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CASE REPORT

Dermatomyositis and HIV infection: case report and review of the literature

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Abstract Since the 1980s, a host of autoimmune phenomena and rheumatologic illnesses have been linked to infection with the human immunodeficiency virus (HIV). Given the broad effects of this virus on both the humoral and cell-mediated arms of the immune system, illnesses such as polymyositis and Reiter's syndrome appear to be more prevalent in HIV-infected individuals and occur in the absence of well-described predispositions. The activities of some rheumatologic illnesses exhibit an inverse relationship with the course of HIV infection, such as rheumatoid arthritis, which becomes more quiescent with advancing disease. Dermatomyositis is a rheumatologic illness that very infrequently occurs and during our review of literature only three other cases were reported. We present the case of a Caucasian male in his mid-20s who presented with acquired immunodeficiency syndrome and subsequently developed dermatomyositis. In this review, we highlight the current relationship between HIV infection and autoimmunity, the possible ways HIV infection may foster an environment favorable for the development of dermatomyositis, and review the previously reported cases of individuals with HIV infection who developed dermatomyositis. The complex issues of how to treat individuals with HIV and dermatomyositis is also discussed.

Keywords Dermatomyositis · Human immunodeficiency virus · AIDS · Immune reconstitution inflammatory syndrome

Introduction

Since the early 1980s, a variety of autoimmune phenomena have demonstrated a well-established link with infection by the human immunodeficiency virus (HIV). In addition to the development of autoantibodies directed against a diverse array of proteins and cells throughout the body, various rheumatologic illnesses have also been found to have a higher prevalence in HIV-infected adults [1–3]. Specific rheumatologic illnesses such as Reiter's syndrome, polymyositis and diffuse infiltrative lymphocytic syndrome (DILS), a Sjögren's-like syndrome, have a well-described association with HIV infection [2]. Other rheumatologic illnesses, such as rheumatoid arthritis, appear to have an inverse relationship with the course of HIV infection, improving as the disease progresses [2, 4]. Dermatomyositis appears to be a member of this latter group of rheumatologic illnesses, as the occurrence of dermatomyositis in HIV infection has only been reported three other times in medical literature. We present the fourth case of a patient who presented with acquired immunodeficiency syndrome (AIDS) and subsequently developed dermatomyositis. In this review, we highlight the current relationship between HIV infection and autoimmunity, the possible ways HIV infection may foster an environment favorable for the

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development of dermatomyositis, and review the previously reported cases of patients with HIV infection who developed dermatomyositis. The complex issues of how to treat patients with HIV and dermatomyositis will also be discussed [5].

Case

A 27-year-old Caucasian male presented in mid-2006 for evaluation of progressive fatigue and muscle weakness. His symptoms first developed in March 2006 as generalized fatigue. Over the course of the next few months, he noted increasing difficulty exercising, putting on a shirt and rising from a chair. During this time, he also experienced generalized muscle aching, mild arthralgias in his shoulders, knees and wrists, and he developed a new rash. The rash initially started on the extensor aspects of both forearms, but rapidly involved the extensor aspects of his metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, the back of his neck and around his eyes. The rash on the extensor aspects of his MCP and PIP joints were raised and the other areas affected were mildly pruritic. The patient presented to several providers in the late spring and summer of 2006 without reaching a diagnosis. He was referred to a dermatologist in August 2006, and a biopsy of his rash and nailfold capillaroscopy were performed. When the skin biopsy demonstrated an interface dermatitis, a diagnosis of dermatomyositis was entertained. An elevated aldolase was noted around this time. Biopsy of the right deltoid muscle was performed in late summer of 2006 and demonstrated changes suggestive of chronic inflammation with macrophages in the endomysium consistent with myositis. The patient was started on prednisone 1 mg/kg daily in October 2006 and experienced rapid improvement in his symptoms, with his strength improving after several weeks of therapy and his symptoms resolving after several months. Antinuclear antibody (ANA) testing was not done during the patient's workup for his dermatomyositis, but was later (after a year of treatment with prednisone) found to be negative.

