Extrapulmonary tuberculosis: an overview

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ABSTRACT

Up to 25% of tuberculosis cases present extrapulmonary involvement. This is produced by hematogenous and lymphatic spread of the M. tuberculosis bacillus to other organs. The most common locations are the lymph nodes, pleura and the osteoarticular system.

The problem with these types of tuberculosis is the difficulty in establishing a definitive diagnosis, since the clinical symptoms and results of imaging tests may be vague. It is often necessary to resort to invasive diagnostic testing such as ultrasound or CAT-guided FNAB, used to collect biological samples for diagnosis. Despite the growing use of and advances in recent years of molecular methods for early detection of mycobacteria DNA, cultures continue to be the gold standard that enables a firm microbiological diagnosis to be made.

Treatment for these types of tuberculosis does not differ from treatment regimens for pulmonary forms of the same disease. The same antibiotic regimens for 6 months are recommended, and any extension of this period is advisable solely in tuberculosis affecting the central nervous system and in Pott's disease.

Key words: Prisons; Tuberculosis; Diagnosis; Therapeutics; Tuberculosis, Pleural; Tuberculosis, Meningeal; Tuberculosis, Miliary; Tuberculosis, Lymph Node; Tuberculosis, Cutaneous.

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Extrapulmonary tuberculosis is defined according to WHO classification criteria as an infection by *M.tuberculosis* which affects tissues and organs outside the pulmonary parenchyma. It represents between 20 and 25% of all TB cases[1].

Extrapulmonary TB (EPTB) results from the hematogenous and lymphatic spread of *M.tuberculosis* bacilli. As a result of that spread and thanks to the development of specific cell-mediated immunity mechanisms, among them the formation of anti-TNF alpha, IL12 and interferon gamma, protective immunity against the bacteria is developed, with the resulting formation of encapsulated granuloma which contain viable bacilli. Although this can happen at any point after primary infection, it most commonly occurs years or decades later, because of the alteration of responsible immune response mechanisms such as extreme ages (children or elderly), concurrent medical conditions or treatments entailing an alteration of cell-mediated immunity. The alteration of the immune mechanisms involved in the formation of granuloma predisposes the reactivation of latent TB and the development of active TB infection[2].

Although throughout recent years we have experienced a constant reduction of the overall number of TB cases, the reduction of extrapulmonary TB cases has not been as relevant[3-4]. The reasons for this have not been thoroughly assessed although it could be due to several causes, among which we can note a reduced use of BCG vaccines and changes involving susceptible populations. However we lack prospective studies assessing the reasons for this increase.

Risk factors involved in the development of EPTB are mainly age, female gender, concurrent HIV infection and comorbidities such as chronic renal disease, diabetes mellitus or immunosuppression. The mean age of EPTB patients is higher than for pulmonary TB. Among EPTB patients those who develop pleural or meningeal affectation are

generally younger than those who present lymphatic, osteoarticular, genitourinary and gastrointestinal forms of the disease[3].

Diagnosis requires a high index of suspicion. Delayed diagnosis of extrapulmonary forms is frequent and it entails an increased morbidity and mortality. Symptoms and signs can be relatively vague and sometimes occur in normal chest x-rays and smear-negative patients, therefore hampering the consideration of the disease in the initial approach. Nevertheless pulmonary tuberculosis always needs to be ruled out by means of chest x-rays and sputum culture. Tuberculin skin test (PPD) or interferon gamma detection needs to be carried out to rule out TB infection.

In Spain positive results are considered for indurations of 5mm or more for BCG non-vaccinated patients. As for BCG vaccinated individuals, the effect of the vaccine can interfere with TB infection, and so it has been established that for high-risk vaccinated populations indurations of 5mm or more are considered positive[6].

Techniques based on the detection of interferon gamma (interferon gamma release assays or IGRA) have additional advantages over PPD tests. They allow to make a difference between those infected by *M. tuberculosis*, BCG vaccinated individuals and patients infected by atypical mycobacteria. They also allow the detection of anergic patients therefore avoiding false negative results. Although these tests support the diagnosis of the disease, a negative result does not exclude the possibility of extrapulmonary forms of TB, since it has been reported that up to 68% of cases may present negative results[7].

In extrapulmonary TB the inherent difficulty to obtain microbiological samples makes radiology and other imaging techniques such as CT or MRI very helpful in the diagnostic approach and in taking samples through biopsy. Isotopic techniques such as positron emission tomography (PET-CT) may early detect inflammatory activity but they are highly unspecific for the diagnosis[6].

