BRIEF ARTICLES

Eosinophilic Annular Erythema- Successful Treatment with Dupilumab

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ABSTRACT

Eosinophilic annular erythema (EAE) is a rare eosinophilic dermatosis with few documented cases in the literature. It is considered either a distinct entity or subtype of Well's syndrome (eosinophilic cellulitis), but EAE, in contrast to Well's syndrome, is characterized by a chronic course and resistance to treatment. Therapies with reported efficacy include anti-malarial medications, suplatast tosilate, and dapsone. We report the first adult case of EAE to respond to dupilumab, an IL-4 receptor antagonist, which targets the type 2 inflammatory response associated with tissue eosinophilia.

INTRODUCTION

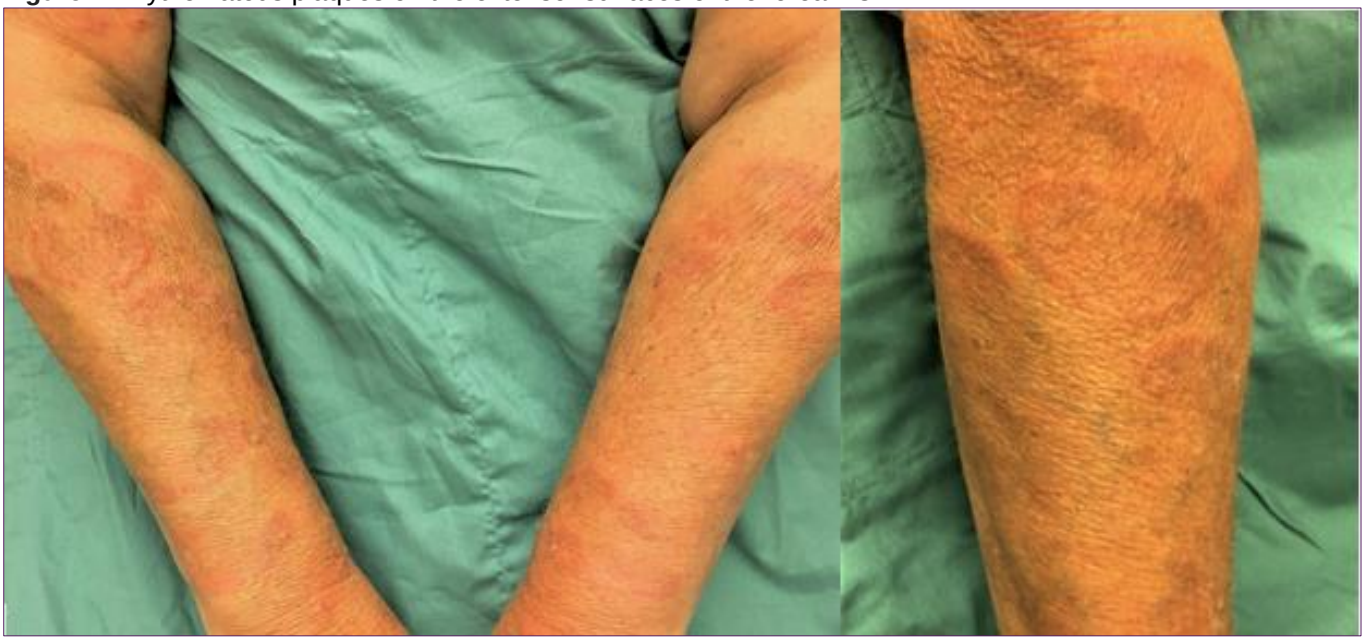
Eosinophilic annular erythema (EAE) is a rare eosinophilic dermatosis characterized by resistance to treatment and high rate of relapse.[1] There are few reported cases in the literature and no standard treatments. Many drugs that work to treat this condition target the Type 2 inflammatory response thought to play a predominate role in its pathogenesis. We report a case of EAE responsive to the IL-4 receptor antagonist, dupilumab.

