Skin puckering and edema during durvalumab therapy

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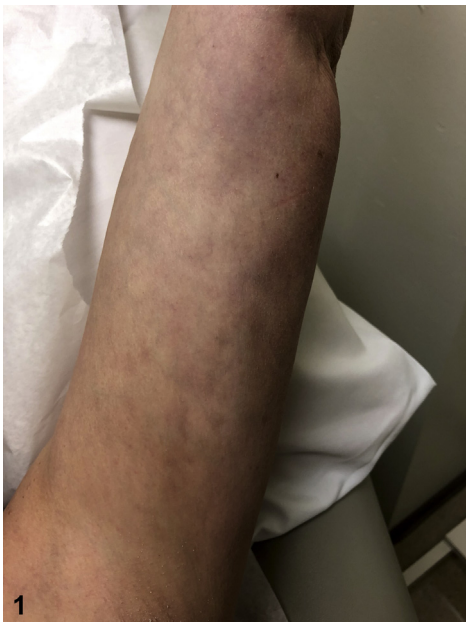

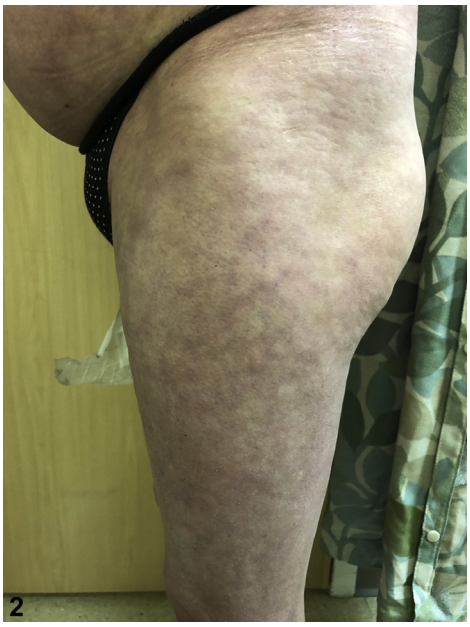

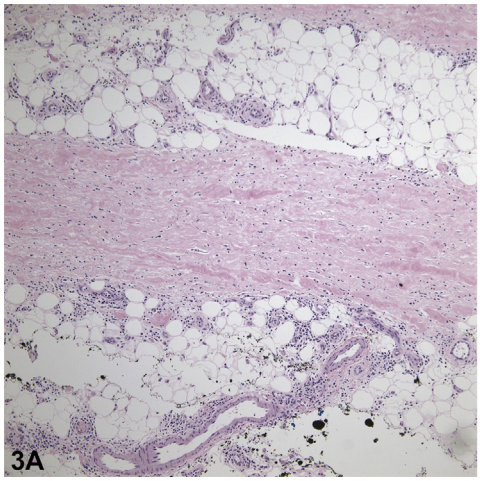

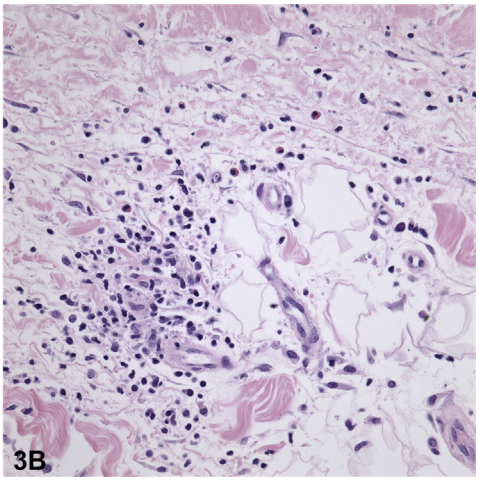

A 41-year-old woman presented with a 2-month history of skin puckering and edema of the bilateral arms (Figs 1 and 2), followed by truncal involvement. Her medical history was significant for metastatic colon cancer while receiving durvalumab and anti-CD73 therapy. Facial and hand involvement, nail changes, and Raynaud phenomenon were absent. Bloodwork revealed an elevated absolute eosinophilic count of 2200 cells/μL. Laboratory workup for antinuclear antibody, anti-RNA polymerase III, and anticentromere antibodies was

negative. Full-thickness skin biopsy showed thickened subcutaneous septa (Fig 3, *A*) and an inflammatory fascial infiltrate composed of lymphocytes, plasma cells, multinucleated giant cells, and eosinophils (Fig 3, *B*).

Question 1: What is the most likely diagnosis?

A. Limited cutaneous systemic sclerosis

B. Generalized morphea

C. Eosinophilic fasciitis

D. Eosinophilia myalgia syndrome

E. Scleromyxedema

Answer:

A. Limited cutaneous systemic sclerosis—Incorrect. Limited cutaneous systemic sclerosis typically presents as progressive tightening of the fingers and hands bilaterally, as well as of the face. The patient did not show signs of Raynaud phenomenon that are usually observed in patients with systemic sclerosis.[1] Some cases of limited cutaneous systemic sclerosis may present with edema of the hands in the absence of progressive tightening. However, as noted, this patient did not have any hand involvement. Additionally, the screening laboratory work for systemic sclerosis was negative, which is important, although it does not automatically exclude the diagnosis.

