

## Severe shortness of breath after PTCA

Saturday, 01 September 2007

A 71-year-old woman was admitted to the hospital due to acute myocardial infarction. Prior medical history included arterial hypertension, insulin-dependent diabetes mellitus, and hyperthyroidism. The patient had no history of tobacco or alcohol use. On admission, she was afebrile. Oxygen saturation was 97 % on room air. Chest x-ray (CXR) was normal. Blood glucose was 288 mg/dl.

She stayed in the Coronary Care Unit (CCU) for 48 h and was treated with aspirin (100 mg per day), clopidogrel (75 mg per day), heparin (1.000 iu/h), and a monoclonal antibody against platelet receptor Gp IIb/IIIa. Percutaneous transluminal coronary angioplasty (PTCA) was performed. Two days following CCU discharge, the patient became febrile (38.5 oC) with non-productive cough and progressive dyspnoea. Three days later, she was readmitted to the medical Intensive Care Unit (ICU) due to severe dyspnea and type I respiratory failure. On admission, she was tachycardic (113 beats / min) and tachypneic (30 breaths/min). The temperature was 38.6 oC and ABG analysis disclosed a PaO<sub>2</sub> of 58.0 mm Hg, a PaCO<sub>2</sub> of 25.8 mm Hg, pH=7.39, and a HCO<sub>3</sub> of 15.6 mmol/L. Chest auscultation revealed end-inspiratory crackles, bilaterally diminished breath sounds, and a grade I apical systolic heart murmur. The patient was intubated and admission-CXR revealed diffuse infiltrates in both lungs and pleural effusions. A white blood cell count of 17.600/iL (89% polymorphonuclear leukocytes) was noted, as well as a hematocrit of 32 %, a platelet count of 344,000/iL, and an erythrocyte sedimentation rate of 110 mm. Liver enzymes, and serum urea and creatinine were within normal limits.

The patient was treated with intravenous piperacillin-tazobactam, ofloxacin and teicoplanin. She remained febrile (39 oC) with no improvement in respiratory function and chest X-ray. Blood, urine and bronchial cultures were negative for common bacterial and fungal pathogens. A chest computerized tomographic (CT)-scan demonstrated confluent opacities in the right upper and middle lobes and in the left lower lobe as well as air-bronchograms, an extensive right pleural effusion and a pathological swelling of pretracheal lymph nodes (Figure 1).

What are possible causes of the pulmonary infiltrates?

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### Diagnosis

The patient continued to deteriorate. A thorough immunological evaluation was performed. Antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies against proteinase-3 and myeloperoxidase (ANCA-C, ANCA-P), and anti-DNA, were negative. Rheumatoid factor was normal, anti smooth muscle antibodies (ASMA) were positive (titer 1:20) and the C3 complement fraction was low. Plasma and urine protein electrophoresis did not reveal any monoclonal bands. Serologic tests for human immunodeficiency virus, and Legionella, Mycoplasma and Chlamydia species were negative. IgG antibodies against cytomegalovirus (CMV) were positive with no IgM antibodies present. Transthoracic echocardiography revealed mild mitral regurgitation, increased left atrial diameter, and normal left ventricular function. Pleural paracentesis revealed an exudate with 570 cells/iL (45% polymorphonuclear leukocytes and 55% lymphocytes) and negative Gram stain and cultures for common bacterial pathogens and fungi.

Bronchoscopy revealed mucosal edema and erythema with no endobronchial mass present. Bronchoalveolar lavage analysis was negative for common pathogens, fungi, CMV, Pneumocystis carinii, and Mycobacterium tuberculosis. Her ICU course was complicated by an Enterobacter cloacae pneumonia and bacteremia on day fifteen. The isolated bacterial strain was sensitive to carbapenems and ciprofloxacin. Additionally, she developed candiduria. The antibiotic regimen was broadened to imipenem, ciprofloxacin, and vancomycin. Repeat Ziehl Nielsen stain of tracheobronchial aspirates, bronchoalveolar lavage and pleural fluid analysis was negative. A new chest CT-scan showed similar findings to the first study. She progressively worsened and developed hemodynamic instability.

