Case Presentation

Dupilumab treatment for pruritus-associated cutaneous sarcoidosis

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Abstract

Sarcoidosis is a chronic multisystemic, inflammatory disease characterized by the formation of noncaseating granulomas, with cutaneous involvement in a fraction of patients. Although existing literature reports dupilumab to cause sarcoidosis-like reactions, we present a 57-year-old man with erythrodermic sarcoidosis and atopic dermatitis refractory to numerous systemic medications that later improved with dupilumab. The improvement of his pruritus and cutaneous lesions after dupilumab initiation, followed by worsening after temporary discontinuation, then re-improvement after re-initiation supported dupilumab's therapeutic role. IL-4 and IL-13 stimulates tissue fibrosis and irreversible tissue damage in sarcoidosis, perhaps explaining dupilumab's therapeutic mechanism in this patient's case. For patients with severe sarcoidosis refractory to numerous medications, clinicians should keep in mind dupilumab as a potential option, particularly for those patients with concomitant atopic dermatitis.

Introduction

Sarcoidosis is often managed with various topical, intralesional, or systemic medications, such as methotrexate, thalidomide, tumor necrosis factor antagonists, and Janus kinase inhibitors.[1,2] Herein, we present the first known documented use of dupilumab as a treatment option for severe refractory cutaneous sarcoidosis associated with atopic dermatitis (AD).

Case Synopsis

A 57-year-old man presented with erythrodermic sarcoidosis, pulmonary sarcoidosis, and severe AD, previously reported as the first documented case of biopsy-proven erythrodermic sarcoidosis in the skin of color population (Figure 1).[3] He reported persistent pruritus throughout the day. Various topical steroids and hydroxyzine 25mg nightly were used without improvement. His exam revealed diffuse pink papules, widespread erythema, dry scale, and poikilodermatous changes (Figure 2).

Previously, his erythrodermic sarcoidosis was resistant to hydroxychloroquine, thalidomide, methotrexate, prednisone, azathioprine, mycophenolate mofetil, cyclosporine, leflunomide, phototherapy (including psoralen-ultraviolet A and narrowband ultraviolet B), adalimumab, allopurinol, dapsone, levofloxacin, ethambutol, azithromycin, and rifampin. Owing to his pruritus and concomitant history of AD, we initiated subcutaneous dupilumab 300mg every two weeks.

His sarcoidosis and AD improved within several months. Conjunctival symptoms, however, led to self-discontinuation of dupilumab. Of note, the patient has a history of hydroxychloroquine-related maculopathy and sarcoid panuveitis treated with corticosteroid eye drops and an oral corticosteroid taper, respectively. Per ophthalmology consultation, his vision changes were not from dupilumab.

The patient decided to stop dupilumab for 11 months. During this time, he noted an exacerbation of skin symptoms, including increased erythema, pruritus, and scaling. Subsequently, dupilumab 300mg every two weeks was reintroduced. Simultaneously, his ophthalmologist increased intensity of treatment for his ocular symptoms with corticosteroid eye drops on a weekly or bi-weekly basis. Following reinitiation of dupilumab, the patient experienced rapid and significant reduction in pruritus, decreasing from severe to mild. Subsequent examinations demonstrated a reduction in the distribution of his generalized sarcoidosis and widespread erythema. At his most recent clinic visit, three years post-reinitiation of dupilumab, only post-inflammatory hyperpigmentation was noted in his examination (Figure 2). Two years later however, he experienced progression of his pulmonary symptoms; thus, mycophenolate mofetil 1500mg twice daily and prednisone 20mg daily was reintroduced.

Discussion

Dupilumab is a monoclonal antibody approved for AD and allergic asthma that inhibits the IL-4/IL-13 pathway via IL-4Rα blockade.[4,5] Emerging literature suggests IL-4

