Case Report

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A Pediatric Case of Leptospirosis Developed after COVID-19 Associated Multisystem Inflammatory Syndrome

Kiana Razavi[1], Leila Shahbaznejad[2], Azin Hajialibeig[2], Mohammad Reza Navaeifar[2], Ali Sadeghi Lotfabadi[2], Mohammad Sadegh Rezai[2]*

1. Student Research Committee, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran.
2. Pediatric Infectious Diseases Research Center, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran.

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ABSTRACT

While presentations of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were observed to be mild in children, multi-system inflammatory syndrome in children (MIS-C) has emerged as one of the most critical phenomena in the era of Coronavirus disease 2019 (COVID-19). We present an eight-year-old boy with prolonged fever, weakness, myalgia, arthralgia, oliguria, hematuria, hemoptysis, and periumbilical pain. With regards to the history of contact with SARS-CoV-2 four weeks prior to symptom onset and prominent gastrointestinal symptoms, MIS-C was highly suspected. Furthermore, based on the compatible symptoms and history of white-water rafting and exposure to contaminated soil two weeks prior to admission, leptospirosis was probable. Of note, Leptospirosis immunoglobulin M and COVID-19 immunoglobulin G were detectable. Lifesaving supportive measures, empirical antibiotic therapy, Remdesivir, Dexamethasone, and Prednisolone pulse therapy were prescribed. Afterward, gradual clinical improvement was shown. We aimed to report a case with MIS-C accompanied by severe leptospirosis to emphasize that in endemic areas of leptospirosis, considering the co-occurrence of MIS-C and other inflammatory disorders is crucial for multidisciplinary management.

Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been declared a pandemic by the World Health Organization (WHO) [1, 2]. Preliminary reports have highlighted that children with COVID-19 tend to have mild upper respiratory presentations, including fever, dry cough, and fatigue [3, 4]. However, in the spring of 2020, severe presentations of a novel entity were identified in a cluster of children. This situation was accompanied by multi-organ dysfunction resembling Kawasaki disease and Kawasaki disease shock syndrome, possibly correlated with SARS-CoV-2 [2, 5-7]. As more cases appeared globally, the Centers for Disease Control and Prevention (CDC) and WHO described these conditions as Multisystem Inflammatory Syndrome in Children (MIS-C) and

*** Corresponding Author:**
Mohammad Sadegh Rezai
Address: *Pediatric Infectious Diseases Research Center, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran.*
E-mail: *drmsrezaii@yahoo.com*

adolescents [8]. Subsequently, the case definition of MIS-C in critically ill patients was determined as prolonged fever for more than 24 hours, at least two organ dysfunctions, elevated biomarkers of inflammation without other obvious microbial etiologies, and evidence of COVID-19 [9].

Of importance, in endemic areas of leptospirosis, its severe multi-organ manifestations, namely Weil syndrome, can be similar to MIS-C. Leptospirosis is a widespread fatal zoonosis that typically presents as a nonspecific, acute febrile illness associated with fever, myalgia, and headache [10, 11]. Although leptospirosis causes less severe manifestations in children [12, 13], in this context, we aimed to report a severe presentation of leptospirosis in combination with MIS-C in a child in Northern Iran.

Case presentation

A previously healthy 8-year-old boy was admitted with a high-grade fever lasting 7 days. His general condition worsened progressively from the day before admission. He suffered from weakness, fatigue, loss of appetite, headache, photophobia, redness of the left eye for 5 days, myalgia, arthralgia, and periumbilical pain with nausea and vomiting. He had respiratory complaints, including cough and hemoptysis. The patient also complained of oliguria and cola-colored urine. The parents mentioned a history of contact with a confirmed case of COVID-19 four weeks ago, in addition to the consumption of unpasteurized dairy products, white-water rafting, and exposure to contaminated soil two weeks ago. During the illness course, he just received Ibuprofen, amoxicillin-clavulanate, and Acetaminophen. Upon admission, his general appearance was toxic, and he was irritable and restless. His weight and height were 28.5 kg (75th percentile) and 132 cm (75th percentile), respectively. On physical examination, he was febrile (39.6°C axillary), and other examinations revealed: pulse rate 128 beats/min, respiratory rate 31 beats/min, and blood pressure 90/45 mmHg. His skin was pale and icteric. Notably, petechiae and purpura were found. Unilateral sub-conjunctival hemorrhage and icteric sclera were observed. One centimeter posterior cervical lymphadenopathy was detected. The liver was palpated at 3-4 cm below the right costal margin. He had generalized tenderness on abdominal examination. Other physical examinations were unremarkable. The patient was hospitalized with a primary impression of sepsis and/or MIS-C. Empirical antibiotic therapy with cefotaxime and lifesaving supportive measures were initiated. Primary laboratory evaluations revealed elevated erythrocyte sedimentation rate (ESR), increased C-reactive protein, increased direct and total bilirubin, elevated urea, increased aspartate aminotransferase, increased ferritin, and lactate dehydrogenase. Additionally, impaired coagulation (PTT: 54 seconds), decreased serum albumin and total protein levels, lymphopenia, and severe anemia were noted. Electrolytes were within normal values except for sodium (128 meq/L). Urine analysis showed blood and ketone. Peripheral blood smear showed hypochromia, anisocytosis, and poikilocytosis. Furthermore, blood and urine cultures were performed, and the results were positive for leptospirosis (Table 1).

