# Unusual Presentation of Erythema Elevatum Diutinum With Underlying Hepatitis B Infection

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## PRACTICE **POINTS**

- Erythema elevatum diutinum (EED) often is associated with an underlying infectious process, including hepatitis B and hepatitis C, or a hematologic or autoimmune condition.
- If EED is suspected clinically, it may be beneficial to perform multiple biopsies from lesions at different stages of evolution to establish the diagnosis.
- First-line therapy includes treatment of any underlying condition and dapsone.

Erythema elevatum diutinum (EED) is a rare, chronic, cutaneous small vessel vasculitis of unclear pathogenesis. Classically, lesions present as symmetric red to purple plaques, papules, and nodules overlying joints. First-line therapy is dapsone. We present a case of EED with widespread lesions involving the hands, extensor arms and legs, and trunk. Multiple biopsies showed concentric intradermal perivascular inflammation with dermal fibrosis and leukocytoclastic vasculitis (LCV) suggesting EED in various stages of evolution. An extensive workup was positive for underlying hepatitis B infection. Our case represents the clinicopathologic spectrum that EED can present and emphasizes the importance of searching for an underlying etiology.

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Erythema elevatum diutinum (EED) manifests on a clinicopathologic spectrum of chronic cutaneous small vessel vasculitis. The lesions typically present as persistent, symmetric, firm, red to purple papules or nodules on the extensor arms and dorsal hands.[1,2] Underlying infectious, malignant, or autoimmune processes are commonly associated with the disease, notably *Streptococcus* infection and IgA monoclonal gammopathy.[2,3] Hepatitis virus also is often implicated in association with EED. Cases of EED have been seen with concomitant human immunodeficiency virus (HIV) infection.[4-6] We report a case of EED presenting in various stages of evolution associated with underlying hepatitis B infection alone.

## Case Report

A 57-year-old man originally presented to an outpatient dermatology practice with a nodular, painful, episodic rash on the trunk and upper and lower extremities. A biopsy revealed leukocytoclastic vasculitis (LCV) with prominent eosinophils. At the time, the skin findings were believed to be a manifestation of drug hypersensitivity, likely to opioid use. The patient was lost to follow-up.

Seven years later, the patient was admitted to the hospital with new-onset burning and stinging red nodules on the dorsum of the hands and persistence of the original episodic rash over the lower legs and bilateral flanks. In the interim, he was briefly treated with an oral

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prednisone taper and topical corticosteroids including triamcinolone cream 0.1% and clobetasol cream 0.05% without improvement.

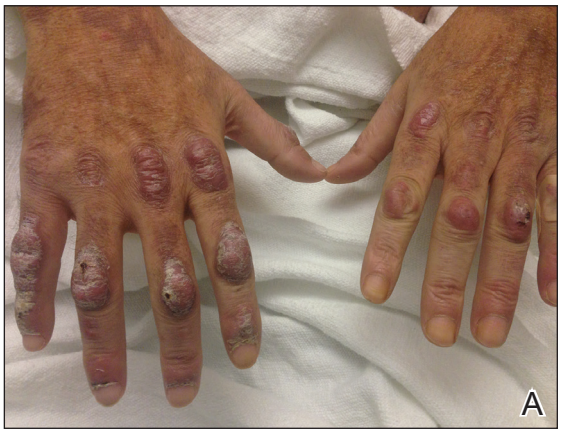
On examination deep red to violaceous discrete nodules and plaques with overlying hyperkeratosis involving all distal and proximal interphalangeal joints of the hands and extensor elbows were seen (Figure 1A). On the bilateral posterior arms (Figure 1B), anterior legs, and periumbilical area were deeply erythematous papules and plaques with background hyperpigmentation. Across his lower back and bilateral flanks were erythematous papules with central hemorrhagic crusting (Figure 1C).

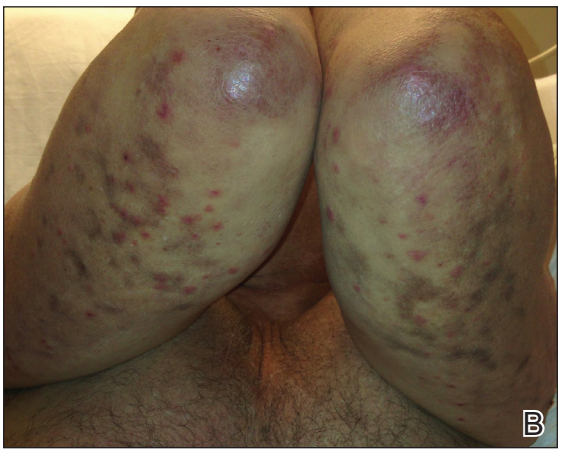
Pertinent laboratory findings included a positive hepatitis B surface antigen with hepatitis B DNA value 4,313,876 IU/mL and a hepatitis B virus quantitative polymerase chain reaction value of 6.64 U. The etiology was suspected to be intravenous drug abuse; however, the patient denied recreational drug use.

