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Case Report

Sulfasalazine induced atypical drug reaction with eosinophilia and systemic symptoms syndrome: a case report

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ABSTRACT

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a type IV b hypersensitivity reaction characterized by cutaneous manifestations, fever, lymphadenopathy, hematologic abnormalities, and multiple organ manifestations. We report a case of sulfasalazine induced DRESS syndrome who was admitted with a complaint of morbilliform rash all over the body, a fever of 100ºF, and severe abdominal pain. Initially the patient did not mention about intake of sulfasalazine while taking the drug history as he could not remember the past medication. The laboratory investigations revealed elevated eosinophils, WBC, and liver function tests. The patient was treated with antibiotics assuming tropical infection, but the patient's condition was not improving. Later while taking proper drug history from a patient representative over the telephone revealed that the patient was in 4th week of tablet sulfasalazine 500 mg treatment for polyarthritis. Further, the J-SCAR scale was used to diagnose it as Sulfasalazine induced atypical DRESS syndrome. The patient was treated with topical and intravenous corticosteroids and antihistamine; the patient exhibited surprising symptomatic improvement. The patient was given a tapering dose of oral corticosteroid tablet prednisolone 20 mg for three weeks and topical corticosteroid mometasone lotion for two weeks upon discharge.

Keywords: DRESS syndrome, Sulfasalazine, Eosinophilia, Polyarthritis

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a potentially life-threatening ADR. It is a severe hypersensitivity reaction to a medication or its reactive metabolites, which may be associated with enzymatic defects in drug metabolism.[1] It has been estimated that the overall population risk is between 1 in 1000 and 1 in 10,000 drug exposures.[2] Dermatologic manifestations of DRESS can be diverse, with morbilliform rash being the most common presentation. It may have significant multisystem involvement, including haematologic, hepatic, renal, pulmonary, cardiac, neurologic, gastrointestinal, and endocrine abnormalities. This syndrome has a 10% mortality rate; most commonly from fulminant hepatitis with hepatic necrosis.[1] Herein report a case of atypical DRESS syndrome in a 39-year-old patient who received sulfasalazine for polyarthritis in the past for but failed to mention during history taking which leads to delayed diagnosis.

CASE REPORT

A 39-year-old male who was a farmer in a remote village of India, presented to the hospital with complaints of morbilliform rash characterized by diffuse, pruritic, and macular rash spreading centrifugally starting from abdomen associated with pyrexia for eight days. The patient also mentioned abdominal pain in the right hypochondriac region. Clinically, the patient's vital signs were typical, yet the temperature was 100ºF. Upon taking drug history, the patient could not mention any drugs as he was an illiterate. On admission, the laboratory values revealed eosinophilia, leucocytosis, elevated bilirubin

levels, liver transaminases, and alkaline phosphatase (Table 1).

Table 1: Laboratory investigations on admission.

Laboratory data	Values
Total WBC	38600 cells/cumm
Absolute eosinophil count	1544 cells/cumm
Total bilirubin	7.3 mg/dl
Direct bilirubin	4.1 mg/dl
Indirect bilirubin	3.2 mg/dl
ALT	253 U/L
AST	154 U/l
ALP	333 U/L

Considering his occupation, upon admission, the physicians suspected a tropical bacterial infection, injection ceftriaxone 1 gm IV twice a day and tablet doxycycline 100 mg PO twice a day was given as empiric treatment. Upon receiving laboratory data, the patient was given treatment for increased liver enzyme levels and all forms of bilirubin levels with tablet ursodeoxycholic acid and tablet glutathione. The same treatment was given for three days, but the patient did not improve clinically. The patient tested negative for scrub typhys, anti-nucleophilic antigens, leptospirosis, cytomegalovirus, Epstein Barr virus, HIV, and blood cultures which rejects the possibility of infections and autoimmune disorders. CT abdomen with contrast showed hepatomegaly, splenomegaly, periportal and paraceliac lymphadenopathy.

Table 2: Treatment recommendations at discharge.

