Case Report

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Stevens–Johnson syndrome and COVID-19: a case report with suspected multisystem inflammatory syndrome in children (MIS-C)

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Introduction and importance: Symptoms similar to diseases such as Stevens–Johnson syndrome (SJS) and multisystemic inflammatory syndrome in children (MIS-C) were reported in pediatric coronavirus infections.
Case presentation: Here, we present a 4-year-old girl with coronavirus disease 2019 (COVID-19), an earlier diagnosis of SJS, and a final diagnosis of MIS-C.
Clinical discussion: Unlike the negative PCR test for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the positive serological test confirmed COVID-19.
Conclusion: The monitoring of this case indicated that higher coronavirus infection can delay immune reaction and cause symptoms similar to SJS.

Keywords: case report, coronavirus infection, MIS-C, Stevens–Johnson syndrome

Introduction

A new type of coronavirus, which is termed *acute respiratory coronavirus syndrome-2*, appeared in March 2020[1]. According to early reports, children are at low risk[1,2] of coronavirus disease 2019 (COVID-19) because of the lower maturity and function of ACE2 compared with adults. Also, there are higher levels of antibodies against viruses due to more respiratory infections and different immune responses in children as to their developing immune system[3]. However, the British Pediatric Intensive Care Society issued a warning about the increase in the number of children with positive COVID-19[1]. Several case reports and small populations have addressed an acute disease associated with multiple organ dysfunction and shock[1,4,5]. Riphagen *et al.*, in 2020, presented a study on eight children with COVID-19 and hyperinflammation that was the first report in the pediatric population. All of these patients had been referred to the hospital with symptoms such as fever, conjunctivitis, peripheral edema, limb pain, diarrhea, vomiting, and abdominal pain. Moreover, they suffered from refractory shock, but none of them showed remarkable respiratory involvement[4]. Pediatric hyperinflammatory syndromes often manifest themselves with pyrexia or fever of unknown origin, unclear nonspecific syndromes, and severe inflammation in multiple organs. Hyperinflammation was first observed in the 2003 SARS (severe acute respiratory syndrome) epidemic[6]. The newest case reports introduce pediatric patients referring to the hospital with symptoms of refractory shock similar to toxic shock syndrome (TSS) instead of Kawasaki disease (KD)[7,8]. Furthermore, patients with COVID-19 and hyperinflammatory syndromes bear similar cytokine profiles, number of lymphocytes, and levels of inflammatory markers. It can result in hemophagocytic lymphohistocytosis (SHLH)/macrophage activation syndrome (MAS), which is important in differential diagnosis[9,10]. MAS, which is the consequence of several systemic inflammatory diseases, can trigger a progressive multiorgan failure. The clinical manifestations of MAS consist of persistent high-grade fever, hepatosplenomegaly, lymphadenopathy, and central nervous dysfunction. The mortality rate of MAS in pediatric systemic lupus erythematosus (pSLE) cases is about 5%[11]. In COVID-19, although mucosal skin manifestations are not original clinical manifestations of infection in children, they are important clinical manifestations in multisystem inflammatory syndrome (MIS-C) in this group[12].

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are diseases with skin complications and mucous

HIGHLIGHTS

- A child presented with the first diagnosis of Stevens–Johnson syndrome (SJS).
- Subsequently, the tests showed coronavirus disease 2019 (COVID-19) and probably multisystemic inflammatory syndrome in children.
- COVID-19 can manifest as SJS at the first visit.
- A severe acute respiratory syndrome coronavirus-2 test is requested for these patients in the early diagnosis.

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membranes as well as prodromal symptoms including fever, general malaise, nonproductive cough, stinging eyes, and a sore mouth. Reasons for SJS in adults often include medications, but infections are commonly the main cause of SJS in children. There is a wide range of skin manifestations like SJS and TEN. In addition, symptoms of these diseases are similar to upper respiratory tract infections[12].

Here, we report a child patient with seizer, fever, rash, and mucosal involvement, having been hospitalized with a first diagnosis of Stevens–Johnson. In the next step and by the persistence of the disease and, resultantly, doing other tests, MIS-C and COVID-19 infections were diagnosed.

Case presentation

This case was reported based on the SCARE 2020 Guideline[13]. A 4-year-old girl suffering from generalized erythematous macular lesions was referred to a hospital on 20 January 2022. She had a history of febrile seizer but was not taking phenobarbital. Phenobarbital is one of the common drugs that is used for treatment seizer. The patient had a negative family history. The physician's diagnosis was the likelihood of a drug reaction. Treatment was started with diazepam and methylprednisolone. She was discharged following hospitalization for 3 days with a considerable improvement in lesions, and the general condition of the patient appeared to be good, so new drugs were not used for her.

