Dermatology Practical & Conceptual

Clinical and Histopathological Evaluation of Forty-one Cases of Pediatric Granuloma Annulare

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Key words: Granuloma annulare, asthma, histopathology, interstitial type, palisadic type

Citation: Koku Aksu AE, İlhan Erdil D, Manav Baş V, Büşra Türk C, Leblebici C, Tellal ES. Clinical and Histopathological Evaluation of Forty-one Cases of Pediatric Granuloma Annulare. *Dermatol Pract Concept.* 2023;13(1):e2023113. DOI: https://doi.org/10.5826/dpc.1301a113

Accepted: January 4, 2023; **Published:** January 2023

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

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ABSTRACT

Introduction: Granuloma annulare (GA) is a non-infectious granulomatous disease that can affect children and adults. Although many studies have been conducted in adult GA patients, the literature on pediatric GA cases is limited.

Objectives: Therefore, this study aimed to examine the demographic, clinical, and pathological features of pediatric GA cases.

Methods: This study was performed retrospectively in a single-center tertiary dermatology hospital. Demographic characteristics and clinical and histopathological features were recorded.

Results: Forty-one participants were included in this study, of which 66% were females. The mean age was 3.8 ± 2.6 years, and the mean lesion duration was 7.5 ± 10.3 months. The involvement of 78% of the patients was localized, and the remaining 22% was generalized. Asthma (30%) was the most common comorbid disease. Histopathological examination was performed on 21 patients, and the infiltrate pattern was interstitial in 71% of the cases and palisadic in 29%. Generalized distribution, trunk involvement, and concomitant disease tended to be higher in patients with an interstitial pattern than in those with a palisadic pattern.

Conclusions: Atopy and asthma should be questioned in pediatric GA cases. There are differences between involvement, distribution, concomitant disease, and histopathological patterns, which may indicate differences in pathogenesis.

Introduction

Granuloma annulare (GA) is a non-infectious granulomatous skin reaction with potential triggers that can affect adult and pediatric populations. The etiology of GA is unknown, but medication, infection, trauma, insect bites, and vaccination have been reported as triggering factors [1–3]. Solitary, erythematous, annular papules, and plaques are found predominantly in the acral regions. Histopathologically, collagen degeneration, mucin deposition, and lymphohistiocytic infiltrate are typically observed [4]. Diabetes mellitus, hyperlipidemia, and malignancy have been associated with adult GA [5–6].

Objectives

While there are many studies on clinical and pathological features and associated diseases in patients with adult GA, few studies have examined pediatric GA patients. Therefore, clinical and histopathological evaluations of pediatric GA cases were planned for our study.

Methods

This study was performed retrospectively in a single-center tertiary dermatology hospital in Istanbul. Ethical approval was obtained from the Clinical Research Ethics Committee of the Istanbul Training and Research Hospital on 11/03/2022 (2011-KAEK-50). Patients under the age of 18 years who were admitted to the dermatology outpatient clinic between 2008–2021 and diagnosed with GA were scanned from the hospital database and patient photograph archive. Cases with an uncertain diagnosis were excluded. Written informed consent was obtained from the parents of the patients participating in the study. Cases with dermatological findings recorded in detail and/or diagnosed histopathologically were included in the study. In total, 41 patients diagnosed with GA were included. Demographic features, lesion localization, lesion characteristics (size, elementary lesion, and color), involvement (localized/generalized), histopathological features, concomitant diseases, differential diagnoses in cases with histopathology, regression time, and recommended treatments were recorded. Missing data were questioned by calling the patients by phone. Age- and gender-matched patients of the pediatric outpatient clinic were included in the study as the control group to evaluate comorbidities.

Statistical analyses were performed using SPSS version 23.0. The conformity of the variables to the normal distribution was examined by histogram graphics and the Kolmogorov–Smirnov/Shapiro–Wilk tests. The mean, standard deviation, median, minimum, and maximum values were used when presenting the descriptive analyses. The Mann–Whitney U test was used when evaluating non-normally distributed (non-parametric) variables between the two groups. When presenting the categorical variables, the frequency and percentage values of the variables were used, and the analysis of the categorical variables was carried out using the chi-squared (exact) test. The Bonferroni multiple comparison test was used to investigate the reason for the significant differences between the groups. Cases with a P value below 0.05 were considered statistically significant.

