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Acute cytomegalovirus hepatitis in an elderly patient: A case report

Hepatite aguda por citomegalovírus em uma paciente de idade avançada: Um relato de caso

Hepatitis aguda por citomegalovirus en un paciente anciano: Reporte de un caso

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Abstract
Introduction: Cytomegalovirus (CMV), also known as human herpesvirus type 5, is transmitted through body fluids and can infect a large number of cells in the individual, enabling systemic transmission within the host. This virus generally causes asymptomatic infections in immunocompetent individuals or mononucleosis-like syndrome, but it can rarely cause systemic infections, such as hepatic manifestation. Objective: This article aims to report a case of hepatitis associated with cytomegalovirus, reinforcing the importance of this agent in the differential diagnosis of acute hepatitis. Methodology: elaborate review of the patient's medical records, as well as a literature review on the subject, indicating epidemiology, pathogenesis, clinical manifestations, diagnosis and treatment. Related to the case: A 60-year-old female patient required care at na care at an emergency room with complaints of malaise, asthenia and fever. Antibiotic therapy was prescribed, without remission of symptoms. Blood count showed low hematocrit levels and red blood cells in Rouleaux. Patient with hypertension, dyslipidemia, ex-smoker and immunocompetent. The patient required hospitalization due to anemia, hepatomegaly and positive IgM and IgG serology for CMV, in addition to an upper abdominal ultrasound showing increased parenchyma. After 10 days of hospitalization, there were no relevant complications, and the case was confirmed as cytomegalovirus hepatitis after a positive viral load (quantitative CMV PCR of 9,770 IU/mL). Conclusion: We highlight the manifestation of cytomegalovirus infection presenting with hepatitis in immunocompetent elderly individuals, demonstrating the importance of analyzing this virus in the differential diagnosis of acute hepatitis and encouraging the exploration of knowledge about this disease.
Keywords: Hepatitis; Cytomegalovirus; Case report.

Resumo
Introdução: O citomegalovírus (CMV), conhecido também como herpesvírus humano tipo 5, é transmitido por fluídos corporais e pode infectar uma grande quantidade de células do indivíduo, possibilitando a transmissão sistêmica no hospedeiro. Geralmente, esse vírus causa infecções assintomáticas em imunocompetentes ou síndrome mononucleose-like, contudo, raramente pode causar infecções sistêmicas, como a manifestação hepática. Objetivo: Este artigo tem

como objetivo relatar um caso de hepatite associada ao citomegalovírus, reforçando a importância desse agente no diagnóstico diferencial das hepatites agudas. Metodologia: Elaborado revisão de prontuário de paciente, assim como revisão bibliográfica sobre o tema, apontando epidemiologia, patogenia, manifestações clínicas, diagnóstico e tratamento. Relato de caso: Paciente de 60 anos, sexo feminino, procurou assistência em pronto atendimento com queixas de mal-estar, astenia e febre. Foi prescrito antibioticoterapia, sem remissão dos sintomas. Hemograma com níveis baixos de hematócrito e hemácias em Rouleaux. Paciente com hipertensão, dislipidemia, ex-tabagista e imunocompetente. Evoluiu com necessidade de internação por anemia, hepatomegalia e sorologia de IgM e IgG positivas para CMV, além de ultrassonografia de abdome superior com aumento de parênquima. Após 10 dias de internação, não houve intercorrências relevantes e o caso foi confirmado como hepatite por citomegalovírus após resultado positivo de carga viral (PCR CMV quantitativo de 9.770 UI/mL). Conclusão: Destaca-se manifestação de uma infecção por citomegalovírus apresentando-se com hepatite em idosa imunocompetente, demonstrando a importância na consideração desse vírus no diagnóstico diferencial de hepatite aguda e incentivo a explorar o conhecimento a respeito dessa doença.
Palavras-chave: Hepatite; Citomegalovírus; Relato de caso.

