The Clinical Uses of Video-assisted Mediastinoscopy – A Preliminary Report

Chih-Shiun Shih, Der-Chuen Shiah*, Chih-Ching Yen*

Liang-Wen Hang*, Der-Yuan Wang*, Nan-Yung Hsu

Our experience with cervical video-assisted mediastinoscopy in 22 cases during the past 2 years is reported. Clinically, all 22 patients had the findings of paratracheal lymphadenopathy on roentgenography and computerized tomography scanning of the chest. The equipment included a videocamera that was connected to a 160 mm mediastinoscope and a TV monitor, a suction-coagulation dissector, a puncture needle connected to suction, and a biopsy forceps. Biopsy was adequately performed piece-by-piece on the tissue (tumor or lymph node) found by mediastinoscopy. Postoperative pathologic studies showed the existence of a hyperplastic change of the lymph nodes in 10 patients, metastatic carcinoma in 4, tuberculosis lymphadenitis in 2, and sarcoidosis in 6. None of the patients had any surgical complications except for one patient with a controllable bleeder. In summary, video technologies can be very helpful when performing mediastinoscopy, leading to an enlarged surgical field, improved operative performance, and an ergonomic position for the surgeon, in addition to providing a good aid for multiple teaching. ***(Thorac Med 2000; 15: 110-114)***

Key words: video-assisted mediastinoscopy

Introduction

Since its introduction by Carlens in 1959 [1], mediastinoscopy has become the standard surgical procedure providing access to the mediastinum, and allowing inspection, palpation, and biopsy of mediastinal tissues for the diagnosis of thoracic disease and the staging of lung cancer [2-4]. Although the efficacy of mediastinoscopy in the preoperative staging of bronchogenic carcinoma is well-established, with a procedural sensitivity greater than 90% and a specificity of 100% [3-5], its shortcomings include its being overly invasive and having a comparatively high rate of morbidity (such as wound infection, mediastinitis, pneumothorax, injury to the left recurrent laryngeal nerve, esophageal perforation, and venous or arterial hemorrhage);

Division of Chest Surgery, Department of Surgery; *Division of Chest Medicine, Department of Internal Medicine China Medical College Hospital, Taichung, Taiwan, R.O.C.
Address reprint requests to: Dr. Nan-Yung Hsu, No 2, Yuh-Der Road, Taichung, Taiwan, R.O.C.

occasional deaths have been reported [4,6]. With advances in endoscopic surgery and instrumentation, this surgical approach has progressed to video-assisted mediastinoscopy [7-9]. We describe our preliminary results in 22 cases involving patients with paratracheal lymphadenopathy who were treated by video-assisted mediastinoscopic surgery.

Materials and Methods

Subjects

From January 1998 through December 1999, 22 patients with paratracheal lymphadenopathy noted by computerized tomography (CT) scanning of the chest were treated with cervical video-assisted mediastinoscopic surgery in the Division of Chest Surgery at China Medical College Hospital. The surgical indications of these 22 patients were as follows: among 12 patients with non-small cell lung cancer, 10 patients were suspected of having N2 disease, and two of having N3 disease; 7 patients had bilateral hilar lymphadenopathy and paratracheal lymphadenopathy identified by chest roentgenography and CT scanning, and sarcoidosis was suspected clinically; two patients had chest roentgenograms, which revealed a widening mediastinum, and subsequent CT scanning of the chest showed enlargement of paratracheal lymphadenopathy; the remaining patient with acute lymphoblastic leukemia had a fever of unknown origin for 2 weeks, and paratracheal lymphadenopathy was noted after a CT scanning of the chest was performed.

Video-assisted mediastinoscopic surgery

Under general anesthesia and tracheal intubation with a single lumen tube, the patient was placed in a supine position. A 3-cm transverse lower neck incision, known as the Carlens' incision, was performed. A 160 mm video-assisted mediastinoscope (Richard Wolf, Wien, Austria) was inserted after the pretracheal fascia was incised, and a finger was slid through this incision down into the mediastinum between the trachea and the sternum and behind the right innominate artery and vein. After the tissue (tumor or lymph node) to be biopsied was identified, a suction-coagulation dissector was inserted through the mediastinoscope for dissecting away the surrounding fat and lymph node capsule. It was necessary to puncture the tissue with a needle connected to suction before the tissue was biopsied, because some vessels, especially veins, looked like lymph nodes, which were black or dark blue due to anthracosis. After the biopsy procedure was finished, the bleeding point could be coagulated with the suction-coagulation dissector or compressed with a gauze pad for 1 or 2 minutes. Then, the platysma and the subcutaneous tissue were approximated in one layer using 3-0 absorbable material, and 4-0 absorbable material was used for intradermic suturing.

Results

In all, 22 consecutive patients have received this video-assisted mediastinoscopy procedure during the past 2 years; twenty were male and the other two were female. Their ages were distributed from 24 to 67 years with the mean age at 45.7 years.

All 10 patients who were suspected of having N2 diseases had reactive lymphoid hyperplasia, and two patients who were suspected of having N3 disease had a proven metastatic adenocarcinoma. Among the 7 patients with bilateral hilar lymphadenopathy, 6 patients had noncaseating granulomas and 1 had a caseating granuloma with positive acid-fast stain. The pathology of each of the 2 patients with a widening mediastinum revealed small cell lung cancer. The patient with acute lymphoblastic leukemia had a caseating granuloma and positive acid-fast stain. None of

the patients had any surgical complications, except one patient who had a controllable bleeder.

Discussion

In general, the surgical indications for video-assisted mediastinoscopic surgery are similar to those for conventional mediastinoscopic surgery. As a very valuable surgical assessment, mediastinoscopy has been used in all cases prior to surgery for patients with non-small cell lung cancer, but in most centers it is now also used selectively to evaluate the mediastinum when CT of the chest suggests the presence of enlarged mediastinal nodes, as in this study. During surgery, all accessible nodal stations, including the pretracheal, paratracheal, subcarinal, and the right and left main stem bronchi, must be explored. In this preliminary study, only the pretracheal and paratracheal lymph nodes for the patients with non-small cell lung cancer were explored. We hope to be able to explore all accessible nodal stations after more experience. As for those patients with findings of enlarged paratracheal lymph nodes on CT scanning, video-assisted mediastinoscopy can help to perform biopsies more easily, resulting in a definitive diagnosis without difficulty.

Technically, the advantages of video-assisted mediastinoscopic surgery include: (1) enlarging the surgical field between the innominate artery and the trachea, and identifying the surrounding anatomy more clearly, which may help in performing biopsies more safely and easily (Figure); (2) allowing the surgeon to assume an ergonomic position to accomplish the procedure, which may result in a greater degree of comfort and, furthermore, may lessen surgical complications; and (3) providing a good aid as a multiple teaching tool, which may make the learning curve more efficient. Although low rates of morbidity and mortality in conventional mediastinoscopic surgery without a video-assisted technique were observed in previously reported series, severe complications have been reported, including aortic laceration, cardiac arrest, pulmonary artery laceration, and an esophageal perforation [2,4,10]. In this preliminary experience, there seems to be no significant differences, including surgical incision, operative time, operative procedure, and postoperative pain, between video-assisted mediastinoscopy and conventional mediastinoscopy, except for operative cost.

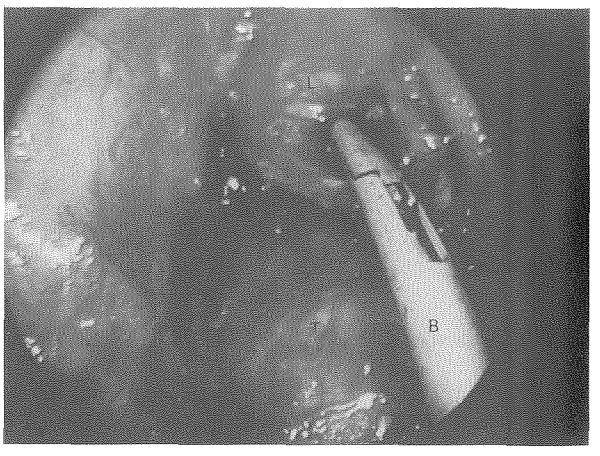


Fig. Under the amplified surgical field of the video-assisted mediastinoscope, the cartilage ring of the trachea (T) and the paratracheal lymph node (L) can be identified without difficulty. (B: biopsy forceps)

To date, no large series of experiences with video-assisted mediastinoscopic surgery have been reported which prove that it is better than conventional mediastinoscopic surgery. However, we believe that surgeons will be encouraged to perform mediastinoscopic biopsies enthusiastically using this modern, advanced technique because of its advantages in improving visualization, dissection, and biopsy maneuvers.

Recently, Roviaro and colleagues have reported that video-assisted thoracoscopic surgery can be a new and useful approach in the management of mediastinal disease, either in diagnosis or in treatment [11]. We agree that videothoracoscopy can offer an alternative that

allows wide exposure of both the chest and the mediastinum, making possible the obtaining of large samples (lung tissues and/or mediastinal samples) and ensuring a precise diagnosis in cases of systemic lymphatic and sarcoidosis diseases. There are still some areas with limitations for using video-assisted mediastinoscopy, such as the lymph nodes located at the A-P window, the anterior mediastinum, periazygous, and deep subcarina, in which we need VATS for more adequate exposures [12]. However, we believe that when the disease is totally confined to the mediastinum, videomediastinoscopy can obtain adequate samples using a small incision wound at the suprasternal site, and not three or four operative ports in addition to a 4- to 6-cm incision for a utility thoracotomy performed by videothoracoscopy.

References

1.Carlens EL. Mediastinoscopy: a method for inspection and tissue biopsy in the superior mediastinum. Dis Chest 1959; 36: 343-52.

2.Luke WP, Pearson FG, Todd TPU, et al. Prospective evaluation of mediastinoscopy for assessment of carcinoma of the lung. J Thorac Cardiovasc Surg 1986; 91: 53-6.

3.Van Schil PEY, Van Hee RHGG, Schools ELG. The value of mediastinoscopy in preoperative staging of bronchogenic carcinoma. J Thorac Cardiovasc Surg 1989; 97: 240-4.

4.Hammoud ZT, Anderson RC, Meyers BF, et al. The current role of mediastinoscopy in the evaluation of thoracic disease. J Thorac Cardiovasc Surg 1999; 118: 894-9.

5.Gdeedo A, Van Schill P, Corthouts B, et al. Prospective evaluation of computed tomography and mediastinoscopy in mediastinal lymph node staging. Eur Respir J 1997; 10: 1547-51.

6.Kirschner PA. Cervical mediastinoscopy. Chest Surg Clin North Am 1996; 6: 1-20.

7.Sortini A, Bresadola V, Navarra G, et al. Video-assisted mediastinoscopy: clinical uses. G Chir 1995; 16(5): 251-2.

8.Sortini A, Navarra G, Santini M, et al. Video-assisted mediastinoscopy. A new application of television technology in surgery. Minerva Chir 1994; 49(9): 803-5.

9.Hutter J, Junger W, Miller K, et al. Subxiphoidal videomediastinoscopy of diagnostic access to the anterior mediastinum. Ann Thorac Surg 1998; 66(4): 1427-8.

10.Puhakka HJ. Complications of mediastinoscopy. J Laryngol Otol 1989; 103: 312-5.

11.Raviaro G, Varoli F, Nucca O, et al. Videothoracoscopic approach to primary mediastinal pathology. Chest 2000; 117: 1179-83.

12.Landreneau RF, Hazelrigg SR, Mack MJ et al.Thoracoscopic mediastinal lymph node sampling: Useful for mediastinal lymph node stations inaccessible by cervical mediastinoscopy J Thorac Cardiovasc Surg 1993; 106(3): 554-8

視訊輔助縱膈腔鏡的臨床運用-初步報告

施志勳 夏德椿* 顏至慶* 杭良文* 王德源* 許南榮

報告最近二年來 22 例經由頸部視訊輔助縱膈腔鏡的經驗。臨床上，所有 22 例在胸部 X 光和胸部電腦斷層檢查都發現有氣管旁淋巴腺病變。使用的設備包括以視訊攝影機連接 160 毫米長的縱膈腔鏡和電視機，抽吸器和電燒剝離器，可連接吸取的探針，以及切片攝子。經由縱膈腔鏡可將組織(包括腫瘤、淋巴腺)以小塊切片摘取。手術後病理報告，包括 10 例為淋巴腺增生反應，4 例為轉移性癌症，2 例為結核性淋巴炎和 6 例類肉瘤。除了 1 例手術當中出血，並順利地加以止血後，其他病例並無併發症發生。總之，我們建議以視訊技術輔助實施縱膈腔鏡檢查手術，此乃有助於擴大手術視野，增進手術者的手術操作舒適性，也可做為手術當中的教學工具。*(胸腔醫學 2000; 15: 110-114)*

關鍵詞：視訊輔助縱膈腔鏡

中國醫藥學院附設醫院 外科部胸腔外科 內科部胸腔內科*
索取抽印本請聯絡：許南榮醫師，台中市育德路 2 號

煤礦工人的通氣功能研究

楊錫欽　林凌芝*　盧國輝*

煤礦工塵肺症(coal workers' pneumoconiosis, CWP)在臨床上會引發多種肺功能異常。為探討台灣礦工CWP患者之通氣障礙型態，本文針對98位煤礦工，依其X光表現並按照國際勞工組織所訂定的標準予以分類，計得無塵肺陰影者(category 0)25位，單純塵肺症(simple pneumoconiosis)者49位，進行性重度肺纖維化(progressive massive fibrosis, PMF)者24位。所有礦工均接受通氣功能、肺容積及氣道阻力測定。觀察的結果顯示CWP患者整體的用力肺活量(forced vital capacity, FVC)及全肺量(total lung capacity, TLC)並無異常；但一秒量(forced expiratory volume in one second, FEV_1)，一秒率(FEV_1／FVC)，及呼氣速率參數(maximal expiratory flow rate at 75% and 50% FVC, Vmax 75 與 Vmax 50)均有低下的現象。單純塵肺症患者約有一半(49%)其最大呼氣流速容積曲線為正常，43%顯現阻塞型通氣障礙，而且此一分佈狀況與X光小陰影形狀(線狀與粒狀)分類無關。用力肺活量在PMF患者才有明顯的下降(至預測值的58.1±17.3%)。氣道阻力在所有的煤礦工，包括X光無塵肺陰影者，均有上升，且其幅度隨著X光等級而加大。本文的結論是台灣CWP在肺功能上是以阻塞型通氣障礙為主要表徵，但不能排除抽煙之因素。

(胸腔醫學 2000; 15: 115-119)

關鍵詞：煤礦工塵肺症，通氣障礙，肺功能

前　言

台灣的礦業人口，以從事煤礦開採者爲最多。這一行業有所謂的煤礦工塵肺症(coal workers' pneumoconiosis)，會使肺功能受到傷害，嚴重者甚至導致殘廢[1-3]。有關台灣CWP患者之肺功能變化的數據，首見於1967年吳[4,5]之論文，其後有謝與汪等人[6,7]之肺瀰散量與閉鎖容積之研究。前者報告矽肺症患者41.8%屬拘束型通氣障礙，只有7.8%屬阻塞型：而後者報告「礦工有肺充氣過高之現象」。是以本土CWP患者通氣障礙的類型，仍有進一步澄清的必要。

病人與方法

本研究起初收集有煤礦開採工作史之礦工126位，包括在職與退休礦工。他們是近來在政府發放職災補償金的誘因下，不論有無呼吸症狀，主動前來門診要求作體檢，以求取職業病證明。每位礦工在經過病史詢問與理學檢查後，都予以用70KV的電壓照標準尺寸(35×42cm)之胸部X光大片。每張X光片至少由兩位專科醫師判讀。判讀的標準依據國際勞工組織ILO U/C所訂定的塵肺症X光攝影分類法[8]。每位礦工的X光片都將之歸屬於下列三組之一，亦即無塵肺陰影組(category 0)，單純塵肺症組(simple pneumoconiosis)與具有直徑1cm以上之大陰影的進行重度肺纖維化(progressive massive fibrosis,PMF)組。單純塵肺症患者再依其小陰影之主要形狀分爲線狀影與粒狀影型。

每一位受測者均接受通氣功能檢查與肺容積測定。在準備好後，先安靜呼吸5次，再按照口令用力吸氣到全肺量(total lung capacity,TLC)，然後用力吹氣到底。流速與容積由體積描記器(CS-828FC,Chest M.I. Inc.Japan)之電腦自動依最大吐氣流速—容積圖形計算。檢查項目包括用力肺活量(forced vital capacity, FVC)；一秒量(forced expiratory volume in one second, FEV_1)；FEV_1／FVC；最

國立台灣大學醫學院　檢驗醫學科　台灣礦工醫院內科*
索取抽印本請聯絡：楊錫欽醫師，台北市中山南路7號

表一 73位煤礦工塵肺症患者整體的通氣功能，氣道阻力及肺容積

	實際值	%預測值
FVC	2.64± 0.77L	81.5± 21.6%
FEV_1	1.78± 0.70L	75.2± 24.7%
FEV_1/FVC	67.2± 13.5%	-
PEER	4.75± 1.96 L/S	62.5± 26.4%
$Vmax_{75}$	2.90± 1.82 L/S	51.6± 28.1%
$Vmax_{50}$	1.73± 1.15 L/S	54.8± 32.2%
Raw	4.54± 1.36 cmH_2O/L/S	181.7± 76.6%
TLC	4.97± 0.92L	93.6± 18.7%
RV/TLC	44.6± 8.6%	-

