

CASE REPORT

A CASE OF CHILDHOOD RECALCITRANT GRANULOMA ANNULARE SUCCESSFULLY TREATED WITH TOPICAL TACROLIMUS

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ABSTRACT: A 5years old boy presented to us with skin colored to erythematous papules which coalesced to form annular plaques with a tendency to spread centrifugally with mild atrophy in the center for a duration of 9 months. The clinical and histopathological findings confirmed the case to be a generalized granuloma annulare of interstitial type. He was successfully treated with topical tacrolimus (0.1%) which was earlier failed to respond satisfactorily with topical and systemic steroid. The case was followed up for duration of another 6 weeks and did not show any signs of relapse or tacrolimus associated adverse effects.

KEYWORDS: Tacrolimus, recalcitrant, granuloma annulare.

INTRODUCTION: Granuloma annulare (GA) is an inflammatory disorder of the dermis and/or subcutis characterized by degeneration of connective tissue and a surrounding infiltrate which is predominantly histiocytic.¹ It can occur at any age but overall is commonest in children and young adults. The most common sites to be involved are the backs of the hands, fingers, dorsum of the feet, legs and forearm.²

The clinical variants of GA are localized, disseminated or generalized, nodular, perforating, and subcutaneous. GA often presents with papules, the centers of which may be slightly hyperpigmented and depressed relative to their borders. Generalized GA is characterized by numerous papules and annular plaques symmetrically distributed on the trunk and extremities. Lesions are usually asymptomatic, but rarely it may be pruritic or painful.

The cause of GA is unknown, but it has been reported to follow trauma, malignancy, viral infections (including human immunodeficiency virus, Epstein-Barr virus and herpes zoster), insect bites and tuberculosis skin tests.³ It is ultimately a self-limiting condition and only very rarely has been associated with tissue destruction and scarring.⁴

Different treatment modalities like cryotherapy, scarification, topical and systemic steroids, antimalarials, chlorambucil, ciclosporin, dapsone, etretinate, fumaric acid esters, isotretinoin, niacinamide, pentoxifylline, photo(chemo)therapy, potassium iodide, zileuton (a 5-lipoxygenase inhibitor), vitamin E have been tried with variable responses.¹ Recent reports suggest topical tacrolimus may be helpful.⁵

History: A 5years old boy weighing 20kgs presented to us with skin colored to erythematous papules which coalesced to form annular plaques with a tendency to spread centrifugally with mild atrophy in the center. Initially, the lesions started over the dorsum of both hands and forearms in a symmetrical fashion and gradually spread to involve both legs and feet in a duration of 9 months (Figure: 2). It was insidious in onset and was not associated with any constitutional symptoms. No history of any seasonal variation, aggravating or relieving factors. No evidence of scaling. General examination did

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not reveal any abnormality. Complete blood count, urine analysis, liver function test, plasma glucose level, chest X-ray, mantoux test, C-reactive protein ASO titre and serology for HIV were all normal.

Histopathological examination of skin biopsy shows the entire reticular dermis was thickened with collagen bundles between which are splayed small collections of histiocytes that partially surround small foci of necrobiosis (Figure. 1). So, the clinical and histopathological findings confirmed the case to be a generalized granuloma annulare of interstitial type.

He was put on moderate potency topical steroid (mometasone 0.1% cream twice daily application) along with systemic corticosteroid (prednisolone 20mg daily i.e. 1mg/kg/day). After 4 weeks of therapy the lesions started regressing in size and completely disappeared in 6 weeks and the steroids were tapered over next 4 weeks. The patient developed topical steroid induced mild atrophy and hypopigmentation around the perilesional areas.

The lesions started relapsing rapidly after stopping the treatment. So, we considered alternate therapy solely with topical tacrolimus 0.1% twice daily application. After 4 weeks of treatment, the lesions started regressing with near complete clearance at the sites with remnant hyper pigmentation over next 4 weeks (Figure. 3). We continued the treatment for another 2 weeks.

The patient remains in a satisfactory clinical remission without any relapse of lesions up to a 6 weeks post therapy follow up. During the treatment with topical tacrolimus, the patient had not reported any side effects such as paraesthesia, burning sensation, itching or skin atrophy associated with tacrolimus as mentioned in literature.

DISCUSSION: The most characteristic histological lesion in granuloma annulare is the necrobiotic granuloma. But there are three histological patterns that may occur: necrobiotic palisading granuloma, an interstitial form, and granuloma of sarcoidal or in tubercular type. Necrobiotic granuloma is characterized by foci of necrobiosis surrounded by histiocytes and lymphocytes with histiocytes commonly forming a palisade pattern.

Analysis of T-cell repertoire and cytokine pattern has shown a T-cell response characterized by a combination of few skin specific clones together with many non-specific T-cells and abundant production of interleukin-2 (IL-2). The high local production of interleukin-2 could be responsible for the non-specific attraction of T-cells to the granuloma.⁶

Histologically, GA is characterized by lymphohistiocytic granulomas, with various degrees of collagen degeneration, micro droplet lipid accumulation and mucin deposition. Immunocytochemical studies have shown a predominance of interleukin (IL)-6 and tumour necrosis factor (TNF- α) in GA and other granulomatous conditions.⁷ Other studies analyzing intralesional cytokine expression in GA revealed abundant production of IL-2^{8,9} which was thought to play an important role in the nonspecific attraction of T cells to the granulomatous site.

Tacrolimus is a macrolide lactone; calcineurin inhibitor, cause inhibition of IL-2 and T-cell derived cytokines like TNF- α , and other interleukins.¹⁰ It also inhibits the transcription and release of other cytokines (e.g. IL-3, IL-4, IL-5, TNF- α and granulocyte/macrophage colony-stimulating factor), which can contribute to allergic inflammation.¹¹ Unlike corticosteroids, which modify functions and growth of many cell types including fibroblasts and keratinocytes, tacrolimus acts specially on inflammatory cells.¹²

The exact mechanism of action of tacrolimus in GA is not known but the capacity of tacrolimus to inhibit the activation of different cytokines (IL-2 and TNF- α) may account for its ability

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to reduce inflammation and to treat GA effectively. And also immunomodulatory effects with suppression of the granulomatous infiltrates, including reduction of chemotactic activity of fibroblasts and the inhibition of collagen synthesis.¹³

Tacrolimus in its topical formulation has been established as a safe and effective alternative to topical corticosteroids because of its mild side effects and its minimal systemic absorption. However, in our case, we are reporting this case, firstly because of its frequent relapses with steroid therapy which was successfully controlled with topical tacrolimus. Secondly, because of its rarity of reporting of successful treatment of childhood disseminated granuloma annulare with topical tacrolimus only.

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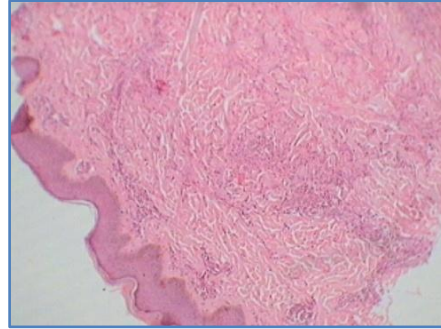


Fig. 1: Histopathology shows the entire reticular dermis has thickened collagen bundles between which are splayed small collections of histiocytes that partially surround small foci of necrobiosis.

Before Treatment



Fig. 2: Multiple erythematous annular Plaques with mild central atrophy on the lateral aspect of leg

After Treatment



Fig. 3: Complete clearance of the lesions with remnant mild hyperpigmentation

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