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MINI-FOCUS ISSUE: HEART FAILURE

ADVANCED

CASE REPORT: CLINICAL CASE

A Novel Treatment for a Rare Cause of Cardiogenic Shock

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ABSTRACT

Drug rash with eosinophilia and systemic symptoms (DRESS)–associated myocarditis is a rare but life-threatening adverse drug reaction with a very high mortality rate and no effective therapies. We report a case of DRESS-associated myocarditis complicated by cardiogenic shock successfully treated with a novel targeted therapy. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2020;2:1461–5) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome is a rare, severe, and potentially life-threatening adverse drug reaction. Visceral organ involvement typically manifests as hepatic dysfunction, but may include lymphadenopathy, nephritis, interstitial pneumonitis, and myocarditis. Eosinophilic myocarditis is a fatal and underrecognized manifestation of DRESS with a mortality rate of more than 80% (1). Currently, there are no effective therapies for this syndrome. Here, we report a case of DRESS-associated myocarditis complicated by cardiogenic shock successfully treated with a novel targeted therapy, Janus kinase (JAK) 1/3 inhibitor tofacitinib (Xeljanz, Pfizer, New York, New York).

LEARNING OBJECTIVES

- To understand the pathophysiology and clinical manifestation of DRESS-associated eosinophilic myocarditis.
- To review the mechanism of tofacitinib and understand its potential role in treatment of DRESS myocarditis.

HISTORY OF PRESENTATION

A 37-year-old Hispanic woman with no cardiac history presented with facial swelling, chills, night sweats, and diffuse morbilliform rash approximately 3 weeks after being started on a course of minocycline for acne vulgaris. She was found to have eosinophilia, transaminitis, and atypical lymphocytes on peripheral smear. At that time, her cardiovascular examination was unremarkable, electrocardiogram did not show any significant abnormalities, and troponin T concentration was within normal limits. A transthoracic echocardiogram demonstrated a normal left ventricular function with left ventricular ejection fraction (LVEF) of 68%.

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ABBREVIATIONS AND ACRONYMS

cTNT = cardiac troponin T

DRESS = drug rash with eosinophilia and systemic symptoms

IABP = intra-aortic balloon pump

JAK = Janus kinase

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

TTE = transthoracic echocardiogram

PAST MEDICAL HISTORY

The patient has a history of acne vulgaris. She does not have any known cardiac history.

DIFFERENTIAL DIAGNOSIS

Cutaneous drug eruptions, viral or bacterial infections, hypereosinophilic syndrome, lymphoma, autoimmune connective tissue disease, and DRESS syndrome were on the differential diagnosis for our patient's presentation. She was diagnosed with definite minocycline-induced DRESS syndrome based on RegiSCAR scoring criteria (2,3).

INVESTIGATIONS

She was initially treated with high doses of methylprednisolone followed by prednisone, with resolution of her rash. She was discharged home. Following 2 weeks of therapy with high-dose prednisone, she was readmitted with chest tightness and dyspnea, and was found to be in cardiogenic shock requiring vasopressors and intra-aortic balloon pump (IABP). TTE demonstrated severe global hypokinesis of the left ventricle, LVEF of <20%, N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of 21,300 pg/ml, and cardiac troponin T (cTnT) of 2.53 ng/ml (Figure 1).

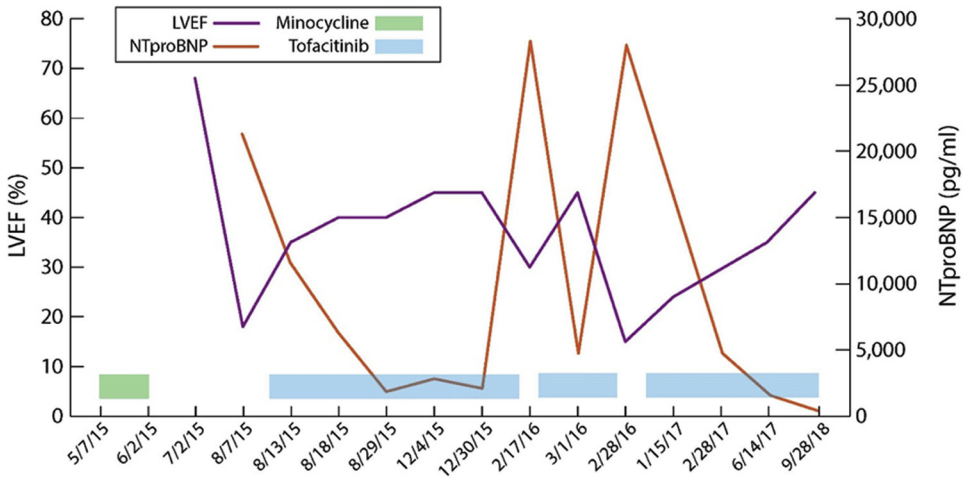
Cardiovascular magnetic resonance imaging demonstrated a nonischemic pattern of delayed enhancement suggestive of myocarditis (Figure 2). An endomyocardial biopsy was not performed due to ensuing clinical instability.

