

HISTOMORPHOLOGICAL SPECTRUM OF CUTANEOUS TUBERCULOSIS IN TERTIARY CARE HOSPITAL- A CASE SERIES

Histopathology

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ABSTRACT

Introduction- Cutaneous tuberculosis constitutes 1-1.5% of all extra-pulmonary tuberculosis. Cutaneous tuberculosis reveals diverse clinical presentation ranging from papules, pustules, papulonecrotic, painful nodules, verrucous lesions, panniculitis, plaques, ulcers, sinuses, scars and may mimic other inflammatory skin diseases hence clinicopathological correlation is necessary for early diagnosis of cutaneous tuberculosis. Histopathology is gold standard for diagnosis of cutaneous tuberculosis; however ancillary tests such as Mantoux test, mycobacterial culture, gene expert studies and amplification of mycobacterial DNA by PCR (Polymerase Chain Reaction) are necessary for confirmation of diagnosis. **Aims-1.** To study clinico-pathological correlation and histological features of various morphological subtypes of cutaneous tuberculosis 2. To record incidence, age-gender distribution and common histological subtype of cutaneous tuberculosis. **Material And Methods -** We studied various morphological subtypes in 12 patients with strong clinical suspicion of cutaneous tuberculosis, out of 602 total skin biopsies received in histopathology department from January 2022 to December 2022. **Results-** On histopathology, 3 cases of Lupus Vulgaris (25%) followed by 2 cases of Lichen Scrofulosorum (16.16%), Erythema Induratum of Bazin (16.16%), Papulonecrotic Tuberculid (16.16%), Erythema Nodosum (16.16%) each and 1 case of Scrofuloderma (8.33%) were diagnosed. Incidence of cutaneous tuberculosis was found to be 1.99%. Age group of the present study ranged from 15-52 years. Most cases occurred in the age group of 20-30 years with female predominance. Most commonly involved site was the lower extremities. **Conclusions-** Cutaneous tuberculosis is an uncommon condition which is associated with significant morbidity. Diagnosis of cutaneous tuberculosis can be challenging due to varied clinical presentation and wide range of differential diagnoses. Early and expeditious diagnosis is important for effective management of patient.

KEYWORDS

Tuberculosis, Cutaneous tuberculosis, Mantoux test, Clinicopathological

INTRODUCTION-

Tuberculosis continues to be one of the major public health problem with worldwide distribution, especially in developing countries like India. ^[1] According to the World Health Organization (WHO), tuberculosis causes 1.5 million deaths every year causing major health crisis. ^[2] The resurgence of tuberculosis in developing countries is associated with low socioeconomic standards, overcrowding, multidrug resistant tuberculosis, immunocompromised states like HIV/AIDS. ^[3] Extra-pulmonary tuberculosis constitutes only 10% of all cases of tuberculosis while cutaneous tuberculosis comprises only 1-1.5% of all these cases. ^[4] Cutaneous tuberculosis was first described by Laennec in 1826. ^[5] Cutaneous tuberculosis is caused by exogenous or endogenous source, by contiguity or autoinoculation and by hematogenous spread. ^[6] The most common etiological agent causing skin manifestations of mycobacterial infection is *Mycobacterium tuberculosis* and occasionally by *Mycobacterium bovis* and the attenuated form of the bacillus calmette Guerin (BCG Vaccine). ^[2, 7] Cutaneous tuberculosis has a wide spectrum of clinical lesions ranging from papules, pustules, papulonecrotic, painful nodules, verrucous lesions, panniculitis, plaques, ulcers, sinuses, scars and may mimic various clinicopathological features of other skin diseases. ^[5, 8] Histopathology is gold standard for diagnosis of cutaneous tuberculosis but ancillary tests like Mantoux test, AFB culture, gene expert studies, QuantiFERON-TB Gold (QFT) and amplification of mycobacterial DNA by PCR (Polymerase Chain Reaction) are necessary for confirmation of diagnosis. ^[9]

MATERIALS AND METHODS-

This study was carried out in the department of pathology of our hospital from January 2022 to December 2022. Out of total 602 skin biopsies received in histopathology section, we studied various morphological subtypes in 12 patients with clinical suspicion of cutaneous tuberculosis.

