ORIGINAL ARTICLE

Spectrum of cutaneous granulomatous lesions: A 5-year experience in a tertiary care centre in Sarawak

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ABSTRACT

Introduction: Granulomatous skin lesions can have various histopathological features leading to diagnostic confusion. The study aimed to determine the frequency and pattern of different granulomatous skin lesions.

Materials and Methods: This was a 5-year retrospective study done between April 2017 and March 2022 at Dermatology Department, Sarawak General Hospital. Subjects with a clinicopathological diagnosis of granulomatous diseases were included in the analysis.

Results: A total of 1718 skin biopsies were done during the study periods, with 49 (2.8%) confirmed granulomatous skin lesions. Most patients were aged 40–60 with a male predominance of 51%. Most of the skin biopsy samples were taken from the upper limb (36%). In this study, epitheloid granuloma was the commonest subtype (21, 43%) followed by suppurative granuloma (12, 24%), tuberculoid granuloma (8, 16%) and foreign body granuloma (5, 10%). The commonest aetiology of granulomatous skin lesions in our study was infections (30, 61%) followed by foreign body inoculation (8, 16%). Fungal infection was the most common infective cause, followed by cutaneous tuberculosis.

Conclusion: The major cause of granulomatous dermatoses in developing countries is still infections, fungal and tuberculosis being the leading causes.

KEYWORDS:
Cutaneous granulomatous, granuloma, cutaneous tuberculosis, cutaneous fungal infection

INTRODUCTION

Granulomatous inflammation is a chronic inflammatory response with a distinctive tissue reaction pattern. It is characterised by focal clusters of epithelioid histiocytes, multinucleated giant cells, and mononuclear leukocytes. It is a type IV or delayed hypersensitivity reaction induced by infection, reactions to autoimmunity, toxins, allergies, drugs and neoplasms.[1] The cardinal tissue reaction patterns seen in granulomatous skin lesions are predominantly epithelioid granulomas.

Granulomatous dermatoses often present as a diagnostic challenge to dermatologists and dermatopathologists. This is because a single histopathological pattern may be caused by several aetiologies and contrarily, a single aetiology may produce diverse histopathological patterns.[2] Good clinical history, close histological examination and clinicopathological correlation are essential in making a final diagnosis.[3]

The present study was undertaken to determine the frequency and pattern of different granulomatous skin lesions in Sarawak, Malaysia.

MATERIALS AND METHODS

This was a retrospective analysis of all skin biopsy results that were done in the Skin clinic, Sarawak General Hospital in Kuching, Sarawak, Malaysia over a 5-year period from March 2017 to April 2022. All reported cases of granulomatous skin lesions were analysed with regard to clinical information and histopathological examination of biopsy samples. Data analysis was done withthe statistical software SPSS version 23.0.

RESULTS

In this 5 years retrospective study, a total of 1718 skin biopsies were evaluated. Granulomatous skin lesions were diagnosed in 49 cases (2.85%).

Histopathological examination revealed several granulomatous patterns. We observed 21 (43%) epitheloid granulomas, 12 (24%) suppurative granulomas, 8 (16%) tuberculoid granulomas, 5 (10%) foreign body granulomas, 2 (4%) xanthogranulomas and 1(2%) of palisaded granuloma. Amongst these 49 cases, 25 (51%) were males, and 24 (49%) were females (Table I). There was no significant difference in the type of granuloma presentation between males and females (Table III).

The age ranges from 14 to 85 years, with a mean age of 53.5 years. A maximum number of cases occurred in the 40–50 age group followed by the 50–60 age group. Epitheloid granulomas were found in all age groups but doubled up after the age of 30, while suppurative, tuberculoid and foreign-body granulomas were presented at age 40 and above. Age group 20–30 was significantly associated with xanthogranulomas (p=0.008), while the age group 30–40 years was significantly associated with palisaded granulomas (p=0.001), and the age group of more than 70 years was significantly associated with epitheloid granulomas (p=0.044).

