CASE REPORT

Role of azathioprine in preventing recurrences in a patient of recurrent erythema nodosum leprosum

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Summary The pathogenesis of erythema nodosum leprosum (ENL) involves both immune complex deposition and dysfunction of cell mediated immunity. Tumour necrosis factor-α (TNF-α) plays an important role in its pathogenesis. Thalidomide and corticosteroids are the mainstay of treatment for ENL. However, there are often severe limitations to their use. We report a case of recurrent ENL treated successfully with azathioprine. A 15-year-old unmarried girl with lepromatous leprosy had recurrent ENL for 2 years. She was treated with WHO-MB MDT and prednisolone in doses of 40–90 mg a day for 2–12 weeks. Her condition was inadequately controlled. The patient was therefore treated with thalidomide 300 mg and prednisolone 40 mg. The symptoms subsided after 5 days and ENL lesions healed in 2 weeks. Prednisolone was reduced by 10 mg per week and stopped, while thalidomide was reduced to 100 mg twice daily after 4 weeks. Azathioprine 100 mg (2 mg/kg per day) daily orally was added to prevent recurrences. Thalidomide was further reduced and stopped after another 4 weeks while she continued with azathioprine in the same doses for 8 months. There was no recurrence of ENL lesions and no side effects of the therapy. MB-MDT was stopped 1 year ago, and she is on follow-up without any relapse. Azathioprine, therefore, appears to be an effective and safe drug to prevent recurrences of ENL.

Introduction

Erythema nodosum leprosum (ENL) is a common and serious immuno-inflammatory complication of multibacillary leprosy. It affects up to 50% of patients with lepromatous leprosy, usually during treatment with anti-leprosy drugs. Systemic manifestations often associated with ENL include fever, malaise, lymphadenopathy, neuritis and arthralgia which...
are often severe, causing significant morbidity in these patients. The condition may be chronic and recurrent. Immune complex deposition and immune dysfunction are the key pathogenic events in ENL, causing activation of complements and migration of polymorphs with release of tissue damaging enzymes. An imbalance of immunoregulatory T-cell subsets has also been demonstrated in ENL. Tumour necrosis factor-α (TNF-α), a pro-inflammatory cytokine, plays an important role in the pathogenesis of ENL. There is activation of T-cells and macrophages, inducing production of large amounts of TNF-α. Plasma levels of this cytokine have been found to be high during the episodes of ENL. Thalidomide and corticosteroids are the two main drugs used for treatment of ENL. Thalidomide is the drug of choice. It quickly controls the condition with relief in signs and symptoms, but it is a teratogenic, poorly accessible and expensive drug. High doses of corticosteroids may control the disease, but their prolonged use is associated with serious side effects. Azathioprine is a known T-cell inhibitor and a potent anti-inflammatory agent. It has been shown to inhibit TNF-α, though the evidence is not conclusive. We used azathioprine in a young girl with recurrent ENL to prevent recurrences.

