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BRIEF REPORT

Mucocutaneous Leishmaniasis in a Pregnant Immigrant

Neima Briggs,[1] Brian M. Wei,[2] Chaarushi Ahuja,[2] Catherine Baker,[3] Carlo Foppiano Palacios,[1] Emily Lee,[2] Niamh O'Grady,[4] Santhi Singanamala,[1] Katelyn Singh,[2] Thilinie D. Bandaranayake,[1] Jeffrey M. Cohen,[3] William Damsky,[3,5] Matthew W. Davis,[4] Rojelio Mejia,[6] Caroline A. Nelson,[3] Jeffrey E. Topal,[1] and Marwan M. Azar[1,7]

[1]Section of Infectious Diseases, Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut, USA, [2]Department of Obstetrics and Gynecology, Yale School of Medicine, New Haven, Connecticut, USA, [3]Department of Dermatology, Yale School of Medicine, New Haven, Connecticut, USA, [4]Department of Pharmacy Services, Yale New Haven Hospital, New Haven, Connecticut, USA, [5]Department of Pathology, Yale School of Medicine, New Haven, Connecticut, USA, [6]Department of Pediatrics, National School of Tropical Medicine, Baylor College of Medicine, Houston, Texas, USA, and [7]Department of Laboratory Medicine, Yale School of Medicine, New Haven, Connecticut, USA

Cutaneous leishmaniasis is a parasitic infection that causes significant maternal morbidity, and even fetal mortality, during pregnancy, yet there are limited therapeutic options. Here, we report a case of leishmaniasis in a pregnant immigrant with exuberant mucocutaneous lesions with favorable response to liposomal amphotericin B.

Keywords. amphotericin B; cutaneous leishmaniasis; host-parasite interactions; mucosal leishmaniasis; pregnancy.

Leishmaniasis is a neglected tropical disease caused by an obligate protozoan parasite that infects >12 million people worldwide. There are >20 species of *Leishmania*, endemic to at least 90 countries across Asia, Africa, Europe, and the Americas [1]. In humans, leishmaniasis manifests as 1 of 3 subtypes: cutaneous, mucosal or mucocutaneous, or visceral disease. Cutaneous leishmaniasis (CL) is the most common and usually presents as localized cutaneous leishmaniasis (LCL). CL may also present as mucocutaneous leishmaniasis (MCL) when mucosal membranes are involved either as a concomitant presentation of cutaneous and mucosal lesions, mucosal lesions following remission of cutaneous lesion, or cutaneous lesions with direct mucosal invasion [2, 3].

Historically, CL cases in the United States (US) have been thought to be mostly imported. While autochthonous transmission within animal reservoirs in the US has been known for decades, locally acquired cases among humans have only been recently recognized. Mcllwee and colleagues reported that 41 of 69 cases (59%) of leishmaniasis identified in Texas between 2007 and 2017 were among individuals with no foreign travel [4]. In 2015, the World Health Organization (WHO) listed the US as a leishmaniasis-endemic country. Yet due to the lack of a federal requirement to report the disease and underrecognition by US physicians, the incidence of leishmaniasis is likely underestimated.

In the Americas, most CL cases occur in adolescent and young adults, including women of reproductive age. The maternal immune system adapts to prevent fetal rejection at the cost of host defenses, leading to increased vulnerability to many infectious agents [5]. CL during pregnancy often presents with more impressive skin lesions, possibly due to an inappropriate type 2 immune response [5, 6]. Furthermore, infection may be associated with an increased risk of adverse fetal outcomes such as preterm birth or spontaneous abortion with CL, yet there are no established systemic treatment options [5–8]. While localized treatment in pregnancy can delay disease progression and spontaneous remission of uncomplicated LCL following delivery has been reported, in complex cases such as MCL, diffuse cutaneous leishmaniasis, visceral leishmaniasis (VL), or in patients with added immunosuppression, systemic therapy should not be delayed, to prevent higher associated rates of morbidity and mortality in both mother and fetus [2, 5, 9].

Here, we report a case of MCL in a pregnant patient who emigrated from Brazil and was treated with liposomal amphotericin B (L-AMB) with a favorable response.

CASE REPORT

A 40-year-old multiparous pregnant female with no significant medical history presented at 34 weeks of gestation with 4 months of progressive skin lesions involving her right arm, nose, and forehead after recent immigration from Brazil to the US (Supplementary Figure 1), traveling primarily by foot or car with minimal prenatal care. The first skin lesion appeared during pregnancy as a plaque on her right arm soon after arriving in Tapachula, Mexico, 5 months prior to presentation. She reported pain and itching of the arm that progressed to a single, large ulcerative plaque (Figure 1*A*, middle row). Two weeks later, she developed a similar itch and pain of her nose that developed into a large exophytic plaque (Figure 1*A*, top row). Finally, 2 months before presentation, grouped papules developed along the forehead hairline (Figure 1*A*, bottom row). She entered the US 2 weeks before

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Correspondence: Neima Briggs, MD, PhD, Yale School of Medicine, PO Box 208022, New Haven, CT 06520-8022, USA (neima.briggs@yale.edu).

