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# 胸腔醫學

# Thoracic Medicine

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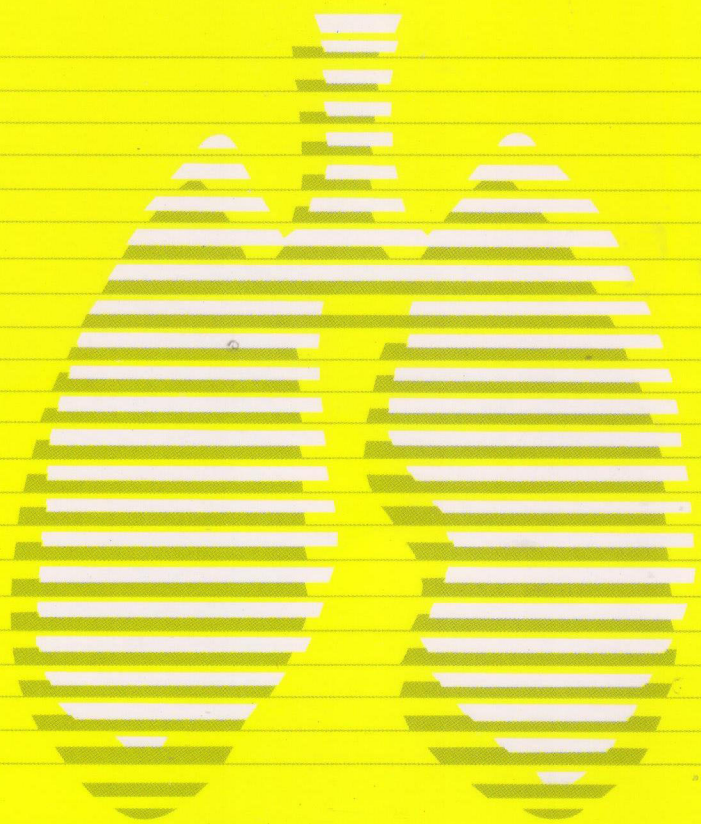

台灣胸腔暨重症加護醫學會

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## 原著



## 病例報告

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# 胸腔醫學
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The Official Journal of Taiwan Society of Pulmonary and Critical Care Medicine

## Orginial Articles



## Case Reports

# Flexible Bronchoscopy-Guided, Self-expandable, Metallic Stents Improve Survival in Patients with Esophageal Cancer Complicated with Esophago-Respiratory Fistula

Tzu-Tao Chen, Chih-Jan Wang***, Chii-Lan Lin, Chun-Nin Lee, H-Eugene Liu*,**
Chih-Cheng Chang

**Background:** Esophago-respiratory fistula, which develops in some esophageal cancer patients, is a devastating and life-threatening complication. When patients are in serious condition, general anesthesia, rigid bronchoscopy and subsequent silicone stent implantation are not feasible. Airway stent implantation can seal the fistula and avoid further complications, such as repeated aspiration. The aim of our study was to evaluate the outcome of airway stent implantation in esophageal cancer patients with esophago-respiratory fistula.

**Patients and Methods:** From April 2002 to October 2009, 16 consecutive patients with esophago-respiratory fistula-associated esophageal cancer were reviewed. Nine patients received airway stent implantation and 7 did not. The outcomes evaluated included emergency department visit episodes, pneumonia episodes, total hospitalized days due to pneumonia, and days of survival after fistula diagnosis.

**Results:** The days of survival after fistula diagnosis were significantly different between the airway stent implantation group and the group without an airway stent implantation (80.22 ± 55.14 versus 32.71 ± 70.86, $p < 0.05$). The other outcomes were not statistically different between the 2 groups.

**Conclusions:** Airway stent implantation improves the number of days of survival in patients with esophageal cancer complicated with esophago-respiratory fistula. ***(Thorac Med 2010; 25: 286-293)***

Key words: esophageal cancer, esophago-respiratory fistula, airway stent

## Introduction

Esophageal cancer that infiltrates surrounding tissue may manifest necrosis with the subsequent development of an esophago-respiratory fistula, which is a devastating and life-threaten-

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ing complication. The usual cause of death in these patients is lung infection resulting from chronic aspiration through the fistula [1]. The prognosis of patients with esophageal cancer remains poor, despite therapeutic progress; the 5-year survival rate was reported as 5-10% [2]. Flexible bronchoscopy therapeutic modalities could be another option for patients with unresectable esophageal cancer or those at high risk for surgical intervention [4]. Moreover, covered self-expandable metallic stents (SEMSs) have been used to seal off tracheo-esophageal fistulas and avoid aspiration symptoms [5]. The aim of this study was to evaluate the outcome of airway stent implantation in esophageal cancer patients with esophago-respiratory fistula complications.

## Patients and Methods

### *Patients*

From April 2002 to October 2009, 16 patients with esophago-respiratory fistula-associated esophageal cancer were reviewed. Nine patients had an airway stent implant and 7 did not. All of these patients were males who had esophageal cancer histologically identified as squamous cell carcinoma. The basic characteristics, including age at the time of fistula diagnosis, site of the fistula (by either bronchoscopy or image study), cancer stage, primary tumor assessment, previous treatment before diagnosis of the fistula, length of the fistula, and performance status, are listed in Table 1 and Table 2. The fistula site in 1 patient in the group without a stent implant could not be identified because the bronchogram was obtained by esophagography at the lower third of the esophagus, and the fistula could not be identified by bronchoscopy. The primary tumor of 1 patient in the stent implantation group could not be assessed but was categorized as stage IV due to distant metastasis. None of the basic characteristics between the 2 groups were statistically different.

### *Statistical analysis*

All data are presented as mean ± SD. All categorical variables were analyzed with the chi-square test. Survival was defined as the duration from the time of diagnosis to death.

**Table 1.** Demography of groups with and without airway stent implantation

| Characteristics | With stent | Without stent |
|---|---|---|
| No. of patients | 9 | 7 |
| Gender | | |
| Male | 9 | 7 |
| Female | 0 | 0 |
| Age (years) | 57 ± 14.47 | 54.57 ± 13.28 |
| Site of fistula | | |
| Trachea | 6 | 2 |
| Left main bronchus | 2 | 3 |
| Right main bronchus | 1 | 1 |
| Stage | | |
| II | 2 | 3 |
| III | 3 | 3 |
| IV | 4 | 1 |
| Primary tumor* | | |
| T2 | 2 | 1 |
| T3 | 2 | 3 |
| T4 | 4 | 3 |
| Previous treatment | | |
| nil | 0 | 1 |
| CCRT | 1 | 1 |
| CCRT and C/T | 4 | 0 |
| CCRT and OP | 2 | 3 |
| CCRT, OP and C/T | 2 | 2 |

* the primary tumor of 1 patient with a stent could not be assessed

**Table 2.** Characteristics of the fistula, stent, and clinical performance status in both groups

| | Age | Gender | Invasion site | Fistula Length | Stent size (OD x Length) | Pre-stent ECOG | Post-stent ECOG | OS days |
|---|---|---|---|---|---|---|---|---|
| Stent group | | | | | | | | |
| Case 1 | 64 | Male | LT | 2 cm | 20 mm x 6 cm | 4 | 4 | 26 |
| Case 2 | 56 | Male | LT | 1.5 cm | 20 mm x 8 cm | 3 | 2 | 106 |
| Case 3 | 45 | Male | LT | 1 cm | 20 mm x 8 cm | N/A | N/A | 91 |
| Case 4 | 68 | Male | MT | 4.5 cm | 20 mm x 8 cm | 4 | 4 | 10 |
| Case 5 | 78 | Male | LM | 1.5 cm | 16 mm x 6 cm | 4 | 4 | 103 |
| Case 6 | 40 | Male | RM | 1 cm | 14 mm x 4 cm | 3 | 2 | 92 |
| Case 7 | 73 | Male | LM | 1.5 cm | 20 mm x 8 cm | 4 | 3 | 39 |
| Case 8 | 39 | Male | UT | 2.5 cm | 20 mm x 8 cm | 3 | 2 | 194 |
| Case 9 | 50 | Male | LT | 2 cm | 18 mm x 6 cm | N/A | N/A | 61 |
| Non-stent group | | | | | | Initial ECOG | | |
| Case 10 | 75 | Male | LM | 1 cm | | 3 | | 2 |
| Case 11 | 32 | Male | Trachea* | 1.5 cm | | 3 | | 13 |
| Case 12 | 59 | Male | LM | 2 cm | | 3 | | 2 |
| Case 13 | 57 | Male | MT | 1.5 cm | | N/A | | 193 |
| Case 14 | 60 | Male | LT | 1.5 cm | | 4 | | 13 |
| Case 15 | 53 | Male | LM | 1.5 cm | | 4 | | 1 |
| Case 16 | 46 | Male | RM | 1.5 cm | | 4 | | 5 |

OD, outer diameter; OS, Overall survival; ECOG: Eastern Cooperation Oncology Group performance status; UT, upper trachea; MT, middle trachea; LT, lower trachea; LM, left main bronchus; RM, right main bronchus; N/A, not available, *diagnosed by esophagography.

**Table 3.** The outcome of groups with and without airway stent implantation

| Outcomes | With stent | Without stent | *p* value |
|---|---|---|---|
| Survival days after diagnosis of fistula | 80.22 ± 55.14 | 32.71 ± 70.86 | < 0.05 |
| Pneumonia episodes | 1.44 ± 0.73 | 1.29 ± 0.76 | 0.6065 |
| Hospitalized days | 51.89 ± 37.92 | 33.71 ± 27.68 | 0.6065 |
| ER consultation episodes | 1 ± 0.87 | 1.14 ± 0.38 | 0.536 |

* Values are means ± standard deviation

Comparisons between the means of the variables used in overall survival days, hospitalized days, and emergency room consultation episodes were made using the Mann-Whitney test. Statistical significance was set at $p < 0.05$.

## Results

The number of survival days (Figure 1) in the group with the airway stent implant was greater than that in the group without the airway stent implant (80.22 ± 55.14 versus 32.71

± 70.86, respectively, $p < 0.05$). However, other results, including emergency department visit episodes (1 ± 0.87 versus 1.14 ± 0.38, $p = 0.536$), pneumonia episodes (1.44 ± 0.73 versus 1.29 ± 0.76, $p = 0.606$), and total hospitalized days due to pneumonia (51.89 ± 37.92 versus 33.71 ± 27.68, $p = 0.606$) were not significantly different (Table 3).

All patients eventually died because of either tumor hemorrhage or infection (Table 4); however, the cause of death of 2 patients in the airway stent implantation group was not identified because they did not expire in the hospital. One patient was transferred to an outside clinic for hospice care, while the other was eventually lost to follow-up.

The origin of infection was either pulmonary or pulmonary and mediastinal; 5 cases (35.7%) progressed to septic shock. Six patients (42.8%) died secondary to tumor hemorrhage from either the airway or the gastrointestinal tract.

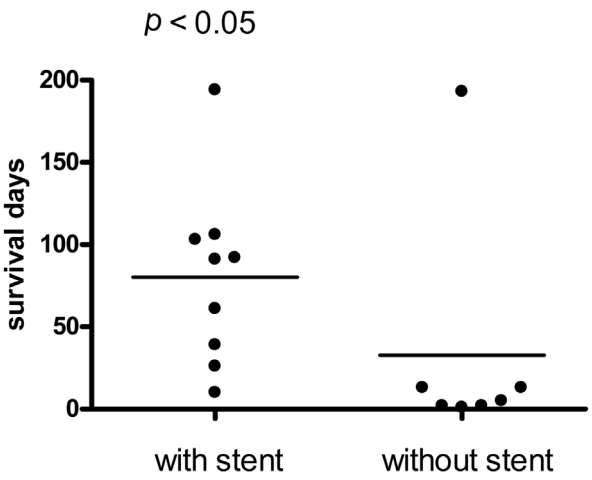


**Fig. 1.** The number of survival days of the patients with and without airway stent implantation.

## Discussion

The incidence of esophago-respiratory fistula development in esophageal cancer patients is 5-13% [6]. Fistulas are the result of tissue destruction by the invasion of carcinoma into normal tissue, and have serious consequences as a result of continuous airway contamination [2]. Most untreated patients die within 1 month of the development of the fistula [7]. The causes of death include asphyxia, repeated aspiration, pneumonia, lung abscess, empyema, mediastinitis, and hemorrhage [8].

Treatment for esophago-respiratory fistula includes concurrent chemoradiation therapy [13], chemotherapy alone, radiation therapy alone [11], several kinds of panendoscopic endoprostheses [1,3,12,14], and surgical inter-

**Table 4.** The cause of death in the 2 groups

| Cause of death | With stent (n)* | Without stent (n) | Total |
|---|---|---|---|
| Hemorrhage | 3 | 3 | 6 (42.8%) |
| Septic shock | | | 5 (35.7%) |
| Pulmonary | 2 | 2 | |
| Pulmonary + Mediastinum | 1 | | |
| Infection | | | 3 (21.4%) |
| Pulmonary | 1 | 1 | |
| Pulmonary + Mediastinum | | 1 | |

* Two patients with a stent did not die in the hospital

vention. Surgical intervention includes bypass treatment to seal the fistula, which is not only invasive but extremely risky, with a mortality rate of up to 41.5% [8]. Because of the high morbidity and mortality rates with surgery, several kinds of panendoscopic endoprostheses have been developed in recent decades. Two endoprostheses have been used for the treatment of fistula: the tracheobronchial prosthesis and the esophageal prosthesis [10,15]. By sealing off the fistula, a successful panendoscopic stent can prevent serious airway contamination and dysphagia, and improve the quality of life and length of survival [2], although its benefit on survival remains to be demonstrated [9]. The complication rate for the panendoscopic prosthesis was reported to be from 17.7% [16] to 36% [20], and includes gastroesophageal reflux disease, food impaction [3], aspiration, perforation [17], hematemesis, chest pain, migration, airway compression, fistula formation in the airway at the ends of the prosthesis, the funnel phenomenon, and stent covering disruption [18].

The bronchoscopic stent may have an outcome similar to the panendoscopic stent, but in our study, survival was the only significant result. The reason for this finding may be that without implantation of the panendoscopic stent dysphagia will persist and cause repeated aspiration. There was no statistically significantly difference in gender, age at fistula diagnosis, site of the fistula, cancer stage, or previous treatment before the diagnosis of fistula between the two groups. The causes of death included tumor hemorrhage with massive hemoptysis or hematemesis, septic shock or infection with either a pulmonary or mediastinal origin, or both. Any of these etiologies of death would be possible due to tumor progression and the natural course of the malignancy.

The study by Earlam *et al*. showed that the malignant esophageal stricture group had a poor outcome, with survival of around 1 month [7]. In our study, all of the patients except 1 in the group without stent implantation expired in less than 1 month after diagnosis of the fistula. The exceptional case survived more than 6 months. The location of the patient's fistula was in the lower third of the esophagus, as revealed by esophagography, and could not be identified by bronchoscopy. This was different from the other cases in that all the other fistulas were identified proximal to secondary bifurcation of the bronchi. This may be the reason why this patient had a longer survival time than the other patients.

The complications of the bronchoscopic airway stent include chest pain, cough, airway secretion retention, granulation formation, hemoptysis, perforation, and migration [22]. Airway stent implantation is frequently followed by airway colonization by potentially pathogenic microorganisms and is not associated with clinical infection signs [19]. Although there has been no prospective study comparing the panendoscopic and bronchoscopic stents, a study showed that delayed complications occurred with panendoscopic stent implantation that might influence the quality of life of about 26.9% of patients [21]. Compared with the panendoscopic stent, the airway stent has fewer complications [23], and subsequently results in a better quality of life.

## Conclusion

Endoscopic endoprosthesis implantation is a feasible method for the treatment of patients with esophago-respiratory fistula [2]. However, a bronchoscopic stent is the alternative choice for patients that have difficulty with panen-

doscopy, fewer complications, and prolonged overall survival. However, further comprehensive and larger studies are needed in order to compare the panendoscopic and bronchoscopic stents.

