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ORIGINAL RESEARCH

Photodynamic Therapy is an Effective Treatment of Facial Pigmented Actinic Keratosis

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ABSTRACT

Background: Actinic keratosis (AK), or solar keratosis, is a precancerous condition of the skin, mainly caused by excessive and chronic exposure to ultraviolet radiation. Pigmented AK (pAK) is a rare variant of AK. Photodynamic therapy (PDT) is widely used to treat the classical variant of AK, but very limited data are available on the use of PDT in patients with pAK. The objective of this study was to assess the usefulness of PDT in the treatment of pAK.
Methods: The study included 16 patients with 20 pAK lesions treated with PDT. All skin lesions were clinically and dermatoscopically assessed for typical features characteristic of pAK. Reflectance confocal microscopy (RCM) was also used to assess keratinocyte atypia, confirm pAK diagnosis, and rule out other disease entities.
Results: After three PDT sessions, the complete resolution of all clinical features of pAK was observed in 80% of the studied lesions. Dermatoscopically, 65% of the lesions achieved 100% response and no cellular atypia was seen in the follow-up RCM images of 85% of lesions.
Conclusions: Photodynamic therapy is an effective treatment modality for pAK in fair-skinned individuals.

Keywords: Pigmented actinic keratosis; pAK; Photodynamic therapy; PDT; Dermatoscopy; Reflectance confocal microscopy; RCM

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Key Summary Points

Why carry out this study?

Actinic keratosis (AK), or solar keratosis, is a common precancerous condition of the skin, and its treatment with conventional and daylight photodynamic therapies (PDT) has been widely studied with high clearance rates reported.

Little is known about PDT effectiveness in different AK subtypes.

Melanin competes with protoporphyrin IX in light absorption, reducing photochemical reaction and desired photodynamic effect.

There have been no studies analyzing the effectiveness of PDT in pigmented AK (pAK).

What has been learned from this study?

PDT has proven to be an effective treatment modality for pAK in fair-skinned individuals.

Reflectance confocal microscopy examination showed superior usefulness in monitoring the PDT results.

INTRODUCTION

Actinic keratosis (AK), or solar keratosis, is a precancerous skin condition, mainly caused by excessive and chronic exposure to ultraviolet radiation [1]. Clinically, AK presents as a rough, scaly papule or plaque on an erythematous base. Seven distinct AK variants can be distinguished using histological features, namely, hypertrophic, atrophic, bowenoid, acantholytic, epidermolytic, lichenoid, and pigmented [2, 3], among which the pigmented subtype is the least frequently reported in the literature [4]. Interestingly, a single lesion can sometimes manifest an overlap of two or even several histological subtypes. However, some authors have suggested that in patients with multiple AK subtypes, lesions tend to present the same dermatoscopic pattern [5]. Pigmented AK (pAK) is a rare AK subtype (approx. 1.7% of all AK cases) [4]. Diagnosis of pAK within the face area can be challenging as it can be mistaken for lentigo maligna (LM), solar lentigo, seborrheic keratosis, or lichenoid keratosis [6–12]. Nevertheless, in daily practice, we can monitor the progression of the pAK with non-invasive methods, i.e., dermatoscopy and reflectance confocal microscopy (RCM) [5, 13, 14].

Conventional and daylight photodynamic therapies (PDT) with 5-aminolevulinic acid (5-ALA) in the form of nanoemulsion or methyl-aminolevulinate (MAL) have been thoroughly studied for AK treatment, with high clearance rates of the lesions reported [15]. However, Kaviani et al. suggested that PDT may have limited value in pigmented lesions. Melanin competes with protoporphyrin IX in terms of light absorption, reducing the photochemical reaction and desired photodynamic effect [16]. To the best of our knowledge, no studies have analyzed the effectiveness of PDT in different AK subtypes. Therefore, the aim of the study reported here was to assess the usefulness of PDT in treating pAK.

