CLINICAL PROBLEM-SOLVING

Caren G. Solomon, M.D., M.P.H., *Editor*

A Gut Instinct

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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 30-year-old woman presented to the emergency department in mid-August, with a 4-day history of anorexia, nausea, vomiting, and diarrhea. She had no fever or respiratory symptoms but had mild abdominal discomfort. She was a physician and worked in a hospital; she reported no travel during the preceding 4 months. On physical examination, she was afebrile. The supine blood pressure was 95/60 mm Hg but dropped to 80/60 mm Hg when the patient stood up. The heart rate was 90 beats per minute, and the respiratory rate was 20 breaths per minute. The abdomen had normoactive bowel sounds and was soft and nondistended, with minimal tenderness in the epigastrium. The rest of the physical examination was normal. A complete blood count was obtained, and the results revealed a white-cell count of 6300 per cubic millimeter, with 77% neutrophils, 11% lymphocytes, and 11% monocytes. The hemoglobin level was 12.6 g per deciliter, and the platelet count was 386,000 per cubic millimeter. No urinalysis was performed. The patient was hydrated with intravenous fluids and given ranitidine and prochlorperazine. Her symptoms improved and the orthostasis resolved, and she was discharged from the emergency department with a presumed diagnosis of acute gastroenteritis.

Infectious causes, particularly viruses (e.g., norovirus), are responsible for most cases of acute diarrhea. The duration of the patient's illness, the negative history of recent travel, and the absence of fever and of bloody diarrhea are important historical features. Her symptoms of anorexia, nausea, and vomiting point to involvement of the upper gastrointestinal tract. Nosocomial spread of norovirus is common; however, systemic manifestations, including fever, are not typically associated with infection, and recovery usually occurs by 72 hours. She had mild orthostasis, and her 4-day illness resulted in some degree of hypovolemia, which was corrected with intravenous fluids. Her hemoglobin level may be lower than it appears, because hemoconcentration is likely. In the absence of signs of severe illness, symptomatic treatment at this time is appropriate.

The following day, the patient returned to the emergency department after an abrupt onset of intractable vomiting, which she described as feculent in appearance. She felt feverish and reported severe abdominal pain. On examination, the body-mass index (the weight in kilograms divided by the square of the height in meters) was 19. The temperature was 40°C. The blood pressure was 90/60 mm Hg, with a drop of 15 mm Hg in systolic pressure when the patient stood up; the heart rate was 110 beats per minute and regular; and the respiratory rate was 16 breaths per minute. She appeared uncomfortable but was alert and oriented. The lungs were clear to auscultation. Cardiovascular examination revealed distinct heart sounds and tachycardia, with no audible murmur. The abdomen was soft and distended, with hypoactive bowel

sounds; slight tenderness was noted in the epigastrium. There was no rebound tenderness or guarding. Murphy's sign was negative. There was no hepatosplenomegaly. She had no palpable lymph nodes. Rectal examination showed a patent rectal vault with no stool.

The patient's abrupt worsening of abdominal pain, in conjunction with vomiting of feculent material, strongly suggest a small-bowel obstruction; abdominal pain out of proportion to physical findings is characteristic of mesenteric ischemia, but she is young and is not known to have any risk factors for this condition, such as valvular heart disease or atrial fibrillation. Inflammatory bowel disease, particularly Crohn's disease, and appendicitis should also be considered in the differential diagnosis. A ruptured ectopic pregnancy or a hemorrhagic cyst must be considered in women of reproductive age with abdominal pain. She requires immediate resuscitation with intravenous fluids while further evaluation is pursued.

On further questioning, the patient recalled noting a single, palpable, nontender lymph node in the anterior neck 1 month before presentation, which resolved on its own. She reported no recent fevers, sweats, or weight loss. Her medical history was remarkable only for pertussis in childhood. She had never been pregnant. She was not taking any medications. She was from the Philippines and had visited there 5 months earlier for 2 weeks. She had finished medical school there but had not practiced as a health care provider, having left immediately for the United States to pursue postgraduate training. She did not smoke or drink and was not sexually active. She had received vaccination with bacille Calmette–Guérin as an infant. On entry into the United States, she had a two-step tuberculin skin test, which was negative, with the standard tuberculin skin test performed annually thereafter. The last tuberculin skin test, performed 7 months before the onset of symptoms, was negative, with an induration of 8 mm (considered negative in an otherwise healthy health care worker).

