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Case Report

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Co-Infection with Cytomegalovirus and *Helicobacter pylori* in a Child with Ménétrier's Disease

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Ménétrier's disease is a rare protein-losing gastropathy characterized by hypertrophic gastric fold, foveolar hyperplasia, and hypoproteinemia with resulting peripheral edema. It is clinically evident as nonspecific gastrointestinal symptoms, including abdominal discomfort, nausea and vomiting, abdominal pain, weight loss, diarrhea, and edema. Pediatric Ménétrier's disease usually has an insidious onset and progressive, chronic clinical course and it spontaneously resolves in weeks or months. The pathogenesis of Ménétrier's disease is not clearly understood. Ménétrier's disease is thought to be associated with some gastric infections. But the cause of Ménétrier's disease is unknown, an association with cytomegalovirus (CMV) and *Helicobacter pylori* has been suggested. In Korea, We present the first a case of pediatric Ménétrier's disease with positive evidence of CMV and *H. pylori*. **(Pediatr Gastroenterol Hepatol Nutr 2013; 16: 123～126)**

Key Words: Ménétrier's disease, Cytomegalovirus, *Helicobacter pylori*

INTRODUCTION

Ménétrier's disease is an uncommon protein-losing hypertrophic gastropathy in childhood. It is clinically evident as nonspecific gastrointestinal symptoms, including abdominal discomfort, nausea and vomiting, abdominal pain, weight loss, diarrhea, and edema [1]. Upper endoscopy reveals giant gastric fold and histologic findings show foveolar hyperplasia and cystically dilated gastric glands. The pathophysiology of Ménétrier's disease is still undetermined [2].

Since the first reported case of Ménétrier's disease in 1888 [3] ,50 to 60 cases have been reported to date worldwide [4]. In Korea, a case of Ménétrier's disease was reported in 1967 [5] and the first pediatric case was reported in 2001 [6]. After that Ménétrier's disease association with cytomegalovirus (CMV) infection was the cases, but we present the first case of childhood Ménétrier's disease in which co-infection CMV and *Helicobacter pylori*.

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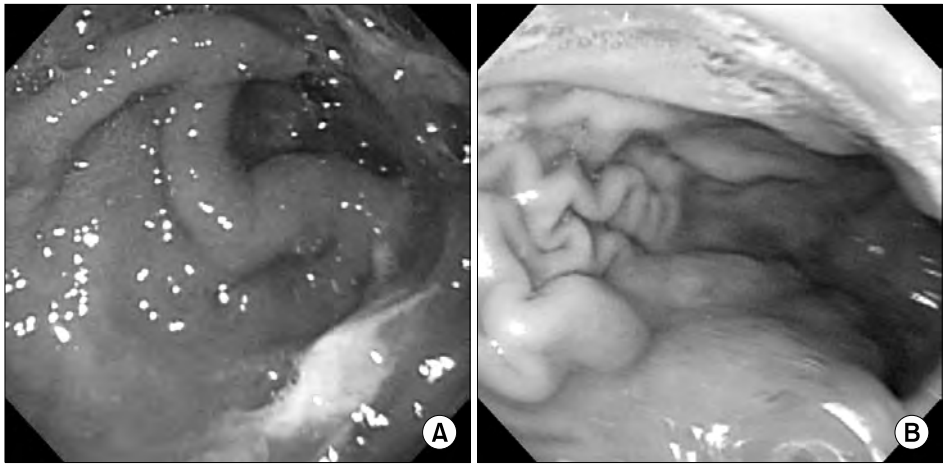

Fig. 1. Endoscopic findings of the present case. (A) Initial esophagogastroduodenoscopy shows enlarged erythematous gastric folds, and exudation in entire stomach. (B) Seven weeks after discharge, endoscopic findings were nearly normalized.

