

## A Retrospective Histopathological Study of Cutaneous Granulomatous Diseases at A Tertiary Dermatology Center in Kuwait

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### ABSTRACT

**Background:** Granulomatous inflammation is a common histological pattern observed in skin biopsy. Due to the overlapping histological features produced by different etiological agents, granulomatous inflammation poses a diagnostic problem for dermatopathologists. This study aimed to determine the frequency and histomorphological patterns of different granulomatous skin lesions in a tertiary dermatology center.

**Materials and Methods:** This is a retrospective observational study of all skin biopsies with granulomatous skin lesions received in the Department of Dermatopathology, As'ad Al-Hamad Dermatology Center, Kuwait, over five years from 2018 to 2022.

**Results:** Over the last five years, 77 patients were found to have a granulomatous reaction. It was common in females (53.2%), with most occurring in the second to fourth decades. Tuberculoid granulomas were the most frequent (45.5%), followed by xanthogranuloma (19.5%). One-third of the granuloma cases were due to infectious causes.

**Conclusion:** Granulomatous skin diseases are a heterogeneous group of conditions that mainly occur in females and have diverse clinical and histopathological presentations. Tuberculoid granuloma is the leading type in this study. The best method for identifying and classifying granulomatous skin lesions is histopathology in combination with special staining.

**Keywords:** Granulomatous inflammation; Histomorphological; Biopsy

## INTRODUCTION

Granulomatous lesions are a diverse group of illnesses characterized by the formation of granulomas in their histopathology<sup>[1]</sup>. The development of distinct granulomas consisting of clusters of epithelioid histiocytes, with a peripheral cuff of lymphocytes and plasma cells and, on rare occasions, a necrotic center, is a characteristic feature<sup>[2]</sup>. Dorland claims that Virchow first used the term "granulomatous" to describe a nodule or mass of granulation tissue that resembled a tumor<sup>[3]</sup>. This type IV, or delayed hypersensitivity reaction, is caused by both infections and in responses to poisons, medications, allergens, autoimmunity, and neoplasms<sup>[4]</sup>. The clinical differential diagnosis can be reduced by identifying and classifying the pattern of granulomatous inflammation. Geographical locations affect the prevalence and various types of granulomatous lesions<sup>[5]</sup>. This study aimed to determine the frequency and histomorphological patterns of different granulomatous skin lesions at a tertiary dermatology center.

## METHODS

A retrospective study of all skin biopsies of granulomatous skin lesions was performed at the Department of Dermatopathology, As'ad K. Al-Hamad Dermatological Center, Al-Sabah Health Area, Kuwait, from 2018 to 2022. The biopsy samples underwent routine tissue processing and section cutting. All cases were stained with H&E, and special stains were applied, as required. Histopathological diagnosis of skin biopsies was performed in our laboratory by a board-certified dermatopathologist. Only histopathologically confirmed cases of granulomatous skin lesions were included in the study. Data collected from the dermatopathology department records included age, gender, and histopathological types of granulomas. All slides were retrieved and examined for morphology. Foreign-body granulomas secondary to ruptured cysts, folliculitis, or suture materials were excluded. Cases of non-granulomatous dermatoses and inadequate samples were excluded from the study. Data were analyzed using the mean, standard deviation, frequency, and percentage, using SPSS version 22. Ethical approval was obtained from the institutional ethics committee before undertaking the study.

## RESULTS

In the 5 years involved in our study, a total of 2299 skin biopsies were evaluated in our Dermatopathology Department. Granulomatous skin lesions were identified in 85 cases, comprising 3.35% of the total. From these, 8 cases were excluded including granulomas secondary to a ruptured cyst, folliculitis, or suture material, leaving a total of 77 biopsies.

Among these 77 cases, 41 (53.2%) were women and 36 (46.8%) were men, with a female-to-male ratio of 1.14:1. Ages ranged from 0.5 to 83 years, with a mean age of 38.5 years and a median of 33.5 years. Maximum numbers of cases were found among the age group of 21 to 40 years (57.1%; n = 44)  $P < 0.0001$ . Age and gender distributions of the included patients are shown in (Table 1). The tuberculoid granulomas category was the most frequent (n=35, 45.5%), followed by xanthogranuloma (n = 15, 19.5%). The distribution of patients according to the different histopathological types of granulomas is shown in (Table 2).

