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Original Article

Challenges in diagnosing COVID-19 related disease in pediatric patients with rheumatic disease

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ABSTRACT

Objectives: Multisystem inflammatory syndrome in children (MIS-C) is a rare but severe condition associated with coronavirus disease 2019. Here we aimed to raise awareness for the symptoms of MIS-C in patients with rheumatic diseases, emphasizing the challenges of the differential features.

Methods: We retrospectively evaluated the demographic and clinical characteristics, laboratory and imaging findings, treatments, and outcomes of six MIS-C patients with previous rheumatic disease.

Results: Three of the patients had familial Mediterranean fever (FMF), one had juvenile dermatomyositis, one had systemic juvenile idiopathic arthritis (JIA), and another patient had oligoarticular JIA. All FMF patients presented with fever and abdominal pain, two also had chest pain. The patient with systemic JIA presented with fever, rash, and myalgia. All patients had elevated inflammatory markers and high d-dimer levels. Chest imaging of two FMF patients showed infiltrations compatible with pneumonia. One FMF patient had mildly decreased systolic functions with a shortening fraction of 48% in his echocardiography. Intravenous immunoglobulin and methylprednisolone were administered to all patients. Anakinra was given to four patients.

Conclusions: Clinical and laboratory signs of MIS-C may overlap with the findings of various rheumatic diseases, and this may cause a delay in diagnosis.

KEYWORDS: Coronavirus disease 2019 (COVID-19); multisystem inflammatory syndrome in children (MIS-C); rheumatic disease

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), usually has a mild course in children [1]. However, children can be severely affected in rare cases, and clinical manifestations may differ from adults. The first time in April of 2020, reports from the United Kingdom documented a presentation in children similar to incomplete Kawasaki disease (KD) or toxic shock syndrome that had termed multisystem inflammatory syndrome in children (MIS-C) [2, 3]. Since then, reports of similarly affected children have been reported elsewhere in the world [4–7].

The timing of onset of symptoms relative to the acute SARS-CoV-2 infection is variable. In children who have a known history of documented or suspected COVID-19, the usual duration between acute infection and onset of MIS-C symptoms is 2 to 6 weeks [8]. MIS-C has a pretty broad clinical spectrum. The various presenting symptoms in MIS-C were as follows: fever, gastrointestinal symptoms, rash, conjunctivitis, mucous membrane involvement (red or swollen lips, strawberry tongue), swollen hands/feet, myalgia, neurocognitive signs, respiratory symptoms, and lymphadenopathy [6, 7, 9–11]. Patients typically present with 3 to 5 days of fever, followed by the development of shock and/or multisystem involvement. Laboratory findings include lymphocytopenia, elevated inflammatory markers (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], d-dimer), elevated troponin, and brain natriuretic peptide. These clinical and laboratory signs of MIS-C may overlap with the findings of various infectious and inflammatory diseases and may pose a challenge in diagnosis.

The aim of this study was to raise awareness for the symptoms of MIS-C in patients with rheumatic diseases, emphasizing the challenges of the differential features.

Methods

The patients admitted with the diagnosis of MIS-C in Hacettepe University Department of Pediatrics between 2020 and 2021 were reviewed. All patients met the MIS-C criteria defined by the United States Centers for Disease Control and Prevention (CDC) or the World Health Organization (WHO) [12, 13]. Among these cases, six patients had a comorbid rheumatic disease. We retrospectively evaluated these six

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patients' demographic and clinical features, laboratory and imaging findings, treatments, and outcomes.

Statistical analyses were performed using the SPSS software v. 24. Descriptive statistics were performed and presented as medians (minimum-maximum) for continuous variables as numbers and percentages for nominal/categorical variables.

The study was approved by the ethics committee of Hacettepe University (GO 21/670). Informed consent was obtained from all parents/patients before inclusion in the study. The study was performed following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Results

Patient characteristics

We reported six MIS-C cases who had a rheumatic disease. The clinical features, treatments, and outcomes of the patients are summarized in Table 1. The median age of the patients was 8 (3–15) years, and four (66.6%) were male. Three of our patients had familial Mediterranean fever (FMF), one had juvenile dermatomyositis (JDM), one had systemic juvenile idiopathic arthritis (JIA), and another patient had a history of oligoarticular JIA. Except for the FMF patients, all patients (patient number-pn:1, 4, 6) were on steroid therapy for their primary disease when diagnosed with MIS-C. *MEFV* gene variants had been analysed by Sanger sequencing in FMF patients. The genotype of patients 2, 3, and 5 were M694V/M694V, M694V/P369S, and M694V/V726A, respectively.