On admission, echocardiography showed mild left ventricular enlargement, mild decreased left ventricular ejection fraction, mild to moderate mitral and tricuspid regurgitation, trivial aortic and mild pulmonary insufficiency, dilated main pulmonary artery, and mild dilated inferior vena cava. CT scan showed mild bilateral pleural effusion with collapse consolidation and patchy ground-glass opacity of the left lower lobe (Figure 1). Based on the hematology consultation, cross-matched leukoreduced packed red blood cells were administered to treat his severe anemia. Nasopharyngeal reverse transcription polymerase chain reaction (RT-PCR) was positive for COVID-19. Additionally, leptospirosis immunoglobulin M (IgM) and COVID-19 immunoglobulin G (IgG) were elevated. According to the COVID-19 assays and compatible signs and symptoms, we initiated Remdesivir, dexamethasone, and prednisolone pulse therapy. Furthermore, dopamine and milrinone were administered to improve cardiac dysfunction.

The patient's condition deteriorated; he was still febrile and irritable. His vital signs revealed: blood pressure 100/50 mmHg, pulse rate 145 beats/min, respiratory rate 36 beats/min, and temperature 40°C. Finally, he was transferred to the pediatric intensive care unit (PICU). On the third day, abdominopelvic ultrasonography was normal, but mild fluid in the sub-hepatic and perisplenic areas was observed. Importantly, serologic findings showed that leptospirosis IgM titer was rising. The second echocardiography reported mild tricuspid and mitral regurgitation, decreased left ventricular ejection fraction, mild right pericardial effusion, normal coronary artery, and no pulmonary hypertension. Since D-Dimer was elevated significantly, imaging studies were performed to exclude thrombotic events. Enoxaparin and captopril were administered.

As the patient's condition improved gradually, on the 9th day, he was transferred from the pediatric intensive care unit (PICU) to the ward unit. The last echocardiography revealed mild left ventricular

Table 1. Laboratory results of the patient on different days.

	Days				
Variable	**1st**	**2nd**	**3rd**	**7th**	**12th**
Total WBC count, ×10³ µL	7.6	6.89	8.6	7.58	10.6
Neutrophil, %	76.8	68.5	77.7	51.4	48.7
Lymphocyte, %	14.1	15.4	17.8	33.1	39.6
Hemoglobin, gr/dL	5.7	7	9.1	9.6	11.5
Platelet count, ×10³ µL	314	318	426	549	612
ESR, mm/hr	42	40	-	12	26
CRP, mg/L	175	170	-	25	2
AST, U/L	47	37	35	31	-
ALT, U/L	20	18	12	21	-
Urea	41	24	19	38	-
Protein total, g/dl	5.8	4.9	-	-	-
Albumin serum, g/dl	3.1	2.8	1.4	3.5	4.5
D-Dimer	-	12458	-	1468	451
Bilirubin total, mg/dL	4.6	3.1	1.9	-	-
Bilirubin direct, mg/dL	2.3	1.5	0.5	-	-
PTT, s	54	32	-	38	-
PT, s	12.5	12.5	-	12.8	-
Ferritin	>1000	-	-	-	-
Widal	1/80	-	-	-	-
2ME (Brucella agglutination test)	Negative	-	-	-	-
U/A (blood and ketone)	Positive	Positive	Negative	-	-
Alkaline phosphatase, U/L	158	-	-	-	-
G6PD	20 min	-	-	-	-
Reticulocyte	0.8	-	-	-	-
coombs wright	1/40	-	-	-	-
GGT, U/L	4	-	-	-	-
Zinc, µg/dL	37	-	-	-	-
Pro-BNP, pg/mL	-	-	338	-	-
Leptospirosis IgM, U	-	-	23 (Normal: 0.02- 20)	-	-
COVID-19 IgG, U	-	-	33.7 (Normal: 0.03- 15)	-	-

