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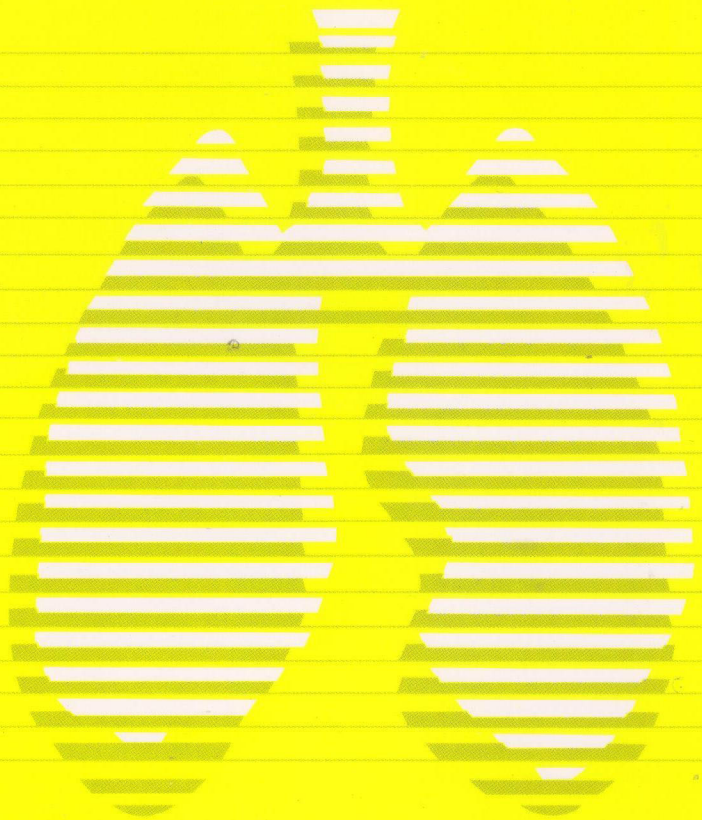

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Review

Case Reports

Management Strategies for Solitary Pulmonary Nodule (SPN)

Chien-Chih Ou, Chang-Yao Tsao*, Der-Ear Huang**, Shi-Ping Luh***,****

Solitary pulmonary nodule (SPN) is seen in about 1 per 500 chest radiographs. The most important goal of its diagnosis is to differentiate benign from malignant lesions. Computed tomography (CT) should be considered for all patients with SPNs, because it can provide more information for subsequent management strategies. Further imaging evaluation, such as positron emission tomography (PET), is generally not recommended because of its limited specificity for the diagnosis of SPN. Tissue diagnosis is usually required, except in cases in which the possibility of finding malignancy is very low. Needle biopsy through the guidance of CT or sonography is not recommended because of its lower specificity and significant complications, such as pneumothorax and hemothorax. Total excision of the SPN through video-assisted thoracic surgery or thoracotomy is usually indicated for specific diagnosis and definite therapy. Many localization techniques, such as hooks, coils, and radiotracer markers can be used to facilitate the subsequent resection procedures. ***(Thorac Med 2011; 26: 1-7)***

Key words: solitary pulmonary nodule, localization, video-assisted thoracic surgery

Definition and Causes of SPNs

A solitary pulmonary nodule (SPN) is defined as an intrapulmonary mass less than 3 cm in size that is not associated with other intrathoracic lesions, such as atelectasis and lymphadenopathy [1]. More than 150,000 patients in the US present annually with SPNs requiring further assessments [2]. The incidence could be higher in upcoming years due to the advances in imaging techniques, especially computed tomography (CT).

The finding of an SPN on a chest radiograph is not uncommon; they are seen in about 1 in 500 chest radiographs. Of the benign lesions, 80% are infectious granulomas, 10% are hamartomas, and the remaining 10% are caused by a variety of rare disorders, including noninfectious granulomas and other benign tumors [3]. The prevalence of malignancy ranges from 10% to 68% in the literature [3]. The probability of malignancy for SPNs increases with the

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size of the lesion, age of the patient, and history of previous cancer [4]. Nodules with a lobular contour or spiculated margin and distorting adjacent vessels are usually malignant. Nodules larger than 1 cm were more likely to be malignant, whereas nodules smaller than 0.5 cm tended to be benign [5]. However, the possibility of malignancy in sub-centimeter SPNs could be up to 30% [6].

Approaches for SPN

Cost-effective differentiation between benign and malignant lesions, early detection and treatment for possible malignancy, and avoidance of unnecessary surgery are the primary goals in the management of patients with SPN [7]. Thus, approaches for SPN include the choice of appropriate imaging modalities and the timing, as well as the type of diagnostic test.

Approaches for SPN depend on the nature of the nodule, the nature of the patient, and the physician or surgeon who assumes responsibility for its further evaluation and treatment [7]. If previous radiographs showed the SPN remained stable in size for at least 2 years and the presence of calcium was in characteristic patterns, and the patients were less than 35 years old without associated risk factors, then serial radiographic follow-up every 3 to 6 months would be appropriate [2, 8]. However, if the SPN were newly diagnosed, malignancy should be considered until proven otherwise. Options in diagnostic approaches include observation, biopsy, and resection, and the choice among them depends on multiple factors, such as age, the characteristics of the lesion, and smoking history [2]. If the SPN were indeterminate after a series of imaging studies, tissue biopsy via a transbronchoscopic or transthoracic approach is recommended in some reported series, whereas direct resection through open thoracotomy or video assisted thoracoscopic surgery (VATS) is recommended by others [8]. Observation would be indicated if the possibility of malignancy was quite low, or the patient refused biopsy or was not suitable for further invasive evaluation [8-9].

By combining appropriate diagnostic studies and close personal attention, unnecessary excision of benign nodules can be kept to a minimum, with the patient's anxiety being allayed and excision of the cancers being undertaken with appropriate staging and without compromise of outcome.

Choice of Imaging Techniques

Imaging evaluations of SPNs are very important to differentiating benign from malignant pulmonary nodules [10]. The expanding availability and use of imaging techniques, such as CT and positron emission tomography (PET), are leading to increased numbers and decreased sizes of nodules detected, and the avoidance of unnecessary surgical resection [11].

With the development of CT for the cancer screening of suspected intrathoracic lesions, more sub-centimeter nodules that cannot be found by conventional radiologic procedures at such an early stage have been detected in recent years. Helical CT, which is not as expansive and time-consuming as standard CT, has gradually replaced chest X-ray as the screening procedure for the early detection of intrapulmonary lesions. Furthermore, CT evaluation can provide more information than conventional imaging to avoid either unnecessary or delayed biopsy procedures [12]. PET can play a role in the evaluation and management of SPNs and

can also be used in combination with CT for tumor and nodal staging for malignancy. In addition, PET also provides additional information for the management of SPNs by estimating the probability of malignancy [3]. However, the value of PET in the diagnosis of SPNs is mostly marginal, since the large discrepancies between CT imaging and other clinical data make judging the risks of malignancy difficult [13-14]. The maximum standardized uptake value (SUV) of 18 fluorodeoxyglucose (FDG) PET/CT is not reliable for the specific diagnosis of SPNs, with false negative rates of about 24% and false positive rates of 20% if the cut-off value is set at 2.5. False negative diagnoses are from bronchoalveolar carcinoma, and carcinoid and metastatic renal cell carcinoma, and false positive diagnoses are from granulomatous inflammation, and bacterial and fungal infection [15]. The specificity of FDG PET for the diagnosis of SPNs is low (around 50% only) because the uptake of FDG occurs not only in malignant tumors, but also in acute inflammatory lesions [16].

The high possibility and significant harmful subsequences of false-negative results from pure imaging evaluations has limited their use in the confirmative diagnosis of SPN. Thus, serial radiographic examinations combined with tissue-diagnostic tests remain necessary in the management of patients with SPNs [14].

Choice of Tissue Diagnosis of SPNs

Once a SPN is detected, image-guided or trans-scopic biopsy is often considered. Image-guided biopsy can be undertaken by using CT, ultrasound or fluoroscopy [17]. A comparative study reviewing over 600 patients who underwent CT-guided or surgical biopsy concluded that CT-guided biopsy is limited in accuracy, especially for benign disease (only 70%), as well as for the inevitability of further surgical intervention for resectable lesions (over 80%) [18]. Biopsy through the fibrobronchoscope or CT-guided biopsy is limited by localization accuracy and the inadequacy of SPN specimens [12], and that it is unsuitable for lung nodules more than 1 cm in diameter, which require tumor resection to establish a definite diagnosis due to the high probability (65%) of malignancy [19]. Previous studies also revealed that histological analysis of resected SPNs found unexpected malignant disease in more than 50% of patients. In these situations, the use of VATS was possible for SPNs, but should be performed in a controlled manner [12, 20-22]. Another large series reviewing over 400 cases concluded that VATS is the approach of choice for both the diagnosis and treatment of SPNs [4].

Previous studies have revealed that VATS, a safe procedure with virtually 100% sensitivity and specificity, could be performed for most small (<3 cm in diameter) and all indeterminate pulmonary lesions [5, 23]. VATS resection of SPN is related to a low conversion thoracotomy rate, a short operation time and fewer postoperative complications, and is well suited for the clarification of SPNs [24-25]. The morbidity and mortality rates with VATS are 3.6-9.6% and 0-0.5%, respectively. Conversion to open thoracotomy in about 15-20% of cases is related to the location of SPNs. Centrally located, larger (>2 cm) and malignant lesions have a greater possibility of conversion [5, 18, 26-27]. VATS for resection of small SPNs was reported to alleviate the need for open thoracotomy in over 80% of patients [6]. Complications with VATS have been reported in relation to the location and size of the lesion, as well as the cardiopulmonary conditions of the patients. SPNs that

were centrally located and larger than 2 cm were reported to have higher rates of complication after VATS biopsy [26].

Localization techniques before the resection of SPNs

Localization techniques include preoperative image-guided injection of methylene blue, placement of hooks, coils, radiotracer markers, intraoperative visual exploration, finger or instrument palpation, and ultrasonographic localization [28-31]. Usually, a combination of CT scan, digital palpation, methylene blue labeling and endosonographic inspections is used.

Preoperative localization is most useful for patients undergoing subsequent VATS resection for small (<10 mm in diameter) and deeply seated (>15 mm from the pleural surface) pulmonary nodules. Even for superficial small nodules, localization can also make VATS resection faster. However, nodules located at apical and diaphragmatic positions are limitations to the procedure [32].

Preoperative localization of SPNs with percutaneous CT-guided hook wire insertion [30-31, 33], and microcoil insertion combined with intra-operative fluoroscopic visualization [34-35] can effectively increase the success rate of subsequent VATS excision.

New localization techniques, such as applying skin fiducials for registration followed by localization by the positioning sensor of the navigation system, have been developed in recent years [36]. Miyoshi *et al*. (2006) [37] reported the use of fluoroscopy-assisted thoracoscopic surgery after CT-guided bronchoscopic metallic coil marking with simulation by means of virtual bronchoscopy.

Treatment of SPNs: The role of VATS

Thoracoscopic wedge excision is a safe and effective procedure in selected patients with an indeterminate SPN. However, malignant SPNs require a minithoracotomy to accomplish a safe operation or to ensure adequate staging and resection for malignancy. Although thoracoscopy reduced postoperative analgesia requirements and shortened hospital stay, total hospital charges were similar to those for a direct resection via open thoracotomy [38]. Previous case studies have revealed that wedge resection with a wide margin for malignant SPNs could achieve 5-year survival, but had a relatively high incidence of local recurrence. Wedge resection can be reserved for patients with resectable lesions but with limited life expectancy or poor cardiopulmonary reserve [39].

Summary

SPNs are not uncommon, and their accurate diagnosis is very important to timely resection for malignant nodules and avoiding unnecessary resection for benign lesions. Since the possibility of malignancy is high for SPNs, tissue diagnosis is usually required for confirmation. Excising SPNs through minimally invasive techniques, such as VATS, is safe and accurate for the diagnosis, and the subsequent definite resection can proceed thereafter (after confirmation by frozen section pathology). Pre- or intra-operative localization for SPNs can facilitate the subsequent resection procedure. Needle biopsy through the guidance of CT or sonography has limited additional effects if subsequent resection is required. In addition, it has lower specificity, and significant complications, such as pneumothorax and hemothorax, develop in

some patients.

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孤立肺結節的處置策略

歐建志　曹昌堯*　黃德兒**　陸希平***,****

孤立肺結節的發生率約為1/500，在診斷上需要注意的就是惡性腫瘤的鑑別診斷，電腦斷層可用為檢查民眾有無肺部孤立結節並提供進一步鑑別診斷已決定處置策略的工具。進一步的影像評估，包括正子攝影，對於孤立結節診斷比起傳統工具並無明顯進一步的診斷價值。組織診斷除非是在臨床判斷惡性機會很低或病人健康狀況不許可的情況下，否則都應執行。使用電腦斷層及超音波針刺切片在診斷上的偽陰性仍高，且其風險也並非極低（其合併症包括氣胸、血胸等）。針對臨床上高度懷疑的病患，使用胸腔內視鏡或傳統外科手術全切除確診後再執行相關處置仍是較為精確即有效率的方法。針對小或深處的腫瘤，我們可以採取許多定位的技術以輔助後續的腫瘤切除，包括鉤針定位，放射同位素註記，螺旋標誌注入等技巧。*(胸腔醫學* ***2011; 26: 1-7)***

關鍵詞：孤立肺結節，定位，胸腔內視鏡手術

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Imipramine Overdose Leads to Acute Respiratory Distress Syndrome: A Case Report

Chun-Yen Cheng*, Chien-Liang Wu*,**, Chao-Hsien Lee*,**

The occurrence of acute respiratory distress syndrome (ARDS) as a result of a tricyclic antidepressant (TCA) overdose is rarely reported, but is of greater interest because of its association with TCA overdose and its reproducibility in animal models. We reported a 43-year-old female who ingested a large amount of imipramine in an attempted suicide. She developed deep coma and hypotension, but did not have cardiac dysrhythmia or seizure. ARDS developed 15 hours later and was treated with extracorporeal membrane oxygenation (ECMO). After a prolonged hospital stay, she was finally discharged uneventfully with moderate restrictive lung disease. We recommended a consideration of the use of ECMO in cases of severe ARDS caused by TCA. ***(Thorac Med 2011; 26: 8-12)***

Key words: tricyclic antidepressant, overdose, acute respiratory distress syndrome (ARDS), extracorporeal membrane oxygenation (ECMO)

Introduction

Tricyclic antidepressants (TCA) are a commonly prescribed medication, as the prevalence of depression has increased in recent years. At the same time, an increasing incidence of attempted suicide with TCA overdose may ensue [1]. Overdose of TCA is distinguished from other medications by its diverse effects on pulmonary vasculature. Therefore, various pulmonary manifestations may develop in cases of TCA overdose [2-3]. Sepsis, trauma, blood transfusion and gastrointestinal aspiration account for most cases of acute respiratory distress syndrome (ARDS), according to a recent review [4]. Drug-related ARDS is rarely reported. Herein, we report a female patient who attempted suicide with a TCA overdose and subsequently (within 1 day) developed ARDS. Conventional ventilator therapy was not sufficient to support her oxygenation. The use of extracorporeal membrane oxygenation (ECMO), however, allowed the recovery of her lung status.

Case Report

A 42-year-old female (weight, 54.5 kg) with a history of major depression was discovered by her family 48 hours after ingesting 160 mg diazepam (80 2-mg tablets), 4 gm quetiapine (40

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100-mg tablets), 400 mg zolpidem (40 10-mg tablets), 300 mg mirtazapine (10 tablets), and 2 gm imipramine (80 25-mg tablets). Previously, the patient had attempted suicide 3 times. There was no history of cardiac dysrhythmia, hypertensive heart disease or thyroid dysfunction, and there was no evidence of aspiration, trauma or infection. She arrived in our medical emergency service in a deep coma (Glasgow Coma Scale of 3), blood pressure (111/71 mmHg), temperature 37.5°C, capillary glucose level 110 mg/dl, sinus tachycardia with 101 bpm, PaO_2 60 mmHg, and respiratory rate 20/min. The chest radiogram showed bilateral interstitial and alveolar pulmonary edema with multiple ill-defined parenchymal densities (Figure 1A). To prevent further absorption of imipramine, a gastric lavage was performed with activated charcoal. Her consciousness recovered gradually in the emergency room. Sandwich immunoassay for urine was positive for benzodiazepines (cut-off 300 ng/mL) and TCA (cut-off 500 ng/mL). Progressive shortness of breath developed 15 hours later. Follow-up chest radiogram revealed diffuse bilateral opacities (Figure 1B). The cardiac sonography showed a preserved global left ventricular contractility function with LVEF 58% and without regional wall motion abnormality. A clinical diagnosis of ARDS was thus made. She was intubated due to persistent hypoxemia despite a high fraction of inspiratory oxygen. Cefpirome, metronidazole and amikacin were given as progression of pneumonia could not be ruled out. A series of infection surveys, including blood, sputum, urine and bronchoalveolar lavage cultures, yielded no growth. The patient remained afebrile with stable hemodynamics during the period in which ARDS was present. Bilateral pulmonary infiltrates persisted, and there was no improvement in oxygenation despite the protective ventilation strategy in the first week (Figure 1C). Arterial blood gas showed pH of 7.449, $PaCO_2$ of 43.8 mmHg, PaO_2 of 49 mmHg, HCO_3 of 29.7 mmol/L, BE of +5 mmol/L with 100% oxygen, and PEEP of 8 cmH_2O on day 5 post-admission. Extracorporeal membrane oxygenation (ECMO) was used from day 5 to day 17 because of severe hypoxia. A step-down steroid regimen for ARDS was used from day 7 to day 38 [5]. ECMO was removed on day 17, and she was extubated on day 23. She received cardiopulmonary rehabilitation after extubation and was discharged on day 51 after admission. The chest radiography (Figure 1D) improved, with some residual interstitial infiltrates only. The pulmonary function test before discharge showed a normal diffusion capacity with a moderately restrictive, but not obstructive ventilation defect.

Discussion

We reported a case of imipramine overdose with rapid development of severe ARDS which was not responsive to a standard protective ventilation strategy, but was successfully rescued with implementation of ECMO and concomitant steroid therapy [6-8]. Although our case was complicated with an overdose of multiple drugs and a prolonged clinical course, the lack of any convincing bacteriologic report, blood transfusion or hemodynamic instability in this case supported our viewpoint that TCA overdose was a reasonable cause of her ARDS [2]. This is the first successful case report in Taiwan using ECMO in the management of a patient with TCA overdose-related ARDS [9].

