CASE REPORT

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Cytomegalovirus colitis in a chronic haemodialysis patient

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ABSTRACT

Cytomegalovirus (CMV) infection is common in humans, usually asymptomatic in the immunocompetent host. In some conditions that reduce cellular immunity, latent CMV may reactivate, and patients are rendered susceptible to systemic CMV disease, characterised by fever, pancytopaenia and inflammatory changes in multiple organs. The gastrointestinal tract is frequently involved, with the colon being the most common site of CMV infection.

The authors report a case of CMV colitis in a haemodialysis patient with persistent aqueous diarrhoea. A rarely described association, of interest is the differential diagnosis to exclude other more common gastrointestinal disorders in these patients, as well as the favourable clinical course and response to antiviral treatment.

Key-Words:
Cytomegalovirus; colitis; ganciclovir; haemodialysis.

INTRODUCTION

Cytomegalovirus is a member of the Herpes viridae family, along with herpes simplex viruses 1 and 2, Epstein-Barr virus and varicella-zoster virus. It is a double-stranded deoxyribonucleic acid (DNA) virus that replicates in the host's cell nucleus. With a seroprevalence ranging between 40 and 100% in the adult population, CMV infection is very common in humans throughout the world[1].

Human CMV infection illness is pleomorphic and mostly dependent on the host. In the immunocompetent host, primary infection is generally asymptomatic or may present as a mononucleosis-like syndrome that is followed by a chronic latent state, in which the virus remains present within host cells, but viral proliferation is prevented by host cell-mediated immunity.

In situations that reduce host T-cell response, such as human immunodeficiency virus (HIV) infection, treatment with immunosuppressive agents after organ or bone marrow transplantation, malignant disease, or therapy with corticosteroids or cytotoxic drugs, latent CMV may reactivate. Patients are rendered susceptible to systemic CMV disease, characterised by fever, pancytopaenia and inflammatory changes in multiple organs, including the liver, lungs, heart, central nervous system and retina. The gastrointestinal tract is often involved, mostly the colon, although any area can be affected[2].

Patients with CMV colitis may present symptoms of acute or chronic aqueous diarrhoea (sometimes bloody), abdominal pain and tenesmus, with or without constitutional symptoms. Complications may occur and include massive bleeding, perforation of the colon, or toxic megacolon.

Sigmoidoscopy or colonoscopy is the definite diagnostic test, allowing colon mucosa direct visu-

alisation and biopsy[3]. Histological findings of characteristic giant cells containing large, central, intranuclear inclusions which stain positively with anti-CMV monoclonal antibody on immunohistochemical techniques are diagnostic[3]. Treatment with antiviral drugs is usually recommended in severe and persistent cases of CMV colitis[4].

CASE REPORT

A 63-year-old female Caucasian patient had a previous history of ovarian neoplasia at the age of 33 years old, treated with chemotherapy and radiotherapy during a two-year period. She also had heart failure, cerebrovascular disease, chronic obstructive lung disease, obesity and pseudogout.

She had been on chronic high-flux haemodialysis with a good dialysis adequacy since August 2004, due to analgesic nephropathy (nonsteroidal anti-inflammatory drugs abuse for chronic pain during several years) and left kidney hydronephrosis secondary to radiotherapy. She had no history of active neoplasias or actual immunosuppressive agents. Viral serologies (hepatitis B and C, HIV) were negative.

She was admitted in the emergency room with a one-week history of fever, anorexia, weight loss, joint pain, abdominal cramps and aqueous diarrhoea (6-8 bowel movements per day). No pulmonary or urinary symptoms were present. Physical examination disclosed a low grade fever (38ºC), hypotension (90/60mmHg) and dehydration. Cardiopulmonary auscultation was normal. Abdominal palpation was diffusely painful, without abdominal mass, organomegalies or signs of peritoneal irritation. Her arteriovenous left arm graft had a surgical thrombectomy performed two weeks earlier, but was nonfunctioning and presented inflammatory signs.

Laboratory tests revealed anaemia [7.7 g/dL], raised white cell count [16.3×10^9/l (normal 3.5-9.5), 79.5 % neutrophils] and raised C-reactive protein [30 mg/dl (normal 0–0.3)]. Liver function test were normal. Thoracic X-ray revealed a slight cardiomegaly.

She was admitted to the Nephrology Department with the diagnosis of vascular access infection and prescribed intravenous antibiotics (vancomycin and gentamycin). A double-lumen catheter was inserted in her right femoral vein to allow dialysis, and one red blood cell unit was administered.

