Dermatology Practical & Conceptual

Reflectance Confocal Microscopy Follow-up of Multifocal Superficial Basal Cell Carcinomas Treated With Imiquimod 5% Cream

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ABSTRACT

Introduction: Patients with multifocal superficial basal cell carcinomas (sBCC) require a non-invasive treatment and follow-up with a non-invasive technique. Imiquimod 5% cream is a new non-invasive therapy for BCC. Reflectance confocal microscopy (RCM) is a non-invasive, real-time imaging technique.

Objectives: To evaluate and describe the feasibility and efficacy of imiquimod 5% cream for the treatment of multifocal sBCC using RCM.

Methods: The efficacy of imiquimod 5% cream for the treatment of multifocal sBCC was evaluated, as well as the potential of RCM for assessing therapeutic effects. We reported four patients with 34 sBCC lesions were treated with imiquimod 5% cream. RCM was performed in the baseline and at 12 weeks, 24 weeks and 52 weeks after starting treatment.

Results: Of 34 lesions treated with imiquimod 5%, 32 responded to the treatment and showed complete clinical clearing. Two subclinical BCC lesions were identified by RCM. The complete tumor clearance rate was 88.2%, and the efficiency rate was 97.1%. No lesion recurred at 24-month follow-up. RCM identified previously described confocal features of BCC and was more sensitive than clinical examination. Local skin reactions were relieved after expectant treatment.

Conclusions: Imiquimod 5% cream may be useful for the treatment of multifocal sBCC, and its side effects are easy to manage. RCM can be used for non-invasive monitoring of treatment response and improved the tumor clearance rate.

Introduction

Basal cell carcinoma (BCC) is the most common skin cancer worldwide. Although surgical treatment of BCC is the gold standard, patients may be reluctant to accept invasive treatment by reason of multifocal BCC-lesions. In recent years, non-invasive therapies have been widely used for the treatment of superficial (s)BCC [1,2]. Imiquimod is a new local treatment that can remove tumor tissues without injuring the surrounding normal tissues. However, histological evidence of tumor clearance is difficult to obtain. In vivo reflectance confocal microscopy (RCM) is a non-invasive, real-time imaging technique that provides near histologic level resolution cross-sectional images of superficial layers of the skin. RCM can be used to diagnose and monitor treatment effectiveness in BCC [3-5].

Objectives

The aim of this study was to evaluate and describe the feasibility and efficacy of imiquimod 5% cream for the treatment of multifocal sBCC using RCM.

Methods

Four patients (3 females and 1 male) with diagnoses of sBCC, with 2 or more lesions, and aged from 27 to 76 years (mean 56 years) were included in the study.

The patients presented with 34 sBCC appearing as mild reddish-brown patches and pigmented patches (Figure 1A). The patients were overall healthy and had no other symptoms associated with Gorlin Syndrome. All lesions were diagnosed clinically, and BCC features were confirmed under RCM. All the lesions were confirmed as superficial (s)BCC histologically (Figure 1B). Each lesion was treated with 5% imiquimod cream (Aldara®; 3M Pharmaceuticals).

Imiquimod 5% cream was applied once daily for 5 days/week for 12 weeks. Treatment visit was performed once every two weeks. Treatment ended when there was no clinical or RCM evidence. If there is no response or insufficient response, treatment was continued and reevaluated every 2 weeks, until complete clinical response was obtained. The imiquimod cream was applied before going to bed and removed with soap and water approximately 8 hours later. The treatment area was not covered except in cases of bleeding or excessive discharge from the wound. Each treatment field encompassed the lesion and 1.0 cm margins surrounding the visible BCC lesion.

Each lesion was followed up by RCM (Vivascope 1500, Lucid Technologies) at 12 weeks, 24 weeks and 52 weeks after the start of imiquimod treatment. Baseline and follow-up images were collected. The RCM images were evaluated by two experienced physicians. If there was discordance between the two evaluators, a consistent interpretation was obtained from a third reviewed. Therapeutic effects were determined by tumor size combined with RCM imaging features.

