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Case Report

Cutaneous Leishmaniasis during Pregnancy, Preterm Birth, and Neonatal Death: A Case Report

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Abstract

Cutaneous leishmaniasis (CL) is an emergent public health concern, particularly in tropical and subtropical regions. Reports of pregnancy complications are scarce; however, as the endemic range of CL expands in Iran, there is concern of possible detrimental effects on fetal development amongst infected mothers through placental transmission of the parasite or enhanced maternal immune responses. We herein describe the first known case of persistent anthroponotic CL, plausibly responsible for pregnancy complications, preterm birth, and neonatal death in a healthy Iranian primigravida woman. Diagnosis was based on physical examinations of the lesions on the back of both calves of the patient and laboratory analyses including direct smear, culture, and PCR. During active CL infection, the patient gave birth to a premature female neonate who passed three days post-delivery due to immature lung development and subsequent respiratory distress syndrome. This report highlights the challenges associated with CL infection during pregnancy, exacerbation of lesions, and subsequent complications.

Introduction

Cutaneous leishmaniasis (CL) is a neglected disease and an emergent public health concern, particularly in tropical and subtropical regions, infecting an estimated one million people worldwide (1). The disease is caused by a group of protozoan parasites in the genus of *Leishmania* and is transmitted by female sand flies, *Lutzomyia* and *Phlebotomus* (Diptera: Psychodidae) in the New World and Old World, respectively (2). CL is endemic in 21 countries; however, it is disproportionately distributed around the globe with greater than 75% of cases reported from Afghanistan, Algeria, Brazil, Bolivia, Colombia, Iran, Nicaragua, Peru, Saudi Arabia, Sudan, and Syria (1).

Because of Iran's semi-arid climate and other risk factors including rapid population growth, displacement, urbanization, and anthropogenic environmental modifications among other contributing issues, CL has developed into an emergent endemic burden in 17 out of 31 provinces (Fig. 1) (3).

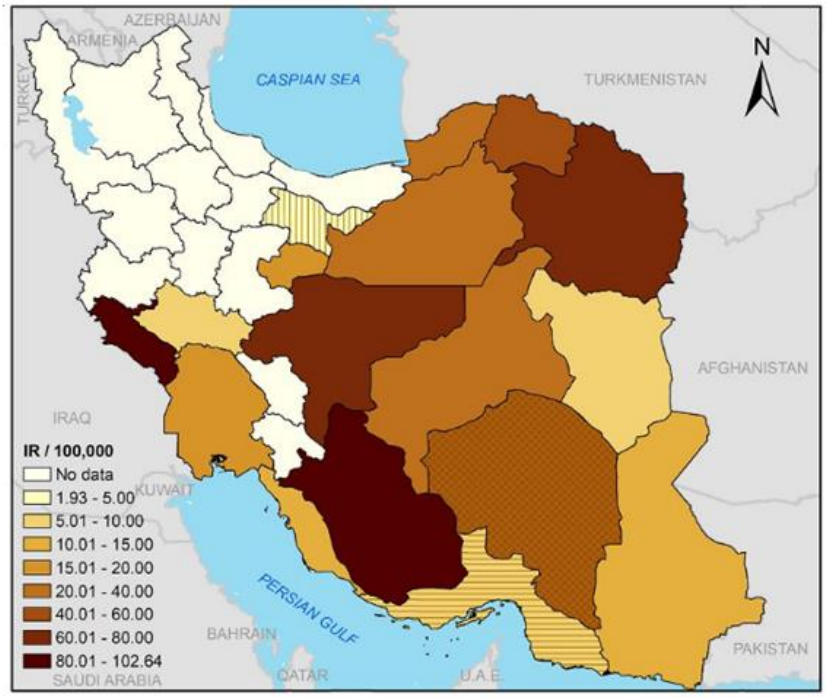

Fig. 1: Cutaneous leishmaniasis incidence rates in endemic provinces in Iran, 2013. Hormozgan Province, where the patient resided, is shown with horizontal lines, and Kerman and Tehran Provinces, where she frequently traveled to, are depicted with outlined diamonds and vertical lines, respectively (4)

