CASE REPORT

The Importance of Early Recognition: a Case of DRESS Syndrome

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This case examines the presentation, diagnosis, and treatment of an otherwise healthy 22-year-old female who presented to urgent care with abdominal pain and fever 27 days after her first exposure to trimethoprim/sulfamethoxazole (TMP/SMX). However, this exposure was not recognized for an extended amount of time. She was initially diagnosed with gastroenteritis and sent home on metronidazole. She failed to improve and presented days later to her primary care physician's office where she was treated with levofloxacin for a suspected urinary tract infection. Her clinical syndrome continued to progress and she developed a widespread rash and generalized edema. She was admitted to the hospital after outpatient laboratory analysis was suggestive of liver and kidney damage. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS syndrome) was suspected in the setting of her fever, rash, elevated liver enzymes, peripheral eosinophilia, and dermatopathological findings. DRESS syndrome is a diagnosis of exclusion and requires a high level of clinical suspicion. The diagnosis was confirmed after review of her history revealed she received two courses of TMP/SMX nearly four weeks prior.

Keywords: DRESS, Drug-induced hypersensitivity syndrome (DIHS), trimethoprim-sulfamethoxazole, Bactrim, Drug reaction

INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is an uncommon, potentially life-threatening, drug-induced hypersensitivity reaction characterized by a triad of dermatoses, hematological abnormalities and internal organ disruptions (1). It should be suspected in patients with exposure to a new drug in the previous two to eight weeks who present with skin eruptions (morbilliform or diffuse, confluent), fever (38˚C to 40˚C), facial edema, and/or lymphadenopathy (2). Peripheral eosinophilia is also suggestive of DRESS. Multiple internal organ involvement can occur and most commonly affects the liver, kidney, and lungs (2) (3).

Several sets of diagnostic criteria have been developed for DRESS, and there is no one universally agreed upon criteria. Three of the most commonly used sets of criteria are outlined. Bocquet et al. were the first to develop criteria in 1996 (Table 1)

(4). In 2007, a European group, The Registry of Severe Cutaneous Adverse Reaction (RegiSCAR), also proposed a new set of criteria for diagnosis to promote increased recognition and diagnosis of DRESS syndrome (Table 2) (5). Shiohara et. al proposed another set of criteria (Table 3) (6). Differing criteria for diagnosis of DRESS can make a challenging diagnosis even more difficult to detect. There has not yet been a consensus on which criteria is superior.

Diagnostic criteria are broad in their definition of drug eruption/rash because of the varied presentation of cutaneous manifestation in DRESS. A diffuse, urticarial, maculopapular rash is most common, but vesicles, bullae, pustules, cheilitis, purpura, target lesions, and erythroderma have been reported (1). The most common organ involvement in DRESS includes hepatic, followed by renal, pulmonary, and cardiac (1). Neurologic, gastrointestinal, and endocrine dysfunction have also been reported (1).

Treatment is primarily focused on the early identification, withdrawal, and avoidance of the offending agent. Supportive treatment is crucial, as systemic involvement is what leads to the morbidity and mortality in DRESS.

Table 1. Bocquet et al. criteria for the diagnosis of DRESS syndrome

Confirmed by the presence of all three
1. Cutaneous drug eruption
2. Adenopathy > 2cm in diameter or hepatitis (liver transaminases > 2 times the normal limit or interstitial nephritis or interstitial pneumonia or carditis)
3. Hematologic abnormalities including eosinophilia >1.5 x 10^9/L or atypical lymphocytes

Table 2. RegiSCAR criteria for the diagnosis of DRESS syndrome

*Three or more required
1. Hospitalization
2. Reaction suspected to be drug-related
3. Acute skin rash*
4. Fever > 38˚C*
5. Enlarged lymph nodes at at least two sites*
6. Involvement of at least one internal organ*
7. Blood count abnormalities* (lymphocytes above or below laboratory limits, eosinophils above the laboratory limits, or platelets below the laboratory limits)

Table 3. Shiohara et al. criteria for the diagnosis of DRESS syndrome

Seven criteria are required for the diagnosis of typical DRESS, or five required for the diagnosis of atypical DRESS
1. Maculopapular rash developing > 3 weeks after starting therapy with a limited number of drugs
2. Prolonged clinical symptoms 2 weeks after discontinuation of the causative drug
2. Lymphadenopathy
3. Fever > 38˚C
4. Liver abnormalities (alanine transaminase > 100 U/L)* Can be other organ involvement such as renal
4. Leukocytosis > 10×10^9/L, atypical lymphocytosis, or eosinophilia
6. Human herpesvirus 6 (HHV-6) reactivation

