HIV-associated erythema elevatum diutinum: a case report and review of a clinically distinct variant

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Abstract

A 24-year-old man with untreated human immunodeficiency virus (HIV) infection consulted our outreach clinic owing to the development of numerous asymptomatic nodules on his palms and fingers. Histopathologic evaluation revealed leukocytoclastic vasculitis and prominent fibrosis with a neutrophilic infiltrate consistent with erythema elevatum diutinum (EED). We referred the patient for initiation of antiretroviral therapy and started him on dapsone. The pathogenesis of EED is not completely understood, but it has been associated with numerous systemic conditions that may be infectious, inflammatory, or neoplastic. Only recently has EED been recognized as a defined reactive dermatosis of HIV. We present an exemplary case of HIV-associated EED and review the differential diagnosis, highlighting clinical features of EED that appear to be more frequently encountered in the HIV-infected population.

Keywords: human immunodeficiency virus, erythema elevatum diutinum, vasculitis

Introduction

EED is a rare form of chronic leukocytoclastic vasculitis (LCV) that manifests as symmetric, red-brown to purple papules, plaques, and nodules that develop on extensor surfaces of extremities, often periarticularly [1]. It is most common in the 4th and 6th decades, although it can present at any age and often develops earlier in the setting of HIV [2]. The majority of EED cases spontaneously resolve in 5-10 years; however, it can persist for decades with an undulating clinical course [3].

EED is currently thought to represent a type III hypersensitivity reaction with immune complex deposition in vessels leading to chronic LCV [1]. Progression to fibroid nodule formation in late-stage EED distinguishes it from generic LCV, which typically presents as self-resolving purpura leaving no residual lesions [4]. EED has been associated with a variety of underlying systemic disorders, of which HIV and IgA gammopathy are the most commonly reported [1, 2], (**Table 1**). Biopsy is essential for diagnosis and histology is typified by leukocytoclastic vasculitis with a predominantly neutrophilic perivascular infiltrate, erythrocyte extravasation, neutrophilic karyorrhectic debris, and fibrinoid necrosis of vessels in the mid-upper dermis [3, 5]. Mature lesions show granulation tissue and perivascular fibrosis with a less pronounced inflammatory infiltrate.

Once the diagnosis is made, careful systemic inquiry should be undertaken to assess for associated symptoms, arthralgia being most common [2]. Ophthalmologic examination should be completed to assess for uveitis and scleritis if symptoms are present [6]. Laboratory evaluation includes complete blood count, comprehensive metabolic panel, serum protein electrophoresis, anti-streptolysin O titer, HIV testing, thyroid function tests, and autoimmune

panel (including anti-neutrophilic cytoplasmic antibodies), [2, 7]. Other specific, organ-based evaluation should be pursued if suspicion is elicited from review of systems. Patients should adhere to close clinical monitoring, as EED can precede an underlying systemic illness, such as hematologic malignancy [7]. Treatment entails management of any underlying associated disease in addition to targeted therapy for EED. Dapsone, a prototypical anti-neutrophilic agent, is currently the treatment of choice and is successful in up to 80% of cases that have not yet reached the late, fibrotic phase [2]. Other therapies to consider include topical dapsone, colchicine, topical or intralesional steroids, chloroquine, tetracyclines, and surgical intervention [5, 8, 9].

Case Synopsis

A 24-year-old male with a history of untreated human immunodeficiency virus (HIV) infection and an unknown CD4 count presented to a rural outreach clinic in Botswana for evaluation of lesions on his fingers and palms. They appeared one year prior and progressively enlarged. Physical examination of the patient's volar hands revealed about 20 discrete, monomorphic, and slightly hyperpigmented nodules that ranged in size from 10-15mm (**Figure 1**). The nodules were firm and non-tender and not associated with systemic symptoms. There were no epidermal changes and the dermatoglyphics were preserved. Conspicuous white foci were scattered haphazardly throughout the lesions.