Although the mechanism of TCA-related ARDS is still not known for certain, results from an animal model suggested that a direct

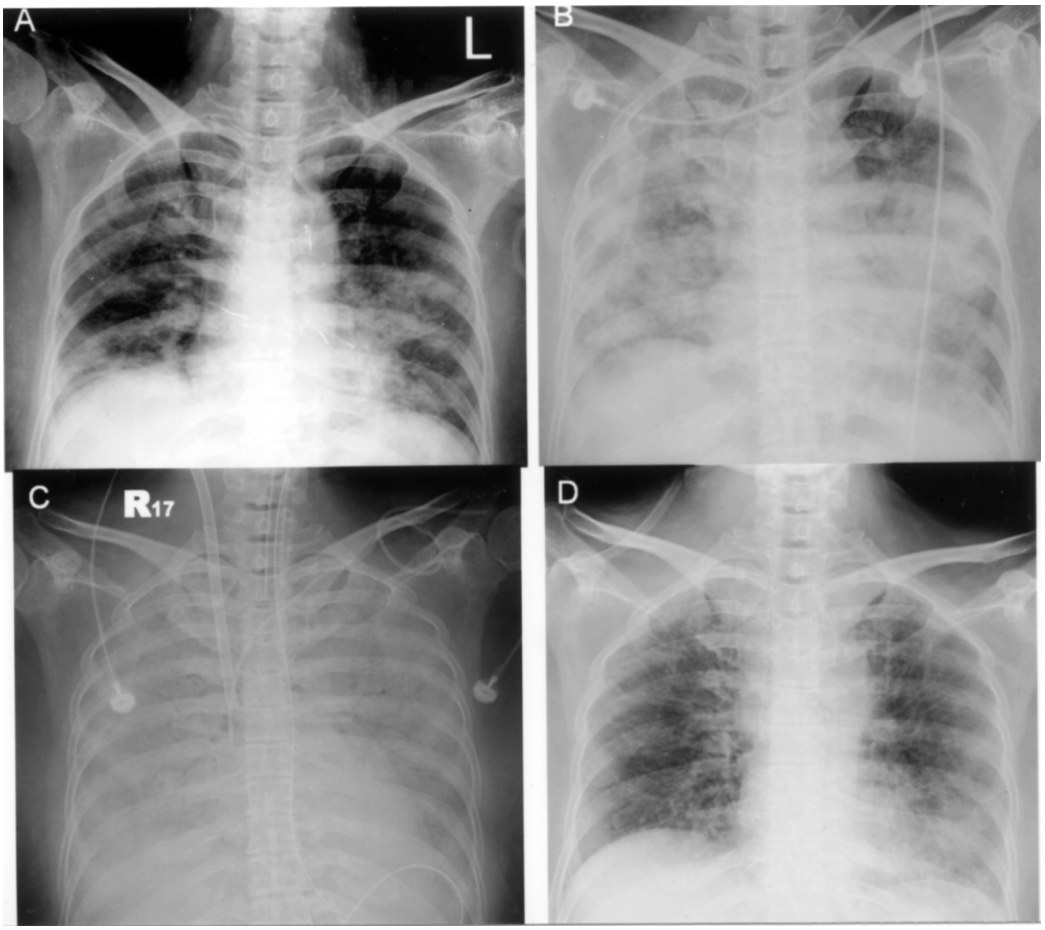

Fig. 1. (A) Chest film at the emergency room. (B) Chest film 15 hours after admission. (C) Chest film while under ECMO. (D) Chest film before discharge.

pulmonary vascular insult from TCA may be responsible for the various manifestations of the TCA-related pulmonary pathology. The severity of pulmonary vasoconstriction is proportionally related to the TCA dose, and this may offer an explanation for the occurrence of ARDS in TCA overdose cases in an animal model [10]. Even though pulmonary abnormalities are common in TCA overdosing, the occurrence of ARDS is rare (9%, according to a large series report) [11]. Although the development of ARDS in patients with TCA ingestion remains hard to predict, our successful experience with ECMO in this patient recommends consideration of a trial using ECMO.

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抗憂鬱三環劑過量合併急性成人呼吸窘迫症候群：一病例報告

鄭俊彥* 吳健樑*,** 李昭賢*,**

在過去的文獻報告中曾有三環抗抑鬱藥過量引致之成人呼吸窘迫綜合症。我們在此報告一名 43 歲的女性服用了大量的 Imipramine 自殺未遂後引起深度昏迷和低血壓，但無心臟心律不整和癲癇發作。她於 15 小時後發生急性呼吸窘迫綜合徵（ARDS），經使用體外膜氧合治療（ECMO），她終於順利出院但罹有中度限制性肺疾病。葉克膜可做為三環抗抑鬱藥過量引致之成人呼吸窘迫症候群拯救生命之暫時治療措施。*(胸腔醫學 **2011; 26: 8-12**)*

關鍵詞：抗憂鬱三環劑，藥物過量，急性成人呼吸窘迫症候群，葉克膜

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Rifampicin-Induced Vasculitis Combined with Thrombocytopenia – Unusual Side Effects in a Patient Receiving Anti-tuberculosis Chemotherapy

Ya-Hui Chiang, Horng-Shin Lin*, Han Chang**, Thomas Chang-Yao Tsao

We reported the case of a 66-year-old male patient with active pulmonary tuberculosis. He suffered from low-grad fever and palpable confluent purpura on the lower limbs and abdomen at 4 months after anti-tuberculous chemotherapy. Thrombocytopenia and eosinophilia were also noted. Leukocytoclastic vasculitis was diagnosed by skin biopsy, which revealed a granular deposition of IgM and C3 at the vascular wall in the superficial dermis, using direct immunofluorescence staining. His skin lesions and fever subsided quickly and the eosinophil and platelet counts returned to normal ranges after rifampicin and corticosteroid treatments were stopped. ***(Thorac Med 2011; 26: 13-18)***

Key words: rifampicin, vasculitis, thrombocytopenia

Introduction

Leukocytoclastic vasculitis (LCV) is 1 of the vasculitic diseases that involve cutaneous small vessels. The etiologies of LCV include infections, autoimmune disorders, food allergens, drugs and idiopathic factors. The clinical symptoms and signs of LCV are fever, malaise and myalgia. The skin lesion is characterized by palpable purpura appearing in crops on the affected dependent parts. The prognosis is usually good, but if LCV involves the kidneys, gastrointestinal tract, lungs, heart, or central nervous system, the result could be fatal [1]. We report a very rare case of rifampicin (RIF)-induced LCV combined with thrombocytopenia and provide more information on the management of such patients.

Case Report

A 66-year-old man was admitted to the pulmonary ward of Chung Shan Medical University Hospital (CSMUH), Taichung, Taiwan, due to a 2-week history of intermittent low-grade fever without chills. He also had had mild exertional dyspnea, cough with scanty sputum, anorexia, malaise and weight loss (6 kg in 1

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month) for a couple of months. A few days before admission, the patient suffered from sore throat and hoarseness, and which was therefore referred to the ear, nose, and throat clinic at CSMUH. Laryngoscopy was performed, which revealed only mild pharyngitis. He was then transferred to the pulmonary outpatient department (OPD) for further management. Physical examinations revealed a thin man with poor nutrition and faint breathing sounds with some coarse crackles in both basal lungs. There was no palpable lymph node or skin lesion. The chest radiograph (Figure 1) obtained at the OPD showed bilateral fibrotic and bronchiectatic changes. Emphysema was also noted in both lungs.

Since the patient had been working in a sand blaster factory for 20 years, pneumoconiosis combined with pulmonary tuberculosis (TB) was suspected. The patient was diabetic, under oral hypoglycemic agent control, and had a history of gouty arthritis.

Blood and biochemical tests performed at admission, on 14 July 2008, showed a white blood cell (WBC) count of 3610/μL, red blood cell (RBC) count of 4,300,000/μL, hemoglobin (Hb) level of 11.7 g/dL, and platelet count of 168,000/μL; renal and liver function tests were normal. A sputum smear revealed 3+ for acid-fast bacilli (AFB) staining. *Mycobacterium tuberculosis* complex was isolated in the sputum culture. The patient was administered anti-TB chemotherapy, including isoniazide (INH), rifampicin (RIF), ethambutol (EMB) and pyrazinamide (PZA). At 12 days after the start of anti-TB chemotherapy, the patient suffered from high-grade fever, and swelling and pain in the right ankle and big toe. Laboratory tests revealed a normal WBC count and eosinophil level, but an elevated uric acid level of 7.0 mg/dL. The patient was diagnosed as having gouty arthritis. The PZA was stopped on 18 July 2008, and he was then treated with colchicin and a non-steroidal anti-inflammatory drug (NSAID). The fever and arthritis subsided after the above treatment. At 3 weeks after admission, the sputum was negative for AFB in 3 subsequent specimens. He was discharged and received regular outpatient management with INH, RIF and EMB.

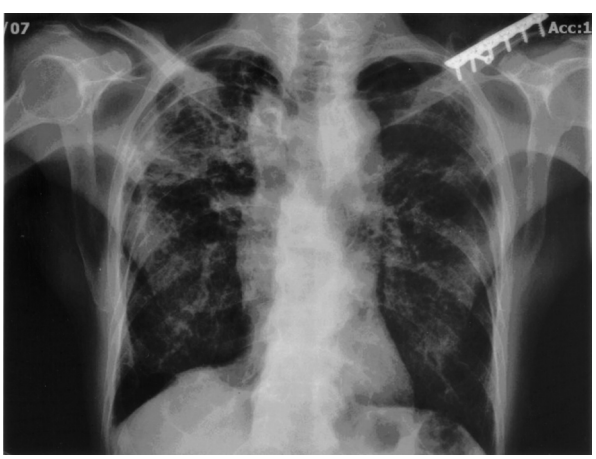
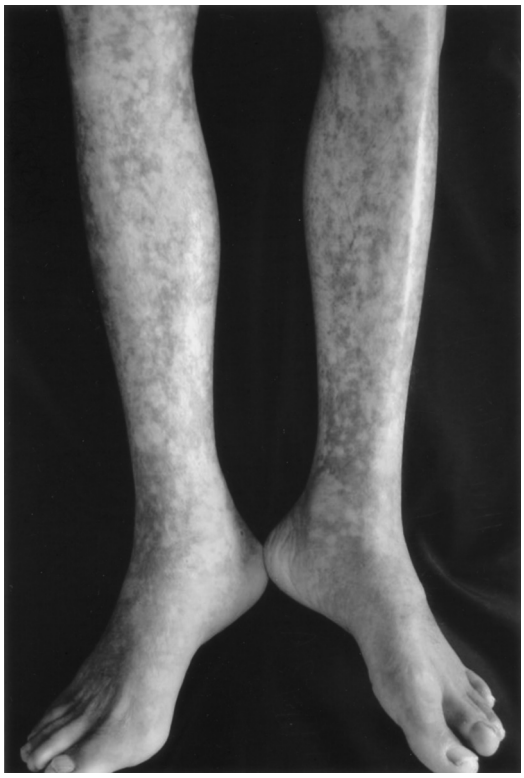


Fig. 1. Chest radiograph showing bilateral fibrotic and bronchiectatic changes. Emphysema is noted in both lungs.

About 4 months after anti-TB chemotherapy, the patient suffered from low-grade fever, and palpable confluent purpura on the lower limbs and abdomen (Figure 2). The hemogram on 14 November 2008 showed eosinophilia and thrombocytopenia, with a WBC count of 8180/μL, eosinophil count of 8.0%, and platelet count of 69,000/μL. The biochemical analysis revealed normal renal and liver functions. We first diagnosed the condition as NSAID-induced skin allergy, but the skin lesions persisted and even exacerbated at 1 week after the medication was stopped. Next, skin biopsy was performed. Direct immunofluorescence revealed granular depositions of IgM and C3 at the vascular wall in the superficial dermis (Figure 3). LCV was

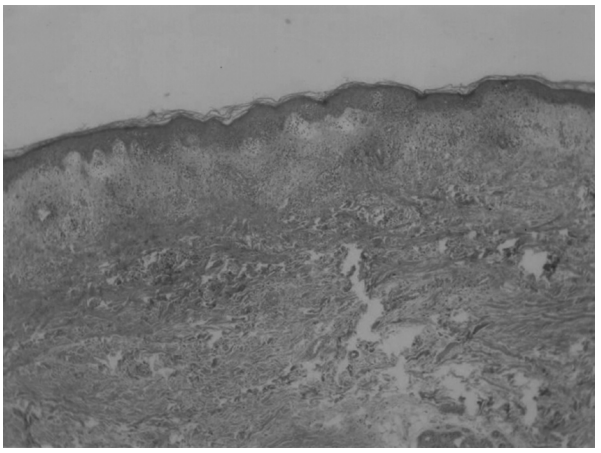


(A)

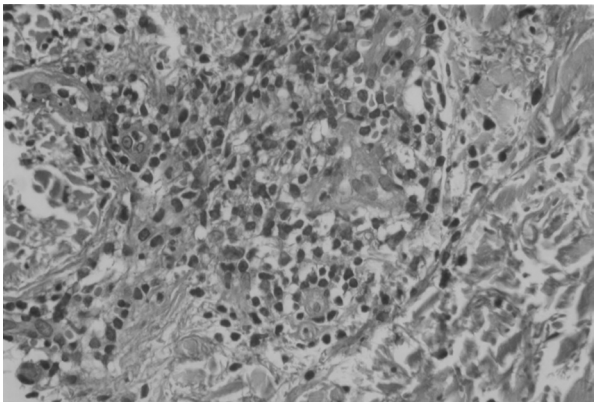
(B)

Fig. 2A, B. Palpable confluent purpura was found on the lower limbs (A) and abdomen (B).

diagnosed. Other immune examinations were positive for antinuclear antibody (ANA)-speckled type 80 X and negative for antineutrophil cytoplasmic antibodies (ANCA); the rapid plasma regain test/venereal disease research laboratories (RPR/VDRL) was negative; and the anti-



(A)



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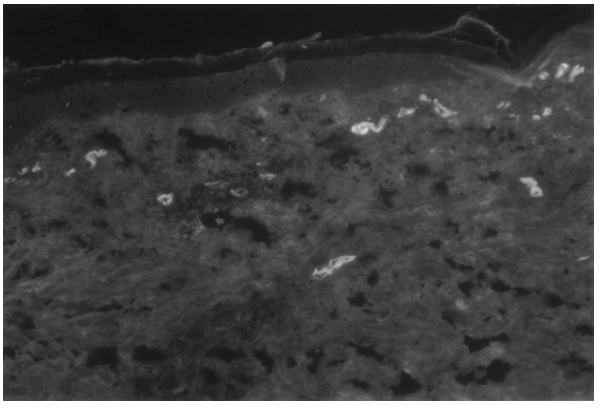

(C)

Fig. 3. A, Interface dermatitis with subepidermal blister and superficial angiocentric infiltration (hematoxylin and eosin stain, 40x). B, Small vessels showing fibrinoid deposition or destruction of the vascular walls (hematoxylin and eosin stain, 200x). C, The combination of vascular changes in the skin biopsy and immun deposition (IgM and C3) in the vascular wall by direct immunofluorescence staining.

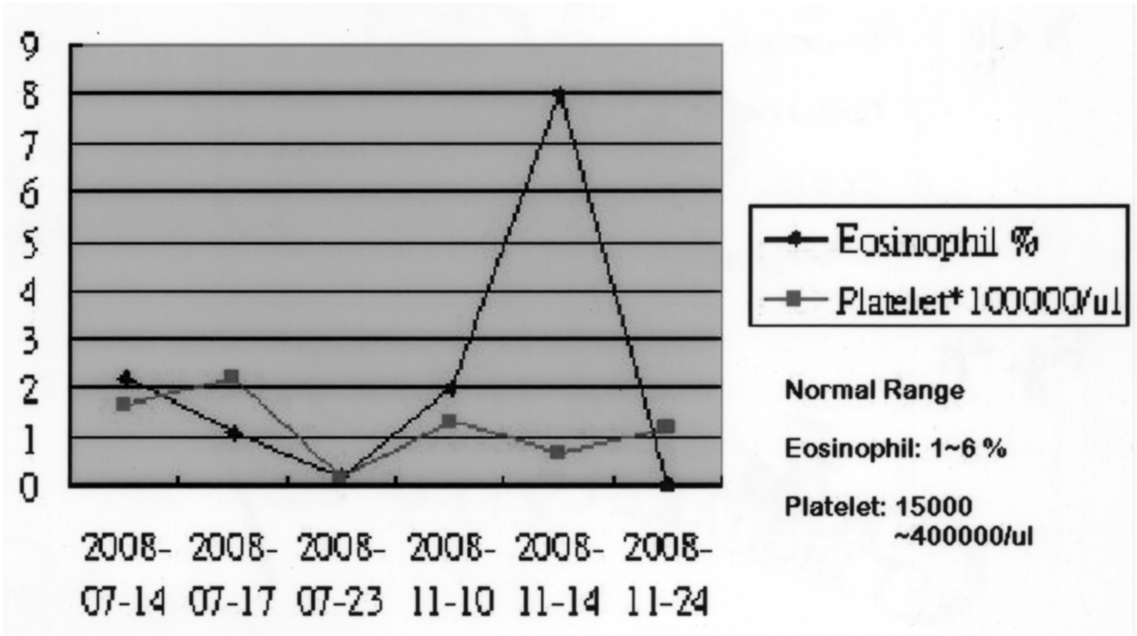

Fig. 4. Eosinophilia and thrombocytopenia occurred on 10 November 2008 and returned to the normal range 10 days after rifampicin and corticosteroid treatment was stopped on 24 November 2008.

streptolysin O test (ASLO) was negative. RIF-induced vasculitis and thrombocytopenia was diagnosed. RIF administration was then stopped and an intravenous injection of corticosteroid was started. The skin lesions improved quickly and the fever subsided; the eosinophils and platelet counts returned to the normal range on 24 November 2008, after corticosteroid treatment (Figure 4). Streptomycin and avelox (moxifloxacin) were added to the treatment protocol after RIF was stopped. No vasculitis or thrombocytopenia recurred during the 9 months of anti-TB treatment without RIF.

Discussion

We report a patient with RIF-induced vasculitis combined with thrombocytopenia. Infection and collagen vascular disease are the most commonly responsible factors in the development of this disease; however, some drugs may also be causative factors [1-2]. RIF is 1 of the most effective anti-TB antibiotics. Its major side effect is liver toxicity. Fewer than 4% of patients may develop an immunoallergic reaction, such as rash, fever, nausea and vomiting. More severe hypersensitivity reactions are uncommon [3]. Drugs implicated in vasculitis include allopurinol, thiazides, sulfonamides, other antimicrobials and several NSAIDs. The symptoms and signs range from cutaneous lesions to glomerulonephritis and pulmonary hemorrhage [3-4]. Our patient had palpable purpura and thrombocytopenia, but his renal function was normal. Skin biopsy revealed granular depositions of IgM and C3 at the vascular wall in the superficial dermis, using direct immunofluorescence staining. These findings were similar to those of RIF-induced thrombocytopenia and renal failure. It is hypothesized that anti-RIF antibodies that are of the IgM, or less frequently of the IgG class, form an immune complex with

RIF. They bind to the platelets, vascular wall or renal tubular epithelium. This binding then induces cellular destruction, with the development of thrombocytopenia, skin lesions and acute renal failure (hypersensitivity III reaction) [5-6].

