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Stevens-Johnson syndrome/toxic epidermal necrolysis associated with natural thyroid medication

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Abstract

Steven-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) is a rare immunologic hypersensitivity reaction to stimuli that presents as widespread eruption with mucocutaneous detachment and involvement of other organs. Multiple causes have been noted in literature, including numerous medications. In this report, we present a 52-year-old woman who arrived at the emergency department with a complaint of rash, malaise, and pruritus. She subsequently developed diffuse cutaneous and mucosal detachment. Work-up supported a diagnosis of SJS/TEN secondary to her thyroid replacement therapy, derived from desiccated pig thyroid glands. The patient's natural thyroid medication was discontinued and she responded well to appropriate treatment. This case is unique in that thyroid replacement therapy is not a commonly reported trigger of SJS/TEN. Providers should be aware of the potential for natural thyroid and other animal-derived natural medications to cause adverse reactions such as SJS/TEN.

Keywords: animal, drug, medication, natural, pig, rash, reaction, SJS, TEN, thyroid

Introduction

Stevens-Johnson syndrome (SJS) is a rare but potentially life-threatening immunologic hypersensitivity reaction to several stimuli—primarily medications—that presents with widespread eruption and mucocutaneous detachment and possible involvement of other organs [1]. Disease pathology is characterized by full-thickness necrosis of the epithelial layer of the involved organ related to immune-mediated apoptosis of the resident keratinocytes. The skin reaction is termed SJS when detachment is less than 10% of the body surface area (BSA). The reaction is termed toxic epidermal necrolysis (TEN) when greater than 30% of the BSA exhibits detachment. Intermediate SJS/TEN describes reactions with 10-30% skin detachment. Stevens-Johnson syndrome/TEN is often triggered by medications but may also be secondary to infections such as pneumonia, herpes virus, and hepatitis [2]. It occurs at higher incidence in patients with human immunodeficiency virus and can have mimics such as in SJS-like acute graft-versus-host disease [3].

Our report details SJS/TEN in a young woman with no known history of recent or chronic illnesses. Her sole medication was a natural thyroid replacement tablet, derived from desiccated pig thyroid glands. After appropriate management, her thyroid hormone supplementation was switched to a synthetic brand with no recurrence of her rash. This case emphasizes the importance of a thorough review of history for patients with SJS/TEN and highlights natural thyroid replacement therapy as a possible culprit for SJS/TEN.

Case Synopsis

Patient is a 52-year-old woman with a history of hypothyroidism who presented to the emergency department for total body erythema and pruritis. She was hemodynamically stable. Complete blood count revealed no leukocytosis. Initial management included diphenhydramine and corticosteroids for a

