Original Article

A histopathological analysis of granulomatous dermatoses – a single centre experience from Sri Lanka

M.P.G.N.S. Jayawardhana[1], R.T.A.W. Gunewardhana[1], N.V.I. Ratnatunga[1] and M. Dissanayake[2]

[1]Department of Pathology, Faculty of Medicine, University of Peradeniya, Sri Lanka; [2]Department of Dermatology, Teaching Hospital Kandy, Sri Lanka.

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Summary

Granulomatous inflammation is a common histological pattern encountered in skin biopsies which pose a diagnostic challenge to pathologists because of overlapping histological features produced by various aetiological agents. We conducted the following study to analyze the aetiological factors and morphological patterns of granulomatous dermatoses in a cohort of Sri Lankan patients from the Central Province. This is a retrospective analysis of skin biopsies dectected to have granulomatous inflammation over a 12 year period at the Department of Pathology, Faculty of Medicine, University of Peradeniya. All biopsies had been assessed using haematoxylin and eosin stain and special stains when necessary. Of the 1547 skin biopsies received, 128 (8.3%) were recognized to have granulomatous inflammation. An infectious aetiology was present in 86.7% (111/128).The most prevalent infectious cause was leprosy, accounting for 39.8% (51/128) followed by the category differential diagnoses in 22 (17.1%) of which had an infectious differential. Cutaneous tuberculosis was the cause in 17 (13.3%) cases. In 102 cases (79.7%) necrosis was absent in the granulomata and when present most were (58%) of suppurative type; typical caseous type necrosis was present in only a few cases. In conclusion, a large majority of granulomatous inflammation is due to infectious causes and leprosy is the leading cause in this study cohort.

Keywords: granulomatous dermatitis, leprosy, cutaneous tuberculosis

Introduction

Granulomatous inflammation is a special type of chronic inflammation, which is often a result of a tissue reaction to an offending agent that is resistant to be eliminated.

Author for correspondence: M.P.G.N.S. Jayawardhana (MBBS, Dpath,MD), Department of Pathology, Faculty of Medicine, University of Peradeniya, Sri Lanka. E mail: sanjeewanijayawardhana77@gmail.com

Granulomatous inflammation in skin biopsies often poses a diagnostic challenge to pathologists because many aetiological agents can produce similar histological changes. However, clues to the aetiology may be obtained by distribution pattern of granulomata such as coalescent large or discrete small, presence of accessory features such as central necrosis, suppuration and necrobiosis and presence of foreign material or organisms (1,2).

Granulomatous inflammation in the skin could be due to infectious or noninfectious causes. In tropical countries infectious aetiology predominates, accounting for up to 90% in some series (1). Common infectious causes of granulomatous skin lesions include leprosy, tuberculosis, leishmaniasis and fungal infections. Use of special stains such as Ziehl Neelsen stain for tuberculosis, Fite's stain for leprosy, Giemsa stain for leishmaniasis and Grocott methanamine silver stain for fungal infections are often helpful in making a definitive diagnosis. However, special stains are specific but relatively less sensitive methods of demonstrating organisms when the organism density is low. Therefore, in some situations, even if the organism is not visualized histochemically, a definitive diagnosis may be given based on the overall histological pattern and the clinical picture. Use of ancillary techniques such as, culture and polymerase chain reaction (PCR) may be helpful in some situations such as tuberculosis.

Analysis of aetiological factors of granulomatous skin diseases has not been reported for Sri Lanka. This knowledge is useful in ordering special stains and ancillary studies when working on a differential diagnosis. Therefore, we conducted this study to analyze the aetiological factors and morphological patterns of granulomatous skin diseases in a cohort of Sri Lankan patients from the Central Province.

Materials and Methods

This is a retrospective study performed on skin biopsies received at the Department of Pathology, Faculty of Medicine, University of Peradeniya, Sri Lanka, from 2000 to 2011. Biopsy reports were retrieved from the archives and those reported to have a granulomatous inflammatory pattern were selected for the study. All biopsies had been assessed on multiple levels using haematoxylin and eosin stain and special stains such as Ziehl Neelsen, Fite, Grocott methanamine silver and Giemsa when necessary. A definitive diagnosis of leprosy was made in the presence of suggestive inflammatory infiltrate casuing neuritis or selective infiltration of neuro-vascular bundle, demonstration of acid fast organisms with Fite's stain or strong clinical correlation with suggestive inflammatory reaction (Figure 1). In the absence of caseous necrosis and positive Ziehl Neelsen stain, cutaneous tuberculosis was diagnosed if clinically suggestive. When a definitive diagnosis could not be made a differential diagnosis was made. Fungal infections, except chromoblastomycosis, were diagnosed by demonstrations of fungi by Grocott methanamine silver stain and leishmania by demonstration of amastigotes confirmed by Giemsa stain. Data relating to morphology, definitive or differential diagnosis and clinical features were collected. Cases with granulomatous reactions to neoplasms and those with diffuse histiocytic infiltration without forming granulomata were excluded. Accordingly, lepromatous leprosy which shows a diffuse infiltration of histiocytes within the dermis was excluded.