Usually, RIF should be withdrawn in patients with any immunoallergic side effects. However, it may have to be prescribed in some patients, such as those with INH-resistant TB. In this condition, the use of a desensitization protocol or the administration of corticosteroids may be effective before the administration of RIF. In our patient, PZA was stopped due to the gouty arthritis. Streptomycin and avelox (moxifloxacin) were then added to the treatment protocol after RIF was stopped. The patient continued with the anti-TB chemotherapy for another 9 months and showed no recurrence of vasculitis or thrombocytopenia.

In conclusion, RIF-induced vasculitis combined with thrombocytopenia is an unusual condition. Physicians should be alert to this rare side effect. RIF should be stopped and corticosteroids administered for the treatment of these side effects. Development of associated immunoallergic reactions, such as thrombocytopenia and acute renal failure, should be monitored.

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Rifampicin 引起的血管炎合併血小板低下症—病例報告

江雅惠　林鴻欣*　張菡**　曹昌堯

Rifampicin引起血管炎合併血小板低下症、噬伊紅性白血球過多症並不常見。這是一個66歲男性在服用抗肺結核藥物4個月後，病人開始出現發燒的症狀，並在四肢、腹部出現紫斑。之後，血液檢驗出現血小板低下症、噬伊紅性白血球過多症等異常現象。皮膚切片在免疫螢光染色下顯現IgM和C3沉積於血管壁，因此，Leukocytolastic vasculitis（LCV）確診。在停用Rifampicin和使用類固醇之後，病人的症狀消失，並且血小板和噬伊紅性白血球的數值均回復到正常值範圍。*(胸腔醫學* ***2011; 26: 13-18)***

關鍵詞：抗肺結核藥物，血管炎，血小板低下症

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Difficulty in Diagnosing Churg-Strauss Syndrome – A Case Report

Jui-Chung Wang, Chung-Huo Chen*, Shin-Hung Huang**, Chih-Yu Hsu

Churg-Strauss Syndrome (CSS) is a very rare form of small vessel vasculitis which could affect any organ system. Untreated, the disease is almost always fatal. Diagnosis is often delayed, which can result in permanent organ damage.

We report a 37-year-old man with cough with sputum, fever, progressive dyspnea. He had a history of mild persistent bronchial asthma, eosinophilia and subacute infective endocarditis. Chest X-ray showed pulmonary opacities and left pleural effusion. He was initially diagnosed with and treated for pneumonia with parapneumonic effusion, but acute cardiogenic pulmonary edema developed 10 days after admission. However, eosinophilic pleural effusion was subsequently demonstrated by cytological examination. CSS with eosinophilic effusion and cardiac involvement was highly suspected. Fortunately, the cardiogenic pulmonary edema resolved after steroid pulse therapy. Endomyocardial biopsy revealed subendocardial infiltration of eosinophils even 17 days after pulse therapy with methylprednisolone. In this complicated patient, the hyper-eosinophilic pleural effusion was recognized as being composed predominantly of polymorphonuclear neutrophils (PMNs), which may have lead to a delayed diagnosis. The physician should be aware of the importance of cytological study, as compared with automated hemocytometric analysis. ***(Thorac Med 2011; 26: 19-26)***

Key words: Churg-Strauss Syndrome, hyper-eosinophilic pleural effusion, delayed diagnosis

Introduction

Allergic granulomatosis and angiitis, also known as Churg-Strauss syndrome (CSS), is a clinicopathological entity which requires a combination of clinical and histopathological findings to be diagnosed with confidence. The hallmarks of the disease are late-onset or worsening asthma and hyper-eosinophilia [1-2]. Other pulmonary findings are reported in 50-70% of cases and include pulmonary opacities with eosinophilia, pleural effusion (often eosinophilic), nodules that are rarely cavitary, and alveolar hemorrhage [3]. Pleural effusions in a patient with CSS are not uncommon (29%) and typically contain large numbers of eosinophils [4-5]. When pleural effusion develops in a patient with CSS and complicates the clinical

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condition, the possibility of a misinterpretation of pleural effusion cell counts by automated hemocytometric analysis may lead to an incorrect or delayed diagnosis [6-7].

Herein, we describe a middle-aged patient with a history of mild persistent bronchial asthma, eosinophilia, and subacute infective endocarditis. The patient suffered from fever and dyspnea. Chest X-ray on admission revealed pulmonary opacity in the left upper lung field with pleural effusion. The differential diagnosis included parapneumonic effusion, hyper-eosinophilic disorder, heart failure, etc. He was treated initially as having pneumonia complicated with left parapneumonic effusion, due to clinical evidence of an exudative pleural effusion with polymorphonuclear neutrophils (PMNs) exclusively, as ascertained by automated hemocytometric analysis and Gram-positive cocci in the sediment. But aggressive therapeutic drainage of the pleural effusion and empiric antibiotics were not able to resolve the symptoms and signs of the patient. A diagnostic dilemma ensued.

Case Report

A 37-year-old man was admitted to our hospital due to non-productive cough, wheezing and dyspnea, and a fever of 38°C for 10 days. He was a mobile phone sales clerk, had never smoked, and had a history of 1) allergic rhinitis and sinusitis; 2) mild persistent bronchial asthma for 4 years under regular medical control by low doses of inhaled corticosteroid; and 3) subacute infective endocarditis as determined by pathological finding from the left atrium 2 years previously, following a 28-day course of antibiotics. He was followed up at our clinics regularly. High serum IgE (2,316 IU/ml) and hyper-eosinophilia (64%, 15,200/cumm) had been found the year before admission. No abnormal skin lesion, abnormal renal function, or heart failure sign was found at that time. On presentation, his body temperature was 37.8oC, with a pulse rate of 120/minute, a respiratory rate of 22/min and blood pressure of 123/64 mmHg. Physical examination revealed crackles in the left lower lung fields, slight diffuse expiratory wheezing, and slight pitting edema in the bilateral legs. The hemogram and biochemical investigations were all within normal limits, except leukocytosis of 17,860/μL and hypereosinophilia of 55%. Chest X-ray on presentation showed opacity in the left upper lung field, and left pleural effusion (Figure 1). Antibiotics with augmentin (amoxicillin trihydrate and clavulanate potassium) were prescribed for 3 days, but intermittent fever up to 37.7°C persisted. On the 4th day of hospitalization, new-onset asymptomatic maculopapular skin rashes developed on the fingers, palms, and soles; septic emboli were favored, and skin biopsy from the right

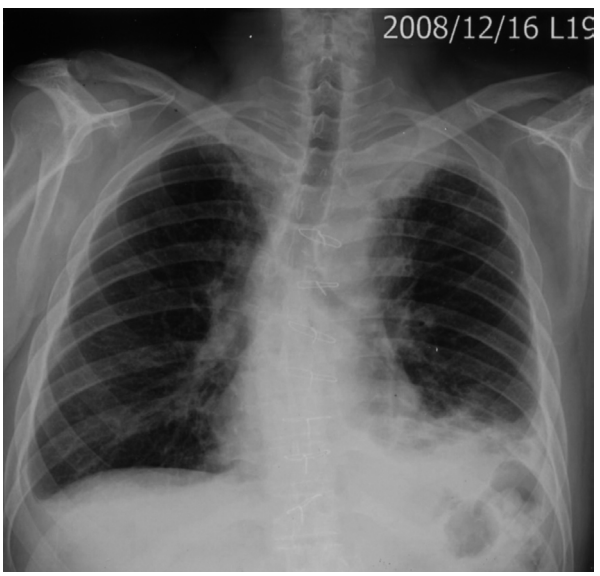
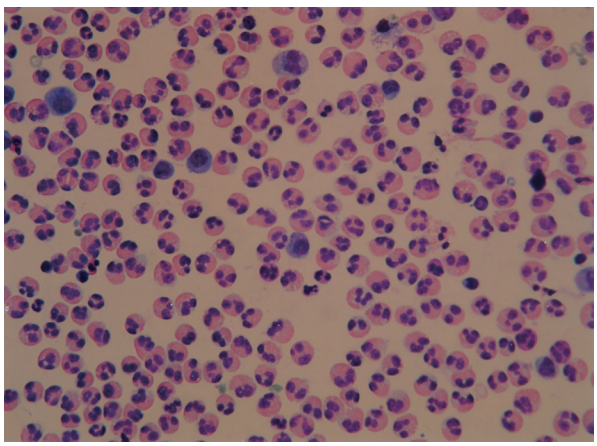
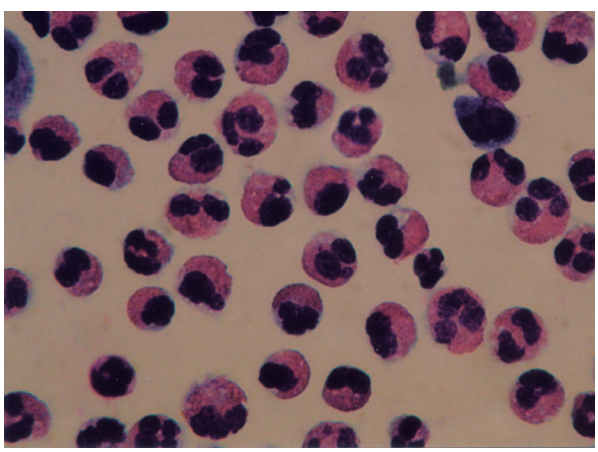


Fig. 1. Chest radiography on admission showing pulmonary opacity in the left upper lobe, and left pleural effusion.

middle finger was taken. Negative serum perinuclear-antineutrophil cytoplasmic antibodies (p-ANCA) and negative anti-myeloperoxidase (anti-MPO) were found. The differential diagnosis included parapneumonic effusion, hypereosinophilic disorder, heart failure, etc. On the 6th day of hospitalization, echocardiography revealed 1) less likely infective endocarditis; 2) no significant valvular dysfunction; and 3) a left ventricular ejection fraction of 58%. A moderate amount of left pleural effusion developed and was characterized by an exudate with a white blood cell count of 19670/μL and 94% PMNs in the automated hemocytometric analysis. There were Gram-positive cocci on the sediment of the pleural effusion. Orthopnea, bilateral moist rales in the chest, hemodynamic shock, and decreasing urine output developed. On the 10th day of hospitalization, electrocardiogram showed sinus tachycardia (135 bpm) with a right bundle branch block, while echocardiography revealed 1) severe left ventricular dysfunction (ejection fraction 25%, compared with that of 58% 4 days previous to this); 2) global left ventricular hypokinesia; and 3) moderate mitral regurgitation. Chest X-ray revealed significant pulmonary congestion, and more and larger pulmonary infiltration. At the same time, the blood test revealed increased creatine kinase (CK), CK-MB, isoenzyme creatine kinase, troponin I, and pro-brain natriuretic peptide (pro-BNP) of 28,027 pg/ml (normal value: 0-900 pg/ml). This patient was intubated with mechanical ventilation, and treated with inotopes because of the unstable hemodynamic status and respiratory failure. His pulmonary capillary wedge pressure was 23 mmHg, with a cardiac index of 1.92 L/min/m^2 (normal range: 2.4 to 4.0), and a systemic vascular resistance index of 2,391 dyne.sec.cm^5/m^2 (normal range: 1,600 to 2,400). Furthermore, incisional skin biopsy from the right middle finger revealed few eosinophils. Systemic vasculitis was suspected. The white cells of the pleural effusion were recognized as exclusively multisegmented eosinophils rather than polymorphonuclear leukocytes, using cytological studies (Figure 2). The characteristic eosinophilic granules found by Liu's stain distinguished the eosinophils from the neutrophils. Eosinophilic cardiomyopathy as



(A)



(B)

Fig. 2. Pleural effusion cytology showing no polymorphonuclear neutrophils (PMNs) but eosinophils exclusively, in which many are multisegmented and were interpreted as PMNs by an automated hematology instrument (Sysmex XE-2100). (Liu's stain, x400, 2A; oil, 2B)

a result of eosinophilic infiltration of the heart was highly suspected, thus steroid pulse therapy (methylprednisolone 1gm/d qd for 3 days) was given. After 14 days of steroid treatment, the heart failure improved and extubation was performed successfully. An endomyocardial biopsy was done after the patient had reached a more stable condition. Histopathologically, the endomyocardial biopsy revealed mild infiltration of lymphocytes and neutrophils with few eosinophils in the myocardium (Figure 3). On the basis of the above clinical history, laboratory data follow-up and the histolpathological findings of the endomyocardial and skin fragments, a diagnosis of CSS was made. During long-term follow-up with oral steroid treatment for 6 months, chest X-ray showed diminished pulmonary opacity in the left upper lung field and left pleural effusion. The blood eosinophilia diminished to 10%. The follow-up electrocardiogram showed 1) poor left ventricular dysfunction (ejection fraction 30%, compared with that of 25% 6 months previous to this); 2) diffuse left ventricular hypokinesia; and 3) moderate mitral regurgitation.

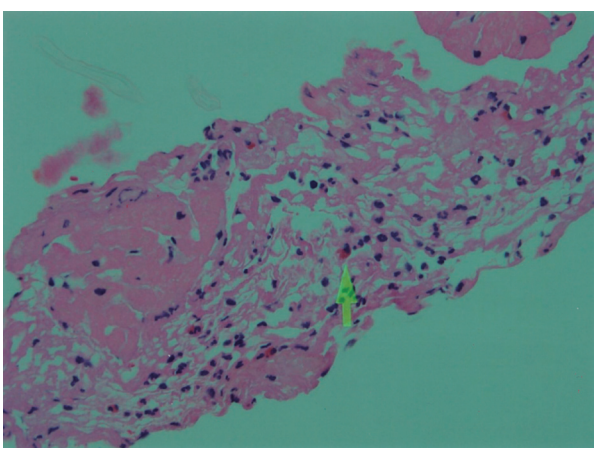


Fig. 3. Endomyocardial biopsy showed subendocardial infiltration of mixed inflammatory cells, including a few eosinophils (arrow). (Hematoxylin and Eosin stain, x100)

Discussion

First described by Churg and Strauss in 1951, CSS is an uncommon vasculitis of unknown etiology also known as allergic angiitis and granulomatosis [1]. The presence of 4 or more of the American College of Rheumatology (ACR) diagnostic criteria [8] had a sensitivity of 85% and a specificity of 99.7% for CSS. This patient had the ACR criteria are 1) moderate to severe asthma (but mildly persistent in this patient); 2) peripheral blood eosinophilia (>10%); 3) paranasal sinus abnormality; 4) transient pulmonary infiltrates detected radiographically; and 5) endomyocardial and skin biopsy containing extravascular eosinophils. The syndrome may be divided into 3 progressive phases which may be arrested with corticosteroid treatment. There is a prodromal phase of asthma and sometimes rhinitis, a 2nd phase of tissue and peripheral blood eosinophilia, and a final life-threatening phase of systemic vasculitis. Asthma is the cardinal clinical feature of CSS and is present in more than 95% of patients [9]. Cardiac involvement is 1 of the more serious manifestations of CSS, accounting for approximately one-half of deaths attributable to CSS [10].

Identification of patients in the early phase is important because they appear to respond well to steroids and have an excellent prognosis. And, early administration of steroid therapy can prevent the acute onset of fatal cardiac involvement. Unfortunately, the diagnosis of CSS is often delayed in different situations. Several cases of CSS have been recognized in patients treated with cysteinyl leukotriene receptor antagonists, omalizumab, and inhaled glucocorticoids, and in those weaned off systemic corticosteroids [11-13]. CSS developed primarily

in those patients taking these medications who had an underlying eosinophilic disorder that was being masked by corticosteroid treatment and unmasked by novel asthma medication-mediated corticosteroid withdrawal [13]. Five cases of CSS provided evidence that inhalation of corticosteroids, even at high doses (500-2,000 ug fluticasone), could not prevent the occurrence of formes-frustes of CSS [11]. Complete or incomplete forms of CSS can become apparent in asthmatic patients when systemic corticosteroids are tapered but can also occur in patients with mild asthma of short duration who use only inhaled corticosteroids [14].

A few cases of CSS without preexisting asthma were encountered in reports of ‘‘atypical,’’ ‘‘limited,’’ or ‘‘forme fruste’’ forms of CSS [15-17]; these situations may lead to a delayed diagnosis. Ohwada *et al*. [15] reported a 52-year-old man diagnosed with CSS during an emergency laparotomy. He had no history of asthma or involvement of 2 or more extrapulmonary organs, but fulfilled the criteria of eosinophilia alone. Sasaki A *et al*. [17] reported an autopsy case of a 54-year-old non-asthmatic patient that was also reported to show CSS. He had died of acute heart failure in the course of the disease, and as a result of delayed diagnosis and lack of corticosteroid therapy. Alper Sevinc *et al*. [18] reported the first case of limited CSS affecting the respiratory system in a patient without a history of asthma or blood eosinophilia. Corradi *et al*. [19] reported the case of a patient who was diagnosed as suffering from CSS shortly after pregnancy and who underwent cardiac transplantation because of severe heart involvement.

Our patient had a history of mild persistent bronchial asthma, subacute infective endocarditis, and eosinophilia. Initially, he presented with toxic signs, and chest X-ray revealed left pulmonary infiltrates with ipsilateral pleural effusion. Although hyper-eosinophilic disorder (such as incomplete CSS) was a differential diagnosis, the patient was initially treated as having pneumonia with left parapneumonic effusion, because an exudative pleural effusion with PMNs exclusively that was found by automated hemocytometric analysis and Gram-positive cocci in the sediment (later proved to be a contamination). Unexpectedly, acute cardiogenic pulmonary edema developed on the 10th hospitalization day. Fortunately, the physician discovered the incorrect automated analysis of the pleural effusion during routine cytological examination. As a corollary, the cardiogenic pulmonary edema resolved after steroid pulse therapy. Endomyocardial and skin biopsy showed extravascular eosinophils. After this event, we replaced the automated analyzer examination of all body fluids with the use of manual microscopic analysis.

Although CSS is classified as a vasculitis, only 40-60% of patients with CSS have ANCA. In a series of 112 patients with newly diagnosed CSS, a positive ANCA at diagnosis was associated with renal involvement, peripheral neuropathy, and biopsy-proven vasculitis, whereas a negative ANCA was associated with heart disease and fever [20].

Current therapies cannot cure the disease, but CSS-targeted therapies seek to minimize tissue and organ damage and prevent relapses. A variety of CSS therapies can dramatically alter the course of the disease: 50% or fewer of those who are untreated die within 3 months of the onset of vasculitis, whereas patients who are treated have a 5-year survival of more than 70% [21]. Corticosteroids (starting at 1 mg/kg and tapering from 3 to 6 months) are the corner-

stone of CSS therapy and result in rapid clinical remission in more than 90% of subjects with CSS [22].

