An Uncommon Presentation of DRESS Syndrome Secondary to Leflunomide Use: A Case Report

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Abstract
Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a constellation of symptoms that manifest as a result of certain medications. Several antipsychotics, antibiotics, and sulfa-containing drugs are known to be implicated in the etiology of DRESS syndrome. The clinical presentation of this disorder consists of a diffuse rash, lymphadenopathy, and systemic organ damage. Our patient presented with symptoms consistent with DRESS syndrome after being started on leflunomide, which is not commonly associated with DRESS. The diagnostic workup comprised of monitoring inflammatory markers on laboratory work, an excisional lymph node biopsy (to rule out malignancy), and a skin biopsy (to assess the etiology of the rash). Our patient received systemic steroids, dose-adjusted based on expert opinion. Further research is required to explore the association between leflunomide and DRESS and address guidelines for the management of DRESS.

Keywords
DRESS syndrome, leflunomide

Background
Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe reaction that presents itself after the initiation of a drug or offending agent.1 Its presentation varies with patient and drug; however, common symptoms are a diffuse blanching rash, multiple end-organ involvement, and lymphadenopathy.2 Immediate diagnosis and appropriate management is necessary in order to avoid progression to severe DRESS symptoms requiring critical care management.3

There have been several antiepileptics, antibiotics, and sulfa drugs that have been heavily associated with DRESS syndrome. However, leflunomide has not been commonly associated with DRESS, as there have only been a few cases, to our knowledge, that have been documented thus far. Our patient was recently started on leflunomide and came in with a diffuse rash, diarrhea, and fever. After a thorough diagnostic approach, he was diagnosed with DRESS. Due to the lack of randomized controlled trials guiding the management of DRESS syndrome, our patient was started on a steroid dose deemed appropriate by expert opinion, which led to the resolution of his symptoms.

Case Presentation
We present the case of a 52-year-old male with past medical history of rheumatoid arthritis, essential hypertension and gastroesophageal reflux disease, who presented to our hospital with chief complaints of fever, diarrhea, and a rash that had been going on for a week prior to admission. He noticed a pruritic skin rash that started at his legs and then rapidly progressed to the rest of his body. He had multiple episodes of diarrhea and 3 episodes of emesis. Review of systems was negative for any possible sick contacts, pulmonary, or other abdominal symptoms.

Four months prior to admission, our patient was worked up for polyarthralgia and was diagnosed with seropositive rheumatoid arthritis. He was started on methotrexate without avail. He was switched to leflunomide, which he started taking 2 weeks prior to admission. His only medications were leflunomide, omeprazole, and ibuprofen.

Physical examination was remarkable for a middle-aged man who appeared his age and was is acute distress. He had a generalized maculopapular blanchable rash present diffusely across the surface of his body. Inguinal lymphadenopathy was noted, with the largest lymph node at 40 mm.

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In the emergency department, he was noted to be tachypneic at a rate of 26 and tachycardic at a rate of 104. His laboratory work was significant for a white blood cell count of $18.7 \times 10^3/\mu L$, elevated eosinophil count at $2.19 \times 10^3/\mu L$, neutrophilia at $14.48 \times 10^3/\mu L$, C-reactive protein of 82 mg/L, erythrocyte sedimentation rate of 20 mm/h, ferritin of 246 ng/mL, and a low complement C4. Rapid strep test, monospot antibody test, and Lyme antibody testing were all negative. He was resuscitated with fluids and started on antibiotics. Computed tomography scan of the thorax, abdomen, and pelvis was done (Figure 1), which showed mediastinal, upper abdominal, axillary, and paraesophageal lymphadenopathy. Rheumatology, hematology/oncology, and dermatology services were consulted.

Further studies showed an elevated rheumatoid factor of 241 IU/mL, an anti-CCP of $>300$ units, speckled pattern antibodies elevated at 160 (/dil), and quantitative immunoglobulin (Ig) E elevated at 20 184 IU/mL. Steroid therapy was deferred until an excisional lymph node biopsy could be obtained. His eosinophil count continued to increase to a peak of $21.34 \times 10^3/\mu L$.

After the excisional left inguinal lymph node biopsy was performed, our patient was started on intravenous (IV) methylprednisolone 40 mg twice daily, which was subsequently increased to 60 mg twice daily. His eosinophil count trended down to $10.70 \times 10^3/\mu L$.

