Fatal mid-gastrointestinal bleeding by cytomegalovirus enteritis in an immunocompetent patient

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Abstract

Cytomegalovirus (CMV) infections are common in immunocompromised patients but rare in immunocompetent individuals. Gastrointestinal disease is frequent in systemic CMV infections but the small bowel is the least common site of involvement.

We present the case of a 66 years-old man, with no evidence of immunological deficiency, hospitalized for unspecific symptoms of diarrhea, fever and abdominal pain, which developed massive mid-gastrointestinal bleeding during hospitalization. Enteroscopy revealed congestive, oedematous mucosa with multiple ulcers in the small bowel. Cytomegalic cells with intranuclear inclusions were found on histologic examination, allowing the diagnosis of CMV infection. Ganciclovir in full therapeutic dose was started and surgery was performed as a last resource treatment, but the patient died.

This case highlights the rare condition of massive gastrointestinal bleeding due to CMV disease of the small bowel, the major importance of enteroscopy and pathologic evaluation for diagnosis and the poor prognosis of this situation. (Acta gastroenterol. belg., **2009**, 72, **245-248**).

Key words : cytomegalovirus disease, cytomegalovirus enteritis, intraoperative enteroscopy, mid-gastrointestinal bleeding, immunocompetence.

Introduction

A new concept in digestive haemorrhage, mid-gastrointestinal bleeding (MGIB), was recently introduced thanks to capsule and double-balloon endoscopy (1, 2). There are multiple causes of MGIB but small bowel infection is a rare one. However, in the immunosuppressed patient with MGIB, cytomegalovirus (CMV) infection must always be considered (3).

CMV is a member of the family Herpesviridae which also includes Epstein-Barr, herpes simplex, varicella zoster and human herpesvirus 6 to 8 (4, 5). It is a widely distributed pathogen with 40% to 100% of the general population being infected at some point in life (6). Primary infection by CMV is usually asymptomatic although a mononucleosis syndrome may occur (7). As with other herpesviruses, CMV establishes a latent infection in the host and may reactivate later during a period of immunosuppression. CMV disease is common in patients with cell-mediated immunity deficiency and may affect almost every organ of the body, causing fever of unknown origin, pneumonia, hepatitis, encephalitis, myelitis, uveitis, retinitis, colitis, neuropathy and others. Prognosis in these patients is poor (8, 9).

Any segment in the gastrointestinal (GI) tract, from mouth to anus, may be infected and the typical manifestation of disease is non-specific ulcerative lesions. Colitis is the commonest disorder and disease of jejunum and ileum is the least frequent (10). Gastric disease may result in abdominal pain and hematemesis. Disease of the colon or small bowel manifests as diarrhea, mid and/or lower GI bleeding and fever. Only a few cases in immunocompetent patients had been described.

We present a rare and disturbing case of enteritis by CMV in an apparently immunocompetent man, with a fatal outcome.

Case report

A 66-year-old man was admitted in a secondary hospital with a two week history of diffuse abdominal pain, watery diarrhea (4 to 5 liquid stools daily), low-grade fever, and nausea. Analgesics and antibiotics (ciprofloxacin) had previously been prescribed but his condition worsened four days before admission. He had well controlled type 2 diabetes mellitus, hypertension, dyslipidemia and nephrolithiasis. Chronic medication included aspirin, omeprazole, furosemide, glibenclamide, metformin, alopurinol, ramipril and simvastatin. Consumption of NSAIDs was frequent. He had no previous history of cancer, major surgery or medication with systemic/topical steroids. On admission, he was febrile, had a systolic bruit II/VI on mitral focus and diffuse tenderness without reboundness on abdominal palpation. Laboratory tests showed raised C-reactive protein, 90 mg/dL (normal range, < 10 mg/dL) but no other alterations. Chest and plain abdominal x-rays were normal. Abdominal ultrasound revealed gastric stasis, gallbladder distension with sludge but no wall thickening and bilateral renal calculi. At esophagogastroduodenoscopy (EGD) bulbar deformation and marked congestion/erythema of duodenal mucosa with yellow

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plaques were found. These alterations suggested an infectious disease so biopsies were taken but only non-specific inflammation was found, with negative cultures, including for mycobacteria.

