ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 9, Issue, 8(E), pp. 28607-28613, August, 2018

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

GRANULOMA REVISITED: A PROSPECTIVE STUDY OF GRANULOMATOUS SKIN LESIONS AT A TERTIARY CARE CENTRE IN GUJARAT

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DOI: http://dx.doi.org/10.24327/ijrsr.2018.0908.2490

ARTICLE INFO

Article History:

Received 13th May, 2018
Received in revised form 11th June, 2018
Accepted 8th July, 2018
Published online 28th August, 2018

Key Words:

Granulomatous reaction, concordance, discordance, Necrobiotic granuloma, Tuberculoid granuloma, Erythema Induratum, Granuloma Annulare, Granulomatous Rosacea and Lupus Miliaris disseminatus Facei

ABSTRACT

Context: Clinico-pathological features of each entity of granulomatous reaction have been evaluated independently. However, considerable clinical and histopathological overlap exists making it diagnostically challenging for the treating physician. We conducted this study, as there is paucity of data in this regard.

Aims: To analyze demographic parameters in patients with granulomatous skin diseases and to detect level of clinicopathological concordance in the study group.

Settings and Design: This is a prospective observational study of 105 cases of granulomatous skin lesions at a tertiary care centre in Gujarat.

Methods and Material: Clinical diagnosis of granulomatous skin lesions was made by two dermatologists and skin biopsy was obtained in each patient. Correlation between clinical impression and histopathological findings was evaluated. Data were analysed using chi-squaretest. P value<0.005 was considered as significant.

Results: There were 62 males (59%) and 43 females (40.9%) with Male to female ratio 1.44:1. Mean age was 32.59 years ± 14.46 SD. Concordance between initial clinical impression and histological diagnosis was found in 69 of 105 cases (65.7%) while 36 (34.2%) were in the discordant and undecided category. Most common type of granuloma was tuberculoid type (n=39,56.52%); Necrobiotic granuloma was detected in 5 cases(7.24%). Miscellaneous 20 cases (28.98%) included 19 cases of Hansen's disease and 1 case of papular xanthoma. In infectious diseases, Erythema Induratum and Hansen's disease were the entities with maximum amount of concordance that is 100% and 85.7% respectively; while in non infectious diseases, cases with Granuloma Annulare, granulomatous rosacea and Lupus Miliaris disseminatus Facei had 100% clinico pathological concordance.

Conclusion: We observed that histopathology alone was not helpful in diagnosis of granulomatous tissue reaction all times, as variable histopathological patterns were observed. Use of other advanced diagnostic methods like PCR; rapid antigen detection etc. should be encouraged. Further studies with larger sample size are needed to confirm the findings and validate new clinical patterns.

INTRODUCTION

The term 'granuloma' means A chronic inflammatory response to a tissue injury, which is evoked by a poorly soluble substance, which is characterized by the accumulation and proliferation of leukocytes primarily mononuclear type[1]. The granuloma is the end result of a complex interplay between invading organism or antigen, chemical, drug or other irritant, prolonged antigenaemia, macrophage activity, a Th1 cell response, B cell over activity, circulating immune complexes, and a vast array of biological mediators (figure 1). Areas of immunological reactivity attract monocyte macrophages, that fuse to form multinucleated giant cells, and macrophages are converted into epitheloid cells. CD4+ Th1 helper cells recognise protein peptides presented to them by antigen presenting cells bearing MHC class II molecules. The T cell induces interleukin-1 on the macrophage and thereafter a cavalcade of chemo tactic factors promote granulomagenesis. Interferon gamma (IFN-γ) increases the expression of MHC class II molecules on macrophages, and activated macrophage receptors carry an Fc fraction of IgG to potentiate their ability to phagocytose. The end result is the epithelioid granuloma

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formation which progresses under the impact of transforming- and platelet-derived growth factor towards fibrosis.[2,3,4] Granulomas can lead to destruction of pre-existing tissues resulting in atrophy, fibrosis or scarring; e.g. fibrinous necrosis or liquefaction[5].

