Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Arrhythmic myocarditis in an adolescent male: A unique presentation of multi-organ inflammatory syndrome (MIS-C)

Grazia Casavecchia, MD, Maria Delia Corbo, Matteo Gravina, Roberta Barone, Michele Magnese, Marco Mele, Domenico D’Alessandro, Riccardo Ieva, Massimo Iacoviello, Luca Macarini, Natale Daniele Brunetti, MD, PhD

A Department of Medical & Surgical Sciences, University of Foggia, Foggia, Italy
b Policlinico Riuniti University Hospital, Foggia, Italy

Abstract

Although children with Covid-19 generally present with mild symptoms or are often asymptomatic, there is increasing recognition of a delayed multi-organ inflammatory syndrome (MIS-C) following SARS-CoV-2 infection. We report the case of MIS-C associated arrhythmic myocarditis which recovered after anti-inflammatory therapy and immunoglobulin infusion.

1. Introduction

The Corona-virus disease (Covid)-19 may present in children with very mild clinical condition and often even as asymptomatic. A possible complication, however, may be represented by an inflammatory delayed syndrome, following the acute phase of SARS-CoV-2 infection by weeks-months, with multi-organ involvement, similar to Kawasaki disease. This SARS-CoV-2 associated Multisystem Inflammatory Syndrome in Children (MIS-C) usually occurs 4–6 weeks after infection and presents with high fever, organ dysfunction, elevated levels of inflammatory markers and signs of shock, in the absence of an alternative explanation [1]. Myocarditis is also possible, with or without signs of coronary arterial inflammation. The pathogenesis is unclear, but some features in overlap with Kawasaki disease (hyperinflammatory syndrome and multiorgan involvement) are suggestive of vasculitis and autoimmune etiology [2].

2. Case report

We report the case of a 15-year-old boy who presented at emergency department for chest pain, relieved by leaning forward, 42 days after SARS-CoV-2 infection. The first antigenic positive test was found on December 23 and confirmed by a molecular test 2 days later; first negative molecular test on January 10. Admission nasopharyngeal swab (molecular test) was negative. Blood pressure was 120/70 mmHg, physical examination unremarkable. Electrocardiogram however showed sinus tachycardia and diffuse ST-elevation (Fig. 1), QRS amplitude attenuation and prolonged QTc values as for myocardial edema; hs-Troponin-I levels were markedly increased (3652 ng/L, n.v. <20). Basal echocardiography showed preserved global systolic function and minimal pericardial effusion (Fig. 2). Chest radiography and blood cell count were normal.

The patient was admitted to acute cardiac care unit. After admission, fever appeared (38 °C), with abdominal pain and diarrhoea. Abdomen echography was normal. A short run (10 beats) of ventricular tachycardia was also found at continuous electrocardiogram monitoring. The boy was treated with aspirin 1500 mg/die and enoxaparin 4000 UI/die. Peak hs-troponin-I level was 12.333 ng/L, NT-proBNP levels 1.570 pg/mL, D-dimer 991 ng/mL, and C-reactive protein 110 mg/L (n.v. <5). Basal echocardiography showed preserved global systolic function and minimal pericardial effusion (Fig. 2). Chest radiography and blood cell count were normal.

