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CASE REPORT

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The role of treatment with plasma exchange therapy in two pediatric toxic epidermal necrolysis cases related to COVID-19

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Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening mucocutaneous reactions characterized by necrosis and detachment of the epidermis. Drugs and bacterial or viral infections are the most common causes of SJS/TEN. Although cases of SJS/TEN have been reported after hydroxychloroquine, vaccine (mRNA [Biontech], and inactivated vaccine [Sinovac]) administration and during the clinical course of active Coronavirus disease 2019 (COVID-19), limited data is indicating the COVID-19 disease as a triggering factor. Also, there are no pediatric cases of SJS/TEN associated with COVID-19 in the literature. Herein we reported two pediatric cases with a diagnosis of TEN related to COVID-19. Therapeutic plasma exchange therapy was applied to both of our patients. Although there are a few adult cases in the literature, our article is the first pediatric case report about patients diagnosed with TEN related to COVID-19 and successfully treated with plasma exchange.

KEYWORDS

COVID-19, plasma exchange, toxic epidermal necrolysis

1 | INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening mucocutaneous reactions characterized by necrosis and detachment of the epidermis.[1] Since these two diseases are defined as the continuation of each other, they are differentiated with body surface area involvement.[2] Although the disease was divided into 5 subgroups in the first international classification, today, involved body surface area is lesser than 10% in SJS and greater than 10% in TEN in standard classification.[3,4] The disease severity score for TEN (SCORTEN) has been used to assess the severity of TEN and consists of seven parameters. There is also a pediatric version of this scoring system.[5] It is reported that 17% to almost 50% of all SJS and TEN patients are younger than 18 years and the mortality rate ranges up to 35% including all ages.[5]

Drugs (anticonvulsants, antibiotics, antiretrovirals, and nonsteroidal anti-inflammatory agents) and bacterial or viral infections (*Mycoplasma pneumoniae*, group A β Hemolytic Streptococcus, Rickettsia, Coxsackie virus, Influenza virus, Ebstein-Barr virus (EBV), Herpes virus 6/7, and Parvovirus, etc.) are the most common causes of SJS/TEN. Malignancies, rheumatologic diseases, and graft-versus-host disease are rare causes of the disease. Also, postvaccination cases have been reported in the literature.[6,7]

Severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) was identified with an outbreak of pneumonia in December 2019 and caused a pandemic with rapid spread.[8] Although it is thought that Coronavirus disease 2019 (COVID-19) affects adults more frequently and severely at the beginning of the pandemic, it is now known to cause serious diseases with various clinical pictures and different organ involvements in children.[9]

Although cases of SJS/TEN have been reported after hydroxychloroquine, vaccine (mRNA [Biontech] and inactivated vaccine [Sinovac]) administration and during the clinical course of active COVID-19 disease, limited data is indicating the COVID-19 disease as a triggering factor.[10-12] Also, there are no pediatric cases of SJS/TEN associated with COVID-19 in the literature.

We present two cases of TEN related to COVID-19, either by molecular tests or radiological proof. The role of COVID-19 in the differential diagnosis of SJS/TEN was also highlighted.

2 | CASE 1

A previously healthy 6-year-old girl presented to the emergency department (ER) with complaints of stomachache and neck swelling and outpatient treatment with amoxicillin-clavulanate was arranged. A day later, she was admitted to ER with an eye discharge, fever reaching 39°, widespread maculopapular rashes, and fatigue. As she had complaints for 3 days, she was hospitalized with a prediagnosis of TEN and methylprednisolone (2 mg/kg/day) and intravenous immunoglobulin (IVIG) (2 g/kg) treatments were administered. Antibiotherapy was arranged as vancomycin, clindamycin, and ciprofloxacin due to high-acute phase reactants. Her rashes worsened during the clinical course and she was referred to our pediatric intensive care unit because of her poor general condition and need for inotropes.

Upon admission to PICU, the patient was conscious and oriented, vital signs were as follows: blood pressure 108/62 mmHg with noradrenalin infusion (0.2 mcg/kg/min), heart rate 140/min, respiration rate 30/min, peripheral oxygen saturation without oxygen support: 100% and body temperature 38°C. There were widespread erythematous, vesiculopustular lesions on the face and body, especially on the distal parts of extremities, and bullous lesions in the edematous oral mucosa. The scalp and acral region are preserved (Figure 1). No other pathological finding was found in the physical examination. Her pediatric SCORTEN was 3 and the percentage of skin involvement was calculated as 44.5% by Modified Lund Browder Scale.

