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Reinfection With Severe Acute Respiratory Syndrome Coronavirus 2 Without Recurrence of Multisystem Inflammatory Syndrome in Children

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Abstract: Multisystem inflammatory syndrome in children is a rare, potentially life-threatening postinfectious complication in children after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. It is currently unknown if multisystem inflammatory syndrome in children (MIS-C) can recur upon reinfection with SARS-CoV-2. Here, we report on a former MIS-C patient who was reinfected with SARS-CoV-2 without recurrence of MIS-C.

Key Words: MIS-C, pediatric COVID-19, reinfection

Multisystem inflammatory syndrome in children (MIS-C) first emerged in Spring of 2020.[1] It is a rare, potentially life-threatening inflammatory condition that can develop in children 4–6 weeks after infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The syndrome has some resemblances to Kawasaki disease (KD), but there are some notable differences. Children with MIS-C are typically older than children with KD.[2] About 5–10% of children with MIS-C have coronary dilation or aneurysms at presentation, which is higher than what has been reported in KD,[2,3] but the coronary dilation may resolve more rapidly in MIS-C.[4,5] Unlike in KD, myocarditis, shock and gastrointestinal symptoms are relatively common presenting symptoms in children with MIS-C.[6] MIS-C is characterized by high levels of proinflammatory cytokines and is treated with IV immunoglobulins and/or high dose corticosteroids.[7,8] More than half of the children with MIS-C are admitted to pediatric intensive care units, and some children have died.[9]

It is not known if children who have recovered from MIS-C are at a risk of recurrence of MIS-C when they are reinfected with SARS-CoV-2. Reassuringly, recurrence of KD is rare, at about 1% for European and North-American populations up to 3.5% for Asian populations.[10] However, because there are many clinical differences between KD and MIS-C, the possibility of recurrence remains an area of concern. One case has been reported of a former KD patient who had a recurrence of KD upon a first infection with SARS-CoV-2.[11] There are no published cases of former MIS-C patients who were reinfected with SARS-CoV-2.

CASE REPORT

Here, we report on a now 16-year-old girl with a history of MIS-C who was reinfected with SARS-CoV-2. In the initial episode of MIS-C in the spring of 2020, she fulfilled World Health Organization and Centers for Disease Control and Prevention criteria of MIS-C.[12] Her MIS-C case was previously reported in a national medical journal.[13] She had no prior medical history. She presented with 5 days of high fever, mild conjunctivitis, malaise, chest pain, coughing, abdominal pain and diarrhea. She was diagnosed with myocarditis, shock and had high inflammatory parameters. Cardiac ultrasound showed a depressed systolic cardiac function with left ventricular (LV) shortening fraction of 15% and mild mitral valve insufficiency. This was confirmed by cardiac magnetic resonance imaging (LV ejection fraction 38%) with diffuse LV elevated native T1 values (1500 ms) suggestive for myocardial edema (Fig. 1A). There were no coronary abnormalities. Polymerase chain reaction for SARS-CoV-2 on nasopharyngeal swab and a fecal sample was negative, but IgG SARS-CoV-2 (Abbott SARS-CoV-2 IgG; Abbott Laboratories, IL) was positive. She needed inotropic support, was treated with IV immunoglobulin and needed 3 days IV methylprednisolone followed by oral prednisone tapered in 3 weeks. She had very high inflammatory markers (C-reactive protein 463 mg/L, ferritin 663 ug/L, interferon gamma induced protein 10 17,519.5 ng/L, chemokine (C-X-C motif) ligand-9 3771 ng/L, interleukin-6 899 ng/L and interleukin-1a 32 ng/L) at diagnosis of MIS-C, which all normalized at follow-up. Cardiac troponin T and N-terminal-pro hormone BNP levels peaked at 120 ng/L and 33,531 ng/L, respectively. She fully recovered (Fig. 1B).

