



Reflectance confocal microscopy for differentiating clear cell acanthoma from squamous cell carcinoma *in situ*

Berrak hücreli akantom ile skuamöz hücreli karsinoma in situ ayırıcı tanısında reflektans konfokal mikroskopi

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Abstract

Background and Design: There are few reports on the *in vivo* reflectance confocal microscopy (RCM) features of clear cell acanthoma (CCA). This study aimed to evaluate the diagnostic ability of RCM in CCAs that are difficult to diagnose clinically and to compare the RCM findings with those observed in squamous cell carcinoma *in situ* (SCCIS) lesions, which exhibit similar clinical morphology.

Materials and Methods: We searched our database and identified three cases of CCA with atypical features and three cases of SCCIS with common morphological features. We described the clinical, dermoscopic, RCM, and histopathological characteristics of these cases.

Results: Both lesion groups showed prominent epidermal hyperplasia on RCM; however, atypia in epidermal cells in CCAs was not as pronounced as that in SCCISs. The general architecture was preserved in the CCAs. In SCCISs, epidermal basal cells were increased in size, and prominent pleomorphism and atypia were observed in the full-thickness epidermis, whereas basal cells in CCAs were normal in pattern and appearance.

Conclusion: We suggest that differentiating CCA from SCCIS on RCM is possible, even in atypical cases, by careful evaluation of the general architecture of the tumor and determination of the degree of epidermal disarray, nuclear features of the epidermal cells, presence of uniformity or pleomorphism of the epidermal cells, and features of the basal cells. A comparison of normal skin and tumor areas may also help in better evaluation.

Keywords: Clear cell acanthoma, dermatoscopy, confocal microscopy, Bowen disease

Öz

Amaç: Berrak hücreli akantomun (BHA) *in vivo* reflektans konfokal mikroskopi (RKM) özelliklerine ilişkin sınırlı sayıda rapor bulunmaktadır.

Bu çalışmada, klinik olarak tanı koymanın zor olduğu BHA'ların RKM tanı yeteneğini değerlendirmeyi ve klinik morfoloji açısından benzer olan *in situ* skuamöz hücreli karsinom (SHKIS) lezyonlarında görülen RKM bulgularıyla karşılaştırmayı amaçladık.

Gereç ve Yöntem: Veritabanımızda arama yaparak atipik özelliklere sahip 3 BHA vakası ve bu BHA'larla ortak morfolojik özellikler taşıyan 3 SHKIS olgusu bulduk. Olguların klinik, dermoskopik, RKM ve histopatolojik özelliklerini tanımladık.

Bulgular: Her iki lezyon grubunda da RKM'de belirgin epidermal hiperplazi gözlemlendi, ancak BHA'lardaki epidermal hücrelerdeki atipi SHKIS'lerde görüldüğü kadar belirgin değildi. BHA'larda genel mimari korunmuştu. SHKIS'lerde epidermal bazal hücreler boyut olarak artmış, belirgin pleomorfizm ve atipi tam kat epidermiste görülmüştü, buna karşın BHA'lardaki bazal hücreler normal bir patern ve görünümdeydi.

Sonuç: Atipik olgularda bile, tümörün genel mimarisinin dikkatli bir şekilde değerlendirilmesi, epidermal düzensizliğin derecesinin, epidermal hücrelerin çekirdek özelliklerinin, üniformluk veya pleomorfizm varlığının ve bazal hücrelerin özelliklerinin belirlenmesi yoluyla BHA ile SHKIS'i RKM'de ayırt etmenin mümkün olduğunu öne sürmekteyiz. Normal deri ile tümöral alanların karşılaştırılması da daha iyi bir değerlendirme yapmaya yardımcı olabilmektedir.

Anahtar Kelimeler: Berrak hücreli akantom, dermatoskopi, konfokal mikroskopi, Bowen hastalığı

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Introduction

Clear cell acanthoma (CCA) is a rare benign epidermal tumor composed of pale, glycogen-rich keratinocytes that are usually normal or large in size. It is usually seen as a slowly growing, sharply demarcated, pink-to-brown, scaly, dome-shaped or plaque-like lesion, most commonly located on the legs¹. Although CCA typically appears as a pink to brown plaque or dome-shaped lesion, rare morphological variants have been reported, including polypoid/pedunculated, cerebriform, cystic, eruptive, and giant types. Color variants include pigmented, purple, gray-white, and hypopigmented forms. Clinical differential diagnoses of CCA include actinic keratosis, warts, dermatofibroma, eccrine poroma, pyogenic granuloma, clear cell hidradenoma, basal cell or squamous cell carcinoma, and metastatic cancer^{2,3}.

