Case report

Multifocal cutaneous leishmaniasis in a patient treated with golimumab for psoriatic arthritis

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Leishmaniasis is a zoonosis caused by protozoans transmitted by sandflies. Immunosuppression is a risk factor for developing leishmaniasis in patients treated with TNF inhibitors for autoimmune diseases. A 65-year-old man with a 14-year history of psoriatic arthritis in treatment with methotrexate, treated with golimumab during the last 2.5 years, presented ulcerations of the buttocks and upper back. Histopathological findings allowed us to yield the diagnosis of cutaneous leishmaniasis. Therapy was suspended and the patient underwent appropriate treatment. Five cases of leishmaniasis in patients treated with golimumab were reported in literature and ten cases were mentioned in retrospective reviews.

Key words: *Leishmania*, psoriasis, psoriatic arthritis, golimumab performance.

Introduction

Cutaneous leishmaniasis is a zoonosis caused by flagellate protozoans of the genus *Leishmania* transmitted by sandflies [1]. Leishmaniasis is a major public health problem in South America, Asia, and Africa, being one of the most important infectious diseases worldwide [2].

Immunosuppression represents an important risk factor for the development and reactivation of severe forms of leishmaniasis. The increasing use of immunomodulatory drugs, such as tumor necrosis factor (TNF) inhibitors, for the treatment of autoimmune disorders has been associated with the disease [3, 4].

We report the case of an Italian patient developing cutaneous leishmaniasis after treatment with golimumab for psoriatic arthritis. As far as we know, only 4 cases of leishmaniasis that occurred in this setting have been thoroughly described so far.

Case report

A 65-year-old Italian man with a 14-year history of psoriatic arthritis with minimal cutaneous manifestations presented to our hospital with bilateral ulcerations of the buttocks and an additional smaller lesion of the upper back that had appeared 8–9 months earlier (Fig. 1). He had been treated with methotrexate (15 mg per week) for the past 14 years, but due to reduced efficacy of this treatment, he also started golimumab (50 mg per month) 2.5 years ago. His last travel abroad (to China) was 8 years earlier.

Punch biopsies from the borders and the inner portions of both gluteal lesions were fixed in 10% buffered formalin and embedded in paraffin to obtain 4-micrometre-thick sections stained with haematoxylin-eosin (HE). Additional slides were cut to be stained with Giemsa, PAS, and Grocott methods, and immunostained with monoclonal antibodies against CD1a (clones 010 and MTB1).

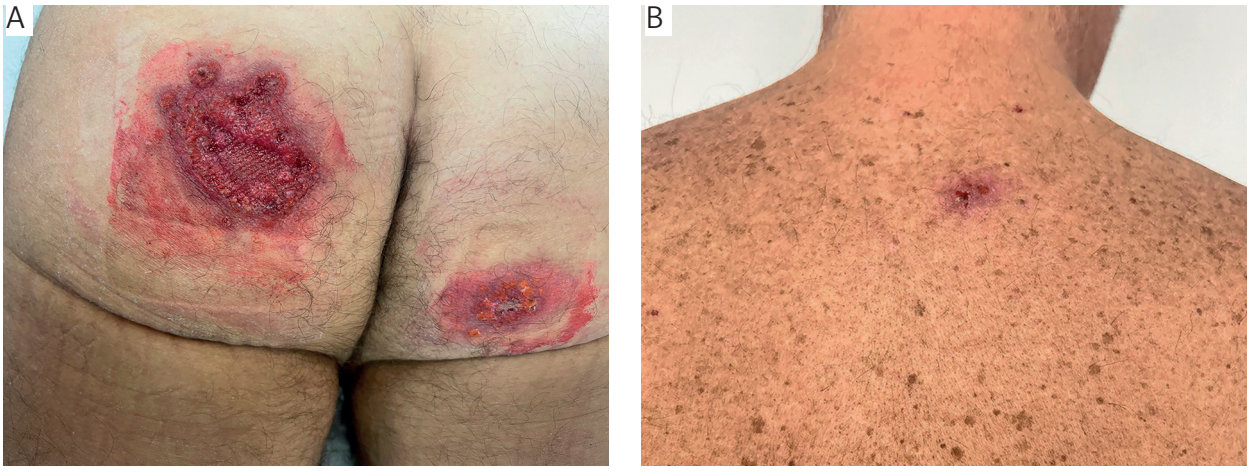

Fig. 1. Clinical presentation of the patient with **A)** huge bilateral ulcerations of the buttocks with erythematous raised margins (reddish coloration enhanced by the empirical treatment with rifampicin); **B)** a smaller raised ulcerated lesion of the upper back

