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Sulfasalazine Induced DRESS Syndrome: A Review of Case Reports

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Authors' contributions

This work was carried out in collaboration between all authors. Author Jasmeen wrote the first draft of the manuscript and managed the literature searches under the supervision of author KV. Authors PK, SV and KV did final editing of the manuscript. Author HK helped in literature retrieval. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Introduction: Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) is designated as a lethal adverse drug effect with characteristic sign and symptoms such as skin rashes, fever, leukocytosis with eosinophilia or atypical lymphocytes, lymph node enlargement, and liver or renal dysfunction. Incidences of the DRESS range from 1/1000-1/10,000 drug exposures and are associated with a mortality rate of 10%. Pathogenesis of DRESS relates to an abnormal immune response in a genetically vulnerable individual, *i.e.* presence of human leukocyte antigen (HLA)*5801 and HLA-B* 5701 genotype and slow acetylation metabolic pathways.
Methods: 48 cases were associated with the "Sulfasalazine-induced DRESS syndrome" reported

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between January 1990- March 2015 in PubMed-MEDLINE and HighWire Press. The "RegiSCAR" scoring system was used to analyze the case reports. Using this system, cases were classified into 4 categories as "no", "possible, "probable" and "definite".

Results: The vast majority of cases were classified as "probable/definite" DRESS cases (83%). Hypereosinophilia, atypical lymphocytes and fever were significantly associated with "probable/ definite" DRESS cases. Liver involvement and skin rash was described in almost all of the cases, including "possible cases". DRESS was found fatal in two cases.

Conclusion: Awareness of DRESS is essential for diagnosis with the presence of skin rash, liver involvement, fever, hyper eosinophilia and lymphadenopathy. Early identification, followed by a prompt withdrawal of the culprit drug is the most essential measure to avoid disease evolution and to restore wellness.

Keywords: Sulfasalazine; DRESS syndrome; adverse drug reaction; RegiSCAR scoring system; skin rash; hypereosinophilia; atypical lymphocytes.

1. INTRODUCTION

Adverse drug reactions (ADRs), a major clinical issue, account for approximately 5% of hospital admissions [1]. Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) is designated as a lethal adverse drug effect with characteristic sign and symptoms such as skin rashes, fever, leukocytosis with eosinophilia or atypical lymphocytes, lymph node enlargement, and liver or renal dysfunction [2]. It is identified by several acronyms, being reported in various literature databases, such as Anticonvulsant Hypersensitivity Syndrome (HSS), Drug Induced Delayed Multi-organ Hypersensitivity Syndrome (DIDMOS) and Drug Induced Hypersensitivity Syndrome (DIHS) [3]. The syndrome has delayed onset and matures 2-8 weeks or longer after administration of the culprit drug [4]. Incidences of the DRESS range from 1/1000-1/10,000 drug exposures and are associated with a mortality rate of 10% [5]. The suggested pathogenesis of DRESS relates to an abnormal immune response in a genetically vulnerable individual, *i.e.* presence of human leukocyte antigen (HLA)*5801 and HLA-B* 5701 genotype [6] and slow acetylation metabolic pathways [7]. It is persuaded by the formation of various reactive drug metabolites [8] and accumulation of drug in the body due to slow acetylation[7], and reactivation of various Human Herpes Viruses (HHV), namely, the Epstein Barr Virus (EBV) [9], Cytomegalovirus (CMV) [10], HHV-6 [11] and HHV-7 [12].

The syndrome ends up with varied early and late phase outcomes. Ushigome et al. [13] had reported formation of autoantibodies and development of autoimmune diseases, such as lupus erythematosus and autoimmune thyroiditis; and development of herpes virus infections and pneumonia, as early and late phase outcomes, respectively. Late-phase outcomes after resolution of DRESS syndrome are not easily recognized due to either inadequacy of long-term follow up or development of new sequelae after a long disease free interval of months to years [14].

DRESS is associated with the use of many drugs [15], but had remarkably noted with the use of aromatic anti-epileptic drugs [16]. Many other drugs also had been reported to cause the severe DRESS syndrome, such as allopurinol [17], aspirin [18], carbamazepine [19], hydroxyl-chloroquine [20], lamotrigine [21], minocycline [22], nevirapine [23], olanzapine [24], oxcarba-zepine [25], phenylbutazone [26], salazo-sulfapyridine [27], spironolactone [28], strepto-mycin [29], sulfasalazine [30], and vancomycin [31], etc. This review mainly focuses on sulfasalazine induced DRESS syndrome. Sulfasalazine, firstly synthesized in 1930, is now currently one of the drugs being employed in the treatment of various rheumatic and inflammatory diseases due to its potential nuclear factor-kappa B (NF-κB) and tumor necrosis factor-alpha (TNF-α) inhibiting activity [32,33]. Recently, its efficacy and safety has also been explored in randomized clinical trials of coronary artery disease patients [34]. But, its long term safety always makes the greatest concern. Although, there is no report of sulfasalazine induced adverse drug effects in cardiovascular disease (CVD) patients, yet, its evaluation in clinical trials for exploring new indications for this old drug, places a need to review on sulfasalazine induced serious adverse drug effects.