Results

Forty-one participants were included in this study, 66% of which were females. Their mean age was 3.8 ± 2.6 years, and their mean lesion duration was 7.5 ± 10.3 months. Seventy-eight% of the patients had localized GA (LGA), while the remaining 22% had generalized GA (GGA) (Figure 1). The lower extremities were the most commonly affected area, and the most common type of lesion was the plaque type (79%). The mean size of the lesions was 3.8 ± 1.9 cm (Table 1). There was no statistically significant difference between clinical criteria and gender ($P > 0.05$). However, upper extremity involvement was significantly more common in patients with GGA compared to those with LGA ($P < 0.004$). No significant differences were found between GGA and LGA in terms of other parameters.

Information on the concomitant diseases was evaluated in 30 of the 41 cases. The evaluation found the following: accompanying disease (30.0%, N = 9), asthma (10.0%, N = 3), and one case each of atopic dermatitis, autoimmunity (type 1 diabetes mellitus, Hashimoto thyroiditis), congenital heart disease, pustular psoriasis, and thalassemia. In addition information on the concomitant disease was evaluated in 146 patients in the age- and gender-matched control group, which resulted in the following: asthma (3.4%, N = 5), hypothyroidism (1.4%, N = 2), atopic dermatitis (0.7%, N = 1), and plaque-type psoriasis (0.7%, N = 1).

The most common differential diagnoses in GA cases were sarcoidosis, tinea corporis, and erythema annulare centrifuge, respectively. Histopathological examination was performed on 21 patients (Table 2). The infiltrate pattern was interstitial in 71% of the cases and palisadic in 29% (Figures 2 and 3). Eosinophil infiltration was observed in 19% of the cases, and lymphohistiocytic infiltration was observed in 90%. Eosinophils were detected in the histopathological examinations of 4 patients, and in 2 of these cases the presence of concomitant asthma was also noted. Trunk involvement was detected in 5 (33%) out of 15 patients with an interstitial pattern, but it was not detected in any of the patients with the palisadic pattern. The difference was statistically significant ($P = 0.01$). All palisadic patterns (N = 6) were LGA, and 6 (40%) of those with interstitial patterns

