Lasers in Surgery and Medicine

CLINICAL REPORT OPEN ACCESS

Efficacy of Alexandrite Laser in the Treatment of Pigmented Actinic Keratoses: A Pivotal Study

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Received: 30 April 2024 | **Revised:** 2 September 2024 | **Accepted:** 15 September 2024

Funding: The authors received no specific funding for this work.

Keywords: actinic keratosis | Alexandrite laser | laser | pigmented actinic keratosis

ABSTRACT

Objectives: Pigmented actinic keratoses (PAKs), a pigmented variant of actinic keratosis, present diagnostic challenges due to their resemblance to both benign and malignant lesions. Conventional therapies have inconsistent outcomes and may cause undesirable side effects. This study investigates the efficacy of the Alexandrite laser, a pulsed laser with selective melanin absorption, for PAK treatment. Through dermoscopic analysis pretreatment, it aims to identify predictive patterns for better treatment outcomes.

Materials and Methods: Patients with PAKs were enrolled in a multicenter study, receiving standardized Alexandrite laser therapy. Detailed dermoscopic evaluations were conducted pretreatment. The Physician's Global Assessment (PGA) and Target Lesion Pigmentation (TLP) scales measured treatment efficacy.

Results: The study included 50 patients with 60 PAKs. Following treatment, there was a statistically significant reduction in TLP scores, particularly in lesions with pigmented pseudo-networks and gray-brownish dots, which were linked to improved outcomes. No adverse effects were reported, suggesting the safety and tolerability of the laser treatment.

Conclusion: The Alexandrite laser emerges as a promising modality for the management of PAK pigmentation, with specific dermoscopic patterns being indicative of a favorable response. This study reinforces the critical importance of dermoscopic expertise in the selection and optimization of treatment for PAKs. Future research should focus on comparative studies with different lasers or combination therapies to develop a more comprehensive treatment framework for PAKs.

1 | Introduction

Pigmented actinic keratoses (PAKs) are a common dermatological condition, representing a pigmented variant of actinic keratosis, which in itself is a marker of chronic sun damage and a potential precursor to squamous cell carcinoma [1, 2]. The identification and management of PAKs are pivotal in dermatologic practice due to their malignant transformation risk [3]. PAKs' pigmentation often results in diagnostic ambiguity, as they exhibit overlapping dermoscopic features with a spectrum of pigmented skin lesions, including benign entities like solar lentigo and malignant conditions such as lentigo maligna [4–8]. This resemblance poses significant challenges for clinicians and dermatologists aiming to implement appropriate treatment strategies. Traditional treatment modalities for PAKs include cryotherapy, topical chemotherapeutics, and photodynamic therapy (PDT), each with variable efficacy and patient tolerance profiles [9, 10]. When employed for facial lesions,

such interventions can be accompanied by notable side effects, ranging from scarring and dyspigmentation to prolonged erythema and discomfort. So, the quest for targeted, less invasive, and cosmetically favorable options has led to the exploration of laser therapy [7]. The Alexandrite laser has garnered attention due to its selective absorption by melanin, making it an attractive therapeutic option for pigmented lesions [11–13]. Its utility has been well-established in treating benign pigmented conditions like SL, but its role in managing PAKs remains under investigation. More recently, novel treatments such as fractional laser and intense pulsed light have also emerged in treating AKs, offering promising results with potentially fewer side effects [14, 15]. However, their long-term efficacy and role in managing PAKs require further investigation.

This investigative study is designed to assess the efficacy of the Alexandrite laser in the treatment of PAKs by employing clinical scoring systems. Our methodological approach involves using dermoscopic analysis to discern whether particular patterns, observed before laser intervention, could serve as reliable indicators for predicting the laser therapy's success.

2 | Materials and Methods

The present multicenter study recruited participants aged 18 years and older from the outpatient clinic of the Dermatology Department at the University Hospital of Brescia and Centro Medico Polispecialistico in Pavia between March 2018 and September 2023. Each subject presented with clinically and dermoscopically confirmed PAK on the face by two expert dermatologists, classified with Olsen criteria. In case of differential diagnostic doubt, a 2 mm skin punch biopsy was performed and lesions that did not have a definite AK histopathologic diagnosis were excluded from the study.

