

CASE REPORT

Allopurinol-induced DRESS syndrome in the elderly: an exceptional form of iatrogenesis

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Abstract: Introduction: The Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a very rare iatrogenic accident that is characterized by its difficult diagnosis due to its clinical latency and heterogeneous clinic. The form induced by allopurinol remains exceptional and often ignored by clinicians, although potentially fatal. We are reporting an original observation of allopurinol-induced DRESS syndrome in elderly. Case report: A 64-year-old woman who had been treated with allopurinol for gout for three weeks, was hospitalized for a diffuse, erythematous and maculopapular cutaneous rash, associated with fever at 39 °C, dyspnea, generalized lymphadenopathy, and a hyperkeratotic and desquamative plantar eruption. The biology showed eosinophilia at 860/mm³ and cytolytic hepatitis without cholestasis or hepatocellular insufficiency with ASAT at 230 IU/l and alanine aminotransferase (ALAT) at 280 IU/l. The infectious, immunological investigation, as well as the search for underlying malignant neoplasia or hematological malignancy were negative. The skin biopsy was inconclusive. The diagnosis of a DRESS syndrome induced by allopurinol was retained. The evolution was rapidly favorable after stopping allopurinol and treatment with systemic glucocorticoids. Conclusion: The incidence of cutaneous reactions to allopurinol is estimated at 1.5/100,000 H/year. The DRESS syndrome, the most serious form of these reactions, remains exceptional. This particular form of toxicity deserves to be known by clinicians, especially since allopurinol is widely prescribed in the elderly.

Keywords: DRESS syndrome, iatrogenesis, allopurinol, cutaneous drug reaction, elderly

1 Introduction

Since its approval in 1966, allopurinol has become a widely prescribed drug, particularly in the elderly, to treat hyperuricemia, gout/gouty arthritis and renal lithiasis.^[1,2]

Dermal adverse reactions to allopurinol are rare and can occur in different aspects: maculopapular rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, cutaneous vasculitis, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome, acute generalized xanthematous pustulosis, pityriasis rosea-like rash, lichenoid dermatitis, fixed drug eruption, and erythroderma. The incidence of these reactions is estimated at 1.5/100,000H/year.^[1]

Of the clinical presentations of allopurinol-induced

allergy, DRESS syndrome remains rare,^[1,3,4] often reported as sporadic cases,^[5,6] and therefore remains unknown to practitioners as a possible complication of this treatment.^[7]

Allopurinol-induced DRESS syndrome can also be seen in young adults (33 years old in the observation of Cooksley T, *et al.*^[7]) and even in children and adolescents (16 years old in the observation Dewan AK, *et al.*^[8]) but seems to be particularly high in the elderly.^[1,3,4] Indeed the average age in the review of Huang CH, *et al.* of allopurinol-related drug injury was 65 years and older in 63.8% of cases.^[2]

The allopurinol-induced DRESS syndrome is characterized by a significantly higher mortality compared to DRESS syndromes induced by other drugs.^[9] This mortality is also particularly high in subjects aged 65 and over compared to those aged 40 to 64 and those under 40: 79.2% versus 17.8% and 3.0%, respectively.^[2]

We are reporting an original case of DRESS syndrome induced by allopurinol in an elderly subject characterized by an unusual plantar eruption.

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2 Case report

A 64-year-old woman with no pathological medical history for whom treatment with allopurinol at a dose of 200 mg/day has been indicated for three weeks for gout, was hospitalized with fever and dyspnea for two days.

The examination noted a fever patient at 39°C, polypnoea at 28 cycles/min, and a generalized pruriginous, erythematous, and maculopapular skin rash in the limbs, abdomen, and back (Figure 1), a bilateral plantar pruriginous, and desquamative hyperkeratosis (Figure 2), and multiple centimeter lymphadenopathies, insensitive, and diffuse at the level of the axillary, inguinal, and spinal ganglionic areas. The specialized Ear, Nose and Throat (ENT) examination noted a discreet diffuse pharyngeal and laryngeal edema. The electrocardiogram and the chest X-ray were without abnormalities.



Figure 1. Diffuse maculopapular rash in the abdomen and back



Figure 2. Bilateral plantar desquamative hyperkeratosis

Biology showed: erythrocyte sedimentation rate at 80mm/H, leukocytosis at 10,500/mm³, eosinophilia at 860/mm³, cytolytic hepatitis without cholestasis or hepatocellular insufficiency with aspartate aminotransferase (ASAT) at 230IU/l and ALAT at 280IU/l. The other basic bioassays were within normal limits (hemoglobin, platelets, C-reactive protein, creatinine, serum calcium, blood glucose, ionogram, direct and conjugated bilirubin, Alkaline phosphatase (ALP), 'YGT, muscle enzymes, lipid parameters, free tetra-iodothyronine (fT4) and Thyroid Stimulating Hormone (TSH), and electrophoresis serum proteins).