CASE REPORT

A 3-year-old boy visited the emergency department with an 11-day duration of anorexia, vomiting, and facial and peripheral edema. He had no previous history of medical problems, surgeries, medication use, or allergies. Family history was not notable. His body temperature was 36.6°C, heart rate was 72 beats/min, respiratory rate was 24/min, and blood pressure was 88/68 mmHg. Physical examination revealed swelling of the face, lower extremities, and scrotum. Breathing sounds were clear bilaterally without crackles or wheezing. His bowel sounds were normoactive and abdominal palpation showed no tenderness or hepatosplenomegaly. Initial complete blood cell count, electrolytes, blood urea nitrogen, creatinine, transaminases and cholesterol were unremarkable. But, serum protein and albumin were decreased (2.9 g/dL and 1.9 g/dL, respectively). The patient displayed no laboratory evidence of acute or chronic inflammation (erythrocyte sedimentation rate 2 mm/hr; C-reactive protein 0.08 mg/dL). No urinary protein was detected in urinalysis. At the second day of admission, esophagogastroduodenoscopy with gastric biopsy was performed, which revealed enlarged erythematous gastric folds in the entire stomach (Fig. 1A). The diagnosis was protein-diminishing gastropathy with giant rugae (i.e., Ménétrier's disease). Along with the gastric biopsy and in-situ hybridization of specific viruses including CMV, Epstein-Barr virus and herpes simplex virus, we also performed an ^{13}C urea breath test. The ^{13}C urea breath test was positive($>2.0‰$: cut-off value $2.0‰$), prompting a 2-week regimen of lansoprazol, amoxicillin, and clarithromycin for *Helicobacter pylori* eradication. During the treatment, we noted the expected positive finding of recent CMV infection. Serologically, CMV immunoglobulin M was positive (IgM 1.19). A subsequent blood CMV polymerase chain reaction was positive and CMV antigenemia also was positive (18/200,000 white blood cells).

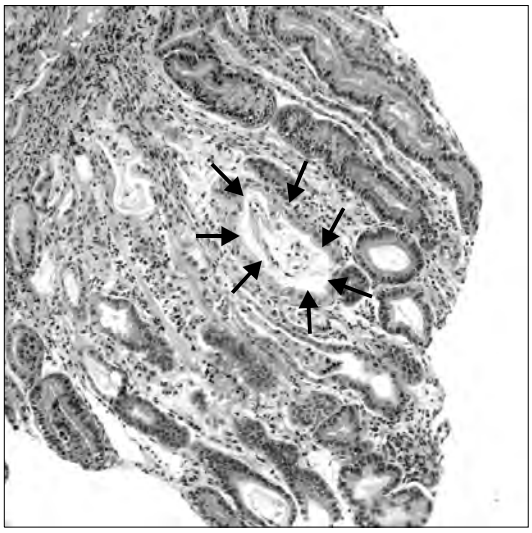

Fig. 2. A gastric biopsy shows the proliferation of the gastric glands (surrounded by arrows) and cystic dilatation without increase of granulocytes or eosinophils (immunostain, ×400).

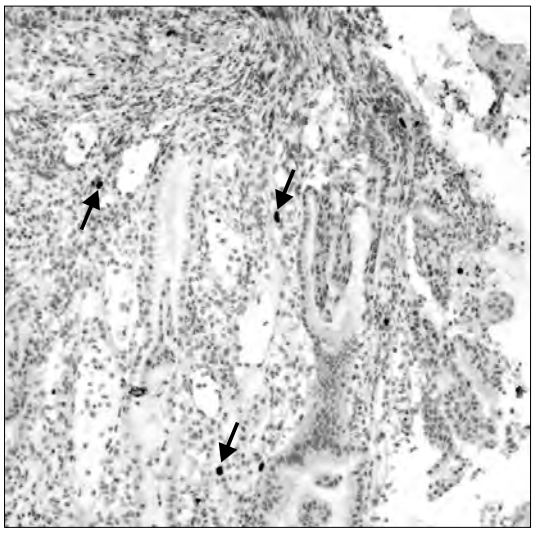

Fig. 3. Cytomegalovirus (CMV) intranuclear inclusions (block dots indicated by arrows) were detected from gastric tissue using in-situ hybridization (H&E stain, ×400).

