



CLINICO-HISTOPATHOLOGICAL CORRELATION OF GRANULOMATOUS LESIONS OF SKIN: A RETROSPECTIVE ANALYSIS OF 111 CASES

Pathology

Dr. Rajani Anand*	M.D, Pathology, Senior Resident, Dept. of Pathology, Dr B.S.A Hospital Rohini, New Delhi-110085. *Corresponding Author
Dr. Pratima Khare	M.D, Pathology, Consultant Pathology, Dept. of Pathology, Dr B.S.A Hospital, Rohini, New Delhi-110085.
Dr. Renu Gupta	M.D, Pathology, Senior Specialist (Pathology) and Head, Dept. of Pathology, Dr B.S.A Hospital, Rohini, New Delhi-110085
Dr Avni Bhatnagar	M.D, Pathology, Senior Resident, Dept. of Pathology, Dr. B.S.A Hospital Rohini, New Delhi-110085

ABSTRACT

Introduction: Granulomatous skin lesions present as wide spectrum of clinical conditions where diagnosis with significant accuracy is possible only through the histopathological examination of biopsy samples. **Aims and objective:** The study was to assess the frequency of granulomatous skin lesions and their pattern in relation to their clinical findings and histopathology. **Material & Methods:** The retrospective study was conducted in the department of pathology of our institute. The data related to the age, gender, clinical presentation, and the biopsy findings was analyzed. **Results:** Amongst 111 histologically proven cases of granulomatous lesions, there was male preponderance. The commonest age group involved was between 21-40 years. The common primary clinical types were plaque, nodule, and macule present in 42.34%, 31.53% and 15.31% cases respectively. The most common diagnosis was leprosy (54.05%), followed by tuberculosis (39.63%). Among the leprosy cases, borderline tuberculoid and borderline lepromatous were the most common types. Histologically, all lesions showed epithelioid cell granulomas, the commonest type being tuberculoid granuloma. **Conclusions:** This study reaffirms that histopathology is a fundamental tool to diagnose granulomatous skin diseases. Type of granulomas, their pattern and associated features suggest about the diagnosis. Infective diseases (leprosy and cutaneous tuberculosis) are still the most common granulomatous skin diseases.

KEYWORDS

Granulomatous Skin Lesions; Leprosy; Tuberculosis; Histopathology; sarcoidosis

INTRODUCTION:

Granulomatous skin lesions are caused by wide spectrum of diseases and are characterized by presence of epithelioid cell granuloma on histopathological examination of the biopsy. The term "granulomatous" was first used by Virchow to describe a granule like tumor mass of granulation tissue [1]. The granulomas contain epithelioid cells. The difference lies in the additional findings of acute inflammation, arrangement of lymphocytes, necrosis, collagen alteration and Giant cells. Reactive substances that are poorly soluble evoke a granulomatous reaction, which is a type IV hypersensitivity reaction, leading to a foreign body granuloma [2]. Based on cellular components and related changes, granulomatous skin lesions are classified into various sub types in the literature namely tuberculoid, necrobiotic, sarcoidal, palisaded, suppurative, histoid type granuloma, foreign body granuloma etc. [3, 4, 5]. These lesions often present as a diagnostic challenge to derma-pathologists, as a single identical histopathological pattern can be produced by several etiologies and on the contrary, a single etiology may produce diverse histopathological patterns [6]. Further different types of chronic granulomatous inflammatory lesions of skin are seen in different geographic locations [7]. The present study aims to define the pattern and frequency of various granulomatous skin lesions in relation to their clinical findings and histopathology.

MATERIAL & METHOD

This retrospective study was carried out in the department of pathology. Analysis of 600 skin biopsies conducted over a period of 5 years from January 2015 to December 2019, was done. These biopsies were carried out by the dermatologist and the tissue was sent for histopathological examination along with clinical details in prescribed proforma. Out of these 600 cases of skin biopsies received during this period, 150 cases were of suspected granulomatous lesion. The biopsy samples were processed. All cases were stained with H&E stain and special stains like Modified Fite-Faraco stain, Ziehl Neelsen (ZN) stain and periodic acid Schiff (PAS) stain wherever required.

Exclusion Criteria:

1. Cases of lepromatous leprosy with large number of foamy histiocytes without granuloma formation. All the cases of Lepromatous Leprosy were Fite positive.
2. Cases of borderline leprosy with presence of only clusters of foamy histiocytes without epithelioid cell granuloma.

