Journal of Pakistan Association of Dermatologists. 2024;**34(4)**:938-946.

Original Article

Granuloma annulare as a leading mimicking granulomatous disease: Clinical and histopathological study in a series of 47 cases

Khalifa E Sharquie[1], Thamir A Kubaisi[2], Inas K Sharquie[3]

[1]Department of Dermatology, College of Medicine, University of Baghdad, Center of Dermatology, Medical City Teaching Hospital, Baghdad, Iraq.
[2]Department of Dermatology, College of Medicine, University of Anbar; Ramadi, Anbar, Iraq.
[3]Department of Microbiology & Immunology, College of Medicine, University of Baghdad, Baghdad, Iraq.

Abstract

Objective To do a full clinical and histopathological evaluation and to present the diverse clinical presentations of different patients to make everybody aware of how it is difficult to establish the right diagnosis in many instances.

Methods This is a cross-sectional descriptive study that was carried out during the period from 2014-2023 where all patients with granuloma annulare were described. All demographic features were reported. A full clinical history and examination were carried out. Biopsy for histopathological assessment was also done.

Results The data of forty-seven patients were analyzed and assessed. All patients were asymptomatic. The commonest sites affected were hands, forearms and trunk in symmetrical ways. To a lesser degree, three patients (6.38%) had penile involvement. Scalp was involved in one (2.12%) patient. The main histopathological picture was palisading granuloma but some patients had little inflammatory reaction while in one patient there was dermal necrobiotic degeneration with no inflammatory reaction.

Conclusion Granuloma annulare presented mainly with typical annular beaded lesions, which were generalized in 87.23%, localized in 8.51% and profundus in 4.25% that might have different clinical distribution. Although some patients had only one site affected like the penis and scalp. The histopathological picture was palisading granuloma. It might imitate many granulomatous diseases both in its clinical and histopathological pictures with many overlapping features but sarcoidosis remains the most important mimicking disease. Still, there is a vague activating triggering factors for GA.

Key words
Granuloma annulare; Granulomatous disease; Annular lesions; Profundus; Palisading granuloma.

Introduction

Granuloma annulare (GA) is a benign granulomatous skin disorder that typically presents as multiple papules grouped in an annular pattern. Typically ranges from skin color to red. There are numerous clinical variants including localized GA tends to involve children; generalized (subdivided into: generalized annular plaques and disseminated papular) that affects adults; perforating; and subcutaneous form.[1,2] There is a lack of large cohort studies assessing the incidence and prevalence of GA.[1,3] The etiology of GA remains unknown and there has been uncertain etiopathogenesis. However, based on the histological features, a delayed-type hypersensitivity reaction is favored.[2,4] Studies

suggest that interferon-gamma producing T helper 1 lymphocytes contribute to the activation of macrophages and subsequent inflammation and tissue destruction.[2]

Although the generalized GA may occur as an isolated cutaneous-limited disorder, numerous potential systemic conditions have been described, such as DM, malignancy, thyroid disease, rheumatoid arthritis, lipid abnormalities, HIV, hepatitis B, hepatitis C, BCG vaccination, and COVID-19. Recently, GA has been reported after receiving the COVID-19 vaccine, moreover, the disease may also be triggered by insect bites or trauma and herpes zoster.[5-11]

There are many clinical patterns of GA, and to get an exact diagnosis of GA, a skin biopsy is recommended for clinicopathological correlation. The differential diagnosis for GA is extensive and includes nummular eczema, psoriasis, sarcoidosis, necrobiosis lipoidica, interstitial granulomatous dermatitis, tinea, lupus, eruptive xanthomas, leprosy, verruca vulgaris, and granulomatous mycosis fungoides. It is important to differentiate subcutaneous lesions from panniculitis, sarcoidosis, rheumatoid nodules, and infection based on the clinical background.[12,13]

Histopathology plays a crucial role in diagnosing GA and the distinctive characteristics include dermal palisading granulomas with collagen degeneration at the center, the existence of mucin, and infiltration of lympho-histiocytes.[14] Histiocytes in GA can be detected in four different patterns: interstitial; palisading granulomas; nodule formation similar to sarcoidosis; and a combination of these patterns. Localized GA usually exhibits more prominent collagen necrosis compared to generalized GA. Perforating GA is distinguished from other variants by the expulsion of collagen through the epidermis.[15,16]

This present study is designed to illuminate full clinical and histopathological characteristics. Also, to present the diverse clinical presentations of different patients to make everybody aware of how it is difficult to establish the right diagnosis in many instances.

