A Case of an 11-year-old With Cough, Diarrhea, and Findings of Concern in His Lungs and Spleen

John B. Darby, MD,a Chris A. Rees, MD, MPH,a Claire E. Bocchini, MD,a Andrea T. Cruz, MD, MPH,a Richard Kellermayer, MD, PhD,a Milton J. Finegold, MD,b Sarah E. Barlow, MD, MPHa

This is the case of a previously healthy, 11-year-old male of Indian descent who presented to the emergency department with a 2-month history of nausea, vomiting, diarrhea, fatigue, cough, and 7-lb weight loss. Acutely, he developed 5 days of fever as high as 39.4°C. He had a remote travel history to the Middle East. On physical examination, he was febrile and tachycardic, was thin but otherwise had a normal examination. His inflammatory markers were elevated: erythrocyte sedimentation rate was 93 mm/hour and his C-reactive protein was 25.4 mg/L. A complete blood count revealed a white blood cell count of 17,000 × 10³/μL with increased bands. His hemoglobin level was 8.8 g/dL with a mean corpuscular volume of 81 fl. Platelets were 556 × 10³/μL. A chest radiograph was concerning for a cavitary lung lesion and an abdominal ultrasound revealed multiple hypoechoic lesions in his spleen. Our panel of experts reviews his case and examines the workup of this patient with diverse symptoms and focal findings on chest radiograph and abdominal ultrasound.

JOHN DARBY, MD, PEDIATRIC HOSPITAL MEDICINE, MODERATOR

This case discusses an 11-year-old, previously healthy Indian-American male who presented to the emergency department (ED) with chronic nausea, vomiting, diarrhea, fatigue, weight loss, cough, and then acutely with fever. Two months before presentation, he began to have nausea and nonbloody, nonbilious emesis. His episodes of emesis occurred typically an hour after each meal. His symptoms seemed to cluster into bouts of daily vomiting lasting 3 to 4 days followed by spans of 2 to 3 weeks without nausea or vomiting. His pediatrician prescribed ondansetron, which alleviated these episodes. He had mild, diffuse abdominal pain associated with vomiting. He also developed nonbloody, watery diarrhea twice daily ~2 months before presentation. He also had a mild cough for 3 months that improved with over-the-counter medications. One week before presentation, he developed worsening cough and persistent vomiting and abdominal pain. His diarrhea increased to 4 times per day and he began to have daily fevers as high as 39.4°C.

Review of systems was positive for fatigue, a 7-lb weight loss over 2 months, and occasional mouth sores. His past medical history was remarkable for a ventricular septal defect noted as an infant that closed without surgical intervention as confirmed by echocardiogram at 1 year of age.

His social history included a visit to a farm a few months before presentation where he played near farm animals. He was born in Texas. Five years before presentation, he traveled to a farm and played near farm animals. He was born in Texas. Five years before presentation, he traveled to a farm and played near farm animals. He was born in Texas.

Saudi Arabia, Dubai, and Pakistan on a family vacation. More recently (within the past year), the patient traveled to Mississippi. He had no known tuberculosis (TB) exposures although his grandparents had visited from Pakistan several times in the preceding years. Neither of his grandparents from Pakistan had a chronic cough or hemoptysis by report. The patient did not have high risk food exposures; he had not consumed unpasteurized milk and cheese products or undercooked meat. He denied sick contacts at school.

His family history was unremarkable.

On physical examination, he was febrile to 39.1°C. He had a heart rate of 130 beats per minute, respiratory rate of 24 breaths per minute, and his blood pressure was 110/70 mm Hg. His oxygen saturation was 98% on room air. His weight was 28 kg (second percentile) and his height was 143 cm (30th percentile). He appeared very thin and pale. On cardiac examination, there was tachycardia. He had a cough, but his lungs were clear to auscultation bilaterally. He had normal respiratory effort with no retractions. He had normal bowel sounds, no distension, no masses, no tenderness, and no organomegaly. His skin examination was normal. He had no lymphadenopathy (Fig 1).

Dr Allen, this patient presented to the ED. What were your initial thoughts?

JOSEPH ALLEN, MD, PEDIATRIC EMERGENCY MEDICINE

He was at the second percentile on the growth curve, and his weight loss was concerning. The persistent nature of the vomiting and the diarrhea made me think of something other than a typical viral illness.

