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Chapter

Extra Pulmonary Tuberculosis: An Overview

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Abstract

Mycobacterium tuberculosis is the bacterium that as a single agent is known to cause the infection with the most morbidity and mortality around the world. It is known to cause pulmonary infection in immunocompetent patient, but its dissemination outside the lungs has been linked to a high degree of cellular immunosuppression as seen in the advance stages of human immunodeficiency virus infection, and after chemotherapy. Despite extensive research, screening, education, and continuous efforts to try to eradicate and control the infection, tuberculosis is still one of the most prevalent infections throughout the world. Even the cases of extra pulmonary dissemination are seen to have increased. Extra pulmonary tuberculous dissemination has a very variable presentation that depends on the organ involved. The diagnosis is difficult and many times a long time passes between diagnosis and initial presentation. In this chapter, we will review how tuberculosis infection presents when the bacilli invades any tissue outside the pulmonary parenchyma, what the literature recommends for the proper work up and diagnosis, and general treatment for major organ system infection.

Keywords: tuberculosis, extra pulmonary, infection, mycobacterium

1. Introduction

Although it is well known that *Mycobacterium tuberculosis* can be pathologic to any organ system, its manifestations can be so variable that sometimes it becomes a challenge for the clinician to identify or even consider it as the cause of the patient's symptomatology. Most of the times, an extensive work up with invasive interventions is required for proper diagnosis.

Extra pulmonary tuberculosis (EPTB), described this way when the tuberculous mycobacterium invades areas outside the pulmonary parenchyma, has nonspecific clinical findings developing insidiously [1] mimicking other noninfectious conditions [2]. It requires a high clinical suspicion and carries a lengthy period from the initial symptoms to the final diagnosis.

Nevertheless, its presentation can be extremely acute causing a life threatening condition [1]. Clinical presentation will vary according to the organ system involved and more than one organ could be involved at the same time. The initial step in early identification is having knowledge of its findings in the proper clinical setting

and including them within the differential diagnosis. Even though some patients do not have the expected risk factors, tuberculosis is identified as the culprit of symptoms associated with other conditions.

This illustrates the ample spectrum of extra-pulmonary tuberculosis manifestations. Vast medical knowledge helps the clinician to identify this condition in the adequate clinical scenario to pursue its diagnosis.

In this chapter, a review of the most important clinical manifestations of extra-pulmonary tuberculosis will be discussed. It will also review the required work up and specific treatment for other organs involved.

2. Epidemiology

Mycobacterium tuberculosis, as a single infectious agent, causes more deaths than any other infection [3]. Outside infectious diseases, it is the ninth leading cause of death worldwide [3]. According to the World Health Organization (WHO) and the Global Tuberculosis report, in 2016, the largest incidence of tuberculosis occurred in areas of Korea and Africa [3]. In 2016, more than 10 millions of people were infected with tuberculosis around the world [3]. Active tuberculosis occurs in approximately 10% of the infected patients, involving lung parenchyma only in approximately 85% of subjects [7], but the incidence of other organ involvement varies widely in endemic and nonendemic areas.

Worldwide, the incidence of extra-pulmonary involvement of tuberculosis occurs in approximately 17–52% of all cases reported [4]. In other publications, the incidence from reported cases varies from 15 to 40%, with approximately 3–3.5 cases per 100,000 of the population from 2002 to 2011 [5]. Although, the incidence has been stable or decreased in some areas, a report from 2003 to 2008 showed an increased worldwide incidence from 30.6 to 37.6% secondary to longer life expectancy of immunosuppressed patients due to better medical care [6]. In the United States, the incidence of EPTB increased from 15.7% of the cases in 1993 to 21.0% in 2006 [8]. Therefore, EPTB continues to be an important presentation within tuberculosis infectious spectrum.

The demography of EPTB cases varies widely among documented case series. A review published in *Clinical Infectious Diseases* in 2009 [6] revealed that from 253,299 of tuberculosis cases reported in the USA from 1999 to 2006, 19% were extra pulmonary, while 8% were disseminated or concurrently pulmonary and EPTB. The mean age of this group was 44 years old, with a proportion of male to female almost one to one. Children (described in this population as less than 15 years old) with reported EPTB were approximately 6% of the cases. This same publication revealed predominance of genitourinary and bone and joint involvement in older patients (more than 60-year old), while children accounted for most of the cases of meningeal and lymphatic involvement.

3. Organ involvement

Tuberculosis can invade practically any organ. The proportions of organ involved in multiple publications suggest that most extra pulmonary tuberculous cases are seen with pleural, bone, and lymphatic involvement [6, 9]. In rare cases, the involvement can be localized to a specific organ [2], while 2–10% of the cases are reported to be disseminated within more than two organ systems [6, 9]. Most cases occur secondary to activation of previous pulmonary contagion.