Resumen
Introducción: El citomegalovirus (CMV), también conocido como herpesvirus humano tipo 5, se transmite a través de fluidos corporales y puede infectar una gran cantidad de células en el individuo, lo que permite la transmisión sistémica en el huésped. Generalmente este virus causa infecciones asintomáticas en individuos inmunocompetentes o síndrome tipo mononucleosis, sin embargo raramente puede causar infecciones sistémicas, como manifestación hepática. Objetivo: Este artículo pretende comunicar un caso de hepatitis asociada a citomegalovirus, reforzando la importancia de este agente en el diagnóstico diferencial de la hepatitis aguda. Metodología: Se realizó una revisión de historias clínicas de pacientes, así como una revisión bibliográfica sobre el tema, destacando epidemiología, patogenia, manifestaciones clínicas, diagnóstico y tratamiento. Informe de caso: Paciente femenina de 60 años de edad consultó atención de urgencia con quejas de malestar, astenia y fiebre. Se prescribió terapia antibiótica, sin remisión de los síntomas. Hemograma con niveles bajos de hematocrito y glóbulos rojos en Rouleaux. Paciente con hipertensión arterial, dislipidemia, ex fumador e inmunocompetente. El paciente requirió hospitalización por anemia, hepatomegalia y serología IgM e IgG positiva para CMV, además de una ecografía abdominal superior que mostraba aumento del parénquima. Tras 10 días de hospitalización no se presentaron complicaciones relevantes y el caso se confirmó como hepatitis por citomegalovirus tras resultado de carga viral positivo (PCR cuantitativa CMV de 9.770 UI/mL). Conclusión: Se destaca la manifestación de una infección por citomegalovirus cursando con hepatitis en una mujer mayor inmunocompetente, demostrando la importancia de considerar este virus en el diagnóstico diferencial de la hepatitis aguda y alentando la exploración del conocimiento sobre esta enfermedad.
Palabras clave: Hepatitis; Citomegalovirus; Informe de caso.

1. Introduction

Cytomegalovirus (CMV), also known as human herpesvirus type 5, was first isolated in 1956. The name of this virus is derived from the increase of the infected cell (cytomegaly) by it, which results in the formation of the inclusion bodies observed in microscopy (Schottstedt et al, 2010). CMV infections are common, presenting high seroprevalence, infecting approximately 30% of children at 5 years of age and more than 50% of adults at 40 years of age in the United States (Fowler et al., 2022). Its prevalence is higher in women, the elderly, people with lower socioeconomic status and in developing countries (Cannon et al., 2010).

This virus is mainly transmitted through close contact with body fluids such as saliva, blood, urine, breast milk, semen and cervical secretions, and also through organ transplantation (Mihalić et al., 2024). From this perspective, CMV can infect a large number of host cells, including epithelial cells, endothelial cells, parenchymal cells, connective tissue cells, as well as hematopoietic cells. Such a phenomenon facilitates both transmission between hosts and systemic transmission within the host (Sinzger et al., 2008).

The clinical manifestations associated with CMV infection are variable depending on the age and immune status of the patient. Congenital transmissions can be severe, with a risk of death and persistent sequelae (Fowler et al., 2022). In adults, it presents asymptomatically in almost 90% of patients, and when symptomatic, it manifests itself with symptoms very similar to infectious mononucleosis. In immunocompetent individuals, infection rarely leads to serious and life-threatening organic

complications. It is described as an often undiagnosed causative agent of hepatitis, with some cases of fulminant hepatitis and cholestatic jaundice reported (Gupta et al., 2014).

In immunocompromised patients, CMV infection can be presented as a serious disease, resulting in colitis, encephalitis, meningitis, myelitis, retinitis, uveitis and Pneumonitis (Chan et al., 2014), including reports in the literature of portal vein thrombosis (Squizzato et al., 2007). In addition, hepatitis is a well-known manifestation of CMV infection in these patients, particularly in patientis with liver transplants, with an incidence ranging from 2 to 34%. However, in immunocompetent patients, hepatic involvement is usually mild and self-limited, manifested by a discrete increase in liver enzyme levels, with severe cases rarely described (Yu et al., 2013).

It is important to understand the epidemiology, pathophysiology, clinical manifestations, and diagnosis of CMV infection, since it can manifest itself nonspecifically in immunocompetent patients and severely in immunocompromised patients. Therefore, in this report, we describe an atypical case of an immunocompetent elderly woman who presented symptomatic infection with acute hepatitis due to CMV infection, which is a frequently undetected and unrecognized cause of hepatitis.

