CHAPTER 3: DIAGNOSIS OF TUBERCULOSIS DISEASE IN ADULTS

INTRODUCTION

Prompt diagnosis and treatment of active tuberculosis (TB) disease improves health outcomes and reduces the spread of TB in the community. Even before the diagnosis is confirmed by laboratory testing, clinicians may initiate TB treatment and recommend that a patient with pulmonary disease restrict social interactions and refrain from work until they are no longer infectious. Recent technological advances enable clinicians to confirm the diagnosis of TB in a more timely and accurate manner, thereby allowing patients to be treated more quickly and minimizing their infectiousness in the community.

DIAGNOSIS OF ACTIVE TUBERCULOSIS DISEASE

Active TB disease can affect nearly any organ of the body. Thus, there are diverse disease presentations that make it difficult to outline a single approach to its diagnosis. The majority of persons diagnosed with active TB disease have pulmonary disease (and are potentially infectious). Nonetheless, a substantial minority of persons have extrapulmonary disease, either with or without pulmonary involvement.

A diagnosis of TB disease is established through a medical history, physical examination, chest radiograph (CXR), and laboratory test results. While a definitive diagnosis of TB disease depends upon a positive culture or nucleic acid amplification (NAA) test result for *Mycobacterium tuberculosis* (*M. tuberculosis*) complex, a high degree of clinical suspicion can be established based on epidemiologic findings, medical history, radiographic findings, and physical examination. Increased clinical suspicion for active TB is warranted for persons with TB risk factors when they fail to improve after initial empiric treatment for conditions such as community acquired pneumonia. Clinicians should consider factors that may affect the typical presentation of TB disease, such as the patient's age and coexisting diseases. TB may present in atypical ways in immunosuppressed patients as well as in young children.

Symptoms of TB disease in extrapulmonary sites may not include cough, but instead reflect the site of disease. For example, individuals with meningeal TB may present with new onset seizures, worsening headache, or meningeal signs.

During an encounter with an individual for whom clinical suspicion for TB disease is high, a complete medical evaluation is performed, including medical history, physical examination, human immunodeficiency virus (HIV) testing, interferon gamma release assay (IGRA) or tuberculin skin test (TST), radiological imaging, and mycobacteriological evaluation (acid-fast bacilli [AFB] smear and culture).

CLINICAL EVALUATION

During the diagnostic process, patients are interviewed to document their medical history. A record of a patient's medical history includes the following:

- **Description and duration of symptoms:** Symptoms of active TB disease are non-specific and may be influenced by the site(s) of disease, but typically include one or more of the following:
  - Cough (including hemoptysis) for several weeks
  - Fever
  - Anorexia
  - Unintended weight loss
  - Night sweats
  - Loss of energy

- **History**

    - Other medical conditions

    - Current or recent medications taken (prescription, over-the-counter, supplements)

    - Other medical care previously obtained for symptoms related to current TB diagnosis

    - TB history, including previous TB treatment, known TB exposure, and/or family history of TB disease

    - If prior treatment for TB disease was obtained in New York City (NYC), the TB electronic surveillance and case management system, Maven, is searched for prior patient records

    - If treatment for TB disease was provided elsewhere in the United States (U.S.) or abroad, efforts are made to obtain relevant information and share with treating providers

    - Social history (e.g., drug and alcohol use, homelessness, incarceration) and occupational history

    - Country of origin and year of entry into the U.S.

- **Physical examination**: A baseline physical exam is conducted for each patient, including a general assessment to detect signs of TB, a directed examination as per symptoms or signs, and an assessment of vital signs (including weight, blood pressure, temperature, and pulse). Although the physical examination cannot be used to confirm or rule out TB disease, it can provide valuable information about the patient's overall condition. Sites of assessment include:

    - Head (including ears, eyes, and throat)

    - Neck

    - Lungs

    - Heart

    - Abdomen

    - Extremities

    - Skin

- **Chest radiograph:** CXRs are obtained for all persons with confirmed TB disease or signs and symptoms consistent with TB disease, including those with only extrapulmonary sites of disease. A baseline posterior-anterior CXR is obtained for all adult patients. Other views (e.g., lateral, lordotic) or additional studies (e.g., computed tomography [CT] scans) are obtained when necessary. A lead shield is used when obtaining a CXR in a pregnant patient or a patient who could be pregnant. Pregnant patients who are being evaluated for TB disease undergo CXR without delay, even during the first trimester.

