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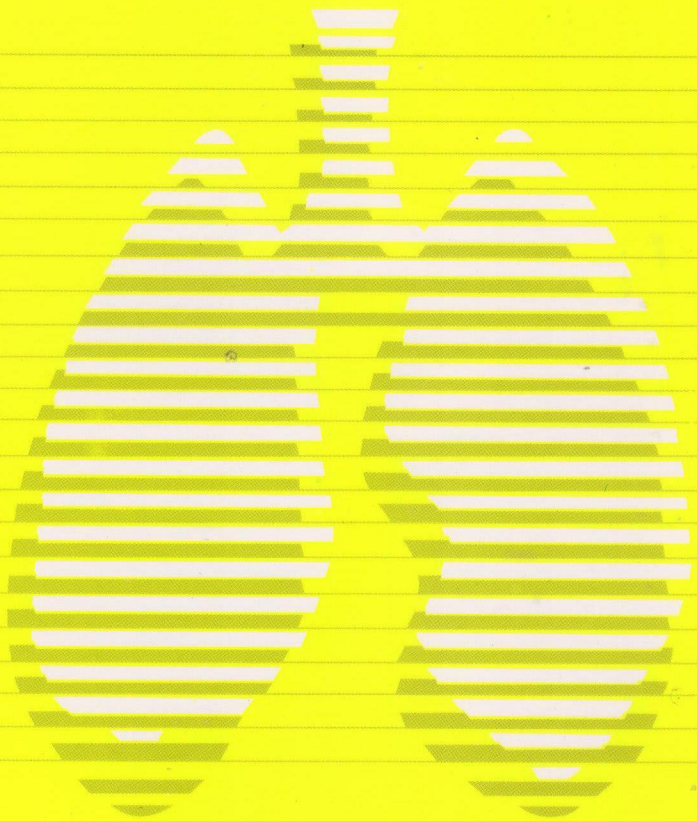

台灣胸腔暨重症加護醫學會

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Orginial Articles

Case Reports

Detecting *Mycobacterium Tuberculosis* in BACTEC MGIT 960 Cultures by COBAS AMPLICOR MTB in Routine Clinical Practice

Kuan-Jen Bai, Fang-Lan Yu, Ruwen Jou*, Mei-Shiang Wang, Ming-Hwei Lin, Chun-Nin Lee, Ming-Chih Yu

Introduction: The rapid, automated cultivation and detection system, BACTEC MGIT 960, is widely used in Taiwan. But the high nontuberculous mycobacteria (NTM) isolation rate is a concern that should be carefully evaluated. The aim of this study was to evaluate the ability of the commercial COBAS AMPLICOR MTB amplification system to identify *Mycobacterium tuberculosis* (*M. tuberculosis*) in positive BACTEC MGIT 960 cultures in routine clinical practice.

Methods: We tested 270 positive BACTEC MGIT 960 cultures with the COBAS AMPLICOR MTB at Taipei Medical University-Wan Fang Hospital from March 1, 2006 through February 28, 2007. The COBAS AMPLICOR MTB results were compared with mycobacterial species identification by conventional biochemical testing.

Results: We found that 207 (76.7%) COBAS AMPLICOR MTB results were regarded as conclusive, and 63 (3 *M. tuberculosis*, 60 NTM) inconclusive. Among 176 conclusive results positive for *M. tuberculosis*, 174 were regarded as true positive and 2 false positive. Among 31 conclusive results negative for *M. tuberculosis*, 30 were regarded as true negative and 1 false negative. After excluding the inconclusive results, we further found that the sensitivity, specificity, and positive/negative predictive values of the COBAS AMPLICOR MTB test were 99, 94, 99, and 97%, respectively.

Conclusion: COBAS AMPLICOR MTB might be suitable for rapid detection and identification of *M. tuberculosis* in BACTEC MGIT 960 cultures in routine clinical practice. ***(Thorac Med 2008; 23: 156-163)***

Key words: *Mycobacterium tuberculosis*, COBAS AMPLICOR MTB, BACTEC MGIT 960

Introduction

Tuberculosis (TB) is a major health problem worldwide. The World Health Organization estimated that there were 8.8 million new cases and 1.6 million deaths resulting from TB in 2005 [1]. TB is also a serious health problem in Taiwan [2]. To prevent and control TB, new cases of

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infectious TB should be diagnosed and reported as early as possible so that curative treatment can be initiated, transmission interrupted, and public health responses (contact investigation and case-management services) promptly arranged [3].

The turnaround time for isolating and identifying *Mycobacterium tuberculosis* (*M. tuberculosis*) should not exceed 21 days [3]. But, conventional solid culture systems (Löwenstein-Jensen [LJ] slant or Middlebrook 7H11 agar plate) have rarely achieved these standards [4]. Recently, the fully automated, non-radiometric and non-invasive BACTEC MGIT system has been introduced and is widely used in Taiwan. The MGIT has a modified Middlebrook 7H9 broth in conjunction with a fluorescent quenching-based oxygen sensor in an atmosphere of 10% CO_2. The BACTEC MGIT system automatically records bacterial growth every 60 minutes, based on O_2-sensitive fluorescence [5]. Compared to conventional solid medium, the BACTEC MGIT system has been found to have the advantages of both increasing the recovery of mycobacteria and shortening the turnaround time [6-10].

Recovering mycobacteria can be accelerated with the MGIT system, but can provide only partial benefit if it not accompanied by rapid species identification [11]. Differentiating *M. tuberculosis* from nontuberculous mycobacteria (NTM) as soon as possible is important, particularly in situations in which NTM represents a considerable share of the clinical isolates. To note, 24% of isolated mycobacteria were identified as NTM in our TB laboratory in 2006 [unpublished data]. Conventionally, identifying *M. tuberculosis* is time-consuming and sometimes ambiguous when using biochemical methods. Therefore, the development of a rapid method of identifying mycobacteria isolated from the MGIT system is urgently needed.

The commercial amplification system, COBAS AMPLICOR MTB, can be used to identify *M. tuberculosis* within several hours. Therefore, the aim of this study was to evaluate the ability and feasibility of identifying *M. tuberculosis* in positive BACTEC MGIT cultures using this commercial amplification system in routine clinical practice.

Materials and Methods

Specimens

The TB Laboratory of Taipei Medical University-Wan Fang Hospital (TMU-WFH) is 1 of the 9 contract laboratories of the Centers for Disease Control (CDC), Taiwan, providing laboratory services for mycobacterial diseases at TMU-WFH and healthcare facilities in northern Taiwan.

We processed sputum specimens from patients with suspected TB with standard *N*-acetyl-L-cysteine-NaOH procedures and concentrated them with centrifugation (3,000 g for 15 min) at the TMU-WFH TB Laboratory [12]. The supernatant was discarded, and the sediment was resuspended with sterile phosphate buffer. This suspension was then inoculated into 2 media: an MGIT culture tube and an LJ slant.

From March 1, 2006 through February 28, 2007, we enrolled 270 positive BACTEC MGIT cultures into this study; 188 were from patients at TMU-WFH and 92 were from patients of other healthcare facilities.

Culture Systems

BACTEC MGIT 960 Culture Systems

The MGIT culture tube contained a 7-ml Middlebrook 7H9 broth base, to which an

enriched supplement containing oleic acid, albumin, dextrose, catalase and polyoxyethylene stearate was added. In addition, BBL MGIT PANTA (an antibiotic mixture of polymyxin B, amphotericin B, nalidixic acid, trimethoprim, and azlocillin) was added to the culture tube [4]. The culture tube contained a fluorescent sensor that detects the oxygen concentration in the culture medium. The level of fluorescence corresponded to the O_2 amount consumed by the organisms in the inoculant. This, in turn, was proportional to the number of bacteria present. When a certain level of fluorescence was reached, the instrument indicated that the tube is positive [4].

After inoculating each tube with 0.5 ml of the processed specimen, we incubated the tubes at 37°C. The instrument automatically read the MGIT tubes hourly for 6 weeks or until positive results were found. We removed the positive samples from the instrument, and examined their smears for acid-fast bacilli (AFB). If the smear was AFB-positive, the broth was then further cultured onto the LJ slant and 7H11 Middlebrook for the species identification.

Solid media method

We inoculated all specimens and the positive MGIT culture fluid onto the LJ slant, and incubated them at 37°C in an atmosphere of 10% CO_2 for 8 weeks or until we saw mycobacterial colonies.

Identifying Mycobacteria

Identifying mycobacteria was based on conventional methods and the COBAS AMPLICOR MTB test. Conventional methods were based on colony morphology, colony pigmentation, rate of growth on conventional solid media, and results of biochemical tests (such as the niacin test and nitrate reduction test) [12]. In our laboratory, we routinely attempt to differentiate *M. tuberculosis* from NTM, but not to further identify the NTM species.

The COBAS AMPLICOR MTB test kit follows 4 main steps: (1) specimen preparation, (2) DNA polymerase chain reaction (PCR) amplification, (3) hybridization, and (4) detection [13]. We did this assay according to the manufacturer's instructions (Roche Diagnostics Corporation, Indianapolis, USA). Briefly, 100 µl of positive MGIT culture fluid was added to 500 µl of wash buffer, and then centrifuged at 12,500 xg for 10 min. We aspirated the supernatant and added 100 µl of lysis reagent to the sediment. The suspension was incubated at 60°C for 45 min and then neutralized by adding 100 µl of neutralization reagent. We transferred 50 µl of each prepared specimen to tubes containing 50 µl of master mix, including all needed components for amplification. Amplification was done by the built-in thermal cycler (Cobas Amplicor Analyzer, Rotkreuz, Switzerland). In addition, we introduced a sequence of plasmid DNA with primer binding regions identical to those of the *M. tuberculosis* sequence into each reaction mixture, and co-amplified it with the target DNA to give an internal control of the PCR reaction.

We prevented carryover contamination by incorporating dUTP in place of dTTP in the amplification reaction and using uracil-*N*-glycosylase (Amperase) to cleave any amplicon carried over from previous reactions. After amplification, the amplified nucleotide sequence for *M. tuberculosis* and the internal control were automatically detected with target-specific DNA probes, and A660 was measured with the built-in spectrophotometer. We interpreted specimens with an absorbance greater than 0.35

as positive regardless of the internal control result, and those less than 0.35 and with an internal control absorbance greater than 0.35 as negative. However, we read specimens with an absorbance less than 0.35 and an internal control absorbance less than 0.35 as inconclusive.

Statistical analysis

We calculated sensitivity, specificity, and positive/negative predictive values to evaluate the COBAS AMPLICOR MTB system, and compared them with conventional biochemical test results.

Results

Table 1 lists the results of 270 mycobacterial strains isolated from patients at TMU-WFH and other health facilities, using the COBAS AMPLICOR MTB and conventional methods. Of them, 65.9% (178 strains) were *M. tuberculosis* and 34.1% (92 strains) were NTM.

Table 2 shows the results of 126 AFB smear-negative isolates from TMU-WFH patients, using COBAS AMPLICOR MTB and conventional methods. After excluding the 35 (27.8%) inconclusive results, the sensitivity, specificity, and positive/negative predictive values of the COBAS AMPLICOR MTB test were all 100%.

Discussion

In Table 1, we showed that the COBAS AMPLICOR MTB test has promising sensitivity and specificity in identifying *M. tuberculosis* in positive specimens from the BACTEC MGIT system. We further found this high performance (sensitivity, specificity, and positive/negative predictive values) in both AFB smear-negative and smear-positive specimens (Tables 1 and 2). Based on these results, we suggest that the COBAS AMPLICOR MTB test should be considered as a tool for rapidly identifying *M. tuberculosis* from positive MGIT culture fluids.

In recommendations from Taiwan and the U.S. CDC, all clinical specimens suspected of having mycobacteria should be inoculated onto culture media for 4 reasons: (1) culture is much more sensitive than microscopy; (2) growth of the organisms is necessary for precise species identification; (3) drug susceptibility testing re-

Table 1. Results of COBAS AMPLICOR MTB and conventional methods with patients at Taipei Medical University-Wan Fang Hospital and other health facilities (n=270)

	AMPLICOR MTB	Conventional methods	
		M. tuberculosis	NTM
Total	270	178	92
Inconclusive	63	3	60
Conclusive	207	175	32
Positive	176	174	2
Negative	31	1	30

Excluding inconclusive results:
Sensitivity: 174/174+1 = 99%
Specificity: 30/2+30 = 94%
Positive predictive value: 174/174+2 = 99%
Negative predictive value: 30/1+30 = 97%

quires culture of the organisms; and (4) genotyping of cultured organisms is needed [12, 14]. Liquid media systems, which can provide information in less time than solid media, should be available in all TB laboratories [3]. If combined with the use of a conventional solid medium, the overall recovery rate of mycobacteria in culture is increased [4-10]. According to Taiwan CDC recommendations, liquid and solid media should be used simultaneously for mycobacteria culture [12]. Non-radiometric MGIT is an automated, sensitive, rapid and less labor-intensive mycobacterial culture system. Therefore, the use of combined LJ and MGIT media has been widely adopted in Taiwan [4-5].

Although the MGIT system can shorten the turnaround time of mycobacterial culture, a higher NTM isolation rate was also reported with this method [4-10]. We also found a 20%~50% NTM isolation rate in the results of 9 contract laboratories of the Taiwan CDC recently [unpublished data]. *M. tuberculosis* can exhibit serpentine cording when grown in liquid medium. This formation could be the rapid presumptive identification of *M. tuberculosis* from positive MGIT culture, but the sensitivity is only 64% [15]. Meanwhile, from the time of positive MGIT culture, several weeks are usually required to obtain mycobacterial species identification by subculture on solid medium and to carry out biochemical testing. Therefore, there is an urgent need to develop a quick method to perform accurate species identification [11, 16]. As shown in Table 1, we found that the COBAS AMPLICOR MTB test was effective in identifying *M. tuberculosis* on positive specimens from the MGIT system, which helped in making the subsequent clinical decision.

For suspected cases of pulmonary TB, positive sputum AFB smears provide a reliable indication of potential infectiousness [3]. A nucleic acid amplification test (NAA) can provide rapid confirmation that the infecting mycobacteria emanated from the *M. tuberculosis* complex [3]. The designation of "sputum smear-negative TB" presents a difficult diagnostic dilemma [17]. Compared with culture and the clinical status, NAA tests have been found to have lower values in AFB smear-negative specimens and are not used as a screen to rule out the disease [18]. In both theoretical considerations and empirical

Table 2. Results of COBAS AMPLICOR MTB and conventional methods from acid-fast smear-negative patients at Taipei Medical University-Wan Fang Hospital (n=126)

	AMPLICOR MTB	Conventional methods	
		M. tuberculosis	NTM
Total	126	76	50
Inconclusive	35	0	35
Conclusive	91	76	15
Positive	76	76	0
Negative	15	0	15

Excluding inconclusive results:
Sensitivity: 76/76+0 = 100%
Specificity: 15/0+15 = 100%
Positive predictive value: 76/76+0 = 100%
Negative predictive value: 15/15+0 = 100%

observations, patients without an AFB smear-positive culture clearly expel fewer organisms than those who are smear-positive, but other characteristics, such as delayed treatment and lack of isolation, contribute to their infectivity [19-20]. Therefore, rapid species identification, which shortens the turnaround time of culture, is important for sputum AFB smear-negative TB patients. In our present study, we found that COBAS AMPLICOR MTB had 100% positive and negative predictive values for positive MGIT culture fluids with initial smear-negative specimens (Table 2). Taken together, we suggest that COBAS AMPLICOR MTB may play a role in assessing patients with a negative AFB smear and positive MGIT culture.

Although many in-house PCR methods have been developed and tested, they vary widely in their accuracy, but the substantial heterogeneity in both sensitivity and specificity of the in-house NAA tests has given clinically useful estimates of test accuracy difficulty [21]. The COBAS AMPLICOR MTB system, which is a U.S. FDA-approved commercial PCR system [22], has been widely used in Taiwan. Based on the findings of our study results (Table 1), we suggest that the COBAS AMPLICOR MTB system has the potential to enhance the use of the BACTEC MGIT system in both speed and accuracy in routine clinical practice.

After excluding the inconclusive results, we found that the COBAS AMPLICOR MTB test was promising in sensitivity, specificity, and positive/negative predictive values (Tables 1 and 2). But, our study has a major drawback for clinical application because of the high percentage (23.3%) of inconclusive results. Interesting to note, the majority (95%) of inconclusive results were due to NTM (Table 1). Of the 178 *M. tuberculosis* isolates, we found that 97.7% were regarded as true positive, 0.6% false negative, and only 1.7% inconclusive; however, of the 92 NTM isolates, 65.2% were regarded as inconclusive (Table 1). We suggest that the reasons may be the existence of some unknown inhibitors related to the NTM in the BACTEC MGIT culture fluids. Based on our results, we suggest that the overall positive/negative predictive values were still favorable if we presumed the inconclusive results were NTM.

Conclusion

In conclusion, COBAS AMPLICOR MTB might be suitable for rapidly detecting and identifying *M. tuberculosis* in BACTEC MGIT cultures in routine clinical practice. But the major drawback for clinical application was the high percentage of inconclusive results, probably due to the NTM in the MGIT culture fluids in our study. This disadvantage may limit the clinical application, and further investigation is needed.

Acknowledgments

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References

1. WHO. Global tuberculosis control: surveillance, planning, financing. WHO report 2007. WHO/HTM/TB/2007. 376. Geneva: World Health Organization, 2007.
2. Hsueh PR, Liu YC, So J, *et al*. *Mycobacterium tuberculosis* in Taiwan. J Infect 2006; 52: 77-85.
3. Centers for Disease Control and Prevention. Controlling tuberculosis in the United States: recommendations from the American Thoracic Society, CDC, and the Infectious

Diseases Society of America. MMWR 2005; 54 (RR-12): 1-81.

4. Lee JJ, Suo J, Lin CB, *et al*. Comparative evaluation of the BACTEC MGIT 960 system with solid medium for isolation of mycobacteria. Int J Tuberc Lung Dis 2003; 7: 569-74.
5. Chien HP, Yu MC, Wu MH, *et al*. Comparison of the BACTEC MGIT 960 with Lowenstein-Jensen medium for recovery of mycobacteria from clinical specimens. Int J Tuberc Lung Dis 2000; 4: 866-70.
6. Hanna BA, Ebrahimzadeh A, Elliott LB, *et al*. Multicenter evaluation of the BACTEC MGIT 960 system for recovery of mycobacteria. J Clin Microbiol 1999; 37: 748-52.
7. Somoskovi A, Kodmon C, Lantos A, *et al*. Comparison of recoveries of *Mycobacterium tuberculosis* using the automated BACTEC MGIT 960 system, the BACTEC 460TB system, and Lowenstein-Jensen medium. J Clin Microbiol 2000; 38: 2395-7.
8. Kanchana MV, Cheke D, Natyshak I, *et al*. Evaluation of the BACTEC™ MGIT™ 960 system for the recovery of mycobacteria. Diagn Microbiol Infect Dis 2000; 37: 31-6.
9. Leitritz L, Schubert S, Bucherl B, *et al*. Evaluation of BACTEC MGIT 960 and BACTEC 460TB systems for recovery of *Mycobacteria* from clinical specimens of a university hospital with low incidence of tuberculosis. J Clin Microbiol 2001; 39: 3764-7.
10. Cruciani M, Scarparo C, Malena M, *et al*. Meta-analysis of BACTEC MGIT 960 and BACTEC 460 TB, with or without solid media, for detection of Mycobacteria. J Clin Microbiol 2004; 42: 2321-5.
11. Katila ML, Katila P, Erkinjuntti-Pekkanen R. Accelerated detection and identification of mycobacteria with MGIT 960 and COBAS AMPLICOR Systems. J Clin Microbiol 2000; 38: 960-4.
12. Laboratory Manual of Mycobacteria, Taipei: Taiwan CDC, 2004.
13. American Thoracic Society Workshop. Rapid diagnostic tests for tuberculosis: what is the appropriate use? Am J Respir Crit Care Med 1997; 155: 1804-14.
14. American Thoracic Society, CDC, Infectious Diseases Society of America. Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 2000; 161: 1376-95.
15. Attorri S, Dunbar S, Clarridge JE. Assessment of morphology for rapid presumptive identification of *Mycobacterium tuberculosis* and *Mycobacterium Kansasii*. J Clin Microbiol 2000; 38: 1426-9.
16. Kontosa F. Petinakia E, Nicolaoub S, *et al*. Multicenter evaluation of the fully automated Bactec MGIT 960 system and three molecular methods for the isolation and the identification of mycobacteria from clinical specimens. Diagn Microbiol Infect Dis 2003; 46: 299-301.
17. Tuberculosis coalition for technical assistance (TBCTA). International standards for tuberculosis care. http://www.who.int/tb/publications/2006/istc_report.pdf
18. Palomino JC. Nonconventional and new methods in the diagnosis of tuberculosis: feasibility and applicability in the field. Eur Respir J 2005; 26: 339-50.
19. Hernández-Garduño E, Cook V, Kunimoto D, *et al*. Transmission of *Mycobacterium tuberculosis* from smear negative patients: a molecular epidemiology study. Thorax 2004; 59: 286-90.
20. Behr MA, Warren SA, Salamon H, *et al*. Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. Lancet 1999; 353: 444-9.
21. Flores LL, Pai1 M, Colford Jr JM, *et al*. In-house nucleic acid amplification tests for the detection of *Mycobacterium tuberculosis* in sputum specimens: meta-analysis and meta-regression. BMC Microbiology 2005; 5: 55
22. CDC. Update: nucleic acid amplification tests for tuberculosis. MMWR 2000; 49: 593-4.

COBAS AMPLICOR MTB於BACTEC MGIT 960之臨床應用

白冠壬　余芳蘭　周如文*　王美香　林明輝　李俊年　余明治

前言：快速、自動的結核菌培養偵測系統BACTEC MGIT 960已在台灣廣為應用；然而，目前非結核性分枝桿菌在臨床實驗室的高分離率也造成診斷上的困擾。此研究主要目的為評估COBAS AMPLICOR MTB在BACTEC MGIT 960陽性檢體的臨床應用。

研究方法：從2006年3月1日到2007年2月28日共有270個BACTEC MGIT 960陽性檢体在台北醫學大學・萬芳醫院進行COBAS AMPLICOR MTB檢驗，並與傳統生化菌株鑑定的結果進行比較。

結果：207(76.7%)個COBAS AMPLICOR MTB 檢驗有決定性結論，63(3株為結核菌，60株為非結核性分枝桿菌)個檢驗無決定性結論。在176個結果為陽性者，174個檢驗為真陽性，2個檢驗為偽陽性。在31個結果為陰性者，30個檢驗為真陰性，1個檢驗為偽陰性。若不考慮檢驗結果為無決定性結論者，此項應用的敏感性、特異性、陽性預測值與陰性預測值分別為99%、94%、99%及97%。

結論：COBAS AMPLICOR MTB可能適合作為BACTEC MGIT 960陽性檢體快速偵測及鑑定結核菌的檢驗工具。*(胸腔醫學* ***2008; 23: 156-163)***

關鍵詞：結核菌，COBAS AMPLICOR MTB，BACTEC MGIT 960

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Mediastinal Hematoma: A Late Complication of Esophageal Reconstruction by Colon Interposition

Sheng-Yueh Yu, Chien-Chih Lu, Chun-hui Lee*, Yun-Hen Liu

Esophageal disruption by foreign bodies is often life-threatening, and emergency surgery may be necessary. Staged reconstruction is 1 of the choices of treatment following the acute stage. The advantages of colon interposition include lower reflux incidence, nearly unlimited conduit length, and preservation of gastric reservoir functions. Late complications, including anastomotic stricture, redundancy on the skin flap, and reflux, are well documented. Spontaneous colic arterial hemorrhage causing mesocolonic hematoma has been reported, but is extremely exceptional. We report a 50-year-old male who developed mediastinal hematoma caused by hemorrhage from a small interposed branch of the colic artery 17 years after colon interposition treatment for esophageal perforation. ***(Thorac Med 2008; 23: 164-168)***

Key words: esophageal reconstruction, colon interposition, complication, middle colic artery hemorrhage

Introduction

Esophageal perforation is a devastating event that causes extravasation of oral secretions and the bathing of mediastinal tissues by gastric content reflux, leading to acute and often fatal infections. Management of esophageal disruption is a formidable challenge for thoracic surgeons. In cases of perforation with severe esophageal necrosis, esophagectomy with immediate or staged reconstruction is the only option [1].

Colon interposition is widely used in reconstruction following benign esophageal disease [2-4]. Anastomotic stricture, reflux, and redundancy are well documented as its later complications [5]. Spontaneous hemorrhage of the colic artery, causing mesocolon hematoma, is rare but reported [6-8]. However, there have been no previous reports of mediastinal hematoma caused by bleeding from an interposed colic arterial branch.

