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Original Research Article

Dermatopathological Presentations of Cutaneous Tuberculosis: A Tertiary Hospital Experience

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Abstract

Background: Even though Cutaneous Tuberculosis (CTB) is quite rare worldwide; in India, it constitutes 1.5% of all cases of extrapulmonary tuberculosis. Though *Mycobacterium tuberculosis, mycobacterium bovis*, and the BCG immunizing agent are the most common causative organisms, in a group of Cutaneous TB lesions called Tuberculids, no organisms may be found. These lesions arise through hypersensitivity reaction to TB antigens and are characterized by sterile, AFB-negative lesions. Diagnosis and identification of these lesions may be difficult, as they may resemble several other dermatological conditions clinically and histopathologically. The present study aims to document the spectrum of clinicopathological findings in Cutaneous Tuberculosis cases presenting at CIMS, Bilaspur, a tertiary care hospital in Chhattisgarh state of India.

Materials & Methods: 20 cases clinically diagnosed as Cutaneous Tuberculosis in the Department of Dermatology and Venereology, CIMS, Bilaspur between July 2017 and Jan 2021 and confirmed at the Department of Pathology, CIMS, Bilaspur on the basis of histopathological and cytopathological examination along with Zeihl-Neilsen staining for acid-fast bacilli (AFB) were retrospectively analyzed. The cases were classified based on clinico-pathological diagnostic criteria as well as various incidental parameters like age, sex, site, clinical presentation etc.

Results: Lupus Vulgaris (LV) and Tuberculosis Verrucosa Cutis (TBVC) were the most commonly diagnosed (30% each), followed by Scrofuloderma (SFD) and Erythema Induratum of Bazin (EIB) (15% each). Papulonecrotic Tuberculid (PNT) and Orificial TB (TBO) were least common (5% each). 30% patients had concomitant Systemic Tuberculosis, out of which one patient simultaneously exhibited features of Cutaneous Tuberculosis (SFD) and Lepromatous Leprosy (LL).

65% patients were males while 35% were females with a male to female ratio of 1.85:1. The mean age at presentation was 36.59 yrs. with the youngest being 9 years old and the oldest 63 years. Lower and upper extremities were the commonest site of involvement (85%) and 20% patients had lesions involving multiple sites. Size of induration on Tuberculin Skin Test (TST) was significant with 90% cases showing induration >10mm. Induration diameter nearabout or exceeding 30mm was particularly seen in Tuberculids like PNT and EIB.

The most consistent histopathological findings were chronic inflammatory infiltrates (100%), epithelioid granulomas (95%), multinucleate giant cells (80%). Hyperplastic epidermal features were observed in 60% cases; most prominently in TBVC and LV. Caseous necrosis (25%) was observed in 2 cases of SFD and 1 case each of PNT, TBO and EIB. Septolobular panniculitis, necrotic fat lobules and perivascular inflammatory infiltrates were the most

prominent histological features of EIB. 80% cases including all the Tuberculids tested negative for AFB. AFB positivity was particularly seen in SFD patients; and where SFD was concomitant with PTB and LL, plenty of AFB were visible in the purulent aspirates and imprint smears.

Conclusion: Due to the diverse clinicopathological manifestations, confusion with other cutaneous disorders and the inability to demonstrate AFB in the lesions, precise diagnosis may be overlooked if a high index of suspicion is not maintained. Suggestive findings in clinical and histopathological examination along with a strong positive TST remains the cornerstone in the diagnosis and treatment of CTB.

Keywords: Cutaneous, Tuberculosis, Lupus Vulgaris, TBVC, Scrofuloderma, Tuberculids, Erythema Induratum of Bazin, Tuberculin Skin Test, AFB.

Introduction

Even though Cutaneous Tuberculosis (CTB) is quite rare worldwide; in India, it constitutes 1.5% of all cases of extrapulmonary tuberculosis. Of all the clinical varieties, Scrofuloderma (SFD) is the most typically encountered variant followed by Lupus Vulgaris (LV) and Tuberculosis Verrucosa Cutis (TBVC). [1] *Mycobacterium tuberculos*is, *mycobacterium bovis*, and the Bacille Calmette-Guérin (BCG) immunizing agent are the most common causative organisms. Infection may be acquired exogenously or endogenously and present as different clinical morphologies. Diagnosis and identification of these lesions may be difficult, as they resemble several other dermatological conditions that are often primarily considered in the differential diagnosis. [2] In this scenario, a pathological confirmation often helps to overcome the diagnostic challenge faced by the dermatologist.

Materials and Methods

20 cases clinically diagnosed as Cutaneous Tuberculosis in the Department of Dermatology and Venereology, CIMS, Bilaspur between July 2017 and Jan 2021 and confirmed at the Department of Pathology, CIMS, Bilaspur on the basis of FNAC, Zeihl-Neilsen (ZN) staining, and histopathological examination were retrospectively analyzed.

Detailed history and physical examination findings were recorded; including age, sex, site and manifestation of the cutaneous lesions. Clinical features suggestive of concomitant presence or absence of systemic tuberculosis was also noted. Tuberculin Skin Test (TST) was performed on each of the patients and the size of induration measured after 72 hours.

Histopathological analysis of biopsy samples from the cutaneous lesions was conducted at the Department of Pathology, CIMS, Bilaspur. H&E-stained slides were examined and diagnosis was confirmed by visualization of epithelioid granulomas, chronic inflammatory infiltrates, giant cells, caseous necrosis and AFB in the lesions. In frankly suppurative lesions, FNAC and imprint smears were collected and stained with MGG, PAP and H&E stains. ZN staining was also performed to elicit AFB.