Results

A total of 34 BCC lesions were included in the analysis. The tumor size ranged from 0.5 to 3 cm in the maximum diameter (mean, 1.4 cm). Lesions were located in the neck area (N = 3), scalp (N = 2), chest (N = 8), abdomen (N = 5), back (N = 5), lower extremities (N = 6), and upper extremities (N = 5). The durations of the drug application period varied from 8 weeks to 28 weeks, with an average of 18.6 ± 6.9 weeks.

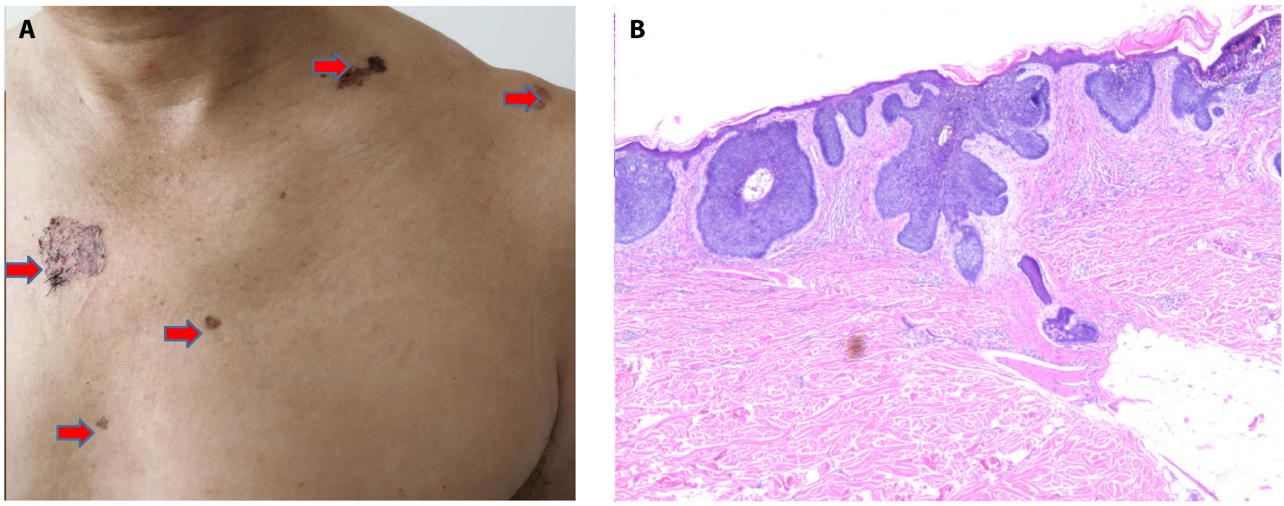

Figure 1. (A) Multifocal BCCs in the chest area before treatment. (B) Histopathology showed the basaloid cords and basaloid island connected to the epidermis (H&E, magnification 40×).

Reflectance Confocal Microscopy Analysis

RCM imaging details are provided in Table 1. RCM criteria previously described were used for the diagnosis of BCC [6-8]. The RCM criteria for the diagnosis of BCC include principal criteria (2 principal criteria present): tumor islands, elongated and polarized nuclei, peripheral palisading; and secondary criterion (3 secondary criterion present): keratinocyte atypia, cords connected to the epidermis, bright particles, peri-tumoral clefting, increased vascularization, and dendritic cells inside tumor islands (Figure 2). At the 12-week, 24-week and 52-week follow-up evaluations, there was no RCM evidence in 22 lesions, 26 lesions, and 30 lesions, respectively (Figure 3). At the 52-week follow-up, residual BCC was detected by RCM in 4 of 34 sites (11.8%), and there was no clinical manifestation in two lesions. The area of three lesions was obviously reduced, but no effect was observed in one lesion. The complete tumor clearance rate was 88.2%, and the efficiency rate was 97.1%. In the residual lesion, treatment with imiquimod 5% cream was discontinued, and surgical treatment was performed. No lesion recurred at 24-month follow-up.

