



RESEARCH ARTICLE

HISTOPATHOLOGICAL SPECTRUM OF NON INFECTIOUS GRANULOMATOUS DERMATOSES AT A TERTIARY CARE CENTRE

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Abstract

Granulomatous dermatoses comprise a wide range of etiologically and clinically distinct skin diseases that share a common histology characterized by the accumulation of histiocytes. Non infectious granulomatous dermatoses includes a wide range of lesions like granuloma annulare, rheumatoid nodule, fat necrosis, granulomatous panniculitis. Aim of present study was to study in detail histopathological spectrum of non-infectious granulomatous dermatoses with respect to their age, sex & site. A total of 770 skin biopsies were received out of which 364 belonged to granulomatous skin disorders from which 64 were diagnosed in category of non-infectious granulomatous skin disorders. Special stains were studies wherever indicated. The commonest skin lesion was calcinosis cutis (23.4%) followed by fat necrosis (20.3%), granuloma annulare (18.7%), rheumatoid nodule, sarcoidosis & granulomatous panniculitis each comprising of 3.1%. All lesions showed female preponderance over males. Histopathology remains the gold standard to diagnose all cutaneous granulomatous dermatoses along with good Dermato-histological correlation.

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Introduction:-

Granulomas were first observed and termed over 200 years ago during the autopsy of a tuberculous lung. The different current definitions of the granuloma are still based on histopathologic observations. The granuloma is defined as a focal, chronic inflammatory tissue response composed mostly of macrophages and their derivatives like epithelioid cells surrounded by cuff of lymphocytes, plasma cells and fibrosis.^{1,2,3} It is a response of immune system to external and internal antigen.⁴ Granulomatous dermatoses comprise a wide range of etiologically and clinically distinct skin diseases that share a common histology characterized by the accumulation of histiocytes. Traditionally, a distinction is made between infectious and non-infectious granulomatous dermatoses.⁵ The present study addresses granulomatous skin diseases for which there is no evidence of a causative infectious agent. Non infectious granulomatous skin disorders include granuloma annulare, annular elastolytic giant cell granuloma, necrobiosis lipoidica, rheumatoid nodulosis, necrobiotic xanthogranuloma, interstitial granulomatous dermatitis, interstitial granulomatous drug reaction, palisaded neutrophilic granulomatous dermatitis, sarcoidosis, and metastatic Crohn

disease.⁶ Because of overlapping features and still a diverse histopathological spectrum, these lesions pose a diagnostic difficulty to naïve and even expert Dermatologists & Pathologists and need a clinicopathological correlation.

Material and Methods:-

Present study was a cross sectional retrospective study carried out over a period of two years in the Department of Pathology, Government Medical College, Akola in association with Department of Dermatology. A total of 770 skin biopsies were received out of which 364 belonged to granulomatous skin disorders from which 64 were diagnosed in category of non-infectious granulomatous skin disorders. Inadequate skin biopsies were excluded. Detailed clinical history of age, sex, duration of site of lesion were noted. Punch biopsies were fixed in 10% formalin, processed and slides were stained with Hematoxyline and Eosin (H&E) stain. Special stains were done if required. Histological features were studied and correlated with the clinical diagnosis.

Results:-

In the present study, 770 skin biopsies were received out of which a total of 64 cases were diagnosed in the category of non-infectious granulomatous skin lesions (NGDS). Out of 64 cases, majority (71.1%) were diagnosed with foreign body type of granuloma from which commonest skin lesion was calcinosis cutis (23.4%) followed by fat necrosis (20.3%). The second most common skin lesion was granuloma annulare (18.7%) followed by rheumatoid nodule, sarcoidosis & granulomatous panniculitis each comprising of 3.1% as shown in table 1.

Table 1:- Incidence of non-infectious granulomatous skin lesions (n=64).