An open lung biopsy revealed distortion of lung parenchyma, moderate inflammation and patchy fibrosis with a subpleural accentuation. The fibrotic areas consisted of dense collagen with focal "honeycomb" pattern alternating with areas of relatively normal alveolar parenchyma. There were also focal alveolar macrophage accumulation, smooth muscle proliferation and focal subpleural fatty metaplasia. The overall pattern was consistent with usual interstitial pneumonia. Some epithelial type II pneumocytes showed cytologic atypia with abundant cytoplasm and large pleomorphic nuclei harboring intranuclear inclusions consistent with CMV infection. Immunohistochemistry with anti-CMV antibodies (Signet) was positive in these cells (Figure 2). Furthermore, a polymerase chain reaction (PCR) on DNA extracted from the paraffin embedded tissue with CMV specific primers showed a band of 110 bps, consistent with the presence of CMV-DNA. Despite treatment with ganciclovir (5 mg/Kg, iv, every 12 hours) the patient died two weeks later from severe acute respiratory distress syndrome and multiple organ failure.

#### Teaching points

1. Ventilator associated pneumonia (VAP) due to CMV is a largely unexpected but probably underestimated diagnosis. In one study 25 of 86 patients with VAP and prolonged ICU length of stay had CMV pneumonia [1]. The presence of CMV IgG antibodies may help to identify a group susceptible to reactivation disease [1]. Recent reports have demonstrated that anti-CMV IgG seropositive ICU patients with severe illness (SAPS II score  $\geq$  41 points) frequently develop active CMV infection [2]. In 10% of the cases examined, active infection progressed to severe and fatal disease [2]. Despite the fact that it is common to see CMV associated interstitial lung disease in post-transplant patients [3], there are only two cases in the literature where CMV related usual interstitial pneumonia has been reported in patients with no transplant history [4, 5]. One referred to a patient compromised by virtue of corticosteroid treatment [4] and the other patient was suffering from a concomitant thymoma [5].
2. In the present case, we speculate that reactivation CMV infection led to the development of usual interstitial pneumonia in a diabetic patient. Infections due to latent viruses, like CMV could theoretically induce immune reactions which activate T-helper cells and type II alveolar cells, thus resulting in local overproduction of growth factors (PDGF and TGF), fibroblast regeneration, and fibrosis. Notably, in the present case, there was no history of chronic interstitial pulmonary disease or fibrosis. One previous report has shown that many patients with pulmonary fibrosis exhibited CMV specific IgG seropositivity and positive complement binding for CMV [6].
3. Previous studies have suggested that CMV is an atherogenic factor predisposing to coronary artery disease. CMV contributed to one third of restenosis cases following angioplasty in recent reports [7, 8]. This was attributed to local CMV reactivation in the injured endothelium resulting in smooth muscle cell hyperplasia, inhibition of apoptosis and induction of atherogenesis [7, 8]. It has been hypothesized that CMV may be reactivated locally as a response to vascular injury in a subgroup of patients undergoing PTCA and in some cases may lead to severe infection [9]. The association between the previous PTCA and the subsequent development of fatal CMV associated usual interstitial pneumonia is of extreme interest in the present case. It could be hypothesized that after the myocardial infarction, the elevated catecholamine titers may have led to CMV reactivation and transient CMV antigenemia, which eventually contributed to the lung injury. That catecholamine infusion or treatment with phosphodiesterase inhibitors, both of which increase c-AMP levels, could contribute to CMV reactivation has been shown in a recent report [10]. In a similar manner, one could see CMV reactivation related disease in ICU patients via blood products transfusion containing leucocytes or the requirement of norepinephrine and other catecholamines infusion [2].
4. An interesting aspect of this case is the diagnostic procedure for the CMV identification. The detection of specific inclusion bodies in alveolar epithelial cells is the most reliable diagnostic criterion for CMV pneumonia. These bodies are rarely found in BAL-fluid, because the virus preferentially attacks alveolar and capillary-endothelial cells. For this reason, open lung biopsy is preferable to BAL and transbronchial biopsy. Although one could potentially diagnose idiopathic pulmonary fibrosis or diffuse interstitial lung disease based on clinical and radiographic criteria, in most cases it is necessary to perform surgical lung biopsy for the diagnosis and determination of the underlying histopathology [11]. However, it is difficult to decide on the performance of a surgical open lung biopsy given the potential complications for an intubated critically ill patient in the ICU setting, unless it is absolutely necessary. Analysis of BAL specimen using the CMV specific polymerase chain reaction measurement of viral load may contribute to diagnosis if open lung biopsy is not feasible [12].
5. CMV pneumonia must be included in the differential diagnosis in the appropriate clinical setting. Even in patients presenting with community-acquired pneumonia (CAP) Marrie et al reported that 4 out of 443 patients (0.9%) had documented CMV pneumonia as the underlying diagnosis [13]. Another fourteen out of 443 patients (3%) had fourfold

increase in CMV IgM titers. From these patients, only six (33%) were immunocompromised, seven needed mechanical ventilation and five (28%) died [13]. In hospitalized patients, CMV is usually transmitted by means of blood products and via transplanted organs [14, 15]. In the presented case, we did not find evidence of recently acquired acute CMV infection. In addition there was no history of recent transfusions or overt immunosuppression besides the diagnosis of diabetes mellitus. We did not find reports of increased incidence of CMV infection in diabetic patients although an increased susceptibility to infection is seen with diabetes.