2. Methodology

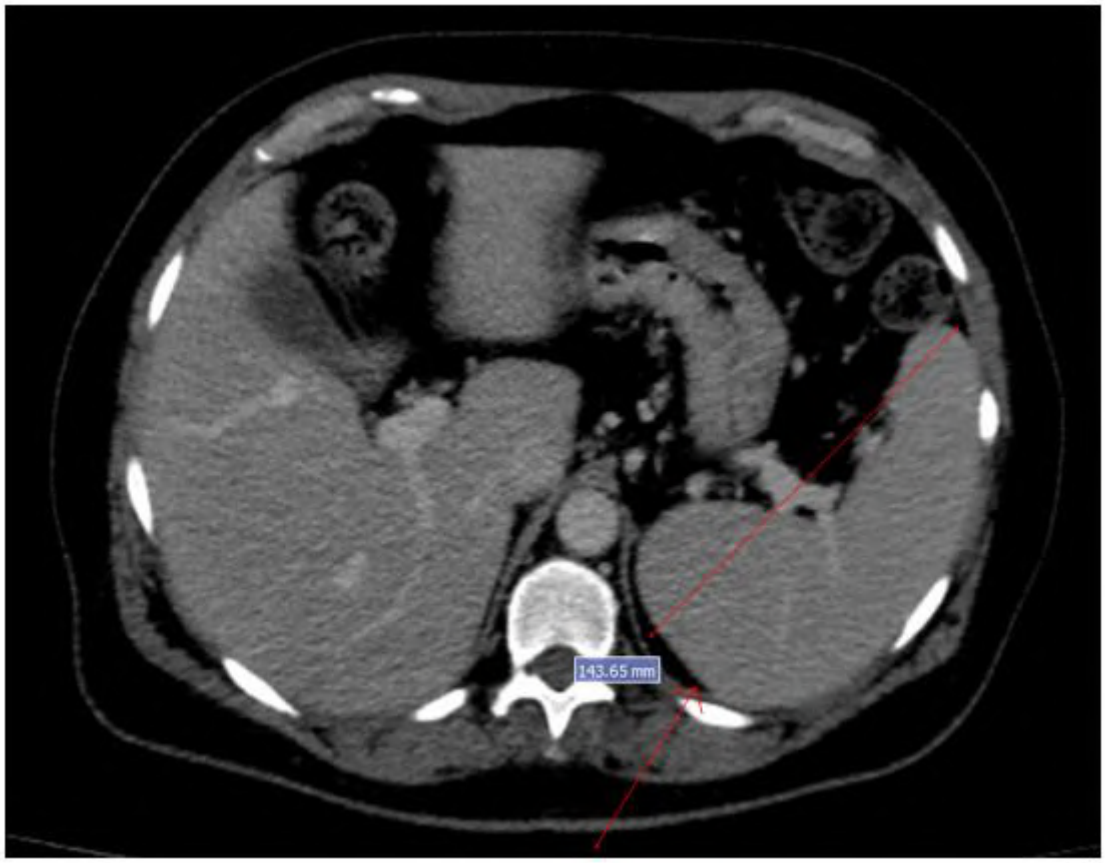
A descriptive research was carried out, of a qualitative nature and a clinical case report type (Toassi & Petri, 2021; Pereira et al., 2018). The study was conducted in accordance with current bioethical standards and was submitted to and approved by the Research Ethics Committee (CAAE 79521024.7.0000.8667; Opinion Nº. 6.843.728).

The research was carried out in 3 stages, the first being the electronic review of the patient's medical record, with collection of clinical data and complementary examinations. The second stage was the literature review of the condition presented by the patient, from the research of scientific articles on digital platforms such as PubMed, ScienceDirect and Google Scholar, with study of its etiology, pathophysiology, clinical manifestations, diagnosis and treatment. And the third stage was the correlation of the case with the findings described in the literature.