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Table I: Distribution of various Histopathological patterns of granuloma according to gender

Type of granulomas	Male	Female	Frequency (%)
Epitheloid	13	8	21 (43)
Suppurative	6	6	12 (24)
Tuberculoid	3	5	8 (16)
Foreign body	3	2	5 (10)
Xanthogranuloma	-	2	2 (4)
Palisaded	-	1	1 (2)
Total	25	24	49

Table II: Site distribution of various granulomatous lesions

Site	Upper limb	Face	Lower limb	Trunk	Neck	Gluteal
Epitheloid	8	7	3	1	1	1
Suppurative	4	2	5	1	-	-
Tuberculoid	5	1	1	1	-	-
Foreign body	1	2	2	-	-	-
Xanthogranuloma	-	2	-	-	-	-
Pallisaded	-	-	1	-	-	-

Table III: Distribution according to the and distribution site

	Total n (%)	Face n (%)	Neck n (%)	Upper limb n (%)	Trunk n (%)	Gluteal n (%)	Lower limb n (%)	*p*-value
Infectious cause								
Fungal infection	12 (40)	0	0	3 (25)	0	0	9 (75)	0.001
Tuberculosis	10 (33)	2 (20)	0	5 (50)	1 (10)	1 (10)	1 (10)	0.254
Atypical tuberculosis	3 (10)	0	0	3 (100)	0	0	0	0.014
Leprosy	4 (13)	1 (25)	0	3 (75)	0	0	0	0.077
Non-infectious								
Foreign body	8 (42)	5 (62)	0	1 (12)	0	0	2 (25)	0.012
Xanthogranuloma	2 (11)	2 (100)	0	0	0	0	0	0.443
Sarcoidosis	2 (11)	0	0	2 (100)	0	0	0	0.048
Granuloma annulare	2 (11)	0	0	1 (50)	1 (50)	0	0	0.100
Others	6 (30)	4 (66)	1 (16)	0	1 (16)	0	0	0.100
Total	49							

Table IV: Distribution according to aetiology and ethnicity

Ethnic	Fungal infection n=12	Tuberculosis n=10	Atypical tuberculosis n=3	Leprosy n=4	Foreign body n=8	Xanthogranuloma n=2	Sarcoidosis n=2	Granuloma Annulare n=2	Others n=6	*p*-value
Malay	2	3	1	1	4	2	0	0	1	0.142
Chinese	4	7	2	2	3	0	0	0	4	0.074
Iban	4	0	0	0	1	0	1	0	1	0.030
Bidayuh	0	0	0	0	0	0	1	1	0	0.080
Melanau	2	0	0	0	0	0	0	0	0	0.011
Pakistan	0	0	0	1	0	0	0	1	0	0.270

Ethnically, Chinese comprised 22 cases (45%), followed by Malay 14 cases (29%), Iban 7 cases (14.2%), and two cases each for Melanau, Bidayuh and foreign nationals (Pakistan). There was no significant association between the type of granuloma presentation and different ethnicities.

The commonest site of granulomas was the upper limb in 18 cases (36%) followed by the face 14 cases (29%) (Table II). Males were significantly associated with a granulomatous lesion on the lower limbs with p=0.025(Table V). There was no significant difference between races in the location of granulomas.

Out of a total of 49 cases, infectious granulomatous dermatoses were seen in 30 (61%) cases and non-infectious in 19 (39%) cases (Table III).

Of 30 infectious granulomatous dermatoses, the most common was fungal granulomatous dermatoses in 12 (40%) cases followed by tuberculosis in 11 (33%) cases. Males and Iban race were significantly associated with fungal granulomatous dermatoses with p=0.025 (Table V) and p=0.030 respectively (Table IV) with a predilection to lower limbs (Table III). Of 12 cases of fungal granulomatous dermatoses, 5 (41%) cases had positive GMS stains. The most common cause of fungal granulomatous dermatoses was chromoblastomycosis 9 (75%), followed by sporotrichosis 2 (16%) and Madura foot 1 (8%). While out of the 10 cases of tuberculosis, only one had positive ZN staining.

