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Case Report

COVID-induced toxic epidermal necrolysis in a 4-year-old female: a case report and literature review

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Abstract: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are conditions characterized by an immune-mediated skin reaction that results in blistering and epidermal detachment. Most cases are caused by drug hypersensitivity; however, recently there have been many publications documenting the association between coronavirus disease 2019 (COVID-19) and SJS/TEN. Our objective is to explore a case of a 4-year-old female who presented with a papular rash on her thighs that progressively worsened and spread to her face, trunk, and genital area. The patient tested positive for COVID-19. She required treatment with intravenous immunoglobulin (IVIG) and IV methylprednisolone, but eventually made a full recovery. This case underscores the need for awareness of the wide spectrum of dermatologic presentations in COVID-19 patients.

Keywords: Toxic epidermal necrosis, pediatric, COVID-19

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are similar conditions characterized by an immune-mediated skin reaction that results in blistering and epidermal detachment. The difference between these two conditions is that TEN is defined as a skin reaction involving more than 30% of the total body surface area (TBSA), whereas SJS involves a TBSA lower than 10% [1].

It has been previously reported that 85-95% of TEN cases are caused by drug hypersensitivity [2], and the pharmaceutical treatment of coronavirus disease 2019 (COVID-19) has induced a number of these cases [3-7]. While multiple studies have been published recently regarding the development of SJS due to COVID-19 vaccinations [8-12], only two incidences of TEN following COVID-19 vaccination have thus far been documented [17]. Even more rare, however, is the development of SJS/TEN induced directly by COVID-19.

The current literature demonstrates primarily adult COVID-19-induced SJS/TEN, with only one pediatric case reported [18]. The TBSA involvement of most cases is not reported and with one exception, the reported TBSA does not definitively place the patient within the range of a TEN-only diagnosis [13-16, 18].

This report explores a case of a 4-year-old female admitted to our Burn Center. Her TEN progressed to include an estimated 65% TBSA, making her surface area involvement significantly larger than any case published in literature thus far.

Case presentation

A 4-year-old female with no prior medical history was transferred from a referring facility to our pediatric intensive care unit (ICU) with a worsening rash. One week prior to her hospital admission, the patient was seen by her pediatrician for a papular rash on her thighs, which was initially believed to be hand-foot-and-mouth disease. A few days later, the patient's mother noticed vesicular lesions within the patient's mouth which had started to slough. Her rash worsened and spread to her face, trunk, and genital area. She was sent to the Emergency

Figure 1. Clinical appearance of patient's (A) anterior and (B) posterior trunk after diagnosis of TEN.

Room for possible TEN where she also tested positive for COVID-19. The patient did not have any respiratory symptoms at that time. She was admitted to the outside referring facility and a skin biopsy was performed. Additional blood tests were ordered, including Hepatitis C Antibody, Hepatitis B Surface Antigen, cytomegalovirus (CMV) IgG, CMV IgM, Herpes Simplex Virus (HSV) 1 and 2, HSV PCR, Varicella PCR, Syphilis, Human Immunodeficiency Virus (HIV), and Mycoplasma PCR. All tests were negative. The rash was treated with triamcinolone acetonide cream, petroleum jelly, and intravenous (IV) methylprednisolone.

Two days later, the patient became febrile to 39.7°C with worsening respiratory symptoms and right upper lobe (RUL) opacities on her chest x-ray. She required two liters per minute of oxygen via nasal cannula and was started on a five-day course of remdesivir. Blood and urine cultures were negative. Patient remained febrile and was found to have a worsening white blood cell (WBC) count, as well as an elevated C-reactive protein (CRP). Oxygen support via nasal cannula was eventually discontinued as the patient had improved from a respiratory standpoint; however, given the fever and elevated WBC count, she was started on IV cefepime and vancomycin at the outside facility. There was no improvement in her rash, and plans were made to transfer her to our Burn Center for further care. Prior to the transfer, the patient underwent bilateral amniotic membrane transplants.

