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Dermoscopic and reflectance confocal microscopy features of cutaneous squamous cell carcinoma.

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Abstract

Background

Squamous cell carcinoma (SCC) of the skin is a highly prevalent neoplasm. The management and the prognosis of this tumor is dependent on its invasiveness and its grade of differentiation.

Objectives

To evaluate whether specific dermoscopic and reflectance confocal microscopy (RCM) criteria can predict the diagnosis of invasive SCC vs in situ SCC and poorly differentiated compared with well- and moderately differentiated SCC.

Methods

Dermoscopic and RCM images of SCCs were retrospectively evaluated for the presence of predefined criteria.

Results

Among 143 SCC, 121 cases had a complete set of images and thus were included in the study set. The head and neck area was the most frequently involved body site (74/121; 61.1%) followed by extremities (36/121, 29.7%) and trunk (11/121, 9.1%). Seventy tumors were in situ (57.8%), while 51 were invasive (42.1%), of these 11 were poorly differentiated (21.5%), 16 were moderately differentiated (31.3%), and 24 were well differentiated (47.0%). Chi-squared analysis demonstrated that invasive SCC were characterized by polymorphic vessels, erosion/ulceration, architectural disarrangement, speckled nucleated cells in the dermis, irregularly dilated vessels and absence of hyperkeratosis. Botton-hole vessels, white structureless areas and dotted or glomerular vessels were significantly associated with in situ lesions. Poorly differentiated SCC were typified by red areas,

erosion/ulceration and architectural disarrangement. Well or moderately differentiated SCC were associated with white areas and speckled nucleated cells in the epidermis.

Conclusion

Clinical, dermscopic and RCM images provide useful information that should be integrated in order to achieve the optimal therapeutic management for the patient.

Introduction

Squamous cell carcinoma of the skin (SCC) is responsible for 20% of skin malignancies [1, 2]. Recent guidelines suggest that the management of high-risk SCC should be as early and aggressive as possible, with surgery considered the optimal choice. [5,6] Tumor aggressiveness and risk of recurrence depend on many factors, in detail: patient's immune efficiency, body site, tumour size, invasion into the subcutaneous tissue, perineural involvement and the grade of histopathological differentiation. [7-9] Poor differentiation is an independent risk factor for recurrence, metastasis and disease-specific death. [5-9] In contrast, well-differentiated SCC is associated with a 5-year recurrence-free survival rate of 83%. [5-9]

Surgical biopsy and histological examination are the gold standard for the diagnosis of SCC [2]. However, there is mounting evidence that dermoscopy and reflectance confocal microscopy (RCM) are useful tools for the bedside diagnosis of AK and SCC, with high sensitivity and specificity values. Dermoscopic criteria have been described for SCC, including keratin, scale, blood spots, white circles, white structureless zones and perivascular white halos. [10,11] In previous studies, keratin and white circles reached a diagnostic sensitivity and specificity for SCC of 79% and 87%, respectively. In addition, keratin, white circles, structureless whitish areas and scales with central distribution were shown to be associated with well- or moderately differentiated tumors. In contrast, poorly

differentiated SCC revealed a predominantly red colour, resulting from the presence of bleeding and/or dense vascularity, in the absence of scale/keratin or other white-coloured criteria [10].

RCM represent an add-on tool for the non-invasive diagnosis and management of SCC. Recent studies demonstrated that RCM image analysis performed by trained (expert) readers, achieved sensitivity values ranging from 80.0 to 93.34 % and specificity values ranging from 88.34 to 98.6% [4,12,13]. RCM grade of honeycomb atypia was highly correlated with the histopatological assessment of keratinocyte atypia in AK. Ulrich et al. found that the most common RCM findings of Bowen Disease (BD) were the disruption of the stratum corneum, an atypical honeycomb pattern in the epidermis, S-shaped blood vessels in the center of the dermal papillae, and 2 types of characteristic targetoid cells [14]. Regarding invasive SCC, large and comprehensive RCM studies are still lacking. Small population sized studies identified that main RCM pattern of invasive SCC are: a disarranged or atypical honeycomb pattern in the epidermis, round nucleated bright cells in the suprabasal epidermis and looping blood vessels in dermal papillae [15,16].

