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Mucosal *Leishmania infantum* leishmaniasis: Specific pattern in a multicentre survey and historical cases

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Summary *Objective: Leishmania infantum* mucosally restricted leishmaniasis was rarely reported, so that diagnostic and treatment strategies remain debated. A long-term multicentric survey appeared thereby necessary.
Methods: Cases were prospectively collected over 12 years in 3 academic hospitals of Southern France. Predisposing factors, clinical findings, diagnostic procedures, treatment and outcome were compared to medical literature.
Results: Ten new cases and 40 historical reports were collected. Respectively 10/10 and 35/40 patients were adult males. Immunodeficiency was frequent (5/10 and 18/40). No previous cutaneous lesion was reported. Leishmaniasis affected mostly larynx (5/10 and 19/40), but also mouth (2/10 and 19/40) and nose (3/10 and 5/40). Lesions were highly polymorph. *Mucosa* histological examination provided respectively 1/10 and 2/40 false negative results, contrary to serum immunoblotting and PCR on mucosal biopsy. Although local response was always

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satisfactory even using topical treatment, subsequent visceral spreading was observed in 2/10 and 1/40 cases.
Conclusion: L. infantum mucosally restricted leishmaniasis exhibits a specific pattern, marked by tropism for adult males, high clinical and histological polymorphism. Immunoblot screening and PCR confirmation of suspected lesions are necessary because of direct examination occasional false negative results. The risk of visceral spreading sustains systemic therapy.
Summary: Leishmania infantum mucosal leishmaniasis mostly affects adult males, half of them immunodeficient. Clinical and histological polymorphism makes the diagnosis difficult, stressing the need for immunoblot screening and *mucosa* PCR analysis of suspected cases. Possible visceralization sustains systemic therapy.

Introduction

Mucocutaneous leishmaniasis is well-known as *espundia*, caused by New World *Leishmania* species, especially *Leishmania braziliensis*. *Espundia* develops within a few months to several years after a cutaneous leishmaniasis. It provokes severe rhino-facial destructions and may relapse despite parenteral treatment.[1] Around the Mediterranean, mucosally restricted leishmaniasis is known for half a century.[2] The disease is due to *Leishmania infantum*, which most often causes visceral leishmaniasis, and seldom cutaneous lesions.[3] Conversely, other Old World species such as *Leishmania major* cause only mucosal extension of cutaneous lesions.[4] In 2003, a review of the literature gathered 31 cases of *L infantum* mucosally restricted leishmaniasis (LIML).[5] However, since 2003, this condition has been increasingly reported.[6–18] Until now, no study reported more than 3 consecutive cases, so that many points remain controversial: predisposing conditions are badly determined, diagnostic efficiency of pathological examination is uncertain,[5,7,8,17] and local treatments are sometimes used although parenteral treatment remains the reference.[5,14] Overall, LIML seems insufficiently evoked: misdiagnosis as neoplasia or vasculitis sometimes leads to undue therapeutics such as radiotherapy or steroids.[5,8,9,16,17] To raise awareness and clarify remaining issues, we conducted a 12-year-long study among the 3 academic hospitals in French endemic zone and updated the literature review.

Material and methods

Cases were collected in all French academic hospitals bordering the Mediterranean: Marseille, Montpellier (National Reference Center for *Leishmania*), and Nice. A prospectively filled-in registry was used from 1997 to 2009. Criteria for inclusion were primarily the presentation of mucosal lesion due to *Leishmania*, then the absence of initial visceral involvement as demonstrated by a negative direct examination of bone marrow, and finally the identification of *L. infantum* or the absence of travel in areas endemic for other *Leishmania* species. ELISA on serum and PCR on mucosal tissue were performed as previously described.[19,20] Immunoblotting was done using LeishWesternBlotIgG from LDBIO Diagnostics®. Strains were typed using multilocus enzyme electrophoresis (MLEE).[21] After informed consent was obtained, TNF promoter of recent patients from Marseille was sequenced using Applied Biosystems™ 3130 Genetic Analyzer to investigate the presence of the mutation associated with New World mucocutaneous leishmaniasis.

The literature was reviewed using MEDLINE (keywords: "leishmaniasis" and "mucosal", "mucocutaneous", "oral", "nasal", "laryngeal", or "tonsil"). We also checked references in the articles collected to detect additional cases and to avoid duplication of reported cases. Reports without documented bone marrow examination were excluded, so as not to include undiagnosed visceral leishmaniasis. Reports with extra-tegumentary lesions were excluded.

Results

Of the 10 patients, 9 lived in endemic foci of Southern France. One patient took holidays there. All patients were adult males, aged between 21 and 65 years (median: 44). Five patients were immunocompromised: 3 HIV infections (when documented, CD4 counts superior to 200/mm^3), one azathioprine and prednisone treatment for renal transplantation, one chronic lymphoid leukemia. Three patients reported smoking. At time of diagnosis, only single lesions were found. Lesions were ulcerative (4/10), polypoid (2/10), infiltrative (2/10), or nodular (2/10). LIML affected larynx (5/10), including three vocal cord lesions (3/10), nose (3/10, Fig. 1), soft palate (1/10), or cavum (1/10). One lesion was painful. One patient with subsequent visceral spreading then presented with multiple mucosal lesions. For all patients, neither history nor scar of cutaneous leishmaniasis was reported. Delay between first sign and diagnosis ranged from 1 week to 3 years (median: 3 months) (Table 1).

Direct examination of mucosal biopsy showed only nonspecific findings in one patient diagnosed by PCR on mucosal biopsy and serology: even with Giemsa staining, only malpighian metaplasia and polymorph inflammation were seen, without granuloma. Direct examination showed *Leishmania* amastigotes in the nine other cases. *In vitro* culture was positive in 4/8 patients, isolating *L. infantum* zymodeme MON-1. Immunoblot was positive in 8/8 cases, while ELISA was negative in 1/8 cases. In case 1, serology was positive for a serum sampled 10 years before the first manifestation, without clinical manifestation evocative of mucosal or visceral leishmaniasis at that time. PCR on mucosal biopsy was positive in 5/5 cases.

Three patients received liposomal amphotericin B, six received meglumine antimoniate, and one left without treatment. One patient discontinued meglumine antimoniate after 7 days because of pancreatitis, but responded well. No local relapse was described during follow-up (median: 8