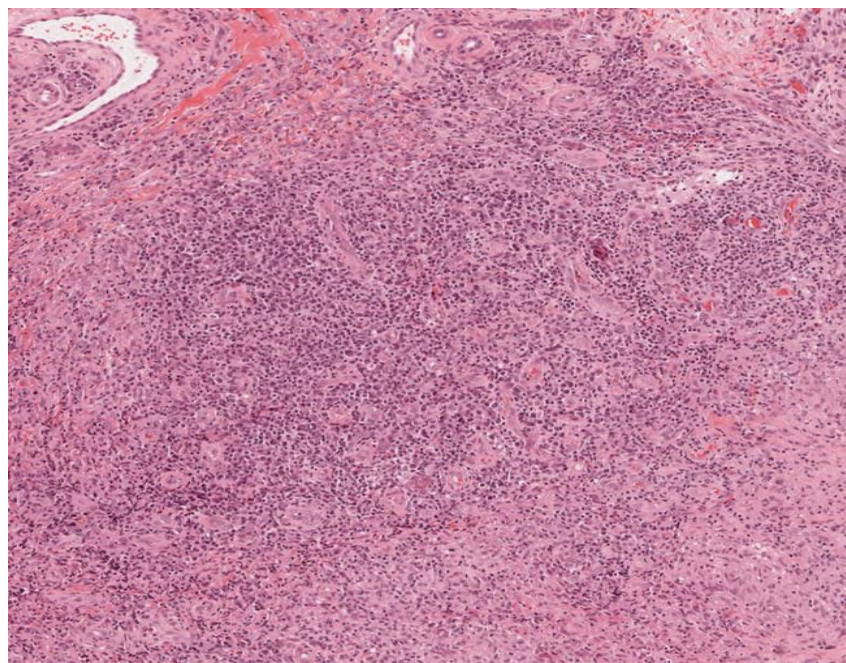
**Table 1:** Age and sex distributions of the patients included in the study

Age Group (Year-Old)	Female (n)	Female (%)	Male n	Male (%)	Total(n)	Total (%)
0.1–10	1	1.3	2	2.6	3	3.9
11–20	2	2.6	2	2.6	4	5.2
21–30	10	13	12	15.6	22	28.6
31–40	9	11.7	13	16.9	22	28.6
41–50	7	9.1	2	2.6	9	11.7
51–60	6	7.8	2	2.6	8	10.4
61–70	3	3.9	2	2.6	5	6.5
71–80	3	3.9	0	0	3	3.9
81–90	0	0	1	1.3	1	1.3
Total	41	53.2	36	46.8	77	100

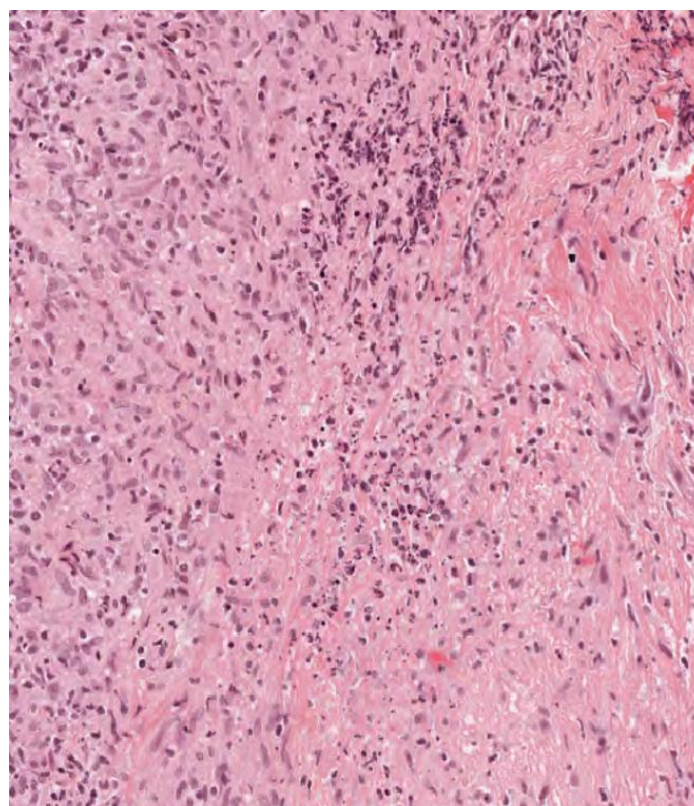
**Table 2:** Distribution of patients according to the type of granulomas observed