The aim of our study was to define the frequencies of the main RCM criteria for the diagnosis of invasive and in situ SCC and their correlations with the histologic grade of differentiation.

Materials and method

SCC cases were retrospectively collected in two centers in Italy (University of Modena and Reggio Emilia, and at the Arcispedale Santa Maria Nuova in Reggio Emilia). Ethics committee approval was waived because the study affected neither the routine diagnostic nor therapeutic management of these cases. Inclusion criteria were a definite histopathologic diagnosis of SCC, including subtype classification, the availability of clinical, dermoscopic, and RCM images of the tumor, and the availability of histopathologic slides. Dermoscopy, RCM and histologic examination were performed

as standards of care in our centers. The pathologic exam was conducted following the routine procedures: all lesions were defined as in situ SCC (intraepidermal carcinoma or Bowen's disease) or invasive SCC, based on the presence of an invasive component of the tumor, and invasive SCC were classified into "poorly differentiated", "moderately differentiated" and "well differentiated", based on the histologic grading of the tumor. Actinic keratosis were excluded from the study. Cases in which RCM images could not be evaluated because of poor image quality or the presence of extensive ulceration or hyperkeratosis were excluded. Dermoscopic images were captured by means of DermlitePhoto equipment (3Gen, Dana Point, CA) at 10-fold magnification. RCM images were acquired by means of a Vivascope 1500 or Vivascope 3000 (Caliber ID, Rochester, NY), which uses an 830 nm laser beam with a maximum power of 20 mW. Instrument and acquisition procedures have been described elsewhere [17,18]. Patient demographics and tumor characteristics were recorded, and two independent investigators (E.M. and M.M.) evaluated all clinical, dermoscopic and RCM images. Both were blinded to the clinical and histopathological diagnosis. If the two investigators failed to reach a consensus, a third investigator was involved (C.L.). Dermoscopic and RCM variables were selected on the basis of previously published data on SCC and our preliminary observations (**Table 1**).

Statistical analysis

The analysis was conducted in order to assess if any dermoscopic or RCM criteria were associated to the different SCC types. The statistical analysis comprised descriptive statistics and Pearson's chi-squared test to analyze the different subgroups. The compared categories were: 1) invasive versus in situ SCC, and 2) well, moderately and poorly differentiated invasive SCC. All statistical calculations were made with SPSS 17.0 (IBM, Armonk, NY, U.S.A.).

Results

143 SCC from 143 patients were retrieved from the databases of the two academic Centers. 121 had a complete set of dermoscopic and RCM images (mean age 78.79 years old), including 77 men and 45

women. The remaining 22 SCC that were excluded from the study (22/143, 15.3%), either lacked some dermoscopic or RCM images or showed abundant hyperkeratosis or ulceration (>85% surface area) that hampered the quality of the images and their evaluation.

The head and neck area was the most frequent body site of tumor development (74/121; 61.1%) followed by extremities (36/121, 29.7%) and trunk (11/121, 9.1%). 70 tumors were in situ (57.8%), while 51 were invasive (42.1%), of these 11 were poorly differentiated (21.5%), 16 were moderately differentiated (31.3%), and 24 were well differentiated (47.0%). Table 2 shows the descriptive results of the dermoscopic features and the RCM criteria and of the analysis performed in order to compare: 1) in situ and invasive SCC, 2) well, moderately and poorly differentiated invasive SCC.

Upon RCM, invasive SCC were significantly characterized by the presence of erosion/ulceration, architectural disarrangement, speckled nucleated cells in the dermis and absence of hyperkeratosis. Regarding the vascular features, the presence of button-hole vessels was significantly associated with in situ SCC, while irregularly dilated vessels were associated with invasive SCC (Fig.1). The assessment of poorly differentiated and other invasive SCC revealed that the RCM images of poorly differentiated SCC were characterized by architectural disarrangement, while well or moderately differentiated SCC showed a more preserved architecture and the presence of speckled nucleated cells in the epidermis (Fig. 1).

