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HIDDEN DANGER OF SARS-COV-2; MULTISYSTEM INFLAMMATORY SYNDROME IN ADULTS (MIS-A): FIRST CASE SERIES IN A SINGLE CENTER FROM TURKIYE

SARS-COV-2'NİN GİZLİ TEHLİKESİ; ERİŞKİNLERDE MULTİSİSTEM İNFLAMATUAR SENDROM (MIS-A): TÜRKİYE'DE TEK MERKEZDEN İLK OLGU SERİSİ

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ABSTRACT

Objective: Multisystem Inflammatory Syndrome (MIS) is a condition seen in the early post-COVID-19 period and thought to develop with an impaired immune response. It has been usually reported in children but rarely in adults. Here we report the first adult MIS (MIS-A) case series from Turkiye.

Material and Methods: Six patients who met the Centers for Disease Control and Prevention's MIS-A diagnostic criteria were included in the study. The demographic, clinical, laboratory, radiological characteristics and therapy regimes and outcomes of the patients were recorded.

Results: All of our cases had a history of mild COVID-19. They presented with fever, severe fatigue and hypotension. Abnormal echocardiography findings were detected in five patients. Only one patient had multiple mucocutaneous findings. Common laboratory features were lymphopenia, markedly increased C-Reaktive Protein, procalcitonin, pro-brain natriuretic peptide (pro-BNP), D-dimer, and ferritin. All patients had positive SARS-CoV-2 antibody result. Corticosteroids and/or anakinra were used in five, and intravenous immunoglobulin was used in two patients. Low-molecular-weight heparin (LMWH) was used for all cases. Empirically initiated antibiotic treatments were discontinued after cultures were negative. After anti-inflammatory treatment, the hypotension of the patients resolved, they did not need intensive care follow-up and no mortality was seen in our cases.

ÖZET

Amaç: Multisistem İnflamatuar Sendrom (MIS), COVID-19 sonrası erken dönemde görülen ve bağışıklık yanıtının bozulmasıyla geliştiği düşünülen sıklıkla çocuklarda görülen bir durumdur. Erişkinlerde nadiren bildirilmiştir. Bu makalede Türkiye'de takip edilen ilk yetişkin MIS (MIS-A) olgu serisi sunulmaktadır.

Gereç ve Yöntem: Centers for Disease Control and Prevention'in MIS-A tanı kriterlerini karşılayan altı hasta çalışmaya dahil edildi. Hastaların demografik, klinik, laboratuvar, radyolojik özellikleri ile tedavi uygulamaları ve sonuçları kaydedildi.

Bulgular: Tüm olgular COVID-19'u hafif şiddette geçirmişti. Hastaların hepsi ateş, şiddetli yorgunluk ve hipotansiyon ile başvurdular. Beş hastada anormal ekokardiyografi bulguları saptandı. Sadece bir hastada çoklu mukokutanöz bulgular mevcuttu. Yaygın laboratuvar özellikleri arasında lenfopeni, C-Reaktif Protein, prokalsitonin, pro-brain natriüretik peptid (pro-BNP), D-dimer ve ferritin artışı vardı. Tüm hastaların SARS-CoV-2 antikoru pozitifti. Beş hastada kortikosteroid ve/veya anakinra, iki hastada intravenöz immunoglobulin tedavisi ve hepsinde düşük moleküler ağırlıklı heparin tedavisi kullanıldı. Ampirik olarak başlanan antibiyotik tedavileri alınan kültürler negatif sonuçlanınca kesildi. Antiinflamatuar tedavi sonrası hastaların hipotansiyonu düzeldi, hiçbirinde yoğun bakım takibi ihtiyacı olmadı ve olgularımızda mortalite görülmedi.

Sonuç: MIS-A, çeşitli klinik tablolara neden olan ve sepsis ile

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Conclusions: MIS-A is a severe and mortal condition that causes various clinical pictures and can be confused with sepsis. Anakinra, a recombinant IL-1 receptor antagonist, is a significant agent that can be used in the treatment of MIS-A since it blocks the cytokine cascade at an early stage. The satisfactory responses will be obtained with early diagnosis and anti-inflammatory treatment. In this period when the pandemic is not over yet, it is necessary to increase the awareness of clinicians about MIS-A, which can be fatal.

