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DERMATOLOGY
DILEMMAS

Column Editor: Nicole Martinez, MSN, RN, FNP-BC, ENP-C, PHN

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Allopurinol-Induced Drug Reaction With Eosinophilia and Systemic Symptoms
A Case Report

Charlene M. Myers, DNP, MSN, CNS, BC-ACNP
Jennifer J. Miller, DNP, ACNP-BC, CVNP-BC
Wesley D. Davis, DNP, ENP-BC, FNP-BC, AGACNP-BC, CEN

ABSTRACT
Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is an uncommon yet serious adverse cutaneous drug reaction that results from a hypersensitivity reaction. Drug reaction with eosinophilia and systemic symptoms is often misdiagnosed because of vague and confounding signs and symptoms. The most common clinical manifestations of DRESS are shared with many other diseases and include rash, lymphadenopathy, and fever. Because the syndrome can be difficult to diagnose, patients are often in the late stages of the disease process before treatment is initiated. The mainstay of treatment is stopping the culprit medication. Drug reaction with eosinophilia and systemic symptoms is associated with a high mortality rate, most often from liver failure and failure to diagnose. Emergency providers should be able to recognize the clinical manifestations of DRESS, know what diagnostic studies are indicated, and be familiar with the appropriate treatment.
Key words: differential diagnosis, drug eruptions, drug hypersensitivity syndrome, eosinophilia

ADVERSE CUTANEOUS DRUG Reactions encompass a number of reactions that vary in clinical presentation and severity. These reactions result from exposure to a drug that may cause an undesirable change in the structure or function of the skin and other adverse events. Adverse cutaneous drug reactions encompass a wide variety of clinical presentations that range from a mild skin rash to life-threatening hypersensitivity reactions. The purpose of this case presentation is to discuss the commonly overlooked syndrome of drug reactions with eosinophilia and systemic symptoms (DRESS) and highlight the importance of early diagnosis to achieve positive outcomes.

Although the name DRESS had not yet been coined, in year 1938 Meriritt and

Author Affiliation: *College of Nursing, University of South Alabama, Mobile, Alabama.*

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Corresponding Author: *Wesley D. Davis, DNP, ENP-BC, FNP-BC, AGACNP-BC, CEN, College of Nursing, University of South Alabama, Mobile, AL 36688 (wesleydavis@southalabama.edu).*

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Putnam described symptoms similar to DRESS in patients taking anticonvulsants. In 1950, drug-induced hypersensitivity syndrome was described as a triad of fever, rash, and multiorgan failure occurring after starting aromatic anticonvulsant therapy (Chaiken, Goldberg, & Segal, 1950). With the discovery of associated eosinophilia and additional causative drugs were noted, the syndrome was later renamed DRESS. Drug reaction with eosinophilia and systemic symptoms is a rare and potentially life-threatening drug reaction that can lead to multiorgan failure (Behera, Das, Zavier, & Selvarajan, 2018). After exposure to a causative drug, reactions may include fever, widespread skin eruptions, hematologic abnormalities, lymphadenopathy, and single- or multiple-organ involvement, which may result in a high mortality rate (Cho, Yang, & Chu, 2017). Many drugs have been associated with this clinical syndrome including anticonvulsants (phenytoin, carbamazepine, phenobarbital, lamotrigine), antibacterial sulfonamides (trimethoprim–sulfamethoxazole), other antibiotics (minocycline, dapsone), antirheumatic drugs (sulfasalazine, gold salts), antiretrovirals (abacavir), and xanthine oxidase inhibitors (allopurinol) being the most common (see Table 1; Behera et al., 2018). Biologically active metabolites from the culprit drugs are thought to be responsible for a delayed-type hypersensitivity reaction leading to the signs and symptoms characteristic of the syndrome.

