Pericarditis as the Main Clinical Manifestation of COVID-19 in Adolescents

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Abstract: Children and adolescents with severe acute respiratory syndrome coronavirus 2 infection usually have a milder illness, lower mortality rates and may manifest different clinical entities compared with adults. Acute effusive pericarditis is a rare clinical manifestation in patients with COVID-19, especially among those without concurrent pulmonary disease or myocardial injury. We present 2 cases of acute pericarditis, in the absence of initial respiratory or other symptoms, in adolescents with COVID-19.

Key Words: pericarditis, COVID-19, adolescent, children

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of the novel coronavirus disease 2019 (COVID-19), has spread rapidly around the world since first identified in Wuhan, China, in December 2019.[1] On March 11, 2020, the World Health Organization declared COVID-19 a pandemic, threatening the global public health and resulting in worldwide severe morbidity and mortality.[2] SARS-CoV-2 may cause a wide range of clinical presentations ranging from asymptomatic infection to severe forms of disease. Typically, COVID-19 presents with respiratory symptoms and pulmonary injury, but there has been increasing awareness of extrapulmonary manifestations and especially cardiovascular involvement as many patients with cardiac symptoms and severe acute cardiovascular injury have been reported.[3] Children infected with SARS-CoV-2 usually have a milder illness, lower rates of mortality and may manifest different clinical entities, compared with adults, such as the multisystem inflammatory syndrome (MIS-C).[4] Herein, we present 2 cases of acute pericarditis in the absence of initial respiratory or other symptoms in adolescents with COVID-19.

CASE REPORT 1

A 14.5-year-old boy presented with a 2-week history of progressive chest pain radiating to the neck and left shoulder and 3 days low-grade fever (Tmax 37.9°C). The pain worsened in supine position and during deep inspiration and coughing. He had no history of travel, but he reported that 4 weeks before admission, he was exposed to a confirmed case of COVID-19. Past medical history was remarkable for allergic asthma, and there was a family history of acute myocardial infection at the age of 40 in the maternal uncle and paternal grandmother.

Due to the persistence of chest pain, he underwent cardiologic evaluation 1 week before admission. An electrocardiogram (ECG) was performed, which was normal, whereas the transthoracic echocardiogram (TTE) showed normal structure and function with mild-to-moderate pericardial effusion of approximately 10 mm. These findings were suggestive of acute pericarditis since 3 of 4 criteria required for the diagnosis were met, namely chest pain, characteristic ECG abnormalities, and pericardial effusion.[5] Treatment with oral colchicine and ibuprofen was initiated immediately. Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for the detection of SARS-CoV-2 nucleic acid was performed in nasopharyngeal swab and was positive. Four days later, he developed low-grade fever with no other symptoms.

On admission, vital signs were within normal range and the physical examination was unremarkable, except for muffled heart sounds and a friction rub. Laboratory investigation revealed normal white blood cell count (WBC: 8200/mL, neutrophils: 61.5%, lymphocytes: 27.5%, monocytes: 6.8%), elevated C-reactive protein (CRP: 36 mg/L) and erythrocyte sedimentation rate (ESR: 100 mm). Blood chemistry and procalcitonin were normal, and blood culture was negative. Coagulation studies revealed elevated D-dimer of 7.26 mg/L (normal range < 0.5 mg/L) and fibrinogen of 6.37 g/L (normal range 1.56–4.00 g/L). Also, rapid test and RT-PCR for SARS-CoV-2 were negative. Chest radiograph revealed cardiomegaly in the absence of pulmonary infiltrates (Fig. 1A). ECG showed T-wave inversion in anteroseptal leads (III, V3, V4) (see Figure, Supplemental Digital Content 1a, http://links.lww.com/INF/E329) and TTE revealed mild-to-moderate pericardial effusion of 10 mm, with normal left ventricular systolic function and coronaries. Troponin I, N-terminal probrain natriuretic peptide (NT-proBNP) and ferritin were within normal range.

Further investigation for the possible etiologies of pericardial effusion was performed, including negative antinuclear antibodies (ANA) titer, extractable nuclear antigen titer, anticyclic citrullinated peptide (anti-CCP2) titer, perinuclear antineutrophil cytoplasmic antibodies (p-ANCA), cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA), QuantiFERON-TB Gold Plus test, serologic assays for Epstein-Barr virus, cytomegalovirus, human herpesvirus 6, herpes simplex virus 1, adenovirus, enterovirus, *Mycoplasma pneumoniae*, parvovirus, hepatitis B and C, syphilis and HIV. Moreover, FilmArray respiratory 2.1 plus panel (BioFire Diagnostics, Salt Lake City, UT), which tests for 19 respiratory viruses and 4 bacteria, including SARS-CoV-2, was negative. Finally, serology for SARS-CoV-2 revealed equivocal IgM and negative IgG and IgA (Euroimmun, Lübeck, Germany) on the 17th day of illness. Treatment with oral colchicine and ibuprofen was continued, and, on the 4th day of hospitalization, the patient was discharged. Overall clinical course was favorable with complete clinical and laboratory resolution. The patient remained

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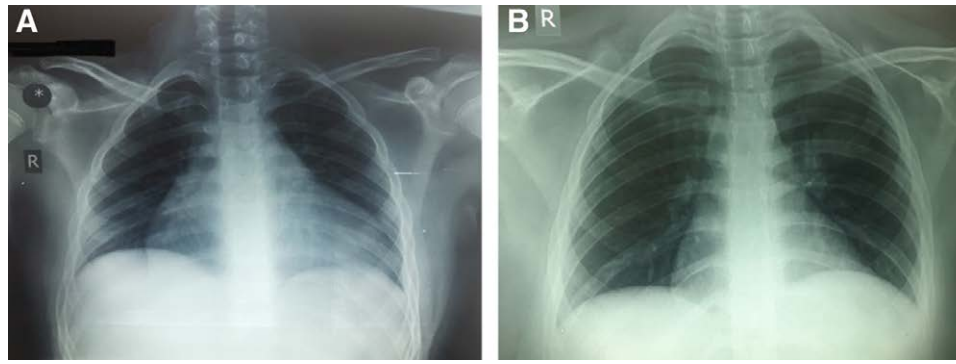

FIGURE 1. Chest radiograph demonstrating (A) the enlarged cardiac silhouette in case 1 and (B) normal chest radiograph in case 2.

asymptomatic after a 4-week follow-up period, with normal cardiologic examination.

