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Annular Plaques in a Woman Receiving Systemic Immunotherapy

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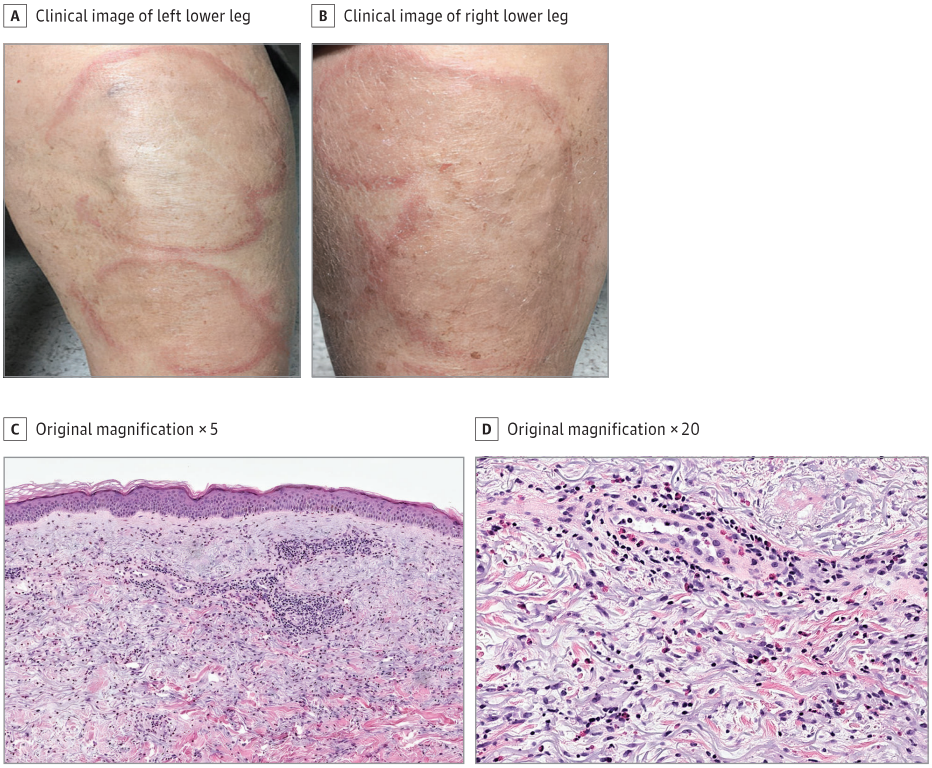

Figure. A, Erythematous annular plaques without scale on the left lower leg. B, Erythematous annular plaques without scale on the right lower leg. C, Hematoxylin and eosin stain demonstrating superficial and deep perivascular and interstitial inflammation. D, Hematoxylin and eosin stain demonstrating numerous scattered eosinophils.

A woman in her 70s with recurrent primary peritoneal carcinoma receiving pembrolizumab and ipilimumab presented to the Division of Dermatology with a pruritic rash that had been ongoing for 2 weeks. The rash started as an erythematous papule on her right arm 2 months after initiation of a new immunotherapy regimen, then gradually enlarged and spread to involve both legs (**Figure**, A and B). She denied any new systemic symptoms associated with onset of the rash. A recent trial of oral terbinafine for possible tinea corporis yielded no improvement. Physical examination revealed erythematous annular plaques without scale on her right arm and bilateral legs. A 4-mm punch biopsy was obtained from the patient's right arm (Figure, C and D), and she was prescribed fluocinonide, 0.05%, ointment. She returned to the clinic 3 weeks later with resolution of pruritus but enlarging lesions. Her last dose of ipilimumab was 2 months prior, and she was scheduled to receive pembrolizumab with doxorubicin, carboplatin, and prednisone for treatment of her underlying malignant tumor. For management of her rash, the patient was prescribed betamethasone dipropionate, 0.05%, ointment (augmented).

WHAT IS YOUR DIAGNOSIS?

