

A Retrospective Study of Histomorphological Patterns of the Cutaneous Granulomatous Lesions in 45 Cases with Review of Literature

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Abstract

Background: Cutaneous Granulomatous lesions comprises a heterogeneous group of diseases caused by the variety of infectious and non-infectious etiological factors and thus often poses a diagnostic challenge to histopathologist as they show similar histological features.

Objective: The present study was aimed at studying the various histo-morphological patterns of cutaneous granulomatous lesions, to determine the relative frequencies and to compare our results with other studies.

Materials and Methods: A retrospective analysis of skin biopsies received over a period of three years from January 2016 to November 2018 was performed and cases of cutaneous granulomatous lesions reported on histopathology were analyzed with respect to age, sex, site, and etiology and histomorphological pattern.

Results: Out of a total of 516 skin biopsies 45 (8.7%) cases were diagnosed as cutaneous granulomatous lesions. It was common in males (60%) with most occurring in the third to fourth decades. Majority of the cases (28 cases, 62.2%) were categorized as infectious granulomatous lesions with the predominance of leprosy (18 cases, 40%) followed by tuberculosis (7 cases, 15.5%).

Conclusion: The present study is a comprehensive, comparative study of cutaneous granulomatous lesions and leprosy is the most common cause of granulomatous skin lesions according to this study. This study concludes that histopathology is the gold standard investigation for diagnosis, categorization, and management of cutaneous granulomatous lesions. Special stains play a supportive role in the diagnosis of infectious granulomas.

Keywords: Cutaneous Granulomatous Lesion; Leprosy; Tuberculosis.

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Introduction

The granulomatous inflammatory reaction is unique in pathology and is the manifestation of many diseases like infective, allergic, autoimmune, toxic, and neoplastic diseases and also conditions of idiopathic etiology. A thorough understanding of the basic pathophysiology of granulomatous tissue reaction is of fundamental importance in the understanding many diseases [1,2].

Granulomas are histologically defined as tiny, 0.5 to 2 mm collection of modified macrophages called "epithelioid cells" surrounded by a rim of lymphocytes. These modified macrophages have abundant, pale-pink, plump cytoplasm, and elongated slipper-shaped nucleus resembling an epithelial cell [3].

Granulomatous reaction belongs to type IV hypersensitivity reaction evoked by poorly soluble reactive substances. Seven types of granulomatous skin lesions are identified according to cellular constituents and associated changes [4].

1) *Tuberculoid type* - granulomas in the tuberculoid group consist of the collection of epithelioid histiocytes, including multinucleate forms, they tend to be less circumscribed than those in the sarcoidal group, have a tendency to confluence, and are surrounded by a rim of lymphocytes and plasma cells. Langhans giant cells are more characteristic of this group but foreign body type giant cells are also seen. There may be areas of caseation in the lesions of tuberculosis

Examples: Tuberculosis, Tuberculids, Leprosy, Later Syphilis, Leishmaniasis, Rosacea, Perioral Dermatitis

2) *Sarcoidal type* - Sarcoidal granulomas are naked granulomas which are discrete, round to oval, and composed of epithelioid histiocytes and multinucleate giant cells which may be of either Langhans or foreign body type and surrounded by a thin rim of lymphocytes and plasma cells, and only occasional lymphocytes are present within them. Generally, the type of multinucleate histiocytes present in a granuloma is not helpful in arriving at a specific histological diagnosis. Giant cells contain asteroid bodies, and Schaumann bodies or crystalline particles.

Examples: Sarcoidosis, Foreign Body Reaction, Blau's Syndrome, Secondary Syphilis, Sezary

Syndrome, Metastatic Crohns, Systemic Lymphomas, and Breast Cancer.

3) *Necrobiotic type* - characterized by

collagenolysis (Necrobiotic) areas which are partially or completely surrounded by a histiocytic rim which may include multinucleate giant cells. Few cases show histiocytes which are spindle-shaped and form a 'palisade'.

