Coxsackie Myocarditis and Hepatitis with Reactivated Epstein-Bar Virus (EBV): A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient:	**Female, 57**
Final Diagnosis:	**Coxsackie myocarditis and hepatitis**
Symptoms:	**Fever • headache • general malaise • sob.**
Medication:	**—**
Clinical Procedure:	**Echocardiography • cardiac MRI**
Specialty:	**Cardiology**

Objective: **Unusual clinical course**

Background: Myocarditis, defined as inflammation of myocardial tissue of the heart, is an uncommon cardiac presentation and is due to a variety of causes. It affects 1% of the US population, 50% of which is caused by coxsackie B virus. Cardiac tissue is the prime target, and destruction of myocardium results in cardiac failure with fluid overload.

Case Report: Our patient was a 57-year-old woman with fever, headache, neck pain, and generalized malaise. Her white blood cell count was 13×10^3 cells/mm³. Interestingly, lumbar puncture ruled out meningitis. An echocardiogram to evaluate elevated troponin revealed an ejection fraction of 30% with severe left ventricular global hypokinesis without valvular vegetations consistent with new-onset systolic heart failure. Cardiac MRI showed a small pericardial effusion with bilateral pleural effusion. As she continued to be febrile, a viral panel was ordered, revealing coxsackie B4 antibody titer of 1: 640 (reference: >1: 32 indicates recent infection) with positive Epstein-Barr virus deoxyribonucleic acid by PCR, consistent with viral myocarditis.

Conclusions: Coxsackie B virus myocarditis is rarely recognized and reported by the general internist in clinical practice, so we would like present our experience with an interesting clinical presentation of the viral prodrome. An estimated 95% people in the US are infected with Epstein-Barr virus by adulthood, but it remains dormant in memory B lymphocytes. Recirculation of these B cells in lymphoid tissue stimulated by antigens, which in our case is coxsackie B virus; they differentiate into plasma cells, and the production of Z Epstein-Barr replication activator protein (ZEBRA) increases viral replication, thus explaining the positive EBV DNA measured by PCR.

MeSH Keywords: **Cardiac Catheterization • Coxsackievirus Infections • Epstein-Barr Virus Infections • Magnetic Resonance Imaging • Myocarditis**

Abbreviations: **ED** – Emergency Department; **CT** – computed tomography scan; **MRI** – magnetic resonance imaging; **ICU** – Intensive Care Unit; **EKG** – electrocardiogram; **CK** – creatinine kinase; **EBV** – Epstein-Bar Virus; **LFT** – liver function tests; **CMR** – cardiac magnetic resonance imaging; **CVA** – Coxsackie virus A; **CVB** – Coxsackie virus B; **CD** – cluster differentiation; **NYHA** – New York Heart Association Classification; **MI** – myocardial Infarction

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/900096

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Background

We describe an unusual presentation of coxsackie B virus causing a viral prodrome. Although widely studied in the literature, it is rarely recognized and reported by the general internist in clinical practice. Our patient presented with symptoms masquerading as meningitis, which led to a delay in diagnosis. Therefore, we emphasize the importance of recognizing the viral prodrome and provide a brief description of how we arrived at the diagnosis. Recognition of this syndrome is critical to initiation of appropriate treatment and preventing fatality.

Case Report

A 57-year-old female health care worker presented with 4 days of progressively worsening fever, headache, neck pain, and generalized malaise. She had a past history of poorly controlled diabetes on insulin. Review of systems was also remarkable for cough and shortness of breath from 1 week, but she denied having blurred vision, passing out, chest pain, or palpitations.

Additional history revealed that she had presented to the ED 3 days before with headache and neck pain, for which she was sent home with acetaminophen. She denied any allergies and had no significant family history. On exam, she had a faint systolic murmur at the apex, fine crackles at the lung bases on both sides, the JVP was not elevated, and she had no lower-extremity edema. Scattered erythematous papules were noted up to the thighs. Vitals: Blood pressure 87/54 mmHg, pulse 100 bpm, oral temperature 38.9°C, resp. rate 18/min, with sat. 97% (Table 1).

She was admitted to the ICU for continued hypotension, despite fluid resuscitation. Further work-up by lumbar puncture to rule out meningitis revealed protein of 94 mg/dL, glucose of 164 mg/dL, with few white cells and no bacteria. Chest X-ray showed cardiomegaly with bilateral pleural effusions. Labs revealed troponin elevated to 1.21 (ref. range: <0.04 ng/mL), CK to 285 (ref. range: 38–234) without any changes on EKG. An echocardiogram was done to further evaluate her elevated troponin, as she had no EKG changes, which incidentally showed an ejection fraction of 30% with severe left ventricular global hypokinesis without valvular vegetations, consistent with new-onset systolic heart failure. Troponin then trended down to 0.9 during her hospital stay (Table 2).

