

Subacute Cutaneous Lupus Erythematosus Associated With Leflunomide

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GOAL

To understand drug-induced subacute cutaneous lupus erythematosus (SCLE) to better manage patients with the condition

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Explain the possible mechanisms of action for leflunomide that may cause SCLE.
2. Describe the side-effect profile of leflunomide.
3. List other drugs that have been reported to induce SCLE.

CME Test on page 193.

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Drs. Elias, Tam, and David-Bajar report no conflict of interest. The authors discuss off-label use for cholestyramine, leflunomide, and prednisone. Dr. Lief reports no conflict of interest.

A skin eruption consistent with subacute cutaneous lupus erythematosus (SCLE) occurred in a patient taking leflunomide for rheumatoid arthritis. The eruption resolved after discontinuation of

the medication. Suppression of tumor necrosis factor (TNF)-effector mechanisms by leflunomide may have played a role in the pathogenesis of this disorder.

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Leflunomide is an immunomodulatory drug indicated for the treatment of active rheumatoid arthritis (RA). Clinical trials have shown its efficacy in both improving the signs and symptoms of RA and delaying progression of the disease.¹ Reports of off-label use suggest the drug is useful in treating several other conditions, including solid organ transplantation, graft versus host disease, certain cancers, systemic lupus erythematosus (LE),

bullous pemphigoid, and psoriasis.²⁻⁷ In clinical trials of leflunomide used to treat RA, cutaneous side effects included alopecia, eczema, pruritus, rash, and dry skin.⁸

We report a case of a patient taking leflunomide for RA who developed a skin eruption consistent with subacute cutaneous LE (SCLE) that resolved after discontinuing the medication. Clinical appearance, histopathologic examination, and direct immunofluorescence findings supported the diagnosis. To our knowledge, this is the first published case of drug-induced SCLE associated with the use of leflunomide.

Case Report

A 64-year-old white woman presented with a month-long history of a pruritic rash on her arms. The patient noted that the rash worsened with sun exposure. Her medical history was significant only for RA. At the time of her evaluation, she had been taking leflunomide 20 mg/d for 4 months, etanercept 25 mg twice weekly for 6 weeks, and prednisone 5 to 7.5 mg/d for one year. She also had been taking rofecoxib for one year, but this was discontinued just prior to being seen by dermatology.

Results of a physical examination showed numerous erythematous scaling plaques on the dorsal aspect of the patient's hands and forearms that extended proximally to the outer aspect of her arms just above the elbows. The face and trunk were spared.

Histopathologic examination results of a biopsy specimen taken from a lesion on the forearm showed vacuolar alteration and scattered necrotic keratinocytes along the dermal-epidermal junction with a sparse superficial and mid dermal perivascular lymphocytic infiltrate that focally obscured the junctional interface. Spongiosis was absent. Direct immunofluorescence examination results showed particulate staining of keratinocytes with immunoglobulin G; granular discontinuous staining at the dermal-epidermal junction with the third component of complement; and diffuse dermal staining with fibrin. Antinuclear antibody test results were positive, with a titer level of 1:320 with a homogeneous pattern using HEp-2 cells. Test results for anti-Ro (anti-SSA) and anti-La (anti-SSB) antibodies were negative by immunodiffusion. Antidouble-stranded DNA, anti-Smith, anti-ribonucleoprotein, and antihistone antibody test results were negative. Complete blood count, basic

metabolic panel, liver function, and urinalysis test results were unremarkable.

The patient was treated with mid- to high-potency topical corticosteroids for 4 weeks without improvement. Results of patch testing with North American standard antigens, preservatives and vehicles, and photoallergens were negative. Etanercept initially was suspected as the cause of the rash because of the temporal relationship between its initiation and the onset of the rash. Despite discontinuing etanercept, the patient's eruption continued to progress with added involvement of the upper back and chest (Figure).

Four weeks after discontinuing etanercept, leflunomide was discontinued and the patient was treated with cholestyramine to hasten clearance of the drug. The patient's prednisone dose was increased to 60 mg and then was tapered over 4 weeks to her baseline dose. The rash markedly improved within 2 weeks and was completely resolved by 8 weeks. The patient was restarted on etanercept without recurrence of the rash.

