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CASE REPORT

Leflunomide-induced DRESS syndrome complicated by diabetic ketoacidosis and autoimmune diabetes: a case report

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Abstract

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is a severe cutaneous adverse reaction with significant multi-organ involvement and potential for delayed autoimmune sequelae, including type 1 diabetes mellitus (T1DM). The occurrence of diabetic ketoacidosis (DKA) in this context is extremely rare. Leflunomide is an uncommon but recognized cause of DRESS. This case report describes a 59-year-old woman with seropositive rheumatoid arthritis who developed fever, facial oedema, a generalized erythematous rash, and eosinophilia 38 days after initiating leflunomide.

She was diagnosed with DRESS and started on systemic corticosteroids. During hospitalization, DKA was confirmed with marked hyperglycemia and ketonuria. Corticosteroids were discontinued, and she required insulin therapy and intensive care support. Anti-glutamic acid decarboxylase (GAD) antibodies were markedly elevated, confirming new-onset autoimmune type 1 diabetes mellitus. Cyclosporine was initiated with clinical improvement. This case underscores the importance of early recognition, metabolic monitoring, and tailored immunosuppression in DRESS.

Keywords: DRESS syndrome; Leflunomide; diabetic ketoacidosis; autoimmune diabetes; Anti-GAD antibodies; Cyclosporine

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Introduction

DRESS is a severe cutaneous adverse reaction (SCAR) characterized by potentially life-threatening multi-organ involvement.[1] It typically occurs 2–8 weeks after exposure to the offending drug. The most common features are fever and a widespread cutaneous eruption, usually morbilliform, often accompanied by facial oedema. Major systemic manifestations include lymphadenopathy, hepatitis, and hematological abnormalities, particularly eosinophilia. Several diagnostic criteria have been proposed, including the RegiSCAR scoring system.[1]

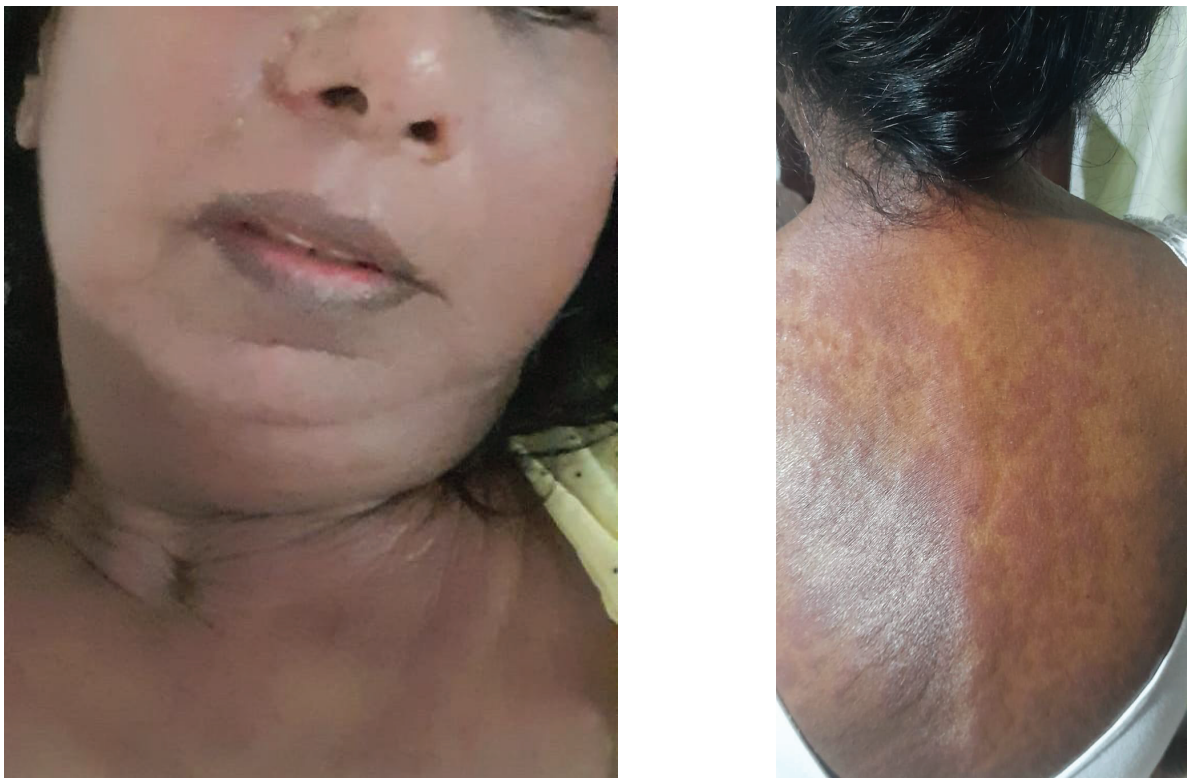
The condition is also associated with delayed autoimmune sequelae, including type 1 diabetes mellitus.[2] The occurrence of DKA in this setting is extremely uncommon and clinically significant. Leflunomide is an uncommon but recognized cause of DRESS.[3]

