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Original Article

Morphological study of different granulomatous lesions of the skin

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Abstract

Objective Morphological study of different granulomatous lesions of the skin to determine the relative frequencies and to compare our results with those of other workers.

Materials and methods A total of 2682 skin biopsies received over a period of 5 years from January, 2001 to December, 2005 at the department of Pathology, Basic Medical Sciences Institute, JPMC, Karachi, were reviewed.

Results Out of a total of 2682 skin biopsies 123 cases were found to have a granulomatous reaction pattern. Out of them, tuberculoid granulomas were seen in 114 cases, foreign body type in 4 and suppurative and sarcoidal each in 2 cases. One case was of necrobiotic granuloma. Cutaneous tuberculosis was the most common lesion (97/123). 47 cases were typified. Out of them 18 were lupus vulgaris, 9 tuberculosis verrucosa cutis, 7 each of tuberculosis cutis orificialis and scrofuloderma and 6 were tuberculous gummas. AFB were seen in 20 out of 79 (25.31%) caseating, and 1 out of 35 (2.85%) non-caseating tuberculoid granulomas.

Conclusion Granulomatous lesions of skin are more common in females. The most common type of granulomas is tuberculoid. The most common lesion in our study was tuberculosis (The incidence is 3.69% of all dermatology patients). The most common subtype of tuberculosis was lupus vulgaris (38.29%) followed by tuberculosis verrucosa cutis and scrofuloderma. AFB is more commonly seen in caseating granulomas.

Key words
Acid fast bacilli, lupus vulgaris, scrofuloderma, tuberculosis, tuberculosis cutis orificialis, tuberculosis verrucosa cutis.

Introduction

Granulomatous dermatoses frequently present a diagnostic challenge. An identical histologic pattern may be produced by several causes, and conversely, a single cause may produce several histologic patterns.[1] The granulomatous reaction pattern is defined as a distinctive inflammatory pattern characterized by the granulomas.[2]

Fully developed granulomas with sheets of epithelioid histiocytes and giant cells are easily recognized, but more subtle lesions containing a few epithelioid histiocytes still qualify as granulomatous.[3] It is difficult to present a completely satisfactory classification of the granulomatous reaction.[4] Many conditions classified as granulomatous lesions may

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show only non-specific changes in the early evolution of the inflammatory process and in a late or resolving stage show fibrosis and non-specific changes without granulomas.

Five histological types of granuloma can be identified on the basis of the constituent cells and other changes within the granulomas:[2]

1. Tuberculoid
2. Sarcoidal
3. Necrobiotic
4. Suppurative
5. Foreign body

The frequency and types of different granulomatous lesions vary according to geographical locations. However, no comparative study, to our knowledge, has been carried out to determine the frequency and types of different granulomatous lesions of the skin in Pakistan, hence this study.

Materials and methods

This was a retrospective study of all the skin biopsies with granulomatous reaction. The study was carried out in Department of Pathology Basic Medical Sciences Institute (BMSI), Jinnah Postgraduate Medical Center (JPMC), Karachi. All the skin biopsies received in the Department of Pathology BMSI/JPMC from 01.01.2001 to 31.12.2005 were reviewed and cases of granulomatous lesions selected for study in detail. Clinical history and relevant data were recorded. Slides stained with haematoxlin and eosin and relevant special stains like periodic acid Schiff (PAS), Ziehl-Neelsen (ZN), Grocott, Gram, Giemsa, modified ZN, alcian blue etc. were studied under the light microscope using scanner (4x10), low power (10x10) and high power (40x10) lenses.

Results

During this five years period a total of 2682 skin biopsies were received in the Department of Pathology. Out of them 123 showed granulomatous lesion. Out of a total of 123 cases, 52 (42.7%) were males and 71 (57.3%) were females. Ages were not mentioned for 3 males. Ages of 120 patients ranged from 6-70 years. The mean age of the patients was 29.258 years. The mean age of the male patients was 33.75 years and the mean age of the female patients was 26.15 years. Maximum numbers of cases i.e. 47 (38.2%) were in second decade. More than 60% of cases were found to be in first 3 decades (**Table 1**).

