

# CUTANEOUS TUBERCULOSIS: CLINICOPATHOLOGICAL SPECTRUM AND DIAGNOSTIC CHALLENGES

## Abstract

Tuberculosis causes morbidity in millions of people per year and is one of the top 10 causes of mortality worldwide. Though pulmonary TB is the commonest form, extra-pulmonary Tuberculosis (EPTB) carries its fair share of morbidity and mortality. The various extra-pulmonary sites are lymph nodes, intestines, bone, joints, meninges, skin, genitourinary tract. Cutaneous tuberculosis (CTB), though accounts for only 1–2% of extra-pulmonary TB (EPTB) cases, is an important cause of mortality and morbidity in developing countries because of high prevalence and huge population. The various types of CTB include Tuberculosis verrucosa cutis (TBVC), Tuberculous chancre, Lupus vulgaris, Scrofuloderma, Orificial Tuberculosis, Tuberculous gumma and Acute miliary Tuberculosis. CTB follows a wide immunological spectrum ranging from low immunity with high bacillary load to high immunity with low bacillary load. The diagnostic techniques like Histopathology, AFB staining, TB Culture and molecular PCR testing remains the mainstay for diagnosis importance of whom may vary type to type basis of CTB.

**Keywords:** Cutaneous Tuberculosis, Clinicopathological Spectrum, Diagnostic Challenges, CTB, Pulmonary TB.

## Authors

### **Dr. Abhishek Yadav**

Assistant Professor  
Department of Microbiology  
North Delhi Municipal Corporation  
Medical College  
Delhi, India.

### **Dr. C. P. Baveja**

Retired Professor of Excellence  
Department of Microbiology  
Maulana Azad Medical College  
Delhi, India.

### **Dr. Tanisha Bharara**

Assistant Professor  
Department of Microbiology  
North Delhi Municipal Corporation  
Medical College  
Delhi, India.

### **Dr. Vasim Ahmad**

Microbiologist  
Rajan Babu Institute of Pulmonary  
Medicine and Tuberculosis  
Delhi, India.

## I. INTRODUCTION

In 2021, eight countries captured more than two thirds of global tuberculosis case share namely India (28%) Indonesia (9.2%), China (7.4%), Philippines (7.0%), Pakistan (5.8%), Nigeria (4.4%), Bangladesh (3.6%) and Democratic Republic of the Congo (2.9%) with India dominating all<sup>1</sup>. Tuberculosis causes morbidity in millions of people per year and is one of the top 10 causes of mortality worldwide, but ranks above HIV/AIDS as one of the leading causes of infectious disease mortality despite the fact that, with a timely diagnosis and treatment, TB disease can be cured in most cases<sup>2</sup>.

Though pulmonary TB is the commonest form, extra-pulmonary Tuberculosis (EPTB) carries its fair share of morbidity and mortality. The various extra-pulmonary sites are lymph nodes, intestines, bone, joints, meninges, skin, genitourinary tract<sup>3</sup>.

The incidence of cutaneous tuberculosis (CTB) is around 0.7% and median duration of disease is 1.25 years<sup>4,5</sup>. The diagnosis of CTB is a daunting task. It is mainly diagnosed by its clinical presentation in combination with substantial histopathological findings. To further make things more complicated the clinical manifestations vary from nodules, warts, and papulonecrotic lesions, to abscesses and ulceration<sup>6</sup>. The clinical presentation is determined by factors such as route of infection and cellular immune status of the host<sup>7</sup>. On histopathology, apart from CTB: epithelioid cell granulomas may also be seen in conditions such as leprosy, sarcoidosis, deep fungal infection, etc. which might clinically also resemble CTB thus making this further more troublesome to diagnose.

Although CTB may remain localized to the skin alone, but frequently involves regional lymph nodes. It might also present as disseminated form with generalized lymphadenopathy and/or involvement of other organs/organ systems<sup>8</sup>. The direct demonstration of *M. tuberculosis* in case of CTB has very low sensitivity because of most lesions being paucibacillary<sup>9</sup>. Culture of *M. tuberculosis* is highly specific but is usually tedious, time consuming and unrewarding.

TB must be included in differential diagnoses of cutaneous infections in developing countries like India due to the high prevalence in these regions. The conclusive results generally cannot be achieved with routine microscopy/culture methods; however, molecular diagnostic methods are considered more sensitive<sup>10</sup> like Polymerase chain reaction (PCR) for IS6110, a conserved sequence<sup>11</sup>.

It is currently a worldwide threat with 9–10 million new active disease cases being reported every year<sup>1</sup>. Cutaneous tuberculosis (CTB), though accounts for only 1–2% of extra-pulmonary TB (EPTB) cases<sup>12</sup>, is an important cause of mortality and morbidity in developing countries because of high prevalence and huge population. It may be acquired through both exogenous inoculation methods or endogenous spread of existing foci<sup>13</sup>.

## II. HISTORY OF TUBERCULOSIS

Greco-Roman civilization named the disease as “*phthisis*” which meant consumption. In the west, the clinical features, infectivity of TB were known before 1000 BC. A team from the University of Tübingen believes that humans acquired TB in Africa about more than

5,000 years ago<sup>14</sup>. Their domestic animals, such as goats and cows then contracted it from them. Seals acquired it when coming up on African beaches during breeding season, and then carried it across the Atlantic. In addition, TB spread via human to human transmission on the trade routes of the old World.