Histological Types	Female (n)	Female (%)	Male (n)	Male (%)	Total n	Total (%)
Tuberculoid	15	19.5	20	26	35	45.5
Xanthogranuloma	8	10.4	7	9.1	15	19.5
Necrobiotic	10	13	2	2.6	12	15.6
Suppurative	2	2.6	6	7.8	8	10.4
Sarcoidal	4	5.2	0	0	4	5.2
Foreign body	2	2.6	1	1.3	3	3.9
Total	41	53.2	36	46.8	77	100

In the group of tuberculoid granulomas, leprosy was the most frequent diagnosis (n = 12; 15.6%), followed by cutaneous leishmaniasis (**Figures 1&2**) (n = 11; 14.3%), granulomatous rosacea (n = 4; 5.2%), and erythema induratum (n = 1; 1.3%). Other nonspecific tuberculoid granulomas (n = 7; 9.1%). Among leprosy cases, lepromatous leprosy (**Figure 3**) predominated (n = 6, 7.8%), followed by tuberculoid leprosy (4 cases, 5.2%). The least common were indeterminate leprosy and borderline tuberculoid leprosy (1 case each, 1.3%). In the case of sarcoid granulomas, only cases of cutaneous Sarcoidosis (**Figure 4**) were detected (n = 4; 5.2%). In the group of necrobiotic granulomas, the most frequent etiology was granuloma annulares (**Figure 5**) (n = 10; 13%), followed by necrobiosis lipoidica (**Figure 6**) and necrobiotic xanthogranuloma (1 case each n = 1; 1.3%). Among xanthogranulomatous reactions (**Figure 7**), adult-type xanthogranuloma predominated (n = 11; 14.3%), followed by juvenile xanthogranuloma (n = 3; 3.9%), and lastly one case in reticulohistiocytoma (1.3%). The most common causes of suppurative granulomatous diseases were pyoderma gangrenosum (n = 4; 5.2%), followed by histoplasmosis (n = 1; 1.3%), and other nonspecific suppurative granulomas (N = 3; 3.9%).

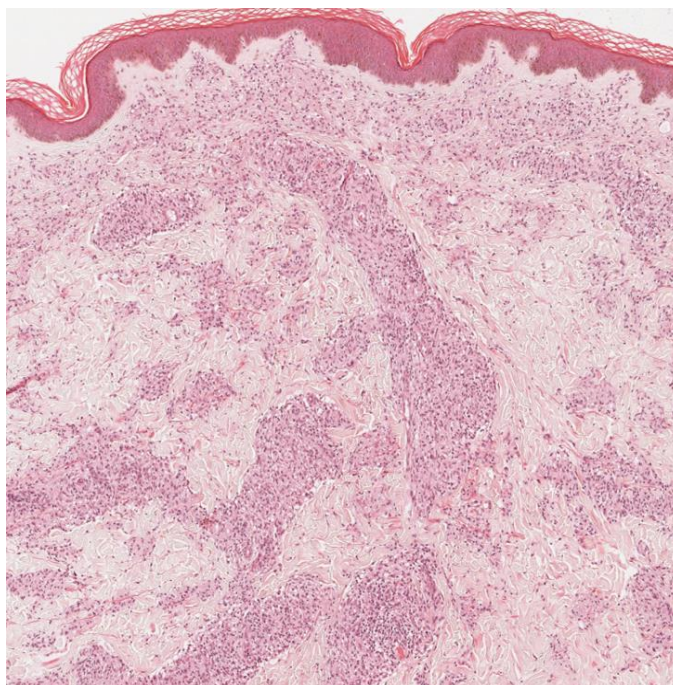


**Figure 1:** (Cutaneous leishmaniasis - H&E stain): Biopsy shows granulomatous dermatitis admixed with macrophages and lymphocytes, with the presence of multinucleated giant cells.

