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LETTER TO THE EDITOR

Anakinra for the Treatment of COVID-19-Associated Pericarditis: A Case Report

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Dear Editor,

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.

A previously healthy 33-year-old male presented to the emergency department (ED) with progressive retrosternal chest pain for the previous 5 days. He described worsening of pain with sitting forward and nonresponse to diclofenac. He also reported severe low back pain that started 1 week before his arrival at the ED on April 16. The physical examination findings were as follows: pulse 90 beats per minute and regular, blood pressure 118/78 mmHg, oxygen saturation 97% whilst breathing ambient air, and temperature 37.9 °C. The rest of the physical examination was unremarkable. The nasopharyngeal swab for SARS-CoV-2 tested positive. Blood tests revealed normal D-dimer (0.26 ng/mL, normal <0.5) and high-sensitivity troponin T (<5 ng/L) and elevated C-reactive protein (CRP, 73.8 mg/dl, $n < 5$), interleukin (IL)-6 levels (43.6 pg/mL, normal <5), and lymphopenia (1060/mm^3). Rheumatoid factor, antinuclear, and anti-extractable nuclear antigen antibodies tested negative. The patient was treated with oral hydroxychloroquine and moxifloxacin as per the local recommended COVID-19 protocol, along with analgesics. The hydroxychloroquine dose was 400 mg bid the first day and then 200 mg bid for 5 additional days. However, on the third day of hospitalization, chest pain did not improve and D-dimer increased 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); biphasic P wave in V1 derivation and J wave in both D3 and V6 derivations; and incomplete right ventricular conduction delay in V1 derivation (rSr pattern) (Fig. 1). The echocardiogram showed normal left ventricular function with

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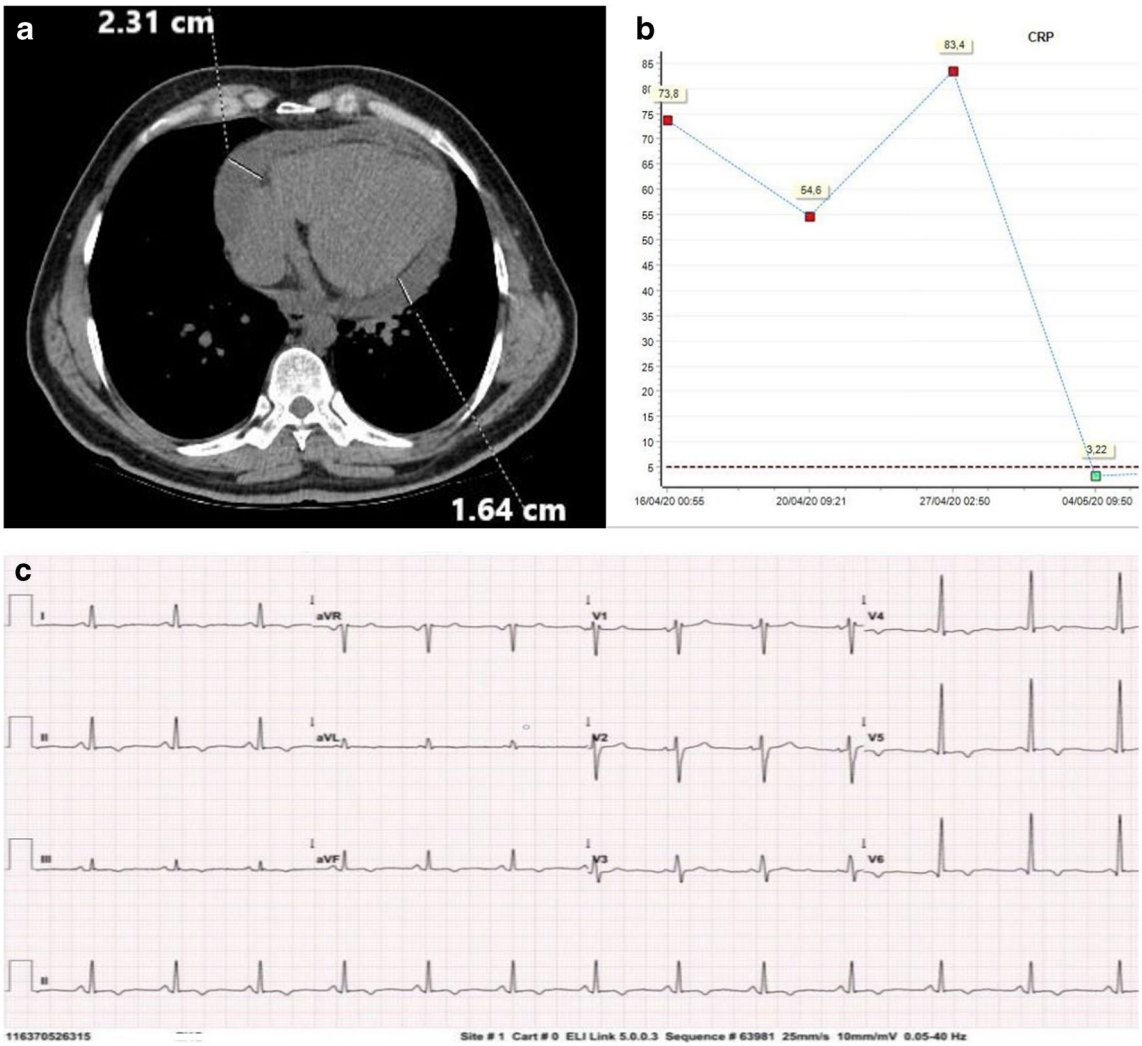

