Eosinophilia-myalgia syndrome presenting with overlapping features of eosinophilic fasciitis and sarcoidal granulomas

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Key words: 5-hydroxytryptophan; autoimmune skin disease; connective tissue disease; dermatopathology; eosinophilia-myalgia syndrome; eosinophilic fasciitis; L-tryptophan; sarcoidal granulomas.

INTRODUCTION

Eosinophilia-myalgia syndrome (EMS), a rare multisystem disorder impacting muscles, skin, and lungs, was initially documented in 1989 after several patients consumed contaminated L-tryptophan.[1] The major diagnostic criteria for EMS includes: (1) swelling, induration, and thickening of the skin and subcutaneous tissue that is symmetric or nonsymmetric, diffuse (extremities, trunk, and abdomen), or localized (extremities); and (2) fascial thickening with accumulation of lymphocytes and macrophages with or without eosinophilic infiltration (determined by full-thickness wedge biopsy of clinically affected skin). The minor criteria includes: (1) eosinophilia >0.5 × 109/L; (2) hypergammaglobulinemia >1.5 g/L; (3) muscle weakness or elevated aldolase levels; (4) groove sign or peau d'orange; and (5) hyperintense fascia on magnetic resonance imaging T2-weighted images. Despite the specific diagnostic criteria, there remains ambiguity because of significant overlap with other infiltrative eosinophilic etiologies. One such condition is eosinophilic fasciitis (EF), which occurs when inflammation leads to debilitating thickening of the fascia. Our case supports the recent literature suggesting EMS and EF share overlapping clinical and histopathologic features complicating their delineation.

Abbreviations used:

5-HTP:	5-hydroxytryptophan
EF:	eosinophilic fasciitis
EMS:	eosinophilia-myalgia syndrome

CASE REPORT

A 44-year-old previously healthy man experienced an asymptomatic macular eruption on both arms, axillae, and back followed by dyspnea and myalgias. Significant edema of the hands and feet prevented flexion leading to a limited range of motion. Symptoms developed 3 weeks after starting a supplement composed primarily of *Griffonia simplicifolia* seed extract. Initial work-up was positive for eosinophilia (10.9%, 1.19 k/μL), aldolase 11.6 (reference range, 1.5-8.1 U/L), and mild elevation in angiotensin-converting enzyme (68 U/L, [reference range, 16-85 U/L]). Negative work-up included antinuclear antibody, antineutrophil cytoplasmic antibodies, serum protein electrophoresis, urine protein electrophoresis, thyroid-stimulating hormone, thyroglobulin antibodies, QuantiFERON gold, and an unremarkable chest computed tomography.

Fascial biopsy revealed a noncaseating sarcoidal granulomatous infiltrate in the deep fascial planes. No epidermal, dermal, or superficial subcutaneous

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Funding sources: None.

Patient consent: The authors attest that they have obtained written consent from patient/s, their legal guardian/s or person/s with legal authority, for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available. Patient consent forms were not provided to the journal but are retained by the authors to be made available upon request.

IRB approval status: Not applicable.

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JAAD Case Reports 2024;50:115-8.
2352-5126

