ORIGINAL ARTICLE

Histomorphological Profile of Non-Infectious Granulomatous Dermatitis: An Appraisal

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Abstract

Introduction: Non-infectious granulomatous dermatitis is a distinctive reactive inflammatory condition. Most of these dermatitis is associated with systemic diseases that impact on overall prognosis. Present study aims at classifying the non-infectious granulomatous dermatitis based on morphology of granulomas.**Aims and Objectives:** To study the histomorphology of non- infectious granulomatous dermatitis of skin and classify them, accordingly into different categories. **Materials and Methods:** It is a descriptive study of 203 cases of non- infectious granulomatous carried over a period of ten years from Jan 2011-Jan 2021. Non-infectious granulomatous dermatitis were diagnosed histopathologically and classified into different types based on morphology, etiology and also compared among different age groups and genders. **Results:** Out of total 2,690 skin biopsies received, 314 cases exhibited granulomatous reaction pattern. Among the granulomatous dermatitis, non-infectious granulomas were seen in 203cases (64.6 %). Among the non-infectious granulomas majority of the cases were foreign body granuloma accounting for 43.3 % followed by interstitial granulomas, Necrobiotic granuloma and sarcoid granuloma in 32.51%, 22.16 % and 1.97 % respectively. **Conclusions:** Knowledge of clinical and histomorphology of non-infectious granulomatous dermatitis is very important to understand and diagnosis early and old lesions of dermatitis. Thus a good clinicopathological correlation in combination with ancillary techniques helps in early and accurate diagnosis.

Key Words

Histomorphology, Skin, Granuloma, Dermatitis, Non-infectious, Foreign Body, Necrobiotic

Introduction

Granulomatous dermatitis is one of the common tissue reaction patterns in day routine dermatopathology practice. [1]Arrival at an exact and appropriate diagnosis is mandatory for successful treatment. Histopathological examination remains gold standard for establishing an accurate diagnosis in various diseases of organ system of the body. [2]

Clinically granulomatous dermatitis defined as infiltrated lesions showing apple jelly - like hue on diascopy. Histopathologically defined as any inflammation to be considered as granulomatous, atleast 50% of infiltration made up of histiocytes / macrophages according to A. B Ackerman. [3] The classification of granulomatous dermatitis is based on pathogenesis and has broadly classified as infectious granulomatous dermatitis and non-infectious granulomatous dermatitis. [4]

Infectious granulomatous dermatitis have underlying

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infectious agent while in non-infectious granulomatous dermatitis it is a part or associated with systemic diseases or neoplastic disorders and mimic granulomatous lesion on histopathology.[5]

It is very essential to differentiate between infectious and non-infectious granulomatous dermatitis as the management and therapeutic interventions differs in both though presents with similar clinical and histopathological findings. Thus good clinicopathological correlation along with histochemical stains, culture, serological tests and ancillary techniques like molecular studies required for accurate diagnosis and therapy.

Hence, giving importance to clinical and histomorphological presentations of non-infectious granulomatous dermatitis the present study was undertaken with following aims and objectives.

1.To study the prevalence non- infectious granulomatous dermatitis.

2. To study in detail the clinical and histomorphological presentations in non- infectious granulomatous dermatitis.

Material and Methods

The study design and setting

It is a descriptive type of study carried over a period of ten years between June 2011-June 2021.

The Sampling technique

Institutional Review Board approval of Multispecialty private hospital Trident, Bangalore was obtained for this study.

The present study was carried out at the Multispecialty private hospital Trident, Bangalore, India. All the patients who visited the dermatology outpatient department (OPD) with skin lesions and diagnosed clinically to have granulomatous dermatitis were included in the study. The punch biopsy/ excisional biopsy were done under aseptic precautionary measures after the informed consent taken. The clinical history and relevant data was recorded from request forms of skin biopsies received.

Clinical and laboratory work-up

The skin biopsies were fixed in 10% buffered formalin and processed with embedding in paraffin wax. Four microns thick sections were cut and stained with haematoxylin and eosin stain (H and E). The stained slides were reviewed under the light microscopy for the detail features of histomorphological diagnosis of non-infectious granulomatous dermatitis.

Statistical Analysis

Data entry and analysis was done using statistical software SPSS of windows version 16.0. The study being descriptive only percentages were calculated for categorical variables.

Following eligible criteria was adopted in our study

Inclusion criteria: All type of skin biopsies diagnosed clinically and histopathologically to have non-infectious granulomatous reaction pattern.

