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### Authors

Maley, Alexander  
Parker, Sareeta

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**Case Presentation**

**Bullous systemic lupus erythematosus in a patient with human immunodeficiency virus infection: a paradox of autoimmunity and immunodeficiency**

**Alexander Maley, MD and Sareeta Parker, MD.**

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**Department of Dermatology Emory University School of Medicine, Atlanta, Georgia**

**Correspondence:**

Sareeta Parker, MD  
Emory Clinic  
Department of Dermatology  
1525 Clifton Road, NE  
Atlanta, GA 30322  
Email: srsingh@emory.edu  
Phone: 404-778-5225  
Fax: 404-778-3337

**Abstract**

Bullous lupus erythematosus is a rare variant of systemic lupus erythematosus (SLE) and is characterized by autoantibodies to type VII collagen. Co-existence of SLE and human immunodeficiency virus (HIV) infection is extremely rare; the development of bullous lupus in the setting of HIV has been, to our knowledge, reported in the literature only once.

We describe a 26-year-old man with an 8-year history of HIV infection who developed bullous SLE. The patient presented with widespread, tense bullae as well as oral ulcerations. Clinical, laboratory, histological, and cutaneous immunofluorescence findings confirmed the diagnosis of bullous SLE.

Given the immunological consequence of HIV infection, the co-occurrence of these two diseases would, theoretically, be unusual. Theories pertaining to the interplay of immunologic mechanisms of the seemingly paradoxical occurrence of autoimmunity in the setting of HIV infection are discussed.

**Keywords: Bullous Lupus, HIV, autoimmunity, blistering disease**

**Case synopsis**

A 26-year-old man with an eight-year history of HIV infection and a remote history of treated syphilis presented with a bullous eruption of several weeks duration. Blisters initially developed on his hands and subsequently generalized to his face, upper and lower extremities, chest, and back. Additional symptoms included oral ulcerations, progressive dysphagia, headache, and a solitary syncopal episode. He was admitted for further evaluation.

Prior to admission, HIV viral load was undetectable and CD4 cell count was 278 cells/mcL (36%). Home medications included an antiretroviral therapy (ART) regimen of emtricitabine-tenofovir, ritonavir, and atazanavir, on which he had been stable on for three years. Family history was negative for autoimmune disease.

Exam revealed discrete oral ulcerations with a narrow erythematous rim affecting the hard palate and lower labial mucosa. On his face, trunk, and extremities were a myriad of fresh and crusted erosions interspersed with intact tense, isolated, and clustered 5-15 mm vesicles with mild surrounding erythema (Figure 1A, 1B). Erythematous, edematous, blanching annular plaques were present on the bilateral medial thighs.



