Tropical regions, including sub-Saharan Africa, the Caribbean, Latin America, India, and Southeast Asia, account for more than 80% of human immunodeficiency (HIV) infections around the globe. The intersection of the HIV pandemic and tropical infectious diseases is inevitable; however, the lack of sophisticated medical infrastructure and diagnostic techniques, along with underreporting from these regions, has limited the understanding of how the epidemiology and clinical course of tropical infections is affected by coinfection with HIV, and much of the existing literature describes cases noted in immigrants to the developed world. As access to highly active antiretroviral therapy (HAART) in tropical regions increases, so does the understanding of its effect on persons coinfected with HIV and tropical infections.

The immune reconstitution inflammatory syndrome (IRIS), also known as immune restoration disease or immune reconstitution syndrome, is a well-documented but poorly understood phenomenon. IRIS occurs in the setting of HAART-induced immune restoration and is best described as a deregulated immunologic response to a previously existing pathogen or antigen, which then causes new or worsening clinical disease. In other words, as the HIV patient’s immune system improves under HAART, it reacts to existing but clinically quiescent pathogens and immunologically ignored antigens in unexpected ways. IRIS typically occurs in the initial weeks or months after starting HAART and subsequent immune reconstitution. There are 2 principal types of IRIS that occur: unmasking IRIS, in which a previously unrecognized infection becomes clinically apparent as immune reconstitution occurs, and paradoxical IRIS, which causes clinical deterioration of a previously recognized and sometimes treated infection. IRIS lacks a clear case definition, and diagnostic biomarkers have remained elusive. The only reliable predictors of IRIS risk are a low CD4^+ nadir and preexisting opportunistic infection. Shelburne and colleagues proposed the following clinical criteria for IRIS: “(1) HIV infection, (2) receiving HAART, (3) decrease in HIV-1 RNA viral load, (4) increase in the level of CD4^+ cells from baseline, and (5) clinical symptoms consistent with an inflammatory process whose clinical course is not consistent with the expected progression of a previously diagnosed opportunistic infection, expected progression of a newly diagnosed opportunistic infection, or drug toxicity.” In reality, IRIS probably represents a collection of unique disorders, each with a distinct immunopathogenesis driven by the interaction of pathogen-specific immune responses and host characteristics (eg, degree of HIV-induced immunosuppression and immunodysregulation, host genetics,
and possibly the inflammatory milieu created by coinfection with other pathogens.\textsuperscript{5} IRIS may be simply a symptomatic inconvenience for a patient or may cause significant morbidity and mortality, affecting vital organs with excessive inflammation (eg, cytomegalovirus retinitis or cryptococcal meningitis). Distinguishing IRIS from opportunistic disease caused by persistent immunodeficiency, treatment failure, or adverse drug reaction presents significant diagnostic and therapeutic challenges.

The emergence of the HIV/AIDS pandemic in the tropical developing world and the subsequent rollout of HAART in these regions have led to numerous reports of IRIS occurring in association with tropical infections. The factors known to predispose to IRIS, such as very low CD4\textsuperscript{+} cell count before initiation of antiretroviral therapy and preexisting opportunistic infection, are far more likely to be encountered in these regions. Although most articles focus on IRIS caused by leprosy and leishmaniasis, IRIS has also been reported with helminthic infections (eg, schistosomiasis, strongyloidiasis) and fungal infections (eg, histoplasmosis, sporotrichosis, and penicilliosis), and many of these infections have cutaneous manifestations. With the massive burden of HIV infection in the tropical world, it is reasonable to anticipate that the range of reported tropical dermatoses with associated IRIS will continue to expand.

Relatively few IRIS events have been reported in association with parasitic helminthic infections endemic to much of the tropical world. This under-reporting may reflect underdiagnosis or result from the helper T cell (T\textsubscript{H}2) 2 immunologic shift caused by advancing HIV, because T\textsubscript{H}2-type cytokines are made during an appropriate response to many parasitic infections.\textsuperscript{6}

This article focuses on dermatoses endemic to tropical regions that have been reported to precipitate cutaneous IRIS events, including leprosy, leishmaniasis, penicilliosis, sporotrichosis, and strongyloidiasis.

**LEPROSY**

Early in the HIV epidemic, HIV was speculated to lead to a significant increase in the prevalence of leprosy in endemic regions.\textsuperscript{7} Although coinfection with HIV and *Mycobacterium leprae* has been reported frequently in tropical regions, mostly in Brazil, India, and sub-Saharan Africa, the HIV epidemic does not seem to have substantially altered the epidemiology of leprosy in these regions.\textsuperscript{8–11} HIV infection does not seem to significantly increase the risk of becoming infected with *M leprae*, and HIV coinfection does not predict a worse outcome.\textsuperscript{12} Furthermore, coinfected individuals experience a similar treatment response rate as HIV-negative patients with leprosy.\textsuperscript{11}

Even in the absence of HIV infection, paradoxic reactions reminiscent of IRIS have long been observed before, during, or after multidrug therapy (MDT) for leprosy. Termined as type I reactions, a subset of individuals experience inflammation of existing leprosy lesions soon after starting antileprous therapy, usually within weeks. These reactions are thought to be caused by increased cell-mediated immunity to the *lepra* bacilli. When type I reactions occur after MDT, they are called reversal reactions. On occasion, type 1 reactions occur even in the absence of therapy and are thought to be caused by a shift in host cell-mediated immunity to the pathogen; these reactions are termed upgrading when the clinical picture shifts toward the paucibacillary end of the spectrum and downgrading when the clinical picture shifts toward the multibacillary pole. Type 1 reactions present clinically with a cellulitis-like inflammation of existing lesions, sometimes with ulceration or necrosis, and can cause significant morbidity because of inflammatory nerve damage. When type 1 reactions occur, they are typically treated with prednisone or other immunosuppressive agents.\textsuperscript{13}

