

CLINICAL PROBLEM-SOLVING

## A Stain in Time

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*In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.*

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**A 45-year-old woman from northern Ontario presented to her local hospital with a 2-year history of asymmetric migratory arthralgias involving the left knee, ankles, elbows, and fingers. She also had morning stiffness, increasing fatigue, an erythematous, nonpruritic rash after sun exposure, and a 3-month history of chest pain that was relieved when she was in an upright position. She did not have fevers, dry eyes or mouth, oral ulcers, or eye irritation or pain.**

This patient presents with a 2-year history of migratory polyarthralgias and, more recently, positional chest pain suggestive of pericarditis. The broad differential diagnosis includes rheumatoid arthritis and seronegative polyarthritis. Seronegative polyarthritis is characterized by the absence of rheumatoid factor and includes reactive arthritis with urethritis and conjunctivitis, systemic lupus erythematosus, psoriatic arthritis, and arthritis associated with inflammatory bowel disease. Photosensitivity often reflects drug toxicity, although it is also a feature of systemic lupus erythematosus.

There was no personal or family history of inflammatory disorders. The patient's medications included fluvoxamine, at a dose of 40 mg once daily, for depression and estrogen therapy (initiated after the patient underwent hysterectomy for benign disease at 32 years of age). She took a nonsteroidal antiinflammatory drug on an as-needed basis. Her blood pressure was 150/84 mm Hg. Her heart rate was 100 beats per minute and regular. There was no malar rash, mucous membrane ulceration, or cervical, supraclavicular, axillary, or inguinal adenopathy. Cardiovascular and chest examinations were normal. Both wrists and the left knee were tender; the left knee had a palpable effusion. The patient's grip strength was normal bilaterally. There were no signs of impaired salivary gland function (i.e., cheilosis or loss of glistening of the tongue or mucous membranes).

None of the patient's medications are likely to explain her symptoms. Although the presentation does not allow us to differentiate between rheumatoid arthritis and seronegative arthritis, her age and sex make the former more probable. At this point, I would order tests for rheumatoid factor and antinuclear antibodies and radiographs of the affected joints to look for destructive changes.

The hemoglobin level was 11.5 g per deciliter, with a mean corpuscular volume of 86  $\mu\text{m}^3$ . The white-cell count was 9500 per cubic millimeter, and the platelet count was 425,000 per cubic millimeter. The erythrocyte sedimentation rate was 100 mm

per hour, and the C-reactive protein level was 3.2 mg per deciliter. Tests for rheumatoid factor and antinuclear antibodies were negative. Serum complement levels were normal (C3, 97 mg per milliliter; C4, 20 mg per milliliter), as were the levels of total bilirubin (0.35 mg per deciliter [6.0  $\mu\text{mol}$  per liter]), haptoglobin (319 mg per deciliter), and lactate dehydrogenase (541 U per liter). Tests for anticardiolipin antibodies, lupus anticoagulant, and cryoglobulin were negative. An echocardiogram revealed normal left ventricular function and a small pericardial effusion.

Laboratory tests, including tests for normocytic anemia, suggest chronic inflammation. Further workup of the anemia is warranted, including a peripheral-blood smear, iron studies, and a reticulocyte count. An anti-cyclic citrullinated peptide antibody test would be of interest, since about one third of rheumatoid factor-negative patients with rheumatoid arthritis have this antibody, but the test is not yet widely available in Canada. In some patients, the development of rheumatoid arthritis is episodic and characterized by transient, recurring episodes of monoarthritis or oligoarthritis with a very sudden onset and without residual joint damage — a condition referred to as palindromic rheumatism. Less common causes of polyarthritis such as sarcoidosis should also be considered. A small pericardial effusion can be a normal finding, but it suggests the possibility of serositis in addition to polyarthritis. The antinuclear antibody test is not 100% sensitive for systemic lupus erythematosus, and it is still possible that the patient has this disorder.

