Generalized morphea/eosinophilic fasciitis overlap after epoxy exposure

Warren H. Chan, MS,[a] Daniel J. Lewis, BA,[a,b] Esther J. Kim, BA,[a,b]
Phyu P. Aung, MD,[c] and Madeleine Duvic, MD[b]
Houston, Texas

Generalized morphea is associated with epoxy resin vapors and is characterized by the development of lesions shortly after exposure. Morphea presenting along with eosinophilic fasciitis (EF), or morphea/EF overlap, is rare and an indicator of poor prognosis and resistance to treatment. Here we present a case of generalized morphea/EF overlap linked to epoxy exposure. Our patient received multiple therapies—ultraviolet A1 phototherapy, prednisone, methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, and rituximab—none of which led to a significant response. The refractory nature of this disease warrants vigilance in its association with epoxy exposure. (J Am Acad Dermatol 2018;4:175-8.)

Key words: azathioprine; eosinophilic fasciitis; epoxy; generalized morphea; phototherapy; ultraviolet A1.

INTRODUCTION

Morphea, also known as *localized scleroderma*, is an uncommon fibrosing skin disorder often presenting with erythematous violaceous patches and plaques in early lesions that resolve into hairless, sclerotic plaques with postinflammatory hyperpigmentation.[1] Eosinophilic fasciitis (EF), characterized by initial pitting edema and erythema of the extremities followed by woody skin induration, is another rare connective tissue disease that may represent a variant of, or present alongside, morphea.[2] A generalized presentation of morphea has been associated with epoxy resins; however, the causative mechanism by which epoxy resins elicit sclerotic changes remains unclear.[3,4] This report describes a rare case of generalized morphea/EF overlap that developed shortly after exposure to epoxy resins.

Abbreviations used:

BAMM:	Bis(4-amino-3-methylcyclohexyl) methane
EF:	eosinophilic fasciitis
EGPA:	eosinophilic granulomatosis with polyangiitis
HES:	hypereosinophilic syndrome
UVA1:	ultraviolet A1

CASE REPORT

A 24-year-old Hispanic man presented to MD Anderson Cancer Center in March 2017 with a 7-year history of diffuse, hyperpigmented sclerosis of his arms, legs, and trunk and accompanying tender edema of the distal extremities. His symptoms began in 2010, 3 weeks after starting a new painting job, during which he used paint with epoxy resins. He quit the job 1 month after the symptoms developed and received a diagnosis of EF after a bone marrow biopsy showed profound eosinophilia (>3000 cells/mm^3). He was started on prednisone, 10 mg daily, which he has since continued. By 2011, the edema had progressed to indurated hyperpigmented patches and plaques, and the patient was administered oral methotrexate 25 mg/d for 1 year with minimal response. From 2012 to 2015, he received regimens of azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, and rituximab, all of which resulted in minimal improvement.

From the School of Medicine, Baylor College of Medicine[a] and the Departments of Dermatology[b] and Pathology,[c] The University of Texas MD Anderson Cancer Center.

Funding sources: None.
Conflicts of interest: None declared.
Disclaimer: Dr Duvic is the Blanche Bender Professor in Cancer Research.

Correspondence to: Warren H. Chan, MS, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030. E-mail: warren.chan@bcm.edu.

2352-5126

https://doi.org/10.1016/j.jdcr.2017.09.006

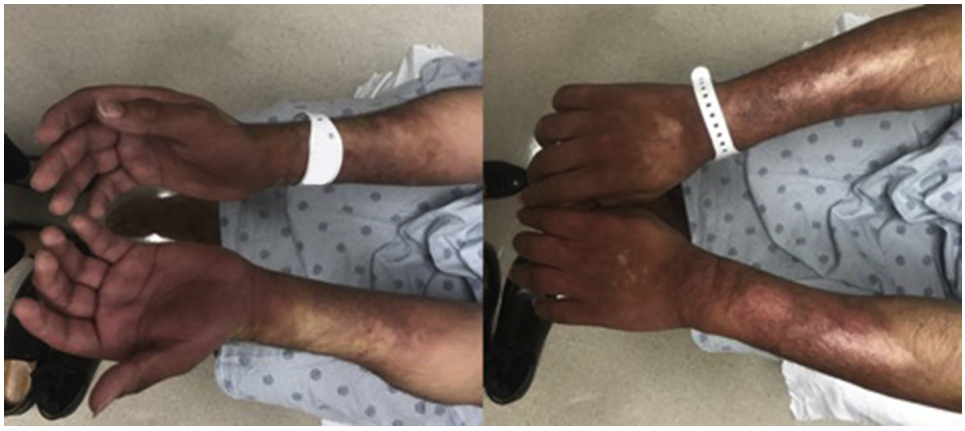

Fig 1. Presentation in March 2017 with diffuse hyperpigmented sclerodermoid lesions of the bilateral upper extremities with palpable fasciitis and tightening of the distal forearm muscles.

