A 71 year old man with malaise, weakness and shortness of breath on exertion

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A 71 year old retired asphalt foreman from a rural center was admitted with a three week history of malaise, anorexia, weight loss and gradual onset of shortness of breath on exertion. One week prior to admission he noted that his chronic unproductive cough was more pronounced. His family physician prescribed erythromycin, but he subsequently developed fever, chills and profuse sweats. A chest x-ray demonstrated right lower lobe pneumonia, and the patient was referred to the Emergency Room. His past history was significant for gout, alcohol abuse and a 75 pack year smoking history.

On examination, the patient was alert, oriented and in mild respiratory distress. Temperature was 39.3°C and vital signs were otherwise stable. No lymphadenopathy or clubbing was found. Breath sounds were diminished on the right side, and coarse crackles were heard over the right mid-lung field and bibasally. Tactile fremitus was normal. Cardiovascular and abdominal examinations were unremarkable. Neurological examination was significant for decreased vibratory sensation to the feet. He had a Duputryn's contracture of the left fourth finger.

The patient's CBC, electrolytes, urea, creatinine and urinalysis were essentially normal. Blood gases on room air revealed: pH 7.45; PCO_2 35 mmHg; PO_2 68 mmHg; HCO_3 24 mmol/L; O_2 sat. of 92%. An EKG showed sinus rhythm with non-specific ST changes. A chest x-ray revealed right upper and lower lobe pneumonia, as well as inferior and right-sided pericardial calcification.

The patient was admitted with the diagnosis of extensive right-sided pneumonia. He was treated with intravenous ceftriaxone, erythromycin and supplemental oxygen. Blood cultures were negative and sputum later showed 2+ WBCs and 1+ Gram positive rods. Rifampin was later added for further Legionella coverage, which was thought to be the etiology of his illness. The patient defervesced after initiation of this treatment. Noting the pericardial calcification suggestive of tuberculosis (TB), an anergy panel was done and was read as non-reactive at 24h. The patient developed left ventricular failure thought to be secondary to pneumonia and volume overload which responded well to diuresis. He also developed urinary retention that required catheterization for several days. The patient was very anxious to return home and, with significant reluctance on the part of the medical team caring for him, he was discharged with prescriptions for erythromycin and rifampin. Unfortunately, he deteriorated and required readmission four days later.

As before, he noted increasing shortness of breath and dry cough. There were no other new symptoms since his last admission. Vitals were stable and he was afebrile. Physical examination was unchanged except for decreased breath sounds bibasally and dullness to percussion in the right upper lobe. An arterial blood gas on room air revealed a pH of 7.51, PCO2 37 mmHg, PO2 53 mmHg, HCO_3 27 mmol/L and an oxygen saturation of 90%. Chest x-ray showed a right upper lobe infiltrate with a reticular pattern. The radiologist noted "improvement in right lower and upper pneumonia compared with last x-ray". Sputum for acid-fast bacilli (AFB) was sent.

The patient was readmitted with a diagnosis of pneumonia and treated with intravenous erythromycin and rifampin. A Mantoux test revealed 8 mm induration four hours after injection. On Day 6, he was noted to have a persisting cough, shortness of breath and weight loss. The Mantoux test was repeated and 20 mm induration resulted. Sputum was found to be positive for Klebsiella and ciprofloxacin was started and rifampin discontinued. On Day 10, the sputum was reported to contain many AFB. The patient was then started on isoniazid (INH), rifampin, pyrazinamide and pyridoxine.

On Day 13, he became confused. The chest x-ray showed increased right upper and middle lobe consolidation. Total parenteral nutrition was begun because he had suffered a significant weight loss (body mass index = 24). On Day 16, he was afebrile but developed respiratory failure secondary to excess secretions and was intubated. Ciprofloxacin was restarted. On Day 23, the patient was once again febrile, but he subsequently became agitated with neck stiffness. A lumbar puncture revealed no white or red blood cells, glucose 4.6 mmol/L, protein 4.7 g/L and no bacteria. By Day 30, the sputum was still positive for AFB. Gallium scans of chest, abdomen and head were found to be normal. A tracheostomy was placed on Day 46. On Day 52, *Pseudomonas cepacia* was isolated from the sputum and ciprofloxacin was restarted. A three week course of steroids was begun on day 56 for possible exaggerated inflammatory response to AFB, and the patient's prognosis was felt to be poor.

At this point, the patient had been intubated for nearly eight weeks. An HIV screen was negative; ciprofloxacin was replaced by ceftazidine for treatment of Pseudomonas, since it was found to be resistant. A small lump found on the patient's back was excised and found to be a lipoma. The patient died on day 92, but an autopsy was not performed.

The final diagnosis was TB with secondary Pseudomonal infection, and possibly an underlying occult malignancy.