    Pulmonary TB disease has a myriad of presentations on the CXR that manifest in the parenchyma and pleura, or that can suggest hilar or mediastinal lymphadenopathy. Classic TB disease findings are seen in the apical and posterior segments of the upper lobe or in the superior segments of the lower lobe. However, abnormalities may appear anywhere in the lungs and may differ in size, shape, and density.

Cavitary lesions, when present, are associated with a higher degree of infectiousness and may influence treatment length. Hematogenous spread of TB causes a miliary pattern (one to five millimeter millet seed-like densities) and when seen, prompts the consideration of additional sites of disease. Finally, the CXR may be entirely normal in persons with HIV infection or other immunosuppressive conditions who have culture-positive pulmonary TB disease.

BACTERIOLOGIC EVALUATION

The diagnosis of TB disease is primarily established by obtaining confirmatory mycobacteriology results (positive culture or NAA test results for *M. tuberculosis* complex). Pulmonary TB disease may be diagnosed through collection of sputum (preferably induced), gastric aspirates, or specimens obtained during bronchoscopy, video-assisted thoracic surgery (VATS), or following other thoracic surgery procedures. Specimens for AFB smear and culture are collected whenever there is a clinical suspicion for TB disease. For optimal results, specimens are collected in sterile containers and stored in refrigerated conditions to reduce the growth of microflora and other contaminating organisms present within the specimen.

Many hospitals, certain commercial laboratories, and the New York City Health Department's Public Health Laboratory (PHL) have incorporated the use of NAA testing on certain raw or processed pulmonary specimens. NAA tests can confirm the presence of *M. tuberculosis* complex DNA and detect mutations associated with drug resistance within hours of specimen receipt at the laboratory. (See *Chapter 4: Laboratory Testing for Tuberculosis Disease.*)

When requesting NAA tests on extrapulmonary specimens or AFB smear-negative respiratory specimens, approval by the Bureau of TB Control (BTBC) is required if the specimen is being tested at PHL.

›› **Sputum:** Sputum induction is the standard procedure for collecting sputum and is performed at all NYC Health Department TB clinics. When inducing sputum, the patient inhales nebulized sterile water, which liquefies airway secretions, promotes coughing, and allows expectoration of respiratory secretions. Sputum is obtained in any individual who is suspected of having pulmonary TB disease.

  • Three sputa specimens are obtained in eight- to 24-hour intervals (over two to three days).

  • At least one sputum specimen is collected in the early morning prior to the patient eating; these specimens have a higher diagnostic yield due to the pooling of respiratory secretions overnight.

  • Sputum induction is especially useful for patients who have trouble producing sputum spontaneously.

  It is important to specify whether the sputum is induced or not, because induced sputum is "more watery" and appears to be just saliva. Some laboratories may throw out induced sputum and report it as an inadequate specimen. (See *Appendix E: Instructions for Performing Sputum Induction*.)

›› **Gastric aspirates:** Gastric aspiration can be considered for any individual with signs and symptoms consistent with pulmonary TB disease who either cannot produce sputum spontaneously or with

induction, or when other methods of collecting respiratory specimens are not practical. While gastric aspirates can be collected in adults, it is more commonly done in children. (See *Chapter 7: Diagnosis and Treatment of Pediatric Tuberculosis Disease*.) Gastric aspirates must be neutralized with sodium carbonate within one hour of collection and submitted to the laboratory for mycobacteria culture and smear microscopy. Rapid diagnostic testing for gastric aspirates is limited by poor sensitivity.

›› **Bronchial washings, broncoalveolar lavage, transbronchial biopsy, and lymph node aspiration:** Bronchoalveolar lavage and/or transbronchial biopsy performed with a fiberoptic bronchoscope may be needed to establish a TB diagnosis in some patients. Mediastinal lymph node aspiration may be done by transbronchial needle aspiration, usually performed using endobronchial ultrasound guidance. Specimens should be sent for culture, cytology, and pathology. Bronchoscopy is used in any of the following situations:

- If a patient has a substantial risk of drug-resistant TB (DR-TB) and has initial routine studies that are negative

- If there is suspicion of endobronchial TB

- If additional clinical specimens for the diagnosis of pulmonary TB disease are needed

The following are considerations when performing a bronchoscopy:

- The topical agents used to anesthetize the airways may be lethal to *M. tuberculosis*; these agents are used judiciously.

