Asymptomatic solitary yellowish red colored plaque on right foot

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CLINICAL FINDINGS

A 13 year old child referred to our clinic with a painless solitary lesion on the dorsum of the right foot for 6 weeks. The child had no systemic complaints like fever, chills, sweating or weight loss during this time. His previous medical history was unremarkable. He received a repeated courses of systemic and topical antibiotics with no response. There was no history of travel outside Kuwait. No similar case in the family. This is the first time he acquired these types of lesions. The lesions increased in size over the period of 1 month.

On examination he had a solitary plaque composed of papules and nodules with central crust on dorsum of right foot with a diameter of approximately 2 cm. The lesion was indurated and firm in consistency (Fig. 1). There were no enlarged lymph nodes and no hepatosplenomegaly. A more detailed examination of his ear, nose and throat did not reveal any mucosal involvement of the lesion.

His full blood count and inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) were normal. Other lab parameters like liver and renal functions were also normal.

What is your clinical differential diagnosis?

Lupus Vulgaris
Chronic Leishmaniasis
Granuloma Annulare
Deep mycosis

PATHOLOGICAL FINDINGS

A 4 mm punch biopsy was taken from the lesion and stained with H&E and Giemsa stains. The histopathology showed dense dermal granulomatous infiltrate formed of lymphohistiocytic cells admixed with plasma cells. (Fig. 2) Leishman bodies were observed within some histiocytes. (Fig. 3) Geimsa stain gave a positive result for Leishman bodies within histiocytes (Fig. 4).

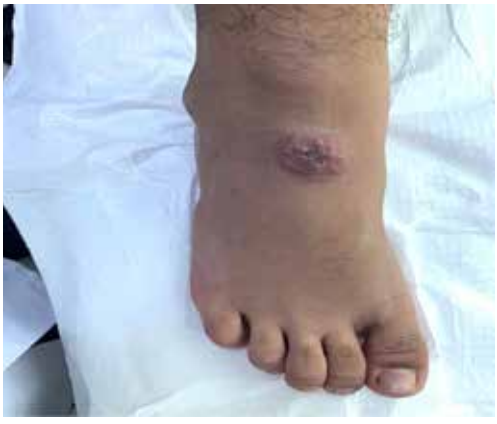

Fig. 1 A skin colored solitary plaque formed of multiple papules and nodules with central crustation.

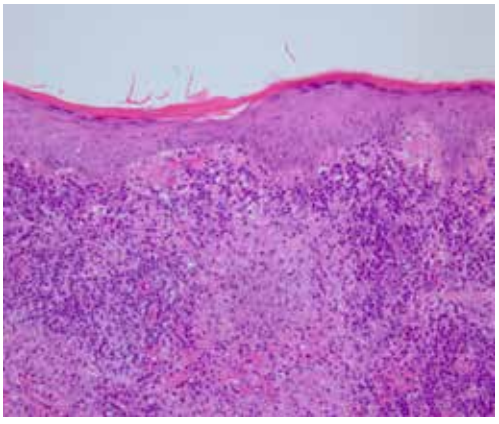

Fig. 2 Granulomatous dermal infiltrate formed of lymphohistiocytic cells admixed with plasma cells.

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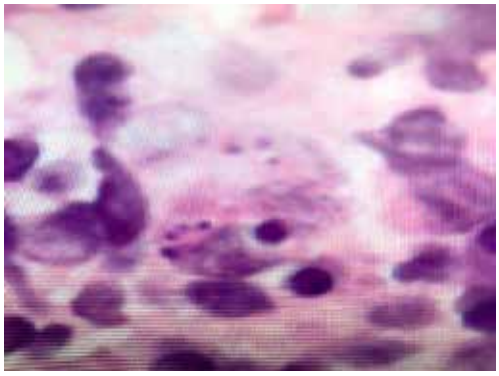

Fig. 3 H&E Histiocytes containing leishman bodeis.

Fig. 4 Positive Geimsa stain for Leishman bodies.