The patient was lost to follow-up and remained on prednisone 1 mg/kg daily until September 2007 when he presented to his physician due to a positive human immunodeficiency virus type 1 (HIV-1) antibody test result performed as part of nuptial screening. HIV-1 antibody testing was positive upon repeat and confirmed by Western blot with all bands positive. The patient's CD4+ T lymphocyte enumerated by flow cytometry (CD4+ count) in September 2007 was 135 per μL, and his burden of HIV-1 viral particles established by polymerase chain reaction (viral load) was 515,824 copies per milliliter; he was clinically diagnosed with AIDS. Further questioning of the patient and review of his medical record demonstrated that he had a negative HIV antibody test result in April 2004, but likely had a seroconverting illness in November 2005 when he presented to his physician with a fever, sore throat and lymphadenopathy. He denied a history of receiving blood transfusions or engaging in sexual intercourse with other men, but he did have multiple lifetime sexual partners with variable condom use. He had two tattoos, both received after 2004, during trips to Mexico and Guam. With his CD4+ count less than 350 cells/μL, he was started on triple therapy with co-formulated emtricitabine, tenofovir and efavirenz. After several months on this therapy, his CD4+ count increased to 388 cells/μL and viral load decreased to <50 copies/mL. With his CD4+ count improving and viral load decreasing on co-formulated emtricitabine, tenofovir and efavirenz, a gradual reduction in prednisone was undertaken over the course of a year, with the patient closely monitored for a relapse of his dermatomyositis. At the time of this report, the patient was continuing a very gradual taper of his prednisone, currently under 10 mg a day, with no relapse of his dermatomyositis given the partial reconstitution of his immune system.

Methods

A review of the published English literature was performed using the Medline® database through the OvidSP Web gateway (http://gateway.ovid.com). The search screened articles from 1950 to March 2009 for the keywords "dermatomyositis" and "human immunodeficiency virus". Screening for both keywords yielded 17 articles. Articles of interest were then selected if a review of the title and/or abstract suggested it described a patient or patients with these concomitant conditions. Basic science and immunology articles on this subject were also reviewed using this search, and additional articles of interest were selected from the bibliographies of the published literature.

HIV and autoimmunity

Since the onset of the HIV epidemic in the early 1980s, it has been recognized that the virus is able to trigger a wide variety of autoimmune phenomena [6]. One of the first reported manifestations of HIV-triggered autoimmunity was the frequent development of hypergammaglobulinemia in patients with AIDS [6, 7]. By the mid to late 1980s, HIV had demonstrated a clear association with multiple rheumatologic illnesses such polymyositis [1, 8] and Reiter's syndrome [2, 9]. Studies over the past two decades suggest that the incidence of rheumatic disease reported in HIV-infected adults approached 72% [1, 10] Autoimmune and

rheumatologic phenomena appear to be more common in women than men, with HIV-infected women more frequently reporting myalgias, photosensitivity and sicca symptoms [10]. At the current time, it appears that the spectrum of autoimmune phenomena in HIV-infected adults is increasing [1], attributable to the complex immunologic deficiency and dysregulation associated with HIV infection [2]. As progressive depletion of CD4+ cells occurs, cell-mediated immunity becomes suppressed in nearly every capacity, whereas humoral immunity becomes hyperactive and uncontrolled [2].

HIV has the capacity to infect multiple immune cell lines, including T lymphocytes, B lymphocytes, dendritic cells and monocytes/macrophages [11]. HIV initially infects mucosal dendritic cells that, in their capacity as antigen-presenting cells (APCs), transmit HIV to monocytes and macrophages within the lymphatics, thus establishing a reservoir [11]. HIV spreads from macrophages and monocytes to B and T lymphocytes [11], leading not only to a rapid depletion of CD4+ cells by virus-induced apoptosis [11, 12], but also to uncoupling of the normal regulation of CD8+ cells [11]. Some CD8+ cells are infected by HIV, and while they do not experience the same cytotoxic effects seen in CD4+ cells, the virus alters the function of memory and effector subsets critical to immune clearance [11]. Memory CD8+ cells also release interferon-γ (IFNγ), a cytokine that induces a potent antiviral state [11]. Regulatory T lymphocytes (Treg), a subset of T lymphocytes important in the peripheral tolerance of naïve T lymphocytes after they encounter cognate antigen, also are early targets of HIV infection [12]; while B lymphocytes are activated through the CD4+ pathway [6] and CD21 (complement receptor 2) receptor [13]. In this milieu, the potential exists for the development of autoantibodies, an effect attributable to activation of the humoral immune response and attempts by B lymphocytes to make antibodies to HIV. Homology of some HIV-1 epitopes with regions on T and B lymphocytes may induce molecular mimicry, and thus while an immune response is generated against the virus, the immune system becomes the target of antibody-mediated autoimmunity [1, 6, 7]. The generation of anti-lymphocyte antibodies is linked to this effect and appears early in the course of infection [1, 3, 6]. A similar phenomenon has been associated with the development of anticardiolipin antibodies, and case reports of the antiphospholipid antibody syndrome developing early in the course of HIV infection have been described [1].

