Idiopathic Pyoderma Gangrenosum as a Novel Manifestation of the HIV Immune Reconstitution Inflammatory Syndrome: A Report of Three Cases

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Abstract
The initiation of antiretroviral treatment for individuals with HIV may be accompanied by a paradoxical flare of underlying inflammatory diseases, the recurrence of dormant infections, or worsening of prior treated opportunistic infections, termed the immune reconstitution inflammatory syndrome (IRIS). Cutaneous manifestations of IRIS are common. Pyoderma gangrenosum is a neutrophilic dermatosis postulated to reflect disrupted innate immune regulation causing altered neutrophil chemotaxis. It is uncommonly reported in association with HIV. In this case series, we present three cases of IRIS manifesting with pyoderma gangrenosum in individuals with HIV from India and the United States to raise awareness of this previously undescribed presentation and discuss the treatment challenges in the management of these patients.

Introduction
HIV continues to account for a significant burden of worldwide disease. While much work remains to be done in earlier disease diagnosis and enhancing access to treatment, the introduction of increasingly sophisticated antiretroviral therapies over the last two decades has saved countless lives. Antiretroviral treatment allows for the reestablishment of the immune system, resulting in enhanced ability to fight off organisms responsible for opportunistic infections in immunocompromised individuals.

By the end of 2011, an estimated 8 million individuals around the world – out of 34 million living with HIV – were on some form of antiretroviral treatment.1 The initiation of antiretroviral therapy in patients with HIV may be accompanied by a paradoxical flare of underlying inflammatory diseases, recurrence of dormant infections, or worsening of prior treated opportunistic infections; this constellation of occurrences, in association with rising CD4 counts or decreasing HIV viral RNA levels, has been termed the immune reconstitution inflammatory syndrome (IRIS). A postulated molecular mechanism of IRIS invokes a treatment-induced dysregulation of effector and regulatory T-cells in the process of immune recovery, leading to an imbalance of cells for particular pathogen-related antigens.2 The resulting inflammation that is observed is thought to be a manifestation of specific immune response targeted at a given pathogen.2

Systematic reviews indicate IRIS is more likely to present in individuals with lower CD4 counts at the time of initiation and may affect up to 22% of individuals started on antiretroviral treatment.3 Other potential risk factors for the development of IRIS include male sex and higher HIV viral load level at time of antiretroviral initiation.4 While any organ system may be affected by IRIS, cutaneous manifestations are seen in more than half of individuals with IRIS.5-8 Frequently encountered skin findings in IRIS include infectious (e.g., primary herpes simplex, herpes zoster, genital warts, molluscum contagiosum, cutaneous mycobacterial infections), inflammatory (e.g. acne vulgaris, eosinophilic folliculitis), and malignant etiologies (e.g. Kaposi’s sarcoma, non-Hodgkin’s lymphoma).9 IRIS can occur de novo or unmask or exacerbate underlying condition in individuals with HIV.

Pyoderma gangrenosum is an inflammatory dermatosis characterized by sterile neutrophilic ulceration with an increased...
prevalence among individuals with underlying inflammatory conditions such as autoimmune arthritis and inflammatory bowel disease, as well as in association with hematologic malignancies. Etiopathologically, pyoderma gangrenosum is postulated to reflect disrupted innate immune regulation causing altered neutrophil chemotaxis. It is uncommonly reported in association with HIV. In this case series, we present three cases of IRIS-associated development and worsening of pyoderma gangrenosum in patients with HIV. None of the patients had any of the characteristic risk factors for pyoderma gangrenosum such as autoimmune arthritis, inflammatory bowel disease or hematologic malignancies, raising the possibility of IRIS-associated idiopathic pyoderma gangrenosum as a distinct entity.

Case Reports

Summary information regarding the three patients with pyoderma gangrenosum is presented in Table 1.

