

COMPELLING COMMENTS

Patch-Type Granuloma Annulare with Clinical and Histological Features of Morphea: A True Overlap?

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ABSTRACT

A 67-year-old woman was evaluated for a worsening asymptomatic rash located on her torso, back, and legs. She denied any chills or fevers and reported feeling otherwise well. Clinically, large brownish, slightly atrophic plaques were seen on the torso suggestive of either morphea or a granulomatous condition. Histopathologic examination revealed an increase in interstitial histiocytes infiltrating between altered collagen fibers, palisaded granulomas with increased mucin, suggestive of granuloma annulare (GA), as well as dermal sclerosis, perineural infiltrates with plasma cells and diminished CD34 counts, that are more typical for localized scleroderma/morphea. Morphea and patch-type GA may be indistinguishable clinically and share some histopathological features. This case demonstrates similarities between these conditions and features of both conditions in the same patient.

INTRODUCTION

GA is a chronic granulomatous disorder that usually presents as erythematous papules or plaques in an annular arrangement¹. Histologically, GA is characterized by mucin deposition, lymphohistiocytic infiltrate, and degeneration of collagen². Numerous inciting factors for GA have been reported, including viruses, arthropods, HIV, and *Borrelia* infection¹. GA often spontaneously resolves and is mostly a cosmetic concern to patients. However, some forms of GA are associated with systemic disease, such as generalized GA and diabetes mellitus (DM)³. Patch-type GA is a distinct variant of this condition, presenting with large asymptomatic annular plaques⁴. This peculiar GA type is often misdiagnosed with other dermatoses, more

commonly tinea, morphea, or mycosis fungoides. Histopathologically, it also differs from classical GA, closely resembling inflammatory stages of morphea and interstitial granulomatous dermatitis of autoimmune disease, and interstitial drug eruption⁴. Herein, we described a case of patch-type GA with overlapping features of morphea and discuss the existing literature of the topic.

CASE REPORT

A 67-year-old woman with a past medical history of essential hypertension, type 2 diabetes, and hypercholesterolemia was evaluated in an outpatient dermatology clinic for an asymptomatic, erythematous rash on the trunk and legs that had been worsening