Keywords: SARS-CoV-2, COVID-19, multisystem inflammatory syndrome, adult, anakinra, steroid therapy

karıştırılabilen ciddi ve ölümcül bir durumdur. Rekombinant IL-1 reseptör antagonisti olan anakinra, sitokin kaskadını erken aşamada bloke ettiği için MIS-A tedavisinde kullanılabilecek önemli bir ajandır. MIS-A'da erken teşhis ve antiinflamatuar tedavi ile olumlu sonuçlar alınacaktır. Pandeminin hız kestiği ancak henüz bitmediği bu dönemde klinisyenlerin ölümcül olabilen MIS-A hakkında farkındalığının artırılması gerekmektedir.

Anahtar Kelimeler: SARS-CoV-2, COVID-19, multisystem inflamatuar sendrom, erişkin, anakinra, steroid tedavisi

INTRODUCTION

In the course of Coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may affect all tissues that express angiotensin-converting enzyme 2 (ACE-2) receptors. Increased cytokine release from infected cells causes local inflammation (1). As it is known, inflammation is a self-limited process through the balance between inflammatory and anti-inflammatory systems of the organism. Somehow, the triggered and activated immune cells may cause a vicious inflammatory circle and some patients develop a cytokine-mediated hyperinflammatory state on the basis of some probable immunogenetic factors. We have learned during the SARS-CoV-2 pandemic that SARS-CoV-2 infection may cause hyperinflammation not only under the title of acute COVID-19 but also in post-COVID-19 period.

Multisystem inflammatory syndrome (MIS) is defined as an immune-mediated complication of COVID-19 in the early stage of post-illness period (2). It has predominantly been reported among children and the first adult case was reported on June 2020 (3). After this time, adult patients with Kawasaki-like illness have been reported. Adult patients who are infected with SARS-CoV-2 can develop MIS days to weeks after the initiation of COVID-19 (4). Clinical features have varied but predominantly included persistent fever, abdominal pain, mucocutaneous signs, edema, cardiac dysfunction, shock, markedly elevated inflammatory markers, hematological involvement and serologically positive COVID-19 (2, 4).

Here we report the first MIS in adults (MIS-A) case series in Turkey, examine the clinical course of the disease and possible pathogenesis, and also present our treatment experiences.

MATERIALS AND METHODS

The hospital files and electronic records of MIS-A cases were retrospectively examined. The administered treatments with the demographic, clinical, laboratory and radiological characteristics of the patients were recorded on the previously prepared forms. Six patients who met the Centers for Disease Control and Prevention (CDC)'s MIS-A diagnostic criteria (5) were included in the study. CDC's MIS-A case definition is: a patient aged ≥21 years with fever hospitalized for ≥24 hours, or with an illness resulting in death, who meets the clinical criteria (three criteria, but at least one primary clinical criteria) and laboratory criteria (laboratory evidence of SARS-CoV-2 infection and elevation of at least two inflammatory markers like C-Reaktive Protein (CRP), ferritin, IL-6, erythrocyte sedimentation rate, procalcitonin). The patient should not have a more likely alternative diagnosis for the illness (e.g., bacterial sepsis, exacerbation of a chronic medical condition). The primary clinical criteria are severe cardiac illness or rash and non-purulent conjunctivitis. The secondary clinical criteria are new onset neurologic signs and symptoms, shock or hypotension not attributable to medical therapy, abdominal pain/vomiting/diarrhea and thrombocytopenia. The transthoracic echocardiography was performed by the cardiologist to the patients. SARS-CoV-2 IgG antibody against Spike protein were tested for all patients, and the informed consent was obtained from the patients on hospital admission. Patients were treated with 40 mg methylprednisolone daily or 6 mg dexamethasone daily as steroid therapy. Intravenous immunoglobulin (IVIG) treatment was administered at a total of 2 g/kg dose divided into five days. In patients with high inflammatory markers, anakinra was administered as an anti-cytokine therapy at a dose of 100-200 mg two or three times a day, subcutaneous (SC)/intravenous (IV), after taking the opinion of rheumatologists according to the follow-up of these inflammatory markers. Prophylactic low-molecular-weight heparin (LMWH) was administered as 40 mg/day SC, LMWH was administered as 1 mg/kg SC twice a day as the treatment dose.

The study was approved by the local ethics committee of Istanbul University, Istanbul Faculty of Medicine (Date: 14.01.2022, No: 2021/2183) and the Turkish Ministry of Health.

