Unpacking the mysteries of Parvovirus B19 Myocarditis

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ABSTRACT

Myocarditis is an inflammatory disease of the heart muscle, most often caused by viral infections. Its diagnosis can be difficult due to the heterogeneity of presentations that often mimic other common cardiological conditions, such as acute coronary syndrome (ACS) and heart failure. Although most cases are benign and self-limiting, it can also take on a more malignant course complicated by life-threatening arrhythmias, cardiogenic shock, and sudden cardiac death (SCD). A certain proportion of patients progress to develop dilated cardiomyopathies (DCMO). The developed world has experienced a shift in viral pathogens detected in patients with acute myocarditis over the past 20 years, and Parvovirus B19 (PVB19) and human herpesvirus-6 (HHV6) are currently the most commonly identified viruses in the myocardium of patients with viral myocarditis. The clinical relevance and pathological roles of these viruses however remain questioned. This focused review aims to use 2 cases of PVB19 myocarditis managed by our unit to explore issues related to the clinical presentation, diagnosis, treatment and prognosis of PVB19 myocarditis along with controversies surrounding the pathogenic role and clinical relevance of PVB19 in myocarditis. SAHeart 2022;19:28-37

INTRODUCTION

Myocarditis is defined by the World Health Organisation (WHO) and International Society and Federation of Cardiology (ISFC) as an inflammatory disease of the heart muscle, diagnosed by established histological, immunological and immunohistochemical (IHC) criteria.[1] Its diagnosis is often difficult due to the heterogeneity of presentations, ranging from symptoms of chest pain with electrocardiogram (ECG) changes mimicking an acute coronary syndrome (ACS), to life-threatening arrhythmias and cardiogenic shock or sudden cardiac death (SCD).[2]

Although the aetiology of acute myocarditis is wide ranging, viral infections are the commonest cause of myocarditis in North America and Europe.[2-9] The most common aetiology of myocarditis in both South Africa and Africa is currently unknown. High-income countries have witnessed a shift in causative viral pathogens isolated from patients with myocarditis in recent years.[2,3,5,7,8] Enteroviruses, including coxsackie virus, were the most prevalent between the 1950s and 1990s, followed by adenovirus in the late 1990s.[2,5-7,10] Parvovirus B19 (PVB19) and human herpesvirus-6 (HHV6) had been increasingly detected on endomyocardial biopsy (EMB) of patients with acute myocarditis over the past 20 years and are now the commonest viral pathogens identified in patients with viral myocarditis.[2,5-7,10] The pathogenic roles of PVB19 and HHV6 however, remains debated. Hepatitis C virus is a common cause of myocarditis in Japan.[2,5-7] The routine evaluation of a broader repertoire of viruses, along with regional climate differences influencing the seasonal variation of viral infections, are thought to be reasons responsible for this shift.[7] A recent local study conducted in Cape Town showed that the commonest viruses identified on EMB of patients with HIV-associated cardiomyopathy and idiopathic dilated cardiomyopathy (DCM) were Epstein-Barr virus (64%) and enterovirus (56%) respectively.[11] PVB19 was only isolated in 14% and 12% of each group.[10] However, histological evidence of active myocarditis was only present in 21% of patients with HIV-associated cardiomyopathy and none in those with idiopathic DCM.[11]

There is no definitive diagnostic finding for acute myocarditis on laboratory blood investigations or transthoracic echocardiography (TTE). Provisional non-invasive diagnosis can be made by cardiovascular magnetic resonance (CMR).[2,12] However, EMB remains the gold standard, as it not only confirms the diagnosis, but also identifies the underlying aetiology and possible viral pathogen.[2] Despite this, EMB has yet to gain widespread acceptance due to its perceived low diagnostic yield and concerns regarding its invasive nature and safety.

Advances have been made in recent years regarding the understanding of the pathophysiology and treatment of myocarditis. Interferon-beta (IFN-ß) had been shown to improve outcomes in patients with entero- and adenovirus cardiomyopathy,[13,14] but these findings were not replicated in patients with PVB19 cardiomyopathy.[14] Registry data have supported the use of intravenous immunoglobulins (IVIG) in patients with PVB19 cardiomyopathy. However, patient selection for therapy remains controversial.[17,15,16] Prognosis varies according to the underlying aetiology, with the majority of cases recovering spontaneously, nevertheless, a significant proportion goes on to develop DCM and SCD.[2-4,6,7]

This narrative review aims to use two cases of PVB19 myocarditis managed by our unit to explore issues related to the clinical presentation, diagnosis, treatment and prognosis of PVB19 myocarditis along with controversies surrounding the pathogenic role and clinical relevance of PVB19 in myocarditis.

