Overlapping Etiologies in a Young Patient with Severe Myocarditis: A Case Report

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Introduction

Etiological identification of young patients with heart failure should always be a medical goal. In this scenario, infectious myocarditis is a possible diagnosis and, when it occurs, it has a benign course in the majority of cases. However, congenital heart diseases or familial forms of cardiomyopathy should be considered in differential diagnosis and/or concomitantly, particularly in more severe presentations of myocarditis. In these cases, in addition to specific investigation for myocarditis, which may include clinical evaluation, imaging exams, laboratory tests, and endomyocardial biopsy with viral agent testing in myocardial tissue, genetic study is also worth considering.[1] Associated etiologies can have an impact on clinical presentation and evolution, but data are still scarce,[2] which means that there is still a gap to be explored in the literature. In this report, we describe the case of a young man with cardiogenic shock secondary to myocarditis caused by Epstein Barr virus (EBV), which led to identification of a pathogenic mutation in the *PKP2* gene.

Case Report

A 17-year-old male patient, with no previous comorbidities, sought emergency care, reporting dyspnea and retrosternal pain during exercise, rapidly progressing to syncope and cardiogenic shock. He required vasopressors, inotropes, and invasive mechanical ventilatory support. Electrocardiogram showed ST-segment elevation in leads V1, V2, and aVR, as well as ST depression in the other leads, which were not characteristic of acute coronary syndrome. Echocardiogram showed increased left atrial volume (41 mL/m^2), left ventricular dilation (59/51 mm), and systolic dysfunction with ejection fraction of 26%. Apical intracavitary thrombus was identified and treated with anticoagulation. Due to clinical suspicion of myocardial inflammation, cardiac magnetic resonance imaging (MRI) was performed, identifying typical signs of acute myocarditis with edema, hyperemia, and delayed enhancement, which was non-ischemic, affecting 45% of the left ventricle (Figure 1A). Antibiotic therapy was initiated due to fever and leukocytosis, but the regimen was suspended after 5 days due to negative blood cultures. Serological evaluation identified recent EBV infection, corroborating the diagnostic hypothesis of viral myocarditis. There was clinical improvement, making it possible to reduce support. The patient had a marked elevation in ultrasensitive troponin I, which remained elevated for a prolonged period: 9,411 ng/L upon admission; 14,760 ng/L peak; and 31.51 ng/L after 30 days.

The patient showed partial improvement in ventricular function at 3 months after discharge from the hospital (ejection fraction 42% with left ventricular dilatation). A second cardiac MRI performed 6 months later demonstrated regression of inflammatory activity, but late enhancement persisted (Figure 1B). In spite of optimized pharmacological therapy with sacubitril-valsartan, metoprolol, and spironolactone, as well as good functional capacity assessed directly by ergospirometry (peak oxygen uptake 34.4 mL^{-1}.kg^{-1}.min), after 1 year of follow-up, elevated troponin, left ventricular dilatation, and moderate systolic dysfunction persisted. The decision was made to implant a cardioverter-defibrillator after a new episode of syncope during recovery from physical exercise, which the patient had been allowed to do. Endomyocardial biopsy with viral testing 24 months after presentation and histopathology identified mild tissue edema, areas of nuclear hypertrophy, and absence of lymphocytic infiltrate on hematoxylin-eosin, but there was lymphocyte activation on immunohistochemistry (Figure 1C). The presence of EBV in the myocardial tissue was identified by qualitative PCR, but not by EBER *in situ* hybridization. Testing for other viral agents (enterovirus, herpes type 6, parvovirus B19, herpes simplex 1 and 2, adenovirus, and cytomegalovirus) was negative.

As the disease had a very prolonged course with intense fibrosis, the decision was made to carry out complementary genetic study (panel of 168 genes for cardiomyopathies). Molecular analysis of the index case (proband) identified a pathogenic variant, c.1440_1444del, (p.Asn480Lysfs*20), in the *PKP2* gene, NM_004572.3 (Invitae Arrhythmia and Cardiomyopathy Comprehensive Panel, Invitae Corp, San

Keywords

Inflammation; Myocardial Injury; Genetics; Arrhythmogenic Cardiomyopathy.

