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The Element of Surprise

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A 64-year-old woman presented to the emergency department with fatigue and shortness of breath. Her symptoms had begun 3 months earlier. During the past few weeks, she had had worsening shortness of breath when walking short distances and climbing stairs. She had no chest discomfort or palpitations; she had a dry cough but no fevers, chills, or sweats. She had had two falls after feeling lightheaded but did not strike her head or lose consciousness. She reported no numbness in the legs, gait imbalance, or weakness.

Fatigue is a common problem with a broad differential diagnosis. The patient should be asked about muscular weakness or excessive sleepiness. Her exertional dyspnea arouses concern about a cardiovascular or pulmonary cause. Her falls and lightheadedness suggest the possibility of low intravascular volume, possibly secondary to anemia, third spacing of fluid (loss of intravascular fluid into the interstitium), or poor oral intake. Clinical history and examination results can be used to differentiate between syncope and falls related to neurologic or gait dysfunction.

The patient had a history of migraines, depression, supraventricular tachycardia, and alcohol use disorder but reported having stopped alcohol consumption 3 years before presentation. Her medications included escitalopram (20 mg daily) and a regimen for migraines — metoclopramide (10 mg four times a day as needed), sumatriptan (100 mg orally as needed), and verapamil (240 mg nightly). She had no known allergies. She had a history of 17.5 pack-years of cigarette smoking and had quit 3 years before presentation.

The patient's history of supraventricular tachycardia arouses concern about a malignant tachyarrhythmia contributing to her presentation. Her former tobacco use raises her risk of pulmonary disorders, including chronic obstructive pulmonary disease and lung cancer.

On further evaluation, the patient reported daily episodes of nausea for 3 months before presentation. She attributed the nausea to migraines, and metoclopramide had provided some relief. She reported poor appetite, loose stools (up to three times daily), and a weight loss of 5.5 kg (12 lb). She reported no hematochezia, melena, or abdominal pain. She did not have nocturnal diarrhea or associate loose stools with particular foods. Previously, she had had

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regular, well-formed bowel movements every other day. She had had an unremarkable colonoscopy 3 years earlier.

The presence of nausea relieved by metoclopramide raises suspicion for gastroparesis; however, gastroparesis is not associated with chronic diarrhea. Chronic diarrhea is often unrelated to infectious causes in an immunocompetent host and can be due to secretory, osmotic, or malabsorptive causes. The clinical history is most consistent with malabsorption, which typically leads to weight loss; loose, foul-smelling stools; and mild gastrointestinal symptoms (anorexia, flatulence, and abdominal discomfort).

On physical examination, the patient was afebrile (with a temperature of 36.3°C); the heart rate was 91 beats per minute, the blood pressure 96/51 mm Hg, and the oxygen saturation 100% while she was breathing ambient air. She was thin and appeared fatigued. She had conjunctival pallor. There was no cervical or supraclavicular lymphadenopathy. Her heart rate and rhythm were regular, and there was a grade 2/6 systolic flow murmur. Jugular venous pressure was not elevated. Her lungs were clear on auscultation, and her abdomen was soft, nontender, and nondistended, without hepatosplenomegaly. She had no edema in the legs and no bruising or petechiae. There was no clubbing or cyanosis of the feet or hands. The gait was normal, strength was intact in the legs and arms, and proprioception and sensation to light touch and temperature were normal. The deep tendon reflexes were 2+ throughout. The Babinski sign was absent. She reported feeling lightheaded when rising from a seated position to standing, but there was no orthostatic change in blood pressure.

The patient's examination arouses concern about intravascular volume depletion, whereas conjunctival pallor raises suspicion for anemia. She does not have evidence of volume overload or a primary pulmonary process.

The sodium level was 133 mmol per liter, the urea nitrogen level 15 mg per deciliter (5.4 mmol per liter), and the creatinine level 1.2 mg per deciliter (106 μmol per liter). The white-cell count was 1990 per cubic millimeter, the hemoglobin level 3.8 g per deciliter, and the platelet count 214,000 per cubic millimeter. The white-cell differential count was 72.8% neutrophils, 10.1% lymphocytes, 16.1% monocytes, 0.5% eosinophils, and 0.5% immature granulocytes. The mean corpuscular volume was 112 fl (normal range, 80 to 95). The red-cell distribution width was 18.6% (normal range, 11.5 to 14.5), and the reticulocyte count 0.7%. The patient received 3 units of packed red cells on admission, which resulted in an increase in her hemoglobin level from 3.8 g to 6.4 g per deciliter. Several days later, she received an additional 2 units of packed red cells, which elicited an appropriate response.