Case Report

A 50-year-old male accidentally ingested a chicken bone in November 1990, leading to a diagnosis of esophageal perforation 2 days

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later. He underwent diverting cervical esophagostomy, esophagectomy and gastrostomy. Mediastinitis and left empyema developed after the first surgical series. He underwent decortication for the empyema and fibrinous debris was removed from the pleural space. After bacteriological examination, antibiotics were administered. With the infection controlled, he was discharged in the following month.

He returned to the hospital for staged reconstruction in March 1991. The cervical esophagostomy was closed and the gastrostomic tube was removed. Esophageal reconstruction with interposition of the left colon flap was performed through the substernal tract. Recovery from this procedure went smoothly.

He was healthy until August 2006, when he developed shortness of breath and sharp pains in the right side of the chest. Chest radiography showed an abnormal right pericardial shadow (Figure 1). A thoracic CT scan revealed a huge, dense and well defined mass (70 x 106 mm) near the interposed colon, in the right hemithorax, with compression of the interposed colon and right lung (Figure 2). Hematoma formation, near the mesocolon of the interposed left colon, was suspected. Angiographies of the superior mesentery artery and celiac trunk demonstrated that the blood supply of the interposed colon came from the middle colic artery, and showed a small contrasting focus of extravasation from a small branch of the interposed middle colic artery at the T7~8 level of the right chest, suggesting pervasive hemorrhage (Figure 3). The conduit could be antiperistaltic, rather than isoperistalic. The patient underwent exploratory thoracic surgery. A blood clot of roughly 1000 ml was aspirated. There was also active bleeding from a small branch of the interposed middle colic artery, which was remedied by suture ligation. The patient recovered uneventfully, and ate solid food easily on the 8th day after surgery. After the residual blood had drained out, the chest tube was removed. The subject was discharged on the 16th day after surgery. Six months later, he was symptom-free and had no problems eating.

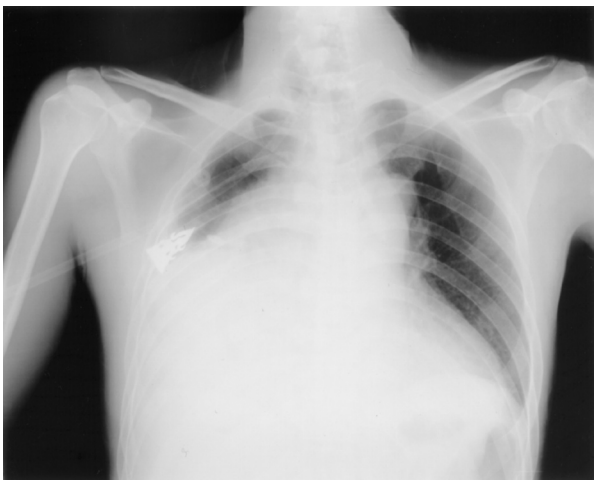

Fig. 1. Chest radiography showing an abnormal right pericardial shadow.

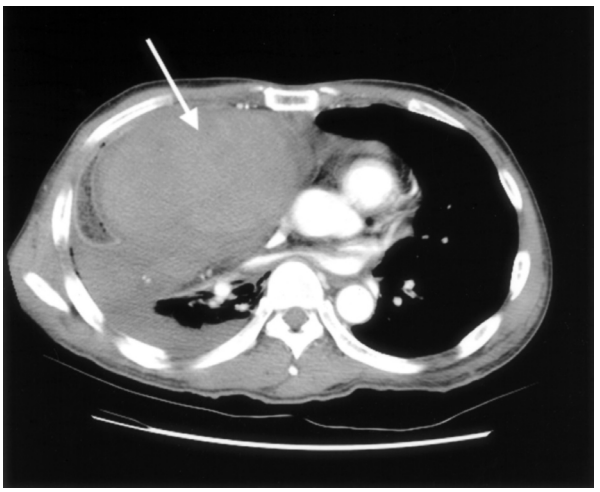

Fig. 2. Thoracic CT scan revealing a huge, dense, well-defined mass (70 x 106 mm) (white arrow) near the interposed colon in the right hemithorax, with compression of the interposed colon and right lung.

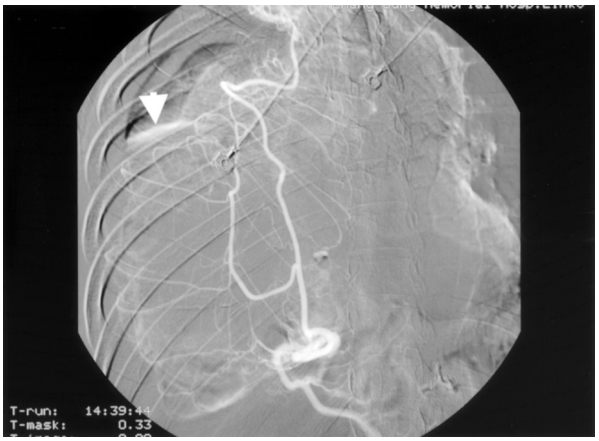

Fig. 3. Angiography revealing a small focus of contrast extrava-sation from a small branch of interposed middle colic artery at the T7~8 level of the right chest, suggesting active pervasive hemorrhage.

Discussion

Esophageal perforation is a potentially fatal symptom, but can be treated by esophagectomy, followed by staged reconstruction for patients with severe esophageal necrosis and mediastinal tissue infection. The choices of immediate or delayed reconstruction depend on the interval between perforation and diagnosis, the severity of mediastinal inflammation, and the extent of pleural infection [9]. Colon interposition has been recognized as a feasible technique for esophageal reconstruction since its first reported application in 1911 [2-4]. The advantages of using colonic tissue for esophageal replacement include a lower incidence of reflux esophagitis, preservation of gastric reservoir functions, nearly unlimited conduit length and potential peristaltic activity [10-13]. The vascular supply of the left colic segment is also very reliable. Transposed colon has been shown to have excellent long-term conduit functions [3, 14]. Post-interposition symptoms have been well documented: they include anastomotic stricture, redundancy, thoracic inlet obstruction, hiatal obstruction, and ulceration.

Jejunal, ileal and colic arterial aneurysms are rare, and account for only 3% of splanchnic aneurysms [15-16]. Mesocolon hematomas, caused by spontaneous colic arterial bleeding, have been reported, though they are rare and mainly caused by aneurysm ruptures [6-8, 17]. The etiology of these aneurysms is not well known. In a literature review, only 28 cases of middle colic artery aneurysm were reported; most presented with rupture [8]. Diagnosis of middle colic artery aneurysms is difficult [15]. They are small, making them hard to identify by ultrasound or CT. However, CT can specify the size and location of the subsequent hematoma following rupture [17]. A degree of skepticism along with a good angiographic technique is thought to be the most valuable diagnostic tool in these situations [18]. In the above review, most of the cases required arterial ligation, and some even bowel resection [8]. Embolization of a ruptured middle colic arterial aneurysm has been infrequently reported, but there is a risk of bowel ischemia [7].

There has been no case reported, thus far, of mediastinal hematoma caused by spontaneous hemorrhage from the vascular supply of the interposed colon. Due to the formation of a significant hematoma, and the threat of interposed colonic ischemia, we performed exploratory thoracic surgery, dissected the hematoma, and ligated the bleeding artery, rather than embolize it.

Although this situation is rare, we present this case to inform clinicians that bleeding from the colic artery can be a late complication of an interposed colon. A thoracic CT scan can identify the mesocolonic hematoma, with subsequent angiography confirming it. Exploratory thoracic surgery, with arterial ligation, is a safe method

that preserves interposed colon flap functions.

References

1. Orringer M.B., Stirling M.C. Esophagectomy for esophageal disruption. Ann Thorac Surg 1990; 49: 35-43.
2. Wilkins Jr. EW. Long-segment colon substitution for the esophagus. Ann Surg 1980; 192: 722-5.
3. Hankins JR, Colet FN, McLaughlin JS. Colon interposition for benign esophageal disease. Ann Thorac Surg 1984; 37: 192-6.
4. Curet-Scott MJ, Ferguson MK, Little AG, *et al*. Colon interposition for benign esophageal disease. Surgery 1987; 102: 568-74.
5. Domreis JS, Jobe BA, Aye RW, *et al*. Management of long-term failure after colon interposition for benign disease. Am J Surg 2002; 183: 544-6.
6. Dravid VS, Sullivan KL, Carter WB, *et al*. Role of selective arteriography in the diagnosis of a ruptured middle colic artery aneurysm. Cardiovasc Intervent Radiol 1994; 17: 167-9.
7. Naito A, Toyota N, Ito K. Embolization of a ruptured middle colic artery aneurysm. Cardiovasc Intervent Radiol 1995; 18: 56-8.
8. Sarcina A, Bellosta R, Magnaldi S, *et al*. Aneurysm of the middle colic artery--case report and literature review. Eur J Vasc Endovasc Surg 2000; 20: 198-200.
9. Brinster CJ, Singhal S, Lee L, *et al*. Evolving options in the management of esophageal perforation. Ann Thorac Surg 2004; 77: 1475-83.
10. Mansour KA, Hansen II HA, Hersh I, *et al*. Colon interposition for advanced nonmalignant esophageal stricture. Ann Thorac Surg 1981; 32: 584-91.
11. Skinner DB. Benign esophageal strictures Adv Surg 1976; 10: 177-95.
12. Corrazziari E, Minco TC, Anzini T, *et al*. Functional evaluation of colon transplants used in esophageal reconstruction. Dig. Dis 1977; 22: 7-12.
13. Clark J, Moraldi AR, Hall AW, *et al*. Functional evaluation of the interposed colon as an esophageal substitute. Ann Surg 1976; 183: 93-100.
14. DeMeester TR, Johansson K, Franze I, *et al*. Indications, surgical technique and long-term functional results of colon interposition or bypass. Ann Surg 1988; 208: 460-74.
15. McNamara MF, Griska LB. Superior mesenteric artery branch aneurysms. Surgery 1980; 88: 625.
16. Reuter SR, Fry WJ, Bookstein JJ. Mesenteric artery branch aneurysms. Arch Surg 1968; 97: 497.
17. Leardi S, Pietroletti R, Di Giuro G, Felici S, De Vita F. Spontaneous hematoma of mesocolon. Chir Ital 2005; 57: 779-81. [In Italian, English abstract]
18. Girishkumar H, Beniwal J, Narasimha V. Aneurysm of the right colic artery. J Cardiovasc Surg 1997; 38: 305-7.

縱膈腔血腫：以結腸重建食道的晚期併發症

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食道異物造成的食道破裂常危及生命而需要緊急的手術治療。急性期之後繼之以階段性食道重建是治療的選擇之一。以結腸重建食道的優點包括：較低的逆流發生率、幾乎不受限制的重建長度及保留原有胃的功能。而晚期的併發症包括：吻合處狹窄、重建的結腸皮瓣贅長及逆流。自發性結腸動脈出血導致結腸系膜血腫已有文獻紀錄但極為罕見。我們的病人為一五十歲男性在行結腸重建食道手術十七年後，因結腸動脈出血而導致縱膈腔血腫。*(胸腔醫學* ***2008; 23: 164-168)***

關鍵詞：食道重建，結腸皮瓣，併發症，中結腸動脈出血

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Critical Illness Myopathy in a Patient with Near-Fatal Asthma – A Case Report

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Neuromuscular weakness is a common occurrence in patients who are critically ill in the intensive care unit (ICU). The prognosis of critically ill patients is significantly influenced by neuromuscular dysfunction. A higher incidence of acute myopathy has been reported in patients with acute severe asthma, especially those paralyzed with neuromuscular blocking agents. Nevertheless, most of the patients in these studies were free of sepsis and lacked a muscle biopsy analysis. Herein, we report a 41-year-old man with near-fatal asthma and sepsis who suffered from prolonged limb weakness without sedative agents after extubation. The clinical diagnosis for critical illness myopathy (CIM) in this patient was based on clinical manifestations, serial clinical electromyographic studies, and muscle biopsy. The muscle strength of this patient improved steadily after extubation and a rehabilitation program. Awareness of the occurrence and prevention of CIM contributes to the reduction of morbidity and mortality, improves life-quality and conserves medical resources. ***(Thorac Med 2008; 23: 169-175)***

Key words: critical illness myopathy, near-fatal asthma, sepsis, electrophysiological test, muscle biopsy

Introduction

Acquired neuromuscular dysfunction after admission to the intensive care unit (ICU) was first reported in 1977 [1], and has been described frequently in the last decade. Neuromuscular weakness in the ICU is most often due to critical illness myopathy (CIM) or critical illness polyneuropathy (CIP). It has always developed in the setting of critical illness in patients admitted to the ICU for trauma, sepsis, systemic inflammatory response syndrome (SIRS), or multiple organ failure [2-3]. Although a detailed history and examination helps in identifying and localizing the weakness originating from the peripheral nerve, neuromuscular junction, or skeletal muscle, there are still many confounding factors. The adverse effects of neuromuscular blocking agents [4-5], high-dose steroids [6-7], antibiotics [7-8], statins and fibrates [9] on neuromuscular function should be carefully

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monitored in patients with critical illness. Patients in the ICU are often confused, sedated, and incubated, leading to difficult communication between patients and clinicians. Thereafter, important clues should be obtained carefully from laboratory data, electrophysiological examination and muscle biopsy. More precise and early identification of the various neuromuscular dysfunctions and risk factors may contribute to future prevention and management. Herein, we present the case of a patient with near-fatal asthma and sepsis who developed CIM.

Case Report

This 41-year-old man was noted to have asthma and hypertension for years, but with irregular medical control. He suffered from shortness of breath and productive cough with yellowish sputum for 3 days prior to admission to the emergency room. At the emergency department of our hospital, tachypnea with the use of accessory muscles and bilateral diffuse wheezing were noted. Asthma with acute exacerbation was initially suspected. Although aggressive bronchodilators were given, he still suffered acute respiratory distress. Subsequently, emergent intubation with mechanical ventilator support was instituted for the near-fatal asthma. No muscle power decrease was detected before intubation. Artery blood gas showed pH: 7.234, PCO_2: 85.8 mmHg, PO_2: 101 mmHg, HCO_3: 35.5 mm/L, and saturation: 96.2% with FiO_2=35%. Intravenous corticosteroids, cisatracurium and midazolam were prescribed simultaneously because of the patient's irritable mood and fighting the mechanical ventilator support. The vital signs were body temperature: 37.5ºC, pulse rate: 97/min, respiratory rate: 40/min, and blood pressure: 133/87 mmHg. The hemogram revealed leukocytosis with white blood cell count: 16200/mm^3, and neutrophils: 89%. Empiric antimicrobial agents (ceftazidime and teicoplanin) were prescribed with the diagnosis of severe asthma with acute respiratory failure and sepsis.

During the period in the intensive care unit (ICU), the patient's respiratory conditions improved gradually with the support of the mechanical ventilator and the usage of antibiotics and corticosteroids (total dose: 2080 mg in ICU). Cisatracurium (total dose: 1008 mg) and midazolam (total dose: 672 mg) were discontinued on hospital day 7.

He was extubated smoothly on hospital day 10. Nevertheless, symmetric limb weakness with flaccid quadriparesis that may affect the proximal more than the distal muscles was noted, even with the discontinuation of the neuromuscular blocking and sedative agents. Muscle strength, using the Medical Research Council Scale of Great Britain was 2/5 in the upper extremities and 3/5 in the lower extremities. Tendon reflexes were areflexia in the leg and hyporeflexia in the upper extremities. Sensory modalities, including pin-prick, touch, vibration, and position sensations were intact. The serum creatine kinase (CK) was 37 u/L (reference: 15-130 u/L).

A neurologist was consulted, and sensory and motor nerve conductive velocity (NCV) tests and electromyography (EMG) were arranged on hospital day 17. Sensory NCV revealed decreased amplitudes and slow conduction velocities of sensory nerve action potential (SNAP) across the wrist in the left median nerve; motor NCV revealed markedly decreased amplitudes and normal conduction velocities of compound muscle action potential (CMAP) in bilateral

peroneal, tibial, ulnar and median nerves; EMG showed an absence of motor unit potential (MUP) in the left biceps and bilateral first dorsal interosseous (FDI) muscles. Early-stage axonal polyneuropathy, myopathy, or a subclinical carpal tunnel syndrome on the left side were suspected. The follow-up EMG 2 weeks later showed mildly increased fibrillations (Fib) and positive sharp waves (PSW) of the resting potentials in the right biceps and anterior tibialis muscles; small amplitude and short-duration with increased recruitment of MUP in the right FDI biceps, anterior tibialis and vastus medium (VM) muscles.

Muscle biopsy was performed 1 1/2 months later. The muscle specimen was taken from the left vastus lateralis muscles. Hematoxylin and eosin (H&E) staining showed a mild degree of increased inflammatory cells around the muscle fiber that resulted in invading nonnecrotic muscle fibers (Figure 1). In addition, there were some pyknotic nuclear clumps and increased internal nuclei. In the adenosine triphosphatase (ATPase) staining, a predominance of type 2 muscular fibers (>80%) and some angulated type 2 fibers were discovered. No evidence of type 2 atrophy was noted in the ATPase staining series (Figure 2). The general weakness improved slowly under rehabilitation, and he was discharged on hospital day 60.

A third EMG was done on discharge day 20 that revealed no evidence of Fib and PSW in all test muscles, increased polyphasic waves, and early recruitment, as well as decreased amplitude of MUP in the right VM and biceps muscles. Follow-up electrophysiological studies were regularly done at the outpatient department after discharge. The clinical symptoms improved, with muscle strength in the upper limbs (grade 4/5) and lower limbs (grade 5/5) about 5 months later. The results of follow-up NCV and EMG studies also showed improvement compared with previous studies.

Discussion

Severe organ dysfunction, major surgery, trauma and other life-threatening events, such as sepsis and acute respiratory failure, may trigger an inflammatory cytokine process and result in

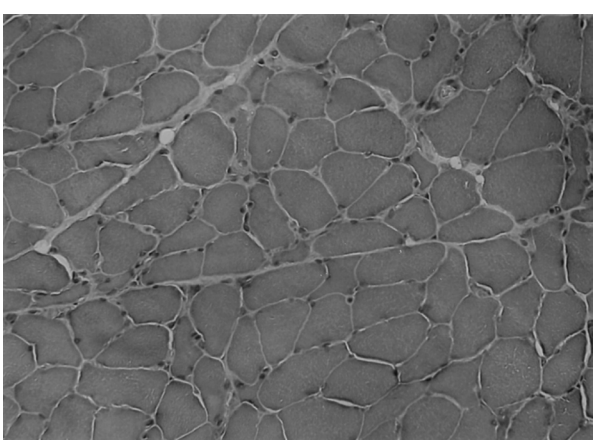

Fig. 1. H&E staining showed a mild degree of increased inflammatory cells around the muscle fiber that resulted in invading nonnecrotic muscle fibers. There were some pyknotic nuclear clumps and increased internal nuclei.

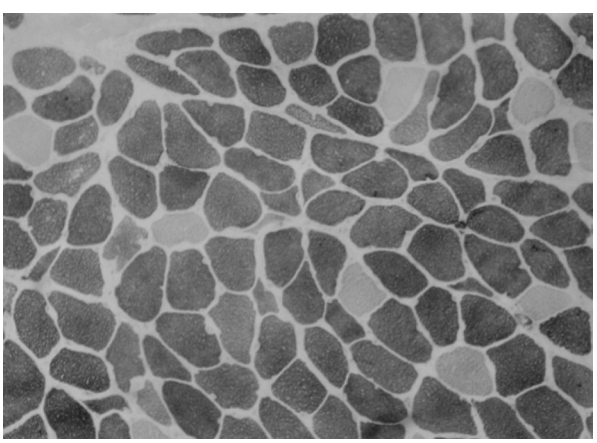

Fig. 2. In the ATPase PH9.4 staining, a predominance of type 2 muscular fibers (dark color) and some angulated type 2 fibers were discovered. No evidence of type 2 atrophy was noted in the series ATPase staining.

activation of mainly T-help 1 cells, monocytes, macrophages, and neutrophils. As a result of this immune activation, the permeability of the endothelial cells is increased. Thereafter, extravasation of inflammatory cells, edema and hypoxia subsequently lead to tissue damage in various systems, including the neuromuscular system, and the development of CIM and CIP [3, 10]. Critical illness neuromyopathy occurs in 25-63% of patients who have been on mechanical ventilation for more than 1 week [2, 10-12]. However, the prevalence is associated with the patient population, diagnostic criteria, and timing of examination. For example, the incidence of CIP and CIM is unreliable in critically ill children [13-14] and gender predilection was inconclusive in different studies [2, 15]. The incidence may increase to 63-100% in patients with sepsis [16-18], and occur as early as the first 3 days of ICU care [11].

Delayed weaning from the ventilator accompanied with prolonged 4-limb weakness in the ICU is a serious condition requiring neurological consultation. The exact onset of the muscular weakness is difficult to determine, due to the use of neuromuscular blockers or sedatives. Clinically, the significantly greater decreases of muscle power in the lower extremities than in the upper extremities and cranial nerve involvement are both rare. Electromyography, nerve conduction, and muscle biopsy are useful for the diagnosis of CIM. In patients with CIM, myopathy may occur independently or in association with CIP. CIM develops in 1/3 of ICU patients treated for status asthmatics [19]. Nerve conduction studies sometimes reveal low-amplitude CMAPs and prolongation of the CMAP duration. The SNAPs should be normal, but may be reduced in amplitude due to tissue edema, especially in the lower legs. MUP is usually decreased or absent. Electrical inexcitability of the membrane can be demonstrated by direct needle stimulation of the muscle, and markedly reduced or absent CMAPs are noted. The major histopathologic finding in CIM is that of a relatively selective loss of myosin, which can be identified as a lack of reactivity to myosin ATPase in non-necrotic fibers. Features of the histopathology in thick filament myosin loss include variation in the size of the muscle fiber and focal loss of ATPase reactivity in type 1 fibers. Necrosis or vascular change is less common.

In our patient, the clinical presentation, electrophysiology and muscle biopsy were compatible with the diagnosis of CIM after the exclusion of autoimmune disorder, neuropathy, encephalopathy, spinal lesions and other types of myopathy. For this patient, the sedative agents were discontinued before extubation, and steroid was tapered gradually after the improvement of the acute asthma. Steroid-induced myopathy in patients with ICU admission has been reported in many studies [2-3, 6], and type 2 fiber atrophy was the most common finding in the histopathology. However, no evidence of type 2 fiber atrophy was noted in the muscle biopsy of our patient, and the duration of steroid use was as short as 2 weeks. Steroid-induced myopathy was less likely in this patient. Other types of myopathy were also excluded, such as acute necrotizing myopathy or cachectic myopathy.

In patients with acute necrotizing myopathy resulting from infective, chemical and other insults, widespread necrosis of the muscle fibers was revealed in the histopathology [3]. In this kind of myopathy, serum CK levels are markedly elevated, myoglobulinuria is present and electrophysiological examinations suggest severe muscular damage [3]. Acute necrotizing

myopathy was less likely in our patient. Cachectic myopathy usually occurs in patients with starvation or malnutrition. Its muscle biopsy results are normal or mild type 2 fiber atrophy [20]. The serum CK level and neurological studies are usually within normal limits. However, no evidence of starvation or malnutrition was noted in our patient.

Many predisposing factors of CIM have been characterized, such as older age [18], hyperosomolarity [12], the use of neuromuscular blockers, steroids, antibiotics, statins and fibrates [6-9], and high Acute Physiology, Age and Chronic Health Evaluation (APACHE) III scores [10]. Patients with severe asthma requiring mechanical ventilation and medication with high-dose corticosteroid and neuromuscular blocking agents may develop myosin-loss myopathy [3-5]. Prolonged weakness after cisatracurium infusion has been reported, although cisatracurium undergoes ester hydrolysis and Hoffman elimination, so it is not likely to accumulate in patients with hepatic or renal dysfunction [4, 21]. In our patient, cisatracurium and concomitant high-dose corticosteroid treatment could not be totally excluded as a predisposing factor for CIM. The above-mentioned drugs should be avoided or used in the lowest possible dosage and for as short a time as possible. In a study by Van den Berfhe *et al*. [12], intensive insulin therapy led to a decrease in the incidence of neuromuscular dysfunction, from 52% to 29%. In addition, intravenous immunoglobulins (IVIG) have been used in an attempt to prevent the development of CIP and CIM [22]. Importantly, controlling SIRS is the main approach to preventing and reducing the severity of CIM [2, 10, 17].

Delayed ventilator weaning, prolongation of hospital days, and neuromuscular dysfunction are the complications of CIM. The recovery period has ranged from 1 month to 3.5 years [2, 23], and overall mortality has varied from 36% to 55% [10, 23], based on the underlying critical illness. Our patient was discharged on hospital day 60, and EMG revealed no evidence of Fib/PSW in all test muscles on discharge day 20. The low level of muscular enzyme and the lack of significant destruction in the muscle pathology may explain the good prognosis in our patient.

