DRESS Syndrome – Rare but Potentially Fatal Drug Reaction

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Abstract

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a rare phenomenon. Review of the literature revealed 2425 DRESS syndrome case reports and only 175 case reports secondary to allopurinol, with this being the first published report of DRESS Syndrome in the state of Hawai'i. This case report describes a Han-Chinese patient diagnosed with DRESS syndrome secondary to allopurinol use, which has been reported to be a high-risk group for allopurinol-related drug reactions. Given Hawaii's unique patient population, compromised of a large Chinese and mixed-race population, it is important to maintain a higher level of suspicion when prescribing allopurinol.

Abbreviations and acronyms

CMV = cytomegalovirus
DHS = drug hypersensitivity syndrome
DIHS = drug-induced hypersensitivity syndrome
DRESS = drug rash with eosinophilia and systemic symptoms
EBV = Epstein-Barr virus
ED = emergency department
HHV = human herpesvirus
PCP = primary care physician
QD = once a day

Introduction

Drug hypersensitivity syndrome (DHS), also known as drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, and drug-induced hypersensitivity syndrome (DIHS) was first encountered during treatment with anticonvulsant drugs in 1936, which remain the predominant cause.[1] The term 'DRESS syndrome' and its diagnostic criteria was proposed in 1996 by Bocquet et al to encompass the association with over 50 drugs.[2] This syndrome is characterized by rash, fever, lymphadenopathy, and single or multiple internal organ involvement.[1] Prompt recognition of this syndrome is crucial given its high associated mortality (10%), as the mainstay of treatment is discontinuation of the offending agent.[3]

DRESS syndrome is a rare but serious delayed T-cell mediated hypersensitivity reaction in response to certain drugs. Most frequently implicated are aromatic anticonvulsants, antidepressants, sulfonamides and sulfones, nonsteroidal anti-inflammatory drugs, antibiotics, and allopurinol.[4] It has a reported prevalence of 2.8 per 100000 adults and is estimated to occur in every 1000 to 10000 drug exposures.[4,5] However, it is thought to be underdiagnosed and underreported due to its broad clinical presentation. Common differential diagnoses include Stevens-Johnson syndrome, toxic epidermal necrolysis, and Kawasaki Disease.[6] With proper knowledge of DRESS syndrome, that usually occurs 2-8 weeks following exposure to an offending agent, the differential can be narrowed.[7,8]

The RegiSCAR criteria is a widely used scoring system for the diagnosis of DRESS syndrome, which includes acute rash, fever >38˚C, involvement of at least 1 internal organ, and blood count abnormalities.[9] Fever ⩾38.5°C is found in 96-100% of cases and usually preceded by cutaneous eruptions, which occur in 85-100% of cases. Eosinophilia occurs in 82-95% of cases.[7,8] Lymphadenopathies are described in 80% of cases. Among internal organ involvement, the liver is the most commonly involved, in 50-84% of cases, and can range from transient elevation of liver enzymes to hepatic failure, which is the primary cause of death in DRESS syndrome.[7,10] The substantial mortality (10%) makes early identification essential to halt disease progression and prevent long-term complications.[7] Suggested treatment is prompt discontinuation of the potential culprit drug, supportive care, and immunosuppressive therapy.[7]

Case Report

A 76-year-old Chinese male with a past medical history significant for diabetes mellitus type II, essential hypertension, stage 4 chronic kidney disease, hyperlipidemia, and coronary artery disease status-post coronary artery bypass graft surgery was seen on 10/03/23 by his primary care physician (PCP) for a regular check-up. His chief complaint at that time was right knee pain of 1 week duration. Arthrocentesis revealed intracellular and extracellular negatively birefringent crystals, consistent with uric acid. The serum uric acid level was 13.4 mg/dL (normal range: 3.4–7.0 mg/dL). The patient was started on 100 mg of allopurinol once a day (QD) on 10/17/23.