The "5-factors score" [23] was developed to assess vasculitis disease activity in patients with CSS and other vasculitides. It is based on the presence or absence of the following 5 clinical factors: cardiac involvement, gastrointestinal disease (bleeding, perforation, infarction, or pancreatitis), renal insufficiency (plasma creatinine concentration >1.6 mg/dL), proteinuria (>1 g/day), and central nervous system involvement. Guillevin *et al*. [23] reported the following 5-year mortality data: 26% when 1 factor (cardiac involvement) was present and 12% when none of the 5 prognostic factors was present.

In conclusion, the physician should be aware of the difference between clinical presentation and laboratory data. Analysis of pleural effusion for determination of the differential WBC count should be performed by microscopic examination and should not be done only by an automated hemocytometric machine. Eosinophilia from CSS can lead to multi-organ damage, including the heart. Therefore, CSS must be considered in the differential diagnosis of peripheral blood eosinophilia and eosinophilic pleural effusion, as early detection and treatment may be critical in decreasing morbidity and mortality.

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困難診斷的 Churg-Strauss 症候群—病例報告

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Churg-Strauss症候群是一種罕見的小血管性血管炎，它能侵犯身體的各個器官。如果沒有給予治療，這個疾病幾乎總是致命的。但是診斷常常被延遲，而這會導致某些器官的永久損傷。

我們報告一個37歲男性，因為咳嗽有痰、發燒，漸進性呼吸困難而住院治療。他曾經有輕度氣喘、嗜伊紅性血球增多症，亞急性心臟瓣膜炎。胸部X光顯示有肺內病灶及左側肋膜積液。起初，他被診斷為肺炎併有肺炎旁肋膜積液，經過10天的住院治療，卻發生急性心因性水腫。然而，嗜伊紅性球增多肋膜積液於細胞學抹片檢查時被證實。我們高度懷疑是Churg-Strauss症候群併有嗜伊紅性球增多肋膜積液，並且侵犯到心臟而致病。幸運地，在使用類固醇脈衝治療後，心因性肺水腫獲得緩解。使用類固醇脈衝治療的十七天之後，心臟內膜切片顯示在心肌組織內仍然有嗜伊紅性球浸潤其中。從這個複雜的病例中我們知道，嗜伊紅性球增多肋膜積液如果被判讀成嗜中性球增多，這會導致一個診斷上的延遲。臨床醫師應該要能警覺地去比較人工讀片和機器讀片的差異性。*(胸腔醫學* ***2011; 26: 19-26)***

關鍵詞：Churg-Strauss 症候群，嗜伊紅性球增多肋膜積液，延遲診斷

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Strongyloides Hyperinfection in a Corticosteroid-Treated Patient – A Case Report and Literature Review

Ko-Hui Hu, Chun-Chi Chang, Ching-Hsiung Lin

Strongyloides stercoralis is a widespread, soil-transmitted, intestinal nematode common in tropical and subtropical countries. The unique ability of this nematode to replicate in the human host permits cycles of autoinfection, leading to chronic disease that can last for several decades without prominent symptoms. However, hyperinfection syndrome caused by *S. stercoralis* in iatrogenically immunocompromised patients may occur. We reviewed the relevant literature and presented a recent case of Strongyloides hyperinfection in a patient treated with corticosteroids for chronic obstructive pulmonary disease (COPD). This patient was a farmer, had initial manifestations of shortness of breath and wheezing breathing sounds that mimicked acute exacerbation of COPD, and chronic gastrointestinal symptoms of anorexia. Subsequent complications of Strongyloides hyperinfection led to ileus, acute respiratory failure, *Trichosporon asahii* fungemia, and aseptic meningitis. Therefore, we should keep the diagnosis in mind when dealing with immunocompromised patients who present with gastrointestinal or pulmonary symptoms or unexplained sepsis caused by enteric pathogens. ***(Thorac Med 2011; 26: 27-32)***

Key words: *Strongyloides stercoralis*, hyperinfection, corticosteroids

Introduction

Strongyloidiasis is an infection caused by *S. stercoralis* with manifestations that can range from asymptomatic eosinophilia in the immunocompetent host to disseminated disease with septic shock in the immunocompromised host. *S. stercoralis* is a widespread, soil-transmitted, intestinal nematode common in tropical and subtropical countries, and was first reported in 1876 in the stools of French soldiers on duty in Vietnam who had severe diarrhea, and the disease the organism produced was known for many years as Cochin-China diarrhea [1].

Strongyloidiasis affects 30 to 100 million people worldwide and is endemic in Southeast Asia, Latin America, sub-Saharan Africa, and parts of the southeastern United States [2]. In contrast to other helminthic parasites, *S. stercoralis* can complete its life cycle entirely within the human host by autoinfection [3]. Most patients have a chronic asymptomatic disease that may last for several decades. However, in patients with impaired cell-mediated immunity,

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autoinfection may give rise to potentially fatal hyperinfection with disseminated disease [4-5]. Herein, we report a patient with *S. stercoralis* hyperinfection who was previously treated with corticosteroids for chronic obstructive pulmonary disease (COPD).

Case Report

A 73-year-old man, a farmer with a smoking history of about 1/2 pack of cigarettes per day for 40 years, had a history of COPD and type 2 diabetes with poor glycemic control; he presented with productive cough, progressive dyspnea and wheezing breathing sounds in November 2009. Combination therapy with inhaled long-acting β2 agonist plus inhaled corticosteroid was prescribed at the outpatient services of our chest division. He was admitted because of shortness of breath, fever, and having experienced anorexia for a period of time before admission. He was a well-nourished man with weight of 70 kg and height of 165 cm. Vital signs on admission showed a temperature of 38.3°C, heart rate of 88 beats/min, respiratory rate of 24 breaths/min, and blood pressure of 142/70 mmHg. Chest auscultation revealed diffuse wheezing breathing sounds. The initial laboratory evaluation revealed a white blood cell count of 13,500 cells/mm^3 (91.4% neutrophils, 0% eosinophils), hemoglobin of 12.2g/dl and platelet count of 424,000 cells/mm^3. Arterial blood gas demonstrated a pH of 7.558, $PaCO_2$ of 34.9 mmHg, PaO_2 of 123 mmHg, and bicarbonate of 31 mmol/L on nasal cannula at 3 L/min. The chest radiograph at admission showed mild increased axial interstitial infiltrates in the bilateral lung fields, as compared with previous chest films.

Medications on admission included intravenous steroids with methylprednisolone 40 mg every 12 hours, nebulized bronchodilator of ipratropium 0.5 mg/salbutamol 2.5 mg every 8 hours, and empiric intravenous antibiotic with ampicillin/sulbactam 1500 mg every 6 hours. Initially, the patient felt abdominal distension, and the abdominal plain film showed paralytic ileus. Besides, multiple ulcerative lesions in the colon, duodenal bulb and second portion of the duodenum had been found by colonoscopy and panendoscopy. Biopsy of the colonic ulcerative lesions revealed non-specific chronic inflammation with leukocytic infiltrates. Several days later, septic shock with acute respiratory failure occurred. The follow-up chest radiograph showed exacerbated bilateral axial interstitial pulmonary infiltrates (Figure 1) and *Trichos-*

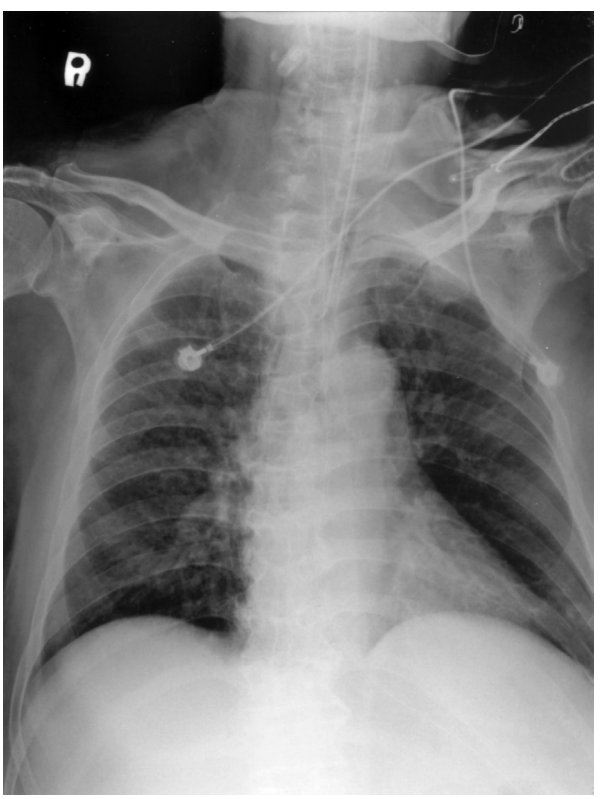
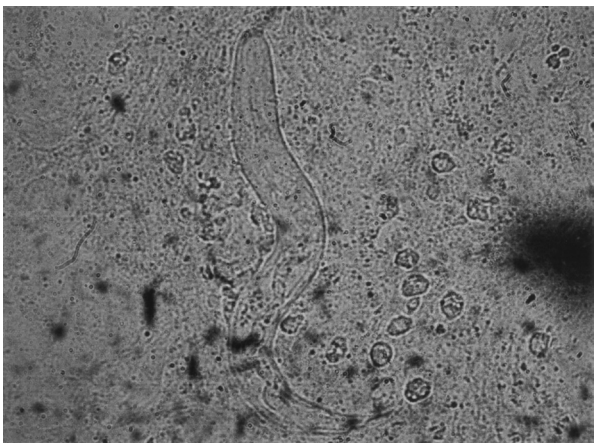


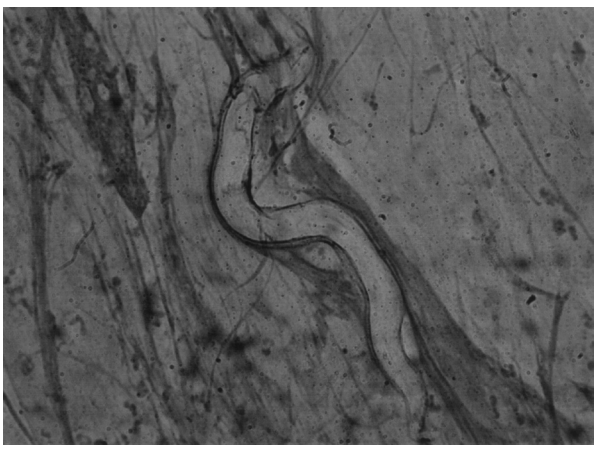
Fig. 1. Chest radiograph shows axial interstitial infiltrates of bilateral lung fields, which were suggestive of atypical pneumonia related to Strongyloides hyperinfection with pulmonary involvement.

poron asahii was isolated from blood culture.

Thereafter, the diagnosis of Strongyloides hyperinfection was made by detection of Strongyloides larvae in the stool and sputum smear (Figure 2). Because of the patient's drowsy consciousness with positive meningeal signs, brain MRI was arranged, but revealed no specific abnormalities except senile brain parenchyma atrophic change. Lumbar puncture was performed and examination showed clear colorless cerebrospinal fluid (CSF) with a pH of 8.0, white blood cell count of 20 cell/mm^3 (0% neutrophil, 98% lymphocyte), protein at 26.96 mg/dL, and glucose at 139.40 mg/dL. India ink stain of the CSF for cryptococcus, a direct smear for fungus (KOH preparation), and serum cryptococcal Ag all yielded negative findings. We prescribed a prolonged 9-day treatment course of ivermectin (200 μg/kg daily) for Strongyloides hyperinfection due to the persistent drowsy consciousness. The patient had a good response to the course of antihelminthic therapy and his consciousness became clear thereafter. Follow-up chest radiography revealed ongoing resolution of the pulmonary interstitial infiltrates. He received regular follow-up at our outpatient services for several months without sequelae of the pulmonary symptoms or neurologic complications.



(A)



(B)

Fig. 2. Microscopic examination of sputum smears demonstrates the *Strongyloides stercoralis* larvae (A: wet mount, B: Gram stain; original magnification 400×)

Discussion

Strongyloides stercoralis is an intestinal nematode endemic to tropical and subtropical areas of the world. Infection of *S. stercoralis* begins when human skin contacts infective filariform larvae of *S. stercoralis*, which are found in soil or other materials contaminated with human feces. Immunocompetent hosts infected by the parasite can be asymptomatic for several decades. Most clinical manifestations of localized strongyloides infection include gastrointestinal symptoms of anorexia, abdominal pain, nausea, vomiting and diarrhea; and pulmonary symptoms of cough, dyspnea and wheezing breathing sounds [2, 6-7]. However, overwhelming hyperinfection can occur in carriers who become immunocompromised, leading to sepsis, respiratory failure, hemoptysis, paralytic ileus, gastrointestinal bleeding, cutaneous lesions, and meningitis [2, 8]. The likelihood of developing the hyperinfection

syndrome is increased if cell-mediated immunity is impaired by congenital immunodeficiency, underlying malignancy, malnutrition, hypogammaglobulinemia, alcoholism, hematopoietic stem cell transplantation, human T-lymphotropic virus type 1 infection or the administration of corticosteroids or cytotoxic drugs [4, 9-11].

Our patient was a farmer, which increased the risk of contact with soil contaminated by human feces. He also had gastrointestinal (anorexia) and pulmonary (shortness of breath) symptoms before admission. We supposed that he may have been previously infected with *S. stercoralis*. Corticosteroid therapy for COPD can play an important role in the transformation of chronic infection to hyperinfection. Moreover, augmentation of intravenous methylprednisolone on admission for acute exacerbation of COPD may have worsened our patient's hyperinfection syndrome, resulting in septic shock with acute respiratory failure several days after admission. Although peripheral blood eosinophilia, a well-known clue of parasitic infection, is a common finding in chronic Strongyloides infection [2], our patient did not show eosinophilia on admission. This tells us that the absence of eosinophilia in patients cannot completely exclude the diagnosis. Furthermore, eosinophil levels of less than 400 cells per microliter are generally considered poor prognostic indicators for patients with severe strongyloidiasis infection [7].

The definitive diagnosis of strongyloidiasis is usually made on the basis of detection of larvae in the stool. However, the standard stool examination is insensitive (<50% sensitivity) [12], especially for uncomplicated cases of strongyloidiasis, since the intestinal worm load is usually low and the output of larvae is minimal [13]. Repeated examination of stool specimens can increase diagnostic sensitivity. In some studies, diagnostic sensitivity increased to 50% with 3 stool examinations, and can approach 100% if 7 serial stool samples are examined [14-15]. In disseminated strongyloidiasis, filariform larvae can be found in stool, sputum, bronchoalveolar lavage fluid, and ascites [16-18]. Currently, the most reliable diagnostic test available to clinicians is a *S. stercoralis* ELISA developed by the Centers for Disease Control and Prevention for detecting serum IgG antibodies to *S. stercoralis*. In 1 study, 2 commercially available ELISAs (IVD-ELISA and Bordier-ELISA) were found to have sensitivity of 89% and 83%, respectively, and specificity of 97.2% for both in the diagnosis of strongyloidiasis [19]. However, ELISA results can be falsely negative in immunocompromised hosts and false positive results may occur in the presence of other helminth infections due to cross-reactivity with hookworms, filariae, and schistosomes [2].

Even in the asymptomatic state, strongyloidiasis must be treated due to the ability of the parasite to replicate in the hosts and its potential for a subsequent fatal hyperinfection. In the past, thiabendazole was the drug of choice for the treatment of strongyloidiasis. Recently, ivermectin (200 μg/kg daily for 2 days) has been found to be the most effective drug in the treatment of disseminated strongyloidiasis and is registered as the drug of choice in the World Health Organization's list of essential drugs for the treatment of strongyloidiasis [20]. For hyperinfection syndrome and disseminated strongyloidiasis, treatment with ivermectin should be extended for at least 5 to 7 days or until the clinical syndrome has resolved and the larvae have not been identified for at least 2 weeks. Follow-up examinations for larvae in stool or sputum are necessary, with repeat dos-

ing if the infection persists [21].

In conclusion, Strongyloides hyperinfection syndrome mostly occurs in immunocompromised hosts who are receiving corticosteroid therapy for underlying disease. It is often associated with sepsis from enteric pathogens and can lead to high mortality rates. Therefore, patients at risk for acquiring *S. stercoralis* infection should always be screened, identified, and treated, especially before administration of corticosteroid therapy.

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接受類固醇治療的病患引發糞小桿線蟲高度感染之病例報告及文獻回顧

胡克輝　張竣期　林慶雄

糞小桿線蟲是一種經由土壤傳播感染且流行於熱帶及亞熱帶許多國家的腸道寄生蟲。這種線蟲擁有獨特的能力可以在人類宿主體內複製而引發自體感染，並可導致持續數十年無明顯症狀的慢性疾病。然而，高度感染症候群可以發生在因接受免疫抑制治療而導致免疫力低下的病人。在此，我們回顧了相關文獻及提出新近因慢性阻塞性肺疾而接受類固醇治療的病患引發糞小桿線蟲高度感染的病例。此病患是一位農夫，他剛開始的表現是類似慢性阻塞性肺疾急性發作的呼吸急促及喘鳴聲，和食欲不振的腸胃道症狀。接下來因糞小桿線蟲高度感染的併發症導致腸阻塞、急性呼吸衰竭、Trichosporon asahii敗血症和無菌性腦膜炎。因此，對於免疫功能低下的病患，如果呈現腸胃道、呼吸道症狀或難以解釋的腸胃道病原菌所引起的敗血症時，吾人應對這個診斷抱持高度警覺。*(胸腔醫學* ***2011; 26: 27-32)***

關鍵詞：糞小桿線蟲，高度感染，類固醇

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Mycobacterium abscessus Empyema in an Immunocompromised Patient: A Case Report

Chieh-Hui Lin, Chun-Shih Chin, Jeng-Yuan Hsu

Thoracic empyema caused by rapidly growing mycobacteria in an immunocompetent patient is rarely reported. A 70-year-old man initially complained about intermittent chest tightness and dull pain at the right chest wall. The patient was diagnosed with and treated for bacterial pneumonia in a community hospital. Anti-tuberculosis agents were given in our ward because of a positive acid-fast stain finding in the sputum. During hospitalization, right thoracic empyema developed, and the pathogens from the sputum and pleural effusion were identified as *Mycobacterium abscessus*. Decortication with chest tube drainage was performed and intravenous cefoxitin, amikacin, plus klaricid therapy was administered for 3 weeks. The patient was continually monitored in our outpatient department, and was maintained in a stable condition with oral-form antibiotics (klaricid, ofloxacin and doxycycline). This case demonstrates that *Mycobacterium abscessus* is a pathogen that can cause thoracic empyema in Taiwan, especially in immunocompromised patients. ***(Thorac Med 2011; 26: 33-38)***

Key words: rapidly growing mycobacteria (RGM), non-tuberculous mycobacterial (NTM), *Mycobacterium abscessus*, thoracic empyema

Introduction

Non-tuberculous mycobacteria (NTM) are common in our environment and have become increasingly apparent in pulmonary infections, especially in immunocompromised patients. Pleuropulmonary disease is 1 of the most common manifestations of a NTM infection in solid organ transplant recipients [1]. Rapidly growing mycobacteria (RGM) have 3 relevant species: *Mycobacterium fortuitum*, *Mycobacterium chelonae*, and *Mycobacterium abscessus*. RGM are also environmental organisms found worldwide, and rapidly grow in culture within 1 week. *M. abscessus* is the most pathogenic of the RGM group and accounts for the majority of pulmonary disease caused by RGM in those that have underlying lung disease [2]. These patients are mostly women, non-smokers, and present with symptoms of bronchiectasis [1].