The exclusion criteria comprised the use of oral and/or topical retinoids in the 6 months preceding the study, significant sun exposure or tanning, presence of active skin or connective tissue disorders with photosensitivity, active herpes simplex infections, usage of photosensitizing cosmetics or medications within 6 months before the study that could affect outcomes, conditions associated with immunodeficiency as evaluated by the attending physicians, uncontrolled diabetes, recent cosmetic or esthetic treatments in the target area as assessed by the physician, conditions like acquired vitiligo or other melanin production abnormalities, tattoos in the treatment area, and the use of anti-inflammatory medications. Additionally, pregnant or breastfeeding women were also excluded.

Each participant underwent treatment sessions with the 755 nm Alexandrite laser (Candela Corp., Wayland, MA, USA) under consistent operational parameters. The parameters were standardized as follows: lesions were treated using a nanosecond pulse duration, with a single pass, a 4 mm spot size, a repetition rate of 2 Hz, and an energy density of 4.5 J/cm^2, with no cooling applied. The clinical endpoint was defined as the presence of erythema, perilesional edema, and darkening or graying of the lesion immediately following laser therapy. Follow-up took place 3 months after laser session. Patients who did not respond to the initial treatment were subsequently treated with traditional methods, such as cryotherapy or topical chemotherapeutics. In the pursuit of a comprehensive evaluation, both dermoscopic and macroscopic photographs were systematically captured before the initiation of treatment and following the conclusion of the therapeutic protocol using a Vidix dermoscope 4.0. In our study, a detailed catalogue of dermoscopic features for each pigmented lesion was chronicled as followed: gray-brownish dots, red pseudo-network, pigmented pseudo-network, inner gray halo, rosettes, yellowish dots, widened follicular openings, linear vessels, double white clods, and scales. To evaluate the therapeutic efficacy and safety of the Alexandrite laser, we employed a two-tiered clinical scoring system as followed.

2.1 | Physician's Global Assessment (PGA)

The PGA score provides a gradation of treatment response in pigmented lesions, ranging from complete clearance (PGA 0) to possible worsening of the condition (PGA 6). Based on clinical and dermoscopic treatment response, PGA is categorized as follows: complete clearance is evidenced by the absence of the treated lesion, while an almost clear rating signals a significant fading of the lesion, with over 90% improvement. A marked improvement reflects a substantial reduction in the lesion's severity, quantified as about a 75% positive change. When the improvement is moderate, it implies that the lesion's severity has been reduced by half. Slight improvements indicate minimal but observable changes, around a 25% betterment. A score signifying no change means the lesion's appearance is largely unchanged posttreatment, and a score for worsening indicates that the lesion has deteriorated beyond its initial state. Patients were categorized into "high efficacy" (PGA $\leq$ 2) and "low efficacy" (PGA $\geq$ 3) groups.

2.2 | Target Lesion Pigmentation (TLP)

The TLP scale is a nuanced scoring system used to assess the pigmentation of a lesion in comparison to the surrounding skin after treatment. A score of 0 on this scale means the treated area is extremely lighter than the surrounding skin, suggesting complete depigmentation. A score of 1 implies that the lesion is markedly lighter but not completely devoid of pigment. Scores of 2 and 3 indicate that the lesion is moderately and slightly lighter than the surrounding skin, respectively, showing a gradient of improvement in pigmentation. A score of 4 is given when the pigmentation of the lesion matches the surrounding skin, indicating neither improvement nor worsening posttreatment. As the scores increase from 5 to 8, they reflect a progression in the lesion becoming darker than the surrounding skin, with 5 being slightly darker, 6 moderately darker, 7 markedly darker, and 8 extremely darker, the latter suggesting significant hyperpigmentation.

2.3 | Statistical Analysis

Encoded and anonymous database was formatted using Microsoft-Excel TM software and subsequently imported from IBM-SPSS TM ver. 29.0. Descriptive statistics, including mean,

standard deviation, median, and range, were calculated for continuous variables, whereas categorical variables were presented as frequency counts and percentages. Differences in TLP scores were analyzed using the paired *T*-test. Differences in pattern and features in dermoscopy between high or low efficacy laser therapy groups were analyzed using chi-square test followed by logistic regression analysis. A p value of < 0.05 was considered statistically significant for all analyses.

