The approach to clinical conundrums by an expert clinician is revealed through presentation of an actual patient's case in an approach typical of morning report. Similar to patient care, sequential pieces of information are provided to the clinician who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.

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Missing the Forest for the Trees

A 56-year-old woman from Colombia presented to the emergency department after 24 hours of abdominal pain. One week before, she had experienced similar pain that lasted for 4 hours and spontaneously resolved. She was nauseated but had no vomiting. She reported an unintentional 14-pound weight loss over the preceding 3 weeks. She denied fever, chills, night sweats, diarrhea, constipation, dysuria, or jaundice.

In a middle-aged woman with abdominal pain and nausea, diagnostic considerations include gallbladder disease, diseases of the bowel (such as a partial small-bowel obstruction or inflammatory conditions), hepatic or pancreatic conditions, and nongastrointestinal ailments such as cardiac ischemia. Knowing the specific location of pain, its quality, precipitating factors, and accompanying systemic symptoms may help to narrow the diagnosis. The unintentional weight loss preceding the onset of pain may be an important clue because it suggests a systemic condition, and in a South American immigrant—particularly if she has traveled recently—it is important to consider parasitic illnesses. The absence of fever makes some infections such as tuberculosis and malaria less likely. At this point, in addition to a thorough history and physical, laboratory tests should include a complete blood count (with quantification of eosinophils) and a metabolic panel with liver enzymes and albumin.

The patient described pain in the midline, just inferior to the umbilicus. The pain was constant, developed without any particular provocation, and was not related to meals or exertion. There were no constitutional symptoms aside from weight loss. She had a history of bipolar disorder, hypothyroidism, osteoarthritis, and chronic sinusitis and had previously undergone cholecystectomy and abdominal hysterectomy. She was taking levothyroxine, montelukast, bupropion, oxcarbazepine, fexofenadine, meloxicam, zolpidem, and, as needed, acetaminophen. She had recently completed a 10-day course of levofloxacin for acute sinusitis. She had immigrated to the United States 10 years earlier and lived with her husband and daughter. She denied the use of tobacco, alcohol or illicit drugs. She had visited Colombia 6 months earlier but had no other recent travel history.

The history of cholecystectomy makes a biliary tract process unlikely. Its location reduces the likelihood of a hepatic or pancreatic

process, but I would like to see the liver enzymes, especially given her recent acetaminophen use. The comorbid illnesses—particularly her bipolar disorder—may be relevant because psychiatric illness might be associated with medication overuse or undisclosed toxic ingestions. For example, excess thyroxine might lead to weight loss while overuse of nonsteroidal anti-inflammatory drugs such as meloxicam can cause intestinal ulceration, not only in the upper tract, but also in the colon. Undisclosed ingestions may also be associated with abdominal symptoms. Her surgical history makes adhesions with a secondary partial bowel obstruction possible. With no travel outside this country in the last 6 months, exotic infections are less likely. Finally, the recent course of levofloxacin may be relevant because many antibiotics are associated with nonspecific abdominal symptoms, and *Clostridium difficile* colitis occasionally presents without diarrhea.

The patient reported taking her medications as prescribed and denied ingesting other medications. On physical examination, she had a temperature of 98.9°F, a pulse of 81 beats per minute, a blood pressure of 110/80 mm Hg, and a respiratory rate of 16 respirations per minute. She had a normal oxygen saturation while breathing ambient air. Her weight was 58 kg. There was no scleral icterus or jugular venous distension. She had a small painless ulcer involving the hard palate. Her lungs were clear to auscultation, and cardiac examination was normal. The abdomen was soft, bowel sounds were present, and there was moderate tenderness to palpation inferior to the umbilicus. There was no rebound or guarding, hepatosplenomegaly or other masses. There was no peripheral edema and no lymphadenopathy. Neurological examination was normal.

The oral ulcer may or may not be related to the clinical presentation because oral ulcers, whether painful or painless, are ubiquitous and may be isolated or may be associated with a wide range of infectious and noninfectious systemic diseases. Although some systemic causes of mucocutaneous ulcers are associated with weight loss (including Crohn's disease, Behcet's disease, celiac sprue, human immunodeficiency virus [HIV], herpesviruses, syphilis, and systemic lupus erythematosus [SLE], among others), the lack of specificity of this finding limits its diagnostic utility. However, it is reasonable to ask whether the patient has noted frequent ulceration in the mouth or genitalia, as recurrent or severe ulcerations may narrow the diagnostic considerations. On the other hand, the focal nature of the pain inferior to the umbilicus suggests a discrete process in the abdomen or pelvis, such as an abscess, mass, or localized area of bowel inflammation. A plain abdominal film is likely to be low yield in this situation, so pursuing computed tomography is appropriate. Not all patients with focal abdominal pain require abdominal imaging, but in the context of weight loss and persistent symptoms for more than a week, imaging is prudent in this case.