Results

There were 1547 skin biopsies received at the Department of Pathology, University of Peradeniya over the 12 year period under study and of them 128 cases (8.3%) were recognized to have granulomatous inflammation. The sex distribution of the sample was similar with 54% men. The age distribution ranged from 7 years to 86 years with a mean of 39.5 years (SD 19.4).

Table 1 shows the aetiological diagnosis pattern of granulomatous dermatoses. An infectious aetiology was present in 86.7% (111/128) cases and the rest were noninfectious categories. In the 22 cases with a differential diagnosis possibilities were of infectious aetiology, which were between leprosy and tuberculosis in most. The most prevalent infectious cause was leprosy, accounting for 39.8% (51/128) of all granulomatous dermatitis, followed by the category differential diagnosis. Cutaneous

Table 1. Causes of granulomatous dermatoses

Diagnosis	Frequency	
Infectious causes	**111**	**(86.7%)**
Leprosy		
Tuberculoid leprosy	43	(33.5%)
Borderline leprosy	06	(4.7%)
Leprosy unclassifiable	02	(1.6%)
*Differential diagnosis	22	(17.1%)
Cutaneous tuberculosis /lupus vulgaris	17	(13.3%)
Leishmaniasis	11	(8.6%)
Chromoblastomycosis	05	(3.9%)
Fungal (not specified)	02	(1.6%)
Fish tank granuloma	02	(1.6%)
Mycobacterium marinum	01	(0.8%)
Noninfectious causes	**17**	**(13.3%)**
Granuloma annulare	07	(5.4%)
Acne rosacea	04	(3.1%)
Sarcoidosis	01	(0.8%)
Acne vulgaris	01	(0.8%)
Acne pulminans	01	(0.8%)
Wegener's granulomatosis	01	(0.8%)
Foreign body granuloma	02	(1.6%)

*all cases had infective causes as the differential diagnosis

tuberculosis was the cause in 17 (13.3%) and a large majority of cutaneous tuberculosis was diagnosed as lupus vulgaris based on the clinical information.

Table 2 outlines the morphological characteristics of granulomatous lesions studied. In 92 (71.9%) cases granulomata were well-formed. Moreover, in most categories, apart from borderline leprosy, granuloma annulare and acne vulgaris, granulomata were well-formed. In 102 cases (79.7%) necrosis was absent in granulomata and when present most were (58%) of suppurative type. Caseous type necrosis was present in only a few cases and when present they took the form of spotty central necrosis (Figure 2). Geographic type necrosis was not a feature in any.

Table 3 demonstrates the clinical features of the skin lesions in each disease category. Clinically, commonly the lesion had been a nodule or a papule accounting for 76 cases (59.4%). The extremities were the most commonly involved site with 60 (46.9%) subjects getting affected, followed by face with 41 (32.0%) affected subjects.

DISCUSSION

According to the study granulomatous inflammation was present in 8.7% of patients undergoing skin biopsy. In a large majority (86.7%) infectious diseases were the cause of granulomatous inflammation and leprosy was the commonest specific cause with at least 39.8% of the subjects in the study affected; the second leading cause lupus vulgaris (13.3%) was much far behind in frequency. A similar aetiological pattern is observed in the other tropical countries in this region. A series from India has shown that 87.8% of granulomatous skin inflammations were of infectious aetiology and 72.4% of them were due to leprosy (3). Similarly, a series from Nepal has shown a 74.5% infectious aetiology and leprosy accounting for 79.7% (4). In both series, similar to our findings, cutaneous tuberculosis was the second leading cause of granulomatous skin inflammation accounting for 23.1% and 7.6% for India and Nepal respectively (3,4). However, another series from India has reported cutaneous tuberculosis as the commonest cause of granulomatous skin inflammation with a prevalence rate of 57.3% (5). The prevalence of granulomatous inflammation in skin biopsies was similar to Sri Lanka in the Nepal series (7.6%) and was significantly higher than the rest in the latter Indian study (14.5%) (4,5).