Examples: Granuloma Annulare, Necrobiosis Lipodica, Necrobiotic Xanthogranuloma, Rheumatoid Nodule, Rheumatic Fever Nodules, Reaction to Foreign Material and Vaccines.

4) *Suppurative type* - are nothing but consist of collections of epithelioid histiocytes, with or without multinucleated giant cells, in the centers of which are collections of neutrophils.

Examples: Chromomycosis And Phaeohyphomycosis, Sporotrichosis, Non-Tuberculous Mycobacterial Infection, Blastomycosis, Paracoccidioidomycosis, Coccidioidomycosis Blastomycosis-Like Pyoderma, Mycetoma, Nocardiosis, and Actinomycosis, Cat-Scratch Disease, Lymphogranuloma Venereum, Pyoderma Gangrenosum, Ruptured Cysts, and Follicles.

5) *Foreign body-* reaction to endogenous or exogenous material like keratin, suture material etc.

6) *Xanthogranulomas* - are granulomas composed of numerous histiocytes with foamy/pale cytoplasm and a variable admixture of other inflammatory cells and some Touton giant cells.

7) *Miscellaneous type granuloma-* are seen in diseases like Chalazion, Melkersson-Rosenthal Syndrome, Elastolytic Granulomas, Annular Granulomatous Lesions, Ochronosis Granulomas, Immunodeficiency [Interstitial Granulomatous Dermatitis, Interstitial Granulomatous Drug Reaction, Super Antigen Id Reaction, and Granulomatous T-Cell Lymphomas]

A cutaneous granulomatous lesion is a diagnostic challenge to histopathologist due to various modes of presentation and similar histological pictures. Recognition of granulomatous pattern on histopathology and finding the etiology in a skin biopsy specimen is very important for specific treatment and outcome of the disease.

The present study was aimed at determining the frequency, histo-morphological pattern of different granulomatous skin lesions; to identify the etiology of all granulomatous skin biopsies; to arrive at a correct diagnosis and to compare the results with the other studies.

Materials and Methods

The present study was a retrospective study of

all the skin biopsies of granulomatous skin lesions received in the Department of Pathology, BGS Global Institute of Medical Sciences and Research center, Bangalore over a period of three years from January 2016 to November 2018.

From institutional ethical committee ethical clearance was obtained before starting the study.

Skin biopsies were taken at Dermatology outpatient Department and specimens were sent to our histopathology laboratory for histopathological examination. The biopsy samples underwent routine tissue processing and section cutting. All cases were stained with H & E stain and special stains (ZN stain, Fite-Faraco, PAS, GMS) were applied as required.

Only the histopathologically diagnosed cases of granulomatous skin lesions were included in the study group. All cases of cutaneous granulomatous skin lesions were analyzed with respect to clinical information and histopathological examination of biopsy samples.

Inclusion criteria: All the skin biopsies showing primary granulomatous lesions are included in this study.

Exclusion criteria: Skin biopsies showing the extension of the granulomatous lesion from adjacent tissues like lymph nodes, intestine, breast etc and infectious and non-infectious; non-granulomatous lesions are excluded from the study.

Results

During this 3 years period, a total of 516 skin biopsies were received in the department of pathology. Out of them, 45 biopsies constituted granulomatous lesion accounting for 8.7%. In the present study out of 45 cases, 27 (60%) cases were males and 18 cases (40%) were females with male predominance. The age distribution ranged from 3 years to 75 years with a mean age of 38 years. The maximum number of cases occurred in the third decade (19 cases, 42.2%) followed by fourth decade (9 cases, 20%).

