Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome Secondary to Furosemide: Case Report and Review of Literature

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Conflict of interest: None declared

Patient: Male, 63
Final Diagnosis: DRESS syndrome
Symptoms: Diarrhea • fever • rash • shortness of breath
Medication: Furosemide
Clinical Procedure: Skin biopsy
Specialty: Internal Medicine • Family Medicine

Objective: Rare disease

Background: DRESS is a rare, life threatening syndrome that occurs following exposure to certain medications, most commonly antibiotics and antiepileptics. While sulfonamide antibiotics are frequently implicated as causative agents for DRESS syndrome, furosemide, a nonantibiotic sulfonamide, has not been routinely reported as the causative agent despite its widespread use.

Case Report: A 63 year old male who started furosemide for lower extremity edema 10 weeks prior presented with diarrhea, fever of 39.4°C, dry cough and maculopapular rash involving >50% of his body. He self-discontinued furosemide due to concern for dehydration. The diarrhea spontaneously resolved, but he developed hypoxia requiring hospitalization. CT scan demonstrated mediastinal lymphadenopathy and interstitial infiltrates. Laboratory evaluation revealed leukocytosis, eosinophilia and thrombocytopenia. He was treated empirically for atypical pneumonia, and after resuming furosemide for fluid excess, he developed AKI, worsening rash, fever and eosinophilia of 2,394 cell/µL. Extensive infectious and inflammatory work up was negative. Skin biopsy was consistent with a severe drug reaction. Latency from introduction and clinical worsening following re-exposure indicated furosemide was the likely inciter of DRESS. The RegiSCAR scoring system categorized this case as “definite” with a score of 8.

Conclusions: We report a case of severe DRESS syndrome secondary to furosemide, only the second case report in medical literature implicating furosemide. Given its widespread use, the potentially life-threatening nature of DRESS syndrome and the commonly delayed time course in establishing the diagnosis, it is important to remember that, albeit rare, furosemide can be a cause of DRESS syndrome.

MeSH Keywords: Acute Kidney Injury • Colitis • Drug Hypersensitivity Syndrome • Exanthema • Furosemide • Lung Diseases, Interstitial

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/907464
**Background**

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, idiosyncratic, potentially life-threatening adverse drug reaction characterized by varying combinations of the following: fever higher than 38.5°C, skin eruptions (usually pruritic maculopapular rash or diffuse erythematous erup- tion), hematologic abnormalities (eosinophilia or/and mononucleosis-like atypical lymphocytes or/and thrombocytopenia), lymphadenopathy, and multiple internal organ involvement (hepatitis being the most common, followed by nephritis, pneumonitis, colitis, encephalitis, pancreatitis, thyroiditis, or myocarditis) [1,2]. Nomenclature of this syndrome has significantly evolved over the last 80 years since its first description. Initially it was named drug induced pseudolymphoma, then subsequently anticonvulsant hypersensitivity syndrome, drug induced hypersensitivity syndrome, and drug induced delayed multiorgan hypersensitivity syndrome. [3–7]. The current name, DRESS, was defined in 1996 by Bocquet et al. [1]. The “R” in DRESS since then has been changed from Rash to Reaction due to the diversity of cutaneous manifestations [7].

DRESS syndrome presents as a spectrum from mild rash with eosinophilia that favorably responds to withdrawal of the offending drug to multiple-organ involvement with high mortality and the need for immunosuppressive medications. The syndrome’s estimated prevalence ranges from 1 in 1,000 to 1 in 10,000 drug exposures, and mortality has been estimated to be up to 10% [2]. Mortality typically results from myocarditis and severe hepatitis leading to liver failure [2,3]. No specific diagnostic test currently exists for this syndrome. It requires a high index of suspicion by clinicians and exclusion of other infectious, inflammatory, autoimmune, and neoplastic conditions as well as other similar cutaneous drug reactions. Due to the variability of its presentation, DRESS is known as a “great mimicker” which contributes to the delay in diagnosis [8,9].