We performed a punch biopsy of one of the nodules and referred the patient to the infectious disease clinic for HIV management. Our differential diagnosis included: nodular granuloma annulare, calcinosis cutis, gouty tophi, sarcoidosis, rheumatoid nodules, keloids, histoid leprosy, atypical mycobacterial infection, cutaneous tuberculosis, Kaposi sarcoma, cutaneous lymphoma, reticulohistiocytosis, and erythema elevatum diutinum. Histologic evaluation of hematoxylin-eosin stained sections showed sclerotic fibroma-like changes with a neutrophilic infiltrate and leukocytoclastic vasculitis, consistent with a diagnosis of erythema elevatum diutinum (EED), (**Figure 2**). At follow-up, his CD4 count was confirmed to be 536 cells/mm^3 and further work-up was deferred owing to the limited resources in this setting. The patient began dapsone 50mg daily and was referred to ophthalmology clinic to rule out ocular complications of EED. The patient

Table 1. *Erythema elevatum diutinum associated conditions [2, 7].*

Infection	1. Human Immunodeficiency Virus (HIV) 2. Group A Streptococcus 3. Hepatitis B virus 4. Tuberculosis **5.** Syphilis
Hematologic	1. IgA gammopathy 2. Hematologic malignancy (Multiple Myeloma, Non-Hodgkin's Lymphoma, Chronic Lymphocytic Leukemia) 3. Waldenstrom's macroglobulinemia 4. Myelodysplasia
Inflammatory	1. Inflammatory bowel disease 2. Celiac disease 3. Systemic lupus erythematosus 4. Dermatomyositis 5. Rheumatoid arthritis 6. Granulomatosis with polyangiitis 7. Relapsing polychondritis
Other	1. Solid malignancies (Breast and Lung) 2. Ophthalmologic disorders 3. Thyroid disease (Hashimoto's thyroiditis)

