



CLINICO-HISTOLOGICAL SPECTRUM OF INFECTIOUS GRANULOMATOUS DERMATOSES AT A TERTIARY CARE CENTRE

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ABSTRACT

Infectious granulomatous dermatoses (IGDS) comprise a large family having various etiologies but sharing the common denominator of granuloma formation. In developing countries like India infectious granulomatous conditions like leprosy and tuberculosis are commonly seen. With the aim to study different types of infectious granulomas with different morphological features along with their clinical correlation, the present retrospective study was conducted. Out of 264 cases of IGDS, Leprosy (84%) was the commonest skin lesion followed by cutaneous tuberculosis (12.8%) and fungal infection (3%). Male predominance was found. Clinico-histological concordance was noted in 85.4% & 94% cases of leprosy and cutaneous TB respectively. Histopathology is a gold standard to diagnose and classify IGDS. It requires microscopic acumen of Histopathologist and its correlation with clinical diagnosis given by Dermatologist. Early diagnosis and proper treatment with multidrug therapy would certainly help WHO mission to "Eliminate TB by 2025" and Accelerating towards "Leprosy Free World 2020".

KEYWORDS : IGDS, leprosy, tuberculosis, fungal.

INTRODUCTION

Infectious granulomatous dermatoses (IGDS) comprise a large family having various etiologies but sharing the common denominator of granuloma formation.¹ Granulomatous dermatoses are distinctive pattern of chronic inflammatory response of skin as a response to variety of organic and inorganic antigens.^{2,3} Granulomatous reaction is a type IV hypersensitivity reaction evoked by poorly soluble antigens.^{4,5} Granulomas are defined as very tiny 0.5-2 mm lesions characterized by focal collection of epithelioid cells (modified histiocytes) admixed with variable number of lymphocytes and multinucleated giant cells.⁶ Granulomas can be hard as seen in Crohn's disease / sarcoidosis or they can be soft as classically seen in tuberculosis. A total of six types of granulomatous dermatoses are known in literature as tuberculoid, sarcoidal, necrobiotic, suppurative, foreign body and lastly histoid according to cellular components and architecture.^{4, 5} Prevalence of types of granulomatous dermatoses differs according to geographic location. In Western countries, non-infectious granulomatous conditions like Crohn's disease and sarcoidosis are common while in developing countries like India infectious granulomatous conditions like leprosy and tuberculosis are commonly seen. In India, granulomatous dermatoses are commonly found in Eastern India.⁷ Many granulomatous skin lesions have similar histomorphology or conversely a single lesion can present with variety of morphological features.⁸ Advanced granulomas with well formed sheets of epithelioid macrophages and giant cells are easily identified but early lesions with only a few epithelioid macrophages still qualify a granuloma. Many a times this diagnostic dilemma between Dermatologist and Pathologist demands for acumen of the

Histopathologist at microscopic levels so that diagnostic confusions can be solved. Thus histopathology is the gold standard for diagnosis and categorization of cutaneous granulomas whether they are infectious or non-infectious. Infectious granulomas can be caused by variety of mycobacteria, fungi and parasites while non-infectious granulomas can be seen in sarcoidosis, Crohn's disease, foreign body type of reaction and granuloma annulare.⁹ There is not a single histological feature that can differentiate between infectious and non-infectious granulomas.⁹ Infectious Granulomatous Dermatoses is a diagnostic challenge for both dermatologist and histopathologist. The microscopic differences are very subtle and it requires knowledge & skill of the Histopathologist. Identification of correct granulomatous pattern after clinical correlation is of utmost importance as treatment modality is disease specific. With the aim to study different types of infectious granulomas with different morphological features along with their clinical correlation, the present retrospective study was conducted.

MATERIAL AND METHODS

Present study was a retrospective cross-sectional study carried over two years from June 2017 to June 2019 in department of Pathology, GMC, Akola in collaboration with department of Dermatology. A total of 709 skin punch biopsies were received, out of which 264 (37.2%) cases were infectious granulomatous dermatoses. All new cases clinically suspected of granulomatous disease were included in the present study. However inadequate skin biopsies were excluded. Detailed clinical history was taken. Punch biopsies were fixed in 10 % formalin, processed and slides were stained with H and E. Special stains like ZN, Fite Foracco,

Reticulin, PAS, Giemsa or Congo red were performed wherever applicable. Following results were obtained and compared with various similar studies in the literature.