MATERIALS AND METHODS

Patients

The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from the patients for participation in the study. The study enrolled 16 patients (13 women, 3 men) with a total of 20 pAKs. Mean (± standard deviation) age of the 16 patients was 74.75 ± 8.89 years. The patients presenting with pAK were diagnosed via (video) dermatoscopic examination based on typical features. To further strengthen the diagnosis and exclude with certainty a possibility of malignant proliferation, each lesion was additionally assessed by RCM. Only patients with unequivocal lesions

(with features typical of pAK) in both the videodermatoscopy and RCM assessments were included in the study. All lesions were located on the face area; the age, gender, phototype, and previous skin cancer history were noted for each participant (Table 1).

Study Design

A total of 20 skin lesions were assessed clinically according to Olsen's 1991 criteria [18], with a videodermatoscope (Canfield D200EVO; Canfield Scientific GmbH, Bielefeld, Germany) and with RCM (VivaScope 1500/3000; MAVIG GmBH, Munich, Germany) before (day 0) and 1 month after (day 112) three sequential PDT sessions at 1-month intervals for 3 months. We included lesions that presented features typical of pAK in terms of dermatoscopy; for inclusion in the study the lesions could not present any features typical of LM in the RCM. The 5-ALA 10% cream (Foto-Dermal® HCl; MagnaPharm, Gdanski, Poland) was applied onto the skin lesions—which had previously been degreased with 70% ethanol and debrided (hyperkeratotic lesions)—in an occlusive light-shielding dressing. After the 180-min incubation period, the dressings were removed, residues of the preparation were washed off with mild soap and water, and the lesions were illuminated with pulsed 630 nm red light (Treviolux; MEDlight GmbH, Herford, Germany). Each patient received three PDT treatments at intervals of 4 weeks. The total dose of light received after three PDT sessions was 111 J/cm^2 for each lesion. Patients were advised on the post-PDT regimen and to avoid prolonged sunlight for 48 h after the treatment. To expedite healing and decrease irritation we recommended cosmetics containing D-panthenol and zinc oxide.

Clinical Assessment

Skin lesions were assessed clinically according to Olsen's 1991 criteria [18]. A grade 1 lesion (mild) was defined as a lesion with mild thickness and slight palpability, with the AK better felt than seen. A grade 2 lesion (moderate) was defined as an AK presenting with moderate thickness that was equally felt and seen, and a grade 3 (severe) was a very thick and/or obvious AK. For study purposes, we added grade 0, which referred to the location of a previous AK lesion that could not be seen and for which no changes could be felt. Clinical cure was claimed when the lesion was not visible by the naked eye and could not be felt with palpation.

Videodermatoscopy

Skin lesions were assessed using a videodermatoscope (Canfield D200EVO; Canfield Scientific GmbH, Bielefeld, Germany) at 20- to 70-fold magnification. The initial examination consisted of "dry dermatoscopy" (without immersion fluid); this was followed by "wet dermatoscopy" (with ultrasound gel). The presence and prevalence of specific dermatoscopic pAK criteria, including gray dots/globules/granularity, structureless brown pigmentation, gray-brown pseudo-network, moth-eaten borders, structureless white areas, annular granular pattern, pigment network, white circles, brown circles, asymmetrical pigmented follicular openings, a hyperpigmented rim of the follicular opening, dots in the line, jelly sign, superficial broken-up network, red pseudonetwork, black blotches, fingerprinting, dotted vessels, grayish areas, rhomboidal pattern, the "star-like" appearance at the periphery of the lesion, scale and crust, rosettes, the double white clods, the dermatoscopic horn, circle in the circle, target-like pattern, "strawberry sign", sharp demarcation, milia-like cysts, comedo-like openings, and yellow opaque homogenous areas, were assessed before (day 0) and after (day 112) the three PDT sessions [8, 13, 19]. On day 112, lesions were considered cured when the videodermatoscopy did not reveal any of the above-mentioned features. To increase the clarity of data presentation in the Results section, we did not include dermatoscopic parameters that were not observed in any of the AK lesions.

