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RESEARCH LETTER

WILEY

Evaluation and treatment monitoring of actinic keratosis using line-field confocal optical coherence tomography

Dear Editor,

Line-field optical coherence tomography (LC-OCT) is a non-invasive real-time 3-dimensional imaging modality that enables high-resolution microscopic visualization of the skin. The integration of reflective confocal microscopy with optical coherence tomography in LC-OCT allows for the creation of two-dimensional vertical and horizontal images, and three-dimensional images of lesions. This capability renders it a promising tool in aiding diagnostics and reducing the need for biopsies. Histopathological correlation with microscopic features observed with LC-OCT have been evaluated for many skin lesions including melanocytic proliferations and non-melanoma skin cancers.[1] However, there are limited studies evaluating the utilization of LC-OCT for treatment monitoring purposes.

Actinic keratosis (AK) is a precancerous lesion, characterized by the proliferation of keratinocytes in the epidermis. These lesions present as erythematous papules and scaly macules on chronically sun-exposed skin.[2] AKs have the potential to progress to cutaneous squamous cell carcinomas (SCC); however, predicting progression of AK to SCC solely by clinical evaluation is difficult. Therefore, clinicians generally opt to treat all AKs. Common treatment options for AK include topical pharmaceuticals (including fluorouracil and imiquimod), destructive therapies (cryotherapy, resection, photodynamic therapy), and/or ablation procedures (laser resurfacing).[3]

Because treatment monitoring is limited to the clinical assessment of lesions, premature discontinuation of treatment can occur. This can lead to residual AKs, recurrence, or progression of AK to SCC. LC-OCT AK criteria have been previously characterized by an irregular epidermis, parakeratosis, erosions/ulcerations, dyskeratotic keratinocytes, hyperkeratosis, disrupted dermal-epidermal junction, and dilated vessels.[4,5] Non-invasive microscopic analysis of epidermal and dermal changes of AK lesions undergoing treatment can aid in evaluating treatment response and guide therapeutic decision-making. Therefore, this study aims to characterize histopathological changes of AKs undergoing treatment with cryotherapy and discuss the effectiveness of LC-OCT for treatment monitoring.

This study was conducted at an independent dermatology office between June and October 2022. This study was conducted in accordance with the Declaration of Helsinki and IRB approval (Pro00035376). Verbal and written consent was obtained. Patients were eligible to participate in the study if they were over 18 years of age, were clinically diagnosed with AK, and elected treatment with cryotherapy. AK lesions that were reoccurring or treatment refractory and patients who elected excision or topical treatments were excluded from the study. LC-OCT images of AK lesions were obtained before cryotherapy treatment. At approximately 4-weeks after treatment, AK lesions were clinically evaluated, and LC-OCT images were obtained. If clinically indicated, patients underwent an additional treatment of elected cryotherapy for residual AK. Patients were followed until complete resolution of AK. Using LC-OCT (DeepLive, DAMAE Medical), vertical, horizontal, and 3D images were obtained. Clinical and image evaluation was conducted by a board-certified dermatologist. This study was conducted with the intention to treat analysis and findings from the study were descriptive.

A total of six AK patients with a total of eight lesions were imaged at baseline, however, one patient with one AK lesion was lost to follow-up so a total of seven lesions were included in this imaging study. A total of two males and four females with an average age of 69.5 years were enrolled, and there was an average of 1.33 lesions/person (Table 1). All patients achieved complete response with cryotherapy treatment (1.43 cycles/lesion). The average time untill follow-up post-cryotherapy was 33.8 days.

LC-OCT imaging findings of patients were collected before cryotherapy (Figure 1A,B) and at follow-up post cryotherapy (Figure 1 A,B). All clinically suspicious lesions of AK had LC-OCT findings that were commensurate with histopathological findings, including hyperkeratosis (7/7), marked acanthosis (5/7), keratinocytic atypia (7/7), parakeratosis (4/7), and dilated vasculature ± inflammatory infiltrate (4/7).

At the ~ 4-week follow-up appointment after initial cryotherapy treatment, LC-OCT images showed normalization of the epithelium, including reduced hyperkeratosis, acanthosis, and keratinocytic atypia (7/7) (Figure 1C,D). Increased pigmentation and evidence of inflammatory cells in the epidermis were also observed. All AK lesions had complete response clinically, and no adverse events were reported.

