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## Case Report

# Eosinophilic Fasciitis with Concurrent Necrobiotic Granulomatous Dermatitis Related to Checkpoint Inhibition Therapy

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## ABSTRACT

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapeutics. However, loss of physiologic tolerance in few cases has triggered rare and novel immune-related adverse events (irAEs). Eosinophilic fasciitis, an infrequently reported diffuse scleroderma-like entity, has been associated with ICI therapy. We report a case of a patient with metastatic melanoma treated with nivolumab who developed eosinophilic fasciitis with concurrent granulomatous dermatitis and lymphadenitis, the latter of which mimicked melanoma recurrence radiographically. Furthermore, this patient had a severe presentation that subsequently proved to be treatment-resistant to both corticosteroid and steroid-sparing therapies. To our knowledge, eosinophilic fasciitis has not been reported concurrently with granulomatous dermatitis in literature. We provide a narrative of this case and a review of therapeutic approaches for severe or refractory irAEs. With the increasing popularity of ICI therapy, we believe it is essential for clinicians to identify novel irAEs and be aware of treatments as late recognition could prove fatal.

Keywords: eosinophilic fasciitis, immunotherapy, immune-related adverse event, nivolumab

### **INTRODUCTION**

First described by Shulman in 1974, eosinophilic fasciitis (EF) was thought to be a "diffuse sclerodermalike illness" with symmetrical distal extremity skin thickening and hardening.<sup>[1,2]</sup> Although the forearms and lower legs are most commonly affected, the fingers and face are always spared.<sup>[2]</sup> Typically, the joints of the affected limbs are involved and have contractures causing limitations in range of motion. Additional findings can include peripheral eosinophilia, hypergammaglobulinemia, and elevated sedimentation rate.<sup>[2–4]</sup> Full-thickness biopsy shows thickened, inflamed fascia with a mixed inflammatory infiltrate containing lymphocytes, plasma cells, histiocytes, and eosinophils.<sup>[2,3]</sup> Many associations have been described in literature, ranging from intense physical exercise to infections with Borrelia species to medication triggers.<sup>[5]</sup> Drugs that have been implicated include monoclonal antibodies such as natalizumab, as well as widely used medications such as statins, and ACE (ACE) inhibitors.<sup>[5]</sup> Herein, we describe a patient treated with ipilimumab and nivolumab for metastatic melanoma of unknown primary who subsequently developed EF with concurrent necrobiotic

granulomatous dermatitis (NGD). The patient provided consent to publish this case.

### **CASE REPORT**

A 56-year-old Caucasian man with a history of metastatic melanoma presented with a 1-year history of swelling and pain in his bilateral lower extremities. His melanoma presented as right supraclavicular lymphadenopathy with subsequent imaging showing mediastinal, right inguinal, and hepatic lesions. A primary melanoma was never identified. Per protocol, he received four cycles of combination ipilimumab and nivolumab after which he was transitioned to single-agent nivolumab maintenance therapy. Imaging at the time of transition and again during maintenance therapy showed no evidence of residual disease. He tolerated nine cycles of nivolumab before developing pain, swelling, and weakness in bilateral lower extremities. Concern at the time was for immunotherapy-related myositis and treatment was promptly discontinued. He received oral prednisone (100 mg/day with taper of 20 mg/2 wk) with partial improvement.

Unfortunately, his symptoms persisted without response to repeated high-dose steroids. The patient was



Figure 1. Clinical image of patient's lower extremities. (A) Bilateral lower extremities with woody induration, joint construction, and ulceration. (B) Left leg depicts *peau* d'orange change and a subtle groove sign (arrow).

referred to our multidisciplinary cutaneous oncology and oncodermatology clinic where he was found to have firmness, thickening, and peau d'orange appearance of bilateral lower extremities from knee to ankle with associated ulceration (Fig. 1). His right medial knee and bilateral volar forearms also exhibited linear depression overlying the course of superficial veins, consistent with a positive "groove sign." An incisional biopsy sample down to the fascia was taken from the left-upper-lateral shin. Histopathologic analysis showed deep dermal, subcutaneous, and fascial sclerosis with rare eosinophils. Interestingly, the biopsy also showed superficial necrobiotic and palisaded granulomatous dermatitis (Fig. 2). A positron emission tomography/computed tomography (Pet/CT) obtained at this time showed fluorodeoxyglucose F 18 (FDG) avidity in the left masseter muscle, lower extremity musculature, and numerous mediastinal and hilar lymph nodes. These findings were concerning for widespread melanoma recurrence, but subsequent nodal biopsies showed granulomatous inflammation without evidence of melanoma.

