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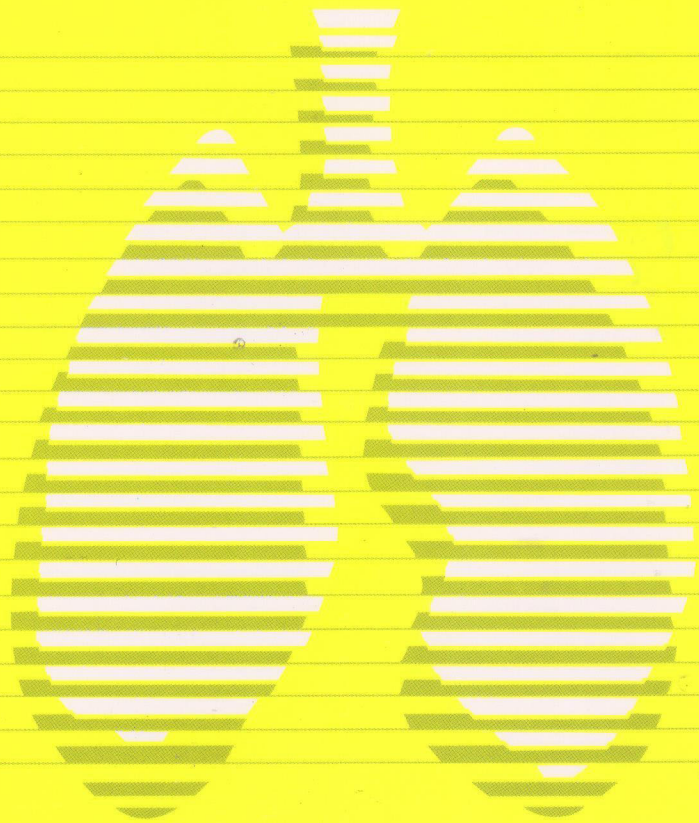

台灣胸腔暨重症加護醫學會

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原著

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Orginial Articles

Case Reports

Palliative Metallic Stent Deployment for Advanced Esophageal Cancer with Airway Invasion

Ching-Yang Wu, Yun-Hen Liu, Hsien-Kun Chang*, Ming-Ju Hsieh, Yi-Cheng Wu, Yen Chu, Hui-Ping Liu, Po-Jen Ko

Background: To determine the clinical roles of metallic airway stents emplaced via rigid bronchoscopy in patients with malignant airway lesion caused by esophageal cancer.

Method: Seventeen patients with malignant airway lesions caused by esophageal cancer were treated by placement of 23 expandable stents (19 airway, 4 esophagus). The clinical evaluations and assessments were completed in all patients.

Result: The procedures were successful in 16 cases. Improvements in dyspnea were achieved in 88% of the patients (15 of 17 patients). The 30-day mortality rate was 18% (3 of 17 patients). The mean survival times were 85 days (5 to 262 days). Seven patients died due to hemoptysis and 9 died with pneumonia and respiratory failure.

Conclusion: The placement of the expandable nitinol stent via rigid bronchoscopy is feasible and effective in achieving a patent airway, relieving dyspnea, and improving the quality of life. ***(Thorac Med 2006; 21: 478-484)***

Key words: esophageal cancer, airway stenosis, tracheoesophageal fistula, airway stent

Introduction

The life expectancy of patients with airway invasion by esophageal cancer is short, the objective of treatment is to provide the best quality of life until the end of the life [1-3]. The metallic airway stent can prevent obstruction caused by tumor ingrowth within the stent lumen, and is widely accepted among many physicians. However, complications of migration, tumor ingrowth, fistula, stent fracture, and hemoptysis have been reported [4-6]. This study reports the results of our experience in using a rigid bronchoscope and metallic stent in patients with malignant airway lesion caused by esophageal cancer. The major goals of this study were to determine the technical and clinical efficacy, clinical course, and survival of these patients.

Materials and Methods

Between January 2002 and May 2004, 17 consecutive patients with inoperable malignant airway lesions caused by esophageal cancer were treated (16 men, 1 woman; average age, 58.7 y; range, 42-88 years). The lesions were airway

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obstructions in 16 patients, tracheoesophageal fistula (TEF) in 5 patients, and airway stenosis complicated with TEF in 4 patients. The lesions were located in the trachea in 10 patients, in the left main bronchus in 5, and in the trachea and main bronchus in 2 patients. Fifteen patients (88.2%) received chemoradiotherapy, 13 (76.5%) before the stent placement and 7 (41%) after. 5 patient received chemoradiotherapy prior and after the procedure. The consent was obtained from all patients before the procedures.

Pre-operative assessment of airway stenosis included panendoscopy, flexible bronchoscopy, and conventional CT scan with 2-D and 3-D reconstruction images. The grade of the obstructions was quantified visually during operation. The length of the stenosis was determined from the 3D reconstruction images, or alternatively, during surgical intervention. For tracheobronchial stenosis, we used self-expanding metallic stents (Covered Ultraflex Airway Stent System, Microinvasive, Boston Scientific Co, Boston, MA) to prevent tumor ingrowth and the recurrence of airway stenosis. For esophageal stenosis combined with TEF, we generally used the Ultraflex airway stent, because only the airway stent is covered by health insurance in our country. The covered esophageal stent was used in 2 patients, however, per their request. In situations of a new TEF occurring after placement of the first stent, we emplaced a second stent (in a different location) or treated the patients conservatively, depending on the patient's general condition.

The procedures took place in the operating room. For tracheobronchial stenosis, the patient was placed in the supine position and general anesthesia was administered in the form of short-acting narcotics and opioid analgesic agents. After adequate sedation, the team introduced the rigid bronchoscope to assess the severity and locations of airway obstruction. The beveled tip of the Dumon scope (Novatech; Aubagne, France) was introduced to dilate the stenotic region and core out the endoluminal tumor. The Ultraflex airway stent was then introduced into the stenotic segment to keep the airway patent. In case of malpositioning after stent deployment, the stent could be manipulated to the best position under direct observation. The stent was dilated with a rigid bronchoscope if the stent expansion was less than 50% of the diameter of the unconstrained stent ends. In contrast, the esophageal metallic stents were placed under local anesthesia. All the stenting procedures were monitored under video endoscopy, which allowed accurate deployment of the Ultraflex stent. The patients were sent to the intensive care unit for further post-operative management. The outcomes were evaluated immediately after the procedures, and included: (1) successful and unsuccessful stent implantation, (2) clinical improvement, (3) complications after stent implantation, and (4) patient survival time. (Table 1)

Adequate nutritional support is an important aspect of management in the palliative treatment of esophageal cancer. Enteral nutrition was delivered via either a nasogastric (NG) tube, nasojejunal (NJ) tube, or surgically placed jejunostomy tubes, based on the patient's condition and technical difficulty.

Results

In this study, 23 covered Ultraflex stents (19 airway stents, 4 esophageal stents) were used. Airway stent sizes were as follows: 4 cm × 14 mm (n=6), 6 cm × 14 mm (n=1), 8 cm × 18 mm (n=11), and 8 cm × 20 mm (n=1). The esophageal stent size was 15 cm × 23 mm (n=4). In 2 cases, 2 airway stents were needed because of the malig-

Table 1. Clinical Data and Treatment Outcome of 17 Patients (under Prognosis, "deceased" would be better than "dead".)

No	Age	Location	Length/ Grade	T-E fistula (pre/ post)	CCRT (pre/ post)	Stent (mm)	Stenting	Improved	Complication	Prognosis
1	57	Lower	4 cm /Gr. 4	- / +	+ / +	18x80*	Success	Yes	Pneumonia UGI bleeding	246 days (Dead)
2	88	Left main	5 cm /Gr. 3	+ / -	- / -	16x60*	Success	Yes	Pneumonia	8 days (Dead)
3	43	Left main	4 cm /Gr. 4	- / -	+ / -	14x40*	Success	No	Pneumonia Hemoptysis	18 days (Dead)
4	72	Middle	3 cm /Gr. 3	- / -	+ / +	18x80*	Success	Yes	Pneumonia Hemoptysis	46 days (Dead)
5	46	Left main	4 cm/Gr. 4	- / -	+ / -	14x40*	Success	Yes	Pneumonia Hemoptysis	43 days (Dead)
6	50	Middle/ lower	6 cm/Gr. 4	- / -	- / +	18x80*	Success	Yes	UGI bleeding, Hemoptysis	39 days (Dead)
7	43	Middle/ lower	6 cm/Gr. 3	- / -	+ / -	18x80*	Success	Yes	Pneumonia	85 days (Dead)
8	55	Left main	2 cm/Gr. 3	+ / -	+ / -	14x40*	Success	Yes	Pneumonia	114 days (Dead)
9	70	Lower/ bil. Main	2 cm/ Gr. 3 3 cm/Gr. 4	- / +	+ / -	14x40* 18x80*	Failed	No	Pneumonia	5 days (Dead)
10	54	Lower	2cm/ Gr. 1	+ / +	+ / +	18x80*	Success	Yes	Pneumonia	246 days (Alive)
11	66	Middle/ lower	6 cm/ Gr. 4	- / -	- / +	18x80*	Success	Yes	Pneumonia	66 days (Dead)
12	52	Lower	6 cm/ Gr. 3	- / -	- / -	18x80*	Success	Yes	Pneumonia	31 days (Dead)
13	76	Left main	3 cm/ Gr. 1	- / -	+ / +	14x40*	Success	Yes	Pneumonia Hemoptysis	50 days (Dead)
14	62	Middle	5 cm /Gr. 3	- / +	+ / +	18x80* 23x150†	Success	Yes	Pneumonia	262 days (Dead)
15	42	Upper	5 cm /Gr. 4	- / +	+ / -	20x80* 23x150†	Success	Yes	Pneumonia	107 days (Dead)
16	53	Lower	3 cm/Gr. 0	+ / +	+ / -	18x80* 23x150†	Success	Yes	Pneumonia Hemoptysis	53 days (Dead)
17	70	Lower/ r't main	2 cm/ Gr. 2 3 cm/ Gr. 3	+ / -	+ / -	14x40* 18x80* 23x150†	Success	Yes	Pneumonia Hemoptysis	34 days (Dead)

*: airway stent; †: esophageal stent

nant stricture involved in the lower trachea and main bronchus.

Stenting was successful in all 17 patients, except 1 with severe carinal, left, and right main bronchus stenosis. Fifteen patients showed respiratory status improvement after stent placement. Of the 14 patients who survived more than 30 days after the procedure, 10 (71%) were discharged from the hospital with a stable respiratory status, and 4 (29%) received supportive treatment and died in the hospital.

Intraoperative complications were observed

in 1 of the 17 patients (5.8%). In this patient, critical airway perforation occurred along the left main bronchus, as noted while coring out the left main endobronchial lesion, and was probably caused by necrotic esophageal cancer entering the wall of the left main bronchus. After meticulous evaluation of the airway status, the perforation was found to be too large, so it was not possible to stent it. Five days later, the patient died with complications of respiratory failure.

Of the 12 patients who had no fistula at the time of placement of the first airway stent, a fistula was detected in 3 patients (27.2%) at 12, 75 and 200 days after stent implantation. The first 2 patients received an airway stent to seal the fistula. Both patients showed clinical improvement and relief of respiratory symptoms, but died 95 days and 187 days (mean 141 days) after the second airway stent. The other patient was treated conservatively because of a generally poor condition and short life expectancy. The 5 patients complicated with TEF before stent insertion all received airway stents. The TEF were successfully closed in 4 patients, and 1 patient died with respiratory pneumonia 8 days later. The TEF was developed in 3 of 4 patients at 20, 45, and 246 days after stent insertion. The first 2 patients received a covered esophageal stent, but both patients died with aspiration pneumonia and respiratory failure at 8 and 14 days (mean 11 days). The remaining patient received a feeding jejunostomy, and he was still alive at this writing.

Fourteen (82.4%) patients with dysphagia symptoms required an esophageal stent (n=4), NG tube (n=7), or surgically placed jejunostomy tubes (n=4) to palliate the dysphagia and facilitate enteral feeding. Three of 4 patients in the esophageal stent group who were intolerant of enteral nutrition resumed feeding via the feeding jejunostomy tube. All patients in both the (NG) tube and surgically placed jejunostomy tubes group successfully tolerated enteral nutrition. One patient had wound dehiscence requiring surgical intervention.

During the follow-up period, all patients (100%) had repeated pneumonia that required admission and further management. Two patients (11%) had UGI bleeding, and 7 (41%) had massive hemoptysis. In 4 of 7 patients (57%) with left and right main bronchus lesions, the hemoptysis occurred at 18, 34, 43, and 50 days. In 3 of 10 patients (30%) with a tracheal lesion (1 middle, 1 lower, and 1 middle/lower), the hemoptysis occurred at 39, 46, and 53 days. All patients passed away within a few hours after massive hemoptysis.

Concurrent chemoradiotherapy was performed in 7 of 14 patients who survived more than 30 days after stent placement. The median survival for patients who underwent concurrent chemoradiotherapy was 136 days (range, 39 to 262 days), compared with 67 days (range, 31 to 114 days) for those who had not received concurrent chemoradiotherapy ($p = 0.318$).

Follow-up was completed in 17 patients. The average follow-up duration was 85 days (range, 5 days to 262 days). Sixteen patients had died at this writing. Three died within 30 days after stent placement, yielding a 1-month mortality rate of 17.6%. One patient (6%) was alive at the completion of follow-up, with an average survival of 85 days (range, 5 days to 262 days). Survival rates were 82.4% at 1 month and 41% at 2 months.

Discussion

Tracheal invasion by cancer is a critical complication for many esophageal cancer patients. It may result in significant obstruction of the trachea with or without an esophagorespiratory fistula.

The treatment is dependent on the severity of respiratory distress symptoms and the extent of luminal involvement of the airway. Endotracheal intubation is the only option when bronchoscopic therapy is not available. The bronchoscopic therapeutic procedures (core out, balloon dilatation, laser therapy, electrocautery, cryotherapy, argon plasma coagulation [APC], endobronchial irradiation, and airway stent) are effective palliative modalities. Wood *et al*. studied 143 patients who underwent airway stenting and reported a significant improvement of 94% (in 94% of patients [7]. Cavaliere *et al*. described a series of 2008 patients with malignant airway. [5] There were good post-operative results in 93% of patients. At our institution, 15 (88%) of the 17 patients had an improvement of symptoms.

The main goal of treatment of inoperable esophageal cancer is to provide enteral nutrition. The conventional palliative therapy for dysphagia with unresectable esophageal cancer required a surgical bypass conduit, but was complicated with high mortality at the time of surgery [8]. Endoscopic palliative treatments for malignant dysphagia include: simple endoscopic dilation of the stricture, laser therapy, and the placement of stents. Stents have the characteristic of allowing a rapid improvement in the swallowing function in comparison with other therapeutic modalities, and are becoming the main means of palliating inoperable malignant stenosis or esophageal fistula. [1,9] In the present series, the benefits and burdens of therapeutic modalities, including surgical bypass, esophageal stent, jejunostomy, gastrostomy, and simple NG feeding, were discussed with the patients. Only 4 patients (23.5%) chose to receive an esophageal stent because of the high cost. Thirteen patients (82.4%) underwent enteral feeding via NG (insertion with the assistance of an endoscope) or a feeding jejunostomy tube. All patients at our institution tolerated enteral feeding. We feel that either NG feeding or feeding jejunostomy is a safe, technically feasible, and useful option for nutrient support in patients with malignant dysphagia.

Patients with malignant TEF usually have a short life expectancy. Control of persistent aspiration and relief of the dyspnea symptoms are the main goals. With an endoscopic procedure, the success rate (closure of the fistula, relief from symptoms of aspiration) after esophageal stenting ranged from 67% to 100%. In our series, airway stent placement was performed as a first treatment, not only for financial reasons, but also because of the associated respiratory symptoms. The stent was successful in sealing the TEF in 4 (80%) of the 5 patients. The results are comparable with those reported in the literature.

Freitag and coworkers inserted an esophageal tube combined with a dynamic airway stent in 30 patients in whom either a tracheal or an esophageal stent failed to seal the fistula, and advocated double stenting as a good option [10]. Taal reported the complete relief of symptoms in 40% and reduction of symptoms in 54% of patients [11]. However, Nomori reported the high risks of enlargement of the fistula with this action [3]. In the present series, 4 patients with TEF were treated with double stenting. The patients with a fistula after airway stent placement were associated with a short survival (mean survival: 11 vs. 141 days). We suggest that patients with TEF after airway stent placement should be followed clinically and treated conservatively. Insertion of the second stent should be reserved for patients with fistula after the esophageal stent.

Life-threatening complications, including hemorrhage, fistulization, perforation, and tracheal compression, occurring in 23.2% of patients with esophageal stent, was reported by Wang [12]

Another researcher reported complications (increased secretion, stent fractures, hemoptysis, and migration or expectoration of airway stents) occurring in 0 to 18% of patients [13]. In our series, massive hemorrhage occurred in 41% of patients, and stent-related perforations and fistulas were detected in 6 patients. All of these suggest a difficult disease in nature.

One study showed a benefit for pre-operative chemotherapy and radiotherapy in 113 esophageal patients [14]. However, other randomized trials failed to demonstrate any survival benefits [15-16]. Survival durations have been reported to be 35 to 121 days after airway stenting. In the present study, the mean survival was 85 days. The concurrent chemoradiotherapy undergone by some of our patients seems associated with their longer survival. With this small number of patients, no statistical significance was noted. We believe that longer survival is related to receiving adjuvant therapy.

This study shows the important palliative role that stenting can have in esophageal malignancies with airway lesions. We believe our patient's quality of life improved markedly after the stents were inserted. With the successful relief of the airway stenosis and closure of the TEF, the patient's respiratory symptoms improved significantly. However, massive hemoptysis was the main cause of death in this extremely difficult disease.

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食道癌合併氣管侵犯之支持性金屬支架置放經驗

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背景：探討經硬式支氣管鏡置放之金屬支架在食道癌合併氣管侵犯的治療角色。

方法：在十七位食道癌併氣管侵犯的病患中，共置放了二十三個金屬支架（十九個氣管支架，四個食道支架）。回溯性的分析治療成果及相關的併發症。

結果：共有十六位病患得到滿意的成果。有 88 % 的病患（15/17）在呼吸急促上有顯著改善。有三位病患在術後三十天內死亡（18 %）。平均存活時間為八十五天（5~262 天）。有七個病患因咳血而死亡,此外有九個病患因肺炎及呼吸衰竭而死亡。

結論：在治療食道癌合併氣管侵犯上，經硬式支氣管鏡置放金屬支架可有效的維持氣道通暢並改善病患的生活品質。*(胸腔醫學* ***2006; 21: 478-484)***

關鍵詞：食道癌，氣管狹窄，氣管食道瘻管，氣管支架

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Clinical Pictures of 28 Cases with Pathology-proven Cytomegalovirus Pneumonia

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Background: The purpose of this study was to review cases of biopsy-proven cytomegalovirus (CMV) pneumonia in a tertiary medical center in Taiwan.

Patients and Methods: From January 1995 to December 2005, 28 patients with biopsy-proven CMV pneumonia were included in this study. The following data were recorded: demographics, clinical manifestations, radiographic and laboratory findings, histopathology, treatment regimens, and outcome.

Results: The study population consisted of 21 male and 7 female patients, with a mean age of 38.9±13.24 years. All were immunocompromised hosts, including 11 patients with acquired immunodeficiency syndrome (AIDS) and 9 who had undergone hematopoietic stem cell transplants (HSCT). The most frequent clinical manifestations were fever (67.9%), cough (57.1%), and dyspnea (89.3%). Elevated levels of C-reactive protein and lactate dehydrogenase were observed in the majority of patients. The ratio of arterial oxygen pressure over inspired oxygen (PaO_2/FiO_2) at diagnosis was 71.9±27.6 mm Hg. The mean CD4 lymphocyte count was 55±61.2 per μL in the AIDS patients. CMV IgM antibody titers were available in 11 cases only, and were all negative. The predominant high resolution computed tomography findings included ground-glass opacity (53.6%) and air-space consolidation (53.6%). Major histological findings associated with CMV pneumonia were fibrosis (39.3%) and *Pneumocystis jirovecii* pneumonia (PCP) (25%). Twenty (71.4%) patients developed respiratory failure, which occurred in 54.5% and 77.8% of the AIDS and post-HSCT groups, respectively (p=0.28). Nearly all of the patients (88.9%) in the post-HSCT group received combination therapy with anti-viral agents and anti-CMV immunoglobulin (CMVIG). In contrast, all of the patients with AIDS received anti-viral agents only. Treatment for 60% of patients was modified after biopsy. The 28-day survival rate was 53.6%, which was higher in AIDS patients than in post-HSCT patients (81.8% vs. 33.3%, p= 0.028).

Conclusions: CMV pneumonia still carries a high risk of mortality in immuno-compromised patients in Taiwan. Our data suggest that no clinical, laboratory, or radiographic features are reliable indicators for diagnosis, and invasive biopsy procedures are often required for definitive diagnosis. Post-HSCT CMV pneumonia is associated with a higher mortality than AIDS.***(Thorac Med 2006; 21: 485-493)***

Key words: cytomegalovirus (CMV) pneumonia, lung biopsy, acquired immuno-deficiency syndrome (AIDS), hematopoietic stem cell transplantation (HSCT)

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Introduction

Cytomegalovirus (CMV) infection is common in the general population, with a reported sero-prevalence of 40-100% [1]. CMV pneumonia, however, is 1 of the most important opportunistic infections in immuno-suppressed patients [2], with an incidence that varies according to the underlying disease, and is associated with considerable morbidity and mortality [3]. CMV pneumonia is not uncommon in allogenic hematopoietic stem cell transplant (HSCT) or bone marrow transplant (BMT) recipients, with an incidence of around 10%-30% [4] and a high mortality rate (>70%) [5], especially when the diagnosis is not made early and the initiation of treatment is delayed [6].

In contrast, the impact of pulmonary CMV infection in patients with acquired immunodeficiency syndrome (AIDS) is controversial. CMV can be found in the bronchoalveolar lavage (BAL) fluid of these patients without evidence of CMV pneumonia [7]. AIDS patients with CD4 cell counts below 100 per μl remain at high risk for CMV disease despite the significant benefits of highly active anti-retroviral therapy [8]. Progress in the diagnosis and treatment of CMV infections has been achieved in recent years, although significant gaps remain in the understanding of the interactions between the virus and its host, the natural history of the infection, and the biological mechanism of its reactivation. The objective of this study was to review patients with biopsy-proven CMV pneumonia in a tertiary medical center in Taiwan.

Patients and Methods

We reviewed the medical records of all patients with a diagnosis of CMV pneumonia admitted to National Taiwan University Hospital (NTUH) from January 1, 1995 to December 31, 2005. Patients were included only if the diagnosis of CMV pneumonia was confirmed on biopsy, whether it was obtained by open lung biopsy, video-assisted thoracoscopic surgery (VATs), or trans-bronchial lung biopsy (TBLB). The criteria for the histopathologic diagnosis of CMV pneumonia included the presence of cytomegalic intra-nuclear or intracytoplasmic inclusions, or positive immunostaining for CMV in lung tissues.

The following data were recorded: demographics, clinical manifestations, radiographic and laboratory findings, histopathology, and treatment regimens. We also determined the incidence of respiratory failure and the 28-day survival rate in these patients.

Statistical analysis

All of the data were reported as mean±standard deviation (SD) unless otherwise specified. All of the categorical variables were analyzed with *chi*-square tests, except when the small size required the use of Fisher's exact test. Means between the groups were compared by the independent Student's *t* test, Mann-Whitney U test, or Kruskal-Wallis method, as appropriate. The statistical difference between the means was calculated by the Pearson Chi-Square test if the population was Gaussian. Otherwise, the Mann-Whitney U test for testing statistical difference between the medians was used. All of the statistical computations were performed using the SPSS for Windows (version 12.0) software. Statistical significance was a p value < 0.05.

Results

Demographic features

From January 1995 to December 2005, 58

patients were diagnosed with CMV pneumonia at NTUH, but only 28 met the inclusion criteria. The demographic data of these 28 patients are shown in Table 1. The study population was composed of 21 males and 7 females, with a mean age of 38.9 years (range: 19-73 years). All were immuno-suppressed, including 11 cases of AIDS and 9 patients who had undergone hematopoietic stem cell transplants (HSCT).

Clinical and laboratory characteristics

Clinical characteristics are shown in Table 2. Most patients presented with dyspnea (89.3%), while more than half had fever (67.6%) and cough (57.1%). The mean WBC count was 7347±7427.4 per μL, mean hemoglobin 10.2±1.6 g/dl, and mean platelet count 147593±145926.3 per μL. The mean levels of C-reactive protein (CRP) and lactate dehydrogenase (LDH) were elevated. The ratio of arterial oxygen pressure over inspired oxygen fraction (PaO_2/FiO_2) at diagnosis was 71.9±27.6 mm Hg. The hepatic transaminases and total bilirubin levels were slightly elevated. There was mild hypo-magnesemia (0.75±0.2 mM/L). Serum CMV IgG antibody was positive in all 13 cases in which data were available (range: 1:4 dilution to 1:256 dilution). CMV IgM antibody titers were available in 11 cases only, and all were negative.

Table 1. Demographic features

Parameters	
Age, years	38.9±13.24
Sex, M/F	21/7
Comorbidities	
AIDS, n (%)	11 (39.3)
Post-HSCT, n (%)	9 (32.1)
Post-solid organ transplant, n (%)	1 (3.6)
Recent chemotherapy, n (%)	2 (7.1)
Others*, n (%)	5 (17.9)
Biopsy method	
Open lung, n (%)	13 (46.4)
VATs, n (%)	7 (25)
TBLB, n (%)	6 (21.4)
Others, n (%)	2 (7.2)

* including: gastric adenocarcinoma post-surgery 8 days (n=1); hypogammaglobulinemia due to T-cell dysfunction (n=1); usual interstitial pneumonitis (UIP) under prednisolone 40 mg per day for more than one year (n=1); ectopic ACTH syndrome refractory to treatment (n=1); Sjogren's syndrome under prednisolone treatment (n=1)

AIDS, acquired immunodeficiency syndrome; HSCT, hematopoietic stem cell transplant; VATS, video-assisted thoracoscopic surgery; TBLB, transbronchial lung biopsy

Table 2. Clinical and laboratory characteristics

Parameters	
Clinical presentation	
Fever, n (%)	19 (67.9)
Cough, n (%)	16 (57.1)
Dyspnea, n (%)	25 (89.3)
Laboratory findings	
White blood cell /μL	7347±7427.4
Absolute neutrophil count /μL	5989±6493.7
Absolute lymphocyte count /μL	723±1141.3
Hemoglobin, g/dL	10.2±1.6
Platelet count /μL	147593±145926.3
AST, U/L	46.4±44.7
ALT, U/L	34.8±27.6
Total bilirubin, mg/dl	1.7±2.8
Albumin, g/dl	3.2±0.6
Globulin, g/dl	2.8±0.9
Alk-P, U/L	284.2±253.9
rGT, U/L	170.1±262.9
BUN, mg/dl	15.0±6.3
Creatinin, mg/dl	0.8±0.3
Mg, mM/L	0.75±0.2
Lactate dehydrogenase, U/L	1073±1010.9
C-reactive protein, mg/dl	8.25±5.7
Initial PaO_2 /FiO_2, mmHg	71.9±27.6
CMV IgG antibody positive	13/13 (100)
CMV IgM antibody positive	0/11 (0)

PaO_2/FiO_2, ratio of PaO_2 over inspired oxygen fraction

Radiographic and histopathologic features

The predominant findings on high resolution computed tomography (HRCT) were ground-glass opacities (53.6%), air-space consolidation (53.6%), and nodular patterns (17.9%). (Table 3) Other HRCT abnormalities included reticulo-linear fibrosis, pleural effusion, pneumothorax/pneumo-mediastinum/subcutaneous emphysema, or mediastinal lymphadenopathy. The histopathologic features are shown in Table 4. Most biopsy specimens had concurrent findings other than CMV pneumonia, including *Pneumocyctic jirovecii* pneumonia (PCP) (25%), fungal thrombi (10.7%), fibrosis (39.3%), and alveolar hemorrhage (14.3%).

