



Original Article

Granulomatous inflammation: A histopathological study

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ABSTRACT

Background: Granulomatous inflammation is a special type of chronic inflammation that is being a manifestation of many infective, toxic, allergic, autoimmune and neoplastic diseases and also conditions of unknown etiology.

Materials and Methods: The study included a total of 418 granulomatous lesions, diagnosed from January 2010 to December 2012 in the department of pathology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal.

Results: The median age of the patients with granulomatous lesion was 29 years and the majority of the patients were in the age group of 20-29 yrs with slight male predominance. Majority of granulomas were seen in lymph nodes (41.1%), followed by skin & subcutis (22%), and bone & joints (11.5%). Tuberculosis was the most common cause of granuloma with 258 (61.7%) cases, followed by fungal infections, foreign body reaction, parasites and toxoplasmosis. Out of 258 cases of tuberculosis, lymph nodes were involved in 140 (54.26%) cases, followed by bone & joints (12.79%) and respiratory system (5.42%). The most common type of granuloma was epithelioid (83.5%), followed by epithelioid with suppuration and mixed inflammatory.

Conclusion: The granulomatous lesion is common in third decade of life with slight male predominance. The commonest site is lymph node with tuberculosis being the most common cause and epithelioid being the most common type of granuloma.

INTRODUCTION

Granulomatous inflammation is a special type of chronic inflammation, that is being a manifestation of many infective, toxic, allergic, autoimmune and neoplastic diseases and also conditions of unknown etiology.¹ In this inflammation, cells of the mononuclear phagocyte system are predominant

and take the form of macrophages, epithelioid cells and multinucleated giant cell. In most instances, these cells are aggregated into well demarcated focal lesions called granuloma.¹ Loose and more diffuse arrangement may be seen. Granuloma formation is usually regarded as a means of defending the host from persistent irritants of either exogenous or endogenous origin.

The provocative agents of granulomatous inflammation appear to be non-degradable by both neutrophils and non-active macrophages. For such degradation, the action of

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transformed macrophages which are formed with the help of the CD 4+ T cells is required. The CD 4+ T cells secrete various mediators such as IL 2, IF γ , TNF and lymphotoxin for the transformation of the macrophages into epithelioid cells and giant cells.²

Causes of granuloma include bacterial, metal-induced, fungal, viral, chlamydial, helminthic, foreign body and unknown cause.³ Other causes of granulomatous inflammation are tumor associated, BCG-instillation, sarcoidosis, Crohn's disease, protozoal (toxoplasma, leishmaniasis) & chalazion.

Granulomas are classified as follows: epithelioid, histiocytic, foreign body, necrobiotic palisading and mixed inflammatory.⁴ Some epithelioid granulomas are necrotizing, while others show suppuration.

There is often no single histologic feature that distinguishes infectious necrotizing granulomas from other granulomas.⁵ Ancillary studies like special stains (Ziehl-Neelsen, Grocott methamine silver), real-time PCR, In situ hybridization can be performed to find the cause of granuloma.⁵ However, some granulomas remain unexplained even with ancillary studies and in these instances, good clinical history and clinicopathological correlation are essential in making a final diagnosis.

Hence, this study was undertaken to find the frequency and cause of granulomatous lesions.

MATERIALS AND METHODS

The study was done from January 2010 to December 2012 in the department of pathology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal. This study included a total of 418 granulomatous lesions, diagnosed on Hematoxylin & eosin stain from all sites. Special stains like Ziehl-Neelsen (ZN), Periodic Acid Schiff (PAS) and Fite-Faraco were used whenever required. The clinical history, other laboratory investigations and radiological findings were collected from the medical records.