EPIDEMIOLOGY

The incidence of DRESS is estimated between one in 1,000 and one in 10,000 drug exposures and has a mortality rate of around 5%–10%, with liver failure being the most common cause of death (Wolfson et al., 2019). In the United States, DRESS prevalence is approximately 2.18 per 100,000 patients (Wolfson, et al., 2019). In the West Indian population, there is an estimated incidence of 0.9/100,000 (Adwan, 2017). Drug reaction with eosinophilia and systemic symptoms is more common in adults and is associated with average median inpatient stay of 9 days (Wolfson et al., 2019).

PATHOPHYSIOLOGY

The pathophysiology of DRESS syndrome is not fully known but is thought to include

Table 1. Drugs associated with drug reaction with eosinophilia and systemic symptoms syndrome

Categories	Common drug names
Antibiotics	Amoxicillin, ampicillin, azithromycin, levofloxacin, minocycline, piperacillin/tazobactam, vancomycin
Sulfonamides	Sulfamethoxazole-trimethoprim, sulfasalazine
Antidepressants	Fluoxetine
Anticonvulsants	Carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin
Antiretrovirals	Abacavir, nevirapine
Anti-hepatitis C agents	Boceprevir, telaprevir
Antituberculosis agents	Ethambutol, isoniazid, pyrazinamide, rifampin
Analgesics	Acetaminophen, NSAIDs
Uric acid lowering agents	Allopurinol, febuxostat
Sodium channel blockers	Mexiletine
Antineoplastic agents	Imatinib, dorafinib, vismodegib, Vemurafenib
Proton pump inhibitors	Omeprazole
Novel oral anticoagulants	Rivaroxaban

Note. NSAIDS = nonsteroidal anti-inflammatory drugs.

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both immunologic and nonimmunologic factors. A key factor is a strong, drug-specific immune response, specifically activation of T cells. Contributing factors may include dysfunctional drug detoxification pathways, which may lead to accumulation of harmful metabolites in the liver leading to a systemic inflammatory state (Sevinc, Tasar, & Buyukkurt, 2019). T-cell activation, possibly drug-specific T cells in some individuals, may be induced by this inflammatory cascade. In particular, $CD4^+$ cells release type 2 cytokines leading to eosinophil activation, which causes eosinophilia and DRESS syndrome.

Hypersensitivity to these metabolites may also cause reactivation of the herpes virus, in particular, human herpes virus 6 and 7 (HHV-6 and HHV-7), Epstein–Barr virus (EBV), and cytomegalovirus (CMV). The offending agent may cause the release of proinflammatory cytokines and chemokines causing a "cytokine storm," leading to HHV-6 reactivation.

This reactivation involves expansion of antidrug specific $CD4^+$ and $CD8^+$ T lymphocytes, which may result in end-organ damage (Adwan, 2017; James, Sammour, Virata, Nordin, & Dumic, 2018).

There is a tendency for genetic predisposition and risk of hypersensitivity reactions to certain human leukocyte antigens (HLAs), particularly HLA-B in certain populations. There is a direct interaction between the drug and antigen-binding cleft of the HLA-B molecule. This HLA-drug (hapten) is presented to the T cells via the T-cell receptor. These molecules are perceived as foreign and elicit a massive activation of CD8 T cells (Behera et al., 2018). The American College of Rheumatology recommends HLA testing in certain populations (Korean, Han Chinese, and Thai) that are at risk of hypersensitivity reactions before starting certain medications such as allopurinol (Papadakis, Stephen, & Rabow, 2019).

CASE

Chief complaint: Rash with fever.

History of Present Illness

The patient is a 68-year-old man of Han Chinese descent presenting to the emergency department (ED) for a rash and fever that started 2 days ago and has gradually worsened. The onset of the fever coincided with the appearance of a rash on his shoulders and neck. Over the last 48 hr, the rash has started itching and it has progressed to involve his chest, abdomen, upper back, arms, and face. His wife notes that his face appears swollen. Now he reports that the rash is intensely pruritic and somewhat painful.

