Azathioprine for the Treatment of Severe Erosive Oral and Generalized Lichen Planus

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Sir,

Lichen planus is usually a benign and self-limiting disease but in some patients the disease may be severe and unremitting, requiring therapeutic interventions. The etiopathogenesis of lichen planus is not exactly known but circumstantial evidence suggests that it is an immunologically mediated disease with an lymphocytotoxic effect (1, 2). Various treatment modalities such as corticosteroids, dapsone, PUVA, griseofulvin, retinoids and cyclosporine, etc., have been tried (3–5). Of these, only systemic corticosteroids have been widely used and usually found to be effective, even in severe disease. However, these treatment modalities often require to be given over a long period, which can result in serious side effects (6). Severe generalized lichen planus also responds to systemic corticosteroids when used in high doses, often resulting in side effects owing to prolonged use. Azathioprine has been shown to be an effective corticosteroid-sparing agent in a few such patients with severe generalized involvement (7–9). We evaluated the effectiveness of this drug in a larger series of patients with severe erosive oral and/or generalized lichen planus.

MATERIAL AND METHODS

Nine patients (4 males, 5 females, 5–54 years of age; mean 32.2 years) with clinical diagnoses of severe erosive oral lichen planus and/or generalized lichen planus were included in the study. The duration of the disease in these patients varied from 3 months to 4 years. The diagnosis in each patient was made on the characteristic morphology of skin/mucosal lesions, confirmed by skin/mucosal biopsy. Baseline investigations including a complete hemogram with platelet counts, renal and liver function tests, blood sugar tests, chest X-ray, routine urine and stool examination and ECG were done in all the patients before starting treatment. Patients with deranged renal/liver function tests, with any focus of infection, and pregnant and lactating mothers were excluded from the study. The patients were treated with azathioprine, 50 mg twice daily orally (about 2 mg/kg day), for a period varying from 3 to 7 months (average 5 months). Complete hemograms with platelet counts, liver and renal function tests were repeated every 4 weeks. All patients were clinically evaluated every 4 weeks to assess the therapeutic response, which was determined by flattening of the lesions, appearance of new lesions and change in severity of itching. Mucosal lesions were assessed in terms of flattening/healing of the lesions and decrease in severity of irritation and burning sensation. The response to therapy was considered to be excellent if there was an overall 75–100% improvement in the lesions and itching/irritation, good if it was 50–75% and poor if it was less than 50%.

RESULTS

Out of 9 patients, 4 patients had only oral mucosal lesions, 3 had oral mucosal as well as skin lesions and the other 2 had generalized skin lesions. Within 3 to 7 months (average 5 months) of azathioprine therapy, 7 (77.8%) patients had an excellent response, which included 4 patients with mucosal lesions, one with oral as well as skin lesions and two patients with generalized skin lesions; one (11.1%) patient who had oral mucosal as well as skin lesions had a good response. One patient with oral mucosal lesions along with generalized skin involvement had a poor response (40%) to the therapy. This patient took the drug for 3 months only and did not report for further follow-up. All the patients who responded to treatment had started showing improvement within 4–6 weeks of initiating the therapy. On follow-up, one patient developed bleeding from the gums due to gingivitis. None of the other patients reported any side effects. There were no changes in laboratory parameters in any of the patients. Out of 7 patients with complete healing of the lesions, none had had a relapse over the 6–9 months' follow-up period after stopping treatment.