In terms of the workup of a patient with these symptoms, a complete blood count and chemistries are a good place to start. I would play close attention to the hemoglobin looking for anemia. Likewise, a low albumin may be a tip that a systemic illness is occurring.

Also, I would check inflammatory markers. If his erythrocyte sedimentation rate (ESR) or C-reactive protein, although they are nonspecific, are elevated it would make one consider a serious infection, inflammatory bowel disease (IBD), or another autoimmune condition. There was an absence of melena and hematochezia; however, given his persistent diarrhea, I would also want to evaluate for bacterial pathogens, such as Salmonella, as well as parasitic infections. I would have liked to order stool cultures and a stool ova and paras.

DR DARBY

Are there any imaging studies you might want at this point?
With a persistent dry cough, weight loss, and a travel history like he had, one should consider TB. In a metropolitan city like Houston with a lot of international travel, one should be prudent about recognizing TB especially given how pervasive its spread can be. I would have liked to see a chest radiograph for this patient.

DR DARBY

The initial laboratories of significance are shown in Table 1.

His electrolytes, albumin, and liver function tests were within normal limits. His stool guaiac was positive. Lactate dehydrogenase and uric acid were both within normal limits as well. His chest radiograph is shown here (Fig 2).

TABLE 1 ED Laboratories

<table>
<thead>
<tr>
<th>ED Laboratories</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count, $10^3$ cells/μL</td>
<td>17, 5–14</td>
</tr>
<tr>
<td>Segmented neutrophils, %</td>
<td>40, 33–76</td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td>14, 15–61</td>
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<tr>
<td>Bands, %</td>
<td>40, 0–1</td>
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<tr>
<td>Hemoglobin, g/dL</td>
<td>8.8, 11.5–15.5</td>
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<tr>
<td>Mean corpuscular volume, fl</td>
<td>81, 76–90</td>
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<tr>
<td>Platelets, $10^3$ cells/μL</td>
<td>556, 150–450</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>93, 0–20</td>
</tr>
<tr>
<td>C-reactive protein, mg/dL</td>
<td>25.4, &lt;1.0</td>
</tr>
</tbody>
</table>

DR DARBY

So there is concern for a cavitary lung lesion, hypoechoic lesions in his spleen, a cough, weight loss, and diarrhea. One of the initial concerns was for infection.

CLAIRE BOCCHINI, MD, PEDIATRIC INFECTIOUS DISEASES

From the infectious disease perspective, the differential diagnosis was broad. I thought about bacterial infections such as endocarditis, which can cause weight loss, cough/cavitary lesions, and splenic lesions. Salmonella can cause diarrhea and systemic disease including splenic lesions, but the pulmonary lesions would be unusual. TB and atypical mycobacteria can cause systemic disease, including pulmonary and splenic lesions and colitis. Fungal infections such as Cryptococcus, Histoplasma, and Coccidioides can cause disseminated disease, although usually in immunocompromised children. Histoplasmosis was also high on my differential given the patient’s travel to Mississippi since histoplasmosis can cause enterocolitis as well as pulmonary and splenic disease.

This patient did not have a history suggestive of a primary immunodeficiency, but infections that can cause pneumonia, splenic lesions, and diarrhea in immunocompromised patients were considered. As mentioned, these include atypical mycobacteria and fungal infections. I recommended a basic workup to determine if this patient was a normal host.

I also felt that noninfectious etiologies should have been considered high on the differential, including IBD, vasculitis, autoinflammatory conditions, sarcoidosis, and oncologic processes. I recommended a computed tomography (CT) scan of the chest, abdomen, and pelvis with contrast to better assess the extent of disease, look for lymph node involvement, evaluate for inflammation of the gastrointestinal tract, and to prepare for a biopsy. For many of the etiologies we were considering, the diagnosis would have been made with a biopsy and histopathology review.

DR DARBY

Dr Rodriguez, will you take us through the CT?