Table 1: Age distribution of all the cases

Age	Number	Percentage (%)
0-10	01	2.2
11-20	01	2.2
21-30	19	42.2
31-40	09	20
41-50	05	11.1
51-60	05	11.1
61-70	03	6.6

71-80	02	4.4
81-90	00	00
91-100	00	00
Total	45	100

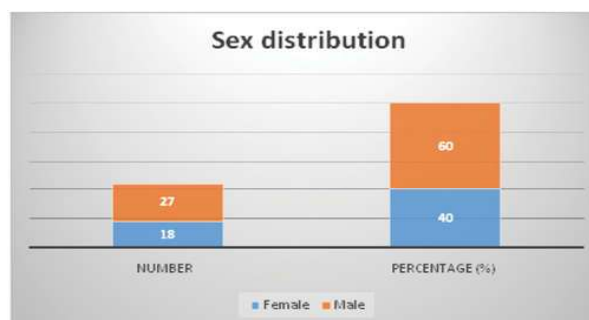


Chart 1: Sex distribution of granulomatous lesions

The extremities were the most commonly involved site with 30 (66.6%) patients getting affected, with lower extremity (20 cases, 44.4%) being most commonly affected, followed by head and neck with (9 cases, 20%) affected patients and other sites being abdomen (3 cases, 6.6%), back (2 cases, 4.4%) and chest (one case, 2.2%).

Table 2: Location of lesions

Site	Number	Percentage (%)
Lower extremities	20	44.4
Upper extremities	10	22.2
Head and neck	09	20.0
Abdomen	03	6.6
Back	02	4.4
Chest	01	2.2
Total	45	100

Table 3 outlines the morphological types of granulomas and in the present study, 28 (62.2%) were tuberculoid type followed by foreign body type in 6 cases (13.3%). Necrosis was present only in 7 (15.5%) cases out of which only one case of scrofuloderma (2.2%) showed caseous necrosis.

Table 3: Frequencies of types of granulomas

Type of granuloma	Number	Percentage (%)
Tuberculoid	28	62.4
Foreign body	06	13.3
Suppurative	05	11.1
Necrobiotic	04	8.8
Sarcoidal	02	4.4
Total	45	100

Majority of the cases were categorized as infectious granulomatous lesions 28 cases (62.2%), while the rest 17 cases (37.7%) as non-infectious granulomatous lesions. The most common cause

of granuloma was leprosy seen in 18 (40 %) cases, followed by tuberculosis in 7 (15.5%) and the common cause of non -infectious granulomas was foreign body reaction accounting for 13.1% (6 cases).

Table 4: Distribution of all granulomatous lesions.

HP diagnosis	Number	Percentage (%)
Leprosy	18	40
Cutaneous tuberculosis	07	15.5
Foreign body reaction	06	13.1
Fungal infection	03	6.6
Sarcoidosis	02	4.4
Erythema nodosum	02	4.4
Non specific	02	4.4
Necrobiotic xanthogranuloma	01	2.2
Necrobiosis lipoidica	01	2.2
Granuloma annulare	01	2.2
Granuloma rosacea	01	2.2
Actinic granuloma	01	2.2
Total	45	100

In the present study 18 (40%) leprosy cases were observed and Tuberculoid leprosy (8 cases, 44.5%) predominated followed by indeterminate leprosy (4 cases, 22.4%), lepromatous leprosy (3 cases 16.6%), one case (5.5%) each of borderline tuberculoid, borderline lepromatous, and histoid leprosy.

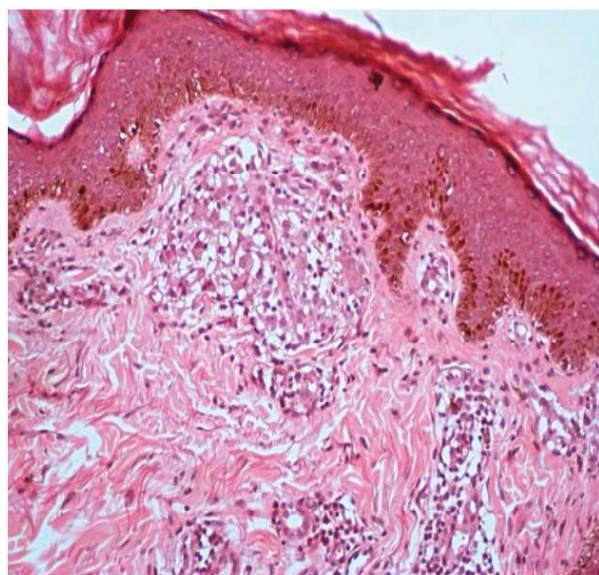


Fig. 1: Histopathology of Lepromatous leprosy showing foamy histiocytic infiltrate in papillary dermis (H&E Stain, X40)

