Intravenous immunoglobulin–refractory necrobiotic xanthogranuloma successfully treated with tofacitinib 2% cream

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Key words: IVIg; JAK inhibition; necrobiotic xanthogranuloma; tofacitinib.

INTRODUCTION

Necrobiotic xanthogranuloma (NXG) is a non-Langerhans cell histiocytosis occurring in association with paraproteinemia. Treatment of NXG is limited given its rarity and lack of robust studies evaluating effective treatments. Successful treatment has been reported with various skin-directed and/or systemic immunomodulatory agents. Tofacitinib is a janus kinase (JAK)1/3 inhibitor approved for the treatment of rheumatoid arthritis and ulcerative colitis.[1] It has recently gained attention for off-label use in a variety of dermatologic conditions, including granulomatous processes, such as sarcoidosis. Here we report the case of a patient with refractory NXG who responded to topical tofacitinib 2% liposomal cream.

Abbreviations used:

IVIg: intravenous immunoglobulin
JAK: janus kinase
NXG: necrobiotic xanthogranuloma

CASE REPORT

A 64-year-old woman first presented to our clinic with a presumed diagnosis of Cogan syndrome and sarcoidosis, having had symptoms of uveitis, facial palsy, labyrinthitis, and skin lesions. Several orange-yellow plaques and nodules in the periorbital and upper portion of the medial cheeks were present (Fig 1) alongside uveitis that was not responsive to up-titration of her medications, which included prednisone 15 mg daily, azathioprine 100 mg daily and infliximab 10 mg/kg every 4 weeks. She had previously failed mycophenolate mofetil as well. On presentation and performance of a biopsy, a diagnosis of NXG was established.

Serum protein electrophoresis and immunofixation revealed prominent IgG kappa paraproteinemia, consistent with monoclonal gammopathy of dermatologic significance. The patient was evaluated by hematology and underwent bone marrow biopsy analysis, which was negative for myeloma. The ultimate plan was for hematology to continue close monitoring for progression.

The lesions were injected with intralesional triamcinolone acetonide (3.3-5 mg/cc) with minimal improvement. Infliximab was discontinued and the patient was started on intravenous immunoglobulin (IVIg) 2 gm/kg, as per previous reports of successful treatment in NXG (Fig 2, *A*).[2] There was an 80% improvement of lesions characterized by thinning and shrinking of plaques after adding IVIg. However, after 9 months, the patient noted the persistence of a plaque on the right temple complicated by ulceration and preseptal cellulitis (Fig 2, *B*). Despite localized treatments with tacrolimus, topical steroids, intralesional triamcinolone acetonide, and mupirocin, the lesion remained recalcitrant. At the time of continuing IVIg treatment, tofacitinib 2% liposomal cream was compounded and the patient was instructed to use it on the temple twice daily. The patient noted significant improvement at her 3-month follow-up visit with complete resolution of

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Funding sources: None.

IRB approval status: Not applicable.

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JAAD Case Reports 2023;32:41-3.

2352-5126

https://doi.org/10.1016/j.jdcr.2022.12.002

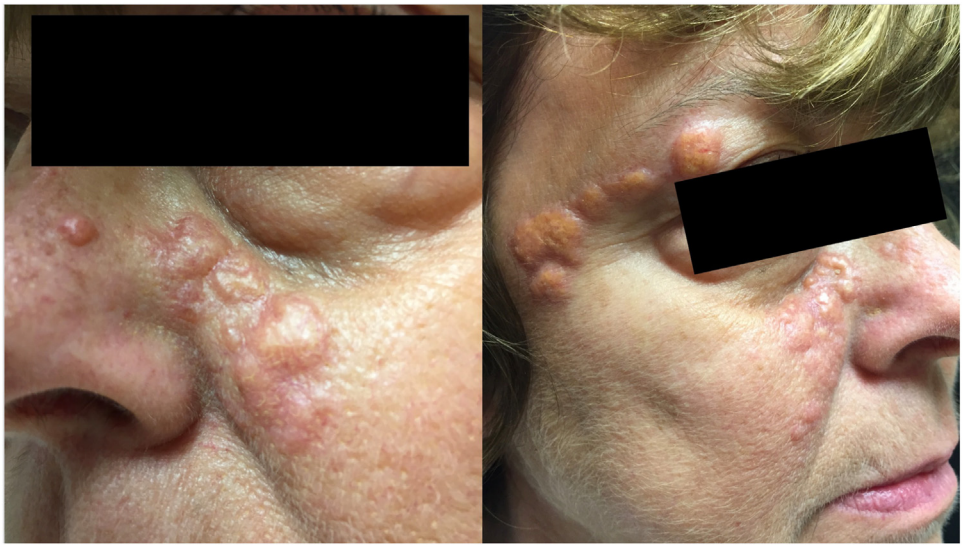

Fig 1. Clinical findings on presentation. Scattered erythematous firm orange-yellow to pink papules and nodules coalescing into larger plaques on the face.

