Palomino • Leão • Ritacco

TUBERCULOSIS 2007

From Basic Science to Patient Care

Chapter 15: Tuberculosis in Adults

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15.1. Introduction

Tuberculosis (TB) is a disease with deep social and economical roots. Low-income people with large families, living in dense urban communities with deficient housing conditions, have a high probability of becoming infected, developing active disease, and dying from TB. Also, the risk of becoming infected and ill with TB is higher among people that live in congregated institutions, such as prisons, youth correctional facilities, nursing homes for elderly people, social shelters, day nurseries and schools; the same is valid for elderly people, diabetics and people living with Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) (Dye 1999, American Thoracic Society 2000, Castelo-Filho 2004, World Health Organization 2006).

The lung is the main entrance gate of the tuberculous bacillus, which causes a focal infection in the site where it is deposited after inhalation. If the infection cannot be contained at the local level, bacilli dissemination is produced initially by hematogenic route, probably inside phagocytic cells, towards different organs and, eventually, to the contiguous pleura. It reaches hilar lymph nodes via the lymphatic route, and from there, a second systemic dissemination can occur, through the thoracic duct and superior vena cava, with the development of local foci in the lungs. Extrapulmonary foci can also be produced by hematogenic and lymphatic dissemination. The clinical manifestations of TB depend on the local organic defenses on the sites of bacilli multiplication (Rich 1944, Bates 1980, Stead 1984). It has been emphasized that the use of bacille Calmette-Guérin (BCG) vaccination may play a role in this phase, avoiding dissemination and the occurrence of extrapulmonary forms of TB.

15.2. The initial lesion

Once inhaled, most tubercle bacilli are trapped in the mucosa of the upper respiratory tract, trachea and bronchi, especially when inhaled in clumps, and are eliminated by the mucocilliary defense mechanisms. Tiny particles or droplet nuclei smaller than 5 μm behave as a gas and overcome this barrier and reach the inferior respiratory tract, especially inside the alveoli, where they are readily phagocytosed by alveolar macrophages.

The survival of the infectious agent in the lung will depend on its pathogenic-ity/virulence and on the ability of the host cells to eliminate it. The alveolar macro-phages are the first line of defense against *Mycobacterium tuberculosis*. This initial response, if completely effective, will cause the elimination of the pathogen through the phagocytic action inherent to such macrophages (see Chapter 5). If the alveolar macrophage is not capable of arresting bacterial growth, a localized pro-inflammatory response is formed through the activity of Toll-like receptor agonists, abundant on the surface of bacteria. Tumor necrosis factor alpha (TNF-α) and in-flammatory chemokines produced by the infected macrophages recruit white blood cells, which phagocytose bacilli and eventually return to the bloodstream causing the primary hematogenic dissemination (Figure 15-1).
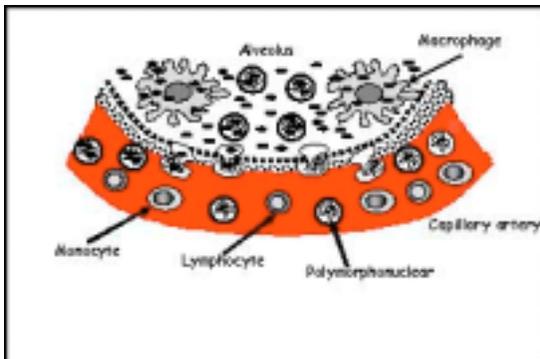

Figure 15-1: Non-specific inflammation with blood white cell migration and primary hemato-genic dissemination

The recruited cells produce their own complement of chemokines and cytokines that amplify cellular recruitment and remodel the infection site into a cellular mass, the tubercle or granuloma. The granuloma initially formed consists of a core of infected macrophages surrounded by foamy macrophages, with an external layer of lymphocytes encircled by collagen and other extracellular matrix components (Russell 2007).

Tubercle bacilli can disseminate by the lymphatic route to regional lymph nodes, constituting the tuberculous primary complex of Ranke, composed by the original granuloma at the inoculation site (Gohn's nodule), the lymphangitis and the hilar lymph node enlargement (Figure 15-2). Although in some cases these lesions may become evident on chest X-ray, most cases of primary tuberculous infection are

clinically and radiologically unapparent, with a positive TST being the only indication of the occurrence of the infection.
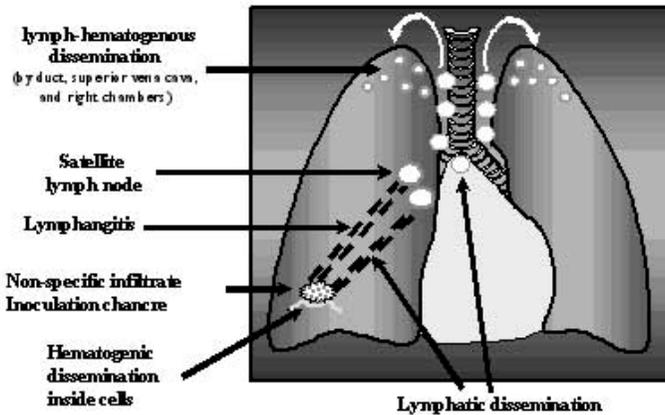

Figure 15-2: Primary infection, inoculation lesion, primary complex, and initial TB dissemination

From the hilar lymph nodes, tubercle bacilli disseminate to tracheal and vertebral lymph nodes. Through the thoracic duct, they reach the blood stream, spreading to the upper areas of the lungs or to different organs, such as kidney, brain, and bones. At these sites, they find a favorable atmosphere for implantation that combines a satisfactory oxygen tension and a low local perfusion: this is an ideal association that hinders the access of defense cells.

15.3. The inflammatory response

With the development of specific cellular immune response and production of interferon-gamma (IFN-γ), a mature stable granuloma is formed, which is responsible for the immune containment of the pathogen. Mature granulomas present neovascularization, epithelioid and giant multinucleated cells. An extensive fibrotic capsule develops and infected macrophages trapped inside granulomas eventually die. Tubercle bacilli tend to locate in the center of the granuloma, but bacteria and antigens are also associated with macrophages in the peripheral infiltrate (Russell 2007). The necrotic material present in the center of TB lesions contains high

amounts of fat representing the lipids liberated from bacillary catabolism. This material, which has a soft, dry and cottage cheese texture, is known as caseous necrosis. On microscopy, large amounts of epithelioid and giant multinucleated cells can be observed in the granulomas, located mainly around the caseous material. The nature of the host immune response will determine whether the infection will progress or be contained.

The discussion regarding the participation of T lymphocytes in the development of infectious diseases has lead to the paradigm, initially developed in the murine model, which characterizes CD4+ T lymphocytes in two subpopulations named T helper 1 (Th1) and T helper 2 (Th2). In the human infection, however, such a clear division into two different cytokine response patterns is not observed. Unlike the murine model, a wide spectrum of cytokines are produced in response to infection by *M. tuberculosis* in the human host, and their function in containing the infection is not yet completely understood (Chacon-Salinas 2005).

Individuals who are able to mount an immune response adequate enough to contain *M. tuberculosis* bacilli at this stage will develop a clinical form of infection, characterized as latent infection, in which bacilli will stay for an undetermined period of time. The risk of progressing to clinical TB is highest during the first 3-5 years after the infection, especially among immunosuppressed individuals.

In view of this, the disease can occur:

- **during the initial phase of infection** - due to excessive bacillary load, increased bacterial pathogenicity/virulence and/or factors that decrease host immune response. In this case, a host-parasite balance is not achieved, which results in the development of **primary TB** a few months after the infection.

- **posterior to the initial phase of infection** – due to a rupture of the host-parasite balance in individuals with latent TB, resulting in **post-primary TB**.

