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Case Study

Drug Reaction with Eosinophilia and Systemic Symptoms Following Sulfasalazine Therapy: A Case Report

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ABSTRACT

A rare and possibly lethal reaction due to an allergic response to medication that presents with fevers, widespread skin rashes, and blood abnormalities like eosinophils, lymphadenopathy and effects on major organs (e.g., liver, kidneys, and lungs) is called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome. Sulfasalazine (a common medication used to treat inflammatory conditions and autoimmune diseases) is one of many drugs implicated (causing) in DRESS Syndrome development. Here we present a case of a 19-year-old female patient with DRESS syndrome secondary to sulfasalazine use, who presented with a high-grade fever, a generalized erythematous (red) rash, periorbital edema (swelling around the eyes), cough associated with (vomiting after) status post-coughing; abdominal pain; and lymphadenopathy. The patient also has a past medical history of epilepsy diagnosed when she was 6 years old and polyarthralgia of one month duration prior to presentation. Laboratory testing revealed leukocytosis, marked eosinophilia and elevated liver enzymes verifying systemic involvement. Based on the time relationship between drug exposure and symptoms; the clinical findings and the laboratory findings we were able to make the diagnosis of DRESS Syndrome. The patient was treated by immediate discontinuation of sulfasalazine and started on systemic corticosteroids, antihistamines and supportive care resulting in her gradual clinical improvement and resolution of her symptoms by the time of her last evaluation.

INTRODUCTION

DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms), or drug-induced hypersensitivity syndrome, is a potentially life-threatening serious adverse drug reaction characterized by widespread cutaneous eruptions, fever, hematological abnormalities, and involvement of internal organs. It occurs 2-8 weeks after exposure to the offending drug and has

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significant morbidity and mortality if not recognized at an early stage [**Error! Reference source not found.**]. The clinical presentation includes, but may not be limited to, widespread maculopapular rash, facial swelling, lymphadenopathy, eosinophilia and atypical lymphocytosis, and multi-organ involvement (liver, kidneys, lungs, and heart) [**Error! Reference source not found.**].

The pathogenesis of the DRESS syndrome is still not fully understood. There are several proposed mechanisms that include immune dysregulation, genetic susceptibility, defects in drug detoxification, and viral reactivation (in particular, by human herpesvirus-6). A number of different drug classes have been implicated in the development of this syndrome, such as anticonvulsants, antibiotics and sulphonamide containing medications [**Error! Reference source not found.**].

Sulfasalazine, which is a disease-modifying anti-rheumatic drug, is frequently used to treat inflammatory bowel disease and rheumatologic disorders, and could be one potential cause of DRESS syndrome. Sulfasalazine is effective at reducing inflammation due to disease, but it is possible (although rare) that sulfasalazine may cause severe hypersensitivity reactions that should be identified and stopped immediately [**Error! Reference source not found.**].

Timely diagnosis and appropriate management of DRESS syndrome is critical to reduce the chances of serious complications, such as complete hepatic failure or multi-organ dysfunction syndrome [**Error! Reference source not found.**]. Therefore, it is important to report individual cases so that clinicians may better understand their potential for DRESS syndrome. A case report is presented to describe a DRESS syndrome patient who presented with DRESS after taking sulfasalazine; she was twenty-five years old.

CASE PRESENTATION

A 19-year-old female was admitted to the hospital with complaints of fever, a widespread red rash on her body, and swelling on her face, and she had difficulty coughing and vomited when she coughed. She also had abdominal pain and felt weak overall. She had been taking Sulfasalazine 500 mg BD for four weeks (starting about 4 weeks before admission) for polyarthralgia. The patient had epilepsy since age six and had been on the same antiepileptic medications throughout this time. There were no previous drug allergy or adverse reactions.