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# 軟式支鏡導引放置呼吸道支架於食道癌併食道—氣管廔管可延長存活

陳資濤　王志冉***　林啟嵐　李俊年　劉興璟*,**　張志誠

**前言：**食道－氣管廔管是一種在食道癌病患上發生並且易有生命威脅的併發症。呼吸道支架放置能封閉廔管避免更進一步的併發症，如反覆性吸入性肺炎，但常因全身麻醉及病況無法進入手術房進行傳統硬式支鏡導引放置氣管支架，本篇的目的在於評估在有此食道-氣管廔管之食道癌病人對於氣管支架放置後的結果評估。

**方法：**本篇回溯2002年4月至2009年10月間，共有16位食道－氣管廔管之食道癌病人被納入評估。總共有9位病人接受此支架放置術，另有7位沒有接受此種術式。評估方式為到急診求診次數、發生肺炎次數，因肺炎住院之總住院天數，及診斷食道－氣管廔管之後的存活期間。

**結果：**食道－氣管廔管診斷後的存活日數在放置與未放置的兩組間有明顯統計上差異（80.22 ± 55.14 與 32.71 ± 70.86, $p < 0.05$），其餘的評估結果並無統計上差異。

**結論：**呼吸道支架放置在於食道-氣管廔管之食道癌病人身上能有效延長存活期。*(胸腔醫學* ***2010; 25: 286-293)***

關鍵詞：食道癌，食道－氣管廔管，呼吸道支架

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索取抽印本請聯絡：張志誠醫師，台北醫學大學　雙和醫院　胸腔內科，235台北縣中和市中正路291號

# Pneumomediastinum and Subcutaneous Emphysema Secondary to Perforated Duodenal Ulcer: A Case Report and Literature Review

Ho-Sheng Lee, Ping-Hung Kuo

Subcutaneous emphysema and pneumomediastinum may be caused by air leakage from an extra-pulmonary source. In this report, we described the case of a 63-year-old man who presented to our emergency department with severe abdominal pain and dyspnea. The chest radiograph showed subcutaneous emphysema, pneumomediastinum, and pneumoperitoneum, but no pneumothorax. An exploratory laparotomy revealed a perforated peptic ulcer at the anterior wall of the duodenum. The subcutaneous emphysema and pneumomediastinum resolved rapidly after the perforation was closed. We also reviewed the literature on this rare complication of peptic ulcer. ***(Thorac Med 2010; 25: 294-298)***

Key words: pneumomediastinum, subcutaneous emphysema, perforated peptic ulcer, duodenal ulcer

## Introduction

Pneumomediastinum (the presence of free air in the mediastinum) is often secondary to a specific responsible pathologic event, such as trauma, intrathoracic infections, or damage to the aerodigestive tract. [1]

Hemorrhage, penetration, and perforation are common complications of peptic ulcers. Perforation occurs in 2-10% of peptic ulcers [2], and free intra-abdominal air is seen in 80% of these peptic ulcers after perforation. However, penetration into the retroperitoneum with pneumothorax and mediastinal emphysema or subcutaneous emphysema is rarely observed. [3-5] In this report, we describe a rare case of pneumomediastinum and subcutaneous emphysema secondary to a perforated peptic ulcer.

## Case Report

A 63-year-old man presented to our emergency department with progressive abdominal pain, abdominal distension, poor appetite, and dyspnea for 3 days. He denied fever, vomiting, a history of trauma, and any underlying diseases. He also denied tarry stool and any change in bowel habit or stool caliber. He had been consuming about 250 ml of alcohol per week for many years, and he sometimes took pain-killers for knee pain. On examination, his consciousness was clear, and his blood pres-

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sure was 143/97 mmHg; pulse rate, 135 beats/min; respiratory rate, 22 breaths/min; and body temperature, 37.2°C. The abdominal wall was distended, with severe tenderness and rebound pain. The bowel sounds were hypo-active. Extensive subcutaneous emphysema involving the neck, both sides of the chest wall, and the upper abdomen were observed. Breathing sounds were present bilaterally. Venous blood gas analysis was performed while oxygen was delivered through a nasal cannula at a flow rate of 5 liters per minute, and the following values were obtained: blood pH, 7.438; $PaCO_2$ and $PaO_2$, 30.3 and 43 mmHg, respectively; and bicarbonate level, 20.5 mmol/L. The pulse oximetry $O_2$ saturation ($SpO_2$) improved from 81% to 98% when the patient used an oxygen mask, with $FiO_2$ 0.98, at a flow rate of 10 l/min.

The following laboratory data were recorded: white blood cell count, 5950 cells/μL (with 50% in band forms); hemoglobin level, 17.9 mg/dL; platelet count, 243 × $10^3$/μL; C-reactive protein, 28.87 mg/mL; creatinine, 1.7 mg/dL; lactate, 4.02 mmol/L; and aspartate aminotransferase, 23 U/L. The chest radiograph showed pneumomediastinum and extensive subcutaneous emphysema involving both chest walls, but pneumothorax or pulmonary infiltrates were not observed (Figure 1). Abdominal computed tomography scans revealed subcutaneous emphysema and pneumomediastinum (Figure 2A), as well as diffuse free air in the intraperitoneal cavity and retroperitoneum (Figure 2B). A pericolorectal abscess about 10 cm in size was also seen. Septic shock was noted and intravenous hydration with 2000 ml of normal saline was given, followed by continual infusion of norepinephrine. The patient was then intubated because of hypercapnic respiratory failure. The post-intubation arterial blood gas showed pH, 7.224; $PaCO_2$, 51.2 mmHg; $PaO_2$, 78.6 mmHg; and $HCO_3$, 21.3 mmol/L, when the patient used a ventilator with $FiO_2$ 1.0.

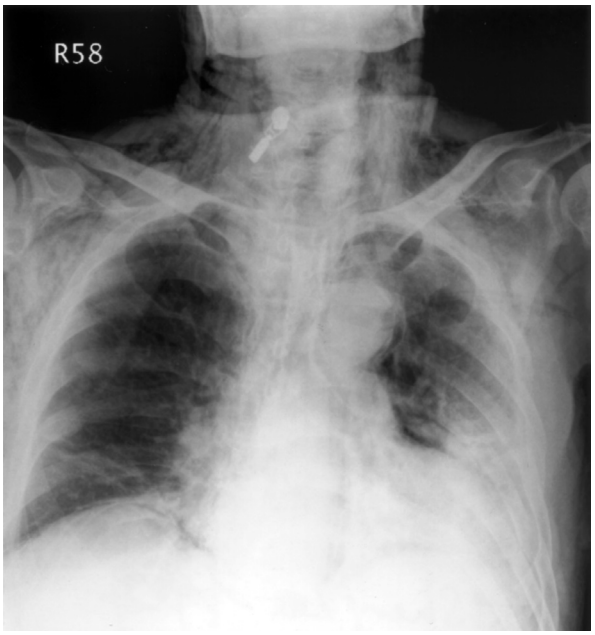
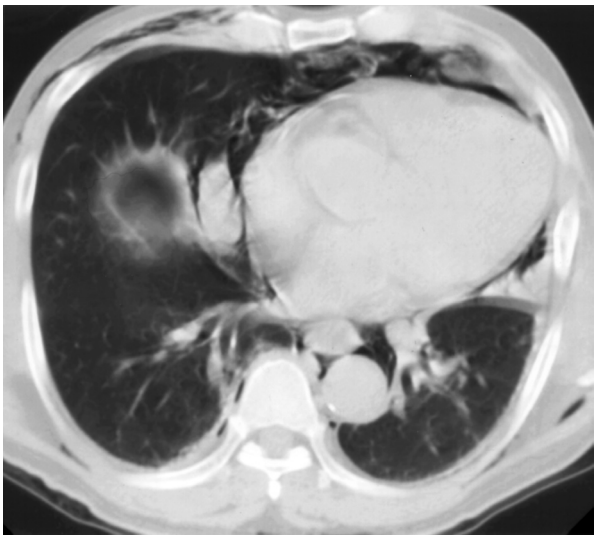
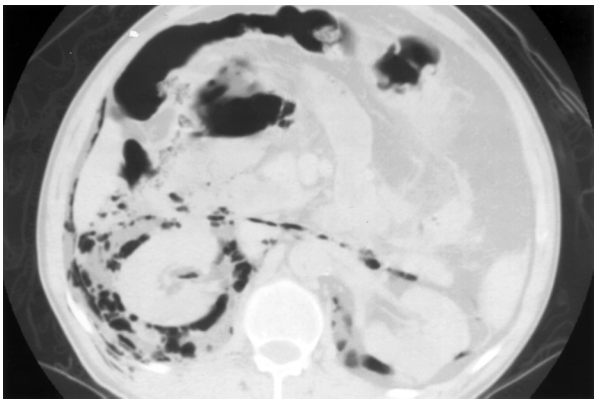



**Fig. 1.** Initial chest radiography in the emergency department showing pneumomediastinum, subcutaneous emphysema, and pneumoperitoneum, but no pneumothorax

An emergency exploratory laparotomy was performed, and a 7-mm perforation at the anterior superior wall of the second portion of the duodenum was found and repaired with simple suture and an omentum patch. The other intraoperative findings included much ascites and an intra-abdominal abscess coated with fibrin, especially in the lesser omentum and hepatic hilum. In addition, an emphysematous retroperitoneal abscess was also noted. These abscesses were drained and the adhesions were released. After irrigation of the abdominal cavity, 4 rubber drain tubes were inserted and a feeding jejunostomy was performed, followed by administration of broad spectrum antibiotic agents. The post-operative course in the intensive care unit was complicated with septic shock with acute renal failure, requiring a short



(A)



(B)

**Fig. 2.** Abdominal computed tomography (2A) showing subcutaneous emphysema, pneumomediastinum, and (2B) free air in the peritoneum and retroperitoneum

course of continuous renal replacement therapy. His fever subsided gradually, and both arterial oxygenation and the subcutaneous emphysema improved rapidly. The follow-up chest radiography performed 3 days after surgery revealed total resolution of the subcutaneous emphysema and pneumomediastinum (Figure 3). The inotropic agents were also tapered off on the 5th post-operative day.

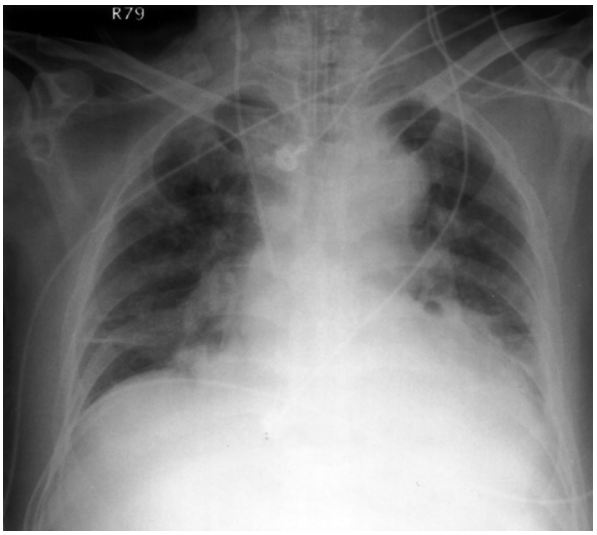



**Fig. 3.** Follow-up chest radiography 3 days after surgery revealing total resolution of pneumomediastinum and subcutaneous emphysema

## Discussion

We have described an interesting case of pneumomediastinum and extensive subcutaneous emphysema as an initial manifestation of perforated peptic ulcer. This case is also notable for the rapid resolution of the air leakage after the perforation was closed.

Two similar cases of simultaneous pneumoperitoneum and pneumomediastinum induced by perforation of duodenal ulcers were reported by Stahl in 1977 [3]. Several mechanisms have been proposed to explain this rare complication, including tension pneumoperitoneum accentuated by vomiting, congenital or acquired peritoneal defects, and the spreading of air through vascular sheaths [3].

Our case showed significant free air accumulation in the retroperitoneum. The possible route of the spreading of the air in our case was from the intra-abdominal cavity to the retroperitoneum, the paravascular sheath, and finally into the mediastinum. However, the retroperi-

toneal air was absent in the 2 cases reported by Stahl, thereby suggesting the existence of other spreading routes. Our patient denied vomiting when he was sent to the emergency department. The absence of vomiting is uncommon because a sufficient pressure gradient between the lumen of the bowel and the subcutaneous space is needed for subcutaneous emphysema of gastrointestinal origin [4].

For patients with extensive air-leak syndrome, bronchoscopy is an important diagnostic procedure that may help identify airway lacerations. However, this procedure was not performed in this patient because there was no history of trauma or airway symptoms suggestive of endobronchial lesion. Moreover, the rapid resolution of subcutaneous emphysema after the surgical repair of a perforated peptic ulcer indicates that the possibility of major esophageal or tracheal lacerations was low.

Pneumomediastinum and subcutaneous emphysema, when not accompanied with pneumothorax, rarely cause significant hypoxemia or shock. In this case, the factors that might have led to the patient's respiratory failure were sepsis, fluid leakage into [a third space, such asclarify], abdominal distension, and respiratory muscle fatigue.

In summary, subcutaneous emphysema and pneumomediastinum can be caused by an extrapulmonary source of air leakage. In the absence of pneumothorax and a history of trauma, special attention should be paid to the possibility of intra-abdominal hollow organ perforation. Rapid resolution of this complication is possible once the source of air leakage is surgically corrected. The treatment course may be prolonged, especially when this condition is complicated by intra-abdominal sepsis and bowel leakage.

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# 十二指腸潰瘍穿孔合併次發性縱膈氣腫及皮下氣腫：案例報告及文獻回顧

李和昇　郭炳宏

縱膈氣腫及皮下氣腫有時是由肺部以外的氣體破出所造成。在此我們報告一位63歲男性，因嚴重腹痛及呼吸困難而來到本院急診，胸部X光呈現皮下氣腫、縱膈氣腫，但並無氣胸。腹部探查手術發現了一個小腸前壁的消化性潰瘍穿孔，並予以修補。皮下氣腫和縱膈氣腫在術後即迅速進步。我們並回顧了與此少見的消化性潰瘍穿孔併發症有關的文獻。*(胸腔醫學* ***2010; 25: 294-298)***

關鍵詞：縱膈氣腫，皮下氣腫，消化性潰瘍穿孔，十二指腸潰瘍

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# Disseminated *Mycobacterium kansasii* Infection with Miliary Lung Lesions and Meningitis: A Rare Case

Jung-Yueh Chen, Chao-Chi Ho, Chong-Jen Yu

Disseminated *Mycobacterium kansasii* infection is a rare complication, and more common in AIDS patients. We reported a 38-year-old woman with underlying autoimmune-related hemolytic anemia (AIHA) and antiphospholipid syndrome. She had had intermittent high fever followed by altered mental status for 2 weeks. A cerebrospinal fluid (CSF) study showed pleocytosis (several atypical lymphocytes). Follow-up chest X-ray showed miliary lesions. Anti-tuberculosis medication was prescribed, but the dyspnea deteriorated. Acid-fast bacilli smear from a bronchial washing specimen was positive. CSF culture grew *Mycobacterium kansasii*. She passed away due to multiple organ failure, despite treatment. The presentation of miliary lung lesions is rare in *Mycobacterium kansasii* infection. This is the second reported case of miliary lung lesions in non-HIV-infected populations with disseminated *Mycobacterium kansasii* infection. Earlier diagnosis and adequate treatment is important to improve the prognosis. ***(Thorac Med 2010; 25: 299-304)***

Key words: *Mycobacterium kansasii*, atypical mycobacterium lung diseases, meningitis

## Introduction

*Mycobacterium kansasii* (*M. kansasii*) as an infectious organism was reported in the early 1950s [1]. *M. kansasii* infection shares many clinical features with tuberculosis. The most common clinical presentations were chest pain, cough, hemoptysis, fever, and night sweats [1]. Disseminated infection is a rare complication, and there are fewer reports of disseminated *M. kansasii* infection in non-HIV infection patients than in AIDS patients.

