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Case Presentation

UVB-Sensitive solar urticaria possibly associated with terbinafine

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Abstract

Solar urticaria is an uncommon condition characterized by erythema and whealing shortly after exposure to ultraviolet (UV) and/or visible light. We report a 25-year-old woman with an erythematous, edematous, pruritic reaction minutes after sun exposure while she was taking terbinafine for onychomycosis. Phototesting revealed a UVB-sensitive urticarial reaction, confirming the diagnosis of solar urticaria. This report describes the first patient with possible terbinafine-associated solar urticaria.

Keywords: terbinafine, solar urticaria, UVB, review, drug-associated

Introduction

Solar urticaria is a rare condition characterized by erythema and formation of wheals shortly after exposure to ultraviolet (UV) and/or visible light. The lesions may itch or burn, but are always transient, lasting 30 minutes to 24 hours [1]. The diagnosis for solar urticaria is confirmed by phototesting, in which the patient is exposed to different wavelengths of light to see which ones trigger a reaction [1]. Solar urticaria is most often triggered by visible or UVA light and less frequently by UVB (Table 1) [2]. The cause of solar urticaria is usually idiopathic and rarely medication-induced. Terbinafine is a commonly prescribed antifungal medication with few reported cutaneous side effects. We describe a patient with UVB-sensitive solar urticaria possibly associated with terbinafine.

Table 1: Summary of Solar Urticaria Cases

<table>
<thead>
<tr>
<th>References</th>
<th>Cutaneous sensitivity</th>
<th>Sensitivity to UVA</th>
<th>Sensitivity to UVB</th>
<th>Treatments</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beattie PE, Dawe RS, et al [43]</td>
<td>87 total pts: 1 pt UVB alone, 5 pts to UVA alone, 17 to UVB/UVA/VL, 35 to UVA/VL, 26 to VL</td>
<td>Yes: MWD N/A</td>
<td>Yes: MWD N/A</td>
<td>Broad spectrum sunscreens, oral antihistamines</td>
<td>12%, 26%, and 36% patients have clinical resolution in 5, 10, and 15 years respectively. There is clinical</td>
</tr>
<tr>
<td>Patient Details</td>
<td>MWD/MED/MUD</td>
<td>Treatment</td>
<td>Notes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------</td>
<td>-----------</td>
<td>-------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beissert S, Stander H, et al [19]</td>
<td></td>
<td>UVA rush hardening</td>
<td>Treatment with UVA not only prevented UVA-induced lesions, but prevented visible light and UVB-induced urticaria in patients 1 and 3, respectively.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botto NC and Warshaw EM [42]</td>
<td>Yes: MWD N/A</td>
<td>Drug therapy (antihistamines, antimalarials, beta-carotene, reserpine, prostaglandin inhibitors, oral steroids), plasmapheresis, hardening, IVIG, sunscreens, protective clothing</td>
<td>No single treatment modality is effective for all patients.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calzavara-Pinton P, Zane C, et al [22]</td>
<td>No MUD, MED BB: 0.23 J/cm², MED NB: 0.32 J/cm²</td>
<td>NB-UVB phototherapy</td>
<td>UVA phototherapy may not be effective for patients with UVB sensitive solar urticaria where tolerance usually lasts only a few days. Effective and well-tolerated prophylaxis for patients with severe solar urticaria; patients sensitive to UVB required more cautious and time-consuming regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dawe RS, Ferguson J. [21]</td>
<td>No</td>
<td>UVA phototherapy</td>
<td>UVA phototherapy can have prolonged duration of improvement, lasting up to a year and steady</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data available for 84 patients.
**Case synopsis**

A 25-year-old healthy woman presented to our clinic in August 2013 with a history of an erythematous, edematous, pruritic, and burning eruption minutes after sun exposure. The patient noted no history of bullae. The rash would resolve after an hour. She had no other symptoms and no previous history of photosensitivity. She noted that her skin would react when her car windows were lowered but not when the car windows were raised. The patient had a history of starting oral terbinafine in May 2013 for onychomycosis, but discontinued it at the onset of her symptoms. The patient did not take any other medications and had no history of any drug allergies.

