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Clinical and Histopathologic Features of Myocarditis in Multisystem Inflammatory Syndrome (Adult)–Associated COVID-19

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BACKGROUND: Multisystem inflammatory syndrome (MIS) associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is a life-threatening condition first described in children (MIS-C). It is characterized by a hyperinflammatory state that involves the cardiovascular, gastrointestinal, dermatologic, and neurologic systems without severe respiratory system involvement. Myocarditis is one of the cardiovascular presentations of MIS that might be complicated with cardiogenic shock. There are few case reports describing SARS-CoV-2-related MIS in adults (MIS-A).

CASE SUMMARY: Three cases of healthy young adults diagnosed with severe acute respiratory syndrome-CoV-2 related (MIS-A). The main presentation was cardiogenic shock secondary to histologically proven myocarditis, which resolved rapidly after initiation of medical therapy including anti-inflammatory and immunosuppressive drugs. All the cases, however, required mechanical circulatory support (MCS) as a bridge to recovery.

CONCLUSIONS: It appears reasonable to treat the patient with fulminant myocarditis in SARS-CoV-2-associated MIS-A with high-dose corticosteroid "pulse" therapy in order to suppress the inflammatory response and MCS to correct initial metabolic derangement and reestablish/maintain vital organ perfusion. Addition of IV immunoglobulin and other immunomodulators should be assessed in a case-by-case basis especially considering the associated cost resource allocation.

Multisystem inflammatory syndrome (MIS) associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is a life-threatening condition first described in children (MIS-C) (1). It is characterized by a hyperinflammatory state that involves the cardiovascular, gastrointestinal, dermatologic, and neurologic systems without severe respiratory system involvement (2). Most patients suffer from cardiogenic shock attributed to myocarditis (2, 3). There are a few case reports describing SARS-CoV-2-related MIS in adults (MIS-A) (2). In the absence of histological evidence, most cases were treated with anti-inflammatory and immunosuppressive agents (2). This case series presents the clinical and histological features of myocarditis in MIS-A associated with SARS-CoV-2 infection and discusses the role of steroids, immunosuppressive drugs, and mechanical circulatory support (MCS) as treatment modalities. This case series was presented after obtaining consent for publication from participants.

CASE 1: EOSINOPHILIC MYOCARDITIS

A 39-year-old healthy woman of African ethnicity presented with fever, dyspnea, chest pain, and diarrhea 4 weeks after she had been diagnosed with SARS-CoV-2, which was asymptomatic.

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She was in cardiogenic shock. The patient had a mean arterial blood pressure (MAP) of 53 mm Hg and a heart rate (HR) of 130/min with an electrocardiogram showing defuse ST segment elevation. She was peripherally malperfused in the context of normal oxygen saturation. She did not have a rash or upper respiratory tract symptoms. SARS-CoV-2 polymerase chain reaction (PCR) (King Fisher Flex System, Thermo-Fisher Scientific, Waltham, MA) nasopharyngeal swab was negative, whereas chest radiograph was normal. Inflammatory markers were high with a peak C-reactive protein (CRP) of 283 mg/L, D-dimer greater than 4 mcg/mL, troponin 11810 ng/L, ferritin 630 ug/L, and a lactic acid (LA) of 6.6 (**Fig. 1*A***). Transthoracic echocardiography (TTE) revealed large pericardial effusion with severe biventricular dysfunction and left ventricular ejection fraction (LVEF) of 10–15%. A diagnosis of cardiac tamponade with concurrent cardiogenic shock from biventricular failure was made. Pericardiostomy was performed yielding 1.5 L of serous fluid. IV methylprednisolone at 1.2 mg/kg/d (40-mg Q8h) was initiated for presumed myocarditis. Despite high doses of inotropic agents and vasopressors (norepinephrine 20 mcg/min, dobutamine 10 μg/kg/min, and milrinone 0.5 mcg/kg/min), she remained in shock with a cardiac index of 1.8 L/min/m^2 and decreasing urine output with rising serum lactate level. Femoral-femoral venoarterial extracorporeal membrane oxygenation (VA-ECMO) was initiated for hemodynamic support, as was continuous renal replacement therapy (CRRT) for refractory acidosis and hyperkalemia. After 48 hours of ECMO support, the patient was transitioned to biventricular assist devices (BiVAD) with ProtekDuo right ventricular assist device (RVAD) (Tandem life, Pittsburgh, PA) and Impella cardiac power (CP) microaxial left ventricular assist device (LVAD) (Abiomed, Danvers, MA). Coronary angiography revealed normal coronary arteries, whereas endomyocardial biopsy revealed eosinophilic infiltrate of the myocardium (**Fig. 2**). Infectious and autoimmune causes of eosinophilic myocarditis were rolled out by the following serological tests: hepatitis B, hepatitis C, cytomegalovirus, syphilis, Epstein-Bar, varicella zoster, Strongyloides, Toxoplasma, antinuclear antibody, anti-DNA antibody, extractable antinuclear antigen profile, and antineutrophil cytoplasmic antibodies. A diagnosis of MIS-A with fulminant myocarditis was made, and steroid treatment plan was changed to high-dose IV methylprednisolone "pulse" therapy of 10 mg/kg/d (1 g/d) for 3 days followed by tapering dose over 8 weeks. Hemodynamic and cardiac function gradually improved 3 days after initiation of high-dose corticosteroid therapy. Follow-up TTE revealed improved left ventricular (LV) systolic function with an LVEF of 30–35% and mild right ventricular (RV) systolic dysfunction. The RVAD and LVAD were explanted on days 8 and 9 of admission, respectively. After 20 days of hospitalization, the renal function partially recovered, and hemodialysis was stopped. The patient was discharged home 28 days after admission.