Seven cases (15.5%) of cutaneous tuberculosis were diagnosed and were typified as lupus vulgaris (4 cases), Erythema induratum (1 case), scrofuloderma (1 case) and tuberculosis verruca cutis (1 case). Stain for acid-fast bacillus was positive in one case of lupus vulgaris.

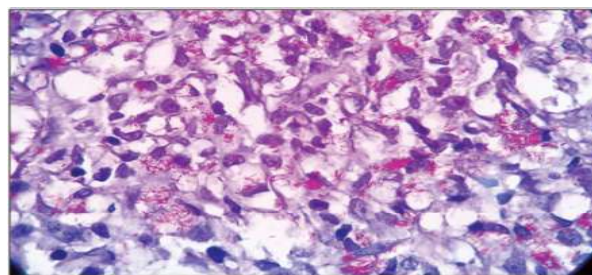


Fig. 2: Wade Fite Feraco stain of Lepromatous leprosy showing lepra bacilli in globi in papillary dermis (X100)

Six cases (13.1%) of the foreign body induced granulomatous dermatitis were observed in this study and 4 cases were those of ruptured epidermal cyst.

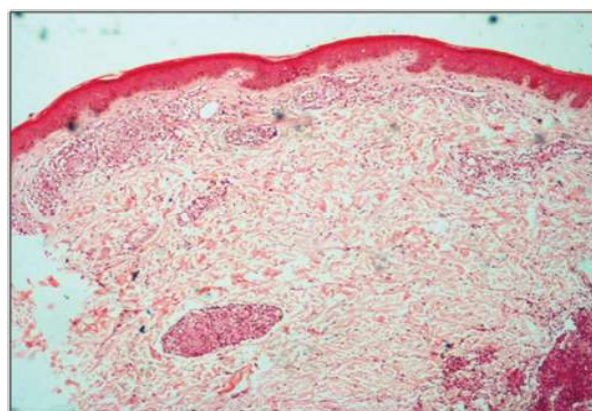


Fig. 3 : Histopathology of tuberculoid leprosy showing epithelioid granulomas around adnexal structures in dermis (H&E Stain, X10)

Cutaneous fungal infection comprised 6.6% (3 cases) in the present study. All the three cases showed suppurative granulomas and were positive for fungal organisms on PAS and GMS satin.

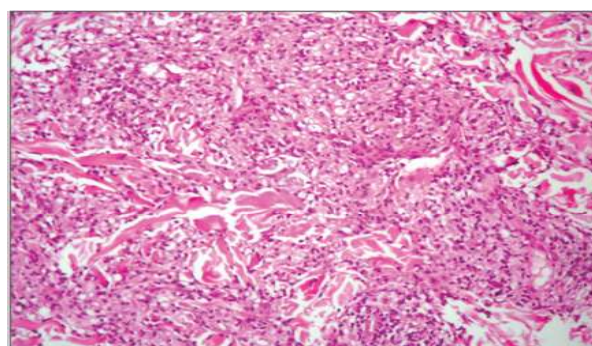


Fig. 4 : Histopathology of histioid leprosy showing spindle shaped histiocytes in dermis (H&E Stain, X10)

Two cases (4.4%) of erythema nodosum were reported in the present study.

Two cases (4.4%) of sarcoidosis involving skin were recorded and both were females in their 4th

decades. Further, the diagnosis was confirmed by serum ACE levels and radiological findings.

