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Diagnosis of Cytomegalovirus Infection in Pediatric Menetrier's Disease by In Situ Hybridization

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A previously healthy 7-year-old boy presented with a protein-losing enteropathy secondary to a hypertrophic gastropathy. The diagnosis of cytomegalovirus (CMV) infection was established by detection of CMV inclusion bodies in gastric biopsy samples and by hybridization with a CMV probe. This report further strengthens the association between CMV and pediatric Menetrier's disease.

Hypertrophic gastropathy, also known as Menetrier's disease, is an unusual cause of protein-losing enteropathy in children and adults. The eponym is derived from the name of the author of its first description, published in 1888 (9).

The course of the disease varies considerably between adults and children. In childhood, the course is typically benign and brief. In adults, the course is more often severe, with persistent protein-losing enteropathy which may require gastrectomy (12, 13). The cause of Menetrier's disease remains uncertain; infectious (2, 5, 7, 8, 10), allergic (1, 11), and immunologic (3, 14) causes have been postulated. In this study, the association of cytomegalovirus (CMV) infection with a protein-losing enteropathy secondary to hypertrophic gastropathy was demonstrated by in situ hybridization.

Case report. A previously healthy 7-year-old African-American boy was admitted with abdominal pain, abdominal distention, and facial edema. His initial symptoms of facial swelling and decreased appetite began 1 week before admission. He had no fever or change in bowel habits.

On physical examination, he was found to be well developed and afebrile. His blood pressure was 94/74. His weight was 27 kg (50 to 75th percentile). His height was 128 cm (50 to 75th percentile). He had mild periorbital and nonpitting lower-extremity edema. His abdomen was soft, nontender, distended, and tympanitic, with a prominent fluid wave and active bowel sounds. He had a transient, blanching, papular erythematous truncal skin rash.

His laboratory tests revealed a hemoglobin level of 150 g/liter (15.0 g/dl) and a leukocyte count of 11.7×10^9/liter, with 44% neutrophils, 3% immature neutrophils, 35% lymphocytes, 9% monocytes, and 6% eosinophils. He had an albumin level of 12 g/liter (1.2 g/dl) and a total serum protein level of 34 g/liter (3.4 g/dl).

We excluded urinary protein loss as a cause of the hypoalbuminemia. His liver synthetic function was assessed; the prothrombin time was 11.4 s (normal limits, 10.7 to 12.9 s). A fecal α_1-antitrypsin level of 6.9 mg/g (normal, <2.0 mg/g) was consistent with enteric protein loss. To determine whether colitis or a parasitic infection was causing the protein-losing enteropathy, stool was examined for fecal leukocytes and for ova and parasites; both tests were negative. After an abdominal ultrasound examination confirmed a moderate amount of ascites, an abdominal paracentesis was performed. The results were as follows: glucose, 5.5 mmol/liter (100 mg/dl); protein, 6 g/liter (0.6 g/dl); albumin, <10 g/liter (<1 g/dl); lactate dehydrogenase, 19 U/liter; triglycerides, 0.85 mmol/liter (75 mg/dl); erythrocytes, 100/mm^3, and leukocytes, 90/mm^3, with 3% neutrophils, 40% lymphocytes, 37% monocytes, 3% eosinophils, and 17% macrophages.

To determine the location of enteric protein loss, an upper-intestinal endoscopy was performed; it revealed giant edematous gastric folds throughout the fundus and body, with areas of superficial punctate erosions and gelatinous secretions (Fig. 1A). The gastric antrum was mildly edematous and erythematous. The duodenum appeared to be normal. Histologic examination of the gastric body and fundus showed hyperplastic gastric glands, with a marked increase in the cellularity of the lamina propria, including neutrophils, eosinophils, plasma cells, and lymphocytes (Fig. 1B). A cell with intranuclear and intracytoplasmic inclusions, characteristic of CMV infection, was seen (Fig. 1C). In addition, in situ hybridization with a DNA-specific probe (Enzo Diagnostics Inc., New York, N.Y.) was positive for CMV (Fig. 1D). No signal was seen in the control sample, which lacked the CMV-specific probe.

After the diagnosis of CMV-associated hypertrophic gastropathy was established, the patient was monitored as an outpatient, having been placed on a high-protein diet. Four weeks after his hospital discharge, his facial edema and ascites had resolved. At that time, his albumin level was 36 g/liter (3.6 g/dl) and his total serum protein level was 62 g/liter (6.2 g/dl). He had no further symptomatic recurrences in the subsequent 6 months.

An association with CMV has been found in 26 of 56 pediatric cases of Menetrier's disease (2, 5, 7, 8, 10). However, in the majority of these cases, the association of CMV was established by either urine culture or serology. Direct evidence of gastric CMV involvement in this disease has been shown, by either culture, antigen detection, or visualization of characteristic inclusion bodies, for 16 patients. We detected gastric CMV infection in a patient with Menetrier's disease by in situ hybridization.