The patient noted no family history of autoimmune disease, porphyria, or other photosensitive disorders. Laboratory testing revealed complete blood count, thyroid stimulating hormone, complement levels, and IgE levels within normal limits. Antibody testing was negative for antinuclear, anti-thyroglobulin, and anti-thyroid peroxidase antibodies. Porphyria testing was planned but not pursued because the patient’s symptoms were already resolving prior to initiation of testing.

Phototesting with a UVA1 lamp and narrowband UVB were performed on the patient’s bilateral forearms (Figure 1, Figure 2). She was not taking any medications at the time of phototesting in August 2013. The patient had a minimal wheal dose (MWD) of 10 mJ/cm² under UVB testing. UVA1 testing revealed no wheal when tested at 5, 10, or 15 J/cm².

A diagnosis of UVB-sensitive solar urticaria was made. Symptoms were managed with broad-spectrum sunscreens, antihistamines, and sun avoidance behavioral changes. However, the patient continued to have recurrent episodes because her studies required significant time outdoors. Her symptoms spontaneously and progressively resolved by October 2013.

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<table>
<thead>
<tr>
<th><strong>Kuo S, Sivamani RK</strong></th>
<th>25 yo F / UVB</th>
<th>No</th>
<th>MWD: 10 mJ/cm²</th>
<th>Broad spectrum sunscreens, oral antihistamines</th>
<th>Resolution each year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Masuoka E, Fukunaga A, et al [20]</strong></td>
<td>Pt 1: 34 yo F / UVA, VL</td>
<td>MWD: 3 J/cm²</td>
<td>No</td>
<td>UVA rush hardening</td>
<td>Successful and long-lasting treatment for serum factor-positive patients with solar urticaria</td>
</tr>
<tr>
<td></td>
<td>Pt 2: 62 yo M / UVA, VL</td>
<td>MWD: 0.5 J/cm²</td>
<td>No</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Uetsu N, Miyauchi-Hashimoto H, et al. [24]</strong></td>
<td>40 total pts: 24 pts VL, 5 pts VL/UVA/UVB, 4 pts UVA, 3 pts UVB, 3 pts UVA/UVB</td>
<td>MUD: 0.1 J/cm²</td>
<td>MUD: 2.5 J/cm²</td>
<td>Antihistamines, sunbathing, PUVA photochemotherapy, sunscreens</td>
<td>No cure, variable treatment, improvement of symptoms with time</td>
</tr>
<tr>
<td><strong>Wolf R, Herzinger T, et al [23]</strong></td>
<td>25 yo M / UVA and VL</td>
<td>MUD: 7 J/cm²</td>
<td>No</td>
<td>NB-UVB 311 nm rush hardening</td>
<td>Treatment with an inhibitory UV spectrum may be more advantageous: low total number of necessary irradiations, prolonged remission</td>
</tr>
</tbody>
</table>
Figure 1. Patient demonstrated a minimal wheal dose (MWD) of 10 mJ/cm² under NB-UVB testing

Figure 2. UVA1 testing revealed no wheal when tested at 5, 10, or 15 J/cm²

Discussion

We present a patient with solely UVB-sensitive solar urticaria, possibly induced by terbinafine. In her history, the patient described not reacting in her car with the windows up, but flaring when the windows were down. This is consistent with sensitivity to UVB light; car windows block all transmission of light in the UVB range, but allow up to 22.4% of UVA radiation [3]. A history concerning flares with the car windows up or down can thus help differentiate between UVA and UVB triggers for solar urticaria.

Medication-induced solar urticaria is rare and has been described with repirinast, tetracycline, coal tar, and benoxaprofen (Table 2) [4-7]. In these cases, symptoms developed after taking the new medication and a diagnosis of solar urticaria was confirmed
with phototesting. The cause of the whealing response in secondary solar urticaria has been suggested to be owing to direct phototoxicity rather than having an immunological etiology [5].

