Recurrent Myocarditis Treated with Intravenous Immune Globulin and Steroids

Brandon H. Schwartz
Nathan R. Stein
Shervin Eshaghian
Alan C. Kwan
Michelle M. Kittleson

Patient: Male, 18-year-old
Final Diagnosis: Myocarditis
Symptoms: Chest pain • palpitation • shortness of breath
Medication: —
Clinical Procedure: Angiogram • cardiac MRI • transthoracic echocardiogram
Specialty: Cardiology

Objective: Unusual clinical course
Background: Myocarditis is an inflammatory process that can present as acute or chronic with either focal or diffuse involvement of the myocardium. Its incidence is approximately 1.5 million cases per year worldwide. In the United States, viral infection is the most common cause of myocarditis. Most of the reported cases are singular and self-limiting in nature. We present the case of severe recurrent myocarditis in a young adult who was transferred to the Intensive Care Unit.

Case Report: An 18-year-old man presented with chest pressure and troponin I 33 ng/mL. He had presented to another hospital with similar symptoms 3 months prior and was diagnosed with myocarditis that had resolved with colchicine. As part of his workup during this admission, coronary angiogram was normal and biopsy obtained without evidence of an inflammatory process; however, cardiac magnetic resonance imaging (MRI) was consistent with myocarditis and Coxsackie B titers indicated prior infection, leading to a diagnosis of clinically suspected recurrent viral myocarditis. He was treated with intravenous immunoglobulin (IV Ig) and a steroid taper, with rapid improvement in symptoms over the ensuing weeks without evidence of further recurrence or sequelae.

Conclusions: We present a case of recurrent Coxsackie B myocarditis based on presentation and imaging. Myocarditis is an important diagnosis to consider when a young, healthy individual presents with chest pain mimicking acute coronary syndrome, especially during the COVID pandemic. If there is evidence of myocarditis on MRI or endomyocardial biopsy, immunosuppressive therapy should be considered in patients with recurrent and severe presentations.

Keywords: Chest Pain • Coxsackievirus Infections • Immunoglobulins, Intravenous • Myocarditis

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/935974
Background

Myocarditis is an inflammatory disease with presentations ranging from asymptomatic to cardiogenic shock. Myocarditis may be autoimmune (systemic lupus erythematosus, sarcoidosis, and giant cell myocarditis), infectious (classically Coxsackie A/B, Streptococcus, Influenza, Parvovirus B19), malignant, or drug-induced [1]. Coxsackie B is an enterovirus that typically results in a benign, febrile illness in children. While Coxsackie B is known to cause myocarditis, recurrent myocarditis due to Coxsackie B has been rarely reported in the literature [2-4].

By the Dallas criteria, an inflammatory infiltrate and associated myocyte necrosis or damage not characteristic of an ischemic event present on cardiac biopsy is the criterion standard for diagnosis of myocarditis [5]. However, the sensitivity of biopsy is low and can lead to false negatives due to sampling error [6,7]. Given the low sensitivity of myocardial biopsy to diagnose myocarditis, cardiac MRI is an alternative diagnostic modality, with the additional advantage of being noninvasive.

Clinically suspected myocarditis can be diagnosed based on a combination of clinical presentation and noninvasive diagnostic findings including typical MRI findings. Based on the 2018 Updated Lake Louise Criteria, the presence of a T1-based abnormality (increased T1 relaxation times, extracellular volume, or positive late gadolinium enhancement [LGE]) and T2-based abnormality (increased T2 relaxation times or T2-weighted signal increase) on cardiac MRI is consistent with myocarditis, particularly in the presence of supportive elements such as pericarditis or LV dysfunction [8,9].

IV Ig has been used for a variety of diseases since its introduction in the 1950's. It’s use for neurologic disorders such as Guillain-Barre syndrome and myasthenia gravis are well known. Additionally, it is useful in hematologic processes including leukemias and lymphomas or post-bone marrow transplant. Lastly, it is commonly used in immunologic deficiency and Kawasaki syndrome [10].