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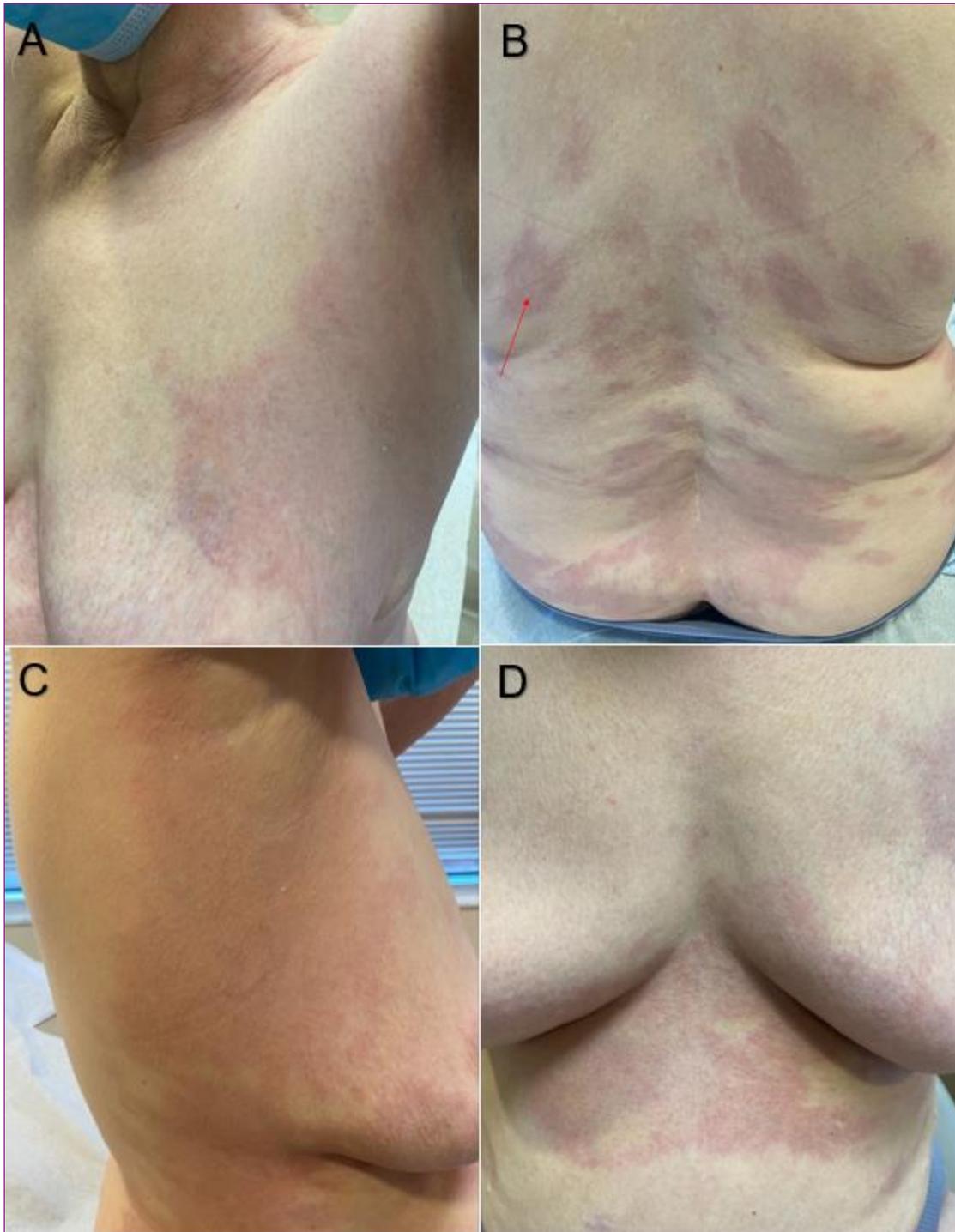


Figure 1. (A): Clinical photograph of left breast exhibiting erythematous skin with sharp border (B): Clinical photograph exhibiting erythematous, annular patches of various sizes, located mostly on the lateral back. Some patches demonstrate central clearing (arrow) (C): Clinical photograph of erythematous, confluent patches that cover the majority of the right side and axilla (D): Clinical photograph of the medial torso featuring a large erythematous patch with sharp borders.

