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CUTANEOUS TRICHOLEMMAL CARCINOMA: A 15-YEARS SINGLE CENTRE EXPERIENCE

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CONFLICTS OF INTEREST

None declared.

ABSTRACT

BACKGROUND:

Clear cell morphology has been described in several cutaneous neoplasms either as a specific feature of some entities either as a morphological variant in the spectrum, and these two entities are frequently considered together in the differential diagnosis.

METHODS:

We reviewed our series of cases occurred in our laboratory in order to further quantify the number of cases showing morphological features of tricholemmal differentiation and to investigate other clinical or histological difference.

We retrieved 91 cases and, for each of them, all the clinical data regarding age, sex, clinical features, and clinical suspicious were collected, when available.

RESULTS:

The revision of the specimens concluded with a final diagnosis of tricholemmal carcinoma in 15 cases (17%), all the other cases were thus considered as squamous cell carcinoma with clear cell features.

No statistically significant correlations were observed with the demografic or clinicopatholagical parameters such as age, sex or dimensions, but morphological revision highlighted a potentially greater “vertical” growth frequently not matched by a concomitant radial one in tricholemmal carcinoma than in squamous tumors.

CONCLUSIONS:

The debate upon the diagnostic distinction of these tumours is still ongoing with authors proposing the tricholemmal carcinoma as a variant of a squamous cell carcinoma rather than a distinct entity.

Further studies are needed to confirm our data and to evaluate the reproducibility of this feature.

KEY WORDS

Clear cell tumors, squamous cell carcinoma, tricholemmal carcinoma, appendageal tumors.

INTRODUCTION

Clear cell morphology has been described in several cutaneous neoplasms either as a peculiar morphological feature of a distinct entity, either as a rare variant of tumors that exhibit squamous morphology: tricholemmal carcinoma and clear cell variant of squamous cell carcinoma represent each an example of the aforementioned scenarios.

Non-surprisingly those two entities are frequently considered together in the differential diagnosis.

The debate upon the diagnostic distinction of these tumours is still ongoing with authors proposing the tricholemmal carcinoma as a variant of a squamous cell carcinoma rather than a distinct entity (1).

Nonetheless recently the 4th edition of World Health Organization (WHO) classification of skin tumours introduced this entity among appendigeal tumours (2).

We reviewed the cases retrieved from our archives in order to quantify the number of tumors showing morphological features of tricholemmal differentiation and to investigate their clinical or histological presentation.

MATERIALS AND METHODS

We retrieved from the database of Dermatopathology Department, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico of Milan, Italy, all the cases diagnosed as squamous cell carcinoma with clear cell features from 2003 to 2018 as in our practice we considered all the tumors showing more than 25% of clear cell component as "squamous cell carcinoma with clear cell features", without using the "tricholemmal carcinoma" wording.

We reviewed 91 cases and, for each of them, all the clinical data regarding age, sex, clinical features, and clinical suspicious were collected, when available.

Ethical approval was not necessary since this work is a retrospective study not involving human subjects but just tissue specimens.

Section stained with hematoxylin and eosins were available in all cases and we performed, in selected cases illustrated in the "Results" section, Periodic acid Schiff (PAS) and PAS-diastase histochemical staining to better evaluate tumor cell cytoplasms and immunohistochemical stain for p53 and Citokeratin 14 to confirm the follicular differentiation.

The five histopathological criteria reported by WHO classification obtainable from hematoxylin and eosins section investigated were: presence of a lobular arrangement, peripheral palisading, presence of tricholemmal keratinization, folliculocentricity and thickened basement membrane.

When all the features were present in the same tumour the lesion was then categorized as tricholemmal carcinoma instead of squamous cell carcinoma with clear cell features.

Major radial dimension, depth of invasion and ulceration was also reported, when available.

Statistical analysis was performed with IBM SPSS Statistics, version 24.0 (IBM Corp., Armonk, N.Y., USA). Statistical significance was defined as $p<0.05$. Distribution normality was assessed with the Shapiro-Wilk Test.

