**Cutaneous Tuberculosis: Clinicopathological spectrum and diagnostic challenges**

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**INTRODUCTION**

In 2021, eight countries accounted for more than two thirds of global tuberculosis cases namely India (28%) Indonesia (9.2%), China (7.4%), the Philippines (7.0%), Pakistan (5.8%), Nigeria (4.4%), Bangladesh (3.6%) and Democratic Republic of the Congo (2.9%).1 Tuberculosis causes ill–health in millions of people each year and is one of the top 10 causes of death worldwide, ranking above HIV/AIDS as one of the leading causes of death from an infectious disease2.

Though pulmonary TB is the most common form, extra–pulmonary Tuberculosis (EPTB) also contributes to significant morbidity and mortality. The various extra–pulmonary sites are lymph nodes, intestines, bone, joints, meninges, skin, genitourinary tract3.

The incidence of cutaneous tuberculosis (CTB) is around 0.7% and median duration of disease is 1.25 years4,5. The diagnosis of CTB is a difficult task. Most of the time, this entity is diagnosed by its clinical presentation in combination with corroborative histopathological evidence. CTB presents with a wide range of clinical manifestations, varying from warty, nodules and papulonecrotic lesions, to ulcerations and abscesses6. The clinical presentation of different types of CTB varies and is determined by factors such as route of infection and cellular immune status of the host7. In association with clinical findings, histopathology is a useful diagnostic test. However, epithelioid cell granulomas may also be seen in other conditions such as sarcoidosis, leprosy, deep fungal infection, etc. which sometimes clinically also resemble CTB.

CTB may remain localized to the skin alone, but frequently involves regional lymph nodes. Disease is considered to be disseminated if there is presence of generalized lymphadenopathy and/or involvement of other organ systems8.

The direct demonstration of *M. tuberculosis* has very low sensitivity because most lesions are paucibacillary9. Culture of the organism from lesion of CTB is again highly specific but is usually tedious and unrewarding.

The challenge increases because of the pathogenic status and minor damage to the affected skin compared to other EPTB forms. TB must be considered a cause of cutaneous infections in developing countries due to the high prevalence of the disease in those regions. The conclusive results generally cannot be achieved with bacteriological methods; however, molecular diagnostic methods are considered more sensitive10.  
Polymerase chain reaction (PCR) has emerged as a promising tool in which IS6110, a conserved sequence, is mostly targeted11.

TB is the ninth leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS. This is despite the fact that, with a timely diagnosis and correct treatment, most people who develop TB disease can be cured. It is currently a worldwide threat with 9–10 million new active disease cases being reported every year1. Cutaneous tuberculosis (CTB), though accounts for only 1–2% of extra–pulmonary TB (EPTB) cases12, it is important cause of mortality and morbidity in developing countries because of high prevalence. It may be acquired through exogenous inoculation or endogenous spread13.

**HISTORY OF TUBERCULOSIS**

Tubercle bacilli have likely lived in symbiosis with mankind since the ascent of homo sapiens on Earth. Greco–Roman civilization recognized the disease as “*phthisis*” or consumption. In the western world, the clinical features and communicability of TB were known before 1000 BC. Paleopathological evidence of TB in prehistoric humans has also been recorded. A team from the University of Tubingen believe that humans acquired the disease in Africa about 5,000 years ago14. Their domesticated animals, such as goats and cows, contracted it from them. Seals acquired it when coming up on African beaches for breeding, and carried it across the Atlantic. In addition, TB spread via humans on the trade routes of the old World.

**ETIOLOGICAL AGENT**

*Mycobacterium tuberculosis*, is a transitional form between actinomycetes and eubacteria. It belongs to class Schizomycetes, order Actinomycetales, family Mycobacteriaceae and genus *Mycobacterium*. Robert Koch first described it on March 24, 1882. It is an aerobic, nonmotile, nonencapsulated, nonspore–forming bacillus that grows most successfully in tissues with high oxygen content. It is an obligate intracellular pathogen that infects human beings as principal hosts. It has an extended growth period and doubling time (18 to 48 hours). These bacilli present acid–alcohol–resistant staining properties – i.e., they stain red by Carbol fuchsin and will not discolour by the actions of specific concentration of alcohol and acid for specific time, hence the name AFB – Acid–Fast Bacilli. Its genome has already been sequenced15,16,17.

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. Although it may cause illness in men, *M*. *bovis* is considered a zoonotic disease that usually affects tonsils, lymph nodes and intestine. It may rarely be the cause of the cutaneous form of TB. When causing lung disease, *M*. *bovis* is not easily transmitted and therefore, there is a tendency for its disappearance18.