Local Skin Reactions

The patient is still under clinical and RCM monitoring. All lesions had good cosmetic outcomes except hypopigmentation in eight lesions (23.5%). Local skin reactions (LSR)

Table 1. Reflectance confocal microscopy characteristics of basal cell carcinomas before (baseline) treatment with imiquimod and at 12, 24 and 52 weeks after treatment.

Reflectance confocal microscopy	Baseline, % (No.)	12-week follow-up, % (No.)	24-week follow-up, % (No.)	52-week follow-up, % (No.)
Tumor islands	82.4 (28)	23.5 (8)	17.6 (6)	2.9 (1)
Elongated and polarized nuclei	79.4 (27)	23.5 (8)	14.7 (5)	2.9 (1)
Peripheral palisading	52.9 (18)	20.6 (7)	8.8 (3)	0 (0)
Keratinocyte atypia	100 (34)	35.3 (12)	23.5 (8)	11.8 (4)
Peri-tumoral clefting	17.6 (6)	5.9 (2)	0 (0)	0 (0)
Dendritic cells inside tumor islands	97.1 (33)	35.3 (12)	20.6 (7)	8.8 (3)
Cords connected to the epidermis	94.1 (32)	32.4 (11)	17.7 (6)	5.9 (2)
Increased vascularization	82.4 (28)	26.5 (9)	5.9 (2)	0 (0)
Bright particles	70.6 (24)	35.3 (12)	23.5 (8)	5.9 (2)

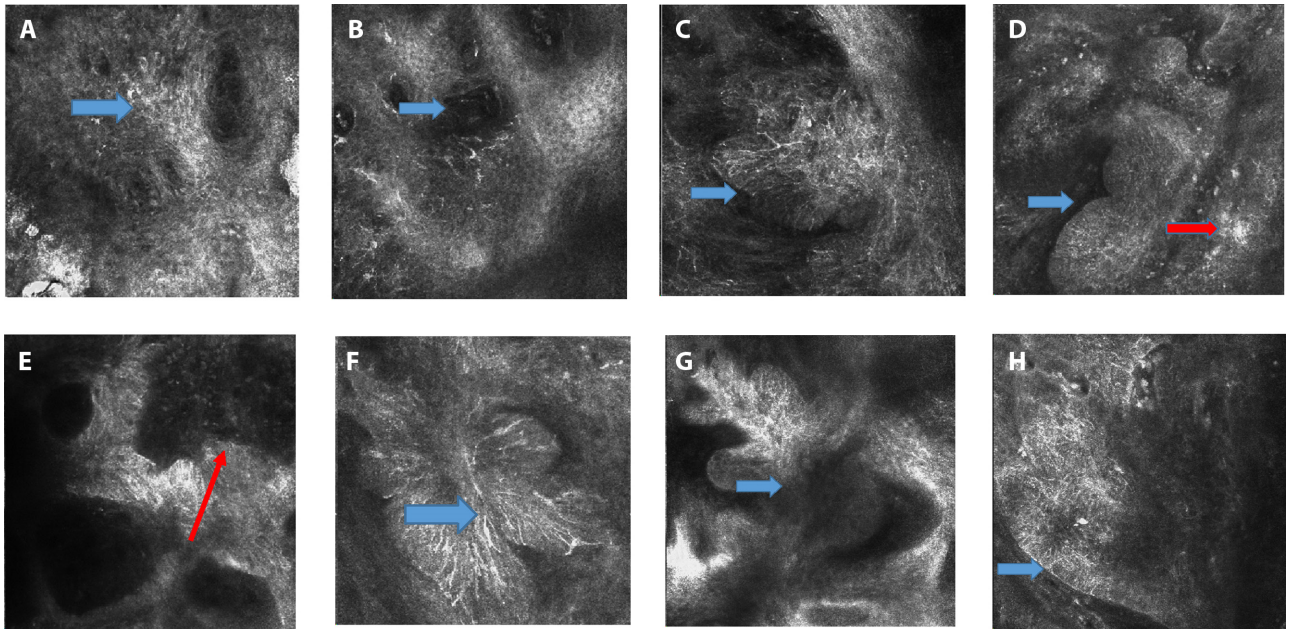

Figure 2. Reflectance confocal microscopy (RCM) image of basal cell carcinoma (BCC). (A) Keratinocyte atypia (blue arrowheads). (B) Increased vascularization (blue arrowheads). (C) Peri-tumoral clefting (blue arrowheads). (D)Tumor islands (blue arrowheads) and bright particles (red arrowheads). (E) Elongated and polarized nuclei (red arrowheads). (F) Dendritic cells inside tumor islands (blue arrowheads). (G) Cords connected to the epidermis (blue arrowheads). (H) Peripheral palisading (blue arrowheads).