CASE REPORT

A 57-year-old woman with medical history notable for moderately-persistent, poorly controlled asthma (requiring high dose inhaled corticosteroid/ long acting beta blocker twice daily) presented with a seven-year history of pruritic arcuate and annular erythematous plaques on the extensor surfaces of the forearms (Figure 1). She denied prior trauma or insect bites and had started no new medications prior to the eruption. The rash was refractory to topical corticosteroids, tacrolimus ointment, and various emollients. Histologic evaluation demonstrated superficial and deep dermal perivascular and periadnexal mixed inflammatory infiltrate containing a significant number of eosinophils and dermal mucin deposition (Figure 2). Due to the persistent and recalcitrant nature of the rash, as well as the annular nature of the lesions and lack of flame figures on histology, the patient was diagnosed with eosinophilic annular erythema (EAE).

Further evaluation of the patient revealed a chronic leukocytosis. Differential showed no eosinophilia but mild persistent neutrophilia which preceded the eruption. Renal and hepatic function were normal.

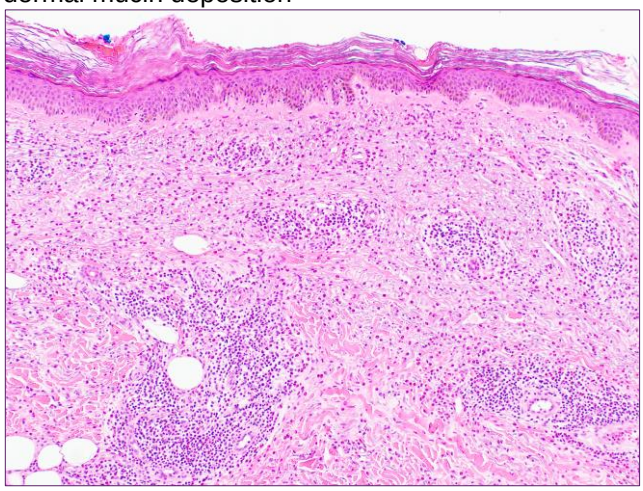
Figure 1. Erythematous plaques on the extensor surfaces of the forearms



Prior to arrival at out clinic, several medications had been ineffective at treating the patient's condition, including: dapsone, azathioprine, prednisone, and topical steroids and tacrolimus. The patient was unaware of the doses or duration of these treatments. A full course of dapsone, however, was not able to be completed, as it was poorly tolerated secondary to the development of fatigue. The patient saw some improvement after one month of treatment with doxycycline 100mg twice a day, with a decrease in the size and number of lesions. This did not last, though, and the condition worsened over the next two months of treatment.

Due to the patient's extensive history of failed medications, we consulted our allergy colleagues to help with approval for Dupilumab, a medication that targets the type 2 inflammatory pathway. This was selected with the goal of treating both the patient's EAE and asthma. The patient was treated with 200mg subcutaneously every two weeks. While the patient's asthma did not improve, she experienced no adverse reactions to the medication, and, in under two months, the rash resolved (Figure 3). She has remained in remission for six months.