RESULTS

Characteristics of the cases

Four of the six cases were men. Mean age of the patients was 43.3 years old (minimum age: 23, maximum

age: 56). All of our cases were middle-aged with a history of mild COVID-19 in the last 2-8 weeks. All had asymptomatic period after COVID-19 until the initiation of the MIS-A symptoms. They were followed after the second COVID-19 wave in Turkiye in November and December 2020. All the patients were unvaccinated against to SARS-CoV-2. The patients presented to emergency room with the symptoms of fever, and severe fatigue. None of the patients had respiratory problems. Five out of six patients developed severe hypotension. Abnormal echocardiography findings were detected in five patients. One patient had no echocardiographic evaluation. Only one patient had multiple mucocutaneous findings, although these findings except livedo reticularis occurred after the diagnosis of MIS-A (Figure 1). Common laboratory features were lymphopenia, markedly increased CRP, procalcitonin, pro-BNP, D-dimer, and ferritin. Mild thrombocytopenia developed in one patient, and moderate thrombocytopenia in another patient. All patients' anti-SARS-CoV-2 IgG antibodies were qualitatively positive (Table 1).

Treatment strategies

Corticosteroids were used in five out of six patients, and we preferred IVIG treatment in two cases who had severe, and IV fluid resistant hypotension (Case 1, and 5). LMWH was used for all cases, interleukin 1 receptor antagonist (Anakinra) was used in five patients (Table 2). Hypotension resolved after a few days with the initiation of anti-inflammatory therapy in MIS-A cases. As a result; none of our patients needed intensive care and none received.