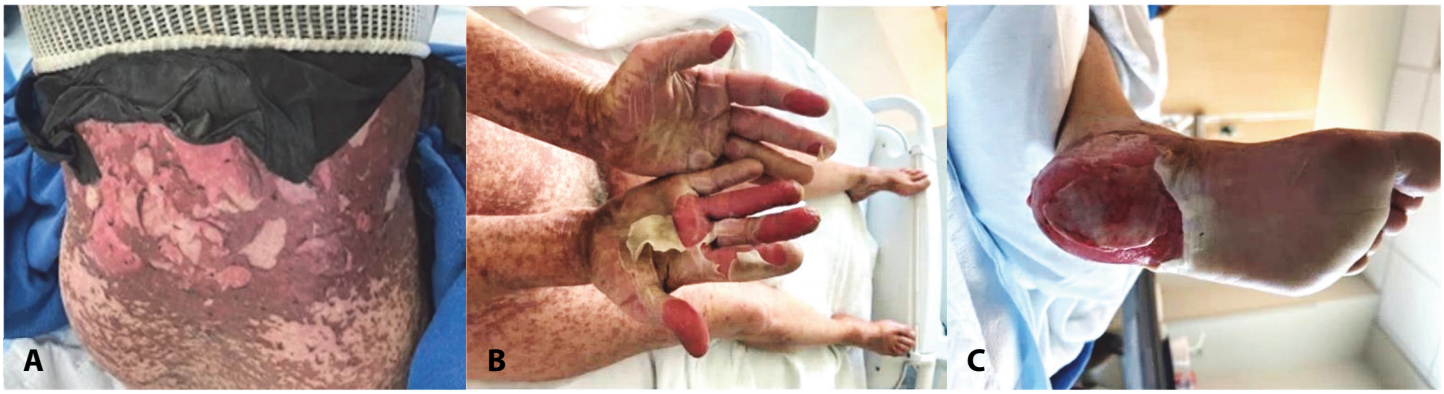

Figure 1. ***A)*** *Truncal rash demonstrating full epidermal necrosis and desquamation consistent with SJS/TEN.* ***B)*** *Palmar epidermal desquamation consistent with SJS/TEN.* ***C)*** *Plantar epidermal desquamation consistent with SJS/TEN.*

presumed allergic reaction. She was discharged home.

She returned the next day with worsening of her eruption with associated tenderness. It was noted that the patient was diagnosed with primary hypothyroidism more than 20 years prior and took synthetic levothyroxine for many years but stopped due to cost. She noted that her thyroid stimulating hormone levels started to rise again following discontinuation of her synthetic levothyroxine and she then was instructed to switch to natural thyroid replacement tablets, a medication derived from desiccated pig thyroid gland. She began this medication a few years prior to this current presentation. She took no other medications. No recent history of upper respiratory infections or other illnesses was elicited.

Physical examination revealed sinus tachycardia (heart rate to 140/s). Her liver function profile revealed an elevated aspartate aminotransferase of 94 U/L (11-40 normal reference range), which increased to a peak of 183 U/L the next day,and an alanine transaminase of 198U/L (5-46U/L normal reference range), which increased to a peak of 295U/L.. Bullae and skin detachment on her trunk, hands, and feet were observed (**Figure 1**). Oral mucosal sloughing was present. There was epidermal sloughing of the lower and upper vermilion border and internal lip mucosa as well as erythema in the posterior oropharynx and associated pain on swallowing.

Our patient had a thorough evaluation for SJS with a severity-of-illness score for toxic epidermal necrolysis (SCORTEN) of 3 and a BSA involvement of 15%. This would correspond to a mortality of 35% (**Table 1**), [4]. Biopsy confirmed changes consistent with late SJS/TEN, demonstrating full epidermal necrosis with scant inflammation (**Figure 2**). Etiology of her SJS was likely secondary to the natural thyroid replacement tablets given it is animal-derived and no other clear causes were apparent. Her thyroid medication was stopped on admission. The patient was started on cyclosporine 3mg/kg for 7 days, dexamethasone 1.5 mg/kg for 3 days, and one dose

Table 1. *Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN) algorithm and related mortality risk based on data from Bastuji-Garin et al., 2013 [9].*

Risk factor	Score of 1 per each risk factor	Mortality risk
Age ≥40 years	0 or 1	Total score of 0 to 1 = 3.2% Total score of 2 = 12.1% Total score of 3 = 35.3% Total score of 4 = 58.3% Total score of 5 or more = 90%
Associated cancer	0 or 1	
Heart rate ≥120	0 or 1	
Serum blood urea nitrogen >28mg/dL (10mmol/L)	0 or 1	
Detached BSA % on day 1 ≥10%	0 or 1	
Serum bicarbonate <20mEq/L (20mmol/L)	0 or 1	
Serum glucose >250mg/dL (14mmol/L)	0 or 1	

