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Case Series

Rings on palms! Clinicopathologic features of 10 cases of palmar granuloma annulare

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ABSTRACT

Palmar granuloma annulare is a rare subtype of granuloma annulare (GA). It can occur along with lesions of granuloma annulare elsewhere or in isolation. However, isolated lesions occurring over the palms possess a diagnostic dilemma because many other cases share similar clinical features.
Therefore, histology is essential to arrive at a correct diagnosis.
Often, palmar GA lesions may lack the characteristic histologic features of palisading granulomas but have an interstitial pattern of inflammation.
Hence it is imperative to be aware with all the morphologic variants of GA in order to make a reliable diagnosis.

1. Introduction

Granuloma annulare (GA) is a common skin disease of undetermined aetiology. Pathogenesis is unknown, although several hypotheses were proposed with limited evidence. Most of them suggest a delayed-type hypersensitivity to an unknown source.[1,2]

Well-delineated subtypes of GA include localized GA, generalized GA and subcutaneous GA. Other rare variants include patch, perforating, pustular, palmar (PGA) and Acute-onset Painful Granuloma Annulare (AOPAGA).[3,4]

A palisading and interstitial infiltrate, typical of generalized GA, is observed on histopathology. GA lesions often resolve spontaneously, although topical corticosteroids have produced good results.[3,4]

Isolated palmar lesions with varied presentations can puzzle clinicians and require histopathology to make an accurate diagnosis. Studies correlating the clinical and histopathological findings of palmar GA are scarce in the literature. The incidence of palmar GA is unknown and probably underestimated, and we sought to identify the clinical features and histopathologic findings of palmar GA (PGA).

2. Case Series

This study was approved by the institutional ethics committee, and a retrospective study was conducted using the dermatopathology reports database from 2013 to 2020. The terms GA and palmar were used to search for patients aged ≥ 18 years. Clinical notes, laboratory data, pathology reports, and clinical images were obtained from the medical records department to confirm the diagnosis of palmar GA.

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Patients were included if they had a clinical diagnosis of palmar GA or GA involving the palms. A pathologist reviewed the histopathological slides. Ultimately, upon review of the histopathology for diagnostic confirmation, we included 10 cases of palmar GA in this study. Ancillary studies were performed using Alcian blue PAS(AB-PAS) and elastic Van Gieson (EVG) in all cases, and special stains such as Ziehl–Neelsen (ZN) staining were performed in cases where an infectious cause was suspected on hematoxylin and eosin (H&E). The evaluated parameters are listed in Table II. We used Microsoft Excel Software was used to tabulate all responses. Descriptive statistics were used to analyze the data.

3. Results

3.1. Clinical and histopathologic characteristics

The study included a total of ten patients with PGA, of which four were male and six were female. Their ages ranged from 40 to 75 years, with a mean was 57.5 years. Pain was the most common symptom in eight of the patients (: Summary of PGA cases). The most common morphological presentation were erythematous plaques 10(100%), of which 2(20%) had pseudovesiculation and 1(10%) had a targetoid appearance. The differential diagnoses suggested were pompholyx, erythema multiforme, secondary syphilis, sweet syndrome, and vasculitis. PGA diagnosis was not considered in eight of ten patients. Two out of ten patients were on treatment with oral hydroxychloroquine for RA, and one received oral corticosteroids for PGA and reported improvement. At the same time, the outcomes of the rest of the patients were unavailable.

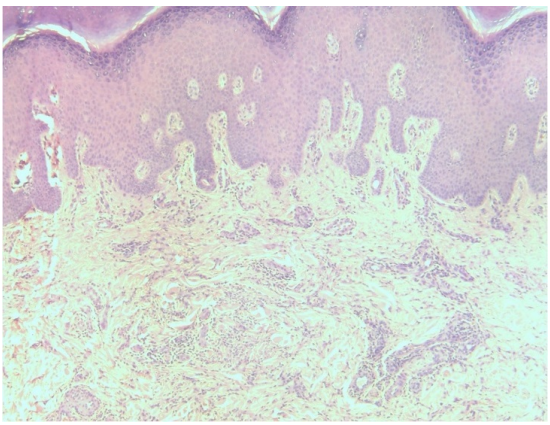

Figure 1: Perivascular and interstitial inflammatory infiltrate (H&E,x10)

We evaluated the histopathologic changes in all cases (Table 2). Epidermal changes observed were parakeratosis in 3 patients (30%), epidermal hyperplasia in 3(30%), and hypergranulosis in 2(20%). The perivascular inflammatory

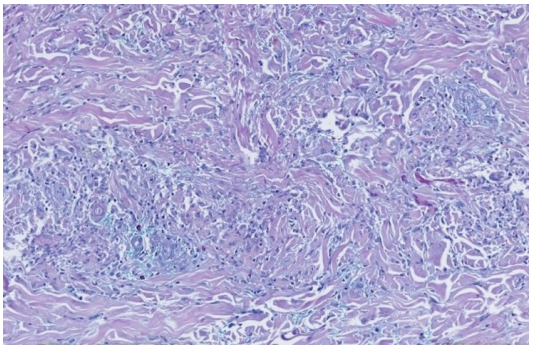

Figure 2: Shows increase in dermal mucin (ABPAS,x40)

