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Case report

Multisystem inflammatory syndrome in children following SARS-CoV-2 infection: A case report

Phuong Ha Nguyen[a], Nguyen Nguyen The Phung[b*], Vinh Than Thanh[a], Manh Van Ngo[a], Thien Thanh Mai[a], Linh Thi Dieu Tran[a], Thanh Viet Nguyen[a], Hung Phi Tran[a], Hieu Sy Cao[a], Thuc Thanh Tran[b]

[a]*Thu Duc City Hospital, Thu Duc city, Ho Chi Minh city, Vietnam;*
[b]*University of Medicine and Pharmacy at Ho Chi Minh city, Ho Chi Minh city, Vietnam.*

Received December 28, 2021: Revised January 25, 2022: Accepted January 25, 2022

Abstract: ***Introduction:*** COVID-19 in children has a diverse clinical presentation, most of which is asymptomatic or mildly symptomatic. In addition, after 2-6 weeks of being infected with COVID-19, children may have the multisystem inflammatory syndrome in children (MIS-C), which is rare but serious condition, death has also been reported despite active treatment. We describe a severe clinical case of MIS-C treated at our hospital in the early stage of the 4th wave of COVID-19 in Vietnam. ***Case report:*** A six-year-old boy admitted to Thu Duc City Hospital on August 27th, 2021. He had a history of COVID-19, which was diagnosed by a positive RT-PCR SARS CoV-2 test on July 24th, 2021. He had no symptoms and was concentrated quarantine with his family. He was discharged on August 12th, 2021. Four weeks after SARS-CoV-2 infection, he had symptoms such as sustained fever (5 days), stomachache (6 days), erythema multiform (8 days), eye and lip swelling (7 days), edema of hands and feet (10 days), dyspnea (5 days), hepatomegaly and shock. After then, he was diagnosed with MIS-C and treated with intravenous methylprednisolone 2 mg/kg/day (3 days), then tapered 1 mg/kg/day (5 days), maintained with prednisone 1 mg/kg/day for 14 days. The patient had no clinical symptoms, was discharged after 14 days of treatment, and continued treatment with aspirin 3 mg/kg/day and prednisolone 1 mg/kg/day. ***Conclusion:*** The MIS-C manifestation following SARS-CoV2 infection needs prompt attention and treatment. Intravenous immunoglobulin plays an important role in treatment. However, when intravenous immunoglobulin is not available where limited resources, early appropriate use of methylprednisolone may be beneficial.

Keywords: MIS-C; SARS-CoV-2; COVID-19; case report.

1. INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused coronavirus disease of 2019 (COVID-19), was first identified in China on late 2019 [1]. The virus then quickly spread into a global pandemic. Children are also subject to infection with COVID-19. The delta variant of SARS-CoV-2 caused the fourth wave of epidemics in Vietnam with 687.063 cases and 17.090 deaths up to September 19th, 2021. There are about 15.000 infected children in Ho Chi Minh City and the mortality rate of 0.1%. Children infected with SARS-Cov2 are mostly asymptomatic or mild. However, in some cases, children may develop a multisystem inflammatory syndrome that presents clinically as Kawasaki syndrome (KD) [2].

Unlike typical KD group, MIS-C mainly affects children of an older age group [3-7]. Symptoms of KD are observed in many patients with MIS-C; however, gastrointestinal symptoms, such as anorexia, nausea, abdominal pain, and

*Address correspondence to Nguyen Nguyen The Phung at the University of Medicine and Pharmacy at Ho Chi Minh city, Ho Chi Minh city, Vietnam; E-mail: nguyenphung@ump.edu.vn

DOI: 10.32895/UMP.MPR.6.3.S8

diarrhea were more common in MIS-C than in KD, as shown in 100% of cases in the French study [3-6]. In cases of MIS-C with symptoms similar to those in KD, treatment and follow-up should be quite similar to those in known KD guidelines, such as intravenous immunoglobulin (IVIG) 2 g/kg and low dose aspirin 3-5mg/kg/day [8]. The current medical literature shows that IVIG and methylprednisolone are the mainstays of treatment for MIS-C [8-10]. However IVIG is not always available, especially in low-middle income countries like Vietnam and in remote and isolated areas. Therefore, treatment with methylprednisolone alone in the presence of heart damage is a real challenge.