Case Series-

We studied various morphological subtypes in 12 patients with clinical suspicion of cutaneous tuberculosis (Table 1). Detailed clinical history,

cutaneous examination with skin biopsy, Mantoux test, AFB culture and CBNAAT/Gene expert (Cartridge based nucleic acid amplification test) were done in all cases. Fine needle aspiration cytology (FNAC) and radiological tests were done in relevant cases. All cases were tested for HIV to see for concomitant HIV/TB; they all were negative. Diagnosed cases were given DOTS therapy with HRZE (Isoniazid, Rifampicin, Pyrazinamide, Ethambutol) drugs for a duration ranging from 6-9 months and response rate of these patients was observed.

On Histopathology, Total 3 Cases Of Lupus Vulgaris Were Reported.

Case 1: 37 year male, presented with single erythematous atrophic scar with peripheral crusted papules over right side of forehead. History of fever spikes and generalized weakness was given by patient. Mantoux test was strongly positive. *Mycobacterium tuberculosis* was not isolated from the culture. Gene expert was negative for *Mycobacterium tuberculosis*. On histopathology it was diagnosed as lupus vulgaris showing confluent epithelioid cell granuloma along with Langhans type of giant cells in the dermis. (Figure 1a, 1b)

Case 2: 10 year female child presented with severe generalized weakness and weight loss with single hyperpigmented annular plaque with central clearing and atrophy over dorsum of right foot since 3 years. Mantoux test was positive with negative culture and gene expert studies. Histopathologically it was diagnosed as lupus vulgaris. (Figure 1c)

Case 3: 52 year female, presented with evening rise of temperature with multiple erythematous waxy papules coalescing to form plaques with atrophic and papulovesicular border over neck. Mantoux test was positive with more than 15mm induration. AFB culture was negative. On gene expert, *Mycobacterium tuberculosis* was not detected. Histopathology revealed features of lupus vulgaris. (Figure 1d, 1e, 1f)

On histopathology, total 2 cases of Lichen Scrofulosorum were diagnosed.

Case 4: 24 year female came with multiple skin coloured papules

coalescing to form plaques over right and left side of abdomen and over lumbar area of back. Clinically presented with high grade fever and dull aching pain over skin lesions. Mantoux test was done which came positive. Gene expert and AFB culture did not detect *Mycobacterium tuberculosis*. On histopathology superficial dermal epithelioid cell granuloma in vicinity of hair follicles with Langhans type of giant cells were seen without areas of necrosis and was diagnosed as lichen scrofulosorum (Figure 2a)

Case 5 : 34 year male visited with red raised skin lesions over trunk and oral cavity along with multiple confluent erythematous skin papules over abdomen, chest and back. He had fever with evening rise of temperature and cough. Mantoux test was positive. AFB culture and gene expert were negative for *Mycobacterium tuberculosis*. Histopathology revealed features of lichen scrofulosorum (Figure 2b,2c,2d)

On histopathology, total 2 cases of Erythema induratum of Bazin were reported.

Case 6: 26 year female having fever and multiple painful nodular swellings over hip and thigh since 1 year. She denied other symptoms like weight loss and cough. Mantoux test was positive. Mycobacterial culture did not isolate *Mycobacterium tuberculosis*. Gene expert was negative for *Mycobacterium tuberculosis*. Histopathology confirmed diagnosis of erythema induratum of Bazin showing septolobular panniculitis with vasculitis and few epithelioid cell granuloma. (Figure 3a,3b)

Case 7: 30 year male showed multiple erythematous nodules over bilateral legs since 4 weeks along with evening rise of temperature and pleuritic chest pain. CECT scan revealed multiple matted necrotic cervical lymph nodes measuring 2.5x1.8cm along with tiny subpleural nodule. Mantoux test was strongly positive. AFB culture was negative. Gene expert detected *Mycobacterium tuberculosis*. Histopathologically it was diagnosed as erythema induratum of Bazin (Figure 3c,3d,3e,3f)

