CASE REPORT

HIV-associated autoimmune blistering and connective tissue disorders: a case report

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Abstract

Introduction: The association of human immunodeficiency virus (HIV) infection with the development of autoimmune disorders or systemic diseases is intriguing. Here, we describe a case of HIV-positive individual, who developed a bullous pemphigoid with several autoimmune disorders.

Case description: A 58 year-old man was admitted to infectious diseases department in June, 2020 due to fever and blistering skin lesions. After several investigations, diagnosis of HIV infection and nodal tuberculosis as opportunistic infection, associated with a bullous pemphigoid was made. Topical corticosteroids and anti-tuberculosis therapy began in June, 2020. Antiretroviral therapy started in August, 2020, with a good virological response. Four months later, in December 2020, the patient developed polyarthralgia and bilateral episcleritis. Testing for anti-nuclear antibodies and rheumatoid factors were positive. Autoimmune diseases were suspected, and the patient was treated with oral corticosteroids for two months with favorable outcome. However, in July, 2021, after the end of corticotherapy, clinical signs reappeared and the patient died of an acute kidney failure.

Conclusions: Pathophysiology of autoimmune diseases in HIV population remains uncertain. There are several issues that need further studies regarding therapy, especially when systemic corticosteroids and immunosuppressive drugs are under consideration.

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Introduction

The interaction between immune dysregulation and human immunodeficiency virus (HIV) infection remains a topic of intrigue. Since highly active antiretroviral treatment (HAART) consequently leads to restoration of T cell immunity and rises life expectancy, the prevalence of autoimmune disorders (ADs) among HIV-infected patients has increased [1]. In HIV population, the type of ADs and their clinical manifestations are poorly described. Here, we describe a case of an association of several ADs developing before and after starting HAART in a 58-year-old man infected with HIV.

Case description

A 58-year-old man, with no significant medical history, was admitted to the Department of Infectious Diseases in

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June, 2020. He presented with a persistent low-grade fever, weight loss, and generalized blistering eruption evolving in the last 8 months, with no apparent cause identified even after extensive tests, including tumor markers, anti-nuclear antibodies, serology for atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Coxiella burnetii*, and *Rickettsia*), cytomegalovirus, Epstein-Barr virus serology, bone marrow biopsy, and radiological investigations. Skin biopsy was not performed at that time. Due to past medical history of herpes zoster involving thoracic dermatomes in 2018 and extra-marital heterosexual intercourses over the past 5 years, the patient was screened, and found positive for HIV infection in June, 2020.

Laboratory findings showed complete blood count, renal and liver functions within normal limits. CD4+ T cell count was 94 cells/mm^3 and HIV viral load was 610,875 copies/ml (by reverse transcription polymerase chain reaction).

A thoraco-abdomino-pelvic computed tomography revealed slightly enlarged spinal, mediastinal, axillar, and inguinal lymph nodes. QuantiFERON-TB Gold test was positive; therefore, the diagnosis of nodal tuberculosis as an opportunistic infection was made. For cutaneous lesions, a skin biopsy was performed, which showed bullous pemphigoid (BP). This was confirmed by direct immuno-fluorescence testing. Topical corticosteroids and an anti-tuberculosis therapy were started in June, 2020. Then, on August 16, 2020, the patient began HAART consisted of tenofovir disoproxil, emtricitabine, and efavirenz, with a good virological response in 3 months. However, there was no improvement in clinical signs, including fever and blistering skin lesions, with fluctuating periods of remission and relapse.

Four months later, in December, 2020, the patient complained of asthenia, pain, and tenderness of extremity joints, affecting mainly small joints of both hands, but also knees, associated with onset of acute redness in both eyes. Slit-lamp examination showed bilateral diffuse bulbar injection with marked vessel congestion (Figure 1), which improved after phenylephrine instillation. Diagnosis of bilateral episcleritis was made. Tests for anti-nuclear antibodies (1/180) and rheumatoid factors (IgM, IgG) were positive. Biological investigations showed a high thyroid stimulating hormone level (10.6 IU/ml) and a slight increase in the serum creatinine level.

