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A case series of Stevens-Johnson syndrome/toxic epidermal necrolysis associated with SARS-CoV-2 infection and COVID-19 vaccination | 1

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a rare, potentially life-threatening, acute hypersensitivity reaction of the skin, and the mucosa of the ocular surface, oral cavity, and genitals. Macules rapidly spread, resulting in epidermal blistering, necrosis, and sloughing. The disease is often drug-related, although it may be triggered by infection or vaccination. Viruses, such as herpes simplex, Epstein-Barr, cytomegalovirus, and influenza have already been implicated in the development of SJS/TENS. In this study, Australian authors presented the largest case series of SJS/TEN associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and COVID-19 vaccination. During six months, the authors from the state-wide burns unit in New South Wales, which serves as a referral center for SJS/TEN, had 14 cases of SJS/TEN, seven times the incidence before SARS-CoV-2 infection and COVID-19 vaccination.



According to a total body surface area (TBSA) desquamation percentage, the disease is classified as Stevens-Johnson syndrome, TEN, and SJS/TEN overlap. In Stevens-Johnson syndrome, the changes affect less than 10% of the TBSA, while in TEN more than 30% is affected. If changes affect between 10 and 30% of the TBSA, the disease is classified as SJS/TEN overlap.

In severe cases of TEN, large sheets of epithelium slide off the entire body at pressure points, exposing painful and erythematous skin. In up to 90% of TEN cases, painful oral crusts and erosions, keratoconjunctivitis, and genital problems accompany skin sloughing.



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The exact pathological mechanism of SJS/TEN is unknown. It is speculated that it is triggered through a T-cell-mediated cytotoxic reaction. The implicated pathways are believed to involve a granule-mediated exocytosis or Fas-Fas ligand (FasL) apoptosis cascade. In the granule-mediated pathway, cytotoxic T cells and natural killer cells release perforin, granulysin, and granzyme B, which destroy keratinocytes. The concentration of perforin, granzyme B, and granulysin in blister fluid correlates with the severity of the disease. It has also been found that interleukin-15, which is elevated in patients with SJS/TEN, enhances the production of granzyme B.

According to the theory of Fas-FasL apoptosis cascade, an interaction between Fas (a cell surface receptor that induces apoptosis) and its ligand, particularly a soluble form of FasL released from activated mononuclear cells, results in apoptosis of keratinocytes and blister formation.

About the study

Authors from the state-wide burns unit in New South Wales, Australia, which serves as a referral center for SJS/TEN, reported a seven-fold increase in SJS/TEN presentations over six months in 2022. In six months, they had 14 cases of SJS/TEN, seven times the incidence before COVID-19.

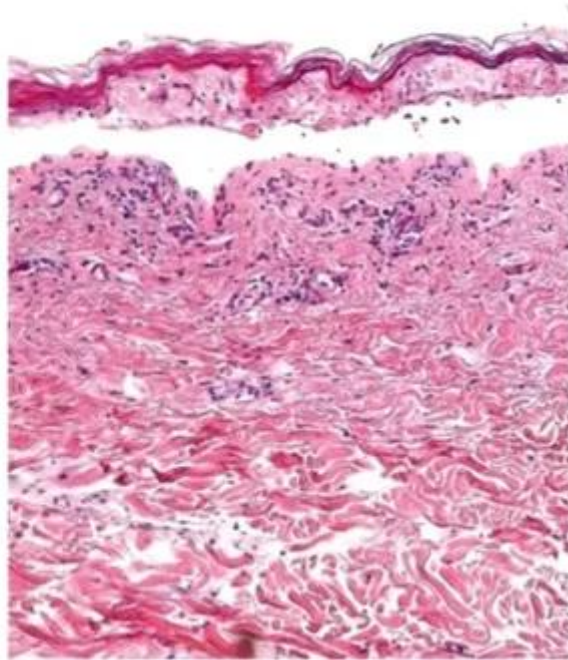
All fourteen cases were vaccinated against SARS-CoV-2. The authors presented eight of the fourteen cases.

