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Case Report

DRESS syndrome; Drug Reaction with Eosinophilia and Systemic Symptoms: A case report and literature review

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Abstract DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) syndrome is a severe, idiosyncratic, T-cell mediated hypersensitivity reaction of drugs characterised by fever, skin manifestations, lymphadenopathy, hematological abnormalities and involvement of internal organs that develops 2-8 weeks after intake of the culprit drug. Its pathophysiology includes genetic susceptibility, defect in the metabolic pathway of drugs and reactivation of human herpes viruses (HHVs). The interaction of these pathogenetic factors is responsible for cutaneous and systemic manifestations of DRESS syndrome. Many cases of DRESS syndrome have been reported globally but to the best of our knowledge DRESS syndrome has not been reported in Pakistan todate. We report a case of DRESS syndrome in which the suspected drug was leflunamide or piroxicam.

Key words
DRESS syndrome; RegiSCAR criteria; Leflunamide; Piroxicam.

Introduction

Adverse drug reactions (ADRs) are the harmful and inadvertent reactions of medicine.[1] The cutaneous adverse drug reactions (CADRs) which account 30% of ADRs are mostly harmless and self-limiting. Some of them are severe and life threatening and need hospitalization, they are termed as severe cutaneous adverse drug reactions (SCARs). SCARs consist of Steven Johnson syndrome/ Toxic Epidermal Necrolysis (SJS/TEN), Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Generalized Bullous Fixed Drug Eruptions (GBFDE).[2] SCARs account for 25-50.4% of total CADRs as mentioned in different studies, however, DRESS syndrome constitute 16% of total cases of SCARs.[3]

DRESS syndrome is one of the SCARs that causes cutaneous and systemic manifestations, approx. 2-8 weeks after drug intake. The most common drugs causing DRESS syndrome are antibiotics, antiepileptics, anti-inflammatory, sulphonamides and antigout medicines. However, many other drugs have been reported recently in the literature that cause DRESS e.g., rifampicin, isoniazid, ACE inhibitors, beta blockers, naproxen, leflunamide.[3,4]

Although there are cases of DRESS syndrome reported worldwide but to the best of our knowledge and data search it has not been reported in Pakistan. We are reporting a case of DRESS syndrome in a young woman in which the suspected drug is leflunamide or piroxicam

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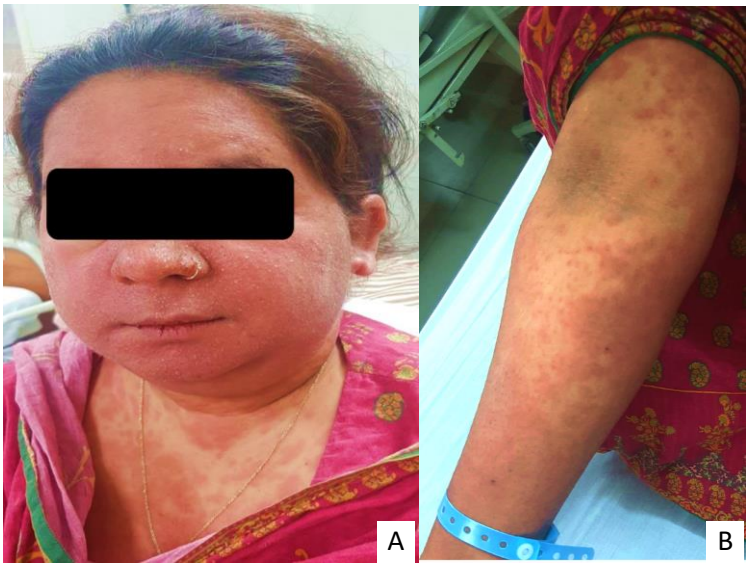

Figure 1 At presentation:
A) Facial edema, erythema, scaling and cheilitis.
B) Urticarted and targetoid erythematous papules and plaques on forearms.