Out of a total of 123 cases, maximum number of biopsies i.e. 29 (23.57%) were from the region of head and neck including 18 from face and 11 from neck region. 20 (16.2%) cases were from lower limbs, 13 (10.5%) from upper limbs, 9 (7.3%) cases were from chest and abdomen and pelvis region, and 8 (6.5%) were from back. Site was not mentioned in 35 (28.4%) cases.

Out of a total of 123 cases 114 (92.7%) showed tuberculoid granulomas, 2 each had suppurative and sarcoidal granulomas, 4 had foreign body type while one had necrobiotic granuloma (**Table 2**). Out of a total of 114 cases of tuberculoid granulomas, 97 were tuberculosis (**Figure 1**), 5 were granulomatous folliculitis, 3 were granulomatous leishmaniasis and its variants (**Figure 2**), 2 were granulomatous vasculitis (not otherwise specified), 2 were fungal infections, and 5 were granulomatous lesions (not otherwise

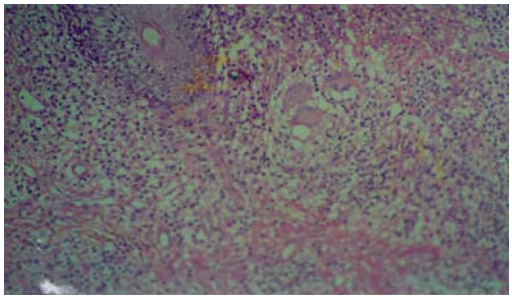

Figure 1 Photomicrograph of a case of lupus vulgaris showing granulomas in upper dermis (H&E X100).

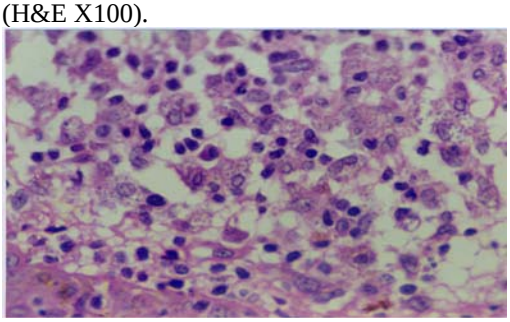

Figure 2 Photomicrograph of a case of leishmaniasis. Upper dermis showing intracellular Leishman-Donovan bodies (H&E x 200).

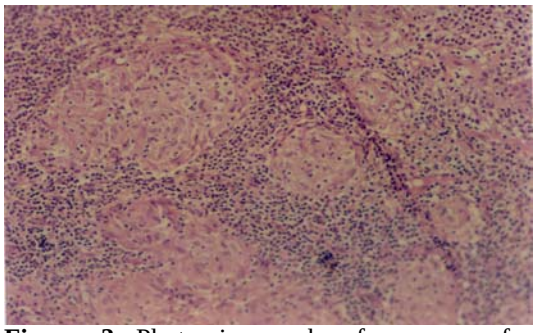

Figure 3 Photomicrograph of a case of sarcoidosis showing discrete non-caseating granulomas (H&E X 100).

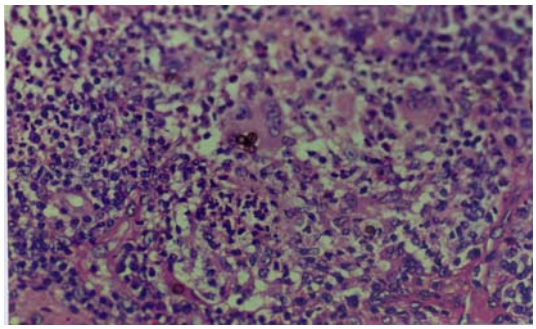

Figure 4 Photomicrograph of a case of chromomycosis showing hyperkeratosis and spores (H&E X 200).

specified). 2 cases with sarcoidal granulomas were sarcoidosis (**Figure 3**). 2 cases of suppurative granulomas were

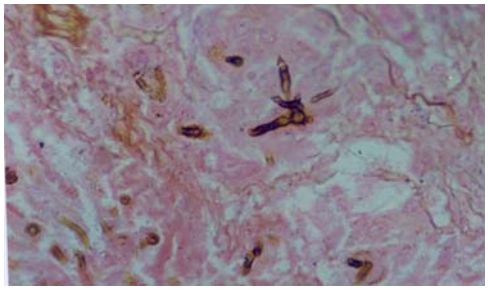

Figure 5 Photomicrograph of a granuloma showing fungal spores and hyphae (Grocott staining)X400.

suggestive of aspergillosis and chromomycosis (**Figure 4**). One case with necrobiotic granuloma was granuloma annulare.