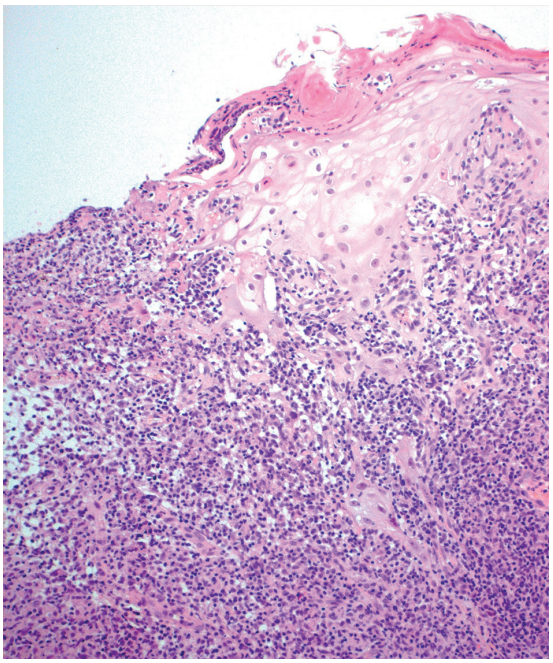

Fig. 2. Microscopic examination of ulcer border with marked dermal infiltrate of histiocytes, lymphocytes, neutrophils, and plasma cells (HE, ×20)

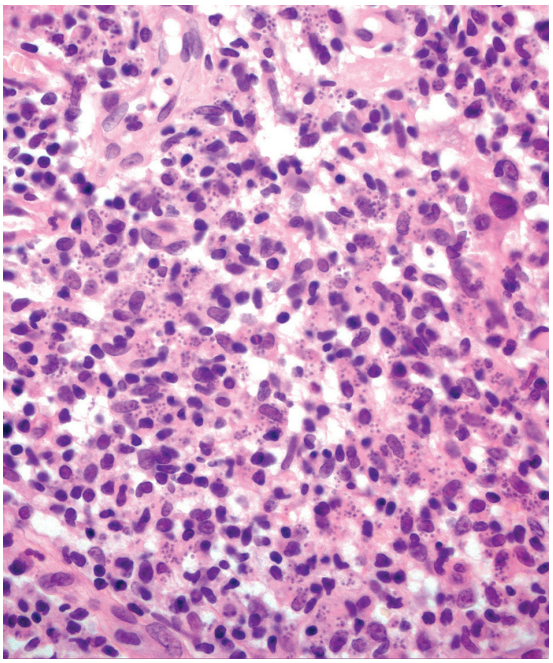

Fig. 3. Numerous amastigotes in the cytoplasm of the histiocytes (HE, ×40)

Histology showed a dense nodular dermal infiltration composed of histiocytes, lymphocytes, neutrophils, and plasma cells, with central ulceration (Fig. 2). Intracellular amastigotes with peripheral nuclei and kinetoplasts were detected within histiocytes (Fig. 3). They were positive with Giemsa stain and negative after staining with PAS and Grocott methods. Amastigotes were strongly immunoreactive for CD1a using MTB1 monoclonal antibody, but not with 010 clone (Fig. 4). These findings allowed us to yield the diagnosis of cutaneous leishmaniasis.

Mucosal and visceral involvement was excluded based on clinical parameters and ultrasonography. Therapy with golimumab and methotrexate was suspended after histologic diagnosis and the patient was referred to another hospital, where he underwent local treatment with paromomycin. After 2 months of local treatment, the lesions are reducing in size.

Discussion

Leishmaniasis is an infection caused by a hemoflagellate parasite of the genus Leishmania. The vector sandfly may belong to the genus Phlebotomus in the Old World and Lutzomyia in the New World. The disease is classified into cutaneous (caused by different