- The procedure may cause the patient to cough; the post-bronchoscopy specimens, which may have a high diagnostic yield, are collected and sent for AFB smear and culture.

URINE

A first morning, voided-midstream collection is used to ensure a high-quality specimen. Multiple specimens are sometimes necessary to detect mycobacteria. White blood cells (WBC) in urine without any bacteria can indicate TB, as can gross or microscopic hematuria; however, urine smears are usually negative and therefore performing them may not be cost-effective. Collection of urine is avoided if the patient is being treated with broad-spectrum antibiotics at the time of collection; many antibiotics concentrate in the urine and may reach levels that inhibit growth of mycobacteria including the fluoroquinolones (FQN).

BODY FLUIDS

Submission of body fluids (e.g., pleural, cerebrospinal fluid [CSF], blood, pericardial, joint, and peritoneal) for AFB smear and culture is recommended when there is body fluid that is accessible and can be sampled in order to determine site of disease. Whenever possible, submit specimen volumes that are greater than 5 ml to increase the sensitivity of detecting the presence of TB disease.

Certain fluids are submitted for additional tests, such as pH, protein, cell count, glucose, and adenosine deaminase (ADA), as these tests may provide data which help make the diagnosis of active TB when the

smear and/or culture results are negative (which is common). The finding of a high protein, elevated WBC count with lymphocytic predominance, low glucose, and elevated ADA are consistent with TB disease; however, these findings are not pathognomonic. Neutrophilic predominance may be seen when the fluid is examined earlier in the disease process.

TISSUE

In certain cases, referrals to specialists are required for invasive methods to obtain a specimen from the lung, pleura, pericardium, lymph nodes, bones and joints, bowel, peritoneum, kidney, fallopian tubes, epididymis, and from other involved sites when non-invasive techniques are not feasible or other methods are not diagnostic. Many of these sites are suitable for closed techniques such as percutaneous needle biopsy or aspiration.

In patients with disseminated disease, bone marrow biopsy, lung biopsy, or liver biopsy for culture and pathological examination may be considered as part of the diagnostic process.

If specimens are taken for pathological examination, a portion of the tissue is placed in normal saline for mycobacterial culture. If the specimen cannot be shipped promptly to the laboratory, it is refrigerated. Avoid fixing or preserving tissues as these specimens cannot be used for mycobacteria culture.

Percutaneous pleural biopsy demonstrates granulomatous inflammation in approximately 60% of patients with TB, and TB can be cultured in up to 80% of pleural tissue specimens. The combined yield of AFB stains of pleural fluid and biopsy tissue, coupled with mycobacterial culture of pleural fluid and biopsy tissue, can be greater than 90%. VATS has become the procedure of choice in diagnosing pleural disease and further increases the diagnostic yield. Providers obtain sputum specimens for patients suspected of having pleural TB disease in order to rule out simultaneous pulmonary TB.

MICROSCOPIC EXAMINATION (ACID-FAST BACILLI SMEAR)

The AFB smear is often the first diagnostic laboratory test performed on a clinical specimen to detect the presence or absence of mycobacteria. The AFB smear has poor sensitivity for detecting pulmonary TB. In NYC, only about 60% of patients diagnosed with pulmonary TB have a positive AFB smear result from a pulmonary specimen.

The mycobacteriology laboratory reports the AFB smear grade in a semi-quantitative fashion: negative, suspicious (rare), 1+, 2+, 3+, or 4+. (See *Chapter 4: Laboratory Testing for Tuberculosis Disease*.) A positive AFB sputum smear is associated with an increased likelihood of infectiousness.

The genus Mycobacterium consists of more than 200 different species, all of which appear similar by acid-fast staining. Although the detection of AFB in a stained smear provides supportive evidence of a TB diagnosis, an NAA test or culture must be performed to differentiate between members of the *M. tuberculosis* complex and other non-tuberculous mycobacteria (NTM). When AFB are observed and grown in a mycobacterial culture, identification can be performed in several ways.