3. Cases with nonspecific dermatosis were also excluded from study.

The records pertaining to the age, gender, clinical lesions type and site were retrieved along with blocks and the slides for reevaluation. The biopsy findings related to the histopathological features of granuloma, necrosis, inflammation, type of granuloma and the final diagnosis were recorded. Cases where slides were subjected to special staining like Modified Fite-Faraco stain, ZN stain and PAS stain were also reevaluated. The exclusion criteria ruled out 39 cases from the study. Thus, the analysis of remaining 111 patients was carried out.

RESULTS.

Among the 111 patients having granulomatous lesions across all age groups, with highest number of patients were seen in the age group of 16-30 followed by those in the age group of 31-45 years [Table1]. Overall, patients in the age group of 16-45 totaling 73 accounted for 65.76% of cases. There was a male preponderance in all the age groups except in age group of 46 to 60 where both males and females were affected equally. Overall, the series had male: female ratio of 7:4. The most common sites of granulomatous skin lesions were upper limb (27.93%), lower limb (25.23%), head & neck and trunk (20.72%) [Table2].

Histopathological examination demonstrated that most common diagnosis was leprosy (60 cases, 54.05%), followed by tuberculosis in 44 cases (39.63%), Actinomycosis 1 case (0.9%), fungal infection in 1 (0.9%), sarcoidosis in 2 (1.8%) cases, granuloma annulare in 2 (1.8%) and foreign body granuloma in 1 (0.9%) case. Among the leprosy cases, borderline lepromatous (BL) leprosy and borderline tuberculoid leprosy (BT) were the most common types, accounting for 46.66% (28 cases) in each subgroup. There were only 2 cases of Tuberculoid Leprosy (TT) and 1 case each of Borderline borderline (BB) leprosy and Erythema nodosum leprosum (ENL).

Among the total tuberculosis cases 44 (39.63%), the commonest lesion was lupus vulgaris (LV) (19 cases, 43.18%) followed by tubercular verruca cutis (TBVC) (14 cases, 31.81%). lichen scrofulosorum (LSCS) (5 cases, 11.36%) and scrofuloderma (4 cases, 9.09%) being less common. There were 2 cases, where diagnosis of cutaneous tuberculosis (Cut.TB) was made due to lack of specific diagnostic features. Among the other infective etiologies leading to granulomatous skin lesions, there were one case each of Actinomycosis and Majocchi.

The non-infectious causes leading to granulomatous disease of skin was uncommon. There were only 5 (4.5%) cases in the series. Two cases each of sarcoidosis and granuloma annulare and one case of epidermal inclusion cyst with granulomatous changes fell into this category.

The commonest clinical picture in the present series was that of plaque in 47 (42.34%) cases, followed by nodule in 35 (31.53%) cases, macule in 17 (15.31%) cases and papule 11 (9.9%) cases. There was only 1 (0.9%) case presenting as soft tissue swelling with serous discharge.

Clinico-histological presentation showed that skin lesions were usually not pathognomonic of a specific granulomatous disorder [Table 3]. The plaques and nodules were present both in infectious etiologies as well as in non-infectious conditions. One case of granuloma annulare presented as papule whereas the other as plaque. Papules and macules were present both in leprosy as well as in tuberculosis. The only case of actinomycosis in the series clinically presented as soft tissue swelling with serous discharge.

Among the 60 cases of leprosy, there were 28 (46.66%) patients each in subgroup of BT and BL. Whereas 10 patients in each of these two groups presented clinically as plaque, and 1 patient each as papule. Macule formation was more common in BT (9 cases) compared to BL (4 cases) (Figure 1). However, the clinical presentation of nodule was more common in BL (13 cases compared to BT (8 cases). There were only 2 cases (93.33%) having tuberculoid leprosy which presented clinically as macule. There was one case of Erythema nodosum leprosum (presenting as nodule) in the series. The Fite Stain was negative in all the cases of BT, TT and in 9 cases of BL, while it was positive in 19 cases of BL, BB and ENL.

