



Drug Induced Reaction: Dilemma of Finding a Real Culprit

Pramod Kumar Sharma, Arup Kumar Misra*, Ajay Gupta, Rajesh Kumar and Surjit Singh

Department of Pharmacology, All India Institute of Medical Sciences, India

Abstract

DRESS syndrome (drug rash, eosinophilia and systemic symptoms) is an idiosyncratic drug reaction characterized by rash, fever, lymphadenopathy and internal organ involvement. This syndrome causes a diverse array of clinical symptoms, anywhere from 2 to 8 weeks after initiating the offending drug. Many drugs including aromatic anticonvulsants can induce DRESS syndrome. We describe a case of this syndrome presented to us with fever, rash, eosinophilia and increase platelet counts after taking lithium. The syndrome resolved with drug withdrawal but co-incidental re-challenge with lithium, syndrome reoccurred within starting lithium. Prompt diagnosis, withdrawal of the offending drug and treatment with corticosteroids remain the cornerstone to the therapy of DRESS. WHO causality analysis scale indicates certain association of this syndrome with lithium.

Keywords: Dress syndrome; Lithium; Lamotrigine; Eosinophilia; Corticosteroids

Introduction

“Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome) is a syndrome, caused by exposure to certain medications, that may cause a rash, fever, inflammation of internal organs, lymphadenopathy, and characteristic hematologic abnormalities such as eosinophilia, thrombocytopenia, and atypical lymphocytosis” [1]. The estimated incidence of this syndrome ranges from 1 in 1000 to 1 in 10,000 drug exposures, Adults are more affected than children [2]. The aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine) and sulphonamides are the most common causative drugs but a variety of other drugs have also been described in this syndrome [3-5]. The pathogenesis is not fully understood and may be multifactorial, involving immunological mechanisms and particular drug detoxification pathways [6,7]. This syndrome causes a diverse array of clinical symptoms, anywhere from 2 to 8 weeks after initiating the offending drug.

Case Presentation

The present case is a 40 year old female with diagnosis of schizoaffective disorder since 2009 had being treated with oral olanzapine, mirtazapine, amisulpride and trihexyphenidyl for past two years. Due to recurrent flare up of her symptoms, her family consulted another psychiatrist in January 2016. She was prescribed oral lithium, lamotrigine, mirtazapine, amisulpride and trihexyphenidyl. After taking the medication for a month, she had fever and body ache for which she took diclofenac, paracetamol and chlorzoxazone as self medication. The following day, she developed diffused erythematous maculopapular and urticarial rash. It developed first on upper limbs followed by involvement of the whole body associated with fever and facial oedema. The following day, she presented with same complain in the Dermatology out-patient department. Her routine blood investigation revealed, hemoglobin to be 9.8 g/dL, TLC ($15.4 \times 10^3/\mu\text{L}$, N=57.7%, L=26.9%, M=8.2%, E=6.9%, B=0.3%), total platelet ($292 \times 10^3/\mu\text{L}$) and absolute eosinophil count ($1.3 \times 10^3/\mu\text{L}$). Peripheral blood smear shows microcytic hypochromic with few macrocytes, neutrophil leucocytosis with shift to the left. Her SGOT (45 IU/L) and SGPT (57 IU/L) values were slightly raised. Serum bilirubin level (total and conjugated), random blood sugar, blood urea and blood creatinine were within normal limits.

On examination, she had diffused erythematous maculopapular and urticarial rash all over the body (Figure 1). There were no other clinically relevant observations.

Based on investigations and symptomatology, she was suspected as a case of drug induced DRESS syndrome. The suspected medication lithium and lamotrigine were stopped from her current treatment regimen. She was put on with oral omnacortil 60 mg in a step-down regimen with oral levocetirizine and advised coconut oil and calamine lotion for tropical application. She was advised to resume lithium once the rash subsides. She had improvement in erythema, scaling

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*Correspondence:

Arup Kumar Misra, Senior Resident,
Department of Pharmacology, All India
Institute of Medical Sciences (AIIMS),
Jodhpur, 342005, Rajasthan, India, Tel:
+91- 9501988533;
E-mail: arup2003m@gmail.com

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Figure 1: First episode of dress syndrome.



Figure 2: Recovery from first episode.

and facial edema following stopping the offending drugs (Figure 2). Except TLC, her repeat investigation showed everything within normal range. However her peripheral blood smear shows similar picture as before.

After 10 days of therapy and improvement in skin rash, lithium with olanzapine, mirtazapine, venlafaxine, armodafinil and prednisolone 30 mg were started. Rash reappeared after 4 weeks of treatment (Figure 3). Investigation showed eosinophil counts (eosinophils 0.9% and absolute eosinophil count - $1.3 \times 10^3/\mu\text{L}$) and total platelet count ($524 \times 10^3/\mu\text{L}$) were raised. Lithium and venlafaxine were stopped and rest of the treatment was continued. Repeat investigation after 4 days showed rising trend for TLC ($19.9 \times 10^3/\mu\text{L}$), eosinophil count (eosinophils 1.9% and absolute eosinophil count $0.4 \times 10^3/\mu\text{L}$) and total platelet count ($620 \times 10^3/\mu\text{L}$).

Discussion

DRESS syndrome is a part of a spectrum of adverse cutaneous drug reactions. Different mechanisms have been implicated in its development, including detoxification defects leading to reactive metabolite formation and subsequent immunological reactions, slow acetylation and reactivation of human herpes viruses. The detection of HHV-6 reactivation has even been recently proposed as a diagnostic marker for DRESS syndrome. It is becoming increasingly apparent that there is a genetic predisposition linked to HLA-B*1502 [6,8].

The case described above met the majority of criteria according to Regis CAR scoring guidelines for a diagnosis of DRESS syndrome [1]. Laboratory testing can help to identify internal organ involvement, which may not be evident clinically. A skin biopsy may help to confirm the diagnosis, but is usually not specific [3].

At the onset of first episode of the reaction, lamotrigine was suspected to be the main offending drug. But to be on the safer side,



Figure 3: Reappearance of Dress syndrome after reintroduction of lithium.

lithium was also temporarily interrupted and thought to be resumed once rash clears. Once rash disappeared, lithium was reintroduced but it proved to be a positive re-challenge for lithium. Surprisingly lamotrigine was the prime suspect initially but rechallange with lithium confirmed it as the main offending agent and proved to be certainly associated with this syndrome when causality analysis was done [9].

Ideally the offending agent should be removed at the earliest as it may be associated with a poor outcome. Corticosteroids remain the agents most widely used for treating the syndrome, although the doses used vary widely according to the seriousness of the disease [10].

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