Dermatology Practical & Conceptual

Interstitial Granulomatous Dermatitis and Palisaded Neutrophilic Granulomatous Dermatitis: Retrospective Clinicopathological Analysis of 16 Cases

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ABSTRACT

Introduction: Reactive granulomatous dermatitis (RGD) is a new entity, which is highly associated with systemic disorders. There is scarce data regarding interstitial granulomatous dermatitis (IGD) and palisaded neutrophilic granulomatous dermatitis (PNGD).

Objectives: We aimed to evaluate clinical and histopathological characteristics of IGD and PNGD as unified entities under the term of RGD.

Methods: Observational, retrospective, single-center study of patients diagnosed with IGD and PNGD between 2012 and 2021 were included in the study.

Results: Of 16 patients (14 females and 2 males) with RGD, 13 had IGD and 3 had PNGD with a mean age of 62.5 years. The most common clinical presentation was plaques 37.5% (N=6), followed by patches 25% (N=4). The most common localization of involvement was lower extremity 75% (N=12), followed by trunk and upper extremity. Multiple localization of involvement was determined in 75% (N=12) of patients. None of the patients had rope sign. Associated comorbidities such as

autoimmune diseases and malignancies were detected in 68.7% (N=11) of patients. In majority of biopsies (87.5%; N=14), there were lymphohistiocytic cell infiltration. Other accompanying cells were scarce neutrophils 31.2% (N=5) and eosinophils 31.2% (N=5). All of the biopsies had interstitially located lymphohistiocytic cell infiltration surrounding with swollen and degenerated collagen. Palisaded pattern was determined in 18.7% (N=3) of patients and floating sign was seen in 18.7% (N=3) of biopsies.

Conclusions: RGD is a rare entity and most patients with RGD had associated disorders such as autoimmunity or malignancy. There is overlapping between IGD and PNGD, therefore supporting the usage of umbrella term as reactive granulomatous dermatitis is compatible with the literature.

Introduction

Interstitial granulomatous dermatitis (IGD) and palisaded neutrophilic granulomatous dermatitis (PNGD) are reactive granulomatous inflammatory skin disorders which were recently proposed to be unified under the term of reactive granulomatous dermatitis (RGD). They are highly associated with systemic disorders with only few and recent large patient population studies regarding the concept of RGD [1,2].

IGD and PNGD are uncommon clinicopathological entities with a wide spectrum of clinical manifestations, and also it can be difficult to establish clinical and pathological correlations of these diseases. IGD usually presents with erythematous to violaceous patches or plaques symmetrically located on the upper trunk or proximal limbs, and PNGD with plaques/papules/nodules sometimes painful with central ulceration or crust distributed on the extensor limbs [3,4]. Despite of initial reporting of classical presentation of IGD with rope sign (linear subcutaneous cords), it is seen rarely in the current reports [2].

Histopathologically a diffuse, interstitial and perivascular, superficial and deep inflammatory infiltrate composed mainly of lymphocytes and histiocytes surrounding foci of collagen degeneration in the dermis with a limited number of neutrophils and eosinophils have been determined. Scarce interstitial mucin deposition can be present. IGD usually does not have leukocytoclastic vasculitis (LV). On the other hand, despite overlapping histopathological findings with IGD, PNGD biopsies are characterized by more intense neutrophilic infiltration, karyorrhexis, more degenerated collagen in dermis, palisading granuloma with or without LV compared with IGD. Interstitial granulomatous drug reaction is also a form of IGD can mimic PNGD and IGD both clinically and histologically with prominent eosinophilic infiltration [2].

Associated comorbidities of RGD include autoimmune diseases (as the most common cause), malignancy and infections. It is reported in the literature that there are not any associated comorbidities at the time of the diagnose in up to 25% of patients however, concomitant disease may also occur after the diagnosis and so follow up is required [2,4].

Objectives

To analyze the clinicopathological findings and the disease associations of RGD.

