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Erythema elevatum et diutinum as a systemic disease

Jeena K. Sandhu, MD [a], Joerg Albrecht, MD [b], Gaurav Agnihotri, BS [c], Maria M. Tsoukas, MD, PhD [d,*]

[a] *University of Missouri–Kansas City School of Medicine, Kansas City, Missouri, USA*
[b] *Department of Dermatology, John H. Stroger Jr. Hospital of Cook County, Chicago, Illinois, USA*
[c] *University of Illinois-Chicago College of Medicine Chicago, Illinois, USA*
[d] *Department of Dermatology, University of Illinois–Chicago School of Medicine, Chicago, Illinois, USA*

Abstract Erythema elevatum et diutinum (EED) is a rare, chronic dermatosis. It has been associated with extracutaneous findings, including arthralgias, scleritis, panuveitis, peripheral ulcerative keratitis, oral and penile ulcers, and neuropathy. Additionally, EED is connected with various systemic diseases, including HIV, IgA paraproteinemia, myelomas, neutrophilic dermatoses, and inflammatory bowel diseases. The presence of such extracutaneous manifestations in EED patients suggests that EED may be a multiorgan entity. Extracutaneous manifestations in EED may involve deposition of circulating immune complexes; thus, patients with EED should be evaluated for systemic manifestations to ensure targeted management.

Historic background and epidemiology

Erythema elevatum et diutinum (EED) was first described in the 1880s,[1] although the term "erythema elevatum diutinum" was first used in 1894 by Henry Radcliffe-Crocker (1845-1909).[2] By 1929, EED had become the accepted term to describe cases with similar cutaneous manifestations.[3] EED commonly occurs in patients 30 to 60 years of age, although patients can develop this disease at any age without any sex or racial predilection.[4]

EED is a rare, chronic dermatosis with less than a thousand reported cases in the literature. Henry Radcliffe-Crocker described the indurated, tender violaceous to red nodules on a patient's hands, elbows, knees, and buttocks.[2] He found similarities between similar lesions previously described by Sir Jonathan Hutchinson (1828-1913)[1] in 1880 and Judson Sykes Bury (1852-1944)[5] in 1889, and named this phenomenon "erythema elevatum diutinum."

The cutaneous manifestations of EED classically consist of red to violaceous papules and plaques.[4] These cutaneous lesions are typically asymptomatic. Extracutaneous manifestations of EED, which are less common, include arthralgias, constitutional clinical manifestations, and ocular disease.[6–9] EED has been linked with several systemic diseases, including systemic infections, autoimmune disorders, and hematologic diseases. This chronic disease is known to have a relapsing and remitting course. EED has been reported to resolve within 5 to 10 years,[4,5] but there are also cases of EED that have remained active for up to 39 years.[10]

* Corresponding author. Tel.: +1 312 996 8666.
E-mail address: tsoukasm@uic.edu (M.M. Tsoukas).

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Cutaneous and histologic findings

EED is characterized as a chronic leukocytoclastic vasculitis. It typically presents as red-brown, violaceous, or yellowish papules, plaques, or nodules (Figure 1).[11] The cutaneous lesions of EED usually favor the extensor surfaces and acral sites. EED can also affect the face, posterior auricular area, axilla, trunk, genitals, buttocks, back, and larynx.[4–13] EED lesions typically begin as more erythematous, soft lesions, becoming red-brown, or violaceous, and indurated over time. There have been cases reporting more atypical cutaneous presentations, such as annular[14] and verrucous plaques.[15]

The histologic findings of EED vary depending on the stage of the cutaneous lesions. Early lesions exhibit findings that are consistent with a leukocytoclastic vasculitis, demonstrating upper dermis to middermis neutrophilic infiltrate with some eosinophils.[15–17] As the lesion progresses, the papillary and periadnexal dermis become involved as well. Additionally, these mature lesions can exhibit granulation tissue, fibrosis with mixed inflammation, and intracellular lipoidosis.[16] Direct immunofluorescence for EED is usually nondiagnostic, demonstrating IgG, IgM, C3, and fibrinogen deposits within vessels in the upper dermis.[18,19]

An analysis of six patients with EED reported that the vascular endothelium in EED stains positive for CD31, CD34, VEGF, and factor VIIIa and negative for factor XIIIa, TGFB, and LANA; however, these findings are not specific to EED,[17] The authors report that the most effective way to differentiate EED from other cutaneous vasculitides is the chronicity and recurrent nature of EED.

