

Microtubule inhibition therapy by colchicine in severe myocarditis especially caused by epstein-barr and cytomegalovirus co-infection during a two-year period: A novel therapeutic approach

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Abstract

The co-infection of Epstein-Barr virus and Cytomegalovirus rarely gains multi-pathogenicity and leads to viral myocarditis. Also, it may lead to progressive heart failure or sudden death. We present a case series of five patients who were monitored for the impact of low-dose colchicine therapy as adjunct to conventional heart failure therapy. Epstein-Barr virus, Cytomegalovirus and other viral antibodies were determined by enzyme-linked immunosorbent assay method. Adjuvant low-dose colchicine therapy (2x0.5 mg twice daily) was prescribed for addition to the conventional heart failure therapy of these patients and it was continued for two years. Ejection fractions of echocardiographic examinations in all patients were 21%, 18%, 25%, 20% and 21% before low-dose colchicine therapy. After two years of treatment, the values increased to 59%, 45%, 40%, 25% and 41%, respectively. The early implementation of low-dose colchicine in these patients seemed to have beneficial effects on overall survival.

Keywords: Epstein-Barr virus/ Cytomegalovirus co-infection, Myocarditis, Colchicine.

Introduction

Myocarditis is an inflammatory cell infiltration with myocardial necrosis and/or degeneration.¹⁻³ Rarely, the form of gaining multi-pathogenicity of Epstein-Barr virus/Cytomegalovirus (EBV/CMV) co-infection leads to severe or fatal viral myocarditis. Also, it may lead to progressive heart failure or sudden death.³⁻⁶ Colchicine has anti-inflammatory and anti-fibrotic properties. It effectively functions as a mitotic poison or spindle inhibitor. It inhibits mitosis by disrupting microtubule formation and tubulin assembly binding to β -tubulin colchicine site and enhances cellular apoptosis.⁷⁻¹⁵

We prospectively investigated and followed up the

impact of low-dose colchicine therapy in a total of five patients diagnosed as EBV/CMV co-infection leading to viral severe myocarditis with extensive myocardial damage that leads to dilated cardiomyopathy (DCM) and this was done according to "expanded criteria for diagnosis of myocarditis" in hospitalisation during a two-year period.¹

Written informed consent was obtained from each patient after the approval of the study protocol by the institutional committee.

Case Reports

A 41-year-old male patient with symptoms similar to infectious influenza for five weeks presented with growing palpitations, shortness of breath, and orthopnoea at night for 10 days. He was hospitalised in our unit.

A 40-year-old male patient with increasing shortness of breath over 15 days was internalised in our unit.

A 48-year-old male patient had upper acute respiratory tract infection for three weeks. He was hospitalised with persistent complaints and increasing shortness of breath.

A 40-year-old male patient had cold-like symptoms with a high fever for a month. He had visited another hospital and medication was prescribed. However, his symptoms did not improve, and he was admitted to our unit. In the physical examination, he had orthopnea, hepatomegaly and gallop rhythm. He had been using alcohol for 15 years.

A 42-year-old male patient was admitted to our emergency unit with palpitation, dyspnoea and chest pain such as needle pricks. His electrocardiogram (ECG) showed atrial fibrillation (AF) and he did not respond to amiodarone treatment protocol and electrical cardioversion. In his Echocardiographic (ECHO) examination, all cardiac chambers were dilated; Ejection Fraction (EF) was 21%. He was diagnosed with idiopathic DCM. He was transferred to a ward with conventional heart failure therapy, but he did not respond.

Physical, serological, biochemical, echocardiography and coronary angiographic examinations of all patients

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suspected from viral severe myocarditis were performed. Immunoglobulin M and G (IgM and IgG) antibodies of EBV, CMV, Coxsackie A and B, Adenovirus, Parvovirus B19, Human Immunodeficiency Virus (HIV), Hepatitis C Virus, Herpes simplex I and II, and Rubella were investigated by enzyme-linked immunosorbent assay (ELISA) method in our patients. We evaluated EBV/CMV co-infection according to IgG antibody positivity.