**An electrocardiogram and chest film were normal. The patient's physicians made a diagnosis of seronegative lupus and started treatment with hydroxychloroquine. The chest pain had resolved and the joint pain had diminished substantially when she was reevaluated 4 months later. The markers of inflammation remained elevated. She remained well for the next 3.5 years, during which time she did not seek further medical attention.**

The diagnosis of systemic lupus erythematosus requires 4 of 11 clinical and laboratory criteria that this patient has not met. At this point, the working diagnosis should be an undifferentiated connective-tissue disease that responded clinically to hydroxychloroquine.

Four years after her initial presentation, the patient presented with a 4-month history of fever, drenching night sweats, abdominal pain, bloating, nonbloody diarrhea, and a decreased appetite leading to a 7-kg weight loss. She had continued to receive hydroxychloroquine. On physical examination, the heart and chest were normal, and there was no hepatosplenomegaly. The examination of the joints was not recorded.

Now the patient has a several-year history of polyarthritis that is partially responsive to an antiinflammatory drug. The development of fever, night sweats, weight loss, and abdominal pain suggests a systemic process. Sarcoidosis remains possible, although this condition would not generally be expected to respond to hydroxychloroquine. Unlike some other drugs used for inflammatory arthritis, hydroxychloroquine is not highly immunosuppressive and should not confer a predisposition to unusual infections. Chronic infection with the human immunodeficiency virus (HIV) can first present as a rheumatic syndrome. Hydroxychloroquine has a well-documented direct effect against HIV type 1 and might improve rheumatic symptoms related to this infection. The current symptoms could be unrelated to her initial presentation. Other possibilities, given her recent symptoms, are lymphoma, infections such as tuberculosis, and inflammatory bowel disease (which may be manifested as arthritis before gastrointestinal symptoms develop).

**The hemoglobin level was 9.1 g per deciliter, with a mean corpuscular volume of 78  $\mu\text{m}^3$ . The white-cell count was 7600 per cubic millimeter, with a normal differential count and a platelet count of 354,000 per cubic millimeter. The serum creatinine level was 0.4 mg per deciliter (35.4  $\mu\text{mol}$  per liter); aspartate aminotransferase, 15 U per liter; alkaline phosphatase, 89 U per liter; total bilirubin, 0.35 mg per deciliter; and albumin, 3.0 g per deciliter. Tests for antinuclear antibodies, rheumatoid factor, and anti-double-stranded DNA were negative. Stool samples obtained for culture and sensitivity testing were negative for ova and parasites, and an assay for *Clostridium difficile* toxin was negative. A urinalysis was normal.**

The patient has become more anemic since her initial presentation. Inflammatory bowel disease could explain the chronic diarrhea and anemia.

I would want to obtain a computed tomographic (CT) scan of her abdomen to look for intraabdominal, retroperitoneal, or mesenteric adenopathy. Endoscopic evaluation of her bowel and iron studies are also warranted.

A CT scan of the abdomen, obtained without the administration of contrast material, showed multiple subcentimeter lymph nodes around the root of the mesentery and around the posterior aspect of the cecum in the absence of evidence of colitis or terminal ileitis; the liver, spleen, pancreas, and adrenal glands appeared normal. A colonoscopy with biopsy showed normal bowel mucosa. Endoscopic examination of the stomach and duodenum showed no abnormalities. Duodenal-biopsy specimens were negative for celiac disease. An upper gastrointestinal series with small-bowel follow-through was normal. Examination of a bone marrow–biopsy specimen revealed normal iron stores and cellularity. On follow-up examination, the surgical consultant who had performed the endoscopic evaluations noted a left axillary lymph node that was 1.5 cm in diameter.

Recurrent fevers, night sweats, abdominal pain, nonbloody diarrhea, and weight loss in the presence of mesenteric and axillary adenopathy (without liver or spleen enlargement) are nondiagnostic but are consistent with a diagnosis of lymphoma, sarcoidosis, or infection such as tuberculosis or fungal infection. Tissue is needed for diagnosis; the axillary node would be most accessible.