- **A.** Erythema annulare centrifugum
- **B.** Eosinophilic annular erythema
- **C.** Granuloma annulare
- **D.** Drug-induced bullous pemphigoid

Quiz at jamacmelookup.com

Diagnosis

B. Eosinophilic annular erythema

Discussion

Histopathologic testing showed superficial and deep perivascular and interstitial inflammation with numerous eosinophils. Periodic acid–Schiff (PAS) stain was negative for fungal organisms. Given the constellation of clinical and histopathologic findings, eosinophilic annular erythema (EAE) was diagnosed. The temporal relationship between onset of the patient's rash and treatment with immunotherapy suggested a drug-induced eruption, although her underlying carcinoma was also a possible trigger.

Eosinophilic annular erythema is a benign, relapsing condition originally described in children.[1] It presents clinically as erythematous papules and plaques without scale on the trunk and extremities, with varying degrees of pruritus. The lesions may assume a polycyclic or annular configuration with central clearing as they expand and usually heal without atrophy or scarring.[2] The cause of EAE remains unknown, but it has been hypothesized that the presence of eosinophils may represent a hypersensitivity reaction to an unknown trigger.[3] Eosinophilic annular erythema has been reported in conjunction with autoimmune diseases such as hypothyroidism[4] and internal malignancies such as renal carcinoma,[5] suggesting that EAE may have a component of autoimmunity or represent a paraneoplastic process. Histologically, EAE is characterized by a dense superficial and deep perivascular and/or interstitial infiltrate with abundant eosinophils. Long-standing lesions present predominantly with histiocytes and eosinophils, with the addition of multinucleated giant cells and occasional flame figures.[5]

Controversy remains as to whether EAE is its own entity or exists on a disease spectrum with Wells syndrome. However, EAE can be differentiated histopathologically from Wells syndrome by the absence of granulomatous inflammation and eosinophil degranulation, as well as the decreased presence of flame figures.[6] In addition, EAE shows an inconsistent response to topical and systemic steroids, which are first-line treatments for Wells syndrome.[6]

The differential diagnosis of EAE includes erythema annulare centrifugum, granuloma annulare, annular sarcoidosis, urticarial vasculitis, and urticarial phase of bullous pemphigoid. Erythema annulare centrifugum presents as an erythematous papule that gradually enlarges to form an annular plaque with central clearing, with the superficial type demonstrating a fine scale inside the advancing edge known as a trailing scale, while the deep type has a firm, cordlike border without scale. Histologically, the superficial type may resemble pityriasis rosea and is characterized by spongiosis, parakeratosis, and a dense infiltrate of lymphocytes and histiocytes in a coat sleeve distribution. The deep type has a similar infiltrate that spans the superficial and deep vascular plexuses, with no spongiosis or parakeratosis.[7,8] Granuloma annulare presents as erythematous papules and annular plaques usually without scale favoring the distal extremities. Histopathology demonstrates palisading granulomas or interstitial histiocytes with increased dermal mucin.[7] Clinically, drug-induced bullous pemphigoid can resemble the urticarial phase of classic bullous pemphigoid, presenting as erythematous urticarial plaques with an annular appearance that can precede the bullous eruption. The histopathology of early erythematous lesions is characterized by superficial papillary dermal edema, perivascular lymphohistiocytic infiltrate, and prominent eosinophils. Eosinophilic spongiosis may also be seen. Immunofluorescence demonstrates linear IgG and C3 along the dermal-epidermal junction.[7]

Eosinophilic annular erythema has a chronic and relapsing course that is resistant to therapy.[5] Successful treatment has been most frequently reported with antimalarials and systemic corticosteroids, although relapse is common after treatment discontinuation.[7] Symptom improvement has also been observed with indomethacin,[6] ultraviolet B phototherapy,[2] dapsone,[7] and dupilumab.[9] One case reported spontaneous resolution within 6 weeks.[3] Concomitant management of associated systemic diseases and prompt treatment of skin lesions can lead to prolonged remission.[5] The present patient experienced complete resolution of her rash after receiving prednisone as part of her chemotherapy regimen and never used the prescribed betamethasone dipropionate ointment. At 3-month follow-up, she had developed hand-foot syndrome secondary to doxorubicin but had no recurrence of EAE.

ARTICLE INFORMATION

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