

Bilateral neck swelling in a 40-year-old woman with HIV

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A 40-year-old African-born woman with HIV presented with a several-month history of progressive, painful bilateral neck swelling. She stated that she had been unable to eat because of the excruciating pain. She reported intermittent fevers as well but denied any shortness of breath or cough. She also reported right upper-quadrant

abdominal pain and mild abdominal distension. She was admitted to the hospital, and her workup included contrast-enhanced computed tomography (CT) of the neck, chest, abdomen, and pelvis (Figures 1–5).

What are the differential diagnostic considerations? What is the most likely diagnosis? What tests can confirm the diagnosis?

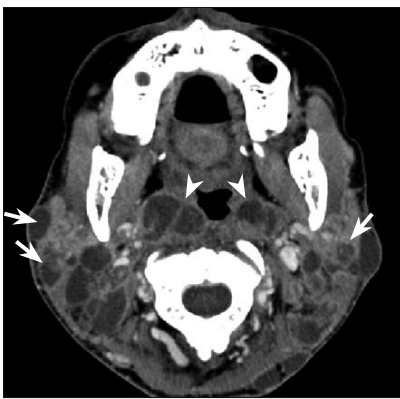


Figure 1. CT image of the upper neck shows innumerable pathologic, enlarged, low-density lymph nodes, which are characteristic (but not pathognomonic) for tuberculosis. Every nodal chain is involved, including retropharyngeal (*arrowheads*) and intraparotid (*arrows*) nodes.

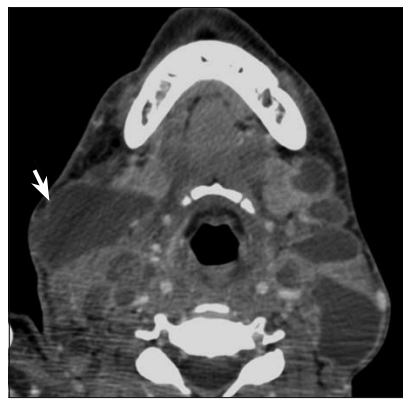


Figure 2. CT image of the lower neck again shows similar pathologic nodes involving multiple nodal chains. The largest node (*arrow*) was aspirated and revealed acid-fast bacilli.



Figure 3. CT image of the chest with lung windows demonstrates an infiltrate within the anterior left upper lobe.



Figure 4. CT image of the upper abdomen demonstrates innumerable low-density lesions within the spleen (*white arrows*), consistent with microabscesses from disseminated tuberculosis. An abscess is present in the hepatic hilum (*black arrow*), and ascites is seen anterior to the liver (*arrowhead*).

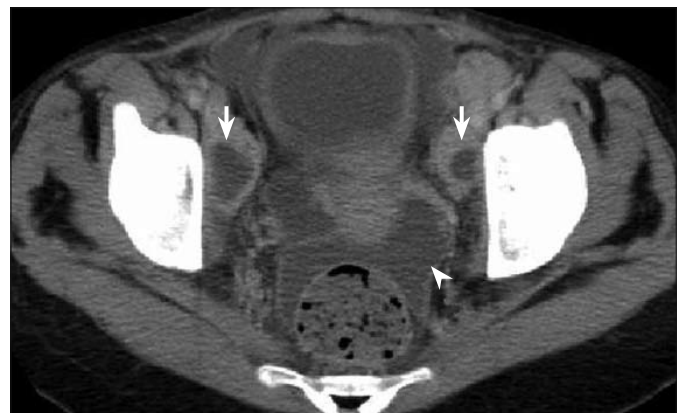


Figure 5. CT image of the pelvis demonstrates characteristic pathologic bilateral iliac lymph nodes (*arrows*). Ascites is also seen in the pelvis (*arrowhead*).