In recent years, conducive environmental conditions for vector activity have resulted in sporadic CL outbreaks in various other regions of the country posing a major public health challenge. From 1986 to 2018, 615,513 CL cases have been reported with the highest annual number of cases recorded at 27,517 in 2004 and the lowest at 11,145 in 1992, respectively, with an average of 18,652 (5-7). The highest and lowest disease incidence rates (cases/100,000) were recorded at 42 and 18.6 in 1987 and 2016, respectively (5-7) (Fig. 2). However, because of misdiagnosis and inconsistent reporting guidelines, the actual number of cases is estimated to be nearly five times greater (6). More recently, 5,714 CL cases have

been reported from the country with incidence rate of 19.1 (7).

Of the two epidemiologic forms of the disease, anthroponotic cutaneous leishmaniasis (ACL) and zoonotic cutaneous leishmaniasis (ZCL), ACL is caused by *L. tropica* and vectored by *Phlebotomus sergenti* while ZCL is instigated by *L. major* and transmitted primarily by *Ph. papatasi*. Anthroponotic CL mainly circulates in humans and occasionally in dogs in major municipalities' suburbs with no known dependency on wild reservoirs (8). Conversely, ZCL is maintained in rural settings among Gerbilidae rodent reservoirs (9, 10).

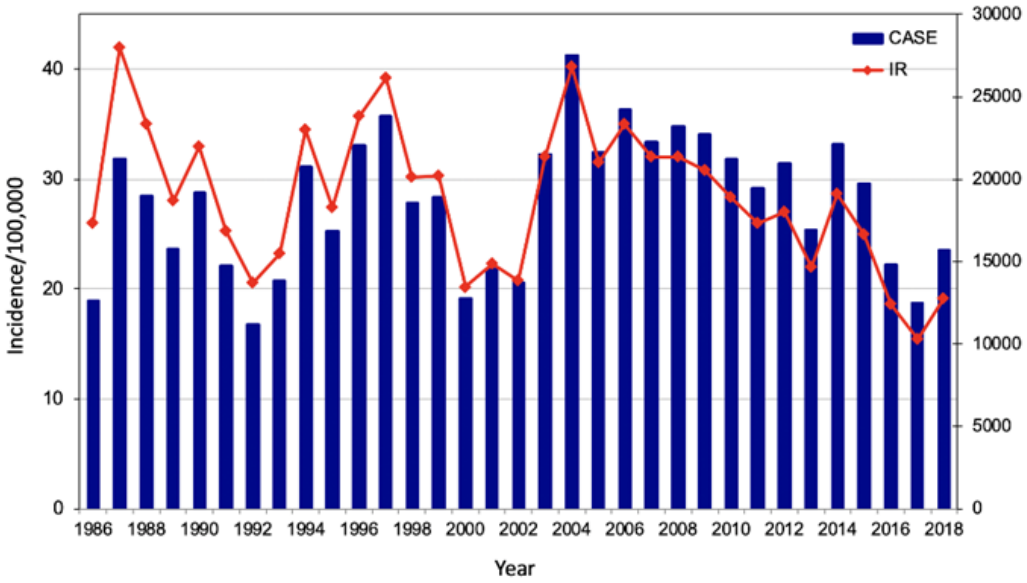

Fig. 2: Cutaneous leishmaniasis cases and incidence rates per 100,000 population in Iran, 1986-2018 (7, 10)

As the number of CL cases continues to rise, there is increasing concern of possible detrimental effects on fetal development amongst infected mothers either through placental transmission of the parasite to the fetus or through enhanced maternal immune responses. Unlike other parasitic infections such as malaria, toxoplasmosis, and trypanosomiasis with documented teratogenic effects, the impact of CL on fetuses is not clearly understood (11). Although pregnancy complications such as preterm birth following infection with CL have been reported occasionally from the New World, to the best of our knowledge such cases have not been documented in the Old World (12).

Herein, we report the first ACL case during pregnancy with subsequent complications, preterm birth, and neonatal death from Iran.