Definite diagnosis however requires the detection of *M. tuberculosis*. Stains to detect acid-fast bacilli such as Ziehl-Nelsen and auramine stains allow a quick diagnosis. Nevertheless quantities of between 5000 and 10,000 bacilli/ml are needed in the sample for them to be detected by these stains. This is why the diagnostic yield of smear in EPTB is higher for samples obtained through biopsy (sensitivity>70-80%) than for biological fluids (5-20%). We must always take into account that a variable percentage (30-50%) of EPTB may be smear-negative. Microbiological culture is the gold standard test. It allows the detection of between 10 and 100 bacteria/ml. Moreover it can identify the determinate species of mycobacteria and it can establish its sensitivity to different drugs. Its main disadvantage is that its results take between 2 and 6 weeks to be ready in solid culture media. As to minimize this period, liquid culture mediums have been developed and they enable the detection of bacterial growth between 7 and 10 days before solid media[6].

Molecular methods based on the amplification of *M. tuberculosis* specific genetic fragments allow a rapid diagnosis over direct samples and they may detect gene mutations responsible for antimicrobial resistance. Most of these techniques use the polymerase chain reaction (PCR) and IS6110 as the genetic target. There are several difference regarding sensitivity and specificity according to the type of sample and there is no universally accepted standardization for the time being [8, 9]. The sensitivity of these techniques depends on the bacterial burden, and therefore in smear-positive samples sensitivity reaches 90-100% while for smear-negative samples this drops down to 60-70%. In extrapulmonary forms of the disease such as pleural, meningeal, urinary, peritoneal and pericardial TB, sensitivity would range between 50 and 70% with a high specificity of between 90 and 95%. As far as other locations are concerned there is not enough evidence to establish the diagnostic yield of these techniques although some studies have reported a sensitivity of around 80% and a specificity of 90% in forms affecting the bone and lymph nodes[2]. Another issue regarding these techniques is the possibility of having false positive results, due to laboratory pollution or to the genetic material produced by dead or dormant bacilli[10]. Current guidelines recommend these techniques as coadjuvant methods for diagnosis of EPTB. Results need to be interpreted jointly with the results of other techniques and the degree of clinical suspicion. When there is a moderate to high suspicion of TB (over 40%) a positive result would indicate TB in 80% of cases, while in low suspicion cases, specificity drops down to 50%[11].

These techniques also allow the detection of specific gene mutations entailing antimicrobial resistance. The vast majority entail the resistance to rifampicin and isoniazid. However, although they provide quick preliminary information, the realization of antibiogram is compulsory, since they do not detect all kinds of resistances[6].

The determination of the enzyme adenosine deaminase (ADA) provides useful information in extrapulmonary TB. It is produced by monocytes and

macrophages involved in the inflammatory response of serous membranes. Its cut-off points are 40U/l in pleural and pericardial fluids, 10U/l in cerebrospinal fluid, and 39U/l in peritoneal fluid. It has a high sensitivity (75-80%) yet its specificity greatly varies and depends on the incidence since according to age and previous pathologies we can have false positive results. For pleural fluid its specificity would be around 90%. We can find high values in this location in inflammatory diseases such as empyema, lymphoma, neoplasms, etc. As for the cerebrospinal fluid its specificity is around 80% and it could present false positive results in the case of lymphoma, cryptococcal meningitis and candidal meningitis[6].

Definite diagnosis of EPTB requires samples from fluids and/or tissues through fine needle aspiration biopsy (FNAB), for smear, culture and PCR testing, even requiring an open biopsy of the affected tissue in case of negative FNAB. Histopathological studies of the biopsies show the typical necrotizing granuloma containing macrophages, lymphocytes and Langhans giant cells. Caseous necrosis can be sometimes found in the central part of the granuloma. Its presence has a high specificity and it could justify the decision to initiate antituberculous therapy. However, the presence of granulomatous lesions without necrosis suggests the diagnosis but it requires the exclusion of other infectious and non infectious diseases. Acid-fast bacilli are only found in 10% of the samples and culture is sometimes impossible since the samples have been preserved in formaldehyde. Polymerase chain reaction of samples fixed in formaldehyde would have a greatly variable sensitivity of between 30 and 60%. It is therefore important to preserve biopsy samples in distilled water [12].

Treatment of extrapulmonary forms of TB does not differ from pulmonary TB treatment regimens. Evidence on the duration of therapy in some forms of EPTB is not unanimous. It has been recommended to use the same regimens of antimicrobial therapy for 6 months and provide extended therapy (12 months) in the case of CNS involvement and (9 months) in the case of tuberculous spondylitis with neurological involvement, since in these patients short regimens have associated a higher risk of relapse [2, 6]. Treatment schemes include a 2 month period on rifampicin, isoniazid, pyrazinamide and ethambutol followed by a 4 month period on rifampicin and isoniazid. Once the sensitivity to standard first-line drugs has been established, ethambutol can be withdrawn [13].