From a dermoscopic point of view, in situ SCC were characterized by the presence of white structureless areas and dotted or glomerular vessels. Polymorphic vessels were associated to invasive SCC (Fig 2). The comparison of the dermoscopic images of poorly differentiated and other invasive SCC showed that the predominance of red areas and the presence of erosion/ulceration were

associated with poor differentiation. Conversely, the presence of white areas was associated with well- differentiated or moderately differentiated tumors (Fig.2).

Discussion

In the current study we focused on the dermoscopic and RCM features of squamous cell neoplasia, in order to correlate the presence of specific descriptors with invasiveness and histologic grade of differentiation. In our analysis, invasive SCC were characterized by erosion/ulceration, architectural disarrangement, speckled nucleated cells in the dermis and irregularly dilated vessels upon RCM examination. These features morphologically reproduce the deregulated growth of the tumor that develops necrotic areas on the epidermal surface and invades beyond the dermo-epidermal junction with abundant neo-angiogenetic phenomena. We introduced the term "Speckled nucleated cells" to define roundish to polygonal cells with speckled appearance and a dark nucleus. Their size is slightly larger than to the one of the surrounding keratinocytes and they can be differentiated from inflammatory because they are larger than the usual size of lymphocytes and have a polygonal shape that is different from the one of dendritic cells or plump bright cells [19,20]. On the other hand, in situ SCCs were characterized by a rich hyperkeratotic component and by the presence of botton-hole vessels inside dermal papillae. Architectural disarrangement was not as marked as in the invasive form, and there was no sign of invasion beyond the dermal epidermal junction. Our dermoscopic findings are consistent with previous studies reporting on the dermoscopic criteria of SCC. [10, 11] In our group of patients, in situ SCCs were characterized by the presence of white structureless areas and dotted or glomerular vessels. Instead, polymorphic vessels were associated with invasive SCC.

The second key point of our study was the identification of RCM or dermoscopic descriptors specific of poorly differentiated tumors. Among invasive SCCs, the recognition of poor differentiated neoplasms is of great clinical and therapeutic relevance [21-23]. It was demonstrated that this feature

is associated to poor prognosis, with higher relapse and nodal involvement rates [5-9]. Even though, given the rarity of this type of neoplasm, only a small number of poorly differentiated invasive SCC were included in the study, we observed that poorly differentiated SCC are characterized by a massive architectural disarrangement and by the absence of round nucleated cells in the epidermis. These features reflected a more chaotic growth and a complete loss of the features associated to the regular epidermal differentiation. Furthermore, the identification of severe atypia of the honeycomb pattern, that was assessed based on previous RCM studies [24], was neither associated to differences between invasive and in situ SCC, nor to the histological grade of the invasive tumors. This is probably due to the fact that, differently from AKs, the honeycomb atypia is often severe in all the SCC, either in situ, invasive, well, moderately or poorly differentiated. Dermoscopically, as previously reported by Lallas and colleagues [10], we confirm that there is a predominance of red colour and of erosion/ulceration in the poorly differentiated tumor, and of white structureless areas in well or moderately differentiated tumors SCC.

Conclusions

Clinical, dermscopic and RCM information should be integrated in order to achieve the optimal therapeutic management for the patient. The clinical information should include tumor size, precise body site location, concurrent scars or chronic inflammation, presence of previous SCC, treatment failure and immunosuppression [6-9, 25]. Based on our findings, dermoscopy and RCM imaging can allow a more accurate pre-surgical assessment of SCC. Further studies are needed in order to define the best surgical margins or therapeutic approaches in relation to the presence of the different RCM patterns.

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TABLE 1

Reflectance confocal microscopy and Dermoscopic pattern and their definition.

TABLE 2

Frequencies and statistical comparison of Reflectance confocal microscopy and Dermoscopic pattern among in situ and invasive SCC.

