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ID TEACHING CASES

Disseminated Skin Lesions in a Patient Living With Human Immunodeficiency Virus

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A 33-year-old man with human immunodeficiency virus (HIV) diagnosed 6 months ago (nadir CD4 count of 23 cells/μL, current CD4 count of 31 cells/μL) presented to the outpatient clinic with a 2-month history of subjective fevers and disseminated skin lesions. He was started on tenofovir, emtricitabine, efavirenz, trimethoprim-sulfamethoxazole, and azithromycin at the time of his HIV diagnosis. However, the patient only took his medications for 1 month and then was lost to follow up. Five months after his HIV diagnosis, he developed several erythematous-violaceous maculopapular skin lesions on upper extremities. Over 2–3 weeks, new lesions appeared over the trunk, lower extremities, and face. The lesions were painless and not pruritic. He denied any history of a similar illness/rash. He was born in Paraguay and worked as a cashier in Asuncion. He denied sick contacts, domestic or international travel, pets, illicit drug use, or allergies to medications. His family history was noncontributory. The patient was sexually active with his wife and reported a mutually monogamous relationship. On exam, the patient had vital signs within normal range and appeared well nourished. Multiple erythematous-violaceous maculopapular lesions (3–7 mm in diameter) were present on extremities, trunk, and face but sparing mucosal surfaces, soles, and palms (Figure 1*A*–*C*). The spleen was firm and palpable to 6 centimeters below the costal margin, and the rest of the exam was unremarkable.

Laboratory studies revealed a white blood cell count of 2180 cells/mL (72% neutrophils, reference range 40–70), platelets 121 000 cubic/millimeter (reference range, 150 000–400 000), hematocrit was 26.9% (reference range, 41–53 in men), HIV viral load was 610 022 copies/mL. Serum venereal disease research laboratory, *Trypanosoma cruzi* immunoglobulin (Ig)G, hepatitis B sAg/sAb/cAb, hepatitis C IgG, and bacterial blood cultures were negative. *Toxoplasma gondii* IgG and cytomegalovirus IgG were positive. A chest radiograph was normal, and ultrasound showed moderate splenomegaly and mild hepatomegaly. A scrape of the skin lesion on the left arm was obtained (Figure 2*A*) and a bone marrow biopsy was performed (Figure 2*B*); both specimens were sent for histopathological evaluation. We obtained written consent from the patient.

WHAT IS YOUR DIAGNOSIS?

Diagnosis

Visceral leishmaniasis with cutaneous dissemination, caused by *Leishmania infantum*.

The differential diagnosis of disseminated erythematous-violaceous skin lesions in a patient with HIV infection with low CD4 count is broad and includes infectious and noninfectious causes. Histoplasmosis, paracoccidioidomycosis, secondary syphilis, leishmaniasis, bacillary hemangiomatosis, and malignant processes such as Kaposi's sarcoma were on the differential diagnosis given the appearance of the rash and laboratory and abdominal imaging findings. The histopathological examination of the skin tissue with Giemsa stain revealed amastigotes suggestive of *Leishmania* spp bone marrow pathology demonstrated macrophages containing multiple *Leishmania* amastigotes. The recombinant kinesin antigen (rK39) for visceral leishmaniasis was positive. Polymerase chain reaction (PCR) of skin tissue identified *L infantum*. The patient received a 28-day course of amphotericin B deoxycholate 0.75 mg/kg per day followed by amphotericin B deoxycholate 0.75 mg/kg every 21 days for approximately 7 months when his repeat CD4 count was 223 cells/μL. Human immunodeficiency virus-antiviral therapy was restarted. Clinical improvement began 4 weeks after anti-leishmania and antiviral therapies, although several lesions became desquamative with no full resolution. The patient did not experience disease relapse during the subsequent 15 months after discontinuing secondary prophylaxis.

