Case report

Arch Argent Pediatr 2023;121(6):e202202893

MIS-C patients who were reinfected with SARS-CoV-2. Report of 2 cases

Ahmet Soysal[a], *Burcu Topçu*[a], *Serkan Atıcı*[b], *Erdem Gönüllü*[c], *Cevat N. Öner*[c]

ABSTRACT

Multisystem inflammatory syndrome in children (MIS-C) is a rare condition. It is still unknown 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. In this study, we aimed to report 2 children who recovered from MIS-C and reinfected with SARS-CoV-2 without recurrence of MIS-C.

Keywords: *pediatric multisystem inflammatory disease, COVID-19 related; recurrence; reinfection; SARS-CoV-2.*

doi: http://dx.doi.org/10.5546/aap.2022-02893.eng

To cite: Soysal A, Topçu B, Atıcı S, Gönüllü E, Öner CN. MIS-C patients who were reinfected with SARS-CoV-2. Report of 2 cases. *Arch Argent Pediatr* 2023;121(6):e202202893.

[a] *Division of Pediatric Infectious Disease, Ataşehir Memorial Hospital. Istanbul, Turkey;* [b] *Division of Pediatric Infectious Disease, Okan University School of Medicine. Istanbul, Turkey;* [c] *Department of Pediatrics, İstanbul Health and Tecnology University. Istanbul, Turkey.*

Correspondence to *Serkan Atıcı: drserkanatici@gmail.com*

Funding*: None.*

Conflict of interest*: None.*

Received*: 10-29-2022*
Accepted*: 2-4-2023*

INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected more than 600 million people since first reported in December 2019. According to data shared by the American Academy of Pediatrics in October 2022, children represent 18.4% of all reported COVID-19 cases in the USA.[1] Peltan et al. reported the incidence of reinfection at 4.3 (95% CI 2.1–7.9) cases per 10,000 COVID-19 patients.[2] Multi-system inflammatory syndrome in children (MIS-C) first emerged in the spring of 2020. Levy et al. reported MIS-C incidences per 100 000 persons younger than 18 years at 54.5, 49.2, and 3.8 during Alpha, Delta, and Omicron variants respectively.[3]

Data on both COVID-19 reinfection with potentially life-threatening MIS-C are very limited. It is unknown if children who had MIS-C are at risk of MIS-C recurrence after a COVID-19 Infection. To the best of our knowledge, there are only two published cases of former MIS-C patients who had SARS-CoV-2 reinfection and no published case of MIS-C recurrence.[4,5] In this study, we report 2 children who recovered from MIS-C with subsequent laboratory-confirmed SARS-CoV-2 reinfection without recurrence of MIS-C.

CASE REPORT

Case 1

The first patient is a 10-year-old girl with a history of MIS-C with SARS-CoV-2 reinfection. She was initially admitted to our hospital after 3 days of high fever, malaise, coughing, abdominal pain, and diarrhea in March 2022. Her physical examination revealed increased bowel sounds with unremarkable findings. Two weeks prior she had Covid-19. At first admission, her laboratory results revealed very high inflammatory markers leading to a diagnosis of MIS-C, which all normalized at follow-up.

CMV-IgM, EBV-VCA-IgM, influenza (A and B variants) and strep A tests were negative. Polymerase chain reaction (PCR) for SARS-CoV-2 on nasopharyngeal swab was negative, but SARS-CoV-2 spike IgG titers (Abbott SARS-CoV-2 IgG; Abbott Laboratories, IL) were positive. The laboratory results of the case are shared in *Table 1*. In the initial MIS-C episode, she satisfied the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) criteria of MIS-C.[6] She was treated with intravenous immunoglobulin (IVIG) (2 g/kg/day single dose), prednisone tapered in 4 weeks, and aspirin.

Four months after the initial MIS-C diagnosis, she developed mild respiratory symptoms. PCR for SARS-CoV-2 was positive. Her laboratory results revealed normal inflammatory markers summarized in *Table 1*. She was followed in an outpatient clinic for about 6 months due to possible recurrence of MIS-C, but no fever or other MIS-C symptoms were observed.

Case 2

The second case is an 8-year-old girl with a history of MIS-C like the first case, who had SARS-CoV-2 reinfection. The patient was admitted to our hospital after 6 days of fever, abdominal pain, diarrhea, and myalgia in January 2022, her physical examination revealed increased bowel sounds, strawberry tongue, conjunctivitis, and left-sided neck lymphadenopathy.