The probability of developing active clinical TB after inhalation of *M. tuberculosis* aerosol from an infectious patient has an estimated lifetime risk of about 10%, the risk being highest within the 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 established disease depends on the interplay of mycobacterial virulence and host immune response.

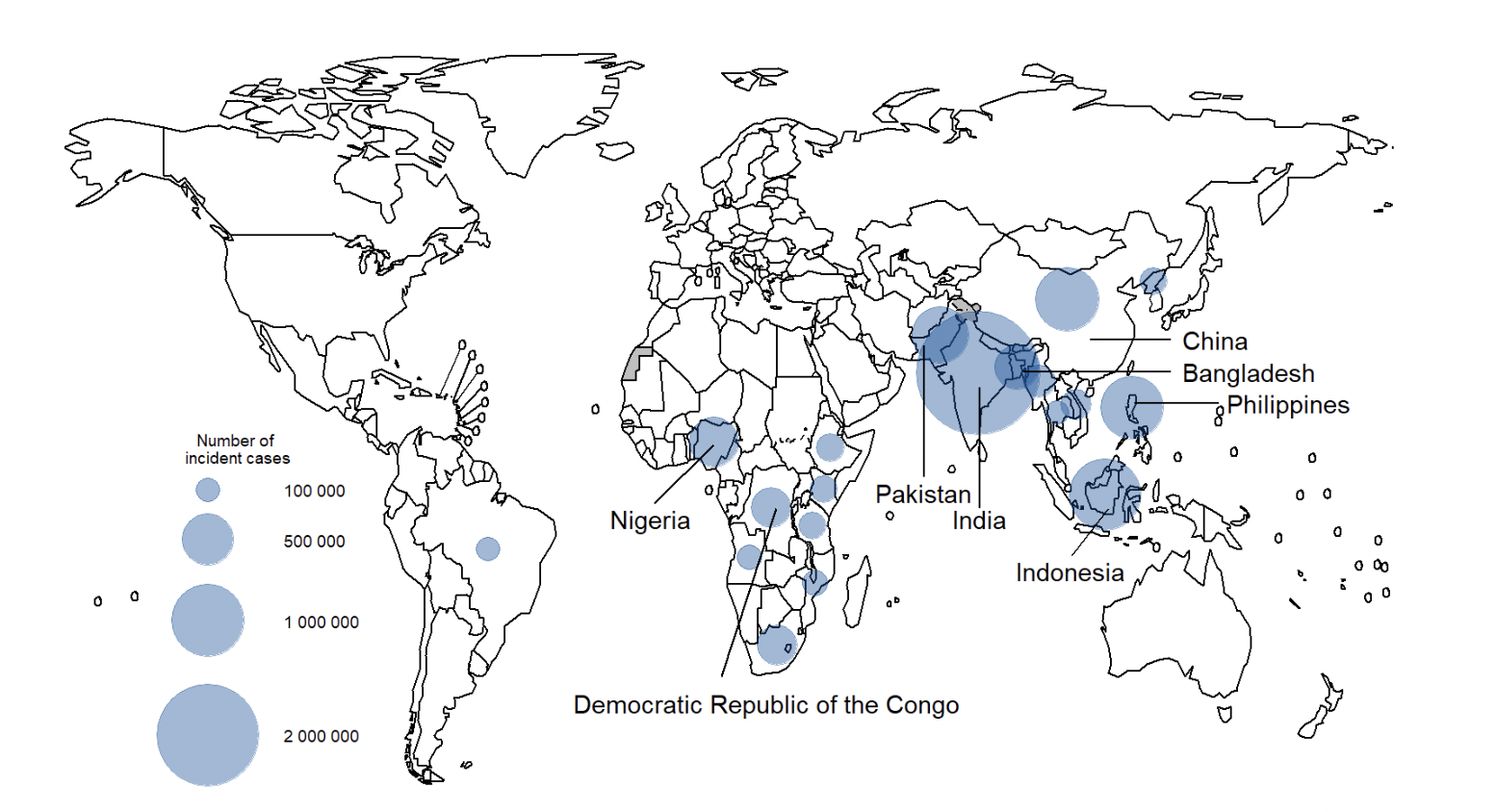
**MODE OF TRANSMISSION – EXOGENOUS V/S ENDOGENOUS CTB**

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 is secondary to a pre–existing 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 reactions such as skin complications are well known and can include local hypersensitivity reactions, cutaneous granulomas, fixed drug eruption and Cutaneous Tuberculosis (CTB). The interval between vaccination and the development of skin lesions may range from several months to years, with an average duration of 1 year19,20.