Table 3. Radiographic features in HRCT

Pattern	
Predominant pattern	
Ground glass opacity, n (%)	15 (53.6)
Consolidation, n (%)	15 (53.6)
Nodules opacity, n (%)	5 (17.9)
Combine with other findings, n (%)	23 (82.1)
Linear/reticular fibrosis, n (%)	15 (53.6)
Pleural effusion, n (%)	5 (17.9)
Cysts or bullae, n (%)	3 (10.7)
Free air*, n (%)	8 (28.6)
Lymphadenopathy, n (%)	5 (17.9)

* such as pneumothorax, pneumomediastinum, subcutaneous emphysema

Table 4. Histopathological findings

Parameters	
Simple CMV, n (%)	7 (25)
Concurrent histological findings	21 (75)
PCP, n (%)	7 (25)
Fungal infection, n (%)	3 (10.7)
Fibrosis, n (%)	11 (39.3)
Hemorrhage, n (%)	4 (14.3)

PCP, *Pneumocyctic jirovecii* pneumonia

Treatment

All of the patients received antimicrobial treatment before undergoing lung biopsy, with anti-CMV agents and anti-PCP therapies administered to 7 and 15 patients, respectively. Antimicrobial agents were changed or modified in 16 (57.1%) patients after biopsy. Twenty-three (82.1%) patients received anti-CMV medications, including ganciclovir, foscarnet, and anti-CMV immunoglobulin (CMVIG). Thirteen received monotherapy and the other 10 received combination therapy.

AIDS vs. post-HSCT patients

The age, gender, symptoms, radiographic abnormalities, and treatment regimens did not differ between the 2 groups (Table 6). The AIDS group had higher white blood cell and platelet counts, hematocrit, and hepatic transaminases than the post-HSCT group. The mean CD4 lymphocyte count in the AIDS group was 55± 61.2 per μL. In the post-HSCT group, the median duration between HSCT and diagnosis of CMV pneumonia was 45.6±19.4 days (range: 21-76 days). Two patients in the AIDS group did not receive anti-CMV therapies. In the post-HSCT group, 88.9% of patients received combination

Table 5. Course, treatment and outcome

Adjusted treatment after pathology proof	
Of total, n/28 (%)	16 (57.1)
Of pre-treatment as PCP, n/15 (%)	9 (60)
Treatment	
Antivirals only*, n (%)	13 (46.4)
Combine with CMVIG, n (%)	10 (35.7)
Outcome	
Respiratory failure, n (%)	20 (71.4)
Overall mortality, n (%)	15 (53.6)
28 days survival, n (%)	15 (53.6)

* Antiviral agent, ganciclovir as first-line choice or alternative foscarnet if neutropenia

Table 6. Comparison of CMV pneumonitis in AIDS and post-hematopoietic stem cell transplant recipients

	AIDS group (N=11)	Post-HSCT group (N=9)	*p* value
Age, years	38.2±9.7	28±7.5	0.22
Sex, M/F	10/1	7/2	0.41
Clinical presentation			
Fever, n (%)	10 (90.9)	7 (77.8)	0.41
Cough, n (%)	8 (72.7)	4 (44.4)	0.2
Dyspnea, n (%)	11 (100)	7 (77.8)	0.1
Laboratory findings			
White blood cell /μL	5417±3170.7	3068±4614.5	0.03
Hemoglobin, g/dL	10.6±1.0	9.4±1.2	0.06
Hematocrit, %	32.4±3.6	24.8±8.9	0.009
Platelet count /μL	233400±160426	45111±32173	0.001
AST, U/L	76.1±60.0	29.3±24.0	0.04
Lactate dehydrogenase, U/L	1486.1±1436.9	796.1±365.5	0.34
C-reactive protein, mg/dl	8.0±4.4	5.2±6.3	0.33
CD4 count per μL	55±61.2	NR	-
Radiographic pattern			
Ground glass opacity, n (%)	7 (63.6)	4 (44.4)	0.39
Consolidation, n (%)	5 (45.5)	5 (55.6)	0.65
Nodules opacity, n (%)	1 (9.1)	2 (22.2)	0.57
Combined with other findings	9 (81.8)	6 (66.7)	0.43
Concurrent histopathologic PCP, n (%)	4 (36.4)	0 (0)	0.09
Treatment			
Antiviral agent*, n (%)	9 (81.8)	9 (100)	0.18
Combine with CMVIG, n (%)	0 (0)	8 (88.9)	<0.001
Outcome			
Respiratory failure, n (%)	6 (54.5)	7 (77.8)	0.28
28-day survival, n (%)	9 (81.8)	3 (33.3)	0.028

NR, not recorded; PaO_2/FiO_2, ratio of PaO_2 over inspired oxygen fraction

PCP, *Pneumocystic jirovecii* pneumonia

* Antiviral agent, ganciclovir as first-line choice or alternative foscarnet if neutropenia

therapy with CMVIG; no patients in the AIDS group received CMVIG (p<0.001).

Outcome

Respiratory failure occurred in 20 (71.4%) patients. The 28-day survival rate of patients with CMV pneumonia was 53.6%; survival was significantly higher for the AIDS patients than the post-HSCT patients (81.8% vs. 33.3%, p = 0.028). We used the 28-day survival rate as an outcome measurement because the duration of our antiviral treatment was 21 days. Two patients died 28 days after biopsy due to new episodes of septic shock.

Discussion

In this study, we retrospectively reviewed the clinical features of 28 patients with biopsy-proven CMV pneumonia. Our data suggest that no clini-

cal, laboratory, or radiographic features were reliable indicators for the diagnosis of CMV pneumonia. Furthermore, invasive procedures were often required for optimal diagnosis and management.

The clinical manifestations and radiographic features of CMV pneumonia in this report were compatible with those of previous reports [2]. The initial symptoms and signs were often non-specific and ranged from asymptomatic or mild dyspnea to severe respiratory insufficiency [5]. These patients tended to have sustained fever, non-productive cough, and dyspnea [5]. Common laboratory findings included mild neutropenia, thrombocytopenia, hypo-magnesemia, and elevated liver enzymes [5].

The radiographic findings of CMV pneumonia were also variable and non-specific. The predominant patterns on HRCT were bilateral diffuse ground-glass opacities (43~69%), multiple and small centri-lobular nodules (57~69%), and areas of air-space consolidation (33~59%) [9-12]. It was interesting to note that the incidence of respiratory failure in our patients was 71.4%, which was higher than those reported by Enright *et al.* [6].

Although CMV pneumonia should be suspected in any immuno-suppressed patient with unexplained lower respiratory complaint or pulmonary infiltrates, the definitive diagnosis is often difficult and delayed. The role of invasive biopsy procedures in the diagnosis remains controversial. In a previous report of 35 bone marrow recipients with diffuse pulmonary infiltrates, Wang *et al.* [13] found that the leading diagnoses were idiopathic interstitial pneumonitis (40%) and CMV pneumonia (20%). Treatment was changed in 22 (63%) patients after biopsy, which led to clinical improvement in 16 (46%). In this study, therapeutic agents were modified in 60% of patients after biopsy.

Recent studies suggest that lung biopsy may be safely performed in AIDS and non-AIDS immuno-suppressed patients with febrile pulmonary infiltrates. Moreover, the diagnostic yield from lung biopsy is higher than in BAL [14-15]. These data suggest that invasive procedures are important for the early diagnosis and management of CMV pneumonia.

For patients with unstable clinical conditions not appropriate for invasive diagnostic approaches, the presence of signs or symptoms, combined with the detection of CMV in BAL fluid, is also indicative. Immunohistochemical staining of BAL fluid with anti-CMV antibodies may enhance the sensitivity and specificity of the diagnosis [16]. It was interesting to note that IgM anti-CMV antibody was of no use in the diagnosis of CMV pneumonia in our patients. This might be due to the serologic conversion that is often delayed and may even be absent in immuno-suppressed hosts [2].

Other virology methods for diagnosing acute CMV pneumonia have been reported [17-19], including viral culture with shell vial techniques (sensitivity 68-100%), pp65 anti-genemia assay, and quantitative nucleic acid detection of CMV genes from sample amplification by PCR. Unfortunately, most of these are time-consuming and are rarely performed in hospital laboratories.

One important clinical dilemma often faced in the management of diffuse pulmonary infiltrates in immuno-suppressed hosts is differentiating CMV pneumonia from PCP. Emoto *et al.* reported that the sensitivity and predictive value of HRCT in diagnosing these 2 infections are not satisfactory [20]. In AIDS patients, McGuinness *et al.* found that the spectrum of HRCT findings in CMV pneumonia is broad and clearly overlaps that of other parenchymal diseases, especially PCP [21]. Therefore, we emphasize that tissue

diagnosis by means of biopsy should be undertaken, especially if a patient does not empirically respond to treatment for PCP [21].

Recently, the incidence of CMV pneumonia has been reduced by routine anti-viral prophylaxis in susceptible populations, especially post-HSCT subjects [2]. The prophylactic combination of ganciclovir and CMVIG has been shown to reduce the incidence of CMV disease and death after organ transplantation [22-23]. Some uncontrolled studies using ganciclovir with CMVIG have also shown survival benefit, with mortality rates ranging from 0% to 47% when therapy is initiated before respiratory compromise [2]. In this study, anti-viral prophylaxis (acyclovir) was administered to all of the patients in the post-HSCT group during the first 30 days after transplantation. Nevertheless, our review showed that CMV pneumonia still resulted in significant morbidity and mortality in these patients.

The reasons for prophylaxis or treatment failure were unknown, but might be due to drug resistance or super-infection by other microorganisms. Development of CMV pneumonia despite prophylaxis or pre-emptive therapy was associated with a high mortality rate in BMT recipients [5]. Caution should be exercised in the early diagnosis and treatment of these patients under appropriate clinical settings.

Some limitations of this study need to be addressed. First, the retrospective design was unable to reveal the incidence and impact of CMV pneumonia in patients with immunity deficiencies. Second, the survival analysis of these patients could not be carried out because of the small sample size. Third, since multiple or concomitant pulmonary infections were common in the immuno-suppressed patients, it was difficult to define the real contribution of CMV pneumonia to respiratory failure and mortality.

In conclusion, CMV pneumonia still remains an important cause of morbidity and mortality in immuno-suppressed patients. There are as yet no specific clinical or radiologic features for this infection, although HRCT findings are helpful in narrowing down the differential diagnosis. Invasive biopsy procedures may be essential for the early diagnosis and disease-modifying therapies for these patients.

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組織病理二十八例証實之巨細胞病毒肺炎之病歷研究

蕭瑤娟　郭炳宏　藍仕政　楊泮池

背景：本篇報告回顧分析臺灣某醫學中心切片證實之巨細胞病毒肺炎病例。

方法：本研究收集從 1995 年 1 月至 2005 年 12 月在此醫學中心接受切片証實為巨細胞病毒肺炎者共二十八例，分析其人口學、臨床表徵、影像學、實驗數據、組織學、治療及預後。

結果：此二十八例皆為免疫不全患者，包含十一例後天免疫不全症候群病患及九例骨髓幹細胞移植接受者。最初主要之臨床表徵包括發燒(67.9%)、咳嗽(57.1%)、呼吸困難(89.3%)。多數患者其 C 反應蛋白與乳酸脫氫酶會上升。動脈血氧分壓平均為 71.9 ± 27.6 mmHg 。後天免疫不全症候群患者之平均 CD4 淋巴球數目為 55 ± 61.2/μL 。有偵測血中巨細胞病毒 IgM 抗體之十一位病患其檢驗報告皆呈現陰性。在胸部高解析電腦斷層呈現型態主要有毛玻璃樣病灶(53.6%)與肺泡型病灶(53.6%)。組織學上有 39.3% 合併纖維化，有 25% 合併肺囊蟲肺炎。有二十例(71.4%)產生呼吸衰竭，佔後天免疫不全症候群病患之 54.5% 與骨髓幹細胞移植接受者之 77.8% (p=0.28)。有 60% 的病患於切片診斷後調整治療計劃。巨細胞病毒肺炎之 28 天存活率 53.6% (後天免疫不全症候群病患為 81.8% 、骨髓幹細胞移植接受者為 33.3% (p=0.028))。

結論：巨細胞病毒肺炎在臺灣仍是造成免疫不全病患死亡之高危險因素。本研究發現除了侵入性的切片檢查之外，並無任何臨床、實驗學或影像學的特徵，可以確定診斷巨細胞病毒肺炎。此外，巨細胞病毒肺炎發生在骨髓幹細胞移植接受者上，其死亡率似乎比發生在後天免疫不全症候群患者上要高。*(胸腔醫學* ***2006; 21: 485-493)***

關鍵詞：巨細胞病毒肺炎，肺部切片，後天免疫不全症候群，骨髓幹細胞移植

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Microscopic Polyangiitis Caused by Propylthiouracil in a Patient with Hyperthyroidism — A Case Report

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Chi-Yuan Tzen***, Jen-Tso Hsiao****

he etiology of hemoptysis can be grouped into 3 major categories: disease from the airways, the pulmonary parenchyma, and the pulmonary vasculature. Small vessel pulmonary vasculitis, such as microscopic polyangiitis (MPA), is 1 of the diseases diffusely affecting the pulmonary parenchyma in the presentation of the hemoptysis. Propylthiouracil (PTU) is 1 of the etiologies of MPA with an unclear mechanism. Herein, we describe a woman with PTU-induced ANCA-positive vasculitis who developed pulmonary hemorrhage with respiratory failure and crescentic glomerulonephritis. We initiated mechanical ventilation, and medical treatment, including high-dose steroid pulse therapy and oral cyclophosphamide, and discontinued PTU. Her condition improved and she was discharged. She has been in stable condition without further sequelae.
(Thorac Med 2006; 21: 494-500)

Key words: peri-antineutrophil cytoplasm antibody, propylthiouracil, vasculitides, microscopic polyangiitis

Introduction

Microscopic polyangiitis (MPA) is a rare disease of unknown mechanism, and has been defined as necrotizing vasculitis primarily affecting the small blood vessels [2]. It is characterized by renal failure due to glomerulonephritis and alveolar hemorrhage secondary to pulmonary capillaritis with a strong association with perinuclear-antineutrophil cytoplasm antibody (p-ANCA) [5]. Recently, propylthiouracil (PTU) has been observed to be an offending agent in causing this rare condition [8-10].

Herein, we describe a rare case of PTU-induced p-ANCA-positive vasculitis. In addition, we also discuss the right moment to suspect vasculitis syndrome, as well as how to utilize laboratory tests to make a diagnosis and the possible mechanisms of PTU-induced MPA.

Case Report

A 33-year-old female was admitted to the hospital with fever of unknown origin for 1 month. The fever, accompanied with an observed chilly sensation, was intermittent without characteristic patterns. In addition, weight loss of 3 kg was also noted. There were no displays of dysuria,

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abdominal pain, arthralgia, skin rash, headache, or animal bite. After seeking medical treatment in the outpatient department, symptomatic treatment was given under the impression of upper respiratory infection, but with no effective results. The patient denied any other respiratory symptoms, such as cough, habitual sputum production, wheezing, rhinorrhea and sore throat. She also denied using tobacco and alcohol. The patient suffered from hyperthyroidism, and ha been under medical control for 10 years; the medications included PTU, methimazole, and propranolol.

On physical examination, the patient was pale and ill. The patient's body temperature measured 40°C, the heart rate was 102 beats per minute, the respiratory rate was 18 breaths per minute, and blood pressure was 111/58 mmHg. Her consciousness was clear. A few basilar crackles were heard in both lung fields. The rest of the physical examination results were within normal limits.

The hemogram showed the following results: hemoglobin, 9.1g/dl; hematocrit, 27.3%; white cell count, 8600/μL with 82.1% neutrophils, 0.6% eosinophils, and 13.3% lymphocytes; and platelet count, 344,000/μL. The blood urea nitrogen level was 20 mg/dl and the creatinine level was 1.2 mg/dl. The urine sample showed gross hematuria, and urinalysis revealed numerous dystrophic red blood cells, a white blood cell count of 9 cells/μl, and protein (++). The chest PA film showed no significant abnormality (Figure 1). However, massive hemoptysis with respiratory distress occurred 2 days after the patient's admission. The arterial blood gas analysis showed pH 7.373, pCO_2 24.6 mmHg, pO_2 43.7 mmHg, HCO_3 14 meq, Sat 79.5%, and FiO_2 21%. An oxygen mask with FiO_2 100% was administered and the subsequent arterial blood gas analysis showed pH 7.357, pCO_2 27.3 mmHg, pO_2 43 mmHg, and Sat 77.7%. The patient was then intubated with mechanical ventilatory support due to acute hypoxic respiratory failure and transferred to the medical intensive care unit for close monitoring.

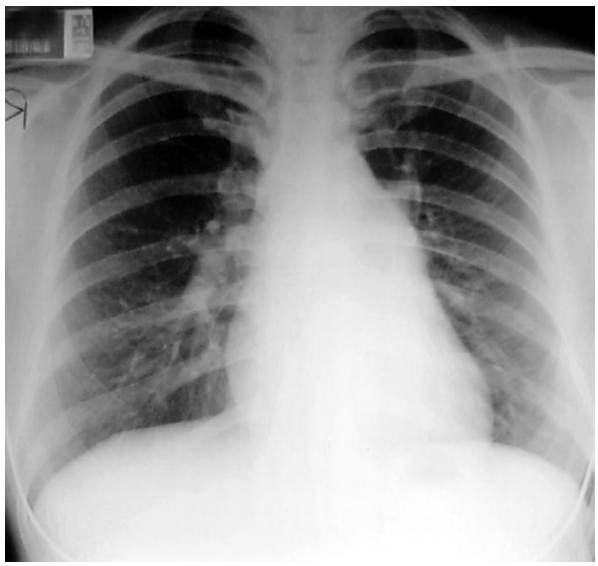

Fig. 1. Chest X-ray, hospital day 1, revealing no significant abnormality.

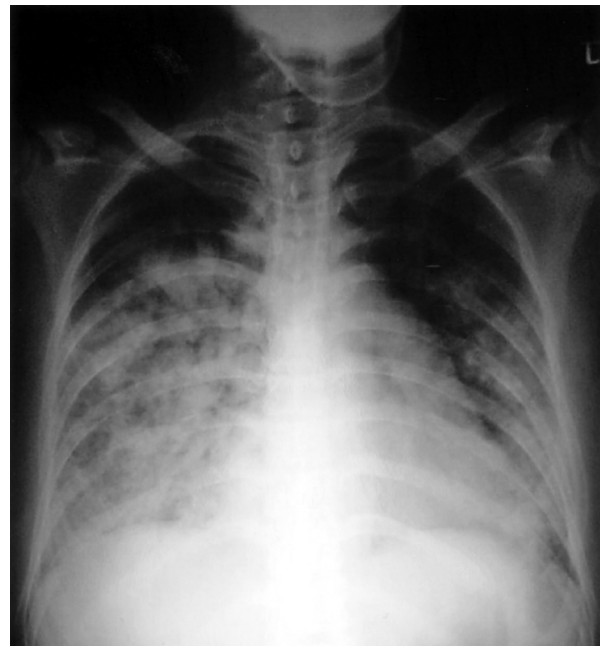

Fig. 2. Chest X-ray, hospital day 3, revealing diffuse alveolar consolidation in the bilateral lower lung field.

The chest X-ray (CXR) taken after intubation revealed diffused alveolar consolidation in the bilateral lung fields (Figure 2). Pulse therapy with high-dose steroid (methylprednisolone 1000 mg/day) was administered for 2 consecutive days under the impression of suspected vasculitis. The hemoptysis then subsided gradually and the following CXRs (days 6 and 8 of hospitalization) revealed gradual resolution of the bilateral patch (Figure 5). The oxygenation was also improved by decreasing the FiO_2 on the mechanical ventilatory setting, and the steroid was tapered gradually.

Under the tentative diagnosis of pulmonary-renal syndrome, a series of immunological studies were carried out and showed that the antinuclear factor (ANA) was at a titer of 1:40, whereas the anti-double strand deoxynucleotic acid (anti-ds-DNA) was negative. The cytoplasmic-antineutrophil cytoplasmic antibody was negative (c-ANCA) but the p-ANCA was positive. The bronchoscopy (day 6 of hospitalization) found multiple reddish spots on the bilateral bronchial tree without an active bleeding site. The patient was successfully extubated after 5 days of close monitoring at the medical intensive unit. A high resolution computed tomography (HRCT) of the patient's chest was subsequently ordered and revealed thickening of the bronchial wall, and infiltration of peribronchial ground glass through the bilateral lung field, predominantly in the central part, favoring residual interstitial infiltration after previous diffuse alveolar consolidation.

Later, the open lung biopsy showed interstitial infiltration with hemosiderin-laden histiocytes, dispersed in the terminal bronchioalveolar space. Definite vasculitis with fibrinoid necrosis was not identified (Figure 3). The immunofluorescence study revealed no deposition of an immune complex. Renal biopsy showed 2 focal segmental necrotizing lesions associated with extracapillary proliferation, a typical presentation of vasculitic glomerulonephritis (Figure 4).

PTU was discontinued based on clinical suspicion with pathological support. The diagnosis of antithyroid drug-related MPA was suspected. The hematuria also improved and became microscopic after the cessation of PTU.

Following treatment with daily oral cyclophosphamide 50 mg, a gradual tapering of the dosage of steroid was carried out until the patient was discharged. She recovered without clinical complication, and was still being following up

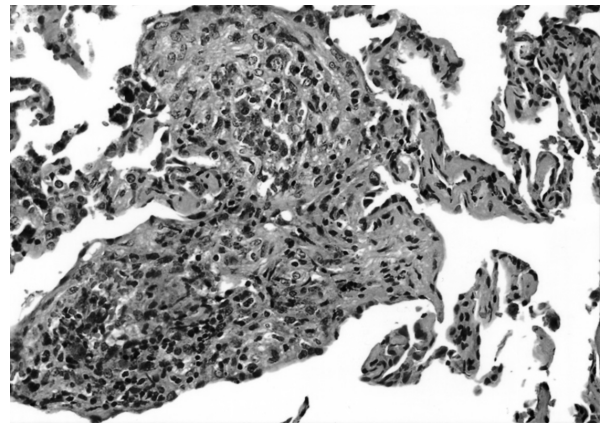

Fig. 3. Lung biopsy, revealing foci of interstitial infiltrates, consisting of lymphocytes, neutrophils and hemosiderin-laden histiocytes. (H&E stain, 100X)

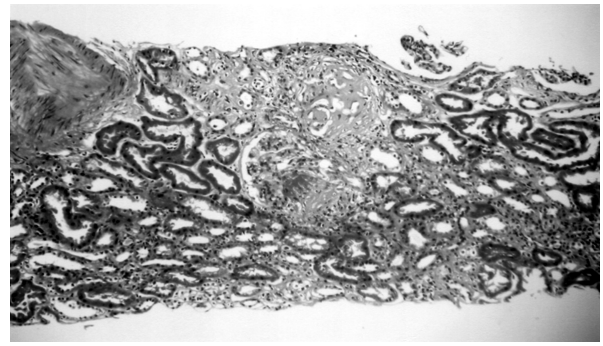

Fig. 4. Renal biopsy, revealing 2 glomeruli with segmental necrosis and thrombi, consisting of focal segmental necrotizing lesions associated with extracapillary proliferation—a typical presentation of vasculitic glomerulonephritis. (H&E stain, 200x)

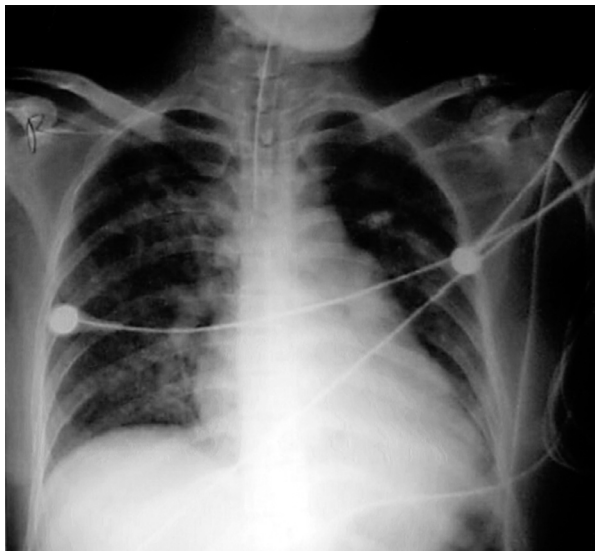

Fig. 5. Chest X-ray, hospital day 8, revealing a resolution of the bilateral alveolar consolidation.

in the outpatient department as of mid 2005.

Discussion

Hemoptysis can be caused by disease from the airways, the pulmonary parenchyma and the pulmonary vasculature. Bleeding from the pulmonary parenchyma, on the other hand, can be caused by either a localized source or a diffuse process [1]. Small vessel pulmonary vasculitis, including Wegener's granulomatosis, Churg-Strauss syndrome, isolated pauci-immune pulmonary capillaritis, and MPA is 1 group of diseases affecting the pulmonary parenchyma diffusely [2].

Vasculitis is a clinicopathologic process characterized by inflammation of/and damage to blood vessels. In addition, the vasculitic syndrome can occur in blood vessels of any type, size and location within the body. The heterogeneity of the vasculitis means that a definite diagnosis usually requires the typical clinical presentations and biopsy from clinically involved tissues. The lungs can be 1 of the target organs in some of these syndromes, such as medium-sized blood vessel vasculitis associated with Behçet's disease and small-vessel pulmonary vasculitis, which includes Wegener's granulomatosis, allergic granulomatosis and angiitis (Churg-Strauss syndrome), isolated pauci-immune pulmonary capillaritis, and MPA. The above-mentioned can present as hemoptysis in Behçet's disease [3], MPA, and diffuse capillaritis, or with periodic dyspnea or a history of asthma in Churg-Strauss syndrome. ANCA testing can greatly assist and facilitate the diagnosis; furthermore, it can also differentiate the types of vasculitis, since PR3 (proteinase-3) ANCA (c-ANCA) is most closely associated with Wegener's granulomatosis, while MPO-ANCA (p-ANCA) is associated with MPA [1,4].

In our case, the patient suffered from hematuria with nonspecific constitutional symptoms, including fever and weight loss; later, massive hemoptysis occurred during the clinical course, but the initial CXR yielded normal results. Based on the consensus guidelines from the Chapel Hill Consensus Conference in 1994 [5], which include the following criteria,

(1) involvement of small blood vessels (capillaries, venules or arterioles)
(2) presence of glomerulonephritis and pulmonary capillaritis
(3) associated with either myeloperoxidase or proteinase-3 ANCAs,

the patient was suspected to suffered from MPA based on the renal biopsy result, which was consistent with vasculitic glomerulonephritis and with the absence of immunofluorescence on renal biopsy. This excluded the possibility of the following entities: Henoch-Schonlein purpura, collagen vascular disease, and Goodpasture syndrome [6]. The clinical picture was also not

consistent with either Wegener's granulomatosis because of the absence of sinus pain and epistaxis, or Churg-Strauss syndrome due to the renal involvement in this case [4].

