SKIN

BRIEF ARTICLE

Case of Generalized Granuloma Annulare Treated with Low Dose Naltrexone + PUVA

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ABSTRACT

Granuloma annulare (GA) is a common, noninfectious granulomatous skin condition that usually presents in its localized form, characterized by flesh-colored to erythematous papules coalescing into annular plaques without scale, commonly on the dorsal hands. Lesions can be pruritic and often resolve without treatment in two years. However, the generalized form of GA has a lower incidence and presents with similar morphology, but with >10 lesions in a widespread distribution. Generalized GA is known to be more symptomatic, longer lasting, and recalcitrant to treatment. The diagnosis is made based on clinicopathological correlation with palisading granulomas around degenerated collagen in the dermis, mucin, and infiltrative lymphocytes and histiocytes. Treatment remains challenging as evidence is limited to case reports, case series, and a few retrospective studies. Here we present the case of a 59-year-old Caucasian female with pruritic rash that began on her abdomen and spread to her extremities over two months. Biopsy revealed superficial histiocytic infiltrates palisading around eosinophilic areas of altered collagen, multiple multinucleate giant cells with elastophagocytosis and lymphohistiocytic perivascular infiltrates, and mucin in the dermis on colloidal iron staining. Overall, this was consistent with generalized GA. The patient was started on a combination of low dose naltrexone (LDN) and psoralen and ultraviolet A (PUVA) therapy. At a five-month follow up visit, she demonstrated near complete resolution of symptoms without any serious adverse effects.

INTRODUCTION

Granuloma annulare (GA) is a common, noninfectious granulomatous skin condition presenting more frequently in women.[1,2] Although the etiology is unclear, histologic features suggest it may be related to a delayed hypersensitivity reaction. GA typically presents in its localized form, characterized by flesh-colored to erythematous papules coalescing into annular plaques without scale, most commonly on the dorsal hands.[1-3] Lesions can be pruritic and often resolve without treatment in two years.[1-3] Generalized GA presents with similar morphology, but with >10 lesions or in a widespread distribution affecting the head, neck, trunk, and limbs. [1-3] Representing about 8-15% cases, it is known to be more symptomatic, longer-lasting, and recalcitrant to treatment.[1-3] The diagnosis is made based on clinicopathological correlation with palisading

