Title page:

COVID-19 could trigger Systemic Juvenile Idiopathic Arthritis: First Case Report

Vadood Javadi Parvaneh[1], Khosro Rahmani[1*]

1Department of pediatric rheumatology, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

*Corresponding author name and email: Khosro Rahmani, email: rahmani.kh88@gmail.com

Abstract:

Background: COVID-19 causesa variety of signs and symptoms.

Case presentation: A boy with COVID-19 presented with acute abdomen. Then he showed features of Kawasaki-like syndrome, a multiorgan inflammatory syndrome in children, and finally systemic juvenile idiopathic arthritis.

Conclusion: We reported the first case presenting systemic JIA triggered by COVID-19.

Keywords: systemic, Juvenile idiopathic arthritis, children, COVID-19

Key Clinical Message: COVID-19 can involve and dysregulate all branches of the immunity system. We reported a 7-years boy who first presented with an acute abdomen, then Kawasaki-like syndrome, and finally systemic juvenile idiopathic arthritis triggered by COVID-19.

Background

The COVID-19 disease can induce secondary vasculitis and/ or presented with vasculitis or hyperinflammation manifestations including Kawasaki-like syndrome and multisystem inflammatory syndrome in children (1-3).After viral entrance to the body, the course of the COVID-19 in symptomatic patients has 3 stages: early infection, pulmonary phase, and hyperinflammation phase. The last phase is responsible for clinical manifestations such as acute respiratory distress syndrome (ARDS), SIRS/shock, cardiac failure, and multisystem inflammatory syndrome in children (MIS-C) (4, 5). This phase may present with a delay of about 2-4 weeks (3).

COVID-19 has been presented with a variety of presentations with an incubation period of 2-14 days, and a median of 5 days. Fever, cough, dyspnea, myalgia, and fatigue are the most

common symptoms. Arthralgia, myalgia, myocarditis, cytopenia (leucopenia, lymphopenia, and thrombocytopenia), secondary hemophagocytic lymphohistiocytosis (macrophage activation syndrome) and cytokine storm, and possible increased risk of venous thromboembolism are features and findings which are well-known figures among the manifestations of rheumatic diseases. (Table-1) Here, we presented a boy with COVID-19 with presentations ranging from the acute abdomen, Kawasaki-like syndrome to finally systemic juvenile idiopathic arthritis (JIA).

Case presentation

A 7 years-old boy referred to our hospital in May 2020 with the impression of resistant Kawasaki disease. He was admitted to another center about 1 month ago with abdominal pain, nausea, vomiting, and fever and operated with an impression of appendicitis. His fever continued and non-pruritic maculopapular rashes appeared on his extremities. He had dyspnea and oral ulcers. With suspicious HRCT and positive PCR for COVID-19, he admitted again. He received supportive care but his fever and rashes continued. He developed edema of limbs and splenomegaly. Therefore, he treated with IVIG (unknown doses) with an impression of Kawasaki-like syndrome. However, due to the prolonged high-fever and rashes, he referred to our hospital and admitted to the COVID-19 ward. At presentation, he had a fever, hypopigmented patches on extremities, hand and foot edema, and arthritis of hips, knees, and ankles. (Figure-1)The cardiac evaluation had no abnormal findings. He was prescribed IVIG 2g/kg and ASA 50mg/kg/day. After two days, the fever relapsed and new punctate erythema appeared in the plantar regions. The second dose of IVIG in addition toa single dose of IVMP (30mg/kg) was given. The signs and symptoms were relieved except for arthritis. The patient was discharged from COVID-19 ward with low doses of prednisolone and ASA. After two weeks the patient was admitted in the pediatric rheumatology ward with polyarthritis, fever, and rising ESR and CRP. He had spiky quotidian fever, punctate erythema in palms, positive Kobner's phenomenon, salmon-pink patches, and a synovial cyst on the posterior aspect of the left wrist. (Figure-1) The patient had a picture of systemic JIA, so he received IVMP pulse (30 mg/kg/day) for three consecutive days, Naproxen 20 mg/kg/day, and Methotrexate 10 mg/m^2. The fever and rashes were subsided dramatically after 24 hours andarthritis, synovial cyst, and elevated acute phase reactants improvrd gradually. After 3 months follow-up the patient had inactive joints, improved synovial cyst, and normal laboratory data. (Table-1, Figure-1)

Discussion and conclusions:

We presented a boy with COVID-19 who presented first with acute abdomen features mimicking appendicitis. His fever continued after appendectomy and manifestations including maculopapular rashes, edema of hands and feet, arthritis, punctate erythema, splenomegaly, and increased level of acute-phase reactants were added. The patient was treated with the impression of Kawasaki-like syndrome which was less known at that time. He was resistant to IVIG, therefore he received the second dose of IVIG plus a single dose of IVMP pulse and ASA. With continuing the high-spiky-fever, splenomegaly, and the presence of polyarthritis, salmon-pink patches, and Kobner's phenomenon the final diagnosis was systemic JIA. So, the patient was treated with medications such as three consecutive days of IVMP pulses (and then oral prednisolone 2 mg/kg/ day), Methotrexate, and Naproxen. His condition improved by time and after 3 months of follow-up, the disease is in remission.

COVID-19 can mimic some aspects of rheumatic diseases. (Table-1) Furthermore, several hyperinflammatory conditions have been reported in COVID-19 patients. The term pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C) was formulated for some aspects of this condition (6).Today, there are increasing reports of this disease from a different area of the world. The patients can be presented with features of complete Kawasaki disease (KD), incomplete KD, atypical KD, KD shock syndrome (KDSS), or multi-organ inflammatory syndrome. There are various clinical presentations: refractory toxic shock syndrome with normal cardiac function, septic and/or cardiogenic shock resembling KD shock syndrome, KD feature, macrophage activation syndrome (MAS), and some with a combination of the above-mentioned features.

Currently, the World Health Organization (WHO) and the US CDC have proposed different and some similar case definition for MIS-C which have shown in table-2 (7,8,9): (Table-3)

Verdoni and colleagues reported a 30-fold increased incidence of Kawasaki-like disease from Italy. In contrast with patients before the COVID-19 pandemic disease, these children were older and showed a higher rate of cardiac involvement and features of MAS (3).The cardiac involvement was in the setting of myocarditis, pericardial effusion, and coronary artery involvement. The increasing cases from the USA and European areas are reported (10). It is not yet clear the full spectrum of disease, and whether the geographical distribution in Europe and North America (in contrast to low reported cases from the traditionallyendemic area

including North-east Asia) reflects a true pattern, or if the condition has simply not been recognized elsewhere.

Our patient had some manifestations compatible with Kawasaki-like syndrome such as prolonged fever, polymorphous rashes, arthritis, edema of the distal part of the extremities , and elevated acute-phase proteins. Furthermore, he had some features which has been reported in KD-like syndrome and not in classic KD such as splenomegaly, persistent fever, arthritis, and rashes, history of oral ulcer, elevated IL-6, D-dimer, and LDH and decreased fibrinogen.Also, he fulfilled both CDC and WHO criteria for MIS-C which had not been recognized at that time. Eventually, the course of the hyperinflammatory phase of the disease led to a picture named as systemic JIA. To the best of our knowledge, there have been no reports of systemic JIA following COVID-19 in the literature.

Systemic JIA could be triggered with several infectious agents such as viral infections. COVID-19 has been reported to induce imbalance in the immunity system and hyperinflammation. We reported the first systemic JIA patient after COVID-19 in children.

List of Abbreviations:

MIS-C:Multisystem inflammatory syndrome in children

COVID-19: coronavirus disease 2019

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

ARDS: acute respiratory distress syndrome

SIRS: Systemic inflammatory response syndrome

JIA: juvenile idiopathic arthritis

HRCT: High-resolution computed tomography

IVIG: intravenous Immunoglobulin G

IVMP: intravenous methylprednisolone

ASA: Acetylsalicylic acid

ESR: erythrocyte sedimentation rate

CRP:C-reactive protein

PIMS-TS: pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2

KDSS: Kawasaki disease shock syndrome

KD: Kawasaki disease

MAS: macrophage activation syndrome

WHO: World Health Organization

CDC:centers for disease control and prevention

Declarations:

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Figure legends

Figure 1. Clinical findings of the patient at presentation and after treatment

A-G. at presentation.H-I. After 3 month follow-up.