Out of a total of 97 cases of tuberculosis 37 were males (38.14%) and 60 females (61.86%). Mean age of male patients was 31.22 years and female patients was 26.63 years. Maximum number of cases i.e. 39, was in second decade. About half of the cases of females (29/60) were in second decade.

Out of a total of 97 cases of tuberculosis 50 were not typified. Out of a total of 47 cases of typified tuberculosis, 18 were lupus vulgaris, 9 tuberculosis verrucosa cutis, 7 each of tuberculosis cutis orificialis and scrofuloderma and 6 were gummas (**Table 3**).

79 cases (69.3%) of tuberculoid granulomas showed caseating and 35 (30.7%) showed non-caseating granulomas. Half of the cases of lupus vulgaris, 71.4%, cases of TCO, 57.2 % cases of scrofuloderma (SFD), 33.3% cases of TVC, and all of the cases of gummas showed caseation. Caseating granulomas were also found in 2 cases of fungal infection (**Table 4**).

Ziehl-Neelsen stain was performed in all

Table 1 Age groups according to gender of granulomatous skin lesion

Age groups (years)	*Male n=52*	*Female n=71*	*Total 123*	*Cumulative %*
0-10	1	2	3(2.4%)	2.4
11-20	12	35	47(38.2%)	40.6
21-30	13	13	26(21.1%)	61.7
31-40	6	11	17(13.8%)	75.5
41-50	6	7	13(10.6%)	86.2
51-60	9	2	11(8.9%)	95.1
61-70	2	1	3(2.4%)	97.5
Age not mentioned	3	--	3(2.4%)	100
Mean± s.d.	33.75±16.481	26.15±13.478	29.258±15.220	

Table 2 Frequencies of various types of granulomas

Type of granuloma	*n (%)*	*95% CI*
Tuberculoid	114 (92.7)	86.9-96.3
Foreign body	4 (3.3)	1.04-7.6
Sarcoidal	2 (1.6)	0.2-5.2
Suppurative	2 (1.6)	0.2-5.2
Necrobiotic	1 (0.8)	0.0-3.9

C.I. confidence interval

Table 3 Frequencies of various clinicopathological types of cutaneous tuberculosis.

Subtype	*n=47*	*95% C.I.*
Lupus vulgaris	18 (38.3%)	25.9-52.7
Scrofuloderma	7 (14.9%)	6.7-27.2
Tuberculosis verrucosa cutis	9 (19.1%)	9.7-32.2
Tuberculosis cutis orificialis	7 (14.9%)	6.7-27.2
Tuberculous gumma	6 (12.8%)	5.3-24.6

C.I. Confidence interval

cases to see the acid-fast bacilli (AFB). Out of 114 cases of tuberculoid granulomas, 21 (18.4%) showed AFB. AFB were seen in 20 out of 79 (25.3%) caseating, and 1 out of 35 (2.8%) non-caseating tuberculoid granulomas, the ratio being 8.8:1 ($p<0.005$) [**Table 5]**. PAS and Grocott's stain was performed on all cases to see the fungus. Out of 123 cases, 4 showed fungal spores/hyphae or both (**Figure 4**). Giemsa stain was performed on selected cases for Leishman-Donovan bodies. Out of 123 cases, 3 were positive for Giemsa stain. Alcian blue stain was positive in one case of necrobiosis. Gram staining was not positive in any case. Retic stain was suggestive of sarcoidosis in 2 cases (**Table 5**).