Results

Table 1: Distribution of cases according to etiology on histopathology (n= 264)

Diagnosis	Number of cases	%
Leprosy	222	84
Tuberculosis	34	12.8
Fungal	8	3
Total	264	100

A total of 300 cases of granulomatous dermatoses were diagnosed on histopathology out of which 264 were of infectious in origin. Leprosy (84%) was the commonest skin lesion followed by cutaneous tuberculosis (12.8%) and fungal infection (3%) as shown in table 1.

Table 2: Age wise distribution of all cases (n=264)

Lesion	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	Total
Leprosy	2	27	57	44	43	26	19	3	1	222
TB	6	4	4	12	4	2	2	-	-	34
Fungal	-	-	-	1	2	3	2	-	-	8

Majority of leprosy cases were observed in 3rd decade while cutaneous TB was common in 4th decade and fungal infections were common in 5th decade as shown in table 2.

Table 3: Sex wise distribution of all cases (n=264)

Diagnosis	Male	Female	Total
Leprosy	141	81	222
TB	22	12	34
Fungal	8	0	8
Total	171	93	

Overall in all cases, male preponderance with male to female ratio 1.83: 1 was noted as shown in table 3.

Table 4: Site wise distribution of all cases (n=264)

Site	Leprosy (222)	TB (34)	Fungal (8)
Upper limb	85	10	-
Lower limb	15	16	8
Head and neck	4	2	-
Face	23	2	-
Trunk	91	4	-
Gluteal	4	-	-
Total	222	34	8

In leprosy, trunk was commonly involved followed by upper limb and face. In cutaneous TB, lower limb was majorly affected and fungal infection was observed only in lower limb as shown in table 4.

Table 5: Distribution of histomorphological features noted in skin biopsy

Features	Leprosy (222)	TB (34)	Fungal (8)
Epidermal atrophy	48	12	-
Epidermal hypertrophy	-	16	8
Destruction of basal layer	21	30	8
Abscess	-	14	8
Granulomas	189	34	8
Giant cells	65	34	8
Caseation	-	20	-
Normal epidermis	174	6	-
Periadnexal granulomas	180	26	-

On histopathology, in diagnosed cases of leprosy, the most common microscopic feature observed was histiocytic granuloma (85.1%). Epidermis was normal in 78.3% cases while 21.6% cases of leprosy showed atrophic epidermis (Fig 1B). Giant cells are also noted in 29.2% cases of leprosy. In

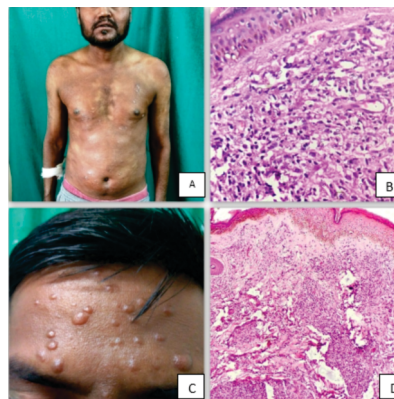
cutaneous TB, microscopic features such as tuberculoid granulomas (Fig 2B), giant cells and destruction of basal layer were common. Caseation is also observed in 58.8% cases of TB (Fig 2B & 2D). In fungal infections, every case showed epidermal hypertrophy, destruction of basal layer abscess formation, foreign body type of granulomas and giant cells as shown in table 5.

Table 6: Distribution of histopathologically diagnosed cases of leprosy (n= 222)

Diagnosis	Number of cases	%
Inderminate	5	2.2
Tuberculoid	21	9.5
Borderline tuberculoid	113	50.9
Mid borderline	11	5
Borderline lepromatous	10	4.5
Lepromatous	38	17.1
Histoid Hansen	18	8.1
Type 1 lepra reaction	5	2.2
Type 2 lepra reaction (ENL)	1	0.5
Total	222	100

In the present study, borderline tuberculoid leprosy (50.9%) was the commonest subtype followed by lepromatous leprosy (17.1%) (Fig 1A & 1B) , tuberculoid (9.5%), histoid (8.1%) (Fig 1C & 1D). Very few cases were fitted in indeterminate type of leprosy as shown in table 6. Special stain Fite Foracco positivity was noted in 45.1% cases of leprosy. Clinico-histopathological correlation was noted in 85.4% cases of leprosy.