The European registry of severe cutaneous adverse reaction (RegiSCAR), the scoring system, had been established by European society to delineate the diagnosis of DRESS

syndrome [3]. It includes toxic epidermal necrolysis, Steven-Johnson syndrome, acute generalized exanthematous pustulosis and DRESS syndrome [11]. RegiSCAR system classifies cases of DRESS into four categories as “no”, “possible”, “probable” and “definite” cases [4,35]. The aim of this review was to report and analyze the cases of sulfasalazine induced DRESS syndrome in the literature by using RegiSCAR scoring system.

2. MATERIALS AND METHODS

A systematic review of case reports of ‘sulfasalazine induced DRESS syndrome’ was prepared by retrieving information from various biomedical databases/search engines such as PubMed-Medline, HighWire Press, Science-Direct and Springer between January 1990-March 2015. The various search terms used for retrieving the information were “DRESS syndrome”, “Sulfasalazine induced DRESS syndrome”, “Sulfasalazine adverse effects”, “Drug-induced hypersensitivity syndrome” and “Sulfasalazine”. Evaluation of published literature was restricted to English language only. Fig. 1 describes the flow diagram of literature selection process.

The “RegiSCAR” scoring system was used to analyze the case reports. Using this system, cases were classified into 4 categories as “no”, “possible, “probable” and “definite” (Table 1).