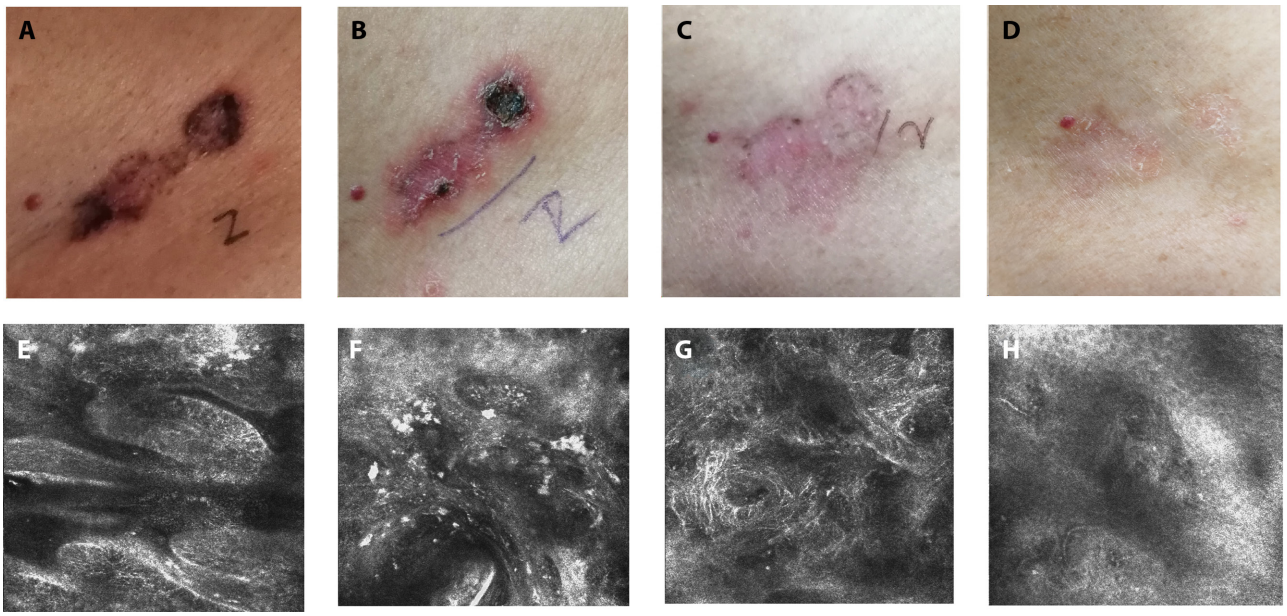

Figure 3. Clinical and confocal images before treatment and during follow-up on the second lesion. (A) reddish-brown and pigmented patches before treatment. (B) At the 12-week follow-up, the lesion presents with erythema and crusting induced by treatment. (C) At the 24-week follow-up, the lesion presents as a small residual tumor on the border. (D) At the 52-week follow-up, complete clearance, with no sign of recurrence. (E)Before treatment, RCM shows tumor islands with peripheral palisading. (F) The12-week RCM follow-up shows increased high-refractive particles inside the tumor. (G) The 24-week RCM follow-up shows irregular tumor islands and increased dendritic cells inside tumor islands. (H) At the 52-week RCM follow-up, RCM showed regularly spaced cells composing a regular honeycomb pattern.

including erythema, edema, dryness, crusting, and erosion were present in nine lesions (26.5%). They were relieved after expectant treatment with moisturizer. Treatment was interrupted for 1 week or 2 weeks for recovery in serious cases.