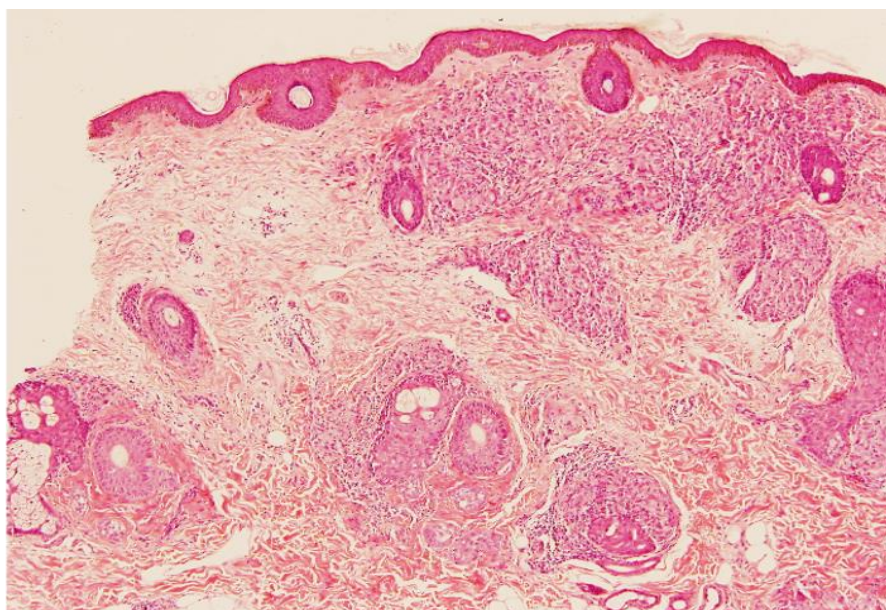


**Figure 2:** (Cutaneous leishmaniasis - H&E stain): Biopsy from the same patient shows macrophages contain tiny, uniform, round, hematoxylinophilic, intracytoplasmic organisms (amastigotes).

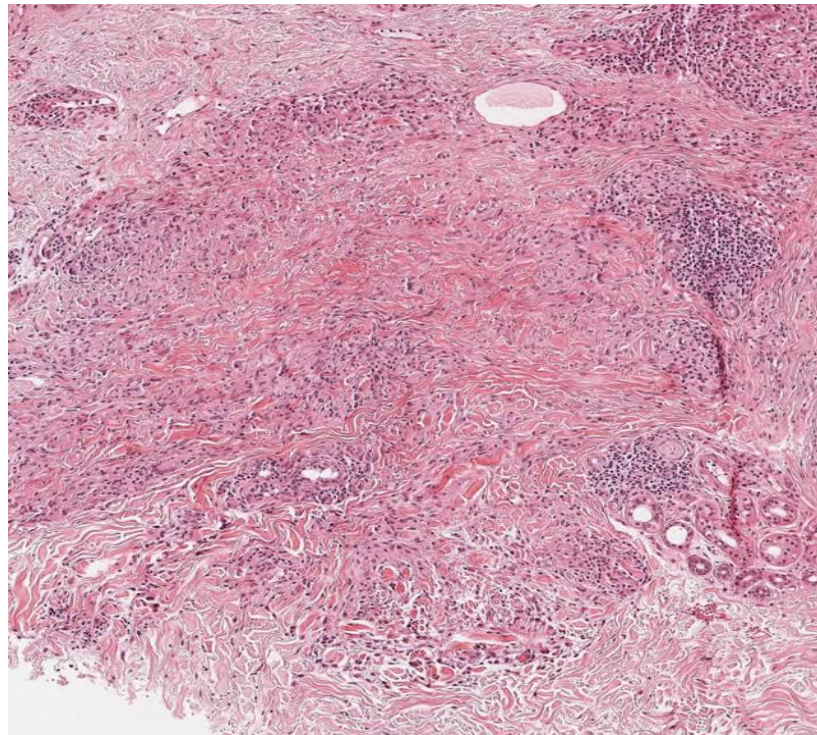




**Figure 3:** (Lepromatous leprosy - H&E stain): Biopsy shows broad band of diffuse granulomas, consisting of foamy histocytes admixed with plasma cells and few lymphocytes. The grenz zone separating epidermis from granuloma.