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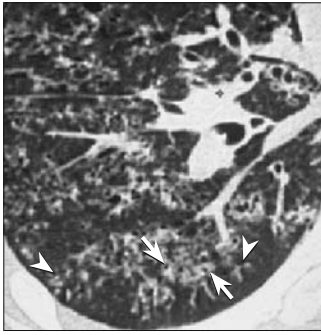


Figure 6. Postprimary tuberculosis. CT image of the lungs demonstrates bronchiolar wall thickening (arrows) and mucoid impaction of contiguous branching bronchioles producing a tree-in-bud appearance (arrowheads). Tree-in-bud is characteristic, but not pathognomonic, for tuberculosis. Reprinted with permission from *Radiographics* (1).



Figure 7. Pott's disease. CT image of the spine demonstrates lytic destruction of the vertebral body (black arrow) with an adjoining soft-tissue abscess (white arrow). Reprinted with permission from *Radiographics* (1).



Figure 8. Ileal tuberculosis. There is irregularity and edema of the terminal ileum with marked narrowing of the lumen, as evidenced by the "string" of contrast (arrows). This appearance is nonspecific and there are many etiologies, with the most common being Crohn's disease. Reprinted with permission from Manpreet Singh Gulati, MD (5).

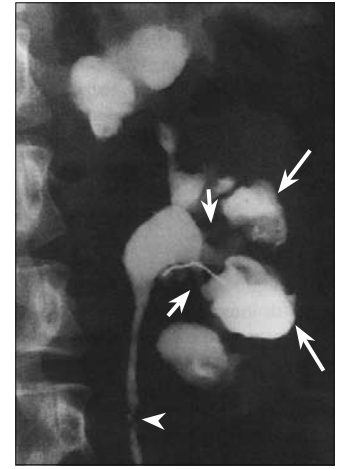


Figure 9. Renal tuberculosis. An antegrade pyelogram shows characteristic calyceal dilation (long arrows) secondary to infundibular stenoses (short arrows). Proximal ureteral stricture (arrowhead) is also seen. Reprinted from *Textbook of Uroradiology* (6) with permission from Lippincott Williams & Wilkins.

DIAGNOSIS: Disseminated tuberculosis. The largest necrotic right cervical lymph node was surgically aspirated; the culture grew *Mycobacterium tuberculosis*. The differential diagnosis would include lymphoma, opportunistic infections (especially fungal), and metastases.

IMAGING FINDINGS

Although manifestations of tuberculosis are usually limited to the site of primary infection within the chest, the disease can affect virtually any organ, with disseminated disease being more common in immunocompromised patients. Here we briefly describe the more common radiological findings found with disseminated tuberculosis (1, 2).

Pulmonary tuberculosis is classically divided into primary and postprimary (reactivation) disease; the former is more common in children, and the latter is more common in adults. Primary tuberculosis is usually demonstrated radiologically by parenchymal consolidation, lymphadenopathy, pleural effusions, miliary nodules, or atelectasis. However, 15% of the time, the chest radiograph is normal. Reactivation tuberculosis usually is evidenced by parenchymal disease with cavitation or endobronchial spread of bacilli leading to a "tree-in-bud" appearance on CT (Figure 6). Tuberculosis rarely affects the heart, but when it does, it often causes a pericarditis evidenced by pericardial fluid and enhancement, best seen on CT.

Skeletal involvement of tuberculosis is frequently manifested in the spine, especially in the thoracolumbar region. Early radiographic changes of tuberculous spondylitis (Pott's disease) include osteopenia and end-plate irregularity, which will progress to vertebral body collapse (usually anteriorly) and lead to an anteriorly wedged body (Gibbus deformity). Osteomyelitis/discitis is best demonstrated by magnetic resonance (MR) imaging. Typically, the affected vertebral body and adjacent disc will have decreased signal on T1, increased signal on T2, and fluid-sensitive sequences such as short tau inversion recovery (STIR) and will demonstrate enhancement on postcontrast

sequences. On CT, cortical irregularity/destruction is evident, usually with an adjacent paraspinous mass or enhancing fluid collection/abscess (Figure 7).