Histologically, a gastric biopsy showed the proliferation of the gastric glands and cystic dilatation without increase of granulocytes or eosinophils, consistent with common histologic findings of Ménétrier's disease (Fig. 2). In addition, CMV intranuclear inclusions were detected from gastric tissue using in-situ hybridization (Fig. 3). *H. pylori* was not detected in Giemsa-stained sections. Although not totally normalized, the patient's appetite, peripheral edema, and hypoalbuminemia improved sufficiently to allow discharge after 8 days of supportive care such as fluid restriction, albumin infusion, diurectics, high-protein diet. Seven weeks after discharge, follow-up esophagogastroduodenoscopy with biopsy and ^{13}C urea breath test were done. The patient did not complain of any notable symptoms and endoscopy was nearly normalized, both grossly and microscopically (Fig. 1B). But the ^{13}C urea breath test was still positive despite 2 weeks of *H. pylori* eradication treatment.

DISCUSSION

Ménétrier's disease is a rare protein-losing gastropathy characterized by hypertrophic gastric fold, foveolar hyperplasia, and hypoproteinemia with resulting peripheral edema. Pediatric Ménétrier's disease usually has an insidious onset and an overall benign course that can be managed with supportive therapy and it typically spontaneously resolves in weeks or months [7].

Ménétrier's disease is thought to be associated with some gastric infections; in pediatric cases, CMV is found frequently [8]. In 1993, Occena et al. [9] reviewed reported pediatric Ménétrier's disease cases and described the association with CMV in 70% (19 of 27) of cases. Subsequently, other reports describing CMV in association with Ménétrier's disease appeared (17 of 22, since 2000 [2,5,6,10-12]. Two Korean cases reported in 2001 and 2004 were also associated with CMV infection in preschool-age boys [6,13]. In adults, *H. pylori* is thought to have a role in Ménétrier's disease, rather than CMV [14].

The pathogenesis of Ménétrier's disease is not clearly understood. Transforming growth factor-α, a ligand to epithelial growth factor receptor, may play a role due to its local growth-stimulating effect via epithelial growth factor receptor binding, leading to foveolar hyperplasia and hypertrophic gastropathy in mice [15]. This specific mediator is over-expressed in adults and children with Ménétrier's disease [16]. The proposed pathogenic mechanism is mucosal damage caused by infection with CMV or *H. pylori*, which may involve the production of abnormal local transforming growth factor-α, which in turn stimulates cell proliferation of gastric mucosa, inhibits gastric secretion, and enhances mucus secretion [17].

Tokuhara et al. [18] reported a case of pediatric Ménétrier's disease involving co-infection with CMV and *H. pylori*. After eradication therapy for *H. pylori*, the thickened gastric folds resolved. The authors concluded that this case of pediatric Ménétrier's disease was secondary to *H. pylori* infection rather than CMV infection. Three years later, in 2010, Iwama et al. [19] reported another CMV and *H. pylori* co-infection in Ménétrier's disease case. They suggested that *H. pylori* had a causative role rather than CMV. In these cases of pediatric in Ménétrier's disease involving co-infection with CMV and *H. pylori*, erad-

ication of *H. pylori* contributed to improvement of not only endoscopy finding, but also clinical symptoms [14]. Because *H. pylori* was thought to be causative pathogen as well as CMV in our case, *H. pylori* eradication was tried. Although follow-up ^{13}C urea breath test was not changed to negative, patient's symptoms was improved and the findings of esophagogastroduodenoscopy were normalized.

One interesting thing about Ménétrier's disease is that all the co-infection cases were Asian pediatric cases, as far as we know. This may reflect the exposure pattern of CMV and *H. pylori* in eastern Asia. Unlike Europe and western countries, the high prevalence of these infections persists in Asia and developing countries [20]. Such higher prevalence of these microbes may increase the chance of infection in children and more commonly result in such co-infection cases.

In summary, we describe another Ménétrier's disease with CMV and *H. pylori* co-infection, which is a very rare case in childhood. The present case information might be helpful for better understanding the nature and course of the disease.

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