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To Study Clinicopathological Correlation of Granulomatous Diseases of Skin

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Abstract
Granulomatous lesions in skin can be due to infectious and non infectious causes. Tuberculosis, leprosy, fungus, HIV, granuloma annulare, sarcoidosis, foreign body etc. all can lead to cutaneous granulomas. They present with a variety of overlapping symptoms like papules, nodules or plaques. So detailed clinical history, a good clinical examination and a close histological examination all can lead to conclusive clinicopathological correlation which is essential in making a final diagnosis. In the present study, 50 cases clinically diagnosed as granulomatous lesions of skin were studied, to find the etiology, clinicopathological correlation and relative frequency of all granulomatous lesions on tissue biopsy sent for histopathological examination. The study was done by routine H & E (Haematoxylin and Eosin) staining. Special stains like Ziehl-Neelsen stain, Gomori's Methenamine silver, PAS, Fite Faraco were also done wherever required. The overall level of concordance between clinical and histopathological diagnosis was noted in 78% cases. Parity for individual type of leprosy was TT (50%), BT (92.3%), BB (0%). Parity for other cases, LV (57.14%), S (66.6%), F (0%) and for GA, TVC, LS, SC 100% each.
Keywords: *Granuloma, Leprosy, Granulomatous Dermatitis*
Keynote: *To find the etiology, clinicopathological correlation and relative frequency of all granulomatous lesions of skin on tissue biopsy sent for histopathogical examination.*

Introduction

Granulomatous inflammation: a distinctive pattern of chronic inflammatory process spectrum which results in varied clinical and histopathologic presentation. Granuloma is a focus of chronic inflammation consisting of microscopic aggregation of macrophages that are transformed into epithelium-like cells, surrounded by a collar of mononuclear leucocytes, principally lymphocytes and occasionally plasma cells[1]. They have a variable histological picture depending on the cause. Granulomatous diseases frequently poses a diagnostic challenge to dermatopathologists, since an identical histologic picture is produced by several causes and conversely a single cause may produce varied histologic pattern[2,3] and are classified based on the etiology and morphology. Also classified as infectious and non infectious according to the presence or absence of pathogenic organisms.

Based on Etiology[4]

- Bacterial
- Fungal
- Viral/ Chlamydial-cat scratch fever, LGV
- Helminthic
- Foreign body type
- Unknown cause

Based on Morphological Criteria[5]

➢ Epitheloid

➢ Histiocytic

➢ Foreign body

➢ Necrobiotic/palisading

➢ Mixed inflammatory/suppurative

- Infectious cause- Tuberculosis, Leprosy, Fungal, HIV
- Non infectious cause- Sarcoidosis, Granuloma annulare, Foreign body granuloma, Necrobiosis lipoidica, Rheumatoid nodule, Palisaded neutrophilic and granulomatous dermatitis.

The provocative agents of granulomatous inflammation are non-degradable by both neutrophils and non-active macrophages. The actions of polymorphonuclear leucocytes, non-activated macrophages and chemical mediators which are associated with the tissue injury are insufficient to completely digest and eliminate the offending agents. For such degradation, the action of transformed macrophages which are formed with the help of the CD4+T cells, is required. The CD4+T cells secrete various mediators such as IL2, IFγ, TNF and lymphotoxin for the transformation of the macrophages into epitheloid cells and giant cells, which are the components of granulomas[6].

Leprosy: Leprosy, or Hansen's disease, is a chronic infectious disease caused by Mycobacterium leprae. Leprosy is primarily a granulomatous disease of the peripheralnerves and mucosa of the upper respiratory tract; skin lesions are the primary external symptoms if left untreated. Leprosy can be progressive and can cause permanent damage to the skin, nerves, limbs, and eyes. India dominates the global picture with 60% of the world's leprosy cases[7]

Leprosy exhibits a spectrum of clinical characteristics that correlate with the histopathological changes and the immunological status of the individual. At one end of the spectrum is tuberculoid leprosy (TT), which is manifested with few lesions and a paucity of organisms (Paucibacillary Leprosy). At the other end is lepromatous leprosy (LL), in which there are numerous lesions with myriad bacilli (Multibacillary Leprosy) and an associated defective cellular immune response. In between these poles are Borderline-tuberculoid (BT), Borderline (BB) and Borderline-lepromatous (BL) leprosy. Polar forms (TT and LL) are the most stable and the Borderline form (BB) the most labile. This categorization is often modified by the addition of subpolar forms at either end of spectrum (TTs and LLs), giving additional categories of subpolar lepromatous leprosy and subpolar tuberculoid leprosy.[8]