### III. ETIOLOGICAL AGENT

The classification of *M. tuberculosis* starts from class Schizomycetes, with order Actinomycetales, belonging to family Mycobacteriaceae and genus *Mycobacterium*. Robert Koch first discovered it on March 24, 1882 as an aerobic, nonencapsulated, nonmotile, nonspore-forming bacillus that prefers growth in tissues with high oxygen content. It is an obligate intracellular pathogen that infects human beings as principal hosts. It has a long growth period and doubling time (18 - 48 hours). These bacilli resist decolorisation when treated with acid-alcohol i.e., they stain red by Carbol fuchsin and will not discolour by the actions of specific concentration of alcohol and acid for specific amount of time, hence named AFB – Acid-Fast Bacilli<sup>15,16,17</sup>.

A very slow rate of cell division and the ability to circumvent host immune responses by the bacteria results in persistence and latency. These two properties mandate the need for prolonged drug therapy in patients with established disease, and prophylactic chemotherapy in susceptible population, most commonly household contacts of active disease. *M. bovis* is a zoonotic disease that usually affects tonsils, lymph nodes and intestine. It may rarely be the causative agent of the cutaneous TB. When lung is involved, *M. bovis* is not easily transmitted and therefore, there is a tendency for it to vanish<sup>18</sup>.

The probability of developing active form of clinical TB after inhalation of *M. tuberculosis* containing aerosol from an infectious patient has an estimated lifetime risk of about 10%, of which risk is highest within first few years of the infection. Most infected immunocompetent individuals either eliminate *M. tuberculosis* or develop latent infection. Latent TB, a hallmark of mycobacterial infection in immunocompetent individuals is characterized by persistence of bacilli in the host's system, with suspended ability to replicate or cause tissue damage and/or clinical symptoms. The clinical presentation of tubercular infection progressing to full blown disease depends on the relationship of mycobacterial virulence with host immune response.

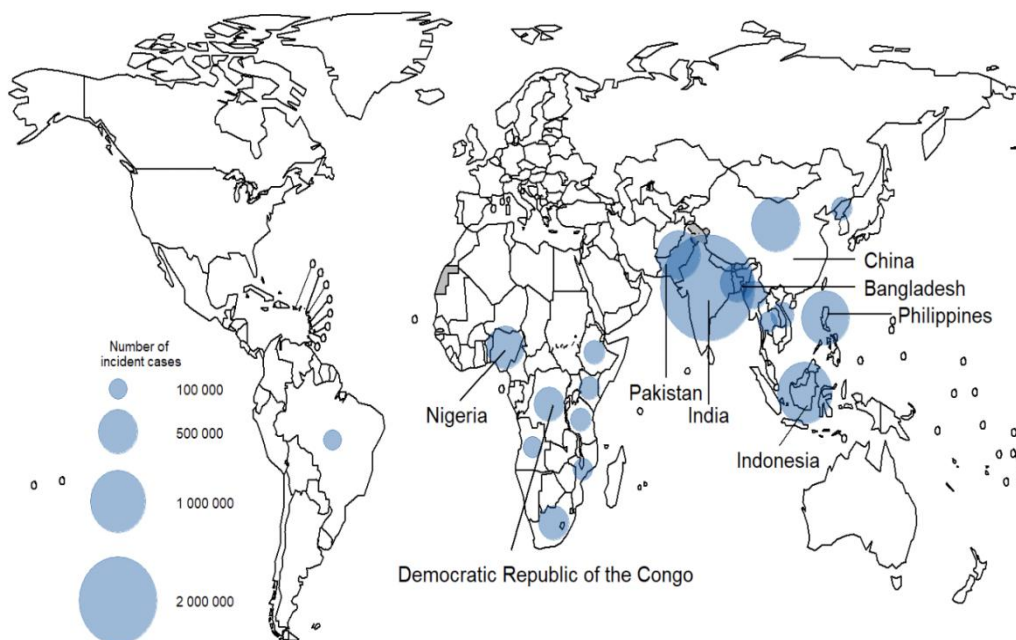
### IV. MODE OF TRANSMISSION – EXOGENOUS V/S ENDOGENOUS CTB

CTB may be acquired exogenously as well as endogenously. Exogenous infection can happen from direct inoculation of tubercle bacilli from infected individual onto the skin of susceptible individuals, leading to tubercular chancre (if poor host immunity) or tuberculosis verrucosa cutis (TBVC) (if good host immunity). Endogenous infection occurs from migration of a pre-existing underlying primary focus. It may present as scrofuloderma (SFD) or orificial TB resulting from locoregional spread from a contiguously infected site, most commonly an infected lymph node. Haematogenous or lymphatic dissemination of a primary systemic focus results in occurrence of lupus Vulgaris (LV), tuberculous gumma or miliary TB. Tuberculids, a separate class of CTB occurs in an individual with concurrent TB elsewhere, as an immune hypersensitivity reaction to *M. tuberculosis* antigens.

Although Bacillus Calmette–Guerin (BCG) is generally safe vaccine, however well-known skin complications are local hypersensitivity reactions, fixed drug eruption, cutaneous granulomas, and Cutaneous Tuberculosis (CTB). The interval between vaccination and the development of skin complications may range to years, with an median duration of 1 year<sup>19,20</sup>.

