Evaluating the Unusual Histological Aspects of Granuloma Annulare: A Study of 30 Cases

Abstract

Background: Granuloma annulare (GA) is an uncommon dermatologic disorder that presents as annular, skin-colored to erythematous plaques. Histopathologically, it is characterized by palisaded histiocytic granulomas. A definitive diagnosis of GA is based on clinicopathologic correlation. **Objective:** The aim of this study was to study the histomorphologic spectrum of GA. **Materials and Methods:** A total of 30 cases reported as GA over 6 years (2012–2017) were retrieved. The detailed clinical profile and histomorphologic findings on the skin biospies were reviewed. **Results:** Majority of the cases (40%) presented in the 6th decade of life with a mean age of 48.3 ± 16.5 years and with a female predominance (77%). The lesions were localized in 22 cases (73%). Asymptomatic to erythematous, annular plaques was the most frequent presentation (60%). GA was not suspected clinically in two cases. Histopathologically, interstitial pattern of infiltrate was most common (44%), whereas granuloma formation and palisaded histiocytes were seen in 4 (13%) and 3 cases (10%), respectively. A mixed pattern was observed in 10 (33%) cases. Collagen degeneration was universal finding (100%) and presence of dermal mucin was noted in 24 cases (80%), both of which were important clues to the diagnosis of GA. Additional features such as presence of plasma cells, eosinophils, and vasculitis were noted in 10 (33%), 6 (20%), and 6 (20%) cases, respectively. **Conclusion:** The diagnosis of GA may be challenging owing to its diverse morphology. Acquaintance with the varied histomorphology of GA is of utmost importance to render a correct diagnosis and understand the pathogenesis.

Keywords: *Eosinophils, granuloma annulare, plasma cells, vasculitis*

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Introduction

Granuloma annulare (GA) is a noninfectious, granulomatous, self-limited dermatologic condition, first described by Colcott Fox in 1895.[1] Most of the patients present with asymptomatic, skin-colored to erythematous papular lesions in an annular configuration. Three forms of clinical presentation are most common: generalized GA, localized GA, and subcutaneous GA.[2] Lesser common clinical variants include perforating GA, palmoplantar GA, blascko-linear GA, pustular, and visceral GA.[3] Localized form of GA is the most common, with lesions limited to the extremities. Generalized form has been defined as involvement of trunk in addition to one or both the extremities.[4]

Establishment of a definitive diagnosis of GA is based on correlation of the clinical and histopathologic findings. Histopathologically, GA is categorized under the noninfectious granulomatous conditions of the skin.[2,5] The characteristic microscopic picture of GA consists of presence of histiocytes in either of the two patterns: palisaded histiocytic granulomas or interstitial pattern; along with dermal mucin, degenerated collagen and sometimes, multinucleated giant cells. Elastophagocytosis and eosinophilic cell infiltrate have been documented in various studies.[3] Vascular changes in the form of vessel wall thickening, vasculitis, fibrinoid necrosis, and vascular occlusion have also been reported in rare cases.[2,3]

Differential diagnoses of GA include other entities under noninfectious granulomas of the skin such as sarcoidosis, necrobiosis lipoidica (NBL), rheumatoid nodule, and interstitial granulomatous drug reaction.[2,5]

As the management of the patient and disease course in all these diseases differ widely, knowledge of the varied morphologic features is essential for

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institution of appropriate therapy. Although a lot of studies have been done on the clinical features, pathogenesis and management of GA, the literature is still scarce on its varied histomorphology, especially in the Indian subcontinent. This study, is therefore, aimed at discussing the spectrum of histomorphologic findings in GA.

