Case Reports and Reviews

Case Report

Usefulness of colchicine for Covid-19 myopericarditis in athletes. A case report and review of the literature

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Abstract

Cardiac injuries, specifically acute myocarditis, are a common complication of COVID-19. Recent studies in the literature have supported the beneficial and safe results of colchicine administration in the general population in cases of COVID-19 infection, especially in cases of myocardial injuries. However, the frequency of occurrence in athletes, its treatment, and management of these individuals concerning the return to competitive sports have not yet been clarified. The present case description is a novelty in that it refers to the onset of a mild form of acute myopericarditis secondary to COVID-19 infection in an athlete that was successfully treated as an outpatient with only colchicine. A 45-year-old marathon runner with no underlying health problems showed clinical symptoms of acute pericarditis and mild febrile infection. The biochemical tests were characterized by an increase in the level of troponin. MRI established the diagnosis of mild myopericarditis. In addition, he has been tested positive for COVID-19 by molecular/PCR test. The patient was treated with colchicine alone for three months. After that time, all the clinical and laboratory findings of myopericarditis were subsided. Six months after the onset of the disease, the athlete returned to full competitive action.

Introduction

Acute pericarditis and/or myocarditis are often complications of a viral infection, especially Coxsackieviruses, in athletes [1]. Regarding COVID-19 infection, a large number (up to 25%) of patients with severe symptoms also have cardiac involvement, such as myocarditis and/or pericarditis [2]. Recently, among the proposed treatments for myocardial injuries caused by the virus SARS-CoV-2, co-administration of colchicine has been proposed [3]. Heart damage because of COVID-19 infection in athletes is usually underestimated if the diagnosis is based solely on the results of the troponin level [4]. A recent report in JACC [5] on 54 athletes with mild COVID -9 who underwent ultrasound and magnetic resonance imaging (MRI), showed that in 39.5% of them, the MRI findings were indicative of pericardial inflammation. In contrast, no imaging evidence compatible with myocardial inflammation was found. Similarly, there was a low prevalence of myocarditis (1.4%) among student-athletes recovering from COVID-19 with mild to moderate symptoms [6]. On the contrary, in another study of athletes participating in competitive sports with COVID-19 infection who had mild symptoms, the MRI showed findings compatible with myocarditis, such as the presence of edema and/or myocardial damage, in 15% of the total sample [7]. Apart from that conflicting information, little is known about the course of myocarditis in athletes, the recommended treatment, as well as the return to play after COVID-19 myocarditis. This study aimed to report the case of a 45-year-old male marathon runner with acute myocarditis and pericarditis secondary to COVID-19 treated with colchicine and to provide a comprehensive review of the literature.

Case presentation

A 45-year-old man who was an experienced long-distance runner participating in many marathon- races was admitted with sudden-onset, severe, stabbing, left anterior chest pain. The pain radiated to the left shoulder, exacerbated by inspiration, and relieved to some extent by leaning forward. Four days before this episode, he reported symptoms of a common "cold" with productive cough and malaise and mild fever without dyspnea. Physical exam showed a well-nourished man. His heart rate was 90 beats per minute, and his blood pressure was 133/84 mm Hg. Heart auscultation revealed a mild pericardial friction rub. Chest auscultation revealed normal bilateral respiratory vesicular sounds with no adventitious sounds. Initial laboratory test results showed a white blood count of

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9.60 cells/mm^3, a high-sensitivity troponin I level of 7.10 mg/dL, creatine kinase level was 230 mg/dL, CK-MB level was 7.6 mg/dL, CRP 15 mg/L, N-terminal pro- B-type natriuretic peptide 810 pg/ml, and normal D-dimer concentration and liver function tests. The SpO_2 level was 95 %, as estimated from a pulse oximeter. He has been tested positive for COVID-19 by molecular/PCR test. Sinus rhythm and lateral wall ST-T wave changes were found in ECG (Figure 1). B-mode echocardiogram showed mild anterior pericardial effusion with minimal basal and lateral wall alterations, and without LV cavity dilatation and dysfunction (Figure 2). No arrhythmias were detected on the 24-h Holter monitoring. Chest radiography revealed mild increased bronchovascular markings with normal cardiac size. Myopericarditis diagnosis, secondary to COVID-19 infection, was made based on clinical, laboratory, ECG, and echocardiogram findings. He refused to be hospitalized. Cardiac Magnetic Resonance Imaging demonstrated a mild pericardial fluid and mild oedema and late gadolinium enhancement of moderate severity in the basal, middle, and lateral wall of the left ventricle (Figure 3). The athlete was subsequently treated with Colchicine (1 mg per day) alone. He was asked to take a rest week. His symptoms disappeared after three days, and the level of troponin I was also significantly depressed. A strict ban on sport and physical activity restriction for six months was recommended. He received colchicine for three months. No side effects were observed. On re-examination, after one month, the ECG and cardiac ultrasound pathological findings were resolved. The cardiac MRI and exercise testing after six months were normal. Therefore, the athlete returned to his complete athletic activities after six months. From his previous personal history, there was no health problem. It should be noted that the patient had undergone coronary angiography a year before due to questionable findings in a nuclear stress test, which showed minimal damage in the anterior descanting branch of the left coronary artery.

