老年人的肺癌

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最近二十年來肺癌一直位居台灣癌症死因的前二名，肺癌是屬於一種較好發於晚年的癌症。發生率隨著年齡增加而逐漸增高，到 80 歲附近到達頂點。由於它是屬於一種老年人的癌症，對於老年肺癌的研究也就相對地顯得重要。 老人肺癌的組織型態與年輕患者稍有差異，鱗狀細胞癌相對比年輕患者多，肺癌的分期也是較早期發現，但是卻較易接受不完整的治療，或是拒絕治療。

雖然我們認為老年人的各種器官功能均較年輕者為差，但是只要小心處理，臨床治療經驗卻發現二者差異不大。一般而言，肺癌的治療原則，不因年紀不同而有明顯差異。 經診斷患有早期非小細胞肺癌的老年患者只要符合手術條件，並且沒有手術禁忌症，均可以施行手術切除，但是宜避免全肺切除手術。至於擴展期或晚期患者均可接受放射治療或化學藥物治療，而且患者耐受性並不比年輕人差。某些文獻報告甚至認為老年人對藥物反應率較年輕人為佳。小細胞肺癌治療原則也不變。台北榮民總醫院自 1987 年至 1996 年共有 6048 位非小細胞肺癌病患。其中 184 人年紀超過 80 歲，另外 127 人年紀小於 40 歲，在小於 40 歲的病患以女性與肺腺癌較多，老年肺癌診斷時的期別相對較年輕人為早。但是，這些小於 40 歲的病患接受較積極治療的方式（如手術切除）比老年人為高。而且，老年病患只接受保守的支持性治療的比率明顯比年輕人為多。其中尚有許多可以改善的空間。台北榮民總醫院胸腔部的肺癌化學治療臨床試驗的經驗也顯示，老年患者接受化學藥物治療的耐受性不比年輕人差，且副作用也沒有明顯增加。

結論：肺癌是一種老人的疾病，只要能夠適當診斷、適當治療，其治療過程與預後和年輕患者並無明顯差異。*（胸腔醫學 2002; 17: 187-193）*

關鍵詞：肺癌，老年人，化學藥物治療，肺葉切除

前　言

最近二十年來肺癌一直位居台灣癌症死因的前二名，自 1999 年起已超越肝癌成為台灣癌症十大死因之首。根據衛生署統計，2000 年台灣地區因肺癌死亡的病例有 6,261 例，死亡率為每十萬人口佔 28.22 人，佔所有癌症死亡率的 19.84%。長期以來，男性肺癌佔男性癌症十大死因之第二位，2000 年男性因肺癌死亡為 4,392 人，每十萬男性人口之 38.69 人；而女性肺癌長期以來都是女性癌症十大死因的第一位，女性因肺癌死亡在 2000 年為 1,869 人，每十萬女性人口之 17.25 人。肺癌是屬於一種較好發於晚年的癌症。發生率隨著年齡增加而逐漸增高，到 80 歲附近到達頂點。[1-2]由於它是一種屬於老年人的癌症，又佔台灣癌症死亡比例約五分之一，對於老年肺癌的研究就相對地重要。

本　文

老年人肺癌的臨床表徵

肺癌是屬於一種較好發於晚年的癌症。發生率隨著年齡增加而逐漸增高，到 80 歲附近到達頂點。只有 5%-10%的病患是在 50 歲以前被診斷出來的。[1-2]一般而言，70 歲以上的肺癌患者與較年輕患者的臨床特徵差異包括有：老年患者初次診斷的期別較早、鱗狀細胞癌較多，合併其他系統疾病的情況也較年輕患者多。[2-3]老年患者接受完整的肺癌分期的檢查的比例較年輕人少、組織學確定診斷的老年病患也比年輕人少。老

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年肺癌較早期別的患者接受手術切除的比例也較年輕人低。[3-4]晚期老年患者接受化學藥物治療的比例也較年輕患者為低。老年肺癌患者經常接受不完整的診斷與治療的原因有可能是因為：患者經常合併有其他疾病，或患者自覺或家屬認為患者年紀已大，不願意再進一步處理，以免增加因診斷與治療帶來額外的痛楚。探討其較少接受化學藥物治療的原因，主要是因為除了患者因年齡因素不願意再接受治療以外，醫師也常常認為患者各個器官（造血功能、腎臟功能、肝臟功能、心臟功能與肺功能等）功能已退化，所以不宜接受化學藥物治療。事實上，只要是合適的患者，老年患者接受化學藥物治療的耐受性不比年輕人差，效果也很好。[5-6]至於為何老年患者診斷出肺癌的期別較早的比例比年輕人多的原因，可能是因為老年人經常有慢性肺部或其他器官的毛病，所以接受定期檢查或健康檢查的機會較多，因而有較高的比例發現較早期的肺癌。[3-4]

老人肺癌的治療原則

有關70歲以上老年患者的治療原則與小於70歲的患者治療原則差異不大，現在詳述於下：

非小細胞肺癌

第一期與第二期非小細胞肺癌的患者還是以開刀手術為原則。荷蘭鹿特丹的癌症中心的學者曾經分析1984-1992年間他們醫院診斷的7,899肺癌病患，他們將患者分為三組，分別是小於60歲、60-69歲之間、70歲或是以上，評估他們接受肺癌切除的比例及手術後30天內的死亡率。結果發現年齡是影響選擇治療方式的因素，而且年齡與手術後的死亡率有關。也就是說，超過70歲的患者接受手術切除的比例較低，手術後死亡率也較年輕人為高（odd ratio = 3.6, 95% confidence interval 1.4-8.9）。所有接受全肺切除手術者的死亡率明顯比接受單肺葉切除或更小範圍的切除者為高（odd ratio = 4.5, 95% confidence interval 2.3-8.8）。經過分析，即使超過70歲病患接受手術切除的危險性還是在可接受的範圍內，故年齡不是決定患者是否接受手術切除的決定因素。[7]近二十年來，大部分胸腔外科的臨床研究報告也均顯示，70歲以上的老年肺癌接受全肺切除的術後30天內或住院內死亡率（8%-21%）均遠高於肺葉或較小範圍切除的死亡率（3%-7%）。[7-12]所以，老年肺癌全肺切除應該要避免，而以肺葉切除為主。在最近的另外一個臨床研究報告也發現，超過70歲的病患接受全肺葉的切除要比接受較小範圍切除預後為差，尤其是合併活動力較差、高血壓、慢性呼吸道性肺疾的病患，如需要進行全肺切除需要審慎考慮。[13]另外，對於此類可以接受手術切除的早期肺癌老年患者也可考慮使用有影像輔助的胸腔鏡手術(video-assisted thoracoscopic surgery)。[14-16]對於因身體因素無法開刀或拒絕開刀的患者，也可以考慮單獨的放射治療。 在 Gauden 等人針對第一期非小細胞肺癌老年患者只接受放射治療（放射劑量50 Gy或更高）的研究裡面發現5年存活率也有34%。[17]

對於第三期非小細胞肺癌老年患者，單獨的放射治療也適合使用於因身體因素無法開刀的 stage IIIA 與 stage IIIB 的患者，甚至較早期的患者。放射劑量可達60 Gy或更高。[18-19] Pignon 等人針對 1,208 位進入歐洲癌症研究與治療組織(European organization for research and treatment of cancer; EORTC)的放射治療臨床試驗的患者所做的研究顯示，年老患者接受高劑量治癒性的放射治療的耐受性以及副作用與年紀較輕的患者並無統計上差別意義。[20]另外，對於因故無法開刀或拒絕開刀的早期老年肺癌病患或是第三期 A 與第三期 B 的病患，除了可單獨施行放射治療以外，也可以同時給予患者化學藥物治療與放射治療。在日本對 40 位 75 歲以上的肺癌患者同時給予化學藥物治療（carboplatin）與放射治療的研究中也發現，在可以評估副作用與效果的38位患者中，主要的副作用是骨髓功能的抑制，而沒有嚴重的食道炎發生。第三期患者的中值生存期（median survival）高達15.1個月，2年存活率也有21%。[21]有關是否值得使用化學藥物治療於晚期非小細胞肺癌老年患者身上，Earle 等人收集 1991 年至 1996 年之間，加入 SEER（surveillance, epidemiology, and end results）計劃的 6,232 位超過 65 歲的第四期非小細胞肺癌患者進行資料分析發現：接受化學藥物治療的患者（2,012位）中值生存期比只接受支持性療法的患者多出33天，一年存活率則增加9%。如果用一般的生存統計（Kaplan-meier method）計算，則中值生存期是 30 週比 23 週。[22] 可見化學藥物治療的效果在老人肺癌也是與較年輕的患者一樣，對患者的延長存活時間是有幫助的。[23-24]

既然化學藥物治療對年老肺癌也有所幫助，我們便須了解哪一種化學藥物是比較好的選擇。一般肺癌病患所接受的治療是以 platinum 類（cisplatin 或 carboplatin）為主的化學藥物治療。[23-24]但是否使用 cisplatin 於老年的肺癌患者則有爭議。[25-26]在 Kubota 等人的研究認為適合使用以 cisplatin 為主的化學藥物治療於活動力良好的老人患者，只要不使用含 mitomycin 的藥物即可。[25]在 Lippe 等人的小型研究裡面，使用 cisplatin 與 gemcitabine 也是可以的。[27]但是，在 Gridelli 的回顧性文章裡面，則認為用 cisplatin 於老年人副作用太

Table 1. Single agent chemotherapy in elderly (≥70 years) NSCLC patients

Agent	Patient No / Evaluable No (schedule)	Median (month) / 1 year survival	Journal / recommend
Vinorelbine	46/41 (25mg/m^2 q week)	7.9	Cancer 2000, yes
Gemcitabine	21 (1250mg/m^2 D1,8 q 3 week)	7.5	Anticancer Res 2000, yes
Docetaxel*	39/38 (36 mg/m^2 /week x 6 q 8 week)	5 / 27%	Cancer 2000, yes
Paclitaxel	28 (210 mg/m^2 3hr D1 q 3 week)	9.8 / 37.1%	Cancer Chemother Pharmacol 2000, yes

*> 65 years.

Table 2. Combination chemotherapy in elderly (≥70 years) NSCLC patients

Agent	Patient No (schedule)	R.R. (%)	Median / 1 year survival	Journal / suggest
GEM + NVB *vs* NVB alone	60 (GEM 1200 mg/m^2 + NVB 30 mg/m^2 D1,8 q 3 week)	22	6.8 / 30%	JCO 2000/ GEM + NVB better than NVB alone
	60 (NVB 30 mg/m^2 D1,8 q 3 week)	15	4.2 / 13%	
GEM + NVB (>65 Yr or *)	43 (GEM 1000 mg/m^2 + NVB 25 mg/m^2 D1,8 q 3 week)	34.9	8.4 / 31.1%	Br J Cancer 2000, yes
GEM + NVB (>70 Yr or *)	49 (NVB 25 mg/m^2 + GEM 1000 mg/m^2 D1,8,15 q 4 week)	26	? / 33%	Cancer 1999, yes

R.R.: response rate; GEM: gemcitabine; NVB: vinorelbine.
*Poor PS or unfit for CDDP.

大，甚至連是否值得使用 carboplatin 都值得考慮。[26] 由於以前的臨床研究已顯示較高或較低的 cisplatin 劑量對一般肺癌患者存活時間並沒有影響，[28] 我們認為低劑量的 cisplatin（例如 60-70 mg/m^2/q 3-4 week，尤其是經過 creatine clearance 修正過時）還是可以使用於年老的患者，而且副作用並不大。另外，最近幾年發展使用的四種新的抗非小細胞肺癌藥物均可使用於年老患者（表一）。[26,29-33] 這四種新藥（vinorelbine, gemcitabine, paclitaxel, docetaxel）裡面，只有 vinorelbine 曾經被拿來與不做化學藥物治療，而只是支持性照顧做臨床隨機試驗比較，結果發現接受 vinorelbine 的老年患者生活品質與壽命均比只是支持性照顧的患者為佳，中值生存期間由 21 週延長為 28 週[34,35]。此外，合併 gemcitabine 與 vinorelbine 治療老人肺癌效果也很好，而且副作用也不大。[36-37] Frasci 等人的臨床隨機試驗則發現使用 gemcitabine 合併 vinorelbine 的治療於老年肺癌比單獨使用 vinorelbine 的效果更好（表二）。[38] 所以，老年非小細胞肺癌適合的化學治療選擇包括：單獨使用新的抗癌藥，或是合併較低劑量的 cisplatin（60-70mg/m^2 q 3-4 weeks; 也可考慮以 carboplatin 取代），或是合併二種新抗癌藥（如：gemcitabine + vinorelbine）的治療。[26,33]

小細胞肺癌

對於一般老年小細胞肺癌患者的臨床表徵與是否接受治療的情況，也是類似於老年非小細胞肺癌患者。老年小細胞肺癌的患者合併其他疾病的比例比較高，活動力可能比較差，接受的治療可能比較不完整，而且很少能夠進入臨床研究。[39-40]由於老年小細胞肺癌患者的預後並不比年輕患者為差，醫界還是需要有針對老年小細胞肺癌患者所做的臨床研究，以找出最適合老年小細胞肺癌的治療。[39-41]

很多學者也發現，老年小細胞肺癌的患者如能承受一般的標準治療，則其預後與一般患者無異，若是無法承受治療，則預後相對較差。[40]所以，針對老年小細胞肺癌的患者所做的治療，其劑量強度得針對個別病患做更細膩的調整。[40]話雖如此，由於未有新藥或舊藥證實其單獨使用效果與傳統的 cisplatin + etoposide (EP) 或 cyclophosphamide + adriamycin + vincristine (CAO) 效果是一樣的；而且單獨使用口服的 etoposide 於老年小細胞肺癌患者的預後比傳統的 EP 或 CAO 治療差，原則上還是以使用 EP 或 CAO 為宜。[42-43]

小細胞肺癌依其侵犯範圍可分為侷限期與擴展期。對侷限期的患者而言，化學藥物治療與放射治療併

Table 3. Paclitaxel plus carboplatin or gemcitabine in chemo-naïve NSCLC patients

		<70 Yr	≧70 Yr	*P* value*
Patient No (%)		46 (51.1)	44 (48.9)	
Performance status	1	26	27	0.401
	2	20	17	
Staging	IIIb	16	19	0.274
	IV	30	25	
Cycle received	≦3	19	13	0.710
	≧4	27	31	
Gr 3 leukopenia		7	3	0.316
Gr 3,4 anemia		4	9	0.14
Gr 3 thrombocytopenia		2	3	0.607

*χ^2 test.

用是最好的治療選擇。這個大原則在老年患者也是一樣。[44-45]加拿大國家癌症組織(National Cancer Institute of Canada)有二個針對侷限期小細胞肺癌的合併化學藥物治療與放射治療臨床試驗(BR.3, BR.6)。這二個臨床試驗的其中一個是檢視 CAO 與 EP 交替使用，或是 CAO 先用，再用 EP，二種治療效果有無差異。這二組病患在治療第 18 週開始給予放射治療。另一個是試驗 CAO 與 EP 交替使用，然後檢視早期就開始同時給予放射治療（第 4 週）與較晚才給予放射治療（第 16 週），這二種治療有無差異。[44]二個研究共收集了 608 位病患，其中有 88 位年齡是 70 歲或是超過 70 歲，經過分析發現，這些老年患者還是可以像年輕患者一樣承受同時的化學藥物治療與放射治療，放射治療的範圍與劑量並不需要減少，只是有些老年患者的化學藥物需減量或暫時取消。而且，老年患者與較年輕患者的效果，復發率與存活情況並無明顯差異。所以，年齡不影響侷限期患者接受化學藥物治療合併放射治療的原則，只要小心劑量（化學藥物與放射治療）不要太重即可。[44-45]

Yuen 等人在另一個大型的臨床試驗（381 位患者）也發現：年老的患者（50 位大於 70 歲）對治療（EP 加上放射治療）的效果與生存情況與年輕患者類似，只是年老患者的骨髓功能的抑制（haematologic toxicity）比年輕人明顯。[46]另外，日本的學者也針對是否可用 carboplatin 取代 cisplatin 做了一些臨床研究，並認為 carboplatin 可以取代 cisplatin 用於老年的小細胞肺癌。[47-48]

總之，對老年小細胞肺癌的治療，宜選擇對造血功能抑制較少的藥物（如：EP），剛開始時可以給予較標準的劑量，再給予較細膩的劑量調整，而不宜一開始就選擇較有造血功能抑制的藥物，再給予減量治療。治療的療程須 4-6 個週期，而且不須要維持性治療（maintenance therapy）。[40-41]

台北榮民總醫院在 1987 年至 1996 年之間，共診斷有 6048 位非小細胞肺癌病患。其中，有 127 位年紀小於 40 歲，有 184 位年紀大於 80 歲。[49]經分析後，可以發現年輕患者（小於 40 歲）女性病患與肺腺癌較多，老年病患（大於 80 歲）鱗狀細胞癌較多。老年病患的期別較早期的比率比年輕人多，但接受手術治療的比率比年輕人少。只接受支持照顧治療的病患比率在老年人也明顯較高。這些臨床特點與外國資料均極相似。

有關台灣老年肺癌患者接受化學藥物治療的耐受性情況，在台北榮民總醫院胸腔部近年來的臨床研究裡面也都有提到。[50-51]以最近發表的研究（paclitaxel + carboplatin 比較 paclitaxel + gemcitabine）為例，這二組病患總共 90 人，二組病患無明顯臨床特徵上的差異，而且治療效果相似。將這二組治療 90 位病患合併一起研究時，可以發現年齡小於 70 歲者有 46 人，70 歲或以上者有 44 人。在這二個年齡別之間並無活動力的差異，接受治療的週期在年老這組則多一點，而且對造血功能的副作用與其他種類的副作用在這二組年齡層之間並無差異（表三）。[51]可見台灣老年肺癌患者接受化學治療的耐受性與年輕人沒有明顯差異。

結　論

老年患者承受檢驗與治療的能力是與年輕人相類似的。對這些患者的治療原則應與年輕人類似，而且須要更多的臨床研究來發掘較適合老年患者的治療。由於老年患者合併其他疾病的機會較高，更細心的照顧與評估將對患者有很大的幫助。

參考資料

1. Schottenfeld D. Etiology and epidemiology of lung cancer. In Pass HI, Mitchell JB, Johnson DH, *et al.* Lung cancer – principles and practice. Philadelphia ; Lippincott Williams & Wilkins, 2000: 367-88.
2. Lee-Chiong TL Jr, Matthay RA. Lung cancer in the elderly patient. Clin Chest Med 1993; 14: 453-78.
3. DeMaria LC Jr, Cohen HJ. Characteristics of lung cancer in elderly patients. J Gerontol 1987; 42: 540-5.
4. Nugent WC, Edney MT, Hammerness PG, *et al.* Non-small cell lung cancer at the extremes of age: impact on diagnosis and treatment. Ann Thorac Surg 1997; 63: 193-7.
5. Ozols RF. Cancer in the elderly. Curr Prob Cancer 1993; 17: 147-217.
6. Hickish TF, Smith IE, Ashley S, *et al.* Chemotherapy for elderly patients with lung cancer. Lancet 1995; 346: 580.
7. Damhuis RAM, Dchutte PR. Resection rates and postoperative mortality in 7,899 patients with lung cancer. Eur Respir J 1996; 9: 7-10.
8. Mizushima Y, Noto H, Sugiyama S, *et al.* Survival and prognosis after pneumonectomy for lung cancer in the elderly. Ann Thorac Surg 1997; 64: 193-8.
9. Whittle J, Steinberg EP, Anderson GF, *et al.* Use of Medicare claims data to evaluate outcomes in elderly patients undergoing lung cancer. Chest 1991; 100: 729-34.
10. Romano PS, Mark DH. Patient and hospital characteristics related to in-hospital mortality after lung cancer resection. Chest 1992; 101: 1332-7.
11. Au J, El-Oakley R, Cameron EWJ. Pneumonectomy for bronchogenic carcinoma in the elderly. Eur J Cardiothorac Surg 1994; 8: 247-50.
12. Thomas P, Piraux M, Jacques LF, *et al.* Clinical patterns and trends of outcome of elderly patients with bronchogenic carcinoma. Eur J Cardio-Thorac Surg 1998; 13: 266-74.
13. Dyszkiewicz W. Early post-pneumonectomy complications in the elderly. Eur J Cardio-Thorac Surg 2000; 17: 246-50.
14. Mentzer SJ, DeCamp MM, Harpole DH, *et al.* Thoracoscopy and video-assisted thoracic surgery in the treatment of lung cancer. Chest 1995; 107: 298S-301S.
15. Jaklitsch MT, Bueno R, Swanson SJ, *et al.* New surgical options for elderly lung cancer patients. Chest 1999; 116 (6 Suppl):480S-5S.
16. Kaga K, Park J, Nishiumi N, *et al.* Usefulness of video-assisted thoracic surgery (Two Windows Method) in the treatment of lung cancer for elderly patients. J Cardiovasc Surg 1999; 40: 721-3.
17. Gauden SJ, Tripcony L. The curative treatment by radiation therapy alone of Stage I non-small cell lung cancer in a geriatric population. Lung Cancer 2001; 32: 71-9.
18. Tombolini V, Bonanni A, Donato V, *et al.* Radiotherapy alone in elderly patients with medically inoperable stage IIIA and IIIB non-small cell lung cancer. Anticancer Res 2000; 20: 4829-34.
19. Hayakawa K, Mitsuhashi N, Katano S, *et al.* High-dose radiation therapy for elderly patients with inoperable or unresectable non-small cell lung cancer. Lung Cancer 2001; 32: 81-8.
20. Pignon T, Gregor A, Koning CS, *et al.* Age has no impact on acute and late toxicity of curative thoracic radiotherapy. Radiother Oncol 1998; 46: 239-48.
21. Atagi S, Kawahara M, Ogawara M, *et al.* Phase II trial of daily low-dose carboplatin and thoracic radiotherapy in elderly patients with locally advanced non-small cell lung cancer. Jpn J Clin Oncol 2000; 30: 59-64.
22. Earle CC, Tsai JS, Gelber RD, *et al.* Effectiveness of chemotherapy for advanced lung cancer in the elderly: instrumental variable and propensity analysis. J Clin Oncol 2001; 19: 1064-70.
23. Souquet PJ, Chauvin F, Boissel JP, *et al.* Polychemotherapy in advanced non small cell lung cancer: a meta-analysis. Lancet 1993; 342: 19-21.
24. Non-small cell lung cancer collaborative group. Chemotherapy in non-small cell lung cancer, a meta-analysis using updated data in individual patients from 52 randomized trials. Brit Med J 1995; 311: 899-909.
25. Kubota K, Furuse K, Kawahara M, *et al.* Cisplatin-based combination chemotherapy for elderly patients with non-small-cell lung cancer. Cancer Chemother Pharmacol 1997; 40: 469-74.
26. Gridelli C. Chemotherapy of advanced non small cell lung cancer in the elderly: an update. Crit Rev Oncol-Hem 2000; 35: 219-25.
27. Lippe P, Silva RS, Monterubbianesi C, *et al.* Advanced non small cell lung cancer (NSCLC) in the elderly: symptoms-reliefs after weekly gemcitabine (G) and cisplatin (P). Proc Am Soc Clin Oncol 1999; 18: 514A
28. Gandara DR, Crowley J, Livingston RB, *et al.* Evaluation of cisplatin intensity in metastatic non-small-cell lung cancer: a

phase III study of the Southwest Oncology Group. J Clin Oncol 1993; 11:873-8.

29. Buccheri G, Ferrigno D. Vinorelbine in elderly patients with inoperable nonsmall cell lung carcinoma: a phase II study. Cancer 2000; 88: 2677-85.
30. Altavilla G, Adamo V, Buemi B, *et al.* Gemcitabine as single agent in the treatment of elderly patients with advanced non small cell lung cancer. Anticancer Res 2000; 20: 3675-8.
31. Hainsworth JD, Burris HA 3rd, Litchy S, *et al.* Weekly docetaxel in the treatment of elderly patients with advanced nonsmall cell lung carcinoma. A Minnie Pearl Cancer Research Network Phase II Trial. Cancer 2000; 89: 328-33.
32. Nakamura Y, Sekine I, Furuse K, *et al.* Retrospective comparison of toxicity and efficacy in phase II trials of 3-h infusions of paclitaxel for patients 70 years of age or older and patients under 70 years of age. Cancer Chemother Pharma 2000; 46: 114-8.
33. Manegold C. Treatment of elderly patients with non-small-cell lung cancer. Oncology 2001; 15 (Suppl 6): 46-51.
34. The elderly lung cancer vinorelbine Italian study group. Effects of vinorelbine on quality of life and survival of elderly patients with advanced non small cell lung cancer. J Natl Cancer Inst 1999; 91: 66-72.
35. Gridelli C. The ELVIS trial: a phase III study of single-agent vinorelbine as first-line treatment in elderly patients with advanced non-small cell lung cancer. Elderly Lung Cancer Vinorelbine Italian Study. Oncologist 2001; 6 (Suppl 1): 4-7.
36. Feliu J, Gomez LL, Madronal C, *et al.* Gemcitabine plus vinorelbine in nonsmall cell lung carcinoma patients age 70 years or older or patients who cannot receive cisplatin. Cancer 1999; 86: 1463-9.
37. Beretta GD, Michetti G, Belometti MO, *et al.* Gemcitabine plus vinorelbine in elderly or unfit patients with non-small cell lung cancer. Brit J Cancer 2000; 83: 573-6.
38. Frasci G, Lorusso V, Panza N, *et al.* Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol 2000; 18: 2529-36.
39. Dajczman E, Fu LY, Small D, *et al.* Treatment of small cell lung carcinoma in the elderly. Cancer 1996; 77: 2032-8.
40. Johnson DH. Small cell lung cancer in the elderly patient. Semin Oncol 1997; 24: 484-91.
41. Stephens RJ, Johnson DH. Treatment and outcomes for elderly patients with small cell lung cancer. Drugs & Aging 2000; 17: 229-47.
42. Clark PI. Oral etoposide alone is inadequate palliative chemotherapy: A randomized trial. Proc Am Soc Clin Oncol 1996; 15: 377 (abstr).
43. Harper P, Underhill C, Ruiz de Elvira MC, *et al.* A randomized study of oral etoposide versus combination chemotherapy in poor prognosis small cell lung cancer. Proc Am Soc Clin Oncol 1996; 15: 27 (abstr).
44. Quon H, Shepherd FA, Payne DG, *et al.* The influence of age on the delivery, tolerance, and efficacy of thoracic irradiation in the combined modality treatment of limited stage small cell lung cancer. Int J Radiation Oncology Biol Phys 1999; 43: 39-45.
45. Siu LL, Shepherd FA, Murray N, *et al.* Influence of age on the treatment of limited-stage small-cell lung cancer. J Clin Oncol 1996; 14: 821-8.
46. Yuen AR, Zou G, Turrisi AT, *et al.* Similar outcome of elderly patients in intergroup trial 0096: cisplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. Cancer 2000; 89: 1953-60.
47. Satoh H, Ishikawa H, Funayama Y, *et al.* Management of small cell lung cancer in elderly. Anticancer Res 1999; 19: 4507-10.
48. Okamoto H, Watanabe K, Nishiwaki Y, *et al.* Phase II study of area under the plasma-concentration-versus-time curve-based carboplatin plus standard-dose intravenous etoposide in elderly patients with small-cell lung cancer. J Clin Oncol 1999; 17: 3540-5.
49. Kuo CW, Chen YM, Chao JY, *et al.* Non-small cell lung cancer in very young and very old patients. Chest 2000; 117: 354-7.
50. Chen YM, Perng RP, Yang KY *et al.* A multicenter phase II trial of vinorelbine plus gemcitabine in previously untreated inoperable (Stage IIIB/IV) non-small cell lung cancer. Chest 2000; 117: 1583-9.
51. Chen YM, Perng RP, Lee YC, *et al.* Paclitaxel Plus Carboplatin, Compared to Paclitaxel plus Gemcitabine, Shows Equal Efficacy While More Cost-Effectiveness – A Randomized Study of Combination Chemotherapy Against Inoperable Non-small-Cell Lung Cancer Previously Untreated. Ann Oncol 2002 (in print).

Lung Cancer in the Elderly

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Lung cancer has been the leading cause of cancer death in Taiwan in the past two decades. It is found in older individuals, as well, with a peak incidence at around 80 years of age. There is more squamous cell carcinoma, at a relatively early staging, among this group, and a higher proportion of elderly patients refuse treatment or receive incomplete treatment, when compared with younger patients. In general, the treatment policy for lung cancer is essentially the same, regardless of age. Surgical intervention, such as lobectomy with mediastinal LN dissection, is the treatment of choice for early-stage non-small cell lung cancer (NSCLC), while pneumonectomy should be avoided if possible. Radiotherapy and/or chemotherapy can also be given to locally advanced and/or metastatic NSCLC patients. The treatment policy for SCLC is also the same, regardless of age. There were 6,048 NSCLC patients diagnosed in Taipei VGH between 1987 and 1996. Among them, 127 patients were younger than 40 years old and 184 patients were older than 80 years old. We found significantly more female patients and adenocarcinoma in the younger group, when compared with the older patients. Younger patients received surgical intervention more frequently than the aged, but older patients received supportive care only more frequently than the younger patients. The chemotherapy clinical trials among NSCLC patients in our hospital have also showed that elderly patients tolerate treatment well. In summary, lung cancer is a common disease among the elderly, and the treatment policy and prognosis are essentially the same as for younger patients.
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Key words: lung cancer, elderly, chemotherapy, lobectomy

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胸部X光像判讀的哲學思考

江自得

人類認知的方式

義大利哲學家克羅齊(B.Croce)曾說：「知識有兩種：一是直覺的，一是邏輯的，直覺的知識是對於個別事物的知識 ，邏輯的知識是對於諸個別事物間的關係的知識」。笛卡爾(R.Descartes)也主張人類經由兩種活動達到對事物的認知，即直觀與演繹。他曾聲稱：「人類除了自明的直覺和必然的推論外，找不到別的通向確定知識之路」。法國哲學家柏格森(H.Bergson)則認為，認知的方法有兩種，一種是直覺的，另一種是分析的。他說，所謂直覺是指一種體驗，它使我們置身於客體對象的內部，與對象內部那個獨特的、不可言傳的東西相契合。而分析的方法則是把客體對象歸納成一些已熟知的、與其他對象所共有的要素。進行分析就是把一件事物用某些不是他本身的東西表達出來，所以，任何一項分析都是一種轉述，一種使用符號的闡述。綜合上述觀點，我們可歸結，人類心靈被賦予兩種認識方式，即"直觀知覺"與"理智分析"這兩種方式，兩種能力具有同等的價值，同等的重要性。直覺用於感知具體情景的總體結構，理智分析則從個別的情景中將實體對象與事件的特性分類、抽象化出來，形成具普遍性、共通性的概念。直覺與理智在認識的過程中是互補的，需要精密的相互配合。

直覺的定義

哲學家懷爾德(K.W.Wild)曾列舉過直覺的三十一種定義。可見對於何謂直覺，各家觀點頗不一致，但從下列諸家的說法，我們亦可得知，雖各家說法不一，但相去不遠。

洛克(J.Locke):「直覺是一種直接看到真理的洞察力，一種無須借助於其他任何概念的知覺。」

朗格(S.Langer):「直覺不是一種推理性的思辨能力，而是一種頓悟能力。」

克羅齊:「直覺是一種脫離理智而獨立的感覺活動，一種賦予本來無形式的物質以形式的心靈活動。只有直覺才能掌握事物的內容。」

笛卡爾:「直覺是毫無屏障的和專注的心靈給與我們的。」

柏拉圖:「直覺是人類智慧的最高層次，因為它可把握先驗的本質，而我們經驗中一切事物之呈現正是由於這些先驗本質。」

胡塞爾(E.Husserl):「本質直觀是通向真理的可靠之路。」

柏格森(H.Bergson):「直覺是一種沒有符號特徵的認識方法，一種感應，且由於這種感應把我們自身投入到客體對象之內，以便與其特有的及不能表達的事物相契合。」

總之，直覺是一種掙脫了理智分析而能直接、整體、本能地把握世界精神和人類意識的能力。

理智的定義

理智是人類的思考方式，人類具有天賦的理智來指導行為。

理智是主體(人)對客體(對象事物)的一種思考方式。

理智是一種分析與重組，理智透過無限的力量去分解任何的法則的同時，也可重組任何的體系。

理智與直覺

形象符號不是約定俗成的，而是訴諸感性直覺的，而感性直覺具有人類大體上相同的普遍性，此普遍性建立在人性的共通性上，人性的共通性則建立在人類身體構造的共同性與生活環境的相類似性之上。從生理學來說，人類視覺始於投射到視網膜上的光刺激，視網膜上的數百萬個光感受器，在觀看一個對象時，這眾多的感受器的點狀記錄需在一個統一的意象中組織起來，這個意象最終由在空間中據有不同位置、大小、形狀、顏色的視覺對象所組成。意象的結構層次藉由理智的駕馭而進行認識活動，然而意象總可以提供一種認識情境的直

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覺把握，不論這些意象是透過圖畫、攝影、漫畫或儀式提供出來。這種對於總情景的直覺領悟是整個認識過程的根本基礎。

理智是從對象事物的外部來認識事物，所以我們只能針對對象事物，將其拆解為更小的、各自獨立的單位，藉由對這些被分解出來的獨立單位的認識而達到對對象事物整體的認識。亦即理智分析是一種把對象事物分解為已知的部分(這個對象事物與其他對象事物所共通的元素)的方法，而在這種由已知元素為基礎的分析上的重組也只能透過已知元素去重組一個事物而已。理智只能處理一些空間化、符號化的事物，是無機的，所以理智的運作需要透過一個媒介 —— 語言。理智在本質上是要依賴語言的，語言是思想的重要工具，藉由語言可思考、描述客觀存在。然而語言是一種形上符號，一種抽象的東西，它是固定的、精簡的、大眾化、非個人的，它具有通用價值，且此通用價值是建築在約定俗成的基礎上。因此，它的固定性及外在性的特徵都只能表達一些靜態的、空間化的事物，只能看到事物的共通性，而對特殊的個體性、內在性則無法掌握。

而直覺是一種完全不需借助任何空間中的任何符號特徵的方法，直覺不是分析的方法，而是對對象事物的一種感應，認知者經由感應，把自己融入對象事物之內，與之合而為一。文藝心理學家安海姆(R.Arnheim)認為直覺是經由"場"的一系列變化而活動(視覺是作為一個"場"作用而活動的)，這意味著作為直覺對象的每一部份之位置和功能是由作為一個整體的結構所決定，在這個展現於時空中的總結構裡，每一組成部分都需互相依賴。猶如在觀賞一幅畫時，我們需對構成一幅畫的整體的各個組成部分特徵的重力和張力之知覺性質進行探討，因此，觀賞者經驗到的意象是一個"力"的系統，而這些力"場"中的構成者最終卻需藉由"直覺"來予以檢證、評價之後，方能達到一種平衡和諧的狀態。亦即在認識的過程中，經由"直覺"來統合總體結構及其組成部分而鑄造成一個統一的知覺意像，因此"直覺"是人類認識對象事物的最重要基礎。

但單憑直覺不足以完全認識世界(對象事物)，這種直覺的認識活動必須承擔每一次在不同情境中出現的直覺結果互異的風險。因此，藉由概括得出"一般性"、"普遍性"仍是認識的一個重要支柱，它使我們認識到我們以前感知到了些什麼，我們因而能將以前學到的東西運用於現在。這種經由探查總體結構中各個組成部分之間的關聯性，且分類、歸納，最後得出一般性、普遍性概念的精神活動是屬於理智的領域。

由是觀之，人類藉由理智進行歸納、分析，因而發展出認識客觀世界的方法—— 科學方法，並經由語言，將理智的作用無限發揮，創造出輝煌的科學文明。但，老子曾說：「為學日益，為道日損」，"學"是經驗知識，"道"是直覺形象本身的能力，對於一件事物的組成部分所知愈多，愈不易專注在直覺它的整體形象。X光判讀的訓練，如何在理智與直覺之間尋求最佳的平衡點，是每一位判讀者需竭力以赴的。

科學哲學簡介

從十六、十七世紀以來，與科學基本概念關聯密切的哲學觀念的發展，成為自然科學發展的前驅，並互為體用，相互影響，培根(F.Bacom)與笛卡爾都是知識論的傳道者。經由培根的鼓吹，歸納法成為確立的科學方法達兩世紀之久，而笛卡爾則把伽利略以降那種特殊的思惟、心靈傾向系統性地建構為哲學系統(主體主義哲學)，試圖把自然看成一個可被數學化的世界，並能以嚴格的邏輯推理而得到像數學結論那般具有客觀普遍性的知識，因而奠定了自然科學發展的哲學基礎。主體主義哲學高舉人自己的主體性優位(Primacy of subjectivity)的思想出發，人不再被視為世界的一部分，而被視為是能以自己的力量來量度世界、征服世界、轉化世界、解釋世界的獨立主體，人與世界分開了，並成為對立的存在(主客二元論)，透過科學、勞動對世界(包括自然世界及人的生活世界)加以系統性的、有目的的、持續的理性化，因而造成近二百年來人類科學文明的高速發展。在西方現代科學發展的過程中，科學哲學和科學之發展，存有一種互為體用的關係，各門科學的發展，變成科學哲學研究反思的題材，促成科學哲學的發展；科學哲學的發展又回過頭來促進科學的發展。

對於現代科學哲學的起始點為何，各家看法不一，但多數認為應從實證論算起。19 世紀中葉孔德(A.Comte)首先提出實證論(Positivism)，採取一種極端經驗論的哲學主張，認為人類知識應僅限於收集事實並找尋其間的相關性，再加以實驗驗證，實證論進一步發展之後在 1920 年代由卡那普(R.carnap)、石里克(M.schlick)等人領導下興起主導本世紀英美科學界的哲學思想——邏輯經驗主義，邏輯與演繹法成為科學驗證的主要方法，他們重視科學理論概念與概念、陳述與陳述間的邏輯結構，以及理論的確證程度等問題。巴柏(K.R.Popper)的素樸否證主義(批判理性主義)則重視科學發現的邏輯，庫恩(T.kuhn)等科學歷史主義者則從科學史、心理學、社會學等角度來研究科學發展的結構，之後又有拉卡托斯(I.Lakatos)的研究綱領方法論、勞丹(L.Laudan)的「研究傳統」等修正的哲學觀點。

在進入八〇年代之後，科學哲學的研究日趨蓬勃，

也產生許多新派別，它們在短期內不太可能達成一致的共識，對未來科學界、哲學界的影響亦未可知。我們若以巴柏作為分界，可發現從實證論到巴柏的批判理性主義，無疑是著重在科學知識的靜態結構分析，找出科學知識的可靠基礎上。而巴柏以降，庫恩、拉卡托斯、費耶拉本(P.Feyerabend)等人則逐漸轉為研究科學的動態面，試圖自科學發展的歷史中找尋它的規律。而勞丹則避開了邏輯實證論的困難，修正了拉卡托斯的「研究綱領」，並將庫恩的「典範」(paradigm)觀念擴大成為「研究傳統」，並提出「合理性就在於接受最能有效解決問題的研究傳統」的主張，其實用主義的精神頗值得吾人進一步思考借鏡。

臨床醫學的哲學

臨床醫學面對的客體對象極為複雜，它包含了太多歧異的事實，其眾多的相關因子或組成元素總會因彼此間之盤根錯節而無法獲致如物理學與數學所擁有的確定性、一致性。至目前為止，仍未有任一學派的哲學觀點能完全適用於醫學，尤其臨床醫學。下列一些臨床醫學的特質與事實是我們在建構醫學哲學時必須慎重思考的。

臨床醫學領域的生命現象也有某些或某種程度的規律性，但這些規律通常不具共通性。

臨床醫學是會受時空限制的，充滿機率性的，是常有例外的。

傳統的科學哲學中之某些方法論諸如歸納法、假說演繹法仍是目前臨床醫學研究中所用的核心方法之一。

邏輯經驗主義所使用的嚴格推論法則，對於充斥機會與偶發事件，且常需解釋獨特現象的臨床醫學而言是不能完全適用的。

否證論(falsificationism)曾經為科學研究發展樹立了一個嚴格的標準，但應用在臨床醫學則甚為不妥，因為在充斥著機率性的臨床醫學，隨機出現的單一例外未必能構成否證，在臨床醫學領域欲尋求沒有例外的普遍定律是相當困難的。

一個學說在臨床醫學中的預測大多是機率性的。對臨床醫學研究者或醫師而言，學說能否通過預測性試驗並不重要，重要的是解決問題的能力。就這一點而言，勞丹的實用主義似乎較能獲得共鳴。

庫恩的歷史主義以及其有關科學發展或變遷的歷程：常態科學→科學危機→科學革命→新常態科學→新科學危機→.....這樣的模式雖被批評與科學發展及變遷的實際情況不盡相符，但在臨床醫學我們卻常可找到大致相符的範例(如結核病的治療、哮喘病的治療等)，故其「相對主義的歷史模型」仍有值得參考之處。

圖像及其解讀

圖像(image)是具有繁複意義的平面，它可將空間與時間組成的四度空間簡化為平面的二度空間，並藉由簡化的過程將做為其表述的具體對象事物的意義凸顯出來。人類具有將四度空間抽象化為平面，並將此抽象重新投射回具體對象事物的能力，這種能力除可製作圖像外，並可解讀圖像 —— 將具體對象事物編成二度空間的象徵符號，之後再將此類符號解碼。圖像是視覺捕捉的，當我們閱讀圖像時是把敘事的時間特質帶入圖像中，我們把侷限在框架裡的意義延伸到過去與未來，此意義常不斷改變，從而建構起一套從圖像轉換成文字符號，從文字符號轉換成圖像的語言。而從圖像中重建的時間——空間特質，就像魔術一樣，一切事物能重複自身，也參與意涵的建構。

除了傳統圖像外，由於人類科技文明的進步，逐漸發展出技術性圖像(technical image)。技術性圖像是由機具製作出來的圖像，圖像的意義能自動浮現到圖像的表面，圖像本身似乎和其意義存在於同一真實層面上。技術性圖像這種明顯的非符號性，即「物體性質」(objective)的特性，促使觀看者在觀看圖像時，不把它們當成真正的圖像，這種對技術性圖像缺乏批判態度是危險的，而其之所以危險，乃是由於技術性圖像的客觀性是一種錯覺，它們事實上是圖像，在作為圖像本位上，它們具有象徵意義。在觀看傳統圖像時，我們很容易明白我們面對的是各種符號，解讀圖像即在轉譯此符號及其象徵之意義。而當我們在觀看技術性圖像時所看到的是與對象事物有關但經過全新轉譯的概念。而解讀是個無底洞，各個解讀出來的層次會揭露出一個更為深入而有待解讀的層次，每一個圖像符號只是在知識的海洋中變動的冰山之一角，我們若意欲將任何一個圖像符號解讀到最完全的程度，則有關一個具體對象事物的完整歷史及知識之全部都將被呈顯出來。

X光像作為一種圖像

透過圖像製作及複製的機器，有愈來愈多的事件進入我們的經驗裡，我們可獲得某種東西作為訊息。X光攝影擁有其他圖像系統不曾擁有的力量，因它不需倚賴一位圖像製作者的存在，基本上它是一種光及化學(或電子)的作用過程，機械操作的目的是為了提供更精細、有用的關於"真實"的圖像，此種技術性圖像的發展已造就了圖像與現實間的一種新關係。X光圖像的力量

來自「它們本身也是一種物性現實」，來自它們是「呈現對象的現實狀態的有效工具」——因為它們把現實化為"影"。藉由被拍照，發生於人體的某件事物成為某一訊息系統的一部份被裝配到醫學診斷上的各種分類及儲存計劃裡頭。

X光像經由機具製成技術性圖像，將人體正常的組織器官顯現出來成為"影"。人體構造雖各個不完全相同，但相似性、類同性極高，又人體罹患疾病時之器官或組織產生病變時，疾病在其特殊結構中依循某種類型而存在，一旦當個人的差異性與種種非本質性的偶然事件已被排除之後，疾病本身便能在器質性之網中完成。在其中，諸結構是空間性的，諸決定因子是因果性的，諸現象是解剖學與生理學的，因此我們可歸納其空間性，因果性及解剖學、生理學特徵，尋出其共通性，如此X光像便成為可理智分析的圖像了。

X光像判讀的哲學

X光像判讀本質上是一種臨床醫學的行為，X光像判讀做為一門學問(科)，毋庸置疑是屬於臨床醫學，其異於一般臨床醫學之處在於其他臨床症狀、徵候、實驗數據等皆非圖像，而X光像卻是一種圖像，具有圖像的特質，它是一種待解讀的符號，它具有象徵性，具有空間性、時間性，它必須借助於直覺來作整體的把握，亦需借助理智來對影像組成之細部作分析、歸納。故X光像判讀的哲學異於一般臨床醫學的哲學之處在於它運用藝術哲學中的直覺遠勝於一般臨床醫學。在認識論上，它持著修正的二元論觀點，同時懷抱主觀主義與客觀主義。為了增進判讀的知識與功力，在方法論方面，它同時運用直覺加上歸納法及/或演繹法，這樣的一門學問在醫學上具有其無可替代的特殊性。而X光圖像本身具有隨情境而改變的特質，圖像及其含義經常在看片燈上彼此輝映，閱讀這樣的X光片，猶如走過掛著一幅幅圖畫的長廊，心中應已體認這是一場永無止境的追尋。

重要參考書目

1. Klee,R.(1997). Introduction to the Philosophy of Science:Cutting Nature at Its Seams. New York： Oxford University Press
2. Ruse, M.(1989).Philosophy of Biology. New York : Macmillan Publishing Company.
3. Levi, A.W.(1977). Philosophy and the Modern World. Chicago：University of Chicago Press.
4. Arnheim, R. (1986). New Essays on the Psychology of Art. Berkeley：University of California Press.
   郭小平、翟燦(譯):《藝術心理學新論》。台北：台灣商務印書館
5. Tarnas, R.(1991). The Passion of the Western Mind : Understanding the Ideas That Have Shaped Our World View. New York：Ballantine Books.
   王又如(譯)：《西方心靈的激情：三千年來西方看世界》。台北：正中書局
6. Kuhn, T. (1969/1990). The Structure of Scientific Revolutions. Chicago: The University of Chicago Press
   王道還等(譯)：《科學革命的結構》。台北：遠流出版公司。
7. Masterman, M. (1970/1993). Criticism and Growth of Knowledge. Cambridge: Cambridge University Press.
   周寄中(譯)：《批判與知識的增長》。台北：桂冠圖書公司。
8. Feyerabend, P.K. (1978/1996). Against Method : Outline of an Anarchistic Theory of Knowledge. London: Verso.
   周昌忠(譯)：《反對方法》。台北：時報文化。
9. Laudan, L. (1992). Progress and its Problems: Toward a Theory of Scientific Growth. London: Routledge & Kegan Paul.
   陳衛平(譯)(1992)：《科學的進步與問題》。台北：桂冠圖書公司。
10. 舒煒光、邱仁宗(編)(1991):《當代西方科學哲學述評》。台北：水牛出版社。
11. 舒光(1987): 《科學哲學導論》。台北：水牛出版社。

Clinical Manifestations of 35 Cases of Narcolepsy

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Background: Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, and hypnagogic hallucinations. This study was designed to evaluate the clinical presentation of narcolepsy patients during the past 10 years at Taipei Veterans General Hospital (Taipei VGH).

Methods: We retrospectively reviewed the medical charts and polysomnographic results of 35 narcoleptics seen between 1992 and 2001 at Taipei VGH. Patient characteristics, clinical symptoms, response to treatment, and a telephone questionnaire regarding quality of life, academic achievement, job performance, and history of automobile accidents, were analyzed.