In conclusion, the differential diagnosis of delayed ventilator weaning and prolonged generalized weakness in critically ill patients is encountered. Consideration of the common causes of neuromuscular dysfunction, a detailed history, adequate electrophysiological study, and muscle biopsy will help to identify a large proportion of these patients with general weakness. Awareness of the occurrence and prevention of CIM contributes to reducing morbidity and mortality, improving life-quality, and conserving medical expenditures. Establishing an adequate surveillance program to monitor neuromuscular dysfunction in ICU patients, in order to detect and manage CIM earlier, is suggested. Although the predominant determinant of outcome is the underlying illness, aggressively removing the predisposing factors, and providing intensive supportive care and rehabilitation are necessary to ensure a satisfactory functional recovery and a reduction in the mortality rate.

References

1. MacFarlane IA, Rosenthal FD. Severe myopathy after status asthmaticus. Lancet 1977; 2: 615.
2. De Jonghe B, Sharshar T, Lefaucheur JP, *et al*. Paresis acquired in the intensive care unit: A prospective multicenter study. JAMA 2002; 288: 2859-67.

3. Bolton CF. Neuromuscular manifestations of critical illness. Muscle Nerve 2005; 32: 140-63.
4. Davis NA, Rodgers JE, Gonzalez ER, *et al*. Prolonged weakness after cisatracurium infusion: A case report. Crit Care Med 1998; 26: 1290-2.
5. Leatherman JW, Fluegel WL, David WS, *et al*. Muscle weakness in mechanically ventilated patients with severe asthma. Am J Respir Crit Care Med 1996; 153: 1686-90.
6. Danon MJ, Schliselfeld LH. Study of skeletal muscle glycogenolysis and glycolysis in chronic steroid myopathy, non-steroid histochemical type-2 fiber atrophy, and denervation. Clin Biochem 2007; 40: 46-51.
7. Bannwarth B. Drug-induced myopathies. Expert Opin Drug Saf 2002; 1: 65-70.
8. Dalakas MC. Peripheral neuropathy and antiretroviral drugs. J Peripher Nerv Syst 2001; 6: 14-20.
9. Baer AN, Wortmann RL. Myotoxicity associated with lipid-lowering drugs. Curr Opin Rheumatol 2007; 19: 67-73.
10. de Letter MA, Schmitz PI, Visser LH, *et al*. Risk factors for the development of polyneuropathy and myopathy in critically ill patients. Crit Care Med 2001; 29: 2281-6.
11. Khan J, Harrison TB, Rich MM, *et al*. Early development of critical illness myopathy and neuropathy in patients with severe sepsis. Neurology 2006; 67: 1421-5.
12. Van den Berghe G, Schoonheydt K, Becx P, *et al*. Insulin therapy protects the central and peripheral nervous system of intensive care patients. Neurology 2005; 64: 1348-53.
13. Banwell BL, Mildner RJ, Hassall AC, *et al*. Muscle weakness in critically ill children. Neurology 2003; 61: 1779-82.
14. Tabarki B, Coffinieres A, Van Den Bergh P, *et al*. Critical illness neuromuscular disease: Clinical, electrophysiological, and prognostic aspects. Arch Dis Child 2002; 86: 103-7.
15. Visser LH. Critical illness polyneuropathy and myopathy: Clinical features, risk factors and prognosis. Eur J Neurol 2006; 13: 1203-12.
16. Latronico N, Peli E, Botteri M. Critical illness myopathy and neuropathy. Curr Opin Crit Care 2005; 11: 126-32.
17. Tennila A, Salmi T, Pettila V, *et al*. Early signs of critical illness polyneuropathy in ICU patients with systemic inflammatory response syndrome or sepsis. Intensive Care Med 2000; 26: 1360-3.
18. Druschky A, Herkert M, Radespiel-Troger M, *et al*. Critical illness polyneuropathy: Clinical findings and cell culture assay of neurotoxicity assessed by a prospective study. Intensive Care Med 2001; 27: 686-93.
19. Douglass JA, Tuxen DV, Horne M, *et al*. Myopathy in severe asthma. Am Rev Respir Dis 1992; 146: 517-9.
20. Hsia AW, Hattab EM, Katz JS. Malnutrition-induced myopathy following roux-en-y gastric bypass. Muscle Nerve 2001; 24: 1692-4.
21. Hunter JM. New neuromuscular blocking drugs. N Engl J Med 1995; 332: 1691-9.
22. Mohr M, Englisch L, Roth A, *et al*. Effects of early treatment with immunoglobulin on critical illness polyneuropathy following multiple organ failure and Gram-negative sepsis. Intensive Care Med 1997; 23: 1144-9.
23. Hund EF, Fogel W, Krieger D, *et al*. Critical illness polyneuropathy: Clinical findings and outcomes of a frequent cause of neuromuscular weaning failure. Crit Care Med 1996; 24: 1328-33.

瀕死性氣喘合併重症肌肉病變—病例報告

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神經肌肉無力的現象常發生在加護病房重症病人身上，病人預後也受神經肌肉病變而影響甚巨。急性肌肉病變常發生在病患有嚴重氣喘，且合併使用神經肌肉阻斷劑者。然而，這些病人大多沒有敗血症且缺乏肌肉切片的證據。在此提出的病例報告是一位41歲的男性病患，因瀕死性氣喘及敗血症而住進加護病房，在拔除氣管內管及停用鎮定劑後仍出現長時間肢體無力的情形。這病人在臨床上診斷重症肌肉病變主要是依據臨床表現、電生理檢查及肌肉切片。病人肌肉的力量在拔管後復健之中持續恢復。臨床上若及早注意及防止重症肌肉病變，則可降低併發症與死亡率，且可改善生活品質及節省醫療支出。*(胸腔醫學* ***2008; 23: 169-175)***

關鍵詞：重症肌肉病變，瀕死性氣喘，敗血症，神經學電生理檢查，肌肉切片

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Muir-Torre Syndrome with Squamous Cell Lung Cancer and Sebaceous Carcinoma

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Muir-Torre syndrome (MTS) is a rare cancer genodermatosis diagnosed by the presence of at least 1 sebaceous neoplasm and at least 1 internal malignancy. Colon cancers and urogenital malignancies account for 75% of the internal malignancies. Others, such as upper gastrointestinal, blood, breast, and, in rare cases, lung malignancies have been reported. Muir-Torre syndrome is considered a variant of hereditary nonpolyposis colorectal cancer and is secondary to germline mutation of the mismatch repair (MMR) genes MSH2 and MLH1. Microsatellite instability is usually observed in patients with MMR gene mutations. Immunohistochemistry studies of MSH2/MLH1 and microsatellite instability evaluations are helpful for screening patients and family members with Muir-Torre syndrome. Early and correct diagnosis of Muir-Torre syndrome is important as patients with Muir-Torre syndrome and family members who are gene carriers are prone to high risks of multiple internal malignancies. Careful survey and regular follow-up can help in detecting visceral lesions as early as possible. Few cases of Muir-Torre syndrome have been reported in Asian and African populations. This case describes a Taiwanese with squamous cell lung cancer and a sebaceous carcinoma with unusual immunochemistry staining results. The patient presents a subclass of Muir-Torre syndrome with different clinical characteristics and potentially different genetic pathways. ***(Thorac Med 2008; 23: 176-181)***

Key words: Muir-Torre syndrome, lung cancer, sebaceous carcinoma, mismatch repair gene

Introduction

Muir-Torre syndrome is a rare cancer genodermatosis characterized by the presence of at least 1 sebaceous neoplasm and at least 1 internal malignancy [1]. The syndrome was first described by Muir, *et al*. [2] in 1967 and by Torre [3] in 1968. An apparent variant of hereditary nonpolyposis colorectal cancer (HNPCC), Muir-Torre syndrome is autosomal-dominant inherited and secondary to germline mutations of mismatch repair (MMR) genes, such as MSH2, MSH6 and MLH1 [4-5]. Microsatellite instabilities also have high concordance with mismatch pair gene defects [6]. However, these genetic characteristics are not found in a

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small subgroup of Muir-Torre syndrome, which may pose different pathogenetic pathways [7].

Although as many as 200 cases [8] of this syndrome have been reported, reports of Asian and African subjects are rare [7]. The visceral cancers involved in Muir-Torre syndrome are usually colorectal cancers and urogenital malignancies. However, breast and upper gastrointestinal tract cancers, as well as blood malignancy diseases are occasionally reported [1]. Few studies have reported lung cancer in Muir-Torre syndrome [1]. The present case describes a 74-year-old male diagnosed with Muir-Torre syndrome after acquiring a squamous cell lung cancer and a sebaceous gland carcinoma in the upper-right eyelid half a year later.

Case Report

A 74-year-old male, who had been a 1-pack-per-day smoker for 55 years, presented at our institute on December 2005 due to nonproductive cough for 8 months. Total collapse of the left lung was noted in the chest radiograph. Computer tomography showed a left upper lung mass with left pulmonary artery encasement and mediastinum invasion. Multiple enlarged lymph nodes were noted at the bilateral mediastinum and right hilum. No abdominal or obvious genitourinary tumors were observed. Bronchoscopy revealed total occlusion of the left main bronchus by an endobronchial mass. Biopsy confirmed squamous cell carcinoma. Although left pleural effusion was noted, repeated cell block cytology failed to identify a malignant pleural effusion. The patient was diagnosed with lung cancer, squamous cell carcinoma, T4N3M0, stage IIIb. Considering the obstructive pneumonitis and advanced age with a borderline performance status, radiotherapy was applied to the main mass and mediastinum, using 6600cGY, from January 2006 to February 2006.

In March, 2006, the patient exhibited an upper-right eyelid mass which progressively enlarged during the following month. It was irregular in margin, palpably firm, and relatively fixed to the peripheral tissue. Intermittent bleeding without purulent discharge was noted. Excisional biopsy performed in May showed a moderately differentiated carcinoma with focal clear cytoplasm in the dermis, and subcutaneous with extension to the epidermis. Sebaceous carcinoma was diagnosed. The tumor cells were immunonegative for CK7 and TTF-1, but positive for CK 5/6 and P53. The co-presence of sebaceous carcinoma and lung cancer indicated this patient was a candidate for Muir-Torre syndrome. Wide excision of the sebaceous carcinoma was not performed due to the deteriorating general condition of the patient. One month later, the patient expired due to pneumonia with sepsis.

Reviewing the family histories, none of the family members had ever been diagnosed with malignant disease or sebaceous gland disease. Immunohistochemistry staining for the mismatch repair gene proteins MSH2 and MLH1 was performed on both paraffin-embedded tumor samples. The tissue from the sebaceous carcinoma expressed both MSH2 and MLH1 proteins, while the lung tissue expressed MSH2 protein normally, but no MLH1. (Figure 1)

Discussion

Muir-Torre syndrome is an autosomal-dominant genodermatosis with variable phenotypes and high penetrance diagnosed by the occurrence of at least 1 sebaceous neoplasm and at

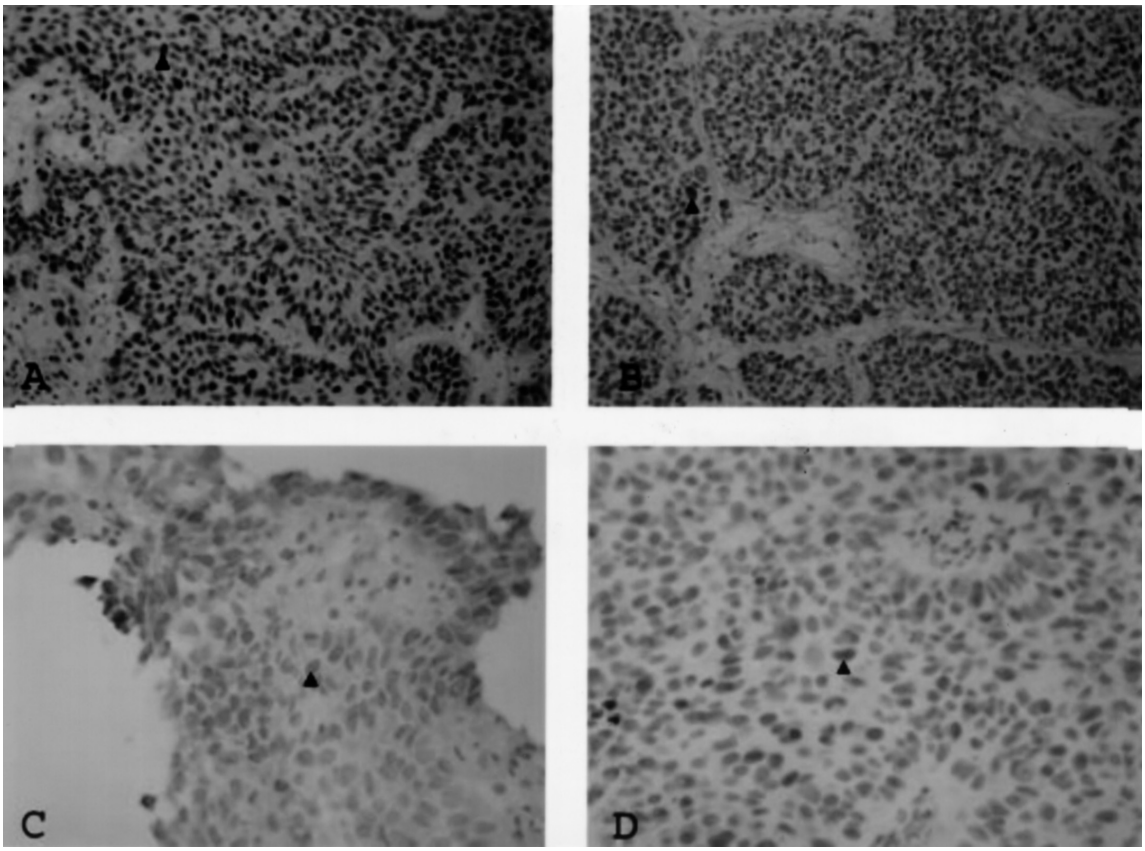

Fig. 1. Immunohistochemical stain for MSH2 and MLH1. [a] Lung squamous cell carcinoma with expression of MSH2 at the nucleus [200x]. [b] Eyelid sebaceous carcinoma with expression of MSH2 at the nucleus [200x]. [c] Lung squamous cell carcinoma with lack of MLH1 expression [400x]. [d] Eyelid sebaceous carcinoma with expression of MLH1 [400x].

least 1 internal malignancy in the absence of other predisposing factors, such as AIDS and radiotherapy for child retinoblastoma [1]. Incomplete forms of this syndrome are indicated in the presence of the following: multiple keratoacanthomas without obvious sebaceous differentiation, multiple internal malignancies, and a family history of Muir-Torre syndrome [1]. New families or sporadic cases of this syndrome could appear due to germline or somatic mutations. Fifty-six percent of subjects with the syndrome had skin lesions after the internal cancers, while the others had cutaneous neoplasms concurrently or before the visceral malignancies [8].

Fifty percent of patients with Muir-Torre syndrome had 1 primary malignancy, while the others had as many as 9 primary malignancies [9]. The most common malignancy is colorectal cancer, which accounts for half of all lesions. The second most common is urogenital malignancies, which accounted one-fourth of visceral malignancies [8]. Furthermore, many other cancers, such as those of the upper gastrointestinal tract, biliary tract, breast, parotid gland, larynx, blood, cartilage, and in rare cases, lung malignancies, have been reported [1]. The visceral malignancies in Muir-Torre syndrome tend to be low grade and less aggressive than their sporadic forms, even though metastasis

is observed at diagnosis. However, few studies have assessed survival [7].

Of the sebaceous neoplasms in Muir-Torre syndrome, sebaceous adenoma and sebaceous epithelioma are more common and are more sensitive markers [1, 10]. Sebaceous carcinoma is apparently less sensitive, but still prompts the consideration of Muir-Torre syndrome. Sebaceous hyperplasia, as well as nevus sebaceous of Jadassohn, though common, are not considered markers of Muir-Torre syndrome. Although many patients have solitary sebaceous tumors, numerous skin tumors are not uncommon [1]. Sebaceous carcinoma is characterized by painless nodules on the inner eyelid surface with occasional bleeding, usually occurring in middle-aged and older persons. It is usually locally aggressive with occasional distal metastasis, especially in extra-ocular sebaceous carcinoma. Excision or cryotherapy could be used with benign lesions, while wide excision using the Mohs procedure is the standard treatment for sebaceous carcinoma [1]. Radiotherapy may be a palliative treatment for metastastic sebaceous carcinomas [7]. Chemopreventive therapies for benign sebaceous lesions using interferon or isotretinoin have been investigated [11].

As a variant of hereditary nonpolyposis colorectal cancer (HNPCC), most cases of Muir-Torre syndrome share a common biomolecular pathogenesis linked to mismatch repair gene mutations (MLH1, MSH2, MSH6), which cause microsatellite instabilities [12-13]. A full concordance between immunohistochemical analysis for MMR proteins and microsatellite instability has been established [7]. However, unlike HNPCC, which exhibits equal proportions of MSH2 and MLH1 mutations, most major mutations in Muir-Torre syndrome are found in MSH2 [7]. More recent studies have suggested analyzing microsatellite instability and immunohistochemical expression of human MSH2 and human MHL1 to identify Muir-Torre syndrome in patients with sebaceous lesions or in patients with family members who have Muir-Torre syndrome [6-7, 14]. Some authors have even proposed germline mutation detection for family members, since cancer risk in gene carriers is as high as 80-100% [7].

A subgroup of Muir-Torre syndrome appearing in sporadic cases without strong family histories has been recognized clinically. Molecularly, 35% of tumors from Muir-Torre syndrome do not show microsatellite instability or MMR gene defects [7, 14]. This group tends to have late-onset and higher grade cancers. Other genetic disorders, such as MUTYH/PMS2 gene defects, somatic mutations of the MMR system, or MLH1 promoter hypermethylations are possible contributors [6, 15]. The exact pathogenesis is still unknown and deserves further investigation.

After diagnosing Muir-Torre syndrome, a regular follow-up plan must be established to examine visceral malignancies and skin lesions in patients and gene carriers [8]. Investigations focusing on the lower gastrointestinal tract, urinary tract and genital organs are suggested. Regular dermatological check-ups, colonoscopy, abdomen/pelvis CT scan, mammography, and endometrial biopsy are also suggested in different intervals [7].

Muir-Torre syndrome is a diagnosis based on clinical characteristics. Several recent studies suggested the definition is not strict enough without a biomolecular evaluation. The patient in this study did not have lung cancer and sebaceous carcinoma just coincidentally. He exhibited no MLH1 expression in the lung tu-

mor and normal MSH2/MLH1 expression in the sebaceous carcinoma. Although patients with Muir-Torre syndrome typically acquire MMR gene mutations in internal tumors and sebaceous lesions, our case could present a sporadic type. In addition, other potential MMR gene mutations, such as MSH6/PMS2, that may have existed in this patient deserve further investigation. Microsatellite instability evaluation and DNA analysis should be helpful in identifying the pathogenesis. Family member evaluations could also help to identify whether a new Muir-Torre syndrome family is being presented.

In conclusion, Muir-Torre syndrome is a rare but distinct syndrome which is probably under-diagnosed. Histological diagnosis and survey for internal malignancies are essential in patients with suspected skin lesions. Immunohistochemistry and microsatellite instability studies may aid the screening and identification of patients and families with Muir-Torre syndrome. Although laborious, detection of germline mutations may be helpful in identifying gene carriers. Conversely, patients with multiple malignancies or a family history of multiple cancers should be evaluated for the possibility of Muir-Torre syndrome. Once Muir-Torre syndrome is confirmed, regular follow-up for internal malignancies can improve survival.

Reference

1. Schwartz RA, Torre DP. The Muir-Torre syndrome: a 25-year retrospect. J Am Acad Dermatol 1995; 33: 90-104.
2. Muir EG, Bell AJ, Barlow KA. Multiple primary carcinoma of the colon, duodenum and larynx associated with kerato-acanthoma of the face. Brit J Surg 1967; 54: 191-5.
3. Torre D. Multiple sebaceous tumors. Arch Dermatol 1968; 98: 549-51.
4. Kruse R, Lamberti C, Wang Y, *et al*. Is the mismatch repair deficient type of Muir-Torre syndrome confined to mutations in the hMSH2 gene? Hum Genet 1996; 98: 747-50.
5. Bapat B, Xia L, Madlensky L, *et al*. The genetic basis of Muir-Torre syndrome includes the hMLH1 locus. Am J Hum Genet 1996; 59: 736-9.
6. Ponti G, Losi L, Di GC, *et al*. Identification of Muir-Torre syndrome among patients with sebaceous tumors and keratoacanthomas: role of clinical features, microsatellite instability, and immunohistochemistry. Cancer 2005; 103: 1018-25.
7. Ponti G, Ponz de LM. Muir-Torre syndrome. Lancet Oncol 2005; 6: 980-7.
8. Akhtar S, Oza KK, Khan SA, *et al*. Muir-Torre syndrome: case report of a patient with concurrent jejunal and ureteral cancer and a review of the literature. J Am Acad Dermatol 1999; 41: 681-6.
9. Coldron J, Reid I. Muir-Torre syndrome. J R Coll Surg Edinb 2001; 46: 178-9.
10. Singh AD, Bhola R, Rundle PA, *et al*. Sebaceous adenoma of the eyelid in Muir-Torre syndrome. Arch Ophthalmol 2005; 123: 562-5.
11. Graefe T, Wollina U, Schulz H, *et al*. Muir-Torre syndrome - treatment with isotretinoin and interferon alpha-2a can prevent tumour development. Dermatol 2000; 200: 331-3.
12. Ponti G, Losi L, Pedroni M, *et al*. Value of MLH1 and MSH2 mutations in the appearance of Muir-Torre syndrome phenotype in HNPCC patients presenting sebaceous gland tumors or keratoacanthomas. J Invest Dermatol 2006; 126: 2302-7.
13. Marazza G, Masouye I, Taylor S, *et al*. An illustrative case of Muir-Torre syndrome: contribution of immunohistochemical analysis in identifying indicator sebaceous lesions. Arch Dermatol 2006; 142: 1039-42.
14. Cohen PR, Kohn SR, Kurzrock R. Association of sebaceous gland tumors and internal malignancy: the Muir-Torre syndrome. Am J Med 1991; 90: 606-13.
15. Ponti G, Ponz de LM, Maffei S, *et al*. Attenuated familial adenomatous polyposis and Muir-Torre syndrome linked to compound biallelic constitutional MYH gene mutations. Clin Genet 2005; 68: 442-7.

合併產生肺癌及皮脂腺癌之Muir-Torre syndrome —病例報告

倪永倫　容世明*　余志騰　陳志弘

Muir-Torre syndrome為一種罕見的顯性遺癌症相關遺傳性皮膚病，臨床上的特徵與診斷依據為在病患身上合併發生皮脂腺腫瘤以及至少一個的內部器官惡性腫瘤。臟器惡性腫瘤以大腸直腸癌及泌尿道系統癌症最為常見，總共佔了四分之三的比例，其他較少發生的惡性腫瘤包括了上消化系統癌症、血癌、乳癌等，只有很少數的肺癌曾經被報告過。皮膚腫瘤及臟器腫瘤可能同時產生，也可能先後產生。Muir-Torre syndrome被認為是遺傳性非息肉性大腸癌（hereditary non-polyposis colorectal cancer）的一個亞型，主要是起因於錯配修復基因（mismatch repair gene）的突變，其中又以MSH2以及MLH1為主。在多數錯配修復基因突變的患部，也可發現有microsatellite instability的現象。臨床上可以藉由針對MSH2/MLH1的免疫組織化學檢查、microsatellite instability的測定、或是DNA序列突變的測定來幫助診斷Muir-Torre syndrome。Muir-Torre syndrome的患者易有多發的臟器惡性腫瘤，早期診斷Muir-Torre syndrome的重要性在於可以幫助患者及家屬監測和及早發現臟器惡性腫瘤，以達到早期治療的目的。我們在此報告一個因合併肺癌以及皮脂腺癌而被診斷為Muir-Torre syndrome的患者以及相關文獻的回顧。*(胸腔醫學* ***2008; 23: 176-181****)*

關鍵詞：Muir-Torre syndrome，肺癌，皮脂腺癌，鱗狀細胞癌，錯配修復基因

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Lung Adenocarcinoma with Penile Metastasis – A Case Report

Wei-Chun Chung, Te-Chun Hsia, Chia-Hung Chen, Chih-Yen Tu, Chuen-Ming Shih, Wu-Huei Hsu

Metastasis to the penis is very rare in lung cancer, especially adenocarcinoma. We describe a patient with adenocarcinoma of the lung who developed a metastatic lesion in the penis. A 66-year-old Taiwanese male was diagnosed with adenocarcinoma of the lung at stage IV (T2N3M1, liver metastasis), and was treated with chemotherapy consisting of gemcitabine, cisplatin and bevacizumab, beginning on 21 September 2005. Three months later, hardness of the penile shaft was noted. A biopsy of the penis was performed, which provided a histological diagnosis of adenocarcinoma. The histology of the specimen was consistent with that of the previous lung cancer, so he was considered to have penile metastasis from adenocarcinoma of the lung. However, a poor performance status was noted, and the patient could not tolerate the chemotherapy. The patient expired 2 weeks later due to cancer progression. We review the reported cases to investigate the clinical characteristics of this rare involvement. ***(Thorac Med 2008; 23: 182-186)***

Key words: lung cancer, adenocarcinoma, penile metastasis

Introduction

Lung cancer, a leading cause of cancer-related death in Taiwan, has a consistent pattern of metastasis. The common sites of metastasis of lung cancer are the regional lymph nodes, the brain, bone, adrenal gland, and lung [1]. Metastasis to the penis from lung cancer is very rare, especially adenocarcinoma of the lung [2-12]. In this report, we describe a patient with adenocarcinoma of the lung who presented penile metastasis. In addition, we review the reported cases to investigate the clinical characteristics of this rare involvement.