4. Risk factors

Multiple populations with tuberculosis have been studied. In a case series described by García-Rodríguez et al., the mean age of patients with EPTB was higher than patients with pulmonary disease [6]. EPTB cases increased with the age, but the anatomical sites varied according to the age [6]. More cases of lymphatic, joint, and bone involvement were seen as patients become older. The female to male ratio varied according to the organ involvement, but in general, the male to female ratio was similar to other publications, which was one to one.

Although immunosuppression seen to be a risk factor for EPTB, a study published in *International Journal Tuberculosis Lung Disease* in 2009 suggested that diabetes mellitus was a risk factor for pulmonary tuberculosis, but not for EXPTB [10]. The protective mechanism for extra pulmonary dissemination of tuberculosis is known. The same study concluded that patients with end stage renal disease had a predisposition for EPTB. A possible mechanism that increases the risk for dissemination is a decrease cell-mediated immune response.

Other risk factors identified for extra-pulmonary dissemination include cirrhosis, malignancy, immunosuppressive drug use, alcoholism, HIV infection, chronic obstructive pulmonary disease (COPD), congestive heart failure, intravenous drug use, previous history of pulmonary tuberculosis, and history of cerebrovascular accident. There is not statistical analysis that linked all those causes as a direct risk factor for disseminated infection [10].

Cell-mediated immunosuppression has been linked to the development of tuberculosis and an increased risk of dissemination. Multiple reports and publications have linked HIV infection to the risk of developing EPTB. Among HIV patients admitted due to tuberculosis, almost 50% have extra pulmonary involvement [11]. Concomitant pulmonary and multi-organ involvement is common. Low counts of CD4 lymphocytic cells, which are in charge of cellular immune response, have been reported to be directly proportional to systemic dissemination, increasing the incidence of central nervous system (CNS) infection. Those patients with CNS involvement have higher mortality. Therefore, HIV infection predispose patients to EPT and its severity increase when CD4 levels decline to 200 cell/mm^3.

5. Pathophysiology

Tuberculosis infection is caused by aerobic bacteria, *Mycobacterium tuberculosis*. Mycobacteria have a cell wall with considerable amount of a fatty acid, mycolic acid, attached to a peptidoglycan-bound polysaccharide arabinogalactan, which provide a strong barrier resistant to antibiotics and (natural) defense mechanisms [12]. Pulmonary tuberculosis is acquired throughout airborne droplets that get into lungs and lead to pulmonary infection. Most of the bacteria are trapped in alveolar macrophages and destroyed. The mechanism of macrophages engulfment includes complement cascade activation when protein C3 binds to the cell wall and enhances recognition of the mycobacteria by macrophages. Mycobacterium phagocytosis initiates a cascade of events that results in either successful control of the infection, followed by latent tuberculosis, or progression to active disease.

After macrophage engulfment, they present the mycobacteria to T cell lymphocytes, which generate the formation of granulomas around the organisms. Granulomas have low levels of nutrients that restrict mycobacteria growth and therefore control the infection. Those patients with decreased immune response fail to control the infection and develop primary pulmonary infection. In patients

infected, droplets produced during coughing can further spread the infection to other patients. Dissemination of the mycobacteria to other organ systems can occur when the bacilli get into a blood vessel or throughout the lymphatic system.

Reports suggest that most tuberculous empyemas and patients with vertebral bone involvement (Pott's disease) develop after the transport of tubercle bacilli from the pleural spaces to the parasternal and the para-aortic lymph nodes and the breakdown of caseous foci in these nodes [13]. These reports also explain investigations in which guinea pigs were injected with various doses of virulent tubercle bacilli inside their pleural cavity, developing granulomas in the liver, parasternal and para-aortic lymph nodes, spleen and kidneys, suggesting systemic dissemination. It all begins after the pleural space is invaded, disseminating to the thoracic lymph nodes and blood vessels, further seeding in distant organs.

6. Tuberculosis and organ system involvement

6.1 Central nervous system

Central nervous system tuberculous involvement occurs in approximately 5–10% of extra pulmonary cases [14]. It is a rare disease within the whole tuberculosis spectrum. This presentation has the most dangerous and catastrophic consequences.

Developing of CNS tuberculous infection has been linked to decreased cellular immune response as seen in HIV patients, malnutrition, alcoholism, malignancies, and the use of immunosuppressive agents [14]. Children and adolescents are more commonly involved with meningitis as the clinical presentation compared to adults (>15-year-old patients). In a study published in 2011, the mean age of patients with meningeal involvement is reported to be lower than those patients with infection in other organs such as lymphatic, bone and/or joint, and genitourinary [6].

