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Acute cytomegalovirus hepatitis in a non-immunosuppressed patient: a case report

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Palabras clave:
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ABSTRACT

Cytomegalovirus (CMV) has high rates of seroprevalence and subclinical infection in the general population. The infection is habitually recognized in immunocompromised patients. However, in a state of immunocompetence, CMV usually presents as asymptomatic and is often revealed fortuitously on routine tests. A case of a 53-year-old female immunocompetent patient with CMV hepatitis is presented. Eight days prior to admission, the patient presented occasional fever, fatigue, myalgia and arthralgia associated with prior upper respiratory tract distress. The percutaneous liver biopsy revealed CMV inclusion bodies; CMV serology and the CMV DNA qualitative PCR test were positives. She was treated with ganciclovir. When patients present non-specific prodromal symptoms pertaining to acute hepatitis with an unclear etiology, CMV infection should be considered.

RESUMEN

El citomegalovirus (CMV) tiene altas tasas de seroprevalencia y la infección subclínica en la población general. La infección se reconoce habitualmente en pacientes inmunocomprometidos. Sin embargo, en un estado de inmunocompetencia, la infección por CMV se presenta generalmente como asintomática y, a menudo se revela fortuitamente en pruebas de rutina. Se presenta un caso de una paciente inmunocompetente con hepatitis por CMV. Ocho días antes de la admisión, la paciente presentó fiebre ocasional, fatiga, mialgias y artralgias asociadas con distrés respiratorio superior. La biopsia hepática percutánea reveló cuerpos de inclusión por CMV, serología para CMV y prueba cualitativa de PCR para ADN del CMV positivas. Por lo anterior, cuando los pacientes presentan síntomas prodrómicos no específicos relacionados con hepatitis aguda de etiología poco clara, la infección por CMV debe ser considerada.

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BACKGROUND

Cytomegalovirus (CMV) is member of the family *Herpesviridae* and subfamily *beta Herpesviridae* that contains a large DNA genome of around 235 kb coding for over 200 genes.[1] Adult infection is transmitted through vaginal secretions, sperm, urine, blood, breast milk, oropharyngeal secretions and iatrogenically.[2] CMV infection is a significant cause of mortality in immunocompromised hosts. However, after primary infection with CMV, the virus becomes latent in several tissues and can later be reactivated and possibly cause esophagitis, colitis, pneumonia, retinitis, encephalitis, myocarditis, portal vein thrombosis, hemolytic anemia and pulmonary embolisms.[3] CMV has high seroprevalence (40-100%) in the general population.[4] Usually, the infection generated by this virus presents as asymptomatic in immunocompetent individuals and is often revealed fortuitously on routine examinations, suggesting high rates of subclinical infections. However, severe illness could be developed by primary CMV infection in such patients.[5] Immunocompetent adult patients infrequently present liver involvement; nonetheless, viral hepatitis is the most common cause of liver inflammation.[6]

CASE REPORT

A 53-year-old female, full-time faculty professor, presented with an 8-day history of occasional fevers, fatigue, myalgia and arthralgia associated with prior upper respiratory tract discomfort. Medical records indicated primary hypothyroidism that is controlled with levothyroxine (125 µg/day). Patient denied use of alcohol, smoking, drugs, or contact with other harmful substances. General physical examination was normal, with the exception of

mild abdominal distension and fever of 105 ºF. Laboratory exams showed chemistry and urinalysis without alterations. The complete blood count revealed leukocytes of 12.53 k/µL (4.50-11.50 k/µL), lymphocytes of 43% (18.0-42.0%), monocytes of 13% (2.0-11%) and normal platelet count. A normal CD4 count (1,600 cell/mm^3). The serum liver profile revealed her bilirubin and prothrombin levels within normal parameters; however, serum aspartate aminotransferase (AST) was of 203 U/L (0-32 U/L), serum alanine aminotransferase (ALT) was of 286 U/L (0-33 U/L) and serum alkaline phosphatase (ALP) was of 160 U/L (35-105 U/L). HIV RNA test, Widal test and hepatitis A, B, and C serology were all negative. Hepatobiliar ultrasound and abdominal CT were normal. Following admission, patient continued to have arthralgia, temperature spikes ranging from 103 to 105 ºF not responding to antipyretics, and semicomatose state. Blood, stool, urine and *M. tuberculosis* cultures showed no bacterial growth. C reactive protein was 44.9 mg/L (0-5 mg/L), erythrocyte sedimentation was 34 mm/h (0-15 mm/h), and liver enzyme levels remained high.