Methods

A cross-sectional descriptive study was carried out during the period from January 2014 to December 2023, at the outpatient dermatology unit at Baghdad Teaching Hospital, and a private clinic (KES), Baghdad, Iraq where all patients were diagnosed with granuloma annulare were described. A full clinical history and examination were carried out. Biopsy for histopathological assessment were also done. Recognized cases of GA were documented regarding age, sex, address, duration of the disease, history of drugs suspected to induce GA, site of involvement, distribution or number of the lesion (generalized >10 lesions or localized <10), and morphology.

Depending on the suitable clinical background and the basis of clinical suspicion, a detailed review of systems, risk factors and thorough physical examination, as well as mandatory additional investigations for underlying situations such as diabetes mellites, thyroid disease, malignancy, lipid abnormalities,

Manuscript: Received: October 06, 2023
Accepted: July 07, 2024
Address for correspondence
Professor Khalifa E Sharquie. Department of Dermatology, College of Medicine, University of Baghdad, Iraqi and Arab Board of Dermatology and Venereology, Center of Dermatology and Venereology, Baghdad Teaching Hospital, Medical City, Medical Collection Office, P.O. BOX 61080, Postal code 12114, Baghdad, Iraq.
Ph: 009647901468515
Email: ksharquieprof@yahoo.com

associated viral infection (HIV, hepatitis B &C), and rheumatoid arthritis were done when suspected. Also, all demographic features and histopathological assessments as GA granulomas on cutaneous biopsy were recorded.

Depending on clinical and histopathological findings, the other mimickers of granuloma include necrobiosis lipoidica diabeticorum, sarcoidosis, eruptive xanthomas, leprosy, granulomatous secondary syphilis, and granulomatous mycosis fungoides were fully examined, studied and omitted. Subcutaneous GA must be distinguished from panniculitis, sarcoidosis, and rheumatoid nodules; therefore, in clinically confusing states, the clinicopathological correlation is recommended. In an appropriate clinical setting, nummular eczema, psoriasis, tinea, lupus, and verruca vulgaris should be excluded. Patients or their parent consents were recorded regarding data or photo publication and no personal information is to be included in this study.

This research was permitted by the Ethical Committee at the College of Medicine, University of Anbar (Ref. No 155 dated December 25, 2023).

Results

Over 10 years, the data of forty-seven patients were analyzed and assessed, their ages ranged from 16-60 years with a mean of 32.8 years with 39(82.97%) females and 8(17.02%) males with a ratio of 4.87:1. All patients were asymptomatic. The mean duration of the disease was 5 (2-12) months. The three different clinical presentations were reported that include **(Table 1)**:

Generalized GA were detected in 41 (87.23%) patients aged more than 30 year, 11 (23.4%) cases with disseminated papular lesions while 30 (63.82%) patients presented with annular beaded granuloma lesions (**Figure 1,2**). The commonest sites affected were hands 16 (34.04%), forearms 12 (25.53%), trunk 10 (21.27%), frequently arranged symmetrically. While the feet, legs, face, arm, and neck were involved to a lesser extent. Four patients (8.51%) had penile involvement, three (6.38%) of them as part of

Table 1 Demographic data and clinical characteristics of patients with granuloma annulare. (n=47)

