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CASE REPORT

The First Multisystem Inflammatory Syndrome in Children (MIS-C) Diagnosis in Our Clinic in the Late Period of the Pandemic: Case Report

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Abstract

COVID-19, which started in China in December 2019 and affected the globe, is seen less frequently in children compared to adults and progresses with milder symptoms. However, some of the children who had COVID-19 infection in Europe in April 2020 were critically ill cases in need of intensive care with shock and multi-organ failure, while others had characteristics similar to Kawasaki Disease. Studies show that SARS-CoV-2 causes multisystem inflammatory syndrome (MIS-C) in children. In this article, a case diagnosed with MIS-C in the early period is presented, which can be frequently confused with Kawasaki Disease and should be considered primarily in the differential diagnosis.

Keywords: Child; COVID-19; Multisystem inflammatory syndrome; MIS-C; SARS-CoV-2.

At the end of December 2019, a pneumonia outbreak of unknown cause occurred in the Wuhan province of China and quickly spread to other countries. Coronavirus disease (COVID-19), caused by a new type of coronavirus called "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)", was declared a pandemic on March 11, 2020 by the World Health Organization (WHO)[1]. Although most children with COVID-19 can recover from the disease mildly and at home, pediatricians in many countries reported that pediatric cases accompanied by fever and multisystem involvement were hospitalized between March and May 2020, and the WHO defined these cases as pediatric multisystemic inflammatory syndrome (MIS-C)[2].

Although the pathogenesis of multisystem inflammatory syndrome is not clearly known, it progresses with findings of multiple organ involvement as a result of uncontrolled inflammation of the immune system and may even result in death if not diagnosed and treated early. When the diagnosis was made, most of the patients had negative polymerase chain reaction (PCR) testing, while the SARS-CoV-2 antibodies were positive[2]. There is no underlying diseases in 52% of children diagnosed with MIS-C. The most common comorbidities are asthma and obesity[3]. More data is needed to understand why these children are more likely to develop the disease.

Diagnostic criteria for multisystemic inflammatory syndrome, which are also used in the guideline created by the Center for Disease Control and Prevention (CDC) and pub-

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Table 1. Diagnostic criteria of the Center for Disease Control and Prevention (CDC) for multisystem inflammatory syndrome in children (MIS-C)

1. Between ages of 0-21 years
2. Fever ≥ 38,0°C, for ≥ 24 hours, or subjective fever lasting ≥ 24 hours
3. Laboratory evidence of inflammation (presence of at least 2 or more evidences)
   - Elevated CRP
   - Elevated ESR
   - Elevated fibrinogen
   - Elevated procalcitonin
   - Elevated D-dimer
   - Elevated ferritin
   - Elevated LDH
   - Elevated IL-6
   - Neutrophilia
   - Lymphocytopenia
   - Hypoalbuminemia
4. Multiple organ system involvement (presence of at least 2 or more)
   - Cardiovascular system (shock, elevated troponin, elevated BNP level, abnormal echocardiography, arrhythmia)
   - Respiratory system (pneumonia, ARDS, pulmonary embolism)
   - Renal involvement (kidney failure)
   - Neurological involvement (seizure, stroke, aseptic meningitis)
   - Hematological involvement (coagulopathy)
   - Gastrointestinal involvement (abdominal pain, vomiting, diarrhea, elevated liver function tests, ileus, gastrointestinal system bleeding)
   - Skin involvement (erythroderma, mucositis, rash)
5. Serious illness requiring hospitalization
6. Exclusion of other microbial diseases that would explain the inflammation, such as bacterial sepsis, staphylococcal/streptococcal toxic shock syndrome
7. Recent or active SARS-CoV-2 infection or history of contact (any of the following)
   - PCR test positivity for SARS-CoV-2
   - Positive serology
   - Positive antigen test
   - COVID-19 exposure in the four weeks prior to the onset of symptoms

lished by our Ministry of Health, in line with the experience gained regarding the disease are given in Table 1[4].

There is no difference in the guide published by the WHO, between the diagnostic criteria except the duration of fever (≥3 days) and the age at which the disease was diagnosed (between 0-19 years)[5].

