# Cutaneous tuberculosis: epidemiologic, etiopathogenic and clinical aspects - Part I*

Josemir Belo dos Santos[1]
Márcia Helena de Oliveira[1]
Ana Roberta Figueiredo[1]
Perla Gomes da Silva[1]
Cláudia Elise Ferraz[1]
Vanessa Lucília Silveira de Medeiros[1]

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**Abstract:** Cutaneous tuberculosis (CTB) is the result of a chronic infection by Mycobacterium tuberculosis, M. bovis and occasionally by the Calmette-Guerin bacillus. The clinical manifestations are variable and depend on the interaction of several factors including the site of infection and the host's immunity. This article revises the current knowledge about this disease's physiopathology and immunology as well as detailing the possible clinical presentations.
Keywords: Erythema induratum; Mycobacterium tuberculosis; Tuberculosis; tuberculosis, cutaneous; Tuberculosis, lymphnode

## INTRODUCTION

Cutaneous tuberculosis was a major public health problem in the nineteenth and early twentieth centuries. With the improvement of hygiene habits in the general population, the improvement of living standards, the use of the BCG vaccine, and the introduction of effective chemotherapy, there was a significant decrease in the number of cases. From the mid-twentieth century onwards, there was a resurgence of the disease with the main causes being the increased incidence of HIV-positive patients, the emergence of multidrug-resistant tuberculosis and the growing number of patients receiving immunosuppressive treatments.[1,2]

## EPIDEMIOLOGY

Tuberculosis (TB) represents a major public health problem in Latin America, since it affects all countries in this macro region. It is estimated that in 2011, the prevalence of TB in Bolivia was 209 per 100.000[3] representing the highest rate, while Uruguay had the lowest prevalence among South American countries with 22 per 100,000 inhabitants.[3] Brazil is the 17th among 22 countries that concentrate 80% of the global burden of TB. In 2011, 71,000 new cases were reported in Brazil, corresponding to an incidence rate of 37.1 per 100,000 inhabitants.[4] Areas considered of low-incidence have rates lower than 25 per 100,000 inhabitants. Regarding gender, 66.5% of the cases in Brazil occur in men and with respect to race there is an increase in the incidence amongst the natives (indigenous population).[4]

About 14% of the affected, corresponding to just over 10,000 patients, present extra-pulmonary forms. When it is assumed that 1-2% of those with extra-pulmonary forms have cutaneous involvement, one can estimate about 100 to 200 new cases of cutaneous tuberculosis per year in Brazil.[3]

## INFECTIOUS AGENT

Cutaneous tuberculosis has as its main etiologic agent the *Mycobacterium tuberculosis* (Mtb) that belongs to the class *Schizomycetes*, order *Actinomycetales*, family *Mycobacteriaceae* and genus *Mycobacterium*. Occasionally it is also caused by *M. bovis* or BCG vaccine (an attenuated strain of *M. bovis*).[5]

*Mycobacterium tuberculosis* is a straight or slightly bent (rod-shaped), non-motile, non sporulated, unencapsulated bacillus, measuring from 1 to 10µm long by 0.2 to 0.6µm wide; its most important feature is that it becomes stained in red by fuchsin and does not discolor under the actions of alcohol and acid (acid-fast bacillus). Its cellular wall has a high lipid content which grants resistance against the action of chemical agents, though, it is susceptible to the action of physical agents (heat and ultraviolet radiation).[5]

This bacillus is a strict aerobic pathogen that requires certain conditions to grow and multiply: oxygen, nutrients and an adequate pH in the medium. It

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[1] Pernambuco Federal University (UFPE) – Recife (PE), Brazil.

has approximately 4,000 genes with most of them involved in the mechanisms of immune system evasion. For example, 200 of the genes are involved in lipid metabolism. So much emphasis occurs because lipids are the main energy source of Mtb and therefore are directly responsible for its ability to multiply in host tissue and form cellular walls. It can also be considered a facultative intracellular parasite, since it is able to survive and multiply both outside and inside phagocytic cells.[6]

## IMMUNOPATHOGENESIS

The immune response in tuberculosis occurs basically via Th1 pathway, with little or no involvement of Th2 pathway. After the mycobacteria are inhaled, alveolar macrophages are activated, the infectious agents are internalized and the bactericidal apparatus, such as the generation of intermediate nitrogen compounds, is triggered in an attempt to eliminate the bacilli at that point.[7,8]

If the mycobacteria survive, a second stage begins, in which they divide within the macrophages. The latter are no longer able to eliminate the infectious agents alone, so they induce the production of cytokines such as IL-6, IL-12, IL-1α and IL-1β, resulting in the recruitment of monocytes, lymphocytes, neutrophils and dendritic cells. CD4 +, CD8 + and NK-cell lymphocytes are stimulated by interleukins (IL-12 and IL-18) produced by dendritic cells to release IFN-γ in order to stimulate the production of RIN (Reactive Nitrogen Intermediates), ROI (Reactive Oxygen Intermediates) and TNF-α. The intensity of IFN-γ production is regarded today as an important marker of effective immune response against Mtb (attenuated or wild) and this is relevant for the development of new diagnostic tests and vaccines for tuberculosis.[7,8,9]