15.4. Tuberculosis infection

In most individuals, TB infection is clinically irrelevant and seldom recognized. It commonly occurs during childhood (see Chapter 16), and may occasionally cause malaise, low-grade fever, erythema nodosum, and phlyctenular conjunctivitis. Erythema nodosum is a toxic allergic nodular lesion 2 to 3 cm large, located in or under the skin. These lesions are spontaneously painful and very painful under

pressure, and are usually located bilaterally on the anterior surface of feet and legs. In most individuals, however, primary TB infection causes no apparent symptoms and the infection stays latent for life or until reactivation (Bates 1980, Melo 1993, Lima 1993). Chest X-rays can present several manifest ations. The classical presentation is known as the primary Ranke's complex, including a calcified peripheral lung nodule (Gohn's primary focus), lymph tracts toward the hilus (lymphangitis), and enlarged local lymph nodes (Figures 15-3 and 15-4).

Figure 15-3: Chest X-ray showing a calcified peripheral nodule in the lower right lung (Gohn's primary focus) (Reproduced from Melo 2005a)
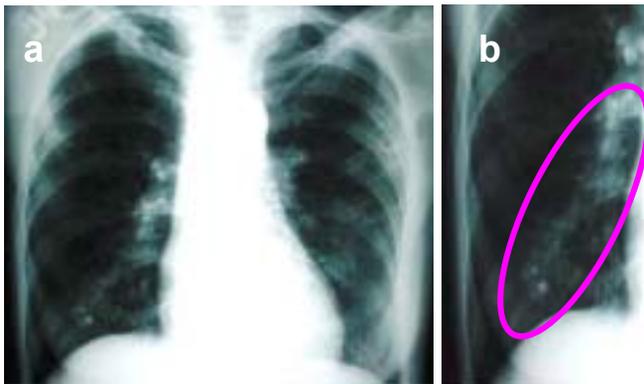

Figure 15-4: a: Chest X-ray showing a calcified peripheral nodule in the lower right lung, lymphangitis (encircled in b) and hilar involvement (Ranke's complex) (Reproduced from Melo 2005a).

In the initial phase of *M. tuberculosis* infection, some tubercle bacilli can reach the upper lobes of the lungs, creating small metastatic foci referred to as Simon foci, visible on chest X-ray (Figure 15-5).
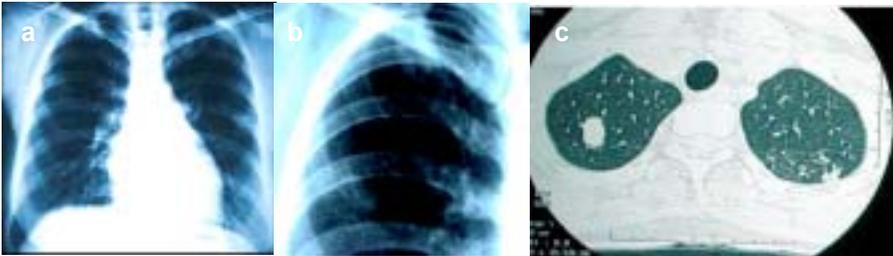

Figure 15-5: Simon nodule in upper lobe of the right lung in an asymptomatic adult. **a** and **b**: chest X-ray, **c**: computerized tomography.

For additional images of TB infection see Presentation 1 at http://www.tuberculosistextbook.com/pdf/Presentation_1.pdf.

15.5. Tuberculosis disease

The development of clinical TB will occur in 5 %-10 % of infected persons at some point in their lives, for reasons that are not completely clear. Some factors involved in increased risk of developing TB have been established, of which the most important are those interfering directly with host immunity.

Diseases and conditions that weaken immunity, such as malnutrition, alcoholism, advanced age, HIV/AIDS, diabetes, gastrectomy, chronic renal insufficiency, silicosis, paracoccidioidomycosis, leukemias, solid tumors, immunosuppressive drug treatments, and hereditary features, are factors that facilitate the development of TB disease. Additional factors include the infective bacterial load, pathogenicity/virulence of bacilli, and host genetic susceptibility (ATS- 2000).

15.5.1. The primary disease

Adult primary TB is paucibacillary, practically non-contagious, difficult to diagnose, and of variable severity, as described in children (see Chapter 16). In seriously immunodepressed patients, but also in individuals with IFN-γ or IL-12 re-

ceptor deficiency, it can develop into a disseminated form, which is sometimes fatal. High morbidity in the primary form was also observed in patients whose ancestors were not previously exposed to the tubercle bacillus, as reported in the Yanomami Indians in the Amazon Region (Sant´Anna 1988, Souza 1997).

For images of primary disease see Presentation 2 at http://www.tuberculosistextbook.com/pdf/Presentation_2.pdf.

15.5.2. The post-primary disease

The existence of post-primary TB, also known as secondary TB, means that the infection can progress after the development of an adequate specific immune response. This TB episode can develop in two ways: by inhalation of new bacilli or by reactivation of the primary focus. Recently, in African countries, using molecular typing methods, it has been shown that the transmission is community driven, and not solely through households, and that reinfection with novel *M. tuberculosis* strains may occur in 40 % of relapsing cases (Verver 2005). The recurrence/relapse caused by new strains highlights the possibility that the progression to disease can be enhanced by multiple infections, especially among high-risk persons, such as HIV infected individuals.

Pulmonary TB is the most common form of post-primary disease. Lymphatic dissemination can occur, but in this case the hilar lymph nodes are usually not affected. The response to bacillary multiplication provokes caseous necrosis that eventually blends and progresses to liquefaction. Tubercle bacilli, whose multiplication had been until then inhibited by granuloma formation, find favorable conditions for population growth after liquefaction of the caseum and subsequent cavitation, and may produce more than 10^8 bacilli per cavity with a diameter of less than 2 cm. The development of tuberculous cavities in the lung characterizes the post-primary TB and, from this lesion, infectious material can spread through bronchi, resulting in the continuous production and elimination of sputum. The natural evolution of post-primary lesions in immunocompetent persons can lead to dissemination and death in about 50 % of cases, and to chronicity in about 25 % to 30 %. Natural cure can also occur in 20 % to 25 % of cases, when the host immune response is able to re-establish control of the disease (Bates 1980, Melo 1993).

In most non-immunosuppressed persons infected by the tubercle bacillus, disease will occur in the first three to five years after the initial exposure. In HIV positive persons infected with the tubercle bacillus, however, 7 % to 10 % will develop active TB annually (ATS 2000). The remaining cases occur at any time during a

lifetime, especially when there are other diseases or weakening conditions, for example malnutrition, diabetes, prolonged treatment with corticosteroids, immuno-suppressive therapy, chronic renal disease, gastrectomy, and others. The post-primary disease presents a great spectrum of manifestations, which are related to the affected organ. The lungs are most commonly affected, usually in the upper lobes or apical segments of inferior lobes. The disease can also affect other organs, including lymph nodes, pleura, kidneys, the central nervous system, and bones.

In pulmonary TB, the patients often present with an insidious clinical onset, some-times with minimal or non-specific complaints in the initial phase. With the devel-opment of the disease, two types of signs and symptoms can be recognized. The most frequent are: lack of appetite, low-grade evening fevers, and night sweats. Additional symptoms are asthenia, irritability and migraine. With respect to respi-ratory signs and symptoms, the patient may complain of cough of insidious evolu-tion, at any hour of the day, which as initially dry and later on productive with purulent or mucous expectoration. Hemoptysis and bloody sputum occur in less than a quarter of patients, with the worst cases originating from lesions invading blood vessels. Chest pain can be localized and dependent on breathing movements (Hopewell 2006). At the beginning of the disease, lung auscultation is of little help. Few crackles can be noticed on auscultation after deep inspiration and also ronchi and tubular sounds. In most cases, the patient may be symptomatic for one to three months before diagnosis. Such delays in diagnosis may be due to low diagnostic suspicion by the medical personnel, lack of access to health services, because the patient may not acknowledge being sick or may not seek medical help due to eco-nomic or cultural reasons. An early diagnosis is critical for controlling transmission of the disease in the community, especially in congregated institutions, such as hospitals, prisons, and shelters.