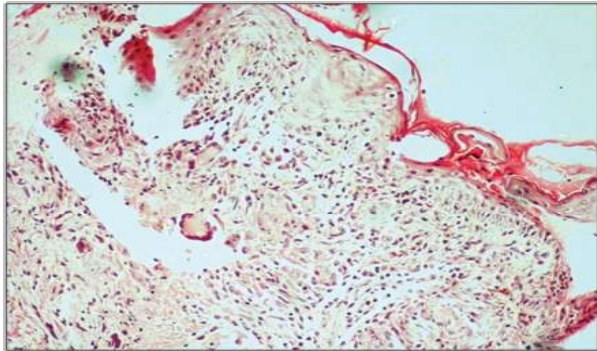


Fig. 5: Histopathology of Actinic granuloma showing epithelioid granulomas with giant cells in dermis (H&E Stain, X10)

Granuloma annulare comprised 2.2% (one case) of the 45 cases studied who was a 75-year-old female, diabetic and presented with a localized lesion on the chest.

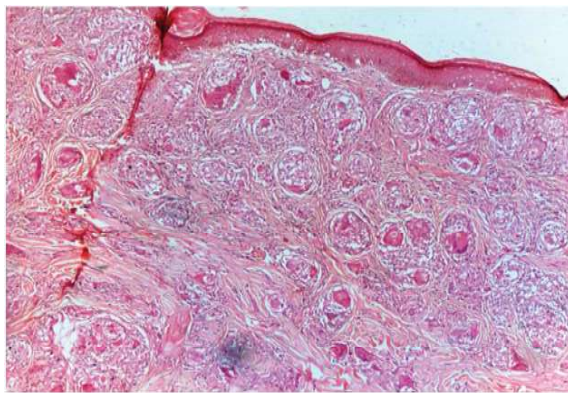


Fig. 6: Histopathology of Sarcoidosis showing naked epithelioid granulomas with giant cells in dermis (H&E Stain, X10)

One case (2.2%) each of granuloma rosacea, Necrobiosis lipoidica, Necrobiosis xanthogranuloma, and Actinic granuloma were observed in the present study.

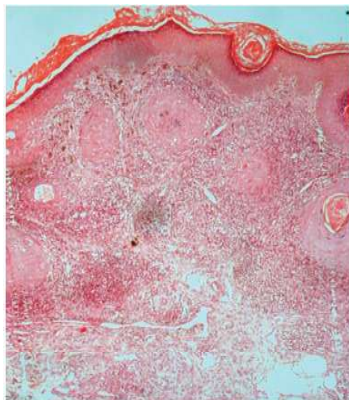


Fig. 7: Histopathology of Granuloma Rosacea showing epithelioid granulomas in dermis (H&E Stain, X10)

Two cases (4.4%) were reported as a non-specific granulomatous lesion in which the specific etiology could not be identified.

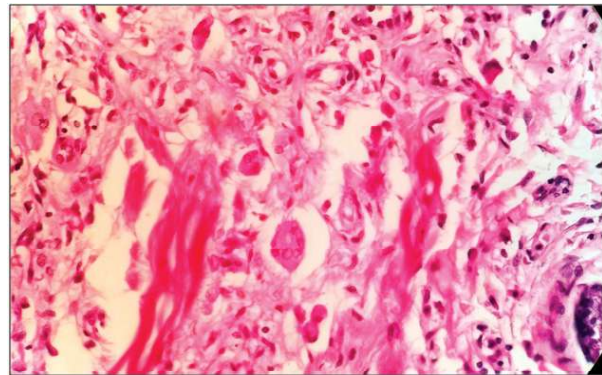


Fig. 8 : Histopathology of Xanthogranuloma showing foamy histiocytes with giant cells in dermis (H&E Stain, X40).

Ziehl Neelsen stain was done in our study for all the cases of cutaneous granulomatous lesions to rule out tubercular etiology.