Sr No	Histopathological Diagnosis	No of cases	%
1	Foreign body type of granuloma	46	71.1
	Calcinosis cutis	15	23.4
	Fat necrosis	13	20.3
	Epidermal cyst with giant cell reaction	12	18.7
	Xanthoma	04	6.2
	Non-infectious granulomatous mastitis	02	3.1
2	Granuloma annulare	12	18.7
3	Rheumatoid nodule	02	3.1
4	Sarcoidosis	02	3.1
5	Granulomatous panniculitis	02	3.1

Table 2:- Age (year) wise distribution of NGDS (n=64).

Sr No	Age groups	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90
	NGDS									
1	Foreign body type of granuloma	-	04	08	07	05	04	15	05	-
2	Granuloma annulare	-	-	04	06	-	-	02	-	-
3	Sarcoidosis	-	02	00	00	-	-	-	-	-
4	Rheumatoid nodule	-	-	-	-	-	01	01	-	-
5	Granulomatous panniculitis	-	-	01	01	-	-	-	-	-

Table 3:- Sex wise distribution of NGDS (n=64).

Sr No	Histopathological diagnosis	Male	Female	Total
1	Foreign body type of granuloma	21	25	46
2	Granuloma annulare	04	08	12
3	Sarcoidosis	02	00	02
4	Rheumatoid nodule	02	00	02
5	Granulomatous panniculitis	01	01	02
	Total	30	34	64

Table 4:- Histological features seen in different lesions (n=64).

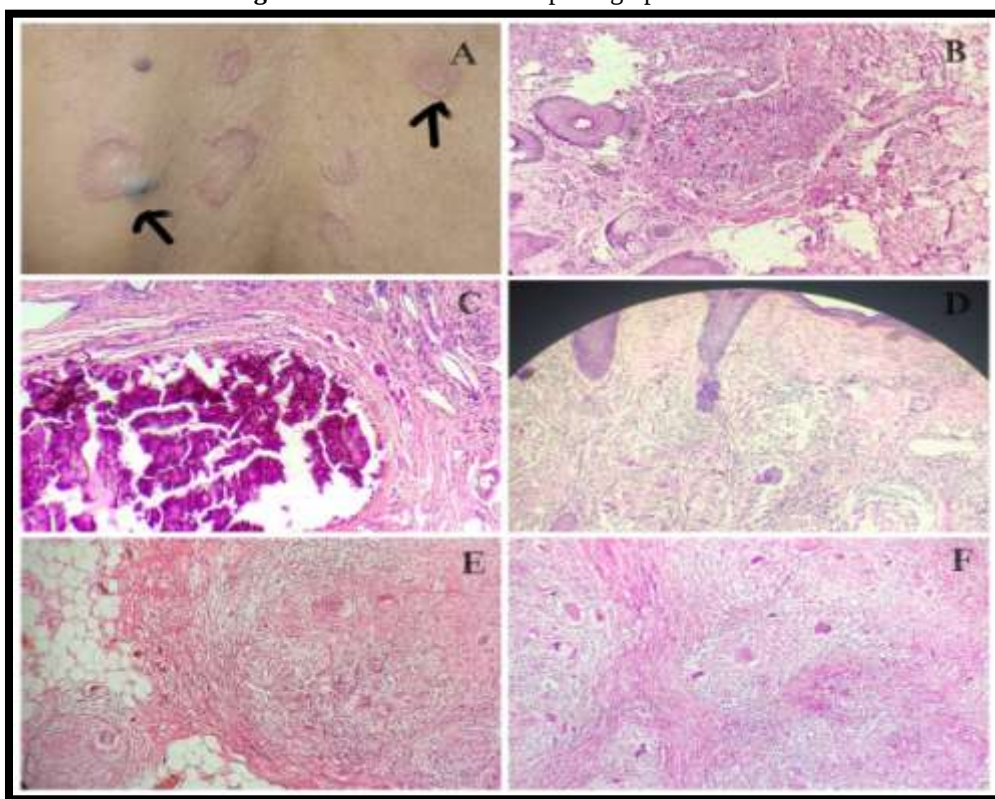
	Foreign body type of granuloma	Granuloma annulare	Sarcoidosis	Rheumatoid nodule	Granulomatous panniculitis
Epidermal atrophy	-	-	-	-	-
Epidermal hypertrophy	40	-	-	1	1
Basal layer destruction	38	-	-	-	-
Abscess	15	-	-	-	-
Normal epidermis	08	12	02	1	1
Granuloma	46	12	02	02	02
Giant cells	46	12	02	02	02
Caseation	-	-	-	-	-
Periadnexal granuloma	-	-	-	-	-