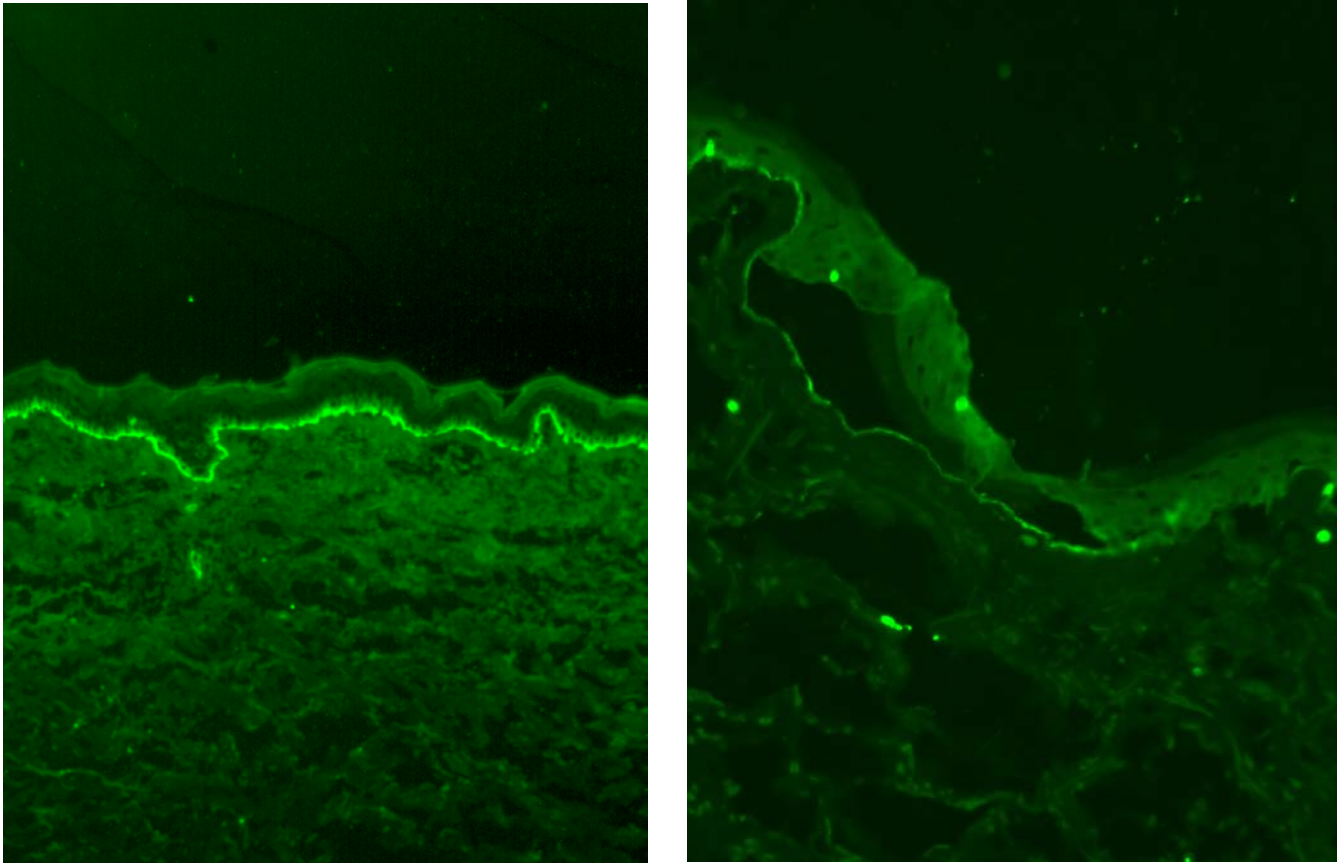
**Figure 1.** Intact vesicles amidst erosions, crusts, and mild background erythema on the neck and chest (A) and the dorsal hand (B)

Laboratory findings were significant for positive antinuclear antibody (ANA), anti-double stranded DNA (302 IU/mL, normal limits (NL) <30), anti-RO (142 AU, NL < 1.0), anti Smith (200 AU, NL < 1.0), and RPR titer (1:4). Complement levels were decreased (C3=35 mg/dL, NL 75-175; C4=4 mg/dL, NL 14-40). Urinalysis at initial evaluation was significant only for trace protein; no cellular casts were identified.