On 12/3/23, the patient was examined in emergency department number 1 (ED-1) for a pruritic generalized macular rash, accompanied by fatigue, of 10-day duration. He reported that the rash began on the extremities, then spread to the torso and face. He denied any swelling, fever, joint pain, discharge, insect bites, exposure to new chemicals, clothing, lotions, or other potential sources for his rash.

He was given one dose of dexamethasone and discharged home. Within 24 hours, he developed anorexia and generalized muscle weakness to the point of being unable to ambulate to the bathroom by himself. Two days after ED-1 visit, he was brought to his PCP by his wife. In his PCP's office, he was noted to have systemic maculopapular rashes including palms and soles, tachycardia, cervical lymphadenopathy, and an 8 lb weight loss since his last office visit two months prior. He appeared weak and dehydrated. He was sent directly to another ED (ED-2) from his PCP's office for further evaluation. Labs were significant for blood glucose level of 990 mg/dL (normal range: 70–99 mg/dL), 22 000 white blood count cells/μL (normal range: 4000– 11 000 cells/μL) with left shift, 36.5% eosinophils (normal range: 0.0–7.0%), reduced estimated glomerular filtration rate of 15 mL/min/1.73 m^2 (normal range: ⩾90 mL/min/1.73 m^2) and mild elevation of alanine transaminase. Hyperglycemia was treated with insulin bolus and drip. Chest x-ray was unremarkable. The patient was admitted to an intesive care unit (ICU) for management of hyperosmolar hyperglycemic state and fluid resuscitation.

During admission the patient experienced fevers with a maximum of 39.9˚C and elevation of liver function tests up to 250 IU/L (normal range: 0-40 IU/L). Dermatology was consulted. Additional history revealed the initiation of allopurinol 5 weeks prior to rash onset. DRESS syndrome secondary to allopurinol was suspected on hospital day 2. Allopurinol was discontinued at this time. Serologies for viruses associated with DRESS syndrome including Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus (HHV)-6, and HHV-7, as well as the a HLA-B*58:01 were obtained. EBV and CMV serologies were consistent with past infection and the patient was positive for the variant HLA-B*58:01 allele. HHV-6 and HHV-7 were negative.

Prednisone was started at 60 mg. Discontinuation of allopurinol and initiation of prednisone was followed by improvement of fever, rash, and liver function tests. The patient was discharged on hospital day 12 with a tapering dose of prednisone and Febuxostat 40 mg PO QD.

Upon follow-up with his PCP 3 days after discharge, the patient noted continued improvement of his rash in itchiness and appearance and endorsed skin peeling. He denied fatigue and reported he was able to ambulate on his own without assistance.

Discussion

This is a case of allopurinol induced DRESS syndrome with a delayed diagnosis due to this patient's 10-day history of symptoms prior to seeking medical treatment as well as an initial missed diagnosis. On admission, 5 weeks after starting allopurinol, this patient met the RegiSCAR criteria for DRESS Syndrome. The correct diagnosis, discontinuation of allopurinol, and initiation of treatment soon resulted in resolution of symptoms and improvement in labs.

The exact pathophysiology is unclear, but mechanisms that are thought to contribute to DRESS syndrome include a T-cell response to a drug or its metabolites after antigen presentation by the major histocompatability complex (MHC), herpes virus reactivation, and genetic susceptibility associated with specific HLA groups in some ethnic groups. Most notable in this case is the association of HLA-B*5801 with allopurinol hypersensitivity in the Han Chinese population.[11] This is a case of allopurinol-induced DRESS syndrome in a HLA-B*5801 positive, Chinese male, with documented past-infection with EBV and CMV, both herpes family viruses. Additionally, the specific pathophysiology of allopurinol-induced DRESS syndrome is thought to be related to the accumulation of oxypurinol. Thus, this patient's renal insufficiency may have contributed to the development of DRESS syndrome.