We report a case of MIS-C with cardiac damage following SARS-CoV-2 infection at Thu Duc City Hospital. Initially, septic shock was diagnosed because it was one of the first MIS-C cases in Vietnam. This case was successfully treated with methylprednisolone alone.

2. CASE REPORT

A six-year-old boy was admitted at Thu Duc City Hospital on August 27th, 2021 for abdominal pain and fever. Three days before admission to the hospital, he had abdominal pain around the navel, intermittent dull ache, not spreading, no pain relief, no vomiting, no bowel movements, sustained fever of 38 - 39ºC for 2 days. The abdominal pain was gradually increased with anorexia, so he was hospitalized. He was completely healthy and had never been hospitalized before.

Table 1. Symptoms of the patient (date of onset and duration of symptoms)

Physical symptoms	Lasting (days)	Date of appearance	Description
Fever	5	Day 1st	Sustained fever
Respiratory failure	5	Day 5th	Progress is getting worse
Rash	7	Day 3rd	Erythema multiform
Swollen eyes and lips	8	Day 3rd	Swollen eyelids, edema around lips
Stomachache	6	Day 1st	Progressing navel pain
Swollen hands and feet	10	Day 3rd	Soft edema, no pain

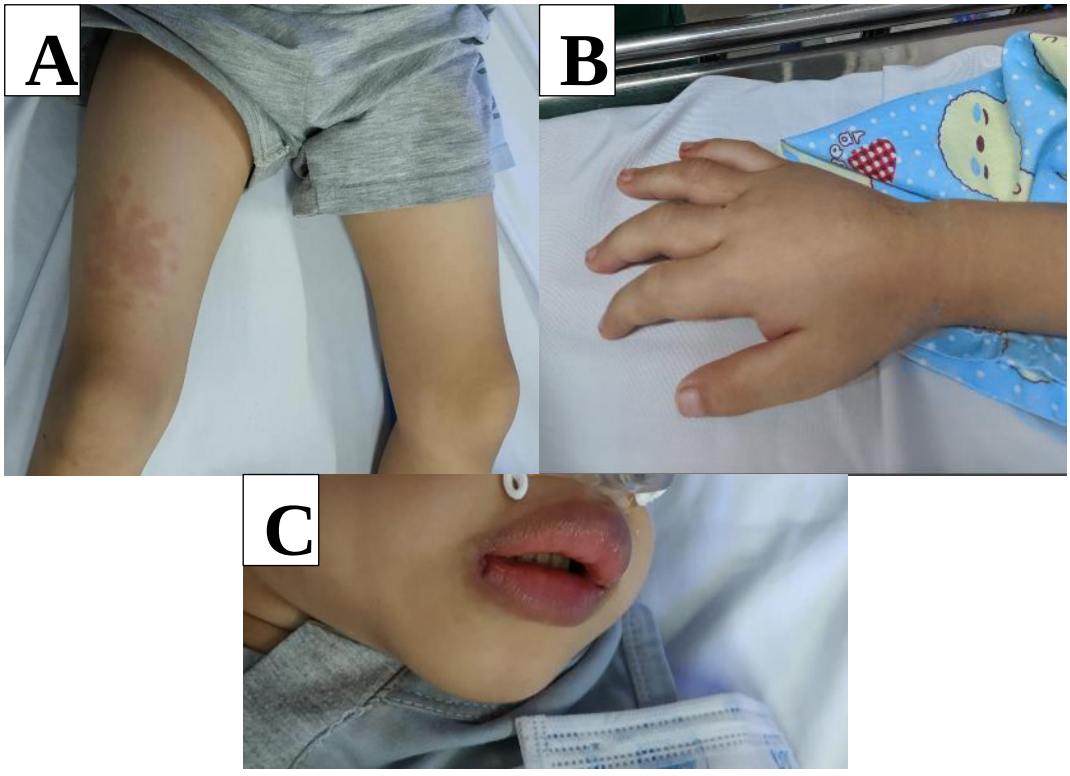

Figure 1. Clinical symptoms of the patient. **A)** Erythema papule of the right thigh. **B)** Dorsal edema of the hand. **C)** Red and swollen lips