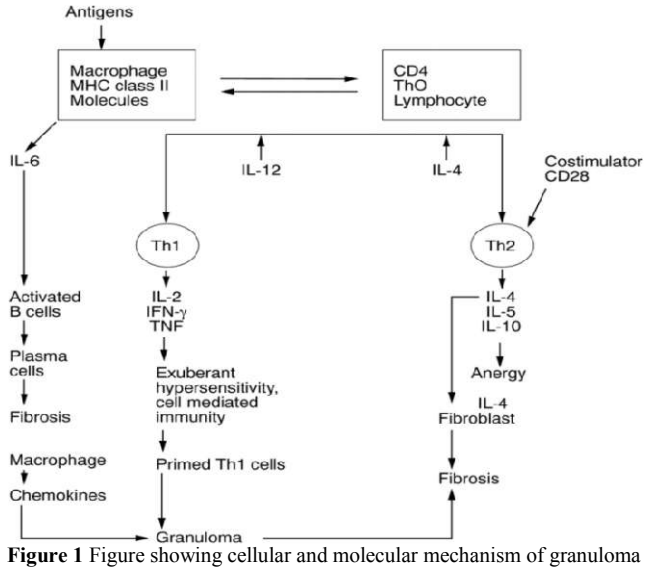

Figure 1 Figure showing cellular and molecular mechanism of granuloma formation

Exact classification of granulomatous reaction is rather difficult. Different types of granuloma can be seen in single area. For example, in reaction to Foreign bodies. A single entity described in this classification may show different types of changes during evolution of disease process; ranging from mild inflammatory infiltrate in early stage to fibrosis or scarring in later stage. Sometimes granuloma is not seen at all. Therefore diagnosis of granulomatous reaction is difficult.

Table 1 Table showing classification of granulomas (based on structural features of granuloma)

Types of granuloma	Example
Sarcoidal granuloma	
	Sarcoidosis
	Reaction to foreign material
Tuberculoid granuloma	
	Tuberculosis
	Tuberculids
	Leprosy
	Late Syphillis
	Leishmaniasis
	Papular Rosecea
	Perioral Dermatits
	Lupus Miliaris Disseminatus et Facei
	Crohn's disease
Necrobiotic granuloma	
	Granuloma Annulare
	Necrobiosis lipoidica
	Rheumatic nodules
	Rheumatic fever nodules
Suppurative granuloma	
	Chromomycosis & Phaeohyphomycosis
	Sporotrichosis
	Non tuberculous mycobacterial infection
	Blastomycosis
	Paracoccidiodomycosis
	Coccidioidomycosis
	Blastomycosis like pyoderma
	Mycetoma,Nocardiosis & Actinomycosis
	Cat Scratch disease
	Lymphogranuloma Venereum
	Pyoderma Gangrenosum
	Ruptured cysts and follicles
Foreign Body granulomas	
	Endogenous material
	Exogenous material
Miscellaneous	
	Orofacial granulomatosis
	Elastolytic granuloma
	Annular granulomatous lesions in oochronosis
	Granuloa in immunodeficiency disorders
	Neutrophilic and palisaded granulomatous disease
	Granulomatous T cell lymphomas

Clinico-pathological features of each entity have also been evaluated independently. [6] However, considerable clinical and histopathological overlap exists making it diagnostically challenging for the treating physician. We undertook this study to evaluate clinical patterns, histopathological patterns and establish clinico-pathological correlation in patients of cutaneous granulomatous diseases at our large tertiary care teaching hospital in west India; as there is paucity of data in this regard.

Aims & Objectives

- To analyze demographic parameters in patients with granulomatous skin diseases.
- To detect level of clinicopathological concordance in the study group.

Subjects and Methods

We conducted a prospective observational study of 105 cases at the Department of Dermatology in a tertiary care centre in Gujarat during period of 2 years between January 2014 and January 2016.

Clinical evaluation

The patients presented with clinical features of granulomatous diseases were enrolled in the study after consent irrespective of age and gender. Patients refusing for biopsy were excluded from study. Detailed history and examination was noted according to proforma. Photographs were taken after written consent. A clinical diagnosis was made by two dermatologists based on characteristic clinical features described for each entity. The features also included 1) sites of predilection of skin lesions, 2) course of disease, 3) sequel of lesions and 4) other associated signs and symptoms.

