CASE REPORT

A BUTTERFLY SHAPED ALVEOLAR HEMORRHAGE CAUSED BY CYTOMEGALOVIRUS

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Abstract. We report here a 35 year-old immunocompetent male, with a fulminantly lethal diffuse alveolar hemorrhage caused by CMV pneumonia. The patient was admitted with fever, rust colored sputum and exertional dyspnea. A chest x-ray revealed bilateral alveolar infiltration in a butterfly pattern. Bronchoalveolar lavage (BAL) was performed which revealed alveolar hemorrhage. Microscopic findings of the lavage fluid revealed large numbers of erythrocytes and hemosiderin-laden macrophages. The patient did not improve with empiric antibiotic treatment. High CMV IgG and IgM titers were found in the serum. The patient died from respiratory failure after detection of inclusion bodies on BAL before initiation of antiviral therapy.

Key words: Cytomegalovirus, pneumonia, alveolar hemorrhage

INTRODUCTION

Cytomegalovirus (CMV) pneumonia can be a life-threatening disease in immunocompromised hosts. Bone marrow transplant recipients can easily become infected with CMV and develop severe pneumonia (Crumpacker, 2000). CMV infection is rarely seen in immunocompetent hosts. It is an even move rare cause of diffuse alveolar hemorrhage (DAH).

CASE REPORT

A 35 year-old male patient was admitted to the hospital with a 3-week history of fever, productive cough, exertional dyspnea and rust colored sputum. He had undergone mitral valve replacement for mitral stenosis due to rheumatic heart disease 12 years previously and had been on warfarin since then. The international normalized ratio (INR) level was 1.9 two days prior to the beginning of his complaints.

On physical examination, his temperature was 37.8ºC. Lung examination revealed bilateral rales in both lung bases. The white blood cell count was $17.5x10^3/\mu l$, the platelet count was $470x10^3/\mu l$ and the hemoglobin level was 13.5 g/dl, but was 16.5 g/dl 1 week prior to admission. Coagulation tests revealed an INR of 1.7. He was negative for human immunodeficiency virus (HIV) antibody. The arterial blood gas results was as follows: PaO2: 54.9mmHg, PaCO2: 26.7mmHg and pH: 7.50 when breathing room air. Auto-antibodies, including ANA (antinuclear anti-

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body), RF (rheumatoid factor) and ANCA (antineutrophilic cytoplasmic antibody), were negative. On chest x-ray, bilateral perihilar alveolar infiltration was detected in a "butterfly pattern" (Fig 1). Echocardiogram revealed normal systolic function and a functionally normal prosthetic mitral valve. Chest computed tomography demonstrated bilateral perihilar consolidation with air-bronchograms in all lung fields. Sputum culture and hemoculture were negative. A sputum smear was negative for acid-fast bacilli. Cefepime and trimethoprim-sulfamethoxazole were initiated empirically. On the third day of therapy there was no improvement in the patient's clinical and radiological findings and the hemoglobin level decreased to 12.5 g/dl from 13.5 g/dl. The INR was 1.9. Bronchoalveolar lavage (BAL) at the time of bronchoscopy was macroscopically suggestive for alveolar hemorrhage. Microscopic examination of BAL fluid revealed large numbers of erythrocytes and hemosiderin-laden macrophages. BAL cultures were negative for bacteria, fungi and acid-fast bacilli. On the 5th day, high titers of IgG (250 AU/ml; N:<15 AU/ml), and IgM (1.79 Index; N:<0.690) antibodies against CMV were detected on serological assays. Cytological examination of BAL fluid smears revealed cytoplasmic inclusion bodies supporting the diagnosis of CMV infection (Fig 2). Unfortunately, on the same day, the patient's condition gradually deteriorated and he died of respiratory failure before initiation of antiviral therapy.

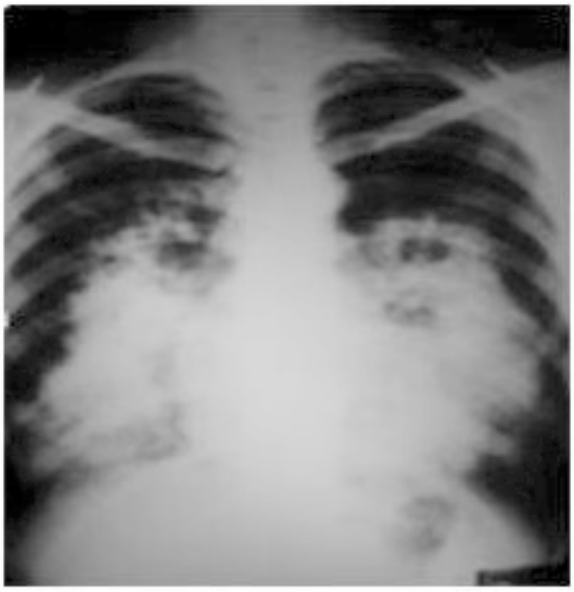

Fig 1–Chest x-ray of the patient revealing "butterfly" alveolar consolidation due to diffuse alveolar hemorrhage.

