Ménétrier's disease and severe gastric ulcers associated with cytomegalovirus infection in an immunocompetent child: a case report

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In pediatric patients, Ménétrier's disease is an uncommon clinical entity that has been rarely described only as sporadic cases, and the etiology is unclear. These patients usually have a self-limiting clinical course. Cytomegalovirus is an important pathogen in the immunocompromised host. However, cytomegalovirus infection can be detected in non-immunocompromised children. We discuss the possible role of cytomegalovirus infection in both Ménétrier's disease and severe gastric ulcers in an immunocompetent child.

Key words: Ménétrier's disease, cytomegalovirus, gastric ulcer.

Ménétrier's disease (MD), consisting of hypertrophic gastric rugal folds complicated by extravasation of serum proteins and consequent hypoproteinemia secondary to a protein-losing gastropathy, is an unusual condition, first described by Menetrier in 1888[1]. Significant differences between adult and pediatric cases in terms of onset, presentation, and prognosis have been observed. In recent years, cases with similar clinical presentation and pathological features have been reported in children[2,3]. In contrast to classic adult MD, however, these childhood cases usually have a self-limiting clinical course, requiring only supportive management with a high-protein, low-salt diet[2]. The etiology of this disorder remains unclear, although several exogenous agents such as chemical irritants and toxins are known to produce gastric mucosal hyperplasia. The pathogenesis of cases with pediatric MD has been associated with viral infections, autoimmune diseases, and allergic process. Cytomegalovirus (CMV) infection has been documented in many of these pediatric patients in the past few decades[2,4].

Cytomegalovirus is an important pathogen in the immunocompromised host. Gastrointestinal (GI) CMV infection has been reported exclusively in the immunocompromised host[5]. However, CMV infection also shows various clinical manifestations, such as hepatitis, meningitis, and pneumonitis, in non-immunocompromised hosts. CMV infection causing multiple gastric ulcers has been very rarely detected in the GI tract of a normal host.

In this report, we present an immunocompetent pediatric case, and emphasize the association of CMV with MD and multiple gastric ulcers.

Case Report

A three-year-old girl referred from a primary care unit had a one-week history of an upper respiratory tract infection, epigastric pain, intermittent vomiting and nausea. Her symptoms were accompanied by occasional emesis, diarrhea and edema. She received non-steroidal anti-inflammatory drug, naproxen, 2 times for 2 days when edema developed; four days later she was transferred to our hospital.

At presentation, the patient's physical examination revealed a well-nourished child [weight 17.5 kg (90 percentile), height 103 cm (90-97 percentile)] with normal vital signs. Mild periorbital edema was found. Her abdomen was soft and nontender. The liver edge was palpated 2 cm below the right costal margin. No ascites was detected.

Laboratory investigations on admission revealed a white blood cell count of 12,400/mm^3 with 40% lymphocytes and no eosinophils, hemoglobin 12.7 g/dl, and platelet count 327,000/mm^3. Hypoalbuminemia (albumin 3.1 g/dl, reference range: 3.8-5) and hypoproteinemia (total protein 4.3 g/dl, reference range: 4.4-7) were also noted. The immunoglobulin (Ig) G, IgA and IgM were elevated (2210 mg/dl, normal range: 345-1236; 220 mg/dl, 14-156; and 300 mg/dl, 43-207, respectively), whereas IgE level was normal (35 IU/L, normal range: 0-170). Her serum electrolytes, blood urea nitrogen, creatinine, C-reactive protein (CRP), and liver function tests were normal. The CMV IgM antibody and CMV DNA by polymerase chain reaction (PCR) were not detected in the patient's blood, whereas CMV IgG antibody was positive. Serum transglutaminase antibodies (IgA and IgG) were negative. The urinalysis was negative for proteinuria. Neither parasites nor bacteria or viruses were detected in the stool microscopic examination. Fasting serum gastrin level was normal (158 pg/ml, normal range: 0-100).