The patient denied genital ulceration but did report painless oral ulcers over the preceding months. Laboratory evaluation revealed a white-cell count of 1000/mm³, of which 6% were neutrophils, 5% were band forms, 36% were lymphocytes, and 47% were monocytes. The absolute neutrophil count was 110/mm³. Hemoglobin level was 10.2 g/dL with a mean corpuscular volume of 90 μm³, and the platelet count was 151,000/mm³. Other results of laboratory studies were: sodium, 140 mmol/L; potassium, 3.8 mmol/L; chloride, 96 mmol/L; bicarbonate, 23 mmol/L; blood urea nitrogen, 13 mg/dL; creatinine, 0.4 mg/dL; lipase, 32 U/L (normal range, 13-60); amylase, 73 U/L (normal range, 30-110); albumin, 4.0 g/dL; aspartate aminotransferase, 779 U/L (normal range, 13-35); alanine aminotransferase, 330 U/L (normal range, 7-35); alkaline phosphatase, 510 U/L (normal range, 35-104); and total bilirubin, 0.9 mg/dL (normal range, 0.1-1.2). The lactate dehydrogenase level was 200 U/L (normal range, 135-214). The corrected reticulocyte count was 1.6% (normal range, 0.3-2.3), and haptoglobin was 190 mg/dL (normal range, 43-212). A direct Coomb's test was positive. The erythrocyte sedimentation rate was 113 mm/hour (normal range, 1-25). Urinalysis was normal without evidence of protein or blood.

Laboratory abnormalities include elevated transaminases and alkaline phosphatase, a markedly elevated erythrocyte sedimentation rate, and profound leukopenia with neutropenia. The patient is anemic, which may elevate the sedimentation rate but not typically to this degree. The patient is not febrile, but if she were to develop a fever, empiric antibiotics would be prudent. The normal albumin and bilirubin suggest that hepatic synthetic and excretory functions remain

intact. Although the direct Coombs test is positive, the reticulocyte and lactate dehydrogenase levels argue against brisk hemolysis; this abnormality may simply be a marker of nonspecific immune activation. A variety of infections can cause neutropenia and liver enzyme abnormalities including parasites (malaria or leishmaniasis), viruses (cytomegalovirus or Epstein-Barr virus [EBV]), tick-borne bacterial infections (ehrlichiosis or rickettsial infection), and granulomatous infections (tuberculosis). Malignant infiltration of the reticuloendothelial system can also lead to cytopenias and liver enzyme abnormalities. Autoimmunity remains a consideration, as SLE may lead to cytopenias, oral ulcers, and nonspecific immune phenomena. Rather than ordering a large number of blood tests, I favor a targeted approach with abdominal computed tomography followed by biopsy of either the liver or bone marrow.

Chest radiography revealed no abnormalities. Computed tomography of the chest, abdomen, and pelvis with intravenous and oral contrast demonstrated concentric wall thickening of the transverse colon, but no evidence of obstruction or free air. The patient was treated with intravenous fluids, morphine, and cefepime. Bone marrow biopsy was performed, which demonstrated a hypercellular marrow with increased myeloid precursors and a left shift and megakaryocytic hyperplasia. Flow cytometry revealed no abnormally restricted clonal populations. A concerted search for an infectious etiology of the patient's neutropenia was unrevealing, including tests for HIV, cytomegalovirus, hepatitis A, hepatitis B, hepatitis C, Mycoplasma pneumoniae, EBV, and parvovirus B19.