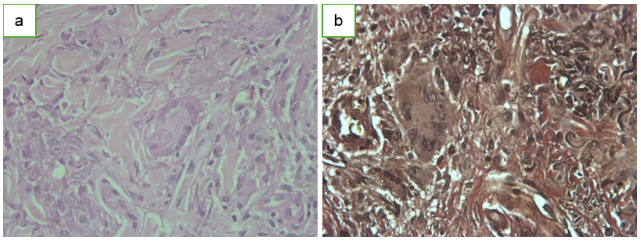

Figure 3: a: Shows elastophagocytosis within a multinucleate giant cell (H&E,x40); **b:** Shows elastophagocytosis and elastic fibre degeneration (EVG,x40)

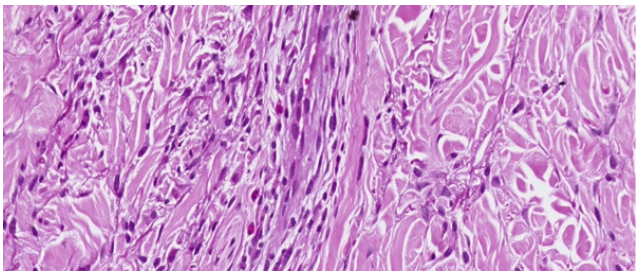

Figure 4: Mixed dermal inflammatory infiltrate with eosinophils (H&E,x40)

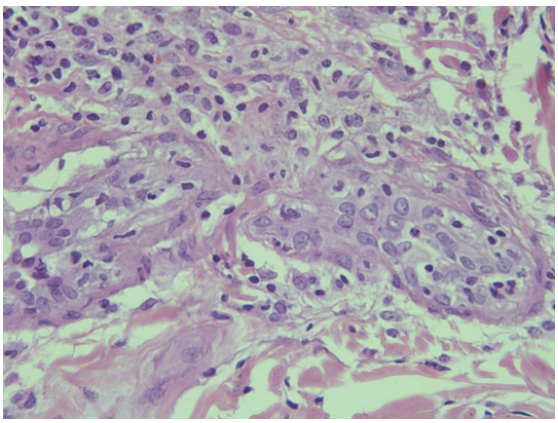

Figure 5: Shows vasculitis with endothelial swelling (H&E,x40)

Table 1: Summary of PGA cases

S.No.	Age	M/F	Symptoms	Comorbidities	Treatment taken	Outcome
1	75	M	Pain	DM	NA	NA
2	48	F	Pain	RA	Methotrexate given for RA	Improved
3	71	M	Pain	DM	NA	NA
4	71	M	Pain	DM	NA	NA
5	60	F	Nil	HT	Oral Prednisolone	NA
6	47	F	Nil	DM,HTN, PTB	Clobetasol propionate ointment	NA
7	53	F	Nil	Nil	NA	NA
8.	59	F	Pain	RA	NA	NA
9.	51	F	Pain	VDD, BP	NA	NA
10.	40	F	Pain	Nil	Oral prednisolone	Improvement

DM: Diabetes Mellitus HTN: Hypertension HT: Hypothyroidism
PTB: Pulmonary Tuberculosis RA: Rheumatoid arthritis VDD: Vitamin D Deficiency BP: Bell's Palsy

Table 2: Histopathological features assessed in palmar granuloma annulare

Feature Total: 10 cases		
Epidermal changes	Parakeratosis	3(30%)
	Epidermal hyperplasia	3(30%)
	Hypergranulosis	2(20%)
	Perforation	0(0%)
Dermal changes	Collagen thickening	10(100%)
	Solar elastosis	2(20%)
	Elastic fibre degeneration	3(30%)
	Elastophagocytosis	3(30%)
Inflammatory infiltrate	Mild	1(10%)
	Moderate	8(80%)
	Severe	1(10%)
Depth of infiltrate	Deep	3(30%)
Inflammatory cells	Lymphocytes	10(100%)
	Macrophages	10(100%)
	Eosinophils	2(20%)
	Plasma cells	1(10%)
	Neutrophils	2(20%)
	Multinucleated giant cells	8(80%)
Pattern of granuloma	Interstitial	6(60%)
	Mixed	3(30%)
	Classical palisading	1(10%)
Necrobiosis and Location	Superficial dermis	1 (10%)
Mucin deposits	Mild/moderate	9(90%)
	Abundant	1(10%)
Peri eccrine granuloma		1(10%)
Peri neural granuloma		0(0%)

infiltrates were moderate in eight (80%) cases, mild in one (10%), and severe in one (10%). Furthermore, the infiltrate extended into the subcutis in 1(10%). All 10 patients (100%) demonstrated collagen thickening. While elastic fiber degeneration was demonstrated using EVG, elastophagocytosis was seen in 3(30%) cases and solar elastosis was seen in 2(20%) cases. The interstitial pattern of infiltrate was seen in 6(60%) cases, followed by a mixed pattern that consisted of interstitial with granulomatous pattern in 3(30%) cases, and classic palisading pattern in 1(10%) case. Granulomas of tuberculoid or sarcoidal type were not observed. Mucin deposition was observed in all 10(100%) cases, abundant in 1/10 (10%), mild to moderate in 9 (90%), and necrobiosis in 1(10%) case. Endothelial swelling of the dermal vessels was observed in 1 case (10%).

