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SARS-CoV-2-induced myocarditis in pediatric patients: A 10-case series from Sanandaj, Iran

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Case Report

Abstract

BACKGROUND: Fever, cough, and acute lung involvement are severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) symptoms. Children can be asymptomatic virus carriers and may contribute to the prevalence of coronavirus disease 2019 (COVID-19). Like other viral diseases, the involvement of different heart parts is also seen in this disease. Myocarditis is an inflammation of the myocardium, usually caused by a virus. The primary aim of this study is to investigate the occurrence and clinical manifestations of myocarditis among pediatric patients infected with SARS-CoV-2 in Sanandaj, Iran.

CASE REPORT: In this study, COVID-19 myocarditis cases in Be'sat Hospital, Sanandaj, were documented. Ten pediatric patients with a definitive diagnosis of COVID-19 who were admitted to Be'sat Hospital in Sanandaj in 2020 were included in this study based on clinical trials after seeking echocardiography and confirming myocarditis. The mean age of these 10 study cases was 7.1 years (2 to 13 years). The most common symptoms were fever, respiratory distress, cough, and vomiting. Ceftriaxone, intravenous immunoglobulin (IVIG), and dopamine were the main interventions in these cases. After these cases, all general practitioners and pediatricians in the province and the country were given the necessary warnings. Based on the results, COVID-19 infections, like viral infections, such as enterovirus and adenovirus, are known as the main causes of myocarditis, which appear as local or general myocardial inflammation, tissue necrosis, and ventricular dysfunction.

CONCLUSION: A direct viral attack and overactive immune responses in viral myocarditis can harm heart tissue. Therefore, in COVID-19-infected individuals, serial symptom evaluation and monitoring are necessary.

KEYWORDS: Myocarditis; SARS-CoV-2; Viral Infections; Pediatrics

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Introduction

In recent years, the world has been grappling with a rise in emerging infectious diseases, a trend fueled by accelerating population growth, expanding urbanization, and increasing globalization. This rapid development creates ideal conditions for the spillover of viruses from animal reservoirs to

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human populations. On average, more than two new strains of human-borne viruses, predominantly ribonucleic acid (RNA) viruses, are identified annually.[1]

The latest pathogen capturing global attention is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent behind the coronavirus disease 2019 (COVID-19) pandemic. This novel coronavirus emerged in late 2019 in China and has since swept across the globe.[2] Molecularly, it shares approximately 79% of its genome with the earlier SARS-CoV virus and uses the angiotensin-converting enzyme 2 (ACE2) receptor as its cellular entry point.[2] While the most prevalent clinical manifestations in adults are fever, cough, and acute pulmonary involvement, children present with a unique clinical profile.[2]

Importantly, children can serve as asymptomatic carriers, posing a significant public health challenge. Special attention should be given to COVID-19-positive children under one year of age and those with preexisting health conditions.[3] Unilateral chest computed tomography (CT) findings are present in roughly 36.4% of pediatric cases, complicating differential diagnoses. The guidelines recommend ruling out other potential causes, such as foreign body aspiration, which underscores the importance of a comprehensive diagnostic approach in children.[3]

One significant area of concern related to SARS-CoV-2 infection is its ability to induce myocardial inflammation or myocarditis. This condition is mediated, at least in part, through the down-regulation of myocardial ACE2, potentially leading to myocardial dysfunction and adverse cardiac outcomes. Recent studies have indicated that children may be particularly susceptible to this form of cardiac involvement, thereby necessitating vigilant clinical monitoring.[4]

Myocarditis is an inflammatory process that primarily affects the myocardium – the heart's muscular middle layer.[5] Symptoms can range from chest pain and arrhythmias to severe heart failure (HF), which, in extreme cases, can result in sudden death.[5] In pediatric populations, myocarditis may also manifest through a spectrum of non-specific symptoms, including fever, fainting, and respiratory distress, making early diagnosis and intervention crucial.[6] The primary aim of this study is to investigate the occurrence and clinical manifestations of myocarditis among pediatric patients infected with SARS-CoV-2 in Sanandaj, Iran.

