

ONLINE FIRST

Progression of Toxic Epidermal Necrolysis After Tanning Bed Exposure

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Background: In addition to recreational tanning bed use, UV radiation exposures are sometimes sought to self-treat skin conditions. The ability of tanning bed radiation exposure to trigger toxic epidermal necrolysis has not been reported.

Observations: A young woman attempted to treat a self-limiting drug hypersensitivity reaction via tanning bed radiation exposure, which resulted in a systemic toxic epidermal necrolysis–like reaction. Studies with cultured keratinocytes and an epithelial cell line reveal that UV-A radiation can synergize with other stimuli such as phorbol esters or interleukin 1 to produce large amounts

of tumor necrosis factor, providing a potential mechanism for this exaggerated reaction.

Conclusion: In addition to inducing photodamage and skin cancer, tanning bed radiation exposure can trigger a toxic epidermal necrolysis–like reaction, possibly via the exaggerated production of keratinocyte cytokines such as tumor necrosis factor.

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DRUG HYPERSENSITIVITY REACTIONS exist on a spectrum from mild self-limiting skin eruptions to the more ominous Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN).^{1,2} The pathogenesis of these reactions involves cytotoxic T cells and cytokines, including tumor necrosis factor (TNF).^{3,4} The different types of UV radiation, including UV-A and UV-B, have profound effects on human skin, and large doses can mimic the epidermal cytotoxic effects seen in a severe drug hypersensitivity reaction.⁵ For instance, UV-B triggers cytokine production, including TNF, in keratinocytes.^{6,7} Recent in vitro studies have demonstrated that UV-B can synergize with other stimuli such as phorbol esters and interleukin 1 α (IL-1 α) to trigger large amounts of TNF.^{8,9} In contrast, UV-A1 (ie, wavelengths of 340-400 nm) exposure does not result in significant TNF release in human keratinocytes.⁷ The present case report describes a young woman who attempted self-treatment for a mild uncomplicated drug hypersensitivity reaction via tanning bed radiation exposure, which resulted in the progression of an uncomplicated drug hypersensitivity reaction to TEN. Moreover, we tested the ability of UV-A to syn-

ergize with other stimuli to induce TNF production in human keratinocytes.

REPORT OF A CASE

A 22-year-old woman with Fitzpatrick type II skin presented to our hospital with a 2-day history of red, burning, and blistering skin, including involvement of oral, ocular, and vaginal mucosa. She was otherwise healthy and did not report taking medications, although she had a history of abnormal reactions to nonsteroidal anti-inflammatory drugs, including swelling of the lips in response to acetaminophen and ibuprofen. The patient had ingested 200 mg of ibuprofen 5 days previously to treat menstrual discomfort. Within 24 hours of its ingestion, she had noticed mild lip swelling and a minimally symptomatic eruption consisting of small red macules and papules on her chest, back, and proximal arms. Two days after the skin eruption had begun, in an attempt to self-treat her stable, nonprogressing rash, she visited a tanning salon she had frequented 4 to 5 times in the past year and received radiation exposure for approximately 8 minutes in a Sundazzler 160 stand-up tanning bed (Heartland Tanning Inc, Lee's Summit, Missouri). The pa-