An additional infectious workup was negative for hepatitis C, streptococcus, syphilis, tuberculosis, and HIV. A complete blood cell count, complete metabolic panel, urinalysis, complement, cryoglobulins, and serum protein electrophoresis were within reference range. Autoimmune serologies were negative including antinuclear antibody, rheumatoid factor, anti-Sjögren syndrome–related antigen A and B, anticyclic citrullinated peptide, anti-Smith, and antineutrophilic cytoplasmic antibodies. Peripheral blood immunophenotyping, lactate dehydrogenase, quantitative immunoglobulins, and age-appropriate cancer screens did not demonstrate evidence for malignancy underlying the disease. Bilateral hand radiographs showed mild periostitis of the proximal phalanges without obvious erosions.

Three 4-mm punch biopsies were performed from the left fifth digit, left posterior arm, and left flank. Tissue of the left fifth digit showed an intradermal vascular proliferation with a concentric pattern resembling onion skin in a background of increased fibrosis. The blood vessels showed focal fibrinoid necrosis (Figure 2A). The biopsy of the left posterior arm showed an intradermal vascular proliferation with an associated mild acute and chronic perivascular inflammation (Figure 2B). The left flank biopsy showed LCV with focal epidermal necrosis (Figure 2C).

The constellation of clinical findings together with the histopathologic changes represented EED in various stages of evolution. The patient was started on dapsone 100 mg daily and referred to the infectious disease service for treatment of chronic hepatitis B; however, he was subsequently lost to follow-up.



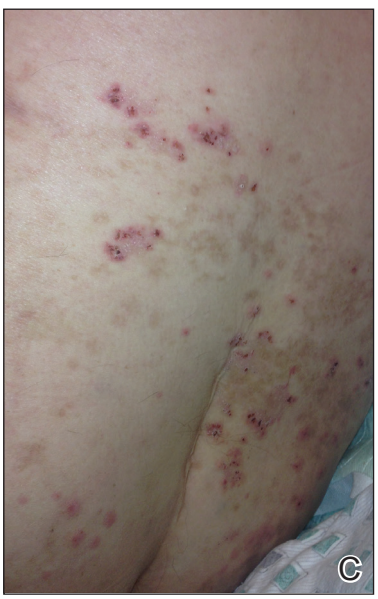




**FIGURE 1.** Erythema elevatum diutinum presenting as deep red, firm plaques and nodules overlying the distal and proximal interphalangeal joints (A); red to violaceous papules and nodules scattered over the posterior arms with background hyperpigmentation (B); and scattered erythematous papules with central hemorrhagic crusting of the left flank (C).

## Comment

*Overview of EED*—Erythema elevatum diutinum represents a rare form of chronic cutaneous small vessel vasculitis. Originally described by Hutchinson[7] and Bury[8] as symmetric purpuric nodules of the skin, it was later