Drug name	Dosage and frequency
Tab. usrodeoxycholic acid	Orally, 300 mg, twice daily for 2 weeks
Tab. glutathione	Orally, 600 mg, twice daily for a week
Tab. prednisolone	Orally, 20 mg, once daily for a week, followed by
	Orally, 10 mg, once daily for a week, followed by
	Orally, 5 mg, once daily for a week and then stop.
Tab. fexofenadine	Orally, 120 mg, once daily for 2 weeks
Mometasone lotion	Topically on rashes once daily for 2 weeks
Lactocalamine lotion	All over the body, thrice daily for 2 weeks

Upon taking drug history by the clinical pharmacist through the patient representative over the telephone, who was living on the other side of the country, it was revealed that the patient was under treatment for polyarthritis with tablet sulfasalazine 500 mg for four weeks along with tablet amitriptyline 10 mg, tablet paracetamol 650 mg. After ruling out every possible way that could cause skin rash, it was evident that the skin reaction was induced by sulfasalazine. On day 4, the patient was started on injection hydrocortisone 100 mg IV thrice a day, tablet fexofenadine 120 mg, lactocalamine lotion and mometasone lotion. The patient improved symptomatically, and laboratory values were slightly abnormal. On day 6, during discharge the laboratory values were slightly high but showed significant improvement compared to laboratory values on admission. The discharge medication of the patient was as mentioned in (Table 1 and 2) (Figure 1).

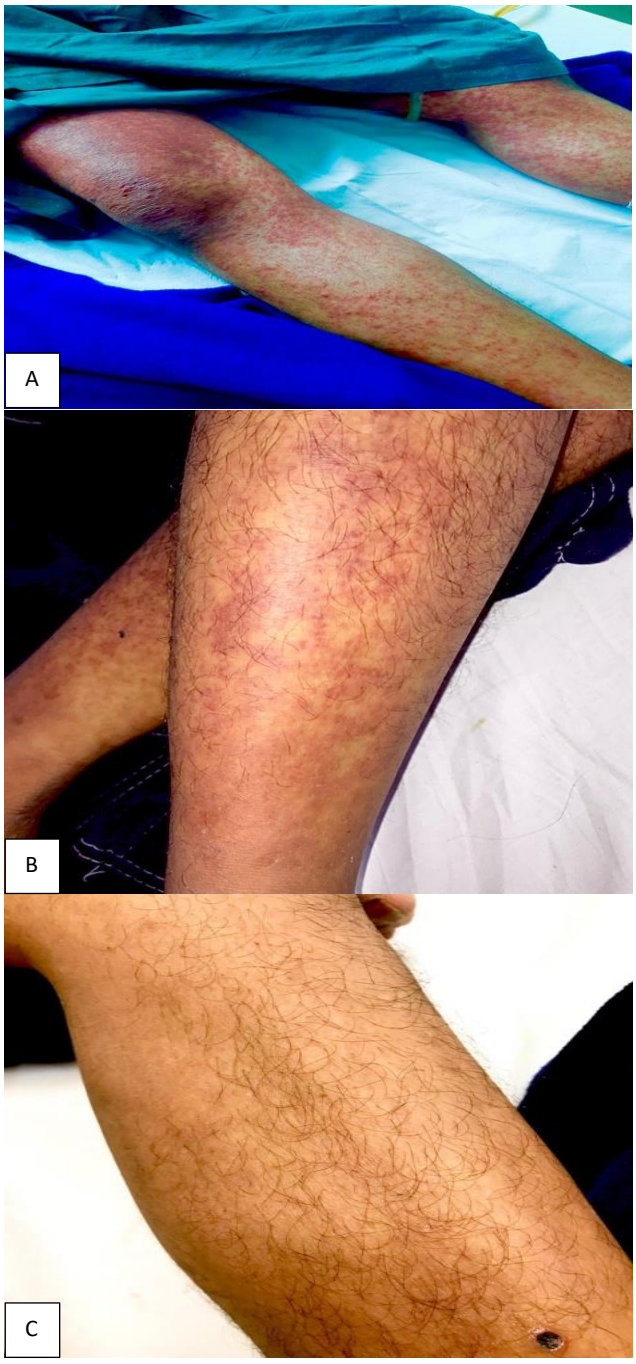

Figure 1 (A-C): Morbilli form rash on admission; resolution of rash after a day of starting intravenous and topical steroids therapy and patient condition upon discharge.