After the failure of the initial containment mechanisms, the body begins a new attempt to control the growth of mycobacteria population through granulomas stimulated by TNF-α.[10] Once again, the release of IL-1, IL-6, RNI, and ROIs by the macrophages will be triggered. The chronic presence of these interleukins stimulating macrophages will ultimately cause their differentiation into epithelioid and giant cells that will organized themselves, to greater or lesser extent, into granulomas according to individual host factors. Laboratory animals with TNF-α deficiency *fail to form effective granulomas, confirming its importance to the efficacy of cellular response*.[7,8]

Containment will lead to stabilization, infection latency or cure, whereas non-containment will cause tissue damage and dissemination. Over time, Mtb persistence inside the granuloma, associated with possible failures in the immune system, keep the chances of focal reactivation a constant concern. In addition to the aforementioned, Th17 cells pathway stimulated by interleukins IL-17 and IL-23, has recently been studied and considered as an essential part in the inducement, formation and maintenance of granulomas in the long-term.[7,8]

Cutaneous tuberculosis can be acquired from hematogenous or lymphatic dissemination of a pulmonary focus or by direct inoculation. However whenever there is a new accretion of bacilli, the entire immunologic cascade will start again and continue until the formation of granulomas.[10]

## FACTORS INVOLVED IN DISEASE PROGRESSION

The development of clinical manifestations in cutaneous tuberculosis should be understood as the outcome of interactions between the environment, the agent and the host.

**A** - Infected person's cellular immunity state: only 5-10% of people infected with the bacilli will develop tuberculosis. The likely explanation for this is the host's ability to contain infection. In 2008, Gaikwad and Sinha performed a study aiming to demonstrate the individual variation in the immune response against Mtb, with volunteers living in an endemic region, immunized with BCG and presenting Mtb antibodies to confirm prior exposure. As the blood of volunteers was exposed to Mtb, the intensity of T-cell proliferation and levels of INF-γ and antibodies were evaluated. Patients classified as strong responders had high levels of antibodies against Mtb cell membrane, high levels of INF-γ and IL-12 and consequently low replication rates of opsonized bacilli. The reverse was found in the other group, classified as weak responders.[11] Another mechanism involved in natural immunity against Mtb, which possibly varies in intensity, is the apoptosis of infected macrophages when the elimination of mycobacteria is no longer possible. The greater capacity for apoptosis is associated with high levels of prostaglandin E2 and conversely low levels of lipoxin A4.[12]

Analogous to leprosy, in 1994 Sehgal *et al*.[5] attributed a spectral character to cutaneous tuberculosis, based on bacteriological, histopathological and immunological parameters. Some case reports describe the patterns of the predominant cytokines for each clinical form, such as lupus vulgaris and tuberculosis verrucosa cutis, however there are still no comparative studies showing variance in the immune status in different forms of TB.[9,10]

**B** – Infection route: the route of infection, the presence or absence of prior contact with the bacilli plus the individual's natural immune response are all decisive factors in the disease clinical presentation. According to the infection route, cutaneous tuberculo-

sis can be acquired by exogenous or endogenous mechanisms. Exogenous infection results from direct inoculation of bacilli into the skin of susceptible individuals (tuberculous chancre, tuberculosis verrucosa cutis).

Endogenous infection is secondary to a preexisting primary focus and may result from contiguous (orificial tuberculosis, scrofuloderma), hematogenous (acute miliary tuberculosis, tuberculous gumma, lupus vulgaris) or lymphatic dissemination (lupus vulgaris). There is not so far an explanation for what causes this influence.[13]

**C** – Bacilli resistance: initially seen as important, but not essential, this factor has progressively been given more attention, especially with the emergence of multidrug resistant (MDR) strains. There were 630 cases of MDR-TB in Brazil in 2011, defined as resistance to isoniazid and rifampicin with or without resistance to another first-line drug. Recently, with the expansion in resistance, a new definition by the World Health Organization (WHO) has emerged, that of extensively drug-resistant TB (XDR-TB), in which the mycobacteria causing the infection are proven resistant to isoniazid and rifampicin, as well as to fluoroquinolones and at least an injectable second-generation drug.[3]

Mutations arise from environmental pressure. Initially, mycobacteria reduce their metabolism, decrease the replication rate and become at the same time tolerant to the antibiotic present in their milieu. This tolerance may be reversed at first, if treatment is kept for the appropriate period with adequate drug concentration. However, inadequate doses, improper discontinuation of treatment, absence of drug association and strains capable of reducing the multiplication in adverse conditions result in spontaneous mutations and resistance to one or more drugs. For isoniazid alone, about 35 different mutations that indicate resistance are already known, although their detailed description is outside the scope of this article.[14]

