

CASE BASED REVIEWS

Cytomegalovirus and rheumatic diseases: cases-based review

Lourenço MH^{1,2,3*} , Borralho J^{4,5*}, Silva I^{1,3}, Alves J^{4,5}, Sampaio R⁶, Mansinho K^{4,7}, Branco JC^{1,2,3}**ABSTRACT**

Cytomegalovirus (CMV) infection is a common and typically benign disease in immunocompetent individuals. However, immunocompromised patients are at a greater risk of reactivation, leading to more severe outcomes. Patients with rheumatic diseases have a particularly high risk of opportunistic infections due to both the inherent immunosuppressive state conveyed by the disease itself and the use of immunosuppressants, although varying in the type of drug, dosage and time of exposure. Limited data are available regarding prophylactic or preemptive treatment of CMV infection in patients with rheumatic diseases. In this article the authors present two cases of rheumatic conditions complicated by CMV infection. The first case describes a patient with eosinophilic granulomatosis with polyangiitis, previously treated with glucocorticoids and cyclophosphamide, who developed CMV colitis with bowel perforation. The second case involves a woman with systemic lupus erythematosus who was diagnosed with CMV meningitis. Both cases reinforce the importance of establishing guidelines for surveillance and prophylaxis of CMV infection in these patients.

Keywords: Immunosuppressants; Systemic lupus erythematosus and autoimmunity; Churg-Strauss Syndrome.

INTRODUCTION

Systemic rheumatic and autoimmune diseases comprise several conditions characterized by an immunological dysfunction associated with primary defects in the adaptive immune system, leading to a loss of self-tolerance¹. Treatment strategies involve the regulation of the immune system using immunosuppressant drugs, which predispose patients to infections. Therefore, patients with rheumatic conditions are at a higher risk of opportunistic infections, and each evaluation demands a careful approach and an exhaustive screening of infectious complications to facilitate early detection and treatment.

Cytomegalovirus (CMV) is a member of the Herpesviridae family, highly prevalent worldwide, with

statistics reporting a global seroprevalence of 83%². It can manifest through various forms, including primary infection, reinfection or reactivation, with main modes of transmission being sexual exposure, direct contact with body fluids (blood, urine, saliva), perinatal exposure and lactation³. In immunocompetent patients, CMV manifestations are generally benign, ranging from asymptomatic to flu-like symptoms with fever, lymph nodes enlargement, and fatigue. However, more severe cases may present elevated transaminases, splenomegaly, cytopenias, pneumonia, esophagitis, colitis and encephalitis. Similar to other herpesvirus, CMV establishes a lifelong latent infection in hematopoietic progenitor cells after the resolution of the acute infection, and, therefore, in immunocompromised patients, reactivation can occur, with potential poorer outcomes, which may eventually lead to organ dysfunction and death³.

Among the most severe complications of CMV, gastrointestinal and central nervous system diseases are of particular importance. CMV colitis is mainly reported in patients with human immunodeficiency virus (HIV) and transplant recipients, with scarce data for patients with rheumatic diseases⁴. Clinical picture is nonspecific, but includes bloody stool, diarrhoea, abdominal pain, and constitutional symptoms. Diagnosis relies on endoscopic studies with biopsy of the affected segments, revealing suggestive findings, such as ulcerations with a punched-out appearance. The gold-standard confirmation involves the observation of typical

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CMV viral inclusions with the characteristic “owl eye” appearance, combined with positive CMV immunohistochemistry^{4,5}.

Involvement of the central nervous system by CMV may adopt several forms, including meningitis, encephalitis, retinitis, seizures, and cranial nerve palsies.⁶ The diagnosis relies on the identification of CMV in the cerebrospinal fluid (CSF) using polymerase chain reaction (PCR), along with either a neutrophilic or lymphocytic pleocytosis, proteins and low levels of glyucose. Analysing CSF is also essential to exclude other common causes of meningoencephalitis⁶.

