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Case report

Cytomegalovirus-associated protein-losing enteropathy in a healthy man

Entéropathie exsudative secondaire à une primo-infection CMV chez un adulte sain

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1. Case presentation

A 35-year-old French man presented to the emergency department with asthenia, vomiting, and global abdominal pain. The patient was a marathon runner. He did not smoke nor did he drink alcohol. He had an 18-month-old healthy daughter. He did not take any medication and had not traveled recently. His medical history was unremarkable apart from an appendicectomy 18 years earlier.

Physical examination at admission revealed fever (38 °C) and an acute abdomen. Laboratory investigations showed WBC count of 12,000 cells/mm^3 with 31% neutrophils, 54% lymphocytes, 15% monocytes, and 0% eosinophils, and a C-reactive protein (CRP) at 58 mg/L. An emergency abdominal CT-scan revealed diffuse peritoneal effusion, and thickening of both the stomach and the small bowel.

Peritonitis was suspected and an exploratory laparotomy was performed and revealed abundant peritoneal fluid. Neither perforation nor ischemia was observed. The stomach was macroscopically normal but inflammation around the duodenum was observed as well as abnormal mesenteric nodes which were sampled for pathological examination.

Two days after surgery, the patient developed massive peripheral edemas and pericardial effusion. Laboratory tests revealed severe hypoalbuminemia (11.9 g/L) and hypoproteinemia (31 g/L), normal creatinine level (0.864 mg/dL), and the absence of proteinuria on repeated exams. Functional coprological examination revealed high fecal protein exudation responsible for severe hypoalbuminemia; thus suggesting protein-losing enteropathy (PLE). Esophagogastroduodenoscopy revealed mild gastritis.

Serological tests were negative for HIV but revealed positive IgM antibodies for cytomegalovirus (CMV) (86.2 IU/mL), while CMV IgG antibodies were negative (9.98 IU/mL), (LIASON^R XL murex CMV IgM/IgG chemiluminescence-based immunoassay, Diasorin, Rome, Italy). High levels of CMV-DNA were observed in the plasma at 4.66 log IU/mL by real-time polymerase chain reaction (RT-PCR) detection, on repeated exams (CMV QS-RGQ Artus® kit, Qiagen, USA). CMV-DNA was also detected in the peritoneal fluid (3.10 log IU/mL).

A positive plasma DNA was also observed for Epstein-Barr virus (EBV) (2.48 log IU/mL), but only EBNA-IgG antibodies were positive, both VCA-IgG and VCA-IgM antibodies were not detected, suggesting EBV reactivation. Moreover, EBV-DNA was not found in the peritoneal fluid.

Pathological examination of the peritoneal biopsies revealed edema of the mesenteric tissues and omentum with no other abnormality. Bacterial cultures of the peritoneal fluid and lymph nodes were negative in the absence of antibiotic therapy.

Histology of the second part of the duodenum highlighted an excess of lymphocytes, compatible with chronic inflammatory duodenitis, and the presence of intra-nuclear CMV inclusions. The immunolabeling was also positive for CMV on 10 nuclei (Fig. 1). Gastric biopsies were normal without *Helicobacter*

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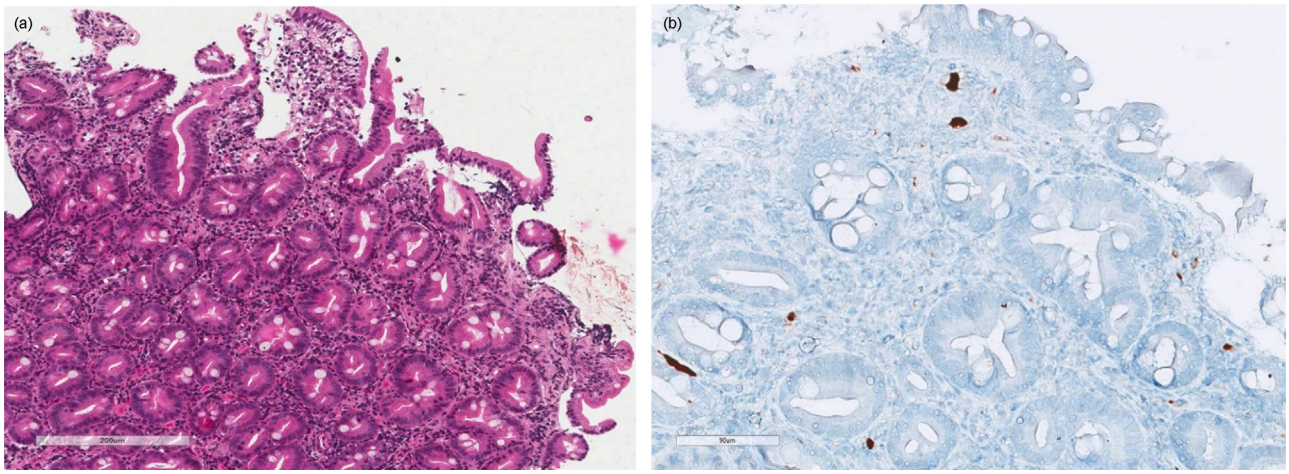