**D** - Virulence factors: the concept of virulence for Mtb is different from that used for other bacteria, since it has no antigens, toxins or well-defined surface molecules leading to an increase in its ability to survive or to inactivate host's phagocytes, but it possesses a numerous and complex set of super expressed genes or mutations that result in proteins, enzymes, lipids, etc. involved in the entire life-cycle of Mtb.[15,16]

The complexity of the subject is such, that many authors consider that, at this time, there is no way of totally separating the virulence factors that influence disease progression from those that cause drug resistance, because both are the result of natural mutations occurring whilst bacilli try to survive in adverse conditions.[6,16] One example is the pathway for production and secretion of mycolic acid, which is important both in establishing resistance to antibiotics (isoniazid and ethambutol) and the direct virulence of bacilli (survival capacity), depending on the point at which mutation or deletion occurs.[16]

To clarify this topic as best as possible, we can allocate the factors comprising the major virulence mechanisms into four groups: first, via lipid metabolism (nutrition); second, cell envelope and secretory system proteins (environmental resistance and drug efflux); third, proteins related to signal transduction, which includes the family of protein kinases, proteases, metal carriers, metalloproteases (various functions) and finally, the production of macrophage effector inhibitors (phagosome inhibitors, apoptosis inhibitors, and oxidative stress responses). Furthermore, there are protein families PE / PE_PGRS and regulatory genes of unknown function and not yet assigned to any of these mechanisms.[16]

**E** – Individual's inherent factors (age, sex, race): children, possibly due to their immune immaturity, present higher frequency of scrofuloderma and primary forms. In adults, in addition to the previously mentioned circumstances, factors that lead to immunosuppression such as malnutrition, alcoholism, silicosis, diabetes mellitus, gastrectomy, and immunosuppressive conditions caused by disease or drugs are also important.[5,17]

**F** - Environmental factors (climate, geography): there is a geographical variation, with prevalence of different clinical types in distinct locations. This is supported by epidemiological observations stating that the most common form of disease in Brazil is scrofuloderma, whereas in Europe and Asia it is lupus vulgaris.[18]

## CLINICAL FORMS CLASSIFICATION IN CUTANEOUS TUBERCULOSIS

The clinical appearance of cutaneous tuberculosis is quite varied; inflammatory papules, verrucous plaques, suppurative nodules, chronic ulcers and other lesions can be identified.[19,20] There are several classifications of CTB variants. The most widely used is based on the inoculation mechanism as previously described in the etiopathogenesis section.[13]

Tuberculosis variants can also be classified according to bacterial load on the skin: multibacillary forms are those in which bacilli are easily detected in cutaneous tissue or isolated in exudate; whereas in paucibacillary forms it is difficult to isolate the organisms, with bacilli being sparse or even not visualized in histology. Among multibacillary forms are: tuberculous chancre, scrofuloderma, orificial tuberculosis, acute miliary tuberculosis and metastatic abscess (tuberculous gumma). Paucibacillary forms are less common and include TB verrucosa cutis and lupus vulgaris.[21,22]

There are also tuberculids, a category of skin disorders associated with TB that represents, most likely, immune hypersensitivity reactions to Mtb antigens. This category includes three variants: papulonecrotic tuberculid, *lichen scrofulosorum* and *erythema induratum* of Bazin (Chart 1).[19,20]

We will approach the clinical aspects of each form according to the mode of infection.

**Chart 1:** Cutaneous tuberculosis classification

| |
|---|
| A. Exogenous cutaneous tuberculosis<br>Tuberculous chancre and Tuberculosis verrucosa cutis |
| B. Endogenous cutaneous tuberculosis |
| a) By contiguity or autoinoculation (Scrofuloderma, orificial tuberculosis and some cases of lupus vulgaris) |
| b) By hematogenic dissemination (Lupus vulgaris, tuberculous gumma and acute miliary tuberculosis) |
| C. Tuberculids<br>- Papulonecrotic tuberculid<br>- Lichen scrofulosorum |
| D. Cutaneous tuberculosis secondary to BCG vaccination |

## EXOGENOUS CUTANEOUS TUBERCULOSIS

Exogenous inoculation of Mtb may originate tuberculous chancre and tuberculosis verrucosa cutis.

## TUBERCULOUS CHANCRE

It is a rare form of TB, also called primary TB inoculation chancre, as it develops in individuals not previously sensitized to the mycobacterium, occurring most often in children in endemic areas of low vaccination coverage.[19,23]

Tuberculous chancre develops by direct Mtb inoculation in the skin after a local trauma, often unnoticed by the patient. There are reports of injuries developing after surgical procedures performed with unsterilized materials, and even after tattoos.[24] After 2 to 4 weeks, a firm, painless, reddish-brown, slow-growing papule or nodule arises, which may develop into an ulcer. The ulcer is friable, has a tendency to bleeding and a base with coarse granular surface.[25]

Lesions measure usually 1 cm or less with the face and extremities being the most frequently involved sites. Occasionally the result of lesion growth is a verrucous plaque, or even lesions resembling scrofuloderma or lupus vulgaris. After 3 to 8 weeks from the onset of TB chancre, there is often bacilli dissemination through the lymph and lymph nodes, analogous to what happens in the lungs with Gohn's complex.[21] Regional lymphadenopathy is evident and occasionally lymph node involvement results in rupture through the skin.[23,26]