On physical exam, the patient was febrile and appeared ill. On dermatological exam, patient had an extensive and diffuse red maculopapular rash over her face, trunk, and extremities, as well as marked swelling of her face. The physician could feel a number of enlarged lymph nodes in the cervical region. Partial examination revealed mild hepatomegaly (enlarged liver). Laboratory test results revealed leukocytosis (increased white blood cell count), marked eosinophilia (increased eosinophils), and elevated liver enzymes, all of which would indicate that there was likely significant systemic involvement.

A diagnosis of DRESS syndrome was made because of the clinical signs and of the chronological relation of the patient's previous medication and the clinical presentation. The diagnosis was also supported by the RegiSCAR scoring system, which scored a total of five points - which indicates a probable case of DRESS Syndrome, or drug reaction with eosinophilia and systemic symptoms.

The suspected offending drug was immediately ceased. The patient was treated with Dexamethasone (Decadrone) Injection 2 cc IV once per day (IV OD) and Bilastine 20 mg tablets, twice a day (BD), in addition to supportive care. The patient developed a gradual improvement in clinical status during their hospital admission, including resolution of skin lesions, facial swelling, normalization of laboratory parameters on followup. The patient was subsequently discharged from the hospital in a stable condition with instructions for follow up and strict avoidance of sulfasalazine.

TABLE 1: Day-Wise Laboratory Investigations

Investigation	Day 1 (Admission)	Day 3	Day 5	Day 7 (Discharge)	Normal Range
Hemoglobin (g/dL)	10.2	10.8	11.4	12.0	12–16
Total WBC Count (/µL)	18,500	15,200	11,800	8,900	4,000–11,000
Eosinophils (%)	18	14	8	4	1–6
Absolute Eosinophil Count (/µL)	3,330	2,128	944	356	40–400
Platelet Count (lakhs/mm³)	2.8	2.9	3.0	3.2	1.5–4.5
ESR (mm/hr)	42	34	24	18	<20
AST/SGOT (U/L)	118	92	58	36	<40
ALT/SGPT (U/L)	136	104	70	42	<45
Alkaline Phosphatase (U/L)	182	164	142	118	44–147
Total Bilirubin (mg/dL)	1.8	1.4	1.0	0.8	0.2–1.2
Serum Creatinine (mg/dL)	1.3	1.1	0.9	0.8	0.6–1.2
Blood Urea (mg/dL)	42	36	30	24	15–40
Sodium (mEq/L)	134	136	138	140	135–145
Potassium (mEq/L)	3.4	3.7	4.0	4.2	3.5–5.0
CRP (mg/L)	48	32	18	8	<10
Peripheral Smear	Eosinophilia present	Improving eosinophilia	Mild eosinophilia	Normal	—

TABLE 2: RegiSCAR Scoring System for DRESS Syndrome

Sr. No	RegiSCAR Criteria	Findings in Present Case	Score
1	Fever ≥38.5°C	Present	+1
2	Enlarged lymph nodes involving at least 2 sites	Cervical lymphadenopathy present	+1
3	Eosinophilia	Marked eosinophilia present	+2
4	Atypical lymphocytes	Not reported	0
5	Skin rash extent >50% body surface area	Generalized diffuse erythematous rash present	+1
6	Skin rash suggestive of DRESS	Maculopapular rash with facial edema	+1
7	Biopsy suggestive of DRESS	Not done	0
8	Internal organ involvement	Liver involvement (elevated liver enzymes)	+1
9	Resolution ≥15 days	Gradual resolution observed	0
10	Evaluation of other potential causes	Other infectious/drug causes excluded clinically	+1

Total RegiSCAR Score: **5**

Interpretation of RegiSCAR Score

- <2 = No case
- 2–3 = Possible DRESS

- 4–5 = Probable DRESS
- >5 = Definite DRESS

TABLE 3: Naranjo Adverse Drug Reaction Probability Scale

Sr. No	Question	Yes	No	Do Not Know / NA	Score
1	Are there previous conclusive reports on this reaction?	+1	0	0	+1
2	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4	Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0	0
5	Are there alternative causes other than the drug that could on their own have caused the reaction?	-1	+2	0	+2
6	Did the reaction reappear when a placebo was given?	-1	+1	0	0
7	Was the drug detected in blood or other fluids in toxic concentrations?	+1	0	0	0
8	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10	Was the adverse event confirmed by any objective evidence?	+1	0	0	+1