Table 1: Age and sex distribution of patients

Age group (years)	Male	Female	Total (percentage)
0-9 year	18	7	25 (6.0)
10-19 year	39	30	69 (16.5)
20-29 year	60	56	116 (27.8)
30-39 year	29	43	72 (17.2)
40-49 year	25	20	45 (10.8)
50-59 year	36	15	51 (12.2)
60-69 year	14	13	27 (6.5)
70 years and above	7	6	13 (3.1)
Total	228	190	418 (100.0)

RESULTS

The median age of the patients with granulomatous lesion was 29 years with a range of 1 to 83 years. The majority of the patients were in the age group of 20-29 years. There was slight male predominance with male to female ratio of 1.2:1 (Table 1).

Majority of granulomas were seen in lymph nodes (41.1%), followed by skin & sub cutis (22%) and bone & joints (11.5%). Other sites were respiratory system, gastrointestinal tract, urinary system, pericardium, male genital system, eye & ocular adnexae, omentum, oral cavity & oropharynx, breast & brain (Table 2).

Granulomas of different etiologies were seen and tabulated in table 3. Tuberculosis (fig.1) was the most common cause of granuloma with 258 (61.7%) cases, followed by fungal infections, foreign body reaction, parasites and toxoplasmosis. Other causes are leprosy, sarcoidosis, cat-scratch disease, Crohn's disease, leishmaniasis, tumors, BCG-instillation and chalazion. Final diagnosis was made based on histomorphology, special stains, other laboratory parameters, clinical & radiological findings and even patient's response to therapy. In 121 (28.9%) cases, histomorphology, special stains, other laboratory parameters and clinic-radiologic findings could not establish the cause of granulomatous inflammation, so, they were just labeled as granulomatous lesion.

In tuberculosis, ZN stain was done in 90 cases, out of which 10 cases were ZN positive (fig.2). Out of 258 cases of tuberculosis, lymph nodes were involved in 140 (54.26%) cases, followed by bone & joints (12.79%), respiratory system (5.42%), gastrointestinal system (4.65%) and female genital system (3.10%). Fungal elements were demonstrated

Table 2: Site wise distribution of granuloma

SN	Site of Granuloma	Number of Cases	Percentage
1	Lymph nodes	172	41.1
2	Skin and Subcutaneous	92	22.0
3	Bone and Joints	48	11.5
4	Respiratory System	32	7.7
5	Gastro-intestinal Tract	23	5.5
6	Female Genital System	10	2.4
7	Urinary System	10	2.4
8	Pericardium	9	2.2
9	Male Genital System	6	1.4
10	Eye and Ocular Adnexae	6	1.4
11	Omentum	4	1.0
12	Oral Cavity and Oropharynx	3	0.7
13	Breast	2	0.5
14	Brain	1	0.2
Total		418	100.0

in five cases with PAS stain, which was performed in 13 cases. Out of five cases, three were aspergilloma (fig.3) and two were sporotrichosis. Lung was the site of aspergilloma and skin revealed sporotrichosis.

The most common type of granuloma was epithelioid (83.5%), followed by epithelioid with suppuration and mixed inflammatory (fig.4). In 97.3% cases of tuberculosis, the granuloma was epithelioid type. However, fungal infection showed epithelioid granuloma with suppuration in 76.9% cases. Histiocytic granulomas were seen in fungal and parasitic infections, whereas mixed inflammatory granulomas were seen in parasitic infestation, tuberculosis, chalazion and leishmaniasis (Table4). Necrobiotic granulomas were not seen in this study.

DISCUSSION

Granulomatous is a distinctive pattern of chronic inflammation encountered in infectious and noninfectious conditions. In this study, granulomatous lesions were common in 3rd decade of life with slight male predominance and this finding corresponds to the finding of other studies.^{6,7} The commonest site was lymph node, followed by skin & subcutis, bone & joints, respiratory system and gastro-intestinal tract. In a study of Permi HS et al⁶ the most common site of granulomatous lesion was skin & subcutis.