The authors report two cases of CMV infection in immunosuppressed patients with rheumatic diseases. The first case involves a patient with eosinophilic granulomatosis with polyangiitis (EGPA), previously treated with high dose corticosteroids and cyclophosphamide, who developed CMV colitis leading to a complicated colonic perforation. The second case describes a woman with systemic lupus erythematosus (SLE) on azathioprine and corticosteroid treatment, who was admitted due to CMV meningitis.

CASE 1

A 78-year-old woman with a 6-month diagnosis of EGPA (adult-onset asthma, sinusitis, bullous hemorrhagic cutaneous vasculitis, symmetric and additive

polyarthritis of hands, elbows and tibiotarsal joints, sensorimotor polyneuropathy and peripheral eosinophilia), previously treated with methylprednisolone 1g/day (3 days), methotrexate 10mg/week (suspended due to hepatotoxicity) and cyclophosphamide (2 cycles; CYCLOPS protocol - stopped because of recurrent urinary tract infections), and presently under prednisolone 20mg/day (weaning scheme from 1mg/kg/day), in clinical remission, was admitted to the emergency room due to abdominal pain, nausea and vomiting, with 2 weeks of evolution.

Blood analysis showed lymphopenia (440 cells/ μ l) (with a CD4+ T cell subpopulation quantification of 235 cells/ μ l), C-reactive protein elevation (8.5 mg/dL) and hyperlactatemia (1.7 mmol/L). Abdominal computed tomography (CT) scan revealed extensive colonic thickening with multiple stenoses of the anorectal junction and extraperitoneal air, suggestive of perforation of the anorectal transition, particularly the anal canal (Figure 1). The patient was hospitalized at the General Surgery department where an exploratory surgery was performed, and a bleeding rectal ulcer was detected. Biopsies were performed, followed by a terminal colostomy and a course of broad-spectrum antibiotics (meropenem 1000mg/day for 5 days). No signs or symptoms of other organ involvement were detected.