Results: There were 19 male and 16 female patients in total. The mean age at onset of symptoms was 21 years. The average delay between symptom onset and the diagnosis of narcolepsy was 12 years. While EDS (100%) was the principal symptom, 22 (63%) had cataplexy, 19 (54%) had sleep paralysis, and 16 (46%) had hypnagogic hallucinations. Only 11 (31%) experienced the full tetrad. Among the 22 patients whose symptoms developed before 20 years of age, 14 (64%) experienced a marked deterioration in academic performance and 10 (45%) had bad grades. For patients older than 20 years of age (n = 26), 10 (38%) reported a poor job performance. Among the 23 who drove a vehicle, 18 (78%) reported falling asleep during driving, and 12 (52%) had had sleep-related driving accidents. Patients with bad grades and bad job performance had significantly shorter mean sleep latency and more sleep onset rapid eye movement periods (SOREMP) on the Multiple Sleep Latency Test (MSLT) than patients with good grades and good job performance. Patients with sleep-related driving accidents had significantly higher Epworth Sleepiness Scale (ESS) scores than patients without driving accidents. All patients were treated with methylphenidate and/or antidepressants. However, 24 patients did not receive regular treatment and follow-up. Of these, 13 reported ineffective treatment and 10 disliked lifelong therapy with medication.

Conclusions: Narcolepsy has a great impact on quality of life. Its diagnosis is often not made until a decade after symptoms develop. During the initial investigation, the MSLT and ESS provide important information about the prognosis. Current drug therapies are symptomatic and only modestly effective. A greater awareness of the pathophysiology and symptoms of narcolepsy may lead to an early diagnosis and an avoidance of serious consequences, such as traffic accidents. ***(Thorac Med 2002; 17: 198-209)***

Key words: narcolepsy, cataplexy, multiple sleep latency test

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Introduction

Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, and hypnagogic hallucinations. The clinical features of narcolepsy usually develop in the second or third decade of life, although they may start as early as 2 years of age [1]. After a relatively brief period of progression, narcolepsy tends to stabilize. However, it rarely completely disappears. Although narcolepsy can have serious consequences, it is frequently under-recognized and under-diagnosed. Not only is the narcoleptic patient's quality of life severely compromised, but psychosocial function, academic performance, and employment are also markedly impaired [2].

Narcolepsy is a relatively common disease with an estimated prevalence of 20 to 60 per 100,000 [3-4]. The disorder has not been extensively studied and has seldom been reported in Taiwan. We herein present a study designed to evaluate the clinical presentation of patients diagnosed with narcolepsy during the past 10 years at Taipei VGH.

Methods

We retrospectively reviewed the medical charts and polysomnographic results of 35 patients with narcolepsy, seen between 1992 and 2001 at Taipei VGH. All patients had received a comprehensive clinical evaluation, and had undergone diagnostic polysomnography and a subsequent Multiple Sleep Latency Test (MSLT). During polysomnography, the following were recorded, using standard techniques: electroencephalogram, electrooculogram, chin and leg electromyograms, electrocardiogram, and respiration monitoring (Alice 4, Respronics, USA). Respiration was measured with oro-nasal thermistors to determine airflow, thoracic and abdominal efforts, and pulse oximetry. All studies were scored manually, by experienced polysomnographic technicians, for sleep stages, leg movements, and respiration. MSLTs were performed using published guidelines [5], and consisted of five nap tests at 2-hour intervals. The mean sleep latency on the MSLT was defined as the mean time from lights-out to the first 30-second epoch scored as sleep. A sleep onset REM period (SOREMP) was defined as one or more epochs of REM sleep occurring within 15 minutes of the first epoch scored as sleep. Our diagnostic criteria for narcolepsy were mainly based on the International Classification of Sleep Disorders Criteria [6], except that a cut-off value for a mean sleep latency < 8 minutes during the MSLT was used, as advocated by Moscovitch [7] (Table 1). Patient characteristics, clinical symptoms, and therapies were analyzed. In order to study the impact on quality of life, we conducted telephone interviews with the patients, and investigated the Epworth Sleepiness Scale (ESS) [8] scores and their influence on academic grades, job performance, and automobile accidents. The ESS, a validated questionnaire, is used to measure the patient's general level of daytime sleepiness. Patients rate the likelihood of falling asleep in each of eight common situations in daily life,

Table 1. Diagnostic criteria for narcolepsy used in our study

A.	Complaint of excessive sleepiness or a history compatible with excessive sleepiness
B.	Cataplexy
C.	Associated symptoms: sleep paralysis, hypnagogic or hypnopompic hallucinations, disrupted night sleep
D.	Mean sleep latency < 8 minutes and two or more sleep onset REM periods on an initial MSLT or on a follow-up MSLT when the initial MSLT was not diagnostic.
E.	No medical disorder, psychiatric disorder, or other sleep disorder sufficiently severe to account for sleepiness, associated symptoms and sleep onset REM periods

Minimal criteria: A + B or A + C + D + E

using a 4-point scale. A score of more than 16 indicates a high level of sleepiness. Academic grades and job performance were classified at three levels (good, average, and bad). Among those patients who drive, incidences of falling asleep during driving and sleep-related driving accidents were investigated. We defined sleep-related driving accidents as driving accidents due to excessive sleepiness or falling asleep while driving. They were classified into major and minor accidents, based on the occurrence of injury. For those patients without regular follow-up, we also analyzed the reasons for being lost to follow-up.

The polysomnographic results of the narcoleptics were compared with those of 31 controls, using a Student's *t* test. The control group was mainly hospital employees who worked during the day, and who gave a history of normal sleep habits. Among patients with differing academic performance, we tested the difference in ESS scores, sleep latency on polysomnography (SL-LAT), mean sleep latency on the Multiple Sleep Latency Test (MSLT-LAT), and SOREMPs, respectively, using one-way ANOVA, and then post hoc Scheffe tests. The same tests were performed to evaluate the differences in the four dependent variables in patients with differing job performances, and in patients with various incidences of sleep-related driving accidents. All data analyses were made using SPSS software, version 10.0. A p value less than 0.05 was considered significant.

Results

Clinical Presentation

The clinical features of our narcolepsy patients are summarized in Table 2. There were 19 male (54%) and 16 female (46%) patients. The mean age at onset of symptoms was 21 years, with a range of 8 to 45 years. The average delay between symptom onset and the diagnosis of narcolepsy was 12 years. While all patients (100%) had EDS as the principal symptom of narcolepsy, 22 (63%) had cataplexy, 19 (54%) had sleep paralysis, and 16 (46%) had hypnagogic hallucinations. Only 11 patients (31%) experienced the full tetrad. All patients initially presented with EDS alone or in combination with sleep paralysis and/or hypnagogic hallucinations. Other less frequent symptoms included disturbed nocturnal sleep (6 patients) and depression (5 patients). In 6 patients, mild obstructive sleep apnea was also diagnosed, but improved after nasal CPAP treatment. However, their sleepiness and the results of repeated MSLTs did not improve after this treatment.

Table 2. Clinical Features of 35 Narcoleptics

Clinical Features	Measurement
Height (cm)	162.9 ± 8.9
Weight (kg)	64.5 ± 14.1
BMI (kg/m^2)	24.3 ± 4.9
Sex (M/F)	19/16
Age of diagnosis (yr)	32.8 ± 16.2
Age at onset (yr)	21.1 ± 11.4
Delay diagnosis (yr)	12.0 ± 13.2
Symptoms— no. (%)	
EDS	35 (100)
Cataplexy	22 (63)
Sleep paralysis	19 (54)
Hypnagogic hallucinations	16 (46)
All four symptoms	11 (31)

Definition of abbreviations. BMI=body mass index; EDS=excessive daytime sleepiness

Polysomnography and the MSLT

The polysomnographic results of the narcoleptics and the controls are shown in Table 3. Compared with the control group, the patients with narcolepsy had significantly more stage 1 and REM sleep, and less slow wave sleep (stage 3 and stage 4 sleep). Sleep efficiencies, sleep stage changes, and the amount of stage 2 sleep did not differ statistically (Figure 1). There was a tendency toward shorter sleep latency and shorter REM latency in patients with narcolepsy, but there was no significant difference (Figure 2). On the MSLT, the average mean sleep latency was 4.6 ± 2.9 (SD)

Table 3. Polysomnographic Results: Narcolepsy vs. Normal Control

	Narcolepsy (n=35)		Control (n=31)		
Measurement	Mean	SD	Mean	SD	p Value
Age (yr)	32.8	16.2	36.4	10.4	0.288
BMI (kg/m^2)	24.3	4.9	24.1	4.2	0.870
Stage 1 (% of SPT)	16.7	7.8	10.8	7.8	0.003★
Stage 2 (% of SPT)	40.7	11.6	43.8	11.2	0.282
Stage 3 (% of SPT)	6.9	5.5	10.4	4.4	0.006★
Stage 4 (% of SPT)	6.0	8.1	11.0	8.8	0.019★
SWS (% of SPT)	13.0	9.6	21.4	10.7	0.001★
REM sleep (% of SPT)	14.8	8.7	9.8	4.4	0.003★
Sleep latency (min)	7.8	6.9	11.2	12.0	0.154
REM latency (min)	80.4	81.5	105.0	51.8	0.154
Sleep efficiency (%)	83.7	11.4	84.8	7.1	0.643
Stage change	164.3	54.0	155.5	37.4	0.455
RDI (RD/HR)	1.8	2.8	1.3	1.9	0.412

★ $p < 0.05$

Definition of abbreviations. SD=standard deviation; SPT=sleep period time; SWS=slow wave sleep; REM=rapid eye movement; RDI= respiratory disturbance index; RD=respiratory disturbance

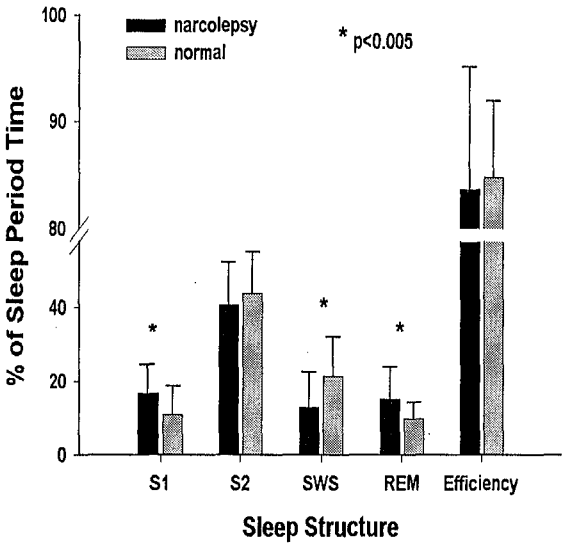

Fig. 1. A comparison of sleep structure between the narcolepsy and the control groups. S1=stage 1; S2=stage 2; SWS=slow wave sleep; REM=rapid eye movement

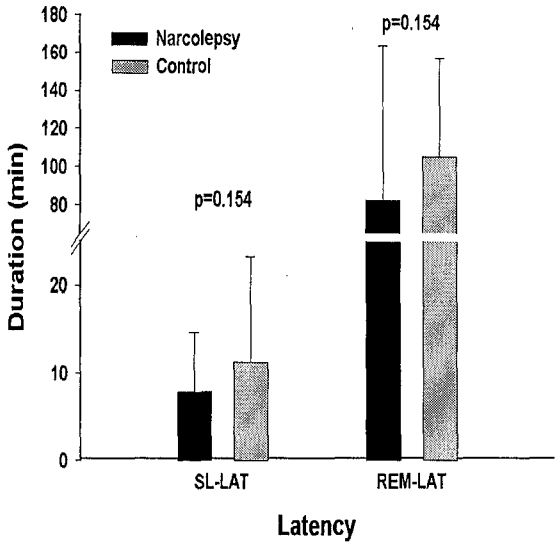

Fig. 2. A comparison of sleep latency and REM latency on polysomnography between the narcolepsy and the control groups. SL-LAT= sleep latency; REM-LAT= REM latency.

and the mean SOREMP was 3.7 ± 1.1 (SD).

Impact on Daily Life

Of the total 35 patients, we were able to complete telephone interviews with 31. Of the narcolepsy tetrad, EDS was the most debilitating symptom in the majority of patients. The mean ESS score was 19.0 ± 2.2 (SD), with a range of 14 to 22. Twenty-eight patients (90%) had ESS scores of 16 or more. According to the original ESS study by Johns MW [8], the mean ESS score for normal controls was 5.9 ± 2.2 (SD) and the mean ESS scores for patients with severe obstructive sleep apnea, or narcolepsy were 16.0

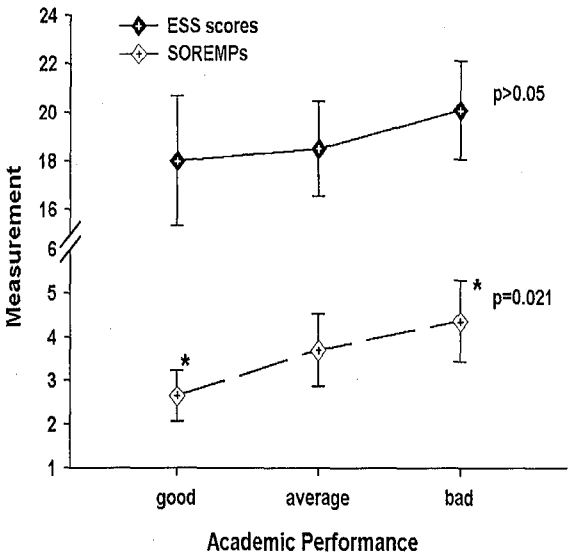

Fig. 3. ESS scores and SOREMPs in patients with differing academic performance. ESS= Epworth Sleepiness Scale; SOREMPs=sleep onset rapid eye movement periods.
SOREMPs: good vs. bad p=0.021

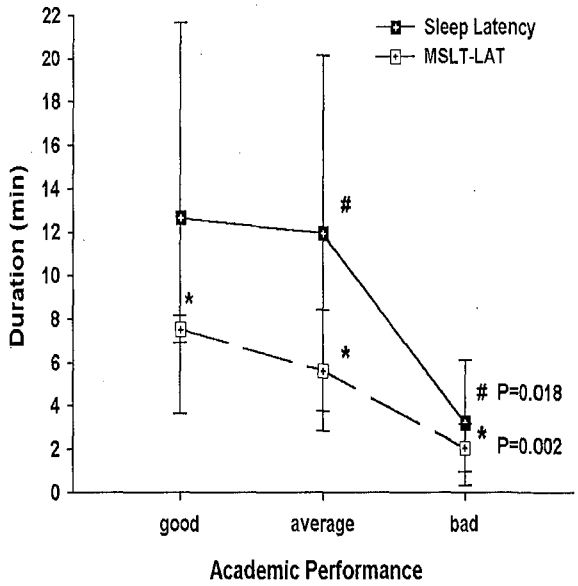

Fig. 4. Sleep latency on polysomnography and mean sleep latency on the MSLT in patients with differing academic performance. MSLT-LAT= mean sleep latency on the Multiple Sleep Latency Test.
Sleep latency: average vs. bad p=0.018.
MSLT-LAT: average vs. bad p=0.002; good vs. bad p=0.002

± 4.4 (SD), and 17.5 ± 3.5 (SD), respectively. Therefore, most of our patients with narcolepsy had a high level of daytime sleepiness. Among the 22 patients whose symptoms developed before 20 years of age, most experienced a severe influence on their academic grades. Ten patients (45%) had bad grades, 9 patients (41%) had average grades, and only 3 patients (14%) reported their grades as good. Moreover, 14 patients (64%) experienced a marked academic decline. In other words, patients achieved at their usual baseline level before symptoms developed or during the early years of symptoms developement. Then, once symptoms had progressed, the deterioration in academic performance was usually obvious and severe. During the time of our investigation, 26 patients were older than 20 years of age. With respect to job performance, 10 patients (38%) reported poor, 13 patients (50%) average, and only 3 patients (12%) revealed a good job performance. In addition, 3 patients were unemployed. Among the 23 drivers, 18 (78%) reported falling asleep during driving and 12 (52%) had had sleep-related driving accidents. Of these 12 patients, 2 experienced life-threatening major accidents and the others minor accidents.

One-way ANOVA demonstrated significant differences in the MSLT-LATs ($F = 13.04$, $df = 2,21$; $p < 0.001$) and SOREMPs ($F = 5.02$, $df = 2,21$; $p = 0.017$) of patients with differing academic performance. Post hoc tests between paired groups showed that the MSLT-LATs for the bad grades group was significantly shorter than those for the average ($p = 0.002$) and good groups ($p = 0.002$). The SOREMPs for the bad grades group were significantly greater in number than those for the good grades group ($p = 0.021$) (Figures 3 and 4).

Between patients with different job performance, one-way ANOVA demonstrated significant differences in the MSLT-LATs ($F = 3.66$; $df = 2,23$; $p = 0.042$) and SOREMPs ($F = 4.14$; $df = 2,23$; $p = 0.028$). Post hoc tests between paired groups showed that the SOREMPs for the bad job performance group were significantly greater in number than those for the good group ($p = 0.033$). But the

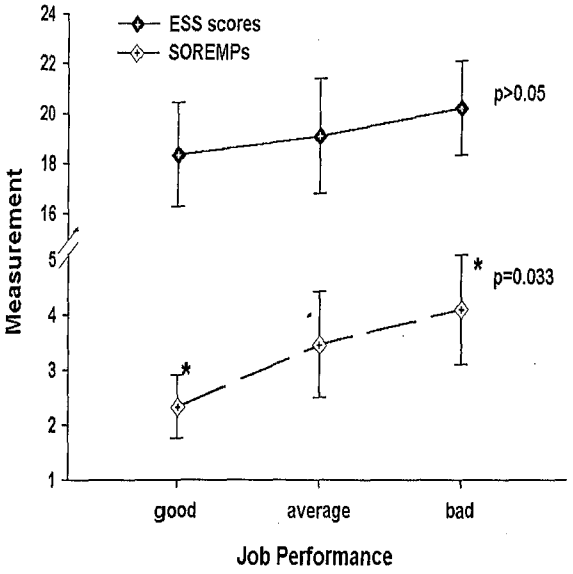

Fig. 5. ESS scores and SOREMPs in patients with differing job performance. ESS=Epworth Sleepiness Scale; SOREMPs=sleep onset rapid eye movement periods.
SOREMPs: good vs. bad p=0.033

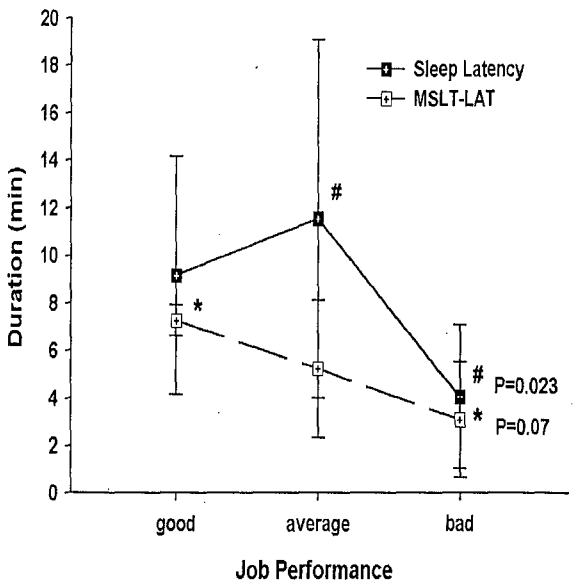

Fig. 6. Sleep latency on polysomnography and mean sleep latency on the MSLT in patients with differing job performance. MSLT-LAT= mean sleep latency on the Multiple Sleep Latency Test.
Sleep latency: average vs. bad p=0.023.
MSLT-LAT: good vs. bad p=0.07

MSLT-LATs for the bad job performance group did not differ significantly from those for the good job performance group during the post hoc tests (p = 0.070) (Figures 5 and 6).

For patients with different incidences of sleep-related automobile accidents, one-way ANOVA showed significant differences in ESS scores between patients with and without sleep-related driving accidents (F = 6.34; df = 3,19; p = 0.004), but the ESS scores showed no linear relationship with the numbers of accidents. Post hoc tests between paired groups showed no significant difference in ESS scores between patients with one, two or three driving accidents. (Figures 7 and 8).

Treatment and Follow-Up

All patients received methylphenidate therapy, initially. The average dosage was 30 mg daily (range, 20-60 mg per day). Patients who frequently suffered from cataplectic attacks, sleep paralysis, or hypnagogic hallucinations also received antidepressant therapies. Although most patients reported a substantial improvement in EDS initially, the effects of long-term treatment with methylphenidate were variable. Only 11 of the 35 patients received long-term treatment, and 24 had neither regular treatment nor follow-up. We analyzed the reasons these 24 patients were lost to follow-up. Thirteen patients reported ineffective treatment, 10 disliked lifelong therapy with medication, and 4 reported side effects when using methylphenidate (irritability, palpitation, and tremor).

Discussion

Narcolepsy is an incurable, debilitating sleep disorder, and is characterized by excessive sleepiness that typically is associated with cataplexy and other rapid eye movement (REM) sleep phenomena such as sleep paralysis and hypnagogic hallucinations. It was first described more than 120 years ago [9], but its etiology is unknown. There have been extensive studies in Western countries. Next to sleep deprivation and obstructive sleep apnea syndrome, narcolepsy is a

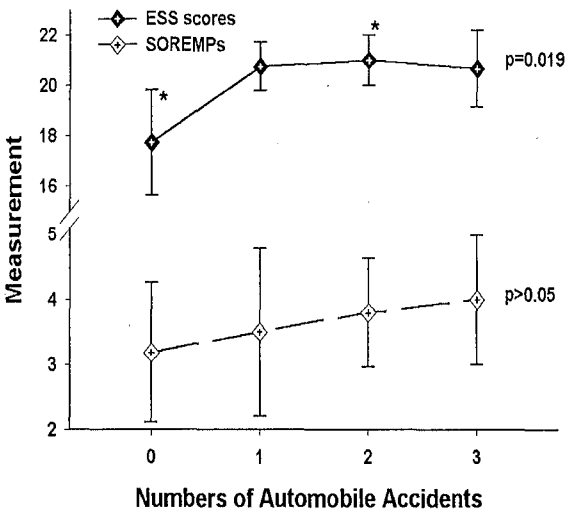

Fig. 7. ESS scores and SOREMPs in patients with differing incidences of sleep-related automobile accidents. ESS=Epworth Sleepiness Scale; SOREMPs=sleep onset rapid eye movement periods.
ESS scores: without accidents vs. 2 accidents p=0.019

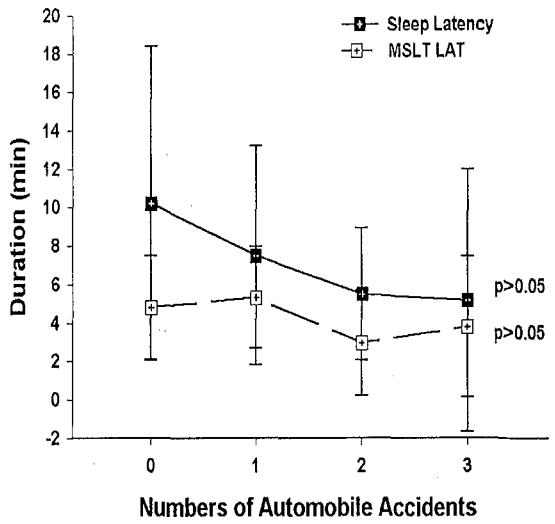

Fig. 8. Sleep latency on polysomnography and mean sleep latency on the MSLT in patients with differing incidences of sleep-related automobile accidents. MSLT-LAT= mean sleep latency on the Multiple Sleep Latency Test.

major cause of excessive daytime sleepiness [10]. According to several studies, narcolepsy has an estimated prevalence of 20 to 60 per 100,000 [3-4]. The highest prevalence is reported in Japan (160/100,000) [11], and the lowest in Israel (0.23/100,000) [12]. According to these data, there may be 4,000 to 12,000 cases of narcolepsy in Taiwan. However, the study of narcolepsy in Taiwan is lacking. This study presents data on the clinical manifestations and our experience with narcolepsy patients at Taipei-VGH during the past 10 years. To our knowledge, our study is the first large report regarding patients with narcolepsy in Taiwan.

Among the 35 cases presented in our study, about half were diagnosed in the past 2 years, indicating the widespread application of sleep studies and the increasing recognition of narcolepsy by clinicians in recent years. As more attention is directed toward understanding narcolepsy, the numbers of cases diagnosed in the future will increase. In our study, the mean age at onset of symptoms was 21 years, and 63% of patients had an onset of symptoms before 20 years of age. The data indicate that more than half of our patients experienced symptoms during childhood or early adolescence. However, the average delay between symptom onset and diagnosis was 12 years. Patients are often diagnosed long after the onset of symptoms, because not only patients and their family members but also teachers and clinicians lack knowledge of the symptoms of narcolepsy. Clinicians often assume that a patient's EDS is due to inadequate nocturnal sleep rather than a medical disorder. The delay in obtaining a diagnosis leads to years of untreated symptoms during the important childhood years.

EDS is the principal symptom of narcolepsy. Most patients are initially identified because of inappropriate, severe daytime sleepiness that interferes with their functioning. EDS is often expressed in two different ways, the first being a continuous feeling of sleepiness, and the second being irresistible sleep attacks. Most patients experience both aspects of sleepiness. Our findings suggest a high level of daytime sleepiness in most patients with narcolepsy (the mean ESS score is 19). Other clinical symptoms (cataplexy, sleep paralysis, and hypnagogic hallucinations) can be

explained by the inappropriate intrusion of "REM sleep" in the awake state. Cataplexy, the most specific symptom of narcolepsy, is a sudden and reversible decrease in or loss of muscle tone, most frequently elicited by an emotional event such as anger or laughter. Cataplectic attacks may range from mild to severe. Mild attacks can cause facial weakness, slurred speech, drooping eyelids, weakened grip, head nodding, or buckling of the knees. Severe attacks can result in physical collapse. In sleep paralysis, a patient becomes transiently unable to speak or move before sleep onset or just after awakening. Hypnagogic hallucinations are vivid, frightening, dream-like experiences that occur during the transition between wakefulness and sleep. Similar experiences that occur upon awakening are termed hypnopompic hallucinations. Although cataplexy is unique to narcolepsy, our study indicates cataplexy occurs in about two thirds of our patients, and the other two symptoms in about one half of them. Only about one third of our patients develop the full tetrad. Therefore, additional ancillary investigations, such as polysomnography and the MSLT, are necessary for the diagnosis of narcolepsy.

Narcolepsy has a great impact on many aspects of life. Controlled questionnaire studies demonstrate that most patients have educational and occupational problems, even when treated properly [2,13]. Moreover, the impact of narcolepsy is often more severe than that of other chronic diseases, such as epilepsy [14]. Our study indicates a severe influence on academic and job performance in our patients. Because the majority (63%) of our patients had an onset of symptoms before 20 years of age, the influence of narcolepsy on children and adolescents is worthy of emphasis. Many of these young patients experience marked academic deterioration once symptoms develop. At the same time, the parents and teachers usually perceive these children and adolescents with narcolepsy as lazy, unmotivated, or intellectually dull. Not only the people around the patients, but also the patients themselves fail to recognize that they have a disease, and do not seek treatment. Over time, they are stigmatized because of their prominent sleepiness, and classmates may use nicknames such as " sleep devil " to ridicule them. Not until several years later are their symptoms finally attributed to narcolepsy rather than laziness.

Persons with narcolepsy are particularly prone to automobile accidents because they easily fall asleep while driving. Eighteen (78%) of the 23 drivers in our patient group have reported falling asleep while driving, and 12 patients (52%) have had sleep-related driving accidents. Our investigation is consistent with a previous study conducted by Cohen FL, et al [15]. They reported that almost 75% of narcoleptic patients had fallen asleep while driving, compared with only 12% of the controls, that 56% had experienced near-accidents, and that another 21% were involved in automobile accidents (compared with 11% and 2%, respectively, among the controls). Our study also demonstrates that patients with higher ESS scores have a significantly higher risk for sleep-related driving accidents. Eighty-five percent of patients with ESS scores 20 or more have experienced sleep-related driving accidents. Because of the high risk of automobile accidents among narcoleptics, driving is prohibited in several countries. Other common accidents experienced by our patients included falls during cataplectic attacks and burns caused by falling asleep while smoking.

The diagnosis of narcolepsy is based primarily on the clinical symptoms and sleep studies. Although some investigators believe that the clinical association of EDS and cataplexy is pathognomonic of narcolepsy, we think objective sleep laboratory diagnosis is imperative for several reasons. First, the history of cataplexy may be difficult to affirm. Absolute cataplexy with physical collapse is uncommon, and most commonly, cataplexy is only partial. Second, only about two-thirds of patients develop cataplexy. Third, cataplexy can occur, though rarely, in association with a variety of other disorders, such as Niemann-Pick disease type C [16], Norrie's

disease [17], and midbrain tumor [18]. Furthermore, the pharmacological treatment for narcolepsy is lifelong and potentially addictive. Therefore, before putting a patient into a chronic, incurable condition, every effort should be made to confirm the diagnosis.

Formal sleep studies for narcolepsy should consist of a nocturnal polysomnography and a MSLT. When narcolepsy is suspected, a nocturnal polysomnography should be performed to eliminate other causes of EDS, such as sleep apnea and periodic limb movement disorder. The specific findings for narcoleptics include short sleep latency and short REM latency [19]. However, our study showed no significant difference in sleep latency between the narcolepsy group and the control group. Several explanations for this exist. First, although sleep latency is a measure of sleepiness, it cannot completely classify narcoleptics and controls, there being some degree of overlap between the groups [20]. Some patients with narcolepsy have less intense EDS and longer sleep latencies than others. On the other hand, some normal controls have short sleep latencies sufficiently similar to the pathological group. Second, the EDS of a narcoleptic fluctuates on a day-to-day basis, which leads to a day-by-day variability of sleep latency [20]. Third, although there is a tendency toward a short sleep latency in narcoleptics (as shown in Figure 2), the relatively small size of our study may hinder the detection of a significant difference between the groups. Fourth, the first-night effect may influence sleep latencies in both groups, and thus decrease their differences.

The MSLT is used to confirm the diagnosis of narcolepsy. According to ICSD criteria, narcolepsy is defined by a mean sleep latency of 5 minutes or less and at least two SOREMPs during five naps. In our study, we used a cut-off value for a mean sleep latency of less than 8 minutes, as Moscovitch et al., have advocated [7]. However, the MSLT cannot be used in isolation to confirm or exclude narcolepsy. According to an investigation conducted by Aldrich et al., only 71% of narcoleptics with cataplexy have a mean sleep latency of < 8 minutes and two or more SOREMPs on the initial MSLT [21]. In another study of 306 narcoleptics, Moscovitch and colleagues showed that a polysomnography evaluation, followed by a MSLT, demonstrated two or more SOREMPs in 84% of cases [22]. These findings suggest that a thorough clinical history, coupled with polysomnography and MSLT evaluation are essential to the diagnosis of narcolepsy.

Our findings suggest that MSLT findings and ESS scores are valuable for predicting impact on quality of life at the time of diagnosis. Patients with bad grades and bad job performance have significantly shorter MSLT-LATs and more SOREMPs than patients with good grades and good job performance. Narcoleptics who have experienced sleep-related driving accidents have significantly higher ESS scores than patients without driving accidents. However, a major limitation of our study is that many confounding variables, besides sleepiness, may affect academic and occupational achievement. Another limitation of our report is the relatively small number of patients in this retrospective study. Therefore, MSLT findings and ESS scores must be interpreted cautiously. They cannot be used independently to predict patient outcome. The results of the MSLT indicate the influence of narcolepsy on grades and job performance. High ESS scores are associated with a high risk of sleep-related driving accidents in narcoleptics.

The management of narcolepsy requires both pharmacologic and non-pharmacologic interventions. Optimizing nocturnal sleep duration and the taking of short daytime naps are important coping strategies. Narcoleptics characteristically wake up refreshed, and there is a refractory period of one to several hours following a nap. A 15 to 20 minute nap taken three times daily helps maintain a satisfactory level of vigilance. Patients frequently report that daytime naps are superior to stimulants for the relief of daytime sleepiness. Pharmacologic interventions include stimulants for EDS, and REM-suppressing antidepressants for REM sleep phenomena (cataplexy, sleep

paralysis, and hypnagogic hallucinations). The majority of patients with narcolepsy require medications for the symptomatic relief of daytime sleepiness. Although the currently prescribed stimulant (methylphenidate) is considered effective, it cannot abolish sleepiness completely. Besides, stimulants for sleepiness are frequently associated with sympathomimetic side effects. Our study indicates that the majority of our patients are unsuitable for methylphenidate therapy. Less than one-third of our patients have received long-term treatment. Because many patients expect a dramatic effect or even "a cure" from taking medication, they dislike enjoying only a modest effect at the expense of lifelong therapy with medication. They are apt to be lost to follow-up and search for other options, such as Chinese herbal drugs or religious support. Therefore, around the time of diagnosis, it is important that patients, as well as their family members, be given accurate information about narcolepsy.

A new wake-promoting agent, modafinil, has been shown to be effective in reducing EDS in large, randomized, placebo-controlled studies [23-24]. Although the exact mechanism of its action is unknown, modafinil differs from the traditional dopaminergic and catecholaminergic-enhancing stimulants. It is generally well-tolerated, with minimal adverse effects and a low abuse potential. When available, it may be an important therapeutic option for the treatment of narcolepsy.

Although narcolepsy is currently defined as a "disorder of unknown etiology", recent advances in narcolepsy research reveal that abnormalities in the hypocretin neurotransmission system play an important role. Nishino et al., showed that hypocretin levels in the cerebral spinal fluid (CSF) were undetectable in seven of nine patients with narcolepsy, suggesting impaired hypocretin production in many narcoleptics [25]. Thannickal et al., reported reduced numbers of hypocretin neurons in the hypothalami of four narcoleptic patients [26]. These findings indicate a loss of hypocretin production in the brains of human narcoleptic patients. Because most cases of human narcolepsy are strongly associated with HLA-DQB1*0602 [3], an autoimmune-mediated destruction of hypocretin-producing cells, analogous to insulin-dependent diabetes, is suggested [27]. But this hypothesis is unproven. Nevertheless, the hypocretin deficiency in narcoleptics suggests that the administration of hypocretins or their agonist may be an effective treatment in the future.

In conclusion, many aspects of the life of narcoleptics are severely compromised, but the diagnosis of narcolepsy is frequently delayed for a decade or more. Besides their role as diagnostic tools, the MSLT and ESS provide important information about the prognosis. The mean sleep latency and SOREMPs on the MSLT are good indicators of the influence of narcolepsy on academic and job performance. The ESS scores help clinicians estimate the risk of sleep-related driving accidents in narcoleptics. Although treatment for narcolepsy remains far from satisfactory, the use of a new treatment modality, including modafinil or a possible hypocretin therapy, combined with appropriate coping strategies, will substantially improve the outlook for patients with narcolepsy.

References

1. Guilleminault C, Pelayo R. Narcolepsy in prepubertal children. Ann Neurol 1998; 43: 135-42.
2. Goswami M. The influence of clinical symptoms on quality of life in patients with narcolepsy. Neurology 1998; 50: S31-6.
3. Mignot E. Genetic and familial aspects of narcolepsy. Neurology 1998; 50: S16-22.
4. Hublin C, Partinen M, Kaprio J, *et al.* Epidemiology of narcolepsy. Sleep 1994; 17: S7-12.
5. Carskadon MA, Dement WC, Mitler MM, *et al.* Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep 1986; 9: 519-24.
6. Diagnostic Classification Steering Committee, Thorpy MJ, Chainman. V International Classification of Sleep

Disorder: diagnostic and coding manual. Rochester, MN: American Sleep Disorder Association, 1990.
7. Moscovitch A, Partinen M, Guilleminault C. The positive diagnosis of narcolepsy and narcolepsy's borderland. Neurology 1993; 43: 55-60.
8. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991; 14: 540-5.
9. Gelineau JB: De la narcolepsie. Gaz des Hop (Paris) 1880; 53: 626-8.
10. Douglas NJ. "Why am I sleepy?" Sorting the somnolent. Am J Respir Crit Care Med 2001; 163: 1310-3.
11. Honda Y. Census of narcolepsy, cataplexy and sleep life among teenagers in Fujisawa city. Sleep Res 1979; 8: 191.
12. Lavie P, Peled R. Narcolepsy is a rare disease in Israel. Sleep 1987; 10: 608-9.
13. Broughton R, Ghanem Q, Hishikawa Y, *et al.* Life effects of narcolepsy: relationships to geographic origin (North American, Asian or European) and to other patient and illness variables. Can J Neurol Sci 1983; 10: 100-4.
14. Broughton R, Guberman A, Roberts J. Comparison of the psychosocial effects of epilepsy and narcolepsy/cataplexy: a controlled study. Epilepsia 1984; 25: 423-33.
15. Cohen FL, Ferrans CE, Eshler B. Reported accidents in narcolepsy. In: Goswami M, Pollak CP, Cohen FL, *et al*, ed. Psychosocial aspects of narcolepsy. New York. Haworth Press, 1992:71-80.
16. Challamel MJ, Mazzola ME, Nevsimalova, *et al.* Narcolepsy in children. Sleep 1994; 17: S17-20.
17. Vossler DG, Wyler AR, Wilkus RJ, *et al.* Cataplexy and monoamine oxidase deficiency in Norrie disease. Neurology 1996; 46: 1258-61.
18. Stahl SM, Layzer RB, Aminoff MJ, *et al.* Continuous cataplexy in a patient with a midbrain tumor: the limp man syndrome. Neurology 1980; 30: 1115-8.
19. Broughton R, Dunham W, Newman J, *et al.* Ambulatory 24 hour sleep-wake monitoring in narcolepsy-cataplexy compared with matched control subjects. Electroencephalogr Clin Neurophysiol 1988; 70: 473-81.
20. Broughton R, Aguirre M, Dunham W. A comparison of multiple and single sleep latency and cerebral evoked potential (P300) measures in the assessment of excessive daytime sleepiness in narcolepsy-cataplexy. Sleep 1988; 11: 537-45.
21. Aldrich MS, Chervin RD, Malow BA. Value of the multiple sleep latency test (MSLT) for the diagnosis of narcolepsy. Sleep 1997; 20: 620-9.
22. Moscovitch A, Partinen M, Patterson-Rhoads N, *et al.* Cataplexy in differentiation of excessive daytime sleepiness. Sleep Res 1991; 20: 301.
23. Laffont F, Mayer G, Minz M. Modafinil in diurnal sleepiness: a study of 123 patients. Sleep 1994; 17: S113-5.
24. Billiard M, Besset A, Montplaisir J, *et al.* Modafinil: a double-blind multicentric study. Sleep 1994; 17: S107-12.
25. Nishino S, Ripley B, Overeem S, *et al.* Hypocretin (orexin) deficiency in human narcolepsy. Lancet 2000; 355: 39-40.
26. Thannickal TC, Moore RY, Neinhuis R, *et al.* Reduced number of hypocrtin neurons in human narcolepsy. Neuron 2000; 27: 469-74.
27. Krahn LE, Black JL, Silber MH. Narcolepsy: new understanding of irresistible sleep. Mayo Clin Proc 2001; 76: 185-94.

三十五例猝睡症之臨床表現

陳信如　蕭光明　劉勝義　彭瑞鵬

猝睡症(narcolepsy)為一種慢性睡眠疾病，其特性為白日過度嗜睡、猝倒(cataplexy)、睡眠癱瘓(sleep paralysis)及臨睡幻覺(hypnagogic hallucinations)。我們回溯性地蒐集民國 81 年至民國 90 年間台北榮民總醫院猝睡症病患之病例紀錄及睡眠檢查資料，並分析病患之特性、症狀及治療情形。我們並以電話問卷方式，調查猝睡症對學業、工作之影響以及因嗜睡引發相關車禍之機率，另外利用 Epworth Sleepiness Scale (ESS)調查病患的嗜睡程度。並以統計之方法分析症狀嚴重度不同的個組之間，其睡眠檢查結果及 ESS scores 是否有差異。

總計 35 位病患包含 19 位男性、16 位女性。症狀發作之平均年齡為 21 歲，但發病到確定診斷的時間則平均達 12 年。病患皆有白日過度嗜睡之症狀，63%之病人有猝倒，54%有睡眠癱瘓、46%有臨睡幻覺。符合全部四項症狀者僅有 31%。猝睡症對生活品質有重大影響。20 歲前發病者，64%有明顯學業成績退步、45%成績很差。已經從事工作的患者，有 38%工作表現不佳。有開車習慣之患者，有 78%曾在駕駛時睡著、52%曾因嗜睡而發生過車禍。我們發現對於猝睡症之病患，多重睡眠潛伏期試驗(Multiple Sleep Latency Test)及 ESS 不僅為主要診斷工具，亦對病患之預後提供了重要的資訊。目前對於猝睡症之治療多為症狀控制的療法，效果不盡理想。亟待更多的研究報告，以增進對猝睡症其致病機轉及症狀之了解，以期早期診斷並避免嚴重之後果，例如車禍。 ***(胸腔醫學 2002; 17: 198-209)***

關鍵詞：猝睡症，猝倒，多重睡眠潛伏期試驗

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CEA is More Useful Than Cytokines in the Differential Diagnosis Distinguishing Malignant Pleural Effusion from Benign Conditions

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Background. We investigated the role of cytokines [tumor necrosis factor-α (TNF-α), interleukin-1 β (IL-1β), macrophage inflammatory proteins 1 β (MIP-1β), granulocyte-macrophage colony stimulating factor (GM-CSF), IL-15] in the evaluation of pleural effusion etiology.

Methods. Using commercially-available ELISA kits, concentrations of these cytokines were measured in the pleural fluid and peripheral blood of patients with malignant effusions (n=51), parapneumonic effusions (n=7), tuberculous pleurisy (n=8), and transudative (n=8) effusions due to congestive heart failure or liver cirrhosis. Carcinoembryonic antigen (CEA) levels were also checked and used for comparison.

Results. The results showed that 75% of blood TNF-α and 50% of effusion TNF-α, 90% of blood IL-1β and 67.5% of effusion IL-1β, and 97.5% of blood GM-CSF and 55% of effusion GM-CSF, were below minimal detectable concentrations, while 92.5% of blood IL-15 and 100% of effusion IL-15, and 95% of blood MIP-1β and 92.5% of effusion MIP-1β, were detectable. There was no significant difference in cytokine levels among a subgroup of patients with benign pleural effusion, in either the pleural fluid or peripheral blood; however, the pleural fluid TNF-α and IL-15 levels were higher in TB pleurisy (p=0.048 and 0.045, respectively), and blood MIP-1β levels were lower in patients with transudates. In general, the pleural fluid cytokine levels were higher than the blood levels, if they were detectable, in both the benign and malignant effusions. However, MIP-1β was higher in the peripheral blood than in the pleural fluid in patients with malignant effusion (p=0.009). None of these cytokines could be used for the differential diagnosis of benign and malignant pleural effusion (p>0.05), in either the pleural fluid or the peripheral blood, except for pleural fluid TNF-α, which was relatively higher in benign disease (p=0.028). On the other hand, there were significant differences in the CEA levels in the peripheral blood (p=0.012) and pleural fluid (p=0.001) of benign and malignant diseases.

Conclusions. These findings suggest that pleural fluid CEA levels are still better than cytokines for the differential diagnosis of benign and malignant pleural effusion. ***(Thorac Med 2002; 17: 210-217)***

Key words: chemokine, cytokine, pleural effusion, malignancy

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Introduction

Cytokines are small molecules involved in the local or systemic tissue reaction to inflammation. The type and degree of cytokine secretion are different in different types of immune or inflammatory reactions, thus, the levels of each cytokine differ in different conditions. Whether or not these cytokines can be detected and used as a differential diagnostic tool to distinguish benign and malignant effusion is still unknown.

Macrophage inflammatory proteins 1 α and β (MIP-1α and MIP-1β) and macrophage inflammatory protein 2 (MIP-2) are heparin-binding proteins that exhibit a number of inflammatory and immunoregulatory activities. While MIPs have been originally identified as the secretory products of endotoxin-stimulated mouse macrophages, these chemokines are also produced by a variety of human cell types including neutrophils, fibroblasts, and epithelial cells. MIP-1α and MIP-1β are chemotactic for monocytes and lymphocytes, and MIP-2 is a potent chemotactic factor for neutrophils. [1] MIPs likely also play a role in regulating hematopoiesis and in stimulating the production of other inflammatory mediators such as interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), and histamine. [1] Studies using animal models of lung injury and inflammation have implicated MIPs as important mediators of lung defense. [1] MIP-1α plays a major role in the recruitment of mononuclear leukocytes from the vascular compartment to the pleural space in the patient with parapneumonic pleural effusion, and pleural mesothelial cells, by their production of MIP-1α, actively participate in this process. [2] An increase in MIP-1β levels has been found in smokers developing chronic obstructive pulmonary disease, suggesting a role in the pathogenesis of chronic bronchitis. [3] However, the role of MIP-1β in pleural disease is less clear.

Silva-Mejias et al [4] found that IL-1β plays a significant role in pyogenic infections of the pleural space, but not in effusions of other etiologies. They also suggested that IL-1β could be used as a diagnostic marker of empyema. [4] Other researchers found that pleural effusion IL-1β levels were low in malignant effusion, but were relatively higher in parapneumonic pleural effusion. [5]

TNF-α and IL-1 are powerful mediators with a key role in inflammation. [6] It has been reported that TNF-α concentrations in pleural effusions are a useful marker in differentiating exudates from transudates. [7] However, the ability of effusion TNF-α levels to differentiate benign from malignant effusion has been less consistent. [6,8-9]

Granulocyte-macrophage colony stimulating factor (GM-CSF) is a hematopoietic growth factor that plays a significant role in the management of neutropenia following myeloablative chemotherapy. [10] GM-CSF is also involved in the maturation and functions of dendritic cells, [11] and has been used in gene therapy against cancers. [12]

IL-15 has been ascertained to have the potential for enhancing cell-mediated immune responses to intracellular pathogens and tumors. [13-15] IL-15 shares many of the biological activities of IL-2, including the induction of the proliferation of phytohemagglutinin-stimulated normal peripheral blood mononuclear cells, natural killer cells, B cells, and T cells, and the generation of allogenic cytotoxic T lymphocytes and lymphokine-activated killer cells in vitro. [13-18] IL-15 has also been detected in rheumatoid pleural effusion. [19]

A tumor marker, such as CEA, is also a useful bio-marker in the differential diagnosis of malignant and benign pleural effusion, in addition to traditional effusion cytology and pathology. [20-21]

There has been no study comparing these cytokines in the differential diagnosis of benign and malignant pleural effusion, nor has there been a study comparing these cytokines and CEA. The objective of the present study was to measure the cytokine levels (TNF-α, IL-1β, MIP-1β,

GM-CSF, IL-15) in the pleural fluid and peripheral blood of patients with pleural effusion of different etiologies. We also tried to verify whether or not these cytokines could be used as a differential diagnostic marker for benign and malignant pleural effusion, with CEA as a reference tool.

Materials and Methods

Between October 1994 and September 1995, samples of pleural fluid and serum were collected from patients with newly diagnosed pleural effusion. Cancer patients with malignant pleural effusion had cytologically-proved neoplastic pleural effusion, and some lung cancer cases with exudative pleural effusion and no evidence of infection were also considered as having malignant pleural effusion. Parapneumonic effusion was diagnosed when patients with bacterial pneumonia had an ipsilateral exudative pleural effusion with a negative bacterial culture result. Tuberculous pleurisy was diagnosed by pleura biopsy, or when TB bacilli were documented on the pleura tissue and/or effusion culture. The effusions from congestive heart failure and viral liver cirrhosis were transudate in nature. Light's criteria were used to separate transudate from exudate. [22]

Pleural fluid and peripheral blood was collected from patients simultaneously, then heparin wad added to prevent clotting, at the first chest sonographic examination and thoracocentesis. The protein, sugar, LDH, CEA, WBC count, and differential count of the pleural fluid and blood, and of the effusion bacterial culture, were sent for laboratory examination. The remaining peripheral blood samples and pleural effusions were then centrifuged at 834 x *g* for 10 minutes at 4°C. The supernatant was collected and stored at -70°C in aliquots of 0.25 ml in microcentrifuge tubes, and was used for the test only once without repeated freeze-thaw cycles. TNF-α, IL-1β, MIP-1β, GM-CSF, and IL-15 were determined in duplicate using a commercially-obtained ELISA kit (Quantikine, R & D System, Inc., Minneapolis, MN, USA) for a solid phase ELISA method that employed the quantitative 'sandwich' enzyme immunoassay technique. The minimally detectable concentrations of TNF-α, IL-1β, MIP-1β, GM-CSF, and IL-15 were 4.4, 1.0, 11, 2.8, and 1.0 pg/ml, respectively. All the samples were determined within one month after collection. Positive and negative controls were included in the assay.