After the initial burst of HIV replication, strong cellular and humoral immune responses contain the virus over the course of several weeks [11], and thus manifests in the partial restoration of CD4+ cells with a significant drop in viremia [11]. The virus is never eradicated, however, and with reservoirs established early in monocyte/macrophage cell lines, HIV eventually escapes immune containment [11]. Progressive HIV disease, due to multiple virus and host factors, leads to CD4+ cells depletion, inversion of the CD4+/CD8+ T lymphocyte ratio [1, 10], and a polarization of the cell-mediated and humoral immune responses [11]. A strong, cell-mediated, antiviral T-helper (Th1) pattern associated with IFNγ (typical of early HIV infection) is steadily pushed toward a Th2 pattern favoring a humoral response [11]. Increasing HIV viral load also leads to increasing exposure of the immune system to HIV antigens, which in turn triggers the host immune system to develop antibodies that favor immune complex formation. This effect becomes especially pronounced as HIV infection progresses to AIDS [2, 6, 14]. Development of immune complexes has been implicated in idiopathic thrombocytopenia purpura and hemolytic anemia seen in HIV-infected patients [14]. Additionally, some antibodies produced in response to HIV epitopes can precipitate antibodies produced against another pathogen [7]. This complementary antibody network has been demonstrated in viral + viral and viral + bacterial antibody combinations for HIV and pathogens such as cytomegalovirus, Epstein-Barr virus, hepatitis B virus, and *Mycobacterium tuberculosis* [7]. Co-infection with these agents can lead to an exaggerated immune response, hypergammaglobulinemia and the increased production of immune complexes [7]. In rheumatoid arthritis, an illness mediated by CD4+ cells and with disease activity associated with a Th1 cytokine pattern, progressive HIV infection is associated with disease stabilization and even remission [3, 4].

Late in the course of HIV infection as the viral load peaks, both cellular and humoral immune responses become most dysfunctional [2, 3]. CD4+ counts, directly depressed by viral-mediated cell toxicity, further decline due to activation-induced cell death [12]. Treg cell counts decline as well, and while the decrease is independent of that seen with CD4+ cells, the suppression further diminishes the ability of the immune system to contain the virus [12]. CD8+ cells experience partial decline, but the overall function of these cells is depressed, including, both, reduced ability to respond to viral infection and increased sensitivity to Fas/CD95 ligand-mediated apoptosis [11]. B lymphocytes become hyperactive and uncontrolled in late HIV disease, spontaneously proliferating [4] and producing copious amounts of gammaglobulins, furthering autoantibody secretion and precipitating immune complex formation [6]. It is at this point that CD8+ cell-mediated rheumatologic illnesses, such as Reiter's syndrome or DILS, may present [1]. In some cases, these rheumatologic illnesses may be the initial manifestation of AIDS [1].

Gradual restoration of the immune system commences with the institution of anti-retroviral therapy (ART), as evidenced by a decline in HIV viral load and an increase in

CD4+ count [5]. Restitution of CD4+ cells leads to a generally incomplete return of the typical interactions between the cellular and humoral immune responses, but some immune cell lineages are able to return close to baseline function. As CD4+ counts increase, interleukin-7 (IL-7) production decreases and this triggers a decline in the number of immature B lymphocytes that arise in late infection with HIV [13]. B lymphocyte activity and survival return to previous baseline, with decreased apoptosis noted [13]. B lymphocytes also become more responsive to T lymphocyte-dependent antigens [6] and CD8+ cell function also normalize, with a return in the ability to mature to a memory phenotype [15]. About 9 months after ART initiation, the paradoxical immune reconstitution inflammatory syndrome (IRIS) may occur, attributable to new (approximately 80%) or quiescent (approximately 20%) autoimmune or rheumatologic disease [5].

