

# Disseminated Tuberculosis in a Patient Taking Anti-TNF Therapy for Crohn's Disease

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## Abstract

A man in his sixth decade with Crohn's colitis and who had been taking infliximab for 18 months presented with fever and weight loss. Chest CT showed numerous nodules in both lungs, and sputum culture grew *Mycobacterium tuberculosis*. Colonoscopy showed circumferential ulcerations from the cecum to the descending colon, and biopsies showed extensive granulomas with central necrosis, positive for acid-fast bacteria. Brain MRI revealed a thalamic ring-enhanced mass with edema, consistent with tuberculoma. Clinicians should be aware of the appropriate screening and close monitoring of tuberculosis before and during anti-tumor necrosis factor (TNF) therapy.

## Introduction

Tuberculosis (TB) remains a major health problem in developing countries. An increasing number of cases of TB in North America since the mid-1980s have been attributed to immigration, coinfection with HIV, and the development of multidrug-resistant TB. The use of anti-tumor necrosis factor (TNF) agents such as infliximab alone and in combination with other immunosuppressants has become more popular in the treatment of Crohn's disease (CD).<sup>1</sup> Reports exist in the literature describing patients developing TB after infliximab therapy.<sup>2</sup> High-risk factors for developing TB with anti-TNF therapy include concomitant use of immunosuppressants, history of latent or active TB, and being born in or spending extensive time in endemic areas.

## Case Report

A man in his sixth decade was admitted to our tertiary hospital for worsening diarrhea. He had been diagnosed with CD 3 years prior, and had been treated with intravenous infliximab for the previous 18 months after failure to respond to treatment with oral mesalamine. Before beginning treatment with the anti-TNF agent, he had a positive tuberculin skin test and a negative chest radiograph. Infliximab was started 2 months after he completed a 9-month course of isoniazid for latent tuberculosis. His CD-related symptoms gradually improved after the initiation of infliximab and had been stable for 16 months.

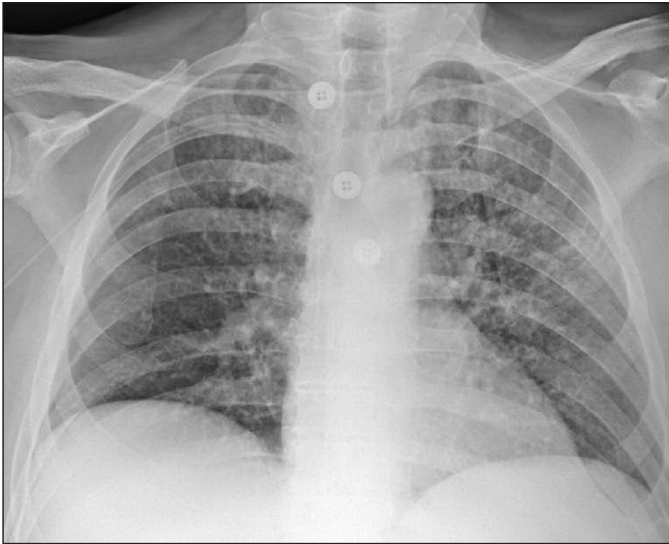
He had a 2-month history of intermittent fever, fatigue, and weight loss of 18 kg. On this presentation, chest radiograph and chest CT showed numerous, bilateral, scattered, small (<5 mm) nodules, with some clustered in a tree-in-bed distribution (Figures 1 and 2). Three consecutive sets of sputum showed acid-fast bacteria, and liquid culture grew *Mycobacterium tuberculosis* (MTB; Figure 3). Colonoscopy showed extensive circumferential ulcerations segmentally distributed from the cecum to the descending colon (Figure 4). Colon biopsies showed large epithelioid granulomas with central necrosis that were positive for acid-fast bacteria (Figure 5).