Case Report

A 66-year-old patient had been in his usual state of good health until 2 months before visiting our outpatient department on 22 August 2005, when a nonproductive cough developed. During the following 2 months, the cough became productive of yellow, blood-tinged sputum. On physical examination, his vital signs were normal. A single node, 2.5 cm in diameter, in the left supraclavicular group was pal-

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pable. The lungs were clear on auscultation and laboratory test results were normal. Chest radiograph revealed a mass, 3.5 cm in diameter, in the lower lobe of the right lung, and computed tomographic (CT) scanning of the thorax identified a 3.5-cm mass in the right lower lobe, with enlarged right hilar, subcarinal and supraclavicular lymph nodes. Bronchoscopic biopsy revealed bronchogenic carcinoma, RLL, adenotype. Consequently, he was diagnosed with adenocarcinoma of the lung at stage IV (T2N3M1) (with supraclavicular lymph nodes and liver metastasis). He then began a clinical trial of chemotherapy with a gemcitabine (1250 mg/m^2), cisplatin (80 mg/m^2) and bevacizumab (15 mg/kg) protocol on 21 September 2005. He received a total course of 4 cycles. CT scanning showed a partial response, but the chemotherapy was held due to thrombocytopenia.

On December 13, he was admitted to our hospital due to weakness and poor appetite for several days. Before admission, he did not complain of urethralgia, priapism, penile pain or urinary retention. During admission, hardness of the penile shaft was noted, and priapism was suspected initially. He denied urinary retention, penile pain and urethralgia. Physical examination revealed a 2 × 2 × 1-cm, well-defined firm mass lesion on the dorsum of the middle penile shaft. The testes and inguinal lymph nodes were both normal. A biopsy of the penis was performed, and the histology of the specimen showed a few irregular nests of polygonal tumor cells with pleomorphic nuclei that had invaded the dense connective tissue (Figure 1). The immunohistochemical study showed positive for cytokeratin (Ck) and thyroid transcription factor-1 (TTF-1) (Figure 2 and Figure 3). The histology of the specimen was consistent with that of the previous lung cancer, so he

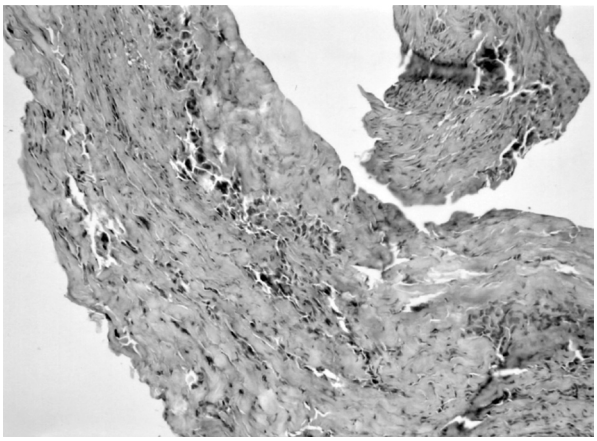

Fig. 1. A few irregular nests of polygonal tumor cells with pleomorphic nuclei invading the dense connective tissue are seen on the penis

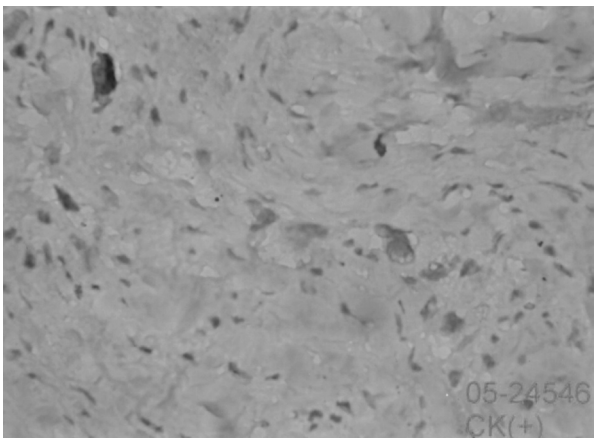

Fig. 2. The immunohistochemical study shows positive for cytokeratin (Ck)

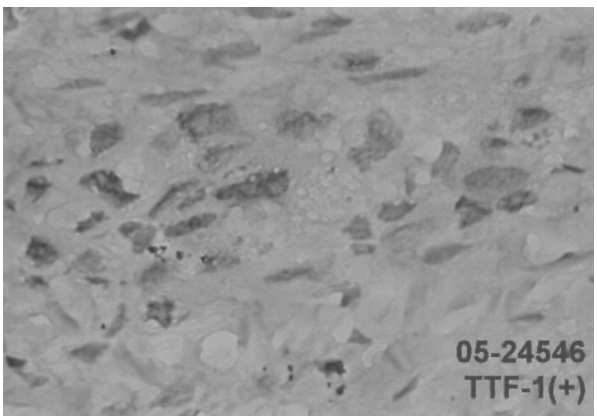

Fig. 3. The immunohistochemical study shows positive for thyroid transcription factor-1 (TTF-1)

was considered to have penile metastasis from adenocarcinoma of the lung. However, a poor performance status was noted, and the patient could not tolerate the chemotherapy. The patient expired 2 weeks later due to lung cancer progression.

Discussion

Despite a generous blood supply in the penis, metastatic tumors to this area are uncommon. The majority of them originate from organs in close proximity of the penis, such as the bladder, prostate, rectum, and sigmoid colon [9-10]. Almost 75% of primary lesions are of pelvic origin; the remaining 25% are from genitourinary, rectosigmoid, or extrapelvic sites [12].

A review (Table 1) of recent literature [2-12] showed that most lung cancers with penile metastasis are combined with other distant metastasis. The symptoms of penile metastasis are various, and include a mass, urethralgia, priapism and urinary retention. A poor prognosis has been observed in lung cancer with penile metastasis, and survival time is usually less than 3 months. Of note, most primary lesions are squamous cell carcinoma. It is generally accepted that adenocarcinoma develops distant metastasis more frequently than squamous cell carcinoma, and yet there is a low incidence of lung adenocarcinoma in penile metastasis. Our reported patient is one such case, and is the first report from Taiwan.

Treatment of penile metastasis is almost always palliative: radiation therapy or limited surgical excision is the most useful modality [7]. Due to their poor prognosis, patients in such a circumstance should be treated with palliative therapy. Our patient did not undergo therapy for penile metastasis due to his poor condition, but palliative therapy should be considered to relieve or prevent the intolerable symptoms.

Metastasis to the penis is usually considered to be a late complication, and is often associated with multiple distant metastases in other organs. Thus, this particular involvement may be an ominous prognostic sign, as was confirmed in our patient, who expired 2 weeks after penile metastasis had become evident.

In summary, metastasis to the penis is extremely rare in lung cancer. The low incidence may be related to the fact that the penis is not examined as routinely as other organs [7, 9]. However, as therapy for lung cancer develops, more cases of penile metastasis will be detected in the future, along with the prolonged survival of lung cancer patients, so early detection and appropriate management of penile metastasis will be important.

References

1. Ginsberg RJ, Vokes EE, Raben A. Cancer of the lung. In: De Vita VT, Hellman S, Rosenberg SA, editors. Cancer Principles and Practice of Oncology, 5th edn. Philadelphia, PA: Lippincott-Raven Publishers, 1997: 858-911.
2. Hayes WT, Young JM. Metastatic carcinoma of the penis. J Chron Dis 1967; 20: 891-5.
3. Silber I. Penile metastases from bronchogenic carcinoma. Urology 1976; 7: 536-7.
4. Van Wyk CE. Bronchogenic carcinoma metastasizing to the heart and penis. S Afr Med J 1983; 64: 255-6.
5. Palfi Z, Zana J, Vilagosi C, *et al*. Carcinoma of the penis as a metastasis. Acta Chir Hung 1988; 29: 323-6.
6. Yokoi K, Miyazawa N, Muraki J, *et al*. Penile metastasis from lung cancer. Jpn J Clin Oncol 1992; 22: 297-9.
7. Belville WD, Cohen JA. Secondary penile malignancies: the spectrum of presentation. J Surg Oncol 1992; 51: 134-7.
8. Bonaminio A, Shingleton WB. Squamous cell carcinoma of the lung with metastasis to the penis. South Med J

1995; 88(7): 761-2.
9. Powell BL, Chaig JB, Muss HB. Secondary malignancies of the penis and epididymis: a case report and review of the literature. J Clin Oncol 1985; 3: 110-6.
10. Peres LM, Shumway RA, Carcon CC III, *et al*. Penile metastasis secondary to supraglottic squamous cell carcinoma: review of the literature. J Urol 1992; 147: 157-60.
11. Fujimoto N, Hiraki A, Ueoka H, *et al*. Metastasis to the penis in a patient with squamous cell carcinoma of the lung with a review of reported cases. Lung Cancer 2001; 34: 149-52.
12. Hizli, Fatih. Berkmen, Ferhat, *et al*. Penile metastasis from other malignancies. A study of ten cases and review of the literature. Urologia Internationalis 2006; 76(2): 118-21.

肺腺癌合併陰莖轉移—病例報告

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陰莖轉移是肺癌中少見的轉移，這類轉移多在肺癌晚期才會出現，因此病人大多預後不佳，過去關於這類病例報告並不多，其中多數為鱗狀上皮細胞癌出現的轉移，我們描述一個六十六歲肺腺癌的患者，初期診斷為第四期併肝臟轉移 (T2N3M1)，在經過四個療程第一線化學治療 (gemcitabine 跟cisplatin) 後，病人因嚴重的噁心嘔吐而暫停治療，之後病人因食慾不佳而入院，住院期間發現病人出現包皮與陰囊腫脹，經檢查發現有陰莖硬塊，切片與免疫螢光染色後發現CK與TTF-1呈現陽性反應，確定為肺腺癌轉移，病人之後因狀況不佳未接受進一步治療並於兩個星期後死亡。*(胸腔醫學* ***2008; 23: 182-186)***

關鍵詞：肺癌，腺癌，陰莖轉移

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Experience with Non-survivors of Acute Carbon Monoxide Intoxication Who Received Hyperbaric Oxygen Therapy and Literature Review

Yu-Sheng Lin*, Te-Chun Hsia*,**, Yu-Lin Tsai*, Wen-Kai Tsai*, Liang-Wen Hang*,**, Chao-I Wu**, Chuen-Ming Shih*, Wu-Huei Hsu*

Purpose: The main purpose of this study was to determine the reason for the carbon monoxide (CO) poisoning-related deaths at out hospital and to describe the demographic data and epidemiology.

Methods: We retrospectively selected this group of acute CO intoxication patients that received emergency hyperbaric oxygen therapy (HBOT) from April 2000 to August 2005 at our hospital. Data regarding age, gender, duration of CO poisoning exposure, cause of the episode, underlying disease, number of HBOT courses, hospital course, cormorbidity, and cause of mortality were obtained from the medical records. We also reviewed the admission data records, including vital signs, Glasgow Coma Scale, arterial blood gas, carboxyhemoglobin level, and intubation or not.

Results: One hundred thirty-seven patients and 5 fatalities related to CO poisoning were reviewed; the mortality rate was 3.65%. The 5 fatalities were all male, in the prime of life (27~37 years old), and without major underlying disease. Four (4/5) patients committed suicide by inhaling CO from burning charcoal. They all received emergent HBOT. Prolonged unconsciousness was noted after series HBOT in 4 (4/5) patients. Four (4/5) patients developed rhabdomyolysis and acute renal failure. The causes of death were multiple organ failure (3/5, 60%) and septic shock (2/5, 40%).

Conclusions: The causes of acute CO poisoning among the fatalities were suicide by inhaling CO from burning charcoal (4/5, 80%) and a fire accident (1/5, 20%) at our hospital. They were in the prime of life without major underlying disease. The brain is an oxygen-dependent organ, and the damage may be severe and irreversible after CO intoxication and hypoxia. Rhabdomyolysis and acute renal failure may also occur. Secondary infection and septic shock may worsen the already poor condition. The cause of death may be considered as multiple organ failure, including the brain, lung, and kidney. ***(Thorac Med 2008; 23: 187-194)***

Key words: acute carbon monoxide poisoning, hyperbaric oxygen therapy, mortality cases, multiple organ failure

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Introduction

Carbon monoxide (CO) is a product of the incomplete combustion of hydrocarbons. CO is a colorless, odorless, and nonirritant toxic gas that is easily absorbed through the lung. Its production does not have a special warning sign. As many as 3,500 people are poisoned and die in the United Sates (US) every year because of CO poisoning related to fire, coal gas, automobile exhaust, and other sources [1]. The amount of gas absorbed is dependent on the minute ventilation, the duration of exposure, and the relative concentration of CO and oxygen in the environment [2]. CO toxicity appears to result from a combination of tissue hypoxia and direct CO-mediated damage at the cellular level [3]. Hyperbaric-oxygen therapy (HBOT) is often recommended for patients with acute CO poisoning, especially if they have lost consciousness or have severe poisoning [4]. The advantages of HBOT include increased dissolved-oxygen content in the blood and accelerated elimination of CO [5]. The potential benefits of HBOT include the prevention of lipid peroxidation in the brain and the preservation of adenosine triphosphate (ATP) levels in tissue exposed to CO [5].

We selected a group of acute CO intoxication patients that had received emergency HBOT from April 2000 to August 2005. The main purpose of this study was to determine the reason for the CO-related deaths and to describe the demographic data and epidemiology of these fatal poisonings.

Materials and Methods

The Hyperbaric Oxygen Therapy Center of China Medical University Hospital (CMUH), Taichung, Taiwan was established in April 2000. We use a multiplace hyperbaric chamber (HPE. 50.2M Model 222.12.AT, Bergamo, Italy).

We retrospectively reviewed the records of the patients who received HBOT at CMUH from April 2000 to August 2005 due to acute CO poisoning. During the 5-year study period, 137 patients who received HBOT for acute CO poisoning were enrolled, and 5 CO poisoning-related deaths are described. Data on the age, gender, duration of CO poisoning exposure, cause of the episode, underlying disease, number of HBOT courses, hospital course, cormorbidity, and cause of mortality were obtained from the medical records. We also reviewed the admission data records, including vital signs, Glasgow Coma Scale (GCS), arterial blood gas, carboxyhemoglobin (HbCO) level, and intubation or not.

Results

The records of 137 patients were reviewed. Seventy-four (73/137, 53%) patients were women, and 64 (64/137, 47%) were men. Eighteen (18/137, 13%) patients had been intubated with mechanical ventilator support due to acute respiratory failure. The causes of CO poisoning included attempted suicide by inhaling CO from burning charcoal (71%, 97/137), bathing accidents with gas inhalation (20%, 27/137), fire accidents (3%, 5/137), attempted suicide by inhaling automobile exhaust (3%, 4/137), barbecue accidents with coal gas inhalation (2%, 3/137), and a work accident with other toxic gas inhalation (1%, 1/137). Twenty-five (25/137, 18%) patients were abusing sedative drugs when they attempted suicide with CO poisoning.

Five patients died due to CO poisoning, with

a mortality rate of 3.65%. All were males, in the prime of life (27~37 years old), and without major underlying disease. They were sent to our Emergency Department (ED) due to attempted suicide through inhaling CO fumes from burning charcoal (4/5, 80%) and a fire accident (1/5, 20%). The duration of exposure to CO could not be clearly ascertained. The level of HbCO ranged from 11.4% to 56.9%. The patients were in a deep coma when they arrived at our ED. Two (2/5) patients were dead on arrival (DOA) and were resuscitated from cardiac arrest; 3 (3/5) were intubated with mechanical ventilator support, and 2 (2/5) used 100% oxygen initially. The patients were treated in the multiplace hyperbaric chamber (HPE.50.2M Model 222.12.AT, Bergamo, Italy), under 2.5 atmospheric pressure absolute (ATA), with 100% oxygen for 23 minutes and an air break for 5 minutes, with the duration averaging 2 hours (1.5~3 hours), and 1~3 times per day. Prolonged unconsciousness was noted after series HBOT in these patients. Three (3/5) patients developed rhabdomyolysis due to extended tissue compression, and 4 (4/5) developed acute renal failure. The length of hospitalization was from 2 to 18 days. Table 1 summarizes the data presented in this study. The causes of death were multiple organ failure (3/5, 60%) and septic shock (2/5, 40%).

Discussion

In Taiwan, suicide has been the 9th leading cause of death in recent years, and CO poisoning is the number 2 cause of successful suicide. CO poisoning accounts for an estimated 40,000 annual ED visits in the US; it is the leading cause of poisoning mortality in the US and may be responsible for more than half of all fatal poisonings worldwide [3]. CO is the commonest and most serious by-product of combustion, and is responsible for smoke-related morbidity and mortality [6]. As it is a colorless, odorless, tasteless and non-irritating gas, the exposed person is usually unaware of its effect until serious disorders occur. CO causes poisoning by its high affinity to hemoglobin (200 to 250 times greater than its affinity for oxygen) and its ability to replace oxygen, which renders the hemoglobin useless in terms of its oxygen carrying capacity. CO also alters the molecular configuration of hemoglobin and decreases the 2-3 diphosphoglycerate (2-3 DPG) of red blood cells, resulting in an unfavorable left shift of the oxyhemoglobin dissociation curve [7]. These alterations result in an impaired release of oxygen at the tissue level, and cellular hypoxia.

The amount of gas absorbed is dependent on the minute ventilation, the duration of exposure, and the relative concentrations of CO and oxygen in the environment. CO is principally eliminated by the lungs as an unchanged gas. CO binds to many heme-containing proteins other than hemoglobin, including cytochromes, myoglobin, and guanylyl cyclase. The disruption of oxidative metabolism via cytochrome oxidase may lead to the generation of oxygen free radicals. Cellular respiration may also be impaired via inactivation of mitochondrial enzymes and impaired electron transport from oxygen radicals (i.e., peroxynitrite) produced after CO exposure [8]. Clinical manifestations of CO intoxication are related to the blood carboxyhemoglobin level, time course of exposure, respiratory rate, age and health of the victim, and concomitant medications (affecting hepatic enzymes) or toxins (drugs, alcohol, etc.) [9]. The duration of exposure appears to be an important factor mediating toxicity. The CO

Table 1. Patient data

No.	Age (y)	Sex	Cause on Arrival	HbCO (%)	G.C.S. on arrival	ET	HBOT Number	Days of Admission	Cormorbidity	Underlying Disease	Cause of Death
1	35	M	Charcoal burning	37.6	E1VEM1	Y	1	2	1. Right leg compartment syndrome S/P fasciotomy 2. Rhabdomyolysis with acute renal failure S/P emergent hemodialysis 3. Aspiration pneumonia	1. Depression 2. Insomnia	CO intoxication with hypoxic encephalopathy and multiple organ failure
2	33	M	Charcoal burning	46.2	E1V1M2	N	2	18	1. Aspiration pneumonia 2. K.P. bacteremia	Major depression	Meningitis with septic shock
3	37	M	Charcoal burning	56.9	E1VEM1	Y	1	2	1. Acute renal failure	Nil	CO intoxication with hypoxic encephalopathy and multiple organ failure
4	27	M	Fire accident	33.2	E1VEM1	Y	1	6	1. Rhabdomyolysis with acute renal failure 2. Refractory seizure	Nil	CO intoxication with hypoxic encephalopathy and multiple organ failure
5	29	M	Charcoal burning	11.4	E4V5M6	N	1	10	1. Rhabdomyolysis with acute renal failure 2. Necrotizing fascitis	1. Mood disorder	Septic shock with multiple organ failure

No.=number; y=years old; ET=intubation; M=male; Y=yes; N=no; K.P.=Klebsiella Pneumoniae; CPCR=cardiopulmonary and cerebral resuscitation; HbCO=carboxyhemoglobin; D.O.A.=dead on arrival; G.C.S.=Glasgow Coma Scale

level is certainly important in diagnosing CO poisoning, but does not predict the immediate or late sequelae. The decision to administer HBOT or not cannot be made solely on the basis of CO levels [10]. By supplying a high concentration of oxygen or HBOT (100 percent oxygen at 2 to 3 times the atmospheric pressure at sea level) in victims of CO poisoning, CO can be replaced by oxygen and tissue hypoxia can be relieved. The half-life of CO in the body is approximately 4-5 hours; this can be reduced to 60-80 minutes by giving 100% oxygen, or to approximately 25 minutes by HBO [3]. HBOT with CO-poisoned individuals is more effective when delivered within 6 hours of removal from CO exposure [11].

Acute CO poisoning is a common event with variable presentations. The symptoms and signs are distributed from headache, dizziness, weakness, nausea, shortness of breath, visual changes, chest pain, difficulty concentrating, and confusion, to loss of consciousness. The clinical effects of CO poisoning are diverse and easily confused with other illnesses, such as nonspecific viral illnesses, benign headache, and various cardiovascular and neurological syndromes [3]. Early neurological manifestations include dizziness and headache. Increasing exposure may produce altered mental status, confusion, syncope, seizure, acute stroke-like syndromes, and coma.

The role of nitric oxide (NO) and other oxygen free radicals has been researched extensively in the setting of CO poisoning. Many animal studies have demonstrated cerebral vasodilation after exposure to CO, which is associated temporally with a loss of consciousness and increased NO levels. This finding has led to speculation that clinical syncope may be related to NO-mediated cerebral vessel relaxation and low blood flow. NO is also a peripheral vasodilator and may result in systemic hypotension [5]. The presence of systemic hypotension in CO poisoning is correlated with the severity of central nervous system structural damage [12]. NO also seems to play a pivotal role in a cascade of events culminating in oxidative damage to the brain, which may be responsible for the clinical syndrome of delayed neurological sequelae (DNS). Brain lipid peroxidation after CO exposure seems to be a post-ischemic reperfusion phenomenon, mediated by alterations in cerebral blood flow and oxidative free radical damage [8].

Due to coma consciousness secondary to CO poisoning, long-term muscle compression and hypoxic encephalopathy with refractory seizure may result in rhabdomyolysis, cell lyses with hyperkalemia, metabolic acidosis, acute tubular necrosis, oliguria, and acute renal failure. CO poisoning may also result in rhabdomyolysis, potentially as a direct toxic effect of CO on skeletal muscles [13].

A number of studies have documented the poor prognosis of patients with out-of-hospital cardiac arrest in general. Rates of survival to hospital discharge in reported series have ranged from 1.4% to 26%, and are estimated to average 20% overall. Discovery of the arrested patient in asystole or bradydysrhythmia has also been described as associated with a worse prognosis [14]. It can be seen that cardiac arrest complicating CO poisoning carries a dismal prognosis, even if resuscitation yields a return of spontaneous circulation and the patient subsequently undergoes HBOT. Neil and Jennette found that cardiac arrest complicating CO poisoning resulted in 100% mortality, despite initial resuscitation in the field with a return of spontaneous circulation and subsequent HBOT

[15].

Case number 4 (Table 1) was poisoned by CO in a house fire. He might have had concomitant poisoning with other toxins, particularly cyanide. In an Australian study, many of the victims died with elevated whole blood cyanide levels, which are significantly correlated with HbCO levels. Further research is required to determine the frequency of toxic cyanide levels in smoke inhalation patients who are transported to the hospital [22]. This was documented in a report of patients undergoing cardiac arrest sustaining CO poisoning from smoke inhalation [23].

In our review of the 5 mortality cases, all patients were healthy and in the prime of life. When they arrived at our ER, an unstable hemodynamic status, deep coma, and acidosis (mixed respiratory and metabolic acidosis) were noted. The brain is the most oxygen-dependent organ and the most sensitive to the toxic effects of CO [3]. Four (4/5, 80%) of the 5 mortalities were persistently comatose; we believe that the damage to the brain was severe and irreversible. Rhabdomyolysis, hyperkalemia, and acute renal failure may occur due to muscle compression, but the course of death is mostly due to multiple organ failure (brain, respiratory, and renal failure).