On histopathology, total 2 cases of Papulonecrotic tuberculid were reported

Case 8 : 15 year female presented with multiple erythematous to violaceous papules over posterior aspect of thigh, legs, face with central crusting and peripheral scaling. Matted lymph nodes noted in cervical region which on FNAC showed granulomatous lymphadenitis. She had a history of weight loss. Mantoux test showed positivity. However, culture and gene expert were negative for *Mycobacterium tuberculosis*. On histopathology it was diagnosed as papulonecrotic tuberculid showing necrosis encroaching upon epidermis along with epithelioid cell granuloma and Langhans giant cells. (Figure 4a,4b,4c,4d)

Case 9 : 38 year male clinically asymptomatic showed erythematous papules with healing, atrophy and hyperpigmentation over right forearm, thigh and back. Mantoux test was positive. AFB culture was negative for mycobacteria. On Gene expert, *Mycobacterium tuberculosis* was not detected. Histopathological diagnosis was papulonecrotic tuberculid showing follicular necrosis and destruction along with epithelioid cell granuloma. (Figure 4e,4f,4g,4h)

On histopathology, total 2 cases of Erythema Nodosum were

Table 2: Clinicopathological Spectrum Of Cutaneous Tuberculosis

Sr no	Age in years/ Sex	Cutaneous examination	Site	Mantoux test	AFB Culture	Clinical history	Gene expert studies	HP changes	HP diagnosis	FNAC of nodes	Follow up of patients
1	37/M	Erythematous atrophic scar with peripheral crusted papules	Forehead	Positive	Negative	Fever spikes and generalised weakness	M. TB not detected	Perifollicular Epithelioid cell granulomas with peripheral cuff of lymphocytes	Lupus vulgaris	-	Lesions started regressing with complete clearance after 5 months of starting anti-tuberculosis treatment
2	10/F	Annular plaque with central clearing and atrophy	Dorsum of foot	Positive	Negative	Generalized weakness, Weight loss	M. TB not detected	Epithelioid cell granulomas , Langhans giant cells without caseous necrosis	Lupus vulgaris	-	Patient was put on CAT I AKT and developed serology proven AKT induced Hepatitis so patient switched to hepatosafe anti tuberculosis treatment after suspension of

diagnosed.

Case 10: 27 year female, presented with high grade fever, generalized weakness and multiple erythematous to violaceous nodules and plaques on bilateral lower limbs. Mantoux test was positive. AFB culture isolated *Mycobacterium tuberculosis*. Gene expert was negative for *Mycobacterium tuberculosis*. Histopathologically it showed septal panniculitis along with epithelioid cell granuloma and was diagnosed as erythema nodosum. (Figure 5a,5b)

Case 11 : 27 year female presented with red raised painful lesions over anterior aspect of both lower legs associated with high grade fever, generalized weakness along with right sided cervical lymphadenopathy. On FNAC it was diagnosed as Tuberculous lymphadenitis. Mantoux test showed positivity and gene expert detected *Mycobacterium tuberculosis* in very low amounts. AFB culture did not isolate *Mycobacterium tuberculosis*. On histopathology, diagnosis given was erythema nodosum. (Figure 5c,5d)

On histopathology, single case of scrofuloderma which is a type of Multibacillary tuberculosis was reported

Case 12- 26 year female, diagnosed case of pulmonary tuberculosis presented with non-healing ulcerative lesion with discharging pus over neck. She had a history of cough, evening rise of temperature along with weight loss. Mantoux test was positive. Mycobacteria was isolated from AFB culture. Gene expert detected *Mycobacterium tuberculosis*. Histopathology revealed variable areas of caseous necrosis along with epithelioid cell granuloma. Special stain for acid fast bacilli (ziehl neelsen stain) showed thin slender tubercle bacilli. (Figure 6a,6b,6c,6d)

RESULTS-

We studied 12 morphological subtypes of cutaneous tuberculosis (Table 1).