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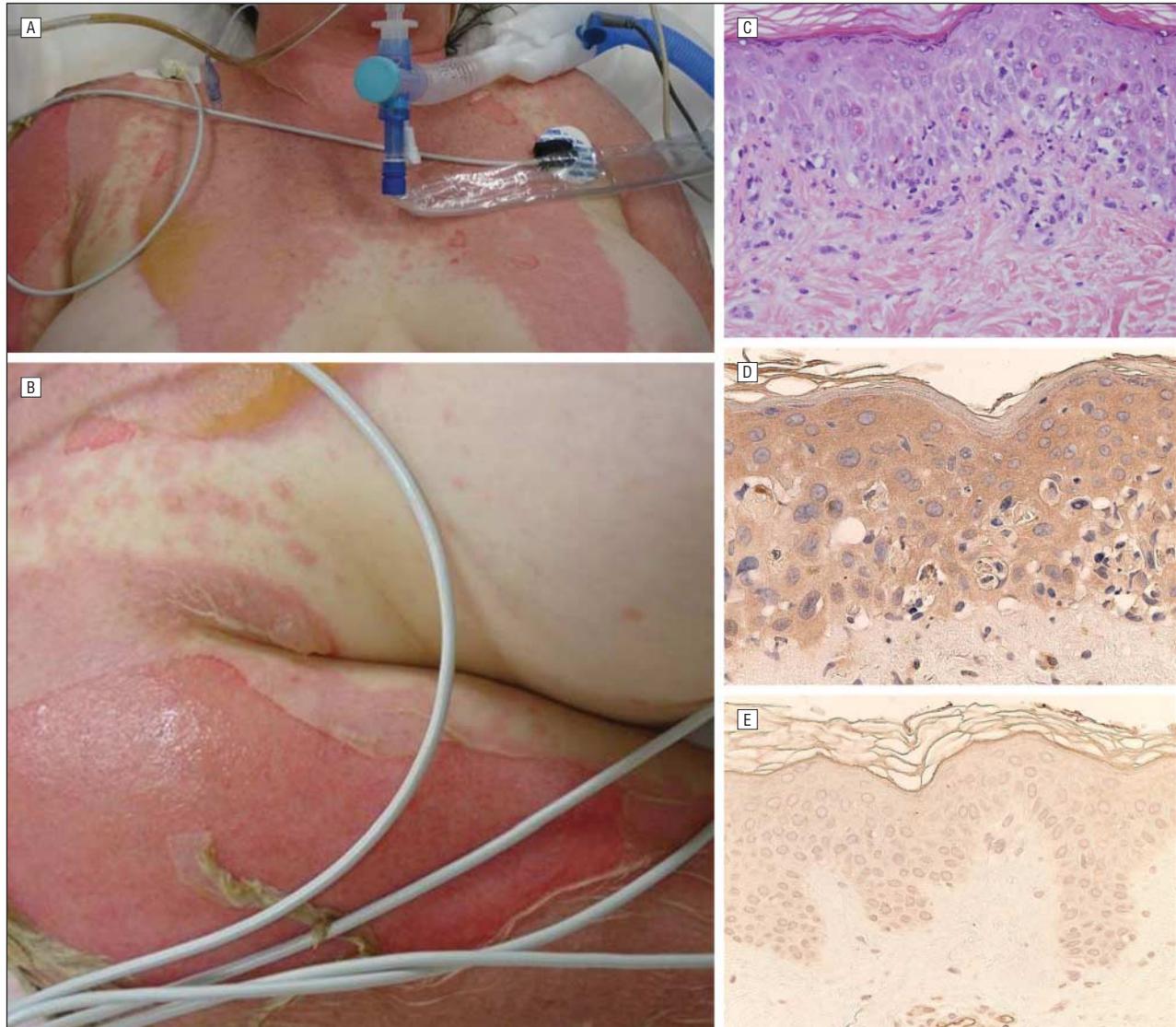


Figure 1. Clinical photographs demonstrating photoaccentuation of blistering skin eruption and skin biopsy specimen showing epidermal necrosis and increased tumor necrosis factor (TNF) immunoreactivity. The patient's upper torso (A) and arm (B) demonstrate blisters in areas of tanning bed radiation exposure and residua of mild morbilliform eruption on the non-radiation-exposed skin (breasts) of the patient. C, Histology of skin biopsy specimen demonstrating necrotic keratinocytes (hematoxylin-eosin; original magnification, $\times 100$). Immunohistochemical studies demonstrating increased cytoplasmic TNF- α immunoreactivity in skin cells from the patient (D) and a control individual (E) (anti-TNF antibody; original magnification, $\times 200$).

tient wore blue jeans and a brassiere and used an ocular shield during the tanning session.

Within approximately 4 hours after the tanning bed radiation exposure, the patient noted increased itchiness of her radiation-exposed skin. The next morning, she experienced severe redness, pain, and the beginnings of blister formations on her radiation-exposed abdomen, back, face, and proximal arms. Moreover, on her lips and in her oral cavity, including in her throat, she developed redness and pain. She also noted mild vaginal irritation. She was afebrile and was able to ingest liquids. The patient then presented to an emergency department at her local hospital. She was thought to have a streptococcal infection or drug eruption and was prescribed intramuscular corticosteroids and oral amoxicillin sodium. She was discharged from the emergency department but she returned approximately 6 hours later

because of worsening symptoms. At this time she was hospitalized and within 24 hours, she was intubated and given fluid boluses for episodes of hypotension. A vaginal culture was performed, which did not reveal *Staphylococcus aureus* or group A streptococcus. Results of a throat culture were negative for the latter. After the cultures were performed, the patient was treated with intravenous vancomycin hydrochloride. Due to her worsening symptoms, the patient was transferred to our medical center. On arrival, she was placed in our burn unit, and dermatology, ophthalmology, and gynecology services were consulted. She was afebrile, and her blood pressure was stable. As shown in **Figure 1** A and B, the patient exhibited blister formation on the areas exposed to tanning bed radiation, especially the chest, abdomen, proximal arms, and upper back (approximately 35% of the body surface area). Laboratory tests results revealed mild transaminitis (as-