Severe macrocytic anemia and leukopenia can result from impaired marrow production or increased destruction of red cells in the peripheral blood. The inappropriately low reticulocyte count suggests impaired marrow production. Potential causes of macrocytic anemia include megaloblastic anemia (most commonly due to vitamin B_{12} or folate deficiency or medications that result in impaired DNA synthesis, such as methotrexate, azathioprine, or hydroxyurea), primary bone marrow disorders (myelodysplastic syndrome [MDS], aplastic anemia, and leukemia), liver disease, long-term alcohol use, and hypothyroidism. Leukopenia with a macrocytic anemia can be seen in patients with primary

bone marrow diseases, megaloblastic anemia, medication-related effects, and copper deficiency.

The peripheral-blood smear showed macrocytosis and anisocytosis but no schistocytes or spherocytes. There was a low number of white cells, and the neutrophils were noted to be hypolobulated (Fig. 1). The platelets were normal in number, size, and granulation.

Bilobed neutrophils are suggestive of pseudo-Pelger–Huët anomaly (acquired Pelger–Huët anomaly). They can be seen in patients with MDS, acute myeloid leukemia, and toxic effects of drug therapy.

The lactate dehydrogenase level was 168 U per liter (normal range, 135 to 225), the iron level 176 μg per deciliter (32 μmol per liter) (normal range, 37 to 158 μg per deciliter [7 to 28 μmol per liter]), the total iron-binding capacity 275 μg per deciliter (49 μmol per liter) (normal range, 220 to 460 μg per deciliter [39 to 82 μmol per liter]), the ferritin level 914 μg per liter (normal range, 10 to 170), the vitamin B_{12} level 281 pg per milliliter (210 pmol per liter) (normal range, 250 to 900 pg per milliliter [180 to 660 pmol per liter]), and the folate level 11.9 ng per milliliter (27 nmol per liter) (normal range, >5.2 ng per milliliter [>12 nmol per liter]). The homocysteine level was 8 μmol per liter (normal range, 5 to 12), and the methylmalonic acid level 0.11 nmol per liter (normal range, <0.40). A direct antiglobulin test (Coombs' test) was negative. The thyrotropin level was 2.28 mIU per milliliter (normal range, 0.50 to 5.70). A complete blood count from 5 months earlier showed a white-cell count of 7610 per cubic millimeter, a hemoglobin level of 11.9 g per deciliter, and a platelet count of 235,000 per cubic millimeter.

The normal level of lactate dehydrogenase, low reticulocyte count, and negative Coombs' test argue against hemolysis. The iron studies do not indicate iron deficiency. The vitamin B_{12} level is near the lower limit of the normal range, but the absence of elevation in the methylmalonic acid and homocysteine levels is inconsistent with vitamin B_{12} deficiency. Bone marrow examination is warranted to determine the cause of the profound anemia and leukopenia; I am concerned about an underlying marrow disorder, particularly MDS, given the pseudo-Pelger–Huët anomaly.

The patient underwent a bone marrow biopsy (Fig. 2A through 2E). The aspirate smear showed vacuoles in myeloid and erythroid precursors. The percentage of blasts was not elevated. An iron stain revealed occasional ringed sideroblasts. The biopsy specimen showed a normocellular marrow with relative myeloid hyperplasia, a low number of erythroid elements, a high number of immature myeloid precursors, and focal dysmegakaryopoiesis. Karyotyping and next-generation sequencing of the marrow aspirate were normal.