Observation

Table 1: Age and Sex Distribution

Sl. No.	Age Range (yrs.)	Male	Female	Total	% cases
1.	0-15	2	1	3	15%
2.	16-30	4	1	5	25%

3.	31-45	2	3	5	25%
4.	46-60	5	1	6	30%
5.	>60	0	1	1	5%
Total		13 (65%)	7 (35%)	20	100%

Table 2: Clinical Diagnosis

Sl. No.	Cutaneous Tuberculosis (CTB) Lesion	No. of Cases			Concomitant Systemic TB
		Males	Females	Total	
1.	Lupus Vulgaris (LV)	4	2	6 (30%)	No (n = 0)
2.	Tuberculosis Verrucosa Cutis (TBVC)	5	1	6 (30%)	No (n = 0)
3.	Scrofuloderma (SFD)	2	1	3 (15%)	Yes (n = 2)*
4.	Papulonecrotic Tuberculids (PNT)	1	0	1 (5%)	Yes (n = 1)
5.	Tuberculosis Orificialis (TBO)	1	0	1 (5%)	Yes (n = 1)
6.	Erythema Induratum of Bazin (EIB)	0	3	3 (15%)	Yes (n = 2) †
Total		13	7	20	6 cases

* 48yr. male with SFD along with concomitant Pulmonary Tuberculosis (PTB) and Lepromatous Leprosy (LL)
†55yr. female with EIB along with concomitant TB Spine

Table 3: Clinical Presentation-Site of lesion

Sl. No.	Site		No. of cases	Clinical Diagnosis
1.	Head and neck	Face	2	LV (n=2)
		Neck	3	SFD (n=2)[a] LV (n=1)
	Total Cases involving Head & Neck		**n=5 (25%)**	
2.	Trunk	Chest wall	2	SFD (n=2)[a,b]
	Total cases involving Trunk		**n=2 (10%)**	
3.	Upper extremity	Arm	1	SFD (n=1)[b]
		Forearm	4	LV (n=2) SFD (n=1)[b] TBVC (n=1)
		Hand (incl. palm)	1	PNT (n=1)[c]
		Fingers	1	TBVC (n=1)
	Total Cases involving Upper Extremities		**n=7 (35%)**	
4.	Lower extremity	Buttocks	1	LV (n=1)
		Calf	3	EIB (n=2)[d]
		Foot	6	TBVC (n=4) PNT (n=1)[c] EIB (n=1)[d]
	Total Cases involving Lower Extremities		**n=10 (50%)**	
5.	Peri-orificial Area	Perianal region	1	TBO (n=1)
	Total Cases involving Periorificial Regions		**n=1 (5%)**	
6.	Lesions at Multiple Sites		n=4 (20%)	

Four cases had lesions at multiple sites:
a) SFD in a 38yr female involving neck and chest
b) Simultaneous SFD and LL in a 48yr. male involving chest wall, arm & forearm
c) PNT in a 51yr. male involving palms and feet
d) EIB in a 55yr. female involving calf and ankle

Table 4: TST (size of induration) & ZN Staining for AFB

Table 4a. Tuberculin Skin Test (TST)								Table 4b. ZN Staining		
Sl. No.	CTB Lesion	Size of Induration (mm)					No. of Cases	AFB		
		None	1-10	11-20	21-30	>30		Positive	Negative	Total
1.	LV	-	1	3	2	-	6	0	6	6
2.	TBVC	-	-	3	3	-	6	0	6	6
3.	SFD	-	-	1	2	-	3	3	0	3
4.	PNT	-	-	-	1	-	1	0	1	1
5.	TBO	1	-	-	-	-	1	1	0	1
6.	EIB	-	-	-	1	2	3	0	3	3
Total		1	1	7	9	2	20	4	16	20
Percentage		5%	5%	35%	45%	10%	100%	20%	80%	100%

Table 5: Histopathological Findings

S. N.	CTB Lesion		No. of cases							% Cases
			LV	TBVC	SFD	PNT	TBO	EIB	Total	
DERMIS										
1.	Epithelioid Granuloma (n=19; 95%)	Caseating	0	1	2	1	1	1	6	31.5
		Non-Caseating	6	5	0	0	0	3	13	68.4
2.	Inflammatory Infiltrates (n=20; 100%)	Lymphohistiocytic	2	3	3	0	1	3	12	60
		Lymphoplamacytic	2	1	0	0	0	0	3	15
		Mixed	2	2	0	1	0	0	5	25
3.	Multinucleate Giant Cells (n=16; 80%)	Langhans Type	3	2	1	0	0	2	8	50
		Foreign-body Type	1	2	2	1	1	1	8	50
4.	Necrosis (n=5; 25%)	Caseous	0	0	2	1	1	1	5	100
		Fat	0	0	0	0	0	1*	1	20
5.	Vasculitis (n=5; 25%)	Lymphocytic	1	0	0	1	0	3	5	100
		Neutrophilic	0	0	0	0	0	1*	1	20
6.	Panniculitis (n=4; 20%)		1	0	0	0	0	3	4	20
7.	Fibrosis (n=6; 30%)		2	0	2	0	0	2	6	30
8.	Infiltration &/or Destruction of Epidermal Appendages (n=7; 35%)		2	1	2	1	0	1	7	35
EPIDERMIS										
1.	Hyperkeratosis, Papillomatosis, Acanthosis, Pseudoepitheliomatous Hyperplasia (n=12; 60%)		3	6	1	1	1	0	12	60
3.	Parakeratosis & Dyskeratosis (n=1; 5%)		0	1	0	0	0	0	1	5
5.	Epidermal atrophy (n=6; 30%)		3	2 (central areas)	0	0	0	1	6	30
6.	Ulceration & Neutrophilic Infiltration (n=10; 50%)		4	2	2	1	1	0	10	50

*1 case of EIB showed both caseating and fat necrosis and also both lymphocytic and neutrophilic vasculitis. The patient had concomitant TB Spine.

