Le Infezioni in Medicina, n. 3, 345-349, 2019

Cutaneous leishmaniasis associated with Systemic Lupus Erythematosus (SLE)

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SUMMARY

Cutaneous Leishmaniasis (CL) is a protozoan disease caused by *Leishmania spp*. and is endemic in the Americas, the Mediterranean basin, Middle East, and Central Asia. There are reports regarding the co-infection of CL with other diseases, especially immune system disorders. Herein, we presented a patient with several leishmania lesions who suffered from Systemic Lupus Erythematosus (SLE). He was a 22-year-old man from Fars province, southern Iran who was treated with corticosteroid drugs to control the manifestations of SLE. The presence of leishmanial bodies was confirmed by microscopic and molecular methods. Treatment was performed based on sodium antimony gluconate (1.5 mg/5ml) for three weeks, resulting in acceptable outcomes. However, recurrence of the lesions was observed after two months when the medication was discontinued. This was the first report of Zoonotic Cutaneous Leishmaniasis (ZCL) in an SLE patient.

Keywords: cutaneous leishmaniasis, systemic lupus erythematosus, Iran, Fars province.

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an inflammatory chronic autoimmune disease characterized by the production of several autoantibodies in different organs. Malfunction in immune system and polyclonal B cell hyperactivity with production of manifold autoantibodies is a serious occurrence in advanced SLE patients. Autoantibodies attack the skin, joints, kidneys, brain, blood vessels, blood cells, lungs, and the heart. Biochemical and hematological abnormalities can be detected in these patients, as well [1-3]. High serum lipase and amylase are the most generally detected biochemical abnormalities [4].

Cutaneous Leishmaniasis (CL) is transmitted to humans by female infected phlebotomine sand fly bites [5]. This skin disease is endemic in 87 countries of the New World as well as in the Old World. According to the World Health Organization (WHO), over 95% of new CL cases live in underdeveloped countries, particularly Afghanistan, Algeria, Brazil, Colombia, Iran, Iraq, and the Syrian Arab Republic. It has also been estimated that 600,000-1,000,000 new cases occur annually [6, 7]. In Iran, CL can be caused by *L. major, L. tropica*, or less commonly *L. Donovani infantum* [8]. The first choices for treating leishmaniasis are pentavalent antimonial compounds although they may result in toxicity and therapeutic failure. At present, liposomal amphotericin B has been introduced as a more effective and safer alternative to antimonial compound drugs in CL treatment, especially in immunocompromised individuals [9-11].

Leishmania parasites multiply in tissue macrophages and extend to other macrophages de-

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pending on diverse parasite and host factors. In CL, the infection is commonly limited to the skin and the lymphatic system [12].
This study aims to report a patient with CL who suffered from SLE.

CASE REPORT

A 22-year-old man from Lamerd, southern Fars province, Iran with several skin lesions in different parts of the body (left heel, right foot, finger point of the right hand, left abdomen, and left elbow) (Figure 1) was referred to the Dermatology Department of Faghihi Hospital in Shiraz. The lesions had appeared 7-8 months before admission. Lamerd is a warm reign located in south of Fars province where people have summer covers most of the year. In this region, leishmaniasis has been reported to be prevalent in both individuals and reservoirs [13-15]. The patient did not have a special job and was studying at the university. He had been suffering from SLE since 2016. In June 2016, physicians suspected SLE according to clinical manifestations such as malar rash, photosensitivity, Raynaud phenomenon, arthritis, keratoconjunctivitis and the following laboratory results: haemoglobin (Hb) 9.5 mg/dL, white blood cells (WBC) 17000/µL, platelets (Plt) 200000/µL, erythrocyte sedimentation rate (ESR) 36 mm/h, red blood cells (RBC) 3310000/µL, and WBC differentiation including polymorphonuclear neutrophils (PMN) 74%, lymph 16%, and mono 9%. Biochemical evaluation revealed normal levels of Creatinine (Cr), albumin, and alanine transaminase (ALT), low levels of C3 and C4, and high levels of lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and blood urea nitrogen (BUN). SLE was also verified by immunological analyses, including seropositivity of antinuclear antibodies (ANA) and anti-double-stranded DNA (Anti dsDNA) antibodies. Then, treatment with corticosteroids was started. After treatment, in September 2018, laboratory analyses revealed Hb concentration 12.5 mg/dL, WBC 5100/µL with normal differential count, RBC 4500000/µl, Plt 268000/µL, and ESR 28 mm/hr. Indeed, the biochemical analysis demonstrated normal levels of Cr, albumin, ALT, AST, BUN, C3, and C4. Moreover, ANA was positive, but Anti dsDNA showed a normal level. These results indicated that the process of the disease was controlled by drug administration. In October 2018, due to the onset of lesions as mentioned above, the patient was referred to the Parasitology and Mycology Department of Shiraz University of Medical Sciences. Therein, smears from different lesions were provided and stained. Leishmanial bodies were seen in light microscopy. For molecular diagnosis, DNA was

Figure 1 - Picture of patient Leishmania lesions: (a) Left heel, (b) On right foot, (c) Finger point of right hand, (d) Left abdomen and (e) Left elbow.

