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Case report

Cytomegalovirus acute infection with pulmonary involvement in an immunocompetent patient

Celina Gonçalves*, Ana Cipriano, Fábio Videira Santos, Miguel Abreu, Josefina Méndez, Rui Sarmento e Castro

Infectious Disease Department, Centro Hospitalar do Porto, Portugal

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ABSTRACT

Introduction: Cytomegalovirus (CMV) infection in healthy adults is usually asymptomatic or causes a mild mononucleosis syndrome, while severe infections are rare in immunocompetent patients and poorly documented. When described, gastrointestinal tract and the central nervous systems are the most frequent sites of severe CMV infection. Lung disease can occur, but it's rare.

Clinical case: A 29 years old man presenting with a 2-weeks history of fever, headache, malaise, dry non-productive cough and thoracic pleuritic pain, without improvement after one-week therapy with levofloxacin. Blood exams showed lymphocytosis of almost 50%, nine percent of atypical lymphocytes and elevated transaminases. Thoracic CT-scan showed bilateral infiltrate with internal air bronchogram. Blood serology showed positivity for CMV IgG and IgM, with low CMV IgG avidity. Serum and bronchoalveolar detection of CMV by polymerase chain reaction (PCR) technique was also positive. Cultures were all negative. The patient became increasingly hypoxemic and the liver transaminases worsening, the reason for which ganciclovir was started. He made a full recovery and was discharged seven days later with oral valganciclovir, completing a 3 weeks antiviral course at home.

Discussion: CMV pneumonia is a rare condition, however it's one of the three most common cause of severe viral community acquired pneumonia (CAP), along with influenza and adenovirus. CMV pneumonia should be considered in patients with atypical lymphocytes and mildly elevated serum transaminases.

Conclusion: In immunocompetent hosts, even with severe CMV-CAP, the prognosis is good. However, antiviral treatment should be considered in the rare occasion of severe CMV infection. Nevertheless, more studies are needed to clarify the clinical benefit of antiviral treatment.

Introduction

Cytomegalovirus (CMV) is a ubiquitous virus of the *Herpesviridae* family, transmitted mostly by contact with infectious body fluids (saliva, urine, genital) or by transplacental route, and it is frequently acquired early in life [1–4]. According to seroprevalence studies, its prevalence ranges between 50% and 85%, with epidemiological differences between different age groups and socioeconomic backgrounds [4,5]. In Portugal, CMV infection is highly prevalent in the population (77%) [6]. Primary CMV infections are usually asymptomatic, or self-limiting diseases, manifested by a mononucleosis-like syndrome or hepatitis. In immunocompromised patients, it is often associated with severe manifestations, causing substantial morbidity and mortality [1,4]. Although there are a few reports describing severe clinical manifestations of the CMV infection in immunocompetent patients, the pulmonary involvement appears to be rare (8%) [1]. CMV pneumonia usually presents with respiratory failure and with diffuse interstitial infiltrates on chest x-ray. The diagnosis is done using serologic testing, molecular biology and histological findings on lung biopsy. Regarding treatment, there are no formal recommendations for the management of severe disease in immunocompetent patients, including in CMV pneumonia [2,7].

Case presentation

In March 2017, a 29 years old man presented a one-week history of fever (38 °C), headache, sweats and malaise. He also complained of thoracic pain and dry cough. Blood exams showed 6620 white blood cells (WBC)/μL (lymphocytes 48% - with 9% atypical lymphocytes, and 10.4% monocytes), C-reactive protein (CRP)

* Corresponding author.
E-mail address: u11200@chporto.min-saude.pt (C. Gonçalves).

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2.9 mg/dL, alanine aminotransferase (ALT) 74 U/L and aspartate aminotransferase(AST) 52 U/L. Urinary antigens for pneumococcus and legionella were negative. Other blood exam results were within the normal range. Chest x-ray showed a small left sided pleural effusion. An acquired community pneumonia was assumed, and the patient was medicated with a course of levofloxacin.

