

Histopathological Spectrum of Cutaneous Granulomatous Lesions

Utkarsh N Pattar¹, Hilda Fernandes², Vasudev Prabhu³

^{1,3}Post Graduate Resident, Department of Pathology, Father Muller Medical College, Mangalore, Karnataka, India

²Professor and Ex Head, Department of Pathology, Father Muller Medical College, Mangalore, Karnataka, India (Correspondence)

Abstract: ***Background:** Cutaneous granulomatous lesions often pose a diagnostic challenge to the pathologists because many of the lesions can clinically as well as morphologically mimic each other. This study was carried out in order to determine the morphology and relative frequency of these lesions and to compare the findings with previously done studies. **Materials and methods:** A retrospective study of the skin biopsies received in the Department of pathology, FMMC, Mangalore was carried out, and cases of cutaneous granulomatous lesions on histopathological examination and special stains were reviewed. **Results:** Out of the 84 cases included in the study, male preponderance was noted (71.43%), Maximum number of cases were observed in the patients of age group in the third and sixth decades. Tuberculoid granulomas were the most common type of granulomas (65.48%). Leprosy was the commonest cutaneous granulomatous lesion in the study. **Conclusion:** In our study, Leprosy was the most common granulomatous skin lesion. Histopathological examination with H and E, aided by special stains is the most valuable tool in the diagnosis, management and prognosis of these lesions.*

Keywords: Cutaneous granulomatous lesions, Leprosy, Tuberculoid granulomas

1. Introduction

The term “granulomatous” was expressed initially by Virchow to describe a tumour-like mass or nodule of granulation tissue.¹

Granulomatous inflammation is a distinctive pattern of chronic inflammation characterised by formation of circumscribed microscopic aggregates of activated macrophages forming epithelioid histiocytes with variable number of admixed multinucleated giant cells and a collar of lymphocytes, known as granulomas.² These are encountered in a certain specific pathological states caused by a variety of offending agents which are often difficult to eradicate, being non degradable by both neutrophils and non active macrophages.³

The actions of polymorphonuclear leucocytes, non-activated macrophages and chemical mediators which are associated with the tissue injury are insufficient to completely digest and eradicate the offending agents.

For such degradation an action of transformed/modified macrophages is required which are formed in response to cell mediated immunity.⁴

The CD4+T cells secrete various mediators such as IL2, IF alpha, TNF and lymphotoxin for the transformation of the macrophages into epithelioid cells and giant cells, which are the components of granulomas.⁵ This is characterised by persistent inflammation, tissue injury, attempted repair by scarring and immune response, mediated by a variety of cytokines secreted by macrophages and T lymphocytes.

Granulomatous lesions can be classified into six types based on the type of participating inflammatory cells, and associated changes i.e 1)Tuberculoid, 2)Sarcoid 3) Necrobiotic 4)Suppurative 5) Foreign body 6) Histoid

There is a high prevalence of cutaneous granulomatous lesions in a developing country like India with leprosy and tuberculosis being the most common causes. However, the frequency of these infections across different regions is variable.⁶

Tuberculosis is the prototype of granulomatous inflammation and should always be ruled out as a cause, whenever granulomas are identified.

Granulomatous inflammations are a common and intriguing problem. The arrival at a proper diagnosis is mandatory, so that the appropriate treatment can be meted out.⁷ Good clinical history, a close histological examination and a clinicopathological correlation is essential in making a final diagnosis.

By combining all the available information, one should be able to arrive at a reasonable differential diagnosis on which to proceed. However, in a minority of the cases, it will not be possible to make a definitive diagnosis, even with all the clinical information being available.

Special stains may also be required to reach a diagnosis. In a small percentage of cases, no definitive diagnosis can be given, other than that of granulomatous inflammation. The morphologic pattern in the various cutaneous granulomatous diseases may be sufficiently different to allow reasonable accurate diagnosis by the pathologist.

Very few comparative studies have been carried out to determine the frequency and types of different granulomatous lesions of the skin. This study was undertaken with the aim of classifying cutaneous granulomatous dermatoses based on its cause, to determine the frequency and pattern of these lesions and to study their clinical and histopathological spectrum.

2. Objectives of the study

- 1) To study the histomorphology of different cutaneous granulomatous lesions.
- 2) To study the relative frequency and to assess the aetiology of the cases based on histomorphology.

