Leflunomide a rare culprit for drug induced subacute cutaneous lupus erythematosus

M N Mahesha[1], B Prashanthi[2], T Dinupa[3], N C Perera[4]

Sri Lanka Journal of Dermatology, 2019/2020, **21**: 81-83

Introduction

Leflunomide is a disease modifying anti rheumatic drug with a manageable safety profile which has received regulatory approval for the treatment of active rheumatoid arthritis and psoriatic arthritis.

It shows anti-inflammatory antiproliferative and immunosuppressive effects.

In clinical trials involving patients treated with leflunomide for rheumatoid arthritis diarrhea is the commonest adverse effect identified.

The more severe adverse effects of leflunomide including life threatening hepatotoxicity leading to liver failure and pancytopenia with bone marrow suppression warrants for monitoring of patients with routine liver transaminases and complete blood count.

Common cutaneous adverse effects include reversible alopecia, rash, pruritus, eczema, and dry skin.

<1% of patients were reported with erythema multiforme, Steven Johnson syndrome and toxic epidermal necrolysis[1].

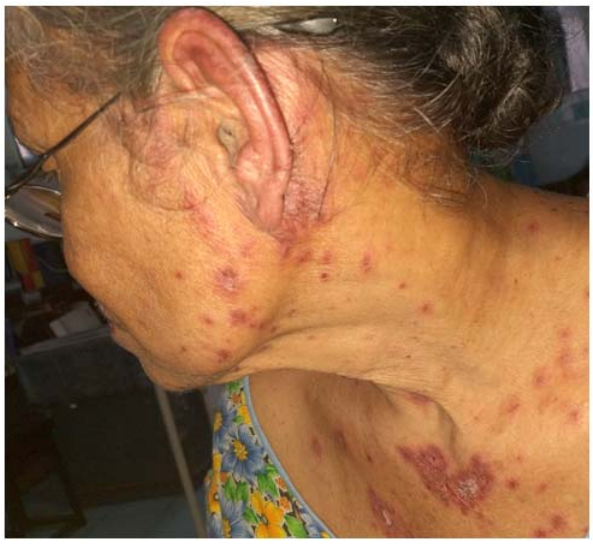
As per literature only very few cases of leflunomide induced SCLE have been reported till time[2].

Case history

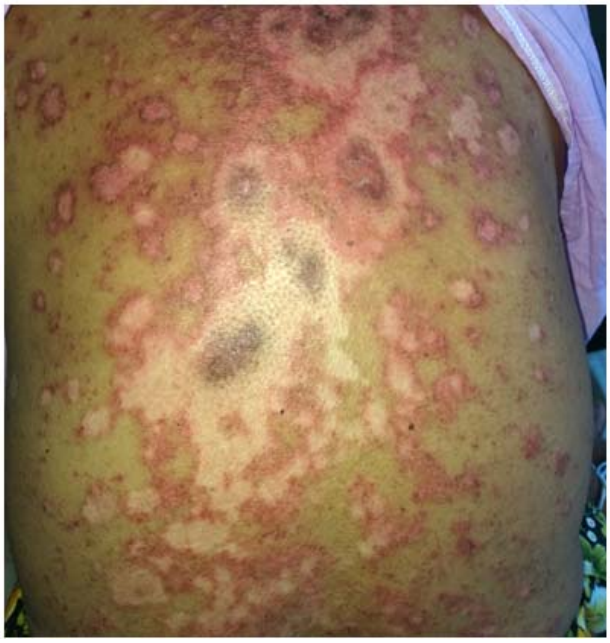
A 70-year-old female with four years history of sero positive rheumatoid arthritis presented with a pruritic and erythematous rash involving the face, neck, upper arms, chest and back for 2 weeks duration along with a history of general malaise and alopecia. She had been taking leflunomide 20 mg/day for a period of 3 months under the care of her rheumatologist.

Clinical examination revealed numerous erythematous papulosquamous lesions on the dorsal aspect of forearms that extended proximally to outer aspect of her arms, also involving the back and the exposed areas of the neck and chest anteriorly. Facial erythema was prominent in the photo exposed parts including malar region and nasal bridge with evidence of non-scarring alopecia on the scalp.

Rest of the clinical examination including mucosae were normal and her rheumatoid arthritis disease activity was well controlled.



[1,2]*Senior Registrar in Dermatology,* [3]*Registrar in Dermatology* [4]*Consultanat Dermatologist, Colombo South Teaching Hospital, Kalubowila, Sri Lanka.*



The possibility of DI SCLE due to leflunomide was considered as the working diagnosis on clinical grounds and the drug was withheld.

Her initial FBC showed a leukopenia with a total WBC of 2.23 x 103 neutrophil 63.3% Hb 9.6g/dl platelets 172. ESR 80mm in 1st hour and CRP was < 5mg/l.

Her serology revealed – positive anti-nuclear antibody (titre 1:100 homogenous type); strongly positive anti-histone antibodies; with positive anti-SSA antibody, but negative anti-dsDNA and anti-SSB.

Urine analysis, and the metabolic profile including liver and renal functions were unremarkable.

Histopathology of a punch biopsy from anterior chest region revealed vacuolar interface dermatitis with formation of focal clefts, mild hyperkeratosis and subepidermal vesicles with necrotic keratinocytes. Dermis revealed edema and perivascular inflammatory infiltrate supportive of a diagnosis of SCLE.