Clinical Features:

Age & Sex: Out of 20 cases, 13 were males (65%) and 7 females (35%); with a male to female ratio of 1.85:1. The patients were divided into 15yr age ranges, the youngest being 9 years old and the oldest 63 yrs. Mean age at presentation was 36.59 yrs. Maximum (30%) patients presented with disease between 46-60 years, with patients in the 16-30 yrs. and 31-45 yr. age groups following at a close second at 25% each. Altogether, 80% of patients were found to be within 15-60 yrs. 15% patients belonged to the pediatric age group (0-15yrs.), whereas only a single patient (5%) was found to be over 60 yrs. age. [Table1.]

Clinical Diagnosis: Lupus Vulgaris (LV) and Tuberculosis Verrucosa Cutis (TBVC) were the most commonly diagnosed (30% each), followed by Scrofuloderma (SFD) and Erythema Induratum of Bazin (EIB) (15% each). We also recorded 1 case each of Papulonecrotic Tuberculid (PNT) and Orificial TB (TBO) respectively (5% each). [Table 2.] [Figure 1.]

Systemic Tuberculosis: 6 patients (30%) had concomitant Systemic Tuberculosis. These included 2 cases of SFD, of which one patient also exhibited simultaneous features of Lepromatous Leprosy (LL) [Fig. 4]. 1 patient with EIB had TB Spine. One patient each of TBO, PNT and EIB were also found to be suffering from concomitant PTB. [Table 2.]

Site of the lesion: Lower extremities were the most commonly affected (50%); followed by upper extremities (35%), head and neck (25%), trunk (10%) and perianal area (5%). 4 cases had lesions at multiple sites; 2 of these were patients with SFD with multiple lesions in neck, chest and upper extremities. [Table 3.]

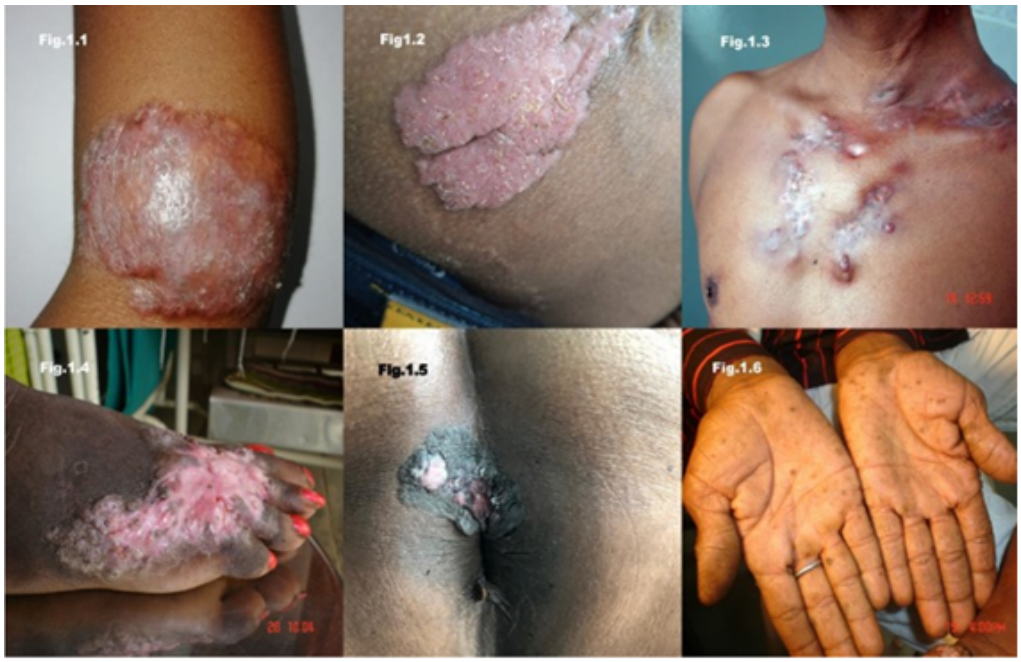

Fig.1.1: LV, Plaque Type
Fig.1.2: LV, Hypertrophic Type
Fig1.3: SFD
Fig.1.4: TBVC with Central Atrophy
Fig.1.5: TBO
Fig.1.6: PNT

Figure 1: Clinical Variants of Cutaneous Tuberculosis

Laboratory Features:

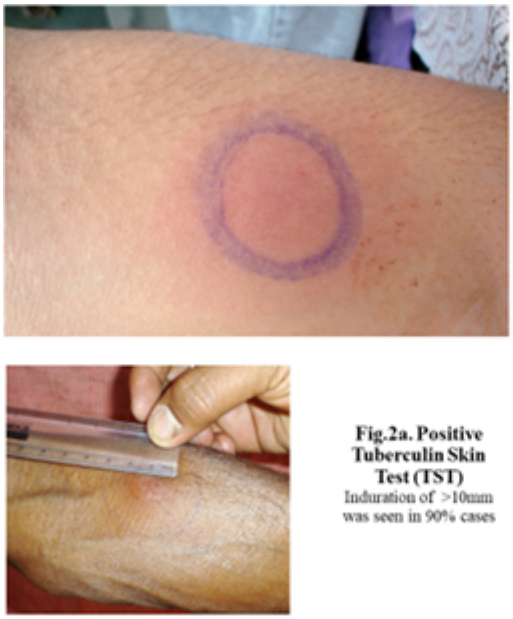

Fig.2a. Positive Tuberculin Skin Test (TST) Induration of >10mm was seen in 90% cases

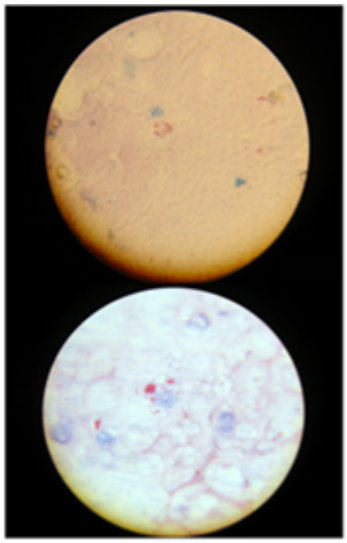

Fig. 2b. Caseous Necrosis with Acid Fast Bacilli (AFB)

Figure 2: TST & AFB

i. Tuberculin Skin Test (TST): 90% cases showed induration exceeding 10mm. In 45% cases induration was in the range of 21-30mm diameter. A single case of TBO with concomitant PTB did not elicit any induration, probably due anergy. 1 case of LV (5%) showed induration of <10mm diameter. 2 cases of EIB (10%) exhibited induration diameter >30mm. [Table 4a.] [Figure 2a.]

ii. AFB: 80% cases tested negative for AFB upon ZN staining. Among the AFB positive cases (20%), there were 3 cases of SFD and 1 case of TBO. Where SFD was concomitant with PTB and LL, plenty of AFB were visible in the purulent aspirates and imprint smears. [Table 4b.] [Figure 2b.]

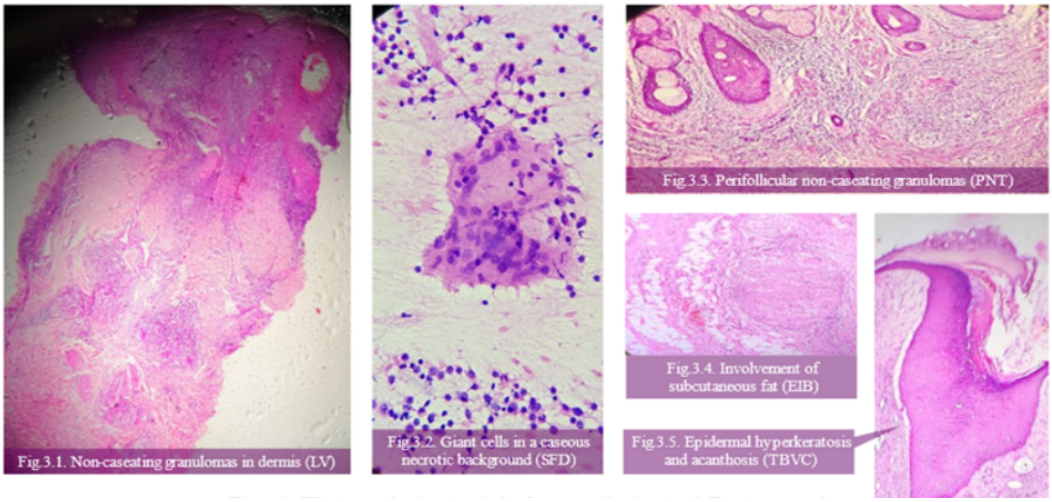

Figure 3: Histopathological & Cytopathological Features of Cutaneous Tuberculosis

iii. Histopathological Examination: The most consistent histopathological findings were epithelioid granulomas (95%) and chronic inflammatory infiltrates (100%) in the dermis. Most epithelioid granulomas were noncaseating (68.4%); caseating granulomas were seen in 31.5% cases. Inflammatory infiltrates were categorized

as lympho-histiocytic, lympho-plasmacytic and mixed, depending on the predominant category of cells present in the infiltrates. Multinucleate giant cells: both Langhans and Foreign-body type, were seen in 80% of cases.

Hyperplastic epidermal features like hyperkeratosis, acanthosis, papillomatosis and pseudoepitheliomatous hyperplasia were observed in 60% cases: most prominently in TBVC (100%) and LV (50% cases). These changes were usually accompanied by epidermal ulceration and neutrophilic infiltration in the epidermis (50% cases). Infiltration and destruction of the epidermal appendages was seen in 35%. Epidermal thinning and atrophy were also found in 30% cases, typically in the atrophic forms of LV and the central hypopigmented portions of TBVC. 1 case of TBVC (5%) also showed parakeratotic and dyskeratotic changes.

Caseous necrosis (25%) was observed in 2 cases of SFD and 1 case each of PNT, TBO and EIB. In 1 case of EIB with concomitant Spine TB, necrotic fat lobules were also observed in association with caseous necrosis.