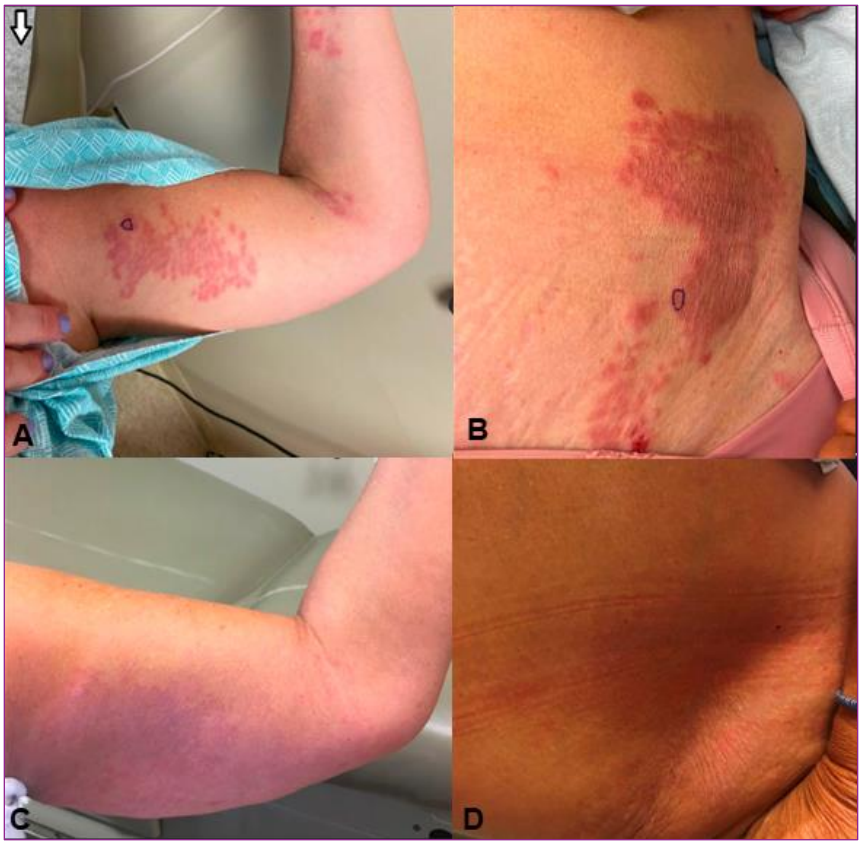

Figure 1. Generalized granuloma annulare presenting as erythematous papules coalescing on medial aspect of left arm (**A**) and left abdomen (**B**). Granuloma annulare status post five months of treatment of LDN + PUVA showing light pink patches on the medial aspect of the left arm (**C**) and left abdomen (**D**).

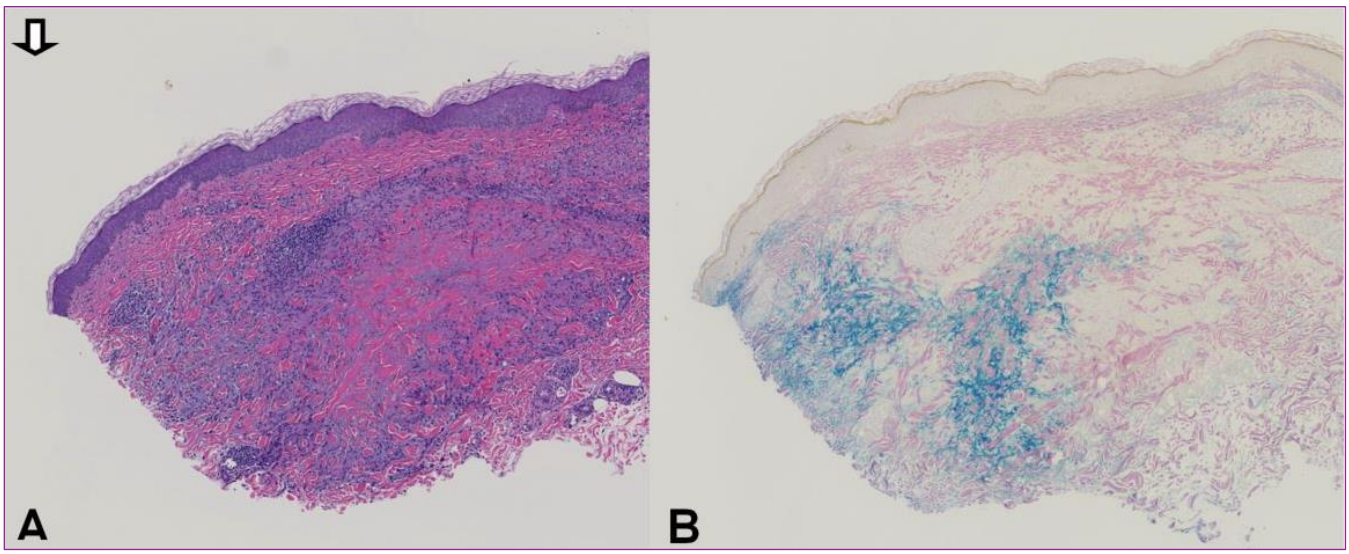

Figure 2. Biopsy of granuloma annulare (**A**) demonstrating superficial histiocytic infiltrates with palisading surrounding eosinophilic areas of altered collagen (hematoxylin-eosin stain; original magnification: X4) and (**B**) colloidal iron stain revealing mucin in the dermis.

granulomas around degenerated collagen in the dermis, mucin, and infiltrative lymphocytes and histiocytes.[1,2] Suggested yet controversial disease associations include dyslipidemia, diabetes mellitus, malignancy, thyroid disease and infections including human immunodeficiency, hepatitis B, and hepatitis C viruses.[1,2]

