# Management of treatment-resistant angiolupoid sarcoidosis with adalimumab and tofacitinib 2% ointment

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***Key words:*** adalimumab; angiolupoid sarcoidosis; cutaneous sarcoidosis; JAK inhibitor; TNF-$\alpha$ inhibitor; tofacitinib.

## INTRODUCTION

Sarcoidosis is a granulomatous disorder of unknown etiology, with diagnosis based on radiographic and/or histologic presence of noncaseating granulomas within organ systems, most commonly pulmonary and lymphatics.[1-5] Angiolupoid sarcoidosis is a subtype of cutaneous sarcoidosis that manifests as erythematous to violaceous telangiectatic papulonodules, characteristically located on the nasal bridge.[1,2] Cutaneous sarcoidosis is reported in approximately 25% of patients with systemic sarcoidosis, but the specific prevalence of the angiolupoid subtype is less well-characterized.[6]

There are currently no US Food and Drug Administration-approved treatments for cutaneous sarcoidosis.[1] Use of topical and intralesional corticosteroids are often attempted, although these therapies are limited by poor efficacy and potential for local side effects, such as hypopigmentation and atrophy. Systemic medications—including immunosuppressants, antimalarials, pentoxifylline, isotretinoin, antibiotics, and tumor necrosis factor (TNF)-$\alpha$ inhibitors—are often implemented but are inconsistently effective.[1,3] Here, we present a case of treatment-resistant angiolupoid sarcoidosis that improved significantly with combination adalimumab and a topical Janus kinase (JAK) inhibitor.

*Abbreviations used:*

JAK: Janus kinase
TNF: tumor necrosis factor

## CASE REPORT

A 44-year-old woman presented to our clinic in 2013 with a 1-year history of violaceous plaques with prominent telangiectasias on the right nasal sidewall and right infraorbital cheek (Fig 1). Punch biopsy from the right nasal sidewall was performed that identified numerous discrete sarcoidal granulomas throughout the dermis with few surrounding lymphocytes and peripheral dermal fibrosis. No foreign bodies were identified on polarized microscopy. Chest x-ray identified mild prominence of bilateral hila with otherwise normal lung parenchyma. Review of systems was negative.

A diagnosis of cutaneous angiolupoid sarcoidosis was made based on clinical and histologic findings. She was prescribed hydrocortisone cream 2.5% and initiated a series of intralesional triamcinolone injections, which were continued over the course of several years. Her disease was sequentially treated with doxycycline 100 mg by mouth twice daily, methotrexate 15 mg by mouth weekly, and hydroxychloroquine 200 mg by mouth twice daily; however, she continued to have progressive disease with development of violaceous plaques and telangiectasias on her nasal dorsum, right mid cheek, and right zygomatic cheek (Fig 2). Violaceous papules and telangiectasias developed at sites distant from previous intralesional triamcinolone injections. In the fall of 2022, she was transitioned to adalimumab 40 mg subcutaneously every other week combined with

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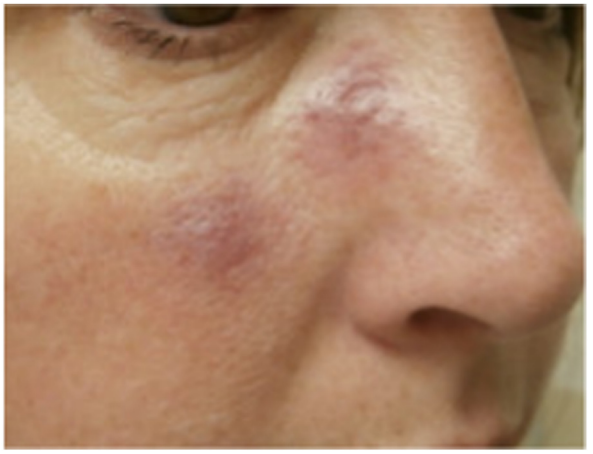

**Fig 1.** Initial presentation of 2 discrete violaceous plaques with overlying telangiectasias on the right cheek and right nasal sidewall.

