Pathologic Quiz Case

Edema and Diarrhea in a 2-Year-Old Boy

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A 2-year-old African American boy was admitted to the hospital for persistent diarrhea, emesis, anorexia, and a 2.7-kg weight loss during 1 month. The patient had a past medical history significant for recurrent sinus infections treated with antibiotics for 2 months prior to admission. Significant findings on physical examination included an erythematous oropharynx consistent with his upper respiratory infections. There were decreased breath sounds at the base of the left lower lung, 1 to 2+ pitting edema on both lower extremities up to the knee, and small hemorrhoids on rectal examination. Abdominal examination revealed normal bowel sounds; no distention, tenderness, hepatosplenomegaly, or mass; and a fluid wave could not be elicited. Laboratory tests revealed a white blood cell count of 11 $\times$ $10^3/\mu L$ (reference range, 5–15 $\times$ $10^3/\mu L$); hematocrit, 50% (reference range, 33%–40%); hemoglobin, 17 g/dL (reference range, 11–14 g/dL); and platelets, 648 $\times$ $10^3/\mu L$ (reference range, 150–375 $10^3/\mu L$). Albumin was measured at 2.8 g/dL (reference range, 3.7–5.7 g/dL) with a total protein level of 3.3 g/dL (reference range, 5.7–7.5 g/dL). Immunoglobulin levels included immunoglobulin (Ig) G of 111 mg/dL (reference range, 492–1269 mg/dL); IgM, 29 mg/dL (reference range, 23–137 mg/dL); and IgA, less than 20 mg/dL (reference range, 49–204 mg/dL). Stool α_1-antitrypsin was slightly elevated at 0.73 mg/g (reference value, $<$0.62 mg/g). Upper gastrointestinal endoscopy revealed prominent folds in the gastric fundus (Figure 1). Gastric biopsies showed pits and foveolar hyperplasia (Figure 2).

What is your diagnosis?

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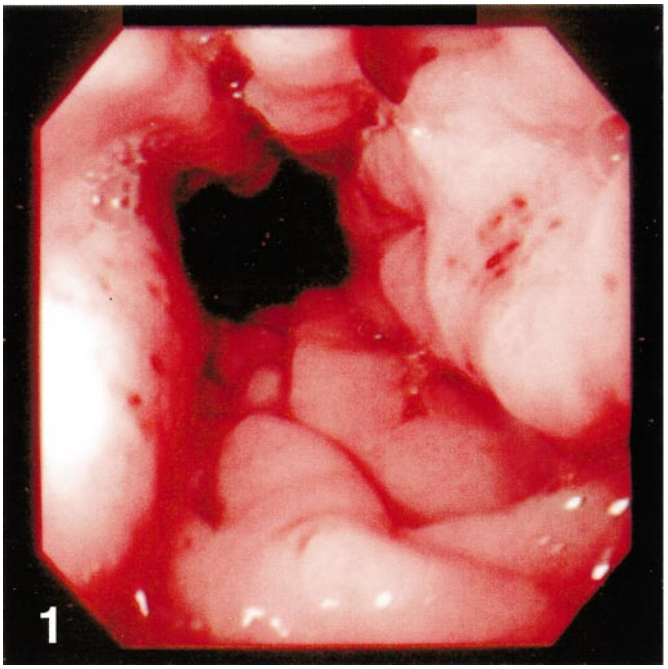

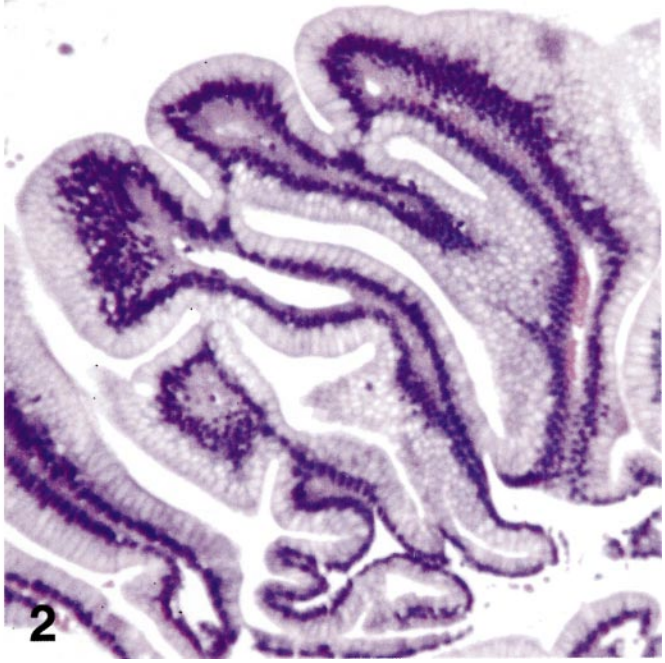

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Pathologic Diagnosis: Menetrier Disease With Cytomegalovirus Gastritis