**EPIDEMIOLOGY**

In 2021, there were an estimated 1.4 million TB deaths among HIV-negative people and 187 000 among HIV-positive people, for a combined total of 1.6 million; this was up compared to estimates of 1.5 million in 2020 and 1.4 million in 2019, and back to the level of 2017. In 2021, 82% of global TB deaths among HIV-negative people occurred in the WHO African and South-East Asia regions; India alone accounted for 36%. The African and South-East Asia regions accounted for 82% of the combined total of TB deaths in HIV-negative and HIV-positive people; India accounted for 32%. 2



**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**](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 proportion of people who develop TB and die from the disease (the case fatality ratio or CFR) was 16% in 2016. Between 2000 and 2016, TB treatment averted an estimated 44 million deaths among HIV–negative people and additional 9 million deaths among HIV–positive people supported by anti–retroviral therapy (ART).

Pulmonary TB has been the most common form in children but there has been a steady increase in the number of EPTB cases, especially tuberculous lymphadenitis. During the last few years, EPTB cases have outnumbered cases of pulmonary TB in children21.

**EPIDEMIOLOGY OF CUTANEOUS TUBERCULOSIS**

CTB is one of the less common clinical forms of TB accounting for approximately 1–2% of the total number of extra–pulmonary cases but contributing to significant morbidity22,23. Its global resurgence parallels the increasing incidence of pulmonary TB and emergence of multidrug resistance24. The prevalence of CTB among Indian dermatology outpatients has ranged from 0.1– 0.9% over the last few decades8,12,23. Kumar et al in their 20–year retrospective survey of patients attending dermatology outpatient department of a tertiary care hospital in India, reported 280 patients suffering from CTB of the total 2,67,420; giving a prevalence rate of 0.1% among dermatology patients23. Parallel to the increase in the overall incidence of EPTB with the HIV epidemic, increase in the incidence of CTB is expected.

**EPIDEMIOLOGY OF CHILDHOOD CUTANEOUS TUBERCULOSIS**

Most published studies in childhood CTB are from developing countries, mainly Southeast Asia. The reported prevalence of CTB in children has varied in different studies depending on the geographical region25. It has ranged from 82% of all CTB cases in Pakistan, 24.3% in Ethiopia, and up to 50% in older surveys from Hong Kong with a downward trend over time6,26. In India, the prevalence of childhood skin TB has ranged from 18% to 54%, 18.7% in Chandigarh, 20.4% in Varanasi, 24.41% in Chennai and a higher prevalence ranging from 31.7% to 53.9% in recent case series from Delhi7,8,25,27,28,29. CTB is common in children aged 10 –14 years, although no age group is resistant. Sex distribution is variable in different studies, but a significant gender predilection is inapparent. The clinical spectrum of CTB in children is comparable to that in adults, except for a higher likelihood of disseminated and systemic involvement21. Childhood CTB has been often reported to develop following BCG vaccination30.

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 Kong6. 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 now12.

**IMMUNOLOGY IN CUTANEOUS TUBERCULOSIS**

Just as in leprosy and pulmonary TB, there is a concept of spectrum in CTB. Based on bacteriological, histopathological and immunological parameters, Sehgal et al proposed a continuous immunological spectrum extending from the greater cellular immunity pole, as seen in LV, with active cellular immunity and normal levels of immunoglobulins, to SFD and cutaneous miliary TB, which present a relatively less active cellular immunity and high humoral response, as evidenced by higher immunoglobulin levels and low levels of C331.

The introduction of more specific and sensitive diagnostic methods may contribute to an efficient fight against TB. Immunosuppression, either due to a poor health, HIV infection or due to immunosuppressive drugs use, represents the main trigger for active disease development, caused by *M*. *tuberculosis*32.

TABLE 1: Types of Cutaneous Tuberculosis

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **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, 2nd 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  Poorly 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 | - | - |

**CLASSIFICATION OF CUTANEOUS TUBERCULOSIS**

(A) EXOGENOUS CTB

**1. Tuberculosis verrucosa cutis (TBVC)**

**Pathogenesis:** TBVC, the most common form of inoculation CTB, is the result of primary inoculation in previously sensitized individuals who maintain moderate to high immunity against *M. tuberculosis.* In tropical zones, TBVC often occurs over the foot and buttocks of children, on account of their habit of walking barefoot on soil contaminated with tuberculous sputum33,34. Extremities and other trauma prone sites are typically involved. It can also be considered an occupational disease, due to self–inoculation possibilities, such as may occur to a dentist treating the mouth of a patient with pulmonary TB or to a butcher handling contaminated meat (in the latter case, usually by *M*. *bovis*). Purified Protein Derivative (PPD) test is strongly positive35,36,37.