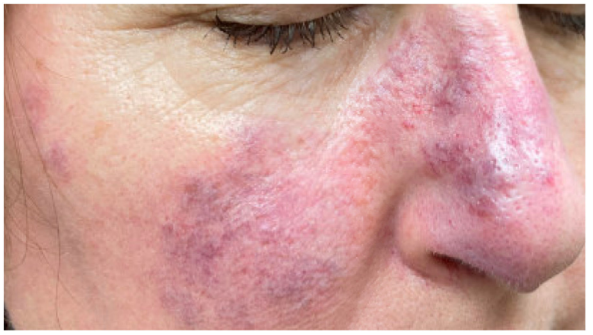

**Fig 2.** Disease progression prior to starting adalimumab and topical tofacitinib 2% ointment.

topical tofacitinib 2% ointment twice daily. She had substantial improvement of the violaceous plaques noted at her 3-month follow-up visit (Fig 3) with only scattered persistent telangiectasias. At 6-month follow-up visit, (Fig 4) there was notable continued lightening of the telangiectasias in previously involved areas.

## DISCUSSION

$CD4^+$ $T_H1$ lymphocytes and macrophages comprise the noncaseating granulomas that are characteristic of sarcoidosis.[4] TNF-$\alpha$ inhibitors are theorized to disrupt this persistent $T_H1$ response.[7,8] There are reports of TNF-$\alpha$ inhibitors successfully treating cutaneous sarcoidosis,[3,4] but evidence is generally mixed, with some cases observing no improvement and others noting worsening disease.[5] $CD4^+$ $T_H1$ lymphocytes also produce interferon gamma, which promotes macrophage activation in sarcoidal granulomas via the JAK/signal transducer and activator of transcription pathway.[1,9] The development of telangiectasias that are characteristic of angiolupoid sarcoidosis is thought to be driven by macrophage production of blood vessel growth factors. Therefore, by preventing macrophage activation by inhibiting the JAK-signal transducer and activator of transcription pathway, tofactinib may also help to reduce the creation of new telangiectasias in this disease process.[1]

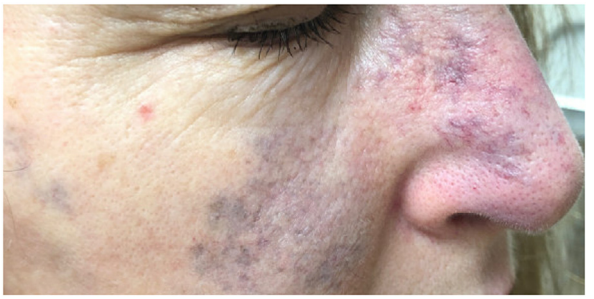

**Fig 3.** Follow-up after 3 months of adalimumab and tofacitinib 2% ointment.

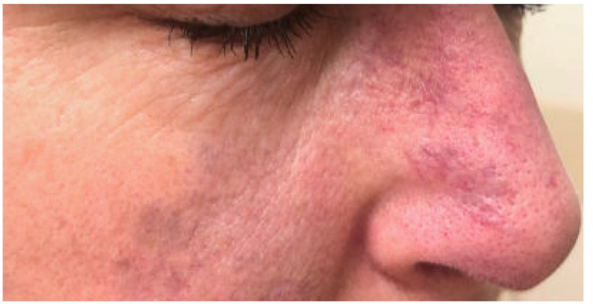

**Fig 4.** Follow-up after 6 months of adalimumab and tofacitinib 2% ointment.

Oral JAK inhibitors, such as tofacitinib, have shown promise in achieving clinical and histologic remission of treatment-resistant sarcoidosis.[9] A case report by Singh et al[1] also demonstrated a notable decrease in erythema and induration of angiolupoid sarcoidosis plaques after 10 weeks of treatment with 2% topical tofacitinib ointment; however, the patient had persistent telangiectasias, which ultimately responded well to treatment with pulsed dye laser. Our patient had similar findings at her 3-month follow-up with persistent telangiectasias, but after 6 months of treatment, these continued to improve.

A concurrent regimen of a TNF-$\alpha$ inhibitor (adalimumab) along with a JAK inhibitor (tofacitinib) is not standard approach to treating angiolupoid sarcoidosis. It is hypothesized that simultaneous disruption of the $T_H1$ polarization within sarcoidal granulomas, as well as downstream inhibition of macrophage activation (and subsequently telangiectasia formation) by interferon gamma, may mitigate the disease process more completely and effectively than using either of these agents as monotherapy.[4,7]

Although drawing any specific conclusions regarding the efficacy of either treatment alone is limited by the patient's concurrent regimen, this case adds to a growing body of literature that topical JAK inhibition may be a viable, low-risk approach for the treatment of angiolupoid sarcoidosis, and may be considered in conjunction with a TNF-$\alpha$ inhibitor for added benefit.

**Conflicts of interest**

None disclosed.

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