Although abdominal tuberculosis is usually secondary to spread from pulmonary tuberculosis, radiologic evaluation often shows no evidence of lung disease. Lymphadenopathy is the most common manifestation of abdominal tuberculosis. The mesenteric, omental, peripancreatic, and upper periaortic nodes are usually involved. There are frequently multiple, large nodes with the characteristic central necrosis (low density on CT) and peripheral enhancement. Although these low-density lymph nodes are typical in disseminated tuberculosis, they are not pathognomonic, as they can be seen in lymphoma, fungal disease, metastases, and Whipple's disease (3, 4). The ileocecal region is the most common area of involvement within the gastrointestinal tract due to the abundance of lymphoid tissue there. Edema and narrowing are often seen in the terminal ileum and cecum, which can be associated with a large, gaping, incompetent ileocecal valve (Figure 8) (5). These findings are best demonstrated on small bowel series and on CT. CT usually also reveals extensive adenopathy and, on occasion, ascites, which may be diffusely distributed or loculated. Tuberculosis of the liver and spleen often demonstrates multiple tiny low-density foci on CT. Less commonly, there may be diffuse hepatosplenomegaly with large low-density areas or a tumorlike mass.

Renal tuberculosis can result in amorphous granular or lobular calcifications within the renal parenchymal. With intravenous pyelography, in the earliest stages, the tips of the papilla will have a "moth-eaten" appearance, which could progress to papillary necrosis. The hallmark of renal tuberculosis is the development of multiple irregular infundibular strictures with subsequent hydrocalycosis (Figure 9) (6). Eventually, chronic disease leads to

parenchymal scarring and loss of function of the affected kidney, termed “autonephrectomy.” Ureteral involvement is demonstrated initially with dilatation of the ureter, possibly with filling defects due to the mucosal granulomas. Progression of disease leads to short- or long-segment ulceration of the ureter and, chronically, to fibrotic strictures, giving a corkscrew or beaded appearance. Strictures, along with fistula formation, are also common with tuberculous involvement of the urethra (6). The most common finding of bladder tuberculosis is a small bladder with wall thickening, which may be irregular and mimic neoplasm. Although classically described, bladder calcification is infrequently seen with tuberculosis. Ureteral calcification is also rare.

Tuberculous involvement of the central nervous system is often manifested by tuberculous meningitis (especially in children) and, on occasion, by intracranial tuberculomas. Meningitis is best demonstrated on MR imaging by intense linear enhancement of the leptomeninges, especially at the basal cisterns. Common complications of tuberculous meningitis are hydrocephalus and ischemia. Tuberculomas may be solitary or multiple and are usually located in the supratentorial brain; they may demonstrate ring enhancement or solid homogenous enhancement. Tuberculomas can easily mimic neoplasm, but associated meningitis, when present, is very suggestive of tuberculosis (Figure 10) (7).

DISCUSSION

Tuberculosis, a historical perspective

Tuberculosis has been ubiquitous in both time and geography. Archeologists have found evidence of the tubercle bacillus in human bones dating back to 5000 BC (8, 9). Spinal column fragments of Egyptian mummies from 2400 to 3400 BC indicate the presence of Pott’s disease. Evidence of tuberculosis appears in biblical scripture, Chinese literature dating to 4000 BC, and religious books in India around 2000 BC. Around 460 BC, Hippocrates wrote about the disease he called “phthisis,” which in Greek translates to “to waste away.” Tuberculosis has also been referred to as consumption, the white plague, king’s evil, and scrofula, among many other names. It was thought that Columbus brought tuberculosis to the New World; however, in 1994, tuberculous DNA was discovered in a Peruvian woman who had died 500 years before Columbus’ arrival.