Three weeks prior she had a history of Covid-19; PCR for SARS-CoV-2 on nasopharyngeal swab was negative, but SARS-CoV-2 spike IgG titers (Abbott SARS-CoV-2 IgG; Abbott Laboratories, IL) were positive. Like the first case, her laboratory results revealed very high inflammatory markers (*Table 1*). Clinical findings and laboratory results were compatible with MIS-C and satisfied WHO and CDC criteria of MIS-C.[6] She was treated with IV immunoglobulin (2 g/kg/day single dose), 3 days high dose pulse methylprednisolone, oral prednisone tapered in 4 weeks, and aspirin.

Six months after the initial MIS-C diagnosis, she developed mild respiratory symptoms. PCR for SARS-CoV-2 was positive. Her laboratory results revealed normal inflammatory markers (*Table1*). Similar to the first case, this patient was followed about 7 months due to possible recurrence of MIS-C, but no fever or other MIS-C symptoms were observed.

DISCUSSION

After the first report of MIS-C cases in April 2020, many cases of MIS-C were reported from different regions of the world. The pathogenesis of the disease is not known and the recurrence of MIS-C is debatable. It is also unknown if immunologic memory will prevent the recurrence of MIS-C after reinfection with SARS-CoV-2. The average time between MIS-C and Covid-19 reinfection, response to the concerns of families in terms of MIS-C recurrence, the relationship of cardiac involvement (severe or mild) with

Table 1. Laboratory values of cases during with MIS-C and reinfection with SARS-CoV-2

	CASE 1			CASE 2		
	First admission (MIS-C)	First discharge (MIS-C)	Second admission (reinfection with SARS-CoV-2)	First admission (MIS-C)	First discharge (MIS-C)	Second admission (reinfection with SARS-CoV-2)
Hemoglobin (g/dL)	11.9	12.4	12.5	12.3	13	13.5
Leucocyte count (cell per mm^3)	6700	14 600	4660	9200	13 700	5660
Platelets (per mm^3)	155 000	288 000	226 000	97 000	242 000	212 000
CRP (mg/L)	148	9.1	7.3	295	0.1	12.5
ESR (mm/h)		None	8	66		-
Procalcitonin (ng/mL)	47.5	0.0.1	0.01		0.01	-
D-Dimer (<0.5 mic/mL)	6.04	0.33	0.24	2.15	0.17	0.33
Ferrritin (ng/mL)	226	121	65	>1675	263	-
Fibrinogen (mg/dL)	410	none	323	666	-	-
Troponin-I (ng/L)	< 10	none	none	<10	-	-
NT-proBNP (pg/mL)	299	none	None	447	212	-
AST (IU/L)	208	22	26	22	27	24
ALT (IU/L)	213	32	14	25	33	16
Creatinine (mg/dL)	0.6	0.7	0.48	0.6	0.5	-
SARS-CoV-2 spike IgG (Au/mL)	Positive (58)	-	-	Positive (1564)	-	-
SARS-CoV-2 spike IgM (Au/mL)	Negative	-	-	Negative	-	-
SARS-CoV-2 PCR	Negative	-	Positive	Negative	-	Positive
EBV VCA IgM	Negative	-	-	Negative	-	-
CMV IgM	Negative	-	-	Negative	-	-
Influenza A and B	Negative	-	Negative	Negative	-	-
Throat culture	No growth	-	No growth	No growth	-	No growth
Blood culture≠∂æææ	No growth	-		No growth	-	No growth

MIS-C: Multi-system inflammatory syndrome in children; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; CRP: C-Reactive protein; ESR: Erythrocyte sedimentation rate; EBV VCA: Epstein-Barr virus viral capsid antigen; CMV: cytomegalovirus.

reinfection caused by SARS-CoV-2 or recurrence of MIS-C, and other rising topics should be examined in light of the published case series and studies.

To our knowledge, only 2 cases of SARS-CoV-2 reinfection have been reported in MIS-C related cases.[4,5] Besides, there is only one reported case of MIS-C rebound and no published case of MIS-C recurrence[7] we aimed to report the 3rd and 4th cases of MIS-C patients reinfected with SARS-CoV-2 and to discuss some questions that need to be answered by a review of the literature on possible MIS-C recurrence, rebound, or relapse.