Methods

We conducted an observational, retrospective study for clinical and histopathological analysis of 16 patients diagnosed with IGD and PNGD between the years 2012 and 2021 by searching the database of the Pathology and Dermatology Departments of a tertiary center. The study has been approved by the Institutional Review Board of the hospital.

Previously defined histopathological criteria, including presence of histiocytic and lymphocytic infiltration through the dermis and surrounding with foci of degenerated collagen was used in the current study [2]. The presence of a "floating sign" was noted, which is the visible clefting in abnormal collagen by the clusters of histiocytes. Mucin deposits should be absent or moderate. Patients who did not meet these criteria, and who had alternative diagnosis (necrobiosis lipoidica, granuloma annulare, interstitial granulomatous drug reaction) were excluded from the study.

For clinical analysis, sex, age at the diagnosis, localization, characteristics of the cutaneous lesions, associated symptoms, medical comorbidities, medication use, laboratory values and treatments were recorded.

Results

Clinical Findings

This study included 16 patients (14 females; 2 males, female:male ratio of 7:1) aged between 42 and 81 years (mean 62.5±11.1 years). Symptom duration ranged from 1 month to 30 months (mean 7.0 ± 8.3 months). The most common

presentation was isolated plaques 37.5%, followed by only patch 25%, papules and plaques in 12.5% patients, one patient with papule and one patient with macule, papule, purpura. "Rope sign" was not present in any of the patients. All lesions were violaceous and/or erythematous in color (Figure 1). Most common localization was lower extremity (mainly medial thigh region) 75%, followed by trunk 50%, upper extremity 43.7%. Multiple site involvement was seen in 75% of patients. One patient had face and neck involvement.

Mycosis fungoides (56.2%) was the most commonly differential diagnosis of IGD/PNGD. IGD/PNGD were among the pathological pre-diagnoses in only 25% of the patients. Associated autoimmune systemic disease or malignancy was observed in 12 patients (68.7%). Associated diseases of PNGD were autoimmune hepatitis in one patient, Sjögren syndrome in one patient, lung cancer and Churg Strauss syndrome in one patient. In a single patient IGD occurred as Wolf isotopic response after herpes zoster (Patient #13). Comorbidities of patients with IGD and PNGD were listed in Table 1. The drugs used by the patients for their associated diseases were listed in Table 1. All of these drugs were used by the patients for many years.

In 31.2% of patients there were no associated disease despite of clinical and laboratory evaluation for an underlying disorder; 12.5% of patients, had both ANA positivity and arthralgia. Rheumatoid factor (RF) positivity was seen in 18.7% of patients and C-ANCA was positive in a single patient. During the follow-up, one of the patients diagnosed with Sjogren syndrome and the other patient with history of thyroiditis was diagnosed with rheumatoid arthritis.

Patients with RGD were treated with topical corticosteroids and also underlying systemic diseases were treated. All the lesions resolved completely with topical therapy in about six months without recurrency in a mean of 39.8 month follow up. The clinical features of the 16 patients are summarized in Table 1.

Histopathological Findings

Epidermis was preserved in 82.7% of the biopsies. Others had hyperkeratosis, parakeratosis, acanthosis and mild increased pigmentation. In all biopsies, there were lymphohistiocytic cell infiltration. Other accompanying cells were scarce neutrophils (31.2%), eosinophils (31.2%) and plasmocytes (12.5%). All of the biopsies had interstitially located lymphohistiocytic cell infiltration surrounding with swollen and degenerated collagen. Palisaded pattern with combination of interstitial pattern was observed in 18.7% of patients. Floating sign was detected in 18.7% of biopsies. None of the biopsies had dermal fibrosis. Alcian blue staining demonstrated interstitial minimal mucin in 56% of the biopsies and moderate mucin in one case, remaining biopsies did not reveal mucin formation. Nuclear debris was seen in 31.2%, vasculitic changes such as fibrinoid

