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Successful miltefosine treatment of post-kala-azar dermal leishmaniasis occurring during antiretroviral therapy

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The first two patients to be treated with miltefosine for post-kala-azar dermal leishmaniasis (PKDL) are reported. One was a 26-year-old Ethiopian man who had been treated with sodium stibogluconate, for relapsing visceral leishmaniasis (VL), four times between August 2002 and March 2004. In January 2004 this patient was found to be seropositive for HIV and began antiretroviral treatment with stavudine, lamivudine and nevirapine. Five months later he developed clinical PKDL, with extensive cutaneous, conjunctival and oral mucosal involvement. The second patient was a 42-year-old Ethiopian man who was treated for relapsing VL in November 2003. He too was subsequently found to be seropositive for HIV and was treated with stavudine, lamivudine and nevirapine from May 2004. He developed a nodular rash of PKDL over his face and upper body 2 weeks after starting the antiretroviral therapy. Treatment of both patients with oral miltefosine, at 100 mg/day for 28 days, led to the complete regression of their PKDL lesions. When checked 3–6 months after the end of the miltesofine treatment, neither patient showed any signs of VL, PKDL or other HIV-associated disease.

In Ethiopia, visceral leishmaniasis (VL) is becoming increasingly common as an HIV-associated opportunistic infection (Ritmeijer *et al.*, 2001; Lyons *et al.*, 2003). In 2005, the World Health Organization included VL as an AIDS-defining clinical event in Africa (http://www.who.int/hiv/pub/guidelines/clinicalstaging.pdf). Just as in southern Europe, where the VL is caused by *Leishmania infantum* (Desjeux and Alvar, 2003), the HIV-associated infection caused by *L. donovani* in Ethiopia often follows a relapsing course. Several cases of post-kala-azar dermal leishmaniasis (PKDL) occurring soon after the initiation of anti-retroviral (ARV) therapy have been observed in Ethiopia and it seems likely that these represent examples of the immune-reconstitution inflammatory syndrome (unpubl. obs.). Two such cases, who were successfully treated with miltefosine (hexadecylphosphocholine), are described below.

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CASE REPORTS

Patient 1

A 26-year-old man, who worked as a daily labourer on a farm in the VL-endemic region of Humera Woreda, Tigray, Ethiopia, was treated for pulmonary tuberculosis in 1998. In August 2002 he was diagnosed as a case of VL (on the basis of prolonged fever, splenomegaly, and the presence of amastigotes of *Leishmania* in a splenic aspirate) and treated with sodium stibogluconate, the only antileishmanial drug then available in Ethiopia, at the

standard dose of 20 mg/kg.day for 30 days (WHO, 1996). Although his symptoms improved and his test-of-cure (TOC) aspirate was negative for amastigotes, he had parasitologically-confirmed relapses of VL in May 2003 and September 2003; on each occasion he was re-treated with sodium stibogluconate. In January 2004, he was diagnosed as having advanced HIV infection and in February 2004 he began ARV therapy, based on stavudine, lamivudine and nevirapine. At that time he was found to have a lymphocyte count of $1.5 \times 10^3/\mu l$ (counts of CD4 cells were not possible). In March 2004, he again developed the signs and symptoms of VL, a splenic aspirate was found to be parasite-positive, and whilst continuing on his ARV therapy, he was treated, for the fourth time, with sodium stibogluconate at 20 mg/kg.day, this time for 40 days. This treatment was closely supervised because of the potential for combinations of ARV drugs and sodium stibogluconate to cause pancreatitis (Delgado *et al.*, 1999). As on all previous occasions, his end-of-treatment splenic aspirate was clear of visible *Leishmania* amastigotes. In May 2004, the patient was found to have 446 CD4 cells/μl. In June 2004 he presented with a new complaint of a rash that had begun on his forehead and then progressively involved his entire face, the upper part of his chest and back, and the extensor surfaces of both arms. Although the rash was not itchy, he subsequently experienced irritation and redness of his left eye and developed a lesion on the mucosal surface of his upper lip.

DIAGNOSIS OF PKDL

When he presented with the rash, patient 1 was found to be moderately malnourished, with a body mass index (BMI) of 19.6 kg/m^2. He had papular and nodular lesions over his face, the upper part of his chest and back, and the extensor surfaces of both arms. Examination of his eyes revealed bilateral conjunctival oedema and injected sclerae, with small nodular lesions on the inner surface of the left lower eyelid and the outer surface of the right upper eyelid. His visual acuity was normal. There was a small ulcer within the left angle of his mouth. His spleen was palpable 3 cm below the left costal margin and his liver was palpable 2 cm below the right costal margin. The rash was clinically diagnosed as PKDL with mucosal involvement.

LABORATORY INVESTIGATIONS

At the time his PKDL was diagnosed, patient 1 was found to have 13.2 g haemoglobin/dl, and approximately 4400 leucocytes, 148,000 platelets and 333 CD4 cells/μl blood. The results of renal- and liver-function tests were normal, and a Giemsa-stained punch biopsy from a lesion on the patients face was negative for *Leishmania* amastigotes.