3. Case Report

A 60-year-old woman was admitted to the emergency room with malaise, asthenia and fever for 2 weeks, being evaluated and initially prescribed antibiotics and being discharged with initial diagnostic suspicion of bacterial infection. After a week, without remission of symptoms, she returned with anemia, as well as the presence of red Rouleaux blood cells, which led to the suspicion of bone marrow dysplasia. The patient was hypertensive, dyslipidemic and a former smoker. She was referred to a tertiary hospital with hepatosplenomegaly on physical examination. In the laboratory evaluation, there was alteration of liver enzymes of mixed pattern, with increase of hepatocellular and canalicular enzymes, without impairment of liver function (Table 1). Further etiological investigation ruled out the hypotheses of hepatitis B or C virus, autoimmune hepatitis and Wilson's disease. Serologies of HIV, syphilis, dengue, zika and chikungunya were negative, presented immunity to toxoplasmosis and Esptein Barr, and IgM and IgG serology was positive for cytomegalovirus. Computed tomography of the abdomen was performed, with the presence of homogeneous splenomegaly with cicatricial foci of calcification. In the following image (Figure 1), in the axial section of the abdomen, splenomegaly (Red Arrow) secondary to viral infection by cytomegalovirus is observed.

Figure 1 – Abdominal tomography with splenomegaly secondary to cytomegalovirus infection.



Source: Radiology Unit. Clinical Hospital – UFTM (2023).

Laboratory tests found protein electrophoresis with monoclonal gamma globulin peak, positive FAN 1: 80 with cross-linked dotted cytoplasmic pattern, hyperferritinemia, in addition to normocytic and normochromic anemia and lymphocyte polymorphism in all blood counts performed. Throughout the hospitalization, the patient progressed with remission of symptoms, remaining only with splenomegaly, and acute CMV infection was confirmed from the quantification of viral load (quantitative CMV PCR - 9,770 IU/mL). In 10 days of hospitalization, there was no progression of the condition, with spontaneous improvement of clinical and laboratory parameters, without the need for specific treatment, thus, the patient was discharged from the hospital. The case was concluded as an acute Cytomegalovirus infection hepatitis. The evolution of the laboratory results is detailed in Table 1.

Table 1 – Evolution of laboratory tests.

	15/10/2023	17/10/2023	18/10/2023	23/10/2023	28/11/2023
ALT	121	124	175	130	37
AST	162	147	207	115	43
ALP	122	123	136	99	-
GGT	118	182	219	143	-
BT/DB	0,48/0,24	-	-	0,62/0,24	0,63/0,22
Albumin	2,9	2,8	-	-	-
INR	1,1	1,0	-	1,0	-

Source: Clinical analysis and pathological anatomy unit. Clinical Hospital – UFTM (2023).

4. Discussion

The symptoms associated with cytomegalovirus (CMV) infection in immunocompetent individuals are not well documented, with only a few reports describing symptoms in these patients. The most described are malaise (67%), fever (46%) and sweating (46%), in addition to alteration of liver enzymes (Wreghitt et al, 2003), as presented by the patient of the case reported. There are few reports of severe or prolonged symptomatic infection in this population. Although CMV infection is generally self-limited in healthy adults, serious complications can occur by mechanisms not yet clarified, including pneumonia, myocarditis, colitis, and hepatitis with impaired liver function (Eddleston et al., 1997).

Liver involvement is rare and can range from sensitive hepatomegaly to fulminant liver failure (Yu et al., 2013). The first case of CMV-associated hepatitis was reported by Lamb and Stern in 1966 (Lamb et al., 1966). Liver involvement differs significantly according to the immune status of the host. In immunocompromised patients, particularly liver transplant patients, CMV usually causes clinically significant hepatitis, while in immunocompetent patients, hepatitis requiring hospitalization is extremely rare (Cunha et al., 2021), with an increase in transaminases up to five times the limit of normal being observed, as well as a discreet increase in bilirubins and alkaline phosphatase (Horwitz et al., 1986).

