

DIAGNOSIS OF TUBERCULOSIS.

Specialty of evaluating patients with tuberculosis. Physical examination of patient.

The key to the diagnosis of tuberculosis is a high index of suspicion. Diagnosis is not difficult with a high-risk patient – e.g., a homeless alcoholic who presents with typical symptoms and a classic chest radiograph showing upper-lobe infiltrates with cavities. On the other hand, the diagnosis can easily be missed in an elderly nursing home resident or a teenager with a focal infiltrate.

Often, the diagnosis is first entertained when the chest radiograph of a patient being evaluated for respiratory symptoms is abnormal. If the patient has no complicating medical conditions that cause immunosuppression, the chest radiograph may show typical upper-lobe infiltrates with cavitation. The longer the delay between the on-set of symptoms and the diagnosis, the more likely is the finding of cavitory disease. In contrast, immunosuppressed patients, including those with HIV infection, may have «atypical» findings on chest radiography—e.g., lower-zone infiltrates without cavity formation.

The evaluation of patient with tuberculosis includes all the pointes of a routine examination of a person with any respiratory disease.

Systemic symptoms and signs of tuberculosis

Although systemic signs and symptoms are classically ascribed to TB in medical textbooks, and are indeed very important for diagnostic suspicion, it should be kept in mind that they are nonspecific and can be present in other diseases of insidious evolution, particularly other bacterial and mycotic bronchopulmonary infections, lung cancer, and chronic diseases with lung involvement.

Fever and sweating

It is believed that bacillary multiplication increases in the afternoon, with the daily circadian rhythm cortisol peak, which is followed by the evening fever characteristic of the disease. *M. tuberculosis* multiplies at a slow pace in comparison with other bacteria and therefore the inflammatory process is moderate and is accompanied by a low-grade fever. The body responds to the evening fever with night sweats to maintain the body temperature. However, when there is massive hematogenous or endobronchial dissemination, peaks of high fever can occur at any time of the day and are accompanied by chills.

Weight loss

Consumption was the name given to TB many years ago because it appeared to consume those affected, and anorexia and weight loss are still frequent in TB patients (about 70 % of the cases). Weight loss is proportional to the duration and extent of the disease and is frequently accompanied by adynamia.

Respiratory symptoms and signs of pulmonary tuberculosis

Cough

Cough is present in virtually all patients with pulmonary TB. Cough results from the stimulus caused by the alveolar inflammatory process or from the granulomatous impingement into the respiratory airways. At the onset of the disease, the cough is dry; but with progression, it becomes productive with mucous or mucopurulent expectoration, generally in small amounts, and sometimes with blood. Cough is less frequent in the pleural form of the disease. It is worth mentioning that cough tends to be ignored or minimized by smokers, who may have a chronic cough, so questions about changes in the usual pattern can be of great value in increasing suspicion of pulmonary TB.

Hemoptysis

When hemoptysis occurs, the blood volume is variable, from bloody streaks mixed in the sputum (hemoptoic sputum) to massive hemoptysis (more than 400 mL/day), which is rare. A higher volume of hemoptysis is generally caused by erosion of Rasmussen's aneurysms, which are free terminations of arteries within lung cavities. Bleeding can also occur in small lesions during the formation of the cavities, when hemoptysis can be the first manifestation of the disease, which was known by the old phthysiologists as alert hemoptysis or bark.

Dyspnea

Although the inflammatory process of TB causes global parenchyma destruction of both alveoli and blood vessels, there is no gross alteration in the ventilation/perfusion ratio, except in cases of atelectasis, large cavities or lesions with a large acute inflammatory infiltration. Therefore, dyspnea is not a common symptom, but can be caused by pleural effusions, pneumothorax or restriction caused by fibrosis in advanced disease. Dyspnea may be more frequent in the miliary form, due to diffuse interstitial disease and consequent hypoxemia. An obstructive pattern of airway disease can result from the bronchial hyperresponsivity that often accompanies TB and its sequels.

Thoracic pain

Thoracic pain occurs when there is pleural involvement, but as the TB pathological process begins in the alveoli, very close to the pleural surface, this is an early and relatively frequent symptom. Generally of low intensity, it disappears within two or three weeks after effective treatment has begun.

