

## CASE REPORT

# Targeted treatment in viral-associated inflammatory cardiomyopathy

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## Abstract

Detection of viruses like HHV-6 in endomyocardial biopsy or serum serology of patients with myocarditis or heart failure features unresponsive to conventional heart failure therapies could be a potential targeted treatment especially in refractory cases.

## KEYWORDS

heart failure, Human herpesvirus 6, inflammatory cardiomyopathy

## 1 | INTRODUCTION

Various viruses affect myocardium in different ways, primary cardiotropic viruses like adenoviruses and enteroviruses that could be cleared from the heart, vasculotropic viruses like parvovirus B19 that have lifelong persistence, lymphotropic viruses like human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV), and human cytomegalovirus (CMV) that have lifelong persistence, and finally viruses leading to myocarditis indirectly via immune system activation like human immunodeficiency virus (HIV), hepatitis C virus (HCV), influenza A and B, Middle East respiratory syndrome-related coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>1</sup>

Patients presenting with severe LV dysfunction secondary to myocarditis have three different trajectories. About 50% experience complete resolution, 25% suffer chronic systolic

dysfunction, and the remaining progress to end-stage heart failure.<sup>2</sup> In general, viral myocarditis is the leading cause of dilated cardiomyopathy.<sup>3</sup>

Notable adverse outcomes in significant proportion of patients with viral-associated cardiomyopathy necessitate searching for effective therapies especially in patients without dramatic response to conventional treatments. Herein, we describe three cases of HHV-6-associated cardiomyopathy refractory to conventional medical therapy with acceptable response to antiviral therapy.

## 2 | CASE PRESENTATION

### 2.1 | Case 1

A 68-year-old woman was admitted with 2 days history of dyspnea and syncope attacks. Temporary pacemaker (TPM)

was inserted due to Mobitz type II AV block. Transthoracic echocardiography (TTE) showed mild left ventricular enlargement (LVE), left ventricular ejection fraction (LVEF) ~45%, mild RVE and dysfunction. Endomyocardial biopsy (EMB) was done due to refractory ventricular tachycardia episodes and reduction in LVEF to 35% despite heart failure guideline-directed medical therapy (GDMT). The remarkable point of samples was HHV-6 positivity by real-time PCR (RT-PCR). Antiviral therapy was initiated regarding undesirable response to GDMT in follow-up besides high viral load of HHV-6 in serum, previous findings of EMB and several arrhythmic episodes. Initiation of oral valganciclovir 450mg bid led to VT cessation and EF improvement. After initiation of valganciclovir, there was no any arrhythmic attack and follow-up echocardiography two months later showed EF~45%.

## 2.2 | Case 2

A 51-year-old man was admitted with acute dyspnea. Transthoracic echocardiography showed severe LVE with EF~10%, moderate right ventricular enlargement and dysfunction. Right heart catheterization (RHC) findings were in favor of low cardiac output and post-capillary pulmonary hypertension. Despite receiving GDMT for about three months, the patient was symptomatic and had several hospitalizations. EMB was done due to refractory heart failure and was positive for HHV-6 using real-time PCR without fibrosis or inflammation of myocardial samples. In cardiac magnetic resonance imaging (CMR), subepicardial late gadolinium enhancement without any edema or hyperemia was noted. Due to LV and RV clots, anticoagulation was initiated. Parenteral acyclovir and then valganciclovir were administered. He was admitted for intravenous immunoglobulin (IVIG) administration due to high viral load of HHV-6 few months later, in follow-up course while he had dyspnea and TTE showed LVEF=20%. Ganciclovir 450 mg bid was added to patient's drugs. Few months later, he had reduction in HHV-6 viral load besides improvement in clinical status and LVEF increased to ~30%.

## 2.3 | Case 3

A 36-year-old man was admitted with aborted sudden cardiac death and severe LV dysfunction (LVEF~10%). GDMT was initiated, and the patient discharged with medical therapy. The patient course was unfavorable due to poor functional capacity and recurrent admissions. At last admission, the patient underwent inotrope administration and was considered for extracorporeal membrane oxygenation (ECMO) due to impending to cardiogenic shock. EMB was done due to

refractory heart failure. EMB was negative for infectious organisms while serum serology PCR was positive for HHV-6. Due to unacceptable response to guideline-directed medical therapy, parenteral ganciclovir for 5 days and IVIG (0.5g/kg) were administered. He discharged in good condition with valganciclovir 450 mg bid besides GDMT for heart failure. At follow-up, he had improvement of LVEF from 10% to 25%, reduction in HHV-6 viral load, and improvement of clinical condition.