Laboratory evaluation

6-mm skin punch biopsy up to the depth of sub cutis was obtained from a representative and active lesions and stained with hematoxylin and eosin (H and E) and, in some cases, special stains as well. Other laboratory tests, including routine biochemistry, urinalysis, chest X-ray, pulmonary function test and tuberculin skin test (TST, Tuberculin PPD RT23 SSI, 2 tuberculin units) and culture were performed on some patients based on individual circumstances. All Biopsies were reviewed for histopathologic features, including the types of granulomas, location of granulomas (dermis, sub cutis or both), the pattern as well as extent of the infiltration and any pathological

findings other than granuloma by pathologist of by pathologist of our institute. The correlation between clinical diagnosis and histopathological findings was evaluated as: (1) Concordance – Histopathological findings consistent with any one of the clinical diagnosis made, (2) Discordance – histopathological findings specific to another disease which was not considered in clinical diagnosis and (3) Undecided – Histopathological findings not specific to any particular disorder.[7] Data were analysed using chi-squaretest. P value<0.005 was considered as significant.

RESULTS

Table 2 Table showing demographic parameters of study group, level of concordance and types of granuloma found in study

Parameter	Frequency
Sex	Males: n=62(59%) Females: n=43(40.9%)
Male to Female ratio	1.44:1
Mean age	32.59 years±14.46 SD
Most common age group:	21-30 years n= 31(29.5%)
Level of concordance	
Concordant biopsy report	69/105(65.7%)
Discordant biopsy report	16/105(15.23%)
Undecided	20/105(19.04%)
Types of granuloma (n=69)	
Tuberculoid granuloma	39/69(56.52%) Hansen's disease(TT and BT)(29), cutaneous tuberculosis(7) ,erythema Induratum(1), Granulomatous Rosacea(1)
Necrobiotic granuloma	5/69(7.24%) Granuloma Annulare(5)
Sarcoidal granuloma	3/69(4.34%) Sarcoidosis(3)
Foreign body	1/69(1.44%) Foreign body reaction at tattoo site(1)
Suppuative/mixed	1/69(1.44%) Mycetoma(1)
Miscellaneous	20/69(28.98%) Hansen's disease(BB,BL,LL)(19), Papular Xanthoma(1)

TT- Tuberculoid leprosy, BT-Borderline Tuberculoid leprosy, BB-Borderline Borderline leprosy, BL-Borderline lepromatous leprosy, LL-Lepromatous Leprosy

A total of 105 patients were recruited. There were 62 males (59%) and 43 females (40.9%) with Male to female ratio 1.44:1. Ages of patients ranged from 5 to 67 years with mean age of 32.59 years ± 14.46 SD. (Table 1) Most common age group was 21-30 years. We found 65.7% (n=69) of biopsy reports concordant with clinical diagnosis showing granuloma in pathology; majority of them comprised of tuberculoid type of granuloma (n=39,56.52%). Necrobiotic granuloma was diagnosed in 5 cases(7.24%). Miscellaneous 20 cases(28.98%) included 19 cases of Hansen's disease and 1 case of papular xanthoma. In 16 cases (15.23%), histopathology didn't match clinical impression, while in 20 cases (19.04%) biopsy was not diagnostic of any particular disease; hence included under Undecided category.

After histopathological examination, concordance between initial clinical impression and histological diagnosis was found in 69 of 105 cases (65.7%) while 36 (34.28%) were in the discordant (n=16) and undecided category (n=20).In infectious diseases, Erythema Induratum and Hansens disease were the entities with maximum amount of concordance that is 100% and 85.7% respectively; while in non infectious diseases, cases with Granuloma Annulare, Granulomatous Rosacea and LMDF had 100% clinico pathological concordance.

DISCUSSION

Granulomatous tissue reactions may be subdivided according to: Arrangement of granulomas, presence of accessory factors such as Caseation or suppuration and presence of foreign material or organisms.

