BRIEF ARTICLE

Erythema Elevatum Diutinum Associated with Tuberculosis

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ABSTRACT

Erythema elevatum diutinum (EED) is a rare small vessel vasculitis with cutaneous manifestations most commonly presenting as red or brown papules, plaques, and nodules on extensor surfaces. It is a chronic, relapsing disease that is often associated with states of immunocompromise, e.g., HIV, gammaglobulinemias, and, more rarely, tuberculosis. Currently oral dapsone is the current treatment of choice, and while most patients respond well, it is imperative that the diagnosis be made early. We report a rare case of EED associated with underlying tuberculosis infection. Recognizing the distinct manifestations of EED and understanding its immunologic and infectious disease associations may enable clinicians to properly recognize, manage, and treat patients with EED.

INTRODUCTION

Erythema elevatum diutinum (EED) is a rare skin disease most commonly presenting as red or brown papules, plaques, and nodules on extensor surfaces.[1] EED was first described in 1888 by Hutchinson and later named by Radcliff-Crocker and Williams in 1894.[2] Lesions are typically asymptomatic, but pain, pruritis, or arthralgias may be present.[3] Adults between the fourth and sixth decades of life are frequently affected with no known sex or racial predilection.[4] EED is a small-vessel leukocytoclastic vasculitis that progresses to perivascular fibrosis.[5] It is thought to be caused by immune complex deposition in small vessels resulting in an inflammatory response.[3] It is a chronic, relapsing disease that has most commonly been associated with HIV and gammaglobulinemias, as well as streptococcal infection, HIV, tuberculosis, rheumatoid arthritis, and celiac disease.[1,3] The differential diagnosis of EED may include Sweet's syndrome, granuloma annulare, Kaposi sarcoma, and bacillary angiomatosis; and thus, histologic correlation is imperative for diagnosis.[1] Oral dapsone is the current treatment of choice while other therapies including colchicine, steroids, antibiotics, and surgery have also been used.[1] We report a rare case of EED associated with underlying tuberculosis infection.

CASE REPORT

A 45-year-old African American female with a past medical history of hypertension and type-2-diabetes presented to our clinic in the fall of 2021 with itchy papules on her legs and ankles for 6 months. She reported that

she had tried petrolatum ointment and over-the-counter hydrocortisone without improvement. She reported having pet cats for several years and denied any sick contacts or recent illness. The patient also denied any bug bites, history of hiking, or possible exposure to plants. Of note, she reported that she recently traveled to the Dominican Republic and had immigrated from Haiti four years prior.

On examination, scattered hyperpigmented-to-erythematous nummular macules and papules were present on her lower legs and ankles with large, flesh-colored nodules on her lateral feet. A punch biopsy was performed, which demonstrated an interstitial granulomatous infiltrate, admixed neutrophils and lymphocytes in the reticular dermis, and a leukocytoclastic small vessel vasculitis with perivascular onion-skinning fibrosis. In addition, of the laboratory tests ordered, a positive QuantiFERON Gold was significant. Based on these findings, EED with underlying tuberculosis (TB) was diagnosed. The patient was treated with oral dapsone and symptomatic management with clobetasol 0.05% ointment and referred to infectious disease for treatment of TB.