Laboratory examinations revealed leucopenia (1.11 10^3/ml), lymphopenia (0.33 10^3/ml), thrombocytopenia (83 10^3/ml), decreased sedimentation rate (3 mm/h), increased pro-BNP (1470 ng/L), C reactive protein (CRP, 60.22 mg/L) and procalcitonin (16,65 μg/L) levels. Other biochemical tests, blood gas analysis, cardiac markers, ferritin and d-dimer levels were normal. Polymerase chain reaction (PCR) test for COVID-19 was positive.

Complement factors, antineutrophil cytoplasmic and antinuclear antibodies, immunoglobulins, blood culture, TORCH panel, viral serologies including hepatitis, EBV, and human immunodeficiency virus were tested for the differential diagnosis considering autoimmune, rheumatological, and infectious etiology. No significant results were found in the test results. Punch biopsy was performed for histopathological diagnosis by dermatology with high-clinical suspicion of TEN due to eye and mucosal involvement, positive Nikolsky sign, and widespread rash. Local oral and eye care was performed. Plastic, reconstructive, and aesthetic surgery recommended washing the wound with antiseptic solutions every other day and covering it with a soft paraffin dressing-containing antiseptic, 5% chlorhexidine acetate BP (Bactigras).

On the second day of her hospitalization, although bone marrow examination could not be performed due to poor general condition and widespread lesions in the body, she was evaluated with macrophage activation syndrome (MAS) due to bicytopenia (leucopenia and thrombocytopenia), hyperferritinemia (316.6 μg/L), hypertriglyceridemia (372.6 mg/dL), high d-dimer levels (3.33 mg/L) and hypofibrinogenemia (176 mg/dL). No hemophagocytosis was observed in the peripheral smear. A temporary hemodialysis catheter was inserted with sedoanalgesia and therapeutic plasma exchange (TPE) was performed on the fifth day of disease, 48 hours after the IVIG and steroid therapies, due to elevated lactate dehydrogenase, thrombocytopenia, worsening of rashes and increased need for inotropes. TPE was performed with the Prismaflex (Baxter) system, and TPE 2000 sets were used. The amount of plasma was calculated as follows: estimated plasma volume (L) = 0.065 × weight (kg) × (1 − hematocrit). We used fresh frozen plasma for the replacement fluid. Saline 0.9% was used to prime the PE circuit. Blood flow was adjusted to 50 mL/min during the TPE procedures. Vital signs were thoroughly monitored during the TPE procedure. Control blood samples were taken immediately before and after TPE. Neither blood products nor electrolyte replacement was not needed. Three sessions of TPE treatment were carried out. Pulse steroid and IVIG treatment were given after each session. After 3 days of pulse therapy, the steroid was continued as maintenance.

Whole-body debridements were performed by pediatric surgery, and lesions seen as third-degree burns were

