Autoimmune blistering disorders in the setting of human immunodeficiency virus infection

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A R T I C L E   I N F O

Article history:
Received 18 October 2017
Received in revised form 30 January 2018
Accepted 15 February 2018

Keywords:
Autoimmune blistering disorder
human immunodeficiency virus
acquired immune deficiency syndrome
pemphigus
pemphigoid
medical dermatology
antiretroviral therapy

A B S T R A C T

The interplay between immune dysfunction and human immunodeficiency virus (HIV) is complex. Reports of autoimmune disorders including autoimmune bullous disorders (AIBDs) have been increasing in prevalence in the HIV population since the introduction of highly active antiretroviral therapy in 1995. We offer a literature review of clinical experiences in various AIBDs with particular emphasis on therapeutic management as well as a brief overview of the mechanisms that explain the relationship between AIBD and HIV. Because immunosuppressants are first-line therapies for AIBD treatment, careful consideration is warranted when considering management in the HIV population.

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Introduction

The association between immune dysfunction and HIV remains a topic of intrigue. Reports of autoimmune disorders in HIV-infected patients have increased in number as the prevalence of HIV reached 36.7 million in 2015 according to the Global AIDS Update by the United Nations Programme on HIV/AIDS (UNAIDS, 2016). This increase in prevalence is attributed to rising infection rates and increased life expectancy since the introduction of highly active antiretroviral therapy in 1995 (Cuellar, 1998). The most commonly reported autoimmune complications in patients with HIV include sarcoidosis, autoimmune thyroid disease, inflammatory arthritis, and connective tissue disease (Calabrese et al., 2005; Chen et al., 2005; Yang et al., 2015).

Autoimmune blistering disorders (AIBDs) comprise a heterogeneous group of diseases that are characterized by autoantibodies directed against adhesion proteins in the skin and mucous membranes. Cases of AIBD in patients with HIV have also been increasingly reported, and in some instances the initial clinical presentation of AIBD compels a workup that reveals a previously unknown positive HIV status (Chou et al., 1991; Lateef et al., 1999; Marfatia et al., 2007; Singh et al., 2014). Interestingly, pemphigus vulgaris and bullous pemphigoid-like antibodies have been reported as detectable in the blood of up to 33% of patients with AIDS. However, not all patients who carry these autoantibodies manifest clinical blistering disease (Kyriakis et al., 1992). AIBDs have been reported to present before, after, and concurrent with a diagnosis of HIV.

Treatment of AIBDs in patients with HIV is complicated by potential further immunosuppression in an already dysfunctional immune system by initiation of long-term systemic immunosuppressants. The possible hastening of opportunistic infections and AIDS-defining illnesses are major risks to weigh against the benefits of treatment (Singh et al., 2014). Therefore, treatment options for AIBD in HIV-positive patients pose a unique clinical challenge. Understanding the relationship between HIV and AIBD may help direct the therapeutic management of these patients.

To further this understanding, we conducted a literature review and examined various AIBDs in the context of HIV by studying the relationship between AIBDs and HIV progression, treatment modalities, and overall clinical outcome. Additionally, we present contemporary theories regarding why AIBDs are on the rise in HIV-infected patients.
Methods

In June 2017, a systematic search of the PubMed Medline database was conducted using the following terms: “pemphigus”, “pemphigoid”, “bullous pemphigoid”, “pemphigus vulgaris”, “pemphigus foliaceus”, “pemphigus vegetans”, “IgA pemphigus”, “paraneoplastic pemphigus”, “epidermolysis bullosa acquisita”, “mucous membrane pemphigoid”, “cicatricial pemphigoid”, “dermatitis herpetiformis”, “pemphigus herpetiformis”, “linear IgA bullous dermatosis”, “autoimmune disorder”, and in combination with “HIV”, “human immunodeficiency virus”, or “AIDS”. Only articles with at least abstracts available in English were included. All original studies and case reports that discussed AIBD in the context of HIV were reviewed. Articles that explored the overall relationship between the emergence of autoimmune disorders and HIV were also reviewed. Information with regard to cluster of differentiation (CD) 4 counts as well as antiretroviral therapies (ARTs) were included when available. Details with regard to antibody titers were limited and often without reference values; thus, they were excluded from our review.

