CASE REPORT

Cytomegalovirus pneumonia after complicated cardiothoracic surgery

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Abstract - An unusual case of cytomegalovirus (CMV) pneumonia in a post-cardiothoracic surgery patient is presented. The diagnosis was made by PCR of CMV, DNA and histopathological examination, which showed bilateral CMV pneumonia, confirmed by immunohistochemical staining. The possibility of CMV reactivation in intensive care unit (ICU) patients is discussed. Clinicians should be aware of CMV as a cause of pneumonia after complicated cardiac surgery if bacterial and cardiac causes are excluded.

Keywords - CMV, pneumonitis, capillary leak, intensive care, cardiothoracic surgery

Introduction
Cytomegalovirus pneumonia in non-immune compromised ICU patients is a largely unexpected and probably underestimated diagnosis. In one study 25 of 86 patients who had a prolonged stay in ICU had CMV pneumonia [1,2]. In studies of septic patients, about one-third of the patients developed CMV reactivation [2,3]. Active CMV infection is associated with prolonged ventilation time and ICU stay [2,3]. Severely ill ICU patients (SAPS 2 score>41 points) seropositive for CMV IgG antibodies frequently develop active CMV infection. Active infection progressed to severe and fatal disease in 10% of the cases examined by Heininger [2]. Although there is conflicting evidence in the literature about the role of CMV reactivation in the ICU, we present a case of CMV pneumonia in a patient who was not obviously immune compromised prior to her admission.

Case report
A 69-year-old woman was admitted to ICU after an urgent mitral valve replacement. Her medical history included Hodgkin’s disease 37 years earlier which had been treated with chemotherapy and local thoracic and brain radiotherapy, fibrotic changes in the right upper lobe, transient ischaemic attacks (TIAs), osteoporosis, recurrent urinary tract infections, splenectomy, gastric ulcer bleeding, lumpectomy for a benign tumour of the right breast and mild normocytic anaemia.

Valve replacement had been a complicated procedure with a long extra-corporeal circulation time of 215 min. She arrived at the ICU on high dose inotropics which were tapered off in the week after her admission. Hydrocortisone therapy was started and tapered off over two weeks. She needed renal replacement therapy because of renal failure due to forward failure. During the first three days of her ICU stay, the patient received ceftazidime simultaneously with topical tobramycin, amphotericin-B and polymyxin, which are components of the selective digestive tract decontamination protocol. She received vancomycin prophylaxis as routine treatment of patients undergoing valve replacement. Postoperative echocardiography revealed peripartate myocardial infarction and showed akinesia of the septum and the inferoposterior region. Eleven days after the operation the patient was extubated, but had to be reintubated because of respiratory insufficiency due to pleural effusion. Because of bradycardia post-surgery a pacemaker was implanted on day twelve.

Using furosemide and continuous venovenous haemofiltration (CVVH), negative fluid balances were achieved and PEEP and pressure support were tapered to minimal values. Then the weaning process stagnated. It was impossible to further mobilize fluids. The clinical picture was that of a patient with persistent peripheral oedema due to capillary leakage. Inflammatory parameters showed elevated CRP levels (76-89 mg/l) with low leucocytes (6-8 *10^9/L). Bacterial cultures of blood remained negative. No serological or virological tests were performed. The patient stayed on low dose inotropics.

Repeat transthoracic and transoesophageal echocardiography revealed a reasonable left ventricular function with some akinesia of the septum and left ventricular hypertrophy (comparable to preoperatively), a good right ventricular function, normal mitral prosthesis valve function and slight pericardial effusion with no signs of tamponade. The capillary leakage was not explained by the results of the echocardiography. As bacterial cultures remained negative, cortisol levels were measured and hydrocortisone was started to exclude relative adrenal insufficiency. The first day after starting steroids she seemed to respond, so these were continued. Twenty-five days after admission on replacing a central venous line Enterococcus faecalis was cultured from its tip, and vancomycin was administered.

Twenty eight days after admission the patient’s condition

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deteriorated. A pulmonary artery catheter was placed which showed a cardiac index of 2.3 l/min/m². Cardiac echocardiography did not explain her deteriorating condition. Re-thoracotomy was performed to exclude tamponade but no tamponade was found. Inflammatory parameters were slightly elevated. A presumptive diagnosis of low grade sepsis was made. An extensive search for an infectious agent followed: radiological investigations did not show any focus of infection. A CT scan of the thorax showed bilateral pleural effusion and atelectasis. No infiltrate suspicious for infection was visible. Repeated blood, sputum and pleural fluid samples were drawn for bacterial and fungal cultures, all of which remained negative.