https://doi.org/10.1016/j.jdcr.2024.05.035

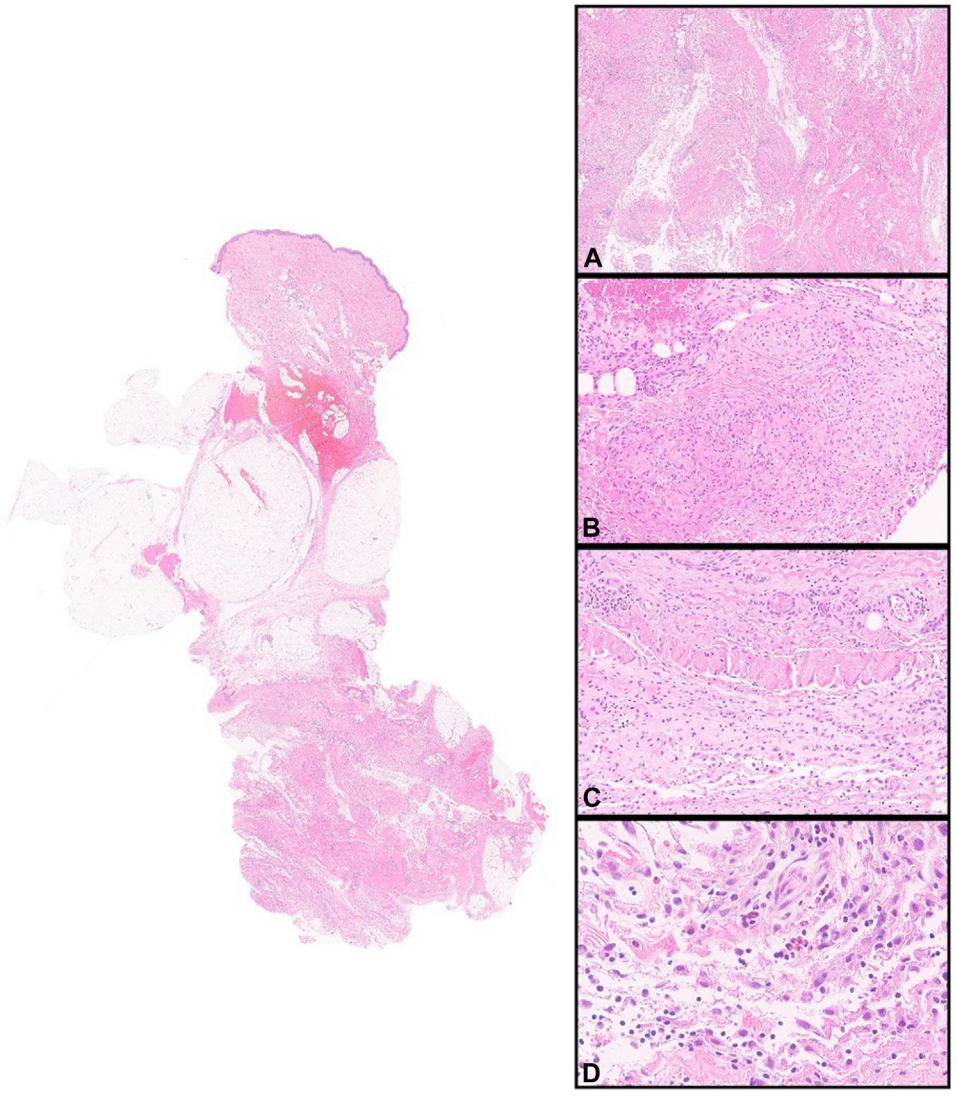

Fig 1. A, On scanning magnification of an excisional biopsy from the left forearm, there is a robust inflammatory infiltrate comprising the deep subcutaneous and fascial planes. **B, C,** Scattered throughout are histiocytes arranged in sarcoidal granulomas and a predominant lymphoplasmacytic infiltrate that are associated with thickened and sclerotic fascia. **D,** There are rare focal areas with several eosinophils in the deep subcutaneous and fascial planes. (Original magnifications: **A,** ×20; **B,** ×100; **C** and **D,** ×200.)

involvement was noted. The infiltrate was primarily histiocytic with few scattered lymphocytes and rare eosinophils (Fig 1). Tissue cultures for mycobacterium and fungal organisms were negative.

Given the patient's reported history of dietary supplement use, EMS was considered in the differential. As EMS has been associated with ingestion of L-tryptophan, there was concern that the patient's supplement, *G simplicifolia* seed extract containing 99% 5-hydroxytryptophan (5-HTP; by label), was contaminated. The sample was subsequently measured using gas chromatography/mass spectrometry to identify its components. 5-HTP was detected and L-tryptophan was not. Lysine was also detected in the sample.

