

Title page

This case series is about three patients presented with heart failure features unresponsive to conventional heart failure treatments. With detection of HHV-6 in endomyocardial biopsies or serum serology and initiation of antiviral treatment, significant improvement was obtained. The concept of considering viruses accusation in selected cases of myocarditis or DCM, could be a potential targeted treatment especially in refractory cases.

This case series was approved to be reported by the ethics committee of Rajaie Cardiovascular, Medical and research center. This paper has not under consideration elsewhere and none of the paper's contents have been previously published. All authors have read and approved it's submission and publication to Clinical case reports Wiley online library. Each author has independent material contribution to this study. The authors disclose that this study have no any relationship with industry and financial association. No person who has right to be recognized as author has been omitted from the list of authors.

Title: Targeted treatment in viral associated inflammatory cardiomyopathy

Key words: Human herpes virus 6, inflammatory cardiomyopathy, heart failure

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Acknowledgments: We would like to thank staff of Rajaie Cardiovascular, Medical and Research Center who supported our study.

Conflict of interest: The authors declare that, there is no conflict of interest.

Word count: 1080

Targeted treatment in viral associated inflammatory cardiomyopathy

Abstract

Though generally self-limited, viral myocarditis can lead to acute cardiac failure or chronic dilated cardiomyopathy. We hereby describe

three cases of human herpes virus 6 (HHV6) associated -myocarditis for the first time from Iran. The first patient was a 68-year-old woman presented with AV block, incessant ventricular tachycardia and reduction of left ventricular ejection fraction, the second patient was a 51-year-old man admitted with severe LV enlargement and dysfunction and the third patient was a 36-year-old man hospitalized with aborted sudden cardiac death and severe left ventricular enlargement and dysfunction. All patients were unresponsive to conventional therapies but with detection of HHV-6 evidences and initiation of antiviral treatment, we observed significant improvement in clinical status of patients. HHV-6 infection can cause significant myocardial disease and endomyocardial Real-Time PCR of patients with acute myocarditis or dilated cardiomyopathy might be helpful in therapeutic approaches.

Key words: Human herpes virus 6, inflammatory cardiomyopathy, heart failure

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 herpes virus 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 HIV, HCV, Influenza A and B, MERS-CoV, SARS-CoV and SARS-CoV-2.¹

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.² In general, viral myocarditis is the leading cause of dilated cardiomyopathy.³

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.

Case presentation

Case 1

A 68-year-old woman was admitted with 2 days history of dyspnea and syncope attacks. Temporary pace maker (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. Endo myocardial biopsy (EMB) was done due to refractory ventricular tachycardia episodes and reduction of 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 Valcyte 450mg bid led to VT cessation and EF improvement.

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. EMB 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 valcyte were administered. He was admitted for 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 of HHV-6 viral load besides improvement in clinical status and LVEF increased to ~ 30%.

Case 3

A 36-year-old man was admitted with aborted sudden cardiac death and severe LV dysfunction (LVEF~10%). RHC findings showed low output state and post-capillary pulmonary hypertension. 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 intravenous immunoglobulin (IVIG) (0.5g/kg) were administered. He discharged in good condition with valcyte 450 mg bid besides GDMT for heart failure. At follow-up, he had improvement of LVEF from 10% to 25%, reduction of HHV-6 viral load and improvement of clinical condition.

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.^{4,5,6}

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.⁷ 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.⁸

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.⁹

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

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.¹¹

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.¹²

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.¹³

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.¹⁴

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

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.

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

References:

1. Tschöpe C, Ammirati E, Bozkurt B, Caforio ALP, Cooper LT, Felix SB, Hare JM, Heidecker B, Heymans S, Hübner N, Kelle S, Klingel K, Maatz H, Parwani AS, Spillmann F, Starling RC, Tsutsui H, Seferovic P, Van Linthout S. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol*. 2021 Mar;18(3):169-193. doi: 10.1038/s41569-020-00435-x. Epub 2020 Oct 12. PMID: 33046850; PMCID: PMC7548534.
2. Heymans S, Eriksson U, Lehtonen J, Cooper LT Jr. The Quest for New Approaches in Myocarditis and Inflammatory Cardiomyopathy. *J Am Coll Cardiol*. 2016; 68: 2348-2364. **Ref.:** <http://bit.ly/2J0QF8S>
3. Pawlak A, Przybylski M, Durlik M, Gil K, Nasierowska-Guttmejer AM, Byczkowska K, et al. Viral nucleic acids in the serum are dependent on blood sampling site in patients with clinical suspicion of myocarditis. *Intervirology* 2016; **59**(3): 143-151.

4. Van Linthout S, Tschöpe C. Viral myocarditis: a prime example for endomyocardial biopsy-guided diagnosis and therapy. *Curr Opin Cardiol.* 2018;33(3):325-333. doi:10.1097/HCO.0000000000000515
5. Dadashi M, Azimi T, Faghihloo E. Global study of viral myocarditis: A systematic review and meta-analysis. *J Acute Dis* 2020; 9(1): 1-13.
6. Kühl U, Lassner D, von Schlippenbach J, Poller W, Schultheiss HP, et al. Interferon-Beta improves survival in enterovirus-associated cardiomyopathy. *J Am Coll Cardiol.* 2012; 60: 1295-1296. **Ref.:**<http://bit.ly/31ZqlDy>
7. Caforio, A.L.P., Pankuweit, S., Arbustini, E., Basso, C., Gimeno-Blanes, J., Felix, S.B. and Elliott, P.M. (2013) Current State of Knowledge on Aetiology, Diagnosis, Management, and Therapy of Myocarditis: A Position Statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 34, 2636-48. <http://dx.doi.org/10.1093/eurheartj/eh210>
8. Escher F, Kuehl U, Lassner D, Poller W, Tschoepe C and Schultheiss H-P. CARDIAC INVOLVEMENT OF HUMAN HERPESVIRUS 6 IN PATIENTS WITH INFLAMMATORY CARDIOMYOPATHY Heart Failure And Cardiomyopathies. *J Am Coll Cardiol.* 2015 Mar, 65 (10_Supplement) A945.
9. Dominguez F, Kühl U, Pieske B, Garcia-Pavia P, Tschöpe C. Update on Myocarditis and Inflammatory Cardiomyopathy: Reemergence of Endomyocardial Biopsy. *Rev Esp Cardiol (Engl Ed).* 2016 Feb;69(2):178-87. doi: 10.1016/j.rec.2015.10.015. Epub 2016 Jan 12. PMID: 26795929.
10. Kuhl U, Schultheiss HP. Viral myocarditis. *Swiss Med Wkly.* 2014;144:w14010.
11. Escher F, Kuhl U, Gross U, Westermann D, Poller W, Tschöpe C, et al. Aggravation of left ventricular dysfunction in patients with biopsy-proven cardiac human herpesvirus A and B infection. *J Clin Virol.* 2015;63:1–5.
12. Bock CT, Klingel K, Kandolf R. Human parvovirus B19-associated myocarditis. *N Engl J Med.* 2010;362:1248–9.
13. Kuhl U, Lassner D, Wallaschek N, Gross UM, Krueger GR, Seeberg B, et al. Chromosomally integrated human herpesvirus 6 in heart failure: Prevalence and treatment. *Eur J Heart Fail.* 2015;17:9–19.
14. Maisch B, Alter P. Treatment options in myocarditis and inflammatory cardiomyopathy : Focus on i. v. immunoglobulins. *Herz.* 2018

Aug;43(5):423-430. doi: 10.1007/s00059-018-4719-x. PMID: 29947834;
PMCID: PMC6096625.