Case analysis

The patient was diagnosed with polyarthritis and was on tablet sulfasalazine 500 mg for four weeks. The treatment regimen was as mentioned in (Table 3).

Table 3: Treatment regimen of tab. sulfasalazine (past medication history).

Duration of administration of the drug	Frequency of administration of the drug
Week-1	Once a day at night
Week-2	Twice a day (morning and night)
Week-3	One pill in the morning and two pills at night (1+2)
Week-4	Two pills in the morning and two pills at night (2+2)

Table 4: Assessment of drug reaction according to J-SCAR criteria to diagnose DRESS syndrome.

Criteria	Present/ absent
Maculopapular rash developing >3 weeks after starting offending drug	Present (+)
Prolonged clinical symptoms after discontinuation of the causative drug	Present (+)
Fever >38^{0}C	Present (+)
Liver abnormalities (ALT >100U/L)	Present (+)
Hematologic abnormalities	Present (+)
Leukocytosis (>11x10/L or 11000 cells/cumm)	(+)
Lymphocytes (>5%)	(-)
Eosinophilia (>1.5x10^9/L or 1500 cells/cumm)	(+)
Lymphadenopathy	Present (+)
HHV-6 reactivation	Absent (-) (not performed)

The patient noticed the allergic reaction when he was on 3rd week of the treatment course but neglected it and anticipated it as a minor allergy. The patient's condition worsened as he started the 4th week treatment course. The onset of allergic reaction in 3rd week of treatment course after its first use establishes DRESS syndrome as a provisional diagnosis. Leukemia cutis, rocky mountain fever. Henoch Schonlein purpura, and autoimmune disorders were considered as differential diagnosis. However, they were ruled out due to negative diagnostic results. The hematologic system is frequently affected when an offending drug is taken, often characterized by leukocytosis and eosinophilia which was clearly evident in the patient. The eosinophil granules are toxic to many tissues and affect visceral organs. The liver is the most commonly affected visceral organ showcasing hepatitis with elevated liver transaminases, alkaline phosphate, and bilirubin levels which was clearly reflected in the patient. Hence patient was treated with tablet ursodeoxycholic acid and tablet glutathione to maintain the levels of liver enzymes within limits. According to the Japanese research committee on severe cutaneous adverse reaction (J-SCAR) scale, the diagnosis of DRESS syndrome can be confirmed if the patient meets the seven criteria mentioned in Table 4 and atypical DRESS syndrome if only 5 criteria were met.

According to the J-SCAR scale, the patient was diagnosed with atypical DRESS syndrome as the patient satisfies 6 out of 7 criteria. The treatment of choice for DRESS syndrome is systemic corticosteroid therapy. It is currently the most widely accepted therapy, and topical corticosteroids can be given for symptomatic relief. The patient's clinical status improved soon after the steroid therapy was given. The liver function tests and hematological values were represented in Figure 2 and Figure 3, respectively, before and after starting the corticosteroid therapy.

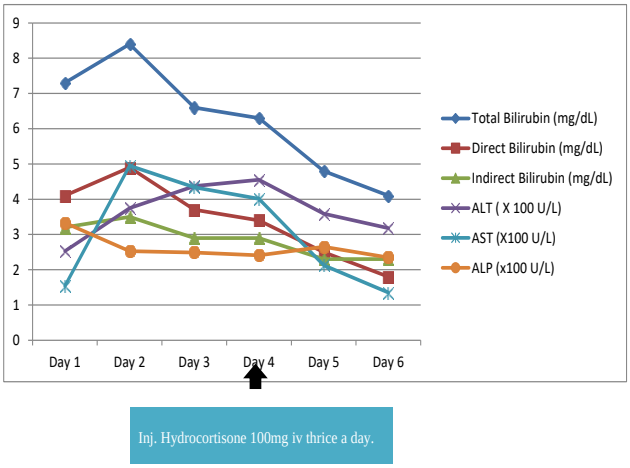

Figure 2: The liver function tests of the patient before and after starting corticosteroid therapy.

