



Case Report

Allopurinol-Induced Skin Reaction, Dress Probable Case: A Case Report

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Abstract

A 75-year-old woman who had taken antihypertensive drugs (ARB+thiazides) and cholesterol-lowering drug (Atorvastatin) had received allopurinol for asymptomatic hyperuricemia for 5 years. He developed pruritic erythematous papules and plaques with rare pustules on extremities after taking allopurinol, this lesions were accentuated in summer during maximum photo exposure. He had no fever, mild eosinophilia ($1.7 \times 10^9/L$) and no systemic abnormalities. Histopathologic: chronic venous insufficiency / stasis. The Doppler echocolor-doppler of the lower limbs showed chronic venous disease. Chronic phlebostasis with reactive vasculitis. The skin rashes have reduced after he stopped taking allopurinol and was treated with steroids. The patient have received steroid treatment without improvement until suspension of allopurinol.



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Allopurinol and Adverse Reaction

Allopurinol, as confirmed by several international studies, is at the basis of various adverse reactions, from less serious to very serious. Allopurinol is the culprit drug cutaneous ADR cases. Clinical forms were maculopapular eruptions (34 cases), Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis, vasculitis, Drug Rash Eosinophilia and Systemic Symptoms (DRESS), Acute Generalized Exanthemata's Pustulosis (AGEP), Pityriasisrosea-like eruption, lichenoid dermatitis, fixed drug eruption, erythroderma. The indication for allopurinol prescription was asymptomatic hyper-uremia in 95% of the patients [1]. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is an idiosyncratic, acute adverse drug reaction [2]. According to the literature, cutaneous adverse drug reactions affect 2-3% of hospitalized patients [3,4]. The incidence of this syndrome is estimated to range from 1:1000 to 1:10000 of drug exposures [5]. The overall mortality rate of this disease is 10-20% [6], but there are studies that present higher mortality rates, up to 40% if organ failure is present [7] fortunately, most of these reactions present as benign maculopapular exanthema or urticarial [4]. However, severe cutaneous adverse reactions (SCARs) affect about 1 of every 1000 inpatients [8]. SCARs to drugs are groups of idiosyncratic hypersensitivity reactions with a heterogeneous clinical presentation [9]. Two of the most notorious SCARs are Stevense Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) due to their rapid progression and high morbidity/mortality rates. With extensive reporting and better education of physicians and patients, the incidence of both has gradually decreased. Another SCAR has begun to attract attention due to its unique clinical features and unknown pathogenesis: drug reaction with eosinophilia and systemic symptoms (DRESS); its description reflects the typical presentation of rash, hematologic abnormalities,

and systemic illness. The incidence of this syndrome is estimated to range from 1:1000 to 1:10000 of drug exposures [5]. The overall mortality rate of this disease is 10-20% [6], but there are studies that present higher mortality rates, up to 40% if organ failure is present [7]. Fever, rash, lymphadenopathy, hematological abnormalities, systemic illness, along with significant multisystem involvement, hepatitis being the most common, followed by nephritis. Highly suggestive of this condition is latency between initial drug administration and specific symptom onset [10]. The pathogenesis of DRESS syndrome is not yet fully understood. Several hypotheses have been proposed which support the involvement of an intricate interplay of multiple factors such as: mutations in genes encoding drug detoxification enzymes leading to the accumulation of drug reactive metabolites, reactivation of human herpes virus 6 and 7, Epstein-Barr virus (EBV), cytomegalovirus (CMV), genetic predisposition associated with certain human leukocyte antigens (HLA), and immunological phenomena [11]. Common drugs associated with DRESS syndrome are anticonvulsants (such as carbamazepine, phenytoin) [12]. Early recognition of this syndrome, withdrawal of suspected culprit drugs, and adequate supportive care are mainstays of improving patient prognosis and reducing morbidities and mortality [13]. Systemic glucocorticoid therapy, intravenous immunoglobulin, antiviral drugs, plasmapheresis, cyclosporine, and symptomatic treatment are part of the appropriate management of this pathology [6]. In DRESS syndrome patients, careful long-term follow-up is crucial and monitoring for autoimmune diseases is required [10].