In the present study, 46 biopsies out of 64 were histopathologically diagnosed in the category of foreign body type of granuloma out of which 15 cases were categorized into calcinosis cutis showing irregular basophilic calcium deposits in deeper dermis and subcutis surrounded by foreign body type of giant cells (Figure 1C). Histopathologically, all cases of lesions foreign body type of granuloma category showed granulomas and giant cells & epidermal hypertrophy in 40 cases as shown in table 4. Thirteen cases were diagnosed as fat necrosis histopathologically upon thigh, arm and breast showing necrosis of adipocytes with focal haemorrhage and infiltrated with lymphocytes, histiocytes and foreign body type giant cells (Figure 1E). 12 cases were diagnosed as epidermal cyst with giant cell reaction which showed keratin material and many multinucleated giant cells with chronic inflammation. 4 cases were diagnosed as xanthoma upon thigh, abdomen and leg showing fat laden histiocytes in dermis and tunon type of giant cells. Lastly, in foreign body type of granuloma, 2 cases were non-infectious granulomatous mastitis; one with silicone implant and one was due to reaction to suture material of old surgery. On analyzing the clinical features of 46 cases of lesions with foreign body type of granuloma, female preponderance was noted and almost found in all age groups. Out of 64 cases of NGDS, 12 biopsies (18.7%) were histopathologically diagnosed as granuloma annulare (GA) showing middermal necrobiotic collagen and mucin surrounded by palisading histiocytes, fibroblasts and multinucleated giant cells with granulomas (Table 4) (Figure1B). GA was found to be common in age group of 31-40 years with maximum 6 cases and female preponderance with an M:F ratio of 1:2 was noted (Table 2,3). GA lesions were widely distributed on extremities. The lesions appeared as flesh-colored papules and nodules arranged in a ring or semicircle fashion on back and legs as shown in figure 1A.

Sarcoidal granulomas (2 cases) were seen as discrete naked epithelioid cell granulomas without central caseation and multinucleated giant cells containing an asteroid body (Figure 1D). Special stains like AFB & PAS stains did not show any organism or foreign body. Both cases of sarcoidosis were noted in 11-20 years age group and were male patients (Table 2, 3) and were clinically suspected of lupus vulgaris and sarcoidosis.

2 cases out of 64 were diagnosed as rheumatoid nodule microscopically showing area of fibrinoid degeneration of collagen in subcutaneous tissue surrounded by a palisading histiocytes and foreign body giant cells (Figure 1F). The surrounding stroma showed a mixed inflammatory infiltrate. Both cases of rheumatoid nodule were elderly and male patients with one having firm nodule on elbow and other near foot.

Granulomatous panniculitis was diagnosed in 2 cases out of 64 cases of NGDS. Histopathologically it revealed the involvement of subcutaneous tissue septae showing widening, histiocytic, and dense neutrophilic infiltrate extending into lobule with variable age groups and equal sex distribution (Table 2,3)

Figure 1:- Clinical and microphotographs of NGDS.

1. **Figure A:** Clinical photograph of Granuloma Annulare showing multiple sharp annular lesions with raised erythematous borders
2. **Figure B:** Microphotograph of Granuloma Annulare showing mucoid degeneration in the center of granuloma (H & E stain, 200X)
3. **Figure C:** Microphotograph of Calcinosis Cutis showing irregular deposits of basophilic dystrophic calcium with surrounding giant cells (H & E stain, 200X)
4. **Figure D:** Microphotograph showing cutaneous Sarcoidosis with Schaumann bodies and discrete naked granulomas (H & E stain, 200X)
5. **Figure E:** Fat necrosis showing necrosis of adipocytes surrounded by fat laden histiocytes and giant cells (H & E stain, 200X)
6. **Figure F:** Rheumatoid nodule with central area of fibrinoid necrosis surrounded by giant cells (H & E stain, 200X)

