PennState Journal of Medicine

An atypical case of recurrent DRESS syndrome

Sa Do Kang, MD, PhD[1]; Erin Bell, MD[1]; Lauren W. Kaminsky, MD, PhD[2]; Gisoo Ghaffari, MD[2]

[1]Pennylvania State College of Medicine, Hershey, PA; [2]Section of Allergy, Asthma, and Immunology, Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Pennsylvania State College of Medicine, Hershey, PA

KEYWORDS: DRESS syndrome, cutaneous drug reactions, iohexol

Abstract

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a severe cutaneous adverse reaction that occurs after exposure to a causative drug. DRESS can be associated with organ involvement and in severe cases can be fatal. We present the case of a 62-year-old woman with a history of recurrent rash with preceding fever and hypotension during three separate hospitalizations. Diagnostic workup revealed findings consistent with DRESS syndrome with atypical features including acute onset of symptoms and hypotension. A chronological history of symptoms and events throughout the three hospitalizations revealed the likely causative agent as intravenous (IV) iohexol. This case highlights the challenge of diagnosing a condition with an etiology that relies heavily on clinical suspicion. Prompt diagnosis of DRESS syndrome is important as outcomes in DRESS syndrome can be severe including end-organ damage and death. Treatment includes cessation of the causative agent and consideration for corticosteroids.

Learning Objectives

1. Identify challenges involved in diagnosing cutaneous drug reactions
2. Distinguish DRESS syndrome from other etiologies of cutaneous drug reactions
3. Recognize atypical features of DRESS syndrome that may confound the diagnosis

Introduction

Cutaneous adverse drug reactions are common causes of skin lesions with an estimated 1.8 to 7 cutaneous adverse drug reactions occurring per 1,000 hospitalized patients[1]. Other etiologies of skin rashes, including infection, malignancy, and autoimmune disorders, should be considered, particularly when a culprit medication is not easily identified. Identifying the etiology of rash is important for providing appropriate treatment.

Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a type IV hypersensitivity reaction that typically occurs 2-8 weeks after drug exposure[2,3]. Most common causative medications include antiepileptic drugs, allopurinol, and antimicrobials[2,4]. Iohexol is an iodinated contrast agent used in computed tomography (CT) imaging, and cases of iohexol-induced DRESS syndrome have been reported[3,5-7]. While symptoms can vary, DRESS syndrome typically presents with rash, eosinophilia, and organ involvement, such as kidney or liver[1-4,8]. Here, we present a case of recurrent episodes of DRESS syndrome with atypical features, including acute onset and hypotension, likely caused by iohexol.

Case Report

A 62-year-old woman with stable retroperitoneal lymphadenopathy (LAD) and previous venous thromboembolism presented with fatigue and dyspnea during a third hospital admission to our medical center. CT for pulmonary emboli (CT-PE) with iohexol was without evidence of new PE. She developed a fever to 38.7° Celsius (C) and hypotension, approximately eight and ten hours after imaging, respectively (**Table I**). Hypotension resolved with IV fluids. Due to concern for infection, she received a dose of IV ciprofloxacin and metronidazole, after which a diffuse, erythematous, macular, and pruritic rash developed covering more than 50% of the body-surface area (BSA). There was no mucosal involvement, blisters, pustules, or skin sloughing.

History was significant for two previous hospitalizations during which she developed similar rashes, fever, and hypotension. Approximately one year prior, she was admitted with a two-week history of cough and

DOI: 10.26209/psjm62458

Table I. Time (in hours) to onset of fever, hypotension, and rash after intravenous iohexol administration during three separate hospital admissions

Sign/Symptom	Admission 1	Admission 2	Admission 3
Fever	32	20	8
Hypotension	38	22	10
Rash	47	30	20

dyspnea and was found to have bilateral PE by CT-PE with iohexol. The following day, she developed a temperature to 38.2°C and hypotension, approximately 32 and 38 hours after the CT-PE, respectively (**Table I**). Subsequently, linezolid, aztreonam, and azithromycin were started due to concern for infection. She developed a diffuse erythematous rash involving >50% BSA and facial edema 47 hours after CT-PE (**Table I**). Fever peaked at 39.1°C on hospital day four, and antibiotics were discontinued as no infection was identified. Laboratory findings included acute kidney injury (AKI) and eosinophilia (1.13 K/μL). DRESS syndrome was diagnosed, and she was discharged on a corticosteroid taper.

Two months prior to this hospitalization, she was admitted with dyspnea with CT-PE with iohexol revealing multiple new PE. She developed fever to 38.6°C and hypotension, approximately 20 and 22 hours following imaging, respectively (**Table I**). Due to concern for infection, she received IV ciprofloxacin and metronidazole, with antibiotics escalated to linezolid and clindamycin on day three and four, respectively. Vasopressors were initiated for hypotension. Approximately 30 hours after CT-PE, she developed diffuse erythema on >50% BSA and facial edema without mucosal involvement, blistering, pustules, or skin sloughing (**Table I**). Bloodwork showed eosinophilia (0.83 K/μL) and AKI. Liver function tests were unremarkable. Skin biopsy showed perivascular lymphocytic infiltrate with numerous interstitial eosinophils in the dermis consistent with DRESS syndrome. Examination and work-up were negative for SJS/TEN, HIV, and Human Herpesvirus (HHV)-6 reactivation. With concern for DRESS syndrome and no infection identified, antibiotics were discontinued on day five. Methylprednisolone was started on day six. The rash, eosinophilia, and AKI resolved by discharge.