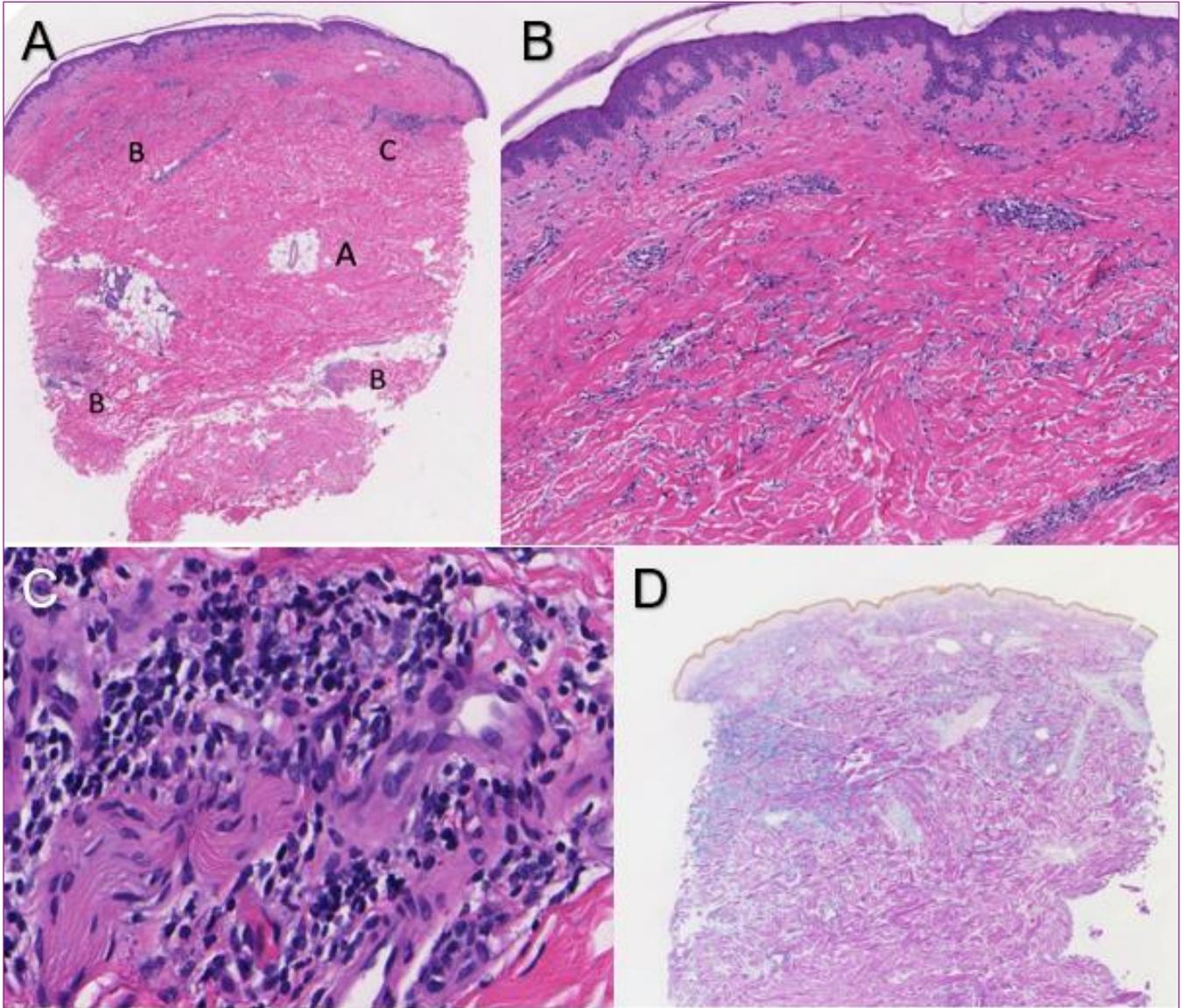


Figure 2. (A): Marked sclerosis and thickened collagen bundles of the superficial and mid dermis zone (zone A) with foci of interstitial granulomatous infiltrate (zone B) and zones of perineural inflammation (zone C), Hematoxylin Eosin stain, x40. **(B)** Higher magnification of the interstitial granulomatous infiltrate and homogenized collagen, Hematoxylin Eosin stain, x200. **(C):** Higher magnification of perineural infiltrate with collections of plasma cells, Hematoxylin Eosin stain, x200. **(D):** Increased amount of interstitial mucin, Alcian Blue stain, x100. **(E):** Loss of CD34 immunostain in the superficial dermis, CD34 immunostain, x100.

over the previous 6 to 8 months (**Figure 1**). The rash was characterized by large, non-scaly, brownish patches with central atrophy/clearing.

Laboratory evaluation was notable for low vitamin D levels. Lyme disease antibodies were negative.

Punch biopsies from the lower back and abdomen revealed significant thickening of the dermal fibers with homogenization in the superficial dermis and thickened fat septae. There was an interstitial infiltrate of spindled histiocytes infiltrating between swollen collagen fibers, and focally increased interstitial mucin. Scattered rare eosinophils were also noted as well as perineural plasma rich cell infiltrate. In addition, there is extensive sclerosis of the superficial and middle dermis with diminished CD34 counts (**Figure 2**). Periodic acid-Schiff (PAS) stain was used to identify any fungal microorganisms and basement membrane changes, both of which were absent. The patient was diagnosed with interstitial GA and possible morphea overlap and started on methotrexate 15 mg per week. The rash showed significant improvement on methotrexate after three months.