The evolution of chancre is variable and healing may occur between three and 12 months, leaving atrophic scarring and calcification in regional lymph nodes. However, if anti-tuberculous medications are not implemented, there is potential risk of developing complications such as lupus vulgaris, scrofuloderma or dissemination (acute miliary TB).[23]

## TUBERCULOSIS VERRUCOSA CUTIS (TVC)

TVC, the most common form of exogenous TB, is the result of primary inoculation in previously sensitized individuals who maintain moderate to high immunity against *M. tuberculosis*.[14,20,26] In the past, professionals like anatomists and physicians were prone to this type of cutaneous TB as a result of direct inoculation of the bacillus through injured skin. [21,25] In tropical zones, TVC is seen more often in children on account of the habit of walking barefoot on soil contaminated with tuberculous sputum; ankles and buttocks being the most affected areas in this group.[19,22]

Lesions are usually solitary, painless and predominate in anatomical locations that are prone to traumas, such as fingers and toes (Figures 1 and 2).[20,23,27,28] They start as erythematous papules surrounded by a purplish inflammatory halo that evolve to asymptomatic verrucous plaques, with 1 to 5 cm in diameter.[19] Growth happens through peripheral extension, sometimes accompanied by central atrophy.[22,23] They may rarely ulcerate.[23]

TVC tends to persist for many years if untreated, although spontaneous resolution might also occur.[14,23] Secondary bacterial infection and elephantiasis are possible complications of extensive lesions affecting extremities.[22] Typically there is a favorable response with anti-tuberculosis therapy.[26]

## ENDOGENOUS CUTANEOUS TUBERCULOSIS

Endogenous cutaneous tuberculosis may occur by contiguity, autoinoculation, lymphatic or hematogenic dissemination. Clinical forms usually found are: lupus vulgaris, scrofuloderma, tuberculous gumma, acute miliary tuberculosis and orificial tuberculosis.

## BY CONTINUITY OR AUTOINOCULATION

Clinical manifestations of cutaneous TB such as scrofuloderma, orificial tuberculosis, and lupus vulgaris may arise from this process.

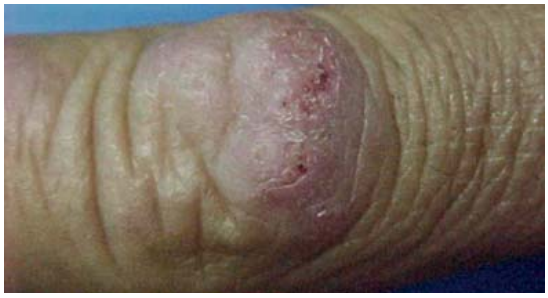

**Figure 1:** Tuberculosis verrucosa cutis

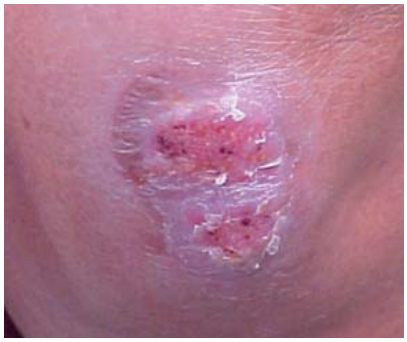

**Figure 2:** Tuberculosis verrucosa cutis

## SCROFULODERMA

Scrofuloderma, also known as *tuberculosis colliquativa cutis*, was the most commonly observed form of CTB before the advent of tuberculostatic drugs and still is the most common form of cutaneous tuberculosis in developing countries such as Brazil and India (particularly in children).[29] It may involve individuals of any age group, however children, teenagers and elders are the most affected ones, because those are the life phases when most immunologic faillures in containing infectious agents occur.[21,26]

It reaches the skin from adjacent structures where infection has developed, such as lymph nodes, bones, joints or testicles (Figures 3 and 4).[22,26] The main sites are cervical lymph nodal chains. Besides these areas, coexistence with pulmonary tuberculosis is frequent.[19] The occurrence of scrofuloderma after BCG vaccination has been rarely reported.[30]

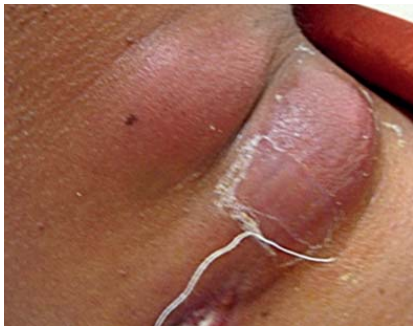

**Figure 3:** Scrofuloderma

**Figure 4:** Scrofuloderma

Lesions may be single or multiple. Intense inflammation leads to formation of painless, cold abscesses that progressively grow, making possible the differential diagnosis with bacterial abscesses, tumor metastasis, histiocytosis and hydroadenitis.[31] As the lesions evolve it is possible to observe purplish ulcerated plaques and latter the appearance of fistulae with draining of caseous material.[22,26] Spontaneous involution may occur leaving keloid scars, retractions and atrophic sequelae.[19] Lupus vulgaris may develop in the scars and next to scrofuloderma areas.[14]