Myeloid hyperplasia, ringed sideroblasts, a high number of immature myeloid precursors, and mild dysplasia can be seen in patients with MDS; however, a diagnosis of MDS is unlikely given the absence of clonal cytogenetic or molecular alterations. There are nonclonal processes that can mimic the dysplasia seen in MDS and be associated with cytopenias, including nutrient deficiencies (vitamin B_{12}, folate, or copper), autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis, and effects of medications including methotrexate and azathioprine. Ringed sideroblasts are a morphologic

finding associated with abnormal iron sequestration in the mitochondria and are also seen in patients with toxic effects of lead exposure, alcohol use disorder, vitamin B_6 deficiency, and copper deficiency. The combination of multilineage dysplasia, ringed sideroblasts, and vacuoles in myeloid and erythroid progenitors has been associated with copper deficiency. Copper levels should be assessed in this patient, along with zinc levels, because zinc excess can contribute to copper deficiency.

Zinc and copper levels were assessed. The zinc level was 247 μg per deciliter (37.8 μmol per liter) (normal range, 66 to 110 μg per deciliter [10.1 to 16.8 μmol per liter]), and the copper level was less than 10 μg per deciliter (<1.6 μmol per liter) (normal range, 75 to 145 μg per deciliter [11.8 to 22.8 μmol per liter]).

Severe copper deficiency manifests with severe hematologic or neurologic abnormalities. The findings of anemia, leukopenia, and dysplastic changes in the bone marrow are consistent with copper deficiency. Common causes of copper deficiency include malnutrition, impaired absorption, and excess zinc consumption. The patient's history of weight loss and loose stools should prompt an evaluation for malabsorptive causes, and additional history should be obtained to determine a source of excess zinc consumption.

The patient reported no use of zinc-containing lozenges, supplements, denture creams, or mouthwashes. Owing to the finding of copper deficiency and her history of loose stools, nausea, and weight loss, the patient underwent esophagogastroduodenoscopy (EGD), which revealed a normal esophagus, diffusely erythematous mucosa in the gastric body and gastric antrum, and diffusely scalloped mucosa in the entire examined duodenum (Fig. 3A and 3B). Biopsy specimens of the gastric body and the duodenum were obtained. The duodenal biopsy (Fig. 4A and 4B) revealed mucosa with partial villous blunting and a high number of intraepithelial lymphocytes (>50 per 100 enterocytes).

The patient had no history of excess zinc intake. Zinc uptake contributes to copper deficiency by promoting the production of metallothionein in enterocytes, which sequesters copper in enterocytes. The patient's EGD and biopsy results are suggestive of celiac disease. Tissue transglutaminase (tTG) IgA antibody testing, which has high sensitivity and specificity for the diagnosis of celiac disease, is recommended to further evaluate the patient.

The patient's levels of tTG IgA and IgG antibodies were elevated, at 68 CU (normal range, 0 to 19) and 28 CU (normal range, 0 to 19), respectively. Copper staining was performed on the patient's duodenal-biopsy specimen and did not reveal any excess copper in the enterocytes.

These findings confirm the diagnosis of celiac disease. Treatment of celiac disease involves careful lifelong adherence to a gluten-free diet. Long-term complications that are associated with uncontrolled celiac disease include nutritional deficiencies, anemia, low bone mineral density, and an increased risk of enteropathy-associated T-cell lymphoma in the small bowel. The absence of excess copper in the enterocytes suggests that this patient's level of zinc excess was not a primary contributor to her copper deficiency.

Over a period of 2 weeks, the patient's anemia responded to 2 mg of intravenous copper chloride administered daily for eight doses. The hemoglobin level increased from 7.7 g to 10.1 g per deciliter. However, she had worsening hypoxemia at rest. She had spontaneous desaturations to 89% on pulse oximetry and was given oxygen supplementation at a rate of 2 liters per minute by nasal cannula; the rate was increased to 6 liters per minute over a period of 2 days. Computed tomography (CT) of the chest revealed mild bilateral interstitial and alveolar edema. She was treated with diuretics for the presumptive diagnosis of volume overload from blood transfusions earlier in the course of illness. A follow-up chest CT after adequate diuresis revealed gradual worsening with an increase in peribronchial and subpleural ground-glass opacities as well as interlobular septal thickening throughout both lungs, particularly in the upper lobes. In terms of symptoms, she continued to have a dry cough and remained hypoxemic. She underwent bronchoscopy with serial lavages, which yielded progressively higher red-cell counts (tube 1 had 1950 red cells per microliter, tube 2 had 2960, and tube 3 had 9650), findings that were consistent with alveolar hemorrhage. Hemosiderin-laden macrophages were detected.

