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Letter to the Editor

Leishmania infection in psoriasis

Dear Editor,

In this Journal Brunet and colleagues¹ discussed reactivation of latent infections in the context of chronic disease, solid organ transplantation or long-term immunosuppressive treatment. We recently observed the reactivation of *Leishmania* infection in a 46-year-old patient receiving methotrexate for psoriasis, who was diagnosed with visceral leishmaniasis (VL) showing a mucocutaneous involvement. We analyzed the epidemiologic and clinical characteristics of all cases of leishmaniasis in patients with psoriasis found through a review of the literature.

Our patient was admitted into the Infectious Disease Unit of Paolo Giaccone hospital, in Palermo, with a painless and ulcerated lesion onto the oral mucosa (Fig. 1a), two nodular ulcerated lesions on the right knee and another one on instep of the right foot appeared one month before (Fig. 1b). The patient did not travel outside Italy during the last year. He had been suffering from low-grade fever in the last month.

Considering the above findings leishmaniasis was suspected and a needle aspiration of oral and cutaneous lesions was arranged in order to perform microscopy and *Leishmania*-PCR, which were positive for *Leishmania*. Laboratory tests exhibited: WBC 4970/mm³, Hb 13.9 g/dl, C Reactive Protein, 26.9 mg/L; positive serology for *Leishmania* (IgG 1/3200) and positive *Leishmania*-PCR test on peripheral blood. Abdominal US examination revealed splenomegaly (14 cm); methotrexate was suspended and liposomal Amphotericin B, 4 mg/kg per day for 10 days, followed by two further administrations two weeks later was started. Cutaneous and mucosal lesions improved at the end of the first 10 days of therapy and completely vanished after two further administrations, 40 days from the beginning of treatment. *Leishmania*-PCR on peripheral blood after 10 days of therapy was negative.

Table 1 shows the literature data about characteristics, therapy and outcome of patients with psoriasis and leishmaniasis.

Leishmaniasis is a vector-borne chronic infectious disease caused by protozoa of the genus *Leishmania* and transmitted to humans by the bite of phlebotomine sandflies. In Europe, the Mediterranean countries are the most affected areas. *Leishmania* parasite establishes chronic intracellular parasitism, survives for an infected person's lifetime and, in the event of major immune deficiency, may be reactivated from sites of latency. Leishmaniasis can present with a spectrum of clinical manifestations and three patterns of infection are described: cutaneous (CL), mucosal or mucocutaneous (ML or MCL) and visceral leishmaniasis (VL). The infecting species of *Leishmania* is very important in determining the clinical manifestations and the host immune response is crucial in determining the clinical outcome of infection². Today, non-HIV related immunosuppressive conditions are becoming increasingly prevalent, mainly because of better medical care of patients with chronic

Figs. 1a and b. Ulcerated lesions by *Leishmania* onto the oral mucosa (a) and right foot (b) in a 46-year-old patient with psoriasis.

illnesses and the therapeutic use of immunosuppressive drugs. In the field of rheumatology, leishmaniasis has been reported in association with the use of various immunosuppressive drugs.³ The introduction of tumor necrosis factor-alpha (TNF- α) antagonist drugs has received much attention recently and several cases of VL have been reported in rheumatic patients who do anti-TNF α drugs.⁴

Psoriasis is a chronic inflammatory autoimmune disease affecting 2–3% of the world's population and characterized by an aber-

Table 1

Detailed characteristics of patients with psoriasis or psoriatic arthritis in whom leishmaniasis developed.

