A previously healthy, 25-year-old man was admitted to the hospital because of abdominal pain, nausea, vomiting, and weight loss. Two weeks before his admission, fever (temperature up to 40°C), chills, and weakness developed. To control his fever, the patient ingested ibuprofen at a dose of 400 mg four times a day for more than a week. Subsequently, abdominal discomfort and nausea developed, and he presented to the emergency department owing to worsening of epigastric pain and vomiting. Since his gastrointestinal symptoms had started, he had lost about 4 kg of body weight. He reported no hematemesis, hematochezia, or melena. His medical history was remarkable only for a left inguinal hernioplasty 3 years earlier. He did not smoke, ingest alcohol, or use illicit drugs.

This patient's symptoms of fever, chills, and malaise are nonspecific and may occur with viral or bacterial infection or noninfectious inflammation. Protracted vomiting or nausea may lead to Mallory–Weiss tears at the gastroesophageal junction, causing epigastric pain and possibly upper gastrointestinal bleeding. Pancreatitis may also explain this constellation of symptoms, although the patient reports no alcohol ingestion and has no known history of gallstones. Intestinal obstruction is another, more remote possibility. The patient's use of ibuprofen puts him at risk for nonsteroidal antiinflammatory drug (NSAID)–induced gastritis; prepyloric edema could lead to partial gastric obstruction and vomiting. Treatment with a proton-pump inhibitor may alleviate his symptoms pending further evaluation.

On physical examination, the patient was pale and weak but did not appear to be in distress. His blood pressure was 125/75 mm Hg in a supine position and 105/70 mm Hg while he was standing. The pulse rate was 96 beats per minute, and the temperature was 36°C. His tongue appeared dry. His tonsils were not enlarged, and there was no exudate. There was no cervical or axillary adenopathy. He had marked epigastric tenderness without rebound or abdominal rigidity. The spleen and liver were mildly enlarged. There was no rash.

The patient's physical examination is consistent with dehydration, but there is no evidence of peritonitis, which would suggest perforation. The mild hepatic and splenic enlargement may be consistent with a viral illness, which could also explain his recent fever and its absence on admission. Alternatively, the patient's fever may be intermittent, as in Hodgkin's disease (Pel–Ebstein fever); the abdominal pain, weight loss, and hepatic and splenic enlargement could also be consistent with this diagnosis.

Laboratory tests revealed an elevated white-cell count, at 11,500 per cubic millimeter, with 34% lymphocytes, 10% monocytes, and 53% neutrophils. The hemoglobin level...
was 16.7 g per deciliter, the hematocrit 48.8%, the mean corpuscular volume 85.3 fl, the platelet count 257,000 per cubic millimeter, and the international normalized ratio (INR) 1.16. The serum level of sodium was 132 mmol per liter, potassium 3.3 mmol per liter, glucose 86 mg per deciliter (4.8 mmol per liter), blood urea nitrogen 33.6 mg per deciliter (12.0 mmol per liter) (normal range, 8.0 to 24.0 mg per deciliter [2.9 to 8.6 mmol per liter]), creatinine 0.83 mg per deciliter (73.4 μmol per liter) (normal range, 0.80 to 1.20 mg per deciliter [70.7 to 106.1 μmol per liter]), total protein 4.2 g per deciliter (normal range, 6.0 to 8.0), albumin 1.4 g per deciliter (normal range, 3.5 to 5.0), alanine aminotransferase 313 U per liter (normal range, 0 to 40), aspartate aminotransferase 192 U per liter (normal range, 0 to 35), alkaline phosphatase 57 U per liter (normal range, 40 to 130), γ-glutamyl transferase 35 U per liter (normal range, 8 to 61), total bilirubin 0.4 mg per deciliter (6.8 μmol per liter) (normal value, <1.0 mg per deciliter [<17.1 μmol per liter]), amylase 64 U per liter (normal range, 20 to 100), lactate dehydrogenase 1091 U per liter (normal range, 240 to 480), creatine phosphokinase 69 U per liter (normal range, 0 to 170), and C-reactive protein (CRP) 2 mg per liter (normal value, <5). The erythrocyte sedimentation rate was 2 mm in the first hour.

The hemoglobin and hematocrit values, though probably elevated by hemoconcentration, do not support a diagnosis of gastrointestinal bleeding. The elevated white-cell count and elevated liver-enzyme levels are suggestive of viral infection and, when combined with the mild enlargement of the spleen and liver, may indicate infectious mononucleosis. However, the severe hypoalbuminemia in this previously healthy young adult is not easily explained by this diagnosis. Hepatic synthetic dysfunction is highly unlikely, given the normal INR and the absence of signs or a history of cirrhosis. Evaluation is warranted for protein loss in the urine or gastrointestinal tract (elevated levels of α1-antitrypsin in the stool are a marker of protein loss). Further history regarding the patient’s nutritional intake is also needed.