NUCLEIC ACID AMPLIFICATION TESTS

Rapid deoxyribonucleic acid (DNA)-based NAA tests have become a routine method for detecting the presence of *M. tuberculosis* complex. NAA tests enable more rapid diagnosis and can decrease the time required for detection of drug resistance from weeks to days. This enables faster reporting and earlier initiation of appropriate treatment by providers, both of which may reduce community transmission of TB. Centers for Disease Control and Prevention (CDC)/American Thoracic Society/Infectious Diseases Society of America guidelines recommend that NAA tests should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test results would alter case management or TB control activities. PHL performs NAA testing on AFB smear positive specimens, but does not routinely perform a NAA test on AFB smear-negative specimen unless requested by BTBC. *(See Chapter 4: Laboratory Testing for Tuberculosis Disease.)*

›› **NAA tests on acid-fast bacilli smear-positive respiratory specimens:** On AFB smear-positive specimens, NAA tests have excellent sensitivity and specificity. New York State regulations require laboratories to perform rapid diagnostic tests using NAA methods on initial AFB smear-positive sputa or respiratory specimens. If the NAA result is positive, the patient is presumed to have TB disease and begins anti-TB therapy. The positive predictive value of the NAA test is > 95% in AFB smear-positive cases.

If the NAA result is negative, clinical judgment is used to determine whether to begin anti-TB treatment and whether additional diagnostic tests are needed. The combination of a negative NAA test result and a positive AFB smear may represent infection with a NTM, especially when a second negative NAA result from a second AFB smear-positive specimen is obtained. For patients who have two AFB smear-positive/NAA-negative sputum test results, airborne infection isolation may be discontinued. *(See Chapter 13: Infection Control.)*

›› **NAA tests on acid-fast bacilli smear-negative respiratory specimens:** If the NAA result is positive on an AFB smear-negative specimen, the patient is presumed to have TB and anti-TB therapy is started pending culture results. If the NAA result is negative, the diagnosis of TB is not excluded and treatment decisions are based on clinical judgment. Current NAA tests are only 50% to 80% sensitive in detecting culture-positive TB in an AFB smear-negative respiratory specimen in patients suspected to have TB. When the clinical suspicion for TB disease is low, NAA testing is not recommended.

> **Processes across individual laboratories differ for AFB smear-negative respiratory specimens. In some instances, the provider may need to specifically request that an NAA test be performed if the clinical suspicion for TB is high.**

›› **NAA tests on extrapulmonary specimens:** For extrapulmonary specimens, NAA testing is only done if the clinical suspicion for TB disease is high. If the NAA test is positive, the diagnosis of TB disease is presumed and is confirmed by culture. If the NAA test is negative, a diagnosis of TB disease is not necessarily excluded.

NAA tests have high sensitivity and specificity on specimens that are AFB smear-positive and are important diagnostic tests, but have some limitations. NAA tests:

- Are not recommended when the clinical suspicion for TB disease is low
- Do not distinguish between live and dead organisms
- Are not recommended after initiation of TB treatment
- Have decreased sensitivity on smear-negative specimens
- Cannot be used to determine biological cure or to monitor response to therapy
- Cannot be used to differentiate between members of the *M. tuberculosis* complex

When a specimen has a positive NAA but no positive TB cultures, the treating provider considers whether the patient has TB disease based on epidemiology and the patient's medical history to determine whether the patient should continue treatment.

NAA tests are interpreted within the context of the patient's signs, symptoms, and risk for TB and are performed in conjunction with AFB smear and culture. Although these direct molecular methods can detect *M. tuberculosis* complex DNA directly from clinical specimens within 24 to 48 hours once received in the lab, mycobacteriology culture remains the gold standard for TB diagnosis.

CULTURE

Public health and commercial laboratories, including PHL, use both liquid (broth) and solid media to culture specimens. When growth is detected in mycobacterial culture, PHL uses various laboratory techniques to aid in the identification of mycobacteria. (See *Chapter 4: Laboratory Testing for Tuberculosis Disease*.) Possible mycobacterial culture results include: *M. tuberculosis* complex (only), one or more NTM, or both *M. tuberculosis complex* and NTM.