MANAGEMENT AND CLINICAL COURSE

Despite initiation of high-dose methylprednisolone and cyclosporine, the patient continued to rapidly decline, and therapeutic options were limited to urgent mechanical circulatory support. With limited treatment options available, we elected for a targeted treatment strategy using tofacitinib (10 mg twice daily), a JAK 1/3 inhibitor, due to its mechanism aimed at suppression of interleukin (IL)-5, a potent eosinophil cytokine. Within days of tofacitinib initiation, she was able to be weaned off of inotropes and the IABP. A repeat TTE revealed an LVEF of 45%, natriuretic peptide levels decreased dramatically (1,860 pg/ml), and cTnT levels were undetectable.

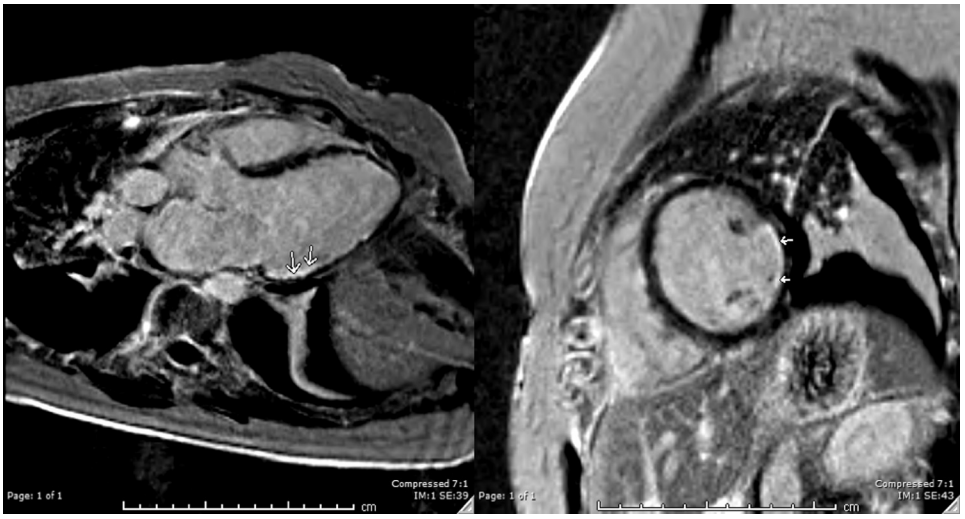
As an outpatient, over the next 6 months, the patient remained free of heart failure symptoms and tolerated up-titration of neurohormonal agents. Of note, during this time she developed near-complete paraplegia with loss of spinal reflexes. Magnetic resonance imaging of the brain and total spine demonstrated leptomeningeal disease involving the lumbar levels and cauda equina as well as the skull base—no clear cause was found, but it was presumed

FIGURE 1 Clinical Course and Treatment With Tofacitinib



Temporal trend in left ventricular systolic function represented by left ventricular ejection fraction (LVEF) and severity of heart failure represented by N-terminal pro-B-type natriuretic peptide (NT-proBNP). Patient was started on tofacitinib during the initial decline; **bars** reveal when therapy was stopped and dosing decreased. All 3 times, reintroduction of tofacitinib led to rapid recovery.