To determine if significant differences existed in the cytokines or CEA levels in pleural effusion as compared to those in serum, a Wilcoxon signed-ranks test was performed. The Mann-Whitney test and Kruskal-Wallis test were used to determine whether or not there existed a significant difference in the cytokines or CEA levels of effusion and peripheral blood found in different clinical conditions.

Results

Pleural fluid and peripheral blood were simultaneously obtained from 74 patients with pleural effusion newly diagnosed during this period, including 51 with malignant pleural effusion, 7 with parapneumonic effusion, 8 with tuberculous pleurisy, and 8 with transudative

Table 1. The proportion of patients with detectable cytokine or CEA levels

Variables (minimal detectable levels)	Benign (%)		Malignancy (%)	
	effusion	blood	effusion	blood
TNF-α (4.4pg/ml)	77.8	22.2	41.9	25.8
IL-1β (1.0pg/ml)	44.4	11.1	29	9.7
MIP-1β (11pg/ml)	100	93.8	87.5	95.8
GM-CSF (2.8pg/ml)	40	0	48	4
IL-15 (1.0pg/ml)	100	87.5	100	95.8
CEA (normal upper limit 4 ng/ml)	0	0	66.7	51.3

effusion (3 with congestive heart failure and 5 with liver cirrhosis). Among the 51 patients with malignant pleural effusion, 45 had lung cancer (36 adenocarcinoma, 5 squamous cell carcinoma, 3 small cell carcinoma, and 1 poorly differentiated carcinoma), 3 had breast cancer (adenocarcinoma), 2 had colon adenocarcinoma, and the last had adenocarcinoma of unknown origin.

Not all patients' cytokines and CEA levels were above detectable concentrations, in both the pleural effusion and peripheral blood (Table 1). The results showed that 75% of blood TNF-α and 50% of effusion TNF-α, 90% of blood IL-1β and 67.5% of effusion IL-1β, and 97.5% of blood GM-CSF and 55% of effusion GM-CSF, were below minimal detectable concentrations, while 92.5% of blood IL-15 and 100% of effusion IL-15, and 95% of blood MIP-1β and 92.5% of effusion MIP-1β, were detectable. Therefore, the majority of TNF-α, IL-1β, and GM-CSF were below minimal detectable concentrations, while MIP-1β and IL-15 were mostly detectable (Figure 1), in both the pleural fluid and peripheral blood of the patients. More than half of the cancer patients had elevated CEA levels in both the pleural fluid and peripheral blood, while the levels were below the upper normal limit in all patients with benign disease. In general, there was no significant difference in cytokine levels among the subgroup of patients with benign pleural effusion, in both the effusion and peripheral blood. However, effusion TNF-α levels were higher in TB pleurisy (p=0.048), effusion IL-15 levels were lower in TB pleurisy (p=0.045), and blood MIP-1β levels were lower in the patients with transudate effusion (p=0.012), among the patients with benign pleural effusion.

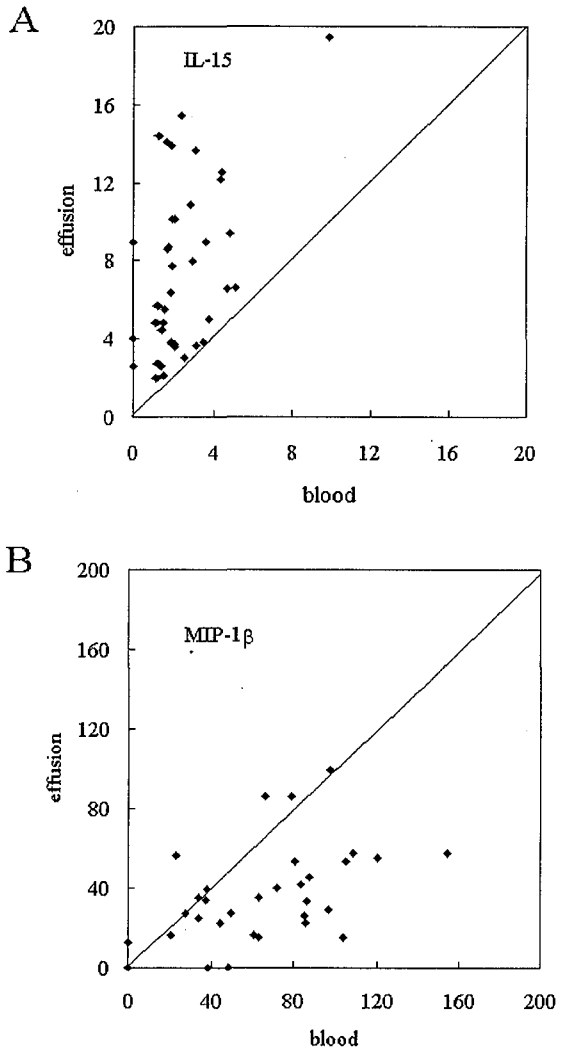

Fig. 1. IL-15 (panel A) and MIP-1β (panel B) data of individual patients. The pleural fluid IL-15 level was higher than the blood level. In contrast, the blood MIP-1β level was generally higher than the pleural fluid level. Note: there were 5 outliers in panel B.

The levels of TNF-α were higher in the pleural fluid than in the peripheral blood, in both benign (p=0.018) and malignant disease (p=0.007). The levels of IL-1β were higher in the pleural fluid than in the peripheral blood in malignant disease (p=0.007), but not in the benign conditions (p=0.5). The levels of GM-CSF were higher in the pleural fluid than in the peripheral blood, in both benign (p=0.028) and malignant disease (p=0.002). The levels of IL-15 were higher in the pleural fluid than in the peripheral blood, in both benign (p<0.001) and malignant disease (p<0.001). The levels of MIP-1β were lower in the pleural fluid than in the peripheral blood in malignant disease (p=0.009), but not in the benign conditions (p=0.255). The levels of CEA were higher in the effusion than in the blood in malignant disease (p=0.012), and all

Table 2. Data of cytokines and CEA levels in 71 patients

		Effusion		Blood	
		Median	Range	Median	Range
TNF-α*	malignancy	4.21	<4 - 1333	<4	<4 - 744
	benign	11.7	<4 – 459.6	<4	<4 - 10
IL-1β	malignancy	<1.0	<1.0 – 546	<1.0	<1.0 – 3.1
	benign	<1.0	<1.0 – 9.7	<1.0	<1.0 – 12.3
MIP-1β	malignancy	34.2	<11 – 2204	84.5	<11 – 1711
	benign	49.5	12.7 – 620.6	75.1	<11 – 834.6
GM-CSF	malignancy	<2.8	<2.8 – 481.5	<2.8	<2.8 – 5.6
	benign	<2.8	<2.8 – 26.6	<2.8	<2.8
IL-15	malignancy	5.2	2.1 – 19.5	1.8	<1.0 – 9.8
	benign	8.4	2 – 15.4	2.1	<1.0 – 5.1
CEA*	malignancy	11.8	<4 - >200	4.3	<4 – 200
	benign	<4	<4	<4	<4

*p=0.028 for pleural fluid TNF-α, p=0.012 for blood CEA, and p=0.001 for pleural fluid CEA.

were below the upper normal limit of 4 ng/ml in the benign conditions.

None of the cytokine contents in the pleural effusion could be used for the differential diagnosis of transudate and exudate (all tested cytokines were p>0.05). None of the cytokines could be used for the differential diagnosis of benign and malignant pleural effusion (p>0.05), either in the effusion or in the peripheral blood, except for effusion TNF-α, which was relatively higher in benign disease (p=0.028). However, TNF-α is still not a good candidate for use in the differential diagnosis because many benign and malignant diseases have TNF-α levels that overlap each other, and many cases have TNF-α levels below detectable concentrations. Using a value of more than 5 pg/ml as an indicator of benign pleural effusion, the sensitivity and specificity of pleural fluid TNF-α were 77.8% and 36.8%, respectively. On the other hand, there was a significant difference in the CEA levels of the peripheral blood (p=0.012) and pleural fluid (p=0.001) of both benign and malignant disease (Table 2). The sensitivity and specificity of blood CEA (≥ 4 ng/ml) for malignant disease were 51.3% and 100%, respectively, and the sensitivity and specificity of pleural fluid CEA (≥ 4 ng/ml) for malignant disease were 66.7 % and 100%, respectively.

Discussion

Based on our studies, GM-CSF, IL-1β, IL-15, and MIP-1β cannot be used as differential diagnostic tools for benign and malignant pleural effusion, when found either in the blood or the effusion.

Even though pleural fluid TNF-α can be used as a differential diagnostic tool (there is a significant difference in the levels of concentration between benign disease and malignancy), it is still not useful in clinical practice. The sensitivity and specificity of pleural fluid TNF-α for benign disease were only 77.8% and 36.8%, respectively. In contrast, 66.7% of malignant pleural effusion had elevated CEA levels, while no cases of benign pleural effusion had elevated CEA (100% specificity), making CEA a useful differential diagnostic marker.

Odeh et al found that effusion TNF-α levels were significantly higher in patients with malignancy than in the pleural fluid of patients with uncomplicated parapneumonic effusions and congestive heart failure (p<0.001). [8] However,

a considerable overlap between all groups was found. [8] This finding differs from this and other studies, [6,9] which have shown no obvious elevation of TNF-α levels in malignant effusion, as compared to other conditions. Alexandrakis et al's study has also shown that there are no statistically significant differences in the serum and pleural fluid TNF-α concentrations of patients with cancer and in those with non-cancer effusion. However, they found that TNF-α concentrations in the pleural fluid are a useful marker in differentiating exudates from transudates. [7]

Mohammed et al found that complicated parapneumonic pleural effusions (empyema) and uncomplicated parapneumonic pleural effusions both contain higher levels of MIP-1α, when compared with effusions resulting from malignancy and congestive heart failure. [2] We found that MIP-1β could be detected in both the effusion and peripheral blood of different etiologies, and that there was no significant difference in the levels of different etiologies. Nevertheless, the level of MIP-1β was significantly lower in the effusion than in the blood sample. In general, effusion had higher cytokine (TNF-α, IL-1β, GM-CSF, IL-15) levels than peripheral blood, when the cytokines could be detected, in both benign and malignant disease. However, when blood MIP-1β is higher than that in the effusion, it is likely that the patient suffers from malignant pleural effusion. Alexandrakis et al reported that IL-6, IL-8 and TNF-alpha might be secreted locally at the site of active disease in both benign and malignant pleural effusions, because the concentrations of these 3 cytokines in malignant and inflammatory benign pleural effusion were significantly higher than their levels in the blood. [23] However, they are not useful in the differential diagnosis of these two disease entities. Wu et al found that the sFasL concentration in TB pleural effusion is significantly higher than that in adenocarcinomatous pleural effusion. [24] FasL is a type II membrane protein with homology to TNF-α, and sFasL is released from the cell surface via a metalloproteinase.

In summary, effusion CEA levels are still better than the cytokines studied here for the differential diagnosis of benign from malignant pleural effusion. An elevated effusion CEA points toward malignant disease. However, neither condition can be ruled out when effusion CEA is below the upper normal limit. Further studies are needed to confirm its usefulness.References

References

1. Driscoll KE. Macrophage inflammatory proteins: biology and role in pulmonary inflammation. Exp Lung Res 1994; 20:473-90.
2. Mohammed KA, Nasreen N, Ward MJ, *et al.* Macrophage inflammatory protein-1alpha C-C chemokine in parapneumonic pleural effusions. J Lab & Clin Med 1998; 132:202-9.
3. Capelli A, Di Stefano A, Gnemmi I, *et al.* Increased MCP-1 and MIP-1beta in bronchoalveolar lavage fluid of chronic bronchitis. Eur Respir J 1999; 14:160-5.
4. Silva-Mejias C, Gamboa-Antinolo F, Lopez-Cortes LF, *et al.* Interleukin-1 beta in pleural fluids of different etiologies. Its role as inflammatory mediator in empyema. Chest 1995; 108:942-5.
5. Yanagawa H, Yano S, Haku T, *et al.* Interleukin-1 receptor antagonist in pleural effusion due to inflammatory and malignant lung disease. Eur Respir J 1996; 9:1211-6.
6. Orphanidou D, Gaga M, Rasidakis A, *et al.* Tumour necrosis factor, interleukin-1 and adenosine deaminase in tuberculous pleural effusion. Respir Med 1996; 90:95-8.
7. Alexandrakis MG, Coulocheri SA, Bouros D, *et al.* Evaluation of ferritin, interleukin-6, interleukin-8 and tumor necrosis factor alpha in the differentiation of exudates and transudates in pleural effusions. Anticancer Res 1999; 19:3607-12.
8. Odeh M, Sabo E, Srugo I, *et al.* Tumour necrosis factor alpha in the diagnostic assessment of pleural effusion. QJM 2000; 93:819-24.
9. Gursel G, Gokcora N, Elbeg S, *et al.* Tumor necrosis factor-alpha (TNF-alpha) in pleural fluids. Tubercle & Lung Dis 1995; 76:370-1.
10. Dempke W, Von Poblozki A, Grothey A, *et al.* Human

hematopoietic growth factors: old lessons and new perspectives. Anticancer Res 2000; 20:5155-64.

11. Holt PG, Stumbles PA. Characterization of dendritic cell populations in the respiratory tract. J Aerosol Med 2000; 13:361-7.
12. Jaffee EM. Immunotherapy of cancer. Ann New York Acad Sci 1999; 886:67-72.
13. Grabstein KH, Eisenman J, Shanebeck K, *et al.* Cloning of a T cell growth factor that interacts with the β chain of the interleukin-2 receptor. Science 1994; 264:965-8.
14. Carson WE, Giri JG, Lindemann MJ, *et al.* Interleukin (IL) 15 is a novel cytokine that activates human natural killer cells via components of the IL-2 receptor. J Exp Med 1994; 180:1395-403.
15. Khan IA, Kasper LH. IL-15 augments $CD8^+$ T cell-mediated immunity against *Toxoplasma gondii* infection in mice. J Immunol 1996; 157:2103-8.
16. Gamero AM, Ussery D, Reintgen DS, *et al.* Interleukin 15 induction of lymphokine-activated killer cell function against autologous tumor cells in melanoma patients lymphocytes by a CD18-dependent, perforin-related mechanism. Cancer Res 1995; 55:4988-94.
17. Chen YM, Ting CC, Whang-Peng J, *et al.* Restoration of cytotoxic T lymphocytes function in malignant pleural effusion: interleukin-15 versus interleukin-2. J Interferon & Cytokine Res 2000; 20:31-9.
18. Lewko WM, Smith TL, Bowman DJ, *et al.* Interleukin-15 and the growth of tumor derived activated T-cells. Cancer Biotherapy 1995; 10:13-20.
19. Yanagawa H, Takeuchi E, Miyata J, *et al.* Rheumatoid pleural effusion with detectable level of interleukin-15. J Internal Med 1998; 243:331-2.
20. Riantawan P, Sangsayan P, Bangpattanasiri K, *et al.* Limited additive value of pleural fluid carcinoembryonic antigen level in malignant pleural effusion. Respiration 2000; 67:24-9.
21. Ferrer J, Villarino MA, Encabo G, *et al.* Diagnostic utility of CYFRA 21-1, carcinoembryonic antigen, CA 125, neuron specific enolase, and squamous cell antigen level determinations in the serum and pleural fluid of patients with pleural effusions. Cancer 1999; 86:1488-95.
22. Light RW, MacGregor MI, Luchsinger PC, *et al.* Pleural effusions: the diagnostic separation of transudates and exudates. Ann Intern Med 1972; 77:507-13.
23. Alexandrakis MG, Coulocheri SA, Bouros D, *et al.* Evaluation of inflammatory cytokines in malignant and benign pleural effusions. Oncology Reports 2000; 7: 1327-32.
24. Wu SH, Chu JJ, Chiang CD. Increased soluble Fas ligand concentration in tuberculous pleural effusion. J Formos Med Assoc 2001; 100: 32-4.

胚胎絨毛抗原(CEA)比細胞激素對區別良性與惡性助膜積水的鑑別診斷有所助益

陽光耀　陳育民　蔡俊明　彭瑞鵬

背景　我們研究是否可以利用細胞激素（TNF-α, IL-1β, MIP-1β, GM-CSF, IL-15）做為評估肋膜積水原因的鑑別診斷。

方法　使用 ELISA 的分析方式，我們測定患者肋膜積水與周邊血液的這些細胞激素的濃度。收集的病例包括 51 例癌症合併惡性肋膜積水的病患、7 例因肺炎引起的肋膜積水、8 例結核性肋膜積水，與 8 例因心臟衰竭或肝硬化引起的積水。我們也同時測定 CEA，以做為比較。

結果　結果顯示 75% 的血液 TNF-α與 50% 的肋膜液 TNF-α, 90% 的血液 IL-1β與 67.5% 的肋膜液 IL-1β, 與 97.5% 的血液 GM-CSF 與 55% 肋膜 GM-CSF 都低於最低可偵測濃度，而 IL-15 與 95% 血液 MIP-1β與 92.5% 肋膜 MIP-1β可以測的到。在不同種類的良性肋膜積水患者之間的肋膜液與血液細胞激素的含量並沒有明顯差異，除了肋膜液的 TNF-α 與 IL-15 在結核性肋膜積水有較高含量，而血液 MIP-1β在 transudates 含量較低。一般而言，如果細胞激素可以測的到的話，病患肋膜積液的細胞激素含量都比周邊血液含量為高，但是，惡性肋膜積水病患的周邊血液 MIP-1β含量則明顯比肋膜液為高（p=0.009）。這些細胞激素在血液或肋膜液的含量均不適合用來區別良性與惡性肋膜積水（p>0.05），除了肋膜液 TNF-α在良性肋膜積水比惡性肋膜積水為高（p=0.028）。相反的，血液與肋膜液的 CEA 含量在良性與惡性肋膜積水則有明顯差異（血液 p=0.012, 肋膜液 p=0.001）。

結論　本篇研究發現，以 CEA 含量做為鑑別良性與惡性肋膜積水的診斷，還是比細胞激素為佳。

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關鍵詞：吸引激素、細胞激素、肋膜積水、癌症

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Determination of Respiratory Disability in Taiwanese Coal Miners

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Coal workers' pneumoconiosis (CWP) is a common occupational lung disease which may be associated with demonstrable pulmonary impairment and can potentially cause disability in miners exposed to coal dust. To promote a better understanding of respiratory disability among Taiwanese coal miners, and to estimate their ventilatory function, conventional spirometry and tests for diffusing capacity (DLCO) were conducted on 125 working or retired miners who had been referred to the hospital by the Bureau of Labor Insurance. Our results show that the 43 miners without radiological evidence of pneumoconiosis had normal ventilatory capacity, and 31 out of the 68 (45.6%) subjects with simple CWP had spirometric indices meeting the extant criteria for disability. Seven additional disabled miners were detected as the result of supplementing DLCO measurement. All of the 14 miners with progressive massive fibrosis (PMF) met the spirometric criteria for disability. Among them, 12 (88.4%) had more than 2 indices of ventilatory capacity that would qualify the subjects for disability benefits. We conclude that it may be worthwhile to carry out DLCO measurement, in addition to spirometry, in workers with simple CWP who are claiming disability compensation, while this is unnecessary for miners with PMF. ***(Thorac Med 2002; 17: 218-225)***

Key words: coal workers' pneumoconiosis, determination of respiratory disability, spirometry, measurement of diffusing capacity

Introduction

Coal workers' pneumoconiosis (CWP) is the most common occupational lung disease. The exposure to and deposition of respirable coal-mine dust, as well as the tissue's reaction to its existence, results in this pulmonary disease [1-2]. Ventilatory function impairment may be of varying degrees of severity, and at its extreme can cause total disability, especially in workers with progressive massive fibrosis (PMF) [3-5]. In Taiwan, there are no stringent measures in practice to reduce the concentrations of coal-mine dust in the pits. However, working miners have been required to undergo an annual health survey since 1970. Moreover, public acts with the aim of compensating miners who have respiratory impairment due to pneumoconiosis have been in effect for more than 35 years. In 1997, the Taiwan Council of Labor Affairs decided to extend the coverage for disability to

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those who had left the industry, because previous data [5-6] has shown that there is a progression of CWP in ex-miners.

In the year 2000, miners with CWP were the most common claimants for benefits due to occupational injuries in Taiwan, accounting for more than 80% of the total compensation paid by the Bureau of Labor Insurance. Occupational history, characteristic radiographic changes, and pulmonary functional abnormalities are evaluated for the recognition of CWP as well as the assessment of disability. The amount of compensation to be awarded depends upon the magnitude of pulmonary dysfunction. Current criteria that qualify a miner for disability benefits are based upon certain lung function indices, e. g., forced vital capacity (FVC), forced expiratory volume in 1s (FEV1), FEV1/FVC, and single- breath carbon monoxide diffusing capacity (DLCO). Should a miner have a normal FEV1 that does not meet the criteria, he can still qualify by meeting another set of standards. Since it is estimated that over NT$ 1 billion has been awarded to miners claiming respiratory disability in the past 2 years, it would be of value to look into the current status of disability determination for pneumoconiosis in Taiwan. To this point, we analysed the respiratory impairment of a group of miners referred to our hospital for functional assessment.

Materials and Methods

The subjects included in this study consisted of a consecutive cohort of 150 coal miners who were claiming respiratory disability, and who were referred by the Bureau of Labor Insurance for an assessment of their functional impairment. They were either working or retired miners. Control workers were selected from among the employees of China Petroleum Company and the Taiwan Railroad Bureau, whose working places were free from dust exposure. They were aged over 40 and were requested by the institutions to undergo periodical medical examinations. Seventy-six normal healthy male workers were included in the final analysis.

All subjects completed a self-administered questionnaire modified from those cited in the Epidemiology Standardization Project [7]. Health information, including the miners' occupational histories, lifetime smoking habits, and past histories of hypertension, diabetes, chronic lung and heart diseases, and neuromuscular disorders, was obtained during subject interviews. Respiratory symptoms were also recorded.

Each subject underwent a full-sized (32 × 44 cm) posteroanterior chest radiograph. Two medically-qualified physicians read the roentgenologic appearances, following the criteria of the International Labor Organization (ILO) classification system [8]. Films showing small irregular and/or rounded opacities without conglomeration were classified as simple pneumoconiosis. The presence of large opacities with diameters exceeding 1 cm indicated PMF. Subjects with abnormal roentgenologic findings other than those caused by occupational exposure were excluded.

Spirometric measurements were carried out by having each subject exhale maximially after full inspiration to total lung capacity. An automated plethysmo-graph (CS-828FC, CHEST Inc., Japan) was used to record the maximal expiratory flow-volume curves. Up to three trials were performed. Values for forced vital capacity (FVC), forced expiratory flow in one second (FEV1), and FEV1/FVC were reported based upon the best of three technically acceptable tests. Predicted values were calculated using equations established by the same laboratory for normal nonsmoking Chinese [9].

Single-breath carbon monoxide diffusing capacity (DLCO) was measured in duplicate for each subject with radiographic evidence of simple pneumoconiosis. Integrated and automated equipment (CHESTAC-55, CHEST Inc., Japan), which consisted of a 10-L rolling-sealed spirometer connected to a 10-L balloon within a box, was used for this purpose. Test procedures were conducted by the method previously

described [10]. Tests with a breath-holding time greater than 11 seconds or less than 9 seconds were discarded. The average of the two DLCO values was used to compare with the predicted data [10].

Since miners might exert a submaximal effort in carrying out the test procedures, the quality assurance of lung function tests was an important issue in this study. All tracings were inspected for effort and reproducibility. Expiratory maneuvers which contained coughing or showed variable flow and early termination were rejected. The extrapolated volume in the measurement of FEV1 should be less than 5% of FVC. For DLCO determination, tests should not show a slow inspiration or an inspired volume < 90% of VC. In addition, venous blood was drawn for a measure- ment of carboxyhemoglobin (COHb) in smokers, to correct the potential effect of CO back pressure.

The extant criteria for disability due to CWP in Taiwan are shown in Table 1. In addition to the functional decrements, radiological signs of CWP with category 2 or above are also required.

All lung function values, except for FEV1/FVC, were expressed as a percentage of the predicted (%p). Data were coded and entered into a computer system, and anal-yzed with the Statistical Analysis System (SAS) software. Values are expressed as mean ± SD. Results were statistically examined using Student's t tests or ANOVA (analysis of variance). A chi-square test was used for comparing the prevalence of cigarette smoking in coal miners and control workers.

Table 1. Extant criteria for disability due to pneumoconiosis (Taiwan , 2000)

Variable	Minimal requirement
FVC	< 80 % p
FEV1	< 80 % p
FEV1/FVC	< 75 %
DLCO	< 80 % p
VO2max	20 – 25 ml/ kg.min

Abbreviations : FVC = forced vital capacity ; FEV1 = forced expiratory volume in 1s : DLCO = carbon monoxide diffusing capacity ; VO2max = maximal O2 uptake during exercise .

Results

Of the 150 claimants, 17 failed to give satisfactory tracings for FVC and FEV1, and 8 had radiological changes unrelated to the occupation. Therefore, analysis was done based on data from the remaining 125 subjects.

Table 2 shows the demographics, smoking habits, radiological categories, as well as the duration of dust exposure in this study population. It is evident from this table that coal-miners were shorter in stature and had a much higher prevalence of smoking than the control group. Approximately one third of the claimants showed no radiographic signs of pneumoconiosis, and more than half of the men were miners with simple pneumoconiosis.

Table 3 shows that FVC, FEV1, and FEV1/FVC were significantly reduced in miners with pneumoconiosis, regardless of the smoking habits. However, miners without radiological signs of pneumoconiosis had similar values for all spirometric parameters compared with those of the control workers. Therefore, functional impair-ments were more likely to be detected when the radiological signs of pneumo-coniosis were present.

Of the 82 subjects with radiographic evidence of CWP, 45 (55%) met the spirometric criteria of disability. More than two-thirds of them had simple CWP.

It is evident from Table 4 that the most common parameter of ventilatory capacity that qualifies a miner for disability benefits is FEV1/FVC. In this group of patients, more than 90% of those with simple CWP, and 78.5% of those with PMF met the FEV1/FVC criteria. None of them met the FVC or FEV1 criteria alone. As was expected, the number of lung function indices with a magnitude of decrement that met the criteria increased with radiological progression. Thus, it is of interest to note that 64.3% and

Table 2. Demographic , radiological and other characteristics of the study population

	Coal miners (n = 125)	Control (n = 76)	p value
Age (yr)			
mean	57.5	54.9	
SD	11.2	13.5	0.16
range	44 – 71	40 – 76	
Height (cm)			
mean	162.0	168.1	
SD	5.8	6.5	< 0.01
range	145 – 176	148 – 182	
Smoking habits	No. (%)		
nonsmokers 28 (22)	40(53)		
smokers	97 (78)	36(47)	< 0.01
Radiological categories	No. (%)	—	
0	43 (34)		
simple	68 (55)		
complicated	14 (11)		
Dust exposure (yr)			
mean	22.6	—	
SD	9.8		
range	3 – 43		

Table 3. Spirometric values (mean ± SD) of men with and without coal-mine dust exposure and men with pneumoconiosis by smoking category

	No exposure	Coal-mine dust exposure	Pneumoconiosis
Nonsmokers			
No.	40	16	12
FVC, %p	102.3 ± 12.6	98.6 ± 13.2	82.7 ± 14.4 *
FEV1, %p	103.5 ± 11.5	99.0 ± 14.4	72.2 ± 13.9 *
FEV1/FVC, %	81.2 ± 7.4	83.5 ± 8.6	67.2 ± 10.3 *
Smokers			
No.	36	27	70
FVC, %p	100.3 ± 12.1	95.6 ± 15.8	80.8 ± 14.7 *
FEV1, %p	94.5 ± 14.0	90.9 ± 16.6	66.7 ± 15.2 *
FEV1/FVC, %	84.6 ± 10.2	80.1 ± 9.5	63.1 ± 12.0 *

* $p < 0.01$ compared to that of either miners without pneumoconiosis or control workers.

21.4% of the men with complicated pneumoconiosis qualified by a combination of 2 and 3 variables, respectively, whereas only 35.5% (11/31) of the men with simple CWP qualified by a combination of at least 2 variables.

Less than half (45.6%) of the claimants with simple CWP met the extant ventilatory criteria. As Table 5 shows, supplementing gas exchange

Table 4. Distribution of pneumoconiotic miners determined to have respiratory disability by lung function variables (n = 45)

Variable	Pneumoconiosis	
	Simple (n = 31)	Complicated (n = 14)
FEV1/FVC (1)	20 (64.5)	2 (14.3)
FEV1 (2)	0	0
FVC (3)	0	0
(1) + (2)	7 (22.6)	6 (42.9)
(1) + (3)	0	0
(2) + (3)	3 (9.7)	3 (21.4)
(1) + (2) + (3)	1 (3.2)	3(21.4)

Table 5. Results of adding DLCO measurement for determining respiratory disability in miners with simple pneumoconiosis (n = 68)

DLCO measurement	Indices of ventilatory capacity *	
	Qualified	Unqualified
Simple pneumoconiosis (n = 68)	31	37
qualified	10	7
unqualified	21	30

*Indices of ventilatory capacity denotes FVC , FEV1 and FEV1/FVC.

studies with DLCO measurement might enable the detection of additional disabled miners. In this sample, approximately 19% (7/37) of the miners with simple CWP, and who had a normal ventilatory capacity that did not meet the criteria, could still qualify if DLCO was reduced, so as to meet another set of standards. Adding a diffusion study is unnecessary for the determination of respiratory disability in miners with PMF and who already have a specified reduction of spirometric parameters. Moreover, the measurement of carboxyhemoglobin in smoking miners disclosed that the mean COHb% was 4.3 ± 0.6% in these subjects. Therefore, DLCO values would be underestimated by less than 5% in smoking miners if we did not correct for the effect of CO back pressure.

Discussion

Pulmonary function testing for occupational lung disease has been frequently utilized since the 1950s. With these tests, functional impairments caused by inhalational exposure can be demonstrated rapidly, in a large number of people, and with a high degree of accuracy. As a consequence, one of the major uses of function tests is to document impairment to help quantify disability. Disability is composed of several parts, of which medical impairment is one. The 1984 American Medical Association (AMA) Guides [11] defines disability as "an alteration of the capacity to meet personal, social, or occupational demands".

CWP, occupational asthma, asbestosis, and siderosis are all examples of occupa- tional lung diseases. Among them, CWP is the one most commonly encountered in daily clinical practice. According to the reports of the Bureau of Labor Insurance (Taiwan) [12], of the 5,385 new cases determined to have occupational injuries between 1987 and 2000, 4,022 (74.7%) were workers with pneumoconiosis or silicosis. In fact, over 85% of the subjects who claimed compensation for disability were coal miners with pneumoconiosis. Because disability means the inability to perform at a specified level of activity, the chief problem is then to decide what amount of loss constitutes impairment sufficient to characterize disability.

Since the ventilatory function test plays a major role in the determination of disability, spirometric criteria for impairment are of vital importance to both coal workers and the Bureau of Labor Insurance, the 2 main parties concerned in the process of disability determination. Our data show that in the presence of PMF, a simple ventilatory test employing FVC, FEV1, and FEV1/FVC as indices of functional change is sensitive enough to detect all disabled miners. However, should a miner with simple pneumoconiosis have either a normal spirogram or a slight decrement that does not meet the criteria, he can still qualify if the DLCO is reduced to such an extent as to meet another set of standards.

Both simple spirometry and a measurement of DLCO are recommended by the American Thoracic Society (ATS) [13] as the primary tests for the evaluation of respiratory impairment, because of their wide availability, reproducibility, and lack of substantial risk. In fact, the FVC, and FEV1, and DLCO tests are often regarded as obligatory, and are first choices [14-16]. However, this is not the case in Taiwan, where tests for DLCO are infrequently conducted for miners. The average cost of a conventional spirometry is about NT$350 (USD10), while that of a test for DLCO is around NT$500 (USD14). It is possible that an additional group of disabled miners may be recognized as a result of DLCO studies. The cost of pulmonary function tests in Taiwan is low relative to that in Western countries. Moreover, it is not borne by the claimant, but by the Bureau of National Health Insurance and the Taiwanese taxpayer. Nowadays, function testing has become a necessity in most occupational cases [17-18]. Therefore, tests for DLCO should be encouraged in miners with simple CWP.

Although we did not perform exercise testing and arterial blood gas analysis in this study, the role of these 2 measurements in the assessment of respiratory impairment needs to be addressed. Indeed, the criteria for disability might include additional indices such as oxygen consumption (VO2) and arterial oxygen tension (PaO2), which must be determined separately. However, the majority of miners being evaluated for respiratory impairment will not require exercise testing, since there is a good correlation between FEV1 and DLCO and VO2 [19-20]. Therefore, such testing should be reserved for those miners in whom the routine tests may have under- estimated the impairment. For example, on the occasion of assessing one's ability to perform a specified level of work, exercise testing may be helpful. Furthermore, Morgan et al [21] have demonstrated that blood gas analyses are unnecessary in the determination of pulmonary disability in coal miners, because only a few disabled men will be detected as a result of the blood gas studies.

Our data show that there was a high prevalence of cigarette smoking in the present study population. Cigarette smoking is known to have a deleterious effect on lung function. However, the interaction between the effects of cigarette smoking and the effects of coal mine dust inhalation is difficult to resolve with epidemiologic studies [22-23]. Of course, we should award equal compensation for equal disability, but respiratory impairment caused by cigarette smoking should not be compensated. However, at the present time, it is impractical to determine how much the pulmonary dysfunction in a miner was due to smoking and how much to occupational exposure [24-25]. Our results indicate that the ventilatory function of nonsmoking miners with CWP is already impaired. Thus, the most important point here is that inhalation of respirable coal-mine dust itself is capable of inducing functional changes in the lung.

In conclusion, experiences from determining respiratory disability in Taiwanese coal miners disclose that those men without pneumoconiosis generally have a normal ventilatory capacity compared to healthy control workers. The functional assessment for disability determination is easily made with conventional spirometry in patients with PMF. However, more sophisticated approaches such as DLCO measurement, in addition to ventilatory capacity, may be required for miners with simple pneumo- coniosis.

References

1. Heppleston AG. The pathological anatomy of simple pneumoconiosis in coal workers. J Path Bact 1953; 66: 235-46.
2. Morgan WKC, Burgess DB, Lapp NL, *et al.* Hyperinflation of the lungs in coal miners. Thorax 1971; 26: 585-90.
3. Lyons JP, Campbell H. Evolution of disability in coal workers' pneumoconiosis. Thorax 1976; 31: 527-33.
4. Love RG, Miller BG. Longitudinal study of lung function in coal miners. Thorax 1982; 37: 193-7.

5. Bates DV, Pham QT, Chau N, *et al.* A longitudinal study of pulmonary function in coal miners in Lorraine, France. Am J Ind Med 1985; 8: 21-32.
6. Yeoh CI,Yang SC. Pulmonary function impairment in pneumoconiotic patients with progressive massive fibrosis. Chang Gung Med J 2002; 25: 72-80.
7. Ferris BG. Epidemiology standardization project. Am Rev Respir Dis 1978; 118: 1-55.
8. International Labour Office. Guidelines for the use of ILO international classification of radiographs of pneumoconiosis. Rev. Ed. 1980. Occupational safety and health series, No 22. Geneva: International Labour Office 1980.
9. Yang SC. Re-evaluation of the ventilatory function in normal Chinese: Com-parison with the results of a survey conducted 15 years ago. J Formosan Med Assoc 1993; 92: S152-9. [In Chinese; English abstract]
10. Yang SC, Yang SP, Lin PJ. Prediction equations for single-breath carbon mon- oxide diffusing capacity from a Chinese population. Am Rev Respir Dis 1993; 147: 599-606.
11. American Medical Association. Guides to the evaluation of permanent impairment (2nd edition). Chicago : AMA, 1984, pp 85-101.
12. Bureau of Labour Insurance (Taiwan). Annual statistical report. 2000.
13. American Thoracic Society. Evaluation of impairment/ disability secondary to respiratory disorders. Am Rev Respir Dis 1986; 133: 1205-9.
14. Bates DV. Respiratory function in disease (3rd edition). Philadelphia: W. B. Saunders, 1989, pp. 333-6.
15. Phillips TJG. Compensation for occupational lung disease in the United Kingdom. Chest 1980; 78 (Suppl.): 141-4.
16. Reichel G. Disability determination and compensation for pneumoconiosis in West Germany. Chest 1980; 78 (Suppl.): 365-6.
17. Ostiguy GL (ed.). Summary of task force report on occupational respiratory disease (pneumoconiosis). Can Med Assoc J 1979; 121: 414-21.
18. Britton MG, Hughes DTD, Phillips TJG. A guide to compensation for asbestos- related diseases. Br Med J 1981; 282: 2107-11.
19. Cotes JE, Poser V, Reed JW. Estimation of exercise ventilation and oxygen uptake in patients with chronic lung disease. Bull Eur Physiopathol Respir 1982; 18: 221-8.
20. Wehr KL, Johnson RL Jr. Maximum oxygen consumption in patients with lung disease. J Clin Invest 1976; 58: 880-99.
21. Morgan WKC, Lapp NL, Seaton D. Respiratory disability in coal miners. JAMA 1980; 243: 2401-4.
22. Marine WM, Gurr D, Jacoben M. Clinically important effects of dust exposure and smoking in British coal miners. Am Rev Respir Dis 1988; 137: 106-12.
23. Hankinson JL, Reger RB, Morgan WKC. Maximal expiratory flows in coal miners. Am Rev Respir Dis 1977; 116: 175-80.
24. Morgan WKC. Industrial bronchitis. Br J Ind Med 1978; 35: 185-9.
25. Ruckley VA, Gauld SJ, Chapman JS, *et al.* Emphysema and dust exposure in a group of coal worker. Am Rev Respir Dis 1984; 129: 528-32.

台灣煤礦工之呼吸障害鑑定

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吸入煤塵會造成煤礦工塵肺症，而塵肺症會損害呼吸功能。當呼吸功能減低到一定程度時，患者的工作能力及日常活動就會受到限制。呼吸功能檢查在塵肺症時之功能損失的評定上非常重要。為瞭解目前台灣煤礦工之呼吸障害等級的狀況，吾人對 125 位由勞保局轉介來院申請呼吸功能檢查之煤礦工進行肺量測定及肺瀰散量測定。結果發現：胸部 X 光片上無塵肺症跡象者 43 位，其肺量測定均為正常；單純塵肺症患者 68 位，其中 31 位(45.6%) 之肺量測定符合勞保局呼吸障害標準，若再加上肺瀰散量測定，則有另外 7 人符合標準；至於進行性重度纖維化患者其肺量測定全部符合標準，而且其中 88.4%的患者至少有 2 項肺量參數達到標準。本文的結論是：除肺量測定外，單純塵肺症患者值得另外加作肺瀰散量試驗，而進行性重度纖維化患者則無此必要。 ***(胸腔醫學 2002; 17: 218-225)***

關鍵詞：煤礦工塵肺症，呼吸障害鑑定，肺量測定，肺瀰散量測定

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Experiences in the Treatment of Recurrent Pneumothorax after VATS: Focusing on Operative Findings

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Background: Although video-assisted thoracoscopic surgery (VATS) is considered to be the first choice for the management of primary spontaneous pneumothorax (PSP), the long-term recurrence rates and the causes of recurrence have not been well evaluated.

Methods: Between January 1993 and July 2001, nine of 216 patients diagnosed with primary spontaneous pneumothorax (PSP) who had received VATS, and latter had recurrent pneumothorax, were reviewed, and the operative findings were evaluated.

Results: All of the patients were male, and aged between 15 and 27 years. Apical blebs were found in all cases, except one, in the first operation. In the re-operation, four patients had blebs in the lower lobe and three patients had apical blebs in the upper lobe. All patients were found to have few or no pleural adhesions. The mean interval of recurrence was 8.3 months (1 to 26 months), and only one patient developed recurrent pneumothorax after the 2nd operation.

Conclusion: The main reasons for recurrent pneumothorax after VATS include failed pleurodesis and unidentified blebs. Better results can be achieved by performing further bleb resection and more extensive pleural abrasion in the re-operation. ***(Thorac Med 2002; 17: 226-231)***

Key words: video-assisted thoracoscopic surgery, recurrent pneumothorax

Introduction

Primary spontaneous pneumothorax (PSP) occurs in more than 1 of 100,000 women, and in 7 of 100,000 men per year, with a peak incidence in adolescence [1]. Video-assisted thoracoscopic surgery (VATS) was first introduced by Levi et al in 1990 to treat pneumothorax. They performed pleurectomy through a 2 to 3 cm posterior incision with the aid of VATS [2]. In 1991, Nathanson was the first to describe the technique of using VATS for ligation of pleural bullae and parietal pleurectomy, in the treatment of spontaneous pneumothorax [3]. Thereafter, VATS represented a new approach for the operative treatment of PSP. However, a somewhat higher long-term recurrence rate, from 2.1% to 13.7%,

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Table 1. Demographic data of 9 patients with recurrent pneumothorax after VATS

Patient	1	2	3	4	5	6	7	8	9
Age (1st op.)	16y/o	22y/o	17y/o	27y/o	17y/o	18y/o	15y/o	17y/o	19 y/o
Sex	Male	Male	Male	Male	Male	Male	Male	Male	Male
Side of PSP	Right	Left	Left	Left	Right	Right	left	Right	Right
Operation finding (1st op.)	RUL apex blebs	LUL apex bleb	LUL apex blebs	LUL apex blebs	RUL apex blebs	Nil.	LUL apex bleb	RUL apex blebs	RUL apex blebs
Operation procedure (1st op.)(VATS)	RUL wedge resection + pleurodesis	LUL wedge resection + pleurodesis	LUL wedge resection + pleurodesis	LUL wedge resection + pleurodesis	RUL wedge resection + pleurodesis	pleurodesis	LUL wedge resection + pleurodesis	RUL wedge resection +pleurodesis	RUL wedge resection + pleurodesis
Chest tube retention	4 days	3 days	4 days	3 days	2 days	8 days	4 days	6 days	2 days
Interval of recurrence	5 M	4 M and 2 M	18 M	1 M	26 M	1 M	7 M	2 M	11 M
Re-operation approach	Right-lateral thoracotomy	Left minimal thoracotomy(1st) Left lateral thoracotomy(2nd)	VATS	VATS	VATS	VATS	VATS	Right axillary thoracotomy	Right-lateral thoracotomy
Re-operation findings	RLL apex bleb few adhesions	LUL apex blebs No adhesions (1st recurrence) Mild adhesions* (2nd recurrence)	LLL superior Segmental blebs	LUL apico-posterior blebs dorsal to the previous resection No adhesions	Mild adhesions*	RUL apex blebs Mild adhesions*	LLL superior Segmental blebs LUL apex Mild adhesions*	adhesions over previous chest tube wound	RLL superior Segmental blebs No adhesions

mild adhesion* : scant adhesion and it was easy to be detached

following VATS, was noted [4-9].

The long-term results following the use of the VATS approach for recurrent pneumothorax have not been well-evaluated, especially with regard to the operative findings during the re-operation. The aim of this report was to analyze the re-operative findings, in order to modify the surgical procedure in the 1st operation.

Patients and methods

From January 1993 to July 2001, patients diagnosed with primary spontaneous pneumothorax, and who had undergone VATS, were reviewed. From a total of 216 patients, nine patients with recurrent pneumothorax following VATS, and who had received re-operation, were analyzed.

The first-time VATS procedure for these cases was performed by experienced thoracic surgeon, under general anesthesia with a double lumen endobroncheal tube that allowed split-lung ventilation. The resection of blebs, if present, was performed with endoscopic stapler, followed by apical pleural abrasion. In the re-operation, bleb resection, if any, was performed followed by a more extensive pleural abrasion (not only ecchymosis but also oozing of the pleura). The operative findings of the first-time surgery and re-operation were recorded (Table 1).

Results

Nine patients with recurrent pneumothorax following VATS were controlled into our series. All of the patients were male, aged between 15 and 27 years. The pneumothorax was on the right side in 5 cases, and the left side in 4 cases. There were no special post-operation complications in this series. The mean length of chest tube retention was 2-8 days.

Fig 1. A mild adhesion in recurrence following VATS

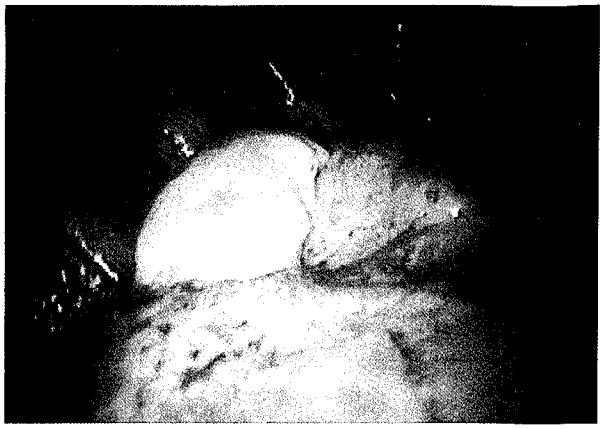

Fig. 2. A bleb over the apex of the upper lobe in recurrence following VATS

Five patients with recurrent pneumothorax underwent re-operation using a VATS procedure. Three patients were treated with a lateral mini-thoracotomy approach, including one patient who received a 3rd operation. Another patient underwent an axillary thoracotomy approach. The decisions regarding surgical approach were made according to the individual preference of the surgeon.

The mean interval of recurrence was 8.3 months (1 to 26 months), and the majority of recurrences developed in the first year (seven patients). One patient developed recurrent pneumothorax 4 months after the VATS procedure. He received a mini-thoracotomy with left upper lobe apical blebs resection and scratch pad pleural abrasion. Unfortunately, he developed another episode of recurrent pneumothorax two months after the 2nd operation. He then received another left lateral thoracotomy with apical pleurectomy and underwent an uneventful post-operation course. No special pathological findings of the lung were evident at the 3rd operation, except for minimal pleural adhesions (Figure 1).

Four patients had blebs of the lower lobe and three patients had apical blebs of the upper lobe in the re-operation (Figure 2). None of the re-operation patients had adequate pleural adhesions, even though routine apical pleural abrasions were performed in the 1st operation.

Discussion

Surgical treatment is indicated in cases of recurrent PSP, and VATS is the most commonly used surgical approach due to its well-known advantages, including short hospital stay, more rapid recovery of postoperative pulmonary function, decreased postoperative pain, and less morbidity. However, most of the criticism concerning VATS for pneumothorax focus on the issue of the higher recurrence or failure rates [7,10].

Patrick et al. demonstrated that the majority of PSP recurrences were due to inadequate pleurodesis [11]. All of our patients with re-operation had few or no adhesions at all, in spite of routine pleural abrasion using a scratch pad. Although some reports have demonstrated that pleurectomy has lower recurrence rates [8-9], we prefer abrasion pleurodesis to pleurectomy due to its simplicity, less bleeding and shorter operation time. One of our patients developed recurrent pneumothorax even though thoracotomy and pleural abrasion were performed in the 2nd operation. He received a 3rd operation, and no specific pathological finding was noted, except mild pleural adhesion. Apical pleurectomy was performed to ensure a solid pleurodesis, and the patient had an uneventful post-operative course. Based on these re-operative experiences, we

believe an extensive pleural abrasion is necessary for the establishment of a solid pleurodesis.

Cardillo et al. compared the success rates among the different techniques of pleurodesis employed in cases of recurrent pneumothorax with patients who had undergone VATS [6]. There were significant differences in the recurrence rates between talc and subtotal pleurectomy (1.79% versus 9.15%). In addition, tetracycline pleurodesis, rotating brush, and fibrin glue also failed to produce a significant decrease in recurrence rates [4,12].