大呼氣流速(peak expiratory flow rate, PEFR)；肺活量呼出 25%與 50%時之呼氣流速(Vmax75 與 Vmax50)。用以計算預測值之回歸方程式是根據本實驗室自行設計者[9]。

通氣障礙類型之認定，依據勞保塵肺症診斷標準，亦即：(1)FVC 正常，FEV_1/FVC 小於 70%者爲阻塞型；(2)FVC小於預測值80%，而FEV_1/FVC正常者爲拘束型；與(3)FVC 小於預測值 80%，而 FEV_1/FVC 小於 70%者爲混合型。

其他肺容積之測定，如 TLC 係由儀器依壓力－容積關係而求出。肺餘容積(residual volume , RV)由 TLC 減除肺活量而得。爲進一步明瞭 CWP 對氣道阻塞的影響，本研究對不同等級之患者均測量其氣道阻力(airway resistance , Raw)。

所有的數據均加以編號，再輸入電腦作統計分析。結果以 mean±SD 或百分比表示。兩組不同 X 光等級 CWP 患者，其各項肺功能參數間差異，以 Student's t test 檢定之。

結 果

原定 126 煤礦工中，有 28 位因爲在作肺功能檢查時未能配合，吹出所要求的圖形，或因肺功能資料欠缺，而不列入統計。其餘 98 位礦工的年齡在 49 到 72 歲之間，平均爲 58 歲。均爲男性，其平均身高爲 162.7±6.1cm，體重爲 61.3±10.1 公斤。有 81 位爲吸煙者，17 位爲不吸煙者，他們暴露於礦塵之工作年數平均爲 29 年。

X 光表徵歸類的結果，有 25 位礦工無任何塵肺症跡象，49 位有小陰影，屬單純塵肺症。若再依小陰影之主要形狀分，則有 28 位屬線狀影型，另 21 位屬粒狀影型。大陰影型者(PMF)則有 24 位，佔相當比例。這些罹患 CWP 之 73 位礦工整體的通氣功能，氣道阻力與肺容積的測定結果見(表一)。表中顯示若不考慮 X 光表現類型，則整體 CWP 患者 FVC 正常，FEV1/FVC 低於 70%，而各項呼氣流速參數如 FEV1，PEFR，Vmax75 等均下降。

表二 單純煤礦工塵肺症與 PMF 患者 X 光變化與通氣障礙類型之比較(n=73)

X 光變化	通氣障礙類型				
	正常	阻塞型	拘限型	混合型	Total
線狀影型	13*(46)**	11(40)	2(7)	2(7)	28(38)
粒狀影型	11(52)	10(48)	0(0)	0(0)	21(29)
PMF	3(12)	12(50)	5(21)	4(17)	24(33)
Total	27(37)	33(45)	7(10)	6(8)	73(100)

* 人數

** 括弧內數字爲百分比。

單純塵肺症對肺功能損害的程度通常比 PMF 爲輕〔10,11〕。但本研究顯示單純塵肺症之 CWP 患者仍有一半左右有通氣功能的低下(表二)，而通氣障礙類型的分析顯示，不論是線狀影或粒狀影型，80%以上都呈現阻塞型通氣障礙，純粹拘束型通氣障礙者不到 10%。即使是 PMF 患者，也有一半是呈阻塞型通氣障礙，但呈拘束型障礙者大幅升高至 27%。須注意仍有 12%的 PMF 患者其通氣功能爲正常。(表三)顯示不同 X 光等級之 CWP 患者經年齡、體型校正後通氣功能的比較。由表中可知 category 0 之礦工通氣功能正常，Raw 略爲上升；單純塵肺症患者其 Raw 與 RV/TLC 比明顯增加；至於 PMF 患者則肺容積如 FVC 開始減少，但 Raw 及 RV/TLC 比則爲所有 CWP 患者中最高者。

表三 台灣 CWP X 光類型與通氣功能之比較(n=98)

	Simple		
	Category 0 (n=25)	Pneumoconiosis (n=49)	PMF (n=24)
FVC(%p.)+	94.5 ± 10.7	90.2 ± 11.5	58.1 ± 17.3*
FEV1(%p.)	88.9 ± 14.6	83.7 ± 15.8	55.6 ± 18.2*
FEV1/FVC, %	81.3 ± 7.2	74.1 ± 14.4**	60.3 ± 16.5*
Raw(%p.)	107 ± 53	162 ± 66**	209 ± 89*
TLC(%p.)	101 ± 8	105 ± 10	88 ± 12*
RV/TLC, %	32 ± 7	41 ± 8	50 ± 7*

* 與無塵肺陰影組(category 0)或單純塵肺症相比，均有顯著之差異，P<0.05。

** 與無塵肺陰影組相比，有顯著的差異，P<0.05。

\+ %p.=預測值百分比。

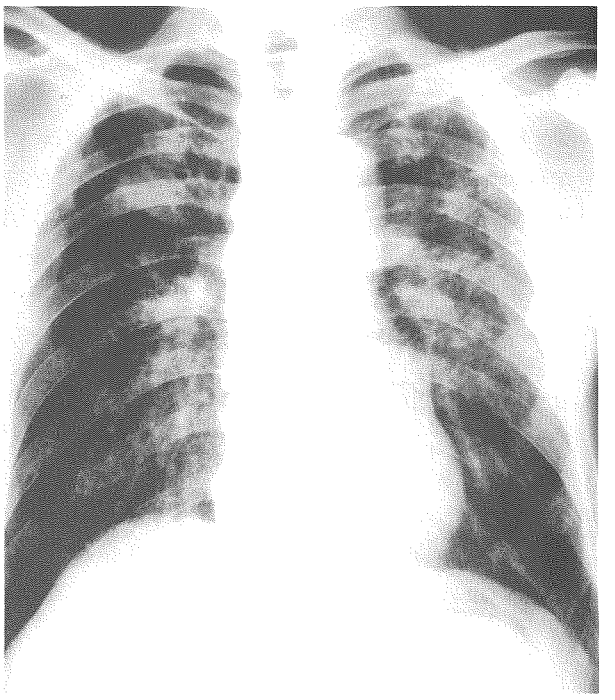
討　論

煤礦工塵肺症之起因是由於在煤礦開採過程中，礦工吸入過量的礦塵所致，礦塵的主要成分是碳粒與二氧化矽。本症在病理上的變化主要是出現煤斑(coal macule)與肺纖維化[12]。單純塵肺症的 X 光表現有不少患者是以線狀影爲主，而線狀影在胸部 X 光判讀上的意義就是代表肺纖維化。再者，嚴重的 CWP 即叫做進行性重度肺纖維化。凡此種種，投射在肺功能檢查結果的顯示上，就讓人以爲 CWP 主要是引起拘束性通氣障礙，其實這和臨床觀察是不符的。本研究顯示 CWP 患者從 category 0 到單純塵肺症即已逐漸有 RV 增加，及顯現阻塞型通氣障礙的趨勢，一直到 PMF 時，FVC 才開始下降。可見純粹拘束性通氣障礙並非 CWP 的主要表徵，而吳之報告[4]中拘束性通氣障礙之所以佔多數的原因是患者係由勞保局轉介，是要辦理傷殘鑑定的，嚴重程度偏高，其中 61%患者爲 PMF 之故。

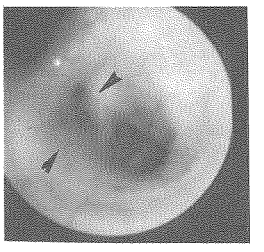
截至目前爲止，有關 CWP 對肺功能損害的研究雖多，但各個研究的結果並非一致。例如 Morgan 等人[12]報告單純塵肺症患者與無塵肺症之礦工相比，其 FVC 較低，但 FEV1 則相仿。Bates[13]等人對煤礦工的肺功能作縱剖式的追蹤，結果發現這些人每年 FEV1 下降的幅度與 FVC 一樣，Ng 等人[14]也有類似的報告。由於 FEV1 數值比 FVC 小，如此下去，自然也是造成阻塞性通氣障礙。不過，文獻上以通氣障礙類型來觀察 CWP 的報告，確實不多。本研究的結果則指出氣道阻塞確是 CWP 在影響肺功能上的一個主要表現。

CWP 之所以產生阻塞性通氣障礙之機制，一般都注重微細礦塵（大小約在 0.5μm 至 5μm 間）之阻塞於呼吸性細小支氣管(respiratory bronchioles)的變化[15]。但是礦塵顆粒有大有小，大顆粒（大小＞20μm）雖然到不了細小支氣管，但卻可能沉積於大支氣管的開口部，造成上呼吸道阻塞。本研究亦觀察到此一現象[圖一(a)及(b)]，因而對 CWP 引起氣道阻塞的原因可提供一新的解釋。

吸煙在臨床上也可以導致慢性氣道阻塞，那麼在本研究中 CWP 患者之阻塞性通氣障礙，由吸煙所扮演的角色如何？此一問題最好是由比較吸煙與不吸煙之 CWP 患者的肺功能來解決。然而台灣礦工的族群特徵之一就是他們大多數都吸煙。例如謝等人之報告[6]中，74% CWP 患者都是吸煙者，而吳之報告[4]則未提及患者的吸煙史。本研究中不吸煙之 CWP 患者人數亦過少，並不適合作這方面的分析。不過文獻上顯示即使排除吸煙的因素，CWP 患者的肺功能還是隨著 X 光等級的加重而惡化[14]，Morgan 等人[12]也認爲 CWP 患者的肺功能異常並非吸煙所能單獨解釋。



圖一(a)　男性煤礦工，工作資歷 28 年，胸部 X 光片呈現大陰影，爲 PMF category A。



圖一(b)　支氣管鏡檢顯示左上葉支氣管口碳粒沉(anthracosis)，注意管口已略有變形（箭頭）。

本文的結論是 CWP 對礦工之肺功能會造成輕、重不等的損傷，單純塵肺症一般而言雖然較輕，但亦有相當嚴重者，不能一概而論，而 CWP 基本上是一種阻塞氣道的疾病，肺纖維化主要是出現在末期。惟本研究並不能完全排除吸煙影響的因素，吸煙在本土 CWP 患者肺功能異常上的角色，有待將來進一步的研究。

參考文獻

1.Love RG, Miller BG. Longitudinal study of lung function in coal-miners. Thorax 1982; 37: 193-7.

2.Morgan WKC, Burgess DB, Lapp NL, et al. Hyperinflation of the lungs in coal miners. Thorax 1971; 26: 585-90.

3.Reichel G. Disability determination and compensation for pneumoconiosis in West Germany. Chest 1980; 78 (suppl. 2): 365-6.

4.Wu MC. Pulmonary function study in silicotics. Part 1. spirometric study. J Formosan Med Assoc 1967; 66: 240-55.

5.Wu MC. Pulmonary function study in silicotics. Part 2. arterial blood gas study. J Formosan Med Assoc 1967; 66: 393-409.

6.謝遠清、汪大衛、沈建業等：煤礦工肺塵症之肺瀰散量、血液氣體分析及通氣功能之研究。中華醫誌 1981; 28: 103-16.

7.汪大衛、謝遠清：68 位煤礦工人閉鎖容積之研究。中華醫誌 1982; 29: 430-9.

8.ILO U/C 1971 International classification of radiographs of the pneumoconioses. Med Radio Photo 1972; 48: 67-76.

9.楊錫欽：正常中國人呼吸功能之再評估：與 15 年前調查結果的比較。台灣醫誌 1993; 92: S152-9.

10.Begin R, Ostiguy G, Cantin A, et al. Lung function in silica-exposed workers. A relationship to disease severity assessed by CT scan. Chest 1988, 94: 539-45.

11.Miller BG, Jacobsen M. Dust exposure, pneumoconiosis, and mortality of coal miners. Br J Ind Med 1985; 42: 723-33.

12.Morgan WKC, Handelsman L, Kibelstis J, et al. Ventilatory capacity and lung volumes of US coal miners. Arch Environ Health 1974; 28: 183-9.

13.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.

14.Ng TP, Chan SL, Lam KP. Radiological progression and lung function in silicosis: a ten year follow up study. Br Med J 1987; 295: 164-8.

15.Hurley JF, Alexander WP, Hazledine DJ, et al. Exposure to respirable coalmine dust and incidence of progressive massive fibrosis. Br J Ind Med 1987; 44: 661-72.

A Study on the Ventilatory Function of Coal Miners

Shieh-Ching Yang, Lin-Chih Lin*, Kok-Wee Low*

Clinically, coal workers' pneumoconiosis (CWP) may result in several pulmonary functional abnormalities. In order to further understand the patterns of ventilatory defect of patients with CWP in Taiwan, this study collected 98 coal miners including 25 with X-ray category 0, 49 with simple pneumoconiosis and 24 with progressive massive fibrosis (PMF)。Tests were conducted to determine their ventilatory function, lung volumes and airway resistance (Raw). Our data revealed that patients with CWP demonstrated a normal FVC (forced vital capcity) and a normal TLC (total lung capacity). However, expiratory flow parameters such as FEV1 (forced expiratory volume in 1s) and FEV1/FVC were decreased. The maximal expiratory flow-volume curves in approximately half (49%) of the patients with simple pneumoconiosis were normal, and were of a obstructive pattern in additional 43% of them. The types of ventilatory defect did not vary with shapes of small opacities in simple pneumoconiosis. Remarkable reduction in FVC and TLC were observed mainly in patients with PMF. However, Raw was consistently elevated in all groups, even in patients with category 0 of CWP. We conclude that CWP in Taiwan, from functional point of view, is primarily manifested with an obstructive ventilatory defect.
(Thorac Med 2000; 15: 115-119)

Key words: coal workers' pneumoconiosis, ventilatory defect, pulmonary function.

Address reprints requests to: Dr. Shieh-Ching Yang, Department of Laboratory Medicine, College of Medicine, National Taiwan University, 7, Chung-Shan South Road, Taipei, Taiwan.

Comparison of Orlowski and APACHE II Scores as Predictors of Outcome in Near-drowning Patients

Jiann-Der Lee, Gwan-Han Shen, Chun-Ming Shih, Chi-Der Chiang

Background

The Orlowski and APACHE II scores have been used to quantify the severity of illness in various groups of patients. The purpose of this study was to compare the clinical usefulness of the two scores in predicting outcome in near-drowning patients.

Methods

Forty-five patients (male: 28; female: 17) with the diagnosis of near drowning were retrospectively enrolled in this study. Patient outcomes were categorized into two groups based on the status at discharge: the intact survival group and the vegetative/non-survival group. The two groups were analyzed and compared using the Orlowski and APACHE II scores. Statistical analysis was carried out using the Student's test and the X^2 test; multiple logistic regressions and Youden's index were used to compare the relative predictive power of the tested Orlowki and APACHE II scores.

Results

Twenty-seven patients emerged with intact survival, five patients with persistent neurological deficit, and 13 patients expired. In comparing the intact survival group (n=27, good outcome) and the vegetative/non-survival group (n=18, poor outcome), we found that an Orlowski score $\geqq$ 3, and an APACHE II score $\geqq$ 15, could predict a poor outcome in near-drowning patients, by 87% and 89% respectively. However, no significant differences were revealed when using both methods to predict outcomes in near-drowning patients.

Conclusion

Our results showed that both the Orlowski score and the APACHE II score were valuable in predicting the outcome of near-drowning patients.***(Thorac Med 2000; 15:120-125)***

Keywords : Near drowning, Orlowski score, APACHE II score

Division of Chest Medicine, Department of Internal Medicine Taichung Veterans General Hospital, Taichung, Taiwan, ROC.

Address reprint requests to: Gwan-Han Shen, Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, No.160, Sec.3, Taichung Chung-Kang Road. Taichung, Taiwan, ROC.

Introduction

Drowning and near drowning are major causes of mortality and morbidity in accidental injuries. As reported, various studies have attempted to use prognostic indicators to predict the outcome of near-drowning patients [1-4]. Among the published papers, the Orlowski score is the most well-known and popular. [5]. In recent years, the APACHE II score has been used widely, and has been shown to be statistically associated with outcome in critically ill patients [6,7], but has never been used to predict the outcome of near-drowning patients. The purpose of this study was to evaluate the Orlowski and APACHE II scores as outcome predictors in critically ill near-drowning patients.

Methods

From January 1983 to December 1997, fifty near-drowning patients were admitted to our hospital. Of those, forty-five patients were enrolled in this study, and the remaining five were excluded due to incomplete clinical data. The enrolled patients included 28 men and 17 women, ranging in age from 1 to 66 years old (mean=10.4). The medical records of the enrolled near-drowning patients were initially evaluated at the emergency room and retrospectively reviewed after admission. Both the Orlowski and the APACHE II scores were calculated and evaluated on the first day of admission, and were based on the worst, but most reliable, component status.

The patients' outcomes were recorded as the status at discharge, and were categorized as intact survival, persistent neurological deficit (including persistent seizure and vegetative status), and death. For a further analysis of these outcomes, we arbitrarily divided these patients into two groups: the intact survival group(n=27, good outcome), and the vegetative/non-survival group (n=18, poor outcome). Then, we compared the results of the two groups by using the independent student's T test and the X^2 test. Multiple logistic regression was used to analyze the predominant predictors of near drowning and Youden's index for rating diagnostic tests was used to compare the relative predictive power of the applied Orlowski and APACHE II scores [8].