It is crucial to perform the diagnosis in the initial phase of this type of presentation in patients with recent symptoms (less than four weeks) (Figure15-6). If diagnosis is delayed, the disease may evolve rapidly, destroying the pulmonary parenchyma (Figures 15-7 and 15-8).

The parenchymal infiltrates from post-primary TB in adults resemble a pyramid, with the base towards the lung periphery and the apex looking at the hilar area. In the past, it was recognized as a sign of the tubercle bacilli seeking a route for air-borne dissemination (Figure 15-7).

Figure 15-6: Parenchymal infiltrate in the upper left lung, in posteroanterior (**a** and **b**) and lordotic position (**c**).
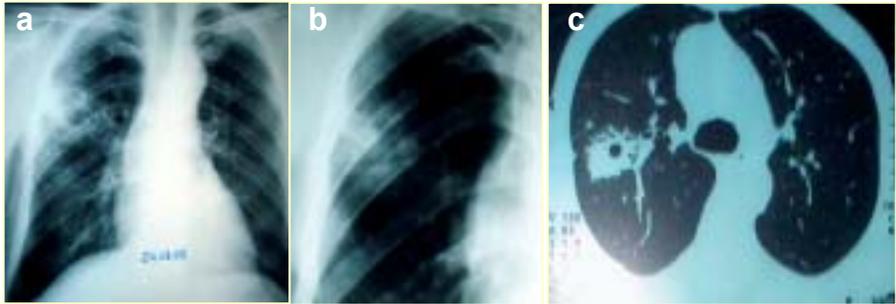

Figure 15-7: Lung infiltrate and cavitation in the upper lobe of the right lung. **a** and **b**: chest X-ray, **c**: computerized tomography (Reproduced from Melo 2005b).
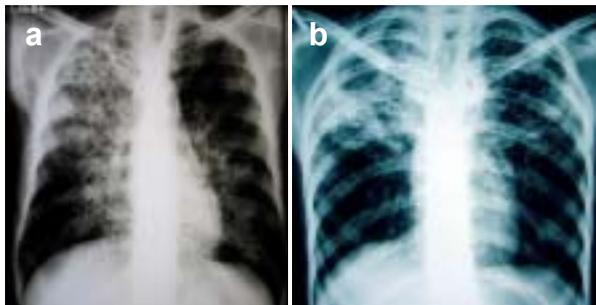

Figure 15-8: Chest X-ray showing parenchymal infiltrate and cavitation in the right upper lobe (**a**) and in both upper lobes (**b**) (Reproduced from Melo 2005b).

For additional images of post-primary disease see Presentation 3 at
http://www.tuberculosistextbook.com/pdf/Presentation_3.pdf.
Sometimes, patients with acquired multidrug resistant TB (MDR TB), after several
treatment schemes with available anti-tuberculosis medication, need to be submit-
ted to thoracostomy, as shown in Figure 15-9.

After achieving cure, respiratory symptoms such as a productive cough persist in
some patients for several years. When the patient refers to recurrent hemoptysis
with elimination of more than 15-50 mL of sputum per day, bronchiectasis and/or a
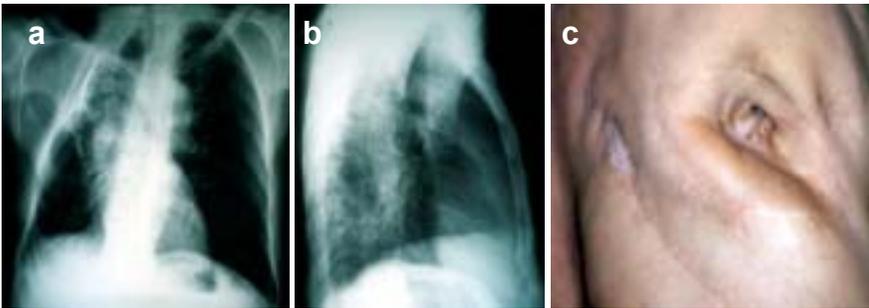fungus ball may be present (Figure 15-10).

Figure 15-9: Patient with MDR TB showing sequelae resulting from chronic disease and thora-
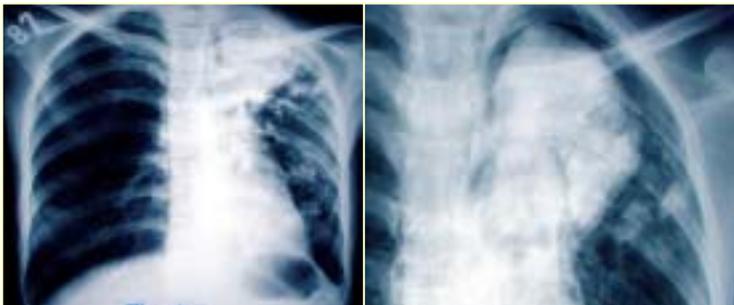costomy.

Figure 15-10: Chest X-ray showing fibrotic infiltrate and cavity with a fungus ball in the upper
left lobe.

For additional images of sequela of TB see Presentation 4 at http://www.tuberculosistextbook.com/pdf/Presentation_4.pdf.

15.5.3. Extrapulmonary tuberculosis

After penetration into the organism through the respiratory route, *M. tuberculosis* can settle and multiply in any organ during the primary infection, before development of the specific immune response. After this, tubercle bacilli can multiply at any time when there is a decrease in the host's immune capacity to contain the bacilli in their implantation sites. The specific signs and symptoms will depend on the affected organ or system, and are characterized by inflammatory or obstructive phenomena. Systemic symptoms are much less frequent than in pulmonary TB, except in the disseminated form of the disease.

The majority of the extrapulmonary forms of TB affect organs with suboptimal conditions for bacillary growth. For this reason, the extrapulmonary disease generally has an insidious presentation, a slow evolution and paucibacillary lesions and/or fluids. Access to the lesions through secretions and body fluids is not always possible, and for this reason, invasive techniques may be necessary in many cases, to obtain material for diagnostic investigation. Tissues and/or body fluids should be submitted to laboratory examination, in particular bacteriological culture for mycobacteria and histopathological analysis. In the immunocompetent patient, the TST response is usually positive (induration ≥ 10 mm).

Imaging studies provide valuable information for the diagnosis of extrapulmonary TB, although specific radiological patterns are not observed. In immunocompetent patients, the extrapulmonary forms only occasionally coexist with active pulmonary TB. Nevertheless, the chest X-ray is mandatory for the evaluation of evidence of primary infection lesions, which provide a good verification to support the diagnosis (Rottenberg 1996).

Miliary tuberculosis

Miliary TB results from the massive hematogenic dissemination of the Koch bacillus during the primary infection. Its onset may be either insidious or abrupt, depending on the bacillary load and/or the host immune situation, with unvaccinated infants, elderly and immunodeficient patients being the most susceptible (Lester 1980, Thornton 1995). The variable and often nonspecific symptoms include fever, anorexia, weight loss, and asthenia. Other specific symptoms depend on the organs affected, and involvement of the central nervous system occurs in 30 % of cases. The physical examination is unspecific, and the patient can present

with variable degrees of wasting, fever, tachycardia and toxemia. The observation of bacilli on smear microscopy examination is rare, and culturing mycobacteria provides a higher probability of bacteriological confirmation of the diagnosis of TB.