Despite resolution of DRESS syndrome with withdrawal of the offending agent, development of autoimmune sequelae has been reported, particularly Grave's disease, autoimmune hemolytic anemia, lupus, alopecia areata, and type one diabetes.[12] Thus, DRESS syndrome patients should be monitored for signs and symptoms of autoimmune disease in the months-to-years following recovery.

This patient's case highlights the importance of considering DRESS syndrome in patients who present with unexplained fever, cutaneous rash and characteristic lab findings in the weeks following intake of a triggering drug. Clinicians should familiarize themselves with the list of drugs associated with DRESS syndrome and maintain a high index of suspicion when prescribing them to patients, particularly of Chinese ethnicity. Patient education should be provided about the symptomatic presentation of DRESS syndrome when prescribing offending agents so that prompt medical treatment can be sought. A team-based care approach with inclusion of a pharmacist could be helpful in the continuum of care for raising awareness and reiterating potential presentations of DRESS syndrome associated with certain drugs.

Conclusion

DRESS syndrome is a rare drug-induced hypersensitivity reaction that can affect multiple organ systems and can be fatal if not recognized early. Due to its rarity and heterogenous clinical picture that mimics many other infectious or autoimmune conditions, diagnosis can be difficult. Thus, physicians should have a high index of suspicion for patients presenting with cutaneous and internal organ involvement after initiation of an offending drug, so as to not miss this critical diagnosis.

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Conflict of Interest and Disclosures

None of the authors identify any conflict of interest.

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References

1. Cardoso CS, Vieira AM, Oliveira AP. DRESS syndrome: a case report and literature review. *BMJ Case Rep*. 2011;2011:bcr0220113898. doi:10.1136/bcr.02.2011.3898

2. Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome. *Semin Cutan Med Surg*. 1996;15(4):250-257. doi:10.1016/s1085-5629(96)80038-1

3. Gianvittorio S, Giovanni C. Allopurinol-induced skin reaction, dress probable case: a case report. *Ann Case Report*. 2022;7(823). doi:10.29011/2574-7754.100823

4. Cacoub P, Musette P, Descamps V, et al. The DRESS syndrome: a literature review. *Am J Med*. 2011;124(7):588-597. doi:10.1016/j.amjmed.2011.01.017

5. Wolfson AR, Zhou L, Li Y, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. *J Allergy Clin Immunol Pract*. 2019;7(2):633-640. doi:10.1016/j.jaip.2018.08.013

6. Mukit W, Cooper R, Moudgil H, et al. DRESS syndrome: an important differential for eosinophilia with systemic organ dysfunction. *BMJ Case Rep*. 2020;13(5):e234251. doi:10.1136/bcr-2020-234251

7. Choudhary S, McLeod M, Torchia D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. *J Clin Aesthet Dermatol*. 2013;6(6):31-37.

8. Prusty BSK, Momin MA, Goud YK, et al. DRESS syndrome- uncommon drug reaction with common disease treatment - a case report. *J Microbiol Infect Dis*. 2020;10(4):225-229. doi:10.5799/jmid.839481

9. Schunkert EM, Divito SJ. Updates and insights in the diagnosis and management of DRESS syndrome. *Curr Derm Rep*. 2021;10(4):192-204. doi:10.1007/s13671-021-00348-z

10. Kim DH, Koh YI. Comparison of diagnostic criteria and determination of prognostic factors for drug reaction with eosinophilia and systemic symptoms syndrome. *Allergy Asthma Immunol Res*. 2014;6(3):216-221. doi:10.4168/aair.2014.6.3.216

11. Hung SI, Chung WH, Liou LB, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci U S A*. 2005;102(11):4134-4139. doi:10.1073/pnas.0409500102

12. Chen YC, Chang CY, Cho YT, et al. Long-term sequelae of drug reaction with eosinophilia and systemic symptoms: a retrospective cohort study from Taiwan. *Journal of the American Academy of Dermatology*. 2013;68(3):459-465. doi:10.1016/j.jaad.2012.08.009