**Clinical features:** Lesions are usually solitary and painless verrucous papules or plaques, with the surface showing fissures or clefts that may extrude pus and, often, perilesional erythema or purplish inflammatory halo25,38. Peripheral extension results in gradual expansion of the lesion that may lead to a serpiginous 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 in the upper dermis and characteristic but sparse tuberculoid granulomas in the mid dermis7. TBVC is a paucibacillary form of CTB, with AFB being rarely detected35,39.

**Course:** Without treatment, extension is extremely slow and the lesions tend to persist indefinitely, although spontaneous resolution might occur rarely40. Secondary bacterial infection and elephantiasis are possible complications of extensive lesions affecting extremities41.



# Figure 2: Tuberculosis verrucosa cutis - image by Rao AG via “https://ijdvl.com/scrofuloderma-associated-with-tuberculosis-verrucosa-cutis/”

**2. Tuberculous chancre (Primary inoculation tuberculosis)**

**Pathogenesis:** It is rare form of inoculation CTB that develops in adults without previous sensitization to the bacillus21. It is rare in children, though frequent in unvaccinated having contact with pulmonary TB patients35,42. 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 procedures38,43. The combination of the chancre and regional lymphadenopathy is equivalent to the Ghon focus in pulmonary TB.

**Clinical features:** After 2–4 weeks of inoculation, a firm more than 1 cm sized painless, reddish–brown papule or nodule arises, which soon evolves into an ulcer which is shallow and friable with undermined bluish margins and a coarse granular base. It is typically painless but tends to bleed. Trauma prone sites like face and extremities are the most frequently involved. Lymphatic dissemination ensues 3–8 weeks after the onset of chancre, resulting in regional lymphadenopathy which may break down to form a discharging sinus39,40. Any painless nonhealing ulcer with regional lymphadenopathy (primary complex) in an adult or child should arouse suspicion of tuberculous chancre.  
**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 with scarring and calcification of regional lymph node may occur or the patient may develop LV lesions and TBVC17.

PPD is initially negative but becomes positive later during the course of the disease (usually post 15 days)17. 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”**

(B)ENDOGENOUS CTB

**1. Lupus Vulgaris (LV)**

**Pathogenesis:** LV is the most common clinical type of cutaneous TB in adults, and the second most common type seen in children25. LV is a chronic and progressive form of CTB that occurs in individuals previously sensitized to *M. tuberculosis* with moderate immunity against the bacillus. Women are affected 2–3 times more often than men. 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 SFD30,44. The most common sites of involvement are the head and neck (disseminating disease), and lower extremities and gluteal region (inoculation–induced LV).  
**Clinical features:** The clinical picture of LV is highly variable with diverse morphology. Typical lesions (also called “classical plaque”) consist of papules and well–defined reddish– brown plaques. The plaque expands peripherally, with serpiginous or verrucous borders, often reaching over 10 cm in diameter with central discolouration and atrophy. 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 LV21,25. 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 encountered in other granulomatous diseases such as sarcoidosis and leprosy34,40. Other morphological variants of

LV include hypertrophic, ulcerative and mutilating**,** vegetative and tumour like, atrophic and

planar. Although regional lymphadenopathy is commonly encountered in LV, systemic involvement is seen less often compared to SFD25. 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, and those mimicking diseases such as discoid lupus erythematous, actinomycosis and mycetoma12,21,25,45,46.

**Laboratory Diagnosis:** Histopathology of LV lesions reveals typical epithelioid granulomas in the upper dermis, with lymphocytes and langhans giant cells in up to 80% of the cases, with the remainder showing nonspecific changes7,8,23. The hypertrophic form also shows epidermal hyperkeratosis, acanthosis and papillomatosis. Necrosis is absent and fibrosis ensues in areas of healing and scarring. AFB is scanty and difficult to detect by staining methods or mycobacterial culture; thus, LV is considered a paucibacillary form of CTB.