Figure 1: Clinico- histological correlation of leprosy subtypes:



- A- Lepromatous Leprosy showing multiple symmetric hypopigmented patches with nodules over trunk.
- B- Lepromatous Leprosy showing atrophic epidermis, grenz zone, and sheets of lepra bacilli. (H&E- 400X)
- C- Histoid Leprosy showing multiple nodules over forehead.
- D- Histoid Leprosy showing storiform arrangement of histiocytes in perineural and perivascular areas of dermis. (H&E-400X)

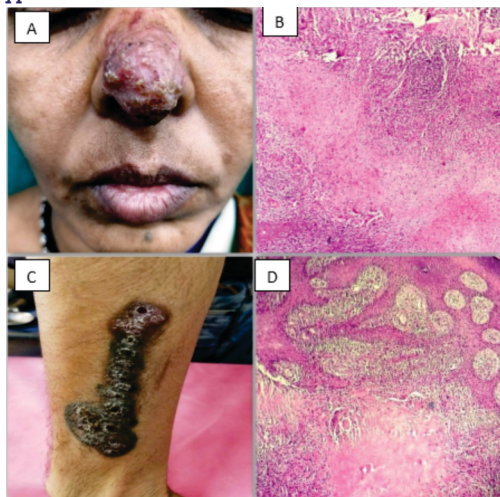
Table 7: Distribution of histopathologically diagnosed cases of cutaneous tuberculosis (n=34)

Diagnosis	Number of cases	%
Lupus vulgaris	18	52.9
Scrofuloderma	6	17.6
TBVC	6	17.6
Papulonecrotic TB	2	5.8
TB cutis orofacialis	2	5.8
Total	34	100

In the present study, the most common cutaneous tuberculosis was lupus vulgaris (52.9%) followed by scrofuloderma (17.6%) and TBVC (Tuberculosis Verucosa Cutis) (17.6%) as shown in

table 7. AFB was positive in 23.5% cases of cutaneous tuberculosis. Clinico-histopathologically 94% cases were correlated.

Figure 2: Clinico- histological correlation of cutaneous TB subtypes:



- 2A – Lupus Vulgaris showing typical “Apple jelly nodules” over nose.
- 2B – Lupus Vulgaris showing caseation with epithelioid cell granuloma. (H&E-400X)
- 2C – TBVC showing single hyperplastic reddish-brown plaque over forearm.
- 2D – TBVC showing hyperkeratotic and hyperplastic epidermis with caseating granuloma in mid dermis. (H&E-400X)

Table 8: Distribution of histopathologically diagnosed cases of cutaneous fungal infections (n=8)

Diagnosis	Number of cases	%
Actinomycosis	3	37.5
Madura mycetoma	3	37.5
Chromoblastomycosis	2	25
Total	8	100

Among fungal infections, actinomycosis and Madura mycetoma each comprised 37.5% of cases and chromoblastomycosis was observed in 25 % cases as shown in table 8.

DISCUSSION

The present study was the retrospective cross-sectional study and compared with various similar studies in literature conducted in different regions of India.

Cutaneous granulomas are classified into infectious & non-infectious depending on presence or absence of pathogenic organisms. The incidence of IGDS in our study was 37.2 % out of all skin biopsies received. It was slightly higher as compared to other studies conducted by Grower et al⁷ from Mumbai (14.5%), Qureshi et al⁴ from Pakistan (14.9%), Gautam et al² from Nepal (6.67%) and Khatib Y et al¹⁰ again from Mumbai (18%). This shows geographical variation of IGDS incidence in different regions.

Table 9: Comparison of incidence of IGDS with other studies

Study	Leprosy (%)	Tuberculosis (%)	Fungal (%)
Present	84	12.8	3
Bal A et al ¹¹	72.4	23.1	-
Grower et al ⁷	77.2	22.7	-
Khatib Y et al ¹⁰	62.7	31.3	3.4
Pawale J et al ³	56.6	7.8	15

In the present study, highest incidence in IGDS was observed in leprosy followed by TB showing high prevalence in Vidarbha, Maharashtra. Similar results were studied by other authors as shown in table 9.