DR RODRIGUEZ

There were multifocal, pleural-based regions of consolidation and a small pleural effusion. When viewed through the lung windows, it was clear that there was not a cavitary lesion in the lung. There were multiple, small ground-glass nodules, inconsistent with what is seen with metastases or other neoplastic changes. There was also hilar lymphadenopathy (Fig 3).
In the spleen, there were multiple, noncontrast enhancing, hypoechoic and cystic lesions, which might suggest a pyogenic infectious process, inflammatory process, malignancy, or a vascular process. One would also consider granulomatous etiologies such as cat scratch, TB, or sarcoidosis (Fig 4).

There was also an inflamed ascending colon with hyperenhancing mucosa that extended into the transverse colon and into the appendix.

**DR DARBY**

Dr Barlow, IBD was mentioned. What were your thoughts at this point?

**SARAH BARLOW, MD, MPH, PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY, AND NUTRITION**

Given the signs of inflammation on the CT and the diarrhea, it is clear that the colon was involved. But the splenic and especially the pulmonary lesions made me think that this may not have been IBD but rather that this was a manifestation of an unusual infection with an underlying immunodeficiency.

**DR DARBY**

Would a calprotectin or lactoferrin be useful in this case?

**DR BARLOW**

Not really. Calprotectin and lactoferrin are signs of inflammation. Those tests are useful when trying to determine whether a child with chronic diarrhea has irritable bowel syndrome rather than IBD or some other inflammatory condition of the bowel. In this case, there was no question that the bowel was inflamed.

**RICHARD KELLERMAYER, MD, PHD, PEDIATRIC GASTROENTEROLOGY, HEPATOLOGY, AND NUTRITION**

It is important to recall that the stool guaiac was positive. When there is blood in the stool, the calprotectin and lactoferrin may also be positive as white blood cells follow red blood cells as they transcend an inflamed bowel, or even uninflamed bowel, as is the case with hemorrhoids. I recommend caution when interpreting calprotectin results if the hemoccult is positive.

**DR BARLOW**

Because his stool was guaiac positive and he was anemic, there was some concern that part of the cause of anemia was blood loss. We decided to proceed with endoscopy and colonoscopy to obtain a tissue sample from the colon. The upper endoscopy looked normal grossly, as did the colonoscopy, surprisingly. The proximal colon was edematous but there was no clear inflammation and no ulceration. The ileal mucosa also appeared normal.

**DR DARBY**

With grossly normal appearing stomach and colon, we waited for
If this was TB then, by definition, this was disseminated TB, which is atypical in a child thought to be immunocompetent. However, it is possible to have a late presentation of vertically acquired HIV. There are also some interferon mutations that can predispose to mycobacterial infection.

Importantly though, when I think of TB, I don’t just think of TB, I think of the cousins of TB. *Mycobacterium bovis* should have been on the differential diagnosis. *M. bovis* is commonly found in unpasteurized milk products, which, by history, this patient had not consumed. When we ask our patients about fresh cheeses coming from Mexico or the Middle East as a source of potential *Brucella* exposure, we fail to think of *M. bovis*. *M. bovis* is known for causing extrapulmonary manifestations. It can cause involvement from the upper to lower gastrointestinal tract and it has a significant predilection for also causing extraintestinal disease. *M. bovis* can be seen both in immunocompromised and immunocompetent hosts.

As part of the workup for mycobacteria, it is important to ask about risk factors in the family. A child is often the first person in the family diagnosed with TB because people have a different threshold for bringing their children to medical attention than they have for seeking care for themselves. When a family tells you that there is no family history of TB, it is not that they are lying; for example, there may be a person in the family with a chronic cough thought to be secondary to smoking.

For a laboratory workup, we typically start with tuberculin skin test, T-SPOT and QuantiFERON tests (interferon γ release assay) and obtain cultures if possible. This was a child in whom I would have done sputum induction by pretreating with albuterol and hypertonic saline to have him cough into a cup if he could not spontaneously produce sputum. Moreover, a biopsy and acid-fast bacillus culture of the pleural-based nodules could be helpful in making a diagnosis. If there is a pleural effusion, a pleural punch biopsy might be the highest yield for a culture, much more so than simply obtaining the serous fluid as that fluid is very inflammatory and there will be a lot of cells but not necessarily TB organisms. It would also be helpful for interventional radiology to aspirate the splenic lesions and send that off for acid-fast bacilli stain and culture along with TB polymerase chain reaction (PCR).