DIAGNOSIS

- Cutaneous leishmaniasis

COMMENT

Leishmaniasis is a protozoal disease transmitted by sandfly vectors. There are several species of vector, each occupying a particular zoogeographical zone. Human leishmaniasis is usually classified as cutaneous or visceral, but the species that cause visceral disease may also cause skin lesions.[1] Transmission may be zoonotic or anthroponotic, by the bite of female phlebotomine sand flies. It includes a wide spectrum of manifestations ranging from localized ulcerative lesions at the site of the sand fly bite (localized cutaneous leishmaniasis, CL) to the potentially fatal disseminated visceral form (visceral leishmaniasis, VL).[2] Tropical infections caused by Leishmania spp. can present diagnostic problems both to physician as well as the dermatologist. The clinical diagnosis is not difficult with typical features of leishmaniasis in the endemic countries. However, in non-endemic countries where cutaneous leishmaniasis (CL) is not common as in Kuwait, it can easily be missed. During the course of the disease, all classical stages of the development of leishmaniasis from small erythematous papules to nodules to ulcerative lesions can be seen. Cutaneous leishmaniasis has several types of lesions, all of which tend to occur on exposed parts because the disease is transmitted by the sandfly. The resulting syndrome depends upon a complex interaction between a specific species of Leishmania and the genetic and immunologic status of the host. Ultimately, either the patient's immune response is able to eliminate the infection and effect a spontaneous cure, or the immune response fails and a chronic form of leishmaniasis develops.[3] Variation in treatment outcome alongside parasite species diversity indicates that the standard therapy (Injection Pentamidine given intramuscularly) may not always be suitable. Therefore, identification of parasite species is important. Nucleic acid amplification tests (NAAT) are the standard techniques for species identification and have a high sensitivity and specificity.[4]

Leishmaniasis is a poverty-related disease caused by several species of the genus Leishmania. It affects the poorest of the poor and is associated with malnutrition, displacement, poor housing, illiteracy, gender discrimination, weakness of the immune system, and lack of resources. Leishmaniasis is also linked to environmental changes, such as deforestation, building of dams, new irrigation schemes and urbanization, and the accompanying migration of non-immune people to endemic areas. Each species tends to occupy a particular zoo-geographical zone.[5] In fact, this is not the case in Kuwait, as Kuwait one of the

Table 1: The clinicopathological challenge of cutaneous leishmaniasis

Diagnosis	Clinical	Pathological
Lupus vulgaris	• Common in young adults; refers to as cutaneous TB; skin lesions with a nodular appearance, usually near the nose, eyelids, lips, cheeks and ears; untreated lesions may develop into disfiguring skin ulcers	• Tuberculoid granulomas with variable caseation necrosis; Acid-fast bacilli are usually easy to find in the early lesions, but are rare once granulomas develop
Granuloma annulare	• Skin colored annular lesion with central clear area or as subcutaneous nodules in legs and feet	• Dermal Central area with collagen necrosis, mucin deposition and surrounded with palisading histiocytes
Deep mycosis	• Solitary or multiples nodules, plaques, verrucous or ulcerative lesion mainly in limbs	• Granulomatous or suppurative infiltrate containinig specific fungi that can be confirmed by PAS, GMS stains

richest countries.

Human leishmaniasis is usually classified as visceral, mucosal, or cutaneous. The different forms of the disease are distinct in their causes, epidemiological features, transmission, and geographical distribution. Visceral leishmaniasis (VL) or kala-azar is caused by *L. Donovani, L. infantum,* and *L. Chagasi*. These species, in contrast with the other species of Leishmania that infect man, are normally viscerotropic and cause a severe systemic infection, often accompanied with gross splenomegaly, anemia, diarrhea, hepatomegaly, lymphadenopathy, and signs of malnutrition.[6] However, a certain percentage of VL may present as post kala-azar dermal leishmaniasis (PKDL) generally after 2-3 years following the treatment for VL, which appears to completely remit. This PKDL also causes a diagnostic dilemma in endemic countries. Mucosal leishmaniasis (ML) is an uncommon but serious manifestation of Leishmania infection, resulting from hematogenous spread to the nasal or oropharyngeal mucosa from a cutaneous infection. It is usually caused by parasites in the L. (Vianna) complex. Approximately half of the patients with mucosal lesions have had active cutaneous lesions within the preceding 2 years, but ML may not develop until many years after resolution of the primary lesion. ML occurs in <5% of individuals who have or had localized cutaneous leishmaniasis caused by *L. (V.) braziliensis*. Cutaneous leishmaniasis (CL) is mainly caused by *L. tropica, L. major*, and *L. aethiopica*.[7] CL is also known as 'Aleppo boil', 'Baghdad boil', 'Bay sore', 'Biskra button', 'Chiclero ulcer', 'Delhi boil', 'Kandahar sore', 'Lahore sore', 'Leishmaniasis tropica', 'Oriental sore', 'Pian bois', and 'Uta' in respective areas. The incubation period in CL is usually measured in months but ranges from a few days to over a year.[8] In our patient, the lesion appeared 3 to 4 weeks after bite of sandflies.

