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CLINICAL REPORT

Immediate Whealing Urticaria in Red Light Exposed Areas During Photodynamic Therapy

Jeanette KAAE[1], Peter A. PHILIPSEN[2], Merete HAEDERSDAL[2] and Hans Christian WULF[2]
[1]Department of Epidemiology Research, Statens Serum Institut, and [2]Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark

One of the recommended first-line treatments for basal cell carcinomas, actinic keratoses and Bowen's disease is photodynamic therapy. Commonly associated side-effects include pain and phototoxicity. Histamine release is a part of this reaction, but whealing urticaria following photodynamic therapy has only been reported by the manufacturer. The aim of this study was to investigate the prevalence of immediate whealing urticaria in exposed areas during photodynamic therapy with topical methylester aminolevulinate and red light. Patients who developed immediate whealing urticaria during photodynamic therapy were prospectively registered in the period from 1 March 2002 to 14 May 2007. Twelve out of 1353 patients (0.9%) treated with photodynamic therapy developed immediate whealing urticaria and itch during red light illumination, which had not been experienced during previous sessions. Urticaria occurred in 3.8% of patients who had received more than 7 sessions of photodynamic therapy. Prophylactic use of systemic antihistamines reduced itch and whealing, permitting photodynamic therapy sessions to be continued. ***Key words: allergy; 5-aminolevulinic acid; methyl aminolevulinate; photodynamic therapy; urticaria.***

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Peter Philipsen, Department of Dermatology, Bispebjerg Hospital, University of Copenhagen, Bispebjerg Bakke 23, DK 2400 Copenhagen NV, Denmark. E-mail: pp01@bbh.regionh.dk

Photodynamic therapy (PDT) involves the use of light to activate a photosensitizer localized in diseased tissues, which results in the formation of cytotoxic reactive oxygen species. It is recommended as first-line treatment for basal cell carcinoma (BCC), actinic keratoses (AK) and Bowen's disease (1). PDT with 5-aminolevulinic acid (ALA) was used previously on an experimental basis. In recent years, methylester aminolevulinate (MAL) has been found to be a more specific sensitizer with less painful side-effects compared with ALA, and it has been approved for use in Europe (2, 3).

PDT is one of several non-surgical treatments for BCC and offers a high cure rate with an excellent cosmetic outcome (4, 5). Generally PDT is well tolerated by the patients, although the action involves a phototoxic reaction causing pain and a skin reaction with inflammation, erythema, oedema and scaling (3). Moreover, cases of allergic eczema to MAL have been described (2). Brooke et al. (6), in a study of healthy persons, have reported ALA dose-related dermal histamine release associated with immediate urticarial response in the skin of all persons. Urticarial responses following PDT have been reported by the manufacturer of MAL (Photocure, Oslo, Norway) to occur at a rate of 1:100 to 1:1.000 treatments. This study determined the prevalence of PDT-induced immediate whealing urticaria, which responded well to antihistamines during subsequent treatments.

METHODS

All patients treated with PDT at the department of dermatology, Bispebjerg University Hospital, Copenhagen, Denmark were registered and examined for immediate side-effects related to the treatments. All PDT-treated patients were prospectively observed for whealing urticaria in direct relation to the treatment. The registration period started on 1 March 2002 and ended on 14 May 2007. The first case was observed in November 2003. All patients with immediate whealing urticaria had additional PDT sessions, which were subtracted in the calculation of prevalence.

Patients had superficial curettage followed by application of 16% MAL cream (Photocure, Oslo, Norway) under occlusion. Red diode light (CureLight 128, Photocure, Oslo, Norway) was given 3 h after cream application at 37 J/cm^2, peak irradiance at 632 nm and 50% at 621 nm and 640 nm, giving a full width at half maximum of 19 nm (7). Nurses observed whether urticarial whealing or itch developed during illumination, in which case a doctor was called to confirm the diagnoses. The files of urticaria cases were reviewed for co-morbid conditions and for their responses to prophylactic systemic antihistamine treatment. The number of treatments was coounted as treatment days. On each day several regions might have been treated. For the urticaria cases we also counted the PDT treatments occurring before 1 March 2002.