Histological examination of the ulcer showed en-

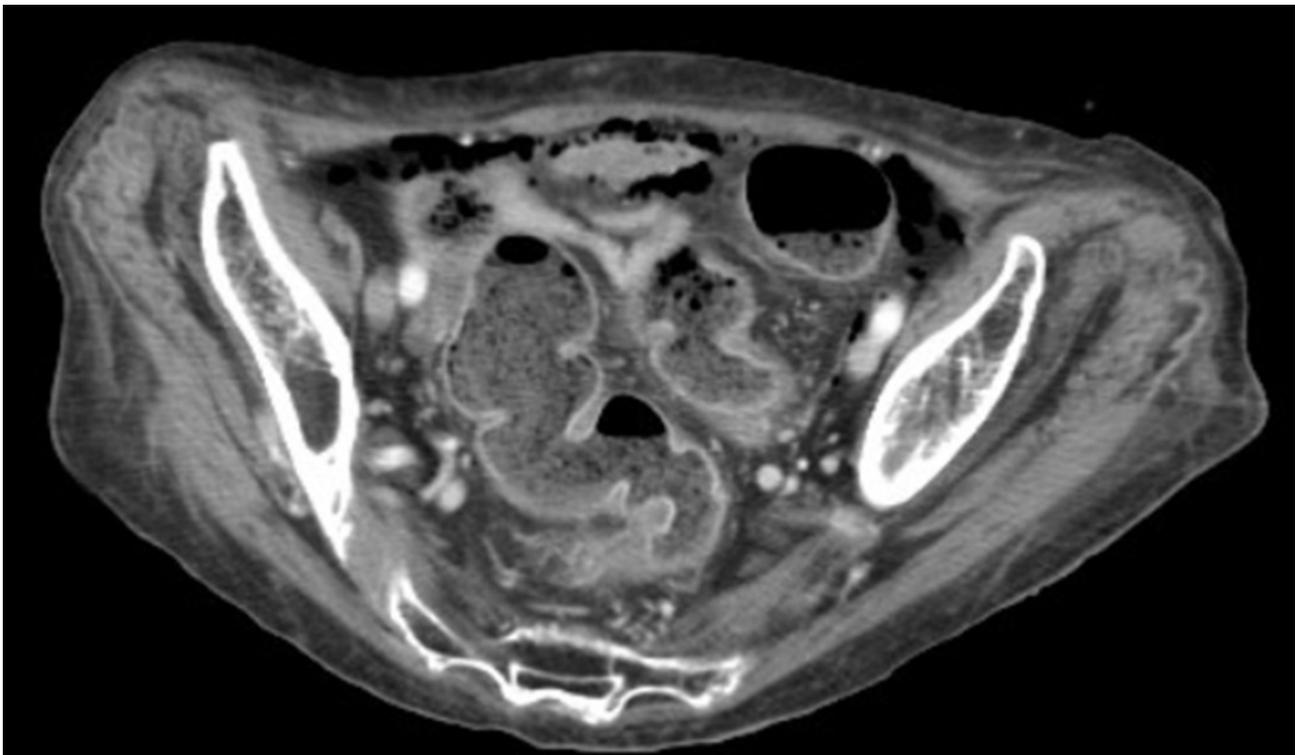


Figure 1. Abdominal computed tomography scan. Transverse abdominal computed tomography scan showing colonic thickening and extraperitoneal air, suggestive of perforation

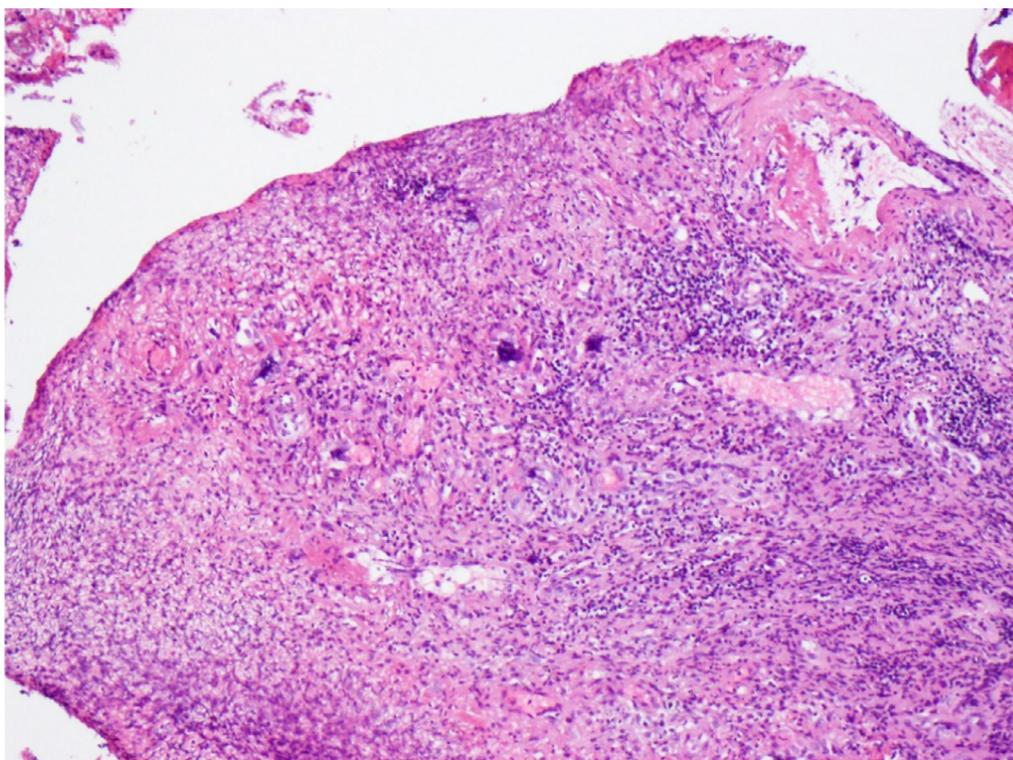


Figure 2. Histopathological slides. Ulcerated granulation tissue with focal cytopathic alterations typical of virus

larged cells (two to fourfold larger than normal) with thickened nuclear membrane containing basophilic intranuclear inclusion bodies (Cowdry bodies) surrounded by a clear halo and granular intracytoplasmic inclusions, very suggestive of CMV infection (Figure 2). Immunohistochemical examination was then applied, confirming this agent (Figure 3). CMV viral load (VL) was 254 IU/mL, compatible with disseminated CMV disease. Three months before, routine evaluation (before starting cyclophosphamide) revealed positive M and G immunoglobulins for CMV, with CMV VL <178 IU/mL and no signs or symptoms of other CMV organic disease were documented at that time.