Clinical Symptoms and Laboratory Findings

DRESS/DIHS symptoms typically occur 2e6 weeks [14] after drug intake; however, reactions may not develop until 3 months later, especially when the syndrome is induced by allopurinol

[15]. A high, spiking fever (usually >38_C) and rash are usually the first signs, and these are followed by other systemic reactions such as cervical, axillary and inguinal lymphadenopathy, arthritis, or general malaise. The rash begins as a nonspecific morbilliform eruption, which is indistinguishable from other less severe drug reactions, but can progress to a generalized form. Facial and accrual edema with periorbital accentuation is an evocative sign for the diagnosis [14]. The cutaneous eruption later becomes confluent and infiltrated with purpuric changes, especially when it affects the lower extremities. As the rash resolves, the end stage involves large sheet desquamation. Occasionally, pinhead-sized pustules. Mucosal regions can be involved in DRESS but in such cases, the symptom is usually mild, and seen as chelates or erythematous pharynx rather than as extensive erosions seen in SJS/TEN [16,17]. Multiple organ involvement is another distinct feature of DRESS but the actual incidence varies. The liver and kidney are the two most frequently involved organs, and the incidence ranges from 50% to 87% and 10% to 53%, respectively [18,19]. Anicteric hepatitis presenting as elevated serum alanine aminotransferase is more common in patients with DRESS, when it becomes icteric, this reduce prognosis [19]. In addition, recurrent elevation of liver enzymes, with or without relapsing fever and rash, may correlate with reactivation of human herpesvirus6 (HHV-6) [20]. Renal involvement usually presents with increased serum creatinine levels and new-onset proteinuria. Chronic renal insufficiency and allopurinol-induced DRESS increased the risk of renal involvement [15]. The severity of renal dysfunction varies from a mild increase in serum creatinine levels to the development of end-stage renal disease. Although the incidence is lower, other visceral organs can be involved during DRESS. Pulmonary involvement presents as nonproductive cough or breathlessness, which may be complicated by acute interstitial pneumonitis, pleuritic, or adult respiratory distress syndrome [21]. Cardiac and muscular complications include myocarditis, [22] rhabdomyolysis [23] and atrioventricular block [24]. Although the cardiac complications are rare, these can easily lead to death. Neurologic symptoms, such as headache, seizure, coma, or disturbed speech are all usually reported, as signs of meningitis and encephalitis. Hypersensitivity syndrome may also results in acute pancreatitis, [25] arthritis, [26] or gastrointestinal bleeding [27]. The severity of organ involvement can vary from subclinical to fatal or can only be recognized months or years later after the development of such organ failures [17]. Various hematologic abnormalities have been described in patients with DRESS. Atypical lymphocytes and/or eosinophilia is the most prominent and characteristic sign [21]; in different previous study, the incidence was 63% and 52%, respectively(studio yi)Other abnormalities include leukocytosis or leukopenia, thrombocytopenia, and hypogammaglobinemia in the early stages [28].Most hematologic changes return to normal without causing significant morbidity.

Diagnosis

In order to define the case, the Regis CAR score and the Japanese Group score, used in the diagnosis of drug-induced hypersensitivity, were applied. The international Registry of Severe Cutaneous Adverse Reactions (Regis CAR) group has suggested a series of inclusion criteria for suspicious DRESS cases, in which hospitalized patients with a reaction suspected to be drug related must have at least three of the following systemic features: acute skin rash; fever above 38C; enlarged lymph nodes; internal organ involvement; and hematological abnormalities, including lymphocytosis or lymphocytopenia, eosinophilia, and thrombocytopenia [29]. Application of these criteria may be limited in a hospital-based setting or used only in expert meetings.

By contrast, the Japanese consensus group established another set of criteria, with the inclusion of HHV-6 reactivation as a diagnostic criterion for DIHS (Table 1) [30]. If all criteria are present, especially evidence of HHV-6 reactivation, the diagnosis of typical DIHS is made; otherwise, atypical DIHS is diagnosed when the first five criteria are present. Compared to the Regis CAR criteria, the Japanese criteria are more easily applied by general physicians or dermatologists working in local clinics because the suggested laboratory tests are easily available, and those tests need not be repeated.

CRITERIA	SCORE
1. Maculopapular rash developing > 3 weeks after starting with a limited number of drugs b	1
2. Prolonged clinical symptoms 2 weeks after discontinuation of the causative drug	1
3. Fever > 38_C	1
4. Liver abnormalities (alanine aminotransferase > 100 U/L)	1
5. Leukocyte abnormalities (at least one present)	1
a. Leukocytosis (>11 _ 109/L)	1
b. Atypical lymphocytosis (>5%)	1
c. Eosinophilia (>1.5 _ 109/L)	1
6. Lymphadenopathy	1
7. Human herpesvirus 6 reactivation	1
0 7=typical DRESS syndrome; 5=atypical DRESS syndrome;	

Table 1: Diagnostic criteria for drug-induced hypersensitivity syndrome (DIHS) established by the Japanese group.