Sarcoidal granulomas are discrete and round to oval in shape. They are composed of epitheloid histiocytes and multinucleated giant cells, which are surrounded by sparse rim of lymphocytes and plasma cells; therefore they are also known as 'naked tubercles'.[8] Multinucleated giant cell may be of Langhans or foreign body type. Sometimes Asteroid bodies and conchoidal bodies may be seen in multinucleated giant cells, but they are not specific for diagnosis. A number of foreign materials can evoke granulomatous response which may mimic sarcoidal granuloma.

Table 3 Table showing level of Clinico-histopathological correlation in different granulomatous skin diseases.

Clinical diagnosis	No. of cases	Histopathological diagnosis		
		No. of cases with Concordant diagnosis	No. of cases with Discordant diagnosis	Undecided
Cutaneous tuberculosis	19	7(36.8%)	3(15.7%) PS(1),BM(1),NCG(1)	9(47.3%)
Hansen's disease	56	48(85.7%)	4(7.14%) SRD(3),MRP(1)	4(7.14%)
Cutaneous sarcoidosis	8	3(37.5%)	4(50.0%) NCG(2),MF(1),LL(1)	1(12.5%)
Cutaneous leishmaniasis	4	0	0	4(100%)
Mycetoma	2	1(50.0%)	0	1(50.0%)
Granuloma annulare	5	5(100.0%)	-	-
Erythema Induratum	1	1(100.0%)	-	-
Foreign Body reaction	4	1(25.0%)	3(75.0%), NCG(3)	-
LMDF	1	1(100.0%)	-	-
Xanthoma	3	1(33.3%)	2(66.7%) ,SRD(1),KLD(1)	-
Granulomatous rosacea	1	1(100%)	-	-
Hidradenitis suppurativa	1	-	-	1(100%)
Total	n=105	69(65.7%)	16(15.23%)	20(19.04%)

PS-Psoriasiform eczema, BM-Blastomycosis, LMDF-Lupus Miliaris Disseminatus Facei, NCG-Non Caseating Granuloma, MRP-Morphea ,SRD-Sarcoidosis, KLD-Keloid ,MF-Mycosis fungoides

For example; Silica, tattoo pigments, Zirconium [9], beryllium etc.

Tuberculoid granulomas consist of collection of epitheloid histiocytes and Langhans giant cells; they are surrounded by dense rim of lymphocytes and plasma cells. They tend to be more confluent than sarcoidal granulomas. In lesions with caseation and demonstration of acid fast bacilli, diagnosis of tuberculosis is becomes easy. In tuberculosis, infiltrate involves lower dermis and may extend to sucutis; while in tuberculoid leprosy, granuloma is found in upper papillary dermis, may destroy basal layer and are typically arranges around neurovascular bundles and arrector pilorum muscle. There may be destruction of nerves, occasional caseation necrosis and M.leprae is usually not detected in lesions. In BT, there is more of foreign body giant cell and no caseation necrosis or destruction of dermis. In BB, granulomas are poorly formed. Differentiation of granulomatous rosacea from lupus vulgaris is difficult. Presence of marked vascular dilatation is suggestive of rosacea. Sometimes follicular and perifollicular inflammation is also seen. LMDF is characterized by caseation necrosis surrounded by epitheloid histiocytes, multinucleated giant cells and lymphocytes. Early lesions show perivascular lymphohistiocytic infiltrate**.** [10]

In granuloma annulare, there are areas of necrobiosis, surrounded by epitheloid histiocytes, giant cells and histiocytes arranged in 'palisaded pattern'[11] in periphery. In areas of necrobiosis, mucin deposition, nuclear fragments and acute or sub acute changes of vasculitis may be seen. Features that differentiate Necrobiosis lipoidica from granuloma annulare are extensive necrobiosis, which also affects intervening areas in dermis and presence of superficial and deep perivascular inflammatory infiltrate that contains plasma cells and occasional eosinophils.

Suppurative granulomas consist of collection of epitheloid histiocytes, multinucleated giant cells and neutrophils in centre. All of the conditions showing suppurative granuloma have similar features. e.g.; pseudoepitheliomatous hyperplasia, micro abscesses, and mixed inflammatory infiltrate; hence special stains and culture may be required to reach specific diagnosis. Essential features of foreign body granuloma are presence of identifiable foreign particle within granuloma. Endogenous materials include calcium deposits, urates, oxalate [12, 13]. keratin and hair.