Case 1

A 60-year-old woman was admitted with TEN, which affected 55% of TBSA. She was infected with SARS-CoV-2 six weeks before the onset of TEN and was double vaccinated with the mRNA COVID-19 vaccine. She received allopurinol for the exacerbation of her gout. She was treated with allopurinol before, with no adverse effects.

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Pictures from the original paper by Stanley EA. et al. Burns (2023). Toxic epidermal necrolysis with 55% of total body surface area desquamation (Case 1). Left: desquamation. Right: frozen section demonstrating necrotic keratinocytes, full-thickness epidermal necrosis, and subepidermal bullae.

Case 2

A 78-year-old woman was admitted with TEN, which affected 60% of TBSA. Five weeks before TEN onset, she was diagnosed with COVID-19 with pneumonitis and received piperacillin/tazobactam. She was double vaccinated with the mRNA COVID-19 vaccine.

Case 3

A 54-year-old woman was admitted with TEN, which affected 40% of TBSA. She had COVID with pneumonitis secondary to *Aspergillus* and received voriconazole four weeks before the onset of TEN. She was double vaccinated with the mRNA COVID vaccine.

Case 4

A 26-year-old man was admitted with TEN, which affected 70% of TBSA. Three weeks before the onset of TEN, he received the mRNA COVID-19 vaccine. He received two doses of a viral vector vaccine before the mRNA COVID-19 vaccination. Due to the vaccine-associated symptoms, he took paracetamol and ibuprofen, which he had used before without



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any adverse effects.

Case 5

A 45-year-old man was admitted with TEN, which affected 70% of TBSA. He had a COVID-19 infection four weeks before the onset of TEN. He was treated with levetiracetam for seizure prophylaxis. The patient was triple vaccinated with the mRNA COVID vaccine.

Case 6

A 53-year-old woman was admitted with TEN, which affected 95% of TBSA. She was quadruple vaccinated with viral vector and mRNA vaccines. The patient was treated with captopril and amlodipine for scleroderma renal crisis.

Case 7

A 47-year-old man was admitted with SJS/TEN overlap, which affected 10% of TBSA. Five weeks before SJS/TEN overlap onset, he had COVID-19 and was treated with amoxicillin. The patient has previously taken amoxicillin without any adverse effects. He was triple vaccinated with the mRNA COVID vaccine.

Case 8

A 53-year-old woman was admitted with TEN, which affected 90% of TBSA. She received the mRNA COVID-19 vaccine four weeks before TEN onset. The patient was treated with piperacillin/tazobactam for bacterial peritonitis. She has previously taken penicillin with no adverse effects. She was triple vaccinated with the mRNA COVID-19 vaccine.

Conclusion

This study reported the largest case series exploring Stevens-Johnson syndrome/TEN associated with SARS-COV-2 infection and COVID-19 vaccination. The researchers proposed three theories to explain the observed increase in the incidence of SJS/TEN: a virus-induced increase, a vaccine-induced increase, and a threshold-lowering pathway. The first assumption is that SARS-COV-2 may directly bind to receptors that trigger T cell-mediated response and induce SJS/TEN. The second theory proposed that vaccines may initiate SJS/TEN. All fourteen patients presented in this work, who developed SJS/TEN, were previously vaccinated with COVID-19 vaccines. The third theory suggests that the SARS-COV-2 virus or a vaccine may reduce the threshold for drugs that trigger SJS/TEN, “priming” the immune system, which may not have happened without this “priming”.



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The authors emphasized that the rarity of SJS/TEN makes it difficult to establish a causal link with COVID-19 or the vaccine, particularly in the context of concomitant medications that are known to initiate SJS/TEN. However, they said that a seven-fold increase in SJS/TEN observed in New South Wales since the pandemic outbreak and immunization is alarming.

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Journal Reference

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