Cases of EPTB are more common in older patients; however, a study from 2011 suggested that patients with ages less than 15 years old accounted for 5.4% of all TB patients. Although children were less likely to have EPTB, 13.8% of them presented as meningitis [6]. Peak of meningeal presentation was higher in patients younger than 24-year old. However, another study suggests that 40–70% of children with meningeal tuberculous involvement were exposed by older patients [15]. Risk factors related to meningitis by tuberculosis in children are similar to those related to infections in other sites, most cases related to some kind of immunosuppression. Median age of young patients with meningitis is approximately 4 y/o, and it is uncommon for children less than 6 months old to present with meningitis [15].

The most common clinical presentation of central nervous system involvement is meningitis. Most patients present with a history of nonspecific symptoms as malaise, anorexia, fatigue, fever, myalgia, and headache for approximately 2–8 weeks prior to the development of meningeal irritation [14]. In addition, neck rigidity and typical meningitis symptoms are more common in adults. These symptoms include depressed consciousness and nonspecific behavioral changes [14]. Tuberculosis can also cause focal nervous system deficits. Intracranial tuberculoma is the least common presentation. They are mass-like lesions that can be found in 1% of extra pulmonary patients with cerebral involvement and present with symptoms and signs of focal neurological deficit without the evidence of systemic disease [17]. Involvement of the spine occurs in less than 1% of TB patients, and it can be secondary to subjacent bone or soft tissue involvement [14]. Approximately 10% of patients with CNS tuberculosis have evidence of pulmonary tuberculosis [16].

Diagnosis of intracranial mycobacterium tuberculosis infection requires cerebral spinal fluid (CSF) cultures or acid fast stains obtained by spinal tap or tissue biopsy. Rates of CSF culture positivity for clinically diagnosed cases range from 25 to 70% [14]. In some cases, large volume spinal tap is required for diagnosis. However, HIV patients usually require less amount of fluid for diagnosis. Drug sensitivity testing is important for appropriate treatment. CSF sensitivity for culture and smear staining decrease significantly after treatment has been started [14], for which rapid diagnosis is essential to warrant the best outcome.

Polymerase chain reaction for *Mycobacterium tuberculosis* has also been used with variable results. Moreover, tuberculin skin tests and interferon gamma release assays could suggest exposure, but has limited utility for active disease diagnosis. Cerebral spinal fluid analysis for adenosine deaminase protein (ADA), an enzyme produced by lymphocytic proliferation differentiation during cell-mediated immunity, has also variable sensitivity for CNS infection. But standardized cutoffs have not been established. It has been used to predict CNS infection sequel that suggests poor outcomes in patients with higher values [14]. However, ADA levels in CNS can be high in other infections and noninfectious CNS pathologies. Therefore, correct diagnosis still requires CSF or tissue sample for AFB stains and cultures for mycobacterium.

Prompt therapy initiation with intravenous medications is extremely important for the treatment of tuberculous meningitis. First, line therapy for tuberculous CNS infection includes a combination of isoniazid, rifampicin, pyrazinamide, and ethambutol, which has to be taken daily. The recommended minimum duration is 10 months of therapy, which can be extended to 12 months if any interruption occurs during therapy. All medications have good hematoencephalic penetrance. On the other hand, monotherapy is not recommended due to the risk of developing an antimycobacterial therapy resistance, especially with isoniazid.

CNS lesions causing mass effect and hydrocephalus may require neurosurgical evaluation and cerebral decompression.

Systemic anti-inflammatory therapy with steroids should be started concomitantly (see **Table 1**). The use of anti-inflammatory medication has shown to decrease mortality without additional risk of adverse events [18]. Based on animal studies, the benefit of steroid therapy results from the reduction of the inflammatory process with a subsequent decrease in cerebral and spinal cord edema and brain pressure [18], with less disruptions in blood flow and cerebral perfusion.

In view of this, early diagnosis and initiation of antituberculous therapy with systemic steroids are vital to decrease mortality and improve outcome in patient with CNS tuberculous infection.

6.2 Thoracic extra pulmonary tuberculosis

It is believed that the development of extra pulmonary manifestation starts after mycobacterium bacilli invade pleural cavity from subjacent pulmonary parenchyma and then migrates to the lymphatic system, blood vessels, and eventually to other organs outside the thoracic cavity. For this reason is important to rule out pulmonary parenchymal tuberculosis when a patient is suspected to have a pleural effusion secondary to pleural invasion. Manifestations of tuberculosis in the pleural cavity could present either as pleural effusion or empyema. Pneumothorax as a result to parenchymal cavitary lesion rupture can also be seen. All pleural tuberculous involvements can end up in pleural tissue fibrosis or fibrothorax.