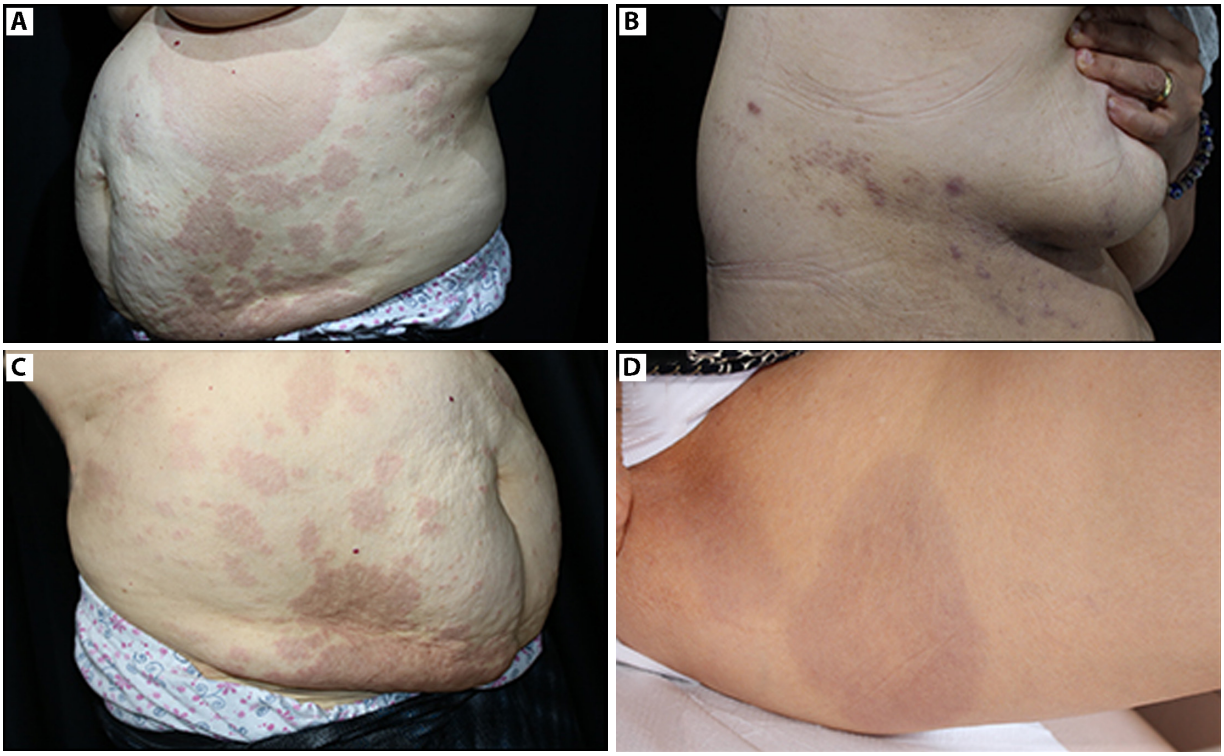

Figure 1. Some clinical presentations of the patients. (A) Erythematous papules and plaques on the anterolateral abdomen. (B) Violaceous papules extending from inframammary region to lateral trunk. (C) Violaceous macules on the arm. (D) Violaceous plaque on the inner thigh.

Table 1. Clinical features of 16 patients diagnosed with interstitial granulomatous dermatitis (IGD) and palisaded neutrophilic granulomatous dermatitis (PNGD).

