



Education

Éducation

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Clinical basics

Tuberculosis: 4. Pulmonary disease

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Case 1

A 22-year-old aboriginal woman presented with a 12-week history of fever, night sweats, weight loss and productive cough.¹ She had no history of lung disease or any condition known to compromise immune function. Plain chest radiography revealed consolidation and moderate volume loss in the left upper lobe of the lung, with at least 2 cavities at the apex, the largest measuring 4–5 cm in diameter (Fig. 1A). This imaging also showed non-cavitary disease in the left lower lobe.

Case 2

An 86-year-old immigrant to Canada from Eastern Europe presented to her family physician with a 3-month history of decreased appetite, weight loss and a mildly productive cough. She was afebrile. There was dullness to percussion and breath sounds were decreased in the right lower lung posteriorly. A chest radiograph revealed bilateral effusions, the right larger than the left, and collapse or consolidation of the right lower lobe (Fig. 1B).

In Canada in 1995, 60% of all cases of tuberculosis (TB) were pulmonary.² From a public health standpoint the lungs are the most important organ involved with TB.³ Patients with pulmonary TB who have a large number of bacilli in their sputum (i.e., those whose smears are positive for acid-fast bacilli) can spread the organism to the lungs of others by coughing, sneezing, laughing or even talking.^{4,5} *Mycobacterium tuberculosis* depends upon human hosts for its survival, and this process of transmission ensures the perpetuation of the organism and the disease. Patients whose sputum smears are negative for acid-fast bacilli and those with TB in organs other than the lung are not likely to infect others.^{4,5}

During the initial infection of immunocompetent people, alveolar macrophages ingest the *M. tuberculosis* organisms, and process and present mycobacterial antigens to lymphocytes bearing CD4 receptors (T-helper cells).⁶ CD4 cells secrete lymphokines, in particular interferon- γ , which enhance the capacity of the macrophages to ingest and kill the mycobacteria. In most people, the infection is contained, and TB does not develop, although small numbers of dormant bacilli may remain in the body. Clinically apparent TB develops in approximately 10% of infected people, either soon after primary infection or years later.⁶

Until the 1990s the incidence of pulmonary TB was declining in Canada, although the proportion of all pulmonary cases that were infectious (i.e., direct smear positive) remained relatively constant (Fig. 2). As the incidence fell, so did the likelihood that pulmonary TB would be considered in the differential diagnosis.^{7–10} The closure of sanatoria and the transfer of TB case management from a small group of specialists to mainstream medicine^{7–10} may have further reduced the likelihood of pulmonary TB being considered as a diagnosis.

A timely diagnosis of pulmonary TB is essential. When the diagnosis is delayed or not made at all, morbidity and mortality rates increase, as does the likelihood that the organism will be transmitted.¹¹ Pulmonary TB is eminently treatable, and the diagnosis must be aggressively pursued in populations at risk.

Characteristics of pulmonary TB

Clinical characteristics

Cases of pulmonary TB are usually found in groups that are at high risk of



carrying the tubercle bacillus in a dormant form, notably aboriginal people, foreign-born people from countries with a high prevalence of TB, poor and homeless people from the inner city, and elderly people. Cases may also be found among the close contacts of people known to have TB and those with a history of TB. TB should be considered in patients in these high-risk groups. Members of these groups are at further risk of active disease if, in addition, they have an underlying illness or other factor known to compromise cell-mediated immunity, such as HIV infection, diabetes, alcoholism, end-stage renal disease or use of immunosuppressive drugs. The discussion that follows is limited to HIV-seronegative adults.

Pulmonary TB is characterized by its insidious onset and its chronic nature; as in cases 1 and 2, symptoms are often present for weeks or months before the patient seeks medical attention. In contrast to acute bacterial pneumonia,

constitutional symptoms of fatigue, anorexia, night sweats and weight loss are common. Weight loss is in fact the second most common symptom, after cough (Table 1).¹² In about 30% of patients, pulmonary symptoms are absent, and constitutional symptoms represent the only clue that the patient is ill. Pulmonary symptoms may be even less common in elderly people,¹³ and the symptoms may be ascribed to pre-existing, non-mycobacterial illness.