Despite the 7 days of antibacterial therapy, no improvement was noted, he started complaining of dyspnea on exertion and he was admitted to the hospital. During this period, he denied gastrointestinal and urinary complaints, arthralgia, exanthema or any other symptoms. He lived with a friend and had no travel history, contact with sick people or pets. He had a history of treated reactive depression (3 years before), without any other significant individual or family medical problems. He did not take any regular medication and he was not on new medication, besides antibacterial therapy (levofloxacin) and paracetamol during this period.

On admission, he was febrile (38 °C), with tachycardia and basal left crackles in pulmonary auscultation. On the blood exams: 12,224 WBC/μL (34.8% neutrophils, lymphocytes 50.5% and 10.4% monocytes), CRP 49 mg/dL, ALT 129 U/L, AST 71 U/L. LDH 554 U/L. Arterial blood gas with pH 7.45, paO2 65 mmHg, paCO2 27 mmHg and lactate 0.8 mmol/L. A CT thorax scan showed parenchymal condensations in the postero-inferior region in both lung lobes, with the condensation on the left being more extensive and presenting some internal air bronchogram; bilateral pleural effusion, more on the left and a small pericardial effusion were also seen. Abdominal ultrasonography (US) showed a 15 cm enlarged spleen without retroperitoneal adenopathy or ascites. Due to the presence of pericardial effusion in the CT scan an electrocardiogram, with normal results, was performed. Echocardiography showed a pericardial effusion with slightly thickened pericardial leaflets without hemodynamic compromise. Cardiac enzymes were normal.

Immunophenotyping in the peripheral blood showed activated lymphocytosis of predominantly alpha/beta + CD8+ type, with phenotype characteristics that strongly suggest acute activation – as seen in the mononucleosis syndromes for Epstein Barr virus (EBV) or CMV. Viral serologies were performed with EBV serology showing a past infection. HIV 1–2 antibodies/antigen assay was negative. Cytomegalovirus (CMV) IgM and CMV IgG antibodies were positive and CMV avidity IgG was negative. Blood PCR CMV was 23 595 cp/mL. Autoantibody screening was negative, except for the IgG antinuclear antibodies, with a titre of 1:160 of uncertain significance. All other serologies were negative: herpesvirus human-6 (HHV-6), hepatitis A, hepatitis C, VDRL, *Toxoplasma gondii*, *Coxiella burnetti*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. He had been vaccinated for hepatitis B. Blood cultures were negative.

Bronchoscopy did not show any bronchial abnormalities. Bronchoalveolar lavage (BAL) cytology showed several alveolar macrophages mixed with lymphocytes but no malignant cells or viral inclusions. The CD4+/CD8+ ratio was 0.547. Bacterial (including mycobacterial) and fungal cultures were negative. CMV polymerase chain reaction (real time PCR) on BAL was positive. All other respiratory virus testing was negative.

No antibacterial therapy was started at the time of admission. During his time in the hospital, on day 6, with 3 weeks of disease, he maintained the same symptomatology, with worsened hypoxemia requiring oxygen supplementation. AST/ALT peaked at 205/384 U/L and albumin decreased (3.24 g/dL).

Based on the clinical features and the result of CMV serology, blood and BAL CMV PCR, IV ganciclovir was started - 690 mg a day (5 mg/Kg IV q12 h) with transition to valganciclovir 900 mg po q12 h after 7 days of IV antiviral.

The clinical condition rapidly improved with apyrexia from day 3 of treatment and with resolution of hypoxemia. Liver function tests normalized and so did the radiological picture during the three-week course of therapy.

Discussion

CMV mononucleosis-like syndrome is more frequent in older patients than EBV infectious mononucleosis (mean of 30 years in the case of CMV, compared to 20 in the case of EBV). Ocular complications (retinitis or conjunctivitis) and gastrointestinal complications (esophageal ulcerations or proctitis), although very rare, are characteristic. The pulmonary involvement is rarely described in immunocompetent hosts [2,9,10].