As far as the administration of corticoids is concerned, they are recommended for tuberculous pericarditis and the first weeks of meningeal forms of the disease, stages 2 and 3 of the British Medical Council (BMC) classification, where several studies have concluded a reduction in mortality of 22% in meningitis and of 18% in the risk of presenting neurological impairment[14-15]. Corticoids can be occasionally used as anti-inflammatory drugs in extensive miliary forms of the disease or those with a poor evolution or rare locations such as pleura, lymph nodes, genitourinary system, peritonitis and uveitis. The recommended dose is 0.5-1 mg/kg/day of methylprednisolone for one month and a progressive reduction until its withdrawal in two months[6].

Surgery for EPTB is used for tuberculous spondylitis involving neurological impairment. Pericardiectomy needs to be considered for persistent and refractory cases of constrictive pericarditis and some severe cases of pleural TB require the realization of thoracotomy when drainage and conservative treatment have been ineffective.

MILIARY TUBERCULOSIS

The term "miliary" refers to innumerable small pulmonary nodules scattered through the lung like millet seeds in the pathology sample. However, today it also refers to progressive and widely spread forms of TB. It entails a hematogenous spread of the disease to several organs and it can be a result of primary infection (especially in children) or of the reactivation of a latent focus. It is a severe manifestation of the disease mainly involving elderly, malnourished patients and individuals with altered cell-mediated immunity such as HIV infected patients, people suffering from chronic kidney disease, solid organ transplant recipients and individuals undergoing anti-TNF therapies. The most frequently affected organs are the liver, the spleen, the lung, the lymph nodes, the meninges, the bone marrow and the adrenal glands. The clinical presentation varies greatly from severe acute forms involving septic shock, multiple organ dysfunction syndrome and acute respiratory distress syndrome (ARDS) to more frequent subacute presentations with insidious symptoms such as general unrest and a trivial physical examination. A micronodular pattern is frequently observed in chest x-rays although up to one third of the cases it can be normal. CT is the most sensitive imaging test to show pulmonary, liver al spleen affectation. Choroidal tubercles can be frequently found upon examination of the ocular fundus and up to 50% are associated to meningeal TB. Diagnosis is difficult and due to its clinical course sometimes delayed. It entails the

collection of several samples in different locations, normally requiring the biopsy of the affected organ for culture and histological testing. Blood cultures are sometimes positive especially in patients with concurrent HIV infection. Necrotizing granuloma are most frequently obtained from liver samples (90-100%) rather than bone marrow (31-82%) or transbronchial biopsy (63-72%)[2, 16].

LYMPH NODE TUBERCULOSIS

It is one of the most common forms of extrapulmonary tuberculosis and it most frequently affects children and young adults. It accounts for between 30 and 40% of all EPTB cases 4. It can be due to a primary form or to the reactivation of a focus. The most common location is cervical lymphadenopathy (63-77%) although it can also affect other areas such as supraclavicular, axillary, thoracic and abdominal nodes[2].

It most frequently involves unilateral laterocervical and supraclavicular swelling with rigid painless consistency. It does not usually imply a systemic involvement. It can eventually present necrosis, fluctuate and produce inflammatory symptoms with ulceration, fistula formation and scrofula. Mediastinal affectation is usually associated with pulmonary forms of the disease (18-42%). Lymph node swelling in this location can compress neighbor structures and produce tracheal bronchial or esophageal obstruction.

Diagnosis requires FNAB of the affected lymph node and microbiological cytological smear testing as well as culture and PCR studies (sensitivity 77%, specificity 80%). Open biopsy is only used when FNAB has not been diagnostic (sensitivity 80%). Viewing caseous granuloma is highly suggestive of tuberculosis[17].

OSTEOARTICULAR TUBERCULOSIS

It accounts for 11% of EPTB forms according to published series[4]. Although it can affect any bone, spondylitis or Pott disease, represents 50% of all cases [2]. Infection generally begins with inflammation of the anterior aspect of vertebral bodies, typically, it spreads behind the anterior ligament to the disc and to adjacent bodies. Eventually the infection can spread to adjacent soft tissues with the formation of paravertebral abscesses and affecting the posterior aspect of vertebral bodies eventually involving the spinal cord which is then at risk of compression. Pott disease most commonly affects the lower thoracic region in younger patients and the upper lumbar region in elder patients. The most common symptom is local pain. Concomitant TB infection in other locations is present in between 20 and 40% of all cases. CT and x-rays are useful in the determination of the extension, the affectation of soft tissues and eventual neurological involvement. MRI is the most sensitive tool in the assessment of neurological commitment. Surgery can be sometimes necessary for patients with symptoms of spinal compression. Diagnosis of skeletal TB requires CT guided biopsy for subsequent culture and pathology study[2, 6].