Table 2: Medications linked to solar urticaria

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of administration</th>
<th>Time after drug started</th>
<th>Light sensitivity</th>
<th>Treatment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benoxaprofen</td>
<td>Oral</td>
<td>3-28 weeks</td>
<td>UVA and UVB</td>
<td>Not stated</td>
<td>[7]</td>
</tr>
<tr>
<td>Coal tar</td>
<td>Topical</td>
<td>Immediate wheal-and-flare response, followed by erythema response peaking at 24-48 hours</td>
<td>UVA</td>
<td>Decreased wheal response after antihistamine injection. Topical and oral corticosteroids had no effect.</td>
<td>[6]</td>
</tr>
<tr>
<td>Repirinast</td>
<td>Oral</td>
<td>1 year and 8 months</td>
<td>UVA (MUD 1.5 J/cm²)</td>
<td>Resolution after stopping repirinast</td>
<td>[4]</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>Oral</td>
<td></td>
<td>UVB</td>
<td>Resolution after stopping terbinafine</td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Oral</td>
<td>2 weeks</td>
<td>UVA and UVB</td>
<td>Resolution after stopping tetracycline</td>
<td>[5]</td>
</tr>
</tbody>
</table>

Terbinafine is an allylamine antifungal medication with few reported cutaneous side effects. More common cutaneous adverse reactions are rash, pruritus, and urticaria, whereas more serious and rare reactions include erythema multiforme, Stevens-Johnson, pityriasis rosea, psoriasis flare, and lupus erythematosus [8, 9]. There has been one reported case of a terbinafine-induced systemic photoallergy [10].

Although a photoallergic reaction is a type of photosensitivity, it differs from phototoxicity (Table 3). The etiology of solar urticaria may either be immunological or non-immunological in different situations. Photosensitivity reactions may produce an eruption after sun exposure and can relate to a variety of causes. Photoallergic reactions are usually caused by topical medications, oral medications, or other agents that lead to erythematous, papular, vesicular, or eczematous eruptions [11]. The photoallergic response occurs when the UV rays cause production of a molecule that elicits an immune response. Because either antibody production or cell-mediated immunity are involved, the rash appears a few days after substance and sun exposure and can spread to all parts of the body [11]. Phototoxic reactions are also caused by exogenous agents, such as oral and topical medications. The eruption generally consists of erythema and pain, like a sunburn. Because there is direct toxicity of the skin after sun exposure with these substances, the reaction occurs within hours and occurs only in sun-exposed areas [11]. These photosensitive reactions differ from the photosensitivity with lupus erythematosus, which is an autoimmune condition [12]. In lupus erythematosus, the response is a macular or diffuse erythematous eruption in sun-exposed areas; the response may be delayed such that the relationship with sun exposure may not be recognized. In addition, in lupus erythematosus sun exposure can also lead to exacerbation of other symptoms such as fever and joint pain.

Table 3: Photosensitive reactions

<table>
<thead>
<tr>
<th>Photosensitivity reaction</th>
<th>Cause</th>
<th>Onset after sun exposure</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photoallergy</td>
<td>Exogenous agent, usually topical agents, immune system mediated</td>
<td>24-72 hours in sensitized individuals</td>
<td>Papular, vesicular, or eczematous reaction after exposure to a photoallergen and sunlight in a sensitized individual.</td>
</tr>
<tr>
<td>Phototoxicity</td>
<td>Exogenous agent (i.e. UVA radiation, minutes to hours) in sun exposed areas. Can also</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
porphyrins, coal tar, psoralens, sulfonamides, tetracycline, amiodarone), not immune mediated
develop dyspigmentation.

Our case suggests the possibility of a terbinafine-associated solar urticaria owing to the timing of the medication and the potential of terbinafine to precipitate different kinds of cutaneous reactions. In the case presented here, the patient had spontaneous resolution of symptoms after four months. It has been shown that terbinafine can concentrate in the sebum and stratum corneum at antifungal doses for up to two months [13, 14]. The half-life for terbinafine redistribution from sebum has been estimated to be $14.5 \pm 8.5$ days [15]. Therefore, terbinafine can last in the sebum and skin for many months, which would fit with the time frame of the patient’s symptoms in this case. It could be a reason for gradual, rather than abrupt, resolution by four months after her initial symptoms.