CASE 2: MIXED-CELL MYOCARDITIS

A 25-year-old healthy Caucasian man presented with dyspnea, fever, and hypotension. There were no gastrointestinal, respiratory, or dermatological symptoms. He was in cardiogenic and vasodilatory shock. He had an MAP of 55 mm Hg and an HR of 155/min (sinus tachycardia). He was febrile (40.5°C) with normal oxygen saturation. At admission, SARS-CoV-2 PCR (King Fisher Flex System, Thermo-Fisher Scientific) nasopharyngeal swab was negative, whereas chest radiograph was normal, and inflammatory markers were high with a peak CRP of 315 mg/L, troponin 1557 ng/L, an LA of 3.8, and D-dimer greater than 4 mcg/mL (**Fig. 1*B***). TTE demonstrated severe LV systolic dysfunction with an LVEF of 15–20% and moderate RV systolic dysfunction. Therapy was initiated with vasopressors, inotropes, piperacillin/tazobactam, and vancomycin. The antibiotics were started for the broad coverage of undifferentiated sepsis. Cultures were sent, and all cultures show no bacterial growth. Considering that the patient had been diagnosed with SARS-CoV-2 5 weeks prior, which was asymptomatic, the diagnosis of MIS-A with fulminant myocarditis was established. The patient was treated with high-dose IV methylprednisolone "pulse" therapy of 15 mg/kg/d (1 g/d) for 3 days followed by tapering dose over 8 weeks. After 48 hours of admission, the patient's hemodynamics nevertheless worsened; he was persistently hypotensive requiring increasing vasopressor and inotropic requirement (norepinephrine 32 μg/min and epinephrin 5 μg/min). There was no improvement in cardiac function in TTE with raising serum lactate and low urine output. An Impella CP microaxial LVAD was implanted, and CRRT was commenced for acute kidney injury. An endomyocardial biopsy was performed revealing mixed