Table 1 Patient characteristics

Patient number	Gender	Age (years)	Skin phototype according to Fitzpatrick grading [17]	Previous skin cancer history
1	Female	89	I	Yes (squamous cell carcinoma)
2	Male	88	II	Yes (basal cell carcinoma)
3	Female	83	II	No
4	Female	83	II	No
5[a]	Female	81	II	No
6	Female	80	II	No
7	Female	79	I/II	No
8	Male	77	II	No
9	Female	74	I	No
10	Female	72	II	Yes (basal cell carcinoma)
11	Female	71	I	Yes (squamous cell carcinoma)
12[a]	Female	68	II	No
13[a]	Female	66	I	Yes (basal cell carcinoma and squamous cell carcinoma)
14[a]	Male	63	II	No
15	Female	61	II	No
16	Female	61	II	No

pAK Pigmented AK
[a]Patients with two pAK lesions

Reflectance Confocal Microscopy

Lesions underwent imaging using a near-infrared reflectance confocal laser microscope (Vivascope 1500/3000; MAVIG GmBH, Munich, Germany) that uses a diode laser at a wavelength of 830 nm. A minimum of three mosaics were obtained per lesion, at the superficial epidermal layer, dermo-epidermal junction, and papillary dermal level, respectively; each mosaic consisted of 16 × 16 images of 500 × 500 μm. A 3000 handheld device was used for lesions located in areas where using the 1500 Vivascope device was technically challenging or impossible; in that case, at least five vivastacks were acquired with around 25–30 images of 750 × 750 μm per stack.

The RCM criteria that we had observed in pAKs included such features as scale, disruption/individual cells, parakeratosis, corneal pseudocysts, keratin-filled invagination, atypical keratinocytes, disarranged epidermal pattern, mottled pigmentation, targetoid cells, intraepidermal dendritic cells, ringed areas/small and bright papillae/densely packed papillae, polycyclic papillary contours, cords, plump bright cells, huddled collagen bundles, coarse collagen bundles, curled fibers, vessels traversing dermal papillae ("bottom-hole"), and linear vessels [14, 20]. To exclude LM, we used RCM criteria included in the lentigo maligna diagnostic algorithm proposed by Guitera et al. [21]. We assessed for the presence of the following features: non-edged papillae, round pagetoid cells > 20 μm, ≥ 3 atypical cells at the

dermo-epidermal junction in five 0.5 × 0.5-mm^2 fields, follicular localization of pagetoid cells and/or atypical junctional cells, nucleated cells within dermal papillae, and broadened honeycombed pattern [21].

To classify the RCM images to determine keratinocyte atypia, we used the classification of Seyed Jafari et al. [22]. According to this classification, an atypia score of "0" corresponds to no cellular atypia, no architectural disruption, normal honeycomb pattern, and well-defined keratinocytes; an atypia score of "1" corresponds to minimal changes to the honeycomb pattern, most keratinocytes with readily detected borders, as well as occasional changes in keratinocyte morphology; an atypia score of "2" corresponds to main characteristics of moderate loss of honeycomb pattern, different cell sizes, areas with blurred cell borders, and several changes with keratinocyte morphology; and atypia score "3" corresponds to the loss of honeycomb pattern, severe cellular atypia, and loss of keratinocyte morphology [22]. Lesions were considered cured when at day 112 the lesion was given a score "0" based on the RCM examination, as proposed by Seyed Jafari et al. [22]

RESULTS

Clinical Evaluation

Of the 20 lesions included in the study, 19 were classified as Olsen's grade 1 (95%) and one lesion as Olsen's grade 2 (5%). After three PDT sessions, we observed the complete resolution of any clinical characteristics of pAK in 80% of the studied lesions; the remaining 20% still presented as flat maculae with no scale, although they were still easily felt with palpation.