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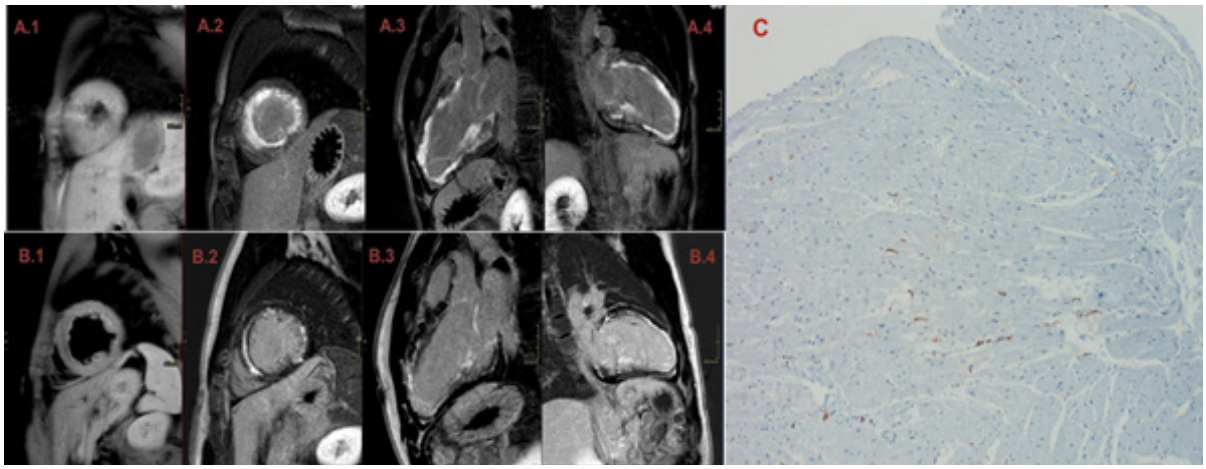

Figure 1 – *A) First cardiac MRI performed. A.1) T2 with fat saturation demonstrating diffuse myocardial edema. A.2) Delayed enhancement in the short axis demonstrating diffuse subendocardial and mesocardial uptake, without defined coronary territory. A.3) Late enhancement in the 3-camera plane demonstrating diffuse subendocardial and mesocardial uptake, without defined coronary territory, including involvement of the papillary muscles. A.4) Delayed enhancement in the 2-camera plane demonstrating diffuse subendocardial and mesocardial uptake, without defined coronary territory. B) Cardiac MRI 6 months after the cardiac MRI in Figure 1A. B.1) T2 with fat saturation in the absence of edema. B.2) Delayed enhancement in the short axis demonstrating ventricular dilatation and reduced uptake, with fine diffuse mesocardial and subendocardial areas of involvement. B.3) Late enhancement in the 3-chamber plane demonstrating ventricular dilatation and reduced uptake, with fine diffuse mesocardial and subendocardial areas of involvement. B.4) Delayed enhancement in the 2-chamber plane demonstrating ventricular dilatation and reduced uptake, with fine diffuse mesocardial and subendocardial areas of involvement. C) Immunohistochemistry showing evidence of lymphocyte activation (CD4-positive).*

Francisco, CA, USA). This variant has a deletion of 3 amino acids, and this deletion promotes the appearance of a premature stop codon, generating a truncated protein. Thus, this messenger DNA undergoes a process called decay and is not transcribed, leading to a lack of this protein. When producing the family genogram, it was possible to observe that several family members were at risk of having inherited the mutation in question (Figure 2).

Discussion

We have reported the case of a young patient with cardiogenic shock due to acute viral myocarditis caused by EBV. Viral agent testing in the tissue demonstrated persistence of the etiologic agent 24 months after presentation. Due to the severity of the clinical condition and the finding of late enhancement on cardiac MRI, a genetic panel of 168 genes for cardiomyopathies was performed, identifying an underlying arrhythmogenic cardiomyopathy due to a pathogenic mutation in the *PKP2* gene.

Myocarditis is an inflammatory heart muscle disease triggered by infectious agents, toxic substances, and/or immune activation.[3] The presentation and clinical evolution are varied, from spontaneous resolution to progression to severe heart failure.[4] Myocarditis caused by EBV, however, is rare.[5] Previous reports have described viral symptoms (fever, prostration, and myalgia) associated with cardiac manifestations such as dyspnea, chest pain, electrocardiography changes, and ventricular arrhythmias.[6] The magnitude of late enhancement in the left ventricle, however, was lower in other series (4% to 10% of left ventricular mass) than in our patient (45%).[6] Our hypothesis is that the identification of a pathogenic desmosomal mutation may have been determinant to the findings in this case (in particular the extent of late enhancement). It is important to underscore that doubts still persist regarding the benefit of treatment with antiviral drugs and immunosuppressive therapy in cases where myocardial inflammatory signs persist in spite of viral elimination.[6]

