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CASE REPORT

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Intravenous immunoglobulin in the treatment of resistant subacute cutaneous lupus erythematosus: a possible alternative

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Abstract Subacute cutaneous lupus erythematosus (SCLE) is a common manifestation of systemic lupus erythematosus. In many cases it appears to be resistant to various systemic or topical treatments. Three cases of resistant SCLE with good response to intravenous immunoglobulin (IVIG) are described here suggesting that IVIG could be an alternative treatment in these patients.

Keywords Intravenous immunoglobulin · Subacute cutaneous lupus erythematosus

Introduction

Cutaneous lesions are a common and often disfiguring manifestation of systemic lupus erythematosus (SLE). Cutaneous lupus erythematosus (CLE) is a broad term, which includes a variety of lesions such as acute cutaneous lupus (ranging from malar erythema to widespread photosensitive eruption), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus (classical discoid lupus, lupus profundus, lupus pernio/chilblains). In addition, nonspecific cutaneous lesions like urticarial or purpuric vasculitis and vascular lesions (periungual erythema, livedo reticularis, Raynaud's, telangiectasia) are associated with SLE. Nevertheless, many patients may present with more than one type of cutaneous lupus at the same time, making the classification into a specific subtype of CLE difficult.

Administration of systemic agents such as corticosteroids, hydroxychloroquine (HCQ), mepacrine, methotrexate (MTX), mycophenolate mofetil (MMF), cyclophosphamide (CPM), and/or azathioprine (AZA) for the underlying systemic disease leads, in many cases, to remission of the cutaneous lesions. The results are better when combined systemic and topical treatment (steroids, sun protection) is used. Nevertheless, many patients suffer from resistant cutaneous lesions despite therapy. On the other hand, cutaneous lesions may be the only manifestation of the disease such as SCLE, making it difficult to justify systemic agents because of their side effects. Alternative systemic (dapsone, thalidomide, retinoids, cyclosporine) and topical agents (thalidomide, intralesional steroids, retinoids, tacrolimus ointment) as well as laser therapy, phototherapy, photopheresis, and cryotherapy were used for resistant cutaneous lesions.

Three patients with SCLE resistant to any previous treatment with good response to intravenous immunoglobulin (IVIG) are described here. All patients gave their consent and the results were documented with photos before and after treatment.

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Case reports

Patient one A 43-year-old lady was diagnosed in 1995 to have SLE based on her clinical and laboratory findings. The cutaneous lesions included an erythematous rash over her hands, legs, and trunk. In 2000, during her pregnancy, the rash deteriorated, especially on the upper trunk, despite oral corticosteroids. In 2001 the patient developed lupus nephritis and she was started on oral CPM (50 mg/day) and prednisolone (5 mg/day). Because of abnormal liver function tests, CPM was substituted with MMF (2 g/day). In August 2003 her treatment was stopped but 3 weeks later, she developed a marked vesicular, papular, scaling rash, affecting her chest and back, and also developed blistering lesions on her hands. A skin biopsy of the upper back showed active cutaneous lupus and her lupus nephritis relapsed clinically. She was restarted on MMF and corticosteroids but the rash gradually worsened and extended to her legs despite increasing prednisolone to 60 mg/day and the addition of Tacrolimus ointment and HCQ. In 2004 she was admitted because of her cutaneous

lesions and a new skin biopsy of the chest was consistent with SCLE. She received IVIG (0.4 g kg^{-1} day^{-1} for 5 days) and the rash responded rapidly in all the affected areas (Fig. 1). One year later her cutaneous lesions still remain under control. Her current treatment is MMF (1.5 g/day) and HCQ (400 mg/day). Throughout her disease course she remained positive for anti-nuclear antibody (ANA), extractable nuclear antigens (ENA) (Ro, La), strongly positive for dsDNA, and had low C_3 and C_4 without significant differences in the titers before and after treatment.