## ORIFICIAL TUBERCULOSIS

Orificial tuberculosis, or *tuberculosis cutis orificialis* often affects middle-aged adults, and seniors who present advanced form of lung, intestinal or genitourinary tuberculosis[32] or severely impaired cellular immunity.[26]

Lesions appear as friable, painful, erythematous-to-yellowish papules and nodules, measuring 1 to 3 cm in diameter, which can lead to painful ulcers with fibrinous bases in the skin near bodily orifices.[20,22,26] Edema and inflammation are evident in perilesional tissue.[23] Affected individuals have a poor prognosis, since there is severe underlying visceral disease. Although there are reports of improvement after initiating therapy, resistance to tuberculostatic treatment is common.[14,26] If the medications are not introduced, lesions progress and contribute to the development of fatal disease.[22]

## BY HEMATOGENIC DISSEMINATION

Hematogenic dissemination from a primary focus of Mtb infection may lead to tuberculous gumma (metastatic tuberculous abscesses), acute miliary TB and lupus vulgaris.

## LUPUS VULGARIS (LV)

It is the most common form of CTB in Europe and India.[27,32] It is a chronic, progressive form of CTB occurring in patients with a high degree of immunity against the bacillus[19,23] being thus a paucibacillary form. For unknown reasons, women are affected 2-3 times more often than men.[14] In addition to the endogenous source, it may develop upon the drainage scar of scrofulodermas or rarely be acquired by exogenous Mtb inoculation.[33]

The clinical findings of lupus vulgaris are varied. Usually there are papules and well-delimited, reddish-brown plaques in facial and cervical areas, which rarely ulcerate.[22] In tropical countries, the development of lesions on the legs and buttocks is common.[26] The plaque grows peripherally, with serpiginous or verrucous borders, often reaching over 10

cm in diameter with central discoloration and atrophy. Diascopy of non-keratotic areas reveals an "apple jelly" aspect. This feature is also seen in other granulomatous diseases such as sarcoidosis and leprosy, and is rarely found in patients with black skin.[22,23] Lesions do not always present in typical forms and there are various descriptions such as nodules, vegetating lesions, ulcerated or tumoriform lesions, and those mimicking diseases such as discoid lupus erythematosus, psoriasis, sporotrichosis, actinomycosis and mycetoma.[34,35]

Untreated, LV lesions persist for years, gradually growing in size up to tens of centimeters and leading to significant aesthetic alterations, with ulcerations and tissue destruction.[19,22,23] The incidence of malignant transformation into squamous cell carcinoma in LV plates ranged from 0.5 to 10.5% and it usually occurs after 25-30 years of untreated disease.[36,37] The development of other malignancies, such as basal cell carcinoma has also been reported.[20]

## TUBERCULOUS GUMMA

Tuberculous gumma, also called metastatic tuberculous abscess, originates from hematogenous spread especially in periods in which there is decreased cellular immunity. Typically, it affects malnourished children and immunocompromised adults, with rare reports in immunocompetent patients.[22,38] Tuberculous abscesses have also been described in individuals with acute miliary TB.[38]

In tuberculous gumma, there are usually few lesions affecting the trunk and extremities, characterized by fluctuating subcutaneous nodules. These may ulcerate and drain caseous secretion. Regional adenopathy is usually not present. Clinically it may resemble scrofuloderma.[23] Patients diagnosed with tuberculous gumma have a poor prognosis because of their compromised immunity. In immunocompetent individuals, abscesses may persist for years without treatment, and eventually resolve spontaneously.[23]

## ACUTE MILIARY TUBERCULOSIS

It is a rare and severe form of tuberculosis that develops in individuals with impaired cellular immunity and children.[22] Individuals are systemically compromised with fever, anorexia, asthenia, and weight loss.[26] Clinically, there is a wide spectrum of cutaneous lesions such as erythema, erythematous-whitish or erythematous-purplish papules, upon which small vesicles appears, subsequently breaking down and resulting in umbilication and crust formation. They tend to regress in 1 to 4 weeks, leaving depressed and hypochromic scars.[22]

As acute miliary TB is usually found in cases of severe immunosuppression, almost always the tuberculin skin test is negative, demonstrating anergy. Despite being a rare form of CTB, the number of cases has been increasing, mainly due to co-infection with HIV when CD4 count is below 100 cells/uL.[39]

## TUBERCULIDS

### PAPULONECROTIC TUBERCULID

It is the most common type of tuberculid often observed in children and young people. It presents as a symmetric and recurrent eruption of erythematous-purplish papules that become pustular and necrotic.[22,26] Lesions affect the face, ears, extensor areas of extremities, trunk and buttocks, associated or not with lymphadenitis (Figure 5). Constitutional symptoms such as fever and asthenia may precede cutaneous manifestations.[14,18]