Comment

Leflunomide is a malononitrilamide drug that exhibits anti-inflammatory, antiproliferative, and immunosuppressive effects through mechanisms that are not fully understood.² Studies have shown that the drug inhibits T-cell proliferation, B-cell proliferation, and antibody production.^{9,10} Leflunomide is a potent inhibitor of dihydro-orotate dehydrogenase, a rate-limiting enzyme in the de novo synthesis of pyrimidines. This may explain the drug's effect on activated lymphocytes, which are dependent on de novo pyrimidine synthesis.¹¹ Another



Erythematous scaling plaques on the upper chest and arms.

mechanism of action may be through the effect of leflunomide on tumor necrosis factor (TNF)-related cellular responses.¹²

In our patient's case, leflunomide was associated with the onset of a photosensitive nonscarring rash that was clinically, histopathologically, and immunohistopathologically consistent with SCLE. Discontinuation of the drug with subsequent resolution of the eruption strongly suggests a key role for the drug in the manifestation of the illness. It is possible, however, that other drugs taken by the patient may have been partly or entirely responsible for her disease. Rofecoxib may have played a role; however, the increasing severity of the disease and the length of time to clear the disease after discontinuing the rofecoxib make this less likely. Etanercept, previously reported to cause SCLE, may have been the cause in this case as well; however, the negative rechallenge with etanercept makes this unlikely. The combination of leflunomide and etanercept is another possible culprit, rather than either drug alone.

To our knowledge, this is the first reported case of SCLE associated with the use of leflunomide. In clinical trials involving more than 1300 patients treated for RA, cutaneous adverse effects included alopecia in 10% of patients, rash in 10%, pruritus in 4%, eczema in 2%, and dry skin in 2%.⁸ There is one

report of cutaneous and renal vasculitis associated with leflunomide used for RA.¹³

SCLE is a subset of LE with distinctive clinical and immunologic features. Clinically, SCLE manifests as a nonscarring papulosquamous eruption that commonly occurs in a characteristic photodistribution. With time, the rash may take on a psoriasiform or annular/polycyclic appearance or may exhibit features of both patterns.¹⁴ On direct immunofluorescence, dustlike particulate deposition of immunoglobulin G in the epidermis, as seen in our patient, has been reported in lesions of SCLE.¹⁵

A number of medications have been reported to induce SCLE (Table¹⁶⁻³¹); however, it is not known how certain medications induce SCLE lesions. A drug's effect on autoantibody formation, cytokine production, or induction of some other immunologic effector mechanism in a genetically predisposed individual may play a role. One possible mechanism for the induction of SCLE lesions by leflunomide may involve the drug's effect on TNF-related effector mechanisms. TNF may play an important role in the manifestation of photosensitive LE.³² Drugs that block the effects of TNF- α , such as thalidomide and etanercept, have been shown to improve SCLE.³³ On the other hand, TNF also may have a protective role against autoimmunity, and its suppression may actually help induce autoimmune disease. Etanercept, previously mentioned as a potential treatment for SCLE, also has been reported to induce SCLE.²¹ The suppressive effect of leflunomide on TNF-related mechanisms may play a similar role in the induction of SCLE.

Drugs Associated With Subacute Cutaneous Lupus Erythematosus¹⁶⁻³¹

Angiotensin-converting enzyme inhibitors
Antihistamines
Calcium channel blockers
Cinnarizine
Etanercept
Glyburide
Gold
Griseofulvin
Interferon β -1a
Naproxen
Penicillamine
Phenytoin
Piroxicam
Psoralen plus UVA
Spironolactone
Terbinafine
Thiazides

Conclusion

We report a case of SCLE associated with the administration of leflunomide for RA. As leflunomide comes into more widespread use in the treatment of RA and other disorders, it remains to be seen whether more cases of SCLE will occur. Fortunately, such a condition appears to be rare and reversible once the drug is discontinued.

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