

## Rare Cardiac Manifestation of a Commonly Prescribed Drug: Takotsubo Cardiomyopathy Caused by Allopurinol Induced Dress Syndrome

Danish Abbasi<sup>1\*</sup>,  
Hina Mannan<sup>1</sup>,  
VineshKumar Patel<sup>1</sup> and  
Syed Farhan Hasni<sup>2</sup>

- 1 Department of Medicine, Division of Cardiology, AtlantiCare Regional Medical Center, Pacific Avenue, Atlantic City, New Jersey, USA
- 2 Department of Medicine, Division of Cardiology, Drexel University College of Medicine, Pennsylvania, USA

### Abstract

It presents a case of 42-year-old male with history of chronic kidney disease stage with rash, itching and swelling. Two weeks before he was started on allopurinol for hyperuricemia. Exam showed swelling of face, extremities with diffuse papular rash. Temperature 99.3, BP 122/93, RR 18. Blood work showed worsening renal function (Cr 3.10), transaminitis (LDH 184, AST 104, ALT 136) and eosinophilia of 13.6%. RegiSCAR score of 6 was highly suggestive of Dress Syndrome. Patient's allopurinol was discontinued. Patient was started on steroids and showed improvement. Patient returned three weeks later with chest pain and shortness of breath. BP 110/68, Pulse rate 132, respiratory rate 30 breaths/min, Sat O<sub>2</sub> 87%. CK-MB 30 and troponin 10. Eosinophil count 19%. EKG showed sinus tachycardia and diffuse ST elevation. Emergent cardiac catheterization showed no coronary artery disease, severe LV systolic dysfunction with apical dilation. Ejection fraction was 20% (EF of 55%-60% baseline). Findings were consistent with Takotsubo Cardiomyopathy (TS). He was continued on steroids and lasix. Skin biopsy showed superficial perivascular dermatitis. Subendocardial biopsy showed mild perivascular and subendocardial infiltrates not suggestive of active eosinophilic myocarditis. Patient condition stabilized, and EF improved to 45%-50%. He was discharged on prednisone taper.

**Discussion:** DRESS syndrome is rare, potentially life-threatening hypersensitivity reaction. Early recognition is important as it has associated mortality of 10%. European Registry (RegiSCAR) is the most commonly used diagnostic criteria. Drug induced Takotsubo cardiomyopathy is mostly associated with medication causing direct or indirect catecholamine stimulation. Although a common association with Dress Syndrome, allopurinol induced takotsubo cardiomyopathy is extremely rare. To our knowledge only one other case has reported. We aim to highlight the importance of clinical suspicion for takotsubo cardiomyopathy in patients with new onset heart failure treated with allopurinol that remains a common prescription medication.

**Keywords:** Takotsubo cardiomyopathy; DRESS syndrome; Allopurinol; RegiSCAR; Hypersensitivity; Hyper eosinophilia

**\*Corresponding author:**  
Danish Abbasi, MD.

✉ D\_perwaiz@hotmail.com

Department of Medicine, Division of Cardiology, AtlantiCare Regional Medical Center, Pacific Avenue, Atlantic City, New Jersey 08401, USA.

**Tel:** 609-464-2555

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**Abbreviations:** TS: Takotsubo Syndrome; DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms; RegiSCAR: European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples

### Introduction

Takotsubo syndrome from allopurinol has been rarely reported. Our case is unusual presentation of Stress induced cardiomyopathy from allopurinol induced dress syndrome.

## Case Report

42-year-old male with past medical history of chronic kidney disease stage IV secondary to focal segmental glomerulosclerosis presented with rash, itching and swelling. He was started on allopurinol for hyperuricemia 2 weeks before. Physical examination showed swelling of face, extremities with generalized diffuse papular rash. Temperature 99.3, BP 122/93, RR 18. Blood work showed worsening renal function (Cr 3.10, baseline 2.3-2.4), elevated LFTs (LDH 184, AST 104, ALT 136) and eosinophilia of 13.6%. Chest X-ray was normal. Renal US showed no obstruction with a prominent lymph node in the left groin measuring 4.1 x 1.4 cm. Hepatitis panel was negative. RegiSCAR score of 6 was diagnostic of Dress Syndrome [1]. Patient's allopurinol was discontinued. He was started on high dose steroids, fluid resuscitation, Pepcid and Benadryl. Patient symptoms started improving. Patient was discharged on steroids.

Three weeks later he returned to the emergency department with complains of chest pain and shortness of breath. Patient was normotensive and tachycardic with BP 110/68, Pulse rate 132 with respiratory rate 30 breath/minute, 87% on room air. Labs were significant for CK-MB 30 and troponin of 10. Eosinophil count increased to 19%. EKG showed sinus tachycardia and diffuse ST elevation more predominant in inferior and anterior leads. Emergent cardiac catheterization showed no coronary artery disease. Patient was found to have evidence of severe LV dysfunction and apical dilatation. Ejection fraction was 20% with the last known EF of 55%-60%. Echocardiogram and cardiac catheter findings were consistent with Takotsubo Cardiomyopathy (TS).