Discussion

Granulomatous inflammation was recognized as a distinct entity in the early nineteenth century and has been of continuing interest since then. It forms a common and intriguing problem. Arrival at a proper diagnosis is mandatory so that appropriate treatment can be meted out. Histopathology remains a time-tested tool for establishing a correct diagnosis like in many other diseases pertaining to various organ systems of the body.[5]

A large number of individual studies on granulomatous lesions of skin were found but still no comprehensive comparative study was found on various granulomatous lesions of skin in our region except a short study of 22 cases of granulomatous lesions of skin done by Dhar in India in 2002.[5] Our study was done on 123 cases with a granulomatous reaction pattern. There were 52 (42.7%) males and 71 (57.3%) females. It showed that females are more susceptible to develop granulomatous lesions of skin. This finding was not in accordance with Dhar who found males to be involved more frequently. He found 12 males out of a total of 22. Ages of our patients ranged from 6-70 years. The mean age of the patients was 29.258 years that is

Table 4 Division of 114 cases of tuberculoid granulomas into caseating and non-caseating granulomas

Type of lesion	*With caseation*	*Without caseation*	*Total*	*Chi square/p value*
Tuberculosis (NOS)	50 (100%)	0(0%)	50	1.0/0.001
Lupus vulgaris	9 (50%)	9 (50%)	18	0.23/0.63 (NS)
Scrofuloderma	4 (57.2%)	3 (42.8%)	7	NS
Tuberculosis verrucosa cutis	3 (33.3%)	6 (66.7%)	9	0.89/0.34 (NS)
Tuberculosis cutis orificialis	5 (71.4)	2 (28.6)	7	1.14/0.28 (NS)
Tuberculous gumma	6 (100%)	0 (0%)	6	8.3/0.005
Leishmaniasis	0	3	3	-
Granulomatous folliculitis and variants	0	5	5	-
Granulomatous vasculitis	0	2	2	-
Granulomatous lesions (NOS)	0	5	5	-
Fungal infection	2	0	2	-
Total	79 (69.3%)	35 (30.7%)	114	33.96/0.001

NOS: not otherwise specific, NS: non-significant *p* value

Table 5 Results of special stains in 123 granulomatous lesions.

Sex	*Total no. of patients*	*Ziehl-Neelsen for mycobacteria*	*Gram*	*Giemsa for leishmania*	*PAS/Grocott for fungus*	*Alcian blue for necrobiosis*
Female	71	13	-	1	1	-
Male	52	8	-	2	3	1
Total	123	21	-	3	4	1

in accordance with Dhar.[5]

Tuberculosis was the commonest granulomatous lesion of skin in our study. Tuberculosis is much common in our population in spite of the active immunization programme through BCG vaccination. With emergence of anti-tuberculosis drug-resistant strains and AIDS epidemic, there has been a world wide rise of tuberculosis in the recent years more so ever in poverty-struck areas of the world due to poor nutrition, poverty, non availability of diagnostic aids and treatment, overcrowding and ignorance about the disease.[6] Tuberculosis can involve any organ or tissue of the body including skin. World-wide incidence of tuberculosis varies from 0.1 to 1% of all cutaneous disorders.[6,7,8,9] In our study the frequency of cutaneous tuberculosis is surprisingly high. We found 3.7% of all dermatology patients having cutaneous tuberculosis. It is alarming to all officials dealing with control and management of tuberculosis. Exact reason for this high frequency could not be identified. However, it may be a possible reflection of increased incidence of systemic tuberculosis due to massive overcrowding, poverty and poor hygienic conditions or it may be due to simply a better referral for biopsy because our center is one of few centers where biopsy facility is freely and easily available.

A sexual predilection was observed in our study in all types of cutaneous tuberculous lesions. Lesions were more common in females. There were 37 males (38.1%) and 60 females (61.9%) out of 97 cases of cutaneous tuberculosis. These results were comparable with Khan *et al.*[10] who also found females preponderance (i.e. 80 %). Yasmeen and Kanji[11] also found females to be involved more by tuberculosis in their study conducted in Jinnah Postgraduate Medical Center in 2005. But

these results were not in accordance with Sengupta[12] and Sehgal[7] who found male preponderance i.e. 54.46% and 60%, respectively. In our study the ages for cases of cutaneous tuberculosis ranged from 6-70 years with a mean age of 28.32 years that was comparable with Zerrin *et al*.[13] who found the mean age 32.46 years.

Out of a total of 97 cases of tuberculosis 17 (17.5%) were children (age <16 years), which is consistent with findings of Kumar *et al*.[14] who observed 75 children (18.7%) out of 402 cases of cutaneous tuberculosis. The type of cutaneous tuberculosis differs from country to country and is closely related to social and health systems developed.[15] In our study, out of 47 typified cases of cutaneous tuberculosis, lupus vulgaris was the commonest form, seen in 18 (38.29%) of these patients, followed by other types. These results were consistent with Khan's study[10] who also found lupus vulgaris the commonest (50%) followed by TVC (30%) and scrofuloderma (20%). Similar results were also seen by Singh[9] and Kumar and Muralidhar[6] who found lupus vulgaris the commonest form in 44% and 48%, respectively.

