INTRODUCTION

Seborrheic Keratosis (SebK) is one of the most commonly observed benign skin tumours in everyday clinical practice. In their typical form, SebK appear as variably pigmented patches and nodules, often affecting elderly people.1-5 Despite an often unsightly appearance which can be frightening for the patient, a dermoscopic examination usually enables a clear-cut diagnosis of the disease with typical features, such as multiple milia-like cysts, comedo-like openings, fissures, finger-print structures and sharply demarcated borders.1-8 However, clinically and dermoscopically unusual cases of SebK have been reported with increasing frequency since the publication of these original features.6-8 This “grey zone” includes lesions presenting without the typical features of the disease, possibly mimicking malignancies, especially melanoma.

Abstract

Background: Seborrheic keratoses (SebK) with atypical dermoscopy presentation are increasingly reported. These lesions do not exhibit typical dermoscopy features of SebK and sometimes mimic melanoma, thus complicating the differential diagnosis. Reflectance confocal microscopy (RCM) is a non-invasive tool, which allows an in vivo imaging of the skin. The study objectives were to evaluate the agreement between RCM classification and histological diagnoses, and the reliability of well-known RCM criteria for SebK in the identification of SebK with atypical dermoscopy presentation.

Materials and Methods: We retrospectively analysed at RCM excised lesions presenting in dermoscopy ≥1 score at revisited 7-point checklist. The study population consisted of cases showing no melanocytic RCM findings. Lesions were investigated for distinct non-melanocytic RCM features, blinded from histopathology diagnoses. Histopathology matching was then performed before statistical analysis.

Results: The study consisted of 117 cases, classified at RCM as SebK (71 cases), dermatofibroma (18 cases), basal cell carcinoma (13 cases), squamous cell carcinoma (2 cases), and “non-specific” (13 cases). Overall K strength of agreement at histopathology matching proved 0.76. Of the 71 cases classified at RCM with SebK, agreement was achieved in 97%.

Conclusion: Reflectance confocal microscopy classification proved high agreement with histopathology for SebK with atypical dermoscopy presentations, allowing an early differential diagnosis. RCM features in this group of lesions were similar to those described for typical cases of SebK, and may assist clinician therapy decision making, whilst avoiding unnecessary excisions.

KEYWORDS
dermoscopy, melanoma, non-invasive diagnosis, reflectance confocal microscopy, seborrheic keratosis
management of these atypical SebK remains undefined, often requiring a final excision of the lesion to reach a correct diagnosis.\textsuperscript{7} To complicate the picture, melanomas mimicking SebK have also been reported.\textsuperscript{7}

Reflectance confocal microscopy (RCM) is a non-invasive technology, which allows in vivo imaging of the skin at a nearly histological resolution. RCM criteria for classic SebK were defined in 2012.\textsuperscript{10}

The aim of our study was to evaluate the reliability of the well-known RCM criteria for SebK identification in a group of lesions with atypical dermoscopy presentation, mimicking melanoma.

2 | MATERIALS AND METHODS

2.1 | Study design and population

We retrospectively analysed all lesions with an initial clinical diagnosis of atypical melanocytic proliferation, excised at the Department of Dermatology of Modena, Italy, between 1st January 2011 and 31st December 2015. Lesions with a complete set of investigations (clinical, dermoscopic imaging RCM imaging, and a histopathological diagnosis) were retrospectively retrieved from a dedicated database. Lesions with at least one of the features of atypical melanocytic lesions at dermoscopy, as defined by the revisited seven-point checklist,\textsuperscript{11} were selected. These features included: atypical pigment network, blue-whitish veil, atypical vascularization, peripheral streaks, regressive structures, irregular blotches and globules. Lesions of the face and lesions without a full set of investigations were excluded. Of the 1142 cases selected, those with known features for melanocytic lesions at RCM were excluded.\textsuperscript{12-22} A total of 117 non-facial lesions without features for melanocytic proliferation were included (Figure 1). All investigations were conducted according to the Declaration of Helsinki principles, with respect to human subjects in biomedical research.