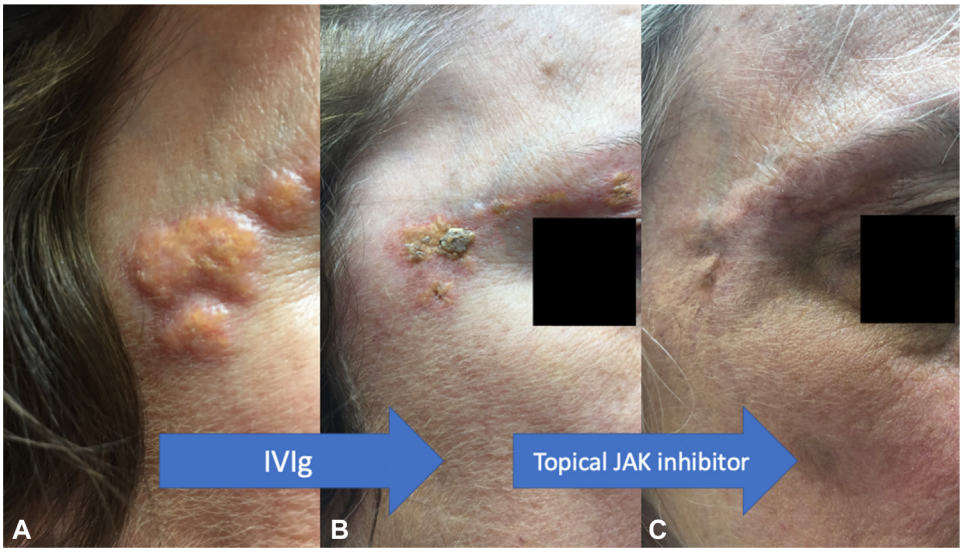

Fig 2. Progression of refractory right temporal necrobiotic xanthogranuloma lesion with treatment. **A,** Active lesion at the time of receiving therapy with infliximab, azathioprine, and prednisone. **B,** After 9 months of treatment with IVIg (in lieu of infliximab). Note the thinning of lesion on the right temple but there is still persistent activity with associated ulceration and crusting. **C,** Complete resolution of lesion on the right temple with the addition of tofacitinib 2% liposomal cream. *IVIg*, Intravenous immunoglobulin; *JAK*, janus kinase.

the lesion at 9 months. The patient no longer required the application of tofacitinib at that time (Fig 2, *C*). No side effects were noted from the topical application of tofacitinib.

DISCUSSION

The treatment of NXG can be challenging given the limited data within the literature. A study with the largest cohort to date did demonstrate a 100% response rate among patients with NXG treated with IVIg, supporting its first-line use.[3] Other treatment options with high response rates included antimalarials (80%), intralesional triamcinolone (75%), surgery (75%), chemotherapy (67%), and lenalidomide/thalidomide (63%).[3]

To our knowledge, no information is available regarding the use of tofacitinib in NXG. Oral tofacitinib has gained attention for off-label use in a variety

of dermatologic conditions including alopecia areata and atopic dermatitis. Topical tofacitinib has mainly shown promise in vitiligo alongside narrowband ultraviolet B.[4] We present the first case to date of the use of topical tofacitinib for refractory NXG. Our patient achieved a great degree of improvement on IVIg; however, her recalcitrant ulcerated lesion only resolved after the use of topical tofacitinib 2% liposomal cream.

Although there are data indicating the upregulation of the JAK-STAT pathway in granulomatous diseases, like granuloma annulare and sarcoidosis,[5,6] to our knowledge, no data in the literature have linked the JAK-STAT pathway directly to the pathophysiology of NXG. However, evaluation of NXG pathophysiology has revealed the upregulation of proinflammatory cytokines, including interleukin 6 and tumor necrosis factor-alpha.[7] Animal studies have shown that JAK inhibitors may impede interleukin 6 transsignaling,[8] potentially explaining the efficacy of tofacitinib on NXG in our patient.

In summary, this case provides evidence for the use of tofacitinib in refractory NXG. Further cases and more studies are necessary to better characterize the effects of JAK inhibitors for the treatment of NXG.

Conflicts of interest

Drs Mazori and Shahriari have no financial disclosures to share. Dr Merola is a consultant and/or investigator for Amgen, Bristol-Myers Squibb, Abbvie, Dermavant, Eli Lilly, Novartis, Janssen, UCB, Sanofi, Regeneron, Sun Pharma, Biogen, Pfizer, and Leo Pharma.

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