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

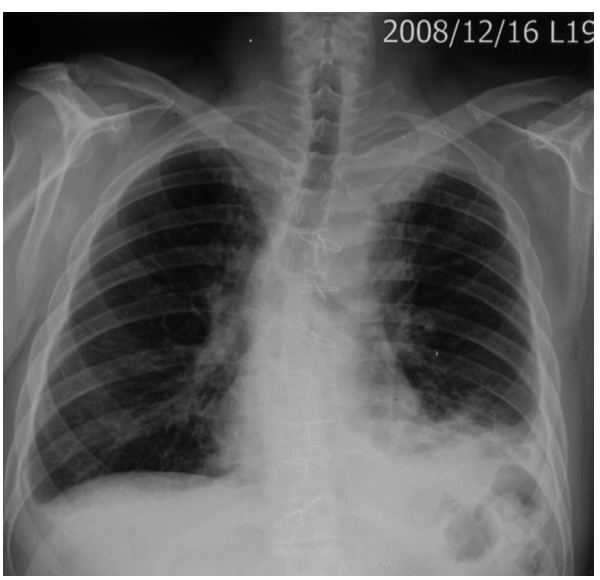
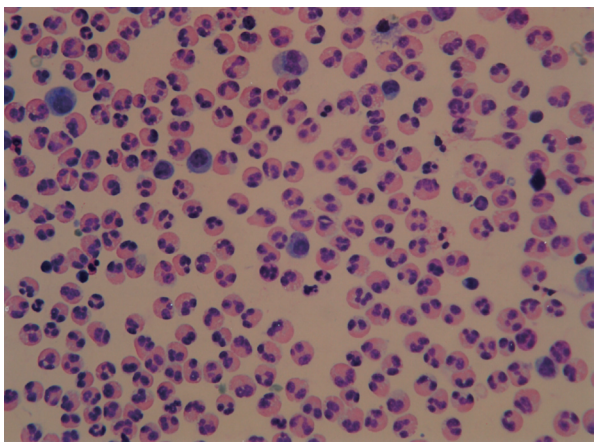
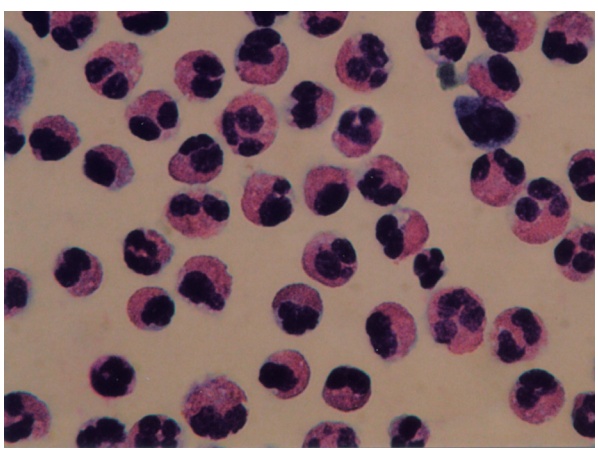


Fig. 1. Chest radiography on admission showing pulmonary opacity in the left upper lobe, and left pleural effusion.

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.

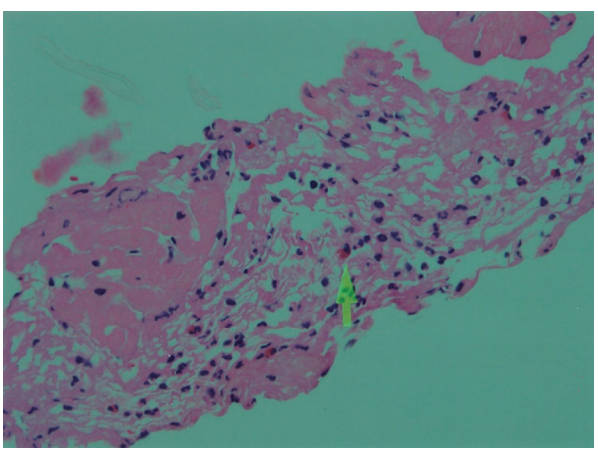


Fig. 3. Endomyocardial biopsy showed subendocardial infiltration of mixed inflammatory cells, including a few eosinophils (arrow). (Hematoxylin and Eosin stain, x100)

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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