Leprosy is endemic in the South East Asian region and 95% of the newly detected leprosy cases have been reported from 16 endemic countries which include Sri Lanka, with India leading (6,7). Sri Lanka has a success story of controlling leprosy reaching the WHO elimination target of one leorpsy case per

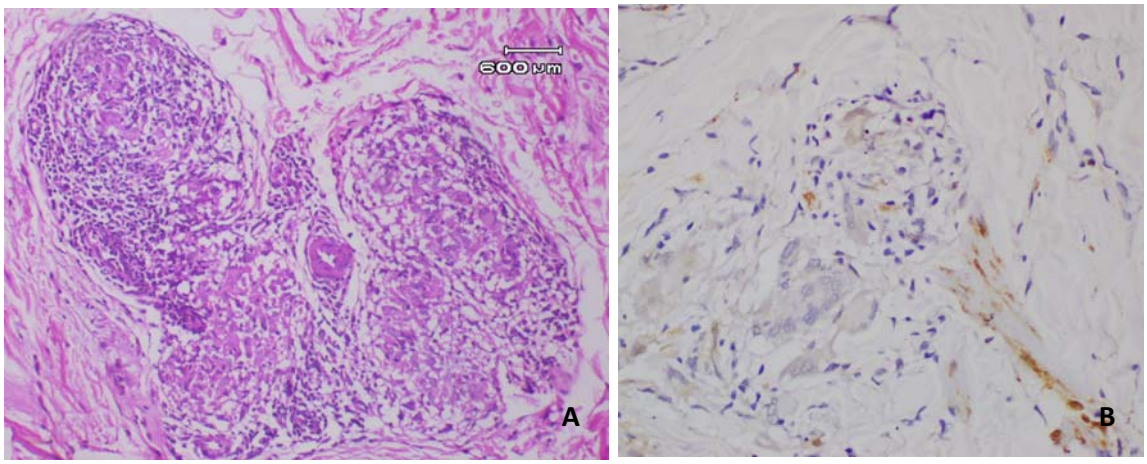

Figure 1. Tuberculoid leprosy. A) Elongated non necrotic granulomata with a lymphocytic cuff in and around a neurovascular bundle (Haematoxylin and eosin stain, x10). B) S 100 staining highlights remnants of a damaged nerve due to neuritis. (S 100 x 20)

10,000 population in 1995 (8). However, the number of new cases reported have been gradually increasing from the lowest reported 7/100,000 population in 1997 to 10.4/100,000 population in 2014 (7). Although a significant majority (40.2%) of granulomatous skin diseases in the present sample from the Central Province is due to leprosy, Central province is one of the less endemic regions in Sri Lanka (4% annual detection rate). Highest number of cases are reported from the Western Province (42% annual detection rate) followed by Eastern Province (13% annual detection rate) (9).

In the present study, 17.2% were differential diagnoses most of which were between tuberculoid leprosy and cutaneous tuberculosis. This indicates the difficulty in reliably differentiating between these two categories in the absence of typical histological features such as neuritis in leprosy and caseating granulomata in cutaneous tuberculosis. Demonstration of M. leprae and M. tuberculosis by Fite's stain and Ziehl Neelsen stains are often difficult with tuberculoid leprosy and cutaneous tuberculosis due to low organism density. Moreover, in cutaneous tuberculosis, particularly in the common form lupus vulgaris, central caseous necrosis is not commonly encountered and even when present, occur as spotty necrosis. In the present study only 3/17 cases diagnosed as tuberculosis had necrosis in granulomata.

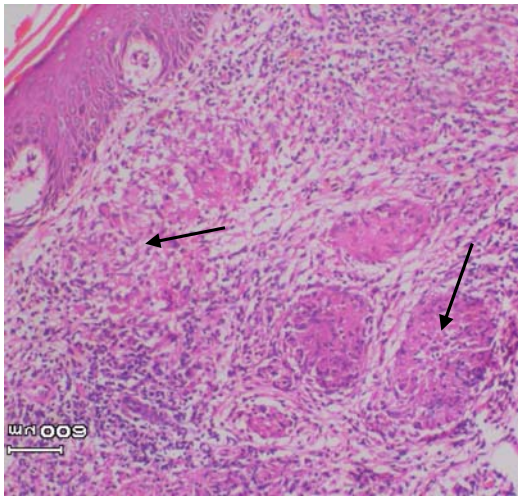

Figure 2. Cutaneous tuberuculosis (lupus vulgaris). Well-formed and ill-formed granulomata with prominent lymphocytic cuff and spotty central necrosis (arrows) (Haematoxylin and eosin stain x4)