**Dr Darby**

In this case, a tuberculin skin test and QuantiFERON test were sent and were both negative. With these tests being negative, why would one need tissue samples?

**Dr Cruz**

We need the tissue sample in a questionable case for a few reasons. First, there is a high rate of false-negative tuberculin skin tests in malnourished children. This child is clinging to the bottom of the growth curve and is certainly not a well-nourished host. Malnutrition can also cause indeterminate QuantiFERON test results. It is notable that most of the data on malnutrition and immunologic tests for TB come from international settings where the definitions of malnutrition vary from those in the United States. As the QuantiFERON test and the tuberculin skin test are tests of immune recognition, it is not surprising that both would be affected by the immunosuppressive state caused by malnutrition. The impact of malnutrition on the sensitivity and specificity of these tests is a difficult question to address in children, as the reference standard would be microbiologically confirmed TB disease.

The other reason that we would need a tissue sample is that the risk of anergy to these tests is actually much higher if you have overwhelming TB disease. Approximately 50% of children with TB meningitis, for example, have negative tuberculin skin tests. TB cannot be ruled out based on a negative tuberculin skin test or interferon γ release assay.

From the standpoint of making a microbiologic diagnosis, there is probably no one in whom it is more important than this child who had an extensive travel history and frequent exposure to family members who live in TB endemic areas. We do not know the exact rates of drug resistance in those areas. It is better to have those data initially and not wait 6 months into treatment without improvement.
However, if a child has a cavitary lesion, regardless of their age, you take precautions as though they were contagious (ie, negative pressure room and N-95 masks). You should take the same infection control precautions with a draining lesion, such as is seen in scrofula, when patients can develop a draining sinus tract. As a general rule, most children who have pulmonary TB are not contagious.

DR DARBY

Regarding additional laboratories that were requested, blood and urine cultures were negative, the bronchoalveolar lavage cultures were negative, and *Bartonella* titers were negative. Serum antibody tests for fungus including *Histoplasma*, *Coccidioides*, and *Blastomyces* were negative. Multiple stool studies were negative, including *Clostridium difficile* PCR, mycobacterial cultures, stool O&P (ova and parasites), *Helicobacter pylori* antigen, and *Giardia* and *Cryptosporidium* antigen. He also had a negative immunodeficiency workup including quantitative immunoglobulin levels, dihydrorhodamine, humoral immunity panel, mitogen stimulation testing, lymphocyte proliferation studies, and HIV.

Several of the requested procedures were completed including endoscopy, colonoscopy, and biopsies of the spleen and lung. Dr Finegold, will you take us through the pathology slides?

MILTON J. FINEGOLD, MD, PATHOLOGY & IMMUNOLOGY AND PEDIATRICS

The stomach revealed nonspecific, chronic, active inflammation with focal erosion in the antrum but no granulomata. The duodenum, ileum, and cecum also revealed diffuse inflammation that was nonspecific without any granulomata. There was marked crypt distortion with cryptitis and abscess formation in the transverse colon and rectosigmoid. From a pathologist’s perspective, these findings were consistent with chronic IBD without granulomata. The fine needle aspirate of the cystic lesions in the spleen was consistent with granulomata, however. No microorganisms were identified by Gram, acid-fast or fungal stains, culture, or PCR for *Bartonella* (Figs 5, 6, and 7).

DR DARBY

Dr Barlow, what was your reaction to the pathology findings?

DR BARLOW

We certainly had high suspicions about Crohn disease (CD) when the pathology revealed diffuse inflammation. However, there remained significant concern for infection despite the negative workup. Additionally, the treatment of diffuse CD is infliximab, which is contraindicated in patients with TB.

There were extensive discussions between the infectious disease and gastroenterology teams surrounding this patient’s diagnosis. Though less common in countries where TB is not endemic, intestinal TB in children has been documented in the literature.7,8 Given the child’s clinical presentation with a cough, diarrhea, weight loss, and the concern for TB exposure, along with the pulmonary nodules, and chronic inflammation in the gastrointestinal tract, the decision was made to start rifampin, isoniazid, pyrazinamide, and ethambutol for empirical TB therapy. He showed initial improvement over the course of a few weeks but he then deteriorated.