It is important to make the differential diagnosis of multisystemic inflammatory syndrome with diseases such as sepsis, Kawasaki Disease, macrophage activation syndrome (MAS) and toxic shock syndrome. It has been observed that 40-50% of children diagnosed with MIS-C meet the diagnostic criteria for Kawasaki disease, but Kawasaki Disease is more common under the age of five, while the average age of occurrence of MIS-C is 9 years and gastrointestinal symptoms (vomiting, diarrhea, abdominal pain) are relatively higher in patients[2,6].

The goal of multisystemic inflammatory syndrome treatment is to restore organ function by reducing systemic inflammation and mortality. Since there is multiple organ involvement, the treatment process should be established and shaped in cooperation with pediatric infection specialists, rheumatologists, cardiologists and intensive care specialists[7].

Case Report

An 8-year-old male patient with no known history of chronic disease admitted to our pediatric emergency department with complaints of fever, fatigue, vomiting, muscle pain and rash lasting for six days. Since the patient's complaints gradually increased, they had applied to another center three days ago and amoxicillin-clavulanic acid combined treatment was started with the diagnosis of tonsillitis. His family declared that they applied to our clinic for a PCR test because his fever did not decrease despite the use of antibiotics and they had COVID-19 positive neigh-

bors. There were no features in his personal and family history. There was a history of close contact with his COVID-19 positive teacher about three weeks ago. The patient, who was followed up closely by his family, did not have any hospital admissions until the previous week because he had no symptoms.

When the patient applied to our center, his body temperature was 37.3°C, heart rate was 120-130/minute, blood pressure was 80/50 mmHg and SpO_2% was 98%. In systemic examination, his skin color was pale, skin turgor was decreased, bilateral conjunctivae were hyperemic, lips were red and cracked, tongue was white, oropharynx was hyperemic; in his neurological examination, there was suspicious nuchal rigidity, and there was an itchy maculopapular rash on the proximal part of the left forearm, in an area of approximately 3x4 centimeters, which faded with pressure. Other systemic examination findings were normal. It was learned that the rash had been in the same area for two or three days and was gradually increasing. The patient was hospitalized with the prediagnoses of COVID-19, MIS-C, Kawasaki Disease and meningitis.

In the laboratory examinations, leukocyte level was 7.720/mm^3, neutrophil 6.160/mm^3, lymphocyte 910/mm^3, platelet 118,000/mm^3, C-reactive protein (CRP) 139.88 mg/L, D-dimer 5270 ng/ml, pro-BNP 7656 pg/ml, fibrinogen 607 mg/dl, ferritin 267.9 ng/ml, troponin T 0.031 ng/ml, ALT 6 IU/L, AST 18 IU/L, sodium 128 mEq/L, potassium 3.9 mEq/L, creatinine 0.36 mg/dl, BUN 13.7 mg/dl; in the blood gas examination, pH was 7.41, pC02 38.3 mmHg, bicarbonate 23.1 mmol/L, lactate 2.1 mmol/L, and his echocardiogram showed sinus tachycardia. With the prediagnosis of MIS-C, 100 mg/kg/day ceftriaxone, 40 mg/kg/day vancomycin, 2 grams/kg/day intravenous immune globulin (IVIG), 80 mg/kg/day acetylsalicylic acid and 1 mg/kg/day enoxaparin sodium treatment were started. He was referred to the pediatric intensive care unit because his general condition worsened and his hypotensive course continued. It was learned that the patient's echocardiogram was normal, he did not need inotropic agents, the current treatment was continued, and he had a mild course of MIS-C.

Discussion

Although China, the origin of the outbreak, had high rates of COVID-19 early in the pandemic, the first case reports of MIS-C were reported in April 2020 in a series of eight children from a tertiary center in South East England[3]. Although the exact incidence of MIS-C is not known, in a study conducted under 21 years of age, the estimated incidence of laboratory-confirmed SARS-CoV-2 infection was 322 per 100,000 and the incidence of MIS-C was 2 per 100,000[6].

In most studies, it has been found that there is a delay of several weeks between the peak of COVID-19 and the period when the number of MIS-C cases increase[2,6]. This delay coincides with the adaptive immune system, suggesting that MIS-C may be a post-infectious complication of the virus rather than active disease in some children. In a case series of 783 children, 60% of patients had positive serology with negative PCR, 34% had positive serology with positive PCR, and 5% had negative serology with negative PCR. This case series further supports the hypothesis that MIS-C is a post-infectious complication of the virus[2]. In our case, there was a delay of three weeks.