This admission, labwork revealed an AKI with creatinine of 2.3 mg/dL (baseline 1.4 mg/dL), leukocytosis (20,900 K/μL), and elevated total bilirubin (2.0 mg/dL). The eosinophil count on admission was unremarkable. Blood cultures showed no growth. Work-up was negative for HHV-6 and HHV-7, cytomegalovirus (CMV), and Epstein-Barr Virus (EBV), suggesting no viral reactivation. Retroperitoneal and mediastinal LAD were unchanged from 1 year prior.

Approximately one hour after the rash erupted, antibiotics were discontinued with concern for drug reaction given her history of two similar episodes diagnosed as DRESS syndrome. She was started on oral corticosteroids. An extended corticosteroid taper was recommended; however, she declined corticosteroids after the second dose. Three days after the last corticosteroid dose, the eosinophil count increased to 710/μL. For pruritus, topical triamcinolone and cetirizine were prescribed as needed. Oncology was consulted due to concern for possible malignancy in the setting of previous venous thromboembolic events, recurrent rash and fever, and LAD. Suspicion for malignancy was low since the LAD remained stable over one year and the fever and rash likely occurred with medication triggers. She declined further malignancy work-up and was discharged on hospital day six with improvement of symptoms.

Discussion

Cutaneous allergic drug reactions account for approximately 3-7% of hospitalizations or referrals from primary care physicians and can pose a challenge as identifying the causative agent can be difficult[8]. Differential for cutaneous eruptions with similarity to DRESS syndrome includes SJS/TEN, acute generalized exanthematous pustulosis (AGEP), hypereosinophilic syndrome, angioimmunoblastic T cell lymphoma, and acute cutaneous drug-induced lupus erythematosus[1,8,9]. We describe a patient who developed fever, hypotension, eosinophilia, AKI, and erythematous macular rash that covered >50% BSA during three separate hospitalizations following iohexol administration. While both SJS/TEN and DRESS are Type IV hypersensitivity reactions, SJS/TEN is characterized by painful rash with bullae or vesicles and mucosal membrane involvement[1,8]. The lack of blistering and mucous membrane involvement made SJS/TEN unlikely. As no pustules were evident, AGEP was ruled out as a possible diagnosis. Angioim-

DOI: 10.26209/psjm62458

Table II. Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) validation scoring system results for this patient.

RegiSCAR Criteria (scoring points)	Patient Score		
	Admission 1	Admission 2	Admission 3
Fever (≥ 38.5 ℃) No=-1, Yes=0, Unknown--1	0	0	0
Enlarged lymph nodes (≥2 sites, ≥1cm) No=0, Yes=1, Unknown=0	1*	1*	1*
Atypical lymphocytes No=0, Yes=1, Unknown=0	0	0	0
Eosinophilia Unknown=0,<700 or <10%=0, 700-1499 or 10-19%=1, >1500 or >20%=2	1	1	1
Skin rash: extent >50% of BSA No=0, Yes=1, Unknown=0	1	1	1
Skin rash: morphology (facial edema, scaling) No=0, Yes=1, Unknown=0	1	1	1
Skin rash: biopsy suggesting DRESS No=-1, Yes=0, Unknown=0	0	0	0
Internal organ involvement Unknown=0, None=0, One organ=1, Two or more organs=2	1 (kidney)	1 (kidney)	1 (kidney)
Resolution in more than 15 days No=-1, Yes=0, Unknown=-1	-1 (unknown)	-1 (unknown)	-1 (unknown)
Exclusion of other causes ≥3 of below are investigated and no positive result found Hepatitis A/B/C Mycoplasma-/Chlamydia pneumoniae Blood cultures Other infections ANA No=0, Yes=1, Unknown=0	0	0	0
Final Score <2=Diagnosis of DRESS not met 2-3 Diagnosis of DRESS Possible 4-5 Diagnosis of DRESS Probable >5 Definite diagnosis of DRESS	**4**	**4**	**4**

ANA, anti-nuclear antibody; BSA, body surface area; DRESS, drug reaction with eosinophilia and systemic symptoms

* the patient had persistent generalized lymphadenopathy, which appeared stable throughout the three admissions, making it difficult to assess the role of lymphadenopathy in this case.

munoblastic T-cell lymphoma, while rare, was considered due to symptoms of LAD, rash, fevers in the setting of previous venous thromboembolism. However, likelihood of lymphoma was low due to stable LAD and association of fever and rash with medication trigger. Hypereosinophilic syndrome can also present with eosinophilia, skin involvement, and end-organ damage; however, this diagnosis was less likely as the eosinophil count never exceeded 1.5 K/μL and eosinophilia did not persist. Acute cutaneous drug-induced lupus erythematosus was considered, but was not consistent with the generalized cutaneous involvement, and the facial rash was not in the characteristic malar distribution[9].