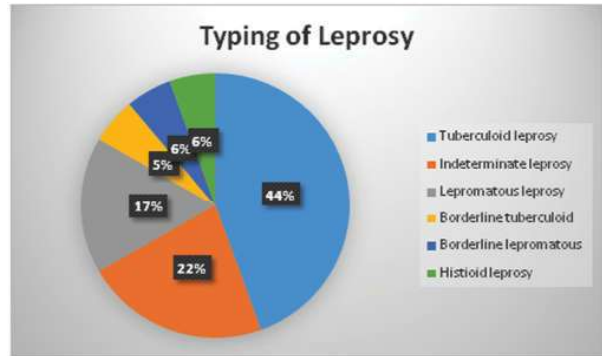


Chart 2: Typing of leprosy

Discussion

Histopathology is considered as a gold standard method to arrive at a correct diagnosis of cutaneous granulomatous lesions. Various authors have done studies on different kinds of granulomatous lesions of the skin.

The present study showed male predominance (27 cases, 60%) and similar results were observed by Gautam K et al. [5]. In our study lower extremity (20 cases, 44.4%) was the most common site of granulomatous dermatosis whereas Gautam K et al. [5] found upper extremity as the common site and Zafar's [6] study found head and neck as the common site. Infectious granulomatous lesions (28 cases, 62.2%) predominated in our study in accordance with a study done by Gautam et al. 5 and Bal et al. [7].

Our study reported 18 cases (40%) of leprosy cases followed by 7 cases (18.7%) of cutaneous tuberculosis whereas Gautam et al's study showed 79.7% of leprosy cases followed by 7.6% of cutaneous tuberculosis and in both the studies leprosy was the most common cause of granulomatous skin lesions.

Leprosy

The Ridley-Jopling classification was applied for classification of leprosy and tissue Wade Fite Feraco stain was carried out for all the leprosy cases before arriving at a diagnosis. Among 18 cases of leprosy in the present study, tuberculoid leprosy was the most common type accounting for 44.5% (8 cases) followed by indeterminate type which contributed to 22.4% (4 cases). Other studies by Gautham et al. [5] and Bal et al. [7] observed borderline tuberculoid as the most common type of leprosy.

Histologically tuberculoid leprosy shows superficial and deep peri-adnexal; noncaseating epithelioid granulomas with many lymphocytes and occasional Langhan's giant cells, infiltrating sweat glands and erector pili muscle. Borderline tuberculoid leprosy shows; superficial and deep periadnexal; noncaseating epithelioid granulomas with moderate lymphocytes and Langhans type giant cells. Lepromatous leprosy shows diffuse dermal foamy histiocytic infiltrate containing lepra bacilli with scant lymphocytes and infiltrates causes destruction of appendages and extends up to subcutaneous tissue. Borderline lepromatous leprosy shows periadnexal; poorly formed granulomas with foamy histiocytes and numerous lymphocytes. Indeterminate leprosy often poses a difficulty to dermatopathologist and the characteristic histological features that are helpful are superficial and deep perivascular, periadnexal and neurotrophic lymphohistiocytic infiltrate. Histoid leprosy is characterized by well-circumscribed lesion composed of spindle-shaped histiocytes with vacuolated cytoplasm arranged in whorls [10].

All the cases of lepromatous leprosy showed lepra bacilli in globi on Wade Fite Feraco stain in this study, while indeterminate leprosy showed only occasional bacilli and most of the tuberculoid were negative for acid-fast bacilli. Overall 37.4% of cases leprosy showed AFB positivity in the present study almost similar to Bal et al. [7] who found 36.4% AFB positivity.

Two cases of Lepromatous leprosy showed type 2 Lepra reaction.

Lepra reactions may be associated with any type of leprosy. Lepra reactions are acute inflammatory reactions to Mycobacteria Lepra bacilli antigens commonly after treatment is started [10]. Three types are observed [10].

1. Type 1 Lepra reaction - represents changes in cellular immunity. This can be upgrading [reversal] or downgrading. Upgrading is toward tuberculoid type and happens usually less than six months after therapy; microscopy shows edema, increased lymphocytes, giant cells and formation of groups of epithelioid cells. Downgrading reactions are towards Lepromatous pole and happen more than 6 months after therapy; microscopy shows decreased lymphocytes and epithelioid cells with replacement by macrophages, fibrosis and more numerous bacteria.

