Case report: Ileocecal tuberculosis

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Abstract

Tuberculosis (TB) can affect any organ system and resemble multiple disease entities, thus it is often called the "great mimicker". We discuss the imaging features and challenges of diagnosing extrapulmonary TB—specifically gastrointestinal manifestations of TB—in our case of a 25 year–old immigrant from Southeast Asia. The diversity of manifestations of TB should alert the reader to keep this elusive disease on their differential diagnosis.

Introduction

Tuberculosis (TB) is frequently thought of as a disease of the developing world, however incidence in Canada is not uncommon, with about 26 and 17 cases per 100,000 persons/year among Aboriginal and foreign–born Canadians respectively, with even higher rates among immunocompromised individuals.[1] While often limited to the pulmonary system, TB may affect the bones, joints, heart, central nervous system, and abdomen—a region involved in up to 11 % of extrapulmonary cases of TB.[2] A brief list of the abdominal manifestations of TB includes: TB lymphadenitis, peritonitis, gastroenteritis, as well as possible masses within and enlargement of the spleen, liver, adrenals, and pancreas.[2] The signs and symptoms of TB are usually generalized and nonspecific, with imaging features frequently resembling other disease entities, giving TB the pseudonym "the great mimicker."[3] The challenging diagnosis of extrapulmonary TB is usually made by the combination of imaging and microscopy. Histopathologic analysis uses a special technique called a Ziehl–Neelsen, or acid–fast bacillus (AFB) stain, as the *Mycobacterium tuberculosis* bacteria are impermeable to Gram staining due to their waxy outer layer.

To highlight the challenges of diagnosing extrapulmonary TB, we discuss a curious case of pulmonary TB which was also found to involve the gastrointestinal system.

Case presentation and workup

A 25–year–old female recent immigrant from Southeast Asia is admitted to hospital for abdominal pain and fever not yet determined. Her history of presenting illness includes a two–year history of productive cough, significantly worsening over the last one month and associated with fevers and chills. She endorses shortness of breath but denies hemoptysis. Other infectious symptoms include worsening diarrhea over the past five days with some bright red blood per rectum.

Her past medical history is unremarkable aside from an appendectomy. Her only risk factors for infectious etiology include travel to China six months prior. She has not traveled to rural areas or had exposure to sick contacts. She is a non–smoker, non–drinker, and is not sexually active. Her review of systems is negative for any rheumatologic or constitutional symptoms.

Her vital signs include a fever of 39.5 ºC, tachycardia, and tachypnea. Her blood pressure is normal and she is saturating well on two liters of supplemental oxygen via nasal prongs. Respiratory exam reveals bronchial breath sounds and decreased air entry to the right lung base. Other components of her physical exam are unremarkable.

Initial laboratory workup shows a white blood cell count of $13.8x10^9$/L and a microcytic anemia with hemoglobin of 88 g/L Her renal function and urinalysis are normal. In regards to her yet to be determined fever, she was started on piperacillin–tazobactam and was sent for a chest x–ray. Her x–ray revealed bilateral nodular opacities and lymphadenopathy (Figure 1). A broad differential for diffuse pulmonary nodules on chest x–ray includes sarcoidosis, granulomatosis polyangitis, septic emboli, as well as tuberculosis. The combination of signs, symptoms, physical exam, and chest x–ray findings in a foreign visitor put this patient at a high pre–test probability of having TB.[4] Our patient was placed in isolation, during which time her sputum sample came back as positive for acid–fast bacteria. The piperacillin–tazobactam was discontinued and she was started on standard quadruple TB therapy: rifampin 600 mg, isoniazid 300 mg, pyrazinamide 1250 mg, and ethambutol 800 mg.

She continued to have persistent fevers and began to complain of worsening diarrhea and rectal bleeding, the clinical differential of which includes inflammatory bowel disease, diverticulitis, ischemic bowel, or infectious causes such as *cytomegalovirus (CMV)* or abdominal manifestation of TB. The six–month lag symptom onset and her travel to China made an acute travel related infection unlikely. Her differential diagnosis was further narrowed by a negative stool culture, ova and parasite examination, and *Clostridium difficile* test. She did not have an elevated lactate and her serology was negative for CMV, Hepatitis, and HIV.