The local ethics committee approved the study (protocol 4277). The committee assessed the study protocol, informed consent forms, and participant information sheets to ensure they met ethical standards, including participant safety, data confidentiality, and the right to withdraw from the study at any time without consequence. The ethics committee required that all researchers comply with these standards and provided conditional approval based on modifications to the study design to further protect participant welfare.

The study adhered to the Declaration of Helsinki's principles and EQUATOR reporting guidelines. These included obtaining written informed consent from each participant after providing detailed information about the study's purpose, procedures, potential risks, and benefits. Participants were also assured of their right to privacy and confidentiality regarding their data.

3 | Results

The cohort consisted of 50 patients, including 9 men and 41 women (18% and 82%, respectively), within an age range of 45–80 years (median age: 68 years). A total of 60 PAKs were treated. Clinical and instrumental characteristics are outlined in Table 1. Out of the PAKs, 45 were classified as Olsen Grade I, 14 as Olsen Grade II, and 1 as Olsen grade III (75%, 23.3%, and 1.7%, respectively). Only 2 (3.33%) PAKs were biopsied. Regarding anatomical locations, 18 PAKs were on the lateral face, 16 on the temples, 14 on the nose, and 12 on the forehead (30%, 27%, 23%, and 20%, respectively). The Fitzpatrick skin-type classification showed that the most common phototypes were II and III, with 28 and 26 cases each (46% and 44%, respectively). Dermoscopic analysis revealed that pigmented pseudo-network was observed in more than half of the cases (31 cases, 51.67%), with red pseudo-networks present in a similar proportion (33 cases, 55%). Gray-brownish dots were noted in 30 PAKs (50%), and rosettes and inner gray halos each in 24 (40%). Yellowish dots were seen in 24 PAKs (40%), widened follicular openings in 21 (35%), and linear vessels in 10 (16.67%). Double white clods were identified in 25 PAKs (41.67%), and scales were present in 31 (51.67%). The median TLP score before laser therapy was 6 (range: 4–8). Scores of 4, 5, 6, 7, and 8 occurred 2 (3.33%), 24 (40%), 20 (33.33%), 10 (16.67%), and 4 times (6.67%), respectively. TLP score decreased to 4 (range: 3–7) posttreatment at the 3-month mark. Scores of 3, 4, 5, and 6 occurred 7 (11.67%), 25 (41.67%), 18 (30%), and 10 times (16.67%), respectively. At follow-up, the median PGA score was 3 (range: 0–4), with 26 (43.3%) PAKs scoring 2 or below and 34 (56.67%) scoring 3 or above. The median number of alexandrite laser spots applied was 48 (range: 9–292). None of the patients experienced a worsening of the lesion or any side effects related to the laser treatment. Of the cohort, 12 patients received alternative traditional treatments for their persistent PAKs; 10 underwent cryotherapy, while 2 were treated with topical chemotherapeutics.

TABLE 1 | Demographics and clinical characteristics.

Sex, *n* (%)	
Female	41 (82)
Male	9 (18)
Age (years), median (min−max)	68 (45–80)
Fitzpatrick phototype, *n* (%)	
I	4 (7)
II	28 (47)
III	26 (43)
IV	2 (3)
Lesion location, *n* (%)	
Lateral face	18 (30)
Temple	16 (27)
Nose	14 (23)
Forehead	12 (20)
Olsen's clinical stage, *n* (%)	
I	45 (75)
II	14 (23.3)
III	1 (1.7)
Pre-laser TLP, median (min–max)	6 (4–8)
Follow-up TLP, median (min–max)	4 (3–7)
Follow-up PGA, median (min–max)	3 (0–4)
Spots alexandrite laser, median (min–max)	48 (9–292)
Subsequent treatment recurrence, *n* (%)	
Cryotherapy	10 (16.7)
Topical chemotherapeutics	2 (3)

A paired *T*-test demonstrated a statistically significant decrease in TLP scores before and after laser treatment ($p < 0.001$). After categorizing the PGA scores as high or low efficacy, we performed a Pearson Chi-Square test to determine any significant differences among the dermoscopic patterns. The results, presented in Table 2, indicate that pigmented and red pseudo-networks, and gray-brownish dots are significantly associated with treatment outcomes ($p < 0.001$, $p < 0.05$, $p < 0.05$, and $p < 0.001$, respectively) (Figure 1). The logistic multivariate regression analysis, as shown in Table 2, reveals that both pigmented pseudo-networks and gray-brownish dots are positive predictors of treatment success (both $p < 0.001$), increasing the odds of PGA being 1 by about 14.46 and 13.14 times, respectively. Conversely, the presence of a red pseudo-network is negatively associated with the likelihood of PGA being 1 ($p = 0.04$) by about 64% (Figures 2 and 3).

