Allergic reactions to meglumine antimoniate while treating cutaneous leishmaniasis

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Sir,

Pentavalent antimonials (meglumine antimoniate, Glucantime® and sodium stibogluconate, Pentostam®) are the gold standard therapy for cutaneous leishmaniasis. Intralesional (IL) therapy is usually the treatment of choice for localized cutaneous disease, whereas intramuscular (IM) and intravenous treatment are recommended for extensive forms and for cases involving the mucosal surfaces.

Cutaneous Adverse Drug Reactions (CADRs) to IM Glucantime® have been reported in less than 1% of the patients.[1-4] They occur more frequently after IL administration, being described in about 3% of over 1000 reported cases.[2-9] These comprise both type-I and type-IV allergic reactions. We report two cases of cutaneous reactions to Glucantime® in two patients diagnosed and treated at Hospital del Mar, Barcelona, that illustrate the clinical and pathogenic heterogeneity of this uncommon side effect.

Case 1: A 35-year-old Caucasian man suffering from ankylosing spondylitis and Crohn's disease and receiving treatment with subcutaneous adalimumab fortnightly developed a small ulcer on the right lower leg one week after a mosquito bite while on vacation in Sri Lanka in February 2013. The patient spent the preceding months in Portugal. Diagnosis of cutaneous leishmaniasis was confirmed by identification of *Leishmania infantum* in cutaneous tissue through molecular techniques. Sri Lanka is known to be endemic for *L. donovani*[10], but considering the clinical history it is very likely that the infection was acquired there. Treatment with adalimumab was stopped and weekly IL Glucantime® (meglumine antimoniate 1500mg/mL, Sanofi-Aventis, France; excipient: potassium metabissulfite) was administered. Few minutes after the third administration, the patient developed erythema, edema and pruritus at the injection site; emesis, dizziness and widespread urticarial lesions (Fig.1) developed after the seventh injection. After presenting this clinical picture the treatment was withdrawn. The cutaneous ulcer showed progressive resolution without any additional treatment. Prick tests and immediate intradermal reaction were positive to meglumine antimoniate (Fig.2a,b). A 4-millimeter punch biopsy obtained from the resulting erythematous papule 48 hours after intradermal infiltration was compatible with hypersensitivity reaction.

Case 2: A 47-year-old Caucasian woman with a personal history of positive serology for hepatitis C virus, developed a solitary ulcerated plaque on the left leg while travelling in Brazil, one month after starting the vacation. The ulcer progressively enlarged and new ulcers appeared in a sporotrichoid distribution. *Leishmania panamensis* was identified in cutaneous tissue confirming the diagnosis of cutaneous leishmaniasis. The patient denied any lesions prior to departure and did not recall any mosquito bite on that area while in Barcelona, where she usually lives. The causal relationship strongly suggests that the infection was acquired in Brazil. Daily IM Glucantime® 20mg/Kg was started in October 2014. During the second week of treatment the patient developed subcutaneous nodules on the injection site, headache and nausea. Treatment was switched to intravenous administration, and after the fourteenth perfusion, self-limited acute generalized urticaria developed. This was suggestive of type-I hypersensitivity, but prick tests and immediate intradermal reaction with meglumine antimoniate 1% were negative. However, the intradermal reaction was positive after 48h, in favor of delayed type-IV hypersensitivity. Treatment was switched to intravenous pentamidine isethionate with favorable evolution.

Two different subsets of cutaneous hypersensitivity reactions to Glucantime® have been reported in the literature. Immediate reactions range from localized and generalized urticaria with or without systemic symptoms to anaphylactic shock and probably represent type-I Ig-E-mediated allergic reactions. This was the case of our first patient, who developed immediate urticaria with systemic symptoms. Positive prick test and immediate intradermal reaction confirmed type-I hypersensitivity mechanism.

Delayed reactions include eczematous lesions and persistent subcutaneous nodules, probably resulting from type-IV allergic reactions. Our second patient developed persistent subcutaneous nodules at the injection sites and had positive delayed intradermal test, which favors a type IV-hypersensitivity mechanism.

Cordoba and co-workers[5] performed intradermal reaction, prick and patch tests in 7 patients who developed eczema at IL Glucantime® injection site. Intradermal reaction with Glucantime® as is and diluted was positive in all 7 patients, whereas prick tests were negative in all of them and patch tests positive in one. No other study reports the use of additional tests to confirm mechanism behind the observed cutaneous lesions.

CARDs to IL Glucantime® might have different clinical presentations depending on the underlying mechanisms. Despite their rarity, the recognition and confirmation of such reactions is important in order to discontinue treatment in due time and prevent further complications.

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Figures

Figure 1 - Papules and plaques scattered over the trunk and upper extremities appearing immediately after intralesional Glucantime® administration. The lesions resolved spontaneously within half an hour.

Figure 2 – a) Prick test with meglumine antimoniate 1%: papule of 5mm and erythema of 10 mm at 30 minutes; b) Positive intradermal reaction to meglumine antimoniate 1% after 48 hours.