Considering this, the patient was transferred to the Infectious Diseases department. After 21 days of treatment with intravenous ganciclovir 5mg/kg (325mg) every 12 hours, CMV VL was undetectable. Subsequently, secondary prophylaxis was initiated with valganciclovir at a daily dosage of 900mg. This prophylactic treatment was maintained for 100 weeks, until CMV VL was undetectable and CD4+ T cell count was above 200 cells/ μ l, alongside with an absence of systemic or organic symptoms, allowing a gradual tapering of prednisone to reach a baseline dose of 5 mg/day. Throughout this 100-week period and even three months after discontinuing valganciclovir, no recurrence of CMV infection was observed.

Furthermore, during the follow-up, the dosage of pred-

nisolone was initially increased until 20mg/day to prevent flares and was subsequently reduced according to a weaning scheme until a daily dose of 5mg, without any EGPA recurrence during the 24-month follow-up period.

CASE 2

A 61-year-old female diagnosed with SLE in 2016 (titres of antinuclear antibodies of 1/320 – nuclear speckled pattern -, leukopenia, polyarthralgias without arthritis, oral ulcers, and non-scarring alopecia), and treated with azathioprine 150mg/day and deflazacort 3mg/day (previously under 9mg/day, in weaning scheme), was admitted in the Rheumatology inward due to a holocranial headache, recurrent low-grade fever, asthenia, anorexia, night sweats, and oligoarthralgias, with one week evolution.

Upon admission, the patient was febrile (38.4°C) and a systolic murmur was audible on the aortic focus; neurological and articular examinations were normal. Blood analysis revealed normocytic normochromic anemia (9,8 g/dL), leukopenia (3100/ μ L) and lymphopenia (840/ μ L), along with elevated inflammatory markers (erythrocyte sedimentation rate 55 mm/h; C-reactive protein 3mg/dL), hepatic cytolysis (aspartate aminotransferase 61U/L, alanine aminotransferase 63U/L; lactate dehydrogenase 555U/L), and normal levels of complement fraction 3 and 4. Anti-double stranded DNA antibodies (dsDNA) titres were within the normal

