

Drug Reaction, Eosinophilia, and Systemic Symptoms (DRESS) syndrome associated with allopurinol leading to acute necrotizing eosinophilic myocarditis and death due to papillary muscle rupture



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Clinical Implications

- There are a few reports in the literature linking Drug Reaction, Eosinophilia and Systemic Symptoms syndrome due to allopurinol and heart failure, but the pathomorphologic basis for this is unclear. We demonstrate one basis for such cardiac complications, namely, acute necrotizing eosinophilic myocarditis and eosinophilic thrombotic microangiopathy, of which treating physicians should be made aware.

TO THE EDITOR:

Drug Reaction, Eosinophilia and Systemic Symptoms (DRESS) syndrome is a well-known severe side effect of a plethora of medications.¹ According to the criteria set up by its first describers, it consists of cutaneous drug eruptions, hematologic abnormalities (increase in eosinophils or abnormal lymphocytosis), and systemic involvements of multiple visceral organs.² In comparison to other organs such as the liver and the kidney, the heart is affected by the DRESS syndrome in a minority of cases.³ Typically, the patients present with first symptoms in an interval of 2 to 6 weeks after initial drug exposure.² Allopurinol, a drug very commonly prescribed for the treatment of hyperuricemia, is known to be a potential cause of DRESS syndrome.⁴ Here, we describe an exceptional case of acute necrotizing eosinophilic myocarditis (ANEM) and

thrombotic microangiopathy complicating DRESS syndrome, which were assumed attributable to a recent addition of allopurinol to the patient's medication regarding the clinical history presented below, and which has not yet been described in this context.⁵

A 78-year-old female patient was admitted to a peripheral hospital because of dyspnea, thoracic pain, and mental confusion. The patient had a medical history of arterial hypertension treated for over 5 years with losartan. Because of recently diagnosed hyperuricemia, allopurinol had been added to the patient's medication 5 weeks before the current hospital admission.

A cranial computed tomography scan showed multiple bihemispheric infarctions. There was no clinical or radiological evidence of myocardial infarction, arterial stenosis, or endocarditis. Four days after admission, she developed a reticular exanthema of the trunk and leukocytosis of $38 \times 10^9/L$ (with 15% eosinophils and 12% monocytes) and thrombopenia of $82 \times 10^9/L$. Skin biopsy showed typical features of toxic epidermal necrolysis/drug-induced exanthema, whereas bone marrow trephine biopsy showed reactive changes with massive excess of eosinophils, CD8+ T cells, and interstitial granulomas, compatible with drug-related changes (Figure 1, A and B). The typical features of human herpes-virus 6 (re-) infection (Exanthema subitum, fever peaks) were not seen. The patient was put on treatment with prednisolone *per os* (1 mg/kg) and allopurinol was withdrawn from her medication because of suspicion of DRESS syndrome, most likely to be caused by allopurinol because this was the only recent change made in her medication and there was no evidence of an infectious disease or malignancy. Skin changes and abnormal blood cell counts quickly improved within the next 2 days. The success of this combined treatment approach was regarded as evidence supporting the assumption that DRESS syndrome in this patient had been caused by allopurinol. However, after 1 day, the patient developed progressive heart failure in need of mechanical ventilation and catecholaminergic medication and died 3 days later despite intensive medical support. Consent for performing an autopsy was given.

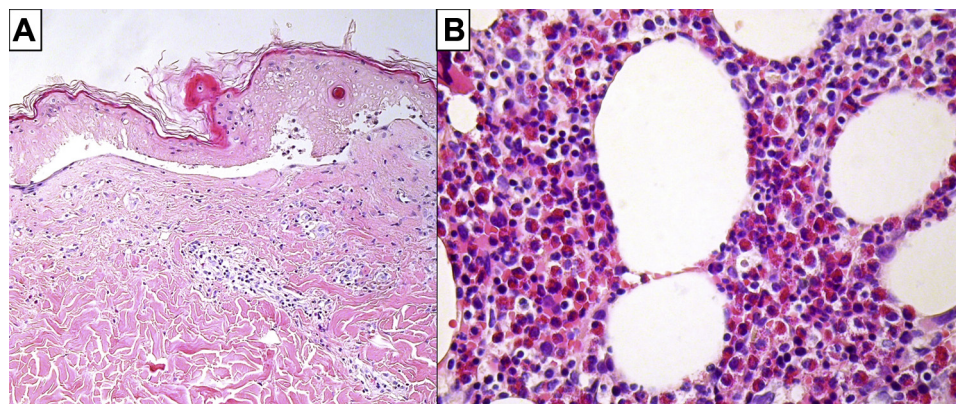


FIGURE 1. Premortal skin and bone marrow biopsies. **A**, Skin biopsy showing necrotic keratinocytes and intraepidermal and subepidermal blistering. There is mild perivascular lymphocytosis and minimal eosinophilia; HE stain, 200 $\times$. **B**, Bone marrow biopsy showing hypercellularity and massive eosinophilia; HE stain, 360 $\times$. HE, hematoxylin-eosin.