Data	*n (%)*
Females	39(82.97%)
Males	8(17.02%)
Age: *Bimodal*	
≥30 years	41(87.23%)
<30 years	6(12.76%)
Generalized. Two types:	**41(87.23%)**
Generalized annular beaded plaques	30(63.82%)
Disseminated papular	11(23.4%)
Sites of involvement	
The hands	16(34.04%)
Forearms	12(25.53%)
Trunk	10(21.27%)
Legs	5(10.63%)
Feet	5(10.63%)
Face	5(10.63%)
Arms	5(10.63%)
Neck	4(8.51%)
Penis	3(6.38%)
Scalp	1(2.12%)
Colors of lesion	
Red	16(34.04%)
Skin-colored	14(29.78%)
Violaceous	11(23.4%)
Localized GA	**4(8.51%)**
Sites of involvement and its features	
Scalp: Skin colored annular plaque & papules	1(2.12%)
Neck: Violaceus, plaques and papules& papules	1(2.12%)
Abdomen: Skin colored annular plaque& papules	1(2.12%)
Penis: Violaceus, single annular plaque& papules	1(2.12%)
Subcutaneous GA (profundus)	**2(4.25%)**
Sites of involvement and its features	
The feet and legs/ Deep nodular lesions	1(2.12%)
The hands/ Deep nodular lesions	1(2.12%)
The histopathological pictures	
Palisading granuloma	36(76.59%)
The interstitial variant	8(17.02%)
Mixed	3(6.38%)

Figure 1 A 30-years-old male patient with papular granuloma annulare.

Figure 2 A 47-years female with annular granuloma annulare of the back (A), A 43-years female showing typical granuloma annulare (B), A 45-years female showing granuloma annulare of the face (C&D).

Figure 3 A 30-years male with annular granuloma annulare of the penis (A), A 27-years-old male showing granuloma annulare of the scalp (B).

generalized annular GA, and another one, the penis was the only site involved. Scalp was involved in one (2.12%) patient **(Figure 3)**. Two (4.24%) patients had linear distribution affecting the forearm and leg in one and the right arm and chest in another patient. Also, one (2.12%) female patient presented with granuloma annulare following herpes zoster **(Figure 4)**.

Localized GA, the rash was described in four (8.51%) cases with a mean age was 21 (16-23) years. One (2.12%) patient for each involved one part including the scalp, penis, neck and abdomen. An encircled plaques and papules that gradually enlarged peripherally with involution at the center, so that grow outwards forming an annular ring. It is characterized by skin-colored or violaceous hue in 3(6.38%), and one (2.12%) case, respectively.

Subcutaneous GA so-called profundus which is characterized by asymptomatic multiple deep firm nodular lesions was reported in two (4.25%) young girls, one of them involved the

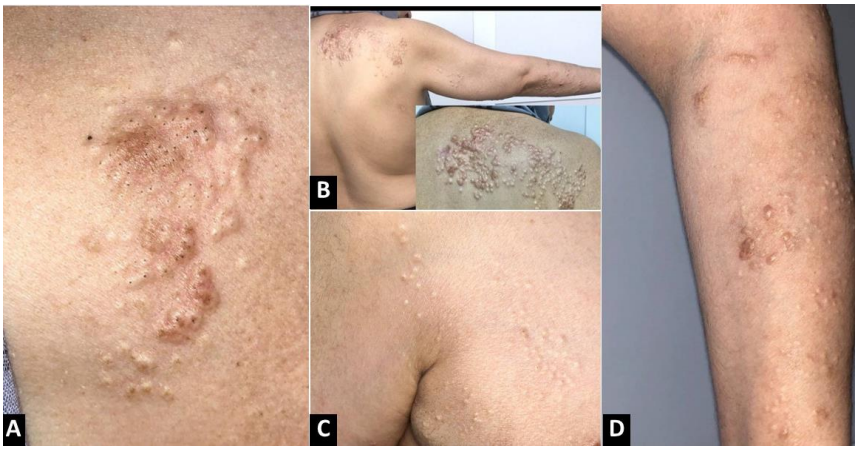

Figure 4 A 50-years-old female showing dermatomal granuloma annulare following herpes zoster rash. Papular lesions involving the back (A &B), the chest (C), and the forearm (D).