Integrating the various autoimmune phenomena that occur throughout the course of infection with HIV, a four-stage system has been proposed by Zandman-Goddard and Shoenfeld, which is summarized in Table 1 [1]. Stage I of this system is typified by acute infection with HIV in which autoimmune phenomena and rheumatologic diseases may first present. Stage II is marked by the gradual decline in CD4+ cells and coincident with immune complex deposition, vasculitis and other autoimmune phenomena rather than new onset rheumatologic diseases. Stage III occurs when CD4+ cells reach a nadir; CD8+ cell-mediated rheumatologic diseases such as polymyositis and Reiter's syndrome may present, even with the initial manifestation of AIDS. The final stage, stage IV, is marked by restoration of the immune system associated with effective ART and a potential for IRIS, manifest as a flare of once quiescent autoimmune disease.

HIV and dermatomyositis

Dermatomyositis is an inflammatory myositis, which clinically presents as proximal muscle weakness and is distinguished from polymyositis and inclusion body myositis by a characteristic facial and/or upper torso rash that accompanies or precedes muscle symptoms [16, 17]. Dermatomyositis is an autoimmune-mediated illness with serologic evidence of autoantibodies found in the majority of patients. These autoantibodies range from the presence of ANA to antibodies directed against various transfer RNA synthetases [16]. The main antigenic targets in dermatomyositis are vascular endothelium components within the endomysial blood vessels and capillaries [16]. Extensive immunologic and microscopic (both light and electron) examination of these vessels demonstrate a complement-mediated microangiopathy [17]. Circulating anti-endothelial cell antibodies directed against the endomysial vascular wall trigger complement activation [16]. Activated complement forms fragments that are deposited in the endomysial vessel wall. This leads to deposition of immune complexes and formation of the membrane attack complex (MAC) [16]. Deposition of the MAC on the endothelial wall leads to osmotic lysis and eventual necrotic destruction of the endomysial capillary [16]. Loss of capillaries in the muscle leads to ischemia and muscle fiber destruction that appears as microinfarcts and inflammation corresponding to perifasicular atrophy on biopsy [17]. In addition to its effects on the endothelial wall, complement deposition also triggers the release of cytokines that upregulate various cellular adhesion molecules by which cells and macrophages leave the blood and enter the perimysial and endomysial spaces [16]. This can be demonstrated on immunologic analysis of muscle biopsy specimens obtained from patients with dermatomyositis. The humoral response seen in dermatomyositis is fueled by B lymphocytes and CD4+ cells, which infiltrate the perimysial and perivascular regions. The cell-mediated response is led by perifascicular CD8+ cell and macrophages that invade myocytes expressing major histocompatibility complex (MHC) class I antigens [16].

While the extent and sequence by which HIV infection promotes an immunological environment favorable for the development of dermatomyositis remains poorly understood, the general mechanisms of how HIV triggers autoimmune phenomena enable some extrapolation of the possible effects the virus may have in this disease. The initial phase in the pathophysiologic process of dermatomyositis is the development of autoantibodies against the endothelial cell wall [16]. Multiple reports have described autoantibodies against a variety of antigens occurring fairly routinely and at higher frequencies in patients with HIV infection compared to those not infected [1–3, 10, 14]. While the avidity of these autoantibodies is typically low [6], the presence of specific autoantibodies can be associated with clinical manifestations, such as thrombocytopenia or leucopenia [1, 3]. Autoantibody production in HIV infection also is antigen driven [4]: as increasing exposure to various antigens from viral or bacterial infections occurs throughout the course of

Table 1 Stages of autoimmune disease as a function of the natural history of treated HIV infection [1]

Stage	CD4+ count	Autoimmunity
I	High (>500)	Initial presentation of some autoimmune diseases
II	Normal/Low (200–499)	Immune complex formation, vasculitis
III	Low (<200)	CD8+ cell predominant rheumatologic illnesses
IV	High (>500)	Resurgence of once quiescent disease

infection, autoantibodies become more numerous [4, 7]. An inverse relationship between the production of autoantibodies and the CD4+ count has been reported [1]. HIV can also have direct effects on the endothelial wall, which through molecular mimicry could trigger an aberrant response from the host immune system to attack specific antigens on the cell [1].