He denies the use of any new bath soaps, laundry detergents, or lotions that would raise suspicion of contact dermatitis. Upon review of his medical history, he states that 3 weeks before the rash began, he was started on allopurinol 100 mg daily by mouth for hyperuricemia that was discovered on routine laboratory work. He denies any known sick contacts or household members with similar symptoms. Over-the-counter remedies such as acetaminophen and diphenhydramine have done little to abate his symptoms.

Past Medical and Surgical History

The patient's medical history is significant for hypertension, hyperlipidemia, coronary artery disease, diabetes mellitus type 2, and hyperuricemia without acute gouty arthritis. Previous surgical procedures include an inguinal hernia repair and coronary artery bypass grafting in the remote past.

Current Medications

Allopurinol 100 mg PO daily (Metoprolol) 50 mg PO twice daily
Lisinopril/hydrochlorothiazide 20/25 mg PO daily, aspirin 81 mg PO daily, atorvastatin 80mg PO daily
Metformin 500 mg PO twice daily

Allergies

The patient describes a nonanaphylactic-type skin rash to penicillin. He denies additional medication, food, or environmental allergies.

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Family and Social History

His family history was noncontributory to the chief complaint. The patient is a former 1.5 pack per day smoker for 40 years, quitting approximately 4 years ago. He denies alcohol and illicit drug use.

Review of Systems

The review of systems is positive for fever, chills, malaise, facial edema, generalized lymphadenopathy of the neck, and a diffuse pruritic rash. He denies headaches, visual changes, trouble swallowing, chest pain, dyspnea, abdominal pain, joint pain, or extremity edema.

Physical Examination—Key Findings

Vital signs: Heart rate 105 beats per minute, blood pressure 150/82 mmHg, temperature 102.2 °F, respiratory rate 22 breaths per minute, O_2 saturation 98% on room air, height 6 ft. 1 in., weight 180 lb

General: An acutely ill appearing, well-nourished male

Skin: An erythematous, maculopapular rash present to the face, trunk, and all extremities. The rash is nontender to palpation and blanches with slight pressure. No desquamation is present.

Face/Mouth: The oral mucosa is erythematous, but no ulcerative lesions are present. Nonpitting and symmetrical facial edema is present; however, there is no oropharyngeal, uvular, lingual, or sublingual edema noted.

Thorax/Lungs: Respirations are regular, even, and nonlabored. Lungs are clear to auscultation in all fields bilaterally.

Cardiovascular: No pericardial friction rub is heard. Radial and pedal pulses are strong and equal.

Abdomen: The liver is palpable at 2 cm below the costal margin with mild tenderness to palpation. No palpable splenomegaly.

Lymphatic: Approximately 1.5-cm lymphadenopathy present throughout the posterior cervical, anterior cervical, and supraclavicular chains.

Neurologic: He is alert and oriented to person, place, time, and events.

Initial Management and Findings

The patient presented to the ED with pyrexia, hypertension, and tachycardia and appeared to be acutely ill. He had mild pain associated with his rash but reported generalized and intense pruritus as the dominating complaint. During the initial assessment, he did not have any signs or symptoms of airway compromise. Given his vital signs and chief complaint, the sepsis alert protocol was triggered and used to help guide his initial evaluation and treatment. There was also a concern for additional life-threatening emergencies, such as anaphylaxis but this was quickly ruled out by a thorough history and physical.

Laboratories were collected according to the sepsis protocol and included a complete blood count with blood smear, comprehensive metabolic panel, C-reactive protein, urinalysis, prothrombin time, partial thromboplastin time, and two sets of blood cultures. Pertinent results included a mild leukocytosis, an eosinophil count of 1,400 per microliter, atypical lymphocytes on the blood smear, creatinine of 3.2 mg/dl, transaminitis, a significantly elevated C-reactive protein, and mild proteinuria. Then, due to the transaminitis, a gamma-glutamyl transferase level and hepatitis A, B, and C panels were obtained. Given the palpable hepatomegaly, a complete abdominal ultrasonogram was obtained and resulted as moderate hepatomegaly. In addition, a chest radiograph and 12-lead electrocardiogram (ECG) were obtained. The chest radiography was negative, and the ECG showed a sinus tachycardia.