In this study, number of male (59%) exceeded from that of female. This result was similar to study by Gautam K *et al* (63.2% male) [14] and Dhar *et al*. [15] Majority of the cases were in 3rd decade of life. In our study group of 105 patients, 65.7% clinico-pathological concordance was detected in biopsy reports, in contrast to other studies e.g. HarishPermi *et al* [16] and Jayshree Paval *et al* [17] which had 92% and 93.5% concordance respectively. Level of concordance may depend on disease pattern prevalent in particular region. In these 69 concordant cases; tuberculoid granuloma was the most common type (56.52%) similar to studies shown in table 4.

Infectious granulomatous lesions were predominant (n=56;81.1%) in the present study in accordance to the study done by Bal *et al*.[18] This group included cutaneous tuberculosis 7 cases(12.5%), Hansen's disease 48 cases(85.7%) and mycetoma 1 case(1.8%). Rubina Qureshi *et al* [19] observed 56 % cases of leishmaniasis in her study as a sole culprit of infectious granulomatous diseases due to endemicity in Pakistan; while we could not find a single case of leishmaniasis out of 4 suspected cases of leishmaniasis. Incidence of leishmaniasis in Gujarat is far lower than that of the Bihar, Jharkhand, West Bengal and eastern Uttar Pradesh. [20]

Non infectious granuloma was observed in 13 cases (18.9%) in our study. Gautam K *et al* [14] has shown 25.5% non infectious origin granuloma in their study. There were sarcoidosis (3, 23.1%), erythema induratum(1,7.6%), xanthoma(1,7.6%) Granuloma Annulare(5, 3.8%), Granulomatous Rosacea(1, 7.6%), Facial idiopathic granuloma with regressive evolution (1 , 7.6%) and foreign body granuloma(1,7.6%) in the Non infectious group.

Cutaneous tuberculosis was considered as a differential diagnosis in 19 patients. Out of them, 7 biopsies were concordant with clinical diagnosis. There were 4 cases of tuberculosis verrucosa cutis and 3 cases of lupus vulgaris (total 7 concordant cases). In a study done by S.Chakrabarti *et al* [21], most common type of cutaneous tuberculosis was Lupus Vulgaris (63.04%). In all cases; classical tuberculoid granuloma without caseation was detected.

Out of 19 discordant cases; In 1 case, epidermal hyperplasia, suppurative granuloma and thick walled dark brown spherical bodies were detected; so was diagnosed as chromoblastomycosis. In a Case report by G Raghurama Rao [22] a child treated as cutaneous tuberculosis with X-ray changes turned out to be blastomycosis in further workup. In 1 patient with verrucous lesion, spongiosis and psoriasiform hyperplasia was observed. In 1 case, pathologist reported non-caseating granuloma and we were asked to correlate clinically. Rests of the cases were included under 'undecided' category.

The most common cause of infectious granuloma(85.7%) detected in the study was Hansen's disease, which is endemic in our region; therefore very less efforts are required to suspect the same in the patients.48(85.7%) out of 56 cases were diagnosed as Hansen's disease in histopathology; showing a fair level of concordance. According to Ridley & Jopling classification, there were 8 cases of tuberculoid leprosy, 21 borderline tuberculoid types, 11 borderline lepromatous type, 1 borderline borderline type and 7 cases of lepromatous leprosy. Most common type of leprosy was Borderline tuberculoid type(21 cases(43.75%).In Studies done by S.Chakrabarti *et al*[21] and Bal *et al*[18] also found borderline tuberculoid leprosy as a most common entity of Hansen's disease, with 57.94% and 55.2% cases respectively.

In 29 cases of Tuberculoid and borderline tuberculoid leprosy, tuberculoid granuloma was detected. In Borderline tuberculoid leprosy, grenz zone was present. In 12 cases of borderline lepromatous leprosy, small collection of macrophages was found, and in 7 cases of lepromatous leprosy foamy macrophages infiltration with abundant acid fast bacilli was seen.