Results

Of the enrolled 45 near-drowning patients, forty victims were fresh-water near-drowning: fish ponds (n=14), ditches (n=10), swimming pools (n=4), creeks (n=3), garden ponds (n=2), bathtubs (n=2), lakes (n=2), and others (n=3); and the remaining 5 were sea-water near-drowning victims. The outcome of the 45 near-drowning patients was as follows: intact survival (n=27), persistent neurological deficit (n=5) (one with persistent tonic-clonic seizure and 4 with vegetative status), and death (n=13). When the patients were divided into an intact survival group (n=27) and a vegetative/non-survival group (n=18), we found that the mean score of the Orlowski and APACHE II scores in both groups were statistically significant (both $p < 0.00001$) (Table 1). However, the age and

Table 1. Comparison of intact survival and vegetative/non-survival near-drowning patients(N=45)

Variable	Intact survival (N=27)	Vegetative/ non-survival (N=18)	P
Orlowski score	1.2± 1.2	3.8± 1.2	$P<0.00001$
APACHE II score	9.5± 7.2	28.2± 8.2	$P<0.0000$

Table 2. Predictions of outcome in near-drowning(N=45)

Score	Intact Survival (N=27)	Vegetative/ Non-survival (N=18)	Correct predictive %	Youden's Index	P*
Orlowski≧ 3	3	15	87%	0.7222	$P<0.001$
< 3	24	3			
APACHE II≧ 15	6	17	89%	0.7222	$P<0.001$
< 15	21	1			

*Multiplelogisticregression

sex distribution in these two groups was not significantly different. The predominant predictors of prognosis, using multiple logistic regression, were an Orlowski score ≧ 3 and an APACHE II score ≧ 15 (P<0.001 vs. P<0.001) (Table 2). The ratios of poor outcome in these two groups are revealed in (Figure 1) and (Figure 2). The correct predictive value of the Orlowski and APACHE II scores was 86.7% and 88.9% respectively. The ability of these scores to predict the outcome of near drowning was compared by Youden's index, but no significant differences could be found (Youden's index: 0.7222 vs. 0.7222). No one method was superior to the other.

Discussion

Accidental drowning accounts for approximately 8,000 deaths each year in the United States, and as many as 150,000 deaths worldwide [9-10]. Although Taiwan is a small island, the number of drowning deaths is more

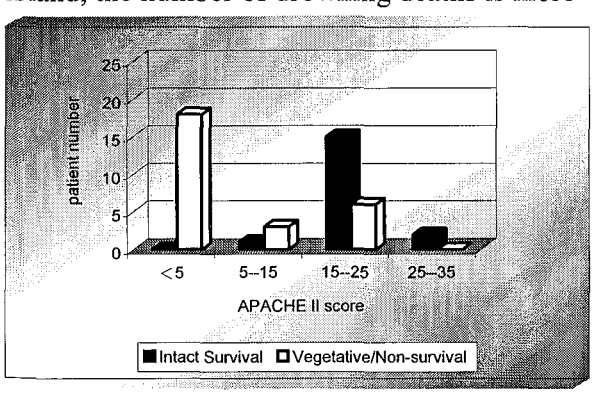


Fig. 1

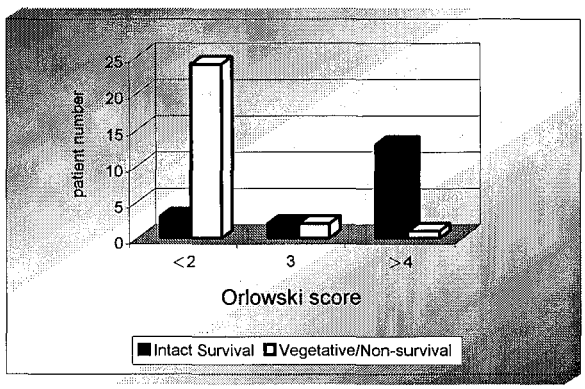


Fig. 2

than 1800 per year. Therefore, drowning is a serious problem in Taiwan. The impact, in terms of the number of lives lost, the handicaps sustained, and the economic ramifications, is devastating to us. Thus, attempts to improve near-drowning care are mandatory. Many papers have reported helpful methods of evaluating the severity of this injury. Of those, the Orlowski and APACHE II scores are the most well-known and popular.

The subject of scoring systems has become an area of active research. The need to assign a relative numeric score to illness is important in every area of medicine. The utility of the Orlowski scoring system has been confirmed as a reliable predictor of outcome in pediatric near drowning [5,11]. Orlowski proposed five unfavorable prognostic factors, including age, estimated submersion time, time to resuscitation, arterial pH, and coma. Patients with two or fewer poor prognostic factors had a 90% chance of a good recovery. Those with

three or more poor prognostic factors had a 5% chance of recovery, only [12-14]. In our series, we used three factors as the cutoff level in the Orlowski score, and the results were impressive. The results of our study support this point of view. An Orlowski score greater or equal to three could correctly predict a 87% poor outcome in near-drowning patients.

The Acute Physiology And Chronic Health Evaluation (APACHE) scoring system was first published by Knaus et al to predict the patient's risk of hospital death after admission to the ICU [6,15-16]. It was later simplified and published as the APACHE II in 1985 [7]. The APACHE II scoring system, in contrast to the 34 acute physiologic parameters measured in the original APACHE, relies on only 12 physiologic parameters, in addition to age and chronic health status. The APACHE II score was developed and tested in a population of predominantly medical ICU patients [17-24]. It has not been used as a predictor of outcome in near drowning before. However, in our series we also confirmed that the APACHE II score is a reliable predictor of outcome in near-drowning patients, and that an APACHE II score greater than or equal to 15 could correctly predict a 89% poor outcome in this study. We also compared the relative predictive power of the Orlowski with that of the APACHE II score as predictors of outcome in near-drowning patients. We used Youden's index for rating diagnostic tests as the measure of comparison. No significant difference could be found between these scores. Both the Orlowski and the APACHE II scores have excellent value as predictors of outcome in near drowning, and no one method is superior to the other.

The APACHE II score is designed as a severity of disease classification system that uses basic physiologic principles to stratify acutely ill patients (both adults and children) prognostically by risk of death [25]. The APACHE II score has also been used to evaluate pediatric patients, no matter whether in the intensive care unit, with trauma, in continuous extracorporeal renal support, or with septic shock [23-26]. Heney et al used the APACHE II score to evaluate the prognosis of his pediatric oncology patients in the intensive care unit [26]. He found the median APACHE II score for patients who died was 27, and for survivors, 16. When we reviewed the literature regarding the use of the APACHE II in children, we found only one paper using the modified APACHE II score [Acute Physiologic Score for children (APSC)] to evaluate prognosis. Gerfried et al used the APSC to evaluate clinical scoring systems in children with continuous extracorporeal renal support [27], and modified the level according to age (<1 month, <1 year, 1-5 year, > 5 year) in the items of heart rate, blood pressure, and respiratory rate. Nonetheless, other reports have used the original APACHE II score to predict prognosis.

As reported in the literature, the Orlowski score as a predictor of outcome in near-drowning patients has been well documented. The APACHE II score, however, has never been used to evaluate outcome in near-drowning patients. In our series, we found that the APACHE II score is valuable as a predictor of outcome in near-drowning patients, and the result is almost the same as that of the clinical implications of the Orlowski score in near-drowning patients (87% vs. 89%). Thus, we concluded that not only the Orlowski score, but also the APACHE II score, could be an excellent predictor of outcome in near-drowning patients.

References

1.Nussbaum E. Prognostic variables in nearly drowned, comatose children. AJDC 1985; 139: 1058-9.

2.David DD, John PS, John RM. Prognosis and management of victims of near drowning. J Trauma 1982; 22(7): 544-9.

3.Jacobsen WK, Mason LJ, Briggs BA, et al. Correlation of spontaneous respiration and neurologi-

cal damage in near drowning. Crit Care Med 1983; 11: 487-9.

4.Peterson B. Morbidity of children near-drowning. Pediatrics 1977; 59: 364-70.

5.Orlowski JP. Prognostic factors in pediatric cases of drowning and near drowning. Ann Emerg Med 1979; 8: 76-9.

6.Kanus WA, Zimmerman JE, Wagner DP. APACHE acute physiology and chronic health evaluation: a physiologically based classification system. Crit Care Med 1981; 9: 591-7.

7.Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. Crit Care Med 1985; 13: 818-29.

8.Youden WJ. Index for rating diagnostic tests. Cancer 1950; 3: 15-25.

9.Spyker DA. Submersion injury: epidemiology, prevention and management. Pediatric Clin North Am 1985; 32: 113.

10.Plueckhahn VD. Drowning: community aspects. Med J Austral 1979; 2: 226-8.

11.Orlowski JP. Drowning, near-drowning, and ice water submersion. Pediatric Clin North Am 1987; 34: 75-92.

12.Dean J, Kaufman N. Prognostic indicators in pediatric near-drowning .The Glasgow coma scale. Crit Care Med 1981; 9: 536.

13.Frewem T. Cerebral resuscitation therapies in pediatric near drowning. J Pediatr 1985; 106: 615.

14.Allman F. Outcome following cardiopulmonary resuscitation in severe pediatric near drowning. AJDC 1986; 140: 571.

15.Knaus WA, Wagner DP. APACHE: a non-proprietary measure of severity of illness [letter]. Ann Intern Med 1989; 110: 327-8.

16.Wagner DP, Draper EA, Abizanda CR. Initial international use of APACHE. An acute severity of disease measure. Med Decis Making 1984; 4: 297-313

17.Giangiuliani G, Gui D, Bonatti P, et al. APACHE II in surgical lung carcinoma patients. Chest 1990; 98: 627-30.

18.Schein M, Gecelter G. APACHE II score in massive upper gastro- intestinal hemorrhage from peptic ulcer: prognostic value and potential clinical applications. Lancet 1989; 2: 201-5.

19.Larvin M, McMahon MJ. APACHE II scores for assessment and monitoring of acute pancreatitis. Lancet 1989; 2: 201-5.

20.Dobkin JE, Cutler RE. Use of APACHE II classification to evaluate outcome of patients receiving hemodialysis in an intensive care unit. West J Med 1988; 149: 547-50.

21.Jacobs S, Chang RW, Lee B. Audit of intensive care: a 30 month experience using the APACHE II severity of disease classification system. Intensive Care Med 1988; 14: 567-74.

22.Chang RW, Jacobs S, Lee B. Predicting outcome among intensive care unit patients using computerized trend analysis of APACHE II score corrected for organ system failure. Intensive Care Med 1988; 14: 558-66.

23.Fedullo AJ, SwinBurne AJ, Wahl GW, et al. APACHE II score and mortality in respiratory failure due to cardiogenic pulmonary edema. Crit Care Med 1988; 16: 1218-21.

24.Wilson C, Heath DI, and Imrie CW. Prediction of outcome in acute pancreatitis: a comparative study of APACHE II, clinical assessment and multiple factor scoring systems. Br J Surgery 1990; 77: 1260-4.

25.William AK, Elizabeth AD, Draper MS. APACHE II: A severity of disease classification system. Crit Care Med 1985; 13: 818-28.

26.Heney D, Lewis IJ, Lockwood L. The intensive care unit in pediatric oncology. Arch of Dis in Childhood. 1992; 67: 294-8.

27.Gerfried Z, Martin K, Ekkehard R. Clinical scoring systems in children with continuous extracorporeal renal support. Child Nephrol Urol 1990; 10: 14-27.

28.Jeffrey RS, John JS, Gail MT. Multiple organ failure in patients with thermal injury. Crit Care Med. 1993; 21: 1673-81.

比較使用 Orlowski 與 APACHE II 計分預測溺水病人的預後

李建德 沈光漢 施純明 江自得

背景 Orlowski計分與APACHE II計分常被用來評估不同患者疾病的嚴重程度。本研究的目的乃在觀察這兩種分數表與溺水病患預後的相關性，同時也比較兩者預測病人預後能力的優劣性。

方法 我們一共搜集了45位溺水病患，其中28位是男性，17位是女性。病人的預後，根據他們出院時的狀況，分成兩組：一組是預後良好的存活者，另外一組則是預後不良的患者，包括有永久性神經障礙者及死亡者。 首先比較兩組病患的Orlowski計分與APACHE II計分的差異性；其次評估兩種計分法預測病人預後的能力。

結果 45位病人中，有27位是預後良好的存活者，有18位患者屬預後不良者(其中有5位具永久性神經障礙，有13位是死亡)。兩組病患的Orlowski計分與APACHE II 計分都有顯著的差異($P<0.00001$ vs. $P<0.00001$)。Orlowski計分≧3與APACHE II計分≧15可以分別正確地預測86.7%與88.9%預後不良者。進一步比較兩種分數表預測病人預後的能力，則無明顯優劣差異。

結論 Orlowski計分與APACHE II計分都是預測溺水病患預後的良好指標，同時兩者的預測的能力不分軒輊。*(胸腔醫學2000; 15: 120-125)*

關鍵詞：溺水，Orlowski計分，APACHE II計分

內科部 胸腔內科 臺中榮民總醫院
索取抽印本請聯絡：沈光漢

Immunohistochemical Study of Hepatocyte Growth Factor in Non-Small-Cell Lung Cancers

Jen-Yu Hung, Jiunn-Jiun Hou, Te-Hung Hsu, Jiuan-Nan Chen *, Tung-Heng Wang, Inn-Wen Chong, Jhi-Jhu Hwang, Eing-Long Kao **, Ming-Shyan Huang

Hepatocyte growth factor (HGF) is a multifunctional growth factor with a broad spectrum of biological effects. However, the physiological role of HGF *in vivo* remains largely unknown. We studied HGF in patients to investigate its clinical significance in non-small-cell lung cancers (NSCLC). Twenty patients with NSCLC were studied. HGF immunohistochemical staining was used to study twenty NSCLC tumor tissue specimens. Sixteen of 20 NSCLC tumors were positive for the anti-HGF immunohistochemical stain, and NSCLC cells showed a diffused cytoplasm immunoreactivity for HGF. The stroma of all specimens showed variable and weak fibroblastic immunoactivity for HGF, but there was strong immunoactivity over the small vascular walls. In conclusion, our results suggest that HGF may play an important role in the growth and behavior of NSCLC. Further investigation may be required. ***(Thorac Med 2000; 15: 126-133)***

Key words: hepatocyte growth factor (HGF), immunohistochemistry, non-small-cell lung cancer

Introduction

Hepatocyte growth factor (HGF) is said to play an important role in tissue repair in liver [1,2] and renal [3,4] injury. In 1989, Miyazawa et al. [5] and Nakamura et al [6] determined the cDNA sequence of human HGF. A later report showed that the lung has an endocrine function which produces HGF after hepatectomy or nephrectomy [7]. The mesenchymal cells of the lung, such as the alveolar macrophages, endothelial cells and fibroblasts, can also produce HGF [2,7]. In 1992, the human lung cancer cell lines that produce hepatocyte growth factor/scatter factor (HGF/SF) were determined by Yoshinaga et al. [8]. Finally, although HGF may be related to tissue regeneration [9,10], wound repair [11], embryogenesis [12] and cancer invasion [13,14], the physiological role of HGF *in vivo* remains largely unknown. Recently, however, Siegfried et al. [15] have suggested that immunoreactive HGF could be a useful prognostic indicator for non-small-cell lung cancer (NSCLC) patients.

C-met has been shown to be identical to the HGF receptor [16]. The c-met receptor is

Division of Chest Medicine, Department of Internal Medicine, Department of Surgery**, Kaohsiung Medical University, *Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, TAIWAN.
Address reprint requests to: Ming-Shyan Huang, M.D., Department of Internal Medicine, Kaohsiung Medical University, 100, Shih-Chuan 1st Road, Kaohsiung, 80708, TAIWAN.

expressed in a variety of tissue and cell types [17,18]. The c-met proto-oncogen encodes the 190-kDa membrane-bound receptor tyrosine kinase, and has also been found to be activated in gastric carcinoma cell lines, where it is amplified and overexpressed [19].

We have studied herein the immunohistochemical stains of HGF in effusion smears and in the paraffin-embedded pathological specimens resected from patients with NSCLC.

Materials and Methods

Twenty patients with NSCLC (16 adenocarcinomas and 4 squamous cell carcinomas) who were admitted to the Department of Internal Medicine or Surgery at Kaohsiung Medical University Hospital were investigated. None of these patients had received previous chemotherapy or/and radiotherapy. Tissue samples were obtained from pathological cases of lobectomy or penumonectomy for resectable non-small-cell lung carcinomas. After fixation in a 10% formal saline, all samples were embedded, using standard methods in a paraffin wax block. Pleural effusion samples taken from 56 patients at the same time the blood samples were drawn, were also measured. Pleural effusion fluid was obtained by aspiration, and cells were removed by centrifugation at 600 *g* for 10 minutes, for subsequent routine cytological investigation and immunohistochemistry stain. All of the pleural effusion samples were exudates. Since this study was done retrospectively, all the samples were stored at -20℃ until analyzed.