At the time of admission, he had a continuously high fever of 39oC, swollen tonsils, red throat, intermittent abdominal pain around the navel, loose yellow stools, twice a day without blood and mucus, mild eyelid edema, lip swelling, dorsal edema of the hands and feet, erythema 4x5 cm on the front and back of the right thigh, scattered in the abdomen (Table 1, Figure 1). Physical examination noted the symptoms as shown in the Table 2. Laboratory tests showed a hyperinflammatory condition (Table 3). Coronavirus real-time PCR was negative, Dengue NS1 quick test and Dengue IgM-IgG ELISA test were also negative too. Abdominal ultrasound showed lymphadenitis right hip mesentery. The patient was preliminarily diagnosed with sepsis accompanied by acute tonsillitis and treated with antipyretic, antibiotics included: ceftazidime 150 mg/kg/day, amikacin 15 mg/kg/day.

Table 2. Physical examination and progression of the patient

Physical symptoms	Date of admission (Day 3rd)	Day 5th	Day 15th
AVPU	A	A	A
Temperature (Celsius)	41	38	37
Pulse (beats per minute)	120	140	95
Blood pressure (mmHg)	100/60	76/50	100/60
Breathing rate (rate per minute)	30	46	24
SpO_2 (%)/ventilation	98/ room air	90/oxygen cannula →98/NCPAP	98/ room air
CRT	<2s	2s	<2s
Eye	Eyelid swelling	Eyelid swelling	Asymptomatic
Mucosa	Red and swollen lips	Red and swollen lips	Asymptomatic
Skin	Erythema multiforme	Erythema multiforme	Asymptomatic
Abdominal	Pain around umbilicus, liver enlargement 2 cm below costal margin P	Pain around umbilicus, liver enlargement 2 cm below costal margin P	Asymptomatic
Extremities	Swollen hands and feet	Swollen hands and feet	Asymptomatic

Table 3. Showing laboratory parameters and progression of the patient

Parameter	Date of admission (Day 3rd)	Day 5th	Day 15th	Standard value
WBC (10^9/L)	5.2	7	6.2	4.5-13.5
NEU (10^9/L)	4	5.2	2.2	1.5-8.5
LYM (10^9/L)	0.2	0.9	2.4	1-6.5
MONO (10^9/L)	0.5	0.4	1.1	0-1.0
EOS (10^9/L)	0.5	0.4	0.2	0-0.4
HGB (g/dL)	10.4	3	10.2	11.5-13.5
HCT (%)	30.6	27	32.6	
PLT (10^9/L)	98	91	405	150-450
Creatinine (mg/dL)	0.5	0.4	0.3	0.5-1.1
GOT (U/L)	59	37	29	< 40
GPT (U/L)	40	44	28	< 37
Na (mmol/L)	122	120	131	135-145
K (mmol/L)	3.7	3.1	2.4	3.5-5.5
Ca (mmol/L)	0.9	1.0	1.1	1.1-1.40
Ferritin (ng/ml)	-	495.7	277.2	12-300
CRP (mg/L)	170.75	325.24	4.42	< 6
Procalcitonin (ng/mL)	-	73.25	-	< 0.25
Troponin Ths (ng/L)	-	54.07	36.65	< 14
NT Pro-BNP (pg/mL)	-	35000	-	< 125
Pro-BNP (pg/mL)	-	35000	22871	< 125
HCO3- (mmol/L)	-	16.2	-	22-30
Lactate (mmol/L)	-	2.1	-	< 2
Albumin (g/L)	-	32.34	-	35-50
PTs	-	15.8	13.3	9-15
PT%	-	79.1	94	70-100
INR	-	1.32	1.08	0.9-1.25
APTT(s)	-	41.2	32	25-35
Fibrinogen (g/L)	-	3.7	-	
SARS-CoV-2 RT-PCR	Negative	Negative	-	
Echocardiography	- Day 6: Normal left ventricular systolic function EF = 58 % Mitral valve regurgitation 1.5/4. Tricuspid regurgitation 1.5/4, PAPs = 20 mmHg Small amount of pericardial effusion - Day 11: Normal left ventricular systolic function EF = 58 % Decreased contractility of the interventricular septum.			
Abdominal ultrasound	Dilated bowel loops, thickened walls, fluid retention, increased peristalsis, mesenteric lymph nodes around the umbilicus.			
Abdominal CT scan	Hepatomegaly 12 cm in diameter, small amount of peritoneal effusion, no appendicitis, small bilateral pleural effusion			
Blood culture	Not detected			
ECG	ST elevation in leads II, III, aVF			
Urinalysis	Normal			
Stool examination	Normal			

