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

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 similar to incomplete Kawasaki disease (MIS-C) 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
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 (≥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 JDM          | 3/M FMF                   | 15/M FMF                  | 14/M Oligoarticular JIA, LRBA deficiency, IBD, TIN | 5/F FMF         | 11/M Systemic JIA         |
| Comorbidities                     |                  |                           |                           |                           |                  |                           |
|                                   |                  |                           |                           |                           |                  |                           |
| Treatments for the primary disease | Prednisolone (1 mg/kg/d) po, methotrexate (12.5 mg/m²/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 × 10³/µl)    | 11.3             | 8.3                       | 3.8                       | 16.7                      | 14.6             | 14.4                      |
| Neutrophil (Ref: 1.8–6.4 × 10³/µl) | 9.9             | 6.1                       | 2.7                       | 15.3                      | 11.9             | 13.2                      |
| Lymphocyte (Ref: 0.8–5 × 10³/µl)  | 0.7              | 1.5                       | 0.3                       | 0.4                       | 1.9              | 0.6                       |
| Platelets (Ref: 150–400 × 10³/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)
| 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: | 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               | Negative                               | Negative                               | Positive                               | Positive                               | Negative                               | Negative                               |
| Nasopharyngeal SARS-CoV-2 PCR    | Negative                               | Negative                               | Positive                               | Negative                               | Positive                               | Positive                               |
| 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 2–4 mg/kg daily for 5 days | 2 g/kg once 2–4 mg/kg daily for 10 days | 2 g/kg once 2–4 mg/kg daily for 10 days | 2 g/kg once 30 mg/kg daily for 7 days | 2 g/kg once 15 mg/kg daily for 5 days | 2 g/kg once 15 mg/kg daily for 5 days |
| Methylprednisolone               |                                        |                                        |                                        |                                        |                                        |                                        |
| 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             | 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-threatening 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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