HIV-leprosy coinfection might be expected to increase the prevalence of multibacillary disease. Instead, HIV infection does not seem to alter the ratio of lepromatous to tuberculoid leprosy; in fact, it seems to predispose to paucibacillary rather than multibacillary disease.\textsuperscript{11,14} Even in advanced HIV infection, the histologic features of leprosy, including granuloma formation, appear to be preserved, indicating that the local cell-mediated immune response is intact.\textsuperscript{11}

Deps and Lockwood\textsuperscript{15} proposed the following case definition for leprosy IRIS: (1) leprosy and/or leprosy type 1 reaction presenting within 6 months of starting HAART, (2) advanced HIV infection, (3) low CD4\textsuperscript{+} cell count before starting HAART, and (4) increase in CD4\textsuperscript{+} cell count after starting HAART. To date, more than 30 reported cases of IRIS associated with leprosy infection have met these criteria. Most cases presented as unmasking of previously unrecognized leprosy, of which most manifested as borderline paucibacillary disease. Several reports have included descriptions of lesions that initially presented with, or later developed, symptoms clinically consistent with type I reactions, including inflammation and ulceration or necrosis of prior typical leprosy lesions; neuritis, however, seems to be rare.\textsuperscript{12,16–31} Talhari and colleagues\textsuperscript{32} reported 2 individuals who had unmasking of multibacillary disease and experienced upgrading to paucibacillary disease accompanied
by inflammation and ulceration of existing lesions. Paradoxical reactions, where a person with known leprosy developed reversal-like reactions within weeks to months of starting HAART, have been reported less frequently.25,26,30,33

Supporting the hypothesis that HAART-induced immune restoration unmasked these events, Couppié and colleagues34 determined in French Guiana the adjusted hazard ratio for a new diagnosis of leprosy in those receiving HAART for 3 months or more over HIV-infected untreated patients was 18.5 (95% CI: 1.6-217; \( P = .02 \)). Nunes Sarno and colleagues14 also found that initiation of HAART was associated with a new diagnosis of leprosy (\( P = .001 \)).

Published case reports that included outcomes consistently described clinical improvement after the initial IRIS event. In addition, patients treated with prednisone had eventual improvement of their disease without serious adverse effects.

LEISHMANIASIS

Leishmania infection in patients coinfected with HIV occurs at anywhere between 10 to 100 times the expected rate.35 In association with HAART-induced immune restoration, 3 clinical variations of leishmaniasis with cutaneous findings have been reported: diffuse mucocutaneous leishmaniasis, post- or para-kala-azar dermal leishmaniasis (PKDL), and sporotrichoid dermal and subcutaneous nodules. Both unmasking and paradoxical reactions are reported. Diffuse mucocutaneous leishmaniasis, an unusual clinical variant of New World disease that typically occurs in anergic individuals, has been described in 3 cases in patients from Brazil and one in a Nicaraguan immigrant to the United States.36–38 From the Old World, 7 cases of leishmanial IRIS events have been reported presenting as PKDL.39–44 In addition, 1 case of paradoxical clinical deterioration of sporotrichoid nodules caused by Leishmania major was reported in a Senegalese immigrant to France.45

PENICILLIOSIS

Penicillium marneffei is a dimorphic environmental fungus that causes infection almost exclusively in northern Thailand and adjacent areas of Southeast Asia. Disseminated infection often presents as multiple crusted molluscum contagiosum-like papules in the skin. To date, three cases of Penicillium marneffei associated IRIS have been reported. Gupta and colleagues46 reported an HIV-infected patient in India, without cutaneous disease, who developed new lymphadenopathy shortly after starting HAART; \( P \) marneffei was isolated from a lymph node aspirate. Saikia and colleagues47 reported another Indian patient with HIV who developed widespread molluscum-like lesions on the face, extremities, and scrotum; culture from his skin and blood grew \( P \) marneffei. Saikia and colleagues48 also reported paradoxical worsening of \( P \) marneffei skin lesions, along with development of fever, arthritis, and lymphadenopathy, in a 12 year old boy 1 month after starting HAART.

SPOROTRICHOSIS

A report from Brazil described 2 patients with cutaneous IRIS associated with Sporothrix schenckii infection. One individual had biopsy-proven, culture-positive sporotrichosis before starting HAART and initially responded to oral itraconazole. After 6 weeks on HAART, the patient experienced paradoxical deterioration with reactivation of old lesions and development of new cutaneous and mucosal lesions. The second patient had no cutaneous findings before HAART but experienced unmasking of sporotrichosis of the left hand 5 weeks into HAART; culture of lesion exudates grew \( S \) schenckii. Both patients recovered well with a combination of amphotericin B and itraconazole.49

STRONGYLOIDIASIS

One report of IRIS-associated disseminated strongyloidiasis describes an Eritrean immigrant to Italy whose infection was unmasked 2 months after initiating HAART. The patient’s symptoms included itchy skin, fever, cough, vomiting, diarrhea, epigastric pain, and eosinophilia. He improved after thiabendazole treatment.50

SUMMARY

IRIS occurs frequently in association with some tropical infections, and clinicians who treat HIV-infected individuals from tropical regions should be aware of the possibility of IRIS after starting HAART. This awareness helps the clinician from mistakenly attributing IRIS-associated signs and symptoms to treatment failure or an adverse drug reaction. More data are needed to understand the etiopathogenesis of IRIS associated with tropical dermatoses and optimize diagnosis and treatment of IRIS symptoms.

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