Histopathologic features of CCA include sharply demarcated compact acanthosis, papillomatosis of varying degrees, enlarged keratinocytes with pale glycogen-containing cytoplasm, focal parakeratosis with reduced or absent granular layer, edematous epidermis, isolated polymorphonuclear leukocyte infiltration in the epidermis, microabscesses in stratum corneum, and dilated vessels and a mixed cellular infiltrate in the dermal papilla².

The dermoscopic features of CCAs have been studied in detail. On dermoscopy, most cases typically demonstrate pinpoint dotted vessels or glomerular vessels distributed in linear, serpiginous, or reticular (string of pearls) formations and variable presence of collarettes of translucent scales, glomeruloid structures, hemorrhagic areas, orange crusts, and crystalline structures. The typical vascular structures may cover the entire lesion or be located in a part of the lesion⁴. The typical vascular structure defined in CCA is not considered pathognomonic because this "string of pearls" has also been reported in non-CCA cases such as lichen planus-like keratosis and seborrheic keratosis⁵. Atypical dermoscopic features have also been reported in a few cases, such as irregularly distributed hairpin, coiled, or dotted vessels. When these atypical features are present on dermoscopy, differential diagnoses include keratoacanthoma, seborrheic keratosis, squamous cell carcinoma, and even amelanotic melanoma⁶. Dermoscopy plays a central role in differentiating CCA from other lesions; however, squamous cell carcinoma *in situ* (SCCIS), which frequently exhibits glomeruloid or dotted vessels, can closely mimic the atypical vascular patterns of CCA. This overlap can pose a diagnostic challenge, which demonstrates the importance of adjunctive tools such as reflectance confocal microscopy (RCM). There is also a case of pigmented CCA demonstrating homogeneous brown pigmentation with a peripheral dark red area and a case of hemosiderotic CCA demonstrating diffuse black/gray pigmentation accompanied by dotted-globular dark red-black structures distributed in a regular reticular arrangement^{7,8}. A definitive diagnosis cannot always be made based on dermoscopy alone, since the typical features defined in CCA may also be seen in non-CCA lesions and may not be observed in every case of CCA. Therefore, histopathology continues to be the most reliable method for diagnosing CCA.

RCM is a non-invasive imaging technique that visualizes skin cells *in vivo* with near-histologic resolution⁹. Three previous reports have defined the RCM findings of clinically and dermoscopically typical CCA cases in the literature. These findings are highly refractile collarette structures,

parakeratosis, psoriasiform hyperplasia, large keratinocytes, epidermal disarray (loss of normal epidermal honeycomb pattern), dilated vessels, psoriasiform epidermal hyperplasia, and inflammatory cells in the epidermis¹⁰⁻¹².

However, the overlapping dermoscopic and clinical features of atypical CCA and SCCIS can lead to diagnostic dilemmas, potentially resulting in unnecessary surgical intervention. In cases where CCA presents with atypical dermoscopic features mimicking SCCIS, an accurate diagnosis may be challenging. We hypothesized that *in vivo* RCM could aid in differentiating these two entities by highlighting specific architectural and cytological features, thereby guiding clinical decision-making in ambiguous cases.

Materials and Methods

We searched our database and found three cases of CCA with atypical features. We then searched for three cases of SCCIS that shared common morphological features with these CCAs. We describe the clinical, dermoscopic (DermLite Foto System, 3Gen, San Juan Capistrano, CA, USA), RCM (Vivascope 1500 Multilaser and 3000 Handheld, Lucid, Rochester, NY, USA, Mavig, Munich, Germany), and histopathological characteristics of the cases.

Statistical Analysis

Because this study was designed as a descriptive case series including a limited number of patients (n=6), no formal statistical analysis was performed. The data were evaluated descriptively and presented in tabular and pictorial form.

Ethical Statement

The study protocol was reviewed and approved by the Ethics Committee of Ege University Faculty of Medicine (decision no: 23-8T/51, date: 24.08.2023). The research was conducted in accordance with the principles of the Declaration of Helsinki.