Subsequently, her Epstein-Barr, influenza, chikungunya, dengue, adenovirus and herpes virus tests were negatives; however, CMV serology was positive with an IgM titre of 2.5 (0-0.99 Index), IgG of 213.9 (0-6 AU/mL), and also positive for a CMV DNA qualitative PCR test. Antinuclear antibody, ceruloplasmin level, liver-kidney microsomal antibody, anti-smooth muscle antibody determinations were negatives; thus, systemic lupus erythematosus, Wilson's disease and autoimmune hepatitis were discarded. A percutaneous liver biopsy was then performed, revealing lobular and periportal infiltration of mononuclear cells *(figure 1A)* and minimal hepatic necrosis with CMV inclusion bodies *(figure 1B)*.

Patient was treated with ganciclovir (5 mg/kd q12hr, x 14d) and intravenous hydration and was checked for fever patterns and liver-renal functions routinely. Fever subsided 10 days after her hospitalization. Repeated hepatic profiles revealed serum AST of 30 IU/L (0-32 U/L), serum ALT of 20 IU/L (0-33 U/L) and serum ALP of 64 IU/L (35-105 U/L). Titres of CMV IgM and IgG performed 15 days after discharge were 0.81 (0-0.99 Index) and 2.20 AU/mL (0-6 AU/mL) respectively, coherent with seroconversion. Two months after hospitalization, hepatic enzymes have remained constant at normal range.

DISCUSSION

CMV has high seroprevalence (40-100%) in the general population.[5] Usually, the infection generated by this virus presents as asymptomatic in immunocompetent individuals and is often revealed fortuitously on routine examinations, suggesting high rates of subclinical infections.[6] However, severe illness could be developed by primary CMV infection in such patients.[7,8] Immunocompetent adult patients infrequently present liver involvement;

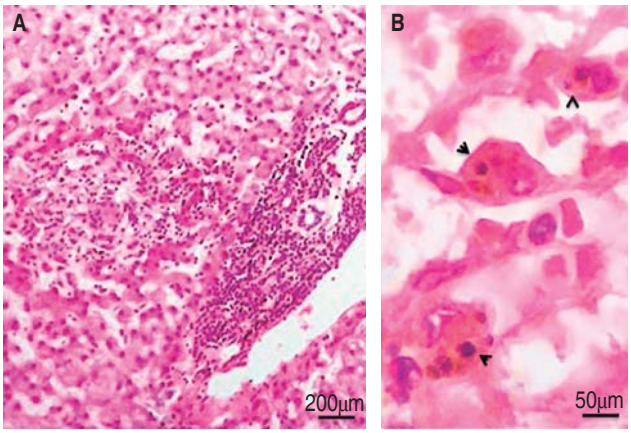

Figure 1. A. Periportal infiltration of mononuclear inflammatory cells (200 µm, haematoxylin and eosin stain). **B.** Cytomegalovirus inclusion bodies were identified. (50 µm, haematoxylin and eosin stain).

Table I. Some cases of cytomegalovirus hepatitis in immunocompetent patients treated with antivirals.[9,10]

Distinctive clinical manifestations	Case 1 Pleuritic chest pain	Case 2 Convulsions, comatose and renal failure	Case 3 Semicomatose with persistent fever
Diagnosis	Serum anti-CMV Ig M + serum pp65 antiginemia	Serum anti-CMV IgM + DNA qualitative PCR + in serum and cerebrospinal fluid	Serum CMV antigen+. Serum DNA qualitative PCR+ and +CMV antigen stain on liver biopsy
Antiviral	Valganciclovir	Acyclovir	Ganciclovir
Recovery time in days	28-35	21	84
Complication	No	No	No

nonetheless, viral hepatitis is the most common cause of liver inflammation.[9]

CMV infection can be detected by a positive anti-CMV IgM or an elevation in IgG titre, qualitative or quantitative PCR, immunofluorescence assay of CMV pp65 antigen in blood or in situ hybridization, and by cytopathology (CMV inclusion bodies).[10,11] In this case, diagnosis of acute CMV hepatitis was made by positive CMV serology and PCR associated with increased rates of liver enzymes (ALT and AST).

Treatment of CMV hepatitis should be adjusted regarding individual patient needs, thus allowing for a personalized treatment approach. Some individuals respond to conservative management;[12] however, in grave cases, the use of antiviral therapy is warranted, in our case the patient presented persistent fever an he was treated with ganciclovir *(table I)*.[13-15] Currently, guidelines for the treatment of CMV hepatitis in immunocompetent patients does not exist.

Essentially, when immunocompetent patients present non-specific prodromal symptoms associate with acute hepatitis from an unknown etiology, CMV hepatitis should be considered as a fundamental diagnosis.

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