Clinical manifestations

Common clinical presentations of patients were as follows: fever ($n=6$), abdominal pain ($n=3$), rash ($n=2$), cough and chest pain ($n=2$), and lymphadenopathy ($n=2$). Only one patient (pn:3) had symptoms similar to KD, such as fever ($\geq$5 days), rash, conjunctivitis, lymphadenopathy. There were fever and abdominal pain among the presentation findings of all FMF patients (pn:2, 3, 5). In addition, one FMF patient had pleural effusion (pn:2), and two had chest pain (pn:2, 5), and they had diarrhea and vomiting, another one had a rash (pn:3), all not expected in the attacks of FMF. The patient with systemic JIA (pn:6) had presented with fever, rash, and myalgia; however, the rash was independent of the fever and was persistent on the abdomen, arms, and legs. Another patient with oligoarticular JIA (pn:4) developed hypertension and seizure at admission, and his cranial magnetic resonance imaging revealed findings consistent with posterior reversible encephalopathy syndrome. On the other hand, clinical findings of MIS-C were relatively mild in the patient with JDM compared to other patients, and additionally, there was a complaint of fever (pn:1).

Laboratory tests and imaging findings

All patients had elevated ESR, CRP, d-dimer, and interleukin-6 levels. Other common laboratory findings were lymphocytopenia ($n=4$), neutrophilia ($n=4$), and thrombocytopenia ($n=4$).

One patient (pn:4) had a history of previous SARS-CoV-2 infection, and three patients (pn:3, 5, 6) had a history of positive contact. All patients were tested using SARS-CoV-2 PCR and COVID-19 serology. Anti-SARS-CoV-2 immunoglobulin G was positive in all cases except one. This patient (pn:4), whose antibody was found to be negative, had SARS-CoV-2 PCR positivity for approximately 1.5 months.

Chest imaging of two patients (pn:2, 5) showed infiltrations compatible with pneumonia and minimal pleural effusion in one of them. Echocardiography (ECHO) was performed on all patients. One FMF patient had cardiovascular involvement (pn:3). This patient had elevated cardiac markers and mildly decreased systolic functions with a shortening fraction of 48%. His ECHO findings improved 2 weeks after.

Treatments and outcome

The median hospital stay was 6 (5–10) days. Neither mechanical ventilation nor vasoactive drugs were required in any of the patients. A single dose of 2 g/kg intravenous immunoglobulin and methylprednisolone were administered to all patients. Methylprednisolone dose and duration were decided according to the patient's clinic and laboratory findings. Two patients had pulse methylprednisolone therapy (15–30 mg/kg/day); others had 2–4 mg/kg/day methylprednisolone. Anakinra (2–4 mg/kg daily, subcutaneous) was given to four patients (pn: 2, 3, 4, 6) due to the severe clinical findings. All patients had short-term anticoagulant therapy since they had abnormal coagulation parameters. All of our patients recovered and were discharged in good clinical condition.

Discussion

This study is the first report of MIS-C cases with underlying rheumatic diseases. The clinical and laboratory findings seen in MIS-C may overlap with the results of various inflammatory diseases, making them difficult to diagnose [9, 11, 14–20]. Based on this hypothesis in our study, we wanted to discuss the difficulties we experienced while diagnosing MIS-C in various rheumatic diseases, most of which have underlying inflammatory disorders.

In only one patient (pn:3), findings similar to KD led us directly to the MIS-C diagnosis. On the other hand, we had difficulty diagnosing MIS-C for the other patients since similar findings can be seen during the attack/activation periods of their primary diseases. All FMF patients (pn:2, 3, 5) had fever and abdominal pain, and two additionally had chest pain. These findings were features that can be seen in a typical FMF attack and easily confused with an attack. Our systemic JIA patient (pn:6) had applied with the complaints of fever, rash, and myalgia. As it is known, these findings can be seen frequently during the activation period of systemic JIA disease and could direct us to a possible disease activation.