2.2 | Instruments

Clinical, dermoscopic and RCM images stored in a dedicated database were previously acquired through a Canfield Nikon D90 Digital SLR,\textsuperscript{12} a Canfield Close-up Scale (Canfield Imaging Systems, Fairfield, NJ, USA) and a RCM laser scanning microscope (Vivascope 1500; MAVIG GmbH, Munich, Germany), respectively. Instruments and acquisition procedures have been described elsewhere.\textsuperscript{12,13} Lesions were first evaluated according to dermoscopic inclusion criteria. Selected RCM images were evaluated by an expert dermatologist in dermoscopy and RCM analyses (F.F.) and lesion features were recorded. RCM evaluations were performed blinded to the histopathological diagnoses.

2.3 | Dermoscopic evaluation

All lesions were first investigated for the presence in dermoscopy of at least one of the well-known criteria for atypical melanocytic lesions proposed by the revisited seven-point checklist.\textsuperscript{11} The following criteria were then evaluated: atypical pigment network, blue-whitish veil, atypical vascularization, peripheral streaks, regressive structures, irregular blotches or atypical globules. Each criterion was scored for its presence or absence. Cases without any criterion for atypical melanocytic proliferation were not included in the study.

2.4 | RCM evaluation

For each case, a complete set of at least three VivaBlock mosaic images, taken at three different standardized levels (epidermal layer, dermo-epidermal junction and upper dermis), was available for evaluation.

For the selected lesions, different criteria were investigated according to RCM features previously outlined in literature.\textsuperscript{21-37} Table 1 shows a brief description of the RCM criteria for non-melanocytic lesions evaluated in the study. The expert dermatologist classified the lesions according to RCM in diagnostic groups: seborrhoeic keratoses (SebK), dermatofibromas (DFs), basal cell carcinomas (BCCs) and squamous cell carcinomas (SCCs). If no RCM diagnostic features could be clearly identified, cases were listed in the “non-specific” group. A regular epidermal pattern, keratin-filled invaginations, epidermal projections, corneal pseudocysts, packed round to polymorphous dermal papillae, a mixed vascular pattern, cords and bulbous projections were characteristic of lesions classified as SebK.\textsuperscript{10,22,24,27} Lesions with dense bright dermal papillary rings and thickened refractile collagen bundles were classified DF.\textsuperscript{22-24} Streaming or pleomorphism of nuclei, cordlike or nodular structures, with or without peripheral palisading, and dark
silhouettes were classified BCC.22,24-32 Finally, lesions with a disruption of the stratum corneum, severe cellular pleomorphism, atypical cells and architectural disarray of the epidermis were classified SCC.22,24-27,33-37

2.5 | Histopathology evaluation

All cases underwent histopathology diagnoses. Lesions were grouped according to histological diagnoses as SebK (hSebK) or histologically proven non-SebK (hnSebK) and matching with RCM classifications and observed RCM features was performed.

2.6 | Statistical analysis

Descriptive statistics and complete case analysis was used for all comparisons between groups. Pearson’s chi-squared test and Fisher’s exact test were used to reveal associations between variables and groups.

### TABLE 1

Reflectance confocal microscopy (RCM) criteria for non-melanocytic lesions evaluated in the study. Lesions with histological diagnosis of SebK are classified as “hSebK” and those with other non-melanocytic histological diagnoses (i.e. dermatofibromas, basal cell carcinomas, squamous cell carcinomas and other diagnosis), are listed as “hnSebK.” Data concerning the frequency of each RCM pattern in the two groups are reported in percentages. A brief description of distinct RCM features is also present, with references to the relevant literature (Ref.)