On admission to our facility, she was afebrile and in no respiratory distress with clear breath sounds. She was noted to have diffuse erythematous macules with scattered vesicles in various stages covering her skin. The patient was evaluated by Dermatology, who confirmed severe mucositis including the ocular, oral, and genital regions. They also noted diffuse skin detachment with at least 30% of TBSA involvement, all of which were consistent with TEN (**Figure 1**). Upon further review, it was noted that the patient had received ibuprofen, melatonin, guaifenesin, dextromethorphan, vitamin C, and a multivitamin over one month prior to her initial presentation. Although all medications had been administered over a month prior to the start of the rash, and therefore beyond the expected time course of implicated medications, the Dermatology team recommended avoidance of all non-steroidal anti-inflammatory drugs (NSAIDs) and listed ibuprofen as an allergy. The patient was started on intravenous immunoglobulin (IVIG) at 2 mg/kg divided over four days in addition to IV methylprednisolone. Detached skin areas were covered with petroleum jelly gauze until re-epithelialization. The face was cleaned with sterile isotonic sodium chloride solution, and bacitracin ointment was applied. She was also evaluated by Gynecology for labial mucositis and mildly adhered proximal labia. The recommendations were to apply daily conjugated estrogen cream with daily labial separation.

The following day, the patient was intubated due to worsening TEN and increasing oral mucosal involvement. She was started on total parenteral nutrition (TPN) with lipids. Tube feeds were paused temporarily due to elevated lactate; however, they were restarted shortly thereafter. Since there were no new signs of infection and all work-up had been negative up

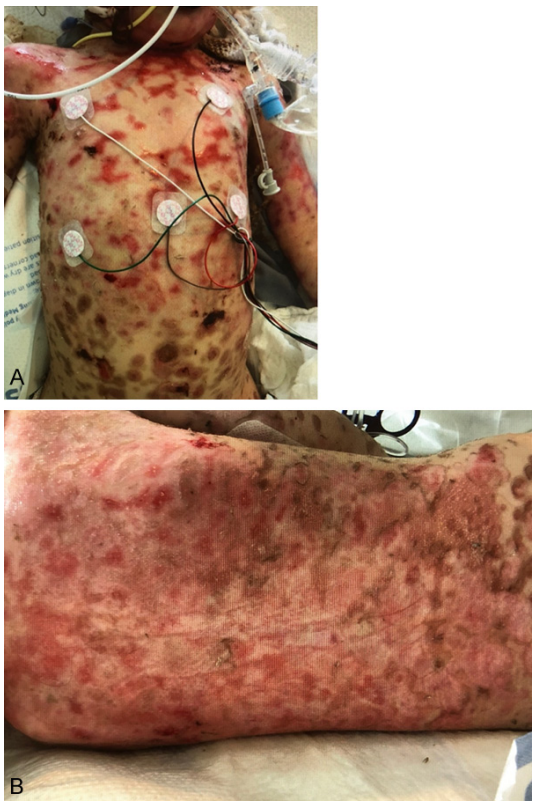

Figure 2. Clinical appearance of patient's (A) anterior and (B) posterior trunk five days after Suprathel application.

to that point, IV cefepime and vancomycin were discontinued.

The patient underwent debridement and placement of Suprathel (PolyMedics Innovations GmbH, Denkendorf, Germany) with Burn Surgery. At the point of the procedure, the patient's TBSA involvement was estimated to be about 65%. Her rash improved gradually (**Figure 2**). She was weaned off sedation slowly, and the methylprednisolone dose was decreased as the rash continued to improve. The patient was eventually extubated. She was transitioned to a full diet prior to discharge, which she tolerated well. The patient received IVIG for four days, high-dose IV methylprednisolone with taper for ten days, and vitamin C for ten days. On subsequent follow-ups with Dermatology, she was treated for paronychia of her nails secondary to onychomadesis from TEN, but otherwise she was doing well.

Discussion

Per the Centers for Disease Control (CDC), about 1.7% of COVID-19 cases reported as of April 2020 occurred in pediatric patients aged < 18 years. In addition, the CDC estimated that 20% of all pediatric COVID-19 patients were hospitalized, compared to 33% of adult patients aged 18-64 years. Many of those adult patients who died due to COVID-19 had underlying comorbidities including obesity, diabetes, hypertension, or other cardiovascular diseases that may have compromised their immune systems. However, the virus has had a milder effect on the pediatric population [18].