There were 44 cases of tuberculosis in the series. Lupus vulgaris was commonest (19 cases, 43.18%) with clinical presentation of plaque, nodules, and papules in 9, 6 and 4 cases, respectively. The plaque type lesions in lupus vulgaris showed erythematous changes in 6 cases, ulceration in 1, hypertrophy in 1 and central clearing with peripheral nodule in 1 case. In nodular type Lupus vulgaris, additional feature of ulceration was seen in 3 cases, whereas in one case of papular lesion erythematous changes were also present. On histopathological examination, epidermis was unremarkable in 5 cases (3 in plaque type lesions, 2 in papule type of lesions) whereas 14 cases LV had typical epidermal changes with 3 of them showing basal layer damage. Ulcerated lesions show intraepidermal neutrophilic infiltration. Typical lupus vulgaris pattern or lichenoid pattern granuloma was found in 5 cases (Figure 2). The rest of the cases show tuberculoid type epithelioid cell granuloma without any distribution along with interstitial infiltration of chronic inflammatory cells in dermis. Necrosis was found in only 1 case and focal fibrosis in dermis was also seen in 1 case of LV.

The second most common presentation of tuberculosis was TBVC seen in 14 (31.81%) cases, all of which presented as plaque. Additional feature of erythema was present in 1 case. Histopathological findings were similar to lupus vulgaris with marked hyperkeratosis and acanthosis present in all the cases along with tuberculoid granuloma with focal necrosis and neutrophilic infiltration both in epidermis and dermis. Basal layer damage was found in 1 case.

There were 5 (11.36%) cases of LSCS (also known as tuberculosis cutis lichenoides) and 4 (9.09%) cases of scrofuloderma in the series. In 2 (4.54%) cases, definitive diagnosis could not be made due to lack of specific diagnostic features, and these were reported as cutaneous tuberculosis. Among 5 cases of LSCS, 4 (80%) cases presented as tiny scaly papules whereas one patient presented as a nodule (20%). Histopathological findings show normal epidermis in 4 (80%) cases and presence of focal ulceration in 1 (20%) case. There is presence of focal perifollicular tuberculoid granuloma in all the cases. All 4 cases of scrofuloderma clinically presented as indurated nodule with discharging and healed sinuses. Histo-pathological examination showed suppurative granuloma along with neutrophilic infiltration in dermis in 2 cases and whereas in other 2 cases there was presence of tuberculoid granuloma.

The only patient diagnosed as actinomycosis clinically presented as soft tissue swelling with serous discharge. In the single case of Majocchi granuloma in the series, the clinical presentation was that of

plaques. Among the non-infective causes of granulomatous skin lesions, sarcoidosis presented as plaques in one patient and as nodule in the other patient (Figure 3). Similarly, 1 patient with granuloma annulare had plaque while the other had papule as clinical presentation. The only case in the series having EIC had clinically presented as nodule.

DISCUSSION:

Granuloma formation is due to type IV hypersensitivity reaction elicited by infectious and non-infectious antigen. Granulomatous dermatitis frequently presents a diagnostic challenge to dermatopathologists as an identical histologic picture is produced by several causes [8]. Granulomatous dermatoses have overlapping clinical presentations. So, definitive etiological diagnoses play a very important role in their treatment. [9].

Our study of 111 patients showed a male preponderance in the series. A similar observation of male preponderance has been reported by many authors [8, 9, 10]. El-Khalawany M. et. al. [9] reported male predominance in their series of 233 cases with male patients accounting for 150 cases compared to female patients (83). Similar male to female ratio of 3/2 have also been reported by many authors [8, 10]. Our series had patients 73 (65.76%) patients between 16-45 age group. Similar observations of lesions being more common in adults between 20-40 years age groups, has also been reported by Kumar and Goswami [10].

Location wise, the most common sites of granulomatous skin lesions were upper limb (27.93%), lower limb (25.23%), and trunk (20.72%) in our series. Many authors have reported that the commonest site of involvement being upper limb by these types of lesions [11, 12].