Both residence in and recent travel to the Philippines raise concern about diseases endemic to the area, including abdominal tuberculosis, melioidosis, food-transmitted bacterial infections (e.g., *Vibrio parahaemolyticus* infection), and parasitic infections, such as ancylostomiasis, amebiasis, fasciolopsiasis, and schistosomiasis. These conditions are typically associated with abdominal pain or discomfort, but obstruction is less common. Abdominal tuberculosis is uncommon and typically indolent in nature. Melioidosis, which can have a presentation that is similar to that of tuberculosis, is infrequently found in the Philippines. Intestinal obstruction is possible with infection from the intestinal fluke *Fasciolopsis buski* or with *Schistosoma japonicum* but is rare.

The white-cell count was 2000 per cubic millimeter, with 64% neutrophils, 12% lymphocytes, and 24% monocytes. The hemoglobin level was 11.8 g per deciliter, and the platelet count was 305,000 per cubic millimeter. The creatinine level was 0.9 mg per deciliter (80 μmol per liter), with a blood urea nitrogen level of 11 mg per deciliter (3.9 mmol per liter). The sodium level was 133 mmol per liter, potassium 3.7 mmol per liter, chloride 95 mmol per liter, and bicarbonate 22 mmol per liter. Results of liver tests were within normal limits, as were amylase and lipase levels. Urinalysis revealed 2+ protein, trace glucose, and a large amount of ketones. A urine pregnancy test was negative. Abdominal radiography revealed markedly dilated loops of small bowel (Fig. 1). Abdominal computed tomography (CT) confirmed this finding and showed a high-grade small-bowel obstruction, with an edematous mesentery and intra-abdominal free fluid. No adenopathy or mass was noted. Imaging of the lung bases revealed small bilateral pleural effusions and right hilar lymphadenopathy. Blood cultures were obtained, and human immunodeficiency virus (HIV) antibody testing was performed. A nasogastric tube was inserted for decompression, and there was immediate output of mixed bilious and fecal material.

The patient's laboratory tests are notable for leukopenia, without a left shift; the absence of eosinophilia; mild anemia; an anion gap of 16 mmol per liter; and proteinuria and ketonuria. Bowel infarction is typically associated with leukocytosis and elevated amylase and lipase levels. Similarly, leukocytosis typically occurs with bacterial infections, but leukopenia can occur with certain infections, including tuberculosis and typhoid fever. The patient's anion gap and ketonuria may be attributable to fasting ketoacidosis, but the serum lactate level should be determined. Substantial proteinuria may confer a predisposition to a prothrombotic state. The results of abdominal imaging are consistent with a small-bowel obstruction, although no tran-

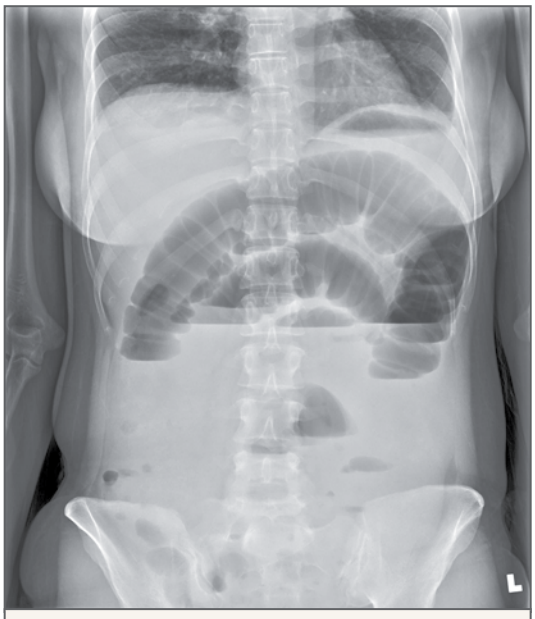

Figure 1. Abdominal Radiograph Showing Markedly Dilated Loops of Small Bowel.

sition point is identified. Postoperative adhesions are the most common cause of small-bowel obstruction; other causes include small-bowel neoplasms (e.g., carcinoid tumors and lymphoma) and congenital hernias. However, no tumorlike lesions or hernias were noted on imaging. Acute ileitis resulting from Crohn's disease continues to be considered in the differential diagnosis; acute ileitis resulting from *Yersinia enterocolitica* infection, intestinal tuberculosis, or amebiasis may present in a similar fashion, with gastroenteritis and mesenteric lymphadenitis. The incidental findings of pleural effusions and probable hilar lymphadenopathy are worrisome and raise concern about a more diffuse process, such as tuberculosis. The initial management of small-bowel obstruction is fluid resuscitation and nasogastric or long-tube decompression, but prompt surgical evaluation is warranted in this patient.