Fluid accumulates in the pleural cavity as a consequence of a hypersensitivity reaction to bacilli mycobacterium in the pleural space. Pleural tuberculosis occurs approximately in 5% of patient with tuberculosis in USA and can reach as high a 30% of patients within high prevalence populations [19]. Tuberculous pleural

Infection site	First line therapy	Duration	Adjunctive therapy
Central nervous system 1. Meningitis 2. Mass like lesion	1. Isoniazid, Rifampicin, Pyrazinamide* Isoniazid, Rifampicin, Pyrazinamide*	1. 9–12 months 2. 9–12 months	1. Systemic steroids 2. Surgical Resection (if mass effect or hydrocephalus)
Thoracic extra pulmonary tuberculosis 1. Tuberculous Pleurisy 2. Empyema	Isoniazid, Rifampicin, Pyrazinamide and Ethambutol	6 months	Percutaneous drainage or surgical evacuation
Gastrointestinal tuberculosis	Isoniazid, Rifampicin, Pyrazinamide and Ethambutol**	9–12 months	
Genitourinary tuberculosis	Isoniazid, Rifampicin, Pyrazinamide and Ethambutol	6–12 months (2 months of the 4 drugs followed by 4 months of Isoniazid and Rifampin)	Surgical resection in case of genito-urinary obstruction
Skeletal tuberculosis	Isoniazid, Rifampicin, Pyrazinamide and Ethambutol*	6–12 months (2 months of the 4 drugs followed by 4 months of Isoniazid and Rifampin)	Surgical resection in case of abscess formation or cord compression
Cutaneous tuberculosis	Isoniazid, Rifampicin, Pyrazinamide and Ethambutol	6–12 months	Colchicine, NSAID's, potassium iodine, dapsone, tetracyclines and antimalarial

**Streptomycin can be added based in susceptibility.*
***Therapy also can be based on susceptibility including Levofloxacin, Linezolid and Streptomycin.*

Table 1.
Extra pulmonary tuberculosis treatment.

effusions usually occur in the right side; these are small to moderate in size and are characterized as an exudate fluid. Fluid analysis is characterized with high protein levels (>5 g/dL), cell count around thousands, and lymphocytic predominance. It usually presents with more than 80% of lymphocytic predominance, and depending on the time of diagnosis, variable amounts of lymphocytes from 20 to 90% has been seen. In addition, low pH and low glucose levels can also be seen in pleural fluid analysis. Long standing effusions result in a highly acidic fluid. Lactate dehydrogenase enzyme (LDH) levels usually range above 500 IU/L [19].

Adenosine deaminase (ADA) levels (see CNS involvement) are of particular utility in suspected tuberculous pleural effusions. The diagnostic use of ADA depends on its sensitivity and specificity and the regional prevalence of the infection. In a high prevalence population, an elevated ADA level (>40 U/L) is considered confirmatory with a clear indication for therapy. In low prevalence populations, a low ADA level (<40 U/L) has a high negative predictive value and therefore, rules out the diagnosis [19]. There are cases where ADA levels are not considered reliable, for example, in patients with pulmonary, pleural or hematologic malignancies, nontuberculous bacterial infections and also in those who underwent pleural procedures.

Acid fast staining and culture test have limited diagnostic utility. Patients with pleural effusions of unknown etiology should be evaluated for a possible infectious

cause, including tuberculosis. This is essential in patients with history of TB exposure, immunosuppression (including HIV), and pleural effusions with nonspecific characteristics, and lymphocytic cell count predominance.

Acid-fast smears are almost always negative. Positive cultures for mycobacterium tuberculosis have been reported in 10–70% of the cases [19], and consequently pleural fluid culture analysis has a low diagnostic yield. Positive culture is directly proportional to the level of immunosuppression. In an HIV patient, the yield doubles (20%) compared to the immunocompetent patient (10%). It is more common to obtain a positive culture in a liquid media versus solid media [19]. Positive pleural fluid cultures are useful for drug therapy sensitivity and should be obtained in every case of suspected tuberculous pleural effusion.

Pleural biopsy is considered one of the best diagnostic methods when tuberculous pleurisy is suspected. Definite diagnosis is obtained if mycobacterial bacillus is detected in the smear, culture or pleural tissue biopsy. In the appropriate clinical setting, the presence of granuloma obtained after pleural biopsy is highly suggestive of tuberculous pleurisy and demands treatment.

Percutaneous biopsy has a yield of almost 90% when guided by ultrasound [18]. When pleural biopsy is performed, the instruments and technique used varies, but the yield improves when at least six samples are taken from different quadrants [20]. More invasive procedures such as thoracoscopy and open surgical biopsies have good diagnostic yields. Access to these techniques is limited in areas of endemic tuberculosis, and for this reason, less invasive work up is the usual diagnostic approach. When a pleural effusion is suspected to be of tuberculosis origin, without evidence of pulmonary parenchymal involvement, a positive ADA in endemic areas is considered diagnostic. A low ADA level (<40) needs further work up including pleural biopsy. In low prevalence populations, a low ADA almost rules out tuberculosis and in these cases other etiologies must be considered [18].