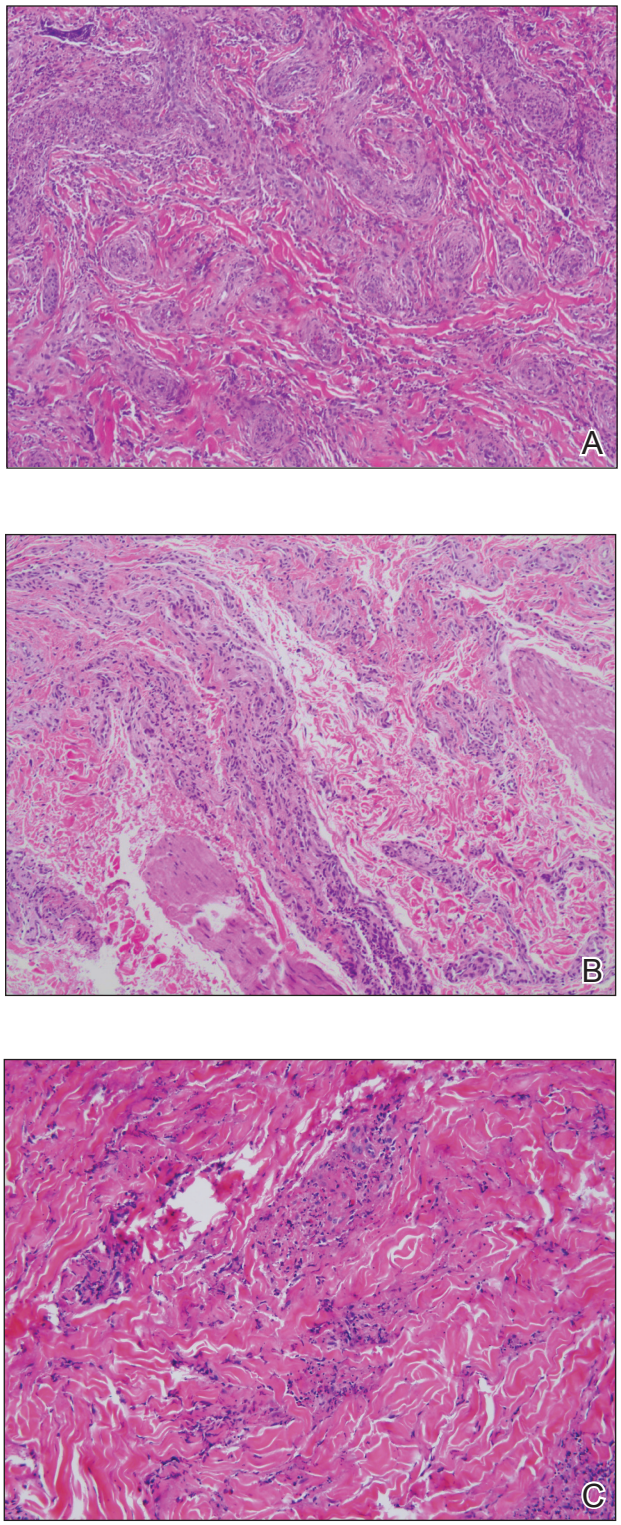



**FIGURE 2.** Punch biopsy of the left fifth digit showed intradermal vascular proliferation forming a concentric pattern resembling onion skin in a background of increased fibrosis (A)(H&E, original magnification ×200); biopsy of the left posterior arm showed an intradermal vascular proliferation on a background of increased fibrosis (B)(H&E, original magnification ×200); and biopsy of the left flank showed leukocytoclastic vasculitis (C)(H&E, original magnification ×200).

named by Crocker and Williams[9] in 1894. The disease classically presents as firm, fixed, red-brown to violaceous papules, plaques, and nodules affecting the extensor upper or lower extremities.[1] Lesions are most commonly found symmetrically overlying joints of the hands, feet, elbows, and knees, as well as the Achilles tendon and buttocks.[3] Less common locations include the palms and soles, face,[10,11] trunk,[12] and periauricular region.[1] Although they are typically asymptomatic, sensations such as burning, stinging, and pruritus have been noted.[1] Our patient was unique because in addition to typical lesions of EED, he presented with crusted papules on the flanks and violaceous papules of the lower legs and periumbilicus.

*Etiology*—Originally associated with *Streptococcus* as isolated from EED lesions,[3,13] additional infectious etiologies include viral hepatitis,[4-6] human herpesvirus 6,[14] and rarely HIV.[1,15] Hepatitis B and C are well known to be associated with EED, with only rare reports in patients with concomitant HIV infection. Erythema elevatum diutinum also has been described in relationship to myeloproliferative disorders and hematologic malignancies such as IgA myeloma,[16] non-Hodgkin lymphoma,[17] chronic lymphocytic leukemia,[18] and hypergammaglobulinemia.[19] In a study of 13 patients with EED, 4 had associated underlying IgA monoclonal gammopathy.[2] Autoimmune conditions such as rheumatoid arthritis,[20] ulcerative colitis,[21] relapsing polychondritis,[22] and systemic lupus erythematosus[23] also have been implicated.

*Pathogenesis*—Although the precise pathogenesis of EED remains unknown, it has been suggested that a complement cascade initiated by immune-complex deposition in postcapillary venules induces an LCV.[24,25] Chronic antigenic exposure or high antibody levels[26] in the face of infections, autoimmune disease, or malignancy may incite this immune-complex reaction. Skin lesions seen in association with hepatitis reflect circulating immune-complex deposition in vessel walls causing destruction. It has been postulated that the duration of immune complexemia may be sufficient to account for the differences in the type of vascular injury seen in acute versus chronic infection.[27]

*Histopathology*—Erythema elevatum diutinum may present on a histopathologic spectrum of LCV, as manifested in our patient. Early lesions show predominantly polymorphonuclear cells with nuclear dust pattern in a wedge-shaped infiltrate with fibrin deposition in the superficial and mid dermis.[2,3] Later lesions show vasculitis in addition to dermal aggregates of lymphocytes, neutrophils, fibrosis, and areas of granulation tissue. The fibrosis may be dense and comprised of fibroblasts and myofibroblasts.[28] Newly formed vessels within the granulation tissue have been postulated to be more susceptible to immune-complex deposition, thus potentiating the process.[1,29]

*Management*—Spontaneous resolution of EED may occur, albeit after a prolonged and recurrent course of

up to 5 to 10 years.[30] Treatment of the underlying cause, when identified, remains paramount. First-line therapy includes dapsone, shown to be effective in reducing lesion size to complete resolution in 80% of the 47 cases reviewed by Momen et al.[31] Dapsone monotherapy tends to be less effective in treating nodular lesions associated with HIV-positivity, likely due to the extensive fibrosis.[4,31] Combination therapy with dapsone and a sulfonamide,[32] niacinamide and tetracycline,[33] colchicine,[34] or surgical excision[35] may be necessary in more resistant cases.

## Conclusion

Our case exemplifies the clinical histologic spectrum that EED can present. The constellation of clinical findings was histologically confirmed to be manifestations of the disease in various stages of evolution. When typical lesions of EED present along with cutaneous findings in less common locations, performing multiple biopsies can be helpful. The clinician should retain a high index of suspicion for an underlying etiology and perform a complete workup for infection, malignancy, or autoimmune disease.

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