Cytomegalovirus-associated protein losing gastropathy in an immunocompetent adult : a case report

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Abstract

Cytomegalovirus infection of the gastro-intestinal tract is frequent and may be serious in the immunocompromised patient. We report a case of cytomegalovirus infection in an immunocompetent young man who presented total food intolerance, pleural effusion and oedema as the result of severe protein losing hypertrophic gastropathy. Hypertrophic gastropathy with severe mucosal protein loss has been described in Menetrier's disease, a condition of unknown cause which involves foveolar hyperplasia of the gastric mucosa. Related hypoalbuminemia is responsible for a clinical picture of diffuse edema. In adults, the natural course of the disease is marked by a chronic course and carries a bad prognosis. In our case, the disease ran a protracted disabling course, likely shortened by ganciclovir therapy, followed by slow clinical, endoscopic and biochemical resolution after several months course. (Acta gastroenterol. belg., **2007**, 70, **296-299**).

Key words : hypertrophic gastropathy, cytomegalovirus, protein losing gastropathy.

Introduction

Hypertrophic gastropathy with severe mucosal protein loss has been described in Menetrier's disease, a condition of unknown cause which involves foveolar hyperplasia of the gastric mucosa. Related hypoalbuminemia is responsible for a clinical picture of diffuse edema (1-2).

In adults, the natural course of the disease is marked by a chronic course and carries a bad prognosis. By contrast, several cases of Menetrier like disease have been described in children, with only transient symptoms and a benign course (3-5). In the same age group an association between cytomegalovirus (CMV) infection and hypertrophic gastropathy has also been documented, in general also running a benign course of limited duration (6-9).

We report the case of an immunocompetent young adult in whom CMV infection was associated with severe disabling protein losing hypertrophic gastropathy which ran a prolong course, likely shortened by ganciclovir therapy

To our knowledge, the present report is the fifth case of CMV associated protein losing hypertrophic gastropathy in an immunocompetent host (10-14).

Case report

A 31 year old Caucasian man was admitted in emergency because of abdominal discomfort, food intolerance and asthenia of four weeks duration. One day before admission, he also complained of epigastric pain, nausea and vomiting. His previous medical history was unremarkable. Recently he had only been treated with a nasal spray and one tablet of ibuprofen for a cold. Upon admission, he appeared with an edematous aspect of the face and eyelid. Clinical examination only disclosed a slight tenderness of the epigastric region. The patient's temperature was 37.2°C.

Laboratory data showed a WBC of 11.6 10/ul (Normal : 4-10) with 64% of neutrophils (Normal : 40-75%) and 25% of lymphocytes (Normal : 20-45%). Serum protein was 4.9 g/dl (Normal : 6.4-8.3), with a normal renal function and normal liver function tests.

Two days later, the liver tests showed a slight increase : AST 51 U/l (Normal : 5-37), ALT 95 U/L (Normal : 10-50), gamma GT 65 U/l (Normal : 5-50) together a marked decrease in proteinemia which reached 3.5 g/dl with an albumin level of 2.3 g/dl (Normal : 3.5-5.0). Hypogammaglobunemia of 0.28 g/dl (Normal : 0.57-1.5) with a decreased IgG levels of 246 mg/dl (Normal : 700-1600) was noted. Urinary protein was negative.

Tests for hepatitis A, B, C, EBV and HIV were all negative. On the contrary, CMV IgM antibodies were positive (1.8 UA) while CMV IgG was negative (< 4 UA).

CMV antigenemia and urine culture for CMV were both negative.

An inversion in WBC formula was noted (neutrophils 34%, lymphocytes 50% with 8% of atypical lymphocytes). The CD4/CD8 ratio was 0.13 (Normal : 1.5-2.5) a pattern being in favour of a viral infection.

Abdominal tomodensitometry showed an important thickening of the stomach wall (18 to 25 mm) while upper gastro-intestinal endoscopy showed the presence of ulcerated and large rugal folds covered with a fibrinous material, especially in the fundic region

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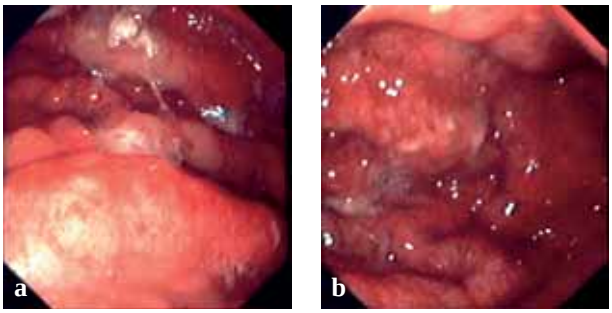

Fig. 1. — Endoscopic appearance of the gastric body showing enlarged polypoid folds (1a) covered with fibrinous membranes and a diffusely congestive mucosa together with scattered erosions (1b).