Immunohistochemical stain for HGF in effusion smears and tissue samples

Cytospin smears obtained from pleural effusions were fixed in acetone and methanol (1 : 1; vol.: vol.). The tissue samples were sectioned at 4μm thick. The sections were deparaffinized in xylene, rehydrated through graded alcohols, and incubated in 2% (vol.: vol.) hydrogen peroxide for 30 minutes to block endogenous peroxidase. Mouse anti-human HGF monoclonal antibody (R&D Systems Minneapolis, MN, USA) and anti-human c-met monoclonal antibody (Santa Cruz Biotech, CA, USA) were used as a primary antibody at concentrations of 10 μg/ml in phosphate-buffered saline (PBS) containing 1% bovine serum albumin, and the specimens were incubated for 60 minutes at room temperature. The DAKO LSAB® 2 Kit (Dako Co., Carpinteria, CA, USA) was used for standard immunoperoxidase stain. The immunostaining was processed according to the manufacturer's instructions. Smears were counterstained with Mayer's hematoxylin, dehydrated, dried, and embedded in Dako glycergel mountant (Dako Co., Carpintera, CA, USA). For HGF negative controls, non-immune immunoglobulins were substituted for the primary antibody for comparison with each tumor examined. The cytological specimen was considered positive when more than 10% of the tumor cells in the specimen showed a positive reaction with the HGF antibody in the pleural effusion cells [20]. For the lung cancer tissue samples, immunohistochemical stains containing more than 10% tumor cells with positive staining with HGF antibody were classified as positive [21].

Results

Immunohistochemistry for HGF of pleural effusion cytological smears:

Immunohistochemical staining for HGF was performed with 56 cytospin smears from pleural effusion smears. Twenty-six patients with benign pulmonary diseases all tested negative on

Table 1. Immunohistochemical stain of HGF in cytological smears of non-small-cell lung cancer patients with pleural effusion

	Immunoreactivity of HGF	
Cytology	+	−
Positive	16	5
Negative	0	9
Total	16	14

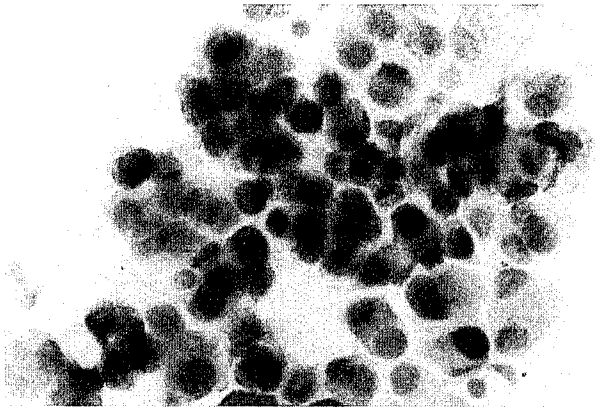


Fig. 1 (A) Immunohistochemical staining with anti-human HGF shows strong positive immunoreactivity in cytoplasm of malignan cells.

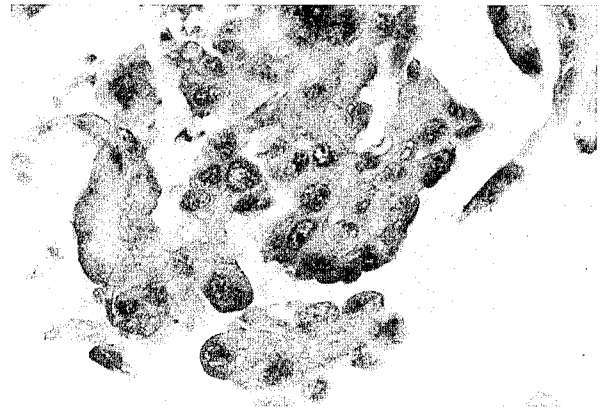


Fig. 1 (B) Negative control. Immunoperoxidase stain with monoclonal anti-human HGF antibody, pleural effusion cytology smear, Mayer's hematoxylin counterstain. (Original magnification, X400.)

conventional cytology and immunohistochemical staining for HGF. Twenty-one of 30 patients with NSCLC showed positive results upon cytological examination. Sixteen of the 21 patients (76%) with NSCLC revealed positive results with the immunohistochemical stain for HGF (Table 1). (Figure 1) demonstrates that HGF is localized mainly in the cytoplasm of NSCLC cells. Inflammatory cells in the pleural effusion were negative on the HGF stain in this study, except for a few polymorphonuclear cells, macrophages, and mesothelial cells revealing a weak stain for HGF.

Immunohistochemistry for HGF of tumor tissues from SCLC:

HGF immunohistochemical staining was used to study twenty tumor tissue specimens from NSCLC. Sixteen of 20 NSCLC were positive on the anti-HGF immunohistochemical stain (Table 2), and NSCLC cells showed diffused cytoplasm immunoreactivity for HGF (Figure 2). The stroma of all specimens showed variable and weak fibroblastic immunoactivity for HGF, but there were strong immunoactivity over the small vascular walls (Figure 3). The bronchial and bronchiolar epithelium showed weak staining.

Discussion

HGF is not only a strong hepatotrophic [1,5] and renotrophic factor [3], but also a pulmotrophic factor [22,23], responsible for airway and alveolar regeneration during lung recovery following acute pulmonary injury. Several reports describe an increased expression of growth factor and growth factor receptors in human tumors. HGF stimulates the migration of various types of

Table 2. Patients' characteristics

			immunoreactivity
Case	Hisotology	Stage	HGF
1	Adenocarcinoma	II	+
2	Adenocarcinoma	I	+
3	Adenocarcinoma	II	+
4	Adenocarcinoma	II	–
5	Adenocarcinoma	II	–
6	Adenocarcinoma	IIIa	+
7	Adenocarcinoma	II	+
8	Adenocarcinoma	IIIa	+
9	Adenocarcinoma	II	+
10	Adenocarcinoma	I	+
11	Adenocarcinoma	II	+
12	Adenocarcinoma	IIIa	+
13	Adenocarcinoma	II	+
14	Adenocarcinoma	I	+
15	Adenocarcinoma	II	–
16	Adenocarcinoma	II	+
17	Squamous cell carcinoma	IIIa	+
18	Squamous cell carcinoma	II	+
19	Squamous cell carcinoma	II	–
20	Squamous cell carcinoma	IIIb	+

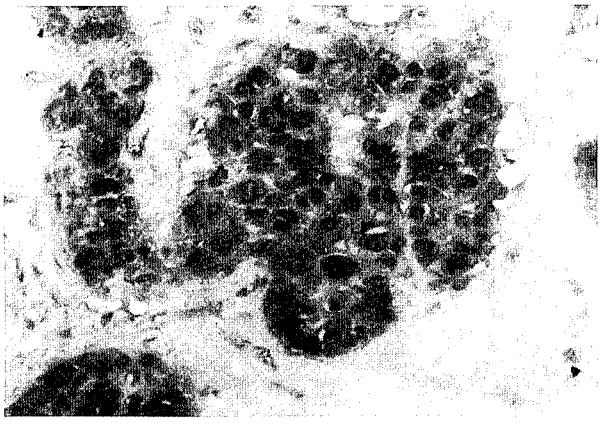


Fig. 2 Immunohistochemical staining with anti-human HGF monoclonal antibody shows positive staining in cancer cells cytoplasm. Immunoperoxidase stain with monoclonal anti-huma HGF antibody, lung tumor tissue specimen, Mayer's hematoxylin counterstain. (Original magnification, X400).

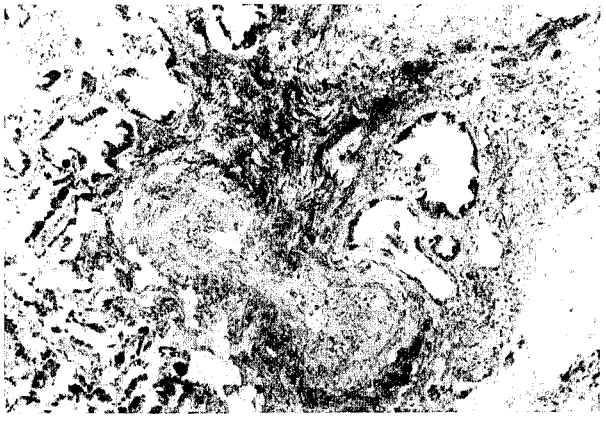


Fig. 3 Immunohistochemical staining with anti-human HGF monoclonal antibody shows positive staining in small blood vessels. Immunoperoxidase stain with monoclonal anti-human HGF antibody, lung tumor tissue specimen, Mayer's hematoxylin counterstai. (Original magnification X200).

carcinoma cells. Recently, Nakamura et al. [24] identified the mutual interactions, as mediated by HGF and HGF inducers, that may play a significant role in the invasion and metastasis of carcinoma cells. Yanagita et al. [25] analyzed serum HGF levels in patients with lung diseases, using radioimmunoassay, and revealed increased HGF levels in these patients. Some cell lines derived from lung adenocarcinomas and squamous cell carcinomas are characterized by both constitutively phosphorylated c-met and the secretion of HGF [22]. So far, there have been only a few immunohistochemical studies of the distribution of HGF and c-met in human lung carcinomas [15,25,26]. Yoshinaga et al. [27] reported strong staining for HGF in the basement membranes of tumors, the bronchial epithelium and small blood vessels, and of the stroma. However, Harvey et al. [28] reported that the cytoplasm of bronchogenic carcinoma cells showed uniform positive HGF and c-met immunohistochemical staining in histological studies. To distinguish these significant differences from these two observations, we studied the HGF immunohistochemical staining in cytological materials, and HGF immunohistochemical staining in NSCLC tumor tissue specimens. In our study, NSCLC malignant cells in pleural effusion showed a positive immunoreactive stain of HGF in the cytoplasm. Increased HGF levels in NSCLC with malignant pleural effusion were observed in our series study [29]. The malignant cells in pleural effusion may produce HGF. As far as we know, our study is the first to report immunohistochemical staining for HGF using the cytological materials of lung carcinomas. Twenty resected NSCLC tumor tissue specimens were studied and a diffused cytoplasm immunoreactivity for HGF in NSCLC was observed in sixteen cases (80%). Our observations are the same as the Harvey. [28] report.

The stroma of all tumor tissue specimens showed variable and weak fibroblastic immunoactivity for HGF in our study. This finding was not unexpected, as human lung fibroblasts secrete HGF *in vitro* [11]. Strong staining of the fibroblast population of HGF in the tumor stroma of malignant mesothelioma, and only sporadic weak staining for HGF in the stroma of lung carcinoma were reported by Harvey.

There was strong HGF immunoactivity over the small blood vessel walls in our tumor tissue specimens. HGF has been found to be a stimulator of angiogenesis [30] and may also

have some role in the enhanced vascularization necessary for tumor growth [28]. Yoshinaga et al. [27] revealed strong immunostaining for HGF in the walls of blood vessels, similar to our results.

Normal bronchial and bronchiolar epithelium samples showed weak immunohistochemical staining for HGF in our study. Previous reports have shown positive immunohistochemical staining for HGF and c-met in normal bronchial epithelium and mesothelium samples [11,28]. Both cytoplasmic and plasma membrane staining were evident [28].

This study also revealed that the alveolar macrophages appeared to weaken the immunohistochemical stain for HGF. Yoshinaga et al. [8] reported that alveolar macrophages synthesize HGF mRNA. Harvey presented similar results to ours.

In previous studies, the presence of HGF mRNA in the human liver [6], placenta [7] fetal pancreas and kidney [31] has been observed. Tsao et al. [22] reported data that revealed that HGF to be an autocrine factor for normal and neoplastic human bronchial epithelial cells in culture. However, Sing-Kaw et al [23] demonstrated that HGF acts as a paracrine growth factor for cells derived from the human bronchus and may play a role in the growth and prognosis of lung cancer. Recently, Siegried et al. [15] measured the immunoreactive HGF tumor content in resectable NSCLC and reported that HGF measurement could be a useful prognostic indicator for NSCLC patients. Olivero et al. [32] observed that HGF overexpression and activation may be the driving factor for NSCLC cell invasive phenotype acquisition.

In conclusion, we demonstrated that the NSCLC cells showed a positive HGF immunoactivity. Our results suggest that HGF may play an important role in the growth and behavior of NSCLC. Further investigations may be required.

Acknowledgment

This work was supported by TAIWAN NSC grant 85-2331-B-037-071. The authors thank Miss Jui-Hsien Kuo and Miss Fei-Chin Huang for their technical assistance.

Reference

1.Nakamura H, Tsubouchi H, Gohda E, et al. Stimulation of DNA synthesis in adult rat hepatocytes in primary culture by sera from patients with fulminant hepatic failure. *Biomed Res* 1985; 6: 231-7.

2.Tsubouchi H, Niitani Y, Hirono S, et al. Levels of the human hepatocyte growth factor in serum of patients with various liver diseases determined by an enzyme-linked immunosorbent assay. *Hepatology* 1991; 13: 1-5.

3.Matsumoto K, Tajima H, Hanamoue M, et al. Identification and characterization of " injurin." an inducer of expression of the gene for hepatocyte growth factor. *Proc Natl Acad Sci USA* 1992; 89: 3800-4.

4.Nagaike M, Hirao S, Tajima H, et al. Renotropic functions of hepatocyte growth factor in renal regeneration after unilateral nephrectomy. *J Biol Chem* 1991; 266: 22781-4.

5.Miyazawa K, Tsubouchi H, Naka D, et al. Molecular cloning and sequence analysis of cDNA for human hepatocyte growth factor. *Biochem Biophys Res Commun* 1989; 163: 967-73.

6.Nakamura T, Nishizawa T, Hagiya M, et al. Molecular cloning and expression of human hepatocyte growth factor. *Nature* 1989; 342: 440-3.

7.Yanagita K, Nagaike M, Ishibashi H, et al. Lung may have an endocrine function producing hepatocyte growth factor in response to injury of distal organs. *Biochem Biophys Res Commun* 1992; 182: 802-9.

8.Yoshinaga Y, Fujita S, Gotoh M, et al. Human

lung cancer cell line producing hepatocyte growth factor/Scatter factor. *Jpn J Cancer Res* 1992; 83: 1257-61.

9.Lindroos PM, Zarnegar R, Michalopoulos GK. Hepatocyte growth factor (hepatopoietin A) rapidly increases in plasma before DNA synthesis and liver regeneration stimulated by partial hepatectomy and carbon tetrachloride administration. *Hepatology* 1991; 13: 743-50.

10.Kinoshita T, Tashiro K, Nakamura T. Marked increase of HGF mRNA in non-parenchymal liver cells of rate treated with hepatotoxins. *Biochem Biophys Res Commun* 1989; 165: 1229-34.

11.Stoker M, Gherardi E, Perryman M, et al. Scatter factor is a fibroblast-derived modulator of epithelial cell mobility. *Nature* 1987; 327: 239-42.

12.Defrances MC, Wolf HK, Michalopoulos GK, et al. The presence of hepatocyte growth factor in developing rat. *Development* 1992; 116: 387-95.

13.Bellusci S, Moens G, Thiery JP, et al. A scatter factor-like factor is produced by a metastatic variant of a rat bladder carcinoma cell line. *J Cell Sci* 1994; 107: 1277-87.

14.Natali PG, Nicotra MR, DiRenzo MF, et al. Expression of the c-met/HGF receptor in human melanocyte neoplasms: demonstration of the relationship to malignant melanoma tumour. *Br J Cancer* 1993; 68: 746-50.

15.Siegried JM, Weissfeld LA, Singh-Kwa P, et al. Association for immunoreactive hepatocyte growth factor with poor survival in resectable non-small cell lung cancer. *Cancer Res* 1997; 57: 433-9.

16.Bottaro DP, Rubin JS, Faletto DL, et al. Identification of hepatocytes growth factor receptor as the c-met proto-oncogene product. *Since* 1991; 251: 802-4.

17.Layer A, Kmiecik TE, Park M, et al. Structure, tissue-specific expression, and transforming activity of mouse met protooncogene, *Cell Growth & Differ* 1990; 1: 87-95.

18.Di Renzo MF, Narsimhan RP, Olivero M, et al. Expression of Met/HGF receptor in normal and neoplastic human tissues. *Oncogene* 1991; 6: 1997-2003.

19.Ponzetto C, Giordano S, Della Valle G, et al. C-met is amplified but not mutated in a cell line with an activated met tyrosine kinase. *Oncogene* 1991; 6: 553-9.

20.Ioakim-Liossi A, Pantazopoulos D, Karakitsos P, et al. P53 protein expression and proliferative activity in imprints of superficial transitional cell carcinoma of the bladder. *Analyt Quant Cytol Histol* 2000; 22: 223-8

21.Yu CJ, Shun CT, Yang PC et al. Sialomucin expression is associated with *erb*B-2 oncoprotein overexpression, early recurrence, and cancer death in non-small cell lung cancer. *Am J Respir Crit Med* 1997: 155:1419-27

22.Tsao M.S, Zhu H, Giaid A, et al. Hepatocytes growth factor/scatter factor is an autocrine factor for human normal bronchial epithelial and lung carcinoma cells. *Cell Growth & Differ* 1993; 4: 571-9.

23.Singh-Kaw P, Zarnegar R, Siegfried JM. Stimulatory effects of hepatocyte growth factor on normal and neoplastic human bronchial epithelial cells. *Am J Physiol* 1995; 268: L1012-L20.