RESULTS

Immediate whealing urticaria occurred in 12 out of 1353 treated patients during the observation period (prevalence 0.9%). All 12 patients had severe itch in connection with the whealing reaction, which developed during the first minute of red light illumination. Whealing disappeared within one hour without any

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Table I. *Characterization of patients with their associated medical diseases and related treatments. Patients are listed in order they developed urticaria*

Patient number	Gender/Age (years)	Medication prior and during PDT treatments	Other diseases
1	M/55	5-fluorouracil cream, thiamine, folic acid, vitamin A, vitamin B, NSAIDs	None
2	F/67	Clobetasol propionate cream, bendroflumethiazide, glucosamine, sumatriptan, acitretin, X-rays	Psoriasis
3	F/48	None	Drug urticaria. Contact allergy to ethylene diamine, potassium chromate, cobalt, nickel
4	F/37	Levothyroxine, injection somatropin, oestradiol, potassium, vitamin D, NSAIDs	Bone marrow transplantation (ALL) in 1979, pituitary gland disorder
5	M/67	Amiloride+hydrochlorthiazide, telmisartan, allopurinol, carvedilol, alfacalcidol	Squamous cell carcinoma
6	F/70	Hydrocortisone cream, methotrexate	Rheumatoid arthritis
7	F/66	None	Squamous cell carcinoma
8	M/58	Prednisolone, budesonide, lithium carbonate, venlafaxine	Lung disease, psychiatric illness
9	F/63	None	Eczema
10	M/45	Prednisolone, cyclosporine, insulin	Kidney transplanted in 1992. Diabetes type 1
11	F/61	None	None
12	M/66	Tolbutamide, metformin, enalapril, statin	Diabetes, hypercholesterolemia

ALL: acute lymphoblastic leukaemia; PDT: photodynamic therapy; NSAIDs: non-steroidal anti-inflammatory drugs.

treatment. No late-occurring urticaria was reported. Three patients (patients 1, 3 and 11, Table I) developed urticaria in spite of ongoing treatment with methotrexate, prednisolone, cyclosporine and non-steroidal anti-inflammatory drugs (NSAID). One of the patients had a known history of urticaria (patient 3, Table I), but none had a history of atopic dermatitis. Nearly all the patients developing urticaria had underlying comorbid diseases mentioned in their treatment records (Table I).

A total of 5713 treatments were performed, with a median number of 3 treatments (range 1–59 treatments) per patient.

One patient developed urticaria at the first PDT treatment (Table II). A median time of 5 weeks (range 1–92 weeks) occurred from the last non-urticaria PDT treatment to the treatment that induced urticaria. All patients were treated with MAL PDT and 3 patients had had ALA PDT in earlier treatments before urticaria developed (patients 2, 4 and 9, Table II). The risk of developing urticaria increased with increasing number of PDT sessions, and the incidence became more frequent during the last part of the observation period. No cases were observed in 2002, one case in 2003 and 2004, 2 cases in 2005, 5 cases in 2006 and 3 cases in the first 4.5 months of 2007. Among patients with 6 or fewer PDT treatments, 0.43% (5/1171) were affected, compared with 3.8% (7/182) who received at least 7 PDT treatments (Fig. 1).

Urticaria and itch developed only at skin sites exposed to both MAL and red light, whereas no adjacent skin areas developed whealing urticaria (Fig. 2). In reacting persons, previously untreated skin, also developed urticaria when PDT treated subsequently.

Table II. *Characterization of patients with skin diseases and details about photodynamic therapy (PDT) treatments. All treatments were performed with red light emitting diodes, 37 J/cm^2. Patients are listed consecutively after the date of developing urticaria*

