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Treatment of disseminated granuloma annulare with pulse therapy upadacitinib

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Abstract

Granuloma annulare (GA) is an idiopathic inflammatory skin condition with a chronic and unpredictable course. Although localized GA is usually cleared with topical or systemic corticosteroids, generalized GA is often difficult to treat owing to the lack of treatment options and recurrence with treatment. Recent evidence has helped to elucidate the etiology behind GA, with growing confirmation for the use of JAK inhibitors as a possible treatment for GA. We present a 61-year-old woman with recalcitrant GA who responded successfully to pulse therapy upadacitinib, a JAK1 inhibitor. Our findings demonstrate the utility of this alternative and practical treatment strategy that may reduce the cumulative toxicity of upadacitinib and optimize its risk/benefit ratio.

Keywords: granuloma annulare, inhibitor, Janus kinase, JAK-STAT, upadacitinib

Introduction

Granuloma annulare (GA) is a benign skin condition that is characterized by a localized or generalized (disseminated) inflammatory, granulomatous reaction [1]. Generalized GA is defined as the presentation of 10 or more widespread annular plaques [1]. Overall, the etiopathogenesis of GA is not well understood, but recent studies have uncovered the upregulation of Th1 and Th2 pathways [2], as well as the activation of JAK-STAT in GA lesions [3]. Limited case reports have shown that the JAK inhibitors tofacitinib, baricitinib, and upadacitinib have successfully cleared recalcitrant cases of GA [4-7]. Although JAK inhibitors are proving to be a viable therapy for various inflammatory skin diseases, the safety profiles of these treatments can cause trepidation for patients. In light of this, we evaluated the efficacy of pulse therapy upadacitinib for disseminated GA.

Case Synopsis

A 61-year-old woman with a medical history significant for hypothyroidism presented with a one-month history of rapidly progressive, pruritic, cutaneous plaques located on her forearms, wrists, thighs, and trunk. The patient had failed a two-week course of triamcinolone 0.1% topical cream prescribed by her primary care physician upon presentation. Clinical examination revealed multiple flesh-toned papules coalescing into plaques located on the posterior neck, dorsal forearms and wrists, abdomen, and posterior thighs (**Figure 1A-C**). A shave biopsy was performed on the right forearm. Histopathology demonstrated superficial and mid-dermal perivascular and interstitial inflammatory cell infiltrate containing lymphocytes, histiocytes, eosinophils, neutrophils, and proliferating histiocytes throughout the dermis (**Figure 2**). These findings were consistent with GA.

Numerous topical and systemic treatments were tried, including clobetasol 0.05% topical cream, triamcinolone 0.1% topical cream alternating with the clobetasol cream, and oral prednisone tapers, all with limited improvement as the patient saw no decrease in the number of plaques and persistent intractable pruritus. However, no new lesions developed. After four months of unsatisfactory response to prior therapies, various treatment options were discussed, including

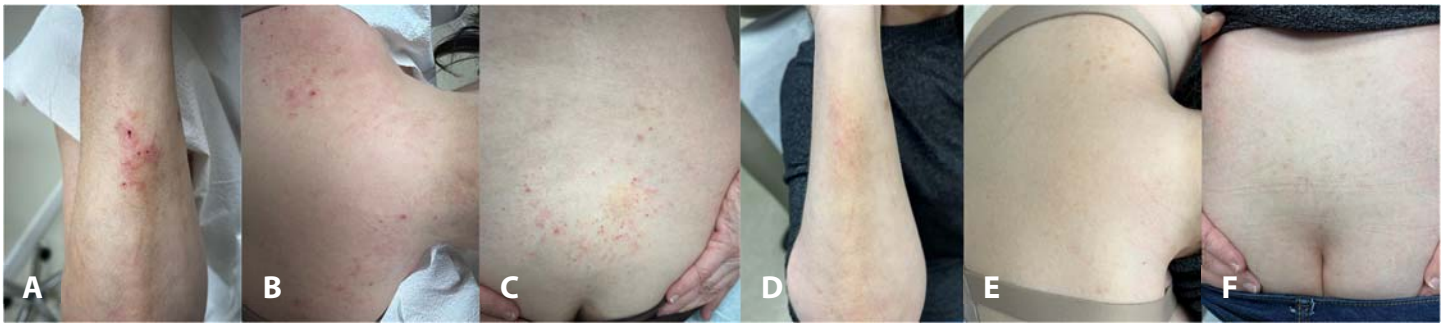

Figure 1. *Effect of pulse therapy upadacitinib treatment for granuloma annulare.* ***A-C****) Clinical photographs prior to upadacitinib pulse therapy, and* ***D-F****) four weeks after upadacitinib pulse therapy showing near complete clearance of granuloma annulare with faint post-inflammatory hyperpigmentation.*

