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Clinical Characteristics, Histopathology and Treatment Outcomes of Granuloma Annulare: A Case Series Review of 15 Patients

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Abstract. Granuloma annulare (GA) is a benign, non-infectious granulomatous skin disorder of unknown etiology, typically presenting as annular or papular lesions. This review analyzes 15 English-language case reports published between 2014 and 2024, retrieved from PubMed, to summarize clinical features, histopathology, associated conditions, treatment responses, and outcomes. The series included 13 females and 2 males, aged 5–69 years (median 48.5 years), with 11 generalized, 3 localized, and 1 subcutaneous case. Lesions appeared as erythematous to skin-colored papules, plaques, or nodules; generalized forms showed widespread distribution, while localized cases were more confined. Histopathology consistently demonstrated palisading or interstitial granulomas, collagen degeneration, and mucin deposition in the dermis. Potential triggers included vaccinations (pneumococcal, SARS-CoV-2), infections, and trauma; comorbidities such as diabetes, dyslipidemia, hypertension, breast cancer, and autoimmune diseases were noted in several patients. Localized GA often resolved spontaneously or with topical/intralesional steroids within months and carried a better prognosis, whereas generalized cases frequently required phototherapy or systemic agents (e.g., dapsone, hydroxychloroquine, adalimumab) with variable success. Most patients improved or cleared, either spontaneously or with treatment.

Keywords: Granuloma annulare, Generalized Granuloma annulare, Case series

1. Introduction

Granuloma annulare (GA) is a harmless and non-infectious skin disease. It was first reported by Colcott-Fox in 1895 as a round rash on children's fingers, and Radcliffe-Crocker gave it the official name in 1905. GA can appear at any age. It is more common in children and young adults, but very rare in babies. More women have GA than men. GA usually shows as small skin-colored or dark-red bumps or ring-shaped skin areas. These skin problems usually do not cause pain, but they may affect how the skin looks.

We do not know the exact cause of GA. It may be a kind of slow immune reaction. It may be related to Th1 cells, macrophage activation, and the JAK-STAT pathway. Possible causes include infections, skin injury, medicines, and vaccines. Some studies say GA may be linked to other health

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problems such as type 1 diabetes, thyroid disease, high blood lipids, HIV, or cancer. But these links are still not sure, and many GA patients do not have other diseases.

There are several types of GA: localized, generalized, subcutaneous, perforating, and plaque. Localized GA often goes away by itself. It can disappear in a few months to two years. For example, one patient had localized GA on the knees and elbows, and it disappeared in 11 weeks [1]. Generalized GA is hard to treat and often comes back. In one case, a patient had GA on the neck, chest, and arms. It did not get better easily, and treatment caused side effects like stomach problems [2].

This study includes 15 GA patients. It tries to describe their clinical features, how they were diagnosed, how they responded to treatment, and the results. The study wants to help people know more about the different signs of GA and possible ways to treat it.

2. Methods

This essay presents an analysis of case reports retrieved from PubMed. The search used the keywords "granuloma annulare" in combination with "case series," "case report," "generalized," or "disseminated," and was restricted to English-language articles published between 2014 and 2024. Case reports were selected based on the completeness of clinical presentation and treatment outcomes. Ultimately, 15 cases of granuloma annulare were included: 11 generalized cases, 3 localized cases, and 1 subcutaneous case, representing the clinical heterogeneity of the disease as shown in table 1.

Table 1. Summary of demographic features, clinical subtypes, treatments and outcomes in 15 patients with granuloma annulare

Author	year	Country	Past medical history	Symptom	Diagnosis	Treatment and outcome
Jicha, Kaitlin I. et al. [1]	2023	USA	6-year-old girl, history of molluscum contagiosum (MC)	Symmetric, erythematous, annular plaques on elbows/knees.	GA-like reaction to inflamed MC.	Cantharidin for MC, triamcinolone for plaques. All resolved in 11 weeks.
Calado, Rita. et al. [2]	2023	Portugal	48-year-old woman, pruritic eruption	Skin-colored papules with "cobblestone" appearance on neck, chest, axilla, arms.	Biopsy: Interstitial GA with mucin. Verhoeff stain ruled out pseudoxanthoma elasticum.	Dapsone (intolerant). Started PUVA phototherapy with good response. Shows gastrointestinal intolerance as side effect.
García-Gil. et al. [3]	2021	Spain	57-year-old woman, 3-year GA history, hypertension	Firm erythematous-violaceous papules in annular pattern on abdomen & legs.	Biopsy: Chronic interstitial inflammation & necrobiosis. Triggers by 13-valent pneumococcal conjugate vaccine	Mometasone furoate cream ineffective. Lesions self-resolved within two months.