Results of the excisional biopsy showed reactive lymphoid hyperplasia with increased polyclonal IgG4 plasma cells, immunoblasts, Langerhans cells, and histiocytes, non-specific findings that could be seen in drug-induced lymphadenopathy (Figure 2). There was no evidence of lymphoma, infection, or IgG4 disease. CD4:CD8 ratio was 8.2, which made the possibility of neoplasm less likely.

Eventually a skin biopsy was done which showed focal granular perivascular C3 and fibrinogen deposition. There was no specific deposition of immunoglobulin or complement in the epidermis or dermal-epidermal junction (Figure 3).

After receiving 7 days of IV methylprednisolone 60 mg twice daily, our patient felt a significant resolution of his rash. He was discharged on a steroid taper.

**Discussion**

DRESS syndrome is a rare phenomenon that has an estimated incidence of 0.9 out of every 100 000 people. There are certain medications that are strongly linked to this syndrome. Antiepileptic drugs such as phenytoin, carbamazepine, and lamotrigine are noted to cause DRESS syndrome. Sulfa-containing medications, minocycline, and vancomycin...
are antibiotics that are linked to this syndrome as well. Other drugs such as allopurinol and mexiletine are associated.\textsuperscript{3,5}

Leflunomide is not usually associated with DRESS syndrome. To our knowledge, there have been very few cases that have been presented similarly.\textsuperscript{6,8} We believe that further investigation is required to explore the association between leflunomide and DRESS, so as to allow safe prescription and education of patients who require leflunomide.

Although the pathogenesis of this disease is still being studied, there are 2 competing hypotheses that aim to explain the syndrome. One hypothesis is that DRESS syndrome occurs through a delayed hypersensitivity reaction whereby CD4 and CD8 T cells are specifically activated by the offending drug to overproduce cytokines and acute phase reactants.\textsuperscript{9} Another theory is that the offending agent leads to the activation of underlying HHV6/HHV7/Epstein–Barr virus or cytomegalovirus, and the ensuing symptoms are secondary to the body’s immune system attacking the virus.\textsuperscript{10} Our patient was tested for HHV6 and Epstein–Barr virus serologies, which came back negative.

Perhaps the most prominent clinical feature of DRESS syndrome is the diffuse, pruritic rash that emerges, as was the case in our patient. The rash can start out as maculopapular and can progress to being erythematous. In severe cases, pustule formation, exfoliation, or mucosal involvement can occur. Fever and lymphadenopathy are common presenting features of the disease as well.\textsuperscript{11}

The following factors are considered as part of the diagnostic criteria in the workup of DRESS syndrome: a measured fever >101.3 °F, lymphadenopathy in 2 different anatomic areas, eosinophilia and atypical lymphocytes on blood work, and skin involvement, with the inclusion of a skin biopsy. Skin biopsy would show nonspecific changes, including vascular wall damage and lymphocytic infiltrate.\textsuperscript{12} Our patient met this criteria; however, the difficulty comes in the overlap of the clinical presentation of DRESS syndrome with multiple other medical conditions. Our patient necessitated an excisional lymph node biopsy in order to rule out lymphoma. Viral infections were excluded through the viral serologies that were obtained on admission. Hyper eosinophilic syndrome was excluded due to lack of multiorgan involvement and nonspecific findings on skin biopsy.

There is a lack of evidence-based guideline directed therapy with regard to the management of DRESS syndrome. Initially, termination of the offending agent in addition to fluid resuscitation and symptom management are crucial. For mild disease without any overt organ involvement, oral prednisone is recommended. For patients with severe DRESS syndrome, with one or more end-organ involvement, systemic steroids, IV methylprednisolone dosed at 1 mg/kg is recommended with a taper of 2 to 3 months or oral steroids after symptoms subside. Other modes of therapy include cyclosporine and intravenous immunoglobulins.\textsuperscript{13} Our patient required the initiation of IV methylprednisolone 60 mg twice daily to alleviate his symptoms of rash, and this regimen helped decrease his eosinophil count as well.

**Conclusion**

DRESS syndrome is an incredibly rare disease that results due to an adverse medication reaction. Our case details the necessity of physicians to be aware of the difficulty in appropriately diagnosing DRESS syndrome, given its overlap to several other rheumatological and hematological conditions, including malignancy. We aim to shed light on the association of leflunomide and DRESS syndrome, calling for further research to assess the strength of association between the two. Further research is required to develop guideline directed therapy for the management of DRESS syndrome.

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**Ethics Approval**

Our institution does not require ethical approval for reporting individual cases or case series.

**Informed Consent**

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