**Examination of a specimen from a left axillary lymph-node biopsy showed a nonspecific lymphadenitis without evidence of lymphoma. Stains for fungus and acid-fast bacilli were negative.**

A sample of the biopsy specimen should also have been sent to the microbiology laboratory for fungal and tuberculosis cultures at the time of the procedure. Surgical specimens are often placed in formalin, which makes subsequent culture growth impossible.

**After this evaluation, the patient did not return for follow-up. Her symptoms continued. Eight months later, she was admitted to a community hospital with persistent, large-volume, watery stools and an additional 15-kg weight loss, despite an**

**intact appetite and reportedly normal food intake. The patient noted shortness of breath and two-pillow orthopnea. Family members reported that she had recent short-term memory loss and a personality change but no other apparent neurologic deficits. She appeared cachectic and required supplemental oxygen at a rate of 2 liters per minute to maintain an oxygen saturation of 97%. The conjunctivae were pale. There was no scleral icterus or oral thrush. The respiratory examination revealed bibasilar crackles. No abnormal heart sounds were noted. Pitting edema to the middle of the shins was noted. There was no joint swelling, erythema, or warmth. The patient was oriented to self, place, and time; however, difficulties with short-term memory were noted.**

The hemoglobin level was 5.9 g per deciliter, with a mean corpuscular volume of 74  $\mu\text{m}^3$ . The white-cell count was 9400 per cubic millimeter, and the platelet count was 192,000 per cubic millimeter. The erythrocyte sedimentation rate was 110 mm per hour; the serum ferritin level, 88 ng per milliliter; serum iron, 16  $\mu\text{g}$  per deciliter (2.9  $\mu\text{mol}$  per liter); total iron-binding capacity, 180  $\mu\text{g}$  per deciliter (32  $\mu\text{mol}$  per liter) (iron saturation, 8.7%); albumin, 2.0 g per deciliter; creatinine, 0.5 mg per deciliter (44  $\mu\text{mol}$  per liter); aspartate aminotransferase, 22 U per liter; and alanine aminotransferase, 11 U per liter. The vitamin B<sub>12</sub> level was normal.

The predominant symptoms are watery diarrhea and weight loss despite a normal appetite, with markers of inflammation still elevated and a more severe microcytic anemia than was noted previously. The low level of serum iron, high total iron-binding capacity, and low level of iron saturation are consistent with iron deficiency; inflammation presumably underlies the elevated ferritin level. I would repeat the gastrointestinal endoscopic examinations to look for a source of occult blood loss. I am also concerned about malabsorption, and I would measure the serum carotene level and obtain a stool sample for the measurement of fecal fat.

**Multiple blood and urine cultures were negative. A 72-hour stool collection showed that the amount of fecal fat was elevated, at 21.2 g per day (normal range, 2.0 to 7.0). Serologic tests for hepatitis B and C virus, HIV, cytomegalovirus, and Epstein–**

Barr virus were negative. The urinary porphyrin level was normal.