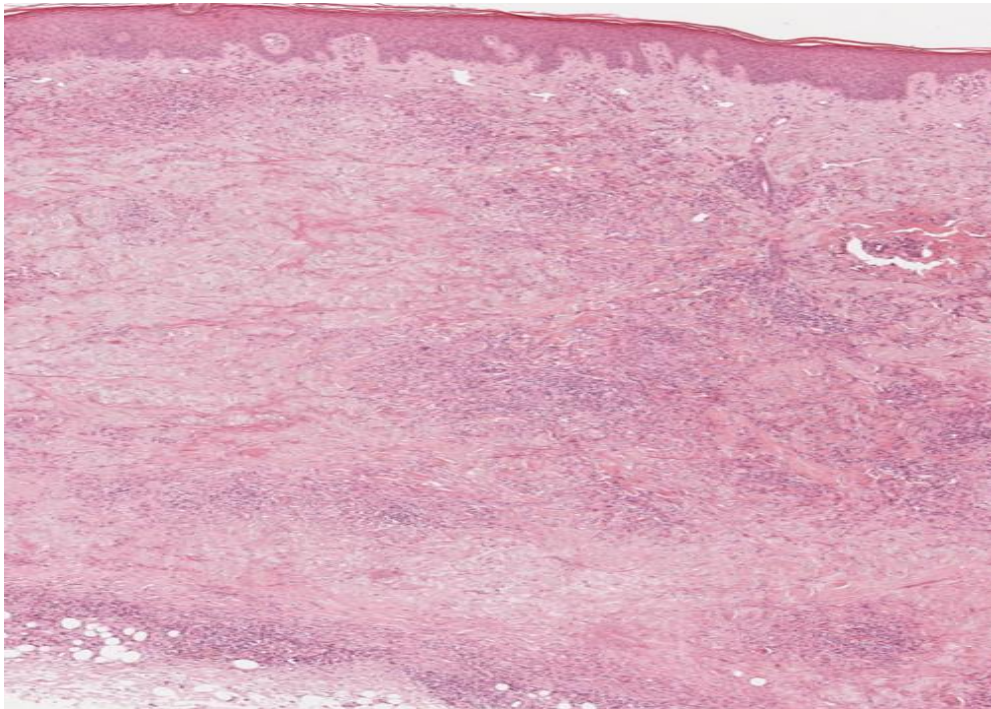


**Figure 4:** (Cutaneous sarcoidosis - H&E stain): Biopsy shows nodular sarcoidal granulomas scattered throughout the dermis, the granulomas are formed of epithelioid histocytes with a sparse number of lymphocytes)

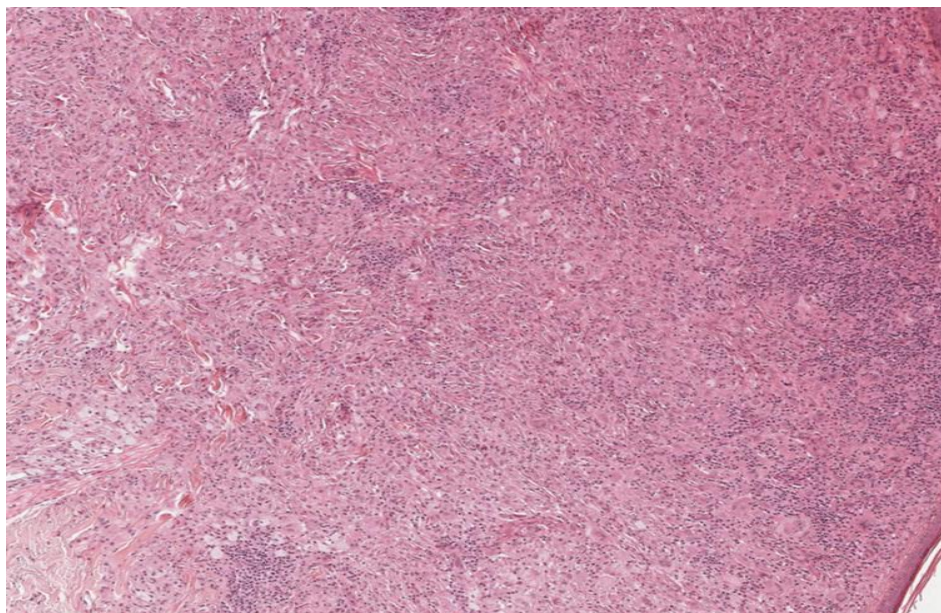


**Figure 5:** (Granuloma Annulare - H&E stain): Biopsy shows palisaded granulomas around areas of collagen necrobiosis. The granulomas are formed of epithelioid histocytes and multinucleated giant cells admixed with lymphocytes.