Case report

A 35 years old lady, known case of hypothyroidism and rheumatoid arthritis, admitted with complaint of itchy cutaneous eruption and high grade fever for 10 days. The eruption was erythematous papules and plaques which started from upper back, chest, and face, then became generalized. Fever was high grade, develop 1-2 days after cutaneous eruption and relieved partially on taking antipyretics. There was associated sore throat, shortness of breath, nausea and vomiting 3 days after developing fever. However, there was no history of productive cough, hemoptysis, orthopnea, PND, chest pain, diarrhea, burning micturition, photosensitivity or mucosal ulcers. She was on thyroxin, deltacortril and HCQ for her comorbid conditions which she discontinued on its own few months ago. However, in the recent past i.e., 3 weeks prior to eruption, two new drugs (leflunamide and piroxicam) had been started by rheumatologist for her arthralgia which she took for few days and discontinued on symptomatic relief.

Cutaneous examination **(Figure 1)** showed facial edema, erythema, cheilitis, and multiple erythematous urticated and targetoid papules and plaques involving >60% of the body surface area, predominantly face, torso and upper limbs. Mucosae, hair and nails were normal. There was no skin tenderness, pustules, petechiae, erosions or malar rash. Nikolsky's sign was negative. She was pale and had mild bronchospasm. Rest of the systemic examination was unremarkable.

Labs showed microcytic hypochromic anemia, leukocytosis with marked eosinophilia (48%). Transaminases were >2-3 times high and alkaline phosphatase and ɣGT were also markedly raised, however, viral markers for hepatitis were non-reactive and ultrasound abdomen was unremarkable. Serum creatinine was mildly raised. CRP was also raised (37.67mg/dL) but FDPs, D-Dimers, PT/INR, platelet count, Urine C/E and blood cultures were normal. CXP-PA view and ECG were also normal and ANA was negative.

The important differentials (autoimmune connective tissue diseases, viral exanthems, sepsis, and other benign and severe cutaneous adverse drug reactions) were ruled out on detailed history, thorough clinical examination and relevant investigations. Diagnosis of DRESS syndrome was made by applying RegiSCAR (Registry of Severe Cutaneous Adverse Reaction) criteria[5] **(Table 1)**. The score of the patient was 7, establishing the diagnosis

Table 11 RegiSCAR[5] DRESS scoring system.

Clinical features	*Total score*	*Patient score*
Extent of rash >50% BSA.	1	1
Eruption suggestive of DRESS (Urticated papular exanthema, morbilliform eruption, erythema multiforme like features, erythroderma).	1	1
Systemic involvement		
a) Lymphadenopathy ≥ 2sites ≥ 1cm.	1	0
b) Eosinophilia.		
10-19% of TLC.	1	
> 20%.	2	2
c) Atypical lymphocytosis.	1	0
d) Organ involvement. (score 1 for each organ involvement; maximal score 2).	2	2
liver; transaminases 2× ULN on 2 successive dates OR bilirubin 2× ULN on 2 successive dates OR ϒGT and alkaline phosphatase 2× ULN on one occasion.		
renal; creatinine 1.5 × pts baseline.		
cardiac; echocardiographic evidence of pericarditis.		
Relevant negative serological test		
≥3 of the following performed and negative: Hepatitis A, B and C, Mycoplasma/Chlamydia, antinuclear antibody, Blood culture (performed ≤ 3days after hospitalization).	1	1
Total	9	7

Interpretation: <2 points = negative case; 2-3 points = possible case; 4-5 points = probable case; >5 points = definite case.

as the definite case of DRESS syndrome. In this case the offending drugs with strong temporal association were leflunamide and piroxicam. The patch test for these drugs was not done due to practical limitations. Hence, either of the drug could be the cause of development of DRESS syndrome in our patient.

The suspected drugs had already been stopped by the patient. During hospitalization the initial symptomatic treatment with antihistamines and bronchodilators was given. Topical steroids followed by oral steroids in the dose of 0.5mg/kg/day (30mg/day prednisolone) was started. Within 4-5 days, the color of the lesions became dusky and desquamation started **(Figure 2)**. Labs also showed improvement in eosinophil count and transaminase levels. The patient was discharged on antihistamine and tapering dose of oral steroids. Desquamation settled completely and all labs became normal at follow up 3 weeks after discharge. Patient is still in follow up and even after 6 months of developing DRESS syndrome she didn't experience similar symptoms, signs or chronic sequelae of the disease yet.