Treatment for isolated pleural tuberculosis does not differ from pulmonary tuberculosis. Unless the effusion is characterized as an empyema, drainage is not required, and the effusion is expected to resolve by itself in weeks after commencement of treatment.

6.3 Gastrointestinal tuberculosis (abdominal tuberculosis)

Gastrointestinal tuberculosis (GI Tb) is relatively rare in the United States and is the sixth most common extrapulmonary location. Populations at risk include immigrants to the United States, the homeless, prisoners, residents of long-term care facilities, and the immunocompromised. The peritoneum and the ileocecal region are the most likely sites of infection and are involved in the majority of cases by hematogenous spread or through swallowing of infected sputum from primary pulmonary tuberculosis. Pulmonary tuberculosis is apparent in less than half of patients.

GI TB is a major health problem in many underdeveloped countries. In those with HIV infection, it is more present.

In those with pulmonary Tb, intestinal involvement was largely present before effective therapy was available.

However, approximately 20–25% of patients with GI TB have pulmonary TB. The ileum and colon are the common sites involved [21].

Other comorbidities associated with lower GI tract TB have been in other series type II diabetes mellitus (23%) and alcoholism (23%). Half of the stool cultures for *Mycobacterium tuberculosis* yields positive for it. This is similar to what is found with biopsy cultures of affected GI tract [22].

Treatment with 6 months antituberculous therapy has been found to be as effective as 9 months of therapy in patients with intestinal TB [23].

6.4 Specific situations

Esophageal Tb is the least common site of Tb in the GI tract [24]. *Stomach and duodenal* involvement by TB is rare because of (1) the high acidity of peptic secretions and (2) diminished amount of lymphoid tissue in the first part of the GI tract. Dyspepsia, diffuse abdominal pain, is frequent.

Clinical features of intestinal TB include abdominal pain, weight loss, anemia, and fever with night sweats. Patients may present with symptoms of obstruction, right sided pain [25].

Malabsorption may be caused by obstruction that leads to bacterial overgrowth, a variant of stagnant loop syndrome. Involvement of the mesenteric lymphatic system, known as tabes mesenterica, may retard chylomicron removal because of lymphatic obstruction and result in malabsorption.

The ileum is more commonly involved than the jejunum. Ileocecal involvement is seen in 80–90% of patients with GI TB. The latter is due to the abundance of lymphoid tissue in the distal ileum [26, 27].

If ascites is present, the measurement of ascitic fluid adenosine deaminase levels is reasonable. Laparoscopic biopsy samples from the peritoneum should be stained for acid-fast bacilli (AFB), and cultures should also be obtained with a reasonable yield [28, 29].

6.5 Genitourinary tuberculosis

Tuberculosis usually goes into the genitourinary system after reactivation of previous acquired disease. This is the second most common presentation of extra pulmonary disease, following lymphatic spread of infection [30]. Tuberculous bacilli infect renal and reproductive organs after they travel through the circulatory system. Genital involvement also occurs by cutaneous lesions during sexual contact or by contaminated instrumentation.

Genitourinary involvement mostly occurs after reactivation of latent disease, and time to reactivation occurs years after primary infection. Cases reported usually involve older patients with a median age above 40 year old and mostly affects male patients [23]. The urinary tract is usually involved and it can manifest as a simple cystitis or pyelonephritis with or without hematuria and renal failure.

When renal function is affected, the patient has urinary tract obstruction or an interstitial nephritis. The prostate, seminal vesicles, and epididymis are rarely affected. Epididymis is the most common genital organ involved in men followed by prostate [30]. Testicles involvement is very rare. In women, fallopian tubes and uterus are the most common genital organs involved and can cause infertility in small percent of young women [30].

Diagnosis is done showing evidence of bacilli in stain or cultures in urine or tissue obtained from the genitourinary tract. Granulomas and acid-fast bacilli can also be seen in tissue specimens from kidneys and reproductive organs [31]. Treatment is usually the same as pulmonary tuberculosis, with approximately 6–8 months as the recommended duration of therapy.

6.6 Skeletal tuberculosis

Skeletal tuberculosis presents with certain variability. It is responsible about 10% of all cases of extrapulmonary tuberculosis in the United States of America, with a highest prevalence among those immigrants who come from endemic areas. The proportion is no different between those patients infected with HIV versus those not infected. The most common affected area is the spine, follow tuberculous

arthritis, and follow by extraspinal osteomyelitis. Young individuals are more likely to be affected in highly endemic are while adult patients are more frequently in low endemic together with a late presentation [32, 33].

The associated pathogenesis resides in disease confinement at the bone and the synovial fluid. It results after seeding during primary infection. Cellular and adaptive response are responsible of disease containment until reactivation which related to immunity failing which can be seen in different settings including older age, renal failure, malnutrition, and acquired immune deficiencies. Skeletal involvement shows histopathological pattern of caseous exudative or granular. The first occurs more frequently in children and it is characterized by inflammatory changes, bone destruction, abscess, and sinus tract formation. The last is much slower and much less destructive. Any bone can be infected with tuberculosis. Clinical manifestations include spondylitis, arthritis, and osteomyelitis [33, 34].