Fibrosis was seen in 30% cases, with extensive and disorganized fibrosis being evident in 2 patients with SFD and one case of LV on the forearm.

Septolobular panniculitis, necrotic fat lobules and perivascular inflammatory infiltrates were as the most prominent histological features of EIB. In 1 case of EIB, neutrophilic infiltrates were also observed along with lymphocytes. [Figure 3.] [Table 5.]

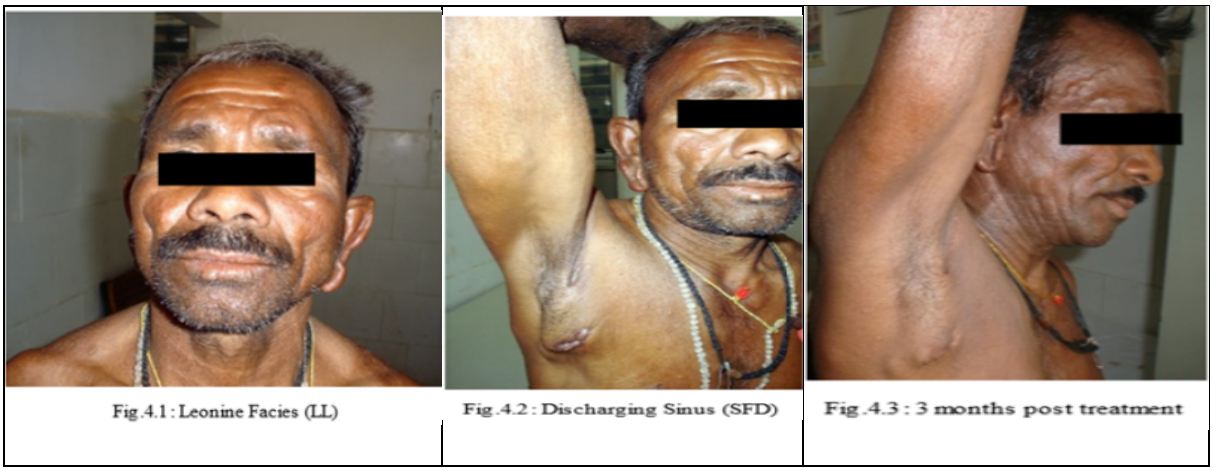

Fig.4.1 : Leonine Facies (LL) Fig.4.2 : Discharging Sinus (SFD) Fig.4.3 : 3 months post treatment

Figure 4 Scrofuloderma with Coexistent Lepromatous Leprosy and Pulmonary Tuberculosis

Discussion:

Age and Sex Distribution: CTB is primarily a disease of young adults, with low incidence in the pediatric and geriatric age groups. [3,4,5] In concordance with the aforementioned, the mean age at presentation in our series was 36.05 yrs. However, in a slight departure from other observations, maximum patients in our study presented between 46 to 60 years age (30 %), closely followed by patients in the 16-30 yr. and 31-45 yr. age group (25% each). A majority of the population in our state is rural and agrarian by nature and has the habit of working in the fields and walking barefoot on soil contaminated with tuberculous sputum. [6] This habit is more evident in the relatively older population who are not comfortable wearing footwear. This is the most plausible reason that majority of patients in the 46-60 yr. age group are males and manifest cutaneous tubercular lesions of TBVC. The incidence of 15% in the pediatric population was well within the

range of 12.8% & 36.3% documented by Sehgal et al. [7] and Wong et al. [8] respectively. Similarly, the low incidence of 5% in the elderly was also corroborated by the studies of Ramesh et al. [4] and Kaur et al. [5]

Sex distribution in our study with males outnumbering the females by a ratio of 1.85:1 was well within the limits observed by other authors. [3,4,5]

Clinical Diagnosis: Several classification systems have been proposed based on the state of host immunity, the amount of bacillary load and mode of inoculation etc. [9] Based on the bacillary load, Cutaneous Tuberculosis may be divided into Multibacillary and Paucibacillary forms. [6] Multibacillary forms include TB Chancre, SFD, TBO, Miliary TB & TB Gumma, while paucibacillary forms include TBVC, LV and Tuberculids. [4,10] Tuberculids are not true cutaneous tuberculous lesions but represent immune hypersensitivity reactions to tubercular antigens [2,10,11] and are characterized by the absence of AFB in culture and PCR. [12]

However, the most widely used classification is the one based on the inoculation mechanism. [10]

CUTANEOUS TUBERCULOSIS CLASSIFICATION[10]

A. Exogenous Cutaneous Tuberculosis
Tuberculous Chancre and Tuberculosis Verrucosa Cutis

B. Endogenous Cutaneous Tuberculosis
a) ***By contiguity or autoinoculation***
- Scrofuloderma
- Orificial Tuberculosis
-some cases of Lupus Vulgaris
b) ***By hematogenic dissemination***
- Lupus Vulgaris
- Tuberculous Gumma
- Acute Miliary Tuberculosis

C. Tuberculids
- Papulonecrotic tuberculid
- Lichen scrofulosorum
- Erythema Induratum of Bazin

D. Cutaneous tuberculosis secondary to BCG vaccination

In India; LV is the commonest variant of CTB [10,13,14] followed by SFD3 or TBVC. [4,5] Even though the incidence of LV and TBVC were found equal (30% each) in our series, it still correlated well with the findings of several other authors. [4,5,15] The high incidence of TBVC in our study could be explained by the lack of health awareness among the population and preference for walking barefoot.16 Most studies report a female preponderance in cases of LV. [17] However, in sharp deviation from the aforementioned, we found an a male:female ratio of 2:1 in the case of LV.