The abdominal ultrasonography revealed mild hepatosplenomegaly. The patient underwent upper GI endoscopy, with the presumptive diagnosis of protein-losing enteropathy. Hypertrophic rugal folds were seen at the gastric body, consistent with MD, as well as multiple gastric ulcers and superficial hemorrhagic erosions at antrum and corpus part of the stomach (Fig. 1). Endoscopic appearance of the duodenal mucosa was unremarkable. Histologic examination of the gastric corpus biopsy revealed superficial mucosal erosions, regeneration, prominent foveolar hyperplasia, and cystic elongation of the gastric glands (Fig. 2). The lamina propria showed a mixed cellular infiltrate and edema. Prominent intranuclear eosinophilic inclusion bodies were noted within multiple gastric glandular cells, consistent with CMV infection (Fig. 3). Antral biopsies were negative for *Helicobacter pylori* both histologically and by direct rapid urease testing.

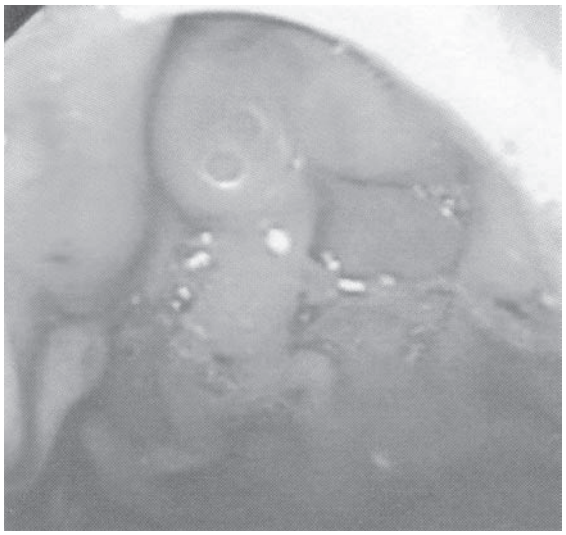

Fig. 1. The hypertrophic rugal folds, multiple gastric ulcers and superficial hemorrhagic erosions at antrum and corpus part of the stomach were visualized.

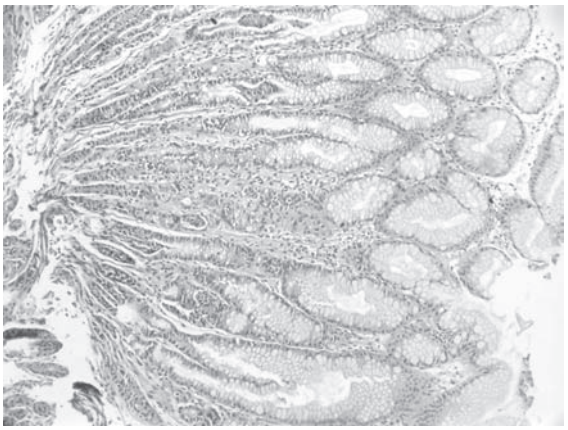

Fig. 2. The prominent foveolar hyperplasia and cystic elongation of the gastric glands in the gastric body and the lamina propria showed a mixed cellular infiltrate and edema.

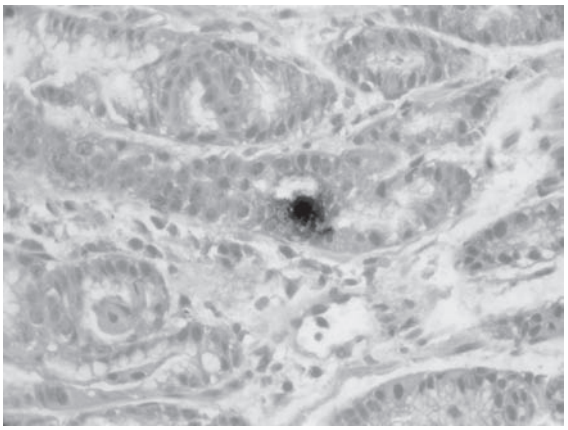

Fig. 3. Cytomegalic inclusion body was within gastric glandular cell.