CASE 1

A 30-year-old male known smoker without previous medical history presented to his local clinic with acute onset typical ischaemic central chest pain and associated autonomic symptoms. Clinical examination was unremarkable. Initial electrocardiogram (ECG) showed ST-segment elevation in the inferolateral distribution along with ST-segment depression in V1 - V3 (Figure 1 A). A diagnosis of an inferolateral ST-segment elevation myocardial infarction with posterior extension was made and the patient was thrombolysed with intravenous streptokinase. He was pain-free and ECG showed resolution of ST-segment elevation (Figure 1 B) at 90 minutes following completion of thrombolytic therapy, and was deemed successfully reperfused and transferred to our centre for early angiography. TTE (Figure 1 C - D) showed a non-dilated left ven-

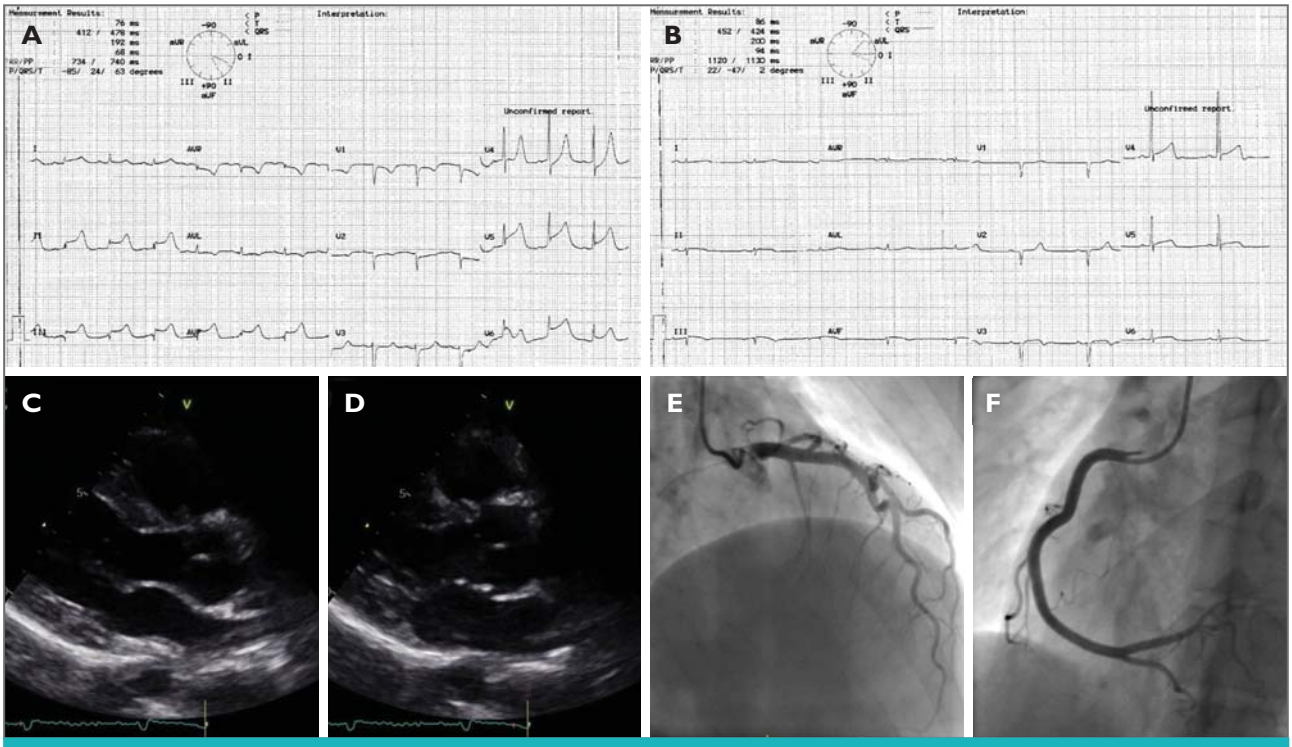

FIGURE 1: Case 1: (A) Electrocardiogram (ECG) on presentation in keeping with an inferoposterior ST elevation myocardial infarction. (B) Repeat ECG 90 minutes following completion of thrombolytic therapy showing >50% resolution of ST segment elevation, in keeping with successful reperfusion. (C) and (D) Parasternal long axis view of the left ventricle (LV) at end diastole (C) and end systole (D) on transthoracic echocardiogram (TTE) performed at initial presentation showing a non-dilated LV with preserved systolic function. (E) and (F) Diagnostic coronary angiogram showing unobstructed epicardial coronary arteries with no evidence of recent plaque rupture.

tricle (LV) with preserved systolic function, estimated ejection fraction (EF) of 57%, and no clear cut regional wall motion abnormalities (RWMA). While awaiting coronary angiography, he developed another episode of chest pain with recurrence of inferolateral ST elevation on ECG and underwent immediate coronary angiography, which showed unobstructed epicardial coronary arteries and no obvious culprit lesions or evidence of recent plaque rupture (Figure 1 E - F). In view of diagnostic uncertainty and concern of possible acute myocarditis, he underwent CMR which showed active myocardial oedema on Short Tau Inversion Recovery (STIR) imaging along with non-ischaemic patterns of early and late gadolinium enhancement (EGE/LGE), fulfilling the Lake Louise Criteria (LLC) for the diagnosis of acute myocarditis (Figure 2 A - C). Uncomplicated right ventricular (RV) septal EMB was performed which demonstrated a lymphocytic infiltrates with myocytolysis histologically (Figure 2 D - F), confirming the diagnosis of acute myocarditis by Dallas criteria. Polymerase chain reaction (PCR) of EMB specimen returned positive for PVB19.