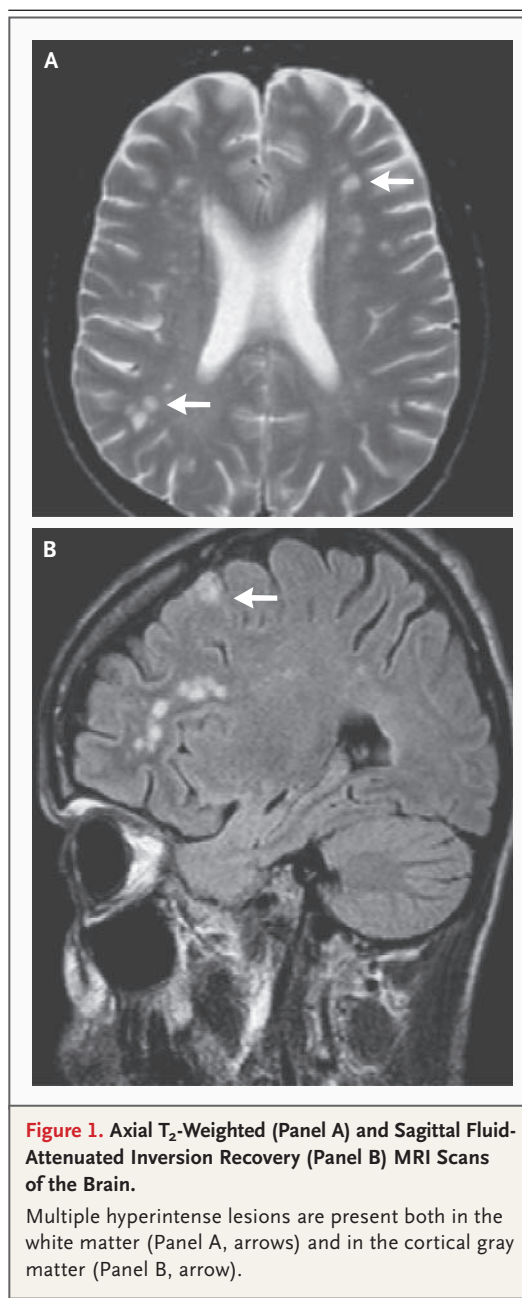
The patient has evidence of severe malabsorption with frank steatorrhea. Celiac disease may cause this condition and can develop in middle age. The 5-year duration of symptoms makes small-vessel vasculitis or bowel infiltration with lymphoma unlikely. Inflammatory bowel disease is also unlikely, given the previously normal endoscopic and small-bowel studies. Few infections persist for 5 years without declaring themselves. One such chronic infection, which can be manifested as polyarthritides, weight loss, night sweats, and abdominal pain, is Whipple's disease. The reported personality change and memory loss are also compatible with this diagnosis. A complete neurologic examination and further cardiac investigations are warranted.

The patient's score on the Mini-Mental State Examination was 25; the highest score (normal) is 30. There was impairment in orientation, short-term recall, and visuospatial tasks. The pupils were equal and reactive to light; extraocular movements and other cranial nerves were normal, and fundoscopic examination showed no abnormalities. Motor strength and all sensory tests were normal. Reflexes were symmetric, and the plantar response was normal bilaterally. A two-dimensional echocardiogram identified left ventricular dysfunction (ejection fraction, 30%) with severe mitral regurgitation and moderate tricuspid regurgitation; there was no pericardial effusion. Fluids were restricted, and treatment with a diuretic was started.

The slowly progressing malabsorption syndrome with central nervous system (CNS), joint, and cardiac involvement strongly suggests Whipple's disease. At this point, I would recommend neuroimaging and examination of the patient's cerebrospinal fluid to look for infection and a malignant disorder. CD4+ T-cell lymphopenia may result from chronic and severe malabsorption, which can cause lymphocyte loss in the gut, and may confer a predisposition to opportunistic infections. Although it is unlikely, syphilis should be considered as well.

**Magnetic resonance imaging (MRI) of the brain showed bilateral, increased signal intensity in the periventricular white matter and subcortical re-**

**gions on T<sub>2</sub>-weighted scans (Fig. 1). Visual, brain-stem auditory, and sensory evoked potentials, assessed to determine whether the patient had multiple sclerosis, were normal. Abdominal angiographic studies of the celiac, superior mesenteric, inferior mesenteric, and renal arteries and a magnetic resonance angiogram of the circle of Willis showed no evidence of vasculitis. The cerebrospinal fluid contained 7 white cells per cubic**



millimeter, with normal glucose and protein levels, and the Venereal Disease Research Laboratory test for syphilis was negative.