TABLE 4: RegiSCAR diagnostic criteria for DRESS/DIHS

Score	-1	0	1	2	MAX	MIN
Fever $\geq 38,5^{\circ}\text{C}$	No / U	Yes			-1	0
Enlarged lymph nodes		No / U	Yes		0	1
Eosinophilia: Eosinophils	No / U		0.7-1.499 x 10^9L^{-1}	≥ 1.5 x 10^9L^{-1}	0	2
Eosinophils, IF leucocytes $< 4.0 \times 10^9\text{L}^{-1}$			10%-19,9%	$\geq 20\%$		
Atypical lymphocytes		No / U	Yes		0	1
Skin Involvement:					-2	2
Skin rash extent (% body surface area)		No / U	$>50\%$			
Skin rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	No / U				
Organ involvement*:					0	2
Liver		No / U	Yes			
Kidney		No / U	Yes			
Muscle / heart		No / U	Yes			
Pancreas		No / U	Yes			
Other organs		No / U	Yes			
Resolution ≥ 15 days	No / U	Yes			-1	0
Evaluation of other potential causes:						
Antinuclear antibody (FAN)						
Blood culture						
Serology HAV / HBV / HCV						
Chlamydia / Mycoplasma						
*If none positive and ≥ 3 of above negative			Yes		0	1
Total score					-4	9

Final scores: <2 : excluded; $2e3$: possible; $4e5$: probable; > 5 : definite. EBV/CMV and HHV6/7 are also recorded; results, however, do not influence the score.

Table 2: Scoring system of Regis CAR for diagnosing drug reaction with eosinophilia and systemic symptoms (DRESS) [30].

The application of diagnostic criteria to the case report would leave to exclude diagnosis of DRESS. The clinical observation associated with response to drug suspension, however, allow believing manifestation observed in the scope of adverb skin reaction to allopurinol [31-34].

Conclusion

DRESS/DIHS is a severe adverse drug reaction with unique clinical features and complex path mechanisms. Early recognition, withdrawal of possible causative drugs, and adequate supportive care are mainstays of improving patient prognosis and reduce morbidities/mortality. In order to carry out a timely diagnosis, we have the duty to always add critical and analytical judgment to the validated scientific instruments to make up for any shortcomings in the means available. From the data reported in the various

articles consulted, a further reflection derives. Considering the potential adverse reactions associated with the use of allopurinol, its use should always be strongly supported by benefits and its prescribing supported by guidelines.

References

1. Atzori L, Pinna AL, Mantovani L. (2011) Cutaneous Adverse Drug Reactions to Allopurinol: 10 Year Observational Survey of the Dermatology Department - Cagliari University (Italy). J Eur Acad Dermatol Venereol, pubblicato on line il 24.
2. Husain Z, Reddy YB, Schwartz AR. (2013) DRESS syndrome: Part I. Clinical perspectives. J Am Acad Dermatol. 68: 693.e1-14.
3. Bigby M, Jick S, Jick H, Arndt K. (1986) Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975 to 1982. JAMA 256: 3358e63.

