Ulcerated Necrobiosis Lipoidica Treated with Cyclosporin A

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Sir,

Necrobiosis lipoidica (NL) is a skin disease of unknown aetiology. It is a relatively rare cutaneous complication of diabetes mellitus, occurring in 0.3% of manifest diabetics (1). The course of NL appears unrelated to duration of the diabetes or to adequacy of the diabetic control. There may be a correlation with diabetic micro-angiopathy (1). NL is characterized by sharply demarcated, smooth surfaced, irregularly shaped plaques of atrophic skin varying in colour from yellowish to reddish brown. The usual location is the anterior lower part of the leg, often bilaterally, but lesions can be seen on the thighs, popliteal areas and feet. The arms, trunk, face and scalp may be affected, but only in rare cases (1). A complication of the more extended lesions is ulceration, which often occurs following trauma and heals with difficulty leaving scars. At present there is no treatment that can be considered satisfactory, although numerous therapeutic protocols have been proposed. The ulcerated forms may need surgical treatment with excision of the affected areas and subsequent grafting. Recently, there have been reports of good results obtained with the use of cyclosporin A (CyA) (2, 3).

CASE REPORT

We report the case of a 44-year-old woman. After a trauma in 1982, she noticed the appearance of well-demarcated, slightly infiltrated, violaceous plaques on the anterior surface of her legs. Subsequently, small ulcers measuring 1 to 2.5 cm in diameter, tending to coalesce and to have a remittent course, appeared within the plaques. In 1992, an histological examination confirmed the diagnosis of NL. For this reason, and on the advice of the specialists she had consulted in the past, the patient tried various topical medications and systemic therapies (retinoic acid, axeroftolo palmitate, betacarotene, D1 tocopherylacetate, melatonine) with only partial and temporary beneficial results. In July 1999 she came to our attention because of the persistence of the lesions, the progressive worsening of the ulcers and the onset of painful symptoms on the legs. During the visit, no significant elements emerged from the physiologic and pathologic history of the patient. She seemed to be in good general health and the haematocchemical tests did not evidence alterations worthy of note. The plasmatic level of glucose before meals was normal (75 mg dl⁻¹) and Hb₁c was 5%. A glucose challenge resulted negative too. On examination, we observed two large oval-shaped plaques aligned in a long axis on the front surface of both legs. The plaque on the right leg measuring 10 × 5 cm, the one on the left leg 15 × 7 cm. The lesions were centred by irregularly shaped ulcers measuring 9 × 4 cm and 2 × 2 cm, respectively. These lesions had an exudative base capped by necrotic tissue, clean raised margins in respect of the surrounding skin, which seemed infiltrated, sclerodermiform in appearance, a smooth surface, a hard-elastic consistency and were brownish-yellow in colour (Fig. 1A). The patient lamented severe pain in correspondence with the ulcerated sites, and had difficulty in walking. Therapy with CyA at a dose of 4 mg kg⁻¹ day⁻¹ was started, the result being progressive improvement of the clinical picture, with the disappearance of pain after a few days’ treatment and complete healing of the ulcers after about 3 months (Fig. 1B). The patient tolerated the treatment well. Periodic haematocchemical controls revealed normal renal and hepatic functions. CyA was gradually reduced until complete withdrawal was reached after 8 months. No relapse has been observed so far.

DISCUSSION

The treatment of NL is particularly difficult because of the complex and uncertain pathogenesis of this disease. Because of its association with diabetes mellitus, it is hypothesized that micro-angiopathy associated with neuropathy may contribute to the necrobiosis of collagen (1). In any case, NL is preceded by a neutrophilic vasculitis even in cases where there is no diabetes association. The release of cytokines from inflammatory cells or of substances of tissue origin deriving from damaged endothelial cells can cause the degeneration of the connective tissue matrix and the diminution of collagen synthesis by the affected fibroblasts (4). The evidence of PAS+ material deposits constituted by IgA, IgM, C3, fibrinogen, inside and outside the dermal vessels of the skin lesion (5) and the predominance of T-helper lymphocytes in the reticular dermis (2) might lead to the assumption that an immunologic mechanism is involved. Although no treatment of choice exists to contrast this disease, therapeutic management seems to be oriented towards reducing the inflammatory state (topical and systemic steroids, PUVA therapy) (6–9),
ameliorating the blood flow (platelet anti-aggregates) (10) and the micro-circulation (pentoxifylline) (11). Tretinoin, which regulates proliferation and differentiation of the tissues, especially those of the epithelia, through a system of genic adjustment, represents yet another therapeutic option (12).

In the past few years, numerous studies have evidenced the immunosuppressive and anti-inflammatory properties of CyA (13, 14). Two recent reports have demonstrated the efficacy of CyA in 4 cases of NL (2, 3). We wanted to try it in a case of long-standing NL which was particularly disabling because of the painful ulcerations and had been resistant to previous treatments. CyA therapy resulted in complete healing of the ulcers after 3 months. At follow-up visit 18 months later, the patient showed no relapses of the ulcerous lesions.

It is well known that CyA has an immunomodulating activity, as it inhibits synthesis of the cytokines by blocking transcription of the gene that codifies the INF-γ and the IL-2 at T-lymphocyte level. Blockage of IL-2 results in inhibition of the maturation of lymphocytes into effective cells. Blocking of the release of INF-γ is responsible for inhibition of the expression of adhesion molecules (ICAM 1) on keratinocytes, antigen presenting cells and endothelium cells. This way the activity of various leucocyte populations is hindered as is the amplification of the inflammatory response (13, 14). It is difficult to establish whether the rapid resolution of the ulcerous lesions and the long period of remittance are to be attributed to the combined anti-inflammatory and immunomodulating activity of CyA or to only one of these two factors.

REFERENCES