Case Report

A 29-year-old Iranian primigravida woman was referred to a dermatological clinic in the city of Bandar Abbas, Hormozgan Province, located along the Persian Gulf, Iran in 2017, for evaluation of lesions on the back of both calves. Lesions first appeared in Feb 2017 before beginning of her pregnancy in May 2017. The patient had no significant medical history, but resided in Hormozgan Province (with CL incidence rates of 5.6, 9.1, and 9.4 in 2016, 2017, and 2018, respectively) (5- 7) and frequently traveled to Kerman (incidence rates of 25.8, 23.8, and 22.2 in 2016, 2017, and 2018, respectively) and Tehran Provinces (5-7), three endemic leishmaniasis foci in Iran (Fig. 1) (6). The physical examination revealed painless dry lesions of 3x2 cm and 2x1 cm on the patient's right and left calves, respectively (Fig. 3A and

B). Laboratory tests were deferred due to concerns they may interfere with her pregnancy. Based on the clinical assumption of CL, the lesions were disinfected with sodium permanganate, and the patient was prescribed a 3-week regimen of paromomycin cream. The lesions proved unresponsive to initial treatment.

Ethics approval and informed consent

This case report was approved by Zoonoses Control Department, Center for Communicable Disease Control, Ministry of Health and Medical Education, Iran.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

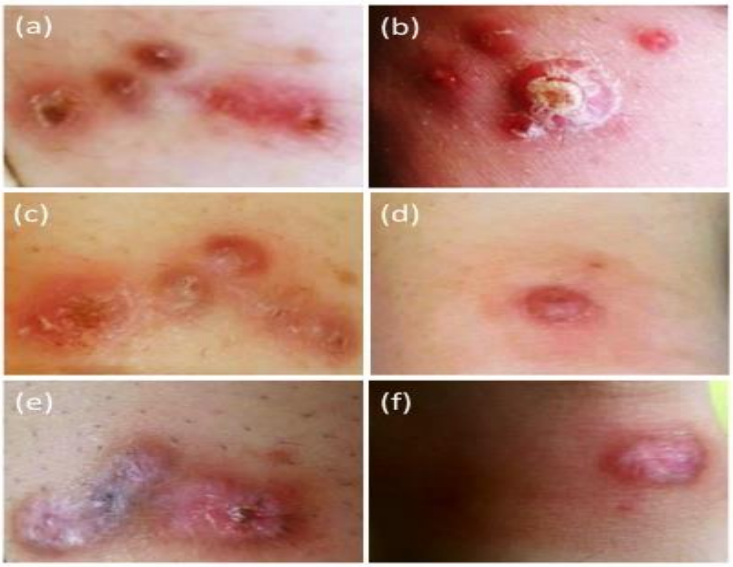

Fig. 3: Manifestation of cutaneous leishmaniasis during pregnancy (Original). "A and B", cutaneous leishmaniasis lesions on the left and right calves of a 29-year-old pregnant woman before treatment; "C and D", and "E and F" 15 and 70 d following treatment, respectively

In Oct 2017, after experiencing contractions, the patient was admitted to a local hospital in Bandar Abbas for premature labor after a 27-week-gestation. She gave birth to a premature female neonate, 850 gr birth weight, 33 cm length, with an Apgar score of 3/4. The neonate passed three days post-delivery due to immature lung development and subsequent respiratory distress syndrome.

After the neonate's death, the patient sought treatment for her lesions at a dermatology clinic in Kerman Province on Nov 30, 2017. Samples were taken for direct smear, culture, and polymerase chain reaction (PCR) analysis. Physical examination revealed new elliptic 1x1cm lesions with rough surfaces around the original bite site. Macroscopic examination revealed epidermis hyperkeratosis with papillomatosis and severe acanthosis. Skin biopsy with histopathological examination elucidated dense and diffusive lymphoplasma cell histiocytes and neutrophils that deepened around hair follicle and eccrine glands. Based on the pathological findings, the patient was diagnosed with pseudoepitheliomatous hyperplasia because of an insect bite and *Leishmania* parasite infection. She was prescribed another daily 4-week regimen of paromomycin cream.