Figure 5 A 21-years-old male with profundus showing granuloma annulare involving the foot (A), and the leg (B).

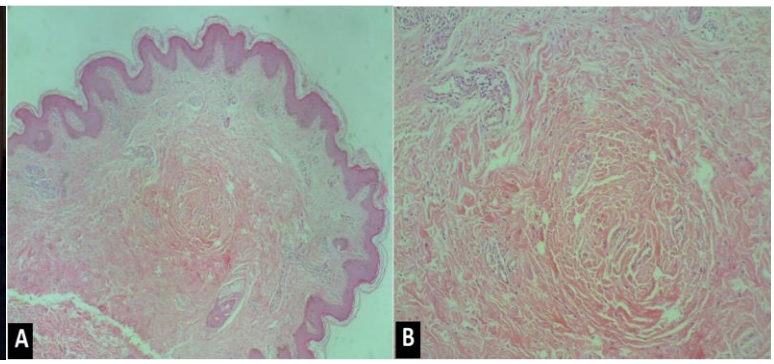

Figure 6 Early granuloma annulare showing palisading granuloma with necrobiotic mass and altered collagen. (Hematoxylin and eosin: A, X10; B, X 40).

feet and legs, while the hands were affected in another patient without joint pain **(Figure 5)**. The histopathological pictures in 36 (76.59%) cases were characterized by palisading granuloma but nearly 5 (10.63%) patients had a little inflammatory lymphohistiocytic reaction that frequently surrounds a focal area of collagen degeneration and mucin deposition. In one patient, there was dermal necrobiotic degeneration with no inflammatory reaction **(Figures 6-8)**. The interstitial histopathologic features were observed in 8(17.02%) patients that contained histiocytes dispersed in the dermis among mucin, bundles of collagen and blood vessels. The combination of these 2 patterns was present in 3(6.38%) cases. Two (4.25%) individuals who complained of the profundus variant showed a granuloma reaching the panniculus **(Figure 9)**.

Furthermore, whenever possible a detailed review of systems and known potential triggering factors were searched for but did not support or report a causal association with almost all cases of GA, apart from one (2.12%) female patient presented with GA following short time after resolution of herpes zoster and was distributed in a dermatomal pattern. And the rash was not on scarred skin.

Discussion

Granuloma annulare is not uncommon idiopathic cutaneous problem characterized by the development of papules and plaques, GA might present with variable clinical types and histopathological pictures.[14] Adding a challenge and difficulty to establish the right diagnosis on many occasions, and it is mandatory and of potential clinical importance to distinguish GA from the other granulomatous inflammatory skin diseases. Overall pathogenesis and the etiology of GA remained unknown, and frequently

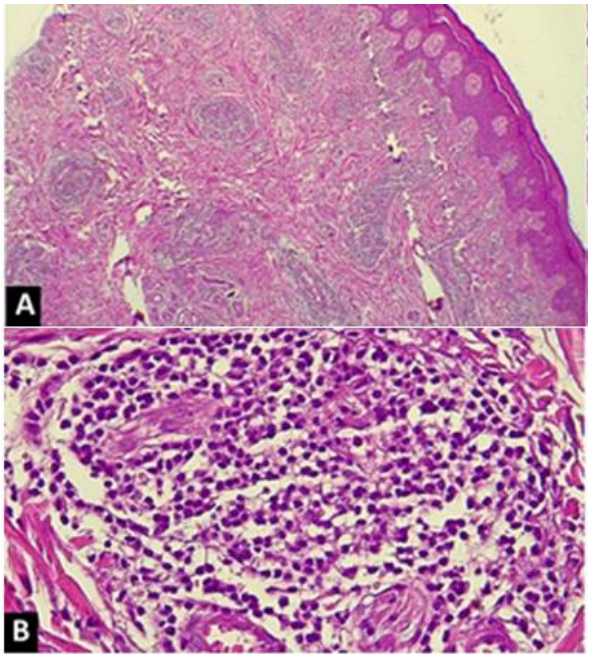

Figure 7 Showing early inflammatory palisading granuloma annulare with lymphohistiocytic inflammation surrounding central palisades of histiocytes with prominent mucin deposition. (Hematoxylin and eosin: A, X10; B, X 40).