The patient's bronchoscopy results arouse concern about pulmonary hemosiderosis. This condition is most often identified in persons who have had recurrent episodes of diffuse alveolar hemorrhage. In this patient's case, an additional consideration is pulmonary hemosiderosis associated with celiac disease, or the Lane–Hamilton syndrome.

The patient's overall presentation was thought to be consistent with diffuse alveolar hemorrhage and pulmonary hemosiderosis associated with celiac disease. She received counseling from a nutritionist regarding maintenance of a gluten-free diet. Her anemia and leukopenia resolved several weeks after intravenous copper supplementation, and she received maintenance therapy with oral copper gluconate (2 mg daily). A gluten-free diet resulted in a reduction in gastrointestinal and respiratory symptoms, and repeat chest radiography showed improvement in bilateral patchy interstitial opacities 4 weeks later and complete resolution 12 weeks after initial imaging.

COMMENTARY

This patient presented with fatigue, shortness of breath, weight loss, nausea, and loose stools. Further evaluation showed macrocytic anemia and leukopenia, leading to a diagnosis of copper deficiency and then of celiac disease. Her course was complicated by pulmonary compromise related to alveolar hemorrhage that was attributed to the Lane–Hamilton syndrome. Overall, malabsorption that was related to celiac disease led to severe copper deficiency.

Copper deficiency is rare in the Western world. There are abundant sources of dietary copper, including dried legumes, whole grains, nuts, raisins, meat, fish, and poultry. Copper is absorbed in the upper gastrointestinal tract by copper transporter 1 (CTR1), which is expressed on the luminal surface of the duodenum. Copper deficiency occurs in persons with a history of gastric bypass surgery, other causes of malabsorption, or zinc overload and in those who receive parenteral nutrition exclusively. Acquired copper deficiency has both hematologic manifestations, which are typically reversible, and neurologic manifestations,

which are unlikely to be reversed. Hematologic manifestations include anemia, neutropenia, and (in rare cases) thrombocytopenia. The anemia can be normocytic, microcytic, or macrocytic; the cause of this variation is unknown. Bone marrow evaluation often reveals a high number of immature myeloid precursors, dysplasia, and ringed sideroblasts. These findings can lead to a misdiagnosis of MDS.[1,2] Neurologic findings include myelopathy affecting the dorsal columns, similar to that of vitamin B_{12} deficiency, as well as peripheral neuropathy and hyporeflexia. Patients can present with spastic gait and sensory ataxia.[3]

This patient was noted to have an elevated zinc level. Excess zinc impairs copper absorption by sequestering copper in enterocytes, which are then sloughed off. However, an elevated zinc level has been reported in persons with copper deficiency even in the absence of excess ingestion of zinc, for unclear reasons.[4] Duodenal-biopsy specimens in this patient did not show excess copper in the enterocytes, which suggests that zinc excess was not a major contributor to her copper deficiency.

The mechanisms of cytopenias that are mediated by copper deficiency are incompletely understood. Copper is an important cofactor for several enzymes, including hephaestin, ceruloplasmin, and cytochrome *c* oxidase. All three enzymes have oxidase functions important in iron transport and heme synthesis.[2,5] The leukopenia in copper deficiency appears to be related to impaired self-renewal and differentiation blockade in CD34+ progenitor cells.[6–8]

Copper deficiency has been reported as a complication of celiac disease in several case series.[4,9,10] Like vitamin B_{12} deficiency, copper deficiency should be considered in persons with leukopenia, anemia, or a myelopathy. This patient also had idiopathic pulmonary hemosiderosis, a rare complication of celiac disease named the Lane–Hamilton syndrome.[11] A gluten-free diet can reverse pulmonary hemosiderosis; glucocorticoids are used in more symptomatic patients.[12]

The present case highlights the importance of considering copper deficiency in patients with dysplasia and cytopenias, with or without a myeloneuropathy. Recognition that this patient was copper deficient led to the diagnosis of celiac disease, and the combination of copper replacement and a gluten-free diet resulted in marked clinical improvement.