INTRODUCTION

TB kills more people than any other infectious disease; one out of 15 people alive today in the world will die of TB. In the late 1970s, the World Health Organization (WHO) set out to eradicate TB, but by the mid-1980s, this did not appear to be possible, and WHO again declared TB to be a global emergency (1). Every year since the 1950s, there have been drops in the rate of TB globally, but since

the 1980s rates have stabilized (to 7.2 - 7.5 per 100 000 in Canada) or actually risen.(2)

Increased incidence recently is attributed to several causes: urbanization, increasing poverty/homelessness, HIV, immigration, poor government health supports and reactivation in the elderly. The latter four are the main factors driving the increased incidence of TB in Canada and the US (2). New immigrants account for approximately 47% of TB cases in Canada, while the elderly represent 25% of cases. In Canada approximately half our health care centres do not see any new TB patients in a given year, which may lead to a low index of suspicion (2).

Of the approximately thirty members of the genus Mycobacterium, *Mycobacterium tuberculosis* and *M. bovis* are the only two that cause TB (3).

AFB in respiratory secretions are spread via droplets during coughing, sneezing, and talking. The number of AFB in sputum is proportional to infectivity and although large numbersof AFB may be expelled, long contact is needed for infection. Fomites are not important, but contaminated milk is an important source of *M. bovis*, which can also cause TB (3).

Initially, there is a non-specific acute inflammatory response that may be asymptomatic. AFB are then ingested by macrophages and transported to lymph nodes, where if not contained, disseminated TB may ensue. Two to eight weeks post-primary infection, the AFB multiply intracellularly, and a delayed-type hypersensitivity is the basis of the Mantoux test which helps diagnose TB. Next, lymphocytes enter infected areas and a multitude of factors (lymphokines, cytokines, interleukins) are released that attract monocytes and ultimately transform them into histiocytes that organize into caseating granulomas.

Healing then occurs and granulomas form, giving rise to the characteristic Ghon complex (calcified peripheral lung lesion and calcified nodes) that is often used to make the radiologic diagnosis. Of all people infected, 90-95% have complete healing. Famine, immunosuppressants, and other stressors cause healed lesions to open, and thus reactivate TB, most likely within three years of primary infection (3).

While TB is often thought of as a respiratory disease, it can affect any organ system (3) as shown in Table 1.

Table 1: Clinical Manifestations

Pulmonary: Up to 80% of people infected with TB have pulmonary manifestations with insidious onset. Patients may note cough, night sweats, weight loss, hemoptysis and fever. They may have post-tussive crackles and apices that are dull to percussion, the latter demonstrated in our patient.

TB easily spreads to involve an entire segment, or the pleural space. The cavities thus formed can persist after cure and secondary pneumonia or aspergilloma may develop here. These cavities may also contain pulmonary arteries that sometimes rupture, causing massive hemoptysis (Rausmaussen's syndrome). TB is a cause of broncho-pleural fistulae.

Cardiac: Acute or chronic cardiac tamponade may occur after pericardial seeding from lymph nodes, and is often heralded by a friction rub. Radiographically, one may note pericardial calcifications, as seen in our patient. Although such calcifications can occur with rheumatic heart disease or any other viral disease of the pericardium, they should always alert one to the possibility of TB, especially in the elderly or those with a history of TB exposure.

Skeletal: The bones and joints are not infrequent sites of TB infection, most frequently the weight-bearing joints. Pott's disease, TB of the spine, usually occurs in the mid-thoracic spin with anterior vertebral body erosions causing a sharp kyphosis. It requires long treatment, and surgical stabilization of the spine may even be needed.

GI: The GI system is an uncommon site of infection, as stomach acidity kills many AFB. Tuberculous ileitis with fistula formation may be difficult to distinguish from Crohn's disease. This disease may be transmitted by consumption of milk contaminated by *M. bovis*.

Adrenal: Extensive TB may cause necrosis of the adrenal cortex, causing Addisonian crisis. Formerly, TB was the most common cause of Addison's disease in Canada.

Genitourinary: TB can involve any part of the urinary tract, often presenting as sterile pyuria. AFB may be cultured from the urine. Salpingitis and prostatic nodules have been reported.

CNS: Meningitis is a relatively frequent complication, especially in children. In addition to typical meningeal signs, cranial nerves may also be involved in this basal meningitis. Lumbar puncture will classically reveal elevated protein, decreased glucose and lymphocytosis. TB reactivation in adults may present as new-onset seizures or mimic a stroke.

Miliary: Patients with this often devastating form of TB may have double quotidian fever with anemia and splenomegaly. Classically, miliary TB follows hematogenous dissemination at the time of primary infection. Illness often precedes radiographic changes (fine, uniform nodules throughout the lung). Diagnosis is often difficult, since the Mantoux test, CXR, and sputum isoften negative (necessitating bronchoscopy or bone marrow aspiration to show AFB). Prognosis is grave without treatment.