## V. EPIDEMIOLOGY

In 2021, an estimated 1.4 million TB deaths reported among HIV-negative and 1.8 lac among HIV-positive, totalling to 1.6 million; compared to 1.5 million in 2020. In 2021, 82% of global TB deaths among HIV-negative occurred in the WHO African and South-East Asia regions (SEAR) out of which India accounted for 36% of this. The African and SEAR accounted for 82% of the combined total of TB deaths; India accounted for 32% of this.<sup>2</sup>



**Figure 1:** Tuberculosis incidence rates around the world - image by WHO 2021  
<https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022/tb-disease-burden/2-1-tb-incidence#:~:text=An%20estimated%20global%20total%20of,among%20people%20living%20with%20HIV%2>

Globally, the case fatality ratio (CFR) for TB was 16% in 2016. Between 2000 and 2016, TB treatment saved an estimated 44 million deaths among HIV–negative and 9 million deaths among HIV–positive in support with anti–retroviral therapy (ART).

Pulmonary TB has conventionally been the most common form in children. During the last few years, EPTB cases especially tuberculous lymphadenitis have surpassed cases of pulmonary TB in children<sup>21</sup>.

- 1. Epidemiology of Cutaneous Tuberculosis:** CTB is a less common clinical form of TB which accounts for approximately 1–2% of the total number of EPTB cases but significantly contributing to morbidity<sup>22,23</sup>. Global resurgence of CTB is in line with the increasing pulmonary TB incidence and emergence of multidrug resistance (MDR)<sup>24</sup>. The prevalence of CTB among Indian dermatology outpatients has ranged from 0.1–0.9% over the last few decades<sup>8,12,23</sup>. Kumar et al reported 280 patients suffering from CTB of the total 2,67,420 patients from a tertiary care hospital in India; giving a prevalence of 0.1% among dermatology patients<sup>23</sup>.
- 2. Epidemiology of Childhood Cutaneous Tuberculosis:** Childhood CTB is mostly studied from developing countries and the reported prevalence varies a lot<sup>25</sup>. It has ranged from 82% in Pakistan, 24.3% in Ethiopia, 50% in Hong Kong with a downward trend over time of all CTB cases<sup>6,26</sup>. In India, the prevalence has ranged from 18% to 54%, out of which state wise distribution being 18.7% in Chandigarh, 20.4% in Varanasi, 24.41% in Chennai and 31.7%-53.9% in Delhi<sup>7,8,25,27,28,29</sup>. CTB is common in children aged 10 – 14 years, although no age group is resistant. A significant gender predilection is not apparent. The clinical spectrum of CTB in children is comparable to that in adults, except for a higher likelihood of disseminated and systemic involvement<sup>21</sup>. Childhood CTB has been often reported to develop following BCG vaccination<sup>30</sup>.

While lupus vulgaris (LV) remains the commonest form of CTB seen in most countries, tuberculids especially lichen scrofulosorum (LS), have recently emerged as the commonest variant in many regions like Hong Kong<sup>6</sup>. Tuberculids are also rapidly becoming one of the most common manifestations of CTB in India. Scrofuloderma (SFD), once reported to be the commonest form in certain populations (e.g., in mexicans), is relatively less frequently encountered now<sup>12</sup>.

## VI. IMMUNOLOGY IN CUTANEOUS TUBERCULOSIS

Just as in leprosy and pulmonary TB, a varied immunological spectrum is seen in CTB ranging from higher cell-mediated immunity (CMI) pole in LV, with active cellular immunity and normal levels of immunoglobulins, to SFD and cutaneous miliary TB, with relatively less active CMI and high humoral response (high levels of immunoglobulins)<sup>31</sup>. Immunosuppression from any reason represents the main driving force for active disease development of the disease<sup>32</sup>.

**Table 1: Types of Cutaneous Tuberculosis (CTB) tabulated on the basis of their properties and diagnostic interpretations.**

	Exogenous Cutaneous TB		Endogenous Cutaneous TB				
	Tuberculosis Verrucosa Cutis (TBVC)	Tuberculous Chancre	Lupus Vulgaris	Scrofuloderma	Orificial TB	Tuberculous Gumma	Acute Miliary TB
Prevalence	Common	Rare	Most common form in adults, 2 <sup>nd</sup> most common in children	Most common form in children	Relatively rare	Rare	Rare and severe
Mode of Infection	Inoculation	Inoculation/trauma	Hematogenous/Lymphatic spread	Contiguous spread from underlying focus	Self-inoculation	Hematogenous spread	Hematogenous spread
Prior sensitisation	Present	Absent	-	-	-	-	-
Immunity against MTB	Moderate – High	Initially none	Moderate	Weak	Immuno-compromised	Immuno-compromised	Poor immune status
Location	Foot, buttocks	Local trauma	Head and Neck	Skin over cervical lymph nodes	Mucocutaneous junctions of orifices	Single multiple lesions on limbs	Generalised
PPD	Strongly positive	Initially negative	Positive	Positive	Negative	Negative	Negative
HPE General	Epidermal hypertrophic changes: pseudo epitheliomatous hyperplasia	Acute neutrophilic inflammation	Typical Epithelioid granulomas + Langhans Giant cell without caseous necrosis	Non Specific ill-formed granulomas with intense caseous necrosis	Necrosis and ulceration	Widespread caseation necrosis	Necrosis and ulceration

Tuberculoid Granulomas	Sparse	Granulomas +	Granulomas +++++	Granulomas +	Granulomas ++	Granulomas ++	Granulomas ++
Bacillary load	Paucibacillary	-	Paucibacillary	Multibacillary	Multibacillary	Multibacillary	Multibacillary
AFB	Rarely detected	-	Rarely detected	Detected	Detected	Detected	Detected
Course	Slow	Chancre heals within 3-12 months	Deep tissue destruction	May heal spontaneously over months-years	Resistant to ATT	Widespread involvement	Poor prognosis
Complication	Elephantiasis, Secondary bacterial infection	LV, Scrofuloderma or miliary TB	Small cell carcinoma	Scars	Fatal	-	-