Case 1

The first patient was a 40-year-old male from India with HIV presenting with a CD4 count of 14. His comorbidities included diabetes mellitus and dyslipidemia. He was initiated with triple antiretroviral treatment with a regimen consisting of tenofovir, emtricitabine, and efavirenz. Twelve weeks after initiating antiretrovirals, he developed extensive vegetative, ulcerating lesions over the penis (Figure 1 A, B). The ulcers were refractory to treatment with systemic antibiotics including clofazimine and minocycline. Biopsies of the ulceration demonstrated dense mixed infiltration of the epidermis and follicular structures with neutrophils and eosinophils (Figure 1C). The dermis also demonstrated dense mixed infiltrate comprising neutrophils, eosinophils, lymphocytes, and plasma cells (Figure 1D). There was no histologic or microbiologic evidence for vegetative herpes simplex. No evidence of microorganisms was detected, and a diagnosis of vegetative pyoderma gangrenosum was made. Additional treatments tried for the ulceration included thalidomide and clindamycin. The ulcer demonstrated 90% healing with this regimen after 6 weeks. At follow-up, after sudden discontinuation of treatment one year after presentation, the lesions recurred and were again responsive to treatment re-initiation.

Case 2

The second patient was a 46-year-old Indian male with HIV with a CD4 count of 171 at the time of diagnosis. His medical
comorbidities included chronic alcoholism. He was started on an antiretroviral regimen of zidovudine, lamivudine, and nevirapine. Thirty-three months after starting antiretrovirals, he developed a non-infected superficial ulcer of the buttocks (Figure 2A). The ulcer did not respond to treatment with topical antibiotics and new ulcerations developed. A trial of systemic steroids was also ineffective. Biopsy demonstrated ulcerated squamous epithelium with a dermal perivascular mixed infiltrate, predominantly neutrophilic. GMS and PAS stains did not reveal any fungal or parasitic organisms. The patient was started on treatment with dapsone, clofazimine, and topical tacrolimus with some initial benefit to the perianal lesion (Figure 2B). However, the patient has had multiple recurrences at other body sites in spite of treatment continuation (Figure 2 C, D).

**Patient 3**

The third patient was a 40-year-old HIV+ African American female who had been initially diagnosed with AIDS several years ago but had discontinued antiretroviral treatment. She re-presented for medical attention with CD4 count of 30. She was initiated on an antiretroviral regimen consisting of ritonavir, darunavir, enfuvirtide, and lamivudine. Within weeks of initiation, she developed a 5-cm ulceration with violaceous undermined borders on her right breast (Figure 3 A). Initial wound swabs grew *Streptococcus viridans*, and she was placed on systemic antistreptococcal antibiotics without improvement. Skin biopsies performed of the ulcer were suggestive of pyoderma gangrenosum. Two separate tissue cultures were negative for bacterial, fungal, and atypical mycobacterial organisms. She was started on systemic cyclosporine to which she responded with some healing of the ulcer, but also experienced the development of several subcutaneous nodules which were also ruled out for infectious etiologies. She developed nephrotoxicity secondary to the cyclosporine and was switched to treatment with dapsone and minocycline – in concert with her antiretrovirals which resulted in stabilization of her ulcer (Figure 3B).

**Discussion**

This case series highlights the rare occurrence of pyoderma gangrenosum as a manifestation of IRIS in three patients with HIV. Pyoderma gangrenosum is an inflammatory dermatosis marked by dense infiltration of neutrophils (hence, pyoderma) in the absence of infectious organisms. Pyoderma gangrenosum has been seen in frequent association with underlying systemic illness, including inflammatory bowel diseases and hematologic malignancies. Clinical variants of pyoderma gangrenosum include...
ulcerative, pustular, bullous, and vegetative types, all of which demonstrate neutrophilic infiltrates on histopathology.\textsuperscript{13}

An important differential diagnosis for pyoderma gangrenosum, given its clinical appearance, is frank infection. Biopsy for both histopathology and tissue cultures must be performed to exclude an infectious etiology when pyoderma gangrenosum is suspected. Other differential diagnoses may include cutaneous vasculitis, vasculopathy, or skin neoplasms, depending on the clinical presentation. In individuals with HIV initiated on antiretrovirals who develop suppurative ulceration, infection must be excluded given the individuals' immunocompromised status as well as the common infectious etiologies that may present as components of IRIS reactions. Pyoderma gangrenosum has been previously reported in association with HIV, but the specific etiopathogenic role that the reconstitution of the immune system which occurs during IRIS plays in the development of pyoderma gangrenosum is an area for further investigation. There are currently no reliable molecular markers for the diagnosis of pyoderma gangrenosum.