HIV and TB: TB is a major opportunist infection in HIV patients, and its rise is one of the reasons for the global increase in TB. Up to 42% of patients hospitalized with TB in New York City were HIV positive, the rate climbs to 66% in Uganda. Up to 50% of patients with HIV acquire TB and they often have extra-pulmonary manifestations. Multi-drug resistance is more common among HIV positive patients (2). The response to tuberculin is often lost early, making diagnosis difficult.

DIAGNOSIS

In the Mantoux test, purified protein derivative (PPD) of *M. tuberculosis* is injected intradermally, usually in the forearm. Induration at the site is measured in 48-72 hours (4). False-negatives (2-20%) may occur in a number of instances including anergy, cachexia, concomitant infection and immunosuppression. The rate of false-positives is unknown and is believed to occur from exposure to non-pathogenic Mycobacteria species (3). Table 2 shows interpretation of the Mantoux test, according to the Draft Canadian Lung Association Guidelines (in press).

An anergy panel, a hypersensitivity test to a variety of antigens, has not been shown to help dramatically in diagnosing TB in anergic patients such as the immunosuppressed (5).

M. tuberculosis demonstrated in sputum by staining and culture remains the cornerstone of diagnosis. At least 104 colonies/mL of AFB are required to visualize them. Up to five sputum samples may be required, but up to one third of TB patients will not show AFB in the sputum. Early-morning gastric washings are another way to make the diagnosis in this group.

Culture of sputum may show as few as 10 to 100 AFB/mL, but takes 2-8 weeks. New dignostic possibilities include detection of radiolabeled carbon when labelled palmitic acid is taken up by mycobacteria and degraded to carbon dioxide. The polymerase chain reaction

Table 2. Reading Mantoux Test Results

Induration	Result
0 -4 mm	Negative in all
5 -9 mm	Positive in: HIV positive,
....	immunosuppressed, those with close
....	contact to TB infected person, evi-
....	dence of TB on chest x-ray
10 + mm	Positive in all patients including those
....	with BCG vaccine

(PCR) is starting to find a diagnostic niche in the diagnosis of TB meningitis, where time is of the essence and only a small amount of CSF is available.

Blood counts with lymphocytosis or monocytosis of uncertain etiology should raise suspicion of TB (3).

TREATMENT

Currently, a regimen of INH, rifampin, pyrazinamide for two months and then INH and rifampin for four months is recommended (6). Ethambutol or streptomycin is added if INH resistance is over 4% in the community. Alternatively, INH and rifampin is used for nine months, adding ethambutol or streptomycin if INH resistance is a concern. All patients are considered for direct observed therapy. This marks a major shift in American treatment programs, the driving force behind it being evidence from various centres around the world and the rise of multi-drug resistant TB. INH and rifampin for four months is acceptable in adults with active TB who are otherwise well and in whom INH resistance is not a concern. Children should be treated as adults but with smaller doses. However, children who have bone, meningeal or miliary TB should be treated for one year. Multi-drug resistant TB needs at least INH and rifampin. Treatment requires individualization and one should consult an expert in TB. The major determinant of success remains patient compliance (6).

Liver function tests (transaminases may quadruple during therapy with no obvious effects), CBC, creatinine and uric acid should be followed. Color vision should be monitored in patients taking ethambutol. Adverse effects of anti-tuberculous therapy are more common in HIV patients, making the issue of potential false-positive testing in this group more crucial.

PREVENTION

In a large randomized, controlled trial INH alone was shown to be of benefit in those presumed to have been infected. The groups for which INH is recommended include the immunosuppressed, HIV positive, household contacts, those whose PPD status has changed, and the elderly. Younger people benefit most. At age 45 years, there is a 1:1 ratio of prevention of TB to INH-induce hepatitis (6).

A vaccine for TB, Bacillus Calmette-Guerin (BCG), an attenuated strain of *M. bovis* that is used in many countries including Canada, is available. Over two billion people have been vaccinated with BCG. Some studies show no effect on mortality, but the vaccine is safe and drastically drops the incidence of disseminated forms of TB (2).

Canada is unique in North America in having a policy for BCG vaccination - albeit only for aboriginal Canadians (7).

Unfortunately, at present, vaccines perform with only limited success against organisms such as TB that affect cell-mediated immunity. Present efforts are being directed toward subunit vaccines and unravelling *M. tuberculosis*'s genome, which is poorly known despite the disease's large impact on life-years lost (8).

In areas of low prevalence, monitoring programs are key. Monitoring of patients and their families, health care workers, occupants of shelters and jails, and new immigrants is most effective. There are high dropout rates (9).

In high prevalence areas, the focus should be placed on BCG vaccination for those younger than 20 years; ambulatory clinics with a low threshold for treatment; free treatment; and improved basic determinants of health.

The Canadian Lung Association recommends that all health care workers have a tuberculin skin test documented prior to starting work, and that a two-step TB test be performed as a screen. These tasks may be formidable given present restraints on health care budgets. Many health care workers, even in tertiary care centres, presently have poorly documented TB screens (Dr. G. Hardy, personal communication).

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