Refractory erythema annulare centrifugum treated with apremilast

Michelle S. Lee, BA,a Nikolai Klebanov, MD,b Daniel Yanes, MD,b and Robert Stavert, MD, MBAc

Boston and Somerville, Massachusetts

Key words: apremilast; erythema annulare centrifugum; treatment.

INTRODUCTION

Erythema annulare centrifugum (EAC) is a reactive eruption that typically presents with annular or polycyclic erythematous lesions on the trunk and proximal extremities, often with a trailing scale. EAC is one of the major figural erythemas, along with erythema marginatum, erythema migrans, and erythema gyratum, and can occur as a paraneoplastic phenomenon called paraneoplastic EAC eruption. EAC is usually self-resolving, assuming that the inciting cause, if any, is addressed. Typical treatment options for the symptomatic disease include topical or systemic corticosteroids, antihistamines, or antibiotics.

Apremilast is an oral phosphodiesterase 4 inhibitor with a favorable safety profile that is currently approved to treat moderate to severe plaque psoriasis, psoriatic arthritis, and Behcet disease. In addition, we report a case of refractory EAC successfully treated with apremilast, which to our knowledge has not been previously reported in the literature.

CASE REPORT

A woman in her 30s presented with 2 years of pruritic arcuate scaling plaques on the arms, chest, and back and was evaluated via teledermatology. She had previously been diagnosed with scalp psoriasis and was prescribed topical clobetasol and ketoconazole 2% shampoo for the scalp but had not used any treatments for the rest of her body. The submitted images showed few erythematous arcuate thin plaques with trailing light white scale on the right upper lateral to the anterior arm and left posterior shoulder to the upper back. The lesions did not appear consistent with psoriasis. Given the initial concern for tinea corporis, a potassium hydroxide scraping was recommended as well as a trial of topical terbinafine cream twice daily for 3 weeks.

At follow-up evaluation 4 weeks later via teledermatology, she had tried terbinafine without response and had new areas of involvement on her left arm. EAC was suspected given the chronicity and previous history of multiple unsuccessful treatments with antifungal creams, and in-person evaluation was recommended. At her in-person visit 4 weeks later, her examination revealed large annular pink patches with a trailing scale on the bilateral upper extremities and back. The presentation and history were determined to be most consistent with EAC. A potassium hydroxide preparation was negative, and a punch biopsy of the right arm was performed. Histologic examination demonstrated parakeratosis, mild acanthosis, spongiosis, and superficial perivascular lymphocytic infiltrate with eosinophils “cuffed” around superficial dermal vessels, consistent with EAC (Fig 1).

She started triamcinolone 0.1% cream twice daily for 14 days per month, which initially provided some relief; however, 1 to 2 months later, she continued to develop new lesions that were unresponsive to treatment. No underlying medical
condition, new medication, or possible trigger of EAC was identified. She trialed econazole cream, doxycycline, minocycline, and high-potency topical corticosteroids with mild improvement; however, her rash did not abate. Given the possible associations between EAC and systemic disease, a laboratory workup was performed, which included a complete blood count, comprehensive metabolic panel, thyroid-stimulating hormone, serum and urine protein electrophoresis, Strongyloides serology, QuantiFERON gold, antinuclear antibody, anti-DNase antibody, mammogram, chest x-ray, and pelvic ultrasound. Previous serologies for HIV and syphilis were negative. Notable laboratory findings included an elevated anti-DNase B of 222 U/mL (reference, 0-120 U/mL), for which she was started on the empiric treatment of potential streptococcal infection with amoxicillin 500 mg twice a day for 10 days. She was found to have elevated serum-free kappa light chains of 28.7 mg/L (reference, 3.3-19.4 mg/L). She was evaluated by a hematologist who had a low suspicion for a malignant process given her normal kappa to lambda ratio, normal flow cytometry, and lack of a monoclonal gammopathy.

Her rash progressed to involve the bilateral arms, breast, abdomen, upper back, and thighs, and she was recommended to use tacrolimus ointment along with triamcinolone cream, in addition to ambient sunlight. However, nearly 4 years after initial presentation, she still had persistent lesions with annular and arcuate pink thin plaques and patches with trailing scale most prominently on the lower extremities (Figs 2, 3, A, and 4, A), less on the upper extremities and trunk.

She was started on a trial of apremilast 30 mg twice daily given its expected systemic antiinflammatory effect with low risk of adverse effects, along with continued use of high-potency topical steroids.