## VII. CLASSIFICATION OF CUTANEOUS TUBERCULOSIS

### 1. Exogenous CTB

#### Tuberculosis Verrucosa Cutis (TBVC):

- **Pathogenesis:** TBVC is the most common form of inoculation CTB. It occurs as a result of primary inoculation in immunocompetent individuals who are previously sensitized to *M. tuberculosis*. In tropical zones, TBVC often occurs over the foot and buttocks of children, on account of their habit of walking/sitting naked on sputum contaminated soil<sup>33,34</sup>. Extremities and other trauma prone sites are typically involved. Occupational exposure due to self-inoculation possibilities in cases like dentist treating the mouth of a pulmonary TB patient or a butcher handling *M. bovis* contaminated meat. Purified Protein Derivative (PPD) test is strongly positive in this case<sup>35,36,37</sup>.
- **Clinical Features:** Lesions are usually solitary and painless verrucous papules or plaques, with fissures/clefts that may exude pus and, often, erythema or purplish inflammatory halo<sup>25,38</sup>. Peripheral extension results in gradual expansion of the lesion that may lead to a serpentine outline with involution at the center. Sometimes extensive form of the disease may result in limb deformities. Lymphadenopathy is less common when compared to SFD and LV.
- **Laboratory Diagnosis:** On histology, it shows striking epidermal hypertrophic changes like pseudo epitheliomatous hyperplasia, the presence of acute neutrophilic abscess formation and sparse tuberculoid granulomas<sup>7</sup>. TBVC is a paucibacillary form of CTB, with AFB being rarely detected<sup>35,39</sup>.
- **Course:** Without treatment, extension of CTB is slow and the lesions persist indefinitely, spontaneous resolution occurs rarely<sup>40</sup>. Complications like secondary bacterial infection and elephantiasis of extensive lesions affecting extremities<sup>41</sup>.



**Figure 2:** Tuberculosis verrucosa cutis - image by Rao AG via <https://ijdv1.com/scrofuloderma-associated-with-tuberculosis-verrucosa-cutis/>



### **Tuberculous Chancre (Primary inoculation tuberculosis):**

- **Pathogenesis:** It is rare form of inoculation CTB that develops in adults without previous sensitization to the bacillus<sup>21</sup>. It is rare in children, though frequent in unvaccinated having contact with pulmonary TB patients<sup>35,42</sup>. Inoculation occurs during local trauma, which may be trivial (often unnoticed), may occur during tattooing, ritual circumcision or ear-piercing, or from exposure to unsterilized material during surgical procedures<sup>38,43</sup>.
- **Clinical features:** After 2–4 weeks of inoculation, a firm more than 1 cm sized painless, reddish–brown papule or nodule arises, which evolves into a shallow friable ulcer with undermined bluish margins and a coarse granular base. It is typically painless but tends to bleed. Trauma prone sites like face, extremities are most frequently involved. Lymphatic dissemination occurs resulting in regional lymphadenopathy which may break to present as a discharging sinus<sup>39,40</sup>.
- **Laboratory diagnosis:** On histopathology, early changes show acute neutrophilic inflammation. After 3–6 weeks, caseous granulomas develop and bacilli begin to disappear.
- **Course:** The chancre tends to heal with atrophic scarring between 3 and 12 months. Spontaneous regression may occur along with scarring and calcification at the level of regional lymph nodes or the patient may develop LV<sup>17</sup>.

PPD initially being negative might later become positive as the disease progresses (usually post 15 days)<sup>17</sup>. However, ATT is strongly recommended, since untreated chancre may become complicated with development of LV or SFD or may lead to dissemination resulting in acute miliary TB.



**Figure 3:** Tuberculous chancre – image by Mariano A  
“<https://www.sciencedirect.com/science/article/abs/pii/S0190962200762189>”

## 2. Endogenous CTB

### Lupus Vulgaris (LV):

- **Pathogenesis:** LV is the commonest CTB in adults, and 2<sup>nd</sup> common type after Scrofuloderma in children<sup>25</sup>. LV is a chronic form of CTB that occurs in immunocompetent previously sensitised individuals. Women are more commonly affected. Although the most common mode of infection is hematogenous or lymphatic dissemination from an endogenous source, it may also develop from direct inoculation, at site of BCG vaccination, or over the drainage scar of SFD<sup>30,44</sup>. The most common sites are the head and neck (disseminating disease), and lower limb and gluteal region (secondary to inoculation).
- **Clinical Features:** LV is highly variable with diverse morphology in the lesions. Typical lesions (also called “classical plaque”) consist of papules and well-defined reddish plaques. The plaque expands with serpentine borders, reaching a diameter of over 10 cm with central discolouration. Presence of involution and scarring in one area and simultaneous progression in another area of the lesion resulting in a geographic or gyrate appearance is characteristic of classical LV<sup>21,25</sup>. Diascopy of the lesion has classically been described to reveal soft reddish-brown “apple jelly” nodules that represent the micro-granulomatous papules that combine to form plaques of LV. However, the ‘apple jelly’ appearance is not specific for LV; it may be seen in other granulomatous diseases<sup>34,40</sup>. Other morphological variants of LV include hypertrophic, ulcerative and mutilating, vegetative and tumour like, atrophic and planar. Systemic involvement in LV is less compared to SFD<sup>25</sup>. Systemic tubercular foci have been reported in the lymph nodes, lungs, and liver. LV may also present with nodules, psoriasiform lesions, vegetating lesions, sporotrichoid lesions, kissing lesions around the gluteal cleft<sup>12,21,25,45,46</sup>.
- **Laboratory Diagnosis:** Histopathology of LV lesions shows typical epithelioid granulomas with lymphocytes and langhans giant cells in most of the cases<sup>7,8,23</sup>. The hypertrophic form also shows epidermal hyperkeratosis, acanthosis and papillomatosis. Necrosis is absent and fibrosis occurs following healing. AFB is scanty and difficult to diagnose. Thus, LV is considered a paucibacillary form of CTB.