Thoracic empyema induced by *M. abscessus* is rarely reported [3]. The following report

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describes an uncommon case of *M. abscessus* pulmonary infection with empyema.

Case Report

A 70-year-old man was diagnosed with tongue cancer, squamous cell carcinoma, and then underwent an operation and radiotherapy on 2007. After the surgery, he was followed up regularly at the community hospital, and no recurrence was found.

Before admission to the community hospital, the patient complained about mild intermittent chest tightness and dull pain in the right chest wall for about 1 month. The dull pain was not related to exercise, diet or position. Twenty days before admission, episodes of fever with an acute onset, up to 38.9°C, began occurring every afternoon. The fever rarely subsided spontaneously, without chills. Productive cough with yellowish sputum also developed 20 days prior to admission. The patient mentioned weight loss (5-6 kg during these 20 days), general malaise, and loss of appetite. There was no hemoptysis, shortness of breath, hoarseness, bone pain, focal muscle weakness, mental status change or night sweating.

When he returned to the community hospital for help, chest X-ray (CXR) showed right middle lobe (RML) consolidation. Community-acquired pneumonia was suspected and levofloxacin was prescribed as an empiric antibiotic. Sputum culture (2009/9/4) yielded methicillin-resistant *Staphylococcus aureus* and group B Streptococcus. A bronchoscopy (2009/09/07) found no endobronchial lesion. Acid-fast stain (AFS) of sputum (3 sets) and bronchial brushing were both negative. Chest computed tomography (CT) (2009/9/11) arranged because of the delayed resolution of RML consolidation revealed numerous small nodules around the consolidation. Malignancy was highly suspected, and the patient asked to be transferred to our hospital on 2009/9/14 for further evaluation.

At our ER, fever was still noted. A CXR image showed consolidation in the RML (Figure 1). Rales were heard in the right lower lung. Lab data presented mild leukocytosis (WBC: 8300/cumm) with a left shift (neutrophil: 86.1%) and a high CRP value (20.58 mg/dl). Later, AFS of sputum (2009/9/14) was positive (1+). He was admitted to our ward for further evaluation.

Repeated bronchoscope (2009/9/17) revealed a strict opening and narrow bronchus in the RML with irregular and erythematous mucosa. Bronchoscopic biopsy and brushing were negative for malignant cells. Sputum culture (2009/9/16, 9/17) yielded *Klebsiella pneumoni-*

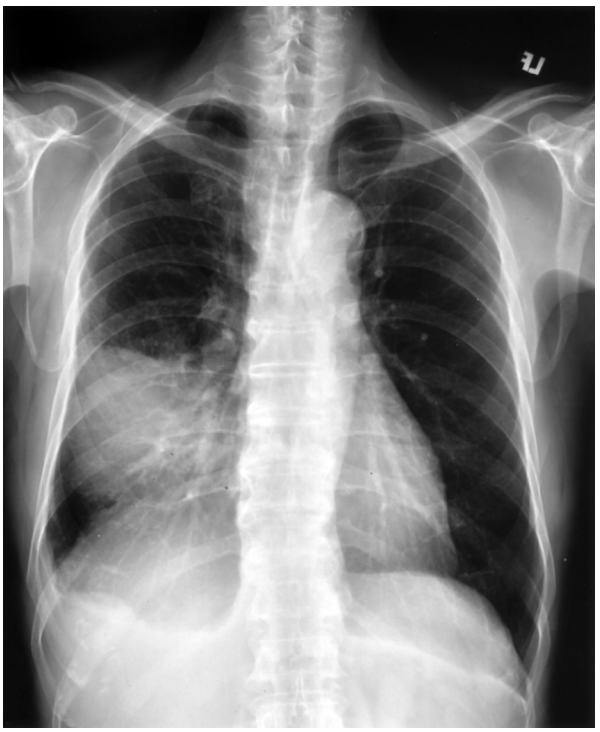

Fig. 1. Initial CXR image at presentation in our hospital reveals consolidation in the RML.

ae. Because of a new onset of fever (2009/9/19), his antibiotic was switched to cefmetazole on 2009/9/20.

AFS of the bronchial brushing yielded 3+, thus anti-tuberculosis therapy with rifinah 600 mg QD and ethambutol 800 mg QD were prescribed on 2009/9/21. Tuberculosis culture of the sputum (2009/9/17) yielded mycobacterium other than tuberculosis (MOTT), but anti-tuberculosis therapy was continued (until the subtype of MOTT was confirmed).

Complaints about tightness in the right chest wall persisted during ward rounds on 2009/9/23 (Figure 2), and the breathing sounds in the right lower lung were decreased. Thoracentesis revealed complicated parapneumonic effusion (neutrophil predominant, N/L: 87:5; LDH: 3217 U/l; glucose: 42 mg/dl; protein: 4400 mg/dl; ADA: 62 U/L). Chest CT presented multiple, massive lobulated right pleural effusion with consolidation of the right lower lobe (RLL) and

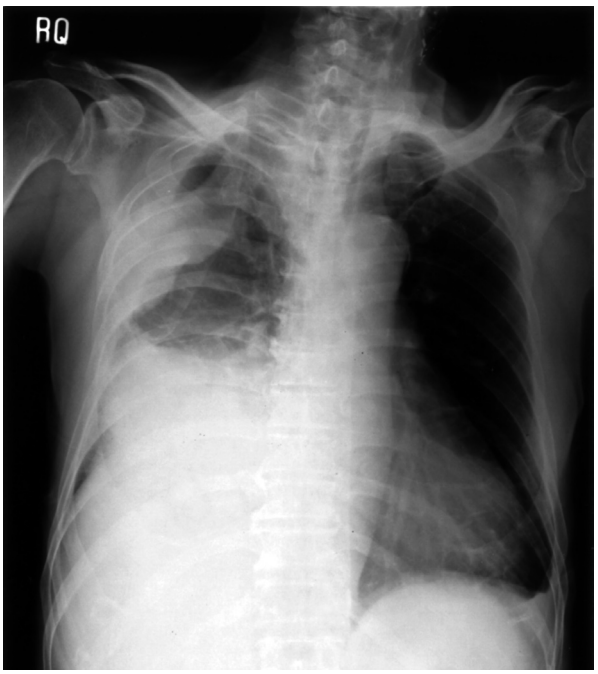

Fig. 2. Right thoracic empyema developed during hospitalization.

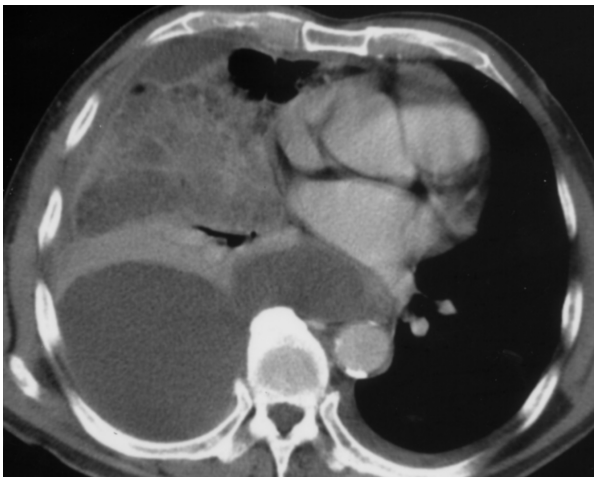

Fig. 3. Computed tomography (CT) showing right thoracic empyema.

RML, and atelectasis of the right upper lobe (RUL). Organized pneumonia with empyema was highly suspected (Figure 3). Pig-tail drainage for pleural effusion was implanted. The thoracic surgeon was consulted for arrangement of debridement and insertion of 2 chest tubes on 2009/9/25.

Rifinah and ethambutol were held and shifted to cefoxitin, amikacin, plus klaricid on 2009/9/26 for the rapidly growing mycobacterium (*M. abscessus*), which was identified by both sputum and pleural effusion culture. Extubation was performed on 2009/9/28 in the respiratory intensive care unit, and the patient was able to tolerate it well. He was transferred back to our general ward on 2009/9/29. One chest tube was removed on 2009/10/8 in the general ward. The other tube was under open-drainage on 2009/10/9. After 3 weeks of intravenous antibiotic treatment for *M. abscessus* infection, the patient was discharged on 2009/10/17 with oral antibiotics (klaricid, ofloxacin and doxycycline). The patient now receives regular follow-up at our outpatient department (OPD).

Discussion

We have reported a rare case of thoracic empyema caused by an RGM infection. Various NTM have been reported, including *M. avium* complex, *M. abscessus*, *M. kansasii*, and *M. chelonae*, but this is not a common infection, and is mostly found in immunocompromised hosts; a lung transplant recipient [4], renal transplant recipient [5], advanced AIDS patient [6], systemic lupus erythematosus (SLE) patient [7], cystic fibrosis patient [8], and solid organ transplant recipient [9] have been reported with NTM infections. Pulmonary infection with empyema induced by RGM or NTM is rare. These pulmonary diseases are mostly caused by *M. abscessus* or *M. fortuitum* [2]. Six cases of thoracic empyema caused by RGM or NTM have been reported. These cases have included *M. chelonae* [3, 10], *M. abscessus* [4], *M. kansasii* [5], *M. avium*-intracellulare complex [6], and *M. fortuitum* [7]. Almost all of these patients had underlying disorders that predisposed them to infection.

Our reported patient, a 70-year-old man, had had a case of squamous cell carcinoma of the left tongue and underwent an operation and radiotherapy, so he could also be considered as an immunocompromised patient. Generally, the clinical and radiological features of NTM infection are not totally similar to those of tuberculosis, and the former is rarely accompanied by pleural involvement. In this case, the initial signs of RGM infection were similar to those of an acute onset of bacterial pneumonia, including the clinical course and presenting images. Even the exudate pleural effusion presented as neutrophil-predominant (N/L: 87:5). It is difficult to differentiate RGM from bacterial pneumonia. Only the ADA value of the pleural effusion and the AFS findings can provide the clues that would lead us to consider this as a highly likely tuberculous mycobacterium in a pulmonary infection disease in Taiwan. Thus, anti-tuberculosis therapy (rifinah 600 mg QD and ethambutol 800 mg QD) was prescribed after obtaining the above findings. When *M. abscessus* was identified by both the sputum and pleural effusion culture, anti-tuberculosis therapy was shifted to intravenous cefoxitin (2 gm Q6H), amikacin (500 mg QD), plus klaricid (500 mg Q12H po) for 3 weeks. The serial CXR revealed obvious improvement. Before discharge, we changed the antibiotics to an oral form (klaricid 500 mg Q12H, ofloxacin 200 mg Q12H and doxycycline 100 mg BID). With no findings in the sensitivity test, we chose 3 antibiotics from those used in anti-RGM therapy. The patient was continually followed up at our

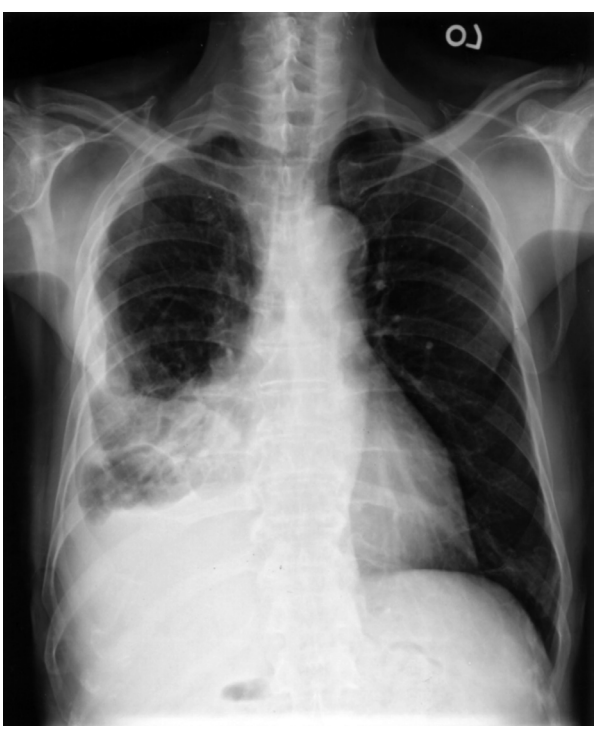

Fig. 4. The follow-up CXR image in the OPD, 7 months after discharge.

OPD, and remained in stable condition (Figure 4). Our therapeutic goal is to use combination therapy during 6 to 12 months of negative sputum culture findings while on therapy. Of interest, during decortication surgery, white material was found coating the entire right thoracic pleural surface (Figure 5A, B), which has not been reported. This case demonstrates that *M. abscessus* is a pathogen that can cause thoracic empyema in Taiwan, especially in immunocompromised patients.

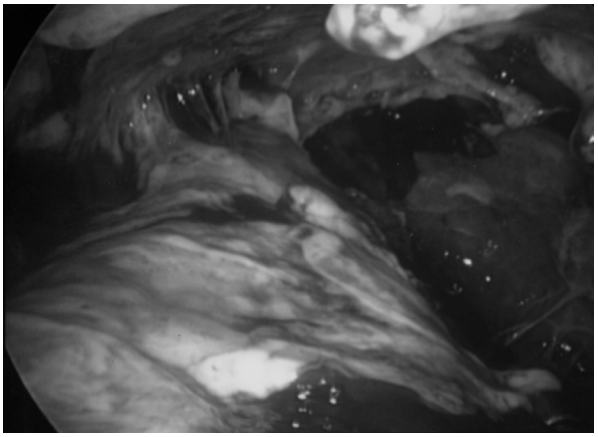

Fig. 5A. White material coating the entire right thoracic pleural surface.

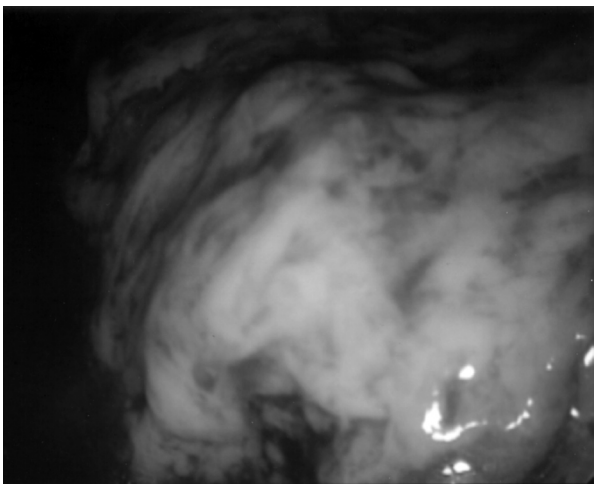

Fig. 5B. White material coating the entire right thoracic pleural surface.

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免疫功能低下病人身上由快速生長型分枝桿菌所造成的膿胸：病例報告

林介惠　覃俊士　許正園

在免疫功能低下病人身上由快速生長型分枝桿菌（rapidly growing mycobacteria, RGM）所造成的膿胸很少被報導。一名70歲男子最初抱怨右側胸壁間歇性胸悶和悶痛。病人在社區醫院以細菌性肺炎治療。轉至我們醫院，由於AFS陽性即給予抗結核菌藥物。住院期間，發生右側膿胸，從痰和胸腔積液結核菌培養，病原體被確定為膿腫分枝桿菌（Mycobacterium abscessus）。我們安排剝除術與胸管引流治療，及靜脈注射cefoxitin，amikacin，及klaricid治療達3週。之後，病人持續以口服抗生素（klaricid, ofloxacin and doxycycline）治療，並於門診追蹤，保持穩定狀態。此案例表明，在台灣，尤其是免疫功能低下患者，膿腫分枝桿菌亦可能是膿胸的病原體之一。*(胸腔醫學* ***2011; 26: 33-38)***

關鍵詞：快速生長型分枝桿菌，非結核性分枝桿菌，膿腫分枝桿菌，膿胸

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An Uncommon Lobar Consolidation of Cryptococcal Pneumonia in an Immunocompetent Host: Case Report and Literature Review

Chung-Hua Kuo, Jia-Horng Wang

Lobar consolidation of cryptococcal pneumonia is rarely reported in immunocompetent hosts. We report a healthy 25-year-old woman who presented with pneumonia in her left lower lobe. A poor response to empiric antibiotics was noted, and a subsequent investigation disclosed high titers of serum cryptococcal antigen (CSA titer >1:1024). Gomori-methenamine silver staining of bronchoalveolar lavage fluid disclosed cryptococci with a cryptococcal antigen titer of 1:128. The patient's symptoms improved with resolution of the consolidation of the left lower lobe of the lung after treatment with fluconazole. We also reviewed the literature. ***(Thorac Med 2011; 26: 39-45)***

Key words: cryptococcal pneumonia, Gomori-methenamine stain (GMS), immunocompetent

Introduction

Cryptococcosis, also known as torulosis or European blastomycosis, is caused by infection with the encapsulated fungus *Cryptococcus neoformans*, a yeast organism with an average 4-8 μm diameter and a worldwide distribution. Pulmonary cryptococcosis is a rare form of pneumonia, with meningoencephalitis being the more common form of cryptococcal infection in immunocompromised individuals. The spectrum of the disease ranges from asymptomatic pulmonary infection to extensive inflammatory pneumonia associated with respiratory failure and disseminated disease in immunocompromised individuals with AIDS, organ transplant recipients, those with Hodgkin's lymphoma, and patients receiving corticosteroids and immune modulating agents [1]. Cryptococcal infection occasionally leads to asymptomatic or self-limited pulmonary disease in healthy individuals. Lobar consolidation of pulmonary cryptococcosis has rarely been reported in immunocompetent hosts [3, 12]. Chest roentgenography findings of cryptococcal pneumonia vary, ranging from solitary to multiple, small to large nodular or mass lesions, and rarely, extensive pulmonary infiltrates in immunocompetent hosts. We herein report the case of an immunocompetent young woman with isolated cryptococcal pneumonia without meningoencephalitis or other systemic diseases. The diagnosis of

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pulmonary cryptococcosis was confirmed by Gomori-methenamine staining (GMS) of bronchoalveolar lavage fluid, which showed a high titer of serum cryptococcal antigen. There was an excellent response to antifungal therapy (fluconazole 400 mg daily), and chest roentgenography showed good resolution 3 months after the therapy.