(Fig. 1a+b). At endoscopic ultrasonography, the thickening of the gastric mucosa was confirmed and there were multiples visible perigastric lymph nodes (3 to 5 mm). The evolution was marked by a weight gain of 9 kg, an accentuation of peripheral edema, the occurrence of pleural effusions and diarrhea. Fecal antitrypsin clearance was increased at 20 ml/24 h (Normal < 12) while stool analysis was normal. Sigmoidoscopy was also unremarkable as was the rectal biopsy.

Histological examination of multiple gastric staged biopsies showed an aspect of active gastritis with foveolar hyperplasia and a marked edema in the lamina propria (Fig. 2a). Direct examination (Giemsa coloration) and culture for Helicobacter pylori were negative.

There were some cytomegalic cells in the regenerative epithelium however without typical viral inclusion. One prominent intranuclear eosinophilic inclusion body was noted within an epithelial cell (Fig. 2b). Immunohistochemical staining was negative for Helicobacter pylori being positive for CMV (Fig. 2c).

The patient was first treated with parenteral nutrition because of complete food intolerance, 40 mg of esomeprazole per day and albumin perfusions. Because of the absence of clinical and chemical improvement after two weeks, a treatment with ganciclovir was initiated and maintained for a total duration of 18 days at the dose of 600 mg per day. This was followed by a progressive clinical improvement. The upper endoscopy performed after three weeks of treatment, showed a marked improvement of hypertrophic gastropathy (Fig. 3). The search for cytomegalic cells and immunohistochemistry for CMV were both negative.

Five months after the onset of symptoms, and in spite of persistent asthenia, serum protein had returned to normal levels. Upper gastro-intestinal endoscopy showed a macroscopic appearance of moderate antral gastritis and two remaining large folds in the fundic region. Serum IgM CMV antibodies disappeared, whereas the anti-CMV IgG titer was positive.

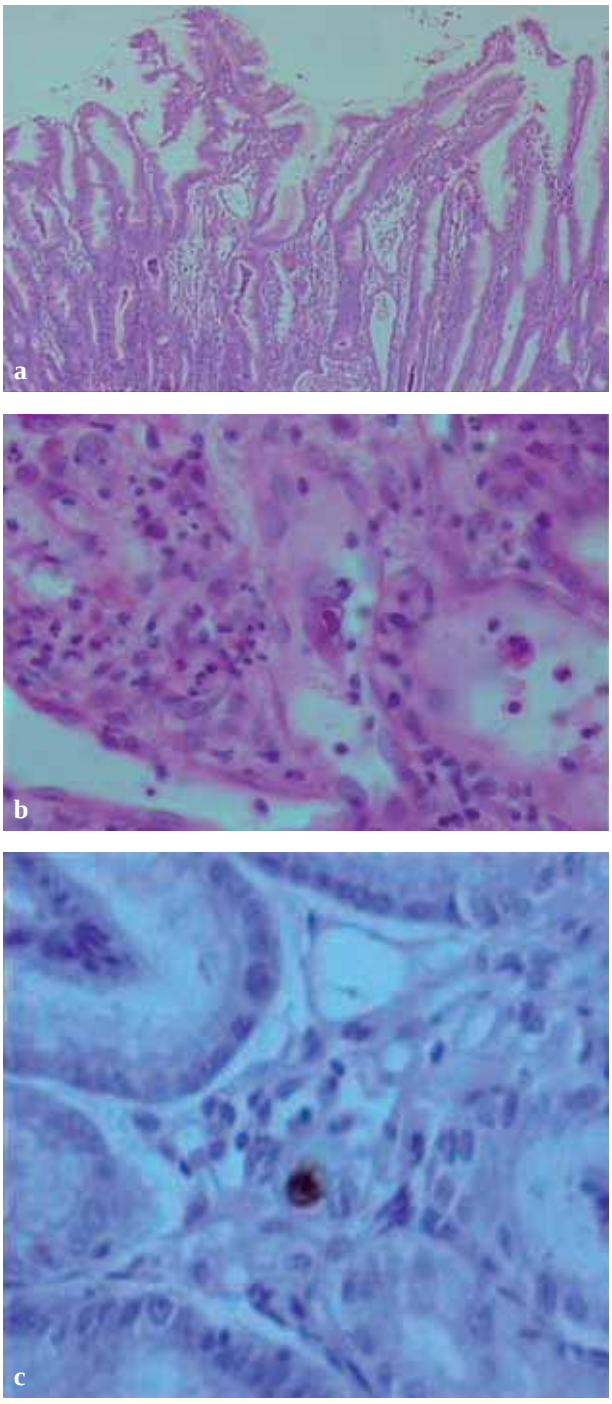

Fig. 2. — Histological appearance of the fundic biopsy showing a marked foveolar hyperplasia (2a – H&E × 40), together with typical CMV cytoplasm inclusions (2b – H&E × 200). CMV immunostaining showing a typical inclusion (2c – × 400).