Eruption may resolve spontaneously after weeks to months, resulting in formation of depressed varioliform scars.[22,23,40] Recurrences are common without tuberculostatic treatment, however when drugs are introduced, it is possible to observe clinical improvement in a few days or weeks.[41]

## LICHEN SCROFULOSORUM

It is a rare tuberculid that most often affects children and young adults with lymph node or bone underlying disease.[22,23,26] There are reports on the onset of *lichen scrofulosorum* after BCG vaccination and in patients infected with *M. avium-intracellulare*.[42,43]

It is characterized by plaques consisting of grouped, asymptomatic, indurated, yellow-red to brown-red follicular or perifollicular papules with 1-5 mm, most commonly observed in the trunks of affected individuals.[19,22,23,26]

Antituberculosis treatment promotes complete resolution of the lesions in weeks.[23,26] Without medication, this dermatosis can regress without leaving scars, after months or years.[14]

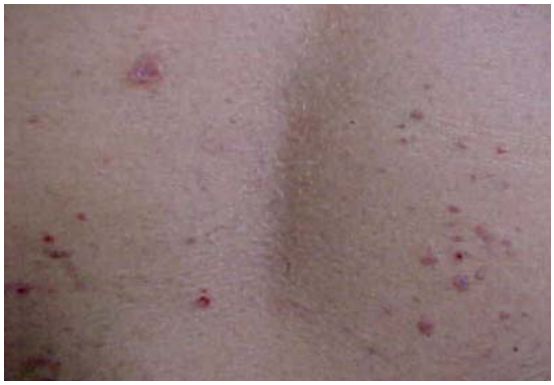

**Figure 5:** Papulonecrotic tuberculid

## ERYTHEMA INDURATUM OF BAZIN

*Erythema Induratum* of Bazin (EIB) is a granulomatous lobular panniculitis associated with tuberculosis, which affects the lower limbs of young and middle-aged women. It appears as slightly painful, erythematous-purplish subcutaneous nodules that persist for several weeks and are usually distributed in the posterior surface of legs and thighs.[44] Nodules may reach a few centimeters in diameter and often rupture, forming deep ulcers that drain secretions.[44,45] Lesions may regress, even without treatment, after weeks to months, leaving depressed post-inflammatory hyperpigmentation and scarring, however recurrences may occur in flares every 3-4 months.

The main clinical differential diagnosis is with *erythema nodosum* (EN), which can be triggered by a variety of infectious and non-infectious agents, and may occur in association with systemic diseases such as sarcoidosis. Histologically, they are different because EN is characterized by septal panniculitis without vasculitis.[14]

One should investigate the possibility of TB through additional tests and when the disease is evidenced, anti-TB treatment is recommended. If the association with TB is not detected, the term "nodular vasculitis" is used to refer to the manifestation of clinically and histologically similar panniculitis.[45] In this scenario, Hepatitis C should be investigated, as it is a potential trigger of nodular vasculitis.[44]

## CUTANEOUS TUBERCULOSIS SECONDARY TO BCG VACCINATION

BCG vaccine is a live virus vaccine derived from attenuated strains of *M. bovis*. It has been widely used to prevent serious tuberculosis infections, such as meningoencephalitis and acute miliary tuberculosis. However, it may cause skin complications like tuberculids, lupus vulgaris, scrofuloderma and even outbreaks of tuberculosis in other organs, and nonspecific reactions, such as fever, local inflammation, abscesses, and lymphadenitis.[30,46] ❑

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*MAILING ADDRESS:*
*Josemir Belo dos Santos*
*Clínica Dermatológica do Hospital das Clínicas da Universidade Federal de Pernambuco (HC/UFPE)*
*Av. Prof. Morais Rego, 1235*
*Cidade Universitária*
*50670-901 - Recife - PE*
*Brazil*
*E-mail: josemirbelo@uol.com.br*

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# QUESTIONS

**1. Choose the correct alternative:**
- **a)** Cutaneous tuberculosis exhibits variable clinical manifestations and only occurs in immunocompromised individuals
- **b)** Cutaneous tuberculosis exhibits variable clinical manifestations, although the infection always occurs by inoculation, and only in immunocompromised individuals.
- **c)** Cutaneous tuberculosis has characteristic clinical manifestations in immunocompromised individuals.
- **d)** Cutaneous tuberculosis exhibits variable clinical manifestations, depending on the mode of infection and the immune status of the host.

**2. Mark the false alternative:**
- **a)** Cutaneous tuberculosis is the result of acute skin infection by Mycobacterium tuberculosis, M. bovis or bacillus Calmette-Guerin.
- **b)** Extrapulmonary tuberculosis constitutes about 10% of all cases, and cutaneous tuberculosis represents a small portion of these, around 1%.
- **c)** The improvement in hygiene and the use of BCG were some of the factors responsible for the decline in tuberculosis during the nineteenth and early twentieth centuries.
- **d)** Currently, cutaneous tuberculosis is in resurgence.