Table 1: Histomorphological Spectrum Of Cutaneous Tuberculosis

Type of Cutaneous Tuberculosis	Number of patients
Lupus vulgaris	3
Lichen scrofulosorum	2
Papulonecrotic tuberculid	2
Erythema induratum of Bazin	2
Erythema Nodosum	2
Scrofuloderma	1

In our study, incidence of cutaneous tuberculosis was found to be 1.99% in 12 patients out of 602 total skin biopsies received. On histopathology, 3 cases of Lupus Vulgaris (25%) followed by 2 cases of Lichen Scrofulosorum (16.16%), Erythema Induratum of Bazin (16.16%), Papulonecrotic Tuberculid (16.16%), Erythema Nodosum (16.16%) each and 1 case of Scrofuloderma (8.33%) were diagnosed. Age group of the present study ranged from 15-52 years. Most cases occurred in the age group of 20-30 years. Females were more affected than males with male to female ratio of 1:2. Most common site involved was the lower limbs. 3 out of 12 cases detected *Mycobacterium tuberculosis* on gene expert studies. Mycobacterial culture was positive in 2 out of 12 cases, of which; one case is of scrofuloderma which is a type of multibacillary tuberculosis and another case is of erythema nodosum caused by *Mycobacterium tuberculosis*. The clinicopathological correlation of these 12 cases shown in Table 2.

											treatment for 1 months till normalization of hepatic function
3	52/F	Erythematous papules coalescing to form plaques	Neck	Positive	Negative	Evening rise of temperature	M. TB not detected	Epithelioid cell granulomas, Langhans giant cells, caseous necrosis with peripheral cuff of lymphocytes	Lupus vulgaris	-	Started on anti tuberculosis drugs and showed drastic improvement of skin lesions at the end of 3 month
4	24/F	Papules coalescing to form plaques	Abdomen, Back	Positive	Negative	Fever	M. TB not detected	Superficial dermal Epithelioid cell granuloma without necrosis in vicinity of hair follicles	Lichen scrofulosorum	-	Favorable clinical response to anti tuberculosis treatment; skin lesions significantly improved after 2 months
5	34/M	Confluent erythematous papules	Abdomen, Back, Chest	Positive	Negative	Fever, cough	M. TB not detected	Epithelioid cell granuloma without necrosis	Lichen scrofulosorum	-	Skin lesions started to resolve after beginning of anti tuberculosis treatment
6	26/F	Painful nodular swellings	Hip, Thigh	Positive	Negative	Fever	M. TB not detected	Septal panniculitis along with vasculitis and epithelioid cell granulomas	Erythema induratum	-	Stated anti tuberculosis therapy showed remarkable improvement with involution of lesions at the end of 9 weeks
7	30/M	Erythematous nodules	Bilateral lower limbs	Positive	Negative	Fever, pleuritic chest pain, Multiple matted cervical lymph nodes	M. TB detected	Septal panniculitis along with vasculitis and epithelioid cell granulomas	Erythema induratum	-	Treated successfully with anti tuberculosis drugs for 6 months with complete resolution of all skin lesions
8	15/F	Erythematous to violaceous papules	Thigh, Legs, Face	Positive	Negative	Weight loss, Matted cervical lymphadenopathy	M. TB not detected	Large areas of necrosis encroaching upon the epidermis along with perivascular lymphohistiocytic infiltrates with epithelioid cells	Papulonecrotic tuberculid	Granulomatous lymphadenitis	After 3 months of treatment with anti tuberculosis HRZE drugs; skin lesions disappeared
9	38/M	Erythematous papules with healing and atrophy	Right forearm, Thigh, Back	Positive	Negative	Asymptomatic	M. TB not detected	Necrosis admixed with dense neutrophilic inflammation destructing hair follicles (Follicular necrosis or destruction) along with tuberculoid cell granuloma and leukocytoclastic vasculitis	Papulonecrotic tuberculid	-	Started with CAT I AKT and skin lesions markedly improved after 1 month of initiation of treatment
10	27/F	Erythematous to violaceous nodules and plaques	Bilateral lower limbs	Positive	Positive	High grade fever and generalised weakness	M. TB not detected	Septal panniculitis with epithelioid cell granuloma without vasculitis	Erythema nodosum	-	Completed 6 months anti-tuberculosis treatment with disappearance of nodules
11	27/F	Red raised painful nodules	Bilateral lower limbs	Positive	Negative	Fever, generalised weakness and right sided cervical lymphadenopathy	M. TB detected in very low amounts	Septal panniculitis with epithelioid cell granuloma	Erythema nodosum	Tuberculous lymphadenitis	Reported clearance of all nodules after completion of anti tuberculosis multidrug therapy
12	26/F	Non healing ulcerative lesion discharging caseous material	Neck	Positive	Positive	Cough, evening rise of temperature and weight loss	M. TB detected	Epithelioid cell granulomas, Langhans giant cells with variable areas of caseous necrosis	Scofuloderma	-	Patient started with anti tuberculosis drugs and his lesion started to regress gradually with no active discharge from lesion