3. Materials and Methods

The present study was a retrospective analysis of all skin biopsies showing granulomatous reaction received in the Department of pathology, Father Muller medical college, Kankanady, Mangalore, over a period of two years, from September 2016 to September 2018. Relevant clinical history and demographics was retrieved from patient case sheet and the hospital record section software. All the slides of the cases were retrieved and studied for morphology.

This study was performed on formalin fixed, paraffin embedded blocks of skin biopsies received in the Department. Special stains such as Periodic Acid Schiff stain, Modified Zeihl Neelson stain, Fite stain, GMS stain and Reticulin etc were used wherever required.

Cases with granulomatous inflammation in superficial dermis were included in the study. Cases with histiocytic aggregates without granuloma formation, and those with granulomatous reaction to endogenous substances, as well as cases with granulomas in the subcutis were excluded.

Data was analysed using the mean, standard deviation, frequency, and percentage.

4. Results

A total of 84 cases were included in this study. Among these, 60 cases were males, accounting for 71.43% of the cases and 24 females which constituted 28.57% of the cases.

The age of the patients in our study ranged from 3 years to 77 years. Maximum number of cases were noticed among age group of 20-30 years and 50-60 years.

Upon subclassifying these granulomatous dermatoses into different subtypes, tuberculoid granulomas constituted the most number of cases (n=55) accounting for 65.48% of the total number of cases.

Distribution of different categories of granulomatous lesions is shown in table 1:

Type of granuloma	Frequency	Percentage
Tuberculoid	55	65.48%
Suppurative	15	17.86%
Histiocytic	12	14.29%
Necrobiotic	1	1.19%
Foreign body	1	1.19%
Sarcoid	0	0

On detailed histopathological examination by H and E staining and special stains wherever required, the cases were subdivided based on the following etiologies, as shown in table 2:

Disease	Frequency	Percentage (%)
Leprosy	49	58.33%
Tuberculosis	9	10.71%
Foreign body	6	7.14%
Fungal Infection	9	10.71%
Juvenile xanthogranuloma	2	2.38%
Lupus miliaris disseminatus faciei	2	2.38%
Cheilitis granulomatosa	1	1.19%
Granuloma annulare	1	1.19%
Erythema nodosum	1	1.19%
Leucocytoclastic vasculitis	1	1.19%
Non specific granulomatous reaction	3	3.57%

Out of a total number of 84 cases, Tuberculoid granulomas were the most common type of granulomas accounting for 65.48% of the total number of cases (n=55). Morphology of these lesions showed well formed granulomas composed of histiocytes, epithelioid cells, Langhans type of multinucleated giant cells, surrounded by a cuff of lymphocytes. Of these, 40 were leprosy, two cases of Lupus miliaris disseminatus faciei, two cases of foreign body reaction, one case each of Cheilitis granulomatosa and granulomatous inflammation associated with Leucocytoclastic vasculitis. Two of the cases could not be assigned specific etiology. A well formed tuberculoid granuloma as seen in a case of tuberculoid leprosy is depicted in figure 1.

Suppurative granulomas formed the second most common type (n=15, 17.86%), comprising of nine cases of fungal infections, three cases of Foreign body reaction, and one case each of Erythema necroticans and granuloma associated with Leucocytoclastic vasculitis. One case could not be classified under any etiological category. These cases showed necrotising granulomas composed of epithelioid cells, multinucleated giant cells, lymphocytes and dense infiltrate of neutrophils. A couple of examples of suppurative granulomas in a case of chromoblastomycosis and a case of foreign body reaction is shown in figure 2a and 2b respectively.

There were 12 cases of histiocytic granulomas, constituting 14.29% of the total number of cases, and comprised of four cases of borderline leprosy, three cases each of Lepromatous leprosy and Erythema nodosum leprosum, and two Juvenile xanthogranuloma. Large sheets of foamy histiocytes were noted in these cases. Figure 3a and 3b shows histiocytic granulomas as seen in case of lepromatous leprosy and Juvenile xanthogranuloma respectively.

Necrobiotic granulomas, and foreign body type of granulomas constituted one case each forming 1.19% of the cases. A necrobiotic granuloma was observed in a case of granuloma annulare, which showed granulomatous infiltrate surrounding collagenolytic foci (figure 4). Figure 5 shows a foreign body granuloma, as observed in a case of foreign body reaction. We did not observe any case with Sarcoidal granulomas in our study.