Based on work-up including the Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) scoring system for DRESS, the most likely diagnosis for all three admissions was DRESS syndrome (**Table II**)[2]. Fever and hypotension may have been the first symptoms of DRESS syndrome caused by iohexol since administration of iohexol directly preceded the onset of fever and hypotension during all three admissions (**Table I**). DRESS syndrome is characterized by skin eruption typically involving 50% or more of the BSA[2,3], and has been associated with reactivation of HHV-6, HHV-7, CMV, and EBV[1,2,4,10]. Common laboratory findings include leukocytosis with eosinophilia and atypical lymphocytes[2-4,8]. Involvement of at least one internal

DOI: 10.26209/psjm62458

organ is common, frequently the liver or kidney[2-4]. In this case, AKI occurred during all three hospitalizations, although hypotension cannot be ruled out as a causative factor. Based on the RegiSCAR criteria, labwork did not meet the definition of liver involvement despite mild hyperbilirubinemia[2]. Hypotension is a less common presentation and can make DRESS syndrome difficult to distinguish from other etiologies of hypotension, such as septic shock[10].

Distinguishing DRESS syndrome from other pathology is important because mortality has been reported in up to 10% of cases[3,4]. Discontinuation of the offending agent is important for treatment[2], and in this case with atypical features, identifying an offending drug proved challenging. Although patch testing and lymphocyte proliferation testing have been piloted for diagnosis, sensitivity is poor making clinical use difficult. Diagnosis of DRESS syndrome still relies heavily on clinical suspicion with careful history and physical examination.

The three episodes of DRESS syndrome occurred within 48 hours after iohexol administration (**Table I**); however, typical onset of DRESS syndrome involves a delay of 2-8 weeks following drug exposure[2,6,7]. There are reports of DRESS syndrome occurring within 15 days of exposure to iodinated contrast, including cases occurring within 2 days of iohexol exposure, demonstrating that iodinated contrast can cause DRESS syndrome with rapid onset[5-7]. In this case, time intervals between iohexol administration and fever, hypotension, and rash onset consistently decreased during each subsequent hospitalization, suggesting possible increased sensitivity with each exposure (**Table I**). While iohexol is the most likely cause of DRESS syndrome in this patient, antibiotics cannot be ruled out as possible contributing factors with antibiotics administered following onset of fever and hypotension, but prior to rash onset.

Conclusion

Cutaneous adverse drug reactions are common but can be difficult to diagnose due to overlapping features among different conditions. In this case, fever, hypotension, diffuse erythematous rash, AKI, and eosinophilia developed after exposure to iohexol during three separate hospitalizations, meeting criteria for DRESS syndrome. The symptoms of fever and hypotension presented within 48 hours of iohexol administration, which is shorter than the typical 2-8 week latency of symptom onset in DRESS syndrome. Initial symptoms of fever and hypotension preceded the typical rash by hours complicating the diagnosis. Diagnosis of DRESS syndrome and identification of the causative agent can be challenging especially with atypical presentation. Discontinuation of the causative medication is a mainstay of treatment, and topical or systemic corticosteroids can be considered depending on disease severity.

Author Information

Corresponding Author

Lauren W. Kaminsky, MD, PhD
lkaminsky@pennstatehealth.psu.edu

Author Contributions

All authors have given approval to the final version of the manuscript.

Funding Sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Disclosures

The authors declare that they have no relevant conflicts of interest.

References

1. Mockenhaupt M. Epidemiology of cutaneous adverse drug reactions. Allergol Select 2017; 1:96-108.
2. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol 2013; 169:1071-80.
3. Wang L, Mei XL. Drug Reaction with Eosinophilia and Systemic Symptoms: Retrospective Analysis of 104 Cases over One Decade. Chin Med J (Engl) 2017; 130:943-9.
4. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, et al. The DRESS syndrome: a literature review. Am J Med 2011; 124:588-97.
5. Alamri Y, Hsu B. DRESS syndrome due to iodinated contrast medium. N Z Med J 2020; 133:93-5.
6. Soria A, Amsler E, Bernier C, Milpied B, Tétart F, Morice C, et al. DRESS and AGEP Reactions to Iodinated Contrast Media: A French Case Series. J Allergy Clin Immunol Pract 2021; 9:3041-50.
7. Soria A, Bernier C, Veyrac G, Barbaud A, Puymirat E, Milpied B. Drug reaction with eosinophilia and systemic symptoms may occur within 2 weeks of drug exposure: A retrospective study. J Am Acad Dermatol 2020; 82:606-11.
8. Balakirski G, Merk HF. Cutaneous allergic drug reactions: update on pathophysiology, diagnostic procedures and differential diagnosic. Cutan Ocul Toxicol 2017; 36:307-16.
9. Okon LG, Werth VP. Cutaneous lupus erythematosus: diagnosis and treatment. Best Pract Res Clin Rheumatol 2013; 27:391-404.
10. Blumenthal KG, Patil SU, Long AA. The importance of vancomycin in drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. Allergy Asthma Proc 2012; 33:165-71.

DOI: 10.26209/psjm62458