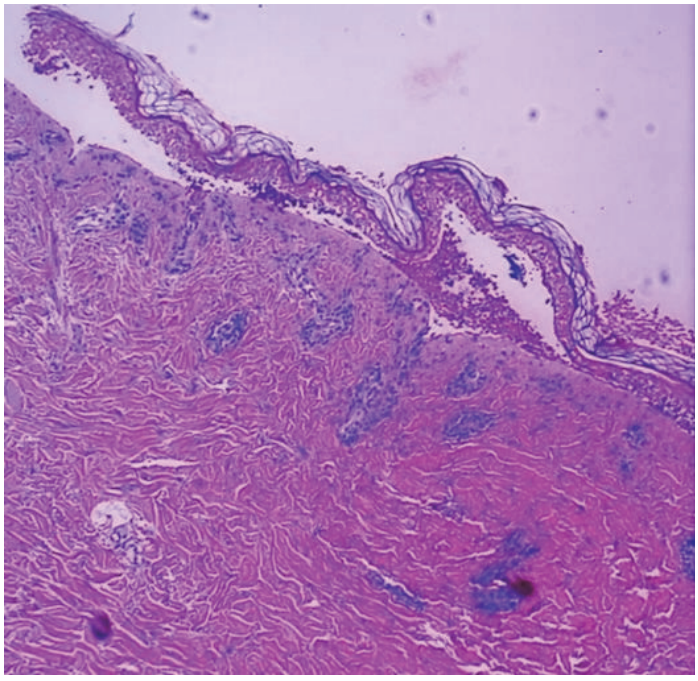

Figure 2. *H&E histopathology of representative lesion demonstrating full epidermal necrosis with scant inflammation consistent with SJS/TEN, 4×.`*

of subcutaneous etanercept (50mg). Her condition stabilized after a few days of admission with no further new blistering/sloughing eruptions or episodes of hemodynamic instability. Her liver function profile normalized to an aspartate aminotransferase level of 25U/L (11-40U/L reference range) after 4 days of treatment, and an alanine aminotransferase of 29U/L (5-46 reference range) after 8 days of treatment.

At one-month follow-up in dermatology clinic, her skin was well-healed with some residual hyperpigmentation in the previous areas of skin detachment (**Figure 3**). She denied any chronic oral or ocular complications. She switched to synthetic levothyroxine as thyroid supplementation with no further complications.

Case Discussion

Stevens-Johnson syndrome/TEN is often confused with other skin conditions, including generalized fixed drug eruption, erythema multiforme major, and autoimmune bullous diseases such as bullous pemphigoid and pemphigus vulgaris [5]. Generalized fixed drug eruption is characterized by widespread red or brown spots or plaques with bullae, rare mucosal involvement; it usually resolves within one-to-two weeks after drug discontinuation [5]. Erythema multiforme major typically presents with target or targetoid lesions, can involve mucosal membranes, but tends to involve less than 10 percent of the body surface area. This is favored to be caused by infection over medications. Bullous pemphigoid results in generalized, itchy, tense bullae on an erythematous base, clinically distinctive and usually in older patients [5]. Pemphigus vulgaris can be mucocutaneous in involvement with painful sloughing and may also be triggered by drugs. However, it has distinct findings on histology with extensive intraepidermal acantholysis rather than epidermal necrosis seen in SJS/TEN. Patients also tend to be more ill with SJS/TEN. Our patient's clinical findings did not match any of these other conditions [5].

Our case presentation adds to the literature to identify culprits to SJS/TEN beyond the common etiologies. Cases of SJS/TEN from animal-derived medications such as certain thyroid replacement therapies are notably rare in the literature but may be underreported given their common use in

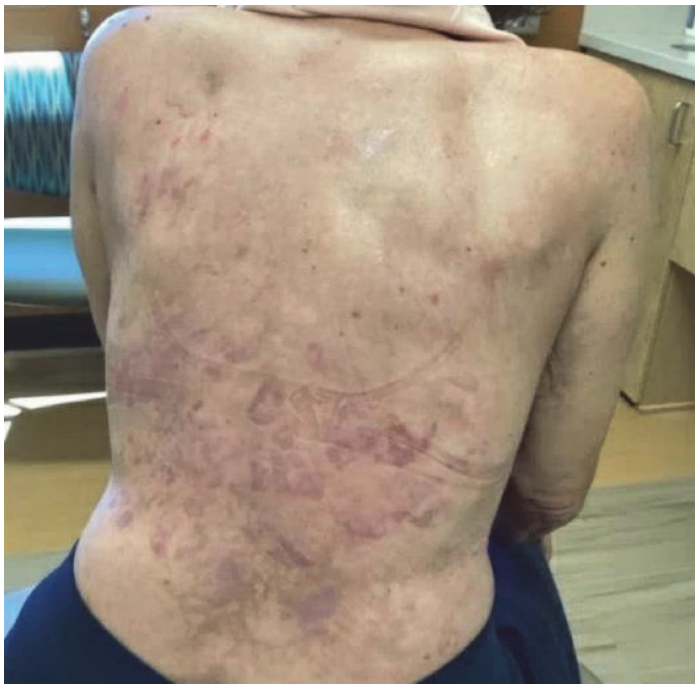

Figure 3. *One month after treatment for SJS/TEN with skin demonstrating reepithelization and post-inflammatory hyperpigmentation.*