Solar urticaria is often difficult to treat. Initial treatments of choice include sun protection and H1-antihistamines. Broad-spectrum sunscreens to cover both UVA and UVB light are recommended. However, some patients are too sensitive to UVA and visible light to benefit from sunscreens [1]. H1-antihistamines can provide symptomatic relief for the itching and whealing, as well as facilitate natural desensitization by allowing the patient to tolerate some sunlight exposure [1]. Higher doses of antihistamines than what is normally prescribed for other skin conditions are needed to control symptoms of urticaria [16] and sometimes combinations of antihistamines are used to act synergistically and reduce side-effect potential [17]. For mild cases, the combination of sunscreen and antihistamines are sometimes enough to control symptoms [18].

When initial treatments fail, hardening can be used to achieve tolerance after repeated exposure to artificial UV lamps. The starting dose is usually less than the determined Minimum Urticarial Dose (MUD) in the patient. Frequency of treatments varies from daily to weekly with dose increments of 10-30% each time depending on relapse occurrence. An average of 15-20 treatments are needed to achieve adequate tolerance [1]. UVA or NB-UVB light can be used for hardening and have long-lasting effects [19-24]. Action-spectrum hardening in which the causative wavelength is used to induce tolerance and inhibitory UV spectrum hardening in which the wavelength used differs from the causative action spectra can both be therapeutic [23].

UVA rush hardening has been used successfully in the treatment of solar urticaria [19, 20]. The mechanisms behind the utility of UVA based hardening are not well understood. Multiple mechanisms have been proposed including blockade of specific IgE from interacting with its receptors [20, 25] and depletion of mast cell mediators [25, 26]. Recent work suggests that impairment or internalization of the mast cell IgE receptor may be the more likely mechanism rather than the depletion of mast cell mediators [20]. Regardless, the mechanism of tolerance appears to cross over different wavelengths as evidenced by the induction of tolerance through the use of wavelengths that differ from the wavelength that elicits solar urticaria [19, 21, 23, 27, 28]. In particular, UVA induced hardening appears to provide protection against other wavelengths that can induce solar urticaria [19, 21, 27, 28]. For that reason, we considered the use of UVA rush hardening in this patient but the patient’s symptoms resolved prior to initiation of any hardening protocols.

For recalcitrant solar urticaria, extracorporeal photochemotherapy (photopheresis) can be tried [29]. Treatment is given on 2 consecutive days every 2 weeks for 8 months. It was found to be well tolerated with a 3 fold increase in MUD.

Other treatment options include plasmapheresis [17, 30, 31] and IVIG [32-34]. Plasmapheresis can also be combined with PUVA [17], but it is not always effective and is not long lasting, making it impractical [1]. IVIG has been shown to be successful in a few cases; significant improvement could be seen after only a single course of 2 g/kg [33] or four cycles of 0.5 g/kg/day for 5 days every 4 weeks [32]. Remission was also seen after 2 g/kg over several 5-day courses a month apart for severe idiopathic SU [34]. Cyclosporin A therapy of 4.5 mg/kg body weight/day showed decreased sensitivity in UVA, UVB, and VL [35]. However, symptoms returned after 1-2 weeks after medication discontinued. Thus, it is recommended when other treatments have failed, especially in the summer months.

There have been new cases in which anti-immunoglobulin IgE treatment with omalizumab was used to treat solar urticaria, but results have been variable. Three cases had successful complete symptom control after one dose [36, 37], one case had only partial improvement after 6 doses [38], and one showed no improvement after 4 doses [39].

Oral polypodium leucotomos (PL), may have potential benefit for solar urticaria patients and serve as an alternative or adjunct to therapy [40]. PL is a natural extract from tropical fern leaves with potent antioxidant and anti-inflammatory properties. Oral
administration of PL has been shown to reduce UV-induced erythema [41]. PL is rich in phenolic compounds that can also act as a filter to absorb ultraviolet rays, making it possibly useful for solar urticaria patients. In the study, 4 patients with solar urticaria exposed themselves to sunlight after taking 480mg/day of polypodium leuocotomos extract daily [34]. There were found to have significant reduction of their skin reaction and subjective symptoms with no side effects.

Despite these treatment options, there is no single modality that is effective for all patients [42]. Overall there is clinical improvement with time and the majority of cases completely resolve within 15 years [43].

Conclusion

We present a patient with possible terbinafine-associated solar urticaria. Terbinafine has been reported to have a number of different cutaneous side effects. Clinicians should be aware that solar urticarial, albeit rare, is another potential side effect of this commonly prescribed medication.

References