The use of dermatoscopy in the diagnosis has been recently suggested, in which linear telangiectasias seen on a yellow-golden background and white streaks. Although it is non-specific, but it may be helpful in combination to other findings<sup>47</sup>.

- **Course:** Untreated LV lesions may grow to become gigantic and often lead to deep tissue destruction with significant aesthetic alterations<sup>33,34,40</sup>. Malignant transformation into squamous cell carcinoma, due to untreated LV for long term, has ranged from 0.5–10.5%<sup>48,49</sup>.



**Figure 4:** Lupus Vulgaris- Image by Thomas M  
<https://www.oatext.com/Cutaneous-lupus-vulgaris-Bringing-the-wolf-out-of-the-darkness.php>

#### **Scrofuloderma (SFD):**

- **Pathogenesis:** SFD is the most common form of CTB in children. SFD can affect any age, extremes of age are commonly affected, owing to relatively weaker immune responses<sup>7</sup>. SFD occurs due to contiguous spread from an underlying primary tubercular focus, usually a lymph nodes or bone, and sometimes joints or testicles<sup>39</sup>. Involvement of overlying skin from an underlying tubercular focus disease causes SFD. The underlying foci can be tuberculous lymphadenitis or tuberculous bone infection. PPD test is usually positive. The most common source of SFD lesions is the cervical group of lymph nodes, which then involves the overlying skin. This might be due to prevalent habit of drinking unpasteurized milk<sup>8</sup>. Other groups of lymph nodes can also be involved which then affect the overlying areas respectively. In addition, tuberculous affliction of bones, joints, testes, and breasts may also give rise to SFD<sup>8,23,50</sup>.
- **Clinical Features:** SFD is characterized by the formation of painless, gradually expanding cold abscesses overlying lymph nodes or bone/joint, followed by the formation of ulcerated plaques and fistula that may discharge caseous material. Ulcers are shallow with undermined edges and blue oedematous margins. In children and immunosuppressed patients, the lesions can be widespread and multiple. Often, a patient presents with active draining lesions of SFD over a background of puckered scarring, reminiscent of previous healed lesions. Uncommon variants of SFD include multifocal lesions, linear sporotrichoid lesions, scrofulous gumma and SFD at the site of BCG vaccination<sup>27,45,50</sup>. Other variants of CTB, most commonly LV, have been reported to develop over and adjacent to the sinuses and scars of SFD<sup>38</sup>. PPD is strongly positive<sup>17,51</sup>. SFD is more often than not, associated with an underlying systemic tuberculous focus, most commonly pulmonary, followed by bone, and abdominal TB<sup>23</sup>.

- **Laboratory Diagnosis:** Diagnosis is usually evident on clinical examination. Biopsy from the margins of lesion may show tubercular granulomas, the histopathology is non-specific in many cases<sup>8,23</sup>. Caseous necrosis, ulcers and abscess are commonly found. Compared to other forms of CTB, SFD shows extensive granulomatous involvement and predominantly with giant cells. SFD is a multibacillary form with abundant AFB as well as positive culture findings compared to other types of CTB<sup>7,23,27</sup>. The tuberculin test is usually positive.
- **Course:** SFD runs a very protracted course, though it tends to heal spontaneously over months and years, leaving behind cerebriform or bridging scars and pockets of retraction.



**Figure 5:** Image by Rambhia KD

“<https://ijdvl.com/multifocal-tuberculous-gummas-and-bilateral-scrofuloderma-followed-by-papulonecrotic-tuberculids-developing-during-anti-tubercular-therapy/>”

#### **Orificial Tuberculosis:**

- **Pathogenesis:** Extension of TB infection at the mucocutaneous junction of orifices (mouth, palate, vulva, anus and urethra), in patients with severe TB on the contiguous area (eg. Intestine for mouth and anus or urogenital tract for urethra). It usually affects immunocompromised patients with well propagated TB and is rare.
- **Clinical Features:** Lesions consist of 1–3 cm sized erythematous-to-yellowish, friable and painful papules and nodules developing more commonly in or around mouth and less commonly surrounding genital or anal mucosa<sup>21</sup>. They progress to painful ulcers with undermined edges perilesional edema.
- **Laboratory diagnosis:** On histopathology, tubercular granulomas with necrosis/ulceration, but with profound AFB is seen. Pain at the orifices with advanced TB disease is hallmark feature. It is a multibacillary form of CTB so the culture is generally positive<sup>17</sup>.
- **Course:** The severity of the underlying visceral disease renders a poor prognosis. Resistance to ATT has been reported in some. Unimpeded progression may result in fatality<sup>34</sup>.