DISCUSSION

Azathioprine has been used in many dermatological diseases such as pemphigus, bullous pemphigoid, connective tissue diseases, chronic actinic dermatitis, psoriasis and pyoderma gangrenosum as a corticosteroid-sparing, immunosuppressive agent (10, 11). A few reports have shown its effectiveness in severe generalized and erosive mucosal lichen planus unresponsive to other modalities of treatment (7–9). When used in this situation, azathioprine probably acts by inhibiting the T-lymphocytes. In the past we used azathioprine in one patient with unresponsive, generalized and severe lichen planus, with a dramatic improvement in 12 weeks and without any side effects (7). Encouraged by the results, we decided to carry out an open study in patients with severe erosive oral and generalized lichen planus. Out of 9 patients, 7 showed excellent responses, one showed a good response and only one patient had a poor response. There were no side effects of the therapy. The drug is metabolized by three competing enzymes, hypoxanthine-guanine phosphoribosyl transferase, xanthine oxidase and thiopurine methyl transferase (TPMT) (12), but its conversion into inactive metabolites is mainly done by TPMT. Therefore the patients with low TPMT levels are at a major risk of developing myelotoxicity, gastrointestinal and hepatic side effects. About one in 200–300 people in the general population are deficient in this enzyme. Determination of TPMT levels in patients before initiating this therapy would facilitate the exclusion of such susceptible individuals. If such a facility is not available, a regular hemogram is recommended to detect early myelosuppression. We used this drug in patients who had air-borne contact dermatitis due to weed Parthenium, with very good results and minimal side effects even when it was continuously used for 2–3 years (13). We also investigated the long-term toxicity of the drug with regular monitoring of hematological, hepatic and renal parameters in these patients (14). We therefore suggest that azathioprine may be used as an alternative drug to systemic corticosteroids in patients with severe/generalized lichen planus. It is safe and better tolerated

than systemic corticosteroids, especially in patients who need prolonged systemic treatment. The drug may be particularly valuable in patients who cannot be given systemic corticosteroids for some reason or other. However double-blind, controlled trials in a larger number of patients are required to establish the efficacy and safety of this drug in these patients.

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Possible Role of Diltiazem in a Recalcitrant Case of Darier's Disease

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Sir,
The gene defect of the genodermatosis Darier's disease (DD), dyskeratosis follicularis, has been identified as the locus for sarco-endoplasmatic reticulum calcium ATPase type 2 (SERCA 2) (1). The exact mechanism by which this gene abnormality leads to dyskeratosis still needs elucidation. We present a case where the calcium channel blocker diltiazem may have played a part in a complicated and severe attack of DD.

CASE REPORT

A 51-year-old woman had suffered from severe DD since 3 years of age appearing first as filiform keratoses and pits on her palms and soles. Apart from a single admission to the hospital in 1989, when she was 38 years old, when the disease had temporarily deteriorated, she was under reasonable control as an outpatient. From 1989 intermittent episodes with superinfections caused by the herpes simplex virus, *Staphylococcus aureus* and hemolytic streptococci complicated the course of the disease. In 1991 she underwent percutaneous transluminal coronary angioplasty (PTCA) and was subsequently prescribed diltiazem (Cardil™) at 120 mg b.i.d. for ischemic heart disease. During the next few years her skin deteriorated, necessitating several yearly admissions. Our patient was convinced that the PTCA had caused the substantial worsening of her disease. In March 1999 she was admitted to hospital because of further exacerbation. The skin was universally covered with greasy crusted papules, especially on the scalp, ears, neck, back and flexural areas. Large erythematous, erosive and fissuring areas were present on the lower back, gluteal regions, lateral aspects of the thighs and pretibial areas (Fig. 1). Bacterial colonization and infections varying between *S. aureus*, *Pseudomonas auruginosa* and hemolytic streptococci complicated the condition. Episodes of septicemia occurred. Her general state of health was weakened with anemia and depletion of zinc and protein.

Neotigason was initiated in 1989 in dosages of 25 to 50 mg daily. This treatment was stopped in June 1999 but reintroduced in August 1999. From 1989 acyclovir had been given intermittently and from 1994 continuously as a prophylactic. Antibacterial therapy was given when indicated according to bacteriology. Cyclosporine was tried for one month at 200 mg/day in 1998 and for one month in May 1999 at 400 mg/day without any response.

In early July 1999 the diltiazem treatment was stopped and one week later replaced with isosorbid-dinitrate, owing to recurrence of ischemic heart symptoms.

Estrogen/gestagen hormone replacement therapy with tibolon was given for 4 weeks but discontinued because of an increase in liver enzymes. Additional treatment included vitamins, oral zinc, iron and a protein-rich diet.

For topical treatment, medical soap and neutral moisturizing and/or dry skin products such as steroids were tried and were either not tolerated or ineffective. From the middle of July, zinc paste was applied to all moist areas, with immediate relief.