The abnormalities on MRI are nonspecific. The negative abdominal and CNS angiograms and the long-term course of the symptoms make vasculitis unlikely. The cerebrospinal fluid may be normal in patients with Whipple's disease or may contain elevated protein levels or increased numbers of inflammatory cells; this diagnosis still remains likely. Whipple's disease does not appear to have been considered at the time of the original upper gastrointestinal endoscopy; if it had been, a biopsy specimen of the distal duodenum or the proximal jejunum with periodic acid–Schiff (PAS) staining probably would have revealed the characteristic histopathological features of Whipple's disease.

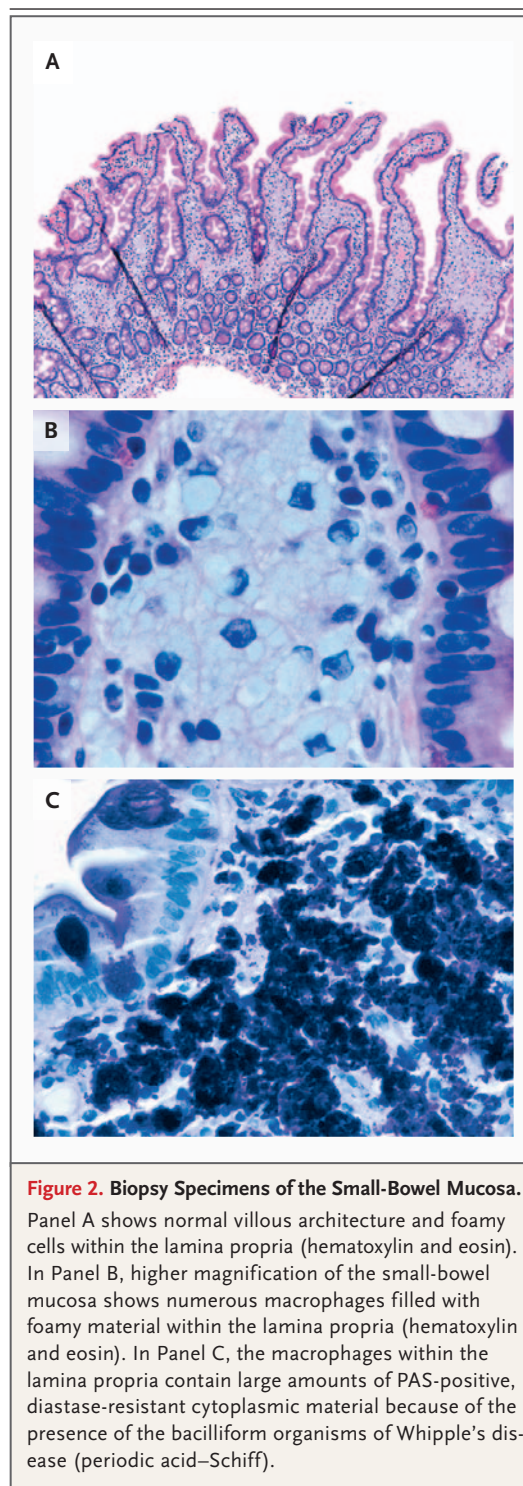
**A repeated esophagogastroduodenoscopy and small-bowel biopsy, with specific instructions to look for Whipple's disease, were performed. Examination of the small-bowel–biopsy specimens revealed normal villi with diffuse infiltration by PAS-positive, foamy macrophages (Fig. 2).**

Positive PAS staining is highly suggestive of Whipple's disease but is not specific; it can also occur in mycobacterial infections and fungal infections such as histoplasmosis and actinomycosis. Confirmation of the diagnosis requires electron-microscopical evidence of the characteristic rod-shaped bacteria with trilamellar membrane or a polymerase chain reaction (PCR) assay of the cerebrospinal fluid showing the presence of *Tropheryma whippelii*.

**Stains of biopsy specimens for acid-fast bacilli and fungi were negative. The cerebrospinal fluid PCR assay for *T. whippelii* was positive.**

The diagnosis of Whipple's disease is confirmed. I would administer intravenous ceftriaxone for at least 2 weeks to ameliorate the intestinal symptoms. Unfortunately, the neurologic symptoms will probably persist despite this treatment.