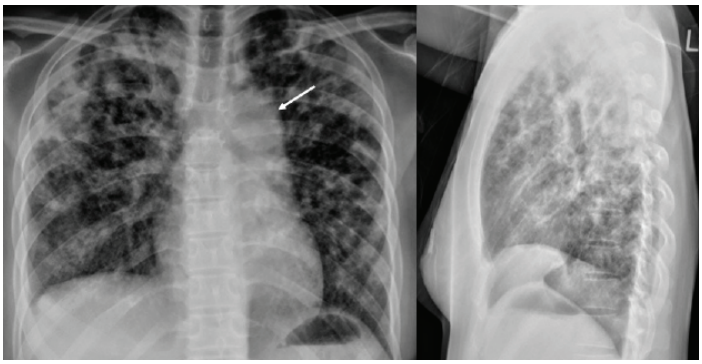

Figure 1 | Postero–anterior and lateral chest radiographs. Numerous and diffuse bilateral soft tissue densities are seen with no evidence of cavitation, in addition to a small right sided pleural effusion. Mild mediastinal lymphadenopathy is indicated by loss of normal aortopulmonary window (white arrow).

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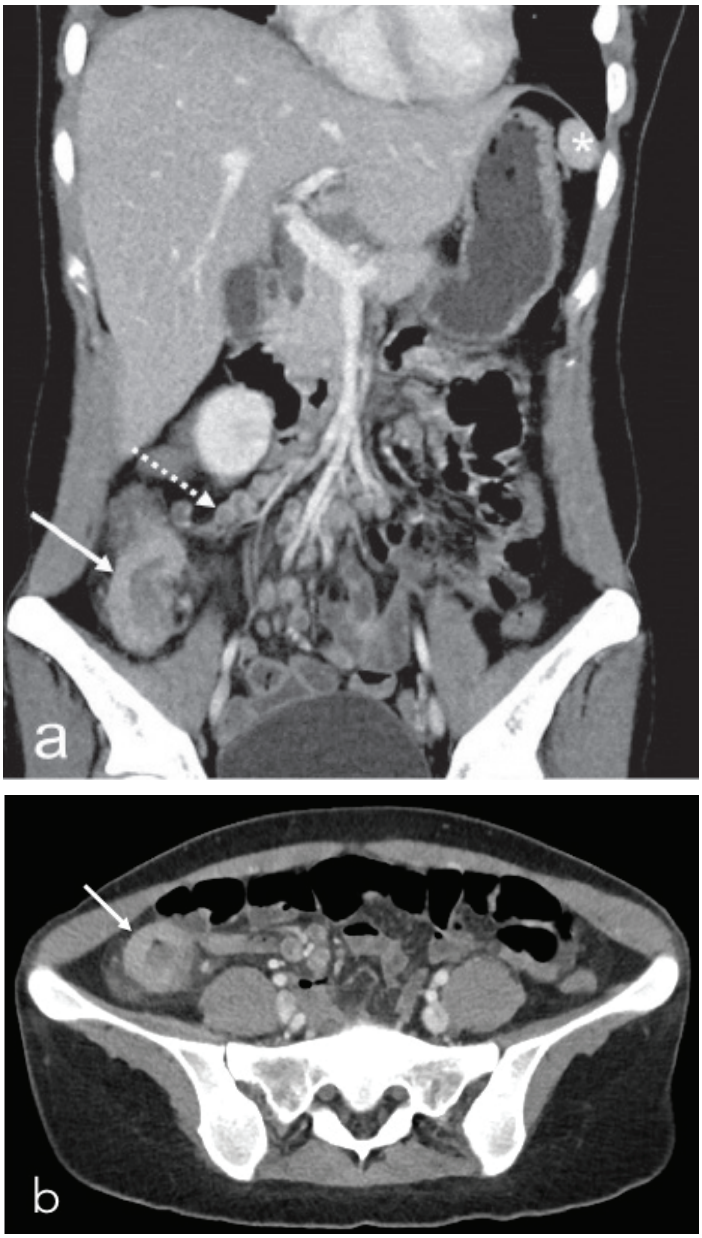

Figure 2 | (a) Coronal and (b) axial contrast enhanced CT abdomen and pelvis. Marked focal mural thickening and enhancement of the right hemicolon and terminal ilieum (white arrow), with multiple small necrotic nodes in the ileocolic fat. Extensive mesenteric lymphadenopathy with nodes measuring up to 1 cm in diameter with central areas of necrosis (dashed arrow). Other than a small accessory spleen (*), there are no focal abnormalities.

An abdominal computed–tomography (CT) scan was requested, which revealed significant ileocecal mural thickening and necrotic lymphadenopathy (Figure 2). The presence of ileocecal thickening on imaging can be present with Crohn's disease (CD), malignancy, or TB, and although necrotic lymphadenopathy can also be seen in malignancy and TB, it is not usually present in inflammatory bowel disease.