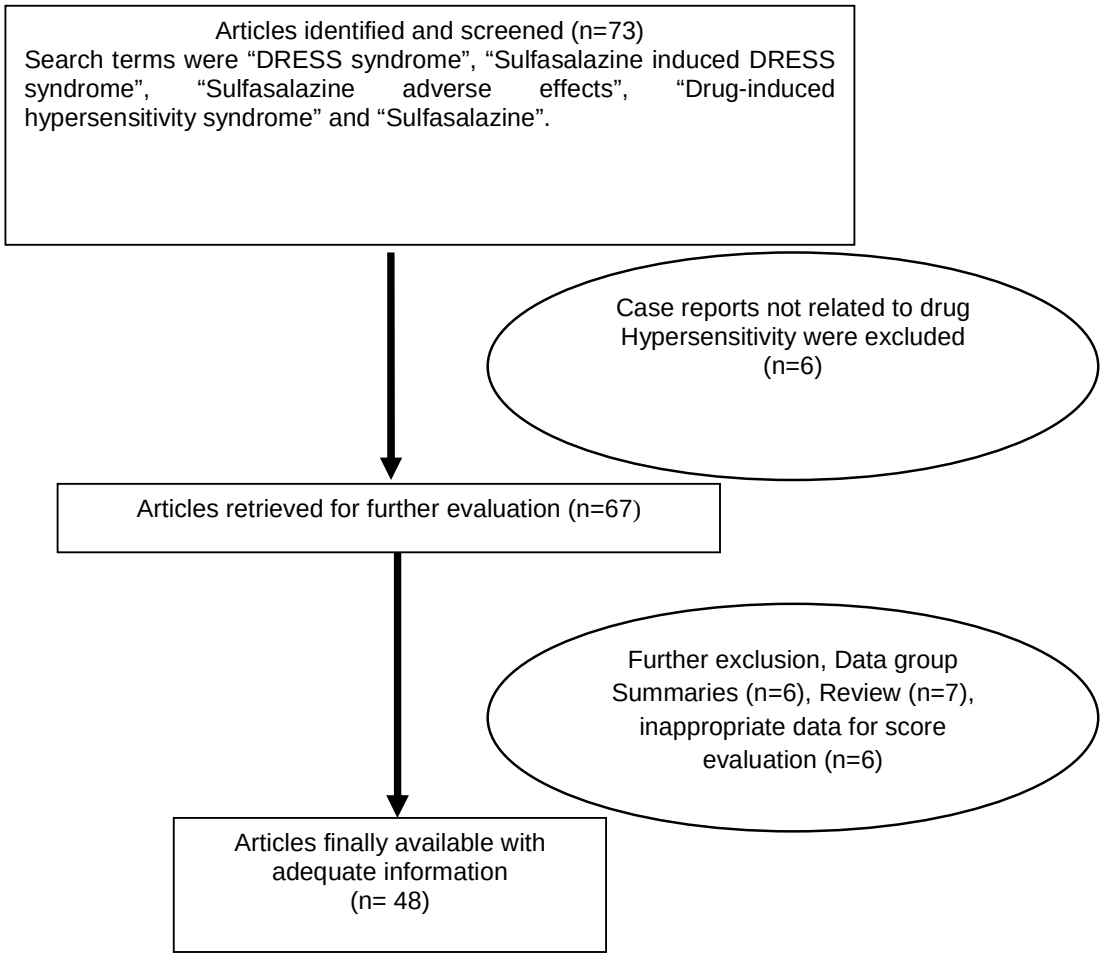

Fig. 1. Flow diagram of literature selection process for DRESS

Table 1. Classification of DRESS cases according to the RegiSCAR scoring system

Initial diagnosis cases (Score)	Rheumatoid arthritis (n=31)	Inflammatory bowel disease (n=8)	Acute lympho-proliferative syndrome (n=2)	Skin eruptions (n=2)	Jaundice (n=1)	Myocarditis (n=1)	Acute tubule-interstitial Nephritis (n=1)
No case (1)		N=1 [55]					
Possible case (2-3)	*N=3 [36,37]	N=2 [56,57]	N=2 [61,62]				
Probable case (4-5)	N=15 [38,39,15,40,41,30,42,43,41,44,45,46,47,48]	N=2 [43,58]		N=2 [63,64]	N=1 [65]	N=1 [66]	N=1 [67]
Definite case (6-8)	N=14 [15,49,50,51,52,53,37,48,43,54]	N=4 [59,48,37,60]					

**Number of cases (reference number)*

The classification was based on presence/or an absence of eight components of the scoring system described as fever, eosinophilia, enlarged lymph nodes, atypical lymphocytes, skin involvement, organ involvement, time of resolution and evaluation of other potential causes. The score of each item ranged from -1 to 2. Each case was scored separately and then scores of all cases were combined together. Finally, two groups were derived as "no/possible cases", "probable/definite cases". The clinical course, onset and resolution time of symptoms, and treatments given were also considered in the evaluation.

Data was recorded on Microsoft excel spreadsheets and evaluated later on. Results were presented as mean ± SD (range) or number (%). The *p value* ≤0.05 was considered statistically significant. Two groups were compared using a Chi-square test for categorical variables and student's t-test for linear variables. Multiple Logistic regression analysis was applied to find independent variables associated with definite/probable cases. Statistical analysis was performed using Sigma Stat 3.5.

3. RESULTS

A total of 73 case reports were screened, but only 48 independent reports of sulfasalazine induced DRESS syndrome, were evaluated. 25 published reports were not included in final analysis due to various reasons such as case reports not related to drug hypersensitivity (n=6), articles displaying data group summaries (n=6), reviews (n=7), and no sufficient data available for an appropriate DRESS score evaluation (n=6) (Fig. 1). Based on RegiSCAR's scoring system, one case was validated as "no case", 7 as "possible cases", 22 "probable cases" and 18 "definite cases". 40/48 cases were classified as probable and definite cases. We also classified distribution of total number of cases as age-wise in to three groups (age <21, 21-60, >60 years). In comparison between three groups according to age, no significant difference was found (p=1.00) (Table 3). The cases in each age group were further sub-categorized into four types of cases based on RegiSCAR's scoring system as described above (Table 2). We found a significant difference in various category of cases based on RegiSCAR's scoring system for patients in age range 21-60 years (p<0.01), but not for other age groups (Table 2).

The major demographic, clinical and treatment characteristics of patients associated with DRESS syndrome are shown in Table 3.

Skin rashes were reported in all cases and were described as most commonly the maculopapular rashes followed by generalized erythematous rashes, and rashes associated with facial edema. In about 72% cases, liver was mainly affected, followed by kidney (35%), heart (19%) and lungs (0.02%). Involvement of the CNS was not reported in any of the cases. Liver involvement was described by either the hepatomegaly or by the elevation of liver enzyme levels [AST (aspartate aminotransferase) and ALT (alanine aminotransferase) ≥ 10 times normal range]. Fever was reported in more than 77% of cases. Hyper-eosinophilia was the third most frequently reported adverse effect. Lymphadenopathy was also reported in the majority of patients. Different pathogenic mechanisms relating to DRESS were not evaluated in the majority of cases, except evaluation of HHV-6. In more than 81% of cases, HHV-6 reactivation was detected by serum antiHHV-6 immunoglobulin titer.