B. Generalized morphea—Incorrect. Generalized morphea classically presents as symmetric, circumscribed indurated plaques in the truncal area.[1] It typically manifests as plaque morphea, which becomes broadly distributed. Of note, deep morphea may result in a pseudo-cellulite appearance similar to the puckering seen in this case, and some cases may have clinical overlap with eosinophilic fasciitis. The combination of peripheral eosinophilia and characteristic histopathologic changes of eosinophils in the fascia is most consistent with another diagnosis.[2]

C. Eosinophilic fasciitis—Correct. Eosinophilic fasciitis presents as swelling and thickening of the skin and soft tissue of the extremities and trunk (puckering or pseudo-cellulite appearance) with fascial thickening on biopsy.[1] It has been recently recognized as an immune-related adverse event secondary to programmed cell death 1 and programmed death-ligand 1 inhibitors.[3] In addition to the classic cutaneous findings, between 10% and 40% of patients may experience concurrent inflammatory arthritis.[1]

D. Eosinophilia myalgia syndrome—Incorrect. Eosinophilia myalgia syndrome is typically associated with cognitive impairment and/or pulmonary involvement. The patient's history does not suggest consumption of contaminated L-tryptophan, which is associated with eosinophilia myalgia syndrome.[1]

E. Scleromyxedema—Incorrect. While scleromyxedema may present as diffuse thickening of the skin, histopathology should reveal mucinous deposition. Scleromyxedema is frequently associated with a paraproteinemia, which this patient did not have.

Question 2: Which of the following is a first-line treatment for this condition?

A. Methotrexate

B. Systemic corticosteroids

C. Azathioprine

D. Mycophenolate mofetil

E. Hydroxychloroquine

Answer:

A. Methotrexate—Incorrect. While methotrexate has been successfully used as corticosteroid-sparing therapy to treat eosinophilic fasciitis, it is not considered first-line therapy.[4]

B. Systemic corticosteroids—Correct. Systemic corticosteroids are considered first-line therapy, usually at 0.5-1 mg/kg/day.[1] Once the cutaneous

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symptoms are well controlled, patients can maintain clearance on corticosteroid-sparing agents. In the setting of immune checkpoint inhibitor therapy, eosinophilic fasciitis is a novel immune-related adverse event that can result in significant morbidity, including joint contracture.[3] Prompt treatment with systemic corticosteroids may reduce the severity. Other choices include corticosteroid-sparing agents, which may be effective upon improvement of initial symptoms.

C. Azathioprine—Incorrect. While azathioprine has been used in patients successfully to treat eosinophilic fasciitis, it is not considered first-line therapy.[4]

D. Mycophenolate mofetil—Incorrect. While mycophenolate mofetil has been used successfully to treat eosinophilic fasciitis and other sclerodermoid disorders, it is not considered first-line therapy.[4] Our patient was started on mycophenolate mofetil after experiencing substantial improvement in her symptoms on prednisone monotherapy, allowing for tapering of systemic corticosteroids.

E. Hydroxychloroquine—Incorrect. While hydroxychloroquine has been used in patients successfully to treat eosinophilic fasciitis, it is not considered first-line therapy.[4]

Question 3: In addition to medications such as immune checkpoint inhibitors, other causes of eosinophilic fasciitis may include all of the following *except*:

A. Muscle trauma

B. Hematologic disorders

C. Infections

D. Autoimmune diseases

E. Primary hypertension

Answer:

A. Muscle trauma—Incorrect. Between 30% and 46% of patients with eosinophilic fasciitis report a history of intense physical exertion or trauma before onset of the condition.[4]

B. Hematologic disorders—Incorrect. Although rare, hematologic disorders such as thrombocytopenia, myelomonocytic leukemia, chronic lymphocytic leukemia, and myeloproliferative disorders have been associated with eosinophilic fasciitis.[4]

C. Infections—Incorrect. Infections such as *Borrelia burgdorferi, Borrelia afzelii,* and *Mycoplasma arginini* have been associated with eosinophilic fasciitis.[4]

D. Autoimmune diseases—Incorrect. Autoimmune diseases such as Hashimoto disease and Graves disease, primary biliary cirrhosis, and lupus erythematosus have been associated with eosinophilic fasciitis.[4]

E. Primary hypertension—Correct. Primary hypertension itself has not been associated with eosinophilic fasciitis. However, some medications used to treat hypertension, such as ramipril,[4] have been associated with eosinophilic fasciitis.

REFERENCES

1. Fett N, Arthur M. Eosinophilic fasciitis: current concepts. *Clin Dermatol*. 2018;36(4):487-497.
2. Onajin O, Wieland CN, Peters MS, Lohse CM, Lehman JS. Clinicopathologic and immunophenotypic features of eosinophilic fasciitis and morphea profunda: a comparative study of 27 cases. *J Am Acad Dermatol*. 2018;78(1):121-128.
3. Chan KK, Magro C, Shoushtari A, et al. Eosinophilic fasciitis following checkpoint inhibitor therapy: four cases and a review of literature. *Oncologist*. 2020;25(2):140-149.
4. Pinal-Fernandez I, Selva-O' Callaghan A, Grau JM. Diagnosis and classification of eosinophilic fasciitis. *Autoimmun Rev*. 2014;13(4-5):379-382.