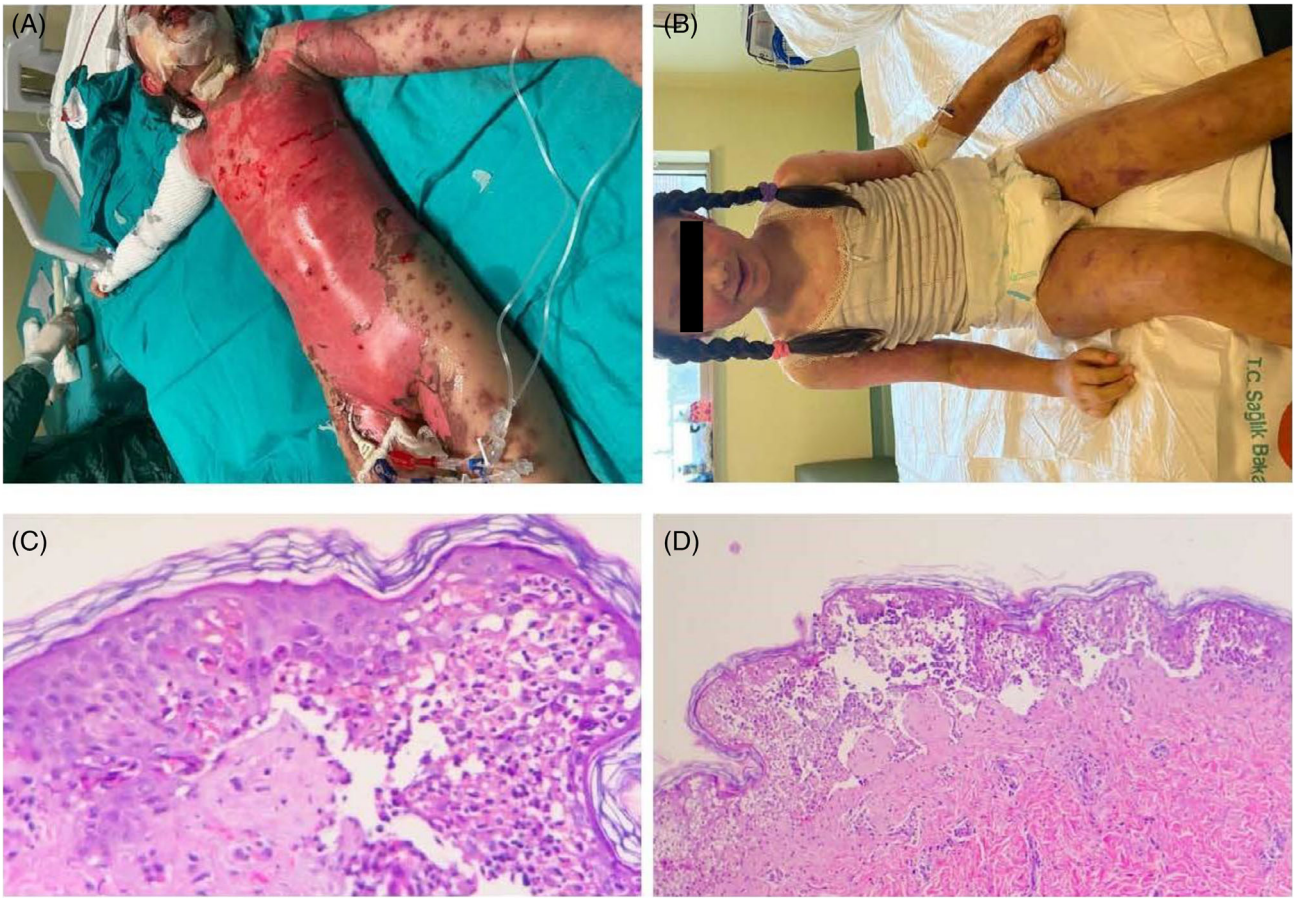

FIGURE 1 Clinical and histopathological features of case 1. A, Presentation of case 1, with widespread maculopapular rashes and detachment of epidermis. B, Healing of rashes and detachment areas with scar tissue, after treatment. C, Extensive necrosis of keratinocytes and polymorphonuclear leucocyte infiltration within epidermis, with bulla formation. H&E × 400. D, Subepithelial detachment due to transmural wide single cell necrosis in epidermis, with polymorphonuclear infiltration. H&E × 20

covered with a synthetic absorbable microcell dressing (Suprathel). After the integration of the synthetic dressing with the skin, a wound care bath was performed. Wound care was performed regularly with Bactigras and antibiotic ointment until skin integrity was achieved. Blood electrolytes and albumin levels were followed. High-calorie diet, zinc, vitamin C, and glutamine supplements were given. Ventilation support was not required during the hospitalization.

The punch biopsy result was consistent with TEN, there were no negative diff results and no accumulation.

On the 21st day of hospitalization, the patient was discharged with complete skin integrity and pediatric allergy control was planned.

3 | CASE 2

A 6-year-old boy without a significant medical history presented to the pediatric ER with complaints of stomachache, nausea, vomiting, and fever. He had widespread vesicular and maculopapular rashes. His family had a history of COVID-19 3 weeks before. He was hospitalized on his third day of complaints, with a prediagnosis of SJS, and IVIG (2 g/kg) and methylprednisolone (2 mg/kg/day) treatments were given. Despite all treatments, his rashes got worse. He was transferred to PICU for further investigation and treatment.

Upon admission to PICU, the patient was conscious and his vital signs were stable except for tachycardia. He had extensive, confluent erythematous vesicles and bullae all over his face and body (Figure 2). His pediatric SCORTEN was 2 and the percentage of skin involvement was calculated as 32.5% by Modified Lund Browder Scale. Laboratory examinations revealed leucopenia (2.83 10^3/mL), lymphopenia (0.54 10^3/mL), hyponatremia (130 mmol/L), increased ferritin (189.8 μg/dL), interleukin 6 (12 pg/mL), CRP (14.26 mg/dL), triglyceride (207.7 mg/dL), blood glucose (230 mg/dL) levels, decreased sedimentation rate (2 mm/h) and fibrinogen (176 mg/dL) and levels. Other