Thirteen months after the initial MIS-C diagnosis, she developed mild respiratory symptoms. Polymerase chain reaction for SARS-CoV-2 was positive, and IgG SARS-CoV-2 was negative (Abbott SARS-CoV-2 IgG; Abbott Laboratories). This time, she was infected with the B.1.1.7 variant (UK variant), which was not yet circulating at the time she was first diagnosed with MIS-C. In the next few weeks, she was closely followed as an outpatient for possible recurrence of MIS-C. She did not develop a fever or any other symptoms of MIS-C, the inflammatory markers were low and the previously restored good biventricular systolic function was maintained. She did not develop any symptoms of MIS-C, and she was well at last follow-up 2 months after the reinfection.

DISCUSSION

To our knowledge, this is the first reported case of a MIS-C patient who was reinfected with SARS-CoV-2. Reassuringly, reinfection did not result in recurrence of MIS-C in our patient. So far, this is the first documented reinfection in our ongoing nation-wide registry of coronavirus disease 2019 and MIS-C patients ("Clinical features of coronavirus disease 2019 in Pediatric Patients" study,

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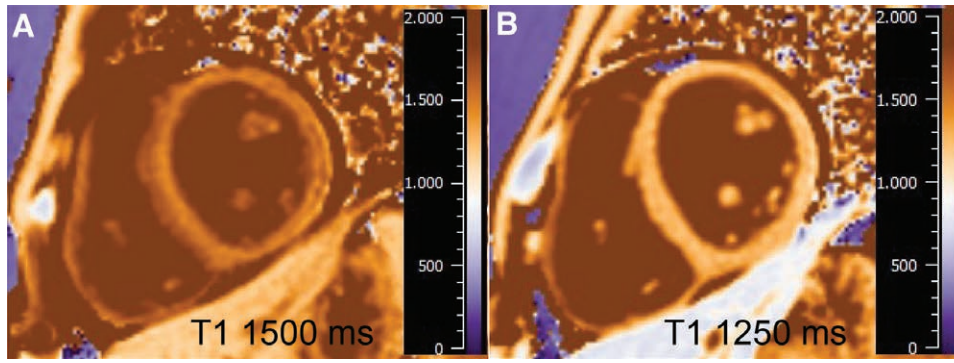

FIGURE 1. A: Cardiac magnetic resonance imaging at diagnosis of MIS-C, showing diffuse LV elevated native T1 values (1500 ms) suggestive for myocardial edema (T1 mapping midventricular short-axis image, 3T Ingenia MR System; Philips Healthcare, Eindhoven, the Netherlands). B: Normalized native T1 values on cardiac T1 mapping at 3-month follow-up.

n = 246 children, including 71 children with MIS-C, www.covid-kids.nl/scientific-dashboard).

SARS-CoV-2 infection has been shown to produce a robust (memory) T- and B-cell response which seems to last for at least 6 months. Nevertheless, an increasing number of reported cases were reinfected with variant SARS-CoV-2 strains.[14] These cases show a high diversity in clinical presentation, varying from asymptomatic infection to severe disease, although a publication bias for more severe cases is certainly conceivable.[15] Because the exact pathogenesis of MIS-C remains elusive, it is currently unknown if immunologic memory will prevent recurrence of MIS-C upon reinfection with SARS-CoV-2.

Many countries have begun to vaccinate children 12 years old and older against SARS-CoV-2. The Centers for Disease Control and Prevention and European Medicines Agency are investigating rare cases of myocarditis after vaccination with messenger RNA vaccines, particularly in young males.[16] It is currently unknown if children with a history of MIS-C might be at increased risk of this possible, rare side effect of vaccination. Both natural (re-)infection and vaccination expose the subject to viral spike protein. Although vaccination and reinfection are not the same, we feel it is reassuring that our patient did not develop myocarditis upon reinfection. Based on this case, we would not advice against vaccination in former MIS-C. We argue that recovered MIS-C patients need to be followed closely to determine the exact risk of recurrence of MIS-C, either after reinfection or vaccination.

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