The patient was placed on 60 mg prednisone for 1 month, then tapered to 40 mg and then placed on 20 mg methotrexate weekly with improvement although significant induration and nodularity persisted. Because of initial concern for sarcoidosis, patient was also started on hydroxychloroquine 200 mg but there was no perceived added benefit. He continues to have repeat flares of disease when steroids are tapered and remains on high dose daily

prednisone. Approval for benralizumab has been denied by insurance.

DISCUSSION

The present case highlights the clinicopathologic spectrum shared by EMS and EF, indicating significant overlap between these conditions. EMS is a disease entity where patients experience disabling myalgia and have eosinophilia after consumption of contaminated products. EF can present similarly and is characterized by early erythema and edema found on the limbs or trunk followed by collagenous thickening of the subcutaneous fascia. Eosinophilia is most commonly observed in the early phases of EF, although it may not always be present initially and is less frequently seen in later phases.[2] Unlike EMS, myalgias are not included in the diagnostic criteria for EF as muscle involvement is less common and milder if observed.[3] In the early phases of EF, deep fascia and subcutis are edematous and infiltrated with lymphocytes, plasma cells, histiocytes with multinucleated giant cells, and eosinophils. As the disease progresses, these structures thicken and inflammatory infiltrates dissipate.[4] Although biopsy typically shows thickening of fascia in EF, these findings are not specific, and EMS can present with diffuse fascial thickening as well.

In this case, the presence of sarcoidal granulomas is highly unique and could potentially be a diagnostic pitfall if the clinical presentation was not taken into account. The sarcoidal granulomas likely represent an exuberant manifestation of the inflammatory infiltrate since extensive work-up for sarcoidosis and atypical infections were negative. Additionally, the presence of a granulomatous component may provide further evidence for a "granulomatous medication eruption" from a dietary supplement.

There are several reports demonstrating the overlap among the clinical and histopathologic features of EMS and EF. For example, Christensen et al[5] described a patient who despite having extremity edema and peripheral eosinophilia, did not have biopsy results confirming EF but instead showed granulomatous inflammation of the fascia. Lewkonia et al[6] reported 2 cases with clinical and histologic features of EF as well as histologic features of granuloma formation. These reports and the present case demonstrate that both EMS and EF can present heterogeneously and there should be consideration for overlapping presentations and mixed subtypes.

One of the main distinguishing factors between these 2 entities is that EMS is temporally related to the consumption of contaminated products, typically L-tryptophan. In 1991, it was suggested that many previously diagnosed cases of EF may have been variants of tryptophan-associated EMS.[7] Interestingly, our patient's supplement did not contain L-tryptophan but instead had 5-HTP. There have been several reports of 5-HTP associated EMS. Michelson et al[8] reports a case of family members who became ill with EMS and eosinophilia after exposure to L-5-HTP. The L-5-HTP was found to have an impurity and once it was replaced without the impurity, the eosinophilia resolved, suggesting the impurities in L-5-HTP may have been related to the development of EMS.[8] Klarskov et al[9] studied the impurities and identified them as peak X. Peak X is a family of contaminants with the same molecular weight (234 Da) and similar high-performance liquid chromatography retention times as L-tryptophan.[9] The contaminants' precise mechanism of action remains unclear, but hypotheses suggest the contaminants could trigger an immunogenic response, with metabolic dysfunction allowing buildup of neurotoxic metabolites, or the contaminants could be toxic themselves, which is the most widely currently accepted theory.[10]

In summary, our patient presented with a macular eruption and an accompanying onset of myalgia and eosinophilia, initially suggesting a diagnosis of EMS. However, notably, his supplement did not contain L-tryptophan but instead 5-HTP. Furthermore, the biopsy demonstrated fascial thickening with sarcoidal granulomas, findings consistent with EF. This patient is currently being managed with prednisone and methotrexate, however, in cases where patients are refractory to first-line treatment, mycophenolate, IVIG, and other immunosuppressants may be considered. This case highlights the clinicopathologic spectrum and heterogeneous nature of EMS and EF.

Conflicts of interest

None disclosed.

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