CASE

A 55-year-old man with a history of HIV, first diagnosed in 2002, presented to our clinic in the spring of 2019 for evaluation of painful nodules on his feet and ankles bilaterally that were present for 7 months. Before the appearance of these lesions, he was untreated for his HIV for 10 months because of lack of follow-up with medical care. At the onset of symptoms, his CD4 count was 287 cells/μL. He resumed treatment for his HIV with bictegravir, emtricitabine, and tenofovir alafenamide combined tablet. At the time of our visit, his CD4 had increased to 452; however, he reported the lesions remained unchanged.

On examination, violaceous, moderately firm, easily movable papules and nodules were present on his feet bilaterally with the largest over his left heel (Fig 1). A punch biopsy was performed, which showed mixed inflammatory perivascular infiltrate with neutrophilic predominance and fibrinoid material within vessel walls and surrounding fibrotic dermis (Fig 2). Based on these findings, erythema elevatum diutinum (EED) was diagnosed. Treatment with oral dapsone is planned.

DISCUSSION

EED is a rare chronic cutaneous small-vessel leukocytoclastic vasculitis that presents initially as soft, nonfixed red/violaceous or brown papules and nodules that later become firm because of fibrosis. The lesions are distributed most frequently on extensor surfaces of the hands, arms, and legs.\(^1\)\(^,\)\(^2\) Involvement of the feet and planter surface (as with our patient) is considered unusual and may represent as few as 4.2% of EED cases.\(^3\) Its presentation may mimic that of Kaposi sarcoma, bacillary angiomatosis, granuloma annulare, and Sweet syndrome among others, and as such, histologic correlation is necessary for diagnosis.\(^1\) Histologically, early lesions may resemble small vessel leukocytoclastic vasculitis from other causes with perivascular inflammation and leukocytoclastic debris within the papillary and mid dermis. As lesions progress to late stage, there is greater involvement of histiocytes and dermal spindle cells leading to fibrosis of lesions that may resemble sclerosing hemangioma.\(^1\) The pathophysiology of this condition is likely caused by immune complex deposition in small vessels leading to an inflammatory cascade.\(^1\)\(^,\)\(^2\)

Dapsone is currently the treatment of choice; however, other therapies have been used including colchicine, intralesional and topical steroids, chloroquine, and surgical intervention.\(^3\)

In their review of the 86 cases published between 1977 and 2012, Momen et al\(^1\) found EED to be associated with many other disease processes including HIV (n = 19/86 [22%]), IgA gammopathy, bacterial infection, and inflammatory bowel disease among others.\(^1\) More recently, Doktor et al,\(^2\) in their 2019 review of 133 cases of EED between 1990 and 2014, found 21 cases associated with HIV. Here we
review the above case as well as the 32 electronically indexed cases of HIV-associated EED with reported CD4 counts that were published between 1986 and 2018.

**EED and HIV**

A search of PubMed, Google Scholar, and the University of Vermont’s Online Library search system literature in June 2019 found 32 reported cases of the concurrence of EED and HIV infection with published CD4 counts (Table I). The remainder of this report focuses on an analysis addressing clinical issues relating to a possible association between these 2 clinical phenomena.

**Age and sex**

The age of patients in Table I ranged between 20 and 60 with a mean of 38.51. Non-HIV—associated EED most commonly presents between the fourth and sixth decade of life. However, there may be an earlier age of onset in patients with HIV, a finding that fits with the data in Table I.

A male sex predominance was noted with 81.8% (27 of 33) of patients in Table I. Men make up 55.6% of all cases of EED; however, the findings of this review are consistent with prior findings of HIV-associated EED. This finding may reflect male/

Table I. Review of published cases of EED occurring in association with HIV infection

| Sex     | Age (years) | CD4 (cells/μL) |
|---------|-------------|----------------|
| This Report | M           | 55             | 287 |
| Cardis et al, 2018 | M           | 24             | 536 |
| Shi et al, 2018 | F           | 60             | Unreported |
| Victoria-Martinez et al, 2016 | M           | 39             | 528 |
| Jose et al, 2016 | M           | 47             | 204 |
| Rao et al, 2014 | F           | 52             | 164 |
| Al Abadie et al, 2012 | M           | 48             | 70  |
| Maksimovic et al, 2010 | M           | 53             | 384 |
| Braun-Falco et al, 2007 | M           | 23             | 185 |
| Kim et al, 2003 | M           | 53             | 618 |
| Martin et al, 2001 | M           | 27             | 114 |
| Fakheri et al, 2001 | M           | 51             | 150 |
| Muratori et al, 1999 | F           | 29             | 114 |
| Al Abadie et al, 2012 | M           | 20             | 332 |
| Maksimovic et al, 2010 | M           | 44             | 305 |
| Braun-Falco et al, 2007 | M           | 41             | 742 |
| Kim et al, 2003 | M           | 34             | 378 |
| Suarez et al, 1998 | F           | 37             | 158 |
| Revenga et al, 1997 | M           | 33             | 102 |
| Dronda et al, 1996 | M           | 32             | 128 |
| C. Bachmeyer et al, 1996 | M           | 58             | 112 |
| LeBoit et al, 1993 | M           | 27             | 168 |
| Momen et al, 2014 and Doktor et al, 2019 | M           | 37             | Unreported |
| Requena et al, 1991 | M           | 32             | Unreported |
| Momen et al, 2014 | 6M, 1F | 36.8 | Unreported |

*Case series.
1Review of 7 cases with unreported CD4 count.
female population disparities with HIV as opposed to a true tendency toward men with HIV.