**Figure 6:** Orificial Tuberculosis – image by Arzu Kilic  
<https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1365-4632.2009.03942.x>

### **Tuberculous Gumma:**

- **Pathogenesis:** Tuberculous gumma, occurs from hematogenous dissemination of TB during low immunity periods resulting in multiple lesions<sup>21,34</sup>. It typically affects immunocompromised adults, malnourished children. Tuberculous abscesses are also seen in patients with acute miliary TB<sup>52</sup>.
- **Clinical Features:** Lesions involve are characterized by subcutaneous nodules that are non-tender that may form sinuses or undermined ulcers. Nodules may ulcerate and drain caseous material. Lesions with overlapping features of SFD and gumma have been called scrofulous gumma. In fact, TB gumma is considered by some to be a severe variant of SFD<sup>21</sup>. Regional lymphadenopathy is usually not present.
- **Laboratory Diagnosis:** Presence of tubercular granulomas with extensive caseous necrosis and profuse amounts of AFB is seen on histopathology.
- **Course:** In immunocompetent individuals, without treatment, the abscess may persist for years followed by spontaneous resolution with scarring. Patients with compromised immunity tend to have a poor prognosis.



**Figure 7:** Tuberculous gumma – image by Parker Louise  
<https://casereports.bmj.com/content/2013/bcr-2013-010462>

### Acute Miliary Tuberculosis:

- **Pathogenesis:** Miliary TB of skin follows generalized miliary TB which occurs after haematogenous dissemination of bacilli into the skin. It is a rare and severe form of TB and affects children with poor immune status<sup>25</sup>. Disseminated miliary TB of the skin has been reported in AIDS patients, and this presentation may become more common owing to the TB–HIV co–epidemic<sup>53</sup>.
- **Clinical features:** Widespread erythematous to purplish papules, pustules, or vesicles develop that break down forming umbilication and crust. Lesions regress in 1– 4 weeks, resulting in depressed and hypopigmented scars. Affected individuals are seriously ill with severe constitutional symptoms like fever, anorexia, asthenia, and weight loss. Affection of internal organs is common, especially the lungs and meninges. The tuberculin skin test is almost always negative, demonstrating energy resulting from severe immunosuppression.
- **Laboratory diagnosis:** It is characterized by tubercle granulomas with necrosis/ulceration, with copious amounts of AFB on histopathology<sup>17,54</sup>.
- **Course:** Poor prognosis is seen although may respond to treatment.



**Figure 8:** Acute miliary TB – image by Daikos G

“<https://www.semanticscholar.org/paper/Disseminated-miliary-tuberculosis-of-the-skin-in-of-Daikos-Uttamchandani/282cacd268131e9e17f1d470a15b41e8e64aa46e>”

## VIII. TUBERCULIDS

Tuberculids are cutaneous representations of immunologic reaction to the presence of *M. tuberculosis* or their products in immunocompetent patient. Their development and presentation fluctuates on the basis of underlying host immune status. There are certain diagnostic features of tuberculids<sup>21,25,38</sup>:

- Skin shows tuberculoid picture on histopathology,
- No AFB in smears,
- No mycobacterial growth on culture,

- Evidence of tubercular focus elsewhere (concurrent or past),
- A Strong positive PPD test and
- Lesions resolve with ATT.

Types of tuberculids – 1) Papulonecrotic tuberculid (PNT), 2) Erythema induratum of Bazin (EIB), 3) Lichen scrofulosorum (LS) and 4) Phlebitic tuberculid.



**Figure 8:** Tuberculid – image by Brinca A  
“<https://www.pagepress.org/journals/index.php/dr/article/view/dr.2011.e29/4865>”

## IX. HIV AND CUTANEOUS TUBERCULOSIS

Concomitant HIV infection has been found to be a predisposing factor for acquiring severe pulmonary and extra-pulmonary forms of TB. However, the relationship of HIV infection and cutaneous TB is not very clear, but it may be more severe in patients with HIV<sup>43</sup>. In various Indian case studies, all children with cutaneous TB tested negative for HIV by enzyme-linked immunosorbent assay (ELISA)<sup>7,23,27</sup>. A single case series of 231 patients from South India reported only two HIV positive cases<sup>28</sup>.

## X. LABORATORY DIAGNOSIS OF CUTANEOUS TUBERCULOSIS

Diagnosis of CTB is primarily based on the clinical appearance of the skin lesions supported by various laboratory tests. The diagnostic accuracy of any single lab test in confirming the diagnosis of CTB is low, therefore it becomes mandatory for the physician to order different tests in order to support positive evidence for the diagnosis and avoid giving empirical treatment.

## XI. MANTOUX TEST

Mantoux test also called tuberculin skin test (TST), is a widely used screening test performed to identify sensitized individuals to *M. tuberculosis*. The test involves injection of 5 tuberculin units (0.1 mL) of PPD derived from *M. tuberculosis*, using 26 or 27 gauge needle, on the volar aspect of left forearm about 2 inches lower than elbow. The reaction, a classical delayed hypersensitivity reaction, results in induration that is read after 48–72 hours.