The most common findings of lung biopsy in MPA are pulmonary hemorrhage and neutrophil capillaritis. In our case, pulmonary hemorrhage caused by MPA was confirmed by p-ANCA (+) and the open lung biopsy which demonstrated interstitial infiltration with hemosiderin-laden histiocytes in the terminal bronchioalveolar space without immune complex deposition. The 1 possibility of finding non-identifiable vasculitis in this case could be due to the high-dose steroid pulse therapy which subsequently improved the natural course of the illness and caused a modification of the lung pathology with the attenuation of capillaritis. Inadequate sampling of lung tissue might be another reason.

Although the pathogenic mechanism of vasculitis remains unknown, most of the vasculitic syndromes are presumed to be mediated at least in part by immunopathogenic mechanisms that occur in response to certain antigenic stimuli. Ultimately however, several factors are involved in the expression of a vasculitic syndrome, including genetic predisposition, environmental exposure, and the regulatory mechanisms associated with the immune response to certain antigens [1].

These autoantibodies are directed against certain proteins in the cytoplasmic granules of neutrophils and monocytes, and are present in a high percentage of patients with certain systemic vasculitis syndromes, particularly Wegener's granulomatosis and MPA. In advanced, ANCA stimulation of neutrophils, the functional importance of the accelerated death that follows the initial activation, such as by the most secure identifiable environmental trigger, the antithyroid drug, PTU, has been highlighted [7]. This is because the failure of phosphatidylserine expression in ANCA-stimulated neutrophils makes them less likely to be phagocytosed and more likely to undergo secondary necrosis, which aggravates the inflammatory response, macrophage-releasing interleukin (IL)-1, IL-8, tumor necrosis factor, and IL-10. Besides, ANCAs may induce different functional responses, leading to inappropriate neutrophil activation and abnormal endothelial damage [7]. T-cell lymphocyte and monocyte recruitment may also be involved in the progression of vasculitic lesions.

The pathogenic mechanism responsible for the generation of ANCA after treatment with antithyroid medication remains unknown. The overall incidence of the important side effects of PTU varies from 1-5% [8]. Variations in the average duration of treatment with PTU in p-ANCA positive patients ranged from 2 to 10 years in previous reports [8-9]. In our case, there was no other definable exposure which could cause MPA, except PTU. Therefore, MPA caused by PTU was the most favorable explanation.

Furthermore, a comparison with p-ANCA-negative patients revealed that prolongation of PTU therapy caused an increase proportion of conversion into p-ANCA positive status for those patients [8,10]. A previous report demonstrated that PTU metabolites may act as a hapten, binding myeloperoxidase and altering its configuration, and promoting the development of autoantibodies in susceptible individuals [11]. There has also been evidence that PTU can accumulate in neutrophils, and increase the risk of the development of ANCA and the presence of hydrogen peroxide, which lead to inappropriately activated primed neutrophils, causing the release of myeloperoxidase. The myeloperoxidase oxidized PTU to cytotoxic products [12], or the PTU sulphonate that further activated B cells through T cell sensiti-

zation, resulting in vascular injury [13]. Since the flu-like symptoms usually appear first, it is presumed that an individual who takes PTU could develop vasculitis only when the neutrophils are appropriately primed by a viral or bacterial infection with a background of genetic susceptibility. In brief, it is possible that the etiology of this condition is multifactorial, and that a viral infection triggers the cascade of events resulting in a dysregulated inflammatory process [14].

In conclusion, we present a case of PTU-induced MPA with pulmonary and renal involvement diagnostically supported by the pathological findings of diffuse alveolar hemorrhage (DAH) and crescentic glomerulonephritis, and the clinical improvement after cessation of PTU administration.

PTU-induced ANCA-positive MPA is a rare condition that may prove lethal if not promptly identified. However, with an accurate early diagnosis, this condition responds well to PTU cessation, corticosteroid, and cyclophosphamide.

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甲狀亢進症病人使用 PTU 誘發 Microscopic Polyangiitis 的病例報告

陳威慎 *　李士毅 **　吳健樑 **　陳培然 **　曾岐元 ***　蕭仁佐 ****

咳血之病因主要細分為三類，包含呼吸道、肺實質性與肺血管性的疾病。而肺部之小血管炎，例如 MPA ，可廣泛影響肺實質。目前，導致 MPA 誘因之一的 PTU ，其致病機轉依然不清楚。

本篇提出一則服用 PTU 所誘發陽性 ANCA 的血管炎的病例。在本案例的治療上，我們給予機械性換氣及包括高劑量類固醇之脈衝療法,口服的免疫抑制劑(cyclophosphamide)併停止使用 PTU 。之後她的症狀好轉後出院，目前狀況穩定。*(胸腔醫學 **2006; 21: 494-500**)*

關鍵詞：核週邊抗嗜中性白血球細胞質抗體，丙硫脲酮，血管炎，多發性小脈管炎

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Surgical Treatment for Boerhaave's Syndrome — Report of Two Cases

Fu-Chi Fang, Yeung-Leung Cheng, Ching Tzao, Chih-Ming Hsieh, Shih-Chun Lee

Boerhaave's syndrome, or spontaneous perforation of the esophagus, is a life-threatening disease. The timing of diagnosis and treatment of this disease is an important factor in determining its outcome. We report 2 consecutive cases of Boerhaave's syndrome with different clinical presentations that were observed in our institution. The first patient was diagnosed and received urgent surgical repair of the esophageal perforation within 16 hours after presentation. Another patient was diagnosed after more than 3 days and esophageal diversion and thoracic drainage were performed to control sepsis. A delayed esophageal anastomosis was performed after the perforation had healed. These 2 patients were treated successfully and recovered uneventfully after a 1-year follow-up. ***(Thorac Med 2006; 21: 501-505)***

Key words: spontaneous perforation, esophagus, surgery, empyema

Introduction

Spontaneous perforation of the esophagus, or Boerhaave's syndrome, is a life-threatening disease associated with an overall mortality rate ranging from 20% to 30% depending on treatment [1]. Herman Boerhaave first described spontaneous rupture of the esophagus in 1724 [2]. The classic history is of a patient with forceful vomiting followed by epigastric or substernal pain. Accurate diagnosis, aggressive early treatment, and vigilant attention to drainage of the esophageal perforation all reduce morbidity, and are essential to the best outcome. We report 2 cases with typical presentations of Boerhaave's syndrome, and discuss the clinical features, management, surgical findings and successful outcomes.

Case Report

Case 1

A 51-year-old healthy male experienced severe vomiting after binge drinking 8 hours prior. He presented with a sharp left chest pain exacerbated by respiratory movement, and epigastric pain. The patient had no history of previous trauma or similar pain. Past medical history was non-contributory. On examination, his body temperature was 35.1ºC, pulse rate was 103/min, and blood pressure was 100/43 mmHg. Chest examination disclosed decreased breathing sounds in the left chest, and bilateral basal rales. The

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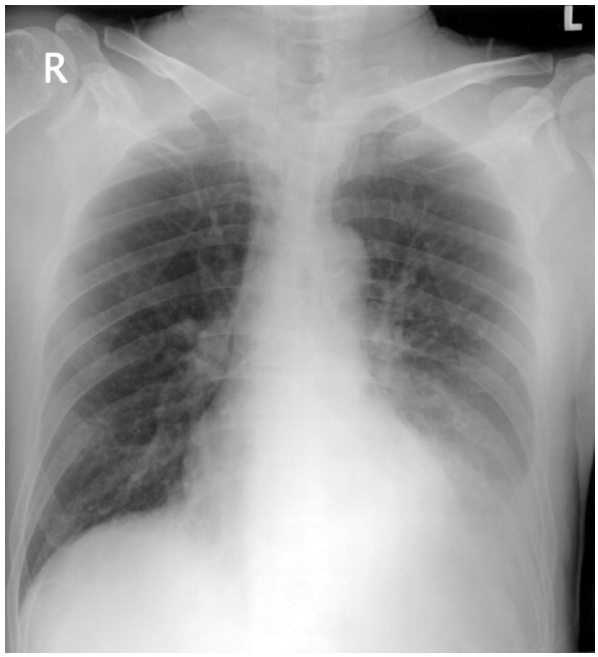

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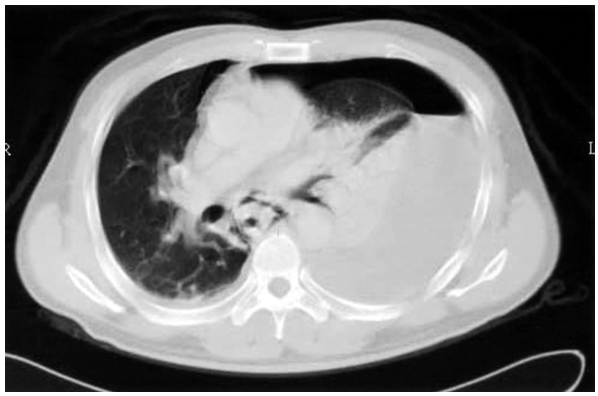


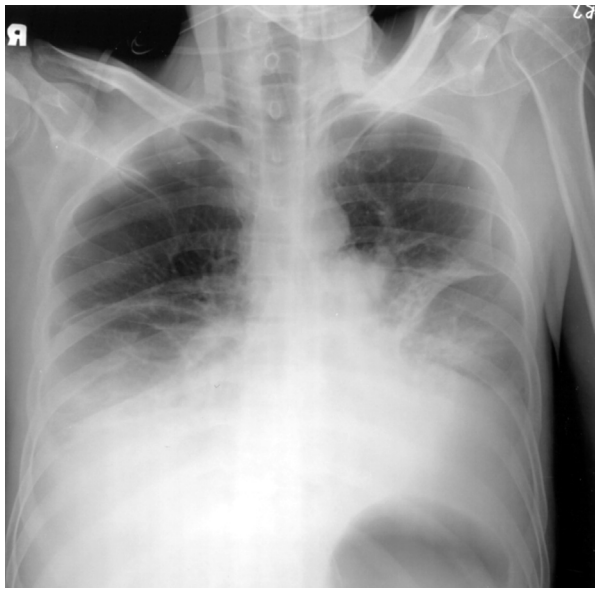
(B)

Fig. 1. A. Chest X-ray showing left pleural effusion with opacities in the left lower thorax. B. CT of the chest showing wall thickening of the lower third of the esophagus with obliteration of the esophageal contour, massive hydropneumothorax, pneumomediastinum, and total collapse of the left lower lobe.

leukocyte count was 22,800 per μL (neutrophils 88.5%, lymphocytes 8.9%); Hb, 14.9 g/dl; and platelet count, 268,000 per μL. Chest X-ray (CXR) and computerized tomographic (CT) scans of the chest showed pneumomediastinum and left hydropneumothorax (Figure 1A and B). A left tube thoracostomy was emplaced and about 1300 cc of foul-smelling turbid pleural fluid drained initially. Because of a suspicion of Boerhaave's syndrome with empyema and sepsis, urgent standard thoracotomy through the left seventh intercostal space was performed. Copious turbid pleural fluid with debris and pleural fragments was noted. A perforation about 2 cm in length in the left posterior aspect of the esophagus was found, and debridement and 3-layered repair were performed. In addition, a gastrostomy was performed to divert gastric contents, and a jejunostomy for enteral feeding. The results of the pleural fluid culture showed mixed bacteria. Antibiotics were administrated. An esophagogram showed intact mucosa without evidence of contrast extravasation 3 weeks after the operation. The patient recovered uneventfully, and could tolerate a solid diet 2 months after the operation.

Case 2

The second patient was a 44-year-old male who presented with progressive chest pain, weakness, chills, and poor intake lasting for 3 days. He had experienced epigastic discomfort after forceful vomiting 3 days prior. He had a history of major depression for 10 years. Initially, the patient's temperature was 37.8ºC, pulse rate was 117/min, and blood pressure was 110/69 mmHg. About 2 hours later, the patient experienced a sudden onset of shortness of breath and severe chest pain accompanied by unstable hemodynamic signs. CXR showed bilateral moderate pleural effusion (Figure 2A). The total leukocyte count was 15,700 per mL (neutrophils, 91.5% with lymphocytes, 7.6%); Hb, 16.8 g/dl; and platelet count, 454,000 per mL. Contrast-enhanced CT scan of the chest showed circumferential wall thickening of the lower third of the esophagus, pneumomediastinum, and massive bilateral pleural effusion (Figure 2B). A diagnosis of spon-



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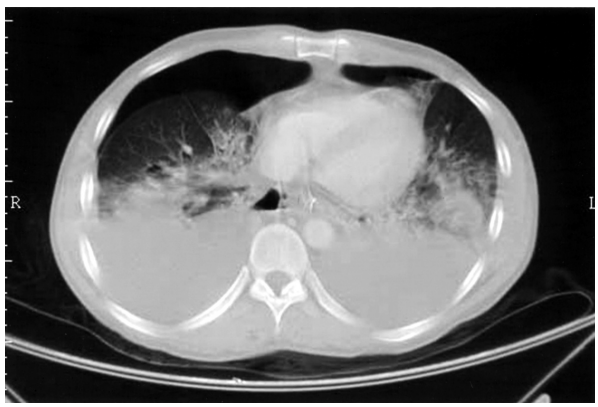

(B)

Fig. 2. A. Chest X-ray showing pneumomediastinum and bilateral pleural effusion. B. CT of the chest showing pneumomediastinum with air bubble retention in the surrounding region of the esophagus, and bilateral hydropneumothorax.

taneous esophageal perforation with mediastinitis, bilateral empyema, and sepsis was first considered. Approximately 1500 ml of turbid, dark, and foul-smelling pleural fluid was noted with bilateral tube thoracostomy with drainage. Diversion procedures, including cervical esophagostomy and gastrostomy, were performed, and copious food-related material was aspirated. A jejunostomy was also performed for feeding. Pleural fluid culture showed mixed bacteria and fungus. Re-anastomosis of the cervical esophagus was performed 1 month later when there was no longer a sign of esophageal leakage and infection had been controlled. The patient was able to eat a liquid diet and was discharged 50 days after admission.

Discussion

Rupture of the esophagus is a critical condition that requires immediate attention, diagnosis, and management. Common causes include spontaneous, iatrogenic, and traumatic factors. Boerhaave's syndrome denotes a spontaneous perforation of the esophagus, which usually occurs in the left pleural cavity or just above the gastroesophageal junction. Due to the lack of a serosal layer in the esophagus, contamination of the pleural cavity and adjacent mediastinum with gastric contents, saliva, and micro-organisms result in empyema, mediastinitis, and severe sepsis, if unrecognized. Mortality is often related to late diagnosis, or misdiagnoses, such as myocardial infarction, peptic ulcer perforation, or acute pancreatitis [3]. A classic triad of symptoms is repeated vomiting, chest pain, and subcutaneous emphysema [4]. However, these symptoms may not be noted in all patients. Our 2 cases both presented with forceful vomiting after heavy eating and drinking, alerting us to the diagnosis of Boerhaave's syndrome. A transmural perforation of the esophagus should be distinguished from a Mallory-Weiss mucosal tear, a non-transmural esophageal tear which is also associated with vomiting. Later stages of the illness may manifest as signs of infection and sepsis, including fever, hemodynamic instability, and progressive obtundation. Establishing a diagnosis in the later stages

can be quite difficult. Laboratory findings, such as leukocytosis, are often nonspecific. Many patients present with pleural effusion. Thoracentesis with examination of the pleural fluid can aid in diagnosis [5].

Abnormalities in the CXR can be variable, with pleural effusion, pneumothorax, pneumomediastinum, and subcutaneous emphysema presenting in most cases, depending on the region of perforation and the time interval [6]. If there are any abnormal findings in the CXR, contrast study, including an esophagogram or computed tomography, should follow immediately. Although the esophagogram helps to confirm the diagnosis and outlines the length of the perforation and its location, computed tomography of the chest with contrast can be a diagnostic tool, especially in atypical clinical presentations, as in our cases [7].

Early diagnosis is critical and yields a better outcome. The interval between perforation and treatment remains a predictor of survival [1]. Management is controversial and in accordance with the presence of associated lesions. Mainstays of therapy include intravenous volume resuscitation, administration of broad-spectrum antibiotics, the early use of nutritional supplementation, and prompt surgical intervention. Primary repair of the perforation and wide drainage of the mediastinum are effective and recommended in patients operated on within 24 hours of rupture [8]. Our case 1 had a perforation hole in the lower third of the esophagus, which was treated with emergency repair leading to a good result. But if therapy of the esophageal perforation has been delayed more than 72 hours, primary repair alone, which often leads to mediastinal leakage, continued sepsis, and death, is not suggested [9]. Our case 2 presented with a delayed diagnosis and was treated by esophageal exclusion and paraesophageal mediastinal drainage, achieving good control of the mediastinal sepsis and healing of the perforation.

In conclusion, this paper reports 2 consecutive cases of typical Boerhaave's syndrome presenting after different time intervals, with successful outcomes after surgical intervention.

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手術治療不同病程的 Boerhaave 氏症候群—兩病例報告

方副吉　程永隆　禚靖　謝志明　李世俊

Boerhaave 氏症候群或自發性食道破裂是一種高死亡率的疾病，從診斷到開始治療的時間對病人的癒後是很重要的因子。我們報告兩例不同病程的 Boerhaave 氏症候群，並成功地手術治療的經驗。第一例從診斷到立即手術修補治療是從病人開始有症狀的 16 小時內。另外一例則是超過三天，緊急手術方式是頸部食道造口、胸腔積液引流來控制敗血症，並且在確定破裂處癒合後行頸部食道吻合。這兩病例在術後一年的追蹤均沒有特別併發症發生。*(胸腔醫學* ***2006; 21: 501-505****)*

關鍵詞：自發性破裂，食道，手術，膿胸

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Misdiagnosis of Swyer-James-Macleod Syndrome as Pulmonary Embolism Leading to a Complication of Extrapulmonary and Rectus Sheath Hematomas — A Case Report

I-Jang Liu, Kam-Chung Lee, Jiunn-Der Lee, David Lin Lee, Hung-Yang Tao

The Swyer-James-Macleod syndrome is one of the causes of unilateral hyperlucent lung. It is thought to be a post-infective form of bronchiolitis obliterans following a lower respiratory tract infection in early childhood. It is comprised principally of hyperlucency, a deficient blood supply, and decreased ventilation in the affected lung, and is sometimes associated with focal bronchiectasis. We present the case of a 61-year-old woman afflicted with Swyer-James-Macleod syndrome that was misdiagnosed as a pulmonary embolism by a cardiovascular surgeon in another hospital. Hemoptysis and severe extrapulmonary hematoma occurred after treatment with anti-coagulants. The literature concerning the differential diagnosis of unilateral hyperlucency on chest X-ray is also reviewed. ***(Thorac Med 2006; 21: 506-511)***

Key words: bronchiolitis obliterans, Macleod's syndrome, pulmonary embolism, Swyer-James syndrome, unilateral hyperlucent lung

Introduction

The first report of Swyer-James syndrome, characterized by a roentgenographic unilateral hyperlucent lung associated with a small pulmonary artery and recurrent respiratory infections in a 6-year-old boy, appeared in 1953 [1]. In 1954, Macleod presented a more detailed report on the same syndrome in 9 patients whose ages ranged from 18 to 41 years [2]. In the Swyer-James syndrome or Macleod's syndrome, which is synonymous with unilateral hyperlucent lung syndrome or unilateral emphysema, unilateral bronchiolitis obliterans (BO) is the most common cause of chronic unilateral hyperlucent lung [3]. At present, the Swyer-James-Macleod syndrome (SJMS) is considered to have a varying spectrum of clinical and imaging features [4-5]. SJMS is usually diagnosed on the basis of its characteristic radiological appearance as follows [6]: (1) a lobar or unilateral hyperlucent lung with air trapping on expiration (a *sine qua non*), (2) diminished pulmonary vascularity with a small hilar shadow, (3) a usually ipsilateral normal or small lung volume with or without proximal bronchiectasis and exclusion of other causes of unilateral hyper-

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lucency, such as unilateral agenesis of a pulmonary artery, massive pulmonary thromboembolism, or endobronchial obstruction. We report a case of SJMS first diagnosed in our hospital but misdiagnosed later as pulmonary embolism in another hospital.

Case Report

A 61-year-old woman without a history of other major diseases was admitted to a local hospital with the chief complaint of exacerbated dyspnea on exertion for 3 years, and was then transferred to our hospital because of shortness of breath with drowsy consciousness. On admission, lethargic consciousness was noted. The physical examination showed her temperature to be 37.5°C, her pulse at 86 beats/min, and respiration at 20 breaths/min. The breathing sounds were faint in the left hemithorax. There was no jugular venous engorgement or peripheral edema. Laboratory studies revealed normal leukocytes, and hematocrit of 43.2%. A sample of venous blood revealed a pH of 7.264, P_vCO_2 79.9 mmHg, and bicarbonate 36.6 mmol/L. The chest roentgenogram disclosed a marked asymmetry in the density of the 2 lungs. The left side was relatively radiolucent and showed a paucity of vascular marking and a small hilum, compared to the right side (Figure 1). The pulmonary function tests (PFT) revealed a forced expiratory volume in 1 second (FEV_1) of 19% of the predicted value (0.27/1.43), a forced vital capacity (FVC) of 38% of the predicted value (0.69/1.8), and a FEV_1/FVC ratio of 0.27/0.69 (39%), indicating an obstructive airway disease. The post-bronchodilator test showed no significant responses with a FEV1 0.30L and a FVC of 0.68L. A subsequent high resolution computed tomographic (HRCT) scan of the chest (Figure 2A) showed obvious hypoattenuation in the entire left lung. It also revealed thin vessels coursing through the hyperlucent areas of the lung. The right main pulmonary arterial system was patent and of a normal size. The left main pulmonary artery and its main branches were patent, but much smaller in size than the right (Figure 2). There was no endobronchial obstruction or bronchiectasis identified by the scan. HRCT performed at end expiration revealed air trapping in the left lung (Figure 2B).

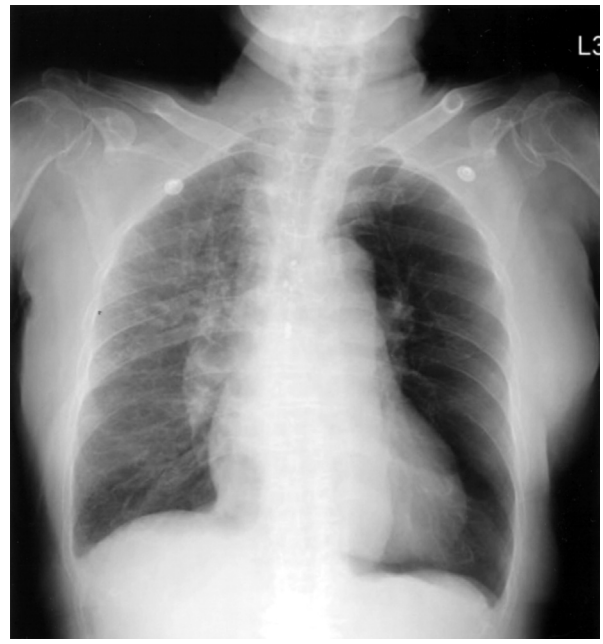

Fig. 1. Chest radiograph showing radiolucency of the left lung with diminished vascular markings and a small hilum.

A ventilation-perfusion (V/Q) scan, inhalation of 99m technetium-labeled diethylene-triaminepenta-acetic acid ($^{99}Tc^m$-DTPA) and injection of $^{99}Tc^m$-labeled macro-aggregated albumin ($^{99}Tc^m$-MAA) were done to rule out pulmonary embolism. There was no evidence of thromboembolism, but of a matched V/Q defect with only 13.8% of the total lung perfusion in the entire left lung. An inhomogeneous matched defect was also noted in the right middle lung field. A diagnosis of SJMS was made, based on

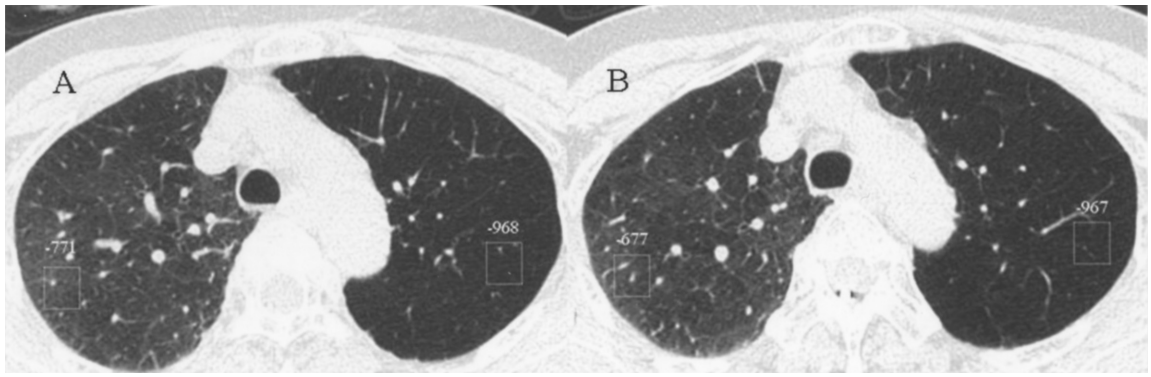

Fig. 2. HRCT of the thorax during inspiration (A) and expiration (B) at approximately the same level, showing hyperlucency and diminished vascularity in the entire left lung. During expiration (B), the vessels on the right appeared more crowded and the mean lung density of the right lung increased from –771 HU during inspiration to –677 HU during expiration (gradient: +94 HU). On the left, the mean lung density showed nearly no change (–968 HU during inspiration and –967 HU during expiration).

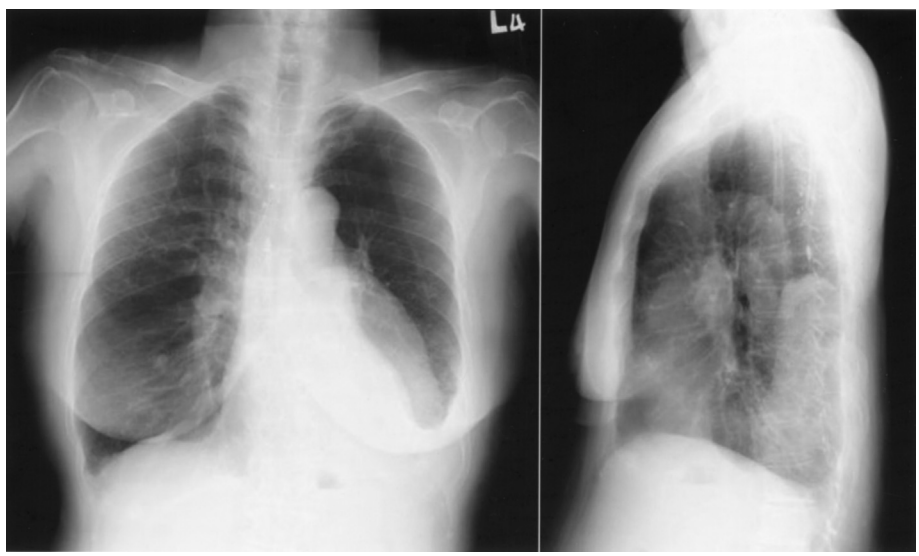

Fig. 3. Chest radiograph showing a mass-like lesion with well-defined convex border, about 10x4 cm in size, in the left posterior lower lung field.

the radiological findings and a pulmonary V/Q scan. The patient improved considerably after corticosteroid and bronchodilator therapy, and was discharged without incident.