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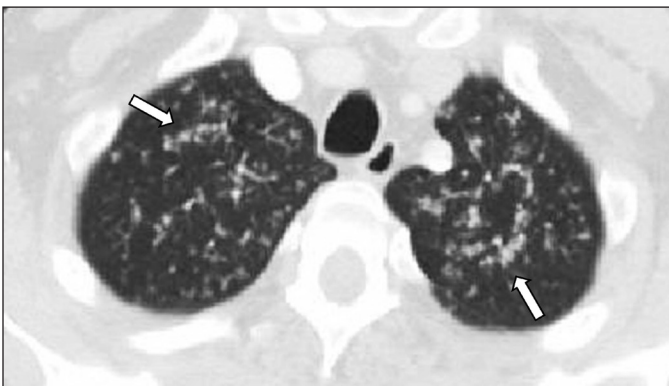
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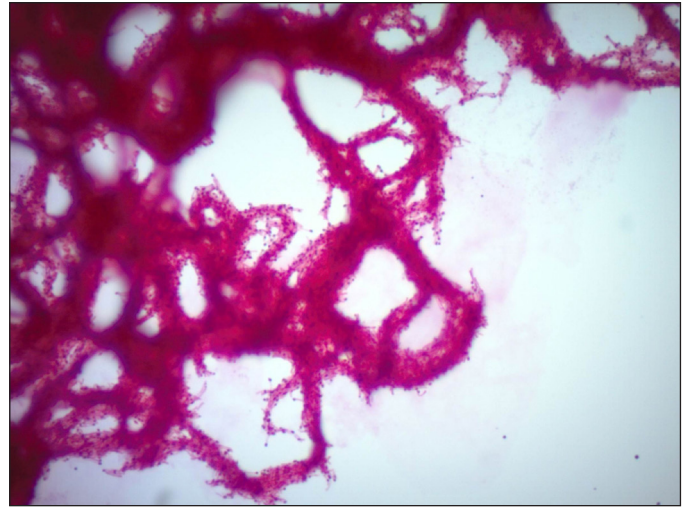
**Figure 1.** Chest radiograph showed numerous small nodules in both lungs.

Stool culture was positive for MTB. A polymerase chain reaction (PCR) test of the colon biopsy specimens confirmed a diagnosis of MTB.

During hospitalization, the patient developed intractable nausea and vomiting. The gadolinium-enhanced MRI of brain revealed a right thalamic ring-enhanced 1.2-cm mass with edema, consistent with tuberculoma, and several smaller punctate lesions in left parietal-temporal lobe and both cerebellar hemispheres (Figure 6). Cerebral spinal fluid analysis revealed high protein and low glucose levels, but a negative MTB culture. Infliximab was discontinued. With the concern of potential isoniazid-resistant tuberculosis (TB), the patient received amikacin in combination with the standard anti-TB regimen for the first 4 weeks before the drug-susceptibility result came back negative for isoniazid resistance. An anti-TB regimen of isoniazid, rifampin, ethambutol, and pyrazinamide for the first 2 months was started, followed by isoniazid and rifampin for an additional



**Figure 2.** Chest CT showed numerous small nodules (black arrows) in both lungs, with some clustered in tree-in-bed distribution.

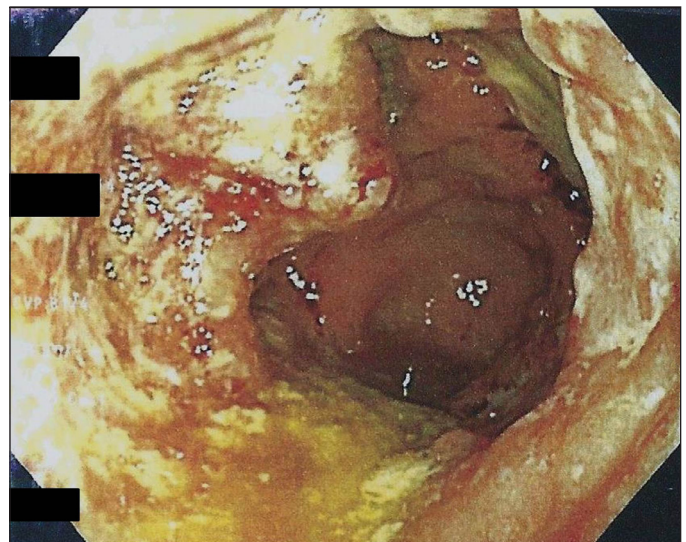


**Figure 3.** *Mycobacterium tuberculosis* can be seen cording in liquid culture (100x magnification).

8 months. After antiemetics and the continuation of anti-TB therapy, the patient's symptoms gradually improved. Subsequent sputum cultures were negative for TB. Repeated MRI of the brain showed a decrease in the size of the tuberculoma. Unfortunately, the patient suddenly became ill and died 8 months after diagnosis, presumably from complications of disseminated TB.

