CASE REPORT

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Localized multisystem inflammatory syndrome in children (mis-c), faster recovery outcome: a case report

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ABSTRACT

Backgrounds: MIS-C cases emerged approximately 4–5 weeks on average after the peak prevalence of COVID-19. The symptoms could be asymptomatic or mildly symptomatic with fever and cough. It was unknown if these infants' exhibited symptoms of Kawasaki disease (KD) or toxic shock syndrome (TSS), or whether they represented a condition associated with the continuing COVID-19 epidemic.

Objective: To describe clinical outcome and examination results of localized multisystem inflammatory syndrome in children.

Case presentation: A 23-month-old boy was brought to the pediatric allergy immunology clinic as a referral from a pediatrician with complaints of lump on right preauricular region, which was redden and painful, feels warm, and difficulty opening mouth. There were also multiple small nodules in peri anal area. There was fever for 1 week before admitted, accompanied by a runny nose with clear secretions with no cough. Fever already resolved at presentation. Tonsils are enlarged to T3/T4 without hyperemic nor injection. The presence of fever, conjunctivitis and cracked lips mimicking Kawasaki disease, but electrocardiography and echocardiography were normal. The MISC panel was shown support for MISC, wherein CBC showed presence of lymphopenia, anemia, neutrophilia, and thrombocytosis. Other panel MISC like the erythrocytes sedimentation rate, quantitative CRP, D-dimer, and quantitative IgG SARS-COV-2 antibodies it was reported to be increased. The patient was treated with intravenous high doses methylprednisolone pulse 10 mg/kg, then tapered off before stopped. The lump was disappeared after the second dose of HDMP, and patient was discharged after 7 days of admission.

Conclusion: We reported a localized *Multisystem Inflammatory Syndrome* (MIS-C) treated with high dose methylprednisolone resulting in fast recovery.

Keywords: *children, localized multisystem inflammatory syndrome, high dose methylprednisolone, outcome*.
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INTRODUCTION

Global pandemic of coronavirus disease 2019 (COVID-19) firstly identified in adult patient in Wuhan, China, on December 2019 with cumulative cases amount 651,918,402 and 6,656,601 deaths worldwide.[1] Cases of COVID-19 have continued in children, included in Indonesia.[2,3] The pediatric of COVID-19 population is frequently characterized by milder symptoms and more favorable outcomes. Pediatric COVID-19 clinical and laboratory presentation may vary in all age group. In the early days of the pandemic, children were either asymptomatic or mildly symptomatic with fever and cough. Recovery is predicted in majority between 1 to 2 weeks and deaths are infrequent.[4–6]

In late April 2020, clusters of children in the Western hemisphere have presented with fever, gastrointestinal symptoms, and myocarditis symptoms, including coronary artery aneurysms (CAAs). It changed the presentation of clinical COVID-19 related manifestation with the emergence of multisystem inflammatory syndrome in children (MIS-C).[3,7,8] The first cases of infants were unknown of exhibited symptoms of Kawasaki disease (KD) or toxic shock syndrome (TSS), or represented a condition associated to the continuing COVID- 19 epidemic.[9]

Multisystem inflammatory syndrome in children cases emerged approximately 4–5 weeks on average after the peak prevalence of COVID-19 in each location.[10,11] Several systematic reviews have found that Afro-Caribbean, Latino/Hispanic, and Black children are more susceptible to MIS-C than children of other ethnicities.[12–14] To date, only 38 cases of MIS-C have been recorded in Asia.[13] Indonesia is severely hit by the COVID-19 pandemic and a case report of MIS-C has been reported showed MIS-C coinfection with severe, atypical dengue infection or MIS-C with a false-positive dengue serologic test resulting in death.[15] Another cross-sectional investigation in a tertiary referral hospital described MIS- C patients. Hypovolemic shock was the most prevalent kind of identified circulatory

failure. Almost half of patients amount suffered circulatory collapse responded favorably to fluid resuscitations.[16]