| RCM pattern                        | RCM description                                                                 | hSebK (%) | hnSebK (%) | P-value | Ref.          |
|-----------------------------------|---------------------------------------------------------------------------------|-----------|------------|---------|---------------|
| **Epidermis**                     |                                                                                  |           |            |         |               |
| Regular epidermal pattern         | Keratinocytes with clearly demarcated cell borders, arranged in a honeycomb pattern | 94.8      | 5.2        | <.001   | [10, 22, 24, 26, 27] |
| Keratin-filled invaginations      | Round to longitudinal invaginations of the lesion epidermal surface, harbouring amorphous material | 100.0     | 0.0        | <.001   | [10, 22, 24, 26, 27] |
| Epidermal projections             | Projections of the epidermal surface of the lesion                              | 100.0     | 0.0        | <.001   | [10, 22, 24, 26, 27] |
| Corneal pseudocysts               | Well-circumscribed, round, bright reflecting structures at various epidermal levels | 95.1      | 4.9        | <.001   | [10, 22, 24, 26, 27] |
| Atypical cells                    | Atypical pleomorphic cells, with atypical nuclei                                | 0.0       | 100.0      | .008    | [22, 24–27, 33–37] |
| Architectural disarray of the epidermis | Disarray of the normal architecture of epidermal layers                      | 0.0       | 100.0      | .008    | [22, 24–27, 33–37] |
| Severe cellular pleomorphism      | Keratinocytes with pleomorphic shape and size                                   | 0.0       | 100.0      | <.001   | [22, 24–27, 33–37] |
| Distruption of the stratum corneum | Various degree of superficial disruption of the stratum corneum with detached keratinocytes and parakeratosis | 0.0       | 100.0      | <.001   | [22, 24–27, 33–37] |
| **Junction**                      |                                                                                  |           |            |         |               |
| Cords / bulbous projections       | Elongated bright tubular structures (cords) and epithelial bulbous projections at the junction | 100.0     | 0.0        | <.001   | [10, 22, 24, 26, 27] |
| Dense bright papillary rings      | Increased density of hyporeflective dermal papillae surrounded by a ring of bright keratinocytes | 5.8       | 94.1       | <.001   | [22–24]        |
| Streaming / pleomorphism of nuclei | Polarization and elongation of nuclei in an aggregate of keratinocytes, with eventually pleomorphic nuclei | 7.7       | 92.3       | <.001   | [22, 24–33]    |
| Dark silhouettes                  | Hyporeflective aggregates of cells imprinting hyporeflective dermal collagen bundles | 0.0       | 100.0      | <.001   | [22, 24–32]    |
| Cordlike/nodular structures       | Variably sized cord-like and lobulated nodular aggregates of neoplastic cells in the dermis, with eventually a single outer layer of cells oriented parallel to each other | 0.0       | 100.0      | <.001   | [22, 24–32]    |
| **Dermis**                        |                                                                                  |           |            |         |               |
| Packed dermal papillae            | Packed round to polymorphous dermal papillae in the dermis, both edged and non-edged | 100.0     | 0.0        | <.001   | [10, 22, 24, 26, 27] |
| Mixed vascular pattern            | Increased density of vessels at the junction                                      | 97.7      | 2.3        | <.001   | [10, 22]        |
| Thicker refractile collagen bundles | Thicker hyporeflective fibrillar structures in the reticular dermis             | 5.9       | 94.1       | <.001   | [22–24]        |
Cohen’s kappa was calculated to evaluate the agreement between RCM classification and histological diagnosis.

The interpretation of agreement adopted is: less than chance agreement ($\kappa < 0$), slight agreement ($0.01-0.20$), fair agreement ($0.21-0.40$), moderate agreement ($0.41-0.60$), substantial agreement ($0.61-0.80$) and almost perfect agreement ($0.81-0.99$). The interpretation of reproducibility adopted is: marginal ($0.00-0.40$), good ($0.40-0.75$) and excellent ($> 0.75$). For all tests, a $P < .05$ was considered statistically significant. Statistical analysis was performed using STATA® software version 14 (StataCorp. 2015, Stata Statistical Software: Release 14; StataCorp LP, College Station, TX, USA).

### Results

#### Study population

The study consisted of 117 cases, with RCM features considered non-diagnostic for melanocytic lesions, in lesions with $\geq 1$ revisited 7-point checklist score. Cases were further classified at RCM as SebK (71 cases), DF (18 cases), BCC (13 cases) and SCC (2 cases). The remaining 13 cases were classified at RCM as “non specific” as no specific RCM features were identified. The same lesions were diagnosed at histopathology and the RCM classifications and histopathological diagnoses were analysed (Table 2).