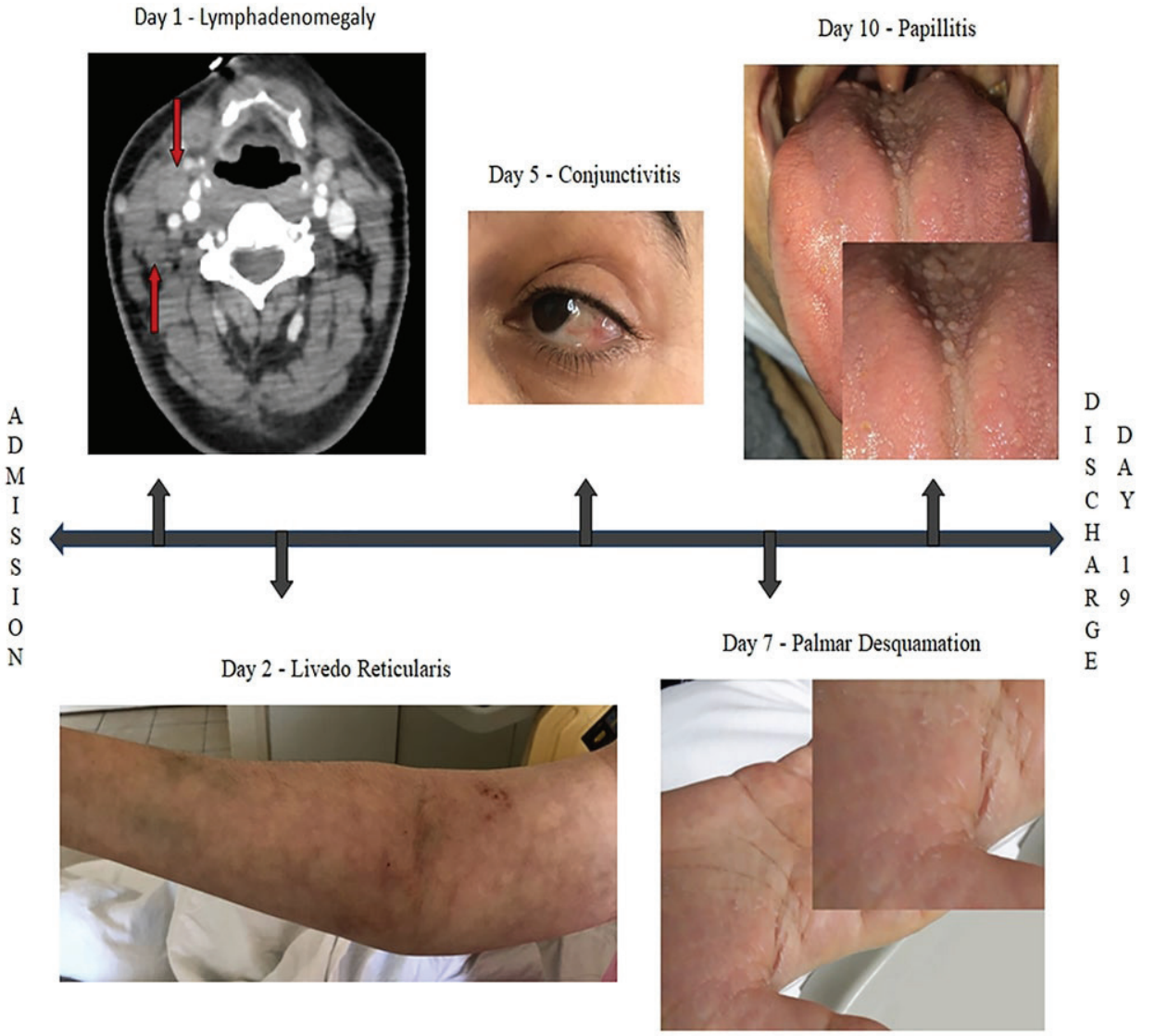

Figure 1: The mucocutaneous and radiological findings of Case 1

Table 1: Clinical, laboratory and radiologic characteristics of MIS-A cases

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age	37	48	45	51	23	56
Gender	Female	Male	Male	Male	Male	Female
Coexisting diseases	Allergic rhinitis	None	Nephrolithiasis	Inactive Hepatitis B	None	Type 2 DM, Hypertension
Severity of COVID-19	Mild	Mild	Mild	Mild	Mild	Mild
Duration between COVID-19 diagnosis and initiation of MIS-A symptoms	29 days	10 days	24 days	29 days	50 days	12 days
Duration of the asymptomatic period	23 days	8 days	20 days	23 days	41 days	9 days
SARS-CoV-2 PCR - on admission for MIS-A	Negative	Positive	Negative	Negative	Negative	Negative
Anti-SARS-CoV-2 IgG antibody	Positive	Positive	Positive	Positive	Positive	Positive
Lymphocyte (absolute count/µl)	300	700	900	800	300	800
Neutrophil (absolute count/µl)	10,000	2,350	25,600	19,100	4,100	24,700
Platelet (absolute count/µl)	75,000	170,000	179,000	127,000	179,000	622,000
C-reactive protein (mg/L)	323.85	280	311.49	205.14	412	111
Ferritin (ng/mL)	426.3	780	3,714	2,748	1,595	998
Procalcitonin (ng/mL)	3.43	19	11.41	0.73	5.31	11.62
D-dimer (µg/L)	12.760	2800	1.400	2090	2900	730
Pro-BNP (pg/mL)	6.831	3600	23.077	>35.000	1006	443
Troponin-T (pg/mL)	3.54	14	54.89	540.5	30.16	6.24
Fever	7 days	6 days	12 days	4 days	4 days	4 days
Fatigue	+	+	+	None	+	+
Lymphadenomegaly	Unilateral cervical	None	None	Unilateral cervical	None	None
Cutaneous and mucocutaneous findings	Livedo Reticularis Conjunctivitis Papillitis Palmar desquamation	Macular rash on legs	Tonsillar hyperemia	None	None	None
Blood pressure (mm Hg)	75/45	85/40	88/60	120/80	70/40	85/60
Edema	Severe-Anasarca	Severe-Anasarca	Slightly	Slightly	Slightly	Slightly

Table 1: Clinical, laboratory and radiologic characteristics of MIS-A cases *(Continued)*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Echocardiographic evaluation	EF: 68% PAP: 43mmHg Pericardial effusion	Not performed	EF: 50% PAP: 32 mmHg Right ventricular dysfunction Septal hypokinesia	EF: 50% Anteroseptal hypokinesia, pericardial effusion	EF: 60% PAP: 27 mm Hg Pericardial effusion	EF: 76% PAP: 27 mm Hg Left ventricular hypertrophy and diastolic dysfunction
Gastrointestinal involvement	Vomiting	None	None	None	Diarrhea	Vomiting/ Diarrhea
Respiratory findings	Mild coughing	Mild coughing	None	None	None	None
Duration of hospitalization	19 days	18 days	15 days	15 days	13 days	12 days

Laboratory results demonstrate the lowest absolute lymphocyte and platelet counts; and highest levels for other parameters.
MIS-A: Multisystem inflammatory syndrome in adults, COVID-19: Coronavirus disease 2019, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, DM: Diabetes mellitus, BNP: Brain natiruretic peptide, EF: Ejection fraction, PAP: Pulmonary artery pressure, PCR: Polymerase chain reaction