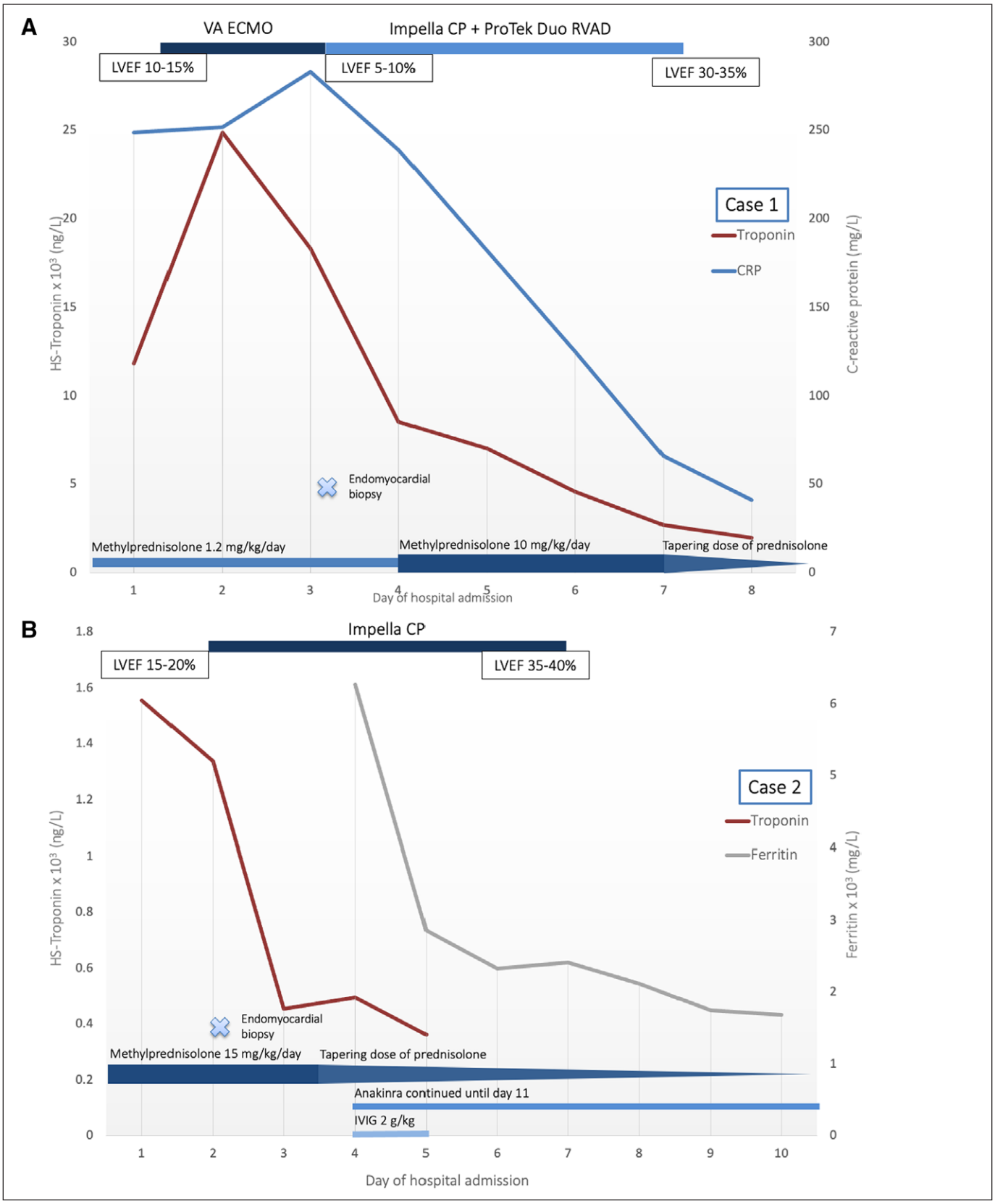

Figure 1. Illustration of the main events from admission until discharge including laboratory, echocardiography finding, and administered therapeutics. **A**, Case 1. **B**, Case 2. **C**, Case 3. CP = cardiac power, CRP = C-reactive protein, HS = high sensitivity, IVIG = IV immunoglobulin, LVEF = left ventricular ejection fraction, RVAD = right ventricular assist device, VA-ECMO = venoarterial extracorporeal membrane oxygenation.

