Case Report

A Rare Case of Rifampicin-induced Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome

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Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is an idiosyncratic adverse drug reaction that can be lethal in up to 20% cases. The commonest culprit drug includes phenytoin, allopurinol, phenobarbital, sulfasalazine and lamotrigine. DRESS syndrome due to antitubercular medicines is rarely reported. In India despite the widespread use of antitubercular medicines, only few cases of DRESS syndrome have been reported. Here we report an interesting case of a 23 year old girl who presented to us with complaints of high grade fever, cough, GI discomfort, numbness, severe pruritus and burning skin sensation. She was receiving antitubercular medicines for tubercular pleural effusion for the last three weeks. She was hospitalised for a suspected adverse drug reaction which was diagnosed as DRESS syndrome on the basis of RegiSCAR criteria. On re-challenge testing the culprit drug was found to be rifampicin. In this case the severity of skin involvement was much higher as compared to organ involvement.

Keywords: *Antitubercular medicine side effects, drug reaction with eosinophilia and systemic symptoms syndrome, drug reaction with eosinophilia and systemic symptoms, rifampicin*

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Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is an idiosyncratic adverse drug reaction characterized by the presence of eosinophilia, systemic symptoms such as fever, rash, lymphadenopathy, any internal organ involvement, atypical lymphocytes, or elevation of liver enzymes. The estimated incidence of DRESS syndrome is around 1/1000–10,000 exposures with a mortality rate up to 20%.[1]

The common culprit medicines for DRESS syndrome are phenytoin, sulfonamides, phenobarbital, sulfasalazine, and carbamazepine.[2] Antitubercular medicines can cause a cutaneous syndrome in the form of mild rashes, pruritus, and on very rare occasions DRESS syndrome (0.7% out of 1600).[3] DRESS syndrome due to antitubercular medicines was first described in 2013 in the United States of America.[4] In the Indian literature, the first description of DRESS syndrome due to antitubercular medicines was in 2016 from Maharashtra.[5] Here, we represent a rare and interesting case of a rifampicin-induced DRESS syndrome in a young female.

Case Report

A 23-year-old female presented to us with complaints of high-grade fever, cough, gastrointestinal discomfort, numbness, severe pruritus, and burning skin sensation all over the body for the past 5 days. She has been receiving antitubercular therapy (ATT) for the past 3 weeks in the following daily doses; isoniazid 300 mg, rifampicin 450 mg, ethambutol 1000 mg, pyrazinamide 1250 mg, and pyridoxine 40 mg in an account of tubercular pleural effusion. She was nondiabetic, nonhypertensive and had no previous history of ATT or any other chronic respiratory illness. She had no history of any drug allergies.

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On examination, she was conscious, oriented and her vitals were within normal limits. She had no pallor, edema, icterus, cyanosis, clubbing, or lymphadenopathy. On respiratory system examination, her breath sounds were reduced on the left side.

She was hospitalized with a provisional diagnosis of adverse drug reaction. At admission, the laboratory parameters were suggestive of eosinophilia (11%), hyperuricemia (9.9), and raised erythrocyte sedimentation rate (32 mm). Her SARS-CoV-2 reverse transcription polymerase chain reaction, HIV, HBsAg, and HCV tests were negative and liver function tests (LFT) were within normal limits. The patient was started on pantoprazole, chlorpheniramine, and paracetamol, and ATT was continued.

The symptoms worsened and there was a new occurrence of multiple wells to ill-defined erythematous plaque (rash) over the back and lower limbs in a few days [Figure 1]. On Day 5, blood investigations showed worsened eosinophilia (24%), and deranged LFT (serum glutamic-oxaloacetic transaminase - 397, serum glutamic pyruvic transaminase - 55 with increased total bilirubin - 1.8, indirect bilirubin - 1.5). She was treated with hydrocortisone and started on modified ATT (ethambutol - 1000 mg and levofloxacin - 750 mg). After modified ATT and hydrocortisone, there was a significant improvement in symptoms in terms of disappearing skin rashes and a reduction in pain and pruritus. Blood parameters became normal by Day 7. We planned to gradually reintroduce other drugs one by one.

The first drug to be introduced was isoniazid followed by pyrazinamide. There were no clinical or blood parameters worsening after the introduction of these drugs.

On the 10th day, we reintroduced rifampicin. After its introduction the patient again developed severe symptoms along with the rashes and her blood parameter showed eosinophilia (13%), leukopenia (3700/mm^3), and deranged LFT.