Discussion:-

NGDS include a challenging group of diseases for diagnosis. An important source of this challenge is the clinical and histologic overlap among these conditions along with the potential for misdiagnosis due to this overlap.⁷ In the present study, our aim was to study the whole histopathological spectrum of NGDS along with their clinical aspects comparing our results with other studies in the literature. Out of 64 cases of NGDS, majority cases were of foreign body type of granuloma (71.1%) in which calcinosis cutis was the commonest lesion (23.4%) followed by fat necrosis and epidermal cyst while in the studies conducted by Grover S et al⁴, Mohan H et al⁸ and Lynch JM et al⁹ the incidence was 19.35%, 14% and 18.3% respectively. This disparity may be explained on the basis of geographical variation of NGDS. In our study, cutaneous Xanthoma was found in 4 cases which was comparable to studies done by Pawale J et al¹⁰ and Srabani C et al¹¹.

The skin lesions of granuloma annulare are single or multiple with annular shape and sharp borders. It commonly affects extremities and young females under 40 years of age. The generalized form is more typical among older patients and mainly involves trunk.¹²

In the present study, all cases were under 40 years of age with a female predilection. GA may clinically resemble tinea corporis, lichen planus, erythema annulare centrifugum, and erythema elevatum diutinum. Histopathologically it shows a necrobiotic area with palisading histiocytes and giant cells.^{4, 7} GA was histopathologically diagnosed in 12 cases out of 364 skin biopsies studied for granulomatous lesions making an incidence of 3.2% similar to Grover S et al⁴ (3.9% incidence out of 276 cases) & Gautam et al¹³ (3.7% incidence out of 106 biopsies studied).

In our study, the incidence was 12 out of 64 cases of noninfectious dermatoses (18.7%) similar to study done by Mohan et al⁸ who found an incidence of 11 cases (15.4%), out of 71 cases of noninfectious dermatoses.

Due to variable histological presentations, sarcoidosis lesions could be misdiagnosed as Leprosy, Syphilis, GA, and foreign body reaction.⁴ In the present study, two cases of Sarcoidosis were diagnosed as diagnosis of exclusion and with support of clinical features & investigations. In both cases, microscopically discrete naked epithelioid cell granulomas with no caseation were noted. Special stains like AFB & PAS stain were negative. These findings were comparable to findings in studies conducted by Grover S et al⁴ and Srabani C et al.¹¹ The incidence of Sarcoidosis in our study was 2 out of 64 cases (3.1%) comparable to Gautam et al¹³ and Zafar et al¹⁴ found an incidence of 1.6% and 1.9%, respectively. In our study, both patients were male in age group of 11-20 years which was similar to studies done by Grover S et al⁴ while Mahajan et al¹⁵ noted most patients presented in age group of 20-40 years with a male predominance.

In the present study, two cases were of Rheumatoid nodule out of 64 cases of NGDS (incidence = 3.1%). Mohan et al⁸ found two cases (2.8%), out of 76 cases, and Grover S et al⁴ (3.4%) which was similar to our study.

In the present study, only two cases of granulomatous panniculitis were diagnosed with nonspecific age group and sex distribution. Histopathologically, subcutaneous lobules along with widened septae were infiltrated with mixed inflammatory infiltrate and multinucleated giant cells which was similar to findings noted by Grover S et al⁴ while Thurber S et al¹⁶ observed neutrophilic lobular panniculitis with suppuration in two cases and lobular panniculitis associated with septal-lobular panniculitis with vasculitis in other two cases.

Conclusion:-

Although histopathology is the gold standard for diagnosis & categorization of non-infectious granulomatous dermatoses, detailed clinical work up and pathological investigations are very important to reach the correct diagnosis. Histopathology helps the Dermatologist for proper approach and accurate treatment to treat the case. Proper site and depth of biopsy along with good Dermato-histological correlation is mandatory. More studies are needed to understand the histopathological variations among NGDS and their clinical behavior along with response to treatment.

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