Pathophysiology and systemic manifestations

Infectious diseases

EED is thought to be secondary to circulating immune complexes that continuously deposit in blood vessels, as the resultant inflammation. In a study of five patients with EED, three demonstrated increased C1q binding, supporting this proposed pathophysiologic mechanism.[20] EED is

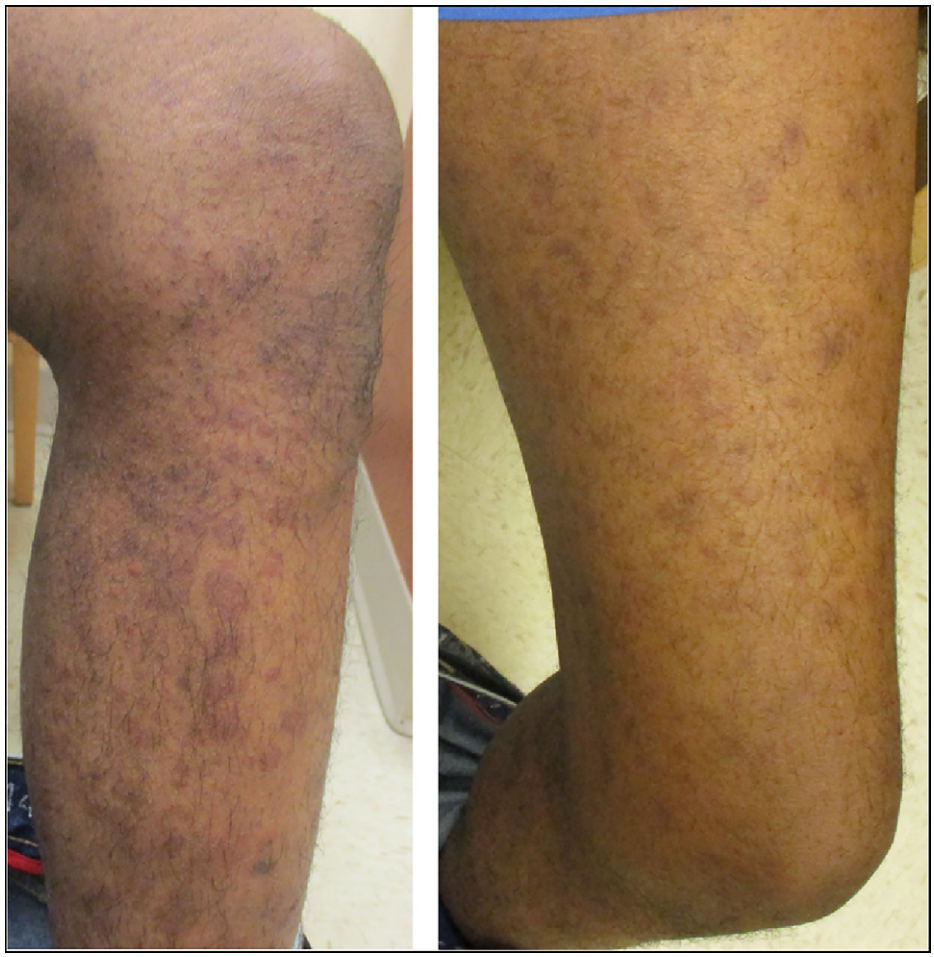

Fig. 1 Atypical erythema elevatum et diutinum in a HIV-positive patient (CD4 500). The skin lesions present with red violaceous papules and flat nodules with itching, burning, and tenderness to touch, disseminated to his lower extremities and with intermittent resolution. Dapsone provided excellent management.

associated with systemic infections, including streptococcal infections, HIV, hepatitis B, tuberculosis, and syphilis, all of which involve elevated levels of antigens or antibodies[7,20] (Figure 1). Intradermal injection of streptococcal antigen into nonlesional skin of patients with EED has resulted in the appearance of lesions both clinically and histologically identical to EED. This further suggests that circulating immune complexes have a role in the pathogenesis of EED.[7] Additionally, in HIV patients, EED is thought to be due to HIV-related antigen-antibody complexes depositing in blood vessels or HIV-induced immunosuppression, which enables other infectious agents to serve as the antigenic stimulus.

Hematologic diseases and malignancies

EED is also associated with IgA paraproteinemia, IgA myeloma, and various gammopathies (IgA, IgG, and IgM).[19,21] It has been linked to other hematologic diseases and malignancies, including hyperimmunoglobulinemia D,[22] other plasma cell dyscrasias,[23] non-Hodgkin lymphoma,[24] myelodysplastic syndrome,[19] hairy cell leukemia,[25] B-cell lymphoma,[26] and chronic lymphocytic leukemia.[27] More studies are required to further analyze the relationship between these diseases and EED, as the role of IgA or other gammopathies remains unclear.[19]

Neutrophilic dermatoses

Other diseases that have been associated with EED include neutrophilic dermatoses such as Sweet syndrome and pyogenic gangrenosum.[28] Neutrophilic dermatoses are a group of heterogeneous diseases that display neutrophilic infiltrate in the skin and other organs, have an association with systemic diseases, and overlap with other neutrophilic dermatoses.[29] EED is considered to be within the spectrum of the neutrophilic dermatoses but can be differentiated from the rest by the presence of vasculitic findings.[19]