Patient was started on intravenous methyl prednisolone 1g daily for 3 days and subsequently oral methylprednisolone was introduced and tapered according to the clinical response. She was given topical corticosteroids and photoprotection to alleviate the symptoms.

A washout procedure with oral cholestyramine (8g tds for 11 days) was initiated to hasten the clearance of leflunomide in the presence of cytopenia.

She recovered from cytopenia during the first week and skin lesions remarkably improved over a course of 4 weeks.

Discussion

Drug induced subacute cutaneous lupus (DI-SCLE) is the commonest entity of drug induced lupus erythematosus (DI-LE).

It is characterized by skin lesions occurring mainly in sun exposed areas, as erythematous annular polycyclic and/or non scarring papulosquamous lesions associated with high titers of anti Ro (SSa) antibody.

Time intervals between drug exposure and appearance of DI-SCLE may vary widely. It has been noted within 3 days or up to 11 years after initiation of the causative medication.

Discontinuation of offending drug causes the lesion of DI-SCLE to resolve within weeks yet, positivity of Ro/SSa persists even after resolution of lesions[3].

Reed *et al* in 1985 first introduced the concept of DI-SCLE when they observed photosensitive eruptions with clinical and histologic features of subacute cutaneous lupus erythematosus and antibodies to SS-A(Ro) antigen in five patients taking hydrochlorothiazide[4].

To date many drugs have been implicated as culprits of DI-SCLE.

Drugs most likely to trigger SCLE include

- Hydrochlorothiazide
- Calcium channel blockers
- Angiotensin-converting enzyme inhibitors
- Proton-pump inhibitors
- Antifungals (terbinafine, griseofulvin)
- Immunomodulators (TNF-α inhibitors)
- Chemotherapeutic agents

Several mechanisms including genetic predisposition, drug biotransformation and epigenetic dysregulation in different immune cells interact with each other resulting in DI-LE.

Majority of patients are slow acetylators who are more prone for antibody accumulation.

Biotransformation generates reactive metabolites which alter epigenetic properties of immune cells resulting in autoreactive T and B cells ultimately leading to photosensitivity and DILE.

This photosensitive state may induce SCLE skin lesions via an isomorphic response in immunologically predisposed individuals (photo pharmacological isomorphic response)[5].

Leflunomide is a prodrug, upon conversion to its active metabolite A771726, reversibly inhibits mitochondrial enzyme dihydroorotate dehydrogenase (DHODH) the rate limiting enzyme in de novo synthesis of pyrimidine ribonucleotides thus the effect on activated T lymphocytes. Another mechanism of action may be through the effect of leflunomide on tumor necrosis factor (TNF)-related cellular responses.

The long half-life of the active metabolite of leflunomide A771726 necessitates for a wash out procedure in addition to withdrawal of the drug in the onset of severe adverse effects.

Indications for a washout procedure.

Severe reactions (inflammation of the buccal or genital mucosa, fever, extensive body rash, including bullous reactions or other signs suggestive of Stevens-Johnson or similar syndromes) or signs of anaphylaxis or severe, poorly tolerated, alopecia and cytopenia

Initiation of the washout procedure.

Following cessation of leflunomide, an 11-day washout period commences, with cholestyramine (8 g tid) or activated charcoal (50 g qds).

The duration of washout may be modified depending on clinical and laboratory variables.

Cholestyramine can facilitate the rapid elimination of leflunomide. One day's treatment with cholestyramine (4 g tid) has been shown to shorten the half-life of leflunomide dramatically so that 90% of patients have undetectable levels after 3 weeks[6].

Conclusion

As leflunomide claims fame as a DMARD among Rheumatologists, Dermatologists should be vigilant for the detection of more cases of leflunomide induced SCLE which is reversible upon discontinuation of the drug. A washout procedure may benefit in some with severe adverse effects.

References

1. Strand V, Cohen S, Schiff M, *et al*. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Leflunomide Rheumatoid Arthritis Investigators Group. *Arch Intern Med* 1999; **159**: 2542-50.

2. Kerr OA, Murray CS, Tidman MJ. Subacute cutaneous lupus erythematosus associated with leflunomide. *Clin Exp Dermatol* 2004; **29**: 319-20.

3. Singh H, Sukhija G, Tanwar V, Arora S, Bhutani J. Rare Occurrence of Drug Induced Subacute Cutaneous Lupus Erythematosus with Leflunomide Therapy. *J Clin Diagn Res*. 2016; **10**(10): OD06-OD07. doi:10.7860/JCDR/2016/14508.8667

4. Reed BR, Huff JC, Jones SK, Orton PW, Lee LA, Norris DA. Subacute cutaneous lupus erythematosus associated with hydrochlorothiazide therapy. *Ann Intern Med*. 1985; **103**: 49-51. doi: 10.7326/0003-4819-103-1-49

5. He Y, Sawalha AH. Drug-induced lupus erythematosus: an update on drugs and mechanisms. *Curr Opin Rheumatol*. 2018; **30**(5): 490-7. doi:10.1097/BOR.0000000000000522

6. van Riel PL, Smolen JS, Emery P, *et al*. Leflunomide: a manageable safety profile. *J Rheumatol Suppl*. 2004; **71**: 21-4.

.