Dyspnea is less common than more acute pulmonary conditions such as bacterial pneumonia.¹⁴ When present, dyspnea suggests advanced fibrocavitary or miliary disease or TB complicated by pneumothorax. Cough may be non-productive at first, but it eventually becomes productive in most patients. Hemoptysis occurs in about 20% of patients, and its presence should alert the clinician to the possibility of TB. Chest pain is common and may not always be pleuritic in character. Fever is present in slightly fewer than half of patients at presentation, and its absence does not rule out the diagnosis of TB.

Physical examination is of limited value, although evidence of chronic disease, such as cachexia, absence of significant dyspnea and the patient's "nontoxic" appearance

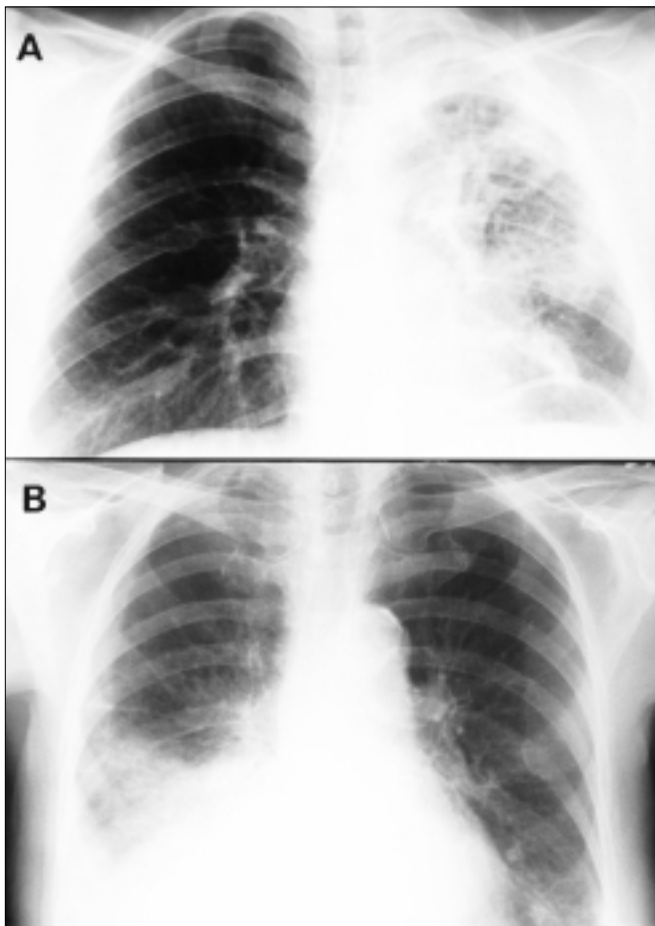


Fig. 1: (A) Case 1. Posteroanterior chest radiograph obtained at the time of diagnosis demonstrates consolidation and moderate volume loss in the left upper lobe with at least 2 cavities at the apex, the largest measuring 4–5 cm in diameter. Reproduced, with permission, from Long and Maycher.¹ **(B)** Case 2. Posteroanterior chest radiograph obtained at the time of presentation to the family physician demonstrates bilateral pleural effusions, the right greater than the left, and collapse and consolidation of the right lower lobe.

Table 1: Frequency of symptoms in adults with pulmonary tuberculosis*

Symptom	No. of patients examined	No. (and %) with symptom
Cough	185	144 (78)
Weight loss	181	134 (74)
Fatigue	165	112 (68)
Tactile fever	183	109 (60)
Night sweats	177	98 (55)
Chills	180	92 (51)
Anorexia	167	76 (46)
Chest pain	179	71 (40)
Shortness of breath	173	64 (37)
Hemoptysis	181	51 (28)
No respiratory symptoms	186	13 (7)
None of the above symptoms	187	9 (5)