Table-1: COVID-19 manifestations which may mimic rheumatic disorders

Clinical symptoms	Laboratory Features	Clinical Diagnosis
Fever	Leucopenia,Lymphopenia	Macrophage activation syndrome
Arthralgia	Thrombocytopenia	Thromboembolism
Myalgia	Increased ESR, CRP, LDH	Arthritis
Chest pain	Elevated AST,ALT	Pleural/ pericardial effusion
Skin rashes	Decreased albumin,fibrinogen	Autoimmune hepatitis
Joint swelling, swelling of hands and feet	Prolonged PT,PTT, INR	Kawasaki like syndrome
Conjunctivitis	Increased Ferritin, d-Dimer, TG	Kawasaki disease shock syndrome
Abdominal pain, nausea, vomiting	Positive ANA, Anti SSA, Anti SSB, anti Scl-70	DIC like syndrome
Hemoptysis, shortness of breath, dyspnea	Positive anti U1-RNP	Skin small vessel vasculitis
Headache	Decreased C3,C4	Reynaud's phenomenon
impairment of consciousness, seizure	High level of serum IL-6	Stroke,encephalopathy

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; LDH: lactate dehydrogenase; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; PT: prothrombin time; PTT; partial thromboplastin time; INR: international normalized ratio; TG: Triglyceride; ANA: anti nuclear antibody; anti U1-RNP: anti-U1 ribonucleoprotein; anti SSA: Anti-Sjögren's-syndrome-related antigen A; anti SSB: Anti-Sjögren's-syndrome-related antigen B ; anti Scl-70: scleroderma and a 70 kD extractable immunoreactive fragment; DIC: Disseminated intravascular coagulation; IL-6: interlukin-6.

Table-2 Laboratory data of the patient from diagnosis to remission

Lab	5-16-2020	5-19-2020	5-23-2020	5-26-2020	5-28-2020	6-23-2020	7-16-2020	8-22-2020
WBC	11200	-	24300	18600	15900	14500	12570	8900
Lymph	3540	-	6318	1860	3340	2976	8120	5960
Hb	8.3	-	8.2	8.2	8.3	13.9	13.7	13.5
MCV	83	-	82.5	89.2	92	86	84.3	85
PLT	688	-	863	809	642	324	359	345
ESR	52	115	85	46	110	30	9	11
CRP	1+	Neg	1+	3+	3+	Neg	Neg	Neg
BUN	10.7	5.7	6.9	-	-	8.2	12.8	14.1
Cr	0.5	0.49	0.5	-	-	0.5	0.51	0.8
AST	121	106	36	211	-	21	15	27
ALT	118	117	67	299	-	19	16	21
ALP	-	750	597	599	-	224	-	-

Ferritin	146	-	752	95	58	-	-	-
Fibrinogen	372(200-400)	-	-	372	600	-	-	-
D-Dimer	>200(pos)	-	-	-	-	-	-	-
Il-6	-	-	-	-	239.6(<7)	-	-	-
Bil	0.9	-	1.2	-	-	-	-	-
TG	90	-	90	-	-	-	-	-
Chol	91	-	112	-	-	-	-	-
LDH	368	-	561	502	-	-	-	-
Uric acid	2.8	-	2.8	-	-	-	-	-
Pr	-	-	-	8.8	-	-	-	-
Alb	-	-	-	3.3	-	-	-	-
U/A	WBC:8-10	-	-	WBC:4-5	-	-	-	-

Table-3: Definition for multisystem inflammatory syndrome in children (MIS-C)

	WHO	**US-CDC**
Age	<20 y	<21 y
Fever	>3 days	≥24h
Multisystem organ involvement	At least 2 of: • Rash or bilateral non-purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet) • Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevated troponin /NT-pro BNP) • Evidence of coagulopathy (by PT, PTT, elevated d-Dimers) • Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) • Hypotension or shock	≥2 of: • Dermatologic • Cardiac • Hematologic • gastrointestinal • renal • respiratory • neurological
evidence of clinically severe illness requiring hospitalization	-	+
Laboratory evidence of inflammation	elevated : CRP ESR	elevated : CRP ESR

	Procalcitonin	Procalcitonin Fibrinogen d-Dimer ferritin LDH IL-6 Neutrophils Reduced lymphocytes albumin
Exclusion of	other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes	alternative plausible diagnoses
Evidence of COVID-19	RT-PCR, antigen test or serology positive, or likely contact with patients with COVID-19	RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms

WHO: world health organization; US-CDC: United States Centers for Disease Control and Prevention; NT-proBNP:N-terminal pro-B-type natriuretic peptide; PT; prothrombin time; PTT; partial thromboplastin time; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase, IL-6: interlukin-6; RT-PCR: Reverse transcription polymerase chain reaction.