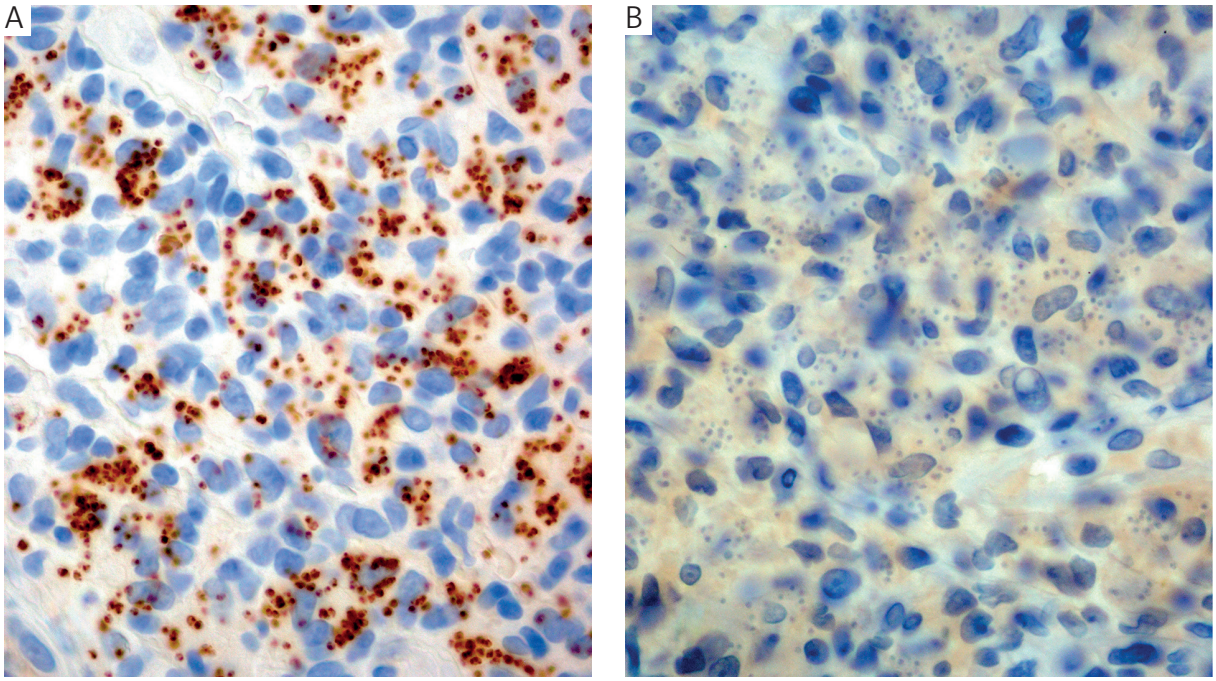

Fig. 4. Immunohistochemical staining with anti-CD1a monoclonal antibodies: **A)** clone MTB1; **B)** clone 010

Leishmania species in Old and New World), muco-cutaneous, and visceral (kala-azar) forms [5]. Cutaneous acute lesions are single pruritic papules at the site of inoculation. Within a few weeks they may become ulcerated nodules [5, 6]. The ulcers have erythematous raised margins that represent the best areas to be sampled to find the organisms. The ulcers heal leaving a residual scar [6].

Infection occurs when sandflies bite and inject flagellated promastigotes. These are phagocytised by macrophages, and within the phagolysosomes of the cells they transform into aflagellated amastigotes and multiply. Dermal dendritic cells phagocytise amastigotes and carry the organisms to lymph nodes, presenting the antigen to trigger a primary immune response. Activated T cells then migrate to sites of infection to kill the amastigotes. During a puncture on an infected human or animal host, new phlebotomes ingest macrophages infected with amastigotes and sustain their life cycle.

Microscopic examination of cutaneous lesions shows a dense dermal inflammatory infiltrate of histiocytes with lymphocytes, neutrophils, plasma cells, and eosinophils. The parasites may be seen in the cytoplasm of the histiocytes, especially at its periphery (marquee sign). They are oval in shape with distinct cell membrane and have a darkly basophilic nucleus on one side and a kinetoplast on the other. Due to their small size (3 μm), they are difficult to see and may be overlooked. The identification of the kinetoplast and PAS/Grocott-negative stainings help to rule out histoplasmosis [5, 6]. The amastigotes may be identified in touch preparations and histologic sections from biopsy specimens, also through immunohistochemistry. The immunohistochemical detection of Leishmania deserves a special mention. The positivity of amastigotes with certain clones of antibodies against CD1a represent an affordable alternative to polymerase chain reaction (PCR) testing on blood or tissue samples. CD1a immunostaining can be extremely useful in difficult cases, when amastigotes are not numerous. Anti-CD1a monoclonal antibodies do not universally stain all species of Leishmania, with a lower sensitivity for New World species [7–9]. CD1a clone MTB1 (Leica/Novocastra) positively labels amastigotes, while 010 clone (DAKO) does not [8]. It has been suggested that Leishmania amastigotes possess a cross-reacting protein with MTB1 clone or may contain a modified form of the protein obtained from host dendritic cells, which no longer reacts with the 010 clone [8]. A more recently investigated CD1a clone (EP3662) appeared as a more sensitive marker for New World cutaneous leishmaniasis [10–12]. In the present case, immunohistochemical staining was performed only as a confirmation test after the diagnosis had been yielded at the HE level. However, the results fully agree with the literature, lacking 010 clone reactivity and displaying marked positivity to MTB1.

