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D. Jiménez-Gallo,[a,*] I. Villegas-Romero,[a]
M.E. Rodríguez-Mateos,[b] M. Linares-Barrios[a]

[a] *Unidad de Gestión Clínica de Dermatología Médico-Quirúrgica y Venereología, Hospital Universitario Puerta del Mar, Cádiz, España*
[b] *Unidad de Gestión Clínica de Farmacia Hospitalaria, Hospital Universitario Puerta del Mar, Cádiz, España*

* Corresponding author.
E-mail address: davidjimenezgallo@gmail.com
(D. Jiménez-Gallo).
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Mucocutaneous Leishmaniasis in Immunocompromised Patients: Report of 4 Cases in Spain☆

Leishmaniasis mucocutánea en pacientes inmunocomprometidos: reporte de 4 casos autóctonos

To the Editor:

Leishmaniasis is a disease caused by parasites of the *Leishmania* genus.[1] Clinically, it can present as cutaneous leishmaniasis, mucocutaneous leishmaniasis, or visceral leishmaniasis.[2] The disease is endemic in a number of Spain's autonomous communities, namely, Madrid, Catalonia, Aragon, Castille-la Mancha, Andalusia, Valencia, Extremadura, Murcia, and the Balearic Islands. In some communities it is a notifiable disease, although not all cases are reported.[1,3] Clinical manifestations depend on the species of *Leishmania*, the inoculation site, and the host's immune status.[4] Immunosuppressed patients have a high risk of severe disease.[5,6]

Between 1% and 10% of all cases of cutaneous leishmaniasis spread to the mucous membranes, and almost 90% of these are caused by *Leishmania braziliensis*, which is rare in our geographic area.

In a retrospective search of the database at our hospital, we identified 18 cases of cutaneous/mucocutaneous leishmaniasis (Table 1). The patients (9 males and 9 females) were aged between 9 and 84 years (mean age, 46 years) and the mean time to diagnosis was 10 months. Six of the 18 patients were immunocompromised for varying reasons (diabetes mellitus, congestive heart failure, liver transplantation, Crohn disease, psoriatic arthritis). Four of them had mucocutaneous leishmaniasis and none of them had been abroad recently.

Case 1

The first patient was a 59-year-old woman with systemic lupus erythematosus under treatment with methotrexate 15 mg/wk, hydroxychloroquine 400 mg/d, trimethoprim-sulfamethoxazole 160/800 mg 3 days a week, acenocoumarol, prednisone, and subcutaneous adalimumab 40 mg every 2 weeks. In the week preceding her visit, she had experienced deterioration in her general health and polyarthritis of the carpal bones and knees. Physical examination revealed thickening of the dorsum of the tongue, multiple ulcers on the palate, and erythematous-violaceous papular lesions on her fingers and palms. She was admitted to hospital. A gastric biopsy performed several weeks earlier showed inclusion bodies consistent with *Leishmania* parasites. Biopsy of the oral mucosa also showed microorganisms consistent with *Leishmania*. Empirical treatment was started with amphotericin 1 mg/kg/d on days 1-5, 10, 17, 24, 31, and 38. Adalimumab therapy was interrupted and the daily dose of prednisone was increased to 20 mg. The patient progressed favorably.

Case 2

The second patient was a 62-year-old man who had undergone liver transplantation and had a history of chronic kidney failure, gout, and chronic obstructive pulmonary disease. He was being treated with mycophenolate, tiotropium, and allopurinol, and presented with

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Table 1 Clinical and Epidemiological Characteristics of Patients With Cutaneous and Mucocutaneous Leishmaniasis.