Exclusion criteria: All biopsies not diagnosed clinically and histopathologically to have non-infectious granulomatous dermatitis, poorly preserved specimens and inadequate skin biopsies.

Patients diagnosed clinically with a non-infectious granulomatous reaction were selected for the study. Samples were collected after the consent is taken using precautionary punch biopsy measuring 4 mm in size under aseptic measures. The biopsy specimens were fixed in 10% buffered neutral formalin for 24 hours and then processed by routine paraffin- section technique and stained with Haematoxylin and eosin (H&E). Special stains like Periodic acid Schiff (PAS), colloidal iron, Giemsa, Alcian blue etc. were done. The slides were examined under the light microscope for epidermal and dermal changes.

The study being descriptive, only percentages were calculated for categorical variables.

Results

Out of the total 203 cases, maximum cases occurred in age group of 31-40yrs with male predominance and showed foreign body granulomas accounting for 43.3 % of the cases as shown in *table 1*. Details of histopathological and histomorphological features of non-infectious granulomatous dermatitis are given in *Table 2& 3.*

In our study maximum number of cases was foreign body type of granuloma accounting for 43.3% of the cases. Histopathologically foreign body granulomas shows foreign material surrounded by histiocytes, foreign body giant cells, lymphocytes and plasma cells (*Fig .1*) Among the necrobiotic type of granuloma most common type observed in our study is rheumatic nodule (*Fig 1*) accounting for 11.33% of cases followed by necrobiosis lipoidica (*Fig 2*) and granuloma annulare accounting for 4.4% and 2.08 % of the cases respectively.

The present study observed interstitial type of granuloma constituting 32.51% of the cases of non-infectious granulomatous dermatitis. Among these, most common is interstitial granulomatous dermatitis accounting for 4.4% of the cases followed by chronic granulomatous vaculities in 3.4% of the cases and papular xanthoma constitute 1.47% of the cases. Sarcoidal type of granuloma accounts for 2.11 % of the cases.

Second common type of non-infectious granulomatous dermatitis observed was palisading type of granulomas, accounting for 24.67 % of the cases. Among these majority were rheumatoid nodule accounting for 14.3%

Table 1: Types of Granulomas in Non-Infectious Granulomatous Dermatitis.

Sl.No	Type of granuloma	No of cases	% of cases
1	Foreign body granuloma	88	43.3%
2	Interstitial granuloma	66	32.51%
3	Necrobiotic granuloma	45	22.16%
4	Sarcoidal granuloma	4	1.97%
5.	Tuberculoid granuloma	-	-
6.	Suppurative granuloma	-	-
	Total	203	100%

Table 2. Histomorphological Diagnosis of Non- Infectious Granulomatous lesions of Skin

Sl. No	Histopathological diagnosis	Number of cases	Percentage
1	Foreign body granuloma	72	35.85%
2	Rheumatic nodule	23	11.33%
3	Discoid lupus erythematous	23	11.33%
4	Suture granuloma	16	7.88%
5	Interstitial granulomatous dermatitis	9	4.4%
6	Necrobiosis Lipidioca	9	4.4%
7	Granulomatous chelitis	9	4.4%
8	Erythema nodosum	7	3.44%
9	Chronic granulomatous Vasculitis	7	3.4%
10	Necrobiotic Xanthogranuloma	7	3.7%
11	Granuloma annulare	6	2.08%
12	Erythema annulare centrifugum	5	2.46%
13	Cutaneous Sarcoidosis	4	2.11%
14	Papular Xanthoma	3	1.47%
15	Morphea	3	1.47%
	Total	203	100%

Table 3. Profile of Histomorphological Changes in Epidermis and Dermis in Various Non-Infectious Granulomatous Dermatitis