2. Type 2 lepra reaction is also called as erythema nodosum leprosum and occurs only in lepromatous leprosy or borderline lepromatous leprosy; microscopy shows papillary dermal edema, intense inflammatory infiltrate of lymphocytes, neutrophils and Virchow cells that extend into subcutaneous tissue.

3. Lucio phenomenon is seen only in Lepromatous leprosy and limited to Mexico and Central America; microscopy shows 2 patterns, one pattern shows thrombotic vasculopathy with skin ulceration, mild mononuclear infiltrate and necrosis and the second pattern shows Leucocytoclastic vasculitis like pattern.

Cutaneous tuberculosis

Cutaneous tuberculosis was reported in 7 cases (15.5%) in the present study. A male preponderance was observed in the present study in contrast to many studies who observed female preponderance. The commonest type was lupus vulgaris (4 cases) in our study similar to other studies [8,9] and one case showed occasional acid-fast bacilli. Lupus vulgaris involved mostly head and neck region.

Three histological patterns can be observed [11]

1. Superficial tuberculoid granulomas with pseudoepitheliomatous hyperplasia and granulomas are very close to the epidermis.
2. Deep tuberculoid granulomas without pseudoepitheliomatous hyperplasia.
3. Superficial and deep tuberculoid granulomas with caseous necrosis without pseudoepitheliomatous hyperplasia.

Top differentials diagnoses that should

be considered are; Leprosy, Leishmaniasis, sporotrichosis, Actinomycosis, Atypical mycobacterial infections, and nodular vasculitis.

Foreign body granulomas

Foreign body granulomas accounted for 5 cases (12.5%) and a majority (4 cases) was ruptured epidermal cyst. Similar findings were observed by Gupta et al. One case of silicone suture granuloma was reported.

Key histological features are giant cells, histiocytes, and lymphocytes forming granuloma surrounding foreign body material which can be easily identified on H&E. Polarized light microscopic examination may help in identifying polarizable material in cases without obvious foreign material [12].

Top differential diagnosis needs to be considered are Sarcoidosis, infectious granulomatous diseases, and ruptured follicular cyst. Sarcoidosis can also show polarizable material so identification of polarizable foreign material is not pathognomic of foreign body granuloma. Polarized light microscopic examination may help in identifying polarizable materials [12].

Fungal infections

Fungal infection of skin was observed in 3 cases (6.6%) in our study and all of them showed suppurative granulomas with fungal elements resembling morphologically Aspergillosis in two cases, Sporotrichosis in one case and all the three patients were diabetic. PAS and GMS stain was done to confirm fungus. However, the culture was advised which is the confirmatory test for fungus and its species.

Sarcoidosis

Two cases of Sarcoidosis were reported in our study. Both the patients were females and similar findings were reported by Gautham et al. [5]. The diagnosis was supported by radiological evidence of lung involvement, negative AFB stain, negative Mantoux, and raised serum calcium and ACE levels.

Differentiating Sarcoidosis from lupus vulgaris on histopathology poses a diagnostic challenge. Naked dermal granuloma with few or absent inflammatory infiltrate around granulomas favors Sarcoidosis than lupus vulgaris. AFB stain doesn't help much as this is negative almost in all cases of

lupus vulgaris with exceptions.

Key histological features of Sarcoidosis are naked, non caseating granulomas with few to no surrounding inflammatory cells; typically they are horizontally oriented to epidermis with presence of Schaumann bodies which are refractile concentric calcium complexes found within giant cells and Asteroid bodies which are pink stellate inclusions which radiate from central core and seen in multinucleated giant cells [12].

Top differential diagnoses need to be considered are foreign body reaction, cutaneous tuberculosis, tuberculoid leprosy, lupus vulgaris, granulomatous rosacea, and Blau syndrome [12].