On the basis of this experience and a review of the available literature, long-term exposure, severe CO poisoning, and multiple organ failure may considered as poor prognostic factors for survival. There are currently no standard recommendations regarding the factors leading to a poor prognosis or the use of HBOT in these patients. Further research is needed to define these factors and help in the decision to institute active cardiopulmonary resuscitation or treatment.

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References

1. Carol W. Runyan, Renee M. Johnson, Jingzhen Yang, *et al*. Risk of Protective Factors for Fires, Burns, and Carbon Monoxide Poisoning in U.S. Households. Am L Pre Med 2005; 28: 102-8.
2. Forbes WH, Sargent F, Roughton FJW. Rate of carbon monoxide uptake by normal men. Am J Physiol 1945; 143: 594-608.
3. Louise W. Kao, Kristine A. Nanagas. Carbon monoxide poisoning. Emerg Med Clin N Am 2004; 22: 985-1018.
4. Ernst A, Zibrak JD. Carbon monoxide poisoning. N Engl J Med 1998; 339: 1603-8.
5. Lindell K. Weaver, Ramona O. Hopkins, Karen J. Chan. Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med 2002; 347: 1057-67.
6. Krenzelok EP, Roth R, Full R. Carbon monoxide: The silent killer with an audible solution. Am J Emerg Med 1996; 14: 484-6.
7. Halebian PH, Corder VJ, Madden MR, *et al*. Whole body oxygen utilization during acute carbon monoxide poisoning and isocapneic nitrogen hypoxia. T Trauma 1986; 26: 110-7.
8. Hardy KR, Thom SR, Pathophysiology and treatment of carbon monoxide poisoning. J Toxicol Clin Toxicol 1994; 32: 613-29.
9. Lindell K. Weaver: environmental emergencies: Carbon monoxide poisoning. Critical Care Clinics 1999; 15: 297-317.
10. Norkool DM, Kirkpatrick JN. Treatment of acute carbon monoxide poisoning with hyperbaric oxygen: a review of 115 cases. Ann Emerg Med 1985; 14: 1168-71.
11. Goulon M, Barois A, Rapin M, *et al*. Carbon monoxide poisoning and acute anoxia due to breathing coal gas and hydrocarbons. J Hyperbaric Med. 1986; 1: 23-41.
12. Okeda R, Funata N, Takano T, *et al*. The pathogenesis

of carbon monoxide encephalopathy in the acute phase-physiological and morphological correlation. Acta Neuropathol 1981; 54: 1-10.

13. Wolff E. Carbon monoxide poisoning with severe myonecrosis and acute renal failure. Am J Emerg Med 1994; 12: 347-9.
14. Becker LB, Ostrander MP, Barrett J, *et al*. Outcome of CPR in a large metropolitan area-where are the survivors? Ann Emerg Med 1991; 20: 355-61.
15. Neil B. Hampson, Jennette L. Zmaeff. Outcome of Patients Experiencing Cardiac Arrest With Carbon Monoxide Poisoning Treated With Hyperbaric Oxygen. Ann Emerg Med 2001; 38: 36-41.
16. Michael J. Yeoh and George Braitberg. Carbon Monoxide and Cyanide Poisoning in Fire Related Deaths in Victoria, Australia. Journal of Toxicology 2004; Vol. 42, No. 6: 855-63.
17. Hantson P, Butera R, Clemessy JL, *et al*. Early complications and value of initial clinical and paraclinical observations in victims of smoke inhalation without burns. Chest 1997; 111: 671-5.

急性一氧化碳中毒病人接受高壓氧治療後死亡病例臨床經驗分析和文獻回顧

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目的：針對急性一氧化碳中毒患者死亡者分析其治療經過及探討其死亡原因。

方法：我們回溯性研究近5年來(從2000年4月至2005年8月)，因為急性一氧化碳中毒送到中國醫藥大學附設醫院，接受高壓氧治療的患者。我們從病歷中收集病人的性別、年齡、中毒原因、一氧化碳中毒時間、高壓氧治療次數、住院時間、併發症、治療經過、以及死亡原因等，並紀錄到院時生命徵象、昏迷指數、一氧化碳濃度、血氧分析、以及有無氣管插管等相關資料。

結果：我們總共收治了137例一氧化碳中毒的患者，其中五例死亡，死亡率為3.65%。五例死亡患者中男性五例，女性零例，年齡27~37歲，正處於青壯年，且無重大疾病;四例為燃煤自殺；一例為火災意外。病人由急診會診後立即進行高壓氧治療。其中四例直到死亡前意識仍無法恢復；四例發生橫紋肌溶解症和急性腎衰竭。死亡原因分別為多重器官衰竭（三例）和敗血性休克（二例）。

結論：本院死亡病例以自殺為主(80%)，且均為青壯年。腦是一個需氧且對缺氧很敏感的器官，在一氧化碳中毒及缺氧後所造成傷害或許是嚴重且不可逆的。橫紋肌溶解症併急性腎衰竭、次發性感染、和敗血性休克或許會使情況更加惡化。但最後死亡原因應該仍為多重器官衰竭，包括了腦、肺、和腎臟。
*(胸腔醫學 **2008; 23: 187-194**)*

關鍵詞：急性一氧化碳中毒，高壓氧治療，死亡病例，多重器官衰竭

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Interventional Bronchoscopy for Treatment of Tracheal Obstruction Secondary to Malignant Thyroid Disease – A Case Report

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Malignant thyroid disorders can cause upper and central airway obstruction. The mechanisms of airway obstruction include extrinsic tracheal compression, tracheal ingrowth, or a combination thereof. Well-differentiated thyroid cancer (WDTC) usually has a better prognosis, but is a less frequent cause of thyroid-induced airway obstruction. However, if WDTC-related tracheal invasion occurs, it is usually associated with a poor prognosis. Surgical resection with tracheal reconstruction remains the mainstay of management of WDTC-related tracheal invasion. In cases with technically or medically inoperable patients with malignant symptomatic airway obstruction, some form of palliative treatment should be considered. Due to recent technical improvements, interventional bronchoscopy with stent placement may provide longstanding airway patency for thyroid cancer-related tracheal obstruction.

We report an 86-year-old female patient presenting stridor because of thyroid papillary carcinoma-related tracheal obstruction. After receiving interventional bronchoscopy with an Ultraflex tracheal stent placement, her stridor symptoms immediately improved. Thus, interventional bronchoscopic procedures with stent implant are valuable alternatives to surgery in inoperable thyroid cancer-induced tracheal obstruction. ***(Thorac Med 2008; 23: 195-199)***

Key words: airway stents, bronchoscopy, thyroid carcinoma, tracheal stenosis

Introduction

Well-differentiated thyroid carcinoma (WD TC) usually has a better prognosis than other human malignancies [1]. Surgical treatment of these cancers is typically associated with a good outcome [2]. Local invasive thyroid cancer is an uncommon disease, but it can display aggressive behavior and also result in tracheal obstruction [3]. When tracheal invasion occurs, it is associated with significant mortality and morbidity [1, 4]; therefore, whether the thyroid cancer has tracheal invasion or not is a significant prognostic factor for survival [5].

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Clinical signs of airway obstruction due to thyroid enlargement are generally considered to be an absolute indication for surgical treatment [3, 6-7], even in elderly patients. When surgery is contraindicated or in medically inoperable patients with malignant symptomatic airway obstruction, palliative treatment should be considered. Herein, we report our experience with bronchoscopic airway stenting in a patient with thyroid papillary carcinoma-induced airway obstruction. The stridor and dyspnea symptoms immediately improved after the interventional bronchoscopic procedure.

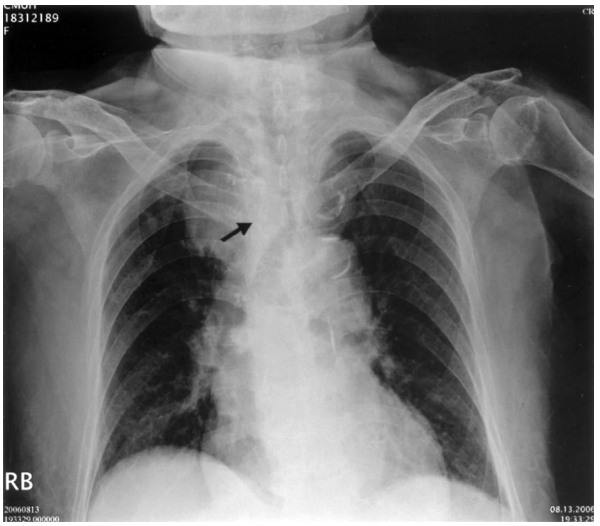

Fig. 1. Chest X-ray showing a right-side thyroid tumor with left-side tracheal deviation and narrowing.

Case Report

An 86-year-old female had a history of hypertension for more than 10 years. She had had intermittent hemoptysis for 3 years, which was usually treated as bronchitis. Then, just before this admission, she suffered from worsening hemoptysis, and 1 day before this admission, she had dyspnea with a high-pitched inspiratory breathing sound. On examination, she was in respiratory distress. Auscultation of the neck showed inspiratory stridor. Chest X-ray (Figure 1) showed a right thyroid tumor with left-side tracheal deviation. Neck and chest computed tomography (CT) (Figure 2A) showed right-side thyroid enlargement with external compression of the trachea and tracheal lumen narrowing. The thyroid function test showed serum thyroid stimulating hormone (TSH): 0.015 mIU/ml (0.465-4.68 mIU/ml) and free T4: 1.42 ng/dl (0.78-2.19 ng/dl). Thyroid sonography revealed multiple hypo- and hyperechoic lesions in both lobes and an ill-defined margin lesion in the right lobe. She was then suspected of having thyroid cancer with tracheal invasion and we suggested operation. However, she and her family refused operation after the surgeon explained the high risk involved, and decided on conservative therapy. She received a bronchoscopic examination which showed the tracheal tumor invading the tracheal lumen, inducing tracheal lumen narrowing. We performed tracheal tumor biopsy and implanted an Ultraflex stent (Boston Scientific; Natick, MA) into the narrowed tracheal lumen. Pathology of the tracheal tumor showed papillary thyroid carcinoma. After tracheal stent implantation, the stridor disappeared and her dyspnea symptoms improved immediately. No further hemoptysis occurred after the interventional procedures. Three months later, the follow-up CT showed the previous tracheal narrowing had improved with the stent (Figure 2B). Unfortunately, her thyroid cancer deteriorated and she passed away due to pneumonia 4 months after the tracheal stent implant.

Discussion

Patients with central airway obstruction

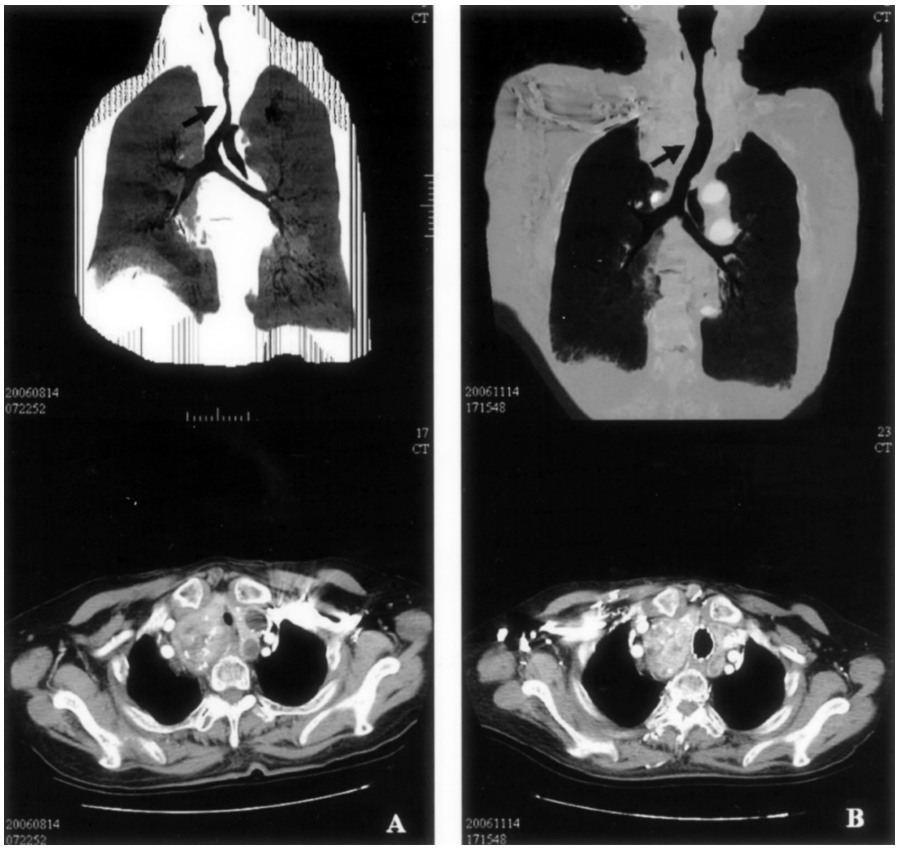

Fig. 2. A. Neck and chest computed tomography (CT) revealed right-side thyroid enlargement with external compression of the trachea and induced tracheal lumen narrowing; B. Three months after interventional bronchoscopy with stent implantation, follow-up CT showed the previous tracheal narrowing had improved with the stent.

from both malignant and benign airway conditions present with disabling symptoms. For some of these patients, the extent of the disease or comorbidities precludes curative surgery. Clinically, the most common neoplasms invading the upper airway include lung cancer (30%) and esophageal cancer (30%) [8-9]. WDTC, including papillary, follicular, and Hurthle cell carcinomas, is a relatively indolent disease compared with other human cancers [2]. It accounts for more than 80% of thyroid cancer and usually has a better prognosis [10]. However, if it invades adjacent structures, especially the central airway, it is associated with a worse prognosis and an increased risk of mortality. The exact frequency of WDTC with central airway invasion is still open to debate. Incidences between 1% and 16% have been reported [1-3]. The manifestations of central airway invasion by WDTC include hemoptysis, laryngeal stridor, hoarseness, laryngotracheal fixation, and vocal cord palsy [1]. Surgical intervention, such as total thyroidectomy with tracheal resection and anastomosis, is the treatment of choice for symptomatic tracheal obstruction due to malignant thyroid disease [3, 6-7]. Radical surgical treatment for patients is associated with a greater overall survival and disease-free interval compared to those with incomplete resections [1].

Only a few therapeutic alternatives are available for inoperative patients; they include external beam radiation therapy, chemotherapy (CT), or radioactive iodine treatment (131I) [6-7, 11]. However, the tracheal stent implants can provide an alternative palliative modality for thyroid cancer-related airway obstruction [7, 12]. Clinically, there are 2 common types of airway stents (silicon stent and self-expanding metallic stent) available for interventional bronchoscopy [7, 13-14]. The use of a silicone stent is preferred in patients with benign conditions who have a relatively better prognosis. However, silicone stents must be implanted using a rigid bronchoscope under general anesthesia, and their complications, such as stent migration and retained secretion, tend to bother patients [7]. This was the basis of our selection of the Ultraflex stent implant under fibrobronchoscopic assistance with local anesthesia.

In our patient, the extent of the disease or the comorbidities precluded curative surgery, so interventional bronchoscopy with an Ultraflex stent implant served as palliative management, relieving her dyspnea symptoms immediately. This management prolonged her survival more than 120 days.

In conclusion, interventional bronchoscopy with an airway stent implant offers an effective and alternative palliation for inoperable thyroid cancer patients with central airway obstruction.

References

1. Kowalski LP, Filho JG. Results of the treatment of locally invasive thyroid carcinoma. Head Neck 2002; 24: 340-4.
2. Kim AW, Maxhimer JB, Quiros RM, *et al*. Surgical management of well-differentiated thyroid cancer locally invasive to the respiratory tract. J Am Coll Surg 2005; 201: 619-27.
3. Patel KN, Shaha AR. Locally advanced thyroid cancer. Curr Opin Otolaryngol Head Neck Surg 2005; 13: 112-6.
4. McCaffrey TV, Bergstralh EJ, Hay ID. Locally invasive papillary thyroid carcinoma: 1940-1990. Head Neck 1994; 16: 165-72.
5. Czaja JM, McCaffrey TV. The surgical management of laryngotracheal invasion by well-differentiated papillary thyroid carcinoma. Arch Otolaryngol Head Neck Surg 1997; 123: 484-90.
6. Avenia N, Ragusa M, Monacelli M, *et al*. Locally advanced thyroid cancer: therapeutic options. Chir Ital 2004; 56: 501-8.
7. Noppen M, Poppe K, D'Haese J, *et al*. Interventional bronchoscopy for treatment of tracheal obstruction secondary to benign or malignant thyroid disease. Chest 2004; 125: 723-30.
8. Cavaliere S, Venuta F, Foccoli P, *et al*. Endoscopic treatment of malignant airway obstructions in 2,008 patients. Chest 1996; 110: 1536-42.
9. Chan KP, Eng P, Hsu AA, *et al*. Rigid bronchoscopy and stenting for esophageal cancer causing airway obstruction. Chest 2002; 122: 1069-72.
10. Shaha AR. Controversies in the management of thyroid nodule. Laryngoscope 2000; 110: 183-93.
11. Ribechini A, Bottici V, Chella A, *et al*. Interventional bronchoscopy in the treatment of tracheal obstruction secondary to advanced thyroid cancer. J Endocrinol Invest 2006; 29: 131-5.
12. Gunasekaran S, Osborn JR, Morgan A, *et al*. Tracheal stenting: A better method of dealing with airway obstruction due to thyroid malignancies than tracheostomy. J Laryngol Otol 2004; 118: 462-4.
13. Vonk-Noordegraaf A, Postmus PE, Sutedja TG. Tracheobronchial stenting in the terminal care of cancer patients with central airways obstruction. Chest 2001; 120: 1811-4.
14. Lund ME, Garland R, Ernst A. Airway stenting: applications and practice management considerations. Chest 2007; 131: 579-87.

利用介入性支氣管鏡治療甲狀腺惡性腫瘤所導致的氣管阻塞—病例報告

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惡性的甲狀腺疾病可以導致上呼吸道的阻塞；造成氣道阻塞的機轉包括由氣管外部的壓迫，腫瘤長到氣管內，或兩者共同造成。細胞分化良好的甲狀腺癌通常有較好的預後，而它造成氣道阻塞的機會較少。然而，假如細胞分化良好的甲狀腺癌(well-differentiated thyroid cancer)已造成了氣管的侵犯，它通常代表預後不佳。治療分化良好的甲狀腺癌所造成的氣管侵犯，手術切除合併氣管重建仍是主要的治療方式。在技術上或身體狀況無法接受手術的病人，若合併有症狀的氣道阻塞，需考慮其他形式的緩和療法。近來，隨著技術的進步，對於甲狀腺癌導致氣管阻塞的病人，介入性支氣管鏡合併支架置放可以提供較長期的氣道通暢度。

我們報告了一位86歲的女性病患，因為甲狀腺乳突狀腫瘤(thyroid papillary carcinoma)導致的氣管阻塞，以喘鳴音(stridor)來表現。她在接受介入性支氣管鏡檢查合併支架置放後，她的喘鳴獲得了立即的改善。因此，在甲狀腺癌所導致的氣管阻塞而又無法開刀的病患，介入性支氣管鏡檢查合併支架置放是一項有用的替代療法。*(胸腔醫學* ***2008; 23: 195-199)***

關鍵詞：氣管支架，氣管鏡，甲狀腺癌，氣管阻塞

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Isolated Tuberculous Mediastinal Lymphadenopathy Mimicking a Tumor

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A previously healthy 53-year-old woman had suffered from chest pain for 2 months, and imaging studies revealed a left mediastinal tumor. Preoperative bacteriological examinations failed to uncover evidence of tuberculous infection. However, after video-assisted thoracoscopic surgery (VATS), the tumor was proved to be tuberculous mediastinal lymphadenopathy. Our experience revealed a unique manifestation of tuberculosis which was neglected by conventional methods and required surgery to establish the diagnosis. Therefore, with the high disease burden worldwide and the various imaging presentations of tuberculosis, we should always take tuberculous mediastinal lymphadenopathy into consideration in the differential diagnosis of intrathoracic lesions. ***(Thorac Med 2008; 23: 200-204)***

Key words: tuberculous mediastinal lymphadenopathy, mediastinal tumor, thoracoscopy/VATS

Introduction

Isolated tuberculous mediastinal lymphadenopathy (TML) in immunocompetent adults is unusual and sometimes presents a diagnostic problem. Despite a variety of diagnostic tools, including clues from the patient's medical history, clinical examinations, chest radiography, sputum examinations and bronchoscopy, one may not be able to distinguish TML from other conditions due to the diverse manifestations [1]. Often, surgical biopsy to obtain a histopathology and tissue culture has to be done to reach the correct diagnosis.

Case Report

A 53-year-old woman, who presented with a 2-month history of intermittent left chest pain, came to our hospital for help. She had no history of contact with tuberculosis (TB) patients, and had been vaccinated with bacillus Calmette-Guerin (BCG) in her childhood. A well-demarcated lesion on the left mediastinum was revealed by chest roentgenogram (*arrow*, Figure 1). She had had no other films in recent years. Thoracic computed tomographic (CT) scan with contrast media discerned a large, homogeneous and well-enhanced solitary tumor located at the left mediastinum lateral to the aortopulmonary

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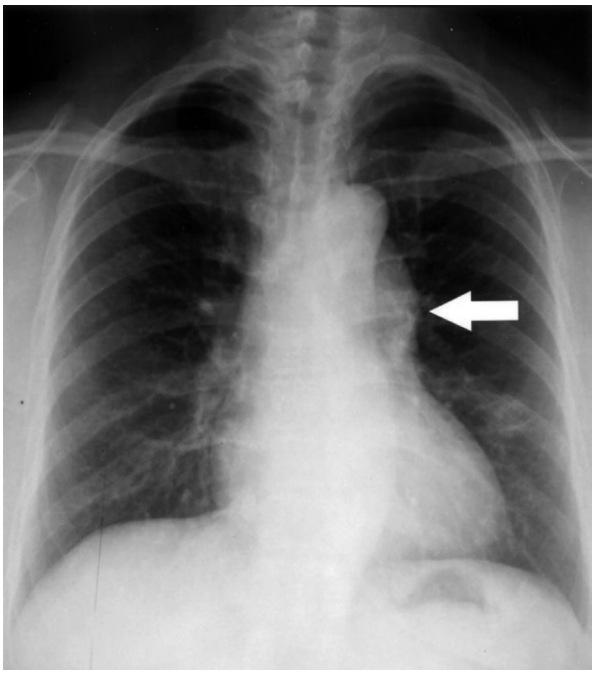

Fig. 1. Chest roentgenogram showed a lesion on the left mediastinum without lung parenchymal lesions (*arrow*).

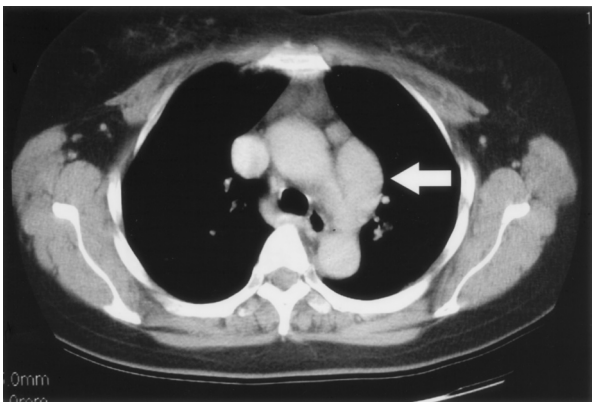

Fig. 2. CT scan of the chest showed a homogeneous and well-enhanced solitary tumor lateral to the aortopulmonary window (*arrow*).

window (*arrow*, Figure 2), without pulmonary lesions. Bronchoscopy showed no endobronchial lesions. Positron emission tomographic (PET) scan demonstrated it to be a hypermetabolic lesion, compatible with malignancy or an inflammatory process (*arrows*, Figure 3).

