Use of photodynamic therapy and acitretin in generalized eruptive keratoacanthoma of Grzybowski

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INTRODUCTION

Generalized eruptive keratoacanthoma of Grzybowski (GEKG), a rare variant of keratoacanthoma (KA),[1] affects widespread areas of the skin and mucous membranes. First described in 1950,[2] this condition is exceptionally difficult to treat. Systemic retinoids or cyclophosphamide, although sometimes effective, may not be well tolerated. We report a case of severe GEKG, unresponsive to multiple systemic agents, in which photodynamic therapy was used successfully along with acitretin for disease management.

Abbreviations used:

GEKG:	generalized eruptive keratoacanthoma of Grzybowski
KA:	keratoacanthoma
PDT:	photodynamic therapy

CASE REPORT

A 46-year-old white woman was first seen in our clinic in 2010 for widespread scaly papules on her chest, back, upper extremities, hands, and in the oral and vaginal mucosa. Hundreds of 1- to 2-mm keratotic, dome-shaped, follicular-based papules were observed on the trunk and extremities, along with 3- to 8-mm scattered crateriform keratotic papules distributed in linear arrays and accentuated in the flexures (Fig 1). These papules were extremely pruritic. Ectropion, xerostomia, and masked facies were also observed. Biopsy results from the forearm were consistent with squamous cell carcinoma, KA type (Fig 2).

The patient was a cattle farmer from Michigan who at age 42 had first experienced the sudden onset of numerous papular lesions on the face and scalp; the eruption then progressed downward to involve her trunk and extremities. Painful palmar and plantar cysts developed. Soon after initial diagnosis, she began receiving acitretin, 50 mg daily, which helped at first but was stopped because of hypertension and headaches. Subsequent courses of methotrexate (5 weeks) and cyclophosphamide (6 weeks) failed to help. When the patient first arrived at our clinic, she had no medical insurance. As a safe, low-cost alternative to systemic agents for ameliorating the worst lesions, we decided to try photodynamic therapy (PDT) because of its reported efficacy in spontaneous KA.[3,4] Red light (635 nm Aktilite, Galderma Laboratories, LP, Forth Worth, TX) at a dose of 60 to 80 J/cm^2 was delivered 2.5 hours after application of 16.8% methyl aminolevulinate cream to her forearms and hands. To minimize severe pain, no occlusion was used. Compared with baseline (Fig 3), significant improvement was observed after 3 monthly sessions (Fig 4), with marked reduction in pruritus. During subsequent months, lesions would flare if treatments were missed or the light dose was lowered to 37 J/cm^2. Between the fifth and 12th PDT session, oral capecitabine was added (Xeloda, Genentech USA, Inc, South San Francisco, CA, 500 mg/d provided on a compassionate basis). However, after marked initial improvement, lesions became worse in areas not receiving PDT treatment. Therefore, capecitabine was stopped and PDT continued for a total of 32 sessions.

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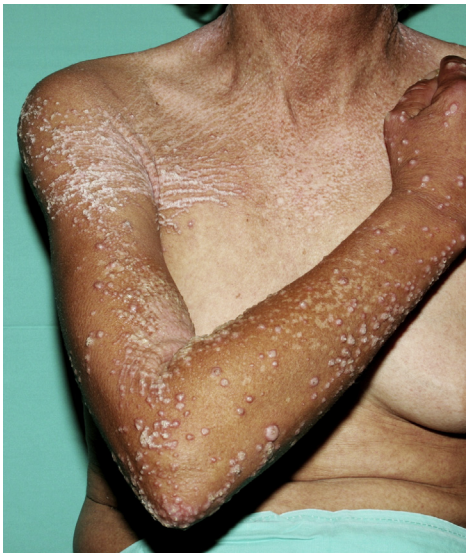

Fig 1. Multiple eruptive keratoacanthoma lesions on the neck, trunk, and upper extremities.

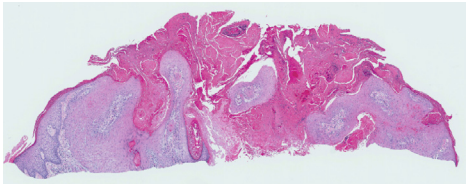

Fig 2. Left arm, atypical squamous proliferation, keratoacanthomatous type. (Hematoxylin-eosin stain; original magnification: ×10.)