WBC: white blood cells, ESR: elevated sedimentation rate, CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, PTT: partial thromboplastin time, PT: prothrombin time, Pro-BNP: pro-brain natriuretic peptide, GGT: gamma glutamine transferase, IgM: immunoglobulin M, G6PD: glucose-6-phosphate dehydrogenase, 2ME: 2-mercaptoethanol

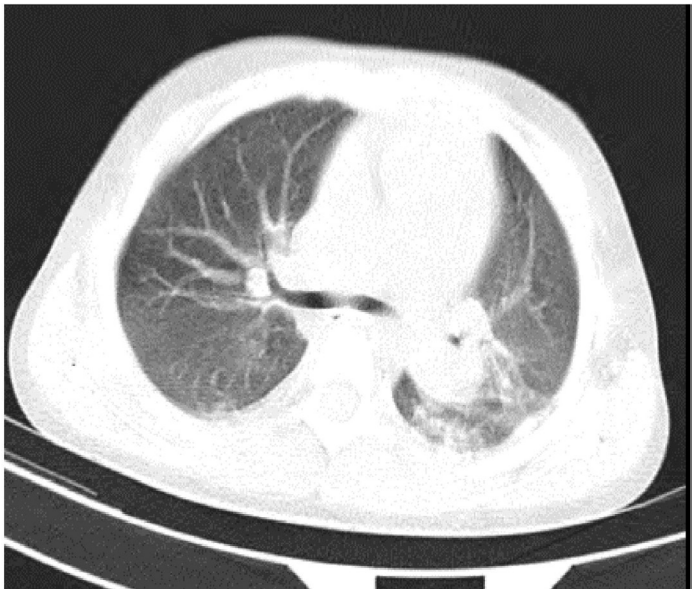

Fig. 1. CT scan of the patient is shown. CT revealed pleural effusion and patchy ground glass opacity.

enlargement, good left ventricular ejection fraction, mild tricuspid regurgitation, mild pulmonary insufficiency, no pericardial effusion, pleural effusion, and arrhythmia. On the 12th day, he was discharged from the hospital and was advised to be followed up for a month. The patient follow-up showed complete improvement, and after 8 weeks from symptom onset, leptospirosis IgG was detectable.

Discussion

In this study, we reported a case of MIS-C accompanied by severe leptospirosis. MIS-C followed by COVID-19 presents with multi-organ involvement, and its exact incidence still needs to be elucidated [3]. Since most of the patients diagnosed with MIS-C have detectable COVID-19 IgG, the underlying mechanism of MIS-C is presumed to be immune-related [14]. However, the likelihood of genetically associated mechanisms requires further illumination in MIS-C children [15]. Similar to our report, in the literature, gastrointestinal symptoms including nausea, vomiting, abdominal pain, and diarrhea have been shown to be prominent in patients with MIS-C, rather than respiratory symptoms [16].

Of note, MIS-C shares a spectrum of similarities with Kawasaki disease, such as rash, conjunctivitis, lymphadenopathy, and increased inflammatory markers. However, particular distinctions have been highlighted to make a considerable difference between MIS-C and Kawasaki disease, including prominent cardiovascular complications and lymphopenia [17]. Regarding the probable mechanism of MIS-C, the utility of immunomodulatory treatment has been discussed in the literature. Recent studies have demonstrated that intravenous immunoglobulin (IVIG) and corticosteroids significantly yield favorable outcomes in critically ill patients [18]. Since MIS-C exhibits various manifestations associated with multi-organ involvement, differentiating between MIS-C and other alternative inflammatory disorders is challenging.