The Cardinal signs of leprosy are:

- Anesthesia
- Thickened peripheral nerves
- Skin lesions
- Presence of Acid-fast bacilli in slit skin smear

For the diagnosis of leprosy, at least two of the three cardinal signs or demonstration of acid-fast bacilli is essential[9]. The histopathological examination is must for confirmation of diagnosis in doubtful cases of leprosy. So, clinicohistopathological correlation of leprosy cases assumes a pivotal role for early diagnosis and for proper labelling of a case.[10]

Aims and Objectives

The present study was planned

1. To study the various clinical cases of granulomatous diseases received.
2. To study the histopathological findings in these granulomatous lesions of skin.

3. To correlate clinical with histopathological findings i.e. to find out clinicopathological correlation.

Materials and Methods

This study was performed on skin samples received from 50 patients of clinically diagnosed cutaneous granulomatous lesions. From each patient, skin biopsy, which includes the lesion and an adjacent normal looking perilesional area, was received in department of Pathology, Government Medical College, Amritsar. Relevant history of the patient was taken. The study was done by routine H & E (Haematoxylin and Eosin) staining. Special stains like Ziehl-Neelsen stain, Gomori's Methenamine silver, PAS, Fite Faraco were also done wherever required.

Tuberculoid Leprosy: Asymmetrical, Scattered, Hypo-pigmented, Well demarcated anesthetic plaques. On Histopathological examination, large epitheloid cells arranged in compact granulomas along with neurovascular bundles and dense peripheral lymphocyte accumulation are seen. Langhans giant cells are typically absent.[11] (Figure 1)

Lepromatous Leprosy: Erythematous papules and nodules, Symmetrical distribution. On Histopathological examination, dense infiltrate of foam cells with lymphocytes, plasma cells with grenz zone. (Figure 2)

Fite Faraco Stain- To Demonstrate Lepra Bacilli (Figure-3)

Tuberculosis (lupus vulgaris): Erythematous, Ulcerated papules, nodules or plaques. On histopathology, epidermal hyperplasia with non caseating granulomas consisting of epitheloid cells, giant cells and lymphocytes seen in upper dermis. (Figure-4)

Fungal Granuloma: Sporotrichosis, eumycetoma, chromoblastosis. Mixed or suppurative granuloma. Best demonstrated with special stains like PAS and gomori methamine. (Figure-5)

Granuloma Annulare: Idiopathic, small firm asymptomatic papules, pale red, grouped in ringlike or circinate fashion. On histopathology, incomplete collagen degeneration surrounded by palisading inflammatory cells-histiocytes, monocytes, giant cells, lymphocytes. (Figure-6)

Sarcoidosis: Systemic granulomatous disease of undetermined etiology. On histopathology, classic well formed non caseating granulomas, composed of aggregates of epitheloid cells, with langhans or foreign body giant cells (Figure- 7). Schaumann bodies and Asteroid bodies 4 seen. (Figure- 8)