TABLE 1 Enrolled patient characteristics and summary of results.

Patient number	Sex/Age	Number of lesions	Actinic keratosis localization	Number of treatments	Follow-up time (days)	Response at follow-up period
1	M/62	3	L01: Right anterior upper arm L02: Pre-sternal chest L03: Pre-sternal chest	2 (3 cycles of LN) [a] per lesion	36 days	Complete response for all lesions
2	F/82	1	L01: Left cheek	1 (3 cycles of LN) [a]	33 days	Complete response
3	F/65	1	L02: Dorsum of right hand	1 (3 cycles of LN) [a]	16 days	Complete response
4	F/61	1	L01: left forehead	1 (3 cycles of LN) [a]	35 days	Complete response
5	F/75	1	L01: left forehead	1 (3 cycles of LN) [a]	49 days	Complete response
6	M/72	1	L01: Right anterior scalp	1 (3 cycles of LN) [a]	Lost to follow-up	Unknown (lost to follow-up)

Abbreviation: LN, liquid nitrogen.
[a]10 seconds per cycle.

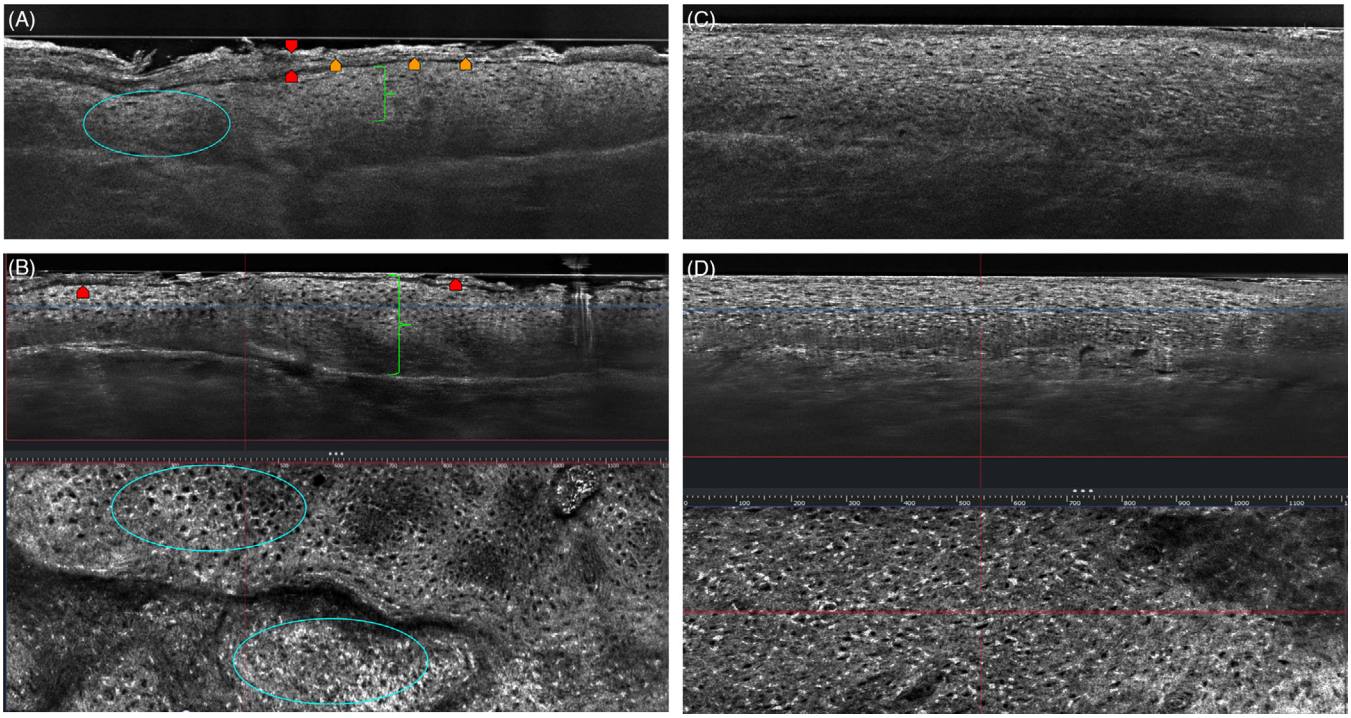

FIGURE 1 (A and B) LC-OCT images of patient three's AK lesion, before cryotherapy, on the dorsum of the right hand. (A) Vertical or OCT view, shows hyperkeratosis (red arrows), parakeratosis (orange arrows), acanthosis (green bracket), and keratinocytic atypia (blue circle). (B) LC-OCT vertical view (top) shows hyperkeratosis (red arrows) and acanthosis (green bracket). LC-OCT en face (bottom) view shows keratinocytic atypia in the epidermis (blue circle) extending into the papillary dermis (blue circle). (C and D) LC-OCT imaging of patient three's AK, after one treatment of cryotherapy (3 cycles), on the right dorsum of the hand. (C) Vertical or OCT view shows a reduction in hyperkeratosis, decreased acanthosis, and minimal keratinocytic atypia. (D) Vertical view (above) and en-face view (bottom) of the epidermis show no atypia extending into the papillary dermis.

Treament monitoring of AK lesions primarily relies on clinical evaluation with dermoscopy. However, in this study, we illustrate the potential of LC-OCT as a non-invasive tool to histopathological assess changes in AK lesions after cryotherapy treatment. The visual changes in histological features observed can aid clinical decision-making by allowing visualization of residual AKs not visible to the naked eye.

Descriptive findings of LC-OCT imaging of AK support the limited previous studies, with evidence of hyperkeratosis, parakeratosis, and atypical nuclei of keratinocytes.[6] We do not see evidence of clear dermal-epidermal borders; however, some images of dermal-epidermal junction were not clearly delineated due to marked acanthosis. Changes in atypia were visible in all pre-treatment lesions assessed. This study is among the first to describe the histopathologic

