PRIMARY CYTOMEGALOVIRUS INFECTION IN A HIV-POSTIVE YOUNG MAN - A CASE PRESENTATION

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Summary

The cytomegalovirus (CMV) causes in immuno-competent patients mostly an asymptomatic disease and very rarely can lead to a severe disease with multiple organ involvement. In contrast, in patients with HIV/AIDS acquired immunodeficiency, it is an opportunistic infection associated with high morbidity and mortality, caused by reactivation of CMV in the presence of severe immunosuppression. There are very few cases of primary CMV infection described in people living with HIV.

We present the case of a 30-year-old male with a history of HIV infection, diagnosed 6 years prior in the B3 clinical and immunological stage, under antiretroviral medication with a good adherence, who was admitted for acute febrile syndrome with gastro-intestinal manifestations, cutaneous eruption and meningeal syndrome. Both CMV IgM antibodies and CMV viral load were performed with positive results. The patient's evolution was favorable under symptomatic treatment. Since the patient's CMV serology and viral load results came back after the resolution of the symptoms, he didn't receive any specific antiviral medication.

In general, CMV infection in HIV-positive patients remains an opportunistic infection which characterizes advanced stages of immunosuppression. However, it can also affect patients with a good immune status, being difficult to diagnose and treat, especially without a consensus regarding antiviral treatment.

Keywords: *primary cytomegalovirus infection, HIV/AIDS infection*

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Introduction

CMV causes in HIV-positive patients with severe immunosupression an opportunistic disease, representing an important cause of morbidity and mortality; it is usually associated with advanced stages of HIV infection. Before the introduction of highly active antiretroviral treatment (HAART) almost half of the HIV-positive patients developed severe disease affecting multiple organs: esophagitis, colitis, pneumonia, retinitis, central nervous system (CNS) disease. It also causes various cutaneous and mucosal lesions which are hard to differentiate from those caused by other opportunistic agents [1].

Nowadays, due to immune restoration under targeted antiviral medication the frequency of occurrence, clinical manifestations and the risk of severity in an infection with an opportunistic pathogen such as CMV requires interpretation in the context of the clinical situation.

We present the clinical picture and the outcome of an HIV-positive patient, but with a good immunological status presenting with an acute CMV infection.

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Case presentation

A 30-year-old male with HIV infection diagnosed 6 years previously, stage B3 (nadir CD4 cell count 159/mm^3), under antiretroviral treatment (ART) with tenofovir, emtricitabine and raltegravir for the last four years, was admitted for headache and photophobia. The patient was adherent to ART, had constantly undetectable HIV viral load for the last 4 years and the last evaluation, performed two months before, showed a CD4 cell count of 702 cells/mmc, CD8 cell count of 600 cells/mmc and a CD4/CD8 ratio of 1.17. The IgM and IgG CMV antibodies were negative since he has been diagnosed with HIV infection.

The symptoms started 10 days before admission, with fever up to 39°C and vomiting (6 to 8 times per day), which the patient had interpreted as a mild case of heat stroke. These symptoms persisted for 4 days and were followed by diarrhea (12-18 watery stools per day without blood, mucus or puss) and a maculopapular rash on the anterior trunk and upper extremities. Two days prior to the admittance he experienced severe occipital headaches and discrete photophobia and decided to present to our clinic.

The physical exam upon admission revealed an afebrile patient with a blood pressure of 110/60 mmHg, oxygen saturation of 98%, a heart rate of 79 bpm, with a non-pruritic maculopapular rash on the trunk (figure 1) and upper limbs, mucosa with a normal appearance and without enanthem, normal chest excursions, normal bilateral respiratory sounds, normal heart sounds and rhythm, normal abdominal findings and nuchal rigidity with positive Kernig's sign.

Blood tests at admission revealed a normal leukocyte count of 6,130 cells/µl with normal differential blood count, lymphocytes = 1,741 cells/µl, hemoglobin = 15.7 g/dL, hematocrit = 45.5%, mild thrombocytopenia with 191,000 cells/µl, mild inflammatory syndrome (CRP = 21.2 mg/L, fibrinogen = 329 mg/dL, ESR = 12 mm/h), normal coagulation tests (PT = 12.1 sec, INR = 102, CP = 97%). ALT, AST, GGT, total bilirubin, urea, creatinine, CK, CK-MB, sodium, potassium, glycemia were all normal.