Total Naranjo Score = 7

Interpretation of Naranjo Score:

- ≥9 = Definite ADR
- 5–8 = Probable ADR
- 1–4 = Possible ADR
- 0 = Doubtful ADR

DISCUSSION

DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms) refers to a rare but deadly hypersensitivity reaction that is characterized by persistent fever, widespread skin rash, eosinophilia (increased eosinophil numbers in the blood), lymph nodes (lymphadenopathy), and multi-organ involvement. Generally, there is an onset of symptoms between 2 to 8 weeks post-exposure to the offending medication. In this particular case, the onset of symptoms occurred four weeks after initiation on sulfasalazine, which is consistent with reported timelines for previous cases. Sulfasalazine is a commonly used DMARD (Disease Modifying Anti-Rheumatic Drug) associated with life-threatening cutaneous adverse effects such as DRESS syndrome [**Error! Reference source not found.**].

Clinically, the patient presented with the classical signs of DRESS syndrome including high fevers (> 38C) and generalized, erythematous, maculopapular rash with facial swelling, cervical lymphadenopathy, eosinophilia, and elevated liver transaminases (enzymes). Hepatic involvement occurs in > 80% of patients with DRESS syndrome and can lead to massive liver injury if not identified and treated timely. The combination of the patient's significant eosinophilia and abnormal liver function tests helped to more clearly substatiate the diagnosis of DRESS syndrome [**Error! Reference source not found.**].

Diagnosis of DRESS syndrome can be quite complicated because its features can be like those found in patient populations with infections or autoimmune conditions. In this instance, the scoring system established by RegiSCAR demonstrated a score of five indicating it was highly likely there will be a diagnosis as a result of DRESS syndrome. Furthermore, upon conducting a Naranjo causality assessment, the score of seven illustrates a high probability that sulfasalazine was the cause of the adverse reaction [**Error! Reference source not found.**].

This pattern was confirmed by the relationship between the exposure of sulfasalazine and the time symmetry of the onset of symptoms and the improvement in symptoms after the termination of sulfasalazine use. The first step in the management of DRESS syndrome will typically be the immediate termination of the suspected causative medication; therefore, in this case, the immediate withdrawal of sulfasalazine was paramount [**Error! Reference source not found.**].

The patient subsequently received a regimen of systemic corticosteroids, antihistamines and supportive care and subsequently demonstrated clinical improvement as well as improvement in some laboratory parameters, including improvement in the level of eosinophils in the blood and the normalisation of liver enzyme levels during the follow-up period. This particular case illustrates the need for early identification of DRESS syndrome associated with the use of sulfasalazine followed by prompt intervention [**Error! Reference source not found.**]. In order to provide optimal patient outcomes and prevent any complications, close monitoring of patients who are receiving sulfasalazine should occur at the outset in addition to being cognisant of common symptoms (e.g., fever, rash, or eosinophilia) associated with the condition.

CONCLUSION

DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome is a rare but severe hypersensitivity reaction to medications that requires urgent identification and management in order to prevent life-threatening complications. This case demonstrates how a 56-year-old male after beginning treatment with Sulfasalazine developed fever, generalized rash, elevated eosinophils, and elevated LFTs. The diagnosis meets the RegiSCAR criteria with a score of 5 (suggesting a likely diagnosis of DRESS syndrome). Discontinuation of the offending medication, combined with systemic corticosteroids by dexamethasone and antihistamines by bilastine, resulted in substantial clinical improvement. This highlights the need to quickly recognize DRESS syndrome, quickly withdraw the causative medication, and use appropriate treatment strategies as methods of decreasing DRESS-associated morbidity. Reporting these types of cases enhances the clinician's ability to recognize DRESS syndrome, therefore providing safer use of medications in clinical practice.

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