The clinical manifestations of leishmaniasis depend on the interaction between the characteristic virulence of the species and the host's immune response.[9] These are transmitted by the bites of female sandflies of the genus Phlebotomotas in the Old World and Lutzomyia in the New World. More than 20 species of Leishmania, pathogenic for humans and other mammals, have been identified

worldwide. About 30 species of sandflies are proven vectors; the usual reservoir hosts include humans and domestic/wild animals. The definitive diagnosis depends on demonstration of the parasites by smears, culture, PCR, and histological examination of suspected specimens.[10] More than 90% of cutaneous leishmaniasis worldwide can be found in Afghanistan, Iran, Saudi Arabia, Syria, Brazil, and Peru. Majority of the cases of cutaneous leishmaniasis are found in adult men between 20 and 40 years. Tourists and workers from endemic areas have an increased incidence of CL. CL is mostly imported to endemic countries by immigrants and returning travelers.[11] Those are some of the surrounding areas of Kuwait.

The list of differential diagnosis is long and includes infective granulomas, such as lupus vulgaris, deep fungal infections, mycobacterium infections, leprosy, sarcoidosis, and squamous cell carcinoma. A high index of suspicion is required for provisional diagnosis.

Sandflies inoculate the infective metacyclic promastigotes when taking a blood meal from the superficial vascular network in the human dermis. Inoculated promastigotes are taken up by histiocytes and newly immigrated monocytes, in which they multiply. Most inoculations do not seem to result in clinical disease as phagocytosis, and complement-mediated killing of Leishmania parasites results in clearing of the infection. A minority of successful parasite inoculations result in localized or disseminated clinical cutaneous leishmaniasis. After a period of time, which depends on parasite species, size of inoculum and the host's cellular immune response, a clinical lesion appears. This lesion comprises parasitized macrophages, lymphocytes and plasma cells, with little structure. With time, piecemeal and focal necrosis of parasitized cells is found, probably the result of antibody-dependent cell-mediated immunity. The overlying epidermis becomes hyperkeratotic and breaks down, causing an ulcer whose surface is covered by a crust composed of hyperkeratotic debris, dried exudate, dead cells, and live and dead parasites. This activity continues for several months, while the lesion appears clinically static. In other, especially chronic cases, the more classical epithelioid cell, and sometimes giant cell granuloma, develops with relatively little necrosis, but with similar epidermal changes. In these cases, parasites are difficult to find. Rarely, when cell-mediated immunity fails to develop, as in diffuse cutaneous leishmaniasis, histology shows masses of parasitized, often vacuolated, macrophages, with little or no lymphocytic infiltrate, and a normal or attenuated epidermis.[12]

A positive diagnosis of cutaneous leishmaniasis (Old World and New World types) can be suggested, and in most cases confirmed, by the presence of one or more of the following criteria.

1. History of exposure to an endemic area in the previous weeks or months.
2. History of sandfly bites in the previous weeks or months.
3. History of high-risk activities such as sleeping outdoors, jungle or desert trekking.
4. Non-healing chronic nodular violaceous ulcer for 4–6 weeks or longer.
5. Demonstration of amastigotes in Giemsa-stained smears from infected skin by direct microscopy.
6. Demonstration of intracellular amastigotes in the dermis of H&E sections of skin.
7. Presence of leishmanial granulomas in the dermis in H&E specimens.
8. Growth of promastigotes in Nicolle–Novy–MacNeal (NNN) culture medium from lesional specimens.
9. Demonstration of leishmanial DNA by PCR.