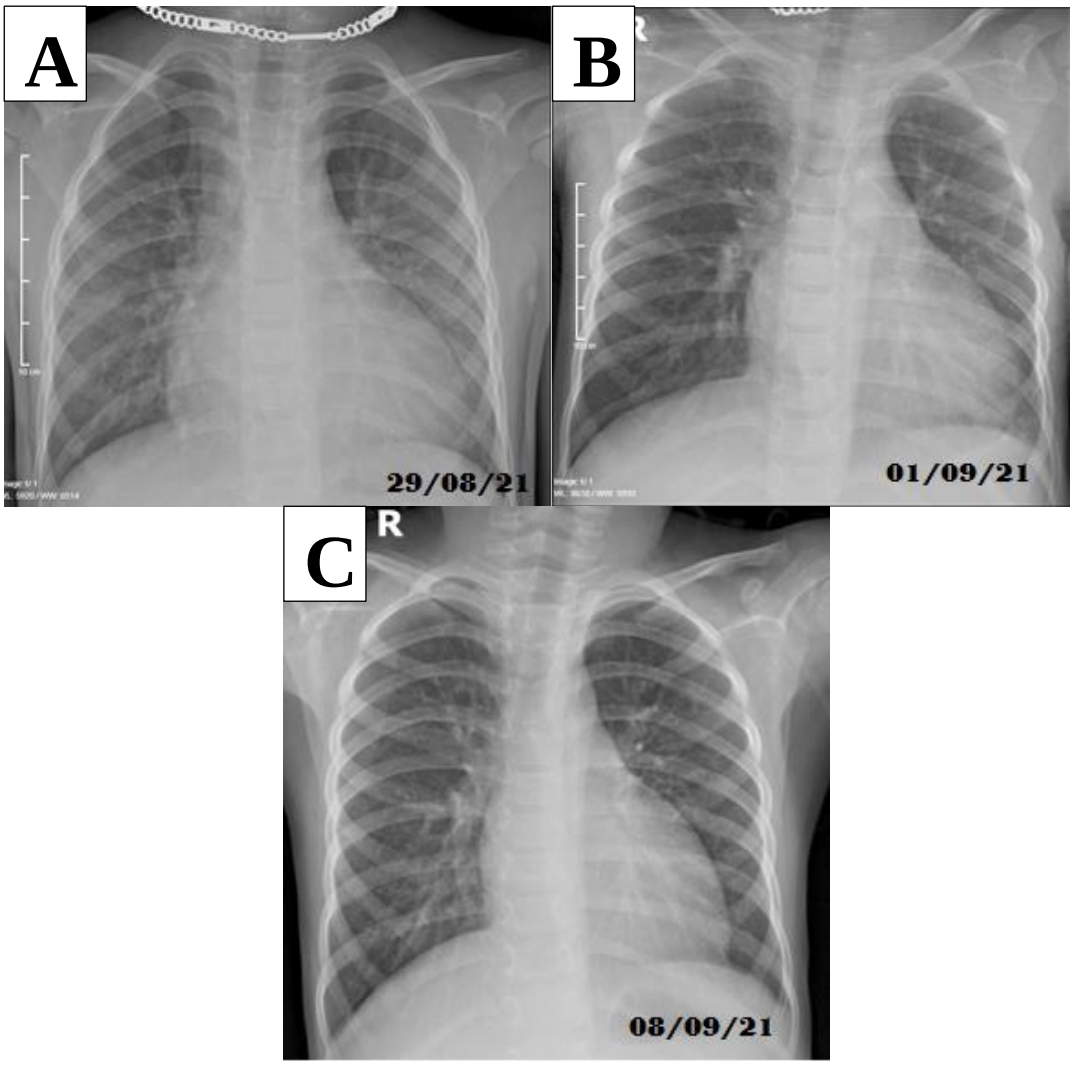

Figure 2. Pulmonary radiography progression. **A)** Heterogeneous opacities on both sides of the lungs with enlarged heart. **B)** After 2 days of anti-inflammatory treatment, the cardiothoracic index decreased. **C)** Normal chest x-ray

Two days after admission, the patient still had fever, abdominal pain around the navel increased, the liver was enlarged 2 cm below the right lower quadrant, red swollen lips, eyelid edema. Then he had vital signs of shock with blood pressure of 76/50 mmHg, pulse rate of 140 per minute, extremities warm, CRT 2s, respiratory rate of 46 per minute and intercostal contractions. Laboratory test showed a strongly inflammatory response (CRP 325.24 mg/l, procalcitonin 73.25 ng/ml, ferritin 495.7 ng/ml); metabolic acidosis with increased anion gap, elevated lactate (18.9 mg/dL), elevated NT pro BNP (35000 pg/ml) and troponin Ths (54.07 pg/ml) (Table 3). Abdominal CT scan showed hepatomegaly 12 cm in diameter, small amount of peritoneal effusion, no appendicitis; chest X-ray had recorded opacity lesion on both sides of the lung (Figure 2). The patient was diagnosed with septic shock - severe pneumonia that blood culture was negative and treated with oxygen therapy via cannula followed by NCPAP, normal saline infusion 50 ml/kg/1h45, vasopressors include noradrenaline 0.3 g/kg/min, adrenaline 0.3 µg/kg/min, dobutamine 10 µg/ kg/min; antibiotics changed to meropenem 120 mg/kg/day, vancomycin 60 mg/kg/day. Despite being treated as aggressively as above, the patient's hemodynamic status is still unstable with blood pressure 85/60 mmHg, pulse rate of 140-150 per minute. Fortunately, when we took a closer look at his medical history, we found