Among a total number of 49 cases of leprosy (58.33% of the total number of cases), Borderline tuberculoid leprosy was the most common subtype (n=14, 28.57%) followed by Tuberculoid leprosy (n=12, 24.49%), Borderline lepromatous leprosy (n=4, 8.16%), and three cases each of Midborderline leprosy and lepromatous leprosy respectively. In addition, we encountered six cases of type 1 lepra reaction and four cases of Type 2 lepra reaction. Two cases of leprosy could not be classified into any of the sub category.

We encountered 9 cases of Cutaneous tuberculides, forming 10.71% of the total number of cases. It comprised of four cases of Lupus vulgaris (44.44%) followed by three cases of Tuberculosis verrucosa cutis (33.33%). Two cases could not be typed.

There were nine cases of fungal infections (10.71% of the total number of cases) and comprised of four cases of Chromoblastomycosis, followed by two cases each of Mycetoma and Actinomycosis, and one case of Phaeoerythromycosis. Out of the total number of six cases associated with foreign body, three cases showed Suppurative granulomas, while there were two cases of Tuberculoid granulomas and one case of foreign body type of granuloma.

5. Discussion

Granulomatous dermatoses pose a diagnostic challenge both to the clinicians and pathologists because, an identical histological picture is produced by several causes and conversely a single etiology can produce different histological patterns. Hence, a clinico- pathological correlation is very important in these cases to arrive at a correct diagnosis for optimum treatment. This can be aided even further by adding some special stains like ZN stain, Fite faraco stain, and GMS stain for specific diagnosis.

Various studies conducted previously have reported a male preponderance.^{6,8} Similar finding was seen in our study, with a Male: Female ratio of 2.5:1. However, Zafar et al has reported a female preponderance with 57.3% males and 42.7% females.⁹

A wide range of age groups is noted in various studies conducted so far.^{6,7,8,9} The age of the patients in our study ranged from 3 years to 77 years. This is similar to the findings of Yasmeeen Khatib et al, with the age range of 2 years to 71 years, although that study includes only infectious granulomatous dermatoses.¹⁰ The most number of cases in his study was in the age group of second decade. Whereas, third decade was the most commonly observed age group in our study.¹⁰

Tuberculoid granulomas constituted most number of cases in our study. This is concordance with the studies conducted by Zafar et al⁹, whereas in a study conducted by Teerthnath Srinivas and Hariprasad S from Mangalore, most common type of granulomas were of Sarcoid type.¹¹

In our study, Leprosy constituted the maximum number of cases with tuberculoid granulomas. This is in concordance with studies by Sabrani et al⁸ and Yasmeeen Khatib et al.¹⁰

Leprosy was also the most common type among the total number of cases, accounting for 58.33% of the cases, similar to the above mentioned studies.^{8,10} However, Khattak et al¹², Zafar et al⁹, Gautam et al⁶ and Dhar et al¹³ have encountered tuberculosis as the most common type in their studies respectively.

Borderline tuberculoid leprosy was the most common subtype of leprosy, supporting the findings of various previously conducted studies.¹⁴

Lepra bacilli could be demonstrated only in 16 cases (four cases of Borderline lepromatous leprosy, three each of lepromatous leprosy, and Type 2 lepra reaction respectively, and one each of Erythema necroticans and tuberculoid leprosy). Sabrani et al⁸ has found AFB in 28.03% and Bal et al¹⁵ in 36.4% of the total number of leprosy cases.

Cutaneous tuberculosis accounted for 10.71% of the cases in our study, whereas Yasmeeen khatib et al¹⁰ and sabrani et al⁸ have reported 31.3% and 24.73% of the cases respectively.

Lupus vulgaris was the most common type of cutaneous tuberculosis in the present study which is similar to the findings of Abdul mamen et al¹⁶, Seneha et al¹⁷, Sabrani et al⁸, and Yasmeeen Khatib et al¹⁰. But few studies have found Scrofuloderma as the most common type of cutaneous tuberculosis.^{6,18}

Special stain for acid fast bacilli is indicated in all suspected cases of cutaneous tuberculosis. In the present study, acid fast bacilli could not be demonstrated in any of the case of cutaneous tuberculosis. However, in a study conducted by Gautam K et al, Acid fast bacilli were demonstrated in 25.3% of caseating and 2.8% of non caseating granulomas in cases of cutaneous tuberculosis.⁶

A foreign body reaction can lead to formation of any of the granulomas, viz foreign body granuloma, suppurative or tuberculoid granuloma. We came across nine cases of granulomatous lesions secondary to exogenous foreign body. Out of which there were three cases with suppurative granulomas, two cases with tuberculoid granulomas and one case showing foreign body granuloma.