Tuberculous arthritis can occur in virtually any joint, but it tends to occur in the hip or in the knee. Clinical manifestations include swelling, pain and loss of joint function that progresses over weeks to months. Patients who present late in the course of disease often have evidence of joint destruction including local deformity and restricted range of motion. The formation of fistula is common in advanced cases. Acute inflammation symptoms are uncommon. Although smear testing is poorly sensitive, positive cultures appear in up to 79% of cases. In case of negative culture, synovial biopsy may be necessary [2, 18].

GASTROINTESTINAL AND PERITONEAL TUBERCULOSIS

Tuberculous enteritis can involve any aspect of the gastrointestinal tract although the ileocecal region is the most common site of intestinal involvement. The pathogenesis of tuberculous enteritis can be attributed to four mechanisms: ingestion of contaminated milk or food in the case of infection by *Mycobacterium bovis*, swallowing of infected sputum, hematogenous spread from active pulmonary or miliary TB or contiguous spread from adjacent organs. The organism penetrates the mucosa and localizes in the submucosal lymphoid tissue, where it initiates an inflammatory reaction with subsequent lymphangitis, endarteritis, granuloma formation, caseation necrosis, mucosal ulceration, and scarring. The symptoms and signs of tuberculous enteritis are relatively vague and nonspecific. Nonspecific chronic abdominal pain is the most common symptom occurring in 80 to 90 percent of patients. A palpable abdominal mass is present in some patients. Anorexia, fatigue, fever, night sweats, weight loss, diarrhea, constipation, or blood in the stool may be present. Fistula and intestinal stricture may occur, and thus differential diagnosis with Crohn's disease

is important. Bowel obstruction is the most common complication and may be due to progressive stricture or adhesions 6, 16. Definitive diagnosis is based on a combination of CT imaging, histology and culture of biopsy material. Colonoscopy with biopsy is the most useful nonoperative diagnostic procedure to obtain material for histology and culture. Biopsy's sensitivity is up to 80%.

Tuberculous peritonitis usually occurs as a consequence of the reactivation of latent foci in the peritoneum following hematogenous spread of the infection or from the contiguous spread from adjacent foci such as genitourinary or intestinal TB. The risk is increased in patients with cirrhosis, diabetes mellitus, HIV infection and in patients undergoing continuous ambulatory peritoneal dialysis. As the disease progresses, the visceral and parietal peritoneum become increasingly studded with tubercles. Ascites develops secondary to "exudation" of proteinaceous fluid from the tubercles. More than 90 percent of patients with tuberculous peritonitis have ascites at the time of presentation, while the remainder present with a more advanced "dry" phase, representing a fibroadhesive form of the disease[2]. The diagnosis usually requires paracentesis with the removal of peritoneal fluid for the determination of ADA, which has a high sensitivity and specificity, and microbiological study. Examination of an acid fast stained smear of ascitic fluid has a disappointingly low yield, it has a reported sensitivity of between 0 and 6%. However, culture of peritoneal fluid is positive in 80% of all cases. If negative, CT guided or laparoscopic biopsy would be needed. Surgery is reserved for complicated cases where perforation, bleeding or obstruction occurs[2, 16].

CENTRAL NERVOUS SYSTEM TUBERCULOSIS

CNS tuberculosis occurs due to hematogenous spread from distal foci or during a disseminated form of the infection. It is a severe form of the disease which entails high morbidity and mortality: 25% of patients can suffer some type of sequelae and between 15 and 40% can pass away despite the initiation of treatment. Tuberculous meningitis is the most common form of the disease, yet the infection can also entail intracranial tuberculoma and periarteritis and vascular thrombosis with the development of ischemic stroke and proliferative arachnoiditis which can eventually produce obstructive hydrocephalus with intracranial hypertension. Tuberculous meningitis typically presents a subacute insidious course. Initially it can present headache, malaise, lassitude and progressively lethargy, coma and for the majority of untreated patients, death ensues within five to eight weeks of the onset of illness. Varying degrees of oculomotor cranial nerve (III, IV and IV) and long-tract signs can also be present. BMC categorizes patients on presentation by the stage of the illness with prognostic value. Intracranial tuberculoma can be asymptomatic or produce headache, seizure or some type of neurological impairment. Early treatment is of paramount importance to avoid complications. MRI is the gold standard test since it detects early lesions more accurately. Hypercaptation of the meninges is highly suggestive of tuberculous meningitis. Other MRI findings are cerebral ring enhancing lesions and peripheral edema together with vascular infarction [2].