Materials and Methods

All cases of GA diagnosed on histopathology over past 6 years (2012–2017) were analyzed. The clinical details of the patients were recorded from the biopsy request form. The slides were retrieved from the archive. In addition to routine hematoxylin and eosin (H and E) stain, all the cases were stained with alcian blue for demonstration of mucin. Special stains like Ziehl–Neelson (ZN) stain and Periodic acid Schiff (PAS) were done in all the cases to rule out infectious etiology. The biopsies were assessed for the following features:

- Pattern of infiltrate (interstitial/palisading/granulomatous/mixed)
- Depth of infiltrate (upper dermal/mid-dermal/pandermal)
- Presence of collagen degeneration
- Multinucleated giant cells
- Perivascular lymphomononuclear cell infiltrate
- Vascular changes
- Presence of dermal mucin (both on H and E-stained sections and on sections stained with alcian blue)
- Additional features such as presence of eosinophils and plasma cells and perivascular infiltrate. These cellular infiltrates were graded as mild (a few cells), severe (heavy infiltrate), and moderate (intermediate between the two) in a subjective manner.

All cases were reviewed separately by two dermatopathologists. In case of any dispute, a consensus was achieved by viewing the slides in multiheader microscope.

Results

Within this study period, a total of 32 cases were diagnosed as GA. Among these, slides and blocks of two cases could not be retrieved and were excluded from the study. Thus, a total of 30 cases were analyzed.

Most of the cases (40%) occurred in the 6th decade of life with a mean age of 48.3 ± 16.5 years (6–76 years). A female predominance was observed with female to male ratio of 2.7:1. There were two children in the study group (6 and 8 years), both with localized lesions on the leg. Most common presentation (60%) was asymptomatic, erythematous, annular plaques [Figure 1]. Papular and nodular forms of disease were seen in 10 (33%) and 2 (7%), patients respectively. The lesions were localized in 22 cases (73%), showing a predilection for the extremities (70%). Generalized disease was seen in 8 (27%) cases as shown in Table 1. Clinically, a diagnosis

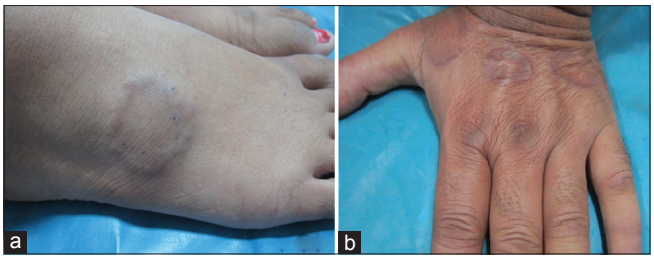

Figure 1: (a) Single skin-colored, annular plaque in a patient of granuloma annulare. (b) Multiple erythematous annular lesions on dorsum of hand

Table 1: Clinical features of granuloma annulare

Feature	Number of cases (%)
Site of involvement	
Localized	22 (73)
Generalized	08 (27)
Type of lesion	
Plaques	18 (60)
Papules	10 (33)
Nodule	02 (7)

of only GA was suspected in 16 cases (53%) but GA was considered as one of the differential diagnoses along with other possibilities in 12 cases (40%). In two cases (7%), GA was not considered clinically.

Histopathologically, an interstitial pattern of histiocytic infiltrate was most commonly observed (44%). Granulomatous pattern and palisaded histiocytes and were seen in 4 (13%) and 3 (10%) cases, respectively [Figure 2a and b]. A mixed pattern of infiltrate, comprising either interstitial with palisading or interstitial with granulomatous pattern was seen in 10 (33%) cases. The granulomas were loose and ill-defined, and of necrobiotic type (around central areas of altered collagen). No case featured a well formed, compact epithelioid cell granuloma. The infiltrate occupied upper and mid-dermis in most of the cases (60%). Pandermal extension of infiltrate was seen in 9 (30%) cases. Biopsies from both the children showed pandermal infiltrate with extension to subcutis. Presence of degenerated collagen was observed in all the 30 cases (100%) whereas 16 cases (53%) showed presence of dermal mucin on H and E staining, which appeared as basophilic stringy material between the collagen bundles [Figure 2c]. Alcian blue staining highlighted the dermal mucin, which identified dermal mucin in another eight cases, which could not be appreciated in H and E stained sections. Thus dermal mucin was present in 24 (80%) cases.