Patient Nr.	Sex	Age (year)	Time to Lesion	Lesion Characteristics	Localization of Lesions	Associated Diseases/Drugs (if available)	Final diagnosis
1	F	77	2 mo	Erythematous plaques	Trunk, lower extremity	Hypertension (calcium channel blockers)	IGD
2	F	42	2 mo	Violaceous papules and plaques	Upper extremity	Rheumatoid arthritis (non-steroid anti-inflammatory drugs)	IGD
3	F	58	1,5 mo	Erythematous to violaceous papules and plaques	Face,neck, upper extremity	Autoimmune hepatitis (azathioprine)	PNGD
4	F	66	9 mo	Violaceous plaques	Trunk, lower extremity	Hypertension (thiazide diuretic+ angiotensin receptor blocker)	IGD
5	F	58	4 mo	Erythematous to violaceous plaques	Upper extremity, lower extremity	Thyroiditis, type 2 diabetes mellitus (levothyroxine)	IGD
6	F	58	24 mo	Violaceous macules, papules and petechies	Lower extremity	Sjögren syndrome	PNGD
7	F	58	6 mo	Violaceous plaques	Upper extremity, trunk, lower extremity	Tubulovillous adenoma with high dysplasia	IGD
8	F	81	12 mo	Erythematous plaques	Upper and lower extremity	Thyroiditis (levothyroxine)	IGD
9	F	71	3 mo	Erythematous patches	Trunk, lower extremity	Hypertension (thiazide diuretic+ angiotensin receptor blocker)	IGD
10	F	68	2 mo	Violaceous patches	Lower extremity	Hypertension (angiotensin-receptor blocker)	IGD
11	M	44	3 mo	Erythematous plaques	Upper extremity, trunk	Rheumatoid arthritis (colchicine)	IGD
12	F	58	30 mo	Erythematous patches	Trunk, lower extremity	Behçet disease (colchicine)	IGD
13	F	69	1 mo	Violaceous papules	Trunk	Rheumatoid arthritis	IGD
14	F	50	6 mo	Erythematous patches	Trunk, lower extremity	None	IGD
15	M	71	1 mo	Erythematous patches, plaques and nodules	Upper and lower extremity	Lung adenocarcinoma, Churg Strauss syndrome	PNGD
16	F	71	6 mo	Erythematous plaques and patches	Trunk, lower extremity	Thyroiditis, hypertension (levothyroxine, thiazide diuretic)	IGD

IGD = interstitial granulomatous dermatitis; mo = months; PNGD = palisaded neutrophilic granulomatous dermatitis.

necrosis was seen in 12.5%, leukocytoclasis in 12.5% of patients. Leukocytoclastic vasculitis was determined in 12.5% of patients. Histopathological information of the 16 biopsies is summarized in table 2 and some examples are shown in Figure 2.

Conclusions

RGD is an umbrella term for IGD and PNGD, which are rarely seen dermatosis with a wide clinical spectrum. IGD and PNGD have overlapping clinical and histopathological

Table 2. Histopathological features of 16 patients diagnosed with interstitial granulomatous dermatitis and palisaded neutrophilic granulomatous dermatitis.

Patient	Epidermal involvement	Lymphohistiocytic cell infiltration	Floating sign	Mucin	Palisading Pattern	Fibrinoid necrosis	Vasculitis	Leukocytoclasia	Nuclear Debris	Neutrophil	Eosinophil
1	+	+	-	minimal	-	-	-	-	-	-	-
2	-	+	-	minimal	-	-	-	-	+	+	+
3[a]	+	+	-	-	+	-	-	-	+	+	+
4	-	+	+	minimal	-	-	-	-	-	-	-
5	-	+	+	-	-	-	-	-	-	-	+
6[a]	-	+	-	-	+	-	-	-	+	-	-
7	-	+	-	minimal	-	-	-	-	-	-	-
8	-	+	-	minimal	-	-	-	-	-	-	-
9	-	+	-	-	-	-	-	-	-	-	-
10	-	+	-	moderate	-	-	-	-	-	-	-
11	-	+	-	minimal	-	+	+	+	+	+	+
12	-	+	+	-	-	-	-	-	-	+	-
13	-	+	-	-	-	-	-	-	-	-	-
14	-	+	-	minimal	-	-	-	-	-	-	-
15[a]	+	+	-	minimal	+	+	+	-	+	+	-
16	-	+	-	minimal	-	-	-	-	-	-	+

PNGD = palisaded neutrophilic granulomatous Dermatitis.[a]Patients with PNGD.