M-Male, F-Female, Sr no- Serial number

DISCUSSION-

Cutaneous Tuberculosis forms small proportion of extra-pulmonary tuberculosis causing significant morbidity. Histopathological features can aid in diagnosis of cutaneous tuberculosis in addition to other investigations. There are different classification systems used for cutaneous tuberculosis. Most recent and widely used classification of cutaneous tuberculosis is based on bacterial load in the skin lesions (multibacillary or paucibacillary). Multibacillary forms reveal numerous mycobacteria on ziehl neelsen stain and can be isolated on culture; it includes primary inoculation tuberculosis (Tuberculous chancre), scrofuloderma, orificial tuberculosis, acute miliary tuberculosis and metastatic abscesses (Tuberculous gumma). Paucibacillary forms of cutaneous tuberculosis are difficult to detect on ziehl neelsen staining and less readily cultured; it includes Tuberculous verrucosa cutis and lupus vulgaris.^[10] Tuberculids represents cutaneous immune hypersensitivity reactions to tuberculous antigens and includes papulonecrotic tuberculids, lichen scrofulosorum, erythema induratum of bazin and nodular tuberculoid.^[11]

In our study 9 cases of paucibacillary tuberculosis (3 cases of lupus vulgaris, 2 cases of papulonecrotic tuberculids, 2 cases of lichen scrofulosorum and 2 cases of erythema induratum of bazin), single case of scrofuloderma which is a type of multibacillary tuberculosis and 2 cases of erythema nodosum associated with tuberculosis were diagnosed. Cutaneous tuberculosis can mimic various infective and inflammatory conditions. There is wide range of differential diagnoses including actinomycosis, blastomycosis, leishmaniasis, sarcoidosis and leprosy.^[12]

Lupus vulgaris (25%) was common morphological subtype in our study; findings are similar to study conducted by Aruna c et al, Mathur et al, Singh et al and Puri et al.^[1, 3, 7,13] Few studies reported scrofuloderma as most common subtype of cutaneous tuberculosis.^{[4,8,}

^{14]} Mean age of patient varied in different studies; most of the studies reported younger age group commonly affected by cutaneous tuberculosis which is same with our study. Most studies in literature reported male predominance over females however; present study showed female preponderance (8 cases /12 cases) with male to female ratio of 1:2 which was similar to studies reported in literature by Supekar BB et al, Marcoval et al, Mann D et al and Spelta et al.^[15,16,17,18] Most cases in our study occurred in 2nd to 3rd decades with maximum cases occurring in 20-30 years age group, findings were consistent with studies conducted by BK Thakur et al and Patra AC et al.^[4,19] Most common reported site in present study was lower extremity followed by neck which was similar to previous studies by Aruna C et al, Mathur et al, Singh et al, Puri et al and Dwari et al.^[1,3,7,12,20] The positivity with mantoux test has been reported from 68-100% in different studies in literature. In our study; mantoux test was done in all patients which came positive (100%), correlating with other Indian studies.^[4,17,21,22]

Histopathology of cutaneous tuberculosis is variable. In this study typical tuberculoid epithelioid cell granuloma was found in 10 cases (83.33%); similar observations were noticed by Aruna c et al and Mathur et al.^[1,3] Scrofuloderma results from spread of tuberculous infection from underlying focus beneath skin especially from lymph nodes, bones and joints.^[14] Initially it presents as nodule which subsequently enlarges and ruptures forming non healing ulcer with discharging pus. We reported one case of scrofuloderma with initial erythematous nodule over neck which ruptured subsequently forming ulcer with discharging caseous material. Most common site for scrofuloderma is neck and axilla. Inguinal region is uncommon.^[23,24] In our study neck was site for scrofuloderma; which was also noticed by other authors BK Thakur et al and Maghwal et al.^[4,8]