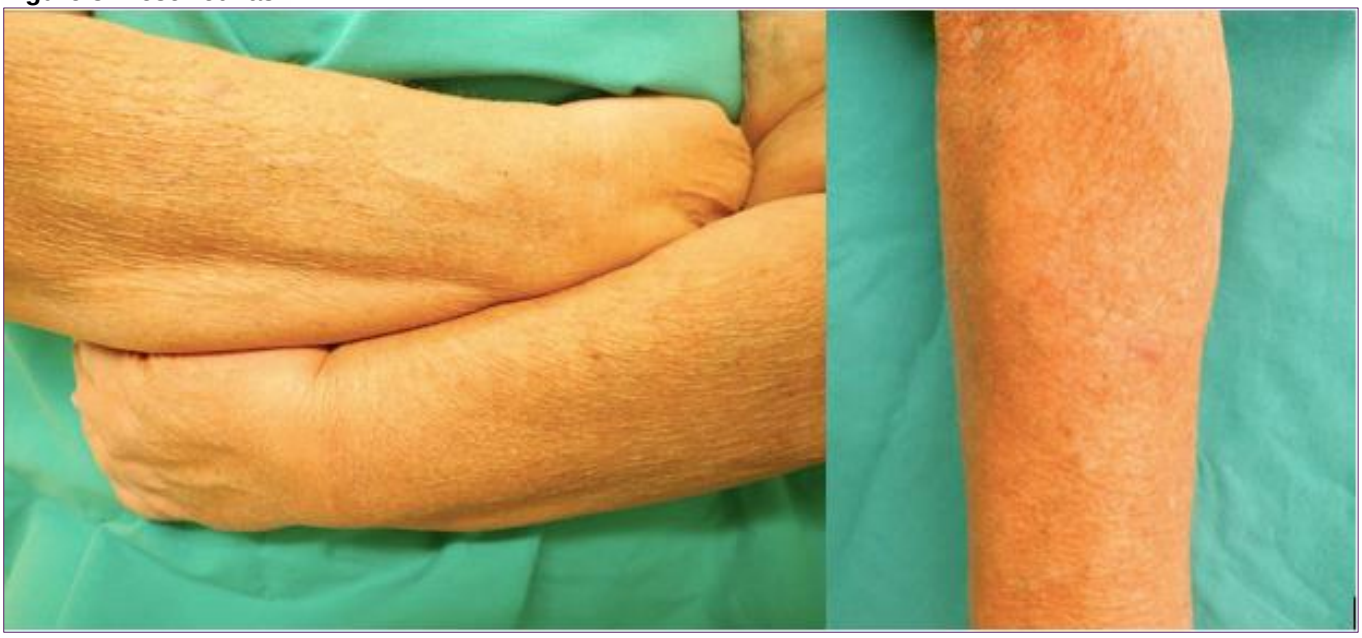
Figure 2. Superficial and deep dermal perivascular and periadnexal mixed inflammatory infiltrate containing a significant number of eosinophils and dermal mucin deposition



DISCUSSION

Eosinophilic annular erythema (EAE) is a rare eosinophilic dermatosis with few reported cases in the literature. EAE was first

Figure 3. Resolved rash



described in the literature in 1999 as a "gyrate erythema" distinct from Well's syndrome due to the lack of blood eosinophilia and "flame figures," deposits of eosinophil basic protein mixed with degenerated collagen fibers, which are both characteristic findings in Well's syndrome.[2] In 2017, Nakazato and colleagues also concluded that EAE was a histologically distinct entity from Well's syndrome due to localization of eosinophils to the superficial and/or deep dermis and absence of flame figures and vasculitis.[3] Other reports argue that EAE is a subtype of Well's syndrome, as flame figures are sometimes seen in biopsies of later lesions.[1,5] Nevertheless, distinct entity or subtype, therapeutic options for EAE, compared to Well's syndrome, have remain limited. This is likely because, while EAE is sometimes self-limited, it is predominantly characterized by a chronic course, high relapse rate, and significant resistance to treatment.[1] This is in contrast to Well's syndrome, which often responds dramatically to oral corticosteroids.

No single drug has been found to be consistently effective for the treatment of EAE, and its relapsing, remitting nature makes true efficacy difficult to determine. Therapies with reported efficacy include prednisone plus or minus hydroxychloroquine or cyclosporine, hydroxychloroquine alone, chloroquine, suplatast tosilate, dapsone, and narrowband ultraviolet B (UVB) treatment.[1,2,5–7] Though the pathogenesis of EAE remains unknown, these drugs may work by targeting the type 2 inflammatory response associated with tissue eosinophilia. Specifically, chloroquine inhibits eosinophilotaxis and the release of pro-inflammatory cytokines; suplatast tosilate suppresses the production of type 2 cytokines, such as IL-4 and IL-5 that promote eosinopoeisis; and, dapsone inhibits eosinophil peroxidase.[2,5,6]