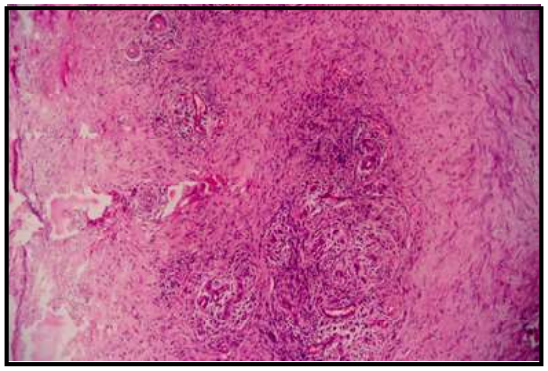
Histopathological Diagnosis	Location of granuloma	Pattern of Distribution	Epidermal changes
Foreign body granuloma (72)	Reticular dermis	Nodular	-
Rheumatic nodule (23)	Papillary (16) and Reticular dermis (17)	Nodular	-
Discoid lupus erythematous (23)	Papillary (18) and Reticular dermis (5)	Nodular	Acanthosis /atrophic/ hyperkeratosis
Suture granuloma (16)	Reticular dermis (16)	Nodular	-
Interstitial granulomatous dermatitis (9)	Reticular dermis (9)	Interstitial	Spongiosis
Granulomatous chelitis (9)	Papillary (4) and Reticular dermis (5)	Nodular	-
Necrobiosis Lipidioca (9)	Reticular dermis (9)	Interstitial	Normal/ atrophic/ hyperkeratosis
Erythema nodosum (7)	Reticular dermis (7)	Nodular	-
Chronic granulomatous Vasculitis (7)	Reticular dermis (7)	Nodular	-
Necrobiotic Xanthogranuloma (7)	Reticular dermis (7)	Nodular	Normal/ atrophic
Granuloma annulare (6)	Papillary and Reticular dermis	Interstitial	-
Erythema annulare centrifugum (5)	Papillary (2) and Reticular dermis (3)	Nodular	Parakeratosis, spongiosis and microvesiculation
Cutaneous Sarcoidosis (4)	Papillary (1) and Reticular dermis (3)	Nodular	Normal/ atrophic
Papular Xanthoma (3)	Papillary (2) and Reticular dermis (1)	Nodular	Atrophic
Morphea (3)	Reticular dermis (3)	Nodular	Atrophic

of the cases. The other group includes epithelioid cell granuloma without necrosis includes granulomatous chelitis accounting for 3.9% of the cases.

Discussion:

Non- infectious granulomatous dermatitis commonly encountered in dermatopathology practice and histopathologically presents with various tissue reactions patterns. Granulomatous inflammation of the skin is associated with wide range of conditions that are confined to the skin and some involve skin as a part of systemic

Fig 1. Microphotograph of Rheumatoid Nodule Showing Areas of Fibrinoid Necrosis, with Degeneration of Collagen Surrounded by Histiocytes in a Palisaded Arrangement



disease. Granulomatous dermatitis is mainly classified into two categories infectious and non-infectious granulomatous dermatitis. Non-infectious granulomatous dermatitis is known to pose difficulty in diagnosis and distinguish between clinical and histologic presentation. Hence it offers diagnostic challenge to both dermatologist and dermatopathologist. [6]

Majority of the non- infectious granulomatous dermatitis are resistant to therapeutic interventions due to polymorphic clinical and histological presentations having chronic and undulating disease courses.[7]

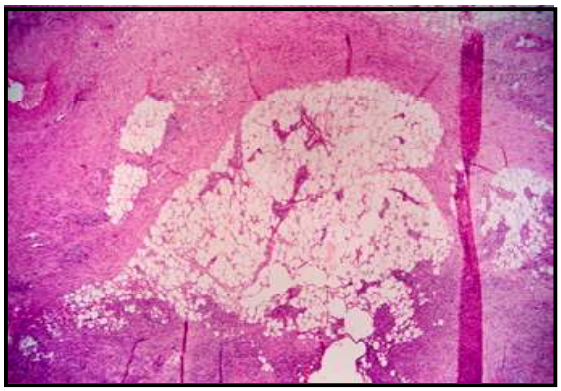
Literature search reveal lack of published data available on non-infectious granulomatous dermatitis that is essential to establish the treatment algorithms for non-infectious granulomatous dermatitis. Hence, an attempt was made to take up the present study on non-infectious granulomatous dermatitis. The study highlights the clinical presentations with emphasizing more on histopathological and histomorphological features of non-infectious granulomatous dermatitis.

In the present study majority of the cases occurred in the third decade. Our present findings are in concordance with Dhar's study [2] Grover's study [8] and Rajeshwari. k *et al* study. [9]

Present study showed female preponderance and susceptible to develop non-infectious granulomatous lesions. Similar findings are seen with Bijjaragi et al study (2021) [10] and Suwarna P *et al* study (2020) [11]. Whereas Dhar's study [2] ,Gautam's study [12] and Grover's study [8] Rajeshwari.k *et al* study [9] showed male preponderance.