CONCLUSIONS-

Cutaneous tuberculosis is an uncommon condition accounting only 1-1.5% of all extra-pulmonary tuberculosis. Cutaneous tuberculosis may cause significant morbidity. Diagnosis of cutaneous tuberculosis can be challenging due to varied clinical presentation and wide range of differential diagnoses. Clinically cutaneous tuberculosis may mimic other inflammatory and infective skin conditions so early and expeditious diagnosis is essential for effective management of patient in prevalent countries like India. Histopathology is the gold standard for diagnosis of cutaneous tuberculosis. Adequate and early treatment with Directly Observed Therapy Short Course (DOTS) in cutaneous tuberculosis will show good therapeutic response.

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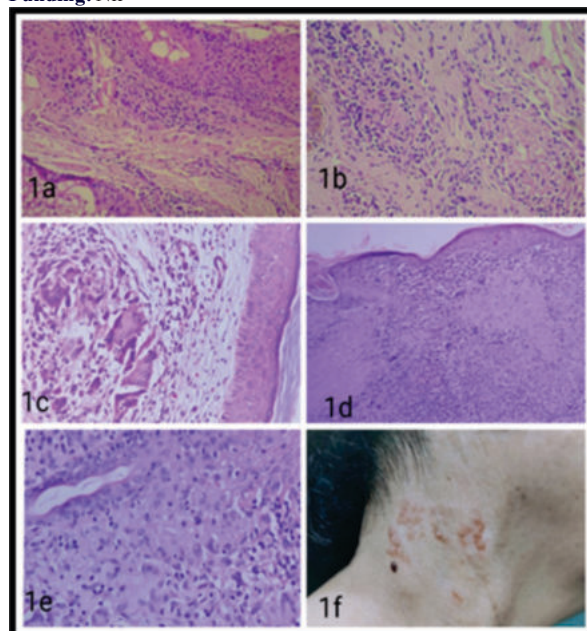


Figure 1a-1f- Case 1, 2 and 3, on histopathology diagnosed as Lupus vulgaris **Figure 1a,1b-** Case 1 showing confluent epithelioid cell granuloma in the dermis (HE, 10x) **Figure 1c-** Case 2 showing epithelioid cell granuloma along with Langhans giant cells in the superficial dermis along with epidermal atrophy (HE, 40x) **Figure 1d,1e-** Case 3 showing Epithelioid cell granuloma, few Langhans giant cells with central areas of caseous necrosis (HE, 4x & HE, 40x) **Figure 1f-** Case 3 clinically presenting as erythematous papules coalescing to form plaques over neck

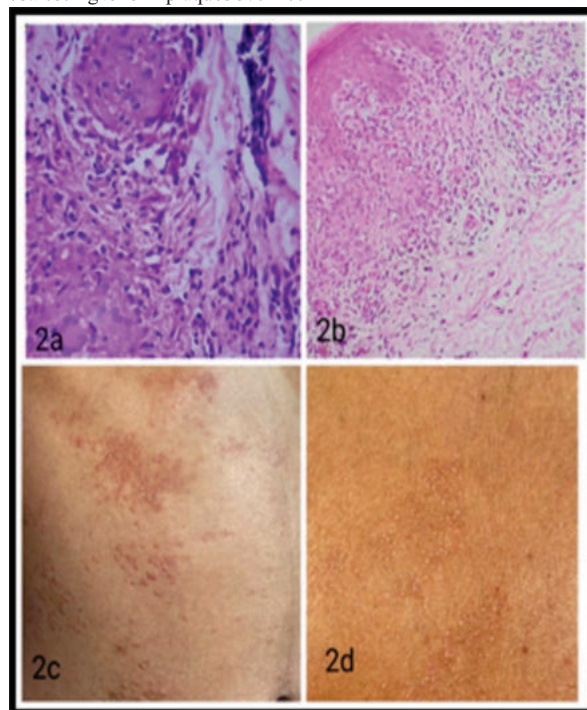


Figure 2a-2d- Case 4 and 5, on histopathology diagnosed as Lichen scrofulosorum **Figure 2a-** Case 4 showing superficial dermal epithelioid cell granuloma in vicinity of hair follicles with Langhans giant cells without necrosis (HE, 40x) **Figure 2b-** Case 5 showing superficial dermal epithelioid cell granuloma with Langhans giant cells (HE, 10x) **Figure 2c,2d-** Case 5 clinically presenting as confluent erythematous papules over abdomen and back