Most cases of SJS/TEN occur due to drug hypersensitivity [2], often triggered by sulfonamides and anticonvulsants, including phenobarbital, lamotrigine, and carbamezapine [18, 19]. Other drugs, including penicillins, cephalosporins, valproic acid, acetaminophen, and NSAIDs may also pose potential risks as triggers [19]. SJS/TEN generally develops about 4-28 days after initial exposure to the drug [5]. There are also multiple cases where SJS was reported to be due to bacterial infections (e.g., Streptococcus group A and mycobacterium), as well as viral infections (e.g., influenza, Epstein-Barr, coxsakie, herpes virus 6 and 7, cytomegalovirus, and parvovirus) [19].

The pathophysiology of SJS/TEN is not fully understood; however, it is generally thought to be a T-cell-mediated disorder. In the early stages of the disease process, cytotoxic $CD8^+$ T cells infiltrate blister fluid and the epidermis, and $CD4^+$ T cells infiltrate the dermis [20]. The diagnosis of SJS/TEN includes an initial clinical evaluation and skin biopsy. The cutaneous presentation is characterized by an erythematous rash, bullae, and erosions that appear on the face, trunk, and the extremities [20]. Early skin lesions may appear as atypical two-ringed, flat targets before blistering occurs [20, 21]. Mucosal involvement may affect oral, ocular, and genitourinary sites [21]. Skin lesions are typically positive for Nikolsky sign, which manifests as epidermal detachment when pressure is applied to the lesions [20].

The treatment of SJS/TEN includes immediate discontinuation of any suspected causative drugs. This is usually followed by supportive care, including fluid replacement, nutritional assessment, and pain relief [20]. The optimal treatment strategy for SJS/TEN remains controversial. Although there have been reports of positive outcomes with the use of systemic corticosteroids, IVIG, cyclosporine, TNF-α antago-

Table 1. Summary of articles reporting cases of COVID-related SJS/TEN

AUTHORS	YEAR LOCATION	AGE (Years)	SEX	CAUSE	ONSET	NEW MEDICATIONS BEFORE ONSET	SYMPTOMS	TREATMENT
Abdelgabar, Elsayed [14]	2021 United Kingdom	23	Male	COVID-19	Day 14	None	Diffuse oral ulcerations with some hemorrhagic areas on upper lips, tongue, and posterior pharynx; Glans penis was erythematous with whitish exudate; Clinical diagnosis: EM/SJS	Supportive care
Jouhar, Yahya, Elsiddiq [18]	2021 Qatar	6	Male	COVID-19	Day 10	Ibuprofen (2 weeks prior to rash)	Fever, oral ulcers; Maculopapular rash on trunk, extremities, palms, and soles; Mild, purulent conjunctivitis and crusted lip lesions; Skin biopsy: SJS/TEN	Supportive care; IVIG 1 g/kg daily for 5 days; IV dexamethasone; Switched to oral prednisolone and cyclosporine 3 mg/kg/day
Muhd Besari, Lim, Vellaichamy, Hussain, Kamaludin, Nor [13]	2021 Malaysia	75	Female	COVID-19	Day 9	Not reported	Oral ulcers, purpuric macules, malaise, poor appetite, conjunctivitis, and genital ulcers; Skin biopsy: SJS	Supportive care
Narang, Panthagani, Lewis, Chohan, Ferguson, Nambi [15]	2020 United Kingdom	53	Female	COVID-19	Day 5	Dexamethasone (Unclear start date prior to rash; Used for brain metastasis)	Previous history of metastatic breast cancer; Maculopapular rash on chest, upper back, and legs; Erosions and hemorrhagic crusting of oral mucosa; Skin biopsy: TEN	Supportive care; Topical corticosteroids and emollients
Tanaka, Isei, Kikuzawa, Hinogami, Nishida, Gohma, Ogawa [16]	2020 Japan	81	Female	COVID-19 (Recurrence)	Day 40	Azithromycin Hydroxychloroquine Ciclesonide Cefmetazole Ampicillin	Widespread erythematous lesions; Skin biopsy: TEN	IVIG; Steroid pulse therapy followed by prednisolone 0.6 mg/kg/day

nists, and plasmapheresis, evidence for systemic therapy remains insufficient [20]. It is likely that the efficacy of systemic treatment strategies depends on the disease phase. For instance, in the acute phase of the disease process, immunosuppressive therapies are considered suitable since a strong inflammation-like "cytokine storm" occurs in the patient [20]. However, once epidermal detachment develops, immunosuppressive therapies may hinder re-epithelization and increase the risk of infection [20].