CASE DISCUSSION

The clinical presentation of acute viral myocarditis is highly variable. A proportion of patients remain asymptomatic or experience non-specific symptoms and do not seek medical help.[17] A viral prodrome including fever, rash, myalgia, respiratory or gastrointestinal symptoms may precede the onset of myocarditis.[17] A chest pain syndrome mimicking acute coronary syndrome is the commonest mode of presentation in patients with PVB19 myocarditis.[18] Patients typically complain of acute onset ischaemic type chest pain often accompanied by autonomic symptoms. ECG may show ST-segment elevation in a coronary distribution. Troponin levels are usually elevated. TTE shows a non-dilated left ventricle with normal

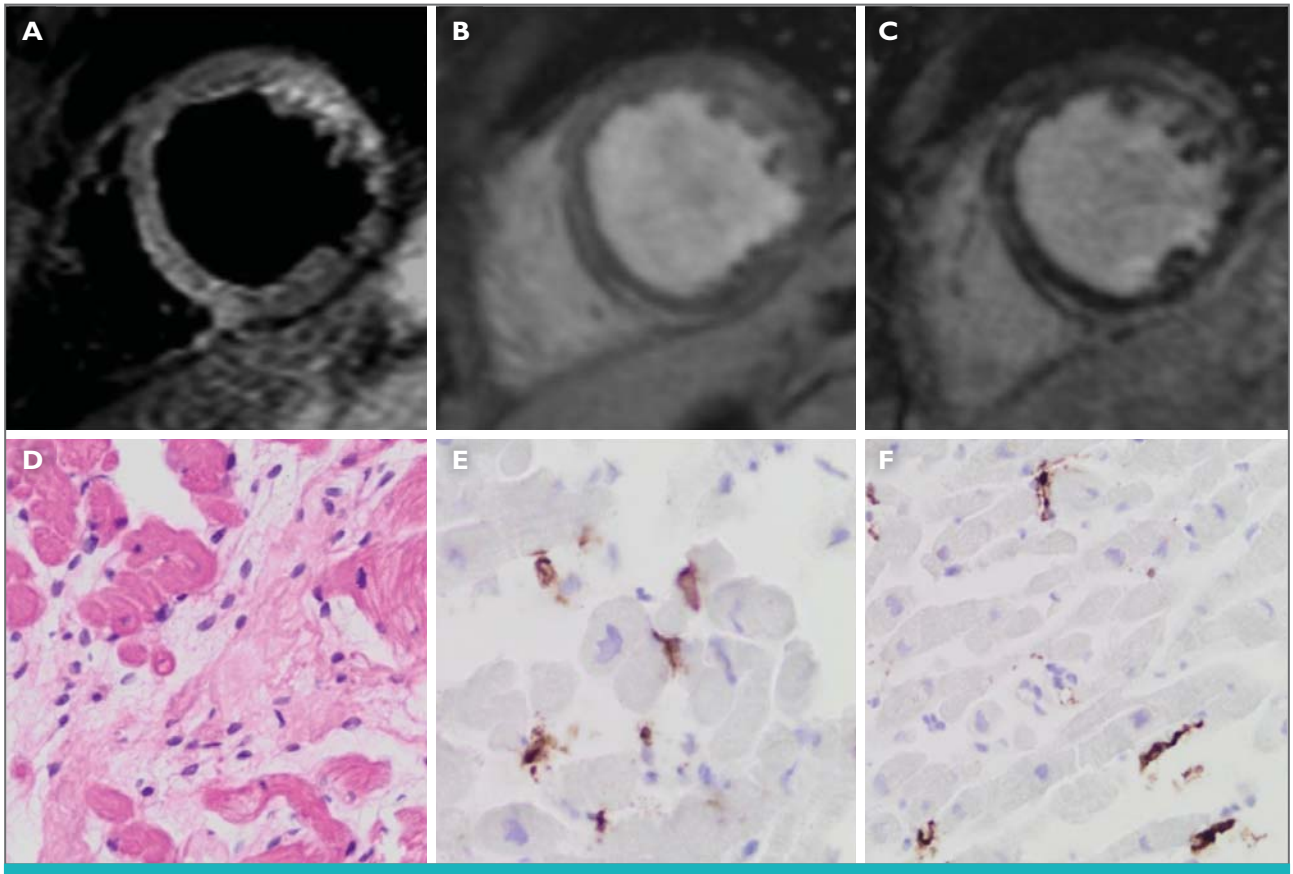

FIGURE 2: Cardiac magnetic resonance imaging (CMR) (top row) and endomyocardial biopsy (EMB) (bottom row) of Case 1. (A) Short tau inversion recovery (STIR) sequence showing active myocardial oedema in the inferior septum and anterolateral wall. (B) Diffuse mid-myocardial early gadolinium enhancement (EGE) involving the septum and posterior wall. (C) Diffuse mid-myocardial late gadolinium enhancement (LGE) of the septum and subepicardial LGE of the inferoposterior wall. (D) Haemotoxylin and eosin statin at 400 x magnification showing a lymphocytic infiltrate and myocytolysis, fulfilling the Dallas criteria for acute myocarditis. (E) and (F) Immunohistochemical staining for CD3+ T lymphocytes and CD68+ macrophages at 400 x magnification, fulfilling the immunohistochemical criteria for acute myocarditis.