In 1679, a German physician, Franciscus de la Boe, more commonly known as Dr. Sylvius, described the many enlarged lymph nodes in afflicted patients as tubercles (Latin for “little swelling”); hence the term “tuberculosis.” In 1720, an English physician named Benjamin Marten hypothesized that tuberculosis might be caused by “wonderfully minute living creatures.” In his publication, *A New Theory of Consumption*, he stated that

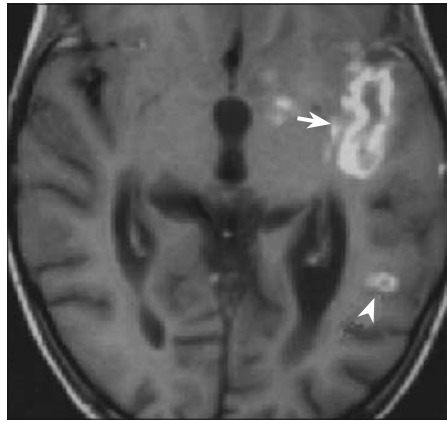


Figure 10. Central nervous system tuberculous meningitis. A postcontrast T1-weighted MR image demonstrates leptomeningeal enhancement along the left sylvian fissure (arrow). There is an accompanying ring-enhancing tuberculoma in the left parieto-occipital region (arrowhead). Reprinted with permission from *Radiographics* (1).

his physicians to seek a healthier climate to combat the disease. He traveled to the Himalayan Mountains, where he continued his studies, and while there, his health improved dramatically. He returned to Germany and studied medicine and in 1854 presented his doctoral dissertation titled *Tuberculosis Is a Curable Disease*. In that same year, he opened an inpatient hospital in Gorbersdorf, Germany, where patients were surrounded by fir trees, supplied with good nutrition, and laid out on balconies to be exposed to continuous fresh air. His hospital became the model for all subsequent sanatoriums which, along with artificial pneumothorax (discussed below), were the main treatment for tuberculosis for almost 100 years. The effectiveness of the sanatoriums was twofold: they treated the ill and isolated the infected from the healthy population.

In 1865, a French military doctor, Jean-Antoine Villemin, demonstrated that the disease could be passed from humans to cattle and from cattle to rabbits. This was a remarkable breakthrough, because despite Marten’s wonderful small organisms, medical theory still held that each case of consumption arose spontaneously within each patient.

Then in 1882, German biologist Robert Koch was the first to visualize the causative organism, *Mycobacterium tuberculosis*, through special staining techniques that he himself developed. He was also able to grow the organism in pure culture. Koch eventually was able to isolate proteins from the bacillus that he thought could cure tuberculosis. Although his hopes for a cure were ultimately not met, his protein isolates would be the basis for the tuberculin skin tests that we now use to screen for patients who may be infected. He was awarded the Nobel Prize for physiology or medicine in 1905 “for his investigations and discoveries in relation to tuberculosis.”

Also in 1882, the Italian physician Carlo Forlanini popularized the method of artificial pneumothorax as a treatment for tuberculosis. Using a portable apparatus that he designed (Figure 11), air would be injected into the pleural cavity with the intention of compressing and eventually scarring the diseased

these creatures could generate the lesions and symptoms of the disease once they gained a foothold in the body. He continued:

It may be therefore very likely that by an habitual lying in the same bed with a consumptive patient, constantly eating and drinking with him, or by very frequently conversing so nearly as to draw in part of the breath he emits from the Lungs, a consumption may be caught by a sound person. I imagine that slightly conversing with consumptive patients is seldom or never sufficient to catch the disease.

One of the first people to view tuberculosis as a treatable disease was a botanical student from Germany named Hermann Brehmer, who suffered from the disease himself. He was advised by