The next phase in the pathophysiology of dermatomyositis is the deposition of complement and immune complexes in the endomysial capillary wall [16]. While overt hypocomplementemia is unusual, complement activation products have been detected in the plasma of adults with HIV infection suggesting that a subclinical, low-grade activation is routinely present [2]. Immune complex formation, incorporating both HIV antibody and antigen, has also been frequently reported in HIV-infected patients and its prevalence inversely related to HIV disease stage [2, 6].

The final phase in the pathophysiology of dermatomyositis is the influx of B and T lymphocytes into the perimysial and perifascicular spaces leading to myocyte destruction. Progressive HIV disease results in gradual depletion of CD4+ cells and a relative predominance of CD8+ cells, the latter potentially interacting with MHC class I antigens on myocytes in a dysfunctional immunologic environment. This effect would be similar to that seen in patients with progressive HIV who develop Reiter's syndrome or DILS as their initial manifestation of AIDS [3, 9]. HIV also impairs B lymphocytes [6], through binding to surface molecules, which leads to altered expression of co-receptor molecules and varied responsiveness to CD4+ cells [6]. Dysfunctional B lymphocytes also produce greater numbers of antibodies and immunoglobulins that can lead to immune complex formation and complement activation [2, 6]. Presumably, it is the concerted effects of multiple immune system failures by which HIV infection can trigger autoimmune phenomena that initiate and sustain the pathophysiologic process characteristic of dermatomyositis.

Review of literature

During our review of the medical literature, only three other patients were identified having HIV infection and subsequently presented with features of dermatomyositis. Table 2 summarizes pertinent clinical, serologic and treatment information about these three cases. In a review by Espinoza et al. in 1991 [8] another patient with HIV infection and dermatomyositis was described, although her diagnosis of dermatomyositis was made 2.5 years prior to detection of HIV infection [8]. The authors of this review recognized that "she most likely had the idiopathic form of dermatomyositis" [8]. A retrospective review of patients in

Table 2 Summary of information from case reports of individuals with dermatomyositis and HIV infection

Reference	Nationality	Age/gender	Rash	Muscle symptoms	CD4+ count/ relationship to symptoms	Maximum CK	ANA Titer	Evaluation	Treatment
Baguley et al. [20]	UK	22/male	Pustular facial rash, Gottron's papules	Intermittent generalized weakness	CD4+ count 117 cells/mm³; muscle weakness present 18 months before HIV was detected	700 Units/L	Negative	Not reported	Prednisolone at various supra-physiologic doses for 3 years, then azathioprine 100 mg daily
Gresh et al. [21]	USA	22/male	Periorbital rash, Gottron's papules	Proximal muscle weakness	CD4+ count 160 cells/mm³; patient infected with HIV for 1 year before onset of rash	5,301 Units/L	1:1,280	Facial rash biopsied, muscle biopsied, and EMG done	Methylprednisolone tapered to prednisone; zidovudine started 2 months after onset of rash
Marfatia et al. [22]	India	30/female	Heliotrope rash, Gottron's papules	Proximal muscle weakness, dysphagia, dysphonia	CD4+ count 379 cells/mm³, HIV viral load not obtained; HIV Ab (+), then rash and muscle symptoms developed 6 months later	Normal (but patient had elevated LDH)	Negative	EMG done; no muscle biopsy	Prednisone 1 mg/kg per day started, then 1 year later ART was added (CD4+ count 251 cells/mm³)

Ab antibody, *ART* antiretroviral therapy, *EMG* electromyography

Zimbabwe in the early 1990s [18] and two recent prospective studies, one from Brazil in 1997 that studied 100 patients [19] and the other from Thailand in 2002 that studied 62 patients [10], did not report patients with HIV infection who also had dermatomyositis.