After 1 year of treatment, she noted resolution of lesions of her bilateral lower extremities and upper back with residual postinflammatory hyperpigmentation, but without plaques or scale (Figs 2, B, 3, B, and 4, B). At follow-up, she had only residual annular brown thin plaques and patches with a minimal trailing scale on her bilateral forearms, a significant improvement from prior visits. Given that she tolerated apremilast well with only mild gastrointestinal side effects, she was recommended to continue apremilast along with tacrolimus ointment.

**DISCUSSION**

While the pathogenesis of EAC is unknown, it is postulated to be a form of hypersensitivity reaction to an underlying antigen. Described triggers include...
fungi (ie, Candida, dermatophytosis, Penicillium), viruses (ie, Epstein-Barr virus, poxvirus, HIV), parasites, bacteria, medications, underlying malignancy, or systemic disease. EAC typically resolves with treatment of the underlying cause; however, symptoms of the eruption can be managed with topical corticosteroids, antihistamines, antibiotics, or systemic corticosteroids. There is also limited evidence for the use of calcipotriene, tacrolimus, narrow-band UV-B, fluconazole, oral metronidazole, and subcutaneous interferon-alpha.

Apremilast is approved to treat plaque psoriasis, psoriatic arthritis, and oral ulcers for Behcet disease and has also been used off-label for lichen planus, hidradenitis suppurativa, pityriasis rubra pilaris, and generalized granuloma annulare. This is the first reported case of its successful use for EAC. Apremilast inhibits phosphodiesterase 4, thereby increasing the concentration of cyclic-adenosine-monophosphate, altering the gene expression of lymphocytes and macrophages. The pathogenesis of EAC is unknown. However, apremilast is likely of value given its ability to upregulate interleukin 10, an antiinflammatory cytokine that inhibits the synthesis of Th1 and Th17 cytokines. Our case suggests that apremilast may represent a novel therapy for refractory EAC with a favorable side effect profile. More extensive and controlled studies may be helpful to further elucidate the utility of apremilast in treating EAC.

**Fig 3.** A, Right upper aspect of the back before treatment with apremilast. B, Right upper aspect of the back after 1 year of treatment with apremilast.

**Fig 4.** A, Right thigh before treatment with apremilast. B, Right thigh after 1 year of treatment with apremilast.
Conflicts of interest
None disclosed.

REFERENCES
1. McDaniel B, Cook C. Erythema annulare centrifugum. In: StatPearls. StatPearls Publishing; 2021.
2. Gniadecki R. Calcipotriol for erythema annulare centrifugum. Br J Dermatol. 2002;146(2):317-319. https://doi.org/10.1046/j.0007-0963.2001.04572.x
3. Kruse LL, Kenner-Bell BM, Mancini AJ. Pediatric erythema annulare centrifugum treated with oral fluconazole: a retrospective series. Pediatr Dermatol. 2016;33(5):501-506. https://doi.org/10.1111/pde.12909
4. Sardana K, Chugh S, Mahajan K. An observational study of the efficacy of azithromycin in erythema annulare centrifugum. Clin Exp Dermatol. 2018;43(3):296-299. https://doi.org/10.1111/ced.13334
5. Naccarato M, Yoong D, Solomon R, Ostrowski M. Erythema annulare centrifugum-like eruption associated with pegylated interferon treatment for hepatitis C. Dermatol Reports. 2013;5(1):e1. https://doi.org/10.4081/dr.2013.e1
6. Bishnoi A, Raj D, Vinay K, Dogra S. Refractory generalized granuloma annulare treated with oral apremilast. JAMA Dermatol. 2019;155(11):1318-1320. https://doi.org/10.1001/jamadermatol.2019.2130
7. Blum S, Altman D. Treatment of generalized granuloma annulare with apremilast: a report of 2 cases. JAAD Case Rep. 2019;5(1):976-978. https://doi.org/10.1016/j.jdcr.2019.09.015
8. Weber P, Seyed Safari SM, Yawalkar N, Hunger RE. Apremilast in the treatment of moderate to severe hidradenitis suppurativa: a case series of 9 patients. J Am Acad Dermatol. 2017;76(6):1189-1191. https://doi.org/10.1016/j.jaad.2017.02.026
9. Paul J, Foss CE, Hirano SA, Cunningham TD, Pariser DM. An open-label pilot study of apremilast for the treatment of moderate to severe lichen planus: a case series. J Am Acad Dermatol. 2013;68(2):255-261. https://doi.org/10.1016/j.jaad.2012.07.014
10. Mavropoulos A, Zafiriou E, Simopoulou T, et al. Apremilast increases IL-10-producing regulatory B cells and decreases proinflammatory T cells and innate cells in psoriatic arthritis and psoriasis. Rheumatology (Oxford). 2019;58(12):2240-2250. https://doi.org/10.1093/rheumatology/kez204