Autoimmune blistering disorders in HIV/AIDS

Bullous pemphigoid

Bullous pemphigoid (BP) is the most common AIBD among the general population. The clinical presentation of BP has been postulated to be variable and delayed in patients with HIV due to a dysfunctional immune system (Kinloch-de Loës et al., 1991). A total of three case reports of patients with both BP and HIV were identified, with HIV diagnosis preceded BP in all three cases (Table 1; Bull et al., 1994; De et al., 2008; Levy et al., 1986). The patients were male and ranging from age 30 to 58 years with an average age of 49 years.

This is in contrast to the average BP demographic, which favors women and elderly patients with an age that is generally >70 years (Alpsoy et al., 2015). One patient with both BP and HIV presented with tense bullae and pruritus 6 weeks after initiating ART with nevirapine, lamivudine, and stavudine. The patient responded to standard oral corticosteroid therapy with temporary cessation of ART (De et al., 2008). Another patient was treated with ritodrine, a beta-2 adrenergic agonist that has been used to treat dermatitis herpetiformis without concerns for immunosuppression. However, ritodrine has since been removed from the U.S. market (Levy et al., 1986).

A prospective study identified a higher prevalence of circulating BP-type autoantibodies in HIV-positive patients with chronic pruritus (38%) compared with HIV-negative patients with chronic pruritus (21%). Furthermore, the incidence of BP-type antibody positivity increased with advanced HIV staging (World Health Organization clinical stages I-IV). Among patients diagnosed with HIV stage II, 21% had detectable levels of BP antibody, as did 37% with HIV stage III and 43% with HIV stage IV (Kinloch-de Loës et al., 1991; Zandman-Goddard and Shoenfeld, 2002). BP-type autoantibodies were identified in 75% of all patients with HIV and a pruritic papulovesicular eruption.

The authors of the study recommended that clinicians consider BP as a diagnosis in patients affected by both HIV and a papulovesicular eruption. Interestingly, six such patients were treated with zidovudine with subsequent undetectable BP antibody levels and improved pruritus. When zidovudine was discontinued, BP antibodies were again detectable, suggesting a correlation between HIV disease activity and autoimmunity (Kinloch-de Loës et al., 1991). This study supports the potential relationship between immune imbalance and autoimmunity phenomena as observed in patients affected by HIV, particularly the risk of developing BP antibodies.

Pemphigus vulgaris

Six cases of pemphigus vulgaris (PV) have been reported in patients with HIV (Table 2; Capizzi et al., 1998; Hodgson et al., 2003; Marfatia et al., 2007; Mignona et al., 2005; Polansky et al., 2015; Splaver et al., 2000). All but one patient was male, and patients ranged from age 29 to 59 years with an average age of 39 years. Those with PV in the general population are generally between 50 and 70 years of age in Europe and between 30 and 50 years in other countries (Alpsoy et al., 2015).

In four cases, HIV preceded PV diagnosis (Capizzi et al., 1998; Hodgson et al., 2003; Polansky et al., 2015; Splaver et al., 2000). Among the reported PV cases, various systemic immunosuppressive therapies have been reported, including systemic corticosteroids, mycophenolate mofetil, azathioprine, cyclosporine, and most recently, rituximab. In three cases, the AIBD treatments were administered concurrently with ART with a positive clinical response of AIBD (Hodgson et al., 2003; Marfatia et al., 2007; Mignona et al., 2005). Some serious complications, including Staphylococcus aureus septicemia and further reduction of CD4 cell count, were reported in another patient (Capizzi et al., 1998). Successful use of systemic cyclosporine has been described in HIV-positive PV but warrants particular consideration in the HIV population because cyclosporine’s renal toxicity may be amplified through interactions with ART medications (Hodgson et al., 2003; Mignona et al., 2005). Therefore, it is recommended that clinicians consider reducing cyclosporine dosing by 5% to 20% in patients on ART (Mignona et al., 2005).