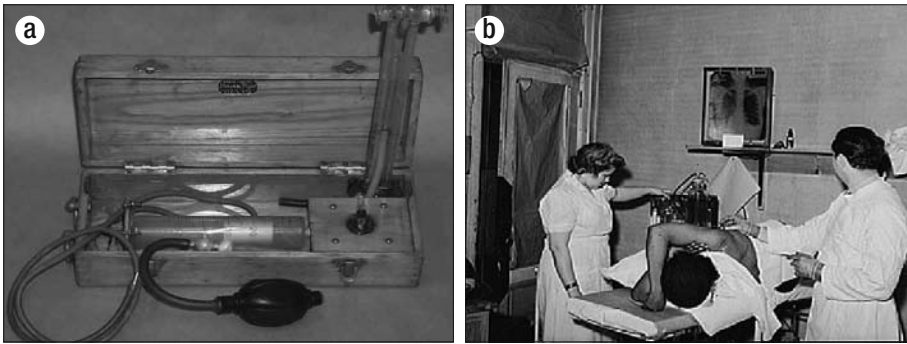


Figure 11. Artificial pneumothorax. (a) An apparatus from the 1930s, based on Forlanini's model. Reprinted courtesy of the Museu d'Història de la Medicina de Catalunya. (b) Depiction of the procedure, designed to collapse the infected lung and allow it to "rest and heal." This procedure was generally repeated every 10 to 15 days and lasted over 3 to 4 years.

lung. The process was repeated once every 10 to 15 days for 3 to 4 years, with the idea that scarring of the affected lung would somehow halt the progression of disease (10). Forlanini's method led to similar forms of lung compression, including thoracoplasty and plombage, where inert substances such as Lucite balls are inserted into the pleural cavity (Figure 12). Another advance came in 1895, when Wilhelm Conrad Roentgen (the founding father of radiology) discovered x-rays that allowed accurate monitoring of the progress and severity of a patient's disease.

From 1908 to 1919, Albert Calmette, a French bacteriologist, and Camille Guérin, a veterinarian, developed a tuberculosis vaccine by serially subculturing *Mycobacterium bovis* over 200 times to result in an avirulent strain called bacilli Calmette-Guérin (BCG). The BCG vaccine was first used in humans in 1921; however, initial public acceptance was lacking, due in particular to one major incident. In Germany, 240 infants were vaccinated in the first 10 days of life; almost all developed tuberculosis, and 72 infants died. It was subsequently discovered that the BCG administered had been contaminated with a virulent strain that was being stored in the same incubator, and legal action was taken against the manufacturers of BCG (11). The BCG vaccine did not gain wide acceptance until after World War II, but since that time, it has been one of the safest and most widely used vaccines. The vaccine has been found to be very effective against childhood tuberculosis, especially meningitis and miliary tuberculosis. It is used in many developing countries with a high prevalence of tuberculosis. However, it has never been widely used in the USA because of the low risk of infection with *Mycobacterium tuberculosis*, the variable effectiveness of the vaccine against adult pulmonary tuberculosis, and the vaccine's potential interference with tuberculin skin test reactivity (12).

The most significant milestone in the fight against tuberculosis came in 1943, when Selman Waksman, a biochemistry and microbiology professor at Rutgers University, discovered streptomycin, the first antibiotic that was effective against tuberculosis. Streptomycin was first administered to a patient on November 20, 1944, and the results were immediate and impressive. The patient's advanced disease was visibly arrested, the bacteria could no longer be found in his sputum, and he made a rapid recovery.

Waksman also won the Nobel Prize for physiology or medicine in 1952 for his discovery of streptomycin. Following streptomycin, p-aminosalicylic acid (1949), isoniazid (1952), pyrazinamide (1954), cycloserine (1955), ethambutol (1962), and rifampin (1963) were introduced as antituberculosis medications. These additional medications were vital because within months of streptomycin's first wide use, strains resistant to it began to appear. Now multiple-drug regimens are utilized in all patients with tuberculosis.