DISCUSSION

Patch-type GA is a poorly described entity. The largest clinic-morphological study of patch GA by Khanna et al demonstrates the challenges in diagnosing this condition⁴. Histopathologically, it was described to have unique features including predominantly interstitial infiltrate and presence of eosinophils and plasma cells⁴. The authors mention that these features were not previously described in the previous reports of patch-type GA and are usually considered features of morphea. We, additionally, found

the presence of perineural infiltrates with plasma cells previously described as features of morphea⁵.

Interestingly, coexisting morphea and GA was described in a few reports in the literature. The first known case described a 62-year-old patient with linear morphea on pretibial surfaces and GA on the medial thigh⁶. Two more patients were reported in 1999: one patient had GA on the thigh and morphea on the chest; the second patient had morphea on the right breast and lateral back and GA on the inner thigh and right shoulder². A third report from 2019 describes a patient with morphea on the lower limbs and GA on the abdomen and dorsum of the feet⁷. Another interesting case report described the development of morphea after granulomatous fasciitis induced by Lyme⁸.

It has been suggested that the coexistence of these conditions may be due to a common etiological link such as autoimmunity or previous injury⁶. Antinuclear antibodies (ANA) may be increased in up to half of all cases of morphea⁹. However, this is a non-specific finding as even healthy individuals can have a positive ANA. In our patient, ANA was negative. Scleroderma and centromere B antibodies, which are ANAs specific for systemic sclerosis, were also within normal limits¹⁰. In regard to previous injury, studies have shown that repeated friction, as occurs along the bra line and waistband area, may play a role in morphea developing at those susceptible sites¹¹. Our patient had patches along the underside of the breast which frequently contacts the bra lining (Figure 1-D). However, our patient also had more diffuse involvement across her back and chest in areas that would not be subject to repetitive friction.

Our patient had several comorbidities that may be risk factors for developing GA,

including diabetes mellitus (DM) and hyperlipidemia. A 2021 study investigated the findings of 5,137 patients with GA. Investigators reported that 21% of patients with GA had DM compared to the 13% seen in the control group. A larger percentage of patients with GA had hyperlipidemia compared to the control group (33% vs 28%)¹². This study suggested that DM and hyperlipidemia may predispose one to GA through T-cell dysregulation. Other studies have found T-helper 1 cells (Th1), T-helper 2 cells (Th2), and the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway to be implicated in dysregulation of GA¹³. Increased expression of cytokines corresponding to the T-cell axes were noted; this is particularly true for IL-4 mRNA (corresponding to the Th2 pathway), which exhibited a 15,600-fold increase in GA lesions versus control skin¹³.

An interesting finding shared by GA and morphea is that both exhibit alterations in collagen and CD34 loss^{2,14,6}. It has been proposed that the collagen degeneration seen in GA is mediated by M1 macrophages, a type of macrophage that initiates inflammation¹⁵. Inflammation is then followed by an M2 macrophage mediated response, resulting in mucin deposition¹⁵. Collagen degeneration can be analyzed by immunohistochemical staining for CD34. CD34 is a marker for vascular endothelial progenitors¹⁶. Endothelial cell damage has been proposed as an inciting factor in developing morphea¹⁷. An important finding in morphea is the loss of CD34 dermal dendritic cells (DDCs)¹⁸. This CD34 loss is also seen in GA¹⁸. Findings from an investigation that analyzed 50 skin lesions from patients with morphea suggest that a phenotypic change of CD34+ DDCs to smooth muscle actin positive (SMA) myofibroblasts is responsible for the disease extent and fibrosis in morphea¹⁹. Because

CD34 counts are decreased in both morphea and GA, phenotypic changes of CD34+ DDCs could play a role in the overlapping nature as seen in our patient. However, it is rare for GA and morphea to occur in the same patient and even more rare for the diseases to occupy the same location. Thus, more studies are needed to further discuss what etiological link, if any, may connect these two disorders.

CONCLUSION

To conclude, we report a case of patch-type granuloma annulare with clinical and histopathological features of morphea. This case presents a challenging clinical and pathologic differential diagnosis and raises the possibility of an overlap of these two conditions. Further studies are needed to better elucidate what etiologic link, if any, exists between these two entities.

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