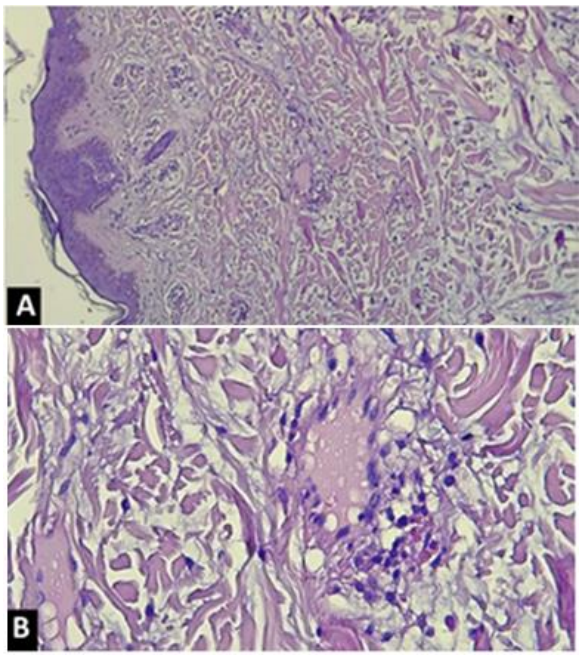

Figure 8 Showing early palisading granuloma with mucin deposition following resolution of herpes zoster. (Hematoxylin and eosin: A, X10; B, X 40).

asymptomatic self-limiting disease.[2,4] Here, the present work will show the full and diverse clinical presentations of different patients that had grown over a decade in this research.

Generally, the mean age of participants was 32.8 (16-60) years while there was bimodal age of involvement, where the younger age group (<30 years) complained of localized or profundus variant, and the middle-aged patient was affected by generalized GA. This outcome was comparable to what was earlier smaller, single-center research, where GA occurred in the initial three to five decades.[2,17] Localized GA arises most commonly in younger age group patients while the generalized GA is more expected to ensue in adults or older patients.[1,18] Until now, there are unavailable large multicenter cohort studies evaluating the incidence and prevalence of GA.[1,3] On the other hand, a preceding retrospective report of 54 Korean cases showed that the generalized GA affecting mostly the subjects lesser than 10 years old and/ or adult of more than 40 years old, and there was a slight male predominance.[19]

In this study, the women were approximately 5 times more predominance to be involved by GA than men, where 82.97% were females and 17.02% were males. Suggesting that GA is common among females. This ratio is higher than previously mentioned in the literature, where the GA prevalent ratio in females to males is around 3:1.[2,17] The reason behind this predominance of females is difficult to explain.

Almost all participants in the current research had no associated pruritus or tenderness apart from the rash in form of papules and/ or plaques, this explained the long duration of the disease and in many instances, the period of their first diagnosis reached to 12 months. This asymptomatic feature is well-recognized in patients with GA. This led to the patients' neglect and delayed seeking medical care,

