Eosinophilic fasciitis as a paraneoplastic syndrome in melanoma

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INTRODUCTION

Eosinophilic fasciitis (EF) is a rare sclerodermoid condition, characterized by acute-onset symmetric limb and trunk erythema, edema, induration, eventual fibrosis, and variable peripheral eosinophilia. EF is typically idiopathic; however, EF as a paraneoplastic condition has been recognized in a variety of hematologic disorders and solid organ tumors,[1] and several cases have been initiated by immunotherapy.[2] The association of EF with melanoma is rarely described.[3]

Below is the case of a woman who developed EF with the initial diagnosis of melanoma, and who later had recurrence of EF when her melanoma relapsed. This case explores possible connections between these 2 conditions.

CASE REPORT

A 72-year-old woman with well-controlled hypothyroidism and no previous history of skin disease developed bilateral leg swelling and discomfort over 5 days. Initial evaluation by her primary care provider included complete blood count, complete metabolic panel, lower extremity venous duplex scan, and thyroid stimulating hormone. All were unremarkable, except for the presence of eosinophilia (0.76 K/μL, normal range: 0.00-0.40 K/μL; 13.8%, normal range: <5%).

Concurrent referral to dermatology for a changing pigmented lesion on the posterior aspect of her thigh resulted in a skin biopsy that revealed invasive melanoma (Breslow depth of 3.5 mm and a mitotic rate of 10/mm^2). Over several weeks, while awaiting definitive surgery for the melanoma, her edema, erythema, and induration worsened on her legs and progressed to involve her forearms (Fig 1).

Abbreviation used:
EF: eosinophilic fasciitis

An incisional biopsy of her arm to fascia showed a moderate-intensity inflammatory infiltrate composed of lymphocytes, histiocytes, and numerous eosinophils located predominantly in the subcutis and fascia. Edema, hemorrhage, and fibrin deposits were also observed, all consistent with EF (Fig 2).[4]

Peripheral eosinophilia persisted at 4 weeks (2.02 K/μL and 23%). Wide local excision with sentinel lymph node biopsy showed metastatic melanoma in 2 of 3 sentinel lymph nodes with no other metastasis on imaging (clinical stage IIIA disease). Sequencing of the tumor revealed a BRAF V600E mutation, and adjuvant dabrafenib and trametinib therapy was started. Immunotherapy was intentionally avoided due to concurrent EF. Synchronous methotrexate and monthly pulsed methylprednisolone infusion (× 3) were started for the EF. Rapid improvement in skin symptoms occurred, and the patient stabilized off all therapy within a year.

Two years later, she developed locally recurrent melanoma. She deferred surgical treatment for 3 months. In that interval, upper and lower extremity induration and peripheral eosinophilia recurred. Following 3-4 weeks of prednisone therapy and repeat wide local excision of the melanoma, the EF symptoms rapidly improved. Fifteen months later,

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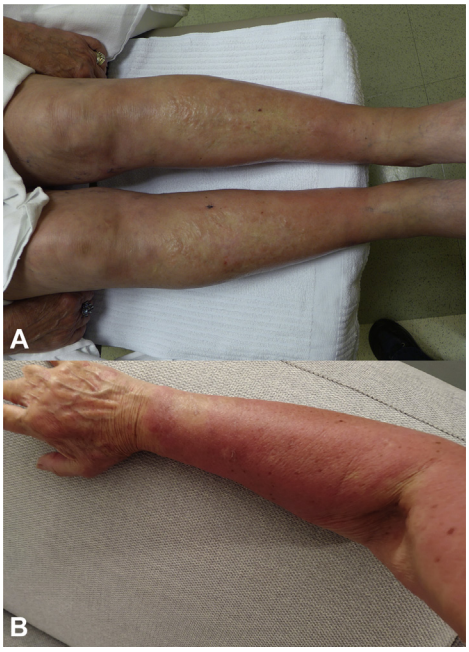

Fig 1. **A**, The patient's legs on presentation, with a shiny, peau d'orange appearance, sparing the feet, which is characteristic of eosinophilic fasciitis. **B**, The patient's arm following recurrence, showing erythema and induration, sparing the hands.

she has no evidence of melanoma and remains off therapy with minimal, stable skin thickening around her ankles and thin plaque morphea lesions at the lower back and hips.