In the advanced stages of HIV/AIDS (CD4+ cell count lower than 200 cells/mm^3 or peripheral blood lymphocyte count lower than 1000/mm^3), the bacilli circulate in the bloodstream, and tubercle bacilli are often isolated from blood when appropriate culture media are used (see Chapter 17). Chest X-ray shows a characteristic diffuse, bilateral and symmetrical micronodular infiltrate (Figure 15-8). Other characteristic TB lesions can be found simultaneously, such as cavities, focal parenchymatous condensations, and pleural effusion. Bilateral involvement is highly suggestive of miliary dissemination. Mediastinal and hilar lymphadenopathy appear more frequently in patients with recent lung infection (primary TB) or HIV co-infection (Figure 15-11). The diagnosis of TB can also be obtained when caseous granuloma is found in biopsy material (Lester 1980, Thornton 1995).
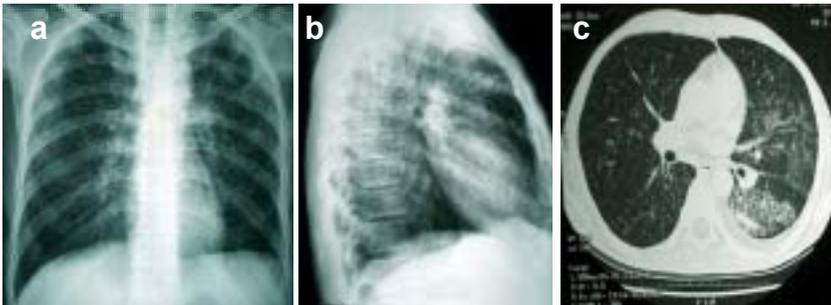
Figure 15-11: Miliary pattern of primary TB in adults. **a** and **b**: chest X-ray, **c**: computerized tomography.

Pleural tuberculosis

This is the most common form of extrapulmonary TB, and can either result from the rupture of a primary sub-pleural lung focus (evident or not on conventional chest X-ray) or be secondary to lymphohematogenic dissemination. The presence of a pleural TB effusion has also been related to hypersensitivity (Light 1990). Most cases occur several months after the primary infection, and frequently the patient relates having contact with an active pulmonary TB case in the two years preceding the current episode. The simultaneous presence of active pulmonary TB

may be related to recent infection followed by disease. The onset of the disease may be insidious or abrupt, with fever, systemic complaints, dyspnea, dry coughs, and pleuritic thoracic pain. The physical examination shows signs characteristic of pleural effusion. With regard to diagnosis, the result of the TST may be negative at the diagnosis of the disease and become positive during anti-tuberculosis treatment. The pleural effusion is generally unilateral and moderate, and can easily be detected by conventional chest X-ray examination (Figure 15-12). In one third of cases, an underlying lung infiltrate can be observed.
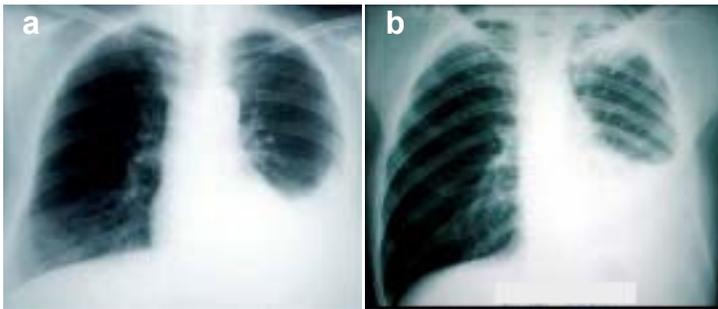

Figure 15-12: Pleural involvement with no parenchymal lesion (**a**) and with upper lobe lung infiltrate (**b**).

Thoracocentesis and puncture pleural biopsy should be indicated. The pleural liquid has a typically citrine yellow aspect and sometimes may be sero-hemorrhagic. It is generally an exudate with a predominance of lymphomononuclear cells, often negative for acid-fast bacilli (AFB) on microscopic examination. The etiological diagnosis is confirmed by the isolation of *M. tuberculosis* by culture of the fluid. The histopathological finding of granulomatous lesions in the pleural biopsy also confirms diagnosis, especially in countries with a high TB prevalence (Light 1990, Uehara 1993).

An important auxiliary method in the diagnosis of pleural TB is the determination of adenosine deaminase (ADA), an enzyme liberated by activated lymphocytes. This examination has a sensitivity and specificity above 90 %. Thus, ADA activity above the cut-off level in the pleural liquid is highly suggestive of pleural TB. If the patient is below 45 years of age and the pleural liquid shows predominance of

lymphomonocytic cells, the specificity and positive predictive value of ADA may approach 100 % (see Chapter 12).

The differential diagnosis for pleural effusions includes para-pneumonic pleural effusions, mycoses, malignant diseases, and, especially in young women, collagen vascular diseases. Most of the time, the effusion is resolved, even if not treated, leaving minimal or no radiological sequelae. Nevertheless, there is a high risk of reactivation of pulmonary TB in the following years if pleural TB is not adequately treated with anti-tuberculosis drugs (Light 1990, Uehara 1993).

Lymph node tuberculosis

This is the second most common form of extrapulmonary TB in HIV seronegative patients and the most frequent in patients living with HIV/AIDS. The preferential localization is the anterior cervical lymph node chain with little predominance of the right side chain. Initially, lymph nodes grow slowly, and are painless and mobile. Later on, as their volume increases, they tend to coalesce and some develop fistulas (Figure 15-13). Patients mainly complain of fever and the increasing volume of lymph nodes, but other symptoms may be absent. In general, the TST is strongly positive, except in immunosuppressed patients.

Figure 15-13: Lymph node TB in cervical area.

The images are similar to those described in primary TB in children: enlargement of hilar and mediastinal lymph nodes (Figure 15-14). The etiological diagnosis can

be made by aspiration puncture biopsy, which is AFB positive in only 10 % to 25 % of cases, but *M. tuberculosis* may be isolated by culture in 50 % to 85 % of cases. Cytopathology may be suggestive of the disease if there is a high proportion of Langhans cells. The histopathological analysis of the lymph node biopsy is usually conclusive, showing granuloma with caseous necrosis in 91 % to 96 % of cases (Lester 1980, Light 1990, Kang'ombe CT 2004, Greco 2004).
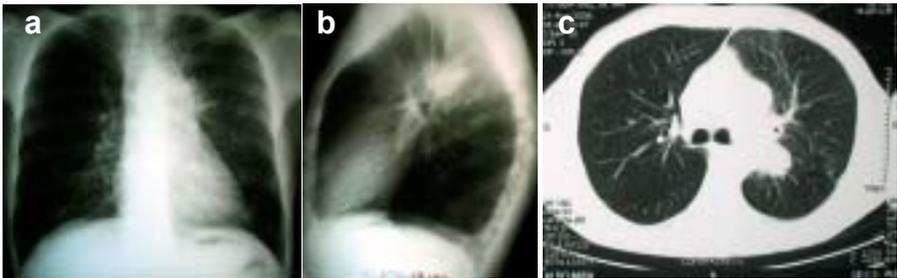

Figure 15-14: Enlargement of left hilar lymph node in an HIV-infected patient. **a** and **b**: chest X-ray, **c**: computerized tomography.

Renal tuberculosis

Renal TB is rare in children and predominantly affects individuals in the fourth decade of life. Renal disease occurs after a long latency period and is frequently secondary to hematogenous dissemination. The localization is almost always bilateral, but can be asymmetric. The lesions often start in the renal cortex and progress slowly toward the central region. Dissemination can occur to the bladder and even to the genital system.