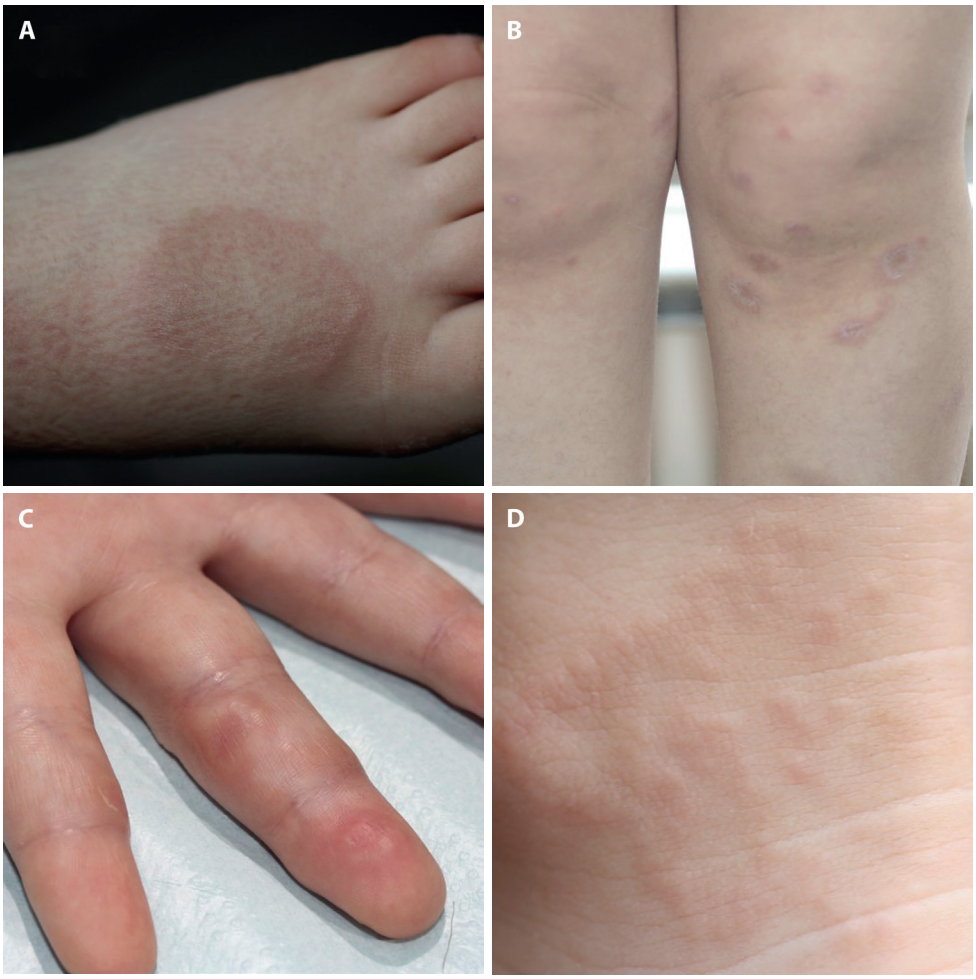

Figure 1. (A) Annular, peripherally raised, pale erythematous, 4 cm in diameter plaque on the dorsum of the left foot (B) Multiple, annular, erythematous plaque lesions around the knee. (C) Annular lesions on the finger. (D) Annular plaque formed by a combination of millimetric papules on the lateral malleolar region of the right foot.

showed GGA. However the difference was not statistically significant ($P > 0.05$). Concomitant disease was present in 5 (33%) out of 15 patients with the interstitial pattern, but it was not detected in any patients with the palisadic pattern.

All of the treated cases received a topical steroid, and the mean duration of the lesions after treatment was 6 ± 5.4 months. When 28 (68%) out of the 41 cases were reached by phone, complaints were still present in 14% (N = 4). The disease regressed in 86% of the cases within one year.

Conclusions

GA can be observed in pediatric and adult populations; however, there are limited data about demographic, clinical, and histopathological features and associated diseases in pediatric GA patients.

In this study, female predominance was evident (66%), similar to adult cases [7]. Notably, male predilection was apparent in two pediatric GA case series [8,9], and no gender difference was detected in another study [10]. Hyperlipidemia and diabetes have been found to be the most common comorbidities in adult GA [5,6]. In our study, unlike in adult GA case series, asthma was found to be the most common accompanying disease.

In our study, 10% of the patients with GA had asthma, a higher rate than the control group (3.4%). Additionally, 13% of the GA cases had atopy (atopic dermatitis and asthma). Previous research has reported even higher rates of atopy (up to 30%) in GA cases [9]. However, to the best of our knowledge, the relationship between pediatric GA and asthma has not been previously reported. The presence of asthma, which is a characteristic of atopic march, suggests that these patients should be evaluated for other atopic conditions such as atopic dermatitis, and allergic rhinitis.

The coexistence of GA and atopy may indicate a common pathogenesis. In recent years, it has been shown that in addition to T-helper 1 and T-helper 2 cell types, the Janus Kinase-Signal Transducer Transcription Activator (JAK-STAT)

Table 1. Descriptive statistics of demographic, clinical, and treatment features of pediatric granuloma annulare cases.

Characteristic			
Gender, N (%)	Girl	27	(66)
	Boy	14	(34)
Age, years, mean ± SD /median (min–max)		3.8 ± 2.6	3.00 (1.0–12.0)
Lesion duration, months, mean ± SD /median (min–max)		7.5 ± 10.4	4.00 (1.0–54.0)
Localization, N (%)	Upper extremity	14	(34.1)
	Lower extremity	30	(75.0)
	Trunk	7	(17.1)
	Gluteal	3	(7.3)
Elementary lesion, N (%)	Papule	5	(14.3)
	Nodule	1	(2.9)
	Patch	6	(17.6)
	Plaque	27	(79.4)
Color, N (%)	Light brown	1	(4.3)
	Brown	9	(39.1)
	Purple	1	(4.3)
	Pink	11	(47.8)
	Orange	1	(4.3)
Mean size of the lesions (cm), ± SD		3.9 ± 2.0	4.0 (1.0–7.0)
Involvement, N (%)	Localized	32	(78.1)
	Generalized	9	(21.9)
Concomitant disease, N (%)	Asthma	3	(10.0)
	Atopic dermatitis	1	(3.3)
	Congenital heart disease	1	(3.3)
	Thalassemia	1	(3.3)
	Pustular psoriasis	1	(3.3)
	Type 1 DM	1	(3.3)
	Hashimoto thyroiditis	1	(3.3)

