Photodistributed eruption with rhabdomyolisis due to leflunomide

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To the Editor,

Leflunomide is a new oral drug licensed for the treatment of rheumatoid arthritis and psoriatic arthritis. Common adverse events reported include gastrointestinal symptoms, reversible alopecia, hypertension and transient alteration in liver function tests. Severe cutaneous drug reactions have been reported recently with its increased clinical used such as vasculitis, erythema multiforme, toxic epidermal necrolysis (1) and drug hypersensitivity syndrome (2). We report a case of photodistributed eruption with rhabdomyolysis due to leflunomide.

This patient was a 60-year-old woman, with a 19-year history of rheumatoid arthritis and Sjögren's syndrome. She was previously treated with gold salts, hydroxychloroquine and salazopyrine. Leflunomide (10 mg/day) and prednisone (18 mg/day) were started in December 2008 after a methotrexate-induced leucopenia. Other laboratory findings revealed positive rheumatoid factor and a high titre (1/2560) of antinuclear antibodies. Anti-DNA and anti-extractable nuclear antigen (ENA; anti-SSA and anti-SSB) antibodies were positive. On 11, May 2009, she developed skin lesions on her face. The administration of leflunomide was stopped and the patient received cholestyramine 8 mg/day. Fifteen days later, she presented to our department, with extensive eruption. Examination revealed erythematous plaques particularly on the face, sparing the eyelids and the area under the nose (physiological shade's areas), on the neck and the upper back with cut-off in the area covered by the bra (Fig. 1). Some lesions were found on the limbs, abdomen and buttocks. There was neither fever nor mucosal involvement. Abnormal routine laboratory findings were as follows: AST, 54 IU/l (normal < 30); ALT, 59 IU/l (normal < 30); serum creatine kinase (CK), 1480 IU/l (normal < 145). Antinuclear antibodies' titre was increased (1/2560), with the detection of anti-DNA and anti-ENA (anti-SSA and anti-SSB) antibodies. Complement C3 and C4 levels were normal. Rheumatoid factor and anti-cyclic citrullinated peptide antibodies were elevated to 419 IU/ml (normal < 20) and 649 IU/ml (normal < 25), respectively. The results of hepatitis B, hepatitis C virus, cytomegalovirus, parvovirus, Epstein–Barr virus, human herpesvirus-6 and immunodeficiency virus analyses were negative. A skin biopsy showed numerous necrotic keratinocytes, vacuolization of the epidermal basal cell layer and lymphocytic perivascular infiltrate. Direct immunofluorescence performed in the skin lesion was negative. The evolution was marked by a normalization of aminotransferases and CK values within 1 month after stopping the drug. Treatment with topical desonide led to the disappearance of the lesions in 2 months without recurrence after a 1-year follow-up. The patient declined photobiological investigations.

The clinical presentation of skin lesions was compatible with photosensitivity supported by occurrence of the rash in spring. The photodistributed eruption, the skin biopsy result and the liver involvement were consistent with drug reaction. Despite a long delay, the temporal relationship between the commencement of leflunomide in winter and the onset of the photodistributed eruption suggests a causative link in this patient.

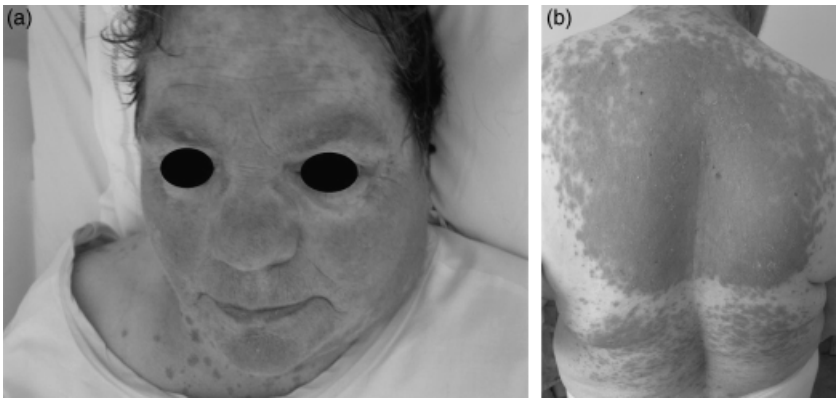

Fig. 1. Erythematous lesions. (a) On the face, sparing the peri-orbital site and the area under the nose. (b) On the back with cut-off in the area covered by the bra.

This is supported by the improvement of symptoms after the withdrawal of leflunomide while the dose of corticosteroid was unchanged. No other drug or parameters of infection or of any other kind of toxicity were detected in this period as possible causes for the patient's condition.

Leflunomide is an isoxazole immunomodulatory agent used as disease-modifying antirheumatic drug. Cases of cutaneous lupus induced by leflunomide have been described recently (3, 4). This drug, through its immunomodulatory effect, can favour the appearance of a Th2 lymphocyte immune response inducing lupus (4). Clinical manifestations are characterized by erythematous and maculopapular eruption associated with annular lesions in a photosensitive distribution. Antinuclear antibodies' titre is increased with the presence of anti-SSA antibodies. In our case, the diagnosis of induced lupus was not made taking account of the absence of immunological profile modification and the skin biopsy result.

In this patient, muscular enzyme concentrations increased tenfold, consistent with rhabdomyolysis that resolved after discontinuation of the drug. Myalgias and renal involvement were not found. Rhabdomyolysis is a syndrome characterized by muscle necrosis and the release of intracellular muscle contents into systemic circulation. Acute renal failure is the most common complication of rhabdomyolysis. Other causes for muscular injury (e.g., infections, muscle compression alcohol or cocaine intake) were not suggested by the clinical history. To our knowledge, one case of rhabdomyolysis with photodistributed lichenoid eruption and oral involvement occurring during leflunomide treatment has been described previously (5). In our patient, the lesions were lichenoid histologically. Furthermore, the lichenoid drug eruptions classically have a long delay of onset and disappearance after stopping the responsible drug like in our case.

In conclusion, prescribers and users of leflunomide should be alerted to the possibility of its potentially severe side effects such as photosensitivity and rhabdomyolysis. Because of the half-life of leflunomide, which is about 2–3 weeks, adverse effects may continue long after the drug has been stopped (5) as in our case in spite of the washout treatment with cholestyramine.

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