After one week, she was again hospitalized due to generalized lesions as popular erythematosus on the upper and lower limbs and abdomen as well as involvement of the mucous membranes of the eyes and mouth. Physical examination showed normal heart and lung auscultations and normal neurological and abdominal examinations. Tests including CBC (complete blood count), DIFF (differential blood count), BUN (blood urea nitrogen), CR (creatinine), ESR (erythrocyte sedimentation rate), and CRP (C-reactive protein) were then conducted (Table 1). Serum therapy was later conducted as well. In this step, a nasopharyngeal swab reverse transcription-polymerase chain reaction test (RT-PCR), as well as serology tests for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [immunoglobulin (Ig)M and IgG] were requested based on the early diagnosis of Stevens–Johnson and the possibility of MIS-C. MIS-C with severe inflammatory responses such as rash and fever involves multiple organs and the cardiovascular system. Intravenous immunoglobulin (IVIG) anticoagulants and steroids are usually used for the treatment of the disease[8]. Although the result of the RT-PCR test was negative, treatment with 0.1 g/kg IVIG and corticosteroids was started based on a positive serology test (IgM: 1.45 and IgG: 0.32) as well as skin–respiratory involvement and contact with a suspected COVID patient. Table 1 shows the results of the related tests. During the regeneration time (3 days), the patient was discharged with improvement of skin symptoms and manifestations, good general condition, and stable vital signs. The treatment process is presented in Figure 1.

The patient's parent has given consent for the possible publication of this case report.

Table 1

The results of related tests in different steps

	First referring	Second referring	Follow-up	Normal range
White blood cell count (WBC)	10 100	3500	6200	4000–11 000 μl
Red blood cell count (RBC)	4.21	4.06	–	4.1–5.1 trillion per liter
Hemoglobin (HB)	10.8	10.1	10.3	Male: 14–18 g/dl Female: 12–16 g/dl
PLT	360 000	327 000	354 000	140 000–440 000/dl
Hct	33.4	33.0	–	Male: 39–52% Female: 36–46%
MCV	79.33	81.28	–	77–97 pg
MCH	25.65	24.88	–	26–32 pg
MCHC	32.34	30.61	–	32–36 pg
Poly (%)	52	37	59	–
Lymph (%)	48	58	38	–
Eosinophil (%)	2	3	3	0–5%
Na	140	–	–	135–145 mEq/l
K	4.1	–	–	3.7–5.2 mEq/l
BUN	7	14	13	5–23 mg/dl
Creatinine	0.7	0.7	0.7	Male: 0.7–1.4 mg/dl Female: 0.6–1.3 mg/dl
ESR	20	89	–	0–20 mm/h
CRP	Negative	Negative	Negative	1–3 mg/l
AST	–	25	–	Male: <37 U/l Female: <31 U/l
ALT	–	18	–	Male: <41 U/l Female: <31 U/l

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Hct, hematocrit; K, potassium; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; Na, sodium.

Discussion

SJS is a disease known as a rare occurrence in the world (1–3 cases per 1 000 000 persons)[14]. Additionally, the frequency of pediatric SJS/TEN is very low, but a high rate of long-term complications appears in children with SJS/TEN[15]. Clinical manifestations of SJS/TEN are similar to SARS-CoV-2 infections, including mucosal damage and many dermatological complications including oral lesions[16,17]. On the other hand, MIS-C is a life-threatening and subsequent syndrome related to COVID-19[6] in the pediatric age[6,18]. Here, we present a child with MIS-C who was first diagnosed with SJS.

In this case report, the patient suffered from diffuse maculopapular erythema, conjunctivitis, and dry, red lips involving the oral cavity. Based on blister skin lesions and mucosal involvement, the main differential diagnosis was SJS–TEN. Nevertheless, the RT-PCR test for COVID-19 was performed due to the COVID-19 pandemic, the history of one of the patient's relatives in the past few weeks, and the likelihood of MIS-C.

Multisystem inflammatory syndrome in children (MIS-C) is a syndrome associated with COVID-19 along with clinical manifestations such as Kawasaki disease and toxic shock syndrome in pediatric patients with SARS-COV-2 infection[19]. No proper data have been obtained on the incidence of MIS-C in children with COVID-19. However, reports suggest the cumulative incidence of MIS-C per 100 000 people and 1 000 000 individuals with SARS-COV-2 aged less than 21 years to be 2.1 and 316,