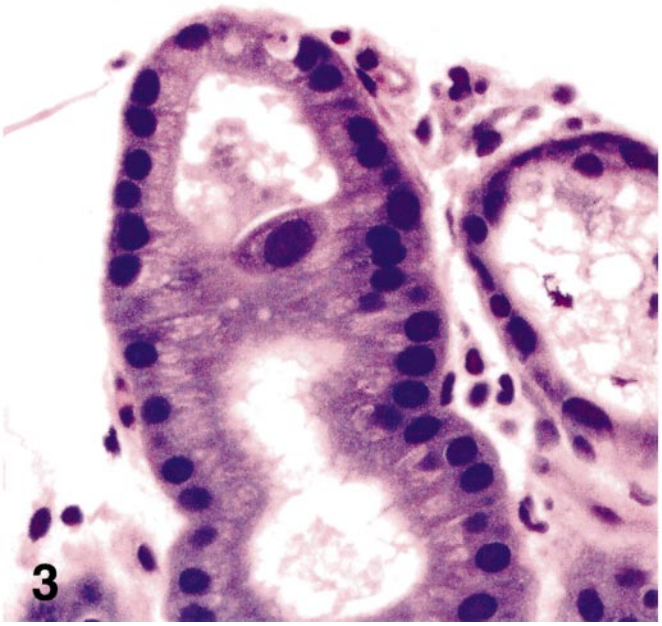
Menetrier disease is a form of hypertrophic gastropathy involving foveolar hyperplasia or hyperplasia of the surface and glandular mucous cells with elongated pit formation.[1–6] These cells replace the normal chief and parietal cells, leading to excessive mucous secretion with little to no acid secretion and subsequent loss of excessive amounts of protein in the mucus with consequent hypoalbuminemia and peripheral edema.[1] Inflammatory cells may or may not be present, and eosinophilia has been observed in up to 61% of cases.[3] Rugal folds are grossly enlarged in a cerebriform pattern, secondary to mucosal hypertrophy. Diagnosis can often be made with contrast radiography, as barium fills the pockets of the dramatically enlarged gastric folds, creating a characteristic image.[2,3] Involvement can be local or can include the entire stomach, but the gastric body and fundus are most often involved, while the antrum is usually spared.[1,4]

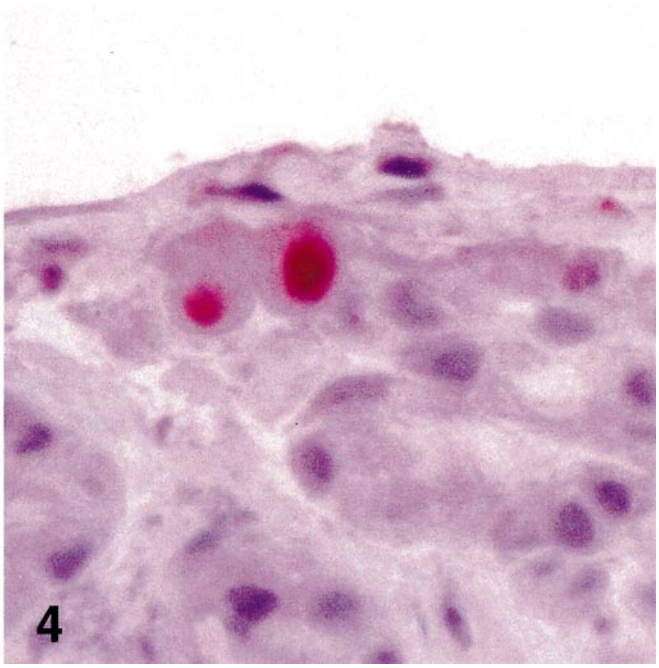
The disease is typically seen in adult men, but more than 40 cases have been reported in children.[1,3–7] Clinical presentation of Menetrier disease in children includes severe edema, vomiting, abdominal pain, anorexia, pleural effusions, and ascites.[2,4] Anemia secondary to erosive blood loss is rare. The adult patient will have similar symptoms along with hematochezia and anemia, but edema (as a result of hypoalbuminemia) is uncommon. The duration and onset of disease is also different in children: an abrupt, self-limited course lasting 5 to 8 weeks is typical. Adults have an insidious onset of disease, which can go undiagnosed for years.[3,5] Only 10% of pediatric cases require surgery, whereas two thirds of adults require gastric resection secondary to hemorrhage or unremitting symptoms.[3]