Combining her clinical and imaging findings, the working diagnosis was Crohn's disease or extrapulmonary manifestation of TB—specifically ileocecal TB (ITB). Using the simplified algorithm in Figure 4, one can see that both CD and ITB are grouped together under granulomatous diseases, thus one cannot differentiate CD from ITB based on bowel wall thickening pattern alone. In addition,

Table 1 | Commonly found features of Crohn's disease and ileocecal tuberculosis on abdominal computed–tomography scan. Fistulas and abscesses are italicized as they are contested to have a similar occurrence in both. Derived from Journal of Digestive Diseases 2016; 17; 155-161.[6]

Crohn's Disease	Intestinal Tuberculosis
Segmental Involvement	Focal involvement
Asymmetric mural pattern	Right colic artery predilection of lymph-adenopathy
Mural stratification	Lymph nodes ≥ 1 cm
Left colon involvement	Central necrosis/calcification of lymph nodes
Comb sign (vascular congestion of vasa recta)	Fistulas and abscesses
Fibrofatty proliferation	
Fistulas and abscesses	

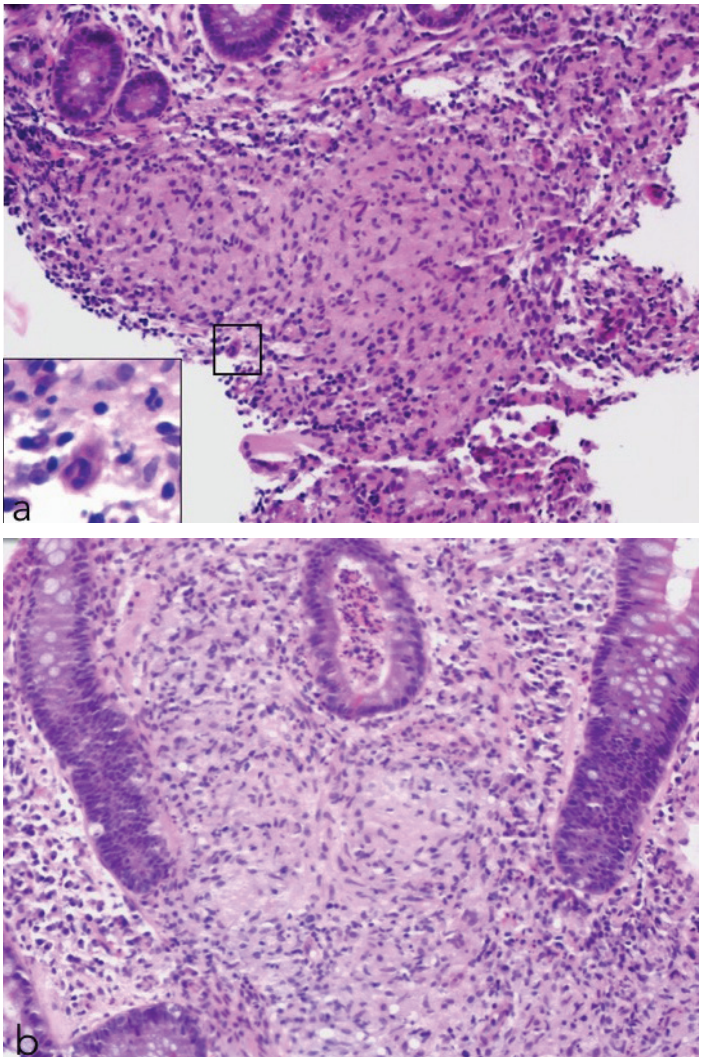

Figure 3 | Hematoxylin and eosin stain of colonic biopsy at (a) low and (b) medium power show multiple concentrations of granulomatous inflammation with central areas of necrosis. A Langhans type giant cell is magnified on the inset of (a).

the absence of intestinal strictures, fistulas, or abscesses associated with Crohn's, or any extraintestinal manifestations such as cirrhosis, cholelithiasis, and nephrolithiasis is neither a sensitive nor specific finding to narrow the diagnosis.