6. The isolation of *Enterobacter cloacae* in the bronchial secretions of our patient during ICU stay may represent coinfection or superinfection, which commonly occur during CMV infection. This could be due to several immunomodulating properties of CMV per se [2, 16].

7. In conclusion, an interesting case of CMV associated usual interstitial pneumonia in a diabetic patient is presented. The potential correlation of the previous PTCA with the reactivation of CMV, which led to a severe fatal CMV infection with the development of pulmonary fibrosis, is discussed. Correct diagnosis of CMV-associated severe bilateral pneumonia, even in a non-overtly immunocompromised patient depends on clinical awareness in the appropriate setting along with definitive proof of viral infection.

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#### References

1. Papazian L, Fraisse A, Garbe L, et al. CMV. An unexpected cause of VAP. *Anesthesiology* 1996;84:280-7.
2. Heininger A, Jahn G, Engel C, Notheisen T, Unertl K, Hamprecht K. Human cytomegalovirus infections in nonimmunosuppressed critically ill patients. *Crit Care Med* 2001;29:541-7.
3. Falagas ME, Snyderman DR, George MI, et al. Incidence and predictors of cytomegalovirus pneumonia in orthotopic liver transplant recipients. *Transplantation* 1996;61:1716-20.
4. Tokimatsu I, Tashiro T, Ichimiya T, et al. A case of idiopathic interstitial pneumonia with cytomegalovirus infection. *Nihon Kyobu Shikkan Gakkai Zasshi* 1992;30:941-6. [article in Japanese]
5. Yonemaru M, Ustumi K, Kasuga I, et al. A case of pulmonary fibrosis associated with CMV inclusion body. *Nihon Kyobu Shikkan Gakkai Zasshi* 1994;32:184-8. [article in Japanese]
6. Yonemaru M, Kasuga I, Kusumoto H, et al. Elevation of antibodies to CMV and other herpes viruses in pulmonary fibrosis. *Eur Respir J* 1997;10:2040-5.
7. Zhou YF, Leon MB, Waclawiw MA, et al. Association between prior cytomegalovirus infection and the risk of restenosis after coronary atherectomy. *NEJM* 1996;335:624-30.
8. Streblov DN, Orloff SL, Nelson JA. Do pathogens accelerate atherosclerosis? *J Nutr* 2001;131:2798-2804.
9. Salomon N, Perlman DC. CMV pneumonia. *Semin Respir Infect* 1999;14:353-8.
10. Prosch S, Wendt CE, Reinke P, et al. A novel link between stress and human cytomegalovirus (HCMV) infection: Sympathetic hyperactivity stimulates HCMV activation. *Virology* 2000;272:357-65.
11. Collard HR, King TE Jr. Demystifying idiopathic interstitial pneumonia. *Arch Intern Med* 2003;163:17-29.
12. Kjellstrom C, Bergstrom T, Martensson G, et al. Relation between PCR findings and morphological changes during CMV infection in transplanted lung. *Diagn Mol Pathol* 1997;6:267-76.
13. Marrie TJ, Janigan DT, Haldane EV, Faulkner RS, Kwan C, Durant H. Does CMV play a role in community-acquired pneumonia? *Clin Invest Med* 1985;8:286-95.
14. Konoplev S, Champlin RE, Giralt S, et al. CMV pneumonia in adult autologous blood and marrow transplant recipients. *Bone Marrow Transplant* 2001;27:877-81.
15. Barbera JA, Martin-Campos JM, Ribalta T, et al. Undetected viral infection in diffuse alveolar damage associated with bone marrow transplantation. *Eur Respir J* 1996 ;9:1195-2000.
16. Falagas ME, Snyderman DR, Griffith J, Werner BG. Exposure to cytomegalovirus from the donated organ is a risk factor for bacteremia in orthotopic liver transplant recipients. *Clin Infect Dis* 1996 ;23 :4-74.