The selection of univariate variables was achieved using the χ^2 test for non-dichotomous quantitative variables and Fisher's exact test for dichotomous quantitative variables and by using the revised diagnosis as a dependent variable.

For continuous variables, the ROC curve was used to calculate the Youden index and obtain a threshold value to be used for a subsequent Fisher exact test.

RESULTS

We reviewed 91 specimens stained with hematoxylin and eosins of 89 patients.

Table 1 shows the clinical and pathologic details of the 91 cases, including sex, age, location, dimension, depth of invasion, clinical diagnosis, clinical features and presence of ulceration.

The average age was 77, with the youngest patient of 57 years old and the oldest one of 92.

In our series 25 out of 89 (28%) patients were female and 64 (72%) were male.

The revision of the specimens concluded with a final diagnosis of tricholemmal carcinoma in 15 cases (17%), all the other cases were thus considered as squamous cell carcinoma with clear cell features.

PAS and PAS-diastase histochemical staining was performed in all these cases and in two cases of SCC with clear cell features in order to evaluate the tumor cell cytoplasms.

In tricholemmal carcinomas, PAS staining showed the presence of glycogen in the neoplastic cells, confirmed by negativity of PAS-diastase staining. In addition, PAS-diastase staining showed focal thickening of the basement membrane.

By the contrary, in SCC with clear cell features, PAS staining was negative.

Immunohistochemical stain for Cytokeratin 14 and p53 was performed to confirm the follicular differentiation in all tricholemmal carcinoma. (Figure 1)

Among the group of patients with tricholemmal carcinoma 10 were male and 5 females, with an average age of 72.2 (range 61 to 87). The average dimension of the lesions was 1.26 cm with the smallest lesion measured 0.5 cm and the biggest one as 3.5 cm. The thickness assessed ranged from 0.3 mm to 3 mm (average of 1.24 mm). The ulceration was also detected in 6 cases (40%).

The number of female patients in the group of squamous cell carcinoma was 20 (27%) meanwhile the 73% of the patients were male. Patients of this group presented average age of 77.77 (range 57 to 92). The dimensional evaluation of the lesion showed a range from 0.5 to 6.6 cm (average of 1.58 cm), meanwhile the thickness of the lesions ranged from 0.1 to 10 mm (average of 0.95 mm).

The 66% of the lesions showed evidence of ulceration.

No statistically significant correlations were observed with the demografic or clinicopatholagical parameters such as age, sex or dimensions.

DISCUSSION

Tricholemmal carcinoma was firstly described by Headington in 1976 (3) as a tumour of clear

cells derived from the outer root sheath in continuity with a coexisting tricholemmoma, glycogen rich (as demonstrated by PAS stains with and without diastase), showing peripheral palisading, thickening of basement membrane and with tricholemmal keratinization (abrupt single-cell keratinization with formation of non-lamellar keratin and absent or minimal granular layer).

Based on this paper other authors started collecting series of cases showing the features described by Headington (4-7).

Few years later the clear cell variant of squamous cell carcinoma was characterized by Kuo (8) interpreted as a degenerative change of tumor cell cytoplasm.

Nowadays since these two tumors show many morphological overlapping their relationship is still controversial.

Some authors investigated the real nature of tricholemmal carcinoma, arguing that actually it could just represent the clear cell variant of squamous cell carcinoma (1).

In 2008 Dalton and LeBoit quantified the occurrence of true tricholemmal differentiation in clear cell squamous carcinoma using Hedington' criteria, stating that the contemporary occurrence of them in the same lesion represents an exceptional event, questioning thus the specificity of many of these criteria.

Moreover the authors showed how immunohistochemical profile and PAS histochemical stain (used to detect intracytoplasmic glycogen and thickening of basement membrane) seemed not to be useful in the diagnostic definition (9). More recently other authors investigated immunohistochemical tools with encouraging results although on a small series of cases (10).