Table 2: Medical therapies of MIS-A cases

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Methylprednisolone	-	-	40 mg/day IV	40 mg/day IV	-	40 mg/day IV
Dexamethasone	-	6 mg qd - 10 days IV	-	-	6 mg qd - 12 days IV	-
Anakinra	100 mg q8h - SC	200 mg q8h - IV	200 mg q8h - IV	100 mg bid - SC	100 mg q8h - SC	-
Tocilizumab	-	-	-	-	-	-

IV: intravenous, SC: subcutaneous

DISCUSSION

Several hypotheses have been suggested to clarify the immunopathogenesis of MIS in children (MIS-C) and MIS-A. Inefficient and reduced neutralizing antibody activity against SARS–CoV-2, hyperinflammation triggered by spike protein which has a superantigen-like motif similar to *Staphylococcal* enterotoxin B, autoantibody mediated cell damage or inflammation and the composition of high viral load, slow viral clearance and delayed interferon response are among the current hypotheses (6-9). Another pathogenesis of MIS in children is the continuation of viral replication in the gastrointestinal system, leading to this strong systemic response in the post-infectious period. Mesenteric lymphadenitis was detected in laparotomy performed in MIS-C patients, and it was shown that enterocytes were infected with SARS-CoV-2 earlier (10, 11). In addition, one study which compared COVID-19, Kawasaki Disease and MIS-C in children; demonstrated that children diagnosed with MIS-C were significantly older, presented with higher CRP and ferritin, lower platelet count and interleukin (IL) 17A, also with different T-cell subsets. Outcomes of the study suggested that these three entity contained differences in immunological and antibody profiles (12).

The characteristics of our cases, and previously reported cases in the literature suggest that this clinical entity has a wide spectrum. Common features of the cases are; high fever, hypotension, systemic findings, lymphopenia, thrombocytopenia, high D-dimer levels, especially significantly higher procalcitonin and increased inflammation markers that mimic severe sepsis. Also, we observed that although patients had mild COVID-19, they had high SARS-CoV-2 antibody levels.

Abnormal echocardiography findings in MIS-C patients are seen in 50-60%, while in the CDC's MIS-A case series, this rate increases to 80% (4,13-15). Similar to this finding, five out of six patients in our study also had abnormal echocardiography findings. Echocardiography findings in patients were evaluated as secondary reactive-hyperdynamic changes to the advanced reduction of peripheral resistance. Pericardial-pleural effusion and peripheral edema were also suggested to develop due to fluid escape associated with reduced resistance, and endothelial damage.

As reported in children, previously reported adult MIS-A patients were mostly African-American and Hispanic, while a small number of patients of Asian descent were reported (2, 4, 15, 16). In the present study all patients were Caucasian.

The aforementioned study examining the COVID-19, Kawasaki, MIS-C and healthy children has shown that SARS-CoV-2 antibodies of several MIS-C patients target the endothelial glycoprotein named endoglin (12). Cellular damage caused by this cross reaction may be perceived by pattern recognition receptors of innate immunity as endogenous damage-associated molecular patterns. It is inevitable that this possible interaction would trigger many signal cascades known from the pathogenesis of sepsis, causing the production of cytokines such as tumor necrosis factor alfa, IL-1β, IL-18 via activation of nuclear factor kappa B and inflammasomes (17). In the light of the data, we have learned about innate immunity over the last decade, there is a possibility of that innate immunity might be trained and triggered with acute COVID-19, and the trained immunity may empower the severity of inflammation that occurs during the post-COVID-19 inflammatory disease (18).

During sepsis, IL-1β levels were shown to be higher in patients who have died compared to the levels of the survivors (19). The IL-1β is known to promote the amplification cascade, and induces the synthesis of various inflammatory genes such as IL-6, IL-8, monocyte chemoattractant protein-1, cyclooxygenase-2, nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha, IL-1α, IL-1β, and mitogen-activated protein kinase (17). Accordingly, we hypothesized that the use of a human recombinant interleukin 1 antagonist would be more effective (Anakinra) to block the cytokine cascade at an earlier stage.