**Figure 6:** (Necrobiosis lipoidica diabetorum H&E stain): Biopsy shows diffuse palisading granuloma formed of epithelioid histocytes arranged in layers with degenerated collagen filling the whole dermis up to subcutaneous fat.



**Figure 7:** (Xanthogranuloma - H&E stain): Biopsy shows dense infiltrate filling the whole dermis that is formed of histocytes with foamy cytoplasm admixed with touton multinucleated giant cells.

During these 5 years, non-infectious granulomatous skin diseases represent approximately two-thirds of the cases and the most frequent types were granuloma annulare (N =10; 13%) and cutaneous sarcoidosis (N= 4; 5.2%). Both diagnoses were more frequent in women (N= 13; 16.9%). The mean age of patients presenting with granuloma annulare and cutaneous sarcoidosis was 41.8 years and 50.6 respectively. On the other hand, infectious pathology was observed in 31.2% of all cases, which included 12 cases of leprosy, 11 cases of cutaneous Leishmania, and 1 case of deep fungal infection. Corresponding to 24 patients with a male-to-female ratio representing 2.75:1. The mean age of this group was 35.4 years. Granulomas caused secondary to infectious diseases were higher among male patients than in female patients representing 73.3%, which was statically significant  $P < 0.05$ .

All the granulomatous skin lesions were correlated with clinical history, examination findings, and lab investigations.

## DISCUSSION

Granulomatous dermatitis has been a subject of interest since the early nineteenth century and remains so today. This disease presents a frequently encountered and interesting challenge in the routine clinical practice of dermatologists. The achievement of an accurate diagnosis is essential in order to administer appropriate therapy. To reach this accurate diagnosis, histopathology continues to be the gold standard diagnostic method.

In our study, the sex distribution pattern revealed that most patients were female (53.2%), which was approximately similar to another study (57.3%) [5] and (62%)<sup>[6]</sup>. Our results were different from other studies results that showed a male predominance (55.38%)<sup>[7]</sup> and (62.2%)<sup>[8]</sup>. The age distribution pattern revealed that the maximum number of granuloma cases was in the age range of 21-40 years, which was in concordance with another study<sup>[9]</sup>.

Tuberculoid granulomas were the most common type noticed in the study (45.5%), our results were in line with other studies conducted in Pakistan (92.7%)<sup>[5]</sup>, Nepal (43%)<sup>[10]</sup>, and India (67.7%)<sup>[7]</sup>. Leprosy disease predominated the tuberculoid granuloma category, our results were in concordance with other studies<sup>[5,7,10]</sup>. Studies conducted in Southern Asia, notably around India and Pakistan, showed the highest number of cases of tuberculoid granuloma, as the prevalence of leprosy remains high in this part of the world<sup>[11]</sup>. The majority of our patients with tuberculoid granulomas were from southern Aisha.

On histology, epithelioid histiocytes encircled by lymphocytes and plasma cells are seen in tuberculoid granulomas. Additionally, they are typically less circumscribed than the sarcoidal ones. Granuloma in tuberculoid leprosy is well-defined and usually distributed around nerves and blood vessels in the dermis and subcutaneous tissue. Tuberculoid leprosy cases can also be similar to non-caseating granulomas of tuberculosis and sarcoidosis<sup>[12]</sup>. Therefore, it is important to consider the clinical context and histology findings when making a diagnosis. For example, tuberculoid granulomas in the context of a history of leprosy are highly suggestive of leprosy disease.