**Figure 9:** Mantoux test

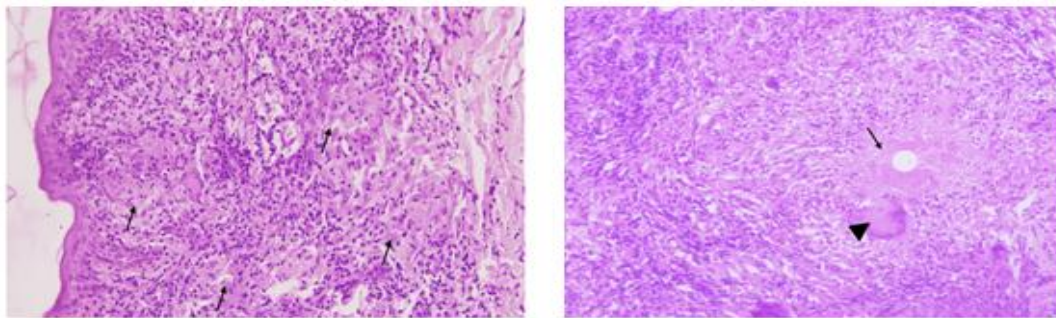
An induration measuring  $\geq 10$  mm is considered significant and indicates infection (i.e. previous sensitization to Tubercle bacilli) but not necessarily the disease. If vesicle or bulla formation or necrosis occurs, it indicates high degree of tuberculin sensitivity and presence of an active infection. A false-positive result may also occur in case of nontuberculous mycobacteria infection or post BCG vaccination<sup>78</sup>.

For cutaneous tuberculosis, TST has sensitivity ranging from 33%-96%, specificity of 62.50% with a cut-off of 10 mm and thus has low accuracy in doubtful cases of CTB. It has also been suggested that for patients with clear evidence of immunosuppression, a lower cut-off of 5 mm may be more suitable. The impact of BCG vaccination on TST positivity in endemic populations cannot be ignored. In unvaccinated individuals, the sensitivity is much higher, reaching 97%<sup>55</sup>. A high mantoux positivity ranging from 91.8% to 97% has been reported in patients with localized CTB in contrast to 50% in those with disseminated disease<sup>23,82</sup>. Tuberculin test shows highest positivity in tuberculids, with common occurrence of exaggerated reactions, as reported by Singal et al in 100% cases of lichen scrofulosorum<sup>56</sup>.

## **XII. HISTOPATHOLOGY**

The hall mark of histology of classic CTB lesion is the presence of characteristic granuloma composed of epithelioid cells, lymphocytes and langhans giant cells. Other features like distribution of granulomas in dermis, their compactness, and presence of caseous necrosis, cellular infiltrate, and epidermal changes varies with different clinical types of CTB. Based on the host immune response, histology of CTB may be grouped into three groups<sup>38</sup>: (1) Well-formed tubercle granulomas without caseous necrosis: LV and LS, (2) Granulomas with caseous necrosis: TBVC, tubercular chancre, acute military TB, tuberculosis orificialis and PNT (3) Presence of poorly formed tubercle granulomas with intense caseation necrosis: SFD and tubercular gumma. The most common histological feature is the presence of tuberculoid granuloma in dermis (57-96% of biopsy samples) followed by epithelial hyperplasia in 57-86% and caseous necrosis in 11.8-57%<sup>28,56,57</sup>. Classical tubercular histopathology is seen more often in LV lesions as compared to SFD. A clinico-histopathological concordance was observed in 64-85.6% of the cases of paediatric cutaneous TB<sup>7,23,29</sup>. Histopathology becomes of prime importance for diagnosis of tuberculids where bacilli cannot be isolated by culture or demonstrated by AFB staining. In 10% of LV cases, superinfection with TB elsewhere will lead to an active disease<sup>58</sup>.

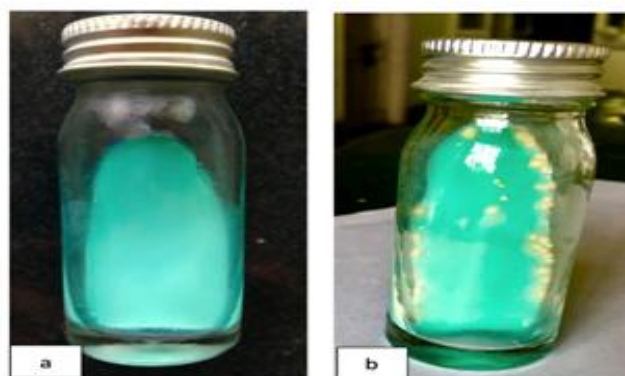




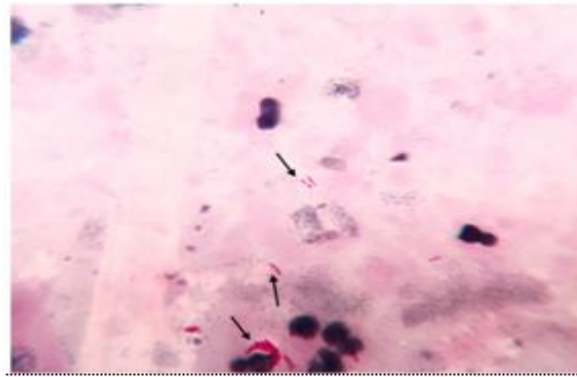
**Figure 10: A (Left) :** Intact epidermis with mild irregular acanthosis. Multiple epithelioid cell granulomas (arrows) in the upper and mid dermis on Haematoxylin & Eosin staining (x 200). **B (Right):** Deeper dermis showing epithelioid cell granuloma with caseation (arrow) and langhan's giant cell (arrow head) on Haematoxylin & Eosin staining (x 400).

