Refractory cardiac myocarditis associated with drug rash with eosinophilia and systemic symptoms syndrome due to anti-bipolar disorder drugs: a case report

Hikaru Hagiwara, Arata Fukushima*, Hiroyuki Iwano, and Toshihisa Anzai

Department of Cardiovascular Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Kita-15 Nishi-7, Kita-Ku, Sapporo 060-8638, Japan

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Background
Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a severe adverse drug reaction accompanied by multiple organ dysfunction. Myocarditis is a manifestation, and once acute necrotizing eosinophilic myocarditis (ANEM) develops, the mortality rate is high.

Case summary
We report the case of a 37-year-old man who developed myocarditis associated with DRESS syndrome after starting treatment with lithium and quetiapine for bipolar disorder. At that time, he presented with fever, morbilliform eruption, lymphadenopathy, eosinophilia with atypical lymphocytes, and liver dysfunction; bipolar drugs were discontinued and oral prednisolone begun. Four months later, he was admitted to our institution with worsening skin rash and dyspnoea. Transthoracic echocardiography revealed reduced systolic function in both ventricles, and endocardial biopsy indicated hypersensitivity myocarditis. Cardiac function was temporarily normalized by high-dose prednisolone. However, the inflammation was persistent as shown by a re-elevation of troponin T and fall of left ventricular ejection fraction several months later; in addition, 18F-fluoro-deoxyglucose positron emission tomography with chest computed tomography (FDG-PET/CT) showed focal FDG uptake in the left ventricle. Despite additional treatment with mycophenolate mofetil, the cardiac function deteriorated further, and the patient eventually manifested refractory heart failure classified as New York Heart Association (NYHA) Class III. Myocardial biopsy showed myocyte necrosis associated with ANEM.

Discussion
This is the first case report of DRESS-associated myocarditis due to treatment for bipolar disorder. Although the pathophysiology remains incompletely understood, lithium and/or quetiapine can induce refractory myocarditis in DRESS syndrome. Regular measurements of troponin T and FDG-PET/CT are useful for assessing disease progression in DRESS-associated myocarditis.

Keywords
Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome • Acute necrotizing eosinophilic myocarditis (ANEM) • Bipolar disorder • Quetiapine • Lithium • Heart failure • Case report

Learning points
• Lithium and/or quetiapine, while both valued treatments for bipolar disorder, can elicit refractory myocarditis associated with drug rash with eosinophilia and systemic symptoms (DRESS) syndrome.
• Repeated assessment of troponin T as well as 18F-fluoro-deoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) can provide important clues regarding the disease progression of myocarditis in DRESS syndrome.

* Corresponding author. Tel: +81 11 706 6973, Fax: +81 11 706 7874, Email: arating77@huhp.hokudai.ac.jp. This case report was reviewed by Ola Jan Magnus Vedin, Sameh Shaheen, Mark Philip Cassar and Peregrine Green.

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Introduction

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, a severe drug adverse reaction, is characterized by fever, erythematous eruption, eosinophilia, atypical lymphocytosis, lymphadenopathy, and dysfunction of multiple organs, including the heart. The cardiac involvement in DRESS syndrome generally consists of an acute form of myocarditis: hypersensitivity myocarditis or acute necrotizing eosinophilic myocarditis (ANEM). Although wide-ranging drugs such as anticonvulsants and sulfonamides have been linked to DRESS syndrome, there is little available data on the link between DRESS-related myocarditis and drugs used to treat bipolar disorder. Herein, we report the case of a patient who suffered from DRESS-associated myocarditis due to de novo lithium and quetiapine administration, which could not be controlled by immunosuppressive treatments. Our case highlights the importance of careful monitoring of cardiac function in DRESS syndrome associated with treatment for bipolar disorder.

Timeline

Case presentation

A 37-year-old Japanese man was admitted to our hospital, because of worsening skin rash and exertional dyspnoea. His dyspnoea gradually worsened over the first week before admission, and in parallel, the erythema spread over his whole body.

He had originally presented 4 months prior with fever, morbilliform eruption, eosinophilia, and liver dysfunction, which had developed 1 month after the prescription of lithium 600 mg and quetiapine 25 mg for his bipolar disorder. When his systemic manifestations appeared, the drug lymphocyte stimulation test (DLST) was negative for quetiapine but positive for lithium. According to the European Registry of Severe Cutaneous Adverse Reaction (RegiSCAR) criteria, he was diagnosed with DRESS syndrome (the DRESS score was seven, indicating definite). Upon diagnosis, lithium and quetiapine were discontinued, and oral prednisolone (1.0 mg/kg/day) was administered for four months, followed by a taper to 0.5 mg/kg/day.

