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CLINICAL VIGNETTE

Culture confirmation of pulmonary tuberculosis: Try, Try, and Try again

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The diagnosis of pulmonary tuberculosis is typically screened with sputum microscopy (AFB staining), and confirmed with sputum culture. These are not felt to be entirely sensitive or specific. If the diagnosis remains uncertain, and these tests are unrevealing or unobtainable, fiberoptic bronchosopy is often used as the next diagnostic test. This case report illustrates how the diagnosis of pulmonary tuberculosis can be elusive even with repeated use of this invasive diagnostic technique.

Case Report

A 46-year-old woman developed fleeting left chest pain and a chest x-ray (CXR) was performed which showed bilateral, nodular, upper lobe opacities (**Figure 1**). The patient's chest pain resolved, and she was entirely without fever, sweats, cough, sputum, shortness of breath, weight or appetite changes. A CT scan was performed which confirmed bilateral bronchocentric opacities, more nodular in the right upper lobe without any adenopathy, effusion, or evidence of prior granuloma (**Figure 2**). The patient was originally from Japan, and had emigrated 2 years before discovery of her CXR infiltrates. She was a non-smoker, and non-drinker. A tuberculosis (TB) skin test in the past was reportedly positive, and this was attributed to receiving Bacille Calmette-Guérin (BCG) vaccination as a child. She could identify no prior tuberculosis exposures, and had not worked in any high-risk occupations. She was hepatitis C-positive from a blood transfusion received many years ago after a motor vehicle accident. She had negligible hepatitis C viral load or transaminitis on blood testing, and was without signs or symptoms of liver disease. She had prior breast implants, but was otherwise without other past medical or surgical history. Physical examination was entirely normal.

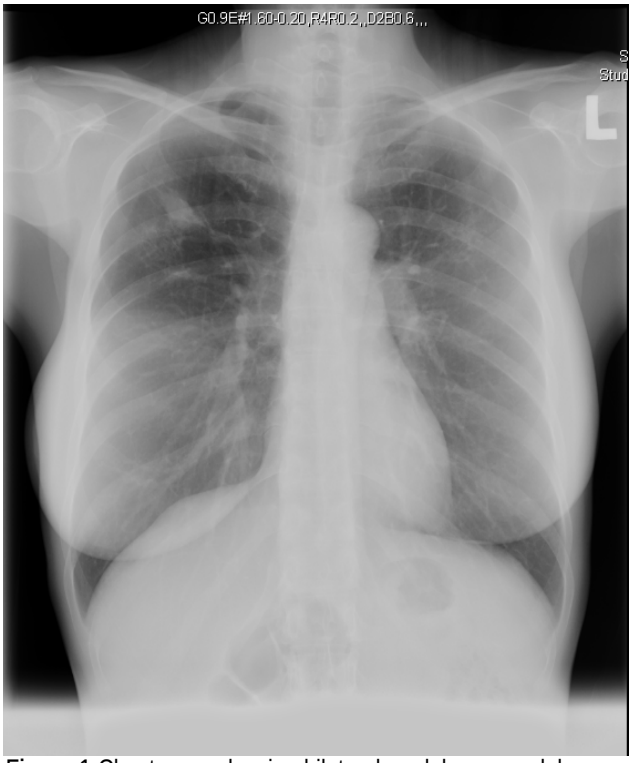

Figure 1 Chest x-ray showing bilateral, nodular, upper lobe opacities.

