Case Report

Superiority of local antimoniate over systemic liposomal amphotericin B therapy in a *Leishmania infantum* cutaneous leishmaniasis

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Introduction: The therapeutic choice for treating cutaneous leishmaniasis (CL) can be difficult, notably in countries where autochthonous cases are rare. In France, CL is mostly due to imported cases. *Leishmania infantum*, which is the endemic species in the French south-eastern region, is usually responsible for visceral leishmaniasis but rarely causes the autochthonous cutaneous form of the disease. Intralesional injection of antimonials seems to be the most recommended therapy in the latter case, but particular situations can justify the use of systemic amphotericin B (AmB).

Case presentation: We report and illustrate a French case of locally acquired CL due to *L. infantum* that was surprisingly unresponsive to systemic AmB, with clinical worsening and parasitic invasion of the lesion. Thereafter, the patient was successfully treated by intralesional pentavalent antimonial.

Conclusion: This case supports the choice of intralesional therapy as the first therapeutic option in *L. infantum* CL, an infrequent situation in France.

Keywords: leishmaniasis; *Leishmania infantum*; amphotericin B; meglumine antimoniate; intralesional treatment; treatment failure.

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Introduction

The therapeutic choice for treating cutaneous leishmaniasis (CL) remains complex, and recommendations depend on the geographical area of contamination, *Leishmania* species and lesion features (WHO, 2010). In France, CL is mostly due to imported cases; the most frequently involved species are *Leishmania major* (cases from northern and sub-Saharan

Africa) and *Leishmania guyanensis* (cases from Southern America, mostly French Guiana) (Lachaud *et al.*, 2013). *Leishmania infantum*, which is the endemic species in the French south-eastern region, is usually responsible for autochthonous visceral leishmaniasis; however, this species rarely causes the cutaneous form of the disease, although it might be underdiagnosed and undernotified.

Here, we report and illustrate a case of CL due to *L. infantum* that was surprisingly unresponsive to systemic amphotericin B (AmB) treatment but was successfully treated by intralesional pentavalent antimonial.

Abbreviations: AmB, Amphotericin B; CL, cutaneous leishmaniasis; LIDL, *Leishmania infantum* cutaneous leishmaniasis; SPC, Summaries of Product Characteristics.

Fig. 1. (a) Clinical aspect at initial presentation. (b) Clinical aspect 2 weeks after completion of systemic AmB therapy. (c–f) Clinical aspect after 8 (c), 13 (d), 19 (e) and 26 (f) days of intralesional treatment. (g, h) Clinical aspect 6 (g) and 15 (h) weeks after completion of intralesional treatment.

Case report

A 67-year-old woman from France presented at our infectious diseases unit in July 2012 with a large (4 cm diameter) erythematous, papulonodular lesion on the forehead (Fig. 1a). The lesion had been growing for 4 months despite several non-specific topical treatments and antibacterial courses. The patient had a recent history of pancreatic carcinoma, treated with complete pancreatectomy and chemotherapy 1 year before, but was considered cured and immunocompetent at the time of presentation. She did not report recent foreign travel but had been on a trip to southern France a few months before the onset of symptoms. A first biopsy, performed before admission to our hospital, showed rare Leishman bodies leading to a diagnosis of CL. A molecular analysis of the sample, performed by the French National Reference Centre of Leishmaniasis (Mary *et al.*, 2004), later detected and identified a dermatropic strain of *L. infantum*.

Treatment

Because of the size of the lesion and its proximity to the eyes, intralesional treatment appeared to be difficult and hazardous. The clinical background of the patient (possible post-chemotherapy residual immunodepression) and the unusual causative species were additional arguments for initiating an intravenous treatment with liposomal AmB. However, despite six courses administered over 1 month (cumulative dose: 18 mg kg⁻¹, according to French official recommendations for visceral leishmaniasis; French National Agency for Medicines and Health Products

Safety, 2015), no clinical improvement was noted. In contrast, the size and inflammation of the lesion increased markedly (Fig. 1b). A new biopsy revealed a considerably increased dermal invasion by abundant *Leishmania* amastigotes (Fig. 2).