*Reproduced, with the permission of the publisher, from Barnes and associates.¹²

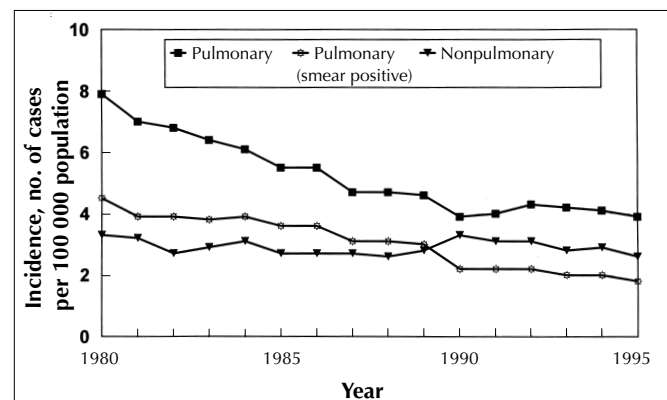


Fig. 2: Reported incidence of pulmonary and nonpulmonary tuberculosis in Canada, 1980 to 1995.



(the patient does not appear acutely ill or in distress) may be helpful. Pulmonary signs are nonspecific. If parenchymal disease is present, there may be crackles, dullness to percussion, decreased breath sounds or bronchial breathing. Dullness, decreased breath sounds and a friction rub may be found with pleural effusion. Often the results of a pulmonary examination are normal.

Most patients in whom pulmonary TB is diagnosed after death are mistakenly thought to have had pneumonia or cancer at the time of death.¹¹

Radiology

The chest radiograph may be particularly helpful in diagnosing pulmonary TB because in a significant proportion of patients symptoms and signs are either nonspecific or absent. The classic description of the chest radiograph of adults with TB is that of "postprimary" TB, with nodular or alveolar infiltrates in the upper lung zones (the apical and posterior segments of the upper lobes and the superior segment of the lower lobes) and evidence of cavitation, as in case 1. This is still a common mode of presentation and, if present, should prompt the physician to consider the diagnosis.¹⁵ Surprisingly, several studies have shown that up to one-third of patients with these classic chest radiographic findings are not initially suspected of having TB.^{8,12}

It is important to note that with the decreased incidence of TB in Canada, it is common for people born in Canada to reach adulthood before they encounter the tubercle bacillus, if they ever do. These people may present not with classic "postprimary" TB but instead with features of the "primary" disease, which reflects the fact that they have only recently become infected with the tubercle bacillus.¹⁶ Therefore in 30% to 50% of cases, the chest radiograph may show patterns previously thought to be rare in adults and more common in children.

The following are descriptions of these atypical but not uncommon patterns.

Lower and mid-lung zone infiltrates can occur in isolation or in association with intrathoracic adenopathy or, as in case 2, pleural effusion. Physicians should suspect TB when the patient's condition has not improved with antibiotic therapy directed at bacterial pneumonia, and the findings on chest radiography remain unchanged.

Pleural effusion is usually unilateral and of moderate size. As in case 2 the fluid is almost always an exudate with a high percentage of lymphocytes in the cell count. In addition to raising the possibility of malignancy, a lymphocytic exudative effusion should always suggest TB.

Miliary TB represents hematogenous dissemination of the tubercle bacillus. When the bacilli spread to the lungs, the chest radiograph shows discrete nodules 1–5 mm in diameter scattered throughout the lungs.¹⁷

Hilar and mediastinal adenopathy is usually unilateral but may be bilateral in 10% of cases. Often there is an adjacent parenchymal infiltrate.

Tuberculoma appears as a solitary coin lesion on the chest

radiograph and is often suspected to represent malignancy. Clues that this finding represents TB include evidence of calcification, adjacent smaller "satellite" lesions and a well-defined border. Lesion diameter generally ranges from 0.5 to 4 cm. This type of lesion may represent either active disease or previous TB that has healed; clinical correlation with the patient's history is required. Lesions greater than 3 cm in diameter are more likely to be active.

Normal results on chest radiography are rare but can occur with endobronchial or laryngeal disease.

In addition to the features suggesting active disease, the chest radiograph also provides valuable clues about past infection. These may include calcified hilar and mediastinal nodes, a calcified focus in the lung parenchyma, pleural thickening and calcification (especially if apical) and scarring in the upper lung zone. If any of these findings are present in association with a new pulmonary process, active TB should be suspected, given that one of the risk factors for active TB is previous disease.