Symptoms and signs may vary in duration and severity. The patient generally complains of dysuria, polacyuria, and lumbar pain, whereas systemic symptoms occur less frequently. Frequently, the disease presents as a urinary infection that does not respond to routine broad spectrum antimicrobial treatment. Purulent urine is frequently found, with urine culture negative for common germs (aseptic pyuria). Hematuria occurs in 10 % to 15 % of the cases.

Excretory urography can either be normal or present a wide variety of alterations that include parenchymatous cavities, dilatation of the pyelocalicial system, renal calcifications of irregular contours, decreased capacity of the urinary bladder, and multiple ureter stenoses (Figure 15-15). Due to the high association between renal

TB and urinary bladder TB, cystoscopy is indicated. In the cystoscopy, edema and diffuse hyperemia are observed, which are more intense around the orifice (golf hole sign), often accompanied by irregular ulcerations and/or infiltrates and vegetations. In these cases biopsy is indicated (Wise 2003).
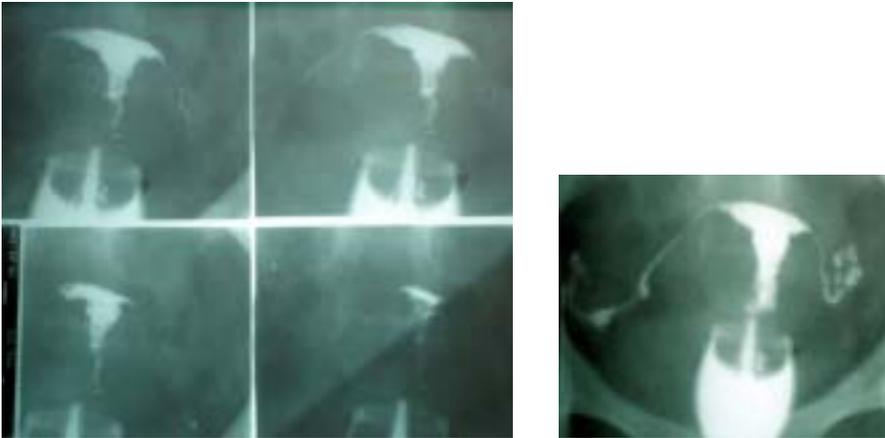
Figure 15-15: Infertility patient hysterosalpingogram, revealing proximal dilatations of the fallopian tubes ("rigid pipe stem" appearance) and distal enlargments/constrictions ("beaded" appearance). Association with antecedents of anterior contagion with TB and TST = 22 mm, allowed the establishment of the diagnosis of TB salpingitis

The diagnosis is confirmed when the urine culture is positive for *M. tuberculosis*. Culture of three to six specimens of first morning urine are together as reliable as the culture of a single 24-hour urine sample. TST is generally positive, except in patients with HIV/AIDS (Smith 1994, Simon 1977, Wise 2003).

Tuberculosis of the central nervous system

The compromise of the central nervous system occurs in two basic forms: meningoencephalitis and intracranial tuberculoma. Since the introduction of modern chemotherapy and especially massive BCG vaccination, a lower proportion of the meningoencephalitis has been observed, but the frequency of this form of TB is higher among young adults with HIV/AIDS (see chapter 17, Simon 1977, Smith 1994).

The clinical manifestations are due to the inflammatory process induced by the mycobacterial infection, and the symptoms depend on the site and intensity of

inflammation. Granulomas can be located in the cerebral cortex or in the meninges. Meningoencephalitis generally has an insidious onset and a slowly progressive course, with symptoms including apathy, lethargy, fever, and mental disturbances such as irritability, understanding difficulties, personality alterations, disorientation, and progressive mental confusion. Vertigo, migraine and vomiting can also be observed.

Findings on physical examination are related to the stage of the disease and the affected area, such as cranial nerve involvement (the most affected are the 2nd, 3rd, 4th, and 8th nerve pairs), focal neurological deficits, and signs of meningeal and cerebellar irritation.

The cerebrospinal fluid is generally clear, with a predominance of lymphocytes, an increase in proteins and a decrease in glucose levels. Microscopic examination for AFB is generally negative and cultures are positive in only 15 % to 30 % of cases.

In the differential diagnosis the following conditions should be considered: other infectious meningitis, vascular pathologies, the collagen vascular disease sarcoidosis, metastatic carcinoma, acute hemorrhagic leucoencephalopathy, and lymphoma.

In the case of intracranial tuberculoma, the clinical manifestations depend on the location of the lesion, which generally grows slowly. When there is no compromise of the sub-arachnoid space, the cerebrospinal fluid is normal and the computerized tomography exhibits a mass, which is generally difficult to differentiate from neoplasia (Azambuja 1993, Kasik 1994, Norris 1995).
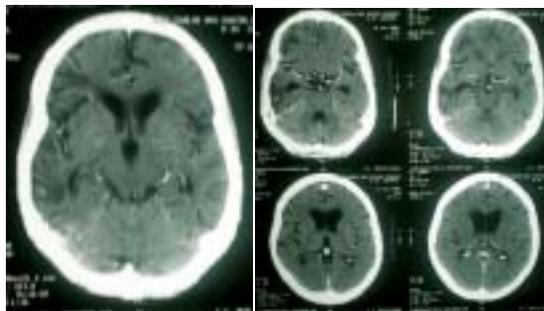

Figure 15-16: Computerized tomography of the skull in young adult patient with cerebral TB, with hydrocephaly, hypodense central areas, and atrophic lesions.

Osteoarticular tuberculosis

Involvement of the osteoarticular system is most commonly found in children and the elderly, and is generally secondary to hematogenous seeding, but can also occur as a consequence of lymphatic dissemination or direct spread from a contiguous lesion. Bone involvement consists of osteomyelitis, and arthritis can occur either by extension of the osseous lesion to the joint or by direct hematogenic inoculation.

The most frequent sites of bone involvement are the vertebrae (Pott's disease) and the proximal extremities of the long bones. Spinal TB frequently affects more than one vertebra. With evolution, it presents a wedged flattening and gibbus formation that can be associated with a paravertebral cold abscess (Figure 15-17). Paresthesia and paraplegia are reported when the cervical and upper thoracic area are affected. Image on X-ray is characterized by erosion of the anterior vertebral body margins with no preservation of the intervertebral space. The definitive diagnosis should be obtained by biopsy for culture and histopathological analysis (Ridley 1998, Schlesinger 2005).

The peripheral joints most frequently affected by TB are the hip and the knee. Pain, with or without movement limitation, fever and systemic symptoms are frequent. Monoarticular involvement is much more frequent than multiarticular disease.

The diagnosis of osteoarticular TB is usually delayed because this etiology is often overlooked in the differential diagnosis of joint disease. In most cases, the TST is positive, and approximately 50 % of cases also have abnormal chest X-rays, suggesting previous pulmonary disease. Cold abscesses occurring in the advanced phase of osteoarticular TB can develop into cutaneous fistulae, which are frequent in this form of the disease. The diagnosis is established by puncture, biopsy, histopathological examination, and culture (Zylbersztejn 1993, Davidson 1994, Ridley 1998, Schlesinger 2005).

Other extrapulmonary localizations

Tuberculous involvement of other tissues, such the eye, skin (*lupus vulgaris*), genital, and digestive tract, may also be the result of hematogenous dissemination, but there are other possible routes of infection.

