Intravenous Immunoglobulin for Recalcitrant Subacute Cutaneous Lupus Erythematosus

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Sir,

Subacute cutaneous lupus erythematosus (SCLE), first described by Sontheimer et al. (1) in 1979, represents a distinct subtype of lupus erythematosus (LE) with specific clinical and serological features. Characteristically, skin lesions appear in a non-scarring papulosquamous, annular, polycyclic or psoriasiform pattern primarily located in the sun-exposed areas such as the upper back and chest. Systemic involvement in SCLE is relatively rare, but the majority of patients have musculoskeletal complaints such as arthralgias. Antinuclear antibodies (ANA) are present in 60–80% of cases, with circulating anti-Ro(SS-A) antibodies as the most characteristic feature (2). Antimalarials are considered to be the first-line drugs in SCLE. However, a minority of patients with resistant disease fail to improve on antimalarials and/or immunosuppressive agents. We here report a patient with highly recalcitrant SCLE who significantly responded to treatment with high dose intravenous immunoglobulin (IVIg).

CASE REPORT

A 55-year-old Caucasian woman was referred to our clinic in 2002 because of widespread skin lesions affecting almost the complete upper trunk and face. Additional dermatological findings included livedo reticularis of the extremities, diffuse alopecia, periungual teleangiectasias and Raynauds phenomenon. Malar eruption was absent. Routine histological examination as well as direct immunofluorescence confirmed the clinical diagnosis of SCLE (2). Laboratory investigation revealed a positive antinuclear antibody at a titre of 1:1280 IU/ml ($<$1:80) in a speckled pattern, positive anti-Ro(SS-A) and anti-La(SS-B) antibodies, low complement C3 (71 mg/dl, 90–180 mg/dl) and C4 (5 mg/dl, 10–40 mg/dl), circulating immune complexes (4.1 μg/ml, 0.0–1.5 μg/ml) and elevated rheumatoid factor (73.9 IU/ml, 0–14.0 IU/ml). There was no evidence of antibodies against dsDNA, Smith, U_1RNP, Scl-70, Jo-1 or antihistone. Further medical check-up disclosed systemic involvement. However, she complained about intermittent arthralgia, myalgia, easy fatiguability and malaise. Further she had a history of heavy cigarette smoking for more than 30 years. Initial treatment included potent topical glucocorticoids and chloroquine (4 mg/kg/day) for several months. Response was poor and therapy was switched to systemic corticosteroids (initial dose of 150 mg/day) and azathioprine (150 mg/day). As she experienced no significant benefit under this regimen, methotrexate at an oral dose of 25 mg/week was started. A slight improvement of skin lesions was observed, but she experienced a strong relapse 4 months later. Further attempts with second-line immunosuppressive agents such as cyclophosphamide (200 mg/day), cyclosporine (4 mg/kg/day) or mycophenolate mofetil (2 g/day) resulted in a marked improvement of skin lesions, but had to be discontinued because of significant gastrointestinal and haematological side effects. Moreover, therapy with dapsone (100 mg/day) and acitretin (40 mg/day) was ineffective. She finally was re-exposed to prednisone (30 mg/day) and azathioprine (150 mg/day) with which a stable disease could be obtained. Skin lesions dramatically worsened at the beginning of December 2003 and prednisone was increased to 50 mg daily (Fig. 1a). After consideration of further treatment options, monthly cycles of IVIg (Intraglobin CP, IgG $>$95%, approx. 59% IgG1, 36% IgG2, 3% IgG3, 2% IgG4) at a dose of 1 g/kg body weight per day over three consecutive days were initiated. Amelioration and brightening of erythematosquamous plaques was observed after the first cycle of IVIg. An almost complete clearance of skin lesions including livedo reticularis was achieved after three cycles of IVIg and prednisone was tapered down to 12.5 mg/day (Fig. 1b). Diffuse alopecia remained unchanged. Also at this time, IVIg was reduced to 0.5 g/kg body weight.