The use of intravenous immune globulin (IV Ig) for severe myocarditis has been documented in case reports but there is conflicting evidence of benefit based on meta-analysis [11] and Cochrane review [12]. The mechanism of action of IV Ig remains unclear, though it appears to have an immunomodulatory effect, suppressing viral replication through antibody-mediated killing and offering an anti-inflammatory role in cytokine release [13]. Similarly, there is a Cochrane review of corticosteroid use in myocarditis which showed minimal to no benefit in prior studies [14]. However, based on potential benefit in patients with Covid-19 has resulted in a resurgence in use with reported benefit in Covid-associated myocarditis [15].

We present a rare case of recurrent myocarditis with classic findings of LGE and edema on MRI, but biopsy without evidence of inflammatory cells. It is important to consider pathologies other than obstructive coronary disease, such as myocarditis, in young patients without risk factors for acute coronary syndrome. Our patient’s severe presentation with elevated troponin and severe chest pain requiring admission to the intensive care unit led the treatment team to use IV Ig and steroids, with subsequent improvement in symptoms and inflammatory markers. In such cases, immunosuppression should be considered.

Case Report

An 18-year-old man with no significant past medical history presented to the emergency department with a 2-day history of non-exertional chest pressure with radiation to his left arm. The episodes initially lasted a few minutes but became unremitting on the day of presentation. The discomfort was slightly relieved by sitting up. He denied shortness of breath, palpitations, or lightheadedness.

On examination, the jugular venous pressure was estimated at 6 cm water. Cardiac auscultation revealed regular rhythm with no murmurs, rubs, or gallops. His extremities were warm without edema. Laboratories on presentation demonstrated troponin I of 33 ng/mL (reference <0.03 ng/mL) and B-Type Natriuretic Peptide of 24 pg/mL (<100 pg/mL). A basic metabolic panel was normal. C-reactive protein was 8.3 mg/L (<5 mg/L) and erythrocyte sedimentation rate was 28 mm/hr (<15 mm/hr). SARS-CoV-2 PCR was negative. Electrocardiogram (ECG) showed sinus bradycardia without Q waves, PR-segment, or ST-segment changes. A transthoracic echocardiogram (TTE) revealed normal left ventricular size and wall thickness with ejection fraction 50% and mild anterior hypokinesis and no pericardial effusion.

Of note, he had been admitted to another hospital 3 months prior with chest discomfort and syncope in the context of upper respiratory tract infection symptoms. Troponin T during that hospitalization peaked at 1.83 ng/mL (reference <0.03 ng/mL). ECG showed no ST-segment changes. TTE revealed normal left ventricular function with no wall motion abnormalities. SARS-CoV-2 PCR was negative. He received a presumptive diagnosis of myocarditis. After discharge, he followed up with a cardiologist who prescribed colchicine daily and acetaminophen as needed. He had near resolution of pain over the subsequent 3 months (Figure 1).

Coronary angiography revealed no coronary artery disease. Cardiac MRI with contrast was consistent with active myocarditis, particularly in the presence of supportive elements such as pericarditis or LV dysfunction. We present a rare case of recurrent myocarditis with classic findings of LGE and edema on MRI, but biopsy without evidence of inflammatory cells. It is important to consider pathologies other than obstructive coronary disease, such as myocarditis, in young patients without risk factors for acute coronary syndrome. Our patient’s severe presentation with elevated troponin and severe chest pain requiring admission to the intensive care unit led the treatment team to use IV Ig and steroids, with subsequent improvement in symptoms and inflammatory markers. In such cases, immunosuppression should be considered. We present a rare case of recurrent myocarditis with classic findings of LGE and edema on MRI, but biopsy without evidence of inflammatory cells. It is important to consider pathologies other than obstructive coronary disease, such as myocarditis, in young patients without risk factors for acute coronary syndrome. Our patient’s severe presentation with elevated troponin and severe chest pain requiring admission to the intensive care unit led the treatment team to use IV Ig and steroids, with subsequent improvement in symptoms and inflammatory markers. In such cases, immunosuppression should be considered.
imaging, mildly elevated T1 and extracellular volume measurements which may be due to injury, necrosis, or edema, and basal/mid-predominant circumferential mid-myocardial and subepicardial late gadolinium enhancement (Figure 2). The high burden of LGE suggested significant myocardial injury and necrosis. Right heart catheterization at the time of endomyocardial biopsy showed normal filling pressures. Endomyocardial biopsy revealed no evidence of inflammation, but the specimen was noted to be insufficient for diagnosis.