Empirical antimicrobial therapy with piperacillin–tazobactam, ciprofloxacin, and vancomycin was initiated. The patient was evaluated by a surgical consultant and underwent emergency exploratory laparotomy, owing to concern about a small-bowel obstruction. Fiberoptic intubation of the trachea was performed, and incidental note was made of a possible endobronchial lesion at the carina. Intraoperatively, multiple serosal, peritoneal, and mesenteric nodules were seen; biopsies were performed and specimens sent to the pathology department. She was found to have a dense adhesive band in her pelvis, which was lysed intraoperatively. Endotracheal aspirates and intraoperative samples from peritoneal nodules were sent for Gram's staining, acid-fast bacilli and fungal smears and cultures, and mycobacterial polymerase-chain-reaction (PCR) testing. Frozen sections taken from intraoperative specimens revealed caseating granulomas.

Caseating granulomas are classically associated with mycobacterial infections but can also occur with fungal infections (e.g., histoplasmosis), tularemia, and, on rare occasions, sarcoidosis. Given the patient's country of origin, the intraoperative findings, and the perihilar lymphadenopathy, the most likely diagnosis is tuberculosis. The abdominal distention in the absence of ascites suggests the fibrotic-fixed form of tuberculous peritonitis, although the patient's fulminant clinical presentation would be unusual for this condition. Peritoneal carcinomatosis, sarcoidosis, Crohn's disease, and endometriosis are associated with peritoneal nodules that resemble tuberculous peritonitis. The latter three disorders may also be associated with endobronchial lesions. The results of pathological examination and culture results should rule out these conditions.

After surgery, the patient was transferred to the intensive care unit and placed in an airborne-infection isolation room. Chest radiography showed bilateral lower-lobe atelectasis and small effusions. CT of the neck and chest was performed and revealed peritracheal, perihilar, and mediastinal lymphadenopathy but no endobronchial lesions (Fig. 2). Lung imaging showed mild bilateral pleural effusions and parenchymal disease. There was no evidence of a miliary disease pattern. Three induced-sputum samples were sent for acid-fast bacilli smear, culture, and PCR testing for *Mycobacterium tuberculosis*.

Given the findings in the lungs, pulmonary and abdominal tuberculosis remain the most important considerations. Antituberculous therapy should be added to the empirical therapy against gram-negative and gram-positive bacteria, pending further results.

An infectious-disease consultant recommended quadruple antituberculous therapy with isoniazid, ethambutol, rifampin, and pyrazinamide, as well

as moxifloxacin to cover possible nontuberculous intraabdominal infection. The other antibiotics that the patient was receiving were discontinued. Final pathological results showed necrotizing granulomatous and histiocytic inflammation. Staining for fungi and mycobacteria was negative.

Staining of tissue for mycobacteria is not sufficiently sensitive to rule out the diagnosis of tuberculosis. The histopathological findings of granulomatous inflammation are still consistent with tuberculosis, and I agree with empirical treatment for tuberculosis.

A few days later, a DNA probe for *M. tuberculosis* from the peritoneum was reported to be positive, and one of three sputum smears for acid-fast bacilli was reported to be positive, with 1 to 9 acid-fast bacilli per 100 oil-immersion fields. The HIV test was negative. Repeat tuberculin skin testing was positive, with 25 mm of induration. Defervescence occurred 2 days after the initiation of antituberculous medications, and the patient was discharged home a week later. Contacts who had been exposed to the patient during the preceding 3 months were identified and tested, and none had a positive tuberculin skin test.

Skin testing has very poor sensitivity even in active cases of tuberculosis, and retesting is not necessary in the case of active disease; the test is negative in up to half of all cases of disseminated tuberculosis. The patient's positive tuberculin skin test 7 months after a negative test could suggest that the infection was acquired recently but may alternatively reflect a "booster phenomenon," which is sometimes seen with two-step tuberculin skin testing. Although health care workers are at higher-than-average risk for tuberculosis, it is more likely that this patient's infection was acquired in the Philippines, perhaps before she moved to the United States. Isolation precautions against airborne transmission should be continued until the patient's clinical condition improves with therapy and she has had three consecutive negative sputum smears for acid-fast bacilli obtained on different days, with at least one being an early-morning specimen.

The patient had a good response to antituberculous therapy. Culture results and results of susceptibility testing showed that her isolate was susceptible to all first-line antituberculous medications. Spoligotyping (a PCR-based system for differentiation of strains of *M. tuberculosis*) showed that her tuberculosis strain probably originated in the Philippines. She received directly observed therapy (at all times), continued receiving quadruple-drug therapy for 2 months, and subsequently completed a 9-month course of isoniazid and rifampin. She was doing well at the time of last follow-up, 5 years after completing therapy.