Tuberculosis today

Since national reporting of tuberculosis cases began in the USA in 1953, the annual incidence of the disease has steadily declined, with the exception of the period of 1985 to 1992. From 1953 to 1985, the annual number of cases reported in the USA dropped 74%, from 84,304 to 22,201. However, the period of 1985 to 1992 saw a resurgence of the disease, with a peak incidence of 26,673 new cases in 1992. This resurgence was due to the HIV epidemic, increased immigration from tuberculosis-endemic countries, increased tuberculosis transmission in congregate settings (e.g., hospitals and prisons), deterioration of the infrastructure for tuberculosis services, and development of difficult-to-treat cases of multidrug-resistant tuberculosis (13). However, from 1993 to 2006, the annual incidence rate has again been in steady decline, with 13,767 tuberculosis cases (4.6 per 100,000 population) reported in 2006, which is the lowest rate recorded since 1953. This reduction is attributed to more effective tuberculosis-control programs that emphasize prompt identification of persons with tuberculosis, prompt initiation of appropriate therapy, and efforts to ensure that therapy will be completed (directly observed therapy).

Despite this fact, there are some alarming trends. First, the rate of decline of tuberculosis has slowed each year since 2000. Also, foreign-born persons continue to be disproportionately affected, with an incidence rate 9.5 times that of US-born persons. The number of cases of tuberculosis in foreign-born persons also increased in 2006 from the previous year. This is troublesome

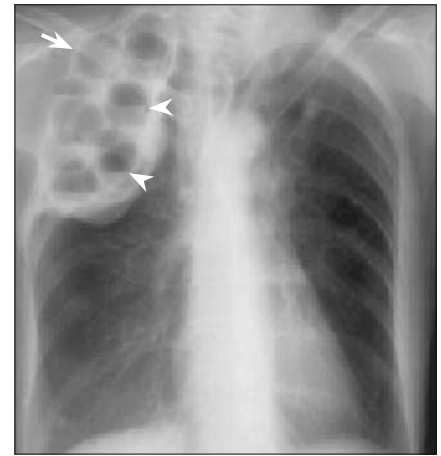


Figure 12. Plombage. A frontal chest radiograph demonstrates typical right-sided Lucite ball plombage. There is thinning and disorganization of the overlying ribs (arrow). Air-fluid levels in the Lucite balls (arrowheads) suggest broncho-pleural fistulas. Reprinted with permission from *Radiographics* (1).

because foreign-born persons are more likely to be infected with difficult-to-treat multidrug-resistant and extensively drug-resistant strains (discussed below).

Lastly, in both 2005 and 2006, the HIV status of one third of the patients with new reported cases of tuberculosis was not known. HIV is the most important risk factor for progression of latent to active disease, and the mortality rate for tuberculosis patients coinfecting with HIV is much higher than that of those who are HIV negative (14). One out of ten immunocompetent people infected with tuberculosis will develop active tuberculosis in their lifetime, but among those with HIV, one in ten *per year* will develop active tuberculosis, while one in two or three *per year* with clinical AIDS will develop active tuberculosis.

One of the most startling developments in the fight against tuberculosis is the recent emergence of extensively drug-resistant tuberculosis (XDR-TB). Multidrug-resistant tuberculosis (MDR-TB) is defined by resistance to the two most powerful first-line antituberculosis drugs, isoniazid and rifampin. XDR-TB is defined as an MDR-TB strain *with additional* resistance to any fluoroquinolone and any one of the three injectable second-line drugs: capreomycin, kanamycin, and amikacin (15). Data from the US National Tuberculosis Surveillance System revealed 49 cases of XDR-TB reported in the USA between 1993 and 2006. This number is a minimum estimate, because only 22% of the reported MDR-TB cases had drug susceptibility testing performed for all the drug combinations in the definition of XDR-TB (16). According to the World Health Organization, 37 countries have confirmed cases of XDR-TB, which again is likely an underestimation (Figure 13). One of the most endemic areas for MDR-TB and XDR-TB is South Africa, which, not by mere coincidence, has one of the highest HIV prevalence rates.