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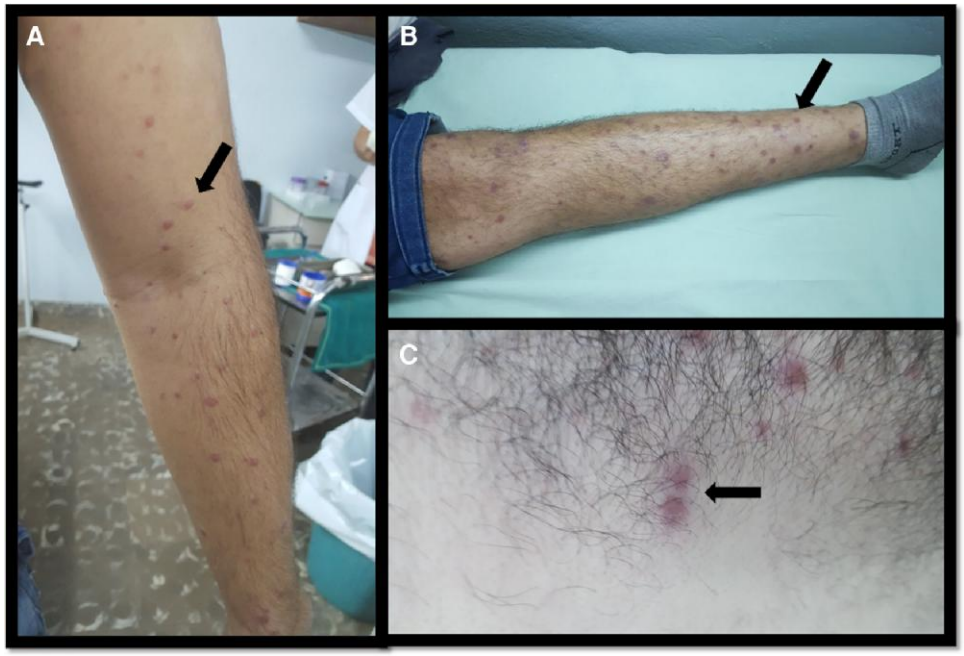

Figure 1. Physical exam showing disseminated erythematous-violaceous maculopapular lesions (black arrows) on the upper extremities (*A*), lower extremities (*B*), and trunk (*C*).

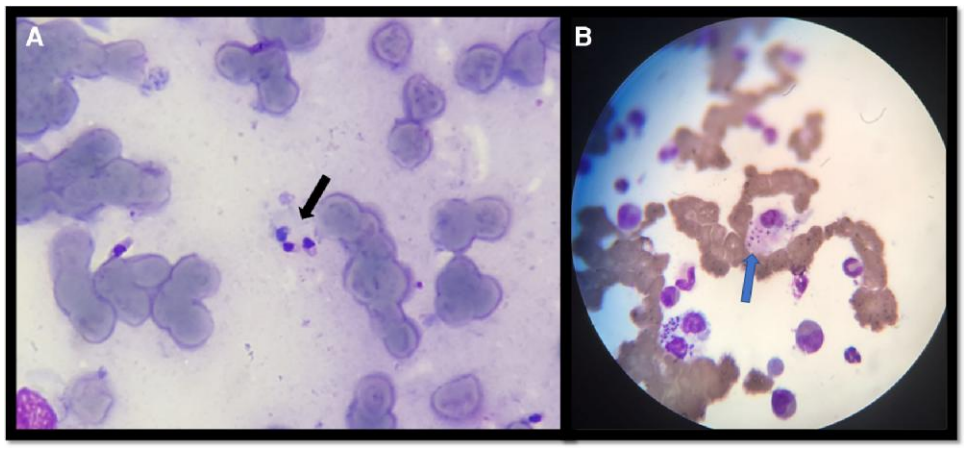

Figure 2. Histopathology of skin tissue scraping of an upper extremity lesion showing oval structures that have a nucleus, kinetoplasm, and cytoplasm compatible with amastigotes (*A*, black arrow), and bone marrow biopsy demonstrating amastigotes present in the cytoplasm of macrophages (*B*, blue arrow). Both specimens were stained with Giemsa.

Leishmaniasis is a vector-borne disease caused by an intracellular parasite of the genus *Leishmania*, endemic in tropical/subtropical regions [1]. Sandfly species transmit the infection to a mammalian reservoir host. More than 20 *Leishmania* species have been linked to human infection, and specific organisms are frequently associated with characteristic clinical features [2]. Our patient was diagnosed with *L infantum (synonym of Leishmania chagasi)*, the primary cause of visceral leishmaniasis in South America, including in Paraguay [3]. In this geographic region, the infection is transmitted by the hematophagous phlebotomine sandflies of *Lutzomyia* spp [4]. Although many leishmania infections remain asymptomatic, HIV coinfection increases the risk of progression to symptomatic disease [5, 6].

