



Toxic epidermal necrolysis after first dose of Pfizer-BioNTech (BNT162b2) vaccination with pharmacogenomic testing

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Abstract

Toxic epidermal necrolysis (TEN) is a rare and acute life-threatening condition and one of the severe cutaneous adverse drug reactions. There are limited data on TEN from the COVID-19 vaccine regarding its pathogenesis, treatment, and prognosis, particularly in children. We report a case of COVID-19 vaccine-induced TEN and the patient's human leukocyte antigen pharmacogenomic profile.

KEYWORDS

COVID-19 vaccine, pharmacogenomics, toxic epidermal necrolysis

1 | INTRODUCTION

Toxic epidermal necrolysis (TEN) is a rare, acute, life-threatening, drug-related disease, which has an estimated mortality rate of 14.8%–48%^{1,2} and an annual incidence of 0.4–1.2 cases per million from various culprit drugs.³

There have been a small number of case reports of patients who have developed Stevens-Johnson syndrome (SJS)/TEN following COVID-19 vaccine. Here we present the case of a 12-year-old girl with TEN after her first dose of Pfizer-BioNTech (BNT162b2) vaccine.

1.1 | Case presentation

A healthy 12-year-old girl with no previous medical history presented 6 days after her first dose of Pfizer-BioNTech (BNT162b2) vaccine.

Two days after vaccination, she developed a low-grade fever with a mild sore throat. The patient did not take any oral prescribed or over-the-counter medications or herbal remedies during the past 8 weeks. On the 6th day after the vaccine, there were erythematous, painful patches and plaques on the chest wall and trunk, which subsequently spread to the face, palms, and soles. Mucocutaneous erosions were observed in the ocular, oral, and genital regions. She was diagnosed with TEN and immediately admitted to the pediatric intensive care unit.

During the first day of admission, the rash rapidly coalesced and she developed tense bullae, prominently seen on both cheeks and left arm. (Figure 1) Multiple, tiny bullae, dusky patches, and macules were observed. Her lips and oral mucosa were covered with painful hemorrhagic crusts and genital mucosal lesions appeared. She had conjunctival and mucopurulent discharge from both eyes. Asboe-Hansen sign



FIGURE 1 Second day of admission, rapid progressive necrosis and denuded area at face and oral mucosa with worsening ophthalmologic symptoms.



FIGURE 2 A wide-spread area of necrotic skin at the back with Nikolsky sign.

was noted all over the body. She was estimated to have epidermal detachment over 40% of the body surface area. (Figure 2).

Complete blood count, standard chemistry panels, transaminases, and urine analysis were all within normal limits. Chest radiography was normal with negative serology for *Mycoplasma pneumoniae*, Epstein-Barr virus, and human immunodeficiency virus (HIV). Pediatric SCORTEN was 2 on the first day of admission, reflecting a heart rate over 120 beats per minute and epidermal detachment area involving BSA >30%. Histopathology showed subepidermal bullae, full thickness epidermal necrosis, patchy areas of basal cell degeneration

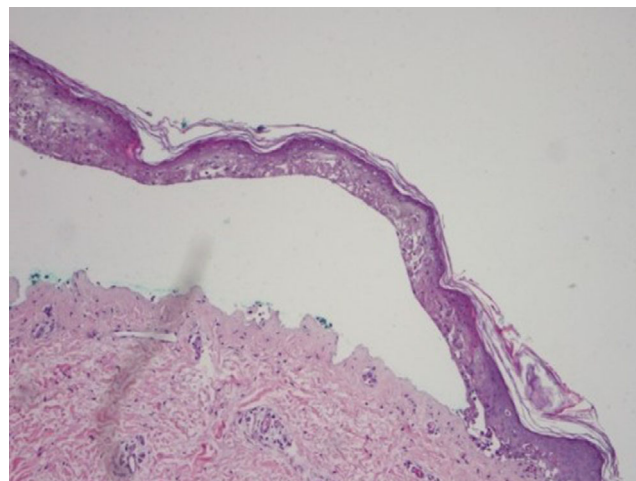


FIGURE 3 Biopsy of full thickness epidermal necrosis with keratinocytes necrosis.

and necrotic keratinocytes and interface dermatitis with perivascular inflammatory cell infiltration (Figure 3). Human leukocyte antigen (HLA) class I and II alleles were determined using PCR sequence-specific oligonucleotide probes. The HLA genotyping in the patient showed *HLA-A*02:03/31:01*, *HLA-B*13:01/15:27*, *HLA-C*04:01/04:06*, *HLA-DRB1*04:06/15:02*, *HLA-DQB1* 03:02/05:01*, *HLA-DQA1* 01:01/03:01*.