First author Year Number of patients	Risk factors for Leishmania infection	Age, y/sex	Disease	Immunosuppressive treatment	Duration months	Form of Leishmania Infection	PCR	Microscopy.	Serology	Treatment	Suspension of immuno- suppressive therapy	Outcome
Romani-Costa et al., 2004, Enferm Infecc Microbiol Clin	Endemic area Spain	55/M	PSA	Infliximab	9	VL				Meglumine antimoniate		Cured
Saha et al., 2006, Br J Dermatol	Traveler returning from Mexico, Spain, Greece, Malta and Turkey	37/M	PSA	Metotrexate Sulfasalazine	36	CL	Pos SB	Pos SB	Pos	Iv sodium stibogluconate	NR	Cured
Balato et al., 2008, Dermatology	Endemic area Italy	42/M	P	Efalizumab cyclosporina	24	VL	Pos BM Pos PB	Pos BM	Pos	None	Yes	Cured
Tektonidou and Skopouli, 2008, Clin Rheumatol	Endemic area Greece	45/M	PSA	Methotrexate Infliximab Prednisolone	60	VL	Pos BM	Neg BM	Neg	Lyophilized amphotericin	Yes	Cured
De Leonardis et al., 2009, Clin Exp Rheumatol	Endemic area Italy	63/M	PSA	Methotrexate Infliximab azathioprine prednisolone	36	VL	ND	PosBM	Neg	Liposomal amphotericin B	Yes	Cured
Khan et al., 2010, BMJ case rep	Traveler returning from Malta	74/F	PSA	Adalimumab methotrexate	21	CL VL	Pos BM Pos SB	pos BM pos SB	pos	Intralesional meglumine antimoniate and liposomal Amphotericin	Yes	Cured
Romero-Mate et al., 2012, Dermatol Online J	Endemic area Spain	59/F	PSA	Adalimumab methotrexate	84	CL	Pos	neg	ND	Intralesional meglumine antimoniate	No	Cured
Besada et al., 2013, Rheumatol Int	Traveler returning from southern Spain	72/F	PSA	Methotrexate Etanercept	288	VL	Pos BM	Pos BM	ND	Liposomal amphotericin B	Yes	Cured
Hernandez-Torres et al., 2013, Scand J Infect Dis	Endemic area Spain	50/M	P	Corticosteroids infliximab	36	CL	Pos SB	Pos SB	Pos	Liposomal amphotericin B	Yes	Cured
Guedes-Barbosa et al., 2013, Semin Arthritis Rheum (two patients)	Endemic area Brazil	39/M 50/M	PSA (2)	Prednisone methotrexate adalimumab (2)	12 14	MCL CL	ND ND	Pos SB Pos SB	NDND	Meglumine antimoniate (2)	No Yes	Cured Cured
Hadjipetrou et al., 2014, Infez Med	Endemic area Greece	65/M	PSA	Methotrexate	24	VL	Pos BM	Pos BM	Pos	Liposomal amphotericin B	Yes	Cured
Catala et al., 2014, Actas Dermosifiliogr	Endemic area Spain	33/M	PSA	Infliximab	24	CL	ND	Pos SB Neg BM	Pos	Intralesional meglumine antimoniate	Yes	Cured
Rakotonarivo et al., 2018, JAAD case rep	Traveler returning from Morocco	62/M	P	Methotrexate ustekinumab	4	CL	Pos SB	Pos SB	ND	Intralesional meglumine antimoniate	Yes	Cured
Guarneri et al., 2017, Wien Med Wochenschr	Endemic area Italy	65/M	PSA	Golimumab cyclosporina metotrexate steroids	48	ML, VL	ND	posBM posSB	Pos	miltefosine for 28 days Liposomal amphotericin B	Yes	Cured
Hernandez Bel et al., 2018, Arch Soc Esp Oftalmol	Endemic area Spain	72/M	PSA	Prednison metotrexate adalimumab	60	CL	Pos	Pos	ND	Intralesional injections of meglumine antimoniate	Yes	Cured
Martinez-Domenech et al., 2019, Br J Dermatol (four patients)	Endemic area Spain	1 pt 34/F 1pt40/F 1pt 71/M 1 pt 53/M	P (3) PSA (1)	Adalimumab (4) Etanercept (2) Metotrexate (2)	17 96 2 24	CL (4)	ND (1) pos SB (3)	pos SB(2) neg SB (2)	neg(4)	Intralesional injections of meglumine antimoniate (4)	Yes (3) No (1)	Cured (4)
Caroleo et al., 2019, Curr Drug Saf	Endemic area Italy	48/M	PSA	Prednisone Metotrexate cyclosporine Adalimumab	12	CL	ND	Pos SB	ND	Intralesional injections of meglumine antimoniate	Yes	Cured
Present case	Endemic area Italy	46/M	P	Methotrexate	180	VL, MCL	pos SB pos PB	ND	Pos	Liposomal amphotericin B	Yes	Cured

Number in parentheses indicates the number of patients of each article reporting the characteristic of the column header. M, male; F, female; P, psoriasis; PSA, psoriatic arthritis; CL, cutaneous leishmaniasis; VL, visceral leishmaniasis; ML, mucosal leishmaniasis; MCL, mucocutaneous leishmaniasis; pos, positive; neg, negative; SB, skin biopsy; BM, bone marrow; PB, peripheral blood; ND, not done.

rant hyper-proliferation of keratinocytes. The pathogenesis of psoriasis is complex. Genetic susceptibility, environmental triggering factors and an over-reaction of local innate immune response initiate inflammation. Subsequent involvement of adaptive immune response with production of Th¹ cytokines, chemokines and growth factors lead to epidermal hyperplasia.⁵

Recently, a functional role of interleukin-17-producing T helper cells (Th17) in psoriasis has been suggested by their reduction during successful anti-TNF treatment.⁶ It is also known that Th17 lymphocytes play an essential role in protecting against intracellular protozoa and in the successful clearance of Leishmania by strengthening the Th1 response.⁷ In view of this, it could be argued that psoriasis may represent a protective factor for Leishmania infection. Indeed, in our review we did not find any case of leishmaniasis in psoriatic subjects who were not under immunosuppressive therapies.