In our study, foreign body granuloma was most common accounting for 35.85% of the cases and our findings are in consistent with Rajeshwari. k *et al* [9] study, Mohan's study *et al* [13] Gautam's study *et al* [12] and Grover's study *et al.* [8]

Fig 2. Microphotograph of Necrobiosis Lipoidica Shows Palisaded Histiocytes Around Necrotic Collagen Fibres



Most of the foreign body granuloma in our study is due to keratin material deposited due to rupture of epidermoid cyst and hair follicle. Few cases were due to dermal deposition of suture material and few calcium salts incites granulomatous reaction.

In our study second most common type of granuloma encountered is necrobiotic type of granulomas. Among these most common was rheumatic nodule accounting for 11.33 % of the cases. Whereas Grover's study observed 3.4% of the cases [8] , Suwarna *et al* [11] noted 3.1% of the cases and Rajeshwari. K *et al* study [9] observed 14.3% of the cases. The cases are high in our study may be due to high detection rate at our centre due to free camps conduction.

Literature reviews states that rheumatoid nodules are the most common extra articular manifestation seen due to immune complex deposition. It occurs in 20-25% of the patients with seropositive rheumatoid arthritis. [14,15] Clinically presents as deep seated, firm nodular masses on external surfaces like proximal ulna, Olecranon process, metacarpophalangeal joint and proximal interphalangeal joint. Histopathologically shows areas of fibrinoid necrosis, with degeneration of collagen surrounded by histiocytes in a palisaded arrangement. Areas of panniculities and fibrosis also noted. The special stain to confirm rheumatoid nodule is Periodic acid Schiff (PAS) that stains positive to large amounts of fibrin.[1] The close differential diagnosis includes subcutaneous granuloma annulare that is mucin positive and lacks areas of panniculities and fibrosis.

Second common type of necrobiotic granuloma noted in our study is necrobiosis lipoidica (NL) accounting for 4.4% of the cases. Our findings are in concordance with Grover's study [8] accounting for 6.9% of the cases and Rajeshwari. K *et al* study [9] accounted 3.9% of the cases. Literature reveals NL shows association with systemic

diseases like diabetes, cardiovascular diseases like hypertension and obesity in 58% of patients and thyroid diseases upto 24% of association noted.[5] Clinically presents as single/multiple, sharply demarcated patches or plaques involving pretibial skin,ankle, calves and thighs. Histopathologically shows areas of necrobiosis surrounded by palisaded/interstitial histiocytes with hyalinization of collagen noted. The differential diagnosis includes subcutaneous granuloma annulare that is mucin positive.

The other types of necrobiotic granuloma in our study is Granuloma annulare (GA) accounting for 2.95% of the cases. Our findings are in accordance with Gautam's [12] study, Rajeshwari. K *et al* study [9] and Mohan's study. [13]

Clinically presents with small, firm, macules or localized annular lesions, pale red in colour. It is of two types of presentation that includes 1. Subcutaneous G A. 2. Perforating G A [4]. In our study all cases were of Subcutaneous GA . Histopathologically shows areas of necrobiosis surrounded by palisaded/interstitial histiocytes with mucin deposition in areas of necrobiosis.

Cytochemical stains like colloidal iron and alcian blue helps in diagnosing the mucin presence. Immunohistochemistry CD 163, CD 68 helps in confirming the diagnosis of GA. Treatment includes 50% of the cases show spontaneous remissions within 2yrs the rest are treated with corticosteroids and immunomodulatory therapy.[5]

In our study, we observed the commonest type of interstitial granuloma is Discoid lupus erythematous (DLE) accounting for 11.3 % of the cases. It is the common cutaneous form of lupus erythematous. Litrature shows 23-28% presents with cutaneous form [9]. Clinically patient presents with dry, indurated red with hyperpigmented plaques with adherent scales. Histopathologically shows epidermal atropy with basement membrane thickening and vacuolar degeneration in the basal layer. Lichenoid infiltrate at dermal and epidermal junction noted. Periadnexal and perivasular lymphohistiocytic and plasma cell infiltration noted with dermal deposition of mucin seen. Special stains like Periodic acid Schiff (PAS) shows the thickened basement membrane. Alcian blue / colloidal iron shows mucin positive. Direct immunoflouroscent test shows IgG, IgM , Ig A and complement at dermoepidermal junction. Antibody titres help in confirming the diagnosis of DLE. [16]

