Case Report

Leflunomide Induced DRESS Syndrome: A Case Report

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Abstract

Drug rash with eosinophilia and systemic symptoms (DRESS) is a severe drug-induced hypersensitivity syndrome. Leflunomide, a disease modifying anti rheumatic drug (DMARD), has been very rarely reported as a cause of DRESS syndrome. We report a case of a 40 year-old woman who presented with DRESS syndrome 5 days after starting leflunomide for Rheumatoid Arthritis. She presented with exfoliative dermatitis, fever and lymphadenopathy along with haematological abnormality, deranged liver and renal function tests. She was treated with long course of steroid and prophylactic antibiotics .Despite optimal management and prolonged hospitalization for 3 months the patient could not be saved. This case highlights the potential of leflunomide in causing DRESS syndrome and the poor prognosis associated with the syndrome.

Keywords: Leflunomide, DRESS syndrome

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Introduction

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome also known as drug hypersensivity syndrome was first introduced in 1996 by Bocquet *et al*.[1] Skin rash and multiorgan involvement with marked eosinophilia constitute the main manifestations. The most frequently involved organ is the liver, followed by the kidney and lungs. The pathophysiology of DRESS syndrome remains unclear, but defects in detoxification of causative drug, immunologic imbalance, and viral infections have been suggested.[2] The overall mortality in DRESS is about 10% and occurs in patients with severe multiorgan involvement.[3] Anticonvulsants such as phenytoin, phenobarbital sodium, or carbamazepine, are the most common causes of DRESS syndrome.[4] Leflunomide is a new immunomodulating agent and disease-modifying antirheumatic drug with anti-inflammatory and immunosuppressive activity, used in the treatment of active rheumatoid arthritis. There are only few case reports of DRESS syndrome caused by leflunomide.

Case history

A 40 year old female presented to us with fever and skin rash for one and half months. She was known case of rheumatoid arthritis since two years and was on treatment with Prednisolone. She was started on methotrexate two months back; however the drug had to be stopped as she could not tolerate it. She was then started on leflunomide 20 mg once daily five days prior to the onset of skin rash. Despite skin eruption she continued leflunomide for 20 days. The eruption had started from lower limb and became generalized in one month. leflunomide was then stopped and the patient referred to our centre. On general examination patient was febrile, there was generalized lymphadenopathy and icterus. On cutaneous examination there was generalized erythematous maculopapular eruption all over the body with few exfoliative flakes interspersed in erythema involving face, palms, and soles sparing mucosa hair and nails. Systemic examination was within normal limit. Investigation showed hemoglobin- 11.2gm%, total WBC count- 28,100/mm3, neutrophils- 45%, lymphocytes- 30%, eosionophils- 10%, atypical lymphocytes- 15%, platelets- 165,000/mm^3 . Liver function was deranged with serum bilirubin- 49micromol/l, AST- 103 IU/L, ALT- 160 IU/land alkaline phosphatase- 747IU/l. Random blood sugar was 8.9 mmol/l. Renal function was deranged with ++ albumin and granular cast in urine, serum urea-5.2 mmol/l and serum creatinine-107 micromol/l. Serum electrolytes was within normal limit. Antinuclear antibodies and viral serology for hepatitis B, C, E and HIV 1 and 2 were non reactive. USG abdomen, chest X- ray and ECG showed no abnormality. Histopathology of skin showed spongiosis along with occasional necrotic keratinocytes, periadnexal and perivascular mixed inflammatory infiltrate with few intraepidermal lymphocytes suggestive of drug reaction. As leflunomide was stopped by rheumatologist we kept patient on tablet prednisolone 50mg per oral single morning dose and supportive proton pump inhibitors, antihistaminic, and prophylactic antibiotics along with moisturizer for skin exfoliation. Gradually in 10-15 days new skin lesion stopped appearing and previous lesion dried up with generalized exfoliation. Fever and abnormal laboratory parameters also settled down. The patient was then discharged on tapering dose of prednisolone. But after 5 days of discharge patient landed up in emergency with similar kind of new skin lesions and fever but this time internal organ involvement was less severe. Patient was re-admitted with high dose of steroid and supportive management. Remission and relapse of the skin rashes continued for 3 months with continue use of steroid. After third episode of erythroderma, patient developed edema with decreasing serum albumin level. With subsequent exacerbation of skin lesion severity of edema increased with decreasing serum albumin up to 17 gm/l despite IV albumin and high protein diet. At 58^{th} day of 2^{nd} admission patient succumbed due to high output cardiac failure.

Discussion

DRESS syndrome has been estimated to occur

in about one in 10,000 cases of exposure to drugs like antiepileptics and sulfonamides.[5] Leflunomide is a new immunomodulatory drug approved by the US FDA in Sept 1998, for the treatment of RA. It inhibits pyrimidine synthesis, resulting in antiproliferative and anti-inflammatory effects. It is a prodrug, which is converted to its active metabolite A771726 and this is highly protein bound with a half-life of 15 to 18 days, the active metabolite undergoes extensive enterohepatic recirculation, and it may take up to two years for the amount of drug in plasma to decrease to an undetectable level. It has been reported to cause various cutaneous adverse drug reactions including SJS, TEN and EM, in less than 1% of the patient population.[3]

Very few reports regarding DRESS syndrome caused by leflunomide is available. Clinical and investigation finding of our patient was consistent with DRESS syndrome and the most probable drug was leflunomide. Recurrent course of the skin manifestation could be due to long half life and highly protein bound nature of the drug. Early withdrawal of the offending medication is needed once the diagnosis is established. The recovery from this condition has been reported to be slow, lasting several weeks to months; recurrences have also been reported.[6] Glucocorticoids remain the most widely used agents for treatment of DRESS syndrome and can result in clinical improvement, although well-controlled clinical trials are lacking. Relapse can occur during the tapering of glucocorticoids.[7]

Conclusion

In conclusion, DRESS Syndrome is a well recognized drug hypersensitivity syndrome. leflunomide , a recently introduced drug for the treatment of Rheumatoid arthritis can cause this syndrome. Despite optimal management of the condition, it can be associated with poor prognosis.

References

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