This patient was later misdiagnosed as having left pulmonary embolism at another hospital. The hemoptysis and lower abdominal ecchymosis occurred after being treated with anti-coagulants in that hospital. Thereafter, she requested transfer to our hospital again. At this second admission, she required O_2 therapy due to desaturation. The chest X-ray (Figure 3) and the CT showed an extrapulmonary mass-like lesion about 10x4cm in size, located at the posterior of the left hemithorax, which resulted in partial atelectasis of the left lower lung. Dark bloody fluid was aspirated from that lesion. A lower abdominal sonography revealed a hypoechoic elliptical lesion measuring

about 4x7cm in size within the rectus sheath. Extrapulmonary and rectus sheath hematomas due to the anti-coagulant therapy were diagnosed. We treated the patient as having a severe obstructive lung disease with acute exacerbation. The dyspnea improved gradually after bronchodilator, corticosteroid, and antibiotics treatment. However, the regular follow-up chest X-rays over a 3-month period revealed no obvious resolution of the extrapulmonary hematoma.

Discussion

SJMS is a rare complication of a lower respiratory tract infection occurring during the first 8 years of life, before the lung has completed its development [4, 7-8]. A variety of organisms may cause the condition, e.g. *Mycoplasma pneumoniae*, measles virus, influenza A virus, *Bordetella pertussis*, and *Mycobacterium tuberculosis*, with adenovirus being the most common [4, 7, 9]. The histopathologic characteristic of SJMS is a bronchiolitis obliterans resulting in peripheral air trapping and eventually in emphysema [6]. SJMS is an obstructive pulmonary disorder. The PFT may show mild to very severe airflow obstruction [5]; our patient demonstrated very severe airway obstruction. An ipsilateral collapsed lobe or bronchiectasis may be present or absent [10-12]. The ultimate fibrosis of the inter-alveolar septum causes obliteration of the pulmonary capillary bed, which results in a decreased blood flow to the major pulmonary arteries, and subsequently results in the hypodevelopment of these arteries [9, 11, 13].

The clinical presentation is variable. Some patients without bronchiectasis or with cylindrical bronchiectasis will be asymptomatic or present symptoms later in adult life. The condition may escape diagnosis until adulthood, as with this patient. However, those with saccular bronchiectasis may have had obvious respiratory symptoms and repeated episodes of respiratory infection since their childhood [4].

The diagnosis of SJMS depends mainly on roentgenographic findings. Unilateral hyperlucency due to the decrease in pulmonary blood flow in the affected lung is the classic finding on the plain chest radiograph. In addition, hyperlucency in 1 segment or lobe of 1 lung or in the bilateral lungs may occur [6, 10, 12-13]. Although this patient was diagnosed with a purely unilateral disease based on the chest X-ray, the V/Q scan demonstrated bilateral involvement. A *sine qua non* for the diagnosis of SJMS is the presence of air trapping [6], which may be proven by an inspiratory-expiratory sequence of chest X-rays or HRCT, or by a radionuclide ^{133}xenon ventilation scan during the washout phase [13]. On post-expiratory HRCT, lung regions trapping air often fail to show a normal increase in the mean lung attenuation and remain more lucent than a normally ventilated lung. On the ^{133}xenon ventilation scan, ^{133}xenon trapping in the washout phase can prove air trapping. In addition, the tidal flow-volume loop can demonstrate the presence of air trapping by a left shift of the loop with increasing end-expiratory lung volume during exercise.

The diagnosis of SJMS requires the exclusion of other causes of unilateral hyperlucent lung. These include radiographic artifacts, chest wall abnormalities, bullae or cysts, central bronchial obstruction, compensatory hyperinflation, congenital lobar emphysema, and pulmonary vascular diseases such as pulmonary artery hypoplasia or aplasia, or massive pulmonary embolism [14]. However, massive pulmonary embolism may present an enlarged proximal pulmonary artery, smaller distal pulmonary arteries, or a filling defect within a dilated pulmonary artery on the

contrast-enhanced CT over the radiolucent areas [15-16]. A V/Q scan may confirm the diagnosis by demonstrating that hyperlucent areas are poorly perfused and normally ventilated. In this case, the HRCT showed a unilateral hyperlucent lung with reduced vascularity, and air trapping was confirmed in the expiratory phases. The left main pulmonary artery and its main branches were patent with smooth mural, but much smaller than the right one. The matched V/Q defect helped us confirm the diagnosis of SJMS, and completely excluded the possibility of massive pulmonary embolism. But a perfusion scan alone may lead to a misdiagnosis of SJMS as a pulmonary vascular disease, such as pulmonary hypoplasia or embolism, because it shows no perfusion of the affected lung [6, 11]. We believe that the misdiagnosis as a pulmonary embolism in this patient was due to the single pulmonary perfusion scan found in the referral sheet from that local hospital.

In conclusion, SJMS is a spectrum disease with variable clinical presentations and radiological features. It is diagnosed on the basis of radiological characteristics. Unilateral pulmonary hyperlucency and air trapping are general features. Variable findings include segmental to bilateral lung involvement, normal or small lung size, lobar atelectasis, and the presence or absence of bronchiectasis. When dealing with a unilateral hyperlucent lung, HRCT and V/Q scans are very useful and can prevent a misdiagnosis.

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將 Swyer-James-Macleod Syndrome 誤診爲肺栓塞以致造成肺外及腹直肌內血腫的併發症—一病例報告

劉宜讓　李錦中　李俊德　李琳　陶宏洋

Swyer-James-Macleod 症候群是單側高透亮性肺野的其中原因之一。它被認為是在幼童早期時，遭受下呼吸道感染之後所形成的阻塞性細支氣管炎（bronchiolitis obliterans)。它主要是由一個單側高透亮性、貧乏血流供應、以及通氣量減低的受損肺葉所組成；偶爾也會合併支氣管擴張症。我們報告一位患有 Swyer-James-Macleod 症候群的 61 歲女性病人，被其他醫院的心臟血管外科醫師誤診為肺動脈栓塞而服用抗凝血劑，以至產生咳血及肺外血腫的併發症。我們並且回顧有關胸部 X 光片呈現單側高透亮性肺野時的鑑別診斷。*(胸腔醫學* ***2006; 21: 506-511)***

關鍵詞：阻塞性細支氣管炎（bronchiolitis obliterans)， Macleod's 症候群，肺栓塞， Swyer-James 症候群，單側高透亮性肺野

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Lung Recruitment Maneuver and High Positive End-expiratory Pressure Setting for Emergency Life-saving in Acute Lung Injury and Acute Respiratory Distress Syndrome — A Report of 3 Cases

Hsuan-Tsung Su, Kun-Ta Chou, Chong-Chen Lu, Reury-Perng Perng

The lung-protective ventilation strategy is well accepted for the management of acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) in adult patients with strongly supportive evidence. However, the role of the lung recruitment maneuver (RM) followed by high positive end-expiratory pressure (PEEP) is still controversial, and the clinical benefits need further evaluation in ongoing trials. This procedure may play an important role as an emergency rescue therapy for ALI/ARDS patients with refractory life-threatening hypoxemia, and provide an opportunity to reverse the clinically almost inevitable fatal outcome of these patients. Herein, we report the cases of 3 severe hypoxemic patients in critical condition. The hypoxemia and unstable condition were both relieved by RM and a high post-RM PEEP setting. The favorable outcome in these 3 patients is a reminder of the importance of using RM and a high post-RM PEEP setting for the rescue of the refractory hypoxemia in ALI/ARDS patients. ***(Thorac Med 2006; 21: 512-523)***

Key words: acute respiratory distress syndrome, acute lung injury, lung recruitment maneuver, high positive end-expiratory pressure

Introduction

The term "acute lung injury" (ALI) was first defined by the American-European Consensus Conference (AECC) in 1994, and currently is widely used by physicians and researchers [1]. As defined, acute lung injury (ALI) is designed for use with patients with significant hypoxemia (partial pressure of arterial oxygenation to fraction of inspired oxygen ratio (PaO2/ FiO2) ≤ 300) and without evidence of elevated left atrial pressure; while "acute respiratory distress syndrome" (ARDS) represents the subset of the most severe ALI patients (PaO2/FiO2 ≤ 200) [1].

The management of ALI/ARDS is largely supportive, and with the use of mechanical ventilation [2]. Although mechanical ventilation is necessary to preserve life, it can also injure the lungs—a condition referred to as ventilator-induced lung injury (VILI) [3-4]. The mecha-

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nisms of VILI include exposure to high inflation pressures or over-distension (barotrauma or volutrauma), repetitive opening and closing of the alveoli, and up-regulated cytokine release and systemic inflammatory response (biotrauma) [5]. Lung-protective ventilation was designed to mitigate VILI with a volume- and pressure-limited ventilator setting. The reported benefits largely support the lung-protective ventilation strategy in ALI/ARDS patient management [5-7].

The lung recruitment maneuver (RM) is a trial with a transiently extremely high airway-pressure to open the atelectatic alveoli and improve hypoxemia. A high positive end-expiratory pressure (PEEP) setting after RM is used to prevent the opened alveoli from collapsing again, and so avoiding VILI due to the cyclical opening and closing of the alveoli. Although the role of RM plus high post-RM PEEP is still controversial, and the benefits need further investigation [5, 8-10], some critical patients may derive benefits from this procedure through the reversal of severe hypoxemia [11-12]. Herein, we report our experience with 3 critically hypoxemic patients who experienced beneficial results from RM plus a high post-RM PEEP setting.

Case Reports

Case 1

A 74-year-old female patient with the underlying diseases of type II diabetes, chronic renal insufficiency, and hypertension, and a history of previous cerebral vascular ischemic stroke, was sent to our emergency department for acute abdominal pain. After the initial diagnosis of perforated peptic ulcer, she received emergency surgical management and was then transferred to the intensive care unit (ICU) for further care. However, difficulty in mechanical ventilation weaning was noted, so she received conservative management with gradually tapering FiO2 from 100% to 25%, but persistent feeding difficulty due to mal-absorption and abdominal distension continued. To further investigate the abdominal condition, an abdominal computed tomography (CT) scan was arranged. Around 1200 cc of contrast medium was fed via a naso-gastric tube approximately 2 hours before the CT scan was performed. After the CT scan examination, and the patient had been transferred back to the ICU, however, cyanosis, shortness of breath, and hypoxemia were found. Physical examination revealed bilateral lung crackles in the breathing, and the chest film showed acute haziness in the bilateral lung fields (Figure 1). Arterial blood gas (ABG) examination showed an acute deterioration of oxygenation (Table 1). Despite the immediate use of pure oxygen, an ambu-bagging procedure, and a trial of elevating the PEEP setting from 8 to 15 cm H2O, poor oxygenation continued to be noted. The follow-up CT scan images showed increased enhancement in the bilateral basal lung fields, and aspiration of contrast medium was highly suspected (Figure 2). For the persistently poor oxygenation, we tried RM plus an empirically high post-RM PEEP ventilator setting:

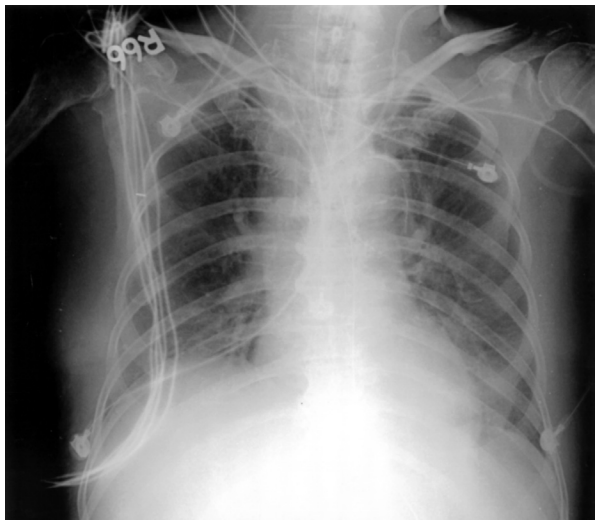
1. Patient sedation with midazolam and paralyzation with atracuronium besylate.

2. RM with pressure-controlled ventilation:

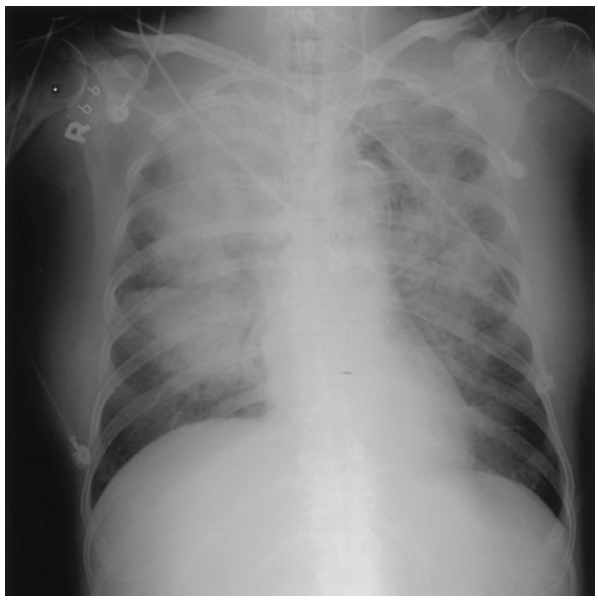
A. Fixed inspiratory pressure 15 cmH2O above PEEP/respiratory rate (RR) 20 per minute with the previous PEEP level (15 cm H2O);

B. Stepwise elevation of the PEEP level from 15 cm H2O to 30 cm H2O (progressively adding 2 cm H2O PEEP in each respiratory cycle), then keeping the peak inspiratory pressure (PIP) at 45 cm H2O/PEEP 30 cm H2O ventilation; the total procedure was about 2 minutes;

C. Stepwise decreasing of the PEEP level



(A)



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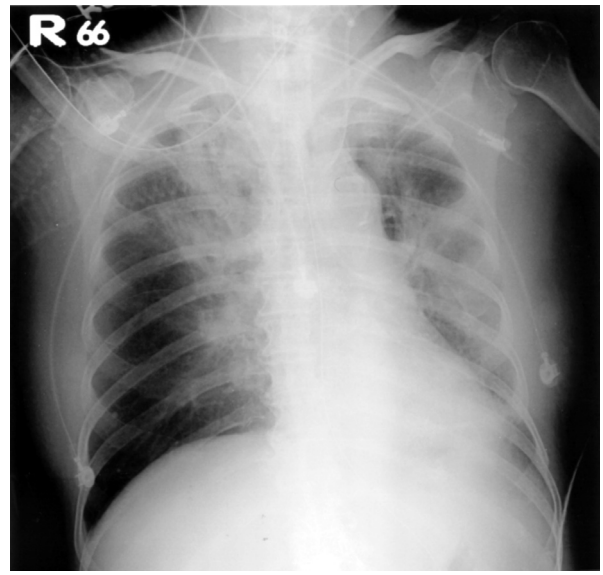


(C)

Fig. 1. Serial chest roentgenograms in case 1. (A) Two days before the aspiration episode, the bilateral lung fields were grossly clear. (B) Immediately after the aspiration episode, severe haziness in the bilateral lung fields can be seen. (C) One day after the recruitment maneuver with partial resolution of the infiltration.

down to 15 cm H2O (progressively decreasing 2 cm H2O PEEP from 30 cm H2O in each respiratory cycle).

3. Changing to the previous volume-controlled ventilation, but keeping the PEEP level at 15 cm H2O.

The pulse oxymeter monitoring showed that the oxygenation improved immediately after RM and the elevated PEEP level. The follow-up ABG showed improvement in hypoxemia (Table 1), and the haziness on the chest film showed rapid resolution (Figure 1). The poor oxygenation due to contrast medium aspiration was reversed by the emergency RM plus high post-RM PEEP setting, and the generalized poor condition resolved within several days without obvious sequela.

Case 2

A 73-year-old female with the underlying diseases of type II diabetes, hypertension, and chronic renal insufficiency was sent to our emergency department due to nausea, vomiting, a sensation of shortness of breath, and decreased urine output for several days. Urosepsis with septic shock and acute deterioration of chronic renal failure was diagnosed at the emergency department. Respiratory failure then developed

Table 1. Ventilator settings and serial ABG results in case 1

Time		Pre-CT exam	Back to ICU after CT scan	RM for 2 mins	10 mins after RM	6 hrs after RM	24 hrs after RM
Ventilator	Mode	V/C	V/C	P/C	V/C	V/C	V/C
Setting	FiO2 (%)	25	100	100	100	60	40
	Vt (ml)	540	540	PC15	500	540	540
	PEEP (cmH20)	8	8 → 15	30	15	10	10
	RR set/Pt (per min)	8/16		20/20	20/20	14/14	14/14
	PIP (cmH20)	32		45	35	32	
	I/E	1:3			1:3.2	1:2.8	
Arterial	FiO2 (%)	25	100		100		40
Blood Gas	PH	7.50	7.29		7.45		7.50
Result	pO2 (mmHg)	70	49.9		67		64
	pCO2 (mmHg)	35.5	45		36		30
	HCO3 (mM/L)	27.9	22.1		24.8		24
	Sat (%)	95	79.8	90*	92	100*	97

V/C: volume-controlled ventilation, P/C: pressure-controlled ventilation, PC15: inspiratory pressure 15 cm H2O above PEEP

*: pulse-oxymeter monitoring result

and oral endotracheal tube intubation with mechanical ventilation support was performed. She was then transferred to our ICU for further management. During the admission period, despite the use of antibiotics, inotropic agents, and mechanical ventilation support, progressive oliguria was still noted, and body weight gain of around 12 kilograms due to a 3-day fluid retention was found. Chest film showed bilateral increased consolidation change, possibly due to pulmonary edema or diffuse pneumonia (Figure 3). A nephrologist was consulted, but aggressive renal replacement therapy was not favored due to low arterial blood pressure, poor oxygenation, and the patient's critical condition. Severe hypoxemia with an air-hunger appearance and a critically low arterial blood pressure level (down to 60/40 mmHg), despite the use of inotropic agents, were then noted (Table 2). At the critical point, RM was tried, as follows:

1. Sedation with midazolam and paralyzation with atracuronium besylate.

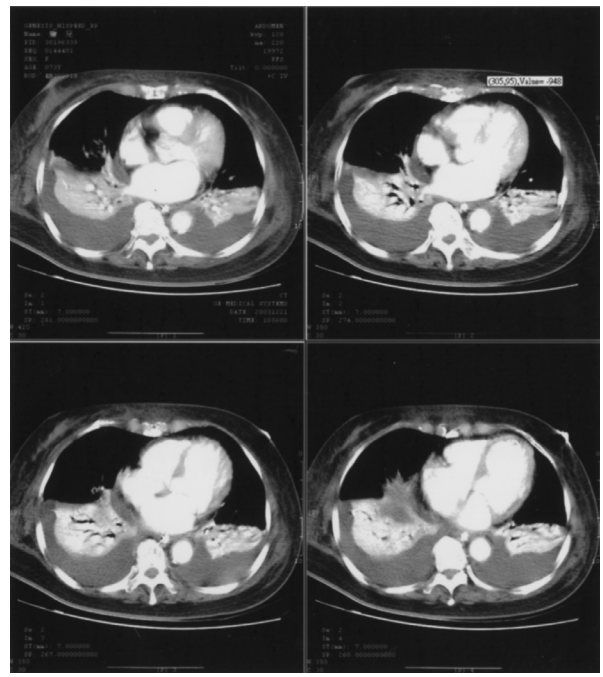


Fig. 2. Computed tomography image in case 1. Bilateral lung fields reveal increased enhancement, mainly at the basal lung fields; aspiration of contrast medium was highly suspected.

Table 2. Ventilator settings and serial ABG results in case 2

Date		0102	0103	0104	0105	0105	0106
Time					1725	RM	0600
Ventilator	Mode	PCV	PCV	PCV	PCV	PCV	PCV
Setting	FiO2 (%)	40	40	50-100	100	100	100
	Insp. Pressure above PEEP (cm H2O)	15	15	18	18	15	17
	PEEP (cmH2O)	5	5	7	10	30	18
	RR (set/Pt)	12/22	12/	12/36	12/30	20/20	20/20
	PIP (cmH2O)	19		31	31	45	35
	I/E	1:2.8		1:1.9			1:3.7
Arterial Blood	FiO2 (%)	40		100	100		100
Gas	pH	7.344		7.284	7.285		7.56
	pO2 (mmHg)	97		131	39.5		259
	pCO2 (mmHg)	15		20	45.6		28.8
	HCO3 (mM/L)	8.3		9.7	21.9		26.1
	Sat (%)	97	96.8*	98	63.8	97-99*	99.8

PCV: pressure-controlled ventilation, *: pulse-oxymeter monitoring result

2. A recruitment maneuver with pressure-controlled ventilation:

A. Fixed inspiratory pressure at 15 cm H2O above PEEP/RR 20 per minute/at the previous PEEP level;

B. Stepwise increase in the PEEP level from baseline up to 30 cm H2O (progressively adding 2 cm H2O PEEP in each respiratory cycle), and keeping PIP 45 cm H2O/PEEP 30 cm H2O ventilation; the entire procedure was about 2 minutes;

C. Stepwise decrease in the PEEP level down to 18 cm H2O (progressively decreasing 2 cm H2O PEEP in each respiratory cycle), and keeping inspiratory pressure at 15 cmH2O/PEEP 18 cm H2O ventilation; the entire procedure was about 30 seconds.

3. Repeat procedure B.

4. Stepwise decrease in PEEP to 18 cm H2O (progressively decreasing 2 cm H2O PEEP in each respiratory cycle)/setting the inspiratory pressure 17 cm H2O above PEEP/RR 20, and maintaining this mode continuously

During the RM procedure, the bedside arterial line monitor showed dramatic improvements in the arterial blood pressure level, and the pulse oxymeter showed improved oxygenation up to 97-99% (Table 2). The follow-up chest film the next day showed a marked resolution in pulmonary infiltrates (Figure 3). ABG also showed a marked improvement (Table 2). The nephrologist was consulted the next day, since the improvement in oxygenation and the clinical condition might be suitable for the arrangement of hemodialysis. The clinical condition improved gradually after hemodialysis and aggressive management. She was finally transferred to the respiratory care unit for further mechanical ventilation weaning 3 weeks later. The clinically inevitable fatal outcome suspected for this patient was dramatically reversed by the RM plus an empirically high post-RM PEEP setting.

Case 3

A 47-year-old male with the underlying

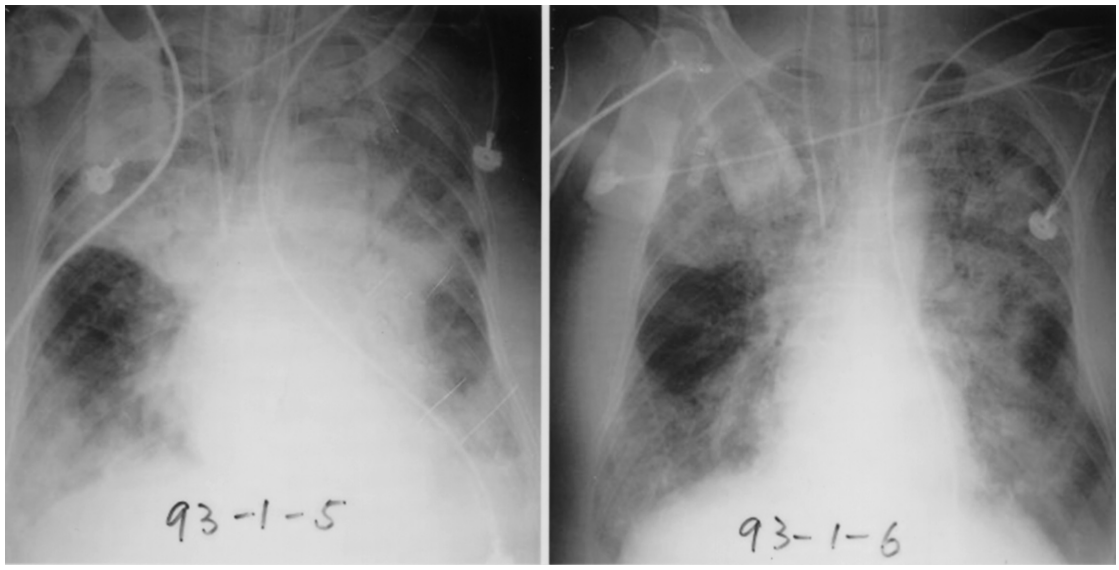


Fig. 3. Serial chest roentgenograms in case 2. (A) Chest film taken on the critical day before the recruitment maneuver was performed. (B) Chest film taken on the day after the recruitment maneuver (before hemodialysis). Resolution of the pulmonary infiltrates and shrinkage of the heart size were noted.

disease of gouty arthritis, and who denied other systemic disease, was transferred to our emergency department due to chest pain and a sensation of shortness of breath for 2 days. Tracing back his history, he had taken herbs recently for management of his gouty arthritis. At the emergency department, the ABG examination showed poor oxygenation (Table 3). The chest film showed bilateral haziness (Figure 4), and the cardiologist was consulted to exclude the possibility of acute pulmonary edema. The cardiologist diagnosed a preserved left-ventricular systolic function after finding a left-ventricular ejection fraction of about 58%, using bedside cardiac sonography examination. Due to poor oxygenation and an acute onset of bilateral infiltrates on the chest film, but with no other infection sign, including fever, shaking chills, or productive cough, and no other infection focus found, ARDS, possibly herb-related, was suspected. He was then transferred to our respiratory intensive care unit (RICU) for further management, with mechanical ventilation support.

Due to the patient's severely refractory hypoxemia, despite pure oxygen and mechanical ventilation support at the RICU, we tried RM and a stepwise increase of the PEEP level up to 25 cm H2O/inspiratory pressure (above PEEP), up to 30 cm H2O, which gradually, but barely maintained the patient's blood oxygenation up to 90% (Table 3). Attempts to lower the PEEP level or the inspiratory pressure to decrease the PIP to less than 55 cm H2O caused an immediate drop in oxygenation, which led us to hesitate in lowering the PIP. The pressure-controlled ventilation with PIP up to 55 cm H2O (inspiratory pressure 30 cm H2O/PEEP 25 cm H2O) persisted for about 4 hours. Unfortunately, subcutaneous emphysema developed later, but the chest film showed no obvious pneumothorax (Figure 4). We decided to sedate and paralyze this patient, and then decreased the PEEP level to 15 cm H2O, while maintaining the inspiratory pressure 30 cm H2O above the PEEP. The respiratory rate was

Table 3. Ventilator settings and serial ABG results in case 3

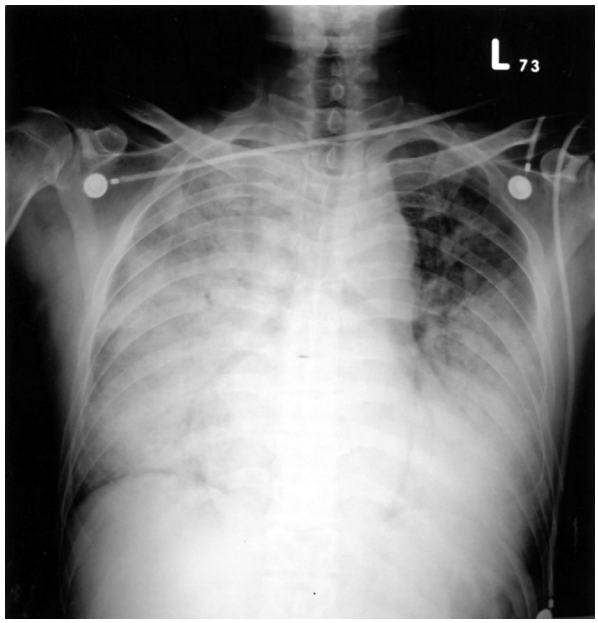
Date		3/30	3/30	3/30	3/30	3/30	3/31	3/31
Time		ER arrival	s/p MV 3 hrs later	RM	RM for 1 hrs	RM for 4 hrs → subcutaneous emphysema	s/p subcut emphysema 4 hrs	s/p subcut emphysema 10 hrs
Ventilator	Mode		PCV	PCV	PCV	PCV	PCV	PCV
Setting	FiO2 (%)	N/C 4L/min	100	100	100	100	100	100
	Insp. Pre. above PEEP (cmH2O)		20	30	30	30	30	24
	PEEP (cm H2O)		10	25	25	Down to 15	15	15
	RR (set/Pt)		15/36	/30	/30	/30 → paralysis to 14	/14	/14
	PIP (cm H2O)		37			45	45	39
	I/E		1:1.1					
Arterial	FiO2 (%)		100		100		100	100
Blood	pH	7.432	7.179		7.51		7.49	7.43
Gas	pO2 (mmHg)	23.7	39		63		69	91
	pCO2 (mmHg)	36.2	56		16		28	32
	HCO3 (mM/L)	23.6	20.5		12		21	21
	Sat (%)	44	55.4	90*	94	90-94*	95	97

PCV: pressure-controlled ventilation, *: pulse-oxymeter monitoring result

also decreased to the setting level of 14 times per minute, after sedating and paralyzing the patient well. Fortunately, the oxygenation level did not drop after the changed setting; no progressive pneumothorax and stable vital signs were noted thereafter. Although the later complications of subcutaneous emphysema, highly suspected barotrauma due to both high PIP setting and hyperventilation with auto-PEEP formation, caused by inadequate sedation and paralyzation, the initially critical hypoxemia was indeed reversed after the RM with PIP up to 55 cm H2O (Table 3). The patient's clinical condition gradually stabilized after the first unstable day. The patient was weaned successfully from mechanical ventilation 21 days later, and was discharged 1 week after this weaning. Despite the complication of subcutaneous emphysema, the RM with high PIP reversed the hypoxemia and supported this patient in overcoming the initially critical condition.