### XIII. MICROBIOLOGICAL TESTS

- 1. Demonstration of Acid-Fast Bacillus (AFB) in the Stained Smear:** Direct demonstration of AFB, on Ziehl-Neelsen staining, in the tissue smear from exudative skin lesions, lymph node aspirates or biopsy specimens, gives faster results than culture although sensitivity gets compromised. The detection sensitivity of smears is higher for exudative lesions of CTB, especially the multibacillary forms because of the obvious higher bacterial load, as in the cases of primary inoculation, SFD, tuberculosis orificialis, or metastatic tuberculous abscess. A higher AFB positivity has been reported in SFD cases (36.8%) as compared to LV lesions (13.6%).
- 2. Mycobacterial Culture:** As for any infection, the definitive diagnosis of Tuberculosis continues to depend on the culture of microorganism. Another advantage of culture is that it can distinguish mycobacterium subspecies and allow drug susceptibility testing. CTB in general is regarded as a paucibacillary infection, therefore mycobacterial isolation from smears and lesion biopsy, on the conventional Lowenstein- Jensen (LJ) medium is reported to be as low as 8.8% and 10.7% in two different studies involving CTB cases exclusively<sup>7,23</sup>. In addition, the time for final negative growth result on LJ medium is 6–8 weeks.



**Figure 11:** Lowenstein-Jensen medium showing: **a)** No growth, **b)** Colonies of *Mycobacterium tuberculosis*



**Figure 12:** Acid fast bacilli (arrows) seen on the direct smear made from processed skin biopsy sample on Ziehl-Neelsen staining (x 1000).

The culture methods are more sensitive than AFB staining and can be positive even with low bacterial load (10–100 bacilli/mL) with sensitivity of 80–85% and specificity of 98%, required for identification of causative organisms. Growth is very slow and usually takes 6–8 weeks. Post growth the same amount of time is required for antimicrobial sensitivity testing. Most commonly used solid culture medium is LJ medium. Other solid media that can be used are Petraghini (egg based) medium, Dorset's medium (egg based), Pawlowsky (potato based), Middlebrook 7H10 and 7H11 medium (agar based).

The inoculated LJ media are incubated at 37°C. The bacilli grow very slowly and colonies appear in about 2 weeks and sometimes upto 6–8 weeks. In positive culture, characteristic colonies appear dry, rough, buff coloured, raised, with a wrinkled surface. They are tenacious and not easily emulsified. *M. tuberculosis* has a luxuriant growth (eugonic growth)<sup>59</sup>.

Liquid culture media reduces the growth time for isolation of tubercle bacilli to approximately 10 days. Growth of mycobacterium in liquid medium requires 5% 10% CO<sub>2</sub>. Besides solid media, liquid media available are Middlebrook 7H9, Dubo's medium, Sula's medium, Proskauer and Becks's medium.

- **Mycobacteria Growth Indicator Tube (MGIT):** MGIT is a type of liquid culture method. It is a rapid method which consists of tubes having 4 mL of modified Middlebrook 7H9 broth which has a fluorescent sensor at the bottom which is sensitive to oxygen in the medium<sup>60</sup>. When mycobacteria grow, they use up the dissolved oxygen in the broth, thus reducing the oxygen content which thus allows the indicator to produce fluorescence under UV light. Generally with this method, positive signals are obtained within 10–12 days. MGIT can also be used for antimicrobial susceptibility testing. An advantage over BACTEC is its lower cost and has no radioactivity issues<sup>61</sup>. MGIT gives higher yield and faster results although it incurs a relatively higher cost<sup>62</sup>.

**3. Serological Tests:** Most serological tests have lower turnaround time. However, the utility of antibody detection frequently appears compromised, firstly due to BCG vaccination and secondly due to immunological sensitization by environmental mycobacteria.

- **Antigen Detection:** Quantitative tests and dipstick method (semiquantitative) to detect lipoarabinomannan (LAM) in pulmonary and extra-pulmonary specimens have been developed. Their utility in the diagnosis of CTB remains to be explored.
- **Interferon Gamma Release Assays (IGRA'S) – Quantiferon TB Gold and T-SPOT TB:** These two tests are commercially available, FDA approved, in vitro serological assays that quantify the amount of interferon-gamma released by blood monocytes upon their stimulation by highly specific *M. tuberculosis* antigen. Both assays have higher sensitivity and specificity compared to the traditional TST. However, previous exposure to atypical mycobacterial infections such as *M. marinum* and *M. kansasii* may give false positive results. The likelihood of indeterminate results is higher (to the tune of 30%) in elderly population (>65 years old), compared to other age groups (3.1%)<sup>38</sup>.

Indeterminate results are also seen in patients with immunosuppression, low CD4 counts, severe systemic diseases, malnourishment with low serum proteins, and increased C-reactive serum proteins. The utility of these assays lies as a screening tests for latent TB especially in patients with kidney disease, planned transplant, under treatment with anti-TNF-alpha therapies, contacts of AIDS patients<sup>38</sup>.

**4. Molecular Tests (NAAT- Nucleic Acid Amplification Test):** A large number of sample organism load of *M. tuberculosis* was required by the above diagnostic methods. Molecular tests comes into the picture which can amplify the genome, even if the sample contains a single organism, which is required for paucibacillary TB cases.

Such tests are real time PCR, LCR (Ligase Chain reaction), CBNAAT (Cartridge Based NAAT), LAMP (Loop Mediated Amplification), LPA(Loop Mediated Amplification). GeneXpert NAAT test boasts a 100% sensitivity and 91.6% specificity for extra-pulmonary specimens<sup>63</sup>. Molecular tests are more so useful in EPTB cases and those cases which have a high clinical suspicion but conventional diagnostic methods have failed.

- **Systemic Screening for Tubercular Focus:** Coexistent systemic focus of TB has been observed in about one fourth of all patients with cutaneous lesions<sup>12</sup>. The range is reportedly higher in paediatric population (21.3–53.4%)<sup>7,8,23,29</sup>. Thus, it becomes mandatory to screen all patients of CTB carefully.

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