Treatment consisted of fluid and salt restriction, high protein diet, and a proton pump inhibitor (lansoprazole). She did not receive antiviral agent as no definite immunodeficiency status was observed. During the six days of follow-

up at the hospital, she remained afebrile, and edema spontaneously resolved. At the time of discharge, only lansoprazole therapy was given. Her condition gradually improved under lansoprazole, with complete endoscopic, histologic and laboratory recovery after 2.5 months. She had no further symptomatic recurrences in the subsequent six months.

Discussion

Ménétrier's disease in children resembles the clinical, radiologic, and histologic features of the adult form; however, there are important differences, especially regarding the course of the illness. In contrast to adults, the initial age of the symptoms in children is in the extremely early period of life. Although generalized edema is seen in less than 25% of adult cases, it is the most common finding in children[2]. While in two-thirds of adult patients, the clinical course is usually unfavorable, with partial or total gastrectomy becoming necessary because of the persistent symptoms, the pediatric form is generally benign and has a self-limiting clinical course. It was reported that only 10% of children required surgery and no malignancy complicating the disease was detected[6]. Our patient also showed complete endoscopic, histological and laboratory recovery after 2.5 months and she did not experience any symptomatic recurrences in the subsequent six months.

Multiple etiologic causal agents of MD have been suggested, including chemical irritants; toxins; dietary factors; neuro-emotional, endocrinologic, immunologic and anatomic abnormalities; allergy; autoimmune disorders; and infectious agents such as CMV and *Helicobacter pylori*. There is no definitive evidence confirming CMV as the etiologic agent in MD in pediatric cases and the diagnosis is based on urine culture and serological studies[7,8]. The serological status for CMV was unknown in these patients. It is not known whether acute infection with CMV produces the characteristic gastric rugal hypertrophy seen in MD at the time of endoscopy. The problem in diagnosis is the fact that the CMV infection may occur as a result of a primary infection, reactivation of a latent infection or a reinfection[3]. CMV excretion may continue intermittently for months to years after primary infection, even in normal children. This may be exacerbated by hypogammaglobulinemia present during a protein-losing enteropathy. Thus, the diagnosis of CMV-associated GI lesions remains speculative. Some investigators consider CMV to be the primary pathogen[9], and have suggested cytomegalic vasculitis to be the major pathogenic mechanism of mucosal damage[10]. Another possible mechanism caused by CMV infection is the production of abnormal local transforming growth factor (TGF)-alpha, a polypeptide that stimulates cell proliferation of gastric mucosa, inhibits gastric secretion, and enhances mucus secretion[11]. A possible role of TGF-alpha was suggested in adult MD[12], but was not investigated in acute hypertrophic gastropathy in children.

The presence of characteristic inclusion bodies in hematoxylin and eosin-stained histological samples, especially for samples from the GI tract, is diagnostic of infection, but is not particularly sensitive given the fact that tissue culture may represent the most sensitive method of CMV diagnosis[13]. Furthermore, the intranuclear CMV inclusions, which were demonstrated in the early stage of the disease, could not be found in the late healing stage[5]. Direct histological evidence was first presented in 1993 by Kovacs et al.[14], who described two children with typical CMV inclusion bodies in gastric biopsy specimens. In a review of the literature[3], an association with CMV was found in 26 of 56 pediatric cases of MD, whereas direct evidence of gastric CMV involvement by visualization of characteristic inclusion bodies in MD was shown in 16/56 patients.

Recent advances in adults with MD showed that patients can be separated into two groups according to histopathologic features: "hypertrophic lymphocytic gastritis" and "massive foveolar hyperplasia (MFH) with minimal inflammation"[15]. Usually, pediatric cases with MD are similar to adult MFH[12]. This patient's gastric histopathological findings revealed prominent foveolar hyperplasia, regeneration, and cystic elongation.