On Dec 2017, the patient was referred to a health center in Bandar Abbas after no significant improvement in her lesions was achieved. Further diagnostic evaluations including a sec-

ond biopsy and examination of lesion secretion revealed *Leishmania* parasite activity, suggesting ineffective paromomycin cream treatment. The patient was treated with intralesional injection of meglumine antimoniate (Glucantime) once a week for 6 wk, followed by 2 wk of intralesional injection and weekly cryotherapy. Clinical examination showed regression of the cutaneous lesions after 15 d (Fig. 3C and D) and further healing after 70 d (Fig. 3E and F). A timeline of the case is presented in Fig. 4.

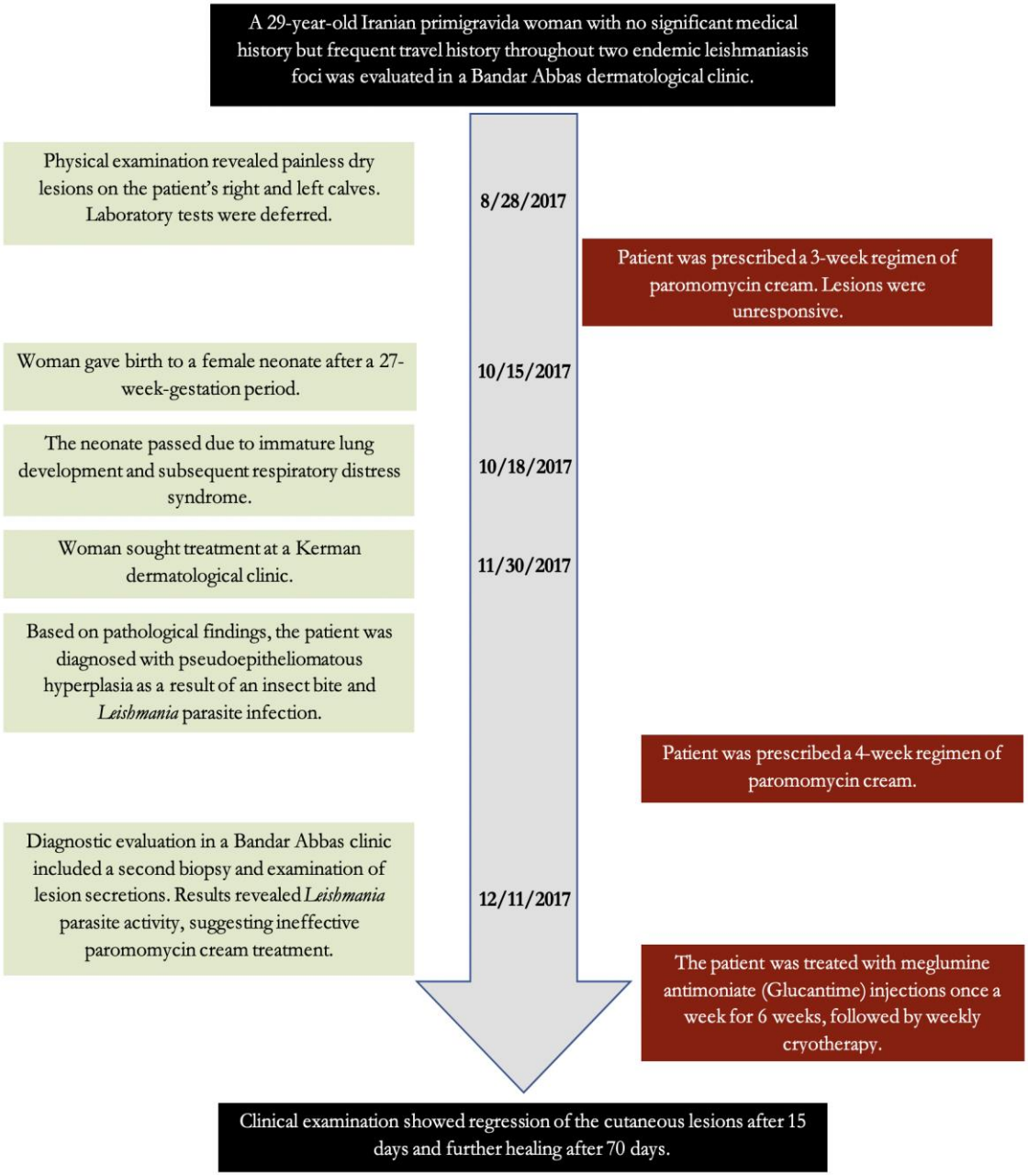

Fig. 4: Timeline of an ACL case during pregnancy with complications, preterm birth, and neonatal death from Hormozgan, Iran

Discussion

We hereby describe the first known case of persistent ACL, plausibly responsible for pregnancy complications, preterm birth, and neonatal death in a healthy 29-year-old woman with no history of contact with *Leishmania* parasites who lived and traveled in endemic areas in Iran.

Exacerbation of CL lesions during pregnancy has been reported mostly from the New World and rarely from the Old World, though maternal and infant health challenges, severity of the disease, and manifestations of the signs and symptoms have not been fully explored (12). Such complications could be due to changes in innate and adaptive maternal immune responses during pregnancy strongly related to gestation and normalize postpartum, among other factors (13).

Results of a retrospective study in a group of matching age and sex pregnant women in Bahia, Brazil indicated markedly larger CL lesions in pregnant women in comparison to nonpregnant patients. Of the 19 women with known pregnancy complications, premature deliveries occurred in 10.5% (n=2), fetal death before or during delivery in 10.5% (n=2), and normal deliveries in 79% (n=15) of the patients (12). While the aforementioned study indicates that normal deliveries make up the majority of cases, there is evidence that postpartum, infected women experience protracted recovery and lesions. In a case report, a 21-year-old pregnant woman with a history of travel to Turkey and residency for one year presented with a lesion after returning to Germany. The lesion had been present for three months and gradually enlarged in size. Clinical and laboratory examinations ruled out other infectious diseases, and histological investigations indicated dermal lymphocytic