Case report

Cytomegalic hepatitis in a patient receiving omalizumab

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ABSTRACT

Cytomegalovirus is a double stranded DNA virus that can be present in nearly all organs and body fluids. The primary infection is usually asymptomatic in the immunocompetent host and it is common among adolescents and young adults. The symptomatic form appears, in the majority of cases, as a mononucleosis syndrome with full recovery without specific treatment. We report a case of a 25 years old woman who presented with hepatitis due to CMV infection and history of omalizumab administration one month earlier. This recombinant monoclonal antibody is used to control refractory asthma and chronic spontaneous urticarial as it inhibits human IgE. Despite that, the long course of the disease lead us to initiate treatment with valganciclovir. The improvement after that was rapid and complete.

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Introduction

Cytomegalovirus (CMV) is a double stranded DNA virus belonging to the family Herpesviridae, which may be present in nearly all organs and body fluids. The infection occurs by contact with saliva, blood, urine, feces, milk, semen or vaginal fluids, with the possibility of vertical transmission or by organ transplantation. The primary infection is most common between 15 and 35 years, and is usually asymptomatic in the immunocompetent individual. In symptomatic forms, the most common presentation is the mononucleosis syndrome: fever, sore throat and lymphadenopathy with hepatosplenomegaly, elevated liver enzymes and the presence of activated lymphocytes. After primary infection the virus enters a state of latency and reactivation may occur in case of immunosuppression.

The diagnosis is based on clinical suspicion and serology, since the virus induces production of IgM and IgG. IgM is the first to appear in the serum and can take up to about 4 weeks, and continues usually between 30 and 60 days. The determination of IgG avidity index allows the confirmation of recent infection in the case of both IgG and IgM are positive. Avidity is weaker the more the infection is recent. The culture of the virus by shell vial method in blood and urine, and determining virus antigenemia are other diagnostic techniques which may be used to monitor response to treatment. Despite the importance of humoral immunity, cellular immunity is considered more important in the virus control [1], with both CD8+ cytotoxic and CD4+ helper cells playing a central role in the resolution of acute infection and in the maintenance of long-term memory. *In vitro* studies demonstrated the association between production of IFN-gamma by the CD8 T lymphocytes and the risk of infection/CMV disease after transplantation [2–5].

Clinical case

A 25 years old Caucasian woman presented to the emergency department with complaints of fever and productive cough for 8 days and several days of anorexia. She had reported mild odynophagia at the onset of her illness which had resolved. She had already received antimicrobials as cefuroxime was prescribed by her family doctor, because of a suspicion of respiratory infection, but she had no improvement in her symptons. Her past history included severe chronic urticarial and had her first omalizumab administration in the previous month. She had no other concomitant medication. She worked in a day care center with daily contact with children and lived in a villa in the countryside, with cats and vaccinated and dewormed dogs. Her vaccination schedule was up to date and she had no recent trips abroad.

On physical examination she was in good general condition with normal respiration rate, body temperature of 38 °C, blood pressure of 113/50 mmHg and heart rate of 89bpm. She had whitish lesions on the left tonsil of 4 mm diameter, but showed no further changes. Blood tests showed elevated aminotransferases (AST 162 U/L, ALT 129 U/L), alkaline phosphatase (163 U/L), LDH (601 U/L), leukocytes $4.7 \times 10 \char`\^ 9$/L with 47.7% lymphocytes, 41% neutrophils, 10% monocytes. An abdominal ultrasound revealed

no abnormalities and the Monospot was negative. The patient was discharged for follow-up with Infectious Diseases consultation two days later.

With no improvement in her symptoms when she was seen by Infectious Diseases as an outpatient, repeated blood analyzes on that day that showed a slight increase in aminotransferases (AST 188 U/L, ALT 165 U/L), alkaline phosphatase (209 U/L), LDH (618 U/L), thrombocytopenia (129 × 10^9/L), elevated ESR (27 mm/1 st h) and lymphocytosis (49%) with activated lymphocytes. It was decided to admit the patient in the ward to maintain under surveillance. Blood and urine cultures and serologies were performed. Of these tests, IgG and IgM were positive for CMV and EBV, as well as IgM for Enterovirus and Coxsackie virus. Those results were interpreted as false positives because of the frequent serological cross reactivity between those viruses [6–10]. She had vaccinal immunity to hepatitis B virus, was hepatitis C antibody negative and had natural immunity to hepatitis A virus. The treponemic test FTA was negative as was the HIV test.

The clinical process of the patient was reviewed with a focus on the previous results and it was possible to conclude that two years before she had already IgG to EBV, but had no antibodies (IgG neither IgM) to CMV. Those past results lead us to request CMV antigenemia, that was positive, and the IgG avidity test for CMV, that was weak. Taking into account the clinical picture and the results obtained it was assumed, as the most probable hypothesis, a diagnosis of primary CMV infection. At the 3rd day in the ward her blood analysis showed declined of both alkaline phosphatase (159 U/L) and LDH (585 U/L), but the aminotransferases continued to rise (ALT of 333 U/L, AST 282 U/L). The clinical case was discussed with the Immunoallergology Unit and we reviewed the literature, and no data allowed us to associate this primary infection with omalizumab administration a month earlier. Despite that and given the persistence of evidence of hepatocyte injury, it was decided to initiate therapy with valganciclovir 900 mg every 12 h, orally. There was a rapid improvement, with resolution of symptoms and progressive decline in aminotransferases. The patient was discharged after 5 days of hospitalization and she was re-evaluated in consultation three weeks later, already with full resolution of the hepatic dysfunction. Six months later she repeated CMV serology, and at that time she had IgG positive and IgM negative, results that confirm primary infection.

Discussion

CMV infection in immunocompetent individuals is usually asymptomatic, with few descriptions of dysfunction of one or more systems. When symptomatic, gastrointestinal manifestations are the most frequent. Due to its low frequency, recommendations for treatment in this population are unclear.

Omalizumab is a recombinant monoclonal antibody that inhibits human IgE, approved by the FDA and European Medicines Agency for use in cases of severe refractory asthma and chronic spontaneous urticaria. The molecule structure allows its binding to FceRI receptor present on mast cells and basophils, the same epitope that is a receptor to free IgE, but do not affect the IgE already bound to the receptor. That way, it prevents the activation of these cells and the consequent liberation of pro-inflammatory mediators [11–14]. On the other hand, it also causes a gradual reduction of FceRI receptor expression, desensitizing cells to

stimulation by allergen [15–17]. Regarded as a relatively safe drug, phase III trials have demonstrated a very low incidence of adverse effects [18,19]. In a study, infectious diseases (respiratory and urinary) were more frequent in the group with omalizumab [18], with reports of a case of influenza virus infection [19].

The authors describe a case of CMV hepatitis in patients receiving therapy with omalizumab. There is no description in the literature of other cases where such infection occurred in this context and it is known that this drug acts specifically on mast cells and basophils. Whether the omalizumab promoted the CMV infection is unclear. Because of the disease persistence and continuing symptoms after several days, we chose to treat the patient with valganciclovir. There was prompt improvement which suggests that the valganciclovir effectively treated the infection.

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