Figure 1:

RCM single images (0.5x0.5 mm) taken at various levels of depth in the epidermis and showing RCM features of SCC. Erosion/ulceration (area between the arrows) (a), hyperkeratosis (arrowhead) (b), speckled nucleated cells in the epidermis (arrow) (c), speckled nucleated cells in the dermis (arrow) (d), architectural disarrangement (e), botton hole (circle) and dilated vessels (arrow) (f).

Figure 2:

In situ SCC characterized by dotted vessels in dermoscopy and pink-white structureless areas (a); well differentiated invasive SCC with central keratin mass and linear vessels at the periphery (b); poorly differentiated invasive SCC with predominant red color and polymorphous vessels in dermoscopy (c).

Table 1

Reflectance confocal microscopy patterns	Definition
Erosion/Ulceration	Dark areas, with sharp borders and irregular contours, filled with amorphous material, cellular debris and small particles
Geographic Surface (0=Absent; 1=Present)	The regular organization of the sulci of the stratum corneum is disrupted and replaced by large areas of hyperkeratosis separated one from another by wide large spaces. The name comes from the map-like appearance of the stratum corneum with the patches resembling the islands of an archipelago.
Hyperkeratosis (0=Absent; 1=Present)	Increased thickness of stratum corneum seen as hype-refractive amorphous material and scales
Parakeratosis (0=Absent; 1=Present)	Individual polygonal cells in the stratum corneum with an irregular nucleus, shown as round highly refractive small structure.
Spongiosis (0=Absent; 1=Present)	Round, highly refractive structures of 8 to 10 µm in diameter corresponding to inflammatory cells
Severe atypia of the Honeycombed Pattern (0=Absent; 1=Present)	Presence of many cells with irregular shape and size showing bright cell borders arranged within a distorted honeycomb structure
Architectural Disarrangement (0=Absent; 1=Present)	Disarray of the normal architecture of superficial layers with unevenly distributed bright granular particles and cells, in absence of honeycombed or cobblestone pattern
Speckled Nucleated Cells In The Epidermis(0=Absent; 1=Present)	Roundish to polygonal cells with speckled appearance and a dark nucleus within the epidermis. Their size is slightly larger than to the one of the surrounding keratinocytes. They are larger than the usual size of lymphocytes and have a polygonal shape that differentiate them from dendritic cells.
Speckled Nucleated Cells In The Dermis (0=Absent; 1=Present)	Roundish to polygonal cells with speckled appearance and a dark nucleus within the dermis. They are larger than the usual size of lymphocytes and have a polygonal shape that differentiate them from plump bright cells.
Targetoid Cells (0=Absent; 1=Present)	Large cell with a bright center and a dark peripheral halo or a dark center and a bright rim surrounded by a dark halo.
Keratin Pearl (0=Absent; 1=Present)	Whorl-shaped accumulation of keratin appearing as highly refractive, speckled structure in the dermis
Dendritic Cells In The Epidermis(0=Absent;	Large elongated cells with clearly visible dendrites connected to the cell

1=Present)	
Nest Like Structures In The Dermis	Cellular aggregates in the dermis with irregular and discohesive margins
Plump Bright Cells	Bright cells with indistinct borders, lacking a clearly defined nucleus, located in the dermis
Dilated Blood Vessels	Dilated horizontal blood vessels in the dermis, with visible blood flow in their inside.
Button Hole Vessels	Dilated blood vessels within the dermal papillae that run perpendicular to the horizontal RCM plane of imaging
Dermoscopic Parameters	Definition
Predominant Red	The criteria was considered present when the red color was observed in >50% of the lesion's surface.
Pink Structureless Areas	Pinkish areas in the absence of any recognizable structure
Rosette Like Structures	Metaphorical term for the Four points in a square criteria, representing four bright white points grouped together akin to a four-leaf clover.
Scales	White or yellow areas lying on the surface, without any recognizable structure
Erosion/Ulceration	Bleeding to clotted materials on a yellowish structureless amorphous areas
Central Keratin Mass	White or yellow keratinized mass in the center of the lesion, without any recognizable structure
White Circles	Roundish structures composed of yellow-to-light brown structureless center and white outer structureless rim
White Structureless Areas	Whitish areas, not corresponding to scales/keratin, in the absence of any recognizable structure
Dotted/Glomerular Vessels	Tiny red dots, usually densely distributed next to each other
Polymorphic Vessels	Presence of vessels with different morphology and dimension

Reflectance confocal microscopy parameters and definitions.