Conclusions

RCM provides a useful, noninvasive tool for the diagnosis of BCC. The presence of two or more RCM criteria is 100% sensitive for the diagnosis of BCC, and with 4 or more RCM criteria present the specificity was 95.7% [9]. In this study, 5 criteria or more present could be diagnosed as BCC, by which diagnostic coincidence rate was 100% comparing with pathological outcome. Our study confirmed that imiquimod 5% cream is highly effective for the treatment of multifocal sBCC. Notably, RCM features were not present after treatment with imiquimod 5% cream in 30 of 34 lesions. Before treatment, the RCM criteria for the diagnosis of BCC were detected as described in Table 1. At 12 weeks after treatment, these RCM parameters were reduced by approximately 64.7 % of the initial values. At the 52-week follow-up, clinical evaluation showed that 94.1% (32 of 34 lesions) achieved complete clearance, whereas RCM showed that 88.2% (30 of 34 lesions) of lesions had lost BCC features. Residual BCC was identified upon RCM examination in two lesions that did not present clinical manifestation. RCM improved the tumor clearance rate during follow-up. The presence of increased dendritic structures and bright particles in the epidermis (Figure 3F) after 12 weeks of imiquimod application indicate that imiquimod 5% has initiated an immune response and is a reliable biomarker for predicting treatment response.

Surgery is the gold standard for treatment of BCC. However, in some cases such as elderly patients who are too frail to withstand excisional surgery, or patients with multifocal BCC-lesions, non-invasive therapies are needed. Studies evaluating BCCs of the trunk or extremities suggest that imiquimod is as effective as surgical treatment regarding clinical cure rates and it achieves good to excellent cosmetic outcomes [10-11]. In this study, we also confirmed that imiquimod 5% is effective for the treatment of multiple sBCCs. The complete tumor clearance rate was 88.2%, higher than those of documents reported [1,2,12], which may be credited to RCM surveillance. The therapeutic regimens were different in the previous studies [12-15]. Consistent with previous studies [16-17], the imiquimod dosing regimen of 5 times per week for 12 weeks is an effective treatment for sBCC.

In this study, the most common side effects were erythema and hypopigmentation, and recovery was gradual. The erythema may be a sign of an immune response in the epidermis. LSRs mainly occurred during the first 3 months of therapy.

The present study had some limitations. This was an open study with no control group and it included only four patients. Larger clinical studies with longer follow-up periods are necessary. In conclusion, we confirmed the efficacy

of imiquimod 5% for the treatment of multiple sBCC and showed that RCM is a valuable tool for non-invasive monitoring of treatment response.