Once culture growth is identified as *M. tuberculosis* complex, additional laboratory methods are used to characterize the *M. tuberculosis* complex isolates, such as drug susceptibility testing and genotyping. NYS conducts testing for *M. tuberculosis, M. africanum, M. bovis, M. bovis-BCG, M. microti, M. canetti, M. caprae,* and *M. orygis.*

BASELINE LABS

The following laboratory tests should be ordered for all patients as part of the evaluation and diagnosis process:

- Complete blood count (CBC)
- Chemistry panel (blood urea nitrogen, creatinine, uric acid, liver function tests [LFT])
- Viral hepatitis screen
- Other tests as clinically indicated

HUMAN IMMUNODEFICIENCY VIRUS TESTING

Knowing a patient's HIV status is vital to the TB diagnosis process. If the patient is not already known to have HIV infection, an HIV test and counseling is provided to all persons with signs and symptoms consistent with TB disease and those with confirmed TB disease according to the most recent local regulations. (See *Chapter 17: Laws Governing Tuberculosis Care in New York City*.) Effective March 2017 in New York, providers are no longer required to obtain informed consent prior to ordering an HIV-related test. Providers performing an HIV test as part of routine medical care must advise patients that an HIV-related test is being performed prior to ordering the test.

If a patient is known to have HIV infection, a complete history of the patient's HIV treatment is obtained and findings are documented in the patient's clinical record. For patients who test positive for HIV, a referral is made to an HIV specialist for appropriate follow-up and care.

> **An HIV test should be obtained for all patients suspected or confirmed to have TB disease**

PATHOLOGY

Although pathology findings can be suggestive of TB, they are not specific enough to be diagnostic of TB. Prior to the availability of mycobacterial culture, pathology findings were a common method for diagnosing TB disease. Because extrapulmonary TB is commonly culture-negative, pathology results may be the primary laboratory result used to diagnose TB.

Common specimens include:

- Lymph node
- Pleural
- Bone/joint
- Kidney
- Peritoneal
- Pericardial

Whenever TB remains in the differential diagnosis for a patient undergoing an invasive procedure to remove tissue for pathological examination, a non-fixed portion of the tissue sample is reserved to submit for AFB smear and culture. Specimens placed in formalin or fixed for pathology cannot be used for culture.

Patients with the following common pathology results should be reported to BTBC:

- Presence of AFB
- Caseating granuloma
- Tubercles
- Necrotizing granuloma

- Necrotizing inflammation
- Chronic granulomatous lesions/chronic inflammation with granuloma formation

EVALUATION OF EXTRAPULMONARY TUBERCULOSIS DISEASE

Each year in NYC, about 20% of patients have an extrapulmonary site of disease, and an additional 13% have both extrapulmonary and pulmonary sites of disease. Extrapulmonary TB disease is more likely to occur among individuals with HIV infection, patients taking immunosuppressive agents, and young children.

Although culture is the gold standard for confirming the diagnosis of TB, the proportion of patients with a culture-positive isolate is lower among those with extrapulmonary disease than among those with pulmonary disease. When possible, extrapulmonary specimens being sent for pathological analysis should also be sent for culture.

LYMPHATIC TUBERCULOSIS

Lymphatic TB disease most commonly affects cervical or supraclavicular lymph nodes, although any set of lymph nodes can be involved.

›› Individuals should be referred for aspiration or biopsy when diagnosing lymphatic TB.

›› Aspiration is useful especially if the node(s) demonstrate fluctuance.

›› Diagnosis can be established if the culture is positive for *M. tuberculosis* complex.

›› Pathology findings of AFB in tissue, caseating granuloma, or caseating necrosis are consistent with, but not diagnostic of, TB disease.

›› On CT scan, the presence of enlarged lymph nodes with hypodense centers is suggestive of necrosis, which is common in TB patients with HIV or other immunosuppressive conditions.

PLEURAL TUBERCULOSIS

TB pleural effusion can be due to a rupture of a subpleural caseous focus in the lung into the pleural space. A delayed hypersensitivity inflammatory reaction results in an increase of the permeability of the pleural capillaries to protein. Over time, pleural fluid accumulates and is usually characterized by a lymphocytic-predominant effusion.