In the fall of 2013, the patient finally received Medicaid insurance to cover medications (amlodipine for hypertension), blood tests, and visits to her local internist for blood pressure monitoring. She was started on oral acitretin (25 mg/d) in January 2014. By March 2014, her skin lesions had cleared completely. PDT was stopped. She remains in remission after 3 years on acitretin.

DISCUSSION

PDT is a nonsurgical modality for skin cancer treatment that takes advantage of the selective uptake and conversion of topical 5-aminolevulinic acid or its methyl ester (methyl-aminolevulinate cream) into the mitochondria of squamous cancerous or neoplastic cells.[5] The topical prodrug is then converted into a porphyrin molecule (protoporphyrin IX) that absorbs light and breaks down and destroys the cancerous cells.[6] Here we report on the novel use of PDT as a palliative treatment for Grzybowski syndrome. GEKG is a rare mucocutaneous disease characterized by spontaneous development of hundreds of

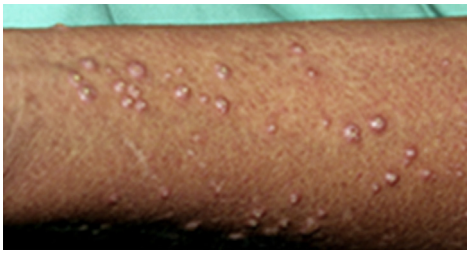

Fig 3. Left volar forearm before PDT shows multiple KA lesions.

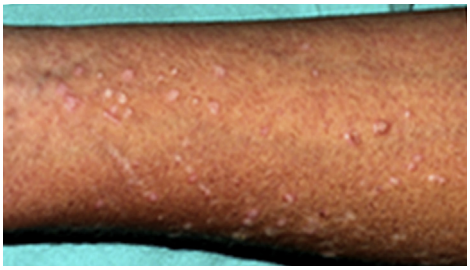

Fig 4. Left volar forearm after 3 PDT sessions shows partial resolution of lesions.

umbilicated papules that histologically resemble KA but generally show no signs of precancerous change or invasion.[1] Rather, the most pressing problem in these patients is often the intense pruritus in lesional skin along with pain and morbidity from palmar and plantar cysts, mucosal ulcers, and ocular ectropion. Our patient's disease was completely unresponsive to methotrexate and cyclophosphamide. She did respond to acitretin but could not continue on the drug because of side effects (exacerbated hypertension) and the need for blood testing and medical monitoring, all of which she could not afford. In that setting, red light PDT proved to be a useful palliative modality. PDT treatments, in the absence of any other therapy, enabled her to function and improved her quality of life to the extent that she was willing to travel 400 miles each month over several years until finally obtaining health insurance. At that point, she could safely resume acitretin therapy, which worked very well and allowed us to discontinue PDT.

There are several reports showing that red light PDT, using either 5-aminolevulinic acid or methyl-aminolevulinate as the prodrug, can treat solitary[7] or multiple KAs[3,4] with reasonable efficacy. However, our case appears to be the first report, to our knowledge, of PDT specifically used in the Grzybowski variant of KA. A relatively high light dose (~75 J/cm^2), similar to that commonly used for basal cell carcinoma, was necessary to achieve a response. Interestingly, an important question raised in the recent literature is whether PDT may promote

neoplasia in some KA patients. Thus, in a few case reports, the use of PDT for actinic keratoses[8-10] was associated with onset of eruptive KA several weeks after treatment. Because of the use of preparation (curettage) of lesions in some cases and the wide range of different light sources and fluences used, it is difficult to say whether pathergy might have played a role in triggering KA development in those cases. However, it also seems entirely possible that lesions in the Grzybowski variant are different than lesions in other types of KA. In support of that assertion, we note that our patient received a total of 32 PDT treatments over 3 years, all in the absence of acitretin and always to the same areas of skin, yet never had any malignant lesions. PDT should be considered a useful palliative modality in severe GEKG, especially when systemic agents are contraindicated or limited by side effects. Although reasonable caution and monitoring for the development of malignant transformation is certainly advisable, this does not seem to be a major risk in GEKG.

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