Table 3: Causes of granuloma

SN	Causes of Granuloma	Number of Cases	Percentage
1	Tuberculosis	258	61.7
2	Fungal	13	3.1
3	Foreign Body	7	1.7
4	Parasites	3	.7
5	Toxoplasmosis	3	.7
6	Leprosy	2	.5
7	Sarcoidosis	2	.5
8	Cat-scratch diseases	2	.5
9	Crohn's Disease	2	.5
10	Leishmaniasis	2	.5
11	Tumors	1	.2
12	BCG Instillation	1	.2
13	Chalazion	1	.2
14	Unknown	121	28.9
Total		418	100.00

The most common cause of granuloma in this study and other studies was tuberculosis. However, the second most common cause is fungal in this study, whereas it is leprosy in study of Pawale JS et al⁷ and Permi HS et al⁶. Rare causes of granulomatous lesion in this study were chalazion, BCG-instillation, tumor-associated, leishmaniasis, Crohn's

Table 4: Types of granuloma and their causes

Causes of Granuloma	Diagnosis					Total (%)
	Epithelioid (%)	Epithelioid with Suppuration (%)	Histiocytic (%)	Foreign Body (%)	Mixed Inflammatory (%)	
Tuberculosis	251(97.3)	6 (2.3)	0	0	1 (0.4)	258(100)
Fungal	2 (15.4)	10 (76.9)	1 (7.7)	0	0	13 (100)
Foreign body	0	0	0	7 (100)	0	7 (100)
Parasites	0	0	1(33.3)	0	2 (66.7)	3 (100)
Toxoplasmosis	3 (100)	0	0	0	0	3 (100)
Cat-scratch diseases	0	2 (100)	0	0	0	2 (100)
Crohn's Disease	2 (100)	0	0	0	0	2 (100)
Leishmaniasis	0	1(50.0)	0	0	1 (50.0)	2 (100)
Leprosy	2(100)	0	0	0	0	2 (100)
Sarcoidosis	2 (100)	0	0	0	0	2 (100)
BCG Instillation	1 (100)	0	0	0	0	1 (100)
Chalazion	0	0	0	0	1 (100)	1 (100)
Tumors	1(100)	0	0	0	0	1 (100)
Unknown	85 (70.2)	11(9.1)	12 (9.9)	0	13 (10.7)	121 (100)
Total	349 (83.5)	30 (7.2)	14 (3.3)	7(1.7)	18 (4.3)	418 (100)

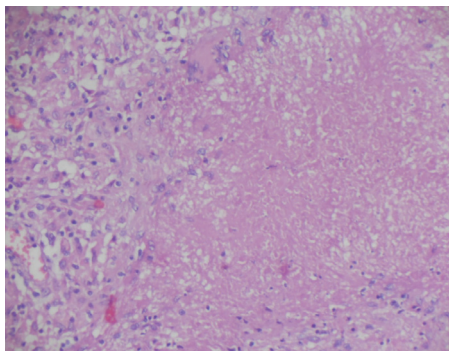


Figure 1: Caseating granulomatous inflammation of lymphnode; consistent with Tuberculosis (HE stain, X100).

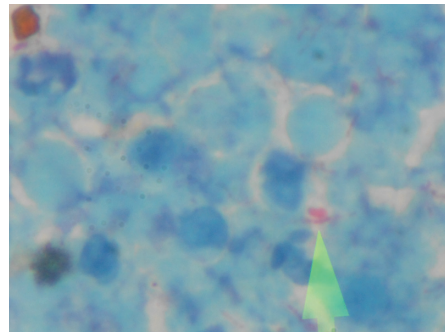


Figure 2: Focus of caseous necrosis showing mycobacterium tuberculosis (ZN stain, X1000).

disease and Cat-Scratch disease.

ZN stain demonstrated acid fast bacilli only in 11.11% cases in this study, whereas it was 20.74% in a study of Permi HS et al, 22.62% in a study of Pawale JS et al and 71% in a study of Krishnaswamy H et al.⁶⁻⁸ The low sensitivity of ZN stain may be due to technical reason. The most common fungal infection is aspergillosis, which is comparable to other studies. Parasitic granulomas were due to cysticercosis and hydatid cyst in this study. In these cases, in addition to granuloma, parasitic structures were demonstrated.