The recurrence is a repeat episode of an illness after the complete recovery of the previous disease. The rebound is defined as a manifestation of disease occurring within 4–6 weeks after treatment is completed or while tapering drugs. The relapse is the worsening of the disease while treatment is continued.[7] The first case of an MIS-C patient who had SARS-CoV-2 reinfection was reported by Budding et al. in a 16-year-old girl who was diagnosed with MIS-C and SARS-CoV-2 reinfection thirteen months later.[4] The second case is a 12-year-old boy who was diagnosed with MIS-C, treated with IVIG, and good subsequent clinical response. He had SARS-CoV-2 reinfection 5 months later with mild symptoms and no recurrence of MIS-C.[5]

Pawar et al. reported an interesting case of MIS-C in a 17-year-old boy with Down syndrome. 8 days after MIS-C treatment (4 weeks after the discharge), her complaints started again, and subsequently clinical and laboratory findings were compatible with MIS-C without SARS-CoV-2 reinfection. This case was not an MIS-C recurrence, and the authors defined it as an MIS-C rebound.[7] In our cases, SARS-CoV-2 reinfection developed 4 and 6 months after MIS-C diagnosis. While 3 cases had cardiac involvement such as acute myocarditis and pericardial effusion without coronary abnormalities, no cardiac problems were detected in our cases. It is unknown if a

relationship exists between children with a history of cardiac involvement and an increased risk of SARS-CoV-2 reinfection or MIS-C recurrence or relapse. These limited cases also cannot provide a clear interpretation.

The pathophysiology of MIS-C is not well understood. The MIS-C may be caused by an abnormal immune response (immune dysregulation) to the virus, with some clinical similarities to Kawasaki disease (KD) and macrophage activation syndrome (MAS). Though there are many clinical and laboratory similarities between KD and MIS-C, the possibility of recurrence remains a matter of concern. Although there are different data about the recurrence rates of KD, the disease can rarely recur. KD and its recurrences have an unknown etiology, but it is theorized some microbial pathogens (including coronavirus) can trigger immune dysregulation causing KD in genetically susceptible children.[8,9] Recurrence of KD usually occurs within 2 years of the first episode. The presence of coronary artery aneurysm, initial resistance to IVIG therapy, longer duration of fever, male sex, young age, lower hemoglobin levels, and high AST levels in the first episode carries a risk for future recurrence.[8]

In conclusion, the number of SARS-CoV-2 reinfection cases after MIS-C may gradually increase, and MIS-C disease could recur like KD. We believe close follow-up of recovered MIS-C patients, especially in the first 2 years, is important in terms of recurrence and identifying risk factors that may cause recurrence. ■

REFERENCES

1. American Academy of Pediatrics (AAP). Children and COVID-19: State-Level Data Report. [Accessed on: September 12, 2022]. Available at: https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/
2. Peltan ID, Beesley SJ, Webb BJ, LopansricBK, et al. Evaluation of potential COVID-19 recurrence in patients with late repeat positive SARS-CoV-2 testing. *PLoS One.* 2021;16(5):0251214.
3. Levy N, Koppel JH, Kaplan O, Yechiam H, et al. Severity and Incidence of Multisystem Inflammatory Syndrome in Children During 3 SARS-CoV-2 Pandemic Waves in Israel. *JAMA.* 2022;327(24):2452-54.
4. Buddingh EP, Vossen ACTM, Lamb HJ, van der Palen RLF, Brinkman DMC. Reinfection with Severe Acute Respiratory Syndrome Coronavirus 2 Without Recurrence of Multisystem Inflammatory Syndrome in Children. *Pediatr Infect Dis J.* 2021;40(12):e491-2.
5. Yori SC, Agrimbau Vázquez J, Berberian G, Curtti T, Urrutia L. Reinfección por SARS-CoV-2 en un niño con antecedente de síndrome inflamatorio multisistémico: a propósito de un caso. *Arch Argent Pediatr.* 2022;120(3):e147-50.
6. Centers for Disease Control and Prevention (CDC.) Multisystem Inflammatory Syndrome in Children (MIS-C) CDC Case Definition. [Accessed on: September 12, 2022]. Available at: https://www.cdc.gov/mis-c/hcp/
7. Pawar RS, Tarkasband VA, Patil RK, Naik AV. Second Episode of Multisystem Inflammatory Syndrome in Children: Relapse, Rebound, or Recurrence? *Pediatr Infect Dis J.* 2021;40(11):e452.
8. Medaglia AA, Siracusa L, Gioè C, Giordano S, et al. Kawasaki disease recurrence in the COVID-19 era: a systematic review of the literature. *Ital J Pediatr.* 2021;47(1):95.
9. Toprak D, Serçe Ö, Türel Ö, Atici S, et al. Is Varicella Zoster Virus an Etiologic Factor in Kawasaki Disease? A Case Report and Review of the Literature. *Glob Pediatr Health.* 2015;2:2333794X14567194.