While both male patients presumably contracted HIV via male-having-sex-with-male exposure, the mode of transmission in the female patient was not described. All three patients had dermatologic findings characteristic of dermatomyositis along with muscle weakness and moderately to profoundly suppressed CD4+ counts. Only two of the three patients had elevated muscle enzymes such as creatine kinase (CK), and only one had an elevated ANA [20–22]. Dermatomyositis occurred approximately 6–18 months after detection of HIV infection. Our patient was of a similar age and gender as the patients in the case reports (male in the mid-20s at the time of development of dermatomyositis), but was infected with HIV through either a sexual contact or, less likely, improperly cleaned tattoo needle. He had a negative ANA test, but did have an elevated aldolase at the time his dermatomyositis was diagnosed.

Treatment

The treatment of dermatomyositis in patients infected with HIV presents two unique challenges. The mainstay of dermatomyositis treatment is supraphysiologic doses of glucocorticoids [16]. This would place HIV-infected patients with depressed CD4+ counts at increased risk of opportunistic infection or neoplasm [20]. The three cases previously described were all treated with prednisone or equivalent, up to 1 mg/kg daily, and/or methylprednisolone 500 mg intravenously at the beginning of treatment. In two of the cases, the severity of the muscular symptoms warranted aggressive immunosuppressive therapy [8, 21, 22]; in the case reported by Baguley et al. [20], HIV infection was not known during the initial treatment course. While our patient had a prompt return in muscle strength with the institution of prednisone, Espinoza et al. [8] reported in their series of seven HIV-infected patients with inflammatory myositis (one with dermatomyositis) that it took longer for a clinical response to occur in HIV-infected patients compared to those with the idiopathic form of the disease. No complications of prednisone usage, such as the development of Kaposi's sarcoma, were reported in their series [8]. The patient reported by Baguley et al. [20] was later placed on azathioprine because his dermatomyositis was refractory to reductions in prednisolone dosage. No complications associated with the addition of this therapy to glucocorticoids were reported aside from leucopenia [20]. While most second-line agents for dermatomyositis include immunosuppressive medications such as azathioprine, methotrexate, or cyclosporine, intravenous immunoglobulin (IVIg) has recently exhibited some promise in the treatment of refractory disease [16, 23]. Given the relative absence of immunosuppression with this treatment, perhaps IVIg will have a more prominent role in the therapy of future patients with HIV infection and dermatomyositis.

The second therapeutic challenge is that of a paradoxical exacerbation in dermatomyositis with effective ART [5, 22]. Autoimmune phenomena and rheumatologic diseases that occur during the IRIS are seen in up to 20% of cases due to more aggressive immune response to mild preexisting disease [5]. In the case reported by Gresh et al. [21], the patient began zidovudine (ZDV) because leukopenia was noted during the dermatologic manifestations of his illness. When his muscle symptoms developed, he was maintained on ZDV while receiving supraphysiologic doses of glucocorticoids [21]. He did not manifest symptoms suggestive of IRIS, but this patient was managed prior to the availability of triple-drug ART. In the case reported by Marfatia et al. [22], the patient began ART 1 year after receiving treatment for dermatomyositis without signs or symptoms suggesting IRIS [22]. Due to concerns about possible IRIS, our patient's prednisone dose was gradually tapered after ART was instituted. Our patient did not exhibit relapse of dermatomyositis signs or symptoms, his HIV viral load became undetectable and his CD4+ count increased appropriately.

Conclusion

The development of dermatomyositis in a patient with HIV infection is exceedingly uncommon, despite a growing body of evidence supporting a link between HIV infection and the secondary development of autoimmune phenomena and rheumatologic diseases. We reported a patient infected with HIV 6 months prior to the onset of his dermatomyositis. Only three other cases have been reported over the last three decades. Treatment of dermatomyositis in HIV-infected patients remains the same as that for immunocompetent adults, including supraphysiologic doses of glucocorticoids as first-line therapy. Special attention must be given to the risk of opportunistic infections or neoplastic complications in HIV-positive patients receiving potent immunosuppressive therapy and the emergence of IRIS when ART is implemented and immune function is partially restored.

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