The patient may present with a rapid onset of dyspnea, fever, and chest pain with dullness to percussion and decreased breath sounds (unilaterally or bilaterally) on physical examination. When considering a pleural TB diagnosis, a thoracentesis is performed and pleural fluid specimens are sent for:

- AFB smear and culture
- WBC count and differential
- pH, protein, and glucose
- ADA (levels > 40 may be suggestive of pleural TB)

Although neutrophils may predominate early in the disease process, > 50% lymphocytes are typically seen with WBC > 1000/microliter (μl). Pleural/serum protein ratio is typically > 0.5; low pH, low glucose levels, and high ADA levels are also consistent with pleural TB. Positive AFB stains are infrequently seen, with positive AFB culture found in approximately 25% to 75% of specimens.

Pleural biopsy for AFB smear and culture, and pathological examination are likely to increase diagnostic yield and are currently obtained most frequently by open methods via VATS, which is nearly always diagnostic of pleural TB. Three sputa for AFB smear and culture are obtained on all patients with pleural TB. Although a CXR may show no visible parenchymal lesions, cultures of sputum or gastric fluid are positive in 25% to 33% of patients.

TABLE 3.1: Evaluation of extrapulmonary tuberculosis

SUSPECTED SITE/TYPE	APPROACH TO DIAGNOSIS[1]
Disseminated	CXR, lumbar puncture[2,3] (to test for meningitis), biopsy[2] of affected sites if possible, blood[1]
Lymph nodes (especially cervical)	Fine needle aspiration, lymph node biopsy[2]
Meningeal	CT, MRI, lumbar puncture[2,3]
Miliary pattern on CXR	Induced sputum,[2] bronchoscopy with bronchial washing and transbronchial biopsy,[2] and gastric aspirates[2] if needed
Pericardial	Echocardiogram, pericardiocentesis,[2,3,4] pericardial biopsy[2]
Peritoneal	Abdominal ultrasound or CT, paracentesis,[2,3] peritoneal biopsy[2]
Pleural	CXR, thoracentesis,[2,3,4] pleural biopsy,[2] VATS[2]
Skeletal (bone and joint)	CT, MRI, arthrocentesis,[2,3] synovial or bone biopsy[2]

1. Conduct tests as clinically indicated; 2. AFB smear and culture; 3. Body fluids are sent for WBC count with differential, protein, glucose, and ADA; 4. Pericardial and pleural fluid should be sent for pH

Abbreviations Used: ADA=adenosine deaminase; AFB=acid-fast bacilli; CT=Computed tomography scan; CXR=chest radiograph; MRI=magnetic resonance imagery; VATS=video-assisted thoracoscopic surgery; WBC=white blood cells

PERICARDIAL TUBERCULOSIS

The onset of pericardial TB may be subtle, characterized by cardiovascular consequences of constrictive effusion, or abrupt, characterized by fever and precordial pain.

›› An echocardiogram is obtained to detect pericardial effusion and assess cardiac dynamics.

›› BTBC recommends pericardiocentesis or surgical biopsy to obtain a specimen for AFB smear and culture and ancillary testing unless there is a positive culture from another source.

›› Positive smears are uncommon.

›› Pericardial fluid is usually a lymphocytic exudate.

›› ADA level > 40 units/liter (U/L) in pericardial fluid may be helpful in making a diagnosis of TB.

›› Cultures are positive in only 25% to 50% of cases.

›› Primary surgical intervention with a pericardial "window" may be indicated.

CENTRAL NERVOUS SYSTEM TUBERCULOSIS

MENINGEAL TUBERCULOSIS: Meningeal TB often has an insidious and variable presentation. Initial signs of personality changes, irritability, and anorexia may be followed by headache, neck stiffness, drowsiness, and cranial nerve palsies with eventual progression to coma. It is important to maintain a high suspicion for TB in patients with meningismus since there is nothing pathognomonic about the presentation of TB meningitis. TB meningitis is classified into stages upon presentation; a higher stage correlates with a poorer outcome:

Stage 1: Isolated meningeal disease without focal neurologic abnormalities

Stage 2: Isolated parenchymal disease and neurologic abnormalities without altered consciousness