#### Table 2

Results of reflectance confocal microscopy (RCM) classifications and histopathology diagnoses of the 117 non-melanocytic lesions included in the study. SebK: seborrheic keratosis; DF: dermatofibroma; BCC: basal cell carcinoma; SCC: squamous cell carcinoma

| Classifications/diagnoses | RCM classification | Histopathology diagnoses |
|---------------------------|--------------------|--------------------------|
| SebK                      | 71                 | 70                       |
| DF                        | 18                 | 16                       |
| BCC                       | 13                 | 13                       |
| SCC                       | 2                  | 8                        |
| Non-specific/other diagnoses | 13               | 10                       |

![A](image1)

![B](image2)

![C](image3)

![D](image4)

![E](image5)

![F](image6)

**FIGURE 2** (A) Dermoscopy of a hyperpigmented SebK (lesion 1), showing thin peripheral streaks (the so called “spitzoid type” of unusual SebK, according to the Squillace classification), diagnosed as SebK at histopathology. (B) Reflectance confocal microscopy (RCM) imaging at the epidermal layer, revealing a regular epidermal pattern with epidermal projections, keratin-filled invaginations and corneal pseudocysts (yellow square). (C) A particular RCM mosaic at the dero-epidermal junction, showing corneal pseudocysts (red arrows) and cords and bulbous projections (red square). (D) Dermoscopy of a SebK (lesion 2) showing peripheral streaks, irregular pigmented blotches and whitish structures (“multicomponent pattern” according to the Squillace classification), diagnosed as SebK at histopathology. (E) RCM imaging of the lesion at the epidermal layer: a regular epidermal pattern is present with invaginations of epidermis and corneal pseudocysts (yellow arrows). (F) A particular RCM mosaic at the dero-epidermal junction with packed round to polymorphous dermal papillae (red square). [Colour figure can be viewed at wileyonlinelibrary.com]
Agreement between RCM classification and histopathological diagnosis

Of the 71 cases classified at RCM as SebK, agreement was achieved in 69, resulting in a 97% agreement; the 2 cases incorrectly diagnosed at RCM with SebK were confirmed SCC at histology. A total of 70 cases were confirmed SebK at histology; the 1 lesion non-identified at RCM was incorrectly classified as "non-specific."

Of the 18 cases diagnosed at RCM with DF, agreement was achieved for 16 cases, resulting in an 89% agreement; the two cases incorrectly diagnosed at RCM with DF were diagnosed at histopathology as a scar and chronic inflammation.

All 13 cases with RCM diagnosis of BCC were confirmed at histopathology, resulting in a 100% agreement.

Interestingly, SCC had a low agreement of only 25%. Of the eight cases diagnosed with SCC at histology, only two lesions were correctly identified at RCM. Four cases were incorrectly classified at RCM as "non-specific" and the other two cases had been incorrectly classified at RCM as SebK, as previously explained.

Of the "non-specific" lesions, histopathology revealed 4 SCC (previously described), 1 SebK (previously described) and varying diagnoses in the remaining eight cases (i.e. cutaneous metastasis, Kaposi Sarcoma, chronic inflammation and no finding of neoplastic cells).

The overall K strength of agreement was 0.76, corresponding to a good strength of agreement. Figures 2-5 illustrate some examples of SebK with atypical dermoscopic presentation patterns in dermoscopy and RCM.