Granulomatous skin lesions are attributed to a very large number of etio-pathological entities. Various methods have been employed to group these entities. James [13] described granuloma as a focal compact collection of inflammatory cells, mononuclear cells predominating, usually as a result of the persistence of a non-degradable product and of active cell mediated hypersensitivity. He attributed this to a complex interplay between invading organism or prolonged antigenemia, macrophage activity, a Th1 cell response, B cell over activity and a vast array of biological mediators. Accordingly, he described these lesions into 7 sub-classes including infections, vasculitis, immunological upsets, leucocyte oxidase defect, hypersensitivity, chemicals, and neoplasia. Alimuddin Zumla [14] grouped these granulomas in 3 categories. The group 1 included infections due to well recognized organisms (Tuberculosis, leprosy, brucellosis, actinomycosis, syphilis, yaws, mycosis, leishmaniasis, Q fever etc.) whereas group 2 causative organism of granuloma was identified by molecular methods but are not readily isolated by conventional microbiological techniques (Cat Scratch disease, Whipple's disease). The group 3 consists of disorders for which the causal organisms were not yet been identified but are strongly suspected (Crohn's disease, sarcoidosis etc.). For convenience purposes and simplicity and having relatively less divergent etiological causes of granuloma formation in our series, we grouped our cases into 2 categories, namely those having infectious etiologies (Comprising of leprosy, tuberculosis, bacterial and fungal etiologies) and non-infectious etiologies (Sarcoidosis, granuloma annulare, foreign body granuloma etc.). The infectious causes leading to granulomatous disease of skin formed the bulk of cases (106 cases, 95.5%) whereas non-infectious causes leading to disease were seen in only 5 (4.5%) cases.

Among the infectious causes of granulomatous lesions of skin, leprosy (56.6%) was the commonest followed by tuberculosis (41.5%). Similar observations have also been reported from the Indian subcontinent by many authors [8, 12]. Bal et al. [8] reported leprosy in 72.4% cases as the causative agent for granulomatous lesion in skin followed by tuberculosis in 23.1% cases. Fungal dermatitis was diagnosed only in 3.3% cases. In a study from Egypt, tuberculosis cases formed the largest granuloma group (40.8%), followed by leprosy (31.7%) [9]. Thus, infections form an important cause of granulomatous dermatitis with leprosy and tuberculosis being the leading causes.

The leprosy may present clinically as plaque, papule, macular, nodular, infiltrative, or diffuse lesions [15]. We also observed this pattern in our series, with nodules being most common (37%) followed by plaque

(33.3%), macule (26.6%) and papule in 3.33% cases. Bhatia et al. [16] considered both TT and BT as paucibacillary and LL or BL as multibacillary for treatment purposes and emphasized that differentiating TT from BT or BL from LL is therapeutically irrelevant. However, we described all these subgroups separately from histological point of view. The commonest type of skin lesions in our series were the BT and BL with 28 (46.66%) cases each, TT 2 case (3.33%) and BB 1 case (1.66%). Thus, the prevalence of paucibacillary (TT+BT) was 50% and multibacillary type (BB+BL) was 48.33%. ENL is characterized by the development of crops of tender cutaneous and subcutaneous nodules in association with generalized malaise, pain, and fever [17, 18] It is a very serious and potentially fatal condition. We had only one case (1.33%) in our series with nodular lesions.

Tuberculosis is the 2nd most common cause of granulomatous lesions in our study. The similar observations have been reported by many authors [18]. The commonest granulomatous lesion caused by tuberculosis in skin present in our series was LV (19 Cases, 43.18 %). Many authors have also reported this to be the commonest tubercular lesion of the skin in Southeast Asia [8, 18, 19, 20]. Kumar et al. [20] described that LV affects primarily the head and neck region but in Southeast Asia it appears to be more common on the extremities and buttocks.

The 2nd commonest lesion in our series was TBVC, seen in 14 cases (31.81%), all of which clinically presented as papule. TBVC is characterized by hyperkeratosis, acanthosis, and acute inflammatory infiltrate along with abscess in upper dermis and caseating granuloma in mid dermis. Chakrabarti et al. [18] had only 13.04% cases of TBVC in their series.

LSCS is also known as tuberculosis cutis lichenoides, is a rare form of tuberculid seen in children and young adults with or without other manifestations of tuberculosis [21]. This uncommon condition presents as lichenoid eruption of minute papules. We had 4 such cases presenting as papule and one as nodule in our series. Whereas 2 of these cases were below 15 years, the remaining 3 were in age group of 16 to 30 years.

Scrofuloderma, also known as tuberculosis cutis colliquativa, begins as a painless subcutaneous nodule, which is called a cold abscess. The diagnosis is often delayed [22]. We had only 4 such cases, all of which presented as nodule. Variable prevalence rate of scrofuloderma had been reported by different authors in their studies [18]. Scrofuloderma is particularly common in childhood and clinical presentation depends upon the underlying immune status of the patients as has been observed by Farina MC et al. [23] and Kumar B et al. [24]. However, we had only 2 cases in age group below 15 whereas remaining 2 were in the age group of 31-45.