Adjuvant low-dose colchicine therapy (2x0.5mg twice daily) was added to conventional heart failure therapy (aspirin 100mg/day, metoprolol 50mg twice daily, and furosemide 40mg once daily) of the five patients. The therapies of the patients continued for two years.

EFs of ECHO examinations in our five patients with EBV/CMV co-infections were 21%, 18%, 25%, 20% and 21% before low-dose colchicine therapy which increased to 59%, 45%, 40%, 25% and 41%, respectively after two years of treatment

Discussion

EBV, CMV, adenovirus, enterovirus and parvovirus B19 are the most common cardiotropic agent pathogens of viral myocarditis. Sometimes, the diagnosis can be demonstrated by postmortem findings. Myocarditis can present itself from a very mild clinical symptom to severe heart failure findings, and sometimes it shows an even fatal spectrum.¹⁻⁶ The clinical course and prognosis of the disease are determined by gender, age, immune response and the causative agent. CMV genome was found to be present in 38% of patients with fatal myocarditis.³

Viral infections may impair myocardium with significant damage on heart cells leading to myocarditis and DCM.

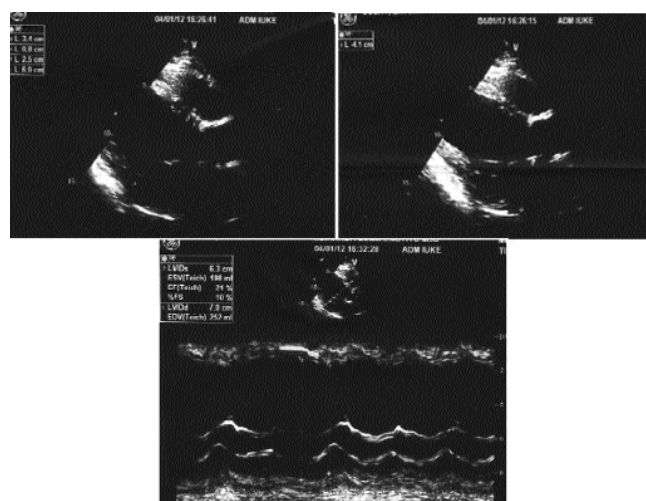


Figure-1: M-Mode and two-dimensional echocardiographic findings of the first case before colchicine treatment (Initial Ejection Fraction was 21%).

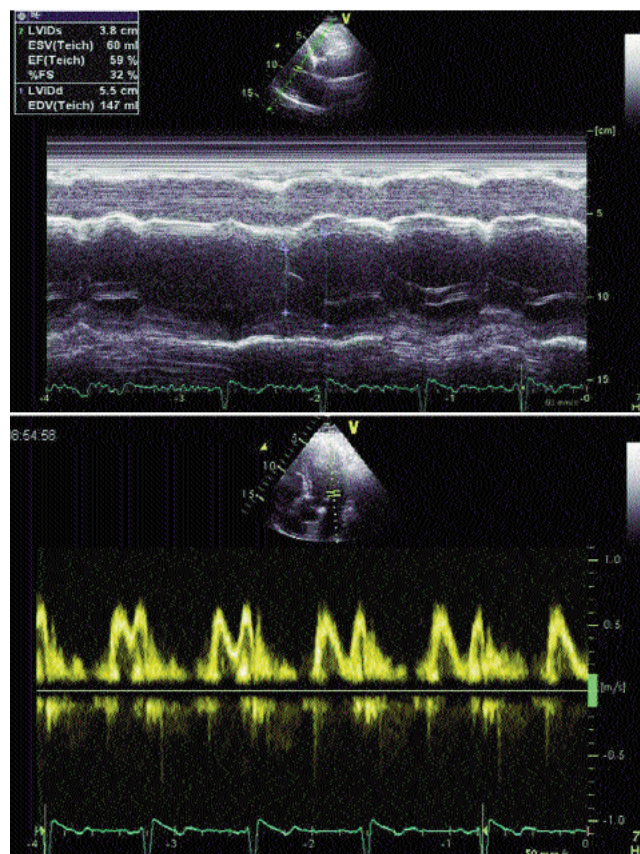


Figure-2: M-Mode and two-dimensional echocardiographic findings of the first case after two years of colchicine treatment (Ejection Fraction was 59%).