Blebs were found in 7 of 9 patients in the re-operation. Previous reports also demonstrated that the unidentified or newly formed blebs were found in the re-operation 1 to 20 months latter [8-9]. Two patients in our study developed recurrent pneumothorax 1 month after the first VATS procedure. The first patient with an apical bleb of the upper lobe in the first operation had apico-posterior blebs just dorsal to the previous resection line in the re-operation. This might have been due to inadequate bleb resection in the first VATS procedure. The second patient with no specific findings in the first VATS procedure had an apical bleb in the re-operation. We believe this patient had unidentified blebs in the first operation which subsequently lead to recurrent pneumothorax. The use of different degrees of thoracoscopes and a thorough examination of the entire lung surface from each thoracic port side are necessary to locate all pathologic lesions.

In this series, the choice of surgical approach for recurrence or treatment failure pneumothorax depended on the individual surgeon's opinion. Five of our patients were treated successfully with redo-VATS without conversion to thoracotomy. There is no general concern in re-treating recurrent pneumothorax after a first-time VATS procedure. However, our experience demonstrated that redo-VATS was an effective procedure in most of circumstances.

The majority of the failure cases were caused by unidentified blebs, inadequate bleb resection, or inadequate pleurodesis. These can be avoided by a thorough examination of the entire lung surface and a more extensive pleural abrasion during the first-time VATS procedure. Furthermore, a redo-VATS approach can be applied to recurrent cases with acceptable results [13].

References:

1. Neal JF, Vargas G, Smith DE, *et al.* Bilateral bleb excision through median sternotomy. Am J Surg. 1979; 138: 794-7.
2. Levi JF, Kleinmann P, Riquet M, *et al.* Percutaneous parietal pleurectomy for recurrent spontaneous pneumothorax. Lancet. 1990; 336: 1577-8.
3. Nathanson LK, Shimi S, Wood, *et al.* Video-thoracoscopic ligation of bullae and pleurectomy for spontaneous pneumothorax. Ann Thorac Surg. 1991; 52: 316-9.
4. Maier A, Anegg U, Renner J, *et al.* Four-year experience with pleural abrasion using a rotating brush during video-assisted thoracoscopy. Surg Endoscopy. 2000; 14: 75-8.
5. Riichiroj M, Takeshi O, Hideaki A. Video-assisted thoracoscopic treatment for spontaneous pneumothorax as two-day surgery. Am J Surg. 2000; 180: 171-3.
6. Giuseppe C, Francesco F, Roverto G, *et al.* Video-thoracoscopic treatment of primary spontaneous pneumothorax: a 6-year experience. Ann Thorac Surg. 2000; 69: 357-62.
7. Bernward P, Christine B, Kah H, *et al.* Efficiency of video-assisted thoracic surgery for primary and secondary spontaneous pneumothorax. Ann Thorac Surg. 1998; 65: 324-7.
8. YIM APC, Ho JKS. One hundred consecutive cases of video-assisted thoracoscopic surgery for primary spontaneous pneumothorax. Surg Endoscopy. 1995; 9: 332-6.
9. Horio H, Nomori H, Fuyuno G, *et al.* Limited axillary thoracotomy v.s. video-assisted thoracoscopic surgery for spontaneous pneumothorax. Surg Endoscopy. 1998; 12; 1155-8.
10. Waller DA, Forty J, Morritt GN. Video-assisted thoracoscopic surgery versus thoracotomy for spontaneous pneumothorax. Ann Thorac Surg. 1994; 58: 372-7.

11. Bertrand PC, Regnard JF, Spanggiari L, *et al.* Immediate and long term results after surgical treatment of primary spontaneous pneumothorax by VATS. Ann Thorac Surg. 1996; 61: 1641-5.
12. Melvin WS, Karsna MJ, McLaughlin JS. Thoracoscopic management of spontaneous pneumothorax. Chest. 1992; 102: 1877-9.
13. Cardillo G, Facciolo F, Regal M, *et al.* Recurrences following videothoracoscopic treatment of primary spontaneous pneumothorax: the role of redo-videothoracoscopy. Eur J Cardio-Thoracic Surg. 2001; 19(4): 396-9

自發性氣胸在胸腔鏡輔助手術術後復發的手術處理經驗

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背景　雖然胸腔鏡的發展已經使得原發性自發性氣胸的處理變得更加容易，至今仍沒有足夠的研究來探討有關胸腔鏡術後的復發率以及復發的原因。

方法　從 1993 年 1 月到 2001 年 6 月，我們一共分析了 216 位原發性自發性氣胸接受胸腔鏡輔助手術的病人。其中有九個復發病人接受第二次手術。資料收集主要是在於第二次手術的發現。

結果　所有病人都是男性，年齡界於 15 到 27 歲之間。有八位在第一次手術發現肺尖小泡的存在。在第二次手術中，四位存在下葉肺泡且三位存在上葉肺泡。 所有的病例均未有足夠之肋膜沾粘形成。平均復發時間為 8.3 個月(1 到 26 個月之間)。其中有一位病人在第二次手術後仍復發。

結論　一般認為造成復發的主要原因是失敗的肋膜沾粘術以及沒有發現的小泡。在第二次手術中，藉由更廣泛的肋膜括除術和進一步的肺泡切除便能改善治療結果。 ***(胸腔醫學 2002; 17: 226-231)***

關鍵詞：胸腔鏡鋪助手術，復發性自發性氣胸

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Performance of the BDProbeTec ET Assay for Identification of *Mycobacterium Tuberculosis* from Clinical Isolates

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To assess the performance of the BDProbeTec assay in the identification of *Mycobacterium tuberculosis*, 60 cultures of *Mycobacterium* from respiratory specimens were tested with *M. tuberculosis* complex probes. Using conventional biochemical tests, 30 of them were determined to be *M. tuberculosis* and 30 nontuberculous mycobacteria (NTM) (13 *M. avium* complex, 7 *M. abscessus*, 2 *M. fortuitum*, 2 *M. kansasii*, 2 *M. phlei*, 2 *M. terrae*, 1 *M. simiae*, and 1 *M. vaccae*). The BDProbeTec detected 100% (30) of the *M. tuberculosis* isolates, while 96.7% (29) of the NTM isolates tested negative. Only 1 NTM isolate, which was *M. phlei*, showed a positive result. The sensitivity, specificity, positive predictive value, and negative predictive value were 100%, 96.7%, 96.7%, and 100%, respectively. We conclude that the BDProbeTec ET system is a robust assay for the identification of *M. tuberculosis* from mycobacterium cultures. Determining the reliability of the BDProbeTec system for the direct detection of *M. tuberculosis* in respiratory specimens requires further study. ***(Thorac Med 2002; 17: 232-237)***

Key words: BDProbeTec ET, *M. tuberculosis*, Nontuberculous Mycobacteria

Introduction

Conventional approaches to the laboratory diagnosis of tuberculosis (TB) are based on acid-fast stains and the recovery of *Mycobacterium tuberculosis* from a cultivation of clinical specimens. However, acid-fast stains are not sufficiently sensitive in most instances, and they cannot distinguish *M. tuberculosis* from non-tuberculous mycobacteria (NTM). Because *M. tuberculosis* is easily spread by aerosols, it is generally recommended that hospitalized patients whose respiratory specimens are smear-positive for acid-fast bacilli be kept in respiratory isolation for 2 weeks until treated. This can be costly, inconvenient, and inappropriate if the isolate is confirmed to be an NTM. NTM are not transmissible from one human being to another, they are frequently colonizers, and the therapy greatly differs. In addition, it is not necessary to isolate patients with NTM infection or to track down people who have had contact.

For many decades, the standard biochemical tests were the only means of identifying mycobacterial species [1]. However, biochemical testing requires an additional 2 to 4 weeks for completion after mycobacteria have appeared in

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culture. The rapid and accurate diagnosis of symptomatic patients is a cornerstone of global TB control strategies [2]. A large number of nucleic acid amplification assays for the diagnosis of TB, many of which utilize the IS6110 repetitive element as a *M. tuberculosis* complex (MTBC)-specific target, have recently been developed [3-7]. False-positive results and cross-reactivity with other species of mycobacteria have been the major problems of these kinds of examinations [8-9].

Recently, the BDProbeTec assay, a fully automated system, has been introduced for the rapid identification of MTBC. The test system utilizes homogenous strand displacement amplifycation (SDA) technology as the amplification method, and fluorescent energy transfer (ET) as the method for detecting the presence of MTBC [10-11]. No studies investigating its performance in the identification of *M. tuberculosis* from culture have been reported. The purpose of this study was to evaluate the performance of the BDProbeTec assay in the identification of *M. tuberculosis* in cultures of *Mycobacterium*.

Materials and Methods

We selected 60 cultures of *Mycobacterium*, which were originally derived from the respiratory specimens of 60 patients, from the *Mycobacterium* laboratory of the Taiwan Chronic Disease Control Bureau, to carry out this study. The identification of these samples was determined by using conventional biochemical methods.

All isolates were tested with the BDProbeTec MTBC probe following the standard procedures provided by the manufacturer.

To process the isolates, 500μl of specimen was added to 1.0 ml of wash buffer solution. This combination was agitated on a vortex mixer for 5s, and centrifuged at 12,200 ×*g* for 30 min. The supernatant was discarded, the pellet was heated for 30 min at 105 °C to render the organisms nonviable, and then the pellet was pulse-centrifuged for 10s. The pellet was resuspended in 100μl of sample lysis buffer, vortex-mixed for 10s, and placed in a 65°C sonic water bath for 45min. The sample was pulse-centrifuged for 10s, and then 600μl of sample neutralization buffer was added. The mixture was vortex-mixed for 5 s, and pulse-centrifuged for 10s. The processed samples (150 μl) were added to priming microwells, which contained the amplification primers, fluorescent-labeled detector probe, and other reagents necessary for amplification. After incubation, the reaction mixtures were transferred to the amplification microwells, which contained enzymes (a DNA polymerase and a restriction endonuclease) necessary for SDA. The amplification microwells were sealed, and the plates were immediately placed in the BDProbeTec ET instrument. Once samples were introduced to the instrument, amplification and detection occurred in 1h. Up to 48 specimens could be analyzed per run. Results were interpreted as positive, negative, or indeterminate. Samples containing the *M. tuberculosis* complex were IS6110 positive and 16S rRNA gene positive.

For each assay, 1 positive and 1 negative control (provided with the kit) were tested. To each control, 600μl of neutralization buffer was added; the mixture was vortex-mixed for 5s and pulse-centrifuged for 10s. Samples and controls were randomly distributed into the sample rack. The corresponding numbers of the priming and amplification microwells were placed into their respective plates. Amplification controls reduce the chance of reporting false-negative results by identifying samples that inhibit the SDA reaction.

Sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

Results

The study was comprised of 30 isolates of *M. tuberculosis* and 30 isolates of NTM, as

Table 1. Distribution of *Mycobacterium* isolates identified by conventional biochemical methods

Organism	No of isolates	%
M. tuberculosis	30	100
NTM	30	100
M. avium complex	13	43
M. abscessus	7	23
M. fortuitum	2	7
M. kansasii	2	7
M. phlei	2	7
M. terrae	2	7
M. simiae	1	3
M. vaccae	1	3

determined by conventional biochemical methods. The 30 NTM included 13 *M. avium* complex (43%), 7 *M. abscessus* (23%), 2 *M. fortuitum* (7%), 2 *M. kansasii* (7%), 2 *M. phlei* (7%), 2 *M. terrae* (7%), 1 *M. simiae* (3%), and 1 *M. vaccae* (3%) (Table1).

Sixty isolates were tested with the MTBC probe, and the total time spent for the entire process was about 8 h. Among the *M. tuberculosis* isolates, 100% (30/30) were interpreted as positive results. Twenty-nine (96.7%) NTM isolates showed negative results in the tests. The only NTM isolate with a positive result was *M. phlei*, confirmed by repeated testing with conventional biochemical methods. None of the tested specimens showed indeterminate results.

The sensitivity, specificity, positive predictive value, and negative predictive value were 100%, 96.7%, 96.7%, and 100%, respectively (Table 2).

Discussion

The results of our study show that the BDProbeTec ET MTBC probe is a reliable assay for the identification of *M. tuberculosis* from *Mycobacterium* culture, with a short turnaround time. Infections due to NTM have been reported to account for 0.5% to 30% of all mycobacterial infections, and there are marked geographic variations [12]. Of all the mycobacteria isolated from patients at National Taiwan University Hospital between January 1996 and June 1996, 19.5% were NTM [13]. Data collected at Taiwan Provincial Chronic Disease Control Bureau from 1996 to 1997 showed that 5.6% of all mycobacteria isolates were NTM [14]. It has become increasingly important to isolate and identify mycobacteria, especially *M. tuberculosis*, as rapidly as possible. Laboratory identification within 17 to 21 days of specimen receipt was recommended at an international conference in 1992 [15]. Rapid methods, such as nucleic acid probes and high-performance liquid chromatography, for the identification of *M. tuberculosis* isolates, were recommended. The use of DNA probes for culture identification have shortened the time required for the identification of certain mycobacteria from 1 to 2 weeks with traditional methods to less than 24 h [16].

The MTBC probe detected all *M. tuberculosis* isolates in this study. The sensitivity, specificity, positive predictive value, and negative predictive value were 100%, 96.7%, 96.7%, and 100%, respectively. This sensitivity and specificity were similar to a previous study using the AccuProbe

Table 2. The results of BDProbeTec MTBC probe testing for clinical isolates

	MTBC probe test		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	Positive (n)	Negative (n)				
MTB	30	0	100	96.7	96.7	100
NTM	1	29				

MTB = *Mycobacterium tuberculosis*, NTM = Non-tuberculous mycobacteria, PPV = positive predictive value, NPV = negative predictive value

[17]. The total time spent for the entire process was about 8 h, which makes it a preferable choice for a rapid diagnosis.

In our study, 1 strain identified as *M. phlei* showed a false-positive result using the MTBC probe. The MTBC probe can detect variants of NTM species that may contain the IS6110 sequence. One false-positive BDProbeTec result from a specimen that grew the *M. fortuitum-chelonae* complex has been reported [18]. In 1991, Torres et al. reported mixed mycobacterial infections, which are difficult to diagnose by conventional methods, in patients with AIDS [19]. Because a DNA analysis was not performed, we cannot be sure if the positive result was related to the presence of the IS6110 sequence or to a mixed mycobacterial infection. However, the patient's clinical symptoms, signs, and chest radiography showed improvement after anti-TB treatment.

A previous study showed discrepant reactions in *M. terrae* isolates using a non-radioactive oligonucleotide probe [20]. We tested 2 *M. terrae* strains with the MTBC probe, but no false-positive reaction was noted. Since the case number is small, further investigation is indicated.

Though the BDProbeTec MTBC probe showed promising results in these tests on clinical isolates, its role in testing clinical samples (e.g. sputum, blood, body fluid) is still not known. The World Health Organization Global Tuberculosis Program supported an international collaborative quality control study among 30 laboratories that showed that nucleic acid amplification methods for the detection of *M. tuberculosis* may be unreliable [21]. Bergmann et al. evaluated the performance of the BDProbeTec ET system for the direct detection of MTBC in respiratory specimens by comparing the results to conventional mycobacterial cultures, and reported an initial overall sensitivity, specificity, positive predictive value, and negative predictive value of 87.5, 99.0, 70.0, and 99.7%, respectively [22]. Nucleic acid amplification to detect *M. tuberculosis* in clinical specimens is increasingly used as a laboratory tool for the diagnosis of tuberculosis. However, the specificity and sensitivity of these tests may be questioned.

We conclude that the BDProbeTec system is a rapid and highly accurate assay for the identification of *M. tuberculosis* in culture. Determining the reliability of the BDProbeTec system for the direct detection of *M. tuberculosis* in respiratory specimens requires further study.

References

1. Kent PT, Kubica GP. Public health mycobacteriology: a guide for the level III laboratory. USDHHS, Center for Disease Control, Atlanta, 1985:71-120.
2. Perkins MD. New diagnostic tools for tuberculosis. Int J Tuberc Lung Dis 2000; 4(12): S182-8.
3. Anderson AB, Thybo S, Godfrey-Fausset P, *et al.* Polymerase chain reaction for detection of *Mycobacterium tuberculosis* in sputum. Eur J Clin Microbiol Infect Dis 1993; 12:922-7.
4. Eisenach KD, Cave MD, Bates JH, *et al.* Polymerase chain reaction amplification of a repetitive DNA sequence specific for *Mycobacterium tuberculosis*. J Infect Dis 1990; 161: 977-81.
5. Eisenach KD, Sifford MD, Cave MD, *et al.* Detection of *Mycobacterium tuberculosis* in sputum samples using a polymerase chain reaction. Am Rev Respir Dis 1991; 144: 1160-3.
6. Kox LFF, Rhienthong D, Medo Miranda A, *et al.* A more reliable PCR for detection of *Mycobacterium tuberculosis* in clinical samples. J Clin Microbiol 1994; 32: 672-8.
7. Nolte FS, Metchock B, McGowan JE, *et al.* Direct detection of *Mycobacterium tuberculosis* in sputum by polymerase chain reaction and DNA hybridization. J Clin Microbiol 1993; 31: 1777-82.
8. Clarridge JE, Shawar RM, Shinnick TM, *et al.* Large-scale use of polymerase chain reaction for detection of *Mycobacterium tuberculosis* in a routine mycobacteriology laboratory. J Clin Microbiol 1993; 31: 2049-56.
9. Noordhoek GT, Kolk AHJ, Bjune G, *et al.* Sensitivity and specificity of PCR for detection of *Mycobacterium tuberculosis* : a blind comparison study among seven laboratory. J Clin Microbiol 1994; 32: 277-84.

10. Walker GT, Frasier MS, Schram JL, *et al.* Strand displacement amplification – an isothermal, *in vitro* DNA amplification technique. Nucleic Acids Res 1992; 20(7): 1691-6.
11. Little MC, Andrews J, Moore R, *et al.* Strand displacement amplification and homogenous real-time detection incorporated in a second-generation DNA probe system, BDProbeTec ET. Clin Chem 1999; 45(6):777-84.
12. Sanders WE Jr, Horowitz EA: Other mycobacterium species. In: Mandell GL, Douglas RG, Bennett JE, eds. *Principles and Practice of Infectious Diseases.* 4th ed. New York: Churchill Livingstone Inc, 1994: 2264-73.
13. Shih JY, Hsueh PR, Lee LN, *et al.* Nontuberculous mycobacteria isolates: clinical significance and disease spectrum. J Formos Med Assoc 1997; 96: 621-7.
14. Yu MC, Wu MH, Suo J, *et al.* Isolation and clinical significance of nontuberculous mycobacteria: the experiences in Taiwan Provincial Chronic Disease Control Bureau, 1996-1997. Thorac Med 1998; 13: 156-60.
15. Hinman AR, Hughes JM, Snider DE, *et al.* Meeting the challenge of multidrug-resistant tuberculosis: summary of a conference. Morbid Mortal Weekly Rep 1992; 41(no. RR-11): 51-7.
16. Salfinger M, Pfyffer GE. The new diagnostic mycobacteriology laboratory. Eur J Clin Microbiol Infect Dis 1994; 13: 961-79
17. Lebrun L, Espinasse F, Poveda JD, *et al.* Evaluation of nonradioactive DNA probes for identification of mycobacteria. J Clin Microbiol 1992; 30: 2476-8.
18. John SB, Gail LW. Clinical evaluation of the BDProbeTec strand displacement amplification assay for rapid diagnosis of tuberculosis. J Clin Microbiol 1998; 36: 2766-8.
19. Torres RA, Nord RF, Labombardi V, *et al.* Disseminated mixed *Mycobacterium simiae- Mycobacterium avium* complex infection in acquired immunodeficiency syndrome. J Infect Dis 1991; 164: 432-3.
20. Lim SD, Lopez J, Ford E, *et al.* Genotypic identification of pathogenic *Mycobacterium* species by using a nonradioactive oligonucleotide probe. J Clin Microbiol 1991; 29: 1276-8.
21. Noordhoek GT, Embden JDA, Kolk AHJ. Reliability of nucleic acid amplification for detection of *Mycobacterium tuberculosis*: an international collaborative quality control study among 30 laboratories. J Infect Dis 1996; 34(10): 2522-5.
22. Bergmann JS, Keating WE, Woods GL. Clinical evaluation of the BDProbeTec ET system for rapid detection of *Mycobacterium tuberculosis.* J Infect Dis 2000; 38(2): 863-5.

BDProbeTec ET 系統由臨床培養檢體中鑑定 *Mycobacterium Tuberculosis* 的臨床運用

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這個研究的主要目的是評估 BDProbeTec ET 系統由臨床培養檢體中鑑定的可靠性。我們從慢性病防治局取得 60 個臨床菌株，其中結核分枝桿菌與非結核分枝桿菌(non-tuberculous mycobacteria)各佔 30 株。非結核分枝桿菌包括(*M. avium* complex 13 株， *M. abscessus* 7 株，*M. fortuitum* 2 株， *M. kansasii* 2 株，*M. phlei* 2 株，*M. terrae* 2 株，*M. simiae* 1 株，*M. vaccae* 1 株)。所有的菌株都用 BDProbeTec ET 系統的 *M. tuberculosis* complex 探針測試。結果發現 30 株結核分枝桿菌全部都呈陽性反應。非結核分枝桿菌菌株只有一株 *M. phlei* 呈陽性反應，其他都呈陰性反應。整個研究的敏感性、特異性、正預估值、負預估值分別是 100%、96.7%、96.7%、100%。我們下了一個結論，BDProbeTec ET 系統的 *M. tuberculosis* complex 探針，在鑑定 *M. tuberculosis* 上，是一種快速又非常準確的方法。 ***(胸腔醫學 2002; 17: 232-237)***

關鍵詞：BDProbeTec ET，結核分枝桿菌，非結核分枝桿菌

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Postoperative Chylothorax Subsequent to Cardiac Surgery

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Objectives: The purpose of this paper is to describe the features of postoperative chylothorax subsequent to cardiac surgery and further discuss the management strategies.

Methods: Reports of postoperative chylothorax after cardiac surgery were collected from the Index Medicus/MEDLINE database of the U.S. National Library of Medicine from 1966 to the present. In all, 198 cases of postoperative chylothorax following cardiac surgery were collected from 61 reports, and included 161 cases (81.31%) of congenital heart defect operations from 28 reports, 24 coronary bypasses (12.12%) from 22, 5 heart valve replacements (2.53%) from 3, 4 aortic aneurysm surgeries (2.02%) from 4, and 4 heart transplantations (2.02%) from 4 reports.

Results: Postoperative chylothorax occurred most often in the correction of coarctation of the aorta (15.70%), more often in patent ductus arteriosus ligation (10.47%), the tetralogy of Fallot correction (8.72%), the Mustard procedure (7.56%), modified Fontan procedure (7.56%), and Blalock shunt (6.98%), in reference to the types of operation for congenital heart defects. As for the 64 cases whose management strategies were recorded, conservative regimens were applied in 41 patients (64.06%), and surgical intervention in 23 (35.94%). Patients recovered due to either medical or surgical treatment with a curative rate of 97.47%. Five patients died with a mortality of 2.53%, and 4 (80%) of these deaths were clearly identified to be unrelated to chylothorax.

Conclusions: Chylothorax is an uncommon complication after cardiac surgery. The diagnosis is mainly based on an examination of the pleural fluid. Once chylothorax is identified, nutritional support is the priority. Surgical treatment is recommanded after a 2-week trial of conservative therapy with chest drainage and diet modulation. ***(Thorac Med 2002; 17: 238-251)***

Key words: chylothorax, complication, heart operation

Introduction

Chylothorax is characterized by the leakage of chyle into the pleural cavity. This condition may have several etiologies classified as congenital, traumatic, obstructed, or spontaneous [1]. The first post-trauma chylothorax was reported by Quinke in 1875, and it was not described as a postopoerative entity until Blalock,

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Cunnuigham and Robinson described it in 1936 [2]. Thoracic duct injury may be incurred in operations on the great vessels, congenital heart corrections, esophageal surgeries, LeVeen shunt placements, and cervical node resections [3].

Chylothorax is an uncommon complication after cardiac surgery. The incidence of chylothorax has been reported as 0.36%-1.5% after cardiothoracic surgery [4], and 0.25%-0.5% after cardiovascular operations performed through a thoracotomy incision [2,5]. Recently, the incidence of this complication following cardiac surgery has changed to 0.2%-0.56% [6,7]. In reference to total admissions after cardiac surgery in neonates, the incidence of chylothorax was 1.2% [8]. Chylothorax after the complete correction of congenital heart disease had a prevalence of 0.9% [9], and was 7.5% in a patient group with a transposition of the great arteries undergoing a Mustard operation [10]. Reports of chylothorax resulting from valve replacement and coronary surgery continue to be anecdotal [11].

To our knowledge, no reports have systemically assessed this complication after various heart surgeries. The purpose of this paper is to describe the features of postoperative chylothorax following cardiac surgery and further discuss the management strategies.

Methods

Reports of postoperative chylothorax, published from 1966 to the present, were collected from the Index Medicus/MEDLINE database of the U.S. National Library of Medicine. Search terms included chylothorax, heart operation, cardioplegia, cardiopulmonary bypass, congenital heart defect, valve replacement, coronary bypass, aortic aneurysm, and heart transplantation. References to cited literature helped further complete the gathering of information. In all, 198 cases of postoperative chylothorax following cardiac surgery were collected from 61 reports, and included 161 cases (81.31%) of congenital heart defect operations from 28 reports, 24 coronary bypasses (12.12%) from 22, 5 heart valve replacements (2.53%) from 3, 4 aortic aneurysm surgeries (2.02%) from 4, and 4 heart transplantations (2.02%) from 4 reports.

Results

Congenital Heart Defects

One hundred and sixty-one cases of congenital heart defect operations from 28 reports were obtained [2,4,5,7,9-10,12-33]. Patient ages ranged from 3 days to 28 years. There were 47 females and 46 males, and the other 72 were sex unrecorded. Postoperative chylothorax occurred most often in the correction of coarctation of the aorta (15.70%), more often in patent ductus arteriosus (PDA) ligation (10.47%), the tetralogy of Fallot correction (8.72%), the Mustard procedure (7.56%), modified Fontan procedure (7.56%), and Blalock shunt (6.98%), with reference to the types of operation for congenital heart defects (Table 1). There were 4 alternative operative incisions (n=16): 7 (43.75%) median sternotomies; 6 (37.50%) left thoractomies; 2 (12.50%) bilateral thoractomies; and 1 (6.25%) right thoractomy. Chylous sites were recorded in 32 cases: 17 (53.125%) left-sided, 7 (21.875%) right-sided, 6 (18.75%) bilateral, and 2 (6.25%) in the mediastinum. Chylothorax occurred 1-42 days after operation. Chyle drained from the incision or the chest tube site occurred in 2 cases (1.23%). The onset of this complication was quite late in 3 patients--up to 2 months following operation [2]. The drainage duration before operation was 4-30 days, and that after operation was 5-16 days. Treatment methods were indicated in 30 cases: 20 (66.67%) with medical management, 10 (33.33%) with surgical procedure.

Coronary Bypass Surgery

There were a total of 24 postoperative chylothorax cases following coronary bypass surgery, found in 22 reports from 1981 to 2001 [1,3,11,34-52] (Table 2). The population included

Table 1. Types of operation of 162 cases of congenital heart defects complicating postoperative chylothorax

Type of operation	No.	Percentage of procedure (%)
Correction of cyanotic congenital heart defects	**63**	**36.63**
TOF correction	15	8.72
Mustard procedure	13	7.56
Senning operation	7	4.07
Switch operation	3	1.74
ECD repair	4	2.33
TAPVD correction	3	1.74
Rastelli procedure	2	1.16
Unknown	16	9.30
Systemic-pulmonary shunt	**43**	**25.00**
Modified Fontan procedure	13	7.56
Bidirectional cavopulmonary connection	8	4.65
Blalock shunt	12	6.98
Gleen operation	3	1.74
Norwood shunt	1	0.58
Waterston shunt	1	0.58
Unknown	5	2.91
Surgery for acyanotic congenital heart defects	**55 (66 procedures)**	**38.37**
Correction of the coarctation of the aorta	27	15.70
PDA ligation	18	10.47
Pulmonary valve stenosis repair	6	3.49
VSD closure	4	2.33
ASD closure	3	1.74
Video-assisted thoracoscopic surgery	3	1.74
Tricuspid annuloplasty	2	1.16
Partial pulmonary venous drainage (concomitant)	1	0.58
Unknown	2	1.16
Total	**161 (172 procedures)**	**100.00**

Note: TOF: tetralogy of Fallot; ECD: endocardial cushion defect; TAPVD: total anormolous pulmonary venous drainage; PDA: patent ductus arteriosus; VSD: ventricular septal defect; ASD: atrial septal defect.

17 (70.83%) males, and 7 (29.17%) females. Their ages ranged from 38 to 77 years, with a mean of 59.63 years (n=24). Twenty-two patients (91.67%) underwent a pure coronary bypass, and 2 (8.33%) had a coronary bypass with concomitant valve replacements [3,35]. One to four grafts of either the internal mammary artery and/or the saphenous vein (SVG) were used, with a mean of 2.39 grafts per patient (n=18). Grafts of the left internal mammary artery (LIMA) + SVG were used in 10 patients (41.67%), LIMA in 5 (20.83%), SVG in 3 (12.5%), bilateral internal mammary arteries in 1 (4.17%), and unavailable in 5 (20.83%). Chylothorax occurred 1-90 days after the initial operation, with a mean of 25.30 days (n=23). It occurred left-sidedly (n=20), much more than either right-sidedly (n=1) or mediastinally (n=2). One of the left-sided chylothoraxes was associated with a chylopericardium [51]. More patients received medical treatment (n=14), while fewer were treated with surgical intervention (n=9). One of these showed a relapse of the chylothorax 2 weeks after the initial medical treatment, and a pleurodesis combined with a diet modulation had

Table 2. Postoperative chylothorax following coronary bypass.

Author	Sex	Age	Graft	Onset of chylothorax (d)	Site of chyle	Treatment
Weber [34]	M	55	3(LIMA+SVG)	2	Mediastinum	C./ pleural drainage
Kshettry [11]	M	51	4(SVG)	60	L.	C./ pleural drainage
Teba [35]	F	51	NA (CABG+MVR)	6	L.	C./ pleural drainage
Di Lello [36]	M	53	1 (LIMA)	9	L.	S./ fibrin glue via a left thoracotomy 31 days later
Zakhour [37]	M	59	2(LIMA +SVG)	2	Mediastinum	C./ pleural drainage
	M	73	3(SVG)	90	L.	C./ pleural drainage
Czarnecki [38]	F	61	3(LIMA+RIMA)	42	R.	S./ lymphatic ligation via right thoracotomy 10 days later
Bogers [39]	M	41	1(LIMA)	1	L.	S./ the chylus leak was closed via a left thoracotomy on 36th postoperative day after the failure of conservative treatment
Chaiyaroj [40]	F	69	3(LIMA+SVG)	6	L.	S./ pleurodesis and lymphatic ligation via a left thoracotomy 18 days later
Smith [41]	M	60	1(LIMA)	14	L.	C./ pleural drainages
	M	47	1(LIMA)	7	L.	C./ pleural drainages
Davies [42]	M	48	NA (IMA+SVG)	29	L.	C./ pleural drainages 4 weeks
Wood [43]	M	69	2(LIMA+SVG)	2	L.	S./ sewing proximal portion of the LIMA pedicle
Janssen [44]	M	58	NA	14	L.	S./ chest tube & thoracoscopic intervention
Zaidenstein [45]	F	70	NA	NA	L.	NA
Yamaguchi [46]	M	64	NA	2	NA	S.
Felz [47]	F	50	2(LIMA+SVG)	60	L.	S./thorecentesis
Pêgo-Fernandes [1]	M	38	2(LIMA+SVG)	90	L.	C./ pleural drainage
Priebe [48]	F	75	3(LIMA+SVG)	30	L.	C./ pleural drainage (a relapse of the chylothorax)
Pérez [3]	M	68	NA (CABG+AVR)	10	L.	C./ pleural drainage
Venturini [49]	M	67	2(LIMA)	70	L.	S.
Sharpe [50]	F	63	4(SVG)	11	L.+ chylopericardium	C./ pleural drainage
Kelly [51]	M	77	3(LIMA+SVG)	18	L.	C./ using somatostatin
Brancaccio [52]	M	64	3(LIMA+SVG)	7	L.	C./ pleural drainage

Note: M: male; F: female; LIMA: left internal mammary artery; SVG: saphenous venous graft; NA: not available; CABG: coronary artery bypass grafting; MVR: mitral valve replacement; RIMA: right internal mammary artery; L.: left-sided; R.: right-sided; C.: conservative treatment; S.: surgical intervention.

to be adopted for recovery [48].

Valve Replacement

Chylothorax after valve replacement is rare, but sometimes occurs with concomitant coronary bypass surgery [3,35]. Five cases of valve replacement from 3 reports were complicated with postoperative chylothorax [2,53-54]. There were 4 mitral valve replacements (80%), one of which was a redo-mitral valve replacement, and one (20%) an aortic valve replacement. All 5 operations (100%) were performed via a median sternotomy incision: 3 (60%) chylothorax occurred in the mediastinum, 1 (20%) was right-sided, and 1 (20%) unknown. The complications occurred early, from 1-2 days after the valve replacement procedures. Three (60%) were managed with medical treatment, and 2 (60%) with surgical intervention for thoracic duct ligation. Brenner et al. [53] reported a relapsed chylothorax, which occurred as a manifestation of severe congestive heart failure resulting from rheumatic mitral stenosis. Chylothorax recurred after valve replacement, and was treated by thoracocentesis initially and then with a diet of medium-chain triglycerides. Ngan et al. [54] reported one case of chylothorax, after mitral valve replacement, which was proved by a lymphogram revealing the leakage of lipiodol from the thoracic duct just below the carina. The thoracic duct was ligated via a right thoracotomy and the drainage of chyle stopped.

Acquired Aortic Surgery

Four cases of postoperative chylothorax following the repair of aortic aneurysms were gathered from 4 reports [55-58]. The ages of the 3 males and 1 female at operation ranged from 59 to 78 years. Chylothorax occurred 2-9 days after operation (n=3). One case was right-sided, 1 left-sided, and 2 unknown. One of the complications was cured with medical regimens, however, a subsequent chylous pseudocyst developed and a surgical intervention was mandatory. Shiono et al. [57] applied fibrin glue, and Willemsen et al. [58] utilized video-assisted thoracoscopic surgery to stop the chylous leakage. All 4 patients recovered uneventfully.

Heart Transplantation

Only 4 cases of chylothorax after heart transplantation, 1 neonate and 3 adults, were reported in 4 separate reports [59-62]. The complications occurred on days 7-21 after the heart transplantation, and were successfully managed with conservative treatment [60,62]. It is considered that injury to the collateral lymphatics in the anterior mediastinal or thymic areas was the probable cause of the chylous fistula. Excessive chyle drainage causes a loss of large amounts of fat, protein, electrolytes, and lymphocytes, which further compromises the nutritional and immunologic status of the transplant patient [60].

Heart Operations of All Sorts

The latent interval from the initial cardiac operation to the diagnosis of the complication was 1-42 days after congenital heart defect correction, and 1-90 days after coronary bypass surgery. In reference to all types of heart operations, the incidence of postoperative chylothorax occurred most often left-sidedly (n=38, 61.29%), more often right-sidedly (n=11, 17.74%), and least often in the mediastinum (n=7, 11.29%) and bilateral (n=6, 9.68%), in the 62 recorded cases. The amount of chylous drainage was recorded in different ways. Some of the cases underwent repeated thoracocentesis, and each single drainage amount was recorded. Those receiving chest tube drainage had their drainage volumes recorded. The mean drainage volumes were 235 ml/kg [33], and 0.91-23.24 ml/kg/day [7]. Pêgo-Fernandes et al. [1] reported the mean volumes of the posterior and anterior drainage of a patient with postoperative chylothorax after coronary bypass were 105 ml/day and 35 ml/day, respectively. The total drainage volumes were reported to be 1300-9000 ml [14], and 40-9580 ml [7] in two different reports. The recovery

period of patients receiving medical treatment ranged from 4 to 90 days [2-3,11,13-15,34,37, 42-43,52,60,62]. As for the 64 cases whose management strategies were recorded, conservative regimens applied in 41 patients (64.06%), and surgical intervention in 23 (35.94%). One hundred and ninety-three patients recovered with either medical or surgical treatment, with a curative rate of 97.47%. Five patients died, with a mortality of 2.53%, and 4 (80%) of them were clearly identified to be unrelated to the open heart surgery.

Discussion

Etiology

Postoperative chylothorax has been confirmed to have 2 distinct causes: (a) direct trauma to the thoracic duct or its lymphatic collaterals and, (b) as a cause to obstruction and/or high pressure in the superior vena cava (SVC) [33].

A direct trauma to the thoracic duct or its lymphatic collaterals

The thoracic duct always receives tributaries from the bronchomediastinal trunk of the right lymphatic channels in the posterior mediastinum [2]. The majority of patients who develop postoperative chylothorax have undergone surgical procedures closely related to the thoracic duct, involving the heart, aorta, esophagus, and left subclavian vessels [3,63]. Cardiovascular and esophageal procedures are the most frequent causes of chylothorax. Malformations of the thoracic duct and other organs of the mediastinum have often been involved in lymphatic injury [64].

Although traumatic chylothorax has occurred after many types of operations for congenital heart defects, it occurs most commonly after subclavian-pulmonary artery shunt, resection of the coarctation of the thoracic aorta, and PDA ligation. Such procedures are carried out in close proximity to the normal anatomic locations of the thoracic duct [14]. There appears to be an increased risk of perioperative pleural effusion and chylothorax when using a superior vena cava-to-pulmonary artery anastomosis [65].

The thoracic duct enters the superior mediastinum and terminates at the junction of the left internal jugular and subclavian veins. The increasing use of the LIMA and the variable anatomy of the lymphatic duct suggest that this complication may occur more frequently in the future [40]. During coronary bypass, lymphatic channels may be disrupted in the region of the thymus or near the origin of the internal thoracic artery. Lymphatic collaterals end at the azygous, brachiocephalic, and intercostal veins, near the subclavian-jugular venous junction. Due to the proximity of the lymphatic tributaries to the origin of the left internal thoracic artery, these lymphatics can be injured during manipulation [1]. Lymphatic injury probably occurs at the time of the dissection to maximize the length of the internal thoracic artery, near the proximal end of the LIMA pedicle [1].

Injury to collaterals from the right bronchomediastinum is a probable cause of chylothorax after intrapericardial surgery [2]. The cause of the chylothorax, in one report, was considered to be injury to the lymphatic collaterals in the anterior mediastinum, which resulted in a retrograde chyle flow; the main duct remained intact [37]. Occult trauma to the lymphatic collaterals during dissection of the internal thoracic artery, or during the cautery of small vessels in the superior left mediastinum, could have allowed the gradual accumulation of chyle and symptomatic onset at a time remote from the thoracotomy [47].

Secondary to obstruction and/or high pressure in the SVC

Injury to the lymphatics can be induced by tapes passing through and around the venae cavae, and increase the SVC pressure during extra-corporeal circulation [34]. The passage of caval tapes, and venous thrombosis causing a venous obstruction to the drainage of chyle at the

subclavian-jugular junction, are possible causes of chylothorax [14]. Patients with an additional source of pulmonary blood flow after bidirectional cavopulmonary shunt have higher postoperative central venous pressures and higher oxygen saturations, and are at risk for the late development of a chylothorax [66]. Chylothorax secondary to acute or chronic venous hypertension was reported following Gleen operations. In 1951, Palken and Weller [67] described one case where thrombosis of the SVC followed a Gleen procedure and produced chylothorax. Edwards and Bargeron [68], in a series of 34 infants undergoing the Gleen operation, reported 5 cases of chylothorax (14.7%), and Hunt et al. [69] in a series of 46 infants and children reported chylothorax in 6 cases (13%).

Diagnosis

The diagnosis of postoperative chylothorax is not very difficult, however, an early diagnosis is critical and correlates closely with the prognosis of this complication. Diagnosis is always made on the the basis of an examination of the pleural fluid. Chyle has a milky appearance only if chylomicrons are present. The appearance of the fluid varies with the type of nutrition, and chyle appears clear and light yellow if the patient has not been fed [33]. Thoracocentesis and a milky fluid microscopic examination will reveal the presence of free fat. Fatty content will be higher in the milky fluid than in the plasma, provided that the protein content is around half of that in the plasma. Pancreatic lipase, amylase, and deoxyribonuclease will be present. Even when the damaged duct is ligated, the possibility of leakage remains, either because of an incomplete occlusion or the presence of other lymphatic channels [1].

The first indication of chylothorax is seen as a mediastinum enlargement in the chest X-ray, and afterwards, as pleural effusion. Symptoms can be weight loss, loss of appetite, and persistent low fever; however, diagnosis cannot be made until circulatory shock and severe respiratory distress have occurred in some cases. Hypoalbuminemia or hypoglobulinemia are usually found [1]. The pleural effusion is delayed in onset, reaccumulates rapidly after initial thoracocentesis, and frequently recurs after apparent resolution. In most patients, a widening of the mediastinum was noted prior to the appearance of the pleural effusion [14]. The diagnostic criteria are listed in Table 3.

The chylothorax was right-sided in 62%, left-sided in 21%, and bilateral in 17% of the cases. If the thoracic duct is damaged below the level of the fifth or sixth thoracic vertebra, the resulting chylothorax will most probably be right-sided. If the injury is above this level, the effusion will most likely be left-sided [70]. Chylous effusion may be bilateral but is more frequently unilateral and seen on the left side [35]. The volume through the drain ranged from 200 to 3200 ml/24h [71]. The average maximal lymph

Table 3. Diagnostic criteria of postoperative chylothorax following cardiac surgery [25,35]

Contents	Criteria
Characteristics	
Description	milky appearance
PH	7.4-7.8
Specific gravity	1.012-1.025
Sudan III staining	fat globules
Electrophoresis	chylomicrons
Lymphocytes	400-6800/mm^3
Erythrocytes	50-600/mm^3
Total protein	21-59 g/l
Albumin	12-41.6 g/l
Globulin	11-30.8g/l
Fibrinogen	160-240 mg/l
Total fat	4-60g/l
Triglycerides	>110mg/dl
Cholesterol	plasma value or lower
Sugar	2.7-11.1 mmol/l
Urea	1.4-3.0 mmol/l
Electrolytes	plasma value
Specific examination	
Chest X-ray	enlarged cardiomediastinal shadow
Lymphagiogram	site of leak or obstruction
Other visualization	site of fistula

leak was 39.4 (range 15 to 130) ml/kg/day. The average duration of a lymph leak was 30 (range 12 to 56) days, and the average maximal lymph leak was 30.1 (range 8.5 to 59) ml/kg/day [4]. Chylothorax usually begins 2-10 days after the surgery, but the initial symptoms often appear weeks or months later. The longest reported latent period was 6 weeks, in the patient with congenital heart defect correction [14], but it was 90 days in patients after myocardial revascularization [1].

Management

The management of chylothorax was controversial before the 1960's [14]. Postoperative chylothorax is treated either surgically or conservatively. The primary method of treatment for chylothorax has been conservative, including nutritional support and chest tube drainage. Initial conservative treatment has consisted of tube thoracostomy drainage ranging from 1 to 62 days [25]. Conservative therapy with chest tube drainage of the chyle fluid and dietary modification (low-fat diet with medium-chain triglycerides, and total parenteral nutrition) is frequently effective [4]. With this regimen, 50% of the cases of traumatic chylothorax resolve spontaneously [72]. Sometimes chest drainage and a low-fat diet will stop the chylous leakage. Once chylothorax is identified, nutritional support is the priority. The first principle in the management of chylothorax is to provide adequate nutrition and to minimize the chyle formation [3]. Approaches such as a hipo or alipoidic diet [71], subcutaneous octreotide (which functions to reduce chyle output, and to decrease the triglyceride content of the pleural fluid) [73-74], and somatostatin [75], have acquired good results.

Surgical intervention is mandatory when medical therapy fails: (1) a chylous drainage greater than 1500 ml/day for the adult and greater than 100 ml/year of age/day for children for more than 5 days; (2) chylous drainage for more than 14 days in spite of medical treatment; and (3) metabolic disturbances, malnourishment, and immunological deficiency occurred due to chylous loss [25,35]. Surgical approaches include: thoracic duct ligation (open thoracotomy or thoracoscopy), pleurodesis with different agents, pleuroperitoneal shunts, pleurectomy, and pleural abrasion. In the past, the most common treatment was right thoracotomy with ligation of the thoracic duct at the aortic hiatus. Actually, a combination of options is often used: pleurectomy and chemical pleurodesis alone or associated with thoracic duct ligation [33]. Some of the patients experienced an unsuccessful conservative treatment and a subsequent surgical procedure. The chylous fistula often occurs in the anterior mediastinum in the region of the thymic tissue, and can be prevented by surgical ligation of the thymic vascular structures at the time of dissection, rather than with the use of electrocautery. The treatment recommended is a 2-week trial of conservative therapy with a diet of medium-chain triglycerides and closed-chest suction. If this fails, surgical division of the fistula is recommended [2].

The pleuroperitoneal shunt was proved to function effectively in patients with moderately elevated right atrial pressures of 10 to 16 mmHg [76]. Mean patient age at the time of shunt placement was 2.1 (0.1 to 11.5) years, and the most common indication (7 of 15) was refractory chylothorax following the surgical correction of congenital heart disease. Mean chylothorax duration before shunt placement was 76 (5 to 810) days, and shunts were in place for an average of 104 (12 to 365) days [76]. A total of 19 chylous effusions (pleural or pericardial) were treated with shunts [77]. Rheuban et al. [76] reported 10 patients who underwent placement of a pleuroperitoneal shunt, with complete resolution of the chylothorax in 90% of the patients. The use of a pleuroperitoneal shunt may control the effusion and shorten the hospital stay by several weeks [78].

Pleurodesis is an option for obtaining pleural adhesion to obliterate the chylous leak in those patients either induced surgically [79], or with agents available for pleurodesis, including

sclerosing agents and other products such as talc [80-81], tetracycline [82], OK432 [63], and fibrin glue [80,83].

Pleurectomy is also a surgical alternative which should be indicated, and has been proved to be the most successful treatment when no distinct chylous leak can be identified [84].

Pleural abrasion has often been integrated with open thoracotomy to manage pulmonary disease in the early stages [85]. Now, it is also utilized in the surgical management of posto-perative chylothorax with the aid of video-assisted thoracoscopic surgery.

Video-assisted thoracoscopic surgery offers the advantages of visualization and manipulation of the mediastinal structures. It allows an easy location and laceration of the thoracic duct with clips, and application of fibrin glue or talc in the pleural space [86]. Percutaneous thoracic duct embolization was performed successfully for the treatment of postoperative chylothorax, and can replace surgical ligation in some patients [87]. Selective lobar-bronchial blockade has successfully managed the thoracoscopic thoracic duct. Video-assisted thoracoscopic surgery reduces the risk of intraprocedural physiologic impairment, facilitating other concomitant procedures [88].

Prognosis

Chylothorax may be associated with delayed extubation [89], prolongation of the hospitalization period of many patients undergoing a Fontan procedure [78], and serious pulmonary and/or pleural functional impairment [45], and result in an impaired immune system and nutritional state [60]. It may cause a previously stable thoracic patient to develop sudden, potentially serious respiratory problems [90]. Sequelae of this complication were reported to be lymphopenia (2 patients) and fungal sepsis (1 patient) [27]. There was one death due to chylothorax after a thrombotic obstruction of the SVC late after switch surgery [22].

Conservative treatment was successful in 80% of the patients. Improvement was defined as a drainage of < 10 ml/kg/day. Failure of treatment was defined as a drainage of > 10 ml/kg/day [25]. Prevention, early recognition, and treatment of potential complications, such as SVC thrombosis or obstruction, may further improve the success rate of conservative treatment [33].