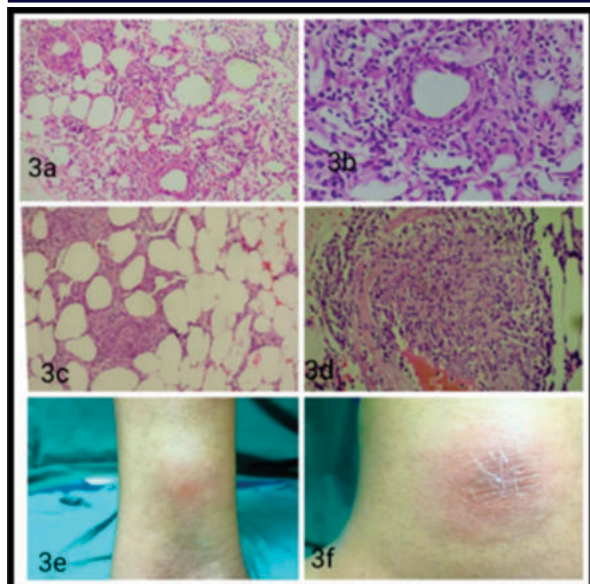


Figure 3a-3f- Case 6 and 7, on histopathology diagnosed as Erythema induratum **Figure 3a,3b-** Case 6 showing septal panniculitis with vasculitis & epithelioid cell granuloma (HE, 10x & HE, 40x) **Figure 3c-** Case 7 showing septal panniculitis (HE, 10x) **Figure 3d-** Case 7 showing vasculitis (HE, 40x) **Figure 3e,3f-** Case 7 clinically presenting as erythematous nodules over bilateral lower limbs

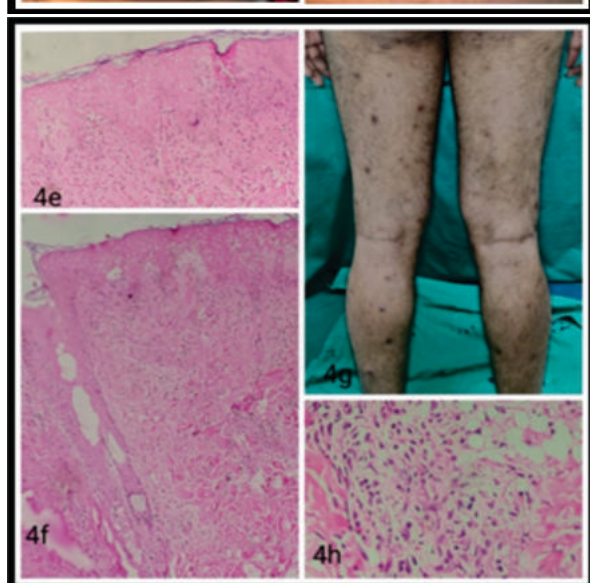
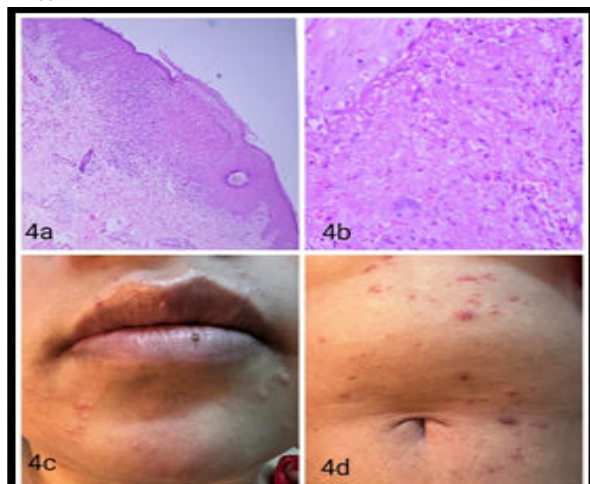