Pleural drainage procedures had only minimal and short-term positive effects on ventilator weaning. Several blood, sputum and pleural cultures were drawn. Bacterial and fungal cultures remained negative. Over the following seven days the patient slowly deteriorated and increasingly needed inotropics and respiratory support. Central venous lines were removed and new ones inserted several times during admission. On day 38 she rapidly developed a severe metabolic acidosis, deep shock, multiple organ failure and then died. Autopsy showed a diffuse acute phase and early organizing pneumonia, with intra-alveolar exudate, granulocytic infiltrate, accumulation of histiocytes, and slight pneumonitis, consistent with a milliary pattern of CMV infection as seen in the haematogenic spread of the virus. Cytopathogenic features characteristic of CMV infection, the so-called owl’s eyes, were easily recognized, and present in all lobes. CMV infection was confirmed by CMV specific immunohistochemical stainings (Fig 2) and PCR. The post mortem PCR (Taqman 7500, applied biosystems) of the lung, heart and kidney were positive for CMV. Cycli times were 31.46;28.78 and 29.27, with a threshold of 0.1. There were signs of chronic cardiac decompensation. Focal CMV immunostaining was found in the myocardium, without the typical owl’s eye morphology, and without tissue necrosis or inflammation. Similarly, few positively stained cells were found in renal glomeruli, again without evidence of tissue damage. No signs of non-Hodgkin lymphoma were found. Blood cultures drawn the day our patient died grew Enterococcus faecium and Bacteroides species.

Discussion
This case shows that CMV infection can occur during a prolonged ICU stay and can be of clinical relevance. It is likely that the recurrence of the CMV in our patient led to persistent respiratory insufficiency and capillary leakage resulting in ventilatory weaning problems.

In general, the clinical significance of CMV recurrence is unknown and its influence on morbidity and mortality in the ICU patient is under debate [4]. After primary infection, there is seroconversion and reactive B-, T- and specific memory cells are formed. Cytotoxic T cells and Natural Killer cells control the primary infection [5]. Primary infection is followed by lifelong CMV latency in cells of the myeloid lineage such as neutrophil granulocytes, and in CD14 monocytes, dendritic cells and megakaryocytes [6]. It is usually asymptomatic and is often acquired during childhood.

Clinical signs vary from asymptomatic in healthy humans to severe disease: pneumonitis, hepatitis, myocarditis, mainly in immunocompromised patients and mostly reported in transplant recipients. In transplant patients CMV disease develops in negative recipients of CMV-positive donors [5].

The severity of the disease is related to viral load, infection

Figure 1.

Haematoxylin and eosin staining of lung tissue showing two examples of cells with characteristic cytopathogenic features of cytomegalovirus infection, the so-called owl’s eye (arrow) an enlarged cell (hence the name of the virus) with a nuclear eosinophilic inclusion surrounded by a halo (white or lighter toned zone), in which a small clump of chromatin can be seen.
route and host factors (the immune compromised state). In bone marrow transplant recipients, who are among the most severely immune compromised, CMV pneumonitis has a high mortality, whereas in renal transplant patients treatment is more successful.

Prevention of CMV in bone marrow-, heart- and liver transplant patients using ganciclovir has been demonstrated to be effective in several studies, and has reduced CMV-associated mortality [5]. Treatment strategies in bone marrow transplant patients, in whom treatment was started as soon as a CMV-positive culture was found at any location in the body, resulted in higher success rates [5], probably due to an earlier start and lower CMV levels.

Muller and Mertens offer a possible explanation for the different clinical course of CMV infections in septic and immune compromised patients [7]. They differentiate between primary CMV infection, CMV reactivation and recurrence. Primary infection is the first contact with the virus. In reactivation there is increased replication of the CMV after an episode of latency of the virus at the cellular level. This can occur due to inflammation or inflammatory cytokines. If, after reactivation the patient has an imbalance in the immune system, this reactivation can result in CMV recurrence of infection with end-organ damage. In reactivation, CMV is replicated at the cellular level and diagnostic blood tests (cell culture, pp65-antigenemia or PCR) can turn positive for CMV. This is a process independent of immunosuppression [6]. Low levels of viral load are measured. In immunocompetent patients reactivation may alert the immune system and show an increase in reactive Th1 cells. The adequate reaction of Th1 cells controls the CMV replication so that the amount of CMV is limited and no direct CMV damage to organs occurs. The T-cell reaction is responsible for the indirect effects of CMV reactivation and local control of the infection. This situation is often seen in septic patients with no end-organ damage.