The usefulness of dermatoscopy in the diagnosis of LV has been recently suggested, since it revealed peculiar characteristics consisting of linear telangiectasias on a yellow–golden background and whitish reticular streaks. Although the observed characteristics are not specific enough alone, their presence in combination may increase the diagnostic sensitivity47.

**Course:** Untreated LV lesions may grow to become gigantic and often lead to deep tissue destruction with significant aesthetic alterations33,34,40. Malignant transformation into squamous cell carcinoma, a dreaded long–term complication of untreated LV, has ranged from 0.5–10.5%48,49.



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

**2. Scrofuloderma (SFD)**

**Pathogenesis:** Also known as tuberculosis colliquativa cutis, SFD was the most commonly observed form of CTB before the advent of ATT and still remains common in developing countries such as Brazil and India, particularly in children. Though SFD can occur in any age group, extremes of age are more commonly affected, owing to relatively weaker immune responses7. SFD occurs as a result of contiguous spread from an underlying primary tubercular focus, usually a lymph nodes or bone, and sometimes joints or testicles39. SFD is due to reactivation of dormant TB. There is contiguous involvement of overlying skin from an underlying tuberculous focus such as tuberculous lymphadenitis or tuberculous bone disease. Tuberculin test is usually positive. A cold abscess is formed and the overlying skin is eroded. SFD from tuberculous lymphadenitis often affects the parotid, submandibular, supraclavicular and both sides of the neck. The most common source of SFD lesions is the cervical group of lymph nodes. This may possibly be due to the prevalent habit of drinking unboiled/unpasteurized milk in many regions, with subsequent infection of the cervical lymph nodes8. Inguinal, axillary, parasternal, preauricular, postauricular, occipital, submandibular**,** epitrochlear and supraclavicular are the other groups of lymph nodes that can be involved. In addition, tuberculous affliction of bones, joints, testes, and breasts may also give rise to SFD8,23,50.

**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 usually shallow with undermined edges and bluish bogged-up margins. In children and immunosuppressed patients, the lesions can be multiple and widespread. 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 vaccination27,45,50. Scrofulous gumma often has multiple swellings and sinuses with irregular finger–like extensions involving larger areas. Other variants of CTB, most commonly LV, have been reported to develop over and adjacent to the sinuses and scars of SFD38. PPD is strongly positive17,51.

SFD is more often than not, associated with an underlying systemic tuberculous focus, most commonly pulmonary, followed by bone, and abdominal TB23.  
**Laboratory Diagnosis:** Diagnosis is usually evident on clinical examination. While biopsy from the periphery of the lesion may show tubercular granulomas, the histopathology is non–specific in many cases8,23. Caseous necrosis, ulcers and abscess formation are commonly encountered. Compared to other forms of CTB, SFD shows granulomatous involvement of the entire dermis, with giant cells as the predominant cell infiltrate. SFD is a multibacillary form of CTB with high likelihood of detection of AFB from stained cytology smears or biopsy samples as well as positive mycobacterial culture compared to other types of CTB7,23,27. 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/**](https://ijdvl.com/multifocal-tuberculous-gummas-and-bilateral-scrofuloderma-followed-by-papulonecrotic-tuberculids-developing-during-anti-tubercular-therapy/)**”**

**3. Orificial Tuberculosis**

**Pathogenesis:** It results from the propagation of TB infection at the mucocutaneous junction of natural orifices (mouth, anus, vulva, urethra and palate), due to self–inoculation from an active focus on deep tissues, in patients with severe TB on the contigous area (eg. Intestine or urogenital tract). This form of CTB is rare and usually affects immunocompromised patients. **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 mucosa21. They evolve into painful ulcers with undermined bluish edges with perilesional edema and inflammation. Severe pain may interfere with eating, micturition, or defaecation.

**Laboratory diagnosis:** On histopathology, it is characterized by the presence of tubercular granulomas with necrosis and ulceration, with profound AFB. Pain is the cardinal feature and there is usually an evidence of advanced TB elsewhere. It is a multibacillary form of CTB so the culture is generally positive, even with a negative tuberculin response (PPD)17.

**Course:** The severity of the underlying visceral disease renders a poor prognosis. Resistance to ATT has been reported in few cases. Unimpeded progression of the disease may result in fatality34.



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

**4. Tuberculous Gumma**

**Pathogenesis:** Tuberculous gumma, results from hematogenous dissemination of TB infection during periods of low immunity resulting in multiple lesions21,34. It typically affects immunocompromised adults, malnourished children. Tuberculous abscesse is also seen in patients with acute miliary TB52.