Viral serologic testing was positive for IgM antibodies to cytomegalovirus (CMV) (2.81 arbitrary units [AU] per milliliter; cutoff value for recent CMV infection, 0.90) and was borderline positive for IgG antibodies to CMV (6 AU per milliliter; cutoff value, 6), whereas testing was negative for IgM antibodies to Epstein–Barr virus or hepatitis A virus, antibodies to hepatitis B surface antigen, total antibodies to hepatitis B core antigen, and IgM and IgG antibodies to hepatitis C virus. A 24-hour urine collection contained 0.14 g of protein (normal range, 0 to 0.25). The patient acknowledged that he had reduced his oral intake during the previous 2 weeks because of epigastric pain. A caloric estimation showed that the patient consumed about 1500 kcal per day.

The presence of anti-CMV IgM antibodies probably indicates either acute CMV infection or reactivation of infection; the concomitant low titer of anti-CMV IgG antibodies favors the former. However, false positive results for anti-CMV IgM antibodies have been reported in cases of cancer or systemic inflammation, causing some doubt about this diagnosis. The absence of clinically significant proteinuria rules out protein loss through the urinary tract. The reduction in the patient’s caloric intake is modest and recent and would not in itself explain his severe hypoalbuminemia, because the serum albumin concentration typically remains normal in short-term and more prolonged fasting. Excessive use of NSAIDs has been reported as a cause of hypoalbuminemia, but this is rare and has been associated with longer courses of NSAID use than reported by this patient. Furthermore, overuse of NSAIDs cannot explain other features of the patient’s disease. Fever, weight loss, splenomegaly, and an elevated lactate dehydrogenase level may suggest an underlying cancer such as lymphoma, though the presence of a normal erythrocyte sedimentation rate and a normal CRP level make the likelihood of lymphoma fairly low. Intestinal involvement of lymphoma may also explain protein loss.

Abdominal and chest computed tomographic (CT) scans showed an enlarged spleen, at 15 cm in diameter, an enlarged liver with four small hypo dense lesions consistent with hemangiomas (the largest one measuring 12 mm in diameter), moderate ascites, and small pleural effusions. In addition, large gastric folds were seen in the stomach (Fig. 1). There was no free air in the abdomen and no lymphadenopathy.

The CT scans do not show evidence of cancer. The pleural effusions and ascites may be due to the hypoalbuminemia, with resultant leakage of
fluid into the third space. The large, edematous gastric folds may be caused by a similar mechanism but could also indicate another disease process. Large gastric folds may be caused by Ménétrier’s disease (foveolar hyperplasia), the Zollinger–Ellison syndrome (parietal-cell hyperplasia), *Helicobacter pylori* gastritis, infiltrative conditions (e.g., sarcoidosis and eosinophilic gastroenteritis), or neoplastic conditions (e.g., primary gastric carcinoma). Ménétrier’s disease has been associated with CMV infection, primarily in children. The patient’s serologic findings for acute CMV infection, along with the large gastric folds and hypoalbuminemia, are suggestive of Ménétrier’s disease.

Serologic testing for celiac disease was negative. The patient underwent gastroscopy, which revealed moderate esophagitis and “raised” gastric folds with severe erosive gastritis; the gastric folds and erosive gastritis were considered likely to be related to NSAID use. No inflammation or lesions were evident in the duodenum. A gastric biopsy showed viral inclusion bodies and foveolar hyperplasia with glandular cystic dilatation (Fig. 2 and 3A). Specific immunohistochemical staining for CMV was positive (Fig. 3B). He was treated with omeprazole (40 mg twice daily) and a high-protein diet (Ensure), without antiviral therapy. After 17 days of hospitalization, the patient was discharged while taking omeprazole at a dose of 20 mg twice daily. He had had gastrointestinal symptoms throughout his hospital stay, but at a follow-up visit 1 month later, his epigastric pain and nausea had disappeared and his serum albumin level had returned to normal. Repeat gastroscopy after 2 more months showed normal gastric folds.

Findings at the initial gastroscopy support the diagnosis of erosive gastritis induced by NSAIDs but also included foveolar hyperplasia, glandular cystic dilatation, and enlarged gastric folds typical of Ménétrier’s disease, which in this case is presumed to be due to CMV infection. The finding of erosive gastritis with viral inclusion bodies and positive staining for CMV suggests that CMV infection may also have contributed to the gastritis.

**Commentary**

Our patient presented with a clinical picture of viral infection and severe epigastric pain. Because

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**Figure 1. Abdominal CT Scan Showing Enlarged Gastric Folds.**

The red circle shows the location of the enlarged folds.

**Figure 2. Gastric-Biopsy Specimen (Hematoxylin and Eosin).**

Visible are active gastritis and gastric-pit hyperplasia (black arrowheads) with glandular cystic dilatation (white arrowheads). The inset shows a cystically dilated gastric pit lined by hyperplastic foveolar cells.
he had ingested high doses of NSAIDs to control his fever, NSAID-induced gastritis was initially suspected as the cause of his abdominal pain. However, the finding of severe hypoalbuminemia was not easily explained by either viral infection or his NSAID use. The identification of this abnormality led to reconsideration of the working diagnosis and a shift from a “probability approach” (identifying the most likely diagnosis) to a “causal reasoning” approach (looking for clinical conditions that could underlie this finding as well as the other presenting symptoms and signs).