In this study, cutaneous leishmaniasis represents 14.3% of all the cases. As the disease incidence varies in different tropical areas, our results were opposite to another study conducted in Pakistan that shows a higher incidence of cutaneous leishmaniasis (56 %) [13]. Histologically, the cases have macrophages containing *Leishmania donovani* (LD) bodies. The LD bodies were positive for Giemsa staining. One study showed that LD bodies could be identified in 50% of cutaneous leishmaniasis cases [14]. Detecting LD bodies in paraffin sections is usually difficult, but plasma cell infiltrates can suggest the diagnosis. Cutaneous leishmaniasis definitive diagnosis relies on the isolation of organisms either by smears and culture, or its identification in tissue sections [15].

Four cases of granulomatous rosacea having tuberculoid granulomatous pattern were identified in the study. Perifollicular granulomas have been observed and vascular dilatation is present in granulomatous rosacea. Our low incidence of granulomatous rosacea is similar to a study finding that showed only one case of granulomatous rosacea [5].

Sarcoidal granulomas were comprising 5.2% of the total cases, similar to other studies that showed a lower incidence 1.6% [5] and 2.7% [10]. On histology, sarcoidal granulomas are discrete, round to oval, and composed of epithelioid histiocytes and multinucleated giant cells. They are usually surrounded by a sparse rim of lymphocytes and plasma cells; hence, they are named as naked granulomas [16]. These are characteristics of sarcoidosis, although this should be a diagnosis of exclusion. Sarcoidal granulomas also appear in response to foreign materials such as silica and, in some cases, granulomatous cheilitis, and Crohn's disease [17]. All of our sarcoidal granulomas were confirmed to have sarcoidosis, and were female patients which is similar to a study conducted in India [7]. The initial diagnosis of sarcoidosis was made based on skin biopsy and further substantiated by radiological evidence of pulmonary involvement and mediastinal lymphadenopathy.

Granuloma annulare comprised 13% of the cases studied, and the majority of the patients were young females. Morphologically, all cases showed necrobiotic foci with palisading histiocytes with central mucin positive for Alcian blue, which was similar to another study [18].

In our study, xanthogranulomatous reaction represents 19.5% of the cases studied, our results were approximately in common with another study conducted in India [7]. Xanthogranulomas are composed of histiocytes with foamy cytoplasm, a variable number of inflammatory cells, and Touton giant cells. Touton giant cells are distinguished by a ring of nuclei encircling a homogeneous eosinophilic cytoplasmic center, with significant xanthomatization at the cell periphery [19]. In one study, these giant cells were observed in 85% of JXG [20].

In this study, suppurative granulomas comprised 10.4% of the cases. Another study conducted in Nepal showed a higher incidence reaching 23% of the cases due to predominating fungal diseases [10]. Our study showed only one case of fungal infection, namely Histoplasmosis. On histology, suppurative granulomas are collections of epithelioid histiocytes, which may include multinucleated giant cells, in the center of which are collections of

neutrophils. They are associated with infectious conditions such as deep fungal and mycobacterial infections<sup>[21]</sup>. Cutaneous histoplasmosis consists of a diffuse infiltrate of histiocytes that contain small uniform dots, these dots representing parasitized fungal organisms. The dots are typically uniformly distributed within the cells, which helps differentiate histoplasmosis from cutaneous leishmaniasis, which is also characterized by a diffuse histiocytic infiltrate containing similar-appearing parasitized organisms, but often randomly spaced or aligning the cell periphery.

Foreign body granulomas comprised 3.6% of the cases, similar to another study showing 2.8%<sup>[18]</sup>. However, the values were much higher in another study conducted in Nepal 12%<sup>[10]</sup>. Foreign body reactions typically cause the cyst wall to disintegrate and may promote pseudocarcinomatous growth in the remaining cyst walls.

## CONCLUSION

Granulomatous skin diseases are a heterogeneous group of conditions that mainly occur in females and have diverse histopathological presentations. Tuberculoid granuloma is the predominated type in this study. The best method for identifying and classifying granulomatous skin lesions is histopathology in combination with special staining.

## ACKNOWLEDGMENTS

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## STATEMENT OF ETHICS

The Kuwaiti Ministry of Health's Standing Committee for Coordination of Health and Medical Research granted the ethical approval number (2032-2022).

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare

## FUNDING

None

## AUTHOR CONTRIBUTIONS

All authors contributed equally to this study.

## DATA AVAILABILITY

Data supporting the findings of this study are available on request.

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