A COMPARISON BETWEEN CUTANEOUS TUBERCULOSIS AND LEPROSY

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SUMMARY

Cutaneous tuberculosis represents a small percent of total extra-pulmonary TB forms, caused mainly by Mycobacterium tuberculosis. Skin tuberculosis can be also highly variable in its clinical appearance, significance, and prognosis. The form of the disease depends on the virulence of the strain, the immune status of the host, the portal of entry, the mode of internal spread, and the adequacy of initial treatment. Lesions in the skin often represent hematogenously or lymphatically dispersed disease from internal foci of infection. Scrofuloderma and lupus vulgaris are much more common and are seen in patients who are less immuno-suppressed and tuberculosis verrucosa cutis is highly seen in patients who are immunocompetent. Leprosy (also known as Hansen’s Disease) is a chronic, infectious disease involving primarily the nerves and secondary the skin, mucosa and the eyes of infected individuals. Leprosy is caused by Mycobacterium leprae. Although this disease is curable since 1948, according to WHO in 2013 there were registered 213,000 new cases of leprosy. Considering the results of skin tests (biopsies, and secretions tests) leprosy can be classified as: paucibacillary - few or absent bacilli (tuberculoid leprosy, and borderline tuberculoid leprosy) and multibacillary - numerous bacilli (lepromatous leprosy, borderline lepromatous leprosy and borderline leprosy). Corroborating clinical data with specific laboratory tests and biopsies of the affected skin and nerves we establish the diagnosis and form of these diseases; the tuberculin test has as correspondent lepromin test. The treatment of cutaneous tuberculosis in most cases is the same as for pulmonary tuberculosis. Early treatment for leprosy prevents disabilities and scarifying.

Key words: cutaneous tuberculosis, leprosy, Mycobacterium tuberculosis, prognosis, skin tests

RéSUMÉ

Comparaison entre la tuberculose cutanée et la lèpre

La tuberculose cutanée avec le principal agent pathogène Mycobacterium tuberculosis représente un très petit pourcentage de la tuberculose extra-respiratoire totale. TB cutanée est extrêmement variable, du point de vue de la signification clinique et pronostique. Le polymorphisme de la lésion dépend de la virulence du bacille, le statut immunitaire de l’hôte, le lieu de passage vers le corps et comment diffuser et mener l’efficacité du traitement initial. Les lésions cutanées se produisent habituellement par diffusion lymphatique ou hématogène d’une épidémie existante. Parmi les formes de tuberculose cutanée et le lupus vulgaris scrofuloderme l’on trouve couramment chez les patients immunodéprimés et la tuberculose verruqueuse est plus fréquente chez ceux présentant une bonne immunité. La lèpre (maladie de Hansen), les maladies infectieuses, granulomatose chronique affecte les nerfs périphériques et les structures tissulaires superficielles primaires et secondaires tels que la peau, les muqueuses et les yeux. L’agent étiologique est Mycobacterium leprae. Bien que la maladie a été déclarée curable depuis 1948 selon l’OMS 2013 il y avait 213 000 nouveaux cas. Les résultats de tests cutanés (sécrétions HP et tests) peuvent classer la lèpre dans: paucibacillaire - bacilles peu ou absents (la lèpre tuberculeuse, la tuberculose et la lèpre borderline) et multibacillaire - de nombreux bacilles (lèpre lépromateuse, la lèpre lépromateuse borderline et la lèpre borderline. Le traitement de la tuberculose cutanée dans la plupart des cas est identique à celui de la tuberculose et de la lèpre pulmonaire; initié au début de l’handicap il empêche la déformation des cicatrices.

Mots clés: tuberculose cutanée, lèpre, Mycobacterium tuberculosis, pronostic, tests cutanés
BACKGROUND

Laennec published in 1826 the first case of cutaneous tuberculosis and described the injury which he called "prosector wart" (1). In 1882, Robert Koch isolated the tubercule bacilli in the lesions of a patient with lupus vulgaris and diagnosed "localized cutaneous tuberculosis". (2,3,4).