Abdominal ultrasound and thoracoabdominopelvic CT were without abnormalities.

The infectious, immunological investigation, as well as the search for an underlying malignant neoplasia or malignant hemopathy were negative. The skin biopsy was inconclusive.

After the pharmacological investigation, and considering the negativity of the explorations, the diagnosis of a DRESS syndrome induced by allopurinol was retained. The specific RegiSCAR score was of 6 classing the diagnosis of DRESS syndrome as "definite".

The evolution was rapidly favorable after stopping allopurinol and treatment with systemic glucocorticoids at a dose of 1 mg/kg/day. Apyrexia is obtained on the second day, the cutaneous signs disappear at the end of the first week, and the transaminases and the hemogram were strictly normal after one month.

3 Discussion

The DRESS syndrome is a real diagnostic challenge, particularly because of its long latency (2-6 weeks) and its significant clinical heterogeneity.^[5,9,10] Its typical clinical presentation combines: rash, blood eosinophilia, and systemic symptoms that vary greatly.^[5,10] Among these systemic symptoms, the most commonly reported are: fever, dyspnoea, cough, polyadenopathy, hepatic injury (acute hepatitis), renal involvement (acute interstitial nephritis), pulmonary involvement (interstitial pneumonitis), cardiac involvement (myocarditis), and central neurological involvement.^[5,9,11] Rarely more severe manifestations can be noted: sepsis-like syndrome,^[10] acute pancreatitis,^[12] acute pseudo-surgical abdomen/cholecystitis-like syndrome,^[13] kidney-limited necrotizing vasculitis,^[14] acute necrotizing myocarditis and papillary muscle rupture,^[15] venous thrombosis,^[16] severe agranulocytosis,^[17] and hemophagocytic syndrome.^[18] This large clinical polymorphism justified the qualification given to DRESS syndrome of "Great Clinical Mimiker".^[10]

Exceptionally DRESS syndrome can occur without any skin lesion^[19] or without eosinophilia^[20] making its clinical diagnosis even more difficult.

As a result, several tools/scores have been proposed for the diagnosis of this syndrome; the most used is the RegiSCAR scoring system (for European registry of Severe Cutaneous Adverse Reaction), which makes it possible to diagnose cases of DRESS syndrome, and to classify them as "possible", "probable", or "definite".^[9]

DRESS syndrome's most common drugs are anticonvulsants, antibiotics, and nonsteroidal anti-inflammatory drugs.^[3,4,9,21] Allopurinol remains exceptional as a cause of the DRESS syndrome;^[21] indeed, it is estimated that generally 2% of allopurinol-treated patients will develop a rash, and only 0.4% of them will experience a severe form of toxicity.^[22] These findings were confirmed by the large study "Lasso Study" of long term allopurinol safety in 1735 patients with 100, 200, or 300

mg/day of allopurinol, where rash incidence and adverse events were reported only in 1.5% of case, and no case of DRESS syndrome was reported.^[23]

This extreme rarity of DRESS syndrome induced by allopurinol, explains that this entity is little known and often misdiagnosed by clinicians: indeed, in the review of the literature made by Cacoub P, *et al* of different cases of DRESS syndrome published between 1997 and 2009, and among the 19 cases of DRESS induced allopurinol only four patients had a "definite" DRESS syndrome (21%), while the remains were judged to be rather "probable" or "possible".^[9]

In addition to the difficulty of the clinical diagnosis, the skin tests contribute little to the diagnosis of DRESS syndrome induced by allopurinol; indeed these tests were negative in 100% of the cases in the series of Santiago F, *et al*.^[24]

Recently in vitro test using the interferon (IFN) enzyme-linked immunospot (ELISpot) and measuring the oxypurinol/anti-PD-L1-inducing IFN- γ -releasing cells, was confirmed to be an excellent test with high value for the diagnosis of allopurinol-induced DRESS syndrome.^[25]

Older age and inappropriate prescriptions of allopurinol in the elderly are the main causes of the frequency of severe allergic reactions associated with this molecule in the elderly.^[1] Indeed, in 95% of the cases in Atzori L, *et al*, the prescription of allopurinol was inappropriate (asymptomatic hyperuricemia),^[1] as well as in several other sporadic observations.^[5]

Comorbidities frequently noted in the elderly such as diabetes, high blood pressure, cardiovascular diseases, pre-existing chronic renal failure, and the use of diuretics are also contributing factors to allopurinol-induced DRESS syndrome in geriatrics.^[2, 11]

Treatment consists of discontinuation of the causative drug and systemic corticosteroids,^[1-5] and the course is usually rapidly favorable.^[4, 5] The evolution can sometimes be fatal, especially in the elderly and fragile subject. This mortality is different depending on the series and can be up to 10%, particularly in severe forms with multi-organ failure.^[9, 11]