Infection with CMV is ubiquitous. While isolation of CMV by urine culture or serology establishes previous infection, it does not identify CMV as the causal agent of acute disease. The difficulty results from the fact that CMV infection may be primary, a reactivation of a latent infection, or a reinfection with a different antigenic strain (15). There is persistent excretion of CMV in nongastric cultures for months to years after primary infection, making these cultures unreliable. Serology may be difficult to interpret and may cause either false-positive or false-negative associations. There is fluctuation of CMV antibody levels in healthy children (4); this may be exacerbated by hypogammaglobulinemia present during a protein-losing

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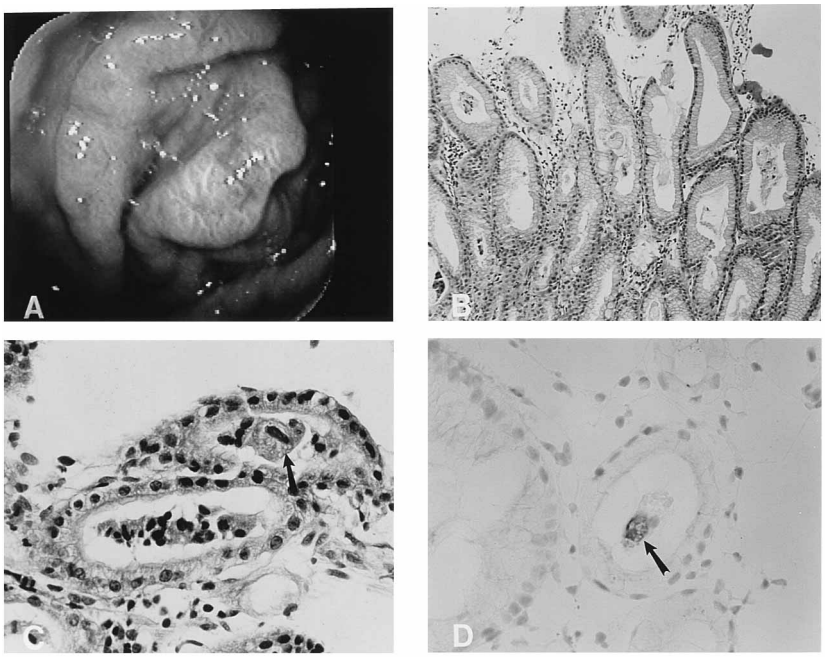

FIG. 1. (A) Endoscopic view (EG 2901 endoscope; Pentax Precision Instrument Corp., Orangeburg, N.Y.) of thickened gastric folds with punctate erythematous erosions. (B) Micrograph (magnification, ×73) showing irregular hyperplastic gastric glands with increased luminal secretions. In addition, an inflammatory infiltrate composed predominantly of neutrophils and plasma cells is seen. (C) High-power micrograph (magnification, ×292) showing a cell with a large intracytoplasmic inclusion body and multiple intranuclear inclusions (arrow). (D) High-power micrograph (magnification, ×292) showing a CMV-positive cell (arrow) by in situ hybridization.

enteropathy. Even CMV immunoglobulin M, usually indicative of acute disease, may reappear during reactivation of a latent infection due to a non-CMV primary illness (4). Direct evidence of gastric infection can be confirmed only by gastric culture, by detection of CMV nucleic acids by in situ hybridization, or by detection of viral antigens by immunocytochemistry with monoclonal antibodies.

In our study, in situ hybridization as well as the presence of intranuclear inclusions provided diagnostic evidence of CMV infection. The reported specificity of the DNA hybridization kit we used is 94 to 100% (6); furthermore, using this kit, we have not seen cross-reactivity with other herpesviruses. Although in situ hybridization and immunocytochemistry have been proposed to be more sensitive (15), in a previous study, neither in situ hybridization nor immunocytochemistry detected gastric CMV infection in two cases of pediatric Menetrier's disease (10). In one of these cases, the gastric culture, the urine culture, and serology were positive for CMV. In the second case, the patient's urine culture was positive for CMV.

Our report provides further evidence of a causal relationship between CMV infection and pediatric Menetrier's disease. We believe that in situ hybridization with a CMV-specific probe may offer an additional highly specific tool to establish the presence of active CMV infection. The predictive value of in situ hybridization for detecting CMV in pediatric Menetrier's disease awaits prospective validation. As no single test has been shown to detect gastric CMV in all cases in which it is associated with this disease, we recommend the use of several approaches to establish the diagnosis of CMV infection in cases of suspected pediatric Menetrier's disease.

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