CLINICAL VIGNETTE

Painless Ulcer in a Traveler

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Case

A 25-year-old female from Los Angeles traveled to Peru for a field trip. During the field trip, she recalls getting bitten by bugs. A month after returning from the trip, she noticed a small papule on her right forearm. Over several weeks, the papule enlarged into a painless ulcerated plaque. She tried and failed Neosporin, as well as two courses of oral antibiotics, before presenting to Dermatology for evaluation. On the exam, there was a one centimeter ulcer with an erythematous firm border on the patient's right forearm. A punch biopsy was performed and H&E showed epidermal ulceration and dermal mixed inflammation with granulomas. The histologic features were highly suspicious for an infectious etiology but special stains failed to reveal infectious organisms. Given the clinical presentation of the lesion and her travel history, leishmaniasis was suspected. Patient returned for another punch biopsy, which was sent to the Center for Disease Control. Polymerase chain reaction of the specimen revealed *L.V. braziliensis*. She was referred to Ear Nose and Throat for examination of nasal mucosal passage, which appeared normal. Patient was referred to Infectious Disease for management. She was initially treated with miltefosine and topical paromomycin without much improvement, before starting intravenous amphotericin. The ulcer began to heal after three infusions of intravenous amphotericin. She was monitored over the next 12 months for relapse.

Discussion

Leishmaniasis is caused by protozoa belonging to the genus *Leishmania*. It is transmitted by sandflies. Leishmaniasis causes a spectrum of diseases ranging from localized cutaneous leishmaniasis to visceral leishmaniasis, which is a systemic multiorgan disease that can lead to death. The incubation period for cutaneous leishmaniasis ranges from weeks to months, while the incubation period for mucosal leishmaniasis may be on the order of years.[1-3]

Our patient presented with a case of localized cutaneous leishmaniasis, which tends to occur on exposed areas of skin after sandfly bites. Localized cutaneous leishmaniasis begins as a pink papule that slowly enlarges into a painless ulcer with an indurated border. Small satellite lesions may develop outside of the ulcer. Lesions can also spread along the draining lymphatics and present as subcutaneous nodules proximally along the lymphatic chain.[4] Our patient was infected with *L.V. braziliensis*, which can cause mucosal leishmaniasis. Mucosal leishmaniasis can present as nasal stuffiness, mucosal bleeding, increased secretions and sloughing of dead tissue. Erosion of the mucosal surface can occur, mostly commonly in the nose, mouth, or nasal septum. Mucosal leishmaniasis can result in significant deformity due to destruction of nasal cartilage and surrounding tissues.[5,6]

The differential for cutaneous leishmaniasis includes other infectious etiologies. Cutaneous leishmaniasis lesions are usually painless, occur in exposed locations where the sandflies bite, and frequently occur in clusters. The ulcers of cutaneous leishmaniasis usually have well-defined indurated borders. Patients usually live or have recently traveled to endemic areas.

Leishmaniasis can be diagnosed using histology, culture, or molecular analysis using polymerase chain reaction (PCR). A full-thickness punch biopsy should be performed at the raised border of an ulcerative lesion. On histopathology, macrophages can be observed containing multiple leishmania amastigotes. Each amastigote has a nucleus and rod-shaped kinetoplast. Visualization of the kinetoplast is essential for diagnosis. In our patient, amastigotes were not visualized on the initial biopsy. Therefore, diagnosis via PCR was key. PCR is one of the most sensitive diagnostic tests for cutaneous leishmaniasis.[7] Another benefit of using PCR is that it can determine the leishmania species causing the lesions. This information may influence treatment.

Treatment of leishmaniasis is determined by the leishmania species as well as whether the infection is considered uncomplicated or complicated cutaneous leishmaniasis.[8] Features of uncomplicated cutaneous leishmaniasis include: infection with species not likely to cause mucosal leishmaniasis, no mucosal involvement, single lesion or few lesions, small lesion size, and immunocompetent host. Features of complicated leishmaniasis include: infection with species that can cause mucosal leishmaniasis, more than four lesions greater than one centimeter, individual lesions greater than five centimeters, subcutaneous nodules, regional lymphadenopathy, lesions on face/fingers/toes/genitalia, immunosuppressed host, and clinical failure of local therapy.

Treatments of leishmaniasis can be divided into local therapy and systemic therapy. Local therapy such as cryotherapy, thermostherapy, and topical paromomycin can be used for patients with uncomplicated cutaneous leishmaniasis. Systemic therapy is indicated for patients with complicated cutaneous

leishmaniasis. Since our patient was infected with a leishmania species that can cause mucosal involvement and she failed local therapy with topical paromomycin, systemic therapy was initiated using miltefosine and amphotericin.

Our patient was initially treated with miltefosine, which is approved by the US Food and Drug Administration for treatment of cutaneous leishmaniasis. Miltefosine kills leishmaniasis by affecting its membrane and by inhibiting Akt, which is part of lipid-dependent cell signaling pathways.[9] Miltefosine is effective for several species of leishmania, though efficacy can depend on the region. For *L.V. braziliensis*, which infected our patient, miltefosine is most effective for this species in Bolivia (70 to 88 percent) and Brazil (75 percent).[10,11] Side effects of miltefosine include nausea, vomiting, diarrhea, and elevated serum transaminases/creatinine.

When our patient failed miltefosine, she started liposomal amphotericin B. Amphotericin B kills leishmania by making its membrane more permeable.[12] Liposomal amphotericin B has a couple of advantages over amphotericin B deoxycholate: liposomal amphotericin B is less nephrotoxic and achieves higher efficacy by delivering the drug to macrophages, which is where the parasite is concentrated. Side effects of amphotericin B include nephrotoxicity, hypokalemia, anemia, peripheral vein phlebitis, and fever. One case series of 34 patients infected with *L.V. braziliensis* and treated with liposomal amphotericin B, healing was observed in 33 or 97%.[13]

In summary, leishmaniasis is caused by a protozoa and transmitted via sandflies. While it affects many people in endemic regions of Africa, Asia, and Latin America, it is relatively rare in the United States. However, with increased global travels, clinicians should suspect leishmaniasis if a patient presents with painless ulcerated plaques on exposed areas of skin and has traveled to an endemic region.

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