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A SUCCESSFUL TREATMENT OF A KENYAN CASE OF UNRESPONSIVE CUTANEOUS *LEISHMANIASIS* WITH A COMBINATION OF PENTOSTAM AND ORAL ALLOPURINOL: CASE REPORT
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SUMMARY

A nine year aged male presented with facial lesions and the problem of responding to conventional treatment of leishmaniasis. Multiple injections of antimony and several topical ointments had been administered in hospital but fresh lesions erupted with potential to disfigure. Smears examined from nodular lesions confirmed presence of Leishmania amastigotes and parenteral pentostam was commenced for over eight weeks. A partial clinical outcome was achieved judged by extent of re-epithelialisation. Combined therapy of pentostam and oral allopurinol at a dose of 7mg/kg/ day was started and finalised at 120 days. All facial lesions receded and 100% re-epithelialisation of the lesions established.

INTRODUCTION

Approximately 1.5 million new cases of cutaneous leishmaniasis (CL) are considered to occur annually (1). Old World CL is endemic in the Middle East, northern, and sub-saharan Africa; the Mediterranean basin; and parts of Indian subcontinent and northwestern China (2). CL is being encountered more frequently in Europe and North America because of increasing travel and immigration from endemic areas but the primary unmet need is finding a rapidly, easily-administered, inexpensive, less toxic, effective species-specific treatment (3). It is argued that the most extensive investigations of treatment of New World CL have been performed against *L. panamensis* disease in Colombia (4). The oral antifungal ketaconazole can be effective for the more rapidly self-curing forms of disease (cutaneous disease caused by *L. mexicana* and *L. panamensis* from Central America) and a short course of antimony may be effective against *L. braziliensis* in Guatemala (5). Its noteworth that the causative species of CL determines the treatments (6). For example, paromomycin ointments are effective in *L. major, L. tropica, L. mexirona*, and *L. panamensis* infections. In *L. braziliensis* localised *leishmaniasis*, both paromomycin and imiquimod may be topically applied.

Both oral fluconazole and zinc sulfate are useful in *L. major* (7). The literature findings indicate that itraconazole given at prolonged period, may be a valid option for the treatment of CL, mainly in those cases unresponsive to conventional drugs (Consigli (8). Miltefosine, which is very effective in VL caused by *L. donovani*, appears ineffective in *L. major* and *L. braziliensis* infections. Intramuscular pentamidine is required for *L. guyanensis* CL, for which systemic antimony is not effective. Ambisome® rould be an alternative to antimony in South American CL with mucosal involvement (especially *L. braziliensis* and *L. guyanensis*). Tested efficacy of thermotherapy or cryotherapy to treat CL and sodium stibogluconate administered intralesionally have shown varied results elsewhere (9-11).

Treatment for CL has not been standardised in Kenya to date. The first-line treatment involves administering pentostam or glucantirne which require multiple injections, are expensive, and can cause reversible electrocardiogram alterations. Hence, WHO recommendation no treatment for uncomplicated CL. The exception to this recommendation would be in most NWCL, where systemic treatment is indicated because of the risk of mucosal spread. Compliance with this recommendation is also poor, as caring practitioners and their patients being anxious, know

that untreated lesions may take several months to heal especially those due to L. tropica, and leave undesirable scars. The parasitologic confirmation of CL by microscopy or species-specific diagnosis using polymerase chain reaction, is obligatory before chemotherapy can be considered. Accordingly, the biochemical basis for effectiveness of antimonials is unknown but may involve inhibition of ATP synthesis (12). Care should be maximised in children with underlying cardiac disease and with low serum potassium (13). Oral allopurinol is usually well tolerated, the most common side effect being rashes, sometimes fever. A rare but serious adverse event being allopurinol hypersensitivity syndrome. Available drug information indicate that allopurinol is not active but undergoes hepatic conversion (about 60-70% of allopurinol) to its active metabolites, oxipurinol and allopurinol riboside. It is the riboside received by patients given concurrently or without probenecid, which is known to show antileishmanial effect in several clinical studies (14,15). Its suggested care should be appropriate in patients with renal disease due to net absorption of oxipurinol (16). Previous studies in vitro have shown synergism between allopurinol and pentavalent antimony in tissue-culture systems and elsewhere randomised controlled trials in humans in Colombia support the view of synergism (17). The simple rationale of combining allopurinol and pentostam was derived from the fact it had been successively used as an adjuvant within the CCR setting in the treatment of those trial cases of VL that did not achieve clinical and parasitological cure with brand pentostam alone at recommended duration of 30 days.