Case Presentation

A 59-year-old female with seropositive rheumatoid arthritis, initially treated with hydroxychloroquine and dexamethasone for two months, was commenced on leflunomide.

After 38 days, she developed oral erosions, facial edema, a generalized erythematous rash, self-reported lymphadenopathy, and intermittent fever (Figure 1A-B). She was initially managed at a local clinic with a short course of methylprednisolone. Due to inadequate clinical response, she was admitted on day 22 of illness with exfoliative dermatitis and cheilitis.

Investigations revealed marked eosinophilia (25.7%; absolute eosinophil count 2264/µL), anemia (Hb 10 g/dL), and mild transaminitis (AST 43 U/L, ALT 73 U/L). Renal function was normal, and infectious screening was negative. Skin biopsy showed non-specific changes.



A B

Figure 1. Cutaneous manifestations of DRESS syndrome following leflunomide therapy. (A) Diffuse erythematous morbilliform eruption with facial oedema during the acute phase of illness. (B) Widespread erythematous rash with scaling and exfoliation involving the trunk and extremities at the time of hospital admission.

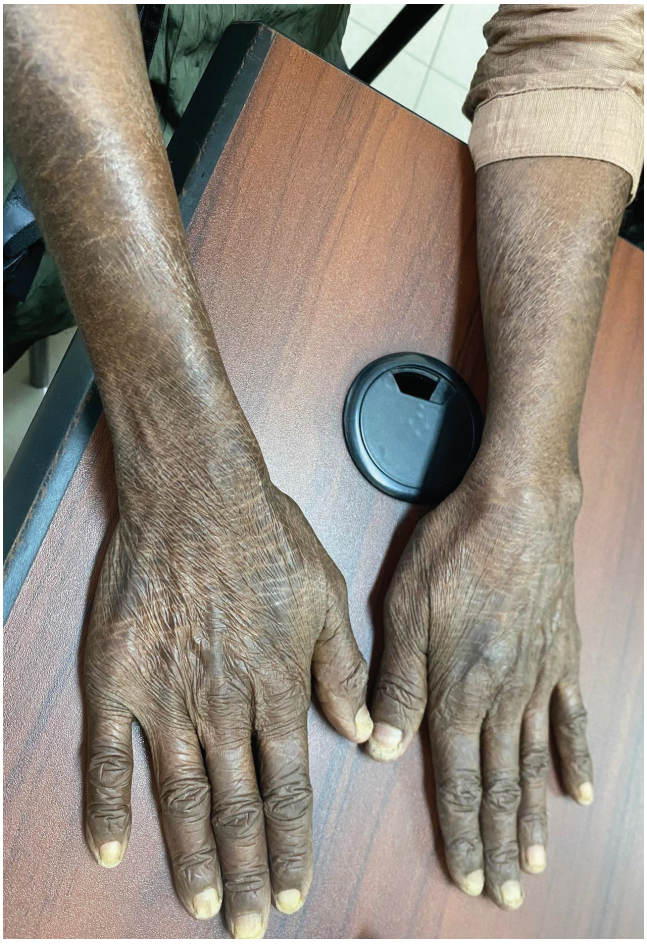


Figure 2. Clinical resolution following treatment. Residual post-inflammatory hyperpigmentation after resolution of the cutaneous eruption following treatment with cyclosporine.