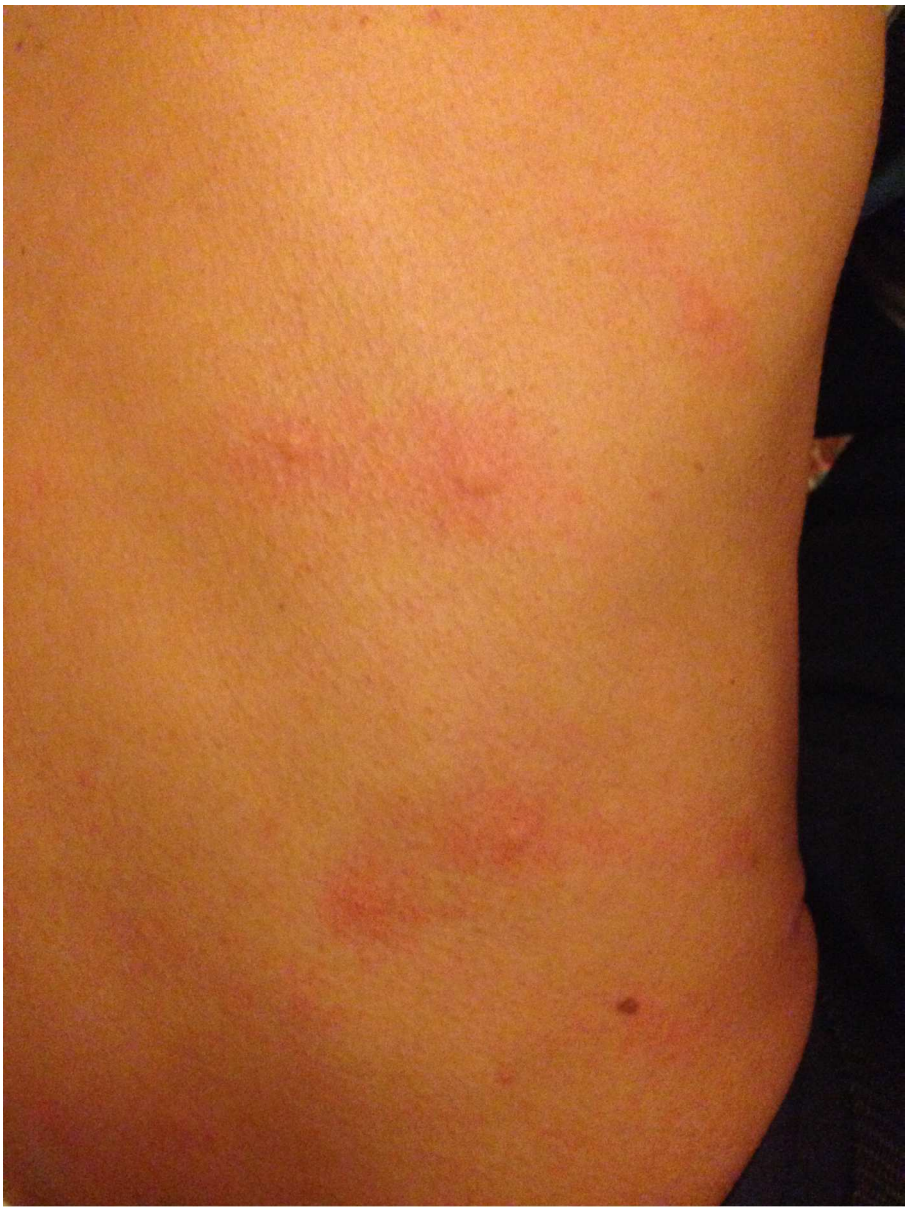

Figure 1 - Papules and plaques scattered over the trunk and upper extremities appearing immediately after intralesional Glucantime® administration. The lesions resolved spontaneously within half an hour.
863x1151mm (72 x 72 DPI)