Spontaneous cessation and cure occurred in 73.1% of the patients, with an average drainage duration of 11.9 (range 4 to 30) days. Those for whom an operation was chosen drained preoperatively for an average of 29.2 (range 25 to 40) days. The amount of drainage per day was not significantly different between patients treated operatively and non-operatively. Failure of non-operative management was associated with venous hypertension from increased right-side cardiac pressures or central venous thrombosis. Presumably this increased pressure is transmitted to the lymphatic system. These patients should be identified early and considered for thoracic duct suture or pleuroperitoneal shunting [27]. Chylo-thorax secondary to venous hypertension and thrombosis has a longer interval between operation and diagnosis compared with direct trauma, as well as a longer duration and larger volume of chylous drainage [91]. Initial conservative treatment, including tube thoracostomy drainage and dietary modification (low-fat diet, total parenteral nutrition), resulted in resolution of the chylothorax in 79% of the patients, and only 21% required ligation of the thoracic duct, with 100% success [25].

Children who develop chylothorax after cardiac surgery should be treated conservatively for at least the early postoperative period when circulatory and/or respiratory conditions are still unstable [23]. Chylothorax of either cause should be treated operatively after a limited trial (1 to 2 weeks) of non-operative therapy [41]. The anatomy of the thoracic duct is extremely variable. And its normal course is rarely seen. Awareness of the variable anatomy of the duct is most important in preventing a chylothorax. Careful dissection of the probable course of the duct, and the meticulous control of suspected chylous leaks at operation are essential.

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References

1. Pêgo-Fernandes PM, Ebaid GX, Nouer GH, *et al.* Chylothorax after myocardial revascularization with the left internal thoracic artery. Arq Bras Cardiol 1999; 73: 383-90.
2. Joyce LD, Lindsay WG, Nicoloff DM. Chylothorax after median sternotomy for intrapericardial cardiac surgery. J Thorac Cardiovasc Surg 1976; 71: 476-80.
3. Pérez J, Casal J, Rodriguez W. Always remember chylothorax. South Med J 1999; 92: 833-5.
4. Nguyen DM, Shum-Tim D, Dobell AR, *et al.* The management of chylothorax/chylopericardium following pediatric cardiac surgery: a 10-year experience. J Card Surg 1995; 10(4 Pt 1): 302-8.
5. Maloney JV, Spencer FC. The nonoperative treatment of traumatic chylothorax. Surgery 1956; 40: 121-30.
6. Sasai T, Kaji M, Morioka H, *et al.* The treatment of traumatic chylothorax. Kyobu Geka 1989; 42: 838-41.
7. Verunelli F, Giorgini V, Luisi VS, *et al.* Chylothorax following cardiac surgery in children. J Cardiovasc Surg (Torino) 1983; 24: 227-30.
8. González de Dios J, García Martín B, Burgueros Valero M, *et al.* Congenital and post-operative chylothorax in the neonatal period. An Esp Pediatr 1992; 36: 109-14.
9. Dagan O, Birk E, Katz J, *et al.* First year's experience of the Post-Operative Cardiac Care Unit, Schneider Children's Medical Center. Harefuah 1998; 134: 101-5.
10. Arciniegas E, Farooki ZQ, Hakimi M, *et al.* Results of the Mustard operation for dextro-transposition of the great arteries. J Thorac Cardiovasc Surg 1981; 81: 580-7.
11. Kshettry VR, Rebello R. Chylothorax after coronary artery bypass grafting. Thorax 1982; 37: 954.
12. Garamella JJ. Chylothorax treated by ligation of the thoracic duct and studies in thoracic ductography. Arch Surg 1958; 76: 46-53.
13. Tandon RK. Chylothorax after repair of ventricular septal defect. J Thorac Cardiovasc Surg 1968;56:378-80.
14. Higgins CB, Mulder DG. Chylothorax after surgery for congenital heart disease. J Thorac Cardiovasc Surg 1971; 61: 411-8.
15. Althaus U, Fuchs W. Chylothorax following cardiovascular surgery. Schweiz Med Wochenschr 1972; 102: 44-8.
16. Lauridsen P, Wennevold A, Efsen F. Anomalous pulmonary venous drainage from the left lung to the right atrium. Successful surgical treatment in an 11-year-old girl. Scand J Thorac Cardiovasc Surg 1979; 13: 17-20.
17. Fairfax AJ, McNabb WR, Spiro SG. Chylothorax: a review of 18 cases. Thorax 1986; 41: 880-5.
18. Okita Y, Miki S, Kusuhara K, *et al.* Massive systemic venous thrombosis after Fontan operation: report of a case. Thorac Cardiovasc Surg 1988; 36: 234-6.
19. Baudet E, al-Qudah A. Late results of the subclavian flap repair of coarctation in infancy. J Cardiovasc Surg (Torino) 1989; 30: 445-9.
20. Okabayashi H, Tamura N, Hirose H, *et al.* Aortic aneurysm associated with coarctation of the aorta. Kyobu Geka 1989; 42: 1032-5.
21. Cooper P, Paes ML. Bilateral chylothorax. Br J Anaesth 1991; 66: 387-90.
22. Krian A, Kramer HH, Quaegebeur J, *et al.* The arterial switch-operation: early and midterm (6 years) results with particular reference to technical problems. Thorac Cardiovasc Surg 1991; 39 Suppl 2: 160-5.
23. Suzuki K, Okada H, Kato T, *et al.* Chylothorax developed after cardiac surgery in children: a report of three cases. Kyobu Geka 1991; 44: 312-5.
24. Chun K, Colombani PM, Dudgeon DL, *et al.* Diagnosis and management of congenital vascular rings: a 22-year experience. Ann Thorac Surg 1992; 53: 597-602.
25. Marts BC, Naunheim KS, Fiore AC, *et al.* Conservative versus surgical management of chylothorax. Am J Surg 1992; 164: 532-4.
26. Minich LL, Beekman RH 3rd, Rocchini AP, *et al.* Surgical repair is safe and effective after unsuccessful balloon angioplasty of native coarctation of the aorta. J Am Coll Cardiol 1992; 19: 389-93.
27. Bond SJ, Guzzetta PC, Snyder ML, *et al.* Management of pediatric postoperative chylothorax. Ann Thorac Surg 1993; 56: 469-72.
28. Miyamura H, Watanabe H, Eguchi S, *et al.* Ligation of

the thoracic duct through transabdominal phrenotomy for chylothorax after heart operations. J Thorac Cardiovasc Surg 1994; 107: 316

29. Laborde F, Folliguet T, Batisse A, *et al.* Closure of patent ductus arteriosus by video thoracoscopy in 282 children. Arch Mal Coeur Vaiss 1996; 89: 547-51.
30. Lavoie J, Burrows FA, Hansen DD. Video-assisted thoracoscopic surgery for the treatment of congenital cardiac defects in the pediatric population. Anesth Analg 1996; 82: 563-7.
31. Minich LL, Tani LY, Olson AL, *et al.* Reversal of flow in the left pulmonary artery after cavopulmonary connection. J Am Soc Echocardiogr 1996; 9: 202-5.
32. Iacona GM, Marianeschi SM, Condoluci C, *et al.* The role of a bidirectional cavopulmonary anastomosis in the correction and palliation of complex congenital cardiopathies. G Ital Cardiol 1998;28:1372-7.
33. Beghetti M, La Scala G, Belli D, *et al.* Etiology and management of pediatric chylothorax. J Pediatr 2000;136:653-8.
34. Weber DO, Mastro PD, Yarnoz MD. Chylothorax after myocardial revascularization with internal mammary graft. Ann Thorac Surg 1981;32:499-2.
35. Teba L, Dedhia HV, Bowen R, *et al.* Chylothorax review. Crit Care Med 1985;13:49-52.
36. Di Lello F, Werner PH, Kleinman LH, *et al.* Life-threatening chylothorax after left internal mammary artery dissection: therapeutic considerations. Ann Thorac Surg 1987;44:660-1.
37. Zakhour BJ, Drucker MH, Franco AA. Chylothorax as a complication of aortocoronary bypass. Two case reports and a review of the literature. Scand J Thorac Cardiovasc Surg 1988;22:93-5.
38. Czarnecki DJ, Kehoe ME, Tector AJ. Lymphangiographic evaluation of chylothorax after myocardial revascularization. AJR Am J Roentgenol 1988;151:1054-5.
39. Bogers AJ, Pardijs WH, Van Herwerden LA, *et al.* Chylothorax as a complication of harvesting the left internal thoracic artery in coronary artery bypass surgery. Eur J Cardiothorac Surg 1993;7:555-6.
40. Chaiyaroj S, Mullerworth MH, Tatoulis J. Surgery in the management of chylothorax after coronary artery bypass with left internal mammary artery. J Thorac Cardiovasc Surg 1993;106:754-6.
41. Smith JA, Goldstein J, Oyer PE. Chylothorax complicating coronary artery bypass grafting. J Cardiovasc Surg (Torino) 1994;35:307-9.
42. Davies MJ, Spyt TJ. Chylothorax and wound lymphocele formation as a complication of myocardial revascularization with the internal thoracic artery. J Thorac Cardiovasc Surg 1994;108:1155-6.
43. Wood MK, Ullyot DJ. Chylothorax. J Thorac Cardiovasc Surg 1994;108:1156.
44. Janssen JP, Joosten HJ, Postmus PE. Thoracoscopic treatment of postoperative chylothorax after coronary bypass surgery. Thorax 1994;49:1273
45. Zaidenstein R, Cohen N, Dishi V, *et al.* Chylothorax following median sternotomy. Clin Cardiol 1996;19:910-2.
46. Yamaguchi T, Watanabe G, Kotoh K, *et al.* The changes in lymphocytes subpopulations of a patient with postoperative chylothorax. Kyobu Geka 1996;49:1085-7.
47. Felz MW, Neely J. Beware the left-sided effusion. J Fam Pract 1997;45:519-22.
48. Priebe L, Deutsch HJ, Erdmann E. Chylothorax as a postoperative complication of aortocoronary bypass operation. Dtsch Med Wochenschr 1999;124:855-8.
49. Venturini E, Piccoli M, Francardelli L, *et al.* Chylothorax following myocardial revascularization with the internal mammary artery. G Ital Cardiol 1999;29:1334-6.
50. Sharpe DA, Pullen MD, McGoldrick JP. A minimally invasive approach to chylopericardium after coronary artery surgery. Ann Thorac Surg 1999;68:1062-3.
51. Kelly RF, Shumway SJ. Conservative management of postoperative chylothorax using somatostatin. Ann Thorac Surg 2000;69:1944-5.
52. Brancaccio G, Prifti E, Cricco AM, *et al.* Chylothorax: a complication after internal thoracic artery harvesting. Ital Heart J 2001;2:559-562.
53. Brenner WI, Boal BH, Reed GE. Chylothorax as a manifestation of rheumatic mitral stenosis: its postoperative management with a diet of medium-chain triglycerides. Chest 1978;73:672-3.
54. Ngan H, Fok M, Wong J. The role of lymphography in chylothorax following thoracic surgery. Br J Radiol 1988;61:1032-6.
55. Mack JW, Heydorn WH, Pauling FW, *et al.* Postoperative chylous pseudocyst. J Thorac Cardiovasc Surg 1979;77:773-6.

56. Yoh T, Ohnuki T, Itaoka T, *et al.* Conservative treatment of postoperative chylothorax in a patient with chronic traumatic aneurysm of thoracic aorta. Kyobu Geka 1994;47:194-7.
57. Shiono S, Sato T, Abiko M, *et al.* Postoperative chylothorax treated with fibrin glue and absorbent mesh: a case report. Kyobu Geka 1998;51:879-81.
58. Willemsen HW, Girbes AR, Borgstein PJ, *et al.* Thoracoscopic clipping of thoracic duct in a woman with persisting chylothorax. Ned Tijdschr Geneeskd 2000;144:2564-7.
59. Repp R, Scheld HH, Bauer J, *et al.* Cyclospnrine losses by a chylothorax. J Heart Lung Transplant 1992;11:397-8.
60. Bowerman RE, Solomon DA, Bognolo D, *et al.* Chylothorax: report of a case complicating orthotopic heart transplantation. J Heart Lung Transplant 1993;12:665-8.
61. Twomey CR. Chylothorax in the adult heart transplant patient: a case report. Am J Crit Care 1994;3:316-9.
62. Conroy JT, Twomey C, Alpern JB. Chylothorax after orthotopic heart transplantation in an adult patient: a case complicated by an episode of rejection. J Heart Lung Transplant 1993;12(6 Pt 1):1071.
63. Shimizu J, Hayashi Y, Oda M, *et al.* Treatment of postoperative chylothorax by pleurodesis with the streptococcal preparation OK-432. Thorac Cardiovasc Surg. 1994;42:233-6.
64. Cevese PG, Vecchioni R, D'Amico DF, *et al.* Postoperative chylothorax. Six cases in 2,500 operations, with a survey of the world literature. J Thorac Cardiovasc Surg 1975;69:966-71.
65. Van Arsdell GS, Williams WG, Freedom RM. A practical approach to 1½ ventricle repairs. Ann Thorac Surg 1998;66:678-80.
66. Frommelt MA, Frommelt PC, Berger S, *et al.* Does an additional source of pulmonary blood flow alter outcome after a bidirectional cavopulmonary shunt? Circulation 1995;92(9 Suppl):II240-4.
67. Palken M, Weller LM. Chylothorax and chyloperitoneum. Report of a case occurring after embolism of the left subclavian vein with thoracic duct obstruction. JAMA 1951;147:566-9.
68. Edwards WS, Bargeron LM Jr. The superiority of the Gleen operation for tricuspid atresia in infancy and childhood. J Thorac Cardiovasc Surg 1968;55:60-9.
69. Hunt D, Edwards WS, Deverall PB, *et al.* Superior vena cava to right pulmonary artery anastomosis. Results in 46 infants and children. Thorax 1970;25:550-5.
70. Schulman A, Fataar S, Dalrymple R, *et al.* The lymphographic anatomy of chylothorax. Br J Radiol 1978;51:420-7.
71. Jatene FB, Bosisio IB, Jatene MB, *et al.* Posttraumatic chylothorax. Experience in the postoperative period following cardiothoracic surgery. Arq Bras Cardiol 1993;61:229-32.
72. Rubin JW, Moore HV, Ellison RG. Chylothorax: therapeutic alternatives. Am Surg 1977;43:292-7.
73. Cheung Y, Leung MP, Yip M. Octreotide for treatment of postoperative chylothorax. J Pediatr 2001;139:157-9.
74. Markham KM, Glover JL, Welsh RJ, *et al.* Octreotide in the treatment of thoracic duct injuries. Am Surg 2000;66:1165-7.
75. Demos NJ, Kozel J, Scerbo JE. Somatostatin in the treatment of chylothorax. Chest 2001;119:964-6.
76. Rheuban KS, Kron IL, Carpenter MA, *et al.* Pleuroperitoneal shunts for refractory chylothorax after operation for congenital heart disease. Ann Thorac Surg 1992;53:85-7.
77. Wolff AB, Silen ML, Kokoska ER, *et al.* Treatment of refractory chylothorax with externalized pleuroperitoneal shunts in children. Ann Thorac Surg 1999;68:1053-7.
78. Sade RM, Wiles HB. Pleuroperitoneal shunt for persistent pleural drainage after Fontan procedure. J Thorac Cardiovasc Surg 1990;100:621-3.
79. Plume SK, Ambrosino D, Boyle W Jr, *et al.* Management of persistent chylothorax. Lancet 1981;2(8243):423.
80. Cerfolio RJ, Allen MS, Deschamps C, *et al.* Postoperative chylothorax. J Thorac Cardiovasc Surg 1996;112:1361-5.
81. Weissberg D, Ben-Zeev I. Talc pleurodesis. Experience with 360 patients. J Thorac Cardiovasc Surg 1993;106:689-95.
82. Good JT Jr, Sahn SA. Intrapleural therapy with tetracycline in malignant pleural effusions: the importance of proper technique. Chest 1978;74:602.
83. Stenzl W, Rigler B, Tscheliessnigg KH, *et al.* Treatment of postsurgical chylothorax with fibrin glue. Thorac Cardiovasc Surg 1983;31:35-6.
84. Browse NL, Allen DR, Wilson NM. Management of

chylothorax. Br J Surg 1997;84:1711-6.
85. Rich RH, Warwick WJ, Leonard AS. Open thoracotomy and pleural abrasion in the treatment of spontaneous pneumothorax in cystic fibrosis. J Pediatr Surg 1978;13:237-42.
86. Fahimi H, Casselman FP, Mariani MA, *et al.* Current management of postoperative chylothorax. Ann Thorac Surg 2001;71:448-50.
87. Cope C, Salem R, Kaiser LR. Management of chylothorax by percutaneous catheterization and embolization of the thoracic duct: prospective trial. J Vasc Interv Radiol 1999;10:1248-54.
88. Takahashi M, Kurokawa Y, Toyama H, *et al.* TOC The successful management of thoracoscopic thoracic duct ligation in a compromised infant with targeted lobar deflation. Anesth Analg 2001;93:96-7.
89. Fischer JE, Allen P, Fanconi S. Delay of extubation in neonates and children after cardiac surgery: impact of ventilator-associated pneumonia. Intensive Care Med 2000;26:942-9.
90. Morey LB, Dungan JM. Chylothorax: a complication of thoracic trauma or surgery. Dimens Crit Care Nurs 1992;11:184-90.
91. Le Coultre C, Oberhansli I, Mossaz A, *et al.* Postoperative chylothorax in children: differences between vascular and traumatic origin. J Pediatr Surg 1991;26:519-23.

心臟外科手術後乳糜胸

袁師敏　郭加強

目的：本文旨在描述心臟外科手術後乳糜胸的特徵，並進一步檢討其治療策略。

方法：搜集 1966 年至今的美國國立醫學圖書館 Index Medicus/MEDLINE 數據庫的心臟外科手術後乳糜胸的文獻，共檢得 61 篇文獻 198 病例。其中包括 28 篇文獻中的 161 例 (81.31%) 先天性心臟病，22 篇文獻中的 24 例 (12.12%) 冠狀動脈繞道手術，3 篇文獻中的 5 例 (2.53%) 瓣膜置換術，4 篇文獻中的 4 例 (2.02%) 主動脈瘤手術，4 篇文獻中的 4 例 (2.02%) 心臟移植手術。

結果：就先天性心臟病的手術種類而言，術後乳糜胸最多發生在主動脈弓中斷手術 (15.70%)，其次爲開放性動脈導管的結紮手術 (10.47%) Fallot 四聯症根治術 (8.72%)、Mustard procedure (7.56%) modified Fontan procedure (7.56%) 以及 Blalock shunt (6.98%)。64 例記錄了治療方法，其中 41 例 (64.06%) 採取保守治療，23 例 (35.94%) 採取外科治療 兩種治療措施的治愈率爲 97.47%。5 例死亡，死亡率爲 2.53%，其中 4 例 (80%) 死因與乳糜胸無關。

結論：乳糜胸是心臟外科手術後少見的併發症。診斷主要依賴胸液的檢查。一旦確診，首先應給予營養支持。包括胸腔引流和飲食控制的保守治療 2 周無效，應採取外科治療。 ***(胸腔醫學 2002; 17: 238-251)***

關鍵詞：乳糜胸，併發症，心臟手術

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Acute Abdomen Due to Unusual Metastatic Manifestation of Pulmonary Squamous Cell Carcinoma —A Case Report and Literature Review

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Acute abdomen due to metastatic primary lung cancer has been reported rarely in the literature, and is associated with a very high operative mortality. Recently, we experienced a patient who presented with a life-threatening complication of small bowel perforation due to the metastasis of primary lung cancer. We reviewed the literature and found that there had been twenty-four cases of lung cancer with small bowel metastasis and perforation since 1961. All patients survived less than 16 weeks and the predominant tumor cell type was squamous cell carcinoma (11/24, 46%). The major site of small bowel perforation was the jejunum (16/24, 67%). In conclusion, lung cancer with metastasis to the small bowel often presents as intestinal perforation and indicates a poor prognosis. ***(Thorac Med 2002; 17: 252-257)***

Key words: acute abdomen, squamous cell carcinoma, small bowel perforation

Introduction

Metastasis as an initial presentation occurs in about one half of all patients with lung cancer [1]. Although the metastasis of lung cancer can spread to virtually all organs, metastasis to the small bowel is a rare condition. An acute abdomen, due to bowel perforation at the site of the metastasis from a lung cancer, is especially infrequent [2]. In general, lung cancer tends to metastasize early. Among the four major histologic types of lung cancer, squamous cell carcinoma has the lowest tendency for extra-thoracic spreading [3]. In this study, we report a case with squamous cell carcinoma of the lung who developed multiple metastases, including small bowel metastasis and perforation.

Case Report

A 74-year-old man was sent to our emergency room, on January 12, 2001, because of a transient loss of consciousness twice without remarkable physical findings and laboratory abnormalities. Then, he was followed up at the neurological outpatient clinic, where a chest radiograph revealed a mass density in the left lower lung field (Figure 1). The chest computerized tomograph showed a lung mass about 7 x 8 cm in the left lower lobe. He was admitted to the chest ward on February 20, due to progressive

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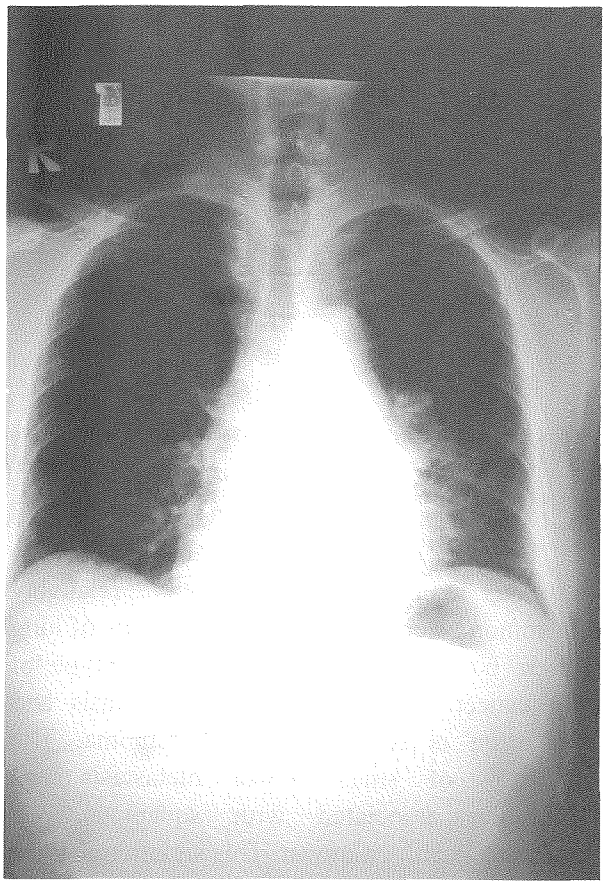

Fig. 1. Chest radiograph (PA) shows a mass lesion in the left lower lung field.

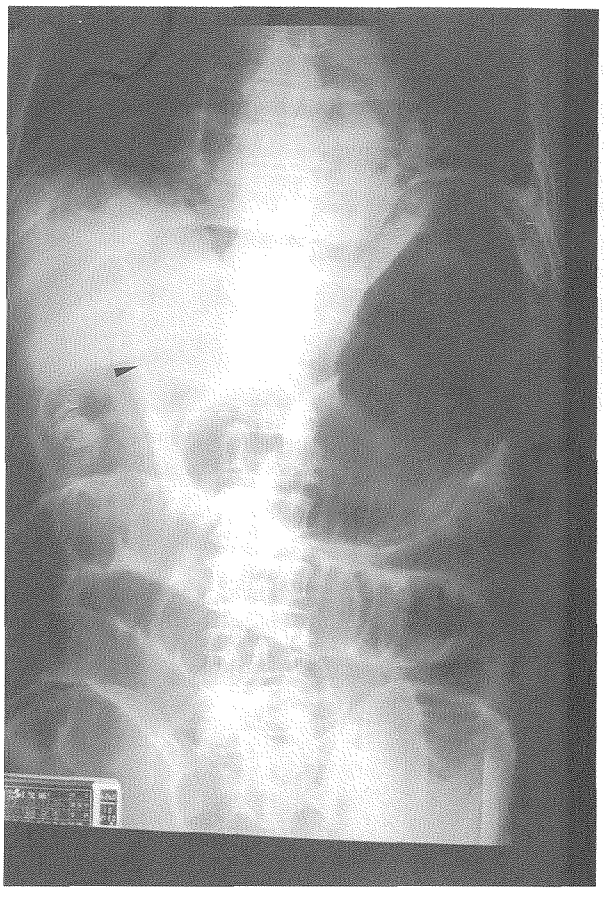

Fig. 2. Plain abdomen shows a massive pneumoperitoneum. Subphrenic free air with a clear outline of the stomach and dilated small bowel loops [double lumen sign] (arrow), and an air-outlined falciform ligament (arrowhead) were also noted.

dizziness and left elbow pain. Bronchoscopic examination showed swelling and hyperemic mucosa on the second carina on the left side. Stenosis of the orifice of the left lower lobe bronchus was also noted. Bronchial biopsy and brushing cytology revealed squamous cell carcinoma. During admission, a right retro-auricular lymph node, about 1 x 1 cm in size, was noted. Lymph node biopsy revealed metastatic squamous cell carcinoma. Due to frequent episodes of syncope, a brain MRI was also performed, which showed a mass lesion, about 3 x 3 cm in size, in the right cerebellar hemisphere.

Under the impression of lung cancer with brain metastasis, he received systemic chem.-otherapy with gemcitabine and concurrent radiotherapy from February 24, 2001 to March 2, 2001. He also underwent a craniotomy on March 6, 2001, and the pathologic examination confirmed metastatic squamous cell carcinoma in the cerebellum.

Consciousness disturbance and abdominal fullness developed on March 12, 2001. Dilated small bowels were found on the plain abdomen film (Figure 2), and the abdominal CT revealed a mass lesion in the small bowel, with obstructive ileus (Figure 3). He then underwent an exploratory laparotomy. A perforated hole noted at 80 cm distal from the ileocaecal valve; diffuse loculated turbid ascites and fibrin organization were also noted during operation. A segmental resection of the jejunum was performed due to small intestine perforation and peritonitis. The histopathologic sections of small intestine revealed nests of well-differentiated squamous cell carcinoma infiltrating throughout the intestinal wall, involving

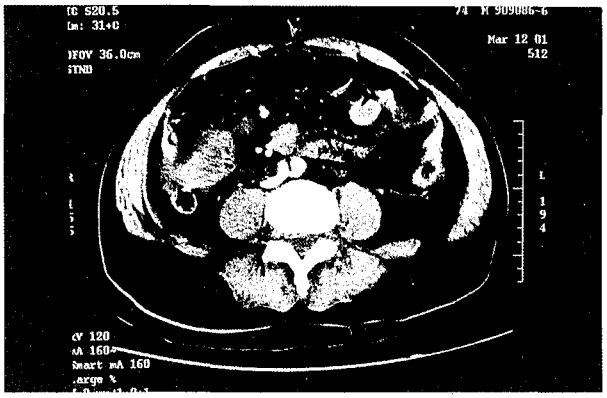

Fig. 3. Post-contrast CT of the abdomen shows a mass lesion, 2 x 3 cm in size, in the small bowel (arrow), with dilatation of the bowel lumen.

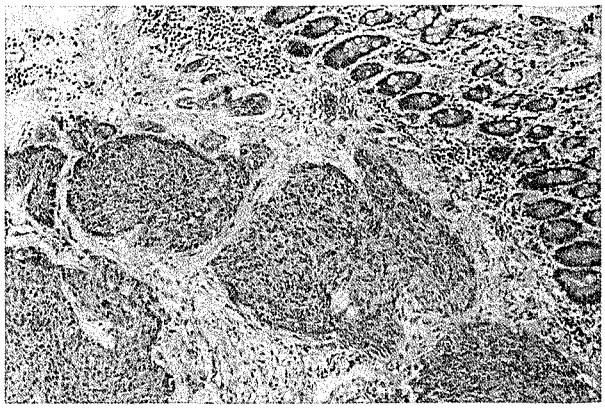

Fig. 4. Non-keratinizing squamous cell carcinoma metastasizing to the small intestine as submucosal nests with focal presence of tumor emboli. Hemotoxylin-eosin stain. Original magnification x100.

the serosa, muscularis propria, submucosa, and lamina propria (Figure 4). Unfortunately, he died of sepsis and respiratory failure on April 27, 2001.

Discussion

More than 6,000 people die of lung cancer annually in Taiwan. Approximately one half of these patients have metastases at the time of initial presentation, and the degree of metastatic disease is related to cell type. Adenocarcinoma and small cell carcinoma have frequent early metastasis, and squamous cell carcinoma usually develops metastasis at a relatively late stage. The most common reported sites of distant metastases are the bone, liver, adrenal gland, and brain [4]. An acute abdomen, due to bowel perforation at the site of metastasis from a lung cancer, occurs infrequently. After reviewing the literature, we found twenty-four reported cases of lung cancer with small bowel metastasis and perforation (Table 1) [1-13,18-19].

Among the twenty-four cases, and including our case, the most frequent histologic type of lung cancer was squamous cell carcinoma (Table 2). The abdominal symptoms were present in eight cases (8/24, 33%), and the major site of small bowel metastasis was the jejunum (Table 3). Usually, as mentioned above, the metastasis of squamous cell lung cancer is relatively uncommon as compared with other types of lung cancer; however, the major histologic type of lung cancer with small bowel metastasis and perforation is squamous cell carcinoma. The frequency of small bowel metastasis and perforation associated with squamous cell carcinoma is still unknown. This situation may be explained by two reasons. First, squamous cell carcinoma has been the most common histological type in the past, and second, tumor necrosis is mostly found in this cell type of lung cancer. In 1957, de Castro *et al.* reviewed 51 cases of tumor metastasis to the small bowel from 1905 to 1954, and found that the cervix, kidney, and skin were the most frequent sites of primary tumor, and obstruction was the most common manifestation. Only seven of the 51 cases presented as perforation [14]. However, primary lung cancer with small bowel metastasis and obstruction was found in only three cases [1,15-16]. From this observation, it is apparent that primary lung cancer with small intestinal metastasis is rare as compared with other cancers.

In our case, multiple metastases were noted and chemotherapy with gemcitabine and concurrent radiotherapy were performed on February 24, 2001. Ten days later, he underwent laparotomy because of perforation of the small bowel. We could not exclude the possibility that the small

Table 1. Clinical data of the patient with lung cancer associated with small bowel metastasis and perforation

Case	First author	Year	Age/sex	Presenting site	Site of small bowel perforation	Histology	Survival (week)
1	Morgan [5]	1961	36/M	Lung	Jejunum	Small cell	7
2	Wootton [6]	1967	65/M	Lung	Jejunum	Squamous cell	10
3	Wellmann [2]	1969	75/F	Abdomen	Jejunum	Giant cell	1
4	Midell [7]	1972	62/M	Lung	Ileum	Giant cell	< 1
5	Inalsingh [18]	1974	59/M	Lung	NA	Squamous cell	16
6	Ramanathan [8]	1976	50/M	Lung	Jejunum	Undifferentiated cell	< 1
7	Winchester [9]	1976	62/F	Lung	Jejunum	Adenocarcinoma	1
8	McNeill [1]	1979	51/M	Abdomen	Jejunum	Giant cell	8
9	Sternberg [3]	1980	81/M	Abdomen	Ileum	Squamous cell	NA
10	Leidich [10]	1981	76/M	Abdomen	Jejunum	Squamous cell	2
11	Rosencrans [19]	1981	43/F	Lung	NA	Squamous cell	2
12	Quayle [11]	1985	78/M	Abdomen	Jejunum	Squamous cell	1
13	McNeill [1]	1987	51/M	Lung	Jejunum	Squamous cell	8
14	McNeill [1]	1987	72/M	Brain	Jejunum	Adenocarcinoma	1
15	McNeill [1]	1987	58/M	Abdomen	Duodenum colon fistula	Giant cell	1
16	McNeill [1]	1987	58/M	Lung	Jejunum	Squamous cell	12
17	McNeill [1]	1987	55/M	Lung	Jejunum	Large cell	1
18	Hwang [12]	1987	63/M	Lung	Ileum	Undifferentiated cell	2
19	Hwang [12]	1987	72/M	Abdomen	Jejunum	Adenocarcinoma	< 2
20	Gitt [4]	1992	71/M	Lung	Ileum	Squamous cell	3
21	Gitt [4]	1992	39/M	Abdomen	Jejunum	Adenocarcinoma	2
22	Gitt [4]	1992	57/M	Brain	Jejunum	Adenocarcinoma	NA
23	Raijman [13]	1994	62/F	Abdomen	Duodenum	Squamous cell	2
24	Lee	2001	74/M	Brain	Jejunum	Squamous cell	6

NA: not available

Table 2. Tumor type with small bowel perforation

Tumor type	No. of patients	percentage
Squamous cell carcinoma	11	46%
Adenocarcinoma	5	21%
Small cell carcinoma	1	4%
Large cell carcinoma	1	4%
Giant cell carcinoma	4	17%
Undifferentiated carcinoma	2	8%
Total	24	100%

bowel perforation was due to tumor necrosis after chemotherapy, but we failed to find any report of chemotherapy-induced hollow organ perforation in the literature. According to the pathologic findings, there was a central perforation hole, measuring 1 x 0.5 x 0.4 cm on the cut section, and the tissue around the perforation manifested a whitish and firm appearance macroscopically. In this case, the mechanism of small bowel perforation may have been as follows: (1) a metastatic tumor cell invaded the intestinal stroma; (2) grew a metastatic tumor nest expanded inwardly and outwardly; and (3) tumor necrosis ensued.

Intestinal perforation caused by metastasis

Table 3. Site of small bowel perforation

Site	No. of patients	Percentage
Jejunum	16	67%
Ileum	4	17%
Duodenum	2	8%
Unknown	2	8%
Total	24	100%

to the small bowel is an ominous sign throughout the course of lung cancer. This unusual problem may occur with increased frequency in the future, as patients with lung cancer may survive longer due to early diagnosis and the introduction of new chemotherapy agents. No patient has survived more than 16 weeks following operation for this problem (Table 1). But in 1986, Schepp *et al.* reported a case with small bowel metastasis and hemorrhage without perforation caused by large cell lung cancer, who survived more than four months due to early diagnosis and early jejunal resection [17]. We think that early diagnosis of the primary lung cancer with small bowel metastasis and early surgical intervention may improve the survival time. In conclusion, lung cancer with small bowel metastasis is a rare condition and usually presents as an acute abdomen due to small bowel perforation. The most frequent histological type is squamous cell carcinoma. This small bowel metastasis usually indicates a poor prognosis.

References

1. McNeill PM, Wagman LD, Neifeld JP. Small bowel metastases from primary carcinoma of the lung. Cancer 1987;59:1486-9.
2. Wellmann KF, Chafiina Y, Edelman E. Small bowel perforation from solitary metastasis of clinically undetected pulmonary giant cell carcinoma. Am J Gastroenterol 1969; 51: 145-50.
3. Sternberg A. Giler S. Segal I, *et al.* Small bowel perforation as the presenting symptom of squamous cell carcinoma of the lung. Clin Oncol 1980; 6: 181-6.
4. Gitt SM. Flint P. Fredell CH, *et al.* Bowel perforation due to metastatic lung cancer. Journal of Surgical Oncology 1992; 51(4): 287-91.
5. Morgan MW, Sigel B, Wolcott MW. Perforation of a metastatic carcinoma of the jejunum after cancer chemotherapy. Surgery 1961; 49: 687-9.
6. Wootton DG, Morgan SC, Hughes RK. Perforation of a metastatic bronchogenic carcinoma to the jejunum. Ann Thorac Surg 1967; 3: 57-9.
7. Midell AI, Lochman DJ. An unusual metastatic manifestation of a primary bronchogenic carcinoma. Cancer 1972; 30: 806-9.
8. Ramanathan T, Skene-Smith H, Singh D, *et al.* Small intestinal perforation due to secondaries from bronchogenic carcinoma. Br J Dis Chest 1976; 70: 121-4.
9. Winchester DP, Merrill JR, Victor TA, Scanlonn EF. Small bowel perforation secondary to metastatic carcinoma of lung. Cancer 1977; 40: 410-5.
10. Leidich RB, Rudolph LE. Small bowel perforation secondary to metastatic lung carcinoma. Ann Surg 1981;193:67-9.
11. Quayle AR, Holt S, Clark RG. Jejunal perforation secondary to metastatic bronchogenic carcinoma. Postgrad Med J 1985; 61: 163-5.
12. Hwang GS, Yeh PF, Lee YC *et al.* Small bowel perforation secondary to metastatic carcinoma of lung . Chung Hua I Hsueh Tsa Chih – Chinese Medical Journal 1988; 41(2): 159-64.
13. Raijman I. Duodenal metastases from lung cancer. Endoscopy 1994; 26(9): 752-3.
14. de castro CA, Dockerty MB, Mayo CW. Metastatic tumors of the small intestine. Surg Gynecol Obst 1957; 105: 159-65.
15. Tillotson PM, Douglas RG Jr. Metastatic tumor of the small intestine. Am J Roentgenol 1962; 88: 702-6.
16. Morris DM, Deitch EA. Clinically significant intestinal metastasis from a primary bronchogenic carcinoma. J surg Oncol 1983; 23: 93-4.
17. Schepp W, Allescher HD, Madaus S, *et al.* A rare source of occult gastrointestinal bleeding: jejunal filiae secondary to metastatic lung carcinoma. Hepato Gastroenterology 1986; 33: 83-5.
18. Inalsingh CH. Hazra T. Prempree T. Unusual metastases from carcinoma of the lung. J Can Assoc Radiol 1974; 25: 242-4.
19. Rosencrans DL. Small bowel perforation caused by metastatic lung carcinoma. Ann Surg 1983;197(1):120.

急性腹痛—扁平細胞肺癌之罕見的臨床表現—病例報告與文獻回顧

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由於原發性肺癌轉移，造成急性腹部併發症，且合併非常高的手術死亡率，在先前的文獻已有零星的報告。最近，我們發現一個原發性肺癌的病人，併發致命的小腸轉移及穿孔。

我們回顧文獻，從 1961 年迄今，原發性肺癌合併小腸轉移且破裂者，共有 24 個病例。所有病患存活不超過 16 週，主要的腫瘤細胞型態為扁平細胞癌(11/24，46%)，主要的小腸破裂部位是在空腸(16/24，67%)。肺癌轉移到小腸，其臨床表現以小腸破裂為主且是一個不良預後的警訊。 ***(胸腔醫學 2002; 17: 252-257)***

關鍵詞：腹部急症，扁平細胞癌，小腸破裂

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Post-Extubation Pulmonary Edema—A Case Report

I-Jen Chen, Chiung-Zuei Chen, Yuan-Chih Chu, Tzuen-Ren Hsiue

Post-extubation pulmonary edema is a critical condition which may be the complication of upper airway obstruction due to post-extubation laryngospasm. Such an episode often develops quickly without warning and results in severe respiratory distress. An extreme intrathoracic negative pressure is considered to be the causative factor. After adequate oxygen supplementation and supportive treatment, patients often recover rapidly, and the prognosis is good. We herein present a case of post-extubation pulmonary edema in a healthy middle-aged male patient. This 34-year-old male patient was admitted to undergo an operation for chronic sinusitis and nasal polyps. The operation course was smooth but the patient developed dyspnea and hypoxemia soon after extubation. The chest radiograph revealed pulmonary edema. After adequate oxygen therapy, he recovered rapidly and the lung fields quickly cleared. The patient was discharged on the fifth postoperative day, with no sequel on the follow-up. ***(Thorac Med 2002; 17: 258-263)***

Key words: pulmonary edema, upper airway obstruction, larygospasm, intrathoracic negative pressure

Introduction

Several etiologies for post-extubation pulmonary edema have been proposed. Acute upper airway obstruction, especially laryngospasm after extubation, is one possible precipitating factor. Post-extubation pulmonary edema is rare but the physician should be able to recognize it and initiate adequate treatment for this potentially critical complication, to minimize morbidity and mortality.

Laryngospasm–induced pulmonary edema has been described since 1980 [1]. Typically, these patients are young and healthy. They develop transient laryngospasm immediately or shortly after postoperative extubation, then abrupt non-cardiogenic pulmonary edema occurs. The pulmonary edema may be due to forced inspiration against the laryngospasm, which induces large negative intrapleural and transpulmonary pressure gradients, then the transudation of the fluid moves from the capillaries into the interstitium. For those etiologies of upper airway obstruction, laryngospasm after tracheal extubation is one of the most common causes. It may be one of the protective responses resulting in reflex glottic closure due to the local irritation of the vocal cords by blood or mucus. It can be transient and self-limited, but it occasionally induces pulmonary edema, with the consequences of severe hypoxia and hypercapnia. Herein, we present a case of pulmonary edema due to post-extubation laryngospasm.

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Case Report

A 34-year-old male patient was 73 kg in weight and 164 cm tall. He denied a history of asthma or COPD and had never smoked. The patient had suffered from bilateral nasal obstruction for years. Chronic sinusitis with nasal polyps was diagnosed by an otolaryngologist, and he was scheduled for bilateral functional endoscopic sinus surgery and septoplasty in an outpatient surgery service. Preoperative laboratory examinations were all within normal limits. Electrocardiography (EKG) showed normal tracing and the chest radiograph did not reveal any abnormality. General anesthesia was induced with robinul 0.2 mg iv, fentanyl 100 μg iv, and propofol 100 mg iv. Endotracheal intubation was facilitated with rocuronium 40 mg iv, and anesthesia was maintained with desflurane in 60% oxygen. The operative course was smooth and blood loss was minimal. The patient was extubated when he could breathe spontaneously, but was not fully awake. Unfortunately, dyspnea occurred soon after extubation, and the patient became cyanotic with oxygen saturation down to 68%, as detected by a pulse oximeter. Systolic blood pressure rose from 120 mm Hg to 160 mm Hg. The patient struggled to breathe, but his breathing sound decreased on auscultation in both lung fields. Positive pressure oxygen was administered by manual ventilation with an anesthesia bag using 100% oxygen. The patient's distress improved after this maneuver for a few minutes, and oxygen saturation returned to 94% with the use of a non-rebreathing mask with a more than 15 L/min oxygen flow supplement. Systolic blood pressure also returned to 120 mm Hg. The patient was alert during this event without an apparent episode of aspiration. At this time, auscultation of the chest revealed diffuse crackles without stridor or wheezing.

A portable chest X-ray (CXR) was performed and showed bilateral alveolar opacification with predominance on the right side (Figure 1). Under the impression of pulmonary edema, diuretic therapy with furosemide 2 amps was given; and a CVP was inserted for fluid status monitoring. The initial central venous pressure level was only –3 cm H_2O. Neither heart murmur nor S_3 gallop was noted during the cardiac examination. The EKG did not show significant ischemic change, and no elevation of cardiac enzymes was found. Fluid overload or congestive heart failure related to pulmonary edema was not considered. The respiratory pattern improved gradually and the supplemental oxygen was tapered off to a simple mask with O_2 6 L/min. The oxygen saturation increased to 98% 3 hours later. Arterial blood gas was drawn 6 hours later and showed PH: 7.365; PCO_2: 43 mm Hg; PO_2: 117 mmHg; HCO_3^-: 24.8 mEq/L; BE_{ecf}: -0.7 mEq/L; and SaO_2: 98.4 %. A low-grade fever of about 37.6 ^{0}C and leukocytosis (white blood cell count: 19900/mm^3) were found, and empirical antibiotics with ampicillin and sulbactam was given. The fever and WBC count returned to the normal range within 2 days. No other sign of infection or infection focus was noted. The lung fields

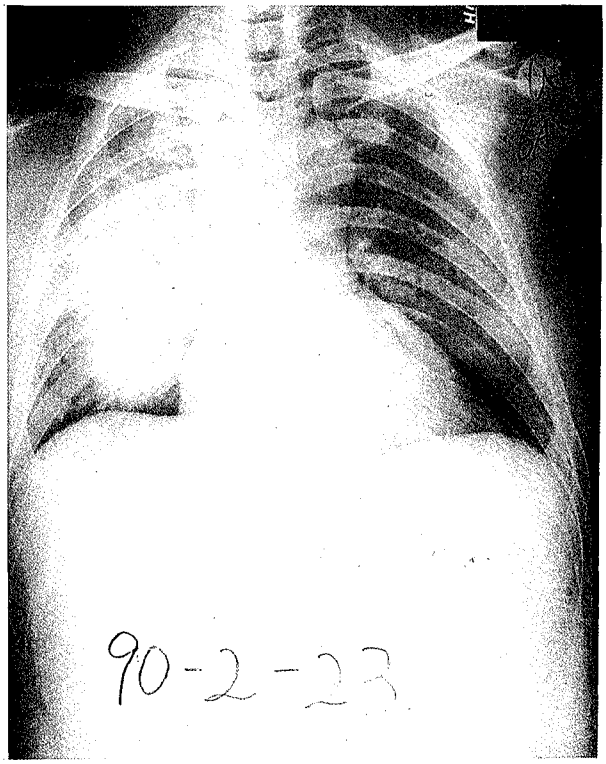

Fig. 1. The initial chest radiograph reveals pulmonary edema, especially on the right side.

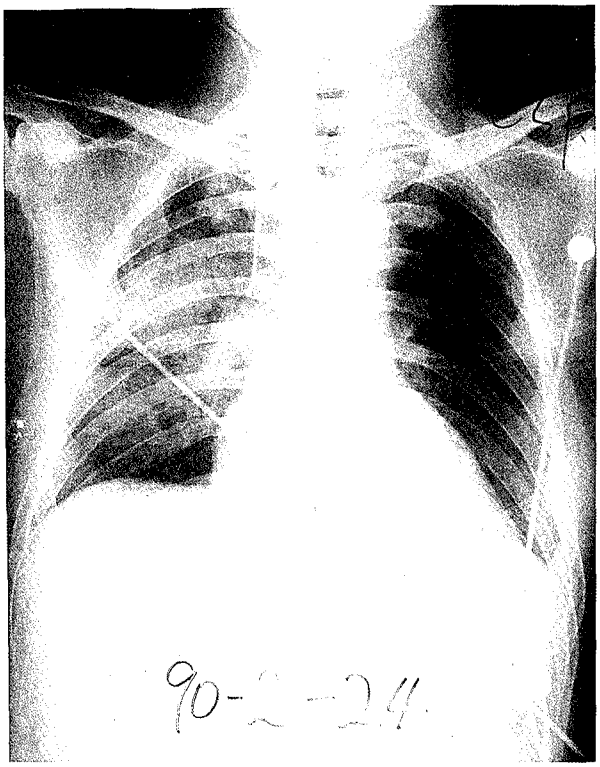

Fig. 2. The pulmonary edema shows resolution one day later.

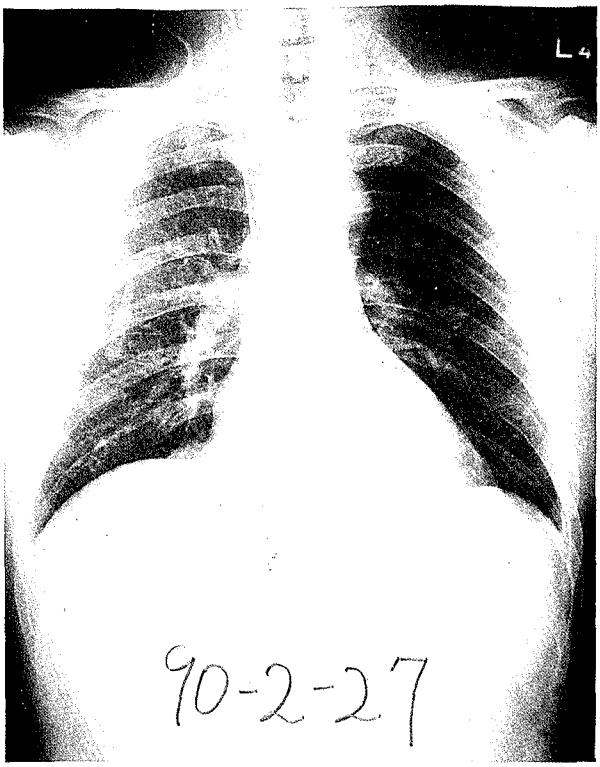

Fig. 3. The chest radiograph becomes completely clear 4 days later

revealed resolution after one day (Figure 2) and became completely clear within 4 days (Figure 3), as revealed in a chest radiography series follow up. The patient was discharged on the 5th postoperative day, and had an uneventful postoperative course after discharge.