References

1. Williams HC, Bath-Hextall F, Ozolins M, et al. Surgery Versus Imiquimod for Nodular and Superficial Basal Cell Carcinoma (SINS) Study Group. Surgery Versus 5% Imiquimod for Nodular and Superficial Basal Cell Carcinoma: 5-Year Results of the SINS Randomized Controlled Trial. *J Invest Dermatol.* 2017;137(3):614-619. DOI: 10.1016/j.jid.2016.10.019. PMID: 27932240.
2. Jansen MHE, Mosterd K, Arits AHMM, et al. Five-Year Results of a Randomized Controlled Trial Comparing Effectiveness of Photodynamic Therapy, Topical Imiquimod, and Topical 5-Fluorouracil in Patients with Superficial Basal Cell Carcinoma. *J Invest Dermatol.* 2018;138(3):527-533. DOI: 10.1016/j.jid.2017.09.033. PMID: 29045820.
3. Kadouch DJ, Schram ME, Leeflang MM, et al. In vivo confocal microscopy of basal cell carcinoma: a systematic review of diagnostic accuracy. *J Eur Acad Dermatol Venereol.* 2015;29(10):1890-1897. DOI: 10.1111/jdv.13224. PMID: 26290493.
4. Torres A, Niemeyer A, Berkes B, et al. 5% imiquimod cream and reflectance-mode confocal microscopy as adjunct modalities to Mohs micrographic surgery for treatment of basal cell carcinoma. *Dermatol Surg.* 2004;30(12 Pt 1):1462-1469. DOI: 10.1111/j.1524-4725.2004.30504.x. PMID: 15606733.
5. Pasquali P, Segurado-Miravalles G, Freites-Martínez A, et al. Cryosurgical management of basal cell carcinoma: in vivo follow-up using reflectance confocal microscopy. *Int J Dermatol.* 2019;58(2):e30-e32. DOI: 10.1111/ijd.14301. PMID: 30456878.
6. Castro RP, Stephens A, Fraga-Braghiroli NA, et al. Accuracy of in vivo confocal microscopy for diagnosis of basal cell carcinoma: a comparative study between handheld and wide-probe confocal imaging. *J Eur Acad Dermatol Venereol.* 2015;29(6):1164-1169. DOI: 10.1111/jdv.12780. PMID: 25338750.
7. Lupu M, Popa IM, Voiculescu VM, et al. A Retrospective Study of the Diagnostic Accuracy of In Vivo Reflectance Confocal Microscopy for Basal Cell Carcinoma Diagnosis and Subtyping. *J Clin Med.* 2019;8(4):449. DOI: 10.3390/jcm8040449. PMID: 30987174. PMCID: PMC6518285.
8. Peccerillo F, Mandel VD, Di Tullio F, et al. Lesions Mimicking Melanoma at Dermoscopy Confirmed Basal Cell Carcinoma: Evaluation with Reflectance Confocal Microscopy. *Dermatology.* 2019;235(1):35-44. DOI: 10.1159/000493727. PMID: 30404078.
9. Nori S, Rius-Díaz F, Cuevas J, et al. Sensitivity and specificity of reflectance-mode confocal microscopy for in vivo diagnosis of basal cell carcinoma: a multicenter study. *J Am Acad Dermatol.* 2004;51(6):923-930. DOI: 10.1016/j.jaad.2004.06.028. PMID: 15583584.
10. Schiessl C, Wolber C, Tauber M, et al. Treatment of all basal cell carcinoma variants including large and high-risk lesions with 5% imiquimod cream: histological and clinical changes, outcome, and follow-up. *J Drugs Dermatol.* 2007;6(5):507-513. PMID: 17679185.
11. Love WE, Bernhard JD, Bordeaux JS. Topical imiquimod or fluorouracil therapy for basal and squamous cell carcinoma: a systematic review. *Arch Dermatol.* 2009;145(12):1431-1438. DOI: 10.1001/archdermatol.2009.291. PMID: 20026854.
12. Schulze HJ, Cribier B, Requena L, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from a randomized vehicle-controlled phase III study in Europe. *Br J Dermatol.* 2005;152(5):939-947. DOI: 10.1111/j.1365-2133.2005.06486.x. PMID: 15888150.
13. Shumack S, Robinson J, Kossard S, et al. Efficacy of topical 5% imiquimod cream for the treatment of nodular basal cell carcinoma: comparison of dosing regimens. *Arch Dermatol.* 2002;138(9):1165-1171. DOI: 10.1001/archderm.138.9.1165. PMID: 12224977.
14. Garcia-Martin E, Gil-Arribas LM, Idoipe M, et al. Comparison of imiquimod 5% cream versus radiotherapy as treatment for eyelid basal cell carcinoma. *Br J Ophthalmol.* 2011;95(10):1393-1396. DOI: 10.1136/bjo.2010.193078. PMID: 21242584.
15. Geisse J, Caro I, Lindholm J, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. *J Am Acad Dermatol.* 2004;50(5):722-733. DOI: 10.1016/j.jaad.2003.11.066. PMID: 15097956.
16. Bostanci S, Kocyigit P, Vural S, et al. Long-Term Follow-Up Results of Topical Imiquimod Treatment in Basal Cell Carcinoma. *Dermatol Surg.* 2018;44(1):36-41. DOI: 10.1097/DSS.0000000000001266. PMID: 29016542.
17. Geisse JK, Rich P, Pandya A, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: a double-blind, randomized, vehicle-controlled study. *J Am Acad Dermatol.* 2002;47(3):390-398. DOI: 10.1067/mjd.2002.126215. PMID: 12196749.