Patient No.	Indication for PDT	Weeks from first PDT to first PDT with urticaria	Weeks from last PDT without urticaria to first PDT with urticaria	Number of sessions		Treatment of urticaria
				PDT without urticaria (*n*)	PDT with urticaria (*n*)	
1	Multiple BCC/AK	11	5	3	7	Cetirizine 10 mg
2	Multiple BCC/AK	318	2	19	28	Fexofenadine 360 mg
3	Hailey-Hailey	77	30	6	2	Fexofenadine 180 mg
4	BCC	10	9	2	7	Cetirizine 10 mg
5	Multiple BCC/AK	51	2	10	24	Loratadine 10 mg
6	Multiple BCC/AK/Morbus Bowen	172	1	9	4	Fexofenadine 240 mg
7	Multiple BCC/AK	78	92	8	7	Fexofenadine 360 mg
8	Multiple BCC/AK	0	*	0	2	Fexofenadine 240 mg
9	BCC	213	2	7	3	Fexofenadine 360 mg
10	Multiple BCC/AK	151	8	25	2	Cetirizine 5 mg
11	Multiple AK	31	29	2	2	Fexofenadine 360 mg
12	Multiple BCC/AK	3	1	2	3	Fexofenadine 360 mg

*Urticaria at first PDT treatment, value not defined.

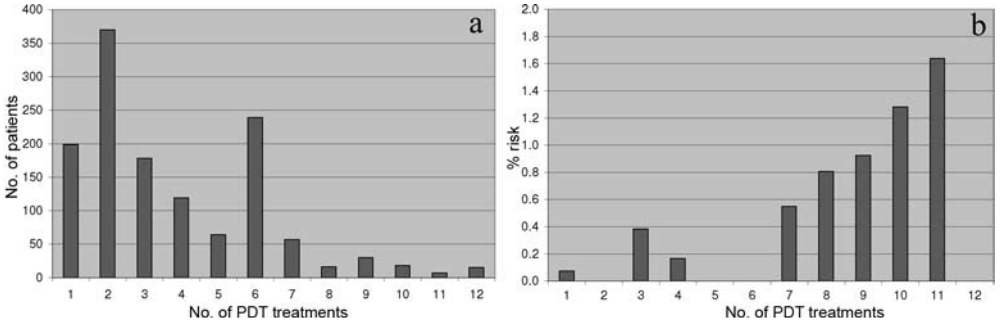

Fig. 1. (a) Number of patients and their total number of photodynamic therapy (PDT) treatments during the registration period from 1 March 2002 to 14 May 2007. (b) The percentage risk of immediate whealing urticaria was related to the number of PDT treatments. Thirty-eight patients had more than 12 PDT treatments. Of these patients, 2 developed urticaria at the 20th and 26th PDT treatment (not included in the figure).

Patients experienced clinical and subjective benefits by prophylactic treatment with systemic antihistamines for future PDT treatment sessions. These included a reduction in the urticarial rash and whealing and an almost total relief from itching. All patients were able to continue further PDT treatments with prophylactic antihistamine treatment.

DISCUSSION

This study documents the occurrence of immediate whealing urticaria during routine PDT. The symptom was itch that had not been associated with previous PDT treatments, and where the patients could clearly feel a new unpleasant event. Contact dermatitis to MAL PDT has been described in case reports (2). During the registration period of this study we recorded only 4 cases of contact dermatitis, which was less frequent than the 12 recorded cases of urticaria. Overall, our department performed more than 5700 PDT treatments during the period of registration. Most patients received several treatments, with the underlying conditions being multiple BCCs and AKs localized on the face and body. Only one of the patients had a history of urticaria and none had atopic dermatitis. The risk of developing urticaria increased considerably with the number of PDT sessions. Among the patients who received more than 6 PDT treatments the incidence was higher than that given in the manufacture's package insert.

Brooke et al. (6) demonstrated in a clinical study that the inflammatory response to PDT in normal human skin consists of 2 phases: first, an immediate short-lived urticarial response; followed by a prolonged erythemal reaction, persisting for 24 h. The immediate urticarial response is mediated mainly by a histamine release acting through H_1 receptors. The PDT-induced dermal