Multisystem inflammatory syndrome in children should be suspected if there is persistent fever without a clear clinical cause. Any child suspected of having MIS-C must also be evaluated for infectious and noninfectious causes. Any fever accompanied by worrying symptoms or coinciding with recent exposure to a person infected with COVID-19 should raise suspicions.[17] Matrisome activation and higher quantities of circulating spike protein were found in MIS-C, although there was no association with SARS-CoV-2 polymerase chain reaction (PCR) status upon admission. In MIS-C, transient expansion of TRBV11-2 T cell clonotypes was related with inflammatory markers and T cell activation.[18]

The characteristic of cytokine storms in MIS-C is represented by abnormality laboratory tests including hematologic conditions such as neutrophilia, lymphopenia, thrombocytopenia, and elevated inflammatory markers. Coagulation parameters as D-dimer and fibrinogen also increased.[19,20] Cardiac markers, such as Troponin, were also elevated and abnormality of INR, PT/aPTT. Imaging investigation showed abnormal chest radiograms including pulmonary opacities/infiltrates, lung edema, pleural effusion, cardiomegaly. atelectasis.[20] Echocardiography alteration including cardiac dysfunction presented a decrease in ejection ventricular fraction.

This disorder can have fatal consequences if not treated immediately. However, the result and its underlying mechanism remain unknown.[21] In this study, we report a case of localized MIS-C with a faster recovery outcome. This case report describes clinical outcome and examination results of localized MIS-C.

CASE PRESENTATION

A 23-month-old boy was referred by a pediatrician to the pediatric allergy immunology outpatient clinic due to suspicion of drug allergy. The patient experiences bumps and redness in the bump area. He also experiences redness in both eyes 1 week after swelling.

Patient experienced fever that had appeared since 27/11/2022 as high as 38.4 Celsius, a temperature that tends to occur at night until dawn. Fever was reported up and down with antipyretic (paracetamol) given 3 times 5 mL per time. There is no cough, but there is a runny nose with clear secretions and snoring while sleeping.