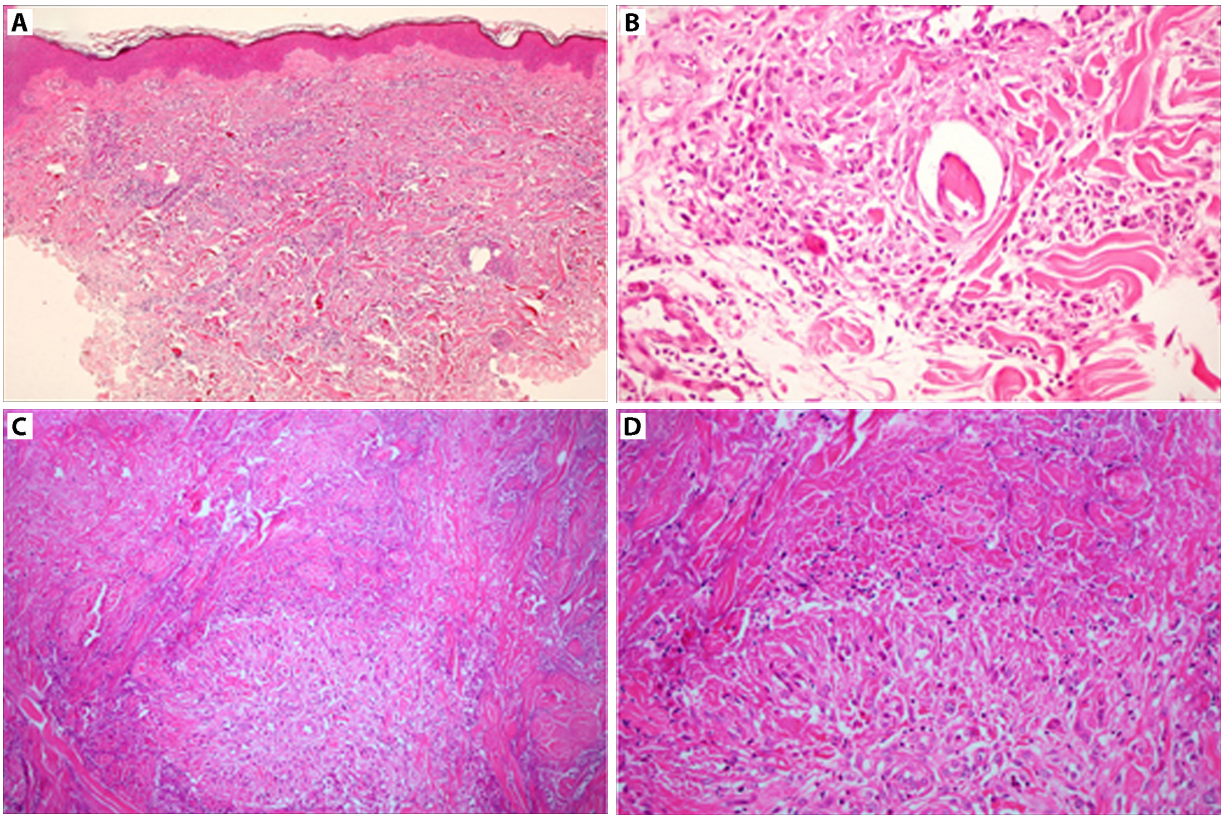

Figure 2. Some histopathological examination of the skin of patients. (A) Interstitial lymphohistiocytic infiltrate with collagen degeneration- interstitial granulomatous dermatitis subtype (H&E, ×100). (B) Collagen degeneration and "floating sign" with lymphohistiocytic infiltrate (H&E, ×200). (C) Palisading granulomas accompanied by neutrophils, lymphohistiocytic infiltration, collagen degeneration (H&E, ×200). (D) Palisading granulomas accompanied by neutrophils, lymphohistiocytic infiltration, collagen degeneration (H&E, ×400).

findings. Therefore, more extensive reports on these diseases are needed.