**3. Mark the alternative that is not correlated with the re-emergence of cutaneous tuberculosis:**
- **a)** Increase in HIV positive population
- **b)** Infection by S. aureus MRSA
- **c)** Multidrug-resistant pulmonary TB
- **d)** Individuals in treatment with immunosuppressive chemotherapy

**4. Regarding the etiological agent of cutaneous tuberculosis, the following statement is false:**
- **a)** Cutaneous tuberculosis is mainly caused by Mycobacterium tuberculosis (Mtb), although occasionally M. bovis and its attenuated strain may be responsible for some cases.
- **b)** Tuberculosis bacillus is recognized to be an AFB (acid-fast bacilli) because it is stained red by fuchsin and does not discolor by the actions of alcohol and acid.
- **c)** Morphologically Mtb is a straight or slightly bent, motionless, non-sporulated, unencapsulated bacillus, measuring from 1 to 10μm long by 0.2 to 0.6μm wide
- **d)** The high lipid concentration on their cell walls makes them fragile, with little resistance to chemical and physical agents.

**5. Regarding the immunopathogenesis of cutaneous tuberculosis, the following is false:**
- **a)** Alveolar macrophages are the first-line of defense against Mtb, internalizing the bacillus and initiating a series of actions with bactericidal intent;
- **b)** The intensity of IFN-γ has significance as an important marker of the effectiveness of immune response against M. tuberculosis;
- **c)** The type of response Th1 or Th2 has an influence on the host's immune response.
- **d)** The stimulation of Th17 cells pathway has been considered an essential part in the induction and maintenance of granuloma formation in the long-term.

**6. Regarding cutaneous tuberculosis, it is incorrect to state that:**
- **a)** It has become a common form of tuberculosis manifestation in the last decade, accounting for 5-10% of all tuberculosis cases in humans.
- **b)** The entry route of the bacteria on the skin, the patient's immune status and the presence or absence of prior host sensitization to M.tuberculosis may influence the clinical presentation of cutaneous tuberculosis.
- **c)** Tuberculous chancre is considered a multibacillary form of tuberculosis, with bacilli being easily detected in cutaneous tissue.
- **d)** Lupus vulgaris may be the result of the dissemination of bacilli from endogenous tuberculosis foci to the skin via self-inoculation, contiguity or hematogenous dissemination.

**7. Examples of exogenous cutaneous tuberculosis are:**
- **a)** Erythema Induratum of Bazin and scrofuloderma
- **b)** Tuberculosis verrucosa cutis and tuberculous chancre
- **c)** Papulonecrotic tuberculid and tuberculous gumma
- **d)** Acute miliary tuberculosis and lichen scrofulosorum

**8. Examples of endogenous cutaneous tuberculosis are:**
- **a)** Lupus vulgaris and tuberculous chancre
- **b)** Acute miliary tuberculosis and tuberculosis verrucosa cutis
- **c)** Tuberculosis verrucosa cutis and scrofuloderma
- **d)** Scrofuloderma and tuberculous gumma

**9. Regarding tuberculous chancre – a form of cutaneous tuberculosis by exogenous inoculation, it can be stated that:**
- **a)** It occurs in individuals previously sensitized by M. tuberculosis.
- **b)** Surgical procedures and tattoos can be ports of entry of bacilli in the skin, in which papules or rapidly growing nodules appear after 2 to 4 days.
- **c)** It usually manifests as a friable ulcer with tendency to bleed and a base with coarse granular surface.
- **d)** Face and trunk are the most frequently sites affected.

**10. Tuberculosis verrucosa cutis is the most common form of exogenous tuberculosis. Which of the following characteristics does not corroborate the suspicion for this clinical form?**
- **a)** Solitary, painless lesions
- **b)** Lesions in the extremities, persisting for years
- **c)** Low intensity of the host's immune response
- **d)** Good therapeutic response to the introduction of anti-tuberculous medications

**11. Regarding scrofuloderma, one cannot state that:**
- **a)** It is the most common clinical form of cutaneous tuberculosis in developing countries like Brazil.
- **b)** The coexistence with pulmonary tuberculosis is infrequent.
- **c)** There is the formation of painless, cold abscesses, that progressively grow and rupture skin, reaching fistulization with discharge of purulent secretion and caseous material.
- **d)** Cervical lymph node chains are the main site of underlying infection, with disease dissemination to the skin of face and neck.

**12. An elderly patient is in the hospital to investigate erythematous-yellowish papular and nodular lesions in anal and perianal mucosal areas, besides some painful ulcers with 1-3 cm in diameter. Orificial tuberculosis was confirmed during diagnostic investigation. Is it correct to inform this patient's family that:**
- **a)** Drugs for tuberculosis need not be introduced, since this clinical form regresses spontaneously.
- **b)** Prognosis tends not to be favorable because of the existence of underlying visceral disease.
- **c)** In most cases there are reports of improvement after initiating therapy, and resistance to antituberculosis treatment is very rare.