Regarding to clinical manifestations, primary CMV infection is often asymptomatic or presents itself with a self-limited fever or sometimes prolonged for 2–3 weeks, except when visceral damage occurs. Pulmonary manifestations of CMV disease are rare and varies from dry cough to a severe interstitial pneumonia. [1,4,9]. In that case, differential diagnosis with influenza and adenovirus must be done. In patients with otherwise unexplained atypical lymphocytosis and increased serum transaminases, clinicians should consider the possibility of CMV pneumonia, even in immunocompetent patients [2].

There is no pathognomonic radiological pattern. The patient can present minimal or no pulmonary infiltrates initially and diffuse interstitial infiltrates. Sometimes the radiological alterations are limited to one lobe or may reveal focal infiltrates on the chest X-ray or CT. Hypoxemia is frequently present. [2,7,8]. The laboratory diagnosis may be based on serological tests or pathological features. The serological diagnosis is based on elevated CMV IgM antibody titer, or on increasing titer of IgG antibodies. In immunocompetent host with primary CMV pneumonia, the blood CMV detection by PCR is usually negative, although it is diagnostic if positive [3]. Lung biopsy can detect CMV inclusion bodies with the typical appearance of an owl's eye. [2]. In the literature review, Grilli et al. [2] found 13 cases of CMV pneumonia in immunocompetent hosts, 12 of them in adult patients (age range 21–73 years old). The diagnosis was made by histology in 6 of the patients, and by serology in the other patients. In our clinical case, the diagnosis was primarily suspected because of the mononucleotide syndrome-like and hepatic cytolysis. Initially, our patient presented few respiratory symptoms that later evolved to a hypoxemic pneumonia, that was later confirmed by serology and PCR on BAL. The diagnosis of CMV pneumonia was based on positive results of serum IgM CMV, the radiological pattern, as well as positive CMV PCR on BAL. The avidity test on CMV IgG antibodies was also negative. Other causes of mononucleosis syndrome and atypical and viral pneumonia were excluded.

No treatment is currently indicated for CMV infection in healthy people (according to Centers for Disease Control and Prevention). Although limited, literature review of current evidence suggests that targeted antiviral therapy with ganciclovir or valganciclovir is appropriate for severe CMV disease in immunocompetent adults. Eddleston et al. reviewed severe cases of CMV infection in immunocompetent patients and, in the 34 patients reported, 7 out of the 19 patients who survived had received ganciclovir or foscarnet, whereas only 1 out of 15 who died had received potentially effective antiviral therapy. The patient who died, and on whom ganciclovir was started, received the treatment after having been in the hospital for 149 days, which was maybe too late. Another six cases of CMV pneumonia have been described more recently. Of those, half received treatment (two with oral valganciclovir only). All of them recovered completely [7,11–16].

The major toxic effect of ganciclovir is myelosuppression, which results in cytopenia, especially severe when other myelotoxic drugs

are co-administered. Both ganciclovir and foscarnet may also cause renal impairment. In immunocompetent hosts the prognosis is good, even with severe pneumonia. The decision to start treatment in CMV pneumonia can be based on hypoxemia severity, since early treatment can lead to a more rapid recovery. As soon as treatment with ganciclovir was started, the clinical condition of our patient improved, with complete resolution of the clinical and radiologic picture. He completed 21 days of treatment and no side effects of antiviral therapy appeared. In conclusion, severe CMV disease with lung involvement may occur, although uncommonly, in immunocompetent patients. Antiviral treatment should be considered in the suspicion of CMV pneumonia supported by laboratory tests. Further studies are needed to clarify the role of antiviral treatment of severe CMV disease in immunocompetent patients.

Conflict of interest

None to declare.

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