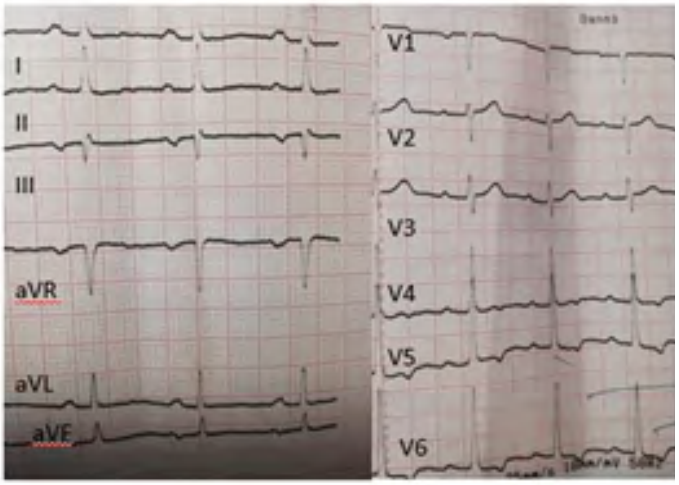

Figure 1. *Electrocardiogram of the patient at his admission. Lateral wall ST-T changes were recorded.*

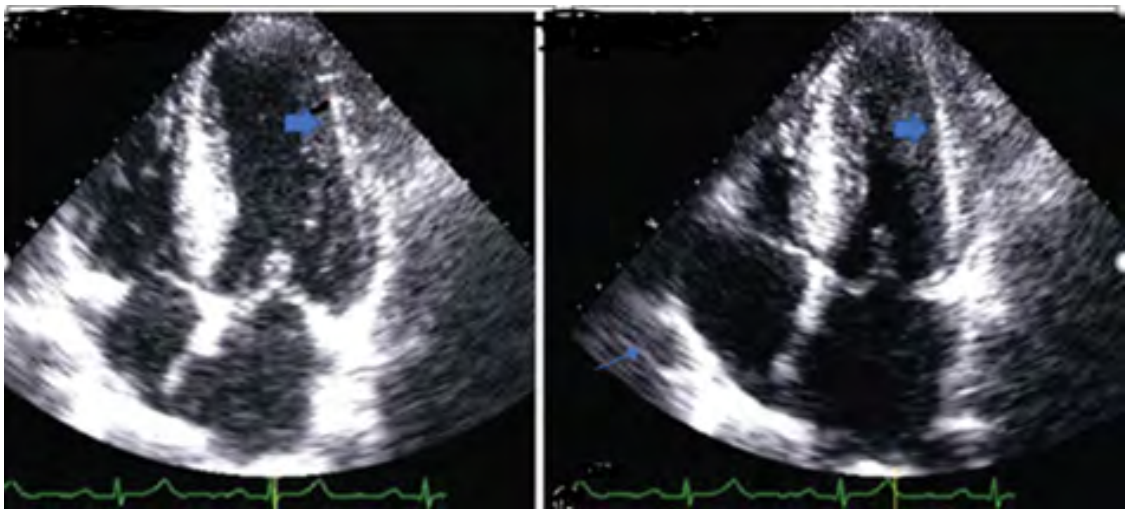

Figure 2. *Four-chamber echocardiogram at the admission showed minimal lateral wall alterations (thick arrow) with mild pericardial effusion (thin arrow). Interventricular septum thickness 12 mm, left ventricular EF 64%, right ventricular EF 62%. Both atria were normal.*