Treatment remains challenging as evidence is limited to case reports, case series, and a few retrospective studies.[1-3] Several treatments have been proposed, including topical or intralesional steroids, cryosurgery, photodynamic therapy, narrowband UVB light therapy, and fumaric acid (not available in the US), but none have been proven to be consistently effective.[1,2]

CASE REPORT

A 59-year-old Caucasian female presented with a pruritic rash that began on her left lower abdomen and spread to her extremities over two months. Physical exam revealed numerous erythematous papules and plaques, coalescing into annular distributions over the trunk and arms without scale (**Figure 1A-B**). A biopsy demonstrated superficial histiocytic infiltrates palisading around eosinophilic areas of altered collagen, and multiple multinucleate giant cells with elastophagocytosis and lymphohistiocytic perivascular infiltrates (**Figure 2A**). A colloidal iron stain showed mucin in the dermis (**Figure 2B**). Overall, this was most consistent with generalized GA.

Treatment was started with topical clobetasol 0.05% with a plan to start hydroxychloroquine. Unfortunately, the patient was found to have latent tuberculosis and started on a two-month course of rifampin instead. During this time, she continued to suffer with pruritis and dyspigmentation from topical steroid use.

The patient was then trialed on low dose naltrexone (LDN), 1 mg daily for two weeks, escalated to 2.5 mg daily for two weeks, and then held continuously at 4.5 mg daily. Once on the dose of LDN at 4.5 mg, she began PUVA treatments, twice weekly. At the five-month follow-up visit after 16 sessions of PUVA, her GA lesions had radically improved and her associated pruritis had completely resolved (**Figure 1C-D**). Her only side effect was occasional vivid dreams.

DISCUSSION

Naltrexone is a non-selective competitive opioid receptor antagonist used to treat substance use disorders at a 50 mg-100 mg dose.[4-6] At this dose, naltrexone completely blocks opioid receptors leading to a pro-inflammatory response. However, at doses of LDN (1-5 mg), naltrexone causes only a partial blockade, leading to receptor upregulation and release of anti-inflammatory molecules, such as β-endorphin and enkephalin.[5] Secondarily, naltrexone acts as an antagonist at toll-like receptor 4, reducing glial and macrophage inflammatory release of cytokines.[4-6]

Several cells of the skin express opioid receptors including keratinocytes, melanocytes, fibroblasts and some adnexal structures.[6] There have also been increasing reports of LDN's ability to reduce pruritis in other dermatologic conditions, perhaps due to inhibition of basophilic histamine release.[6] Studies have found success in Hailey-Hailey disease, systemic sclerosis, guttate psoriasis, and lichen planopilaris, as well as a host of diseases affecting other body systems.[5,6] Side effects include vivid dreams, insomnia, headache, and anxiety. To date,

however, no serious adverse effects have been reported. [4-6]

In addition to LDN, this patient received PUVA therapy. Studies have demonstrated mixed results on the efficacy of PUVA on GA.[3,7] In a retrospective study, Browne et al determined that PUVA was successful in clearance or at least improvement in 66% of 44 cases of generalized GA.[7] Cunningham and colleagues supported this finding with a small cohort of 8 out of 12 patients experiencing total or near total clearance of generalized GA.[3] Adverse effects of PUVA include phototoxicity, nail damage, nausea, and reactivation of HSV in the short-term, while long-term treatment has been associated with development of lentigines and keratoses, increased risk of squamous cell carcinoma, and altered immune function.[8]

CONCLUSION

LDN plus PUVA should be considered an alternative treatment for generalized GA. This case demonstrates that although the mechanism is unclear, the combined therapy led to improvements in cutaneous manifestations and associated pruritis with few side effects. A further investigation in larger cohorts is needed to explore the therapeutic potential of LDN plus PUVA in this treatment-refractory condition.

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