Patient two A 40-year-old lady presented with SCLE since childhood. In 1998 she had a temporary deterioration of her cutaneous lesions during her pregnancy with good response to prednisolone of 20 mg/day (AZA failed to diminish the rash). She then had a gradual extension of the rash over her face, neck, arms, and hands despite treatment with HCQ (400 mg/day) and mepacrine (100 mg/day). In 2000, she developed vasculitic lesions on her hands and feet with thinning of the skin and a healing crust over the arms and legs. She was started on MTX (10 mg/day), which was discontinued because of dizziness and vomiting. She remained on HCQ (400 mg/day) and prednisolone (35 mg/day). She was admitted for 3 IV methyl-prednisolone 500-mg pulses without any improvement (bright red painful eruptions involving face, arms, upper trunk, and legs). She continued on MMF, which caused headaches and diarrhea and was substituted for thalidomide (50 mg/day). One year later, thalidomide was discontinued as the rash remained active and she was admitted for 5 pulses of IVIG (0.4 g kg^{-1} day^{-1}). Four months later there was a significant improvement on the hands and feet (almost complete remission) but an active rash remained on the upper arms and trunk. She was admitted again for a single dose of 20 g of IVIG with further improvement especially on her upper arms (more than 80% decrease in the extent of the rash). She continued with Tacrolimus ointment 0.1%, which was stopped 18 months later as her rash almost disappeared. She was always positive for ANA, ENA (Ro), rheumatoid factor, and negative for dsDNA without any change before and after treatment.

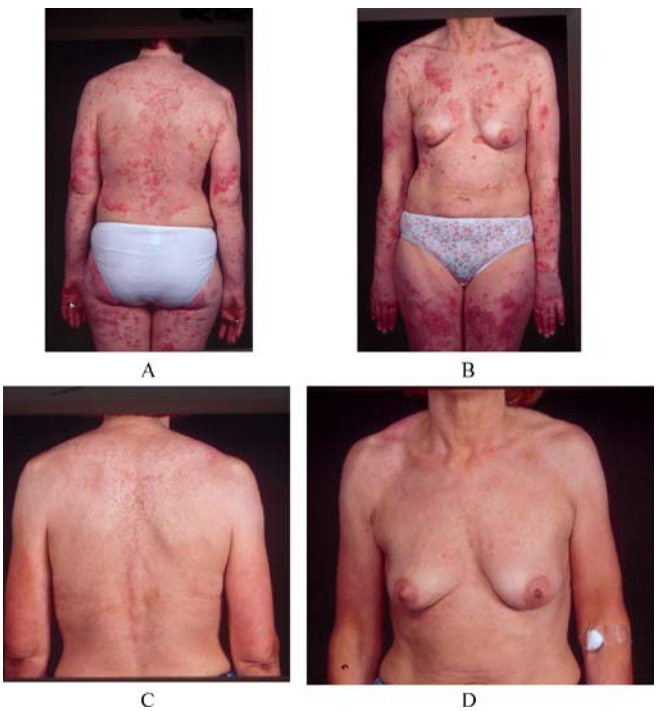

Fig. 1 Photos of patient one before (**a**, **b**) and after (**c**, **d**) the administration of IVIG

Patient three A 35-year-old lady developed a polymorphic rash on her face and hyperkeratotic eruptions on her soles in 1992. Skin biopsy of the face was compatible with SCLE and she was started on mepacrine (discontinued because of skin discoloration), HCQ (400 mg/day), and AZA (100 mg/day). In 1995 the rash extended over her arms and trunk and she had great difficulty in walking. AZA was discontinued and thalidomide was started (100 mg/day) with improvement of the rash except on the soles. One year later, she developed sensory neuropathy and thalidomide was stopped. In 1998, she had a widespread rash over her face, scalp (one lesion), trunk, arms, and soles. Pulses of IV methyl-prednisolone, MTX, and HCQ failed to improve it and the patient was admitted in 2004 for IVIG (0.4 g kg^{-1} day^{-1} for 5 days). The improvement was quite significant over trunk and arms (almost 50%) but lasted only for 2 months. The patient refused repeated IVIG pulses every 3–4 months and she continued on MMF and Tacrolimus ointment without improvement. Recently however, she has had a good response to Acitretin (25 mg/day). She was positive for ENA (Ro) and weakly positive for ANA. It is interesting to note that after treatment she became negative for those autoantibodies.

Discussion

SCLE represents a widespread, photosensitive, nonscarring form of lupus erythematosus. This cutaneous lesion is highly associated with an immunogenetic background and the production of anti-Ro antibodies. The etiopathogenesis [1] includes many factors such as the inheritance of susceptibility genes (C_2, C_4, and C_{1q} deficiency; TNF-α 308A polymorphism), induction of autoimmunity (ultraviolet light, smoking, infections, psychological stress, or photosensitizing drugs like taxotere, thiazides, and calcium channel blockers), triggering of apoptosis as this is expressed by reduction of Bcl-2, and increase of Fas antigens, which correlate directly with the extent of apoptosis in the epidermis. The most frequent histopathological findings are epidermal atrophy, hydropic degeneration of the basal layer, and perivascular lymphocytic infiltrate with deposits of immunoglobulin and C_3 at the dermo-epidermal junction in 86% of the patients with SCLE [2].