On initial presentation, a 30 ml/kg bolus of 0.9% normal saline and acetaminophen 1 g orally were administered. After consultation with other health care providers, and based upon the history of recent allopurinol initiation, the patient presentation, and preliminary diagnostic data, a presumptive diagnosis of DRESS syndrome was suspected. At this time, the allopurinol was stopped,

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and diphenhydramine 50 mg and methylprednisolone 125 mg were administered intravenously. Specialty consultations were obtained, and he was admitted to the critical care unit for further treatment.

Treatment Course and Outcome

Upon admission, the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) criteria, a tool designed to aid the diagnosis of DRESS, was used and revealed a score of 7, corresponding with a definite case of DRESS syndrome (see Table 2). Polymerase chain reaction testing for EBV, CMV, and HHV-6 and -7 was performed and reported negative, thus increasing the RegiSCAR score to 8. Dermatology performed punch biopsies of the rash and revealed infiltration of atypical lymphocytes, eosinophils, and leukocytoclastic vasculitis. Nephrology performed a renal biopsy that demonstrated interstitial nephritis. An echocardiogram was obtained to rule out cardiac involvement and was reported as negative.

The patient was started on hydrocortisone 0.1% topically twice daily and prednisolone 80 mg (1 mg/kg) daily with plans to gradually taper over several months. On hospital day 2, exfoliation of the lower extremities ensued, and the patient's temperature maxed at 103 °F. Supportive treatment was continued and on hospital day 3, hemodialysis was required because of worsening renal function

Table 2. RegiSCAR score

	Score			
Criteria	**−1**	**0**	**1**	**Additional information**
Temperature greater than 101.3 °F	N/U	Y		
Lymphadenopathy		N/U	Y	More than 1 cm and more than two different areas
Eosinophils greater than 0.7×10^9/L or greater than 10% if white blood cell count is less than 4.0×10^9/L		N/U	Y	Score 2 points if greater than 1.5×10^9/L or greater than 20% if white blood cell count is less than 4.0×10^9/L
Atypical lymphocytosis		N/U	Y	
Skin rash greater than 50% of body surface area		N/U	Y	Rash suggestive of DRESS:
Suggestive of DRESS	N	U	Y	More than two of the following: purpuric lesions (other than legs), infiltration, facial edema, psoriasiform desquamation
Skin biopsy suggestive of DRESS	N	U/Y		
Organ involvement		N	Y	Score 1 point for each organ involved with a maximum of 2 points
Rash resolution in more than 15 days	N/U	Y		
Other causes excluded		N/U	Y	Score 1 point if three of each of the following are negative: Hepatitis A, hepatitis B, hepatitis C, mycoplasma, chlamydia, antinuclear antibody, blood cultures

Note. DRESS = drug reaction with eosinophilia and systemic symptoms; N = no; RegiSCAR = Registry of Severe Cutaneous Adverse Reactions; U= unknown; Y= yes. Retrieved from Creative Commons Attribution 4.0 International. https://creativecommons.org/licenses/by/4.0/. No changes were made.

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and severe hyperkalemia. After 1 week, the patient's laboratory results improved, the fever resolved, and the cutaneous manifestations were significantly improved. At the 2-week interval, the patient had a relapse of cutaneous symptoms and fever corresponding to the first trial of prednisone reduction. The prednisone dose was increased and the patient improved again. The patient was discharged on day 20 with the rash completely resolved and normalized liver function. Renal dysfunction persisted for approximately 5 weeks after discharge, requiring intermittent hemodialysis. At the 3-month interval, he was still on low-dose corticosteroid therapy and was off dialysis with a return of renal function to near baseline. There were no further relapses found during follow-up.