Long-term studies have found that about 20% patients who present with acute myocarditis may develop DCM.³⁻⁶ The process by which this occurs appears to be divided into three distinct phases: In phase 1, the virus causes direct destruction of cardiomyocytes. Lysis of the cells allows further entry of virus into the myocytes. During phase 2, an immune response to myocyte injury becomes dysregulated. A study⁶ reported that T cells and antibodies were directed against viral and some cardiac epitopes such as myosin and beta-1 receptors (anti-heart auto-antibodies), leading to a powerful inflammatory response. In many patients, the pathogen is eliminated and the immune response diminishes. However, in some patients the autoimmune response persists (phase 3) and extensive myocardial damage leads to DCM.^{5,6}

The condition of some patients with fulminant viral myocarditis deteriorates despite optimal pharmacological management and immunotherapy. Such patients may need mechanical circulatory support, such as intra-aortic balloon pump, ventricular assist devices (VAD) or extracorporeal membrane oxygenation (ECMO) as a

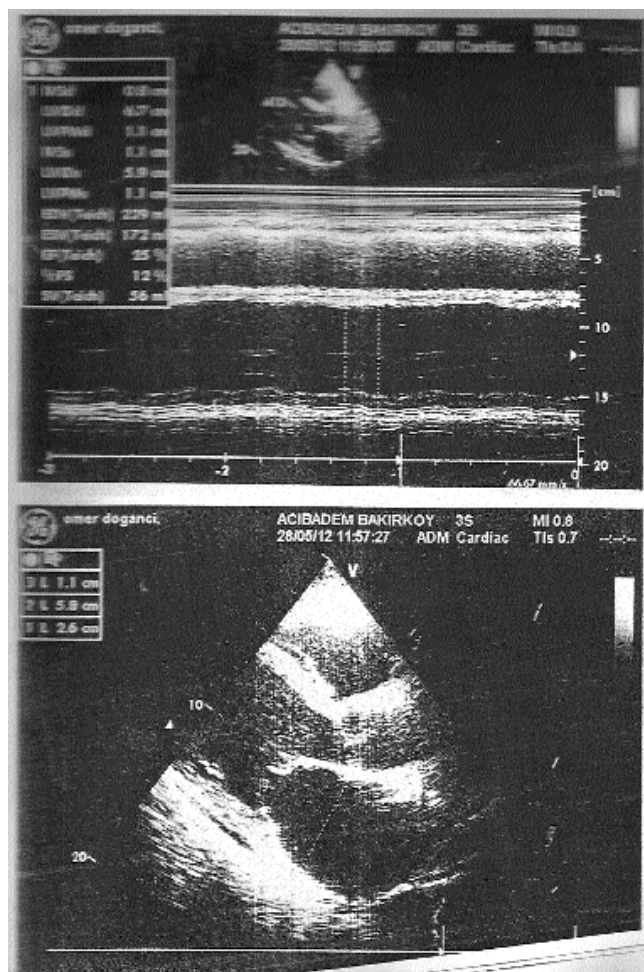


Figure-3: M-Mode and two-dimensional echocardiographic findings of the second case after first month of colchicine treatment (Ejection Fraction was 24%) (Initial Ejection Fraction was 18%).

bridge to transplantation or recovery (destination therapy).^{5,6} Also, various stem-cell therapies are tried in severe myocarditis.¹³

Our two-year follow-up study showed a dramatic disappearance of symptoms and improvement in the clinical status of these patients with EBV/CMV co-infection leading to viral myocarditis with the use of low-dose colchicine as adjunct to conventional therapy. Also, EFs of ECHO examinations in our clinical cases of acute viral severe myocarditis caused by EBV/CMV co-infection were 21%, 18%, 25%, 20% and 21% before low-dose colchicine therapy. After two years of treatment with low-dose colchicine, EFs increased to 59%, 45%, 40%, 25% and 41%, respectively (Figure-1-4). In our opinion, these improvements were not spontaneous or incidental.