patients with many other comorbid conditions, medications, and confounders. Historically, cases of SJS/TEN most frequently occur six-to-eight weeks post-exposure to a new medication, although some reports of reactions have been noted months-to-years later. It is unclear if this is due to a new insult resulting in hypersensitivity to a medication that the patient was previously tolerating. In our case, no clear inciting triggers were elicited by our patient. Identification and early withdrawal of offending agents improves the prognosis [6].

Although there is no current test to confirm the culprit medications, researchers have developed the algorithm of drug causality assessment for epidermal necrolysis (ALDEN) for assessing drug causality in patients with SJS/TEN. This tool provides a rapid assessment of drug causality, particularly in patients who have been exposed to multiple medications [7]. The scoring system ranges from -12 to +10 and considers several factors, such as the time it took for the drug to cause a reaction, the likelihood that the drug was present in the patient's body at the time of the reaction, previous use of the drug, drug discontinuation when the disease worsened, the drug's level of recognition, and other potential causes of the reaction [7]. The scores are grouped into categories that aim to indicate causality. A score of 6 or higher is considered *very probable*, whereas a score of 0-1 indicates *unlikely*, and a score less than 0 indicates *very unlikely* [7]. Notably, levothyroxine is listed as a drug with a probable causality score of "0." This score indicates that there is *no evidence of association* between levothyroxine and epidermal necrolysis, based on the lack of evidence in current literature [7]. It is worth noting that the ALDEN algorithm does not mention the use of thyroid hormone replacement derived from animals. This underlines the significance of this case in making people aware that this medication could be responsible for SJS/TEN. The ALDEN scoring system is based on expert opinion and other classification systems, such as the Naranjo scale [7]. According to the Naranjo scale, our drug would receive a score of 6, on a scale ranging from -4 to 13, with higher scores indicating a higher likelihood of causality [8]. Given that our patient takes no other medications and has responded well after treatment and switching to synthetic levothyroxine, it is highly likely her natural thyroid supplementation was the culprit.

Conclusion

In conclusion, our report entails a rare case of SJS/TEN associated with natural thyroid hormone supplementation. Early diagnosis, discontinuation of offending agent, and treatment are vital to managing SJS secondary to medication use.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Stern RS, Divito SJ. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Associations, Outcomes, and Pathobiology-Thirty Years of Progress but Still Much to Be Done. *J Invest Dermatol*. 2017;137:1004-1008. [PMID: 28411832].
2. Zang X, Chen S, Zhang L, Zhai Y. Toxic epidermal necrolysis in hepatitis A infection with acute-on-chronic liver failure: Case report and literature review. *Front Med (Lausanne)*. 2022;9:964062. [PMID: 36213642].
3. Hung YT, Chen YW, Huang Y, Lin YJ, Chen CB, Chung WH. Acute graft-versus-host disease presenting as Stevens-Johnson syndrome and toxic epidermal necrolysis: A retrospective cohort study. *J Am Acad Dermatol*. 2023;88:792-801. [PMID: 36280000].
4. Fracaroli TS, Miranda LQ, Sodré JL, Chaves M, Gripp A. Toxic epidermal necrolysis induced by lansoprazole. *An Bras Dermatol*. 2013;88:117-120. [PMID: 23539016].
5. Frantz R, Huang S, Are A, Motaparthi K. Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: A Review of Diagnosis and Management. *Medicina (Kaunas)*. 2021;57:895. [PMID: 34577817].
6. Garcia-Doval I, LeCleach L, Bocquet H, Otero XL, Roujeau JC. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death?. *Arch Dermatol*. 2000;136:323-327. [PMID: 10724193].
7. Sassolas B, Haddad C, Mockenhaupt M, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis. *Clin Pharmacol Ther*. 2010;88:60-68. [PMID: 20375998].
8. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239-245. [PMID: 7249508].
9. Bastuji-Garin S, et al. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol*. 2000;115:149-53. [PMID:

10951229].