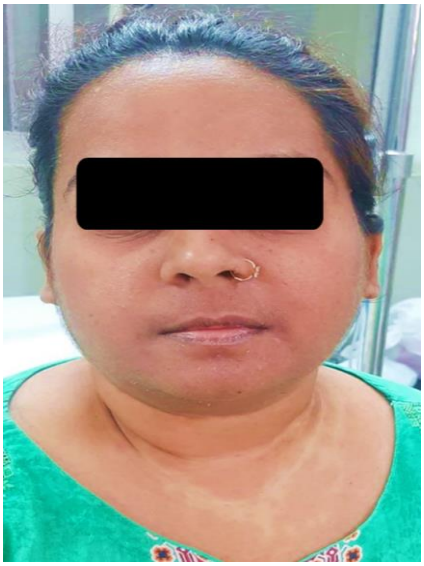

Figure 2 Resolving phase: Settling edema and erythema leading to desquamation (at the time of discharge).

Table 2 Drug groups associated with DRESS syndrome [3-6].

Groups	*Drugs*
Anti-convulsants	Carbamazepine, lamotrigine, phenytoin, phenobarbital, valproate, oxcarbazepine, gabapentin
Anti-bacterials	Amoxicillin, ampicillin, trimethoprim-sulfamethoxazolem-azithromycin, levofloxacin, minocycline, doxycycline, piperacillin/tazobactam, vancomycin, linezolid, cephalosporins
Anti-retroviral agents /Anti Hepatitis C virus agents	Abacavir, teleprevir, nevirapine, boceprevir
Anti-gout medicine	Allopurinol, febuxostat
NSAIDs	Aceclofenac, celecoxib, ibuprofen, aspirin, piroxicam, naproxen,
Antituberculous medications	Ethambutol, isoniazide, rifampicin, pyrazinamide, streptomycin
DMARDs/ Immunomodulatory drugs	Sulfasalazine, dapsone, hydroxychloroquine, leflunamide, azathioprine, daclizumab,solcitinib
Anti-depressants	Despiramine, amitriptyline, fluoxetine
ACE inhibitors	Captopril,enalapril
Others	Atorvastatins, omeprazole, atenolol, celiprolol

Discussion

DRESS syndrome is a severe, idiosyncratic, Type 4 hypersensitivity reaction of drugs, characterised by fever, skin manifestations, lymphadenopathy, hematological abnormalities and involvement of internal organ that develop 2- 8 weeks after intake of culprit drug[4]. The estimated worldwide incidence of DRESS syndrome is between 1:1000 to 1:10000 drug exposures. In Asia, among all the drug hypersensitivity reactions, DRESS incidence is 10% and mortality ranges from 3-10%.[4] There are many drugs reported in the literature causing DRESS syndrome **(Table 2)**.[3-6]

The pathophysiology of DRESS syndrome involves three factors: genetic susceptibility, defect in the metabolic pathway of drugs and reactivation of human herpesviruses (HHVs). In a genetically predisposed individual, the defect in detoxification pathway of drugs results in the formation of reactive oxygen metabolites leading to cellular damage. This activate antigen presenting cells and T cells, resulting in the release of pro inflammatory cytokines (TNF α, ɣ IFN, IL-4, IL-5, IL-6 & IL-13). This immune response against drug or drug metabolites leads to recruitment of inflammatory cells especially eosinophils, hence causing inflammation in skin and internal organs. In addition to this, the T cell activation suppresses B cells and decreases immunoglobulin levels, creating immuno-suppression resulting in reactivation of HHVs. So, reactivation of HHVs (particularly HHV-6) is an additional phenomenon in the pathogenesis of DRESS syndrome which occurs directly by transcription of viral DNA through drug metabolites and indirectly through immunosuppression. This complex interaction of the three pathogenetic factors is responsible for cutaneous and systemic manifestations of DRESS syndrome.[6,7]