Case Report

In this case series, we assessed 85 pediatric patients who received a definitive diagnosis of COVID-19 via nasopharyngeal swab polymerase chain reaction (PCR) testing and were subsequently admitted to Be'sat Hospital in Sanandaj during the year 2020. Upon admission, a comprehensive record of clinical signs, symptoms, and laboratory results was maintained for each patient.

Of the initial cohort, 10 patients demonstrated signs of respiratory distress syndrome, including symptoms such as dyspnea, tachycardia, and low blood pressure, as well as a general deterioration in condition during their hospital stay (Tables 1 and 2). These clinical findings, along with specific responses to treatment and laboratory test results, raised the suspicion of myocarditis among the attending medical team (Table 3). Diagnostic confirmation for myocarditis was obtained through echocardiography for these 10 patients, who were subsequently included in this study. At the time, echocardiography was recommended for all critically ill patients; however, apart from these 10 cases, none exhibited clinical findings indicative of myocarditis.

Notably, these were the first documented cases of pediatric myocarditis induced by COVID-19 in our province (Kurdistan) and among the first in the country. Treatment protocols for this specific complication were still under development during this period.

Table 1. Clinical signs of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced myocarditis in pediatric patients

Case	Age (year)	Gender	Duration of hospitalization (day)	Intubated	Death	PICU care	Fever	Cough	Distress	Diarrhea
1	7	Boy	10	Yes	Yes	Yes	Yes	No	Yes	No
2	7	Girl	10	No	No	Yes	Yes	Yes	Yes	Yes
3	4	Girl	13	No	No	No	Yes	Yes	Yes	Yes
4	2	Boy	2	Yes	Yes	Yes	Yes	Yes	Yes	No
5	6	Girl	8	No	No	No	Yes	No	No	No
6	10	Boy	8	No	No	No	Yes	Yes	Yes	No
7	13	Boy	10	No	No	No	Yes	No	No	No
8	2	Boy	6	No	No	Yes	Yes	Yes	Yes	No
9	13	Boy	7	No	No	No	Yes	No	No	No
10	7	Boy	10	No	No	Yes	Yes	No	Yes	No

PICU: Pediatric intensive care unit

Patient demographics and clinical characteristics: Seven of the ten cases were boys (70%), with a mean age of 7.1 years [standard deviation (SD): 3.95]. All presented with fever, while other symptoms included skin lesions (50%), respiratory distress (70%), and headaches (30%). All patients tested positive for COVID-19 via PCR.

Laboratory findings: Hypernatremia was observed in 10% of the patients, while 50% had hyponatremia, and another 10% exhibited hyperkalemia. Additionally, 60% were anemic, 20% showed leukopenia, and 10% had leukocytosis (Tables 2 and 3).

Therapeutic interventions: Treatment regimens varied but primarily involved ceftriaxone (90%), intravenous immunoglobulin (IVIG) (80%), and dopamine (50%). Other drugs used included vancomycin (40%), meropenem (10%), milrinone (20%), and aspirin (40%). The average length of hospital stay was nine days (SD: 2.2 days).

Post-case follow-up: Following the identification of these myocarditis cases, advisories were issued to all general practitioners and pediatricians in the province to raise awareness and guide the management of similar cases.

Case 1

A 7-year-old boy from Saghez, Iran, showed mild fever and headache symptoms two days before the visit with no past medical history. The patient's consciousness suddenly dropped, and his Glasgow Coma Scale (GCS) was 3.2 mydriasis at admission. After intubation and cardiopulmonary resuscitation (CPR), early laboratory tests and procedures, including two PCR tests, were performed according to hospital protocols.