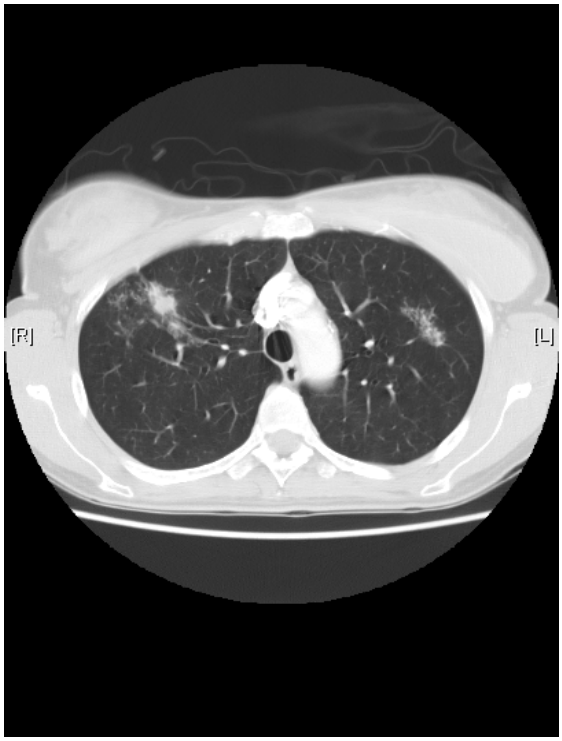

Figure 2 CT scan confirming bilateral bronchocentric opacities, more nodular in the right upper lobe without any adenopathy, effusion, or evidence of prior granuloma.

Cocci serologies and HIV were tested and were negative, and complete blood count showed no left shift or eosinophilia. The patient could not produce sputum, and fiberoptic bronchoscopy was performed with bronchial washings. These showed no acid-fast bacilli (AFB) or other organisms on stain or culture. A follow up CT scan was performed 6 weeks later, which showed mass-like infiltrate with slight progression in the right upper lung. A follow-up bronchoscopy was performed, this time with both biopsy and washings. Again this showed no organisms on stain or culture. The transbronchial biopsy did show "granulomas with some necrosis, no organisms seen". The patient remained asymptomatic. Laboratory rheumatologic markers were negative. A third chest CT scan was performed after an additional 4 months had passed, which showed some further progression of nodular, peribronchial infiltrates. The patient was still asymptomatic and without constitutional symptoms (fevers, sweats, weight loss) but agreed eventually to a third bronchoscopy. This was again stain-negative for AFB organisms, but ultimately did grow mycobacterium tuberculosis.

The patient was treated with 4 drugs initially, and then completed 2 months of INH, rifampin and pyrazinamide (the ethambutol discontinued when the tuberculosis was shown to be sensitive to all drugs on culture testing). This was followed by an additional 4 months of INH and rifampin. Follow-up lab testing showed no transaminitis, and follow-up CXR showed resolution of infiltrates with biapical scarring. Her husband was screened with a PPD skin test, which remained negative 8 weeks after treatment had begun for the index patient. The patient herself remained asymptomatic throughout her treatment and follow-up.

Results of three bronchoscopies:

Date	Bronchoscopy washing AFB microscopy	Bronchoscopy washing AFB culture	Bronchoscopy biopsy AFB culture
5/4/2004	negative	negative	
6/29/2004	negative	negative	negative
1/12/2005	negative	positive	

Discussion

Like any test, the predictive power of bronchoscopy to search for lung infection is determined by the pre-test probability. The difficulty in interpreting repeated negative results for this patient was the increasing clinical suspicion that this might be tuberculosis. The sputum microscopy and culture results began to lose their "negative predictive power". The discordance between clinical suspicion and test results was ultimately resolved by repeated testing.

Pulmonary tuberculosis remains a worldwide problem, but thankfully the incidence has gradually declined over the last 10 years in this country. In 2008 there were 12,898 cases in the United States, for a case rate of 4.2 per 100,000 population. More than half (59 %) of these were diagnosed in patients who were born in foreign countries[1]. Most of these cases came from countries with high tuberculosis rates. Japan has a low rate of tuberculosis similar to the United States[2]. This patient's recent emigration from Japan would not necessarily have increased suspicion. This patient had no other risk factors such as residence in high-risk congregate settings, medical work, or known exposure to contacts with active tuberculosis.

The history of a positive PPD does raise the possibility of latent tuberculosis. Patients who are exposed and infected by tuberculosis often have minimal symptoms, and develop clinically silent, "latent" disease. These patients are often reactive when tested with PPD skin testing, and have a risk of reactivation/ post-primary tuberculosis later in life. The role of childhood BCG vaccination contributing to false positive skin testing has long been debated. In present practice it is typically disregarded when interpreting skin test results in adults, although it is known to cause lingering skin test reactivity for some patients who have received the vaccine earlier in life[3]. Newer interferon release assays have been developed as an alternative to skin testing. These blood tests may be able to discriminate prior tuberculosis exposure from BCG immunization. They may also be able to help predict risk of reactivation[4]. These blood tests are just becoming available clinically.