Because of the obvious failure of systemic therapy, and despite the large size of the lesion, intralesional meglumine antimoniate injections were initiated. Five sessions, with injections of 750 mg per session, were conducted over 1 month. This led to a gradual regression of the lesion (Fig. 1c–f); the patient completely recovered in 3 months (Fig. 1g, h) with no side effects or sequelae.

Discussion

This case illustrates the high efficacy of intralesional antimonial treatment in CL due to dermatropic strains of *L. infantum*. In France, CL due to the autochthonous species *L. infantum* (LI CL) are infrequent: out of the 78 annual cases of CL that were reported in France between 1999 and 2012, only 3.6 % were due to *L. infantum* (Lachaud *et al.*, 2013). In addition, the therapeutic choice for treating CL is complex, as few well-conducted studies have been published (WHO, 2010). The antifungal AmB is one of the few compounds that has been successfully used in leishmaniasis; other drugs are miltefosine, triazoles, pentamidine and pentavalent antimonial derivatives (Blum *et al.*, 2004). In Mediterranean Europe, liposomal AmB is the reference treatment for visceral leishmaniasis with *L. infantum* (WHO, 2010). However, as with other systemic treatments,

Fig. 2. May–Grünwald–Giemsa stain of a skin biopsy after systemic therapy showing numerous Leishman bodies, after intense intralesional proliferation of *L. infantum*.

AmB can also be considered in cases of CL, notably in countries where mucocutaneous forms exist (Goto & Lindoso, 2010). Moreover, success in treating LICL with liposomal AmB has already been reported (Paradisi *et al.*, 2005; Rongioletti *et al.*, 2009; del Rosal *et al.*, 2010). In metropolitan France, according to proposed therapeutic guidelines, AmB is currently recommended in particular cases with multiple or large lesions, metastatic spread or that are unresponsive to local treatment (Buffet *et al.*, 2011).

In the current case, the size of the lesion was close to that defined to require systemic treatment (5 cm diameter) (Blum *et al.*, 2004). After the European and French Summaries of Product Characteristics (SPC) of meglumine antimoniate, intralesional injection of this compound was not a first-line option, as the lesion was located in an area where scarring could cause disfigurement or disability (Sanofi-Aventis, 2011). Consequently, the initial treatment with systemic liposomal AmB of the current case appeared to be justified and the worsening of the lesion was unexpected.

A previous case of LICL unsuccessfully treated by AmB was published in 2012 in Spain (Hervás *et al.*, 2012), where the lesion was unresponsive to two courses of AmB (cumulative doses: 39 and 18 mg kg⁻¹, respectively) following other treatments including intralesional antimoniate; imiquimod was finally used with success.

The current case together with this latter one reflect the difficulty in achieving a high drug concentration in the lesion. Thus, the dose and duration of the treatment may be critical; however, there is no consensual regimen. The recommended cumulative dose in the French SPC for liposomal AmB for visceral leishmaniasis ranges from 18 to 24 mg kg⁻¹ (French National Agency for Medicines and Health Products Safety, 2015), whereas the British SPC states 21–30 mg kg⁻¹ (Electronic Medicines Compendium, 2015); the latter recommends treatment over a 10–21-day period, while the former provides a protocol of six injections over 10 days. For CL, similar regimens appeared to be efficient in most published cases (Paradisi *et al.*, 2005; Rapp *et al.*, 2003; Solomon *et al.*, 2011). However, increasing the cumulative dose to 40–50 mg kg⁻¹ as reported by some authors may solve some cases (Brown *et al.*, 2005; del Rosal *et al.*, 2010).

Alternative explanatory hypotheses for the treatment failure presented here are: (i) a lower susceptibility to AmB of dermatropic strains compared with viscerotropic strains; and (ii) the emergence of strains resistant to AmB. In favour of the latter hypothesis, *L. infantum* strains showing high inhibitory concentrations (IC₅₀) to AmB have been reported in humans and dogs (Maia *et al.*, 2013). However, no standardized, easy-to-use tests are currently available for *Leishmania* strain susceptibility assessment, and more data in this field would be of interest.

In conclusion, this report emphasizes the need for developing susceptibility testing on *Leishmania* strains and supports the choice of intralesional therapy as the first therapeutic option in LICL.

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