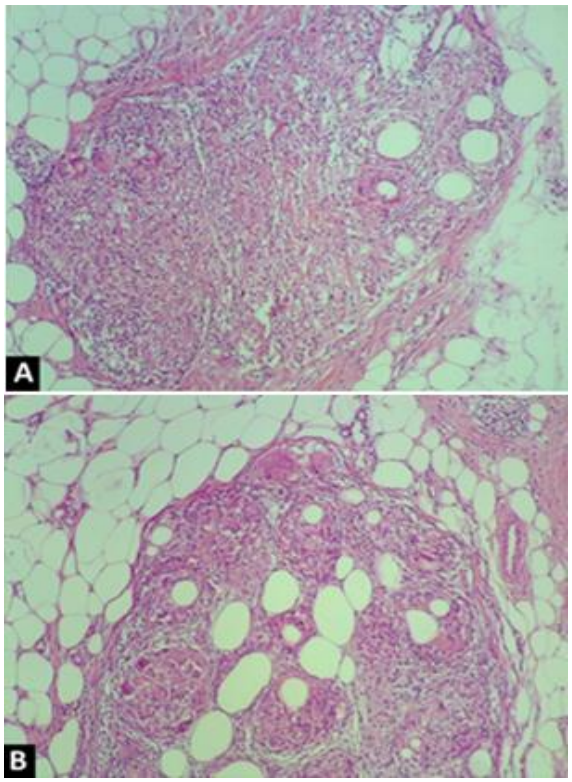

Figure 9 Showing granuloma annulare profundus reaching the panniculus. (Hematoxylin and eosin: A, X10; B, X 40).

therefore, the patients were unconcerned about the treatment. Previous retrospective cross-sectional research elucidated those patients had encountered GA during 6 months of their first medical consultation.[17] The polymorphic cutaneous manifestations of GA are due to their several variants are well documented in the present our work. Diverse three clinical presentations were reported: Generalized type, localized GA, and subcutaneous profundus GA. This finding is in the same line with other studies, except for the perforating variant of GA that was not described in the current research. As well as other informed sporadic variants of GA include photo-distributed, palmar, macular type, and pustular GA.[1,20,21]

The present work showed a generalized GA in 87.23% of older patients and subdivided into 2 types: generalized annular beaded granuloma and disseminated papular in 63.82% and 23.4% of cases, respectively. The color of the lesions either was red in 34.04%, skin colored in 29.78%, or violaceous in 23.4% of patients. These results were compared with previous reports that revealed generalized GA defined by widespread or the concurrent existence of at minimum ten skin lesions and occurs in less extent in about 8–15% of patients. It is either widespread annular plaques or disseminated skin-colored to red papules. Another report documented that approximately 15% to 25% of patients will have generalized variant.[2,22,23]

Also, the current study described localized GA in 8.51% of young cases. They presented with encircled plaques and papules that grow outwards forming an annular ring. The scalp, penis, neck and abdomen were the validated sites of involvement. The characteristic color ranged from skin-colored to violaceous hue. However, previous studies revealed that the localized variant was the most common form and accounted for 75% of cases of GA.[2,23,24] Otherwise, the features of localized GA were nearly comparable to that in the other studies, where commonly observed on the hands and/or feet and occurred in young age group below the of 30 years old and it is characterized by annular skin-colored to red papules.[1,24]

The subcutaneous GA so-called profundus variant was observed in 4.25% of healthy young girls in the present work and it is characterized by asymptomatic multiple deep firm nodules involving the feet, legs, and hands. This finding was similarly reported and described as subcutaneous GA, so-called pseudo-rheumatoid nodules and it is commonest on the lower legs of children and characterized by firm subcutaneous nodular lesions.[25]

The present research showed a wide clinical differential diagnosis of GA; therefore, an incisional biopsy of the skin lesion is recommended for histopathological study when somebody suspects GA. Interestingly, the histopathological pattern in almost 76.59% of cases is characterized by palisading granuloma. In one patient there was dermal necrobiotic degeneration with no inflammatory reaction. The interstitial histopathologic features are present in 17.02% of patients. The mixed combination of these 2 patterns was present in 6.38% samples. Two (4.25%) individuals who complained of the profundus variant showed a granuloma reaching the panniculus. The demonstration of mucin deposition in nearly all cases is the vital histological finding to distinguish GA from other granulomatous (non-infectious) diseases. These features of the present work are on line with other studies, where collagen necrosis is usually less prominent in generalized GA than in localized GA. Mucin sedimentation joined with an interstitial or palisading pattern of granulomatous formation signifies the principal feature in all types of GA. Typically, the granuloma in subcutaneous GA was composed of nodules in the subcutaneous layer and deep

reticular dermis.[1,15,26] Winkelmann described 207 patients of GA and established that 26% showed palisading granulomas, while 71% exhibited the interstitial pattern. On the other hand, a study on 54 Korean patients with GA found that the 2 dominant histologic pictures were closely equal in numbers, and mucin was realized in 94% of samples.[2,19]