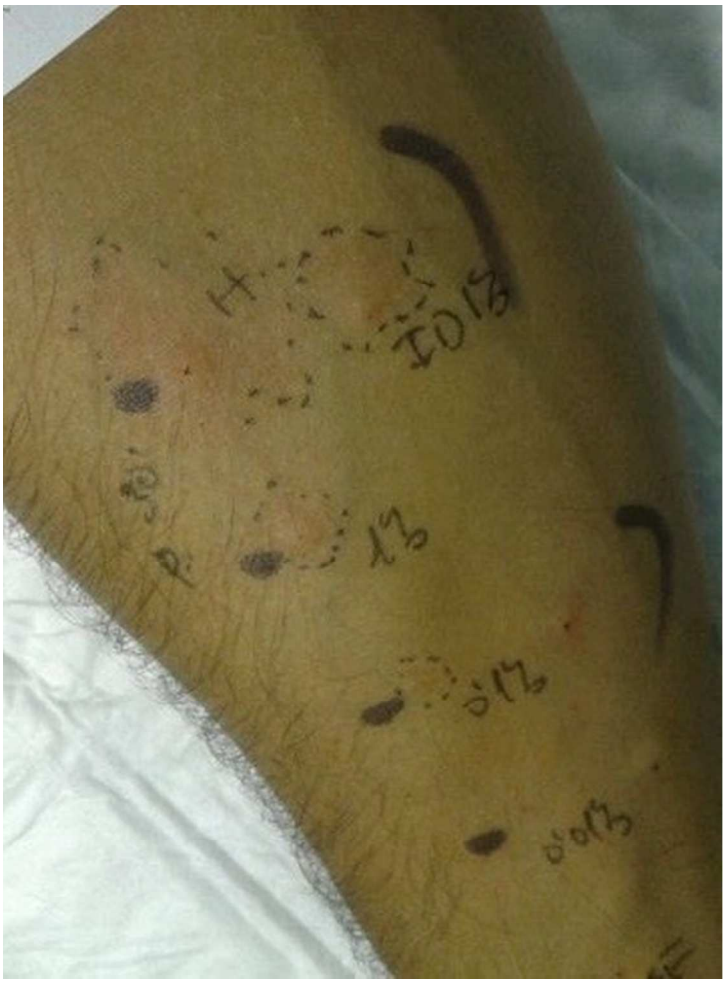

Figure 2 – a) Prick test with meglumine antimoniate 1%: papule of 5mm and erythema of 10 mm at 30 minutes
126x171mm (72 x 72 DPI)

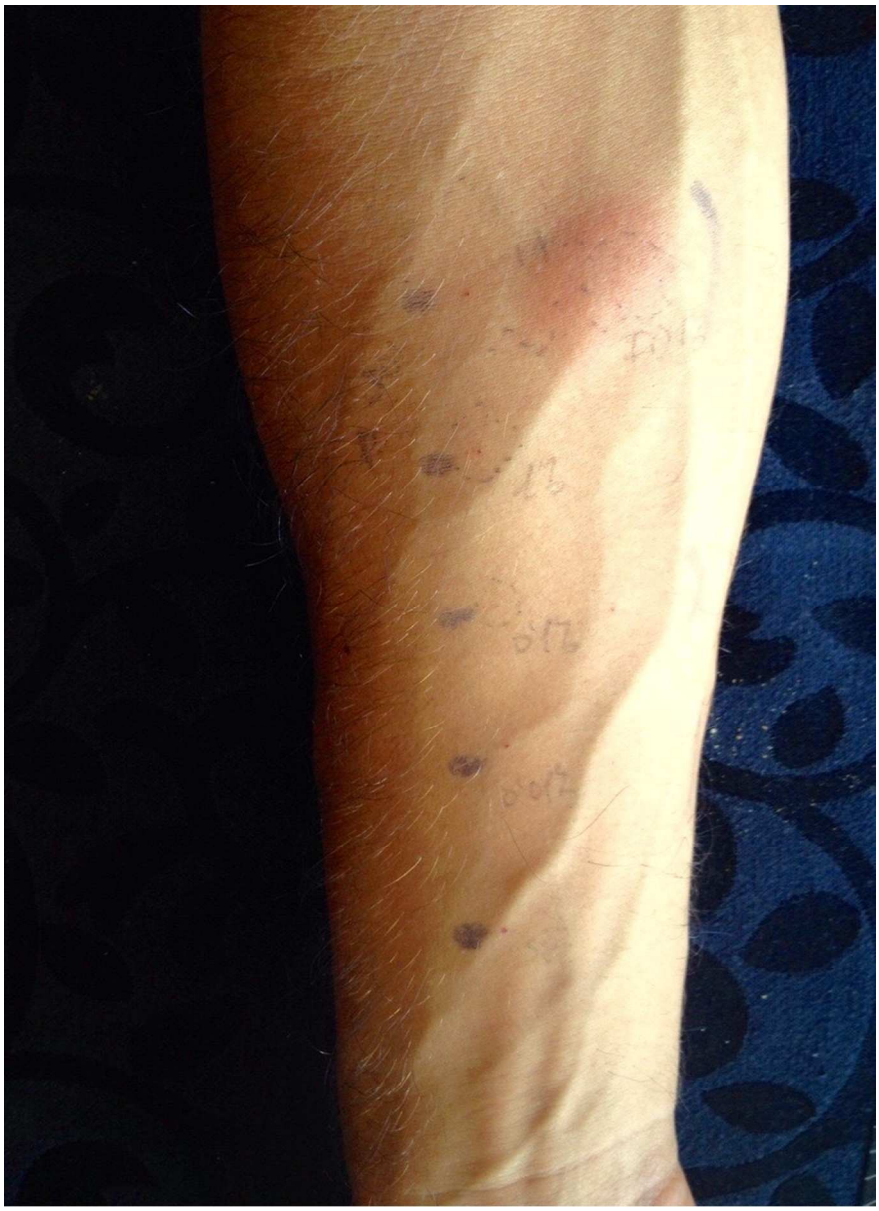

Figure 2 - b) Positive intradermal reaction to meglumine antimoniate 1% after 48 hours.
309x426mm (72 x 72 DPI)