RegiSCAR (European Registry of Severe Cutaneous Adverse Reactions) is a scoring system developed to more accurately define different entities including Steven-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and DRESS [2,10]. Depending on the score, cases of DRESS are categorized into four groups: no case, possible case, probable case, and definite case [10]. Another score developed by a Japanese consensus group for DRESS incorporated reactivation of human herpes virus (HHV)-6 as a criterion in addition to those included in RegiSCAR. The Japanese consensus group score classifies cases as either typical DRESS or atypical DRESS [11].

DRESS has later onset and longer duration than other drug reactions [3]. Latency between exposure to medication and onset of symptoms is a well-defined characteristic of this syndrome. It usually ranges from two to six weeks; however, latency periods up to 105 days have been described [12]. More than 40 medications have been described to cause DRESS, among which aromatic anticonvulsants (phenytoin and carbamazepine) and antibiotic sulfonamides (dapsone, sulfasalazine, and sulfamethoxazole) are the most common [2,3,5,12]. Furosemide, a nonantibiotic sulfonamide, has rarely been cited as a cause of DRESS syndrome and, to the best of our knowledge, this is the second case published in the literature [13]. Here, we present a severe case of DRESS syndrome caused by furosemide that was manifested by typical rash, fever, hematologic abnormalities, and unusually extensive visceral organ involvement including nephritis, pneumonitis and colitis. Using RegiSCAR, it scored 8 points (maximum possible score 9) classifying it in the definite DRESS case category [10]. The Japanese consensus group score classified it as atypical DRESS due to the absence of documented HHV-6 reactivation [11].

**Case Report**

A 63-year-old male with a history of hypertension, chronic back pain secondary to spinal stenosis, and lower extremity edema was transferred to our hospital for further management of fever, diffuse maculopapular rash, and cough. His medications included oxycodone for back pain, losartan for hypertension, and furosemide which had been started for lower extremity swelling approximately 10 weeks prior to hospitalization. He was fully employed and in good overall health. He was a married resident of the USA Midwest who rarely drank alcohol, did not smoke, and did not use illicit drugs. He had not recently traveled outside the USA and had no pets.

His symptoms started two weeks prior to admission with profuse watery diarrhea without vomiting, hematochexia, or abdominal pain. One week prior to admission, he developed a diffuse, itchy maculopapular rash. At the same time, he noticed a dry, nonproductive cough, as well as fevers up to 38.6°C, and he stopped taking furosemide on his own because of concern for further investigation and management.

On admission, his physical examination revealed a man in moderate distress. Vitals signs were notable for temperature of 38.6°C, blood pressure 126/59 mm Hg, heart rate 103 beats per minute, respiratory rate 22 breaths per minute, and oxygen saturation was 95% on 2 L oxygen via nasal cannula. Diffuse erythematous maculopapular rash was present on his face, upper torso, back, and both upper and lower extremities sparing palms and soles. There was no conjunctival injection or mucosal involvement. Apart from tachycardia, his cardiovascular examination was normal without murmur. His lungs were clear bilaterally without crackles or rhonchi. His abdomen was soft...
and nontender, without hepatosplenomegaly. There were no focal neurological deficits.

The laboratory workup was significant for leukocytosis of $11.8 \times 10^9/L$ and elevated eosinophil count of $1.29 \times 10^9/L$. Hemoglobin and platelets were normal. Creatinine, electrolyte, and liver enzymes tests were all normal. Inflammatory markers were elevated with C-reactive protein (CRP) of 229 and erythrocyte sedimentation rate (ESR) of 31. Blood gas showed hypoxemia, and partial oxygen was 66 mm Hg. Computed tomography (CT) scan of the chest showed significant hilar lymphadenopathy and interstitial changes consistent with pneumonitis (Figure 1).

Empiric treatment initiated included levofloxacin for community-acquired pneumonia and intravenous (IV) fluids for presumed sepsis while awaiting blood and sputum culture results. The following day his rash worsened, cough and fevers persisted, and he developed thrombocytopenia. Doxycycline for empiric coverage of tick-borne pathogens was added and a diagnostic panel for tick-borne illnesses sent. Skin biopsy was performed. The next day the patient was feeling slightly better; he was afebrile though cough and eosinophilic leukocytosis persisted. The patient’s home dose of furosemide 20 mg by mouth was resumed for chronic lower extremity swelling, which resulted in significant clinical deterioration 12 hours following re-exposure. His rash worsened, hypoxia and dyspnea progressed, fevers returned up to 39.4°C, and both leukocytosis and eosinophilia worsened. Additionally, he developed acute kidney injury and atrial fibrillation with rapid ventricular response. DRESS syndrome secondary to furosemide was suspected.