IgA pemphigus

There have been three reported cases of IgA pemphigus in patients with HIV (Table 3; Barnabas et al., 1997; Muldrow et al., 1997; Myers and Rico, 1994). In two cases, dapsone and short-term oral corticosteroids rapidly cleared the skin lesions (Muldrow et al., 1997; Myers and Rico, 1994). In the other case, high-potency topical

Table 1
BP and its relationship to HIV

| Reference          | Age (years); sex | Timing of HIV diagnosis | CD4 (count/mm³) | Treatment and/or intervention | Outcomes                                                                 |
|--------------------|------------------|-------------------------|-----------------|-------------------------------|--------------------------------------------------------------------------|
| Levy et al., 1986  | 58; male         | HIV preceded BP diagnosis by 1 year | NA              | Ritodrine                    | Disease suppression but recurrence immediately after therapy discontinuation |
| Bull et al., 1994  | 58; male         | HIV preceded BP diagnosis by 5 years | NA              | Oral corticosteroid medications | Remission when therapy reintroduced                                       |
| De et al., 2008    | 30; male         | HIV preceded BP diagnosis by 10 years | 116             | Oral and topical corticosteroid medications; ART discontinuation | Remission sustained through therapy taper and reintroduction of ART       |

ART, antiretroviral therapy; BP, bullous pemphigoid; CD, cluster of differentiation; HIV, human immunodeficiency virus; NA, not available.

* Last line addresses ART therapy. If not listed, this information was not explicitly addressed.
The patient had been exposed to the same anti-tuberculosis medication without skin complication (Morice et al., 2013). Another case report described a case of LABD in a patient who was recently diagnosed with HIV. The patient responded to dapsone (Chaudhry et al., 2015).

Pemphigus vegetans

In the two reported cases of pemphigus vegetans (PVe), patients’ HIV-positive statuses were established during workup for PVe diagnosis (Table 5; Lateef et al., 1999; Mahe et al., 1994). Systemic therapies included successful use of oral dapsone and oral gold salts, in addition to systemic corticosteroids. The oral lesions were effectively treated with topical corticosteroids.

Pemphigus foliaceus

There is one report of endemic pemphigus foliaceus (PF) in a 32-year-old Brazilian man with HIV (Table 5; Cunha et al., 1995). Interestingly, the skin disease initially improved after the patient

| Table 2 |
| PV and its relationship to HIV |

| Reference | Age (years); sex | Timing of HIV diagnosis | CD4 (count/mm³) | Treatment and/or Intervention* | Outcomes |
|-----------|-----------------|------------------------|----------------|---------------------------------|----------|
| Capizzi et al., 1998 | 50; male | HIV preceded PV by 2 years | 1014 (315 after treatment) | IV and oral corticosteroid medications; cyclophosphamide | Remission but development of Staphylococcus aureus septicemia and decrease in CD4 |
| Splawer et al., 2000 | 30; female | HIV preceded PV diagnosis by 7 years | 104 | IV corticosteroid medications; ampicillin/sulbactam; azathioprine | Remission |
| Hodgson et al., 2003 | 29; male | HIV preceded PV diagnosis | 760 (640 after treatment) | Topical and oral corticosteroid medications; thalidomide; azathioprine; cyclosporine; ART initiation | Topical corticosteroid medications: Disease persistence Or oral corticosteroid medications, thalidomide, azathioprine: Initial improvement Cyclosporine, ART: Remission |
| Mignona et al., 2005 | 29; male | HIV diagnosed after PV diagnosis | 186 (244 after treatment) | Cyclosporine; oral corticosteroid medications; ART initiation | Remission but acute renal dysfunction Or oral corticosteroid medications: Disease suppression as maintenance therapy Systemic corticosteroid medications: Disease persistence Systemic corticosteroid medications combined with ART: Remission |
| Marfatia et al., 2007 | 30; male | HIV and PV diagnosed concurrently | NA | Intramuscular corticosteroid medications; ART initiation | Systemic corticosteroid medications: Disease progression Systemic corticosteroid medications and mycophenolate mofetil: Disease persistence |
| Polansky et al., 2015 | 54; male | HIV preceded PV diagnosis by 14 years | 1672 (444 after mycophenolate mofetil and azathioprine but before rituximab) | Oral corticosteroid medications; mycophenolate mofetil; azathioprine; rituximab; continuation of ART already initiated for HIV | Remission but development of Staphylococcus aureus septicemia and decrease in CD4 |