Discussion

The lung recruitment maneuver was designed using high inflation airway-pressure to open the atelectatic lung area in ALI/ARDS patients. The effects of RM were reported mostly as an improvement of oxygenation and static compliance [8-9, 13-15] in ALI/ARDS patients or animal models mimicking the ARDS condition, but also were reported in other groups of patients or specific instances, such as desaturation in ARDS patients after open endotracheal suctioning [16]; hypoxemia in patients after pulmonary thromboendarterectomy for chronic pulmonary thromboembolism [17]; and hypoxemia in patients during laparoscopic bariatric surgery [18]. Besides the



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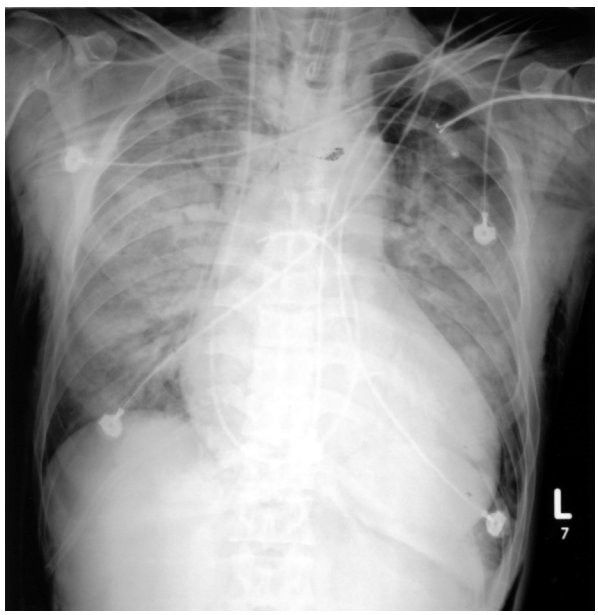

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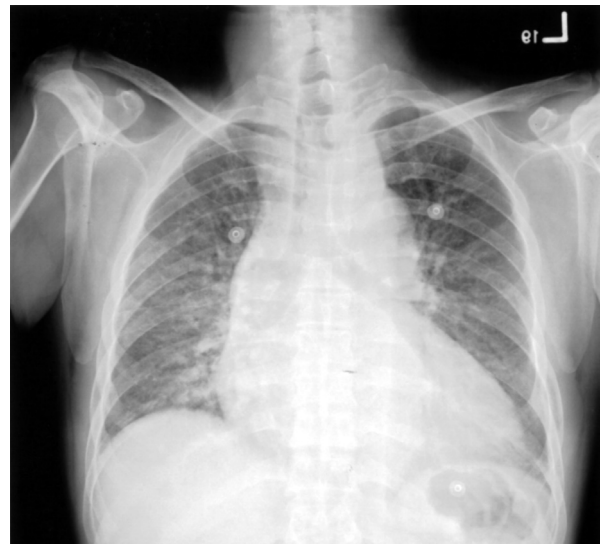

(C)

Fig. 4. Serial chest roentgenograms in case 3. (A) Chest film on arrival at the emergency department. (B) Chest film after subcutaneous emphysema was found. Chest film before discharge showing resolution of the pulmonary infiltrates.

improvements in oxygenation and static compliance, the opening of the atelectatic alveoli by RM was also observed in the CT scans of ARDS patients [19] and animal models [20]. The major side effects observed were the suppression of cardiac output, a drop in arterial blood pressure, and alveolar hyperinflation [8-9, 15, 17-19, 21]. Severe complications, such as pneumothorax, arrhythmia, or bacteria translocation, although not common, have also been reported [5]. Clinically, RM can be performed through various methods, including high continuous positive airway pressure (CPAP), intermittent sighs, pressure-controlled ventilation (PCV) with a fixed PEEP level and high inspiratory pressure, or PCV with fixed inspiratory pressure and a high PEEP level [12]. The commonly used peak inspiratory pressure (PIP) in RM was reported to be mainly around 40 cm H2O to 60 cm H2O [12], but an extremely high PIP, up to 80 cm H2O, was reported in 1 successful rescue RM for a difficult recruited lung [11].

An optimal PEEP level setting after RM is important. Without enough PEEP support, recollapse of the RM-opened alveoli could be observed with CT scan monitoring [19], or observed directly in animal models with in vivo

microscopy [22]. With excessive PEEP, however, suppression in cardiac output and over-stretching of the lung, especially in the well-aerated regions, can also be seen [14]. Clinically, the post-RM PEEP level could be set at 2 cm H2O above the lower inflection point (Pflx) obtained with the static pressure-curve method [6, 23]. It could also be set empirically, such as the reported level of 15/16 cm H2O, since it is clinically difficult to obtain the Pflx from the static pressure-volume curve [6, 13]. Other trials, such as the "post-RM optimal PEEP setting", referred to as the PEEP titration method, were performed by pressure-controlled ventilation with fixed inspiratory pressure (above PEEP) and a high PEEP level in RM. After the RM procedure, the PEEP level was decreased stepwise, with close monitoring of the ABG result at each PEEP level. The post–RM optimal PEEP was set at the lowest point without causing a significant drop in PaO2 obtained at the RM [8, 14].

Although the combination of the lung-protective ventilation strategy, the recruitment maneuver, and an adequately high post-RM PEEP setting obtained an impressive result in 1 study [6], many authors consider the role of RM plus a high post-RM PEEP setting as undetermined and requiring further investigation [5, 9-10]. However, the abundant reported evidence of improvement in hypoxemia suggests that this combination can provide an opportunity for critically ill patients. Zigelman and colleagues reported a 27-year-old male patient in a critical state of severe hypoxemia [11]. The almost inevitable fatal outcome was reversed by aggressive RM, with the peak airway pressure up to 84 cm H2O. Marini's reply to Zigelman's experience was that the "aggressive recruiting maneuver must be taken cautiously, but it also has the potential to be life-saving" [11]. In our experience, the improvements in oxygenation seen as a result of RM and a high PEEP setting have not been rare in ARDS/ALI patients, but the final outcomes were not always so dramatic, due to the complexity of ARDS itself. However, for responsive patients, this maneuver provides more opportunities to overcome the unstable condition of hypoxemia, and more importantly, to reverse the almost inevitable fatal outcome due to hypoxemia, as in our second case report.

One of the most common concerns about RM and a high PEEP level--the complication of barotrauma or air-leakage—was demonstrated in our third case. The mechanism of barotrauma in this patient was suspected to be not only the high PIP setting, but also the inadequate sedation and paralyzation. Auto-PEEP may arise in patients at hyperventilation, due to inadequate expiratory time, if they are not sedated and paralyzed well. The elevated PIP/PEEP level further increases the risk of barotrauma. Although not routinely recommended in the RM procedure, we believe that adequate sedation and paralysis would mitigate the risk of barotrauma, as seen in our third patient. Despite the complication of subcutaneous emphysema, the severe hypoxemia in this patient was indeed immediately reversed by RM. Lowering the PIP level to less than 55 cm H2O, yielding an immediate drop in the oxygenation level, might imply that an opening pressure of 55 cm H2O was needed to open the atelectatic lung area. The decrease in the PIP level by lowering the PEEP down to 15 cm H2O after subcutaneous emphysema developed, however, did not bring on the worsening oxygenation. This divergent result may be attributed to the improved ventilator-patient synchronization by proper sedation and paralyzation. Another possible contributing factor was the opening of the atelectatic alveoli by the previously aggressive RM. A lower PEEP was

then sufficient to keep the alveoli opened.

In conclusion, although the role of RM plus a high post-RM PEEP level needs further investigation, this procedure can act as a rescue maneuver in refractory hypoxemic patients. Further investigation is needed on the most appropriate method of RM, the method of finding the optimal post-RM PEEP level, and the timing and indication for the performance of this procedure.

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肺泡撐開法合併高呼氣末陽壓設定在急性肺損傷與急性呼吸窘迫症候群病人的瀕危急救使用—三例病例報告

蘇鉉宗　周昆達　盧崇正　彭瑞鵬

肺保護換氣策略(lung-protective ventilation strategy)是在成人急性肺傷害與急性呼吸窘迫症候群的呼吸器使用上，目前普遍的共識。而肺泡撐開法(lung recruitment maneuver)與撐開肺泡後高呼氣末陽壓(high positive end-expiratory pressure)的設定，目前在此類病人臨床上的預後效果則尚未確立，有待進一步的研究與探討。儘管如此，肺泡撐開法與高呼氣末陽壓的設定，在急性肺損傷與急性呼吸窘迫症候群病人因為氧合不足而瀕臨危險時，卻有可能扮演一個重要的角色。透過這樣的呼吸器使用方法，有可能因為改善病患的氧合度，而逆轉因缺氧造成的不穩定狀態或死亡結果。在此我們報告三例因缺氧而瀕危的急性呼吸窘迫症候群病人，因為這樣的方法，而逆轉臨床上的不穩定狀況，同時也對這樣的呼吸器設定做一個簡單的探討。*(胸腔醫學* ***2006; 21: 512-523)***

關鍵詞：急性呼吸窘迫症候群，急性肺損傷，肺泡撐開法，高呼氣末陽壓

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Chest Tube Malpositioning-related Hemothorax and Intra-abdominal Bleeding — A Case Report

Po-Kuei Hsu*, Chien-Ying Wang, Mu-Shun Huang

Chest tube insertion is a standard procedure for pneumothorax, massive hemothorax, and hemopneumothorax in emergency departments. The 2 common techniques used for the insertion of chest tubes are the trocar method and blunt dissection. Although the trocar method is simpler, it is associated with a higher incidence of complications. In contrast, blunt dissection is safer and minimizes trauma to neurovascular bundles. The complications of chest tube insertion include infection, tube malpositioning, and injury to internal organs. Inadvertent malpositioning of chest tubes may cause unnecessary trauma to patients. We report a complication due to chest tube malpositioning.

Computed tomography disclosed an intra-hepatically malpositioned chest tube in a patient who had undergone thoracostomy for right-side hemopneumothorax, with a continuous drainage of blood from the chest tube and hemodynamic instability. Tube thoracostomy-related hemothorax and intra-abdominal bleeding were suspected. Immediate removal of the chest tube and insertion of a new chest tube were performed. The hemopneumothorax condition stabilized after conservative management and the chest tube was removed 11 days later. Complications of tube thoracostomy are reviewed in this report. ***(Thorac Med 2006; 21: 524-528)***

Key words: chest tube, complication, hemothorax, internal bleeding

Introduction

In 1876, Hewett [1] first described the drainage of the chest through intercostal tubes. Currently, tube thoracostomy is indicated for a variety of pleural disorders in the emergency department. Although simple, this old technique can be life-saving. However, instrumentation of the thoracic cavity without proper instruction can result in devastating complications. The importance of careful tube thoracostomy can never be overstressed. Herein we report a case with a chest tube malpositioning-related complication.

Case Report

A 44 y/o male involved in a motor vehicle traffic accident was sent to a regional hospital with a loss of consciousness. Subcutaneous emphysema at the right-side chest wall was noted, so, under the suspicion of right-side hemopneumothorax, tube thoracostomy was performed

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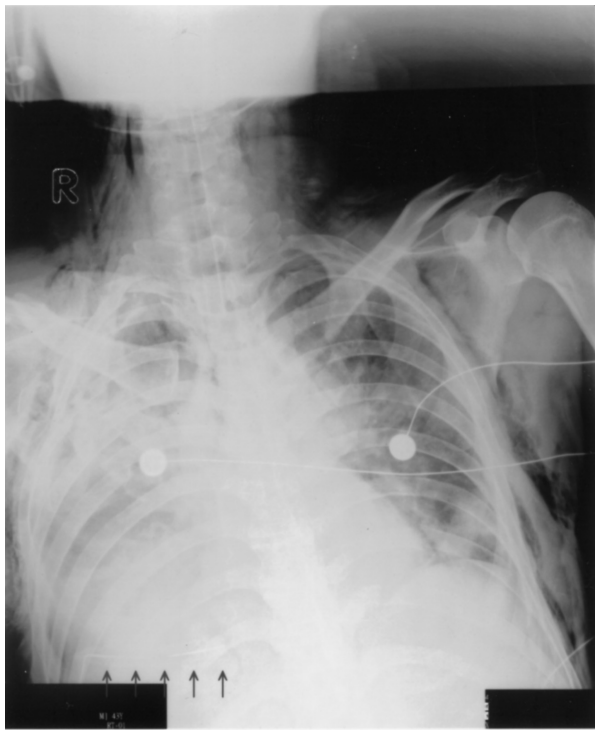

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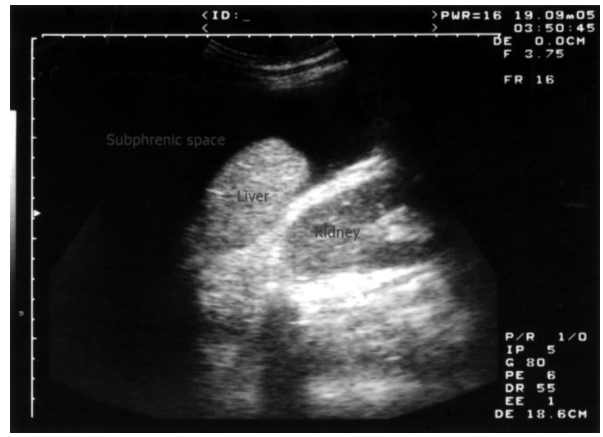

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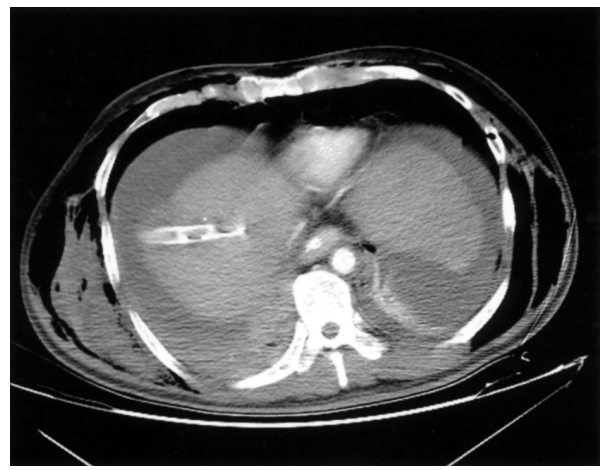
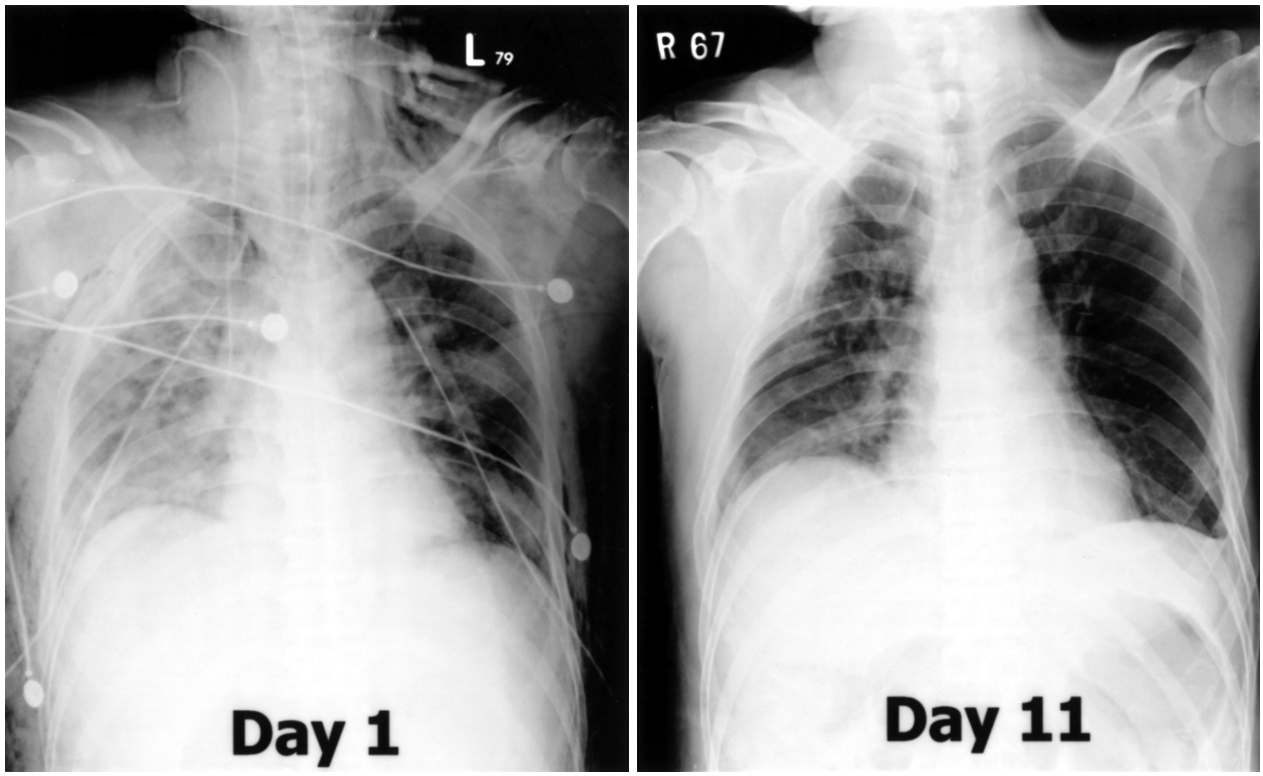


(C)

Fig. 1. (A) The first chest film at the ER showed extensive subcutaneous emphysema, multiple thoracic cage fractures, bilateral hemothorax, and chest tube malpositioning. (B) Intra-abdominal fluid accumulation in the subphrenic space, found by sonography. (C) Abdominal CT scan showing the chest tube in the liver parenchyma.

using the trocar method via the seventh intercostal space. However, continuous drainage of fresh blood from the chest tube and hemodynamic instability ensued. Therefore he was referred to our emergency department.

Emergency personal arrived to find the patient supine and unconscious. The patient's Glasgow Coma Scale score was E2V$_T$M4. Initial vital signs were as follows: blood pressure, 105/52 mmHg; heart rate, 105/min; and body temperature, 33.3ºC. The patient's hemoglobin level was 2.5 g/dL. Fluid resuscitation with normal saline, 4500 ml; Ringer's lactate solution, 1000 ml; packed red blood cells, 8 units; and fresh frozen plasma, 6 units, was initiated to maintain the blood pressure. Image studies revealed right-side hemothorax, right-side middle third clavicular fracture, right-side second to sixth ribs fracture, right-side femoral neck fracture, and right-side acetabular fracture. Chest tube malpositioning was suspected in the chest film (Figure 1A). A focused assessment with sonography for trauma (FAST) showed right-side hemothorax and massive intra-abdominal fluid accumulation (Figure 1B). A contrast-enhanced computed tomography (CT) was indicated for intra-abdominal fluid accumulation evaluation. Our previous suspicion was confirmed by CT scan and an intrahepatically malpositioned chest tube was noted (Figure 1C). The chest tube was removed imme-



(A) (B)

Fig. 2. (A) Bilateral chest tubes were inserted toward the apex for hemothorax. (B) Chest film 11 days later showing good recovery.

diately in the trauma room and the liver parenchyma was accessed with a finger through the chest tube opening. Another tube thoracostomy, using the blunt dissection method, was performed via a new opening at the fifth intercostal space (Figure 2A). Since the clinical condition was not deteriorating and no other internal organ damage could be found on the CT scan, the patient was managed conservatively in the ICU and was transferred to the general ward 11 days later. The chest tube drainage output decreased day by day and we removed the right-side chest tube 11 days later (Figure 2B).

Discussion

In a thoracic trauma patient, a chest tube is indicated with the presence of pneumothorax or hemothorax. The relatively wide and avascular second intercostal space in the midclavicular line has been recommended as the insertion site for the treatment of pneumothorax [2]. The third to fifth intercostal space in the midclavicular line below the pectoralis major muscle has also been recommended to avoid an obvious surgical scar [3]. The triangle of safety, bordered by the anterior axillary line, the lateral margin of the pectoralis major muscle, and a horizontal line through the nipple has been proposed to be the optimum site of chest tube insertion [4]. Since the diaphragm can rise as high as the fourth intercostal space on expiration [3], drains below the nipple increase the risk of intra-abdominal organ damage, such as spleen, liver, and stomach injury [5]. Millikan,

et al. retrospectively reviewed the complications of tube thoracostomy. Four of 447 (1%) patients suffered a technical complication, including laceration injury to the diaphragm, lung, stomach and liver [6]. Two common techniques used in chest tube insertion are the trocar method and blunt dissection [3, 7]. A chest tube with a central trocar can be inserted into a skin incision and forced into the pleural space. Although this simple and fast procedure provides an opening that is better fitted to the chest tube, it is associated with a higher incidence of internal organ damage [3, 7]. Pulmonary parenchymal injury and perforation of the right atrium have been reported with trocar-type thoracostomy [8-9]. In contrast, the blunt dissection method is safer. The pleural cavity is entered using the tip of a mosquito clamp to minimize the possibility of lung parenchymal injury. Then a finger is inserted to confirm the pleural cavity and lyse any adhesions. Precise placement of the tube is achieved with the aid of digital exploration. The incidence of chest tube malpositioning was reported to be higher with the trocar technique than the blunt dissection method in emergency tube thoracostomy (29% vs. 19%) [10]. Spanjersberg reported that the chest tube with a rigid trocar was abandoned in the emergency department in order to prevent iatrogenic complications [11].

In this case, trocar-type tube thoracostomy resulted in hemothorax and liver parenchymal injury with intra-abdominal hemorrhage. Since no other intra-abdominal injury was found by CT scan and an improving clinical condition was noted, the liver injury was treated conservatively without surgical intervention. Although chest tube malpositioning is not rare, it should be keep in mind that trocar-type thoracostomy carries a higher incidence of tube malpositioning and internal organ injury, especially in the presence of severe subcutaneous emphysema, poor patient cooperation, and an emergency situation. Under these circumstances, we suggest the blunt dissection method, rather than the trocar method, in performing tube thoracostomy.

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胸管誤置引起血胸及腹腔內出血—病例報告

徐博奎 * 王鑑瀛 黃睦舜

插胸管是在急診室及胸腔科病房常施行的處置，用以處理肋膜腔不正常的空氣或液體積留，胸管誤置雖不少見，卻可能對病人造成極大併發症。我們報告一位 44 歲男性，因騎機車車禍送到急診室，由於皮下氣腫，便在懷疑氣胸的存在下快速插上胸管，因為血壓不穩及持續有鮮血引流，於是病人被轉往本院。胸部 X 光懷疑胸管誤置，外傷重點腹部超音波可見血胸及腹內積水，為評估腹內狀況，安排電腦斷層檢查，結果證實胸管誤插至肝臟之中，緊急拔除誤置的胸管並重新插入胸管。病人經保守治療 11 天後拔除胸管，肺部復原良好。常用插胸管的方式包括套管穿刺法及手指剝離法，前法雖然較為簡單方便，但在緊急狀況，嚴重皮下氣腫及病人無法正確配合時，我們建議使用手指剝離法較為安全。*(胸腔醫學 **2006; 21: 524-528**)*

關鍵詞：胸管，併發症，血胸，腹內出血

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Extramedullary Hematopoiesis: A Forgotten Cause of Mediastinal Mass

Yin-Kai Chao, Ming-Ju Hsieh, Yun-Hen Liu, Hui-Ping Liu

Extramedullary hematopoiesis (EMH) is a rare disorder, and is defined as the appearance of hematopoietic elements outside the bone marrow. Although it tends to be microscopic and asymptomatic, EMH may sometimes manifest as organomegaly or tumor-like mass. We report the case of a patient with a posterior mediastinal mass with unexplained weight loss. Extramedullary hematopoiesis was diagnosed via surgical resection. Alpha thalassemia minor was confirmed after the diagnosis of extramedullary hematopoiesis. Keys to the accurate pre-operative diagnosis and proper management of this condition are discussed. ***(Thorac Med 2006; 21: 529-533)***

Key words: extramedullary hematopoiesis, mediastinal mass

Introduction

Extramedullary hematopoiesis is generally considered to be the result of a compensatory response to either chronic hemolytic conditions or a disturbance of the bone marrow. Herein, we present a case of extramedullary hematopoiesis presenting as a posterior mediastinal tumor in response to chronic hemolytic anemia.

Case Report

A 49-year-old male patient with a 60-pack-year smoking history and alcoholism presented with dry cough and acute weight loss (7 kg in 1 month). Physical examination revealed a thin man with normal physical activity and with bilaterally clear breathing sounds. Preoperative laboratory findings included microcytic anemia (Hb: 10.3, MCV: 72). Prothrombin time and activated partial thromboplastin time were in the normal range. Routine chest PA and lateral views showed hyperinflation of the lung and a suspected abnormal retrocardiac shadow. Chest CT revealed a bilateral posterior mediastinal mass (Figure.1). Systemic survey, including bronchoscopy and abdominal echo, were all negative. However, due to unexplained weight loss and a suspicion of malignancy, surgical exploration for diagnosis was arranged.

