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Journal
Dermatology Online Journal, 25(3)

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Publication Date
2019

DOI
10.5070/D3253043334

Unilateral granuloma annulare in association with pyoderma gangrenosum and chronic lymphocytic leukemia

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Abstract

Granuloma annulare (GA) is a fairly common inflammatory skin condition with a range of clinical subtypes. We describe an unusual case of unilateral GA confined to the thigh on a previously amputated limb. A man in his 80s with a past medical history of below-knee amputation of the left leg owing to severe leg ulcers from pyoderma gangrenosum, chronic lymphocytic leukemia, and dyslipidemia developed a slowly spreading eruption on the distal stump spreading proximally. On physical examination, he had numerous non-scaly violaceous papules and annular plaques from the stump to the lateral, medial, and anterior thigh. Histology confirmed a diagnosis of GA. The extensive, chronic lesions make this presentation of GA very unusual in that it shares features of both localized and generalized forms. Moreover, the temporal and spatial association with pyoderma gangrenosum is unique and may reflect a related inflammatory pathway.

Keywords: granuloma annulare, pyoderma gangrenosum, chronic lymphocytic leukemia

Introduction

Granuloma annulare (GA) is a self-limited inflammatory skin condition, with a variety of clinical subtypes, including localized, generalized, perforating, subcutaneous, and patch types [1]. Localized GA, which typically presents as a non-scaly, red, annular plaque confined to the distal extremities, is the most common form of GA, comprising around 75% of cases. Lesions are single or few in number and tend to resolve within a couple of years [2]. Association between GA and malignancy has not been elucidated. However, it has been reported that atypical presentations of GA may be associated with malignancy [3]. We present an unusual case of unilateral GA confined to the thigh of a previously amputated limb associated with chronic lymphocytic leukemia (CLL).

Case Synopsis

A man in his 80s with a history of below-knee amputation (BKA) of the left leg owing to severe ulcers from pyoderma gangrenosum (PG) 14 years prior, chronic lymphocytic leukemia (CLL) diagnosed 6 years ago, and dyslipidemia, was treated at our wound care clinic for recurrence of PG on his left leg stump. The diagnosis of PG was made clinically and by excluding other causes by histology and tissue cultures. Shortly after the BKA, the patient developed a rash on the distal stump that has been slowly spreading proximally up his left thigh. On physical examination, he showed multiple non-scaly red to violaceous papules and annular plaques from the stump base up to the lateral, medial, and anterior thigh (**Figure 1**). Histology showed collection of lymphocytes and histiocytes with scattered giant cells associated with mild dermal fibrosis (**Figure 2**). Colloidal iron staining was positive for mucin. AFB and Fite stains were negative. Therefore, these features were consistent with the diagnosis of GA.