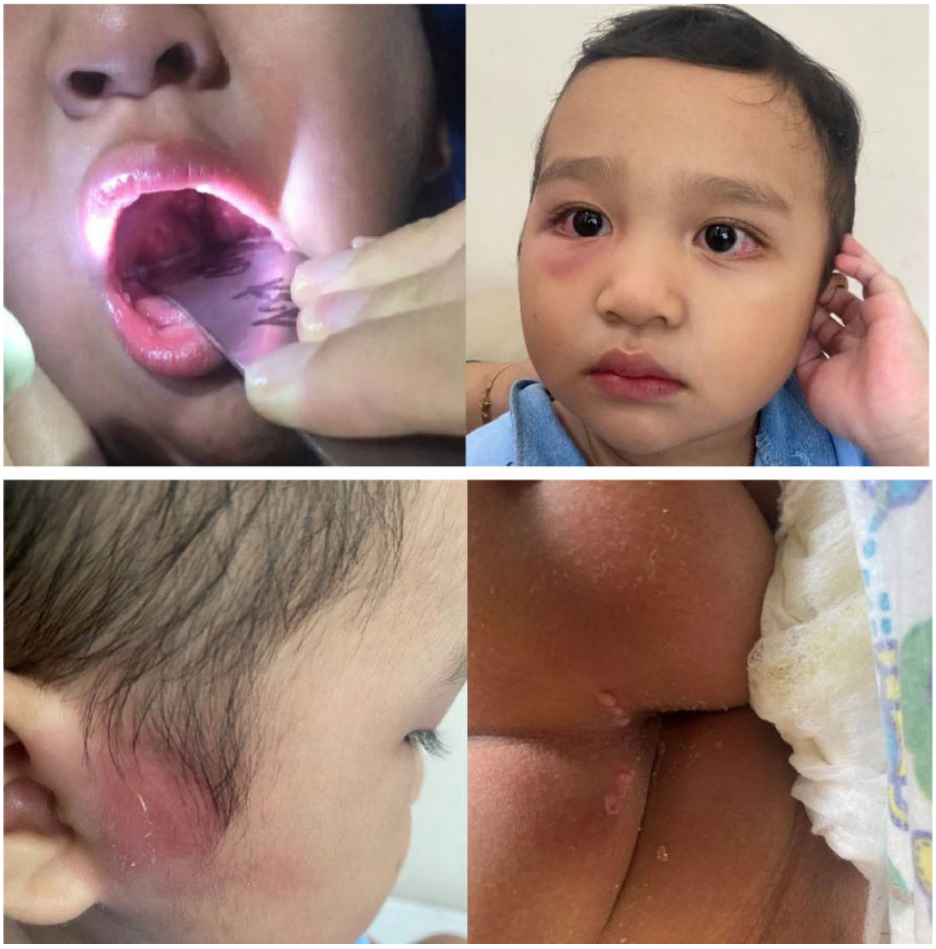

Figure 1. General examination of the patient.

The parents reported a lump that had appeared in front of the ear since 27/11/2022 with a hard consistency, felt warm with slight redness, and severely painful when touched which caused the patient difficulty to open mouth. The lump was reported to be getting bigger and redder, then the patient was taken to a pediatric specialist practice, and given Erysanbe® syrup 3.8 mL every 8 hours and proris syrup 3x5 mL. After being given the initial medicine, the swelling was reduced and there was no pain or fever. Swollen eyes have been reported to have appeared since 4/12/2022 accompanied by localized redness, itching, and discharge without pain. Despite the clinical presentation, patients are active and communicate well during physical examination.

The patient's appetite reportedly decreased since the illness. The stool was reported soft, accompanied by dregs, frequency of 1-2 times a day. No nausea and vomiting. The last urination at the children's polyclinic, with a large volume (XL size pampers), was clear yellow. The patient is the first single child with a birth weight of 3000 grams, was born spontaneously, and immediately cried. There is no history of drug and food allergies.

On generalist examination, the pulse 96 beats/minute, RR: 24 beats/minute, temperature: 36.7, and SpO_2: 97-98% in room air, weight 15 kg (weight/age 2-3 SD) and height of 90 cm (height/age 2-3 SD) and weight/height: 2-3 SD, both sclera were redden with clear border from the healthy area and there was edema of right upper and low eyelid. There was a lump on the right preauricular region, redness, no pain, felt warm, no secretions. Tonsils are enlarged to T3/T4 without hyperemic nor

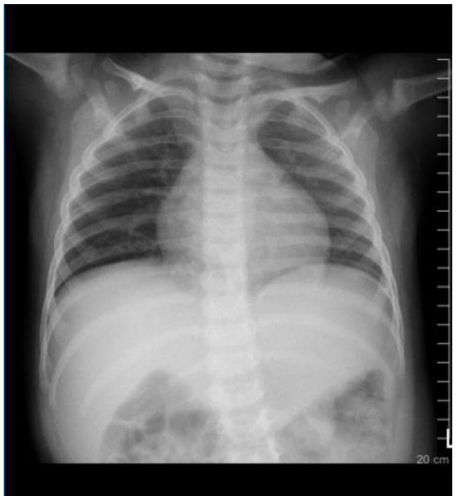

Figure 2. Plain chest X-ray.

injection. Lips are dry and cracked. Chest and abdomen were normal, but anal area showed multiple linear nodules. Upper and lower extremities were normal.