Discussion

Post-extubation laryngospasm, a spasm of the glottis and bronchi after extubation, occurs via laryngeal reflexes. The laryngeal reflexes may be stimulated at sites from the nasal mucosa to the diaphragm, especially when the patient is not fully conscious after anesthesia. The onset of post-extubation pulmonary edema usually occurs within minutes. However, delays in presentation of about 1-2 hours have also been reported. One patient was reported to have developed signs of pulmonary edema 85 min after arrival in the recovery room [2]. Post-extubation lung edema usually occurs in young and athletic patients. The common clinical manifestations of these patients are a sudden onset of respiratory distress, progressive oxygen desaturation, tachycardia, and a frothy pink secretion immediately after extubation. The chest radiograph often shows bilateral consolidation. If treated properly, the condition usually improves completely within 24 hours.

Pulmonary edema secondary to upper airway obstruction has some predisposing factors, such as obesity and a short, thick neck [1]; nasal obstruction and palatal mass [3]; symptoms of obstructive apnea and post-nasal surgery [4]; and obesity and observed sleep apnea [5]. The mechanism of upper airway obstruction-induced pulmonary edema is multifactorial. Forced inspiration against a closed glottis (Mueller maneuver), resulting in large negative intrapleural pressure, is the predominant factor. Normal breathing produces inspiratory intrapleural pressures ranging from –2 to –5 cm H_2O, but intrapleural pressure may drop to as low as -100 cm H_2O during severe airway obstruction [6]. This marked negative intrapleural pressure will alter Starling forces across the pulmonary capillary by lowering

the pulmonary interstitial hydrostatic pressure. This leads to decrease pulmonary capillary perivascular pressure and induces the hydrostatic transudation of fluid into the interstitium of the lung. Pulmonary venous return is enhanced after the relief of the airway obstruction, when the airway pressure drops, and pulmonary blood flow increases.

Cardiovascular physiology is also disturbed by intrapleural negative pressure. The left ventricular afterload is increased and performance is adversely affected by increased negative transmyocardial pressure [7-8]. The increasing pulmonary blood flow combined with an impaired left ventricular function will further contribute to the transudation of fluid into the interstitial space. Upper airway obstruction can result in hypoxemia due to the lack of alveolar ventilation. This hypoxemic status can develop a central nervous system-mediated alpha-adrenergic release with peripheral vascular constriction, and redistribute blood from the systemic venous to the pulmonary circulation [9]. Hypoxia also results in pulmonary arterial vasoconstriction and further compromises cardiac function. All these factors aggravate the tendency to pulmonary edema formation.

In our case, the chest radiograph also showed bilateral central alveolar consolidations on the right side predominantly. Unilateral post-extubation pulmonary edema has been reported previously, and was due to the lateral position of the dependent lung and interscalene block with diaphragm paralysis [10-11]. In the lateral decubitus position, the dependent lung shares more of the pulmonary blood flow and elevated hydrostatic pressures. The diaphragm is elevated more at the dependent side while under anesthesia, and that may generate a more negative pressure compared to the non-dependent side with a greater excursion. Therefore, predominant pulmonary edema develops in the dependent lung. In addition, postobstructive pulmonary edema needs a functional hemidiaphragm to generate a negative pressure. When the diaphragm is paralyzed on one side, pulmonary edema may develop only on the contralateral side. Our patient did not move to the right lateral position during the operation, nor did he have left diaphragm paralysis. Aspiration pneumonia should be distinguished in this condition. However, aspiration with gastric content or blood clots sufficient to make such a large lung parenchymal injury is unlikely to resolve completely within a few days. This manifestation cannot be explained by congestive heart failure, due to the patient's young and healthy condition, with no previous heart disease history. In addition, EKG and cardiac enzyme examinations did not show abnormal findings. The initial central venous pressure was as low as –3 cm H_2O. This might be related to the extremely negative intrathoracic pressure [12]. Therefore, we think that this condition was postobstructive negative pressure pulmonary edema.

The management of postobstructive pulmonary edema aims at relief of the upper airway obstruction and supportive treatment for the pulmonary edema. The therapy includes an oxygen supplement for the possible hypoxemia with or without an application of positive pressure support, such as nasal BiPAP, mask CPAP or intubation with mechanical ventilation with or without PEEP, if indicated [13]. The administration of diuretics is also recommended, but the role is uncertain. Some short-acting neuromuscular blocking agents can be used to relieve the laryngospasm and prevent further negative intrathoracic pressure [12]. In fact, the prognosis of most patients is good: the majority of patients recover rapidly and completely, without significant sequel.

In conclusion, postobstructive pulmonary edema is a well-recognized syndrome, but may be underdiagnosed clinically. Physicians should have a high suspicion of this syndrome when patients suffer from sudden respiratory distress after postoperative extubation. The condition may lead to unplanned postoperative intensive care in young and healthy patients. The prognosis is

usually good with an early diagnosis and rapid treatment.

References

1. Jackson FN, Rowland V, Corssen G. Laryngospasm-induced pulmonary edema. Chest 1980; 78:819-21.
2. Glasser SA, Siler JN. Delayed onset of laryngospasm-induced pulmonary edema in an adult outpatient. Anesthesiology 1985; 62:370-1.
3. Cass N. Pulmonary oedema due to respiratory obstruction. Anaesth Intensive Care 1981; 9:78-9.
4. Melnick BM. Post-laryngospasm pulmonary edema in adults. Anesthesiology 1984; 60:517-8.
5. Lorch DG, Sahn SA. Post-extubation pulmonary edema following anesthesia induced by upper airway obstruction. Are certain patients at increased risk? Chest 1986; 90:802-5.
6. Timby J, Reed C, Zeilender S, *et al.* "Mechanical" causes of pulmonary edema. Chest 1990; 98:973-9.
7. Buda AJ, Pinsky MR, Ingels NB, *et al.* Effect of intrathoracic pressure on left ventricular performance. N Engl J Med 1979; 30:453-9.
8. Rowbotham JL, Scharf SM. Effects of positive and negative pressure ventilation on cardiac performance. Clin Chest Med 1983; 4:161-83.
9. Lang SA, Duncan PG, Shepahrd dae, *et al.* Pulmonary edema associated with airway obstruction. Can J Anaesth 1990; 37:210-8.
10. Sullivan M. Unilateral negative pressure pulmonary edema during anesthesia with a laryngeal mask airway. Can J Anaesth 1999; 46(11): 1053-6.
11. Betts A, Eggan JR. Unilateral pulmonary edema with interscalene block. Anesthesiology 1998; 88:1113-4.
12. Virolainen J, Ventila M, and Turto H, *et al.* Influence of negative intrathoracic pressure on right atrial and systemic venous dynamics. Eur Heart J 1995;16:1293-9.
13. McConkey P.P. Postobstructive pulmonary oedema-a case series and review. Anaesth Intensive Care 2000; 28:72-6.

拔管後之肺水腫——病例報告

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拔管後引起之肺水腫為一臨床急症。其可能是因拔管後喉部筋攣引起上呼吸道阻塞所造成。它的發生經常是快速而無預兆，並有可能導致嚴重的呼吸窘迫。極度的胸內負壓被認為是可能的發生機制。在適當的氧氣供應及支持性治療後，患者大都能迅速痊癒並且預後十分良好。我們在此提出一發生於健康中年男性之拔管後肺水腫病例報告。這位 34 歲男性病人因慢性鼻竇炎及鼻息肉而入院接受手術。手術過程順利，但病患拔管後突然發生呼吸困難並血氧濃度下降，胸部 X 光呈現雙側肺水腫，以右側肺野較為明顯。在適當的氧氣治療後，病患病況迅速回復並且肺野也很快變乾淨。該患者於術後五天出院，於門診追蹤並無發現任何不適後遺症。 ***(胸腔醫學 2002; 17: 258-263)***

關鍵詞：肺水腫，上呼吸道阻塞，喉部筋攣，胸內負壓

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Scrub Typhus Complicated with Acute Respiratory Distress Syndrome, Meningoencephalitis and Disseminated Intravascular Coagulation —A Case Report

Hung-Jen Chen, Liang-Wen Hang, Te-Chun Hsia

Scrub typhus can be found everywhere in Taiwan, especially in Kinmen, Nantou, Penghu, Hualien, and Taitung Counties. The clinical manifestations are persistent high fever, headache, lymphadenopathy, and a painless eschar at the site of chigger feeding. The illness varies in severity from mild and self-limiting to fatal.

We report a 42-year-old farmer who lived in Shinyi Shiang, Nantou County, and who suffered from fever, dry cough, and severe headache for one week, complicated with disturbed consciousness and acute respiratory failure. A 0.5 x 0.5 cm^2 eschar was found near the patient's navel. A radiograph of the chest showed air-space disease involving the bilateral lungs. A cerebrospinal fluid (CSF) study revealed mononuclear leukocytosis, an increased protein concentration, and decreased glucose concentration. Hematological values showed thrombocytopenia (platelets: $119x10^3$/ul), an abnormal prothrombin time (PT 19.93 seconds), partial thromboplastin time (PTT 65.50 seconds), FDP (>20 ug/ml), and D-Dimer (>2.0 ug/ml). The patient's critical condition dramatically improved after urgent intravenous minocycline therapy. The final laboratory diagnosis was proved to be scrub typhus, using a serum antibody, in the Center for Disease Control, Department of Health, Taiwan. ***(Thorac Med 2002; 17: 264-270)***

Key words: scrub typhus, ARDS, meningoencephalitis, DIC

Introduction

Scrub typhus is an acute febrile illness caused by rickettsia tsutsugamushi (from the Japanese: tsutsuga, "dangerous"; mushi, "bug"). Scrub typhus can be found everywhere in Taiwan. The clinical manifestations are a persistent high fever, headache, lymphadenopathy, and painless eschar. The illness varies in severity from mild and self-limiting to fatal [1]. Serious complications include pneumonitis, acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), myocarditis, and septic shock [1-8]. Timely tetracycline therapy can reduce the mortality to practically zero. Herein, we report a case of scrub typhus with multiple complications because of a delay in diagnosis and treatment. The critical condition dramatically improved after urgent intravenous minocycline therapy.

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Case Report

On September 3rd 2001, a 41-year-old male was brought to the emergency service because of dyspnea and disturbed consciousness lasting for two days.

The patient had been well until seven days earlier, when he suffered from influenza-like symptoms, manifested with intermittent fever, headache, and non-productive cough. Three days later, he was admitted to a local hospital under the impression of pneumonia. Cephradine and gentamicin were administered. On the third day of admission, disturbed consciousness and shortness of breath were noted. He was then referred to this hospital.

The patient was a farmer, living in Shinyi Shiang, Nantou County. He had smoked one pack of cigarettes daily for 20 years. In addition, he abused alcohol.

On admission, he had a blood pressure of 79/42 mmHg, pulse rate of 126/minute, respiration rate of 40/minute, and body temperature of 38℃. The Glasgow coma scale (GCS) showed E4V2M5. The patient appeared shallow with quick breathing. Cold limbs with cyanosis were also noted. His neck was stiff, with a positive Kernig's sign. Icteric conjunctiva was also noted. Crackles were heard throughout the lungs. An eschar around 0.5 x 0.5 cm^2 was found near the navel (Figure 1). There was a disseminated erythematous maculopapular skin rash on the trunk and extremities, and there was no definite lymphadenopathy. Other physical findings were unremarkable.

A radiograph of the chest showed air-space disease involving the bilateral lungs (Figure 2). The EKG showed sinus tachycardia with QS waves at lead III and aVF. Laboratory tests were performed (Tables 1 and 2).

A specimen of arterial blood, drawn while the patient was breathing room air, showed that the partial pressure of oxygen was 46.5 mm Hg (Sat O_2 85.3%), the partial pressure of carbon dioxide was 28.2 mm Hg, HCO_3^- was 20.8 mmol/L and PH was 7.471.

An emergency endotracheal tube was inserted. The ventilator mode used pressure control with full sedation, and central venous pressure was around 12~16 cm H_2O. After fluid hydration and the administration of high-dose dopamine (8 ug/kg/min), the blood pressure rose to 100/60 mmHg.

A lumbar puncture was performed, with an opening pressure of 245 cmH_2O. The appearance of the cerebrospinal fluid (CSF) was xanthamatous, with a cell count of 180/ul, a lymphocyte to polymorphonuclear cell ratio of 70:30, glucose of 32 mg/dl, and protein of 183 mg/dl.

Ceftriaxone 2 gm intravenously every 12 hours and minocycline 100 mg intravenously every 12 hours were administered.

On day 2, PO_2 was 65 mmHg using 70% FiO_2, PCV 20 cmH_2O, and PEEP 12 cmH_2O, in

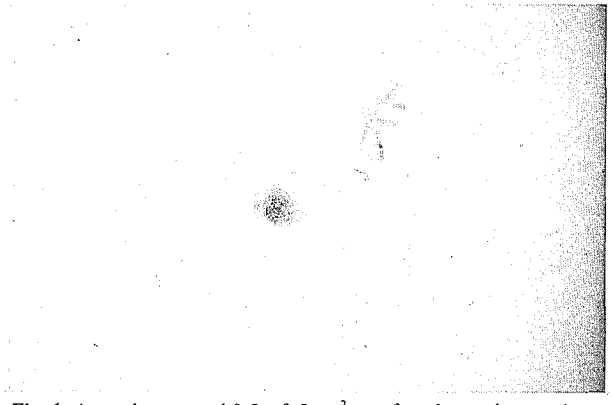

Fig. 1. An eschar around 0.5 x 0.5 cm^2 was found near the navel.

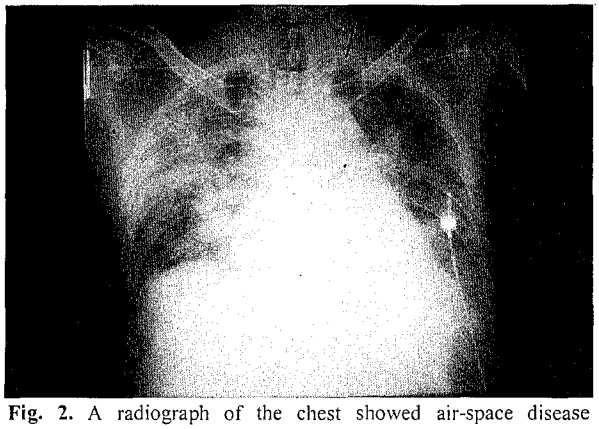

Fig. 2. A radiograph of the chest showed air-space disease involving the bilateral lungs.

Table 1. Hematological Values

Variable	Values	Reference values
Hematocrit (%)	30.2	
White-cell count (per mm^3)	11700	
Differential count (%)		
Neutrophils	96	
Lymphocytes	2.4	
Monocytes	1.23	
Eosinophils	0.103	
Basophils		
Platelet count (per mm^3)	119000	
Prothrombin time (sec)*	19.93	
Partial-thromboplastin time (sec)**	65.50	
Fibrinogen (mg/dl)	177.6	(150-450)
F.D.P. (ug/ml)	>20	(<5)
D-Dimer (ug/ml)	>2.0	(<0.5)

*control values, 11.80 secs

**control values, 28.10 secs

Table 2. Blood Chemical Values

Variable	Values	Reference Values
Urea nitrogen (mg/dl)	31	5-26
Creatinine (mg/dl)	1.4	0.5-1.3
Sodium (mmol/liter)	130	135-147
Potassium (mmol/liter)	3.3	3.5-4.9
Chloride (mmol/liter)	98	98-107
Bilirubin (mg/dl)		
total	4.79	0.2-1.3
direct	3.20	0.0-0.4
Glucose (mg/dl)	54	70-110
Aspartate aminotransferase (U/liter)	201	5-34
Alanine aminotransferase (U/liter)	49	0-40
Alkaline phosphatase (U/liter)	174	38-126
Creatine phosphokinese (U/liter)	1154	38-174
CKMB (U/liter)	6.3	3-10
Troponin I (ng/ml)	0.015	0.8
C-Reactive Protein (mg/dl)	17.37	<0.8

the prone position. The Proteus OXK titer was only 1:20x. On day 3, the ceftriaxone was discontinued due to the CSF negative gram stain.

On day 5, the inotropic agents were discontinued due to the stable hemodynamic condition. PO_2 was 60.2 mmHg using 30% FiO_2, PCV 18 cmH_2O, and PEEP 10 cmH_2O. The sedative drug was discontinued, and the patient was allowed greater movement.

On day 6, the patient's consciousness cleared. On the day 8, extubation was performed smoothly. Minocycline had been continued for a

total of 14 days.

An indirect immunofluorescence assay for antibody to Orientia tsutsugamushi, at the Center for Disease Control, Department of Health, Taiwan, showed a higher IgM titer (>1:80)

On day 12, he suffered from massive hematemesis, tarry stool, and delirium. He was then transferred to the intensive care unit again. Panendoscopy showed erosion, with a visible vessel with spurting. Dieulafoy's lesion was suspected. Treatment with a heat probe and epinephrine for local infection were performed. Omeperazole was administered and blood was transfused. The platelet count, prothrombin time and partial-thromboplastin time were all within normal limits.

On day 19, he was discharged due to stable condition.

Discussion

The pathogen of scrub typhus is Orientia tsutsugamushi, an obligatory intracellular organism. The vector is the chigger, a kind of mite. The incubation period is from one to three weeks (usually eight to ten days) after the bite of a chigger which carries Orientia tsutsugamushi.

This disease begins with the sudden onset of chills, fever, headache, and cough, all influenza-like manifestations. Gastrointestinal upset may also occur. Some patients develop no further distress and recover spontaneously in a few days, but others progress to severe complications, including myocarditis, meningoencephalitis, pneumonitis, and disseminated intravascular coagulation (DIC) [1-8]. There is still no definite conclusion on how long a delay in treatment will give rise to complications [1,3].

All the symptoms mentioned above could be explained pathologically by vasculitis [9]. This is because Orientia tsutsugamushi invades the endothelial cells lining the small blood vessels, followed by inflammatory responses, producing generalized vasculitis.

This article reports a farmer who lives in the mountains of Nantou County, and who was transferred to our hospital due to fever, dyspnea, and disturbed consciousness. DIC was diagnosed based on thrombocytopenia (Platelet $119x10^3$/ul) and abnormal prothrombin time (PT 19.93 seconds, control values: 11.80 seconds), partial thromboplastin time (PTT 65.50 seconds, control values: 28.10 seconds), F.D.P (>20 ug/ml, normal range: <5 ng/ml), and D-Dimer (>2.0 ug/ml, normal range: <0.5 ng/ml). Coagulopathies may be occasionally demonstrated in scrub typhus, but DIC is extremely rare [1,7-8].

The patient's CSF showed pleocytosis (180/ul) with a predominance of mononuclear cells (70%), an increased protein concentration (183 mg/dl), and decreased glucose concentration (32 mg/dl). This result is compatible with those of previous reports [8,10]. Pai H et al studied twenty-five cases of scrub typhus and discovered that half the cases had mild pleocytosis in the cerebrospinal fluid. White blood cells averaged $16/mm^3$, and were half lymphocytes. The protein level was greater than 50 mg/dl in seven cases [10].

Chest radiographs were reported to show abnormalities in about 70% of patients with scrub typhus [11]. But the mortality rate elevates greatly if there is a complication with ARDS [2-6]. Chayakul P reported five cases of scrub typhus associated with ARDS in 1987; three of them expired [12]. The American-European Consensus Committee recommends as criteria for ARDS: (1) timing: acute onset; (2) oxygenation: PaO_2/FiO_2<200 mmHg; (3) chest radiograph: bilateral infiltrates seen on the frontal chest radiograph; and (4) pulmonary arterial wedge pressure (PAWP)<=18 mmHg when measured, or no clinical evidence of left arterial hypertension [14]. The respiratory failure in our patient fulfilled the criteria of ARDS. Despite the lack of cardiogenic wedge pressure data, myocarditis with pulmonary edema was unlikely because the cardiac enzymes were not elevated.

Even if all these complications could be avoided by early diagnosis and treatment with

tetracycline, we would have difficulty diagnosing them. Most symptoms have no specificity, and routine laboratory studies are not of value. The classic case description includes an eschar at the site of chigger feeding, regional lymphadenopathy, and a maculopapular rash. The scrub typhus rash begins on the trunk and spreads peripherally on the fifth to ninth days [1].

A descriptive study of eighty-seven US soldiers in Vietnam who had scrub typhus, showed that all cases had fever and headache, 46% had an eschar, 35% had a rash, and 85% had generalized lymph node enlargement [13].

In Taiwan, Tsay RW *et al* reported that the most common signs and symptoms were: fever (100%), chills (39%), cough (24%), headache (21%), diarrhea (18%), dyspnea (18%), eschar (60%), adenopathy (33%), and rash (21%). Nineteen percent (6/32) had obvious leukopenia (WBC < 4000/ mm^3), 34% (11/32) had leukocytosis (WBC > 10,000/mm^3), and 44% (14/32) had thrombocytopenia (platelet count < 100,000/mm^3). The elevation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were 81% (26/32) and 75% (24/32), respectively [3].

The patient's condition dramatically improved after the prompt administration of minocycline based on the evidence of a prominent eschar near the navel. In addition, oxygenation improved when the patient was put in a prone position two hours later [15].

Thereafter, this patient was admitted to the intensive care unit due to a Dieulafoy's lesion with massive gastric bleeding. A few papers have discussed the relationship between Dieulafoy's lesion and vasculitis [16-17], but there is no mention of scrub typhus. In our opinion, any Dieulafoy's lesion should be related to an underlying problem rather than scrub typhus.

Scrub typhus exists everywhere in Taiwan, especially in Kinmen, Nantou, Penghu, Hualien and Taitung Counties. According to statistics from the Center for Disease Control, Department of Health, Taiwan, about 1200 cases of scrub typhus have been registered and around 250 have been proven in the most recent two years [18]. Actually, the real cases in one year number more than 250 if we estimate the non-registered, spontaneously recovered, and misdiagnosed cases. There is a lack of official statistical data regarding misdiagnosed scrub typhus followed by severe complications, or even mortality.

The early diagnosis and treatment of scrub typhus is very important. As an example, although this case was complicated with meningoencephalitis, ARDS, and DIC, the patient's entire condition improved as soon as we gave him minocycline for treatment. The endemic foci of scrub typhus and whether or not the patient has traveled or worked in such areas, constitute important epidemiological information. If a patient has a fever of unknown origin and comes from an area of scrub typhus prevalence, a thorough physical examination should be performed, especially detailed with regard to lymphadenopathy, skin rash, or eschar. A therapeutic trial of tetracycline is indicated in patients in whom the diagnosis of scrub typhus is suspected.

References

1. Sayen JJ, Pond HS, Forrester JS, *et al.* Scrub typhus in Asia and Burma. Medicine 1946; 25: 155-214.
2. Park JS, Jee YK, Lee KY, *et al.* Acute respiratory distress syndrome associated with scrub typhus: diffuse alveolar damage without pulmonary vasculitis. J Korean Med Sci 2000; 15(3): 343-5.
3. Tsay RW, Chang FY. Serious complications in scrub typhus. J Microbiol . Immunol Infect 1998; 31(4): 240-4.
4. Chi WC, Huang JJ, Sung JM, *et al.* Scrub typhus associated with multiorgan failure: a case report. Scand J Infect Dis 1997; 29(6): 634-5.
5. Fang CT, Ferng WF, Hwang JJ, *et al.* Life-threatening scrub typhus with meningoencephalitis and acute respiratory distress syndrome. J Formosa Med Assoc 1997; 96(3): 213-6.
6. Lee WS, Wang FD, Wang LS, *et al.* Scrub typhus

complicating acute respiratory distress syndrome: a report of two cases. Chin Med J (Taipei) 1995; 56(3): 205-10.

7. Ognibene AJ, O'Leary DS, Czarnecki SW, *et al.* Myocarditis and disseminated intravascular coagulation in scrub typhus. Am J Med Sci 1971; 262(4): 233-9.
8. Ben RJ, Feng NH, Ku CS. Meningoencephalitis, myocarditis, and disseminated intravascular coagulation in a patient with scrub typhus. J Microbiol Immunol Infect 1999; 32(1): 57-62.
9. Allen AC. Spitz S. A comparative study of the pathology of scrub (tsutsugamushi disease) and other richettsial disease. Am J Pathol 1945; 21: 603-81.
10. Pai H, Sohn S, Seong Y, *et al.* Central nervous system involvement in patients with scrub typhus. Clin Infect Dis 1997; 24: 436-40.
11. Choi YH, Kim SJ, Lee JY, *et al.* Scrub typhus: radiological and clinical findings. Clin Radiol 2000; 55(2): 140-4.
12. Chayakul P, Panich V, Panich V, *et al.* Scrub typhus pneumonitis: an entity which is frequently missed. QJ Med 1988; 256: 595-602.
13. Berman SJ, Kundin WD. Scrub typhus in Vietnam: a study of 87 cases. Ann Intern Med 1973: 79:26-30.
14. Bernard GR, Artigas A, Brigham KL, *et al.* The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994:149: 818-24.
15. Slutsky AS. The acute respiratory distress syndrome, mechanical ventilation, and the prone position. N Engl J Med 2001; 345(8): 610-2.
16. Usui J, Takemura H, Yuhara T, *et al.* Dieulafoy's lesion of the esophagus as a probable complication of Takayasu's arteritis. J Rheumatol 1999; 26(2): 454-6.
17. Arendt T, Kloehn S, Bastian A, *et al.* A case of Behcet's syndrome presenting with Dieulafoy's ulcer. Z Gastroenterol 1997; 35(10): 935-8.
18. Center for Disease Control, Department of Health, Taiwan R.O.C. Cases of Notifiable Disease, III, Taiwan, R.O.C. Epidemiology Bulletin 2001; 17(1): 18.

恙蟲病併發急性呼吸窘迫症候群、腦膜腦炎及血管內凝血病變——一病例報告

陳鴻仁　杭良文　夏德椿

恙蟲病存在於台灣各縣市，尤其好發於金門縣、南投縣、澎湖縣及花東等地區。其發病特徵為持續性高燒、頭痛、淋巴腺腫大、螯口處形成特有的無痛性焦痂。病況由多數的自限性痊癒到少數的嚴重致死皆有可能。本文報告一例居住於南投信義鄉的 42 歲農夫，在持續約一星期的發燒、乾咳和劇烈頭痛後，因併發意識不清及呼吸衰竭而轉診至本院。理學檢查發現臍旁有一 0.5x0.5 cm^2 的焦痂。胸部 x 光呈現雙側肺野瀰漫性浸潤，腦脊髓液分析呈現白血球增多（180/ul）、蛋白質上升（183 mg/dl）及糖份下降（32 mg/dl）。血液檢查呈現血管內凝血病變。在高度懷疑為恙蟲病的情況下，投予 minocycline 治療，症狀獲得迅速改善並脫離呼吸器之使用。本例最後經衛生署疾病管制局證實為恙蟲病感染。 ***(胸腔醫學 2002; 17: 264-270)***

關鍵詞：恙蟲病、急性呼吸窘迫症候群、腦膜腦炎、血管內凝血病變

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Silicone Fluid-Induced Pulmonary Emboli — A Case Report

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Silicone fluid is a good substitute for human subcutaneous fat, but has been associated with many complications, including local tissue granulomatous reaction, systemic sclerosis, connective tissue disease-like syndromes, granulomatous hepatitis, and systemic involvement. It is a well-known illegal procedure for mammary augmentation in Taiwan. Pulmonary involvement in human beings has been reported in a few cases, and presents as acute pneumonitis, pulmonary emboli, and acute respiratory distress syndrome after the silicone injection. We report a 30-year-old previously healthy female who received a silicone fluid injection for mammary augmentation and developed an acute onset of cough, hemoptysis, and progressive dyspnea. Pulmonary embolism was diagnosed from the histopathology of lung tissue obtained from a wedge biopsy, which revealed variably-sized vacuoles within the pulmonary vessels, alveolar septal capillaries and intra-alveolar spaces, extensive intra-alveolar hemorrhage, and a few foamy histocytes infiltrating into the alveolar spaces. After steroid treatment, the patient gradually improved. One month after the silicone fluid injection, the pulmonary function test showed a moderate reduction in the diffusing capacity. The patient had reached a nearly complete recovery without any lung sequence as determined by a follow-up chest roentgenogram and the normal pulmonary function test after eight months. ***(Thorac Med 2002; 17: 271-275)***

Key words: silicone fluid, pulmonary emboli

Introduction

Silicones (Dimethylpolysiloxane) is a liquid polymer, which alternates silicon and oxygen atoms with organic groups (methyl). It has been widely used in breast augmentation and other cosmetic procedures during the past three decades, due to its predictable physical properties and a high degree of thermal stability. Silicone was initially believed to elicit a minimal tissue reaction and lack immunogenicity, but numerous studies have reported wide-ranging local and remote clinical symptoms in patients with silicone implants. The most frequently reported symptoms are fatigue, joint and muscle pain, neuritits, lymphadenitis, rheumatism, and cutaneous lesions [1]. Pulmonary involvement including pulmonary interstitial fibrosis years after silicone implant augmentation mammoplasty [2], acute pneumonitis, acute respiratory distress syndrome, and pulmonary emboli [3-9], have

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been reported after local silicone fluid injection. We herein report a female patient who developed pulmonary hemorrhage directly related to a subcutaneous injection of silicone fluid. The pulmonary histopathology disclosed diffuse, variably-sized vacuoles in the pulmonary vessels, alveolar septal capillaries and spaces, with extensive intra-alveolar hemorrhage and a few foamy histocyte infiltrates.

Case Report

A 30-year-old, previously healthy woman came to our chest outpatient department with a complaint of progressive dyspnea and hemoptysis lasting for 3 days. She had received an illegal silicone fluid injection for mammary augmentation 3 days before, but the volume of the injection was unknown. She had undergone a similar procedure before, but without any discomfort. A sudden onset of dry cough during the injection course then progressed to dyspnea and hemoptysis the next day. She was admitted due to an exacerbation of the dyspnea.

On examination, her body temperature was 37.3℃ and her respiratory rate was 32 per minute. A physical examination revealed small injection marks on the lower margin of the left breast, and diffuse expiratory wheezes and basal crackles could be heard on auscultation. The blood test revealed mild, normocytic normochromic anemia: hemoglobin was 9.5 g/dl and hemocrit was 30.1%, the leukocyte count was 8400/cumm (77% neutrophils, 19% lymphocytes, 1% eosinophils, and 4% monocytes), and platelets were $3.45*10^5$/cumm. The serum biochemistry was within normal range. The chest X- ray showed a diffuse alveolar process (Figure 1). A computerized tomography of the chest revealed the alveolar consolidation of both lungs (Figure 2). A bronchoscopic examination performed 4 days after admission showed diffuse blood retained in the bilateral bronchial lumen. No advanced procedure, including bronchoalveolar lavage, was performed due to the deterioration of the O2 saturation found during the bronchoscopic examination. The patient underwent a thoracoscopic lung biopsy on the 10th day of hospitalization. A wedge resection of the upper and middle right lobes was done, and the histopathologic picture showed variably-sized vacuoles in the pulmonary vessels and alveolar septal capillaries, and extensive alveolar hemorrhage with some foamy

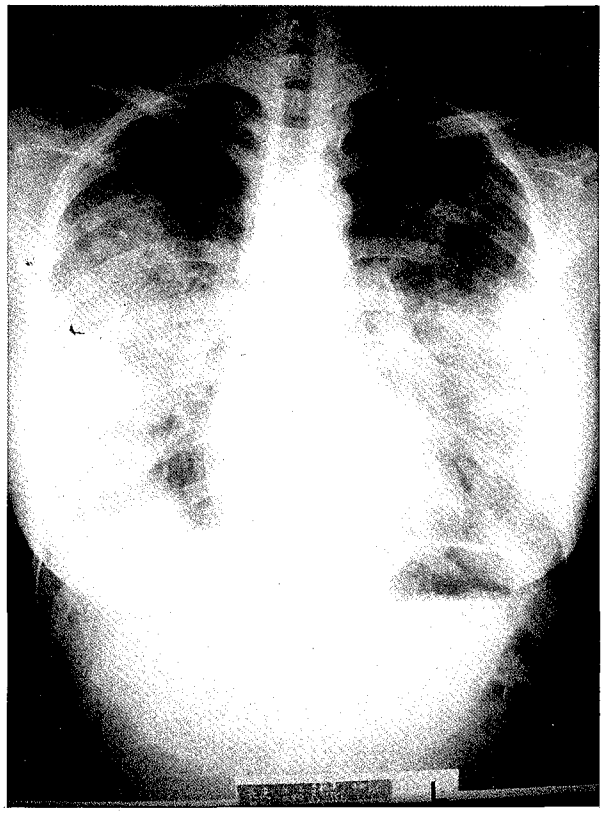

Fig. 1. The CXR shows diffuse alveolar infiltration in both lungs

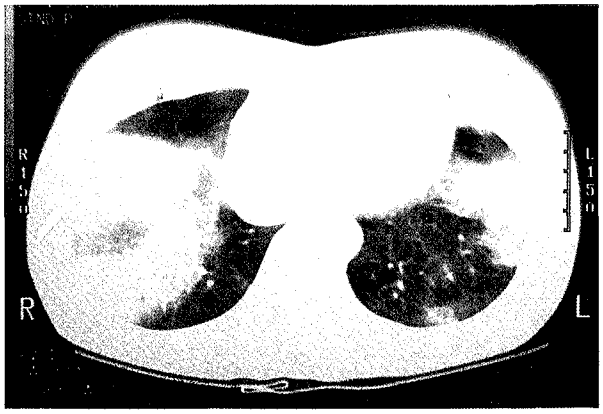

Fig. 2. The Chest CT shows the diffuse alveolar consolidation of both lungs

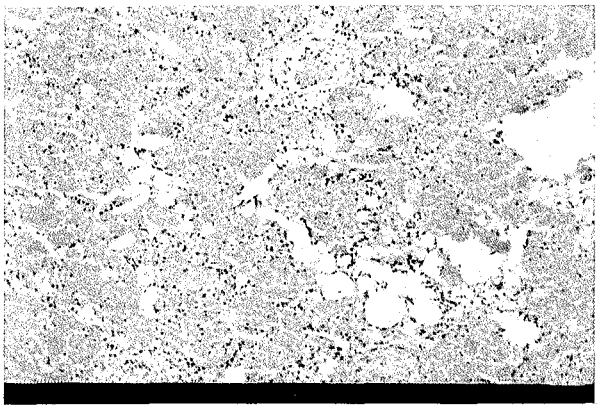

Fig. 3. The microscopic examination reveals variably-sized vacuoles in the pulmonary vessels and alveolar capillaries, and extensive alveolar hemorrhage.

histocyte infiltration (Figure 3).

Parenteral corticosteroid therapy with hydrocortisone 100 mg every 6 hours was given on the day of admission. Treatment was then shifted to oral prednisolone 40 mg per day 5 days later. The patient was discharged in stable condition three weeks after admission, and was followed up regularly at our outpatient clinic. One month after the silicone fluid injection, the pulmonary function test disclosed normal ventilatory functioning, but a moderate reduction of the diffusing capacity (FVC 3.07 L, 97% of predicted; FEV1 2.70, 99% of predicted; FEV1/FVC 88.1%; and DLco 12.5 ml/min/mmHg, 43% predicted). The latter had returned to normal (22.9ml/min/mmHg, 80% of predicted) after eight months of follow-up. There was a nearly complete resolution of the lung lesion on the follow-up chest roentgenogram at that time.

Discussion

Pulmonary emboli induced by silicone fluid injection usually occur after more than one injection; most of the patients have had a history of previous silicone fluid injection [3,8]. The reason for this is not clear. The major clinical manifestations are dyspnea, cough, fever, chest tightness or pain, and hemoptysis; disturbance of consciousness is a poor prognostic factor [3,8,11]. The symptoms have an acute onset, and usually develop hours to days after the silicone fluid injection. The mechanism is probably related to a direct intravascular silicone injection, which forms a silicone embolus in the lung, to high local tissue pressure induced by a large-dose and high-pressure injection which forces the silicone into the bloodstream, or to a migration effect [8-10].

The tissue reaction to silicone fluid is strikingly different from that to silicone elastomer (rubber). When the silicone fluid is introduced into the soft tissue, the exuberant foreign body giant cell reaction seen with silicone elastomer is less common. Silicone liquid in tissue usually shows the presence of round or oval vacuoles of varying sizes, which often appear empty on light microscopic examination and sometimes are surrounded by histocytes of multivacuolated cytoplasm [10]. Most silicone is lost in the processing of the pathological procedure, but a tiny residual amount can be detected by scanning electron microscopy. The histopathologic pictures of this case disclosed diffuse variably-sized vacuoles filling within the pulmonary vessels and the alveolar septal capillaries, and multiple silicone particles migrating across the damaged alveolar-capillary membrane. The inflammatory reaction wasn't predominant but alveolar macrophages with silicone inclusions could be found. Chastre *et al* [3] described three cases of acute silicone pneumonitis and showed that two of their patients had detectable silicone content in the supernatant of the bronchoalveolar lavage (BAL) fluid, and silicone inclusions in the alveolar macrophages. Intra-alveolar hemorrhage is significant because of the destroyed alveolar-capillary membrane. The final pathway of the silicone particles leading to pulmonary vascular damage isn't clear, based on the literature review, and some reports state the mechanism may be similar to that of fat embolism syndrome [12], which is induced by free fatty acid and serotonin from platelet degradation.

Lung perfusion and ventilation scans in these pulmonary emboli cases usually get negative results because the silicone doesn't occlude large segmental vessels but forms small particles to make microvascular emboli. The results of the pulmonary function tests may vary from normal to restrictive ventilatory function, but the single-breath diffusing capacity for carbon monoxide is usually reduced [3,8-9]. The pulmonary function test of gas exchange of our patient showed a reduced diffusing capacity one month after the silicone fluid injection, but returned to normal after eight months of follow-up.

The many long-term sequelae of augmentation mammoplasty with silicone bag gel implantation have been discussed elsewhere, and the pulmonary involvement mainly involves interstitial change in the lungs [2]. However, the long-term pulmonary sequelae of silicone fluid pulmonary embolism have only rarely been reported. In this case, we didn't find any abnormal pulmonary infiltration on the chest film taken 8 months later.

Corticosteroid therapy has been suggested for the treatment of fat embolism syndrome and for the local skin reaction induced by silicone. Therefore, early corticosteroid treatment for silicone fluid-induced pulmonary embolism may be helpful in reversing the clinical course, according to some reports [7-8], but the proper duration of steroid use is still controversial.

Conclusions

Because of the potentially high risk and the complications of silicone fluid injections, this procedure has been abandoned for cosmetic breast augmentation purposes. If the patient develops pulmonary symptoms after silicone fluid injection, silicone-induced pulmonary embolism should be considered. Silicone inclusion in the alveolar macrophages can be found by BAL or the lung biopsy of a tissue specimen, thus confirming the diagnosis. Early corticosteroid therapy and supportive care are effective for most cases.

References

1. R.Vaamonde, J.M. Cabrera, R.J. Vaamonde-Martin, *et al.* Silicone granulomatous lymphadenopathy and siliconomas of the breast. Histology and Histopthology 1997; 12: 1003-11.
2. John Varge, H. Ralph Schumacher, Sergio A, *et al.* Systemic sclerosis after augmentation mammoplasty with silicone implants. Annals of Internal Medicine 1989; 111: 377-83.
3. Chastre J, Basset F, Viau F, *et al.* Acute pneumonitis after subcutaneous injection of silicone in transsexual men. N Engl J Med 1983; 308: 764-7.
4. Chastre J, Basset F, Gibert C, *et al.* Acute pneumonitis after subcutaneous injection of silicone . N Engl J Med 1983; 300: 856.
5. Lee CM, Kou HT, Lin CC, *et al.* Adult respiratory distress syndrome following augmentation of breast. Taiwan I Hsueh Hui Tsa Chih 1982; 81: 1047.
6. Editorial. Silicone pneumonitis. Lancet 1983; 2: 833.
7. Manresa JM, Manresa F. Silicone pneumonitis. 1983; 2: 1373.
8. Chen YM, Lu CC, Perng RP. Silicone fluid-induced pulmonary embolism. Am Rev Respir Dis 1993; 147: 1299-302.
9. Celli B, Textor S, Kovnat DM. Adult respiratory distress syndrome following mammary augmentation. Am J Med Sci 1978; 275 : 81-5.
10. Travis WD, Balogh K, Abraham JL, *et al.* Silicone granuloma: Report of three cases and review of the literature. Human pathology 1985; 16: 19-27.
11. Ellenbogen R, Ellenbogen R, Rubin L. Injectable fluid silicone therapy, human morbidity and mortality. JMAM 1975; 234: 308-9.
12. Besuow V, Hinds CJ. Fat embolism syndrome. Br J Hosp Med 1989; 42: 304-11.

矽膠液注射引發肺栓塞之病例報告

曾若琦 花仲涇 謝文斌 張良慈*

矽膠因為有穩定的物理及耐熱特性，而且被認為具有低免疫刺激性及最少的組織反應度。因此在臨床上被使用於人體皮下組織脂肪的填充，如隆乳及其它美容性用途。但經過數十年的應用，有許多併發症已被報告，包括局部的及全身系統的反應，如肉芽腫，硬化症，類結締組織症候群。對肺部的影響，有使用矽膠隆乳數年後，產生纖維性變化的報告。回顧文獻，僅有少數的報告是因局部液態矽膠注射後引發之急性肺炎，急性呼吸窘迫症候群，或肺栓塞的病例。目前國內使用液態矽膠局部注射隆乳已被禁止。但仍有少數小針美容的非法醫療行為時有所聞。我們報告一位三十歲女性，進行局部胸部隆乳液態矽膠注射後，引發肺栓塞及廣泛性肺泡出血。以類固體治療後，症狀獲得改善。在八個月後追蹤，肺功能及胸部 X 光，恢復正常，無明顯併發症產生。 ***(胸腔醫學 2002; 17: 271-275)***

關鍵詞：液態矽膠，肺栓塞

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Nodular Pulmonary Amyloidosis Mimicking Metastatic Malignancy—A Case Report

Yih Chou, Yuan-Chih Chu, Fen-Fen Chen*, Tzuen-Ren Hsiue

Amyloidosis is a disorder associated with the extracellular deposition of characteristic insoluble protein fibrils which interfere with tissue structure and function. Amyloidosis may be focal, localized, or systemic. The deposits can be localized in the respiratory tract, especially the larynx, tracheobronchus, and lung parenchyma.

We herein report a case of a 67-year-old female who had suffered from a cough with bloody sputum for a month. The image studies, including chest radiograph and computed tomograph, revealed bilateral multiple nodular lesions with a predilection for the basal lung fields, mimicking metastatic malignancy. Pathological examinations revealed dense pale-pink amorphous deposits and an apple-green color on Congo-red staining viewed under polarized light. Based on the above results, pulmonary amyloidosis was diagnosed. The disease was found to be localized within the respiratory tracts after a series of studies. ***(Thorac Med 2002; 17: 276-281)***

Key words: amyloidosis, pulmonary nodules, Congo-red stain, polarized light

Introduction

Amyloidosis is a pathological condition in which protein is deposited extracellularly in the form of insoluble fibrils [1]. In 1928, Divry and Florkin first reported a green birefringence when Congo-red stained specimens were viewed under polarized light [2]. Amyloid deposition localized to the respiratory tracts was recognized by Lesser in 1877. Since then, various classifications have been proposed based upon radiographic or bronchoscopic findings [3-5]. The treatments of choice for respiratory tract amyloidosis mainly depend on the symptoms and the severity of illness.

Case Report

A 67-year-old female, a housewife, visited the Chest Department of our medical center, presenting a history of intermittent hemoptysis for one month. She also had suffered from anorexia with a body weight loss of 4 kg during the previous 3 months. Her blood pressure was 126/72 mmHg, pulse rate 82/min, respiratory rate 21/min, and body temperature 36.7^{0}C. Chest examination revealed diminished breathing sounds in the bilateral lower lung fields, and no evident palpable lymphoadenopathy was noted. Arterial blood gas analysis in room air showed that pH was 7.395, PO_2 82.4 mmHg, and PCO_2

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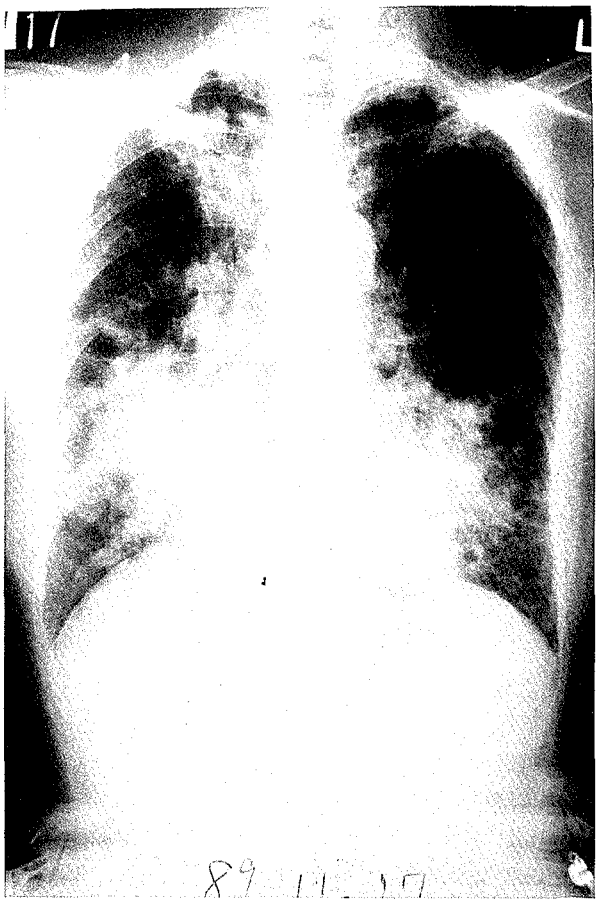
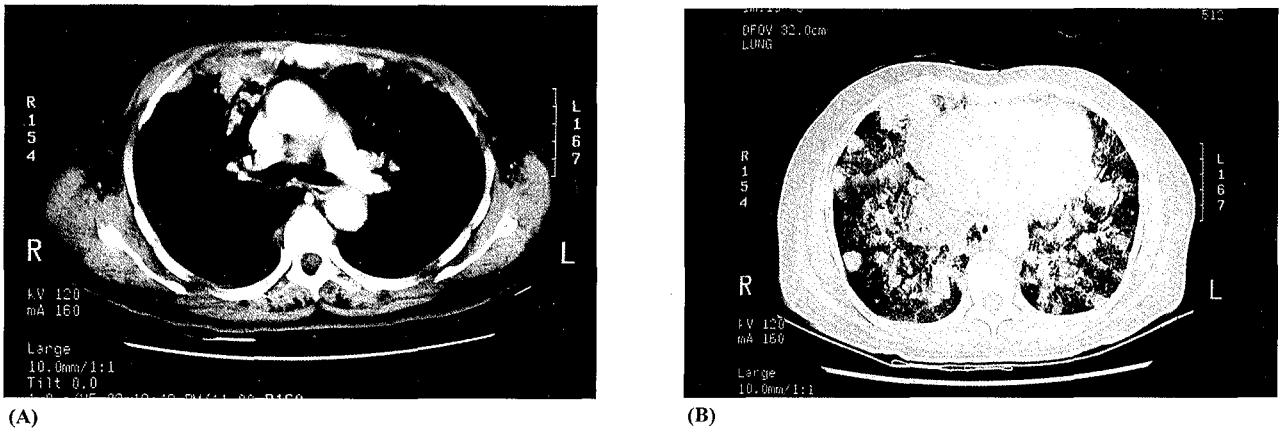


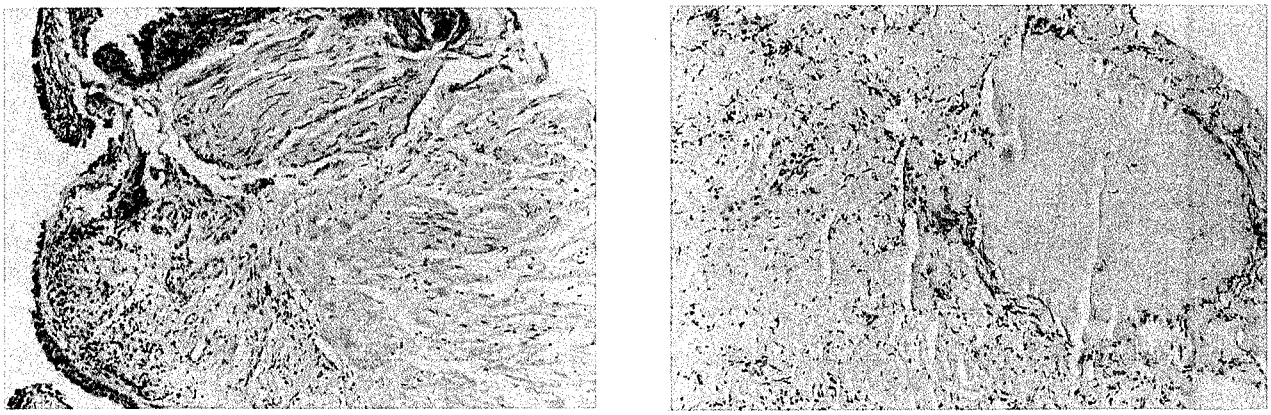
Fig. 1. Bilateral multiple variable-sized nodular lesions, some with a confluent tendency and a predilection for the lower lung fields, were noted in the chest radiograph.