In the presence of MIS-C diagnosis (acute myocarditis with intestinal symptoms) intravenous immunoglobulin were infused; after while, a marked improvement of laboratory tests and hs-troponin I levels reduction (5749 ng/L) were observed (Fig. 3).
Cardiac magnetic resonance showed diffuse signal increase in the left ventricular walls in the sequence T1 Native for the Mapping study (Fig. 2a–b), signal increase with “patchy” distribution of the left ventricular walls in the T2-STIR sequences edema (Fig. 2c–d), multiple areas of increased signal with middle and subepicardial distribution within left ventricular walls in the sequences for Early Gadolinium Enhancement (Fig. 2g–h), and signal increase with “patchy” distribution of the left ventricular walls in the sequence T1 Native for the Mapping study (Fig. 2a–b), signal increase with “patchy” distribution of the left ventricular walls in the T2-STIR sequences edema (Fig. 2c–d), multiple areas of
Fig. 2. Serial imaging assessment a–b). Diffuse MRI signal increase of the left ventricular walls in the sequence T1 Native for the Mapping study. c–d) Signal increase with “patchy” distribution within left ventricular walls in the T2-STIR sequences for edema. e–f) Signal increase with “patchy” distribution within left ventricular walls in the PSIR sequence for Late Gadolinium Enhancement study compatible with myocardial necrosis in acute myocarditis. g–h) Multiple areas of increased signal with mid- and subepicardial distribution within left ventricular walls in the sequences for Early Gadolinium Enhancement. i) Normal basal 2-dimensional echocardiogram. j–k) Two-month follow-up: Reduction of signal in the sequence T1 Native for the Mapping study. l–m) Absence of edema within left ventricular walls in the T2-STIR sequences. n–o) Remodeling and reduction of Late Gadolinium Enhancement areas compatible with fibrosis.
ventricular walls in the PSIR sequence, compatible with myocardial necrosis in acute myocarditis (Fig. 2e-f).

At discharge, the electrocardiogram showed sinus rhythm with negative T-waves and decreased levels of inflammatory markers (CRP) and hs-troponin-I. The boy was discharged 12 days after admission, asymptomatic, with a wearable cardioverter-defibrillator. Echocardiogram, again, was normal.

At 3-month follow up cardiac magnetic resonance showed reduction of signal in the sequence T1 Native for the Mapping study (Fig. 2j-k), absence of edema within left ventricular walls in the T2-STIR sequences (Fig. 2l-m) and reduction of Late Gadolinium Enhancement areas compatible with fibrosis (Fig. 2n-o). Echocardiography was normal, without pericardial effusion. Electrocardiogram was normal, while CRP levels still increased. Aspirin therapy was reduced to 1000 mg/die. Continuous electrocardiogram monitoring with wearable cardioverter-defibrillator did not show any episode of ventricular tachy-arrhythmias. Rest electrocardiogram was normal.

3. Discussion

We report the case of MIS-C presenting with myocarditis, ventricular tachycardia and intestinal symptoms. Clinical conditions improved after aspirin therapy and immunoglobulin infusion.

Typically, children were less severely affected by SARS-CoV-2 infection than adults [3, 4]. The incidence of severe clinical presentation in children varies between 2 and 6%, with a greater risk in patients with previous respiratory, cardiological and neuromuscular comorbidities [3, 5]. However, on May 8, 2020, the Center for Disease Control (CDC) in the United States issued an alert describing a new entity termed MIS-C (Multisystem Inflammatory Syndrome in Children Associated with Covid-19). The definition of MIS-C includes [6]: a) an individual aged <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND b) No alternative plausible diagnoses; AND c) Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or exposure to a suspected or confirmed COVID-19 case within the 4 weeks prior to the onset of symptoms.

MIS-C may begin weeks after SARS-CoV-2 infection, with the patient unaware of the infection. Patients with MIS-C usually present with persistent fever, abdominal pain, vomiting, diarrhoea, skin rash, mucocutaneous lesions and, in severe cases, with hypotension and shock. Some patients develop myocarditis, cardiac dysfunction, and acute kidney injury. Not all cases share the same signs and symptoms: some require hospitalization and multi-specialist evaluations, sometimes intensive care.

The pathogenesis of MIS-C is still unknown. Some features overlap with Kawasaki disease, an acute medium vessel vasculitis, with specific predilection for the coronary arteries, that occurs in infants and children. MIS-C and Kawasaki disease could share a cytokine dysregulation, while they differ in the regulation of platelet and coagulation factors [7]. MIS-C is characterized by a cytokine storm driven by interleukin-6 and by a dysregulation of cytotoxic lymphocytes with depletion of CD8+ T lymphocytes and CD56 and CD57 NK cells. Consiglio et al. demonstrated that the subtypes of lymphocyte T cells differ between two diseases and interleukin-17A mediates hyperinflammation in Kawasaki disease, but not in MIS-C [8]; one study has found evidence of microangiopathy in MIS-C [9].