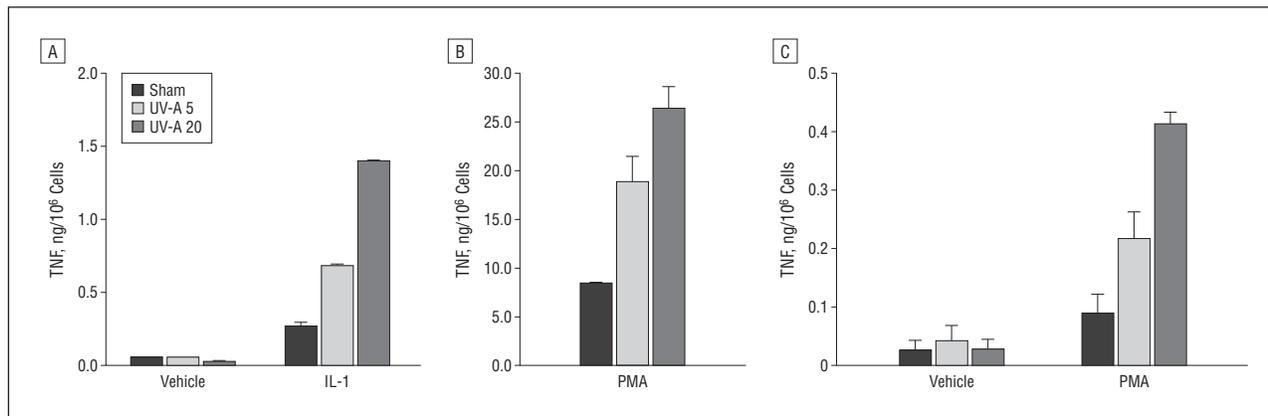


Figure 2. Augmentation of tumor necrosis factor (TNF) production in human keratinocytes (A) and KB cell line (B) by UV-A radiation. Primary cultures of human keratinocytes or KB cell line were treated with vehicle control, 1-ng/mL interleukin 1 α (IL-1 α) or 10nM phorbol myristic acetate (PMA), followed 30 minutes later by treatment with sham (5 or 20 kJ/m² UV-A). The TNF released into the supernatants was measured 6 hours after UV-A exposure by enzyme immunoassay. The data depicted are mean (SD) from triplicate samples of a representative experiment from at least 4 trials with similar results.

partate aminotransferase, 80 U/L [normal, <45 U/L]), but were otherwise normal.

The dermatology service suspected TEN and performed skin biopsies that revealed a lymphocytic infiltrate at the dermoepidermal junction with some apoptotic keratinocytes consistent with TEN (Figure 1C). The ophthalmology service noted ocular involvement also consistent with TEN, and the gynecological service found erythema and swelling of the patient's vaginal introitus with several small ulcerations. She was given intravenous cyclosporine, 5 mg/kg/d, and was treated supportively in the burn unit. After 2 days, owing to lack of response and some extension of the blisters onto the groin and proximal thighs, treatment with cyclosporine was discontinued, and the patient received 3 days of treatment with intravenous IgG (1 g/kg/d). She slowly recovered and was extubated after 1 week. After a total of nearly 3 weeks, she was discharged home and reported no discomfort except mild ocular light sensitivity.

METHODS

IMMUNOHISTOCHEMISTRY

Immunohistochemistry with a human anti-TNF antibody (Assay Designs Inc, Ann Arbor, Michigan) was performed on a formalin-fixed, paraffin-embedded tissue sample from the patient's skin biopsy, as previously described.¹⁰ Healthy skin from a different individual was used as a control for TNF immunohistochemistry.