Table 2. Clinical signs of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced myocarditis in pediatric patients

Case	Abdominal pain	Vomiting	Conjunctivitis	Skin lesions	Headache	Impaired consciousness	O_2 saturation (%)	Temperature (°C)
1	No	No	No	No	Yes	Yes	70	39
2	Yes	No	Yes	Yes	Yes	No	87	39
3	No	Yes	Yes	Yes	No	No	88	39
4	No	Yes	No	No	No	Yes	85	39
5	Yes	Yes	No	No	No	No	90	38
6	No	No	Yes	No	No	No	90	39
7	Yes	Yes	Yes	Yes	No	No	93	39
8	No	No	No	No	No	No	90	39
9	No	No	Yes	Yes	No	No	94	39
10	No	Yes	Yes	Yes	Yes	No	89	39

Table 3. Clinical trials of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced myocarditis in pediatric patients (Part I)

Case	WBC (× 10^9/L)	PMN (%)	Lymphocyte (%)	Hb (g/dl)	MCV (fl)	MCH (pg)	MCHC (g/l)	PLT (× 10^3/µl)	ESR (mm/hr)	CRP (mg/l)	AST (U/l)	ALT (U/l)	Urea (mg/dl)	Cr (mg/dl)	Na (mmol/l)	K mmol/l)	CPK (µg/l)	LDH (U/l)
1	43	90	10	14.0	74.0	27.0	31.0	125	15	1+	110	150	50	1.0	160	2.5	2000	6300
2	10.3	90	10	10.0	83.0	27.0	32.0	100	30	1+	100	90	11	0.4	137	4.0	297	530
3	11.5	87	13	9.9	82.0	26.0	31.6	152	50	2+	27	10	10	0.5	138	4.4		
4	6.6	87	13	7.0	76.0	25.0	28.0	135	51	1+	72	50	110	1.1	130	5.9	281	1318
5	15	80	20	13.0	76.0	24.0	32.0	358	4	Negative	230	120	12	0.5	133	4.7	7641	1090
6	24.5	89	11	11.6	79.0	25.4	32.1	215	18	Negative	95	121	15	0.7	132	4.3	577	522
7	100	93	7	11.0	78.0	26.0	31.0	115	40	2+	100	50	10	0.5	132	4.0	230	500
8	7.60	51	49	11.0	78.0	24.0	32.0	311	4	Negative	25	10	10	0.6	135	3.6	200	350
9	5.8	80	20	11.0	78.0	25.0	31.0	1700	27	1+	82	63	20	1.1	141	4.0	930	1100
10	2.9	67	27	9.0	82.3	26.7	32.5	89	70	2+	110	90	17	0.8	138	4.2	70	573

WBC: White blood cells; PMN: Polymorphonuclear neutrophils; Hb: Hemoglobin; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; PLT: Platelet count; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CPK: Creatine phosphokinase; LDH: Lactate dehydrogenase

We rolled out the causes of loss of consciousness (LOC). His lab test results showed normal blood glucose, no sign of meningitis, or a history of head trauma, malnutrition, drug use, and electrolyte imbalance. The first PCR was negative, but the second was positive. According to the patient's condition, we showed depleted ejection fraction (EF) as a myocarditis symptom due to low blood pressure and cardiac monitoring changes, cardiac evaluation, and echocardiography. The patient underwent ceftriaxone, vancomycin, and dopamine therapy but expired after five days of hospitalization in pediatric intensive care unit (PICU).

Case 2

A 7-year-old girl from Saghez with fever, diarrhea, vomiting, abdominal pain, conjunctivitis, and skin lesion with no past medical history was admitted to the pediatric ward for Kawasaki evaluation. During hospitalization, the patient developed severe tachycardia and respiratory distress; following echocardiography, myocarditis was confirmed. The patient underwent IVIG, ceftriaxone, vancomycin, Lasix, dopamine, and dobutamine therapy programs. Finally, the patient was discharged 15 days after hospitalization with overall good health status.

Case 3

A 4-year-old girl from Qorveh, Iran, with early symptoms of fever, cough, respiratory distress, decreased O_2 saturation, diarrhea and vomiting, conjunctivitis, and skin lesions with a positive PCR test and with no past medical history was hospitalized with inadequate overall health status. Myocarditis was reported on echocardiography examination, and IVIG, dopamine, ceftriaxone, and vancomycin therapy was performed on the patient. The patient was discharged 13 days after hospitalization in good overall health status.