4 | Discussion

The results of our multicenter study have provided valuable insights into the application of Alexandrite laser therapy for the

TABLE 2 | Dermoscopic features and statistical analysis.

Dermoscopic features, *n* (%)		Chi-square test *p* value	OR (interval)
Pigmented pseudo-network	31 (51.67)	0.00*	14.46 (2.46–31.43)
Red pseudo-network	33 (55)	0.05*	0.36 (0.035–0.86)
Gray-brownish dots	30 (50)	0.00*	13.14 (2.02–21.26)
Inner gray halo	24 (40)	0.09	
Linear wavy vessels	10 (16.67)	0.29	
Rosettes	24 (40)	0.92	
Yellowish dots	24 (40)	0.18	
Widened follicular openings	21 (35)	0.82	
Double white clods	25 (41.67)	0.78	
Scales	31 (51.67)	0.22	

*p-value statistically significant.

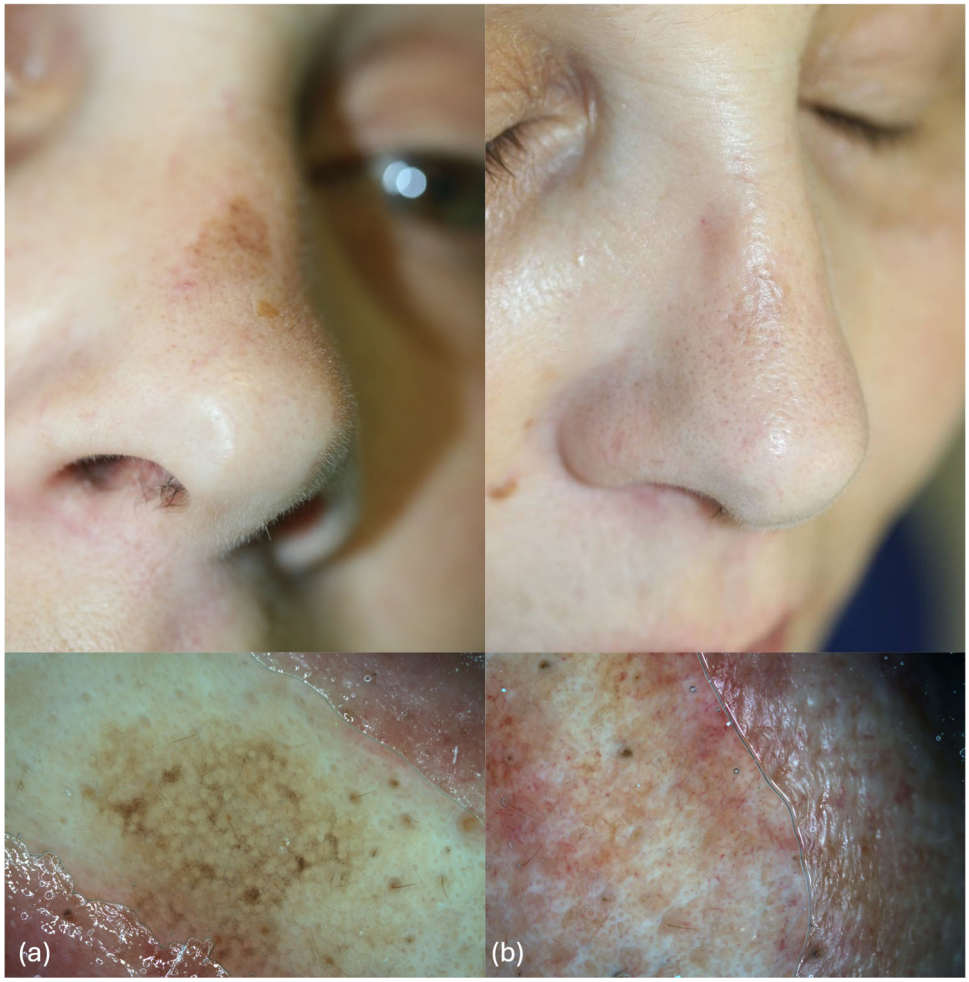

FIGURE 1 | Clinical and dermoscopic images of a PAK of the nose treated with Alexandrite laser (a) pretreatment, characterized by gray-brownish dots, pigmented pseudo-netiwork and widened follicular openings (b) posttreatment with complete resolution.