In the present work whenever possible a detailed review of systems and known potential triggering factors were done, fortunately, did not support or report a causal association with almost all cases of GA, a part of one (2.12%) female patient presented with GA following short time healing of herpes zoster but not on scarring. The same suggestion has been mentioned in a previous case report of GA over an old scar of herpes zoster.[9] Similarly a case–control research of 126 participants failed to discover an association between GA and the majority of reported systemic associations.[27] Another study's outcomes do not support a relation between generalized GA and malignancy.[28]

Several preceding studies elucidate numerous systemic disease associations with generalized GA including DM, thyroid disease, malignancy, rheumatoid arthritis, lipid abnormalities, viral infection (HIV, hepatitis B &C), trauma, and herpes zoster.[1,9] As well as an original study results suggested that hyperlipidemia and diabetes may be risk features for the advance of GA.[17] But these findings have not been studied using a case-controlled technique. They were based on case reports and insignificant retrospective studies. Despite a great number of studies available about GA and DM, the final evidence for an association is absent.

Conclusion

The clinical features of granuloma annulare in the Eastern population do not differ markedly from those of overseas studies. GA presented mostly with typical annular beaded lesions, that were generalized in 87.23%, localized in 8.51% and profundus in 4.25% that might have different clinical distribution. Although some patients had only one site affected like the penis and scalp. The histopathological picture was palisading granuloma. GA might mimic many granulomatous diseases like sarcoidosis both in its clinical and histopathological pictures and there are many overlapping features among them. The triggering factors were rarely reported in GA.

Declaration of patient consent The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship None.

Conflict of interest Authors declared no conflict of interest.

Author's contribution

KES, TAK: Substantial contribution to study design, acquisition of data, manuscript writing, has given final approval of the version to be published.

IKS: Substantial contributions to analysis and interpretation of data, critical review, has given final approval of the version to be published.

References

1. Thornsberry LA, English JC. Etiology, diagnosis, and therapeutic management of granuloma annulare: an update. *Am J Clin Dermatol*. 2013;**14**:279-90.
2. Piette EW, Rosenbach M. Granuloma annulare: pathogenesis, disease associations and triggers, and therapeutic options. *J Am Acad Dermatol*. 2016;**75(3)**:467-79.
3. Rubin CB, Rosenbach M. Granuloma annulare: A retrospective series of 133 patients. *Cutis*. 2019;**103(2)**:102-6.
4. Fayyazi A, Schweyer S, Eichmeyer B, Herms J, Hemmerlein B, Radzun HJ, *et al*. Expression of IFNγ, coexpression of TNFα and matrix metalloproteinases and apoptosis of T lymphocytes and macrophages in granuloma annulare. *Arch Dermatol Res*. 2000;**292**:384-90.