The clinical manifestations of DRESS syndrome start with prodromal symptoms followed by skin manifestations,lymphadenopathy, hematological abnormalities and involvement of internal organ/s. Prodromal symptoms include malaise, itching and fever which develops several days prior to cutaneous eruption. Skin involvement comprises of morbilliform eruption, urticated papules, scaling, erythroderma, vesiculobullous lesions, erythema multiform (EM) like lesions and rarely purpura and pustule formation.[6] Urticated papular exanthem is the most common cutaneous presentation followed by morbilliform eruption.[8] Skin manifestations start from face followed by upper trunk, upper limbs and then become generalized, involving >50% of body

surface area. It persists for weeks and months after discontinuation of the offending drug and resolves with desquamation. Facial edema and mucosal involvement (cheilitis, pharyngeal erythema, hypertrophied tonsils or rarely erosions) occurs in 50% of the cases of DRESS syndrome. Lymphadenopathy which develops in 75% of the cases usually involve more than 2 sites (cervical, axillary, inguinal).[5-7]

Among hematological abnormalities the most common finding is leukocytosis with markedly raised eosinophils and it is seen in approximately 60-70% of cases of DRESS syndrome. Other findings are atypical lymphocytosis, lymphopenia, thrombocytopenia and anemia. Among internal organ involvement, liver is the most commonly affected one, followed by renal, pulmonary, cardiac, GIT, neurological and endocrine involvement[7]. Liver injury (in 60-80% of the cases) may present in the form jaundice, hepatomegaly, raised transaminases, ↑alkaline phosphatase, ↑ɤGT and can lead to hepatic necrosis which is one of the causes of mortality in DRESS syndrome. Renal impairment (in 30%) can cause moderate and transient increase in urea and creatinine levels and rarely severe interstitial nephritis, acute tubular necrosis and kidney failure. Pulmonary impairment (in 25%) includes interstitial pneumonitis, pleuritis and ARDS. Liver, kidney and lung damage usually occurs early during the course of disease however, cardiac involvement in the form of eosinophilic myocarditis or pericarditis develops months after discontinuation of drug. GIT (diarrhea, dehydration and GI bleed), endocrine (thyroiditis, pancreatitis, Type 1 DM) and neurological manifestations (meningitis, encephalitis, cranial nerve palsy) are rare but can occur in DRESS syndrome.[5,6]

In some patients more severe or life-threatening complications may develop i.e., Fulminant liver failure requiring liver transplantation, renal failure requiring dialysis, ARDS requiring ventilatory support and myocarditis leading to cardiac insufficiency. Thyroid dysfunction also occurs in convalescent phase. There is an increased risk of development of autoimmunity in patients with DRESS syndrome and can occur months to years after remission of cutaneous manifestations. Associated autoimmune diseases include thyroiditis, hemolytic anemia, alopecia, DM, SLE, autoimmune blistering disorders. This occurs due to loss of regulatory T lymphocyte function and subsequent loss of tolerance to autoantigens.[5,6]

To diagnose DRESS syndrome is always challenging because of its varied and delayed clinical presentation, and mimicking autoimmune connective tissue diseases, viral exanthems and other cutaneous adverse drug reactions. So, diagnosis is made by applying RegiSCAR criteria,[5] proposed in 2007. RegiSCAR is the most valid, detailed and frequently used criteria for clinical diagnosis, through scoring system based on clinical and laboratory data.

Treatment of patient with DRESS syndrome includes discontinuation of the offending drug, use of emollients, antihistamines, topical and/ or systemic corticosteroids. In addition to this, patients may require IVIG, immunosuppressive drugs (ciclosporin, mycophenolate mofetil or cyclophosphamide), plasma exchange and antivirals. These medications are given depending upon the severity of the disease and according to various guidelines.[6,8] The use of the systemic corticosteroids is currently the most accepted treatment although it has not been studied in a randomized trial. Early administration and gradual tapering (3-6months) of systemic corticosteroids is recommended in most of the patients. It not only controls acute phase of disease, avoids relapse, but also helps reduce the chances of development of autoimmunity.[5,6,8]