Age (y) and Sex	Lesion Type	No.	Location	Time to Diagnosis (mo)	Origin	Immune Status	Treatment	Outcome at 1 Year
20 M	Nodular	1	Upper arm	2	Autochthonous	Immunocompetent	Excision	Uncertain
62 F	Ulcer	1	Lip	36	Imported	Immunodepressed (liver transplantation)	Excision and antimoniate	Adequate
12 F	Nodular	1	Cheek	4	Autochthonous	Immunocompetent	Excision	Uncertain
46 F	Nodular	1	Upper arm	2	Autochthonous	Immunocompetent	Excision	Adequate
21 M	Psoriasiform	2	Upper arm	8	Imported	Immunocompetent	None	Adequate
56 M	Psoriasiform/ eczematous/ papular	3	Ear	6	Imported	Immunodepressed (Crohn disease under treatment with adalimumab)	Antimoniate	Adequate
45 M	Macular	1	Face	34	Imported	Immunocompetent	Excision	Adequate
59 F	Ulcer	3	Palate	4	Autochthonous	Immunodepressed (SLE)	Amphotericin B	Adequate
44 F	Papular	1	Cheek	5	Autochthonous	Immunocompetent	Excision	Adequate
49 M	Nodular	3	Arms and legs	Uncertain	Autochthonous	Immunocompetent	Excision	Adequate
45 M	Large plaque	1	Hand	Uncertain	Autochthonous	Immunocompetent	Antimoniate	Adequate
82 F	Macular	1	Cheek	6	Imported	Immunodepressed (HIV)	Excision	Adequate
42 M	Nodular	1	Upper arm	12	Autochthonous	Immunocompetent	Imiquimod	Adequate
84 F	Papular	1	Eyelid	12	Autochthonous	Immunodepressed (DM, CHF)	Excision + cryotherapy	Adequate
9 M	Large plaque	1	Leg	9	Autochthonous	Immunocompetent	Excision + imiquimod®	Adequate
34 F	Psoriasiform	3	Upper arm	3	Autochthonous	Immunocompetent	Cryotherapy	Residual lesion
60 M	Papular-nodular	3	Sublingual	3	Autochthonous	Immunodepressed (psoriatic arthritis under treatment with adalimumab)	Amphotericin B	Adequate

Abbreviations: CHF, congestive heart failure; F, female; HIV, human immunodeficiency virus; M, male; SLE, systemic lupus erythematosus.

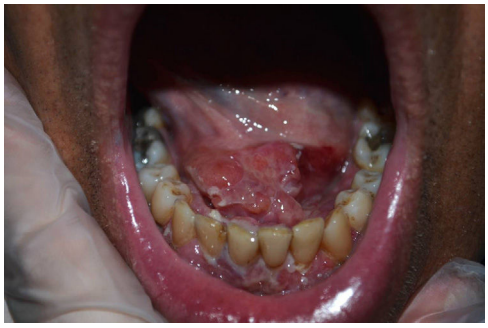

Figure 1 Friable erosive lesions on the base of the tongue.

an ulcerated lesion measuring 2 cm on the upper lip. The lesion was excised and biopsied, and the histopathology report described a granulomatous lesion with intracellular microorganisms consistent with *Leishmania*. The patient was prescribed intramuscular meglumine antimonate 20 mg/kg/d for 20 days. Response was favorable and he experienced no recurrences.

Case 3

The third patient was a 90-year-old woman with high blood pressure, type 2 diabetes mellitus, dyslipidemia, heart failure, obesity, and Parkinson disease. She presented with a hard papular lesion of 1 year's duration accompanied by slight swelling on the lower right eyelid. It was decided to excise the lesion, which had a raised surface area of 1.5×1.5 cm and an excavated base involving the conjunctival mucosa. The histopathologic study confirmed the diagnosis of mucocutaneous leishmaniasis. No additional studies or follow-up were performed as the finding was incidental.

Case 4

The fourth case involved a 60-year-old man with psoriatic arthritis under treatment with subcutaneous adalimumab 40 mg every 2 weeks and methotrexate 12.5 mg every week. He presented with papulonodular lesions of approximately 3 months' duration in the sublingual region accompanied by gingival enlargement and erosions (Fig. 1). Biopsy of the mucosa showed intracellular microorganisms consistent with *Leishmania*. Treatment with adalimumab was suspended and replaced with liposomal amphotericin B at a dosage of 3 mg/kg/d on days 1 to 5 and days 14 and 21. The treatment was well tolerated and the mucocutaneous lesions resolved.

Discussion

Leishmaniasis is endemic in several autonomous communities in Spain,[7] and a rise in incidence has been described in immunodepressed patients.[8] Mucosal involvement is very uncommon in the old world,[9] and most of the cases reported to date have been in immunocompromised individuals.[8] Mucocutaneous involvement is due to *L braziliensis* in approximately 90% of cases, and this species is found almost exclusively in South America. Nevertheless, there has been a gradual increase in the number of cases involving mucosal lesions caused by *Leishmania infantum* or *Leishmania major*.[1]

In our retrospective review of cases at our hospital, we found that the 4 patients with mucocutaneous leishmaniasis were all immunodepressed, indicating that leishmaniasis must be ruled out in patients with lesions of an unknown origin affecting different mucous membranes. The 4 patients were also all Spanish, which is a noteworthy finding considering that mucocutaneous leishmaniasis is very uncommon in Spain and other parts of Europe.[9] Although we were unable to identify the species responsible for the 4 cases described, *L braziliensis* is a highly unlikely candidate as it is very uncommon in our area.