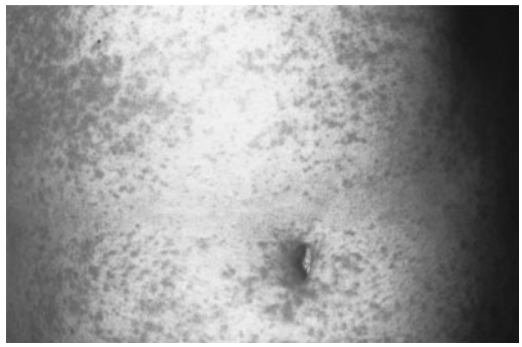

Figure 1. Cutaneous rash.
Note. From "Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS): An Interplay Among Drugs, Viruses, and Immune System," by Cho, Y.-T. & Yang, C.-W., & Chu, C.-Y, 2017, *International Journal of Molecular Sciences, 18*, p. 1243. doi:10.3390/ijms18061243. Retrieved from the CDC Image Library.

DISCUSSION

This case illustrates an aggressive presentation of DRESS syndrome. With DRESS, the symptoms are highly variable, which often leads to a missed diagnosis. The prodromal symptoms of DRESS are typically fever, malaise, pruritus, and tender lymphadenopathy that occur 2–8 weeks after the initiation of a new medicine. As the condition progresses, the patient may have a combination of high fever, skin eruptions, eosinophilia, lymphadenopathy, and visceral organ involvement.

Although the skin may not be involved in rare cases, most patients develop a characteristic rash that starts as a morbilliform eruption and spreads diffusely over the body (see Figure 1). Typically, the face and upper extremities have the first lesions. Drug reaction with eosinophilia and systemic symptoms should be considered with more than 50 percent of the body surface area involved. In a subset of patients, the erythematous rash will progress to an exfoliative dermatitis evidenced by flaking or scaling of the skin. The mucosa may be involved but is usually limited to a single site such as the mouth, throat, or lips. In contrast to Stevens–Johnson syndrome and toxic epidermal necrolysis, the mucosal involvement of DRESS does not progress to erosions or skin sloughing. Symmetric facial edema associated with erythema is also a hallmark feature, which can be found in up to 76% of patients (Cho et al., 2017).

Internal organ involvement is commonly observed in patients with DRESS syndrome (see Table 3). Approximately 90% of patients will have at least one organ affected and approximately 60% of patients will have two or more organs involved (Kardaun et al., 2013). Liver involvement is the most common, tends to be the most severe, and lasts longer. In patients with DRESS and acute liver failure, there is increased mortality (Martinez-Cabriales, Shear, & Gonzalez-Moreno, 2019). Renal involvement is noted in up to 40% of DRESS cases. In contrast to liver injury, renal injury is usually mild and recovers without any sequelae. Lung, cardiac, and neurologic involvement is the least prevalent (Cho et al., 2017).

Diagnosis

Although a gold standard for diagnosis of DRESS syndrome is lacking, prompt recognition is imperative to prevent possible organ failure and death. A thorough history should

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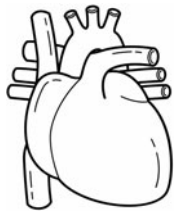
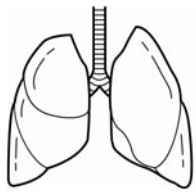
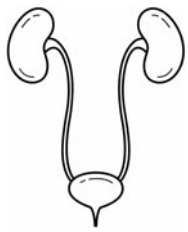
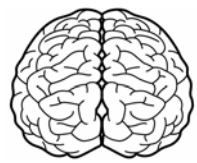
Table 3. Organ involvement in drug reaction with eosinophilia and systemic symptoms syndrome