IVIG was widely used in the treatment of dermatomyositis, polymyositis, Guillain–Barré syndrome, myasthenia Gravis, idiopathic thrombocytopenic purpura, and many other conditions. It is a powerful immunomodulatory agent, although the mechanism of its action is not completely defined. It inhibits complement binding and prevents membrane attack complex formation, neutralizes pathogenic cytokines, downregulates antibody production, modulates Fc-receptor-mediated phagocytosis, T cell function, and antigen recognition [3]. Side effects of IVIG include thromboembolic events, skin reactions, headaches, occassional renal failure, aseptic meningitis, and hemolysis. Recent publications suggest the use of IVIG in various diseases such as atopic dermatitis, SLE [4], multiple sclerosis [5], Churg–Strauss syndrome [6], lupus nephritis [7], autoimmune neuromuscular diseases [8], bullous pemphigoid, scleroderma, and malignant conditions [9]. There is also evidence that IVIG may be useful during pregnancy as in recurrent neonatal hemochromatosis [10] and dermatomyositis [11].

The usefulness of IVIG in CLE is not well established. There are very few reports suggesting good efficacy of IVIG in resistant cases [12, 13]. In our three patients with SCLE, IVIG administration led to significant improvement of the skin rashes. The duration of the remission ranged from 2 months to more than 1 year. A second injection in one patient further improved the cutaneous lesions suggesting that repeated pulses of IVIG could be used as maintenance therapy. Further prospective studies are needed to evaluate the importance of IVIG in SCLE and cutaneous lupus. Although this is only an observational, noncontrolled study, we suggest that IVIG should be considered in patients with SCLE and resistant or extensive cutaneous lesions to achieve a rapid remission of the rash and to be followed by maintenance therapy, either classical systemic and topical agents or repeated pulses of IVIG.

References

1. Sontheimer RD (2005) Subacute cutaneous lupus erythematosus: 25-year evolution of a prototypic subset (subphenotype) of lupus erythematosus defined by characteristic cutaneous, pathological, immunological and genetic findings. Autoimmun Rev 4:253–263
2. Parodi A, Caproni M, Cardinali C, Bernacchi E, Fuligni A, De Panfilis G et al (2000) Clinical, histological and immunopathological features of 58 patients with subacute cutaneous lupus erythematosus. A review by the Italian group of immunodermatology. Dermatology 200:6–10
3. Dalakas MC (1998) Mechanism of action of intravenous immunoglobulin and therapeutic considerations in the treatment of autoimmune neurologic diseases. Neurology 51:S2–S8
4. Toubi E, Kessel A, Shoenfeld Y (2005) High-dose intravenous immunoglobulins: an option in the treatment of systemic lupus erythematosus. Hum Immunol 66:395–402
5. Stangel M, Gold R (2005) Intravenous immunoglobulins in MS. Int MS J 12:5–10
6. Danieli MG, Cappelli M, Malcangi G, Logullo F, Salvi A, Danieli G (2004) Long term effectiveness of intravenous immunoglobulin in Churg–Strauss syndrome. Ann Rheum Dis 63:1649–1654
7. D' Cruz DP, Hughes GR (2005) The treatment of lupus nephritis. BMJ 330:377–378
8. Dalakas MC (2004) Intravenous immunoglobulin in autoimmune neuromuscular diseases. JAMA 291:2367–2377
9. Shoenfeld Y, Katz U (2005) IVIg therapy in autoimmunity and related disorders: our experience with a large cohort of patients. Autoimmunity 38:123–137
10. Whitington PF, Hibbard JU (2004) High-dose immunoglobulin during pregnancy for recurrent neonatal haemochromatosis. Lancet 364:1690–1698
11. Mosca M, Strigini F, Carmignani A, D' Ascanio A, Genazzani AR, Bombardieri S (2005) Pregnant patient with dermatomyositis successfully treated with intravenous immunoglobulin therapy. Arthritis Rheum 53:119–121
12. Ruetter A, Luger TA (2004) Efficacy and safety of intravenous immunoglobulin for immune-mediated skin disease: current view. Am J Clin Dermatol 5:153–160
13. Goodfield M, Davison K, Bowden K (2004) Intravenous immunoglobulin (IVIg) for therapy-resistant cutaneous lupus erythematosus (LE). J Dermatolog Treat 15:46–50