DM = diabetes mellitus; SD = standard deviation.

pathway is involved in the pathogenesis of GA [11]. Treatment with JAK-STAT inhibitors resulted in the downregulation of cytokine levels and clinical improvement in GA [12]. In addition, topical JAK-STAT pathway inhibitor administration is clinically effective in the treatment of GA [13]. The pathway is also involved in the pathogenesis of atopy and asthma. Similarly, JAK-STAT pathway inhibitors have been effective in the treatment of atopic dermatitis and asthma [14,15]. JAK-STAT pathway is also related with eosinophils, in our study the presence of eosinophils in histopathological examinations was associated with an increased probability of concomitant asthma. Further studies on this subject may contribute to the understanding of GA pathogenesis.

Regarding histopathology, GA comprises granulomatous inflammation in a palisading or interstitial pattern accompanied by mucin. A palisading pattern comprises a central zone containing necrobiotic collagen surrounded by palisadic histiocytes, while an interstitial pattern comprises histiocytes localized to the papillary or middle dermis distributed between collagen fibers and blood vessels [16]. There is a paucicellular appearance, with minimal mucin traces in the interstitial pattern [17].

In this study, histopathological examination of 21 patients was performed. The histopathological pattern was palisading in 6 patients, while the remaining (N = 15 patients) showed interstitial pattern. Trunk involvement was detected in 5 (33%) out of 15 patients with an interstitial pattern, but it was not detected in any patients with a palisadic pattern. Another striking finding was that all of the palisadic patterns were LGA, and 6 (40%) of those with an interstitial pattern showed GGA. The concomitant disease was present in 5 (33%) out of 15 patients with an interstitial pattern, whereas none of the patients with a palisadic pattern had concomitant disease. As a result, trunk involvement, GGA,

Table 2. Descriptive statistics of histopathological features of pediatric granuloma annulare cases.

Histopathological features		N	%
Epidermal findings	Regular	14	(73.7)
	Hyperkeratosis, Acanthosis	1	(5.3)
	Hyperplasia	1	(5.3)
	Orthokeratosis, Acanthosis	1	(5.3)
	Pigmentation increase	2	(10.5)
Pattern of infiltrate	Interstitial	15	(71.4)
	Palisadic	6	(28.5)
Depth of infiltrate	Deep dermis	3	(17.6)
	Dermis	3	(17.6)
	Medium	2	(11.7)
	Middle and lower	1	(5.9)
	Medium and deep	5	(29.4)
	Upper and middle	2	(11.8)
	Superficial and deep	1	(5.9)
Collagen degeneration	Absent	0	(0.0)
	Present	21	(100.0)
Multinuclear giant cells	Absent	18	(90.0)
	Present	2	(10.0)
Mucin	Absent	1	(5.6)
	Present	17	(94.4)
Eosinophils	Absent	17	(80.9)
	Present	4	(19.1)
Lymphohistiocytic	Absent	2	(9.5)
	Present	19	(90.5)

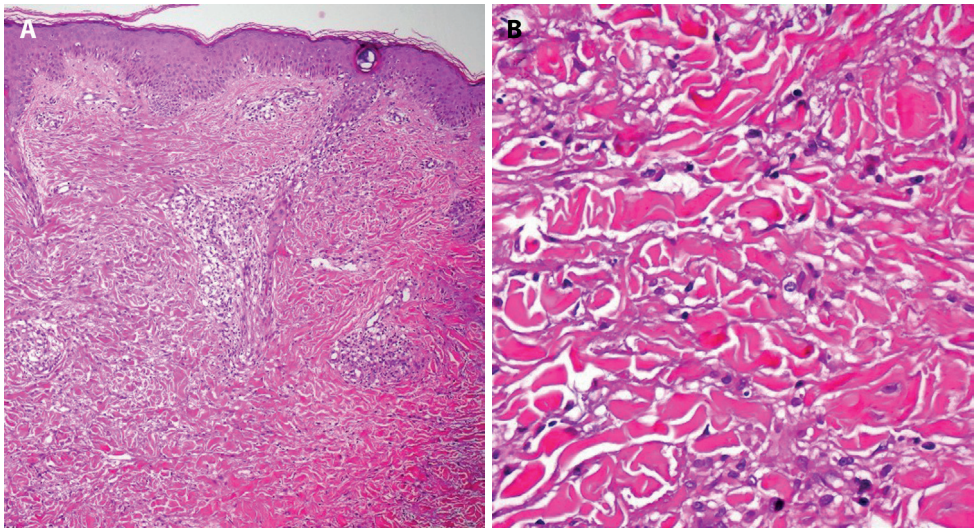

Figure 2. (A) Palisading granuloma with a necrobiotic center in dense dermal infiltration (H&E,x100). (B) histiocyte palisade around fragmented and partially granular collagen structures and sparse lymphocytes and karyorrhectic debris (H&E, x400).