Fig. 1. Duodenal biopsy. Erosive duodenitis (a) with multiple nuclear CMV inclusions confirmed with specific immunostaining (b).
Biopsies duodénales. Duodénite érosive (a) avec de nombreuses inclusions nucléaires CMV, confirmées par immunocoloration (b).

pylori (HP) and CMV-immunolabeling was negative. The diagnosis of PLE associated with primary CMV infection was made. The patient was symptomatically treated with diuretics, painkillers, and proton pump inhibitors. He recovered spontaneously and his albumin level normalized within three months.

2. Discussion

We report the case of a young immunocompetent adult presenting with CMV-associated PLE, a disease usually described in children. The diagnosis is straightforward and was based here on the clinical presentation, biological and pathological findings. The patient presented with typical primary CMV infection, including asthenia, lymphocytosis, positive IgM antibodies, high CMV plasma viral load, and enteritis with CMV inclusions on histology. Severe hypoalbuminemia with fecal loss of protein, in the absence of any other cause of hypoalbuminemia or proteinuria, is consistent with PLE. Laparotomy was performed because of suspected peritonitis, which in retrospect was ascites secondary to hypoalbuminemia. Of note, the patient also had positive EBV-DNA in the plasma but no EBV in the peritoneal fluid and a serological profile suggesting EBV reactivation which was probably the result of the relative immunosuppression caused by the concomitant CMV infection.

Albumin loss through the gastrointestinal tract increases from less than 10% of the total body degradation of albumin in normal situations to 60% of the total albumin pool in patients presenting with severe PLE [1]. This condition results from abnormal mucosal permeability, mucosal desquamation, ulcerations, inflammation, or lymphatic obstruction. It has been described in various diseases such as inflammatory bowel disease, celiac disease, neoplasm, sarcoidosis, Zollinger–Ellison syndrome, intestinal lymphangiectasia, and cardiac diseases like constrictive pericarditis, structural heart disease, or cardiomyopathy. Some viral infections can also be involved, including CMV infection [1].

CMV-associated PLE has been more extensively reported in children and primary CMV infections should be systematically evoked in cases of PLE in children. To our knowledge, only 10 cases of CMV-associated PLE in immunocompetent adults have been reported, including ours (Table 1). Most patients were young men who presented with abdominal pain, fever, diarrhea, edemas, hypoalbuminemia, hepatic cytolysis, and often lymphocytosis. In 5/10 patients, thickening of the gastric mucosal folds and foveolar hyperplasia was described, a presentation mainly known in children as Ménétrier's disease (MD). MD is a rare protein-losing hypertrophic gastropathy characterized by the thickening of the gastric mucosal folds and foveolar hyperplasia. MD may complicate primary CMV infection but also HP infection, and rarely other viral infection such as HSV infection (one case patient in the literature) but has never been reported with EBV. The remaining five patients, including ours, had CMV-associated PLE without hypertrophic gastropathy, related to erosive gastritis with HP co-infection [2], pancolitis [3], ileitis [4], or jejunitis [5] and duodenitis in this case. Although these cases do not appear to involve the stomach, the pathophysiology of the disease is likely to be quite similar, underlining the heterogeneous clinical presentations of CMV-associated PLE.

The case patient presented here differs both in terms of clinical presentation, pathophysiology, management, and prognosis from the situation of immunocompromised hosts presenting with CMV-associated intestinal involvement which may cause severe colitis, gastritis, and proctitis. Indeed, in immunocompromised hosts, the pathological examination often reveals diffuse ulcerations and necrosis with CMV inclusions. Two main mechanisms are believed to be involved in immunocompromised hosts: an invasion of the endothelial cells by the virus, leading to endothelial ischemic injury, and an increased vascular permeability, leading to PLE. Such immunocompromised patients often require antiviral therapy with ganciclovir or foscarnet.

However, even in immunocompetent hosts, primary CMV infection may be severe, as shown here by the severity of the hypoalbuminemia. In most cases of pediatric MD disease, spontaneous recovery was prompt and no treatment was needed, but ganciclovir seems to be an alternative for severe or prolonged

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