Case report

A 15-year-old unmarried girl, a resident of Bihar, India, had had hypopigmented and hypoaesthetic patches over the extensor aspect of her left arm for 7 years. Three years later, she noticed similar lesions on both forearms and the lateral aspect of thighs and legs, which gradually increased in size. Within 2 years of the appearance of these lesions, she developed multiple, tender, erythematous nodules on both the extremities associated with fever, joint pain and redness of both eyes. She was diagnosed to have multibacillary leprosy, and started on (WHO) MB MDT by a local medical practitioner. Prednisolone 40 mg once daily orally was added for treatment of ENL, which was tapered over 3 months and stopped. The ENL was controlled with this treatment and the patient became asymptomatic. One month after stopping prednisolone, she developed a recurrence of ENL as erythematous, tender nodules with fever and joint pain. She was again started on prednisolone 40 mg once daily orally by the same practitioner, which she continued for 3 months on his advice. There was no adequate control of ENL with this treatment. Moreover, she continued to develop similar new lesions with fever and the joints pain persisted. The dose of prednisolone was increased to 60 mg daily for 2 weeks, then 80 mg daily for 2 weeks, and finally 90 mg daily orally for 2 weeks. The dose of clofazimine was also increased to 100 mg thrice daily for 4 weeks. Even with this treatment, there was no control and she developed severe ENL with erythematous necrotic lesions. Thereafter the patient was referred to us. She presented to us with hypoaesthetic macules and erythematous nodules over both extremities, with fever and joint pain. On examination, she had diffuse infiltration of both ear lobes and face with multiple hypoaesthetic patches of varying sizes on the trunk and proximal parts of the extremities, peripheral hypoaesthesia and symmetrical nerve thickening involving both ulnar, radial, lateral popliteal and right posterior tibial nerves, without significant nerve tenderness and no clinically detectable nerve function impairment. There were multiple erythematous, tender nodules and a necrotic ulcer over both forearms and legs. Ocular examination did not reveal any abnormality. Examination of other systems was unremarkable. All the routine investigations, including haemogram, liver and renal function tests, urine, stool and chest X-ray, were within normal limits. Slit skin smear examination revealed a bacteriological
index of 2+ from the ear lobes and 3+ from the patch. Electrophysiological studies showed asymmetrical axonal sensorimotor neuropathy. Skin biopsy from a nodule showed histopathological features consistent with lepromatous leprosy with erythema nodosum leprosum. A urinary pregnancy test was performed twice and was negative, and ultrasonography of the abdomen did not reveal a gestational sac. The patient was treated with (WHO) MB MDT, prednisolone 40 mg daily and thalidomide 100 mg thrice daily orally. The patient was informed about the teratogenic effects of the drug and counselled about complete abstinence while on therapy. After 5 days of this treatment, there was no fever and the joints pain were alleviated. The ENL lesions also started healing, with complete relief in 2 weeks. Prednisolone was reduced by 10 mg every week and then stopped after 4 weeks while thalidomide was reduced to 100 mg twice daily. Azathioprine at a dose of 50 mg twice daily orally (2 mg/kg per day approximately) was added (her body weight was 55 kg). One week later, thalidomide was further reduced to 100 mg daily for 4 weeks and then stopped. The patient received thalidomide for 9 weeks. During the first 6 weeks, she was given thalidomide as an in-patient followed by 3 weeks outpatient treatment. Urine pregnancy test was repeated monthly while she was on thalidomide. Azathioprine was continued in the same dose for 8 months. During azathioprine therapy complete blood count, liver and renal function tests were repeated every month which remained unremarkable. She did not develop any further episodes of ENL. There were no significant side effects of the treatment. The patient continued (WHO) MB MDT for 2 years, due to clinical activity of leprosy but without any ENL episodes (Figure 1).

Discussion

The management of ENL is still a challenge for clinicians. Out of the various drugs used for treatment of ENL, thalidomide and corticosteroids remain the mainstay of therapy. Thalidomide is a highly effective drug for acute severe ENL. It causes rapid improvement in clinical symptoms with reduction in TNF-α levels. It also acts on T-cells, reducing the CD4 cells and increasing the CD8 cell counts. There are, however, serious limitations to its use due to its teratogenic effects and potential neurotoxicity. The drug has a very restricted availability and a high cost in India which further limits its use. We used thalidomide in this young unmarried teenage girl in addition to prednisolone to control ENL, which was not getting better even with high doses of corticosteroids alone. The patient was informed about the teratogenic effects of the drug and counselled about complete sexual abstinence while on therapy. She was also treated as an in-patient for 6 weeks out of 9 whilst on thalidomide therapy. With a combination of prednisolone and thalidomide, her ENL completely subsided in 2 weeks; prednisolone and thalidomide were gradually tapered and stopped, while she continued azathioprine for 8 months without any further recurrences.

Azathioprine is a 6-mercaptopurine derivative, which inhibits purine synthesis and is a potent T-cell inhibitor. It also inhibits B-cell proliferation and antibody production, and probably monocyte and polymorphonuclear cell function as well. It also has a strong anti-inflammatory effect and has also been shown to inhibit TNF-α, a procytokine primarily responsible for ENL lesions. Therefore, we tried azathioprine in this patient to prevent recurrences. Azathioprine with corticosteroids has also been used in ENL by other workers. Marlowe et al. have used azathioprine with prednisolone to treat severe type 1 reaction. They used azathioprine as a steroid-sparing agent. The drug has been effectively used on a
Figure 1. ENL treatment and response.
long-term basis in patients with Parthenium dermatitis as a corticosteroid-sparing agent.\textsuperscript{11} Its long-term safety, adverse effects and monitoring have been well studied.\textsuperscript{12} We arbitrarily decided to continue azathioprine for 8 months. There were no adverse effects of the drug. Azathioprine probably prevented further recurrences of ENL in this patient. Further studies, however, are needed to confirm its role in this condition.

References