KERATINOCYTE STUDIES

Primary cultures of human keratinocytes were grown from human neonatal foreskin cells as previously described,¹⁰ and the human epithelial cell line KB was used and culture conditions replicated, as previously reported.¹¹ Keratinocytes with approximately 80% to 90% confluence were treated with 10nM phorbol myristic acetate (PMA) (Sigma Chemical Co, St Louis, Missouri) or 1-ng/mL IL-1 α (PeproTech Inc, Rocky Hill, New Jersey) for 30 minutes before exposure to UV-A. The KB cells were approximately 50% to 70% confluent and were treated similarly with PMA with or without exposure to UV-A. The broadband UV-A source (range, 315-400 nm; peak, 350 nm) con-

sisted of a bank of 4 Philips PL-L 36-W bulbs (Philips International BV, Amsterdam, the Netherlands). The intensity of the tanning bed radiation and the UV-A source used for the experiments were measured using an IL1700 radiometer, a SED240 UV-B detector, and an SED033 UV-A detector (International Light Technologies, Inc, Peabody, Massachusetts) at a distance of 8 cm from the radiation source. The cells were incubated for 6 hours, and TNF was measured in supernatants using an enzyme immunoassay kit (Assay Designs Inc). Cells were then treated with trypsin and counted.

RESULTS

Two studies have reported that the combination of UV-B radiation and the cytokine IL-1 α or the phorbol ester PMA results in synergistic TNF production in human keratinocytes.^{8,9} Given that TNF has been implicated in the pathogenesis of TEN,^{3,12} we hypothesized that exaggerated keratinocyte cytokine production by the combination of UV radiation and IL-1 α or PMA could explain how tanning bed radiation exposure in the setting of a mild uncomplicated drug reaction could result in the patient's symptoms. Immunohistochemical staining of the patient's skin biopsy revealed significant cytoplasmic TNF immunoreactivity (Figure 1D) in comparison to healthy skin from a control individual (Figure 1E). Next, we measured the UV output of a Sundazzler tanning bed using a radiometer; the output was 20 W/m² of UV-A and 0.13 W/m² of UV-B. Thus, the patient had received approximately 9.6 kJ/m² of UV-A and 62 J/m² of UV-B during her 8-minute exposure. These findings fit with values in the literature for a mild tanning bed radiation exposure.^{13,14}

To test the ability of UV-A to trigger a synergistic response as seen in response to UV-B, we exposed primary cultures of human keratinocytes to either vehicle, the phorbol ester PMA (IL-1 α only) or 30 minutes before irradiation with sham or 2 doses (5 or 20 kJ/m²) of UV-A. In other experiments, the human epithelial cell line KB was treated with PMA only or 30 minutes of ethanol vehicle (0.1%) before UV-A radiation. At 6 hours after radiation exposure, TNF protein released into the supernatants was measured by enzyme-linked immunosorbent assay. As shown in **Figure 2**, UV-A did not stimu-

late appreciable TNF production in primary cultures of HK or KB cells. However, the combination of UV-A with IL-1 α or PMA resulted in the synergistic (approximately 4- to 6-fold increased) production of TNF protein. It should be noted that the synergistic TNF production seen with UV-A is less than that reported for UV-B with these stimuli.^{8,9} These studies indicate that the combination of UV-A and other stimuli such as IL-1 α or PMA induce synergistic TNF production in human keratinocytes.

COMMENT

Tanning bed radiation exposure has been linked to various types of skin cancer, including malignant melanoma.^{15,16} Moreover, such exposure is involved in approximately 700 emergency department visits per year.⁵ The present case report describes a patient who apparently developed an uncomplicated mild drug reaction from ingesting ibuprofen, and several days after developing the eruption, attempted to self-treat via tanning bed radiation exposure, resulting in TEN. Although a severe sunburn reaction would be in the differential diagnosis, the history of a cutaneous exanthema preceding the tanning bed radiation exposure and the mucous membrane involvement more strongly suggest TEN. In addition, the fact that almost 72 hours had passed between the ingestion of ibuprofen and the tanning bed radiation exposure also suggests this was not a phototoxic reaction to ibuprofen. Of note, there is a previous report of photoaccentuated TEN with high levels of TNF measured in blister fluid from the affected patient, although tanning bed radiation exposure was not involved.¹⁷ The present study also suggests a mechanism by which this photoaccentuated reaction could have occurred, namely, that UV-A exposure in the setting of keratinocytes already activated from the preexisting drug reaction resulted in an exaggerated production of epidermal cytokines such as TNF. Results of the current in vitro studies that use keratinocytes to demonstrate that combining IL-1 α or PMA with UV-A results in the synergistic production of keratinocyte TNF fit with this notion. Of interest, other keratinocyte-derived cytokines, including the T-cell chemokine CCL-20, are also highly upregulated in response to the combination of UV-A and PMA/IL-1 α (data not shown). The present in vitro studies probably would underestimate the exaggerated TNF response from tanning bed radiation exposure because the low amount of UV-B found in the radiation was not tested.