In the case of SJS/TEN due to COVID-19, the diagnosis and treatment of the cutaneous lesions remains the same. However, the use of immunosuppressive agents in this patient population needs to be carefully considered and weighed against the potential progression and worsening of COVID-19 symptoms if such therapy is initiated.

Currently, there are four incidences of SJS/TEN in adults due to COVID-19 reported in literature [13-16]. One case involves a 75-year-old female with confirmed COVID-19 who on day 9 of her illness began developing mucocutaneous ulcers which eventually progressed to biopsy-confirmed SJS [13]. Another case is that of a 23-year-old male with confirmed COVID-19 and dermatologic lesions who received a clinical diagnosis of overlapping erythema multiforme (EM) and SJS, though this diagnosis was not confirmed with a biopsy [14]. A third published case described a 53-year-old female who developed a maculopapular rash 5 days after a positive PCR test for COVID-19 that eventually progressed to biopsy-confirmed full thickness epidermal necrosis involving greater than 10% of her TBSA, and thus giving her a diagnosis of SJS/TEN overlap [15]. The final case in literature is of an 81-year-old female who was hospitalized for COVID-19, recovered with a negative PCR on day 33 after onset, and then on day 40 developed widespread dermatologic lesions that progressed to biopsy-confirmed TEN with an unreported TBSA involvement. She was subsequently diagnosed with COVID-19 again 44 days after initial onset, making her recurrent COVID-19 infection the suspected culprit [16].

Most literature published so far demonstrates only adult COVID-19-induced SJS/TEN, and the TBSA of the reported cases does not definitively place them within the range of a TEN-only diagnosis. Recently, a case of a 6-year-old male with SJS-TEN was published [18]. This case, along with the other COVID-19-associated SJS/TEN reports, is summarized in **Table 1**.

Our report presented the case of a 4-year-old female with a recent history of COVID-19 infection and subsequent development of TEN. Her TEN progressed to include an estimated 65% TBSA, making her involved surface area significantly larger than any case published in literature thus far. Although our patient did have a history of ibuprofen use one month prior to the development of her rash, this occurred beyond the expected time course for implicated medications. Thus, it is very likely that COVID-19 was the trigger in this case.

Conclusion

The purpose of this case report was to raise awareness of the possibility of significant COVID-19-induced TEN in the pediatric population, and to document our institution's successful management of the condition. TEN is a life-threatening skin disorder in which treatment involves immunosuppression, though the treatment itself can be dangerous in the setting of a viral disease state [17]. Because of the impaired immune function of the skin in TEN, patients are at risk for further illness beyond COVID-19, particularly if de-epithelialization is allowed to progress before treatment is initiated. Thus, this case report can serve as a valuable example to inform other providers of an effective treatment strategy for a previously unknown sequelae of COVID-19 infection among pediatric patients.

Disclosure of conflict of interest

None.

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References

[1] Bakir M, Almeshal H, Alturki R, Obaid S and Almazroo A. Toxic epidermal necrolysis post