24.Nakamura T, Matsumoto K, Kiritoshi A, et al. Induction of hepatocyte growth factor in fibroblasts by tumor-derived factors affects invasive growth of tumor cells: in vitro analysis of tumor-stromal interactions. *Cancer Res* 1997; 57: 3306-13.

25.Yanagita K, Matsumoto K, Sekiguchi K, et al. Hepatocyte growth factor may act as a pulmotrophic factor on lung regeneration after acute lung injury. *J Biol Chem* 1993; 268: 21212-7.

26.Ohmichi H, Matsumoto K, Nakamura T. In vivo mitogenic action of HGF on lung epithelial cells: pulmotrophic role in lung regeneration. *Am J Physiol* 1996; 270 (*Lung Cell Mol Physiol* 14): L1031-L9.

27.Yoshinaga Y, Matsuno Y, Fujita S, et al. Immunohistochemical detection of hepatocyte

growth factor/scatter factor in human cancerous and inflammatory lesions of various organs. *Jpn J Cancer Res* 1993; 84: 1150-8.

28.Harvey P, Warn A, Newman P, et al. Immunoreactivity for hepatocyte growth factor/scatter factor and its receptor, met. In human lung carcinomas and malignant mesotheliomas. *J Pathol* 1996; 180: 389-94.

29.Huang MS, Tsai MS, Wang TH, et al. Serum hepatocyte growth factor levels in patients with inflammatory Lung Diseases. *Kaoshiung J Med Sci* 1999; 15: 195-201.

30.Rosen E, Nigam S, Goldberg I. Scatter factor and the met receptor: a paradigm for mesenchymal/epithelial interaction. *J Cell Biol* 1994; 127: 1783-7.

31.Selden C, Jones M, Wade D, et al. Hepatotropin mRNA express in human fetal liver development and in liver regeneration. *FEBS Lett* 1990; 270: 81-4.

32.Olivero M, Rizzo M, Madeddu R, et al. Overexpression and activation of hepatocyte growth factor/scatter factor in human non-small-cell lung carcinomas. *Br J Cancer* 1996; 74: 1862-8.

非小細胞肺癌之肝細胞生長因子免疫組織化學研究

洪仁宇 侯俊君 許德宏 陳俊男* 王東衡 鍾飲文 黃吉志 高英隆** 黃明賢

肝細胞生長因子被認為是一種多功能性之生長因子具有多種生物學功能作用。但是至今肝細胞生長因子在人體內的生理功能機轉及所具有的角色尚未十分明白。我們用免疫組織化學方法研究肝細胞生長因子在非小細胞肺癌之表現。二十位非小細胞肺癌病例進入比研究，針對這二十個肺癌腫瘤標本，進行肝細胞生長因子之免疫組織化學染色。結果有十六位病例免疫組織化學染色呈現陽性反應，非小細胞肺癌細胞的細胞質呈現肝細胞生長因子之免疫組織化學陽性反應，肺癌組織間質及纖維細胞亦有弱的肝細胞生長因子之免疫組織化學陽性反應，組織的小血管壁呈現強度的肝細胞生長因子之免疫組織化學陽性反應。由我們的研究結果，顯示肝細胞生長因子可能在非小細胞肺癌細胞的繁殖生長上具有重要的角色，可能在非小細胞肺癌的腫瘤血管增生上亦具有其作用功能。今後需要作更進一步深入研究。*（胸腔醫學 2000; 15: 126-133）*

關鍵詞：肝細胞生長因子，免疫組織化學，非小細胞肺癌

高雄醫學大學內科部胸腔內科，外科部**，高雄市立大同醫院內科*
索取抽印本請聯絡：黃明賢醫師，高雄市三民區十全一路 100 號

Disseminated *Strongyloides stercoralis* Infection in a Patient with Chronic Obstructive Pulmonary Disease – A Case Report

Shen-Chun Chen, Hung-Yang Tao, Jiunn-Der Lee, Lin Lee, Kam-Chung Lee, Chia-Jung Chen*

Disseminated *Strongyloides stercoralis* infection occurs in the immunocompromised host. This infection can repeat its particular life cycle indefinitely and result in chronic infection in the patient. The filariform larvae can carry enteric bacteria and fungi on their outer surface and induce severe infection with sepsis when the larvae migrate through the whole body. We herein present a case of chronic obstructive pulmonary disease (COPD) with disseminated *S. stercoralis* infection involving the lungs, small intestine, colon, kidneys, thyroid gland, lymph nodes, and heart, which was proved by autopsy. The patient was admitted because of COPD with acute respiratory failure. Severe *Strongyloides* infection with gastrointestinal and pulmonary involvement was diagnosed by observing the living larvae in the sputum and stool during the premortum period. The patient was treated with mebendazole 200 mg twice per day. He subsequently expired due to disseminated *S. stercoralis* infection and sepsis with acute respiratory distress syndrome. To the best of our knowledge, this is the first case report of COPD complicated with disseminated strongyloidiasis receiving postmortum examination in Taiwan. ***(Thorac Med 2000; 15: 134-140)***

Key words: *Strongyloides stercoralis*, chronic obstructive pulmonary disease

Introduction

Strongyloides stercoralis is an intestinal nematode with worldwide distribution. It is endemic in tropical and subtropical regions, and affects 100 million humans [1]. It has the ability to multiply within a host, and complete entire life cycles within one human being indefinitely. In immunocompetent persons, it usually induces a silent or limited intestinal reaction [2]. It is also known to cause a hyperinfection syndrome characterized by a massive parasitic invasion of the gastrointestinal tract and lungs, or disseminated disease in immunocompromised persons when multiple organs, such as the kidneys, liver, and central nervous system, have been invaded by this nematode [3]. Strongy-

Division of Respiratory Therapy, Department of Medicine, *Department of Pathology and Laboratory Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan
Address reprint requests to: Dr. Hung-Yang Tao, Division of Respiratory Therapy, Department of Medicine, Kaohsiung Veterans General Hospital 386 Ta-Chung 1st Road, Kaohsiung, Taiwan

loidiasis is potentially fatal if not treated early [4]. It is important to have a high degree of suspicion with patients who have gastrointestinal and pulmonary symptoms and have traveled or lived in endemic areas. Herein we present a patient with chronic obstructive pulmonary disease (COPD) complicated with disseminated *Strongyloides* infection involving the small intestine, colon, mesentery, lungs, kidneys, thyroid gland, lymph nodes, and heart, which was proved by autopsy.

Case report

A 70-year-old man was sent to our emergency department because of increasing dyspnea for several days. He had visited our outpatient clinic due to exertional dyspnea one year previous, and a pulmonary function test showed severe obstructive ventilatory impairment with FEV_1 = 0.64 L (24% predicted value), FVC = 1.97L (54% predicted value), and FEV_1/FVC = 32%. He was admitted to our hospital because of COPD with acute exacerbation one month earlier, and had received corticosteroid treatment with a regime ranging from hydrocortisone 200 mg q8h parenterally to prednisolone 10 mg orally within 2 weeks. Inhaled corticosteroid (beclomethasone dipropionate 200 mcg bid) was adminstrated for another 2 weeks after discharge.

He was a former sergeant who had been retired since 1979. He had a two-year history of multiple gallstones without clinical symptoms. There was no history of diabetes mellitus, hypertension, pulmonary tuberculosis or major operation. He used to smoke about 30 packs a year, but had quit smoking 3 years ago.

At the emergency department, his vital signs were a temperature of 38.7°c, pulse rate of 148/ min, respiratory rate of 32/ min, and a blood pressure of 167/ 73 mmHg.

On examination, the patient was an overweight man with severe cardiopulmonary embarrassment. No rash or lymphadenopathy was found. Wheezes were heard over bilateral lungs. The heart was not enlarged, but the rhythm was irregular and rapid. The abdomen was soft, and ovoid in shape, without rebounding tenderness or hepatosplenomegaly. The extremities showed no pitting edema. Neurologic examinations were negative. A chest roentgenogram revealed mild hyperinflation only. An electrocardiogram showed multifocal atrial tachycardia with a rate of 144/ min. Laboratory values on admission included a leukocyte count of 7000 /mm^3 with 93% segmented neurtophils, 5% lymphoytes, 1% eosinophils, and hematocrit at 28.7%. Initial results of the liver and renal function tests were normal.

Due to impending respiratory failure, endotracheal intubation was installed immediately and the patient was admitted to our ward. He then was treated with hydrocortisone, aminophylline, penicillin, and an inhaled bronchodilator. On the third hospital day, he was extubated and shifted to nasal canula oxygen use due to his improving clinical condition. Diarrhea was also noted 6 days after admission.

Unfortunately, on the ninth hospital day, increasing dyspnea developed, accompanied by fever and consciousness disturbance. The patient was intubated again and mechanically ventilated. The antibiotic therapy was shifted to imipenem-cilastatin (500mg q8h). The chest roentgenogram showed mixed alveolar and interstitial infiltration over bilateral lungs, and progressive changes were noted in the subsequent films. The sputum culture on the 11th hospital day disclosed Xanthomonas maltophilia.

Because of his unstable hemodynamic status, the patient was transferred to the medical intensive care unit for further management under the impression of COPD with pneumonia, complicated with sepsis and acute respiratory distress syndrome. On the 13th hospital day, a few *S. stercoralis* larvae were found in a wet mount examination of a sputum specimen (Fig. 1) and also in a stool specimen smear. Mebendazole 200 mg twice per day was administered. Unfortunately, septic shock developed on the 17th

Fig. 1 The photomicrograph of a sputum smear showing a larva of *Strongyloides*. (Gram's stain, x 250)

hospital day and he finally expired three days later.

The postmortum examination revealed overwhelming *S. stercoralis* infection of the lungs, subcarinal lymph nodes, heart, mesentery, kidneys, thyroid gland (Fig. 2- A, B, C, D, E, F), small intestine, and colon. Variable extents of mixed leukocyte infiltration containing eosinophils were noted in the specimens of multiple organs on light microscopy.

Discussion

S. stercoralis is ubiquitous in subtropical and tropical regions [1]. Infection begins when filariform larvae, from contaminated soil, penetrate the exposed skin and migrate through lymphatic and venous circulation [5]. The larvae pass through the right side of the heart, settle in the capillary bed of the lung, and penetrate the capillary walls into the alveoli [5]. Then, the larvae ascend the tracheobronchial tree to the larynx, and are swallowed. When they reach the duodenum and the upper part of the small intestine, they mature into adult female worms. They then burrow into the submucosa, and lay eggs in the intestinal lumen. The eggs produced by parthenogenesis hatch into rhabditiform larvae, and may either metamorphose into infective filariform larvae or mature into adult worms in the environment [1]. These filariform larvae can penetrate the intestinal mucosa or perianal skin, reenter the venous system, and repeat the life cycle within the host indefinitely (autoinfection), resulting in chronic infection. This parasite may exist in the host for up to 65 years or longer, and eventually induce massive parasitic infestation [6].

The clinical spectrum of *S. sterocoralis* infection may be asymptomatic, mildly symptomatic, hyperinfection syndrome, or disseminated disease [2]. The usual gastrointestinal symptoms include diarrhea, bloating, nausea, vomiting, gastrointestinal bleeding, and weight loss with evidence of malabsorption or of protein-losing enteropathy. Respiratory symptoms such as cough, dyspnea, asthma-like wheezing, and hemoptysis may be predominant in some cases [1]. Hemorrhagic pulmonary infarction, pulmonary edema, bronchopneumonia, lung abscess, inflammatory pneumonitis, pleural effusion, and exacerbation of underlying pulmonary disease may develop when the larvae migrate through the lungs [7].

The hyperinfection syndrome reveals a massive infection of *S. sterocoralis* which is restricted to the organs in the migratory pathways of the larvae, such as the gastrointestinal tract and lungs [3]. Disseminated strongyloidiasis is defined as a widespread *Strongyloides* infection affecting organs not ordinarily involved in the life cycle of the parasite, such as the entire small bowel, colon, peritoneum, central nervous system, pancreas, biliary tract, liver, kidneys, thyroid gland, parathyroid glands, adrenal glands, prostate, ovaries, lymph nodes, skeletal muscles, heart, and skin [3]. Known risk factors for severe *Strongyloides* infection, in addition to residence in or travel to an endemic area, include age greater than 65 years, chronic lung disease, achlohydria, the use of antacids or Histamine-2 blockers, surgically created intestinal blind loops, and altered cellular immunity through the use of corticosteroids or immunosuppressive drug therapy, and AIDS [7]. In our patient, the possible risk factors included age, chronic obstructive

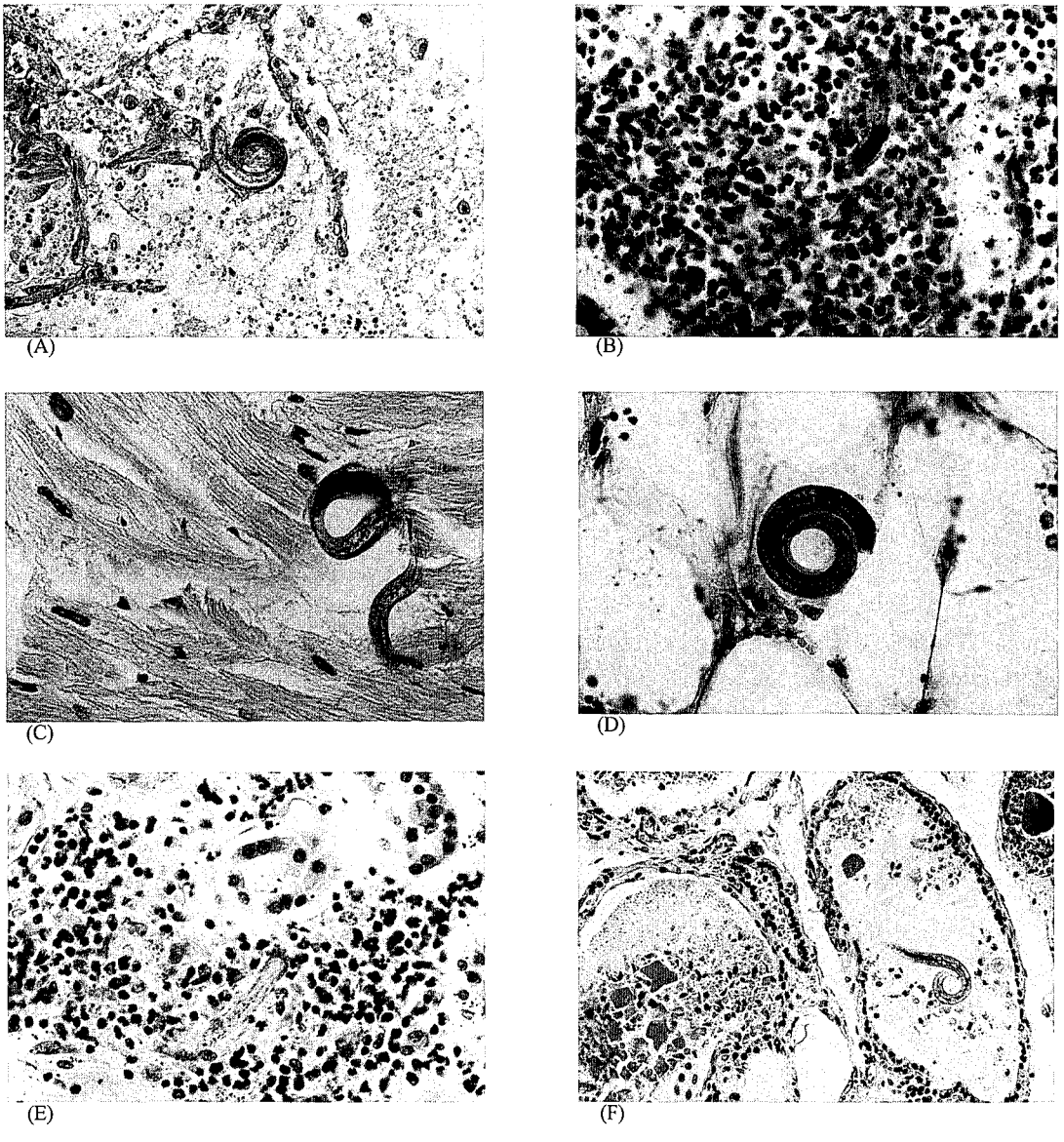


Fig. 2 The photomicrographs of histologic sections of multiple organs stained with hematoxilyn and eosin disclosing *Strongyloides* larvae in the (A) lung (x 250), (B) subcarinal lymph node (x 500), (C) heart (x 500), (D) mesentery (x 500), (E) kidney (x 500) and (F) thyroid gland (x 250), with variable degrees of inflammatory cell infiltration, including eosinophils

pulmonary disease, and the use of corticosteroids. However the actual doses of steroids could not be traced due to irregular follow-up. The filariform larvae of *S. stercoralis* are known to carry enteric bacteria and fungi piggyback on their outer surface, resulting in bacterial or fungal sepsis, meningitis, and disseminated bacteremia or fungal infection in many part of the body. Serious secondary bacterial infections are often the immediate cause of death in patients with hyperinfection syndrome, and account for death rates as high as 80% [8].

The first and most important step in diagnosing *S. stercoralis* infection is to consider it in the differential diagnosis of recurrent skin lesions, multiple pulmonary infiltrates, diarrhea, abdominal pain, and malabsorption [1]. The definite diagnosis may be made by examination of body fluids, such as sputum, stool, cerebrospinal fluid, ascites [9] and other body

fluids, containing larvae.