I hope blood cultures were drawn prior to the initiation of antibiotics. Hypercellularity of the bone marrow in the context of leukopenia raises concern that white blood cells are being destroyed peripherally. Autoimmunity against neutrophils can be transiently induced by viruses such as HIV, hepatitis B, and EBV, but these infections have been excluded. Testing for antinuclear antibodies is reasonable. A normal-sized spleen on the abdominal CT excludes hypersplenism. Colonic thickening can be associated with infection, ischemia, inflammatory bowel disease, and malignancy. The question is whether the colonic thickening is part of the same disease process causing the leukopenia and liver enzyme elevation or whether it represents a secondary infectious process in the setting of neu-

tropenia (such as *Clostridium difficile* infection or typhlitis). Testing for stool pathogens (including ova and parasites) is certainly appropriate, and consideration of a colonoscopy with biopsy is reasonable, provided that appropriate antimicrobial coverage remains in place.

Blood cultures obtained prior to starting antibiotics were negative. The patient's abdominal pain improved, and she was discharged home to have close follow-up with a hematologist. The results of her liver function tests improved, and her absolute neutrophil count was 230/mm^3 at the time of discharge. Her neutropenia was believed to be secondary to peripheral destruction from a viral, drug-mediated, or autoimmune process. Oxcarbazepine (Trileptal) was discontinued, as it was believed to be the medication most likely to be responsible. She returned to the hospital 3 days later with recurrence of her abdominal pain and diarrhea. She remained afebrile. Additional history revealed arthralgias over the previous 2 months, mild alopecia, and prior symptoms suggestive of Raynaud's phenomenon. Stool studies failed to establish an infectious etiology for the diarrhea, and her continued neutropenia responded appropriately to treatment with subcutaneous filgrastim. Colonoscopy could be performed only to the hepatic flexure and revealed no abnormalities. A serologic test for antinuclear antibodies was positive at a titer of 1:640 in a homogenous pattern, and a test for antineutrophil cytoplasmic antibodies was negative. Complement levels were normal, and tests for cryoglobulins, rapid plasma reagin, anticardiolipin antibody, lupus anticoagulant, rheumatoid factor, and antibodies to extractable nuclear antigens were all negative.

Raynaud's phenomenon is consistent with lupus. Double-stranded DNA antibodies should be sent, although the urine did not demonstrate protein or an active sediment. Systemic sclerosis and the CREST syndrome is strongly associated with Raynaud's phenomenon and high-titer ANA, but the patient does not have sclerodactyly, which is generally the earliest skin involvement. Autoimmune hepatitis is often associated with high-titer ANA but does not fit this clinical picture. Given that the patient's presentation included segmental bowel wall thickening and a transient but marked liver enzyme elevation with AST predominance, I am concerned about vasculitis of the abdominal

vasculature and would strongly consider a mesenteric angiogram.

To exclude mesenteric vasculitis, the patient underwent magnetic resonance angiography of the abdomen, the results of which were normal. A repeat test for antinuclear antibodies was positive at a titer of 1:2560 in a uniform pattern. A test for anti-double-stranded DNA was positive at 1370 U/mL. The patient was diagnosed with systemic lupus and probable lupus enteritis, and therapy with oral prednisone (10 mg daily) and hydroxychloroquine was initiated. She had prompt improvement in her abdominal pain, and was discharged home. Five months later she developed proteinuria and underwent a renal biopsy, which showed minor, nonspecific glomerular abnormalities, suggesting possible mild lupus nephritis. Eight months after her initial presentation, she remains free of abdominal pain and has regained the weight she had initially lost. Her oral ulcers have resolved, and her blood counts have normalized. Her serum creatinine has remained normal. She is now maintained on prednisone (15 mg daily), hydroxychloroquine, and mycophenolate mofetil.

COMMENTARY

A diagnosis of systemic lupus erythematosus (SLE) provided a unifying explanation for the patient's findings. Indeed, she manifested 4 of the 11 American College of Rheumatology criteria for systemic lupus (oral ulcers, leukopenia, positive anti-DNA, and positive ANA), meeting criteria for a definite diagnosis of SLE. She additionally had multiple other features suggestive of lupus including Raynaud's phenomenon, arthralgias, alopecia, mild thrombocytopenia, and a positive Coombs' test (although the normal reticulocyte count, lactate dehydrogenase, and haptoglobin were most consistent with anemia of a chronic disease).