It is not surprising then that dupilumab, an IL-4 receptor alpha antagonist which blocks IL-4 and IL-13 signaling involved in the type 2 inflammatory response, worked to improve our patient's EAE. To our knowledge, this is the first adult case with response of EAE to dupilumab, though similar efficacy was noted in a pediatric case of EAE in 2018.[8] Although

FDA-approved only for atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis, dupilumab has shown efficacy in several dermatologic diseases of the type 2 inflammatory pathway, including allergic contact dermatitis, bullous pemphigoid, and prurigo nodularis.[9–11]

In summary, our patient experienced a dramatic and lasting improvement with dupilumab. Although further studies are certainly necessary to assess the true benefit of this medication for EAE and other eosinophilic dermatoses, dupilumab offers a mechanistically compelling therapy for an often refractory condition.

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References:

1. El-Khalawany M, Al-Mutairi N, Sultan M, Shaaban D. Eosinophilic annular erythema is a peculiar subtype in the spectrum of Wells syndrome: a multicentre long-term follow-up study. *J Eur Acad Dermatol Venereol*. 2013;27(8):973-979. doi:10.1111/j.1468-3083.2012.04616.x
2. Kahofer P, Grabmaier E, Aberer E. Treatment of eosinophilic annular erythema with chloroquine. *Acta Derm Venereol*. 2000;80(1):70-71. doi:10.1080/000155500750012685
3. Nakazato S, Fujita Y, Shinkuma S, Nomura T, Shimizu H. Eosinophilic annular erythema is clinically characterized by central pigmentation reflecting basal melanosis: a clinicopathological study of 10 cases. *J Eur Acad Dermatol Venereol*. 2017;31(11):1916-1923. doi:10.1111/jdv.14350
4. Howes R, Girgis L, Kossard S. Eosinophilic annular erythema: a subset of Wells' syndrome or a distinct entity? *Australas J Dermatol*. 2008;49(3):159-163. doi:10.1111/j.1440-0960.2008.00456.x
5. Kanameishi S, Goto K, Ogawa M, Fukumoto T, Tanabe H. Efficacy of suplatast tosilate in a case of recurrent eosinophilic annular erythema. *Int J Dermatol*. 2018;57(9):e66-e68. doi:10.1111/ijd.13973
6. Manriquez J, Berroeta-Mauriziano D, Andino-Navarrete R, Vera-Kellet C. Eosinophilic annular erythema: complete clinical response with dapsone. *Int J Dermatol*. 2015;54(4):e96-98. doi:10.1111/ijd.12736
7. Thomas L, Fatah S, Nagarajan S, Natarajan S. Eosinophilic annular erythema: successful response to ultraviolet B therapy. *Clin Exp Dermatol*. 2015;40(8):883-886. doi:10.1111/ced.12668
8. Gordon SC, Robinson SN, Abudu M, et al. Eosinophilic annular erythema treated with dupilumab. *Pediatr Dermatol*. 2018;35(4):e255-e256. doi:10.1111/pde.13533
9. Goldminz AM, Scheinman PL. A case series of dupilumab-treated allergic contact dermatitis patients. *Dermatol Ther*. 2018;31(6):e12701. doi:10.1111/dth.12701
10. Kaye A, Gordon SC, Deverapalli SC, Her MJ, Rosmarin D. Dupilumab for the Treatment of Recalcitrant Bullous Pemphigoid. *JAMA Dermatol*. 2018;154(10):1225-1226. doi:10.1001/jamadermatol.2018.2526
11. Beck KM, Yang EJ, Sekhon S, Bhutani T, Liao W. Dupilumab Treatment for Generalized Prurigo Nodularis. *JAMA Dermatol*. 2019;155(1):118-120. doi:10.1001/jamadermatol.2018.3912