Hoarseness

This occurs when the larynx is affected, which is frequent with pulmonary TB. It rarely occurs in other forms of the disease. When cough and other symptoms are over looked by the patient, hoarseness may be the sole reason for seeking medical assistance.

Physical examination

Physical signs in TB are related to the extent of the lesions, the duration of the disease and the form of presentation. The longer the duration of the disease, the more evident are the classic signs of consumption, such as pallor and weight loss. The extent and the form of the disease in the lung parenchyma determine the presence of specific pulmonary signs.

The most common auscultation findings are:

- coarse crackles in the area corresponding to the lesion (generally apical and posterior);
- wheezing and ronchi in the area of compromised bronchi; clinical signs of lung condensation in the forms with caseous pneumonia;
- decreased vesicular murmur and broncophony or tubular blow when pleural effusion is present;
- as well as the classic amphoric breath sounds near cavities.

Hepatosplenomegaly can occur in the disseminated forms.

Some findings are caused by delayed-type hypersensitivity to tubercle bacilli components, although the lesions themselves do not contain *M. tuberculosis*.

These TB associated conditions are:

- erythema nodosum (inflammation of the subcutaneous adipose tissue),
- phlyctenular conjunctivitis,
- erythema induratum of Bazin (nodular vasculitis)
- polyserositis.

These lesions are mostly associated with primary TB infection, although they may also be observed in re-activation TB disease and sometimes are recurrent.

Table 2-1 – TB symptoms

Respiratory symptoms	General symptoms (tuberculous intoxication)
+++Cough	++Loss of weight

+++Sputum	++Fever and sweating
++ Hemoptysis	+Tiredness
+Chest wall pain	+Loss of appetite
+Breathlessness	
+Localized wheeze	
+Frequent colds	
The number of plus (+) shows which symptoms are most important	
Note that all the symptoms could be due to other illnesses. To make sure, you must examine the sputum for TB	

One of the most important signs, which should make to think of possible tuberculosis, is that the symptoms have come on gradually over weeks or months. This applies particularly to the general symptoms of illness: loss of weight, loss of appetite, tiredness or fever.

Radiographic procedures in diagnosis (chest radiography, computer tomography, magnetic resonance imaging). Certain radiographic abnormalities are consistent with tuberculosis.

Chest X-ray in diagnosis

Pulmonary tuberculosis in adults can present with a wide variety of radiographic features. Chest radiography is not a method of diagnosis. When it is available, it can be used to screen patients with respiratory symptoms to identify features that might be caused by tuberculosis, or that are consistent with other diseases, or to demonstrate the absence of abnormality.

Indications for CXR

Positive sputum smear

The first screening test for PTB suspects is sputum smear microscopy. In most cases of sputum smear-positive PTB a CXR is not necessary. In a few cases, a CXR may be necessary; the indications are as follows:

- a) suspected complications in a breathless patient, needing specific treatment, e.g. pneumothorax, pericardial effusion or pleural effusion (note that a positive sputum smear is rare in pericardial effusion and pleural effusion);
- b) frequent or severe haemoptysis (to exclude bronchiectasis or aspergilloma);

c) only 1 sputum smear positive out of 3 (in this case, an abnormal CXR is a necessary additional criterion for the diagnosis of sputum smear-positive PTB).

Negative sputum smear

Reassess patients who continue to cough despite a course of broad-spectrum antibiotic, and who have had at least two (and preferably three) negative sputum smears. If you still suspect TB despite negative sputum smears, the patient needs a CXR.

A few principles can aid student in viewing films.

First, the appearance of any structure on a radiograph depends on the structure's density; the denser the structure, the whiter it appears on the film. At one extreme is air, which is radiolucent and appears black on the film. At the other extreme are metallic densities, which appear white. In between is a spectrum of increasing density from fat to water to bone. The viscera and muscles fall within the realm of water density tissues and cannot be distinguished in radiographic density from water or blood.

Second, in order for a line or an interface to appear between two adjacent structures on a radiograph, the two structures must differ in density. For example, within the cardiac shadow the heart muscle cannot be distinguished from the blood coursing within the chambers because both are of water density. In contrast, the borders of the heart are visible against the lungs, because the water density of the heart contrasts with the density of the lungs, which is closer to that of air. However, if the lung adjacent to a normally denser structure (e.g., heart or diaphragm) is airless, either because of collapse or consolidation, the neighboring structures are now both of the same density, and no visible interface or boundary separates them. If an expected border with an area of lung is not visualized or is not distinct, the adjacent lung is abnormal and lacks full aeration.