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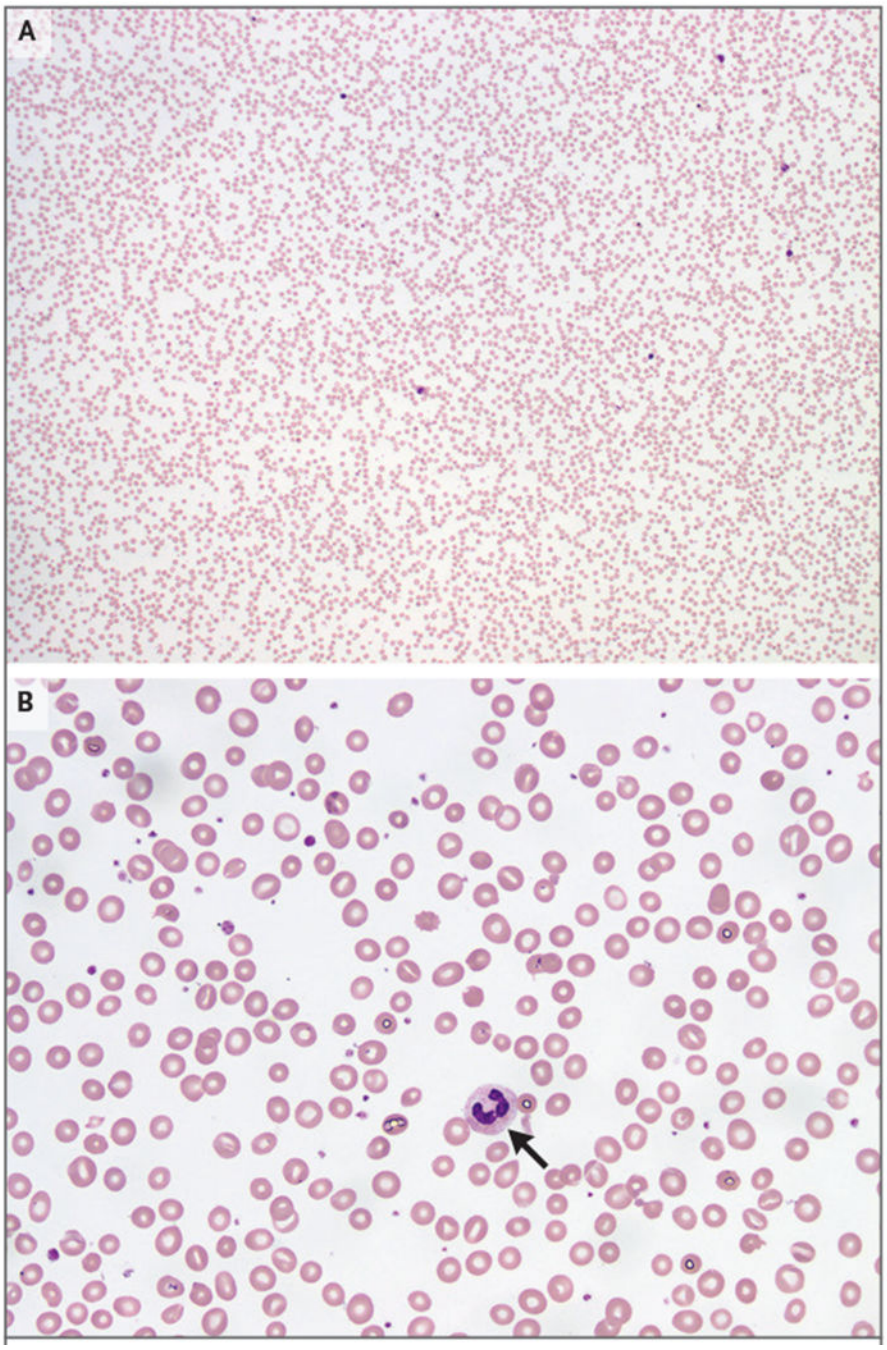

Figure 1. Blood Specimens.

A peripheral-blood smear at low magnification (Panel A) shows evidence of hypochromia. At higher magnification (Panel B), a representative hypolobulated polymorphonuclear granulocyte (arrow) is noted, along with macrocytosis, anisocytosis, and hypochromia.

