Photodistributed toxic epidermal necrolysis in association with lamotrigine and tanning bed exposure

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Key words: drug-related side effects and adverse reactions; photodermatosis; photosensitivity disorders; Stevens–Johnson syndrome; toxic epidermal necrolysis.

INTRODUCTION

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, life-threatening immune-mediated conditions characterized by mucocutaneous epidermal necrosis. In 80% to 95% of SJS/TEN cases, exposure to an offending drug can be identified approximately 6 to 14 days prior to the presentation. The eruption classically begins as scattered, dusky, erythematous macules distributed on the head, neck, and trunk, and it progresses to the extremities in larger confluent patches, which can be detached with lateral pressure (Nikolsky sign). As necrosis spreads, flaccid bullae develop, leading to a diffuse epidermal detachment. Painful erosions of the oral, ocular, and genital mucosa are present in 87% to 100% of TEN cases. The pathogenesis of SJS/TEN is incompletely understood; however, a high density of CD8+ lymphocytes within the epidermis and blister fluid has been demonstrated. It has been hypothesized that CD8+ T lymphocytes drive a complex inflammatory response, leading to expansive keratinocyte apoptosis.

It has occasionally been reported that SJS/TEN occurs in a photodistribution. Sulfasalazine, antimalarials, ciprofloxacin, clobazam, itraconazole, and naproxen have been reported in association with photodistributed SJS/TEN. At present, little is known about the effects of ultraviolet (UV) radiation on the metabolism of culprit drugs, or drug–immune system interplay. We present a case of photodistributed TEN associated with lamotrigine and tanning bed use and discuss the possible pathogenesis of this distinct presentation.

CASE REPORT

A 22-year-old Caucasian woman having Fitzpatrick skin type 2 with bipolar disorder presented to the emergency department for evaluation of a blistering eruption. The patient began treatment
with lamotrigine 2 weeks prior and denied having taken any other prescription or over-the-counter medications or supplements. Ten days after initiation, she noticed a diffusely pruritic eruption involving her upper back and chest that later extended to the face and extremities, including the palms and soles. Her symptoms evolved to include dysphagia that was interfering with eating, prompting the presentation to the emergency department. At the time of evaluation, she also complained of stinging of her eyes, swelling of the genitalia, and dysuria. Notably, she reported daily tanning bed use until 3 days prior to the arrival, a habit that she believed alleviated the symptoms of her mood disorder.

On physical examination, dusky pink macules and papules with overlying flaccid bullae were present in a sharply demarcated photodistributed pattern (Figs 1 and 2). There was a prominent conjunctival injection, in addition to bullae involving the vermillion and mucosal lips, buccal mucosa, and tongue. A punch biopsy, submitted for hematoxylin-eosin staining, showed interface dermatitis with scattered dyskeratosis, consistent with SJS/TEN (Figs 3 and 4). Direct immunofluorescence was negative. Result of a blood test, including a complete blood count with differential and comprehensive metabolic panel, was within normal limits. The patient was promptly admitted to the intensive care unit with a 5-day regimen of oral cyclosporine 5 mg/kg/d. Her condition ultimately improved, and she was discharged on the day 12 of hospitalization. She has been followed up over the past 12 months, and although her condition has improved significantly, she still has tenderness and photosensitivity in the areas that were most disproportionately affected.

DISCUSSION

Classically, SJS/TEN presents as a symmetric and bilateral desquamative process without any striking variants in distribution. Photodistributed SJS/TEN was initially described in 1989 and has been sporadically reported since then. The pathogenesis remains poorly understood. We propose multiple theories that may explain this phenomenon, including an isomorphic response of evolving SJS/TEN, accumulation of phototoxic metabolites of offending drugs, alteration of intercellular adhesion molecule 1 (ICAM-1) expression, and activation of resident memory T cell.

Erythema multiforme can be induced by sunburn and is thought to be a UV-dependent variant of the isomorphic response (Koebner phenomenon). There may be some similarities to be drawn between the effects of UV radiation on evolving erythema multiforme and SJS/TEN. By increasing vascular permeability, UV radiation ultimately may cause increased deposition of immune complexes within
the skin, resulting in exaggerated involvement of the exposed areas.7 It is conceivable that UV radiation precipitated Koebnerization of the evolving TEN, leading to the observed photodistributed pattern.