We diagnosed nine cases of fungal granulomatous lesions in our study which accounted for 10.71% of the cases, similar to the finding of Pawale et al¹⁹ (11.32%). Chromoblastomycosis was the most common type of fungal infection in the study (n=4). The presence of Copper penny bodies helped to distinguish Tuberculosis verrucosa cutis, which is a differential diagnosis for the same.

There were two cases of Lupus miliaris disseminatus faciei which showed tuberculoid granulomas in the dermis. Originally it was thought to be a tuberculid. However recent studies have contradicted that idea as AFB were not demonstrable nor there was any evidence of systemic tuberculosis in the affected patients.

Granuloma annulare was diagnosed in one of the cases (1.19% of the cases in our series). Gautam K et al, S

Chakrabarthy et al, and Pawale et al have found 3.7%, 4.83% and 3.7% respectively.

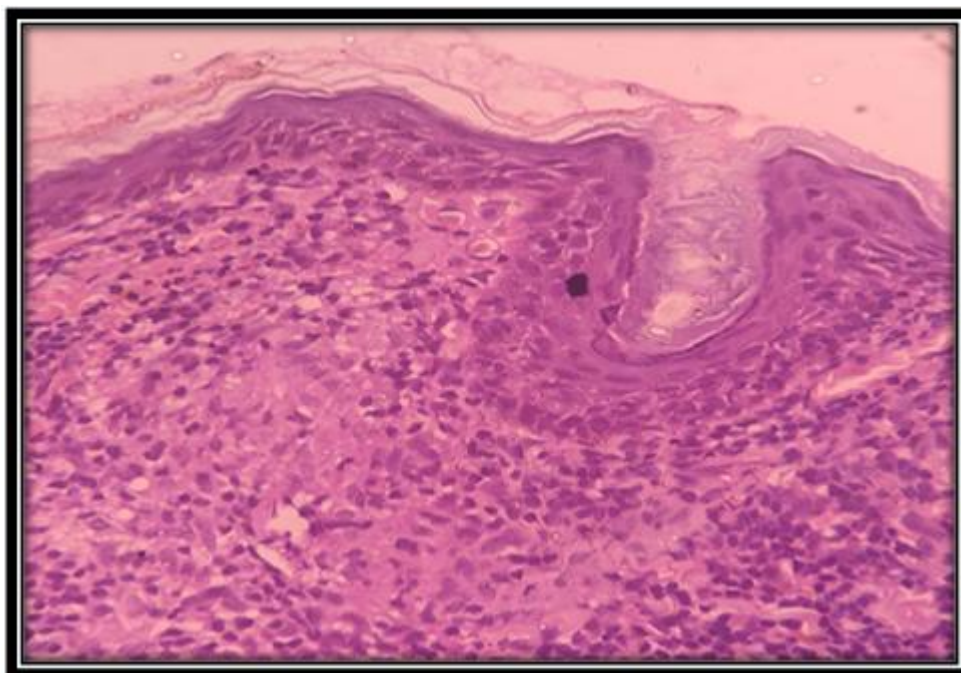


Figure 1: Tuberculoid leprosy showing well demarcated tuberculoid granulomas

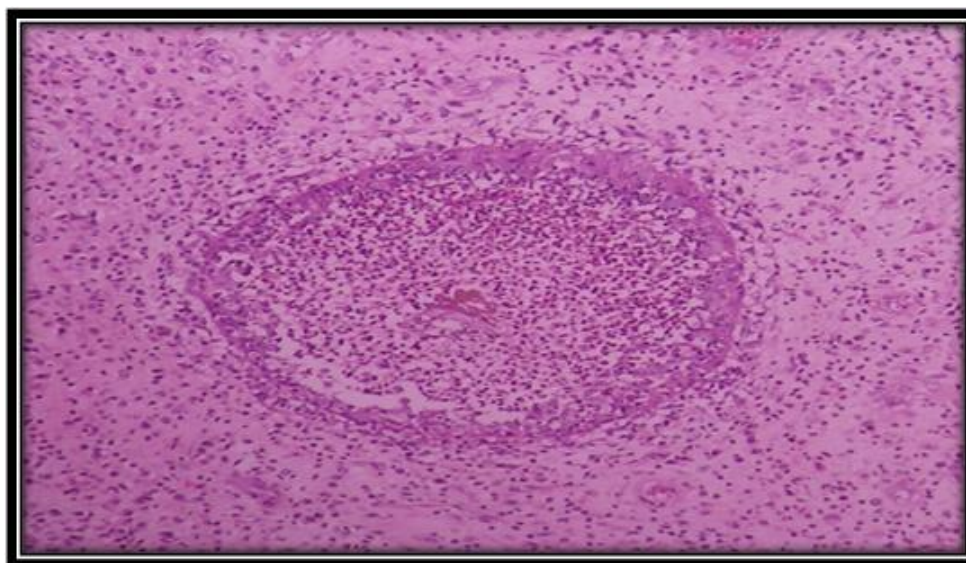


Figure 2 (a): Suppurative granuloma surrounding a foreign body

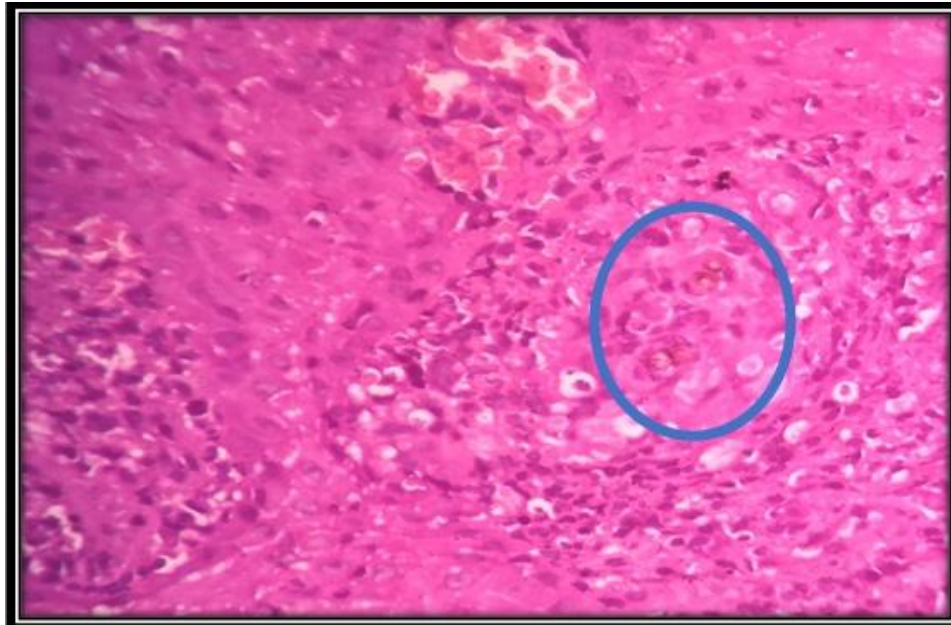
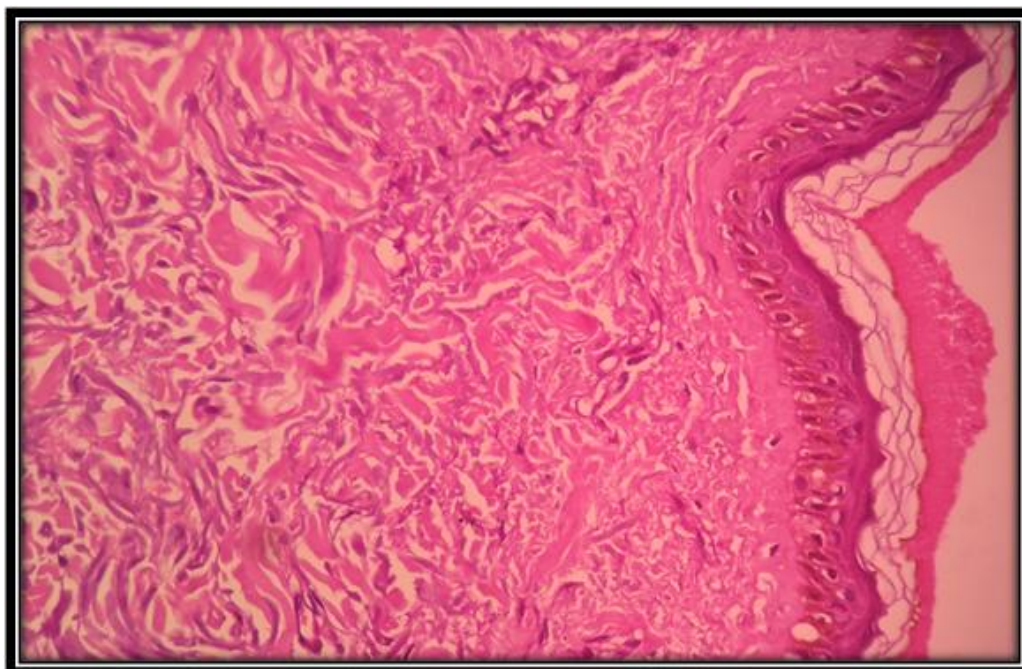