Treatment of CL is often difficult. Multiple treatment options are used throughout the world for cutaneous disease. Besides oral and parenteral

medications (pentavalent antimonials, liposomal amphotericin B, miltefosine, and some others), local cryotherapy, intralesional infiltration of sodium stibogluconate, local heat therapy, and various topical paromomycin preparations are in practice for many years. Antimonials are still the first-line drug in the treatment of CL. Sodium stibogluconate (Pentostam) and meglumine antimonite glucantime are essentially similar drugs which contain pentavalent antimony (Sb). Sodium stibogluconate can be administered intravenously or intramuscularly while meglumine antimonite should only be given via the intramuscular route. The recommended dose is 20 mg/kg/day for 20-28 days.[7] Treatment with antimonials is associated with some side-effects, such as myalgia as well as possible liver or cardiovascular toxicity, which fortunately is rare. A study using intralesional sodium stibogluconate showed that alternate daily or weekly administration of intralesional sodium stibogluconate was effective in the treatment of CL.[13] Dapsone and allopurinol have also been used for the treatment of CL. The mechanism is unclear, although basic biomedical studies have shown that Leishmania cannot make all of their own nucleic acids and thus, it uses the host's purine through the purine salvage pathway.[5] Besides systemic treatment, local measures, such as cryotherapy, local excision of a small focus and topical treatment using 15% paromomycin ointment, have also been shown to be effective in some cases.[14] That's what we used in our patient repeated Cryo sessions with a good response.

Vaccines for prophylaxis and immunotherapy have been developed and are currently undergoing trials in many countries, including Venezuela, Brazil, and Iran.[5]

The development of molecular biology techniques is also improving knowledge on the structure, evolution, and expression of the Leishmania genome, and the study and definition of the mechanisms that regulate the parasite's biochemical and molecular features will certainly contribute to the development of new and more effective strategies for leishmaniasis treatment. So far, chemotherapy with systemic and intralesional sodium stibogluconate is effective without any major side-effects.

CONCLUSIONS

Cutaneous leishmaniasis is a rare disease in Kuwait as it is not an endemic area. However, due to the multinational workers in Kuwait, we have to keep Leishmaniasis in mind as a differential diagnosis even with negative history of travelling as in our case.

REFERENCES

1. Reithinger R, Dujardin JC, Louzir H, Pirmez C, Alexander B, Brooker S: Cutaneous leishmaniasis. Lancet Infect Dis 2007; 7(9):581-96.
2. Reithinger R, Mohsen M, Aadil K, Sidiqi M, Erasmus P, Coleman PG: Anthroponotic cutaneous leishmaniasis, Kabul, Afghanistan. Emerg Infect Dis 2003; 9(6):727-29.
3. Hepburn NC. Cutaneous leishmaniasis. Clin Exp Dermatol. 2000; 25:363-70.
4. Schonian G, Nasereddin A, Dinse N, Schweynoch C, Schallig HDFH, Presber W, Jaffe CL, PCR diagnosis and characterization of Leishmania in local and imported clinical samples. Diagn Microbiol Infect Dis 2003; 47:349-58.
5. Tan HH, Wong SS, Ong BH. Cutaneous leishmaniasis: a report of two cases seen at a tertiary dermatological centre in Singapore. Singapore Med J 2000; 41:179-81.
6. Bryceson ADM, Hay RJ. Parasitic worms and protozoa. In: Champion RH, Burton JL, Ebling FJG, editors. Textbook of dermatology. 5th ed. Oxford: Blackwell, 1991:1252-53.
7. Kliegman RM, Behrman RE, Jenson HB, Stanton BMD. Nelsion textbook of paediatrics. 18th ed. Philadelphia, PA: Saunders, 2007:1468-71.
8. James WD, Berger TG, Elston DM. Andrews' diseases of the skin clinical dermatology. 10th ed. Philadelphia, PA: Elsevier Health Sciences, 2006. 961 p.
9. Marsden PD. Mucosal leishmaniasis ("espundia"

Escomel, 1911). Trans R Soc Trop Med Hyg 1986; 80:859-76.
10. Ridley DS. A histological classification of cutaneous leishmaniasis and its geographical expression. Trans R Soc Trop Med Hyg 1980; 74:515-21.
11. Hengge UR, Marini A. [Cutaneous leishmaniasis]. Hautarzt 2008; 59:627-32. [German]
12. Weatherall DJ, Ledingham JGG, Warrell DA, eds. Oxford Textbook of Medicine, 2nd edn. Oxford: Oxford University Press, 1987.
13. Schwarz KJ. [Diagnosis and differential diagnosis of cutaneous leishmaniasis. Report on seven cases observed in Zurich]. Schweiz Med Wochenschr 1970; 100:2073-78.
14. Herrmann A, Wohlrab J, Sudeck H, Burchard GD, Marsch WC. [Chronic lupoid leishmaniasis. A rare differential diagnosis in Germany for erythematous infiltrative facial plaques]. Hautarzt 2007; 58:256-60.