The diagnosis of tuberculous meningitis requires the spinal fluid examination, which typically shows elevated protein and lowered glucose concentrations with a mononuclear pleocitosis. ADA levels over 9.5-10.5U/l have a sensitivity of between 81 and 87% and a specificity ranging between 80 and 90%. Smear testing has a low diagnostic yield. As for intracranial tuberculoma, stereotactic biopsy may be needed [16, 19]. Surgery would be indicated for hydrocephalus.

URINARY TUBERCULOSIS

Genitourinary tuberculosis is a common form of extrapulmonary disease, it has been estimated to account for 6.5% 4 of all cases. It is more common in men than in women. Hematogenous seeding at the time of primary pulmonary infection can lead to renal involvement; infection can also occur in the setting of late reactivation disease or miliary disease. Of patients with miliary infection, 25 to 62% have been documented to have concomitant renal lesions [20].

The onset on genitourinary TB is often asymptomatic but eventually with the spread if the disease to the ureter and the bladder lower tract symptoms may appear together with sterile pyuria and microscopic hematuria in up to 90% of cases. Ureteral stricture can occur and may cause obstructive uropathy with the development of hydronephrosis. By means of imaging tests such as echography, intravenous pyelogram or CT calcifications, papillary necrosis, calyx involvement, ureteral stricture and pelvic dilation can be demonstrated. Microbiological diagnosis is established by demonstration of tubercle bacilli in the urine though stain and culture. As to improve diagnostic yield, between 3 and 6 serial

samples should be collected every early morning (30% sensitivity for one sample, and 80-90% for several determinations). Although data on sensitivity and specificity of interferon gamma determination in urine are limited some studies have reported figures of 100% and 67% respectively[21]. The use of polymerase chain reaction (PCR) for detection of *M. tuberculosis* in urine or renal tissue is improving diagnostic capabilities; sensitivity and specificity are 87 to 100 percent and 93 to 98 percent, respectively[22].

GENITAL TUBERCULOSIS

In men, the involvement of the prostate, epididymis and testicles is common with the development of subacute prostatism and epididymo-orchitis. Microbiological testing of urine, prostatic fluid samples or FNAB or open biopsy samples is necessary for the establishment of the diagnosis. In women, the Fallopian tubes are bilaterally involved in up to 80% of cases. This is a common cause of abdominal pelvic pain and in developing countries it is a common cause of infertility. Diagnosis requires the realization of hysterosalpingography and culture of menstrual fluid, endometrial biopsy and sampling of other affected tissues by means of laparoscopy[2, 16].

LARYNGEAL TUBERCULOSIS

Laryngeal tuberculosis usually entails the development of masses, ulcers or nodules in the larynx and vocal cords, which are usually mistaken as laryngeal neoplasms. The most common clinical manifestation is dysphonia but it can also produce coughing, stridor and hempoptysis. It is usually associated with concomitant pulmonary TB, and it is thus a highly bacilliferous and contagious form[6] of the disease.

TUBERCULOUS PERICARDITIS

Pericardial infection with *Mycobacterium tuberculosis* may occur via extension of infection from the lung or tracheobronchial tree, adjacent lymph nodes, spine, sternum, or via miliary spread. It is usually associated to concomitant infection in other locations. Ecocardiography can be useful in the establishment of the diagnosis as well as in the assessment of potential complications such as constrictive pericarditis and cardiac tamponade. Tuberculous pericardial effusions are typically exudative and characterized by high protein content and increased leukocyte count, with a predominance of lymphocytes and monocytes. Acid fast bacilli are observed infrequently (6% sensitivity) and the yield is increased by culture (25-75% according to published series). The determination of interferon gamma is more sensible and specific (92% and 100% respectively) than the elevation of ADA levels (sensitivity of 87% and specificity of 89%). Although the specificity of polymerase chain reaction is high, its sensitivity is low for the diagnosis (32%) according to published studies. If necessary, pericardial biopsy should be carried out for culture and pathology study[2, 23].