Fig. 1 (**a**) Thorax computed tomography showing pericardial effusion. (**b**) C-reactive protein time-table graph. (**c**) A 12-lead electrocardiogram (ECG) showing T-negative in D2, D3, and AVF derivations (more prominent in the inferior lateral derivations). Biphasic P wave in V1 derivation and J wave in both D3 and V6 derivations. Incomplete right ventricular conduction delay in V1 derivation (rSr pattern)

circumferential pericardial effusion. Thorax computed tomography showed minimal ground-glass opacification, subpleural curvilinear lines, and pericardial effusion (greatest thickness 23.1 mm), while it did not find indirect suggestive signs of pulmonary embolism. Nonetheless, 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. A regimen of 0.5 mg colchicine twice daily and 25 mg indomethacin thrice daily was initiated on April 21. Five days later, fever and chest pain persisted, while CRP and D-dimer increased significantly to 83.4 mg/L and 5.65 ng/mL, respectively, despite ongoing treatment with colchicine and indomethacin. Because his condition did not improve, subcutaneous administration of anakinra 100 mg/day was started. Chest pain was promptly relieved. CRP and D-dimer values normalized 7 days after anakinra commencement, as well as echocardiogram. Anakinra was discontinued 7 days later and the patient was discharged in good clinical condition. He was doing well in his follow-up visit 2 weeks after the hospital discharge.

This is the first case in the literature showing the efficacy and safety of anakinra in a COVID-19-associated pericarditis 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 the 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 cases [5]. According to recent findings, inflammasome activation is one of the main immunopathogenic pathways leading to pericardial inflammation. Interleukin (IL-1) β is the predominant cytokine activated by inflammasomes and stimulates the synthesis of cyclooxygenase-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 treatment 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-1β, IL-18, and the pro-pyroptotic factor gasdermin D [7]. In a previous study, SARS-CoV-2 was 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 [8]. COVID-19 is now considered a virus-induced immune disorder due to a constellation of features observed in cytokine storm syndromes. Hypercytokinemia is believed by many to be the main driver of morbidity and mortality in COVID-19 [1, 9]. Therefore, anti-cytokine treatments such as tocilizumab (targeting IL-6) and anakinra (targeting IL-1) are being investigated for the treatment of patients with severe COVID-19 [1]. Based on these common pathogenetic mechanisms between idiopathic pericarditis and COVID-19, we suggest that the therapeutic approach in this clinical setting might be the same as for COVID-19-associated pericarditis [1]. In our case, we unsuccessfully tried colchicine and indomethacin, while obtaining rapid recovery with anakinra as for refractory cases of idiopathic recurrent pericarditis.

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

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Written informed consent was obtained from the patient.

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