The outcome of DRESS syndrome is variable due to its expected recurrences (complete/ partial), chronic sequelae of the disease and development of autoimmunity. Most of the patients usually recover completely within 6-9 weeks on withdrawal of the offending drug and management of the acute stage. In >20% of the cases the disease persists for several months due to chronic sequelae of the organ/s involved. The poor prognostic factors of the syndrome are eosinophilia, atypical lymphocytosis, pancytopenia, thrombocytopenia, coagulopathy, sever liver injury and reactivation of HHV-6 and CMV. The mortality in DRESS syndrome is mainly due to fulminant hepatitis and liver necrosis. As patients are at increased risk of development of autoimmunity so long term follow up is required.[6]

Though, it is reported in the literature that skin eruption succeeds prodromal symptoms,[6] but in our case clinical manifestations started with skin involvement followed by prodromal symptoms and shortness of breath. Skin involvement began from trunk, then involved face and upper limbs, however, in literature review the involvement of face usually occurs initially followed by trunk.[5,6] In this patient the cutaneous eruption was urticated papular exanthem which is the most common presentation of DRESS syndrome reported in the literature.[5] Mucosal involvement i.e. cheilitis, pharyngeal erythema, hypertrophied tonsils or rarely erosions is reported in literature,[5] however, in our case only cheilitis was seen. Lymphadenopathy which is usually the most common presentation of DRESS syndrome, was not found in our case. Eosinophilia and liver involvement are again the most frequently occurring hematological and internal organ involvement in DRESS syndrome and similar findings were seen in our patient.

In our case, although patient was on treatment for her comorbid diseases for a long period of time but she did not develop similar clinical manifestations in the past, moreover, she had already stopped taking her previously prescribed medications few months before developing this ailment. She had recently started taking new drugs for her joint pains. So, the intake of these new drugs i.e., piroxicam and leflunamide followed by development of current clinical and laboratory findings had strong temporal association of causing DRESS syndrome in this patient.

The first suspected drug in our case was leflunamide (Disease-modifying antirheumatic drugs DMARDs). There are case reports of leflunamide causing cutaneous adverse drug reactions (CADRs) that includes lichenoid drug eruption[9] and subacute cutaneous lupus erythematosus.[10] Among SCARs; SJS/TEN[11] and few cases of DRESS syndrome[12-16] are also reported. The other suspected drug causing DRESS in our case was piroxicam (oxicam class of non-steroidal anti-inflammatory drugs). There are CADRs reported with piroxicam that includes photosensitivity, erythema multiforme, urticaria, fixed drug eruption, pemphigus vulgaris and Lyell's syndrome[17] and a case report of DRESS syndrome along with severe acute hepatitis had been reported in 2014.[18] Since then, there isn't any other case of DRESS syndrome reported in humans so far, however, a single case has been reported in cat in 2018.[19] No case of DRESS syndrome has been reported by other drugs of oxicam class of NSAIDs, however, many cases of DRESS syndrome have been reported by other classes of NSAIDs (diclofenac, ibuprofen, naproxen and aceclofenac).[20-24]

DRESS syndrome is a potentially fatal condition if not identified early and manage promptly. Early diagnosis, identification and withdrawal of suspected drug and timely treatment will help reduce the mortality and morbidity of the

disease. Moreover, the confirmation of the offending drug with patch test should be considered to confirm the diagnosis and to replace the offending drug with alternatives that alleviate patient symptoms without causing adverse effects. Long term follows up of patient for cardiac and endocrine dysfunction and development of autoimmunity should also be done to identify and treat the chronic sequelae of the DRESS syndrome.

Declaration of patient consent The authors certify that they have obtained all appropriate patient consent.

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Conflict of interest Authors declared no conflict of interest.

Authors' contribution

BM: Identification, diagnosis and management of the case, manuscript writing, has given final approval of the version to be published.

ATZ: Identification of the case, manuscript writing, has given final approval of the version to be published.

TZ: Diagnosis and management of the case, critically review, has given final approval of the version to be published.

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