Perivascular lymphomononuclear cell inflammation was observed in all the cases, which was graded as mild (40%), moderate (47%), and heavy (13%). Multinucleated giant cells were found in 23 (77%) cases. The biopsies were also examined for the presence of eosinophils, plasma cells, and vasculitis. Presence of plasma cells was observed in 10 cases (33%) and graded as mild, moderate

and heavy in 5, 4, and 1 cases, respectively [Figure 2d]. Eosinophils were present in six cases (20%), with mild infiltrate seen in four cases, and moderate infiltrate in two cases [Figure 2e]. None of the cases showed heavy eosinophilic infiltration. Six of the 30 cases (20%) showed features of vasculitis [Figure 2f]. Small capillary-sized blood vessels in the upper as well as lower dermis were predominantly involved and showed infiltration of their wall with neutrophils and lymphocytes with extravasation of erythrocytes. Fibrinoid necrosis was less commonly observed.

Special stains performed to rule out differential diagnoses including infections (e.g., mycobacteria and fungi) were negative in all the cases.

The histopathologic findings have been summarized in Table 2.

Discussion

Onset of GA has been reported mostly in the first 3 decades of life in the literature.[6,7] In the present study, however, most of the cases presented in the 6th decade. A female preponderance with a female to male ratio of 2.7:1 was found in this study, similar to previous observations.[6-8] Clinically, a diagnosis of GA was suspected in 28 of 30 cases. In two cases, GA was not considered in the clinical differentials. The clinical diagnoses in these cases were sarcoidosis and erythema multiforme in the first case, and discoid lupus erythematosus, lichen planus, and photosensitive dermatitis in the other case. So a high index of suspicion by the pathologist is required to diagnose the cases with atypical clinical presentation.

Table 2: Histopathologic features

Histopathologic feature	Number of cases (%)
Pattern of infiltrate	
Interstitial	13 (44)
Granulomatous	04 (13)
Palisaded histiocytes	03 (10)
Mixed	10 (33)
Depth of infiltrate	
Upper dermis	03 (10)
Upper + mid-dermis	18 (60)
Pandermal	09 (30)
Degenerated collagen	30 (100)
Mucin	24 (80)
Perivascular infiltrate	
Mild (1+)	12 (40)
Moderate (2+)	14 (47)
Severe (3+)	04 (13)
Giant cells	23 (77)
Plasma cells	
Mild (1+)	05 (17)
Moderate (2+)	04 (13)
Heavy (3+)	01 (3)
Eosinophils	
Mild (1+)	04 (13)
Moderate (2+)	02 (7)
Heavy (3+)	Nil
Vasculitis	06 (20)