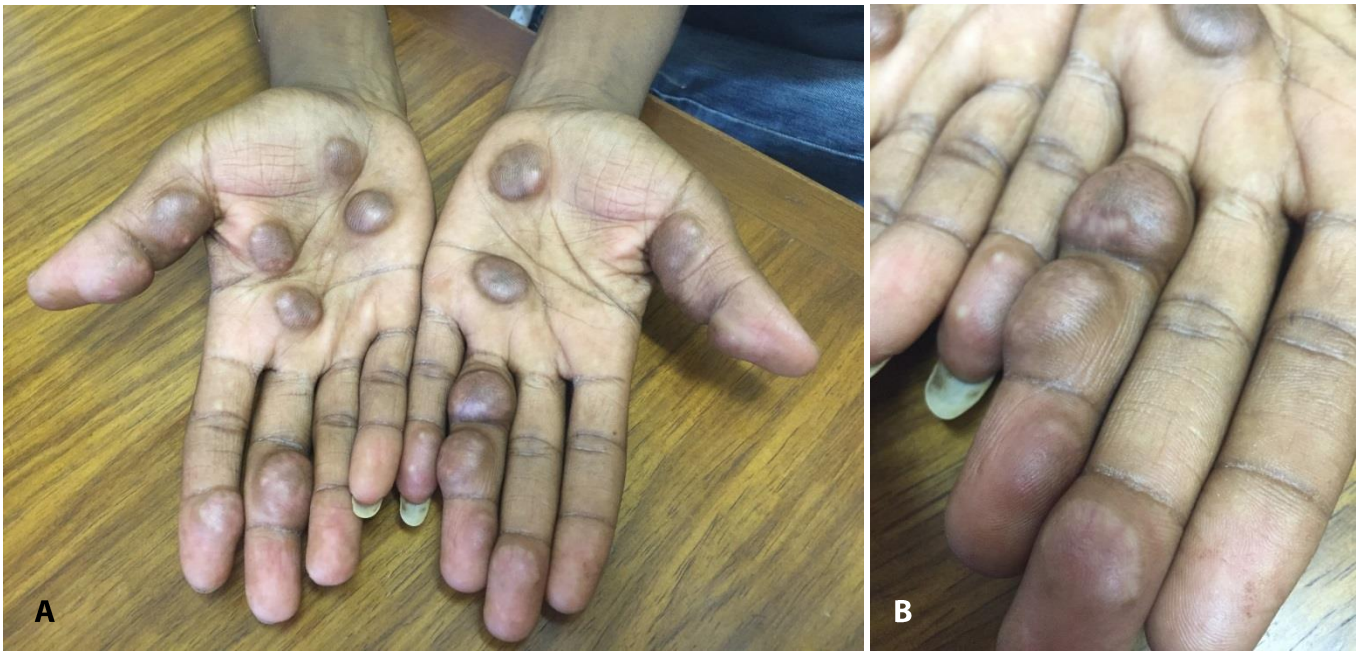

Figure 1. ***A)*** *Volar hands display about 20 discrete, monomorphic, and slightly hyperpigmented firm nodules that range in size from 10-15mm.* ***B)*** *Close up view of the firm, fibrotic nodules with preservation of the dermatoglyphics and scattered white foci.*

discontinued dapsone after two weeks due to headaches.

Case Discussion

EED has recently been recognized as a defined reactive dermatosis of HIV infection. Since the discovery of HIV in 1983, about 25 cases of HIV-associated EED have been reported [5, 9]. HIV patients that develop EED tend to have CD4 counts less than 200 cells/mm^3 EED can be the first clinical evidence of HIV infection, necessitating that patients diagnosed with EED undergo testing [5, 10]. EED has been reported as part of immune reconstitution inflammatory syndrome). Thus, it should be considered in the differential diagnosis when a suggestive eruption develops in the setting of antiretroviral therapy initiation [5].

HIV infection has been suggested as a predisposing factor for a number of vasculitides, including polyarteritis nodosa, microscopic polyarteritis,