Eosinophilia, while common in normal hosts (70% of infected patients), is uncommon in the immunocompromised host such as our patient, and is present in only 17% of the cases [10]. This may be due to the suppression of eosinophils by corticosteroids or by associated bacterial infection [11,12]. The sensitivity of stool examination ranges from 27% to 73% [13]. Duodenal fluid examination for nematodes has a wide range of sensitivity, from 39% to 76% [9].

Due to the lack of sensitivity of the above measures, a serological test with an enzyme-linked immunosorbent assay to detect antibodies to *S. stercoralis* filariform larvae has been developed. Sensitivities and specificities of the test vary from 85% to 88% and 97% to 99%, respectively [14,15]. A positive result indicates that past or current infection and cross-reactivity with other helminthes, such as *Loa loa* filaria, *Ascaris lumbricoides*, and hookworm, may occur occasionally [14,15]. The pathologic features of strongyloidiasis, including vascular congestion, edema, inflammatory cell infiltration containing eosinophils, and larvae in the specimens of the involved organs, were noted in our patient.

The drug of choice for *S. stercoralis* infection is thiabendazole 25 mg/kg orally twice daily, and the duration of therapy varies, depending on the severity of disease. For simple autoinfection, treatment for 2-3 days is usually adequate, but in patients with chronic lung disease or hyperinfection syndrome, the duration of therapy should be longer than 5 days [5]. The end point of therapy should be the eradication of viable parasites in excretions [16]. Because thiabendazole is not available at our hospital, mebendazole at a dose of 100-200 mg twice daily for 1-2 weeks can be used alternately [5]. Although the eradication rate of thiabendazole is about 90%, this therapy may not be sufficient for infection because the relapse rate is up to 15%. Close follow-up is needed after completion of initial therapy [17,18].

The prognosis of strongyloidiasis is dependent on the severity of the disease [7]. While most patients with autoinfection survive well if treated properly, the prognosis of those patients with hyperinfection syndrome is poor. HIV-infected patients have a greater risk for widespread dissemination of *S. stercoralis*, a greater tendency to be refractory to standard treatment regimens, and their mortality rates may be as high as 90% [12].

In conclusion, dissemination of *S. stercoralis* can be life-threatening in the immunocompromised host. This is the first case report of disseminated *Strongyloides* infection involving the small intestine, colon, mesentery, lungs, subcarinal lymph nodes, kidneys, thyroid gland, and heart proved by autopsy in Taiwan. Early diagnosis and proper treatment is mandatory and can be life-saving.

References

1. Mahmoud AA. Strongyloidiasis. Clin Infect Dis 1996; 23: 949-52.
2. Makris AN, Sher S, Bertoli C, et al. Pulmonary strongyloidiasis: An unusual opportunistic pneumonia in a patient with AIDS. Am J Roentgenol 1993; 161: 545-7.
3. Wehner JH, Kirsch CM. Pulmonary manifestation of strongyloidiasis. Semin Respir Infect 1997; 12: 122-9.
4. Kothary NN, Muskie JM, Mathur SC. *Strongyloides stercoralis* hyperinfection. Radiographics 1999; 19: 1077-81.
5. Woodring JH, Halfhill H 2nd, Reed JC. Pulmonary strongyloidiasis: clinical and image features. Am J Roentgenol 1994; 162(3): 537-42.
6. Leighton PM, MacSween HM. *Strongyloides stercoralis*: The cause of a urticaria–like eruption of 65 years' duration. Arch Intern Med 1990; 150: 1747.
7. Woodring JH, Halfhill H, Berger R, et al. Clinical and imaging features of pulmonary strongyloidiasis. South Med J 1996; 89(1): 10-19.

8.Simpson WG, Gerhardstein DC, Thompson JR. Disseminated *Strongyloides stercoralis* infection. South Med J 1993; 86: 821-5.
9.Wu MP, Ko LY, Chen KC, et al. Disseminated strongyloidiasis: Report of a case. J Formos Med Assoc 1988; 87: 402-5.
10.Igran- Siegman Y, Kapila R, Sen P, et al. Syndrome of hyperinfection with *Strongyloides stercoralis*. Rev Infect Dis 1981; 3: 397-407.
11.Chu E, Whitlock WL, Dietrich RA. Pulmonary hyperinfection syndrome with *Strongyloides stercoralis*. Chest 1990; 97: 1475-7.
12.Lessnauk-D, Can S, Talavera W. Disseminated *Strongyloides stercoralis* in human immunodeficiency virus-infected patients: Treatment failure and a review of the literature. Chest 1993; 104: 119-22.
13.Goka AKJ, Rolston DDK, Mathan VI, et al. Diagnosis of *Strongyloides* and hookworm infections: Comparison of faecal and duodenal fluid microscopy. Trans R Soc Trop Med Hyg 1990; 84: 829-31.
14.Genta RM. Predictive value of an enzyme-linked immunosorbent assay (ELISA) for the serodiagnosis of strongyloidiasis. Am J Clin Pathol 1988; 89: 391-4.
15.Lindo JF, Coneway DJ, Atkins NS, et al. Prospective evaluation of enzyme-linked immunosorbent assay and immunoblot methods for the diagnosis of endemic *Strongyloides steroralis* infection. Am J Trop Med Hyg 1994; 51: 175-9.
16.Wong B. Parasitic disease in immunocompromised hosts. Am J Med 1984; 76: 479-86.
17.Berk SL, Verghese A, Alvarez S, et al. Clinical and epideminologic features of strongyloidiasis: a prospective study in rural Tennessee. Arch Intern Med 1987; 147: 1257-61.
18.Williams J, Nunley D, Dralle W, et al. Diagnosis of pulmonary strongyloidiasis by bronchoalveolar larvage. Chest 1988; 94: 643-4.

慢性阻塞性肺病合併播散性糞小桿線蟲感染－病例報告

陳勝群 陶宏洋 李俊德 李琳 李錦中 陳家榮*

播散性糞小桿線蟲感染常發生於免疫力低下的病人。幼虫於全身游走時，會合併有嚴重的細菌感染，死亡率高達百分之八十。在這裏，我們報告一位慢性阻塞性肺病的病人，曾經使用過類固醇。由於散播性糞小桿線蟲感染，併發肺炎、敗血症及急性呼吸窘迫症候群致死的病例。死後的病理解剖顯示蟲體於肺、小腸、大腸、腎、甲狀腺、淋巴結和心臟，合併有嗜伊紅性血等白血球的浸潤。據我們所知，這是台灣第一個死後接受病理解剖的播散性糞小桿線蟲病例。*(胸腔醫學 2000; 15: 134-140)*

關鍵詞：糞小桿線蟲，慢性阻塞性肺病。

高雄榮民總醫院 內科部呼吸治療科 病理部*
索取抽印本請聯絡：陶宏洋醫師，高雄市左營區大中一路 386 號 高雄榮民總醫院呼吸治療科

Aspiration of A Broken Metallic Tracheostomy Tube– An Unusual Cause of Tracheobronchial Foreign Body

Puh-Shen Yeh, Yeong-Long Hsu , Ping-Hung Kuo

We here report a rare case of a tracheobronchial foreign body due to metallic tracheostomy tube breakage. A 77-year-old male patient was presented to the emergency room because of a sudden onset of dyspnea. The patient had been a chronic user of a metallic tracheostomy tube. Degradation of the braced joint apparently resulted in an external tube component detaching from the tracheostomy plate. This external tube component was aspirated and became lodged in the left main bronchus. We removed the foreign object without complication using biopsy forceps through a flexible bronchoscope under topical anesthesia. In this report, we also review related literature to identify the mechanism and management of this rare complication. ***(Thorac Med 2000; 15: 141-145)***

Key words: metalic tracheostomy tube, biopsy forcep, tracheobronchial foreign body, flexible bronchoscope.

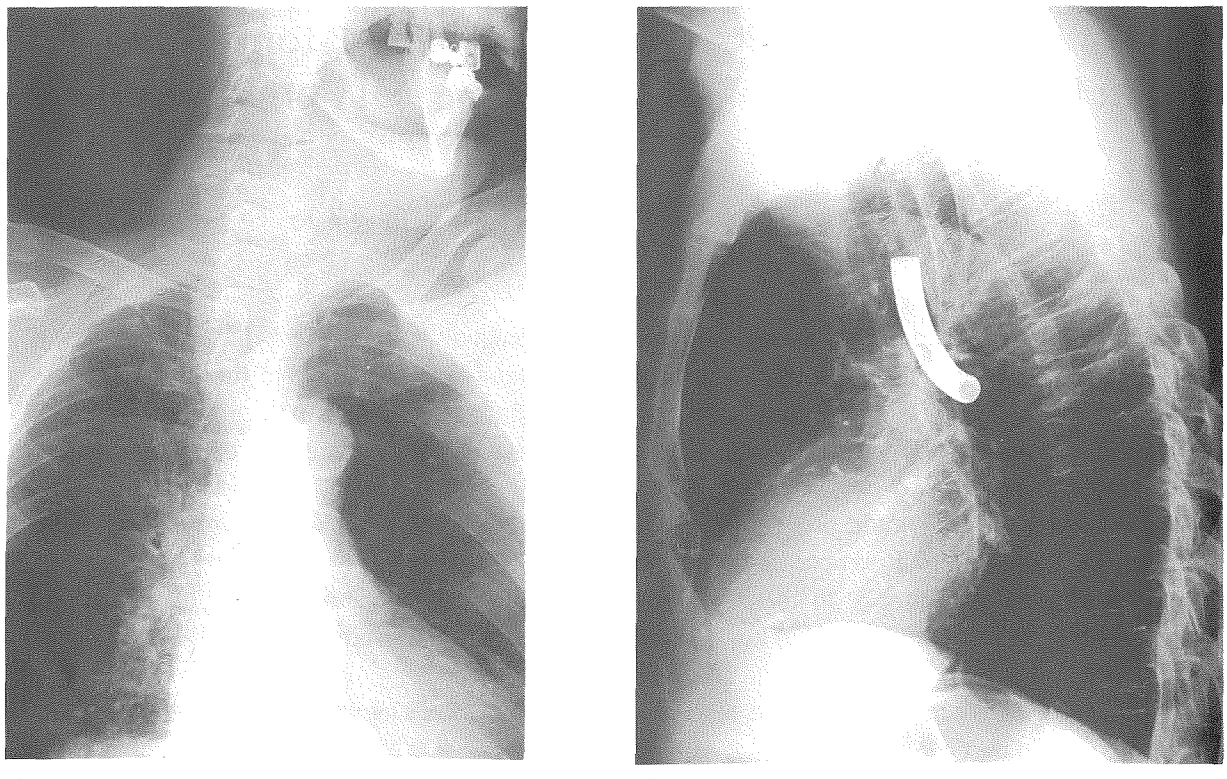
Introduction

Tracheostomy is commonly indicated for the relief of an upper airway obstruction, and is also used as a pathway for ventilatory support and for control of secretion. Metallic tracheostomy tubes are preferred for long-term use because of their durability and the convenience of daily care. Aspiration of metallic tracheostomy tube components is a rarely reported complication [1]. We here report a case of a tracheobronchial foreign body as a result of metallic tracheostomy tube disintegration after prolonged use.

Case Report

A 77-year-old male patient with a history of cerebrovascular accident and recurrent aspiration pneumonia underwent tracheostomy in 1990, and had been on a metallic tracheostomy tube ever since. On January 1, 2000, he was presented to the emergency room (ER) complaining of dyspnea and chest discomfort while at his nursing home. His condition improved upon arrival at the ER. At admission, his blood pressure was 146/74 mmHg, his heart rate 62 per minute, and his respiratory rate 20 per minute. Oxygen saturation

Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
Address reprint requests to: Ping-Hung Kuo, M.D., Department of Internal Medicine, National Taiwan University Hospital, 7, Chung-Shan South Road, Taipei 100, Taiwan



(A) (B)

Fig. 1 The posterior- anterior (A) and left lateral (B) chest radiographs showing a broken metallic tracheostomy tube lodged in the left main bronchus.

(SaO_2) was 98 per cent when breathing room air. Physical examination revealed the absence of the metallic tube from a widened, well-defined tracheostoma. No stridor, wheezing, or bronchial sounds were observed. Chest radiographs showed an external tube component of the tracheostomy tube lodged in the left main bronchus (Figure 1). After a plastic tracheostomy tube was inserted, a fiberoptic bronchoscopy (Olympus, BF P2000, Japan) procedure was performed with a topical anesthesia of 2% lidocaine aerosol. The foreign object was found in the left main bronchus, without evidence of mucosal damage or bleeding in the tracheobronchial tree. The bronchoscope could pass through the broken tracheostomy tube and reach the left secondary carina. However, all attempts to pull the tube upward were unsuccessful, as there was no room to bend the tip of the bronchoscope in the left main bronchus. During the procedure, the patient had a violent cough and the metallic tube was expectorated out into the middle third portion of the trachea (Figure 2). The foreign body was grasped using biopsy forceps (Olympus, FB-15C-1, ID 1.8 mm, Japan) inserted through the bronchoscope, and successfully removed. No complication, such as laceration or bleeding, was found. Careful examination revealed degradation and total disintegration of the braced joint between the plate and the external tube. This patient was discharged on the second day with a new plastic tracheostomy tube with a low-pressure cuff.

Discussion

Major complications of tracheostomy include infection, hemorrhage, and airway obstruction due to granulation. Breakage of a tracheostomy tube and its subsequent presentation as a foreign object in the tracheobronchial tree are rare. Bassoe and Boe reported the first such case in 1960 [2]. The largest series, including nine cases,

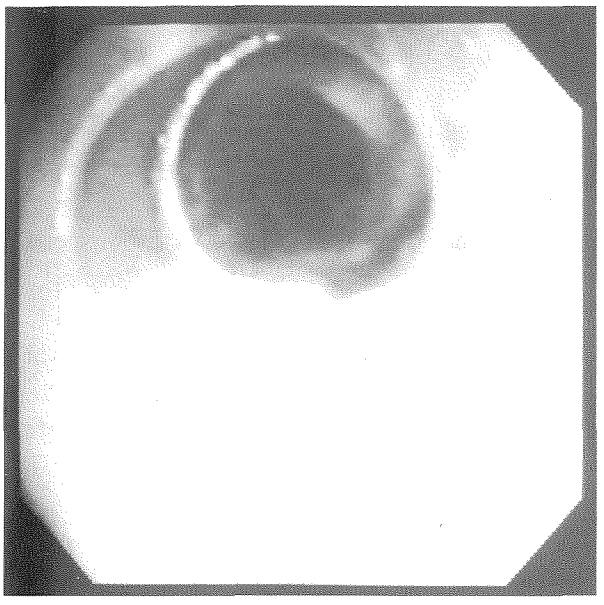


Fig. 2 Bronchoscopic view of the broken metallic tracheostomy tube in the middle-third portion of the trachea.

was reported in 1987 [3]. In that series, both metallic and plastic tubes were included. Among the 62 reported bronchoscopic procedures to remove foreign objects [4], only one (1.6%) was due to a plastic tracheostomy tube. In one report, the breakage of a stainless steel tracheostomy tube had resulted in the death of a 19-year old man [5]. Various factors might contribute to the fracture of a tracheostomy tube [6]: long, continued high internal stress on the surface; erosion by alkaline tracheobronchial secretions; long duration of usage; defects in braising and manufacture; mechanical stress and fatigue caused by repeated removal; and repeated cleaning and reinsertion.

To our knowledge, the case reported here involves a patient older than any other patient with this complication reported in literature. The duration of use of his metallic tracheostomy tube may have been more than ten years. Therefore, metal fatigue and the degradation of the plate-external tube braced joint may be the main causes of breakage in this instance. Repeated boiling and inadequate care might have also facilitated its breakage.

Chevalier Jackson pioneered the techniques for the endoscopic management of tracheobronchial foreign bodies over 79 years ago. He stated that open surgery was not indicated for the removal of airway foreign bodies [7]. Until 1970, however, hollow, rigid instruments were the only access to the tracheobronchial tree. General anesthesia was necessary for most patients undergoing rigid bronchoscopy. In 1993, Malhotra et al [8] described the first successful removal of a metallic tracheostomy tube in the right main bronchus using flexible bronchoscopy. Though a foreign body dislodgment was observed once in 55 children undergoing diagnostic fiberoptic bronchoscopy [9], a high success rate (68-95%) for foreign body extraction with few and unimportant complications [3, 10] have been reported. This approach is usually safe and timesaving in emergency settings, and should be considered for any patient with a broken tracheostomy tube lodged in the tracheobronchial tree. If flexible bronchoscopy fails, the opinion on alternative techneques varies from secondary bronchoscopy to thoracotomy [11].

In summary, aspiration of a broken tracheostomy tube can be a serious, long-term complication of tracheostomy. As a precaution, the regular examination of tracheostomy tubes for signs of wear and tear is therefore indicated. In particular, the braced joint between the external tube and the tracheostomy plate should be checked frequently for structural integrity. In the rare and unfortunate incidence of a broken tracheostomy tube and the subsequent presentation of a tracheobronchial foreign object, therapeutic bronchoscopy is the mainstay of treatment.