It is still unclear whether the processes that mediate MIS-C are different from those leading to severe respiratory failure and shock in case of Covid-19 [9]. The delay in the presentation after Covid-19
infection, the low rates of SARS-CoV-2 positive, and the high proportions of antibody positive suggest that this inflammatory syndrome is not presumably mediated by direct viral infection but may represent an acquired immune response to SARS-CoV-2, mediated by antibodies or T-cell-mediated cell attacking cells expressing viral antigens or host antigens which cross-react or mimic viral antigens. Autoantibodies involvement in MIS-C is supported by the efficacy immunomodulatory and anti-inflammatory therapies: children with MIS-C typically respond well to therapy with intravenous immunoglobulins, that prevent membrane-attack complexes by complement factors and mitigate autoantibody-mediated pathology [8]. Prior immunity to other viruses (respiratory syncytial virus, rhinovirus, viruses of the herpesvirus family) could modulate the response to SARS-CoV-2 infection and anticipate hyperinflammation. The lack of IgG antibodies to common coronaviruses may modulate the immune response to SARS-CoV-2 infection and play a role in the pathogenesis of MIS-C [8]. Patient with MIS-C may have elevated laboratory markers of inflammation (CRP, fibrinogen, D-dimer, ferritin, lactate dehydrogenase, IL-6, neutrophils, lymphocytes, and albumin), and develop kidney injury, anemia, thrombocytopenia, hypertriglyceridemia, proteinuria, coagulopathy, and cardiac dysfunction [6, 10].

Patients with cardiac involvement could have elevated levels of troponin, BNP, and CK-MB [11]. Given the frequent association of MIS-C with cardiac involvement (over 80%), cardiac testing (echocardiogram, electrocardiogram, troponin and B-type natriuretic peptide (BNP) or NT-proBNP) must be considered. The cardiac injury involves systolic-diastolic biventricular dysfunction, mitral regurgitation, arrhythmia and pericardial effusion, while coronary involvement has been described in 6–24% of cases (as mild or as coronary ectasia) [11]. Left ventricular systolic dysfunction has been described in most patients affected by MIS-C, from 38% to 100%, with the need for supportive treatments, including ventilatory support, use of inotropes and ECMO [12]. Non-specific electrocardiogram anomalies of the ST segment, prolongation of the QTc segment, atrial and ventricular ectopic beats can be observed in MIS-C, while cases of L- and II-degree atioventricular block and supraventricular and ventricular arrhythmias are more rare. Serologic testing should be performed prior to intravenous immunoglobulins (IVIG) infusion or any exogenous antibody treatments.

The optimal treatment is still not known for a patient with MIS-C; however, a multidisciplinary approach is needed to guide individual treatment, that could be different and is based on the evaluation of symptoms and laboratory values. Patients with MIS-C are usually treated with IVIG, 2 g/kg (max of 100 g), by slow infusion (16–24 h). Patients have also been treated with steroid therapy (2 to 30 mg/kg/day of methylprednisolone depending on severity of illness) and biologics [13]. A recent observational study found that the initial treatment with both IVIG and steroid therapy led to earlier resolution of fever compared to IVIG alone [14]. Antithrombotic prophylaxis should be considered in all MIS-C patients and, unless contraindications, should be started with enoxaparin [15]. Antiplatelet therapy should only be considered if platelet or coronary involvement is present [16]. In our case the therapy was limited to the use of IVIG, after a rapid response to infusion therapy.

Noteworthy, we can observe in this case a delayed onset of MIS-C, although previously reporte [17], and, given the arrhythmic presentation, a prolonged outpatient monitoring with a wearable ICD in a young boy with myocarditis.

4. Conclusions

Although children with Covid-19 generally present with mild symptoms or are asymptomatic, there is increasing recognition of a delayed MIS-C following SARS-CoV-2. We report the case of MIS-C associated arrhythmic myocarditis.