Although the diagnostic dignity of tricholemmal carcinoma continues to be a matter of debate, the 4th edition of World Health Organization (WHO) classification of skin tumours introduced this entity among appendigeal tumors (2).

The histological criteria proposed by the authors basically retrace the original Headington's criteria: lobular arrangement, peripheral palisading, tricholemmal keratinization, folliculocentricity and thickened basement membrane.

By following those criteria, we were able to characterize 15 tricholemmal carcinoma out of 91 cases showing clear cell morphology.

In our series, the population features in the two group were found basically similar: both tumours occurred mostly among male patients during their 7th decade.

Also, the anatomical site was also not helpful in the differential diagnosis, both tumours indeed involved mostly face, scalp and neck.

Those evidence are easily explained by the shared pathogenesis of the two entities related to the actinic damage.

The histological revision of the slides and the macroscopic features allowed to notice a grater trend of a radial spreading of the tumours resulting in a greater maximal dimension of 6.6 cm for squamous cell carcinoma compared to tricholemmal carcinoma (maximal dimension of 3.5 cm).

Moreover, the depth of invasion for squamous cell carcinoma reached greater value by reaching 1 cm of thickness, compared to 3 mm reached by the thickest tricholemmal carcinoma.

However, when depth and radial dimensions are considered together this data suggest an opposite trend between them: the thickest squamous cell carcinoma (1 cm) reached 2.5 cm in radial dimension, way more than the average of 1.58 cm of other squamous cell carcinoma in the series meanwhile the opposite occurred for the thickest tricholemmal carcinoma (equal to 3 mm) was just 0.8 cm in radial dimension, almost the half of the averaged recorded (1.26 cm).

Considering these data, we can speculate that the tricholemmal carcinoma of our series could potentially show a greater “vertical” growth frequently not matched by a concomitant radial one.

Evaluation at low-power magnification showed several cases with convincing different pattern of growth among the two group with a more radial-oriented growth for squamous cell carcinomas versus a more vertical-oriented growth among tricholemmal carcinomas (Figure 2).

This trend, albeit not translatable in a cut off, seemed in our series a interesting hint for tricholemmal differentiation retracing the folliculocentricity and the postulated origin from adnexal skin structures of this entity.

Further study and evidence are needed to confirm this tendency and to asses the reproducibility among pathologist since our data were strongly affected by the numerosity discrepancy of cases in the two group.

Although, on the other hand, we confirmed the lower incidence of tricholemmal carcinomas compare to squamous cell carcinoma already described in literature. Moreover, we confirmed how no clinical presentation regarding site, age, sex can represent useful hint in the differential diagnosis.

Lastly the presence of ulceration was more frequently spotted among cases of squamous cell carcinoma, however not confirmed by statistics. This lower occurrence of ulceration seemed in line with the higher tendency to expand vertically before growing in an exofitic and radial direction.

Nevertheless, the higher propensity of a vertical growth recorded in tricholemmal carcinoma of our series could represent a new useful hint in the differential diagnosis of challenging cases.

Further studies are needed to confirm our data and to evaluate the reproducibility of this feature.