Nowadays cutaneous tuberculosis represents a small percentage (<1%) of all extrapulmonary TB cases, its incidence being inversely proportional to the social-economic status and directly proportional to the pulmonary TB incidence. (1) The pathogenesis of cutaneous tuberculosis is similar to pulmonary tuberculosis: direct mechanism, after direct contact with a patient with tuberculosis or indirectly after reactivation of previously infected areas already existing in the body. Five factors that are important for the clinical presentation of cutaneous tuberculosis are 1) the pathogenicity of the organism, 2) its antibiotic resistance profile, 3) the portal of infection, 4) the immune status of the host, particularly the presence or absence of acquired immunodeficiency syndrome (AIDS) secondary to infection with human immunodeficiency virus (HIV), and 5) various local factors in the skin (eg, relative vascularity, trauma, lymphatic drainage, and proximity to lymph nodes). (5)

Leprosy (Hansen’s disease) was first described in 680 b. C., the first cases being identified in the valleys of the Nile and the Ganges. Current disease is more common in subtropical areas of Africa, Southeast Asia and Latin America, predominantly affecting men. In most European countries leprosy disappeared even before the introduction of specific drugs. There were identified some factors that contributed to this: better living conditions, better food, better hygiene, less overcrowded housing and even emigration of the population likely to contract leprosy to America. World Health Organisation (WHO) estimates total number of leprosy cases around the world between 10 and 12 million. According to data from WHO the number of newly discovered cases was below 300,000 in 2005 reaching 215,000 in 2013, of which 10% are children. In Romania the last case of leprosy was diagnosed in 1977; admitted and treated to Leper House Tichilesti Hospital. (6)

Leprosy is a chronic infectious granulomatous disease which first affects the peripheral nerves and secondary superficial tissue structures such as skin, mucous membranes and the eyes. The etiologic factor is the Mycobacterium leprae, an acid-alcohol resistant bacillus (AARB) from Mycobacteriaceae family. The gateway to this pathogen in the body is the skin or respiratory mucosa. Untreated patients spread bacilli through nasal secretions. The average incubation period of the disease is about five years, but in some cases can expand to 20-30 years.

Leprosy can affect individuals of different ages. Children are most frequently affected by infection with M. leprae, a fifth of cases being registered under 10 years; in infants the disease is very rare. (6)

Histopathological and immunological aspects

The presence of tuberculoid granuloma is pathognomonic for histopathological diagnosis. A sequence from nonnecrotic epithelioid cell granulomas with no acid-fast bacilli (high-immune), through necrotic epithelioid granulomas with some acid-fast bacilli, to necrosis with abundant acid-fast bacilli (low-immune) can be arranged. Lupus vulgaris typifies the high-immune pole; tuberculoid-sis cutis orificialis and acute milliary tuberculosis, the low-immune pole. (5)

There have been described seven patterns associated with inflammation: 1) classic tuberculoid granuloma with Langhans cells and peripheral cuff of lymphocytes, 2) abscess formation with inflammatory cells in different degrees of necrosis and rare giant cells, 3) diffuse infiltrate of histiocytes with necrosis, 4) panniculitis accompanied by an infiltrate of acute inflammation, chronic inflammation or both, 5) nonspecific chronic inflammation which includes chronic inflammatory cells predominantly of histiocytes and lymphocytes but giant cells are absent, 6) sarcoidal granuloma described as "naked" granuloma due to the absence of peripheral lymphocytes cuffing and 7) rheumatoid like nodules in the dermis or subcutaneous tissue consisting of central necrosis surrounded by histiocytes; giant cells are absent in this pattern. (5,8, 9, 10)

One or more histopathological patterns can be found in the same patient, and it may change over time; also, the presence of tuberculoid granuloma, does not always mean cutaneous TB, because similar histopathological aspects can be seen in some type of infections (syphilis) or noninfectious granulomas (with zirconium). (11,12)

Cell-mediated immune deficiency is specific for lepromatous patients. In leprosy, bacilli entering human body do not influence early clinical manifestations. M. leprae bacilli are surrounded by a lipid coated dense, inert capsule and are not able to produce exotoxins, generating a low grade of inflammatory response. Only a fifth of those infected will develop signs of indeterminate leprosy, and half of them will develop into a form of leprosy with clinical signs.