## Case Report

We report a 38-year-old woman who was admitted to National Taiwan University Hospital, a tertiary referral hospital in Taiwan, with high fever and altered mental status. She had been diagnosed with autoimmune-related hemolytic anemia (AIHA) and antiphospholipid syndrome 3 years prior to admission. Immunomodulatory medications such as prednisolone, hydroxychloroquine and mycophenolate were prescribed. She had intermittent high fever, nausea and postprandial vomiting 2 weeks be-

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fore admission. No shortness of breath, cough, dysuria or skin rash was noted. She denied recent travel or an animal contact history. At admission on 16 September 2008, her temperature was 37.7°C; blood pressure, 112/82 mmHg; pulse, 135 beats per minute; respiratory rate, 26 breaths per minute; and oxygen saturation, 96% in ambient air. The conjunctiva was slightly pale. The respiratory pattern was rapid and shallow without obvious crackles or wheezing. No neck stiffness, Kernig's sign or Brudzinski's sign was noted during physical examination. Pancytopenia (white blood cell count of 1000/μL, hemoglobin 7.4 g/dL, and platelet count of 67 K/μL) was found. The differential count revealed 62% neutrophils, 14% lymphocytes, 23% monocytes and 1% basophils. Bone marrow study favored myelodysplastic syndrome. Because of the altered mental status, lumbar puncture was performed on the 25$^{th}$ hospital day, and the cerebrospinal fluid (CSF) study showed an elevated opening pressure, high protein content (162 mg/dl) and pleocytosis (18/μl, all were lymphocytes, including several atypical lymphocytes). Brain MRI revealed a suspicious, increased leptomeningeal enhancement of the bilateral cerebral hemispheres. Further study, including acid-fast bacilli smear, Gram's stain, cryptococcal antigen, Aspergillus antigen, and bacterial and fungal culture were all negative. Fever, altered mental status and pancytopenia did not improve with imipenam and corticosteroid treatment. Follow-up chest X-ray on the 32$^{nd}$ hospital day showed miliary lesions, especially at the lower lung fields (Figure 1). Diffuse small lung nodules and interstitial opacities were disclosed by high-resolution computed tomography (Figure 2). Anti-tuberculous treatment was initiated, but fever persisted, and consciousness and dyspnea deteriorated. She received endotracheal intubation because of hypoxic respiratory failure on the 40$^{th}$ hospital day. Seizure developed on the day after respiratory failure, and was controlled by lorazepam and phenytoin infusion. Repeated bone marrow studies showed hemophagocytosis and suspected NK/T cell lymphoma. Acid-fast bacilli smear from a bronchial lavage specimen was positive, but TB polymerase chain reaction (PCR) from the same specimen was negative. At the same time, CSF culture grew *M. kansasii*. Amikacin, moxifloxacin, meropenam and linezolid were prescribed instead of isoniazid and rifampin for *M. kansasii* treatment due to hepatic failure. However, multiple organ failure deteriorated and she passed away on the 48$^{th}$ hospital day.

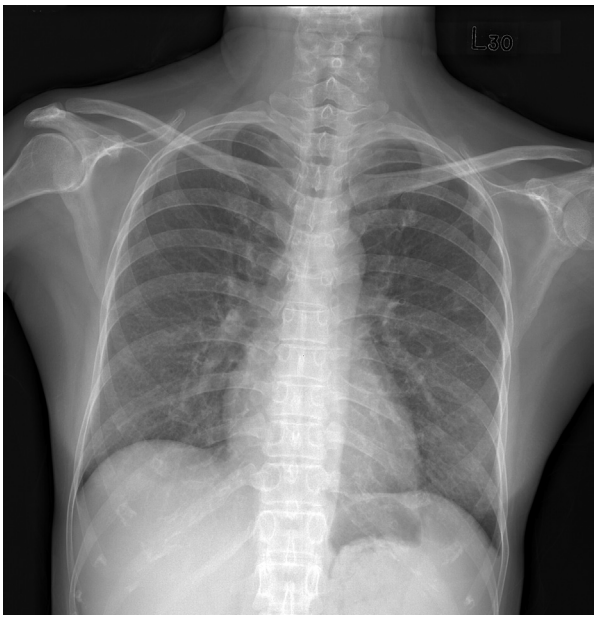


**Fig. 1.** Chest radiography revealed miliary shadows at the bilateral lung area

## Discussion

*M. kansasii* is the non-tuberculous mycobacterium most frequently found in immunocompetent patients. It is also the second most

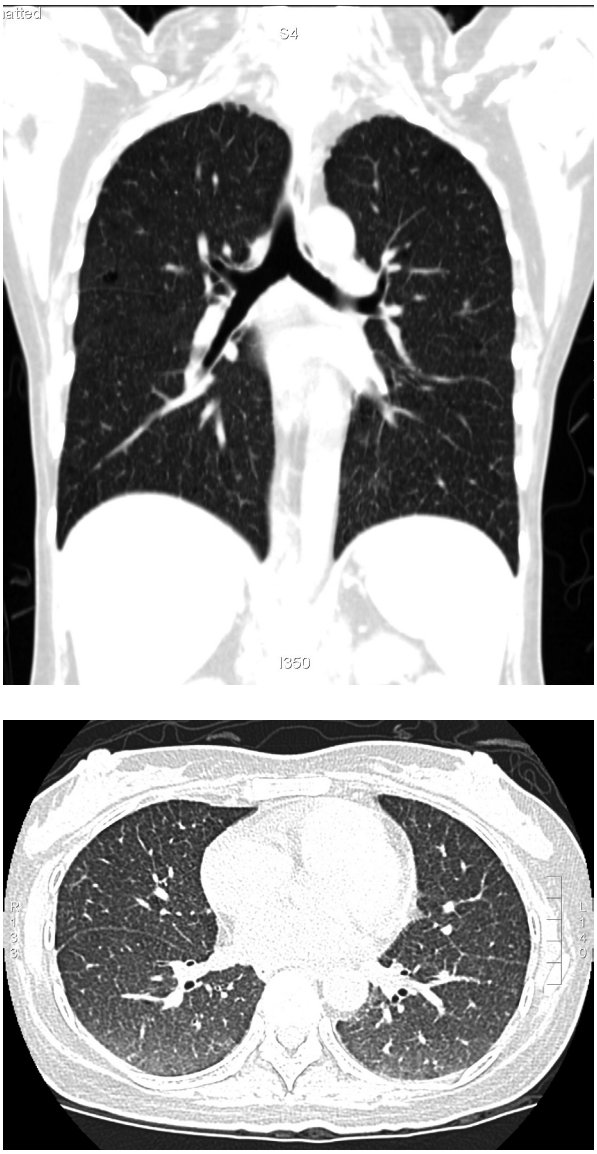

**Fig. 2.** Chest HRCT (coronal and cross-sectional views) disclosed diffuse small lung nodules and interstitial opacities

frequent Mycobacterium found in HIV-infected patients and is surpassed only by *M. avium* complex [12]. The most common clinical presentations have been chest pain, cough, hemoptysis, fever, and night sweats [13]. Apical or subapical, thin-walled cavitary infiltrate was the characteristic radiological feature of *M. kansasii* pulmonary infection [1,8]; this presentation was similar to that of post-primary pulmonary tuberculosis [2]. The *M. kansasii* findings on chest radiography of HIV-infected patients have varied, and included diffuse interstitial infiltrations, consolidations or nodules [9,10]. Adithya C *et al*. analyzed the radiographic presentations of *M. kansasii* lung disease in patients with HIV infection [4], and among 83 patients, consolidation (n = 55, 66%) and nodules (n = 35, 42%) were the most common radiographic abnormalities identified, especially at the middle and lower lung zones [4]. Compared to non-HIV infected patients, cavitary infiltrates in HIV-infected patients were a less common finding (7%) [4,8]. A miliary or interstitial pattern was uncommon in HIV patients with disseminated *M. kansasii* infection, as well. Of 96 patients reported by Fishman *et al*., interstitial opacities were found in only 6% [5]. However, in another case series, interstitial infiltrates noted by chest radiography were found in 33.3% of patients. The discrepancy was possibly due to the small number of cases (n=15) [11]. In another study analyzing HIV-infected patients, a miliary pattern was found in only 4% of the *M. kansasii* group, compared with 12% of the *M. tuberculosis* group [3]. In non-HIV patients, disseminated *M. kansasii* with miliary lung lesions has been reported only in an 81-year-old man who had short-bowel syndrome [6]. In our hospital, Lai *et al*. reviewed the records of 15 non-HIV disseminated non-tuberculous mycobacteria (NTM)-infected patients from January 1997 to December 2004, and no miliary lesions had been found by chest radiography [7]. The mean time from presentation to anti-NTM treatment was 130 days. And, among the reported patients, only 3 had been infected with *M. kansasii*. One of them received antimicrobial therapy and none survived. When *M. kansasii* infection was confined to the lung only, the

prognosis was much better [1]. Among 302 patients who had pulmonary infection caused by *M. kansasii* during a 50-year period, only 11% of 224 deaths were attributed to *M. kansasii* [1]. In this case report, we have described only the second case of *M. kansasii* miliary lung lesions in non-HIV-infected populations.

The American Thoracic Society recommends a 3-drug combination for the treatment of *M. kansasii* infection, including isoniazid, rifampin and ethambutol. Therapy is given for a minimum of 12 months with culture negativity [14]. The fluoroquinolone, moxifloxacin, also has good *in vitro* activity against *M. kansasii* [15]. Because of the good efficacy of clarithromycin against other non-tuberculous mycobacteria, the triad of clarithromycin, rifampin, and ethambutol may be a reasonable alternative for patients unable to tolerate isoniazid [16].

Due to the increasing number of immunocompromised hosts who are older, have HIV infection and cancer, and have undergone steroid therapy, this type of infection will become more common and its earlier diagnosis and adequate treatment will be important to improve the prognosis.

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# *Mycobacterium kansasii* 粟粒性肺部感染及腦膜炎：罕見病例報告

陳鍾岳　何肇基　余忠仁

在非愛滋病的病患族群中瀰漫性*Mycobacterium kansasii*感染是極少見的。我們報告一位38歲女性病患，本身具有自體免疫溶血性貧血及抗磷脂症候群等疾病。病患兩週前開始有高燒及意識不清的症狀。腦脊髓液檢查發現一些非典型淋巴球細胞。追蹤X光及電腦斷層檢查發現雙側肺野充滿粟粒性結節。抗結核藥物針對粟粒性結核病開始治療，但發燒及呼吸急促的狀態未見改善。支氣管鏡肺沖洗液的抗酸性染色為陽性，而且腦脊髓液的培養結果為*Mycobacterium kansasii*。儘管接受治療，病患仍因多重器官衰竭而去世。此病患為文獻中第二位在非愛滋病患族群瀰漫性*Mycobacterium kansasii*感染並且以粟粒性肺部感染為主要表現之個案。及早診斷並及早正確治療對於改善病人預後至為重要。*(胸腔醫學* ***2010; 25: 299-304)***

關鍵詞：*Mycobacterium kansasii*，非典型肺分枝桿菌感染，腦膜炎

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# Central Diabetes Insipidus: An Unusual Initial Presentation of Lung Cancer

Szu-Chun Yang, Chien-Chung Lin, Chin-Chung Tseng*, Han-Yu Chang

Central diabetes insipidus (DI) rarely occurs as the initial presentation of lung cancer. Lung cancer patients with the presentation of central DI often exhibit other central nervous system (CNS) symptoms. We reported a 54-year-old man with polyuria for 3 months. His physical and neurological examination results were unremarkable. Water deprivation test confirmed the diagnosis of central DI. A magnetic resonance image of the brain revealed multiple lesions consistent with metastases, including a lesion in the posterior lobe of the pituitary gland. A chest radiograph showed a nodule in the left upper lobe of the lung. Computed tomography-guided needle biopsy of the nodule confirmed the diagnosis of lung adenocarcinoma. The patient was treated with a nasal spray of desmopressin, cyber-knife radiosurgery followed by whole brain radiotherapy, and chemotherapy. His polyuria improved markedly and he was well without significant complications. In conclusion, if a patient initially presents with central DI without other CNS symptoms, physicians should consider the possibility of metastatic disease, especially that resulting from lung cancer. ***(Thorac Med 2010; 25: 305-310)***

Key words: diabetes insipidus, lung cancer, pituitary metastasis

## Introduction

Central diabetes insipidus (DI), occurring from injury to the hypothalamic-neurohypophyseal system, commonly results from head trauma, neoplasms, and granulomatous disease [1]. Pituitary metastasis frequently results from breast and lung cancer [2]. However, patients with pituitary metastases are often asymptomatic, and the metastasis is discovered accidentally. Symptoms of central DI are often complicated with other central nervous system (CNS) symptoms that are caused by multiple CNS metastases. Central DI as the initial presentation of lung cancer has hitherto been reported in only a limited number of cases [3-6]. In most of these patients, central DI was accompanied by other neurological symptoms. We report a patient in whom the initial presentation of lung adenocarcinoma was central DI without other neurological symptoms.

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## Case Report

A 54-year-old non-smoking man presented to our nephrology outpatient department with a 3-month history of polyuria and polydipsia. He did not experience cough, shortness of breath, feverishness, or weight loss, and had an uneventful medical history except for diabetic mellitus. He took 500 mg of oral metformin twice daily.

The physical examination was unremarkable. Neurological and visual field examinations revealed no focal deficit. Initial investigation showed normal plasma glucose, and his hemoglobin A1c was 7.4%. His 24-hour urine volume was 5,800 ml; urine osmolality, 92 mOsm/kg; and plasma sodium, 149 mmol/L. These levels were consistent with those for DI. We therefore performed a water deprivation test (Table 1). After administration of desmopressin, urine osmolality increased (and urine output concomitantly decreased) by more than 100%. This result confirmed the diagnosis of central DI [7]. The patient's growth hormone, adrenocorticotropic hormone, prolactin, follicle-stimulating hormone, luteinizing hormone, and thyroid stimulating hormone levels were within normal limits.

A magnetic resonance image (MRI) of the brain showed multiple lesions consistent with metastases, including a lesion in the posterior lobe of the pituitary gland (Figure 1). Chest radiographs showed a nodule in the left upper lobe of the lung (Figure 2). A chest computed tomographic (CT) scan (Figure 3) showed a 2.8 cm × 1.9 cm speculated nodule in the left upper lobe of the lung with several fine nodules in both lungs, indicating metastases.

We performed a CT-guided needle biopsy of the nodule; the morphology confirmed the diagnosis of lung adenocarcinoma (Figure 4). A technetium-99m whole body bone scan showed multiple bony metastases. The disease was classified as stage IV according to the tumor-node-metastasis stage ($T_{1b}N_0M_{1b}$).

The patient was treated with a nasal spray of 10 μg desmopressin twice daily, which markedly improved his polyuria. He underwent cyberknife radiosurgery (12-24 Gy; pituitary metastatic tumor, 24 Gy) followed by whole-brain radiotherapy (3000 cGy/10 fractions for 2 weeks) and 4 cycles of cisplatin (60 mg/m$^2$) and

**Table 1.** Water deprivation test

| Time (hr) | Plasma osmolality (mOsm/kg) | Plasma sodium (mmol/L) | Urine osmolality (mOsm/kg) | Urine volume (ml) | Urine sodium (mmol/L) |
|---|---|---|---|---|---|
| 0 | 295 | 141 | 112 | 250 | 18 |
| Subcutaneous desmopressin 2.5 μg | | | | | |
| 0.5 | 291 | 143 | -- | 110 | -- |
| 1 | 297 | 142 | 503 | 80 | 86 |
| 2 | 288 | 143 | 510 | 60 | 112 |
| 3 | 290 | 143 | -- | 0 | -- |
| 4 | 291 | 144 | 544 | 80 | 110 |

--: Not applicable

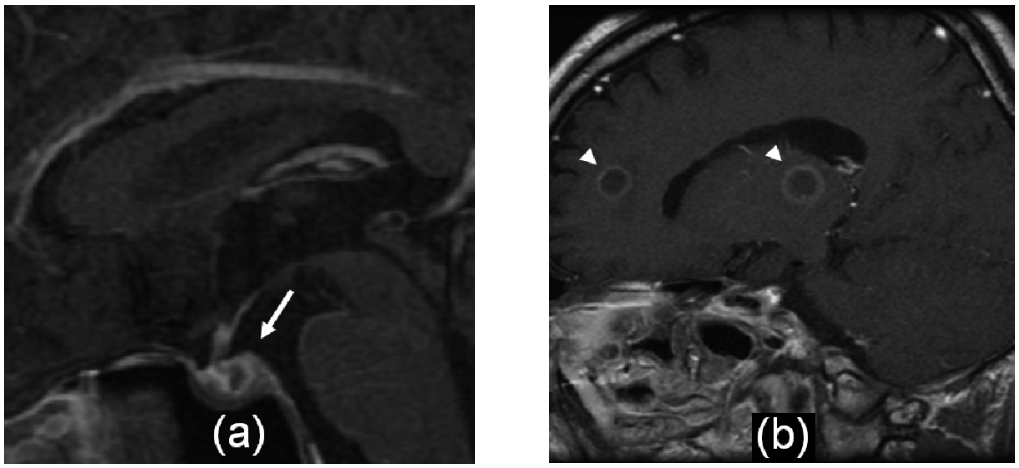


**Fig. 1.** MRI of the brain (sagittal view) shows: (a) A peripherally enhanced lesion (arrow) in the posterior lobe of the pituitary gland on a post-Gd T1-weighted image (T1WI). (b) Several lesions (arrow heads) with rim-enhancement are seen on a post-Gd T1WI, located at the right thalamus and the right frontal lobe. These findings are consistent with the presence of metastases.