Worldwide, leptospirosis as a neglected zoonosis disorder is associated with a significant prevalence of mortality. The clinical presentation of leptospirosis is diverse and ranges from an asymptomatic subclinical form to multi-organ involvement or even failure. Icteric leptospirosis, also known as Weil syndrome, commonly manifests with heterogeneous presentations with multi-system involvement, including shock, jaundice, acute renal dysfunction, sub-conjunctival suffusion, and respiratory distress. Identification of the severe presentation of leptospirosis in patients is necessary for the prompt initiation of lifesaving management [19]. Leptospirosis typically does not cause severe manifestations in children. However, host-associated variables are considered to play a pivotal role in the severity and intensity of the leptospirosis illness course [1, 13].

In the current patient, it was presumed that underlying MIS-C could potentially aggravate the clinical presentation of leptospirosis due to the dysregulation of the immune system. Although the exact pathogenesis of leptospirosis is still unknown, studies have shown that vasculitis and endothelial damage are attributed to multi-organ impairment [20].

The differential diagnosis in this patient included MIS-C, leptospirosis, glucose-6-phosphatase deficiency (G6PD), severe COVID-19, toxic shock syndrome (TSS), Kawasaki shock syndrome (KSS), brucellosis, and typhoid fever. Based on the clinical manifestations and incompatible laboratory evaluations, TSS, typhoid fever, brucellosis, KSS, and G6PD were considerably ruled out.

In the current patient, during hospitalization, hypoalbuminemia was observed despite receiving albumin. Cytokine storm and immunologic reaction caused by MIS-C can lead to hypoalbuminemia [21]. However, proteinuria, protein-losing enteropathy, and failure to thrive were excluded in our case.

In some reports of children with complaints of right upper quadrant pain who were diagnosed with leptospirosis, acalculous cholecystitis has been observed [22]. In the current patient, abdominal ultrasonography was performed, which revealed mild fluid in the sub-hepatic and perisplenic areas.

Consistent with a study conducted by Sethi et al. [23], hematuria in this patient could be attributed to the acute kidney injury caused by MIS-C based on probable mechanisms such as dysregulated immune response, cytokine storm, and direct injury. Furthermore, Yang L. [24] in a review showed that renal dysfunction in leptospirosis occurs in about 10-85% of patients.

At admission, the patient presented with severe anemia. Concerning the co-occurrence of MIS-C and leptospirosis, severe anemia could not be considered unexpected. Anemia is perceived as a common manifestation of leptospirosis, especially in Weil syndrome, due to the hemorrhagic phase of the illness and renal failure [25]. Almoosa et al. [26] in a multicenter case series showed that acute anemia could be caused secondary to MIS-C, necessitating

the importance of multidisciplinary management in patients with MIS-C. Notably, the presence of anisocytosis and poikilocytosis in the peripheral blood smear of the patient mostly suggested microcytic anemia. Nevertheless, the patient did not have iron deficiency, thalassemia, or chronic disease.

Pleural effusion is less common in COVID-19 and leptospirosis, especially in children. However, in our case, it is supposed that pleural effusion may be caused by hypoalbuminemia or systemic inflammatory reaction [21, 27, 28].

Conclusion

Regarding the heterogeneous manifestations of MIS-C, it is crucial to note that MIS-C can potentially resemble other inflammatory diseases. Of importance, in the era of COVID-19, the co-occurrence of MIS-C and leptospirosis must be considered in endemic regions of leptospirosis to improve the management of critically ill patients through multidisciplinary treatment.

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Ethical Considerations

Ethics approval and consent to participate

Since this is a case report, the ethics committee of Mazandaran University of Medical Sciences exempted our report from approval. Consent for publication of this case report was obtained from the patient's parents.

Consent for publication

Informed consent was obtained from the parents of the patient before manuscript submission for their clinical details.

Author contributions

MS R contributed to the design of the study. MS R, A SL, MR N, LS, and ZS managed the patient. SK RA contributed in collecting the data of the illness course and drafting the manuscript. SKRA and MS R critically evaluated the study. All authors approved the submitted manuscript to be published.

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Conflict of Interests

The authors have no conflicts of interest to disclose.

Abbreviation

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Corona virus disease 2019; MIS-C: Multisystem inflammatory syndrome in children; PICU: pediatric intensive care unit; CT: computed tomography; RT-PCR: reverse transcription polymerase chain reaction; IVIG: intravenous immunoglobulin; TSS: Toxic shock syndrome; G6PD: Glucose-6-phosphate deficiency.

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