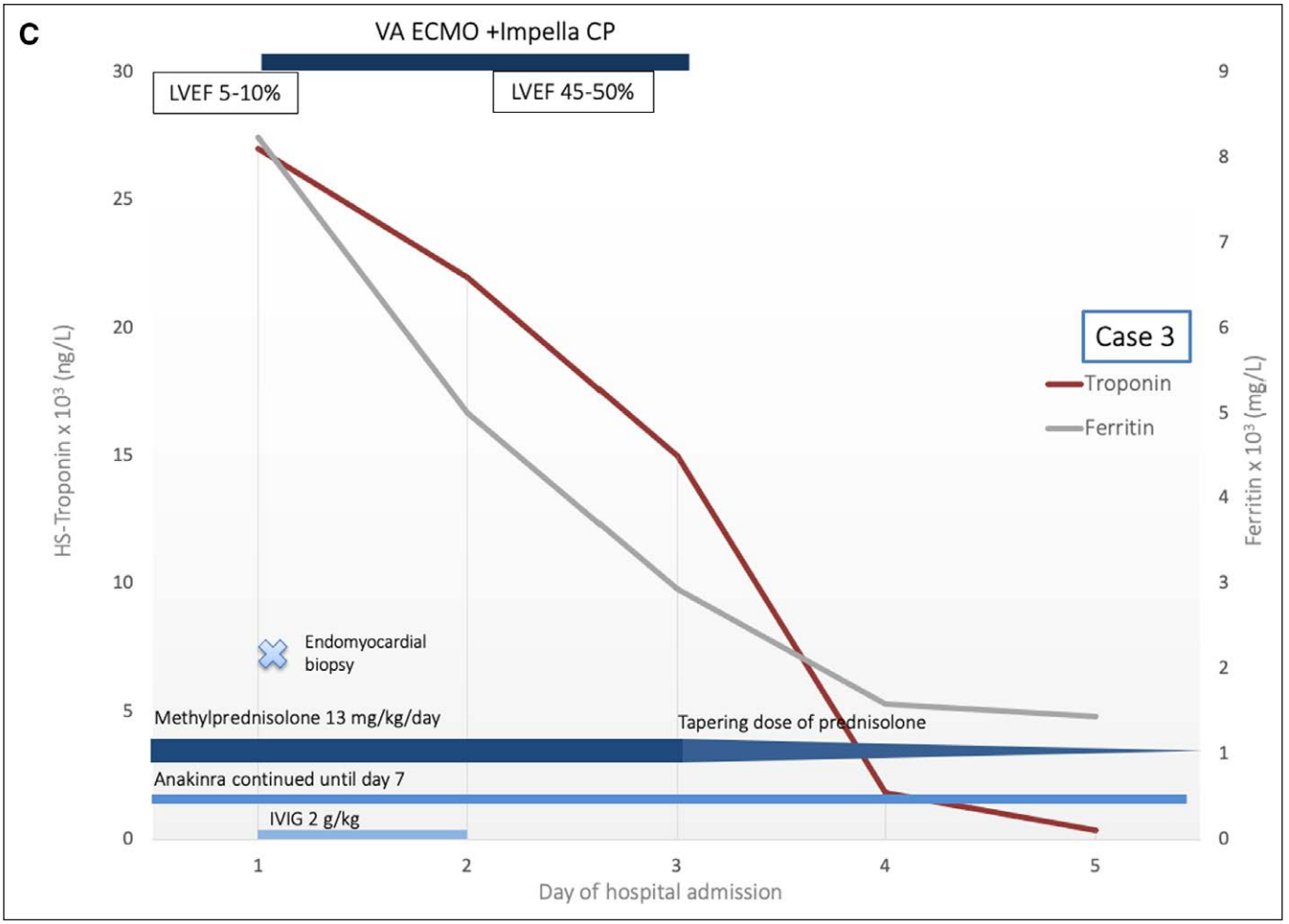

Figure 1. (*Continued*).

inflammatory cells with some eosinophils (**Fig. 3**). As there was no improvement in cardiac function early after the administration of high-dose corticosteroid pulse therapy, anakinra (interleukin-1 receptor antagonist) IV 100 mg tid for 7 days and IV immunoglobulin (IVIG) 2-g/kg single dose were added to the treatment regimen.

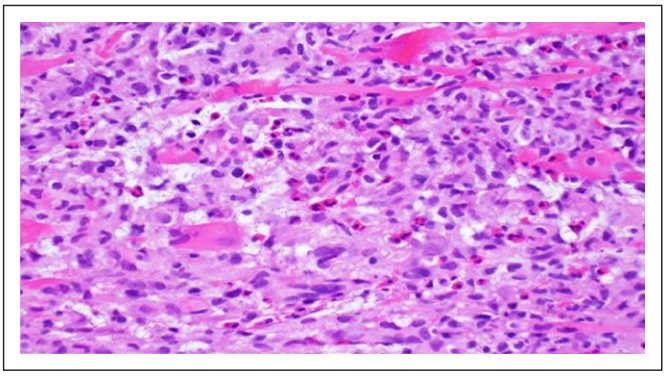

Figure 2. High-power field showing the infiltrate consisting predominantly of mononuclear cells (few lymphocytes and histiocytes with many eosinophils).

Seven days from following admission, the cardiac function improved significantly; TTE showed normal RV and improving LV systolic function with an LVEF of 35–40%, and the LVAD was explanted. The patient was discharged home 23 days after admission on intermittent hemodialysis, which was stopped 3 weeks later after improvement of the renal function.