References

1.Bhattacharjee N. Fractured tracheostomy tubes: 3 case reports. Bangladesh Med Res Council Bull 1994; 20: 8-11.

2.Bassoe H.H. , Boe J. Broken tracheostomy tube as a foreign body. Lancet 1960; 1: 1006-7.

3.Gupta S.C. Fractured tracheostomy tubes in the tracheobronchial tree: a report of nine cases. J Laryngol Otol 1987; 101: 861-7.
4.Debeljak A, Sorli J, Music E, et al. Bronchoscopic removal of foreign bodies in adults: experience with 62 patients from 1974-1998. Eur Respir J 1999; 14: 792-5.
5.Kock KF, Thomsen JL. Safety in using metal tracheostomy tubes. Ugesk Laeger. 1994; 156: 1960-2. [In Danish English abstract]
6.Gupta S.C. Fractured tracheostomy tube: an overlooked foreign body. J Laryngol Otol 1996; 110: 1069-1.
7.Jackson C. Are there cases of foreign bodies in the lungs impossible of bronchoscopic removal? Laryngoscope 1921;31: 528-38.
8.Malhotra B. Kallan BM. An unusual foreign body in tracheobronchial tree: removed by fiberoptic bronchoscope. Indian J Chest Dis Allied Sci. 1993; 35: 85-8. [In Indic English abstract]
9.Martinot A, Closset M, Marquette CH et al. Indications for flexible versus rigid brochoscopy in children with suspected foreign body aspiration. Am J Respir Crit Care Med 1997; 155: 1676-9.
10.Donado Una, de Miguel Poch E, Casado Lopez ME, et al. Fiberoptic bronchoscopy in extraction of tracheobronchial foreign bodies in adults. Arch Bronchopneumol 1998; 34: 76-81. [In Spanish English abstract]
11.Steven C. Bernard R. David L. Indications for open surgical removal of airway foreign bodies. Ann Otol Rhinol Laryngol 1993;102: 690-4.

吸入斷裂之金屬氣切套管－氣管及支氣管異物罕見之原因

葉步盛　許永隆　郭炳宏

我們描述一位76歲男性，因為陳舊性中風及反覆吸入性肺炎而接受氣管切開術，並長期使用金屬氣切套管。因氣切套管斷裂而導致危及生命的呼吸道阻塞。臨床上病人有突發性呼吸困難的現象。胸部X光顯示斷裂之金屬氣切套管正好卡在左主支氣管。我們嘗試局部麻醉並使用軟式支氣管內視鏡配合有齒之切片鉗成功的取出此異物，病人免除了全身麻醉並於隔天順利出院。金屬氣切套管斷裂後造成呼吸道阻塞之病案報告並不多見。我們回顧過去的文獻報告並探討其原因及處理方式。***(胸腔醫學 2000; 15: 141-145)***

關鍵詞：金屬氣切套管，切片鉗，氣管及支氣管異物，支氣管內視鏡

國立臺灣大學附設醫院胸腔科
索取抽印本請聯絡：郭炳宏醫師，台北市中山南路7號

Papillary Thyroid Carcinoma with Pleural Metastasis – A Case Report

Chen-Hsing Chou, Kuo-An Chu, Jau-Yeong Lu, Hong-Chung Wang

Papillary carcinoma of the thyroid generally follows an indolent course, with slow growth and a low metastatic rate. The most common sites of metastases are the cervical lymph nodes, the lungs' and bone. Pleural metastasis is a rare condition, but a poor prognostic sign when it appears. We present a female who had a history of papillary thyroid carcinoma, and who developed massive right side pleural effusion one year after total thyroidectomy. Papillary thyroid carcinoma with pleural metastasis was considered due to elevated thyroglobulin (Tgb) in the pleural effusion and a positive pleural uptake in the iodine I-131 whole-body scan. The diagnosis was proved by thoracoscopic biopsy. Systemic I-131 therapy was given, but no significant improvement was noted. She died 8 months after the pleural metastasis had presented. ***(Thorac Med 2000; 15: 146-151)***

Key words: Papillary thyroid carcinoma, pleural metastasis, thyroglobulin.

Introduction

Thyroid cancer is uncommon, with about 12,000 new cases occurring each year in the USA space [1], and shows a female predominance [1]. The age at diagnosis of thyroid cancer is distributed from 5-87 years [2]. The peak age distribution of papillary thyroid cancer in Taiwan is 21 to 40 years [3]. Patients with well-differentiated thyroid cancer have an excellent prognosis, even in the presence of a persistent tumor [1]. The patient age at diagnosis, tumor cell types and the presence of distant metastasis all influence the prognosis [2,4]. Distant metastasis shortens life expectancy: the 10–year overall survival rate with distant metastasis ranges from 24% to 36% [4]. Pleural metastasis is a rare condition. It may develop many years after the initial diagnosis, and indicates a poor prognosis and death within 1 to 20 months (median 11 months) [1].

An elevated thyroglobulin level of the blood after total thyroidectomy means recurrence or distant metastasis of thyroid cancer. The serum Tgb level combined with I-131 whole-body scan can be used to follow up thyroid cancer patients who have received total thyroidectomy, and effectively detect early tumor recurrence or distant metastases.

Division of Chest Medicine, Department of Medicine, Veterans General Hospital -Kaohsiung, Taiwan, ROC
Address reprint requests to: Kuo-An Chu, MD, Division of Chest Medicine, Department of Medicine, Veterans General Hospital Kaohsiung, 386, Ta-Chiung 1st Road, Kaohsiung, Taiwan, ROC.

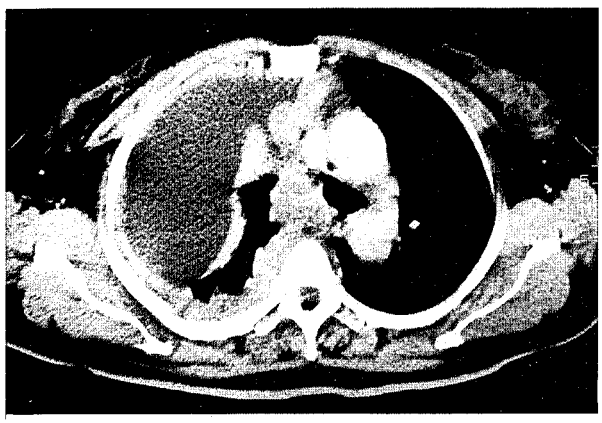


Fig.1 Chest computed tomographic scan showing diffuse enhancing pleural thickness with multiple nodularities, massive right-sided pleural effusion, and collapse of the right lung.

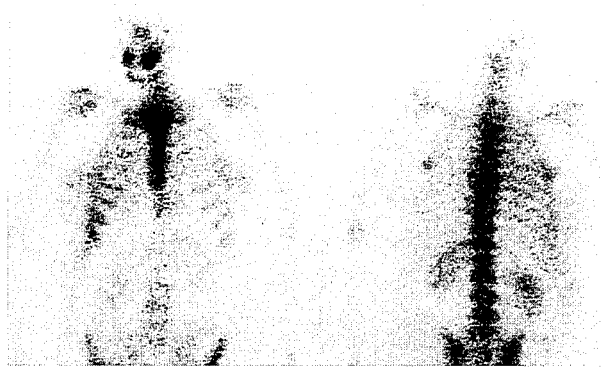


Fig. 2 I-131 whole body scan showing an increased right thoracic uptake, compatible with thyroid cancer with pleural metastasis.

In this report, we present the case of a papillary thyroid carcinoma patient, who had pleural metastasis one year after initial diagnosis. A positive post-therapy I-131 whole-body scan, an elevated Tgb level of the blood, and pleural effusion were present. She received local and systemic treatment, but had a poor response.

Case report

A 45-year-old female patient called at our emergency room due to progressive dyspnea for one month. She had a history of cervical cancer and bilateral ovarian cysts, and had received an abdominal total hysterectomy 6 years ago and a bilateral salpingo-oophorectomy one year ago. She was diagnosed as papillary thyroid carcinoma over the bilateral neck in May 1998, and then received a total thyroidectomy with radical neck dissection. The pathological examination of the resected specimen showed papillary carcinoma of the thyroid gland with multiple cervical lymph nodes and adjacent muscle involvement. She received a thyroxine supplement after the total thyroidectomy, but didn't receive systemic I-131 therapy. She suffered from dyspnea in February 1999, and visited a local physician. The chest X-ray at that time showed massive right-side pleural effusion, and a pelvic sonography revealed no abdominal tumor growth. She was then referred to our hospital for further management.

She called at our emergency room one month later, when a chest X-ray was performed, and showed massive right-side pleural effusion. She received a chest CT scan then, which showed a diffuse right pleural thickness with nodularity and a large amount of pleural effusion (Fig. 1).A neck CT scan was also done, and showed only residual post-operation change, with no thyroid cancer recurrence. Then she was admitted for further study.

After admission, the physical examination revealed a diminished breathing sound over the right chest field, and no palpable abnormal abdominal mass lesion. Thoracentesis was performed, and the pleural effusion analysis showed exudative effusion with a white blood cell count: 4060/cumm, neutrophil/lymphocyte: 8/92, and a red blood cell count: 50000/cumm. No acid-fast bacilli were found within the pleural effusion. The repeated cytology examination of the pleural effusion showed no malignant cells. The carcinoembryonic antigen (CEA) of the effusion was 1.01 ng/ml, and the thyroglobulin, 115.9 ng/ml. The CEA of the blood was 1.42 ng/dl, and the thyroglobulin was 71.4 ng/ml. She received a thoracoscopic pleural biopsy for pathological diagnosis, which revealed metastatic papillary adenocarcinoma, with a positive thyroglobulin stain. Papillary thyroid carcinoma with pleural

metastasis was then confirmed. She received pleurodesis with minocycline, and after discontinuing the oral thyroxine supplement for one month, she received iodine I-131 therapy with a dose of 150 mCi. The I-131 whole-body scan was performed 10 days after the systemic iodine I-131 therapy was administered, and showed a warm area over the right thyroid, and a diffuse right thoracic uptake (Fig. 2). After one course of iodine I-131 therapy, a series of chest X-rays and CT scans showed progressive pleural metastasis with chest wall involvement, and new-developed pulmonary metastasis and mediastinal lymph node metastasis was noted in August 1999. She received local palliative radiotherapy over the chest wall lesion for pain control. However, the patient's condition progressively worsened, and she died eight months after the pleural metastasis was found.

Discussion

Thyroid cancer is a relatively uncommon malignancy. Well-differentiated thyroid carcinoma is a slowly growing neoplasm, and patients with this disease usually have a good prognosis. Even with postoperative tumor recurrence, patients still can be cured. With distant metastases, the patients have a 40-50% chance of a 5-year survival rate. [1,4,5,6] Papillary thyroid carcinoma is the most common type of thyroid cancer, accounting for about 70% of all thyroid cancer. Distant metastases of papillary thyroid carcinoma seldom develop. The most common sites of metastases are the cervical lymph nodes, the lungs, and bone [7]. Pleural metastasis rarely occurs, developing in 0.6% of adults with well-differentiated papillary thyroid carcinoma [1]. The prognosis has been associated with patient age at diagnosis, tumor extent, sex, multiple organ metastases, radioiodine uptake of the metastases, and the serum Tgb level [2,3,4,6]. Recurrence or distant metastases may occur many years after the initial diagnosis. Regular lifelong follow-up with measurements of Tgb and clinical examinations may be required.

Thyroglobulin is synthesized in both benign and differentiated malignant thyroid tissue. It is a good tumor marker and is no longer detected after a complete total thyroidectomy, except with tumor recurrence. But patients without a total thyroidectomy can have a wide range of thyroglobulin concentration [8]. Although thyroglobulin is not a good marker for preoperative diagnosis in well-differentiated thyroid cancer, the postoperative thyroglobulin level may be used as a prognostic factor and tumor recurrence marker [3,8]. Patients with post-therapy (surgery or thyroid ablation with I-131) Tgb levels less than 2 ng/ml rarely have tumor recurrence [8]. Post-therapy Tgb levels above 60 ng/ml may indicate the development of distant metastases [9] .A poor prognosis was reported with a Tgb level higher than 25 ng/ml [3]. In our case, the patient's serum Tgb was 71.4 ng/ml, which was compatible with distant metastases, and might demonstrate the possibility of the metastatic adenocarcinoma of the pleura being of thyroid origin, with a poor prognosis.

The pleural effusion cytology of papillary thyroid carcinoma with pleural metastasis frequently shows positive malignant cells [1], with features similar to a primary tumor. These cells are often associated with psammoma bodies [1], which are not a pathognomonic feature of papillary thyroid carcinoma, as they also appear in other tumors, mainly adenocarcinoma of the lung, kidney, and ovaries. In our case, repeated pleural effusion studies didn't reveal malignant cell and psammoma bodies. The histological features of the pleural biopsy showed a moderately differentiated papillary carcinoma, with a positive thyroglobulin stain. Although occasional cases of ovarian carcinoma may show weak staining for thyroglobulin [10], the pleural metastasis of thyroid carcinoma in our patient could still be confirmed because of her previous thyroid cancer history and elevated serum Tgb level.

Tgb is only synthesized by thyroid tissue.

Diseases other than thyroid disorders resulting in elevated serum Tgb occur via the stimulation of thyroid tissue secretion [11,12,13] or the reduction of Tgb metabolism [14]. In cases of total thyroidectomy, no other diseases, except tumor recurrence or struma ovarii (a very rare teratomatous ovarian tumor containing functioning thyroid tissue), can result in elevated serum Tgb. Combining elevated serum Tgb and a positive Tgb stain of the carcinoma in cases of total thyroidectomy, we can almost confirm the carcinoma to be of thyroid origin.

The iodine I-131 whole-body scan has been one of the most important diagnostic tools in the follow-up of differentiated thyroid carcinoma. Its utility in detecting metastases may be interfered with by residual thyroid tissue, whose metabolic activity may mask possible secondary tissue. The I-131 whole body scan can be done with the diagnostic dose (about 3-5 mCi) or as a post-therapy scan 5 days after ablative therapy [9]. This examination can detect residual tumors and distant metastasis. About 21.7% of patients' metastases were not detected by the I-131 whole-body scan [9]. The combined use of the I-131 whole-body scan and Tgb allowed for the detection of the presence of metastases in 83% of patients [9]. In our case, the patient received a post-therapy whole body scan, which showed a residual tumor over the right neck area and distant metastases of the pleura and lung. This finding further confirmed that the thyroid carcinoma was the origin of the pleura metastatic carcinoma.

The first treatment of choice for papillary thyroid carcinoma is surgical removal. Total thyroidectomy is preferred. I-131 therapy should be performed if residual thyroid tissue is found (with a thyroid-ablation dose, about 50 to 60 mCi) or if metastases are present (the dose is double). In patients with papillary thyroid carcinoma with pleural metatstasis, the principal treatment is systemic therapy with radioiodine I-131, but this has little potential in treating metastatic lesions in the chest cavity [1]. Local therapy with tetracycline or radioactive gold, or phosphorus instilled into the pleural cavity for palliation, may be tried, but fail to prevent the recurrence of pleural effusion. In our case, the pleural metastastic lesion progressively enlarged, and persistent pleural effusion was noted even after receiving I-131 therapy and pleurodesis with minocycline. Unfortunately, till now, no definitively effective therapy has been reported for these patients.

Pleural metastasis and pleural effusion, if present, usually occur within 3 years from the time of diagnosis of thyroid cancer, but it may develop many years after diagnosis [1]. However, regardless of the timing of pleural effusion, its appearance means a poor prognosis. After the development of malignant pleural effusion, the survival time was around 11 months in one report [1]. In our case, the patient died 8 months later after the malignant pleural effusion was noted.

In patients with a history of differentiated thyroid carcinoma, regular follow-up serum Tgb is necessary for the detection of tumor recurrence. If pleural effusion develops during regular follow-up, a pleural effusion Tgb study may help to determine its cause. Further evaluation, with measurement of the blood Tgb level and a diagnostic I-131 whole-body scan, are suggested to evaluate the metastatic condition. A pleural biopsy with a Tgb stain may be required in some patients if the above examination fails to prove a thyroid tumor origin. Systemic I-131 therapy may be tried for pleural metastasis of papillary thyroid carcinoma, but the response has been poor. A grim prognosis is indicated when pleural metastasis is found, regardless of the timing and treatment.

Reference

1.Vassilopoulou-Sellin R, Sneige N. Pleural effusion in patients with differentiated papillary thyroid cancer. Southern Med J 1994; 87: 1111-6.

2.Samaan NA, Schultz PN, Haynie TP, et al.

Pulmonary metastasis of differentiated thyroid carcinoma: treatment results in 101 patients. J Clin Endocrinol Metab 1985; 65:376-80.

3.Lin JD, Huang HS, Chen SC, et al. Factors that predict metastasis of papillary and follicular thyroid cancers in Taiwan. Otolaryngol head neck surg 1997; 116:475-82.

4.Ruegemer JJ, Hay ID, Bergstralh EJ, et al. Distant metastases in differentiated thyroid carcinoma: a multivariate analysis of prognostic variables. J Clin Endocrinol Metab 1988; 67:501-8.

5. Massin JP, Savoie JC, Garnier H, et al. Pulmonary metastases in differentiated thyroid carcinoma- study of 58 cases with implications for the primary tumor treatment. Cancer 1984; 53:982-92.