**d)** This patient has a clinical manifestation of recent and localized cutaneous tuberculosis infection; specific treatment against M. tuberculosis should be introduced.

**13. Regarding lupus vulgaris, it can be stated that:**
- **a)** It can be acquired either from endogenous or exogenous infection by M. tuberculosis and even by BCG inoculation, especially in patients with PPD anergy.
- **b)** It is characterized most commonly by poorly delimited, reddish-brown papules and plaques on extremities that rarely ulcerate.
- **c)** The plaque grows peripherally with central atrophy and discoloration, often reaching over 10 cm in diameter, and there is a tendency to spontaneous regression and cure months after the onset of lesions.
- **d)** There are descriptions of lesions with several presentations from plaques, papules and nodules to vegetative, tumoriform and ulcerated lesions, mimicking diseases such as discoid lupus erythematosus, psoriasis, sporotrichosis, actinomycosis and mycetoma.

**14. Regarding possible complications of cutaneous tuberculosis, one cannot state that:**
- **a)** Lupus vulgaris lesions can be sites of squamous cell carcinoma after decades of disease.
- **b)** Secondary bacterial infection and elephantiasis are complications of tuberculous chancre that affect the face.
- **c)** Scrofuloderma can develop into keloid scars, retractions and atrophic sequelae.
- **d)** Fatal outcome can occur in immunocompromised patients with miliary tuberculosis.

**15. Regarding tuberculous gumma it is not correct to say that:**
- **a)** It affects mainly immunocompromised adults and malnourished children.
- **b)** It is characterized by fluctuating nodules that may ulcerate and discharge serohematic secretion.
- **c)** It usually affects the trunk and extremities.
- **d)** Although it is characterized by few skin lesions, it has a poor prognosis.

**16. Regarding tuberculids it is incorrect to state that:**
- **a)** Papulonecrotic tuberculid is a symmetric and recurrent eruption of erythematous-purplish papules that become pustular and necrotic and evolve into depressed varioliform scars.
- **b)** In cases of papulonecrotic tuberculid, tuberculostatic treatment provides clinical improvement in a few days or weeks.
- **c)** Lichen scrofulosorum is characterized by plaques composed of asymptomatic, indurated, grouped perifollicular or follicular papules, with 1 to 5 mm, most frequently observed in the trunk.
- **d)** Erythema induratum of Bazin is a septal panniculitis associated with tuberculosis with detectable extracutaneous clinical infection.

**17. The following characteristics are common to tuberculids except:**
- **a)** Tendency to spontaneous involution.
- **b)** Failure to detect M. tuberculosis in cultures of affected tissues.
- **c)** Histopathology of cutaneous lesion with granulomatous inflammation.
- **d)** Common resolution of cutaneous lesions with the initiation of tuberculosis treatment.

**18. The link between immunology and clinical presentation of cutaneous tuberculosis has been gaining attention. In this context it is true to affirm that:**
- **a)** The frequency of clinical forms distribution is similar in all countries.
- **b)** Paucibacillary forms are rare and include lupus vulgaris and lichen scrofulosorum.
- **c)** The clinical forms of tuberculosis can be disseminated in a spectral manner, reflecting the host-agent relationship.
- **d)** The form of inoculation has little or no influence on the clinical presentation.

**19. As it happened in leprosy, a spectral behavior was attributed to cutaneous tuberculosis. In this context it is true to affirm that:**
- **a)** Patients able to produce humoral immune response against M. tuberculosis represent the pole of resistance to cutaneous tuberculosis;
- **b)** Patients progressing to tuberculosis verrucosa cutis probably would present an exacerbation of the humoral response;
- **c)** Scrofuloderma represents those patients with immunological failure in the containment of infectious agents;
- **d)** Despite the high correlation of immune profile and clinical presentation, no correspondence between immune profile and histopathology of cutaneous tuberculosis lesion was observed.

**20. Regarding the immunopathogenesis of cutaneous tuberculoses, check the wrong answer:**
- **a)** The tuberculosis' bacillus is an aerobic pathogen that has approximately 4000 genes, 200 of which are involved in lipid metabolism;
- **b)** Lipids are the main energy source of Mtb;
- **c)** Mycobacteria survive and divide within lymphocytes;
- **d)** The presence of lymphokines such as TNF-α, IL-1 and IL-6 stimulates macrophages to differentiate into epithelioid cells and giant cells.

**Answer key**

Incontinentia pigmenti. An Bras Dermatol. 2014;89(1):26-36.

| | | | |
|---|---|---|---|
| 1) C | 6) A | 11) A | 16) C |
| 2) C | 7) C | 12) B | 17) B |
| 3) A | 8) B | 13) C | 18) B |
| 4) B | 9) B | 14) D | 19) C |
| 5) D | 10) A | 15) A | 20) D |

**Papers**

Information for all members: The EMC-D questionnaire is now available at the homepage of the Brazilian Annals of Dermatology: www.anaisdedermatologia.org.br. The deadline for completing the questionnaire is 30 days from the date of online publication.