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TABLES

Table 1 – Clinicopathological characteristics of the series

#	Diagnosis	Sex	Age	Site	Dimension (cm)	Thickness (mm)	Clinical suspicious	Clinical presentation	Ulceration
1	SCC	M	57	Left shoulder	2	0.3	BCC	Erythematous and erosive plaque	no
2	SCC	M	58	Right arm	1	NA	SCC	Keratotic nodule	no
3	SCC	M	60	Right leg	1.6	0.5	SCC	Ulcerated nodule	yes
4	SCC	M	60	Right gluteus	1.3	1	SCC	Keratotic nodule	yes
5	SCC	M	61	Scalp	3.5	0.7	SCC	Ulcerated nodule	yes
6	SCC	M	62	Right temple	1.5	0.5	SCC	Erythematous and erosive plaque	yes
7	SCC	M	65	Nose	1.5	0.8	SCC	Ulcerated nodule	yes
8	SCC	M	65	Right lip	0.8	0.7	Cutaneous horn	Keratotic nodule	no
9	SCC	F	66	Right breast	0.8	IN SITU	Cutaneous horn	Erosive and erythematous plaque	yes
10	SCC	F	67	Right cheekbone	0.5	IN SITU	SCC	Ulcerated nodule	yes
11	SCC	M	68	Right pre-auricolar	1.2	0.3	SCC	Erosive nodule	yes
12	SCC	F	68	Right arm	1.5	NA	BCC	Erosive plaque	yes
13	SCC	F	69	Right scapula	2	IN SITU	Seborrheic keratosis vs BCC	Nodule	no
14	SCC	M	70	Left retroauricolar	2.2	2	BCC	Keratotic nodule	yes
15	SCC	M	70	Forehead	0.6	1	BCC	Keratotic nodule	no
16	SCC	M	70	Left pre-auricolar	1.7	3	SCC	Erythematous plaque	no
17	SCC	M	71	Left temple	1.5	0.3	BCC	Ulcerated nodule	yes
18	SCC	M	71	Right temple	1.3	0.55	SCC	Ulcerated nodule	yes
19	SCC	M	72	Right helix	1.2	0.8	BCC	Nodule	no
20	SCC	M	72	Forehead	1.5	1	BCC	Keratotic nodule	no
21	SCC	M	73	Left forehead	NA	NA	Cutaneous horn	Erosive nodule	yes
22	SCC	M	73	Left forehead	2	0.25	Cutaneous horn	Erosive nodule	yes
23	SCC	M	73	Chest	1	0.15	BCC	Erythematous nodule	no
24	SCC	F	73	Right arm	2.5	0.6	KA	Necrotic nodule	yes
25	SCC	M	75	Parietal scalp	1.2	0.7	SCC	Crateriform lesion	yes
26	SCC	F	75	Right eyebrown	0.7	0.1	BCC	Papular lesion	yes
27	SCC	M	75	Left temple	1.5	0.3	SCC	Keratotic and erythematous plaque	no
28	SCC	M	75	Left temple	2.5	0.8	SCC	Nodule	yes
29	SCC	M	77	Forehead	0.6	1	BCC	Ulcerated nodule	yes
30	SCC	M	77	Right helix	0.5	0.3	Cutaneous horn	Keratotic nodule	no
31	SCC	F	77	Right arm	1.9	0.4	SCC	Erosive nodule	yes
32	SCC	M	78	Right hip	1.5	2	SCC	Erythematous and erosive plaque	yes
33	SCC	M	78	Parietal scalp	2	0.8	SCC	Ulcerated nodule	yes
34	SCC	M	78	Scalp	2	0.25	SCC	Erythematous and erosive plaque	yes
35	SCC	F	79	Left arm	1	IN SITU	SCC	Ulcerated nodule	yes
36	SCC	M	79	Right forehead	1	0.2	SCC	Erythematous and erosive plaque	yes
37	SCC	M	79	Left leg	0.5	0.3	SCC	Keratotic nodule	yes
38	SCC	F	80	Left gluteus	0.8	0.2	UD Nodule	Nodule	no
39	SCC	M	80	Left parietal scalp	1.6	IN SITU	SCC	Erythematous nodule	no
40	SCC	M	80	Left arm	0.6	0.3	SCC	Ulcerated nodule	yes