Intravenous immunoglobulin (IVIG) (2 g/kg) was given within 24 h after diagnosis, in conjunction with nonpharmacologic treatments, such as fluid, electrolyte and nutritional support, and wound management. No prophylactic antibiotics were prescribed.

Clinical improvement occurred on the second day after IVIG administration, with defervescence of fever and no new skin lesions. Reepithelialization of the skin was noticed on the 7 day after admission. The patient had complete skin reepithelialization on the 12 day after admission, with a total hospitalization of 18 days. She had a full recovery without sequelae.

2 | DISCUSSION

SJS/TEN is an extremely rare adverse event from basic vaccination. In addition, cases of SJS/TEN associated with the COVID-19 vaccine have been rarely reported and are summarized in Table 1.⁴⁻¹²

There have been only nine reported cases of SJS/TEN after COVID-19 vaccine. Five of these patients had underlying diseases, such as hyperlipidemia, diabetes mellitus and breast cancer with a history of medication use.^{6-8,11,12} Most cases of SJS/TEN occurred following the first dose of COVID-19 vaccine. The onset of SJS/TEN after vaccination was about 1-2 weeks (1-14 days). However, underlying diseases, vaccine type, concomitant factors (medication type and duration of treatment, and probably infection) could be additional predisposing factors for SJS/TEN. From the literature review, treatments included anti-tumor necrosis factor-alpha (anti TNF- α), prednisolone, cyclosporine, and IVIG.

TABLE 1 Reported cases of COVID-19 vaccine induced SJS/TEN

Author's name, Reference	Age (years)	Gender	Underlying diseases, drug	Vaccine	Dose	Onset duration after vaccination (days)	Diagnosis	Skin biopsy	SCORTEN	Laboratory	Treatment	Recovery time (days)	Prognosis
Bakir M, et al. ⁴	49	F	No	Pfizer-BioNTech (BNT 162b1)	First dose	7 days	TEN	Confirmed	2 (1 day)	AST 178 U/L ALT 90 U/L CXR-normal	Etanercept × 2 doses	22 days	Good
Elborae MO, et al. ⁵	"Middle-age"	F	N/R	Pfizer-BioNTech (BNT 162b1)	Second dose	5 days	SJS	Not done	N/R	N/R	Oral prednisolone (30 mg/day)	N/R	Good
Dash S, et al. ⁶	60	M	DM+metformin, teneligliptin HT- amlodipine	Astra Zeneca (ChAdOx1 nCoV-19)	First dose	3 days	SJS	Confirmed	1 (1 day)	N/R	Cyclosporine 300 mg	7 days	Good
Mansouri P, et al. ⁷	49	F	Breast cancer (tamoxifen, sodium valproate, alprazolam)	Sinopharm, (China National Biotech Group)	Second dose	3 days	SJS (mild symptoms)	Confirmed	N/R	N/R	Oral prednisolone (30 mg/day)	14 days	Good
Mardani M, et al. ⁸	76	M	Hyperlipidemia (atorvastatin)	China National Biotech Group)	First dose	1 day	TEN	Confirmed	N/R	AST 90 U/L ALT 82 U/L CXR-normal	Oral prednisolone	14 days	Good
Aimo C, et al. ⁹	65	M	No	Vaxvetria (AZD1222)	Second dose	10 days	SJS	Confirmed	N/R	-Thrombocytopenia -Elevated CRP, LDH, fibrinogen, D-dimer -Sagittal sinus thrombosis	Oral prednisolone (1 mg/kg/day)	Within 8 weeks	Good
Kherlopian A, et al. ¹⁰	48	F	N/R	Astra Zeneca (ChAdOx1 nCoV-19)	First dose	14 days	TEN	Confirmed	2 (day-not reported)	-Serology: M, pneumoniae, herpes simplex virus, adenovirus, HIV, hepatitis B, C- negative	Etanercept × 3 doses	35 days	Good
Mansouri P, et al. ¹¹	63	F	Psoriasis, DM- Sitagliptin, metformin	Sinopharm, (China National Biotech Group)	First dose	1 day	SJS	Confirmed	N/R	-CBC, BUN, Cr- normal -HbA1C 6.4% (normal 4%-5.6%)	Oral prednisolone (40 mg/day)	3 weeks	Good
Padniewski JJ, et al. ¹²	46	F	Hyperlipidemia- atorvastatin Obesity DM- metformin	Moderna (Moderna Inc., MRNA 1273)	First dose	3 days	SJS	Confirmed	N/R	-Serology: M, pneumoniae, herpes simplex virus, varicella, tuberculosis, hepatitis B, C- negative -CXR-normal	Oral prednisolone (80 mg/day)	6 days	Good
Our case	12	F	No	Pfizer-BioNTech (BNT 162b2)	First dose	6 days	TEN	Confirmed	2 (1 day): Pediatric SCORTEN	Normal	IVIg 2 g/kg/day	12 days	Good