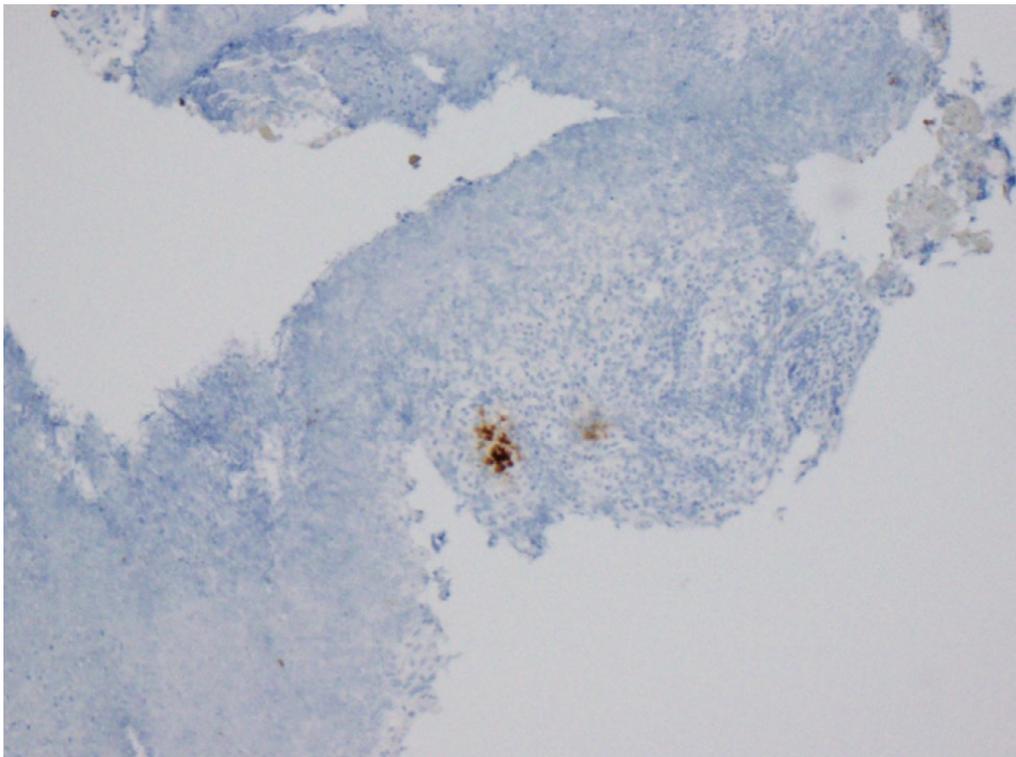


Figure 3. Immunocytochemistry. Positive immunocytochemistry for cytomegalovirus.

range, and there were no antiphospholipid antibodies detected; blood cultures were negative as well.

Brain CT scan and magnetic resonance were normal. Considering this and the absence of suggestive analytical findings or other symptoms, the hypothesis of neurological involvement of SLE was dismissed. Bone marrow biopsy excluded a myeloproliferative syndrome. To investigate the sustained fever and heart murmur, a transthoracic echocardiogram was performed and excluded valvular vegetations or any intracavitary masses or thrombi.

In the meantime, viral serologies revealed a positive CMV immunoglobulin M and G in the serum, with a high plasmatic CMV VL (10442 UI/mL) and the CSF analysis revealed a slightly hematic CSF with pleocytosis (leukocyte 18 cells/ μ L, with no cell predominance), normal levels of proteins and glucose and a positive CMV PCR (100 copies/mL) with no other neurotropic infectious agents detected. Lymphocyte subpopulation quantification revealed 267 CD4+ T cells/ μ L. CMV meningitis was assumed as in the context of either an acute disseminated CMV primoinfection or reactivation and the patient was started on ganciclovir treatment (5mg/kg every 12 hours). Endoscopic studies excluded gastrointestinal involvement and ophthalmological evaluation ruled out retinitis.

Following a 17-day course of ganciclovir therapy, there was no recurrence of headache or fever;

inflammatory markers became negative, including serum CMV VL. Lumbar puncture was repeated and did not detect CMV in the CSF. The patient was discharged without need for further therapy or prophylaxis and with SLE Disease Activity Index (SLEDAI-2K) of 1 due to persistent leukopenia – 2100 cells/ μ L with 590 lymphocytes/ μ L - associated with the disease). Azathioprine was suspended, as it was assumed it could be a potential risk factor aggravating lymphopenia, and hydroxychloroquine was started (400mg/day). The patient remained asymptomatic in a 3-year follow-up, with no recurrence of CMV disease.

DISCUSSION

EGPA is a vasculitis of small- and medium-sized vessels characterized by lung, paranasal sinus, skin, kidney, nervous system, and joints involvement, associated with peripheral eosinophilia. It is a potential life-threatening disease, and high-dose glucocorticoids, cyclophosphamide, rituximab, and more recently mepolizumab, are often used to induce remission of the severe forms^{1,7}.

The second case reports a patient with SLE, a multisystemic autoimmune disease which may potentially affect any organ or system; its pathophysiology is complex but involves dysregulation of both innate and

adaptive immune system, and there is a clear and well-studied affection of both B and T lymphocytes. The key treatment of SLE, besides the non-medical approaches such as the sun exposure protection, like EGPA, also rely on immunosuppressant drugs which modulate the immune system. These drugs range from the antimalarials like hydroxychloroquine, glucocorticoids, methotrexate, azathioprine, mycophenolate mofetil, calcineurin inhibitors and biotechnological treatments like belimumab, rituximab and anifrolumab.⁸ Mirroring what happens with most rheumatic autoimmune diseases, these immunosuppressant drugs used in both diseases predispose patients to opportunistic infections.