LC-OCT findings of inflammation and hyperpigmentation of the epidermis post-cryotherapy.

Advantages of LC-OCT as a clinical diagnostic aid and treatment monitoring tool include real-time imaging results, improved diagnostic accuracy, treatment efficacy monitoring, non-invasiveness, and potential reduction in the need for biopsy. Limitations to this study and the use of LC-OCT include a limited number of patients/lesions, limited availability of LC-OCT devices, and physicians limited experience interpreting LC-OCT images. Although this study demonstrates the potential of LC-OCT to assist clinicians in the treatment monitoring of AKs, future studies with larger cohorts are needed to corroborate findings. In summary, LC-OCT is a non-invasive imaging technique that can identify morphological characteristics of AK including keratinocytic atypia, acanthosis, and parakeratosis, and visualize changes in response following cryotherapy including clinical response, inflammation, and hyperpigmentation.

CONFLICT OF INTEREST STATEMENT

Dr. Babar Rao is a speaker for Incyte. All other authors have no disclosures.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

PATIENT CONSENT

Not applicable.

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REFERENCES

1. Verzi AE, Micali G, Lacarrubba F. Line-field confocal optical coherence tomography may enhance monitoring of superficial basal cell carcinoma treated with imiquimod 5% cream: a pilot study. *Cancers (Basel)*. 2021;13(19):4913.
2. Reinehr CPH, Bakos RM. Actinic keratoses: review of clinical, dermoscopic, and therapeutic aspects. *An Bras Dermatol*. 2019;94(6):637-657.
3. Del Regno L, Catapano S, Di Stefani A, Cappilli S, Peris K. A review of existing therapies for actinic keratosis: current status and future directions. *Am J Clin Dermatol*. 2022;23(3):339-352.
4. Verzi AE, Russo A, Castellino N, et al. Line-field confocal optical coherence tomography of eyelid margin growths: a case series. *Skin Res Technol*. 2024;30(1):e13559.
5. Cinotti E, Bertello M, Cartocci A, et al. Comparison of reflectance confocal microscopy and line-field optical coherence tomography for the identification of keratinocyte skin tumours. *Skin Res Technol*. 2023;29(1):e13215.
6. Cinotti E, Tognetti L, Cartocci A, et al. Line-field confocal optical coherence tomography for actinic keratosis and squamous cell carcinoma: a descriptive study. *Clin Exp Dermatol*. 2021;46(8):1530-1541.