LVEF in the majority of cases. Coronary arteries are however unobstructed on angiography. The resemblance of presentation to acute myocardial infarction is thought to be related to the pathogenic mechanism of PVB19 in myocarditis.[18-20] PVB19 is a vasculotropic virus which infects the endothelial cells of myocardial vessels and not myocytes directly, leading to endothelial dysfunction and vasospasm along with inducing the migration of inflammatory cells into the myocardial interstitium resulting in damage to myocytes.[7,8,19,20] The myocardial inflammation and injury may however remain focal, with relatively preserved global LV function.[21]

There are no pathognomonic findings of acute myocarditis in laboratory investigations or TTE. Non-specific markers of inflammation such as leucocyte count, C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) may be elevated but are neither sensitive nor specific for the diagnosis of acute myocarditis.[2,4] Troponin T and I are usually elevated in patients with infarct-like presentation but may be negative in up to ⅔ of patients with biopsy confirmed myocarditis.[22] Viral serology for cardiotropic viruses, besides HIV and Hepatitis C, are not useful in the diagnosis of acute viral myocarditis, as it does not reflect infection at myocardial level.[2,23] TTE is useful for the assessment of cardiac chamber sizes, wall thickness, systolic and diastolic function, RWMA, valvular function and to exclude intracardiac thrombi.[2,24]

CMR is the imaging modality of choice in the diagnosis of acute myocarditis and should be routinely performed in haemodynamically stable patients.[2] It allows for non-invasive tissue characterisation of the myocardium to evaluate the 3 markers of myocardial injury, namely, acute myocardial oedema on T2-weighted imaging, and T1 and T2 mapping sequences, hyperaemia and capillary leakage with early gadolinium enhancement (EGE), and necrosis and fibrosis with late gadolinium enhancement (LGE), native T1 mapping and extracellular volume (ECV) mapping.[12,25] The Lake Louise Criteria (LLC), originally published in 2009, were the standard for CMR diagnosis of acute myocarditis and takes into account these 3 markers of myocardial injury.[12] Its specificity and positive predictive value have been reported to be as high as 91% when 2 out of 3 markers of myocardial injury are present.[12,26,27] However, the sensitivity and negative predictive value are somewhat lower at 67% and 69% respectively.[12,26,27] Subsequent EMB-based studies found that removing EGE did not appear to substantially hamper the diagnostic performance of the LLC.[27,28] Specific patterns of LGE can differentiate between myocarditis, which is usually subepicardial or mid-myocardial in distribution, from other causes of LV dysfunction such as myocardial infarction (subendocardial or transmural) and cardiac amyloidosis (diffuse).[29] Furthermore, the presence and distribution of LGE were shown to be predictors of poor long term outcome.[30,31] However, despite allowing for a provisional non-invasive diagnosis, CMR cannot determine the specific underlying aetiology of acute myocarditis.

EMB is the gold standard for the diagnosis of acute myocarditis, as it allows the direct microscopic visualisation of inflammatory infiltrates and cardiac myocyte necrosis (Dallas histopathological criteria).[1-3,24] It also identifies the specific type of inflammatory infiltrate (lymphocytic, eosinophilic, giant cell) and can determine the underlying aetiology, which may be important in guiding therapy.[2-7,9,10,24] Despite this, EMB has yet to gain widespread acceptance due to its perceived low diagnostic yield and concerns regarding its invasive nature and safety. Diagnostic accuracy can be improved by performing EMB early in the course of the disease and taking at least 3 samples for histological evaluation.[2,7,32] Additional samples should be taken for routine viral genome detection by polymerase chain reaction (PCR).[2,7,32] Sensitivity of EMB can be further improved by the routine addition of immunohistochemical staining for CD3 (T cells), CD68 (marcophages) and human antigen class II antigens, to the standard Dallas histopathological criteria.[2,5,7,17,32] Furthermore, immunohistological evidence of inflammation is associated with poor outcome.[33] The safety of EMB when performed by experienced operators in high-volume centres is well established, with major complication rate of less than 1%.[34-38] Unpublished data from our centre showed that in a low volume centre, safety can be ensured by the routine use both fluoroscopic and real-time echocardiographic guidance, with no major complication reported in a series of 87 RV EMB performed over a period of 3 years.