Rasburicase, a genetically engineered enzyme derived from the uricase of *Aspergillus flavus* (Febuxostat[®]), can be proposed as a therapeutic alternative for subjects with gout who have developed a DRESS syndrome under allopurinol.^[26]

Moreover, preferential associations according to the ethnic groups with HLA haplotypes and the DRESS syndrome have been recently demonstrated, explaining the dysimmunitary bases of the physiopathology of these reactions, and let hope for the eventuality of the possi-

ble prevention via screening before prescription (pharmacogenetic screening).^[27-30] For allopurinol-induced DRESS syndrome, the combination is described with the HLA-B*5801, HLA-A*303, and HLA-C*0302 alleles.^[27, 29, 30]

4 Conclusion

As rare as it is, this particular and potentially fatal form of toxidermy associated with allopurinol deserves to be known by clinicians, especially geriatricians. A rationalization of the prescription of allopurinol in the elderly and a possible pharmacogenetic screening will prevent the occurrence of DRESS syndrome induced by this molecule.

Our observation is distinguished by the unusual appearance of the plantar skin reaction.

5 Conflicts of interest:

The authors declare that they have no competing interests.

References

- [1] Atzori L, Pinna AL, Mantovani L, *et al*. Cutaneous adverse drug reactions to allopurinol: 10 year observational survey of the dermatology department - cagliari university (Italy). *J Eur Acad Dermatol Venereol*. 2012, **26**(11): 1424-1430. <https://doi.org/10.1111/j.1468-3083.2011.04313.x>
- [2] Huang CH, Chu MP, Chen WW. Examining the use of allopurinol: Perspectives from recent drug injury relief applications. *J Formos Med Assoc*. 2018, pii: S0929-6646(17)30905-1. [Epub ahead of print] <https://doi.org/10.1016/j.jfma.2018.06.006>
- [3] Ding WY, Lee CK, Choon SE. Cutaneous adverse drug reactions seen in a tertiary hospital in Johor, Malaysia. *Int J Dermatol*, 2010, **49**(7): 834-841. <https://doi.org/10.1111/j.1365-4632.2010.04481.x>
- [4] Um SJ, Lee SK, Kim YH, *et al*. Clinical features of drug-induced hypersensitivity syndrome in 38 patients. *J Investig Allergol Clin Immunol*, 2010, **20**(7): 556-562.
- [5] Hassan S, Wetz R, Zouein E. Allopurinol causing drug rash with eosinophilia and systemic symptoms syndrome: a challenging diagnosis. *Int J Gen Med*, 2011, **4**: 789-792. <https://doi.org/10.2147/IJGM.S24953>
- [6] Kim MS, Lee JH, Park K, Son SJ. Allopurinol-Induced DRESS Syndrome With a Histologic Pattern Consistent With Interstitial Granulomatous Drug Reaction. *Am J Dermatopathol*, 2014, **36**(2): 193-196. <https://doi.org/10.1097/DAD.0b013e3181c0e14d>
- [7] Cooksley T, Iqbal J, Robertson C, *et al*. DRESS Syndrome caused by allopurinol. *Acute Med*. 2010, **9**(3): 122-123.
- [8] Dewan AK, Quinonez RA. Allopurinol-induced DRESS syndrome in an adolescent patient. *Pediatr Dermatol*, 2010, **27**(3): 270-273. <https://doi.org/10.1111/j.1525-1470.2009.00983.x>