SFD is the most common form of CTB in developing countries, particularly in children. [10,15,18] The incidence of SFD in different studies from the Indian subcontinent exhibited vastly divergent ranges from 14% to 36.6%. [3,4,5,15,19] The 15% incidence of SFD recorded in our series almost mirrors the 14% incidence recorded by Dwari et al. [15]

Barring a few authors like Chong et al. [11], and Zhang et al. [20], most Asian studies record much lower incidences of EIB. [3,4,5,15] Our finding of a 15% incidence; though higher than others, correlated well with the 18.7% incidence

reported by Mann et al. from Brazil. [21] All the patients were young and middle-aged females with lesions in their lower extremities. [10,22]

The 5% incidence each of TBO and PNT found in our study also correlated well with the range reported by most authors. [3,5,19] In our study, 30% patients also had associated systemic disease, most common of which was PTB. Wide variations in the incidence of concomitant systemic involvement in CTB cases (12.7% - 53.4%) have been reported. [1,4,5,17,18,23] Systemic TB is more commonly associated with SFD, [4,19] EIB [1,23] and TBO [10,24] compared to high immunity variants like LV or TBVC [4]; a fact also reflected in our study. Likewise, coexistent spine TB [5] and Lepromatous Leprosy [15] has also been reported by other authors.

Site Distribution of Cutaneous Tuberculosis:

In western countries, the majority of cutaneous tubercular lesions are located in the head and neck region. However, in India, due to poor hygiene and the habit of walking barefoot, lower extremities are more commonly affected. [1,3,4,9,13,19] In concordance with these observations, we found the lower extremities to be affected in ≥ 50% cases, followed by upper extremities (35%), head and neck (25%), trunk (10%) and perianal area (5%). SFD was exclusively found in the neck region and chest wall [1,4] while LV and TBVC showed a predilection for the extremities. [4,11,19] As the primary infection in SFD is a cervical lymphadenitis secondary to consumption of un-boiled/unpasteurized milk, the preferential distribution of SFD in the neck and chest regions can be explained by the spread of infection to contiguous supraclavicular lymph nodes and the rib bones giving rise to cold abscesses and discharging sinuses. [9,19]

More than 90% of LV lesions in western countries involve the head and neck region, but in tropical countries, lower extremities or buttocks are more commonly affected. [19,25] However, in our series, 50% of LV cases showed preference for the head and neck region, with only a single case affecting the buttocks [13]. Maximum predilection for the lower extremities was shown by TBVC (66.6%). Usually, LV and TBVC affect the exposed trauma-prone body parts, i.e.; hands and fingers in adults, and, buttocks and the lower extremities in children who walk barefoot on soil contaminated with TB sputum. [9,10,13]

EIB lesions are typically distributed in the posterior surface of legs and thighs, which was corroborated by our study as well. [12,22,26,27] PNT commonly affect the face, ears, extensor areas of extremities, trunk and buttocks, [10,28] but the unusual location of the lesions on the palms and soles seen by us has also been reported by Sirka et al. [28]

Though the most common location of TBO is the oral mucosa, other well-documented sites of disease include the perianal skin [24,29], vulva, urinary meatus, and glans penis after autoinoculation of AFB during defecation or urination. [9] The single case of perianal TBO reported by us was therefore in concordance with the aforementioned findings.

Tuberculin Skin Test:

The Tuberculin Skin Test is a good screening test to detect the presence or absence of tubercular infection as it identifies individuals sensitized to *Mycobacterium tuberculosis*. [1,6] Induration of 10 mm or more is considered significant for those without immune deficiency, while induration of 5mm or more is indicative of reactivity for patients with AIDS. [6] However, induration indicates infection and not necessarily the disease. [1] False-positive results may occur due to exposure to environmental and atypical mycobacteria as well as within 1 year of BCG vaccination. [1,6]

False negative reactions can occur in extremes of age, immunosuppressed states, chronic diseases and disseminated disease (miliary tuberculosis). [1,6] TST is typically negative because of anergy in up to 50% cases of disseminated disease and acute cutaneous miliary tuberculosis [1,2,6,9,12] whereas the strongest reactivity; due to cutaneous immunological reactions to TB antigens, is seen in case of Tuberculids (Papulonecrotic Tuberculid, Lichen Scrofulosorum, Erythema Induratum of Bazin). [1,6,9,12,22] TBO commonly shows negative results for TST due to a decrease in tuberculo-host defense and also due to being commonly associated with AIDS. [6,12,24,29] SFD and LV more often present strongly reactive tests. [2,4,6,9,12]

TST has a sensitivity between 33% and 96% and specificity of 62.50% with a cutoff of 10 mm, with much higher sensitivity rates in unvaccinated population (>97%). [6,12] Most studies from the Indian Subcontinent have reported significant TST results (>10mm) [1,3,5,15,19,12] with incidences ranging from 33% (Puri et al.) [3] to as high as 96-97% (Singhal et al. & Dwari et al.) [1,14] In our study, 90% cases showed significant induration exceeding 10mm, with maximum no. of cases (45%) showing induration in the range of 21-30mm diameter. The high incidence can be explained by the widespread lack of public health awareness and insubstantial data regarding BCG vaccination in the underprivileged and predominantly rural population of Chhattisgarh.