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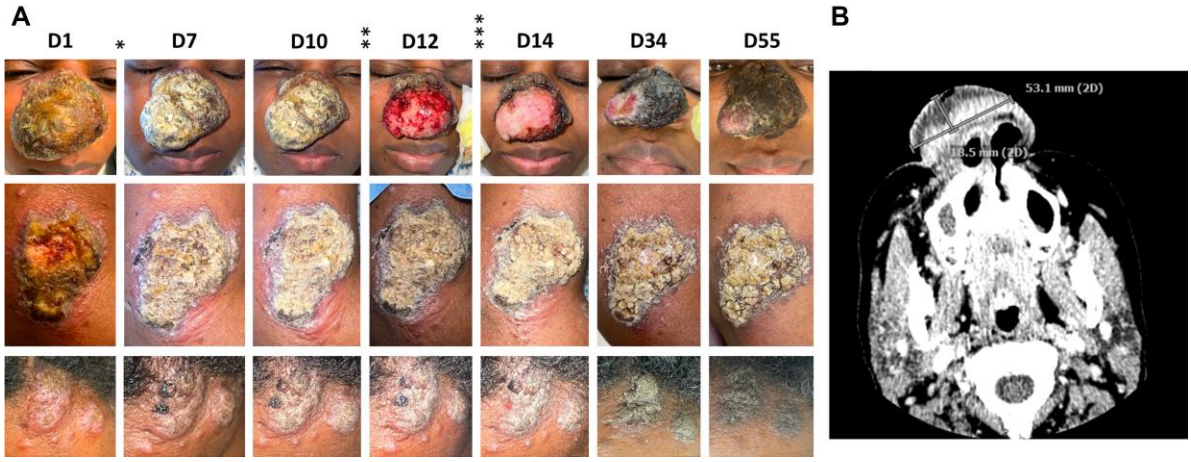

Figure 1. Time-course clinical photographs and imaging of the patient's cutaneous lesions. *A*, Clinical photographs illustrating the progression of the patient's nose lesion (top row), right arm 8 × 6 cm ulcerated vegetative plaque (middle row), and forehead lesion (bottom row). Photograph of the nose lesion shows a large, exophytic 5 × 4 cm vegetative plaque with yellow-brown crust obscuring the entirety of the nose, developing a verrucous appearance following initiation of liposomal amphotericin B treatment (*). Following debridement (**), delivery (***), and continued treatment, all 3 lesions decreased in size and developed an overlying dark brown crust with reepithelization along the borders. *B*, Computed tomographic imaging of the facial bones with intravenous contrast demonstrating a complex 5.31 × 1.85 x 4.30 cm soft tissue lesion centered at the middle-to-right nasal soft tissues without an associated drainable fluid collection or osseous erosions.

presentation, with admission to our hospital for her first detailed medical evaluation.

On admission, she was afebrile and at 34 weeks' gestation. Basic laboratory findings were unremarkable. Computed tomography of the facial bones revealed a complex 5.31 × 1.85 × 4.30 cm nasal soft tissue lesion (Figure 1*B*). An abdominal ultrasound showed no evidence of hepatomegaly or splenomegaly. On flexible fiberoptic nasopharyngolaryngoscopy, there was visualization of a necrotic mass involving the inferior third of nose with ulcerative extension into the nasal mucosa but no evidence of osseous, nasal septum, nasopharynx, or larynx involvement.

DIAGNOSIS

Histopathologic evaluation of a punch biopsy of the right elbow plaque showed a dermal infiltrate composed predominantly of lymphocytes, histiocytes, and plasma cells (Supplementary Figure 1*A* and 1*B*). Microorganisms could not be definitively identified on initial touch prep or on permanent sections, including with the use of a CD1a stain (Supplementary Figure 1*C*). A second punch biopsy from a forehead lesion showed similar histopathological findings and no microorganisms. A fresh-frozen sample of the initial biopsy was sent to the University of Washington Medical Center for polymerase chain reaction (PCR) testing and returned positive for *Leishmania* (*Viannia*) *guyanensis* species complex [*L (V) guyanensis, L (V) panamensis*, and *L (V) shawi*], confirming the diagnosis of MCL. In addition, enzyme immunoassay for leishmaniasis immunoglobulin G total was reactive (1.61, positive cutoff >1.00, Quest Diagnostics). Multiple peripheral buffy coat smears were negative for amastigotes. Workup for endemic mycoses and human immunodeficiency virus (HIV) infection was negative.

Molecular Evaluation of Skin Lesions

RNA in situ hybridization staining was performed on both biopsy samples to evaluate the expression of cytokines (Supplementary Material). Staining for *IFNG* showed diffuse strong positivity, whereas *IL4*, *IL5*, and *IL13* showed only occasional, weakly positive cells (Supplementary Figure 2*E–G*). Staining for *IL17A* and *IL17F* showed no positivity (not shown).