	Liver is the most common organ involved.	• Hepatomegaly • Transaminitis • Hepatitis • Hepatic failure • Jaundice
	Cardiac manifestations are often missed in the work-up.	• Myocarditis • Pericarditis
	Pulmonary abnormalities are present in 5%–25% of cases.	• Interstitial pneumonitis • Spontaneous pneumothorax and pneumomediastinum • Interstitial pneumonia • Adult respiratory distress syndrome
	The kidneys are involved in approximately 10% of cases.	• Elevated blood urea nitrogen • Elevated creatinine • Eosinophils in the urine • Low-grade proteinuria • Interstitial nephritis
	Neurologic abnormalities are rare.	• Meningitis • Encephalitis • Cerebral edema • Seizures • Cranial nerve palsies

be performed to help determine the cause. Clinicians should suspect DRESS in any patient who presents with fever, rash, and a new medication or change in medication within the last 2 months. If DRESS is suspected, ask in detail about all medications taken recently by the patient. Because of the variation in presentation, the clinical diagnosis can be difficult and, in many cases, requires a high degree of suspicion and clinical judgment especially if the patient has been taking the high-risk medications or if the patient has eosinophilia and elevated liver enzymes.

Because of the complexity of the syndrome and often vague presentation, several tools have been proposed to help standardize the diagnosis and management of DRESS. Using a scoring system, the RegiSCAR group developed a system to aide clinicians in making the diagnosis of DRESS. The RegiSCAR scoring system is the most used and widely accepted tool. The tool distributes scores on the basis of clinical features and classifies them as "no"

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(score less than 2), "possible" (score 2–3), "probable" (score 4–5), and "definite" (score greater than 5; Kardaun, et al., 2007). Another tool developed by a Japanese consensus group offers a different set of diagnostic criteria (Shiohara, Iijima, Ikezawa, & Hashimoto, 2007). Use of this Japanese model is limited because it requires laboratory measurement of HHV-6, a test that is not routinely available. The main difference between the RegiSCAR tool and the Japanese model is that in the Japanese model, patients who test negative for HHV-6 do not meet the criteria for diagnosis of DRESS syndrome. We recommend using the RegiSCAR tool for all patients who may have DRESS.

Standard diagnostic testing is essential in patients suspected of having any type of drug-induced hypersensitivity reaction and is aimed at helping confirm the diagnosis, rule out other conditions, and detect the extent and severity visceral organ involvement (see Table 4). Laboratory tests should include a complete blood cell count with differential and peripheral blood smear, liver function tests, electrolytes, serology for viral hepatitis, serum creatinine, C-reactive protein, and testing for viruses such as EBV and HHV-6 and -7 IgG titers when available. As previously mentioned, based on the Japanese criteria for diagnosing DRESS, laboratory results positive for reactivation of HHV-6 may be used as confirmation of the diagnosis (Shiohara et al., 2007).

Imaging of the heart, lungs, and abdominal organs should be considered. In patients with pulmonary symptoms, a chest radiograph or computed tomographic (CT) scan should be obtained to assess for pleural effusions, pneumonia, and pneumonitis. An ultrasonogram or CT scan of the abdomen may be necessary to rule out other causes of elevated liver enzymes. If the patient has any symptoms suggestive of cardiac involvement, an ECG should be obtained.

Differential Diagnosis

Differentiating DRESS syndrome from other similar clinical conditions is complicated because it is a diagnosis of exclusion. The cardinal features of DRESS, such as rash and fever, are shared with a near-infinite number of other disease processes. The differential diagnosis of DRESS syndrome includes other severe cutaneous drug eruptions, such as Stevens–Johnson syndrome and toxic epidermal necrolysis (see Table 5). Viral or bacterial infections (viral exanthemas, staphylococcal and streptococcal shock syndromes,

Table 4. Laboratory results suggestive of DRESS

Test	Findings suggestive of DRESS
Complete blood count with differential	Eosinophilia greater than 700 per microliter Lymphocytosis greater than 4,500 per microliter
Peripheral blood smear	Atypical lymphocytes
Liver function	ALT more than twice the upper limit Alkaline phosphatase more than 1.5 times the upper limit
Urinalysis	Proteinuria Hematuria Eosinophils in the urine
Kidney function	Creatinine more than 1.5 times the basal level
Serology for viral hepatitis (hepatitis A IgM antibody, hepatitis B surface antigen, hepatitis B core IgM antibody, hepatitis C viral RNA)	Negative

Note. ALT = alanine aminotransferase; DRESS = drug reaction with eosinophilia and systemic symptoms.