Care Report

A 25-year-old woman suffering from fever, cough, and dyspnea for several days had been treated for pneumonia with antibiotics at a local hospital for 2 weeks before admission to our hospital. On admission, she presented with intermittent fever (around 38°C), dry cough, dyspnea and chest pain. A physical examination revealed no finger clubbing, lymphadenopathy or cyanosis. Chest auscultation detected fine crackles in the left lower lung. Detailed examinations of the cardiovascular, gastrointestinal and neurological systems were normal. Chest radiography showed lobar consolidation with an air-bronchogram in the left lower lobe of the lung (Figure 1). She denied travel to the United States or European countries in recent months, as well as symptoms of nausea, vomiting or headache. Laboratory data showed WBC: 11400/uL, segments: 78%, lymphocytes: 9.1%, and CRP: 7.44 mg/dL. She was treated for bacterial lobar pneumonia with cefpirome and teicoplanin for 10 days. However, an intermittent fever still persisted after an adequate duration of antibiotic treatment. Cefpirome was then shifted to imipenem/cilastatin combined with teicoplanin on the 10th day of hospitalization. Chest computed tomography (CT) was therefore performed because of the delayed resolution and poor response to antibiotic treatment, and revealed consolidation with an air-bronchogram in the left lower lobe of the lung, favoring an inflammatory process (Figure 2).

Because of the poor response to empiric antibiotic treatment for 2 weeks, atypical pneumonia, subacute or chronic infection was highly suspected; serial examinations excluded the possibility of pulmonary tuberculosis, *Legionella* pneumonia and mycoplasma pneumonia. The level of serum cryptococcal antigen was high, with a titer >1:1024, and a sputum culture dis-

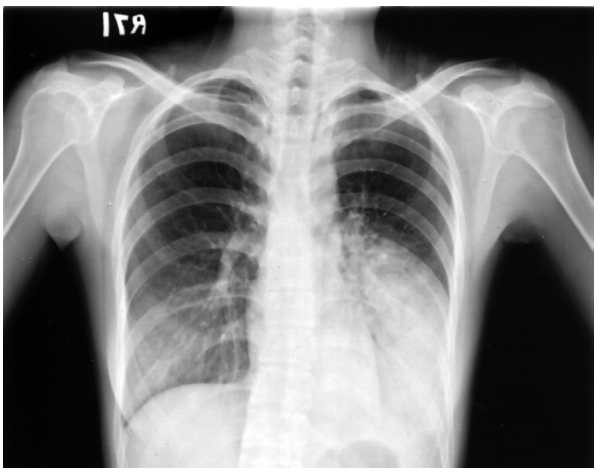

Fig. 1. Chest X-ray (posterior-anterior view) of the patient showing extensive ground glass consolidation with an air-bronchogram in the left lower lobe on presentation.

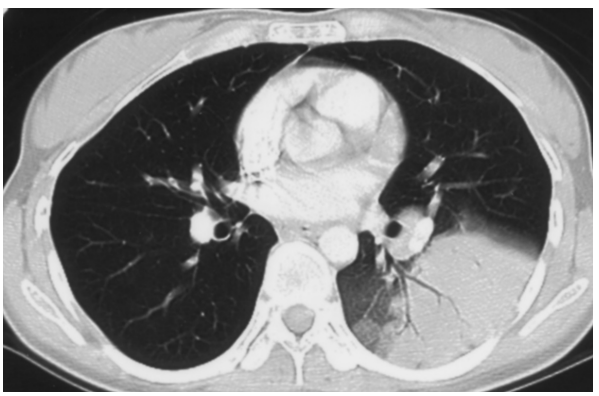

Fig. 2. Chest CT was performed because of the poor response to antibiotic treatment after admission, and revealed lobar consolidation of the left lower lobe with an obvious air-bronchogram.

closed normal mixed flora. The patient received a bronchoscopic examination, and bronchoalveolar lavage (BAL) was performed via the LB8 bronchus. Cryptococcal antigen of the BAL fluid was positive, with a titer of 1:128. Neither tuberculous bacilli nor malignant cells were identified in Liu's or Papanicolaou's stains. Moreover, cryptococci were readily identified by GMS staining of the BAL fluid, and a dense-black yeast stain was demonstrated in the microscopy (Figure 3). Cryptococcus yeast budding was occasionally identified. A bacterial culture of the BAL fluid disclosed *Pseudomonas aeruginosa* and *Burkholderia cepacia*, both of which were sensitive to cefpirome and imipenem/cilastatin. A fungal culture of the BAL fluid showed *Candida famata*, and fluconazole iv 400 mg qd was given initially. The fever subsided on the 7th day of treatment with fluconazole 400 mg daily. Fluconazole 400mg iv was then shifted to oral fluconazole 400 mg. Later, due to the high titer of serum cryptococcal antigen, a lumbar puncture was performed to exclude disseminated meningitis. CSF analysis was negative for cryptococcal antigen with WBC 0/uL, a negative Indian ink stain, and no CSF bacterial or fungal growth.

We also checked the patient's HIV and autoimmune profile because of the uncommon isolated lobar cryptococcal pneumonia. The laboratory data were negative for anti-HIV antibodies and normal for ANA and ANCA. Serum immunoglobulin for IgG, IgA and IgM were also normal. Peripheral lymphocyte subpopulation analysis revealed normal T-helper cells (CD4: 50%, CD8: 33%) and B cells (CD20: 7%). No evidence of immune suppression or malignancy was identified in this patient.

Chest radiography at the outpatient follow-up disclosed regression of the left lower lobe consolidation after daily fluconazole 400 mg therapy for 3 months, which correlated with clinical improvement (Figure 4).

Discussion

Pulmonary cryptococcosis is rarely reported

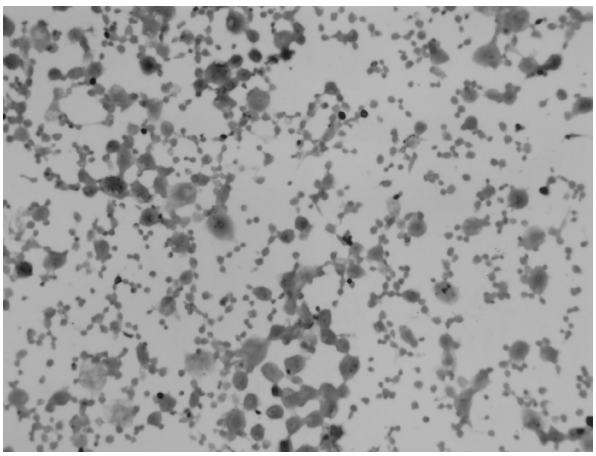

Fig. 3. Bronchoalveolar lavage fluid was obtained via LB8, and 74 cc of BAL fluid was retrieved after 150 cc normal saline injection with a 50% yield rate. With Gomori-methenamine silver stain, dark dense granules of *C. neoformans* were clearly seen in the field x 400.

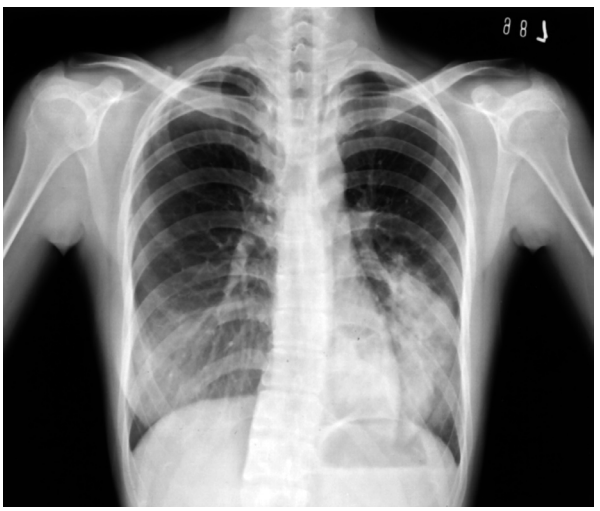

Fig. 4. Chest X-ray correlated with clinical improvement of the left lower lobe consolidation with fluconazole 400 mg qd 3 months after treatment.

in non-AIDS patients. Lam *et al*. reported a few cases of pulmonary cryptococcosis in immunocompetent patients in the Asia-Pacific region (Hong Kong, Singapore, Malaysia, New Zealand and Taiwan) [2]. Pulmonary cryptococcosis accounts for just over 30% of cryptococcosis cases and is therefore a rare disease, particularly in immunocompetent hosts. Extensive lobar pneumonia is even rarer and seldom reported worldwide [2]. One study did report 23 pregnant women with pulmonary cryptococcosis as a result of immunosuppression during pregnancy [3].

Pulmonary cryptococcosis can appear as cryptococcoma, atelectasis, lobar pneumonia and lymphadenopathy in chest plain radiography, and is not very specific in imaging. Chest radiographs of patients with pulmonary cryptococcosis offer a variety of presentations, ranging from 1 or more spherical nodules or masses, patchy consolidation, to multiple small nodules and even irregular shadows, with or without hilar and mediastinal adenopathy, and pleural effusion. Multiple nodules may resemble metastatic carcinoma and a consolidated mass is often difficult to distinguish from bronchial carcinoma in radiologic imaging [4-6]. Patchy consolidations can vary greatly in mass, size and location. Extensive consolidation is more frequently seen in immunocompromised patients [4]. Cavitation occurring within nodules or focal consolidations is relatively rare and seen in only 10% to 15% of cases. In addition, it seems that younger patients are more likely to present with cavitary nodules [6-7]. Widespread small nodules or irregular shadows are the least common, and have to be differentiated from miliary tuberculosis or other interstitial lung diseases. Pleural effusion is relatively rare in pulmonary cryptococcosis, in both radiographs and CT. Single or multiple well-defined pulmonary nodules are more common than segmental or lobar consolidations in pulmonary cryptococcosis. A disseminated pattern of broncho-pneumonia is rarely seen in immunocompetent patients [4, 6-7].

Clinical manifestations of pulmonary cryptococcal disease include fever, malaise, chest pain and cough. Many patients have no pulmonary symptoms, but infiltrates are seen on routine chest radiography, suggesting that asymptomatic pulmonary cryptococcosis may be common [8]. Meningitis is the most common clinically significant pattern of cryptococcosis. Patients may present with fever, confusion, headache, nuchal rigidity, cranial nerve palsy, papilledema and coma [9].

Besides meningitis and pulmonary cryptococcosis, cryptococcal infection also leads to extrapulmonary dissemination, most commonly hepatosplenomegaly and bone marrow suppression. Less than 10% of patients may also exhibit skin, eye, bone or joint involvement [10].

The diagnosis of pulmonary cryptococcosis is established by positive culture or the presence of the *C. neoformans* organism in specific staining of lung biopsy tissue or pulmonary secretions, positive serum cryptococcal antigen, and a history of exposure to pigeon droppings; pulmonary cryptococcosis has an excellent therapeutic response [2]. A CSF examination is recommended if the patients have any symptoms of meningitis or brain involvement, or if they are immunocompromised, and even in normal hosts according to the Infectious Disease Society of America (IDSA) guidelines.

Specific stains for *C. neoformans* include GMS stain, periodic acid-Schiff (PAS) stain and Indian ink stain. Some more specific stains are Mayer's mucicarmine stain (staining of the

fungal capsule) and Masson-Fontana melanin stain (capsule-deficient cryptococcus). With GMS stain, cryptococci are densely stained as dark granules (Figure 3). In immunocompetent hosts, fungal stains of BAL fluid and high titers of serum cryptococcal antigen are rarely positive. Serum cryptococcal antigen is usually not detected in those with cryptococcal pneumonia unless extrapulmonary dissemination has occurred, the patients are immunocompromised, or there is extensive lobar pneumonia.

No randomized controlled trials on the treatment of isolated pulmonary cryptococcosis in immunocompetent patients have been conducted, and there is no clear consensus on treatment in this patient population at present. Nadrous *et al*. reviewed 42 immunocompetent patients who had had cryptococcosis during a 26-year period; 36 of the patients had pulmonary involvement alone. Eleven of the 36 patients underwent lumbar puncture, and in all, findings were negative; of the 22 patients in whom serum cryptococcus antigen was measured, only 3 had positive titers [11].

Treatment is indicated in patients with symptomatic pulmonary infection if they are immunocompromised and have meningitis or disseminated infection. For asymptomatic immunocompetent patients with pulmonary cryptococcosis, antifungal therapy may be withheld for a month if the patients can be followed closely. Fluconazole 200-400 mg once daily for 6-12 months is the standard treatment recommended by the invasive fungal infections guidelines in Taiwan for cryptococcal pneumonia in immunocompetent patients [12].

A prospective comparison of fluconazole with a standard amphotericin B/flucytosine regimen in non-AIDS patients has not been done, but the trend is clearly toward fluconazole for most patients because of its lower toxicity, ease of administration and good results [13].

Treatment recommendations for cryptococcosis have been published by the IDSA. Immunocompetent patients who have isolated pulmonary cryptococcosis may be observed only, without therapy, if meningitis has been excluded; however the IDSA recommends treating all patients who are symptomatic. The recommended treatment is oral fluconazole (itraconazole is an alternative choice) for 3 to 6 months [14].

Our patient had high titers of cryptococcal antigen in both the serum and BAL fluid, and GMS staining of the BAL fluid also disclosed cryptococci. She also had a good response to fluconazole treatment. This was a rare pulmonary manifestation of cryptococcal infection in an immunocompetent patient.

In summary, pulmonary cryptococcosis is still rare, especially when presenting as extensive lobar cryptococcal pneumonia in immunocompetent patients. The clinical symptoms and presentations are variable and similar to those of community-acquired pneumonia. Consequently, a high index of suspicion is required for patients not responding to empiric treatment for pneumonia. Further investigations are necessary to confirm the diagnosis, as in this case.

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罕見大葉性隱球菌肺炎在免疫正常患者的臨床表現 病例報告及文獻回顧

郭仲華　王家弘

大葉性隱球菌肺炎在免疫正常病患文獻鮮少提及且相當罕見。我們提出一位25歲免疫功能正常的女性病患藉由高效價隱球菌血清抗原（SCA>1:1024）以及支氣管肺泡沖刷術（Bronchoalveolar lavage, BAL），Gomeri methenamide silver（GMS）細胞學銀染色確診為大葉性隱球菌肺炎。在免疫不全病人或臨床懷疑腦膜炎患者皆需要施行腰椎穿刺腦髓液分析以排除隱球菌腦膜炎的可能性。高效價隱球菌血清抗原很少表現在單獨隱球菌肺炎患者，在肺外散播或中樞神經感染或免疫不全、甚至嚴重大葉性肺炎等患者較為常見。在免疫功能正常的隱球菌肺炎患者，目前台灣感染症醫學會黴菌治療指引建議Fluconazole每日200-400 mg 持續治療6至12個月。*(胸腔醫學* ***2011; 26: 39-45)***

關鍵詞：隱球菌肺炎，GMS銀染色，免疫健全

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Pulmonary Malignant Melanoma with Occult Primary – Case Report

Tsu-Hui Shiao*, Jang-Ming Lee**, Yeun-Chung Chang***, Li-Na Lee*,****, Chong-Jen Yu*

Malignant melanoma is a fatal skin malignancy with uncontrolled growth of melanocytes. The incidence in Taiwan was 0.76-0.91 per 100,000 people in 2007 [1]. The lung is one of the visceral organs to which melanoma frequently metastasizes. Some patients show only a pulmonary tumor at diagnosis. If they fulfill certain criteria, these patients can be diagnosed as having primary pulmonary melanoma. If not, they are categorized as pulmonary melanoma with occult primary. We reported a 51-year-old man with a solitary pulmonary melanoma found incidentally at admission for thyroglossal ductal carcinoma. Bronchoscopy showed a dark-green endobronchial tumor obstructing the posterior segmental bronchus of the right upper lobe. Subsequent work-up showed no primary lesion in the skin, mucus membrane or eyes. Positron emission tomography showed negative results. The patient underwent right upper lobe and middle lobe bilobectomy and the diagnosis of melanoma with occult primary was established. We reviewed the literature and summarized the epidemiology, clinical and pathological features, treatment and prognosis of pulmonary melanoma. In diagnosing a solitary pulmonary melanoma, the primary site should be carefully sought, and surgical intervention should be performed if possible. ***(Thorac Med 2011; 26: 46-53)***

Key words: melanoma, pulmonary melanoma with occult primary, endobronchial metastasis

Introduction

Malignant melanoma is a fatal skin malignancy that predominantly arises from pigment-producing melanocytes of sun-exposed skin. Sometimes, a tumor may also develop from the oral cavity, esophagus, larynx, ano-genital mucosa and eyes. The incidence of malignant melanoma differs among ethnic groups. The yearly crude incidence from 1997 to 2005 was 41.5-58.3 per 100,000 New Zealand Europeans, but only 0.8-1.3 per 100,000 New Zealand Asians [2].

Melanoma may show pulmonary involvement. Pulmonary metastasis usually presents as multiple pulmonary nodules with an extra-pulmonary primary site. For solitary pulmonary melanoma, care must be taken to distinguish

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between a primary pulmonary melanoma and a single metastasis. Pulmonary melanoma with occult primary is a term used to describe metastatic pulmonary melanoma with no detectable extra-pulmonary primary lesion, probably because of the regression of the primary tumor. The distinction between pulmonary melanoma with occult primary and primary pulmonary melanoma can be very difficult. Therefore, certain criteria have been proposed to assist the establishment of a diagnosis of primary pulmonary malignant melanoma. Using the criteria, primary pulmonary malignant melanoma is extremely rare and the diagnosis is sometimes controversial [4].

In previous studies, chemotherapy, immunotherapy and molecular target agents failed to improve the survival of patients with metastatic pulmonary melanoma. Surgical intervention, if feasible, improved the outcome substantially [3]. Herein we present a patient with a large solitary pulmonary melanoma found incidentally at admission for thyroid surgery. The patient was diagnosed with pulmonary malignant melanoma with occult primary. Because of its rarity in the Taiwanese population and the distinguishing endobronchial presentation, we present this case and review the epidemiology, clinicopathology, treatment and prognosis of such patients.

Case Report

A 51-year-old man visited our ear-nose-throat outpatient clinic for a submandibular neck mass that had been noted for 4 days. He also had intermittent blood-tinged sputum for 1 year, but no dyspnea, hoarseness, cough, dysphagia or body weight loss. An ex-smoker of 20 pack-years, he quit smoking 20 years ago. The submandibular mass, 3 x 3 cm in size, was located along the midline, between the hyoid bone and the thyroid cartilage. It was elastic, non-tender and movable. Sonography presented a thyroglossal duct cyst. Fine needle aspiration obtained yellowish fluid, and thyroglossal duct papillary carcinoma was diagnosed by cytology. He was scheduled for total thyroidectomy and thyroglossal duct cyst excision.