Extensive infectious and autoimmune workup was negative including the following: no growth on blood and sputum cultures, negative respiratory panel (influenza A and B, respiratory syncytial virus (RSV), parainfluenza, adenovirus, and human metapneumovirus), negative streptolysin O antibodies, negative gamma interferon release assay for tuberculosis, negative urine Legionella and streptococcal antigens, negative mycoplasma and chlamydia serologies, negative tick-borne illness panel (Lyme disease, rickettsia, human monocytic ehrlichiosis, human granulocytic anaplasmosis, and Babesia), negative HIV test, negative syphilis by IgG, negative stool cultures, negative stool for ova and parasites including Strongyloides, negative viral and parasite serologies (Epstein-Barr virus (EBV), cytomegalovirus (CMV), parovovirus B19, toxoplasma, hepatitis A, B, and C), negative HHV-6 PCR, and negative testing for endemic mycoses (histoplasmosis, blastomycosis, coccidioidomycosis, and cryptococcosis).

Inflammatory workup was also negative including negative or normal antinuclear antibody (ANA) and antiphospholipid antibodies, complement levels, C-ANCA, P-ANCA, tryptase levels, and angiotensin converting enzyme (ACE) levels. Urine analysis showed no casts or eosinophils but was significant for hematuria and proteinuria (100 mg/dL). Finally, protein electrophoresis was negative for monoclonal spike, and flow cytometry for leukemia/lymphoma was negative. Skin biopsy was consistent with severe drug reaction (Figure 2).

Workup for atrial fibrillation included echocardiogram that showed normal left ventricle (LV) ejection fraction without pericardial effusion or wall motion abnormalities. Troponin T, creatine kinase (CK)-MB, and thyroid-stimulating hormone (TSH) were negative. He did not respond to diltiazem and metoprolol, so amiodarone was used for rate control. Use of amiodarone coincided with initiation of steroids.

On hospital day 5, following clinical worsening with resuming furosemide and after extensive workup ruled out infectious, inflammatory, and neoplastic etiologies, the diagnosis of DRESS syndrome secondary to furosemide was made and the patient was started on 1 mg/kg of oral prednisone daily.

Figure 1. Computed tomography without contrast demonstrating diffuse mediastinal and hilar lymphadenopathy with conglomeration of lymph nodes in the subcarinal region.
Levofloxacin and doxycycline were discontinued. The patient dramatically improved in the next few days. The trajectory of selected tests is shown in Figure 3. He was discharged on a slow taper decreasing dose of prednisone by 10 mg every two weeks. Atovaquone was given for pneumocystis jirovecii pneumonia prophylaxis during his course of steroid treatment. Bactrim (for the same indication) was avoided due to concern for cross-reaction to the sulfa component. He was discharged on spironolactone as a diuretic for treatment of his lower extremity edema. At his primary care follow-up visit six weeks after onset of symptoms, he had improved symptomatically, and his laboratory testing normalized (Figure 2). At that time of last follow-up, he continued to have fatigue, mild shortness of breath, and insomnia from steroids.

**Discussion**

The pathogenesis of DRESS syndrome is not completely understood. Multiple authors agree, however, that a complex interplay between a patient’s genetic predispositions, abnormalities...
in metabolic pathways leading to accumulation of drug metabolites, as well as drug-virus interactions leading to reactivation of HHV-6 and HHV-7, EBV, and CMV are likely responsible for the syndrome [2,3,7,15,16]. The association between specific human leukocyte antigen allele (HLA) groups in some ethnic populations and the development of DRESS with exposure to certain medications has been described [16,17]. For example, minocycline induced DRESS syndrome seems to be more prevalent in Caribbean blacks [17]. Similarly, HLA-B*5701 is associated with abacavir-induced DRESS syndrome and HLA-B*5801 is associated with allopurinol-induced DRESS syndrome in certain Chinese groups [18,19].