Kedia et al. attempted to develop criteria differentiating CD from TB and showed that lymph nodes greater than 1 cm and ileocecal involvement had odds ratios favouring ITB, however due to multiple outliers and exceptions, there are ultimately no exclusive imaging predictors.[5] A 2016 review of ITB and CD describes

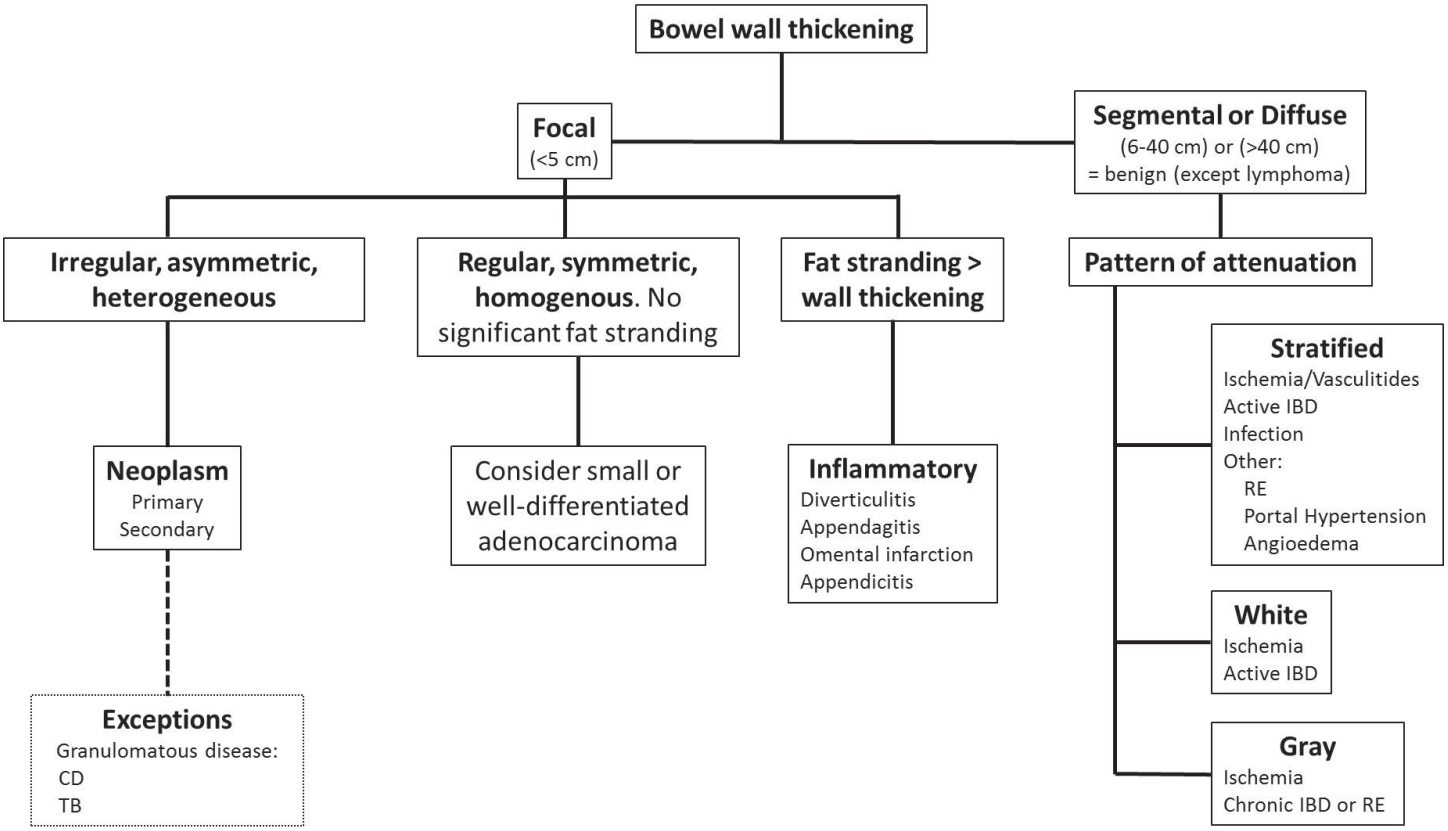

Figure 4 | Simplified algorithmic approach to bowel wall thickening. IBD; inflammatory bowel disease. RE; radiation enteritis. CD; Crohn's disease. TB; tuberculosis. Modified from Insights Imaging (2014) 5:195-208.[8]

imaging characteristics more commonly found in one disease process versus another (Table 1), but confirms the lack of specific criteria to reliably differentiate the two.[6]

Case conclusion

To arrive at a definitive diagnosis, the patient underwent a colonoscopy and ileocecal biopsy. Microscopy exhibited extensive areas of granulomatous inflammation (Figure 3). Granulomatous inflammation in itself is a nonspecific finding, as it can be observed in a multitude of fungal, bacterial, and viral infections in addition to Crohn's disease, sarcoidosis, and granulomatous polyangitis. However, given the presence of Langhans type giant cell, characteristically found in TB granulomatous inflammation, and the lack of crypt abscess or mucosal ulceration to suggest Crohn's disease, her diagnosis was most in keeping with *TB enteritis*. Although an AFB stain of the biopsy was negative – not uncommon after initiation of *TB antibacterials* – the sample was subsequently found to be culture positive for *M. tuberculosis*.