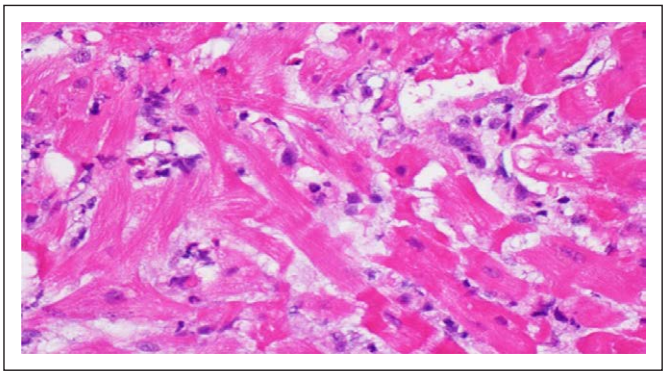

Figure 3. High-power view showing mixed inflammatory infiltrate with lymphocytes, histiocytes neutrophils, and eosinophils.

CASE 3: LYMPHOCYTIC MYOCARDITIS

A 21-year-old Caucasian man presented with dyspnea and fever. He was in cardiogenic and vasodilatory shock. He had an MAP of 55 mm Hg and an HR of 135/min (sinus tachycardia). He was febrile (39.8°C) but not hypoxemic. Patient was treated empirically on piperacillin/tazobactam and vancomycin for undifferentiated sepsis. Cultures were sent, and all cultures show no bacterial growth. There were no gastrointestinal, respiratory, or dermatological symptoms. The patient was in direct contact with SARS-CoV-2-positive family members 4 weeks prior to this admission. He developed upper respiratory tract symptoms; however, he refused SARS-CoV-2 testing. In this admission, chest radiograph was normal; however, SARS-CoV-2 PCR (King Fisher Flex System, ThermoFisher Scientific) nasopharyngeal swab was positive. The inflammatory markers were high with a peak CRP of 185.9 mg/L, a troponin of 27,000 ng/L, a ferritin of 8241 ug/L, a D-dimer of 3.5 µg/mL, and an LA of 5.1 (**Fig. 1*C***). TTE revealed severe biventricular systolic dysfunction with an LVEF of 5–10%. Despite support with inotropic agents (milrinone 0.375 mcg/kg/min and dobutamine 2.5 µg/kg/min), vasopressors (norepinephrine 20 mcg/min), and antibiotics, the patient was persistently in a low-perfusion state. The diagnosis of MIS-A with fulminant myocarditis was made, and femoral-femoral VA-ECMO was implanted for circulatory support. Venting with an Impella CP was performed for LV dilatation, flow stasis, and complete closure of the aortic valve. Endomyocardial biopsy was performed revealing lymphocytic infiltrate (**Fig. 4**), and the patient was treated with combination of high-dose IV methylprednisolone "pulse" therapy of 13 mg/kg/d (1 g/d) for 3 days followed by tapering dose over 8 weeks, anakinra (interleukin-1 receptor antagonist) IV 100 mg tid for 7 days, and IVIG 2 g/kg single dose (Fig. 1). After 3 days, a significant recovery was observed in his cardiac function. TTE revealed improving LV systolic function with an LVEF of 45–50% and mild RV dysfunction. At this time, both MSC devices were explanted. After 14 days of hospitalization, the patient was discharged home.

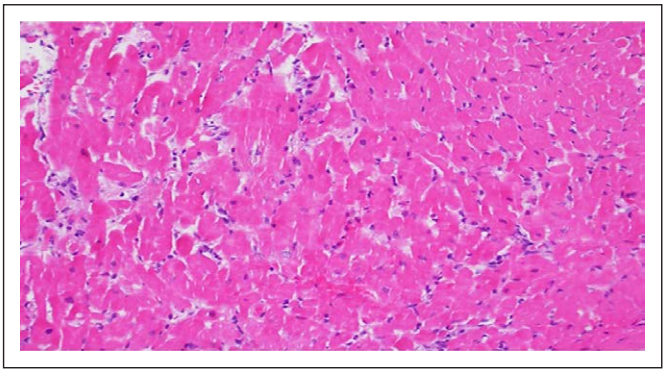

Figure 4. High-power view showing mild lymph-histiocytic interstitial myocardial infiltrate with occasional neutrophil.

DISCUSSION

The report presents three cases of healthy young adults diagnosed with MIS-A associated with COVID-19. The main presentation in each case was cardiogenic shock secondary to fulminant myocarditis without obvious signs of respiratory compromise. Endomyocardial biopsy showed varying type of cellular infiltrate. Although the cardiogenic shock resolved rapidly after the initiation of immunosuppressive agents, all cases required MCS as a bridge to recovery because of profound circulatory collapse at presentation.