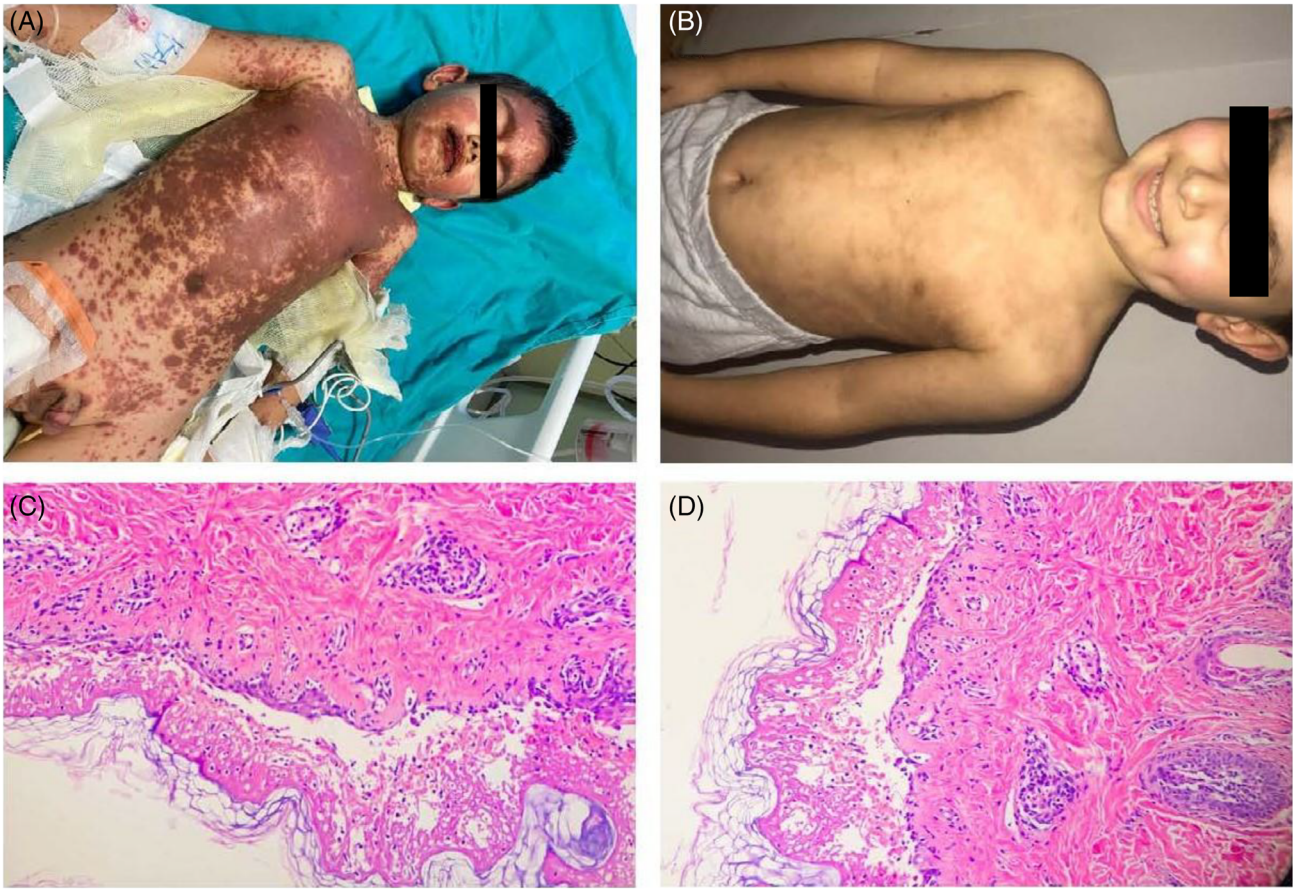

FIGURE 2 Clinical and histopathological features of case 2. A, Presentation of case 2, with widespread vesicular and maculopapular rashes. B, Healing with rudimentary scar tissue, after treatment. C, Transmurally observed single cell necrosis within epidermis, with lymphocyte and sparse polymorphonuclear leucocyte infiltration. Subepithelial and suprabasal irregular detachment with due to extensive keratinocyte necrosis. H&E × 100. D, Acantholytic detachment due to epidermal necrosis, also seen in hair follicles

biochemical tests, blood gas analysis, cardiac markers, and d-dimer levels were normal. COVID PCR test was negative, but COVID-19 antibody analysis was positive. Influenza A was detected in the nasopharyngeal swab test. The punch biopsy result was also compatible with TEN.