1.2 mmHg. Hematologic evaluation revealed no leukocytosis, with WBC 6500/mm^3 and a differential count of 0% band form, 70% neutrophils, 2% eosinophils, 22% lymphocytes, hemoglobin 12 g/dl, hematocrit 42%, and a platelet count of 162000/mm^3. Blood biochemical studies, including electrolytes, hepatic enzymes, renal function, and albumin/globulin ratio, were all within normal ranges. Bleeding profiles, including bleeding time, prothrombin time, and partial thrombin time, were all normal. The chest radiograph (CXR) revealed bilateral multiple nodules, with sizes varying from 2 mm to more than 10 cm in diameter. These nodules were mainly distributed in the lower lung fields, with some having a confluent tendency (Figure 1). The chest computed tomograph (CT) also showed lesions and distribution similar to the CXR, without mediastinal lymphoadenopathy (Figure 2). Based on the above findings, metastatic or primary malignancy and subacute infections such as fungal or *Mycobacterium tuberculosis*, were considered. Sputum examinations, including cytology, acid–fast stain, and fungus stain, were negative. The bronchofiberscopic findings showed diffuse erythematous mucosa with multiple whitish jelly-like miliary nodules along the trachea and bilateral bronchial trees. The bronchial brushing and biopsy pathological findings revealed no malignant cell, but showed dense pale-pink amorphous deposits and apple-



(A) (B)

Fig. 2. Chest CT (A) mediastinum window, (B) lung window showing confluent nodules and masses distributed diffusely in the bilateral lung fields. The size of the nodules varied from 2 mm to more than 10 cm in diameter. There was no mediastinal lymphoadenopathy.



(A) (B)

Fig. 3. The pathological examinations of the bronchial biopsy (A) and the CT-guided needle biopsy of the lung (B) revealed the deposition of orange-colored, dense amorphous materials stained with Congo-red. They also showed the characteristic apple-green birefringence viewed under the polarized light (200X).

green birefrigence on Congo-red staining viewed under polarized light. A CT–guided lung biopsy was also performed and yielded pathological results similar to the bronchial biopsy (Figure 3). A subsequent bone marrow examination disclosed normal findings. Serum immunoglobulins were IgM 1.14 g/L (normal range 0.6-2.8), IgG 23.3 g/L (normal range 8.1-16.9), and IgA 8.2 g/L (normal range 0.9-4.5). Immunoelectrophoresis of the serum and urine showed no monoclonal gammopathy, and the serum β_2-microglobulin level was normal. Urine Bence–Jones protein and sputum culture for fungus and *M. tuberculosis* were both negative. Abdominal echo, cardiac echo, and radioisotope skeletal studies were all negative. Based on the above studies, the disease was localized within the respiratory tract and the final diagnosis was primary pulmonary amyloidosis. The patient was followed up at the outpatient clinic, and her general condition was stationary one year after discharge.

Discussion

The term amyloid was coined by Schleien in 1838 to described a normal constituent of plants, and adopted by Virchow in 1854 to describe the similarity of an infiltrative substance to cellulose when stained with iodine and sulfuric acid [6]. Amyloidosis is a generic term for a heterogenous group of disorders associated with the extracellular deposition of characteristic insoluble protein fibrils which interfere with tissue structure and function [3]. Opinions differ as to the best way to classify amyloidosis. Classification in the older literature was based on clinicopathologic findings, whereas more recent reports recommend a classification scheme based on the constituent protein fibrils [7].

Diagnosis of amyloidosis requires a tissue specimen showing the amyloid deposits, and is primarily accomplished by demonstrating the characteristic apple-green birefringence with Congo-red staining viewed under polarized light. Though the presence of an amorphous substance in the sputum cytology specimen is suggestive of amyloidosis, the definite diagnosis requires a tissue specimen. In our case, we performed a CT-guided transcutaneous lung biopsy even though the pathology of the bronchial biopsy showed a positive amyloid stain. There were two reasons for this relatively invasive procedure: the first was the discrepant findings of the bronchoscopic examinations and the chest radiograph, and the second was that some literature had reported that amyloidosis could be associated with malignancy [8,9]. Amyloidosis may be hereditary or acquired, primary or secondary, and the deposits may be focal, localized, or systemic. The deposits can localize

in the respiratory tract especially the larynx and tracheobronchus, or involve the lung parenchyma. The symptoms, varying from asymptomatic, hemoptysis, to airway obstruction with impaired gas exchange, depend on the anatomic location of the deposits and their severity. In our patient, the predominant symptom was hemoptysis. Amyloid deposits involving the lung parenchyma can also be distinguished radiologically as solitary/ multiple nodules or a diffuse alveolar-septal pattern. The former are usually found in the localized AL type, and the later usually is a manifestation of systemic amyloidosis [3]. Based on the above description, our case should be classified as a localized AL type.

Amyloid nodules in the lung parenchyma need to be distinguished from neoplasia. They are usually peripheral and subpleural in location, and occur more frequently in the lower lobes. The amyloid nodules may be bilateral, and range in diameter from 0.4 to 15 cm. They grow slowly, and cavitation or calcification are frequently present [10-13]. The image findings in our case were bilateral parenchymal nodules without cavitation or calcification, with sizes varying from 2 mm to more than 10 cm in diameter, and distributed with a predilection for the lower lung fields. This picture is very similar to the usual presentation of metastatic malignancy and was the first impression at the beginning of the evaluation of this patient.

In contrast to the diffuse alveolar-septal pattern of pulmonary amyloidosis, which is usually a systemic involvement with a poor prognosis, nodular parenchymal amyloidosis rarely requires active intervention. The median survival of patients with systemic involvement was 16 months after diagnosis and active management [4]. The lack of controlled clinical trials means the management decisions have to be made on an individual empirical basis. The treatments of choice for amyloid deposits within the respiratory system include simple observation with supportive care, local intervention with endoscopic excision, laser evaporation, stenting,

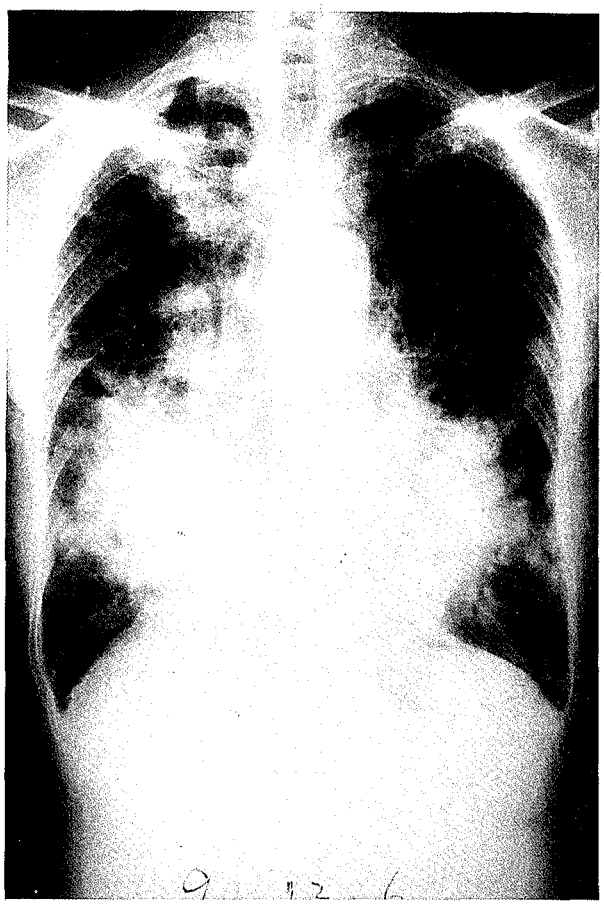


Fig. 4. The chest radiograph demonstrated no obvious progression one year after discharge.

or systemic chemotherapy with or without an autologus peripheral blood stem cell transplantation [14]. New approaches to treatment with an "anti–amyloid" agent are under development, and may be available for clinical use in the near future [15]. Our patient was managed at the outpatient clinic with supportive care, because there was no evident airway obstruction or abnormal gas exchange. She maintained a stable clinical condition and the chest radiograph demonstrated no obvious progression one year after discharge (Figure 4).

References

1. Vittorio Bellotti, Giampaolo Merlini. Current concepts on the pathogenesis of systemic amyloidosis. Nephrol Dial Transplant 1996; 11 [Suppl 9]: 53-62.

2. Gertz MA, Lacy MQ , Dispenzieri A. Amyloidosis. Hematology / Oncology Clinics of North America 1999; 13: 1211-33.
3. Gillmore JD, Hawkins PN. Amyloidosis and the respiratory tract. Thorax 1999; 54: 444-51.
4. Utz JP, Swensen SJ, Gertz MA. Pulmonary amyloidosis: the Mayo Clinic experience from 1980–1993. Ann Intern Med 1996; 124: 407-13.
5. Thompson PJ, Citron KM. Amyloid and the lower respiratory tract. Thorax 1983; 38: 84-7.
6. Alterman K. A historical note on the iodine-sulfuric acid reaction of amyloid. Histochemistry 1976; 49: 131-43.
7. Husby G. Nomenclature and classification of amyloid and amyloidosis. J Intern Med 1992; 232: 511-2.
8. Melato M, Manconi R, Falconieri G. Amyloidosis and lung cancer. Morphol Embryol 1981; 27: 137-42.
9. Halliday BE, Silverman JF, Finley JL. Fine-needle aspiration cytology of amyloid associated with nonneoplastic and malignant lesions. Diagn Cytopathol 1998; 18: 270-5.
10. Kyle RA, Gertz MA. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. Semin Hematol 1995; 32: 45-59.
11. Himmelfarb E, Wells S, Rabinowitz JG. The radiologic spectrum of cardiopulmonary amyloidosis. Chest 1977; 72: 327-32.
12. Rubinow A, Celli BR, Cohen AS, *et al.* Localized amyloidosis of the lower respiratory tract. Am Rev Respir Dis 1978; 118: 603-11.
13. Ayuso MC, Gilabert R, Bombi JA, *et al.* CT appearance of localized pulmonary amyloidosis. F Comput Assist Tomogr 1987; 11: 197-9.
14. Sezer O, Eucker J, *et al.* New therapeutic approaches in primary systemic AL amyloidosis. Ann Hematol 2000; 79: 1-6.
15. Kisilevsky R. Anti–amyloid drug: potential in the treatment of diseases associated with aging. Drugs and Aging 1996; 8: 75-83.

肺部結節性類澱粉沉著症仿似轉移性惡性病變—病例報告

周翊 朱遠志 陳芬芬* 薛尊仁

類澱粉沈著症是於細胞外沈積大量特異，難溶性的蛋白纖維，因而破壞正常組織結構及功能。類澱粉的沈積可以是局部性或是系統性的，當類澱粉沈積局限於呼吸道時可侵犯咽喉、氣管－支氣管或肺實質。在此我們報告一位 67 歲家庭主婦主訴咳嗽合併血痰已有一個月的時間。影像檢查包括胸部 X 光及電腦斷層掃瞄皆呈現兩側多發性結節病灶並傾向分佈於兩側下肺葉—仿似轉移性惡性病變。病理上的發現包括支氣管鏡切片及電腦斷層導引細針肺切片皆未顯示惡性細胞，反而呈現大量無定形物質沈積於細胞外，且在剛果紅染色並以偏光鏡檢查下呈現特異性蘋果綠的顏色，最後診斷為“類澱粉沈著症”而後續的檢查顯示除了呼吸系統外並無其它系統的侵犯。 ***(胸腔醫學 2002; 17: 276-281)***

關鍵詞：類澱粉沈著症、肺結節、剛果紅染色、偏光

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Amiodarone Pulmonary Toxicity—A Case Report

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Amiodarone, an iodinated benzofuran derivative, is frequently used for the treatment of cardiac arrhythmia. However, a variety of adverse effects have been reported. Among them, pulmonary toxicity is one of the most life-threatening complications. Because amiodarone pulmonary toxicity is relatively uncommon, and there is a lack of specific clinical features, it is easily missed or undiagnosed. A high index of suspicion and awareness of the various adverse effects associated with amiodarone are of clinical significance, because lung toxicity may be serious and fatal.

We report a 70-year-old male with ischemic ventricular tachycardia who received amiodarone to control the arrhythmia. He developed nonspecific symptoms, such as cough with blood-tinged sputum, shortness of breath, and fever, after amiodarone therapy. The chest radiograph showed multiple mass-like lesions in both lungs. A non-contrast chest CT revealed several mass- or consolidation-like lesions containing non-homogeneous high density in the bilateral lung fields. Under an electron microscope, the lung tissue biopsy taken by video-assisted thoracoscopic surgery (VATS) disclosed excessive lamellar bodies in the pneumocytes and intraalveolar macrophages. Amiodarone pulmonary toxicity was diagnosed. The patient's condition, follow-up chest radiographs, and serial pulmonary function tests showed improvement after the discontinuation of amiodarone. ***(Thorac Med 2002; 17: 282-289)***

Key words: amiodarone, pulmonary toxicity

Introduction

Amiodarone, an iodinated benzofuran derivative, is frequently used to treat various cardiac arrhythmias. There are a variety of adverse effects associated with amiodarone therapy, including cardiovascular, pulmonary, gastrointestinal, neural, ocular, and dermatologic toxicities, as well as thyroid dysfunction [1-2]. Of these, pulmonary toxicity appears to be the most serious and potentially life-threatening drug reaction. In this paper, an unusual case of amiodarone pulmonary toxicity presenting with multiple mass-like lesions on imaging studies is reported, and related literature is reviewed.

Case Report

A 70-year-old male non-smoker with a history of coronary artery disease and ischemic ventricular tachycardia presented with episodic

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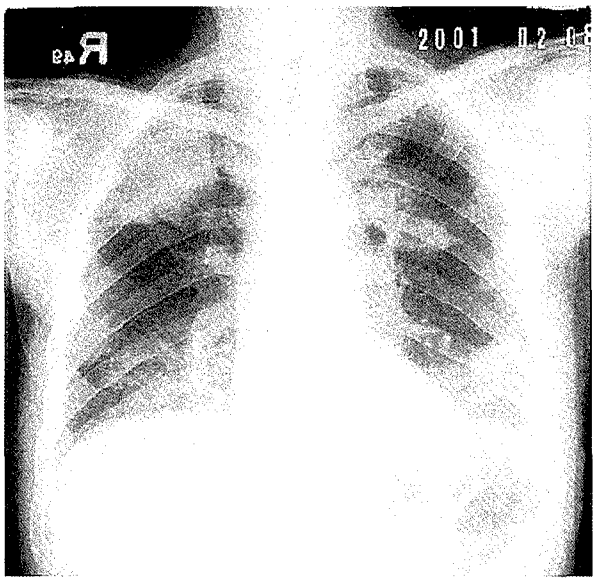
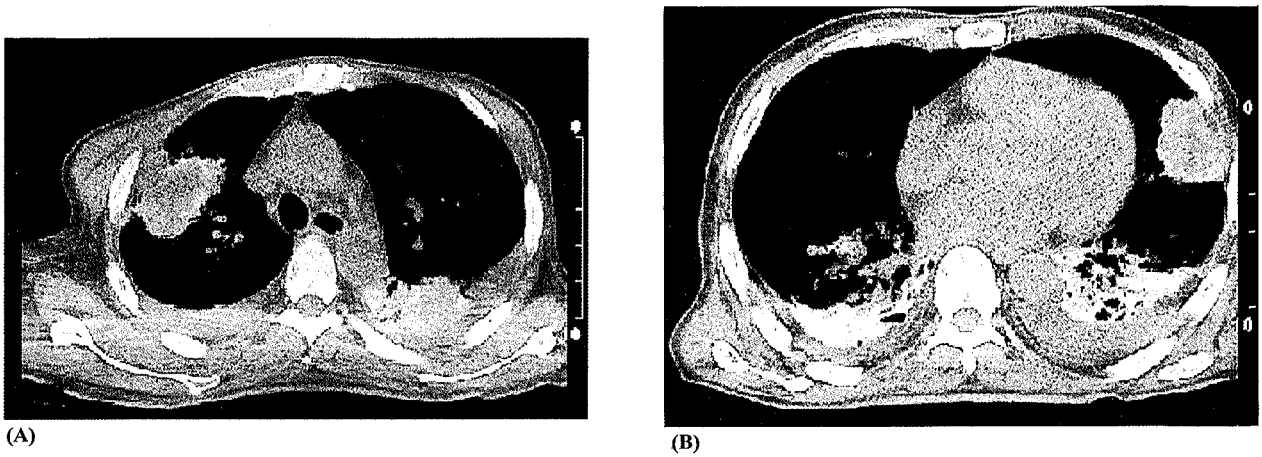


Fig. 1. The chest radiograph obtained on Feb. 8, 2001 shows multiple consolidation or mass-like lesions in both lungs.

attacks of syncope. Amiodarone had been administered in April 1999 at an initial dose of 600 mg per day, and was decreased to 400 mg daily in June 1999 and again increased to 600 mg daily 2 months later. In late 2000, the patient began to notice body weight loss and increased dyspnea. In January 2001, the patient began to have a productive cough with blood-tinged sputum and fever, and was admitted to a local hospital in early February 2001. During hospitalization, the chest radiograph showed multiple mass-like lesions in both lungs. The post-contrast enhanced thoracic computed tomography (CT) disclosed multiple mass-like lesions with peripheral heterogeneous enhancement in the lungs. Lung cancer with lung-to-lung metastases was highly suspected. Because no definite diagnosis could be reached, the patient was referred to our hospital and admitted on February 8, 2001.

On physical examination, he appeared acutely ill and in moderate respiratory distress. His temperature was 37.1°C; pulse rate, 68/min; respiratory rate, 24/min; and blood pressure, 120/70 mmHg. Another significant physical finding was crackles heard bilaterally in the basal lungs. The results of a complete blood count were as follows: WBC count, 13,900/mm^3 (88.6% neutrophils, 5.2% lymphocytes, 4.7% monocytes and 1.4% eosinophils); hemoglobin, 8.6 g/dL; and platelet count, 632,000/mm^3. The relevant data from the blood biochemistries are summarized as follows: albumin, 2.4 gm/dL; total protein, 5.5 gm/dL; sodium, 129 mEq/L; and chloride, 91 mEq/L. The CRP was 45.71 mg/dL. Tests for thyroid function were normal except for a mild decrease in T3 (< 20.00 ng/dL). The microbiological studies, including smears and cultures of sputa, blood, and lung aspiration for bacteria, mycobacterium tuberculosis, and fungus, yielded no substantial findings. The latex test for the cryptococcal antigen was negative.

The frontal chest radiograph on admission (Figure 1) showed multiple consolidation or mass lesions in both lungs, and suspected bilateral pleural effusions. Thoracentesis was done with the aid of chest ultrasonography, and 30-ml of clear fluid was aspirated. The pleural fluid was transudate in nature. Both cytologic and pathologic studies of the sono-guided percutaneous lung aspiration and biopsy specimens were negative for malignancy, and failed to provide a diagnosis. The non-contrast chest CT (Figure 2), done on February 20, 2001, revealed several mass- or consolidation-like lesions containing a non-homogeneous high density in the bilateral lung fields. The results of the pulmonary function testing done on February 22, 2001, showed a restrictive ventilatory defect with FEV_1 (forced expiratory volume in one second), 1.52 L (63% pred.); FVC (forced vital capacity), 1.69 L (51% pred.); FEV_1/FVC, 90%; and TLC (total lung capacity), 4.17 L (79% pred.). The arterial blood gas results were as follows: pH: 7.467; PO_2: 96.9 mmHg; PCO_2: 35.8 mmHg; and HCO_3^-: 25.3 mEq/L (with an O_2 supplement of 3 L/min by nasal cannula). Bronchoscopy was performed with a bronchoalveolar lavage (BAL) on February 23, 2001. A return of 95 ml of fluid was collected using three 50-ml aliquots of normal saline solution. The cell count was 12.0 x 10^4 cells/mL, a marked increase above our normal

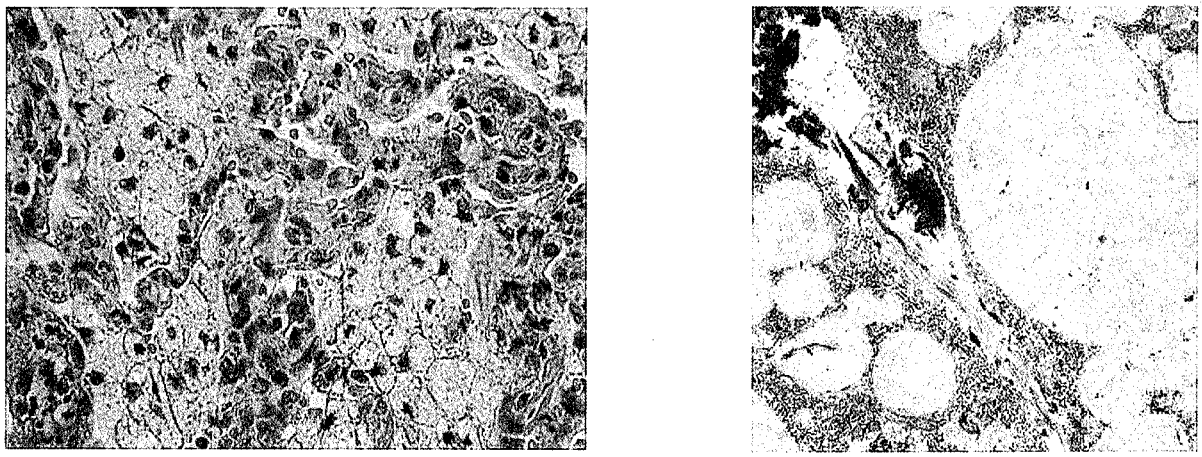


(A) (B)

Fig. 2. A Non-contrast chest CT scan obtained on Feb. 20, 2001 discloses several non-homogeneous soft tissue masses containing high density infiltrates in the bilateral upper and lower lobes (A, B). Bilateral pleural effusion is also noted.

range ($5.5 \pm 2.8 \times 10^4$ cells/mL). The cyto-preparation was stained with Riu's stain and revealed that most of the alveolar macrophages were foamy in appearance. The alveolar macrophages showed a positive Sudan black staining in the smear that was used to detect phospholipids. The pathologic examination of the transbronchial lung biopsy specimen was unremarkable.

An ophthalmologic examination was done on February 20, 2001, and amiodarone-induced deposits in both corneas were found. Because the clinical features, and the results of imaging studies, pulmonary function testing, and the BAL examination were highly suggestive of amiodarone pulmonary toxicity, and because of the poor response of the patient to empirical antibiotic treatment, amiodarone was discontinued on February 28, 2001. Since a progression of the pulmonary lesions was shown on chest radiographs during hospitalization, the patient was subjected to video-assisted thoracoscopic surgery (VATS), with a wedge resection of the lesions in the RML and RLL on March 15, 2001. Under light and electron microscopes (Figure 3), the lung tissue specimen revealed prominent alveolar exudates containing many macrophages, desquamated pneumocytes, and fibrin material;



(A) (B)

Fig. 3. Pathological findings under light (A) and electron (B) microscopes. Under a light microscope, many foamy macrophages in the alveolar sacs are seen (H&E stain, x 400). Under an electron microscope, numerous lamellar bodies in the pneumocytes and intraalveolar macrophages are seen (magnification x 10000).

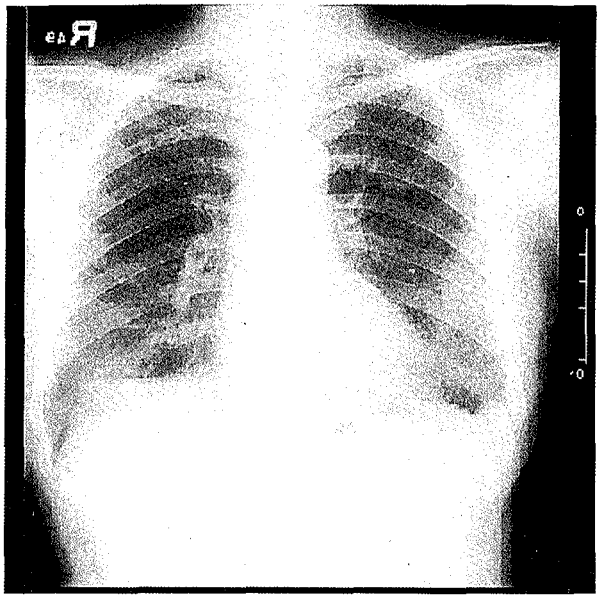


Fig. 4. A chest radiograph obtained on Jun. 15, 2001. Resolution of the lung lesions is noted.

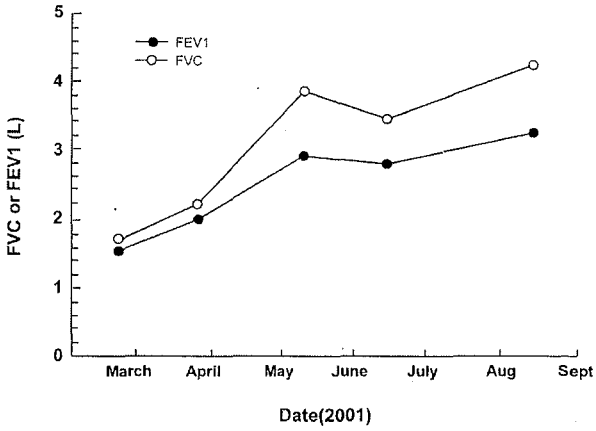


Fig. 5. The changes in FEV_1 and FVC. A gradual improvement of pulmonary function as expressed by FEV_1 and FVC can be observed.

interstitial inflammation and fibrosis; and the presence of excessive lamellar bodies in the pneumocytes and intra-alveolar macrophages. The microscopic findings and ultrastructural features were compatible with those of amiodarone pulmonary toxicity.

The patient's condition showed improvement after discontinuation of the amiodarone. He was then discharged on March 28, 2001, and followed up at our outpatient clinic regularly. The follow-up chest radiographs in May and June 2001 (Figure 4) showed a gradual resolution of the pulmonary lesions. The results of serial pulmonary function tests showed a return to normal, as expressed by FEV_1 and FVC (Figure 5).

Discussion

Pulmonary toxicity or pneumonitis is the most serious noncardiac side effect, and a potentially life-threatening drug reaction, ascribable to amiodarone. The incidence of amiodarone pulmonary toxicity varies widely [3-5]. A realistic estimate of its incidence would be 5 to 10% [1-2,6], and death has been reported in approximately 5 to 10% of those patients who developed pulmonary toxicity [2,7-8]. Amiodarone pulmonary toxicity has rarely been reported in Taiwan, although the drug is commonly used clinically. This may be explained by the fact that amiodarone is relatively new in Taiwan, and the experience and alertness of clinicians in making a diagnosis of amiodarone pulmonary toxicity is still inadequate.

Amiodarone pulmonary toxicity has been reported more frequently in patients receiving maintenance doses of more than 400 mg/day, which suggests an increased risk of pulmonary toxicity with higher maintenance dosages [5-6,9]. Other risk factors include advanced age, lower pretreatment DLco (diffusing capacity for carbon monoxide), and higher plasma desethylamiodarone concentrations [9].

The mechanisms of amiodarone-induced pulmonary toxicity are probably multifactorial [8]. Both direct cytotoxic effects and indirect immunological mechanisms have been reported [6-8,10]. Amiodarone may induce an accumulation of phospholipids in the tissue, which has a direct cytotoxic effect on the alveolar-capillary membrane in the lungs [11]. The cells retrieved by BAL from most patients with amiodarone pulmonary toxicity demonstrate CD8+ and cytotoxic lymphocytic alveolitis, which might suggest a cell-mediated immunologic mechanism in the development of amiodarone pulmonary

toxicity [12-14].

The clinical features of amiodarone pulmonary toxicity are nonspecific [6-7]. Dyspnea, especially occurring with exertion, is the most common clinical symptom [7,15-18]. Nonproductive cough, low-grade fever, and pleuritic chest pain are also common. Other constitutional symptoms, which have been reported occasionally, include general malaise and body weight loss. There are two distinct kinds of clinical illness in patients with amiodarone pulmonary toxicity [7,15,17]. Most patients have an insidious presentation with dyspnea, cough, and sometimes weight loss. Others may present with a more acute illness, with a fever and cough that mimics pneumonia. The physical findings of amiodarone pulmonary toxicity are inconsistent, and help to identify the presence of lung disease only [15]. Crackles and occasionally a pleural friction rub may be heard. Other physical findings, such as skin discoloration or corneal micro-deposits, merely confirm that the patient is taking amiodarone, but does not help to evaluate amiodarone pulmonary toxicity [7,15].

The chest radiographic findings of amiodarone pulmonary toxicity are varied and include a peripheral and apical or bilateral diffuse alveolar and/or interstitial pattern of infiltrates [7,15,17-18]. Of these, diffuse interstitial infiltrates appear to be the most common, although airspace opacities are not uncommon [15-18]. In contrast, nodule-mass or consolidation-mass like lesions [19-21] have been reported in some patients. Pleural effusion can be found occasionally. However, the presence of pleural effusion can be due to an underlying cardiac problem or adverse reaction to the drug. A CT scan of the chest can provide more evidence suggestive of amiodarone pulmonary toxicity. Since amiodarone has a high iodine content, which is radiopaque, amiodarone pulmonary toxicity shows a high CT attenuation of pleural-parenchymal lesions [22-25].

The results of pulmonary function testing in patients with amiodarone pulmonary toxicity disclose a reduction of DLco and a restrictive ventilatory defect [5,18,26-27]. The decline of DLco appears to be the most consistent physiologic abnormality [15]. Arterial hypoxemia is relatively common. However, a reduction of DLco and a restrictive ventilatory defect can also be observed in patients with congestive heart failure. Accordingly, these physiologic abnormalities are not specific to amiodarone pulmonary toxicity.

The histopathological findings of amiodarone pulmonary toxicity include interstitial abnormalities with a thickening of the alveolar septal membrane by connective tissue and/or inflammatory cells [15,17]. Diffuse alveolar damage has also been found. The presence of intra-alveolar foamy macrophages and intracytoplasmic lamellar inclusion bodies due to phospholipidosis are characteristic, however, the above features do not distinguish toxic and nontoxic patients [7,15,17]. These foamy alveolar macrophages containing intracytoplasmic lamellar inclusion bodies can also be observed in the bronchoalveolar lavage fluid (BALF) from patients with amiodarone exposure or those with amiodarone pulmonary toxicity [15].

Based on the diversity of the clinical presentation and radiographic features shown on chest radiograph and CT, and in the lung pathology, a diagnosis of amiodarone pulmonary toxicity can be made on clinical grounds. Amiodarone pulmonary toxicity should be considered in those patients receiving the drug therapy, if 3 or more of the following are present: (1) new or worsening respiratory symptoms; (2) new abnormalities on the chest radiograph, or chest radiograph change; (3) a 15% reduction in DLco or TLC; (4) an increase in foamy cells in the BALF; (5) diffuse alveolar damage with interstitial pneumonitis or fibrosis on lung biopsy; and (6) clinical improvement after withdrawal of the drug [2,26].

The therapeutics for amiodarone pulmonary toxicity is limited. The preferred treatment is discontinuation of the drug and employment of an alternate drug. Resolution of amiodarone pulmonary

toxicity with drug elimination has been reported [28-29]. However, there is a risk that life-threatening arrhythmias will recur. Another option for treatment is the use of corticosteroids. In a number of cases, apparent benefits have been reported after employment of corticosteroids with or without drug elimination [16-18, 29]. Since there has been no control trial for comparison of this therapy, the role of steroids in the treatment of amiodarone pulmonary toxicity remains uncertain. In our reported case, a spontaneous resolution of amiodarone pulmonary toxicity after discontinuation of the drug was observed.

In summary, we present a case of amiodarone pulmonary toxicity which resolved spontaneously after discontinuation of the drug. The value of steroids in the treatment of amiodarone pulmonary toxicity requires further study for clarification.

References

1. Wilson JS, Podrid PJ. Side effects from amiodarone. Am Heart J 1991; 121: 158-71.
2. Martin WJ II, Rosenow EC III. Amiodarone pulmonary toxicity: Recognition and pathogenesis (Part I). Chest 1988; 93: 1067-75.
3. Smith WM, Lubbe WF, Whitlock RM, *et al.* Long-term tolerance of amiodarone treatment for cardiac arrhythmias. Am J Cardiol 1986; 57: 1288-93.
4. Haffajee CI, Love JC, Canada AT, *et al.* Clinical pharmacokinetics and efficacy of amiodarone for refractory tachyarrhythmias. Circulation 1983; 67: 1347-55.
5. Magro SA, Lawrence EC, Wheeler SH, *et al.* Amiodarone pulmonary toxicity: Prospective evaluation of serial pulmonary function tests. J Am Coll Cardiol 1988; 12: 781-8.
6. Jessurun GAJ, Boersma WG, Crijns HJGM. Amiodarone-induced pulmonary toxicity: Predisposing factors, clinical symptoms and treatment. Drug Safety 1998; 18: 339-44.
7. Pitcher WD. Southwestern internal medicine conference: Amiodarone pulmonary toxicity. Am J Med Sci 1992; 303: 206-12.
8. Martin WJ II, Rosenow EC III. Amiodarone pulmonary toxicity: Recognition and pathogenesis (Part II). Chest 1988; 93: 1242-8.
9. Dusman RE, Stanton MS, Miles WM, *et al.* Clinical features of amiodarone-induced pulmonary toxicity. Circulation 1990; 82: 51-9.
10. Martin WJ II. Mechanisms of amiodarone pulmonary toxicity. Clin Chest Med 1990; 11: 131-8.
11. Martin WJ II, Standing JE. Amiodarone pulmonary toxicity: Biochemical evidence for a cellular phospholipidosis in the bronchoalveolar lavage of human subjects. J Pharmacol Exp Ther 1988; 244: 774-9.
12. Israel-Biet D, Venet A, Caubarrere I, *et al.* Bronchoalveolar lavage in amiodarone pneumonitis. Chest, 1987; 91: 214-20.
13. Akoun GM, Cadranel JL, Blanchette G, *et al.* Bronchoalveolar lavage cell data in amiodarone-associated pneumonitis. Chest, 1991; 99: 1177-82.
14. Cherniak RM, Banks DE, Bell DY, *et al.* Bronchoalveolar lavage constituents in healthy individuals, idiopathic pulmonary fibrosis, and selected comparison groups. Am Rev Respir Dis 1990; 141: S169-S202.
15. Kennedy JI. Clinical aspects of amiodarone pulmonary toxicity. Clin Chest Med 1990; 11: 119-29.
16. Gefter WB, Epstein DM, Pietra, *et al.* Lung disease caused by amiodarone, A new antiarrhythmic agent. Radiology 1983; 147: 339-44.
17. Kennedy JI, Myers JL, Plumb VJ, *et al.* Amiodarone pulmonary toxicity: Clinical, radiologic, and pathologic correlations. Arch Intern Med 1987; 147: 50-5.
18. Marchlinski FE, Gansler TS, Waxman HL, *et al.* Amiodarone pulmonary toxicity. Ann Intern Med 1982; 97: 839-45.
19. Patel P, Honeybourne D, Watson RDS. Amiodarone-induced pulmonary toxicity mimicking metastatic lung disease. Postgrad Med J 1987; 63: 393-4.
20. Arnon R, Raz I, Chajek-Shaul T, *et al.* Amiodarone pulmonary toxicity presenting as a solitary lung mass. Chest 1988; 93: 425-7.
21. Piccione W Jr, Faber LP, Rosenberg MS. Amiodarone-induced pulmonary mass. Ann Thorac Surg 1989; 47: 918-9.
22. Ren H, Kuhlman JE, Hruban RH, *et al.* CT-pathology correlation of amiodarone lung. J Comput Assist Tomogr

1990; 14: 760-5.

23. Kuhlman JE, Teigen C, Ren H, *et al.* Amiodarone pulmonary toxicity: CT findings in symptomatic patients. Radiology 1990; 177: 121-5.
24. Kuhlman JE, Scatarige JC, Fishman EK, *et al.* CT demonstration of high attenuation pleural-parenchymal lesions due to amiodarone therapy. J Comput Assist Tomogr 1987; 11: 160-2.
25. Nicholson AA, Hayward C. The value of computed tomography in the diagnosis of amiodarone-induced pulmonary toxicity. Clin Radiol 1989; 40: 564-7.
26. Kudenchuk PJ, Pierson DJ, Greene HL, *et al.* Prospective evaluation of amiodarone pulmonary toxicity. Chest 1984; 86: 541-8.
27. Gleadhill IC, Wise RA, Schofeld SA, *et al.* Serial lung function testing in patients treated with amiodarone: A prospective study. Am J Med 1989; 86: 4-10.
28. Fraioli P, Barberis M, Montemurro L. Spontaneous regression of amiodarone pulmonary toxicity. Sarcoidosis 1990; 7: 58-62.
29. Rakita L, Sobol SM, Mostow N, *et al.* Amiodarone pulmonary toxicity. Am Heart J 1983; 106: 906-16.

Amiodarone 引起之肺毒性——一病例報告

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Amiodarone 是一種 iodinated benzofuran 的衍生物，常用於治療心律不整。但此藥已有許多副作用被發現，肺毒性是其中對生命最具威脅的副作用之一。由於 amiodarone 引起之肺毒性並不常見，而且缺乏特異的臨床特徵，因此容易被臨床醫師所忽略。由於此肺毒性可能是嚴重而足以致死的，臨床醫師有必要認識 amiodarone 所引起的各種副作用，並且對其要有高度的警覺性。

我們的病例是一位 70 歲男性，因患缺血性心室性頻脈而服用 amiodarone。經過一段時間後，病患出現一些呼吸道的症狀，如咳嗽帶有血絲痰，呼吸急促，發燒等。胸部 x 光發現兩側肺野有多處腫塊狀陰影。未打顯影劑之胸部電腦斷層發現兩側肺野有多處腫塊狀或實質化之病變，其中並呈現不均勻的高亮度之浸潤。病患接受影像輔助胸腔鏡術，取得的肺切片在電子顯微鏡下顯示在 pneumocytes 及肺泡內巨噬細胞中有相當多的層狀結構，因此診斷病患為 amiodarone 引起之肺毒性。病患的症狀，放射線學上的異常，以及肺功能檢查等，在停止服用 amiodarone 後有明顯改善。 ***(胸腔醫學 2002; 17: 282-289)***

關鍵詞：amiodarone，肺毒性

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Chronic Necrotizing Pulmonary Aspergillosis —A Case Report

Paw-Loong Ang, Te-Chun Hsia, Liang-Wen Hang, Tze-Yi Lin*, Shwen Yang

Chronic necrotizing pulmonary aspergillosis (CNPA), also known as semi-invasive pulmonary aspergillosis, is a rare pulmonary infection caused by the genus *Aspergillus*, and usually is found in immunosuppressed patients. We report a 38-year-old man presenting with dyspnea, fever, anemia, and thrombocytopenia prior to admission. Acute myeloid leukemia (AML), M1, was diagnosed at the base of his bone marrow study. During the course of hospitalization, he developed neutropenic fever after induction chemotherapy. Initially, he was treated with a regimen of broad spectrum antibiotics, and then an anti-fungal agent was added for the prolonged neutropenic fever. Chest radiography showed multiple cavitary nodular lesions in both lungs. The transbronchial biopsy could not yield a diagnosis. Therefore, the patient underwent an exploratory thoracotomy, and the pathology confirmed a diagnosis of semi-invasive pulmonary aspergillosis. In order to reach a diagnosis of chronic necrotizing pulmonary aspergillosis, a high degree of clinical suspicion is required. Pulmonary tuberculosis and anaerobic infections should be carefully excluded. Treatment is based on the administration of anti-fungal drugs. In the event of a failure of medical treatment, thoracic surgery may be indicated. ***(Thorac Med 2002; 17: 290-296)***

Key words: chronic necrotizing pulmonary aspergillosis, semi-invasive pulmonary aspergillosis, aspergillosis

Introduction

Chronic necrotizing pulmonary aspergillosis (CNPA), also known as semi-invasive pulmonary aspergillosis, is a rare infection encountered mainly in immunocompromised patients. In the 1980s, Gefter and associates [1] and Binder and colleagues [2] independently described a distinct type of aspergillus lung disease known today as "semi-invasive aspergillosis" or "chronic necrotizing pulmonary aspergillosis" (CNPA). CNPA often occurs in middle-aged and older persons who are immunocompromised to some degree: for example, those with diabetes mellitus, connective tissue disease, alcoholism, and chronic obstructive pulmonary disease, or those on steroid therapy. Clinical symptoms at presentation include cough, fever, sputum production, and weight loss. In one study, ninety-three percent of patients had more than one symptom, and 76% had three or more [3]. To reach a diagnosis of CNPA, a high degree of clinical suspicion is required. A differential diagnosis should be done

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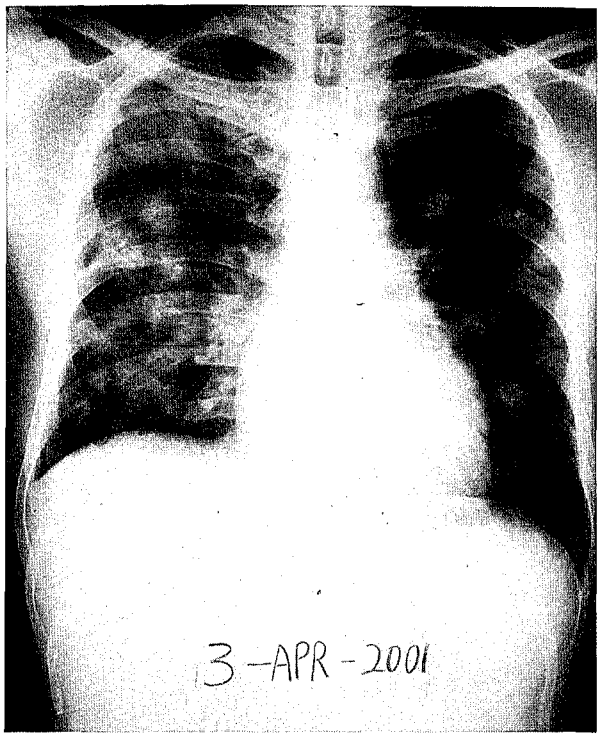

Fig. 1. Chest X-ray shows increased infiltration in the right lung field, and right pleural effusion.

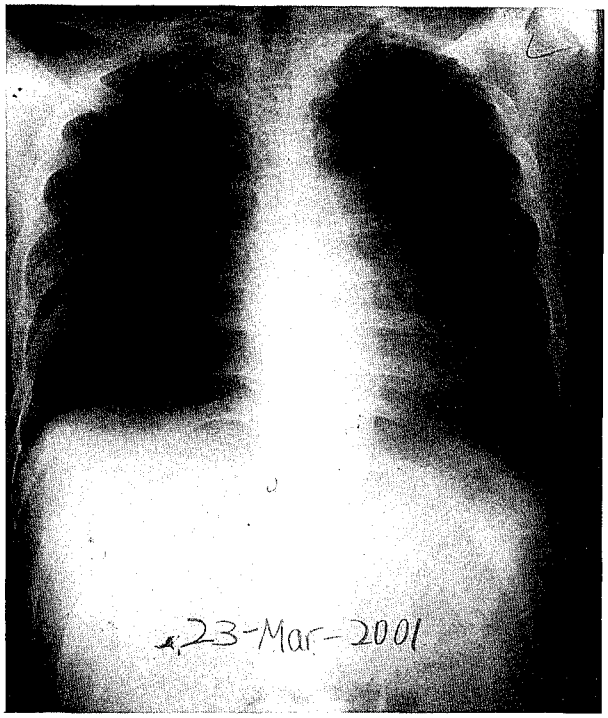

Fig. 2. Improvement on the chest X-ray after antibiotic treatment and pig-tail drainage.

with pulmonary tuberculosis and anaerobic infections. We herein report a case of pathology-proven semi-invasive aspergillosis in a leukemic patient. This patient died of relapsing leukemia complicated with leukemic meningitis, despite amphotericin B treatment which led to an initial improvement.

Case Report

A 38-year-old male patient was admitted to the hospital with the chief complaints of dyspnea and right chest pain lasting for several days. He had experienced fever and productive cough 2 weeks before admission, followed by increasing right chest pain and dyspnea. On admission, he presented with right pleural effusion (Figure 1), leukocytosis, anemia, and thrombocytopenia. The patient's blood pressure was normal and body temperature was 37.9℃. The physical examination showed decreased breathing sounds in the right lower lung. The hematologic study showed: white blood cell count, 19,400/μl; hemoglobin, 8.29 g/dl; platelet count, 34,300/μl; neutrophils, 11%; lymphocytes, 7.75%; and monocytes, 72.3%. Diagnostic thoracentesis showed an exudative pleural effusion with a predominance of neutrophils. After appropriate cultures were obtained, he was treated with broad spectrum antibiotics and pig-tail drainage for his probable parapneumonic effusion.

The fever subsided after one week of antibiotic treatment, and his chest radiograph showed an improvement in the infiltrate and pleural effusion (Figure 2). He was diagnosed with acute leukemia via the bone marrow study for his thrombocytopenia and anemia. Chemotherapy with idarubicin and cytosar was started after the diagnosis of acute myeloid leukemia (AML), M1. His leukopenic status persisted for 17 days after the 3rd day of chemotherapy, despite the administration of granulocyte-colony stimulating factor (G-CSF). Therefore, an anti-fungal agent was added for his prolonged neutropenic fever.