CASE REPORT 2

A 15.5-year-old obese girl presented with a 6-hour history of chest pain that worsened during deep inspiration and coughing. She had no history of travel, but he reported that 2 weeks before admission, she was exposed to a confirmed case of COVID-19. Past medical and family history was unremarkable.

On admission, vital signs were within normal range and the physical examination was unremarkable. Laboratory investigation revealed normal WBC: 8100/mL (neutrophils:78.4%, lymphocytes: 15.3%, monocytes: 6.2%), and mildly elevated CRP: 14 mg/L and ESR: 25 mm. Blood chemistry, coagulation studies, D-dimer and fibrinogen were normal and blood culture was negative. A rapid test and RT-PCR for SARS-CoV-2 were performed and they were positive. Chest radiograph was normal (Fig. 1B), while ECG showed T-wave inversion in inferolateral leads (III, aVF, V5, V6) (see Figure, Supplemental Digital Content 1b; http://links.lww.com/INF/E329) and TTE revealed normal structure and function, echo contrast pericardial effusion, with normal left ventricular systolic function and coronaries. Troponin I, NT-proBNP and ferritin were within normal range. These findings were suggestive of acute pericarditis since 2 of 4 criteria required for the diagnosis were met, namely chest pain and characteristic ECG changes.[5]

Treatment with oral ibuprofen was initiated immediately. On the second day of hospitalization, the patient developed fever (Tmax 38.2°C). Further investigation for the possible etiologies of pericardial effusion was performed, including serologic assays for Epstein-Barr virus, cytomegalovirus, adenovirus, enterovirus, *Mycoplasma pneumoniae*, that were all negative. On the 4th day of hospitalization, the patient was discharged. Overall clinical course was favorable with complete clinical and laboratory resolution. The patient remained asymptomatic after a 4-week follow-up period, with normal cardiologic examination.

DISCUSSION

The association between cardiovascular disease and COVID-19 has been established. Despite the profound severe pulmonary damage of SARS-CoV-2 infection, it can also lead to cardiovascular abnormalities, including myocardial injury, myocarditis and pericarditis, arrhythmia and cardiac arrest, cardiomyopathy, heart failure, cardiogenic shock and coagulation abnormalities.[6] Furthermore, COVID-19 patients with preexisting cardiovascular diseases are at higher risk of increased morbidity and mortality.[6] Acute effusive pericarditis is a rare manifestation in adults with COVID-19, especially without concomitant pulmonary disease or myocardial injury, with a prevalence reported to 0.71‰.[7] Viral infections are common causes of pericarditis in developed countries and it is evident that SARS-CoV-2 has cardiotropic properties.[3] Although the mechanism of effusive pericarditis in COVID-19 is unknown, it is hypothesized that it occurs secondary to the inflammatory response and the subsequent cytotoxic and immune-mediated effects related to SARS-CoV-2.[5,6,8] COVID-19 may activate cascades of inflammatory pathways, which can potentially result in multiorgan injury and particularly, in pericarditis and pericardial effusion similarly to other viral infections.[5,6,8]

The clinical diagnosis of acute pericarditis can be made with at least 2 of the following criteria (i) chest pain, (ii) pericardial friction rub, (iii) ECG changes and (iv) pericardial effusion.[5] Approximately 90% of acute pericarditis cases are idiopathic or viral. Viral pericarditis typically has a benign course and is selflimited, as most patients recover within 2–4 weeks with treatment, including nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine and corticosteroids.[5] For NSAIDs, there is no clear scientific evidence linking ibuprofen and other NSAIDs to worsening of COVID-19; therefore, it seems prudent to use them to control pericarditis, in combination with other treatments, including corticosteroids, colchicine and anakinra, as they are currently considered potential therapeutic options for COVID-19 infection at different disease stages.[9] To date, there are no established guidelines for the management of pericarditis secondary to COVID-19.

The data about the spectrum of clinical presentation of COVID-19 infection in children is limited. Only one case has been previously reported in the literature of a 7-year-old female with COVID-19 and acute pericarditis presenting with pericardial tamponade in the setting of cough, chest pain, and orthopnea.[10] To our knowledge, COVID-19 presenting as pericarditis in the absence of evident respiratory or myocardial involvement in adolescents has not been described. It is difficult to determine whether pericarditis was a postinflammatory immune-mediated presentation or an active COVID-19 infection-causing pericardial inflammation.

In conclusion, acute pericarditis and pericardial effusion can occur in adolescents with COVID-19, even in the absence of pulmonary disease. These cases highlight the importance of recognizing COVID-19 infection with atypical clinical presentations such as pericarditis, which can be underdiagnosed during the pandemic. In particular, we underline the need to include pericarditis in the differential diagnosis of adolescent patients with cardiac symptoms, ECG or TTE abnormalities, with or without cardiac enzyme elevation, to prevent potential complications and enhance rapid symptom resolution with appropriate management.

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