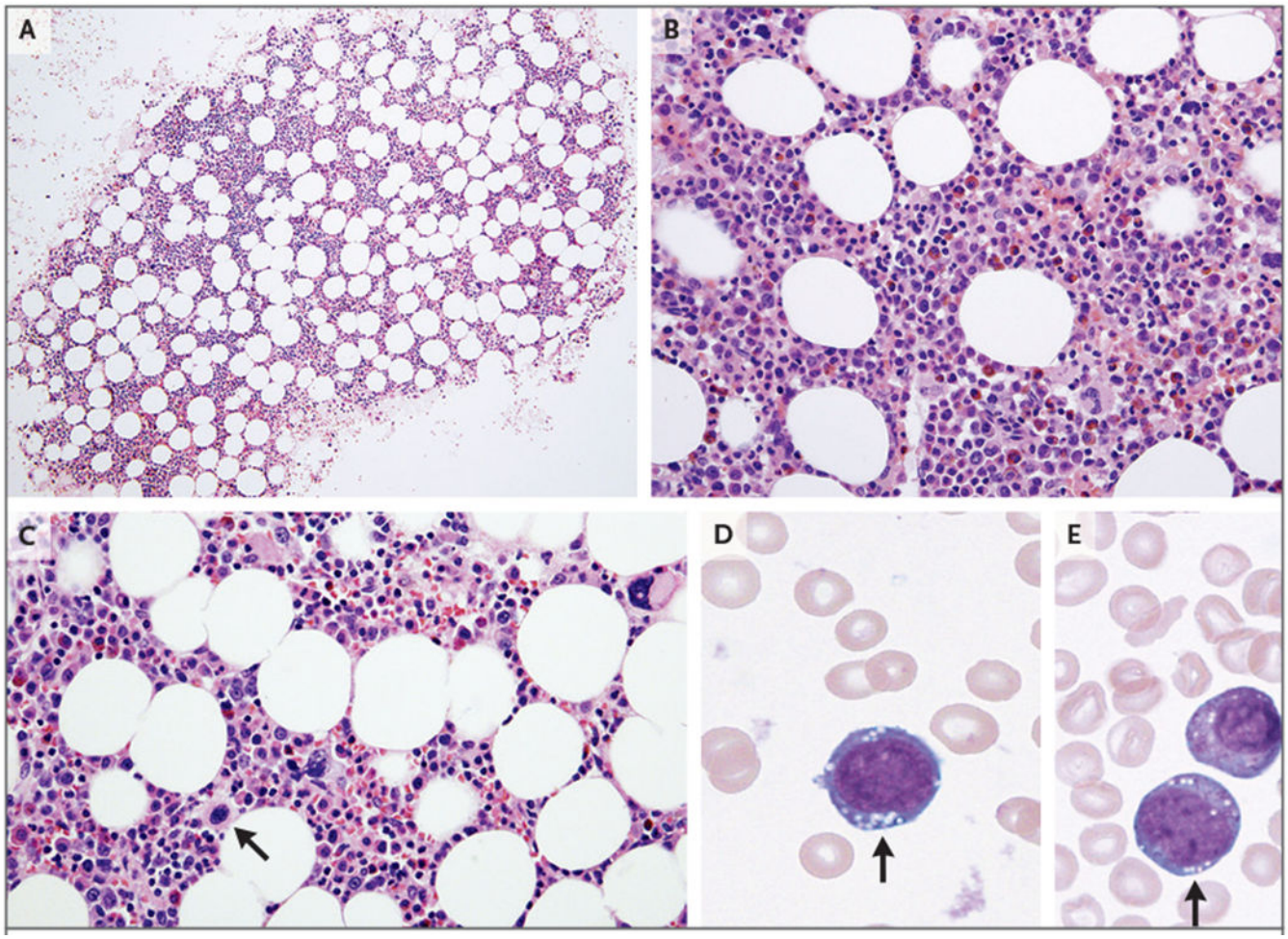

Figure 2. Bone Marrow Specimens.

In Panel A, the core biopsy specimen shows 50% cellularity, normocellular to mildly hypercellular for the patient's age. In Panel B, a high number of immature myeloid precursors with mild myeloid predominance and a relative decrease in erythroid maturation are noted. In Panel C, closer examination of the bone marrow core reveals atypical, small hypolobulated megakaryocytes (arrow) with a high nuclear-to-cytoplasmic ratio. In Panels D and E, cytoplasmic vacuoles (arrows) are noted in erythroid and myeloid precursors, respectively.