Based on multiple variations of involvement, MISC was suspected and the MISC panel was withdrawn. With clinical suspicions in the form of MISC, right preauricular region abscess, and obesity. The patient underwent complete blood count, blood smear, SGOT/PT, complete bilirubin, PT/APTT INR, D-dimer, BUN SC, SARS COV-2 antibodies, UL, and chest x-ray examination. Laboratory result shown a decrease in lymphocytes (27.30%; normal range 30.00-64.30), RBC (3.87x106/uL; normal range 4.10-5.3), hemoglobin (10.10 g/dL; normal range 12.0- 16.0), HCT (29.40%; normal range 36.0-49.0), MCV (76.00 fL; normal range 78.00-102.00), accompanied by an increase in neutrophils (60.10%; normal range 18.30-47.10), monocytes (7.50%; normal range 0.00-7.10), neutrophils ($7.06x10^3$/uL; 1.10-6.60), as well as a very high increase in platelets ($966.00x10^3$/uL; normal range 140-440).

The blood smear showed a form of poikilocytosis (ovalocytes) in erythrocytes. The leukocyte picture is normal, but there is an increase in the number of platelets greatly increasing, the erythrocyte sedimentation rate increased (101.0 mm/h; normal range <20) and quantitative CRP increased (29.50 mg/dL; normal range <5). On examination of the quantitative IgG SARS-COV-2 antibodies it was reported to be increased (126.3 AU/mL; non-reactive if <50). There was also a decrease in total bilirubin (0.20 mg/dL; normal range 0.3-1.2), creatinine (0.43 mg/dL; normal range 0.72-1.25), accompanied by an increase in D-dimer (3.34 ug/mL; normal range <0.5). Plain chest X-ray was carried out, which showed normal cardiac and lung impressions, as shown in the following figure.

Based on clinical manifestation of both cracked lips and the lesion on anal area as well as obesity, differential diagnosis of Kawasaki disease was also considered hence consultation to cardiology division was carried out. ECG results show sinus tachycardia. ECG results showed normal limits, which rules out the possibility of Kawasaki disease.

The patient was treated with intravenous administration of high doses of methylprednisolone (10 mg/kg equals to 150 mg). The preauricular abscess was improved after single 10 mg/kg methylprednisolone, hence the methylprednisolone was tapered off to intravenous 5 mg/kg methylprednisolone (equals to 75 mg), then further tapered off to intravenous methylprednisolone 2 mg/kg (30 mg) methylprednisolone 1 mg/kg (15 mg), intravenous methylprednisolone 0.5 mg/kg (7 mg) every single day. The route was switched to oral whe the dose achieved 4 mg and continuously tapered off until 2 mg and then stopped. The patient adapted to the treatment regimen and no additional complaint was reported hence discharged when oral methylprednisolone was started.

DISCUSSION

Multisystem Inflammatory Syndrome in Children (MIS-C) was first given the terminology of Paediatric Multisystem Inflammatory Syndrome Temporally Associated with COVID-19 through findings by the Royal College of Paediatrics and Child Health (RCPCH) in the United Kingdom.[22] Since, it has been more widely referred to as MIS-C due to its prominent use by the Center for Disease Control and Prevention (CDC) and the American College of Rheumatology (ACR).[23,24] MIS-C is a relatively complex and incapacitating collection of illness with a widespread distribution across different organ systems, proposed to be induced by a cytokine storm that occur two to four weeks after the onset of COVID- 19 infection.[23,25]

MIS-C in general was severe, but in our case was mild. This mild presentation is probably the ability of the immune system to localize the inflammation process preventing it from spreading systemically. The ability to localize the inflammation process was shown in the form of abscess and localized sharp border conjunctivitis. The cracked lips conjunctivitis, and fever, with perianal lesion was mimicking Kawasaki disease. Each of the components, however, was not classic such as clear border of conjunctivitis, nodule form of perianal lesion, leading the consultation to cardiologic as form of diagnosis exclusion. This process was supported by normal ECG and echocardiography. The clinical presentation and symptoms of Kawasaki Disease and MIS-C are very similar, making Kawasaki disease to be listed on the differential diagnosis whenever the presentation appropriate.[26]