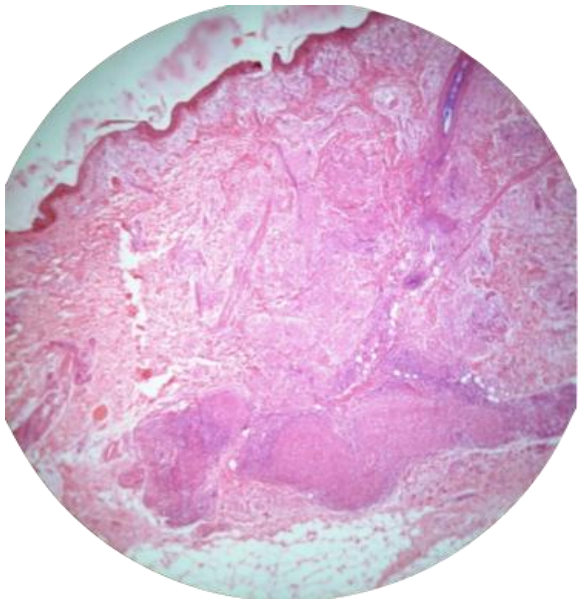
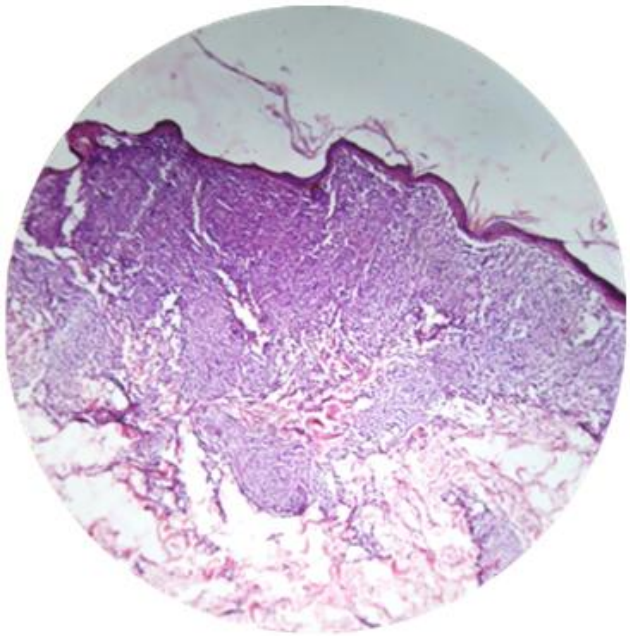


Figure 1



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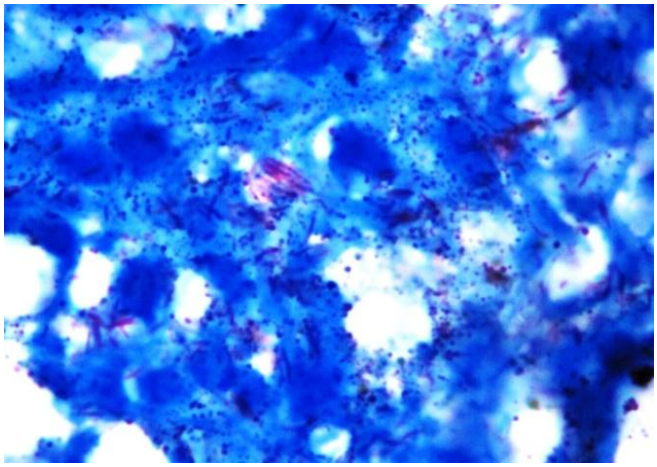

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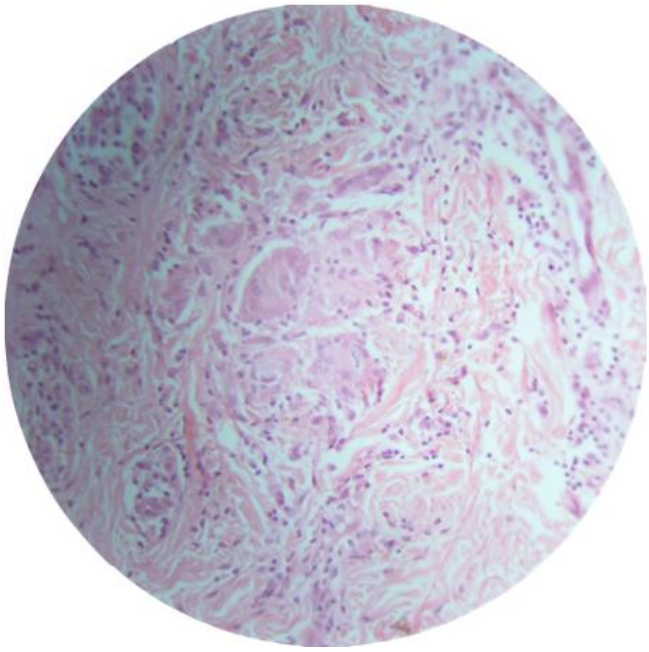