Results

Table 1 and Figure 1 present the clinical and dermoscopic characteristics of the cases, respectively. Both lesion groups showed prominent epidermal hyperplasia on RCM. However, cytological atypia was less pronounced in CCAs than in SCCISs (Figure 2). The general architecture was preserved in the CCAs. Epidermal basal cells were increased in size, and prominent pleomorphism and atypia were observed in the full-thickness epidermis in SCCISs, whereas basal cells in CCAs were normal in pattern and appearance. Figure 3 presents the RCM features of the pigmented variants of CCA and SCCIS (cases 2 and 5). Histopathological sections of the cases are shown in Figure 4.

Discussion

In this study, we highlighted the utility of RCM in distinguishing atypical CCA from SCCIS, particularly in cases where clinical and dermoscopic features overlap. Atypical presentations of CCA can closely resemble those of SCCIS, making histopathological confirmation essential in numerous instances. Based on our observations, RCM may serve as a valuable non-invasive tool to aid in the differentiation of these two entities before surgical intervention.

Table 1. Clinical, dermoscopic and *in vivo* reflectance confocal microscopy features of the cases

Cases age/sex	Clinical examination	Dermoscopic findings	<i>In vivo</i> reflectance confocal microscopy findings
Case 1-CCA 62/F Figure 1a	Right lower leg skin-colored plaque 8x7 mm	White lines arranged linearly from the center to the periphery on a light brown background, focally located grouped vessels Figure 1g	Large bright keratinocytes, preserved honeycomb pattern with mild disarray, dilated dermal vessels Figure 2a
Case 2-CCA 38/F Figure 1b	Left waist brown, plaque 7x5 mm	Thick brown curved lines forming a cribriform pattern, occasionally located near linear brown globular structures Figure 1h	Mild epidermal disarray, bright keratinocytes, dilated vessels, preserved DEJ, and comparison with adjacent normal skin. Figure 2c Figures 3a, 3b
Case 3-CCA 52/F Figure 1c	Right abdomen pink, keratotic plaque 15x10 mm	Multiple yellow homogenous polygonal structures, hairpin and coiled vessels irregularly distributed throughout the lesion on a pink background, linearly arranged vessels at the periphery, and focal hemorrhages. Figure 1i	Psoriasiform thickening, distorted honeycomb pattern, bright enlarged keratinocytes, and dilated dermal papillae. Figure 2b
Case 4-SCCIS 68/F Figure 1d	Left upper arm Pink, scaly plaque 15x10 mm	Irregularly distributed light brown structureless areas, focal grouped dotted vessels and focal linear irregular vessels, a few brown clods, and radial brown lines at the periphery Figure 1j	Full-thickness disarray, atypical honeycomb pattern, pleomorphic nucleated cells, and S-shaped vessels. Figure 2d
Case 5-SCCIS 67/M Figure 1e	Pubic region brown, plaque 10x7 mm	Pigment network diversity (brown, black, gray), scar-like depigmentation, gray areas, dotted vessels on an erythematous base, and a few linear irregular vessels Figure 1k	Atypical and targetoid cells, disorganized epidermis, dendritic cells, and bright-edged dermal papillae. Figure 2e Figure 3c, 3d
Case 6-SCCIS 71/M Figure 1f	Left chest pink, keratotic plaque 7x5 mm	Central yellow crust on a pinkish background, hairpin and coiled vessels Figure 1l	Epidermal disarray, nuclear atypia, targetoid cells, disrupted DEJ, bright pleomorphic keratinocytes. Figure 2f

CCA: Clear cell acanthoma, SCCIS: Squamous cell carcinoma *in situ*, F: Female, M: Male, DEJ: Dermal-Epidermal junction