Autoimmune and inflammatory diseases

Several autoimmune and inflammatory diseases are associated with EED. These include inflammatory bowel disease, granulomatosis with polyangiitis,[30] cryoglobulinemia,[31,32] relapsing polychondritis,[33] celiac disease,[34] dermatitis herpetiformis,[35] systemic lupus erythematosus,[36,37] and rheumatoid arthritis.[38,39] There have also been cases reporting possible associations between EED and hypothyroidism,[40] Hashimoto thyroiditis,[41] dermatomyositis,[42] myasthenia gravis,[43] and ankylosing spondylitis.[44] The underlying mechanism for most of the previously referenced diseases is also due to the deposition of immune complexes; for example, there is a known association between IgA and EED; hence, the presence of IgA deposits in diseases such as dermatitis herpetiformis found to be associated with EED justifies the common underlying mechanism.[45]

Extracutaneous manifestations of EED

Extracutaneous findings in patients with EED support the concept that EED can be reviewed as a systemic entity. Arthralgias,[4] scleritis,[9,46] panuveitis,[46] peripheral ulcerative keratitis,[8,47–49] neuropathy,[50] and ulceration (oral,[51] esophageal,[52] and penile[53]) all have been reported in patients with EED, with joint disease being most common.[54]

The response of these extracutaneous manifestations to the treatments used for EED suggests a common underlying pathophysiologic mechanism. A patient with EED associated with severe arthritis and scleritis responded very well to oral dapsone, the first-line therapy for EED.[46] Additionally, in another patient with EED and associated progressive neuropathy, dapsone helped to improve both the cutaneous and neurological clinical manifestations.[50]

Treatment

Dapsone, an antimicrobial that impairs neutrophil chemotaxis and function, is currently the treatment of choice for EED.[4] Treatment with dapsone, however, may not be as effective in HIV-positive patients and for patients with late-stage fibrotic lesions.[7] Antiretroviral therapy is typically added to the treatment regimen for HIV-positive patients. Other treatments consist of anti-inflammatory, antimicrobial, and immunosuppressive agents.[54,55] These therapies include NSAIDs, niacinamide, tetracyclines, chloroquine, colchicine, and plasmapheresis. Additionally, for fibrotic nodules that respond poorly to dapsone, surgical excision is considered if the extent of lesions is limited.

Is EED a distinct entity?

The question of whether EED can be classified as a distinct entity has been prone to contentious debate among dermatologists. Even though Radcliffe-Crocker had described the distinguishing clinical and histologic characteristics of EED originally in 1902, the disease was not accepted as a separate entity until 1929,[3] a concept that is still sometimes challenged.

Although most cutaneous leukocytoclastic vasculitides resolve, the chronic nature of EED appears to be due to the formation of granulation tissue, which is more likely to be continuously injured.[56] The disease holds a unique position in the spectrum of cutaneous leukocytoclastic vasculitides. The acute presence of leukocytoclasis and perivascular neutrophil infiltration, and the chronic development of fibrosis and granulation tissue is popularly thought to truly differentiate EED from other cutaneous leukocytoclastic vasculitides on the spectrum.[57] Although EED may clinically and histologically be a distinct entity, etiologically it may not be, because it shares similar hypothesized pathophysiologic mechanisms with other diseases.[3,7,19–21,28]

The evolving nature of the clinical and histologic findings makes the diagnosis of EED initially difficult, as it may mimic other cutaneous leukocytoclastic vasculitides at a point in time, potentially delaying diagnosis; for example, the two major conditions associated with chronic leukocytoclastic vasculitides include EED and granuloma faciale (GF). By histology alone, one may not be able to distinguish between the two, as they both present with similar sequential changes from leukocytoclastic vasculitis to neutrophil infiltration to eventual fibroplasia.[58] Clinically, the most important clue to differentiating between EED and GF seems to be anatomic location[58]; EED seems to prefer extensor surfaces and acral sites, whereas GF lesions mainly appear on the face. There have been cases where GF presented with extrafacial manifestations[59,60] and lesions of EED appeared on the face.[61] This raises the question of whether EED and GF are different entities or different names for the same condition emerging at different locations on the body.[58]

A review of EED and presentation of 41 cases of GF concluded that granulomatous nodules are only present in EED, and a predominance of eosinophils in the interstitial infiltrate strongly supports a diagnosis of GF.[58] It is yet to be determined whether these findings are unique to their respective diseases, as additional cases of EED and GF emerge. Until more evidence is available, it may be beneficial to identify EED as a distinct entity from GF as the recommended first-line treatment for the two conditions differs.[4,62]

Conclusions

EED represents chronic leukocytoclastic vasculitis with systemic manifestations. It can present with extracutaneous findings and is associated with several systemic diseases, including infectious diseases, hematologic diseases, malignancies, neutrophilic diseases, autoimmune diseases, and inflammatory disorders. In patients with EED, it is important to look for extracutaneous findings and workup for potential underlying infections or diseases to optimize management.[4]

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