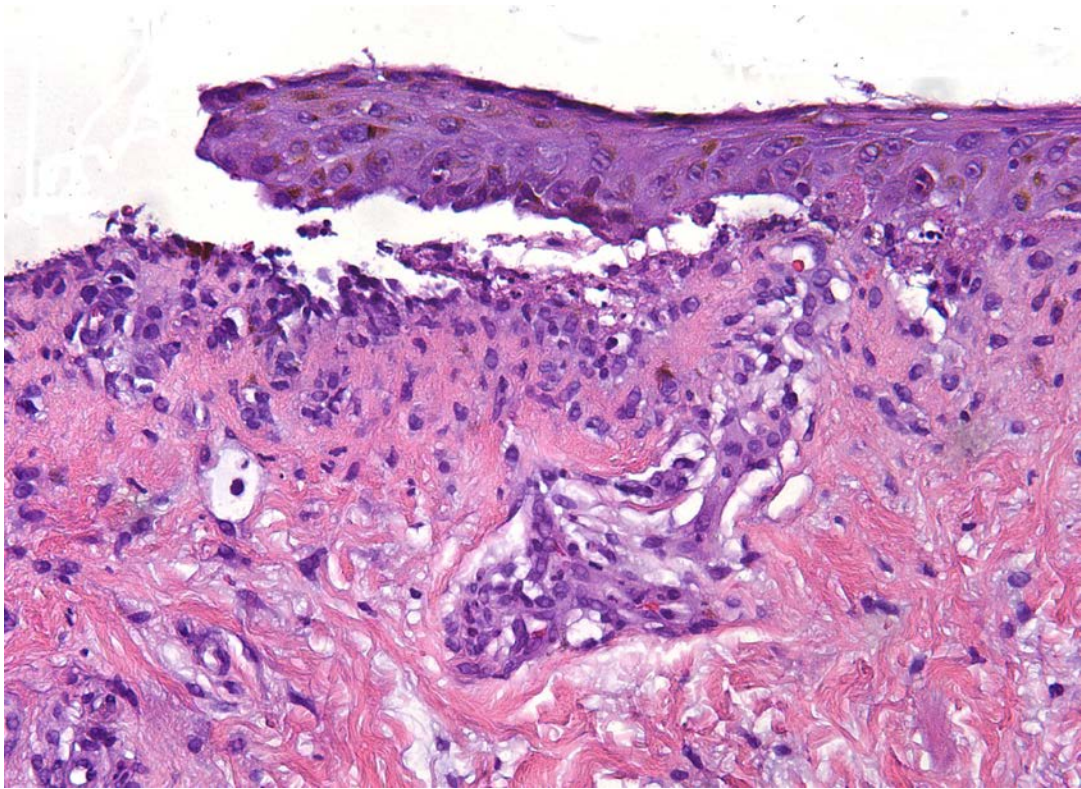
Herpesvirus cultures from the oral mucosa and an intact blister showed no growth. An esophageal biopsy was negative for CMV and candida. Varicella IgM was negative. Brain MRI and cerebrospinal fluid evaluation were unremarkable.

Skin histology from the edge of a bulla on the left arm revealed subepidermal bullae with a mixed inflammatory infiltrate with rare eosinophils. Direct immunofluorescence of perilesional skin revealed bright bands of IgG, IgM, IgA, and C3 along the basement membrane zone. Serum indirect immunofluorescence was positive at the base on salt split skin with IgG and IgA at a

titer of 1:40 and 1:20, respectively (Figure 2A and 2B). ELISA for type VII collagen antibodies was strongly positive at 209 (NL <9).



**Figure 2.** Direct cutaneous immunofluorescence revealing linear IgM along the basement membrane zone of perilesional skin (10X) (A): A similar pattern of staining was seen with IgG, IgA and C3. Indirect immunofluorescence reveals IgG staining at the base of salt split skin at a dilution of 1:20 (10X) (B).