TB cannot be diagnosed with certainty from the chest radiograph alone; a CT scan of the thorax may help.¹⁸ It is true that an open cavity or an enlarging alveolar infiltrate suggests that the disease is active, and it is also true that cavities tend to be associated with a high sputum load of acid-fast bacilli and a high degree of infectivity. However, when the physician ordering the chest radiograph receives a report of "old healed TB" from the radiologist, this interpretation must be accepted with caution — active disease cannot be absolutely excluded on the basis of the chest radiograph alone. If any suspicion exists, active TB must be ruled out by bacteriologic means.

Laboratory

Ease of performance, widespread availability, low cost and a considerable diagnostic yield make examination of sputum by microscopy an essential component of any diagnostic evaluation of pulmonary TB. Most studies report a sensitivity of 40% to 60% and a specificity of 99%, with some of the variability explained by different presentations.¹⁹ For example, positive smear results have been reported in 52% of patients with cavitary disease but in only 32% of those with local infiltrates.²⁰ In Canada in 1995, 46% of pulmonary cases were smear positive (Table 2). Canadian-born patients were significantly more likely to have positive smear results than foreign-born people. Most smear-positive cases occurred in adults. The importance of ordering sputum cultures as well as smears is underscored by the fact that 30% to 40% of all cases in 1995 were smear negative but culture positive. A recent review found that the sensitivity and specificity of sputum cultures were 82% and 98% respectively.¹⁹

Specimens of sputum should be collected first thing in the morning on each of 3 consecutive days (for both smear examination and culture, 95% of the positive results are obtained by examining 3 samples).¹⁹ A separate sterile container with a wide mouth and a screw cap should be used



for each specimen. Specimens should be transported to the laboratory as soon as possible after collection. If for any reason transport is delayed, the specimens should be refrigerated at 4°C to reduce overgrowth of contaminants.

In any laboratory that performs a substantial number of mycobacterial sputum cultures, an enhanced, broth-based culture detection and identification system should be in place. The most widely used of these is the BACTEC 460TB system (Becton-Dickinson Diagnostic Instruments Systems, Maryland).²¹ This system employs a metabolic substrate, palmitic acid, labelled with carbon-14, which in the presence of viable mycobacteria is metabolized to ¹⁴CO₂. The amount of radioactive CO₂ released in the culture vial can be quantified and used to detect mycobacterial growth well before conventional cultures would show positive results. Distinguishing *M. tuberculosis* from other mycobacterial species is accomplished presumptively by selective growth in the presence of para-nitro- α -acetylaminob- β -hydroxypropionophenone (the NAP test). Definitive rapid identification of mycobacteria is possible with species-specific probes (e.g., AccuPROBE, Gen-Probe Inc., San Diego). Using systems such as BACTEC, the time to identification of a positive culture can be shortened to as little as 2 weeks. By combining systems such as BACTEC with specific probes for nucleic acids, a substantial proportion of cultures can be identified more quickly.

For patients in whom the clinical and radiographic findings suggest a diagnosis of pulmonary TB and the sputum smear is positive for acid-fast bacilli, a working diagnosis can be made and antituberculous drug therapy commenced. The drug therapy should include 4 drugs (isoniazid, rifampin, pyrazinamide and either ethambutol or streptomycin) to allow for the possibility of drug resistance (more likely in people from countries with a high prevalence of TB,^{22,23} those with a history of antituberculous drug use and those with known exposure to a drug-resistant case). Ideally, sputum-smear-positive patients should be isolated for 2 weeks in a room with adequate ventilation to prevent nosocomial spread of infection.

For patients in whom TB is suspected but whose smear

results are negative, one alternative is to begin therapy and wait for culture results. A recent investigation of presumptive therapy of patients with negative smear results indicated that about half of such patients actually had active TB.²⁴ Although physicians with substantial clinical background in TB may recommend presumptive treatment for many patients, establishing a definitive diagnosis as early as possible is generally preferred.