The chest radiograph at admission unexpectedly showed a round, homogenous and well-defined opacity in the right upper lung (Figure 1). Computed tomography (CT) revealed a lobulated tumor in the right upper lobe, 7.1 x 4.5 cm in size (Figure 2). Under the provisional diagnosis of primary lung cancer, he underwent bronchoscopy, which revealed an endobronchial tumor with a dark-green color and smooth, shining surface, almost completely obstructing the right upper lobe bronchus. There were tiny dark spots in the bronchial mucosa near the tumor (Figure 3). Melanoma was suspected at first, but out of concern for the possible differential diagnosis of melanocytic carcinoid tumor

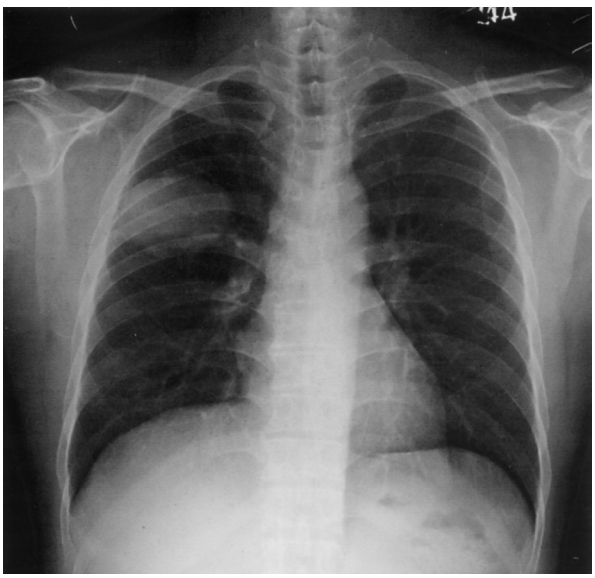


Fig. 1. Chest X-ray. A round, homogenous, well-defined solitary pulmonary nodule noted on the right upper lung chest X-ray image.

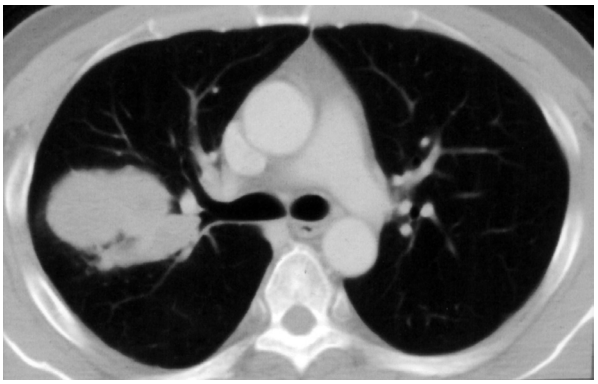
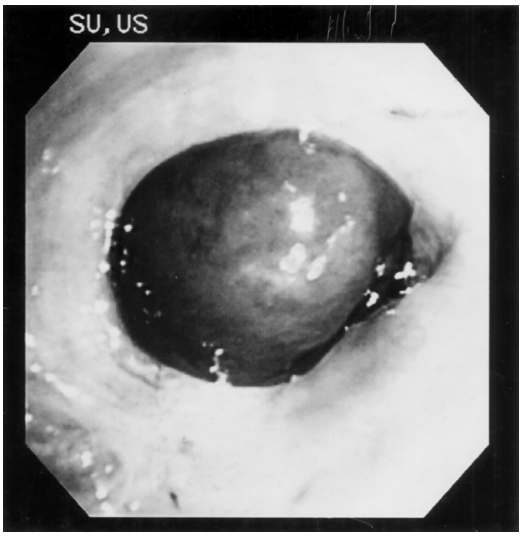
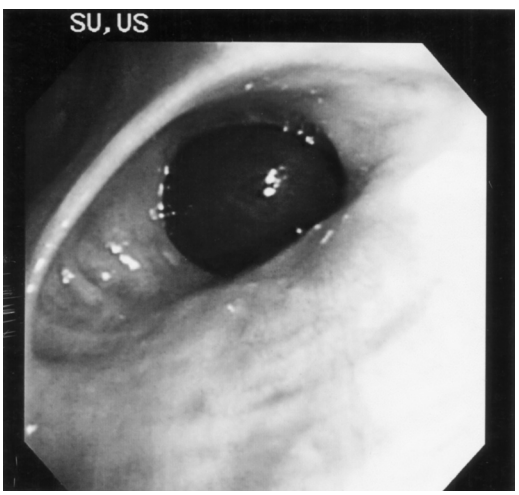


Fig. 2. Computed tomography. Under lung window of computed tomography, a lobulated tumor noted in the right upper lobe, measuring about 7 x 4.5 cm in size.



(A)



(B)

Fig. 3. Bronchoscopy. Bronchoscopy revealed an endobronchial tumor with a dark-green color and smooth, shining surface, almost completely obstructing the right upper lobe bronchus. There were tiny dark spots in the bronchial mucosa near the tumor.

with high vascularity, bronchoscopic biopsy was withheld. Instead, a percutaneous echo-guided aspiration/biopsy was performed. The imprint cytology showed clustered and scattered atypical cells with brown-black pigment, favoring the diagnosis of melanoma. Histological examination revealed melanin pigment only, with no viable cells.

Because primary pulmonary melanoma is so rare, we speculated that this tumor could be a metastatic melanoma, and began looking for a possible primary site. We conducted a comprehensive cutaneous, mucosal and ophthalmic examination, but failed to identify a primary site. The patient recalled that he underwent excision of a nevus on his back 10 years ago, but the nevus was said to be benign at that time. After a pre-operative positron emission tomography (PET) examination showed no extra-pulmonary lesion, the surgeon was consulted for surgical intervention.

The patient underwent video-assisted thoracoscopic surgery and right upper/middle bilobectomy under the provisional diagnosis of pulmonary melanoma. On gross examination, the resected right upper lobe contained a black, ill-defined, homogeneous soft tumor 8 x 7 x 7 cm in size. Microscopic examination showed that the tumor was composed of pleomorphic, spindle-to-polygonal cells, with melanin pigments in the eosinophilic cytoplasm and irregular nuclei. The tumor cells were arranged in a solid growth pattern, with a high mitotic index, and exhibited endobronchial growth and further invasion into the adjacent pulmonary

parenchyma. Immunohistochemistry staining showed strong and diffuse positive for HMB-45 (a monoclonal antibody against human melanoma cells) and S-100 (an antibody that stains schwannomas and melanomas) in the cytoplasm, and negative for cytokeratin, thyroid transcription factor-1 (TTF-1), chromogranin A and synaptophysin (Figure 4). The diagnosis of malignant melanoma was confirmed. The surgical margin was free and there was no lymph node metastasis.

He then underwent total thyroidectomy and neck dissection, followed by I^{131} treatment for the thyroglossal duct papillary carcinoma. He was free of disease 6 months after the surgery for melanoma.

Discussion

We presented a patient with a large lung tumor detected incidentally at admission for thyroid surgery. Bronchoscopy showed a dark-green polypoid endobronchial tumor, which is rarely seen in bronchoscopic practice, and the color was the first suggestion of melanoma. After surgical resection, the pathological diagnosis of melanoma was established, but we found no evidence of melanoma in the skin, mucosa and

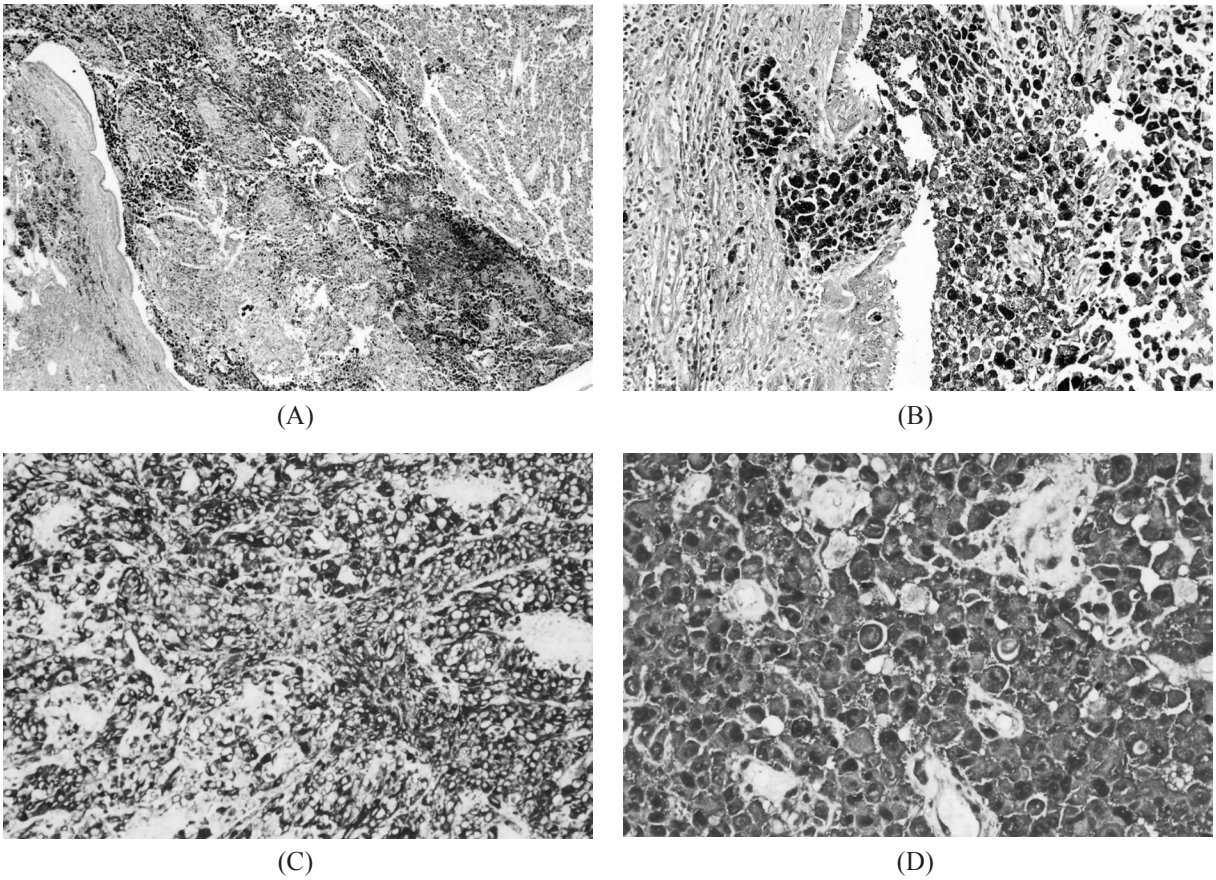


Fig. 4. Pathology of surgical lobectomy. Under 40x and 200x hematoxylin and eosin stain, the surgical lobectomy specimen showed highly pleomorphic, spindle-to-polygonal cells with prominent melanin pigments and a high mitotic index (Fig. 4A, B) Immunochemistry showed diffuse cytoplasmic staining for HMB-45 (Fig. 4C) and S-100 (Fig. 4D) under 400x microscopy.

eyes. We then thought this might be an exceedingly rare primary pulmonary melanoma, which constituted only 0.01% of all primary lung tumors [5-6], and was reported only once in Taiwan [7].

Jensen and Egedorf [8] defined the criteria for diagnosing primary pulmonary melanoma as: 1) no previous removal of pigmented or any kind of skin tumor, 2) no removal of eye tumors, 3) surgically removed lung specimen with a solitary tumor, 4) morphology of the tumor corresponding to the primary origin, 5) no detectable melanoma in any other organ, and 6) pathological criteria, including nesting melanoma cells beneath the bronchial epithelium. Our patient recalled that 10 years ago he had a nevus excised. Although the nevus was said to be benign and his current pulmonary melanoma was solitary and endobronchial, by definition his pulmonary melanoma was not primary, but had an occult primary.

Malignant melanoma is a skin malignancy with uncontrolled growth of melanocytes. Worldwide, there were about 160,000 cases reported yearly [6]. The crude incidence in Taiwan was 0.91 per 100,000 in 2007 [1]. Of all primary melanomas, 13.8-50% have been observed to show spontaneous regression of the primary site [9]. Occult primary of malignant melanoma, defined as histologically confirmed primary subcutaneous, nodal or visceral metastatic melanoma with no known cutaneous, mucosal or ocular primary lesion, accounted for 2-16% of the melanoma population [10].

The lung is one of the organs in which melanoma is frequently involved. In a study that included 146 melanoma patients with occult primary, 77 (53%) showed a pulmonary presentation [10]. Metastatic pulmonary melanoma was present in 19-23.5% of melanoma patients [11-12]. Most lesions were multiple, and solitary metastasis was less than 1% [13]. Patients often presented with cough, hemoptysis, and dyspnea, or were asymptomatic. Chest radiograph may show bilateral multiple nodules, a single, large, well-defined tumor, or lobar collapse. Sixteen cases of endobronchial metastasis of melanoma have been reported in the literature [14].

Endobronchial metastasis from extrapulmonary neoplasms is involved in 2-50% of pulmonary metastases. The most frequent primary tumors were cervical, breast and renal cell carcinoma. Other frequently observed primary sites included colorectal, head and neck cancer and lymphoma [15-16]. Endobronchial metastatic melanoma has been reported rarely [17-18], and often presented as a polypoid or fungating tumor showing a dark color and obstructing a lobar or segmental bronchus, as in our patient. The unusual dark color has often been the first clue to the diagnosis of melanoma.

The diagnosis can be established by a typical histology showing medium-sized tumor cells forming a solid growth, containing hyperchromic nuclei and numerous brownish pigment granules. Immunohistochemical study further confirms the diagnosis by showing positive staining for S-100 protein and HMB-45 antigen. Surgery plays an important role in pulmonary melanoma treatment, whether primary or metastatic. Systemic treatment such as chemotherapy, immunotherapy and molecular target therapy usually failed to improve survival in stage IV disease [19]. The criteria for pulmonary metastasectomy included a controlled primary site with prolonged disease-free survival, less than 2 pulmonary metastases, a good performance status, and negative extrathoracic metastasis as seen in PET or CT examinations [3, 19].

The prognosis of stage IV melanoma with

pulmonary metastasis is poor. The median survival is 7-8 months and the 5-year survival rate, without surgical treatment, is merely 3-6%. With metastasectomy, median survival can be prolonged to 19 months and 5-year survival can be increased to 18-39% [3, 20-21]. The independent predictors of overall survival included nodular histological type, disease-free interval, number of pulmonary metastases, presence of extrathoracic metastasis, and performance of pulmonary metastasectomy [3]. Pulmonary melanoma with occult primary may have an even better prognosis, with 5-year survival of 42% [4]. As for thyroglossal ductal papillary carcinoma, an extensive literature review did not find a direct association between that and melanoma.

In summary, we reported a patient with pulmonary melanoma with occult primary that presented as a large pulmonary neoplasm and a dark-green endobronchial tumor. The incidence and outcome of primary pulmonary melanoma, pulmonary melanoma with occult primary, and metastatic pulmonary melanoma are different. Surgical treatment should be performed whenever appropriate.

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無原發腫瘤的肺部惡性黑色素細胞瘤——病歷報告

蕭慈慧* 李章銘** 張允中*** 李麗娜*,**** 余忠仁*

惡性黑色素細胞瘤是一種黑色素細胞不正常增生造成的致命皮膚腫瘤，2007年在台灣每十萬人發生率是0.91人。肺臟是惡性黑色素細胞瘤常轉移的臟器，有些人在診斷時只有肺部腫瘤被發現，如果進一步符合特定的臨床條件，則可以診斷為原發性肺部惡性黑色素細胞瘤，如果沒有符合該臨床條件則被歸類成為無原發腫瘤的肺部惡性黑色素細胞瘤。我們提出一位51歲男性在入院治療甲狀舌管囊腫乳突癌時意外發現肺部單一腫瘤，支氣管鏡檢查顯示一個深綠色光滑球狀的腫瘤阻塞右上葉後段的支氣管；後續檢查顯示全身的皮膚、黏膜以及眼睛並無病灶，正子掃描亦未發現其他病灶，病人接受右上及右中肺葉切除手術治療，診斷為無原發腫瘤的肺部惡性黑色素細胞瘤。我們回溯文獻並對肺部惡性黑色素的流行病學、臨床、病理、治療、預後做一整理；針對單一肺部黑色素瘤，診斷上必須仔細尋找原發病灶，而治療上則應盡可能讓病患接受手術治療。*(胸腔醫學 **2011; 26: 46-53**)*

關鍵詞：惡性黑色素細胞瘤，無原發腫瘤的肺部惡性黑色素細胞瘤，支氣管內轉移

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Tuberous Sclerosis Complex Suspected in Young Female Presenting with Spontaneous Pneumothorax

Frank Cheau-Feng Lin*,**, Yung-Wei Tung*** , Stella Chin-Shaw Tsai****

Spontaneous pneumothorax is a commonly encountered medical condition that may often require emergency treatment. It has a predilection to occur in tall, thin, young males. A high degree of suspicion for other etiologies should be had when spontaneous pneumothorax occurs in young females, especially in non-smokers. This case report presents a non-smoking young female patient who was neither tall nor thin, and who experienced repeated attacks of spontaneous pneumothorax. Her other presentations included dyspnea, hematuria, urinary tract infection, mild mental retardation, seizure disorder, and acidosis. Thoracoscopy revealed multiple diffuse lung cysts. Lung biopsy was performed, and lymphangioleiomyomatosis (LAM) was diagnosed based on the pathologic results. The concurrent presence of renal angiolipomas, facial angiofibromas, ungual fibromas, hypomelanotic macules, shagreen patches, cortical tuber, subependymal nodules, and an ovarian cyst in this patient led to the diagnosis of tuberous sclerosis complex (TSC). With detailed history taking and physical examinations, we discovered that her mother and daughter also fulfilled some of the criteria of TSC. We therefore made the diagnosis of familial TSC. LAM should be suspected in female patients of childbearing age presenting with pneumothorax. TSC, though rare, ought to be considered in LAM patients. ***(Thorac Med 2011; 26: 54-61)***

Key words: female nonsmoker, lymphangioleiomyomatosis, pneumothorax, tuberous sclerosis

Introduction

Pneumothorax is a relatively common disease afflicting both the young and old, and both males and females. It could be primary, secondary, traumatic or iatrogenic in etiology [1]. Primary pneumothorax typically occurs in tall, thin, young males [1]. When a patient presents with pneumothorax, secondary causes should first be surveyed and excluded. The patient could be diagnosed as primary only after confirming that there were no previous traumatic or iatrogenic events. The etiologies of secondary pneumothorax include chronic obstructive pulmonary disease, asthma, bronchiectasis, cystic fibrosis, lung infections, lung tumors, pulmonary fibrosis, allergic alveolitis, histiocytosis X, lymphangioleiomyomatosis (LAM),

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sarcoidosis, Marfan's syndrome, Ehlers-Danlos syndrome, catamenia, adult respiratory distress syndrome, and immunologic diseases [2]. The incidence of primary pneumothorax is around 6.3 and 2.0 out of 100,000 persons per year for males and females, respectively [2]. The occurrence of pneumothorax in females is relatively uncommon, and should therefore always require more attention in clinical practice. Previous published studies on female pneumothoraces have been focused on catamenia and pneumothorax during pregnancy. In Sweden, 80% of female spontaneous pneumothorax cases were related to smoking [3]. Hagaman first suggested that female non-smokers between the ages of 25 and 54 years and without obvious reasons for pneumothorax should be screened for LAM [4]. The estimated prevalence of LAM is 0.5-4.8% amongst female pneumothorax patients, 1-2.6 per 1,000,000 women, and 1-3% of the population of tuberous sclerosis complex (TSC) patients [4-6]. We herein report a young adult female nonsmoker with familial TSC presenting with pneumothorax.