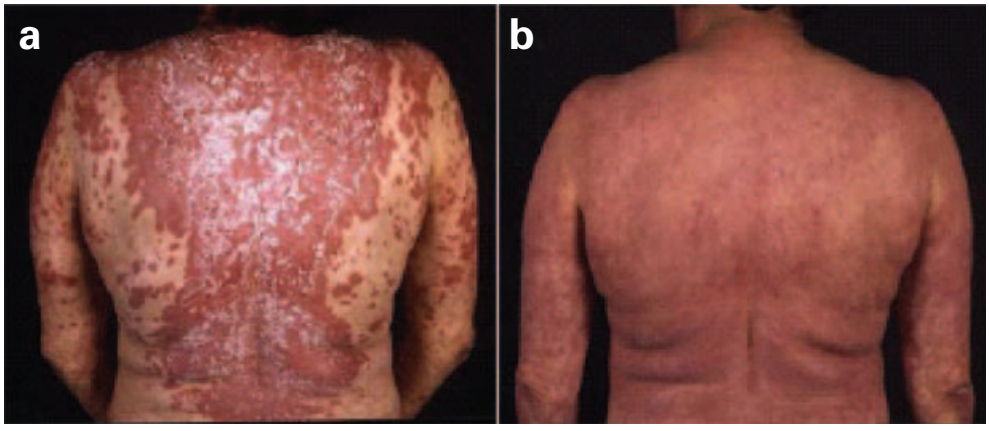

Fig. 1. (a) Widespread subacute cutaneous lupus erythematosus located on the upper back. (b) Remarkable improvement after the third cycle of IVIg.

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New skin lesions appeared after the sixth cycle of IVIg when prednisone was decreased to 10 mg daily. Five months after finishing IVIg she apparently experienced a transition to systemic LE with pulmonary involvement resulting in a severe worsening of her general condition. At this time, anti-Smith and -U_1RNP antibodies were detectable as well. She finally died in October 2004 because of acute lupus pneumonitis.

DISCUSSION

It has been suggested that risk factors that are more likely to signal transition of cutaneous into systemic LE are nephropathy, high ANA titres (>1:320) and the presence of arthralgias. The original clinical features of SCLE as well as the later occurrence of anti-Smith and -U_1RNP antibodies and acute pneumonitis observed in the present case demonstrate that there is indeed a risk of certain patients experiencing a transition of SCLE into systemic LE with fatal outcome (3). However, a rebound of autoantibodies after discontinuation of IVIg treatment cannot be fully excluded from involvement in the exacerbation of disease (4).

Antimalarials are broadly considered the treatment of choice for cutaneous LE. In SCLE, response rates of 50–80% have been reported (5). Smoking significantly decreases the effectiveness of antimalarials, as confirmed in our patient (6). In this subgroup of patients, disease activity can usually be controlled with 'second-line' immunomodulatory or suppressive drugs, e.g. azathioprine or methotrexate. However, if these agents are intolerable due to toxicity or side effects, therapeutic alternatives are limited.

Experiences with IVIg in immune-mediated or autoimmune dermatoses have been obtained for almost two decades. There is clear evidence for the efficacy of IVIg in dermatomyositis resistant to conventional therapies. So far, only one report about IVIg in three patients with rapidly deteriorating systemic sclerosis has been published. Wollina et al. observed good effects in one case of disabling morphoea of childhood (7). In 1995, Piette al. (8) for the first time reported IVIg therapy (1 g/kg body weight monthly) in five patients with recalcitrant discoid LE. A complete response was achieved in three patients, whereas the remaining two showed no improvement. Interestingly, all patients relapsed 2–10 months after finishing IVIg. In contrast, de Pita et al. (9) reported seven patients with LE (five had systemic LE, two had SCLE) in which IVIg was unable to control disease efficiently. Moreover, skin lesions in SCLE even enlarged. IVIg was administered at a dosage of 300 mg/kg/day for five consecutive days each month for a 12-month period. Genereau et al. (10) successfully treated a 30-year-old woman with SCLE, applying IVIg at a dose of 2 g/kg monthly. In a study of 20 systemic LE patients treated with IVIg, one had discoid LE lesions and a significant improvement was observed after six cycles of IVIg (11). Recently, Goodfield et al. (12) performed an open prospective study on 12 patients receiving an initial dose of 1 g/kg body weight followed by 400 mg/kg monthly for a maximum of 6 months. Five patients experienced complete clearing, two had partial and three had limited response. One patient developed cutaneous vasculitis and IVIg therapy was terminated. IVIg was only of temporary benefit and a severe rebound occurred shortly after finishing IVIg therapy and reducing oral steroids, respectively. The dosage of IVIg in these publications was adapted to the recommendations for IVIg in autoimmune blistering diseases (13). However, the optimal dose of IVIg in cutaneous LE still has to be elucidated. In our patient, 0.5 g/kg after the initial dose of 1 g/kg was used and resulted in a transient healing of all active lesions. This observation is in accordance with our recent findings on IVIg in livedoid vasculitis, where the dose of 0.5 g/kg body weight was sufficient to achieve an excellent response (14).

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