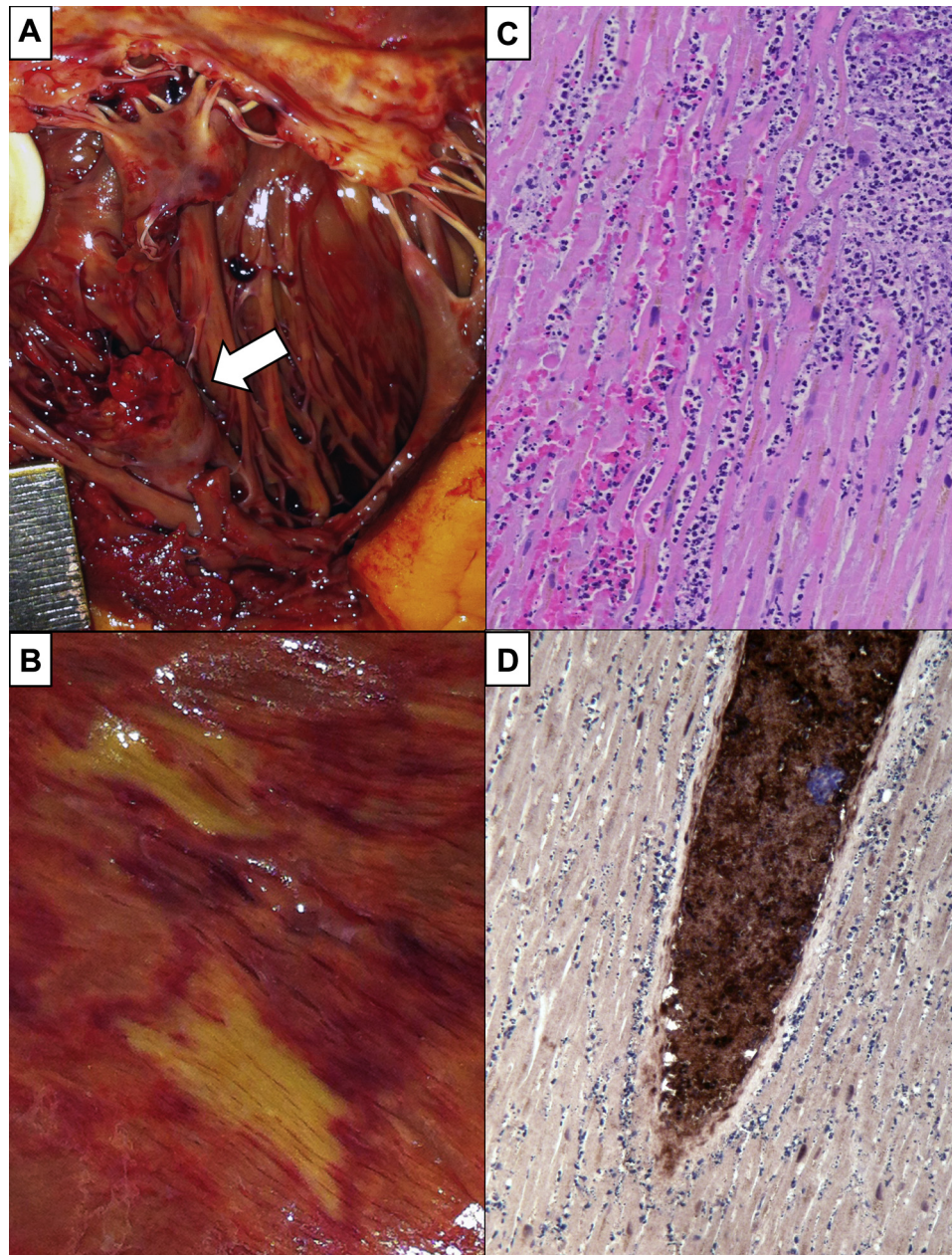


FIGURE 2. Autopsy findings. **A**, Gross image showing ruptured papillary muscle (white arrow). **B**, Area of subacute myocardial necrosis (yellowish discoloration). **C**, Myocardium showing an infiltrate of eosinophils on the left adjacent to necrotic cardiomyocytes on the right which are infiltrated by neutrophils; HE stain, 100 $\times$. Eosinophils are mainly responsible for causing the death of cardiomyocytes due to the release of various enzymes and cytotoxic agents. Neutrophils are mainly seen in areas of necrosis removing the debris of necrotic cells. **D**, Intravascular eosinophilic thrombus causing thrombotic microangiopathy of a myocardial microvessel; staining with anti-eosinophilic peroxidase antibodies and confirming the necrotic intravascular granulocytes to be eosinophils; most of the granulocytes in the necrotic myocardium in this area are neutrophils, which do not stain for antieosinophilic peroxidase; immunoperoxidase stain, 100 $\times$. HE, hematoxylin-eosin.

Autopsy macroscopically showed rupture of the left posterior papillary muscle and subacute necrosis of the left ventricular myocardium in the surrounding area (see Figure 2, A and B). Microscopic evaluation of the heart tissue showed severe ANEM and thrombotic microangiopathy caused by eosinophilic thrombi (Figure 2, C and D). Other organs showed signs of shock

including pericentral necrosis of hepatocytes, acute hemorrhagic pancreatitis, acute ischemic necrosis of the renal tubuli, and involvement of the small lung vessels by thrombotic microangiopathy. The brain displayed multiple hemorrhagic infarctions. The sudden rapidly progressive heart failure was attributed to the extensive necrosis caused by ANEM, finally

leading to a rupture of the papillary muscle next to the infarcted area.

At first glance, the patient described here shows the classical features of DRESS syndrome developing few weeks after initial drug exposure, with skin eruptions being preceded by general malaise and fever.⁶ However, the malignant clinical course despite immediate immunosuppressive treatment and drug withdrawal is remarkable. The main pathophysiology of DRESS syndrome comprises a drug-specific immune response in a genetically predisposed patient, the presence of toxic drug metabolites, and reactivation of viruses.⁴ Most cases of visceral complications due to DRESS syndrome comprise liver, kidney, and the bone marrow, whereas cardiac involvement is rarer, so far mainly reported on the basis of case reports.