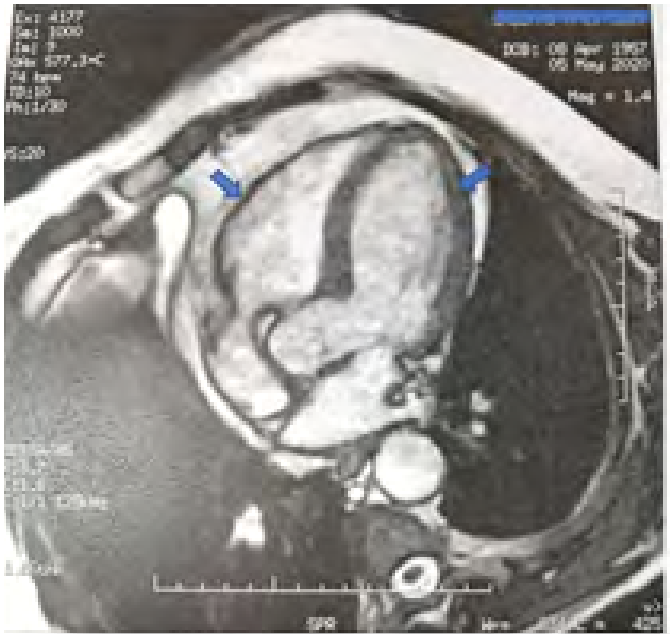

Figure 3. *Four-chamber view in MRI enables visualization area of mid myocardial oedema and late gadolinium enhancement of moderate severity in the lateral wall (right arrow). Moreover, mild pericardial effusion was fount (left arrow).*

Discussion and conclusion

The novelty of this interesting case lies in the fact that it concerns an acute myopericarditis involvement caused by COVID 19 infection in an athlete who was successfully treated with the administration of colchicine alone.

It is well known that moderate-intensity exercise reduces upper respiratory virus infections while high-intensity exercise increases them. Thus, a J -shaped correlation model between varying exercise intensity and upper respiratory tract infection was designed. Concerning COVID 19 infection, it has not yet been established whether this association remains. The spectrum of viruses involved in causing myocarditis is shifted from the "traditionally" expected viruses, mainly Coxsackie virus type B, to other viruses, such as parvovirus B19 and herpesvirus. The ARS-CoV-2 is a single-stranded RNA virus, which has similarities to previous coronaries (SARS and MERS) but shows greater transmissibility and frequent mutations. The infectious disease, called Coronavirus Disease 2019 (COVID-19), is accompanied by cough, fever, myalgia, or fatigue, and often causes pneumonia. Its clinical course in people having specific health problems is particularly severe. Cardiac injury, especially myocarditis, occurred in COVID-19 infection, usually associated with increased disease severity [2]. More often, COCID-19 myocarditis is fulminant, leading to acute heart failure, cardiogenic shock, and life-threatening arrhythmias [8,9]. Less commonly, pericardial inflammation (acute pericarditis) alone or in combination with myocarditis was described [9]. As already mentioned, the incidence of pericarditis and especially myocarditis after COVID 19 infection in competitive athletes is still unclear.

The pathophysiology of viral myocarditis presupposes the "synergy" of two factors: the viral myocardial damage and the subsequent immune response. Thus, the initial invasion of myocardial cells by the virus (acute phase) leads to mobilization of the immune system, ultimately the production of antibodies against the virus that is, however, cross-reactive with antigens of myocardial cells and thus cause the final myocardial damage (subacute phase), leading to either complete cure or development of dilated cardiomyopathy (chronic phase) [10]. Experimental studies have shown that myocardial injury by certain viruses presupposes the presence of specific receptors in the myocardial cell, such as the CAR receptor (Coxsackie and Adenovirus Receptor), the absence of which appears to act as a protection against Coxsackie type B [11]. It is possible that appropriate genetic predisposition is a prerequisite for myocardial cell infection by viruses. Halushka et al. [12], in a large postmortem examination study in patients with SARS-CoV2, reported that the most common cardiac findings were a nonspecific non-myocarditis inflammatory infiltrate and single-cell ischemia occurring in 12.6% and 13.7% of cases, respectively. Acute myocardial infarctions were noted in 4.7% of individuals, and myocarditis was reported in 7.2% of cases. Endomyocardial biopsy studies in patients with SARS-CoV2 myocarditis observed the infiltration of myocardial macrophages in the autopsy samples [13]. That infiltrate is lymphocyte-predominant [12]. A second probable mechanism is the indirect involvement of the myocardium by the accumulation of cytokines, as evidenced by the increase of interleukin (IL) IL-6, IL-10, IL-2 receptor, and tumor necrosis factor [13]. A third mechanism described is the manifestation of downregulation of angiotensin-converting enzyme 2 (ACE2) receptors that weaken the protective role of angiotensin in the myocardium [13]. The cell entry of SARS-CoV-2 depends on the angiotensin- converting enzyme 2 (ACE2) receptors, which are found in the endothelial cells of the heart and lead to the onset of inflammatory processes [12].