Diagnosis of DRESS syndrome is difficult to establish, and it requires a high level of suspicion as well as ruling out other etiologies. Multi-system involvement and febrile skin eruption makes the list of differential diagnoses quite extensive. It includes infectious disease (e.g., viral exanthemas, staphylococcal and streptococcal shock syndromes, meningococcemia), noninfectious drug eruptions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis), autoimmune disease (e.g., Kawasaki disease, Still's disease, hypereosinophilic syndrome) and neoplastic diseases (e.g., leukemia cutis, mycosis fungoides). Depending on the specific organs involved, the differential diagnosis also includes viral hepatitis (liver), glomerulonephritis, vasculitides, pre- and post-renal causes of acute kidney injury (kidney), Kawasaki disease and eosinophilic myocarditis (heart), parasitic infection (gastrointestinal (GI) tract), and bacterial, viral and fungal pathogens (lung). There is no pathognomonic sign or diagnostic test for DRESS. The diagnosis is clinical and established by taking into account drug exposure in the appropriate clinical setting and latency between drug exposure and symptom onset. While re-challenging with the causative drug has been the gold standard to diagnose drug eruptions, it should not be used in suspected DRESS cases due to the life-threatening nature of this syndrome [7].

Our patient was unintentionally re-challenged with furosemide, and shortly following re-exposure his clinical symptoms worsened. Following re-exposure to furosemide, he developed worsening rash and hypoxia as well as increased fever, eosinophil count, and creatinine. This was when we suspected DRESS while simultaneously confirming that furosemide was the causative agent. Shorter latency period after re-challenging has been described in DRESS [15]. Antibiotic sulfonamides have been previously described as causative agents for DRESS, and are one of the most common classes of antibiotics to cause the syndrome. The nonantibiotic sulfonamide furosemide has not commonly been reported to cause DRESS syndrome. In our review of the literature, we found only one case linking furosemide to DRESS [13]. In that case, as in our case, the patient developed visceral involvement including hepatitis and nephritis. That case scored 7 on RegiSCAR and the patient responded favorably to oral steroids with prednisone 1 mg/kg daily as initial therapy [13]. Our case further substantiates furosemide as an inciting agent of DRESS considering the acute worsening of symptoms with re-exposure to furosemide. The sulfonamide group of furosemide is likely responsible for the reaction, yet it remains an enigma why furosemide has been remarkably less frequently associated with DRESS in comparison to sulfonamide antibiotics despite it containing a sulfa component. One possibility is that different metabolic pathways of various sulfa-containing compounds lead to different reactive metabolites which differ in immunogenic reactivity. For example, metabolite formation is stereospecific to the N4 amino nitrogen of the sulfonamide antibiotics, a structure not found on any nonantibiotic sulfonamide drugs [20]. The leucocyte transformation/activation test (LAT) has been used sporadically to confirm the causative drug and confirm cases of DRESS. The test measures the proliferation of T cells to a drug in vitro. Unfortunately, it is not standardized for many medications, is difficult to perform, usually yields a negative result early in the course of the syndrome, and lacks sensitivity [21]. A positive LAT is useful to confirm the diagnosis due to very low false positive results (only 2%), however, a negative test cannot exclude diagnosis [22]. All of these factors prevent widespread use of this test.