CASE PRESENTATION

D.O. is a 22-year-old female with no significant past medical history who presented to urgent care with complaints of fever, lower abdominal pain, nausea, and malaise for one day. She was febrile to 39.4˚C. Blood pressure was 136/88, pulse 120 beats per minute, respirations 20 per minute, and oxygen saturation 98% on room air. Physical exam at the time noted the patient's face was plethoric and erythematous with overlying xerosis. There was a confluent, erythematous rash on the face, chest, and legs and non-blanching erythematous targetoid lesions over the bilateral feet, palms, and soles. The patient's abdomen was diffusely tender to palpation, most severe in the right upper quadrant. No lymphadenopathy was appreciated. She was diagnosed with gastroenteritis and treated with metronidazole. Despite three days of treatment, her symptoms continued to worsen. Laboratory tests performed by her primary care physician were remarkable for acute hepatic injury with alanine transaminase (ALT) and aspartate transaminase (AST) 20 times greater than the upper limit of normal (see table 4 and table 5 for progression of laboratory values). Computerized tomography (CT) of the abdomen demonstrated a small amount of fat stranding around the bladder but was otherwise normal. She was instructed to present to the emergency department for admission after liver function tests and creatinine were elevated.

Upon admission, laboratory tests were notable for worsening transaminitis without leukocytosis or other abnormalities. Acetaminophen and alcohol levels were undetectable. Ultrasound of the liver was unremarkable and chest x-ray showed no evidence of pathology. She was started on levofloxacin and continued on metronidazole to treat a presumed urinary tract infection. On hospital day #4, she developed a diffuse, pruritic eruption and facial edema. She was treated with prednisone, diphenhydramine cream, and hydroxyzine. Her abdominal pain persisted, and liver enzymes remained elevated. On

hospital day #6, additional laboratory tests demonstrated newly elevated lactate greater than twice the normal limit. Other laboratory results included: Ebstein-Barr virus (EBV) negative, cytomegalovirus (CMV) IgM negative, Parvovirus B19 IgM negative, positive Parvovirus IgG, herpes simplex virus (HSV) 1/2 negative. All blood cultures were negative for growth. She was transferred to a higher level of care for further workup.

The patient was transferred with a diagnosis of rash of unknown origin and abnormal lab values. She continued to complain of abdominal pain without clear etiology as extensive laboratory and radiological assessment prior to transfer were negative for an identifiable cause. Her liver enzymes were known to be elevated, despite normal liver morphology on imaging.

Upon transfer, she was followed by dermatology and immunology teams as prior workup failed to identify the etiology of the diffuse rash, swelling, and hepatic injury. The revised differential diagnosis included erythema multiforme, viral exanthem, cholangitis, acute hepatitis, rocky mountain spotted fever (RMSF), and syphilis. Skin biopsy was performed. Serological assay was positive for human herpes virus 6 (HHV-6). Additional testing was largely unremarkable with antinuclear antibodies, antineutrophil cytoplasmic antibodies, antimitochondrial antibodies, and anti-smooth muscle antibodies within normal limits. Repeat viral hepatitis panels, including hepatitis C (HCV) RNA and human immunodeficiency virus (HIV) were also negative. Serological assays were negative for syphilis, ehrlichia, and HSV. The differential was further reduced to erythema multiforme in the setting of acute viral illness versus DRESS secondary to levofloxacin and metronidazole exposure prior to the rash.

On hospital day #8, her eosinophils peaked at 4900 cells/μL and her white blood cell count peaked at 29.6 $x10^3$/μL but was only elevated after starting steroids. Physical exam at the time was significant for a diffuse maculopapular rash that was mostly confluent in nature. She had edema evident on her face and all extremities. Skin biopsy from the dorsum of the right foot returned and showed spongiotic dermatitis. DRESS syndrome became the most likely diagnosis given her pathology results, roaring eosinophilia, and liver enzymes nearly 20 times greater than normal at admission.