Videodermatoscopy

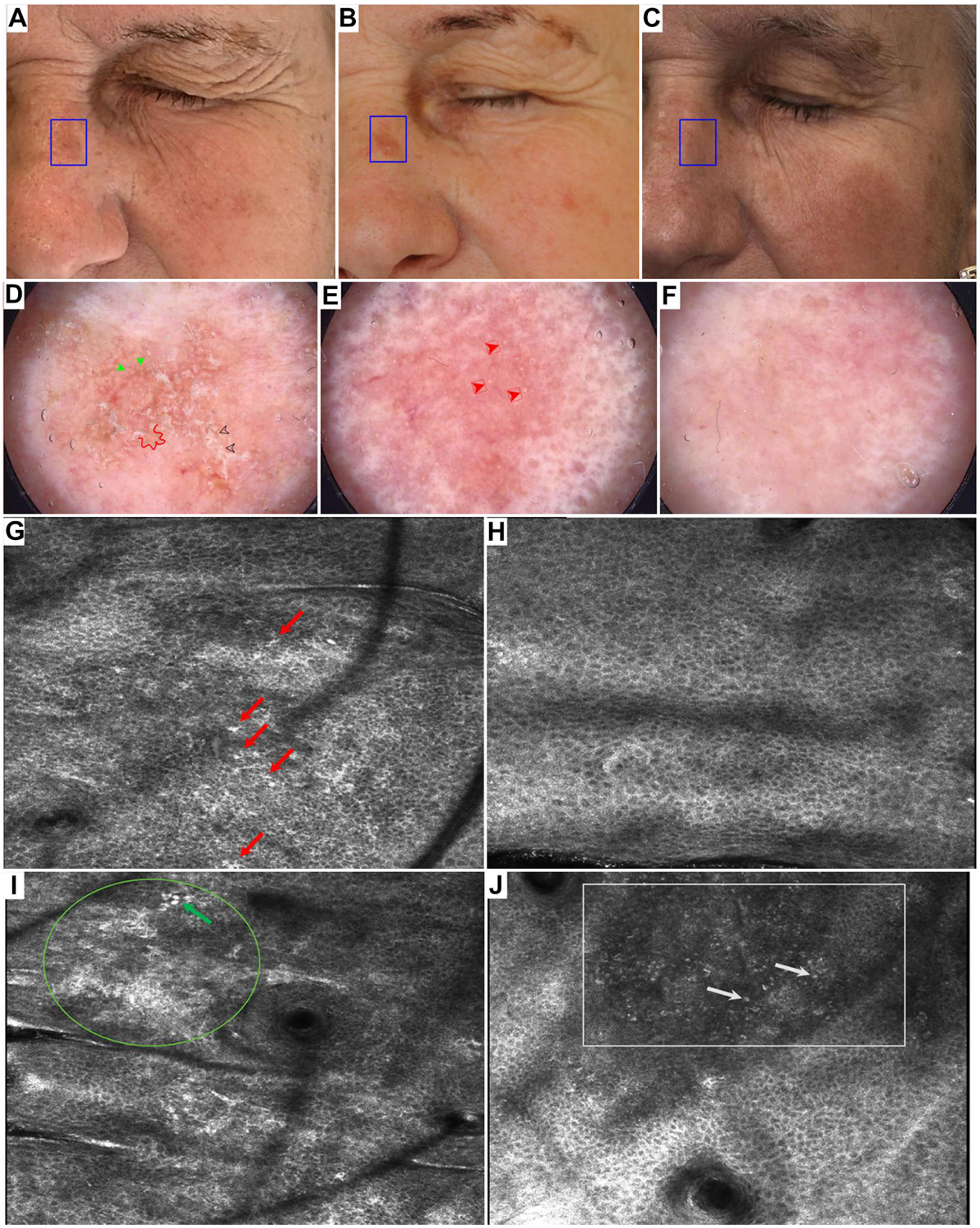
All assessed skin lesions showed typical features of pAK on dermatoscopy. In our study population, the most prominent pAK features were rhomboidal pattern (80%), scale (60%), presence of white globules (50%), jelly sign with superficial pigmentation (40%), inner gray halo (35%), and white circles (30%).