In lepromatous form of the disease macrophages "ingest" M. leprae bacilli but do not destroy them. Patients with lepromatous form of the disease present an increased number of CD 8+ circulating lymphocytes that will be activated by specific antigens.Since lesional T lymphocyte type and number vary depending on the type of disease, cytokine production in lepromatous lesions is significantly different from that developed in tuberculoid lesions. (5, 6)

Histologically, in the lesions of tuberculoid leprosy form, we identify non-caseous granulomas with an increased number of lymphocytes, epithelioid cells and giant cells (8). Frequently, in this form of lesions, bacilli are not present or can be scarcely found.

Lepromatous leprosy manifests as a diffuse granulomatous reaction with numerous macrophages, foam cells and multiple large intracellular pathogens; epithelioid cells
and giant cells are absent. In the composition of granuloma in the borderline tuberculoid leprosy cases epithelioid cells are predominant, but in borderline lepromatous form of the disease there is a predominance of macrophages with an increased number of bacilli in the skin lesions.

Histological features of the lesions of erythema nodosum leprosum are characterized by the presence of an infiltrate rich in PMN leukocytes, IgG class antibodies and complement factors. Interferon gamma and tumor necrosis factor alpha (TNF-\(\alpha\)) play a very important role in the initiation and development of clinical and immunological manifestations.

There is evidence that Mycobacterium tuberculosis and other mycobacteria play an important role in the occurrence of leprosy. This is probably due to antigenic overlapping. Different degrees of protection provided by BCG against leprosy in different geographical areas and limited protection observed in people with tuberculin reactivity in BCG trials conducted in Uganda Stanley et al. (1981) support this hypothesis. Rook and others in the same year, went further and suggested that the protective efficacy of BCG's in different areas may increase or decrease depending on the mycobacteria in that environment, some acting synergistically with BCG and other antagonistic.

**Forms of Cutaneous TB and Leprosy**

Cutaneous tuberculosis clinical polymorphism is due to multiple pathophysiological mechanisms. There are forms of cutaneous tuberculosis in which Koch bacillus is present in cutaneous lesions and forms in which it is absent. Based on this criterion cutaneous TB can be classified into:

- **Typical tuberculosis**: Koch bacillus is present in the lesions and can be isolated in cultures. Histological features of the lesions are tuberculous ones. This group includes: primary cutaneous TB (tuberculosis chancre), cutaneous tuberculosis of superinfection (lupus vulgaris tuberculosis, tuberculosis verrucosa cutis, scrofuloderma, tuberculous ulcer and vegetant cutaneous tuberculosis);
- **Atypical tuberculosis**: tuberculin skin test is positive, Koch bacillus is present in skin lesions, but is present in other organs, too. This category includes: lichen scrofulosorum, papulonecrotic tuberculids, milliary tuberculids of the face, erythema nodosum in children, ulcerous tuberculids.

Direct innoculation with M. tuberculosis of the skin or mucous membranes from an external source may cause a primary injury called tuberculosis chancre. This is a superficial ulceration with a firm, granulous base, which develops in 2-4 weeks after mycobacteria penetrated through skin lesions. (4)

The most common form of the disease is lupus tuberculosis or lupus vulgaris often mistaken for Systemic Lupus Erythematosus. Small sharply defined reddish-brown lesions with a gelatinous consistency (called apple-jelly nodules) frequently seen on the face or nasal or mouth mucosa. (Fig. 1).

Another form of cutaneous TB is tuberculosis verrucosa cutis, with rough and hard structure frequently seen on hands and legs (Fig. 2). The immune response of the patient and the aggressiveness of Mycobacterium determine the type and severity of skin TB skin.