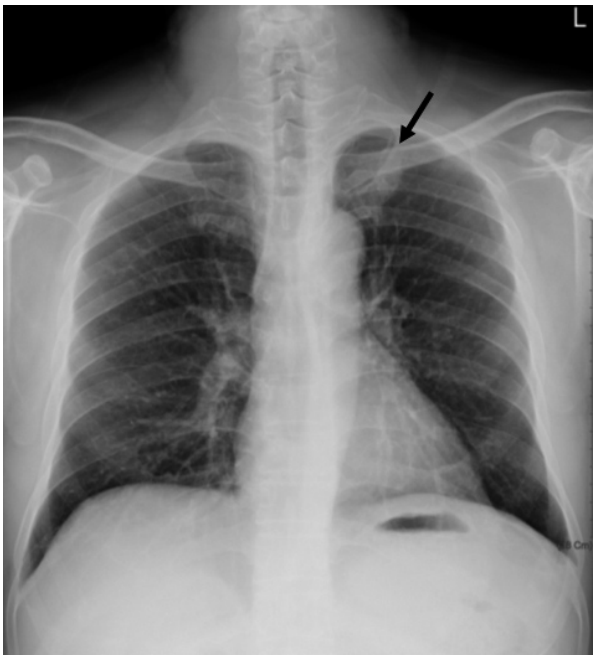


**Fig. 2.** Chest radiograph of the patient shows an obscure nodule (arrow) in the left upper lobe of the lung.

pemetrexed (500 mg/m$^2$). As of this writing, the patient was well and had not developed significant complications.

## Discussion

Pituitary metastases are observed at the time of autopsy in 1% to 5% of patients with advanced cancer [8]. The breast and lung are the most frequent primary sites in woman (66.0%) and men (62.9%), respectively [2]. However, pituitary metastases in most patients remain asymptomatic and are usually discovered as a postmortem finding [2]. More than 60% of pituitary metastases primarily affect the posterior lobe, 10% to 20% affect the anterior lobe, and only 1 to 2% involves the infundibulum [2]. The posterior pituitary receives blood supply from the systemic circulation, whereas the anterior pituitary is supplied by its portal system [3]. Symptoms of central DI are rare (6.8%) among patients with pituitary metastases [2]. These patients often experience other CNS complications, such as headache, cranial nerve palsy, and visual changes [9-11] that are caused by multiple CNS metastases.

Polydipsia, polyuria with hypotonic urine, low serum antidiuretic hormone (ADH) levels,

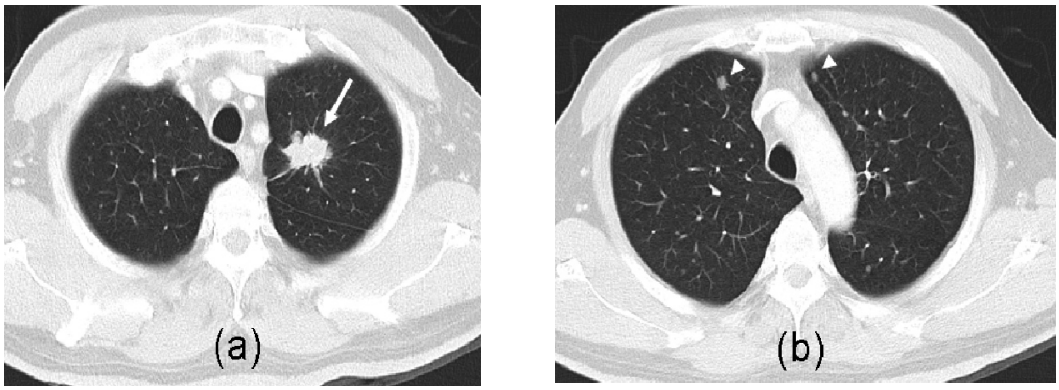


**Fig. 3.** CT scan of the chest. (a) A speculated nodule (arrow) in the left upper lobe, 2.8 cm × 1.9 cm in size. (b) Innumerable nodular lesions in both lungs (arrow heads).

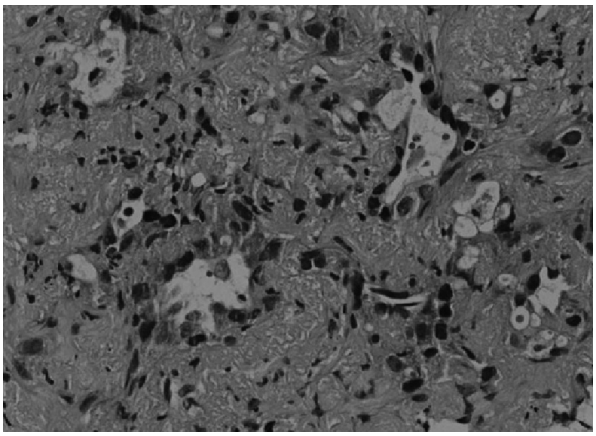

**Fig. 4.** Section shows adenocarcinoma composed of tumor cells with hyperchromatic nuclei and pale cytoplasm arranged in a glandular pattern (hematoxylin & eosin, 200×)

and correction of symptoms upon exogenous ADH administration are the clinical hallmarks of central DI. Among patients with central DI, 10% to 20% have pituitary metastases [1]. CT scans cannot detect pituitary abnormalities in many patients; however, MRI scans are an effective tool to identify pituitary metastases [12]. In MRI of the pituitary tumor, T1-weighted images do not show the normal physiological bright spot for the posterior lobe, and post-gadolinium (Gd) imaging reveals abnormal enhancement in the posterior lobe [13]. On the basis of factors such as patient age of more than 50 years, rapid onset or progression of symptoms, presence of cranial nerve palsy, history of malignancy, and failure of bromocriptine treatment, clinicians can differentiate pituitary metastases from pituitary adenomas [6, 14].

Administration of exogenous ADH usually improves the symptoms of central DI. However, most patients require lifelong administration because of the destructive, irreversible nature of the pituitary lesions. Resolution of central DI after brain radiotherapy has been observed in a few cases [12, 15-16]. Piedra et al. also reported a patient in whom the DI medication could be reduced 3 months after gamma knife surgery for a solitary metastasis in the pituitary stalk [17]. Early radiotherapy or surgical decompression do not change the overall poor prognosis associated with pituitary metastases. However, they may improve the quality and quantity of life of symptomatic patients [10].

In conclusion, if a patient initially presents with central DI but no other CNS symptoms, physicians should consider metastatic disease from lung cancer.

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# 中樞性尿崩症：肺癌一不尋常的最初表現

楊思雋　林建中　曾進忠*　張漢煜

肺癌最初以中樞性尿崩症為表現的實為罕見。這些患者通常合併有其它中樞神經系統的症狀。我們在此報告一個病例：一位五十四歲的男性，主訴多尿已三個月，住院接受理學及神經學檢查皆正常。經限水試驗（water deprivation test）證實是中樞性尿崩症（central diabetes insipidus）。腦部核磁共振影像發現多處轉移性病灶，包括一位於腦垂腺後葉的病變。胸部X光片看到一左上肺葉結節。電腦斷層導引細針切片術證實它是肺腺癌。之後患者接受desmopressin鼻噴劑，數碼導航刀暨全腦部放射線治療及化學治療。多尿的症狀明顯地改善而且無相關的併發症。我們藉由這樣的病例報告，對於最初表現僅是中樞性尿崩症的患者，即使無中樞神經系統的症狀，臨床醫師亦須考慮腦部轉移的癌症，尤其是肺癌的可能性。*(胸腔醫學* ***2010; 25: 305-310)***

關鍵詞：尿崩症，肺癌，腦垂腺轉移

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# Non-endemic Pulmonary Coccidioidomycosis in Taiwan – A Case Report

Hsin-Yi Chiu*, Yih-Gang Goan*,**, Yo-Wen Chang*, En-Kuei Tang*, Hong-Shen Lin*, Huang-Chou Chang*

Coccidioidomycosis is a dustborne infection caused by the dimorphic fungus *Coccidioides immitis*. Infections are endemic to certain regions of the southwestern United States. Most patients with primary pulmonary coccidioidomycosis are asymptomatic. Inhalation of fungal spores is the only established mode of infection, and spores may be carried on dust particles.

Coccidioidomycosis is frequently unrecognized as a diagnosis because of the lack of suspicion in a non-endemic area. We described a case of coccidioidomycosis manifesting as a persistent pulmonary mass and diagnosed in Taiwan, a non-endemic area. This patient initially was treated with anti-tuberculosis drugs owing to the presence of necrotizing granulomatous inflammation on repetitive lung biopsies. The diagnosis of coccidioidomycosis was confirmed after wedge resection of the right middle lobe of the lung through mini-thoracotomy.

We also reviewed the related literature concerning the epidemiology, clinical manifestations, diagnosis and treatment of coccidioidomycosis. ***(Thorac Med 2010; 25: 311-316)***

Key words: coccidioidomycosis, non-tuberculosis, respiratory infection

## Introduction

Coccidioidomycosis is a fungal infection caused by *Coccidioides immitis* (*C. immitis*), which is native to the southwestern United States and found in soil penetrated by rodents. Human *C. immitis* infection is caused by inhaled airborne fungal spores. The disease is not transmitted from person to person. Most infected patients are asymptomatic. The common clinical manifestations are flu-like illness, pneumonia, and even septic shock. Pulmonary nodules with or without cavitation and diffuse reticulonodular pneumonia are the major pulmonary manifestations. This kind of infection is often diagnosed by the presence of spherules of *Coccidioides* spp. in body fluids, exudates, sputum and biopsy-tissue. However, the diagnosis is often missed or delayed due to a low index of suspicion. In this report, we describe the clinical entity and review the literatures on coccidioidomycosis.

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## Case Report

This 61-year-old female patient was a teacher who had frequently spent her summer and winter vacation in the United States, especially in California, during the last 40 years. Her medical history was unremarkable, except a calcified lesion in the right lung field found on chest X-ray film during a physical check-up 30 years ago. However, she did not pay much attention to it, and no further survey or management had been scheduled since that time. She began suffer from occasional palpitations 2 years ago and underwent another physical check-up. There was no cough, no hemoptysis, no body weight loss, no headache, and no fever at that time. A repeated plain chest X-ray showed a patchy density at the right lung field (Figure 1), and a solid tumor mass lesion at the right middle lobe (RML) of the lung was found on computerized tomography of the chest. As the possibility of malignancy could not be completely ruled out, she was admitted to another institution for tissue diagnosis. The pathologic result of lung biopsy was consistent with necrotizing granulomatous inflammation. Therefore, an anti-tuberculosis regimen using a combination of 4 anti-tuberculosis drugs was planned for treatment. However, the regimen was switched to isoniazid and rifampin 3 months later due to the side effects of impaired liver function and general malaise. Since the tumor mass did not regress, even after taking medication for 9 months, a 2nd lung biopsy was done and the result also showed necrotizing granulomatous inflammation. Continuous anti-tuberculosis treatment was suggested, but she requested a referral to our institution for a second opinion. Therefore, she was admitted to our chest surgery ward for further evaluation and management.

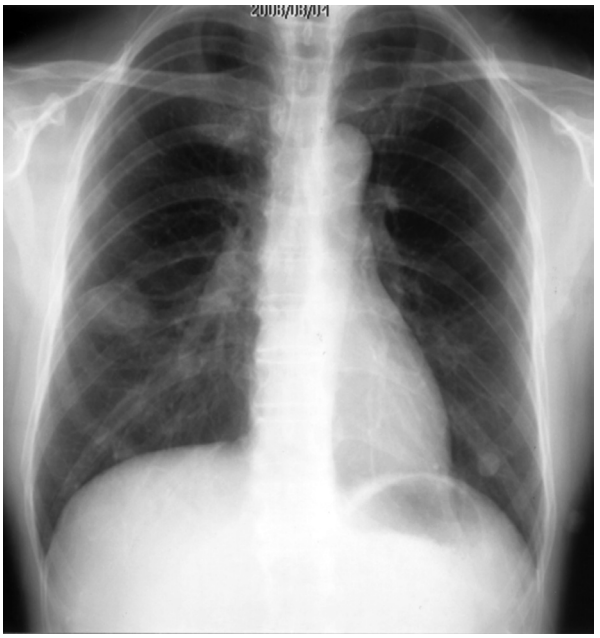

**Fig. 1.** Patchy density at right middle lung field

On admission, nothing in particular was found during physical examination and serum biochemistry analyses, except mild impairment of the liver function. Owing to the possibility of malignancy, the patient underwent a wedge resection at the RML of the lung through a right mini-thoracotomy. During operation, a mass lesion about 5x3x2 cm in size was identified at the RML of the lung. One piece of tumor tissue was sent for frozen section and the result was benign. Several small pieces of lung tissue were sent for fungal, mycobacterial and bacterial cultures. The rest of the tissue sample was sent for pathologic diagnosis. Several granulomas with extensive caseous necrosis and oval shaped yeast-like cells were identified in necrotic areas on microscopic examination (Figure 2, 3). Combined with the result of *Coccidioides* spp. growing on fungal culture, the diagnosis of coccidioidomycosis was confirmed. (Figure 4) This patient was discharged uneventfully on the 4$^{th}$

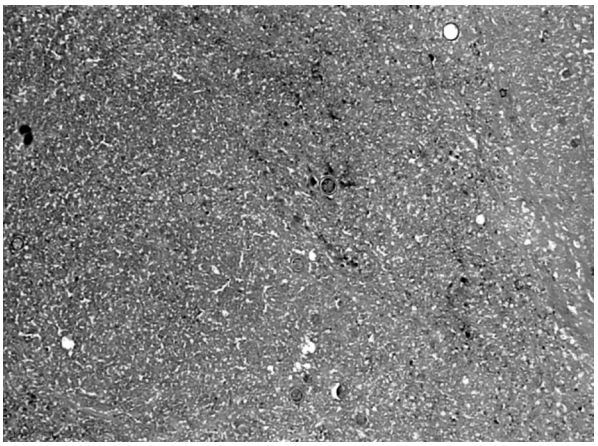

**Fig. 2.** Several granulomas with extensive caseous necrosis, Langhans' giant cells and epithelioid histiocytes (H&E stain, 100X)

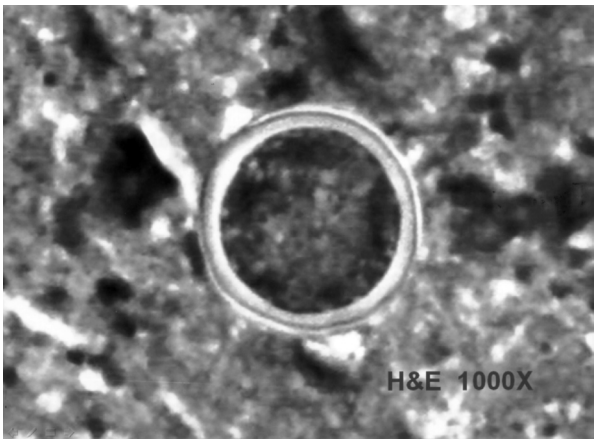


**Fig. 3.** Large, round to oval shaped yeast like cells with thick walls can be identified in the necrotic areas (H&E stain, 1000X)

postoperative day and remained in good condition 1 year after surgery.