Abbreviations: F, female; M, Male; N/R, not reported.

All patients had a good prognosis, with a complete time of resolution ranging from 7 days to 35 days. The hospitalization time of drug-induced SJS/TEN in a previous study was 11.8 ± 10.6 days.¹³ However, long-term sequelae should be monitored.

Our case was treated with IVIG due to concern regarding the side-effects of other treatments, including systemic corticosteroids and cyclosporine. Being in a resource-limited setting, we were unable to use anti-TNF-alpha agents in Thailand. Despite clinical data from a systematic review and meta-analysis in 2017¹⁴ regarding the non-usefulness of IVIG, other systematic reviews and meta-analyses in 2012 and 2015 suggested that IVIG was beneficial in reducing mortality in children when compared to studies in adults.¹⁵ Dosages of ≥ 2 g/kg appeared to significantly decrease mortality in patients with SJS or TEN.¹⁶ Thus, IVIG use in pediatric patients is another option in a country with limited resources.

The COVID-19 vaccine is comprised of virotopes and excipients (L-histidine, L-histidine hydrochloride, sucrose, sodium chloride, polysorbate 80, ethanol, water, polyethylene glycol [PEG-2000] and others). The most likely causative vaccine component in one case report was thought to be the virotopes.⁶ The presumptive hypothesis of SJS/TEN from routine vaccination was proposed by Chahal et al.¹⁷ The expression of virotopes on the surface of keratinocytes is similar to drug antigens on keratinocytes that can potentially activate a CD8+ T-cell lymphocyte response. This activation induces the release of chemokines, cytolytic molecules, cytotoxic agents, and enzymes, such as granulysin, granzyme B, and perforin, leading to keratinocyte apoptosis and detachment of epidermis.^{17,18}

mRNA vaccines initially activate toll-like receptor-7/8 (TLR7/8) and retinoic acid-inducible gene-1-like (RIG-I-like) receptors (RLRs), inducing a cellular immune response embraced by CD8+ T cells and macrophages with a T-helper 1 cell profile (Th1). Key cytokines include interferon- γ (IFN- γ), tumor necrosis factor- α (TNF- α), and interleukin(IL)-2 and IL-6.¹⁹

The implementation of pharmacogenomics in clinical practice represents a feasible and likely useful enhancement to the therapeutic management of medication-induced adverse events. Pharmacogenomics may have a role in personalized vaccination plans and potentially could reduce adverse events. HLA encoded by the HLA gene are an important modulator of the immune response and drug hypersensitivity reactions. HLA variants can be a risk factor for developing potentially fatal drug and vaccine-induced hypersensitivity reactions. Interestingly, specific HLA genotypes that confer genetic susceptibility to SCARs have been found in this patient (HLA-A* 31:01-carbamazepine, HLA-B*13:01-cotrimoxazole and dapsone, HLA-DRB1*15:02-allopurinol).²⁰ We hope that the HLA-pattern of this patient might be beneficial for future research on drug susceptibility, particularly of vaccines.

3 | CONCLUSION

The impact of COVID-19 infection is well-recognized all over the world. To date, 3.15 billion doses of vaccines have been provided with

only 10 cases (including our reported case) of SJS/TEN. The occurrence of SJS/TEN is extremely rare and the benefits of vaccination clearly outweigh the risks.

In our case, we describe how early IVIG administration was as an effective and safe treatment for TEN induced Pfizer (BNT162b2) vaccination. We also report the HLA pharmacogenetic biomarkers of this patient: HLA-A* 02:03/31:01, HLA-B* 13:01/15:27, HLA-C* 04:01/04:06, HLA-DRB1* 04:06/15:02, HLA-DQB1* 03:02/05:01, HLA-DQA1* 01:01/03:01.

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CONFLICT OF INTEREST

None declared.

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