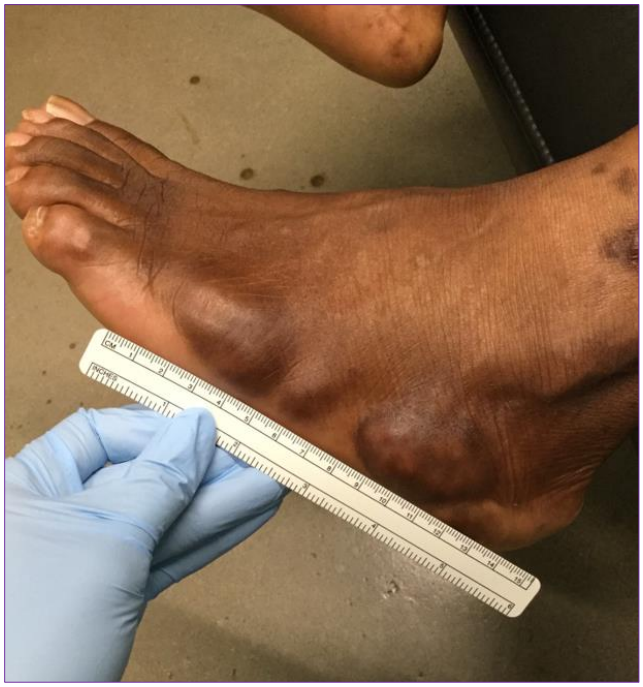

Figure 1. Nodules on left lateral foot

Figure 2. Nodules, macules, and papules seen on left lower extremity

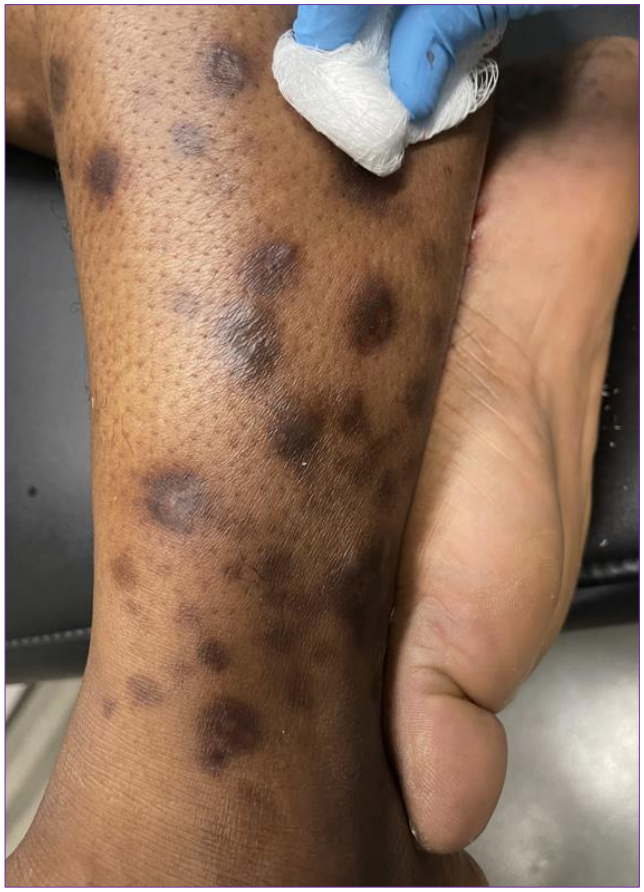

Figure 3. Close up visualization of macules and papules on left lower extremity

DISCUSSION

EED is a rare, chronic cutaneous leukocytoclastic vasculitis of small vessels that presents as red-brown soft papules that progress to firm nodules due to perivascular fibrosis.[6] Only several hundred cases of EED have been described in the literature.[7] While an association between EED and other diseases such as HIV, TB, paraproteinemias, and malignancy is often described, very few cases of EED associated with TB are reported, especially when compared to the other associated diseases.[3] In their review of 133 cases published from 1990 to 2014, Doktor et al[3] found just two cases of EED associated with TB.

The pathogenesis of EED is not fully understood but is most likely due to the deposition of immune complexes in small blood vessels leading to an inflammatory reaction. The underlying etiology is thought to be related to high circulating antibody levels produced after recurrent infections.[3] Classically, streptococcal infection and rheumatoid disease have been cited as causes for these immune-complex formations.[8] However, as mentioned previously, reports have shown EED to be associated with autoimmune diseases such as ulcerative colitis, Crohn's disease, relapsing polychondritis, diabetes mellitus, Celiac disease, and pyoderma gangrenosum; as well as infectious diseases including HIV, hepatitis, syphilis, and tuberculosis.

Tuberculosis is caused by *Mycobacterium tuberculosis* and is responsible for up to two million deaths each year.[9] TB is a multi-system disease affecting various organ systems including the musculoskeletal system, skin, and nervous system, but is most notable for its effects on the lungs. Common symptoms include cough, hemoptysis, weight loss, fever, and night sweats. TB is typically spread person-to-person via inhalation of aerosol droplets.[10] An infected individual first develops primary tuberculosis in which the bacteria localize to the lungs and form a Gohn focus, which typically then enters a state of latency, known as latent tuberculosis. Latent tuberculosis may be reactivated during a state of immunosuppression. Primary progressive tuberculosis occurs when individuals develop active disease following first exposure to TB and is seen in immunocompromised hosts. Typically, however, most people develop secondary tuberculosis several years after the initial primary infection due to reactivation.[11]

M. tuberculosis is an acid-fast, non-motile, obligate-aerobic, non-spore forming, catalase-negative, intracellular bacillus that is neither gram-positive or gram-negative.[11] TB is a type-IV delayed hypersensitivity reaction stimulating CD4+ T lymphocytes, which recruit and activate macrophages. Cytokines interferon-gamma, interleulin-4, interleukin-6, and tumor-necrotic-factor-alpha play a major role in the pathogenesis of TB. TB is notable for its formation of granulomas, defined as aggregations of macrophages fused together to form giant cells, which are subsequently surrounded by lymphocytes.[9] Screening tests for TB include the PPD skin test and interferon release assay. Confirmatory tests include chest x-ray, acid-fast staining, culture, and nuclear amplification tests. First-line treatment for TB includes rifampin, isoniazid, pyrazinamide, and ethambutol. [10]

The prognosis for EED patients varies based upon the underlying disorder.[8] Proper and timely treatment of the underlying cause or infection should significantly improve EED lesions. Of note, patients with EED are not at increased risk for developing systemic vasculitis. Moreover, most patients with TB have a favorable outcome due to adequate treatment. Without treatment, however, there is a 50% mortality rate for tuberculosis. Patients at risk for worse outcomes include the very young and elderly, as well as factors of delayed treatment, severe respiratory compromise, immunosuppression, and multi-drug resistance. These patients may experience prolonged EED as well as lung damage and associated conditions, dissemination of disease, and systemic amyloidosis, among others.[11]

CONCLUSION

This case demonstrates an exceedingly rare presentation of erythema elevatum diutinum caused by tuberculosis in a middle-aged woman. With only several hundred cases of reported EED, we hope to raise awareness of this rare disease process associated with TB so dermatologists may properly identify and manage EED in an uncommon clinical setting. Practitioners should have a high index of suspicion for individuals presenting with reddish-brown papules and plaques on extensor surfaces, especially during the fourth through sixth decades of life. Recognizing the distinct manifestations of EED and understanding its immunologic and infectious disease associations may enable clinicians to properly recognize, manage, and treat patients with EED.

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