Common clinical manifestations of MIS-C may be categorized into systemic inflammation, hematologic manifestations, cardiopulmonary symptoms, gastrointestinal symptoms, mucocutaneous disorders, renal symptoms, and neurologic manifestations.[24,27,28] Symptoms appearing in MIS-C is highly similar to those seen in Kawasaki disease (KD) and some characteristics of toxic shock syndrome (TSS) may be present in some pediatric patients.[10,29–31] The pattern of fever accompanied by conjunctivitis in patients can be similar to that of Kawasaki disease. The point of difference between MIS-C and KD or TSS is the intensity of inflammatory or cytokine storm which was found to be higher in MIS-C. Some differing clinical features also include age and gastrointestinal symptoms, such as abdominal pain, diarrhea, and vomiting. A higher percentage of cardiovascular collapse is found in children with MIS-C.[32]

The most common presentation in MIS-C is fever with an average maximum temperature (T_{max}) of 39.4 ± 0.7 °C with mean duration of 11.6 ± 5.7 days based on a study by Sokunbi *et al.* in 2021.[33] Other systemic inflammation symptoms may also be present, namely myalgia, tachycardia, hypo- or hyper- perfusion, and lymphadenopathy.[28]

Hematologic manifestations may be present in the form of anemia, thrombocytopenia, and thrombocytosis.[33] Cardiopulmonary symptoms include chest pain, respiratory distress, left-heart dysfunction, heart failure, pericarditis, hypertension, peripheral edema, coronary symptoms, and conduction disorders.[24,33,34] The predominance of cardiac presentation is significant in MIS-C, as opposed to KD.[35] Gastrointestinal disorders are important in the diagnosis of MIS-C and has been reported to be abdominal pain which may be so severe that appendicitis was suspected, vomiting, diarrhea, and some that are not as common being pancreatitis, hepatomegaly, and acute liver failure.[11,33,36–39] Mucocutaneous lesions are also common in MIS-C patients and range from oral lesions (ulcers, cheilosis, oral erythema, strawberry tongue), non-suppurative conjunctivitis, pharyngitis, palmar and plantar erythema to generalized desquamating rash. Renal symptoms may manifest as oliguria with proteinuria and/or hematuria as presentations of acute kidney injury, dysuria, periorbital edema, and ascites.[33] Neurologic manifestations may also be an important differentiator between MIS-C and KD.[24] In MIS-C, patients often present with headache, change in mental status (restless, agitated, confused), meningism, focal deficits, and convulsions.[24,40–42] In this case, patient first presented with fever of 38.4 °C mostly present during nighttime until dawn, runny nose, and a hard lump on the right pre auricular region with tenderness that is warm to the touch, with edema without erythema. The patient's right eye became swollen a week after the first admission with redness, itchiness, and eye discharge. Patient then developed auricular swelling and cracked bright red lips.

Children who are overweight or obese are in higher risk of MIS-C due to the suggested mechanisms including accumulation of inflammatory cells in adipose tissue, adipose tissue-associated cytokines being proinflammatory, higher number of SARS-CoV-2 binding receptors in adipose cells, and impaired respiratory functions.[43–46] In this case, patient's weight was above normal in relation to both age and height. Patient was a 22 months old male who weighed 15 kg and was 90 cm tall, placing the patient at 2 -3 SD according to the body weight/age and body weight/body height table issued by the Indonesian Ministry of Health.

The diagnosis of MIS-C is not guided by one specific definitive test, instead it varies based on the guidelines underlying the proposed case boundaries. Boundaries for case definition according to World Health Organization (WHO) is children less than 19 years of age with history of more than three days of fever and a minimum of two of the following: rash, bilateral non-purulent conjunctivitis, or signs of inflammation in the mucocutaneous system (in the mouth, on hands or legs); hypotension or shock; pericarditis, valvulitis, dysfunction of the myocardium, or coronary abnormalities (including increased troponin/NT-proBNP level or abnormalities in the echocardiography result); coagulopathy (PT, PTT, elevated D- dimers); acute gastrointestinal symptoms (abdominal pain, diarrhea, vomiting); increase of inflammatory markers (ESR, CRP, procalcitonin); no clear evidence of pathogen that might cause inflammation (bacterial and staphylococcal sepsis, streptococcal shock syndrome); and evidence of SARS-CoV-2 infection (RT-PCR, antigen or serology testing) or exposure to a patient diagnosed with COVID-19.[47]