3.3 RCM criteria for SebK identification

All RCM features considered are listed in Table 1. Keratin-filled invaginations, epidermal projections, packed round to polymorphous dermal papillae, cords and bulbous projections were observed in hSebK only, and not in hnSebK \( (P < .001) \). A mixed vascular pattern \( (97.7\%, P < .001) \) along with corneal pseudocysts \( (95.1\%, P < .001) \) and a regular epidermal pattern \( (94.8\%, P < .001) \) were also found indicative of hSebK compared to hnSebK. These patterns were observed at RCM with varying high frequencies in the 70 hSebK; interestingly keratin-filled invaginations were detected in 83%, corneal pseudocysts in 79%, a regular epidermal pattern in 79%, cords and bulbous projections in 77%, epidermal projections in 74%, packed round to polymorphous dermal papillae in 67%, and a mixed vascular pattern in 61%.
Typical dermoscopic features that we commonly use to identify SebK, were systematically described and included in a dermoscopic algorithm in 2003 by Argenziano et al.1 As a consequence, when multiple milia-like cysts and comedo-like openings are observed at dermoscopy, a differential diagnosis is simplified. However, unusual dermoscopic patterns or patterns common to many lesion types have been increasingly reported in association with the diagnoses of SebK with atypical dermoscopy presentation. The main objective in differential diagnosis is to discriminate SebK from malignant conditions, and especially melanoma, in order to determine correct treatment pathways as early as possible. Misclassification at dermoscopy of pigmented SebK was discussed by Braun et al.28 A series of additional dermoscopic criteria to increase diagnostic accuracy, underlining fissures, hairpin vessels, sharp demarcation and moth-eaten borders were proposed. Later, Scope et al observed that some typically melanocytic dermoscopic features, such as pigmented network, aggregated globules, streaks and homogeneous blue colour, were also present in SebK and other non-melanocytic lesions.6 Recently, in a large series of SebK cases, Lin et al compared dermoscopy with histopathology, proposing additional dermoscopic features for differential diagnosis, including the presence of globular-like structures and network-like structures, which may mimic the well-known globular and network patterns of melanocytic lesions.6 Squillace et al proposed a series of 10 dermoscopic classifications for “unusual SebK,”7 concluding that histopathology should remain mandatory for SebK with atypical dermoscopy and without a clear differentiation from other malignancies at dermoscopy.

The current study aimed to evaluate whether the use of RCM could improve the differential diagnosis of SebK with atypical dermoscopy presentation, mimicking melanoma, from melanocytic lesions. All cases included in the study showed at least one of the 7-point checklist criteria at dermoscopy for atypical melanocytic proliferation, thus leading to a possible dermoscopic misclassification. In this clinic however, patients with uncertain diagnosis are evaluated with RCM prior to histology, enabling an analysis of RCM features with microscopic outcomes, and the potential identification of specific features favourable to a differential diagnosis.

The current study confirmed that RCM features previously described for classic SebK,8 were also present in SebK with atypical...
dermoscopy presentation. As shown in Table 1, these patterns were significantly more frequently observed in hSebK, compared to hnSebK. The resulting agreement between the RCM diagnosis and hSebK was high (97%), and suggestive of a good diagnostic accuracy.

Interestingly, the presentation of atypical dermoscopy SebK compared well with the RCM features identified by Ahlgrim-Siess et al for typical dermoscopy SebK.10 With the exception of the corneal pseudocysts (present in 79% of the atypical SebK and in only 42% of the typical SebK), the epidermal projections (74% vs 96%), keratin filled invaginations (83% vs 80%) and the regular epidermal pattern (79% vs 100%) were all frequently observed in the epidermal layer in both studies, respectively. Deeper in the dermis, the densely packed round to polymorphous dermal papillae (67% vs 100%) and the mixed vascular pattern (61% vs 47%) were similarly observed, again with the exception of the cords and bulbous projections being more frequent in atypical SebK (77% vs 31%, respectively).

In the current study, two cases of SCCs were incorrectly classified as SebK at RCM. A retrospective analysis of these lesions revealed the presence of marked hyperkeratosis, covering more than 50% of the lesions, and limited a correct visualization of the RCM features. Marked hyperkeratosis is known to be highly refractile at RCM, thus possibly affecting the correct visualization of RCM features.20

The main limit of the present study was the sample size. Only lesions with atypical dermoscopy presentation and RCM imaging, excised and sent for histopathological analysis, were selected and included. Furthermore, as RCM was installed as a non-invasive analysis tool at our centre, many SebK with atypical dermoscopy presentation were assessed at RCM only and are not always sent for histopathological analysis.

5 | CONCLUSION

Reflectance confocal microscopy classification has a high agreement with histopathological diagnoses for SebK with atypical dermoscopy presentations. RCM features for the selected lesions were similar to those observed in typical SebK. Data suggest that RCM is an optimal non-invasive examination for early differential diagnosis of SebK with atypical dermoscopy presentations. Therefore, RCM may be able to assist in differential diagnosis and avoid unnecessary excisions.
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