that he had a history of COVID-19, which was diagnosed by a positive RT-PCR SARS CoV-2 test on July 24th, 2021. He had no symptoms, was concentrated quarantine with his family in COVID-19 isolation area at The Dormitory of The Vietnam National University of Ho Chi Minh City and was discharged on August 12th, 2021. After expert consultation and department discussion, we confirmed the diagnosis of MIS-C following SARS-CoV-2 infection and decided to administer intravenous methylprednisolone at a dose of 2 mg/kg/day in two divided doses and enoxaparin subcutaneously 0.5 mg/kg twice a day. Treatment results showed that the condition improved and maintained stable hemodynamics after the first dose of methylprednisolone. After 10 hours of shock management, the patient's vital signs improved with pulse rate of 100-110 mmHg, blood pressure of 110/72 mmHg; noradrenaline and adrenaline vasopressors were stopped, and dobutamine was maintained at 5 µg/kg/min.

In the following days of treatment: The patient's vital signs got back to the normal range, vasopressors and oxygen

therapy was wean off. Other symptoms, such as fever, abdominal pain, erythema, swelling of the lips and edema of the eyelids, or edema of the hands and feet, recovered and disappeared. Further treatment was intravenous methylprednisolone 2 mg/kg/day for 3 days following 1 mg/kg/day for 5 days; then maintain oral prednisolone 1 mg/kg/day for 4 days, enoxaparin subcutaneously 0.5 mg/kg twice a day for 12 days, aspirin 3 mg/kg/day for 9 days. He was discharged on the 16th day of the illness (September 9th, 2021), and continue to take prednisolone 1 mg/kg/day plus aspirin 3 mg/kg/day as an outpatient therapy, see a follow-up appointment 2 weeks later.