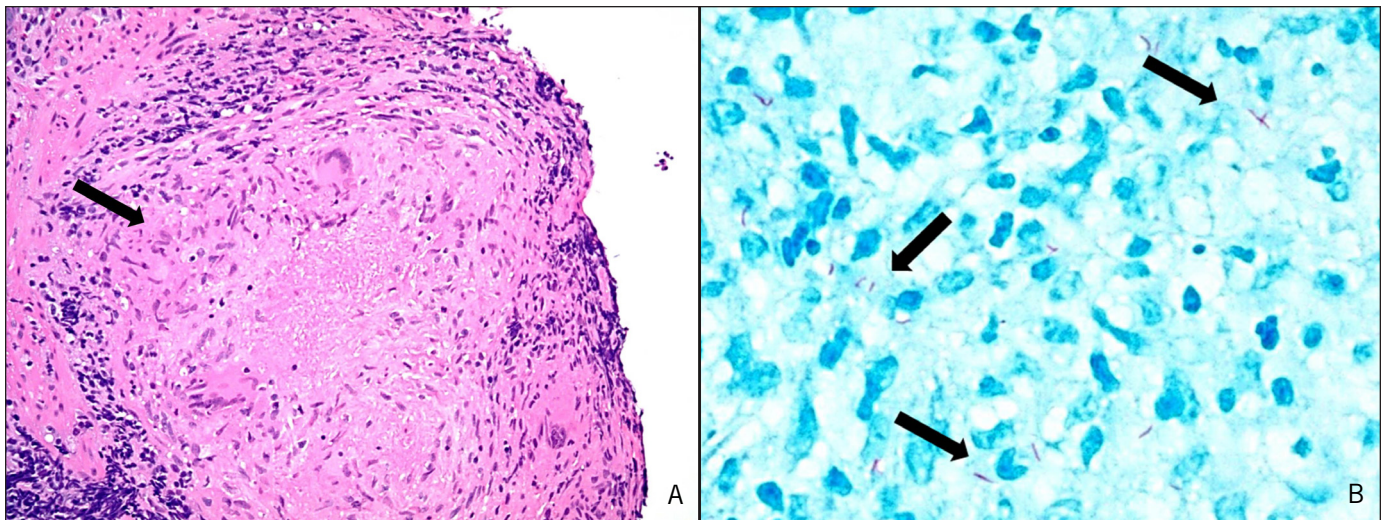
## Discussion

Patients with a positive tuberculin skin test should receive chemoprophylaxis with either isoniazid for 6–9 months, or rifampin for 3–4 months.<sup>3</sup> Shorter regimens might avoid poor adherence and hepatotoxicity; however, rifampin-containing



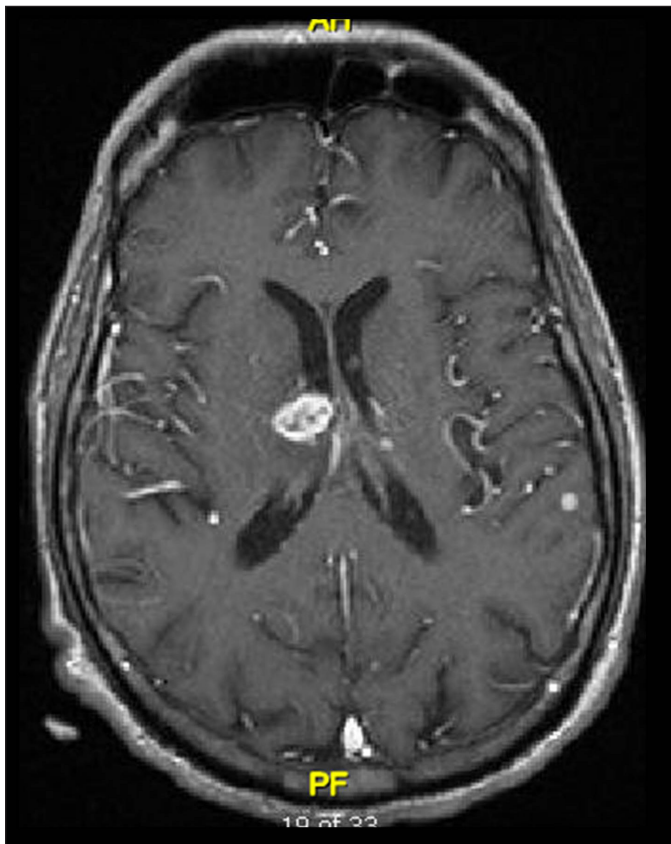
**Figure 4.** Large circumferential ulcerations surrounded by inflamed mucosa at right colon.





