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Case report

Cytomegalovirus (CMV)-related cutaneous necrotizing vasculitis: case report and literature review

Ferhat Arslan[a,*], *Ayse Batirel*[a], *Ali Mert*[b], *Serdar Ozer*[a]

[a] *Department of Infectious Diseases and Clinical Microbiology, Dr. Lutfi Kirdar Kartal Education and Research Hospital, Istanbul, Turkey*
[b] *Department of Infectious Diseases and Clinical Microbiology, Cerrahpasa Medical Faculty, Istanbul University, Istanbul, Turkey*

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ABSTRACT

Cytomegalovirus (CMV) infection is usually asymptomatic in immunocompetent patients. A mononucleosis-like syndrome may develop in some patients. Various organ involvements (eg: encephalitis, meningitis, retinitis, myocarditis, pneumonia, hepatitis, enterocolitis, neuritis), which rarely occur in immunocompetent patients, have also been reported. Cutaneous necrotizing vasculitis caused by CMV infection has been reported very rarely in the literature. Here, a case with a very rare clinical form of CMV infection, presenting with persistent fever and livedo reticularis on the extremities and cutaneous necrotizing vasculitis of the toes, is described, and the relevant literature is reviewed. This case report aims to highlight the possibility of CMV infection to be a cause of cutaneous necrotizing vasculitis.

Introduction

Cytomegalovirus (CMV) infection is usually asymptomatic in immunocompetent patients.[1] A mononucleosis-like syndrome may develop in some of the patients. Apart from that, various organ involvements (e.g.: encephalitis, meningitis, retinitis, myocarditis, pneumonia, hepatitis, enterocolitis, neuritis), which are rare in immunocompetent patients, have also been reported.[2] Cutaneous necrotizing vasculitis caused by CMV has been reported very rarely.[3–5] In this report, a very rare clinical form of CMV infection, presenting with persistent fever and livedo reticularis on extremities and cutaneous necrotizing vasculitis of toes, is described, and the literature regarding this case is reviewed.

Case presentation

A 17 year-old female had been treated with amoxicillin-clavulunic acid, and clarithromycin for complaints of fever and cough. Her cough resolved within a month, but the fever persisted, and she started to present additional symptoms such as nocturnal sweating, livedo reticularis-like rash on hands and feet, and weight loss (12% of total body weight). There were no enlarged peripheral lymph nodes on physical examination. Laboratory investigation results during the first month of her illness were as follows: white blood cell count (WBC): 8,700/mm^3, hemoglobin (Hgb): 9.7 g/dL, hematocrit (Htc): 30%, platelets (PLT): 534,000/mm^3, erythrocyte sedimentation rate (ESR): 70 mm/hr, C-reactive protein (CRP):

* *Corresponding author at:* Infectious Diseases and Clinical Microbiology, Lutfi Kirdar Kartal Training and Research Hospital, TR 34863 Kartal, Istanbul, Turkey.
E-mail address: ferhatarslandr@hotmail.com (F. Arslan).
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44 mg/L, alanine aminotransferase (ALT): 13 U/L, aspartate aminotransferase (AST): 12 U/L, creatinine kinase (CK): 19 U/L, total protein: 8.1 mg/dL, albumin: 3.9 mg/dl, ANA (antinuclear antibody): negative, anti-dsDNA (anti-double-stranded DNA): negative, urea: 30 mg/dL, creatinine: 0.9 mg/dl, urinary sediment: normal. Since this patient had been considered as a "fever of unknown origin" case and had the symptoms of fever, weight loss, and nocturnal sweating, thoracic and abdominal computed tomography (CT) scans were performed, along with bone marrow aspiration and biopsy to exclude lymphoma or any other malignancy. However, these exams revealed no abnormality. Suspecting the diagnosis of sustained mononucleosis syndrome, CMV serology was performed by ELISA. CMV IgM was 7.85 AU/mL (Abbott Architect i1000SR) and CMV IgG was 130.4 AU/mL (Abbott Architect i1000SR), and CMV IgG avidity was 4% (Abbott Architect i1000SR). CMV PCR was not initially tested. Human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), toxoplasma and parvovirus serology were investigated for the differential diagnosis of mononucleosis syndrome, as well as hepatitis B virus (HBV) and hepatitis C virus (HCV) serology. Tests for EBV VCA IgM, toxoplasma IgM and IgG, anti-HIV, and parvovirus IgM, HBsAg, anti-HBc IgM and anti-HCV were all negative.