Figure 2 (b): Suppurative granuloma in a case of Chromoblastomycosis, showing Copper penny bodies



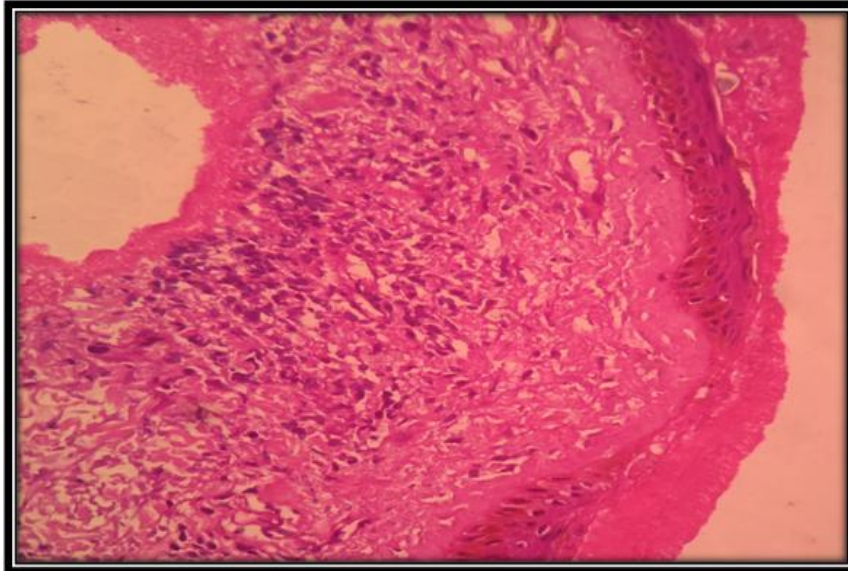


Figure 3 : Necrobiotic granuloma in a case of Granuloma annulare
3 (a): Degenerating collagen fibres **3 (b):** Necrobiotic granulomas