DR BARLOW

When he deteriorated despite TB treatment, a mycobacterial infection seemed unlikely and our concern for CD further increased. Because his symptoms of diarrhea, vomiting, and weight loss continued despite undergoing TB treatment, the decision was made to start infliximab therapy. He had another endoscopy and...
colonoscopy to establish a baseline before treatment. Unlike the first studies, these procedures revealed gastritis and colitis both grossly and histologically, though granulomata remained absent.

He was then started on infliximab and he responded in a matter of days. His appetite improved, his fevers resolved, his diarrhea stopped and he felt much better. Given his clinical response to infliximab, we felt confident of the diagnosis of CD. Moreover, he had an abdominal ultrasound after 3 infusions of infliximab, and his splenic lesions had abated.

There have been case reports of splenic lesions in CD. In some of the cases they are abscesses that could be due to contiguous bacterial spread or possibly from hematologic spread.9–12 Aseptic abscesses have been reported as well.13–18

DR KELLERMAYER

Regarding the pulmonary lesions, there have been incidental case reports of CD presenting primarily as pulmonary disease.19–25 Identification of noncaseating granulomas would have been helpful though those were not present on the tissue sample.

One of the most important things that we can all learn from a case like this is how important it is for a pediatrician to take accurate longitudinal measurements of growth. The patient’s height was at the 30th percentile and his weight was at the second percentile. Such growth parameters are red flags and indicate the potential presence of a chronic disorder. After receiving 3 treatments of infliximab, he grew at least an inch and gained back all of his acutely lost weight.

It is also important to recall that his ESR was initially 93 mm/hour. With an ESR approaching 100 mm/hour, it is important to consider noninfectious inflammatory processes.

Summary

CD is an inflammatory condition that is increasing in incidence and prevalence worldwide.26,27 It primarily affects the intestinal tract, but can be complicated by extraintestinal manifestations that can present in almost any organ. Noncaseating granulomas are
considered pathognomonic for this disease but, as in this patient, they are not always present. The etiology of CD is currently unknown, and there is no cure available for the disorder.

Infectious etiologies were important considerations in this case for several reasons. First, the extraintestinal manifestations were unusual. Although CD may not be limited to the intestine, the more common extraintestinal manifestations are arthralgia, arthritis, uveitis, erythema nodosum, and pyoderma gangrenosum. In this case, the constellation of pulmonary and splenic lesions was an unusual presentation of CD. Antibiotics can reduce the inflammation seen in CD, and we speculate that the anti-TB medications given led to transient improvement in his colonic inflammation.

The prolonged time between exposure to an unusual infection and the onset of symptoms often hinders consideration of these rare infectious conditions. However, when they are considered, the differentiation of CD from a number of disseminated infectious processes can be challenging.

Finally, the treatment regimen for moderate to severe CD is likely to worsen an infection. The foundation of CD treatment is immunosuppression. The antitumor necrosis factors-α agents that became available ~15 years ago are generally well tolerated, they do not always present. The etiology of CD is currently unknown, and there is no cure available for the disorder.

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Finally, the treatment regimen for moderate to severe CD is likely to worsen an infection. The foundation of CD treatment is immunosuppression. The antitumor necrosis factors-α agents that became available ~15 years ago have greatly improved the ability to control inflammation in moderate to severe CD. Although these agents are generally well tolerated, they do increase susceptibility to infection and, in particular, can activate latent TB. The risk is significant enough that standard protocol before initiating infliximab or other biologics is robust. The risk is significant enough that standard protocol before initiating infliximab or other biologics is to assess for TB, even in patients without identified risk factors.

In this case, the comprehensive evaluation by the multispecialty team was essential to exclude infectious causes. Despite the lack of a simple positive test for CD, the evaluation supported the safety of infliximab, and the patient’s response has validated the treatment.

ACKNOWLEDGMENTS

We thank Drs Joseph Allen, MD, and Danella Rodriguez, MD.

ABBREVIATIONS

CD: Crohn disease  
CT: computed tomography  
ED: emergency department  
ESR: erythrocyte sedimentation rate  
IBD: inflammatory bowel disease  
PCR: polymerase chain reaction  
TB: tuberculosis

REFERENCES


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