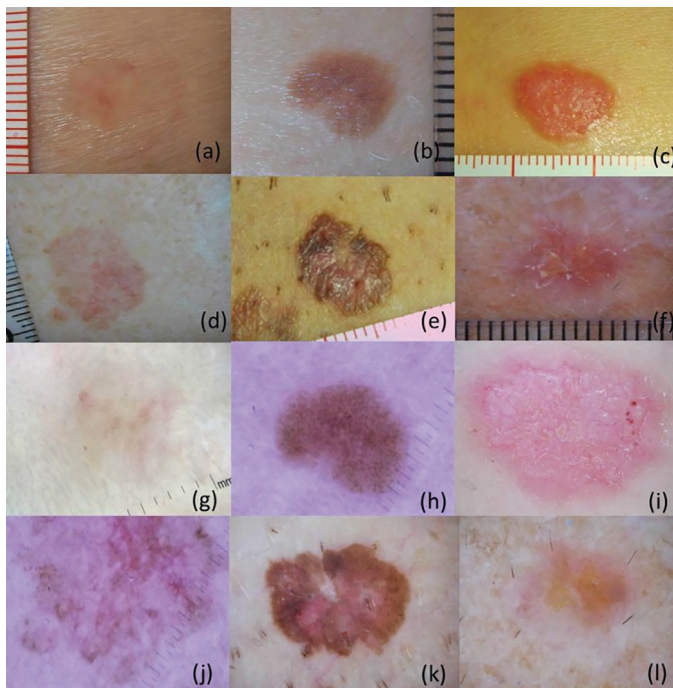


Figure 1. Clinical images of CCA (a-c) and SCCIS (d-f). Dermoscopic images of CCA (g-i) and SCCIS (j-l)

CCA: Clear cell acanthoma, SCCIS: Squamous cell carcinoma *in situ*

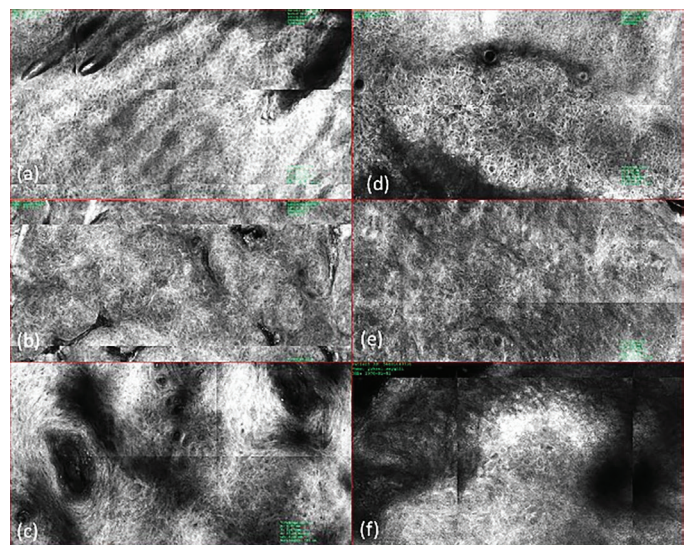


Figure 2. RCM images. Epidermal features in CCA (a-c) and SCCIS (d-f)
RCM: Reflectance confocal microscopy, CCA: Clear cell acanthoma, SCCIS: Squamous cell carcinoma *in situ*

While histopathology continues to be the primary diagnostic method, RCM reveals several key features that highlight the fundamental architectural and cytological distinctions between CCA and SCCIS. In CCA, RCM typically shows large keratinocytes, preserved basal layer structures, and mild-to-moderate epidermal disarray without significant pleomorphism. On the other hand, SCCIS exhibits full-thickness disarray, atypical honeycomb patterns, pleomorphic basal keratinocytes, and architectural disruption, all of which are also visible on RCM. These findings are consistent with previously published RCM features: Ardigò et al.¹⁰ described highly refractile collarette structures, parakeratosis, psoriasiform hyperplasia, large keratinocytes, and focal epidermal disarray in CCA, while Ulrich et al.¹³ reported atypical honeycomb patterns, targetoid cells, and superficial epidermal disruption as characteristics of SCCIS. Our observations also support that, despite