6.Brown AP, M.R.C.P. BS, Greening WP, et al. Radioiodine treatment of metastatic thyroid carcinoma: the Royal Marsden hospital experience. BR J Radiol 1984; 57:323-7.

7.Rasmusson B. Carcinoma of the thyroid – A survey of 227 cases. Acta Radiologica Oncology 1978; 17: 177-88.

8. Ruter A, Smeds S, Lennquist S. Value of serum thyroglobulin measurement in patients operated on for well-differentiated thyroid carcinoma. Eur J Surg 1998; 164:665-71.

9. Filesi M, Signore A, Ventroni G, et al. Role of initial iodine-131 whole-body scan and serum thyroglobulin in differentiated thyroid carcinoma metastases. J Nucl Med 1998; 39:1542-6.

10.Keen CE, Szakacs S, Okon E, et al. CA125 and thyroglobulin staining in papillary carcinoma of thyroid and ovarian origin is not completely specific for site of origin. Histopathology 1999; 34: 113-7.

11.Van Herle AJ, Klandorf H, Uller RP. A radioimmunoassay for serum rat hyroglobulin, physiologic and pharmacological studies. J Clin Invest 1975; 56:1073-81

12.Van Herle AJ, Chopra IJ, Hershman JM. Serum thyroglobulin in inhabitants of an endemic goiter region of New Guinea. J Clin Endocrinol Metab 1976; 43:512-6.

13.Feldt-Rasmussen U, Petersen PH, Date J. Sex and age correlated reference values of serum thyroglobulin measured by a modified radioimmunoassay. Acta Endocrinol (Copenh) 1979; 90:440-50.

14.Hegedus L, Kastrup J, Feldt-Rasmussen U. Serum thyroglobulin in acute and chronic liver disease. Clin Endocrinol (Oxf) 1983; 19:231-7.

乳凸狀甲狀腺細胞癌併肋膜轉移及肋膜積液－病例報告

周振興　朱國安　盧朝勇　王鴻昌

乳凸狀甲狀腺細胞癌是一種進展緩慢的腫瘤，有較低的轉移比例。最常見的轉移部位為頸部淋巴腺，肺部及骨頭。併發肋膜轉移是一種很少見的情況，且常是病患預後不好的指標。我們報導一個女性病患，先前有乳凸狀甲狀腺細胞癌接受甲狀腺全切除手術。手術一年後發生大量右側肋膜積液。積液檢查顯示甲狀腺球蛋白(Thyroglobulin)升高，且碘-131 全身掃描亦顯示肋膜有攝取。吾人懷疑此為甲狀腺癌併肋膜轉移，後經胸腔鏡切片檢查證實。雖然給予碘-131 治療，病情仍無改善。病患於八個月後死亡。***(胸腔醫學 2000; 15: 146-151)***

關鍵詞：乳凸狀甲狀腺細胞癌，肋膜轉移，甲狀腺球蛋白

高雄榮民總醫院　內科部　胸腔內科
索取抽印本請聯絡：周振興醫師，嘉義市世賢路二段 600 號　嘉義榮民醫院內科

Recurrent Juvenile-Onset Laryngotracheal Papillomatosis With Pulmonary Parenchymal Spread – A Case Report

Jiann-Der Lee, Gee-Chen Chang, Chih-Mei Huang, Gwan-Han Shen, Chi-Der Chiang

A 33-year-old female patient with juvenile-onset laryngotracheal papillomatosis had presented with hoarseness and upper airway obstruction at 7 years old, and received a CO2 laser papillectomy and tracheostomy. Papillomatosis recurred and underwent repeated CO2 laser and local acyclovir cream treatments, but with no appreciable improvement. During the last month, progressive shortness of breath, dyspnea on exertion, and fever had developed. Multiple cavitary lesions were found incidentally on chest radiography. A bronchoscopy was performed and papillomatosis was confirmed, with bronchial and lung spread. A review of the literature has shown that respiratory tract papillomas distally extending into the trachea, bronchi, and lung parenchymal are rarely seen. ***(Thorac Med 2000; 15: 152-156)***

Key words: laryngotracheal papillomatosis

Introduction

Juvenile-onset laryngotracheal papillomatosis of the respiratory tract is a benign neoplastic disease that involves the larynx and trachea, but rarely the bronchi and lungs. It occurs more commonly in children and adolescents as multiple papillary tumors on the vocal cords, though rare cases of tracheal and bronchial involvement without laryngeal disease have been reported [1,2]. The mechanism of intra- parenchymal spread is unknown, but peripheral seeding [3] and the multicentric origin of papillomas have been postulated as causes. Tracheostomy or other operative manipulations may induce or exacerbate spreading [4]. Papillomatosis of the upper respiratory tract can lead to hoarseness, stridor, dyspnea, hemoptysis, and respiratory distress; a tracheostomy may be necessary if obstruction of the airway is severe enough. Involvement of the lower respiratory tract can lead to bronchiectasis, alelectasis, pneumonia, tissue destruction, cyst formation, and pneumothorax [5]. Another complication of papillomatosis is squamous cell carcinoma arising in the larynx, trachea, and around the tracheostomy site in patients who have received radiation therapy or smoked cigarettes [6]. A transformation to squamous cell carcinoma of the

Chest Division, Department of Internal Medicine Taichung Veterans General Hospital
Address reprint requests to: Dr. Jiann-Der Lee, Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, No.160, Section 3, Chung-Kan Road, Taichung City, Taiwan, R.O.C.

lung has been reported in non-irradiated, non-smoking patients [7].

Case Report

The patient was a 33-year-old female with no history of smoking or irradiation. At age 7, she suffered from hoarseness, stridor, dyspnea, intermittent cough, and recurrent upper respiratory tract infection. She was diagnosed with laryngotracheal papillomatosis and subsequently treated with multiple local excisions and a temporal tracheostomy. She had annual CO2 laser ablation therapy for the recurrent tracheal lesions, using a local acyclovir cream 5%, in the otorhinolaryngologic department of our hospital. Twenty-six years after the diagnosis of papillomatosis, a chest X-ray film showed two suspicious mass densities in the upper lobe of the right lung and the lower lobe of the left lung (Fig 1). Fever, purulent sputum, stridor, and dyspnea developed, and she was referred to our chest medicine out-patient department. Computed

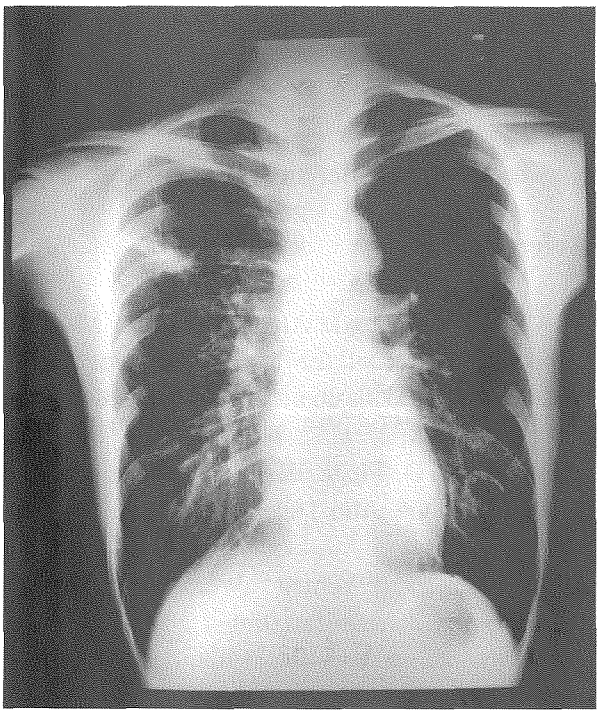


Fig. 1 Cavitary lesions in bilateral lungs with enlargement to mass-like formation.

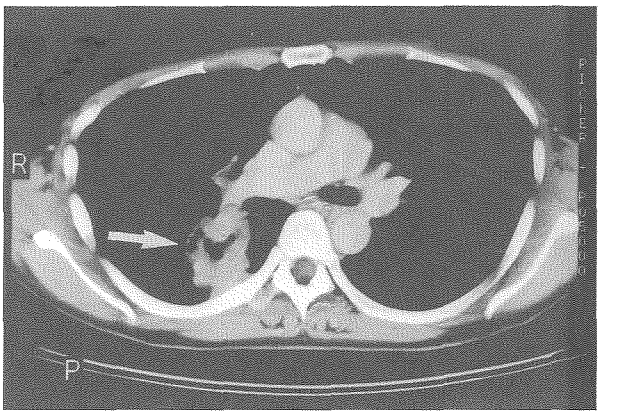


Fig. 2 Chest CT scan shows multiple cavitary lesions (arrows) within the parenchyma of the lungs.

tomography (CT) showed multiple necrotic masses of variable sizes in both lungs (Fig 2). She received a bronchoscopy examination transorally, with the finding of several papilloma lesions over the residual larynx and upper third of the trachea which caused upper airway diffuse narrowing. There was copious mucopurulent secretion present, some of which has been removed by suction. The bronchoscopy was stopped due to her inability to tolerate the hypoxia aggravated by the bronchoscope. She was admitted to our ward and an otolaryngologist was consulted for a tracheostomy and CO2 laser ablation therapy of the recurrent trachea lesions. A bronchoscopy was repeated via the transtracheostomy tube with the finding of one tumor lesion obstruction in the right anterior sub-branch (Fig 3). A transbronchial biopsy was then done. Histopathology showed squamous cell papilloma (Fig 4). The sputum culture yielded pseudomonas aeroginosa sensitive to piperacillin/ tazobactam. After antibiotics treatment, her condition improved and she was discharged.

Discussion

The viral etiology of respiratory papillomatosis has been well-established, but the precise manner in which it spreads is not known. Of the more than 60 types of human papillomavirus that have been identified, HPV 6 and 11 are primarily

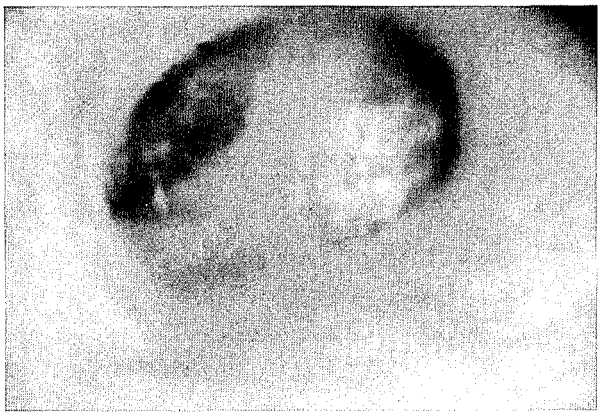


Fig. 3 Bronchoscopy disclosed one tumor lesion obstruction in the RB3 sub-branch.

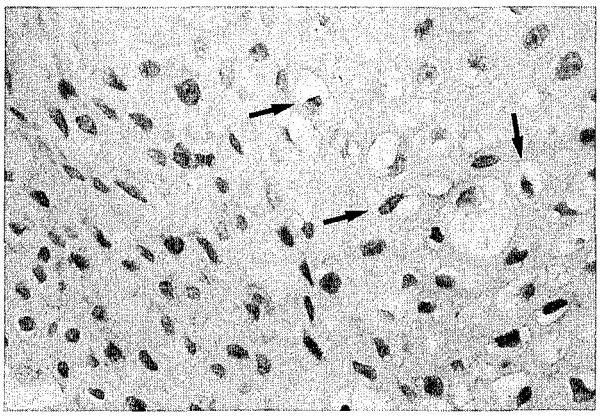


Fig. 4 Bronchus biopsy: the papillae are covered by a well-differentiated non-keratinizing squamous epithelium containing koilocytes (arrows). (H & E x400)

associated with papillomatosis [7]. Numerous studies have shown HPV 6 or 11 in laryngeal, tracheal, bronchial, and pulmonary papillomas, and in uninvolved sites in patients with active disease or in clinical remission [8-9].

Patients with juvenile-onset papillomatosis probably acquired the HPV 6 or 11 during birth, from mothers with genital condyloma [10-11]. It is not known if adult-onset papillomatosis represents a delayed manifestation of a perinatal infection or one acquired later, possibly through oral contact with infected genitals or secretions [12].

Papillomas typically spread from the larynx by direct extension to the trachea and bronchi. This aggressive pattern of growth by a neoplasm lacking the cytologic features of malignancy has been termed "invasive papillomatosis" by Fechner et al [13]. In situ transformation of bronchiole mucosa infected with HPV is another possible mechanism by which papillomas arise in the lower respiratory tract. Almost all patients with juvenile-onset laryngotracheal papillomatosis have needed a tracheostomy within 1 year of diagnosis [14].

Most radiographic findings in the involved lung include initial solid nodules or the cavitary lesions coexisting with a predilection for the lower lobes. Cavities tend to enlarge slowly, and areas of consolidation or atelectasis may be superimposed upon cavitary lesions. Less typical presentations have included consolidation, a large solitary mass, and bronchiectasis. Bronchiectasis may reflect endobronchial papillomatosis [15].

Specific treatment directed to the lung involved has included resection, antibiotics, steroids, and chemotherapy in combination with human leukocyte interferon-alpha. A sustained benefit has yet to be demonstrated. Patients with chronic and extensive papillomatosis involving the bronchi, or bronchioles, are at risk for spontaneous malignant transformation without prior therapeutic irradiation. Clearly, for all patients with long-standing respiratory papillomatosis, squamous cell carcinoma must be considered in the differential diagnosis.

References

1.Al-Saleem T, Peale AR, Norris CM. Multiple papillomatosis of the lower respiratory tract. Clinical and pathologic study of eleven cases. Cancer 1968; 22:1173-84.

2.Aylward TD, Flege JB Jr. Primary papilloma of the trachea. Ann Thorac Surg 1973; 16:620-3.

3.Kramer SS, Wehunt WD, Stocker TJ. Pulmonary manifestations of juvenile laryngotracheal papillomatosis. AJR 1982; 139: 1036 (Abstr).

4.Runckel D, Kessler S. Bronchogenic squamous carcinoma in nonirradiated juvenile

laryngotracheal papillomatosis. AM J Surg Pathol 1980; 4: 293.
5.Anderson KC, Roy TM, Fields CL, et al. Juvenile laryngeal papillomatosis: a new complication. South Med J 1993; 86: 447-9.
6.Majuros M. Laryngeal papillomas: malignant transformation after radiation therapy. Surg Clin North Am 1963; 43: 1049-61.
7.Yantsos VA, Gist H. Farr, JR., Michael McFadden et al. Recurrent juvenile-onset laryngotracheal papillomatosis with transformation to squamous cell carcinoma of the lung. South Medical J. Oct 1999; vol. 92, No 10: 1013-16.
8.Byrne JC, Tsao MS, Fraser RS, et al. Human papillomavirus-11 DNA in a patient with chronic laryngotracheobronchial papillomatosis and metastatic squamous-cell carcinoma of the lung. N Engl J Med 1987; 317: 873-8.
9.Guillou L, Sahli R, Chaubert P, et al. Squamous cell carcinoma of the lung in a nonsmoking, nonirradiated patient with juvenile laryngotracheal papillomatosis. Evidence of human papillomavirus-11 DNA in both carcinoma and papillomas. Am J Surg Pathol 1991; 15: 891-8.
10.Hajek E. Contribution to the etiology of laryngeal papilloma in children. J Laryngol Otol 1956; 70: 166-8.
11.Quick CA, Faras A, Krzyzek R. The etiology of laryngeal papillomatosis. Laryngoscope 1978; 88: 1789-95.
12.Katial RK, Ranlett R, Whitlock WL. Human papilloma virus associated with solitary squamous papilloma complicated by bronchiectasis and bronchial stenosis. Chest 1994; 106: 1887-9.
13.Fechner RE, Geopfert H, Alford BR. Invasive laryngeal papillomatosis. Arch Otolaryngol 1997; 99: 147-51.
14.T. Kawanami, A. Bowen. Juvenile laryngeal papillomatosis with pulmonary parenchymal spread, case report and review of the literature. Pediatric Radiology 1985; 15: 102-4.
15.Justus J, Baerthold W, Preibisch-Effenberger R. Juvenile larynxpapillomatose mit Ausbreitung uber das Trcheobronchialsystem und maligne Entartung ohne Strahlentherapie. HNO 1970; 18: 349.

復發性幼年型喉與氣管的乳頭狀瘤病併肺擴散－病例報告

李建德　張基晟　黃枝梅　沈光漢　江自得

一位 30 歲女性病人於七歲時被診斷為幼年型喉與氣管的乳頭狀瘤病，初期症狀為聲音沙啞與上呼吸道阻塞，隨後接受二氧化碳雷射切除及氣切手術。復發後再多次接受二氧化碳雷射切除術及局部 acyclovir 藥膏塗抹，但效果並不令人滿意。最近因呼吸困難與發燒症狀求診，意外發現 X 光檢查肺部有多處空洞病灶，支氣管鏡檢証實有支氣管內乳頭狀瘤病擴散。回顧過去的文獻，呼吸道乳頭狀瘤病擴散至氣管，支氣管及肺部是相當罕見。*(胸腔醫學 2000; 15: 152-156)*

關鍵字：laryngotracheal papillomatosis

台中榮民總醫院　胸腔內科
索取抽印本請聯絡：李建德醫師，台中市中港路三段 160 號