As inferred by numerous Indian studies, [1,3,15,19] almost all CTB cases in our study exhibiting moderate to high Tuberculin hypersensitivity (LV, SFD and TBVC) showed induration 11-20mm. Maximum induration (near about and exceeding 30mm) was observed in all the 3 cases of Tuberculids (1 case of PNT and 2 cases of EIB), proving that Tuberculids exhibit the greatest degree of Tuberculin hypersensitivity among all cases of CTB. [1,2,9,12,22] The single case of Perianal TB which also had concomitant PTB did not elicit any induration on TST, probably due anergy. [24,29]

Demonstration of AFB:

Compared with culture by Lowenstein–Jensen medium, direct AFB staining is inferior due to lesser sensitivity, but has the advantage of presenting faster results than culture. [1,6,12] However, AFB staining is not diagnostic of CTB, since the other pathogens like Nocardia, Corynebacterium, nontuberculous mycobacteria, and even artifacts may reveal acid-fast characteristics. [19] AFB positivity on cytology is depends on the mycobacterial load in the tissue and varies over a wide range- from 2.1% reported Singhal et al. [1] to 18.4% as reported by Vashisth et al. [17] Pandhi et al. additionally noticed that identification of AFB was higher (10.3%) in cytology smears from lymph nodes compared with detection on histological sections of skin biopsies (2.9%) and suggested that culturing the organisms from cytology smears may be a good alternative to biopsy. [1,23]

Multibacillary forms like SFD, TBO, Miliary TB, etc. exhibit significant numbers of acid-fast bacilli due to low degree of immunity and/or immunocompromised state; while paucibacillary forms like TBVC and LV, as well as Tuberculids resulting from a hypersensitivity reaction to mycobacterial antigens are typically negative because of the high degree of immunity in these patients. [2,4,6,9,15,19,24] In keeping with the afore-cited studies, all cases of LV, TBVC, EIB and PNT tested negative for AFB upon ZN staining. Among the AFB positive cases, 3 were seen in SFD, while one was a case of TBO.

The diagnostic yield of smears is particularly higher for wet or exudative lesions due to higher bacterial loads; [1,6]

a feature consistently observed in case of SFD [4,6,9,19] and also corroborated by our study. Similar to Dwari et al. [15] and Varshney et al. [19], we also found a single case where SFD coexisted with PTB and Lepromatous Leprosy. As postulated by the aforementioned authors, in this patient too, the marked lack of immunity was evidenced by finding plenty of acid-fast bacilli in the purulent aspirates and imprint smears taken from the suppurative nodules and discharging sinuses. In case of TBO, AFB positivity may be variable. While most studies including ours report positive findings, [24,30,31] few authors have also reported negative yields. [3,24,30,31]

Therefore, in case of justifiable clinical suspicion, finding AFB in tissue or secretions warrants the commencement of empiric ATT trial even in the absence of diagnostic histopathological features. [19]

Histopathological Examination:

Histopathological examination is essential to complement the investigation of CTB cases. However, in most samples, the bacillus cannot be observed even when special staining techniques are performed. [3,6,15] Besides the absence of the bacillus, confirming a CTB diagnosis based on histology alone is limited by the fact that otherwise characteristic diagnostic features are not always found, making it impossible to predict the diagnosis solely from histology. [6,15,32] This occurs because of the histological similarity between CTB and other infectious granulomatous diseases like cutaneous leishmaniasis, tuberculoid leprosy, superficial granulomatous pyoderma, and chromomycosis; as well as some granulomatous disorders of unknown etiology like cutaneous sarcoidosis, lupus miliaris disseminatus faciei and granulomatous rosacea. [6,13,12]

The most common histological finding in CTB is the tuberculoid granuloma in the dermis, observed in 57% to 96% of biopsies. [3,6,15] At 95%, our findings conform to the upper limits of the aforementioned spectrum. In concurrence with the higher incidence of LV (30%), TBVC (30%) and Tuberculids (20%) in our study, 68.4% of the granulomas were noncaseating; while caseating granulomas were seen in only 31.5% cases, primarily in SFD and TBO. [1,2,6,9,12,13,24] Some authors [7,32] report the finding of other types of granulomas in CTB, such as sarcoid granulomas, suppurative granulomas and annular-like granuloma formations, but none of these variants were found in our study. However, granulomas may not be found in all cases. As reported by Kaur et al. [5] and Dwari et al. [15], and also corroborated by our findings; in up to 19.44% cases [5], a non-specific chronic inflammatory infiltrate may be found in the absence of cutaneous granulomas.

Chronic inflammatory inflammation is a hallmark of cutaneous tubercular lesions [1,5,6,13,15,19] and was found in 100% cases in our series. Most common type is a lymphohistocytic infiltrate made up of lymphocytes, epithelioid histiocytes and giant cells of Langhans and/or foreign-body type, [3,5,6,13,12,15,19,22,24] and also substantiated by our study (lympho-histiocytic infiltrate- 60% cases, giant cells-80% cases). Though relatively uncommon; the presence of mixed acute and chronic inflammatory infiltrates (25% cases), and chronic inflammatory infiltrates in exclusion of giant cells (15% cases) found in our study has also been ratified by other authors. [6,12]

The other two most important findings, in decreasing order of frequency, are epidermal hyperplasia (57% - 86%) and caseous necrosis (11.8% - 57%). The first is more common in verrucous forms, and the second is observed in inflammatory forms. [6,32,33,34] With a 60% incidence of epithelial hyperplastic lesions (hyperkeratosis, papillomatosis, acanthosis, pseudoepitheliomatous

hyperplasia) and 25% incidence of caseating necrosis, our findings are well within the respective ranges cited previously.