Due to the clinical findings, a lumbar puncture was performed that showed clear, normotensive cerebrospinal fluid (CSF), with 25 elements/mmc and a predominance of lymphocytes, with a slightly positive Pandy reaction, with lactic acid within normal ranges (10.7 mg/dL), normal CSF protein count (53 mg/dL), CSF glucose of 53 mg/dL with a CSF glucose/glycemia ratio of 0.56. PCR for enteroviruses in the CSF were negative; the CSF was tested for enteroviruses in the genetics lab with a negative result after 5 days. We could not perform PCR for the detection of herpesviruses in the CSF. Lab tests for CMV IgM antibodies were performed and the result was highly positive. The CMV blood viral load was 57,247 copies per ml, but the result was available after the symptoms resolution.

The case was interpreted as acute viral meningitis and the patient was given osmotic agents, acetaminophen and NSAIDs. Initially the patient's evolution was favorable, he remained afebrile and headache has improved, but after five days he developed fever (38.2°C), nausea, vomiting, sore throat, epigastric pain and abdominal bloating; the main symptom was odynodysphagia. Upon physical examination rare ulcerative lesions on the oral mucosa were found (figure 2). Blood tests showed lymphocytosis (6,030 lymphocytes/µl out of 12,560 leucocytes/µl) and mild hepatic cytolysis with ALT=243 U/L and AST=141 U/L suggesting a mononucleosis-like syndrome.

It was considered to be a CMV primary infection with gastroesophageal manifestations and the patient was given symptomatic treatment with esomeprazole 40 mg p.o. every 12 h and sucralfate 1 g p.o. every 8 h for 2 weeks. The patient did not receive any specific antiviral medication for the CMV infection.

The outcome was good and the subsequent evaluations performed in our clinic highlighted undetectable HIV viral load, with satisfactory immune status and normalization of the cerebrospinal fluid.

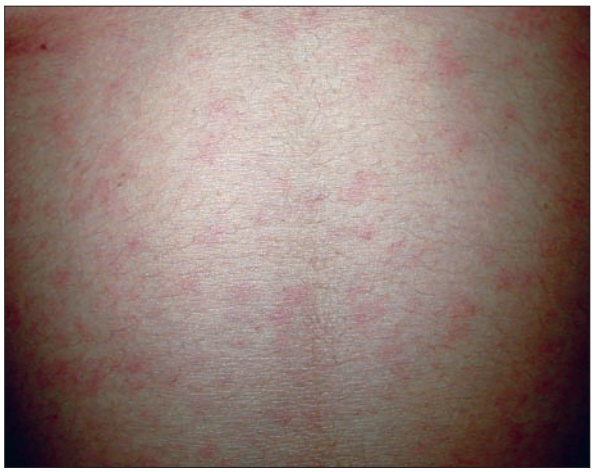

Figure 1. Non-pruritic maculopapular rash on the thorax.

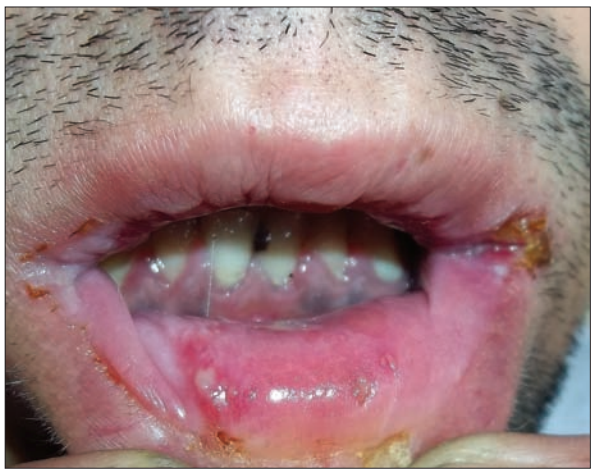

Figure 2. Ulcerative lesions on the oral mucosa.