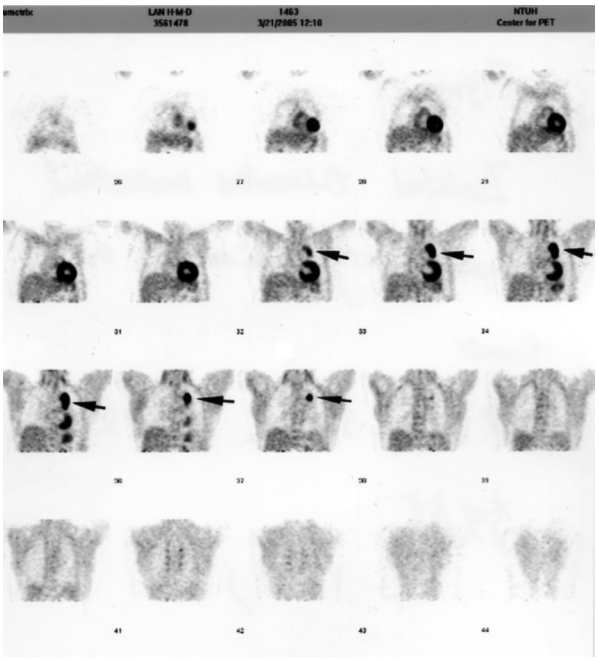

Fig. 3. PET revealed a hypermetabolic lesion on the left anterior mediastinum, compatible with malignancy or an inflammatory process (*arrows*).

Three sets of sputum acid-fast stains and TB cultures were all negative. The serum level of carcinoembryonic antigen was within the normal range. To attain a definite diagnosis, a video-assisted thoracoscopic (VAT) excisional biopsy was performed via a camera port and 2 working ports. The large tumor, measuring 5.5 x 5.0 x 2.0 cm in size, was elastic and firm (Figure 4). Beyond our expectation, it showed granulomatous inflammation with acid-fast bacilli microscopically, and TML was diagnosed. The post-operative course was smooth and she was discharged 6 days after surgery. Anti-TB chemotherapy was soon initiated for a complete course of 12 months. As of this writing, the patient had been followed up for 27 months at our outpatient department with no other evidence of tuberculous infection.

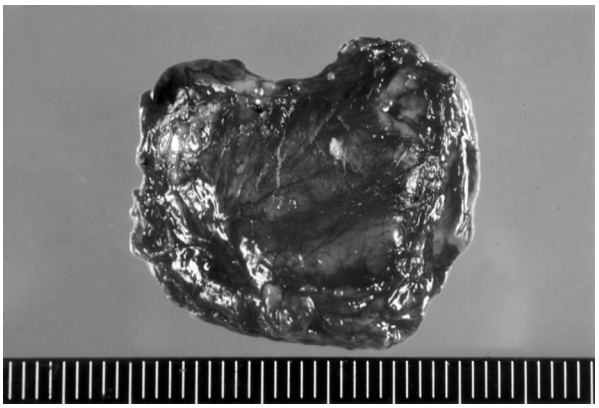

Fig. 4. Grossly, the large mediastinal mass, measuring 5.5 x 5.0 x 2.0 cm in size, was yellowish, elastic and firm.

Discussion

Tuberculosis is still one of the leading causes of death in many developing countries. In Taiwan, the high disease burden and high resistance rates of TB represent increasingly serious health problems [2]. The incidence of TB has also been increasing in developed countries since 1985 due to a higher number of immunocompromised patients, especially human immunodeficiency virus (HIV) seropositive patients [3]. Thus, it appears that the clinical and radiological presentations of TB have changed to more unusual manifestations. Among them, isolated hilar and mediastinal lymphadenopathy is a common sign of tuberculous infection in children and in adults with HIV infection [4]. However, in immunocompetent adults, TML without a parenchymal lung lesion is unusual and is more common in non-Caucasians [5]. This has been attributed to environmental factors, previous exposure to tuberculous infections, and differences in susceptibility and immunological reactions [6]. The incidence of isolated TML in a study conducted by Ayed *et al*. was 2% of 1700 new cases of TB over a 3-year period [1]. In a study by Dhand *et al*. [7], the incidence was 5.8%, while Baran *et al*. [8] reported a lower incidence of 0.25%.

While isolated mediastinal lymphadenopathy may be caused by malignancy, many benign diseases, such as TB or fungal infection, sarcoidosis, Wegener's granulomatosis and Castleman's disease should also be considered in the differential diagnosis. Typical images of tuberculous lymphadenopathy are contrast-enhanced thoracic CT findings of nodules with central low attenuation and peripheral rim enhancement, corresponding pathologically to caseation or liquefaction necrosis and granulation tissue with inflammatory hypervascularity, respectively, and are indicators of active tuberculous disease [9]. Non-homogeneous nodal enhancement is also a relatively common sign of tuberculous lymphadenopathy [9]. However, in our patient, the thoracic CT scan showed a single, large, homogeneous, and well-enhanced solitary mediastinal tumor without pulmonary parenchymal lesions. The radiological manifestation was quite unique. Furthermore, due to its active inflammatory condition, the functional image modality with PET falsely regarded it as a malignant tumor. In Asia, the accuracy of PET for lung cancer diagnosis and staging is hampered by the high prevalence of TB, and because tuberculoma may have a high metabolic rate that is almost indistinguishable from malignancy, either by visual assessment or standard uptake value (SUV) [10-11]. Therefore, it demonstrated the unusual clinical and radiographic findings of TB, which caused difficulties in determining the diagnosis. Moreover, the diagnostic yield from sputum examinations is low in these patients, ranging from 0% to 24%, which may be explained by the lack of parenchymal lesions [1, 7]. Further procedures,

such as bronchoscopy, CT-guided fine needle aspiration biopsy, mediastinoscopy or VATS for pathogen culture and histopathology may be required to establish a definite diagnosis [12]. In our patient, CT-guided fine needle aspiration biopsy or mediastinoscopy was not suggested because the tumor was located near the aortopulmonary window.

In summary, the TML in our patient uniquely mimicked an isolated mediastinal tumor radiologically. The pathophysiology was not clear in this immunocompetent woman, but may have been due to airborne transmission in this endemic area. That conventional diagnostic tools were unable to distinguish TML from other causes made the differential diagnosis difficult before operation. VATS excisional biopsy was necessary to establish a definite diagnosis, followed by appropriate anti-TB treatment. Therefore, due to the various manifestations of pulmonary TB and its high global disease burden, TML should be kept in mind during the differential diagnosis of unknown intrathoracic lesions, not only for patients who live in an area with a high prevalence, but also for those in economically well-developed countries and who are immunocompetent.

References

1. Ayed AK, Behbehani NA. Diagnosis and treatment of isolated tuberculous mediastinal lymphadenopathy in adults. Eur J Surg 2001; 167(5): 334-8.
2. Hsueh PR, Liu YC, So J, *et al*. Mycobacterium tuberculosis in Taiwan. J Infect 2006; 52(2): 77-85.
3. Narain JP, Raviglione MC, Kochi A. HIV-associated tuberculosis in developing countries: epidemiology and strategies for prevention. Tuber Lung Dis 1992; 73(6): 311-21.
4. Gabbay E, Cameron D, Lake FR. Tuberculous lymphadenitis: revisiting an old foe. Aust N Z J Med 1996; 26(4): 561-2.
5. Short course chemotherapy for lymph node tuberculosis: final report at 5 years. British Thoracic Society Research Committee. Br J Dis Chest 1988; 82(3): 282-4.
6. Domingo P. Isolated mediastinal tuberculous lymphadenitis. Arch Intern Med 1996; 156(14): 1582.
7. Dhand S, Fisher M, Fewell JW. Intrathoracic tuberculous lymphadenopathy in adults. JAMA 1979; 241(5): 505-7.
8. Baran R, Tor M, Tahaoglu K, *et al*. Intrathoracic tuberculous lymphadenopathy: clinical and bronchoscopic features in 17 adults without parenchymal lesions. Thorax 1996; 51(1): 87-9.
9. Anand J, Khanna SP, Menon MPS. Computed tomography features of tuberculous mediastinal lymphadenopathy. Indian Journal of Tuberculosis 1992 Oct; 39(4): 229-34.
10. Ho CL. Clinical PET imaging--an Asian perspective. Ann Acad Med Singapore 2004; 33(2): 155-65.
11. Low SY, Eng P, Keng GH, *et al*. Positron emission tomography with CT in the evaluation of non-small cell lung cancer in populations with a high prevalence of tuberculosis. Respirology 2006; 11(1): 84-9.
12. Chen JS, Chang YL, Cheng HL, *et al*. Video-assisted thoracoscopic surgery for the diagnosis of patients with hilar and mediastinal lymphadenopathy. J Formos Med Assoc 2001; 100(3): 213-6.

以腫瘤表現之單一結核性縱膈腔淋巴病變：一病例報告

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結核性縱膈腔淋巴病變並不常發生在免疫正常的人，且診斷上也往往是困難的。雖然以病史詢問、身體檢查、胸部X光片、痰液培養與支氣管鏡檢，我們仍常常無法診斷出結核性淋巴病變。通常這時就需要藉由手術切片、病理檢查與檢體組織培養來證實這個診斷。

在本文中，我們報告了一位以兩個月胸痛來表現的53歲家庭主婦。她因此求醫並接受胸部X光與電腦斷層檢查，意外發現了一個異常的左前縱膈腔腫瘤。這個單一的邊緣平滑之圓形腫瘤位在主動脈與肺動脈窗的旁邊，大小為5.5 x 5.0 x 2.0公分。肺部或其他器官均無異常現象。一系列的檢查都沒有辦法確認診斷，故她接受了胸腔鏡腫瘤切除手術。在病理檢查中，意外發現了有肉芽腫性炎症以及抗酸性染色陽性的結核桿菌之出現，故結核性縱膈腔淋巴病變才得以診斷確認。此病人經過12個月的抗結核菌藥物治療後，結核菌感染已完全康復。*(胸腔醫學* ***2008; 23: 200-204)***

關鍵詞：結核性縱膈腔淋巴病變，縱膈腔腫瘤，胸腔鏡手術

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Alpha-Fetoprotein-Producing Hepatoid Adenocarcinoma Originating in the Lung – A Case Report

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Hepatoid adenocarcinoma (HAC) is a rare extrahepatic malignant disease with a histopathologic pattern similar to that of hepatocellular carcinoma (HCC). Most hepatoid carcinomas generate a high level of alpha-fetoprotein (AFP). To date, only 11 cases of HAC in the lung have been reported in the literature. Herein, we report a 44-year-old man with an incidentally-found lung mass accompanied by an elevated serum level of AFP as high as 82,714 ng/mL; the mass was confirmed to be HAC on histopathologic examination via a specimen obtained from percutaneous computed tomography-guided biopsy. The CT scan and ultrasonography of the abdomen revealed no evidence of hepatoma or other intraabdominal abnormalities. The follow-up serum AFP level declined to 28,461 ng/mL after a cycle of chemotherapy and radiotherapy. ***(Thorac Med 2008; 23: 205-210)***

Key words: hepatoid adenocarcinoma, alpha-fetoprotein

Introduction

Hepatoid adenocarcinoma (HAC) is a rare extrahepatic malignant disease with a histopathologic pattern similar to hepatocellular carcinoma (HCC). Most hepatoid carcinomas manifest as increased alpha-fetoprotein (AFP) in the serum, but normal levels of AFP have also been reported [1]. In 1981, Yasunami *et al*. first reported a primary lung cancer producing AFP as high as 19,000 ng/mL, but with no evidence of hepatic neoplasm [2]. In 1985, the term "HAC" was coined by Ishikura *et al*. for an AFP-producing gastric carcinoma with features of hepatic differentiation in histology [3]. Although the most common location of HAC is in the stomach, it has also been described in other organs, such as the lung [4], esophagus [5], pancreas [6], papilla of vater [7], and colon [8]. In 1990, Ishikura *et al*. defined HAC, and presented 5 cases of HAC in the lung after reviewing 7 cases of AFP-producing lung cancer [4]. To date, only 11 cases of HAC in the lung have been reported in the literature; HAC is generally associated with a poor prognosis.

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Case Report

In May 2007, a previously healthy 44-year-old man with a 40-pack-year history of cigarette smoking presented with a sudden onset of right-side extremities numbness and aphasia of a 5 minutes' duration. He was brought to the emergency room (ER) of this hospital immediately, where the physical and neurologic examination revealed no abnormalities. However, the routine chest roentgenogram showed a huge mass in the right upper zone (Figure 1). He also reported a 4-month history of nonpurulent productive cough and an episode of hemoptysis with blood-streaked sputum 1 day before presentation, but no fever or weight loss. The routine laboratory investigations, including testing of liver and renal function, were unremarkable. The computed tomography (CT) scan of the chest obtained without the administration of intravenous contrast material at the ER demonstrated a 10-cm tumor in the right upper lobe (RUL), closely abutting the right main bronchus, and multiple small nodules ranging from 4 mm to 1 cm in the subpleural regions in the RUL and right lower lobe (RLL) (Figure 2).

He was subsequently admitted to the pulmonary ward of this hospital 2 weeks after presentation for a scheduled percutaneous trans-

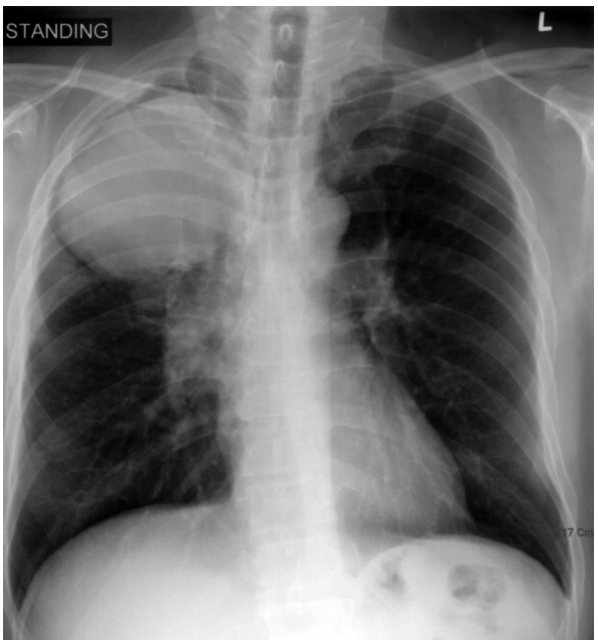

Fig. 1. The chest roentgenogram in the emergency department showed a huge mass in the right upper zone.

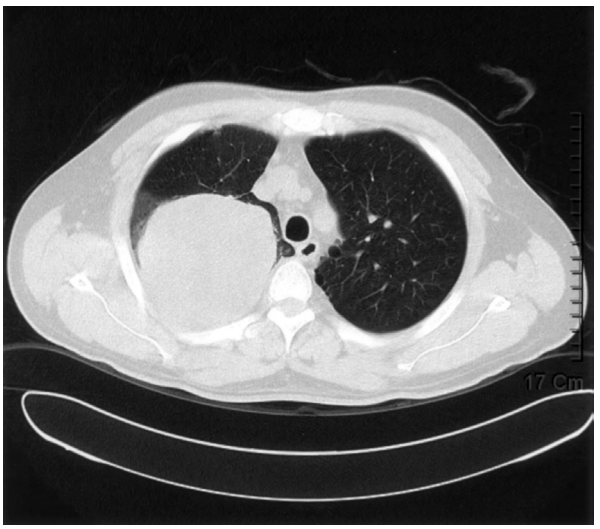

Fig. 2. The computed tomography (CT) scan of the chest without the administration of intravenous contrast material at the ER demonstrated a 10-cm tumor in the right upper lobe (RUL), closely abutting the right main bronchus.

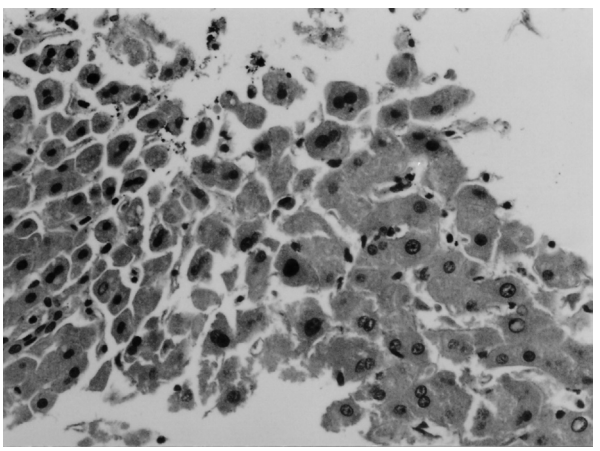

Fig. 3. The histopathologic examination of the biopsy specimens revealed degenerative tumor cells with ample eosinophilic cytoplasm and large nuclei with prominent nucleoli.

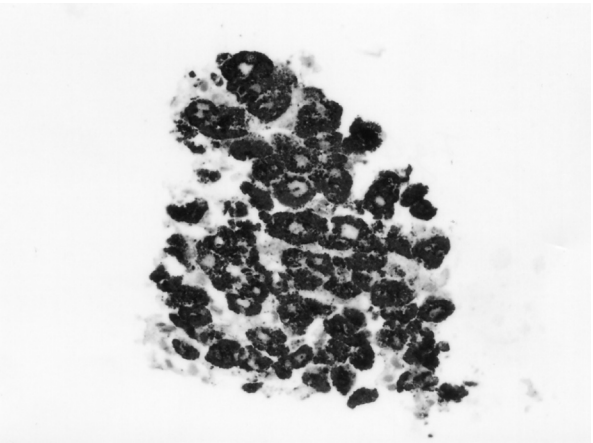

Fig. 4. Immunohistochemical study of the specimen with hepatocyte paraffin 1 (Hep Par 1) antibody was positive.

thoracic CT-guided biopsy of the RUL mass, which was performed uneventfully 1 day after admission. During hospitalization, the serum AFP level was checked and was found to be surprisingly high (82,714 ng/mL; normal range: 0-20 ng/mL). Pathological examination of the biopsy specimens revealed degenerative tumor cells with ample eosinophilic cytoplasm; large nuclei with prominent nucleoli and binuclear cells were occasionally observed (Figure 3). The histologic patterns on the standard hematoxylin and eosin stains were consistent with HCC. Immunohistochemical study of the specimen with hepatocyte paraffin 1 (Hep Par 1) antibody was also positive (Figure 4). The preliminary pathologic diagnosis of the metastatic HCC was thus established, and hepatic evaluation for the primary neoplasm was suggested by the pathologist. However, the clinical examinations and imaging study, including abdominal CT and ultrasound examinations, revealed no evidence of hepatoma or other abnormal focal space-occupying lesion. Tests for hepatitis B and C virus antibodies and hepatitis B antigen were negative. As a consequence, the pathologist revised the diagnosis, and HAC was eventually confirmed.

The patient underwent a cycle of chemotherapy with a regimen of gemcitabine and cisplatin and concomitant radiotherapy 1 month after presentation. The follow-up serum AFP level declined to 28,461 ng/mL 10 weeks after presentation.

However, progressive bilateral visual loss developed 3 months after presentation, and CT of the head with and without contrast medium showed multiple brain metastases with tumor hemorrhage. The patient experienced an unrelenting downhill course and died 14 weeks after presentation.

Discussion

HAC in the lung is an uncommon tumor, and was first reported by Yasunami as a primary lung cancer producing AFP as high as 19,000 ng/mL in 1981. In 2002, Yasufumi *et al*. reported the 9th case of HAC of the lung [9], followed by reports of the 10th case by Genova *et al*. in 2003 [10] and the 11th case by Oshiro *et al*. in 2004 [11]. In other words, to our knowledge, our patient is the 12th reported case of HAC of the lung (Table 1). From the database, the ages of these patients ranged from 36 to 82 years, with an average of 61 years. Interestingly, all 12 cases were male and almost all the reported cases, including the present case, manifested a raised serum level of AFP. The tumor diameter ranged from 3.5 cm to 11.0 cm, revealing that the tumor was large when it was found. On the whole, the prognosis was dismal.

In 1956, AFP was initially recognized by Bergstrand and Czar in serum from the human fetus [12], which was subsequently found to be significantly increased in hepatoma [13-14]. Measurement of the serum level of AFP is now

Table 1. Reports of hepatoid adenocarcinoma of the lung

Number	Age	Sex	Clinical location	Tumor diagnosis	Size (cm)	Serum AFP (ng/mL)	Prognosis	Initial report
1	67	M	LUL	Ad	8.0	19,000-160,000	16 months, D	1981 Yasunami
2	69	M	RLL	Large	11.0	5,050-88,000	6 months, D	1981 Yokoyama
3	40	M	RUL	Ad	9.0	3,090	14 months, D	1986 Miyake
4	55	M	RUL	Ad	5.0	2,123	4 days, D	1986 Miyake
5	73	M	LUL	Ad	6.0	1,039	19 months, D	1987 Miyake
6	36	M	LUL	Epi	10.0	11,600	7 months, D	1997 Arnould
7	63	M	RUL	Large	8.0	14,000	11 months, D	1998 Nasu
8	82	M	LLL	-	3.5	-	-	2000 Carlinfante
9	55	M	RUL	Ad	6.0	(89)	30 months, D	2002 Yasufumi
10	71	M	LUL	Ad	7.7	-	-	2003 Genova
11	77	M	RLL	Ad	-	3,890	18 months, D	2004 Oshiro
12	44	M	RUL	Ad	10.0	82,714	3 months, D	Present case

* M, male; F, female;

+ RUL, right upper lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe;

II ad, adenocarcinoma; large, large cell carcinoma; epi, epidermoid carcinoma;

π D, death; A, alive.

diagnostic of HCC and yolk sac tumor. Reported cases with elevations of AFP, other than HCC, include gastric cancer [17-18], pancreatic cancer, other nonseminomatous cellular tumors [19], and ovarian cancer. Most HAC presents with increased AFP [1]. In the present case, increased AFP was an incidental finding before the percutaneous CT-guided biopsy. Although we reasonably evaluated whether hepatoma was present, due to the abnormally high APF level, there was no radiographically and ultrasonographically detectable primary hepatoma.

Two microscopic criteria for the diagnosis of HAC have been described by Ishikura [4]. The first criterion is a mixture of tubular or papillary adenocarcinoma with a sheet-like or trabecular proliferation of neoplastic cells within an AFP-producing carcinoma. The second criterion is the presence of cells with abundant, eosinophilic cytoplasm and centrally located nuclei in sheet-like or trabecular portions. These definitions have pathologic characteristics resembling those of HCC. In the present case, the histopathological findings were also in accord with the above definitions.

Hep Par 1 antibody was developed by Wennerberg *et al*., who used fixed liver as an immunogen [15]. The Hep Par 1 antibody was commercially developed recently to stain normal and neoplastic hepatocytes. Zhen *et al*. found that Hep Par 1 is a useful marker for HCC, although it is not totally specific for HCC, which frequently also stains in gastric carcinoma [16].

The pathologist for the present patient originally diagnosed HCC based on the microscopic histopathological finding and the Hep Par 1 stain result, but revised the diagnosis to HAC after observing that the liver was intact. Together with the raised serum AFP level, therefore, the diagnosis of HAC for this patient was solid.

In addition, the patient's serum AFP also declined in response to the 1 cycle of chemotherapy and radiation therapy, suggesting that the

AFP level may be a reasonable follow-up tumor marker for evaluation of the response to treatment. However, the 14 months' survival of the present patient also reflects the grim nature and poor prognosis of HAC in the lung.

References

1. Ishikura H, Kishimoto T, Andachi H, *et al*. Gastrointestinal hepatoid adenocarcinoma: venous permeation and mimicry of hepatocellular carcinoma, a report of four cases. Histopathology 1997; 31: 47-54.
2. Yasunami R, Hashimoto Z, Ogura T, *et al*. Primary lung cancer producing alpha-fetoprotein: a case report. Cancer 1981 Mar 1; 47(5): 926-9.
3. Ishikura H, Fukasawa Y, Ogasawara K, *et al*. An AFP-producing gastric carcinoma with features of hepatic differentiation: a case report. Cancer 1985; 56: 840-8.
4. Ishikura H, Kana M, Ito M, *et al*. Hepatoid adenocarcinoma: a distinctive histological subtype of alpha-fetoprotein-producing lung carcinoma. Virchows Arch A Pathol Anat 1990; 417: 73-80.
5. Motoyama T, Higuchi M, Taguchi J. Combined choriocarcinoma, hepatoid adenocarcinoma, small cell carcinoma and tubular adenocarcinoma in the esophagus. Virchows Arch 1995; 427: 451-4.
6. Paner GP, Thompson KS, Reynes CV. Hepatoid carcinoma of the pancreas. Cancer 2000; 88: 1582-9.
7. Gardiner GW, Lajoie G, Keith R. Hepatoid adenocarcinoma of the papilla of Vater. Histopathology 1992; 20: 541-4.
8. Lattes C, Carella R, Faggioli S, *et al*. Hepatoid adenocarcinoma of the rectum arising in ulcerative colitis: report of a case. Dis Colon Rectum 2000; 43: 105-8.
9. Hayashi Y, Takanashi Y, Ohsawa H, *et al*. Hepatoid adenocarcinoma in the lung. Lung Cancer 2002 Nov; 38(2): 211-4.
10. Genova S, Dikov D, Peshev Zh, *et al*. Hepatoid adenocarcinoma of the lung: a case report. Khirurgiia (Sofiia) 2003; 59(4): 45-7.
11. Oshiro Y, Takada Y, Enomoto T, *et al*. A resected case of metachronous liver metastasis from lung cancer producing alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist II (PIVKA-II). Hepatogastroenterology 2004 Jul-Aug; 51(58): 1144-7.
12. Bergstrand CG, Czar B. Demonstration of a new protein fraction in serum from the human fetus. Scand J Clin Lab Invest 1956; 8(2): 174.
13. Abelev GI, Perova SD, Khramkova NI, *et al*. Production of embryonal alpha-globulin by transplantable mouse hepatomas. Transplantation 1963 Apr; 1: 174-80.
14. Tatarinov YS. Alpha-fetoprotein in the laboratory testing for cancer. Gann 1979 Apr; 70(2): 133-9.
15. Wennerberg AE, Nalesnik MA, Coleman WB. Hepatocyte paraffin 1: a monoclonal antibody that reacts with hepatocytes and can be used for differential diagnosis of hepatic tumors. Am J Pathol 1993 Oct; 143(4): 1050-4.
16. Fan Z, van de Rijn M, Montgomery K, *et al*. Hep par 1 antibody stain for the differential diagnosis of hepatocellular carcinoma: 676 tumors tested using tissue microarrays and conventional tissue sections. Mod Pathol 2003 Feb; 16(2): 137-44.
17. Ishikura H, Kirimoto K, Shamoto M, *et al*. Hepatoid adenocarcinomas of the stomach. An analysis of seven cases. Cancer 1986 Jul 1; 58(1): 119-26.
18. Nagai E, Ueyama T, Yao T, *et al*. Hepatoid adenocarcinoma of the stomach. A clinicopathologic and immunohistochemical analysis. Cancer 1993 Sep 15; 72(6): 1827-35.
19. Childs WJ, Goldstraw P, Nicholls JE, *et al*. Primary malignant mediastinal germ cell tumours: improved prognosis with platinum-based chemotherapy and surgery. Br J Cancer 1993 May; 67(5): 1098-101.