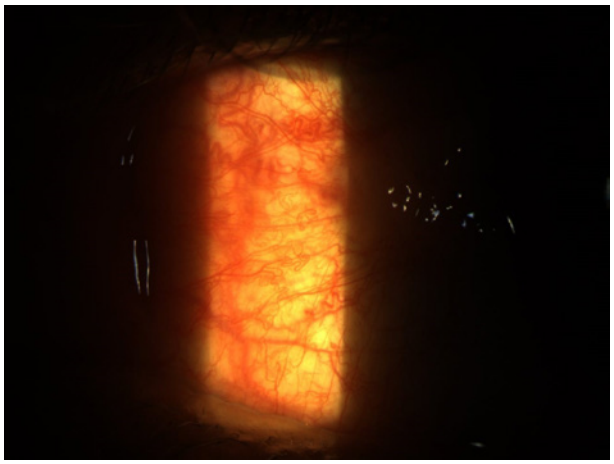

Figure 1. Slit lamp photography showing diffuse redness with dilated superficial episcleral vascular network

Based on the American College of Rheumatology/European League Against Rheumatism classification criteria, rheumatoid arthritis was the most likely diagnosis, and the patient was treated with oral corticosteroids for 2 months (from April, 2021 to June, 2021) with favorable clinical outcome. However, 2 weeks after the end of corticotherapy, fever and polyarthralgia re-appeared (Figure 2).

In July, 2021, the patient was re-admitted to the infectious diseases department due to acute kidney failure (AKF) with high anion gap severe metabolic acidosis. Renal affectation secondary to rheumatoid arthritis or tenofovir-related nephron-toxicity were the possible etiologies of AKF. We prescribed abacavir instead of tenofovir disoproxil, but no percutaneous renal biopsy was performed because of the presence of a left renal atrophy. The patient died one month later, and autopsy was not performed.

Discussion

The association of HIV infection and the development of autoimmune diseases is intriguing. Yet, several studies showed an increase in the prevalence of autoimmune phenomena in HIV population. A large French multicenter cohort study (from January, 2000 to July, 2013) among 33,403 HIV-positive patients had identified 1,381 patients with an autoimmune disease, which represented a prevalence of 4.1% [2]. The most commonly reported autoimmune complications in these patients included sarcoidosis, inflammatory arthritis, connective tissue disease, Graves' disease, idiopathic thrombocytopenic purpura, and autoimmune thyroid disease [2, 3]. Moreover, there was an array of auto-antibodies reported in HIV patients even without clinical manifestations, including anti-nuclear, anti-cardiolipin, anti-thyroglobulin, anti-thyroperoxydase, and anti-myosin antibodies [4].

Our patient had positive anti-nuclear antibodies and rheumatoid factors with chronic articular manifestations and an episcleritis. Based on the American College of Rheumatology/European League Against Rheumatism classification criteria, the diagnosis of rheumatoid arthritis was made. Additionally, he developed a hypothyroidism, but no anti-thyroid antibodies tests were performed.

Several theories have been proposed to explain the development of autoimmunity in the setting of HIV infection. These include molecular mimicry (structural similarities of HIV virion to a self-antigen), persistent antigenic simulation, and a restoration of the immune system with HAART [5].

Zandman-Goddard *et al.* proposed a staging to assess the occurrence of autoimmune diseases related to HIV manifestations, total CD4+ count, and viral load. In stage I of acute HIV infection with intact immune system, the ADs may develop. However, during the quiescent period (stage II), with a decline of CD4+ count, and in the stage III with a pro-