In this study, majority of cases were found in third decade and male predominance was present which was also observed by Gautam K et al², Grower et al⁷, Manandhar U et al¹² and Jayalakshmi¹³. This could be because of more OPD visits of male patients as compared to females due to socio-economic barriers in most of the regions in India.

In the present study, most common site involved in leprosy was trunk followed by upper limb and face while Grower et al⁷ noted upper limb to be the commonest and Jha et al¹⁴ observed neck to be the common site. In the present study, amongst the subtypes of leprosy, borderline tuberculoid (50.9%) was the commonest followed by lepromatous leprosy (17.1%) concluding that BT & LL are common subtypes of leprosy observed in Vidarbha. While Grower et al⁷ from Mumbai, Khatib et al¹⁰ from Mumbai, Bal et al¹¹ from Punjab and Gautam et al² from Nepal noted BT and TT to be the common subtypes. Whereas LL was the major subtype as reported by Jindal et al¹⁵ from Himachal Pradesh. Special stain Fite Foracco positivity was noted in 45.1% cases of leprosy in the present study which was comparable to Bal et al¹¹ (36.4%) and Khatib et al¹⁰ (33.3%) . In the present study, clinically 85.4% cases of leprosy were well correlated with histopathological diagnosis while Khatib et al¹⁰ observed it in 51.8% cases.

Among 34 cases of cutaneous TB, lupus vulgaris (52.9%) was the commonest subtype followed by scrofuloderma (17.6%) & TBVC (17.6%) (Tuberculous verrucosa cutis) in the present study which was correlated with the study conducted by Grower et al⁷ Bal et al¹¹. Whereas Kaur et al¹⁶, Zafar et al⁵, Dwari et al¹⁷ found TBVC to be the commonest subtype after lupus vulgaris. In the present study, the majority of cases of cutaneous TB were found in the age group of 31-40 years while Khatib et al¹⁰ found 11-20 years to be major age group and many studies observed 21-30 years as the common age group for cutaneous TB. In this study, male preponderance was observed which was also noted by Sengupta et al¹⁸ and Sehgal et al¹⁹ while Khatib et al¹⁰ and Zafar et al⁵ noted female preponderance. Cutaneous TB can present in different ways giving a varied spectrum depending on the route of infection, immune status and previous sensitization by TB.⁷

TB is one of the deadliest disease which is increasing worldwide more so in poor socioeconomic group with poor hygiene & overcrowding. Incidence of cutaneous TB worldwide is 0.1-1% of all cutaneous disorders. We found it to be 4.8%. It could be due to high incidence of systemic TB in our area with patients referred to our tertiary care center with a specialized Dermatology department, biopsy facilities and a good access to free treatment. Cutaneous TB has to be differentiated from non-infectious granulomatous dermatitis which can be made possible with the help of chest X ray, sputum sample examination and mantoux test. AFB was positive in 23.5% cases which was comparable to other studies conducted by Khatib et al¹⁰ (14.8%) and Agrawal et al²⁰ (17.19%). Clinico-histopathological concordance in this study was noted in 94% cases which was comparable to Khatib et al¹⁰ and Chaudhari N et al.²¹

In the present study we found 3% cases of cutaneous fungal infection which was similar to that noted by Khatib et al¹⁰ while El-Khalawany et al²² noted 5.6% cases of fungal dermatitis.

In the present study, the most common site involved was lower limb and most were presented with draining ulcer, could be because lower limbs are more injury prone. Special stains like PAS and GMS are very helpful for the diagnosis. Chromoblastomycosis can be confused with TBVC clinically but specific feature such as Copper penny bodies confirms chromoblastomycosis.

CONCLUSION

Histopathology is a gold standard to diagnose and classify IGDS. It requires microscopic acumen of Histopathologist and its correlation to clinical diagnosis given by Dermatologist. Appropriate approach, site and technique of skin biopsy is mandatory. Special stains like PAS, ZN stain & Fite Foracco are very useful. Bacteriological and morphological index for Hansen disease is a good protocol for paucibacillary and multibacillary leprosy cases as the treatment and duration varies. Early diagnosis and proper treatment with multidrug therapy would certainly help WHO mission to "Eliminate TB by 2025" and acceleratin towards "Leprosy Free World 2020". IGDS cause much of morbidity & crippling deformities. Hence early histomorphological diagnosis would help reducing the social stigma associated with leprosy and TB.

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