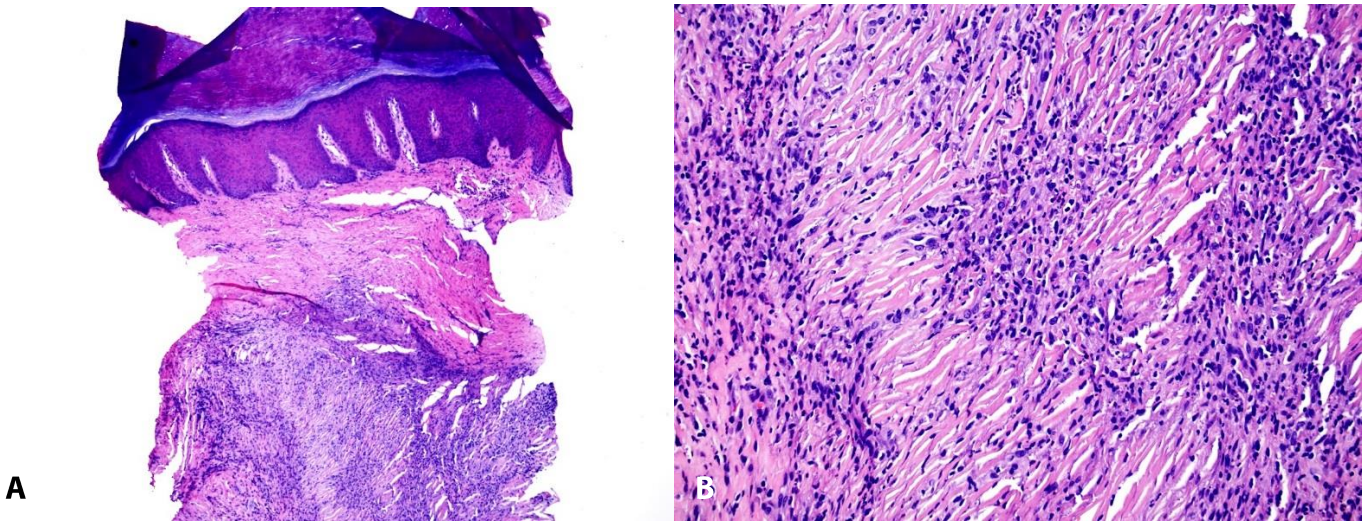

Figure 2. ***A)*** *Histologic sections demonstrate acral skin with dermal fibrosis and inflammation. (H&E, 40×).* ***B)*** *Higher power demonstrates sclerotic fibroma-like changes with a neutrophilic infiltrate and leukocytoclastic vasculitis. (H&E, 200×).*

Kawasaki-like syndromes, and EED [11]. Several mechanisms have been proposed to explain the relationship between EED and HIV, most of which hinge upon chronic antigenic exposure (from HIV or opportunistic infections) leading to lymphotaxis, immune complex formation, and subsequent vasculitis [5, 12]. This hypothesis is underscored by the reported efficacy of antiretroviral therapy in the treatment of EED [3]. Furthermore, beta-hemolytic streptococcal infection was proposed to initiate the development and exacerbation of EED in HIV patients; in such cases, antibiotics were helpful in controlling disease [13]. It has also been suggested that the association of HIV infection with IgA gammopathy may play a role in EED development [5, 9]. Whatever the underlying mechanism, it is known that in EED abnormalities in neutrophil migration occur in response to interleukin-8 and bacterial peptides, which leads to the development of this neutrophilic dermatosis [2, 6].

The clinical presentation and differential diagnosis of EED in the setting of HIV infection have several distinct features that are useful in attaining an accurate diagnosis (**Table 2**). Of the reported cases of HIV-associated EED, the majority are males and EED often presents at a younger age in HIV-infected individuals [2, 10]. When considering the diagnosis of EED in an HIV-positive patient, Kaposi sarcoma and bacillary angiomatosis must be ruled out as potential mimics, both clinically and histopathologically [4, 9, 12]. EED typically spares the mucosa and trunk, but involvement of these areas may raise suspicion for Kaposi sarcoma [6]. Furthermore, in HIV patients, EED tends to display extensive and advanced involvement with nodular, fibrotic, and bulky lesions on the palms and soles [13, 14]. Blistering and ulcerating lesions of EED have also been reported in the setting of HIV [6]. Of the previously listed features, nodular and fibrotic appearance is most suggestive of HIV-related disease, possibly related to the chronic nature of HIV infection resulting in protracted antigenic exposure [6].

Table 2. *Features of HIV-Associated erythema elevatum diutinum.*

Nodular/fibrotic lesions*
Extensive disease
Poor response to dapsone
CD4<200
Involvement of the palms and soles
Younger age of onset
Male sex

*Strongest association

First line treatment of EED in HIV patients is initiation of antiretroviral therapy and dapsone [5, 15]. Dapsone appears to be less efficacious in HIV-infected patients, possibly related to the more advanced, fibrotic lesions that tend to develop in HIV [12, 14]. Even when dapsone is effective, relapse may occur with cessation of therapy requiring long-term treatment [13].

Conclusion

EED has been recognized as a defined reactive dermatosis of HIV and EED related to HIV has distinctive clinical features and a nuanced differential diagnosis compared to EED presenting in the seronegative population (**Table 2**). Owing to the rarity of this condition, our report and the deductions therein are limited by a small subject number and lack of clinical trial data. However, our observational accounts combined with the reports in the literature have indicated that this is an important association to recognize because 1) EED can be the first indicator of HIV infection, 2) in the setting of HIV, it is important to distinguish EED from other life-threatening mimics, and 3) EED can both develop as a result of antiretroviral therapy (in the setting of immune reconstitution inflammatory syndrome) or be treated by starting ART in conjunction with targeted therapy. Our understanding of this condition and its underlying association to systemic disease will continue to benefit from further investigation.

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