CMV has glycoproteins that can interact with a vast number of cell surfaces, which gives it broad cellular tropism, with its systemic dissemination through the hematogenous pathway (Jean Beltran & Cristea, 2014). It presents direct and indirect cytopathogenicity in several organs, and the mechanism of liver injury is mainly associated with indirect pathogenicity by the cytotoxicity of TCD8+ lymphocytes, triggering an inflammatory response with the release of hepatotoxic cytokines (Pape et al., 1983). It has also been evidenced more recently, from an experiment with murines, that TCD4 + lymphocytes perform an important function by producing several cytokines (IL - 17 IFN-γ and TNF), contributing to the enhancement of adaptive immune response (Livingston-Rosanoff et al., 2012).

The variability of clinical manifestation according to the immunological status of the patient can be justified by its pathophysiology. It was evidenced that, in immunocompetent patients, liver damage occurred earlier and was mediated by T lymphocytes and natural Killer cells, however, the reduction of enzymes was also earlier, reflecting the immune control capacity of the host. In immunocompromised patients, the elevation of enzymes was observed later, as well as was more prolonged (Stahl et al., 2018), with a higher risk of progression to severe conditions. It was observed in the patient that the transaminases returned to their normal value one month after discharge from the hospital, which was compatible with her immunocompetence status.

In a study of liver biopsies of patients with CMV Hepatitis, it was observed that the infection began in the cells lining the sinusoids, such as Kuppfer cells and endothelial cells, proposing that, already in early stages, hepatic dissemination by the agent occurs (Theise et al., 1993). In relation to infected liver cells, it was evidenced that the most affected lineage was hepatocytes, with the identification of only one case with bile duct involvement (Sano et al., 1991). Although the most common hepatic involvement is hepatocellular, there are reports of collective conditions, including manifestation with acute cholangitis, characterized by abdominal pain in the right upper quadrant, fever and jaundice (Alibegovic et al., 2021), which demonstrates the diversity of clinical manifestations that can occur in CMV infection.

CMV infection can also result in hematological changes. The predominant characteristic is lymphocytosis, with atypical lymphocytes being evidenced in 78 to 98% of cases (Schattner et al, 2024). Anemia is common, affecting up to 67% of patients, but it is mild and secondary to the systemic inflammatory process (Weiss et al., 2019), as well as thrombocytopenia, so that such changes are transient and self-limited. The patient in the reported case presented normocytic and normochromic anemia, as well as leukocytosis, which resolved spontaneously after the resolution of the condition.

Diagnosis of CMV infection should be carried out from the clinical evaluation with laboratory confirmation. Serology can be used, being considered probable acute infection or reactivation, with the detection of specific IgM antibody and increase of at least four times the IgG value in samples compared with an interval of two to four weeks (Sy et al., 2013). However, this methodology can give a false positive result. The detection of the virus DNA is carried out by molecular assays, via qualitative or quantitative PCR. Since qualitative PCR does not have the ability to differentiate a latent infection from an active infection, the ideal is to dose the quantitative examination (Caliendo, 2013). In addition, there are antigenemia assays to detect CMV proteins in leukocytes and peripheral blood, as well as histopathological and immunohistochemical studies that can assist in the diagnosis. It is worth noting that in cases of acute hepatitis in immunocompetent individuals, the finding of typical cytomegalovirus nuclear inclusions and immunohistochemical staining for cytomegalovirus antigen may be absent (Snover et al., 1984).

Guidelines for the treatment of cytomegalovirus hepatitis in immunocompetent adults have not been published, and should be carried out individually, weighing the risks and adverse effects of medications (Rafailidis et al., 2008). Usually, the infection is resolved spontaneously without complications. Since the criteria for specific antiviral therapy are not well established, therapy is reserved for those who evolve with severe or persistent form of the disease (Nangle et al., 2018).

5. Conclusion

The report presents a case of acute hepatitis by cytomegalovirus in an elderly and immunocompetent woman. Although most cases of CMV hepatitis in immunocompetent individuals are mild and self-limited, understanding its clinical manifestations, its underlying pathogenic mechanisms, including T-cell-mediated cytotoxicity and cytokine-mediated inflammatory response, are essential for the diagnostic and adequate management of this condition, since it can rarely present in severe form. This report highlights the importance of considering CMV as a possible etiological agent in cases of acute hepatitis, especially when other more common causes have been excluded, highlighting the complexity and variability of clinical presentations of this viral infection.

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