Recent studies indicate that PCR may be sensitive for early diagnosis of active CMV infection in immunocompetent patients[16]. The direct detection of CMV in nucleic acids by in situ hybridization or of viral antigens by immunocytochemistry using monoclonal antibodies is more sensitive and specific, and is as sensitive as viral culture[17]. Recently, Xiao et

al.[4] demonstrated overexpression of TGF-alpha and TGF-beta receptor II in gastric specimen in an adult with MD. Electron microscopy is limited by the number of infected cells in gastric tissue and does not permit discrimination between CMV and other related viral agents[18].

Impaired blastogenic response, hypersensitivity reactions, and cell-mediated immunity have been included among the immunologic abnormalities in children with MD. The presence of increased numbers of eosinophils in peripheric blood cells suggests either a hypersensitivity or coinfection with an organism that induced eosinophilia. The abnormal helper:suppressor T lymphocyte ratio noted in three of the pediatric cases with MD and the increased absolute number of suppressor cells are changes that occur with acute CMV infection[14]. The presence of decreased immunoglobulins resulting from the protein-losing enteropathy adds to this immunosuppression. In our patient, no lymphocytopenia or hypogammaglobulinemia was detected.

Gastrointestinal (GI) CMV infection most often afflicts immunocompromised hosts. This infection may involve the GI tract as part of the spectrum of disseminated infection in immunocompromised cases. However, a few cases in non-immunocompromised hosts were recently reported[5]. Colon, stomach and esophagus are the most frequent sites of CMV infection in the immunocompromised host, whereas the stomach is the most frequently reported site of GI CMV infection in the non-immunocompromised host[5,19]. GI disease has occurred in association with perinatal CMV infection in a few immunocompetent infants[20]. Patra et al.[19] showed that the prevalence of CMV inclusion was 0.9% in the GI mucosal biopsies from an unselected group of patients. Ulcerated lesions were detected in 32 of the 54 patients with GI CMV infection, whereas 70% of the 37 immunocompromised individuals and 35% of the 17 patients with normal immune status showed ulcers.

Pediatric cases with MD typically follow a benign and self-limited course, with recovery time ranging from weeks to months. Our patient was managed conservatively, without a specific therapy, with ganciclovir, and fully recovered within 10 weeks of presentation. Faure et al.[11] showed that despite the disappearance of CMV during ganciclovir therapy, clinical and histologic manifestations did not improve. However, Hoffer et al.[21] showed improvement of symptoms including hypoalbuminemia, severe edema, and oliguria after treatment with intravenous ganciclovir within five days in a two-year-old girl with CMV-associated MD.

Reports with non-steroidal anti-inflammatory drugs (NSAIDs) indicate that nonselective cyclooxygenase (COX)-1 inhibitors, including aspirin, are by far the most common causes of drug-induced mucosal injury of the stomach in children, even at low doses of NSAID. The mechanisms are multifactorial (i.e., increased platelet activating factor and oxygen free radicals, platelet dysfunction, enhanced mast cell histamine release, and increased mucosal capillary damage), but most likely involve inhibition of COX in the mucosa of the stomach, thereby reducing mucosa-protective prostaglandins. Risk factors for developing NSAID-induced gastroduodenal ulcers include advanced age, past history of ulcer, use of concurrent corticosteroids, higher NSAID doses, multiple NSAID use, anticoagulant use, and serious systemic disorder[22]. In our patient, these risk factors were not found, and she had ingested only two doses of naproxen. Therefore, we were less inclined to consider NSAID-induced gastric ulcer in our case, but this cannot be ruled out.

To our knowledge, there is no report associating CMV infection and MD and severe gastric ulcers in an immunocompetent child. This is the first such reported case.

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