## Discussion

Coccidioidomycosis is also known as Valley fever, San Joaquin Valley Fever, California Valley fever, and desert fever. It is a fungal infection caused by soil-borne *C. immitis* or *C. posadasii*. *Coccidiodes* spp. are endemic to certain lower deserts of the Western Hemisphere, including southern Arizona, central California,

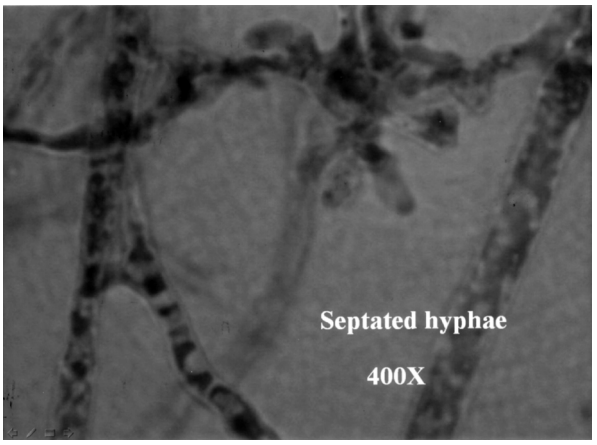


**Fig. 4.** Fungal culture revealed septate hyphae and thickened wall arthroconidia

southwestern New Mexico, and west Texas in the United States [1]. The *C. immitis* infection is caused by inhaled airborne fungal spores. It has a high infectivity rate, which is increased in immunosuppressed patients. Factors governing the recent increases in coccidioidomycosis are environmental rather than genetic. Outdoor activity is associated with an increased risk of infection [2]. Travel to endemic areas increases the chance of coccidioidomycosis infection, so travel history should always be considered in the evaluation of patients.

Most patients with coccidioidomycosis infection are asymptomatic. Symptomatic infection occurred in 40% of cases, and usually presented as a flu-like illness with fever, cough, headaches, rash, myalgia, etc. [3]. Serious complications include severe pneumonia, pulmonary nodules and disseminated disease causing skin ulcers, severe joint pain, heart inflammation, urinary tract problems, and meningitis. Pulmonary nodule, pulmonary cavity, and diffuse reticulonodular pneumonia are 3 major pulmonary manifestations of coccidioidomycosis infection [4].

The period between the onset of symptoms

and the diagnosis is relatively long. An accurate diagnosis will be difficult if this infection is not considered initially [5]. The results of most routine laboratory examinations are unremarkable. Analysis of the erythrocyte sedimentation rate (ESR) is a common but non-specific test for diagnosis. It is often 1-2 times above the upper limits of normal in approximately 1/4 of patients [6]. The mainstays of diagnosis are culture, serologic testing, histopathological examination, and polymerase chain reaction. *C. immitis* with endospores can be identified by hematoxylin and eosin stain, periodic acid-Schiff stain, or Grocott-methenamine silver stain, which has the highest sensitivity. The surrounding tissue may show a granulomatous reaction.

In this report, our patient had been treated as having a pulmonary mycobacterial infection for nearly 1 year, resulting from the presence of necrotizing granulomatous inflammation on repeated lung biopsies. However, the tumor mass did not regress, even after complete treatment. Under these circumstances, other differential diagnoses should be considered and more advanced procedures used to obtain a larger tissue specimen to confirm the diagnosis. Identification of spherules in tissue specimens on microscopic examinations cannot be ignored, especially in patients with an unsatisfactory outcome after initial treatment and a travel history to endemic areas.

Clinically, the *C. immitis* infection in most patients is self-limited. Those patients with coccidioidomycosis who have clinical signs and symptoms should be treated with anti-fungal agents. Patients at high risk for complications include those with AIDS, immunosuppressive medication use for transplants, glucocorticoids use, lymphoma, chemotherapy for solid tumors, diabetes mellitus, pregnancy, and preexisting cardiopulmonary conditions. Intravenous amphotericin B is indicated in patients with disseminated disease or prolonged chemotherapy. The azoles have less toxicity than amphotericin B, but similar therapeutic response rates in patients with coccidioidomycosis, although their therapeutic role in coccidioidomycosis has not yet been approved by the Food and Drug Administration [7]. Surgical intervention is indicated in *Coccidioides*–infected patients with severe hemoptysis, enlarged or ruptured cavities, empyema, persistent bronchopleural fistula and a suspicion of malignancy.

In conclusion, several important messages emerge from our case. First, other differential diagnoses should be taken into account when the outcome of treatment is unsatisfactory. Second, a detailed travel history is required for accurate diagnosis, especially when the patient has traveled to areas with an increased incidence of emerging infections. Third, the positive fungal culture contributed to the microscopic detection of typical spherules and led to a definitive diagnosis. Therefore, specimen cultures should not be omitted in patients with unresolved benign pulmonary diseases.

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# 在台灣地區非地方性之肺部球孢子菌感染—病歷報告

邱欣怡* 管毅剛*,** 張耀文* 湯恩魁* 林鴻生* 張晃宙*

球孢子菌感染是一種經由在土壤裡的雙形性黴菌“*Coccidioides immitis*”所造成之感染，這種感染盛行於美國的西南區域。大多數原發性肺部球孢子菌感染的病人是沒有症狀的，目前唯一確定的感染模式是經由散佈於土壤內的黴菌孢子。

在非盛行區域，常因沒有想到這個疾病而沒有診斷出來。我們要報導一個在台灣這個非盛行區域，以肺部腫塊來表現的球孢子菌感染病例。這個病例因為反覆的肺部切片都顯示為壞死性肉芽組織發炎，所以剛開始是以抗結核菌藥物治療。最後經由開胸手術進行右中肺葉楔形切除後，才確定診斷為球孢子菌感染。

在這篇病例報告裡，我們也回顧了一些文章，關於球孢子菌感染的流行病學，臨床表現，診斷與治療。*(胸腔醫學* ***2010; 25: 311-316)***

關鍵詞：球孢子菌感染，非結核感染，肺部感染

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# Huge Malignant Solitary Fibrous Tumor of Pleura with Cardiopulmonary Distress

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Malignant solitary fibrous tumors of the pleura (SFTP) are rare mesenchymal cell tumors in the thoracic cavity. A 59-year-old woman presented with dry cough, exertional dyspnea, and palpitation. Chest CT scan disclosed a huge and heterogeneous tumor mass in the left pleural cavity. She received surgical intervention through a sternotomy combined with a left anterior thoracotomy (modified hemi-clamshell) approach. The pathology revealed malignant solitary fibrous tumor.

For malignant SFTP, complete surgical resection is the mainstay of treatment. However, we described another surgical approach for the resection of huge thoracic tumors. In addition, we reviewed the literature with particular attention to the clinical features, histopathological characteristics, and management of these tumors. ***(Thorac Med 2010; 25: 317-321)***

Key words: malignant solitary fibrous tumor

## Introduction

Primary tumors of the pleura are commonly divided into 2 major categories: diffused and localized. Diffused pleural tumors are known for their association with asbestos and their poor outcome. Because of the results seen with electron microscopy and immunohistochemistry, the term "localized mesothelioma" has been abandoned and these tumors are now called "solitary fibrous tumors of the pleura" (SFTP) [1]. Solitary fibrous tumors are also described in other sites with mesenchymal tissue, such as the peritoneum, pericardium, mediastinum, upper respiratory tract, thyroid and orbit [2].

Malignant SFTPs show an increased cellularity with crowding and overlapping nuclei, cellular pleomorphism, and a high mitotic count. Surgical resection is the treatment of choice. We present our experience with the resection of a huge malignant solitary fibrous tumor of the pleura.

## Case Report

A 59-year-old woman who complained of a progressive dry cough, exertional dyspnea, and palpitation for 4 months was admitted to a

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nearby hospital where the chest X-ray revealed a huge mass lesion in the left pleural cavity (Figure 1). Further investigation by computed tomographic (CT) scanning (Figure 2) disclosed a huge heterogeneous opacity occupying the whole left pleural cavity with mediastinal compression. She was then transferred to our hospital for further evaluation and management. On initial clinical examination, we noted a thin female with cardiopulmonary distress. Her temperature was 37°C, pulse rate was 116/minute, respiratory rate was 24/minute, and blood pressure was 120/80 mm-Hg. The pulmonary function test showed the following results: forced expiratory volume in 1 s, 0.57 (24%) and vital capacity, 0.71 (25%). The laboratory results included a normal blood sugar level and no specific findings. Extra-thoracic investigation included a normal bone scan, and sono-guided biopsy of the tumor revealed negative results for mycobacterium and a suspected solitary fibrous tumor or sarcoma. Surgery was scheduled and performed with supine positioning for fear of cardiopulmonary compression. Extracorporeal membranous oxygen (ECMO) was prepared in the event of cardiopulmonary decompensation. Following median sternotomy, which was performed to make sure the pulmonary and intrapericardial vessels were under control, a left anterior lateral thoracotomy was performed (Figure 3). A huge mass was found that was firmly adherent to the lingular segment of the left upper lobe (LUL) of the lung and diaphragm without invasion into the pericardium. Many feeding vessels from the lingular segment of the LUL of the lung and diaphragm were noted (Figure 4). The tumor was completely resected with wedge resection of the lingular segment of the LUL of the lung and dissection with vessel ligation from the diaphragm. The excised tumor mass was 30x18x15 cm in size and 3500 gm in weight. The postoperative recovery showed marked clinical improvement, and disappearance of the clinical signs of cardiopulmonary distress. The postoperative histological examination revealed a tumor with the classical histological pattern of SFPT with necrosis and high

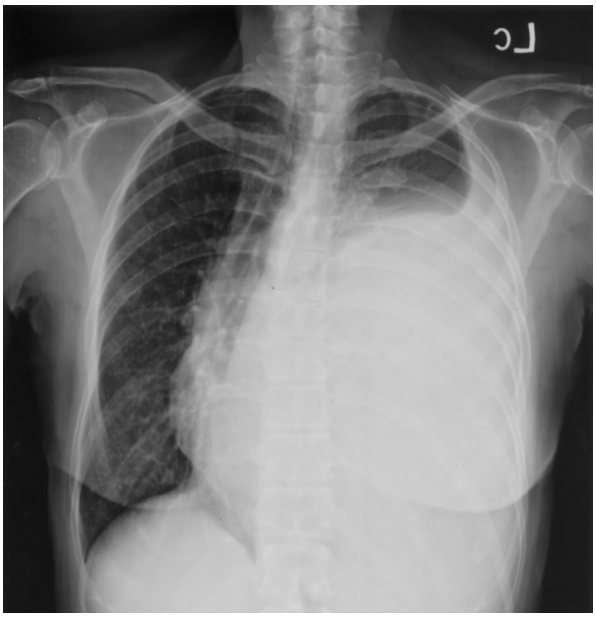

**Fig. 1.** Chest roentgenogram revealed a huge mass in the left pleural cavity with mediastinal shifting.

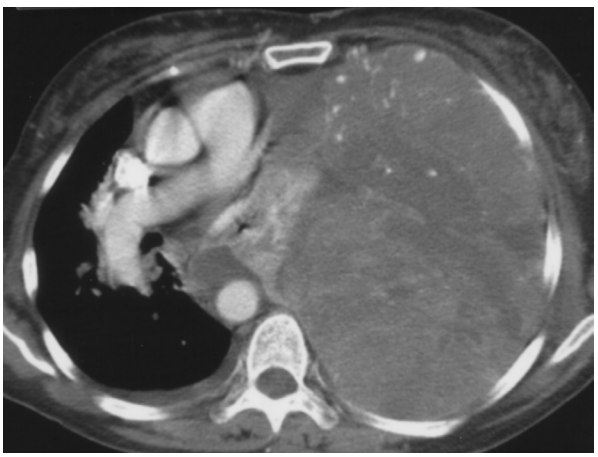

**Fig. 2.** Computed tomographic scan disclosed a huge and heterogenous mass in the left pleural cavity with mediastinal compression.

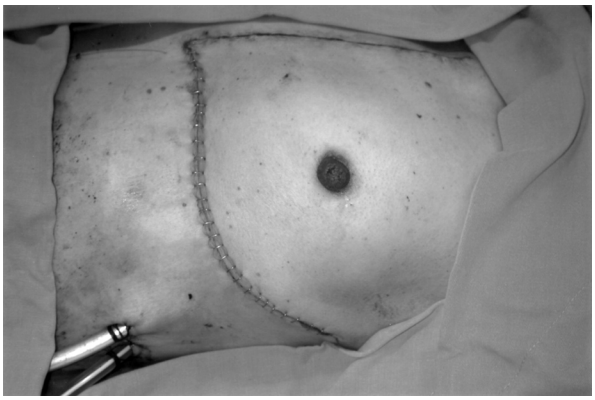

**Fig. 3.** The cutaneous incision used for the modified hemi-clamshell approach.

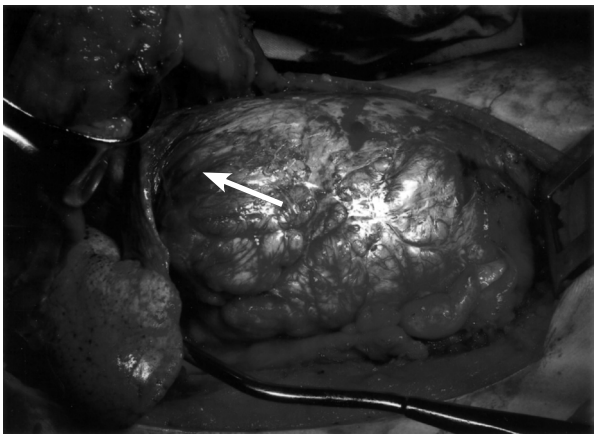

**Fig. 4.** The surgical view offered by the modified hemi-clamshell approach. Feeding vessels from the lingular segment of the LUL of the lung to the huge tumor were noted (arrow).

mitotic activity (19 mitoses in 50 high power field). The immunohistochemical study of the tumor mass showed strong positive for CD34. The final diagnosis was a malignant SFTP.

## Discussion

Malignant SFTP is a rare soft tissue tumor. The first SFTP was described by Wagner in 1870 [1]. The incidence of SFTP is approximately 2.8 cases per 100000 registered hospital patients; two-thirds of these tumors arise from the visceral pleural and one-third from the parietal pleura [2-3]. In SFTP, about 50% of patients are asymptomatic. The most frequent symptoms of SFTP are cough, dyspnea, and chest pain. Digital clubbing and hypertrophic osteoarthropathy (Pierre-Marie-Bamberger syndrome) have been described in 10% to 20% of patients and are thought to be the result of an abnormal production of hepatocyte growth factor or an excessive release of hyaluronic acid by the tumor [1-3]. In less than 5% of patients, SFTP can secrete insulin-like growth factor II, which causes refractory hypoglycemia (Doege-Potter syndrome) [1-4]. These clinical features will resolve within 2 to 5 months after removal of the tumor, but they may reappear with recurrence of the tumor.

England *et al*. have defined the criteria of malignant SFTP, including (1) high mitotic counts, defined as more than 4 mitoses per 10 high power fields; (2) mild to marked pleomorphism based on nuclear size, irregularity, and nuclear prominence; (3) bundles of high cellularity with crowding and overlapping of nuclei; (4) the presence of necrotic or hemorrhagic zones; and (5) stromal or vascular invasion [1, 3-4]. Malignant SFTP may be misdiagnosed as pleural mesothelioma, neurogenic sarcoma, synovial sarcoma, hemangiopericytoma, fibrosarcoma, and malignant fibrous histiocytoma. Immunohistochemistry is an extremely useful tool to differentiate SFTP from mesotheliomas and other sarcomas. Indeed, SFTP by definition is vimentin-positive and keratin-negative, as opposed to mesothelioma, which is keratin-positive and often vimentin-negative. In addition, CD34 is positive in most benign and malignant SFTP, whereas it remains negative for most other pulmonary tumors [1]. Occasionally, malignant SFTP may be CD34-negative. Further-

more, nestin is only detected in malignancies that are negative for CD34 [5].