Discussions

In immunocompetent patients, ***primary CMV infection*** is usually asymptomatic. In some cases it can cause a *mononucleosis-like syndrome* presenting with malaise, prolonged fever, minimal to moderate elevation of hepatic transaminases and lymphocytosis with atypical lymphocytes in peripheral blood; lymphadenopathy and splenomegaly are not usually striking. In up to a third of cases, there is a maculopapular, rubelliform, follicular or urticarial eruption, often affecting the legs and lasting several days. As in Epstein-Barr virus infectious mononucleosis, ampicillin commonly triggers a widespread eruption. Lipschutz ulcers, more commonly associated with EBV infection, have occurred with primary CMV infection. *Mononucleosis-like syndrome* occurs in 10% of the cases and is usually a mild illness with a self-limiting course [2,3]. However, very rarely, severe, fulminating infections were reported in non-immunocompromised patients presenting with multiple organ involvement resulting in meningitis, encephalitis, neuritis, myocarditis, pneumonia, hepatitis, retinitis or enterocolitis. Primary infection is followed by lifelong carriage of the virus with intermittent shedding in various secretions; this may be increased by physiological stimuli such as pregnancy, and by immune suppression.

At the beginning of the HIV epidemic approximately 40% of HIV infected patients with advanced disease developed clinical manifestations due to CMV infection during their lifetime [1,4]. Even after the introduction of HAART therapy, CMV infection remains a challenge although the number of cases declined to almost 5-10% of the original number. Cytomegalovirus infection can affect different organs causing chorioretinitis, meningoencephalitis, pneumonia, esophagitis, colitis, hepatitis, rash, etc.[5]. The CMV infection diagnosis in HIV-seropositive patients requires most times thorough investigations, at times difficult to conduct, usually involving tissular biopsies to highlight viral inclusions and inflammation [6].

The patient we presented was immunosuppressed secondary to an HIV infection, but with a good immunological status. He developed a primary CMV infection with multiple clinical involvement: *mononucleosis-like syndrome* (asthenia, fever, odynodysphagia, lymphocytosis without atypical lymphocytes), central nervous system involvement – meningoencephalitis (with clinical symptoms, meningeal syndrome and minimal CSF abnormalities), digestive system involvement (possible esophageal and colonic lesions, vomiting, loose stools in the beginning and lesions on the oral mucosa), mild hepatic dysfunction (mild hepatic cytolysis developed during the hospital admission) and muco-

cutaneous manifestations (erythematous maculopapular rash on the trunk and upper extremities).

Although the patient was immunosuppressed and had multiple organ involvement, overall he had a mild form of disease with a favorable outcome even in the absence of specific CMV antiviral medication due to a good immune status secondary to the ART taken for the last six years. Actually, his CD4 cell count was over 500 cells/mmc on admission, which was a lower value than previous measurements during the biannual immunological and viral evaluations.

Even though in HIV patients who develop CMV infection the first suspicion is that of an immunological and viral failure by a lack of adherence to the treatment and/or by developing drug resistance mutations which allow high viral replication and immunological collapse with CMV infection reactivation and organ dysfunction, in our patient's case a primary acute CMV infection was confirmed.

In a review published by Eddleston *et al*. [7] 34 cases of severe CMV infection were identified in apparently healthy adults, with no significant personal pathological history, without any identified cause of immunosuppression. The authors divided the patients into two groups. The first group included patients with involvement of one or more organs, but without infection of the central nervous system (n=24). The other group included ten patients with only central nervous system involvement and only four patients out of ten diagnosed with encephalitis received specific antiviral treatment. Unlike patients in the latter group, where no deaths were recorded, the evolution of patients with multiple organ involvement was unfavorable, with only nine patients out of twenty-four surviving [7].