Immunomodulatory drugs constitute an important basis for the treatment of dermatological, rheumatological, and gastroenterological autoimmune disorders. Immunobiologicals specifically block important mediators of the immune system, such as TNF-α and other cytokines, thereby enhancing the risk of leishmaniasis infection or reactivation. Although the increased risk of tuberculosis was the initial focus regarding infections

in patients treated with immunosuppressive drugs, there have been a substantial number of reports on leishmaniasis, which is usually diagnosed after several months of treatment [2, 13]. Significantly increasing numbers of cutaneous, muco-cutaneous, and visceral leishmaniasis have been reported during immunomodulatory therapy for rheumatoid arthritis, ankylosing spondylitis, or severe psoriasis/psoriatic arthritis. The TNF inhibitors involved in the development of leishmaniasis includes methotrexate, adalimumab, etanercept, infliximab, efalizumab, certolizumab, and golimumab [13–20]. The geographical distribution of leishmaniasis in immunosuppressed patients is significantly different from the one observed in the general population. About 76% of cases in immunosuppressed individuals has been reported in Europe, where chronic rheumatic conditions and access to immunosuppressive treatments are more common, while European leishmaniasis accounts for only 2% of all cases worldwide [2]. Also, increasing rates of travel and migration play a significant role in the distribution of leishmaniasis in non-immunosuppressed patients [20].

Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF-α, preventing TNF-α binding to its receptors. First approved in April 2009, golimumab demonstrated significant efficacy for treating psoriasis, psoriatic arthritis, and nail disease, with a positive impact on quality of life. Although protozoal opportunistic infections are only generically mentioned between rare adverse reactions to this immunobiological drug, a case of cutaneous and visceral leishmaniasis was firstly reported in 2017 [21]. Three additional fully documented reports of leishmaniasis occurring in patients on golimumab were published in the following years [22–24]. The clinical data of these patients are summarised in Table I.

In addition to these single reports, 10 additional cases of leishmaniasis that arose after golimumab therapy were mentioned in retrospective investigations dealing with leishmaniasis in European patients treated with TNF inhibitors [19, 20]. Unfortunately, no individual data about the single patients were reported in these studies. Case reports are to be preferred because the description of the features related to each individual case provides accurate documentation of the differences observed between distinct TNF blockers.

Regarding our patient, he used to live in Milan, Italy, and it seems quite likely that he contracted the infection during his seaside stays on the Adriatic coast of the Abruzzo region, where he used to spend his summer vacations. His only recent trip abroad was to China, a country where leishmaniasis is not an endemic disease. As in 2 of the cases reported in the literature, our patient also had a long history of treatment with methotrexate [21, 22]. Given the lapse of time since the start of treatment with the 2 drugs, the infection appears to be more likely related to golimumab. However, we cannot exclude a pre-existing Leishmania infection reactivated after the beginning of golimumab treatment.

As for other TNF inhibitors, immunosuppression with golimumab can be followed by the development or reactivation of leishmaniasis. The most reasonable hypothesis is that people living in endemic regions have Leishmania infection in a latent stage, which then progress to symptomatic disease after immunosuppression [21–23]. In fact, persistence of Leishmania has been documented in the scar tissue and blood of successfully treated patients, confirming that persisting infection may upsurge following immunosuppression [13]. The management of these patients may be problematic, also due to the lack of precise guidelines. Discontinuation of the biologic agent seems to be the best therapeutic approach, and its re-administration may be performed only after successful treatment for leishmaniasis [21, 23].

Table I. Details of the reported cases

Ref.	Age/ Gender	Country	Disease	Therapy	Duration	Golimumab	Leishmaniasis
[21]	65/M	Italy	PsA	Cyclosporine Methotrexate Steroids	20 years	2 years	Cutaneous, visceral
[22]	73/F	Brazil	RA	Methotrexate Steroids	NA	6 months	Mucocutaneous (reactivated)
[23]	71/M	Spain	PsA	NA	NA	NA	Cutaneous
[24]	72/F	Sweden (visiting Spain)	PsA	NA	NA	NA	Cutaneous
PC	65/M	Italy	PsA	Methotrexate	2.5 years	2.5 years	Cutaneous

PsA – psoriatic arthritis; RA – rheumatoid arthritis; NA – not assessed; PC – present case

Healthcare professionals must be aware of the increasing prevalence of leishmaniasis in countries where the disease is endemic, due to the growing population of immunosuppressed patients, and in non-endemic areas, due to the frequent cases related to people travelling and migration [24].

Conclusions

To the best of our knowledge, this case represents the fifth fully documented report of leishmaniasis in a patient treated with golimumab. Ten additional cases were mentioned in retrospective reviews, but their individual data are not available.

As observed for other TNF antagonists, the use of golimumab has been associated with new cases of leishmaniasis. Lesions may be due to infection during immunosuppressive therapy or reactivation of latent leishmaniasis. Physicians should be aware of this disease in patients on this biotechnological drug, especially when they have previously lived in endemic areas.

Disclosures

1. Institutional review board statement: Not applicable.
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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