All patients with acute myocarditis should be advised to avoid strenuous physical activity for 6 months from the onset of symptoms.[2,3] Increased physical activity during the acute phase of myocarditis has been shown in animal models to worsen myocardial inflammation and necrosis, along with increased risk of cardiac remodeling and death.[39] The role of angiotensin converting enzyme inhibitors (ACE-i) and ß-blockers in patients with infarct-like presentation but without LV systolic dysfunction is unclear.[7] It is the current practice at our centre to initiate all patients with myocarditis on ACE-i and ß-blockers if tolerated and not contraindicated.

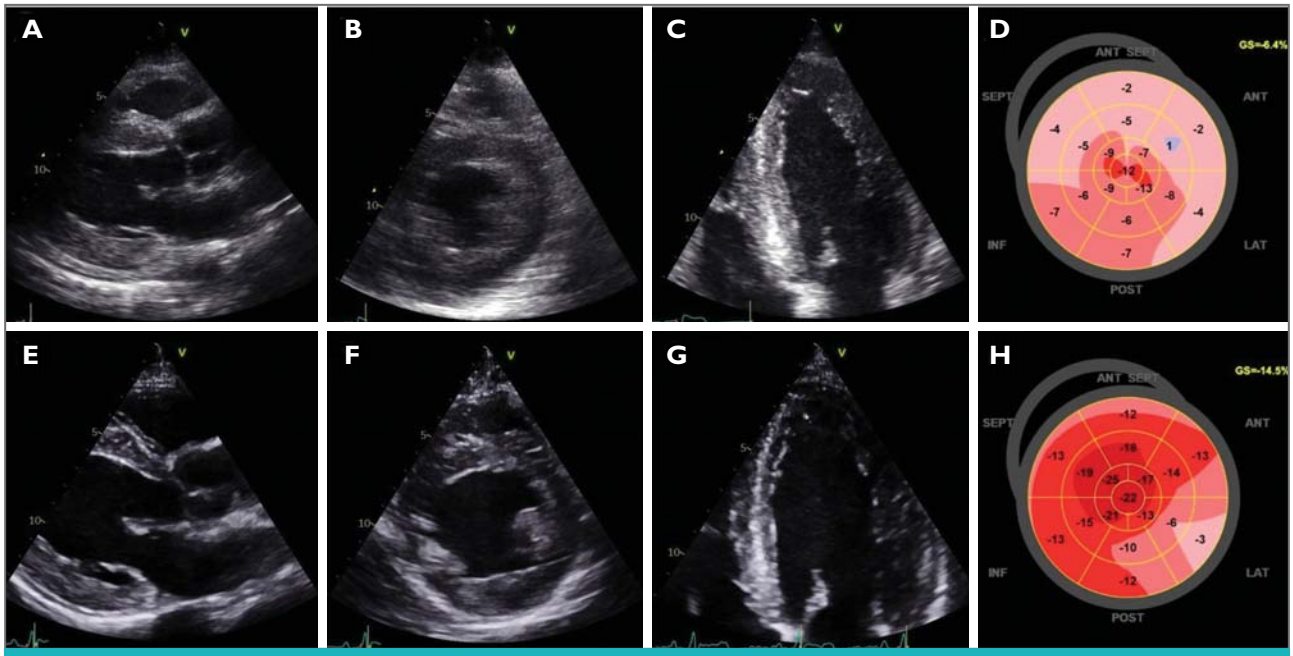

FIGURE 3: Transthoracic echocardiogram (TTE) of Case 2 performed during initial presentation (top row) and at 1 month follow up (bottom row). (A) to (C) Parasternal long axis (PLAX), short axis (PSAX) and apical 4 chamber (A4C) views showing diffuse left ventricular hypertrophy (pseudohypertrophy) secondary to diffuse myocardial oedema. (D) Speckle tracking showing severly reduced global longitudinal strain of the left ventricle. (E) to (G) Corresponding TTE windows to (A) to (C) performed at 1 month follow up showing significant reduction in left ventricular wall thickness. (H) Repeat speckle tracking at follow up showing significant recovery in global longitudinal strain.

Patients with PVB19 myocarditis who present with pseudo-infarct presentation or with mild symptoms and preserved LV function have an excellent prognosis and usually recover spontaneously without residual sequelae.[4]