Our study observed interstitial granulomatous dermatitis accounting for 4.4% of the cases. Our findings are in concordance with Rajeshwari. K et al study observed 7.8% of the cases [9]. Literature review shows association with systemic diseases like Rheumatoid arthritis, lupus erythematous and thyroiditis having autoimmune and immune complex formation etiology. It is also seen to associate with malignant disease like lymphoproliferative disorders. [17-19] Clinically patient presents with multiple, symmetric, cord like indurations, plaques or papules. Histopathologically dermis shows interstitial infiltrate of macrophages, lymphocytes and neutrophils around degenerated collagen fibres. However mucin deposition and vasculitis are not encountered.[1]

Present study showed seven cases of erythema nodosum (EN) also known as granulomatous panniculitis accounts for 3.44% of the cases and our findings are in accordance with Grover's study [8] accounting for 6.9% of the cases and Rajeshwari. K *et al* study observed 3.9% of the cases.[9] Clinically patient presents with red painful bilateral symmetrical nodules or plaques. Commonly it presents in third decade of life, in females with lower extrimities involvement noted.[8] Histopathologically subcutaneoud tissue shows marked septal fibrosis infiltrated with dense neutrophils, lymphocytes, histiocytes, granulomas and multinucleated giant cells noted.

We found five cases of Erythema annulare centrifugum (EAC) accounting for 2.46% of the cases. Our findings are in consistent with Rajeshwari. K *et al* study observed 3.9% of the cases. [9] EAC is an idiopathic skin disorder clinically presents as ring shaped lesions with central clearing. Histopathologically revealed spongiosis, parakeratosis and microvesiculation in the epidermis. Dermis shows perivasular lymphohistiocytic infiltrates.[9]

In our study, the incidence of sarcoidosis observed is 2.11% of the cases. Among the four cases three were males and one was female. Our findings are in accordance with Gautam et al study [12] and Zafar *et al* study [20] who found an incidence of 1.6% and 1.9% respectively.

Cutaneous involvement seen in 15% of the cases of sarcoidosis. Clinically patient has polymorphic presentation, commonly seen as popular, plaque and scar variants. Histopatologically shows dermal non-caseating, epitheliod, histiocytic granulomas and multinucleated giant cells with lack of areas of inflammatory infiltrates.[7]

Recent modern literature search reveals the pathogenesis of non-infectious dermatitis. It states that the exact pathogenesis is not fully understood, the pathogenetic mechanism involved may be due to reaction pattern to immunogenic stimulus. This immunogenic stimulates the antigen presenting cells to release large amount of TNF - alpha and interleukins. Hence most of the non-infectious granulomatous dermatitis is treated with

immunosuppressants and immunomodulatory therapy. [21]
The diagnosis of non-infectious granulomatous dermatitis requires detailed medical history, clinical examination and histopathological evaluation and thorough proper clinicopathologic correlation. Recent ancillary diagnostic techniques include Immunohistochemistry and molecular genetics for accurate diagnosis.

Along with clinical and histopathological diagnosis, dermoscopy can also aid in non-infectious granulomatous dermatitis diagnosis. On dermoscopy, dermal granuloma appears as structureless, yellowish to orange areas It helps in diagnosing the various vascular patterns that help in differential diagnosis. [22] Histopathological examination requires detail examination of 1.Location of granuloma superficial/deep. 2. Pattern of distribution of granuloma - interstitial/nodular. 3. Intensity. 4. Composition of dermal infiltrate - lymphocytes plasma cells, histiocytes and type of giant cells. [23]

Our study has highlighted the various histomorphological spectrum of non-infectious granulomatous dermatitis with overlapping clinical and histopathological findings. Literature search showed limited information regarding incidence and prevalence of non-infectious granulomatous dermatitis. Hence that provoked us to take up the present study and to the best of the author knowledge it is the study conducted over large population and has got large, varied, profile of non-infectious granulomatous dermatitis cases. In order to provide. The clinician should provide detailed clinical history which includes age, sex, sit, type and colour of skin lesions with list of differential clinical diagnosis. [24]

Conclusion

The present study emphasis on various spectrum of clinical and histomorphological features of non-infectious granulomatous dermatitis. It has highlighted the overlapping histomorphological features and recent modern adjuvant techniques used for early diagnosis. The accurate diagnosis of granulomatous dermatitis requires cooperation between clinician and histopathologist for the greatest benefit from the biopsy. Hence early and accurate diagnosis is required for appropriate therapy and outcome of specific non-infectious granulomatous dermatitis.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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