There is an increasing trend for patients to seek tanning bed radiation exposure as a means of self-treatment because, among much of the general public, the perceived benefits of tanning bed radiation include its ability to treat rashes. Of note, a recent report of more than 1200 study participants indicated that almost 10% of those who frequented tanning salons did so in response to treatment of skin disease and 5% were doing so on the recommendation of their physician.¹⁸ The current report should provide caution to those who recommend tanning bed radiation exposure for the treatment of undiagnosed skin conditions.

In summary, these studies describe a clinical case report of a woman who developed TEN from the combination of a cutaneous drug reaction and tanning bed radiation exposure. Treatment of cultured keratinocytes activated by IL-1 α or PMA with levels of UV-A approximately similar to that to which the patient was exposed resulted in an exaggerated production of TNF, providing a potential mechanism for this clinical scenario.

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Author Contributions: Drs Gatson, Travers, and Al-Hassani and Mr Travers had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Drs Gatson and Travers and Mr Travers. *Acquisition of data:* Drs Gatson, Al-Hassani, Warren, and Hyatt and Mr Travers. *Analysis and interpretation of data:* Drs Gatson, Travers, Al-Hassani, and Warren and Mr Travers. *Drafting of the manuscript:* Dr Travers. *Critical revision of the manuscript for important intellectual content:* Drs Gatson, Al-Hassani, Warren, Hyatt, and Travers and Mr Travers. *Statistical analysis:* Dr Travers. *Obtained funding:* Dr Travers. *Administrative, technical, and material support:* Drs Gatson and Travers and Mr Travers. *Study supervision:* Drs Gatson, Al-Hassani, and Travers.

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Notable Notes

Galen Disease: Delusions of Grandeur in an Authoritative Clinical Investigator

Most modern physicians believe that the concept that the practice of medicine should be based on experimental evidence (as opposed to anecdotes) is relatively new. Nevertheless, the 12th century physician/scientist/theologian Moses Maimonides¹ in his textbook on medicine stressed the requirement for evidence-based practice of medicine.²

Maimonides paralleled his text to that of Galen, a first-century Roman physician.³ Despite the 11 centuries between them, Maimonides knew that Galen's publications on medicine remained authoritative. Maimonides agreed that Galen in his early years had relied on experiments to become an expert in anatomy, physiology, and therapeutics. Galen, he states, "reached such a level, he demanded visual proof for everything." Maimonides praised "Galen, who was truly extremely wise, and who provided experimental evidence [to support his contentions], and even composed a book on [experimental] signs." In fact, Galen went further and "repulsed Aristotle," the Greek medical authority who had preceded him for centuries,⁴ for Aristotle's failure to perform such experiments. Over his lifetime and thereafter, Galen became esteemed and recognized as an authority of general medicine, equal to or greater than Aristotle.

According to Maimonides, as Galen's reputation grew, so did his ego. Galen stopped performing experiments and just pontificated as fact his personal unsubstantiated thoughts on any topic. He believed that what he thought must be true, because he thought of it. Eventually, Galen declared that he un-

derstood perfectly all aspects of medicine, because he directly learned from "an angel of God." Thus, Maimonides explains that he (Maimonides) was obligated to write his own medical text to identify and elucidate where Galen's writings asserted non-evidence-based opinions as fact. He then replaced Galen's descriptions with those based on experiments.

Maimonides felt that Galen had succumbed to an illness: one common to those "considered to be in the category of a foremost authority, and one of the great masters." One common among "people who are otherwise clever and wise, who have already learned one of the physical or theoretical sciences or one of the traditional sciences and have become proficient in that science. Such a person then gives opinions not only in the science he has mastered, but also in other sciences concerning which he knows nothing at all." Alas, Maimonides offers no treatment. He issued a warning to fellow physicians to be careful about accepting data from others without first considering whether or not they were healthy or succumbing to Galen disease.

Perhaps we should institute clinical trials to determine whether Galen disease still afflicts medical authorities. If so, we must assign it an *International Statistical Classification of Diseases, 10th Revision* code. Then, perhaps, my colleagues, we can fulfill Maimonides' 12th-century dream of discovering a treatment for Galen disease.

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