Tuberculous spondylitis (also known as Pott's disease) is the most common presentation. It is responsible for one half of the bone-related cases and most commonly affects the lower thorax and upper lumbar region. The infection starts at the anterior area of the vertebral joint and locally spreads to the anterior ligament after that it will affect the local vertebral body. Once the adjacent vertebra is affected, it proceeds to involve the intervertebral disk space with vertebral narrowing and further collapse. This finding may lead to distortion of the spinal canal anatomy and possible neurologic compromise. Although continuous spinal infection is uncommon, it has been documented [35]. Less than 40% of the patients presents with fever and weight loss. Symptoms include progressive local pain over the weeks with associated muscle spam and rigidity. The patient may present with an erect posture with associated short steps. Unfortunately, due to the lack of medical access on endemic regions, many of these patients will present with cord compression. Radiography changes are first appreciated in the anterior part of the vertebral body showing areas of demineralization and loss of margin contour. Findings of next vertebral involvement are common. Sclerotic changes persist but the rest of the vertebra remains without involvement [36]. Although the disk is commonly obliterated, collected data show that multiple sites and sparing of the disk are possible [37].

Arthritis may occur as part of direct infectious process to the joint or due to an inflammatory response. The infectious process is monoarticular and may affect any joint but most commonly the hip. The symptoms progress from weeks to months and presents with chronic swelling, pain, and loss of function without erythema. Constitutional symptoms occur in less than 30% of the cases [38]. The joint presents with effusion and loss of function with associated granulomatous changes, such changes lead to distortion and deformity of the joint. Treatment may include total hip replacement if debridement and antituberculous treatment is given [39]. Prosthetic joints can also be affected but it is very rarely. While arthroplasty may have an adequate outcome, infections related to hardware may co-exist with other bacterial infections. The same is painful, and hardware needs to be removed. On the other hand, symmetrical polyarthritis may involve large and small joints without local evidence of active TB, despite the presence of military, pulmonary, or extrapulmonary manifestations of the disease. Poncet's disease, other name given to the condition, seems to be immune-mediated and related to HIV co-infection. The inflammation resolves after starting antitubercular treatment without evidence of joint destruction [40]. Phemister triad may be observed in this case. The same consists of juxta-articular osteopenia or osteoporosis, peripheral osseous erosions, and gradual narrowing of the joint space. Although there is also evidence of local swelling and bode destruction, there is a preservation of the cartilage space.

Osteomyelitis may occur in any bone of the body, and it is more commonly insidious but the case has described acute and subacute onsets, which are very rare.

Clinical scenarios may include suspected malignancies or metastasis, but those findings are due to lytic tubercular lesions. It presents in unusual areas such as symphysis pubis, elbow, and sacroiliac joint [41]. Small bones may be affected without evidence of active pulmonary disease [38]. Ribs and sternum may also be affected. The firs may be confused as a breast or chest wall mass. The second may occur after coronary bypass surgery due to previous mediastinal involvement or as primary focus [42]. Radiological evident is usually present at the time of clinical presentation. There is osteolytic changes with minimal or none inflammatory changes, periarticular osteopenia, soft tissue swelling, and minimal or periosteal elevation [43].

Musculoskeletal involvement may also be seen at the epidural space, as an extraspinal mass or psoas abscess. The presentation may cause cord compression, rib erosion, and sinus tracts to the groin, respectively.

The diagnosis of musculoskeletal tuberculosis is challenging considering its indolent progression and clinical presentation. Caliceal suspicion is warrant and detail travel history and exposition in needed. In addition, although, a chest X-ray neither includes nor excludes the presence of extrapulmonary manifestation, and it may give a clue of current situation or evidence of previous infection. Other studies such as computer tomography, myelography, and MRI help to describe in detail joint and spinal cord involvement. Biopsy with microscopy and culture of the suspected or infected area is need for drug testing and identification of isolates. Synovial biopsy is needed in case of TB arthritis is considered. The fluid may be aspirate and verified but findings and usually nonspecific. In case of findings or with draining sinus, culture of the latter may help to identify the pathogen, although polymicrobial isolates and fungal results may be present and misleading [44].

Treatment is very similar to pulmonary TB. However, the course of therapy relies in whether the drug regime includes rifampin or not. Data suggest that dose that include rifampin may be shorter and as equally as effective as longer treatments (6–9 vs. 9–12 months). Shorter courses such as 6 months may be suitable on those cases that involve radical surgical resections [45]. Also, randomized clinical trials show comparable results after 5 years of treatment on those patients who received isoniazid with rifampin for 6–9 months vs. those who received isoniazid with either paraminosalicylic acid or ethambutol. Sixteen surgeries are required in different settings such as chest wall abscess, spinal diseases with a kyphosis of more than 40°, and spinal disease with progressive neurological deficits while on treatment or just advance neurological deterioration. This would lead to different alternatives such as decompression, drainage, debridement, and hardware placement for spine stabilization [46].