**Clinical features:** Lesions involve both trunk and extremities and are characterized by subcutaneous nodules that are non-tender and may later break down forming 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 SFD21. Regional lymphadenopathy is usually not present. **Laboratory diagnosis:** Presence of tubercular granulomas with widespread 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”**

**5. Acute Miliary Tuberculosis**

**Pathogenesis:** Miliary TB of skin develops in association with generalized miliary TB due to haematogenous dissemination of mycobacteria into the skin. It is a rare and severe form of TB

and affects children with poor immune status25. 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–epidemic53.  
**Clinical features:** Widespread erythematous to purplish papules, pustules, or vesicles develop that subsequently break down forming umbilication and crust formation. 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 the presence of tubercule granulomas with necrosis and ulceration, with copious amounts of AFB on histopathology17,54.  
**Course:** The overall prognosis is poor 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”

**TUBERCULIDS**

Tuberculids are cutaneous representations of immunologic reaction to the presence of *M. tuberculosis* or their products in a patient with significant amount of immunity. Their development and presentation fluctuates on the basis of underlying host immune status. There are certain diagnostic features of tuberculids21,25,38:

• Tuberculoid histology on skin biopsy,

• Absence of AFB in smears,  
• No mycobacterial growth on culture,  
• Evidence of tubercular focus elsewhere (concurrent or past),  
• A Strongly positive tuberculin skin test and  
• Resolution of the lesions 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”**

**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. Cutaneous TB, tubercular ulcers, PNT and disseminated miliary forms may be more severe in patients with HIV43. In various Indian case studies, all children with cutaneous TB tested negative for HIV by enzyme–linked immunosorbent assay (ELISA)7,23,27. A single case series of 231 patients from South India reported only two HIV positive cases28. Thus, larger studies are required to assess the impact of HIV co-infection on cutaneous TB.

**LABORATORY DIAGNOSIS OF CUTANEOUS TUBERCULOSIS**

Diagnosis of CTB is primarily based on the characteristic clinical appearance of the skin lesions supported by various lab 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.

**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 gauze needle, on the volar aspect of left forearm about 2 inches below the elbow crease. The reaction, a classical delayed hypersensitivity reaction, results in induration that is read after 48–72 hours.



**Figure 9 : Mantoux test**

An induration measuring ≥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 be due to nontuberculous mycobacteria or BCG vaccination78.

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%55. 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 disease8,23. Tuberculin test shows highest positivity in tuberculids, with common occurrence of exaggerated reactions, as reported by Singal et al in 100% cases of lichen scrofulosorum56.

**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 groups38: (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%28,56,57. 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 TB7,23,29. Histopathology becomes of prime importance for diagnosis of tuberculids where bacilli cannot be isolated by culture or demonstrated by AFB staining.

In early lesions, there is non–specific inflammation consisting of polymorphonuclear cells and macrophages. Tubercles appear after 3-6 weeks as immunity develops. The tubercle consists of a collection of epithelioid cells at the centre with a number of langhans giant cells which are in turn surrounded by a rim of lymphocytes. As the inflammation progresses, the centre of the granuloma undergoes caseous necrosis, which is a distinctive feature of tubercular infection.

In patients with adequate cell mediated immunity (CMI), the granuloma is well able to contain the infection with progressive fibrosis and finally calcification ensues. In 10% of cases, superseded TB infection will lead to active disease58. In LV, there is effective CMI, granulomas are formed with little caseation and AFB are scarse.

In SFD, there is moderate CMI in the host, the granulomas are less well formed and are located at the periphery of the lesion with more caseation at the centre with some AFBs. In TBVC, changes like warty hyperkeratosis or pseudoepitheliomatous hyperplasia with epithelioid and giant cells in the mid–dermis can be seen.

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**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).

**Figure 10B (Right):** Deeper dermis showing epithelioid cell granuloma with caseation (arrow) and langhan’s giant cell (arrow head) on Haematoxylin & Eosin staining (x 400).

At the other end of the immunological spectrum, there is miliary TB with poor or absent granuloma formation and marked tissue necrosis with numerous AFBs. The histological picture is similar in primary tuberculous chancre, but as CMI develops, well-formed tuberculoid granulomas are seen.

In patients with poor CMI such as in acute disseminated miliary TB, mycobacteria are present. There is massive necrosis and non–specific inflammation. Culture might help in differentiation from other types of mycobacteria. Sarcoidosis may be distinguished from tubercule infection by the scarcity of lymphocytes around the granuloma; called naked granulomas. Tertiary syphilis is characterised by plasma cell infiltration and vascular changes. In tuberculoid leprosy, the granulomas usually form around cutaneous nerves.