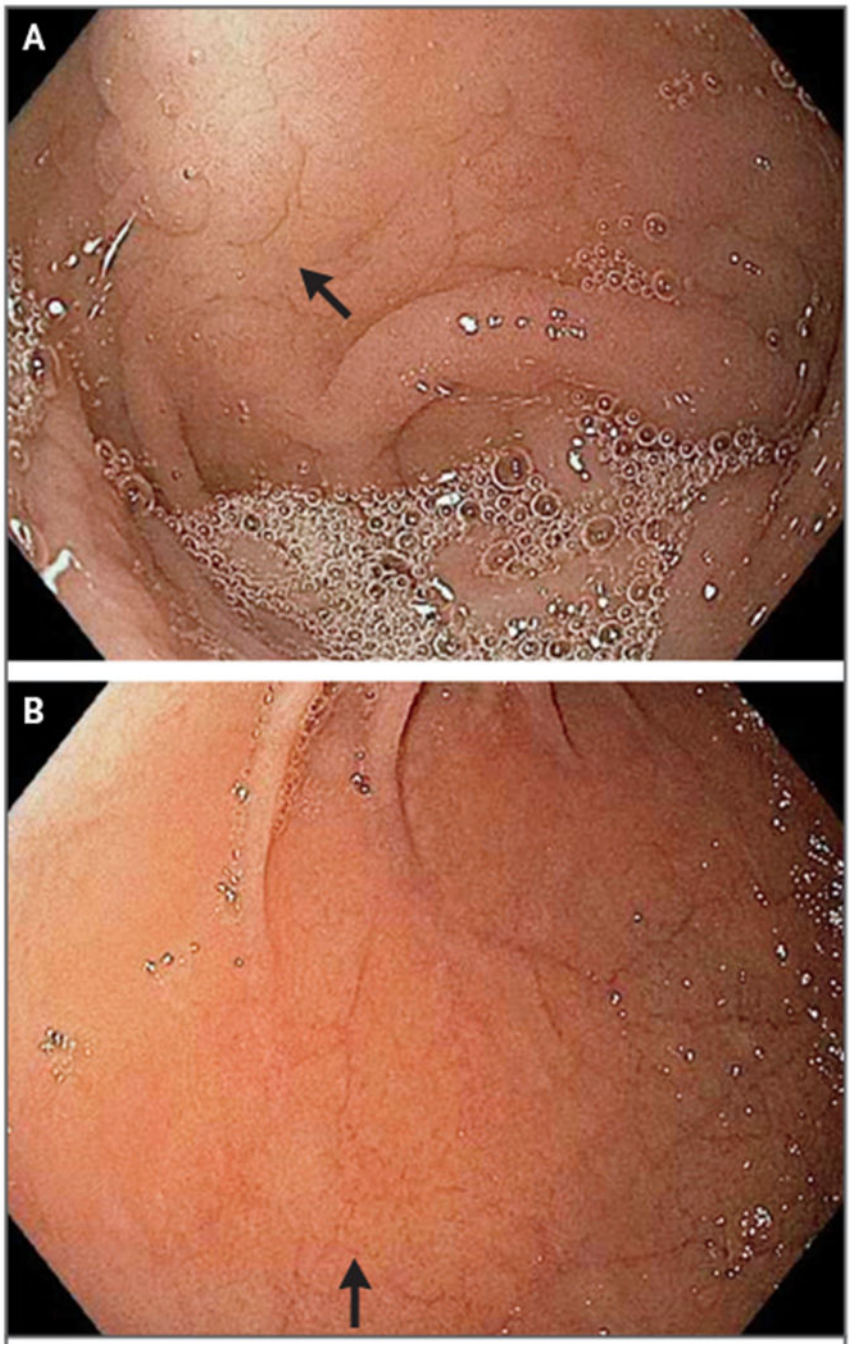

Figure 3. Esophagogastroduodenoscopic Images.

Panel A shows a scalloped appearance in the duodenal bulb (arrow). Panel B shows a smooth appearance of the duodenum (arrow), a finding suggestive of loss of villi in segment 2 of the duodenum.