According to RCPCH 2020 guidelines, diagnosis of MIS-C may be made for a child experiencing fever, inflammation (neutrophilia, increased CRP, lymphopenia), evidence of one or more organ system(s) dysfunction (cardiac, respiratory, gastrointestinal, renal, nervous system disorder, or shock), and additional presentations (clinical, electrocardiogram, laboratory, imaging). It also mentioned, "a complete and partial picture of Kawasaki Disease".[22]

Diagnosis made using the CDC case boundaries requires an individual younger than 21 years old presenting with fever, inflammation evident by laboratory testing results, evidence of serious clinical presentations requiring inpatient treatment in the hospital with involvement of two or more organ systems (hematologic, cardiac, respiratory, renal, gastrointestinal, dermatologic, or neurologic), with the presence of evidence of SARS-CoV-2 infection (RT-PCR, serology, antigen testing, or exposure in four weeks before manifestation of MIS-C), and the absence of other possible differential diagnoses.[23]

Some guidelines require all cases to show laboratory findings including fibrinogen abnormalities, high CRP, high D-dimer, high ferritin, lymphopenia, low neutrophils, hyponatremia, hypoalbuminemia, and no evidence of infection by specific microorganisms. Other laboratory findings that might be reported, namely anemia, neutrophilia, thrombocytopenia, coagulopathy, elevated troponin, elevated IL-6 and IL-10, proteinuria, elevated ferritin, elevated CK and LDH, and transaminitis.[14,22–24,38,48–51] The cases were recommended to be screened for infection due to pathogens, such as bacteria (Staphylococcus, Streptococcus which also cause TSS) or virus (enterovirus-associated myocarditis) through blood culture and viral markers.[22] Imaging such as chest radiographs may show pleural effusion, lung consolidation, pneumonic changes, interstitial pneumonitis, and cardiomegaly. Abdomino-pelvic ultrasound may detect presence of ascites, hepatomegaly, splenomegaly, and renomegaly.[33] Patients also had echocardiogram done with findings include coronary dilatation and/or aneurysm, pericardial effusion, and atrioventricular valve regurgitation.[52] Electrocardiogram results also reported certain features on MIS-C patients, namely prolonged QTc interval, non-specific ST/T changes, reduced QRS voltage, dysrhythmia, and first-degree atrioventricular block.[48,53] In this case, patient underwent some laboratory testing namely complete blood count (CBC), blood smear, liver function test, PT/APTT INR, D-dimer, BUN SC, SARS-CoV-2 antibody, urinalysis, and imaging in the form of thorax radiography. CBC showed presence of lymphopenia, anemia (decreased number of RBC and hemoglobin), decreased HCT, decreased MCV, neutrophilia, and thrombocytosis. Blood smear examination highlighted a form of poikilocytosis (ovalocytes) in RBCs. Blood smear analysis reported that the patient had normocytic normochromic

anemia, increased sedimentation rate and quantitative CRP. IgG SARS-CoV-2 was found to be increased from the normal value. A decrease in total bilirubin, creatinine, and increase in D-dimer were also found. Chest radiograph showed normal cardiac and pulmonary impressions.