Reported clinical presentations of RGD in the previous studies are annular plaques, erythematous-violaceous papules or nodules [4,5], non-scaly annular plaques (similar to most of our patients) [4,6,7], linear-shaped plaques [8,9] and arciform-non scaly nodules [10]. Most of our patients presented with MF like, erythematous to violaceous plaques on the sun-protected sites such as axilla, lateral chest or inner thighs. Since RGD is a rare disease, this diagnosis can be underestimated by clinicians, thus in only 25% of the patients in our study, pre-diagnosis of IGD/PNGD was possible due to a wide spectrum of presentations. According to our results RGD should be considered in the differential diagnosis of plaque lesions on sun-protected areas. It has been reported that the rope sign is rarely seen in studies, similar to these studies, this finding was not found in any of the patients in our study, despite of initial reporting of classical presentation of IGD with rope sign [2].

Due to possible accompanying diseases, correct and early diagnosis of RGD is important. In our study, autoimmunity and/or malignancy (lung adenocarcinoma) were accompanied in all (100.0%) PNGD patients, in 7 of 13 (53.8%) patients with IGD had autoimmunity and 1 (7.7%) had malignancy (tubulovillous adenoma with high dysplasia). Neutrophilic infiltration was determined in all patients with palisading pattern and all of them were associated with autoimmunity or malignancy. However, we could not detect any clinical and/or histopathological data that can definitely distinguish between these two entities due to a small number of PNGD patients and overlapping features of IGD and PNGD. For this reason, the term proposed as RGD in the current studies will be appropriate.

Comorbidities associated with our patients were similar to the literature (60-76%) [1,2,4]. In one 69-year-old female patient with a history of herpes zoster, IGD developed in the same localization after one month. We evaluated this patient as Wolf's isotopic response. One patient with Wolf isotopic response was reported in the literature. This patient was an 11-year-old boy diagnosed with IGD possibly to herpes zoster [11]. Autoimmune hepatitis associated with IGD was previously reported [3,12,13]. In our series, the patient with

PNGD was accompanied by autoimmune hepatitis. In literature, other diseases which may accompany were autoimmune disorders such as; rheumatoid arthritis [3,4], systemic lupus erythematosus [1,3,4,16], autoimmune thyroiditis, primary biliary cirrhosis [7], malignancies such as hematological or solid cancers [14,15], infections such as HCV and related cryoglobulinemia [10], coccidiomycosis [17] or medications [4,5]. In 31.2% of patients, there were no associated autoimmunity or malignancy despite of clinical and laboratory evaluation for an underlying disorder. Due to high association with systemic disorders, follow-up of the patient for the possible development of autoimmunity or malignancy is important despite of having no associated features at time of diagnosis.

In addition to reported comorbidities, we had a patient with Behçet disease and IGD in our case series. When we search for the literature, Behçet's disease accompanies only two patients with PNGD [18,19]. Kim et al. reported a 32-year-old female with papular lesions on legs [18]. Shin et al. reported a 60-year-old female with also popular lesions on extremities, buttocks, and ear lobes [19]. In our study the patient with IGD and Behçet disease was 58-year-old female, and her lesions were erythematous patches on her trunk and legs.

Angiotensin receptor antagonists, thiazide diuretics, calcium channel blockers are thought to be associated with interstitial granulomatous drug reaction [3]. Like mentioned in methods, interstitial granulomatous drug reaction was excluded from the study. However, when the drugs used by the patients, especially the antihypertensive drugs were evaluated, they were not considered to be associated with IGD development in this study, as the duration of the drugs were more than four years in our study.

RGD is a rare clinicopathological entity. This is one of the larger case series presenting new disease associations. Since there is a high association with systemic disorders, follow up of patients is required. Due to overlapping features between IGD and PNGD, the term proposed as RGD in the current studies will be appropriate.

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