Table V:Comparison of granulomatous dermatoses clinical characteristics between male and female patients

Clinical characteristic	Male	Female	*p*-value
Location of lesions			
Face	5	9	0.173
Neck	1	0	0.342
Upper limb	7	11	0.234
Trunk	2	1	0.480
Gluteal	1	0	0.283
Lower limb	9	3	0.025
Types of granulomas			
Epitheloid	13	8	0.336
Suppurative	6	6	0.807
Pallisaded	0	1	0.342
Foreign body	3	2	0.537
Tuberculoids	3	5	0.559
Xanthogranuloma	0	2	0.174
Causes of granuloma			
Infectious	17	13	0.086
Fungal	9	3	0.025
Tuberculosis	4	6	0.622
Atypical tuberculosis	1	2	0.626
Leprosy	2	2	0.898
Non-infectious	6	13	0.086
Foreign body	3	5	0.559
Sarcoidosis	0	2	0.174
Xanthogranulomatous	0	2	0.174
Others (including Granuloma Annulare	4	4	0.850

In the non-infectious category foreign body inclusion reactions, 8 (42%) was the most common, followed by xanthogranuloma 2 (11%), sarcoidosis 2 (11%) and others with one case each was granulomatous type rosacea, ruptured epidermal inclusion cyst, granulomatous cheilitis, mycoses fungoides and pseudolymphoma. One case had an indeterminate cause.

All patients were treated based on diagnosis, with antifungal therapy for cutaneous fungal dermatoses, anti-tuberculosis therapy for cutaneous mycobacterium infection and Bactrim (Trimethoprim/Sulfamethoxazole) for atypical mycobacterium infection. Excision, mainly in non-infectious granulomatous dermatoses, e.g., foreign body granulomas, was performed in 9 cases, resulting in complete resolution of the granulomas. 29 (55.8%) patients recovered, 16 (30.8%) defaulted, 3 had a change of diagnosis and 1 was a non-responder to treatment.

DISCUSSION

Granulomatous skin disease is a distinctive pattern of chronic cutaneous inflammation associated with infectious and non-infectious causes. The distribution of granulomatous dermatoses varies depending on geographic location.[4] Sarawak, which is located in East Malaysia is a highly agricultural state and agriculture and poultry activities dominate the local populace. There is a strong reliance on foreign workers in the palm oil and timber industries.

We observed that epithelioid granulomas were the most common granuloma in our population predominantly in the fifth decade of life with distribution mainly over the upper limbs. Most were infectious in origin. This was in concordance with other studies. In contrast, patients with granulomatous lesions in our population had equal gender distribution. Fungal infection was the most common of the infectious granulomas. These findings were in contrast to previously conducted studies.

Different type of classifications was used by different authors worldwide for granulomatous skin lesions. We have classified granulomatous lesions based on constituent cells and other changes within the granulomas based on George et al., where granulomatous skin lesions are classified as epithelioid, palisaded, suppurative, xanthogranulomatous, foreign body and other granulomatous patterns.[5] They are classified based on characteristic findings found in the histology. Epitheloid granulomas consist of epitheloid histiocytes, or macrophages, a few of which fuse to form cells admixed with lymphocytes and occasional plasma cells with or without features of necrosis.[5] Suppurative granulomas are characterised by epitheloid histiocytes and multinucleated giant cells with a central collection of polymorphonuclear leucocytes and can occur with necrotising or non-necrotising granulomatous inflammation.[6] On the other hand, tuberculoid granulomas are composed of mixed macrophage phenotypes which include epitheloid histiocytes marked by abundant cytoplasmand foamy macrophages with intracellular lipids accumulation. The macrophages can coalesce into multinucleated giant cells, called Langhans' cells.[7] Foreign body granulomas are characterised by the zonal type of granulomatous inflammatory reaction surroundingthe foreign body. Palisading granulomas surround a central focus of degenerated connective tissue, mucin accumulation or fibrin.[8]