Hypoalbuminemia can result from reduced production of albumin by the liver or increased loss through the kidneys or the intestines. In this patient, the normal INR argues against abnormal liver synthetic function. The urine did not contain protein, ruling out the kidneys as a source of protein loss. Therefore, the gastrointestinal system became the main focus of investigation. In most cases, the syndrome of protein-losing enteropathy is associated with diseases localized to the small intestine. In some cases, however, protein loss originates in the stomach. In this case, the identification of large gastric mucosal folds and areas of erosive gastritis on abdominal CT and gastroscopy, respectively, provided an explanation for both the hypoalbuminemia and the epigastric pain.

Large gastric mucosal folds are recognized in a variety of conditions and may reflect mucosal hyperplasia (i.e., an excessive number of mucosal epithelial cells confined to the rugae in the gastric body and fundus) or mucosal hypertrophy. Because these conditions have the same gross appearance, a biopsy is often necessary to determine the cause. Large nonhyperplastic gastric folds may be caused by chronic H. pylori gastritis, neoplasms (e.g., lymphoma, adenocarcinoma, and carcinoma), lymphocytic gastritis, sarcoidosis, eosinophilic gastroenteritis, and the Cronkhite–Canada syndrome. Hyperplastic gastropathies include the Zollinger–Ellison syndrome, in which there is an increased number of parietal cells, and Ménétrier’s disease, in which the number of surface and foveolar mucous cells is increased. Although the term “Ménétrier’s disease” has been used (inappropriately) to describe any condition with enlarged gastric folds, the majority of patients with enlarged gastric folds do not have classic Ménétrier’s disease.

The pathogenesis of Ménétrier’s disease is incompletely understood. However, the observation of elevated levels of transforming growth factor α (TGF-α) in gastric mucous cells of patients with this condition has suggested a role for TGF-α–induced hyperplasia. Ménétrier’s disease affects men more often than women and is most common between 40 and 55 years of age. Clinical manifestations of the disease include epigastric pain, weight loss, nausea, vomiting, gastrointestinal bleeding, diarrhea, and protein-losing gastropathy. Hypoalbuminemia is present in 20 to 100% of patients, according to a different series; this feature helps distinguish Ménétrier’s disease from the Zollinger–Ellison syndrome. The diagnosis of Ménétrier’s disease is usually established by extreme foveolar hyperplasia with glandular atrophy and decreased numbers of parietal cells on biopsy in a patient with large gastric folds on endoscopy. Treatment includes medications to relieve nausea and gastric pain. A high-protein diet is prescribed to offset the loss of protein. Partial or total gastrectomy is sometimes advocated for patients with intractable pain, hypoalbuminemia, edema, hemorrhage, or pyloric obstruction, or in cases in which cancer cannot be ruled out. A small, single-blinded
trial involving patients with severe Ménétrier's disease who were treated for 1 month with cetuximab (a monoclonal antibody that blocks epidermal growth factor receptor signaling) showed significant improvement in quality of life and in biochemical indexes (increased parietal-cell mass and gastric acidity)\textsuperscript{9}; however, more data are needed to inform the role of this medication in treatment.

Although our patient had morphologic findings of the stomach that are characteristic of Ménétrier's disease, this condition would not explain the viral prodrome or the course of his illness. A Ménétrier's disease–like condition with transient protein-losing gastropathy, hypoalbuminemia, and marked gastric rugal hypertrophy has been reported in association with CMV infection, mainly in children.\textsuperscript{9} Ménétrier's disease has also been reported in association with \textit{H. pylori}.\textsuperscript{10} CMV-associated Ménétrier's disease differs from classic Ménétrier's disease in its acute self-limited course and more focal involvement of the gastric fundus, antrum, or both.\textsuperscript{11} The histologic picture resembles idiopathic Ménétrier's disease, with the addition of viral cytoplasmic inclusion bodies. Isolated case reports have described CMV-associated protein-losing gastropathy in immunosuppressed\textsuperscript{12} and immunocompetent\textsuperscript{13,14} adults. Although the gastropathy resolved spontaneously in several patients with supportive treatment only,\textsuperscript{12,13} one reported case—in a 69-year-old immunocompetent man with features of Ménétrier's disease—resulted in death despite antiviral treatment.\textsuperscript{14}

In the present case, the finding of inclusion bodies in the gastric mucosal cells that stained positively for CMV confirmed the diagnosis of CMV-associated Ménétrier's disease (Fig. 3). This diagnosis reasonably explains all the patient's presenting features: a prodrome of viral infection, splenomegaly, abdominal pain, erosive gastritis, large gastric folds, and hypoalbuminemia.

Antiviral treatment for CMV infection is usually reserved for immunocompromised patients.\textsuperscript{15} However, in immunocompetent patients with severe, debilitating disease (specifically, protracted symptoms or organ-specific complications), antiviral therapy may be indicated. In our patient, symptomatic and supportive nutritional therapy resulted in rapid improvement of symptoms, without the need for antiviral therapy.

This case underscores the need to consider underlying causes, including viral infection, in patients with findings that are consistent with Ménétrier's disease. No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES


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