CASE 2

A 42-year-old male, known with human immunodeficiency virus (HIV) infection on anti-retroviral therapy (ART) but no other cardiovascular risk factors, presented with a 1 week history of sudden onset New York Heart Association (NYHA) Class III dyspnoea, 3-pillow orthopnoea and paroxysmal nocturnal dyspnoea (PND). On clinical examination, his jugular venous pressure (JVP) was elevated to the angle the jaw, apex was undisplaced and bibasal inspiratory crackles were audible on auscultation of the lung fields. ECG showed T wave inversion in the inferior leads and early repolarisation abnormalities. Laboratory investigations revealed a mildly elevated hsTnT of 168ng/L (normal <100 ng/L) but all other parameters were within normal limits, including a normal white cell count and CRP. TTE showed a non-dilated LV with severe concentric hypertrophy measuring 15mm (normal <10mm), global LV hypokinesia, severely impaired LV systolic function with estimated EF <20% and a sliver of pericardial effusion (Figure 3 A - D). Coronary angiography revealed unobstructed coronaries. CMR was performed to further characterise the myocardium and showed diffuse myocardial oedema on T2-weighted imaging, absence of EGE or LGE, but elevated T1 and T2 relaxation times, thus fulfilling the modified but not the classic LLC for the diagnosis of acute myocarditis (Figure 4 A - E). In view of ongoing diagnostic uncertainties and imaging findings suggestive of an acute inflammatory process of the myocardium, a decision was taken to perform RV EMB, which confirmed acute lymphocytic myocarditis by Dallas Criteria. PCR of EMB specimens returned positive for PVB19. The patient was initiated on heart failure therapy consisting of enalapril, carvedilol and spironolactone, and was discharged as his heart failure symptoms had resolved. On follow up a month after diagnosis, his heart failure symptoms had completely resolved and his clinical examinations were otherwise normal. Repeat TTE showed normalisation of LV wall thickness to 10mm and complete recovery of LV systolic function with estimated EF of 55% (Figure 4 E - H). Follow up CMR confirmed the complete resolution of myocardial oedema (Figure 4 F - J).

CASE DISCUSSION

Heart failure is another manner in which patients with PVB19 myocarditis can present.[2-4,6,7,17,24,32] Onset is typically acute (less

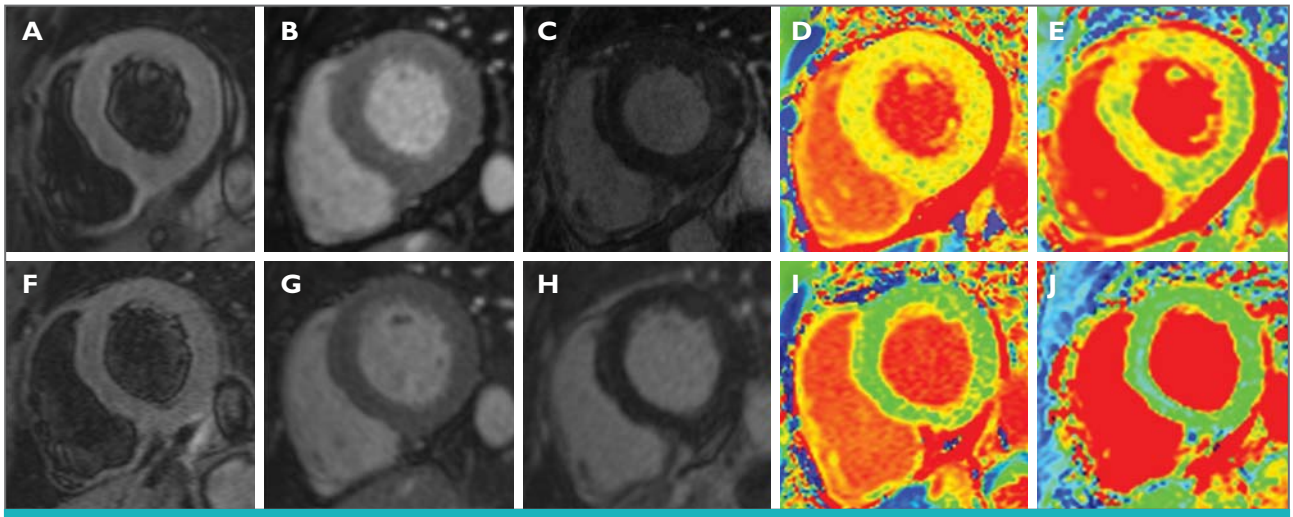

FIGURE 4: Cardiac magnetic resonance imaging (CMR) performed during initial presentation (top row) and at follow up 1 month after diagnosis (bottom row). (A) Short tau inversion recovery (STIR) sequence showing increased signal throughout the left ventricle (LV) in keeping with diffuse active myocardial oedema. (B) and (C) The absence of both early and late gadolinium enhancement (EGE/LGE) meant that the classic Lake Louise diagnostic criteria for acute myocarditis was not fulfilled. (D) and (E) Parametric myocardial mapping showing both increased T1 and T2 relaxation times (yellow/red areas) in keeping with active myocardial oedema. These parameters were added to the 2018 update of the Lake Louise criteria to improve specificity and diagnostic accuracy of CMR in myocarditis. (F) Repeat CMR 1 month after diagnosis showing complete resolution of myocardial oedema on STIR imaging. Note also the reduction of LV wall thickness. (G) and (H) EGE and LGE remained absent at follow up. (I) and (J) Parametric myocardial mapping showed normalisation of both T1 and T2 relaxation times (green/blue areas) in keeping with resolution of myocardial oedema.

than 2 weeks duration) or subacute. In the minority of patients onset may also be more gradual and persists for more than 3 months present.[2-4,6,7,17,24,32] A distinct group of patients with fulminant myocarditis generally presents with severe heart failure symptoms and rapid progression to haemodynamic compromise and cardiogenic shock.[2-4,6,7,17,24,32]