In the single case series of antiviral therapy use in humans

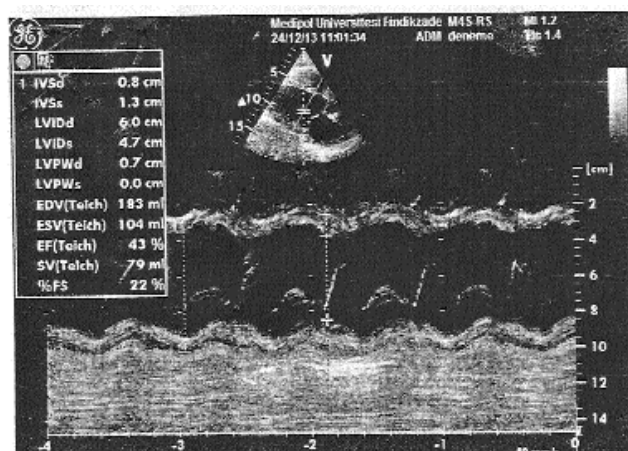


Figure-4: M-Mode and two-dimensional echocardiographic findings of the second case after two years of colchicine treatment (Ejection Fraction was 43%; next: 50%).

with fulminant myocarditis, ribavirin therapy did not prove effective.¹⁴ Colchicine is a medication with a relatively low therapeutic index that has been used to treat acute gout, familial Mediterranean fever (FMF), dermatologic and auto-inflammatory diseases. Colchicine has been recommended to treat patients with recurrent pericarditis and viral infections such as acquired immunodeficiency syndrome (AIDS) and chronic active hepatitis.^{7,11} Colchicine (Avicenna's magic and mysterious drug) which has been used for many centuries, binds to tubulin, blocks mitosis, and inhibits a variety of functions of polymorphonuclear leukocytes both in vivo and in vitro. In addition, colchicine binding to β -tubulin results in curved tubulin dimer and prevents it from adopting a straight structure, due to steric clash between colchicine and β -tubulin, which inhibits microtubule assembly and enhances cellular apoptosis.^{7-12,15} Thus, cells infected with the virus are quickly eliminated. Intact cells would dominate the myocardial tissue in severe viral myocarditis.

Colchicine also interferes with the transcellular movement of collagen. The close proximity of lymphoid components and fibroblasts at inflammatory sites and the production of lymphokines, which influence fibroblast chemotaxis, proliferation, and protein synthesis, are now well recognised. Thus, colchicine may reduce immunopathic anti-fibroblastic properties. To our knowledge, colchicine treatment of acute severe myocarditis has not been reported previously. Furthermore, colchicine mobilizes β -amyloid and prevents deposition kappa (κ) and lambda (λ) light-chain protein.^{7-12,15} We foresee that aside from cardiac hereditary diseases, it might also be a new therapeutic

approach in primary amyloidosis, cardiac sarcoidosis, neurodegenerative and psychiatric disorders such as Alzheimer disease and autism.^{10,15}

Conclusion

The early implementation of low-dose colchicine in patients may have beneficial effects on overall survival and offers a new therapeutic approach in the treatment of this rare and severe form of viral myocarditis with extensive myocardial damage that leads to DCM. Also, low-dose colchicine may be safe and effective in patients with severe myocarditis and may reduce its related complications and relapse by turning back and preventing adverse remodelling.

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