Tuberculids are another form of cutaneous TB looking like generalized exanthema that is generally seen in patients with increased immunity to TB due to previous infection. Among them erythema induratum (Bazin disease) presents as recurring nodules or lumps on the back of the legs (mostly women) that may ulcerate and scar. It is a type of nodular vasculitis. Papulonecrotic tuberculids results in crops of recurrent crusted skin papules on knees, elbows, buttocks or lower trunk that heal with scarring after about 6 weeks. (Fig. 3) Lichen scrofulosorum is an extending eruption of small follicular papules in young persons with active TB.

Several classifications have been proposed for leprosy over the years as new knowledge about the disease was gained. In the International Leprosy Congress, held in Madrid in 1953, leprosy is classified as: 1) indeterminate leprosy – first erythematous skin phase 2) tuberculoid leprosy - hair loss, nodular swellings appear in the nerve line, tissue necrosis 3) borderline leprosy – unstable form defined by the immune system that can later transform into a serious form of leprosy, 4) contagious serious form of leprosy when reddish brown spots appear, “lion head” aspect of the face, inflammation in
A COMPARISON BETWEEN CUTANEOUS TUBERCULOSIS AND LEPROSY - NITU et al

vol. 50, no. 1, 108

the line of the lymphatic and nervous system along with tissue necrosis with swelling and ulcerations. These processes can extend into muscle, bone, tendons and internal organs, death being caused by secondary bacterial infections (13, 14).

Later a new system of classification divides leprosy into two immunologically unstable groups (indeterminate and borderline) and two stable polar types (tuberculoid and lepromatous).

**Early or indeterminate leprosy**

The first signs of illness are the cutaneous manifestations and can be identified when examining patient contacts leprosy. Infected individuals present macular lesions with hypochromic or hyperchromic boards. Usually the macular aspect of the skin is accompanied by sensory disturbances in this region: anesthesia or paresthesia. Sometimes, after two years evolution, primary lesions may heal spontaneously. Specific therapies will stop earlier the progression of the disease. (15).

**Tuberculoid leprosy**

The disease begins with a hypopigmented hyposthetic macular lesion, well defined, extending peripherally. The edges are infiltrated and erythematous while the central area becomes atrophic and depressed. Loss of sensation may occur from the start at site of some lesions and sweat glands or hair follicles are absent in this areas. Tender, thickened nerves with subsequent loss of function are common, especially affecting large peripheral nerves (ulnar, peroneal, auricular) that can be identified easily by touch. (16) The patient presents neuritic pain, with secondary muscle atrophy and risk for secondary limb infections after minor trauma. After a long evolution, repeated skin infections, the patient will lose some parts of the fingers. Facial nerve damage determines the occurrence of various events: lagophthalmos, exposure keratitis and corneal ulceration leading to blindness. (10)

**Lepromatous leprosy**

Lesions are disposed along the midline of the body, bilaterally and symmetrically in this extreme form of disease. Patches appear on the skin, also nodules, plaques or papules with imprecisely defined edges, and a hard convex shaped central portion. Dermal inflammation contains bacilli evidenced by staining on slide exams. Regions affected are mainly the face (nose, cheeks, eyebrows), ears, elbows, buttocks and knees. The infection can go unnoticed and undiagnosed for a long time if skin lesions are discrete. In time, patient may lose the side portion of the eyebrow, the skin on the face becomes thin and wrinkled and the ears become pendulous. (16,17, 18)

**Borderline leprosy**

Borderline Leprosy is a form of disease with intermediate symptoms of tuberculoid and lepromatous form. There are three clinical borderline types of leprosy: borderline tuberculoid leprosy, borderline form (dysmorphic type), borderline lepromatous leprosy. Borderline forms characteristics of the disease are incompletely defined; there is polymorphism of cutaneous lesions without local hair loss; symptoms of tuberculoid and lepromatous borderline forms were more clearly defined (16). In borderline lepromatous type the number of lesions is higher but their size is smaller, but in borderline tuberculoid type the aspect of the lesions is similar to the one in tuberculoid leprosy (increased number and imprecisely defined edges). Tuberculous borderline leprosy affects a much larger peripheral nerve structures in comparison with tuberculous disease.