Case 4

A 2-year-old boy from Baneh, Iran, was referred to the center with fever, severe respiratory distress, an episode of seizure with LOC, depressed O_2 saturation, and severe condition with no past medical history. He was intubated due to his severe respiratory distress. On echocardiography, myocarditis and an extreme increase in pulmonary artery pressure were reported. The patient treatment protocol was started with meropenem, vancomycin, Lasix, dobutamine, IVIG, and milirinone. The patient expired less than 24 hours after admission.

Case 5

A 6-year-old girl from Saghez was admitted with abdominal pain and vomiting symptoms. With the diagnosis of appendicitis, she underwent an appendectomy. Because of developing tachycardia, cardiac complications were suspected during her hospitalization. Echocardiography results showed myocarditis and HF. Besides, the PCR test result was positive for coronavirus. At the time of admission, the patient was in a critical condition and had severe tachycardia and HF with no past medical history. The patient was treated with ceftriaxone, IVIG, and aspirin and was discharged with good overall health status after eight days of hospitalization.

Case 6

A 10-year-old boy from Sanandaj with symptoms of fever, cough, respiratory distress, and ocular conjunctivitis was admitted with a positive PCR test result for SARS-CoV-2. Cardiac examination and echocardiography confirmed myocarditis. The patient underwent ceftriaxone, IVIG, and aspirin therapy and was discharged after eight days of hospitalization with good overall health status.

Case 7

A 13-year-old boy from Sanandaj, with a known case of asthma presented with fever, abdominal pain, vomiting, conjunctivitis, and skin rashes and was hospitalized with a positive PCR test for SARS-CoV-2. The patient underwent a cardiac examination suspected of multisystem inflammatory syndrome (MIS)

and was diagnosed with myocarditis. The patient then underwent ceftriaxone, IVIG, and aspirin therapy and, after three days, was discharged with good overall health status.

Case 8

A 2-year-old boy from Sanandaj with symptoms of fever and mild respiratory distress without any signs of cough was admitted and hospitalized. O2 saturation at the time of admission was 94%, and early procedures were done. The results of the early chest radiography showed pulmonary edema. Echocardiography results showed a 10% EF of myocarditis. The PCR test for SARS-CoV-2 turned out to be positive. The patient underwent a regimen of ceftriaxone, IVIG, and dopamine. The patient then developed severe respiratory distress and, as a result, was intubated and went on a ventilator. Still, because of his clinical condition, after a week of dobutamine, milrinone, Lasix, and broad-spectrum antibiotic therapy, he died of severe HF.

Case 9

A 13-year-old boy from Sanandaj with fever, conjunctivitis, and skin lesions was admitted with a positive PCR test for coronavirus and O2 saturation of 94%. Results of echocardiography reported myocarditis. The patient was treated with ceftriaxone, aspirin, and IVIG. After seven days of hospitalization, the patient was discharged with good overall health.

Case 10

A 7-year-old boy from Sanandaj with clinical symptoms of fever and cervical lymphadenopathy and a positive coronavirus PCR test was admitted to our clinic. During hospitalization, he underwent antibiotic therapy for his purulent cervical abscesses, and gradually patient developed skin lesions, respiratory distress, and tachycardia. Results of echocardiography reported myocarditis. The patient then underwent ceftriaxone, vancomycin, IVIG, and aspirin therapy. After ten days of hospitalization, the patient was discharged with good overall health.

Discussion

The primary objective of this case series was to investigate the incidence and clinical manifestations of myocarditis among pediatric patients diagnosed with COVID-19. Conducted at Be'sat Hospital in Sanandaj in 2020, our study identified 10 cases of myocarditis among 85 hospitalized pediatric patients, marking them as the first documented instances of COVID-19-induced myocarditis in children in our province and among the first nationally. Predominantly affecting boys (70%), with a mean age of 7.1 years, the patients exhibited various symptoms like respiratory distress and dyspnea and were primarily treated with ceftriaxone, IVIG, and dopamine. The mean length of hospitalization was nine days. These findings add vital information to the clinical understanding of the cardiac complications associated with COVID-19 in pediatric patients and highlight the urgent need for comprehensive diagnostic and treatment guidelines for this emerging complication.