An alternative theory speculates that phototoxic metabolites of the culprit drug may precipitate the response. Lamotrigine accumulates in both the eyes and skin and undergoes slow photodegradation, releasing chloride anions and free radicals, which may modify the proteins and contribute to phototoxic responses.8 It is plausible to draw a causal relationship between a phototoxic metabolite of lamotrigine and the development of photodistributed TEN. It is unknown whether lamotrigine itself or its phototoxic metabolites are more potent in the stimulation and progression of SJS/TEN. It is conceivable that areas of skin that were exposed to UV radiation developed higher concentrations of a phototoxic metabolite, which subsequently triggered the exaggerated necrosis in this distribution.

Although the 2 aforementioned theories would seem to necessitate UV exposure in an acute temporal relationship with the initiation of the drug, there are some mechanisms by which the UV exposure could conceivably occur long before the initiation of the offending medication and development of SJS/TEN. One such mechanism is via alterations in ICAM-1 expression. Ultraviolet B radiation induces keratinocyte secretion of tumor necrosis factor-alfa and interleukin 1, which in turn increases the expression of ICAM-1, ultimately trafficking CD8+ T lymphocytes to UV-exposed skin.7 Upregulation of ICAM-1, either secondary to UV exposure or UV-induced cytokines, may also explain a photodistributed clinical presentation.

Finally, it has been postulated that drug hypersensitivity reactions are driven by the generation of neoeptopes on keratinocytes, which tissue-resident memory T (T\textsubscript{RM}) cells then target with a cytotoxic response.9 Unlike other types of memory T cells, T\textsubscript{RM} cells indefinitely reside in the epithelial barrier tissues, including mucosae and skin, and are important for cutaneous repair mechanisms and immunity. In a study, it was noted that UV radiation, by way of a dangerous signaling molecule, extracellular adenosine triphosphate, activates T\textsubscript{RM} cells by initiating a myriad of downstream effects, including the release of interleukin 17, an important driver of pathogenic inflammation, and upregulation of apoptotic pathways.10 It is feasible that an increased UV-mediated T\textsubscript{RM} cell activation in photoexposed sites potentiated the keratinocyte apoptosis in SJS/TEN, resulting in a photodistributed disease.

Photodistributed SJS/TEN is a rarely reported phenomenon, and there are multiple conceivable theories that explain the relationship between UV radiation and the accentuation of SJS/TEN caused by medications. Knowledge about the relationship between UV radiation, T cell response, and the role of drug metabolites may ultimately shed light on the pathogenesis of photodistributed SJS/TEN that, in turn, may help us to better understand the conventional SJS/TEN and allow us to identify therapeutic targets.

**Conflicts of interest**

None disclosed.
REFERENCES

1. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: Part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. J Am Acad Dermatol. 2013;69(2):173.e1-173.e13 [quiz: 185-186].

2. Borrás-Blasco J, Navarro-Ruiz A, Matarredona J, Devesa P, Montesinos-Ros A, González-Delgado M. Photo-induced Stevens—Johnson syndrome due to sulfasalazine therapy. Ann Pharmacother. 2003;37(9):1241-1243.

3. O r t e lB ,S i v a y a th o r nA , H € o n igsmann H. An unusual combination of phototoxicity and Stevens—Johnson syndrome due to antimalarial therapy. Dermatology. 1989;178(1):39-42.

4. Moghaddam S, Connolly D. Photo-induced Stevens—Johnson syndrome. J Am Acad Dermatol. 2014;71(3):e82-e83.

5. Redondo P, Vicente J, España A, Subira ML, De Felipe I, Quintanilla E. Photo-induced toxic epidermal necrolysis caused by clobazam. Br J Dermatol. 1996;135(6):999-1002.

6. Eloranta K, Karakorpi H, Jeskanen L, Kluger N. Photo-distributed Stevens—Johnson syndrome associated with oral itraconazole. Int J Dermatol. 2016;55(9):e508-e510.

7. Mansur AT, Aydingöz I A. A case of toxic epidermal necrolysis with lesions mostly on sun-exposed skin. Photodermatol Photoimmunol Photomed. 2005;21(2):100-102.

8. Bilski PJ, Wolak MA, Zhang V, Moore DE, Chignell CF. Photochemical reactions involved in the phototoxicity of the anticonvulsant and antidepressant drug lamotrigine (Lamictal). Photochem Photobiol. 2009;85(6):1327-1335.

9. Iriki H, Adachi T, Mori M, et al. Toxic epidermal necrolysis in the absence of circulating T cells: a possible role for resident memory T cells. J Am Acad Dermatol. 2014;71(5):e214-e216.

10. MacLeod AS, Rudolph R, Corriden R, Ye I, Garijo O, Havran WL. Skin-resident T cells sense ultraviolet radiation-induced injury and contribute to DNA repair. J Immunol. 2014;192(12):5695-5702.