A report published in the October 2006 issue of *Lancet* demonstrated the devastation that XDR-TB and HIV can exact on a community (17). Gandhi and colleagues obtained sputum samples of 1539 patients from a hospital in the KwaZulu-Natal Province of South Africa from January 2005 through March 2006. Five hundred forty-two patients were found to be culture positive for tuberculosis, with 221 patients meeting criteria for MDR-TB and 53 patients meeting criteria for XDR-TB. Again, this is likely an underestimation of the true prevalence of XDR-TB because susceptibility testing was performed for only one fluoroquinolone, ciprofloxacin, and only one injectable drug, kanamycin. Forty-four of the 53 patients were tested for HIV, and they were all coinfecting. Fifty-two of the 53 patients died, with a median survival of 16 days from the time of sputum collection. Due to this alarming study, there is new increased awareness of an old disease by both public officials and health officials worldwide. In June 2007, the World Health Organization and the Stop TB Partnership launched a \$2.15

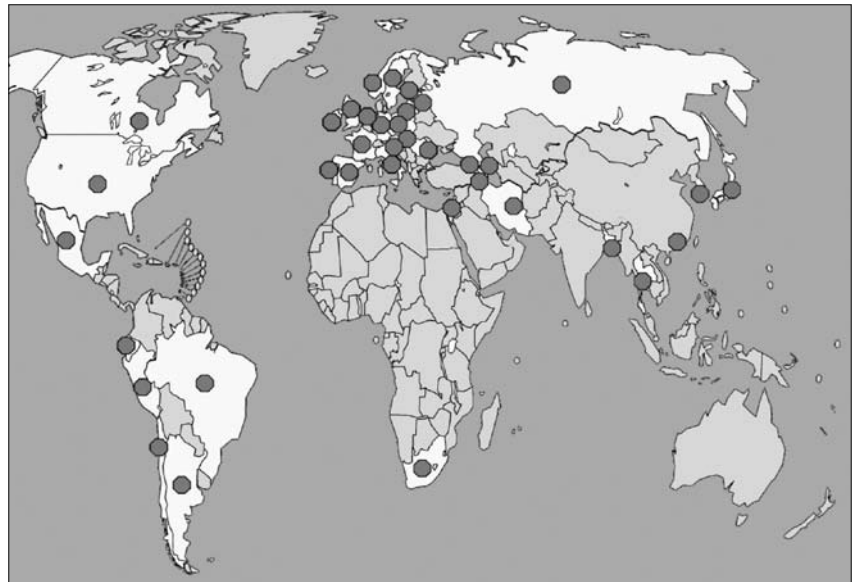


Figure 13. Countries with confirmed cases of extensively drug-resistant tuberculosis as of May 2007. The countries are Argentina, Armenia, Azerbaijan, Bangladesh, Brazil, Canada, Chile, China–Hong Kong SAR, Czech Republic, Ecuador, Estonia, France, Georgia, Germany, Ireland, Islamic Republic of Iran, Israel, Italy, Japan, Latvia, Lithuania, Mexico, Netherlands, Norway, Peru, Poland, Portugal, Republic of Korea, Romania, Russian Federation, Slovenia, South Africa, Spain, Sweden, Thailand, United Kingdom, and USA. Reprinted with permission from the World Health Organization.

billion 2-year program that is projected to prevent hundreds of thousands of cases of drug-resistant tuberculosis and save as many as 134,000 lives. In addition, six new antituberculosis drugs are in various stages of testing.

CLINICAL OUTCOME

This admission was actually the patient's second hospital admission for disseminated tuberculosis. She was admitted 2 years earlier when she initially developed neck masses. A few of the masses were aspirated and revealed acid-fast bacilli. She has been on triple therapy consisting of isoniazid, rifabutin, and ethambutol; in addition, she has been on highly active retroviral therapy. On this admission, the largest lymph node, on the right, was surgically aspirated and once again showed acid-fast bacilli. Pyrazinamide, streptomycin, and levofloxacin were added to her therapy, for a total of six antituberculosis drugs. The patient's condition improved with the new regimen, and she was discharged home. Unfortunately, she was lost to follow-up. Drug susceptibility testing revealed pan-sensitivity to all six of her tuberculosis medications.

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