Treatment of Recalcitrant Generalized Granuloma Annulare With Adalimumab

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ABSTRACT

Granuloma annulare is a benign, usually self-limited, dermatosis of unknown cause. Generalized lesions occur in approximately 15 percent of patients with GA and may cause mild to severe cosmetic disfigurement. The treatment of generalized granuloma annulare can be challenging. We report the case of a 36-year-old male patient with a generalized granuloma annulare who had failed topical and systemic glucocorticoids, systemic retinoids, dapsone, minocycline, PUVA therapy, and hydroxicloroquine and was successfully treated with adalimumab, an anti-TNF-α monoclonal antibody. Adalimumab may be an additional option in the treatment of recalcitrant forms of granuloma annulare.

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INTRODUCTION

Granuloma annulare (GA) is a benign inflammatory skin disease characterized by marginated erythematous plaques or nodules that are usually localized to the distal extremities. Although generalized, perforating and subcutaneous variants have also been identified.[1] Additionally, although GA tends to be idiopathic, several case reports have shown an association with diabetes mellitus and several malignancies. Localized forms of GA are usually asymptomatic and self-limited with spontaneous resolution occurring often within 2 years. However, generalized GA (GGA) tends to be more chronic and pruritic, may last for decades, and may cause mild to severe cosmetic disfigurement. The treatment of GGA can be challenging. Systemic steroids can often benefit patients; however high doses are required and usually patients relapse after stopping treatment. Moreover, as GGA is occasionally associated with diabetes mellitus, some patients are contraindicated to steroids therapy. Other systemic treatments include nicotinamide, PUVA therapy, UVA1, dapsone, pentoxifylline, systemic retinoids, cyclosporine, alkylating agents, and antimalarials.

CASE REPORT

A 36-year-old male patient presented with disseminated erythematous plaques on the trunk, upper, and lower extremities that had persisted for more than five years (Figure 1a). He was otherwise healthy. He had the diagnosis of disseminated granuloma annulare, histopatologically confirmed. He had been treated unsuccessfully with topical and systemic glucocorticoids, systemic retinoids, dapsone, minocycline, PUVA therapy, and hydroxychloroquine. It was evident that the disease created a high psychological discomfort, mainly for aesthetic reasons.

A new cutaneous biopsy was performed, confirming the diagnosis (Figure 2), and diabetes mellitus was excluded. Treatment with adalimumab was started, with a subcutaneous injection 80 mg at week 0 and then 40 mg every other week at week 1. Before initiating therapy, the patient was screened for tuberculosis, hepatitis B, and hepatitis C, which were negative. A rapid response to treatment was observed, and at week 4 most of the lesions had showed a remarkable regression. At week 8 all lesions had completely regressed, showing only residual hyperpigmentation (Figure 1b). After 6 months of therapy, without recurrence of the lesions, the treatment was stopped. At the 9-month follow-up after stopping adalimumab, the patient continues to be free of lesions.

DISCUSSION

The use of TNF-α inhibitors (infliximab, adalimumab and etanercept) in the treatment of recalcitrant GGA has been reported, showing an effective and rapid response.[2-5] TNF-α is critical in the formation of granulomas due to infectious and non-infectious

FIGURE 1. Clinical features of the lesions **a)** before treatment; **b)** 8 weeks after treatment with adalimumab.

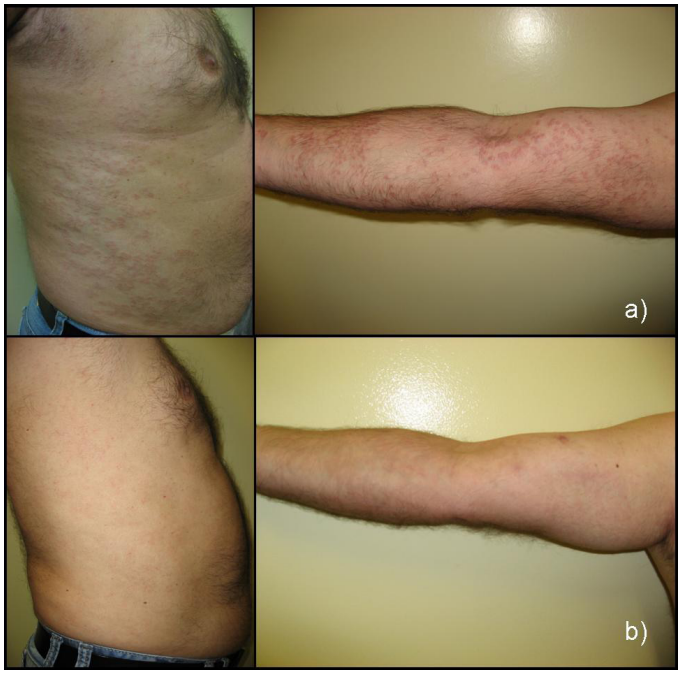
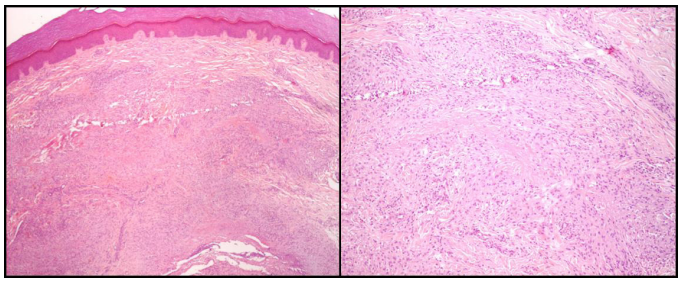


FIGURE 2. Histopathological features: palisades of histiocytes admixed with scant lymphocytes and surrounding foci of necrobiosis admixed with subtle strands of mucin in the superficial and mid dermis.



agents. Granulomas are composed predominantly of mononuclear cell with lymphocytes and macrophages secreting TNF-α and interferon-gamma. Moreover, some investigations have shown that an overexpression of TNF-α by peripheral mononuclear lymphocytes and macrophages may play a role in the development of GA.[6] Therefore, interfering with TNF-α can lead to breakdown of the granuloma structure.

Adalimumab is a fully human anti-TNF-α monoclonal antibody that binds specifically to soluble and membrane-bound TNF-α, blocking its interaction with p55 and p75 cell surface TNF receptors. Adalimumab is currently approved for psoriasis, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, adult rheumatoid arthritis, and Crohn's disease. Adalimumab, like infliximab, inhibits not only soluble TNF-α but also transmembrane TNF-α, while etanercept mainly binds soluble TNF-α.[7]

The ability to adalimumab and infliximab to bind transmembrane TNF-α may explain why adalimumab and infliximab—but not etanercept—induce apoptosis of monocytes and T-lymphocytes in Crohn's disease.[8]

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This partially different mechanism of the TNF-α inhibition between etanercept and anti-TNF-α monoclonal antibodies might justify the lower clinical efficacy of etanercept, but not infliximab and adalimumab, in the treatment of granulomatous diseases as Crohn's disease and Wegener's granulomatosis, and the more pronounced propensity of the monoclonal antibodies in comparison with etanercept in reactivation of latent tuberculosis. It could also explain the treatment failure of 4 patients with GGA treated with etanercept reported by Kreuter et al.[9] In fact, several recent reports have demonstrated that infliximab was highly effective in the treatment of other granulomatous skin disorders such as cutaneous sarcoidosis and necrobiosis lipoidica, which are sometimes difficult to treat.

This case is another example that anti-TNF-α inhibitors (mainly the monoclonal antibodies adalimumab and infliximab) because of their slightly different mechanism of action relatively to etanercept, should be considered a therapeutic option in refractory GGA.

DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

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