Figure 4a-4h- Case 8 and 9, on histopathology diagnosed as

papulonecrotic tuberculid **Figure 4a-** Case 8 showing necrosis encroaching upon epidermis (HE, 4x) **Figure 4b-** Case 8 showing epithelioid cell granuloma along with Langhans giant cells (HE, 40x) **Figure 4c, 6d-** Case 8 clinically presenting as erythematous to violaceous papules over face and abdomen **Figure 4e, 4f-** Case 9 showing necrosis admixed with neutrophils along with follicular necrosis and destruction (HE, 40x & HE, 10x) **Figure 4g-** Case 9 clinically presenting as erythematous papules with healing and atrophy over thigh and back **Figure 4h-** Case 9 showing epithelioid cell granuloma (HE, 40x)

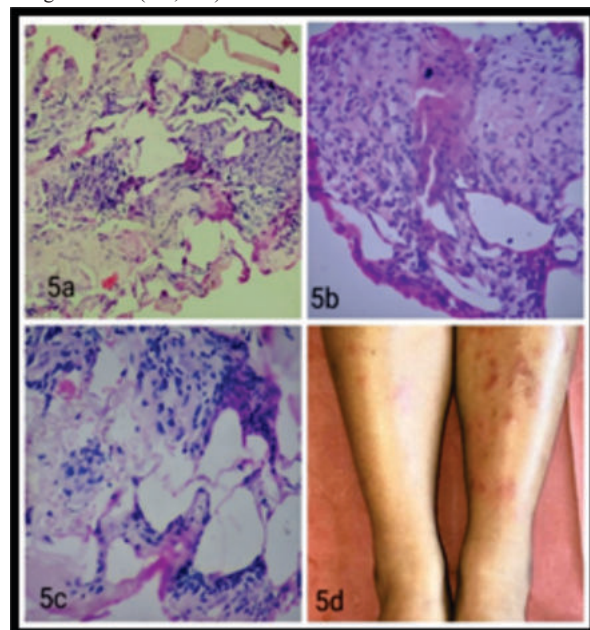


Figure 5a-5d- Case 10 and 11, on histopathology diagnosed as Erythema nodosum **Figure 5a,5b-** Case 10 showing septal panniculitis with epithelioid cell granuloma (HE, 10x & HE, 4x) **Figure 5c-** Case 11 showing septal panniculitis (HE, 40x) **Figure 5d-** Case 11 clinically presenting as red raised painful lesions over anterior aspect of lower legs

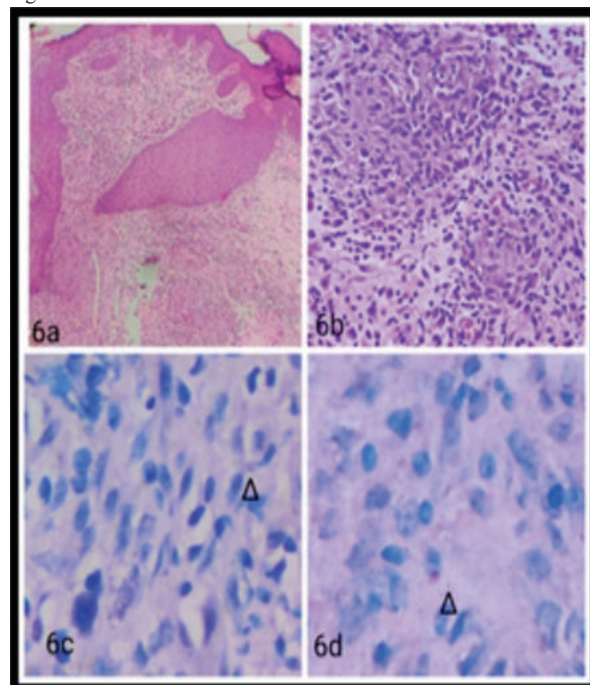


Figure 6a-6d- Case 12, on histopathology diagnosed as Scrofuloderma **Figure 6a-** Case 12 on low power showing epidermis and dermis with variable areas of necrosis (HE, 4x) **Figure 6b-** Case 12 showing epithelioid cell granuloma with areas of necrosis (HE, 40x) **Figure 6c,6d-** Case 12 showing slender tubercle bacilli on Ziehl Neelsen stain (HE, 40x) (Arrow head)

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