**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%). Also, cytology smears showed 18.44% AFB positivity, with majority of them being SFD7. Pandhi et al observed that the identification of AFB was higher in cytology smears from lymph nodes compared to biopsy specimens (10.3% vs. 2.9%)23.

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 exclusively7,23. In addition, the time for final negative growth result on LJ medium is 6–8 weeks.

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| **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 when bacterial load is low (10–100 bacilli/mL) with sensitivity of 80–85% and specificity of 98%, required for identification of causative organisms. Growth is 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 Petragnini (egg based) medium, Dorset’s medium (egg based), Pawlowsky (potato based), Middlebrook 7H10 and 7H11medium (agar based).

The inoculated LJ media are incubated at 37oC. 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)59.

Liquid culture media – The use of 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% CO2. 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 round bottom tubes containing 4 mL of modified Middlebrook 7H9 broth which has an oxygen sensitive fluorescent sensor at the bottom60. When mycobacteria grow, they use up the dissolved oxygen in the broth and allow the indicator to produce fluorescence brightly in a 365 nm UV light. Positive signals are obtained within 10–12 days. MGIT can also be used as a rapid method for the detection of drug resistant strains of *M. tuberculosis* directly from smear positive samples as well as for indirect drug susceptibility studies. An advantage over BACTEC is its lower cost and has no radioactivity issues61.

In a study conducted in South Africa, among 1267 specimens, MGIT versus LJ medium gave a higher yield of tubercle bacilli (29.7% vs. 22.8%), higher contamination rates (16.7% vs. 9.3%) and shorter time to positivity (median 14 vs 25 days for smear–negative specimens). Among smear–negative samples that were positive on MGIT culture but negative on LJ culture, 77.3% were non–tuberculous mycobacteria (NTM). Thus, MGIT gives higher yield and faster results but also at a relatively higher cost62.

**3. Serological tests:**

Most serological tests have lower turnaround time and higher negative predictive value. However, the utility of antibody detection frequently appears compromised, firstly due to BCG vaccination and secondly due to immunological sensitization by environmental mycobacteria.

**i) 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.

**ii) 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 release of interferon–gamma by blood monocytes upon their stimulation by highly specific *M. tuberculosis* antigen. Both assays have higher sensitivity and specificity compared to TST. However, previous exposure to atypical mycobacterial infections such as *M. marinum and M. kansasi* 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%)38.

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 patients38.

**4. Molecular tests:**

**i) Polymerase Chain Reaction (PCR)**

A large number of sample organism load was required by all the above methods which is the major limitation in detection of *M. tuberculosis*. A single test, which can amplify the genome, even if a single organism is present in the sample, would be ideal for detection of paucibacillary TB cases. PCR is mainly used to complement clinical and histological examination in CTB, especially for undefined cases. In this test, *M. tuberculosis* DNA (most commonly targeting the IS 6110 gene specific for the MTC) present in the fresh tissue sample or paraffin block is amplified and then can be identified to detect mycobacterial infection. The DNA can be amplified by several techniques such as: conventional or in–house PCR, PCR with hybridization or real–time PCR. Though mRNA PCR has been used in monitoring therapeutic efficacy and/or susceptibility to antibacterial agents in sputum samples, it has not found to be useful in diagnosing CTB. The sensitivity of DNA PCR varies from 25%-100%, and specificity from 73.7%-100% in CTB10,38,63,64. Tan et al, observed PCR to be 100% sensitive and specific in immunocompromised patients with multibacillary forms and 55–60% in paucibacillary forms with overall positivity of 73% in a case series of 105 cases10. In a recent prospective study comparing PCR with other diagnostic methods, though a higher sensitivity (88%) and specificity (83%) rates were attributed to PCR, authors advocated clinical presentation to be the main key in diagnosing CTB65.

**ii) Ligase chain reaction (LCR)**

A variant of PCR, in which a pair of oligonucleotides is made to bind to one of the DNA target strands, so that they are adjacent to each other. A second pair of oligonucleotides is designed to hybridize to the same regions on the complementary DNA which in turn increases specificity. The action of thermostable DNA polymerase and thermostable ligase in presence of nucleotides results in the gap between the adjacent primers being filled with the appropriate nucleotides and ligation of the primers. It is mainly used for respiratory samples, and its use in paucibacillary forms such as cutaneous TB is under nascent stage.