Diagnosis of cutaneous tuberculosis certainly requires evidence of the presence of the tubercle bacilli either in the smear or in the tissue section or its recovery *in vitro.*[16] Looking for AFB in ZN staining is a time consuming and laborious procedure. Establishment of the diagnosis in cutaneous tuberculosis is achieved by the correlation of the various relative and absolute criteria.[7] In our study, AFB were found by the staining method in pathologic sections in 21 cases. AFB were more positive in caseating granulomas 20/79 (25.3%) than non-caseating granulomas 1/18 (5.5%). The ratio was statistically significant.

Cutaneous leishmaniasis is present worldwide. It is of considerable clinical importance due to its chronicity and its potential for local destruction and disfigurement. It is endemic in various regions of Pakistan but the disease manifests mainly in the young local population or the outsiders (travelers, military troops).[17] Karachi, being a populous city, comprises multiethnic population, from different regions of country, who frequently visit their native areas off and on. So, sporadic cases of leishmaniasis are seen here. A total of 9 cases of leishmaniasis were found in the skin biopsied examined. Of these, 3 were granulomatous and 6 non-granulomatous lesions on the basis of formation of epithelioid cells granuloma. The tissue section remains the backbone of the diagnosis of leishmaniasis and is considered to be the most sensitive test.[18]

We found 5 cases of granulomatous folliculitis. 2 cases were clinically correlated and diagnosed as granulomatous rosacea and lupus miliaris disseminatus faciei (LMDF), respectively. Rest of the cases did not have any supportive data. In our study 2 cases were found with granulomatous vasculitis but informative clinical data was not available. So, they were reported as granulomatous vasculitis. In another 5 cases histological findings were not so conclusive and clinical data were not informative to put them in an appropriate class. So, they were labeled as chronic granulomatous lesions.

Fungal infections of humans are divided somewhat arbitrarily into the superficial mycoses and the deep mycoses. We found 4 cases of fungal infections (3.25%) in our

study. Two of them showed suppurative granulomas including one case with fungal elements suggestive of aspergillosis and one with features suggestive of chromomycosis. The patients were advised for culture, which is a definitive tool for confirmation of causative fungus. In other 2 cases caseating tuberculoid granulomas were found with giant cells showing small, rounded and few segmented elongated bodies on H & E stain which were proved to be spores and hyphae of fungus on PAS and Grocott stain. Fungal elements could not be further specified. In such cases histopathology can give only a clue to the referring dermatologist that he is dealing with a granulomatous lesion consistent with fungal infection. Patients were advised for culture, which is a definitive tool for confirmation of fungus and its species.

Internationally, granuloma annulare is an uncommon dermatosis whose frequency in the general population is unknown. Most cases resolve without adverse medical sequel. We found only one case of granuloma annulare who was 70 year-old-male.

In order to apply the knowledge effectively when examining biopsy sections, it is essential that submitting physicians provide detailed clinical information. This must include age and sex of the patient, shade of skin color essential for judging pigmentary change, the exact site of the biopsied lesion, and a concise history and description of the dermatoses. Clinical diagnosis or a list of differential diagnosis should be given.[19] By comparing the clinician's list with his own, the pathologist may be able to rule out certain diagnoses, to favour others, and perhaps to come up with a single one that fits clinical and pathologic data alike. Cooperation between clinician and pathologist is more important in the field of skin disease than in almost any other field if the patient is to derive the greatest benefit from the biopsy.[19]

Conclusion

Our study shows that granulomatous lesions of skin are more common in females and tuberculoid is the most common of granulomas. Tuberculosis, especially lupus vulgaris, is the leading cause; however, AFB could be demonstrated in less than 20% cases. Other granulomatous diseases are less frequent.

Cooperation between clinician and pathologist is more important in the field of dermatology than in any other field if the patient is to derive the greatest benefit from the biopsy. Even after relevant special stains, etiological diagnosis could be confirmed in only 28 (22.7%) cases. This percentage can be further consolidated, if culture, serological investigations and PCR are done.

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