* Last line addresses ART therapy. If not listed, this information was not explicitly addressed.

Corticosteroid monotherapy was sufficient for disease control (Barnabas et al., 1997).

Mucous membrane pemphigoid or cicatricial pemphigoid

In the three published case reports of mucous membrane pemphigoid (MMP) or cicatricial pemphigoid in patients with HIV, CD4 counts were normal or near normal (Table 4; Demathe et al., 2008; Lish et al., 1997; Singh et al., 2014). Patients were successfully treated with dapsone and topical or intralesional corticosteroids.

Linear IgA bullous dermatosis

There are two reported cases of linear immunoglobulin (Ig)A bullous dermatosis (LABD) diagnosed in patients with established HIV diagnoses. One patient with untreated HIV developed LABD days after initiating treatment for multisystemic tuberculosis. The authors suspected tuberculosis as the trigger for LABD given that years earlier, the patient had been exposed to the same anti-tuberculosis medication without skin complication (Morice et al., 2013). Another case report described a case of LABD in a patient who was recently diagnosed with HIV. The patient responded to dapsone (Chaudhry et al., 2015).

Pemphigus foliaceus

There is one report of endemic pemphigus foliaceus (PF) in a 32-year-old Brazilian man with HIV (Table 5; Cunha et al., 1995). Interestingly, the skin disease initially improved after the patient

| Table 3 |
| IAP and its relationship to HIV |

| Reference | Age (years); sex | Timing of HIV diagnosis | CD4 (count/mm³) | Treatment and/or Intervention* | Outcomes |
|-----------|-----------------|------------------------|----------------|---------------------------------|----------|
| Myers and Rico, 1994 | 28; female | HIV preceded IAP diagnosis by 5 months | NA | Dapsonle; oral corticosteroid medications | Remission |
| Muldown et al., 1997 | 48; male | Advanced HIV preceded IAP diagnosis | NA | Dapsonle; oral corticosteroid medications | Remission |
| Barnabas et al., 1997 | 35; male | HIV preceded IAP diagnosis by 1.5 years | NA | High-potency topical corticosteroid medications; topical gentamicin | Remission |

* Last line addresses ART therapy. If not listed, this information was not explicitly addressed.
contracted HIV, despite the need for high-dose systemic corticosteroids for disease control prior to HIV infection. Clinical improvement was associated with a 16-fold improvement of PF antibody titers. The patient’s autoantibody response is speculated to have been attenuated by the concomitant HIV infection.

Paraneoplastic pemphigus

There is one case report of paraneoplastic pemphigus (PnP) in a patient with known HIV (Table 5). The patient’s PnP was attributed to diffuse B-cell lymphoma that was identified after further evaluation. The skin disease was characterized difficult to treat despite systemic corticosteroids and intravenous immunoglobulin (IVIg), and the patient eventually succumbed to sepsis (Tull et al., 2014).

Epidermolysis bullosa acquisita

There is one reported case of epidermolysis bullosa acquisita (EBA) in a patient with HIV (Table 5). The diagnosis of HIV was made during the course of the AIBD workup. Cutaneous disease was successfully managed with systemic corticosteroids (Chou et al., 1991).