Abdominal ultrasound showed gall bladder sludge and normal appearance of the liver. CT abdomen showed small pelvic ascites. LFTs subsequently improved during the hospital stay. There was no angiographic evidence of coronary atherosclerosis, with elevated right and left ventricular pressures on cardiac catheterization. Because of her viral constitutional

Table 1. Laboratory investigations.

WBC – 12.9×10³ cells/mm³
AST – 61
ALT – 220 IU/L
ALP – 461 IU/L

AST – aspartate transaminase; ALT – alanine transaminase; ALP – alkaline phosphatase.

Table 2. Echocardiographic findings.

Normal left ventricular chamber size
Left ventricular end diastolic volume=99 ml
Left ventricular end systolic volume=70 ml
Left ventricular ejection fraction=30%
Severe global hypokinesis of the left ventricle

symptoms with elevated troponin, cardiac MRI was done to rule out myocarditis, which showed small pericardial effusion with bilateral pleural effusion. She was treated with symptomatic and supportive therapy. On consultation with cardiology, she was started on Metoprolol XL 12.5 mg OD, Lisinopril 5 mg OD, Furosemide 40 mg OD, and spironolactone 12.5 mg OD during her hospital stay. As she continued to be febrile with temperature >39°C and without a focus for bacterial infection and negative blood cultures, a viral panel was ordered, which interestingly revealed a coxsackie virus B4 antibody titer of 1: 640 (ref. >1: 32 indicates recent infection) with positive EBV DNA, consistent with viral myocarditis. The patient subsequently improved, with marked resolution of symptoms and received outpatient follow-up.

Discussion

Myocarditis is an inflammatory disease of the myocardium, affecting 1% of the US population 50%, of which are caused by coxsackie B virus [1,2]. Most cases are middle-aged men, with an average age of onset at 42 years. The World Health Organization/International Society and Federation of Cardiology (WHO/ISFC) [3] definition specifies diagnosis by established histological, immunological, and immuno-histochemical criteria. The criterion standard for diagnosis is a myocardial biopsy; however, given the invasive nature of the procedure, serology is more widely used. CMR serves as an important diagnostic non-invasive imaging test to confirm (and exclude) suspected myocarditis given its high specificity and positive

predictive value, especially within 1–2 weeks of symptom onset [4]. Unfortunately, there is no criterion standard test for non-invasive diagnosis.

Microbiology

Coxsackie viruses are members of the genus Enterovirus, family Picornaviridae, further subdivided into CVA and CVB. There is a total of 23 serotypes of CVA and 6 serotypes of CVB [5], although most cases are attributed to CVB [6]. The incubation period is about 2–10 days and onset of cardiac symptoms typically occurs 2 weeks after viral infection. It is transmitted fecal-orally and through direct contact with mucosal secretions. Coxsackie B virus initially replicates in the gut and spleen and eventually spreads to its target organ, the heart [7]. Once in the heart, replication of the virus causes damage to the heart cells and induces migration of white blood cells into the heart tissue. The white blood cells subsequently activate an autoimmune process in which the white blood cells kill the virus-infected heart cells and normal heart cells, which are not infected. This autoimmune process persists long after the viral particles are no longer detected. The destruction and damage to the heart cells results in myocarditis and heart failure.

Pathogenesis

The pathogenesis of myocarditis can be divided into 3 phases [8]: 1) Nonspecific innate immune response causing destruction of myocardial cells along with viral-mediated cell lysis [9]; 2) The second phase is more specific, with CD 8+ lymphocytes acting to eliminate the virus and causing more destruction of infected cardiac myocytes, leading to heart failure; and 3) A few weeks later, destroyed cardiac myocytes are replaced by fibrosis, with progressive biventricular dilation and heart failure. Chronic myocarditis develops in 50% of cases and dilated cardiomyopathy in 21%.

Diagnosis

Biomarkers (such as troponins or creatine kinase) lack specificity, but may help to confirm the diagnosis of myocarditis [10,11]. In patients with acute myocarditis, serum concentrations of troponin I and T are elevated more frequently than creatine kinase myocardial band fraction [12], and higher levels of troponin T have been shown to be of prognostic value. EKG is used as a screening tool despite low sensitivity [13]. EKG changes vary from nonspecific ST and T wave changes to ST elevation myocardial infarction mimicking an acute myocardial infarction [14]. Echocardiography is helpful, but not diagnostic. Echo shows left ventricular dysfunction that may be segmental, reflecting the focal nature of myocardial necrosis [15]. According to the Dallas criteria [16], biopsy evidence of active myocarditis shows: "*an inflammatory infiltrate of the myocardium with*

or without degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease." While biopsy does not necessarily alter the management plan, it confirms the diagnosis, but is now rarely performed.