The best therapy for malignant SFTP is complete resection with a margin of 1-2 centimeters. Tumors adherent to the parietal pleura require an extrapleural dissection [1]. In 3% or less of cases, the tumor can be "inverted" and grow inside the lung parenchyma. These tumors may occasionally require a lobectomy or a sleeve lobectomy [1]. Although most tumors can be excised through video-assisted thoracoscopic surgery, thoracotomy or sternotomy is necessary for a large tumor. In the present case, the tumor was too huge to remove through thoracotomy only. Furthermore, the vessels in the pulmonary hilum were compressed by the tumor and mediastinal invasion was highly suspected. The tumor was also difficult to approach through sternotomy only. Therefore, we decided to make sure the cardiopulmonary function was under control first through sternotomy. After confirming that the tumor could be resected safely, a further incision using anterior lateral thoracotomy was made to remove the tumor. This modified hemi-clamshell incision allows lengthy access to the thoracic cavity, enabling the excision of large masses with greater safety, as the pulmonary and intra-pericardial vessels can be easily controlled [6].

Since fibrous tumors of the pleura may rapidly enlarge and are potentially malignant, surgical resection is recommended in all cases. Preoperative transthoracic needle biopsy may be not necessary because it does not exclude malignant variants and does not influence the need for surgical resection [3].

Recurrence of SFTP was found in 60% of sessile histologically malignant tumors, 19% of pedunculated histologically malignant tumors, and 2% of benign tumors [1]. Therefore, long-term clinical and radiological follow-up is highly recommended. SFTP are readily curable with careful, complete resection, but malignant SFTP have a relatively poor outlook despite a complete resection. Multifocal local recurrence is usually not amenable to surgical intervention and carries a poor prognosis. Although Veronesi and colleagues have observed significant reduction of an inoperable recurrent SFTP using ifosfamide and adriamycin, the benefits of adjuvant chemotherapy and/or radiotherapy remain unproven [1-2]. Additional therapies, such as brachytherapy and photodynamic therapy, have rarely been reported, and their utility also remains unproven [1].

In conclusion, malignant solitary fibrous tumor of the pleural cavity should be resected whenever possible. Close follow-up is needed and the benefit of adjuvant therapy remains unproven.

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# 巨大之肋膜惡性單發性纖維瘤伴隨心肺窘迫症狀

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肋膜之惡性單發性纖維瘤是罕見的間質細胞腫瘤。我們報告一位59歲之女性病人，因乾咳、呼吸困難及心悸而前來就診。電腦斷層顯示左下肺葉有一巨大的異質性腫瘤。我們藉由左側前位開胸術及胸骨正中切開術（改良式hemi-clamshell），成功移除腫瘤，病理報告證實為肋膜之惡性單發性纖維瘤。

對於肋膜之惡性單發性纖維瘤，手術切除是唯一的治療方式。在此，我們提供了另一種可行之術式來切除巨大的腫瘤。此外，我們特別針對肋膜之惡性單發性纖維瘤的臨床表徵、病理特徵及處置方法，做了文獻整理與回顧。*(胸腔醫學* ***2010; 25: 317-321)***

關鍵詞：惡性單發性纖維瘤

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# Small Cell Lung Cancer with Hilar Lymphadenopathy Mimicking Pulmonary Embolism in Conventional Computed Tomography: A Case Report

Ke-Min Chen, Tsung-Ying Yang, Jeng-Yuan Hsu

A 69-year-old male was admitted because of intermittent chest tightness and shortness of breath for several months. Chest radiography showed a ground-glass lesion in the left middle lung field. The chest computed tomography showed a partial filling defect in the left pulmonary artery and peripheral wedge-shaped consolidation. Pulmonary embolism with pulmonary infarction was highly suspected from the computed tomography results. Because of the discordance between the clinical symptoms and the images, a multidetector computed tomographic pulmonary angiography was performed, and showed left hilar lymphadenopathy with external compression to the left pulmonary artery, mimicking a pulmonary embolism. Small cell carcinoma was proved by transthoracic lung biopsy from the peripheral lung lesion under sonographic guidance. ***(Thorac Med 2010; 25: 322-327)***

Key words: pulmonary embolism, pulmonary angiography, multidetector computed tomographic (MDCT) pulmonary angiography

## Introduction

Early and accurate diagnosis of pulmonary embolism has been discussed before and is still a real challenge because the clinical symptoms and laboratory findings are neither sensitive nor specific for diagnosis [1-3]. A combination of clinical assessments, including a review of the risk factors for venous thrombosis, clinical scoring systems, like Wells' criteria, and imaging studies can lead to a more precise diagnosis of pulmonary embolism [3, 5-7]. However, in some situations, the clinical symptoms are discordant with the imaging findings, so the diagnosis of pulmonary embolism is vague. Pulmonary angiography has been the gold standard in confirming pulmonary embolism. However, not all patients can tolerate this procedure [8]. In recent years, multidetector computed tomographic (MDCT) pulmonary angiography has been widely used as an alternative examination, due to the advantage of its convenience and high sensitivity and specificity [13-14]. Herein, we report a 69-year-old male with small

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cell lung carcinoma and left hilar lymphadenopathy mimicking pulmonary embolism and pulmonary infarction on the conventional chest computed tomography (CT), which presented clearly on MDCT pulmonary angiography combined with venous-phase imaging.

## Case Report

A 69-year-old male was admitted because of intermittent chest tightness and shortness of breath for 6 months. He had no history of cardiovascular disease, orthopnea, paroxysmal nocturnal dyspnea, pitting edema in the bilateral lower limbs, fever or productive cough. No remarkable body weight loss, no poor appetite and no night sweating were mentioned. He had been smoking 0.5 packs of cigarettes per day for more than 30 years. Physical examination revealed no specific abnormal finding. The laboratory examinations were all within normal limits, except mild leukocytosis. The serum cryptococcal antigen was negative. The chest radiography on 18 March 2010 showed a ground-glass lesion in the left middle lung field as shown in Figure 1.

CT of the chest revealed a wedge-shaped consolidative lesion in the left lingular lobe, 2.2 x 3 x 3.5 cm in size, with a filling defect at the left pulmonary artery (Figure 2a). Pulmonary artery embolism with lung infarction was highly suspected from the CT images. D-dimer was within the normal range. Due to the discordance between the clinical symptoms and the CT findings, MDCT pulmonary angiography combined with venous-phase imaging was performed to confirm the diagnosis of pulmonary embolism. MDCT showed (1) a 33 mm consolidative mass at the left lingual lobe with the left pulmonary artery compressed by an enlarged left hilar lymph node, instead of a filling defect. (Figure 2b, 2c), and (2) patent vessels inside the consolidative lesion, rendering infarction unlikely. Lung cancer with left hilar lymphadenopathy was highly suspected. Transthoracic sono-guid-

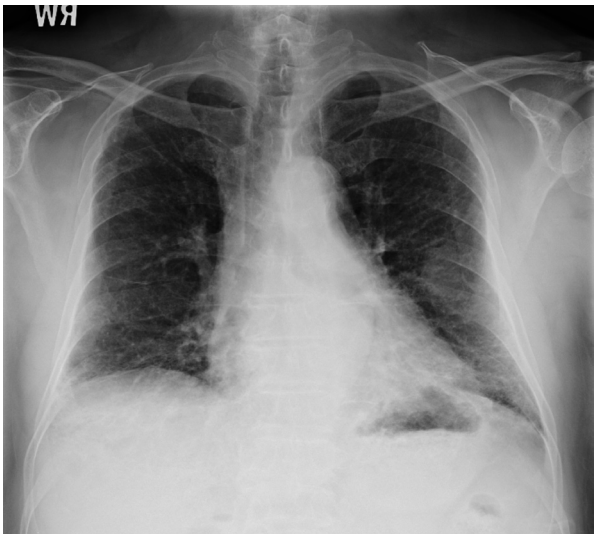


**Fig. 1.** Chest radiography (18 March 2010) revealed a ground-glass lesion in the left lung field

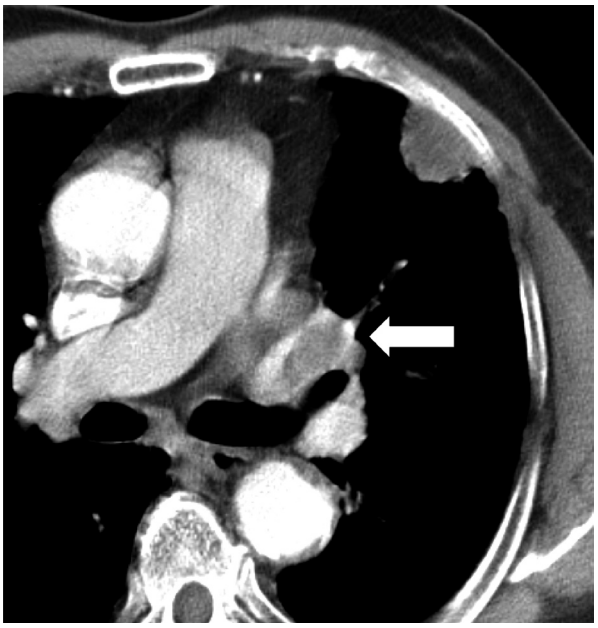

**Fig. 2a.** Conventional chest computed tomography showing a filling defect in the left pulmonary artery

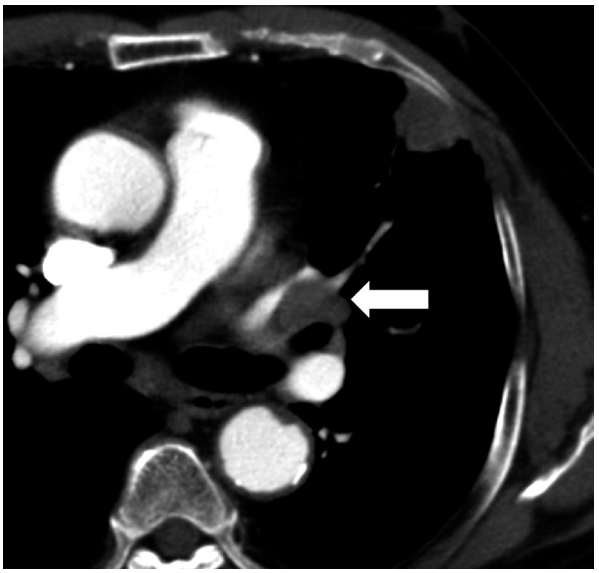

**Fig. 2b.** Multidetector computed tomographic angiography reveals left hilar lymphadenopathy with external compression on the left pulmonary artery

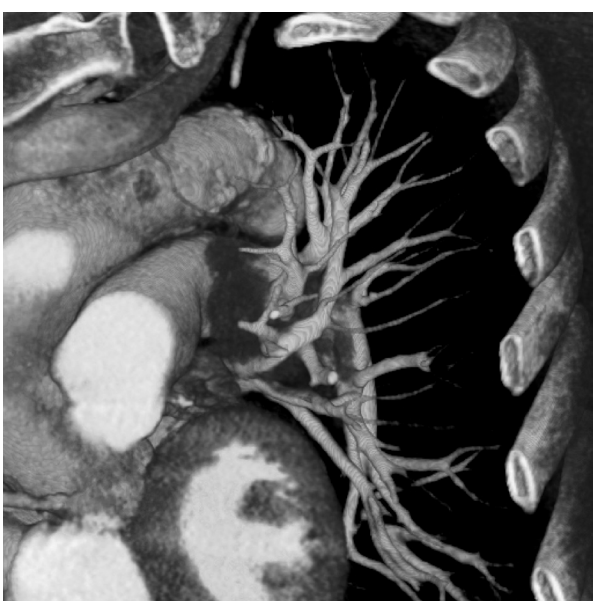

**Fig.2c.** 3D volume rendering reconstruction

ed lung biopsy from the peripheral lung lesion proved small cell carcinoma.

## Discussion

The question of how to diagnose acute pulmonary embolism early and accurately in clinical practice has been discussed during the past decades [1]. Symptoms such as chest pain, dyspnea, tachycardia, fever and hemoptysis are not sensitive or specific enough for diagnosis [2]. The differential diagnosis of pulmonary embolism is extensive, and includes cardiovascular problems, pneumonia, chronic obstructive pulmonary disease, and costochondritis [3], so the early diagnosis of pulmonary embolism is still a challenge. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) in 1990 emphasized the importance of incorporating clinical assessment into the evaluation of patients with suspected acute pulmonary embolism. A combination with ventilation-perfusion scanning would improve the accuracy of diagnosis. But still, about 10% of patients with pulmonary embolism were not diagnosed initially and the disease recurred within 3 months of follow-up [4]. This, then, means that clinical signs combined with other imaging studies and risk factors for venous thromboembolic disease (inherited and acquired factors) would make the diagnosis more accurate. However, those people without typical symptoms cannot be excluded from the diagnosis [3-5].

The Wells' criteria, 1 of the clinical scoring systems that determine the pretest probability (PTP) of pulmonary embolism, help clinical doctors decide what kinds of follow-up tests should be done. The Well's score system, which contains 7 variables, each of which was assigned scores (in parentheses), was used in clinical prediction. The variables and their scores were: clinical symptoms of DVT (3.0), no alternative diagnosis (3.0), heart rate >100 (1.5), im-

mobilization or surgery in the previous 4 weeks (1.5), previous DVT/PE (1.5), hemoptysis (1.0) and malignancy (1.0). The Wells' criteria divide the patients into 3 groups, according to their scores: high (>6), intermediate (2-6) and low (<2) clinical probability for pulmonary embolism. The lower the Wells' scores were, the lower the possibility of pulmonary embolism [6-7]. Blood D-dimer was also used for prediction of pulmonary embolism. The combination of a negative whole blood D-dimer and a Wells' score less than 2 points can be used to exclude pulmonary embolism safely [6-8].

Pulmonary angiography has been a gold standard in the diagnosis of pulmonary embolism, but not all patients can tolerate the procedure. It is an expensive and invasive procedure which requires a large amount of contrast medium and a long examination time. Some complications, like contrast medium intolerance or bleeding, have been reported [9]. CT pulmonary angiography has become the first-line method to confirm or exclude the diagnosis of pulmonary embolism in clinically suspicious patients over the years [10]. The sensitivity and specificity of the single detector CT angiography (CTA) for diagnosing pulmonary embolism varied from 53% to 91% and 78% to 97%, respectively, in a previous report [11]. The CTA criteria for diagnosing pulmonary embolism are similar to the classic arteriographic signs of pulmonary embolism, and include partial or complete filling defects [12]. Two other studies compared the diagnostic accuracy of pulmonary embolism between pulmonary angiography and MDCT pulmonary angiography [13-14]. Qanadli *et al*. reported that the sensitivity and specificity of the dual-section CT were 90% and 97%, respectively, in a study of 157 patients [13]. Winer-Muram *et al.*, also mentioned 100% sensitivity and 89% specificity when using 4-slice MDCT [14]. MDCT pulmonary angiography seemed better than single detector CTA for diagnosing pulmonary embolism. Stein *et al*. reported that the use of MDCT angiography combined with venous-phase imaging in patients suspected of having pulmonary embolism had high diagnostic sensitivity and specificity [15].

In this patient, the conventional chest CT showed a central filling defect of the left pulmonary artery and a peripheral wedge shaped lesion, which were highly suspicious of pulmonary embolism with infarction. Due to the discordance between the CT images and the clinical presentation, MDCT was performed to confirm the diagnosis. Unexpectedly, MDCT showed external compression of the left pulmonary artery by a lymph node rather than there being a clear embolism inside. Compared with conventional CT, MDCT angiography has some advantages in diagnosing vascular disease. It scans faster which decreases the effect of breath-holding time, improves the temporal resolution and decreases the variability with respiration. It has thinner sections that decrease the partial volume and improve the diagnostic accuracy. In providing images of the vasculature, MDCT has faster scanning (shorter acquisition time), which allows us to obtain near isotropic spatial resolution and clear separation between arterial and venous phases, better than conventional CT or single detector CT angiography. Besides, MDCT offers 3-dimensional (3D) volume rendering reconstruction which allows us to observe the vascular structure from different imaging planes [16-17].

## Conclusion

In diagnosing pulmonary embolism, the

combination of clinical assessment, D-dimer, risk factors of venous thrombosis and imaging studies leads to a more accurate diagnosis. If the symptoms and imaging studies are discordant, MDCT pulmonary angiography combined with venous-phase imaging can be used to exclude inaccurate diagnoses.