COVID-19 vaccination-first reported case. Cureus 2021; 13: e17215.
[2] Schwartz RA, McDonough PH and Lee BW. Toxic epidermal necrolysis: part II. Prognosis, sequelae, diagnosis, differential diagnosis, prevention, and treatment. J Am Acad Dermatol 2013; 69: 187, e1-16.
[3] Punyaratabandhu P and Vanitchpongphan S. Favipiravir-induced cutaneous adverse reactions in patients infected with COVID-19. Clin Exp Dermatol 2022; 47: 573-577.
[4] Bulat V, Likic R, Pondeljak N and Azdajic MD. Pholcodine-induced Stevens-Johnson syndrome in a patient with COVID-19. Postgrad Med J 2022; 98: 499-500.
[5] Rossi CM, Beretta FN, Traverso G, Mancarella S and Zenoni D. A case report of toxic epidermal necrolysis (TEN) in a patient with COVID-19 treated with hydroxychloroquine: are these two partners in crime? Clin Mol Allergy 2020; 18: 19.
[6] Davoodi L, Jafarpour H, Kazeminejad A, Soleymani E, Akbari Z and Razavi A. Hydroxychloroquine-induced Stevens-Johnson syndrome in COVID-19: a rare case report. Oxf Med Case Reports 2020; 2020: omaa042.
[7] Shahraki T, Hassanpour K, Arabi A, Ansari I and Sadoughi MM. Coronavirus disease 2019-associated Stevens-Johnson syndrome: a case report. BMC Ophthalmol 2021; 21: 274.
[8] Aimo C, Mariotti EB, Corrà A, Cipollini E, Le Rose O, Serravalle C, Pimpinelli N and Caproni M. Stevens-Johnson Syndrome induced by Vaxvetria (AZD1222) Covid-19 vaccine. J Eur Acad Dermatol Venereol 2022; 36: e417-e419.
[9] Boualila L, Mrini B, Tagmouti A, El Moubarik N, Benchekroun Belabbes M, Boutimzine N and Cherkaoui LO. Sinopharm COVID-19 vaccine-induced Stevens-Johnson syndrome. J Fr Ophtalmol 2022; 45: e179-e182.
[10] Mansouri P, Chalangari R, Martits-Chalangari K and Mozafari N. Stevens-Johnson syndrome due to COVID-19 vaccination. Clin Case Rep 2021; 9: e05099.
[11] Elboraey MO and Essa EESF. Stevens-Johnson syndrome post second dose of Pfizer COVID-19 vaccine: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol 2021; 132: e139-e142.
[12] Dash S, Sirka CS, Mishra S and Viswan P. COVID-19 vaccine-induced Stevens-Johnson syndrome. Clin Exp Dermatol 2021; 46: 1615-1617.
[13] Muhd Besari A, Lim JA, Vellaichamy PT, Hussain FA, Kamaludin Z and Nor M. Stevens-Johnson syndrome as a primary skin manifestation of COVID-19. Postgrad Med J 2021; postgradmedj-2021-140778.
[14] Abdelgabar A and Elsayed M. Case of erythema multiforme/Stevens-Johnson syndrome: an unusual presentation of COVID-19. J R Coll Physicians Edinb 2021; 51: 160-161.
[15] Narang I, Panthagani AP, Lewis M, Chohan B, Ferguson A and Nambi R. COVID-19-induced toxic epidermal necrolysis. Clin Exp Dermatol 2021; 46: 927-929.
[16] Tanaka A, Isei M, Kikuzawa C, Hinogami H, Nishida K, Gohma I and Ogawa Y. Development of toxic epidermal necrolysis in a coronavirus disease 2019 patient with recurrence of positive SARS-CoV-2 viral RNA. J Dermatol 2021; 48: e144-e145.
[17] Shahidi-Dadras M, Shahrigharahkoshan S, Yazdi E, Fatemi A, Mahboubi-Fooladi Z and Dadkhahfar S. Sulfasalazine-induced toxic epidermal necrolysis: a challenging case during the COVID-19 pandemic. Adv Emerg Nurs J 2021; 43: 194-197.
[18] Jouhar L, Yahya M and Elsiddiq S. Toxic epidermal necrolysis associated with COVID-19 infection: a case report. Clin Case Rep 2022; 10: e05565.
[19] Ferrandiz-Pulido C and Garcia-Patos V. A review of causes of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. Arch Dis Child 2013; 98: 998-1003.
[20] Hasegawa A and Abe R. Recent advances in managing and understanding Stevens-Johnson syndrome and toxic epidermal necrolysis. F1000Res 2020; 9: F1000 Faculty Rev-612.
[21] Ramien M and Goldman JL. Pediatric SJS-TEN: where are we now? F1000Res 2020; 9: F1000 Faculty Rev-982.