The dermatoscopic examination showed complete resolution of all assessed features after three PDT sessions in 65% of the lesions (Fig. 1). In the remaining cases, a significant reduction in the size of the lesions and their color intensity was observed (Fig. 2). In addition, such features as the presence of white globules resolved in almost half of the lesions (5/11), while the annular-granular pattern resolved in one-third of the lesions (3/9). At the same time, the only dermatoscopic feature that presented with an increase in incidence after the three PDT sessions was the presence of grayish areas (5–10% of patients).

Reflectance Confocal Microscopy and Keratinocyte Atypia

According to the recommendations proposed by the panel of experts on the multidisciplinary management of cutaneous squamous cell carcinoma in 2022, RCM may be used in selected patients for the differential diagnosis of complex lesions, especially in the head and neck area [23]. In our study, RCM was used to exclude the possibility of LM diagnosis and to assess keratinocyte atypia. None of the lesions included in the study showed features typical for LM (20% of the lesions scored 1 point and 80% scored 0 points) as proposed by Guitera et al. in the RCM diagnostic algorithm for LM [21].

All lesions (100%) presented varying degrees of keratinocyte atypia before PDT. The most prevalent keratinocyte atypia (85%) was characterized by keratinocyte atypia score 2 (moderate loss of honeycomb pattern, with several changes in keratinocyte morphology and different cell sizes, areas with blurred cell borders), followed in prevalence (10% of cases) by atypia with score 3 (loss of honeycomb pattern, severe cellular atypia, and loss of keratinocyte morphology). The least observed atypia were those with atypia score 1 (minimal changes to the honeycomb pattern, occasional changes in keratinocyte morphology, and the most keratinocytes with readily detected borders), with a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◀**Fig. 1** An example of a patient who achieved a complete cure of pigmented actinic keratosis (pAK) lesion after three photodynamic therapy (PDT) sessions. **A–C** Clinical images of pAK on the left side of the nose (blue rectangle) before PDT treatment (**A**), after the first PDT session (**B**), and after the third PDT session showing the disappearance of the lesion (**C**). **D–F** The disappearance of the characteristic dermatoscopic pAK features during PDT treatments, including the rhomboidal pattern (red line), the double white clods (green arrowhead), scale (black arrowheads), white clods (red arrowheads), before PDT (**D**), after the first PDT session (**E**), and after the third PDT session (**F**). **G–J** Single RCM pictures of pAK before (**G**, **I**) and after (**H**, **J**) three PDT sessions, showing keratinocyte atypia with the presence of dendritic cells and processes (red arrows) probably corresponding to Langerhans cells (**G**), normal honeycomb pattern (**H**), presence of pigment incontinence (green circle) and pigment granules (green arrows) in the spinous layer (**I**), and area of numerous melanophages (white rectangle) depicted as small plump bright cells (white arrows) (**J**)

5% prevalence. After three PDT sessions, the absence of cellular atypia was achieved by 85% of lesions (n = 17), as determined in the follow-up RCM images. Only three lesions (15%) still presented with some keratinocyte atypia, with minimal changes to the honeycomb pattern of the epidermis (Fig. 3).

Overall Cure Rates

Photodynamic therapy success rates according to the different methods of evaluation are summarized in Table 2. In our study of the treatment results, the RCM examination was characterized by the highest pAK cure rates (85%), followed by clinical examination, amounting to 80%. The lowest complete lesion resolutions (65%) were achieved while using dermatoscopy.