Intravenous fluids, proton pump inhibitors and antibiotics (ciprofloxacin and metronidazole) were started but the situation worsened with persistent fever, diarrhea, abdominal distension and oliguria. By the sixth day, renal and respiratory insufficiency supervened and determined admission in a polyvalent intensive care unit (ICU). Mechanical ventilation was necessary for three days. By day 19, while renal and respiratory failure were subsiding, hematochezia occurred, becoming increasingly frequent and abundant. A second EGD showed a slight improvement of duodenal lesions with some dark fluid and a small blood clot in the lumen. A complete colonoscopy with adequate visualization of colonic mucosa and ileocecal valve was performed and revealed no lesions. No biopsies were taken. A new ultrasound scan revealed a marked thickening of terminal ileum suggesting a possible inflammatory bowel disease (IBD) and systemic corticosteroids were started.

Several nosocomial infections (urinary infection by *Acinetobacter baumanii* and by *Candida albicans*, blood cultures positive to *Staphylococcus aureus*) occurred and the patient received different antibiotics and antifungals. Multiple relevant exams were negative including fecal cultures and parasitological exams, toxin of *Clostridium difficile*, serology for Yersinia, Shigella, Salmonella, HAV, HBV, HCV and HIV.

Given the persistent blood loss with transfusion of 30 red blood cell (RBC) units, fresh frozen plasma and platelets, the patient was transferred to a specialized gastroenterology intensive care unit in a tertiary hospital at day 39. Since he was unstable, an abdominal angiography was performed but no active bleeding was found. However, at EGD some blood and clots were observed in duodenum suggesting that the bleeding source was located in the proximal small bowel. Given the patient's instability, the impossibility to perform an adequate bowel preparation, the results of the recent colonoscopy and the presumed bleeding origin we assumed that an intraoperative enteroscopy with oral approach was the best working out strategy. The first 80 to 100 cm of small bowel were explored and two areas of congestive mucosa with marked oedema, friability and multiple erosions were found, one in the third and 4th portions of duodenum (Fig. 1) and the other beginning 40 cm after the angle of Treitz. Biopsies were taken but since there was no active bleeding at the moment and the nature of the lesions was unknown no therapeutic intervention was performed. By day 43, the GI bleeding recurred with need for massive transfusion of RBCs, plasma and platelets, so a second intraoperative enteroscopy became necessary. By now, the mucosal alterations described above extended throughout the first 100 cm of small bowel. A surgical biopsy was taken but no therapeutic intervention was possible. All serologic and autoimmune studies were negative apart from serology for cytomegalovirus (CMV) with a positive IgG and a dubious IgM. No CMV-PCR was performed in the blood and tissue specimens because this technique was unavailable. By day 47 the histologic study of the biopsies revealed a florid cytomegalovirus enteritis (Fig. 2) and therapy with Ganciclovir IV 5 mg/kg twice per day was initiated. Unfortunately, there was no response to antiviral treatment and we even tried a third total enteroscopy, with the purpose to eventually remove the most affected segments, but by now, the proximal jejunum and proximal ileum were severely affected. The patient died on day 54.

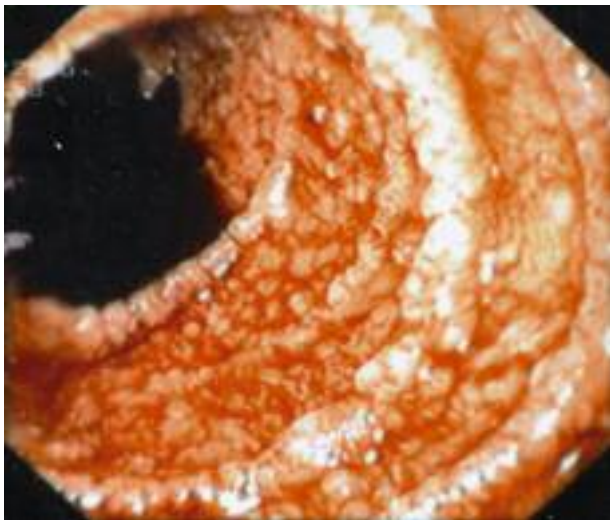

Fig. 1. — Marked congestion and erythema of duodenal mucosa with multiple erosions and spontaneous diffuse bleeding.

