Case Presentation
Missed Opportunities

Medical History
A 52 year old Hispanic female presented in January 2006 with left upper quadrant (LUQ) pain. An abdominal x-ray series revealed a density in the left upper lung; there was no hilar, mediastinal or axillary adenopathy. She denied cough, fever or night sweats. She had no prior history of tuberculosis. She immigrated to the US from Mexico 20 years ago and occasionally returns there to visit family. She is a diabetic and a non-smoker. She was referred to the local public health department where a tuberculin skin test (TST) was done and had an induration of 25 mm. Three sputums were negative for *M. tuberculosis* by direct staining and culture. A CT scan revealed a 2.4 cm slightly irregular cavitary mass in the left upper lobe. After the negative cultures, she was started on a 9 month course of isoniazid (INH) and vitamin B6.

Six months later in August of 2006, a CT showed a thick-walled cavitary lesion. She was referred for thoracotomy and surgical removal of the mass. A left upper lobectomy was performed which showed a thick walled cavitary lesion (4.5 x 3.5 x 3 cm in size) with no evidence of malignancy. The cavitary lesion had focal extension into the surrounding bronchiole. A direct smear was 2+ positive for Acid Fast Bacilli (AFB) on the tissue specimen; *Mycobacteria tuberculosis* was isolated by culture and confirmed by mycolic acid analysis within 9 days. The patient's physician made a diagnosis of old granulomatous disease (tuberculosis). The patient had an unremarkable surgical recovery; she was discharged with diabetic medication and continued on her INH and vitamin B6. Three repeat sputums were obtained by the local public health department after her release from the hospital; they were all AFB smear and culture negative. The state TB public health department initiated a 4 drug regimen; INH, rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB); also referred to as RIPE. Subsequently, drug susceptibility studies showed her isolate resistant to INH.
• The differential diagnosis of latent TB infection (LTBI) or TB disease is critical in the treatment and management of TB-infected patients. LTBI patients are not infectious and have no symptoms consistent with tuberculosis. They can go on to develop TB disease if untreated; certain sub-populations of people are more at risk to advance to full-blown TB disease. Patients with pulmonary TB disease usually present with symptoms (mild to severe) and are generally infectious; this infectiousness makes these patients a public health threat; see Table below.

### Table: Differential Diagnosis of LTBI vs. TB Disease

<table>
<thead>
<tr>
<th>Latent TB Infection</th>
<th>TB Disease</th>
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<tbody>
<tr>
<td><strong>Infectivity</strong></td>
<td>Can be highly infectious to others depending on the body site of the TB infection; i.e. laryngeal or pulmonary</td>
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<tr>
<td>NOT infectious to others</td>
<td></td>
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<tr>
<td><strong>Symptoms</strong></td>
<td>Range from asymptomatic to severe; site of TB disease determines symptoms; i.e. pulmonary infection - cough, hemoptysis</td>
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<tr>
<td>Asymptomatic</td>
<td></td>
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</table>
| **Diagnosis**       | • Positive TST but may be negative in immunocompromised patients and in some with disease  
|                     | • Abnormal CXR or CT  
|                     | • Positive AFB smears in >70% and culture in >90% (some may have a diagnosis of culture negative disease)  
| Positive Tuberculin Skin Test (TST); positive cutoff determined by patient risk factors; i.e. HIV+, age, recent contact of infectious TB case |  
| Negative Chest X-ray (CXR) |  
| Negative AFB sputum and cultures |  
| **Treatment**       | • Preferred – INH daily for 9 months  
|                     | • Alternative regimens available due to drug resistance, adverse drug reactions and patient intolerance  
| Preferred - INH daily for 9 months |  
| Alternative |  
| **Failure to Treat** | Usually results in progressive disease, may result in death in >25% of individuals |
| Risk of advancing to TB disease; lifetime risk dependent on many factors; i.e. recent infection, immune status, recent immigration in foreign-born persons, other concurrent medical conditions |  
| **Public Health Risk** | High; site of TB disease determines infectivity to others |
| None unless patient advances to pulmonary or laryngeal TB disease |  

- The following medical conditions are associated with an increased risk of progression from LTBI to TB disease:
  - HIV infection
  - Injection drug use
  - Radiographic evidence of prior healed TB
  - Low body weight ($\geq 10\%$ below ideal)
  - Silicosis, diabetes mellitus, chronic renal failure or on hemodialysis, gastrectomy, jejunoileal bypass, solid organ transplant, head and neck cancers, conditions that require prolonged use of immunosuppressive agents such as prednisone or TNF-alpha antagonists
- The size of the TST induration (in mm) and patient factors determine whether the TST is considered positive. A positive TST requires further testing to differentiate LTBI or TB disease:
  - TST $\geq 5$ mm induration is positive in: HIV+ persons; recent contacts of infectious TB cases; persons with fibrotic changes on CXR consistent with prior TB; organ transplant patients; persons on immunosuppressive agents (prednisone $\geq 15$ mg/day for 1 month or TNF-alpha antagonists)
**Teaching Points continued**

- **TST ≥ 10 mm induration** is **positive** in: recent immigrants (within last 5 years) from high prevalence countries; injection drug users, residents or employees of high-risk congregate settings; Mycobacteriology lab personnel; concurrent medical conditions (silicosis, **diabetes mellitus**, chronic renal failure or on hemodialysis, gastrectomy, jejunoileal bypass, solid organ transplant, head and neck cancers); children younger than 4 years of age; children or adolescents exposed to adults at high risk for TB disease

- **TST ≥ 15 mm induration** is **positive** in: persons with no risk factors for TB

- The following diagnostic measures should be employed to rule out TB disease if the TST is considered positive:
  - Chest x-ray (posterior-anterior views; children less than 5 years of age should have a lateral view also); additional studies (such as CT) maybe added to fully view the chest area
  - Sputum examination by AFB smear and culture is indicated when the patient has an abnormal CXR or respiratory symptoms. Three sputums should be collected at least 8 hours apart and at least one should be an early morning specimen.
  - Physical exam and complete patient medical history noting all risk factors. A written documentation of a previously positive TST is required; a patient’s verbal history is not sufficient.

- **TB infection in older diabetes mellitus patients** is usually due to reactivation of an old focus rather than through a fresh contact. The usual signs and symptoms of TB disease may be absent or mild with the lack of a fever or cough. The absence of respiratory symptoms may delay diagnosis; radiographic changes in the lungs can be atypical or limited. Abdominal tuberculosis and other rare manifestations such as pseudotumors in the lungs and papulonecrotic tuberculid tuberculosis of the maxilla, zygoma and sinus can be more common in diabetic patients.

- When a radiographic abnormality is present that is possibly consistent with active tuberculosis, radiographic stability should be determined before starting treatment for LTBI. A repeat CXR is suggested after 2 to 3 months. If the CXR is stable, that is usually an indication, along with negative sputum cultures, for a diagnosis of LTBI. When there is a radiographic manifestation that is worrisome for active disease, even with radiographic stability, a more aggressive attempt at a diagnosis should be made. Consultation with an expert in the treatment of tuberculosis is recommended for patients who have such radiographs.

- When active tuberculosis is a possibility, it is best to start four drug standard therapy (RIPE) pending the results of cultures. Treatment of active disease with a single drug leads to resistance to that drug.

**References**