Clinical recurrence of infection occurs if there is an imbalance of the immune system. In clinical recurrence a high CMV viral load can be established (pp65 antigenemia, positive PCR), which is correlated with direct and indirect signs of end-organ disease. These effects can be inhibited by pre-emptive antiviral therapy and prophylaxis, as is shown in haematopoietic stem cell transplant recipients [7].

In a prospective study, CMV reactivation with low pp-65-antigenemia was seen in 32% of septic shock patients [3]. Proinflammatory cytokines, transient immune paralysis (compensatory anti-inflammatory response syndrome) and drugs are indicated as factors related to CMV reactivation in sepsis [3,7].

One of the cytokines reported to induce CMV reactivation is tumour necrosis factor alpha (TNF-a) [4] Although in the CMV group of 80 ICU patients Jaber et al. found a significantly longer period of mechanical ventilation and an increased ICU length of stay, they found no significant differences in morbidity and mortality between treated and untreated patients [4]. In our patient, who was in severe shock on admission, the cytokine storm and systemic inflammatory response syndrome (SIRS) may have resulted in the CMV reactivation: shock induces release of catecholamines and glucocorticoids into the circulation. During the inflammatory response syndrome and the compensatory anti-inflammatory response syndrome the immune function may be impaired, resulting in reactivation, and recurrence of CMV infection with organ damage [4].

In our patient the PCR was positive in several organs (heart, kidney and lung). Histological examination showed only end-organ damage/infection of the lung and not of the other organs. This illustrates the diagnostic difficulties of CMV in the ICU patient.

Figure 2.

Immunohistochemical staining for CMV: 2 examples of characteristic owl’s eyes (A and B) showing brown staining of the nuclear inclusion and nuclear membrane, separated by the lighter halo (arrow) (best seen in A). The is also some staining of the cytoplasm.
Renal failure, corticoid therapy, dialysis and the amount of blood transfused, have also been reported to be significantly associated with CMV re-infection [4]. We think that these risk factors, in combination with the locally depressed immune function of the lung due firstly to radiation therapy and fibrosis and the chronic congestion of the lung, resulted in an immunosuppressed state, evoking the recurrence of the CMV infection.

Primary infection can occur through saliva, sexual contact, placental transfer and breast feeding [6]. In hospitalized patients, CMV is usually transmitted as a primary infection by means of blood products and through transplanted organs [8]. Although our patient received several blood transfusions, we could not find any evidence of a recently acquired CMV infection. The positive IgG and negative IgM tested post-mortem underscores the low probability of primary infection and the high probability of CMV reactivation.

Prior to her admission, our patient was not immune compromised. The CMV recurrence with end organ damage occurred weeks after admission. Pappazian reported a series of ICU patients with CMV pneumonia who were not immunocompromised before admission. In this study, CMV pneumonia was histologically diagnosed 22.4±8.8 days after admission to the intensive care unit [1].

The autopsy revealed numerous CMV-specific owl’s eyes: nucleolar inclusion bodies of CMV (Figure 2). This, together with acute early organizing stage of pneumonia and mild pneumonitis fits in well with CMV infection of the lungs. Combined with the clinical picture of respiratory failure and the positive PCR we postulate that in retrospect the CMV infection played an important pathogenic role in the deterioration and the prolonged capillary leakage from day 28 onwards. Our patient finally died of CMV pneumonia complicated by Enterococces faecium and Bacteroides sepsis with multiple organ failure.

In organ transplant patients, antiviral treatment could reduce CMV-associated illness and death, especially if started early after detection. In critically ill patients with clearly established CMV infection who have organ damage, there is no clear evidence of the effect of antiviral therapy. Short reports have not shown any benefit from therapy [3]. It can be postulated that treatment at an earlier phase would result in better effects, as is the case in the transplant patients. However, the effects of early treatment or antiviral prophylaxis remain to be tested in critically ill patients.

In conclusion, in ICU patients with a prolonged length of stay and persistent infectious capillary leakage after complicated surgery, clinicians should be aware that CMV infection may be a possible complicating factor if bacterial and cardiac causes have been excluded.

References

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