In borderline lepromatous disease lesions are arranged asymmetrically, bilateral (versus polar lepromatous disease in which lesions were bilaterally symmetrical). Borderline clinical forms of the disease are unstable, and in the

![Figure 3 - Papulonecrotic tuberculids (1)](image)

![Figure 4 - Ocular damage in leprosy (6)](image)
absence of right and proper treatment can turn in lepromatous or tuberculoid polar form of leprosy. (10)

Whatever form of leprosy, peripheral nerves will always be affected in variable degrees. Peripheral nerve structures will be more severely affected by the infection, compared to other types of tissues involved. Tissue destruction is due to granulomatous reactions developed by the ill host. The absence of skin lesions does not exclude the presence of nerve lesions, pathologic situation called "pure neural leprosy" (18).

**DIAGNOSIS**

The diagnosis of cutaneous tuberculosis is complex and requires physical examination, careful medical history, tuberculin skin test, QuantiFERON test (and other specific tests if possible), skin biopsy with histopathological exam, special staining methods for identification of Koch bacilli, and other investigations including chest X-ray and sputum exams. According to the guidance of Diagnosis and control centers for tuberculosis in 2005, QuantiFERON test can be used instead of the tuberculin test because of its high specificity and no cross-reaction with BCG. High costs do not justify efficiency. (9)

Culture of provided samples remains the most effective method for determining the presence of Mycobacterium. Using PCR, fragments of tissue can be analyzed to confirm the presence of mycobacterial specific DNA sequences. (17)

Coexisting TB outbreaks can be identified using chest and bone radiographs, blood, sputum and urine tests. (5)

For positive diagnosis of leprosy it is necessary the identification of AARB in samples from skin lesions (with specific stains) or specific microbiological exams. We draw attention that, in tuberculoid leprosy, mycobacteria may be missing in skin lesions. Even in the absence of bacilli, peripheral nerve structures will always be affected.

Polymerase chain reaction (PCR) is used to identify microbial DNA, but it doesn’t have superior sensitivity for the identification of pathogens, compared to the conventional microscopic methods (19).

Lepromin bacillary suspension was created using specific lab methods and samples from heavily infected persons. In infected individuals appears the dermal reaction, tuberculin-like, after more than 48 hours since intradermal injection of a lepromin suspension.

High-performance serological tests are also used for leprosy diagnosis with 95% sensitivity. These tests identify antibodies against M. Leprae Phenolic Glycolipid I (17). The level of serum antibodies is directly proportional to the amount of bacilli present in the human body. Serological tests are useful for determining the etiology of lepromatous disease and are used in the epidemiologic studies. (10)

As a characteristic of leprosy skin lesions will be accompanied by peripheral nerve hypoesthesia due to neural damage. Peripheral nerve damage can easily be demonstrated by neurological exam. There are other diseases with peripheral neuropathy but without skin damage.

**Treatment**

The basic treatment in cutaneous TB is the antituberculous chemotherapy for 6-12 months. Generally for adults it is used a treatment regimen for 9 months but immunocompromised patients require treatment for at least 12 months.

Treatment of leprosy is particularly complex due to multiorgan damage and involves the participation of
several medical and surgical specialties: orthopedic surgery, ophthalmic surgery, physical therapy and chemotherapy. Leprosy treatment is done in special clinics for this condition. The risk of transmission of the disease is relatively small and does not require taking drastic measures of protection and control. (20, 21)

CONCLUSIONS

Cutaneous tuberculosis and leprosy are increasingly rare, mainly due to BCG vaccination and specific treatment of patients in isolation during the contagious period of the disease.

The diagnosis of these diseases is done corroborating clinical symptoms with specific serological tests, lab cultures of secretions and also with biopsies of the skin and nerve affected.

Tuberculin test has lepromin test as correspondent. To avoid sequelae treatment must begin as early as possible (in the case of leprosy using a multidisciplinary team). The results of treatment are affected by the immune status of the patient and the form and progression of the disease. Contacts of cutaneous TB and leprosy patients require specific chemoprophylaxis and periodic controls.

A number of new vaccines are currently under study; they need to be highly effective in both leprosy and tuberculosis.

All the authors have the same contributions.

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