Diagnosis and Management: A diagnosis of DRESS was based on a RegiSCAR score >5 (definite case), and she was started on oral prednisolone. Previous investigations showed fasting blood glucose of 108 mg/dL and HbA1c of 6% three months prior.

During hospitalization, she developed altered consciousness and hyperventilation. Evaluation confirmed diabetic ketoacidosis with severe hyperglycemia and ketonuria. Corticosteroids were discontinued, and she was managed with insulin and intensive care support.

Immunosuppression was switched to cyclosporine, resulting in gradual clinical improvement. Further evaluation revealed markedly elevated anti-GAD antibodies (107.5 U/mL), confirming new-onset autoimmune type 1 diabetes mellitus. Endocrinology follow-up was arranged for long-term management, along with rheumatology follow-up.

Cardiac and thyroid evaluations were normal. Cyclosporine was tapered over four months, with resolution of symptoms and only residual pigmentary changes (Figure 2).

Discussion

DRESS syndrome is a severe hypersensitivity reaction characterized by delayed onset, with 70–90% of adult cases being drug-induced.[1] Although commonly associated with aromatic anticonvulsants, antibiotics, and allopurinol, leflunomide remains a rare but recognized trigger.[3] Its long half-life and enterohepatic circulation may contribute to prolonged clinical manifestations.[4]

Autoimmune sequelae of DRESS include systemic lupus erythematosus, thyroiditis, and diabetes mellitus, which may present as fulminant type 1 diabetes mellitus (T1DM) or diabetic ketoacidosis.[2] The interval between the onset of DRESS and the development of diabetes mellitus is variable,

ranging from a few weeks to several months.[5] Reported causative drugs for DRESS associated with subsequent diabetes mellitus include anticonvulsants, antibiotics, sulfonamides, and allopurinol.[2] To date, there are no reported studies linking leflunomide-induced DRESS specifically to the development of diabetes mellitus. Moreover, leflunomide has been shown in some studies to reduce blood glucose levels. Therefore, in such cases, diabetes is best considered a rare autoimmune sequela of DRESS rather than a direct effect of leflunomide.

Islet-related autoantibody testing, such as anti-GAD antibodies, confirms autoimmune β-cell destruction, establishing the diagnosis of new-onset T1DM rather than steroid-induced hyperglycemia or type 2 diabetes. In this patient, markedly elevated anti-GAD levels supported the diagnosis.

Distinguishing steroid-induced hyperglycemia from true autoimmune diabetes is crucial, as management and long-term implications differ significantly.

Management of DRESS primarily involves withdrawal of the offending drug and initiation of systemic corticosteroids. However, in this case, corticosteroids likely contributed to metabolic decompensation, necessitating their discontinuation. Cyclosporine, a calcineurin inhibitor that suppresses T-cell activation, was successfully used as an alternative immunosuppressive agent, leading to clinical resolution.[5]

Conclusion

DRESS syndrome can be complicated by life-threatening metabolic and autoimmune conditions. Early recognition of these complications, careful metabolic monitoring, and individualized immuno-suppressive therapy with long-term endocrinology follow-up are essential in cases complicated by type 1 diabetes mellitus.

Importantly, when initiating any new drug with the potential to cause SCARs, patients should be thoroughly educated about early warning symptoms and advised to discontinue the medication immediately and seek urgent medical attention if such symptoms develop, particularly during the first 2 months of treatment.

Ethics statement

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Patient confidentiality has been strictly maintained.

Authors' contribution

TK contributed to case identification, data collection, literature review, manuscript drafting, and final manuscript preparation. All authors were involved in patient management, manuscript revision, and approved the final version for publication.

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