All cases were hospitalized and the culprit drug was discontinued immediately on the first day of hospitalization. Treatment course was also found reported in the case reports. Corticosteroids were given as the core treatment, mainly prednisolone (1 mg/kg/day), and in some cases, intravenous immunoglobulin (IVIG) - 0.4 gm/kg was also prescribed. Symptoms recovery was achieved completely almost in two weeks to maximally 3 months. However, DRESS was found fatal in two cases. Characteristics of patients resulting in death are shown in Table 4.

Table 2. Age-wise classification of DRESS cases

Age in years (number of cases)	No case	Possible case	Probable case	Definite case	*P* value
<21 (n=9)	0	2	5	2	0.056
21-60 (n= 30)	1	4	10	15	<0.001
>60 (n= 9)	0	1	4	4	0.056

Table 3. Demographic, clinical and treatment characteristics associated with DRESS

Parameters	N	%
Age (years)		
Mean ± SD (range)	38.34±19.54 (4-83)	
<21	9	18.75
21-60	30	62.5
>60	9	18.75
Sex		
Male	21/48	43.7
Female	27/48	56
Onset (weeks)*		
Mean ± SD (range)	2.27±1.9 (0.2-8)	
Skin rash	39/48	81
Maculopapular rash	18/48	37
Generalized erythematous rash	9/48	19
Facial edema	15/48	31
Internal organ involvement	44/48	92
Liver	35/48	72
Kidney	17/48	35
Lung	1/48	2
CNS	0/48	0
Hyper-eosinophilia (>0.7 × 10^9 L^{-1})	35/48	72
Fever >38.5ºC	37/48	77
Atypical lymphocytes	28/48	58
HHV-6 infection		
Detection	39/48	81
Positive	11/48	23
Serology findings (EBV, Hepatitis A, B and C, CMV) positive	4/48	18
Treatment		
Corticosteroid	30/48	62
IV immunoglobulin	15/48	31

In both the cases, death occurred within 24 hour of onset of symptoms and was found associated with skin rashes and liver involvement. Corticosteroid treatment was started but failed badly.

Case reports, classified into two groups "No/Possible cases", and "Probable/Definite cases", differed significantly for some of the clinical variables. Definite/Probable cases were differed significantly from other group by the presence of hypereosinophilia, fever and atypical lymphocytes. Multivariate logistic regression analysis further supported the hypereosinophilia and atypical lymphocytes as independent factors associated with definite/probable cases of DRESS syndrome (Table 5).

4. DISCUSSION

In this review, we have systematically analyzed 48 case reports of sulfasalazine-induced DRESS syndrome. Data from Japanese patient population studies had revealed that eight different drugs are mainly held responsible for the development of DIHS, including carbamazepine, phenytoin, phenobarbital, zonisamide, mexiletine, dapsone, sulfasalazine and allopurinol [68]. Diagnosis and management of DRESS syndrome has become comparatively easier after the introduction of RegiSCAR's scoring system in 2007 [3]. Although, DRESS is presented with characteristics sign and symptoms but these may reflect other disease such as viral hepatitis, idiopathic hyper-eosinophilia and other connective tissue disorders [5]. The diagnosis of DRESS was confirmed by ruling out the presence of other diseases on the basis of negative results of laboratory investigations such as anti-nuclear antibody (ANA) test and, blood culture for EBV, CMV, viral hepatitis A, B and C. Positive serology findings (EBV, CMV, Hepatitis A, B and C) were found in only 4/48 cases.

Table 4. Characteristic of death cases

Parameters	N = 2
Age (years)	
Mean ± SD (range)	58±2.82 (56-60)
Sex	
Male	1
Female	1
Onset (weeks)	
Mean±SD (range)	4.5±2.12 (3-6)
Skin rash	2
Liver involvement	2
Time between onset of symptoms and death	2 hrs.-24 hrs.
Corticosteroid treatment	2

We found that skin rashes, including maculopapular rashes and generalized erythematous rashes; high fever, hyper-eosinophilia, lymphadenopathy, and atypical lymphocytes were present in almost all cases of sulfasalazine induced DRESS syndrome. In present review, majority of cases (83%) were "probable/definite" cases based on RegiSCAR's scoring system. Kardaun et al. [4], had also reported a few cases (n=8) of sulfasalazine induced DRESS syndrome using RegiSCAR's scoring system. The author also revealed that sulfasalazine was one of the culprit drug mostly involved in causing both DRESS as well as Steven Johnson Syndrome.