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Table 5. Differentiating DRESS from Stevens–Johnson syndrome and toxic epidermal necrolysis

	DRESS	SJS and TEN
Onset after drug exposure	2–8 weeks	A few days
Duration	2–4 months	2–4 weeks
Skin manifestations	Facial edema, no bullae, morbilliform rash, pustules, exfoliative dermatitis	Necrosis, bullae, target lesions
Mucosal involvement	Absent	Severe
Fever	Severe	Minimal to absent
Lymphadenopathy	Localized or generalized	Absent
Hepatic involvement	Severe	Minimal
Eosinophilia	Severe	Absent
Organ involvement	Heart, lungs, kidneys	Absent
Mortality	10%	30%

Note. DRESS = drug reaction with eosinophilia and systemic symptoms; SJS = Stevens–Johnson syndrome; TEN = toxic epidermal necrolysis.

meningococcemia), autoimmune connective disease (Kawasaki disease, Still's disease, hypereosinophilic syndrome), and neoplastic disease (lymphoma, leukemia cutis, mycosis fungoides) may also present with skin eruption, fever, and systemic symptoms that mimic DRESS (James et al., 2018). Regardless of signs and symptoms, an important factor in diagnosing DRESS is establishing a correlation between the signs and symptoms and a causative drug. Often, the signs and symptoms of DRESS appear after a long latency period or patients have paradoxical worsening after the offending drug has been discontinued.

Treatment

There are no specific treatment guidelines for the management of DRESS syndrome. The mainstay of treatment in the ED is prompt recognition and discontinuation of the offending drug (Mockenhaupt, 2019). Early withdrawal of the causative agent leads to better outcomes and is the most important intervention. In mild to moderate cases, without organ involvement, patients can be treated symptomatically. Topical steroids for the rash and topical or systemic antihistamines for pruritus are usually sufficient (James et al., 2018).

For patients with visceral organ involvement, systemic corticosteroids are the mainstay of treatment. Medium to high doses of systemic corticosteroids are recommended (e.g., 0.5–1.0 mg/kg/day of prednisone or prednisone equivalent) until there is clinical improvement and laboratory normalization and stabilization (Sevinc et al., 2019). A gradual tapering dose of the corticosteroid is recommended over the next 8–12 weeks to avoid a risk of relapse and development of long-term autoimmune consequences. There is no consensus on which patients should receive systemic corticosteroids.

In life-threatening cases, intravenous immunoglobulin may be used; however, the evidence has conflicting results. Intravenous immunoglobulin has been beneficial to some and detrimental to others; therefore, the decision should be made on a case-to-case basis (Cho et al., 2017). Additional supportive measures may include antipyretics for fever, fluid, and electrolyte replacement; nutritional support and skin care with warm baths; wet dressings; and emollients (Behera et al., 2018).

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CONCLUSION

Drug reaction with eosinophilia and systemic symptoms syndrome is a rare, complex, and potentially fatal drug-induced hypersensitivity reaction that includes skin eruption, hematologic abnormalities, fever, lymphadenopathy, and internal organ involvement. The diagnosis of DRESS, especially in the early stages, can be a challenge because of the wide variation of clinical presentation and similarity with other commonly seen conditions. Emergency providers should be suspicious of DRESS in anyone who presents with a fever, rash, and a change in medication over the past 2 months, especially high-risk medications. A thorough history and physical examination are critical to making the diagnosis. In the ED, the lifesaving intervention is stopping the culprit drug.

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