In conclusion MIS-A is a severe and mortal condition that causes various clinical pictures and can be confused with sepsis. Anakinra, a recombinant IL-1 receptor antagonist, is an agent that can be used in the treatment of MIS-A since it blocks the cytokine cascade at an early stage. Since this clinical picture can be fatal, our clinical strategy was an earlier diagnosis and rapid anti-cytokine treatment. We suggest that there was a demonstrative response to anakinra and corticosteroid therapy in our case series and it is worthwhile. We assume that there is a need to increase the awareness of clinicians about MIS-A.

Ethics Committee Approval: The study was approved by the local ethics committee of Istanbul University, Istanbul Faculty of Medicine (Date: 14.01.2022, No: 2021/2183).

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REFERENCES

1. Iwasaki M, Saito J, Zhao H, Sakamoto A, Hirota K, Ma D. Inflammation triggered by SARS-CoV-2 and ACE2 augment drives multiple organ failure of severe COVID-19: Molecular mechanisms and implications. Inflammation 2021;44(1):13-34. [CrossRef]
2. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem inflammatory syndrome in US children and adolescents. N Engl J Med 2020;383:334-46. [CrossRef]
3. Sokolovsky S, Soni P, Hoffman T, Kahn P, Scheers-Masters J. COVID-19 associated Kawasaki-like multisystem inflammatory disease in an adult. Am J of Emerg Med 2021;39:253.e1-2. [CrossRef]
4. Morris SB, Schwartz NG, Patel P, Abbo L, Beauchamps L, Balan S, et al. Case series of multisystem inflammatory syndrome in adults associated with SARS-CoV-2 infection-United Kingdom and United States, March-August 2020. MMWR Morb Mortal Wkly Rep 2020;69(40):1450-6. [CrossRef]
5. Centers for Disease Control and Prevention. Multisystem inflammatory syndrome in adults (MIS-A): case definition. Available at: https://www.cdc.gov/mis/mis-a/hcp.html#:~:text=Case%20Definition%20for%20MIS%2DA,following%20clinical%20and%20laboratory%20criteria. Accessed 19 December 2021.
6. Weisberg SP, Connors T, Zhu Y, Baldwin M, Lin WH, Wontakal S, et al. Antibody responses to SARS-CoV2 are distinct in children with MIS-C compared to adults with COVID-19. medRxiv 2020. [CrossRef]
7. Cheng MH, Zhang S, Porritt RA, Rivas MN, Paschold L, Willscher E, et al. Superantigenic character of an insert unique to SARS-CoV-2 spike supported by skewed TCR repertoire in patients with hyperinflammation. Proc Natl Acad Sci U S A 2020;117(41) :25254-62. [CrossRef]
8. Rowley AH. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. Nat Rev Immunol 2020;20(8):453-454. [CrossRef]
9. Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis 2020;20(11):e276-88. [CrossRef]
10. Belhadjer Z, Meot M, Bajolle F, Khraiche D, Legendre A, Abakka S, et al. Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. Circulation 2020;142(5):429-36. [CrossRef]

11. Lamers MM, Beumer J, Vaart J, Knoops K, Puschhof J, Breugem TI, et al. SARS-CoV-2 productively infects human gut enterocytes. Science 2020;369(6499):50-4. [CrossRef]
12. Consiglio CR, Cotugno N, Sardh, F, Pou C, Amodio, D, Rodriguez L, et al. The immunology of multisystem inflammatory syndrome in children with COVID-19. Cell 2020;183(4):968-81. [CrossRef]
13. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020;324(3):259-69. [CrossRef]
14. Davies P, Evans C, Kanthimathinathan HK, Lillie J, Brierley J, Waters G, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. Lancet Child Adolesc Health 2020;4(9):669-77. [CrossRef]
15. Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr 2021;180(2):307-22. [CrossRef]
16. Dufort EM, Koumans EH, Chow EJ, Rosenthal EM, Muse A, Rowlands J, et al. Multisystem inflammatory syndrome in children in New York State. N Engl J Med 2020;383(4):347-58. [CrossRef]
17. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. In Seminars in immunopathology. Semin Immunopathol 2017;39(5):517-28. [CrossRef]
18. Netea MG, van der Meer JWM. Trained immunity: an ancient way of remembering. Cell Host Microbe 2017;21(3):297-300. [CrossRef]
19. Mera S, Tatulescu D, Cismaru C, Bondor C, Slavcovici A, Zanc V, et al. Multiplex cytokine profiling in patients with sepsis. APMIS 2011;119(2):155-63. [CrossRef]