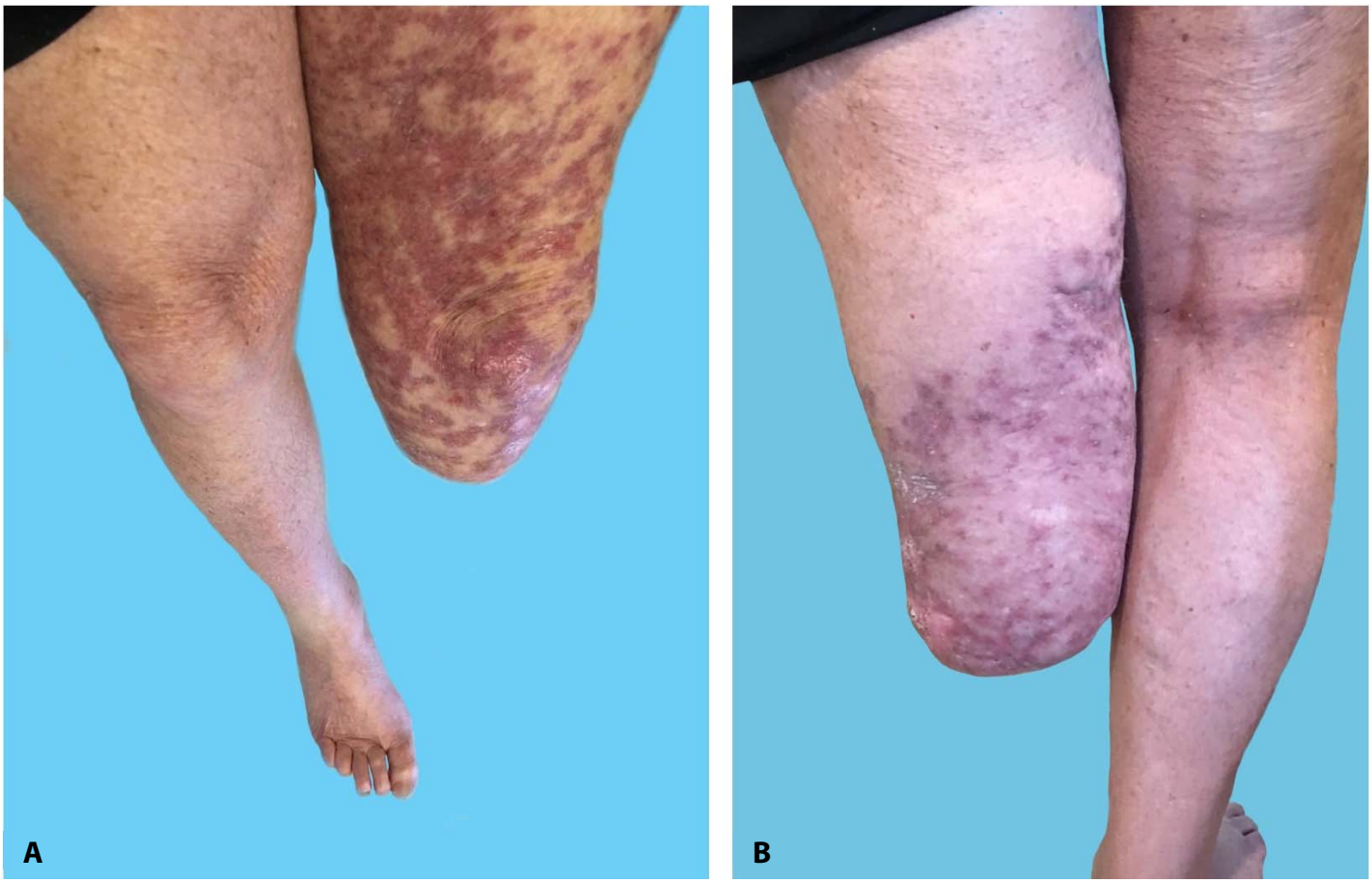

Figure 1. *Clinical manifestation. Non-scaly multiform erythematous patches and plaques involving the medial, anterior, lateral, and posterior sides of left thigh and leg stump approximately 3 years ago.* ***A)*** *anterior view, and* ***B)*** *posterior view.*

Previous treatment for PG included cyclosporine and prednisone, which prevented the spread of the GA. Moreover, the patient was started on adalimumab 40mg subcutaneously every two weeks for approximately two years that stopped progression but did not result in resolution of the GA. Additionally, he has been receiving 20mg IVIG every other month for management of CLL. Current medications include IVIG, adalimumab, atorvastatin, and gabapentin.

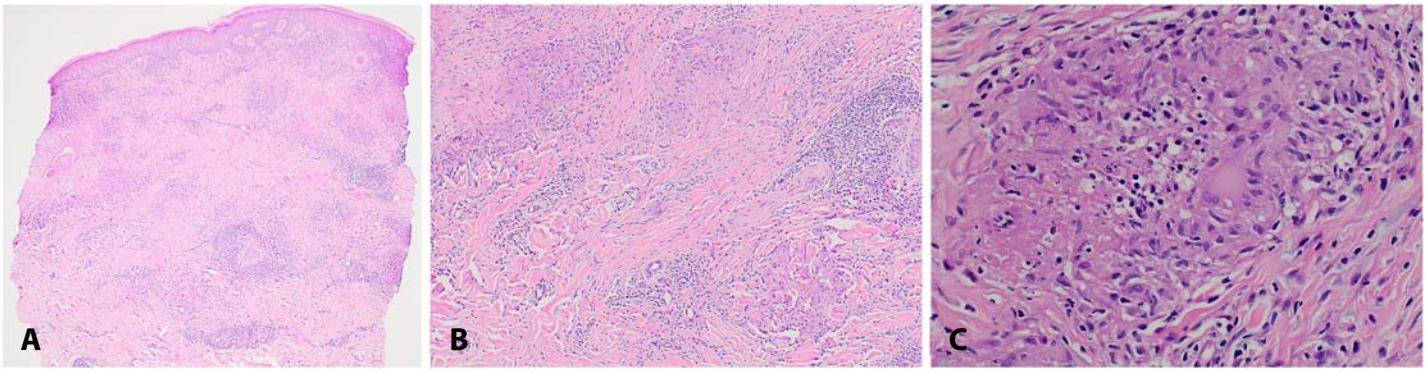

Figure 2. *Dermal granulomatous mixed infiltration. Low and high-power images of H&E stain show upper and mid dermis with connective tissue degeneration (necrobiosis) and interstitial histiocytes, as well as lymphocytes, fibroblasts, and giant cells. Additionally, colloidal iron staining was positive for mucin (not shown) consistent with the diagnosis of granuloma annulare.* ***A)*** *4×;* ***B)*** *10×;* ***C)*** *40×.*