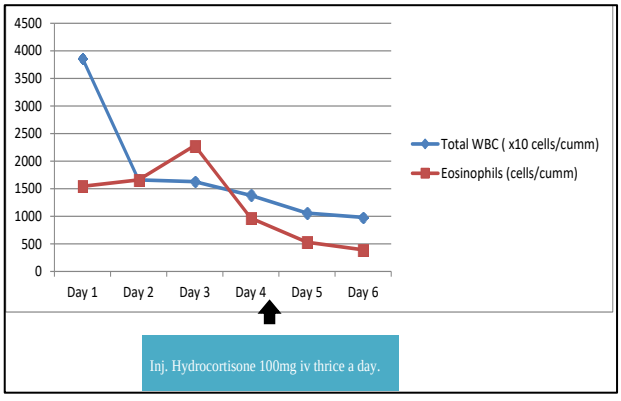

Figure 3: Haematological values of the patient, before and after starting corticosteroid therapy.

DISCUSSION

DRESS syndrome is a rare, potentially fatal adverse drug reaction that manifests as cutaneous signs and internal organ involvement in both adults and children.[3] DRESS is thought to be caused by a strong hypersensitivity to a treatment and its reactive drug metabolites, which may be linked to enzymatic abnormalities in drug metabolism. The most common causes of DRESS include aromatic anticonvulsants like phenytoin, carbamazepine, and phenobarbital, as well as sulfonamides like dapsone and sulfasalazine.[2,5] Immunosuppression may predispose individuals to develop this condition, especially when accompanied by a primary or reactivation human herpesvirus-6 (HHV-6) infection.[6-8] DRESS syndrome normally develops within two months after the offending drug's consumption, with symptoms appearing 2 to 6 weeks following the first usage. Re exposure, on the other hand, may cause symptoms to appear more quickly and to be more severe.[4,9] Our patient presented with symptoms of rash and fever during 4th week of treatment course. The pathogenesis of DRESS syndrome is not fully understood. Several hypotheses have been proposed; one theory is that deficient drug metabolism and reactive metabolites play a major role in the development of DRESS.[4,9-13] Individuals carrying specific mutations in genes that encode drug detoxification enzymes have been shown to have a higher risk of DRESS.[9] These genetic polymorphisms appear to be inherited in an autosomal dominant fashion, which may explain familial distribution of the disease and possible racial predisposition, as suggested by the many cases reported in black patients.[12,14,15] Mutations of genes encoding drug detoxification enzymes lead to the accumulation of drug reactive metabolites, which can biochemically interact with and modify cellular proteins, trigger autoimmune responses against skin or liver cells, alter immune responses, and induce the reactivation of viral infections.[13] An immunologic mechanism is also widely believed to underlie a major component of DRESS syndrome.[9] There are several characteristics of this condition that support an immune mediated model, including the fact that it occurs in only a limited number of patients and is accompanied by eosinophilia and modification of the lymphocytic system. DRESS often begins with prodromal symptoms of pruritus and pyrexia. The fever generally precedes cutaneous eruptions by several days, with temperatures ranging from 38ºC to 40ºC, and may last for several weeks. Although there can be various cutaneous manifestations, a morbilliform rash is the most common and is characterized by a diffuse, pruritic, macular, and occasionally erythrodermatous exanthema. [16] It usually first involves the face, upper aspect of the trunk, and upper extremities, and later spreads to the lower extremities, becoming infiltrative and indurated with associated edema.[17] Approximately 25% of patients have prominent facial swelling, which can be so marked that the patient becomes disfigured.[18] Multiple organ systems can be affected in DRESS syndrome. The most common systemic findings involve the:

Lymphatic system: It is characterised by limited lymph node involvement or generalised lymphadenopathy with localised tenderness involving the cervical axillary and inguinal lymph nodes.[19]

Hematologic system: The hematologic system is frequently affected. There can be marked leukocytosis, up to 50×10^9 leukocytes/L and, there is eosinophilia with $>2.0x10^9$ eosinophils/L, but it can be delayed for 1 to 2 weeks.[4,16]

Liver: The liver is the most frequently affected visceral organ in DRESS syndrome. Hepatosplenomegaly can be present and is often accompanied by hepatitis elevated liver transaminases (ALT and AST), alkaline phosphatase.[20]

Kidney: Clinical symptoms are usually absent, but patients can present with mild hematuria and proteinuria. Laboratory abnormalities reflect renal dysfunction and include elevated blood urea nitrogen and creatinine levels and low creatinine clearance. However, severe interstitial nephritis can develop and progress to kidney failure.[16]

Pulmonary system: Reported pulmonary complications include impaired pulmonary function, acute interstitial pneumonitis, lymphocytic interstitial pneumonia, pleuritis, and acute respiratory distress.[16]

Cardiovascular system: DRESS syndrome associated myocarditis is potentially fatal and can present months after withdrawal of the offending drug and resolution of the clinical and laboratory abnormalities. Two forms of myocarditis are recognized in DRESS syndrome: hypersensitivity and acute necrotizing eosinophilic myocarditis.[21]

Neurologic system: Neurologic manifestations of DRESS syndrome are infrequently encountered. They include meningitis and encephalitis, which often develop 2 to 4 weeks after onset of DRESS syndrome and may be related to HHV-6 reactivation.[16]

Bocquet et al proposed the original criteria to establish the diagnosis of DRESS syndrome, which include the following:[5] (1) drug eruption; (2) hematologic abnormalities i.e., eosinophilia $1.5x10^9$/L and the presence of atypical lymphocytes; and (3) systemic manifestations i.e., adenopathy with lymph nodes 2 cm; hepatitis with transaminase levels twice the normal values; interstitial nephritis; pneumonitis, and carditis.[4] The presence of at least 3 criteria is required to establish the diagnosis of DRESS syndrome. The European registry of severe cutaneous adverse reaction study group expanded on the diagnostic criteria proposed by Bocquet et al J-SCAR group that highlights the role of HHV-6 in DRESS syndrome, which they refer to as DIHS and Regi SCAR. [22] Therapy of DRESS syndrome is challenging the most important measures are early recognition of this syndrome and immediate withdrawal of the suspected drug. Delay

may be associated with poorer outcomes.[23] Systemic corticosteroid therapy for DRESS syndrome is currently the most widely accepted and used treatment.[24] The significant improvement in both clinical symptoms and laboratory abnormalities is often seen within several days after initiating steroid therapy. The early administration of systemic steroids is generally recommended for all cases of DRESS syndrome.[24] Topical corticosteroids may be applied to skin lesions for symptomatic relief.[25] Systemic steroid therapy should begin with a minimum dose of 1.0 mg/kg/day of prednisone or equivalent. Gradual taper over 3 to 6 months after clinical and laboratory stabilization is recommended to avoid relapse. There is often significant improvement of symptoms and laboratory abnormalities within several days after initiating steroid treatment.[26]

CONCLUSION

DRESS syndrome is a type IVb hypersensitivity reaction characterized by eosinophilia and ultimately affects the visceral organ, most probably the liver. Treatment typically consists of discontinuation of the offending drug, but additional supportive measures may be necessary depending upon the severity of the reaction. However, the mainstay for the treatment of DRESS syndrome is oral corticosteroids if the level of allergic reaction is mild, whereas intravenous corticosteroids must be considered in case of severe allergic reaction.

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