Magnetic resonance imaging (MRI) was subsequently performed showing diffuse perifascial and intermuscular fascial edema in bilateral upper extremities, lower extremities, and imaged portions of the chest wall, rotator cuff musculature, and pelvic musculature compatible with diffuse fasciitis. A muscle biopsy was performed also showing fasciitis and excluding myositis. Amitriptyline and gabapentin were started for symptomatic relief, followed by infliximab. Owing to persistence, he was then switched to mycophenolate mofetil and intravenous immune globulin after which he started to slowly improve clinically and radiographically but with persistent pain and limited mobility.

#### DISCUSSION

Although there are no validated diagnostic criteria for EF, the most commonly cited criteria proposed by Pinal-Fernandez et al<sup>[5]</sup> and Chan et al<sup>[6]</sup> require two major criteria or one major and two minor criteria to be met. The major criteria include swelling, induration, and thickening of the skin and subcutaneous tissue; and fascial thickening with an accumulation of lymphocytes, macrophages, with or without eosinophils.<sup>[5]</sup> The minor criteria include eosinophilia >  $0.5 \times 10^9$ /L, hypergammaglobulinemia > 1.5 g/L, muscle weakness, and/or elevated aldolase levels, groove sign and/or peau d'orange change, and hyperintense fascia on MR T2-weighted images.<sup>[5]</sup> Our case met both major criteria as well as four of five minor criteria, including eosinophilia up to  $1.0 \times$  $10^{9}$ /L, elevated aldolase levels (9.3 units/L), clinically evident groove sign and peau d'orange change, and the MRI findings as stated above confirming the diagnosis of EF.



**Figure 2.** Histopathologic images displaying necrobiotic and granulomatous dermatitis in the superficial dermis (A), with extensive necrobiosis of subcutaneous and fascial septae (B). A rare eosinophil is observed in the deep fascial plane (C) (H&E–stained tissue sections at 40×, 100×, and 400× original magnification).

Although definitive pathogenesis has not been elucidated, literature review revealed reports of granulomatous reactions (GRs) and EF associated with immune checkpoint inhibitor (ICI) therapy. However, we discovered no previous reports of EF with concurrent NGD or GRs. Cornejo et al,<sup>[7]</sup> in a 2019 review, found 72 patients with GRs to ICI therapy. Most patients (59/72) developed sarcoid-like GR. Additional GRs, including four with granulomatous dermatitis, were also reported.<sup>[7]</sup> The reactions rarely required withdrawal of ICI therapy but are clinically relevant given their propensity to mimic melanoma metastases on imaging. Nonetheless, few cases with more severe presentations have required topical or systemic steroids and withdrawal of ICI therapy.<sup>[7]</sup> Literature review also revealed eight cases of EF in association with nivolumab and one other in association with ipilimumab.<sup>[6,8,9]</sup> In seven of eight cases the offending agent was discontinued.<sup>[6,8–10]</sup> Of the cases that reported treatment, six of seven initiated immunosuppressive therapy with steroids and five of seven also initiated a second agent such as methotrexate, mycophenolate mofetil, and/or cyclosporine.<sup>[6,8–10]</sup> Although no treatment guidelines have been established, glucocorticoids are considered first-line.<sup>[6]</sup> There is no established "second-line treatment" but methotrexate, mycophenolate mofetil, cyclosporine, and infliximab

have all been described in literature often used in combination with steroids.<sup>[6]</sup> Varying degrees of efficacy have been reported with use of combination high-dose steroids and methotrexate. A large study of 63 patients reported 64% of patients achieved full remission, while smaller studies with the same drugs have reported rates of remission as high as 100%.<sup>[6,11]</sup>

This patient's presentation is particularly unique in that immunotherapy triggered not only EF but also a granulomatous response in both the skin and lymph nodes. To our knowledge, this is the first case to report these histopathologic findings concurrently. While widespread use of ICIs in the field of oncology has provided lifesaving treatment for many patients, immune-related adverse events (irAEs) such as EF may become more prevalent. Unfortunately, these conditions may be life altering. It is critical clinicians continue to monitor for and identify adverse reactions to immunotherapy and remain aware of options for aggressive treatment.

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