CMV primary infection occurs when a non-immune person is infected for the first time, after which CMV remains latent in CD34+ myeloid progenitor cells⁹. This latent state poses a particular risk, especially in immunocompromised hosts, as reactivation of CMV can lead to severe end organ disease. CMV is a common and well characterized infectious agent among patients with Acquired Immune Deficiency Syndrome (AIDS) and solid organ and hematopoietic stem cell transplant recipients. It has been also described in patients with rheumatic disorders, and previous studies have shown that SLE and antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis patients are thought to be at higher risk, especially if more severe disease which require higher dosage of immunosuppressants^{10,11}.

Conversely, viral infections can also be triggers for the appearance of rheumatic diseases, and this association is more studied for Epstein-Barr virus and SLE^{12,13}.

CMV reactivation in rheumatic diseases is estimated to be between 31-50%, with Ota *et al.* showing a prevalence in their study of 39.7%¹⁴. Several clinical and analytical markers have been studied as potential risk factors and predictors of CMV infection in patients with rheumatic disorders. Studies have showed a significant association between CMV infection and certain factors, including the presence of oral candidiasis, hypoalbuminemia, and the detection of CMV antigenemia specifically the virus-specific protein pp65 antigen in polymorphonuclear leukocytes. Moreover, higher viral load, lymphopenia (as detected in the patient from case 2) observed four weeks before CMV reactivation, and co-infections with other pathogens have also been linked to increased susceptibility to CMV infection. Conversely, factors like older age and the use of methylprednisolone have also been identified as possible predictors of CMV reactivation, which were observed in the first case report^{11,15}. Some cohorts tried to find differences among various immunosuppressants but only high/moderate-dose corticosteroids were independently associated with CMV reactivation regardless the use of additional drugs.¹⁴ Shimada *et al.* showed recently

that cyclosporine was a risk factor for CMV¹⁶. For hematological conditions, data shows that irradiation, purine analogues, alemtuzumab, phosphoinositide 3-kinases inhibitors, and, again, high-dose corticosteroids, increase the risk of CMV infection¹⁷. The European Society of Clinical Microbiology and Infectious Diseases elaborated recommendations about certain immunosuppressants, namely anti-CD20 and anti-tumor necrosis factor- α agents, interleukin and kinase tyrosine inhibitors, although information about antimetabolites is unclear¹⁸⁻²¹. The American Society of Hematology reported that azathioprine was associated with a higher risk of CMV infection and cyclophosphamide with reactivation of latent infections (not specifically CMV)²².

The cases described reflect rare manifestations of CMV disease in patients with rheumatic disorders. To our knowledge, there have been only three published cases of patients with SLE who developed CMV meningitis or encephalitis, although one of them had a demyelinating disease underneath²³⁻²⁵. Regarding ANCA-associated vasculitis patients, as EGPA, there is a greater number of reported cases involving CMV colitis, however only scarce publications have documented colonic perforation as a complication of CMV disease^{26,27}.

The mortality rate associated with CMV infection seems to be high mainly in patients with severe immunosuppression, with higher doses of oral corticosteroids and more severe lymphopenia. This underscores the critical importance of early detection and timely intervention in such vulnerable patients. Prompt diagnosis and efficacious treatment are essential in improving survival outcomes and preventing potentially life-threatening complications associated with CMV infection¹⁰.

Prophylactic measures play a crucial role in the management of rheumatic patients; however, they are currently routinely implemented for only a small fraction of infectious agents, primarily targeting *Pneumocystis jirovecii*^{7,8}. The use of prophylactic approaches for other infectious agents, such as CMV, remains limited due to sparse data regarding to prophylactic or preemptive treatment. These cases reinforce the importance of guidelines concerning surveillance and prophylaxis of CMV infection in patients with rheumatic autoimmune and systemic diseases, especially when treated with high risk immunosuppressants.

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