3. DISCUSSION

This is the first case of MIS-C treated at Thu Duc City Hospital and in the southern part of Vietnam from starting of the COVID-19 pandemic. The diagnostic of MIS-C, in this case, was based on the WHO case definition (WHO 2020) [2]. The WHO criteria can easily be applied for diagnosis of MIS-C in low-resource settings if all the options in the criterion are followed. Cardiac injury is one of the critical features in the diagnosis and treatment of MIS-C [5-7]. In this case, we monitored the progress of cardiac enzymes (Troponin Ths, NT pro-BNP, pro-BNP), performed echocardiography every day to monitor this complication (Table 3).

Bacterial infection cannot be excluded due to the high prevalence of bacterial infections in Vietnam, high inflammatory response, and abnormal abdominal ultrasound and chest x-ray. However, the use of antibiotics for 2-3 days did not show improvement in either the clinical or inflammatory status of the patient. Some children with MIS-C may experience distributive shock, with reducing vessel myogenic tone and cardiac contractility. Epinephrine or norepinephrine are the preferred vasopressors for shock management. Milrinone may also be helpful in cases of severe reduction in left ventricular contractility [9].

The use of glucocorticoids as a sole treatment option in under-resourced settings has also been reported by Ahmed et al (2020) [10] mentioned in their report. The favorable outcome with glucocorticoid alone in this patient is consistent with that reported by Riphagen et al (2020) for cases in the UK [4]. For patients with cardiovascular damage, a combination of glucocorticoids and IVIG should be used [9, 11-15]. However, IVIG was not available during social distancing times, it is more difficult to transfer serious patients to a higher facility. We monitored the patient till hospital discharge and re-examination showed no abnormalities afterward. Evidence for IVIG therapy was proved in a series of studies, 70-95% of patients were treated with IVIG (with or without an alternative) and the majority of patients in the study group improved and restored cardiovascular function [4-7, 12, 13, 15-20]. For MIS-C graded moderate to severe, in addition to IVIG and aspirin, bolus of methylprednisolone is recommended - at a dose of 2 mg/kg/day in divided doses for three days; some life-threatening cases require a loading dose of 10-30 mg/kg/day (maximum 1 g)[14]. Compared with IVIG alone, the combination of corticosteroids and IVIG has shown more benefit across many studies, especially when heart injury [12, 13, 15]. The use of glucocorticoids for MIS-C was described in many case series. Corticosteroids were used in approximately 30 to 60 percent of patients in these series and most of them recovered rapidly [12, 13, 15, 16, 18-22]. Biological agents will be considered in cases of poor response to treatment with IVIG and glucocorticoids. The use of anticoagulants in MIS-C is unclear. In mild to moderate cases of MIS-C, prophylactic doses of enoxaparin (0.5 mg/kg every 12 hours) can be used, and in severe cases, therapeutic doses may be used [23, 24].

Conclusion

MIS-C is a rare and novel syndrome, occurring after SARS-CoV-2 infection. When a child had a history of COVID-19 admitted to the hospital with a high fever, gastrointestinal manifestations and skin rashes, and increased inflammatory response, the diagnosis of MIS-C should be considered. When intravenous immunoglobulin is not available, early appropriate use of methylprednisolone may be beneficial.

ETHICAL STATEMENT

The study was approved by the Ethics Committee of Thu Duc City Hospital. Patient's informations are provided for scientific purposes and are completely confidential.

FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors had a role in patient treatment, information collection, and completion of this manuscript.

ORCID ID

Phuong Ha Nguyen https://orcid.org/0000-0001-7967-6561
Nguyen Nguyen The Phung https://orcid.org/0000-0003-2444-1876
Vinh Than Thanh https://orcid.org/0000-0003-2540-9913
Manh Van Ngo https://orcid.org/0000-0001-5604-128
Thien Thanh Mai https://orcid.org/0000-0002-6662-1438
Linh Thi Dieu Tran https://orcid.org/0000-0001-7504-0574
Thanh Viet Nguyen https://orcid.org/0000-0001-8212-5314
Hung Phi Tran https://orcid.org/0000-0001-8512-9820
Hieu Sy Cao https://orcid.org/0000-0001-7323-6055
Thuc Thanh Tran https://orcid.org/0000-0001-8809-2699

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