Dermatitis herpetiformis

Four cases of dermatitis herpetiformis (DH) have been reported in patients with HIV (Bull et al., 1994; Conri et al., 1990; Krishna and Kavitha, 1999; Pincelli et al., 1992), but only a single case has been published in English (Table 5) (Bull et al., 1994). Successful disease management has been reported with oral prednisolone and oral dapsone (Bull et al., 1994).

Therapeutic considerations and management

AIBDs in HIV-infected patients present a clinical challenge with regard to medical management. Topical corticosteroids are the gold standard in limited AIBD (Hooten et al., 2014). However, systemic corticosteroids and other steroid-sparing immunosuppressives are often necessary for generalized or refractory disease. Ultimately, the

### Table 4
MMP and its relationship to HIV

| Reference        | Age (years); sex | Timing of HIV diagnosis | CD4 (count/mm³) | Treatment and/or intervention* | Outcomes                     |
|------------------|------------------|-------------------------|-----------------|-------------------------------|------------------------------|
| Lish et al., 1997| 51; male         | HIV preceded MMP diagnosis by 7 years | 428             | Dapsone                       | Death from unrelated adenocarcinoma |
| Demathe et al., 2008 | 48; male        | HIV preceded MMP diagnosis by 13 years | 1970            | Topical corticosteroid medications | Remission                   |
| Singh et al., 2014 | 48; male        | HIV and MMP diagnosed concurrently | 1180            | Topical and intralesional corticosteroid medications | Remission                   |

| Reference        | Age (years); sex | Timing of HIV diagnosis | CD4 (count/mm³) | Treatment and/or intervention* | Outcomes                     |
|------------------|------------------|-------------------------|-----------------|-------------------------------|------------------------------|
| LABD; reference  |                  |                         |                 |                               |                              |
| Morice et al., 2013 | 50; female    | HIV preceded LABD by years | 10              | Discontinuation of anti-tuberculosis medications | Remission                   |
| LABD: Chaudhry et al., 2015 | 50; male | HIV preceded LABD by 7 months | 421             | Dapsone                       | Remission                   |
| PVe; Mehe et al., 1994 | 31; male       | HIV and PVe diagnosed concurrently | 936             | Dapsone; gold salts; topical corticosteroid medications | Remission                   |
| PVe; Lateef et al., 1999 | 23; male      | HIV and PVe diagnosed concurrently but PVe symptoms preceded HIV diagnosis by 2 years | 372             | Not attempted due to loss to follow-up | Patient lost to follow-up |
| PF; Cunha et al., 1995 | 32; male       | HIV diagnosed after PF diagnosis and improved PF symptoms 10 years later | 816             | Oral corticosteroid medications (prior to HIV diagnosis) | Disease self-resolved after HIV infection |
| PnP; Tull et al., 2014 | 40s; male     | HIV preceded PnP diagnosis by 6 years | 403             | Intravenous immunoglobulin and corticosteroid medication; ART discontinuation | Death from diffuse B-cell lymphoma and sepsis |
| EBA; Chou et al., 1991 | 20; male     | HIV and EBA diagnosed concurrently | NA              | Oral corticosteroid medications (10 days) | Remission with relapses |
| DH; Bull et al., 1994† | Male          | HIV preceded DH diagnosis by 3 years | 300             | Oral and topical corticosteroid medications; dapsone | • Corticosteroid medications alone: Disease persistence | • Oral corticosteroid medications and dapsone: Remission with maintenance on oral corticosteroid medications alone |