PLEURAL TUBERCULOSIS

It is a common form of EPTB, accounting for almost 20% of all cases. It is caused by a set of hypersensitivity reactions against mycobacterial antigens in the pleural space. These organisms and/or their antigens probably enter the pleural space due to leakage or rupture of a subpleural focus of disease. Tuberculous pleural effusions are typically unilateral and self-limited resolving spontaneously without treatment. However they can also entail the development of empyema. Tuberculous pleural effusions can occur in association with pulmonary TB. Its diagnosis begins with pleural fluid effusion examination through thoracentesis. The pleural fluid in pleural tuberculosis is uniformly exudative with low glucose concentrations. Microscopic assessment of pleural effusions have low diagnostic yield since only 10 to 25% of samples are positive. Pleural fluid cultures are positive in between 25 and 75% of patients. The determination of ADA in pleural fluid has a sensitivity of 92% and a specificity of 90% but it greatly depends on the prevalence of the disease in the population. It countries where there is a high prevalence of this form of the disease its positive predictive value is 99% while for countries with lower prevalence rates it drops down to 41% [24]. The determination of interferon gamma in pleural effusions has the highest yield with 89% sensitivity and 97% specificity rates[25]. Sensitivity and specificity values for PCR are heterogeneous depending on the specific test used; some studies have reported figures of 62% and 98% respectively[26].

SKIN AND SOFT TISSUE TUBERCULOSIS

Cutaneous tuberculosis is a rare condition which accounts for between 0.5 and 2% of all EPTB cases in developed countries 27-28. Although *M. tuberculosis* is the main agent involved in the development of the disease, other cases have been reported associated to *M. bovis* or the *Bacillus Calmette Guerin*. The association with visceral tuberculosis is observed in up to 28% of cases.

Clinical manifestations of cutaneous tuberculosis greatly vary depending on the pathogenic form, the route of infection, previous sensitization and patient's immunological condition[29]. For over twenty years now, the most widely accepted classification is that by Tappeiner and Wolff[30], which takes into consideration the route of infection and the immunological condition of patients.

With regard to the mode of infection there are the following: inoculation from an exogenous source (primary inoculation TB and tuberculosis verruca cutis); endogenous spread by contiguous extension in previously infected patients (scrofuloderma and tuberculosis cutis orificialis) and hematogenous spread to the skin (metastatic tuberculous abscesses and lupus vulgaris). The latter can also be due to lymphatic spread or contiguous spread from adjacent foci. There are paucibacillary forms of the disease such as tuberculosis verrucosa cutis and lupus vulgaris. Multibacillaty forms include the remainder forms. In Western countries the most common cutaneous manifestation of tuberculosis is lupus vulgaris while in developing countries scrofuloderma remains the most common form of the disease[30-31]. Positive tuberculin skin test is inversely proportional to the degree of immunosuppression[32].

A characteristic histopathological finding in cutaneous TB is the tuberculoid granuloma that demonstrates a variable degree of central caseation necrosis and a peripheral rim composed of numerous lymphocytes. The presence of M. tuberculosis can be demonstrated by means of staining, culture or molecular diagnostic techniques although direct visualization and isolation of the etiologic agent may be more complicated in paucibacillary forms of the disease. There are other lesions, tuberculids, which are thought to be the consequence of hypersensitivity reactions against mycobacterial antigens. Patients most commonly have a history of active tuberculosis with intensely positive tuberculin skin tests. Lesions show granulomatous inflammation and improve with antituberculous treatment, yet M. tuberculosis is not identified with stain or culture techniques. Nevertheless, M. tuberculosis DNA has been identified by means PCR developed in recent tears although not consistently enough[29, 33]. Real tuberculids are scrofulosorum and papulonecrotic tuberculids. Bazin's disease or erythema induratum has been considered a facultative tuberculid since it can be associated to other non-tuberculous processes[34].

The article by Dr. Marco[36] presents the case of an immunocompetent patient with a metastatic tuberculous abscess as the initial manifestation of a disseminated form of tuberculosis. Metastatic tuberculous abscesses also known as tuberculous gummas usually arise as a consequence of hematogenous spread of the bacillus from a primary focus of infection to the subcutaneous tissue during a state of reduced cell-mediated immunity[34]. These lesions typically occur in malnourished children and immunosuppressed adults, although cases have also been reported in immunocompetent individuals[32, 35]. This form of the disease is more typically observed in highly endemic regions, however we have been observing an upturn in developed countries due to the expansion of HIV infection and to a progressive increase of immunosuppressive treatments. Therefore, before the suspicion of tuberculous gumma, subjacent immunosuppression and visceral affectation will need to be ruled out.