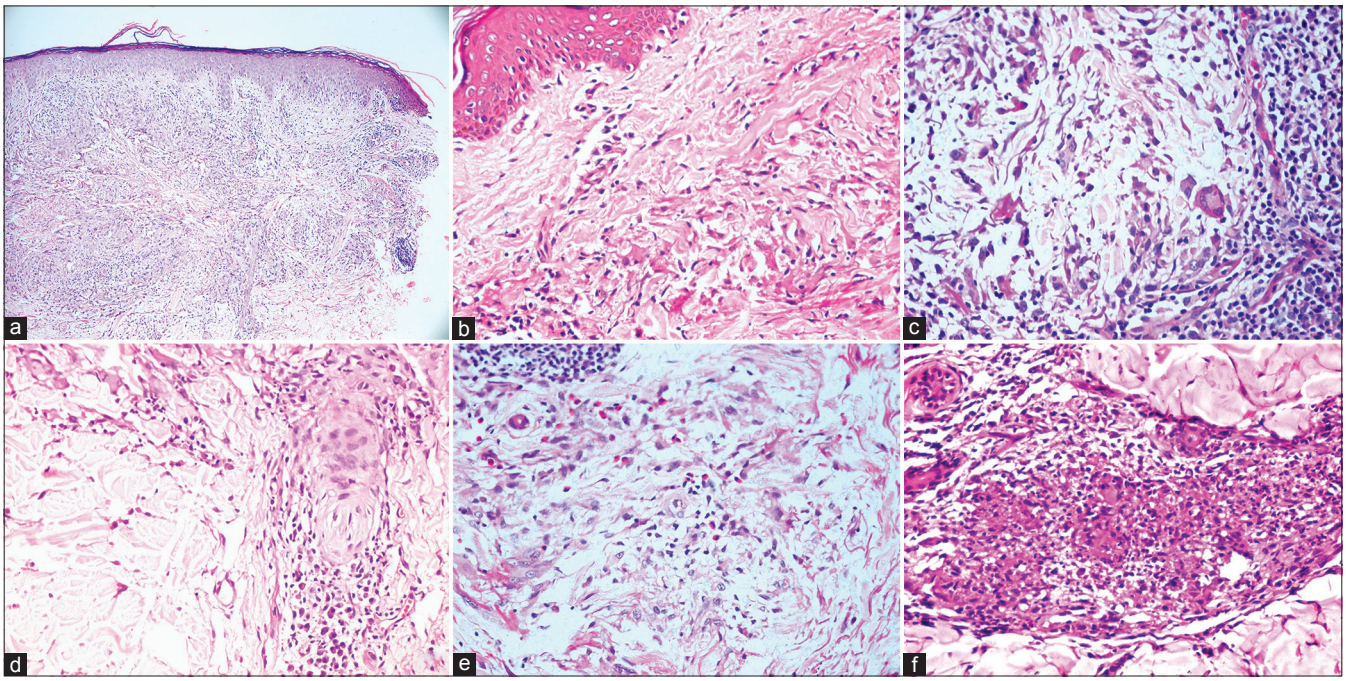

Figure 2: (a) Photomicrograph showing pandermal inflammation with lymphohistiocytic infiltrate and formation of granulomas. (H and E, ×40). (b) Altered collagen with palisaded histiocytes and presence of giant cells. (H and E, ×400). (c) Interstitial accumulation of mucin along with giant cells and palisaded histiocytes. (H and E, ×400). (d) Case of granuloma annulare with interstitial accumulation of plasma cells. (H and E, ×400). (e) Palisaded and interstitial infiltrate of histiocytes with prominence of eosinophils. (H and E, ×400). (f) Small vessel vasculitis in a case of granuloma annulare. (H and E, ×400)

On histopathologic examination, interstitial, palisading, and granulomatous are the various patterns of inflammation. The most common pattern of infiltrate in this study was interstitial (44%). In a large study conducted by Umbert *et al*. on 207 patients of GA, interstitial pattern was found in as many as 71% of the cases.[9] Cheng *et al*., however, found palisading histiocytes to be the predominant pattern of infiltration.[10] Although nomenclature of disease includes the word "granuloma", well-formed granulomas are rarely encountered in GA. Most of the cases show interstitial or palisaded pattern of histiocytic infiltrate around central area of altered collagen (necrobiotic granuloma). Thus, a pathologist should not discard the diagnosis of GA in the absence of well-formed granulomas. Presence of degenerated collagen was observed in all the 30 cases (100%) consistent with the findings in literature.[10,11] Dermal mucin was present in 24 (80%) cases, which has been found in other studies to be present in as much as 93% of the cases on application of special stains.[10] One should carefully examine for features like collagen alteration and mucin production, which provide vital diagnostic clue.

Most of the cases (60%) showed the infiltrate involving upper and mid-dermis with pandermal inflammation in nine cases (30%). Biopsies from two children included in the study showed pandermal infiltrate with extension to subcutis. Subcutaneous GA is seen exclusively in pediatric age group and is characterized by presence of firm, painless subcutaneous nodules predominantly on the extremities, which may either occur alone or in association with lesion in the dermis.[2] Stefenaki *et al*. studied the histologic pattern of GA in children and found subcutaneous extension of inflammation in 6 of 13 cases (46%).[12] Two pediatric cases included in this series showed pandermal infiltrate and did not qualify for subcutaneous GA.

