

Systemic allergic contact dermatitis caused by methyl aminolaevulinate in a patient with keratosis–ichthyosis–deafness syndrome

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Photodynamic therapy (PDT) is used for the treatment of non-melanoma skin cancers. A photosensitizer [aminolaevulinic acid (ALA) or methyl aminolaevulinate (MAL)] is applied to the skin and activated by light to produce cytotoxic oxygen species. Keratosis–ichthyosis–deafness (KID) syndrome is a form of ichthyosis caused by mutations in the *GJB2* gene (1). Patients present with vascularizing keratitis, hearing loss, and increased susceptibility to some cancers. We report systemic allergic contact dermatitis caused by MAL in a patient with KID syndrome.

Case Report

A 53-year-old female with KID syndrome presented with a long history of extensive hypertrophic lesions on both legs. Skin biopsies showed benign acanthosis and hyperkeratosis, which was treated with 15 sessions of PDT with ALA as a photosensitizer. Seven years later, new biopsies revealed multiple *in situ* squamous cell carcinoma on



Fig. 1. Erythematous papules in the mid-back region appearing with subsequent photodynamic therapy sessions and older hyperkeratotic hyperpigmented lesions in the lower back at the site of a preceding eruption.

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the legs. PDT with MAL (Metvixia[®] cream; Galderma, La Défense, France) was initiated. The topical drug was applied exclusively on the legs.

The first session was unremarkable. However, 2 h after the second session, performed 1 week later on the same skin area, the patient developed a generalized symmetric eruption (multiple erythematous and oedematous pruritic plaques on the trunk, arms, and legs). No obvious eczematous lesions were noted on treated sites. The eruption partially improved within 2 weeks, with the use of topical steroids. A similar eruption accompanied by intense pruritus occurred after the three following sessions, despite premedication with oral steroids. The eruption progressively resolved (older lesions becoming hyperkeratotic and hyperpigmented as newer lesions appeared following subsequent sessions) (Fig. 1). A lesional skin biopsy, performed at a late stage of the eruption, showed papillomatous epidermal hyperplasia with hyperkeratosis and superficial lymphocytic infiltrate.

As photoallergy to Metvixia[®] was suspected, photopatch tests were performed: a non-irradiated control patch and two patches irradiated 24 h after the application of Metvixia[®] with ultraviolet (UV) A (5 J/cm²) and three-quarters of the UVB minimal erythema dose, respectively. A photo-aggravated contact allergy was evident, yielding a +2 reaction at 24 h and a +3 reaction at 48 h for the UVB Metvixia[®] photopatch test, and a +1 reaction at 48 h and a +2 reaction at 72 h for the non-irradiated control patch test (Fig. 2a,b). Skin biopsies of the Metvixia[®] patch and the UVB Metvixia[®] photopatch were indicative of a contact allergic reaction. Photo tests with visible light, with irradiation for 5 and 10 min, gave negative results. We also performed a modified photopatch test with Metvixia[®] applied under occlusion for 3 h, in an attempt to mimic the PDT protocol, at two sites. We then irradiated one site with visible light for 5 min, and there was no immediate reaction up to 30 min after irradiation; the other (control) site was left unirradiated. The reading at 48 h of both the irradiated site and the non-irradiated site showed +2 reactions

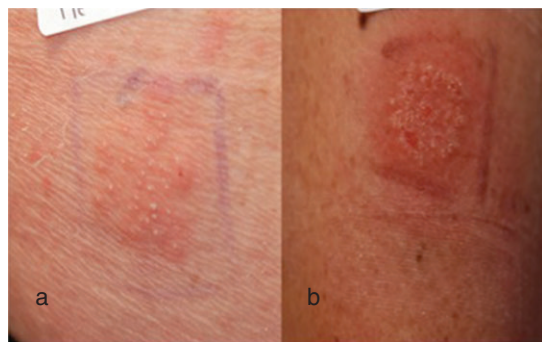


Fig. 2. Patch tests for: (a) Metvixia[®] control site – erythematous papules (+2) at 72 h; and (b) Metvixia[®] irradiated with ultraviolet B – erythematous papules and vesicles (+3) at 72 h.

Table 1. Results of different photopatch tests performed in our patient

Patch test	Source of irradiation	Results
Metvixia [®] applied 48 h	None	+1 at 48 h (and 72 h)
Metvixia [®] + UVA 5 J/cm ²	UVA1 range (340–400 nm)	+2 at 48 h
Metvixia [®] + three-quarters of UVB minimal erythema dose	Polychromatic (approved for the study of UVB photosensitivity)	+3 at 48 h
Metvixia [®] applied 3 h	None	+2 at 48 h
Metvixia [®] applied 3 h	Visible light (400–800 nm)	+2 at 48 h

UV, ultraviolet.

with similar intensities [several erythematous papules (Table 1)]. Patch tests performed with the components of Metvixia[®] supplied by the manufacturer showed weak positive reactions (+) on day (D) 2 and D3 with MAL 21% pet. All the other components, tested at concentrations higher than that in Metvixia[®], gave negative results, including the vehicle tested 'as is'.

A diagnosis of systemic allergic contact dermatitis caused by MAL was made. The lesions disappeared within 10 months.

Discussion

The immediate side-effects of PDT include pain, burning, and, rarely, urticarial reactions limited to treated sites. Allergic contact dermatitis has rarely been described at the application site, and there is no evidence of cross-reactivity between MAL and ALA (2, 3). Systemic contact allergic reactions occur when an individual sensitized to a contact allergen is exposed to this allergen or a cross-reacting molecule through a systemic route. It needs to be distinguished from a localized reaction with secondary spread. Lesions appear within 2 days following exposure. Clinical lesions may include 'dyshidrotic' hand eczema, flexural dermatitis, exanthematous eruptions, and erythroderma. Generally, systemic exposure to a contact allergen can occur by transcutaneous or transmucosal absorption, inhalation, or by oral, intravenous or intramuscular administration (4). In our case, the skin at the application site of Metvixia[®], that is, the legs, was abnormal in terms of being inflamed and hyperkeratotic. It was hence impossible to identify any possible localized eczematous reaction. To our knowledge, systemic allergic contact dermatitis caused MAL has not been described in the literature. In our patient, the transcutaneous absorption may have been enhanced by the skin barrier defect associated with the KID syndrome.

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