Patients with metastatic tuberculous abscesses present with single or multiple, non-tender, fluctuant, subcutaneous nodules. The nodules eventually penetrate the skin, resulting in the formation of ulcers and draining sinuses. Lesions may occur at any skin site but frequently develop on the extremities. Associated regional adenopathy usually is not present[31,34].

Differential diagnosis includes syphilitic gumma, infections by atypical mycobacteria, cutaneous leishmaniasis and deep fungal infections [34].

Lesions typically disappear after the initiation of treatment although bigger abscesses may require percutaneous drainage or surgical excision, as in the aforementioned case [29].

To sum up, a high degree of suspicion is necessary for the diagnosis of extrapulmonary tuberculosis forms. Conventional diagnostic techniques provide different degrees of sensitivity and specificity according to location and bacterial load. Invasive methods are often needed to obtain samples for microbiological and histological testing. The yield of IGRA and the standardization of molecular techniques still remain to be established. Treatment regimens do not differ from those recommended for pulmonary TB, although in some locations treatment should be extended to avoid the appearance of relapses.

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BIBLIOGRAPHICAL REFERENCES

1. Who report 2009. Global Tuberculosis control: epidemiología, strategy, financing. Geneva: World Health; 2009.
2. Fisher D, Elwood K. Nonrespiratory tuberculosis. In: Canadian Thoracic Society, Canadian Lung Association, and the Public Health Agency of Canada, editors. Canadian Tuberculosis Standards. 7th Edition. Ottawa: Canadian Thoracic Society; 2013.
3. García Rodríguez JF, Álvarez Díaz H, Lorenzo García MV, Mariño Callejo A, Fernández Rial A, Sesma Sánchez P. Extrapulmonary tuberculosis: epidemiology and risk factors. Enferm Infecc Microbiol Clin. 2011; 29(7): 502-9.
4. Peto HM, Pratt RH, Harrington TA, LoBue PA, Armastrong L. Epidemiology of extrapulmonary tuberculosis in the United States, 1993-2006. Clin infect Dis. 2009; 49: 1350-7.
5. Yang H, Field SK, Fisher DA, Cowie RL. Tuberculosis in Calgary, Canada, 1995-2002; site of disease and drug susceptibility. Int J Tuberc Lung Dis. 2009; 49: 1350-7.
6. González Martín J, García García JM, Anibarro L, Vidal R, Esteban J, Blanquer R, et al. Documento de consenso sobre diagnóstico, tratamiento y prevención de la tuberculosis. Enferm Infecc Microbiol clin. 2010; 28(5): 297.e20
7. Mert A, Bilir M, Tabak F, Ozaras R, Ozturk R, Senturk H, et al. Miliary tuberculosis: clinical manifestation, diagnosis and outcome in 38 adults. Respirology. 2001; 6(3): 217-24.
8. Ganavalli SA, Praveen CS, Raghavendra DK, Umesi B. PCR as a diagnostic tool for extra-pulmonary tuberculosis. J Clin Diagnc Rese. 2013; 7(6): 1012-5.
9. Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis.MMWR [Internet]. 2009 Jan [cited 2014 Jan 12]; 58(01); 7-10: [about 3 p.]. Available from: www.cdc.gov/mmwr/preview/mmwrhtml/mm5801a3.htm.
10. Makeshkumar V, Madhavan R, Narayanan S. Polymerasa chain reaction targeting insertion sequence for the diagnosis of extrapulmonary tuberculosis. Indian J Med Res. 2014; 139: 161-6.
11. Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, et al. A systematic review of a rapid diagnostic tests for the detection of tuberculosis infection. Health Technol Asses. 2007; 11: 1-196.
12. El-Zammar AO, Katxenstein ALA. Pathological diagnosis of granulomatous lung disease:a review. Histopathology. 2007; 50: 210-89.
13. Tuberculosis. Clinical diagnosis and managemente of tuberculosis, and measures for its prevention and control [Internet]. London: National Institute for Health and Clinical Excellence; 2011 [cited 2014 Feb 22]. Available from: http://www.nice.org.uk/guidance/cg117/resources/cg117-tuberculosis-full-guideline3
14. Prasad K, SinghMB. Corticoistereroids for managing tuberculous meningitis. Cocharane Database Sys Rev. 2008; (1): CD002244.
15. Critchley JA, Young F, Orton L, Garner P. Corticosteroids for the prevention of mortality in people with tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis. 2013; 13: 223-37.
16. Espinosa-Gimeno A, Martínez-Sanz J, Asong-Engonga L. Rodríguez-Zapata M. Protocolo diagnóstico y terapéutico de las tuberculosis extrapulmonares. Medicine. 2014; 11(52): 3091-7.
17. Fontanilla JM, Barnes A, Fordham von Reyn C. Current diagnosis and Management of Peripherals tuberculous lymphadenitis. Clin Infect Dis. 2011; 53(6): 555-62.
18. Colmenero JD, Ruiz-Mesa JD, Sanjuan-Jiménez R, Sobrino B, Morata P. Establishing the diagnosis diagnosis of tuberculous vertebral osteomielitis. Eur Spine J. 2013; 22 Suppl4: S579.
19. Thwaites GE, Van Toorn R, Johan Schoeman J. Tuberculous meningitis: more questions, still too few answer. Lancet Neurol. 2013; 12: 999-1010.
20. Figueiredo AA, Lucon AM. Urogenital tuberculosis: update and review of 8961 cases from the world literature. Rev Urol. 2008; 10(3): 207.
21. Feng Y, Diao N, Shao L, Wu J, Zhang S, Jin J, et al. Interferon-gamma release assay performance in pulmonary and extrapulmonary tuberculosis. PLoS One. 2012; 7(3): e32652.
22. Chawla A, Chawla K, Reddy S, Arora N, Bairy I, Rao S, et al. Can tissue PCR augment the diagnostic accuracy in genitourinary tract tuberculosis? Urol Int. 2012; 88(1): 34-8.
23. Reuter H, Burgess L, Van Vuuren W, Doubell A. Diagnosing tuberculous pericarditis. QJM. 2006; 99(12): 827-39.