VATS was used for an initial exploration of the left hemithorax, and a 2x2 cm, hourglass-shaped, soft, dark-red tumor at T-7 was noted (Figure 2A, B). It was covered with parietal pleura

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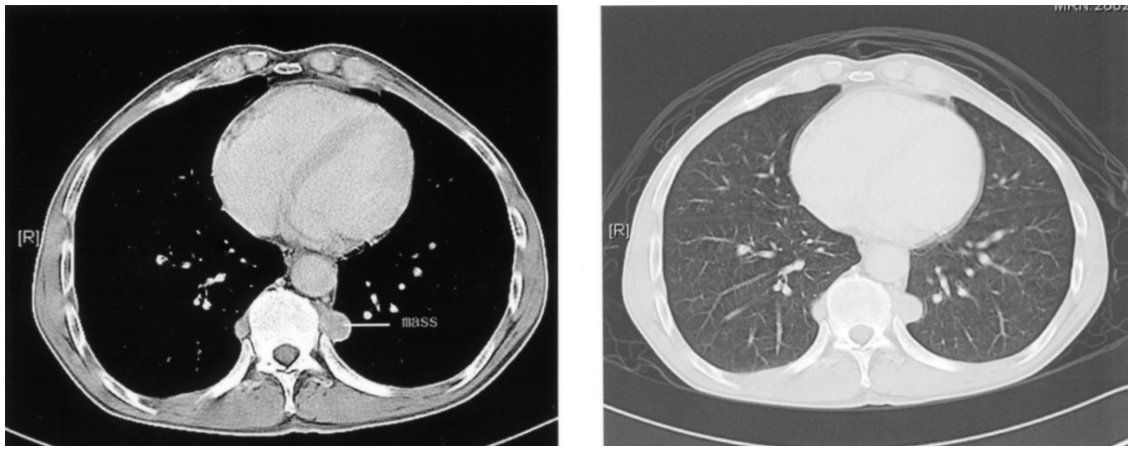

Fig. 1. CT scan showing a bilateral paraspinal mass

and overlaid the descending thoracic aorta. Ennucleation was performed for diagnosis. Profuse low-pressure bleeding at the tumor base was noted, and was controlled with electro-coagulation and local compression (Figure 2C). Estimated operative blood loss was 50cc. The postoperative course was smooth and the patient was discharged 5 days after operation. Pathology proved the diagnosis of extramedullary hematopoiesis, and alpha thalassemia was confirmed by Hb electrophoresis later.

Because of the infrequent association of acute weight loss with extramedullary hematopoiesis, the patient was referred to the oncology clinic for a further systemic survey. Serial workup for cancer, non-malignant GI disorder, and endocrine disease were all negative. The patient remained asymptomatic with stationary body weight during the next 8 months' follow-up.

Discussion

EMH occurs due to the production of blood cells outside the bone marrow and is a compensatory mechanism for bone marrow dysfunction. EMH develops as a reactive process in various types of chronic anemia, especially thalassemia [1], sickle cell anemia [2] and hereditary spherocytosis [3]. Most EMH presents with organomegaly; the most common sites are the liver and spleen. Only a small subset of patients will have a tumor-like mass outside the bone marrow. Atypical areas, such as the mediastinum [1], CNS [4], skin, sinus, and adrenal gland [5] have been reported.

Thalassemia is a common genetically inherited disease in Taiwan with multiple clinical variants. Alpha thalassemia minor is a less severe form and patients are asymptomatic with only mild microcytic hypochromic anemia and do not require blood transfusion. Reviewing the literature, most EMH were reported in cases of thalassemia intermedia [1, 6]. However, bone marrow hyperplasia and an extramedullary focus of hematopoiesis may also occur in patients with thalassemia minor due to constantly decreased blood oxygen load-related bone marrow hyperplasia. In geographical areas where thalassemia is prevalent, mediastinal extramedullary hematopoiesis should be considered in the differential diagnosis of patients who have an abnormal mediastinum mass.

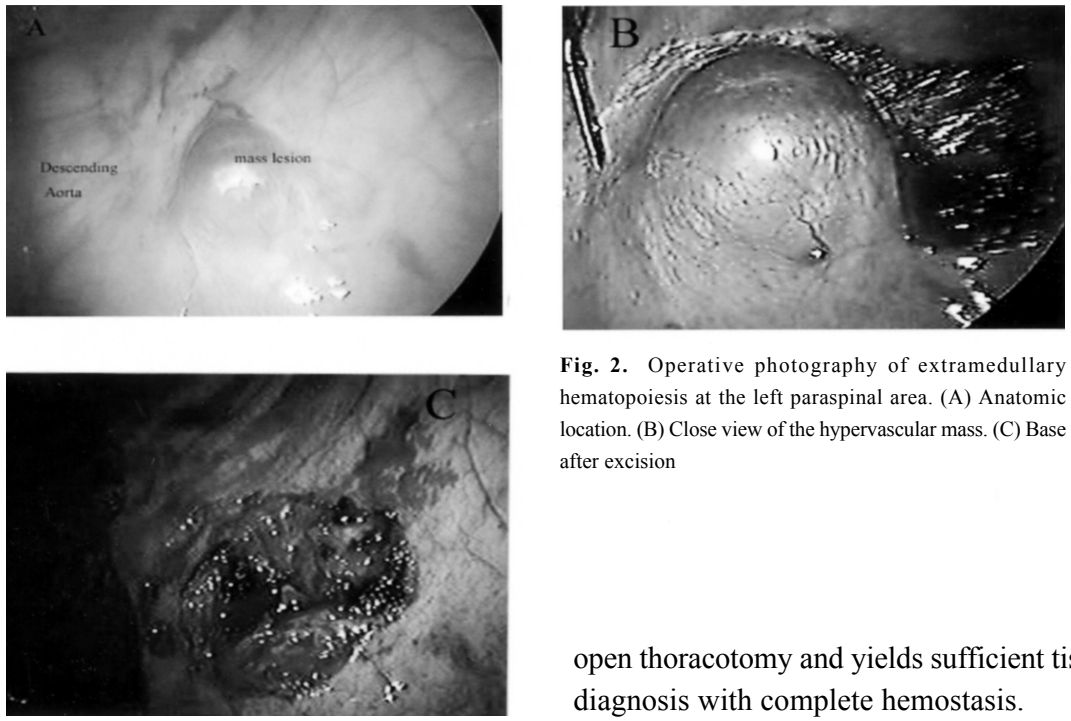

Fig. 2. Operative photography of extramedullary hematopoiesis at the left paraspinal area. (A) Anatomic location. (B) Close view of the hypervascular mass. (C) Base after excision

Intrathoracic EMH is a rare condition that is usually asymptomatic. When the bone marrow dysfunction is obvious and intrathoracic EMH is suspected, the presence of the characteristic findings on a chest roentgenogram and chest CT scan should suffice to make the diagnosis [1, 8]. The typical radiological appearance of intrathoracic EMH includes a well circumscribed lobulated mass without calcification or erosion to the vertebra. It is often accompanied with widening of the ribs or periosteal elevation. Radionuclide bone marrow scanning using Tc^{99m} sulfur colloid was also helpful in establishing the diagnosis [7]. In cases of clinical doubt, transthoracic needle biopsy and open biopsy should be considered. Using a needle biopsy to forestall surgery, however, may not yield sufficient tissue for diagnosis [8]. Further, it should be noted that the needle can cause dangerous hemorrhage from the tumor. VATS is a safe and efficient method for establishing diagnosis, as it eliminates the need for an open thoracotomy and yields sufficient tissue for diagnosis with complete hemostasis.

Most patients with EMH are asymptomatic, and aggressive diagnostic and therapeutic procedures are rarely needed. Aggressive intervention is reserved for when complications occur. When spinal cord compression was treated with low-dose radiotherapy, hydroxyurea, hypertransfusion therapy [9-10] and spontaneous hemothorax were required for surgical exploration and drainage [6].

Conclusion

In geographical areas where thalassemia is prevalent, intrathoracic extramedullary haematopoiesis should be considered in the differential diagnosis of patients who have chronic anemia with asymptomatic intrathoracic masses and abnormal chest roentgenograms, in order to avoid unnecessary surgical interventions. Diagnosis by noninvasive means is desirable, and invasive intervention such as radiotherapy or hypertransfusion is rarely needed, unless symptoms occur. In cases with clinical doubt, VATS is an efficient and safe procedure for establishing the diagnosis.

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以後縱膈腔腫瘤來表現的骨髓外造血：病例報告及文獻回顧

趙盈凱　謝明儒　劉永恆　劉會平

骨髓外造血在慢性貧血的病患常以肝脾腫大來表現，極少數會以腫瘤狀增生做為臨床表徵，本文報告一例以後縱膈腔腫瘤來表現的骨髓外造血，並討論如何術前診斷及治療的時機。*(胸腔醫學* ***2006; 21: 529-533)***

關鍵詞：骨髓外造血，縱膈腔腫瘤

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Clinical Features and Outcomes of Cryptococcal Pleural Effusion in Liver Cirrhotic Patients

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Cryptococcus neoformans can cause infection in individuals with both normal and impaired immune function, especially in cases of human immunodeficiency virus infection. Pleural involvement is not common in cryptococcosis, even with disseminated infection. Liver cirrhosis is a disease known to lead to immunodeficiency. Herein, we report 4 cases of liver cirrhosis diagnosed as cryptococcosis with pleural involvement. The patients comprised 3 females and 1 male, and their ages ranged from 53~75 years. There were 3 hepatitis-related cases and 1 primary biliary-related case of cirrhosis. The characteristics of pleural effusion in our cases were all transudative, and the cellular response of the pleural effusion was neutrophil or lymphocyte-predominant. The prognosis of isolated pleural involvement is somewhat better than that of disseminated infection, although all our cases expired within 3 months. Three cases from the literature are also reviewed in this case series report. In summary, early diagnosis of cryptococcal pleural effusion in cirrhotic patients is still a challenge in clinical practice. ***(Thorac Med 2006; 21: 534-542)***

Key words: *Cryptococcus neoformans*, pleural effusion, liver cirrhosis

Introduction

Cryptococcus neoformans is encapsulated yeast that can cause infection in individuals with both normal and impaired immune function, especially in cases of human immunodeficiency virus (HIV) infection. In addition, hematological and oncologic disease, collagen vascular disease, solid organ transplantation, immunosuppressive drug usage, and diabetes mellitus have been identified as underlying disorders associated with cryptococcosis [1-3]. However, 22% of non-HIV patients with cryptococcosis have no apparent immune suppression [1]. The commonly infected sites are those with meningitis and pneumonia, although invasion to any organ is possible [4-5]. Unlike pulmonary tuberculosis, pleural involvement is not common in cryptococcosis, even with disseminated infection [6-7]. Pleural effusion, if present, is almost always associated with underlying lung parenchymal lesions [8]. An immunocompromised status and immunosuppressant use

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are important underlying conditions of patients with cryptococcal pleural effusion [6].

Liver cirrhosis is a disease known to lead to immunodeficiency [9-11]. It has been documented in several reports that liver cirrhosis is a potential risk factor for cryptococcal infection. [12-14]. Poor outcomes have been reported in many case series, no matter whether disseminated or not. Pleural effusion is not uncommon in liver cirrhotic patients; however, there have been only a limited number of cryptococcosis-related pleural effusion cases reported [12, 15-16]. Herein, we present 4 cases of Cryptococcus pleural effusion in liver cirrhotic patients and review the clinical presentation, characteristics and outcomes of the pleural effusion.

Case Reports

Case 1

A 75-year-old woman with hepatitis B-related liver cirrhosis and Child-Pugh C was hospitalized on 5 November 2000, due to a new onset of fever up to 38.9°C for 2 days. On arrival, the chest X-ray (CXR) showed focal patch opacity in the left middle lung field, and reticular infiltrations in the bilateral lung fields with bilateral sharp costophrenic angles. The white blood cell (WBC) count was 5,600/μL with 72% neutrophils, the platelet count was 59 K/μL, and hemoglobin (Hb) 7.8 g/dL. Serum aspartate aminotransferase (AST) was 202 IU/L (normal range: <37 IU/L), alanine aminotransferase (ALT) 71 IU/L (normal range: <37 IU/L), blood urea nitrogen (BUN) 20 mg/dL (normal range: 4.5~24 mg/dL), creatinine 0.9 mg/dL (normal range: 0.6~1.3 IU/L), lactate dehydrogenase (LDH) 989 U/L (normal range: 230~460 U/L), globulin 2.6 mg/dL (normal range: 2.3~3.5 mg/dL), albumin 2.2 mg/dL (normal range: 3.5~5 mg/dL) and total bilirubin 4.6 mg/dL (normal range: 0.2~1.2 mg/dL). Amoxicillin/clavulanate (1.2 g per 8 hours) was prescribed, but fever was persistent after 4 days' use. A new onset of pleural effusion was disclosed by follow-up CXR. The preliminary isolation of blood culture yielded yeast, and fluconazole 200 mg per day was given parenterally. Paracentesis was performed, yielding yellowish, turbid fluid, and analysis showed portal hypertension-related ascites without evidence of infection. The patient received thoracocentesis, and analysis of the pleural fluid revealed LDH: 152 U/L, glucose: 156 mg dl, protein: 1.3 g/dl, cytology: 1300 WBC/μl, 12% lymphocytes, 15% mesothelial cells, 73% macrophages, an absence of neoplastic cells, and a negative culture for bacteria and mycobacteria. One set of blood culture and pleural fluid culture revealed *C. neoformans.* Then, the dosage of fluconazole was escalated to 400 mg per day. Liver function deteriorated with progressive jaundice (total bilirubin: 19.6 mg/dL) despite the fact that infection seemed under control. She expired on the 22nd hospital day, due to decompensation of liver cirrhosis and a suspected new-onset episode of sepsis.

Case 2

A 67-year-old man with hepatitis C-related liver cirrhosis, Child-Pugh C, and hepatic hydrothorax was admitted on April 22, 2003 due to progressive dyspnea for 3 months. On arrival, the initial CXR revealed massive right pleural effusion with left deviation of the heart and trachea (Figure 1). The WBC count was 7,720/μL, with 80.1% neutrophils, a platelet count of 51 K/μL, and Hb 8.6 g/dL. Serum AST was 42 IU/L, ALT 28I U/L, BUN 23.7 mg/dL, creatinine 1.14 mg/dL, albumin 2.98 mg/dL, globulin 5.1 mg/dL, LDH 536 U/L, total bilirubin 10 mg/dL. and direct bilirubin 4.4 mg/dL. Thoracocentesis was perfor-

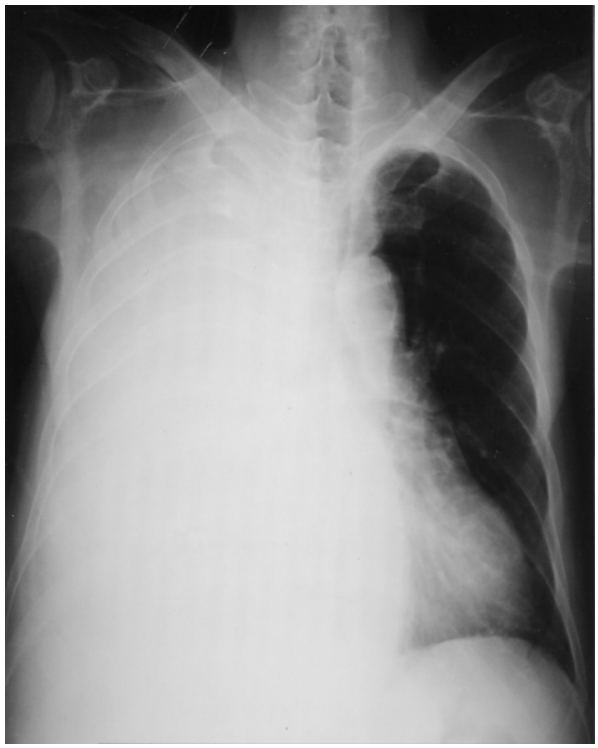

Fig. 1. Anterioposterior chest X-ray on the day of admission showing complete haziness in the right hemithorax with tracheal and mediastinal shifting

med, yielding 1000 ml of reddish serosanguinous fluid. Analysis of the pleural fluid revealed glucose: 112 mg dl, protein: 1.23 g/dl, cytology: 90,000 RBC/μl, 300 WBC/μl, 26% lymphocytes, 58% mesothelial cells, 16% macrophages, absence of neoplastic cells, and a negative culture for bacteria and mycobacteria. Five days after admission, an episode of fever with shortness of breath occurred, followed by septic shock 1 day later. Ampicillin/sulbactam (1.5 g per 8 hours) and an inotropic agent, dopamine, were administered for septic shock. One set of blood culture yielded *Aeromonas hydrophila*. Antibiotics were shifted to Cefuroxime (1.5 g per 8 hours), and his hemodynamic status improved gradually. However, pleural effusion yielded *C. neoformans,* with an elevation of serum antigen (>1:1024) and urine cryptococcus antigen (1:256). Empirical fluconazole with a dosage of 400 mg per day had been given since the 14th day of admission. The patient received video-assisted thoracic surgery for pleural tenting on the 21st hospital day, due to refractory pleural effusion. No Cryptococcus was identified in the operational specimens, and he received a total of 7 days of anti-fungal therapy. He was discharged on the 33rd hospital day, and the CXR upon discharge showed ill-defined consolidation in the right lower lung field with focal obliteration of the right hemidiaphragm.

However, reaccumulation of pleural effusion with shortness of breath, an unstable homodynamic status and leukocytosis were noticed 34 days after discharge. He was admitted to the surgical intensive care unit (ICU) with intubation. Analysis of pleural fluid revealed LDH: 235 U/L, glucose: 164 mg dl, cytology: 300,000 RBC/μl, 900 WBC/μl, 27% lymphocytes, and 72% macrophages. Cefmetazole (1 g per 8 hours) was given, but progressive deterioration of the liver function with hepatorenal syndrome was observed. He expired on the 18th day of admission. The post-mortem fungus culture of pleural effusion revealed *C. neoformans*.

Case 3

A 55-year-old woman with primary biliary cirrhosis, Child-Pugh C, under treatment with prenisolone 15 mg per day, was hospitalized on December 4, 2003 due to abdominal distension and abdominal pain for several days. On arrival, CXR showed bilateral pleural effusion (Figure 2). The WBC count was 26210/μL with 72% neutrophils and 21.5% band forms, the platelet count was 89K/μL, and Hb 8.6g/dL. Biochemistry study revealed AST: 139IU/L, ALT: 108IU/L, BUN: 36.7mg/dL, creatinine: 0.7 mg/dL, albumin: 2.4mg/dL, and total bilirubin: 23.5mg/dL. Ceftazidime (1 g per 8 hours) and metronidazole

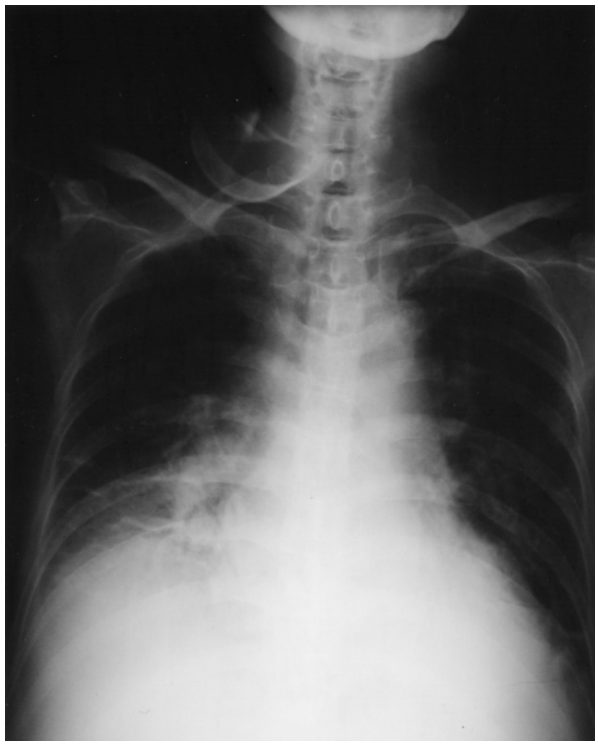

Fig. 2. Anterioposterior chest X-ray on the day of admission showing bilateral pleural effusion with increased lung marking

(500 mg per 8 hours) were prescribed. An episode of a sudden onset of consciousness change, fever up to 38°C, and dyspnea were noted on the 4th day of admission. Cardiomegaly with increased lung markings, multiple patches at both lungs, and blurring of the bilateral costophrenic angles were disclosed by follow-up CXR. Due to respiratory failure and shock, she was admitted to the surgical ICU on the 5th hospital day, with intubation and an inotropic agent, dopamine. The pleural fluid study revealed LDH: 142 U/L, glucose: 60 mg/dl, protein: 0.4g/dl, cytology: 1200 WBC cells/μl, 44% lymphocytes, 7% mesothelial cells, 49% macrophages, absence of neoplastic cells, and a negative culture for bacteria and mycobacteria. Analysis of ascitic fluid showed portal hypertension-related ascites, with 1600 WBCs and 94% neutrophils. Fungal culture of ascites yielded yeast initially, and an empirical antifungal agent with fluconazole 200 mg per day was given beginning the 5th day of admission. Despite the use of antifungal agents, she expired on the following day of ICU stay. Post-mortem, 2 sets of blood culture, a pleural effusion culture, and ascites culture all revealed *C. neoformans.*

Case 4

A 53-year-old woman with hepatitis C-related liver cirrhosis, Child-Pugh C, and hepatic hydrothorax was admitted on September 7, 2005, due to recurrent dyspnea for 3 days and 1 episode of fever. Upon arrival, massive right-side pleural effusion with respiratory distress was disclosed by physical examination and proved by CXR. The WBC count was 9,520/iL with 92.4% neutrophils, the platelet count was 112 K/μL, and Hb 11.2 g/dL. Serum AST was 127 IU/L, ALT 50 IU/L, BUN 25.9 mg/dL, creatinine 1.0 mg/dL, globulin 3.32 mg/dL, albumin 3.03 mg/dL, LDH 634 U/L, total bilirubin 24.26 mg/dL, and direct bilirubin 14.13 mg/dL. Thoracocentesis was performed, yielding 1000 ml of yellowish serosanguinous fluid. Analysis of the pleural fluid revealed LDH: 254 U/L, glucose: 154 mg dl, protein: 1.7 g/dl, cytology: 20000 RBC cells/il, 2900 WBC cells/μl, 5% lymphocytes, 7% mesothelial cells, 88% macrophages, and absence of neoplastic cells. Ceftrioxone (1 g per 8 hours) was given for possible spontaneous bacterial pleuritis. One blood culture set yielded *Salmonella O4.* After 5 days of treatment, fever persisted and antibiotics were switched to cefepime (1 gm per 12 hours). On the 8th day of admission, Cryptococcus was identified from the initial sampling of urine. The antifungal agent, Ambisone, at 3 mg/kg/day, was started on the 8th day of admission. Three sets of blood culture and the pleural effusion study also yielded *C. neoformans* with elevation of pleural cryptococcal antigen (>1:512). She was trans-

ferred to the ICU due to unstable hemodynamics, and intubation was begun due to respiratory failure. Her renal function deteriorated gradually and an episode of profound shock with a full dose of dopamine and norepinephrine was observed on the 15th day of admission. *Enterococcus faecium* bacteremia was reported on the following day, and Teicoplanin was added. She expired on the 18th hospital day, due to profound septic shock.

Discussion

Cryptococcus neoformans is a ubiquitous saprophytic fungus with worldwide distribution. Pleural involvement is not common in cryptococcosis, even in disseminated infection [6-7]. Pleural effusion, if present, is almost always associated with underlying lung parenchymal lesions which may manifest as subpleural nodules, interstitial infiltrates, pulmonary masses, miliary nodules, focal or widespread alveolar consolidation, and lymphadenopthy [8]. The involvement is considered as occurring from an extension of a subpleural lesion into the pleural space [17]. HIV infection is the predisposing factor in approximately 80-90% of cryptococcal infections [18]. An underlying immunocompromised status and malignancy are identified as underlying disorders associated with cryptococcosis in non-HIV patients [1, 3]. Many reports have shown that some types of selective defects in the immune system may relate to Cryptococcus infection [1, 19-21]. Liver cirrhosis is a disease known to lead to immunodeficiency, including depression of cell-mediated immunity, hypocomplementemia, and the reduction in opsonization activity and IgM antibody activity [9-11]. Several reports have documented that liver cirrhosis is a potential risk factor for Cryptococcus infection [12-14].

We identified 3 other cases of Cryptococcus-related pleural effusion in liver cirrhosis patients in a MEDLINE search of reports from 1965 to

Table 1. Clinical characteristics and outcomes of cryptococcal pleural effusion in cirrhotic patients

Case No	Sex	Age	Underlying disease	Child Score	Identified site	PE culture	Treatment	Outcome
Previous report [reference]								
1 [12]	F	55	Cryptogenic LC	B	PE	positive	Flucon	Survival
2 [15]	M	65	Alcoholic LC; steroid use	NR	Disseminated	negative	NR	NR
3 [16]	F	63	LC	NR	Disseminated	NR	Ampho B	Survival
Our cases								
4	F	75	Hepatitis LC	C	Disseminated (B, PE)	positive	Flucon	Death
5	M	67	Hepatitis LC	C	PE	positive	Flucon	Death*
6	F	55	PBC; steroid use	B	Disseminated (B, PE, A)	positive	Flucon	Death
7	F	53	Hepatitis LC	C	Disseminated (B, U, PE)	positive	Ampho B	Death

Definition of abbreviations: M= male; F= female; LC= liver cirrhosis; PBS= primary biliary cirrhosis; B= blood; U= urine; PE= pleural effusion; A= ascites; NR= non-record; Flucon= fluconazole; Ampho B= amphotericin B.

*death 85 days after diagnosis

Table 2. The characteristics of cryptococcal pleural effusion

Case No	RBC (/μL)	WBC (/μL)	L/N/M (%)	Glucose (mg/dL)	Protein (g/dL)	LDH (U/L)
Previous report						
1 [12]	NR	900	4/74/22	91.7	1.4	253
Our cases						
4	0	1300	12/73/15	156	1.3	152
5	90000	300	26/16/58	112	1.23	NR
6	0	1200	44/49/7	60	0.4	142
7	<10000	1000	58/10/32	79	1.5	150

Definition of abbreviations: NR= not recorded; WBC= white blood cell count; RBC= red blood cell count; L/N/M= the ratio of lymphocy-tes: neutrophils: methothelial; LDH= Lactate dehydrogenase

2005 [12, 15-16]. The pleural effusion culture was documented in only 1 case, and this was the only case in which pleural effusion characteristics were recorded [12]. The clinical characteristics are summarized in Table 1. The presentation of cryptococcal pleural effusion includes fever, cough and dyspnea. Five of the total 7 patients had disseminated cryptococcal infection, and the other 2 had documented pleural effusion only. The characteristics of cryptococcal pleural effusion are summarized in Table 2. According to Light's criteria, all of the cases had the pleural characteristics of transudative effusion. The differential count of cytology in the pleural effusion revealed neutrophil predomination and lymphocyte predomination in 2 cases each. Most patients (5/7) received fluconazole therapy, and 2 received amphotericin B. All our patients expired within 3 months; the median documented survival after Cryptococcus is 15.5 days, with a range of 1~85 days. In contrast, in 2 of the 3 reported cases in the literature, the patients survived.

The diagnosis of cryptococcal pleural effusion may be achieved by pleural biopsy, culture and/or detection of cryptococcal antigen in the pleura or pleural fluid. The detection of cryptococcal antigen is considered a good alternative diagnostic method [6, 22]. The fluid itself may be transudate, exudate or even empyema in nature, tending to be lymphocytic in cellular response [17, 23]. However, in the cirrhotic patients in our review, the characteristics of pleural effusion were usually transudative, and differential counts of pleural effusion were neutrophilic or lymphocytic. This presentation is considered related to a cirrhotic status as the possible origin of effusion. This may make diagnosis of cryptococcal pleural effusion more difficult in cirrhotic patients. Two of our cases had lung parenchyma lesions, and the others had unilateral massive pleural effusion. No matter if there are parenchymal lesions or not, cryptococcal infection should be considered in cirrhotic patients with pleural effusion under febrile conditions.