In our study of 48 cases of leprosy, FiteFaraco stain demonstrated lepra bacilli in 27 (56.3%) cases and was negative in 21 (43.7%) cases, the result was in contrast with study by Harish *et al*[16] and Nayak SV *et al*, [23] which showed

FiteFeraco stain positive in 25.7 % and 74.2% of leprosy cases respectively. In 1 case of papulo-nodular lesions resembling lepromatous leprosy/ENL revealed sarcoidal granuloma; detailed work up revealed final diagnosis of cutaneous sarcoidosis. Tuberculoid leprosy is an important histopathological differential diagnosis of Sarcoidosis showing perineural invasion.[24, 25] 1 out of 2 discordant cases of leprosy was presented with hypo pigmented patch; pathological features of morphea were seen.

The Variants of cutaneous sarcoidosis in literature are papules, nodules, plaques, annular plaques, subcutaneous nodules, infiltrative scars and lupus pernio.[26] .Clinical findings in 3 confirmed cases of sarcoidosis included subcutaneous nodule in one male, single erythematous infiltrated plaque on chin in one female and discrete papular lesions on upper trunk in a female. In a study by C.Bansal *et al*, only 1 case of sarcoidosis was noted.[27] cases had discordant biopsy reports. In 1 patient with erythematous plaques over face and upper trunk, lepra bacilli with diffuse macrophage infiltration was found, In 1 case with disseminated papules, epidermotropism was seen and serial biopsies were advised by the pathologists .Due to patients' refusal for serial biopsies, proper follow up of pathological findings was not done. In 2 patients non caseating granuloma was described, which was then correlated clinically and treated accordingly.

Highest level of concordance was found in 5 cases of granuloma annulare; Mucin deposition, necrobiotic changes with palisading grauloma in dermis was revealed in almost all the cases. Study by jayshree *et al*[17] showed 2 cases (18.18%) of granuloma annulare in their study.

In the present study, we had 1 case of papular xanthoma, in which histopathology showed toutan giant cells with foamy macrophages. S.Chakrabarti *et al*[21] also had only 2 cases of xanthoma in their study; as it is a rare entity.

There was a single case chronic ulcer with pus discharge and granules over foot. Biopsy from ulcer showed suppurative granulomatous reaction along with spetate hyphae.Thus diagnosis of Eumycotic mycetoma was established.Patients were advised for culture, which is a definitive tool for confirmation of fungus and its species. There were 4 cases of deep mycosis in a study done in Pakistan by M Naved Uz Zafar *et al*[28].

Table 4 Table showing comparison of different studies

	Tuberculoid	Sarcoidal	Suppurative	Foreign body	ecrobio	Miscellaneous
Dhar and Dhar	77.3%	13.7%	9%	-	-	-
Bal *et al*.	87.7%	2.6%	2.9%	1.7%	2.7%	2.4%
Zafar *et al*.	92.7%	1.6%	1.6%	13.3%	0.8%	-
Gautam K *et al*	68.9%	1.9%	2.8%	18.9%	3.7%	3.7%
Present study	56.52%	4.34%	1.44%	1.44%	7.24%	28.98%

Atypical presentations of various dermatological conditions lead to difficulty in providing nearest differential diagnosis. Other factors for discordant results are lack of detailed clinical information while submitting the specimen as well as inappropriate selection of lesion. In most of the cases fresh or newly appeared lesion is required for biopsy. Clinical picture may be altered due to application of topical drugs; therefore leading to misinterpretation of histopathology.

Cutaneous granulomatous diseases are a challenging group of disorders. We can improvise these drawbacks by providing detailed clinical information to pathologist. Discussion between dermatologists and pathologists is necessary for final diagnosis. In our attempt to establish a clinico-pathological correlation, we observed that histopathology alone was not helpful in differentiating one entity from another at all times since variable histopathological patterns were observed. Only 65.7% clinico-pathological concordance could be found in this study. Use of other advanced diagnostic methods like PCR; rapid antigen detection etc. should be encouraged, if enough resources are available. Special staining may be helpful to aid in the diagnosis.

Studying patterns of granulomatous diseases will help understanding epidemiology as well most common types of granulomatous inflammations that we should not miss in routine practice. Further studies with a larger sample size for each of the groups are required to confirm these findings and to validate the new clinical patterns observed in this.