Intestinal TB can be acquired by the oral route, and in countries with a high prevalence of bovine TB. Before the generalization of milk pasteurization, this was a rather common form of zoonotic TB (produced by *Mycobacterium bovis*), particularly in infants.
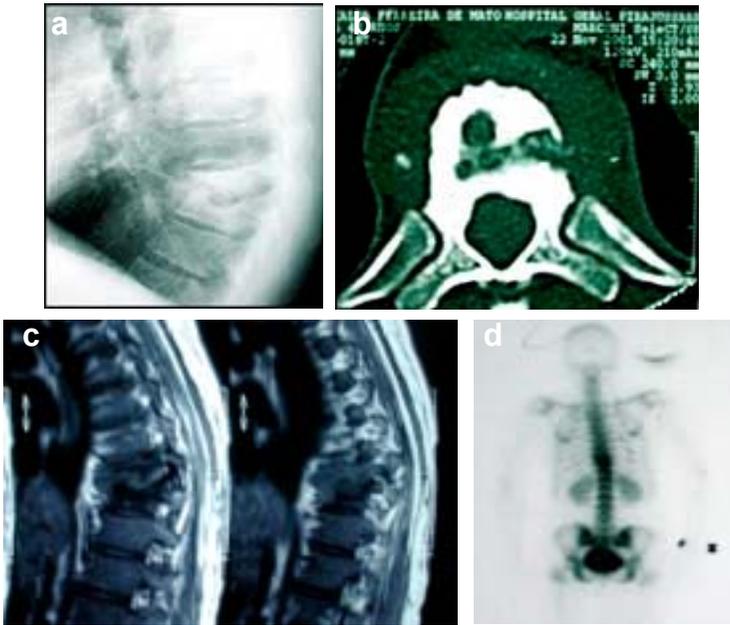
Figure 15-17: X-ray (a), computerized tomography scan (b), nuclear magnetic resonance (c), and scintilography (d) showing images of spondylitis and meningocele in a patient with Pott´s disease (from the archives of Instituto Clemente Ferreira, Brazil)

Eye and skin TB may be the consequence of accidental inoculation, particularly among medical and veterinary professionals, and genital TB may be produced by spread from renal TB.

15.5.4. Special conditions

During the past few decades, TB has been observed in association with immuno-suppression, malignant neoplasms (i.e. lung cancer, head and neck cancer, Hodg-kin's lymphoma), malnutrition (more than 15 % loss of usual weight), old age, diabetes mellitus and silicosis. The occurrence of TB in these patients is likely to be the result of both increased susceptibility and longer patient survival, due to the increased frequency of organ transplantation and the accompanying immune sup-pression, more effective cytotoxic treatments for neoplastic disease, and immuno-

suppressive treatment of autoimmune diseases, such as systemic lupus erythemato-sus or the anti-TNF antibodies used against chronic inflammatory arthritis.

In many low-income countries, patients with these immunosuppressed conditions receive care in large urban health centers (ambulatory or hospitalized) where health professionals are insufficiently trained in the diagnosis and treatment of TB. Meanwhile, the staff in TB clinics has scarce information about the management of immunosuppressed patients, other than those infected with HIV. Particularly in the elderly (> 60 years old), there has been an increase in morbidity and mortality from pulmonary TB in patients with diseases such as chronic renal failure, chronic liver diseases, malignant neoplasm, diabetes mellitus and organ transplant (Carvalho 2002). The clinical, radiological and laboratory presentation of these patients tend to be atypical, making diagnosis very difficult, delaying the start of anti-tuberculosis treatment, and increasing TB transmission within the hospital or am-bulatory clinic environment.

In countries with a high TB prevalence, TB occurs 30 to 40 times more frequently among patients receiving organ transplantations such as heart, kidney and bone marrow. The immunosuppression may be caused by the original disease (i.e. chronic renal insufficiency), by the immunosuppressive radiotherapy/chemotherapy necessary to avoid transplant rejection, or by a combination of both. In these pa-tients extrapulmonary TB is more frequent than pulmonary disease, and the disease manifests itself in the first or second year after transplantation. The mortality rate is especially high when the diagnosis and treatment are delayed.

Tuberculosis in patients with diabetes mellitus

Before the advent of anti-tuberculosis chemotherapy and the generalized use of insulin therapy, the incidence and mortality rates of TB among patients with dia-betes mellitus were high. In patients whose diabetes is difficult to control, the im-mune defects are presumably more severe, and pulmonary TB tends to be more aggressive producing cavities and extensive lesions in the lower third of the lungs (Ikezoe 1992, Al-Wabel 1997, Singla 2006).

Tuberculosis in patients with chronic renal insufficiency

In patients with chronic renal insufficiency, TB often has a slow onset with low-grade fever, dry cough, dyspnea, pleuritis and/or pericarditis. TB occurs frequently in patients undergoing long periods of dialysis (on average, after 22 months), and extrapulmonary presentations (i.e. ganglionar) are common. As the mortality rate is high when the diagnosis is delayed, TB must always be considered a possibility,

and appropriate invasive and non-invasive procedures should be employed to ensure an early diagnosis (Moore 2002, John 2002, Erkoc 2004).

Tuberculosis in elderly patients

In middle-income countries, the increased survival rates have resulted in larger elderly populations, which can be expected to lead to an increase in TB reactivation. However, TB in the elderly may be due to a newly acquired infection. The lack of attention given to TB in the elderly in these countries is due to:

- disinformation of healthcare personnel, because TB is considered a problem of young adults

- inexperience of health personnel in diagnostic and therapeutic approaches to tuberculosis in elderly patients

- unavailability of laboratory facilities to diagnose TB in nursing homes and/or support houses

- confusing TB symptoms with other pulmonary, heart or malignant diseases

- impaired communication ability of some elderly patients

Chest X-ray findings can be similar to those observed in young adults with pulmonary TB, although with a lower frequency of cavitation and higher frequency of pleural involvement. Other diseases, especially lung tumors among smokers, can also be located in the lung apices, mimicking TB; so a prompt diagnosis is critical. Patients with neoplasia in the lung apex often present with referred pain, while this symptom is rare in patients with TB (Perez-Guzman 1999, Zevallos 2003).

It should be stressed that undetected pulmonary TB in the elderly commonly results in the transmission of the disease to close contacts in households, hospitals or nursing homes. The mortality rate is high among elderly patients who develop TB in nursing homes and support houses, probably because inadequate diagnostic procedures and facilities lead to a late diagnosis, which is followed by inadequate therapeutic measures. Standardization and legislation on the appropriate procedures for diagnosis and management of TB in these specific settings are required. A chest radiograph should be performed in every elderly patient admitted in a health center, complemented by bacteriological tests (AFB smear microscopy and, when available, culture for mycobacteria) in patients with pneumonia not responsive to broad spectrum antibiotics, fever of obscure origin, or a productive cough of more than three weeks duration, with or without associated weight loss.

15.6. Diagnostic approaches

15.6.1. 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.

15.6.2. Respiratory symptoms and signs of pulmonary tuberculosis

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. In the WHO Guidelines, it is recommended that in low and middle income countries, community TB screening be performed by AFB

smear microscopy in all respiratory symptomatic persons, defined as those with a productive cough of at least three weeks duration. The diagnostic yield in this population ranges from 4 % to 10 %.

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 sequelae.

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 overlooked by the patient, hoarseness may be the sole reason for seeking medical assistance.

15.6.3. 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) and polyserositis (Figure 15-18). These lesions are mostly associated with primary TB infection, although they may also be observed in re-activation TB disease and sometimes are recurrent.

Fig 15-18: Erythema nodosum (**a**) and erythema induratum of Bazin (**b**).

15.6.4 Sputum smear microscopy and culture

The principal method of pulmonary TB diagnosis is microscopic examination of Ziehl-Neelsen stained sputum samples for AFB. In low-income countries, under routine conditions, sputum smear is positive for AFB in 30 % to 60 % of respiratory TB cases. When this is thoroughly performed on two sputum samples collected on consecutive mornings in patients with pulmonary cavities on chest X-ray and respiratory symptoms, the sensitivity of the sputum smear microscopic examination can be higher than 70 % (WHO 2005, Stop TB/WHO 2007). If the sensitivity of AFB smear microscopy does not approach these levels, the quality of the mycobacteriology laboratory or of the TB diagnosis itself should be questioned (see Chapter 12).