Recent guidelines from the Infectious Disease Society of America recommended treatment with amphotericin B plus flucytosine, followed by consolidation therapy with fluconazole for 10-12 months in immunocompromised HIV-negative patients [24]. Treatment of patients with extraneural or extrapulmonary sites is 1 of the most problematic issues, and this group of patients has the worst prognosis and worst therapeutic response [1]. In case 2, the treatment duration was

1 week due to the lack of isolation from pleural effusion. However, the relapse of cryptococcal pleural effusion indicated that the treatment duration was a critical point in this patient. There are many reports showing a good clinical response with the use of fluconazole only, even in non-AIDS patients [25-26]. In cirrhotic patients, the potential drug-related adverse side effects in renal or liver function are major concerns for cryptococcosis treatment. In the report of Franca *et al*., patients with cryptococcal pleural infection received fluconazole only, and these patients had at least a 1-year survival [12]. The choice of antifungal agents still needs further evaluation in cirrhotic patients. Due to the limited case number, the prognosis factor could not be identified. However, we found that patients with isolated pleural infection effusion seemed to have a better prognosis than those under disseminated infection.

In conclusion, the diagnosis of cryptococcal pleural effusion in cirrhotic patients is still a challenge for clinicians. Pleural cryptococcal infection should be considered in liver cirrhotic patients with pleural effusion under febrile conditions.

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肝硬化病人合併隱球菌肋膜感染之臨床表現及其預後

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無論是否為免疫功能缺陷，隱球菌都可以造成人類的感染，尤其是在後天免疫不全的病人。隱球菌造成肋膜感染的比率並不高，即使在全身性的感染，這樣的表現依然是少數。肝硬化是一個會造成免疫功能低下的後天疾病，亦有一些報告關於這些病人得到隱球菌的病例，但關於隱球菌造成肋膜炎的病例少見，且其臨床表現及胸水的特徵亦多未描述。我們報告四個病例在過去五年中藉由胸水培養，確定有隱球菌造肋膜炎的肝硬化患者：包括三位女性和一位男性，其年齡範圍為 53~75 歲；形成肝硬化的原因，其中三例為肝炎病毒所造成，一例為原發性膽汁性肝硬化症；臨床表現為發燒及呼吸困難，而其胸水的特徵全部皆為濾出液，其中白血球的分類有二例是淋巴球為主，另一例則以嗜中性球為主；其中只有一例其隱球菌感染侷限在胸水中，其他皆為全身性的感染；所有的病例皆有接受抗黴菌藥物的治療，但唯有侷限肋膜感染的一例，存活超過一個月但亦於三個月內死亡。回顧過去文獻中總共有三例的病例報告，唯一一個有胸水分析的病例亦為濾出液。肝硬化的病人發生肋膜隱球菌症並不常見，如何適當的予以早期診斷是個相當重要但不容易的課題。*(胸腔醫學* ***2006; 21: 534-542)***

關鍵詞：隱球菌，胸水，肝硬化

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Lupus Erythematosus (LE) Cells in Pleural Effusion: Initial Diagnosis of Systemic Lupus Erythematosus by Cytological Examination — Two Case Reports and Review of the Literature

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Systemic lupus erythematosus (SLE) is an autoimmune disease involving multiple organs. The diverse manifestations can be confusing and may obscure the diagnosis, especially when few clues are present at the beginning. Serositis is 1 of the various presentations, and the presence of LE (lupus erythematosus) cells in the body fluid may be a hint leading to the final diagnosis of SLE.

Herein, we present 2 male patients diagnosed with SLE with an initial presentation of pleuritis. Although SLE is unusual in this population, the finding of LE cells in the pleural effusion prompted an immunologic survey. The diagnosis of SLE was confirmed with the high titer of ANA and anti-ds ANA. The literature regarding LE cells is reviewed, and we conclude that cytologic examination of the body fluid is not only a useful tool for detecting malignant cells, but also has a role in detecting benign diseases, such as SLE. ***(Thorac Med 2006; 21: 543-550)***

Key words: lupus erythematosus (LE) cell, systemic lupus erythematosus (SLE), pleural effusion, serositis

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease involving multiple organs. The 1997 revised American College of Rheumatology (ACR) criteria for SLE included malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal disorder, neurologic disorder, hematologic disorder, immunologic disorder, and anti-nuclear antibody. The diverse manifestations may be confusing and obscure the diagnosis, especially when few clues are present at the beginning. Serositis, especially pleural involvement [1-2], is not an uncommon manifestation of SLE, with reported incidences of 30% to 54% [3-5]. The task is how to diagnose serositis in a fresh patient. The presence of LE (lupus erythematosus) cells in body fluid may be a helpful guide.

Herein, we present the cases of 2 male patients diagnosed with SLE with an initial presentation of pleuritis. Though confidence in an autoimmune etiology is weak in this population, the finding of LE cells in the pleural effusion prompted an immunologic survey. The high titer

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of ANA and anti-ds ANA was confirmation of a diagnosis of SLE.

Case Reports

Case 1

A 62-year-old male patient was admitted with the chief complaint of dry cough and pleuritic pain in the left side for several weeks. Fever, body weight loss of 6 kg in the most recent 3 months, and general myalgia were also complained of. He had a 3-year history of diabetes mellitus and took oral hypoglycemic agents (OHA) regularly. Other systemic diseases were denied. He was a current smoker, and had consumed 1 pack per day for more than 40 years.

Physical examination disclosed decreased breathing sounds in the right lower lung field without audible adventitious sounds. No supraclavicular lymphadenopathy, jugular vein engorgement, leg edema, joint deformity, or arthritic change was observed. The chest radiograph (CXR) (Figure 1) showed cardiomegaly, left-side costophrenic angle blunting, and increased infiltration in the left lower lung field. Laboratory data revealed normocytic anemia (hemoglobin level: 10.1 g/dl, MCV: 81.9 fl). No leucocytopenia (WBC: 8400/μL) or thrombocytopenia (platelet count: 300000/μL) were noted. The chest computed tomography (CT) showed clustered small mediastinal lymph nodes (Figure 2A, arrows) and a moderate amount of pleural effusion on the left side with mild pleural thickening (Figure 2B). Thoracocentesis was done, and 30

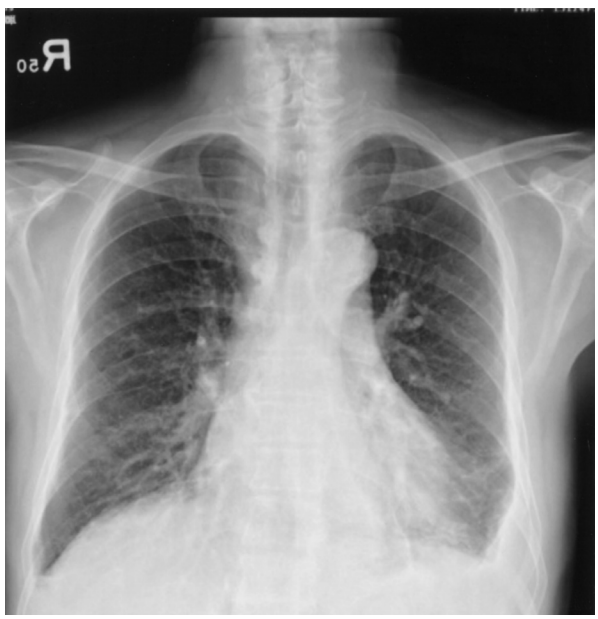


Fig. 1. CXR showing cardiomegaly, left-side costophrenic angle blunting, and increased infiltration in the left lower lung field.

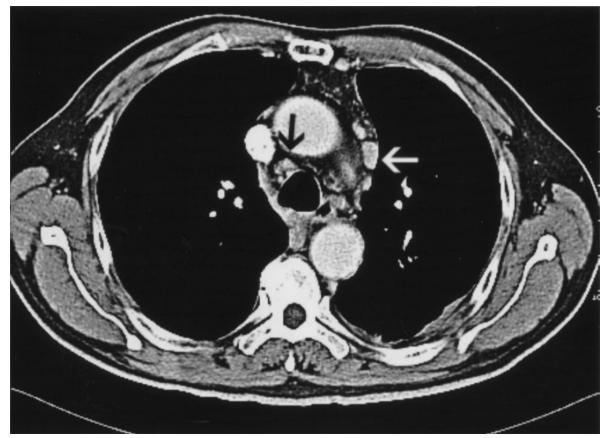


Fig. 2A. CT image showing clustered small mediastinal lymph nodes (arrows)

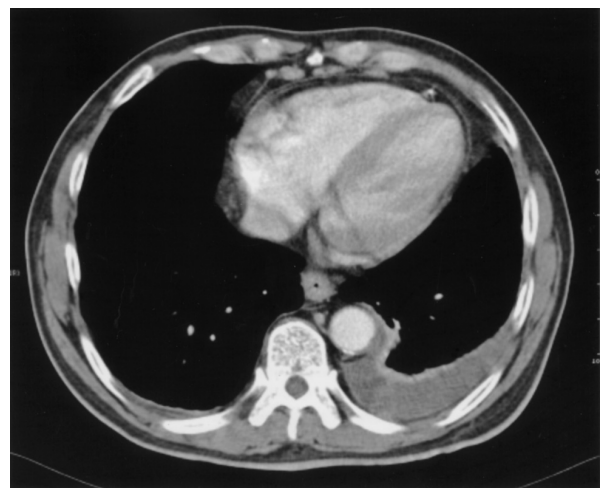


Fig. 2B. CT image showing a moderate amount of pleural effusion with mild pleural thickening on the left side

ml amber color fluid was aspirated. The pleural fluid was analyzed as exudative in nature (protein: 4600 mg/dl, LDH: 967 U/L, WBC: 1429/μL, N/L=51/49). The pleural effusion cytology demonstrated numerous neutrophils with large homogeneous smooth inclusions, typical for LE (lupus erythematosus) cells (Figure. 3-6). No malignant cells were observed.

Serologic survey revealed a markedly elevated anti-nuclear antibody (ANA) titer of 1:2560 in a peripheral type, and a significantly elevated titer of antibody to double-stranded DNA (469 IU/ml, normal < 30 U/ml). Oral ulcers were also observed after examination. With these findings, systemic lupus erythematosus was diagnosed. His discomfort subsided after oral steroid administration.

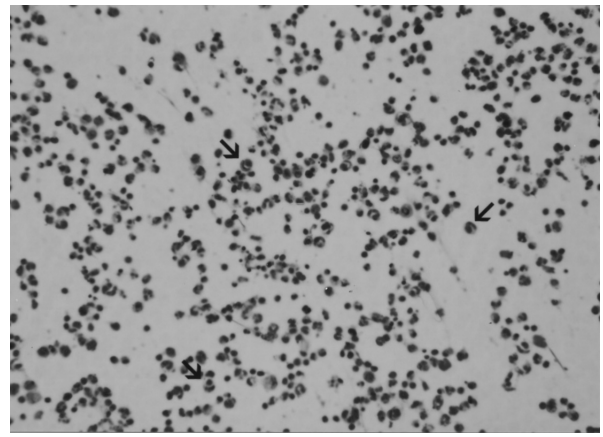


Fig. 5. LE cells in pleural fluid in the pleural effusion cytology (arrows; Papanicolaou stain, 400X)

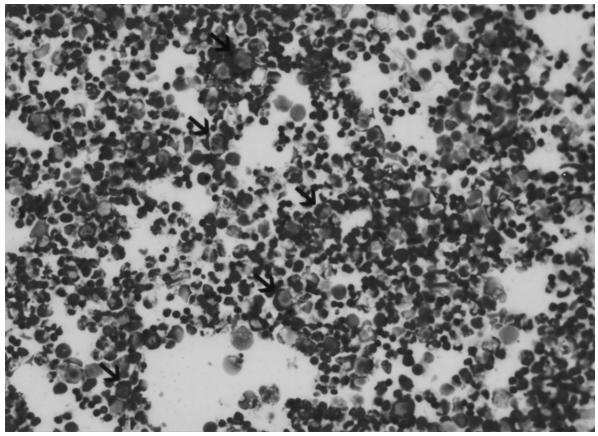


Fig. 3. LE cells in pleural fluid in the pleural effusion cytology (arrows; Liu's stain, 400X)

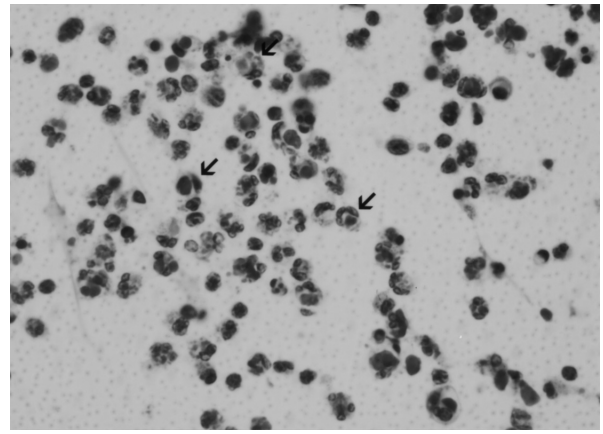


Fig. 6. Typical LE cells (arrows; Papanicolaou stain, 1000X)

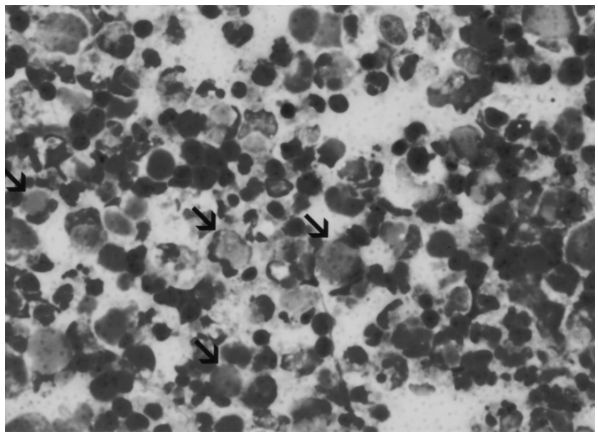
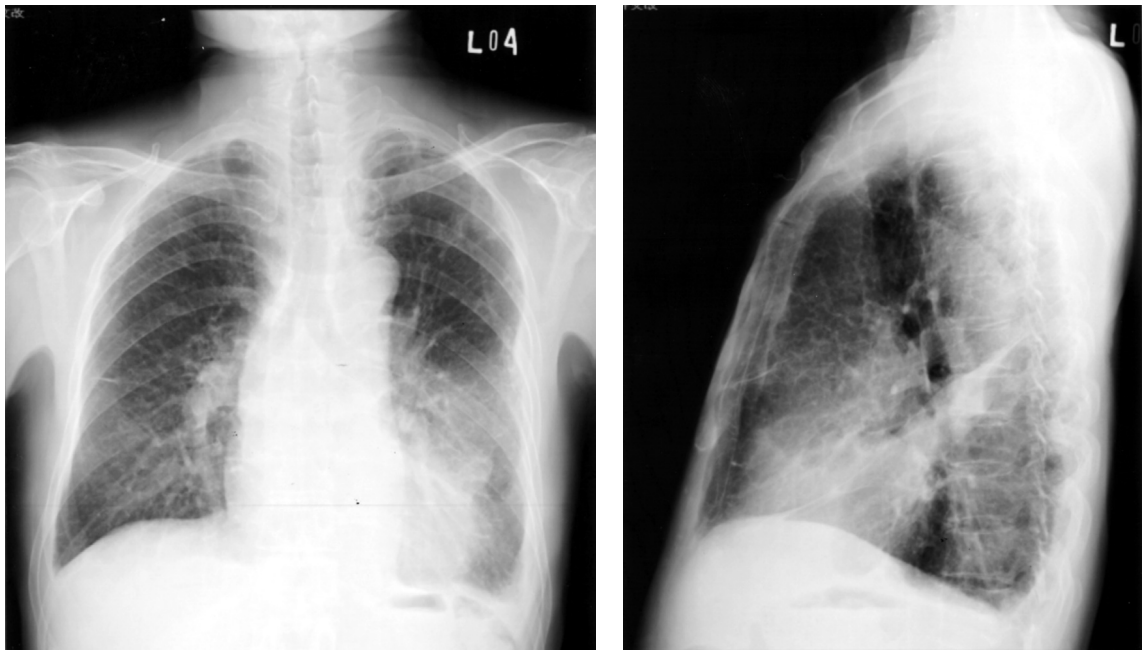


Fig. 4. Typical LE cells in pleural fluid demonstrate a single large homogeneous inclusion within neutrophils (arrows; Liu's stain, 1000X)

Case 2

A 58-year-old male patient was admitted due to general edema for several months. He had a past history of hypertension and chronic hepatitis B with regular medical control. He had visited another hospital due to edema 8 months prior to this admission, and immunotactoid glomerulone-



(A) (B)

Fig. 7A/B. The chest radiograph showing bilateral costophrenic angle blunting, increased infiltration in the left lower lung field, and left-side interlobar effusion

phritis was diagnosed after renal biopsy was performed. Oral steroid was prescribed, but the patient did not take the medication. He then came to our hospital for help because of persistent discomfort. Physical examination disclosed oral ulcers, anemic conjunctiva, and general anasarca. Laboratory data revealed normocytic anemia (hemoglobin level: 7.4 g/dl, MCV: 95.6 fl), hypoalbuminemia (Alb: 2.5 gm/dl), hypercholesterolemia (chol: 288 mg/dl), BUN: 21 mg/dl, and Cr: 1 mg/dl. Direct and indirect Coombs' tests were negative. Urinalysis showed positive findings for protein (> 300 mg/dl) and red blood cells (2+/HPF). The extent of proteinuria was measured as up to 10.9 g/day. Nephrotic syndrome was suspected. The initial chest radiograph (Figure 7A/7B) showed bilateral cardio-phrenic angle blunting, increased infiltration in the left lower lung field and left-side interlobar effusion. Cardiac echocardiography revealed a preserved LV systolic function with an ejection fraction of 71%. Unfortunately, right-side massive pleural effusion (Figure. 8) with dyspnea developed 1 week later. Sono-guided thoracocentesis and chest drainage were done, yielding 1000 ml of yellowish fluid. The pleural fluid was analyzed as transudative in nature (protein: 246 mg/dl, LDH: 35 U/L, WBC: 100/μL, N/L = 85/14). The pleural effusion cytology demonstrated several neutrophils with large homogeneous smooth inclusions, suspicious of LE cells (Figure. 9-11). No malignant cells were observed.

Serologic survey revealed an elevated anti-nuclear antibody (ANA) titer of 1:640 in a diffuse type, and a significantly elevated antibody titer to double-stranded DNA (106 IU/ml, normal < 30 U/ml). Renal biopsy was performed and reported as compatible with lupus nephritis, V+IVc. With these findings, SLE was diagnosed. Due to recurrent pleural effusion, a pig-tail was inserted

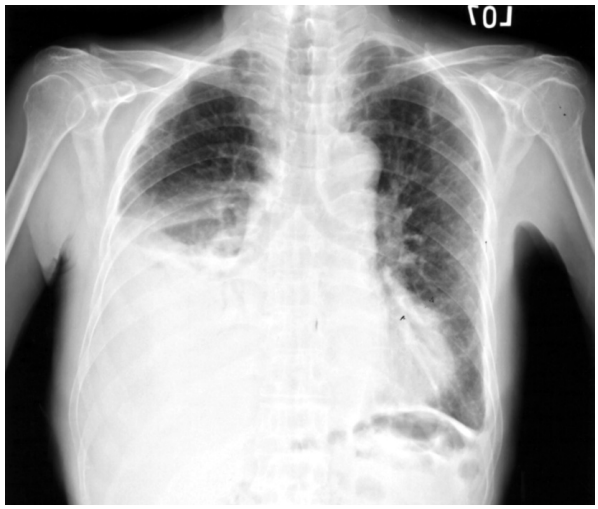


Fig. 8. The chest radiograph 1 week later

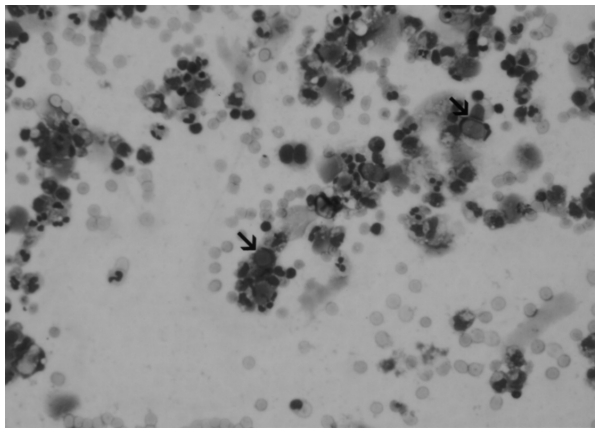


Fig. 9. LE cells in pleural fluid in the pleural effusion cytology (arrows; Lieu stain, 400X)

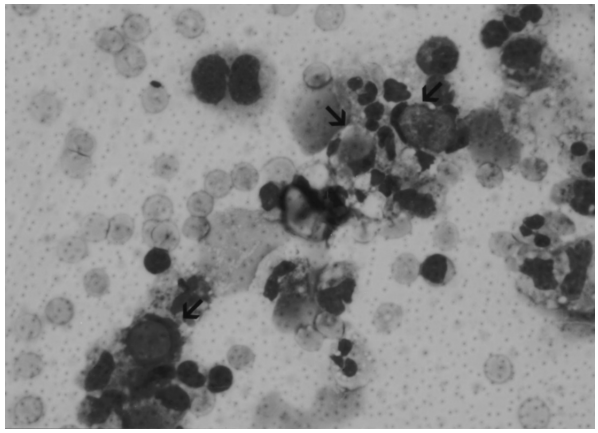


Fig. 10. LE cells in pleural fluid in the pleural effusion cytology (arrows; Liu's stain, 1000X)

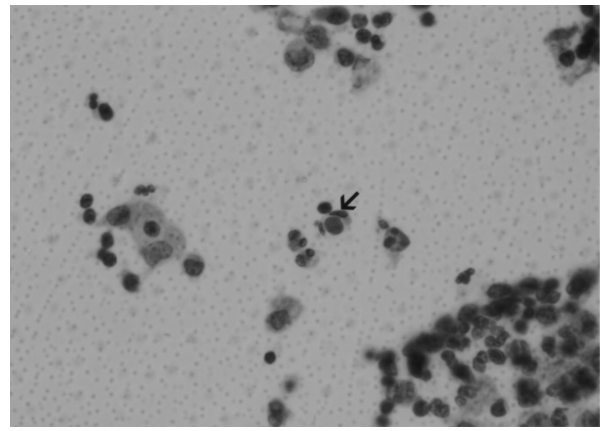


Fig. 11. LE cells (arrows; Papanicolaou stain, 1000X)

for drainage. Parenteral pulse therapy with high-dose steroid and cyclophosphamide were administrated for SLE. His condition improved gradually and he was discharged.

Discussion

SLE is an autoimmune disease involving multiple organs. Serositis is one of the various presentations, and was included first in the 1982 revised American College of Rheumatology (ACR) criteria for SLE [6]. Lupus serositis can involve the pleura, pericardium, peritoneum, and serosal membrane of the bowels. In the current criteria, pleuritis is defined by a characteristic history (pleuritic pain), physical findings (pleural rub), or evidence of pleural effusion [6].

The prevalence of serositis in patients with SLE varies widely, depending on the criteria used, screening methods used, and the patient selection. In a recent retrospective study of 310 patients with SLE, the prevalence of serositis according to ACR criteria was reported to be up to 12%. Pleural involvement is the most common, followed by peritoneal and pericardial involvement [7]. A much higher incidence was reported in previous studies. The prevalence of pleuritis has ranged from 30%

to 54% [3-5]. In 3% to 6% of patients with SLE, serositis was 1 of the initial manifestations [4, 7]. The clinical presentation of pleuritis included typical pleuritic chest pain (47%), dyspnea (30%), dry cough (47%), unilateral pleural effusion on CXR (60%), and bilateral pleural effusion on CXR (33%) [7].

Diagnosis of lupus pleuritis in a fresh case without a specific presentation of SLE is complex. Even if the diagnosis of SLE has been established, the possibility of other etiologies evoking the production of pleural effusion, such as infection, uremia, and congestive heart failure, should be excluded. In the 2 cases reported herein, cytology results put us on a short cut toward the final diagnosis. The presence of LE cells raised our level of suspicion of an autoimmune etiology, especially SLE. Serial work-up, including autoantibody testing, was thus initiated.

The pleural effusion produced in lupus pleuritis was reported as exudates in most cases [8-10], but transudates were also reported [8-9]. Both neutrophil predominance and lymphocyte predominance have been reported [10-11]. The pleural effusion was exudative in our first case, and transudative in the other. The component of fluid overloading should be taken into account, as well. That is, lupus pleuritis per se is exudative in nature, but the concomitant production of transudates due to lupus nephropathy, heart failure, or other causes may turn the overall fluid to meet the criteria of transudate.

The LE cell was first described in the bone marrow of cases of acute disseminated lupus erythematosus by Hargraves in 1948 [12]. Its appearance in peripheral blood [13] and body fluid was observed later [14-18]. Most of the illustrated examples of LE cells in the body fluid of patients with SLE were from pleural fluid [17-21], followed by pericardial fluid [14, 19] and ascites [16, 22]. The presence of LE cells in the body fluid often indicates an active disease status. The process of LE cell formation starts with the interaction of serum gamma globulin with cell nuclei. In the presence of a complement, the loss of molecular structure in the nucleus and the swelling of the nucleus, which are chemotactic for polymorphonuclear cells, can be observed. These denatured, homogenous structures are then engulfed by polymorphonuclear cells, which results in LE cells [23]. It is known that anti-histone H1 antibody plays a central role in LE cell formation [24-25].

Initially, the LE cell was considered specific for SLE. Over the succeeding years, the LE cell was also found in cases of adult and juvenile rheumatoid arthritis, liver cirrhosis, scleroderma, periarteritis nodosa, polymyositis, lymphoma, and tuberculosis, and following therapy with some drugs [26]. The sensitivity and specificity of LE cells for SLE were reported as 73% and 96%, respectively [6]. In contrast, ANA possesses higher sensitivity (99%) and lower specificity (49%). Even though the LE cell is a relatively specific marker for SLE, it was deleted from the ACR criteria and replaced by ANA to increase the overall sensitivity [27].

With respect to cytological examination, this old marker still has its role in the early detection of SLE and in explaining the autoimmune pathogenesis of SLE. The cytological examination is not only helpful in identifying malignant cells, but also some benign diseases, such as SLE.