Figure 2 Mycetoma

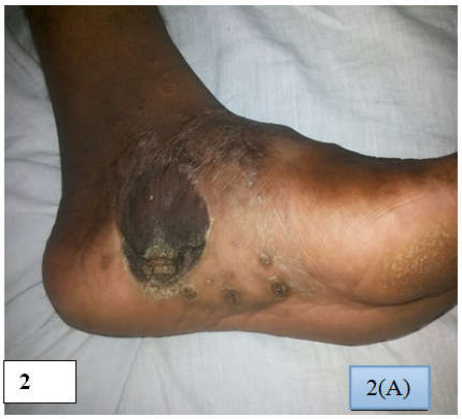

Figure 2(A) Clinical photograph of 32 years old farmer presented with chronic nonhealing ulcer showing pus and granules discharge, crust over surface

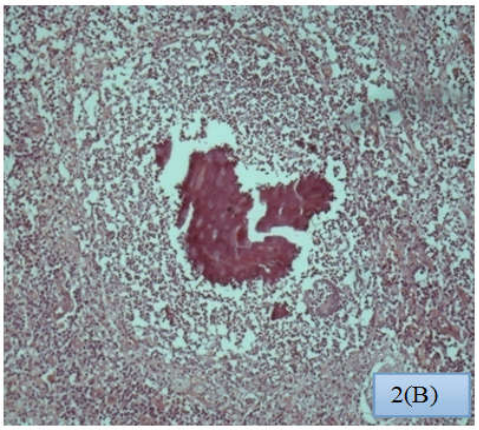

Figure 2B H & E section 40x showing ray fungus and foreign body granuloma

Figure 3 Tuberculoid leprosy

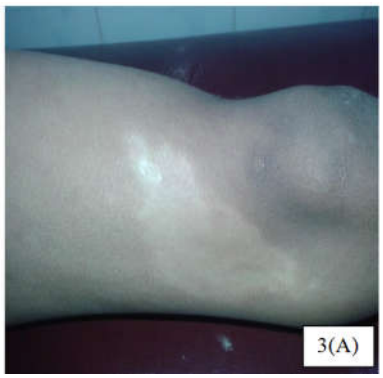

Figure 3 A clinical photograph showing single hypopigmented anaesthetic patch over left thigh

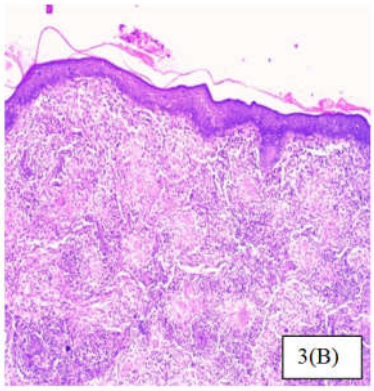

Figure 3 B H & E 10x showing location of infiltrate in upper dermis reaching up to basement membrane zone

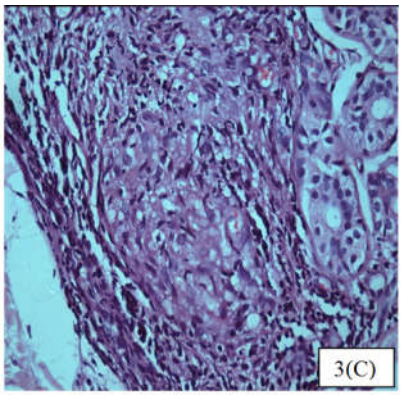

Figure 3 C H & E section 40x showing tuberculoid granuloma

Figure 4Tuberculosis Verrucosa Cutis

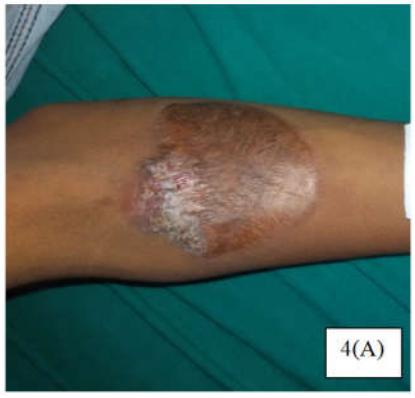

Figure 4 A clinical photograph showing single infiltated plaque with atrohy over lower part and verrucous appearance in upper part over right forearm

