Successful use of anakinra in a patient with COVID-19- associated pericarditis

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Case Report

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Abstract

Since its recognition in December 2019 as a cause of pneumonia, SARS-CoV-2 infection has rapidly spread globally, causing a pandemic. Although it is an infectious disease, several distinct manifestations have been described in the setting of COVID-19, which result from the immune perturbations caused by this new Coronavirus. The heart is frequently involved in COVID-19 and is associated with severe outcomes. Pericarditis is rarely reported in COVID-19 patients and no reports on its treatment and outcome are available so far. Herein, we present a 33-year-old man with COVID-19-related pericarditis (COVID-19-RP) who was unresponsive to colchicine and nonsteroidal anti-inflammatory drugs, but was successfully treated with the IL-1R antagonist anakinra.

Introduction

Since its recognition in December 2019 as a cause of potentially severe pneumonia, SARS-CoV-2 infection has rapidly spread globally, causing a pandemic. Although it is an infectious disease, several distinct manifestations have been described in the setting of the new Coronavirus disease (COVID)-19 resulting from the hyperimmune response caused by the virus [1]. The heart is frequently involved in COVID-19 and is associated with severe outcomes. Numerous distinct cardiac complications have been reported in COVID-19 patients, including arrhythmia, myocarditis, and coronary thrombosis [2]. Pericarditis is rarely reported in COVID-19 patients and no reports are available on its treatment and outcome [3]. Herein, we describe the case of a patient affected by COVID-19 complicated by pericarditis successfully treated with the IL-1R antagonist anakinra.

Case Report

A previously healthy 33-year-old man presented to Emergency Department (ED) with a progressive retrosternal chest pain lasting for 5 days. He described a pain worsening with change position and unresponsive to painkillers. In the past few days, he had decided to go to sleep sitting because of the pain. He also reported severe low back pain that started one week before his arrival on April 16, at the ED. The physical examination findings were as follows: his pulse was 90 beats per minute and regular, his blood pressure was 118/78 mmHg, oxygen saturation was 97% whilst breathing ambient air, and his temperature was 37.9 °C. The rest of the physical examination was unremarkable. Blood tests revealed normal D-dimer (0.26 ng/mL, normal <0.5) and high sensitive troponin T (<5 ng/L). On the contrary the patient had high levels of C-Reactive Protein (CRP, 73.8 mg/dl, nv <5) lymphopenia (1060/mm³) and elevated interleukin (IL)-6 levels (43.6 pg/mL, normal <5). Rheumatoid factor, antinuclear and anti-extractable nuclear antigen antibodies tested negative. The nasopharyngeal swab for SARS-CoV-2 tested positive. The patient was treated with oral hydroxychloroquine and moxifloxacin as per the recommended COVID-19 protocol along with analgesics. However, on third day of hospitalization chest pain did not improve and D-dimer raised to 3.15 mg/mL. A 12-lead electrocardiogram (ECG) showed T-negative in D2,

D3, and AVF derivations (more prominent in the inferior lateral derivations). Biphaseic P wave in V1 derivation and J wave in both D3 and V6 derivations. Incomplete right ventricular conduction delay in V1 derivation (rSr pattern). (**Figure 1**). The echocardiogram showed a normal left ventricular function with circumferential pericardial effusion. Thorax computed tomography showed minimal ground glass opacification, subpleural curvilinear lines and pericardial effusion while excluding pulmonary embolism. However, enoxaparin 40 mg twice daily was added to his treatment due to increased d-dimer. Given the clinical manifestations, laboratory results and ECG findings, a diagnosis of pericarditis was made. 0.5 mg colchicine twice daily and 25 mg indomethacin thrice daily were initiated on April 21. Five days later fever and chest pain persisted, while CRP and D-dimer significantly increased to 83 mg/L and 5.65 ng/mL, respectively despite ongoing treatment with colchicine and indomethacin. Because his condition did not improve, anakinra 100 mg/day subcutaneously was started. Chest pain promptly relieved. CRP and D-dimer values normalized seven days after anakinra commencement, as well as echocardiogram. Anakinra was discontinued seven days later and the patient was discharged in good clinical conditions. He was doing well in his follow-up visit two weeks after the hospital discharge.

Discussion

This is the first case in the literature showing the efficacy and safety of anakinra in a COVID-19-RP after failure of colchicine therapy. Although rarely reported in COVID-19, pericarditis is an expected complication of viral infections. According to the 2015 European Society of Cardiology (ESC) Guidelines, diagnosis of pericarditis can be made using two of the following four criteria: (i) pericardial chest pain, (ii) widespread saddle-shaped or concave upward ST segment elevation or PR-segment depressions on ECG (iii) new or worsening pericardial effusion and (iv) pericardial friction rub that is auscultated by placing diaphragm of the stethoscope over the left sternal border. Additional supportive findings were fever, positive inflammatory markers (leukocytosis, CRP) and evidence of pericardial inflammation by imaging [4]. Most patients with acute pericarditis have an idiopathic form which accounts for more than 80% of the cases [5]. According to recent findings, inflammasome activation is one of the main immunopathogenic pathway leading to pericardial inflammation. Interleukin (IL-1) β is the predominant cytokine activated by inflammasomes which stimulates the synthesis of cyclo-oxygenase-2 (COX-2) and prostaglandins thus leading to pericarditis [5]. Hence, treatments targeting inflammasome (colchicine), COX-2 (aspirin, ibuprofen, indomethacin) and IL-1 (anakinra) constitute the treatments options for idiopathic pericarditis [6]. Viral components and cytosolic danger signals, such as mitochondrial injury, protein aggregates, and aberrant ion concentrations can activate NLR Family Pyrin Domain Containing 3 inflammasome which in turn releases IL-1 β , IL-18 and the proapoptotic factor gasdermin D [7]. In a previous study, SARS-CoV-2 has been shown to activate the NLRP3 inflammasome and induce the production of IL-18 by human macrophages by its ion channel-forming E protein and ORF8b, which are also the structural components of SARS-CoV-2 [1]. Therefore, pericarditis is an expected clinical condition in COVID-19 [9]. COVID-19 is now thought as a virus-induced immune disorder due to constellation of features observed in cytokine storm syndromes. Hypercytokinemia is considered by many to be the main driver of morbidity and mortality in COVID-19 [1]. Therefore, anti-cytokine treatments, as tocilizumab

(targeting IL-6), and anakinra (targeting IL-1) pathways are being investigated for the treatment of severe COVID-19 patients [1]. Based on these common pathogenetic mechanisms between idiopathic pericarditis and COVID-19, we suggest that therapeutic approach in this clinical setting might be the same also for COVID-19-RP [1]. In our case we unsuccessfully tried colchicine and indomethacin, while obtaining a rapid recovery with anakinra as for refractory cases of idiopathic recurrent pericarditis.

Conclusion

Nowadays, COVID-19 related cardiovascular disease in conjunction with lung involvement represents one of the leading cause of death and morbidity in worldwide. As far as we have experienced in this case, anakinra could be an effective and reliable option in COVID-19-RP owing to complete remission of pericarditis and prevention of long-term hospitalization, along with the absence of adverse effects.

Declarations

Conflict of interest: Written informed consent was obtained from the patients. The authors declare that they have no conflicts of interest.

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Figures

Figure 1

A 12-lead electrocardiogram (ECG) showing T-negative in D2, D3, and AVF derivations (more prominent in the inferior lateral derivations). Biphasic P wave in V1 derivation and J wave in both D3 and V6 derivations. Incomplete right ventricular conduction delay in V1 derivation (rSr pattern)