Chest radiographs usually are taken in two standard views—posteroanterior (PA) and lateral. Knowledge of radiographic anatomy is fundamental for interpretation of consolidation or collapse (atelectasis) and for localization of other abnormalities on the chest film. Lobar anatomy and the locations of fissures separating the lobes are shown in **Figure**.

Lobar anatomy as seen from anterior and lateral views. In anterior views, shaded regions represent lower lobes and are behind upper and middle lobes. Lingula is part of the left upper lobe; dashed line between the two does not represent a fissure.

Certain radiographic abnormalities are consistent with tuberculosis:

- Nodules are round shadows (or «densities») with clearly defined borders; their size varies from a micronodule (less than 3mm in diameter), to a nodule (more than 3 mm and less than 1 cm in diameter), to a round shadow (more than 1 cm in diameter);
- Patchy shadows, or infiltrations, have irregular borders that are not as clearly defined. They are of varying size, sometimes extending to large parts of the lungs.
- Cavities are the most characteristic sign of tuberculosis. A cavity is an area of lucency with a fairly thick wall (more than 1mm), in which an area of bronchial drainage, demonstrated by opaque parallel lines, may be evident at the pole closest to the hilum of the lung. Cavities sometimes contain liquid at the base (liquefied caseous material), evident as an «air fluid level».

In tuberculosis, a wide variety of abnormalities may be present on the same film. In films taken at least 2 weeks apart, changes in the abnormalities can be detected: growth of the cavities, confluence and spread of the nodules, or the formation of a cavity inside a patchy shadow. This kind of evolution of the radiographic features suggests that the tuberculosis is clinically active.

When the tuberculosis has progressed over several months, the destruction of the lung parenchyma and gradual fibrosis lead to retraction of the neighbouring structures: the trachea may be displaced, the hilum may become elevated, the diaphragm may be pulled upward and the cardiac silhouette may change shape and place.

Lesions due to tuberculosis can be unilateral or bilateral; they are most frequently observed in the upper zones of the radiograph. The extent of the abnormalities may vary from a minimal lesion (an area less than the size of a single intercostal space), to far advanced lesions, with extensive involvement of both lungs.

Some radiographs show tuberculosis sequelae

Pulmonary tuberculosis lesions may have various types of sequelae:

- nodules that are fully or partially calcified
- stellate abnormalities
- fibrous retraction
- fine-walled bullae/cavities

In some cases the retraction may be extensive, and may affect a whole lobe or even a whole lung.

Tuberculin skin test. Value of a positive and negative result. False-positive reactions. TST suppressing factors. IFN- γ Release Assays (IGRAs). Diaskin-test.

Tuberculin Skin Test

Tuberculin is a purified protein derived from tubercle bacilli. Another name for tuberculin is PPD (purified protein derivative). Following infection with *M. tuberculosis*, a person develops hypersensitivity to tuberculin. Tuberculin injected into the skin of an infected person produces a delayed local reaction after 24–48 hours. This reaction is quantified by measuring the diameter of skin induration (thickening) at the site of the reaction. Various conditions can suppress this reaction. The reaction indicates hypersensitivity. In other words, the reaction only shows that the person has at some time been infected with *M. tuberculosis*. False-positive reactions may be caused by infections with nontuberculous mycobacteria and by bacille Calmette-Guérin (BCG) vaccination.

The standard amount of tuberculin used is 5 units, injected as 0.1 ml into the anterior surface of the forearm at the junction of the middle and upper thirds. It is very important that the tuberculin is injected intradermally so that it is well localized. If correctly given, the injection should raise a small bump of 5 mm or more in diameter, which disappears within 1–2 hours.

Value of a negative tuberculin test

A tuberculin test is not significant, or “negative”, when the diameter of skin induration is less than 10 mm (or less than 5 mm in an HIV-infected patient). A negative tuberculin skin test does not exclude TB. Thus, it is of no help in deciding that someone does not have TB. The table below shows the conditions that can suppress a tuberculin skin test in a person with active TB.