Sputum smear examination should be requested when (Castelo-Filho 2004, Hopewell 2006):

- the patient seeks assistance at the health services complaining of respiratory symptoms with cough and expectoration for more than three weeks

- chest X-ray alterations are present that are consistent with pulmonary TB

Whenever it is possible from an operational point of view, and especially when there is a high clinical suspicion, sputum should also be cultured for mycobacteria, as it increases the diagnostic yield by 15 % to 20 %. Cultures are most commonly performed on solid media (Löwenstein-Jensen or Ogawa Kudoh), giving results on an average of 30 days. Cultures in liquid media give faster results and may be more sensitive (see Chapter 12). Drug susceptibility testing is indicated when infection with drug resistant strains is suspected (see Chapter 19), but as suspicion for drug resistance is not always easily evaluated, susceptibility testing should be systematically performed on isolates from patients with associated risk factors:

- previous history of anti-tuberculosis treatment

- failure of chemotherapy given with direct supervision

- contact with patients with multi-drug resistant TB [*M. tuberculosis* strain resistant to at least rifampicin (RIF) and isoniazid (INH)].

15.6.5. Induced sputum

When the patient does not produce expectorant, it is advisable to induce sputum by nebulization with hypertonic (3 % to 5 %) saline solution. Recent studies showed that induced sputum has a diagnostic yield equal to or higher than that of material

collected by fiberoptic bronchoscopy. When miliary TB is suspected but the smears are negative for AFB, fiberoptic bronchoscopy with bronchial biopsy is recommended for a definitive diagnosis (Al Zahrani 2001).

15.6.6. Radiological examination

The chest X-ray examination may help to make the diagnosis in respiratory symptomatic patients that are repeatedly negative on direct microscopy sputum examination. It may also help in those individuals that cannot produce sputum for the bacteriological examination. In patients with positive smear microscopy, the chest X-ray exam may be indicated to exclude an associated lung disease, and also allows the evaluation of the disease evolution, especially in patients not responding to TB treatment (Rottenberg 1996).

Initial chest X-ray studies should include posteroanterior and lateral views. Lordotic and oblique views may be helpful for further evaluation of the extent of lung involvement, especially in patients with apical lesions or extensive hilar adenopathy (Figure 15-6). If pleural effusion is present, lateral decubitus views may aid determination of the nature of effusion (i.e. free moving, loculated) (Correa 1997, Schluger 1994, Vallejo 1994).

The results of the chest X-rays may be described as:

- **Normal**: absence of pathological images in the lung fields

- **Sequelae**: presence of images suggestive of old scarred lesions

- **Suspect**: presence of images suggestive of active TB

    - single or multiple condensations in the upper third of one or of both lungs and in the apical segment of the lower lobe

    - cavities in the upper third or in the apical segment of the lower lobe

    - unilateral or bilateral pleural effusion

    - miliary pattern

- **Other diseases**: presence of images suggestive of non-tuberculous pneumopathy.

15.6.7. Computerized tomography and ultrasonography

Computerized tomography of the chest is mainly used for diagnosis of pulmonary TB in patients who do not expectorate or that have a negative AFB sputum smear, and are suspected of having tuberculous lymphadenitis or miliary TB. It can also be useful for the differentiation of pulmonary sequelae due to old, inactive TB from active disease. Also, when the presence of an associated lung cancer is suspected, high-resolution computerized tomography with the analysis of the secondary lung lobule becomes an important diagnostic aid (Sinan 2002, Busi-Rizzi 2003).

Both abdominal computerized tomography and ultrasonography are useful for the investigation of fever in HIV/AIDS patients suspected of having disseminated TB. Visceral focal lesions and heterogeneous, low density adenomegalies are common in patients with TB and HIV/AIDS (see Chapter 17). In diseased lymph nodes, pathological images are preferentially located in the peripheral areas. Computerized tomography of the skull in patients with cerebral TB reveals hydrocephaly in 60 % of cases, lesions with hypodense central areas and "ring image" in 45 %, and atrophic lesions or lack of alteration in 30 % of cases.

15.6.8. Tuberculin skin testing

A positive tuberculin skin testing (TST) only indicates infection and by itself is not diagnostic of TB disease (Huebner 1993, Menzies 1999, WHO 1999, Castelo 2004). The tuberculin, PPD RT23, in a 0.1 mL dose, equivalent to 2 TU (tuberculin units), or PPD-S, equivalent to 5 TU, is applied intradermally in the medium third of the anterior surface of the left forearm. When kept at a temperature between 4°C and 8ºC, tuberculin remains active for six months, but it should not be frozen or exposed to direct sunlight.

The TST test is read 72 to 96 hours after its application, measuring the largest transverse diameter of the palpable hardened area with a millimeter ruler.

Interpretation of tuberculin skin test results

In developed nations, TST induration is interpreted on the basis of a ruler showing 5, 10, and 15 mm divisions. For persons exposed to highly contagious TB patients, or HIV infected persons, with a history of previous TB, or with fibrotic images consistent with TB on chest radiography, a reaction equal or greater than 5 mm diameter is classified as positive. For other groups, the cut-off of 10 mm has been proposed.

Table 15-1: Tuberculin skin test cut-off of reactive area for a positive tuberculin reaction

Cut off area (mm)		
≥ 5 mm	≥ 10 mm	≥ 15 mm
Contacts of infectious case with or without symptoms	Residents or professionals at hospitals, shelters, prisons, long-term facilities, mental institutions, nursing homes	Persons who do not meet any of these criteria
Fibrotic image on chest radiography consistent with TB	Seronegative intravenous drug use	
HIV infected	At higher risk of TB development: high-dose corticosteroid therapy, bone marrow and solid organ transplant, chronic renal failure, lymphoma, Hodgkin disease, diabetes mellitus, head and neck carcinoma, weight loss of ≥ 10 % below ideal body weight	

In low and middle income countries, the tested persons may be grouped according to the resulting induration registered in millimeters:

- **non reactor** (0 to 4 mm induration): not infected with *M. tuberculosis* or on immunosuppression

- **weak reactor** (5 to 9 mm): vaccinated with BCG or infected with *M. tuberculosis* or other mycobacteria

- **strong reactor** (10 mm or more): infected with *M. tuberculosis*, with or without clinical disease

Positive TST decreases as the interval between vaccination and tuberculin skin testing increases (because vaccination-induced reactivity wanes over time and is unlikely to persist for > 10 years). It has been proposed by some authors from developing nations, that TST indicates infection with *M. tuberculosis* when the induration area is greater than 10 mm in adults not vaccinated with BCG or those vaccinated more than two years prior to the examination; or the induration is greater than 15 mm in adults vaccinated with BCG less than two years prior to the examination (Castelo 2004). In adults who have been revaccinated with BCG, interpretation is difficult. In summary, for high burden countries, the TST should be recommended:

- in contacts of smear-positive TB cases

- in persons with radiographic or clinical findings consistent with TB, especially extrapulmonary forms

- in HIV infected persons

- as part of the medical examination of all health personnel.

In some circumstances, the sensitivity of the TST can be reduced, for instance:

- Immunosuppressive diseases, such as sarcoidosis, HIV/AIDS, head and neck cancer, lymphoproliferative diseases and other neoplasias

- Transient or age-related immunodeficiencies, such as after live virus vaccination, pregnancy, corticosteroid and immunosuppressive therapy, children less than two months old and persons above 65 years old.