DISCUSSION

To the best of our knowledge, no studies on PDT for pAK, which is a rare subtype of AK, are available in the literature, particularly on PDT from pAK in fair-skinned individuals [6]. The etiology of pAK is unclear; nevertheless, several theories have been proposed. Dinehart et al. demonstrated that there are no differences in the number of melanocytes in the basal layer of the epidermis in pigmented versus non-pigmented AK. Electron microscopy studies, on the other hand, showed enhanced melanosome formation in epithelial keratinocytes [24]. According to Labadie et al. [25], pAK color in histopathology is associated with pigment incontinence, basilar pigment presence, and absence of inflammation. Chung et al. studied a series of 167 cases of pAK and reported that histopathologically one-fifth of the lesions (19%) were bona fide pAK and that 81% of the cases were a collision between adjacent or coexisting non-pigmented AK and pigmented lesions (most frequently solar lentigo) [26]. Moscarella et al. also detected in assessed pAKs features typical for solar lentigines and seborrheic keratoses. However, no clear-cut collision pigmented lesions were found [14].

Dermatoscopic and RCM features of pAK have been described previously [5, 13, 14, 27–33]. Similar to our results, Kelati et al. found that the most prevalent dermatoscopic pAK features were a rhomboidal pattern, inner gray halo, scale, jelly sign, and superficial pigmentation. Moreover, researchers noted that the presence of $\geq$ 2 dermatoscopic features from both follicle surroundings (1) and follicle keratosis (2) categories were observed in 99.1% of the lesions. Therefore, the diagnosis of pAK in flat lesions should be based on the presence of a combination of at least two dermatoscopic features rather than on a single criterion. In addition, these authors noted that jelly sign with a superficial pigmentation characterized thin plates of AKs, whereas central crust and scale were more characteristic of thick plates and lower skin phototypes; these results are in agreement with our findings in the present study.

A recently published systematic review and meta-analysis of noninvasive diagnostic techniques for melanoma detection [34] computed RCM performance and found an average sensitivity and specificity of 88.2% and 65.2%, respectively, with small 95% confidence intervals (CI) of 80.3–93.1% and 55–74.2%,