Epithelioid type granuloma was similarly the most common type in other studies which were conducted in India, Pakistan and Nepal.[2,3,9-12]

Upper limbs were the commonest site of the lesions followed by the face, similar to a study from Gupta et al.[1] The site of the lesion showed variations in different studies. The most common site of lesion was the trunk followed by the lower limb in India by Kumar, Lalit et al.[13], and in Pakistan, Zafar et al.[11] found the head and neck region to be the most common site followed by lower limb. In our study, atypical mycobacterium infection had predilection in the upper limb, foreign body inclusion in the face and cutaneous fungal infection in the lower limb. This could be job-related such as mycobacterium marinum in a fisherman's hand; however, proper correlation cannot be established due to small numbers.

We observed that granulomatous lesions were common in the 5th decade of life which was similarly reported by Vimal Chander et al.[14] which was a contrast to reports in the third decade in Nepal and India.[3,9,10] There was equal gender distribution in our study, while in other reports from Nepal, Nigeria, Sri Lanka and India there was male gender predominance.[10,15-17] These could be due to geographical differences.

Infectious granulomatous dermatoses (61%) were more common than non-infectious granulomas in our retrospective analysis. Similar results were found by other authors in India.[2,13] Fungal infection was the most common followed by tuberculosis in infectious granulomatous dermatoses. There was no concordance with other reports from India, Nepaland Pakistan. Pawale et al., Adhikari et al., Zafaret al. and Kumar, Lalit et al.[3,10,11,13] found tubercular most common. Gupta et al. from India found leprosy to be more common than tubercular.[2] Pawale et al.[3] found 11.32% fungal lesions in their study while Zafar et al., Bal et al. and Chakrabarti et al. reported 3% granulomatous fungal dermatoses comparatively much lower than our study.[11,18,19] They can manifest as epitheloid and suppurative granulomas. Geographic location probably affected the result as a study conducted in different cities in India yielded different results. Similarly in Sarawak, Malaysia, in the Northern part of Sarawak there is a higher number of cases of leprosy amongst the indigenous Penan people.[20] Thus, if the study was conducted in the Northern part of Sarawak the most common cause of infectious granulomatous dermatoses could be leprosy. Another possibility for the differences could be because cutaneous tuberculosis with concomitant pulmonary tuberculosis may have been treated at a primary care centre leading to lesser referrals to the tertiary centre while all cutaneous fungal infections will generally be referred to Dermatology clinic tertiary hospital for confirmation of diagnosis and management. This could explain the reasons for the high incidence of cutaneous granulomatous fungal infection in our study. Cutaneous fungal granulomatous dermatoses were found in higher proportion in the indigenous Iban male on the lower limbs. Traditionally, the Iban natives are involved in farming. They plant hill paddy, vegetables and fruits and also in oil palm plantations which exposed them to soil. Prolonged work in warm and humid climates, sweating and exposure to infected soil without proper working attire and shoes make them at risk of cutaneous granulomatous fungal infection.

The positivity rate of Grocott-Gomori's methenamine (GMS) staining in cutaneous granulomatous fungal infection is not well described. 5 (41%) fungal granulomatous dermatoses had positive staining with GMS. Two of these had positive cultures with Cladosporium species. Another three patients had negative GMS staining but had fungal bodies seen in histopathology which aided our diagnosis of cutaneous granulomatous fungal infection. The remaining cases were treated with antifungals based on their history and clinical correlation. Amongst them, one patient had no response and required a repeat biopsy and a change of treatment. However, amongst those with either positive staining or fungal body seen in the histopathology, two patients did not respond to antifungal therapy; with one revised diagnosis based on repeat biopsy and another requiring surgical excision. Further study is needed to look into the positive rate of staining and its correlation to fungal cultures. It is a diagnostic and management challenge for cutaneous granulomatous fungal infection.