The protean manifestations of SLE can present significant diagnostic challenges. In this case, physicians were immediately drawn to the patient's acute abdominal pain and severe neutropenia and failed to recognize more subtle disease manifestations that may have aided in establishing a unifying diagnosis sooner. The initial history and review of systems did not disclose arthralgias, alopecia, or Raynaud's phenomenon. In an era of increasing use of hospitalists, which creates potential discontinuity between inpatient and outpatient physicians, a thorough history and review of systems may be particularly important in diagnosing acute manifestations of chronic systemic disease. Inpatient physicians may be overly focused on the small subset of acute complaints leading to hospitalization, without considering the larger constellation of symptoms that may facilitate accurate diagnosis. Our discussant quickly recognized the multisystem nature of the patient's illness and appropriately focused on infectious, neoplastic, and autoimmune categories of disease as being most likely. When infectious and neoplastic conditions were excluded with reasonable certainty, a directed serologic investigation for autoimmune disease was requested, culminating in a diagnosis of SLE.

Involvement of the skin as well as hematologic, renal, and musculoskeletal systems in SLE is commonly recognized, whereas gastrointestinal involvement is perceived to occur much less frequently. However, abdominal pain occurs in up to 40% of patients with lupus.[1–4] Abdominal pain in lupus patients can arise from non-lupus-related conditions as well as lupus-related entities, including serositis, mesenteric vasculitis with or without infarction, mesenteric thrombosis, pancreatitis, inflammatory bowel disease, and adverse medication effects including peptic ulcer disease. Abnormal liver chemistries, as seen in our patient, occur in 20%-50% of patients with lupus and may be due to lupus hepatitis, concomitant autoimmune hepatitis, or medications including NSAIDs.[5,6] Oral ulcers and leukopenia are likewise common in SLE, with each seen in up to half of patients.[4,7,8] Leukopenia in SLE may a result of neutropenia, lymphocytopenia, or both. However, severe neutropenia (ie, absolute count less than $500/\mu L$), as seen in our case, is more often a result of myelotoxicity from immunosuppressive therapy, rather than SLE itself.[9]

Lupus enteritis represents bowel microischemia from small-vessel arteritis or venulitis that often is not evident on conventional mesenteric angiography.[4,10,11] The reported prevalence of intestinal vasculitis in patients with SLE varies widely, depending on the characteristics of lupus patients sampled in individual studies. Intestinal vasculitis affects 0.2%-0.5% of SLE patients in general,[4,12] whereas among SLE patients with active disease and an acute abdomen, vasculitis has been reported in up to 53% of patients.[10] Antiphospholipid antibodies, antibodies to extractable nuclear antigens, the SLE Disease Activity Index, complement levels, erythrocyte sedimentation rate, C-reactive

protein, and anti-double-stranded DNA do not reliably differentiate lupus enteritis from acute abdominal pain due to other etiologies in patients with SLE.[11] However, a concomitant drop in the white blood cell count at the onset of symptoms may be useful in distinguishing lupus enteritis from other causes of acute abdominal pain among lupus patients.[11] Computed tomography findings consistent with lupus enteritis are nonspecific and include bowel-wall thickening, submucosal edema (eg, target sign), dilatation of intestinal segments, engorgement of mesenteric vessels, and increased attenuation of mesenteric fat.[13] Colonoscopy may reveal areas of ischemia and ulceration, and biopsy can confirm intestinal vasculitis. However, intestinal involvement may be segmental, and pathologic confirmation may be difficult. Contrast enema, gallium scanning, and indium-labeled white cell scanning may be useful, but lack specificity. No controlled trials to date have evaluated the optimal therapy for lupus enteritis, but pulsed methylprednisolone is often recommended.[4] Cyclophosphamide, azathioprine, methotrexate, and cyclosporine have also been used as adjunctive agents. Patients may progress to intestinal infarction and perforation, which augurs a poor prognosis, and early surgical exploration should be considered in severely ill patients.[10] Death may occur in more than two-thirds of patients whose disease progresses to intestinal perforation.[1]

In summary, a multisystem disease such as SLE requires a comprehensive history, physical exam, and review of systems to establish a correct diagnosis. In our case, an extensive evaluation was necessary to exclude other etiologies of abdominal pain and systemic illness, particularly as infectious and neoplastic conditions occur far more often than lupus enteritis in the general population. However, profound laboratory abnormalities may have preoccupied the attention of treating physicians, leading them to overlook less obvious but important historical and physical findings suggestive of SLE. The cohesively abnormal "forest" may thus have been obscured by erratically abnormal individual "trees." Gastrointestinal symptoms may be under-recognized in SLE. When these result for lupus enteritis, timely recognition may be lifesaving.

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