New patches on his chest and upper back appeared in 2016.

Physical examination found hyperpigmented sclerotic patches of the upper back and bilateral upper and lower extremities, indurated hyperpigmented plaques with erythematous borders extending from the upper and mid–lateral chest to the neck and shoulder, and palpable fasciitis and tightening of the bilateral distal forearm muscles (Fig 1). Laboratory tests found positive antinuclear antibody levels, peripheral eosinophilia, hypergammaglobulinemia, and increased erythrocyte sedimentation rate and C-reactive protein levels; however, systemic involvement and antiscleroderma-70 and anti-centromere antibody levels were negative. Biopsy and histopathologic examination found homogenization and thickening of collagen fibers, fragmentation of elastic fibers, atrophy of skin appendages, and focal lymphocytic infiltrate with eosinophils throughout the dermis (Fig 2). These findings, together with the clinical presentation, were consistent with a diagnosis of EF/generalized morphea overlap. The patient received ultraviolet A1 (UVA1) phototherapy thereafter for 1 month with no signs of improvement.

DISCUSSION

Morphea is characterized by an early inflammatory stage followed by subsequent sclerosis and atrophy. The depth of involvement may be primarily dermal or may extend into the deep dermis including the subcutis, fascia, muscle, and bone. Lesion distribution varies with morphea subtype: circumscribed (trunk, waist, submammary region), deep (symmetric lower extremities), generalized (trunk, extremities), linear (extremities, face), and en coup de sabre (forehead, face).[1,5]

EF, characterized by trunk and extremity edema and erythema followed by sclerosis of the subcutaneous fascia, is often regarded as a part of the morphea spectrum.[2,5] Because EF involves the deep fascial layers, differentiation from deep morphea can be especially challenging both clinically and histologically. A more acute inflammatory phase, symmetric skin involvement, and peripheral eosinophilia point to EF.[2,5] Other differential diagnoses to consider include eosinophilia-myalgia syndrome, toxic oil syndrome, hypereosinophilic syndrome (HES), eosinophilic granulomatosis with polyangiitis (EGPA), and systemic sclerosis. The presence of internal organ involvement in eosinophilia-myalgia syndrome, toxic oil syndrome, HES, EGPA, and systemic sclerosis and the absence of cutaneous sclerosis in HES and EGPA distinguish these conditions from EF.[6-8] Raynaud's phenomenon and sclerodactyly, characteristic of systemic sclerosis, are absent in both morphea and EF.[1,2]

Biopsy depth is important in the diagnosis of morphea and EF. A punch biopsy extending into the subcutaneous fat is reserved for superficial morphea lesions of unclear presentation. For deep morphea and EF, a full-thickness incisional biopsy down to the muscle is recommended. Magnetic resonance imaging, ultrasound scan, and positron emission tomography to assess lesion depth and fascial involvement may also aid in diagnosis.[5]

Generalized morphea, defined by the presence of ≥ 4 morphea lesions (circumscribed or deep) in ≥ 2 anatomic locations, has been described in several workers engaged in the polymerization process of epoxy resins.[3,4,9-11] The mechanism of pathogenesis is unclear but may be caused by the accumulation of the amine, Bis(4-amino-3-methylcyclohexyl) methane (BAMM), derived from epoxy fumes, or to

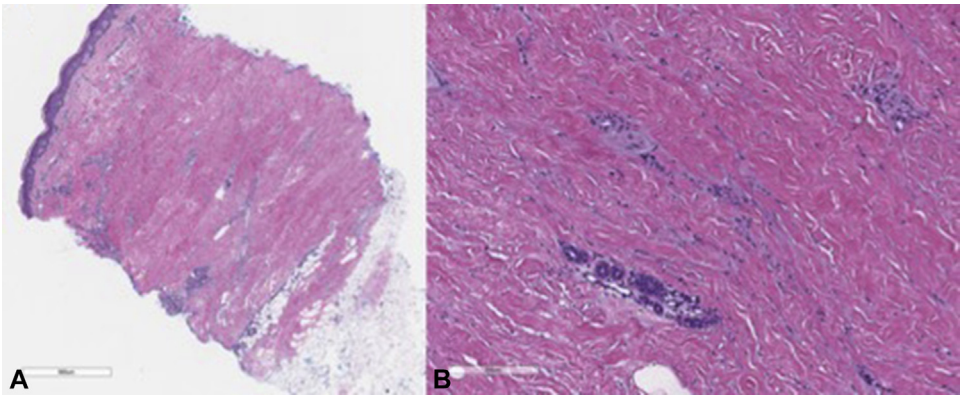

Fig 2. Markedly hyalinized and thickened dermis and atrophic eccrine glands (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, ×20; **B**, ×200.)