The management of pyoderma gangrenosum should first involve the treatment of any underlying systemic comorbidity, followed by treatment directed at the cutaneous manifestations with either topical, intralesional, or systemic medications. Local treatments, including appropriate wound care, are a cornerstone of pyoderma gangrenosum management and crucial to prevent secondary infectious colonization and infection. Topical or intralesional immunosuppressive medications, including corticosteroids, calcineurin inhibitors, and antibiotics have been used with varying success in the treatment of pyoderma gangrenosum. Systemic immunosuppression with corticosteroids, dapsone, azathioprine, and several biologic agents has been tried with varying success in patients refractory to local treatments. Treatment of pyoderma gangrenosum in the context of HIV presents a special therapeutic challenge, given the balance between immune reconstitution and medical immunosuppression. In all three patients, clinical improvement was noted with some form of immunomodulatory therapy in contrast to immunosuppression, raising consideration for a protective inflammatory role in keeping pyoderma gangrenosum controlled.

While mild or superficial pyoderma gangrenosum will often respond to treatment with corticosteroids alone, the deep ulcerations as seen in our patients often require a multiagent immunosuppressive or immunomodulatory approach.\textsuperscript{11} The slow healing of deep ulcerations in response to immunosuppressive or immunomodulatory treatment, as seen in Case 3, are in keeping with the clinical history of pyoderma gangrenosum. The chronic relapsing course with development of new lesions, as seen in Case 2, is not uncommon for patients with pyoderma gangrenosum as well.

In our patients with HIV, treatment of their underlying immunocompromised condition with antiretrovirals and the resulting IRIS may have paradoxically led to the development or worsening of pyoderma gangrenosum. Other inflammatory conditions such as sarcoidosis have been noted to flare in association with IRIS, at times even greater than 1 year after antiviral initiation.\textsuperscript{14} As one of our patients presented here developed pyoderma gangrenosum more than two years after antiretroviral initiation, the timeline is still in keeping with other reported IRIS-associated worsening of inflammatory disease. Pyoderma gangrenosum is a diagnosis of exclusion which may be seen in the setting of other underlying systemic diseases such as hematologic malignancies or inflammatory bowel disease. None of the patients presented in this report demonstrated any history or physical findings suggestive of these conditions, and as such invasive diagnostic procedures such as bone marrow biopsies or endoscopies were not performed in the absence of such findings.

Initiation of antiretrovirals targeting the HIV virus results in several changes within the immune system; most notable is the restoration of CD4+ T-lymphocyte counts and function. However, antiretroviral therapy has also been noted to impact neutrophil numbers and function as well. The incidence of neutropenia in individuals with HIV is estimated to be as high as 44% based on large population studies.\textsuperscript{13} Neutrophil function is also markedly reduced in advanced HIV.\textsuperscript{15} The start of antiretroviral therapy has been demonstrated to increase neutrophil counts, as well as result in enhanced neutrophil chemotaxis and antimicrobial activity.\textsuperscript{13,16} The exact mechanism of such neutrophil enhancement by antiretrovirals remains to be fully elucidated. In our patients, this neutrophil activation may have served to catalyze the development of pyoderma gangrenosum as a manifestation of IRIS.

These cases raise several important lessons for dermatologists and other clinicians caring for patients with HIV who develop cutaneous ulceration. First and foremost, in addition to raising awareness of IRIS-associated idiopathic pyoderma gangrenosum, we hope to stress the importance of ruling out infectious etiologies in patients with HIV. As pyoderma gangrenosum does have the potential to exhibit pathergy, we would caution against vigorous surgical debridement, as this has the potential to worsen the disease.
Immunosuppressive medications in patients with HIV may present particular challenges, both from the basic immune physiology as well as in the form of drug-drug interactions or side effects (such as the impact of cyclosporine on renal failure in individuals on antiretroviral medications, seen in Case 3). Antibiotic agents used for their inflammatory properties, such as minocycline, may have a useful therapeutic role here, as seen in our series of patients. Finally, immunomodulatory drugs that have been explored for the treatment of pyoderma gangrenosum such as anti-TNF biologic agents may not be as readily available or easily dispensed globally in areas with high prevalence of HIV (such as in India and sub-Saharan Africa) and the prevalence of significant infectious diseases such as tuberculosis and hepatitis B may limit their utility in such settings. Future work dedicated to better understanding the molecular mechanisms underlying our observation is necessary to fully characterize this rare occurrence and shed light on future diagnostic and therapeutic options for pyoderma gangrenosum presenting as a manifestation of HIV associated IRIS.

References