Table 2. Histopathological features of granulomatous dermatitis

Diagnosis	Nature of granuloma		Presence or absence of necrosis			
	Well-formed	Ill-formed	Caseous	suppurative	Others	Absent
Infectious causes						
Leprosy						
Tuberculoid leprosy	33	10	00	00	02	41
Borderline leprosy	02	04	00	00	00	06
Leprosy unclassifiable	02	00	00	00	01	01
Differential diagnosis	15	07	00	05	00	17
Cutaneous tuberculosis	14	03	03	00	00	14
Leishmaniasis	08	03	00	01	00	10
Chromoblastomycosis	03	02	00	02	00	03
Fungal (not specified)	02	00	00	02	00	00
Fish tank granuloma	02	00	00	02	00	00
Mycobacterium marinum	01	00	00	01	00	00
Noninfectious causes						
Granuloma annulare	02	05	00	00	05	02
Acne rosacea	04	00	00	00	00	04
Sarcoidosis	01	00	00	00	00	01
Acne vulgaris	00	01	00	00	00	01
Acne pulminans	01	00	00	00	00	01
Wegener's granulomatosis	01	00	00	01	00	00
Foreign body granuloma	01	01	00	01	00	01

Therefore, often definitive diagnosis of these two entities can be made by correlation of suggestive histological pattern with clinical findings. On the other hand, demonstration of fungal organisms in fungal skin infections and amastigotes in leishmaniasis are not that difficult. It is also interesting to note, that in the 50% of the cases with a differential diagnosis granulomata were ill-formed and 33% had suppurative necrosis. Although this is the typical histological picture in fungal infections and less often in leishmaniasis, failure to demonstrate organisms may have led to a differential diagnosis. In such situations, borderline leprosy, tuberculosis, atypical tuberculosis and partially treated fungal infections should be considered. Furthermore, it is also important to note that secondary bacterial infections, following scratching etc. in the lesions can produce suppurative lesions and alter the typical histological picture.

Overall, in the present study, necrosis is not a prominent feature and was absent in about 80%; when present the most common type of necrosis was suppurative type of necrosis. Of those with a definitive diagnosis, fungal infections and atypical mycobacterial infections were the common aetiological factors. Caseous type necrosis has been an infrequent finding.

In conclusion, this analysis shows that a large majority of granulomatous inflammation is due to infectious causes; hence, in our setting, an infectious cause should be ruled out in all granulomatous skin lesions. Even though Sri Lanka has achieved successful

Table 3. Clinical characteristics of granulomatous skin lesions

Diagnosis	Shape of the lesion			Site/s of involvement				
	Nodule/ papule	Plaque	Other	Face	limbs	Trunk	Multiple	Other
Infectious causes								
Leprosy								
Tuberculoid leprosy	24	14	05	12	21	06	02	02
Borderline leprosy	04	01	01	02	02	01	00	01
Leprosy unclassifiable	00	00	02	01	00	00	00	01
Differential diagnosis	15	04	03	07	11	02	00	02
Cutaneous tuberculosis	09	06	02	07	07	00	00	03
Leishmaniasis	05	06	00	05	04	01	01	00
Chromoblastomycosis	02	02	01	01	04	00	00	00
Fungal (not specified)	02	00	00	00	01	01	00	00
Fish tank granuloma	00	02	00	00	02	00	00	00
Mycobacterium marinum	01	00	00	00	01	00	00	00
Noninfectious cause								
Granuloma annulare	06	01	00	01	03	02	01	00
Acne rosacea	04	00	00	03	00	00	01	00
Sarcoidosis	01	00	00	00	01	00	00	00
Acne vulgaris	01	00	00	01	00	00	00	00
Acne pulminans	00	01	00	00	01	00	00	00
Wegener's granulomatosis	00	00	01	00	01	00	00	00
Foreign body granuloma	02	00	00	01	01	00	00	00

control of leprosy, still it is the leading cause of granulomatous inflammation of the skin in this cohort. Furthermore, this study also highlights the importance of clinico-pathological correlation in making a definitive diagnosis of granulomatous skin inflammation due to overlapping histological features, particularly between tuberculoid leprosy and cutaneous tuberculosis.

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