**CD4 count and EED**

Many reports associated EED in the setting of HIV with a CD4 count of less than 200. However, our review of the reported data and our case does not support this finding. The mean CD4 count of EED cases in Table I (in which CD4 counts were reported) was 266.41, 50% (11 of 22) of cases being associated with CD4 counts higher than 200. This finding is complicated by the fact that only 66.7% (22 of 33) HIV-associated EED cases reported CD4 counts. These findings indicate that more data are needed from more cases before a clinically significant association between CD4 counts and EED can be established. We encourage further reports on EED in the setting of HIV that include CD4 counts whenever possible. Until more such data are available, it may be more appropriate to consider a CD4 count of less than 300 to be a risk factor for EED in patients with HIV.

**Treatment**

Dapsone was the most common treatment in 75.6% (24 of 33) of the EED/HIV cases in Table II. Of these, 70.8% (17 of 24) were able to achieve complete or partial remission with the remainder either experiencing adverse events, failing to respond, or having unknown results. Of note, one patient achieved complete remission with combination topical dapsone and intralesional corticosteroids following oral corticosteroids. Topical therapy may represent a treatment option following nonhyper-sensitivity adverse effects to oral dapsone.

Other reported treatments included colchicine, corticosteroids (oral, topical, and intralesional), surgical excision and antibiotics (fusidic acid, erythromycin, tetracycline, clarithromycin, and penicillin), pegylated interferon, and soft tissue radiotherapy. Three cases utilized colchicine as treatment, all of which achieved partial or complete remission. Corticosteroids in any preparation, when successful, were used in combination with other treatments. Surgical excision was performed in 18.2% (6 of 33) cases, with 50% (3 of 6) achieving complete resolution, although one of these patients was also treated with dapsone. Surgical excision may be appropriate in the setting of late-stage, fibrotic lesions. However, of the 10 late-stage lesions treated with dapsone with known response, 5 completely or partially resolved, 3 discontinued dapsone because of adverse events, and 2 did not respond to treatment. This finding may indicate that surgical excision (or other therapy) is more appropriate after treatment failure with dapsone.

Although use of dapsone was efficacious, it is limited by adverse events. Topical dapsone, colchicine, and surgical excision may warrant further study as rescue therapy following dapsone or even monotherapy.

### EED occurring in the context of HIV—Disease association, concurrence, coincidence or causation?

Doktor et al., in their 2019 review of reported cases of EED, found 15.8% (21 of 133) of cases of HIV-associated EED. With the additional cases detailed in this report added to that number, HIV-associated EED may represent as much as 22.8% (33 of 145) of published cases. The prominence of HIV-associated EED in the literature is striking; however, it is possible that this is overreported compared with isolated EED, EED with mild presentation, or factors that may incline practitioners to not publish cases.

EED in the setting of HIV may represent an immune reconstitution inflammatory syndrome in which symptoms of infectious or inflammatory conditions worsen after initiation of antiretroviral therapy. In many reports in this review (including this report), patients were either untreated or on unchanged maintenance treatment at onset of EED symptoms. This finding does not represent a clear pattern of increased prominence of symptoms...
related to starting antiretroviral therapy. Many reports did not discuss the course of therapy for HIV, making it difficult to fully support or refute immune reconstitution inflammatory syndrome as a component of this condition.

SUMMARY AND CONCLUSIONS
The association between HIV and EED remains to be confidently characterized. When compared with all cases of EED, EED occurring in HIV might have a greater male predominance and a younger age of onset. Accordingly, patients presenting with EED, particularly younger male patients, may warrant screening for HIV as a possible comorbidity. Based on our analysis of the published literature, a CD4 count of less than 300 may represent a more appropriate risk factor for the development of EED in HIV patients than the prior suggestion of CD4 less than 200. However, the validity of this suggestion is limited by the small number of cases (22 of 33).

Dapsone was the most commonly used treatment option for EED in HIV patients and completely or partially treated both early and late stage lesions. Other therapies, including topical dapsone, colchicine, topical clobetasol/fusidic acid combination therapy, and surgical excision may warrant consideration as alternate treatment options. Further reports of EED occurring in the context of HIV infection could better refine the relationship between HIV infection and this rare form of chronic cutaneous small-vessel leukocytoclastic vasculitis.

This work is dedicated to the memory of Steven I. Katz, MD, PhD. Dr. Katz was the long-time Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) before his recent unexpected sudden death. Dr. Katz had an early-career clinical interest in EED. He and his colleagues were among the first to examine the underlying immunologic basis of this clinical disorder in his 1977 report entitled “Erythema elevatum diutinum: skin and systemic manifestations, immunologic studies, and successful treatment with dapsone.”

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