and accompanying diseases were detected in the interstitial pattern in a ratio of approximately 30%–40%, while these features were not present in the palisadic pattern.

The differences found between the involvement, distribution, and concomitant disease in interstitial and palisading patterns of GA may indicate the possibility of different pathogenic mechanisms underlying these patterns. The palisading pattern may be induced by external factors, such as trauma or insect bites [1,18]. This may explain localized clinical involvement and a predilection for the extremities.

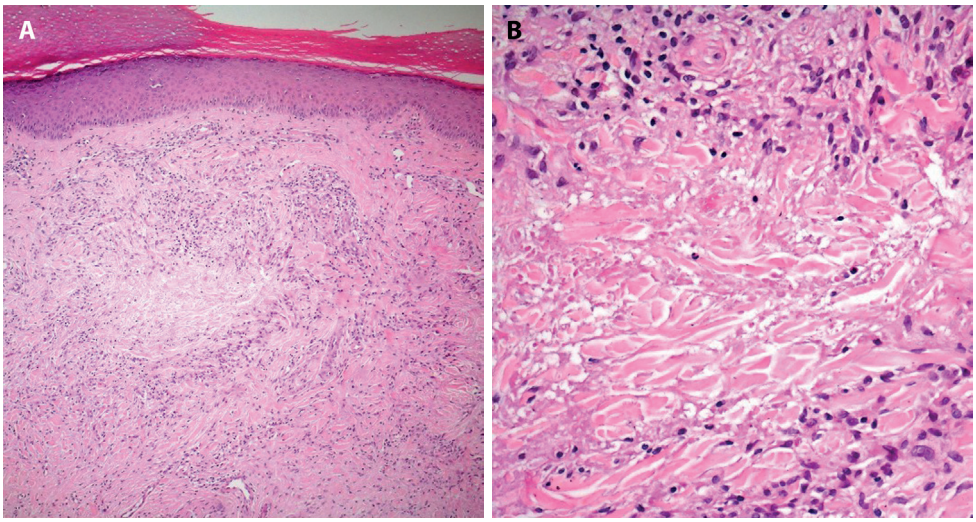

Figure 3. (A) Busy dermis with dermal infiltration at low magnification (H&E,1x00). (B) Histiocytic dissemination in the interstitial space between degenerated (thick/swollen) collagen fibers (H&E, x400).

Conversely, the concomitant disease ratio was higher in the interstitial pattern than in the palisadic pattern. Intrinsic stimuli in the immune system due to concomitant diseases may be related to the generalized clinical involvement and trunk localization detected in the interstitial pattern.

Pediatric GA cases can be followed-up without treatment. Topical corticosteroids are the most common option when treatment is preferred. In two previous studies on pediatric GA cases, most patients were managed without treatment, except for one case that received topical steroids. These studies observed complete regression in 92% of cases within the first two years [8,19]. In contrast, our study all patients received topical steroid treatment, and regression was observed in 86% of cases within a shorter timeframe (one year) compared to the previous literature. This difference in treatment approach and outcome may be related to the use of treatment in our study, compared to the management without treatment in the previous literature.

The etiology and pathogenesis of GA has not been clarified, and it is a clinical entity that requires further study. In pediatric GA cases, the data are even more limited than those for the adult population. This study contributes to the literature by reporting the presence of asthma in pediatric GA cases for the first time. The findings regarding histopathological involvement and clinical features may guide future studies. The limitations of the study are that it was conducted retrospectively (ie, there may be a lack of data), and the number of patients who underwent histopathology was relatively low.

In conclusion, atopy and asthma should be questioned in pediatric GA cases. There are differences between the involvement, distribution, concomitant disease, and histopathological patterns, which may indicate differences in pathogenesis.

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