There is some controversy surrounding the treatment of mucocutaneous leishmaniasis. Although favorable outcomes have been reported following excision, some authors recommend systemic treatment due to the risk of visceral involvement.[10,11] Current treatment options are pentavalent antimonials, pentamidine, amphotericin B, azoles, and miltefosine. All immunosuppressive treatments should be suspended until the leishmaniasis has been successfully treated.[10] There is also a lack of consensus on the reintroduction of immunosuppressants, (and TNF-α blockers in particular) following treatment due to the risk of recurrence.[10] In most of the cases described in the literature, TNF-α blockers were reintroduced following completion of leishmaniasis treatment.

In conclusion, leishmaniasis must be considered in the differential diagnosis of mucosal lesions in immunocompromised patients in leishmania-endemic areas.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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S. Habibi Naderizadeh,[a,*] C. Valcárcel Sierra,[a]
L. Medrano Gallego,[a] B.J. Flores Robles,[b]
L.G. Roustán-Gullón[c]

[a] *Servicio de Medicina Familiar y Comunitaria, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, España*
[b] *Servicio de Reumatología, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, España*
[c] *Servicio de Dermatología, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, España*

* Corresponding author.
E-mail address: shabnamhab@hotmail.com
(S.H. Naderizadeh).
1578-2190/

Bullous Sweet's syndrome with myositis

Síndrome de Sweet ampollar con miositis

Dear Editor:

A 79-year-old female, who had suffered from myelodysplastic syndrome (MDS) (RAEB-1), was referred to our department complaining of painful lesions on the neck, chest and lower extremities with fever-up which appeared three weeks previously. She had received occasional transfusion for her MDS, but granulocyte-colony stimulating factor (G-CSF) was not administered. Physical examination showed ill-defined, tender edematous erythemas with bullous and erosive lesions on the chest (Fig. 1a). In addition, painful fresh-colored erythematous plaques were scattered on the lower extremities. Laboratory examination showed slightly elevated white blood cell counts (9100/μl with 27% Band, 29% Seg, 12% Lym, 4% Mono, 4% Eo, 9% Baso, and 10% Meta), and increased levels of erythrocyte sedimentation rate (136 mm/h) and C-reactive protein (9.0 mg/dl). A biopsy specimen from the chest showed dense neutrophilic infiltration throughout the edematous dermis (Fig. 1c). Bacterial culture resulted sterile. Bone marrow biopsy revealed severe hypocellular bone marrow with a marked decrease of erythroblasts and megakaryocytes. After admission, systemic prednisolone (20 mg/day) was started which resulted in the improvement of skin lesions. However, during the course, she complained of severe muscle pain of the right thigh along with fever up to 39 °C. Examination by MRI showed edematous swelling on the right gluteus maximus muscle (Fig. 1d). Unfortunately, muscle biopsy was not performed, because her general conditions worsened. Serum creatine kinase level was not elevated and myositis was gradually improved without dose-up of prednisolone. However, her general condition was worsened, and she died of disseminated intravascular coagulation, renal failure, and complete A-V block one month after admission.

Sweet's syndrome is characterized by tender erythematous skin lesions accompanied by fever-up, in which inflammatory cells predominantly consisted of neutrophils infiltrate diffusely in the dermis. Sometimes Sweet's syndrome presents with atypical variants,[1] and bullous variant is histologically characterized by extensive neutrophilic exocytosis and severe edema of the upper dermis. Whether cases of bullous Sweet's syndrome are commonly associated with hematological disorders is controversial.[2,3] In the present case, bullous lesions were developed in a patient with active and severe MDS. The patient had no other apparent triggers such as upper airway or gastrointestinal infections and the use of new drugs, for the induction of Sweet's syndrome. Also, the patient developed non-bullous infiltrative erythema on the knee, and muscle tenderness during the course. So far, several cases of extracutaneous manifestations of Sweet's syndrome have been reported involving the lung, digestive tract, joints, lymph nodes, liver, spleen, eyes, central nervous system, and bone.[4] Only several cases of neutrophilic myositis have been reported in association with neutrophilic dermatosis[5]; however, to our knowledge, there have been no reports of neutrophilic myositis in association with bullous Sweet's syndrome. A previously reported case developed severe sterile neutrophilic myositis as the first manifestation of acute myelogenous leukemia.[6] In the present case, myositis was developed soon after admission, which occurred almost concurrently with cutaneous manifestations. Because of the increased risk of infection, we did not escalate the dose of prednisolone; however, muscle lesions were transient and gradually improved. Because muscle biopsy was not carried out, it is uncertain that the patient developed neutrophilic myositis during the course. Hematoma was unlikely, but other factor such as infection was not denied, because drainage procedures were not performed. In such cases as immunocompromised patients like ours, it is often difficult to decide whether other organ involvement is caused by aseptic neutrophilic infiltration or infection.