### Table 5
Other AIBDs and their relationships to HIV

| AIBD; reference | Age (years); sex | Timing of HIV diagnosis | CD4 (count/mm³) | Treatment and/or intervention* | Outcomes                     |
|-----------------|------------------|-------------------------|-----------------|-------------------------------|------------------------------|
| LABD; reference |                  |                         |                 |                               |                              |
| Morice et al., 2013 | 50; female    | HIV preceded LABD by years | 10              | Discontinuation of anti-tuberculosis medications | Remission                   |
| LABD: Chaudhry et al., 2015 | 50; male | HIV preceded LABD by 7 months | 421             | Dapsone                       | Remission                   |
| PVe; Mehe et al., 1994 | 31; male       | HIV and PVe diagnosed concurrently | 936             | Dapsone; gold salts; topical corticosteroid medications | Remission                   |
| PVe; Lateef et al., 1999 | 23; male      | HIV and PVe diagnosed concurrently but PVe symptoms preceded HIV diagnosis by 2 years | 372             | Not attempted due to loss to follow-up | Patient lost to follow-up |
| PF; Cunha et al., 1995 | 32; male       | HIV diagnosed after PF diagnosis and improved PF symptoms 10 years later | 816             | Oral corticosteroid medications (prior to HIV diagnosis) | Disease self-resolved after HIV infection |
| PnP; Tull et al., 2014 | 40s; male     | HIV preceded PnP diagnosis by 6 years | 403             | Intravenous immunoglobulin and corticosteroid medication; ART discontinuation | Death from diffuse B-cell lymphoma and sepsis |
| EBA; Chou et al., 1991 | 20; male     | HIV and EBA diagnosed concurrently | NA              | Oral corticosteroid medications (10 days) | Remission with relapses |
| DH; Bull et al., 1994† | Male          | HIV preceded DH diagnosis by 3 years | 300             | Oral and topical corticosteroid medications; dapsone | • Corticosteroid medications alone: Disease persistence | • Oral corticosteroid medications and dapsone: Remission with maintenance on oral corticosteroid medications alone |

### Notes
- AIBD, autoimmune blistering disorders; ART, antiretroviral therapy; CD, cluster of differentiation; DH, dermatitis herpetiformis; EBA, epidermolysis bullosa acquisita; HIV, human immunodeficiency virus; LABD, linear immunoglobulin A bullous dermatosis; MMP, mucous membrane pemphigoid; NA, not available; PF, pemphigus foliaceus; PnP, paraneoplastic pemphigus; PVe, pemphigus vegetans.
- * Last line addresses ART therapy. If not listed, this information was not explicitly addressed.
- † Three other studies reported a relationship between dermatitis herpetiformis and HIV but were not available in English (Conri et al., 1990; Krishna and Kavitha, 1999; Pincelli et al., 1992).
risk-benefit ratio of immunosuppression must be deemed acceptable with a commitment to vigilant monitoring for possible opportunistic infections, particularly in patients already in immuno-compromised states (Bull et al., 1994).

Our literature review revealed that most patients who were affected by both HIV and an AIBD required systemic therapy. A single case of IgA pemphigus and two of three cases of MMP were managed with topical corticosteroids without the need to escalate to systemic therapy (Barnabas et al., 1997; Demathe et al., 2008; Singh et al., 2014). Systemic corticosteroids are the most frequently utilized therapy among patients with AIBD and HIV and are considered first-line therapy in patients with BP and PV. Therefore, it is not surprising that all but one patient with BP and all patients with PV received systemic corticosteroids based on our review (Hooten et al., 2014).

In several instances, systemic corticosteroids were used in conjunction with other systemic immunosuppressants, such as cyclosporine and azathioprine. Systemic corticosteroids were also successfully used to treat HIV-infected patients with IgA pemphigus, EBA, and with dapsone, DH (Bull et al., 1994; Chou et al., 1991; Muldrow et al., 1997; Myers and Rico, 1994). In addition to infection, other side effects associated with long-term use of systemic corticosteroids included weight gain, high blood pressure, osteoporosis, fluid retention, elevated blood sugar levels, cognitive disturbances, cataracts, and glaucoma (Hooten et al., 2014). We recommend that systemic corticosteroids only be utilized in HIV-infected patients in collaboration with an infectious disease specialist under close monitoring.