In this study, epithelioid granuloma was the most common type of granuloma, followed by epithelioid with suppuration, mixed inflammatory, histiocytic and foreign body granulomas. Similar to this study, epithelioid type granuloma was most common type in other studies.^{6,7} However, in contrast to this study, the second most common is either foreign body type or histiocytic type in these studies.

Epithelioid granulomas were seen in tuberculosis (97.3%), toxoplasmosis, fungal, Crohn's disease, leprosy, sarcoidosis, BCG-instillation and tumor associated. In our study, urothelial carcinoma of urinary bladder, testicular seminoma, Hodgkin lymphoma, mature cystic teratoma and adenocarcinoma of lung showed granulomatous inflammation. In a study of Permi HS et al, granulomas were seen in squamous cell carcinoma of skin, infiltrating ductal carcinoma of breast, papillary carcinoma of thyroid gland, dysgerminoma, Hodgkin lymphoma, seminoma, ameloblastoma and benign cystic teratoma.⁶ Tumor associated granulomatous reaction has largely been attributed to the cytokine milieu of the main tumor or the other cells of the background.⁹ Epithelioid granulomas with suppuration were seen in fungal infection (76.9%), tuberculosis, cat-scratch disease and leishmaniasis. Histiocytic granulomas were found in parasitic infestation and fungal infections. Foreign body granulomas were seen as a reaction to foreign body. The causes of mixed inflammatory granulomas were parasitic infestation, tuberculosis, leishmaniasis and chalazion.

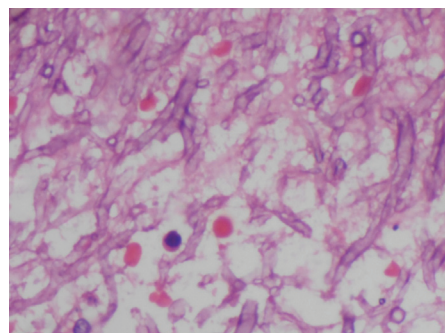


Figure 3: Clumps of dichotomously branching *Aspergillus* species in lung (HE stain, X400).

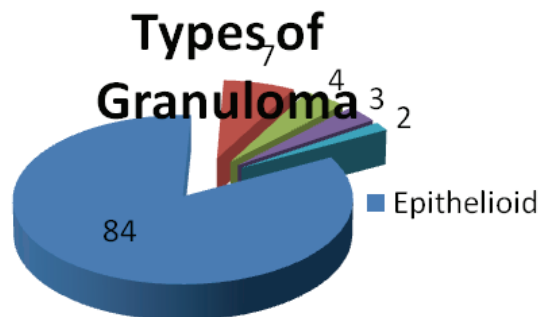


Figure 4: Types of Granuloma

Most of the epithelioid granulomas were necrotizing. As per study of Aubry MC et al⁵, the most common cause of necrotizing granulomatous inflammation is infectious and even with ancillary studies, cause of few necrotizing granulomas remain unexplained. Ulbright TM et al¹⁰ suggested that these cases represent infectious granuloma in which micro-organisms have been killed and/or removed by the inflammatory process. Alternative stains i.e. auramine / auramine-rhodamine using fluorescence technique¹¹, in-situ hybridization¹² and real-time polymerase chain reaction¹³ are useful tools to find the cause of granulomatous inflammation.

In significant number of cases (28.9%), the cause of granuloma was not known in this study. It may be due to

limited special stains and unavailability of PCR or ISH like techniques. The use of auramine / auramine-rhodamine using fluorescence technique, in-situ hybridization and real-time PCR may provide specific diagnosis.

CONCLUSION

The granulomatous lesion is common in third decade of life with slight male predominance. The commonest site is lymph node with tuberculosis being the most common cause and epithelioid being the most common type of granuloma.

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