treatment of PAKs situated on the face. The significant decrease in TLP scores posttreatment suggests a pronounced pigmentary alteration attributable to the laser intervention. Notably, the stratification of PGA scores and subsequent Pearson Chi-Square analysis have elucidated the dermoscopic patterns that could be instrumental in predicting treatment efficacy. The pigmented pseudo-network and gray-brownish dots, with their strong association to positive treatment outcomes, could potentially serve as indicators of the lesion's amenability to laser-induced melanin disruption. Conversely, the presence of a red

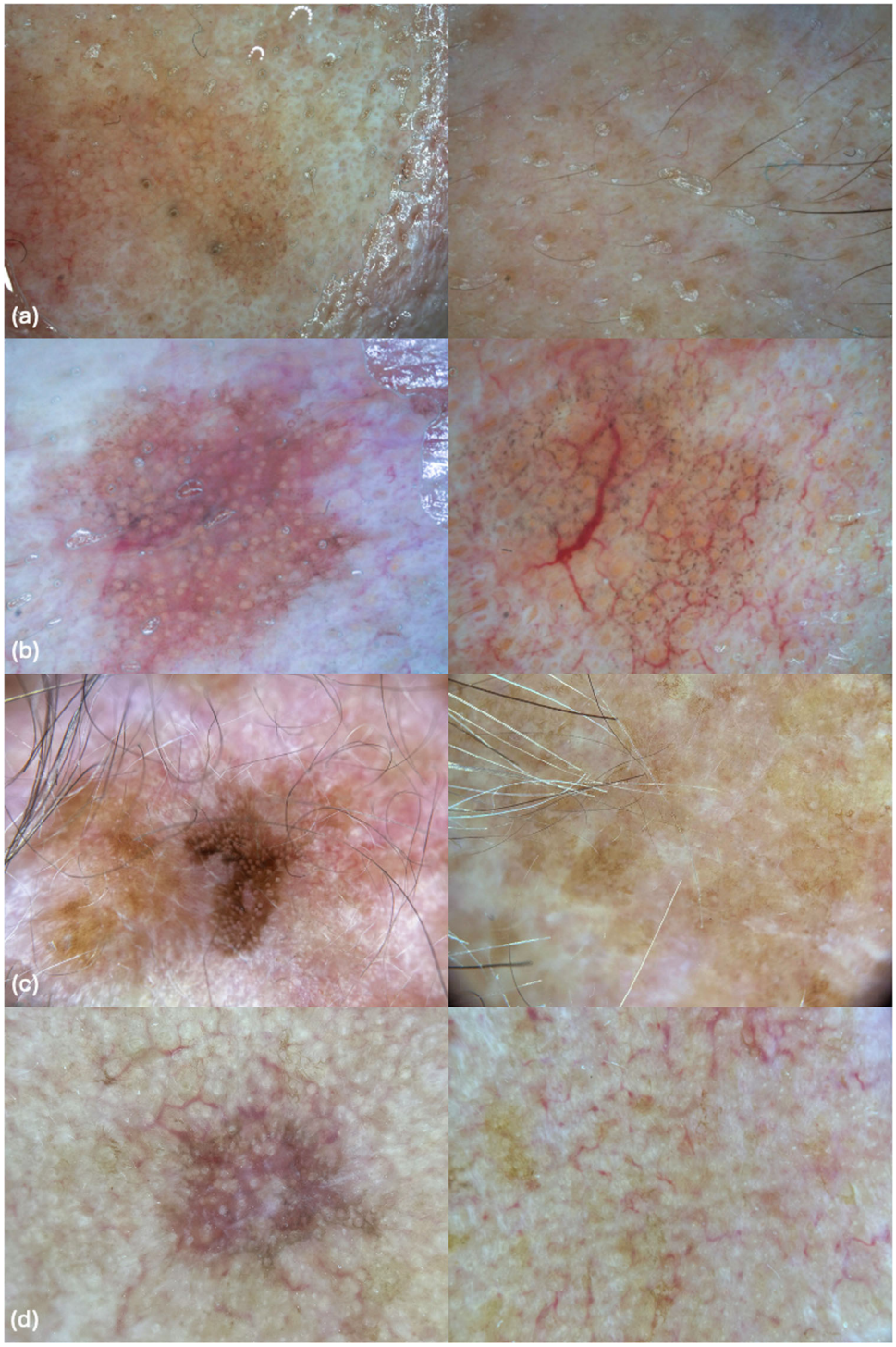

FIGURE 2 | Dermoscopic images of PAKs before treatment (left side) and after 3 months treatment (right side). (a) Pigmented pseudo-network along with widened follicular openings and double white clods. (b) Red pseudo-network with gray brownish dots, yellowish dots, and linear wavy vessels (right side) with partial response after treatment (left side). (c) Rosettes, peripheral scales, and central pigmentation. (d) Fine scale, double white clods, linear wavy vessels, and rosettes.

pseudo-network, which negatively correlates with PGA being 1, might imply a distinct pathophysiological underpinning less responsive to the wavelength and energy density parameters employed in this study.

The Alexandrite laser operates at a wavelength of 755 nm, situating it comfortably in the near-infrared region of the light spectrum. This specific wavelength corresponds to a peak of melanin absorption, rendering the Alexandrite laser particularly effective for targeting pigmented lesions [11]. Histologically, pigmented pseudo-networks in PAKs align with hyperpigmentation in the Malpighian layer, while grayish-brown dots match melanin accumulations, designating them as primary Alexandrite laser targets. However, in the context of PAK, which straddles the continuum between pigmentation and keratosis, the results intimate a disparity in response,