Nonimmunosuppressive therapies without the risk of increased opportunistic infections should be strongly considered in the treatment of patients with AIBDs and concurrent HIV. Dapsone is a systemic steroid-sparing nonimmunosuppressive agent that has been reported to successfully treat PV, IgA pemphigus, MMP, LABD, and DH in the HIV population (Bull et al., 1994; Chaudhry et al., 2015; Lish et al., 1997; Mahe et al., 1994; Muldrow et al., 1997; Myers and Rico, 1994). In consultation with an infectious disease specialist, one of the authors (A.Y.C.) has also successfully used dapsone in the treatment of BP in a patient with HIV. Furthermore, dapsone can be used as a prophylactic medication for Pneumocystis jiroveci pneumonia in the HIV population, especially in those who cannot tolerate trimethoprim-sulfamethoxazole (Goldie et al., 2002). Therefore, dapsone may be a safe alternative systemic therapy in patients with HIV and AIBDs. Prior to initiating oral dapsone, all patients should be screened for glucose-6-phosphate dehydrogenase deficiency. While on dapsone, all patients require monitoring for hemolytic anemia, methemoglobinemia, agranulocytosis, hepatic abnormalities, and distal motor neuropathy (Hooten et al., 2014).

IVIg has been shown in numerous small studies and case reports to be beneficial in patients with BP, PV, LABD, PF, MMP, and EBA without the risk of immunosuppression (Czernik et al., 2012). Because the use of IVIg in the treatment of AIBD is recent, our literature search only revealed one case of IVIg treatment in a patient with both HIV and AIBD. IVIg and systemic corticosteroids were administered, along with ART cessation in a patient with PnP. Unfortunately, the patient succumbed to underlying malignancy and sepsis (Tull et al., 2014).

IVIg may be a safe alternative overall to immunosuppressive therapy in patients with HIV because side effects are generally minor or can be minimized by decreasing the infusion rates and/or administering prophylactic medications prior to infusions. The side effects of IVIg include headache, acute cutaneous reactions, renal failure (minimized by using sucrose-free preparations), and thromboembolic events. Anaphylaxis is possible in patients with an IgA deficiency. Therefore, IgA levels should be checked prior to starting IVIg (Czernik et al., 2012).

Interestingly, no report of tetracycline and niacinamide use in patients with HIV and AIBD was identified in our literature search even though this combination has been shown to be an effective therapy for patients with BP who cannot tolerate long-term systemic corticosteroids (Fivenson et al., 1994). Additionally, colchicine is a nonimmunosuppressive alternative in patients with EBA but this was not the elected therapy in the one patient identified with concomitant EBA and HIV (Chou et al., 1991; Cunningham et al., 1996; Hooten et al., 2014).

Based on our literature review, it is unclear whether adding ART itself can improve clinical outcome in patients with both HIV and AIBD. Screening for HIV should be a part of routine laboratory workup for patients with AIBD who are being considered for immunosuppressive therapy. Furthermore, the U.S. Preventive Services Task Force currently advises all people ages 15 to 65 years be screened for HIV at least once and then be regularly screened if at high risk for new HIV infection (U.S. Preventive Services Task Force, 2013). Although immunosuppressive therapy is not explicitly listed as a risk factor by the Task Force, clinicians should consider this element when treating and screening patients. All patients with untreated HIV should be referred to HIV specialists for treatment regardless of their AIBD disease status.

**Mechanisms for development of autoimmune disorders in HIV-infected patients**

Several theories have been proposed to explain the development of autoimmunity in the setting of HIV infection. These include molecular mimicry to a self-antigen, persistent antigenic stimulation, and restoration of the immune system with ART.