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Table 1. (continued)

Russo, Daniela. et al. [4]	2020	Italy	69-year-old woman, post SARS-CoV-2 vaccination	Reddish papules forming plaque at injection site, enlarged over 10 days.	Biopsy: Interstitial GA. Attributed to post-vaccination immunopathology.	Signs of resolution at 3-month follow-up.
Stefaniak, Aleksandra A. et al. [5]	2021	Poland	8-year-old boy, type 1 diabetes	First lesion on dorsum of right foot appeared 5 years prior, shortly after diabetes diagnosis.	Unique non-annular, unilateral morphology confined to right foot/calf.	Cryotherapy and mild topical corticosteroids partially effective (improved but did not resolve).
Clapé, Antoine. et al. [6]	2018	France	45-year-old woman, 4-month rash, DM, dyslipidemia	Widespread erythematous papules/plaques, fever, weight loss, polyarthritis.	Diffuse interstitial GA. Breast biopsy: invasive papillary carcinoma.	Breast cancer treatment initiated. GA outcome not specified.
Hyde, Jessica. et al. [7]	2021	USA	60s man, psoriasis, dyslipidemia, 3- week history of ankle joint pain	Non-pruritic targetoid plaques on trunk/limbs, preceded by fever, myalgia.	Biopsy: Interstitial histiocytic dermatitis. Triggered by Lyme disease.	Not mentioned.
Horoub, Yamen A. & Walker, Kelcie [8]	2024	USA	59-year-old woman, e-year GA history, hypertension	Lesions on upper/lower extremities & trunk, refractory to prior therapies.	Clinical & histopathological diagnosis of GA.	Adalimumab 40mg. Controlled within 2 years with continued improvement.
Saber, Maryam. et al. [9]	2021	Iran	51-year-old woman, breast cancer	1-month history of annular eruption of erythematous papules/plaques.	Lesional biopsy: lymphohistiocytic infiltration.	Topical corticosteroids and intralesional triamcinolone gave incomplete regression. Oral isotretinoin (intolerant). Ultimately no treatment.
Navea, Olivia Vega. et al. [10]	2023	Spain	66-year old woman, not past medical history recorded	Lesions on lower abdomen, buttocks, proximal thighs.	Clinical diagnosis, concomitant subtypes (macular & perforating).	Topical corticosteroids ineffective. Phototherapy (PUVA/PDT) noted as effective option.
Kaune, K. M. et al. [11]	2014	Germany	13-year-old girl, 16-month solitary nodule	Asymptomatic, slow-growing skin-colored nodule on thigh.	Initial biopsy suggested interstitial GA. Final diagnosis: Angiomatoid fibrous histiocytoma.	Surgical excision.
Abbas, Omar & Kurban, Mazen [12]	2014	Lebanon	5-year-old girl, 2-month history	Asymptomatic eruption on trunk and extremities	Punch biopsy: Granulomatous dermatitis with collagen degeneration & mucin deposition	No treatment. Resolved spontaneously after 11 months.

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Table 1. (continued)

Mohaghegh, Fatemeh. et al. [13]	2023	Iran	6-year-old girl, with alopecia areata	Lesions on soles/palms/face; patchy alopecia on scalp.	Clinical diagnosis of GA.	Alopecia treated with topical minoxidil/betamethasone & intralesional steroids. GA treatment not detailed.
Osman, Shireen & Traboulsi, Diala [14]	2023	USA	61-year-old woman, 20 year history of alopecia universalis (AU)	Rash on right thigh spreading to torso/legs over 18 months.	Biopsy: Palisaded granuloma with increased dermal mucin.	Hydroxychloroquine added to ongoing nbUVB for GA.
Wang, Hong. et al. [15]	2022	China	65-year-old woman, 4-year history, Sjogren's syndrome	Irregular annular plaques on trunk & lower limbs; dry eyes & mouth. Hypertension.	Skin biopsy: Granulomatous infiltration. Lab findings consistent with Sjogren's.	No treatment provided for GA.

Inclusion criteria were cases of granuloma annulare confirmed clinically or histopathologically, with reports providing information on patient demographics, clinical presentation, complications, treatment, and outcomes. Exclusion criteria included perforating cases or reports lacking essential details.

The extracted data included patient age, gender, subtype, lesion distribution, complications, treatment, and follow-up outcomes. All data were obtained from publicly available articles, so no ethical approval was required. The analysis focused on descriptive summaries rather than statistical testing.