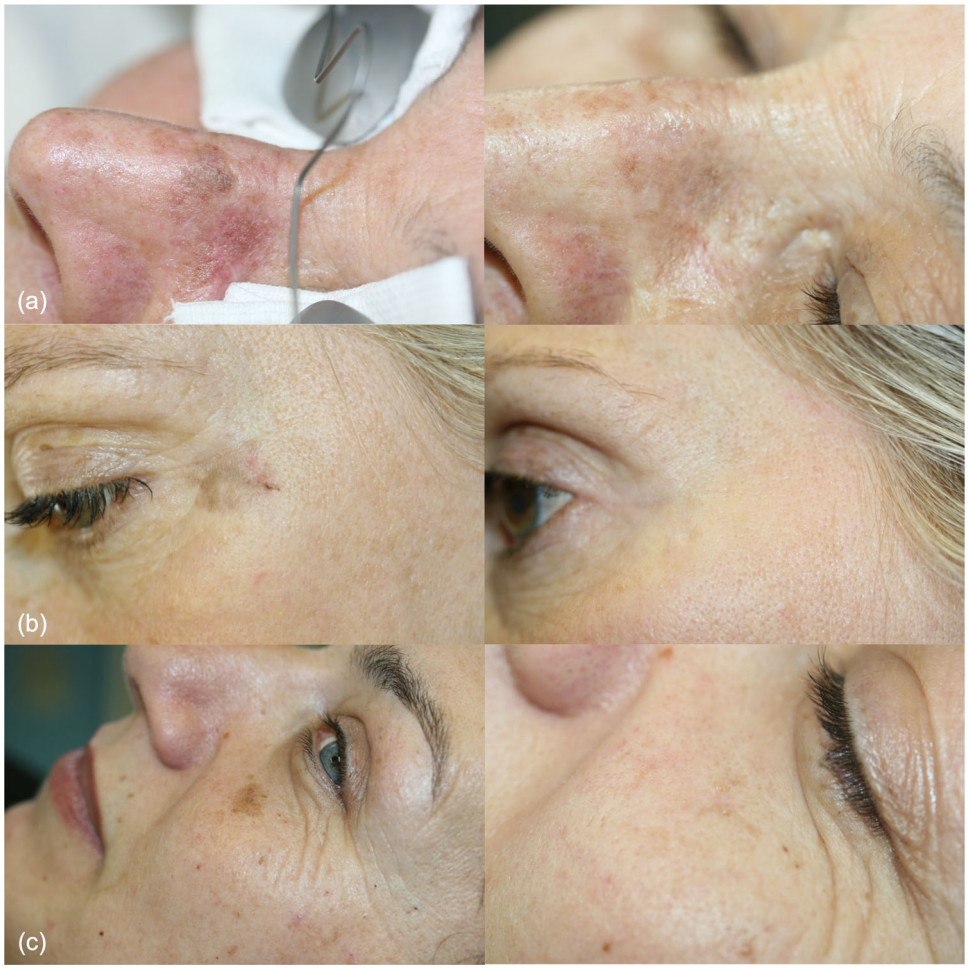

FIGURE 3 | Clinical images of PAKs before treatment (left side) and after 3 months of treatment (right side). (a) PAK on the nose, (b) PAK on the temple, and (c) PAK on the lateral face.

favorable for pigmentation alteration but not significant for the keratotic aspect. Additionally, the red pseudo-network is associated with poorer outcomes. This could be due to a stronger vascular component within the lesion. Alexandrite lasers specifically target melanin, and although they may impact superficial blood vessels, their effectiveness could be diminished in the presence of a significant vascular component. Moreover, a red pseudo-network might indicate an underlying inflammatory process, which can alter the skin's absorption properties and potentially modify the lesion's response to the laser, leading to less than optimal results.

Clinically, the discernment of these dermoscopic patterns pretreatment could guide in tailoring patient-specific management plans. By identifying the patterns associated with a high likelihood of improvement, clinicians can offer a more informed prognosis, thereby optimizing the therapeutic strategy.

Despite the Alexandrite laser's established efficacy in treating various pigmented skin lesions, its role in managing PAKs has not been documented. Mazur and Reich investigated the efficacy of PDT in treating PAKs. The study included 16 patients with 20 PAKs treated with pulsed 630 nm red light and the results showed that 80% of lesions had a complete resolution of clinical features after three PDT sessions. However, the effectiveness of PDT in PAKs where melanin could potentially interfere with the activation of the photosensitizer, has been less clear.

While this pivotal study makes significant strides in the therapeutic management of PAKs, it is not devoid of limitations. Firstly, there is a need to expand the cohort size to strengthen the reliability of the findings. Importantly, our study included only one case of Olsen III thick hyperkeratotic PAK, which may bias the evaluation of keratotic characteristics. However, this is considered in the context of Olsen II PAKs that typically present with moderate hyperkeratosis. It is important to acknowledge that the single Olsen grade III PAK included in the study required cryotherapy after the 3-month follow-up. Due to the limited number of grade III PAKs in this study, no definitive