HIV virion molecular mimicry is one proposed mechanism in the development of autoimmune diseases in patients with HIV. The HIV virion may exhibit structural similarities to a self-antigen and therefore induce an (auto)immune response (Etzioni, 2003). Specifically, HIV-1 env-products have structural homology to functional molecules that are involved in self-tolerance: HLA-DR4 and DR2; T cell receptor alpha-, beta- and gamma-chain; the Fas protein; and several functional domains of IgG and IgA. Through such molecular mimicry, HIV may promote immune dysregulation and subsequent autoimmunity (Silvestris et al., 1995).

Persistent antigenic stimulation due to an inherently defective immune system has also been hypothesized as a primary precipitant of autoimmune disorders in the setting of immunodeficiency (Etzioni, 2003). Continuous, unrestricted stimulation of memory B-cells is a plausible mechanism by which antibody production may be sustained in the absence of a specific antigen. In the early stage of HIV infection, nonspecific polyclonal B-cell stimulation is driven by cytokines that are released from HIV-infected macrophages (Bernasconi et al., 2002; Demathe et al., 2008; Montes et al., 2007). This mechanism could explain the increase in autoimmune disorders with the growing population of HIV-infected individuals.

Finally, it has been hypothesized that HIV-infected patients are prone to developing autoimmune disorders during immune restoration after implementation of ART. Zandman-Goddard and Shoenfeld (2002) proposed a clinical staging system to further categorize autoimmune diseases in HIV and their relationship to total CD4 counts and viral loads: 1) Stage I/clinical latency (CD4 > 500 with high viral load) associated with autoimmune disease, 2) Stage II/cellular response (CD4 200-499 with high viral load) associated with immune-complex disease and vasculitis, 3) Stage III/immune deficiency (CD4 < 200 with high viral load) associated with spondyloarthropathy, and 4) Stage IV/immune restoration (CD4 > 500 with low viral load) associated with autoimmune disease. The authors argue that autoimmune diseases require preservation of the
immune system (ie, normal CD4 counts as seen in defined Stages I and IV). If this is the case, the incidence of autoimmune diseases would be expected to decrease as CD4 counts decrease (ie, as a patient’s HIV status deteriorates, he or she would be at a lower risk of acquiring an autoimmune disease; Zandman-Goddard and Shoenfeld, 2002).

However, the risk of AIBD cannot alone be explained by CD4 counts or immune restoration. In fact, we identified four cases in which an AIBD was diagnosed in patients with CD4 < 200 (De et al., 2008; Mignona et al., 2005; Morice et al., 2013; Splaver et al., 2000). Although CD4 counts normalize in HIV-positive patients on therapy, the broader milieu of immune restoration is believed to remain altered (Zandman-Goddard and Shoenfeld, 2002). Studies have shown that levels of memory-phenotype CD4+ T-cells that express CD28 (which facilitates cellular activation after antigen exposure) do not normalize in HIV-infected patients on ART (Lange and Lederman, 2003). This suggests that normalization of CD4 counts alone does not fully explain the increase in comorbid AIBDs.

Limitations

We acknowledge the limitations of our review. A plethora of valuable information, including CD4 counts, details on therapeutic regimens for either AIBD or HIV, antibody titers, and patient outcomes, was not always routinely specified in case reports. Overall, few publications exist that examine AIBDs in the context of HIV. As additional reports of autoimmune disorders in patients with HIV emerge, we hope to better understand the protean ways in which AIBDs in individuals who are infected with HIV.

Conclusions

Even though there is presently a limited understanding of the complex relationship between HIV and autoimmunity, emerging reports further illuminate the impact of immune dysfunction and restoration in the pathogenesis of autoimmune diseases. Herein, we reviewed the 23 reported cases of AIBD in HIV-positive patients. Dermatologists should work closely with infectious disease specialists and cautiously weigh the benefits and risks of immunosuppression when treating AIBDs in individuals who are infected with HIV.

Studies are needed to explore alternative treatments for patients who cannot tolerate immunosuppressant therapies. Expanding the arsenal of effective AIBD therapies, in addition to optimizing immune restoration, will be necessary for the future directions of the treatment of AIBD patients with HIV.

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