Treatment

Recent data support the possible role of administration of immune globulin in patients with new-onset dilated cardiomyopathy secondary to myocarditis [17] with improvement in EF from 25% to 41%, as well as also improvement of functional class of NYHA from II/IV to I/II. Current management of patients with acute heart failure secondary to myocarditis should be treated in the same way as heart failure secondary to ischemic heart disease or other myocarditis causes. Once the patient is stabilized, conventional treatment with ACE inhibitors, beta blockers, and spironolactone are initiated. These agents can be discontinued if there is clinical or echocardiographic evidence of complete recovery.

Prevention

While coxsackie virus infection cannot be prevented, it can be controlled through sanitary measures. As a fecal-orally transmitted virus, spread of the virus can be limited by improving sanitation and thoroughly washing hands.

Myocarditis can be managed by reducing inflammation with analgesics and thus limiting the amount of heart damage that occurs. As myocarditis impairs the functioning of the heart, activity should be limited and excessive dietary intake of salt should be avoided. Oxygen can also be given to reduce the workload on the heart and, in cases of heart failure, heart transplants can be performed.

Conclusions

It is important to understand the common etiologies of biventricular heart failure. Although widely studied in the literature, coxsackie B virus is an uncommon cause of myocarditis and acute-onset heart failure. The initial work-up should include EKG, ECHO, cardiac MRI, CK, and troponins. Myocarditis should be suspected in patients with or without cardiac signs and symptoms who have a rise in cardiac biomarkers (e.g., troponin), electrocardiographic changes suggestive of acute myocardial injury, arrhythmia, or abnormalities of cardiac function (typically on echocardiogram or cardiac magnetic resonance [CMR]), particularly if the clinical findings are new and unexplained. An estimated 95% of people in the US have been infected with EBV by adulthood, but the virus remains dormant in memory B cells. Stimulation of these B cells by antigens leads to viral replication.

Endomyocardial biopsy, although rarely done, is indicated if the patient has hemodynamic instability, ventricular tachycardia, heart block, or fails to respond to standard therapy. The treatment is the same as in treating for heart failure secondary to MI. This case illustrates the potential of coxsackie B virus to cause myocarditis with hepatitis and other masquerading symptoms.

Competing of interests

The authors declare that they have no competing interests.

Acknowledgements

References:

1. Feldman AM, McNamara D: Myocarditis. N Engl J Med, 2000; 343: 1388–98

2. Maisch B, Seferović PM, Ristić AD et al: Guidelines on the diagnosis and management of pericardial diseases executive summary. Eur Heart J, 2004; 25: 587–610

3. Richardson P, McKenna W, Bristow M: Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies. Circulation, 1996; 93: 841–42

4. Friedrich MG, Marcotte F: Cardiac magnetic resonance assessment of myocarditis. Circulation, 2013; 6: 833–39

5. Baboonian C, Treasure T: Meta-analysis of the association of enteroviruses with human heart disease. Heart, 1997; 78: 539–43

6. Andréoletti L, Lévêque N, Boulagnon C et al: Viral causes of human myocarditis. Arch Cardiovasc Dis, 2009; 102: 559–68

7. Wilson FM, Miranda QR, Chason JL, Lerner AM: Residual pathologic changes following murine Coxsackie A and B myocarditis. Am J Pathol, 1969; 55: 253–66

8. Kawai C: From myocarditis to cardiomyopathy: mechanisms of inflammation and cell death: Learning from the past for the future. Circulation, 1999; 99: 1091–100

9. Bergelson JM, Cunningham JA, Droguett G et al: Isolation of a common receptor for Coxsackie B viruses and adenoviruses 2 and 5. Science, 1997; 275: 1320–23

10. Cooper LT Jr.: Myocarditis. N Engl J Med, 2009; 360: 1526–38

11. Smith SC, Ladenson JH, Mason JW, Jaffe AS: Elevations of cardiac troponin I associated with myocarditis. Experimental and clinical correlates. Circulation, 1997; 95: 163–68

12. Lauer B, Niederau C, Kuhl U: Cardiac troponin T in patients with clinically suspected myocarditis. J Am Coll Cardiol, 1997; 30: 1354–59

13. Morgera, Di Lenarda A, Dreas L: Electrocardiography of myocarditis revisited: Clinical and prognostic significance of electrocardiographic changes. Am Heart J, 1992; 124: 455–67

14. Pauschinger M, Noutsias M, Lassner D et al:I nflammation, ECG changes and pericardial effusion: Who to biopsy in suspected myocarditis. Clin Res Cardiol, 2006; 95: 569–83

15. Chandraratna PAN, Nimalasuriya A, Reid CL et al: Left ventricular asynergy in acute myocarditis. JAMA, 1983; 250: 1428–30

16. Aretz HT, Billingham ME, Edwards WD et al: Myocarditis. Am J Cardiovasc Pathol, 1986; 1: 3–14

17. McNamara DM, Rosenblum WD, Janosko KM et al: Intravenous immune globulin in the therapy of myocarditis and acute cardiomyopathy. Circulation, 1997; 95: 2476–78