原發性肺臟內肝樣腺癌—病例報告

王博中　張漢煜　薛尊仁

肝樣腺癌是一種罕見的肝外惡性腫瘤，而在病理組織學上的表現與原發性肝細胞癌十分相似。大部份的肝樣腺癌會產生極高量的甲型胎兒蛋白。到目前為止，在現有的文獻上，只有正式提出十一位原發性肺臟內肝樣腺癌。我們在此報告一個病例：一位四十四歲的男性，被意外發現有一個肺部腫瘤與合併血清中有大量的甲型胎兒蛋白，並在經由電腦斷層掃描指引下所取得的切片，經病理組織學的檢查，證實是肝樣腺癌。而他的肝臟的檢查並沒有發現肝癌的證據或是其他的異常。在經過化學治療與放射線治療後，病人血清中的甲型胎兒蛋白有明顯的下降。*(胸腔醫學* ***2008; 23: 205-210****)*

關鍵詞：肝樣腺癌，甲型胎兒蛋白

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Delayed Onset of Acute Respiratory Distress Syndrome Following Intravenous Rituximab in a Rheumatoid Arthritis Patient: A Case Report

Huang-Chih Chang*, Yu-Hsiu Chung*,**, Yi-Hsi Wang*,**, Meng-Chih Lin*,**

Rituximab is a humanized monoclonal antibody found to be effective and safe in its use with malignant lymphoma and various humoral autoimmune diseases in which B lymphocytes play a role, such as rheumatoid arthritis. Most of the adverse events are modest, including flu-like illness, fever, chills, cough and rhinitis. However, more serious adverse effects have been reported, such as interstitial pneumonitis, pleuritis, bronchospasm and acute respiratory distress syndrome. We report a woman with rheumatoid arthritis who was treated with intravenous rituximab because her symptoms were refractory to standard treatment that included cyclosporine, methotrexate and steroid pulse therapy. Unfortunately, she suffered progressive dyspnea resulting in acute respiratory failure 18 days after the second administration. She was subsequently diagnosed with acute respiratory distress syndrome (ARDS), and this was attributed to a delayed hypersensitivity reaction to the medicine. It is important to keep in mind that rituximab may induce this fatal adverse effect, even though it is rare and delayed in its onset. ***(Thorac Med 2008; 23: 211-216)***

Key words: acute respiratory distress syndrome, delayed hypersensitivity reaction, rheumatoid arthritis, rituximab

Introduction

Rituximab is a humanized monoclonal antibody that selectively depletes CD-20 positive B-cells. It is approved in the United States for the treatment of hematologic malignancies and autoimmune disease, including rheumatoid arthritis, lupus, multiple sclerosis and anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis [1]. The adverse effects of rituximab usually develop following the first administration. Patients often recover soon after medical intervention. Serious complications, including hypoxia, pulmonary infiltration, acute respiratory distress syndrome, and myocardial infarction, as well as cardiogenic shock and severe mucocutaneous skin reactions, tend to develop during the first 2 hours after the first administration [1]. Although the pathogenesis of these adverse events is uncertain, cytokine release

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syndrome (CRS) [2], tumor lysis syndrome (TLS) [3], complement activation [2] and hypersensitivity reaction were all considered as possible mechanisms.

We report a case of rheumatoid arthritis that was refractory to several treatments with disease modifying anti-rheumatic drugs (DMARDS). The patient unexpectedly developed acute respiratory distress syndrome (ARDS) 18 days after the second administration of rituximab. To our knowledge, this is the first report of a patient suffering a delayed onset ARDS after the second dose of intravenous rituximab for a non-hematologic disorder.

Case Report

A 59-year-old female was diagnosed as having had rheumatoid arthritis for more than 20 years. She had a history of hospital admissions due to flare ups of symptoms. Initially, pulse therapy was given with methylprednisolone 500 mg intravenously once daily for 3 days. Other oral medications were prescribed concomitantly, including hydroxychloroquine sulfate 200 mg twice daily, prednisolone 5 mg twice daily and methotrexate 15 mg once weekly for arthritis.

She received intravenous rituximab due to refractory multiple joint pain. After the first administration, the patient felt no discomfort. Then, 2 weeks later, she received a second dose, and unfortunately suffered severe dyspnea and persistent fever 18 days after that. There was no chest tightness, chest pain, orthopnea or paroxysmal nocturnal dyspnea. No decrease in the amount of urine output was noted. Due to worsening dyspnea, she was sent to our emergency department for management. The initial chest radiograph showed consolidations in the bilateral lung fields (Figure 1). Hypoxemia (PaO_2: 50 mmHg in room air) and impending respiratory failure were noted. Emergent endotracheal intubation was performed immediately, and then she was transferred to the intensive care unit (ICU).

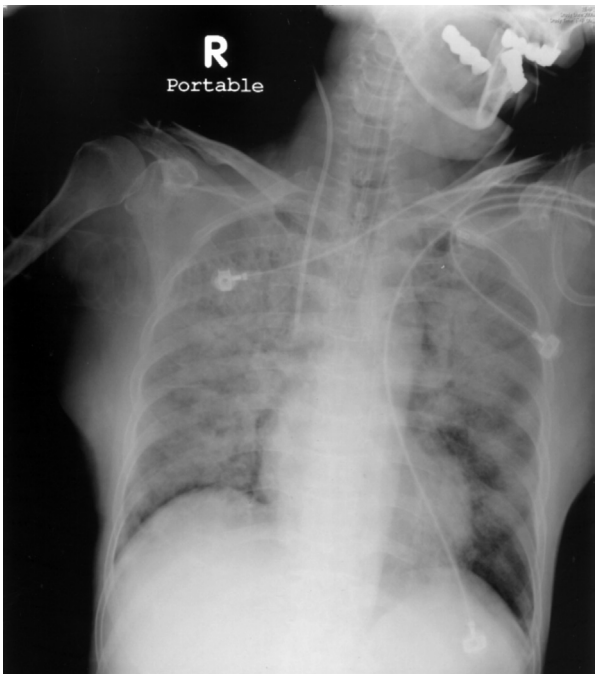

Fig. 1. Chest radiograph showed consolidations in bilateral lung fields.

Her complete blood count showed a leukocyte level of 11.3 k/uL with differential counts of 81% neutrophils, 2% band forms, 12% lymphocytes, and 5% monocytes, a hemoglobin concentration of 10.9 g/dL, and a platelet count of 27.5 k/uL. Blood chemistry values were blood urea nitrogen, 29 mg/dL, and creatinine, 1.7 mg/dL. Her serum level of aspartate transaminase was 63 U/L; alkaline phosphate, 54 U/L; lactate, 34.2 mg/dL; C-reactive protein (CRP), 233.5 mg/dL; CK-MB, 1.7 U/L; and troponin I, 0.02 ng/dL. Hepatits B markers were normal. After endotracheal intubation, her level of PaO_2 rose to 105.2 mmHg under 100% FiO_2, representing a PaO_2/FiO_2 ratio of 105.2 mmHg.

Initially, pneumonia associated with septicemia was suspected, so clarithromycin, meropenem, teicoplanin and a low dose of hydrocortisone sodium succinate were administered. However, no pathogens were discovered in the pooled sputum. Bronchoalveolar lavage was performed under video-assisted bronchoscopy, and results from bacterial, fungal and mycobacterial cultures, as well as cytology, were all negative; no virus, neither Legionella nor fungus were found in the sample of serum. Infection was excluded conclusively.

The central venous pressure was 12 mmH_2O and the echocardiography showed adequate left ventricular performance (EF: 74%). Initial cardiac enzymes were within the normal range. There was no obvious ST-T wave change in the electrocardiogram. Coronary artery disease and congestive heart failure complicating pulmonary edema could be excluded. A high resolution computed tomography (HRCT) scan (Figure 2) was performed due to persistent bilateral pulmonary consolidations on the chest radiograph. Bilateral diffuse ground glass opacification was revealed, and interstitial disease was suspected. Excluding infection and acute cardiogenic pulmonary edema, an adverse effect of rituximab was highly suspected. So methylprednisolone 40 mg was administered intravenously every 6 hours. After 7 days of treatment, the hypoxemia had improved (PaO_2: 68.9 mmHg), and she was weaned from the mechanical ventilator and extubated successfully. She was discharged in a stable condition 40 days later. At that time, her chest radiograph showed little mixed alveolar and interstitial infiltration in the bilateral lungs, without consolidation (Figure 3). A pulmonary function test and diffusing capacity (DLco) were performed 6 months after she was discharged, and revealed only mild restrictive ventilatory impairment.

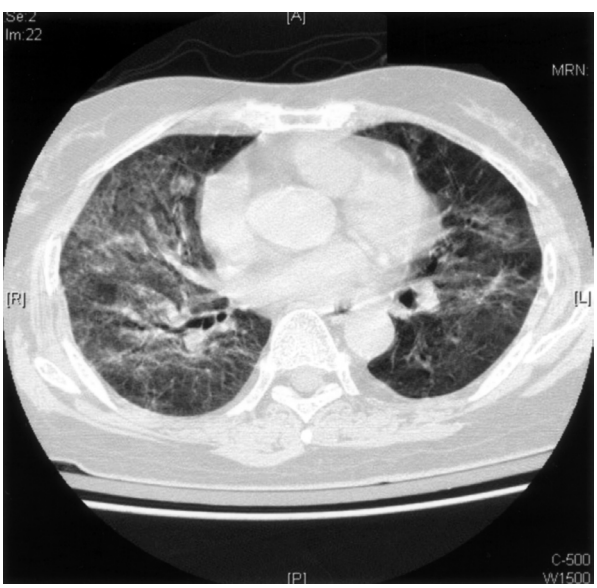

Fig. 2. Computed tomography showed bilateral ground glass opacification.

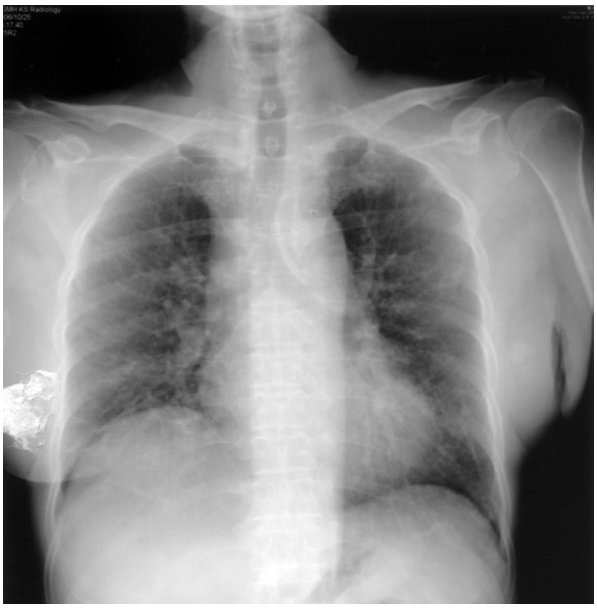

Fig. 3. Chest radiograph showed little mixed alveolar and interstitial infiltration in the bilateral lungs.

Discussion

ARDS is defined as a syndrome of acute and persistent lung inflammation with increased vascular permeability and impaired lung diffusion that produces hypoxemia. More than 60 causes of ARDS have been identified. Sepsis is a most common cause of ARDS. Other etiologies include aspiration of gastric contents, infectious pneumonia, severe trauma, surface burns, transfusion-related lung injury, and drug overdose or the adverse effects of medication.

Rituximab, a humanized monoclonal antibody, has been safely used for malignant lymphoma and various humoral autoimmune diseases. The most frequently reported pulmonary events included a flu-like illness, cough, rhinitis, bronchospasm and dyspnea. The severe pulmonary reaction, generally occurring during the first 2 hours following the first administration, presents as bronchospasm, hypoxia, interstitial pneumonitis, pleuritis and ARDS. These symptoms vary in severity and usually are reversible with medical intervention. The mortality rate is approximately 0.04 to 0.07% among patients who are treated with rituximab [4].

The diagnosis of late drug-induced ARDS relies on the initial exclusion of other causes, such as typical and atypical infection, a relapse of the underlying disease, and cardiogenic pulmonary edema. A history of current or recent exposure to drugs is a hint of drug-induced lung disease. When there is an early positive response to high doses of corticosteroids or if symptoms subside upon drug discontinuance, this may support the notion that the syndrome is related to drugs.

Respiratory distress syndrome is rare with intravenous administration of rituximab [5], and the causative mechanisms of this adverse effect remain unclear. Rituximab therapy is associated with several adverse events like tumor lysis syndrome (TLS); it often occurs in patients with hematologic malignancies. Rituximab appears to have a severe infusion reaction among patients with peripherally higher tumor cell numbers, especially with numbers above 50,000/mm^3 [6-7]. The cytokine release syndrome (CRS), is characterized by a transient release of proinflammatory cytokines such as interferon γ, tumor necrosis factor α, interleukin 6 and interleukin 8. Progressive CRS potentially leads to cytokine-related systemic inflammatory response syndrome (SIRS) and an increased incidence of septicemia. This usually occurs after the first infusion and within the first 24 hours [8]. The rare hypersensitivity anaphylactic reaction with acute onset of hypotension, tachycardia, and hypoxia is frequently associated with increased eosinophil counts and serum immunoglobulin E, and may also produce a severe mucocutaneous skin reaction [5]. Rapid activation of both classic and alternative complementary pathways may promote neutrophil binding to the pulmonary vasculature and may also induce the production of proinflammatory cytokines by monocytes [9].

The case reported herein involved a patient with a non-hematologic disorder who was unlikely to have TLS, and who had no evidence of infections and negative results from bacterial, fungal and mycobacterial cultures using bronchoalveolar lavage. Additionally, the serum level of methotrexate was low (0.02 uM/L), so other drugs likely to induce respiratory distress could be excluded. The cause of the immediate onset of ARDS and the eosinophilia or skin rash in this patient was not likely to be CRS with SIRS, an anaphylactic reaction, or an activation of a complementary pathway. However, the patient's

ARDS improved dramatically after steroid administration. Therefore, a delayed onset of ARDS due to rituximab was more likely to have occurred.

The human antichimeric antibody (HACA) and the human antimouse antibody (HAMA) are like second antibodies in some immunochemical applications, such as the indirect immunohistochemistry of human tissue using mouse antibodies. HACA and HAMA are used to eliminate the possibility of the second antibody reacting directly with endogenous immunoglobulin G [10]. HACA and HAMA may play a role in the development of the adverse event of delayed hypersensitivity reaction, but serum levels of HACA and/or HAMA may not necessarily be correlated with adverse reactions in patients receiving rituximab [11]. Others have reported that a delayed hypersensitivity reaction induced ARDS in a patient with Crohn's disease 10 days after the second infliximab administration [12]. However, our case developed a delayed onset of ARDS 18 days after the second administration of rituximab for a non-hematologic disorder rheumatoid arthritis; this is very rare.

Rituximab is more frequently being prescribed for hematologic and non-hematologic disorders. We hope this case report will alert us to the late occurrence of this seriously disabling and rare adverse effect of ARDS in individuals who receive rituximab treatment. This will enable the initiation of appropriate therapies with a high dose of corticosteroids.

References

1. Genentech: Products – Product information – Rituxan Full Prescribing Information: [www.gene.com/gene/products/information/oncology/rituxan/insert.jsp]
2. van der Kolk LE, Grillo-Lopez AJ, Baars JW, *et al*. Complement activation plays a key role in the side-effects of rituximab treatment. Br J Haematol 2001; 115: 807-11.
3. Yang H, Rosove MH, Figlin RA. Tumor lysis syndrome occurring after the administration of rituximab in lymphoproliferative disorders: high-grade non-Hodgkin's lymphoma and chronic lymphocytic leukemia. Am J Hematol 1999; 62: 247-50.
4. Kunkel L, Wong A, ManeatisT, *et al*. Optimizing the use of rituximab for treatment of B-cell non-Hodgkin's lymphoma: a benefit-risk update. Semin Oncol 2000; 27: 53-61.
5. Alexandrescu DT, Dutcher JP, O'Boyle K, *et al*. Fatal intra-alveolar hemorrhage after rituximab in a patient with non-Hodgkin lymphoma. Leuk Lymphoma 2004; 45: 2321-5.
6. Abou Mourad Y, Teher A, Shamsedddine A. Acute tumor lysis syndrome in large B-cell non-Hodgkin lymphoma induced by steroids and anti-CD 20. Hematol J 2003; 4: 222-4.
7. Boye J, Elter T, Engert A. An overview of current clinical use of anti-CD 20 monoclonal antibody rituximab. Ann Oncol 2003; 14: 520-35.
8. Seifert G, Reindl T, Lobitz S, *et al*. Fatal course after administration of rituximab in a boy with relapsed all: a case report and review of literature. Haematologica 2006; 91: 27-9.
9. Montero AJ, McCarthy JJ, Chen G, *et al*. Acute respiratory distress syndrome after rituximab infusion. Int J Hematol 2005; 82: 324-6.
10. Thorpe SJ, Turner C, Heath A. Clonal analysis of human antimouse antibody response Scand J Immunol 2003; 57: 85-92.
11. Satio B, Nakamaki T, Adachi D, *et al*. Acute respiratory distress syndrome during third infusion of rituximab in a patient with follicular lymphoma. Int J Hematol 2004; 80: 164-7.
12. Riegert-Johson DL, Godfrey JA, Myers JL, *et al*. Delayed hypersensitivity reaction and acute respiratory distress syndrome following infliximab infusion. Inflamm Bowel Dis 2002; 8: 186-91.

類風濕性關節炎病人使用 Rituximab 治療後延遲引起急性呼吸窘迫症：病例報告

張晃智* 鍾聿修*,** 王逸熙*,** 林孟志*,**

Rituximab是一種人工合成的單株抗體能安全有效的治療惡性淋巴瘤和以B淋巴球為主的自體免疫疾病，如類風濕性關節炎。大部分的副作用僅是輕微的表現，包括感冒症狀、發燒、畏寒、咳嗽和鼻炎。不過也有一些較嚴重的病例報告，如間質性肺炎、肋膜炎、支氣管痙攣和急性呼吸窘迫症。我們報告的這位類風濕性關節炎女性在標準的藥物治療無效下使用Rituximab靜脈注射治療。不幸的患者在接受第二劑注射的18天後，病人發生漸進性的呼吸困難結果造成呼吸衰竭。最後的診斷歸咎於延遲性的藥物過敏反應造成急性呼吸窘迫症。因此我們在使用Rituximab必須留意可能產生的副作用，儘管是一些罕見或是延遲發生的症狀。我們回顧並整理過去的相關文獻提出此報告。*(胸腔醫學* ***2008; 23: 211-216)***

關鍵詞：急性呼吸窘迫症，延遲性過敏反應，類風濕性關節炎，Rtuximab

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Delayed Massive Hemothorax – A Rare Late Complication after Recurrent Pectus Excavatum Repaired by Nuss Procedure

Hsu-Kai Huang, Jen-Chih Chen, Hung Chang, Shih-Chun Lee, Yeung-Leung Cheng

The Nuss procedure is a popular new technique for the correction of pectus excavatum (PE) [1-2]. Delayed hemothorax is an extremely rare complication which often occurs within 1 to 2 months postoperatively [3-5]. Emergent tube thoracostomy is mandatory and surgery is indicated if the hemodynamic status remains unstable or continuous hemorrhage is noted [6]. We report a patient who experienced delayed hemothorax 6 months after a Nuss procedure for recurrent PE. This condition was caused by injury to the rib under the pectus bar with active bleeding. ***(Thorac Med 2008; 23: 217-220)***

Key words: hemothorax, pectus excavatum, Nuss procedure

Case Report

A 19-year-old male came to the emergency department of our hospital complaining of serious chest pain with shortness of breath that developed after a tennis competition. Dyspnea, fever (38ºC), tachycardia (105 beats/min), and decreased breathing sounds in the left hemithorax were noted. Oxygen and fluid resuscitation were given. The chest film revealed partial opacity of the left hemithorax, which favored the finding of massive fluid accumulation (Figure 1). Emergent tube thoracostomy was performed with subsequent drainage of 1000 ml of fresh blood. The blood examination showed decreased hemoglobin, from 13.5 g/dl to 12.0 g/dl, and a decreased hematocrit, from 42.8% to 36.3%, within 1 hour. The platelet count and partial thromboplastin times were normal. Blood transfusion was administered immediately.

The patient had undergone a xyphoid stenting operation when he was a 13-year-old student, but it failed. The funnel index was 5.39, according to a CT scan 6 months before this incident. At that time, we performed a modified Nuss procedure in which a pericostal wire 5-point fixation was done, instead of the stabilizer implantation innovated by Park [7]. One Nuss pectus bar (11 inches, Walter Lorenz Surgical, Inc. Jacksonville, Florida, USA) was placed via the bilateral 6th intercostal space, with the

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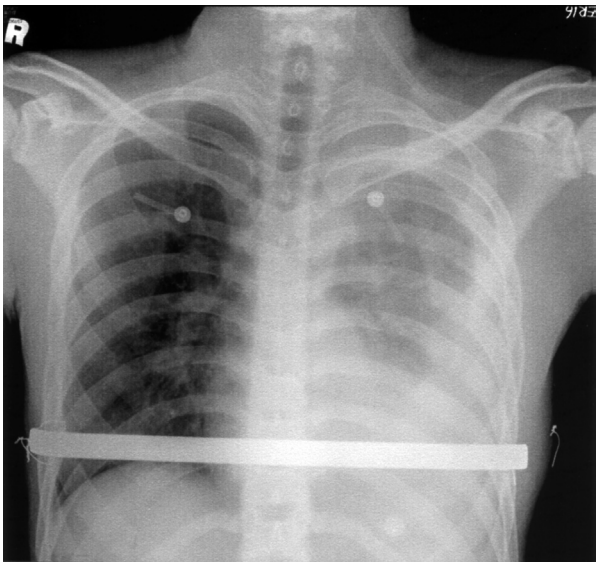

Fig. 1. Fluid accumulation in the left pleural space with fragmentation and migration of the Nuss bar fixation wire.

assistance of thoracoscopy. The operation and hospitalization were uneventful.

During this admission, Nuss bar retention and fragments of fixation wire were noted on chest film. The total drainage amount was 2000 ml. Surgical intervention for hematoma and removal of the fragmented wire was performed 2 days later. Erosion of the rib under the bar with bleeding and blood clot formation were discovered. He was discharged on the 5th hospital day, and was advised to avoid strenuous exercise. The patient had recovered well by the 6-month follow-up.