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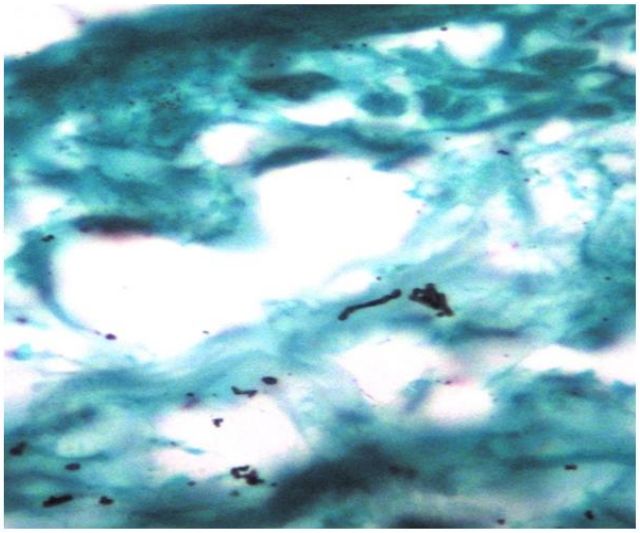

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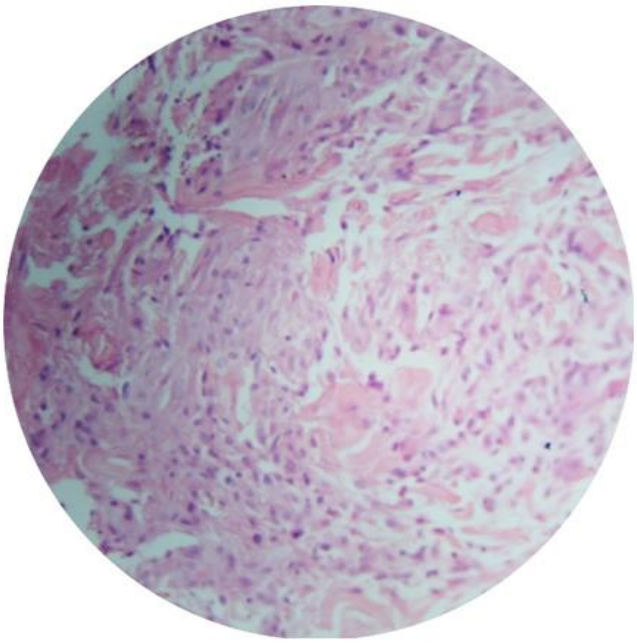

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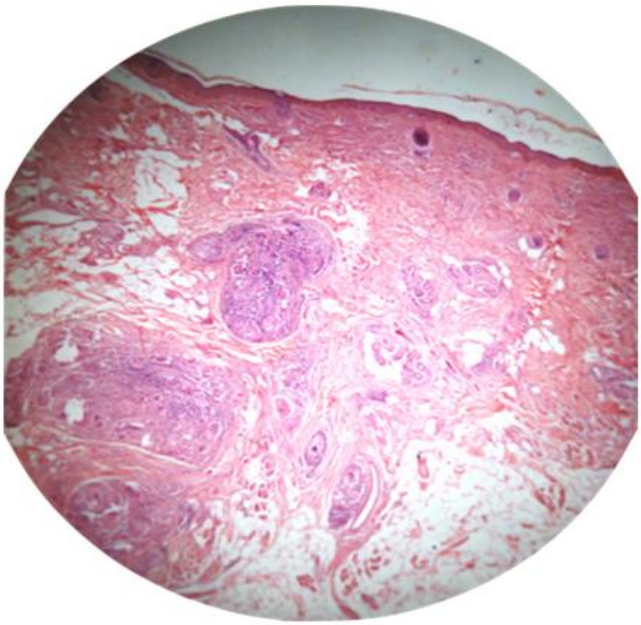