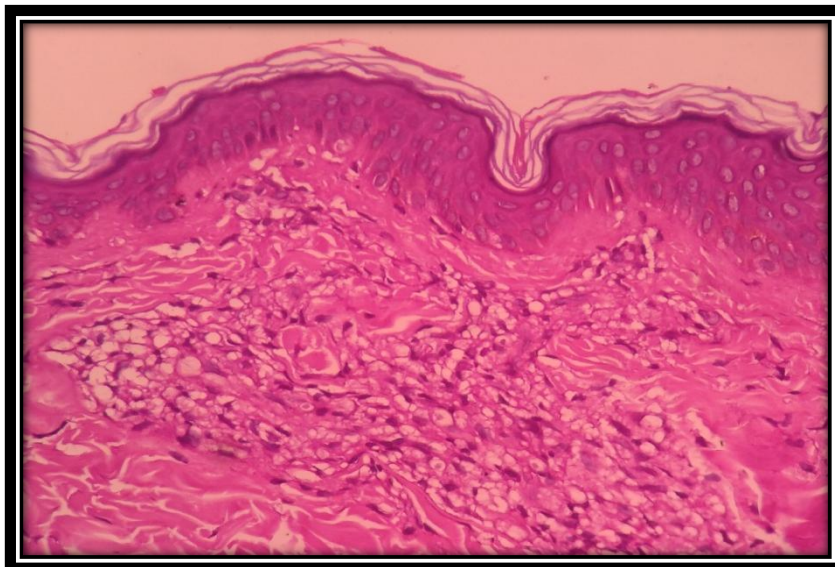


Figure 4 (a): Histiocytic granulomas in a case of Lepromatous leprosy

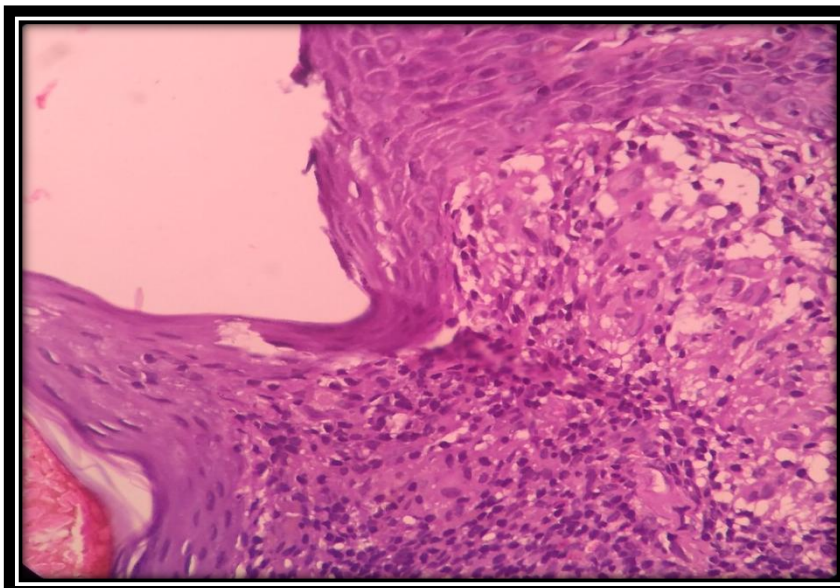


Figure 4 (b): Histiocytic granulomas in a case of Juvenile xanthogranuloma

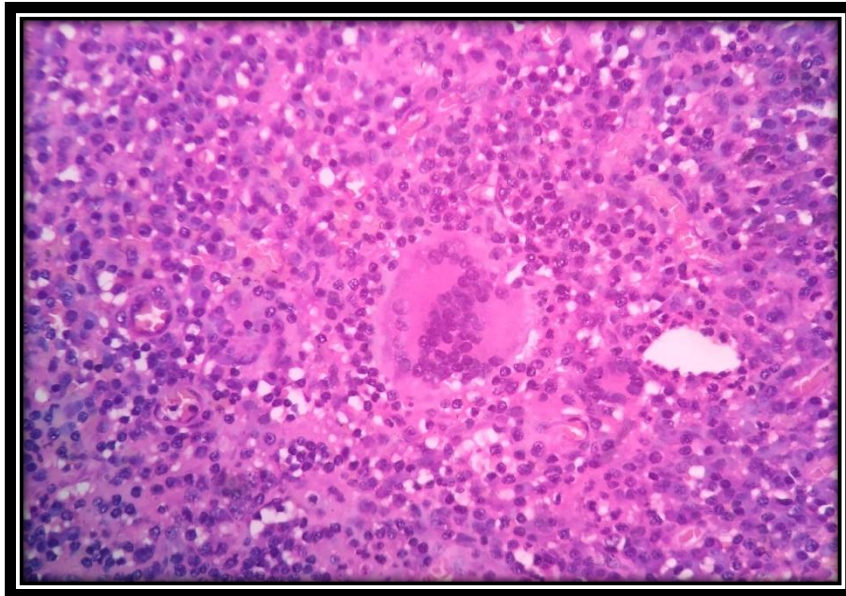


Figure 5: Foreign body granuloma

CONCLUSION

In our study, Tuberculoid granulomas were the most common type of granulomas. Overall, Leprosy was the most common granulomatous skin lesion. This is in concordance with many of the previously conducted studies. Histopathological examination with H and E stain can be considered as the valuable tool in the diagnosis of the cutaneous granulomatous lesions. Special stains aid in the diagnosis whenever required.