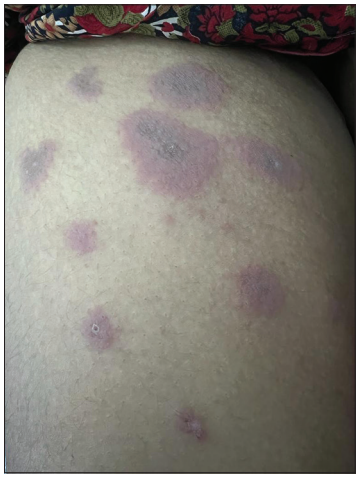

Figure 1: Skin lesion

A diagnosis of rifampicin-induced DRESS syndrome was established by RegiSCAR criteria (score = 3, possible category) and the patient was started on a nonrifampicin-containing regimen.[6] She underwent a close follow-up during her treatment. A nonrifampicin regimen (isoniazid, ethambutol, pyrazinamide, and levofloxacin) was continued for 6 months. She showed complete resolution of skin rashes by 3 months and itching by 4 months. Her LFT remained normal after discharge from the hospital.

Table 1 shows the change in various laboratory parameters during her hospital stay.

Discussion

The diagnosis of DRESS syndrome is suspected if any patient presents with late-onset (usually 3 weeks) skin rashes, eosinophilia, and any internal organ involvement after the introduction of the suspected drugs. The characteristic features of DRESS syndrome are skin lesions, hematological manifestation, and internal organ involvement. The severity of skin lesions and internal organ involvement may not correlate with each other. The diagnosis is usually based on the clinical criteria, and a skin biopsy is not usually required for the establishment of the diagnosis.[7] The most widely used and sensitive criteria is the RegiSCAR criteria.[6]

The skin is usually involved in the form of morbilliform rash which rapidly progresses and becomes infiltrating. Vesicles, small sterile pustules, purpuric lesions, symmetrical facial edema (up to 50%), and mucous membrane involvement (up to 50%) may be there in DRESS syndrome.[8,9] These clinical manifestations can persist for weeks to months after discontinuing the offending drug.[10]

The hematological manifestations include most commonly eosinophilia (>10%), thrombocytopenia, neutropenia, and the presence of atypical lymphocytes. On rare conditions, a hemophagocytic syndrome (fever, jaundice, hepatosplenomegaly, low ferritin, elevated lactate dehydrogenase, and increased triglycerides) may occur.[11]

Internal organ involvement may occur in the form of hepatitis, myocarditis, nephritis, pneumonitis, colitis, or sometimes multiorgan involvement.[8] The liver is the most commonly (60%–80%) involved organ which generally manifests as asymptomatic elevation of liver enzymes, not hepatomegaly and jaundice may also be present.[11]

The possible explanation of DRESS syndrome is abnormal production and detoxification of active

Table 1: Various laboratory parameters during hospitalization

Date	Eosinophil count (%)	Absolute eosinophil count	TLC	SGOT	SGPT	Remarks
D1	11	660	6000	16	18	At the time of admission
D5	24	1272	5300	397	55	Modified ATT started
D7	3	183	6100	34	28	
D10	13	111	3700	58	66	Rifampicin reintroduced, severe reaction with rash and itching along with severe pain and burning sensation all over the body especially the back and the lower limbs
D12	2	708	5900	30	25	Presence of mild symptoms

SGOT: Serum glutamic-oxaloacetic transaminase, TLC: Total leukocyte count, SGPT: Serum glutamic pyruvic transaminase, ATT: Antitubercular treatment

metabolites, genetic predisposition caused by epoxide hydrolase deficiency and reactivation of human herpes virus-6 (HHV-6) has been demonstrated in many patients with DRESS syndrome and may be considered prognostic factors for identifying patients at high risk of DRESS syndrome. Reactivation of HHV-6 may be considered one of the diagnostic criteria of DRESS syndrome proposed by a Japanese consensus group.

In our case, the skin symptoms were severe enough to make the patient cry but systemic involvement was not so severe. In our case, the systemic involvement was in the form of asymptomatic slight elevation of liver enzymes.

The DRESS syndrome can be treated by the stoppage of culprit medications and the use of glucocorticoids, which can result in clinical improvement, although any specific clinical guidelines are lacking.

In India, despite the widespread use of antitubercular medicines, only few cases have been reported. The possible reasons may include a lack of awareness among clinicians, overlapping symptoms of various conditions such as infections, neoplasm, and rheumatologic conditions, and difficulty identifying the culprit antitubercular medicines.

Conclusion

As the mortality due to DRESS syndrome may be up to 20%, a high degree of suspicion is required for the diagnosis. A diagnosis of DRESS syndrome should be considered when there are high eosinophil counts, multisystem involvement, and skin eruption, especially 3 weeks after initiation of the culprit drug. Skin eruption sometimes may not correlate with the severity of symptoms.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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