Discussion

We have reported the case of a young immunocompetent adult who developed a severely symptomatic protein losing hypertrophic gastropathy which required prolong hospital stay, parenteral nutrition and ganciclovir therapy at the time of CMV primo infection.

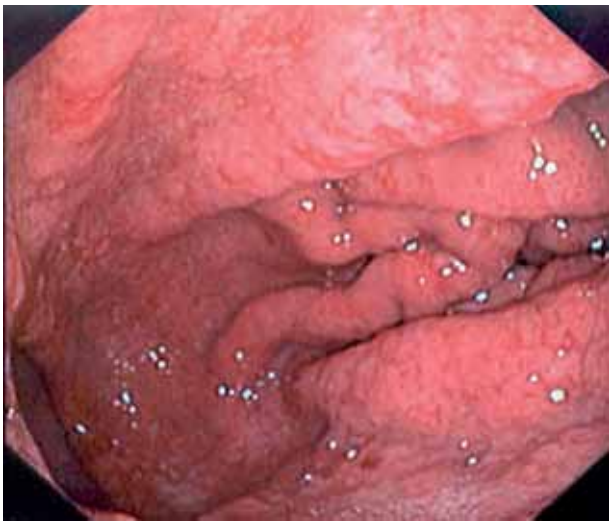

Fig. 3. — Endoscopic aspect of gastric body 3 weeks after completion of treatment showing the improvement in mucosal fold hypertrophy.

Recovery eventually occurred after a 6 months course being likely shortened by antiviral therapy. The diagnosis of CMV induced hypertrophic gastropathy was based on endoscopical, serological and histological criteria while that of protein losing enteropathy was based on biochemistry (15) and the result of fecal antitrypsin clearance.

The diagnosis of CMV infection is quite difficult because of the high frequency of asymptomatic and relapsing infections. Multiples modalities for diagnosis should be used. For immunocompromised patients, CMV isolation, CMV antigenemia and CMV DNA detection by PCR are preferred. Detection of CMV immunoglobuline antibodies (ELISA) alone is not specific of primary infection. Histologically, the presence of the distinct "owl's eye" inclusion bodies on tissue sample can be a highly specific method for determining organ involvement of CMV.

For immunocompetent patients the diagnosis of CMV infection is based on IgM antibodies, which should be positive in the majority of the patient during the symptomatic phase of the illness and the monitoring of IgG antibodies during acute infection.

Hypertrophic gastropathy with mucosal protein loss is a rare disease, first described by Menetrier in 1888. The disease is usually limited to the fundic region, is associated with reduced gastric acid secretions and protein loss from the mucosa, followed by hypoalbuminemia and peripheral edema (1-2).

Menetrier's disease is typically seen in adult man. More than 50 cases have however been reported in children. The natural history of the disease is also different in adults, and children (5). In adults the disease exhibits an insidious onset and two third require gastric resection due to hemorrhage or unremitting symptoms. On the contrary in children, the onset of the disease is abrupt and it generally turns a lasting for 5 to 8 weeks.

In adults and according to histopathologic features, patients with Menetrier's disease can be separated into two groups : those with hypertrophic lymphocytic gastritis (HLG) and those with massive foveolar hyperplasia and minimal inflammation (MFH). The term Menetrier's disease should likely been used only in patients with MFH (14).

The aetiology of the disease remains unknown. Infectious, allergic and immunologic causes have been postulated. The pathogenesis of mucosal changes seems to involve an overproduction of transforming growth factor α (TGFα) in the stomach (16).

In children, an association between Menetrier's disease and CMV infection has been described in more than twenty cases (5-9).

On the contrary, in immunocompetent adults only a few cases of protein losing gastropathy due to CMV infection have been described (10-14). Out of the 4 cases, only one presented with gastric mucosal CMV inclusions (13). None was treated by antiviral therapy.

In the immunocompromised patients, severe gastrointestinal CMV infection constitutes an indication for specific antiviral therapy. In the immunocompetent adult on the contrary treatment remains ill defined. In the reported cases, therapy includes only supportive and symptomatic medications and in two, resolution occurred after 4 and 9 months, respectively (12-10). On the contrary, in our case and due to disabling and persistent gastrointestinal symptoms a treatment with ganciclovir was instituted with an apparent clinical and morphological favourable and also likely a shortening the course of the disease.

In conclusion, CMV induced hypertrophic and protein losing gastropathy may occur in the immunocompetent adult and be the source of edema together with severe and prolonged disabling gastrointestinal symptoms. Search for histological viral signature should be performed as early since as possible the virus can readily be missed due to the scarcity of viral presence. As suggested by the rapid symptomatic and endoscopic improvement following therapy, ganciclovir is likely effective in shortening the course of the disease.

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