Coxsackie B2 and B5 antibody titers were positive at 1:16 (reference <1:8), which at that level is often indicative of prior infection. ANA was 1:80, but no other specific markers were reactive, including SSA, Smith, Scl-70, Jo-1, SRP, double-stranded DNA, proteinase-3 antibody, and mitochondrial antibody.

Over the course of the next 12 h, troponin I rose to 142 ng/mL. Based on the significantly elevated troponin, ongoing chest pain, cardiac MRI findings, and pending endomyocardial biopsy results, he received intravenous immune globulin 1 g/kg daily for 2 days and methylprednisolone 500 mg daily for 3 days, followed by a prednisone taper over the next 2 months.

He noted near resolution of chest pain after 5 days. By the time of discharge, troponin was 6.46 ng/mL. Two months after discharge, he had completed a prednisone taper. He reported minimal chest discomfort. An echocardiogram showed normal left ventricular function with EF 60% and normal wall motion. He did not have follow-up cardiac MRI, troponin, or Coxsackie titers.

Discussion
The diagnosis of clinically suspected myocarditis was based on the patient’s clinical presentation of chest discomfort with antecedent viral symptoms, troponin elevation with normal angiogram, inflammation, and injury on MRI with elevated inflammatory markers and positive Coxsackie B titers. Although biopsy is considered the criterion standard for diagnosis, in this case it was important to avoid anchoring bias and focus on the patient’s clinical context rather than solely on the negative biopsy with an insufficient sample.

The decision to treat viral myocarditis with IV Ig and corticosteroids was based on the patient’s severe presentation and concern for recurrence given that prior studies for both corticosteroids and IV Ig treatments elicited mixed outcomes in retrospective analyses [16,17]. Since our patient’s timeline of infection was not apparent and no previous titers were drawn, the clinical team decided to treat as both an acute and more subacute process. While IV Ig may be more useful for acute cases of fulminant myocarditis, steroids can offer a more sustained immunosuppressive effect for later phases of host immune response. Given the paucity of data regarding IV Ig
monotherapy versus combination with steroids, we decided to treat more aggressively given the severity of the patient’s symptoms and troponin level. However, this illustrates the need for more randomized data to determine the best treatment for varying levels of disease.

This case offers diagnostic and management lessons for clinically suspected myocarditis. First, on the initial presentation months prior, a more in-depth evaluation with cardiac MRI or endomyocardial biopsy might have been considered given the unexplained elevated troponin. While colchicine may be used to treat pericarditis, pericarditis alone would not explain the troponin elevation and acetaminophen is not used to treat myocarditis. It is possible that a cardiac MRI performed earlier in the disease course may have shown a greater degree of myocardial inflammation and a biopsy might have been higher-yield. While other potential etiologies of subepicardial LGE on MRI exist, including genetic variations of desmoplakin mutation like arrhythmogenic left ventricular cardiomyopathy, the patient did not have a family history of cardiomyopathy and the ECG and echocardiogram did not have classic findings of this condition [18].
Figure 2. Cardiac MRI images demonstrating evidence of myocarditis. (A) STIR acquisition of mid-ventricular short axis: increased T2 signal intensity (SI) in the myocardium (SI myocardium: 275, SI skeletal muscle: 100). (B) MOLLI T1 map of mid-ventricular short axis: diffusely and focally (green arrows) increased T1 values (T1 mid-septal: mean 1170 msec, maximum 1364 msec). (C) T2-prepped SSFP T2 map of mid-ventricular short axis: diffusely- and focally-increased (blue arrows) T2 values (T2 mid-septal: mean 67 msec, max 80 msec). (D) PSIR late gadolinium enhancement (LGE) 4-chamber view. (E) Short axis stack: dense regions of mid-myocardial LGE (red arrows) consistent with acute injury, necrosis, and possible scarring.
Second, the diagnosis of recurrent Coxsackie B-related myocarditis could not be definitively confirmed in this patient based on the lack of Coxsackie B titers checked during the first hospitalization and the inability to perform biopsy viral genome analysis. Given the concern for recurrent myocarditis, the use of intravenous immune globulin and corticosteroids for empiric therapy appeared justified even though no prior randomized trials using the combination exist.