hydroxychloroquine, dapsone, and upadacitinib. The patient agreed to pulse therapy of upadacitinib (15mg/d for three days per week) in order to reduce the risk of immunosuppression and other possible side effects. Four weeks after initiating pulses of upadacitinib, clinical examination revealed complete clearance of her bilateral forearms, trunk, and thighs (**Figure 1D-F**). The patient noted complete resolution of pruritus within days of initiating therapy. Sustained clearance of skin lesions and pruritus was noted even upon tapering to upadacitinib 15mg/d twice weekly at month two. If the patient remains clear on this treatment schedule then further tapering to upadacitinib once weekly will be initiated at month three.

Case Discussion

Granuloma annulare is a granulomatous, inflammatory skin disease that can be characterized as either localized or disseminated, dependent on lesion formation and distribution. First-line therapies typically include topical and intralesional corticosteroids owing to their low safety risk and cost effectiveness [1]. Disseminated GA is often recalcitrant and unresponsive to corticosteroids, leading to second line therapies such as dapsone, hydroxychloroquine, pentoxifylline, or methotrexate [1]. Although the etiology of GA is still largely unknown, the recent discoveries of Th1 and Th2 upregulation and activation of the JAK-STAT pathway provide an alternative approach to treatment [2,3]. Several case reports have demonstrated successful treatment of disseminated GA with the JAK inhibitors upadacitinib [6,7], tofacitinib [4], and baricitinib [4]. In the previous case presentations of disseminated GA treated with upadacitinib, one patient with rheumatoid arthritis was given upadacitinib 15mg daily and was nearly clear in four months [6]; the other patient with a history of diabetes mellitus was given upadacitinib 15mg daily and saw almost complete clearance in two weeks [7]. Our patient saw almost complete clearance within days of completing just three pulses of upadacitinib 15mg/d, demonstrating the lowest effective dose of upadacitinib for disseminated GA to date. It is important to note that GA has been linked to numerous comorbidities, including rheumatoid arthritis and diabetes mellitus, which may have contributed to the differences in treatment time between the three cases [8].

Although JAK inhibitors are proving to be a promising treatment for GA, concerns of their safety profiles and recent black box warning by the FDA may contribute to hesitation from prescribers and patients alike [9]. Common adverse effects of JAK inhibitors include infections such as upper respiratory tract infections, nausea, and headaches;

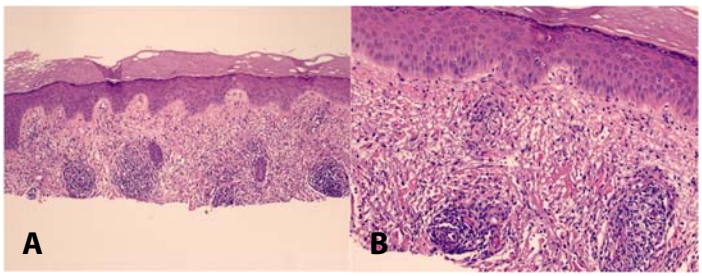

Figure 2. *H&E histologic examination of granulomatous dermatitis from skin biopsy consistent with granuloma annulare.* ***A)*** *Mixed dermal infiltrate with perivascular and interstitial infiltrate, 10×;* ***B)*** *perivascular and interstitial infiltrate of histiocytes, lymphocytes, and neutrophils, 20×.*

less common but possible serious side effects include major adverse cardiovascular events, increased malignancy risk, and serious infections such as pneumonia [9]. For individuals with recalcitrant disseminated GA who have concerns or comorbidities that raise their risks for these side effects, pulse therapy upadacitinib provides a safer, more sustainable approach to potentially long-term therapy.

Conclusion

Granuloma annulare is an inflammatory skin condition characterized by annular plaques that can be localized or generalized. Disseminated GA is often resistant to treatment and owing to the recent discovery of the JAK-STAT activation of GA lesions, JAK inhibitors have emerged as a new treatment. We believe that the decreased risk of immunosuppression and other possible side effects from pulse therapy upadacitinib could make it a suitable treatment option for those with recalcitrant disseminated GA who have comorbidities or intolerance to standard therapies.

Potential conflicts of interest

The authors declare no conflicts of interest.

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