On a biochemical level, it appears that endothelial growth factor is increased and is responsible for the morphologic changes of the gastric mucosa seen in Menetrier disease.[7] An experimental treatment designed to neutralize the endothelial growth factor receptor relieved symptoms of Menetrier disease in one patient.[7] Also, it is believed that transforming growth factor α (TGF-α) mediates the hyperplastic gastric mucosal changes seen in this disease.[5] Transforming growth factor α is produced by normal gastric epithelium and stimulates gastric epithelial cell proliferation and mucin secretion, and inhibits parietal cell acid production, which is characteristic of Menetrier disease. Transgenic mice that overexpress TGF-α appear to develop Menetrier disease.[8] This polypeptide has also been identified in elevated levels in both adults and children with disease.[5]

Focal gastric hyperplasia has been associated with several stimuli, including toxins, dietary factors, immunologic abnormalities, autoimmune disorders, allergic reactions, and infectious agents.[4] A pattern of autosomal dominant inheritance has been suggested in a few cases.[4] There does not appear to be a connection between *Helicobacter pylori* and Menetrier disease, as the microorganism causes gastritis without hypoproteinemia. Eradication therapy for *H pylori*, however, does appear to resolve symptoms of protein-losing hypertrophic gastropathy.[4,9] *Campylobacter* and Herpes gastritis have also been weakly associated.[4]

A consistent association first reported in 1971 in nearly every pediatric case, but not in adults with Menetrier disease, is cytomegalovirus (CMV) infection.[3–5] While many authors conclude that there appears to be a causal relationship between CMV and pediatric Menetrier disease, it has been argued that the association is only circumstantial, because CMV infections are ubiquitous in children.[4,5] However, investigators have not determined whether the infection with CMV is acute, reactivated, or latent in these children. Sferra et al[5] found that CMV was not found in pediatric controls (children with other forms of gastritis or prostaglandin-induced antral hypertrophy), while it was present in their patients with Menetrier disease, suggesting that CMV is not incidental or commensal within the inflamed or damaged mucosa of children. They also





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found that the histologic localization of CMV in Menetrier disease differed from that in opportunistic infection in immunocompromised individuals. Cytomegalovirus is found exclusively within the gastric mucosal epithelial cells in Menetrier disease, as shown in Figure 3. It is also seen in endothelial and muscle cells of immunocompromised patients. In cases of Menetrier disease in which CMV was not found, it is likely that not all possible diagnostic procedures were used.[4] Cieslak et al[4] suggested that performing gastric cultures, urine cultures, and serology may be necessary to accurately determine the presence of CMV, as the virus can readily be missed with any one of these methods. In this patient, the diagnosis was confirmed with CMV polymerase chain reaction (2600 units; reference value, <200) and immunostaining for CMV (Figure 4).

Treatment with anticholinergics or H_2 receptor antagonists can help relieve symptoms of protein loss by decreasing mucous secretion.[2–9] Cimetidine specifically appears to reduce paracellular protein secretion by constricting the tight junctions of the gastric epithelium, which are widened in Menetrier disease.[9] Gastric ulcers are treated with standard protocols and a high-protein diet may also be recommended.[1–3] As discussed above, *H pylori* eradication therapy appears to be of use in reducing symptoms.[9] Ganciclovir should also be used to treat the CMV infection. Severe cases of hemorrhage may require gastrectomy.

The differential diagnosis for Menetrier disease includes eosinophilic gastritis, which can exhibit enlarged rugal folds, but will often involve the antrum. Zollinger-Ellison syndrome is also in the differential, but classic Menetrier disease does not involve excessive acid production. Malignancy and lymphoma are possible considerations in the presence of hypertrophic gastropathy. In adults, this has been of great concern and some patients have undergone gastric resection for the purpose of removing or avoiding associated malignancy, as hyperplasia in Menetrier can evolve to neoplasia. In children, it is believed that malignancy does not occur in the context of Menetrier disease. While there have not been any cases of cancer documented after Menetrier disease in a child, there has been 1 case of gastric plasmacytoma in a child initially believed to have Menetrier disease.[6] Full-thickness gastric biopsy may be necessary in children with hypertrophic gastritis who have prolonged or unremitting symptoms to rule out a neoplastic process.

Menetrier disease appears to run a benign course in children, in comparison to adult disease. This difference raises many questions as to what causes this pathology and why adults and children have such a different disease manifestation. It does appear that cytomegalovirus is a consistent factor in pediatric cases. As research continues to elucidate the role of growth factors and TGF-α in the disease process, the etiology of Menetrier disease may become clearer. Further identification of any genetic associations also may be helpful in discovering predisposing or causative factors.

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