**Figure 3.** Subepidermal bulla with predominantly neutrophilic inflammatory infiltrate, H&E 200X

Based on the above results, the diagnosis of bullous systemic lupus was rendered. A glucose-6-phosphate dehydrogenase level was checked and was normal. Oral dapsone 50-mg and topical triamcinolone acetonide 0.1% were initiated and the patient was discharged. At first follow up, the skin had improved, but acrocyanosis and mild dyspnea developed. This methemoglobinemia was managed by dapsone reduction to 25-mg and addition of daily oral cimetidine (400-mg) and vitamin C (500-mg). The dapsone was then titrated to 50-mg without incident and the skin disease remained stable. Several months later asymptomatic thrombocytopenia (64,000/mcL, NL 150,000-450,000) was noted. Three months later the patient developed non-scarring scalp alopecia, cutaneous vasculitis, worsening proteinuria, and worsening dysphagia. EGD revealed esophageal stricture; esophageal biopsies were again nondiagnostic, but esophageal dilatation was required. Oral prednisone 60-mg and hydroxychloroquine were initiated and the patient's symptoms temporarily improved. However, within two months, the patient returned with anasarca, worsening proteinuria, creatinine of 2.1 (NL 0.7-1.3 mg/dL), and BUN of 56 (NL 7 - 20 mg/dl). He was re-admitted and underwent renal biopsy, which showed diffuse global proliferative lupus nephritis (International Society of Nephrology/Renal Pathology Society working group class IV-G(A)), lupus vasculopathy, and lupus interstitial nephritis. There was no overt evidence of HIV associated nephropathy. Therapy with intravenous cyclophosphamide (750mg/m<sup>2</sup>) and prednisone 50 mg was initiated, with the plan of delivering six cycles. He has shown clinical and laboratory improvement to date.

## Discussion

We present a patient with bullous SLE developing in the setting of HIV disease. A search of the literature reveals only one other instance of these two diseases co-occurring [1]. The patient described by Carguati et al. had a five-year history of SLE prior to the development of bullous lesions and the bullous LE developed 20 days following resumption of ART. In contrast, our patient was HIV infected and stable on ART for years; his bullous lesions were the presenting sign of SLE.

Bullous lupus is characterized by tense blisters of varying size in the setting of SLE. Blister formation is attributed to autoantibodies directed against type VII collagen, the major component of anchoring fibrils in the sublamina densa region of the basement membrane zone of stratified squamous epithelia. Disruption of the integrity and/or function of type VII collagen results in loss of epidermal adhesion and the formation of subepidermal blisters [2]. In the absence of clinical and/or laboratory findings to fully support the diagnosis of SLE, the distinction between bullous SLE and epidermolysis bullosa acquisita (EBA) can be difficult because the target antigen is the same in both diseases. It has been proposed that bullous SLE may be more readily responsive to therapy with dapsone than EBA.

Recently, the criteria for diagnosis of SLE have been updated by the Systemic Lupus International Collaborating Clinics group (SLICC) [3]. The newly proposed criteria have been revised and validated; 4 of the clinical and immunological criteria with at least one clinical and one immunological are required. Our patient unequivocally met several clinical criteria: acute cutaneous lupus (bullous lupus), oral ulcers, non-scarring alopecia, lupus nephritis, and thrombocytopenia. Additionally, he fulfilled several immunological criteria: positive ANA, Anti-dsDNA, Anti-Sm, and low complement.

Co-existence of autoimmunity in the setting of immunodeficiency would seem paradoxical. However, reports of autoimmune diseases, including skin-limited diseases, have been reported in the setting of iatrogenic immunosuppression as well as in acquired immunodeficiency states. Our case is of particular interest given the development of SLE in the setting of HIV.

Despite the high incidence of HIV infection among African Americans in the US and the relatively high prevalence of SLE among African Americans, (2.5-3.5 fold compared to whites), the co-occurrence of SLE and HIV is much rarer than expected [4, 5]. The increased availability of ART, which allows for immune restoration and prolonged survival, would additionally be expected to increase the incidence of autoimmunity.

Based on a review by Carugati et al. [1] of the literature from 1981-2012 and on the recently published cases by Iordache [6] and Scherl [7], only sixty-five cases of SLE in HIV patients have been reported; in only 35 of these cases SLE followed HIV infection.

The relative paucity of SLE in HIV may be attributed to the inhibition of the development of T-cell driven autoimmunity. T-cell driven autoimmunity is thought to be instrumental to the pathogenesis of SLE. A case report in a patient with SLE in which the exact timing of HIV seroconversion was determined using stored serum, indicated that infection with HIV resulted in the disappearance of SLE autoantibodies [8]. The paucity of cases of concurrent HIV and SLE could also relate to the development of antibodies with HIV neutralizing activity among patients with SLE [7]. A case has recently been reported of a chronically HIV-infected patient who subsequently developed SLE. She developed broadly HIV-1 neutralizing antibodies similar to autoantibodies found in SLE. From this patient the authors isolated an antibody to the CD4 binding site of the HIV gp120 viral protein. This patient was able to control her viral load/HIV infection without ART [9].