6.7 Cutaneous manifestations of tuberculosis

Although uncommon, tuberculosis also has skin manifestations. The same have been documented since 1826 and occurs in 1–2% of the infected individuals. Cutaneous classification varies, and it depends not only on clinical appearance but also on the method of infection, predisposing factors, and pre-existing TB exposure. The bacterial load may be variable, the same may be easily or difficult to detect [47]. Mode of infection may be due to inoculation secondary to exogenous source, endogenous (continue infection), or hematogenous spread.

Exogenous inoculation can occur due to primary inoculation or due to tuberculosis verrucosa cutis (TBVC). Primary inoculation is rare and occurs after direct skin invasion of a previous nonsensitized patient. Children of endemic areas are more affected. However, surgical procedure with infected equipment, piercing, and tattoos has been identified as causals. The infection is clinically apparent by the fourth week. A painless brown papule or nodule shallow about 1 cm affecting the

face and extremities. The lesion progresses slowly, and regional painless lymphadenopathy develops. The same may cause sinus draining tracks following skin perforation. Diagnosis relies on the tissue sample, acid fast, and culture. If left untreated, the patient became sensitize to tuberculin test. Hematogenous spread is possible resulting military pattern [48].

On the other hand, TBVC occurs after direct inoculation in a patient who is already sensitized with TB. Children of endemic areas are at high risk and those who are occupationally related. In children, the buttocks and ankles are more commonly affected, while in adults, it occurs more frequently at the fingers and the dorsum of the hands. It also presents with red-brown painless but warty plaques that grows peripherally. Ulceration and regional lymphadenopathy is not common, it may co-exist with bacterial infection. Diagnose may be challenge. Culture form the lesion are usually negative, tuberculin test is positive, and interferon gamma assay may play a role in the diagnosis. Biopsy superficial dermal pseudoepitheliomatous hyperplasia with hyperkeratosis and microabscess in the dermis or pseudoepitheliomatous rete pegs. The upper and middle dermis shows inflammatory infiltrates of giant and epithelioid cells. Patient usually responds to anti-TB treatment. If left untreated, lesions may persist [49].

Cutaneous involvement may also be causes by contiguous spread presenting as Scrofuloderma, tuberculosis cutis orificialis, and lupus vulgaris. Scrofuloderma are painless red-brown nodules subcutaneously located most commonly at the axillar, neck, and groin areas. The infection occurs because of direct extension of the infection from deeps structures invading the skin. Cervical nodes are the most common site of infection. They tend to enlarge forming ulcers and sinus tracts and may follow a line lymphoid distribution. Although the infection has been related to *Mycobacterium tuberculosis*, it has been described in other in mycobacterial infections other than tuberculosis such as bovis and following BCG vaccination [49]. The lesion may be healed spontaneously, but it may take a long time to leave a scar. Lupus vulgaris may be developed in association to the later. Children, adolescents, and older adults are more commonly affected. Diagnosis is made by smear, culture, and biopsy. Tuberculin test is usually positive, and concomitant pulmonary disease is common [50].

Tuberculosis cutis orificialis (TBCO) is a rare manifestation of characterized by painful ulcers with pseudomembranous fibrous base from a prior red-yellow nodule with associated inflammation. The lesion may be sited at the oral, nasal, or anogenital area. It affects middle age and older adults with advance immunodeficient disease (cell-mediated). Most of these patients already have a progressive, pulmonary, gastrointestinal, or genitourinary advance TB disease. Tuberculin test is usually positive. Clinical course is usually poor leading to disseminated military TB. Diagnosis relies on biopsy smear and bacilli identification with the identification of them at the ulcer. The same is also associated with tubercular granulomas at the edge of the ulcer and deep dermis.

Lupus vulgaris results as a manifestation of TB reactivation. Is a chronic manifestation that can occur by direct extension, lymphatics, or hematogenous spread? It occurs more frequently on females than males, and it is the most common for old TB skin manifestation in Europe. Despite this, it has a different distribution which varies with geographical location. For example, in western countries, the distribution is more common located at the head and neck areas, while in subtropical or tropical areas is more common at the lower extremities [49]. The skin lesion is red-brown papule that progresses into a nonpainful plaque. The same grows up to 10 cm developing areas of atrophy with associated central clearing. There are also variations of the lesion, where it can develop hypertrophy and ulcerations. It may also infect with other infections. As can be appreciated in other forms of granulomatous disease, lesion can have a yellow-brown contour with "apple jelly" appearance [49]. Diagnosis may be difficult, since it cannot be detected by culture or histopathology. PCR plays

a role in the identification of the mycobacteria. Although some cases have described, *Mycobacterium bovis* has potential pathogen. Pathology will show tuberculoid granulomas with central caseated lesions at the dermal area. The epidermal area may reveal atrophy acanthosis, hyperkeratosis. The disease, also known as Lupus TB, requires the use of anti Tb treatment. If not, the size of the lesion progresses developing ulceration of the skin with loss of architecture. Also, progression to skin-related cancer, such as squamous cell carcinoma, has been documented [50].