the binding of oligomers of epoxy resins with BAMM or biogenic amines in tissue. These changes in turn damage blood vessels and sympathetic nerve endings, eliciting sclerosis.[3,11,12] Strong allergenicity associated with epoxy resin oligomers leading to immune hyperactivation has also been proposed.[3,4]

The resulting scleroderma has been characterized by homogenization of collagen fibers, atrophy of skin appendages, fragmentation of elastic fibers, focal lymphocytic infiltrates, muscle weakness and thickening fascia, and indurated erythematous patches and plaques without visceral involvement.[4] Additionally, a distinctive feature of epoxy-induced scleroderma is the development of skin sclerosis shortly after epoxy exposure.[3,4] The characteristic timing and clinical and histologic similarities of our patient's sclerodermalike syndrome strongly suggest an epoxy-related etiology. If epoxy was the causative factor, our patient represents one of the few documented cases of generalized morphea activated by epoxy resin exposure and is, to our knowledge, the first reported case of EF/generalized morphea overlap linked to epoxy.

Although treatment of EF can be achieved with systemic glucocorticoids,[2,13] and morphea often involves a combination of glucocorticoids and methotrexate or UVA1 phototherapy usually to good effect,[14] morphealike lesions presenting with concomitant EF indicate poor outcome and therapeutic resistance.[15] One report describes a patient who experienced successful treatment of EF/generalized morphea with azathioprine.[16] Our patient did not show a significant response to azathioprine or to multiple other therapies including glucocorticoids, methotrexate, UVA1, mycophenolate mofetil, and cyclosporine. Because of the refractory nature of EF/generalized morphea, care in preventing disease through limiting exposure to epoxy resins is imperative, and renewed vigilance on the subject is recommended.

REFERENCES

1. Fett N, Werth VP. Update on morphea. *J Am Acad Dermatol*. 2011;64(2):217-228.
2. Antic M, Lautenschlager S, Itin PH. Eosinophilic fasciitis 30 years after—what do we really know? Report of 11 patients and review of the literature. *Dermatology*. 2006;213(2):93-101.
3. Yamakage A, Ishikawa H, Saito Y, Hattori A. Occupational scleroderma-like disorder occurring in men engaged in the polymerization of epoxy resins. *Dermatologica*. 1980;161(1):33-44.
4. Haustein UF, Ziegler V. Environmentally induced systemic sclerosis-like disorders. *Int J Dermatol*. 1985;24(3):147-151.
5. Mertens JS, Seyger MMB, Thurlings RM, Radstake TRDJ, de Jong EMGJ. Morphea and eosinophilic fasciitis: an update. *Am J Clin Dermatol*. 2017;18(4):491-512.
6. Kaufman LD, Krupp LB. Eosinophilia-myalgia syndrome, toxic-oil syndrome, and diffuse fasciitis with eosinophilia. *Curr Opin Rheumatol*. 1995;7(6):560-567.
7. Noth I, Strek ME, Leff AR. Churg-Strauss syndrome. *Lancet*. 2003;361(9357):587-594.
8. Roufosse F. Hypereosinophilic syndrome variants: diagnostic and therapeutic considerations. *Haematologica*. 2009;94(9):1188-1193.
9. Inachi S, Mizutani H, Ando Y, Shimizu M. Progressive systemic sclerosis sine scleroderma which developed after exposure to epoxy resin polymerization. *J Dermatol*. 1996;23(5):344-346.
10. Asquier E, Degenne D, Boissinot E, et al. Relationship between occupational risk factors and severity markers of systemic. *J Rheumatol*. 2005;3232(5):1713-1718.
11. Thorgeirsson A, Fregert S, Ramnäs O. Sensitization capacity of epoxy resin oligomers in the guinea pig. *Acta Derm Venereol*. 1978;58(1):17-21.
12. Stachów A, Jabłońska S, Skiendzielewska A. Biogenic amines derived from tryptophan in systemic and cutaneous scleroderma. *Acta Derm Venereol*. 1979;59(1):1-5.
13. Lebeaux D, Francès C, Barete S, et al. Eosinophilic fasciitis (Shulman disease): new insights into the therapeutic management from a series of 34 patients. *Rheumatology (Oxford)*. 2012;51(3):557-561.
14. Zwischenberger BA, Jacobe HT. A systematic review of morphea treatments and therapeutic algorithm. *J Am Acad Dermatol*. 2011;65(5):925-941.

15. Moulin C, Cavailhes A, Balme B, Skowron F. Morphoea-like plaques revealing an eosinophilic (Shulman) fasciitis. *Clin Exp Dermatol*. 2009;34(8):e851-e853.

16. Alonso-Castro L, de las Heras E, Moreno C, et al. Eosinophilic fasciitis/generalized morphea overlap successfully treated with azathioprine. *Int J Dermatol*. 2014;53(11):1386-1388.