As in the first case, he was tested for differential diagnoses of autoimmune, rheumatological, and infectious etiology. Wound care, local care, antibiotics, and supportive treatments were applied in the same way as the first patient.

TPE was performed on the seventh day of disease, 96 hours after the IVIG and methylprednisolone treatments, as his rashes worsened and signs of MAS occurred despite IVIG, methylprednisolone, and oseltamivir treatments. Pulse steroid and IVIG treatment were also given after each TPE session. After three sessions of TPE treatment, the steroid was continued as maintenance.

On the twelfth day of hospitalization, the patient was discharged and pediatric allergy control was planned.

4 | DISCUSSION

SJS/TEN are clinical conditions with severe skin involvement; it may affect all age groups. Drugs are mainly held responsible for etiology and immunosuppressive agents such as IVIG and cyclosporine were used for treatment.[1,4] Also, positive outcomes were reported with tumor necrosis factor (TNF-α) inhibitors and plasma exchange in the management of SJS/TEN.[13] Along with the studies emphasizing the success of IVIG treatment, several case series have shown that the plasma exchange decreases serum cytokine levels and is effective for the treatment of SJS/TEN patients who were refractory to supportive therapy or systemic corticosteroid therapy.[13] Since the beginning of the COVID-19 pandemic, different clinical conditions and various amounts of skin signs due to coronavirus infection were reported.[14] According to a review study of 113 articles mostly including case reports, by Conforti C. et al, the erythematous maculopapular rash is

reported to be the most frequent sign of skin involvement.[15]

In the literature, the role of coronavirus infection in skin lesions is not clarified yet and it is emphasized that it may worsen the rashes due to drug side effects.[15,16] Data related to SJS/TEN among the skin signs related to COVID-19 are present according to the limited case reports. In the past studies, there are SJS/TEN case reports related to COVID-19 vaccination[10,17] and drugs for COVID-19 treatment.[18] Also, there are studies in which primarily coronavirus infection is mainly held responsible for the etiology of SJS/TEN.[12,19,20] In addition, SJS/TEN was detected in two cases with acute respiratory distress syndrome compatible with COVID-19 despite a negative COVID-19 PCR test.[21] Like in the classical SJS/TEN, various opinions about immunosuppressive treatments are present in COVID-19 related SJS/TEN cases, due to its effect on coronavirus infection.[4,13] In all these opinions, IVIG seems to be the best choice among treatment options similar to non-COVID-19 SJS/TEN patients.[22] In the literature, it has been reported that TNF-α inhibitors and TPE are used in the treatment of a few cases of COVID-19-related TEN/SJS.[23,24]

It is known that the Influenza virus is involved in the etiology of classical SJS/TEN and these cases generally respond to treatment.[1] In our second case, the development of SJS/TEN is affiliated with Influenza A, which was positive in molecular analysis, and IVIG and steroid therapies were given. In this case, despite the conventional therapies for TEN and adequate antiviral therapy for Influenza with the right timing, rashes got worsened and MAS signs occurred both in clinical and laboratory assessments. As he had a family history of COVID-19 and the presence of SARS-CoV-2 antibodies, it is suspected that COVID-19 infection may have a role in etiology due to poor response to conventional therapies. There is some uncertainty regarding the etiology of SJS/TEN in this case, but we believe it was caused by COVID-19 due to the presence of COVID-19 antibody and the family is known to have had COVID-19 3 weeks prior to patient presentation. In either of our cases, TPE was performed with pulse steroid therapy due to worsening clinical condition and unresponsiveness to IVIG and steroid therapies and we had successful outcomes. All other etiological factors were investigated in both cases and neither of the cases has no other suspected factor. MAS developed in both of our cases during the clinical course meets the HLH-2004 diagnosis criteria and a good clinical outcome was achieved with plasma exchange therapy. We suggest that it is the first reported pediatric SJS/TEN/Hemophagocytosis case related to COVID-19.

AUTHOR CONTRIBUTIONS

Yasar Yusuf Can, Ceyhan Sahin, Fatima Gursoy, Tugba Akin, Ebru Sahin, and Fatih Varol had a role in the patient's diagnosis. Yasar Yusuf Can, Cansu Durak, and HC had a role in the literature overview. Fatih Varol, Ebru Sahin, and Aziz Kilic played a role in case documentation and table preparation.

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CONFLICT OF INTEREST

None of the authors of this article has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Our patient's parents obtained detailed informed consent. The photographs of the children are being used with the permission of the parents/guardians of the children.

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