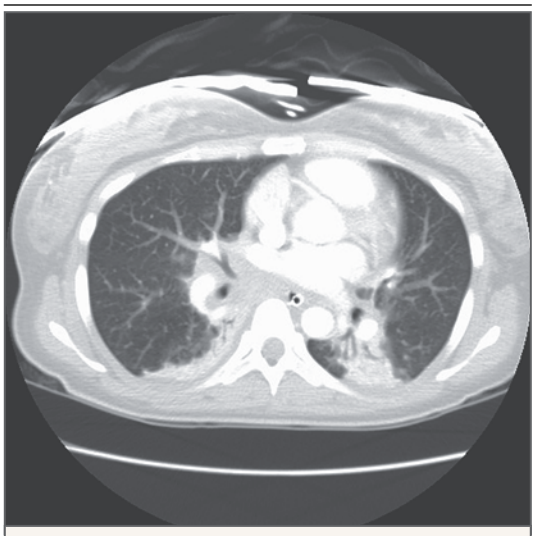

Figure 2. Computed Tomographic Scan of the Lungs.
The scan shows perihilar and mediastinal lymphadenopathy, bilateral pleural effusions, and parenchymal disease.

COMMENTARY

Tuberculosis is a well-recognized occupational hazard of health care. In a systematic review[1] that included 15 studies conducted in high-income countries, health care workers had a median annual risk of pulmonary tuberculosis infection of 1.1% (range, 0.2 to 12), as compared with a risk of 0.1 to 0.2% in the general population. In this case, however, it is most likely that the patient's foreign-born status posed a greater risk of tuberculosis infection than that associated with her work in health care.

There has been a steady decline in cases of tuberculosis in the United States, from 52.6 cases per 100,000 population in 1953 to 3.6 cases per 100,000 population in 2010.[2] However, the proportion of extrapulmonary tuberculosis increased from 7.6% in 1962 to 20% or more since the late 1990s.[3,4] The risk of extrapulmonary tuberculosis is reported to be increased among women,

Asian and foreign-born persons, and health care workers[4]; as a female physician from the Philippines, our patient had several risk factors.

Intraabdominal tuberculosis, including peritoneal and mesenteric lymph-node involvement, is the sixth most common type of extrapulmonary tuberculosis reported in the United States.[5] The diagnosis of intraabdominal tuberculosis is challenging, owing to its protean and nonspecific manifestations.[6] In a large case series,[7] up to two thirds of patients had negative tuberculin skin tests, and many did not have respiratory symptoms; our patient also had a negative skin test initially and despite abnormal findings on chest imaging had not reported associated symptoms. Systemic and constitutional symptoms are frequent, as are abdominal pain and distention. The majority of patients with tuberculous peritonitis have ascites, which results from fluid exudation from peritoneal surfaces; only about 10% of patients present as our patient did, with the "dry type" of tuberculous peritonitis, characterized by a doughy abdomen, adhesions, fibrosis, and the absence of ascites.[8] Often there is a long delay between symptom onset and diagnosis.[9] Our patient, however, noted no symptoms until peritoneal inflammation triggered an intestinal obstruction.

Our patient was born in the Philippines, a country with a high incidence of tuberculosis and one in which vaccination with bacille Calmette–Guérin is the standard. Her annual tuberculin skin test was negative. Our discussant proposes that given the conversion of the tuberculin skin test to positive after the disease became symptomatic, this patient may have been exposed recently, during her trip to the Philippines; however, it is more likely that this was a reactivation of latent disease and that her initial exposure had occurred much earlier, because most acute presentations of tuberculosis in adults are thought to result from reactivation rather than primary infection.[10]

In the case of active tuberculosis, the reported sensitivity of tuberculin skin testing is highly variable and is generally estimated from culture-confirmed cases; false negative test results are reported in up to 25% of cases.[11] Tuberculin skin tests should not be considered to be reliable tests for the diagnosis of active disease.

Extrapulmonary involvement carries little risk of transmission, but concomitant pulmonary disease, as was present in this patient, poses a risk of transmission. Fortunately, none of the patient's contacts who were tested had a positive tuberculin skin test. Guidelines for the treatment of extrapulmonary tuberculosis closely mirror those for the treatment of pulmonary tuberculosis.[12] Currently, for susceptible tuberculosis, four-drug therapy for 2 months is recommended, followed by two-drug therapy for 4 months or longer, depending on the extrapulmonary site (e.g., the meninges require longer therapy).

This case highlights the need to consider the possibility of tuberculosis in persons who have lived in areas in which the disease is endemic, including in those who present with disease manifestations outside the pulmonary system.

Dr. Moseley reports providing expert testimony in a case related to chronic hepatitis B virus infection; Dr. Crnich, receiving fees for serving on a data and safety monitoring board from Covance; and Dr. Saint, receiving fees for board membership from Doximity and Jvion. No other 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.

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