4. Discussion

PGA is a rare form of localized GA of undetermined etiology, with only 3 case series and 8 case reports in the

literature. Our case series is the largest to date, with a clinical presentation similar to that of previous studies in the form of erythematous to skin-colored papules and plaques, with or without pseudo-vesiculation. However, perforating and keratotic papules were not seen.[5] Our patients were older with a female predominance, contrary to a male predominance seen by Gutte et al.[6] None of our patients had symptoms suggestive of AOPAGA[4] or simultaneous presence of sarcoidosis and malignant lymphoma.[7,8] PGA in our patients was more often observed in diabetics and hypertensives. Although the presence of GA with diabetes mellitus is well documented, the association between PGA and diabetes is sparse in the literature and remains to be proven.

In most cases, the infiltrate was interstitial (Figure 1). Therefore, it is essential to notice the interstitial arrangement of the infiltrate in doubtful cases of PGA lesions, because these are histologically not similar to the accepted form of the disease. This is supported by Ronen et al., who found that 71% of GA cases showed an interstitial pattern of infiltrate.[9] Furthermore, it is essential to identify this pattern because this variant can be misdiagnosed as normal skin on histology. Ronen et al. suggested the use of antibodies for CD163 to identify atrophic histiocytes.[9] It is also necessary to be aware of the mixed pattern of infiltrates observed that can occur infrequently in PGA.[6] Abundant dermal mucin is a hallmark of GA (Figure 2). Although mucin deposition was seen in all of our cases, it was mild in 90% of the cases and abundant in 10%. Similar findings were reported by Gutte et al.[6] It is said that the palisading pattern of inflammation represents the active phase of GA, with the deposition of abundant mucin. The interstitial form of GA corresponds to the burned-out phase of the disease with scant or absent mucin. This reiterates the fact that most of our cases had an interstitial pattern of inflammation, thereby having minimal mucin.[9,10] Therefore, the presence of mucin alone is not a reliable histopathological feature of GA. A consistent feature in most PGA's is necrobiosis, noted in only 10% of our cases situated in the superficial dermis. This feature helps differentiate GA from necrobiosis lipoidica (NBL), which presents with necrobiosis in the lower dermis, along with the presence of extracellular lipids and decreased mucin.

In our study, elastic fiber degeneration was observed in 30% of the cases. (Figure 3a and b), which is similar to the findings of Gutte et al. All PGA cases showed minimal epidermal changes;only 20% of our cases showed solar elastosis and elastophagocytosis, similar to Gutte et al.[9] This feature was earlier called annular elastolytic giant cell granuloma (AEGCG).[11] However, it is most likely not a separate entity, but granuloma annulare occurs in sun-exposed areas.[9] The presence of eosinophils is well-known in GA. We observed only 20% of the cases with eosinophilic infiltrate (Figure 4), with one extending into the subcutis, as noted by Gutte et al. Therefore, eosinophils are probably mere bystanders in the inflammatory process of GA, and are less helpful in differentiating GA from other disorders of granulomatous inflammation.[12]

The presence of vasculitis in the dermal blood vessels in GA is debatable, with Dahl et al. supporting this view and Thyresson et al. failing to demonstrate any[13] Similarly, in our case series, only 1(10%) patient demonstrated endothelial cell swelling (Figure 5) without any other features of vasculitis such as fibrin thrombi and extravasation of RBC, which corroborates the findings of Gutte et al.[9]

Similar to Gutte et al., perieccrine granulomata was also noted in 10% of patients who complained of pain over the affected lesions.[9] None of the samples showed changes in the vacuolar interface or lymphoid atypia, as reported in drug-induced PGA-like eruptions.

5. Conclusion

The present study had some limitations. First, we included only cases that were histopathologically diagnosed as PGA. Second, we did not propose an association between diabetes mellitus and PGA because the necessary investigations were not performed in all cases. Furthermore, our data were cross-sectional without follow-up; therefore, we cannot comment on the disease course and treatment outcome.

In summary, this study is relevant because it is the largest PGA case series compiled to date. We emphasize that the interstitial pattern of inflammation in PGA has an acceptable definition to prevent it from being easily missed.

6. Author Contributions

SB, AN, PJ and MT contributed to the design and implementation of the research, RT and AN to the analysis of the results and to the writing of the manuscript. SB conceived the original and supervised the project.

7. Source of Funding

None.

8. Conflict of Interest

None.

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