⁵ Myocarditis occurring in DRESS syndrome can be further subdivided into hypersensitivity myocarditis/acute eosinophilic myocarditis, which has a benign and self-limiting course once the causative drug is stopped and immunosuppression is given, and the more severe variant ANEM. The latter has a mortality rate of more than 70% and a median survival of 3 to 4 days.⁵ The pathogenesis of ANEM is based on the occurrence of toxic drug metabolites in conjunction with an alteration in the patient's immune system and reactivation of viruses such as human herpes-virus 6.⁷ These factors might serve as a prerequisite leading to accumulation, activation, and degranulation of eosinophils in the myocardium and subsequent tissue necrosis, formation of intravascular thrombi, and microangiopathy.⁸

The largest summary of myocarditis in DRESS syndrome comprises 22 cases derived from literature searches.³ There is a plethora of causative drugs listed ranging from anticonvulsants to antibiotics and antiphlogistics. It also lists a report of 2 cases that led to fatality due to heart failure after allopurinol-induced DRESS syndrome,⁹ yet no morphological evaluation of the heart had been performed in these cases. Both patients were described to have had myocardial infarctions, and the authors speculated whether this was attributable to either coronary vasculitis or myocarditis. Both deaths occurred 2 and 4 months after the diagnosis of DRESS syndrome and thus not as fast as in the case presented here. In our patient ANEM and thrombotic microangiopathy were the obvious cause of the myocardial infarction, and there was no evidence of vasculitis of the larger coronary arteries. By morphologic documentation of ANEM accompanied by an eosinophilic thrombotic microangiopathy leading to heart muscle necrosis and finally rupture of the left posterior papillary muscle in a patient with DRESS syndrome

caused by allopurinol, we document a sequela that should be kept in mind. ANEM has been well described in association with DRESS syndrome, yet no other case of ANEM in the context of allopurinol-induced DRESS syndrome can be found in the literature, so this case report might raise the awareness for this potential life-threatening complication. Finally, our case also impressively illustrates the value of postmortem examinations to explain sudden deteriorations in patients' states.

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