Although patients present with fever lasting for a maximum of three to five days, they may present with gastrointestinal symptoms such as abdominal pain, diarrhea, vomiting, rash, conjunctivitis, headache, neurocognitive symptoms such as lethargy, respiratory symptoms, sore throat, myalgia, swelling in the hands and feet and lymphadenopathy[2,6,8]. Gastrointestinal symptoms may be particularly common and pronounced to mimic acute appendicitis. Terminal ileitis and colitis have been found in some children undergoing abdominal imaging[6,8]. Our case also had symptoms of fever, vomiting, myalgia and rash. Patients may present with different clinical presentations such as shock, myocardial dysfunction, arrhythmia, acute respiratory failure, acute renal failure, serositis, hepatitis/hepatomegaly, encephalopathy, seizures, coma, or meningoencephalitis[8]. The first case series generally reported the most severe end of the spectrum, and this was reflected in the reports as increased myocardial involvement, respiratory failure and shock. It is predicted that the incidence of these cases will decrease as the recognition of milder forms of the disease increases[2].

Empirical antibiotic therapy, intravenous immunoglobulin (IVIG) and antithrombotic agents are used in the treatment of children with multisystemic inflammatory syndrome, depending on their clinical situation[3,7]. MIS-C may present with signs and symptoms that mimic septic shock and toxic shock syndrome. Therefore, patients with severe multisystem involvement should receive empirical broad-spectrum antibiotic therapy while awaiting culture results. Appropriate empirical antibiotic regimen consists of ceftriaxone and vancomycin[7]. American Rheumatology Association recommends giving IVIG at a single dose of 2 g/kg as an infusion for 8-12 hours, in the presence of shock, suppressed left ventricular function on echocardiogram,

coronary artery abnormalities (dilation or aneurysm) on echocardiography, arrhythmia, elevated BNP/NT-Pro BNP and/or troponin levels, and severe symptoms requiring pediatric intensive care unit care[9]. A second dose of IVIG is not recommended in refractory MIS-C patients and in patients who do not respond to a single dose of IVIG, due to hemolytic anemia and volume overload. Instead, methylprednisolone at a dose of 1-2 mg/kg/day can be applied as an alternative treatment[7]. Pulse glucocorticoid therapy can be used in life-threatening situations (IV methylprednisolone 10-30 mg/kg/dose, maximum 1 gram)[9]. Patients with MIS-C are at risk of experiencing thrombotic complications. Therefore, all patients presenting complete or incomplete Kawasaki criteria should receive at least low-dose aspirin, and all patients with moderate or severe left ventricular dysfunction should receive systemic anticoagulant therapy[7]. Anakinra, canakinumab, and tocilizumab are alternative options for patients who are unable to receive glucocorticoids and resistant to glucocorticoids[7]. Children who develop shock are treated according to shock protocols. Epinephrine can be used, especially in those with left ventricular dysfunction. Those with significant left ventricular dysfunction are treated with intravenous diuretics, agents such as milrinone, dopamine, and dobutamine. Mechanical hemodynamic support in the form of extracorporeal membrane oxygenation or a ventricular assist device may be required in cases of fulminant disease[9]. In our case, aspirin, 1 mg/kg/day enoxaparin sodium and 2 gr/kg IVIG were used together with ceftriaxone-vancomycin combination in the treatment. There was no coronary involvement in our case. IVIG was given to our case within the first seven days. It is known that the development of coronary aneurysm can be prevented with early diagnosis and treatment[9].

It was found appropriate to present our case as a case report, since it is the first MIS-C case diagnosed in our hospital within 9 months since the first COVID-19 case was seen in Turkey. Early diagnosis and treatment of MIS-C, which is rare but can be fatal when it occurs, will significantly reduce the mortality and morbidity of the disease. Therefore, it would be appropriate for pediatricians to manage the disease by keeping in mind the possibility of MIS-C in cases where they encounter a picture similar to Kawasaki disease.

Informed Consent: Written, informed consent was obtained from the patient's family for the publication of thís case report and the accompanying images.

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