Induction of sputum, bronchoscopy, gastric aspiration and needle aspiration are available to aid in rapid diagnosis in the smear-negative patient. Techniques of molecular biology such as polymerase chain reaction offer promise, but their exact clinical role has not yet been determined.²¹ Sputum induction is performed with hypertonic saline delivered by an ultrasonic nebulizer. The patient is seated in a cubicle or small room with adequate ventilation to prevent nosocomial spread of infection. In a recent study, sputum induction was found to be well tolerated and inexpensive, and its diagnostic yield was the same as, if not better than, that of bronchoscopy.²⁵ When sputum induction is not possible, bronchoscopy may be performed. If the latter procedure includes transbronchial biopsy, there is the opportunity for an immediate tissue diagnosis. Again, precautions to prevent nosocomial spread of infection are necessary. In uncooperative patients, who are not candidates for sputum induction or bronchoscopy, early morning gastric aspiration is an alternative.²⁶ Mass lesions or nodules may be sampled by needle aspiration. Physicians who are uncertain as to how to proceed should consult a respirologist or infectious disease specialist.

The tuberculin test may be helpful in confirming that a patient is at risk, particularly when pulmonary TB is suspected but the results of a sputum smear are negative. However, the results of a tuberculin test must always be interpreted with caution. In many patients with active TB, including immunosuppressed and elderly people, false-negative results are common because of impaired cell-mediated immunity and anergy. Other patients may have a positive tuberculin test result but not active TB. They may simply be harbouring dormant tubercle bacilli and, depending on age and other factors, may be candidates for prophylaxis.

Table 2: Bacillary status of the 1145 cases of pulmonary tuberculosis reported in Canada, 1995*

Bacillary status	Ethnic origin; no. (and %) of cases				Total
	Aboriginal	Canadian-born non-aboriginal	Foreign-born	Unknown	
Smear positive, culture positive	90 (8)	148 (13)	245 (21)	8 (1)	491 (43)
Smear positive, culture negative or not done	2 (< 1)	18 (2)	18 (2)	2 (< 1)	40 (3)
Smear negative or not done, culture positive	75 (7)	102 (9)	244 (21)	11 (1)	432 (38)
Unknown	20 (2)	36 (3)	121 (11)	5 (< 1)	182 (16)
Total	187 (16)	304 (27)	628 (55)	26 (2)	1145 (100)

*Source: *Tuberculosis in Canada 1995 annual report*.⁵



Routine laboratory tests are rarely helpful in establishing or suggesting the diagnosis. Mild normochromic normocytic anemia may be present. The leucocyte count is often normal, and counts over 20 000/ μ L suggest another infectious process, although a leukemoid reaction may occasionally occur in miliary TB. A "left shift" in the leucocyte count or an elevated sedimentation rate may occur, but these findings are nonspecific. Physiologic data, such as those in case 1, support the concept that pulmonary TB causes parallel reductions of ventilation and perfusion.^{1,18} The resulting preservation of gas exchange may actually extend the life of the patient within the community, thereby allowing dissemination of the organism and survival of the species.¹⁸

Conclusion

The lung is the organ most commonly affected by the tubercle bacillus. Identification of patients with active pulmonary disease is important to the health of both the affected individuals and the public at large. Early diagnosis and treatment will cure the patient and interrupt the spread and persistence of TB.

Case resolutions

Case 1

Examination of a sputum smear revealed large numbers of acid-fast bacilli. Cultures were positive for *M. tuberculosis* susceptible to all first-line antituberculous drugs. The patient was successfully treated with directly observed therapy. Contact follow-up identified 1 secondary case and 4 tuberculin converters.

Case 2

Sputum was collected for routine and acid-fast bacilli smear and culture. A diagnostic tap of the right pleural effusion was performed, and the patient was given a broad-spectrum antibiotic. Routine cultures of sputum and pleural fluid were negative for respiratory pathogens, as was acid-fast bacilli smear. The effusion was an exudate with 92% lymphocytes. Three weeks later, after no clinical or radiographic improvement, cultures of sputum were positive for *M. tuberculosis* resistant to isoniazid but susceptible to all other first-line antituberculous drugs. Although a closed pleural biopsy might have been helpful, the fact that the family physician considered the diagnosis of TB and submitted a sputum specimen as well as the specimen from a pleural tap was commendable, given the nonspecific radiographic abnormalities.

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