There are 2 main mechanisms by which viruses induce myocarditis and LV dysfunction. Cardiotropic viruses such as entero- and adenoviruses infect cardiomyocytes directly and induce cell lysis by viral replication inside host cells, triggering an immune response and inflammation which leads to viral clearance and complete recovery in about 50% of cases.[7,10,17,32] Persistence of these viruses in the myocardium leads to LV dysfunction and poor long term outcomes.[7] Respiratory viruses such as influenza and coronaviruses, including SARS-CoV-2, do not directly infect cardiomyocytes but trigger myocarditis indirectly via cytokine-mediated cardiotoxicity and inducing an autoimmune response against components of the myocardium by molecular mimicry.[7,10,32] The pathogenic mechanism by which PVB19 induces myocarditis and subsequent progression to dilated cardiomyopathy is less well understood, as there are no established animal models, but is thought to be a triphasic process involving a combination of the above mechanisms.[7,20]

Initial infection of the endothelial cells of intramyocardial arterioles and post-capillary venules by PVB19 leads to increased expression of proinflammatory cytokines, endothelial dysfunction, and apoptosis of the infected endothelial cells.[7,8,20] The second phase involves intravascular accumulation, adhesion and penetration of inflammatory cells consisting predominantly of macrophages and T-lymphocytes.[7,20] Sustained severe cardiac inflammation results in myocyte necrosis. However, cytotoxic T-cell response assists with viral clearance and resolution of acute myocarditis.[7,8,20] In a proportion of patients, there is an absence of PVB19-specific T cells, which results in inadequate viral clearance and persistence of PVB19 in the myocardium, leading to chronic myocardial inflammation.[40-42] Even in patients with complete viral clearance, ongoing myocardial inflammation can result from an autoimmune response against host myocardial antigens induced by molecular mimicry.[43] The resultant chronic myocarditis secondary to either viral persistence or autoimmunity can lead to dilated cardiomyopathy.

TTE in patients with PVB19 myocarditis presenting with acute or subacute heart failure typically shows a non-dilated LV with impaired systolic function.[24,44] However, those that present more insidiously may have a dilated LV. Myocardial oedema can result in pseudo-hypertrophy of the LV, with LV wall thickness

returning to normal once the oedema resolves.[24,44] RV dysfunction is rare,[4] but is an important predictor of poor long term outcome if present.[45]

The diagnostic performance of CMR in this sub-group of patients presenting with heart failure tends to be lower than those with pseudo-infarct presentation,[46,47] with reported sensitivity of 57% in a small cohort of patient.[47] In our experience, myocardial oedema on STIR imaging and myocardial mapping is the predominant finding on CMR in the majority of these patients, with EGE or LGE much less prominent, if present at all. When present, LGE tends to be subtle and of low signal intensity, appearing quite bland, and is usually present in a mid-myocardial distribution. This is in contrast to the bright subepicardial LGE that is commonly seen in patients with a pseudo-infarct presentation. As a result, the CMR findings in patients presenting with heart failure rarely fulfils the classic LLC for acute myocarditis. However, the LLC was updated in 2018 with the incorporation of the assessment of both T1 and T2 relaxation times using parametric myocardial mapping techniques, requiring the fulfilment of both a T2-based imaging criterion for oedema and a T1-based tissue characterisation criterion (increased T1 relaxation time or extracellular volume (ECV), or EGE, or LGE). This is thought to significantly improve both its specificity and diagnostic accuracy,[25,47] especially in this distinct group of patients where the presence of prominent gadolinium enhancement is unusual. It also potentially allows for the diagnosis of myocarditis even if the administration of gadolinium is contraindicated.

EMB remains a very important modality for confirming the diagnosis and guiding therapy in the management of patients with PVB19 myocarditis presenting with heart failure.[48-50] As discussed above, the CMR findings in the majority of this group of patients tend to be bland and frequently do not fulfil either the classic of modified LLC for the diagnosis of myocarditis. In contrast, it is our experience that the diagnostic yield of EMB tend to be higher in these patients compared to those with pseudo-infarct presentation. Furthermore, new onset heart failure of uncertain aetiology of less than 2 weeks duration with normal-sized or dilated LV and haemodynamic compromise, and new onset heart failure of uncertain aetiology of 2 weeks to 3 months duration with a dilated LV and new ventricular arrhythmias, high degree atrioventricular nodal blocks, or failure to respond to optimal heart failure therapy are class I recommendations for the performance of EMB by the American Heart Association (AHA), American College of Cardiology (ACC) and European Society of Cardiology (ESC).[51]