Actinomycosis is a rare, chronic disease caused by a group of anaerobic Gram-positive bacteria, usually *Actinomyces israeli*, seen after mucosal disruption and may mimic malignancy due to its capacity to invade surrounding tissues and to form masses [25]. It may affect skin in some cases leading to granulomatous skin lesion. We had only one (0.9%) such case in our series.

Majocchi's Granuloma was described in 1883 in Italy by Domenico Majocchi [26]. It is a rare skin infection caused by fungus (Dermatophyte) which has tendency of invading keratinous tissue. This rare infection is possibly associated with depilation or with use of high potency topical corticosteroid therapy in areas of dermatophyte infection in immunocompetent patients [27]. We had one (0.9%) such young male patient in our series presenting as papule.

Sarcoidosis is characterized by non-caseating epithelioid cell granuloma with very few surrounding lymphocytes and a rim of mild dermal fibrosis, often described as naked non-caseating granuloma. It usually begins around 40 years of age and affects females more often than males. Skin lesions may mimic various other common dermatologic conditions [28] We had 2 such female patients, one presenting as papule whereas the other one presented as nodule. One of these two patients was a young adult, the other one was an elderly.

Granuloma annulare is a benign and self-limited cutaneous disease. Subcutaneous granuloma annulare is an uncommon variant seen almost exclusively in young children, usually presenting as firm

nodules, appearing more frequently in lower extremities, buttocks, hands, and scalp. In most of the cases a biopsy and histopathology are required to confirm the diagnosis [29]. There were only 2 (1.8%) cases in our series presenting as plaque in one patient and papule in the other patient. While one patient was an adolescent, the other one was an elderly male, which is a rare presentation of this benign disease.

Foreign body granulomas are not uncommon. Commonest cause of this pathology is due to granulomatous reaction occurring against the ruptured keratin material of epidermal cyst, resulting in numerous multinucleated giant cells and granuloma formation surrounding the cyst wall [18]. Variable percentage of these lesions has been reported in the literature [8, 11, 18]. Symptomatic lesions may develop years after the injury, and the patient may not remember a specific injury event [30]. We had only one case (0.9%) of foreign body granuloma in a young adult in our series.

CONCLUSION:

The present study reaffirms that the granulomatous skin lesions can be caused by a wide range of disease processes including the infective and non-infective etiologies. We had leprosy and tuberculosis as the leading causes of granulomatous lesions of skin. The clinical spectrum of presentation was so variable that a particular causative disease presented as different lesion at different sites in the same individual. Conversely, different disease processes also presented as similar types of lesions in different individuals. The nonspecific types of clinical lesions like plaque, papules, macules, nodules made differential diagnosis difficult. Further, a large number of rare conditions also produce such skin lesions that add to the difficulties in arriving at diagnosis. A detailed history, local and general physical examinations, clinical presentation of the lesions along with histopathological studies in many such situations is essential tools for the clinician to arrive at final diagnosis and proper management of patients.

Acknowledgement:

Special Thanks to the Medical Records Technician and laboratory staff Technicians Mr Arun Bhardwaj and Mr Ashwani Kumar for their continued technical support in providing old records, blocks, slides and re-staining wherever required.

Informed Consent:

Taking informed consent in writing from the patients, as per standard operating protocol, is mandatory for carrying out any surgical procedure including biopsies, FNAC etc.

Statement of Ethics:

This retrospective study had the approval of the institutional ethics committee vide file no. F.5(50)/2020/BSAH/DNB/Committee/22301, dated 01/10/2021, issued by Member Secretary (Ethics Committee) Dr Rajeev Ranjan.

Conflicts of Interests: None.

Funding Sources:

Ours being a Government of Delhi hospital, all services are provided free of cost to all the patients. No funding was taken from any organization.

Table 1: Age & Sex Correlation with Histopathological Diagnosis

Histopathological diagnosis	Age (< 15y) n=17	Age (16-30) n=42	Age (31-45) n=31	Age (46-60) n=12	Age (61-75) n=9	Total n=111
A. Infectious Causes (n=106)						
1. M. leprae (Leprosy) (n=60)	M/F	M/F	M/F	M/F	M/F	M/F
TT (n=2)	--	0/1	--	0/1	--	0/2
BT (n=28)	1/0	8/3	8/2	1/2	1/2	19/9
BB (n=1)	--	--	0/1	--	--	0/1
BL (n=28)	3/0	6/3	4/3	5/0	3/1	21/7
ENL (n=1)	--	--	1/0	--	--	1/0
2. M. tuberculosis (T.B.) (n=44)						
LV (n=19)	4/3	6/1	3/2	--	--	13/6
TBVC (n=14)	1/1	3/2	3/1	0/2	1/0	8/6
Cut.TB (n=2)	0/1	--	1/0	--	--	1/1