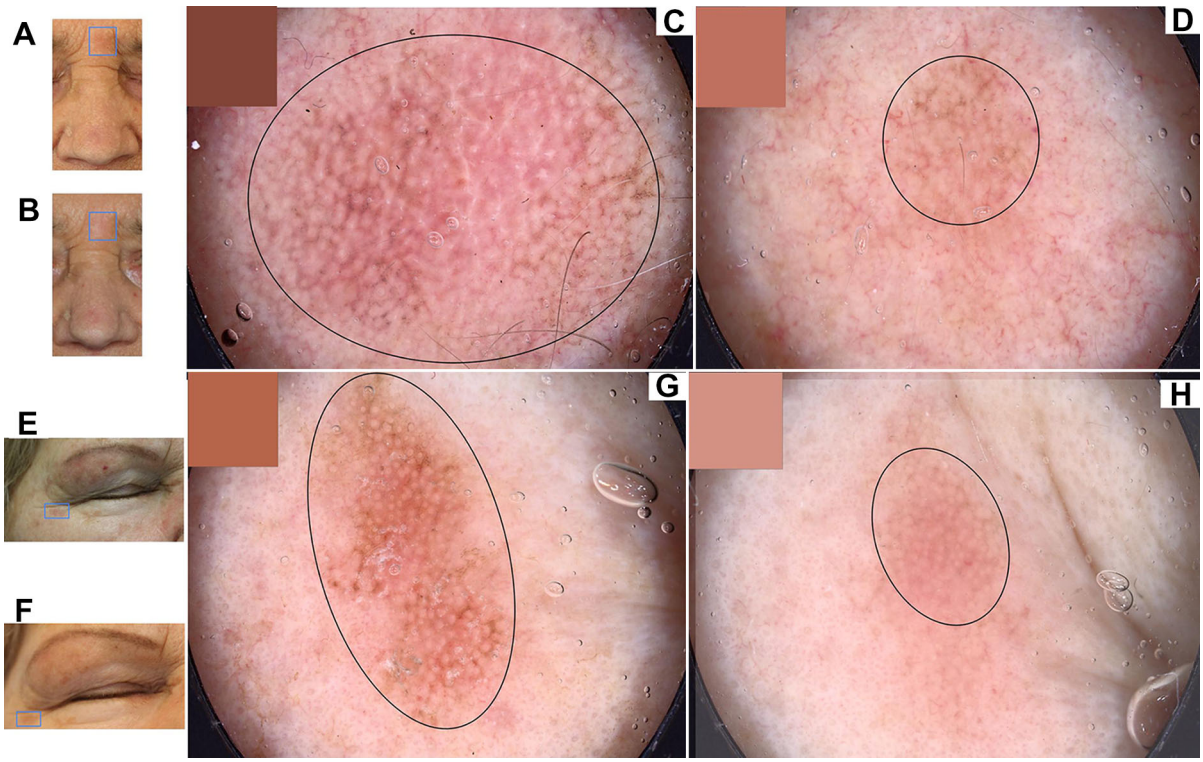

Fig. 2 An example of a patient achieving a reduction in the size and color of the pAK after three PDT sessions. **A**, **B**, **E**, **F** Clinical images of pAK (blue rectangle) on the nasal bridge (**A**, **B**) and the left eyelid (**E**, **F**) before PDT (**A**, **E**) and after the third PDT session (**B**, **F**) showing a reduction in the size of the lesions and their color intensity. **C**, **D**, **G**, **H** Dermatoscopic pictures of pAK, showing diminishing of the size (black circle) and color (upper left corner) of pAK before (**C**, **G**) and after (**D**, **H**) three PDT treatments

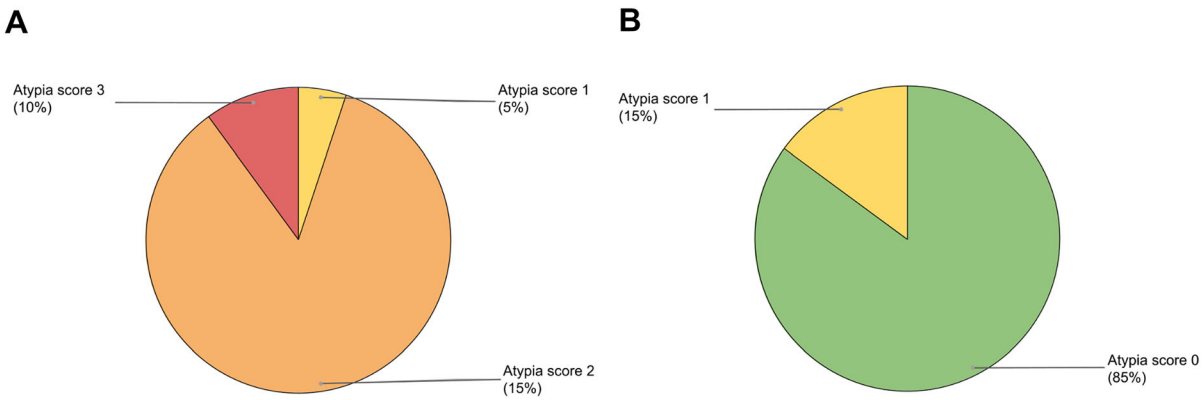

Fig. 3 Reflectance confocal microscopy keratinocyte atypia before (**A**) and after (**B**) three PDT sessions of pigmented actinic keratosis

respectively. Moreover, RCM achieved the highest performance when paired with dermatoscopy (sensitivity: 98%, 95% CI 92–99%; specificity: 92%, 95% CI 87–96%) [35], exceeding dermatoscopy-alone diagnostic performance [36].