Skin lesion may also result from hematogenous spread from primary site of infection leading to metastatic tuberculous abscess, acute military TB, or lupus vulgaris. The first, metastatic tuberculous abscess occurs after developing cell-mediated immunodeficiency occurring in adults and malnourished children. The abscess may be single or multiple forms subcutaneous nontender nodules that progress to ulcer and sinus tract formation without lymphadenopathy [49, 51]. Any part of the skin may be affected more commonly the extremities. The metastatic infection usually confers a poor prognosis in the predispose individuals. Diagnosis is done after the findings of bacillus formation in culture, smears, or biopsies. Histopathological, there is evidence of ample skin necrosis, may show granulomas at the dermis. Unfortunately, tuberculin test results are variable [51].

Acute miliary TB is a rare manifestation that occurs more frequently in patients with deficient cell-mediated immunity such as infants and acquired immunodeficiency syndrome. Lesions are pinpoint red-bluish or purpuric papules with associated vesicles that furtherly become crusted. The lesion may resolve in the following weeks leaving hypopigmented scar like tissue. Skin biopsy plays a role in the diagnosis where mycobacteria are frequently identified. TST is usually negative [51].

Patient who have a higher immunity may develop hypersensitivity reaction manifestation as tuberculid. The lesions may be papulonecrotic, lichen scrofulosorum, and erythema induratum of Bazin (EIB). The identification of a tuberculid is supported after the following: presence of detectable infection such a TST and interferon gamma release assay, identification of granulomatous lesion in the skin, failure to identify *Mycobacterium tuberculosis* in cultures and stains, and noted, the resolution of the skin lesions after anti-Tb treatment.

Papulonecrotic tuberculid is the most common. It occurs more frequently in children and young adults. It is a dark violaceous papule that progress to pustular and necrosis. It is more commonly located in the face, neck, extremities extensor areas, and buttocks. It may be recurrent if left without treatment [51]. Constitutional symptoms occur prior the lesions and lymphadenitis can be appreciated [51]. The lesions may resolve alone leaving residual scars. Diagnosis is based on history of TB and evidence of wedge necrosis at the dermal and epidermal areas with granulomatous inflammation, mycobacterial DNA identification, and probable focus. TST is usually positive, and lesion resolves with anti-TB treatment.

Lichen scrofulosorum is rare and presents more frequently in children and young adult with previous infection at the lung, bone, lymph nodes, or intracranial. The lesion is small 1–5 mm red-brown -yellow commonly located at the truncal area [49, 51]. The lesions may resolve spontaneously without treatment. It does not leave a scar, and anti-TB treatment brings complete resolution. As other tuberculid, the diagnosis is based on clinical presentation, histopathologic findings (tuberculid granulomas at the upper dermis and tuber, glands, and hair follicles). TST is usually positive with negative mycobacterial culture.

Panniculitis of the lower extremity (EIB) may be seen in patients with TB. The manifestation usually occurs in middle age young females. The lesion is tender, red, subcutaneously located at the posterior aspects of the leg. The nodules may progress forming draining ulcers. Its course is chronic and resolves alone leaving scars. Anti-TB treatment is recommended. If panniculitis is associated to TB, TST is

often positive. Diagnosis is based on clinical history and histopathological findings. Mycobacterial DNA may be identified by PCR but not always. Biopsy needs to include subcutaneous fat in a wedge fashion. The sample should reveal lobular with or without septal panniculitis, poorly form granulomas, necrosis of the fat with mixed inflammatory cells. Vasculitis may also. Other treatment alternatives include colchicine, NSAID's, potassium iodide, dapsone, tetracyclines, and antimalarial. Other kind of tuberculid, similar to EIB, is the nodular pattern occurs at the same areas but the granulomatous findings occur at the dermal-subcutaneous fat junction without ulceration or evidence of panniculitis.

7. Conclusions

Tuberculosis can invade almost any organ through the lymphatic system and blood dissemination. The manifestations of extra pulmonary tuberculosis can be variable depending on the organ and the system involved. The diagnosis is made through a high suspicion in the predisposed populations, and many times, extensive diagnostic tests that usually involve cultures and/or biopsies of the infected tissue. This is one of the infectious affections with a greater range of presentations, capable of pretending to be other noninfectious diagnoses.

Conflict of interest

No conflict of interest.

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