Discussion

There are many conventional approaches to the surgical repair of pectus excavatum. Among them, the modified Ravitch procedure and sternum turnover are the most popular. Ravitch reported an operation that included the excision of costal cartilage with perichondrium, division of the xiphoid, and a transverse sternal osteotomy in 1949. The sternal turnover technique was first reported by Judet in 1954. The sternum is removed and re-implanted after being rotated 180 degrees. Wada and colleagues reported a large series from Japan in 1970 [8]. A method elevating the sternum with a retrosternal bar without massive destruction or dissection of costal cartilage and the sternum was reported by Nuss [1]. Due to the advantages of minimal invasiveness and a good surgical result, the Nuss procedure has been much more acceptable than traditional operations for pectus excavatum. Usually, the bar is removed after 2 years, once permanent remodeling of the costal cartilage has occurred. Park and associates reported a complication rate of 16.1%, which included mostly minor conditions [3]. However, some major problems may cause remarkable consequences, including perforation of the heart, pericardium, great vessels, and diaphragm. Most major complications are noted immediately, with a subsequent need for emergent operation. Of 335 reported cases in 1 study, only 3 patients were noted to have experienced late-onset hemothorax [3]. Thus, late-onset hemothorax is a rare complication noted after the Nuss procedure. A further review of the literature revealed only 2 similar cases [4-5]. The possible causes of late-onset hemothorax may be injury to the intercostal vessels or erosion of the internal mammary artery by the Nuss bar.

Based on our experience with the case described herein, late-onset hemothorax can be a problem in the patient who has undergone a prior Nuss procedure, even without blunt or penetrating injury to the chest wall. The symptoms depend on the amount of blood accumulated in the pleural cavity. After airway establishment and oxygen supplementation have been

performed, fluid resuscitation and preparation for blood transfusion are necessary. Chest tube placement should be performed immediately on every hemothorax patient, for drainage and monitoring of hemorrhage. In most cases, the bleeding ceases when the lung is re-expanded. In the event of drainage of an initial amount of 1500 ml or persistent drainage above 200 ml per hour, operations such as thoracotomy or sternotomy may be required. Video-assisted thoracic surgery may be considered if the hemodynamic status is stable.

Dr. Nuss invented a stabilizer with submuscular sutures to secure the bar, but a 5-point pericostal fixation was used in our division; the reasons are as follows: First, a stabilizer may not be suitable in very thin patients because of protruding and wound erosion, and because of the cost. Second, the submuscular fixation technique may not provide enough support, and causes much worse complications, such as bar migration. We believe that the periosteal wire fixation technique may be helpful to relieve the pressure of the pectus bar, especially in children and adolescent patients. If needed, additional wire or a stabilizer can be used in selected patients.

In our patient, erosion and bleeding of the rib under the Nuss bar was probably caused by intense exercise. The patient recovered well after emergent resuscitation and adequate surgical intervention. The Nuss bar and fixation wires are foreign bodies retained in the chest wall for patients undergoing the procedure. Strenuous and excessive exercise may contribute to migration and fragmentation of the bar or wires, resulting in injuries to adjacent structures, such as the ribs, intercostals vessels, and even the mediastinal structures. These patients should be educated and advised to avoid intense sports to prevent trauma, in an effort to prevent the development of late-onset hemothorax.

References

1. Nuss D, Kelly RE Jr, Croitoru DP, *et al*. A 10-year review of a minimally invasive technique for the correction of pectus excavatum. J Pediatr Surg 1998; 33: 545-52.
2. Croitoru DP, Kelly RE Jr, Goretsky MJ, *et al*. The minimally invasive Nuss technique for recurrent or failed pectus excavatum repair in 50 patients. J Pediatr Surg 2005; 40: 181-6; discussion 186-7.
3. Park HJ, Lee SY, Lee CS. Complications associated with the Nuss procedure: analysis of risk factors and suggested measures for prevention of complications. J Pediatr Surg 2004; 39: 391-5.
4. Kosumi T, Yonekura T, Owari M, *et al*. Late-onset hemothorax after the Nuss procedure for funnel chest. Pediatr Surg Int 2005; 21: 1015-7.
5. Hoel TN, Rein KA, Svennevig JL. A life-threatening complication of the Nuss procedure for pectus excavatum. Ann Thorac Surg 2006; 81: 370-2.
6. Symbas PN. Acute traumatic hemothorax. Ann Thorac Surg 1978; 26: 195-6.
7. Park HJ, Lee SY, Lee CS, *et al*. The Nuss procedure for pectus excavatum: Evolution of techniques and early results on 322 patients. Ann Thorac Surg 2004; 77: 289-95.
8. Shamberger RC. Chest wall deformities, in Shields TW, General thoracic surgery, 6th ed., U.S., Lippincott Williams & Wilkins, 2005; 658-65.

延遲性大量血胸—罕見復發性漏斗胸經納氏矯正術術後之併發症

黃敘愷　陳仁智　張　宏　李世俊　程永隆

納氏矯正術是對胸廓畸形之漏斗胸的一種新式微創手術，延遲性之血胸是極少見的併發症，通常在術後一至二個月發生。緊急之胸管引流術為首要之治療，若病人之生命徵象或血行動力學狀態不穩定，手術確認並控制出血即為必要。本文報告一位十九歲男性漏斗胸復發病患，接受納氏矯正術六個月後併發大量血胸。原因是激烈運動後，固定矯正板之鋼絲斷裂，造成肋骨及肋間血管之傷害及活動性出血。病患接受胸管引流、輸血，微創開胸止血，並重新固定矯正板後出院。*(胸腔醫學* ***2008; 23: 217-220)***

關鍵詞：血胸，漏斗胸，納氏矯正術

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Occult Thyroid Cancer Presenting as Endotracheal Invasion Report of Two Cases and Literature Review

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Occult thyroid cancer presenting initially as endotracheal invasion is extremely rare. Two patients presented to our chest clinic with hemoptysis and cough. The chest radiograph showed a filling defect in the tracheal air column. Physical examination of the neck and thyroid revealed unremarkable findings. An endotracheal tumor was noted by bronchoscopy. The pathologic examination of the surgical specimens confirmed the diagnosis of occult papillary thyroid carcinoma with transmural tracheal invasion. One patient had long-term survival after radical surgery, while the other expired because of the complication of progressive upper airway obstruction. No similar cases have been described in the literature. We believe endotracheal invasion by occult thyroid cancer should be considered in the differential diagnosis of endotracheal tumor. The absence of a clinically detectable thyroid abnormality does not exclude the possibility of locally advanced thyroid cancer. Aggressive surgical resection of the primary tumor and the involved trachea can provide the opportunity for long-term survival. ***(Thorac Med 2008; 23: 221-227)***

Key words: endotracheal invasion, endotracheal tumor, occult thyroid cancer, papillary thyroid carcinoma

Introduction

Although thyroid cancer with endotracheal invasion is not rare [1], its presence in recurrent, clinically apparent, or locally advanced thyroid cancers is extremely rare. It is a well-established fact that occult thyroid cancer can present initially as cervical lymph node metastasis, but clinically undetectable thyroid cancer presenting as direct endotracheal invasion is extremely rare. Herein, we report 2 patients who experienced hemoptysis and cough. Fiberoptic bronchoscopy revealed an endotracheal tumor, and occult papillary thyroid carcinoma (PTC) with transmural tracheal invasion was diagnosed. We briefly review the clinical spectrum of

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endotracheal invasion by thyroid cancer. Since potentially curative resection of locally advanced PTC is possible, aggressive surgical resection of the primary tumor and the involved trachea should be considered.

Case Reports

Case 1

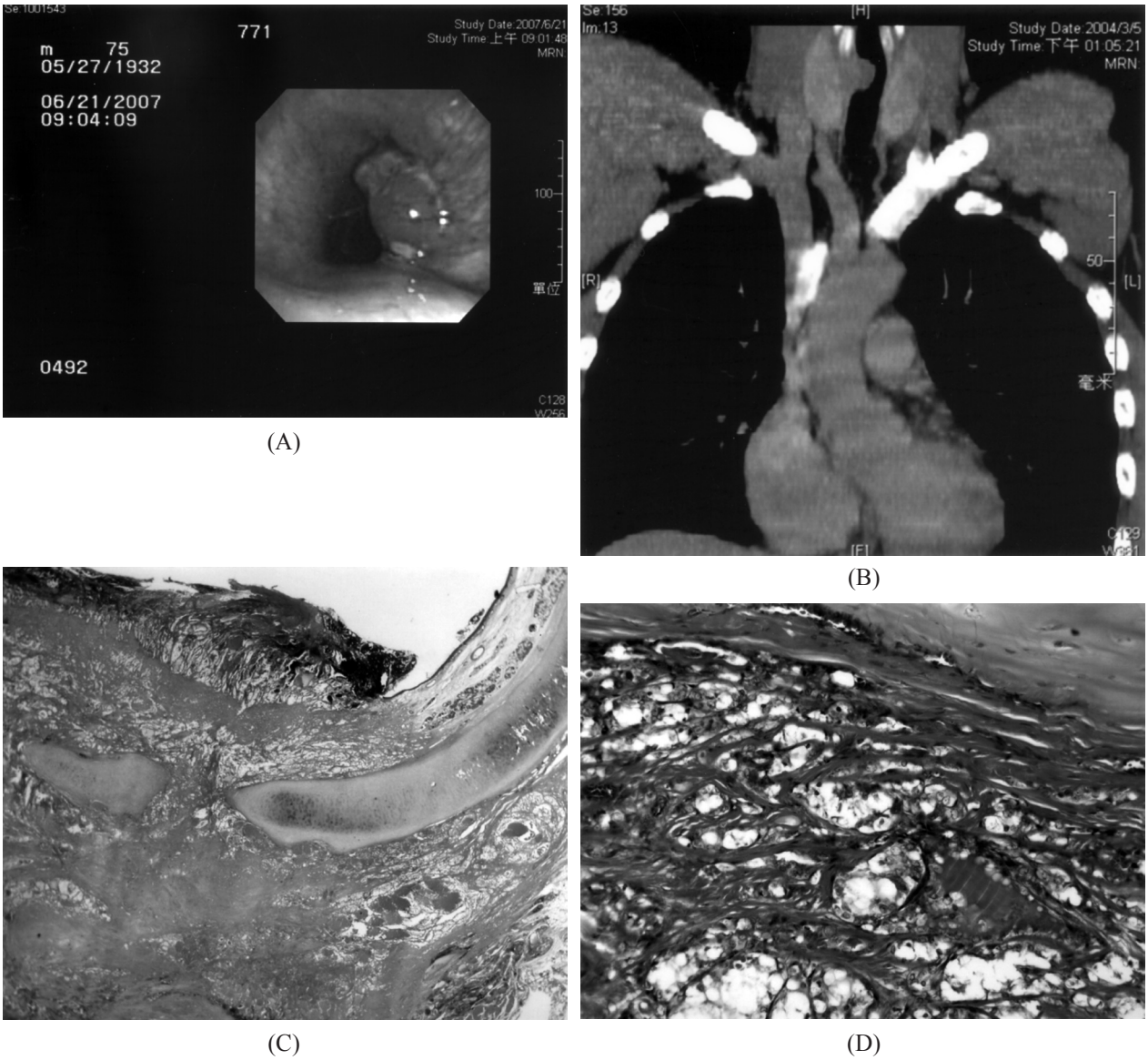
A 42-year-old man presented to our chest clinic with dyspnea, cough and hemoptysis. He had had intermittent hemoptysis in the last 2 years. The physical examination revealed mild inspiratory stridor. Palpation of the thyroid revealed no abnormality, and no cervical lymphadenopathy was palpable. The chest roentgenogram showed a filling defect in the tracheal air column consistent with endotracheal lesion. Bronchoscopy demonstrated a protruding endotracheal tumor located 2 cm below the vocal cords (Figure 1A). A bronchoscopic biopsy was not performed due to the high risk of bleeding and airway obstruction. A computed tomography (CT) scan (Figure 1B) confirmed the presence of an endotracheal tumor originating from the right thyroid gland. Moreover, neither the CT scan nor the thyroid ultrasonography demonstrated enlargement of the right thyroid gland. Thyroid ultrasonography also revealed no evidence of a right thyroid nodule.

Thyroid cancer with endotracheal invasion was highly suspected as a result of the CT scan. Due to the impending airway obstruction and no evidence of distant metastasis, the patient underwent operation. Intra-operative frozen section of the endotracheal tumor disclosed PTC. Total thyroidectomy and laryngectomy were then performed. Complete resection of the tumor was achieved and the surgical margin was free of tumor involvement. On pathologic examination, the tumor measured 1.3 × 1.0 cm at the right first to second tracheal rings. The bilateral vocal cords and bilateral arytenoids cartilage were free of tumor involvement. A cut of the tumor revealed that tumor cells had invaded and infiltrated the entire thickness of the trachea (Figure 1C). High magnification photomicrograph (Figure 1D) showed optically clear and ground-glass nuclei. These histopathological findings were consistent with PTC. No evidence of ectopic normal thyroid tissue was noted in the specimen, so the PTC apparently arose in the thyroid gland, rather than ectopic thyroid tissue.

The patient was followed in the outpatient department. A CT scan 2 years after the operation showed no local recurrence. After 3 years of follow-up, the patient remained clinically asymptomatic without endoscopic evidence of recurrence. Serum thyroglobulin remained undetectable during the period of follow-up.

Case 2

A 74-year-old man with a history of end-stage renal disease under maintenance hemodialysis therapy was admitted because of hemoptysis for 3 days. Cough had been noted for 3 months. Physical examination revealed no abnormal finding, including thyroid and neck palpation. No stridor was noted. The chest radiograph revealed right upper lobe fibrotic change and a filling defect in the trachea (Figure 2A). Bronchoscopy showed an endotracheal tumor 3 cm below the vocal cords (Figure 2B). The CT scan revealed an endotracheal tumor originating from the right thyroid gland (Figure 2C). Bronchoscopic biopsy of the endotracheal tumor confirmed the diagnosis of PTC. A mildly enlarged right thyroid gland with calcification was also documented by CT scan. Thyroid ultrasono-



(A)

(B)

(C)

(D)

Fig. 1.

A) Bronchoscopy reveals an endotracheal tumor with an irregular and friable surface. Superficial vessel engorgement and adherent blood clots are also noted.

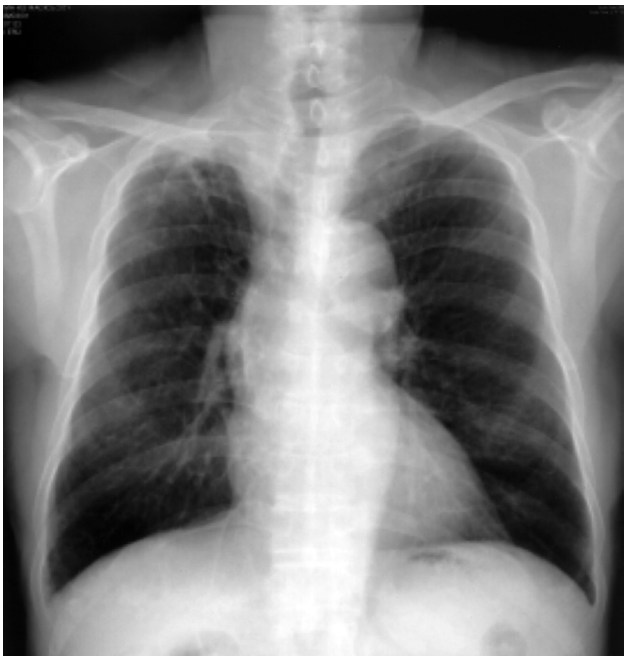
B) Computed tomography demonstrates the endotracheal tumor originating from the right thyroid gland.

C) Photomicrograph of the trachea (hematoxylin and eosin stain x 40) demonstrates infiltrative nests and follicles of neoplastic epithelial cells.

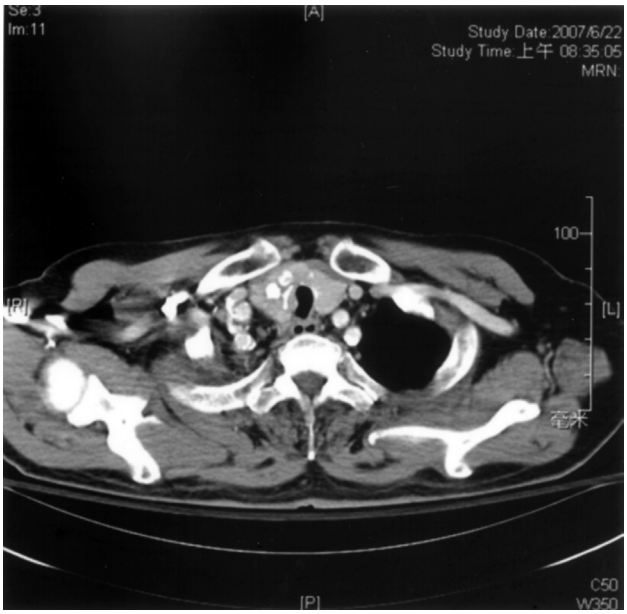
D) High-magnification photomicrograph (hematoxylin and eosin stain x 400) shows that the tumor cells are characterized by optically clear and ground-glass nuclei. These characteristics are consistent with papillary thyroid carcinoma.

graphy revealed focal calcification of the right thyroid without definite nodule.

This patient refused further treatment, so he was discharged with follow-up. However, he was found to have progressive dyspnea and stridor 1 year after the diagnosis. He was admitted again, and enlargement of the endotracheal tumor was demonstrated bronchoscopically



(A)



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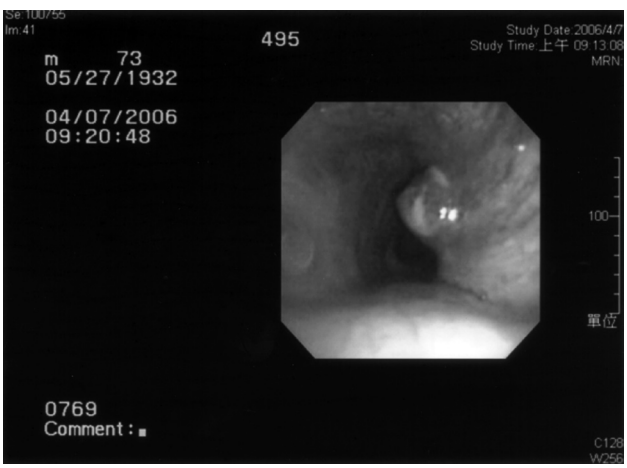

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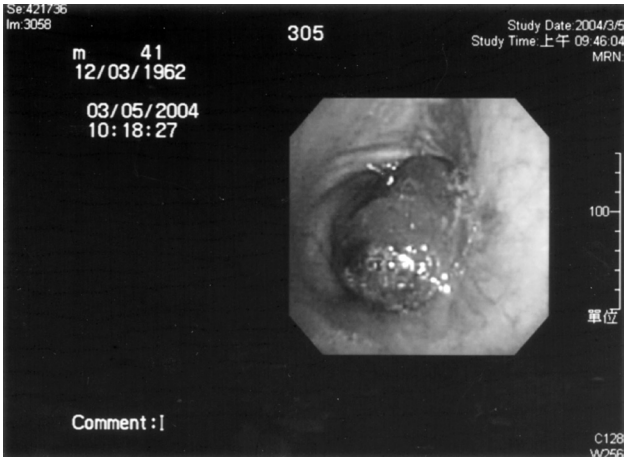

(D)

Fig. 2.

A) Chest radiograph shows a filling defect in the tracheal air column.

B) Bronchoscopy confirms a protruding endotracheal tumor.

C) Computed tomography demonstrates the endotracheal tumor originating from the right thyroid gland. Calcification in the thyroid gland is also noted.

D) Bronchoscopy 1 year later reveals progressive enlargement of the endotracheal tumor.

(Figure 2D). Nosocomial pneumonia with acute respiratory failure was noted during hospitalization. The patient expired due to refractory septic shock.

Discussion

PTC is the most common histologic type of differentiated thyroid cancer. Most patients with PTC are asymptomatic and subclinical, and the diagnoses are often based on fine needle aspiration of incidental thyroid nodules. Occasionally, regional (cervical lymph nodes or parapharyngeal area) or distant hematogenous spread (pulmonary or endobronchial) may be the first manifestation of PTC.

PTC grows slowly and spreads early, from lymphatic ducts to cervical lymph nodes. Local extrathyroidal extension (such as trachea, larynx, or pharynx) often occurs in locally advanced diseases. Although the long-term prognosis of PTC is excellent (5-year survival rate > 90%), local tracheal invasion is associated with significant morbidity and mortality. In fact, about 50% of deaths from thyroid carcinomas result from uncontrolled airway obstruction [2].

Thyroid carcinoma with tracheal invasion is not a rare clinical condition; an incidence of up to 6% is reported [1]. The clinical spectrum of tracheal invasion by thyroid carcinoma ranges from subclinical microscopic invasion to clinically apparent tracheal obstruction. Since more aggressive surgical policies are crucial for tracheal involvement, routine screening for tracheal invasion in patients with thyroid carcinomas is suggested. Bronchoscopy, thyroid ultrasonography [3], CT, magnetic resonance imaging [4], and endobronchial ultrasound [5] are currently available screening methods to detect thyroid carcinoma with tracheal invasion preoperatively.

However, significant endotracheal invasion often occurs in recurrent or clinically overt thyroid carcinomas. Occult thyroid cancer presenting initially as endotracheal invasion is extremely rare. Intratracheal tumor as the initial presentation of PTC was reported in 1 case, with no primary tumor found in the thyroid gland radiologically or pathologically [6]. Herein, we report 2 cases initially presenting as an endotracheal tumor. Both patients had a history of mild clinical symptoms (cough and hemoptysis) for 1 to 2 years before the onset of significant airway obstruction (stridor and dyspnea). Despite intraluminal tracheal invasion, no goiter was palpable in these 2 patients, even with clinically overt airway obstruction. In the first patient, pathologic examination of the surgical specimen offered direct support of a transmural tracheal invasion by PTC. Complete resection of the primary thyroid tumor and adjacent organ invasion was performed in this patient and long-term survival was noted. This intensive surgical policy was also reported in another recent study [1]. In the second patient, PTC-related endotracheal invasion led to progressive airway obstruction without aggressive treatment. The negative thyroid ultrasonography results in these 2 cases may have been due to intra-thyroid calcification [3] or intraluminal tracheal invasion.

In summary, endotracheal tumor can be the first manifestation of occult thyroid cancer. The absence of clinically detectable thyroid abnormality does not exclude the possibility of locally advanced thyroid carcinoma. We think that occult thyroid cancer with endotracheal invasion should be considered in the differential diagnosis of tracheal tumor. Aggressive surgical intervention can provide the opportunity for long-term survival in this circumstance.

References

1. Gaissert HA, Honings J, Grillo HC, *et al*. Segmental Laryngotracheal and Tracheal Resection for Invasive Thyroid

Carcinoma. Ann Thorac Surg 2007; 83: 1952-9.
2. Ishihara T, Yamazaki S, Kobayashi K, *et al*. Resection of the trachea infiltrated by thyroid carcinoma. Ann Surg 1982; 195: 496-500.
3. Tomoda C, Uruno T, Takamura Y, *et al*. Ultrasonography as a method of screening for tracheal invasion by papillary thyroid cancer. Surg Today 2005; 35: 819-22.
4. Wang JC, Takashima S, Takayama F, *et al*. Tracheal invasion by thyroid carcinoma: prediction using MR imaging. Am J Roentgenol 2001; 177: 929-36.
5. Wakamatsu T, Tsushima K, Yasuo M, *et al*. Usefulness of Preoperative Endobronchial Ultrasound for Airway Invasion around the Trachea: Esophageal Cancer and Thyroid Cancer. Respiration 2006; 73: 651-7.
6. Paksoy N, Oztürk H, Demircan A, *et al*. Occult papillary carcinoma of the thyroid presenting as an intratracheal tumour. Eur J Surg Oncol. 1994; 20: 694-5.

以氣管內侵襲爲起始表現的隱性甲狀腺癌 —二病例報告及文獻回顧

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以氣管內侵襲(endotracheal invasion)為起始表現的隱性甲狀腺癌(occult thyroid cacner)極為罕見。我們提出兩個因為咳嗽與咳血的病例，胸部X光片顯示在氣管的部位有腫塊的陰影；頸部與甲狀腺的理學檢查並無異常的發現。支氣管鏡檢查發現有一氣管內腫瘤(endotracheal tumor)，手術與切片證實為甲狀腺乳突癌(papillary thyroid carcinoma)併發氣管內侵襲。其中一位病人在積極的外科治療後達到長期存活；然而另一位病人則因上呼吸道阻塞而死亡。回顧英文文獻，只有一個相似的病例被發表過。我們認為隱性甲狀腺癌應列入氣管內腫瘤的一個鑑別診斷。即使頸部的理學檢查缺乏明顯的甲狀腺異常，亦不能排除局部侵襲性甲狀腺癌的可能性。積極的外科治療，包括原發腫瘤與受影響氣管的局部切除，可以提供病人長期存活的機會。*(胸腔醫學* ***2008; 23: 221-227)***

關鍵詞：氣管內侵襲，氣管內腫瘤，隱性甲狀腺癌，甲狀腺乳突癌

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