Another systematic review published by Rafailidis *et al*. [8], considered to be the most comprehensive evaluation of severe CMV infection in immunocompetent adults to date, identified 290 immunocompetent patients with severe CMV disease reported between 1950 and 2007. In a decrescendo order of frequency severe organ involvement included: the gastrointestinal tract, the central nervous system (meningitis, encephalitis, myelitis, nerve palsies, myeloradiculopathy), hematological manifestations, the eye, liver, lung and thrombosis of the arterial and venous system. There were 56 patients reported with CNS infection, with 37 being reported in previous reviews and 19 patients that were first identified in this review. Nine of the 19 patients were administered specific antiviral therapy and none of the patients died. Among the 37 patients that were previously reviewed, 15 received specific treatment and 3 died while 22 did not receive any antiviral treatment and 4 of them died. The conclusion of the authors is that there is no clear answer regarding the use of antiviral treatment for immunocompetent patients with severe CMV infection [8].

There is no general consensus regarding treatment of CMV disease in immunocompetent patients. There has been a great expanse in knowledge of management of CMV infection in the last 20 years, particularly in the immunocompromised population. Nevertheless, few studies have evaluated the use of these antiviral agents for the treatment of severe CMV disease in immunocompetent patients.

Among the ***muco-cutaneous manifestations*** determined by CMV in HIV-seropositive patients a variety of lesions were described – from localized ulcerations to miscellaneous rashes. Sharply demarcated ulceration may occur, mostly around the genitalia, perineum, buttocks and thighs and there may be associated *livedo reticularis*; severe oral and skin ulceration have been reported, especially in AIDS. A nonspecific widespread maculopapular eruption may be seen that may become papular and purpuric; vesiculous or bullous eruptions (difficult to differentiate from infections caused by herpesviruses), indurated pigmented nodules or plaques, pustular or verrucous lesions, perifollicular papules, papules covered with crusts, urticarial or morbilliform eruptions, etc. may also occur. All these aspects can raise difficulties in the diagnosis [9]. Even more, the CMV can be highlighted by skin biopsies in the absence of visible lesions. In some cases, the skin can be the first one affected and it can predict an

unfavorable outcome with up to 85% mortality in immunodeficient hosts [10,11,12].

Most authors usually describe cases of systemic involvement caused by CMV infections, with scarce data involving cutaneous manifestations. This can be due to the difficulties in diagnosing cutaneous lesions both clinically and paraclinically given the large variability of their appearance.

There are also differences with regards to the ***histopathological aspect***. Therefore, in cutaneous involvement, the characteristic nuclear inclusions (*„owl eyes"* nucleus) of the CMV infection can be present within mesenchymal cells, endothelial cells, fibrocytes and in inflammatory cells as well, like macrophages. However, when the infection occurs in other organs, the inclusions caused by the CMV are found within ductal epithelial cells [13].

In patients with HIV infection and associated immunosuppression, the anogenital mucosa is the most common site involved. The lesions are usually ulcerative and multiple. Biopsies performed at this level highlight cytopathic changes in the dermis, especially in the cells of the vascular endothelium, but also in macrophages, with specific *„owl eyes"* inclusions in the nucleus. These eosinophilic inclusions, surrounded by a halo, located in the nucleus of the host cell, can be observed using hematoxylin-eosin staining [14]. In these patients with significant immunosuppression due to HIV infection, the presence of other members of the *Herpesviridae* family, usually *Herpes simplex virus 1* or *2*, was highlighted in the ulcerative lesions, leading some authors to ask if the lesions were caused by *Herpes simplex virus* or CMV. A study by Choi *et al*. [15] including nine patients with immunosuppression without HIV infection, demonstrated clinical and histopathological aspects similar to those present in HIV/AIDS patients. In contrast to HIV/AIDS patients, the presence of *Herpes simplex* virus was determined in only one of the nine patients, the authors concluding that the skin lesions were most likely caused by CMV [15].

Most adults have positive serology for past CMV infection, with more than 90% of people in certain risk groups. Unlike most patients living with HIV, our patient never had a latent CMV infection with reactivation at the moment of admission, but an acute CMV infection. This highlights the importance of applying preventive measures for CMV infection in HIV-seropositive patients without proof of prior CMV infection along with continuing antiretroviral therapy for immune status restoration. Regarding treatment, more studies are needed in order to have a ferm recommendation.

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Conflict of interest
NONE DECLARED

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