Lichen scrofulosorum (n=5)	1/0	1/3	--	--	--	2/3
Scrofuloderma (n=4)	1/1	--	1/1	--	--	2/2
3. Other Bacterial causes (n=1)						
Actinomycosis	--	1/0	--	--	--	1/0
4. Fungal (n=1)						
Majocchi	--	1/0	--	--	--	1/0
B. Non-infectious Causes (n=5)						
1. Sarcoidosis (n=2)	--	0/1	--	0/1	--	0/2
2. Granuloma annulare (n=2)	--	0/1	--	--	1/0	1/1
3. Foreign Body Granuloma (EIC with Granulomatous Changes) (n=1)		0/1				0/1
Total (n=111)	11/6	26/16	21/10	6/6	6/3	70/41

Abbreviations:

TT-Tuberculoid Leprosy; BT-Borderline Tuberculoid; BB-Mid borderline; BL-Borderline Leprosy; ENL- Erythema nodosum Leprosy; LV-Lupus Vulgaris; TBVC-Tuberculosis verruosa cutis; Cut. TB- Cutaneous Tuberculosis; LSCS-Lichen Scrofulosorum; GA-Granuloma annulare; EIC-Epidermal inclusion cyst

Table 2: Site distribution of the lesions (n=111).

S.NO	Sites	Total No. of cases	Percentage
1.	Upper Limb	29	26%
2.	Lower Limb	31	28%
3.	Head & Neck	13	12%
4.	Trunk	20	18%
5.	Generalized	18	16%

Table 3: Etio pathological and clinical picture co-relation (n=111)

	Clinical presentat ion					Total
Etio-pathological diagnosis	Plaque	Papule	Macule	Nodule	Soft swelling with serous discharge	
A. Infectious Causes (n=106)						
1. M. leprae (Leprosy) (n=60)						
TT	--	--	2	--	--	2
BT	10	1	9	8	--	28
BB	--	--	1	--	--	1
BL	10	1	4	13	--	28
ENL	--	--	--	1	--	1
2. M. tuberculosis (T.B.) (n=44)						
LV	9	4	--	6	--	19
TBVC	14	--	--	--	--	14
Lichen scrofulosorum	--	4	--	1	--	5
Scrofuloderma	--	--	--	4	--	4
Cutaneous	1	--	1	--	--	2
3. Other Bacterial causes (n=1)						
Actinomycosis	--	--	--	--	1	1
4. Fungal (n=1)						
Majocchi granuloma	1	--	--	--	--	1

B. Non-Infectious Causes (n=5)	--	--	--	--	--	
1. Sarcoidosis	1	--	--	1	--	2
2. Granuloma annulare	1	1	--	--	--	2
3. Foreign Body Granuloma (EIC with Granulomatous Changes)	--	--	--	1	--	1
Total (n=111)	47	11	17	35	1	111

Abbreviations:

M. leprae- Mycobacterium leprae; TT-Tuberculoid Leprosy; BT-Borderline Tuberculoid; BB-Mid borderline; BL-Borderline Leprosy; ENL- Erythema nodosum Leprosy; M. tuberculosis- Mycobacterium tuberculosis; LV-Lupus Vulgaris; TBVC-Tuberculosis verruosa cutis; LSCS-Lichen Scrofulosorum; Cut TB – Cutaneous Tuberculosis; GA-Granuloma annulare; EIC-Epidermal inclusion cyst