Granuloma annulare

One case of granuloma annulare was reported in the present study. This is an idiopathic granulomatous disease.

Histologically two patterns are observed [12].

1. Interstitial pattern with interstitial histiocytes and perivascular lymphocytes in the dermis;
2. Palisaded pattern showing central mucin surrounded by a palisade of histiocytes, giant cells and the occasional presence of elastophagocytosis.

Top differential diagnoses need to be considered are interstitial granulomatous dermatitis and interstitial mycosis fungoides for interstitial pattern showing cases; for palisaded pattern necrobiosis lipoidica, annulare elastolytic giant cells granuloma, rheumatoid nodule, palisaded neutrophilic and granulomatous dermatitis [12].

Necrobiosis lipoidica

One case of Necrobiosis lipoidica was reported and it was located in the popliteal fossa.

The most common site it affects is shins. Histologically the key features are lesions are centered in the lower dermis with alternate layers of necrobiosis and inflammation composed of giant cells, plasma cells, histiocytes, and lymphocytes. Epithelioid granulomas and cholesterol clefts may be seen [12].

Top differential diagnoses need to be considered are granuloma annulare, necrobiotic xanthogranuloma, Rheumatoid nodule, and Sarcoidosis [12].

Necrobiotic xanthogranuloma

One case of necrobiotic xanthogranuloma was reported and the site involved was left eye.

This disease is a chronic progressive disease presenting as yellow to red to purple plaques and nodules and highly associated with paraproteinemia. Most common location is the periorbital region. Key histological features are necrobiosis with inflammatory infiltrate consists of histiocytes, Touton giant cells, and bizarre, atypical giant cells [12].

Top differential diagnosis needs to be considered are Necrobiosis lipoidica, foreign body granuloma, Juvenile xanthogranuloma, plane xanthoma, and granuloma annulare [12].

Actinic granuloma

One case of actinic granuloma was reported in the present study involving scalp which is a rare site.

Clinically this disease presents as annular plaques with atrophic centers, most common site involved are dorsal hands, forearms, neck, and shin. Key histological features are fibrotic areas with total loss of normal elastic tissue surrounded by giant cells granulomas with elastophagocytosis [12].

Top differential diagnosis needs to be considered are granuloma annulare, Sarcoidosis and granulomatous slack skin [12].

Erythema nodosum

In the present study, two cases of erythema nodosum in chronic form were observed.

Erythema nodosum is a type of panniculitis without prominent vasculitis and it can be of an acute form and chronic form. Chronic form shows granulomatous reaction, lipogranulomas with vasculitis extending up to subcutis on histopathology [13].

Granuloma Rosacea

One case of granuloma Rosacea was reported in a 40 year old male involving forehead in this study.

It's a granulomatous acne form inflammatory condition characterized histologically by granulomas with vascular dilatation of upper and mid-dermal vessels with perivascular and perifollicular lymphohistiocytic infiltrate and caseous necrosis can be observed in 10% of them [14]. Histologically this mimics mycobacterial infections and in such cases, other ancillary tests

like tissue culture need to be used.

Non-specific granulomatous inflammation

In the present study 2 cases were reported as nonspecific granulomatous inflammation where we failed to identify the cause and all them showed illformed granulomas, absent necrosis and negative for bacilli on ZN stain, absent fungal structures on PAS and GMS and also absent bacteria on Gram's stain.

Conclusion

Granulomatous skin lesions are caused by various infectious and non-infectious diseases and present with identical, overlapping, histological features, which often poses a diagnostic challenge to histopathologist. However, availability of proper clinical details, added with special stains, culture and PCR studies wherever indicated helps in arriving at a proper diagnosis and appropriate treatment. The present study concludes that infectious cutaneous granulomatous lesions are the most common cause of cutaneous granulomatous lesions, among which leprosy stands first in developing countries like India and special stains play a very important role in arriving at a specific diagnosis for histopathologist.

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