Proposed mechanisms of autoimmunity in the setting of HIV include immune reconstitution inflammatory syndrome attributable to ART, interaction of HIV with endogenous retroviruses, and dysregulation of the immune system following HIV infection.

Following treatment with ART, HIV patients restore the ability to mount an inflammatory response, which can result in clinical deterioration despite an improvement in T-cell count and reduction in viral load. This syndrome, known as immune reconstitution inflammatory syndrome (IRIS), has been associated with the development of autoimmunity. Multiple pathogenic mechanisms have been postulated for the development of de novo autoimmune disease in IRIS including B-cell activation by reconstituted T-cells and a disruption in self tolerance resulting in the failure to delete autoreactive T-cells. De novo development of SLE and tumid lupus has been reported after T-cell reconstitution following ART [10].

Evidence exists that endogenous retroviruses, defective proviruses found in the human genome, may be triggers for SLE immunopathology. Proposed mechanisms include encoding autoantigens, immune dysregulation owing to insertional mutagenesis, loss of self-tolerance via disruption of the Fas receptor, and by molecular mimicry and epitope spreading through viral proteins [11]. These endogenous retroviruses are not typically active. However, HIV-induced change can result in the induction of endogenous retrovirus transcription, often leading to protein expression and potentially the development of SLE.

Infectious agents have been implicated in the initiation of autoimmunity in SLE. Thus, consequences from infection with HIV and the subsequent immune activation could predispose to the development of SLE. Infection with HIV activates human dendritic cells, which results in an increase in T-cell stimulatory activity and production of type I interferons. Misregulation and sustained hyper activation of this innate viral defense can result in the development of autoimmunity and SLE [11]. Studies have suggested that as HIV destroys CD4 T-cells, protein fragments are released that promote the formation of autoreactive CD8<sup>+</sup> T cells [12]. Macrophages infected with HIV produce IL-1 and IL-6, which results in B-cell stimulation that could lead to the production of autoantibodies [13]. Additionally, loss of specific immunomodulatory CD4 T cells may allow for expansion of B-cell clones responsible for the autoantibody formation. A study by Deas et al. showed that up to a third of patients with Sjogren syndrome or SLE with no history of HIV react to HIV p24 antigen, implicating molecular mimicry as an additional potential mechanism of autoimmunity [14]. A similarly proposed mechanism involves structural homology between HIV proteins and the molecules responsible for self tolerance, HLA-DR4 and DR2 [13].

Dapsone is generally recognized as first-line therapy for bullous SLE [2]. The symptomatic methemoglobinemia that developed in our patient was managed with vitamin C, cimetidine, and dapsone dose restriction, and his bullous lesions remained under fair control. However, he developed more serious systemic manifestations of SLE while on this regimen. His HIV status complicated selection of immunomodulatory therapy, but given his severe renal disease, intravenous cyclophosphamide and corticosteroids were initiated. Owing to several factors, belimumab, a human monoclonal antibody inhibiting soluble B-lymphocyte stimulator, was not selected as the initial agent but is under consideration as therapy for our patient. Belimumab has been found to reduce serum levels of autoantibodies and improve serum complement levels without affecting memory B-cell or T-cell populations [15].

## Conclusions

We report a patient with bullous SLE occurring in a patient with HIV. Although autoimmunity in HIV patients appears to be rare, the practicing clinician should be aware of its potential co-occurrence. Investigating the interplay of autoimmunity in the setting of immunodeficiency will invariably enhance our understanding of the pathogenetic mechanisms leading to disease.

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