During the second month of her illness, fever, and bilateral livedo reticularis on her feet, more prominent on the left, continued. Repeated blood cultures remained sterile. No vegetations were detected on transthoracic echocardiography. No abnormality was detected on thoracic and abdominal CT. Arterial and venous Doppler ultrasonography of the upper and lower extremities and MRI (magnetic resonance imaging)-angiography of the aorta and its branches were normal. Markers for autoimmune diseases including ANA, anti-ds-DNA, RF (rheumatoid factor), anti-CCP (anti-cyclic citrullinated peptide), anti-LA (anti-SSB), anti-RO (anti-SSA), anti-ENA (anti-extractable nuclear antigen), Sm-antigen (Smith antigen), anti-ENA U1-RNP (U1-ribonucleoprotein), anti-cardiolipin IgM and IgG, MPO-ANCA (myeloperoxidase-anti-neutrophil cytoplasmic antibody), p-ANCA (perinuclear-ANCA), c-ANCA (cytoplasmic-ANCA) were all negative. CMV IgM was negative, but CMV IgG was >250 AU/mL (Abbott Architect i1000SR) with low avidity (CMV IgG avidity: 4%, low avidity if less than 20%), PCR assay for CMV was negative. Other laboratory test results were as follows; WBC: 7.200/mm3, Hgb: 8.7 g/dL, Htc: 28.7%, PLT: 524,000/mm^3, ESR: 76 mm/hr, CRP: 39 mg/L (negative if <3 mg/L) and biochemical tests were within normal limits. As any infectious focus had not been detected, treatment with methylprednisolone 1 mg/kg was begun. Although her fever resolved and ESR and CRP values decreased to normal levels, the tip of the second toe of her right foot had become necrotic (Fig. 1). The biopsy of this lesion revealed necrosis in the epidermis and dermis, necrotizing vasculitis, and occlusive vasculopathy of the small-sized vessels (Fig. 2). Inclusion bodies were not observed in the tissue specimen and CMV PCR was negative. Azathioprine 50 mg twice a day and methylprednisolone 48 mg was given to the patient. After the first month of immunosuppressive therapy, necrosis of the toes had begun to regress. She had no other systemic signs and symptoms, and she is still under follow-up at the outpatient clinic.

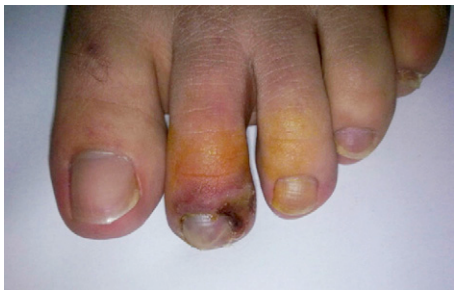

Fig. 1 – Necrotic appearance of the tip of the second toe of patient's right foot with purple to bluish discoloration.

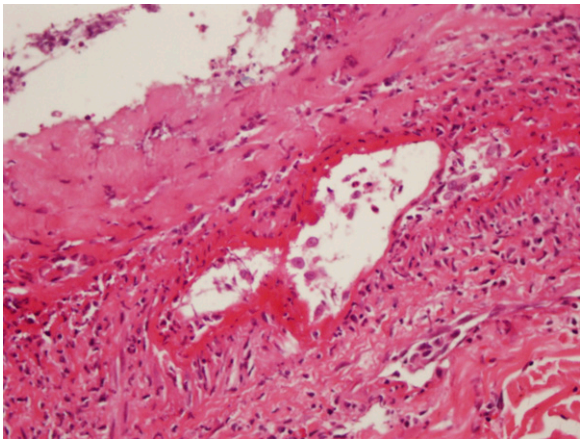

Fig. 2 – Histopathological slide of the biopsy of tip of the second toe of the patient's right foot, revealing necrosis in the epidermis and dermis, and necrotizing vasculitis and occlusive vasculopathy of the small vessels.

Discussion

In recent years, some laboratory data regarding the association between viral infections and some autoimmune diseases have been obtained. Particularly, CMV-related conditions are remarkable. High CMV prevalence in systemic lupus erithematous patients, CMV antigen positivity in synovial fluid of rheumatoid arthritis patients, and presence of UL94-related apoptosis in vascular endothelium of systemic sclerosis cases are some examples.[6–8]

During the course of viral infections, viruses have been thought to cause vasculitis and vasculopathy either directly by replication in the vascular endothelium or indirectly by induction of autoimmunity.[9] Some well-known examples are intra-synovial deposition of immune complexes against hepatitis B virus surface antigen or anti-HBsAg in polyarteritis nodosa, and hepatitis C virus-related cryoglobulinemic vasculitis.[10,11] Despite conflicting results, studies describing parvovirus and herpes virus infections to cause temporal arteritis and giant-cell arteritis have been reported.[12]

CMV infection causes vascular endothelial damage either by causing direct cell injury and death or by means of immune-mediated injury via induction of autoimmunity (molecular mimicry). Other reported mechanisms of vascular injury are