All of our patients had high acute phase reactants (CRP and ESR). Elevated inflammatory markers were among the laboratory findings that can be seen in both MIS-C and rheumatic diseases [2, 5, 21–27].

The signs and symptoms of MIS-C may be suppressed in patients on steroid therapy. Three of our patients (pn:1, 4, 6) were having steroids for their primary disease. MIS-C symptoms and laboratory findings were milder, particularly in the JDM patient (pn:1) on high-dose (1 mg/kg/day) steroid, which might have indirectly affected the treatment and hospitalization process positively.

Table 1. Clinical features, treatments and outcomes of six children with MIS-C.

Clinical feature	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)/sex	4/F	3/M	15/M	14/M	5/F	11/M
Comorbidities	JDM	FMF	FMF	Oligoarticular JIA, LRBA deficiency, IBD, TIN	FMF	Systemic JIA
Treatments for the primary disease	Prednisolone (1 mg/kg/d) po, methotrexate (12.5 mg/m^2/weekly) sc	Colchicine (0.04 mg/kg/d)	Colchicine (0.03 mg/kg/d)	Prednisolone (0.5 mg/kg/d) po	Colchicine (0.03 mg/kg/d)	Prednisolone (0.2 mg/kg/d) po
Time to presentation	2 days	3 days	5 days	1 day	2 days	3 days
Presenting symptoms	Fever, extremity edema, lymphadenopathy	Fever, abdominal pain, diarrhea, cough, chest pain, dyspnea	Fever, abdominal pain, rash, conjunctivitis, lymphadenopathy	Fever, headache, hypertension, seizure, PRES	Fever, abdominal pain, emesis, cough, chest pain	Fever, rash, myalgia
Laboratory findings						
Hemoglobin (g/dl)	11.6	11.0	12.9	10.6	11.4	13.9
Leukocyte (Ref: 4–11 × 10^3/μl)	11.3	8.3	3.8	16.7	14.6	14.4
Neutrophil (Ref: 1.8–6.4 × 10^3/μl)	9.9	6.1	2.7	15.3	11.9	13.2
Lymphocyte (Ref: 0.8–5 × 10^3/μl)	0.7	1.5	0.3	0.4	1.9	0.6
Platelets (Ref: 150–400 × 10^3/μl)	130	170	119	135	379	128
CRP (Ref: 0–0.8 mg/dl)	7.1	23.6	21.2	32.2	13.8	14.6
ESR (Ref: 0–20 mm/h)	33	83	41	45	52	57
Interleukin-6 (Ref: 0–6.4 pg/ml)	12	1157	136	1682	39	379
Ferritin (Ref: 11–307 mg/l)	323	109	268	10.578	45	431
d-dimer (Ref: 0–0.55 mg/l)	1.2	7.5	0.9	3.4	2.6	13.1
Troponin (Ref: 14–42.9 ng/l)	6.9	4.3	7.200	93.6	3.2	48
BNP (Ref: 0–100 pg/ml)	46	314	878	153	10	57

(continued)

Table 1. (Continued)

Clinical feature	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Kidney function tests	Normal	Normal	Normal	Elevated	Normal	Normal
Liver enzymes	Minimal elevated	Moderately elevated	Normal	Normal	Normal	Normal
Chest imaging	Chest radiograph: Normal	Chest CT scan: bilateral infiltrations with minimal pleural effusion	Chest radiograph: Normal	Chest radiograph: Normal	Chest radiograph: right pericardiac infiltration	Chest radiograph: Normal
Echocardiographic findings	Ejection fraction: 80%. No pathological finding was detected	Ejection fraction: 82%. No pathological finding was detected	Mildly decreased systolic function with a shortening fraction of 48%	Ejection fraction: 64%. No pathological finding was detected	Ejection fraction: 76%. No pathological finding was detected	Ejection fraction: 73%. No pathological finding was detected
SARS-CoV-2 testing						
Nasopharyngeal SARS-CoV-2 PCR	Negative	Negative	Negative	Positive	Negative	Negative
Anti-SARS-CoV-2 immunoglobulin G	Positive	Positive	Positive	Negative	Positive	Positive
Known exposure or history of SARS-CoV-2 infection	None	None	Present	Present	Present	Present
SARS-CoV-2 exposure or history time before presentation	–	–	3 weeks ago	6 weeks ago	5 weeks ago	4 weeks ago
Treatments						
IVIG	2 g/kg once	2 g/kg once	2 g/kg once	2 g/kg once	2 g/kg once	2 g/kg once
Methylprednisolone	2–4 mg/kg daily for 5 days	2–4 mg/kg daily for 10 days	2–4 mg/kg daily for 10 days	30 mg/kg daily for 3 days followed by 2–4 mg/kg daily for 10 days	2 mg/kg daily for 7 days	15 mg/kg daily for 3 days followed by 2 mg/kg daily for 5 days
Anakinra	–	2 mg/kg daily for 4 days	2–4 mg/kg daily for 5 days	2–4 mg/kg daily for 8 days	–	2–4 mg/kg daily for 5 days
Mechanical ventilation	None	None	None	None	None	None
Vasoactive drugs	None	None	None	None	None	None
Exitus	None	None	None	None	None	None