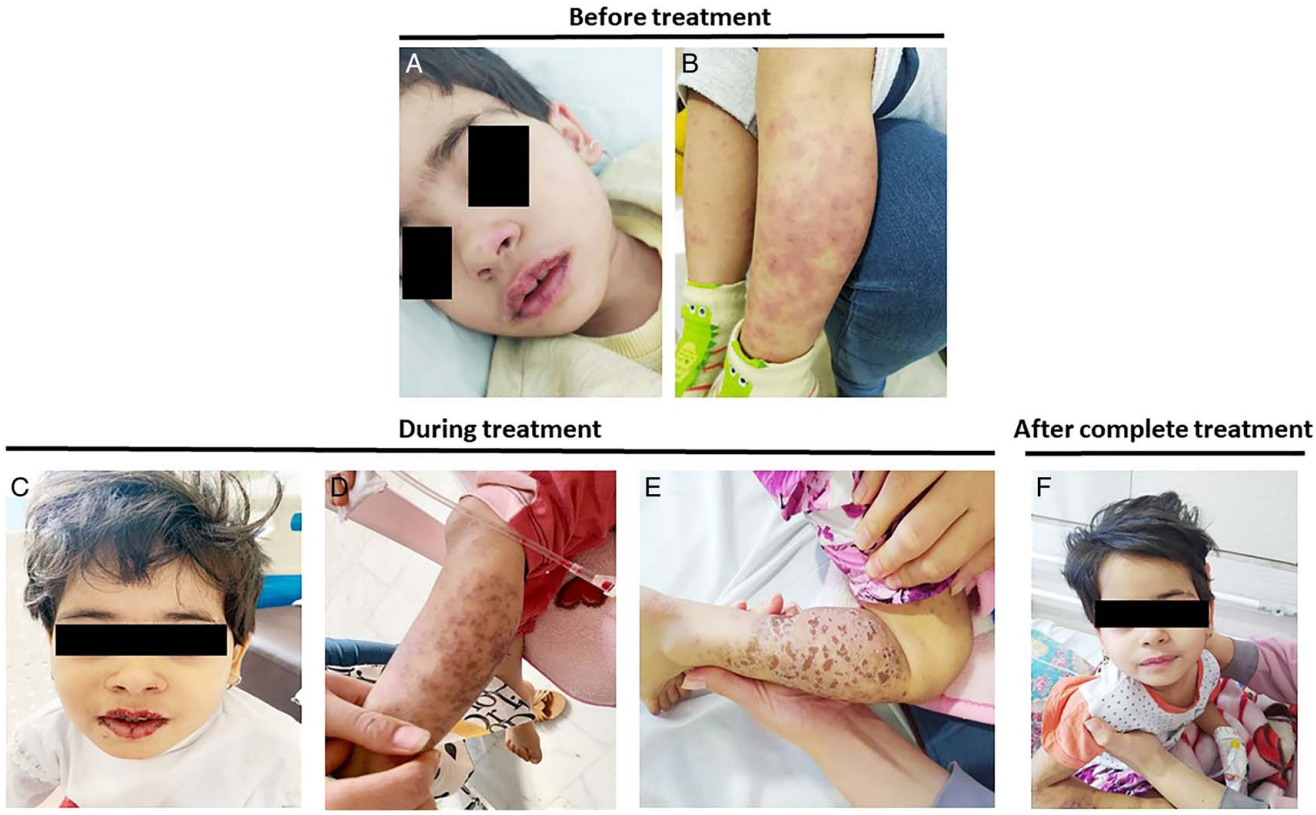

Figure 1. The treatment process of a girl with early diagnosis of Stevens–Johnson syndrome and suspected COVID infection and properly multisystem inflammatory syndrome in children. (A) and (B) before treatment, papules and erythematous purpura plaques of the lower extremities in some parts of the back of the bullous, erosive legs, and lip crust. (C), (D) and (E) during treatment. (F) After complete treatment.

respectively[20]. The result of the RT-PCR test was negative. However, positive serologic tests, long-term fever, laboratory results, involvement of both dermatologic and hematologic organs, and the result of a computed tomography scan confirmed COVID-19.

Literature review projects some adult cases with SJS associated with COVID-19[21,22]; however, according to reports, the disease seems to be rare in children[16]. Shahraki *et al.* in 2020 reported SJS in an adult patient with acute pneumonia secondary to SARS-CoV-2 infection in Tehran, Iran. The patient received azithromycin and naproxen and improved during 3 weeks[21]. In another study, Lagziel *et al.*[22], reported a 58-year-old female with SARS-CoV-2 and suspected SJS/TEN.

For the first time, Katlan *et al.*, reported two children with MIS-C associated with COVID-19 who were presented with SJS and had kidney and liver function abnormalities. Despite all the treatments, severe hypoxia resulted in the death of one of the cases[23]. Also, Karimi *et al.*[16], reported a 25-month-old boy presented with fever, malaise, diffuse maculopapular rashes, and mucosal involvement with COVID-19. In the first visit, he was diagnosed with SJS.

Conclusion

We reported a case with an earlier diagnosis of SJS associated with COVID-19. Despite the early reports of the low prevalence of symptomatic COVID-19 infection in children, the higher level of infection induced by coronavirus reveals a delay in immune reaction after being associated with COVID-19 infection. MIS-C is diagnosed through mucosal skin manifestations, which are similar to several other diseases like SJS/TEN. However, an extensive differential diagnosis should be considered when visiting a child with mucosal eruption and a suspected history of COVID-19. This suggests that COVID-19 can manifest itself as SJS at the first visit of a patient, and the SARS-CoV-2 test is thus more appropriate to be requested for such cases at the early phase of diagnosis.

Ethical approval

Ethical approval for this study (IR.GOUMS.REC.1401.386) was provided by the Ethical Committee of Golestan University of Medical Sciences Research on 27 November 2022.

Consent

Written informed consent was obtained from the patient's parents/legal guardian for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

M.E. and S.A.A.: presented the idea and were involved in reviewing the manuscript; A.R. and M.M.: joined in writing the manuscript and literature review.

Conflicts of interest disclosure

There are no conflicts of interest.

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