Diagnosis of MIS-A

MIS is a rare but life-threatening complication associated with SARS-CoV-2 infection. The syndrome was first reported in the pediatric population (1); since then, a few case series and reports have described this syndrome in adults. Five criteria have been proposed to define patients with MIS-A: 1) severe illness requiring hospitalization in a person over 21 years old, 2) positive test result for current or previous SARS-CoV-2 infection during admission or in the previous 12 weeks, 3) severe dysfunction of one or more extra pulmonary organ systems, 4) laboratory evidence of severe inflammation (e.g., elevated CRP, ferritin, D-dimer, or interleukin-6), and 5) absence of severe respiratory illness (2).

Histological Pattern of Myocardial Biopsy

Although myocarditis is a common presentation of MIS-A associated with SARS-CoV-2, most cases were not confirmed histologically (2, 4). The reported histopathological presentations of SARS-CoV-2-associated myocarditis are variable with different cell infiltrates (5, 6). In this case series, two endomyocardial biopsies revealed mainly eosinophilic infiltration (Figs. 1 and 2), whereas in the third case, the infiltrate was lymphocytic (Fig. 4). The reason behind the inconsistencies in

the histological features of the myocardium in MIS-A associated with SARS-CoV-2 is yet to be ascertained.

Treatment With Immunosuppression

There are currently no available guidelines for the treatment for SARS-CoV-2-associated MIS-A. Contemporary treatments are extrapolated from the guidelines used for the treatment of SARS-CoV-2-associated MIS-C and other viral myocarditis (7). The recommended management is supportive therapy in addition to suppression of the acute inflammatory response. In severe cases with myocardial involvement, the recommendation was to commence steroids in addition to IVIG and anakinra (interleukin-1 receptor antagonist) (8). Several studies have shown a good response to steroids (8, 9). The dose of steroids, however, is determined based on the severity of the disease (9). In the first presented case, the cardiac function and hemodynamics did not improve until the dose was augmented to the "pulse" regimen. The response to high-dose corticosteroid "pulse" therapy in this series was varied. The first patient rapidly responded to high-dose corticosteroid pulse therapy as a sole therapy, whereas the second did not until IVIG and anakinra were administered. It is not clear if the improvement was related to the addition of IVIG and anakinra or it was a delayed response to corticosteroid therapy. Anakinra was reported to be beneficial if the treatment of MIS-associated SARS-CoV-2 with corticosteroids and IVIG was insufficient (10). The approach to SARS-CoV-2-associated MIS-A in the third case was different. A combination of high-dose corticosteroid "pulse" therapy, IVIG, and anakinra was administered on day 1. To date, data comparing the use of only high-dose corticosteroid "pulse" therapy versus high-dose corticosteroid "pulse" therapy combined with other anti-inflammatory or immunosuppressive agents in fulminant myocarditis in SARS-CoV-2-associated MIS-A are absent.

Role of MCS Devices

In cases of fulminant myocarditis with severe cardiogenic shock, the recommendation is to start MCS as a bridge to transplant or recovery (11). The early implantation of MCS in the form of VA-ECMO or a percutaneous BiVAD restored vital organ perfusion and allowed time for investigation and initiation of definitive management. There were limited reports describing the use of MCS devices for fulminant myocarditis in MIS-A associated with SARS-CoV-2 (5, 12, 13). To our knowledge, there were only three cases of MIS-A associated with SARS-CoV-2 with fulminant myocarditis that required ECMO and four cases that required intra-aortic balloon pump (5, 12–14). The reported duration of MCS ranged between 5 and 50 days, whereas in this case series, the duration was between 3 and 8 days.

It is important to state that in the presented series, MCS was not limited to ECMO, but rather included appropriate MCS devices such as the ventricle-unloading devices whose utilization expedited recovery of cardiac function. In cases 1 and 3, VA-ECMO was implanted as the patients were in a profoundly metabolically deranged state secondary to cardiogenic shock from severe biventricular dysfunction refractory to medical therapy. In case 2, only an LVAD was implanted as RV was not severely dysfunctional. To decrease the risk of complication from VA-ECMO, our center adopted a "short-term run" protocol for VA ECMO preferring early conversion to ventricle-unloading MCS devices as bridge to recovery or cardiac transplantation.

In conclusion, it appears reasonable to treat the patient with fulminant myocarditis in SARS-CoV-2-associated MIS-A with high-dose corticosteroid "pulse" therapy in order to suppress the inflammatory response and MCS to correct initial metabolic derangement and reestablish/maintain vital organ perfusion. Addition of IVIG and other immunomodulators should be assessed in a case-by-case basis especially considering the associated cost resource allocation.

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