The incidence of cutaneous tuberculosis in the present study was 0.6%, similar to the worldwide incidence of 0.1-1% of all cutaneous lesions.[3]

Ziehl-Neelsen stain demonstrated acid-fast bacilli only in 10% of our study population. One other study showed a different positivity rate. It can be as low as 5% by Bal et al. whereas it was 11.1% by Adhikari et al., 20.74% in a study by Permiet al., 22.62% in a study by Pawale JS et al., and as high as 71% in a study of Krishnaswamy et al.[3,9,10,18] Cutaneous tuberculosis was diagnosed in the remaining patients based on the presence of positive acid-fast bacilli in tissue culture in two patients and positive tuberculosis polymerase chain reaction (PCR) in one patient and others were empirically treated with anti-tuberculosis medication. Amongst the cutaneous atypical mycobacterium infection, one had positive acid-fast bacilli and one was treated empirically based on history and clinical correlation. Both patients were treated with Bactrim, a sulphonamide antibiotic, with complete resolution. All patients with cutaneous tuberculosis treated with anti-tuberculosis responded favourably.

Detection of tuberculosis, especially in the tissue slides is still based on the histological characteristics of granuloma, which has several differential diagnoses. Ziehl–Neelsen staining has low sensitivity, especially in tissue sections and requires the presence of intact tubercle bacilli.[21] Considering the limitations in sensitivity and specificity of Ziehl–Neelsen staining for mycobacterial detection, mycobacterial culture and molecular and serological techniques, the histomorphological analysis appears to be the only important and feasible technique for the diagnosis of tuberculosis in some patients.[22] However, some tests are not readily available and may have negative results, which leads to the empirical treatment of cutaneous tuberculosis despite the results.

In the present study, foreign body granuloma was the most common type of non-infectious granulomatous dermatoses. This was compatible to Zafar et al.[11] and Pawale et al.[3]

In cases where the staining and cultures were negative, other relevant factors such as occupation and history of exposure to infection may be able to pinpoint the probable aetiology. The morphology of skin lesion might be able to give a clue as well. In the event of a lack of probable aetiology, empirical treatment can be considered, and patients need to be monitored closely on treatment respond. Alternative diagnosis needs to be considered if treatment response is not observed. All the granulomatous skin lesions were correlated with clinical history, examination findings and ancillary investigations before definitive treatment were instituted. 29 (55.8%) patients recovered, 16 (30.8%) defaulted, 3 had a change of diagnosis and 1 was a non-response to treatment. There was difficulty in ascertaining predisposing factors such as comorbid, occupation and history of exposure in developing different cutaneous granulomatous lesions in our population due to incomplete documentation in a retrospective assessment. One-third of patients defaulted to follow-up causing difficulty in ascertaining their treatment outcome. These limitations need to be addressed as they rely on previous documentation on patients' medical records. Therefore, a larger, prospective cohort study in collaboration with the histopathology team is recommended to look specifically into the occupation, socio-economic differences, and comorbidities; different staining, histopathological details and their correlation clinically, which can provide better information, especially on predisposing factors to developing granulomatous lesions. This information would be useful in developing treatment strategies for each granulomatous reaction and in formulating preventive strategies for occupational-related granulomas.

CONCLUSION

Epitheloid granulomas are the most common granuloma pattern in our population. Infectious causes were the major cause of granulomatous dermatoses in developing countries with fungal infection being the most common followed by tuberculosis. The incidence and prevalence of different types of granulomatous dermatoses depend on geographic location. Successful treatment of infectious granulomas would depend on identifying the organism causing each granulomatous reaction and targeted to the infectious disease source. Non-infectious granulomas usually respond well to surgical excision.

ETHICAL APPROVAL

This study was registered via the National Medical Research Register, Ministry of Health Malaysia

CONFLICT OF INTEREST

The authors declare no competing interests

FUNDING

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AUTHOR'S CONTRIBUTION

IPLT was responsible for the study design, data collection and manuscript writing. HZT and HGT participated in data collection and discussion. JWK and MP were involved in manuscript editing and language proofreading. All authors read and approved the final manuscript.

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