24. Liang QL, Shi HZ, Wang K, Qin SM, Qin XJ. Diagnostic accuracy of adenosine deaminase in tuberculous pleurisy: a meta-analysis. Respir Med. 2008; 102(5): 744-54.
25. Jiang J, Shi HZ, Liang QL Qin SM, Qin XJ. Diagnostic value of interferon gamma in tuberculous pleurisy. A metaanalysis. Chest. 2007; 131: 1133-41.
26. Pai M, Flores LL, Hubbard A, Riley LW, Colford JM Jr. Nucleic acid amplification tests in the diagnosis of tuberculous pleuritis: a systematic review and meta-analysis. BMC Infect Dis. 2004; 23: 4: 6.
27. Pérez B, Pifarre R, de Vera CV, García JM, Baradad M, Vila M, et al. Cutaneous tuberculosis caused by Mycobacterium tuberculosis, an uncommon pathology. An Med Interna 2006; 23 (11) 560-1.
28. García-Rodríguez JL, Monteagudo-Sánchez B, Mariño-Callejo A. Tuberculosis cutánea: estudio descriptivo de 15 años. Enferm Infecc Microbiol Clin 2008; 26(4): 205-11.
29. Santos JB, Figueiredo AR, Ferraz CE, Oliveira MH, Silva PG, Medeiros VL. Cutaneous tuberculosis: epidemiologic, etiopathogenic and clinical aspects. An Bras Dermatol. 2014; 89(2): 219-28.
30. Tappeiner G, Wolff K. Tuberculosis and other mycobacterial infections. In: Fitzpatrick TB, Eisen AZ, Wolff K, editors. Dermatology in general medicine. 5th ed. New York: McGraw Hill; 1999. p. 2274-92.
31. Barbagallo J, Tager P, Ingleton R, Hirsch RJ, Weinberg JM. Cutaneous tuberculosis: diagnosis and treatment. Am J Clin Dermatol. 2002; 3(5): 319-28.
32. Parker L, Babu S. Tuberculous gumma: a forgotten entity in the UK. BMJ Case Rep. 2013 Sept 26. doi:10.1136/bcr-2013-010462
33. Tan SH, Tan HH, Sun YJ, Goh CL. Clinical utility of polymerase chain reaction in the detection of Mycobacterium tuberculosis in different types ofcutaneous tuberculosis and tuberculids. Ann Acad Med Singapore. 2001; 30(1): 3-10.
34. Frankel A, Penrose C, Emer J. Cutaneous tuberculosis: a practical case report and review for the dermatologist. J Clin Aesthet Dermatol. 2009; 2(10): 19-27.
35. Almagro M, Del Pozo J, Rodríguez-Lozano J, Silva JG, Yebra-Pimentel MT, Fonseca E. Metastatic tuberculous abscesses in an immunocompetent patient. Clin Exp Dermatol. 2005; 30(3): 247-9.
36. Marco A, Solé R, Raguer E, Aranda M. Goma o absceso tuberculoso metastásico como diagnóstico inicial de tuberculosis en un paciente inmunocompetente: una presentación inusual. Rev Esp Sanid Penit. 2014; 16: 59-62