4. Hunziker T, Künzi UP, Braunschweig S, Zehnder D, Hoigné R. (1997) Comprehensive hospital drug monitoring (CHDM): adverse skin reactions, a 20-year survey. *Allergy* 52: 388e93.
5. Cacoub P, Musette P, Descamps V. (2011) The DRESS syndrome: a literature review. *Am J Med.* 124: 588-597.
6. Behera SK, Das S, Xavier AS, Selvarajan S. (2018) DRESS syndrome: a detailed insight. *HospPract.* (1995). 46: 152-162.
7. Tsyrlunik A, Landman A. (2011) Drug rash with eosinophilia and systemic symptoms: two emergency department cases. *West J Emerg Med.* 12: 559-562.
8. Roujeau JC, Stern RS. (1994) Severe adverse cutaneous reactions to drugs. *N Engl J Med* 331: 1272e85.
9. Roujeau JC. (2005) Clinical heterogeneity of drug hypersensitivity. *Toxicology* 209: 123e9.
10. Descamps V, Ranger-Rogez S. (2014) DRESS syndrome. *Joint Bone Spine.* 81: 15-21.
11. Walsh SA, Creamer D. (2011) Drug reaction with eosinophilia and systemic symptoms (DRESS): a clinical update and review of current thinking. *ClinExpDermatol.* 36: 6-11.
12. Cho YT, Yang CW, Chu CY. (2017) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): An Interplay among Drugs, Viruses, and Immune System. *Int J Mol Sci.* 18: 1243.
13. Yi-Chun Chen, Yung-Tsu Cho, Chia-Ying Chang, Chia-Yu Chu. (2013) Drug reaction with eosinophilia and systemic symptoms: A drug-induced hypersensitivity syndrome with variable clinical features. *DERMATOLOGICA SINICA* 31: 196e204.
14. Bocquet H, Bagot M, Roujeau JC. (1996) Drug induced pseudolymphoma and drug hypersensitivity syndrome (drug rash with eosinophilia and systemic symptoms: DRESS). *Semin Cutan Med Surg* 15: 250e7
15. Chen YC, Chiu HC, Chu CY. (2010) Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. *Arch Dermatol* 146: 1373e9.
16. Bachot N, Roujeau JC. (2003) Differential diagnosis of severe cutaneous drug eruptions. *Am J Clin Dermatol* 4: 561e72.
17. Shiohara T, Inaoka M, Kano Y. (2006) Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesviruses and antiviral and antidrug immune responses. *Allergol Int* 55: 1e8.
18. Chiou CC, Yang LC, Hung SI. (2008) Clinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: a study of 30 cases in Taiwan. *J Eur Acad Dermatol Venereol* 22: 1044e9.
19. Vittorio CC, Muglia JJ. (1995) Anticonvulsant hypersensitivity syndrome. *Arch Intern Med* 155: 2285e90.
20. Tohyama M, Hashimoto K, Yasukawa M. (2007) Association of human herpesvirus 6 reactivation with the flaring and severity of drug-induced hypersensitivity syndrome. *Br J Dermatol* 157: 934e40.
21. Kano Y, Ishida T, Hirahara K, Shiohara T. (2010) Visceral involvements and long-term sequelae in drug-induced hypersensitivity syndrome. *Med Clin North Am* 94: 743e59.
22. Shaughnessy KK, Bouchard SM, Mohr MR, Herre JM, Salkey KS. (2010) Minocycline-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome with persistent myocarditis. *J Am Acad Dermatol* 62: 315e8.
23. Engel JN, Mellul VG, Goodman DB. (1986) Phenytoin hypersensitivity: a case of severe acute rhabdomyolysis. *Am J Med* 81: 928e30.
24. Zhu KJ, He FT, Jin N, Lou JX, Cheng H. (2009) Complete atrioventricular block associated with dapsone therapy: a rare complication of dapsone-induced hypersensitivity syndrome. *J Clin Pharm Ther* 34: 489e92.
25. Descamps V, Mahe E, Houhou N. (2003) Drug-induced hypersensitivity syndrome associated with Epstein-Barr virus infection. *Br J Dermatol* 148: 1032e4.
26. Morito H, Ogawa K, Kobayashi N, Fukumoto T, Asada H. (2012) Drug-induced hypersensitivity syndrome followed by persistent arthritis. *J Dermatol* 39: 178e9.
27. Asano Y, Kagawa H, Kano Y, Shiohara T. (2009) Cytomegalovirus disease during severe drug eruptions: report of 2 cases and retrospective study of 18 patients with drug-induced hypersensitivity syndrome. *Arch Dermatol* 145: 1030e6.
28. Kano Y, Inaoka M, Shiohara T. (2004) Association between anticonvulsant hypersensitivity syndrome and human herpesvirus 6 reactivation and hypogammaglobulinemia. *Arch Dermatol* 140: 183e8.
29. Kardaun SH, Sidoroff A, Valeyrie-Allanore L. (2007) Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 156: 609e11.
30. Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. (2007) The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. *Br J Dermatol* 156: 1083e4.
31. Brennan TA, Laird N, Lawthers AG. (1991) The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Engl J Med* 324: 377e84.
32. Peyrière H, Dereure O, Breton H. (2006) Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 155: 422e8.
33. Mockenhaupt M. (2009) Severe drug-induced skin reactions: clinical pattern, diagnostics and therapy. *J Dtsch Dermatol Ges* 7: 1
34. Cristina Scavone. (2020) D Severe Cutaneous Adverse Drug Reactions Associated with Allopurinol: An Analysis of Spontaneous Reporting System in Southern Italy *Drugs Real World Outcomes.* 7: 41-51.