Abbreviations: BNP, brain natriuretic peptide; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; F, female; FMF, familial Mediterranean fever; IBD, inflammatory bowel disease; IVIG, intravenous immunoglobulin; JDM, Juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; M, male; PCR, polymerase chain reaction; PRESS, posterior reversible encephalopathy syndrome; po, perioral; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; sc, subcutaneous; TIN, tubulointerstitial nephritis.

Although aforementioned factors made it difficult to diagnose accurately, some signs led us to think of MIS-C. Two FMF patients described gastrointestinal symptoms not characteristic of their usual attacks, such as diarrhea and nausea (pn:2, 5), which suggested a feature more specific for MIS-C. Moreover, in these patients, features suggesting lower respiratory tract infections such as cough and dyspnea were not signs of FMF attacks. Another FMF patient had diffuse maculopapular eruptions all over the body, which is not typically seen in attacks (pn:3). Infiltrative findings suggesting pneumonia in the lung X-ray of two FMF patients (pn:2, 4) and the detection of decreased systolic functions in the ECHO imaging of another FMF patient (pn:3) led us to the diagnosis of MIS-C. On the other hand, in the systemic JIA patient, the rash was independent of the fever and was persistent. This patient also had severe myalgia, which again was in favour of MIS-C rather than disease activation. Furthermore, the ferritin value was not as high as would expect in sJIA activation, and there was lymphopenia. Among the laboratory findings, thrombocytopenia, lymphocytopenia, and high d-dimer were not characteristic during the disease course of FMF and sJIA. Cytopenia could be seen only in the case of possible macrophage activation syndrome (MAS) development in the systemic JIA patient (pn:6). However, MAS was not considered with the clinical and laboratory findings of the patient at that time [28]. In addition, most of our patients (66.6%) had a previous history of patient contact with or passing on Covid-19 which directed us to the diagnosis of MIS-C.

The retrospective nature and the small sample size were the major limitations of this case series.

Conclusion

The clinical and laboratory signs in MIS-C may overlap with the findings of various infectious and inflammatory diseases, complicating the diagnosis. Clinicians should be aware of MIS-C which is a life-threating disorder, in the differential diagnosis of other inflammatory conditions. We hope that our research will raise awareness for identifying clinical and laboratory features that distinguish MIS-C from other similar diseases.

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Conflict of interest

None declared.

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References

[1] World Health Organization. *Director-General's Remarks at the Media Briefing on 2019-nCoV on 11 February 2020*. http://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020 (12 February 2020, date last accessed).

[2] Riphagen S, Gomez X, Gonzalez-Martinez C *et al.* Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020;**395**:1607–8.

[3] Paediatric Intensive Care Society. *PICS Statement: Increased Number of Reported Cases of Novel Presentation of Multi System Inflammatory Disease*. https://picsociety.uk/wp-content/uploads/2020/04/PICS-statement-re-novel-KD-C19-presentation-v2-270420 20.pdf (15 May 2020, date last accessed).

[4] Health Alert Network (HAN): *Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)*. https://emergency.cdc.gov/han/2020/han00432.asp (15 May 2020, date last accessed).

[5] Verdoni L, Mazza A, Gervasoni A *et al.* An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet* 2020;**395**:1771.

[6] Whittaker E, Bamford A, Kenny J *et al.* Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA* 2020;**324**:259.