and plasma cell-rich infiltrates, accompanied by epithelioid cells and multinuclear giant cells. Giemsa staining confirmed infection with *Leishmania* spp. Following eight sessions of cryotherapy treatment, a complete clearing was achieved, and follow-up after 6 months showed only residual postinflammatory hyperpigmentation (14). Although clinical examination of the patient in our case report study showed regression of the lesions, changes and further healing only occurred several months after preterm birth.

Vertical transmission of CL species with adverse fetal effects has rarely been reported in humans; however, recent evidence suggests that it may occur in animal models. In a laboratory study, infecting hamsters with *L. panamensis* during the first week of pregnancy resulted in infection of 24 of 93 (25.8%) offspring, as verified by PCR at one and two months following birth (15). Results of a separate laboratory investigation to determine the potential of vertical transmission of *L. mexicana* in a group of BALB/c mice indicated that in addition to fatality in infected animals, the infected group's offspring body weight was lower than that of the control group. All placentas and maternal spleens as well as 35% (total n=110) of fetal spleens obtained from the infected mothers' offspring tested positive for the parasite by PCR (16). Unfortunately, in the present case report, the status of infection and the potential of vertical transmission were not investigated after the preterm birth.

Conclusion

Despite expanding endemic range of CL in Iran, reports of complications in pregnant women are scarce, limiting proper assessment of the disease impact on mothers and its consequences on newborns. There are no clear recommended forms of treatment, and effectiveness of the available medications and other treatment methods has not been systematically evaluated. Considering persistent deficiency in drugs and other treatment methods, investment and multifaceted collaborations for research and development of new therapeutics for CL are required. Although we cannot rule

out the contribution of other factors to the pregnancy complications, the CL case reported here emphasizes the importance of prevention in endemic regions, particularly in areas where the inadequacy of resources and healthcare costs may impede prompt and effective treatments.

Acknowledgements

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Conflict of interest

We declare that we have no conflict of interest.

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