Table 1. *Granuloma annulare and associated lymphomas and/or chronic lymphocytic leukemia.*

Case No.	Age/Sex	Location	GA Type	Associated Lymphoma/CLL	References
1	39/M	Trunk and buttocks	Generalized	Hodgkin lymphoma	[5]
2	69/M	Hands	Localized	Follicular lymphoma	[6]
3	64/F	Back and limbs	Localized	Lennert lymphoma	[7]
4	85/F	Scalp and sacral	Subcutaneous	Hodgkin lymphoma	[8]
5	37/F	Generalized	Generalized	Nshd	[9]
6	51/F	T3 dermatome	Perforating	Lennert lymphoma	[10]
7	57/F	Hands	Localized	Nshd	[11]
8	25/M	Neck, hands, arms	Localized	Nshd	[11]
9	40/M	Trunk and limbs	Generalized	Hodgkin disease	[12]
10	68/M	Generalized	Generalized	Granulomatous MF	[13]
11	75/M	Palms, fingers, soles	Atypical	Nshd	[14]
12	20/M	Dorsum of hand	Localized	Nshd	[14]
13	75/M	Fingers	Atypical	Cll	[14]
14	68/M	Dorsum of hand	Localized	Cll	[14]
15	68/F	Knees, face, arms, legs, trunk	Atypical	Cll	[14]
16	64/F	Chest, trunk, and limbs	Generalized	Follicular lymphoma	[14]
17	66/M	Forearm, helix	Localized	Follicular lymphoma	[14]
18	59/F	Back and limbs	Generalized	Follicular lymphoma	[14]
19	52/F	Arms and legs	Atypical	Diffuse small cell lymphoma	[14]
20	66/F	Fingertips	Atypical	Diffuse small cell lymphoma	[14]
21	73/F	Fingers, palms, soles, limbs, occipital head	Atypical	Diffuse small cell lymphoma	[14]
22	46/F	Back, flank, palms, and limbs	Atypical	Sezary syndrome	[14]
23	59/M	Face, scalp, trunk	Not Stated	Mf	[15]
24	60/F	Arms and legs	Localized	Nshd	[14]
25	64/F	Head, neck, chest, arms, and dorsa of hands	Generalized	Non-hodgkin's lymphoma	[16]

*CLL: Chronic Lymphocytic Leukemia; NSHD: Nodular Sclerosing Hodgkin's Disease; MF: Mycosis Fungoides
&Atypical GA: Lesions in unusual locations or painful lesions (or both).

Case Discussion

The clinical presentation of the case described herein has some features of localized and generalized GA, but it is unique in its unilateral distribution confined to one leg for 14 years without generalization to the trunk. To our knowledge, this finding of extensive, chronic GA located solely on a single limb without additional lesions ever appearing on the trunk or any other location has not been reported before. Interestingly, the presence of a dermal lympho-histiocytic infiltrate as seen in GA may also be observed in PG. Given the inflammatory nature of these conditions and overlapping distribution in our patient, one must consider whether a correlation exists. However, GA has not been previously reported in association with PG.

Although PG is occasionally associated with hematologic malignancies, the potential association between GA and malignancy remains unclear. Li et al. reported that cases linked to malignancy typically occurred in patients with an atypical presentation of GA [3]. Lymphoma is the most commonly associated malignancy. Nevertheless, GA in the setting of CLL has rarely been reported (**Table 1**). Most GA cases associated with lymphoma surpassed the age of 50 years, whereas all GA patients with CLL were more than 65 years old. Interestingly, two out of the three GA patients with CLL had atypical features in GA presentation.

GA has also been associated with dyslipidemia. Wu et al. revealed that dyslipidemia was significantly more prevalent among adults with GA [4], which is

observed with our patient as well. The reason for this association is unclear, though some have theorized that chronic microvascular inflammation related to dyslipidemia may play a role in the pathogenesis of GA [4].

In relation to the differential diagnosis, the red to violaceous plaques combined with the histologic findings could also have suggested an early presentation of necrobiosis lipoidica. Necrobiotic xanthogranuloma, characterized by red-brown, violaceous, or yellowish papules/plaques and palisading histiocytic infiltration that may be associated with CLL also was considered in the differential diagnosis. Granulomatous dermatitis and sarcoidal granulomas would also be included in the differential diagnosis. However, the lack of xantho-granulomas in the histologic examination and the positivity of colloidal iron staining confirmed the diagnosis of GA.

Conclusion

This case exemplifies that clinician's suspicion for GA should be present even though the clinical manifestation does not fit any exact type, specifically in a patient with history of malignancy. Even though no definite relationship is found between GA and malignancy, in older patients with atypical skin lesions of GA or that histologically are similar to GA, investigation for lymphoma/CLL or other malignancies could be considered.

Potential conflicts of interest

The authors declare no conflicts of interests.

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