Discussion

CMV disease has an enormous impact on immunosuppressed patients, and it is the most common infectious complication in transplant recipients being extremely rare in immunocompetent individuals (11, 12). In immunocompromised patients CMV can cause an unspecific syndrome (fever with myelosuppression) or a compartmentalized, tissue-invasive disease which most often involves the gastrointestinal tract, although virtually any organ system can be involved (13). In addition to immunosuppression, there are immune-modulating conditions such as endocrinopathies (particularly diabetes mellitus), lymphoproliferative and nonhematologic malignancies, renal failure, autoimmune diseases and pregnancy that can favour primary infection or reactivation of CMV. These conditions are also associated with increased mortality in CMV disease (8).

In fact, our case reflects a rare situation of small bowel infection by CMV in an immunocompetent man with an immune-modulating condition : type 2 diabetes mellitus. There were no alterations in lymphocyte subpopulations, no HIV-related infection, no previous

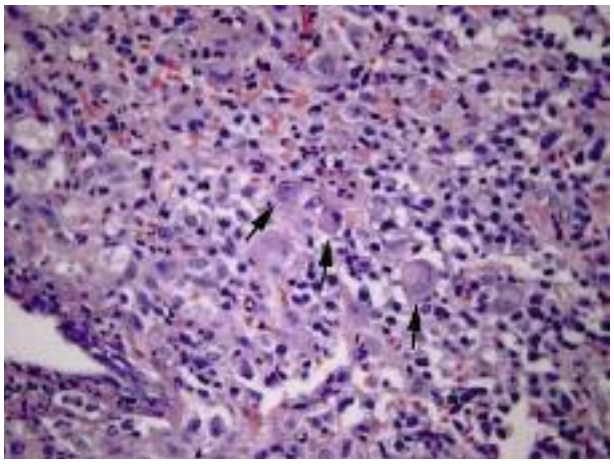

Fig. 2a. — Biopsy specimen from the patient's jejunum showing typical "owl's eye" appearance of CMV-infected cells (arrows), including large intranuclear inclusions surrounded by a clear halo (hematoxylin and eosin, ×400).

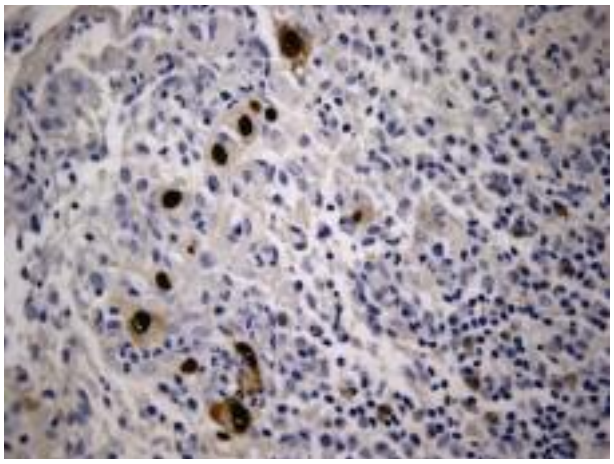

Fig. 2b. — Immunoperoxidase staining confirmed the nature of these inclusions (Immunoperoxidase, antibody anti-CMV, ×400).

history of hematologic malignancy, chemotherapy, radiotherapy, no use of immunosuppressive drugs. In fact, systemic steroids were given on the presumption of an IBD and they only potentiated the infection already present.

The appearance of such a rare disease in an immunocompetent man is an interesting point. Irigoin *et al.* (10) reported only 36 cases of enteritis by CMV, 10 of which were in patients with HIV infection. On the other side, it seems that age is important for immune status since the elderly may suffer a relative immunodeficiency, resulting from age-related dysfunctions of B and T cell lymphocytes, impaired cytokine regulation and perturbation of mucosal immunity. These alterations predispose older people to various infectious and inflammatory diseases (14). The higher prevalence of CMV disease in elderly individuals might also be related to the increased comorbidities in these patients (8, 15).

CMV colitis in immunocompetent patients is also mostly community-acquired (8) and this applies to our case of CMV enteritis.