During hospital stay, fever subsided within two days, arteriovenous graft inflammatory signs regressed and C-reactive protein values lowered to 5.0 mg/dL. However, she maintained aqueous diarrhoea (5-6 bowel movements per day) and oral ulcers appeared on the fourth day of her stay. Piperacillin-tazobactam was added to her regime. Repeated blood and stool cultures were negative as well as Clostridium difficile cytotoxin assay on stool sample. Thoracic and abdominal computerised tomography scan was normal. A colonoscopy revealed a segmental colitis with a rectal ulcer, suggestive of infectious or inflammatory colitis. Colon mucosa and rectal ulcer biopsies were performed. Loperamide and mesalazine were prescribed with a good clinical response (2-3 bowel movements per day). The patient was discharged with a double-lumen right jugular vein tunnelled catheter, awaiting biopsy reports.

Colon biopsies revealed an active inflammation with local erosion of the surface epithelium (Fig. 1),

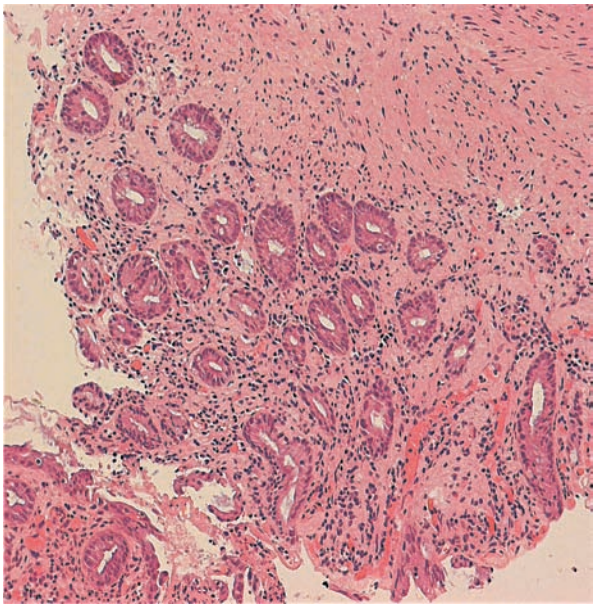

Figure 1

Haematoxylin and eosin staining (×100) of colonic mucosa, showing intense inflammatory infiltrate and mucosal ulceration.

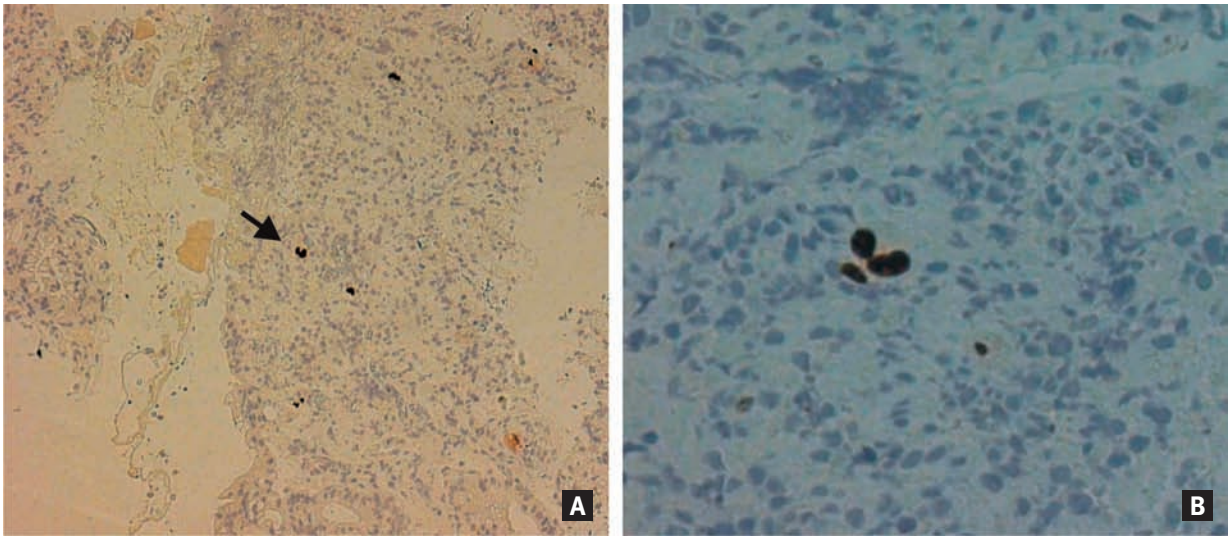

Figure 2

Immunohistochemical staining with anti-CMV monoclonal antibody, showing giant cells with intranuclear inclusion bodies and prominent nucleoli in some colonic mucosa cells (A: ×100, B: ×200).

associated with giant cells with prominent nucleoli infiltrating the lamina propria. Immunohistochemical staining with an anti-CMV monoclonal antibody revealed intranuclear inclusion bodies in some colonic mucosa cells (Fig. 2). These features were regarded to be consistent with CMV-associated colitis.