Table 5. Comparison of clinical and outcome parameters between "no/possible" cases and "probable/definite" cases of DRESS

	Univariate analysis			Multiple logistic regression			
Parameters	**No/possible cases (n=8)**	**Probable/definite cases (n=40)**	**P value**	**B**	**Odds ratio**	**95 CI**	**p**
Age, Mean ± SD	28.87±10.02	41.88±20.89	0.095				0.0
Sex							
Male	5	16	0.423				
Female	3	24					
Internal organ involvement							
Liver	4	31	0.211				
Kidney	2	15	0.713				
Lung	0	1	0.384				
Hyper-eosinophilia (>0.7* 10^9 L^{-1})	2	31	0.010	2.929	18.703	163.53	0.008
Fever >38.5ºC	3	34	0.018	0.879	0.415	2.241	0.307
Lymphadenopathy	7	30	0.949				
Atypical lymphocytes	1	26	0.018	3.178	24.00	488.39	0.039
HHV-6 Infection	3	11	0.956				
Skin rash	4	26	0.768				
Onset (Weeks), Mean ± SD	2.219±1.081	2.708±2.125	0.532				
Resolution (Weeks), Mean ± SD	4.8±4.2	4.6±4.6	0.853				

The liver is the most commonly affected visceral organ due to DRESS syndrome and involves elevated levels of serum ALT in approximately 72% of cases and with different degrees of hepatitis [69]. It has also been previously reported that sulfasalazine was associated with causing severe acute hepatitis in women of age 20-40 years [70]. In present reports, internal organ participation was also seen with mainly liver involvement, where the liver enzymes were found to increase 10 times more than normal value. Moreover, renal dysfunction described as increased serum creatinine and urea and, decreased creatinine clearance has been reported to occur in 11% of cases [71]. Similarly, renal dysfunction was noted in 35% of cases, while only 1 case report was found of lung dysfunction. Bourgeois et al. [72] had reported a case of sulfasalazine-induced DRESS associated myocarditis, a fatal and under-recognized manifestation of DRESS, which exhibits multifactorial pathogenesis involving patient factors, drug metabolites, and viral reactivation. Present review, too had found cardiac involvement (n=9) in 19% cases including tachycardia (n=3), cardiac failure (n=1), hypotension (n=3), coronary artery disease (n=1) and pericardial effusion (n=1). Other organ involvement such as the CNS was not at all reported in any of the cases. Hematological abnormalities like hypereosinophilia and atypical lymphocytes were common and well described, emphasizing the importance of complete blood count (CBC) in the DRESS syndrome. Atypical lymphocytes and lymphadenopathy often observed as distinctive for DRESS were found in 58% and 77% cases, respectively. Poland et al. 1986 [41] too had found marked atypical lymphocytosis, hepatitis and skin rashes in patients of sulfasalazine induced drug allergy. Thrombocytopenia or thrombocytosis was rarely noted. In only one case report classified as "no case", above discussed clinical features were not meaningfully associated as with "possible cases" or "probable/definite" cases.

Apart from the contribution of drugs, reactivation of herpes virus (HHV-6) is also considered a persuader for DRESS [42], which mainly plays a role by interfering with drug detoxifying enzymes [10]. We found a low rate of positive HHV-6 infection. In this review, HHV-6 detection was carried with 81% of cases, but in only 23% cases reactivation was found positive.

Delayed onset and a longer resolution time is the characteristic feature of DRESS [73].The time taken for onset and resolution of symptoms was not different in both the groups. Although corticosteroids or IVIG were prescribed, but

different dosage regimen were followed, depicting the lack of standard consensus guidelines for the management of DRESS. Till now only 2 fatal cases of sulfasalazine-induced DRESS has been reported as compared to the highest number of fatal cases by allopurinol-induced DRESS syndrome being reported by Cacoub et al. [5] and, Eshki et al. [36].

5. LIMITATIONS

Present review was based on retrospective analysis of published case reports, which were subjected to publication bias. Moreover, in some case-reports, clinical outcome parameters were not described in detail. So, interpretation was subjected to some missing data gaps.

6. CONCLUSION

In conclusion, near 50 independent case-reports of the sulfasalazine induced DRESS syndrome had been registered till date and being analyzed in this review. Diagnosis of DRESS was confirmed with the help of RegiSCAR scoring system. Among all clinical features, atypical lymphocytes and hyper-eosinophilia were only independent predictors associated with definite cases of DRESS. Analyses of the reports revealed that standard treatment consensus guidelines were not followed in its management. Some clinical parameters were also not reported in all the reports such as detection of HHV-6, HLA-genotype, and different viral infections etc. Overall, sulfasalazine induced mortality rate was found very low.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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