The case was confirmed to be dissemination and extrapulmonary manifestation of TB within the gastrointestinal tract. The treatment for abdominal TB is the same as for active pulmonary TB, thus the patient was kept in isolation and received daily quadruple therapy. Due to persistent fevers and continued positive sputum cultures, the dose of her rifampin, isoniazid, and ethambutol were increased to 900 mg, 600 mg, and 1200 mg respectively. She underwent two months of in–hospital therapy under this regime, and at six weeks was deemed non–infectious as a result of negative sputum cultures. She was discharged on a six–month course of daily isoniazid 600 mg, rifampin 900 mg, ethambutol 1200 mg, and pyridoxine 50 mg.

Discussion

Our patient presented with features quite typical for an active pulmonary TB infection. She was a visitor from an area with a high endemic rate of TB and endorsed a history of chronic productive cough associated with dyspnea, fevers, chills, and general malaise. A positive sputum AFB stain combined with evidence of pulmonary involvement on chest x–ray confirmed an active infection and warranted isolation and initiation of quadruple TB therapy. Our initial workup of her gastrointestinal symptoms (as described above) narrowed our differential diagnosis to that of inflammatory bowel disease or intestinal manifestation of TB—entities which can be so similar they received special attention in a 2016 review "Intestinal tuberculosis and Crohn's disease: challenging differential diagnosis."[6]

Our case was made especially challenging given that our patient already had an active pulmonary TB infection. While an active TB infection increases the likelihood that abdominal symptoms are related to ITB, the presence of mycobacterium in patients with CD is theorized to act as an inflammatory nidus triggering a CD flare.[6] Furthermore, positive sputum cultures or serologic tests for TB, such as an interferon gamma assay that measures cytokine release from immune cells exposed to *M. tuberculosis* antigen, would not help distinguish ITB from CD in our patient. Even stool analysis with polymerase chain reaction (PCR) for *M. tuberculosis* DNA—considered more specific for ITB—could yield false positive results given the possibility of patients with active pulmonary TB swallowing infected sputum. Serologic tests for CD, such as anti-*Saccharomyces cerevisiae* antibody (ASCA) test, could help in the diagnosis of CD and even differentiate CD from ulcerative colitis, however similar positive rates occur in patients with ITB as in CD,

limiting its usefulness in our setting.[6]

Another diagnostic tool that could be used includes aspiration and analysis of ascitic fluid in patients with suspected gastrointestinal TB. Findings suggestive of TB in peritoneal fluid include an exudate with > 300 white blood cells/mm3, a serum–ascites albumin gradient < 1.1 g/dl, or a positive adenosine deaminase assay (ADA).[7] Unfortunately, our patient did not have a clinically significant level of peritoneal fluid for safe paracentesis.

As discussed in our case presentation, cross–sectional imaging alone cannot accurately differentiate ITB from CD. Histopathalogic analysis is required for confirmation of ITB with the gold standard being the presence of caseous granulomas and a positive AFB. Here again, our diagnosis was made more challenging secondary to initiation of antibiotic therapy for active pulmonary TB producing a negative AFB stain of our patients' ileal biopsy. A confirmatory diagnosis for ileocecal TB was only possible after several weeks when her specimen was found to be mycobacterium culture positive.

The diagnostic challenges presented herein can be quite common, with a misdiagnosis between ITB and CD quoted to be between 50-70 %.[6] And although treatment for CD and ITB differ, the treatment of extrapulmonary TB is the same as for pulmonary TB (daily quadruple drug regime). Because our patient was already started on TB antibiotics, she was concomitantly receiving appropriate empiric therapy for her abdominal symptoms even amidst her diagnostic dilemma. Current literature recommends that when considering CD versus ITB, and where ITB is highly suspicious, that anti–TB chemotherapy be initiated with a therapeutic trial of two to three months and monitoring for clinical improvement.[6]

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