Hyperplastic epidermal features were observed in 100% cases of TBVC6,15 and 50% cases of LV, [2,14,34,35] while epidermal thinning and atrophy9,13 was found in the atrophic variants of LV and the central hypopigmented portions lesions of TBVC lesions (30% cases). 1 case of TBVC also showed parakeratotic and dyskeratotic changes. Similar findings have been reported by Pai et al., [13] albeit in a case of LV. Similarly, other documented secondary epidermal abnormalities like ulceration, neutrophilic infiltration and destruction of epidermal appendages have also been validated by others. [2,6,9,13]

Necrosis in CTB can be graded along an immunopathological spectrum.15 Necrosis is virtually non-existent at the high end of the spectrum (LV and Lichen Scrofulosorum) while being evident extensively at the low immune end (SFD, Metastatic Abscesses and TB Gumma). [1,2,6,9,12,13,15] Extensive caseous necrosis was observed in 66.66% cases of SFD and the single case of Perianal TB, with cytological smears from the lesions also showing fragmented granulomas, epithelioid histiocytes and plenty of AFB. In both these lesions, concomitant Pulmonary Tuberculosis was found, 1 case of SFD additionally manifested features of LL (Fig. 4), bearing further testament to the extreme degree of immunocompromise associated with the two aforementioned variants of CTB. [4,6,10,15,24] Fibrosis was most prominently noted in chronic lesions of SFD & EIB [2,5,13,22] and atrophic scars of LV.[1,13]

Out of all types of CTB, histopathology is particularly useful for diagnosis of Tuberculids where bacilli cannot be isolated by culture or demonstrated by AFB staining. [1] Tuberculids comprise of a heterogeneous group of Cutaneous Tuberculosis cases that arise through immune-mediated pathogenesis and are characterized by sterile lesions where the bacilli are destroyed owing to the hypersensitivity reaction against TB antigens.9 These patients typically have a highly positive TST result. Histology from skin biopsy specimens are negative for AFB smears and cultures fail to identify *M. tuberculosis*. [2,6,9]

Some authors also consider Erythema Nodosum to be a Tuberculid as it is sometimes associated with Tuberculosis, especially in India. [1,9] Erythema Nodosum; characterized by painful subcutaneous nodules on the shins, and septal panniculitis without vasculitis, is considered to be the primary differential diagnosis of EIB. [1,9,22] All Tuberculids exhibit granulomatous inflammation and some degree of necrosis and vasculitis; a consequence of mycobacterial antigens released in the setting of a concurrent or distant infection. [2,6,9] By finding evidence of Systemic TB in 75% cases of Tuberculid lesions, our study could corroborate the aforementioned findings.

In our study, we encountered Tuberculid lesions in 1 case of PNT and 3 cases of EIB. In the case of PNT, we found evidence of non-caseating perifollicular granulomas and necrosis in the upper dermis. [2,6,9] Leucocytoclastic vasculitis is considered a distinguishing feature of PNT, [1,6,9] but we found a nonspecific perivascular lymphocytic infiltrate in all the Tuberculid lesions including PNT, putting our findings at a variance with other notable authors. [1,6,9]

Frankel et al. [2] mandate the presence of at least three out of four of the following elements to establish a diagnosis of Erythema Induratum of Bazin: 1) septal panniculitis, 2) fat necrosis, 3) small or large vessel vasculitis; and 4) granulomas; By documenting all the aforementioned features, all EIB cases in our series were able to fulfil the requisite diagnostic criteria. [1,2,9,15,22]

Treatment:

CTB treatment is the same as that for systemic TB and consists of 6 to 9 months long multidrug therapy. [2,6] Second line drugs are to be considered in case of failure/clinical resistance. [36,37] In doubtful cases, 5-6 weeks of therapeutic trial in an adequate dose is helpful in obtaining a favorable response. [36]

All the patients in our series were put on ATT as per the National Tuberculosis Elimination Programme. [37] Good clinical response was observed in patients with LV, SFD, and TBVC after a 6-month course. Clinical cure was defined as the absence of active skin lesions. Extended therapy for 9 months was required in 2 cases of LV and 1 case of SFD due to persistent signs of clinical activity. The SFD-LL co-infected patient [Fig 4.1 & 4.2] was started with anti-leprotic MDT drugs [38] Clofazimine and Dapsone except Rifampicin. The patient demonstrated marked improvement of clinical features after three months of treatment [Fig.4.3]. [39]

Conclusion:

Tuberculosis is a major health problem worldwide, and Cutaneous Tuberculosis, although uncommon, is frequently encountered in patients in endemic areas. Due to the diverse clinicopathological manifestations, features overlapping with other cutaneous disorders and the inability to demonstrate AFB in the lesions, precise diagnosis may be overlooked if a high index of suspicion is not maintained by both dermatologists and pathologists. A simple way to increase the sensitivity of histopathology is to add the Tuberculin Skin Test (TST) and/or serum PCR. However, since easy access to nucleic acid amplification techniques like CBNAAT is still out of reach of many health care facilities in our country, suggestive findings in clinical and histopathological examination along with a strong positive TST remains the cornerstone in the diagnosis and treatment of CTB.

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