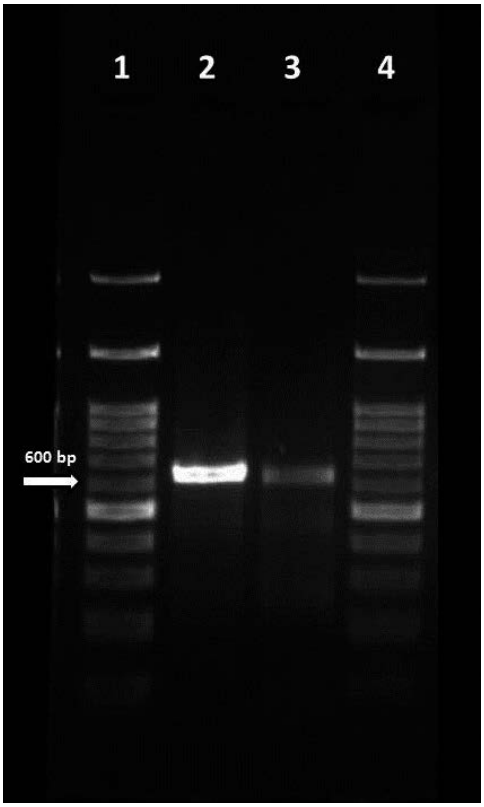

Figure 2 - Electrophoresis of PCR product on 1.5% agarose gel: (1,4) ladder; (2) positive control and (3) sample of patient.

extracted from the smears using kits (FAVERGEN, Tiawan). Then, specific Polymerase Chain Reaction (PCR) was done by a specific primer for *L. major* and 650 bp band was yielded in agar gel electrophoresis (Figure 2) [16, 17]. Sodium antimony gluconate (1.5 mg/5 ml) was administered to the patient intralesionaly for twice a week for two months (20 mg/kg), leading to acceptable results. However, recurrence of the lesions was observed two months after discontinuing the medication at the edges of the site of a previously cured lesion and subcutaneous nodules (Figure 3). Thus, the patient was treated with sodium antimony gluconate intramuscularly once again and the wounds progressed to healing.

DISCUSSION

Leishmaniasis presents a clinical spectrum ranging from a self-resolving cutaneous ulcer to a lethal systemic disease. Mononuclear cells, specifically macrophages and monocytes, are a particular host for aetiological agents. Macrophages, as effector cells of protective immunity, are able to destroy intracellular organisms [18, 19]. The cytokine profile characterizes CD4 and T cells into two subsets; Thl cells make IL-2 and lFN-γ in response to antigens, while Th2 cells make IL-4, IL-5, and IL-10 [20]. Monocytes, macrophages, and B cells make

Figure 3 - Picture of lesions recurrence at the edges of the site of a previously cured lesion and subcutaneous nodules.

IL-12 that provokes the development of Thl and NK lymphocytes. These immune cells affect the synthesis of lFN-γ [21].
SLE is an autoimmune disease characterized by production of various autoantibodies [22]. Laboratory investigations for SLE have shown hemolytic anemia, leucopenia or lymphopenia, and thrombocytopenia, because of production of autoantibodies [23]. SLE diagnosis can be confirmed via positive ANA and positive Anti dsDNA [24]. Furthermore, high levels of monocytes in SLE patients lead to disease-causing activities. It has been reported that monocytes and macrophages have effector functions in immune activation in SLE [25, 26]. SLE is most commonly treated by immunosupressive drugs, such as glucocorticoids. Glucocorticoids have suppressive impacts on immune responses mediated by T- and B-cell lymphocytes. They affect monocytes and neutrophils, as well [27].
CL is generally self-limiting, but can display a spectrum of clinical features, such as atypical lesions, disseminated forms, and even severe clinical forms due to visceralization, in immunosuppressed individuals [28]. The chance of *Leishmania* infection is expected to decrease in SLE patients who take immunosuppressive drugs due to immune responses, such as inhibition of monocyte and macrophage cells that are a specific host for *Leishmania*. In this report, a case was presented with a three-year history of SLE and immunosuppressive therapy. Therefore, it can be concluded that high affinity of promastigotes to macrophages through common receptors might be a good reason for macrophages infection despite their inhibition [29-31]. On the other hand, in SLE patients infected with *Leishmania*, the duration of treatment increases and the possibility of self-healing decreases because of treatment with immunosuppressive drugs.
In the patient presented in this report, self-limitation had not occurred 7-8 months after the appearance of lesions. He was treated with sodium antimony gluconate (1.5 mg/5mL) intramuscularly for three weeks and improvements were observed in lesions healing.
Villamil-Gómez et al. in 2019, Silva et al. in 2015, and Ossandon et al. in 2006 presented an association between Visceral Leishmaniasis (VL) and lupus in patients who lived in endemic areas [32-34]. Mutengo et al. also reported an SLE case associated with HIV infection with different pathogeneses and opposed managements [35]. Moreover, co-infection of VL and psoriatic arthritis was reported by Hadjipetrou et al. [36]. It seems that this report presented the first association between SLE and CL in the world.
Autoimmune diseases, such as SLE, created due to immune system disorders can lead to the host's susceptibility to infectious diseases. Therefore, the manifestations of the disease should be considered in immunodeficient individuals in CL endemic areas.

Acknowledgements
The authors would like to thank Ms. A. Keivanshekouh at the Research Improvement Center of Shiraz University of Medical Sciences for improving the use of English in the manuscript.

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