In turn, arrhythmogenic cardiomyopathy is an inherited disease characterized by myocardial liposubstitution and interstitial fibrosis. It is expressed by means of ventricular arrhythmias, and it may progress with ventricular dilation and heart failure. This pathology increases the risk of sudden death, which may be the first clinical manifestation. However, it has incomplete penetrance and variable clinical presentation.[7] Most mutations have been described in desmosomal genes, *PKP2* being the most frequent.[8] Loss of PKP2 protein expression disrupts sodium channel traffic in the intercalated disc, facilitating the emergence of arrhythmias.[9]

Although previously asymptomatic, the presence of structural left ventricular changes may have predisposed the tropism of EBV to the myocardium.[2] In fact, a higher prevalence of cardiotropic viruses has been described in patients with arrhythmogenic cardiomyopathy. Furthermore, the occurrence of viral infections may play a role in disease progression, contributing to morbidity and mortality.[10] Finally, inflammation plays a central role in the pathophysiology of arrhythmogenic cardiomyopathy, and the presence of lymphocytic infiltrates is a common finding, even when there is no viral genome identification. In some cases, the active

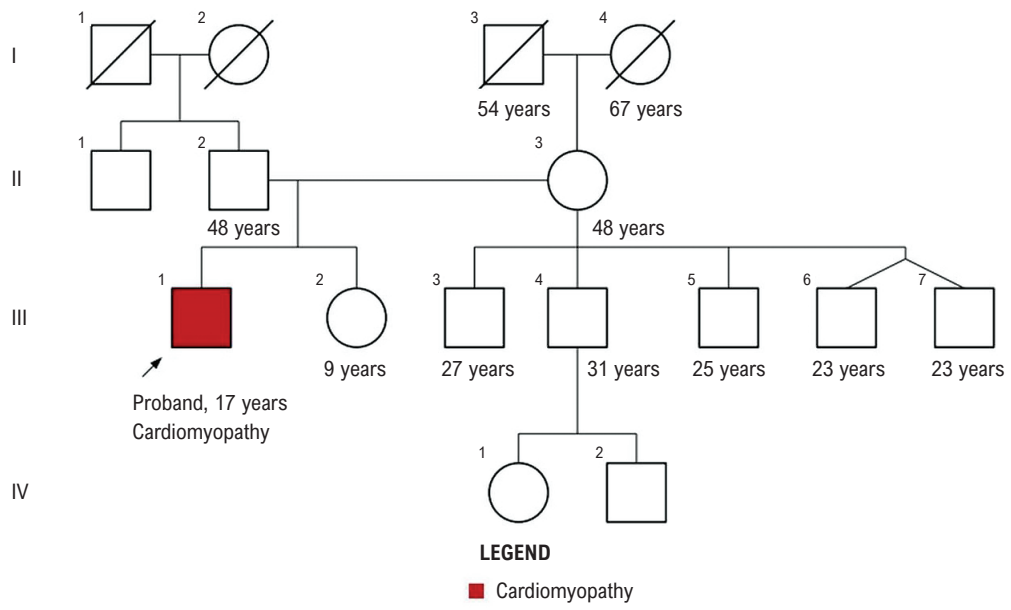

Figure 2 – *Genogram. Note that patients III.2, III.3, III.4, III.5, III.6, and III.7 were at a 50% risk of having inherited a pathogenic variant in the event that patient II.3 was heterozygous.*

phase of the disease may present as clinical myocarditis, which reinforces the very probable overlap between both conditions.[11]

Conclusion

We have reported the case of a young patient admitted for cardiogenic shock caused by EBV myocarditis, who was also the carrier of a pathogenic mutation in the *PKP2* gene, which is the one most frequently involved in familial arrhythmogenic cardiomyopathy. Severe presentations of myocarditis caused by infectious agents can occur in parallel with different hereditary cardiomyopathies and, in these cases, cascade screening and family genetic counseling can assist in therapeutic management from the perspective of the best available evidence allied with the emerging concept of personalized medicine.

Author Contributions

Conception and design of the research: Oliveira TM, Goldraich LA; Acquisition of data: Oliveira TM, Oliveira FH; Analysis and interpretation of the data: Oliveira TM, Scolari FL, Poswar FO, Oliveira FH, Stein R; Writing of the manuscript: Oliveira TM, Scolari FL, Poswar FO, Goldraich LA; Critical revision of the manuscript for intellectual contente: Scolari FL, Poswar FO, Stein R, Goldraich LA.

Potential Conflict of Interest

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Study Association

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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