conclusions can be drawn regarding their treatment outcomes. Moreover, the variability inherent in the multifaceted presentation of PAK necessitates a larger data set to capture the full spectrum of dermoscopic patterns and their respective responses to laser therapy. Noninvasive diagnostic tools such as reflectance confocal microscopy (RCM) could provide deeper insights into treatment response beyond what is achievable with dermoscopy alone and should be considered for integration in future studies. Additionally, a comparative study involving other laser types or combined therapeutic modalities could offer

a comparative efficacy landscape, potentially steering toward a multimodal treatment paradigm for PAKs. Although the 532 and 1064 nm wavelength lasers effectively target melanin and oxyhemoglobin or hemoglobin, respectively, and could potentially be useful in treating PAKs, the literature on laser use for this specific condition is limited. Therefore, we opted for the 755 nm Alexandrite laser, which is well-established and widely used for targeting melanin in pigmented lesions. This choice ensures a more reliable and evidence-based approach to treating PAKs.

5 | Conclusion

In conclusion, the Alexandrite laser shows promise as a therapeutic option for targeting the pigmentation component of PAKs. However, it is crucial to emphasize that PAKs, unlike solar lentigines, represent precancerous lesions requiring careful consideration by a certified dermatologist. Our study underscores the importance of recognizing specific dermoscopic patterns associated with treatment response in PAKs. This highlights the critical role of dermatological expertise in guiding personalized treatment approaches. The translation of these findings into practice could signify a significant advancement in the management of PAKs, particularly by emphasizing the necessity of expertise in dermoscopic interpretation to ensure optimal outcomes.

Ethics Statement

The study, approved by the ethics committee (protocol: 4277), upheld ethical and regulatory standards. Participants provided informed consent, with the option to withdraw anytime. The study was conducted in accordance with the principles of the Declaration of Helsinki. The patients in this manuscript had given written informed consent to publication of their case details.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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