Case Report

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Internal Medicine Section

Rare Occurrence of Drug Induced Subacute Cutaneous Lupus Erythematosus with Leflunomide Therapy

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ABSTRACT

Leflunomide is an immunomodulatory drug exhibiting anti-inflammatory, anti-proliferative and immunosuppressive effects. It has been widely used for treatment of active rheumatoid arthritis. Despite its good safety profile cutaneous side effects like alopecia, eczema, pruritis and dry skin have been reported with Leflunomide use. Skin ucleration, vasculitis, lichenoid drug rash and Subacute Cutaneous Lupus Erythematosus (SCLE) have been rarely reported with its use. A rare case of Leflunomide induced SCLE is being reported in a female patient with rheumatoid arthritis. The clinical features, histopathological and immunological characteristics were consistent with drug induced SCLE. Withdrawal of Leflunomide along with short course of topical steroids resulted in resolution of symptoms suggesting the drug to be the culprit. As this drug comes into widespread use, it remains to be seen whether more cases of DI-SCLE will occur/be reported. Fortunately, such a condition till times appears rare and is reversible once the drug is discontinued thus avoiding over evaluation and over treatment if the triggering drug is recognized.

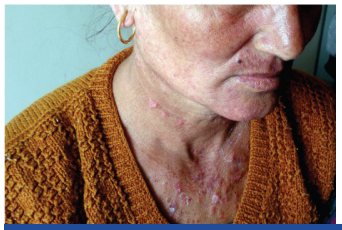
Keywords: DI-SCLE, Immunomodulatory drug, Rheumatoid arthritis

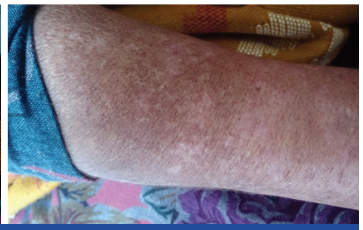
CASE REPORT

A 50-year-old female, known case of hypothyroidism (for past six years) and seronegative Rheumatoid Arthritis (RA) (for four years), presented to the Rheumatology Department at Pt. B.D. Sharma, PGIMS, Rohtak, with two months history of pruritic and erythematous rash on her arms, neck and anterior chest along with history of alopecia. She was on leflunomide 20mg/day for past three years (as she developed GI intolerance with Methotrexate then) and levothyroxine 25µg/day. Etoricoxib as anti-inflammatory she was using on SOS basis.

Her clinical examination revealed numerous erythematous lesions on the dorsal aspect of forearms that extended proximally to outer aspect of her arms, also involving the upper part of the exposed areas of the chest anteriorly and neck. The face was spared and she had evidence of alopecia [Table/Fig-1,2]. Rest clinical examination was normal and her RA disease activity was well controlled. A possibility of overlap with Subacute Lupus Erythematosus (SLE) or Drug Induced Subacute Cutaneous Lupus Erythematosus (DI-SCLE) due to leflunomide was kept.

Her serology revealed – positive anti-nuclear antibody (titre 1:320 homogenous type); strongly positive anti-Histone antibodies; positive Anti-SSA antibody; but negative Anti-dsDNA and Anti-SSB and normal complement levels. Complete blood count, urine analysis, liver and kidney function biochemistry were unremarkable. Her skin biopsy was performed and histopathological report revealed hyperkeratosis in epidermis, hydropic degeneration of basal layer, formation of focal clefts and subepidermal vesicle; dermis revealed edema and perivascular inflammatory infiltrate with changes suggestive of histopathological diagnosis of SLE.





[Table/Fig-1]: Erythematous rash and annular lesions with crusted borders over face and anterior chest. **[Table/Fig-2]:** Erythematous erosive skin lesions on the exposed forearm.

Leflunomide and Etoricoxib were withdrawn and patient was put on Methotrexate 15mg/week alone along with topical corticosteroids. Patient improved in symptoms. Etoricoxib was reintroduced with no exacerbation of her symptoms after introduction.

The clinical profile, drug history, serology and histopathology with response to drug withdrawal suggested that patient had Leflunomide induced SCLE in a background of RA and hypothyroidism.