The clinical manifestations leishmaniasis vary according to the specific *Leishmania* spp and geographic location and range from subclinical infection, cutaneous (cutaneous leishmaniasis), mucocutaneous (mucocutaneous leishmaniasis), and

systemic multiorgan disease (visceral leishmaniasis) [7]. Similar to immunocompetent hosts, patients with HIV coinfected with visceral leishmaniasis may develop fever, malaise, weight loss, splenomegaly, hepatomegaly, over weeks to months (also known as kala-azar syndrome) [6, 8, 9]. In profoundly immunosuppressed patients (HIV infection with CD4 <50 cells/μL), atypical manifestations affecting lung, pleura, peritoneum, and gastrointestinal tract are reported [6, 9]. Unlike immunocompetent populations, patients with HIV infected with visceral leishmaniasis can present with cutaneous dissemination. Patients can also develop cutaneous manifestations during or after treatment of visceral leishmaniasis (post-kala-azar dermal leishmaniasis); most of these cases occur in East Africa and the Indian subcontinent [10]. Skin lesions can have various forms ranging from scant to multiple pigmented maculopapular rash, desquamative lesions, or nodules [11]. Cutaneous manifestations of visceral leishmaniasis can mimic Kaposi's sarcoma and other opportunistic infections [11, 12]. In patients with visceral leishmaniasis-HIV coinfection, concomitant opportunistic infections have been reported in 42%–68% of cases, highlighting the importance of ruling out additional infections [7].

The diagnosis of visceral leishmaniasis is made by visualizing parasites on smear or tissue biopsy of affected organs or parasite isolation in culture. In this patient, PCR was a useful tool for the identification of the *Leishmania* species [1]. Molecular assays are sensitive, particularly in spleen and bone marrow tissues, and peripheral blood samples of patients with a high parasite burden [13]. Serologic testing is a less invasive diagnostic tool; however, the sensitivity is less than 50% among patients coinfected with HIV [14].

Visceral leishmaniasis is fatal in almost all cases if left untreated [1]. The treatment for patients with HIV-visceral leishmaniasis coinfection varies by geographic region. Our patient received amphotericin B deoxycholate due to the high cost of the liposomal formulation in Paraguay, which is an alternative therapy in many endemic countries. In the United States, the preferred therapy is liposomal amphotericin B 2–4 mg/kg IV daily or in an interrupted schedule on days 1–5, 10, 17, 24, 31, and 38 to achieve a total cumulative dose of 20 to 60 mg/kg body weight [15]. In East Africa and Southeast Asia, the World Health Organization recommends combination therapy with liposomal amphotericin B plus miltefosine based on emerging evidence from clinical trials [16–18]. In addition to anti-leishmania treatment, antiretrovirals should be initiated or optimized without delay. Until effective immune reconstitution, secondary prophylaxis with antiparasitic therapy could be considered to prevent disease relapse; the optimal regimen remains uncertain [19]. In the United States, experts suggest liposomal amphotericin B 4 mg/kg intravenously every 3–4 weeks until the CD4 count is >200 to 350 cells/μL [15]. However, others suggest that prophylaxis should be continued indefinitely due to visceral leishmaniasis relapses even with a CD4 count of 350 cells/μL [15]. There are documented cases of leishmaniasis-associated immune reconstitution inflammatory syndrome in patients infected with HIV after initiation of antiretroviral therapy [20]. Although patients with visceral leishmaniasis-HIV coinfection may respond poorly to therapy, our patient had a favorable and sustained response to the treatment. It is unclear whether the positive outcome in our patient was due to a less virulent *L infantum* variant, an isolate with high susceptibility to amphotericin B, or genetic and environmental factors [7].

Visceral leishmaniasis should be considered in the differential diagnosis of immunocompromised patients presenting with skin lesions from endemic areas. Healthcare providers should be familiar with the clinical features of visceral leishmaniasis because atypical cutaneous manifestations can mimic opportunistic infections found in patients coinfected with HIV. Clinical suspicion is essential for early diagnosis and prompt therapy because visceral leishmaniasis is usually fatal if left untreated.

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