Patient was subsequently transitioned to critical care. He required Levophed for support. VQ scan was negative for pulmonary embolism. No infectious source was identified. He was continued on high dose steroids [2] and IV Lasix. Skin biopsy showed superficial perivascular dermatitis. Subendocardial biopsy showed mild perivascular and subendocardial infiltrates not suggestive of active eosinophilic myocarditis. Patient condition stabilized. Patient was taken off vasopressor support. Patient was continued on Lasix and steroids. Patient did not require any supplemental oxygen. Echocardiogram on discharge showed improved EF of 45-50%. He was discharged on prednisone taper.

## Discussion

Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) is rare, potentially life-threatening hypersensitivity reaction [3]. Fever, eosinophilia, lymphadenopathy and swelling are the most common features [4]. Typical latency period is 2-6 weeks. Overall mortality rate is around 10% which makes early identification and management of paramount importance [1]. The incidence of DRESS syndrome is not unknown. A 7 years prospective study of West Indian population by Muller et al. estimated the incidence rate at 0.9/100,000 [5]. Ethnic distribution in this study did not reach significance conclusion.

The diagnosis of DRESS syndrome is challenging because of multiple patterns of drug eruption and variable organs involved.

To assist in this regard scoring systems have been developed. European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples (RegiSCAR) criteria is the most commonly used diagnostic criteria [1,4]. European registry of severe cutaneous adverse reaction (SCAR) includes Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and DRESS. The registry aims to identify all four as separate entities. Scoring system includes fever, enlarged lymph nodes, atypical lymphocytes, eosinophils, skin rash, internal organ involvement, resolution in >15 days, 3 investigations to rule out alternative diagnosis. Score of greater than 5 is considered definite case. Patient in this case presented with fever, lymphadenopathy, rash, eosinophilia, multiple organ involvement and more than 3 negative investigations. Patient RegiSCAR score in this case was 6. Based on the criteria diagnosis of allopurinol induced DRESS syndrome was made. Kim et al. compared RegiSCAR, Bocquet and atypical DIHS criteria from the Japanese group. They concluded that Bocquet's criteria are efficient and appropriate to diagnose DRESS syndrome in clinical practice [6].

Early recognition of the syndrome, withdrawal of suspected drug and adequate supportive care are the mainstays of treatment. Topical corticosteroids can be used for symptomatic relief in patients with limited skin involvement. Systemic steroids are required in most cases [7]. Most patients recover completely after drug withdrawal and appropriate therapy. Corticosteroids are often prescribed when organ involvement is suspected [8]. Long-term sequelae include autoimmune disease and end organ failure [9]. Overall mortality incidence is around 10%. Severe cases of DRESS syndrome should be managed in critical care or burn units when appropriate.

Allopurinol is one of the drugs commonly associated with DRESS syndrome [3]. Results from the prospective RegiSCAR study showed Antiepileptic drugs were involved in 35%, allopurinol in 18%, antimicrobial sulfonamides and dapsone in 12% and other antibiotics in 11% [3]. Hiransuthikul et al. in a retrospective review concluded that phenytoin, nevirapine, allopurinol, and cotrimoxazole were the drugs most commonly associated with DRESS syndrome. DRESS induced by allopurinol had the longest onset time. Allopurinol induced DRESS syndrome was also associated with higher eosinophilia and incidence of renal involvement in this study [10].

Takotsubo syndrome is defined by transient systolic dysfunction of left ventricle in absence of obstructive coronary artery disease [11]. Heart Failure Association of the European Society of Cardiology recommended Takotsubo syndrome' as the formal name for this condition [12]. TS accounts for 1.7%-12.2% cases presented with suspected ST elevation infarction [13]. TS predominantly affects females [14]. Pathophysiology is not completely understood. Catecholamine excess along with coronary artery vaso-spasm has been increasingly proposed as underlying mechanisms. Patients with neurologic or psychiatric disorders were found to have a higher prevalence [14].

Drug induced takotsubo syndrome has been reported in the literature. Drugs associated with direct or indirect

overstimulation of the sympathetic nervous system are more commonly associated Takotsubo cardiomyopathy. A systemic review of drug induced TS determined that over two thirds of drug-induced cases were due to drugs causing direct or indirect catecholamine stimulation [15].

TS from allopurinol has rarely been reported. Our literature search showed only one other reported case of allopurinol induced cardiomyopathy [16]. Takotsubo cardiomyopathy developed in that patient after 5 days of restarting allopurinol as compared to our patient who had a more typical latency period of 4-6 weeks after initial exposure to allopurinol.

We hope to highlight the importance of clinical suspicion for

takotsubo cardiomyopathy in a patient with new onset heart failure previously treated with allopurinol that remains a common prescription medication.

## Conclusion

Dress syndrome is a life-threatening hypersensitivity reaction. Allopurinol is one of the drugs most commonly associated with DRESS syndrome. Allopurinol induced takotsubo cardiomyopathy has been rarely reported in literature. The purpose of this case report is to highlight the importance of clinical suspicion for takotsubo cardiomyopathy in patients with new onset heart failure treated with allopurinol that remains a common prescription medication.

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