**iii) Cartridge Based Nucleic Acid Amplification Test** (**CBNAAT**)  
The new, rapid and also fully automated intervention free CBNAAT Xpert MTB/RIF test is a real–time cartridge–based automated DNA amplification test. It was co–developed by David Alland at the University of Medicine and dentistry of New Jersey, Cepheid, Inc. and Foundation for Innovative New Diagnostics, with additional financial support from the US National Institutes of Health66. GeneXpert NAAT test boasts a 100% sensitivity and 91.6% specificity for extra–pulmonary specimens67. It is highly sensitive for smear negative samples also. It uses three specific primers and five unique molecular probes to ensure a high degree of specificity in the diagnosis. Assay targets *rpoB* gene in *M. tuberculosis*. In addition to detecting the presence of TB, this test also detects rifampicin resistance. The results of the GeneXpert test in a study on EPTB are available within 48 hours compared to weeks for cultures. In a study by Held et al*,* all cases of multi–drug resistant TB (MDR–TB) were diagnosed with GeneXpert test68. The MDR–TB rate was calculated to be 5.8%.  
Similarily, in the study on rapid molecular detection of TB and rifampicin resistance by Boehme et al, among culture–positive patients, a single, direct MTB/RIF test identified 551 of 561 patients with smear–positive TB (98.2%) and 124 of 171 with smear–negative TB (72.5%). The test was specific in 604 of 609 patients without TB (99.2%)68.  
Also, a study done on evaluation of CBNAAT for rapid diagnosis of TB by Zeka et al with extra–pulmonary specimens, reported 100% sensitivity for smear– positive specimens69.

**iv) Loop–mediated isothermal amplification (LAMP) test**

LAMP is a novel nucleic acid amplification method in which reaction occurs under isothermal conditions i.e. without thermocycling with high specificity, efficiency, and rapidity. LAMP is used for detection of MTC, *M. avium*, and *M. intracellulare* directly from sputum specimens as well as for detection of culture isolates from samples. The whole procedure is simple, which starts with mixing of all reagents in a single tube, followed by an isothermal reaction. The resulting amplicons are visualized by adding SYBR Green dye to the reaction tube. The only equipment needed for the amplification reaction is a regular laboratory water bath or heat block that furnishes a constant temperature of 63°C. The limit of detection of assay is 5 to 50 copies of purified DNA with a 60–min incubation time70.

**v) Line probe assay (LPA)**

WHO recommended use of LPA for rapid screening of MDR– TB in low and middle–income countries and regions71. LPA uses multiplex PCR amplification and reverse hybridization to identify MTC and its mutations to genes associated with resistance to rifampicin and isoniazid. LPA can be performed directly from AFB smear– positive sputum, or from the culture isolates, and provides results in 1–2 days. A recent systematic review gave conclusion that LPA is highly sensitive and specific for detection of rifampicin resistance (≥97% and ≥99% respectively) and isoniazid resistance (≥90% and ≥99% respectively) on culture isolates and smear–positive sputum. It has been documented that the agreement of LPA with conventional drug susceptibility testing (DST) for detection of MDR–TB was 99%72.

**Antitubercular Drug Trial (Therapeutic Trial):**When the clinical picture of CTB is uncertain, and laboratory results are indecisive but the suspicion of diagnosis of CTB is high, the concept of therapeutic challenge as a valid diagnostic method has been discussed73. Four–drug ATT (consisting of isoniazid, rifampicin, pyrazinamide and ethambutol) is initiated and the clinical response is monitored in 4–6 weeks. It has been suggested that adequate duration of a therapeutic trial is 5 weeks in cutaneous TB suspects. If there is no significant response after 5 weeks, it is unlikely that further treatment may be beneficial5. So, either the diagnosis should be reviewed or possibility of MDR–TB should be considered.

However, patients with tuberculids and those with latent disease might take longer; around 8–9 weeks to respond, and thus prolonging the therapeutic trial in such cases may be considered before considering alternative diagnosis56.

**Systemic Screening for Tubercular Focus**

Coexistent systemic focus of TB has been observed in about one fourth of all patients with cutaneous lesions12. The range is reportedly higher in paediatric population (21.3–53.4%)7,8,23,29. Thus, it becomes mandatory to screen all patients of CTB carefully. Associated TB focus elsewhere in the body is a guide to the duration of ATT. A thorough clinical assessment of lymph nodes, pulmonary, extra pulmonary and gastrointestinal system, nervous system, eyes and musculoskeletal system and reproductive system should be performed.

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