In their review of the literature, Cacoub et al. showed that probable/definite cases consistently demonstrated more delayed onset of symptoms when compared to possible cases [2]. Additionally, time to resolution of symptoms was longer in probable/definite cases when compared to possible cases. This is consistent with our case that exhibited a quite long latency period of 10 weeks and resolved over the course of three weeks. This case scored 8 points on RegiSCAR which indicates a "definite" DRESS case. The Japanese consensus group criteria, however, characterized it as "atypical" DRESS due to the lack of demonstrated HHV-6 reactivation. Reactivation of HHV-6 has not been routinely tested. In the era of increasing healthcare cost and increasing pressure to cut down on spending it is important to evaluate utility of testing for HHV-6 reactivation in routine cases outside of research purposes since it does not affect management. In fact, Cacoub et al. found that reactivation of HHV-6 was tested in only 41% of cases, however, when HHV-6 reactivation was tested, 80% of cases tested positive [2]. The severity of DRESS syndrome and mortality appears to be tightly related to the extent of involvement of visceral organs [2,3]. Multiple organs and systems of organs have been described to be affected in DRESS syndrome, which can make DRESS a difficult diagnosis to make because of both the extent and diversity of presentation. Previously identified affected visceral organs include liver, kidney, lung, intestines, and heart. Hence, we describe the manifestations of these involved organs. The liver is the organ most commonly affected in DRESS syndrome [3]. Liver involvement is considered if the patient has exhibited hepatomegaly.
and/or increase in liver enzymes. In a study of 25 patients by Lee et al. [23], the liver was affected in 80% of cases. Among these, 24% of patients had hyperbilirubinemia, while the rest had elevation in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). A study by Chen et al. of 60 consecutive patients from Taiwan between 1998–2008 re-demonstrated liver involvement in 80% of cases [24]. Interestingly, our patient did not have significant liver involvement despite extensive involvement of other visceral organs.

Renal involvement in DRESS is common with 11%–28% of patients being affected [23,25]. Renal involvement is usually manifested as elevation in creatinine, decrease in glomerular filtration rate (GFR), proteinuria, and hematuria. Our patient exhibited all of these indicators. Allopurinol is the medication most commonly associated with renal involvement [3,26]. Several case reports documented favorable outcomes in renal recovery following treatment, even in the patients who temporarily required renal replacement therapy [27,28]. Our patient recovered completely three weeks following discharge, with resolution of hematuria and proteinuria and return of GFR and creatinine to pre-morbid levels.

Unlike liver and kidney, lungs are rarely affected in DRESS syndrome. The most commonly described findings are interstitial pneumonitis, pneumonia, pleural effusion, and acute respiratory distress syndrome (ARDS) [3,23]. Exact incidence of lung involvement in DRESS is unknown but it ranges from 2.6% in a study by Chen et al. [24] to 5% as documented by Cacoub et al. [2]. Minocycline and abacavir are the medications most often associated with lung involvement [26,29]. Interestingly, in a study of 15 patients with severe DRESS syndrome (with mortality rate of 20%) admitted to a critical care unit, 10 patients (67%) had lung involvement. In this group of critically ill patients, allopurinol and minocycline – known to be associated with high mortality and lung involvement – were the most common offending agents, respectively [30]. Our patient had interstitial pneumonitis with significant mediastinal lymphadenopathy on admission, which led to empiric treatment for community-acquired pneumonia. Due to persistent fevers, worsening leukocytosis and eosinophilia despite appropriate broad-spectrum antibiotics, we confidently concluded that lung involvement was part of DRESS syndrome in this case after infectious workup was negative for viral, bacterial, and fungal pathogens and serology was negative for vasculitides that commonly involve lungs and renal parenchyma concomitantly (systemic lupus erythematosus, Goodpasture’s syndrome, antiphospholipid antibody syndrome and ANCA associated vasculitis). Following administration of steroids, his lymphadenopathy and hypoxia completely resolved.

Non-specific GI symptoms including diarrhea have been described as part of DRESS, however, they are rarely investigated which might contribute to underestimation of the prevalence of GI involvement [31]. Out of 25 patients described by Lee et al., only two patients (8%) had colitis. Several case reports have described colon involvement in DRESS [32–34]. Colon involvement in DRESS ranges from mild self-resolving diarrhea to profuse diarrhea leading to severe electrolyte abnormalities. One case was also complicated with hemophagocytic syndrome resulting in death from massive GI hemorrhage [35]. Chung et al. described a case where the patient had significant diarrhea as part of DRESS syndrome, who failed to improve on oral prednisone and required IV hydrocortisone to improve. Hence, they argued that hyper motility of the digestive tract lead to poor absorption of steroids and suggested that in cases with significant GI involvement initial treatment should be with IV steroids [36]. It is important to rule out infectious causes of diarrhea, especially parasitic, inflammatory, and ischemic causes. In our patient, infectious diarrhea had been ruled out and we believe that diarrhea was his first symptom of DRESS syndrome. It is prudent to keep in mind DRESS in the differential diagnosis for patients with fever, eosinophilia, diarrhea, and negative infectious workup since diarrhea might be the presenting symptom of DRESS colitis.