The diagnosis of DRESS syndrome is difficult and requires a high degree of suspicion and clinical judgement. Clinical suspicion of DRESS syndrome can be enhanced by a history of exposure to a high-risk medication. D.O. had documented exposure to metronidazole and levofloxacin, however, these drugs are unusual causes of DRESS syndrome. Further review of the patient's history revealed that she had pierced her right ear 4 weeks prior to presentation at urgent care. Days later she felt as though it were getting infected, and she was started on trimethoprim/sulfamethoxazole (TMP/SMX). After no improvement with the first round of TMP/SMX, she requested a refill and completed a second round TMP/SMX. About 27 days after her initial exposure to the drug, she began to "feel sick" characterized by a fever of 39.4˚C and "stomach flu" symptoms.

Management of DRESS syndrome is primarily focused on the identification and withdrawal of the offending drug. Supportive measures were also employed to maintain proper fluid status and electrolytes. Given the time frame of her exposure, TMP/SMX was identified as the most likely cause of D.O.'s symptoms. The patient was instructed to avoid TMP/SMX in the future. Intravenous steroids were given during her

admission. She was discharged on an eight-week taper of oral prednisone. Topical steroids, diphenhydramine, and hydroxyzine were also prescribed for symptom management. At her two-month follow-up, D.O. was feeling well with no complaints. The rash had resolved. Her laboratory values had normalized, including AST and ALT which were 28 Units/L and 53 Units/L, respectfully.

Table 4. Complete Blood Count (CBC) laboratory findings throughout the course of illness.

Labs	Urgent Care	Admission	Hospital day 8	Outpatient follow up	Reference Range*
White Blood Cells (WBC)	5.4	5	29.6	11	3.0-11.4x10*3/µL
Red Blood Cells (RBC)	4.05	3.65	3.5	4.34	3.80-5.00x10*6/µL
Hemoglobin	13	11.5	10.8	13.7	11.3-15.0 g/dL
Hematocrit	37.5	34.5	33.8	41.6	34.0-45.0 %
Mean Corpuscular Volume	92.6	94	96.6	95.9	83.0-98.0 fL
Mean Corpuscular Hemoglobin	32.1	31.5	30.9	31.6	27.0-34.0 pg
Mean Corpuscular Hemoglobin Concentration	34.7	33.5	32	32.9	31.0-35.0 g/dL
Red Blood Cell Distribution Width	52.1	46	50.7	48.1	36.4-50 fL
Platelet Count	208	191	209	292	135-370x10*3/µL
Mean Platelet Volume	10	10.2	10	9	9.0-12.0 fL
Nucleated RBC			0.05	0	0-0.1 / 100 (WBC)
Lymph %	36		25.4	36.8	15-44%
Mono %	5		5.3	5.7	4-13%
Neutrophils %	42		32.4	54.4	42-76%
Bands%	9			1.4	1-10%
Eosinophils %	8		16.7	1.1	0-6%

Basophils%			1	0.6	0-1.5%
Lymph absolute	1.9		12.7	4.1	0.6-3.5x10*3/µL
Monocyte Count	0.3		1.6	0.6	0.2-0.9x10*3/µL
Neutrophil Count	2.8		9.6	6	0.85-7.8x10*3/µL
Bands Absolute				0.15	0-1.0x10*3/µL
Eos Count	0.4		4.9	0.1	0-0.5x10*3/µL
Basophil Count	0				0-0.1x10*3/µL
RBC Morph	normal				

*Reference ranges from admitting hospital

Table 5. Comprehensive Metabolic Panel (CMP) laboratory findings throughout the course of illness.

Labs	Urgent Care	Admission	Hospital day 8	Outpatient follow up	Reference Range*
Sodium	134	137	141	140	136-144 mmol/L
Potassium	4.6	4.1	3.9	3.3	3.4-4.8 mmol/L
Chloride	106	107	105	106	98-108 mmol/L
CO2 (venous)	18	21	29	22.8	22-30 mmol/L
Glucose Level	86	93	134	104	65-100 mg/dL
Blood Urea Nitrogen	7	7.3	8	8	7.0-24.0 mg/dL
Creatinine	0.6	0.5	0.62	0.8	0.5-1.2 mg/dL
Total protein	6.5	5.6	4.8	6.8	6.3-8.0 g/dL
Albumin	3.3	3.2	2.7	3.6	3.5-5.1 g/dL
Calcium	8.5	8.3	7.7	9.7	8.6-10.2 mg/dL
Bilirubin, Total	2.1	1.9	5.9	0.5	0.3-1.2 mg/dL
Bilirubin, Direct		1.1			0.0-0.2 mg/dL

Alkaline Phosphatase	140	130	427	60	35-104 U/L
AST/GOT	741	1152	256	28	9-35 U/L
ALT/GPT	838	1151	627	53	5-40 U/L

*Reference ranges from admitting hospital

DISCUSSION

The exact incidence of DRESS syndrome is unknown but is thought to occur in adults without predilection for gender (7). As evident in this case, the diagnosis of DRESS syndrome is often delayed due to the wide scope of clinical features and extended latency of presentation (typically 2-8 weeks). The mean onset of other drug hypersensitivity reactions such as Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) is 6.8 days from first drug administration (8). D.O. fulfilled criteria for DRESS syndrome at the time of her initial presentation, however, the diagnosis was delayed due to the lack of apparent exposure to a known offender.