Patient 2

A 42-year-old man who, like patient 1, worked as a daily farm labourer in the VL-endemic area of Tigray, was treated for parasite-proven VL in November 2003. He responded satisfactorily to a 30-day course of sodium stibogluconate. He was found seropositive for HIV in August 2003 and started on ARV therapy (stavudine, lamivudine and nevirapine) in May 2004, when his CD4 count was found to be 154 cells/μl. Two weeks after starting ARV therapy, a nodular, non-itchy rash appeared over the peri-oral region of his face, and then progressively involved his entire face, the upper part of his chest and both upper arms.

DIAGNOSIS OF PKDL

On examination when he presented with the rash, patient 2 was found to be afebrile and malnourished (BMI=15.7 kg/m^2) and to show no splenomegaly but mild (2-cm) hepatomegaly. He had hypopigmented papular and macular lesions over his face (mainly over the forehead, nose and

peri-oral region) and these extended over the extensor surface of the upper arms. There was an ulcerated crusted lesion within his right nostril and a nodular lesion over his left nostril. His conjunctivae were hyperaemic, with a nodular lesion on the lower lid of the right eye. The rash was clinically diagnosed as PKDL with mucosal involvement.

LABORATORY INVESTIGATIONS

At the time his PKDL was diagnosed, patient 2 was found to have 11.2 g haemoglobin/dl, and approximately 3700 leucocytes, 185,000 platelets and 182 CD4 cells/μl blood.

Management of Both Cases

The clinicians attending patients 1 and 2, assuming that both had severe PKDL, possibly as a manifestation of an immune-reconstitution inflammatory syndrome, decided that both patients required urgent systemic antileishmanial therapy. At the time this decision was made, the clinicians already had considerable experience in the use of miltefosine to treat VL, and were able to offer the patients miltefosine free of charge, on a compassionate basis. A discussion was held with the patients, at which they were fully informed of the treatment options (i.e. intravenous sodium stibogluconate or oral miltefosine). They chose to try miltefosine (Impavido®; Zentaris, Frankfurt, Germany) and were therefore treated with this drug, either as an inpatient (patient 1) or outpatient (patient 2), in the standard regimen that has been used against VL in Ethiopia — 100 mg daily for 28 days.

Outcomes

PATIENT 1

On his third day of treatment with miltefosine, patient 1 experienced itching of his lesions, with mild swelling of the dorsum of each hand; these effects responded to oral chlorphenamine (4 mg twice daily for 5 days). After 2 weeks of treatment, patient 1's skin and mucosal lesions began to improve, and by the end of treatment his eye and mouth lesions had disappeared and his skin lesions were crusted, flattened, and slightly hypopigmented. Six months later, his skin appeared normal, he felt well on the ARV therapy, and he had a normal CD4 count. He showed no signs of VL or other HIV-associated disease.

PATIENT 2

Patient 2 reported no adverse effects during or after miltefosine treatment and his skin lesions began to regress within 2 weeks of the first dose. At follow-up 3 months after the end of treatment, his CD4 count was 204 cells/μl, his skin appeared normal, and he felt well and showed no signs of VL or other HIV-associated disease.

DISCUSSION

Miltefosine is an oral antileishmanial agent that was licensed for the treatment of VL in India in 2002 and in Germany in 2003. In the largest trial conducted so far, miltefosine was found to cure 94% of 299 VL cases (Sundar *et al.*, 2002). The drug has been well tolerated in AIDS patients with VL, who received it on a compassionate basis (Sindermann *et al.*, 2004). In a study in Colombia, 40 out of 44 patients with cutaneous leishmaniasis were cured when given 2.5 mg miltefosine/kg.day for 28 days (Soto *et al.*, 2004). The drug has also been successfully emplyed to treat diffuse cutaneous leishmaniasis caused by *L. major*, in an HIV-positive patient (Schraner *et al.*, 2005). PKDL is particularly common in Sudan and Ethiopia, where approximately 50% of all treated VL cases develop the complication to some extent (Zijlstra *et* al., 2003) and about 9% develop it sufficiently severely to require treatment (Collin *et al.*, 2004). There have been no new developments in the treatment of PKDL for many

years, and the standard treatment is still based on the antimonial drugs that have been used since 1915. A combination of oral terbinafine and itraconazole was not found to be very effective (Khalil *et al.*, 1996). In southern Sudan, a retrospective analysis of 205 cases of PKDL, who were probably all HIV-negative, revealed that 39–88 days (median=45 days) of sodium stibogluconate were required for an effective treatment (Collin *et al.*, 2004). Less than 1% of current VL cases from southern Sudan but 23% of such cases in Humera, Ethiopia, are HIV-positive (Lyons *et al.*, 2003). In Ethiopia, Ritmeijer *et al.* (2001) found that PKDL of grade 2 or 3 was twice as frequent in those who were co-infected with HIV (and survived treatment) than in those who were HIV-negative. In addition, PKDL has been increasingly reported, as part of an immune-reconstitution syndrome, soon after ARV treatment was initiated in patients with HIV and *L. infantum* or *L. chagasi* infection (Rios-Buceta *et al.*, 1996; Ridolfo *et al.*, 2000; Gilad *et al.*, 2001; Bittencourt *et al.*, 2003). These reports are particularly intriguing because *L. infantum* and *L. chagasi* are not usually associated with PKDL.

In conclusion, this is the first reported use of miltefosine for the treatment of PKDL. Miltefosine was effective in two HIV-positive patients with PKDL who had recently commenced ARV therapy. Miltefosine appears to be a promising treatment for PKDL, and its use in this context merits further investigation.

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