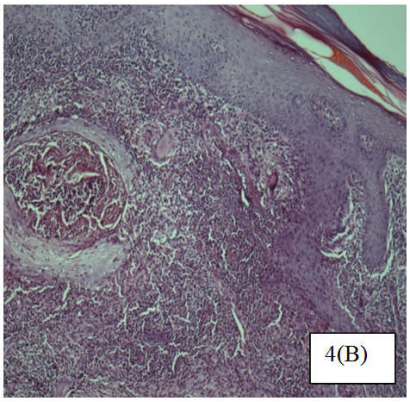

Figure 4 B H & E section 10x showing tuberculoid granuloma

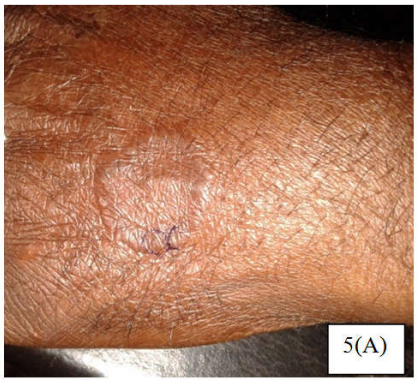

Figure 5 A clinical photograph showing single skin coloured annular plaque with central clearing and normal texture over dorsum of right hand in 52 years old diabetic female

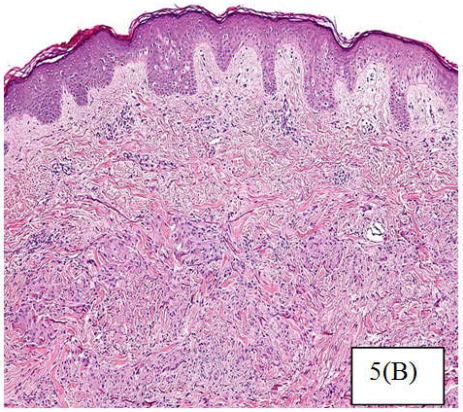

Figure 5 B H & E sectio n: 10 x showing palisading arrangement of lyphocytes surrounding epitheloid cells, Langhans giant cells.

Figure 6:Foreign body reaction

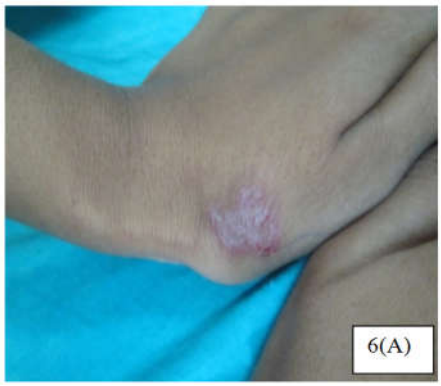

Figure 6 A clinical photograph of 18 years old male patient presented with eczematization over tattoo site

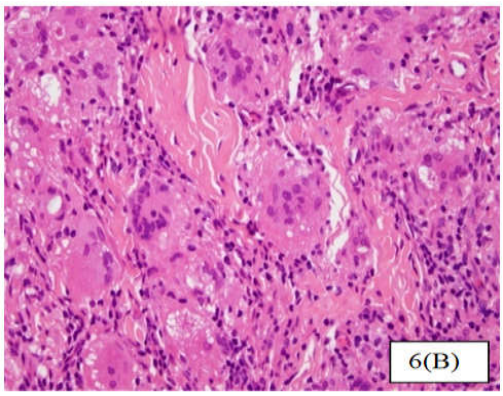

Figure B H & E section:40x showing foreign body granuloma formation

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How to cite this article:

Vaishali R Makwana *et al*.2018, Granuloma Revisited: a Prospective Study of Granulomatous Skin Lesions at a Tertiary Care Centre In Gujarat. *Int J Recent Sci Res.* 9(8), pp.28607-28613.DOI: http://dx.doi.org/10.24327/ijrsr.2018.0908.2490

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