There are currently no clinical trials to support the optimal therapeutic approach in cases of secondary to COVID-19 acute myocarditis and/or pericarditis; the decision is recommended to base on the clinical findings [8,9]. In patients with fulminant myocarditis, heart failure, and arrhythmias,

optimally management should include the use of diuretics, ACE inhibitors, beta-adrenergic blockade, antiarrhythmic, immunomodulatory therapy using anti-viral medications, many novel anti-inflammatory agents, steroids, with unclear results, azathioprine, and cyclosporine.

Colchicine is an old anti-inflammatory drug derived from Colchicum autumnale. It is a microtubule polymerization agent, an inhibitor of interleukins 1 and 6, and a granulocyte-macrophage colony- stimulating factor. Many studies have provided strong evidence of colchicine's effectiveness in treating pericarditis, often recurrent pericarditis cases [14]. The treatment is usually administered up to 12 weeks (0.5- 2 mg / daily) but can be prolonged up to 1-year, recurrent pericarditis. Indeed, some reports supported the efficacy of colchicine to treat patients with viral myocarditis. Interestingly, the study of Morgenstern et al. [15] demonstrated that 63% of the patients with viral myocarditis who received colchicine showed complete resolution of myocarditis on their previous CMR study. On the contrary, only 38% of the patients who did not receive colchicine had a resolution of myocarditis. However, in an experimental study, the administration of colchicine aggravated coxsackievirus infection in both the myocardium and the pancreas [16]. Recently, the use of colchicine in the treatment of COVID-19 infections has been supported by several studies [3,17,18]. It is found to reduce the admission of patients to hospitals since it plays a significant role in the prevention of myocardial injury-related complications of COVID-19. Deftereos et al. [3] demonstrated that patients with biochemical evidence of myocardial injury who received colchicine had significantly less clinical deterioration. The researchers suggested that colchicine's mechanism of action in the treatment of COVID-19 cardiac complications may be antithrombotic as well as anti-inflammatory. They hypothesized that colchicine's effectiveness was based on the blunted inflammatory waterfall mediated by the cytokines leading to interference from viral endocytosis. However, a limitation of the study was the co-treatment with other investigational agents, such as hydroxychloroquine and azithromycin. Papadopoulos et al. [18] mentioned that the effect on inflammatory cardiac biomarkers could be observed within hours of administration of colchicine in COVID- 19 cases. The administration of colchicine, as a monotherapy, in the case of our athlete with myopericarditis following COVID-19 infection, had excellent results, inducing rapid response and remission, and achieving its complete cure.

There are currently no randomized trials studies suggesting the optimal time to return to sport following myopericarditis. According to guidelines, for confirmed cases of pericarditis and/or myocarditis, it is recommended that athletes refrain from exercise training for 3-6 months after the complete clinical resolution of the disease [19]. Since there is no specific test to support complete recovery from myocarditis, the decision to return to competitive sports will be based on the severity of the initial illness the absence of arrhythmias during exercise.

In mild symptomatic athletes with COVID-19 infection without complications, return to regular exercise training is allowed after ten days from the onset of symptoms and seven days after their resolution, i.e., a total of 2-3 weeks, without additional testing. Baggish et al.[20] recommended that before to returning to sports after COVID-19 infection, all asymptomatic competitive athletes should undergo a history and physical examination; primarily, for those who were mild symptomatic, ECG should be performed. There is no evidence that myocarditis secondary to COVID-19 infection is substantially clinically different from other forms of viral myocarditis that would advocate a different attitude to participate in competitive sports. As a rule, returning to sports is permitted after the 3-6 months' period of restriction due to COVID-19 myocarditis, when symptoms are absent, LV function has normalized, and there are not arrhythmias on ECG exercise stress testing and ECG ambulatory monitoring. According to these recommendations, we allowed the athlete to participate in long-distance running six months after the onset of COVID-19 myopericarditis. There were no symptoms, arrhythmias, and abnormal laboratory findings. Our practice was to recommend a gradual return to entire intensity exercise.

In conclusion, as monotherapy the administration of colchicine, in cases of mild, uncomplicated myo-pericarditis in athletes resulting from COVID-19 infection, is an effective, safe, and cheap treatment.

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