CASE REPORT

A nine year aged male from Muruku village, Salama location, Laikipia west was referred to the CCR with fulminating facial lesions. The boy had inflamed papulonodular and fungated lesions spread over the face. A previous histological report was available of facial biopsy removed from the boy at the Nakuru general hospital in December 2005. The report indicated the lesions were cystic epidermoid lesions. A parasitological re-examination of the stored specimen in the same hospital in December 2006, confirmed presence of *Leishmania amastigotes*. During the one year period, varied treatment options were used including, brand sodium stibogluconate (Pentostam®) injections given for 52 days and topical ointments such as ketoconazole. While on treatment, the patient continued to experience fresh facial lesions which erupted with potential to disfigure. Hence, the patient was referred to the CCR where an informed consent was obtained for skin slit sample collection for study. Microscopy examination of Giemsa stained skin slit material from selected nodular lesions on the face were positive for *Leishmania amastigotes* and graded 4+ using methodology described by Bryceson and Chulay (18).

Parenteral pentostam was started at a dose of 20mg/kg once daily for 60 days on outpatient basis. A partial clinical outcome was achieved with no new lesions observed on assessment as the definition of lesion cure and failure were based on both clinical and parasitological criteria. Complete clinical response was defined as 100% re-epithelialisation of lesions. A combined therapy of pentostam at similar dose and oral allopurinol at a dose of 7mg/kg/ day was started and finalised after 120 days. No adverse events were reported while the patient was on treatment. Facial lesions receded and 100% epithelialisation of lesions established. Healing left a thin smooth scarring with reversed hypopigmentation. While it was possible to conclude that a clinical cure had been achieved, a parasitological assessment could not be done on a completely healed scar. A series of medical photography as evidence was created to document the visual changes on the patient before, during and after the treatment period (fig 1, 2, 3)

Figure 1

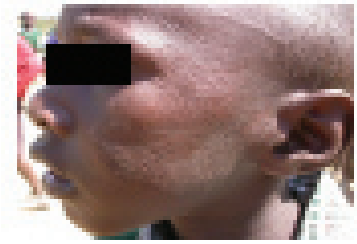


Figure 2

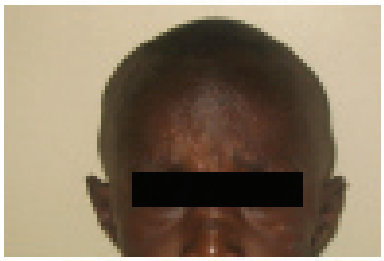
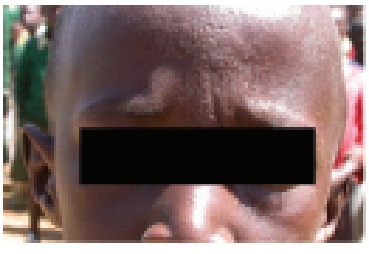


Figure 3



DISCUSSION

In primary care most CL cases are often mistaken for other common dermatological disorders such as fungal infections, bacterial, eczema, or chronic ulcers that leads to a delay in appropriate treatment. In some places patients consulted from one to seven physicians before CL was diagnosed (19). This can also lead to delay in the correct diagnosis and inadvertent exposure to adverse events of inappropriate treatment. Overall, the median time from noticing of lesions to the release of drugs can be unexpectedly prolonged. However, even when making the correct diagnosis the choice of drugs for treating CL is important as commonly used anti-Ieishmanial drugs such as antimony medications are often not sufficient as single therapies. This may cause a prolonged course of disease and exposure to undesirable effects of antimony drugs and may be associated with disfiguring scars.

The use of combination therapy using recommended doses of allopurinol and antimony drugs can shorten the duration of treatment. Prior to the described case, combination therapy for leishmaniasis in the model clinic had only been used in successful treatment of unresponsive cases of VL (20).

The use of combination therapy to treat VL has been reported in several countries. Combination of allopurinol and low dose antimony drugs has been shown to be as effective as a high dose of the antimony drug alone or even more effective than single therapy (21,22)). There are other drugs in process of investigation, for example, oral miltefosine, amBisome, generic sodium stibogluconate, azithromycin, sitamaquine, artemisinin and fluconazole. There is evidence in literature that some topical applications such as 15% paromomycin plus 10% urea in white paraffin is effective when applied ≥ 4 weeks (23).

In the meantime, we suggest that following confirmed CL diagnosis the combination regime should be considered as first-line choice of therapy to prevent prolonged exposure to single antimony therapy which may lead to non-healing and resislilnt cases of CL. Although the report is limited to one case, it is possible to have these observations being transferable to similar populations and settings.

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