Cardiovascular involvement in DRESS is usually manifested as myocarditis and, although rare, is associated with high mortality (55%). One of the distinct features of DRESS myocarditis is that it can occur late after resolution of all other symptoms and after normalization of laboratory values. It has been documented to occur up to four months following successful treatment of DRESS [37]. The most common medication associated with DRESS myocarditis is ampicillin. Manifestations include chest pain, non-specific electrocardiogram (ECG) changes or gross ST segment elevation or depression, tachycardia and arrhythmias, and decrease in LV ejection fraction [3,37]. Definite diagnosis is made by endomyocardial biopsy, however, due to the invasive nature of the biopsy, diagnosis is most often made clinically based on ECG findings, echocardiography (ECHO) and laboratory results. Troponin and CK-MB are elevated in the majority of myocarditis cases, though neither was elevated in our case. Our patient developed atrial fibrillation with rapid ventricular response shortly after being re-exposed to furosemide, which we considered possible cardiovascular involvement as part of DRESS syndrome, even though the ECHO did not show evidence of reduced LV ejection fraction or wall motion abnormalities.

There have been no prospective clinical trials done to guide treatment for DRESS syndrome. Current recommendations are based on case reports and expert opinion. The first and most important step in treatment is withdrawal of the inciting medication. Without this step, other treatment will be futile. Earlier withdrawal of the drug is associated with better prognosis [38]. In mild to moderate cases without visceral
involvement, withdrawal of the causative agent together with topical steroids for rash and topical or systemic antihistaminic agents for itchiness is usually adequate. However, in cases of visceral involvement, systemic steroids are indicated [6,9,15]. Optimal dose, route of administration, duration of treatment, and rapidity of dose tapering of steroid treatment have not been verified in controlled trials. The majority of case reports have suggested initiating prednisone 1 mg/kg orally with subsequent slow taper over three to six months. Rapid taper can be associated with relapse [31]. Proposed mechanism by which corticosteroids benefit the patient is inhibition of IL-5, which is essential for accumulation of eosinophils and which, in turn, is responsible for visceral organ damage in DRESS syndrome. Some authors, however, suggest that corticosteroids should not be used in cases of documented viral reactivation due to the potential to exacerbate the reactivation disease [25,39]. The benefit of antiviral medications is unclear in cases of documented viral reactivation, yet some authors have used it successfully [40]. Dramatic improvement in symptoms and frequent relapses associated with quick prednisone taper strongly argues in favor of systemic steroid therapy in cases of moderate to severe disease. In severe and corticosteroid-resistant cases, more potent immunosuppressant medications including cyclosporine, azathioprine, and mycophenolate have been used, sometimes alongside adjunctive treatment with intravenous immunoglobulin (IVIG) and plasmapheresis [37]. Our patient responded favorably to oral prednisone 1 mg/kg daily for 14 days with subsequent taper down 10 mg every two weeks without relapse. It took at least six weeks for all symptoms to gradually resolve.

Long-term sequelae of DRESS syndrome include development of autoimmune disease including thyroiditis, diabetes mellitus type I, systemic lupus erythematosus (SLE), systemic sclerosis, or adrenal insufficiency. These manifestations can occur months to years following the initial episode and careful follow-up and awareness of this association is crucial for timely recognition and treatment should they occur [41,42].

Conclusions

We present a case of severe DRESS syndrome with multiple visceral organ involvement caused by furosemide that favorably responded to systemic steroids. Apart from classically described involvement of the skin and hematologic system, our patient exhibited colitis, pneumonitis, and nephritis—a combination that hasn’t been reported thus far. DRESS can be life-threatening and delay in diagnosis is associated with worse outcome. Hence, it is important to recognize that furosemide, albeit rare, can cause DRESS syndrome. Increased awareness regarding the association between DRESS and furosemide will help with diagnosing future cases in timely manner and avoiding the morbidity of delayed diagnosis.

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