Conditions that may suppress the tuberculin skin test:

- HIV infection
- malnutrition
- severe bacterial infections, including TB itself
- viral infections, e.g. measles, chickenpox, glandular fever
- cancer
- immunosuppressive drugs, e.g. steroids
- incorrect injection of PPD

Value of a positive tuberculin skin test

The criterion for a significant or “positive” tuberculin test depends on whether a child has previously had BCG vaccination or not. This is because a reaction to tuberculin is usual after a previous BCG, at least for several years. The reaction is usually weaker (diameter often less than 10 mm) than the reaction to natural infection with *M. tuberculosis*. A tuberculin test is considered significant or positive when the diameter of skin induration is 10 mm or more. However, if the child is HIV-infected,

the tuberculin test is considered positive if the induration is 5 mm or more. A positive tuberculin test is only one piece of evidence in favour of the diagnosis of TB. The younger the child and the greater the diameter of induration, the stronger is that one piece of evidence.

IFN- γ Release Assays (IGRAs)

Recently, two in vitro assays that measure T-cell release of IFN- γ in response to stimulation with the highly tuberculosis-specific antigens ESAT-6 and CFP-10 have become commercially available. QuantiFERON-TB Gold is a whole-blood enzyme-linked immunosorbent assay (ELISA) for measurement of IFN- γ , and T-SPOT.TB is an enzyme-linked immunospot (ELISpot) assay.

IGRAs are more specific than the TST as a result of less cross-reactivity due to BCG vaccination and sensitization by nontuberculous mycobacteria. IGRAs also appear to be at least as sensitive as the TST for active tuberculosis (used as a surrogate for LTBI). Although diagnostic sensitivity for LTBI cannot be directly estimated because of the absence of a gold standard, these tests have shown better correlation than the TST with exposure to *M. tuberculosis* in contact investigations in low-incidence settings.

Other potential advantages of IGRAs include logistical convenience, the need for fewer patient visits to complete testing, the avoidance of unreliable and somewhat subjective measurements such as skin induration, and the ability to perform serial testing without inducing the boosting phenomenon (a spurious TST conversion due to boosting of reactivity on subsequent TSTs among BCG-vaccinated persons and those infected with other mycobacteria). Because of the high specificity and other potential advantages, IGRAs are likely to replace the TST for LTBI diagnosis in low-incidence, high-income settings where cross-reactivity due to BCG might adversely impact the interpretation and utility of the TST. Direct comparative studies in routine practice thus far suggest that the ELISpot has a lower rate of indeterminate results and probably a higher degree of diagnostic sensitivity than the whole-blood ELISA. Further studies are under way to assess the performance of these tests in contact investigations and in persons with suspected tuberculosis disease, health care workers, HIV-infected individuals, persons with iatrogenic immunosuppression, and children.

Serologic and Other Diagnostic Tests for Active Tuberculosis

A number of serologic tests based on detection of antibodies to a variety of mycobacterial antigens are marketed in some countries. Careful independent assessments of these tests suggest that they are not useful as diagnostic aids, especially in persons with a low probability of tuberculosis. Various methods aimed at detection

of mycobacterial antigens in diagnostic specimens are being investigated but are limited at present by low sensitivity. Determination of ADA levels in pleural fluid may be useful in the diagnosis of pleural tuberculosis; the utility of this test in the diagnosis of other forms of extrapulmonary tuberculosis (e.g., pericardial, peritoneal, and meningeal) is less clear.

Additional Diagnostic Procedures

Other diagnostic tests may be used when pulmonary tuberculosis is suspected. Sputum induction by ultrasonic nebulization of hypertonic saline may be useful for patients who cannot produce a sputum specimen spontaneously. Frequently, patients with radiographic abnormalities that are consistent with other diagnoses (e.g., bronchogenic carcinoma) undergo fiberoptic bronchoscopy with bronchial brushings and endobronchial or transbronchial biopsy of the lesion. Bronchoalveolar lavage of a lung segment containing an abnormality may also be performed. In all cases, it is essential that specimens be submitted for AFB smear and mycobacterial culture. For the diagnosis of primary pulmonary tuberculosis in children, who often do not expectorate sputum, specimens from early-morning gastric lavage may yield positive cultures.