References

- [1] Hirsh BC and Johnson WC. Concepts of granulomatous inflammation. *Int J Dermatol* 1984; 23: 90-9
- [2] Weedon D. The granulomatous reaction pattern. In: Weedon D (ed). *Skin Pathology*, 2nd ed. Philadelphia: Churchill Livingstone; 2002. pp193-220
- [3] Kumar V, Abbas AK, Aster CJ. Inflammation healing and repair. In: *Robin's pathological basis of diseases*. 9th ed. Philadelphia: WB Saunders, 2013; 160-78.
- [4] Rosai J, Ackerman. Inflammation. In: *Rosai and Ackerman's Surgical Pathology*. 9th edn. St. Louis: Elsevier Mosby, 2004; 1718-27
- [5] Adams D O. The granulomatous inflammatory response. *American Journal of Pathology* 1976; 84: 164-87
- [6] Gautam K, Pai RR, Bhat S. Granulomatous lesions of the skin. *Journal of Pathology of Nepal*. 2011; 1:81-6.
- [7] Blessing K. Mini-Symposium: Inflammatory skin Pathology: cutaneous granulomatous inflammation. *Current Diagnostic Pathology* 2005; 11: 219-35.
- [8] Chakrabarti S, Pal S, Biswas B, Bose K, Pal S, Pathak S. Clinico-Pathological Study of Cutaneous Granulomatous Lesions- a 5 yr Experience in a Tertiary Care Hospital in India. *Iran J Pathol* 2016; 11(1): 54 - 60.
- [9] Zafar M N, Sadiq S, Menon MA. Morphological study of different granulomatous lesions of the skin. *Journal of Pakistan association of dermatologists*. 2008; 18:21-8
- [10] Khatib Y, Khair S, Makhecha M, Kamat A, Rathod R, Kapoor K. Clinicopathological study of infectious dermatoses in a peripheral hospital of Mumbai. *International journal of contemporary medical research*: 2016; 3:3311-4
- [11] Srinivas T, Hariprasad S. Granulomatous dermatosis: histopathological study in a tertiary care hospital. *Int J Res Med Sci* 2017; 5:3869-74
- [12] Khattak MS, Ahmad S, Ahmad M. Distribution of histopathological variants of cutaneous granulomatous inflammation. *Gomal J Med Sci* 2017; 15(2):74-7.
- [13] Dhar S. Histopathological features of granulomatous skin diseases: an analysis of 22 skin biopsies. *Indian J Dermatol* 2002; 47(2):88-90.
- [14] Premi HS, K JS, Padma SK, Srinivas T, Mathias M, Y SK, L KPH, Chandrika. A histopathological study of granulomatous inflammation. *NUJHS* 2012; 2(1):15-9.
- [15] Bal A, Mohan H, Dhama GP. Infectious granulomatous dermatitis: a clinicopathological study. *Indian J Dermatol* 2006; 51(3):217-20.
- [16] Bhutto AM, Solangi A, Khaskhely NM, Arakaki H, Nonaka S. Clinical and epidemiological observations of cutaneous tuberculosis in Larkana, Pakistan. *Int J Dermatol*. 2002; 41(3):159-65.
- [17] Sehgal VN, Srivastava G, Khurana VK, Sharma VK, Bhalla P, Beohar PC. An appraisal of epidemiologic, clinical, bacteriologic, histopathologic, and immunologic parameters in cutaneous tuberculosis. *Int J Dermatol*. 1987; 26(8):521-6.
- [18] Farina MC, Gengundez MI, Pique E et al. Cutaneous tuberculosis: a clinical, histological and bacteriological study. *J Am Acad Dermatol* 1995 Sep; 33(3):433-40.
- [19] Pawale J, Belagatti SL, Naidu V, Kulkarni MH, Puranik R. Histopathological study of cutaneous granuloma. *Int J Public Health Res Develop* 2011 July; 2(2):74-9.
- [20] Hirsh BC and Johnson WC. Concepts of granulomatous inflammation. *Int J Dermatol* 1984; 23: 90-9.
- [21] Weedon D. The granulomatous reaction pattern. In: Weedon D (ed). *Skin Pathology*, 2nd ed. Philadelphia: Churchill Livingstone; 2002. pp193-220.

- [22] Kumar V, Abbass AK, Aster CJ. Inflammation healing and repair. In: Robin's pathological basis of diseases. 9th ed. Philadelphia:WB Saunders,2013; 160-78.
- [23] Rosai J, Ackerman. Inflammation. In: Rosai and Ackerman's Surgical Pathology. 9th edn. St.Louis:Elsevier Mosby,2004:1718-27
- [24] Adams D O. The granulomatous inflammatory response. American Journal of Pathology 1976; 84: 164-87
- [25] Gautam K, Pai RR, Bhat S. Granulomatous lesions of the skin. Journal of Pathology of Nepal. 2011;1:81-6.
- [26] Chakrabarti S, Pal S, Biswas B, Bose K, Pal S, Pathak S. Clinico-Pathological Study of Cutaneous Granulomatous Lesions- a 5 yr Experience in a Tertiary Care Hospital in India. Iran J Pathol 2016; 11(1): 54 - 60.
- [27] Zafar M N, Sadiq S, Menon MA. Morphological study of different granulomatous lesions of the skin. Journal of Pakistan association of dermatologists. 2008;18:21-8
- [28] Srinivas T, Hariprasad S. Granulomatous dermatosis: histopathological study in a tertiary care hospital. Int J Res Med Sci 2017;5:3869-74.
- [29] Blessing K. Mini-Symposium: Inflammatory skin Pathology: cutaneous granulomatous inflammation. Current Diagnostic Pathology 2005; 11:219-35.