Significant cardiac complications have been observed in patients with COVID-19. Clinical cardiac manifestations include myocarditis, arthritis, and HF. The first case of elevated cardiac serum markers was observed in Wuhan, China.[7] Possible mechanisms of cardiac damage in COVID-19 and related cardiac phenotypes include viral myocarditis, coronary ischemia, stress cardiomyopathy, and tachyarrhythmias due to endogenous or exogenous adrenergic stimulation.[8] Myocarditis due to myocyte invasion by the virus can lead to cardiac dysfunction, arrhythmia, and death. Acute myocardial infarction (MI) has been reported in 22% of hospitalized myocarditis patients.[9] The mechanisms of acute myocardial injury are numerous in patients with COVID-19. Inflammatory reactions act with

cytokine storm, immunological factors, and signaling pathways associated with the ACE2. Hypoxia and heart damage occur through direct viral invasion.[10]

The cause of myocarditis is diverse and includes various infectious agents, systemic diseases, drugs, and toxins.[11] Most common viral infections are Coxsackievirus B, adenovirus, parvovirus B19, hepatitis C virus, Epstein-Barr virus (EBV), cytomegalovirus, and human herpesvirus (HHV).[12] Family members of the SARS-CoV-2, SARS-CoV, and Middle East Respiratory Syndrome (MERS) have also been reported to cause myocarditis.[13] Cardiac damage appears to be greater in patients infected with COVID-19 than in patients infected with various coronaviruses. The first case of coronavirus myocarditis was seen in 1980. Blood test of a 43-year-old man from Helsinki, Finland, showed higher levels of coronavirus antibodies, indicating that coronaviruses could cause myocarditis in addition to the initial upper respiratory infection.[14]

As a result, SARS-CoV-2 has a more significant heart involvement. The virus uses its spike protein with transmembrane protease serine 2 (TMPRSS2), heparan sulfate (HS), and other proteases to target the ACE2 receptor throughout the body, allowing cell entrance. One of the most strongly expressed organs of ACE2 is the heart. Furthermore, SARS-CoV-2 has a much stronger affinity for ACE2 than SARS.[15] Tropism to organs other than the lungs was investigated using autopsy specimens. The lungs had the highest quantities of SARS-CoV-2 genomic RNA, but the heart, kidneys, and liver also had considerable levels.[16]

Diagnosis of myocarditis in current clinical practice may be difficult. A 2013 article from the European Society of Cardiology (ESC) Working Group on Cardiovascular Diseases diagnosed myocarditis, both clinically suspected and defined myocarditis. Clinically suspected myocarditis is based on patient clinical presentations (mainly chest pain), electrocardiogram (ECG), ST-section, laboratory test, and imaging findings, including those using echocardiography or cardiovascular magnetic resonance imaging (CMRI). Increased cardiac enzymes and alterations in ECG and echocardiography have been found in patients with COVID-19, indicating acute myocardial injury.[17] Studies have shown that patients with COVID-19 infection with cardiac injury have significantly higher plasma concentrations of interleukin (IL)-6, 3, 4 endotracheal endothelial peptide [N-terminal probrain natriuretic peptide (NT-proBNP)], and cardiac troponin T (cTnT) and cardiac troponin I (cTnI).[18] In our study, because of existing pressure due to the peaks of COVID-19, the diagnostic basis was clinical manifestations and echocardiography and troponin tests were not requested.

Only a few investigations have produced endomyocardial biopsy (EMB) (or, in some cases, autopsy) results to differentiate between sterile myocardial damage and myocarditis. The first instance of full COVID-19-associated myocarditis was described in a 63-year-old man who originally showed pneumonia and had no history of cardiac disease or hypertension (HTN). Further blood tests revealed elevated IL-6 levels as well as high levels of cardiac injury markers such as troponin I (TnI), myoglobin, and N-terminal brain natriuretic peptide (NT-BNP). Left ventricular (LV) enlargement, decreased left ventricular EF (LVEF), widespread myocardial dyskinesia, and pulmonary HTN were all seen on echocardiography.[19] A study of COVID-19 patient's autopsies revealed single-nucleation infiltration, primarily of lymphocytes, along with localized myocyte necrosis.[20] In addition to identifying myocardial damage, an essential step in diagnosing myocarditis is to rule out coronary artery disease, especially when the clinical manifestations are similar to those of acute coronary syndrome.[12] Extensive