Figure 15-19: Phlyctenular tuberculin reaction with 2UT of PPD RT-23

15.6.9. The use of alternative methods for diagnosis of latent TB.

IFN-γ release assays are alternatives to TST now available for detection of latent TB. They have been used in developed nations, but data about the evaluation of its usefulness in high burden countries are scarce (Oxlade-2007, see Chapter 13).

15.6.10. Use of nucleic acid amplification for TB diagnosis

In industrialized countries, the advent of rapid nucleic acid amplification (NAA) tests for tuberculosis is seen as a major breakthrough in the management of PTB (Brodie 2005). Several commercial NAA tests have undergone validation and are licensed for routine testing of sputum. They have specificities of > 95 % for smear-positive specimens, but sensitivities are variable, especially in smear-negative disease, where a rapid diagnostic test is most needed. *In house* NAA tests have been proposed for developing countries due to their low cost. In a recent meta-analysis of *in house* NAA tests for the detection of *M. tuberculosis* in sputum specimens, the use of *IS6110* as the target appeared to be associated significantly with higher diagnostic accuracy (Flores 2005).

The majority of studies on the use of NAA for TB diagnosis have been performed in industrialized countries, where there is low burden of TB/HIV and history of pulmonary TB, and where false positive NAA results may occur due to *M. tuberculosis* DNA detection in the absence of active TB (Sloutsky 2004). Few series have estimated the potential clinical utility of these tests in relation to different levels of clinical suspicion and pretest probability (Cantazaro 2000).

For developing countries, where almost 100 % of smear-positive results represent TB disease, it has been emphasized that NAA tests increase sensitivity among smear-negative pulmonary TB cases. In these settings, the published evaluations of NAA techniques for smear-negative TB diagnosis have mainly been based on laboratory criteria for the diagnosis of disease (Kivihya-Ndugga 2005), with or without the use of clinical records to evaluate discrepant results (Laifer 2004). In addition, it has been emphasized that many laboratories in those countries did not use adequate quality controls to evaluate the performance of PCR (Suffys 2000).

Automated NAA or *in house* PCR might be more widely introduced in developing nations only after a proper evaluation of cost-effectiveness, together with analysis of clinical and radiographic characteristics, to refine estimates of the likelihood of TB disease in those settings, as proposed by others (Van Cleef 2005).

15.7. Treatment of latent tuberculosis infection

Treatment of latent TB infection with INH (10 mg/kg/day or, at most, 300 mg/day) for six to nine months is indicated in every adult person with a high risk of developing active disease (International Union Against Tuberculosis and Lung Disease 1994, Horsburgh 2004, Castelo-Filho 2004, Hopewell 2006).

The treatment of latent TB with INH reduces the risk of developing disease from endogenous reactivation, but it does not protect against exogenous exposure. Therefore, when there is the possibility of recent new exposure to the tubercle bacillus, the patient must be evaluated for the need to extend the treatment of latent TB (when receiving INH) or the instauration of a new treatment (in case the previous one has already been discontinued).

The candidates for treatment of latent TB infection are:

- household contacts of AFB smear-positive pulmonary TB patients, who have not recently been vaccinated with BCG and who have TST induration > 10 mm; or contacts that were BCG vaccinated within the previous two years with TST induration > 15 mm

- individuals with TST conversion (a positive test with > 10 mm induration after a previously negative test, applied 12 months earlier)

- HIV-infected individuals with a reactive TST of > 5 mm

- HIV-infected individuals that report close contact with a smear-positive TB patient, regardless of the TST response

- individuals with a chest X-ray image consistent of residual TB, without a history of previous anti-TB treatment

In every case, before starting preventive chemotherapy with INH, the physician should confirm the absence of active TB disease:

- the chest X-ray should be normal

- the individual should be asymptomatic

Before beginning preventive chemotherapy, it is important to exclude active TB, either pulmonary or extrapulmonary, particularly in patients with moderate/severe immunodeficiency. Moreover, appropriate follow-up of the patient is necessary to ensure a regular drug supply and at least 70 % adherence to the preventive treatment regimen.

Risk-benefit analyses demonstrated cost effective benefits for INH preventive therapy of low risk reactors and substantial cost effective benefits in higher risk reactors (Rose 1992, Jordan 2001), in addition to substantial long-term public health

benefits (Salpeter 1993). However, the overall effectiveness of INH preventive therapy in low or middle income countries has not been well established.

15.8. Contact tracing and control

Even for developed nations, competing demands restrict the resources that can be allocated to contact tracing. Therefore, public health officials must decide which contact investigations should be assigned a higher priority (Guidelines for contact investigation 2005). The WHO proposes that the control of contacts and treatment of latent TB should be considered a priority only in areas of high prevalence of TB and HIV co-infection, where TB control programs are using DOTS, and have cure rates higher than 85 % or defaulting of treatment lower than 5 %. A decision to investigate an index patient depends on the presence of factors used to predict the likelihood of transmission. When exposure is related to households, congregate living settings, or cough-inducing medical procedures, contacts are designated as high priority. Household contacts are defined as anyone who lived with a patient with pulmonary TB during their symptomatic phase, or shared the same bedroom at least once a week. The contacts of AFB smear-positive patients are at higher risk of becoming ill with TB and therefore a priority for active case finding (Arnadottir 1996, International Union Against Tuberculosis and Lung Disease 1991, Reichler 2002, Guidelines for the Investigation of Contacts 2005). In regions with high TB prevalence, assuming that the threshold for acquiring TB infection is 10 % means that 50 hours of contact with index cases could be used as a limit.

In the last years, it has been demonstrated that TST results helped identify persons in a BCG-vaccinated population who had had recent exposure to persons with pulmonary TB, were probably infected with *M. tuberculosis*, and could benefit from treatment of their latent TB (Garcia Sancho 2006).

The following contacts could be investigated with TST, chest X-ray and smear microscopy/culture, according to each group included in contact investigation procedures

- Household contacts of AFB smear-positive pulmonary TB and larynx TB patients

- Contacts under 15 years old (particularly < 5 years) and over 60 years old in settings where DOTS has not yet been well implemented

- Contacts with conditions that predispose them to develop the illness (HIV/AIDS, severe malnutrition, diabetes mellitus, patients under pro-

longed corticosteroid therapy or other immunosuppressive drugs, and patients with primary immunodeficiency)

- Contacts at congregating living settings, such as healthcare workers or medical students that report contact with AFB smear-positive pulmonary TB cases in their routine activities in the absence of biosafety measures

15.9. The limits between infection and disease

In developed countries is fairly easy to distinguish TB infection from TB disease. TB infection is characterized by the presence of a positive TST in the absence of symptoms and/or progressive lesions consistent with TB disease. This classification is useful for control strategies in areas of low prevalence of infection and low incidence of new cases. Chemoprophylaxis is indicated for recently infected persons in high risk groups in order to protect them from primary TB.

The application of such control strategies is very difficult in low and middle resource countries with high rates of infection and high incidences of new infectious TB cases. Wide-scale TST and chemoprophylaxis for all tuberculin-positive individuals would be neither innocuous nor cost-effective. Large scale TST testing demands a sophisticated system of production, quality control, distribution, handling and application of reagents. This strategy is not feasible in low resource countries where health attention systems have scarce economic, operational and human resources. In such countries, contact investigation should be introduced more widely after an evaluation of its cost-effectiveness and refined estimates of the likelihood of TB infection and TB disease in different settings.

In summary, in low and middle income countries, whenever possible, the control of the contacts should be done during the follow-up period of the index case, and at least all contacts younger than 15 years old (or particularly under 5 years old) with a TST > 10 mm (if not vaccinated with BCG or vaccinated more than two years before), asymptomatic and with normal chest X-ray, should be given prophylactic INH for at least six months.

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