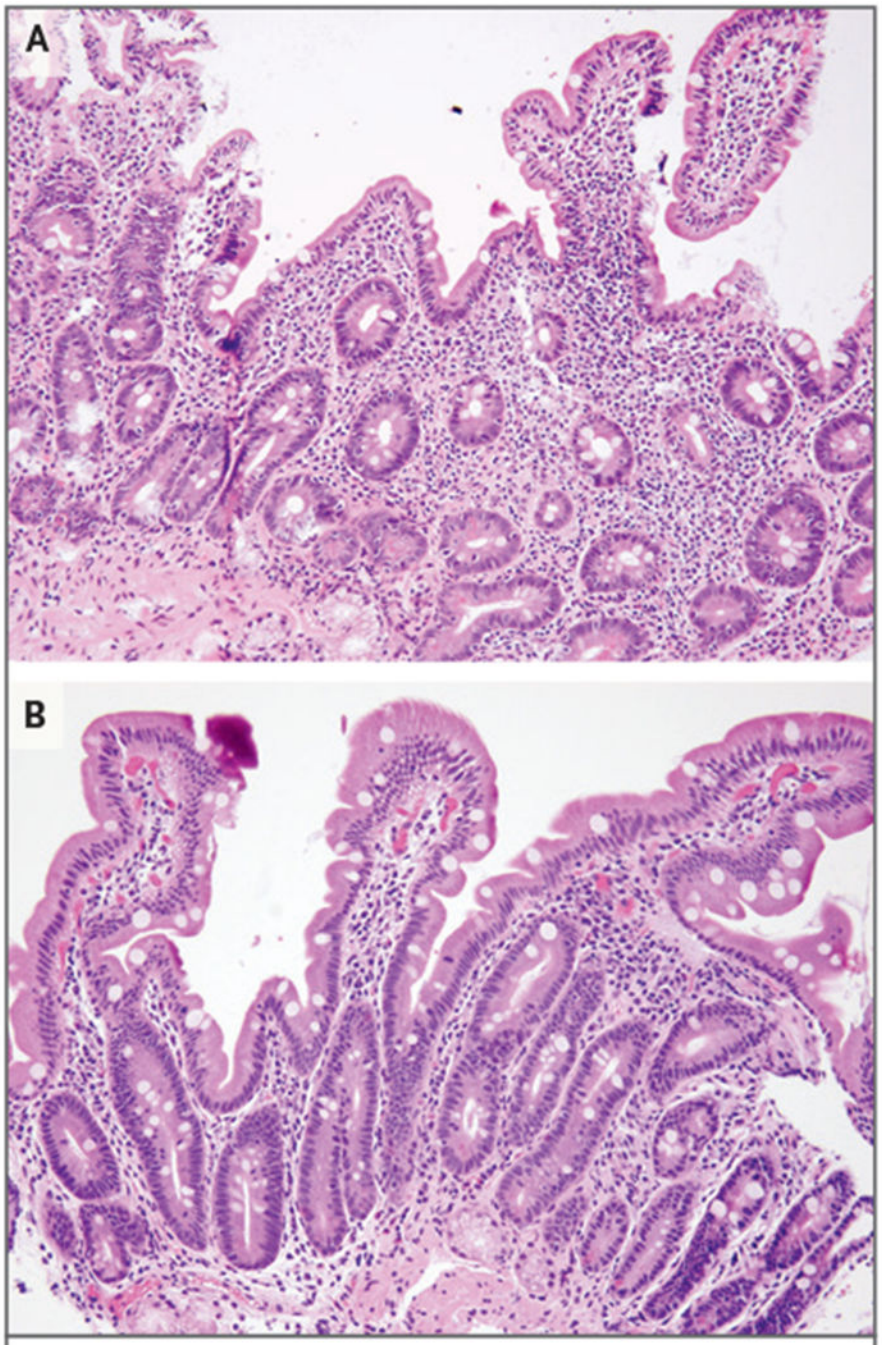

Figure 4. Duodenal Specimens.

A duodenal-biopsy specimen obtained at the time of diagnosis (Panel A) shows duodenal mucosa with partial villous blunting and a high number of intraepithelial lymphocytes (>50 per 100 enterocytes). A duodenal-biopsy specimen obtained 6 months after the initiation of a gluten-free diet (Panel B) shows improvement in villous blunting and no increase in the number of intraepithelial lymphocytes.