## 3 | DISCUSSION

In recent decades, a shifting change has occurred in the type of prevalent cardiotropic viruses of EMB samples, from adenoviruses and enteroviruses to parvovirus B19 (B19V) and HHV-6. In a recent meta-analysis, B19, non-polio enteroviruses, and HHV-6 had the highest prevalence in viral myocarditis cases, respectively. Persistence of entro- and adenovirus in myocardium has been shown to be associated with ventricular dysfunction, and on the other hand, clearance of viral genome had association with ventricular function improvement and better 10-year outcome. The prognosis of HHV-6 persistence in myocardium supposed to be better than adeno /enteroviruses and even from B19V in terms of less inflammatory response.<sup>4-6</sup>

Since HHV-6 infection has lifelong persistence, finding of this virus in myocardium or serum could be just an association and not a cause and effect relationship. Based on recent statements, antiviral therapy is not routinely recommended for treatment of viral-associated myocarditis due to unproven efficacy.<sup>7</sup> However, scarce evidences are in favor of possible benefits of viral targeted treatment in viral-associated cardiomyopathies especially in refractory cases. In a study on 73 patients with cardiac biopsy-proven HHV-6 infection, persistence of the virus in EMB samples at a median follow-up of 8.8 months was associated with cardiac dysfunction and HHV-6 clearance was associated with improvement in hemodynamic parameters.<sup>8</sup>

After an active myocarditis, myocardium could be affected in several forms depending on some factors including viral clearance, persisting inflammation, and extent of myocardial injury. For differentiating these entities and defining the dominant pathology, EMB is helpful for appropriate treatment. Among viruses, HHV-6 has the potential to integrating its genome into human chromosomes leading to germ line transmission probability. Considering previous investigations, antiviral treatment benefit was evident only in reactivated chromosomally integrated HHV-6; however, it is recommended that this therapy could be considered as an alternative treatment in symptomatic patients despite GDMT.<sup>9</sup>

The most common entity in HHV-6 is persistent latent infection with episodes of reactivation.<sup>10</sup>

Reactivation of HHV-6 during adulthood could cause heart failure symptoms. Escher F et al in their study showed that persistence of HHV-6 could lead to worsening of myocardial function and viral clearance could result in improvement of it.<sup>11</sup>

In viruses with lifelong persistence like HHV-6 and B19, it is important to differentiate between latent infection manifesting with positive DNA alone and reactivation with positive mRNA in addition to positive DNA.<sup>12</sup>

Although we did not perform evaluation regarding mRNA of the HHV-6, dramatic response to antiviral treatment could be a rationale for this treatment in these cases.

Since IFN beta is not effective in HHV-6 infection, in a study, valganciclovir was administered in unexplained symptomatic heart failure patients with reactivated chromosomally integrated HHV-6 and resulted in improvement of symptoms.<sup>13</sup>

Efficacy of intravenous immunoglobulins has been shown in different spectrum of myocardial injuries including peripartum cardiomyopathy, acute and chronic fulminant myocarditis, dilated cardiomyopathy, enteroviral and B19V-associated heart disease.<sup>14</sup>

Considering the abovementioned data, it seems that the antiviral treatments like valganciclovir and ganciclovir and also IVIG are among the optional choice for targeted treatment in HHV-6-associated inflammatory cardiomyopathy.

## 4 | CONCLUSION

In conclusion, evidences of viral traces in myocardial samples of patients with myocarditis and dilated cardiomyopathy along with acceptable efficacy of antiviral treatment in reported cases may be rational for searching of viruses footprints in selected cases as a causative or triggering factors.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

AA involved in critical revision of the manuscript. ST involved in data collection. MCH involved in corresponding author. EZ involved in data collection. MK involved in data collection. NN drafted of the manuscript.


## ETHICAL STATEMENT

This case series was approved to be reported by the ethics committee of Rajaie Cardiovascular, Medical and research center.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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