5. Andreu-Barasoain M, Gómez de la Fuente E, Pinedo F, Gamo-Villegas R, Sánchez-Gilo A, López-Estebaranz JL. Long lasting interstitial generalized granuloma annulare on sun-exposed areas. *Photoderm Photoimmun Photomed*. 2012;**28(4)**:216-8.
6. Toro JR, Chu P, Yen TS, LeBoit PE. Granuloma annulare and human immunodeficiency virus infection. *Arch Dermatol*. 1999;**135(11)**:1341-6.
7. Kakurai M, Kiyosawa T, Ohtsuki M, Nakagawa H. Multiple lesions of granuloma annulare following BCG vaccination: case report and review of the literature. *Int J Dermatol*. 2001;**40(9)**:579-81.
8. Houcke-Bruge C, Delaporte E, Catteau B, Martin De Lassalle E, Piette F. Granuloma annulare following BCG vaccination. *Ann Dermatol Venereol*. 2001:**128(4)**:541-4.
9. Ohata C, Shirabe H, Takagi K, Kawatsu T. Granuloma annulare in herpes zoster scars. *J Dermatol*. 2000;**27(3)**:166-9.
10. Monte-Serrano J, García-Gil MF, García-García M, Casas-Flecha I, Matovelle-Ochoa C, Ara-Martín M. Granuloma annulare triggered by SARS-CoV-2 infection: Immunohistochemical staining. *Dermatol Ther*. 2021;**34(3)**:e14897.
11. Nguyen TH, Gabros S, Friefeld S, Gupta A, Skopit S. Generalized granuloma annulare after COVID-19 vaccination. *JAAD Cas Rep*. 2022;**25**:18-21.
12. Mizuno K, Suzuki A, Kato N, Isei T, Okamoto H. CD8-positive granulomatous mycosis fungoides mimicking generalized granuloma annulare. *J Dermatol*. 2012;**39(12)**:1068-9.
13. Wu H, Barusevicius A, Lessin SR. Granuloma annulare with a mycosis fungoides–like distribution and palisaded granulomas of CD68-positive histiocytes. *J Am Acad Dermatol*. 2004;**51(1)**:39-44.
14. Wang A, Rahman NT, McGeary MK, Murphy M, McHenry A, Peterson D, *et al*. Treatment of granuloma annulare and suppression of proinflammatory cytokine activity with tofacitinib. *J Allergy Clin Immunol*. 2021;**147(5)**:1795-1809.
15. Güneş P, Göktay F, Mansur AT, Köker F, Erfan G. Collagen-elastic tissue changes and vascular involvement in granuloma annulare: a review of 35 cases. *J Cutan Pathol*. 2009;**36(8)**:838-44.
16. Penas PF, Jones-Caballero M, Fraga J, Sánchez-Pérez J, García-Díez A. Perforating granuloma annulare. *Int J Dermatol*. 1997;**36(5)**:340-8.
17. Barbieri JS, Rodriguez O, Rosenbach M, Margolis D. Incidence and prevalence of granuloma annulare in the United States. *JAMA Dermatol*. 2021;**157(7)**:824-30.
18. Plotner A, Mutasim D. Successful treatment of disseminated granuloma annulare with methotrexate. *Br J Dermatol*. 2010;**163(5)**:1123-4.
19. Yun JH, Lee JY, Kim MK, Seo YJ, Kim MH, Cho KH, *et al*. Clinical and pathological features of generalized granuloma annulare with their correlation: a retrospective multicenter study in Korea. *Ann Dermatol*. 2009;**21(2)**:113-9.
20. Izikson L, English JC. Noninfectious granulomatous diseases: an update. *Adv Dermatol*. 2006;**22**:31-53.
21. Suárez O, Pérez-Pérez L, Pereiro MM, García CP, Toribio J. Disseminated granuloma annulare located on photoexposed areas. *Actas Dermo-Sifiliograficas*. 2006;**97(7)**:448-50.
22. Bansal M, Pandey SS, Manchanda K. Generalized papular granuloma annulare. *Indian Dermatol Online J*. 2012;**3(1)**:74-6.
23. Dabski K, Winkelmann R. Generalized granuloma annulare: clinical and laboratory findings in 100 patients. *J Am Acad Dermatol*. 1989;**20(1)**:39-47.
24. Cyr PR. Diagnosis and management of granuloma annulare. *Am Fam Physician*. 2006;**74(10)**:1729-34.
25. Requena L, Fernández-Figueras MT. Subcutaneous granuloma annulare. *Sem Cut Med Surg*. 2007:96-99.
26. Grogg KL, Nascimento AG. Subcutaneous granuloma annulare in childhood: clinicopathologic features in 34 cases. *Pediatrics*. 2001;**107(3)**:e42-e42.
27. Nebesio C, Lewis C, Chuang TY. Lack of an association between granuloma annulare and type 2 diabetes mellitus. *Br J Dermatol*. 2002;**146(1)**:122-4.
28. Gabaldón VH, Haro-González-Vico V. Lack of an association between generalized granuloma annulare and malignancy: A case-control study. *J Am Acad Dermatol*. 2019;**80(6)**:1799-1800.