Table 2 Absolute and relative frequencies of the Reflectance confocal microscopy and Dermoscopic patterns evaluated.

Reflectance confocal microscopy parameters	In situ SCC	%	P value: Invasive vs In situ SCC	Well or moderately Differentiated Invasive SCC	%	Poorly differentiated invasive SCC	%	P value: Poorly differentiated vs Other invasive SCC
Erosion/Ulceration	**9**	**12.9% *[1]**	**0,01**	12	30.0%	4	36.4%	0,21
Geographic Surface	36	51.4%	0,30	16	40.0%	2	18.2%	0,83
Hyperkeratosis	**51**	**72.9% *[1]**	**0,00**	13	32.5%	1	9.1%	0,31
Parakeratosis	56	80.0%	0,49	26	65.0%	3	27.3%	0,39
Spongiosis	33	47.1%	0,49	28	70.0%	4	36.4%	0,91
Severe atypia of the Honeycombed Pattern	65	92.9%	0,40	35	87.5%	11	100.0%	0,30
Architectural Disarrangement	**29**	**41.4% *[1]**	**0,00**	**26**	**65.0% *[2]**	**11**	**100.0% *[2]**	**0,02**
Speckled Nucleated Cells In The Epidermis	30	42.9%	0,35	**17**	**42.5%*[2]**	**1**	**9.1% *[2]**	**0,04**
Speckled Nucleated Cells In The Dermis	**5**	**7.1%*[1]**	**0,01**	15	37.5%	4	36.4%	0,08
Targetoid Cells	18	25.7%	0,88	15	37.5%	0	0.0%	0,08
Keratin Pearl	27	38.6%	0,83	17	42.5%	2	18.2%	0,49
Dendritic Cells In The Epidermis	24	34.3%	0,49	16	40.0%	5	45.4%	0,33
Nest Like Structures In The Dermis	31	44.29%	0,53	18	45.0%	5	45.4%	0,68
Plump Bright Cells	27	38.6%	0,37	15	37.5%	1	9.1%	0,31

Dilated Blood Vessels	**35**	**50.0% *[1]**	**0,02**	31	77.5%	6	54.5%	0,98
Botton Hole Vessels	**42**	**60.0% *[1]**	**0,00**	11	27.5%	1	9.1%	0,48
Dermoscopic Parameters								
Predominant Red	13	81.4%	0,18	**14**	**65.0%*[2]**	**0**	**100.0% *[2]**	**0,02**
Pink Structureless Areas	59	84.3%	0,23	24	60.0%	6	54.5%	0,88
Rosette Like Structures	16	22.9%	0,24	7	17.5%	2	18.2%	0,50
Scales	53	75.7%	0,46	21	52.5%	7	63.6%	0,37
Erosion/Ulceration	39	55.7%	0,68	**16**	**40.0%*[2]**	**8**	**72.7%*[2]**	**0,01**
Central Keratin Mass	16	22.9%	0,16	8	20.0%	1	9.1%	0,63
White Circles	28	40.0%	0,30	16	40.0%	2	18.2%	0,56
White Structureless Areas	**34**	**48.6% *[1]**	**0,02**	**31**	**77.5%*[2]**	**5**	**45.4% *[2]**	**0,04**
Dotted/Glomerular Vessels	**41**	**58.6% *[1]**	**0,01**	15	37.5%	2	18.2%	0,63
Polymorphic Vessels	**25**	**35.7% *[1]**	**0,04**	21	52.5%	9	81.8%	0,06

***[1]** P value of the chi-square analysis between invasive and in situ SCC was significant (<0.05).

***[2]** P value of the chi-square analysis between poorly differentiated and other invasive SCC was significant (<0.05).