- [9] Cacoub P, Musette P, Descamps V, *et al.* The DRESS syndrome: a literature review. *Am J Med*, 2011, **124**(7): 588-597.
<https://doi.org/10.1016/j.amjmed.2011.01.017>
- [10] Fleming P, Marik PE. The DRESS syndrome: the great clinical mimicker. *Pharmacotherapy*, 2011, **31**(3): 332.
<https://doi.org/10.1592/phco.31.3.332>
- [11] Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. *Arch Dermatol*, 2010, **146**(12): 1373-1379.
<https://doi.org/10.1001/archdermatol.2010.198>
- [12] Roquin G, Peres M, Lerolle N, *et al.* First report of lamotrigine-induced drug rash with eosinophilia and systemic symptoms syndrome with pancreatitis. *Ann Pharmacother*, 2010, **44**(12): 1998-2000.
<https://doi.org/10.1345/aph.1P350>
- [13] Batista M, Cardoso JC, Oliveira P, *et al.* Allopurinol-induced DRESS syndrome presented as a cholecystitis-like acute abdomen and aggravated by antibiotics. *BMJ Case Rep*, 2018, pii: bcr-2018-226023.
- [14] Esposito AJ, Murphy RC, Toukatly MN, *et al.* Acute kidney injury in allopurinol-induced DRESS syndrome: a case report of concurrent tubulointerstitial nephritis and kidney-limited necrotizing vasculitis. *Clin Nephrol*, 2017, **87**(6): 316-319.
<https://doi.org/10.5414/CN108966>
- [15] Menter T, Tzankov A. Drug Reaction, Eosinophilia, and Systemic Symptoms (DRESS) syndrome associated with allopurinol leading to acute necrotizing eosinophilic myocarditis and death due to papillary muscle rupture. *J Allergy Clin Immunol Pract*, 2016, **4**(6): 1262-1264.
<https://doi.org/10.1016/j.jaip.2016.07.005>
- [16] Medhioub Kaaniche F, Allela R, Ben Algia N, *et al.* Venous thrombosis, unrecognized complication of DRESS. *Ann Dermatol Venereol*, 2017, **144**(2): 121-124.
<https://doi.org/10.1016/j.annder.2016.06.011>
- [17] Kato M1 Kano Y, Sato Y, Shiohara T. Severe Agranulocytosis in Two Patients with Drug-induced Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms. *Acta Derm Venereol*, 2016, **96**(6): 842-843.
- [18] Korbi M, Youssef M, Ben Brahim H, *et al.* Allopurinol-induced DRESS complicated by hemophagocytic lymphohistiocytosis. *Ann Dermatol Venereol*, 2015, **142**(12): 767-770.
<https://doi.org/10.1016/j.annder.2015.03.026>
- [19] Sasidharanpillai S, Binitha MP, Manikath N, *et al.* Drug reaction with eosinophilia and systemic symptoms without skin rash. *Indian J Pharmacol*, 2015, **47**(6): 687-689.
<https://doi.org/10.4103/0253-7613.169580>
- [20] Rakusa J, Lautenschlager S, Chmiel C. Allopurinol induced DRESS syndrome without eosinophilia and pronounced mucosal involvement. *J Eur Acad Dermatol Venereol*, 2016, **30**(5): 865-867.
<https://doi.org/10.1111/jdv.13033>
- [21] Jeung YJ, Lee JY, Oh MJ, *et al.* Comparison of the causes and clinical features of drug rash with eosinophilia and systemic symptoms and stevens-johnson syndrome. *Allergy Asthma Immunol Res*, 2010, **2**(2): 123-126.
<https://doi.org/10.4168/aaair.2010.2.2.123>
- [22] Miederer SE, Miederer KO. Allopurinol hypersensitivity syndrome: Liver transplantation after treatment of asymptomatic hyperuricaemia. *Dtsch Med Wochenschr*, 2014, **139**(49): 2537-2540.
- [23] Becker MA, Fitz-Patrick D, Choi HK, *et al.* An open-label, 6-month study of allopurinol safety in gout: The LASSO study. *Semin Arthritis Rheum*, 2015, **45**(2): 174-83.
<https://doi.org/10.1016/j.semarthrit.2015.05.005>
- [24] Santiago F, Gonçalo M, Vieira R, *et al.* Epicutaneous patch testing in drug hypersensitivity syndrome (DRESS). *Contact Dermatitis*, 2010, **62**(1): 47-53.
<https://doi.org/10.1111/j.1600-0536.2009.01659.x>
- [25] Klaewsongkram J, Thantiworasit P, Suthumchai N, *et al.* In vitro test to confirm diagnosis of allopurinol-induced severe cutaneous adverse reactions. *Br J Dermatol*, 2016, **175**(5): 994-1002.
<https://doi.org/10.1111/bjd.14701>
- [26] Calogiuri GF, Satriano F, Muratore L, *et al.* Therapeutic alternatives in a patient with DRESS syndrome induced by allopurinol. *J Investig Allergol Clin Immunol*, 2009, **19**(4): 333-334.
- [27] Nakkam N, Konyoung P, Kanjanawart S, *et al.* HLA Pharmacogenetic Markers of Drug Hypersensitivity in a Thai Population. *Front Genet*, 2018, **9**: 277.
<https://doi.org/10.3389/fgene.2018.00277>
- [28] Phillips EJ, Chung WH, Mockenhaupt M, *et al.* Drug hypersensitivity: pharmacogenetics and clinical syndromes. *J Allergy Clin Immunol*, 2011, **127**(3 Suppl): S60-66.
<https://doi.org/10.1016/j.jaci.2010.11.046>
- [29] Aihara M. Pharmacogenetics of cutaneous adverse drug reactions. *J Dermatol*, 2011, **38**(3): 246-54.
<https://doi.org/10.1111/j.1346-8138.2010.01196.x>
- [30] Jung JW, Kim JY, Park IW, *et al.* Genetic markers of severe cutaneous adverse reactions. *Korean J Intern Med*, 2018, **33**(5): 867-875.
<https://doi.org/10.3904/kjim.2018.126>