Allopurinol Therapy in Post-kala-azar Dermal Leishmaniasis

Sir,

Presently, parenteral administration of pentavalent antimonial compounds is the only effective therapy for post-kala-azar dermal leishmaniasis (PKDL). Unfortunately the high dose and duration hamper regular treatment, particularly in lean individuals. Oral ketoconazole proved toxic when used in the desired dose and duration in PKDL (1). The efficacy of oral allopurinol is here reported in 3 patients.

CASE REPORTS

Case no. 1

A 17-year-old boy presented with pea-sized eruptions of 7 months' duration. Past history was significant for an episode of kala-azar (KA) 4 years earlier, treated elsewhere. The skin lesions had commenced as asymptomatic papules on the face. Later the genital area was affected, followed by the appearance of light coloured macules on the trunk and extremities. On examination the general condition appeared normal. Cutaneous examination revealed discrete, erythematous papulonodules on the cheeks, the ear lobules and penile shaft. Similar lesions were seen on the glans penis and inner prepuce. Erythematous induration was present on the forehead and chin, which were studded with small papules. Multiple 1–1.5 cm-sized irregular hypopigmented macules were seen scattered on the trunk and extremities. Systemic examination revealed no abnormality. Routine blood and urinalysis, liver function tests, renal function tests and chest X-ray were within normal limits. Blood VDRL was nonreactive. Biopsy of a papule revealed a thinned-out epidermis on histopathology. A dense inflammatory infiltrate occupied 90% of the dermis. It comprised sheets of lymphocytes and plasma cells interspersed with macrophages. No definite pattern of the granuloma was seen. There were dermal oedema and vascular dilatation. With Weigert's iron hematoxylin Leishman-Donovan bodies (LDB) were seen inside some macrophages.

The patient, who weighed 42 kg, was given allopurinol (20 mg/kg) 800 mg in divided doses daily and reviewed every month. The facial and genital lesions started regressing toward the end of 3 months, the latter showing a better response. At the end of 14 months the genital lesions had regressed completely. The facial eruptions had subsided but the erythematous induration persisted. Hypopigmented macules also showed a decrease in size and number. A repeat biopsy from the face revealed a marked decrease in inflammatory infiltrate, which now occupied 40% of the dermis. Few macrophages with granular bodies (?LDB) were seen. Allopurinol was continued and after 6 more months the facial skin returned to normal. The hypopigmented macules had also decreased considerably. Skin biopsy confirmed the impression of clinical cure. He has completed 4 years of follow-up with no signs of relapse.

Case no. 2

An 11-year-old girl reported generalised hypopigmented lesions of 2 years' duration. One year before appearance of the skin lesions she had suffered from an attack of KA that was fully treated. History revealed that the lesions started from the face and in a short time involved the rest of the body. On examination the girl was of lean build and weighed 40 kg. There were numerous macules with irregular borders on the face, trunk, buttocks and the extremities. The facial lesions showed erythema and some induration. The laboratory investigations were within normal limits. A 4-mm punch biopsy from the chin showed features similar to case 1, but the infiltration was less dense and LDB were found after a prolonged search.

Allopurinol was given as in case no. 1. After 4 months of treatment some changes could be noticed – no new lesions appeared and the macules on the trunk had regressed. At the end of 1 year of therapy with allopurinol more regression was seen, but erythema and infiltration of the face were still present. A repeat biopsy from the chin showed reduction in the infiltrate and no LDB could be detected. After another 12 months of therapy considerable improvement was seen (Fig. 1a, b). Some hypopigmented macules were seen scattered on the body. Biopsy showed features of subsided disease. Knowing that hypopigmentation takes much longer to regress after clinical cure, we stopped allopurinol and the patient has now completed 6 months of follow-up.

Case no. 3

A 15-year-old boy had eruptions which had started 3 months after receiving treatment for KA. On examination there were numerous erythematous hypopigmented macules on the extremities, with relative sparing of the trunk and buttocks. Some discrete papules were seen on the face and right ear lobule. After completion of investigations and histopathological confirmation of PKDL, he was given allopurinol 800 mg/day in divided doses. Following 3 months of therapy the lesions showed signs of regression. During the 6th month he developed bilateral gynecomastia, more evident on the right side. Allopurinol was discontinued. Alkaline phosphatase was 41 units (normal 3–13 units). Other tests revealed no abnormality. Two months after stopping allopurinol the liver function tests returned to normal and gynecomastia had almost regressed. He was then advised to take intramuscular injections of sodium antimony gluconate as the only alternative.

DISCUSSION

Following the demonstration of the antileishmanial effect of allopurinol in preventing growth and division of the protozoal cells (2), it was experimentally shown that the *Leishmania* species were more susceptible to allopurinol-1 ribonucleoside, a mammalian metabolite of allopurinol (3). Pharmacokinetic studies established the safety of the drug at very high doses (4), and in KA the dose administered has been up to 20 mg/kg. Allopurinol was successfully used in Indian KA caused by *Leishmania donovani*, the uncertainty of the response in some cases being attributed to the differing rates of conversion of allopurinol into the riboside compound (5). Other studies indicated that allopurinol alone was effective, but for complete cure in KA it had to be combined with antimonials (6). The combination proved

Fig. 1. Facial macules in case 2 before (*a*) and after (*b*) allopurinol therapy.

effective in KA otherwise unresponsive to antimonial compounds (7) and in those with associated HIV (8).

PKDL is a refractory dermatosis in which the duration of antimonial therapy is almost four times longer than in KA. In our previous experience with antimony (9) we had to persuade the patients to continue the injections and at times had to stop therapy for brief periods to relieve pain at the injected sites. We anticipated more problems with antimony in the patients reported here and hence opted for oral allopurinol therapy. It was seen that with regular intake the indurated lesions in the covered sites were the first to respond after 3 months of therapy, followed much later by the hypopigmented macules. The facial lesions took more time to regress. A total of 20 to 24 months of therapy was required for clinical and histopathological cure. No serious side-effects were seen. Hepatotoxicity is an uncommon reversible complication and gynecomastia, the causative mechanism of which is unclear, is a rarer side-effect, seen in less than 1% of patients on allopurinol therapy (10).

It is concluded that allopurinol may be given in situations where patients cannot tolerate parenteral antimony therapy. The long duration of treatment and follow-up need to be emphasized.

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Accepted January 2, 1996.

V. Ramesh
Department of Dermatology, Safdarjang Hospital, New Delhi, -110029, India.