On admission, he was afebrile and had a systemic cutaneous eruption, presenting with keratinizing erythema, papules, and oedematous erythema on the back and dorsum of his hands and fingers (Figure 1). A dermatologist diagnosed the rash as a manifestation of DRESS.

Patient timeline: refractory cardiac myocarditis associated with DRESS syndrome due to anti-bipolar disorder drugs

| Time                        | Events                                                                 |
|-----------------------------|------------------------------------------------------------------------|
| 5 months prior to admission | Lithium 600 mg and quetiapine 25 mg were begun for bipolar disorder.  |
| 4 months prior to admission | The patient presented with fever, morbilliform eruptions, lymphadenopathy, eosinophilia with atypical lymphocytes, and liver dysfunction. The drug lymphocyte stimulating test (DLST) was negative for quetiapine but positive for lithium. Lithium and quetiapine were discontinued. Oral prednisolone was started (1.0 mg/kg/day) for 4 months, tapered to 0.5 mg/kg/day. |
| First admission             | Worsening skin rash and exertional dyspnoea. Echocardiography indicated moderate global hypokinesis in both ventricles with a left ventricular ejection fraction (LVEF) of 43%. The 18F-fluoro-deoxyglucose positron emission tomography with computed tomography (FDG-PET/CT) showed diffuse FDG uptake in both ventricular walls. Endomyocardial biopsy revealed a mixed eosinophilic and lymphohistiocytic infiltration without necrosis and fibrosis. |
| 5 days after admission      | High-dose prednisolone (1.0 mg/kg/day) was started.                    |
| 3 weeks after admission     | Endomyocardial biopsy revealed the attenuation of eosinophil accumulation. |
| 2 months after admission    | The LVEF was improved to 61% together with reduced troponin T.         |
| Discharge                   | The dose of prednisolone was reduced to 0.5 mg/kg/day.                 |
| 3 months after admission    | The dose of prednisolone was decreased to 0.25 mg/kg/day.              |
| 5 months after admission    | FDG-PET/CT showed focal FDG uptake in the left ventricular anterior to anteroseptal wall. Echocardiography indicated reduced LVEF of 43% with elevated troponin T level (0.287 ng/mL). The dose of prednisolone was increased to 0.5 mg/kg/day. |
| 9 months after admission    | Mycophenolate mofetil (MMF) was started on top of the 0.5 mg/kg/day prednisolone. |
| 15 months after admission   | FDG uptake was moderately improved. LVEF improved to 50%, but then fell again to 44%. |
| Second admission (17 months after the first admission) | Readmission due to worsening heart failure with New York Heart Association (NYHA) Class III. Echocardiography showed a dramatic decline in LVEF at 20%. Endocardial biopsy revealed myocyte necrosis associated with an eosinophilic and lymphocytic infiltrate. |
| 27 months after the first admission | Patient died of uncontrolled heart failure. |
syndrome. The patient's blood pressure was 105/63 mmHg, and his heart rate was 53 b.p.m. An S3 gallop rhythm, a pan-systolic heart murmur, and moist lung crackles were noted. Electrocardiography showed sinus bradycardia. On chest X-ray, his cardiothoracic ratio was 52% with pulmonary congestion (Figure 2A).

Haematological examination indicated a marked increase in cardiac troponin T (cTnT) to 2.35 ng/mL (reference range 0–0.014). No increase in human herpesvirus (HHV)-6 IgG or DNA in paired-serum samples was found. Transthoracic echocardiography (TTE) revealed reduced systolic function in both ventricles, with a left ventricular ejection fraction (LVEF) of 43% and pericardial effusion (Figure 2B). Acute coronary syndrome was excluded by the coronary angiography. Results of cardiac 18F-fluoro-deoxyglucose positron emission tomography with chest computed tomography (FDG-PET/CT) showed diffuse FDG uptake in both ventricular walls (Figure 3A), indicating active myocardial inflammation.

An endomyocardial biopsy revealed a mixed eosinophilic and lymphohistiocytic infiltration without necrosis or fibrosis (Figure 4A).
The patient was managed in the general ward after diagnosis of DRESS-associated myocarditis. We treated the patient with high-dose prednisolone (1.0 mg/kg/day) for 2 weeks with a slow taper to a maintenance dose of 0.5 mg/kg/day. Concomitantly, an angiotensin converting enzyme inhibitor (enalapril, 2.5 mg/day) was started as a treatment for heart failure; the patient was intolerant of β-blockers due to his symptomatic bradycardia. An endomyocardial biopsy at 3 weeks after initiation of treatment confirmed the attenuation of eosinophil accumulation (Figure 4B). The LVEF evaluated by TTE improved to 61% as cardiac enzymes decreased, and the patient was discharged on the second month.