DISCUSSION

Drug induced SLE presents uncommonly with lupus erythematous specific skin changes (including SCLE) and more oftenly with systemic symptoms such as fever, arthritis, myalgias and serositis in a background of positivity of antinuclear antibodies (including specific anti-Histone antibodies) [1]. The clinical concept of drug induced SCLE (DI-SCLE) is just two decades old and was reported by Reed et al., in 1985 [2]. They speculated that DI-SCLE is the photosensitive drug reaction in which the culprit photoactive drug produces cutaneous lesions of SCLE in synergism with anti-SSA antibodies [2]. Since the initial report, various drugs of different pharmacological classes have been identified to trigger DI-SCLE and these trigger drugs with few exceptions do not trigger SLE suggesting a fundamentally different underlying disease mechanism [3].

DI-SCLE presents with skin lesions occurring mainly in sun exposed areas, as erythematous annular and/or papulosquamous lesions with or without scales. DI-SCLE resembles clinically, histopathologically and immunologically (including Ro/SSa positivity) like idiopathic SCLE. Time intervals between drug exposure and appearance of DI-SCLE vary. Discontinuation of offending drug, unlike idiopathic SCLE, causes the lesion of DI-SCLE to resolve within weeks. Interestingly, positivity of Ro/SSa persists even after resolution of lesions.

Arbuckle et al., have suggested the persistence of positivity of Ro and/or La antibodies even after lesion of SCLE resolves, may be due to crescendo of auto-immunity which culminates into clinical

illness i.e., DI-SCLE skin lesions and so may persist to some degree after resolution of symptoms [4]. Unlike drug induced SLE, only one third cases of DI-SCLE have evidence of anti-Histone antibodies (as was in the present case) [5]. Interestingly progression of DI-SCLE to full blown SLE or Sjogren's syndrome, despite the above mentioned antibodies positivity has not been reported in majority of patients [3].

Speculation regarding DI-SCLE pathogenesis has always been there. Probably in a genetically predisposed individual, the culprit drug effects on autoantibody formation/ cytokine production or induces immunologic effecter mechanism. The induction of photosensitive state is the common feature of these drugs which trigger DI-SCLE. This photosensitive state may induce SCLE skin lesions via an isomorphic response (syn. Koebner Response) in immunologically predisposed individual i.e., photopharmacological isomorphic response [3,4].

In most cases DI-SCLE is reversible without treatment once the triggering drug(s) is recognised and withdrawn although besides withdrawal of drug for early relief topical steroids, oral Prednisolone, Hydroxychloroquine or topical Tacrolimus have been used for DI-SCLE [1,3].

The present case of DI-SCLE associated with administration of Leflunomide for RA. In the present case, Leflunomide associated photosensitive non-scarring rash was clinically, histopathologically and immunihistopathologically (positive ANA, anti-Histone antibodies and antiRO antibodies) was consistent with a diagnosis of SCLE. Discontinuation of the drug with subsequent resolution of the eruption strongly suggests a key role for the drug Leflunomide in the manifestation of skin lesions of SCLE. As per literature only six cases of Leflunomide induced SCLE have been reported till time [6-10]. As Leflunomide comes into more widespread use in the treatment of RA and other disorders, it remains to be seen whether more cases of DI-SCLE will occur/be reported. Fortunately such a condition till times appears rare and is reversible once the drug is discontinued thus avoiding over evaluation and over treatment if the triggering drug is recognized.

CONCLUSION

Authors would like to conclude that Leflunomide can cause a subacute cutaneous lupus like syndrome which is reversible with discontinuation of the drug or with a short course of steroids and its action on the tumour necrosis factor alpha may have some role in its pathogenesis or unmasking of SCLE in predisposed individuals.

ABBREVIATIONS

SCLE – Subacute Cutaneous Lupus Erythematosus

GI – Gastrointestinal

RA – Rheumatoid Arthritis

DI-SCLE – Drug Induced Subacute Cutaneous Lupus Erythematosus

SLE – Systemic Lupus Erythematosus

ANA – Anti Nuclear Antibodies

syn. – Synonymous

i.e. – That is

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