[7] Feldstein LR, Rose EB, Horwitz SM *et al.* Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med* 2020;**383**:334.

[8] Cirks BT, Rowe SJ, Jiang SY *et al.* Sixteen weeks later: expanding the risk period for multisystem inflammatory syndrome in children. *J Pediatric Infect Dis Soc* 2021;**10**:686.

[9] Godfred-Cato S, Bryant B, Leung J *et al.* COVID-19–associated multisystem inflammatory syndrome in children — United States, March–July 2020. *MMWR Morb Mortal Wkly Rep* 2020;**69**:1074.

[10] Feldstein LR, Tenforde MW, Friedman KG *et al.* Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. *JAMA* 2021;**325**:1074.

[11] Davies P, Evans C, Kanthimathinathan HK *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**:669.

[12] World Health Organization Scientif Brief. *Multisystem Inflammatory Syndrome in Children and Adolescents with COVID-19*. https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19 (17 May 2020, date last accessed).

[13] Centers for Disease Control and Prevention Health Alert Network (HAN). *Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)*. https://emergency.cdc.gov/han/2020/han00432.asp (15 May 2020, date last accessed).

[14] Sperotto F, Friedman KG, Son MBF *et al.* Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. *Eur J Pediatr* 2021;**180**:307.

[15] Dolhnikoff M, Ferreira Ferranti J, de Almeida Monteiro RA *et al.* SARS-CoV-2 in cardiac tissue of a child with COVID-19-related multisystem inflammatory syndrome. *Lancet Child Adolesc Health* 2020;**4**:790.

[16] Abdel-Mannan O, Eyre M, Löbel U *et al.* Neurologic and radiographic findings associated with COVID-19 infection in children. *JAMA Neurol* 2020;**77**:1440.

[17] Hanson KE, Caliendo AM, Arias CA *et al.* Infectious Diseases Society of America guidelines on the diagnosis of COVID-19: serologic testing. *Clin Infect Dis* 2020 ciaa1343.

[18] Choi NH, Fremed M, Starc T *et al.* MIS-C and cardiac conduction abnormalities. *Pediatrics* 2020;**146**:e2020009738.

[19] Woo P. Systemic juvenile idiopathic arthritis: diagnosis, management, and outcome. *Nat Clin Pract Rheumatol* 2006;**2**:28–34.

[20] Cassidy JTPR. *Juvenile Rheumatoid Arthritis. Textbook of Pediatric Rheumatology*, 4th edn. Philadelphia: WB Saunders, 2001, 219–20.

[21] European Centre for Disease Prevention and Control Rapid Risk Assessment. *Paediatric Inflammatory Multisystem Syndrome and SARS CoV 2 Infection in Children*. https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-risk-assessment-paediatric-inflammatory-multisystem-syndrome-15-May-2020.pdf (17 May 2020, date last accessed).

[22] Belhadjer Z, Méot M, Bajolle F *et al.* Acute heart failure in multisystem inflammatory syndrome in children in the context of global SARS-CoV-2 pandemic. *Circulation* 2020; **142**:4.

[23] Toubiana J, Poirault C, Corsia A *et al.* Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ* 2020;**369**:m2094.

[24] Royal College of Paediatrics and Child Health Guidance. Paediatric multisystem inflammatory syndrome temporally associated with COVID-19. https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf (17 May 2020, date last accessed).

[25] Tunca M, Kırıkali G, Soytürk M *et al.* Acute phase response and evolution of familial Mediterranean fever. *Lancet* 1999;**353**:1415.

[26] Lin SJ, Huang JL, Chao HC *et al.* A follow-up study of systemic-onset juvenile rheumatoid arthritis in children. *Acta Paediatr Taiwan* 1999;**40**:176–81.

[27] Pelkonen P, Swanljung K, Siimes MA. Ferritinemia as an indicator of systemic disease activity in children with systemic juvenile rheumatoid arthritis. *Acta Paediatr Scand* 1986;**75**:64–8.

[28] Behrens EM, Beukelman T, Gallo L *et al.* Evaluation of the presentation of systemic onset juvenile rheumatoid arthritis: data from the Pennsylvania Systemic Onset Juvenile Arthritis Registry (PASOJAR). *J Rheumatol* 2008;**35**:343–8.