Case Report

A 28-year-old female Formosan aboriginal was transferred to the Emergency Department due to dyspnea which failed conservative medi-

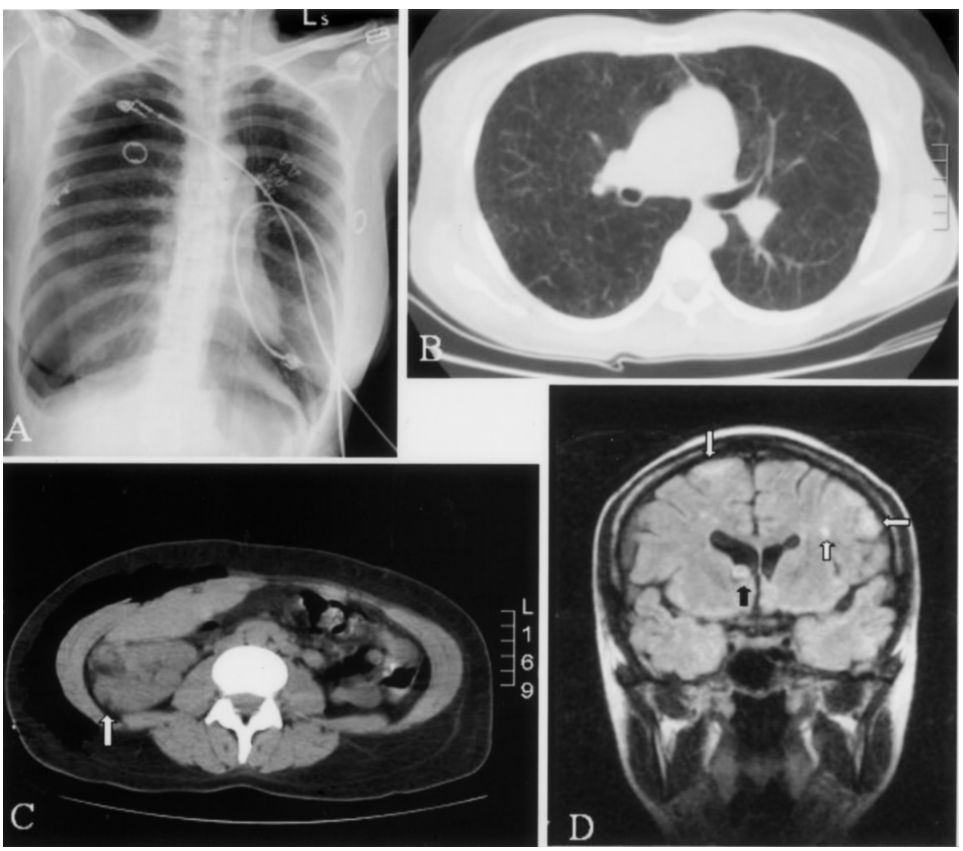

Fig. 1. Radiologic images. A. CXR. Pneumothorax in the right side, and increased lung volume with a flap of the diaphragm in the left side of the lung. B. HRCT. Multiple cystic lesions in the bilateral lungs. C. CT scan of abdomen without enhancement. Right renal angiomyolipoma (arrow): huge mass with fat and soft tissue densities. D. MRI of the brain. Subependymal nodules or giant cell astrocytomas in the ventricle (black arrow), and tubers (white arrows) in the cortex of the brain.

cal treatment. She had been treated for left-side pneumothorax surgically a year prior to this at another hospital. She was 1.52 m tall and weighed 52 kg. Vital signs at presentation were: pulse 143/min, respiratory rate 36/min, and blood pressure 82/46 mmHg despite 100% oxygen use. Breathing sounds could not be detected in the right chest on chest auscultation, and right tension pneumothorax was revealed by chest X-ray (CXR) (Figure 1A). Arterial blood gas data showed: pH 7.28, $PaCO_2$ 47.6 mmHg, PaO_2 75.2 mmHg, HCO_3^- 22.6 mmol/L, and oxygen saturation 92.8%. As this recurrent pneumothorax was on the opposite side, thoracoscopy was arranged immediately. Hundreds of bullae (Figure 2A) throughout the lung, especially the right upper lung and right middle lung, were disclosed intraoperatively. In consideration of the existence of specific lung diseases, lung biopsy was undertaken at the same surgery. The post-operative course was uneventful. The pathologic results of the lung lesions confirmed the diagnosis of LAM (Figure 2B). The aberrant smooth muscle in the septum of the lung was strongly immunoreactive for HMB45, progesterone receptor, desmin, smooth muscle actin, and S-100 focally, but was negatively stained for estrogen receptors. High resolution computed tomography (HRCT) of the chest was arranged following the surgical course, and revealed multiple cystic lesions in the bilateral lungs (Figure 1B).

The patient's detailed history was carefully reviewed after the operation. Her family history was significant in that her mother had similar facial lesions, and her only daughter suffered from dementia. Prior to admission, the patient had complained of exertional dyspnea, and she lived on the first floor to avoid climbing stairs. She had mild mental retardation which was confirmed by our psychiatrist after in-hospital consultation. The patient had received a left nephrectomy 3 years previous to this in another hospital due to hematurea. Previous pathologic slides and reports were obtained which revealed the diagnosis of renal angiomyolipoma. The other kidney also showed the presence of a similar tumor, as noted in the CT scan (Figure

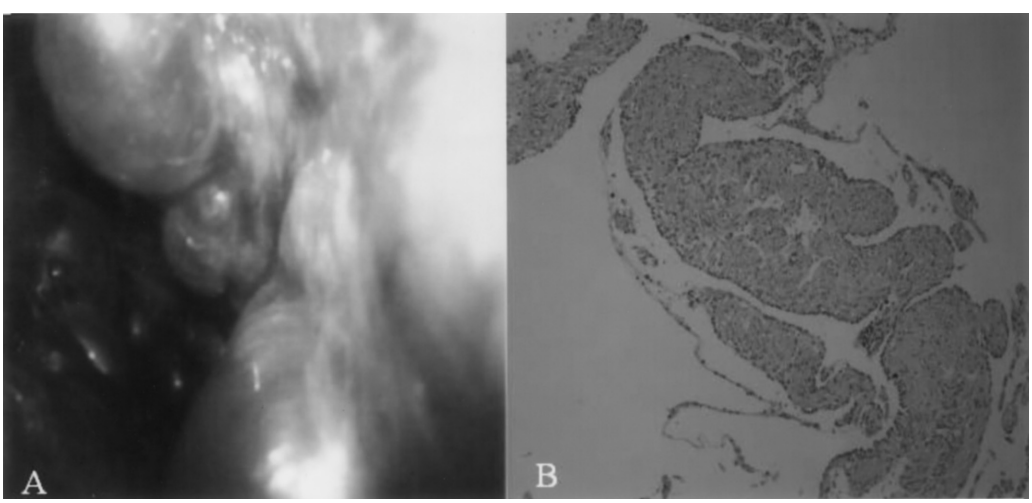

Fig. 2. Surgical findings. A. Thoracoscopy showed diffuse, multiple cystic lesions of different sizes throughout the right lung. B. Histopathology showed diffuse and irregular dilatation and thickened change of the bronchioloalveolar spaces, which are proliferations of smooth muscle tissue mixed with numerous small lymphatic and vascular vessels (H & E, 100×).

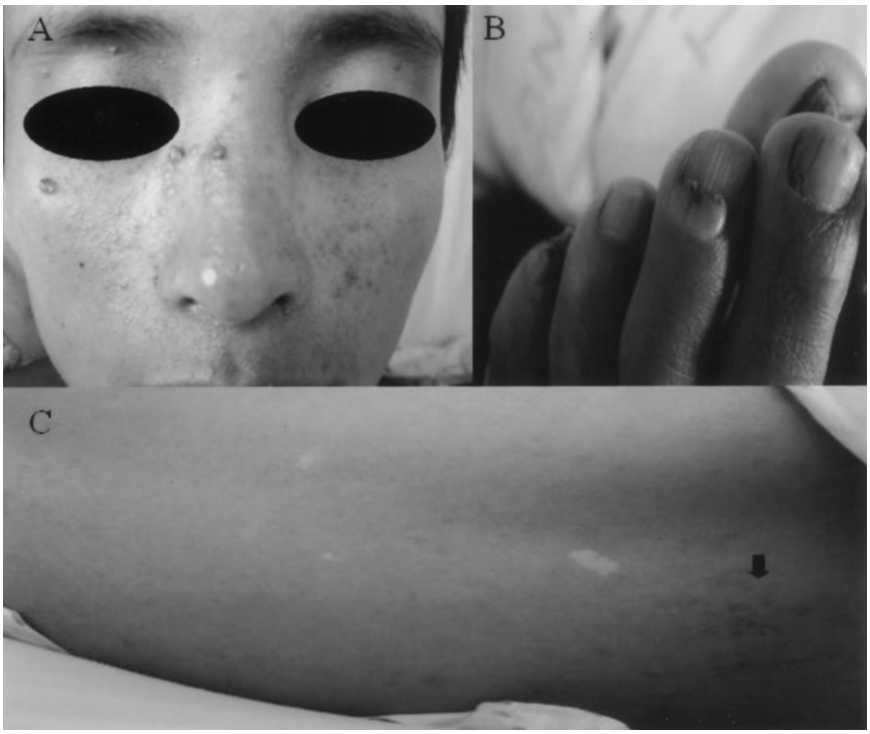

Fig. 3. Skin phenotypic presentations. A. Angiofibromas, face. Different-sized firm nodules around the nose and eyes. B. Ungual fibromas, toes. Whitish pearl-like tumor at the base of the 3rd toe occupying half of the nail. Smaller ones were seen on the 2nd and 5th toenails. C. Hypomelanotic macules ("ash-leaf" spot) and shagreen patch (arrow), back. Hypomelanotic macules: zigzag margins, elongated hypopigmented macules on the skin of the back. Shagreen patch: pigmented nevus with an elevated clear margin was also noted in this photo.

1C). A 5×5 cm left ovarian cyst was also noted in the CT scan. Brain tubers and subependymal nodules were seen in the magnetic resonance imaging (Figure 1D). Biopsy was performed on one of the facial lesions, and showed angiofibroma (Figure 3A). Ungual fibromas were seen on her fingers and toes (Figure 3B). 'Ash leaf' hypomelanotic spots were found on her back (Figure 3C) and extremities. Shagreen patches were noted on her back (Figure 3C) and forehead. Severe pulmonary obstructive impairment and alveoli diffuse function impairment, with FEV1 0.53L (20%, reference 2.69L), FVC 2.69L (87%, reference 3.08L), FEV1/FVC 20%, TLC 6.09L (142%, reference 4.31L), and DLCO 3.1 mL/mmHg/min (16%, reference 19.3 mL/mmHg/min), were detected 1 month after the pneumothorax.

We recommended that the patient undergo an oophrectomy in order to treat the underlying LAM and the ovarian cyst. However, due to the previous nephrectomy, the chance of using laparoscopic surgery was slim. Consequently, the patient refused further surgical intervention. She was therefore treated medically with bronchodilators and progesterone.

The patient was admitted 2 months later due to metabolic acidosis and seizure attack. Three months later, she was again hospitalized due to recurrent right-side pneumothorax, and 4 months later, for urinary tract infection and seizure. An anticonvulsant was used. Lung and kidney transplantations were suggested but the patient refused.

Discussion

Tuberous sclerosis (TS) is an autosomal dominant disease [7]. Two thirds of TS are sporadic. Familial TS on the other hand is relatively uncommon. Mutations in the TSC1 or TSC2 tumor suppressor genes are the known causes of this harmatomatous systemic disease, and were detected in 80% of TSC patients [7]. TSC1 located in chromosome 9q34 encodes harmartin, and TSC2 located in chromosome 16p13.3 encodes tuberin. They can form TSC1-TSC2 complexes, which are proteins involved with cellular differentiation, tumor suppression, intracellular signaling, cell cycle passage and intracellular vesicular trafficking [8]. Impairments of these proteins will promote cell responses to growth factors and nutrients, and result in cell proliferation and growth [9].

There are 11 major and 9 minor criteria to diagnose TSC. The presence of 2 major or 1 major and 2 minor criteria fulfills the diagnosis [10]. Of the 11 major criteria, this woman met 8, including renal angiolipoma, facial angiofibroma, ungual fibroma, hypomelanotic macules, shagreen patches, cortical tuber, subependymal nodules and LAM of the lung. One of the major criteria, cardiac rhabdomyoma, almost always regresses before adolescence [11], and was not found in this patient. The patient did not complain of visual problems, so the eye fundus was not examined. In the brain MRI, we found at least 3 large and 3 tiny nodules in the ventricle. Without pathologic evidence, astrocytoma could not be confirmed, but the nodule shown in Figure 1D radiographically resembled a subependymal giant cell astrocytoma. With that, she fulfilled almost all of the major criteria. Minor criteria include multiple renal cysts, nonrenal hamartoma, hamartomatous rectal polyps, retinal achromic patch, cerebral white matter radial migration tracts, bone cysts, gingival fibromas, 'confetti' skin lesions and multiple randomly distributed dental enamel pits [10]. The minor phenotypes were not apparent in this patient.

The most common manifestation of TSC is skin lesions [12]. Though always harmless, these skin lesions will distinguish the patient from others. Seizure attack, mental retardation and behavioral abnormalities are the neurological manifestations observed in 80% of TSC patients [9]. Of these neurological manifestations, our patient had mild mental retardation and seizure disorder, which was well controlled with medication.

Hypertension and hemorrhage are the commonly encountered renal problems in TSC patients [13]. Unfortunately, hematurea led to the need for a left nephrectomy in this patient. Worse still, her remaining right kidney also had angiomyolipoma. She suffered from occasional urinary tract infection and metabolic acidosis which might have induced seizure. However, her kidney functions were preserved without having to receive dialysis treatment. She had no cardiovascular abnormalities, such as dysarrythmia.

Even though not frequently present in TSC patients, LAM was a major problem for this patient. The prevalence of LAM is 1-2.6 cases per 1,000,000 women, mostly sporadic, and affecting women of reproductive age [5]. LAM is also related to the impairment of the TSC1 or TSC2 gene [14-15], and is a cystic lung disease caused by the abnormal proliferation of alveolar smooth muscles (or smooth muscle-like LAM cells). Subsequent destruction of the alveoli has led to the formation of cysts, and obstruction of the airway and lymphatic channels [16]. Half

of the sporadic and 70% of the TSC-associated LAM patients had renal angiomyolipoma [15]. Henseke et al. suggested that pulmonary LAM may be caused by metastasis from the kidney lesion, and the impairment of harmartin and tuberin may play a role [17]. Dyspnea, chest pain, pneumothorax and chylothorax have been reported in LAM patients [5], but asymptomatic patients are not uncommon [6]. CXR may not show significant findings except in cases with pneumothorax or pleural effusion. Nevertheless, CT of the chest will reveal multiple thin-walled cystic lesions in the bilateral lungs. The pulmonary function tests will show the presence of obstructive lung disease and impairment of the capacity to diffuse carbon monoxide [18]. The standard diagnostic method is biopsy with pathologic proof. The finding of myofibroblast-like spindle-shaped cells in the core surrounded by epithelioid-like polygonal cells is a pathognomonic feature. Immunhistochemistry studies showed positivity for smooth muscle actin, desmin, human melanoma black 45 (HMB45), and vimentin [16]. This patient's lung tissue was stained positive for the first 3 of the 4 markers.

As most LAM cases occurred in women of childbearing age, it was thought to be related to estrogen and progesterone. Progesterone receptor was present more frequently than estrogen receptor in one study, as with this patient [19]. Anti-estrogen therapy has been used in LAM patients, with 5, 10, and 15-year survival rates of 91%, 76%, and 65%, respectively [4]. Progressive deterioration of the pulmonary function, the involvement of a bigger area and increased severity of cystic lesions of the lung are related to a poor prognosis. Patients who have survived through their reproductive age have a good chance to survive well through the rest of their life [18]. The treatments for TS are often symptomatic and tailored towards involved organs. The development of targeted therapy is underway and may help these patients in the future [9].

The presentation of this 28-year-old female with repeated bilateral pneumothoraces differed from that of the typical tall and thin young male candidate. With a high degree of suspicion of a secondary etiology, further detailed history-taking, a careful physical examination and a workup revealed LAM in a patient with familial TSC. For reproductive-aged nonsmoking females presenting with spontaneous pneumothorax, secondary etiologies should be screened. LAM and TSC should be included in the differential diagnoses to be considered. Correct treatment can then be administered.

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結節性硬化症應列入年輕女性自發性氣胸患者之鑑別診斷

林巧峯*,** 童詠偉*** 蔡青劭****

自發性氣胸為一常見且常需緊急處理之疾病，好發於瘦高之年輕男性。若發生於年輕、未抽煙之女性，則要懷疑是否有其它原因造成。本例為一年輕不高不瘦不抽煙之女性反覆氣胸發作。其症狀包括喘、血尿、尿路感染、輕度智能障礙、癲癇、酸中毒。胸腔鏡下看見瀰漫性多發肺囊泡。肺臟切片之病理報告為淋巴管平滑肌增生症。病人亦有腎臟血管脂肪瘤，臉部血管纖維瘤，指甲纖維瘤，皮膚鯊魚皮斑，灰葉狀白斑，腦部皮質結節，腦室下結節及卵巢囊腫，故診斷為結節性硬化症。病人之母親及女兒亦有結節性硬化症之徵兆。自發性氣胸之育齡女性應懷疑是否有淋巴管平滑肌增生症，結節性硬化症雖稀少，但亦應列入鑑別診斷。*(胸腔醫學 **2011; 26: 54-61**)*

關鍵詞：女性，非吸煙，氣胸，結節性硬化症，肺淋巴管平滑肌增生症

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索取抽印本請聯絡：蔡青劭醫師，童綜合醫療社團法人童綜合醫院 醫學研究部，台中縣梧棲鎮中棲路一段699號