**Treatment with high-dose intravenous ceftriaxone was started, followed by trimethoprim–sulfamethoxazole. One month after the initiation of antibiotic treatment, the patient had normal stools and had gained weight. However, her memory deficits had not improved and gait ataxia had recently**



**developed. Six months after the initiation of antibiotic treatment, the gastrointestinal symptoms and fever had not recurred, but the cognitive difficulties and impairment of balance persisted.**

## COMMENTARY

When this patient initially presented with polyarthritis and pleuritic chest pain, her physicians diagnosed systemic lupus erythematosus (and initiated treatment accordingly), presumably because systemic lupus is commonly linked with these symptoms. However, this conclusion was premature; the patient did not meet formal criteria for the diagnosis, antinuclear antibody–negative lupus is rare, and other more common conditions (such as inflammatory bowel disease and chronic infections) warranted consideration first. As the case unfolded over a period of several years, the chronic nature of the illness, the evolution of new constitutional symptoms, and the manifestations of malabsorption led to reconsideration of the initial diagnostic hypothesis and ultimately to conclusive diagnostic testing of duodenal tissue and cerebrospinal fluid.

Since Whipple's disease is uncommon and patients present with nonspecific symptoms, the diagnosis is challenging and is often delayed. PAS staining of small-bowel–biopsy specimens reveals characteristic PAS-positive macrophage granules,<sup>1,2</sup> but this staining may not be performed unless it is requested by the clinician. Thus, a high index of suspicion is required.

On histopathological examination, small-bowel–biopsy specimens can exhibit villous atrophy, empty spaces containing neutral fat, and infiltration by foamy macrophages.<sup>1,3</sup> Because of the difficulty of *in vitro* culturing of *T. whipplei* and the poor specificity of serologic tests, the diagnosis is generally made by means of PCR amplification of *T. whipplei* DNA from biopsy specimens of the small bowel<sup>4,5</sup> or lymph nodes<sup>6</sup> or from samples of cerebrospinal fluid.<sup>7</sup> Although one report noted *T. whipplei* DNA in duodenal–biopsy specimens and gastric fluid from healthy controls,<sup>8</sup> this finding has not been confirmed, and the test is generally considered to be diagnostic.

Up to 60% of patients with Whipple's disease

have a history of migratory arthritis that may antedate other symptoms by years.<sup>1</sup> Other common features include weight loss, diarrhea, abdominal pain, and fever.<sup>9</sup> Hepatomegaly, splenomegaly, lymphadenopathy, pericarditis, pleural effusions, dermatologic changes, ocular abnormalities, and myocarditis with valvular involvement have all been described.<sup>2</sup> Thus, this patient's heart failure and valvular disease may have been related to Whipple's disease. Neurologic symptoms, which occur in 20 to 43% of patients at the time of diagnosis, include personality changes and dementia, as observed in our patient, as well as supranuclear ophthalmoplegia and myoclonus.<sup>2,3,9,10</sup> It is often the appearance of neurologic manifestations that prompts consideration of the diagnosis.

Data that can be used to guide therapy are limited to case reports and observational studies.<sup>1</sup> Currently, the administration of ceftriaxone followed by long-term maintenance treatment with cotrimoxazole is favored by most experts because of the ability of these agents to penetrate the cerebrospinal fluid.<sup>11</sup>

The combination of joint and gastrointestinal signs and symptoms (especially if there are also CNS findings) should prompt the consideration of Whipple's disease. To make the diagnosis, tests that are not routinely performed must be requested. Had PAS staining been performed with the initial lymph node and small-bowel–biopsy specimens, the diagnosis might have been made much earlier, although it is uncertain whether earlier treatment would have affected the course of the CNS manifestations of Whipple's disease in this patient.

Dr. Vellend reports having equity in Abbott Laboratories, Pfizer, and Johnson & Johnson. No other potential conflict of interest relevant to this article was reported.

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