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肋膜液中發現 LE 細胞：藉由細胞學檢查診斷系統性紅斑性狼瘡—病例報告與文獻回顧

周昆達 * 施振甫 *,** 李毓芹 *,** 彭瑞鵬 *,**

系統性紅斑性狼瘡是自體免疫疾病，可影響許多器官。多樣性的表現會混淆我們的目光，特別是初到院時只有少量的証據存在。漿膜炎也常在系統性紅斑性狼瘡病人身上表現。困難處在於如何在一個沒有診斷而且年紀大的男病人身上得到一些蛛絲馬跡，引導我們向免疫疾病的方向追查。在體液中發現LE細胞，也許是一個不錯的線索。

我們報告兩位年紀大的男病人，一開始以肋膜炎為最初表現。在男性老年族群中，系統性紅斑性狼瘡是比較少見的。在他們的肋膜積液中，我們藉由常規的細胞學檢查，意外發現 LE 細胞的存在。病人血清中也呈現高濃度的的 ANA 及 anti-ds DNA ，從而確立了系統性紅斑性狼瘡的診斷。這兩位病人接受類固醇治療後，症狀得到不錯的改善。我們回顧有關 LE 的文獻，並提出體液細胞學檢查不僅是偵測惡性細胞的常規檢查，對於良性的疾病，如系統性紅斑性狼瘡也扮演一定的角色。*(胸腔醫學 **2006; 21: 543-550**)*

關鍵詞：LE (lupus erythematosus) 細胞，系統性紅斑性狼瘡，肋膜積液，漿膜炎

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Catamenial Pneumothorax: An Example of a Porous Diaphragm — Case Report

Yi-Heng Liu, Chih-Yen Tu, Chia-Hung Chen, Hung-Jen Chen, Chuen-Ming Shih, Chih-Yi Chen*

Catamenial pneumothorax is currently considered to be a very unusual clinical condition. It has been defined as a spontaneous and recurrent pneumothorax occurring within 72 h from the onset of menstruation. The first attack usually occurs in women during the 3rd or 4th decade of life, and is mostly involved in the right lung. However, the exact incidence, pathogenic mechanisms, and optimal management of catamenial pneumothorax remain unclear. We report a 36-year-old female patient with right catamenial pneumothorax that recurred 5 times, and who was found, at surgery, to have many diaphragmatic holes without signs of diaphragmatic or thoracic endometriosis. After the diaphragmatic holes had been closed with sutures, the patient no longer suffered recurrent right-side pneumothorax. Thus, a consideration of catamenial pneumothorax in women of reproductive age with recurrent spontaneous pneumothorax is warranted. Evaluation of the diaphragm is necessary, and if holes are seen, they should be sutured closed to prevent recurrence. ***(Thorac Med 2006; 21: 551-555)***

Key words: catamenial pneumothorax, porous diaphragm

Introduction

Catamenial pneumothorax (CP) is a rare clinical condition. It is found classically in women in the 3rd or 4th decade of life, and occurs within 72 hours of the first day of menstruation. The site of involvement in 95% of cases is the right lung [1]. Several case reports have been published [2-3], thus demonstrating an improved recognition of the disease and an increased interest in the medical community. However, the etiology of CP is unknown, the management is largely variable, and the optimal management remains unclear.

CP occurs more frequently than expected, because physicians usually mistake the historical relationship between pneumothorax and menstruation, as in our case. Herein, we report a patient with right catamenial pneumothorax recurring 5 times, whose diaphragmatic holes were noted during thoracotomy. The pneumothorax no longer recurred after the holes had been closed with sutures.

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Case Report

A 36-year-old female officer (BH=165 cm, BW=56 kg) had a past history of allergic sinusitis and ovarian tube obstruction-related infertility. She suffered from dyspnea and persistently sharp right chest pain in May 2004. The chest radiography (CXR) revealed right hydropneumothorax (Figure 1); she was treated with a 12F pig-tail insertion and her symptoms resolved. The follow-up CXR revealed right lung full expansion, and the pigtail was successfully removed. We diagnosed her as having right spontaneous primary pneumothorax. Unfortunately, she again suffered from persistent right chest pain in December 2004, and the CXR showed right-side pneumothorax. She was then suspected of having recurrent right-side spontaneous primary pneumothorax, and we suggested operation. She received video-assisted thoracoscopy and wedge resection of the right upper and lower lobes with talc pleurodesis. The operative findings were a ruptured and healed bulla of the lung with fibrous thickening, and 2 dark brown, firm, nodules located at the right upper lobe and right lower lobe, with some scarring formation at the apical segment. The pathology finding was fresh hemorrhage of the pleura, myxoid degeneration, and reactive mesothelial hyperplasia. Hyperplasia of type II pneumocytes in the lung tissue beneath the thickening pleura was also noted.

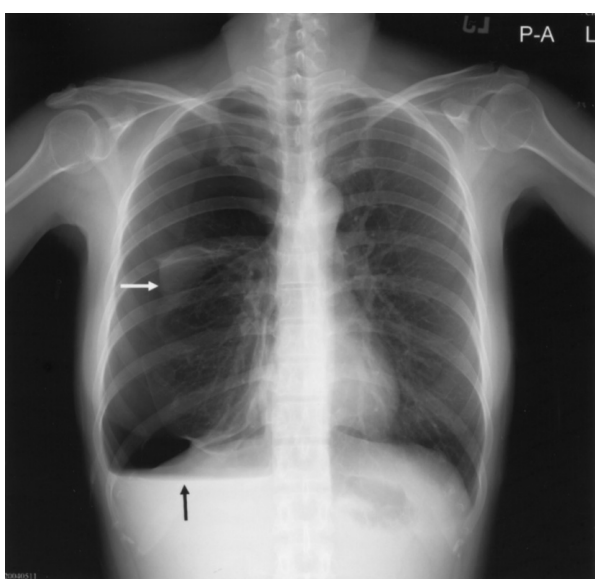

Fig. 1. The initial chest radiography showing right lung shrinkage (white arrow site) and an air-fluid level in the basal area (black arrow site).

The right-side pneumothorax recurred in July 2005, and the patient was treated again with 12F pigtail drainage and repeated pleurodesis with minocycline. At the 4th instance of right-side pneumothorax in August 2005, we made a detailed review of the relationship between her menses and chest pain. The patient recalled that she suffered right chest pain on each 1st day of menstruation, so she was suspected of having catamenial pneumothorax. Due to the small area of pneuemothorax and no obvious dyspnea symptom, she was treated with only an oxygen supply; her follow-up CXR showed no pneumothorax. We consulted a gynecologist about hormone therapy, but the patient still wanted to bear children and refused. However, she suffered a 5th right pneumothorax on the 1st day of another menstrual cycle in September 2005. Due to the frequent recurrence, a second right thoracotomy was suggested. Chest computed tomography in the lung window showed a radio-opaque lesion at the right upper lobe, and operative findings were multiple small holes (about 0.5-0.8 cm) found on the tendinous part of the diaphragm (Figure 2). Multiple brown pigmentation spots were also noted in the right parietal pleura, and the pleural biopsy revealed chronic inflammation with fibrosis. The diaphragmatic holes were closed with sutures, and wedge resection of the right lower lung was performed. After operation, and up to this writing, no more chest pain or pneumothorax has occur-

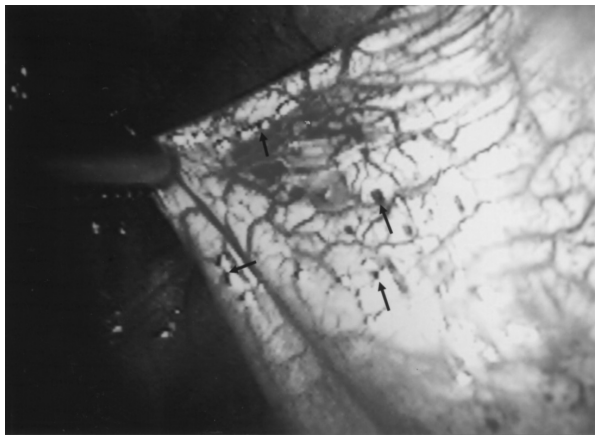

Fig. 2. Multiple small holes were found on the tendinous part of the diaphragm (black arrow site).

red.

Discussion

Catamenial pneumothorax (CP) is generally considered to be a very rare clinical entity found in women of reproductive age and occurring within 72 h from the onset of menstruation. The temporal relationship with menstruation defines the "catamenial" character of recurrent pneumothorax. Menstruation has been considered a rare cause of spontaneous pneumothorax, but interestingly, has accounted for about 25% of the spontaneous pneumothorax in women [4].

The exact pathogenesis of thoracic endometriosis remains unknown. Many hypotheses regarding the cause of CP have been put forth, and include: (1) sloughing of endometrial implants involving the visceral pleura, with a subsequent pulmonary air leak; (2) passage of air from the genital tract through congenital or acquired defects in the diaphragm; (3) alveolar rupture caused by prostaglandin-induced bronchiolar constriction; (4) spontaneous rupture of blebs [1, 5-6]. Therefore, it is well known that CP would be a typical presentation of thoracic endometriosis. However, CP could occur also in the presence of diaphragmatic defects without signs of diaphragmatic or thoracic endometriosis (ie, porous diaphragmatic syndrome).

The most common theory is the movement of endometrial implants to the right diaphragm. Peritoneal circulation up from the pelvis to the right diaphragm has been recognized. These implants then create channels or holes through the diaphragm that will allow further implants to move into the chest or allow the transgression of air [6]. The timing of pneumothorax around menstruation is postulated to occur because of the passage of the cervical mucous plug that allows the retrograde movement of air. In our case, we did not find the endometrial implantation in the diaphragm or parietal pleura. This means that some air may have been retrograded up to the subdiaphragm area, and that some mechanism may have induced pneumothorax.

The second most common theory is congenital or acquired defects of the diaphragm. The right-side predominance of the thoracic manifestations of this phenomenon is the result of the anatomic difference between the 2 upper quadrants of the abdomen. In the right upper quadrant, the solid, more or less fixed liver acts as a piston when the right hemidiaphragm contracts, raising the intraperitoneal pressure locally, trapping the offending substance (ie. air, fluid, etc), and forcing substances through preexisting or acquired holes in the diaphragm. In the left upper quadrant, the relatively loose stomach, colon, and spleen are not mechanically likely to produce the same pressure changes as on the right side [5, 7]. So, the right lung is involved in the great majority of cases [1]. In our case, we found multiple diaphragmatic holes. We believe that there was some air retrograde from the cervical mucous plug up to the subdiaphragm area which was related to

the right diaphragmatic hole-induced recurrent pneumothorax.

In a prospective study by Alifano [4], 32 women with CP were referred for surgery. The catamenial character of the pneumothorax was recognized by clinical history in 8 cases. Of this group of patients, diaphragmatic abnormalities (holes) were found in 1 case, endometrial implants were found in 3, and both were found in 4 cases. In some of these cases, it seemed possible to explain this phenomenon by the transphrenic passage of gas. Nevertheless, not all cases can be explained by the pore hypothesis. In our case, there were no pleural or diaphragmatic endometrial implants, but diaphragmatic holes that played an important role in her recurrent catamenial pneumothorax were found. A detailed history-taking is important in women of reproductive age with recurrent pneumothorax, in order to ascertain if there is a historical relationship between pneumothorax and menses, since this relationship is commonly overlooked.

In conclusion, catamenial pneumothorax treatment usually involves the achieving of 2 goals, the closure of the holes and hormone treatment for the endometriosis. The options for closure of the holes are to perform pleurodesis of the chest, resect the portion of the diaphragm involved, or suture closed the individual holes. Treatment for each case must be individualized.

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月經性氣胸—橫隔膜破洞之病例報告

劉奕亨　涂智彥　陳家弘　陳鴻仁　施純明　陳志毅 *

月經性（catamenial）氣胸臨床上是一個很少見的疾病。它通常發在三十到四十歲的女性病人，並且在月經第一天的前後七十二小時內發生。另外，大部分發生在右邊（95%）。它的致病機轉雖然不明，但有很多論點在討論之中。因此我們報告了這則病例。

本篇文章我們介紹一個病例為 36 歲女性每次月經來時常合併右側氣胸，經由 pig-tail 引流、甚至開刀和肋膜沾黏術後右側氣胸仍然反覆發作。在第二次開刀時發現右側橫膈有很多個約 0.5 至 0.8 公分破洞，並且壁側肋膜有數個棕色色素斑點。病理切片為慢性發炎，並無發現子宮內膜異位。經縫合橫膈破洞之治療後，至今未再復發。同時希望藉由本篇文章之討論能引起更多臨床醫師注意，因為我們在女性病患併有氣胸作病史時常常忽略月經與氣胸之間的關係。橫膈膜破洞可能在月經性氣胸扮演重要的角色。*(胸腔醫學 **2006; 21: 551-555**)*

關鍵詞：月經性氣胸，橫隔膜破洞

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Isolated Pleural Cryptococcosis in an Immunocompetent Patient — A Case Report

Po-Tsung Feng, Wen-Chia Chuang, Chia-Mo Lin, Diana Yu-Wung Yeh, Shang Jyh Kao, Jiunn-Song Jiang

Pleural effusion is an unusual manifestation of cryptococcal infection, and when it does occur, it is almost always accompanied by pulmonary parenchymal disease, usually in the form of infiltrates or nodules. A subpleural nodule is often found immediately subjacent to the effusion, suggesting that the pathogenesis of such an effusion involves direct spread from the subpleural focus. Pleural effusion occasionally occurs in immunocompromised patients with cryptococcosis and suggested disseminated disease. In hosts with a normal immune status and cryptococcosis, pleural effusion is rarely seen.

We report a case of isolated pleural involvement by cryptococcus in an immuncompetent patient. A 53-year-old male suffered from chest pain and dyspnea for 1 week. Chest X-ray on presentation showed left-side pleural effusion, and chest CT revealed a small amount of fluid in the left pleural space. There were no pulmonary parenchymal lesions. The pleural biopsy revealed cryptococcosis and chronic granulomatous inflammation. ***(Thorac Med 2006; 21: 556-561)***

Key words: *Cryptococcus neoformans*, pleural effusion, empyema, immunocompetent

Introduction

Cryptococcosis is caused by *Cryptococcus neoformans*, which is a thin-walled, nonmycelial, budding yeast that is characterized by a thick polysaccharide capsule best seen on India ink stain. *C. neoformans* has a worldwide distribution and is particularly abundant in soil contaminated by pigeon droppings [1-2]. It may also be found in pigeon roosts and nests on window ledges and tall buildings in urban areas. Viable organisms may survive in dried material and dust for months. The respiratory tree is the portal of entry [3-5].

Cryptococcosis may occur in patients with normal immunity; however, most patients who develop cryptococcosis are immunocompromised. Pulmonary cryptococcosis is often clinically silent. The infection may be disseminated hematogenously to involve any part of the body [6-8]. Patients with impaired cell-mediated immunity, such as those with AIDS, rheumatological conditions requiring chronic steroid therapy, organ transplantation and hematological malignancies, are more prone to disseminated cryptococcosis [9].

Cryptococcosis was first reported in Taiwan

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in 1959 [10]. The incidence of pulmonary cryptococcosis in Taiwan is ill-understood, and cryptococcal pleural effusion is even less often discussed. In a review of the English literature, reports of isolated pleural involvement with Cryptococcus were rare [11-12]. We describe an isolated case of pleural cryptococcosis in an immunocompetent patient who presented with chest pain and left-side pleural effusion.

Case Report

In October 2005, a 53-year-old male was referred to our chest outpatient department with a 1-week-history of left pleuritic chest pain. He denied having cough, sputum production, hemoptysis, fever, shortness of breath, or headache. His past history was unremarkable, with no claimed past systemic disease. He was an active smoker with a history of smoking 1 pack per day for 30 years. There was no history of contact with tuberculosis or pigeons. On presentation, he had a body temperature of 37.5°C, blood pressure 140/86 mmHg, respiratory rate of 20/minute, and a pulse rate of 84/minute. Physical examination revealed left-side coarse breathing sounds and tenderness on the left lower chest wall. No lymphadenopathy was noted.

A chest X-ray showed a left pleural-based hazy shadow with interstitial thickening in the left lower lung field (Figure 1). The computed tomography showed a small amount of fluid loculated in the left pleural space with enhancing pleural layers (Figure 2). There was no evidence of disease outside of the pleural cavity. A chest-sonography revealed a small amount non-complex pleural effusion on the left side and pleural thickening. Thoracentasis and pleural biopsy were performed under sono-guidance. Serosanguinous pleural effusion was obtained. The pleural effusion work-up revealed a RBC count of 21850 per cubic millimeter, WBC count of 675 per cubic millimeter (14% polymorphonuclear cells and 86% lymphocytes), glucose of 52 mg/dl, LDH of 272 IU/L, and total protein 4.75 gm/dl. A Gram stain and a stain for acid-fast bacilli were negative. A cell block preparation demons-

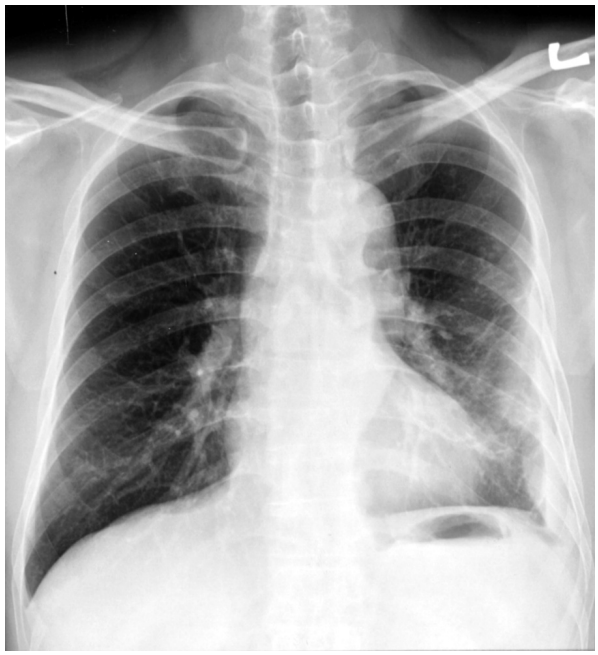

Fig. 1. Chest X-ray revealing left-side pleural-based hazy shadows with interstitial thickening in the left lower lung fields.

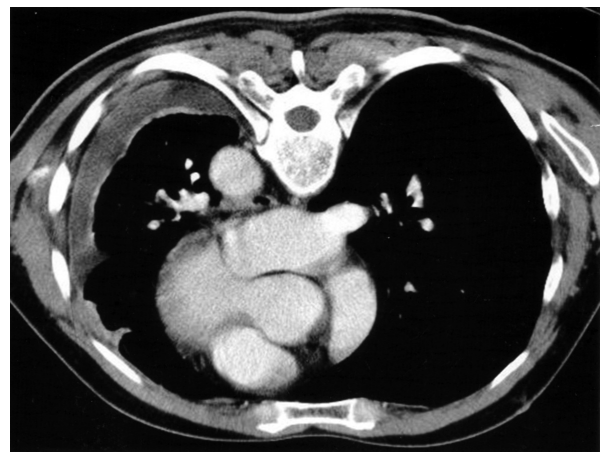

Fig. 2. Contrast-enhanced chest CT scan revealing a small amount fluid loculated in the left pleural space with enhancing pleural layers.

trated benign mesothelial cells intermixed with lymphocytes and inflammatory cells, and was negative for malignancy. The pleural fluid culture was negative. The pleural biopsy specimen report favored a fungus infection, in particular that caused by Cryptococcus. Histochemical studies of mucicarmine, periodic acid Schiff (PAS) (Figure 3) and Grocotal's methenamine silver nitrate (GMS) (Figure 4) stains showed numerous yeast forms, compatible with cryptococcal species. The serum cryptococcal antigen test was positive at a titer of 1:16. The patient was not in a human immunodeficiency virus (HIV) risk group and displayed negative HIV serology.

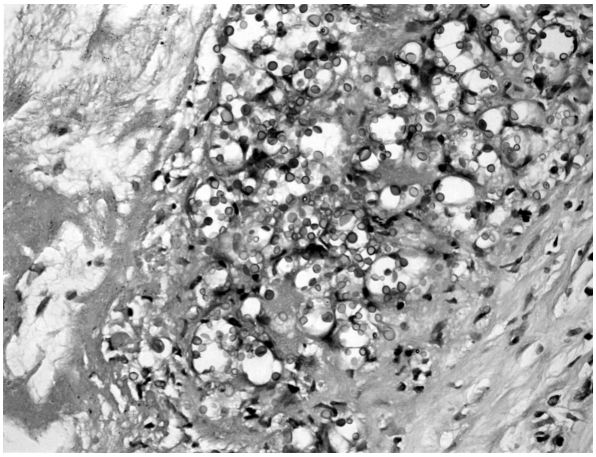

Fig. 3. Section of left pleural specimen stained with PAS demonstrated encapsulated cryptococcal yeast forms, (x400).

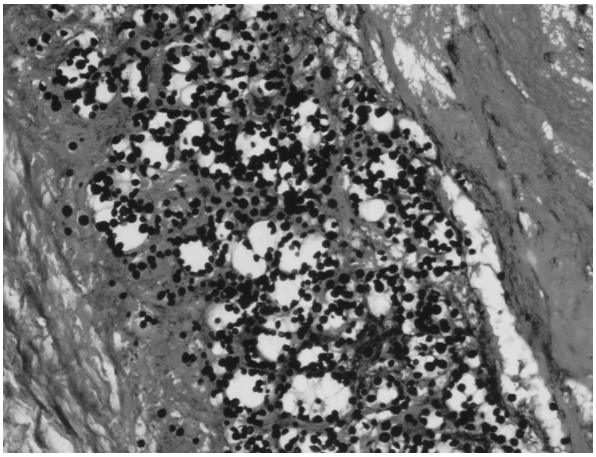

Fig. 4. Cryptococcal yeast forms in the focus of pleural infection (GMS stain, x400).

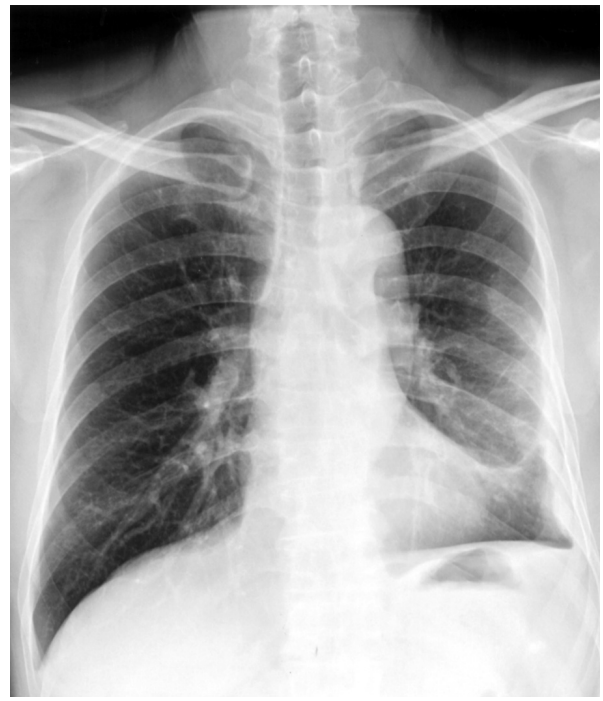

Fig. 5. Chest X-ray revealing left-side pleural effusion resolution with pleural thickening after treatment with oral fluconazole for 1 month.

Therapy with fluconazole 400 mg/day was prescribed for 6 months. The patient gradually improved with complete relief of the chest pain. A chest X-ray (Figure 5) obtained after 1 month of therapy revealed pleural thickening. To date, there have been no signs of further infection.

Discussion

In Taiwan, pigeons are frequently kept as pets and for racing. Their exercise flights are believed to be a means of their dispersing microorganisms. *C. neoformans* was isolated from 62% of pigeon excreta in Taipei, Taiwan [13-14]. Infected patients usually contract the infection directly from the source, and almost always via inhalation. Our case could not be traced to any specific exposure

to pigeons; therefore, it seems reasonable to assume that varying degrees of fungi exposure are possible in our community [13].

Pulmonary cryptococcosis may affect persons of any age, but is more common in middle-aged males. There is no occupational predilection. It is generally accepted that the organism enters the host by the respiratory route in the form of a dehydrated haploid yeast or as basidiospores. In Taiwan, human-to-human transmission of the disease has been documented [15].

The severity of the host's disease results from a combination of several virulence factors superimposed on the host innate and immune resistance status [16]. Between 40% and 85% of patients with cryptococcal infections also have severe underlying diseases or immunodeficiencies. The frequency of cryptococcal disease in steroid-treated individuals, allograft recipients, and AIDS victims highlights the importance of the T lymphocyte-dependent host defense [17].

In Taiwan, the characteristic radiographic findings of pulmonary cryptococcosis were the following: (1) a single, well-circumscribed nodule or mass (64.3%); (2) a well-defined lobar or segmental consolidation (7.1%); (3) infiltration (21.4%); (4) rare cavitation or calcification; and (5) rare pleural effusion [13].

Pleural effusion is an unusual manifestation of cryptococcal infection [1-3], and when it does occur, it is almost always accompanied by pulmonary parenchymal disease, usually in the form of infiltrates or nodules. A subpleural nodule is often found immediately subjacent to the effusion, suggesting that the pathogenesis of such an effusion involves direct spread from the subpleural focus [4]. In a review of the English literature, isolated pleural involvement without pulmonary lesions was found to be very rare in immunocompetent hosts. The first case of epipleural cryptococcosis without pulmonary involvement was reported by Potenza *et al*. [18]. The natural history of cryptococcal pleural disease is poorly understood. In patients with progressive pulmonary cryptococcosis, pleural effusion and parenchymal disease may coexist. Pleural effusion alone may be the presenting manifestation of cryptococcosis, and may resolve without recurrence if the patient's immune response is appropriate [5]. The patient presented herein had a normal immune status and did not have pulmonary cryptococosis.

The pleural fluid of cryptococcal infection varies greatly, from serous to hemorrhagic. Cellular response is lymphocytic. There is no consensus on the definition of empyema associated with fungal disease, nor are there uniform criteria for cryptoccoccal empyema or specific recommendations for treatment, including indications for drainage [12].

As the overall incidence of cryptococcal disease has increased, so has the number of treatment options available to treat the disease. At the present time, in addition to amphotericin B and flucytosine, other drugs, namely fluconazole, itraconazole, and lipid formulations of amphotericine B, are available to treat cryptococcal infections. These agents can be used alone or in combination with other agents with varying degrees of success. The choice of treatment for disease caused by *C. neoformans* depends on both the anatomic sites of involvement and the host's immune status. For immunocompetent hosts with isolated pulmonary disease, careful observation may be warranted. For those with symptomatic infection, non-CNS-isolated cryptococcemia, or a positive serum cryptococcal antigen titer of >1:8, recommended treatment is oral azole therapy for 3 to 6 months [19]. Our case presented with acute cryptococcal pleural disease, and the diagnosis was based on the demonstration of *C. neoformans* in pleural

biopsy specimens and a positive serum cryptococcal antigen titer of >1:16. The patient responded to oral fluconazole therapy without aggressive chest tube drainage or surgical intervention.

In conclusion, isolated cryptococcal infection of the pleural spaces with effusion in an immunocompetent patient is regarded as unusual. Thus, in immunocompetent patients with unexplained pleural effusion, cryptococcal disease should be considered, particularly when there is no evidence of other illnesses that may account for pleural fluid formation.

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新型隱球菌在一免疫力正常病人的肋膜感染—病例報告

馮柏綜　莊文嘉　林嘉謨　葉育雯　高尚志　江俊松

新型隱球菌單純只有在肋膜感染是很少見的，通常在合併有胸水發生的新型隱球菌感染的情況下，常是有肺實質的感染，常可見以肺結節、肺浸潤或肋膜下的結節來表現，間接說明胸水的致病機轉，可能是由肋膜下的病灶直接散佈而來。在免疫力低下的病人，若有胸水發生的新型隱球菌感染，同常表示有散播性的全身感染，而在正常免疫力的病人發生新型隱球菌的感染，很少發生胸水。我們在此提出單純肋膜感染合併胸水，而無肺實質感染新型隱球菌的病歷報告。一個 53 歲的男性，因為胸痛、喘而到胸腔內科求診，胸部 X 光片檢查顯示左肋膜腔積水，胸部電腦斷層顯示無肺實質病灶，經肋膜切片證實為新型隱球菌感染。*(胸腔醫學 2006; 21: 556-561)*

關鍵詞：新型隱球菌，肋膜腔積水，免疫力正常，膿胸

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