Stage 3: Parenchymal and meningeal disease with obtundation or stupor

Prompt identification of TB meningitis is crucial, as the clinical outcome is influenced strongly by the stage at initiation of treatment. The key diagnostic procedure is the examination and culture of the CSF. Characteristic CSF findings are:

- Elevated WBC count (mean of 200 with range of 6-500/µl)
- Lymphocytic predominance
- Low glucose (less than 50% of serum)
- High protein

These findings are consistent with, but not diagnostic of, TB meningitis. The diagnosis may be supported by a positive AFB smear, or confirmed by a positive NAA test; however, negative AFB smears or negative NAA and culture tests do not rule out the diagnosis if clinical criteria are highly suggestive. Performing more than one lumbar puncture or submitting more than five milliliters (ml) of CSF increases

the likelihood of obtaining a positive CSF culture. AFB-positive cultures may be observed in 45% to 70% of patients with meningeal disease.

TUBERCULOMA: Patients with intracranial tuberculoma(s) may present with cranial nerve deficits, altered mental status, hemiparesis, seizures, or headache. Concomitant meningitis may be present.

Diagnosis depends on CT or magnetic resonance imaging (MRI) findings and biopsy of the lesion. On imaging studies, tuberculomas usually appear as ring-enhancing lesions.

Patients who are taking appropriate therapy for meningeal, pulmonary, or disseminated TB disease may paradoxically develop intracranial tuberculomas or worsening of symptoms either as a result of immune reconstitution inflammatory syndrome (IRIS), or to tapering of steroids.

DISSEMINATED AND MILIARY TUBERCULOSIS: Although the terms "disseminated" and "miliary" are used interchangeably by some, BTBC considers them to be distinct. BTBC considers TB disease to be disseminated when TB occurs in two or more non-contiguous sites such as in an individual with meningeal and pulmonary TB disease. TB may disseminate either through the blood or lymphatic systems. Miliary TB refers to the pattern of TB within an organ, such as the findings on a CXR of millet seed-like (one to five mm) round/ovoid nodular opacities throughout the lung fields, and represents hematogenous spread.

Confirming disseminated TB disease may require invasive procedures, such as transbronchial biopsy, or tissue biopsy of other organs, such as the lymph nodes, liver, or bone marrow. In patients who are severely immunocompromised or have advanced acquired immunodeficiency syndrome (AIDS), urine or blood cultures obtained by appropriate techniques may yield *M. tuberculosis*. These patients are assumed to have disseminated TB disease, even in the absence of radiologically- or pathologically-demonstrated TB lesions in other organs. If disseminated TB is confirmed, the length of treatment may need to be prolonged. (See *Chapter 5: Treatment of Drug-Susceptible Tuberculosis Disease in Adults*.)

SKELETAL TUBERCULOSIS

Bone or joint TB disease most often occurs in the spine (Pott's disease), followed by TB of the hip and knee. The typical presenting symptoms are pain, and when in a weight-bearing joint, difficulty with locomotion. The diagnosis of skeletal TB disease is prompted by abnormal findings on radiological imaging of the involved joint. The diagnosis is confirmed by collecting and culturing tissue or pus if there is an abscess.

GENITOURINARY TUBERCULOSIS

Untreated genitourinary TB disease can lead to scarring of the ureters and chronic renal failure in some patients. For women, untreated TB disease of the reproductive organs is a leading cause of infertility in some parts of the world. A biopsy and/or culture is performed on the affected sites to collect tissue for testing. Urine is also collected for urinalysis (hematuria or pyuria are frequently observed). Three morning urine specimens are collected for AFB smear and culture. Pathology specimens may be indicated, especially if patient has infertility.

GASTROINTESTINAL TUBERCULOSIS

TB can affect any part of the gastrointestinal (GI) tract, from the tongue or oropharynx to the anus. The cecum is the most common GI site. The most common symptoms are anorexia, early satiety, abdominal pain or symptoms of intestinal obstruction. Evidence of coexistent pulmonary TB disease is present in about 25% to 50% of cases. Many patients with GI TB have a stool culture that is positive for *M. tuberculosis*. It is important to note that a positive stool culture could represent organisms either from a GI source or organisms from a pulmonary source that were swallowed. Endoscopy and/or colonoscopy can be used to examine the lumen and obtain specimens for AFB and other cultures. Pathology specimens may also be suggestive of TB disease.