DISCUSSION

The symmetric acral fibrosis, peripheral eosinophilia, and distinctive involvement of the fascia observed on biopsy strongly support the diagnosis of EF in our patient. The concomitant development of thin plaque morphea in our patient is not unique. EF is considered by some to be on the spectrum of morphea, representing a severe variant of the disease. One case study of 63 EF patients showed concomitant morphea in 35% of the patients.[5]

EF is usually idiopathic, and although numerous case reports of EF as a paraneoplastic syndrome exist in the literature, a paraneoplastic association is observed in only a small number of cases. Reports of paraneoplastic EF have been suggested in the setting of hematologic malignancy or in association with breast, lung, prostate cancer, and choroidal melanoma.[1,3] Like EF, morphea has rarely been reported as a paraneoplastic phenomenon, usually in the setting of hematologic malignancy.[6]

This case adds to other emerging clinical data that implicate cutaneous melanoma as a potential cause of paraneoplastic EF. As of 2019, 15 cases of fasciitis

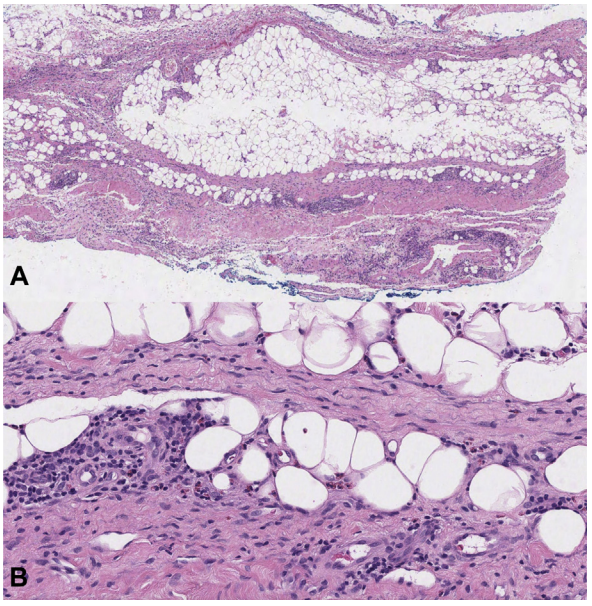

Fig 2. **A**, Scanning magnification showing inflammation in the subcutaneous tissue and fascia. **B**, Higher power view revealed the infiltrate to be composed of lymphocytes, histiocytes, and numerous eosinophils, consistent with eosinophilic fasciitis.

were documented following treatment with anti-CTLA4, anti-PD1/PD-L1 checkpoint inhibitor therapies, and none occurred using BRAF and MEK inhibitors. In 9 of the 15 cases, treatment was given for melanoma.[2] In the patient presented here, the EF occurred prior to any treatment and recurred with melanoma relapse. This suggests that when EF occurs in association with immunotherapy, EF may not be a direct toxicity of therapy; rather, immunotherapy may be unmasking relevant tumor biology (eg, tumor neoantigenic mimicry) or augmenting host responses that trigger skin inflammation and fibrosis. Dysregulation of the extracellular matrix facilitates metastasis in cancer and is implicated as a possible mechanism of fibrosis in EF, posing another possible link between the two.[7] Progression of melanoma and EF have both been linked to altered expression of tissue inhibitor of metalloproteinase, which may represent a common pathomechanism for these 2 phenomena. The simultaneous recurrence of EF with melanoma relapse in this patient suggests that these 2 disparate phenomena share pathophysiology to some extent.[7,8] It remains to be seen, whether the development of EF predicts improved outcomes in melanoma, as has been shown with other immunologic reactions.[9]

First-line treatment for EF has long been administration of systemic corticosteroids and referral to physical therapy. More recent data show improved outcomes with combination therapy using

corticosteroids and methotrexate.[5] Our patient achieved rapid disease remission with a combination of systemic corticosteroids, methotrexate, and treatment of her melanoma. The clinical course of EF after treatment of an associated malignancy has not been well described. Delay in diagnosis is common with EF, and experience suggests that quick diagnosis and treatment of EF portend a better prognosis, with many patients achieving complete remission with appropriate therapy.[5]

This case effectively demonstrates the concurrent onset and parallel clinical course of EF and melanoma, supporting EF as a paraneoplastic process. The added context of recent reports of EF observed in patients with melanoma on immunotherapy and possible shared pathomechanisms for these 2 conditions is enticing and further suggests a link between paraneoplastic EF and melanoma.

Conflicts of interest

None disclosed.

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