**Figure 5.** (A) Extensive large epithelioid granulomas with central necrosis at colon biopsy. (B) Acid-fast bacteria stained by Ziehl-Neelsen in colon biopsies (400x magnification).

regimens should be prescribed with caution to people who are on antiretroviral treatment due to potential drug-to-drug interactions. In general, anti-TNF therapy may be started 2 months after completion of chemoprophylaxis. During the



**Figure 6.** A 1.2-cm ring-enhanced mass with peripheral edema at right thalamus in the gadolinium-enhanced brain MRI.

anti-TNF therapy these patients should be closely monitored at least annually with TB screening tests, starting 12 months after completion of chemoprophylaxis, to identify reactivation of latent TB or new TB infection. Up to a 19% risk of TB reactivation has been reported, mostly during the first year of anti-TNF therapy after completion of chemoprophylaxis.<sup>4</sup> A case series of 130 patients who developed TB after infliximab between 2001 and 2006 was reported; 45% of cases had extrapulmonary involvement.<sup>2</sup> In the subset analysis, only 3 of the 23 patients with documented normal pretreatment chest radiographs developed disseminated TB after infliximab. T-cell interferon-gamma release assays (IGRAs) are more sensitive and specific than the tuberculin skin test for the diagnosis of latent or new TB infections.

Endoscopic features of intestinal TB and CD are similar, and the distinction between the presentations of these disease entities can be challenging.<sup>5</sup> Endoscopic findings of transversely placed ulcers surrounded by diffusely inflamed, nodular mucosa, and patulous ileocecal valves favor TB; in contrast, aphthous and longitudinal, deep, fissuring ulcers, cobblestone appearance, normal surrounding mucosa, and stricturing ileocecal valves suggest CD. Endoscopic examination provides the advantage of obtaining multiple biopsies, especially at ulcer margins, to increase the chance of identifying MTB. Pathological features suggest that granulomata in intestinal TB tend to be multiple, large, and confluent, often with caseating or central necrosis. In contrast, granulomata in CD tend to be less numerous, smaller, and lack necrosis. Identification of acid-fast bacilli on intestinal biopsy tissue followed by PCR provides a definitive diagnosis. Other diagnostic methods include MTB cultures of stool or biopsy tissue, though these methods are time consuming.

Our patient had been diagnosed with Crohn's colitis 3 years prior with colonic biopsies reporting no evidence of TB. His primary CD-related symptoms improved after the initiation of an anti-TNF agent and had been stable until 2 months before this admission. Although it is less likely, we can't completely exclude the possibility of primary intestinal TB imitating IBD. For cases of intestinal biopsies showing suppurative or caseating granulomas, pathologists, incorporating the clinician's concern, should bear a high index of suspicion and examine the acid-fast bacilli stains thoroughly with an appropriately reactive positive control. In cases with negative acid-fast bacilli stain on initial intestinal biopsy, close clinical correlation and follow-up should be attempted to avoid an unnecessarily delayed diagnosis of intestinal TB.

## Disclosures

Author contributions: M-H Wang wrote and revised the manuscript. X. Liu described the histopathology and edited the manuscript. B. Shen supervised the process and is the article guarantor.

Financial disclosure: None to report.

Informed consent was not obtained for this case report, as the patient is deceased. Next of kin contact information was unavailable. All patient identifying information has been removed.

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