While we continued to slowly taper the prednisolone to 0.25 mg/kg/day, no exacerbation of clinical symptoms was observed at a regular outpatient visit. By month 5, his cTnT level had risen again to 0.287 ng/mL in parallel with a return to a 43% LVEF. FDG-PET/CT showed focal FDG uptake in the LV anterior to anteroseptal wall (Figure 3B), indicating persistent inflammation. The follow-up endomyocardial biopsy demonstrated sustained infiltration of mixed inflammatory cells, including lymphocytes and eosinophils (Figure 4C). In response to this, we increased prednisolone to 0.5 mg/kg/day, and the LVEF improved to 50% but was not completely normalized. Since this case seemed to be steroid-resistant, mycophenolate mofetil was started on top of the prednisolone at month 9. At month 15, FDG uptake was moderately improved (Figure 3C), but was not completely diminished, and the LVEF fell again to 44%.

At month 17, the patient was readmitted due to worsening heart failure [New York Heart Association (NYHA) Class III]. TTE showed a dramatic decrease in LVEF to 20%. Repeat endomyocardial biopsy revealed myocyte necrosis associated with an eosinophilic and lymphocytic infiltrate, compatible with ANEM (Figure 4D). He was managed symptomatically using an inotropic agent with increased prednisolone (1.0 mg/kg/day). At month 27, he died of uncontrolled heart failure.

**Discussion**

Cardiac involvement has been reported in 4–21% of DRESS syndrome cases, and its manifestations range from asymptomatic to cardiogenic shock. Although a definite diagnosis of DRESS syndrome is sometimes challenging, our case fulfills all seven criteria of the RegiSCAR score. Notably, a series of myocardial biopsies further confirmed DRESS-related myocarditis. The causative medications consist primarily of anticonvulsants and sulfonamides, but also include allopurinol and non-steroidal anti-inflammatory drugs. However, this is the first report showing that drugs used for the treatment of bipolar disorder were causative for DRESS-associated myocarditis.

The histological findings of DRESS-associated myocarditis occur in two forms: hypersensitivity myocarditis and ANEM. The latter is associated with severe clinical symptoms with 50% mortality, such as cardiogenic shock and refractory heart failure. In our case, the initial myocardial biopsy findings consisted of mainly hypersensitivity myocarditis, and thus we expected that the patient would respond to steroids or immunosuppressants. To our surprise, chronic inflammation in the myocardium was sustained and refractory, leading to the progression to ANEM. It remains undetermined whether the persistent myocardial inflammation was due to insufficient doses of immunosuppressants or the inherent reactions to lithium and quetiapine.
As clozapine, another serotonin-dopamine antagonist, has been shown to induce myocarditis, a common pharmacological feature of clozapine and quetiapine as multi-acting receptor targeted antipsychotics (MARTAs) might be associated with the pathogenesis of myocarditis. Indeed, there was no evidence of reactivation of HHV-6, a common cause of DRESS-associated myocarditis. The cytokine release and catecholamine hyperactivation suggested to be associated with clozapine administration may have been the aetiological mechanism. Importantly, clozapine-induced myocarditis often occurs two to four weeks after treatment, which is consistent with the present case.

Unfortunately, we could not determine which drug, lithium or quetiapine, was causative for the DRESS-associated myocarditis, although lithium was more suspicious from the results of DLST. It was noteworthy that an increase in serum cTnT and sustained accumulation of FDG after the introduction of immunosuppressive treatments appeared to reflect the activity of myocardial inflammation as sensitively as histopathological examination. Specifically, FDG-PET/CT is a promising modality for the identification of disease activity in myocarditis as reported by the previous study. Further investigations will be needed in order to optimize the assessment and treatment strategies for DRESS-related myocarditis.

**Conclusion**

This case raises a concern about drug therapy for bipolar disorder as a potential cause of DRESS syndrome and subsequent myocarditis. Once myocarditis develops, close monitoring of serum troponin levels and FDG-PET/CT, as well as serial myocardial biopsies, could provide crucial information on DRESS-related myocarditis disease activity.

**Supplementary material**

Supplementary material is available at European Heart Journal - Case Reports online.

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**Slide sets**: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

**Consent**: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

**Conflict of interest**: none declared.

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