The differential diagnosis of GA includes other granulomatous inflammation, such as NBL, sarcoidosis, rheumatoid nodule, palisaded neutrophilic granulomatous dermatitis, and various infectious dermatosis. In most of the cases, the diagnosis is straight forward, presence of collagen degeneration and stromal mucin deposition confirm the diagnosis.[13] However, diagnosis may be challenging in cases lacking mucin deposition. GA can closely resemble NBL histologically, however these two diseases differ in clinical presentation. Histologically, NBL shows predominantly lower dermal involvement as compared to upper dermal involvement in GA, and it lacks abundant mucin deposition. Rheumatoid nodule usually involves lower dermis and subcutaneous tissue. Histologically, it is characterized by central area of fibrinoid necrosis, surrounded by palisading histiocytes. Mucin deposition is extremely rare. It should be differentiated from subcutaneous GA. Sarcoidosis shows compact, well-formed granulomas, with minimal lymphoid infiltrate. Necrosis is unusual feature, but some cases of sarcoid can show presence of fibrinoid necrosis. A possibility of infectious granuloma should be carefully excluded in all cases using special stains such as ZN, PAS, etc.

A number of studies in the literature have found eosinophils in the cases of GA. The frequency (18–44%) and the extent of eosinophilic infiltrate is variable in different studies.[7,10,13-15] In this study, eosinophils were present in six cases (20%), all of which showed pandermal extension of inflammation. However, no association with a specific pattern of infiltrate was found. In a retrospective study conducted by Romero *et al.*, eosinophils were present in 66% (51/77) of the biopsies, more commonly associated with a palisaded pattern of infiltrate.[14] Cheng *et al.* found eosinophils to be more frequent in subcutaneous GA.[10] The presence of eosinophils in GA is known since long, most commonly attributed to inflammatory mediators released during granuloma formation. However, their role in the pathogenesis of the disease remains unexplained.[7,15,16]

Small-vessel vasculitis was observed in 20% of the cases in this study. In a study of GA by histopathology and immunofluorescence, Dahl *et al*. found vascular changes such as vessel wall necrosis, fibrinoid change, thickening, and occlusion in 33 of 38 GA patients (86%).[17] This, however, is an exceptional finding as no other study has reported such high frequency of vasculitis in GA. Chaitra *et al*. found vasculitis in 10% of the cases and postulated that collagen alteration and histocytic reaction in GA might be explained by the formation of micro infarcts in the dermis, as a consequence of vasculitis.[13] However, leukocytoclastic vasculitis was not detected in any of the cases by Gunes *et al.*, who, therefore suggested that pathogenesis of GA does not involve vascular changes.[18]

Presence of plasma cells was observed in 10 cases (33%). Only one study has previously observed the plasma cells to be present in two of seven cases (28.5%) of GA.[19] To the best of our knowledge, such a high percentage of cases of GA showing plasma cells has not been reported in the literature till date. The exact pathogenesis of plasma cells in GA is not clear. CD4+ T cells producing interleukin-2 have been thought to play a central role in the pathogenesis of GA.[20] The increased local production of interleukin-2 might also play an important role in the attraction of plasma cells. No correlation of plasma cell infiltrate with other findings like eosinophilic infiltrate and vasculitis was found in this study.

To conclude, the diagnosis of GA may be challenging because of its diverse clinical and histopathologic features. Pointers toward the correct diagnosis include presence of degenerated collagen and dermal mucin. Acquaintance with the varied histomorphology of GA is of utmost importance to render a correct diagnosis. One should carefully look for other histologic features like vasculitis and eosinophil and plasma cell infiltrate, as they can provide critical clue toward understanding the pathogenesis of this disease.

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Conflicts of interest

There are no conflicts of interest.

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