3. Results

A total of 15 patients were included in this study. There were 13 women and 2 men. Their ages were from 5 to 69 years old. The middle age was 48.5 years old. Among these patients, 11 had generalized GA, 3 had localized GA, and 1 had subcutaneous GA. No patients had perforating GA. The time they had GA was from 11 weeks to three years. Many things can start GA. In this study, one patient got GA after the 13-valent pneumococcal conjugate vaccine [3]. Another patient may have got GA after the SARS-CoV-2 vaccine [4]. GA can appear with other health problems. In this study, six patients had other diseases: one had diabetes [5], two had dyslipidemia [6,7], two had high blood pressure [3,8], and one had breast cancer [9].

3.1. Clinical presentation

All patients had skin bumps or patches. These were skin-colored, red, or dark red. The shapes were mostly round or not regular. The skin surface was smooth. Generalized GA appeared on many parts of the body. Localized GA only appeared on one or two nearby areas. Subcutaneous GA was different. It usually was one skin-colored bump deep under the skin, and the skin surface looked normal.

Generalized GA had many different looks. It could be many hard red bumps in rings, or skin-colored bumps on both sides of the body. For example, in one serious case [8], big red bumps and dark red patches were on the patient's arms, legs, and body. In another case [10], red patches covered half of the lower stomach, hips, and upper legs.

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Localized GA only appeared in small areas as ring-shaped patches. These were dark red or skin-colored. One typical example [4] was one red patch only at the place where the patient got the SARS-CoV-2 vaccine on the arm. This is a common place after skin injury. Another case [5] was a child who had long-term bumps only on the top of the foot.

Subcutaneous GA was different from the other two types. It formed bumps deep in the skin, not near the surface. Only one patient in this study had it. It was one slow-growing bump on the left upper leg. The skin surface looked smooth and normal, but the bump was deep in the skin [9].

3.2. Histopathology examination

GA happens when certain skin cells called macrophages are activated in the wrong way. We do not know what starts this. These cells release things that hurt the collagen in the skin. They do not fight outside germs. This makes collagen break down. Then mucopolysaccharides fill the empty spaces. This is called mucin deposition.

Broken collagen and mucin cause the skin bumps and patches we can see. The broken collagen brings more immune cells. This keeps the inflammation going. Mucin makes the skin thicker and changes the normal skin structure. These changes cause more immune cells to gather. Small blood vessels become wider. This forms the bumps, patches, or nodules.

The type of GA depends on how strong and where the inflammation is. Generalized GA means the inflammation is strong and wide. Localized GA means the inflammation is small and in one area. Subcutaneous GA affects deep fat tissue. The inflammation can be in the upper skin, all over the skin, or deep in the skin. Each place causes different skin looks, like bumps, patches, or nodules.

All patients had a small skin test called punch biopsy. The results all showed granuloma in the middle and upper skin. Immune cells were around them. The middle part had broken collagen and mucin. This was shown by Alcian blue staining. These findings are typical for GA.

3.3. Treatment and follow up outcomes

Localized GA is easier to treat than generalized or subcutaneous GA. Skin problems can go away in three months to two years. Some patients got better without treatment. One adult with generalized GA got well in three months [4]. One child got well in 11 months [12]. Among patients who had treatment, one got well in 11 weeks [1]. Another needed two years [8]. Some patients had side effects, like stomach problems [2], but this was not common. No patients had the disease come back or long-term problems.

4. Discussion

Many things can affect how well GA is treated. Age is very important. Two children—one 6-year-old girl [1] and one 5-year-old girl [12]—got better by themselves quickly. This shows that children's immune systems work better. But older patients, especially women who are 50 or 60 years old and have had GA for a long time, often need long treatment or many different treatments. Sometimes they cannot get better completely. The type of GA also affects the result. Localized GA, especially when it is caused by vaccines, may get better by itself in a few months. But generalized and subcutaneous GA are harder to treat. They often need many different treatment ways. For example, a 66-year-old woman with generalized GA did not get better with corticosteroids [10]. Doctors had to change her treatment many times to find a way that worked. Other health problems, like diabetes and dyslipidemia, may make GA harder to treat. More women have long-term or

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complicated GA cases. But the current study does not have enough evidence to show that gender really makes a difference.

5. Conclusion

In short, GA is a relatively rare disease. There are many things we do not know about it, because it has many different causes and many different treatment ways. It can happen to people of all ages, which makes it harder to treat. Even though GA is not dangerous and does not cause death, we need to study it carefully and pay close attention to patients. This can help improve treatment results and make it more likely for the skin problems to go away.

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