Table 2 Clinical, dermatoscopic, and reflectance confocal microscopy complete cure rates and partial effect of photodynamic therapy in pigmented actinic keratosis

Assessment	Complete cure (%)	Partial effect (%)
Clinical	80	20
Dermatoscopic	65	35
Reflectance confocal microscopy	85	15

Pellacani et al. [37] correlated RCM with histopathology for grading keratinocyte atypia in AK. Their findings showed good concordance between raters in terms of grading RCM and histopathological atypia of keratinocytes, for both the detection of keratinocyte atypia and the identification of 'key' RCM images; both of these features are usable for grading keratinocyte atypia [37]. Because of the growing number of articles on RCM use in different non-melanocytic skin lesions, Navarete Dechent et al. performed a systematic review pooling all of the literature terms used to describe the same RCM findings. These authors found out that actinic changes in honeycomb, an architectural disorder of the overlying epidermis, mild keratinocyte atypia, and atypical honeycomb pattern were the most frequently used terms to describe keratinocyte atypia in RCM [38]. Curiel-Lewandowski et al. [39] assessed the usefulness of RCM as a non-invasive monitoring tool in AK treatment. According to these authors, RCM has the potential to standardize the therapeutic monitoring of AK over time. Features such as atypical honeycomb patterns, hyperkeratosis, disarranged epidermal patterns, and stratum corneum disruptions in RCM were the most reliable criteria for assessing AK treatment response. These authors also emphasized the importance of the utility of RCM for the non-invasive monitoring of subclinical disease and for the identification of early post-treatment AK recurrence. However, they consistently stressed the importance of simplifying the RCM criteria used to date and the need for extensive standardization efforts [39].

A clearly defined keratinocyte atypia score was proposed by Seyed Jafari et al. [22]. The Swiss team created a grading system in which a score of 0 corresponds to no cellular atypia; a score of 1 corresponds to occasional changes in morphology (< 10%), with minimal changes to the honeycomb pattern; a score of 2 represents several changes in keratinocyte morphology and moderate loss of honeycomb pattern (10–50%), with blurred cell borders and different cell sizes; and a score of 3 corresponds to a loss of keratinocyte morphology (≥ 50%) and honeycomb pattern with severe cellular atypia as the most important characteristics. The study showed acceptable intra/inter-rater agreement with an intraclass coefficient (ICC) > 0.7, and the Spearman correlation coefficient showed a significant positive correlation with clinical response ($p = 0.006$, $r = 0.619$) [22].

We found RCM to be the most helpful device for monitoring PDT results in pAK. To the best of our knowledge, this is the first study to present an evaluation of the disappearance or diminishing of videodermatoscopic and RCM keratinocyte atypia features of pAK during PDT treatment. We hypothesize that the low resolution of the "annular granular pattern" in our dermatoscopic analysis together with the increase in the presence of so-called "grayish areas" might be explained by the Tyndall effect, possibly evoked by the presence of melanophages in the upper layer of the dermis that became activated during the PDT sessions. Thus, the remaining minimal dermatoscopic features of pAK do not necessarily mean that the treatment was ineffective, and RCM may help to properly assess the doubtful lesions, as used in our study when four of seven patients with residual dermatoscopic abnormalities no longer demonstrated any keratinocyte atypia.

Although we consider our treatment results valid and encouraging, they have to be considered with some caution. Limitations of the current study include small sample size, single-center design, and inclusion of only Caucasian patients (Fitzpatrick skin phototype I–II). Thus, further research is needed to reliably evaluate the applicability of PDT in the treatment of pAK and of non-invasive skin imaging methods in its treatment monitoring.

CONCLUSIONS

Photodynamic therapy seems to be an effective treatment modality for facial pAK in fair-skinned individuals, and RCM examination is a useful tool for monitoring PDT results. However, this hypothesis needs to be supported by a larger study population, preferably with a control group.

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Author Contributions. Ewelina Mazur conceived the research idea, designed the study, supervised the data collection and analysis, interpreted the results, redacted the scientific content of the manuscript, and reviewed and validated the final version. Adam Reich supervised the study, redacted the scientific content of the manuscript, and reviewed and validated the final version.

Disclosures. Ewelina Mazur declares that she has no conflict of interest. Adam Reich is a member of the journal's Editorial Board.

Compliance with Ethics Guidelines. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from the patients for participation in the study and publication of the article, including the publication of clinical photographs.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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