When there is CMV disease, GI tract is frequently involved (10). The most common site is the colon followed by the upper GI tract and the least common is the small intestine (15-18). Concerning clinical manifestations, diarrhea, abdominal pain, fever, malaise, anorexia and GI bleeding are frequent, but massive bleeding is rare (19, 20). As occurred with our patient, manifestations of severe CMV disease such as hemorrhage or perforation are often preceded by vague GI symptoms for up to 2 weeks (11, 21).

Diagnosis of CMV GI infection in immunocompetent patients can be difficult (19). Serologic markers may be useful since in primary CMV infection IgM antibodies may be found as early as 4-7 weeks after initial infection and may persist for 16-20 weeks and in reactivation there is seroconversion of CMV IgM or a fourfold increase in CMV IgG titers, but they are not sufficient to make the diagnosis of CMV-associated disease (4, 11, 22-24). Viremia can be detected by shell vial cultures, CMV antigenemia, CMV pp65 or pp67 antigen assays or polymerase chain reaction (PCR) amplification but compartmentalized disease can occur with minimally detectable or undetectable virus in the blood (25). The macroscopic hallmarks of GI tract infection by CMV are erosions, ulcers and mucosal hemorrhage. The pathogenesis of lesions is not completely understood, but it involves tissue inflammation and necrosis, ischemic mucosal injury from endothelial involvement and local autoimmune effects (9). The macroscopic lesions are not diagnostic and biopsy is fundamental. In fact, diagnosis of CMV GI disease depends on the demonstration of intranuclear CMV inclusions or evidence of CMV on immunostaining, immunofluorescence, in situ hybridization or PCR in a biopsy specimen and the absence of other pathogens (4, 18). In our patient, the serology was suggestive, but the histologic examination of the biopsies obtained during enteroscopy was irrefutable. In the first biopsies, during the initial EGD, there was no apparent evidence of CMV infection. We must remember that this diagnostic hypothesis was only considered when the histology guided us towards diagnosis, so it was possible that some aspects in the first biopsies were undervalued. However, these negative biopsies were obtained from the 2nd portion of the duodenum in an early stage of the disease and the positive biopsies were obtained afterwards in the jejunum. For technical reasons it was not possible to re-examine the first biopsies. In addition, cytomegalic cells are not always observed in biopsy specimens of patients with GI disease (4, 26). On the other side, presence of cytomegalic cells or other evidence of CMV in GI biopsies is only indicative of CMV GI disease if there are macroscopic lesions (27). DNA amplification

by PCR, histopathology, shell-vial assay and tube culture, in this order, have a decreasing sensitivity for diagnosis of CMV infection in the intestine (27).

CMV disease has a high mortality rate in immunocompromised hosts but in immunocompetent patients CMV disease is rarely associated with death (<1%) (4). However, a meta-analysis of CMV colitis in nonimmunocompromised hosts showed a higher mortality rate among male patients older than 55, with immune-modulating comorbidities and need for surgical intervention (8). Our patient had all these unfavourable conditions, and the mortality rate for patients with CMV enterocolitis has been quoted as being as high as 71% (28).

Ganciclovir is the treatment of choice in immunosuppressed patients with CMV disease. In CMV pneumonia, CMV-specific Immunoglobulin is also important. Foscarnet and Cidofovir are effective when the virus is resistant to Ganciclovir, but they are highly nephrotoxic (4). Use of antivirals in an immunocompetent patient is controversial since the disease is normally self-limiting. In our patient, the disease was so severe that using Ganciclovir was obligatory but insufficient. The natural history and impact of this disease in such group of patients is unknown so it is not possible to establish which patients would potentially benefit from antiviral therapy. We assume that such therapies should be offered to patients with higher mortality rates such as the older ones, with immune-modulating conditions and criteria of severe disease, including the need for surgery, multiple organ disease or admission in an intensive care unit (29, 30). The overall response to Ganciclovir in severe enteritis in nonimmunosupressed patients is unknown.

In conclusion, a high index of suspicion is crucial for early diagnosis of CMV enteritis in immunocompetent patients. Endoscopic studies with biopsies are essential, and, when the initial tests are inconclusive, they must be repeated and some pathologic specimens should be sent for PCR detection, or at least for culture in Shell-vial, even if the chance of CMV infection is remote. This is the only way to achieve a diagnosis in time to initiate therapy. We think that, given the rarity and poor prognosis of this pathology, anti-viral treatment must be offered to all patients as soon as possible.

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