Biological agents, which are powerful immunosuppressive drugs, have been more and more used in rheumatic patients and Leishmania infections have been reported among anti-TNF-agents users.⁸ Recently Maritati et al. found higher prevalence of subclinical leishmaniasis in patients with inflammatory rheumatic diseases receiving biological drugs than those treated with other immunosuppressive drugs.⁹ However, leishmaniasis has also been reported in psoriatic patients not receiving biological drugs, as occurred to our patient (Table 1).

Diagnosis of CL in psoriatic patients is challenging, as it mimics many other infections or a flare-up of psoriasis itself that can lead to ineffective and harmful changes of therapy. Immunosuppressive therapies cause atypical manifestations of leishmaniasis with large lesions spread over large cutaneous areas and associated to a possible mucosal involvement. ML by *L. infantum* is very rare and only sporadically described in patients receiving powerful immunosuppressive therapies or in HIV-coinfected patients. MCL is mostly observed in Latin America where *L. braziliensis* accounts for most cases, but *L. panamensis*, *L. guyanensis*, and *L. amazonensis* have also been implicated. Only rarely cutaneous lesions extend to areas of skin distant from the mucosa involved, as in our case in which two lesions on the foot and knee were associated with the oral lesion. In the context of impaired immunity, it is also advisable to rule out VL by PCR-Leishmania on peripheral blood so as to establish the most appropriate therapy: intralesional or intravenous.

Finally, there is no agreement on appropriate screening for leishmaniasis before immunosuppressive treatments and on the strategy to be followed after the diagnosis of leishmaniasis in rheumatic patients taking immunosuppressive drugs.¹⁰ Molecular methods are highly sensitive and specific tools for the diagnosis of visceral leishmaniasis and a screening with Leishmania-PCR in immunosuppressed patients living in endemic areas could be useful to identify patients at highest risk of reactivation.⁹

Specific leishmaniasis treatment followed by suspension of the immunosuppressive therapy was adopted by most of the authors. Overall even if the treatment response is not as good as seen in the immunocompetent population, our review reports a good outcome in all cases and patients remained relapse-free without maintenance therapy and despite the ongoing use of immunosuppressive medication.

In conclusion physicians must be alert to the possibility of development of leishmaniasis in immunosuppressed rheumatic patients. Adequate screening for VL should be incorporated into the list of baseline studies to carry out before initiating biologic therapies, at least in endemic areas.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.jinf.2020.01.019](https://doi.org/10.1016/j.jinf.2020.01.019).

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Claudia Colomba*, Laura Saporito, Silvia Bonura
Department of Health Promotion, Mother and Child Care, Internal
Medicine and Medical Specialties "G. D'Alessandro", University of
Palermo, Via Liborio Giuffrè, Palermo, Italy

Giuseppina Campisi
Department of Surgical, Oncological and Stomatological Disciplines,
University of Palermo, Via Liborio Giuffrè, Palermo, Italy

Paola Di Carlo
Department of Health Promotion, Mother and Child Care, Internal
Medicine and Medical Specialties "G. D'Alessandro", University of
Palermo, Via Liborio Giuffrè, Palermo, Italy

Vera Panzarella
Department of Surgical, Oncological and Stomatological Disciplines,
University of Palermo, Via Liborio Giuffrè, Palermo, Italy

Valentina Caputo, Antonio Cascio
Department of Health Promotion, Mother and Child Care, Internal
Medicine and Medical Specialties "G. D'Alessandro", University of
Palermo, Via Liborio Giuffrè, Palermo, Italy

*Corresponding author.

E-mail addresses: claudia.colomba@libero.it (C. Colomba),
laura.sapo@tin.it (L. Saporito), giuseppina.campisi@unipa.it (G.
Campisi), paola.dicarlo@unipa.it (P. Di Carlo),
panzarella@odonto.unipa.it (V. Panzarella),
valentina.caputo@unipa.it (V. Caputo), Antonio.cascio03@unipa.it
(A. Cascio)

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