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# 小細胞肺癌合併肺門淋巴結—仿造急性肺栓塞

陳克旻　楊宗穎　許正園

一位69歲的男性，這幾個月來因為感覺胸口悶及呼吸急促，而住院做檢查。胸部X光片顯示在左邊的肺中葉有個毛玻璃樣的病灶；胸部電腦斷層檢查（CT）顯示左邊的肺動脈有部分的顯影缺損及週邊楔形實質化病變。由影像的變化，高度懷疑為急性肺部血管栓塞合併肺梗塞。由於臨床症狀和電腦斷層圖像不一致，多探頭斷層攝影（MDCT）肺血管造影被安排檢查並且顯示了左邊的肺動脈有部分的顯影缺損其實是左門的淋巴結病向外壓迫到左邊的肺動脈，仿造肺栓塞(非真正的肺栓塞)。在超音波的導引下經胸廓的肺切片檢查，證實為小細胞肺癌。*(胸腔醫學* ***2010; 25: 322-327)***

關鍵詞：肺栓塞，肺血管攝影，多探頭斷層攝影（MDCT）肺血管造影

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# Malignant Thymoma-Related Agranulocytosis Resolved after Thymothymectomy

Chun-Chien Wang, Tsung-Ying Yang, Cheng-Yen Chuang*, Jeng-Yuan Hsu

Thymoma has been associated with many kinds of paraneoplastic syndromes, the most common of which is myasthenia gravis. Hematological abnormalities such as pure red cell aplasia, hypogammaglobulinemia, and thrombocytopenia can be seen sometimes, but agranulocytosis is a rare condition associated with thymoma. We examined a 47-year-old woman with thymoma who complained of fever, chills and sore throat that had persisted for 4 days. Recurrent febrile neutropenia episodes were noted with an initial peripheral absolute neutrophil count of zero. A bone marrow biopsy revealed moderate myeloid hypoplasia. Antibiotics and granulocyte colony-stimulating factor (G-CSF) were prescribed. The neutropenia improved with the administration of G-CSF, but not with radiotherapy. Thymothymectomy, following radiotherapy, was performed and no further neutropenia was reported. ***(Thorac Med 2010; 25: 328-333)***

Key words: malignant thymoma, agranulocytosis, thymothymectomy

## Introduction

With an overall incidence of 0.15 per 100,000 person-years, malignant thymoma was considered to be a rare neoplasm in the United States [1]. Thymoma can be associated with various autoimmune disorders, such as myasthenia gravis, pure red cell anemia, oral lichen planus and other hematological abnormalities [2]. An immunodeficiency associated with thymoma was first described by Robert Good in 1954, and was subsequently known as Good syndrome [3]. Good syndrome is a thymoma with hypogammaglobulinemia, which is associated with recurrent infections with encapsulated bacteria, fungi and viruses due to immunodeficiency [2, 4]. However, thymoma with agranulocytosis is a rare condition. Few cases have been mentioned in previous reports [5-12]. We herein describe a patient with thymoma presenting with recurrent neutropenic fever. Her absolute neutrophil count (ANC) was zero on first admission. The neutropenia did not improve significantly with radiotherapy, but resolved with thymothymectomy.

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## Case Report

A 46-year-old woman had a past history of iron deficiency anemia and thalassemia. She was hospitalized after 4 days of intermittent fever, chills and sore throat. A physical examination revealed blood pressure: 146/79 mmHg, heart rate: 129 beats per minute, respiratory rate: 18 per minute, body temperature: 38.5°C, and oral candidiasis. Laboratory examinations showed microcytic anemia and agranulocytosis: white cell count 1000/cumm (lymphocyte: 60%, neutrophil: 0%, monocyte: 40%), hemoglobin 7.6 g/dl, MCV 67.4 $\mu m^3$, and platelet count 320000/cumm. The C-reactive protein level was high at 19.8 mg/dL (reference range: less than 0.5 mg/dL). Liver and renal function tests were within normal limits, except for a low serum albumin level (2.8 g/dl, reference range: 3.5-5.0 g/dl). Her immunoglobulin levels, including IgG, IgA, IgM, were all within normal limits; the CD4:CD8 ratio was also within normal limits at 0.89 (reference range, 0.8-2.4). The HIV-ELISA test was negative. Antinuclear antigen (ANA) and antineutrophil cytoplasmic antigen (ANCA) were negative. Abdominal sonography showed no significant abnormality except mild splenomegaly. Chest plain film (CXR) disclosed an anterior mediastinal mass and alveolar infiltration in the right lung field (Figure 1). Pneumonia and an anterior mediastinal tumor were suspected. Antibiotics with piperacillin/tazobactum and amikacin were administered for pneumonia. Fluconazole was also prescribed for oral candidiasis with an immunodificient status. Filgrastim, a recombinant human granulocyte colony-stimulating factor (G-CSF), 300 ug, was also given in an attempt to restore the white blood cell count. Two weeks later, a follow-up CXR revealed resolution of the pneumonia patch, but the anterior mediastinal mass was still present. A chest computed tomography (CT) scan showed a heterogeneous mass in the anterior mediastinum (Figure 2). Herpes zoster at the left S2-3 dermatome developed after the pneumonia had resolved. She received intravenous acyclovir for 1 week without significant sequelae. A bone marrow biopsy revealed mildly hypocellular marrow with histiocytosis and moderate hypoplasia of the myeloid series. A real-time sonography-guided cutting biopsy of the anterior mediastinal mass disclosed thymoma, World Health Organization type B3. Surgery was not performed due to the immunocompromised condition and agranulocytosis. Radiotherapy with a dose of 1500 cGy in 5 fractions was given as the first treatment for thymoma. However, episodic neutropenia was noted if no G-CSF had been administrated even 1 month after radiotherapy (Figure 3).

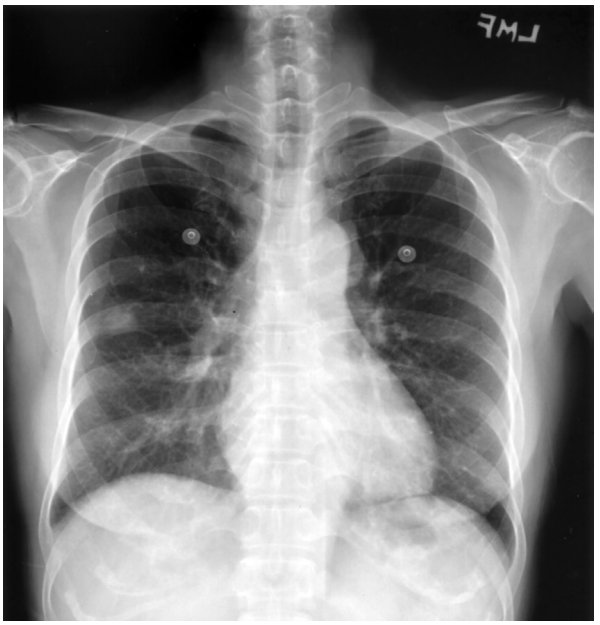


**Fig. 1.** Chest plain film reveals an alveolar patch in the right middle lung field and a mass in the left upper mediastinum.

She received a thymothymectomy after the

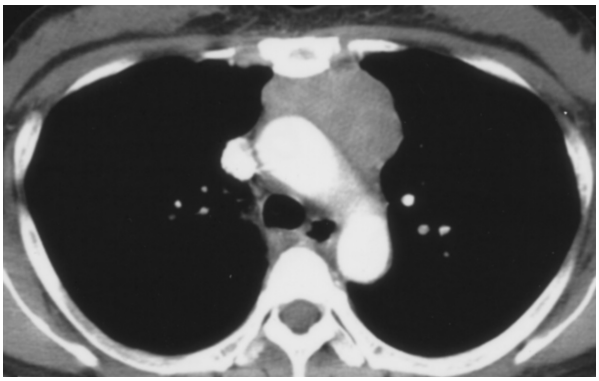
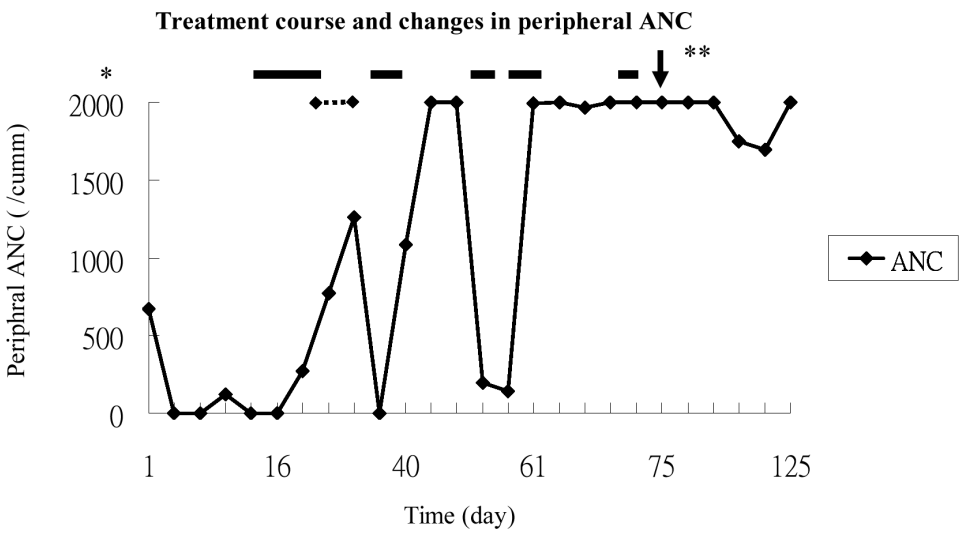


**Fig. 2.** Chest CT shows a heterogeneous mass in the anterior mediastinum

ANC had increased to a normal range with G-CSF support. Pathological findings included tumor invasion of the pulmonary parenchyma and skeletal muscle, adherent to the perivascular soft tissue of the innominate vein. Malignant thymoma, Masaoka's stage III, was diagnosed. She received adjuvant radiotherapy with a dose of 4500 cGy in 25 fractions after surgery. After completion of treatment, she received regular follow-ups for 6 months, which revealed no further neutropenia episodes.

## Discussion

Thymoma is associated with a variety of paraneoplastic disorders. About 40% of patients with thymoma have at least 1 paraneoplastic autoimmune disorder, and myasthenia gravis is the most common [13]. Other paraneoplastic diseases include neurological, hematological, and cutaneous abnormalities, such as neuromyotonia, Lambert-Eaton syndrome, pure red cell aplasia, hypogammaglobulinemia, T-cell deficiency syndrome, lichen planus and pemphigus [13-15].




* Peripheral absolute neutrophil count (ANC) greater than 2000/cumm is shown as 2000/cumm in this figure.
** Arrow shows the day of operation
Thick bar (▬) represents days of G-CSF administration
◆-◆ Time of receiving radiotherapy

**Fig. 3.** The entire treatment course and changes in the ANC level after administration of G-CSF

The commonly seen state of thymoma with immunodeficiency is Good syndrome. It is characterized by hypogammaglobulinemia, low or absent B cells in the peripheral blood, a low level of $CD4^+$ T cells, and an inverted $CD4^+$/$CD8^+$ cell count T-cell ratio [2, 16]. It often presents as a recurrent infection with bacteria, fungi or viruses. Sinopulmonary infections, in which hemophilus influenza, pseudomonas aeruginosa, and Klebsiella spp. are the usual pathogens, are most common. Some frequently seen opportunistic infections are mucocutaneous oral candidiasis, *Pneumocystis jirovecii* pneumonia, herpes zoster, recurrent herpes simplex and CMV infections [2, 17].

Thymoma-related agranulocytosis is a rare hematological condition. Affected patients often suffer from severe infections [5-6, 8, 10], similar to our patient. The cause of agranulocytosis is not known. The treatment for thymoma-related agranulocytosis includes steroids, cyclophosphamide, vicristine, plasmapheresis and thymectomy [6-13]. Alvares *et al*. successfully used monoclonal antibody Campath-1H for thymoma-associated agranulocytosis unresponsive to thymectomy [12]. Palliative radiotherapy was used for the thymoma in our patient, but without a good response in the peripheral white blood cell count. Leukopenia still occurred 1 month later, despite radiotherapy. The agranulocytosis responded to G-CSF administration, so the patient was able to undergo a thymothymectomy. The agranulocytosis was resolved after the thymothymectomy, as was also seen in a case described by Weir AB [10].

G-CSF has been effective in restoring ANC in some patients, but not all. Desmond Yip *et al*. suggested that the thymoma-related agranulocytosis is unlikely to respond to therapy if complete myeloid aplasia is found in a bone marrow examination. However, there is a chance to recover from agranulocytosis after treatment with G-CSF if promyelocyte arrest is noted in a marrow biopsy [5]. In our patient, the bone marrow biopsy revealed moderate myeloid hypoplasia and potential recovery from agranulocytosis after G-CSF administration.

In conclusion, thymoma-associated agranulocytosis is a rare condition with a potentially fatal outcome and often presents as recurrent febrile neutropenia. G-CSF should be used if the bone marrow function is reversed. Surgery could be the method to achieve long-term remission.

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# 惡性胸腺瘤相關之顆粒性白血球缺乏症—經胸腺瘤切除後緩解

王俊傑　楊宗穎　莊政諺*　許正園

胸腺瘤與許多腫瘤附屬症候群相關，其中最常見的是重症肌無力。在胸腺瘤造成的腫瘤附屬症候群中，偶爾可以見到血液系統異常，例如單純紅血球再生不良性貧血、免疫球蛋白低下、血小板減少症，但是胸腺瘤造成的顆粒性白血球缺乏症卻是很罕見的情況。我們報告一位47歲胸腺瘤的女生，一開始以發燒，發冷和喉嚨痛4天來就診。之後反覆發生嗜中性球低下所導致的發燒（febrile neutropenia），而且這位病人一開始周邊血液絕對中性球數目是零。骨髓切片檢查顯示放中度骨髓系列血球發育不全。一開始，我們使用抗生素和顆粒細胞刺激生長因子（G-CSF）作治療。在放射線治療失敗後進行胸腺瘤切除手術。顆粒性白血球缺乏症於胸腺瘤切除後消失，之後再也沒有發現嗜中性球低下所導致的發燒。*(胸腔醫學 **2010; 25: 328-333**)*

關鍵詞：惡性胸腺瘤，顆粒性白血球缺乏症，胸腺瘤切除術

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# Air Crescent Sign: A Rare Presentation of Varicose Bronchiectasis with Hemoptysis

Shan-Yueh Chang, Hsian-Her Hsu*, Chih-Feng Chian, Chien-Wen Chen, Wann-Cherng Perng, Wen-Lin Su

The most common cause of the air crescent sign is aspergilloma resulting from saprophytic aspergillosis. The fungal ball consisting of condensed hyphae can vary in both size and number. Although saprophytic aspergillosis can be asymptomatic, patients may occasionally experience severe, life-threatening hemoptysis. Other causes of the air crescent sign include pulmonary hydatid cysts; lung colonization by other fungi; Rasmussen aneurysms in a tuberculous cavity; lung abscesses; bacterial necrotizing pneumonia caused by *Staphylococcus aureus*, *Klebsiella pneumoniae*, or *Pseudomonas aeruginosa*; and cavitating neoplasm of the lung. Bronchiectasis has not yet been reported as a cause of the air crescent sign. In this paper, we present a case of varicose bronchiectasis complicated with massive hemoptysis; a chest computed tomography (CT) scan of the patient showed the air crescent sign. Clinicians should therefore be aware that while there are several well-known causes of the appearance of the air crescent sign in a chest CT scan, varicose bronchiectasis complicated with severe hemoptysis should be considered as a diagnosis if rapid changes in the image occur during the follow-up period. ***(Thorac Med 2010; 25: 334-340)***

Key words: air crescent sign, computed tomography, varicose bronchiectasis, hemoptysis

## Introduction

The air crescent sign, which appears on a chest radiograph or computed tomography (CT) scan, is crescenteric and radiolucent and is formed when a lung cavity between the normal parenchyma and a round radiopaque mass is filled with air [1]. It may move or remain fixed when the patient's position changes, and may seem to protrude into the cavity like a polyp [2]. The air crescent sign can be visualized in a pulmonary cavitary process, which results from crescent-shaped air lucency interposed between an intracavitary mass and the cavity wall. There are many causes of the air crescent sign, including pulmonary hydatid cysts; fungal infections (especially aspergillosis); Rasmussen aneurysms in a tuberculous cavity; lung abscesses;

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bacterial necrotizing pneumonia caused by *Staphylococcus aureus*, *Klebsiella pneumoniae*, or *Pseudomonas aeruginosa*; and cavitating neoplasm of the lung [3].