The drugs most frequently associated with DRESS syndrome include allopurinol, antiepileptics (carbamazepine, lamotrigine, phenytoin, phenobarbital), vancomycin, minocycline, and sulfamethoxazole (1). In this case, a fluoroquinolone (levofloxacin) and metronidazole were initially suspected as the offending agents. The diagnosis of DRESS syndrome secondary to TMP/SMX was made on hospital day 16 of 18, when repeat history revealed the patient had two courses of TMP/SMX with exposure beginning nearly 27 days prior to symptom onset.

Although the exact mechanism of DRESS syndrome is not yet fully elucidated, the suggested pathophysiology involves a drug induced immune response and reactivation of the herpesvirus family (9). T-cells are thought to mediate the immune response to the offending drug or drug metabolite, leading to a delayed T-cell-mediated hypersensitivity reaction (9).

Human leukocyte antigens (HLA) alleles can predispose individuals to DRESS syndrome and other severe cutaneous adverse reactions. For example, HLA-A*31:01 has been found to be associated with carbamazepine induced cutaneous adverse drug reactions including SJS, TEN and drug-induced hypersensitivity syndrome (DIHS) in a Japanese population (10), and HLA-A*32:01 allele is associated with the development of vancomycin induced DRESS in a European population (11). Although particular HLAs have been found to be associated with DRESS syndrome, it is important to note that they are also associated with other severe cutaneous adverse reactions, and none have been found that are predictive solely of DRESS syndrome (9). Additionally, HLA alleles seem to be drug dependent and ethnicity dependent in their predisposition to DRESS.

DRESS is often associated with the reactivation of HHV-6, and this reactivation often correlates to a worsening of symptoms even after cessation of the offending drug (9). Studies have detected HHV-6 DNA in blood and solid organs of DRESS patients after initial HHV-6 testing was negative (12), (13). EBV, HHV-7, and CMV reactivation have also been reported (14), (13), (9). How the reactivation of herpes viruses contribute to the pathophysiology and mechanism of DRESS is not yet fully understood and remains an area of further study.

The mainstay for treatment of DRESS syndrome involves identification and immediate cessation of the offending drug if the patient is still taking it. If the patient is no longer taking the drug, strict avoidance of future use is advised. As DRESS syndrome is thought to be an aberrant immune response, systemic corticosteroids are the recommended treatment. Prednisone is the common first line agent, but intravenous methylprednisolone may be used in refractory cases (1). Due to the high tendency for relapse, steroids should continue a lengthy taper for 6-8 weeks (1). Supportive therapy is a crucial element of treatment, and should include stabilizing hemodynamics, fever reduction, and emollients and topical steroids (1). Other immunosuppressants have been utilized, and recent literature suggests there may be a role for the use of cyclosporine in DRESS syndrome, as it is an area of current investigation (15).

Prognosis of DRESS varies, with the majority recovering completely, but others suffering long term organ and treatment related damage (1,16). DRESS syndrome carries a mortality rate of 10% (16). Outpatient follow up is important for corticosteroid tapering and long term sequelae including organ damage and infections from immunosuppression (16). Follow up recommendations include a review of systems and laboratory evaluation with a complete blood count with differential and liver function testing every 1-2 weeks until normalization (17). Monthly monitoring of glucose and thyroid function are recommended for 3 months post-discharge (17).

This case highlights the importance of a thorough investigation into patient history. This is especially true in the fast-paced environment of hospital medicine. Now more than ever, medicine relies on predetermined order sets, checklists, and increasing technology. However, it is imperative we do not forget about the power of an in-depth history at bedside. Patient's will often lead the clinician to the diagnosis if they take the time to listen. This patient had the opportunity to be started on treatment much sooner, had her medication history been initially elucidated upon hospital admission.

Notes

Potential conflicts of interest: The author reports no conflicts of interest in this work.

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