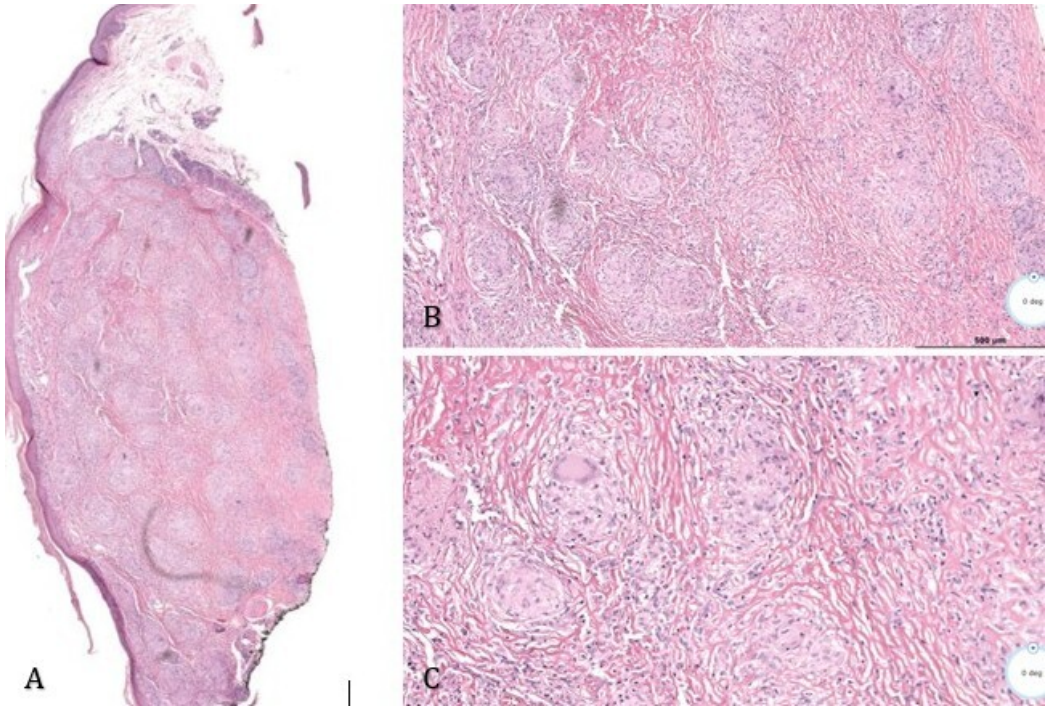

Figure 1. *Biopsy specimen from the back demonstrates non-caseating granulomatous inflammation, with well-formed epithelioid granulomas and sparse lymphocytic infiltrates. Hematoxylin and eosin stain, starting from left-hand side, clockwise:* ***A)*** *x1,* ***B)*** *x5,* ***C)*** *x10.*

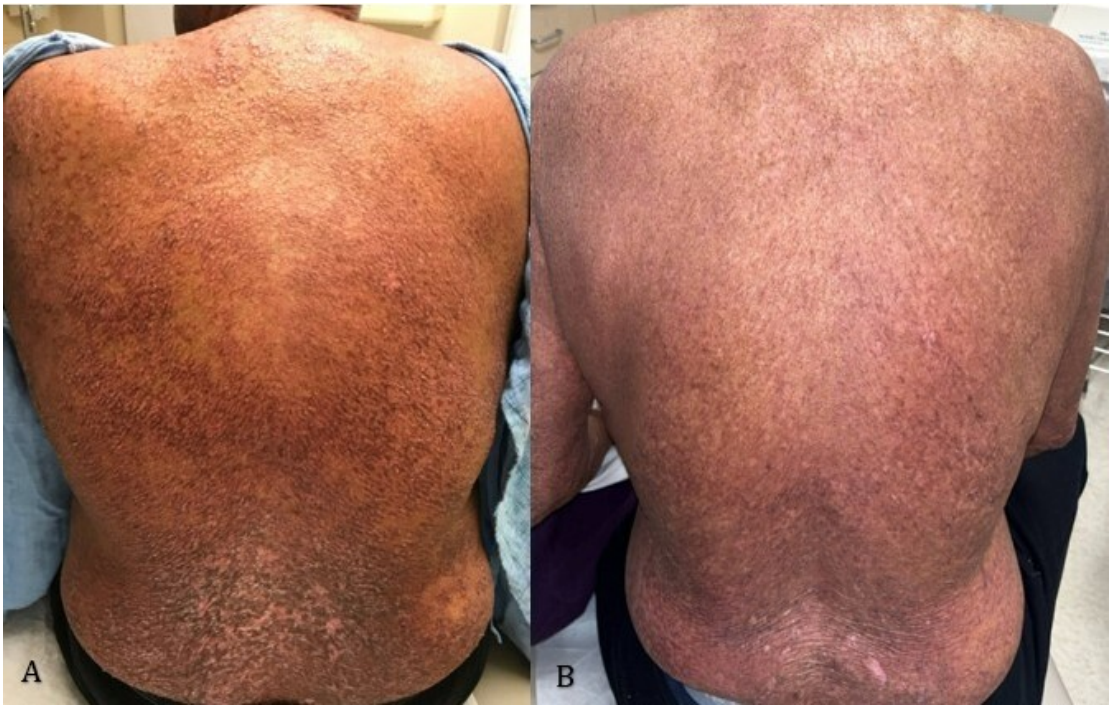

Figure 2. ***A)*** *Left image represents the patient's concomitant sarcoidosis and atopic dermatitis prior to initiation of dupilumab.* ***B)*** *Right image represents the patient's skin after two consecutive years of dupilumab. Note the decreased eczematous papules and decreased lichenification.*

and IL-13, both Th2 cytokines, stimulate polarization toward alternatively activated (M2) macrophages, which promote irreversible tissue damage, fibrosis, and early granuloma formation in sarcoidosis.[6,7] Increased thymus and activation-regulated chemokine expression in the peripheral circulation and in cutaneous granulomas also suggest an active Th2 response.[8] Inhibition of the Th2 pathway may therefore explain the significant reduction in cutaneous symptoms and pruritus observed in our patient.[9] However, careful monitoring is warranted as

dupilumab can result in drug-induced sarcoidosis-like reactions.[10]

Imbalance of the Th1/Th2 pathways in sarcoidosis is linked to granuloma formation and subsequent classical (M1) macrophage activation.[6] Interestingly, our patient had worsening pulmonary sarcoidosis around the time of dupilumab introduction. Nguyen et al demonstrated elevated interferon-inducible protein 10 (IP-10) and Th1 predominance in pulmonary tissue of patients with sarcoidosis.[8] Monitoring of dupilumab-induced progression of pulmonary sarcoidosis is warranted as Th2 depression by dupilumab may further shift the Th1/Th2 balance towards a Th1 response and promote pulmonary granuloma formation.[10]

Conclusion

In summary, to our best knowledge, we describe the first case of dupilumab as a treatment option for cutaneous sarcoidosis in the skin of color population. Although dupilumab is associated with inducing sarcoidosis-like reactions, we discuss how the imbalance of the Th1/Th2 pathway may explain dupilumab as a treatment option for cutaneous sarcoidosis. Nonetheless, dupilumab should not be used as a first-line option for sarcoidosis and should be monitored carefully for drug-induced sarcoidosis-like reactions.

Potential conflicts of interest

The authors declare no conflicts of interest.

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