Bronchiectasis has not been reported as a cause of the air crescent sign, but intracavitary hemorrhage may produce a similar image. In this paper, we present a case of varicose bronchiectasis complicated with severe hemoptysis; a chest CT scan of the patient showed the air crescent sign.

## Case Report

A 64-year-old-man had symptoms of severe dry cough and sore throat for 2 weeks before admission. Hemoptysis with a large amount of blood clotting followed by fresh bleeding of approximately 200 ml developed 1 day before admission. The patient denied symptoms of body weight loss, fever, chest pain, chest tightness, dyspnea, and arthralgia. He had a history of type 2 diabetes and had been treated with subcutaneous insulin injection for approximately 20 years. End-stage renal disease developed 7 years before admission, and he had been receiving maintenance hemodialysis since then. Pulmonary tuberculosis with pleuritis was diagnosed 3 years before admission, and he had received a full course of anti-TB therapy for 1 year. He also had a history of hypertensive cardiovascular disease and had been under medical treatment for 8 years. Parathyroidectomy was performed 2 years before admission due to tertiary hyperparathyroidism. He had no significant family history and no history of drug abuse or allergy.

On examination, his body temperature was 36.6°C; pulse rate, 72/minute; respiratory rate, 18/minute; and blood pressure, 180/85 mmHg. Petechiae or ecchymosis on the skin, jugular vein engorgement, murmurs, tenderness in the abdomen, and an obvious pitting edema in the bilateral pedal area were all absent. An arteriovenous fistula in the right forearm with a good thrill was observed. All other physical examination findings were normal. The initial white blood cell count was $12.59 \times 10^3/mm^3$ (72.3% neutrophils, 11.8% lymphocytes, 2.3% monocytes, 13.3% eosinophils, and 0.3% basophils); hemoglobin, 9.6 g/dL; MCV, 91.6; and platelet count, $274 \times 10^3/mm^3$. Blood biochemistry findings were as follows: BUN, 70 mg/dL; creatinine, 9.3 mg/dL; sodium, 133 mg/dL; potassium, 4.5 mg/dL; and liver function, normal. The initial chest radiograph revealed patches of airspace consolidation with cavitation in the left upper lobe (Figure 1).

The patient was admitted to an isolation room, since recurrent pulmonary tuberculosis could not be excluded. A sputum culture, an acid-fast smear, and a tuberculosis culture were performed. Empiric antibiotics with ampicillin, sulbactam, and clarithromycin were prescribed for a probable lung abscess. Three consequent sputum specimens for acid-fast smear and bacterial and fungal culture tests revealed negative results. A high-resolution computed tomography (HRCT) of the chest revealed a cavity in the left upper lobe with an intracavitary mass-like soft tissue density surrounded by a rim of air lucency (Figure 2). The specific air crescent sign observed in the CT scan suggested the presence of infectious material, including fungus, bacteria, and mycobacterium. Bronchoscopy showed a considerable amount of blood-coated sputum retained in the left main and segmental bronchus with no visible bleeding spot. A brushing cytology and biopsy were performed at the left upper lobe bronchus (LB3), but no evidence of

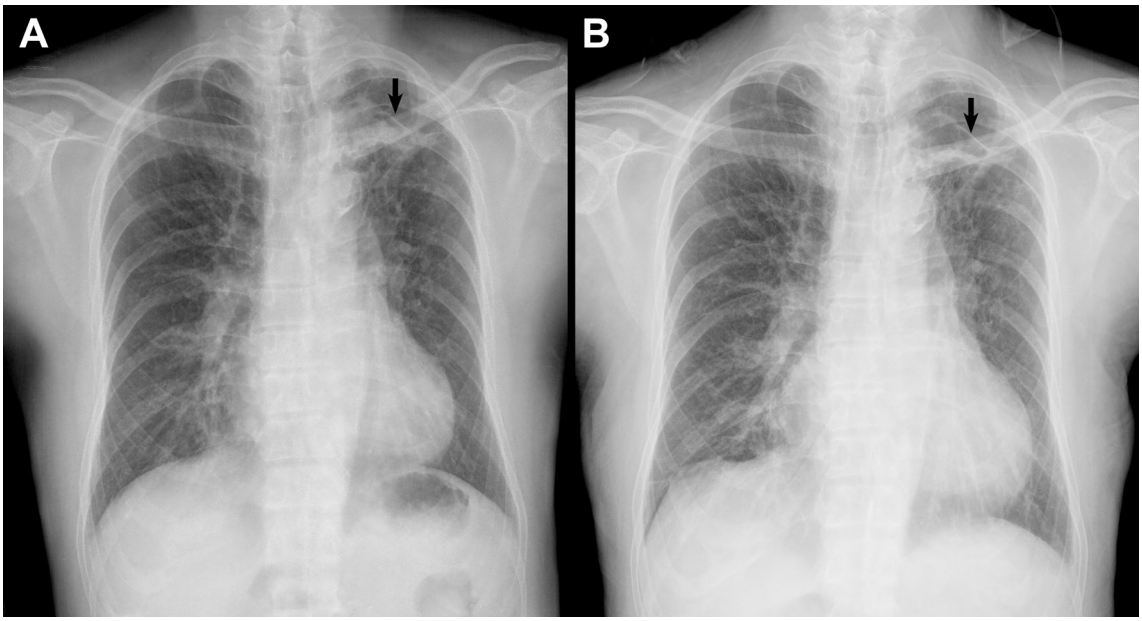


**Fig. 1.** On admission, chest radiography revealed a radiopaque mass-like lesion with surrounding air lucency, suggesting an air crescent sign (black arrow), and some fibrocalcified nodules located at the left upper lobe (A). Seven days after admission, the previous intracavitary mass at the left upper lobe disappeared with only a residual fibrotic scar and thin wall cavity (black arrow) (B).

fungal hyphae, mycobacterium, or malignancy was found. Blood carcinoembryonic antigen (CEA, 2.42 ng/ml (normal range, 0-5)) and squamous cell carcinoma antigen (SCC, 3.40 ng/ml (normal range, 1-1.5)) were within normal limits. By the 7$^{th}$ day after admission, the hemoptysis had improved, and the patchy opacity at the left upper lobe disappeared after the patient expectorated a large amount of blood clot-like material. Follow-up chest radiography revealed a mild residual fibrotic scar and a cavity-like lesion (Figure 1). The patient was discharged 10 days after admission and was followed up regularly in the outpatient department. An HRCT of the chest was performed 6 months after discharge, and the clinical diagnosis of varicose bronchiectasis was confirmed (Figure 2).

## Discussion

A detailed PubMed search of the English literature available on the subject revealed no published cases in which varicose bronchiectasis had led to the appearance of the air crescent sign on a chest HRCT scan. Ours is the first reported patient with varicose bronchiectasis and severe hemoptysis showing the air crescent sign. The clinical symptoms of a large number of blood clots, followed by fresh bleeding of more than 200 ml of blood developed before admission. In adults, bronchitis, bronchogenic carcinoma, and pneumonia are the most common causes of hemoptysis. Other etiologies include pulmonary parenchymal diseases such as bronchiectasis, and vascular diseases, approximately 30% of which are cryptogenic.

The air crescent sign, also called the meniscus or cap sign, can be found in the pulmonary cavitary process, and is often associated

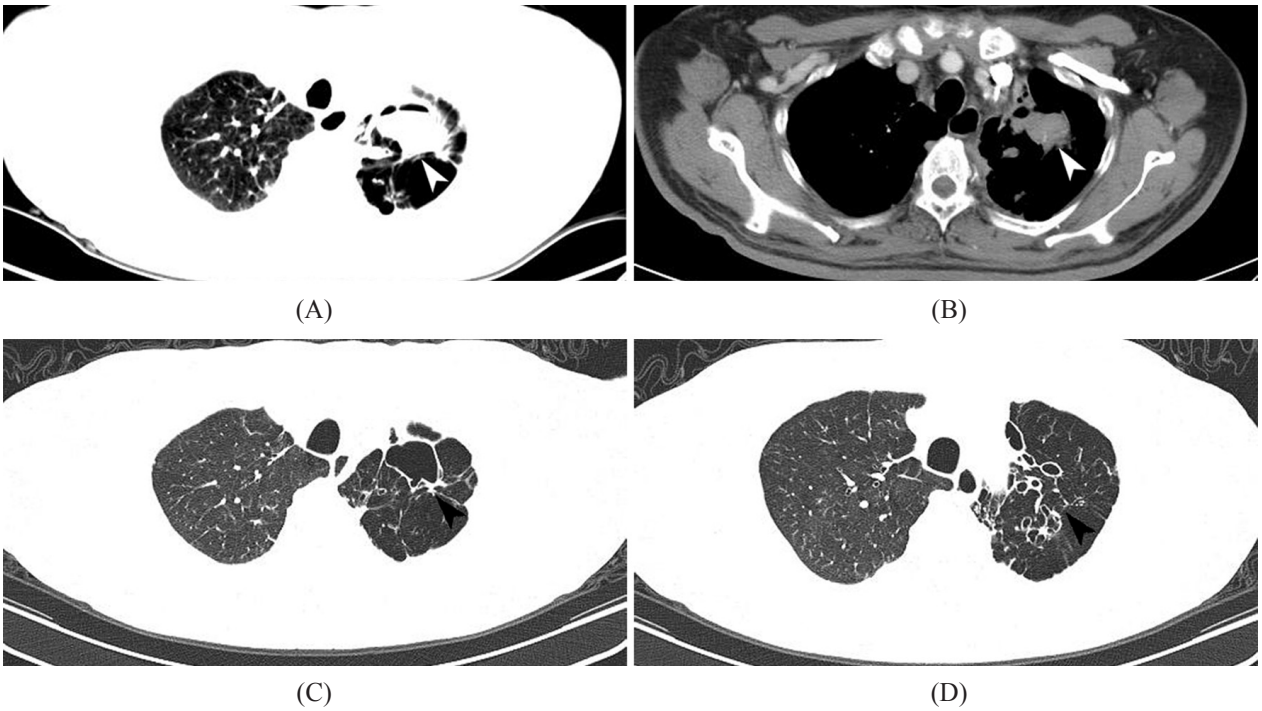


**Fig. 2.** Contrast-enhanced CT of the chest showed an air crescent between the central mass and the thin wall cavity (white arrowhead) without obvious pleural thickening at the lung window (A). The mediastinal window showed a lobulated mass at the left upper lobe (white arrowhead) (B). HRCT of the chest obtained 6 months after discharge revealed cyst-like air lucency with surrounding wall thickening (black arrowhead) at the left upper lobe (C), and dilated, beaded airways with wall thickening (black arrowhead) (D). Both were compatible with varicose bronchiectasis at the left upper lobe.

with ischemic necrosis and thrombosis due to the angio-invasive nature of the fungus infection, followed by infarction at the center of the consolidation. Its shape ranges from crescent-like to that of total encapsulation on an HRCT of the chest, and is characteristic of invasive pulmonary aspergillosis in appropriate clinical situations, such as hemotologic disorders (leukemia, lymphoma) and bone marrow or other organ transplants [4]. When the air crescent sign appears on a chest HRCT scan, it is usually the result of a complication of necrotizing pneumonia or even pulmonary gangrene, which often occurs in patients infected with *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, polymicrobial anaerobes, *Mycobacterium tuberculosis*, and *Aspergillus* species [3]. None of the typical presentations of necrotizing pneumonia, such as high fever, productive cough, and leukocytosis, were found in our patient. The air crescent sign may also be found in cavitating neoplasm, pulmonary tuberculosis, bacterial lung abscesses, and hydatid cysts. The most common underlying causes of the saprophytic aspergillosis-related air crescent sign are tuberculosis and sarcoidosis [5]. Other diseases that may occasionally be related to the cavity of the air crescent sign are bronchogenic cysts, pulmonary sequestration, and pneumatoceles post-*Pneumocystis jirovecii* infection in immunocompromised hosts [6]. Although the air crescent sign may be indolent and without obvious symptoms, it may also occur with hemopty-

sis and may sometimes be fatal.

Bronchiectasis involves permanent and abnormal dilation of the bronchi, often occurring secondary to chronic airway inflammation and infection [7]. There are many etiologies of bronchiectasis, but we may consider these as risk factors rather than definitive causes. Mucociliary disorders (Kartagener's syndrome, Young's syndrome), immune disorders (hypogammaglobulinemia, allergic bronchopulmonary aspergillosis), rheumatic disease (rheumatoid arthritis), alpha 1-antitrypsin deficiency, and chronic obstructive pulmonary disease are other important risk factors for bronchiectasis [8]. There is a long history of frequent lower respiratory tract infections in patients with bronchiectasis, and hemoptysis is also common. HRCT has become the gold standard for a definite diagnosis of bronchiectasis [9]. Varicose bronchiectasis is characterized by focal constrictive areas along the dilated airways resulting from defects in the bronchial wall [8]. If life-threatening hemoptysis occurs, interventional radiology with embolization of the supported bronchial artery can be performed [10].

The most well-known cause of the air crescent sign, saprophytic aspergillosis with aspergilloma formation in a previously-existing cavity, was not considered in this case for the following reasons. First, the multiple sputum cultures, fungal cultures, and bronchial brushing cytology showed negative results for *Aspergillus* spp. Second, the first choice of treatment for aspergilloma is surgical intervention [11]. Medical therapy with itroconazole is commonly used as an adjunctive therapy after surgical resection [6]. In our case, although the patient did not receive the abovementioned treatment, the air crescent sign resolved within 7 days. According to the laboratory report and the clinical course, it is less likely that the air crescent sign was produced by aspergilloma. Thus, in the present case, the air crescent sign observed on the chest CT scan may have been caused by an intracavitary hemorrhage in obscured varicose bronchiectasis, and its rapid changes may be related to the removal of blood clots after hemoptysis.

In conclusion, clinicians should be aware that while there are a number of possible causes for the appearance of the air crescent sign on a chest CT scan, varicose bronchiectasis with hemoptysis should be considered as a diagnosis when rapid changes occur during the follow-up period. Consequently, monitoring a series of chest radiographs is mandatory during treatment to avoid misdiagnosis. As the lesion detected by chest X-ray film overlaps with the left clavicle and posterior ribs, a follow-up chest CT scan should be necessary to rule out fungus colonization in the bronchiectatic cavity, complicated by blood clot formation during massive hemoptysis.

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# Air crescent sign—支氣管擴張症合併咳血之罕見表現

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當影像學上出現Air crescent sign最常見的原因就是麴菌感染後形成麴菌球。麴菌球的成因是由許多菌絲聚集而成，通常不會造成明顯的症狀，但有些病人仍可能會以致命性的咳血來表現。其他可能造成air crescent sign的原因包括胞蟲囊體、其他黴菌感染、產生於之前結核病空洞中的血管瘤（Rasmussen aneurysm）、肺膿瘍、因金黃色葡萄球菌、綠膿桿菌或克雷白氏肺炎桿菌造成的壞死性肺炎、合併開洞表現之惡性腫瘤等疾病。支氣管擴張症合併嚴重咳血，過去並未曾被報導會在影像上呈現air crescent sign之變化。我們提出一位病患因支氣管擴張症合併嚴重咳血，而在胸部電腦斷層影像上呈現了air crescent sign。此病例可提醒臨床醫師，雖然臨床上有許多常見原因會導致電腦斷層影像上呈現air crescent sign，一旦發現病人影像上有air crescent sign且合併嚴重咳血，但在影像上卻有異乎尋常的快速變化時，除了考慮常見的鑑別診斷外，也應考慮病人可能有潛在的支氣管擴張症之問題。*(胸腔醫學* ***2010; 25: 334-340)***

關鍵詞：Air crescent sign，電腦斷層，支氣管擴張症，咳血

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