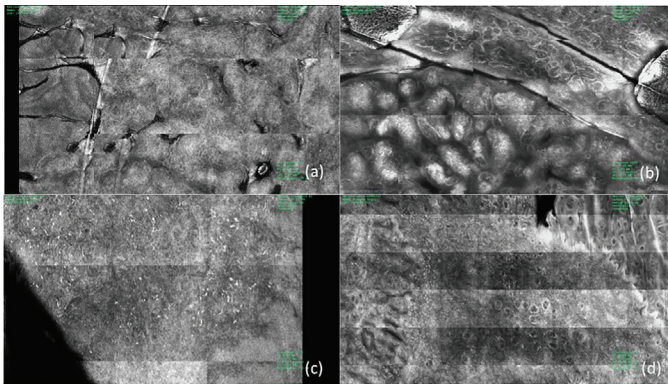


Figure 3. RCM features of the pigmented variants of CCA (case 2) (a-b) and SCCIS (case 5) (c-d). Tumoral and normal skin features can be seen in the same image, and comparison is possible
RCM: Reflectance confocal microscopy, CCA: Clear cell acanthoma, SCCIS: Squamous cell carcinoma in situ

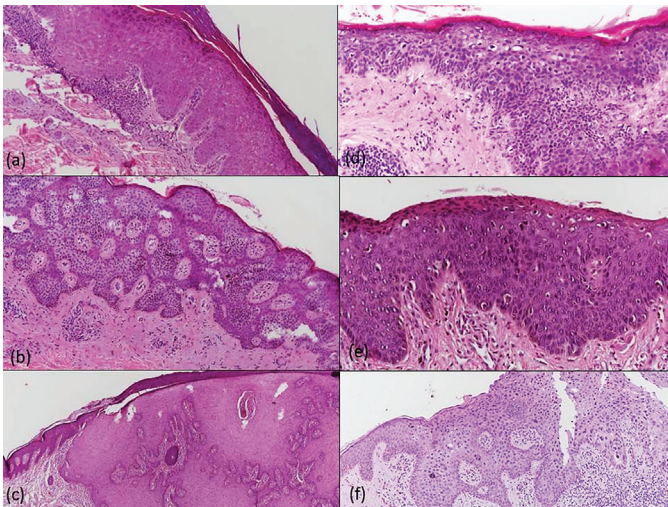


Figure 4. Histopathological sections of the cases are presented in the same order as in Figures 1 and 2. (a-c) CCA and (d-f) SCCIS cases. (a-c) Large eosinophilic nonpleomorphic spinous layer cells in the clear cell acanthomas (H&Ex100, Cases 1-2 and 3, respectively); (d-f) Epidermal full-thickness atypia and pleomorphic cells in the SCCIS cases (H&E x200, x200, x100; Cases 4-5 and 6, respectively)
CCA: Clear cell acanthoma, SCCIS: Squamous cell carcinoma in situ

some degree of epidermal disarray in CCA, the overall architectural integrity is better preserved than in SCCIS, a point not emphasized in the previous literature.

Additional RCM findings reported in SCCIS include intraepithelial atypical dendritic cells and bright-edged dermal papillae due to pigmented keratinocytes at the dermoepidermal junction, particularly in pigmented Bowen's disease^{14,15}. These features may serve as ancillary clues in difficult-to-diagnose cases.

Study Limitations

This study had several limitations. First, the sample size was small (n=6), which limits the generalizability of the findings. Second, the absence of statistical analysis and blinded evaluation of RCM images may introduce interpretation bias. These limitations are inherent to the descriptive case series design, especially when dealing with rare entities such as atypical CCA. Nevertheless, we believe that the consistent RCM features observed in these cases provide valuable preliminary insights and illustrate the possible role of RCM in differentiating CCA from SCCIS. Future studies with larger cohorts and controlled settings are required to validate our findings.

Conclusion

In conclusion, features such as the degree and distribution of epidermal disarray, presence or absence of pleomorphism, nuclear morphology, basal cell features at the dermoepidermal junction, and overall architectural preservation are key parameters visible on RCM that may support the differentiation of CCA from SCCIS. Additionally, comparing adjacent normal skin with the lesional area during RCM examination can enhance diagnostic accuracy. Further studies with an expanded case series should confirm the reproducibility of our findings.

Ethics

Ethics Committee Approval: This study was approved by the ethics board of the Ege University, Faculty of Medicine (approval number: 23-8T/51, date: 24.08.2023).

Informed Consent: The patients in this manuscript have given written informed consent to the publication of their case details.

Footnotes

Authorship Contributions

Concept: N.D., B.Y., I.K., Design: N.D., B.Y., I.K., Data Collection or Processing: G.O., Analysis or Interpretation: N.D., B.Y., I.K., Literature Search: N.D., B.Y., I.K., Literature Search: G.O., Writing: G.O.

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