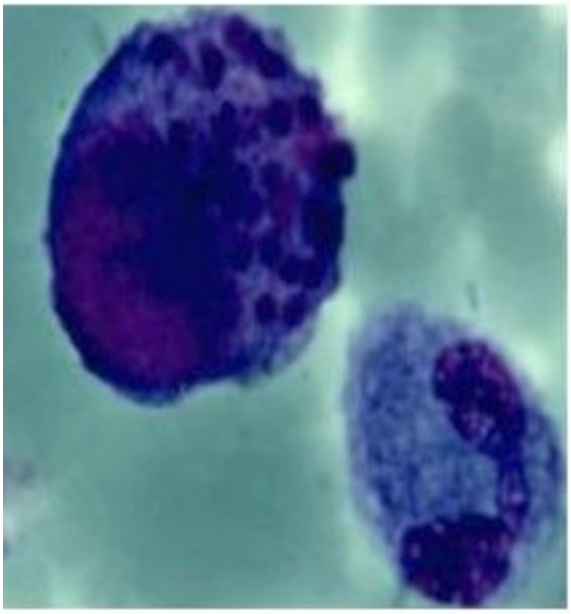

Fig 2–Cytoplasmic inclusion bodies revealing CMV infection (May-Grunwald-Giemsa, x 400).

DISCUSSION

Although CMV infections are prevalent in the general population, symptomatic pneumonia in immunocompetent hosts is rarely reported (Salomon and

Perlman, 1999). Eddleston *et al* (1997) reviewed the literature and found 34 reported cases of severe CMV infection in immunocompetent individuals. Karakelides *et al* (2003) reported an immunocompetent patient with a cavitary mass due to CMV pneumonia, confirmed by surgical lung biopsy. There was no evidence of diffuse alveolar hemorrhage in these cases.

Chest x-ray usually reveals diffuse interstitial infiltrates but this may be limited to a single lobe or it may appear consolidative. In the present case the chest x-ray revealed bilateral perihilar butterfly shaped alveolar infiltrates. To our knowledge, this radiological pattern has never been reported in a host with CMV pneumonia. This is a characteristic feature of alveolar filling along with hemorrhage resembling pulmonary edema.

The diagnosis of CMV infection can be established by either the detection of CMV-specific IgM antibodies (suggesting recent seroconversion) or the observation of at least a four-fold increase in CMV-specific IgG titers on paired specimens obtained at least two to four weeks apart. While the sensitivity and specificity of the serologic tests are adequate, the requirement for paired serum samples limits the utility of these tests in establishing a timely diagnosis. Nuclear and cytoplasmic inclusion bodies seen on conventional BAL cytology are the hallmarks of CMV disease; although the sensitivity is only 36.3%, it is very specific for CMV infection, up to 99.3% in advanced stage CMV infection with full virus replication (Tamm *et al*, 2001). Cell cultures, early antigen detection, CMV antigenemia (*ie*, CMV pp65) assays and molecular amplification (CMV DNA detection) are the other methods to detect active CMV infection. Drew (2007) found assays for CMV DNA or antigens in the blood are superior to culture for documenting viremia and pneumonia.

In this case, there was no time to detect a four-fold rise in IgG. Acute hemoglobin loss, fever, alveolar hemorrhages, alveolar infiltration associated with high titers of CMV IgM antibodies with BAL fluid showing cytoplasmic inclusion bodies are highly suggestive of CMV infection.

Diffuse alveolar hemorrhage (DAH) is a syndrome characterized by the presence of widespread hemorrhage from the pulmonary microvasculature (Primack *et al*, 1995). There are reports about the association between CMV pneumonia and alveolar hemorrhage. Herry *et al* (1996) reported five cases of alveolar hemorrhage associated with intravascular hemolysis in patients with AIDS; CMV was the only pathogen recovered from the lungs of these patients. Vincent *et al* (2001) studied 243 HIV-infected patients undergoing BAL who had pulmonary symptoms and/or fever. Alveolar hemorrhage was most commonly observed in patients with AIDS-related pulmonary disorders; pulmonary Kaposi's sarcoma, CMV pneumonia and hydrostatic pulmonary edema were the leading diseases identified as independent risk factors for alveolar hemorrhage. Tsushima *et al* (1999) described an immunocompromised patient with α1-antitrypsin deficiency and pulmonary hemorrhage due to CMV infection. Magro *et al* (2005) reported CMV infection may be of pathogenetic importance in some cases of alveolar hemorrhage in immunocompetent hosts.

Warfarin is the most commonly used oral anticoagulant and the most important adverse effect is hemorrhage. DAH is a rare complication in patients receiving warfarin. It may have also contributed to the hemorrhage in our case. However, no

patient with a therapeutic INR range has yet been reported to develop DAH.

In conclusion, although very rare, in a patient with acute hemoglobin loss, butterfly shaped alveolar infiltration, fever, alveolar hemorrhage and rusty sputum, CMV pneumonia should be considered.

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