Figure 7

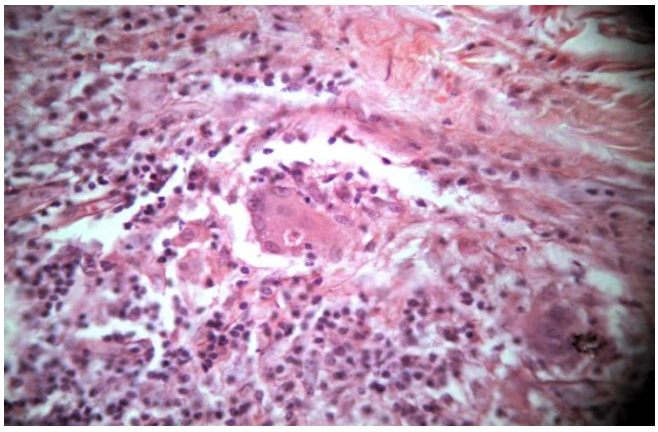

Figure 8

Results and Discussion

In the present study, there was good correlation between clinical and histopathological findings in leprosy. BT leprosy was most common lesion encountered. Cutaneous tuberculosis was 2nd largest group with 9(18%) histologically confirmed cases. Out of these, lupus vulgaris was the commonest, seen in 5 patients. There were 7 clinically diagnosed cases of lupus vulgaris. On histopathology, 4 were LV,1 was fungal,1 was FB granuloma, 1 was sarcoidosis.AFB were seen in 6 out of 30 cases of leprosy(20%). The overall level of concordance between clinical and histopathological diagnosis was noted in 78% cases.

The youngest patient in the present study was 5 yrs old while the eldest being 72 yrs old. The cases showed maximum incidence in the age group of 21-30 yrs comprising 16 (32%) of cases followed by age groups 31-40 yrs (22%). The least number of cases were seen in 0-10 yrs old group. Mean age in the present study was 32.44 years. In a study by Permi et al the mean age was 33.26 years[12]. (Table I)

In the present study, 64% patients were males and 36% females with a male to female ratio (M:F) of 1.7:1. Similar results were obtained in a study conducted by Gautam et al and there were 63.21% males and 36.79% females. The male:female ratio was 1.7:1[13] Similarly Nadkarani and Rege[14], Moorthy et al [15] in their studies on leprosy also found males to be involved more by leprosy of the skin. (Table II)

In present study, 30 out of 50 patients were of leprosy. 20 out of 30 (64.5%) presented with hypopigmented patches/ macules followed by Erythematous plaque in 23.3% (7/30). Similar results were seen in a study by Mittal et al 63/102 (61.76%) cases had hypopigmented macules and 38.24% cases had erythematous nodules[18]. Hypopigmented skin lesions were the mostcommon clinical feature in the study by Murthy NB et al[19]. (Chart A)

In the present study, 31 cases clinically presented as Leprosy with BT (26), TT (2) and BB (3) Cases. 11 cases as Tuberculosis with LV (7), TVC (2), LS (1) and SC (1) case. 4 cases as GA, 3 cases as Sarcoidosis and 1 as Fungal granuloma. In the present study clinical diagnosis was made according to Ridley-Jopling criteria and it was found that maximum number of cases seen were of BT (52%) followed by BB(6%) and TT(4%). In comparison to this, a study conducted by Kumar et al on 61 patients clinical diagnosis of BT was made in 48 (78.7%) cases, IL in 4 (6.6%), BL in 5 (8.2%), LL in 3 (4.9%) and pure neuritic in 1(1.6%) case. Clinically there was no patient with TT or BB disease[20]. Clinical presentation varies with immune status of individuals. (Chart B)

Of the 50 skin biopsies taken, on histopathology 30 were typified as leprosy, 9 as tuberculosis of skin, 4 out of 50 cases were diagnosed on histopathology as sarcoidosis, 4 as granuloma annulare, 2 as fungal granuloma and 1 as foreign body granuloma. (Chart C)

On histopathology out of 50 skin biopsies, Tuberculoid granulomas were seen 34 (68%) cases, both Sarcoidal and Necrobiotic/palisading granulomas in 4 (8%), histiocytic granulomas 5 (10%), suppurative granulomas in 2 (4%) and Foreign body granulomas also in 1 (2%) cases. (Chart D).