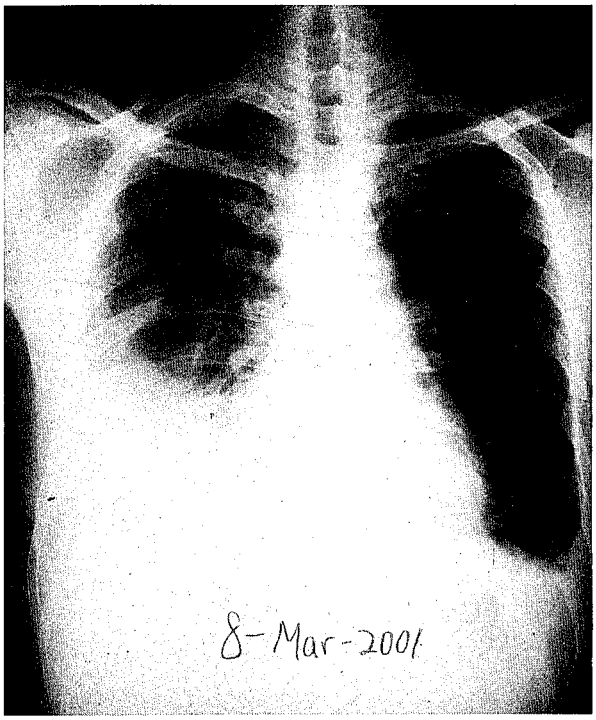

Fig. 3. Chest X-ray shows multiple cavitary nodular lesions in both lungs.

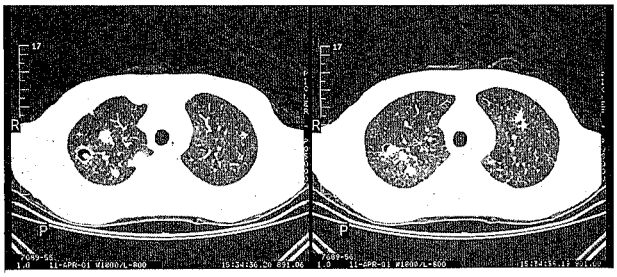

Fig. 4. Chest computerized tomography reveals multiple cavitary nodular lesions, with a "ball in the hole" in both lungs.

The chest X- ray (Figure 3) and chest computerized tomography (Figure 4) revealed multiple cavitary nodular lesions in both lungs. The results of multiple cultures of sputum, urine, and blood samples were negative. The results of sputum smears for acid-fast bacilli and mycobacterial cultures were also negative. A resection of the right upper and middle lobes was performed after the transbronchial biopsies failed to make a diagnosis. The pathology of the resected lung specimens revealed multifocal peribronchial acute necrotizing and chronic xanthogranulomatous inflammation with scattered peribronchial hemorrhage, adjacent early organizing pneumonia,

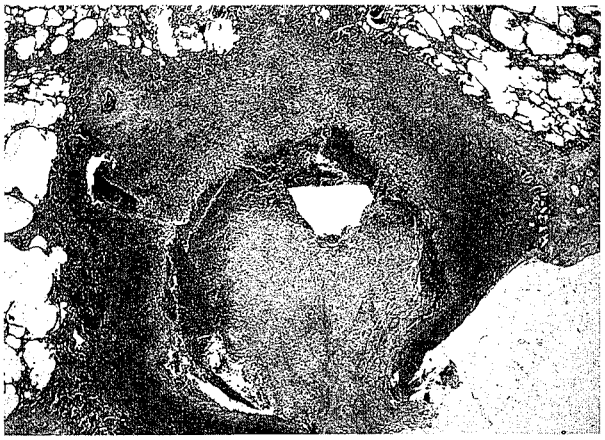

Fig. 5. Pathology shows necrotizing and cavitary aspergilloma.

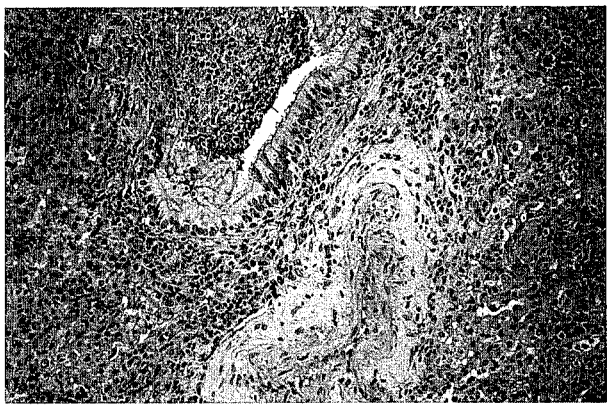

Fig. 6. Focal bronchiolar epithelial destruction with intact adjacent vascular wall

and focal intrabronchial aspergilloma with bronchial epithelial destruction (Figure 5, 6). An aggregate of narrow-angled, septated, fungal hyphae and spores with scattered foci of fruiting bodies were demonstrated by Periodic Acid Schiff (PAS) (Figure 7) and Gormorine Methenamine Silver (GMS) stains (Figure 8), while the acid-fast, mucicarmine, and Gram stains failed to disclose any microorganisms. Thus, the diagnosis of semi-invasive aspergillosis was confirmed. Amphotericin B, 50mg/day, was then begun, and he was discharged after the fever had subsided. Amphotericin B, 50mg/day, was continued at our OPD. Improvement was noted in the follow-up chest radiographs (Figure 9).

One month after discharge, he was admitted to the hospital again with a presentation of headache and fever. The examination of his cerebrospinal fluid (CSF) showed leukemic cells

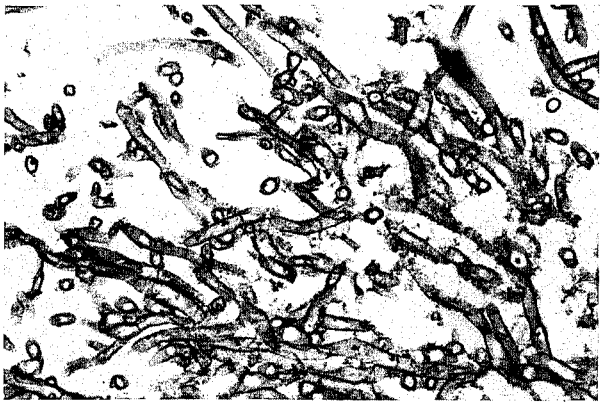

Fig. 7. PAS stain shows narrow-angled septated hyphae.

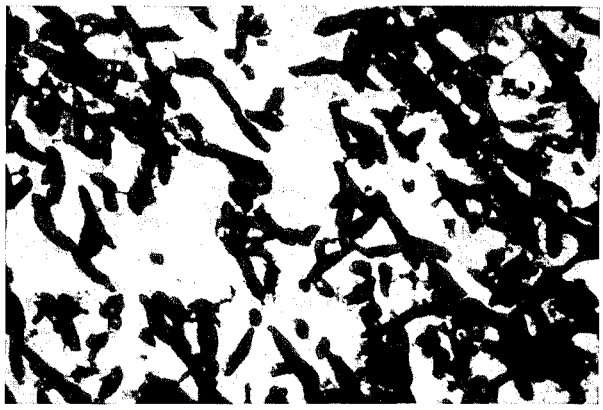

Fig. 8: GMS stain shows narrow-angled septated hyphae.

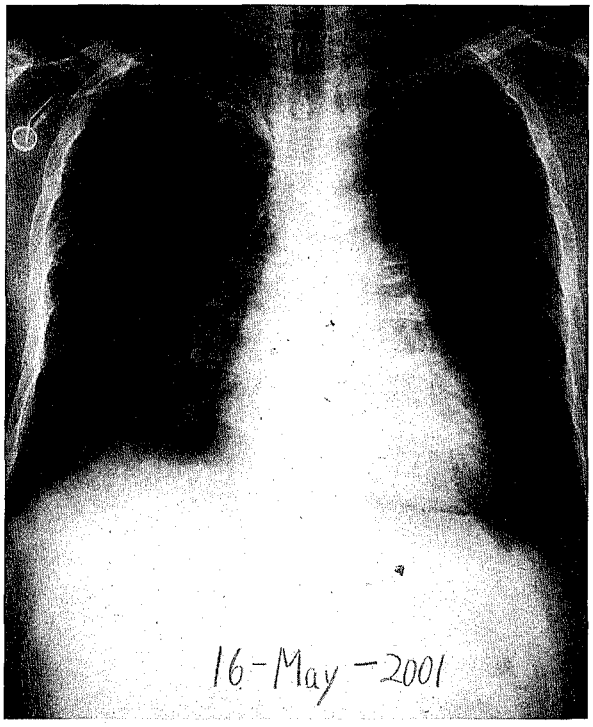

Fig. 9: Chest X-ray shows an improvement in the cavitary nodular lesions after amphotericin B therapy.

and acid-fast bacilli on the acid-fast stain. There was no fungal growth in the CSF culture. Anti-tuberculous agents were given pending the mycobacterial cultures of the CSF and sputum. The results of these cultures ultimately were negative. Bacteremia with *Enterobacter cloacae* infection was noted during hospitalization, and he was again treated with antibiotics. Despite antimicrobial therapy and chemotherapy, he finally died of relapsing leukemia with meningitis.

Discussion

Pulmonary aspergillosis has been traditionally classified into three types: invasive broncho-pulmonary aspergillosis (pneumonia type) [4-5], aspergilloma (non-invasive type, saprophytic), and allergic aspergillosis [6]. Binder et al, proposed the concept of chronic necrotizing pulmonary aspergillosis (CNPA) in 1982 [2]. Gefter reported five cases with chronic cavitary pulmonary aspergillosis as "semi-invasive" pulmonary aspergillosis [1] to emphasize a disease process overlapping an extremely colonizing and frankly invasive disease, very similar to CNPA. Thus CNPA could be the same entity as "semi-invasive" pulmonary aspergillosis.

Chronic necrotizing pulmonary aspergillosis is an unusual entity within the spectrum of pulmonary aspergillosis. Diagnosis is based on a chronic, locally invasive, cavitary lesion with *Aspergillus* species, found either on repeated cultures or in biopsy specimens of the lung tissue. There are three distinct forms of the histom-orphology of CNPA: necrotizing granulomatous pneumonia, granulomatous bronchiectatic cavity, and bronchocentric granulomatosis [9]. Tissue invasion without vascular involvement defines CNPA, and distinguishes this condition from simple mycetoma [1, 7-8].

CNPA affects middle-aged individuals, with

a predilection for men [1-3, 12]. Patients with CNPA have local defects in their pulmonary defenses stemming from structural lung diseases, such as chronic obstructive pulmonary disease, antecedent tuberculosis, bronchiectasis, sarcoidosis, radiation fibrosis, lung resections, and lung disease attributable to ankylosing spondylitis. Other systemic immunosuppressive factors are diabetes mellitus, alcoholism, debilitation, chemotherapy, and the long-term use of corticosteroids [1-3, 12]. Constitutional as well as pulmonary symptoms are typically present in CNPA. Cough, fever, sputum production, and weight loss are the most commonly reported signs and symptoms [1-3, 12]. Ninety-three percent of patients had more than one symptom on admission and 76% had three or more [1-3]. Most patients had signs and symptoms of a 1- to 6-month duration, which tended to become worse over time. Delayed diagnosis is common, and may contribute to the morbidity and mortality associated with CNPA. The average delay in diagnosis reported was seven months [1-3, 10-11].

Chest roentgenographic abnormalities in CNPA were largely localized to the upper lobes [2], where an alveolar or nodular infiltrate was the initial abnormality. In 80% of cases, there was evidence of cavitation or necrosis, and this observation was occasionally accompanied with a marked pleural fibrotic reaction [1-2, 10]. Progressive cavitation or superimposed new infiltrates often precipitate lung biopsy and resection.

Amphotericin B has been the mainstay of pulmonary aspergillosis therapy in the immuno-compromised host, and it is the most frequently employed therapy reported in the literature. Itraconazole is the most effective therapy currently available for CNPA [3, 12]. In the event of medical treatment failure, thoracic surgery may be indicated. Pulmonary resection may be curative if sufficient ventilatory reserve is present, although controversy exists regarding the effectiveness of this procedure [13-15]. The role of pulmonary resection in CNPA appears to be limited to a small subset of patients with local infection, adequate pulmonary reserve, and acceptable surgical risk. A good outcome would be expected in this group of patients who are less severely ill [1, 3, 10]. The prognosis of CNPA is affected by chronic underlying diseases, any delay in diagnosis, and delay in initiating treatment with a drug that is toxic and only variably effective. Mortality is related to the underlying co-morbid condition and reflects the high degree of illness in these patients [2].

References

1. Gefter WB, Weingrad TR, Epstein DM, *et al.* "Semi-invasive" pulmonary aspergillosis: a new look at the spectrum of Aspergillus infections of the lung. Radiology 1981; 140: 313-21.
2. Binder RE, Faling LJ, Pugatch RD, *et al.* Chronic necrotizing pulmonary aspergillosis: a discrete clinical entity. Medicine 1982; 61: 109-24.
3. Saraceno JL, Phelps DT, Ferro TJ, *et al.* Chronic necrotizing pulmonary aspergillosis: an approach to management. Chest 1997; 112: 541-8.
4. Finegold SM, Will D, Murray JF. Aspergillosis, review and report of twelve cases. Am J Med 1959; 27: 463-82.
5. Hinson KFW, Moon AJ, Plummer NS. Broncho-pulmonary aspergillosis, a review and a report of eight new cases. Thorax 1952; 7: 317-33.
6. Rosenberg M, Patterson R, Minezer R *et al.* Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Ann Intern Med 1977; 86: 405-14.
7. Rohatgi PK, Rohatgi NB. Clinical spectrum of pulmonary aspergillosis. South Med J 1984; 77: 1291-301.
8. Stanley MW, Davies S, Deike M. Pulmonary aspergillosis: an unusual cytologic presentation. Diagnostic Cytopathology 1992; 8(6): 585-7.
9. Yousem SA. The histological spectrum of chronic necrotizing forms of pulmonary aspergillosis. Human Pathology 1997; 28(6): 650-6.
10. Caras WE, Pluss JL. Chronic necrotizing pulmonary aspergillosis: pathologic outcome after itraconazole

therapy. Mayo Clinic Proceedings 1996; 71: 25-30.
11. Bennet MR, Weinbaum DL, Fiehler PC. Chronic necrotizing pulmonary aspergillosis treated by endobronchial amphotericin B. South Med J 1990; 83: 829-32.
12. Dupont B. Itraconazole therapy in aspergillosis: study in 49 patients. J Am Acad Dermatol 1990; 23: 607-14.
13. Soltanzadeh H, Wychulis AR, Sadr R, *et al.* Surgical treatment of pulmonary aspergilloma. Ann Surg 1977; 186: 13-6.
14. Hamamoto T, Watanabe K, Ikemoto H. Endobronchial miconazole for pulmonary aspergilloma. Ann Intern Med 1983; 98: 1030.
15. Varkey B, Rose HD. Pulmonary aspergilloma. Sabouraudia 1971; 9: 30-5.

慢性壞死性肺麴菌病—病例報告

洪保龍　夏德椿　杭良文　林智一* 楊　蕙

慢性壞死性肺麴菌病又稱為半侵入性肺麴菌症，是一由麴菌屬所造成的罕見肺部感染且通常發生於免疫缺乏患者身上。在此我們報告一位38歲男性患者，以呼吸困難，發燒，貧血及血小板缺乏症表現來院。經骨髓檢查證實為急性白血病之後，他開始接受化學治療。化學治療後發生嗜中性顆粒細胞減少性發燒，因此他接受廣效性抗生素治療。但由於持續的嗜中性顆粒細胞減少性發燒，因此加上抗黴菌藥物。此時病患胸部 X 光片顯示雙側多發性結節病兆。氣管鏡檢查並未得到確診，因此建議病患接受進一步胸廓切開術檢查。後來病理報告證實為慢性壞死性肺麴菌病。診斷慢性壞死性肺麴菌病，須靠臨床上的高度警覺性，並且須小心的排除肺結核及其他厭氧性感染等。治療上以抗黴菌藥物為主，若是內科療法失敗則可考慮外科手術治療。***(胸腔醫學2002; 17: 290-296)***

關鍵詞：慢性壞死性肺麴菌病，半侵入性肺麴菌症，麴菌病

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Vocal Cord Dysfunction Mimicking Asthma —A Case Report

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Vocal cord dysfunction (VCD) is a respiratory condition characterized by an adduction of the vocal cords, with a resultant airflow limitation at the level of the larynx. The previously reported cases with VCD have been predominantly young women. We herein present an uncommon, elderly case of VCD. This 75-year-old male had been suffering from intermittent inspiratory difficulty and chest discomfort for about 6 years. He had been diagnosed as having asthma for 3 years. Since diagnosis, he has had repeated exacerbations despite aggressive therapy that included corticosteroids, theophylline, and inhaled bronchodilators. However, in the current evaluation, a methacholine inhalational challenge revealed a negative result. The spirometry indicated remarkable flattened inspiratory loops on the flow volume curve while he was experiencing acute symptoms aggravated by an exercise test. Direct visualization, by bronchoscopy, of paradoxical adductive vocal cords movement in the inspiratory phase during a symptomatic period further confirmed the diagnosis. After undergoing maneuvers directed at laryngeal relaxation, and receiving anxiolytic agents from the psychiatrist, he has demonstrated a significantly improved quality of life. ***(Thorac Med 2002; 17: 297-302)***

Key words: asthma, flow volume curve, vocal cord dysfunction

Introduction

Vocal cord dysfunction (VCD) is a symptomatic functional disorder characterized by the paradoxical adduction of the vocal cords during the inspiratory phase of the respiratory cycle in the absence of organic disease. Its clinical characteristics are similar to other acute or chronic respiratory disorders, and usually masquerade as severe asthma unresponsive to standard therapy. It is crucial to identify such patients and treat them properly because a significantly improved quality of life can be gained. Failure to diagnose VCD may lead to unnecessarily escalating therapies and the development of related complications, such as iatrogenic Cushing's syndrome or tracheostomy. Herein, we report a rare elderly male patient with VCD, and discuss the clinical features, diagnostic methods, and management of this disease.

Case Presentation

A 75-year-old retired male soldier had no history of cardiovascular disease or diabetes mellitus. He also denied the habit of smoking, and any drug or food allergy. He had been in good health until 1994, when his voice quality changed. However, he did not pay attention to it.

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In 1995, he began to experience difficulty in breathing and chest discomfort. Intermittent episodes of dyspnea with wheezing occurred predominantly at rest rather than on effort. Between episodes, he was noted to be healthy. He had visited several clinics, and the asthma-like symptoms persisted despite treatment. In 1996, he was hospitalized because of experiencing an episode of convulsion. The hyperventilation syndrome was considered to be a contributor to his dyspnea. However, his symptoms persisted, and he was admitted again for further evaluation in 1998. During that hospitalization, the chest examination showed bilateral diffuse wheezing, and the dyspnea was partially relieved by salbutamol inhalation. Meanwhile, a coronary arteriographic examination was performed because of the frequent bouts of chest discomfort, and it disclosed no abnormality. He was tentatively diagnosed with clinical asthma. However, his wife reminded us that he seemed to have emotional problems. The psychiatrist was then consulted and the patient was diagnosed as a victim of anxious depression. After discharge, the patient was followed up irregularly at an outpatient clinic. In addition to a salbutamol easyhaler used on an as-needed basis, his asthma regimen included a fluticasone accuhaler, theophylline, and a salmeterol accuhaler. However, short bursts of oral corticosteroids were prescribed for the instances of exacerbated symptoms, and generally resulted in transient clinical improvement. Despite these therapies, the patient continued to have numerous episodes of respiratory difficulty, leading to four emergency room visits within four months in 1999.

In the two-day hospitalization due to exacerbated dyspnea and chest tightness, in September, 2000, he was afebrile and generally in mild distress, with oxygen saturation greater than 90% in room air. The physical examination on admission demonstrated predominantly inspiratory wheezing in the larynx area. Chest radiographic findings showed clear lung fields, and the blood biochemical results were within normal range. The resting pulmonary function test revealed normal expiratory flows (forced vital capacity [FVC]: 3.12[l] and 84% of predicted value; forced expiratory volume in 1 second [FEV_1]: 2.41[l] and 87% of predicted value; FEV_1/FVC: 78%). A methacholine inhalational challenge failed to demonstrate a significant fall in FEV_1 and FVC (FVC decreased 10% and FEV_1 decreased 8%). The cardiac examination was unremarkable. During this hospitalization, he spoke in a hoarse voice and experienced several abrupt episodes of dyspnea during the day. However, the wheezing was variably responsive to salbutamol inhalation. An exercise test with cycle riding was also performed. After 4 minutes of testing, he was noted to have severe respiratory distress, so simultaneous measurements of flow volume curves were done for 4 trials. The measurements revealed truncated inspiratory loops associated with a progressive reduction in the peak inspiratory flow rate (Figure 1). Bronchoscopy, performed while he was symptomatic in the absence of topical anesthesia spraying, demonstrated a complete apposition of the anterior two thirds of the vocal cords, and a small posterior orifice during the inspiratory phase (Figure 2). Having established the diagnosis, we consulted the psychiatrist for the purpose of distraction and reassurance. Finally, all asthma

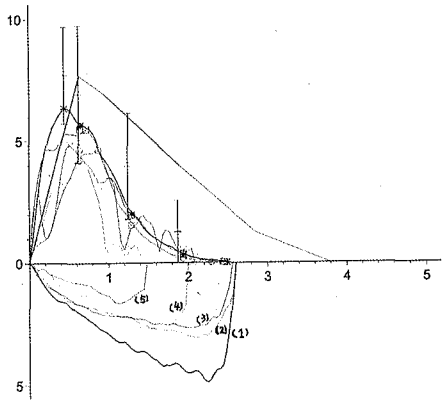

Fig. 1. Spirometry, before [trial (1)] and after an exercise test [trial (2) to trial (5), sequentially with an interval of 10 seconds], showing truncated inspiratory loops during a single session. Note the progressively declining peak inspiratory flow rate from trial (2) to trial (5).

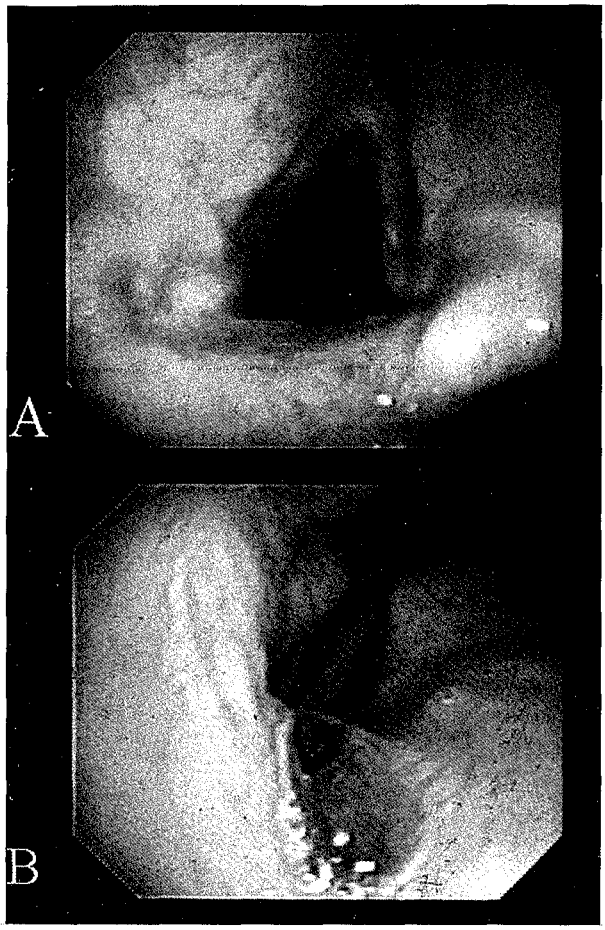

Fig. 2. Photographs of the larynx obtained by bronchoscope during a symptomatic period. Note the normal appearance of the vocal cords at expiration (A) and the complete apposition of the anterior cords, leaving a small posterior opening at inspiration (B).

medications were stopped and he was discharged with administrations of anxiolytics and antidepressants. He has had a remarkably improved quality of life since then.

Discussion

The true incidence and prevalence of VCD are unknown. In the study of Newman and associates, about 10% of referred admissions for intractable asthma had a diagnosis of VCD [1]. Another study of childhood's VCD reported by Brugman and colleagues indicated that this disorder was common in young girls (68%), and that one third of them had prior psychiatric illness [2]. Our patient presented with asthma-like features clinically. Coincidentally, he was also noted to have psychiatric problems. However, he was an older male, which is different from the other reported cases in the English medical literature.

The pathophysiology of VCD is mostly speculative. Upper respiratory tract infection may contribute to VCD because of the possible altering of the sensitivity of the normal dilated vocal cord reflexes. Gavin disclosed that coexistent psychiatric disorders, such as anxiety or depression, were common in VCD patients [3]. Our patient was a victim of anxious depression, and his symptoms could be relieved dramatically by psychotherapy. This suggests that VCD is a functional disorder, rather than organic, which has been accepted by the worldwide medical community. However, VCD sometimes can be complicated with other medical disorders, such as post-nasal drip resulting from rhinosinusitis [4]. Occasionally, VCD may develop in patients with neurologic disease, including amyotropic lateral sclerosis, multiple sclerosis, encephalitis, myasthenia gravis, and movement disorder [5]. Although our patient had an episode of a suspected seizure attack (or just a breathlessness-related twitch), none of the above neurologic diseases were identified.

The common symptoms of VCD include cough, wheeze, stridor, dyspnea at rest, hoarseness, a choking sensation, dysphonia, and chest pain. Symptoms are episodic in nature and may be provoked by emotional factors, physical exertion, inhaled irritants, and respiratory tract infection. During an acute episode, the clinical picture resembles an asthma attack. However, unlike asthma, an episode of VCD often consists of an abrupt onset followed by rapid resolution. Several clues suggestive of VCD have been described, including, 1) patients showing little anxiety about the severity of the clinical manifestation, 2) some patients flexing their necks while symptomatic, 3) symptoms are relieved when the patients are unattended, speaking, or sleeping. and 4), localized wheezing or stridor in the larynx area,

with a diminution toward the peripheral lung fields [6]. All clinicians should be alert to distinguishing VCD from refractory asthma by using the above specific clinical manifestations, or to identifying other possible coexistent obstructive airway disease [7].

The diagnosis of VCD requires the exclusion of organic causes of upper airway obstruction, such as congenital airway defects, foreign body aspiration, neoplasm, inflammatory and infectious processes, and vocal cord paralysis. The arterial blood gas analysis and chest radiography provide little help in the diagnosis of VCD because the results are mostly unremarkable. Computerized tomographic scans of the chest are also not useful except for evaluating a possible anatomic disorder of the upper airway. Blood laboratory evaluations are not imperative, but helpful in differentiating VCD from acute attacks of asthma (eosinophilia).

Spirometry may define the presence of extrathoracic airflow obstruction (truncated inspiratory loop) in patients with VCD. However, variability between trials is common, and spirometric results are often normal between episodes. If VCD is highly suspected and the baseline spirometry is nondiagnostic, broncho-provocation techniques with either pharmacologic agents (methacholine or histamine) or an exercise test will serve to identify abnormal vocal cord motion and spirometric abnormality consistent with VCD.

Direct visualization by bronchoscopy of the paradoxical vocal cords movement during a symptomatic period is the standard of diagnosis for VCD. Ideally, upper airway anesthesia should be avoided before a procedure because the dilatory reflex of the vocal cords is likely to be abolished [8]. The classical appearance of the vocal cords is a complete apposition of the anterior cords and a small posterior opening with tidal breathing or maximal inspiratory maneuver [6,9]. Patients are unable to produce such paradoxical movement volitionally.

During the acute state, and until the diagnosis is confirmed, patients suspected of having VCD should be treated as if they had an asthma exacerbation. Several maneuvers [10], such as reassurance, distraction, speech, extension of the neck, and relaxing the neck and shoulder muscles, may relieve symptoms in the acute setting. A mixture of helium (70%) and oxygen (30%) has been reported to be effective for relieving symptoms [11]. The lower density of the mixture generates less turbulence across the vocal cords, and relieves the perception of dyspnea. Continuous positive airway pressure has also been described as being effective, and is based on the hypothesis of stenting the glottic orifice with positive airway pressure [12].

Long-term treatments include speech therapy [13] and psychological counseling. The goal of speech therapy is to direct the patient's attention away from the larynx. Patients are taught how to control their breathing pattern without constricting the larynx, and to focus on exhalation rather than inspiration. The role of psychiatric evaluation with anxiolytic medication and relaxation techniques is also important. In some patients, biofeedback and hypnosis have been successful [14]. For extremely intractable cases, an injection of botulinum toxin into the vocal cords has been reported [15].

The clinical presentations of VCD are highly variable, and diagnosis can be easily missed. Considerable morbidity can be avoided with appropriate diagnosis and therapies. We urge that all clinicians with patients with asthma-like symptoms who fail to respond to asthma therapy evaluated them for underlying VCD.

Reference

1. Newman KB, Mason UG, Schmaling KB. Clinical features of vocal card dysfunction. Am J Respir Crit Care Med 1995; 152: 1382-6.
2. Brugman SM, Howell JH, Rosenberg DM, *et al.* The spectrum of pediatric vocal cord dysfunction. Am J Respir Crit Care Med 1994; 149: A353.
3. Gavin L, Wamboldt M, Brugman S, *et al.* Psychological

and family characteristics of adolescents with vocal cord dysfunction. J Asthma 1998; 35: 407-17.
4. Irwin R, Pratter M, Holland P, *et al.* Post nasal drips causes cough and is associated with reversible upper airway obstruction. Chest 1984; 85: 346-52.
5. Hanson DG. Neuromuscular disorders of the larynx. Otolaryngol Clin North Am 1991; 24: 1035-51.
6. Francis J, Damien S, Peter S. Vocal cord dysfunction. Clin Pulm Med 2000; 7(3): 111-9.
7. O'Connell MA, Sklarew PR, Goodman DL. Spectrum of paradoxical vocal cord motion in ambulatory patients. Ann Allergy Asthma Immunol 1995; 74: 342-4.
8. Liistro G, Stansescu DC, Veriter C, *et al.* Upper airway anesthesia induces airflow limitation in awake humans. Am Rev Respir Dis 1992; 146: 581-5.
9. Leonard BB, Robert CS. Vocal cord dysfunction – A practical approach to diagnosis. J Respi Dis 2001; 22(2): 93-103.
10. Kattan M, Ben-Zvi Z. Stridor caused by vocal cord malfunction associated with emotional factors. Clin Pediatr (phila) 1985; 24: 158-60.
11. Reisner C, Borish L. Heliox therapy for acute vocal cord dysfunction. Chest 1995 ; 108: 1477.
12. Todisco T, Eslami A, Baglioni S, *et al.* Inspiratory vocal cord dysfunction (VCD) in myasthenia gravis : efficacy of n-CPAP treatment. Eur Respir J 1997; 10: 150S.
13. Martin RJ, Blager FB, Gay ML, *et al.* Paradoxic vocal cord motion in presumed asthmatics. Semin Respir Med 1987; 8: 332-7.
14. Smith MS. Acute psychogenic stridor in an adolescent athlete treated with hypnosis. Pediatrics 1983; 72: 247-8.
15. Grillone GA, Blitzer A, Brin MF, *et al.* Treatment of adductor laryngeal breathing dystonia with botulinum toxin type A. Laryngoscope 1994 (suppl 1, pt1); 104: 30-3.

似氣喘病之聲帶功能異常—病例報告

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聲帶功能異常是指在呼吸時，聲帶不正常地內收而導致氣流在喉部受阻。文獻上之病例大都為年輕女性，而且常被誤診為氣喘病。我們報告一罕見之老年男性聲帶功能異常之病例。一名年齡七十五歲之病人患有間歇性呼吸困難及胸悶六年之時間，被誤診為有氣喘病三年。雖然已接受氣管擴張劑與類固醇之積極治療，其病情並無改善。在最近的一次住院當中，支氣管誘發測驗顯示陰性反應。我們利用電子腳踏車來進行運動測驗，以誘發病患症狀發作。結果發現在吸氣期，其氣流與肺容積曲線圖有明顯之截平現象。在症狀發作時，氣管鏡檢查亦發現在吸氣期，聲帶有反常之內收現象，這更進一步幫我們確定診斷。之後病患接受精神科醫師所提供之喉部放鬆技巧及投予抗焦慮藥物，其生活品質獲明顯之改善。 ***(胸腔醫學 2002; 17: 297-302)***

關鍵詞：氣喘病，氣流與肺容積曲線圖，聲帶功能異常

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Pulmonary Lymphangioleiomyomatosis—A Case Report and Review of the Literature

Kun-Ming Wu, Chin-Yin Sheu*, Chi-Yuan Tzen**, Pei-Jan Chen

Pulmonary lymphangioleiomyomatosis (LAM), a rare disorder of unknown cause that occurs almost exclusively in women of childbearing years, and is characterized by a proliferation of abnormal smooth muscle cells within the lung parenchyma and elsewhere, leading to a progressive loss of lung function and death.

We report a 44-year-old female presenting with the characteristic clinical, radiographic, and histologic features of LAM. In the examination, renal and hepatic angiomyolipoma (AML), and a unique histopathologic feature were found in this patient. The literature is reviewed for further discussion. ***(Thorac Med 2002; 17: 303-308)***

Key words: lymphangioleiomyomatosis, angiomyolipoma

Introduction

Lymphangioleiomyomatosis (LAM) is a rare disease that almost exclusively affects premenopausal women. It mainly involves the lungs, where, as its name suggests, lymphatics (*lymph*), blood vessels (*angio*), and airways are surrounded by smooth muscle (*leiomyo*) proliferation [1]. The two most common presenting symptoms of LAM are dyspnea on exertion and pneumothorax. Other common signs and symptoms include non-productive cough, hemoptysis, chylous pleural effusion, and chylous ascites [2]. We present a patient who suffered from dyspnea and recurrent pneumothorax, which was finally diagnosed as LAM, with an unusual histopathologic feature.

Case Report

A 44-year-old female was admitted because of shortness of breath lasting for six months and radiographic evidence of bilateral multiple air-cyst formation with a reticular pattern. The patient had had a left nephrectomy in 1982 for left renal tumors, but the pathological report was unknown. She has had 5 to 6 episodes of spontaneous pneumothorax since then, and underwent a bilateral blebectomy and pleurodesis more than ten years ago. She denied other systemic disease or a smoking history. There was no mental retardation or seizure history in her family. She complained about progressive dyspnea on exertion and left chest pain of about one-half year's duration.

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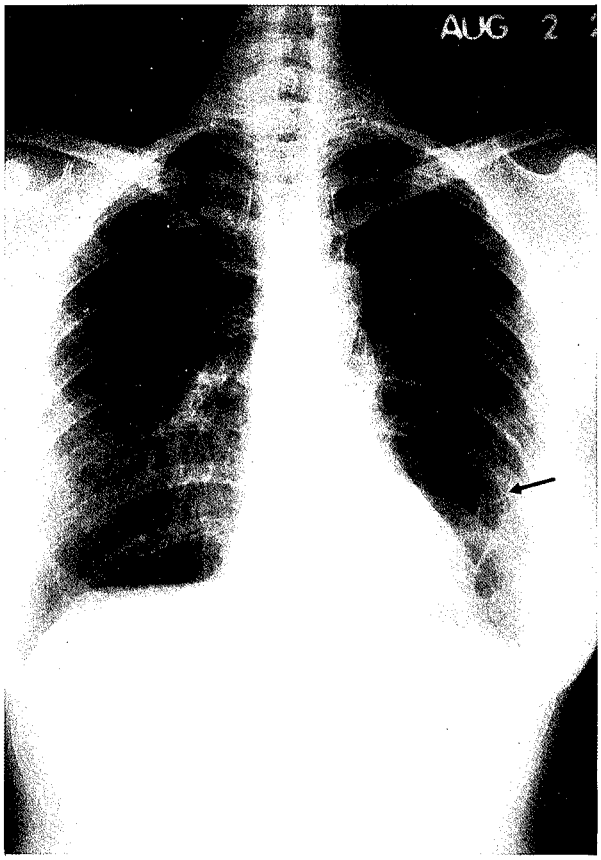

Fig. 1. Chest radiograph showing reticular opacities in both lungs, and a big air cyst (arrow) about 10 x 6 cm in size in the left lung field. There is pneumothorax in the right upper lung.

On admission, her temperature was 36.8℃, pulse rate 76/min, respiratory rate 18/min, and blood pressure 130/80mmHg. Physical examination revealed no skin lesion or clubbing of the fingers, and no hepatosplenomegaly. The breathing sound had bilateral diffusely fine crackles without wheezes. Routine laboratory data were within normal limits.

The chest radiography (Figure 1) on admission disclosed a reticular pattern with multiple cystic structures. High resolution computerized tomogaphy (HRCT) revealed multiple thin-walled cysts throughout the lung field, and right side pneumothorax; the intervening parenchyma appeared normal (Figure 2). Pulmonary function tests (PFT) showed mild obstructive and moderately restrictive defects (FEV1: 1.25L, 50% of predicted value; FVC: 1.69L, 56% of predicted

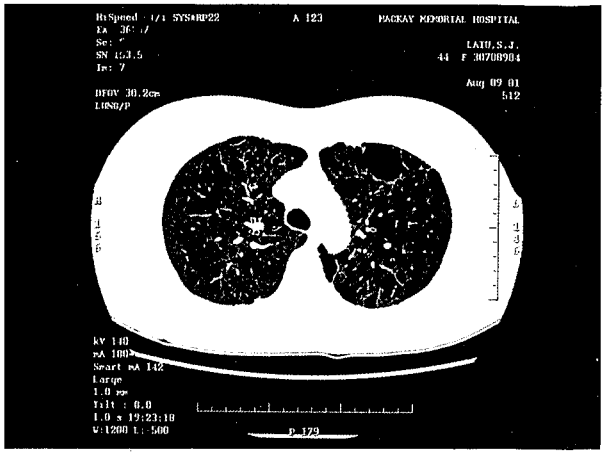

Fig. 2. HRCT showing multiple thin walled cysts evenly distributed throughout the lung fields; the intervening parenchyma appears normal.

value; FEV1/FVC: 74%; TLC: 2.58L, 58% of predicted value). The diffusing capacity for carbon monoxide (DLCO) was impaired (10.5 ml/mmHg/min, 59% of predicted value). Abdominal ultrasound showed multiple hyperechoic nodules in the liver, and abdominal computed tomographic (CT) scans revealed multiple hypodensity nodules scattered in the right lobe of the liver, with lipid content; the abdominal CT also revealed the left nephrectomy status and a residue fatty mass that was identified there, showing a partial enhancement post-contrast-enhanced. A brain CT was done to exclude any central nervous system (CNS) lesions. The findings were negative.

Based on the clinical presentation, pulmonary function tests and radiological findings, we strongly favored a high probability of lymphangioleiomyomatosis (LAM). For a definite diagnosis, an open lung biopsy was performed. Microscopically, the lungs were characterized by cystic air spaces and a nodular proliferation of abnormal smooth muscle cells (LAM cells) (Figure 3). They stained positively for vimentin, desmin, α- smooth muscle actin and the monoclonal antibody HMB 45 (Figure 4). Interestingly, a focus of fat component existing with the abnormal smooth muscle cells proliferation was found. With the diagnosis of

Fig. 3. Open lung biopsy showing cystic airspaces and a nodular proliferation of abnormal smooth muscle cells.

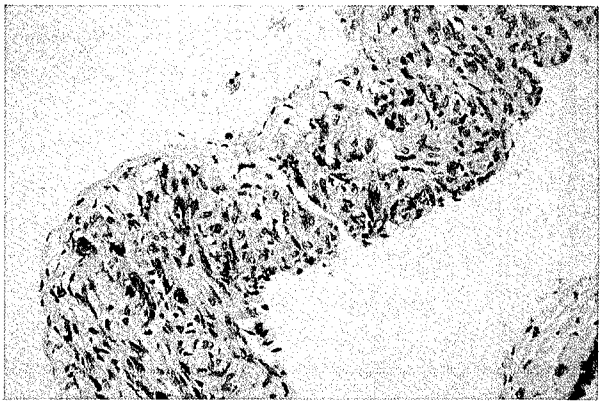

Fig. 4. HMB-45 staining of a specimen.

LAM, the patient was treated with medroxyprogesterone 10mg daily, and was discharged. She received regular follow-up at the outpatient department, after discharge with a stable clinical course.

Discussion

The reported prevalence of LAM is around one per million in the United Kingdom, France, and the United States [1]. LAM affects primarily young women of childbearing age, with an average age in the fourth decade; it is rare in women after menopause [3]. Recently, however, LAM in a phenotypic and genotypic male was reported [4].

Pulmonary LAM can occur as part of the tuberous sclerosis complex (TSC). TSC, an autosomal dominant disorder, is characterized by hamartomas in one or many organs, particularly in the skin, central nervous system, retina, and kidneys [5]. The incidence of pulmonary involvement in TSC estimates are <0.1 to 2.3% [2]. Histologically, pulmonary TSC is identical to pulmonary LAM [5]. The striking similarities between the two entities have led many to believe that LAM is a *forme fruste* of TSC [6]. TSC should be suspected in all patients with the diagnosis of LAM [5]. We excluded the possibility of TSC in our patient because she was mentally healthy, with no history of seizures, a negative brain CT, no classic features such as skin lesions [1,7], and no family history of TLC.

LAM is a multisystem disorder that frequently involves other organs, such as the kidneys, retroperitoneal lymph nodes, liver, uterus, and pancreas, in addition to the lungs. Renal angiomyolipoma (AML) is often seen in patients with LAM. In five recent case series, renal AML was present in 33% to 60% patients with LAM [8-12]. Renal AML usually have no symptoms, but they may be associated with flank pain, hematuria, or a palpable mass [2]. Renal AML, like LAM, also demonstrates immune-oreactivity with HMB-45 [3]. Our patient had a left nephrectomy for a renal tumor twenty years ago, due to a palpable mass. She had no hematuria or flank pain, and the renal function was normal. A left residue fatty mass compatible with AML was identified in the abdominal CT of our patient. This suggested that she had received a left nephrectomy owing to renal AML.

In the series by Avila *et al*, hepatic AML was found in only 3 of 80 (4%) patients [8]. Our patient, though with no pathological confirmation, had fatty hepatic lesions consistent with AML. This is rare in patients with LAM.

Lung function tests in patients with LAM show airflow obstruction, and decreased DLCO is the most frequent abnormality [3,14]. Restrictive lung defects are sometimes seen, but usually in combination with airflow obstruction, and often as the result of pleural effusion, pleurectomy, or thoracotomy [15-16]. Our patient had undergone

a bilateral blebectomy and pleurodesis which may explain the restrictive abnormalities in addition to the airflow obstruction and decreased DLCO.

The striking histopathological finding in our patient was the coexisting of the abnormal smooth muscle cells proliferation and a fat component in a nodule. Pathologically, this feature resembles that of angiomyolipoma (AML), but lacks the classic *angio* manifestation, and is found only occaisionally. There have been only four reported cases of pulmonary AML, and none are related to LAM [17-20].

Hormonal manipulations, such as progesterone, oophorectomy, tamoxifen, and gonadotropin-releasing hormone (GnRH) agonists, have been used in an effort to prevent the progressive lung destruction. Progesterone can be given by intramuscular injection or in tablet form. Side effects include tenderness at the injection site, decreased libido, weight gain, mood swings, headache, and fatigue. Long term negative effects on bone density, serum lipoproteins, and atherosclerosis have been reported [3]. None of above side effects occurred in our patient. Despite hormonal therapy, a progressive deterioration of the pulmonary function occurs. In 1996, Boehler et al [21] discussed lung transplantation for LAM. Survival figures were similar to those in other diseases.

Earlier reports have described a poor prognosis, with death from respiratory failure coming after 10 years of symptoms. Recent series have demonstrated improved survival, with the probability of being alive at 91% after 5 years, 79% after 10 years, and 71% after 15 years of disease duration [14].

In conclusion, LAM should be suspected in premenopausal women presenting with dyspnea, recurrent pneumothorax, and typical radiological features. With improved understanding of the natural history as well as the genetic, molecular, and cellular biology of LAM, we hope new therapies will soon emerge.

References

1. Johnson S. Lymphangioleiomyomatosis: clinical features, management and basic mechanisms. Thorax 1999; 54: 254-64.
2. Sullivan E. Lymphangioleiomyomatosis- a review. Chest 1998;114:1689-703.
3. Kelly J, Moss J. Lymphangioleiomyomatosis. Am J Med Sci 2001; 321 (1):17-25.
4. Aubry M-C, Myers JL, Rye JH, *et al.* Pulmonary lymphangioleiomyomatosis in a man. Am J Respir Crit Care Med 2000; 162: 749-52.
5. Castro M, Shepherd CW, Gomez MR, *et al.* Pulmonary Tuberous Sclerosis. Chest 1995; 107:189-95.
6. Jao J, Gilbert S, Messer R. Lymphangiomyoma and tuberous sclerosis. Cancer 1972; 25: 1188-92.
7. Roach ES, Smith M, Huttenlocher P, *et al.* Report of the diagnostic criteria committee of the National Tuberous Sclerosis Association. J Child Neurol 1992; 7: 221-4.
8. Avila NA, Kelly JA, Chu SC, *et al.* Lymphangioleiomyomatosis: Abdominopelvic CT and US Findings. Radiology 2000; 216: 147-53.
9. Kerr LA, Blute ML, Ryu JH, *et al.* Renal angiomyolipoma in association with pulmonary lymphangioleiomyomatosis: forme fruste of tuberous sclerosis? Urology 1993; 41: 440-4.
10. Maziak DE, Kesten S, Rappaport DC, *et al.* Extrathoracic angiomyolipomas in lymphangioleiomyomatosis. Eur Respir J 1996; 9: 402-5.
11. Bernstein SM, Newell JD Jr, Adamczyk D, *et al.* How common are renal angiomyolipomas in patients with pulmonary lymphangiomyomatosis? Am J Respir Crit Care Med 1995; 152: 2138-43.
12. Chu SC, Horiba K, Usuki J, *et al.* Comprehensive evaluation of 35 patients with lymphangioleiomyomatosis. Chest 1999; 115: 1041-52.
13. Avila NA, Kelly JA, Chu SC, *et al.* Lymphangioleiomyomatosis: Abdominopelvic CT and US Findings. Radiology 2000; 216: 147-53.
14. Urban T, Lazor R, Lacronique J, *et al.* Pulmonary Lymphangioleiomyomatosis- a study of 69 patients. Medicine 1999; 78: 321-32.
15. Kitaichi M, Nishimura K, Itoh H, *et al.* Pulmonary lymphangiomyomatosis; a report of 46 patients including a clinicopathologic study of prognostic factors. Am J

Respir Crit Care Med 1995; 151: 527-33.
16. Burger CD, Hyatt RE, Staats BA. Pulmonary mechanics in lymphangioleiomyomatosis. Am Rev Repir Dis 1991; 143: 1030-3.
17. Guinee DG, Thornberry DS, Azumi N, *et al.* Unique pulmonary presentation of an angiomyolipoma. Analysis of clinical, radiographic, and histopathologic features. Am J Surg Pathol 1995; 19(4): 476-80.
18. Ito M, Sugamura Y, Ikari H *et al.* Angiomyolipoma of the lung. Arch of Pathol and Lab Med 1998; 122(11):1023-5.
19. Wu K, Tazelaar HD. Pulmonary lymphangiomyomatosis and multifocal micronodular pneumocyte hyperplasia associated with tuberous sclerosis. Hum Pathol 1999; 30(10): 1266-8.
20. Gloeckner-Hofmann K, Krismann M, Feller AC. Angimyolipoma of the lung. Pathology 2000; 21(3): 260-3.
21. Boehler A, Speich R, Russi EW, *et al.* Lung transplantation for lymphangioleiomyomatosis. N Engl J Med 1996; 335: 1275-80.

肺淋巴管平滑肌增生症—病例報告及文獻回顧

吳崑明　許清寅*　曾歧元**　陳培然

肺淋巴管平滑肌增生症是一種原因不明且罕見的疾病，幾乎都發生在停經前的婦女身上。其特徵為肺實質異常平滑肌細胞增生，造成肺功能逐漸惡化乃至死亡。肺外的病灶也可見於此病患者。

我們報告一位四十四歲的女性，其臨床表徵、放射學檢查和組織切片皆符合本病。同時在病人身上也發現腎臟及肝臟有血管肌肉脂肪瘤。此外，本病患的病理組織切片亦有一獨特的發現。我們回顧了相關的文獻並予以探討。 ***(胸腔醫學2002; 17: 303-308)***

關鍵詞：肺淋巴管平滑肌增生症，血管肌肉脂肪瘤

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