Treatment

The patient was initiated on liposomal amphotericin B at 5 mg/kg/day (using ideal body weight) for days 1–7 for treatment of MCL. She was planned for continued weekly outpatient infusions but was delayed until safe discharge could be met including arrangements for hospital-sponsored insurance, safe housing, pediatric supplies, and transportation for follow-up. She received 5 additional weekly infusions at a reduced dose of 4 mg/kg (using adjusted body weight), completing the treatment course (total 55 mg/kg) outpatient with progressive improvement in the skin lesions (Figure 1) and a plan for long-term follow-up for the possibility of recrudescence.

Throughout her treatment course, fetal monitoring remained reassuring. At 35 weeks and 3 days of gestation and day 8 of therapy, she progressed to preterm labor and received 12 mg of betamethasone for neonatal benefit. She had an uncomplicated preterm vaginal delivery of a healthy male infant. Treatment was otherwise well-tolerated and without

appreciated adverse events. Histopathologic examination of the placenta was negative for evidence of infection or *Leishmania* amastigotes and the neonate exhibited no signs of vertical transmission.

DISCUSSION

The *Leishmania* subgenus *Viannia*, to which *L (V) guyanensis* and *L (V) panamensis* belong, is a well-established cause of MCL, a severe disseminated manifestation of several New World *Leishmania* species [2]. There is a higher incidence of New World leishmaniasis among reproductive-age women. Pregnancy may affect the presentation and evolution of the disease and has been associated with a higher rate of disseminated lesions, mucosal disease, recurrent disease, and exophytic lesions compared to nonpregnant patients, as well as an increased risk of preterm birth or spontaneous abortion [5]. Severe presentations of New World *Leishmania* strains may be due to underlying host factors, including forms of cellular immunocompromise besides pregnancy such as HIV coinfection, as well as impaired nutritional status, parasite genetic polymorphisms, and vector saliva components [2, 10]. Furthermore, coinfection with *Leishmania* double-stranded RNA virus 1 (LRV1) is considered a risk factor for developing mucosal and metastatic lesions, although its mechanism in parasite virulence is still under investigation; in 1 study of mucocutaneous leishmaniasis in northern Brazil, >70% of cases were associated with LRV1 [10]. Compared to nonpregnant patients with CL, biopsies of lesions in pregnant patients demonstrate a slightly stronger type 2 response (mainly interleukin 4 and interleukin 10) but overall similar, robust type 1 interferon-γ production by predominately $CD4^+$ cells, as demonstrated in our patient, as well as similar number of *Leishmania*-positive cells [6]. Emerging evidence suggests that disease severity and risk for relapse go beyond a simple type 1 vs type 2 immune response and are instead related to a complex interaction of numerous immune players, including T-helper 17 cells, regulatory T cells, and even humoral immunity [10].

Despite our patient's large, exophytic lesions and significant inflammation on microscopic examination, no definitive amastigotes of *Leishmania* were visualized by hematoxylin and eosin (H&E) stain or CD1a immunohistochemistry. The sensitivity of H&E and CD1a is considerably lower for New World *Leishmania* species, including *L (V) guyanensis* species complex in which a paucity of organisms may be present despite significant tissue inflammation [11]. It is plausible that an exuberant inflammatory response akin to that seen with tuberculoid leprosy may render the parasites harder to visualize on histopathology. Ancillary stains, such as Weigert iron hematoxylin and anti-*Leishmania* (G2D10) antibody, modestly improve sensitivity (to approximately 51%) but are not routinely available [11]. PCR testing of biopsied CL lesions offers a rapid, highly sensitive, and species-specific approach to diagnosis and management. Although increasingly considered the standard of care, PCR testing is expensive and limited to a few reference laboratories [12]. The PCR testing employed in this study identified *L (V) guyanensis* as a species complex, including *L (V) panamensis*, which many consider a subspecies of *L (V) guyanensis* but does have variations in treatment guidance that need to be reconciled with the updated classification, and *L (V) shawi*, a pathogen of nonhuman mammals [2].

While amphotericin B, particularly its liposomal derivative (L-AMB), is considered safe and effective in the treatment of VL in pregnancy, and has been widely used for cutaneous and mucosal leishmaniasis in South America, this is the first published report of its use in CL in a pregnant patient [6, 13]. There is no standard dosage regimen of L-AMB for either VL in pregnancy or MCL in any host. The 2010 WHO Expert Committee on the Control of Leishmaniases suggests regimens for MCL such as L-AMB 2–3 mg/kg/day for a total dose of 40–60 mg/kg [8]. Bruschi and Gradoni provide a more detailed approach for MCL, using L-AMB at 3–4 mg/kg/day on days 1–5, 10, 17, 24, 31, and 38 for a total dose of 21–40 mg/kg [2]. Given the lack of data for MCL in pregnancy, we selected a more aggressive and extended dosing regimen due to the presence of multiple large lesions with extension into the mucosa. Fortunately, our patient had a rapid and favorable response to therapy; however, close monitoring is recommended over the next year for signs of relapse, especially with *L (V) guyanensis* [14]. Prospective studies are needed to elucidate the pathophysiologic basis of more severe presentations in pregnancy and to ascertain the efficacy and safety of L-AMB regimens for CL in pregnancy.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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