Table I Showing Age Wise Distribution

AGE GROUP	NO. OF CASES	PERCENTAGE (%)
0-10 yrs	3	6
11-20 yrs	7	14
21-30 yrs	16	32
31-40 yrs	11	22
41-50 yrs	9	18
>50 yrs	4	8

Table II Showing Sex Distribution

SEX	NO. OF CASES	PERCENTAGE (%)
Male	32	64
Female	18	36
Total	50	100

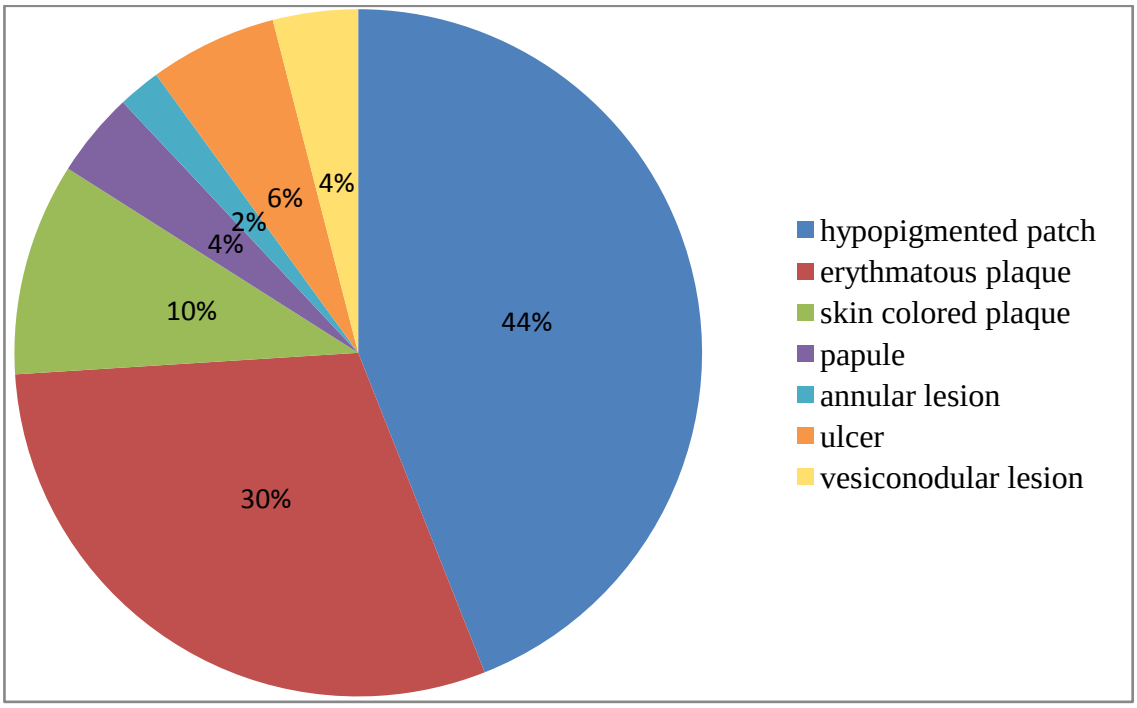

Chart A - Relative Proportions of Various Clinical Symptoms in Granulomatous Diseases