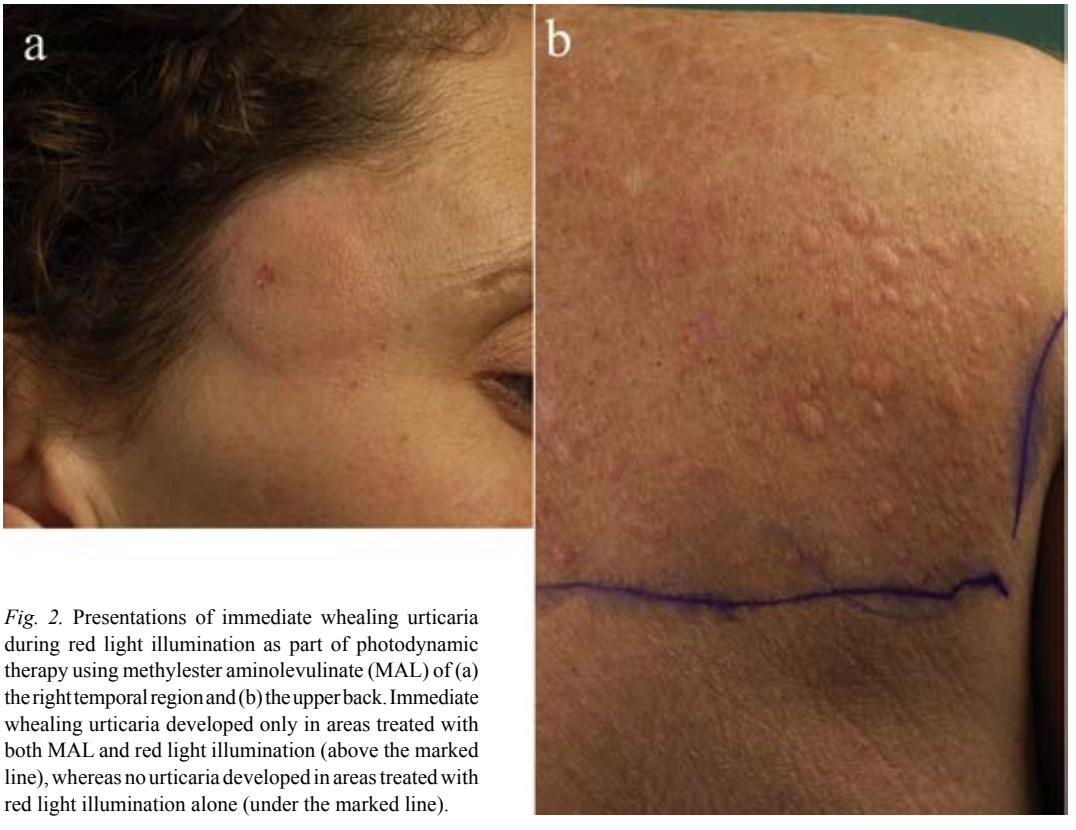

Fig. 2. Presentations of immediate whealing urticaria during red light illumination as part of photodynamic therapy using methylester aminolevulinate (MAL) of (a) the right temporal region and (b) the upper back. Immediate whealing urticaria developed only in areas treated with both MAL and red light illumination (above the marked line), whereas no urticaria developed in areas treated with red light illumination alone (under the marked line).

release of histamine was confirmed by direct measurements of histamine in the skin and was considered of major importance. However, PDT-induced immediate whealing urticaria does not seem to be a part of the normal clinical reaction.

All but one case developed urticaria after several PDT treatments, indicating that urticaria may be initiated by an IgE-mediated reaction with histamine release from intracellular mast cell granulas in the dermis. This pathogenesis is in accordance with the recurrent nature of the reactions for subsequent treatments and with the appearance of immediate urticaria in areas that had not been previously PDT-treated. For subsequent treatments, all patients were given a H_1 receptor blocker, which resulted in both subjective and objective relief of symptoms. Although this was not a formal randomized trial and other explanations might be considered, the strong benefits of antihistamine suggest that the H_1 block was responsible for the effect.

Three patients had been treated with ALA before MAL PDT, but developed their first case of urticaria after MAL PDT. It is surprising that the majority of patients had one or several co-morbidities. Two patients were organ transplanted, but no other common features were found. However, our material does not allow further analysis for common features. A high number of special cases are referred to our clinic, and the high number of co-morbidities may merely be a consequence of that fact.

It was not possible to draw any conclusions in this study about whether ALA PDT played a role in the risk of developing urticaria, as the number of ALA-treated patients was not sufficiently high. It is concluded that it is important to be aware of acute urticaria as a side-effect of PDT. However, treatments with PDT are generally well tolerated and can be continued with prophylactic antihistamines.

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