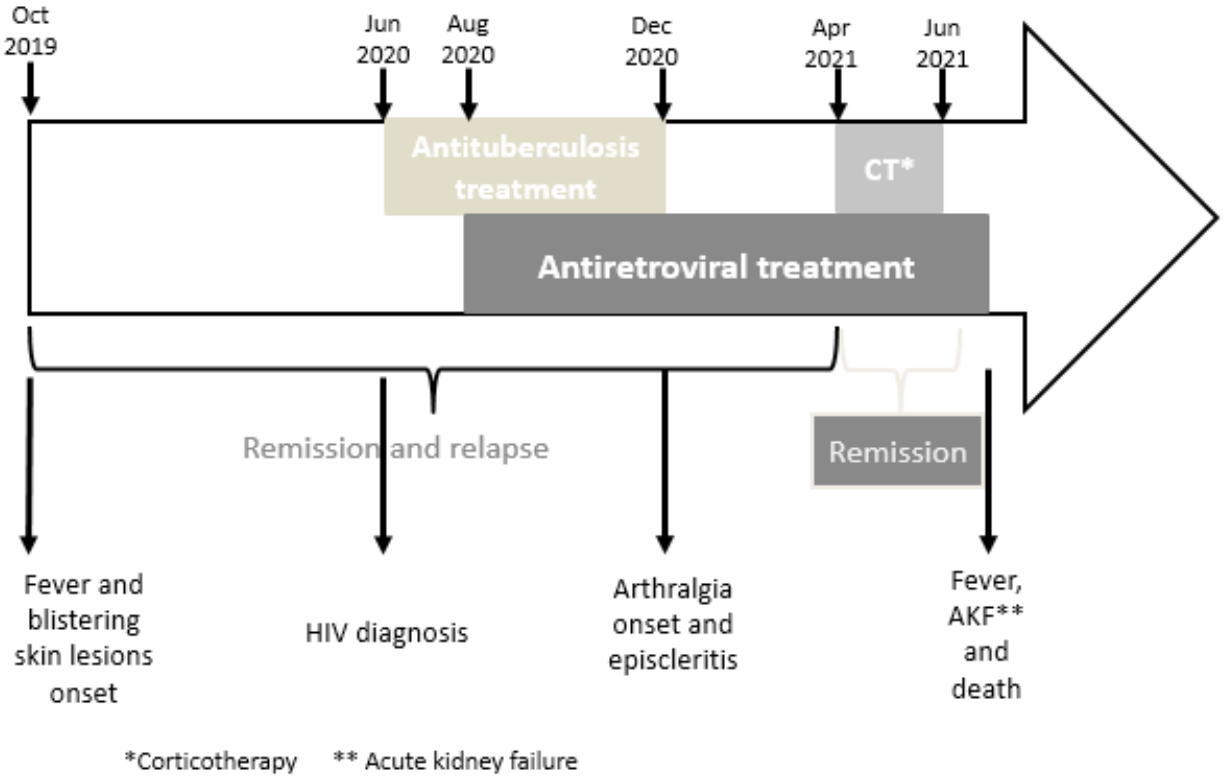

Figure 2. Timing of important events

Table 1. Bullous pemphigoid in HIV-infected patients

No.	Author(s) [Ref.]	Age (years)/ gender	Timing of HIV diagnosis	CD4+ count (mm³)	Treatment	Outcome
1	Levy *et al.* [6]	58/Male	HIV preceded BP diagnosis by 1 year	N.A.	Ritodrine	Relapses and remissions
2	Bull *et al.* [7]	58/Male	HIV preceded BP diagnosis by 2 years	N.A.	Prednisolone	Relapses and remissions; died of PCP
3	De *et al.* [8]	30/Male	HIV preceded BP diagnosis by 10 years	116	Prednisolone	Under remission with treatment, no long-term follow-up
4	Braiteh *et al.* [9]	65/Female	HIV preceded BP diagnosis by 28 years	517	Prednisolone	Remission with 3-month follow-up
5	Present case	58/Male	PB preceded HIV diagnosis by < 1 year	94	Topical corticosteroids	Relapses and remission; died of AKF

AKF – acute kidney failure, PCP – pneumocystis pneumonia

found immunosuppression (acquired immunodeficiency syndrome), ADs occur rare and mainly mediated by CD8+ lymphocytes and immune complexes. In stage IV, there is a restoration of immune competence following HAART, leading to an increase in the prevalence of ADs [4].

In our case, the autoimmune blistering disorder (bullous pemphigoid) had developed before the diagnosis of HIV infection and starting HAART, probably in stage II or III of Zandman-Goddard staging, with a low CD4+ T cell count (94 cells/mm³). However, this disorder usually occurs when CD4+ T cell count level is above 200 cells/mm³. The incidence of BP auto-antibodies increased with advanced HIV stages: from 21% in HIV infection stage II to 37% and 43% in stages III and IV, respectively [4, 5]. Pathophysiology of autoimmune blistering disorders (ABID) in HIV population has not yet been clarified. Rheumatoid arthritis had occurred after initiating antiretroviral therapy.

Cases of AIBD in HIV-infected patients have also been increasingly reported. BP belongs to the group of AIBD, and may present with different clinical presentations. A total of

4 case reports of patients with both BP and HIV infection were identified, with HIV diagnosis preceded BP in all four cases. There were 3 men and one woman, with a median age of 52.75 years (Table 1) [6-9].

Autoimmune diseases in HIV-infected patients are a challenge. Their main treatment include systemic corticosteroids and immunosuppressive agents. However, these agents may cause a rapid progression of HIV infection, especially when CD4+ cell count level is less than 200 cells/mm^3, and HIV viral activity is not completely suppressed [10].

Conclusions

The pathophysiology of autoimmune diseases in HIV population remains uncertain. To the best of our knowledge, the current case of a bullous pemphigoid developed before starting HAART and then associated with other Ads, has not been reported previously. There are some issues that need further studies regarding therapy, especially when systemic corticosteroids and immunosuppressive drugs are under consideration.

Conflict of interest

The authors declare no conflict of interest.

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