interstitial edema and limited foci of necrosis were observed. EMB also showed the presence of virus particles in cardiac macrophages in patients who died of cardiogenic shock, interstitial inflammation, and low-grade endocarditis but showed no signs of the virus in cardiomyocytes and endothelium and no signs of myocardial necrosis.[21] The SARS-CoV-2 genome was discovered using a reverse transcriptase-PCR (RT-PCR) in five cases. However, determining the cell type exposed to SARS-CoV-2 infection in the heart muscle was impossible. According to histopathological alterations in cardiac tissue, the inflammatory process appears to infiltrate the artery wall, leading to destruction and minor arterial injury.[17] Autopsies were performed on 21 patients with COVID-19 in an international multicenter trial, and multifocal lymphocytic myocarditis was found in three cases (14%).[22] As well as enhanced macrophage infiltration into the myocardium (86%), there was no myocyte damage associated with the left or right ventricles.[17]

Furthermore, incidences of COVID-19-associated myocarditis and sudden HF have been described in patients with no previous pneumonia or those who had overcome COVID-19, indicating a late onset of cardiovascular problems.[23] There was no previous cardiovascular disease except HTN (8%) in 26 relatively young patients (mean age: 36) who recovered from moderate COVID-19 pneumonia (85%). They underwent CMRI after recovery at the start of heart symptoms. Patients with MI (n = 15) accounted for 58% of the cases, whereas patients with late gadolinium enhancement (LGE) accounted for 31%. Fourteen patients (54%) had myocardial edema. Myocardial involvement was evident outside the LGE region, with just one out of 15 patients having LV dysfunction.[24]

The most exciting topic is why some people develop cardiac disease after being infected with SARS-CoV-2. Cardiac involvement was expected to arise mostly in patients with severe COVID-19 months after the epidemic discovery. Its frequency has been exaggerated, but its true extent remains unknown. It is critical to figure out what causes this pathophysiology, whether this is due to a person's inflammatory response, an autoimmune phenomenon, or another explanation. The goal is to avoid cardiovascular involvement in addition to preventing SARS-CoV-2 infections. COVID-19 distinct variability, from asymptomatic to fatal, is not understood. This challenge is made even more difficult by a new virus circulating widely throughout the human population, with many illness signs that are often disguised.[25]

While echocardiography was employed for diagnostic confirmation, more advanced diagnostic modalities like CMRI were not used, potentially leading to underdiagnosis or misclassification. Moreover, it was better to check troponin for patients. Finally, long-term follow-up data on cardiac function or other potential sequelae are not available, restricting our understanding of the chronic impacts of myocarditis in these pediatric patients.

Suggestions for future research are as follows:

- *Multi-center collaborative studies across multiple healthcare centers to increase the sample size and improve the generalizability of the findings:* This approach would also allow for more diverse patient demographics, thereby making the results more universally applicable.
- *Prospective design with control groups:* Adopting a prospective study design that includes control groups, such as children with other viral illnesses or asymptomatic children, would provide a more robust framework for drawing specific conclusions about the myocardial impact of COVID-19.
- *Longitudinal follow-up:* A long-term follow-up component can be incorporated to assess the chronic impacts and potential complications of myocarditis in children who have recovered from COVID-19. This would be invaluable for understanding long-term cardiac function and outcomes.

Conclusion

Based on the results, COVID-19 infection, like other viral infections, such as enterovirus and adenovirus, is known as the main cause of myocarditis, which appears as local or general myocardial inflammation and ventricular dysfunction. A direct viral attack and overactive immune responses in viral myocarditis can harm heart tissue. Therefore, in COVID-19-infected individuals, serial symptom evaluation and monitoring is necessary. Although the mechanisms of myocardial involvement and myocardial damage secondary to COVID-19 infection are still not precise, the authors of this study hope that this case report and mini-review will further expand on the possible manifestations of COVID-19 in pediatric patients.

Conflict of Interests

Authors have no conflict of interests.

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