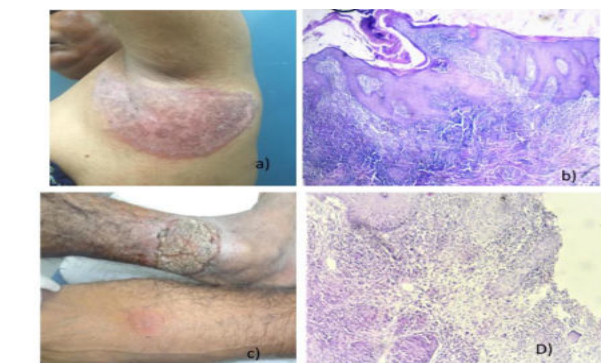
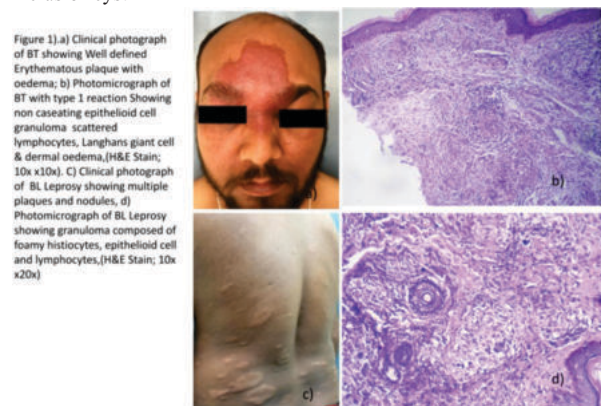


Figure 2: a) Clinical photograph showing Erythematous indurated plaque with central atrophy and raised margins of Lupus vulgaris; b) Photomicrograph of Lupus Vulgaris showing Lichenoid granuloma, (H&E Stain; 10x x 4x) c) Clinical photograph showing well defined erythematous verrucous indurated plaque of Tuberculosis verrucosa cutis; d) Photomicrograph of Tuberculosis verrucosa cutis showing epithelioid giant cell granuloma, necrosis and neutrophils in dermis, (H&E Stain; 10x x10x)

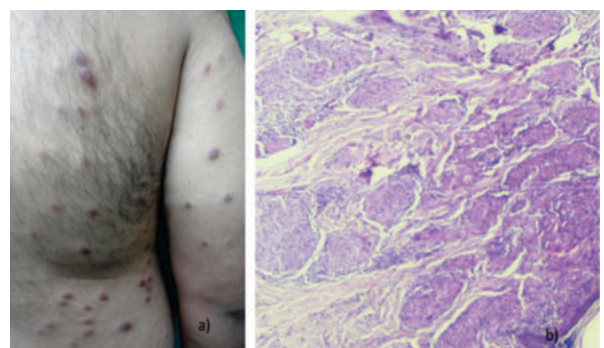


Figure 3: a) Multiple erythematous indurated nodules of Sarcoidosis; b) Photomicrograph of Sarcoidosis showing multiple naked non caseating epithelioid cell granuloma, (H&E Stain; 10x x10x)

REFERENCES:

1. We J. Concepts of granulomatous inflammation. *Int J. Dermatology*. 1984;23:90-99
2. Yadav D, Ramam M. Epithelioid cell granuloma. *Indian J Dermatopathol Diagn Dermatol* 2018; 5:7-18.
3. Qureshi R, Sheikh RA, Haque AU. Chronic granulomatous inflammatory disorders of skin. *Int J Pathol* 2004;2(1):31-4.
4. Ackerman BA, Chongchitnant N, Sanchez J, et al. *Histologic Diagnosis of Inflammatory Skin Diseases*. 2nd Ed. Baltimore, MD: Williams & Wilkins; 1997:64.
5. Grant-Kels JM. Granulomatous dermatitis. *Color Atlas of Dermatopathology*. New York, NY: Informa Healthcare; 2007:105-129.
6. Gupta K, Kumari A, Mangal K. Granulomatous lesions: a diagnostic challenge to dermatopathologists. *Int J Med Res Prof* 2016;2(4):33-39.
7. Zaim MT, Bordell RT, Pokorney. Non-Neoplastic Inflammatory Dermatoses: A Clinicopathologic Correlative Approach. *Mod Pathol*. 1990; 3:381-414.
8. Bal A, Mohan H, Dhami G P. Infectious granulomatous dermatitis: A clinico pathological study. *Indian J Dermatol* 2006; 51:217-20
9. Mohammed EK, Ibrahim M, Bayoumi E, Hussein HEN. Clinicopathological Features and the Practice of Diagnosing Infectious Cutaneous Granulomas in Egypt. *Int J Infect Dis*. 2011;15: 620-626.
10. Vivek Kumar and Hansa M. Goswami: Spectrum of Non-neoplastic Skin Lesions: A Histopathological Study based on Punch Biopsy. *Int. J. Cur Res Res V* (10) Issue 6 March 2018 43-48
11. Gautam K, Pai RR, Bhat S. Granulomatous Lesions of Skin. *J Pathol Nepal*. 2011;1(2):81-86. DOI: <http://dx.doi.org/10.3126/jpn.v1i2.5397>
12. Ahmad F, Mittal A, Arora D, Awasthi S, Dutta S, Kumar A. Histopathological study of cutaneous granulomatous lesions. *Indian J Pathol Oncol* 2019;6(4):526-529.
13. D Geraint James. A clinicopathological classification of granulomatous disorders: *Postgrad Med J* 2000; 76:457-465.
14. Alimuddin Zumla, D. Geraint James, Granulomatous Infections: Etiology and Classification, *Clinical Infectious Diseases*, Volume 23, Issue 1, July 1996, Pages 146-158, <https://doi.org/10.1093/clinids/23.1.146>
15. George VP, Srinivasan S. Histopathological Spectrum of Granulomatous Skin Lesions: A Review. *J Basic Clin Appl Health Sci* 2019;2(3):95-104.
16. Bhatia AS, Katoch K, Narayanan RB, Ramu G, Mukherjee A, Lavana RK. Clinical and histopathological correlation in the classification of leprosy. *Int J Lepr Other Mycobact Dis*. 1993 Sep;61(3):433-8. PMID: 8228443.
17. Lockwood DNJ (2004) Leprosy. In: Burns DA, Breathnach, S.M., Cox, N.H., Griffiths, C.E.M., editor. *Rook's Textbook of Dermatology* 7th ed. Oxford: Blackwell Publishing. pp. 29.21-29.21.
18. Chakrabarti S, Pal S, Biswas BK, 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.
19. Yasmeen H, Kanjee A. Cutaneous tuberculosis: a three-year prospective study. *J Pak Med Assoc* 2005; 55:10-3.
20. Kumar B, Muralidhar S. Cutaneous tuberculosis: a twenty-year prospective study. *Int J Tuberc Lung Dis* 1999; 3: 494-500.
21. Joshi, Harshal S et al. "Lichen scrofulosorum." *BMJ case reports* vol. 2014 bcr2013200858. 30 Jan. 2014, doi:10.1136/bcr-2013-200858
22. Kim GW, Park HJ, Kim HS, Kim SH, Ko HC, Kim BS, Kim MB, Sim EK. Delayed diagnosis of scrofuloderma misdiagnosed as a bacterial abscess. *Ann Dermatol*. 2012 Feb;24(1):70-3. doi: 10.5021/ad.2012.24.1.70. Epub 2012 Feb 2. PMID: 22363159; PMCID: PMC3283855.
23. Farina MC, Gegundez MI, Pique E et al. Cutaneous tuberculosis: a clinical, histological, and bacteriologic study. *J Am Acad Dermatol* 1995 Sep;33(3):433-40.
24. Kumar B, Rai R, Kaur I, Sahoo B, Muralidhar S, Radotra BD. Childhood cutaneous tuberculosis: a study over 25 years from northern India. *Int J Dermatol* 2001;40(1):2632.
25. Francisco Acevedo, Rene Baudrand, Luz M. Letelier, Pablo Gaete. Actinomycosis: a great pretender. Case reports of unusual presentations and a review of the literature: *International Journal of Infectious Diseases* Volume 12, Issue 4, July 2008, Pages 358362
26. Coelho WS, Diniz LM, Sousa JB, Filho, Castro CM. Case for diagnosis. Granuloma trichophyticum (Majocchi's granuloma) *A Bras Dermatol*. 2009; 84:85-86
27. Bressan AL, Silva RS, Fonseca JC, Alves M de F. Majocchi's granuloma. *An Bras Dermatol*. 2011; 86:797-798
28. Reddy RR, Shashi Kumar B M, Harish M R. Cutaneous sarcoidosis - a great masquerader: A report of three interesting cases. *Indian J Dermatol* 2011; 56:568-72
29. Reyes-Baraona F, Hasbún P, González S, Zegpi MS. Granuloma anular subcutáneo: reporte de un caso [Subcutaneous granuloma annulare: a case report]. *Rev Chil Pediatr*. 2017;88(5):652-655. Spanish. doi: 10.4067/S0370-41062017000500013. PMID: 29546952.
30. El Bouchti I, Ait Essi F, Abkari I, Latifi M, El Hassani S. Foreign body granuloma: a diagnosis not to forget. *Case Rep Orthop*. 2012; 2012:439836. doi: 10.1155/ 2012/439836