It is believed that primary pulmonary tuberculosis infection leaves a parenchymal scar, such as tuberculoma or area of fibrosis on radiograph in approximately one third of patients who contract the disease. Evidence of old tuberculosis scars or granuloma can provide radiographic evidence of possible latent disease. This patient's CT scan did not suggest prior granulomatous disease. Post primary tuberculosis (or "re-activation of latent disease") typically presents as patchy, poorly-defined segmental consolidation in the well-aerated upper lobes, and superior segments of the lower lobes. These consolidations often have a nodular appearance, and ultimately cavitate in many cases. There is often a "tree and bud' pattern seen on chest CT scan which represents spread of granulomatous inflammation down bronchioles.[5] The evolution of this patient's chest CT scan did show many of these features.

This patient had a surprising lack of clinical symptoms. Classic symptoms of tuberculosis are cough, fever and weight loss. Modern population-based studies show these symptoms may be less common than traditional teaching. One study of over 500 cases of tuberculosis identified in Los Angeles over 6 months in 1993 showed[6] cough present in only 48%, weight loss reported in 44% and fever in 29%. Clearly, tuberculosis should not be dismissed as a possibility when "typical" symptoms are not present.

The most common screening test for pulmonary tuberculosis (either primary disease or reactivation of latent disease) is sputum microscopy for AFB-staining organisms. The gold standard for confirming diagnosis is isolation of the organism on sputum culture. Spontaneous sputum samples are typically collected 3 times (preferably on separate days) and processed in an experienced lab. The sensitivity of sputum stain for culture confirmed tuberculosis varies from 45% to 80% depending on the population studied[7]. Newer nucleic acid amplification tests may improve this sensitivity further, and may be particularly useful in quickly differentiating mycobacterium tuberculosis from other non tuberculosis mycobacterium which stain positive in sputum samples[8].

Unfortunately, many patients with possible clinical and/or radiographic evidence of pulmonary tuberculosis are unable to expectorate sputum spontaneously. Options to obtain specimens in patients who can not cough up a specimen include gastric washings, induced sputum or fiberoptic bronchoscopy. Gastric washings are rarely performed in the adult. Broncohscopy is commonly used in this situation (at least in developed countries). The sensitivity of bronchial washings obtained via bronchoscopy for AFB culture has been described as high as 82% in older studies[9]. Induced sputum is performed less often in most centers, but is also reported to be effective in sampling the lower airway for stains and culture. Interestingly, recent comparisons of bronchoscopic sampling to induced sputum show no clear additional benefit to bronchoscopy in identifying tuberculosis when sputum induction is well-performed [10-12].

Bronchocsopy does have the additional benefit of obtaining biopsy samples, as were performed in this patient. Necrotizing granuloma is a well-known histology for tuberculosis, although other infectious or non-infectious illness can mimic this pattern of inflammation. In one retrospective study of 105 trans-bronchial biopsies which showed necrotizing granuloma, the large majority were ultimately diagnosed with tuberculosis. The authors estimated this pathologic finding on biopsy gave a sensitivity in their population of 76% for culture-positive tuberculosis[13].

With positive PPD history, evolving CT scan and suggestive pathology, it would have been reasonable to pursue empiric treatment of tuberculosis in this patient after the second bronchoscopy. Empiric treatment has the advantage of forestalling further morbidity in the patient and interrupting any community disease transmission. Without positive culture results, however, the diagnosis would remain presumptive, and drug sensitivities would not be able to guide a drug treatment regimen. In this case the patient ultimately underwent a third bronchoscopy, which, although negative again on microscopy, ultimately grew mycobacterium tuberculosis. This case demonstrates the imperfect sensitivity and specificity of bronchoscopy, even on repeated sampling, in making culture diagnosis of mycobacterium tuberculosis. It also emphasizes the importance of prior probability and clinical suspicion in interpreting any test result.

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