Common, but non-specific findings from a CT scan of the abdomen and pelvis are lymphadenopathy, especially in the retroperitoneum, and bowel wall thickening with associated lymphadenopathy. The presence of enlarged lymph nodes with a hypodense center is suggestive of necrosis, which is especially common in patients with HIV or other immunosuppressive conditions.

PERITONEAL TUBERCULOSIS

Peritoneal TB disease typically presents with weeks to months of abdominal pain often accompanied by distention. Ascites is a common and predominant finding, though systemic symptoms such as fever, night sweats, fatigue, and weight loss may also occur. A paracentesis is performed, a specimen is collected for AFB smear and culture, and a WBC count is obtained with differential, protein, and glucose to aid in the diagnostic process.

›› WBC counts are typically 1000 to 2000/µl with > 80% lymphocytes.

›› Protein levels are typically elevated (greater than three g/dl), but are lower when underlying liver disease is present; ADA is elevated, and glucose is typically low.

›› Culture is positive in up to 70% of cases, though AFB smear is infrequently positive.

›› Laparoscopic findings (gross appearance, pathology, or culture) also aid in diagnosis.

CUTANEOUS TUBERCULOSIS

Cutaneous TB disease is rare and presents with chancres and wart-like lesions. These lesions may be the result of direct inoculation of TB in the skin or from hematogenous or lymphatic spread. Cutaneous lesions may be confused with those seen in systemic diseases such as sarcoidosis. Autoinoculation from underlying infected tissues or secretions can also occur.

Staff who work in mycobacteria labs or who work with autopsy specimens occasionally receive an inoculum of TB, which can lead to a condition called "Prosecutor's Wart." The diagnosis can be confirmed by performing a biopsy of the lesion and sending the specimen for AFB smear and culture, and pathologic analysis.

DISEASE DUE TO INTRAVESICAL BACILLE CALMETTE-GUÉRIN FOR BLADDER CANCER

BCG is a live attenuated strain of *M. bovis*, which is used as immunotherapy for superficial transitional cell carcinoma of the bladder. The mechanism of action appears to be modulation of the immune response in the bladder, with localized inflammation induced by BCG leading to destruction of cancer cells. Occasionally, treatment for bladder cancer is complicated by disseminated or localized BCG-related disease. A case of *M. bovis*-BCG is not counted as a case of TB by either BTBC or the CDC.

BCG-related disease may present early (i.e., within 12 weeks of the initiation of intravesical therapy) or late (i.e., more than a year after initiation of intravesical therapy). Early disease may be associated with fever, malaise, chills, sweats, weight loss, shortness of breath, and arthralgia. The clinical picture is often consistent with disseminated disease with pneumonitis and/or hepatitis; however, disease may also be localized. The diagnosis is supported by the finding of granulomas on biopsy of affected organs, and while culture may be positive for *M. bovis*-BCG, a negative culture does not exclude the diagnosis.

Late disease is more likely to present locally in the genitourinary tract without associated generalized symptoms of fever, malaise, and weight loss. It is the result of reactivation following initial immunologic control. Biopsy often yields non-caseating granulomas. Culture may or may not be positive for *M. bovis*-BCG. The individual should be tested for TB infection and sputa obtained for AFB smear and culture, as the patient will have an abnormal CXR. Bronchoscopy with biopsy may be indicated. Molecular techniques distinguish *M. bovis*-BCG from *M. tuberculosis*.

M. bovis strains, including *M. bovis*-BCG, are universally resistant to PZA. Some *M. bovis* strains are also resistant to INH. Therefore, susceptibility results are used to guide treatment. Corticosteroids have been used to treat pneumonitis associated with BCG disease, as it may contribute to rapid resolution of symptoms.

SUMMARY

The prompt and accurate diagnosis of active TB disease is essential to improving patient health outcomes and preventing TB transmission. TB disease may present in atypical ways, particularly among those who are immunosuppressed or have extrapulmonary TB disease. Knowledge of local TB epidemiology and TB risk factors are key to promptly identifying those who may have active TB disease. Obtaining adequate diagnostic samples and initiating presumptive treatment when indicated is imperative.

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