Initial management of haemodynamically stable patients with myocarditis and impaired LV systolic function involves the initiation of standard heart failure therapy consisting of an ACE-I, ß-blocker and mineralocorticoid receptor blocker (MRA) as per the relevant society's guidelines on heart failure.[2-4,6,17,24] Whether to discontinue treatment once LV function has recovered and the timing of discontinuation is unknown, and the decision should be made on an individual basis.[5] Recent studies have shown the benefits of the combination of azathioprine and corticosteroids in patients with myocarditis and LV dysfunction or inflammatory cardiomyopathy that have failed conventional heart failure therapy, with improvement in event-free survival and LVEF.[52-55] However, safe immunosuppression requires the exclusion of viral genomes in the myocardium by EMB, as immunosuppressive therapy could worsen outcomes of patients with viral myocarditis (Ref immunosuppression viral myocarditis). Immunosuppression should therefore be considered in patients with impaired LV and ongoing inflammation but without viral genomes on EMB who do not respond to conventional heart failure therapy. Although there is no specific antiviral therapy in the treatment of PVB19 myocarditis and cardiomyopathy, there is evidence to support the use of IVIG in patients with PVB19 myocarditis and persistent LV dysfunction.[7,10,15,16,39] IVIG has both antiviral and immunomodulatory effects. It can stimulate anti-inflammatory cytokines, suppress pro-inflammatory cytokines, interrupt the complement cascade and inhibit leucocytes adhesion and apoptosis.[10] IVIG is often used in patients with severe PVB19 viraemia and its associated complications.[7] Registry data have shown that IVIG therapy in patients with PVB19-associated inflammatory cardiomyopathy was associated with clinical improvement and reduction of myocardial inflammation on EMB, but not viral clearance.[16] These findings were confirmed in a Dutch pilot study, which showed significant improvement in LVEF and NYHA class in a small group of patients with DCM and presence of PVB19 on EMB.[15]

PARVOVIRUS B19 - CULPRIT OR BYSTANDER?

Despite the high prevalence of PVB19 in EMB of patients with myocarditis and DCM, questions remain regarding its pathogenic role and the relevance of its presence in the myocardium.

Primary PVB19 infection usually occurs in childhood and manifests as erythema infectiosum.[20,56,57] Although infection in most individuals is transient, there is evidence to suggest lifelong persistence of the virus in certain tissue types including liver,

synovium and skin.[20,56,57] This is further supported by the detection of a genotype of PVB19 that had stopped circulating in Europe more than 50 years ago only in specimens obtained from patients born before 1973,[57] proving infection occurred long before sampling. In contrast, earlier studies into myocarditis and dilated cardiomyopathy showed a low prevalence of PVB19 in the myocardium of control subjects, supporting the hypothesis that PVB19 plays an important role in the pathogenesis of myocarditis and dilated cardiomyopathy.[20] More recent studies conducted in Germany have however shown prevalence of between 60% - 85% in patients undergoing cardiac surgery and in post-mortem subjects without evidence of myocarditis.[20,56,57] However, the background prevalence of PVB19 appears to vary depending on population studied, as it was detected in only 26% and 44% of post-mortem cohorts without histological evidence of myocarditis in the United States[58] and Denmark[59] respectively, and 44% of an Italian cohort undergoing cardiac surgery.[60] These findings would suggest that similar to other tissue, PVB19 might also persist lifelong in the myocardium, and its mere presence might be insufficient to prove a direct causal role in disease.

Subsequent studies have attempted to establish a marker for active viral replication, which leads to myocyte necrosis and active myocarditis, as a surrogate for clinical relevance. The most widely accepted approach currently is the determination of viral load by quantitative PCR on EMB specimens, with a threshold of more than 500 copies per microgram of DNA (copies/mcg DNA) deemed clinical significant.[7,8,20,32,] This cut-off had been successfully used to guide the safe immunosuppression in a small cohort of patients with PVB19 inflammatory cardiomyopathy.[61] However, whether this threshold is applicable to all populations is currently unknown. In the Dutch pilot study demonstrating the clinical benefits of IVIG in patients with DCM and presence of PVB19 on EMB, the investigators used a threshold of 250 copies/mcg DNA to determine clinical significance.[15] This was derived by determining the background prevalence and mean viral load in the hearts of a small post-mortem cohort without histological evidence of myocarditis.[15] This underscores the importance of using locally relevant data as "one size may not fit all".

The burden of PVB19 myocarditis, background prevalence of PVB19 in the general population and the viral load threshold for clinical significance in South Africa is unknown. In view of the fact that treatment options for patients with dilated cardiomyopathies are extremely limited locally, and a single course of IVIG at the recommended dose costing R90 000 per patient,[62] it is imperative that we determine the relevance and threshold for clinical significance of PVB19 in South Africa to guide selection of patients mostly likely to benefit from therapy.

CONCLUSION

Myocarditis is an under-recognised condition with a wide range of clinical presentations, often mimicking other common cardiovascular disorders. Although the majority of patients recover fully, a significant proportion can develop dire consequences, including dilated cardiomyopathy and sudden cardiac death. There has been a shift in viral pathogens identified over the past decades with PVB19 currently the most commonly isolated. Its pathogenic role in myocarditis and clinical significance however, remains debated. Further research into the local burden of disease and background prevalence is pertinent to improve our understanding and clinical management of patients with PVB19 myocarditis in South Africa.

Authors contribution

All authors contributed equally to the manuscript.

Conflict of interest: none declared.

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