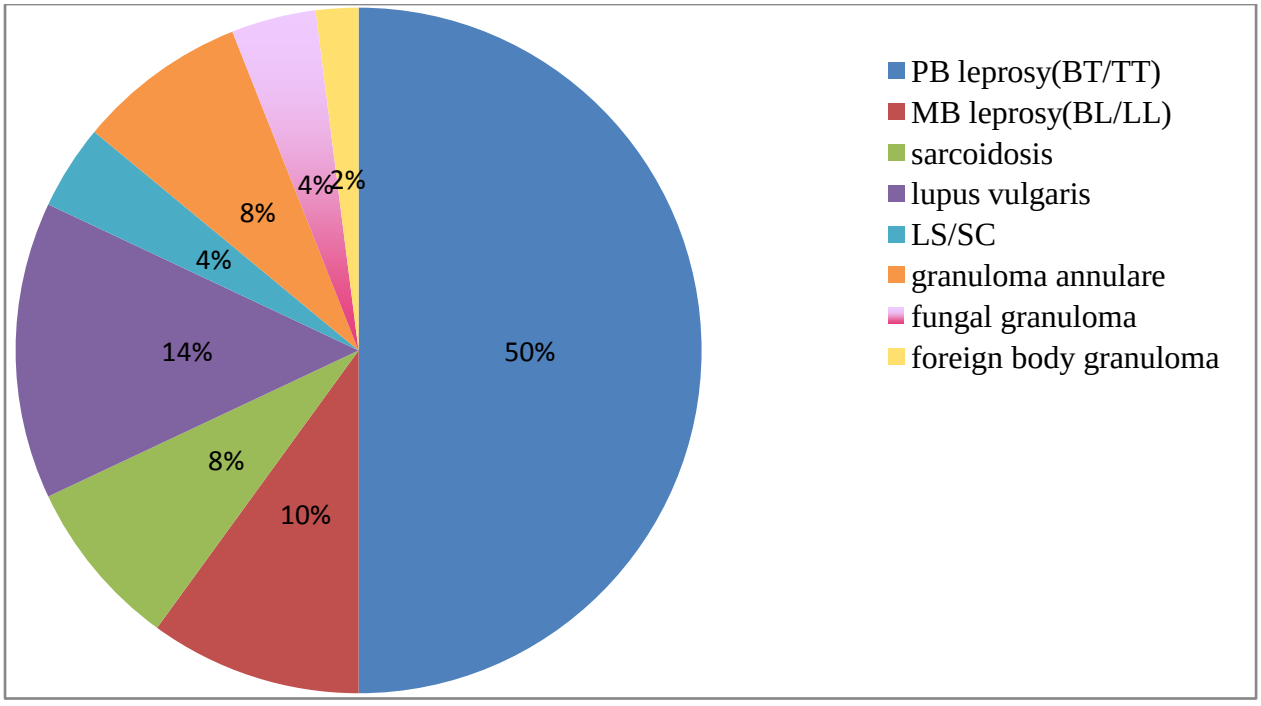

Chart B - Spectrum of Histopathological Diagnosis for the skin Biopsies

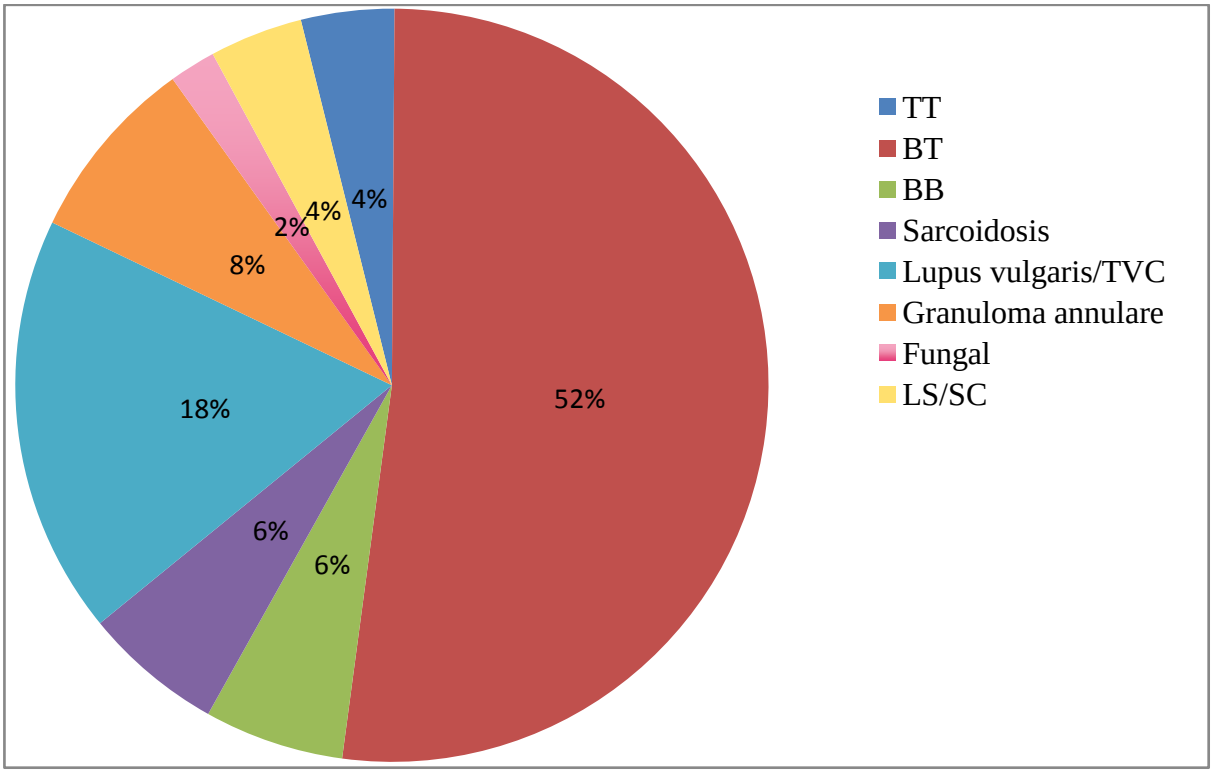

Chart C - Showing Proportion of Various Clinical Diagnosis

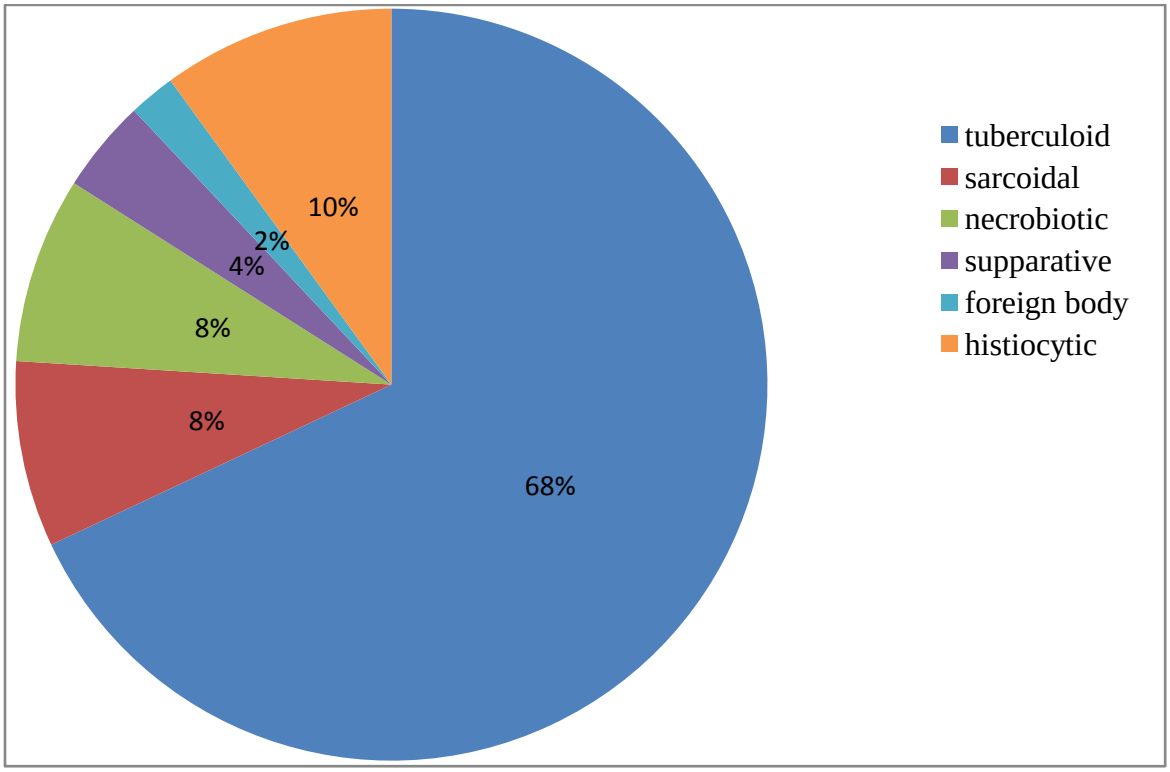

Chart D Showing Relative Proportion of Various Types of Granulomas

Conclusion

There is no independent gold standard test for the diagnosis of granulomatous diseases of the skin. It is therefore difficult to present a completely satisfactory classification of granulomatous dermatitis. In the present study a combination of etiology and morphology of granuloma was used to classify granulomatous dermatitis. It was observed that an important cause of granulomatous dermatitis is infections, with

leprosy and tuberculosis constituting the leading etiology. There is significant overlap seen in histopathological presentation of different granulomatous reactions. Adequate clinical data and workup in combination with pathological resources can help in finding specific etiology. We conclude from our study that histopathological examination should be carried in all cases of clinically labelled granulomatous pathology to aid arrive at a definite diagnosis. Cooperation between clinician and pathologist is more important in the field of skin disease than in almost any other field if the patient is to derive the greatest benefit from the biopsy[17].

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