Conclusions

In conclusion, we present lessons learned from a case of presumed recurrent Coxsackie B-related myocarditis. When a young patient presents with unexplained troponin elevation, a detailed evaluation to exclude myocarditis is essential. If evidence of myocarditis is present, empiric immunosuppressive therapy may be considered, especially if there is concern of recurrence. This successful treatment signifies the need for further data for optimal treatment of myocarditis and whether IV Ig should be used in combination with steroids or as monotherapy for severe disease.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Sagar S, Liu PP, Cooper LT. Myocarditis. Lancet. 2012;379(9817):738-47
2. Karavidas A, Lazaros G, Noutsias M, et al. Recurrent coxsackie B viral myocarditis leading to progressive impairment of left ventricular function over 8 years. Int J Cardiol. 2011;151(2):e65-67
3. Nikolaou M, Lazaros G, Karavidas A, et al. Recurrent viral myocarditis: The emerging link toward dilated cardiomyopathy. Hellenic J Cardiol. 2018;59(1):60-63
4. Rose HD. Recurrent illness following acute coxsackie B 4 myocarditis. Am J Med. 1973;54(4):544-48
5. Aretz HT, Billingham ME, Edwards WD, et al. Myocarditis. A histopathologic definition and classification. Am J Cardiovasc Pathol. 1987;1(1):3-14
6. Baughman KL. Diagnosis of myocarditis: Death of Dallas criteria. Circulation. 2006;113(4):593-95
7. Chow LH, Radio SJ, Sears TD, McManus BM. Insensitivity of right ventricular endomyocardial biopsy in the diagnosis of myocarditis. J Am Coll Cardiol. 1989;14(4):915-20
8. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: Expert recommendations. J Am Coll Cardiol. 2018;72(24):3158-76
9. Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: A JACC White Paper. J Am Coll Cardiol. 2009;53(17):1475-87
10. Jolles S, Sewell WA, Misbah SA. Clinical uses of intravenous immunoglobulin. Clin Exp Immunol. 2005;142(1):1-11
11. Huang X, Sun Y, Su G, Li Y, Shuai X. Intravenous immunoglobulin therapy for acute myocarditis in children and adults. Int Heart J. 2019;60(2):359-65
12. Robinson J, Hartling L, Vandermeer B, et al. Intravenous immunoglobulin for presumed viral myocarditis in children and adults. Cochrane Database Syst Rev. 2020;8:CD004370
13. Takada H, Kishimoto C, Hiraoka Y. Therapy with immunoglobulin suppresses myocarditis in a murine coxsackievirus B3 model. Antiviral and anti-inflammatory effects. Circulation. 1995;92(6):1604-11
14. Chen HS, Wang W, Wu SN, Liu JP. Corticosteroids for viral myocarditis. Cochrane Database Syst Rev. 2013(10):CD004471
15. Kamarullah W, Nurcahyani, Mary Josephine C, et al. Corticosteroid therapy in management of myocarditis associated with COVID-19: A systematic review of current evidence. Arch Acad Emerg Med. 2021;9(1):e122
16. English RF, Janosky JE, Ettedgui JA, Webber SA. Outcomes for children with acute myocarditis. Cardiol Young. 2004;14(5):488-93
17. Amabile N, Fraisse A, Bouvenot J, et al. Outcome of acute fulminant myocarditis in children. Heart. 2006;92(9):1269-73
18. Augustine JB, Erios R, Nakou E, et al. Dilated cardiomyopathy and arrhythmogenic left ventricular cardiomyopathy: A comprehensive genotype-imaging phenotype study. Eur Heart J Cardiovasc Imaging. 2020;21(3):326-36