She was readmitted to the Nephrology Department, maintaining aqueous diarrhoea (5-6 bowel movements per day), weight loss and dehydration. CMV-specific IgG and IgM antibody tests were positive as was polymerase chain reaction (PCR) assay for CMV-DNA in blood (256 copies/ml of plasma). Intravenous ganciclovir (1.25 mg/kg/3 times per week following haemodialysis) was prescribed. Diarrhoea reverted within four days, and PCR assay for CMV-DNA became negative at day 14. She underwent four weeks of ganciclovir treatment that was suspended because of progressive leucopaenia.

After a one year follow-up, she remained asymptomatic and with no CMV colitis relapse.

DISCUSSION

Chronic renal disease, while not usually appreciated as an immunodepressive state like HIV infection, treatment with immunosuppressive agents after organ or bone marrow transplantation, malignant disease, or therapy with corticosteroids or cytotoxic drugs, is associated with severe acquired disturbances of the immune system.

Patients with end-stage renal disease present paradoxically with an overactivated but functionally compromised immune system, with alterations in neutrophil number and function, mononuclear cell activation, cytokine production, complement activation, T-cell function and adhesion molecule expression[5]. Immune dysfunction is accentuated rather than corrected by chronic dialysis[5].

Specific immune defence is particularly altered in uraemia, with a greatly diminished activation of T-cells due to a defective function of costimulation derived from antigen presenting cells[6,7]. Several mechanisms have been described. Firstly, there is a low activation of T-cell receptors on helper T-cells caused by impaired expression of the costimulatory molecule B7-2 (CD86) on monocytes[6,7]. Secondly, there is an increased production of inflammatory cytokines such as interleukin-1beta, interleukin-6 and tumour necrosis factor-alpha by activated monocytes and of soluble CD23 by B lymphocytes which correlate with low effector activation[6].

Thirdly, there is a reduced bioavailability of interleukin-2 secondary to its overconsumption by activated T-cells[2]. Fourthly, a functional pattern of T-cell activation toward T helper-1 differentiation is caused by inflammatory cytokines such as interleukin-12, which leads to an additional reduction of T helper-2 and B-cell function[6]. Finally, the presence of uraemic toxins *per se* directly causes immune cellular dysfunction[8].

In haemodialysis patients, other factors such as blood-membrane interaction during dialysis (especially when bioincompatible membranes are used), dialysis dose and nutritional state[5] may also play a role. All these events that impair T-cell lymphocyte-dependent immune response predispose uraemic patients to infections, particularly viral infections[7], and are associated with an increased risk of mortality in haemodialysis patients[9].

Although relatively frequent in renal transplantation, CMV colitis has rarely been reported in dialysis patients[2]. The authors describe a haemodialysis patient who was admitted with a suspected vascular access infection and gastrointestinal symptoms of aqueous diarrhoea, abdominal cramps and oral ulcers persisting despite broad-spectrum antibiotic therapy. The most common agents of gastrointestinal disorders in immunocompetent patients were excluded. Definitive diagnosis was established by colon mucosa biopsies and confirmed with positive CMV-specific IgG and IgM antibodies serological tests, suggesting viral reactivation instead of a primary CMV infection. The PCR assay for CMV-DNA was also positive, although with a small number of copies regarding the symptomatology presented by the patient. This finding has also been reported in a study[10] performed in cardiac and renal transplant recipients, where clinical symptoms of CMV infection, although more frequently observed in patients with higher number of CMV-DNA copies detected, were also present in patients with lower number of CMV-DNA copies (50-100 copies/ml of plasma).

Treatment of CMV colitis in immunocompetent patients is not consensual[2,11], as many cases are managed with supportive measures only. However, treatment with antiviral drugs is recommended in patients over 55 years old with chronic diseases (diabetes mellitus, chronic renal failure) who present severe and persistent cases of CMV colitis, with significant patient morbidity[4,11]. The prolonged evolution of abdominal symptoms in our patient, associated with the consideration of haemodialysis as an immunodepressive state, supported our decision to treat this patient with antiviral drugs, with a good clinical response and a complete remission of symptoms, without clinical evidence of relapse on follow-up.

Our case shows that CMV gastrointestinal disease is not restricted to severely immunocompromised patients. Although uncommon, it can occur rarely in supposedly immunocompetent patients with some conditions where an immunodeficiency state is present. Chronic renal disease is associated with severe acquired disturbances of the immune system, which are accentuated by chronic dialysis. Therefore, CMV colitis should be included in the differential diagnosis of persistent abdominal complaints in haemodialysis patients whenever an infectious colitis is suspected.

In the diagnostic workup, although serological tests are important for the diagnosis of CMV infection, colonoscopy with biopsy of colonic mucosa is the definite diagnostic test of CMV colitis, with characteristic findings of giant cells with intranuclear inclusions.

Treatment of CMV colitis with antiviral drugs is not consensual in immunocompetent patients, and it should be tailored to the individual according to clinical severity and evolution.

Conflict of interest statement. None declared.

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