FIGURE 2 **Active Myocarditis on Cardiovascular Magnetic Resonance Imaging**

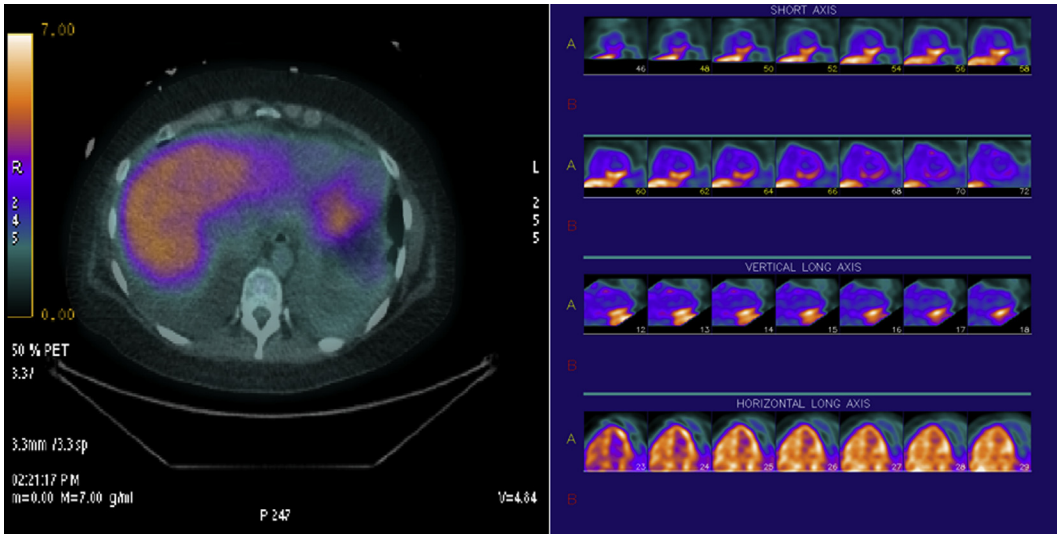


Cardiovascular magnetic resonance imaging with contrast and velocity flow (vertical long-axis view **[left]** and short-axis view **[right]**) demonstrated nonischemic patterns of delayed enhancement suggestive of myocarditis **(arrows)**.

to have the same pathophysiological basis as her cardiac dysfunction.

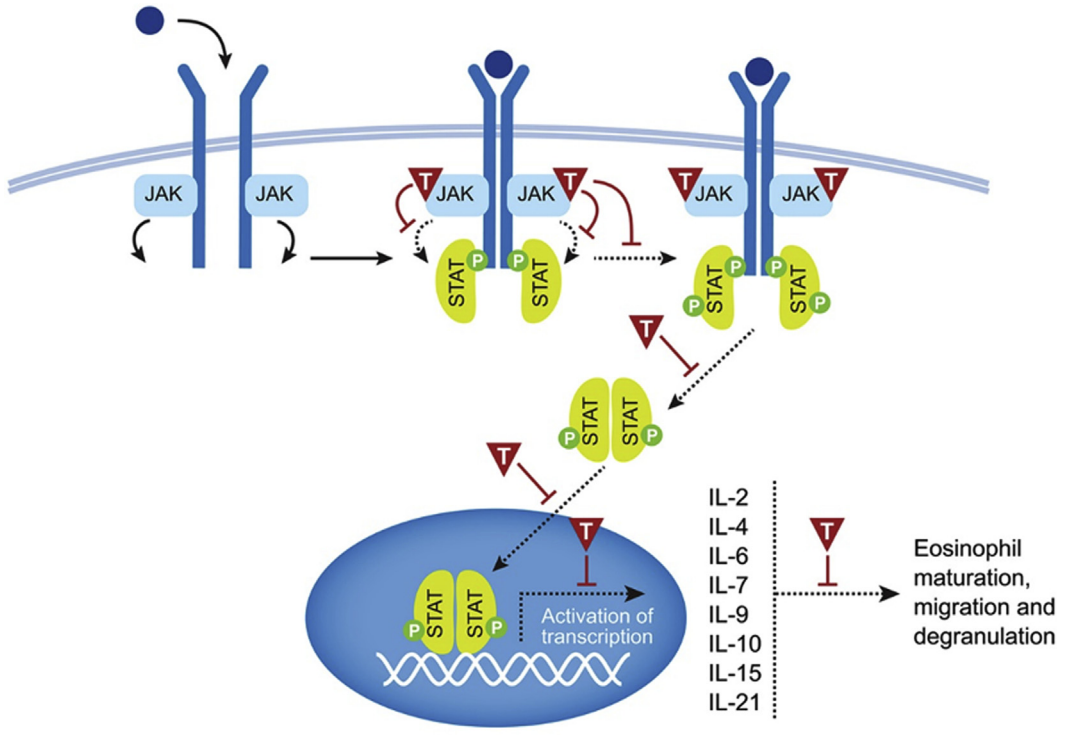
Due to her continued off-label use, the patient had insurance denial for tofacitinib. She was unable to afford the out-of-pocket cost of therapy, was forced to self-discontinue tofacitinib for 2 weeks, and was readmitted with profound cardiogenic shock requiring inotropes and IABP. A repeat TTE showed

FIGURE 3 **Active Inflammation Demonstrated on ^{18}F-Flurodeoxyglycose-Positron Emission Tomography**



^{18}F-flurodeoxyglycose positron emission tomography demonstrated active inflammation in the mid to apical inferior left ventricle, right ventricle, right atrium, and liver.