The goals that physicians try to reach in the management of MIS-C are the reduction of systemic inflammation, restoration of organ function, and reduction of long-term sequelae and death. Many of the current treatment guidelines recommended the use of standard KD therapies, namely intravenous immunoglobulin (IVIG) and high dose corticosteroids as MIS-C's first line of therapy due to their highly similar nature.[53–55] Management of MISC involve IVIG and methylprednisolone with range of variation depend on disease severity. Patients with severe MIS-C and hypotension who have been brought to the PICU should be given IVIG together with methylprednisolone as a treatment option.[56] Intravenous immunoglobulin as an infusion at dose 1-2g/kg over 12 to 24 hours may be given under careful supervision.[57,58] Steroid in the form of high dose intravenous methylprednisolone may be given at 10 mg/kg for two days. Prednisolone then may be given at 1-2 mg/kg daily for five to seven days then tapered down over the next week.[33] Immunomodulating agents such as IL-1 receptor antagonist (anakinra), IL- 6 receptor antagonist (tocilizumab), and TNF-a antagonist (infliximab) had also been given as adjunct therapy.[14,38,48,52,59]

High dose aspirin as antiplatelet may also be given at 30-60 mg/kg daily in four doses for five to seven days then reduced to 3-5 mg/kg daily single dose for 6 weeks or until the patient is discharged or the inflammatory picture has improved.[22–24,49,60] The administration of high dose steroid and aspirin called for intravenous Omeprazole for gastric protection.[33]

In this case, patient was given Paracetamol syrup 4mL each for three doses daily, Erysanbe syrup 3.8mL every 8 hours, and Proris syrup 5mL each for three doses daily as supportive treatment for their fever and pre auricular swelling by a pediatrician before the diagnosis was established (27/11/2022). Patient was then prescribed Optiflox eye drops 4 x 1 drops for both eyes, Lyteers eye drops 4 x 1 drops, and was given as supportive treatment for the suspected conjunctivitis (06/12/2022). Intravenous immunoglobulin could not be given due to the high scarcity and price point of the substance in Indonesia. Methylprednisolone was then administered in high dose, 10 mg/kg (08/12/2022), followed by intravenous administration of 15 mg, 1 mg/kg methylprednisolone (10/12/2022); 7 mg intravenously, methylprednisolone 0.5 mg/kg (11/12/2022); 7 mg intravenously, methylprednisolone 0.5 mg/kg (12/12/2022), and 4 mg orally (13/12/2022). Patient was then discharged eight days after initial admission and got home medication methylprednisolone 2mg and then stopped.

The outcome of the patients was excellent in early recognized cases and prompt management was instituted. Mortality of MIS-C in previous study reach almost 6% of all cases with each median of hospital stay and ICU stay are 9 (7–13) and 7(4–9.5) days.[61] This is similar to another study reported that there was a 9 % mortality rate in their study with the group that did not survive had the disease for a longer period of time before being admitted to the PICU.[62] Our case outcome was excellent in short period with length of stay eight days. This is probably explained by early recognition and prompt management.

CONCLUSION

We reported a localized multisystem inflammatory syndrome with good outcome presumably related to early recognition and prompt management. A 23- month-old pediatric patient came to the pediatric allergy immunology polyclinic as a referral from a pediatrician with complaints of fever. Next, the MISC panel was examined with clinical suspicions in the form of MISC, right preauricular region abscess, and obesity. In addition, the pattern of fever accompanied by conjunctivitis in patients can be similar to that of Kawasaki disease. On blood smear examination, it shows that there is a form of poikilocytosis (ovalocytes) in erythrocytes. The leukocyte picture is normal, but there is an increase in the number of platelets greatly increasing with a normal distribution. Based on blood smear analysis, it was reported that the patient had normocytic normochromic anemia with thrombocytosis. The patient was treated with high doses of 10 mg/kg methylprednisolone, followed by intravenous administration of 15 mg, 1 mg/kg methylprednisolone; 7 mg intravenously, methylprednisolone 0.5 mg/kg; and 4 mg orally, continuous with 2mg and then stop. In the end, complaints of colds, and swelling of the ears and eyes were reported to decrease. Examination of vital signs and generalist status also showed normal limits. The patient is declared to be on an outpatient basis (home).

ETHICAL CLEARANCE

Patient approval was obtained in this study, and ethics approval was fulfilled by the International Committee of Medical Journal Editors (ICMJE).

CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

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AUTHOR CONTRIBUTIONS

The authors confirm sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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