FIGURE 4 Mechanism of Action of Tofacitinib



Tofacitinib (T) binds to Janus kinase (JAK) 1/3 preventing phosphorylation (P) of signal transducer and activator of transcription (STAT) proteins translocation of STAT to the nucleus thus prevents downstream gene transcription, which leads to reduction in inflammation. IL = interleukin.

severe left ventricular dysfunction with an LVEF of 30%, her NT-proBNP level was 28,300 pg/ml, and troponin T was 9.44 ng/ml. 18F-flurodeoxyglycose positron emission tomography performed at the time demonstrated focal uptake in the mid to apical inferior wall, mild diffuse update in the right atrium and right ventricle, and diffuse uptake in the liver (Figure 3). This was consistent with active cardiac and hepatic inflammation in a pattern consistent with eosinophilic myocarditis and hepatitis. Tofacitinib (10 mg twice daily) was promptly reintroduced. She rapidly recovered; she was weaned off of cardiac support, she tolerated neurohormonal blockade, and TTE performed 2 days after tofacitinib reintroduction demonstrated an EF of 45% with NT-proBNP levels that had decreased to 4,750 pg/ml and undetectable cTnT.

The patient was started on higher-dose steroids for her neurological symptoms. In this setting, the decision was made to decrease tofacitinib dosing by one-half (from 10 mg twice daily to 5 mg twice daily). With this, she developed symptomatic heart failure and needed hospitalization. Her LVEF was noted to be 15% and NT-proBNP level was 28,000 pg/ml; cTnT was not checked. Tofacitinib at the higher dosing (10 mg twice daily) was initiated and symptoms of heart failure improved rapidly over the course of days.

DISCUSSION

Eosinophilic myocarditis is an uncommon but often fatal late complication of DRESS that can occur up to several months after the original diagnosis. It is due to delayed hypersensitivity reaction rather than direct toxicity of the drug. The mechanism of eosinophilic myocarditis is due to eosinophilic tissue infiltration followed by eosinophilic degranulation leading to cardiomyocyte necrosis (4). Inflammatory cytokines are responsible for multiple steps in the pathways of eosinophilic infiltration, migration, and granular release. These cytokines transmit intracellular signaling for downstream gene expression through JAK signal transducer and activator of transcription proteins pathways. Cytokines bind to an

extracellular receptor, which dimerizes and phosphorylates signal transducer and activator of transcription protein that translocates to the nucleus, binds DNA, and initiates gene transcription. Currently, there are no effective therapies for eosinophilic myocarditis, and global immunosuppression is utilized as the mainstay of therapy. However, with the previously mentioned understanding of the pathophysiology, it is reasonable to hypothesize that inflammatory cascade leading to cardiomyocyte necrosis can be blunted or reversed by implementing a therapy that causes direct inhibition of eosinophilic migration, maturation, and degranulation.

Tofacitinib (Xeljanz) is an oral JAK1/JAK3 inhibitor that is approved for the treatment of rheumatoid arthritis and is undergoing trials for other autoimmune diseases. Tofacitinib has structural similarity to adenosine triphosphate, which enables it to act as a reversible, competitive inhibitor of adenosine triphosphate binding site in the catalytic cleft of the kinase domain of JAK proteins. By inhibition of the phosphorylation and activation of JAK1/JAK3 proteins, tofacitinib blocks signaling through the common chain-containing receptors for cytokines, including IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, which leads to its antieosinophilic effects (**Figure 4**). The use and practice of targeted therapy precision medicine has become common practice in the field of oncology, and rheumatology and is now emerging in cardiovascular medicine. The effectiveness of a targeted therapy, which proved to be life-saving in this case, underscores the importance of investigating the utility of tofacitinib for the treatment of eosinophilic myocarditis.

FOLLOW-UP

Within 6 months, the patient's LVEF had improved to 35% and NT-proBNP had decreased to 1,573 pg/ml. The last set of cardiovascular parameters (1.5 years post-initial hospitalization) revealed an LVEF of 45% and NT-proBNP of 406 pg/ml. She remains on tofacitinib through the manufacturer compassionate use program. She has not experienced any adverse events related to the drug.

CONCLUSIONS

To our knowledge, this is the first reported case of using a targeted JAK inhibitor to treat DRESS-associated myocarditis. Our case highlights the novel mechanism and potential for targeted therapy for the treatment of eosinophilic myocarditis, a rare but fatal illness.

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KEY WORDS cardiomyopathy, DRESS, eosinophilia, myocarditis, shock, tofacitinib