41	SCC	M	80	Left forehead	2.2	0.3	Cutaneous horn	Erosive nodule	yes
42	SCC	M	81	Right cheekbone	1.1	8	BCC	NA	yes
43	SCC	M	81	Neck	1.5	0.2	BCC	NA	no
44	SCC	M	81	Right leg	3.5	0.7	KA	Ulcerated nodule	yes
45	SCC	M	81	Left forehead	1.5	0.5	SCC	Nodule	yes
46	SCC	M	81	Right scapular region	1.2	0.5	SCC	Nodule	yes
47	SCC	F	81	Right periorbital region	1	0.2	SCC	Papular lesion	yes
48	SCC	F	81	Left cheek	1.5	0.4	Cutaneous horn	Keratotic and eruthematous nodule	no
49	SCC	M	82	Scalp	4	IN SITU	SCC	NA	no
50	SCC	M	82	Scalp	1.5	0.6	BCC	Keratotic nodule	no
51	SCC	M	82	Forehead	2	0.5	BCC	Keratotic nodule	no
52	SCC	M	82	Right temple	3.5	0.7	SCC	Ulcerated nodule	yes
53	SCC	M	82	Left abdomen	1.5	NA	Seborrheic keratosis	Keratotic and erythematous nodule	no
54	SCC	F	83	Right leg	6.6	0.5	SCC	Ulcerated nodule	yes
55	SCC	M	83	Right helix	0.5	0.5	Cutaneous horn	Keratotic nodule	no
56	SCC	M	83	Right pre-auricolar	0.8	0.3	BCC	Keratotic nodule	yes
57	SCC	M	83	Left forehead	1	0.45	BCC	Ulcerated nodule	yes
58	SCC	F	84	Left cheek	0.8	IN SITU	BCC	Ulcerated nodule	yes
59	SCC	M	84	Left temple	0.9	0.4	BCC	Nodule	yes
60	SCC	M	85	Right leg	1	0.15	BCC	Keratotic nodule	no
61	SCC	M	85	Left parietal scalp	2	0.8	SCC	Nodule	yes
62	SCC	F	85	Nose	1.5	IN SITU	BCC	Keratotic nodule	no
63	SCC	M	85	Scalp	2.5	10	SCC	Keratotic nodule	no
64	SCC	M	86	Chest	1	1	BCC	NA	yes
65	SCC	M	86	Right cheekbone	1	NA	SCC	Keratotic nodule	yes
66	SCC	M	86	Left shoulder	1.1	0.3	BCC	Erythematous and erosive plaque	yes
67	SCC	M	87	Nose	NA	3	UD Nodule	Ulcerated nodule	yes
68	SCC	F	88	Left supraclavear region	2	0.5	SCC	Keratotic nodule	yes
69	SCC	F	88	Left temple	1	0.6	KS	Nodule	no
70	SCC	M	89	Left temple	2	1	SCC	Erythematous nodule	yes
71	SCC	F	90	Left leg	0.8	2	BCC	Erythematous nodule	no
72	SCC	F	91	Forehead	1.8	1	SCC	Ulcerated nodule	yes
73	SCC	F	91	Scalp	1.8	1	Cutaneous horn	Ulcerated nodule	yes
74	SCC	M	92	Left temple	2	0.5	BCC	Erythematous nodule	yes
75	SCC	M	92	Scalp	1.8	0.3	SCC	Nodule	yes
76	SCC	F	92	Chest	2.7	0.6	Cutaneous horn	Erosive nodule	yes
77	TC	F	61	Nose	1	2	SCC	Ulcerated nodule	yes
78	TC	M	61	Left leg	3.5	0.5	Skin tag vs BCC	Nodule	no
79	TC	F	69	Left cheekbone	0.8	3	BCC	NA	no
80	TC	M	69	Left temple	1	0.3	SCC	Ulcerated nodule	yes
81	TC	M	73	Right ear	1	0.45	BCC	Ulcerated nodule	yes
82	TC	M	74	Left parietal scalp	0.5	1	BCC	NA	no
83	TC	M	74	Nose	1	2	Cutaneous horn	Ulcerated nodule	yes

84	TC	M	75	Left supraclaverar region	1	0.5	BCC	Erythematous and erosive plaque	yes
85	TC	M	76	Right clavear region	1.3	0.4	BCC	Keratotic and erythematous plaque	no
86	TC	F	78	Left eyebrown	1	0.4	BCC	Nodule	yes
87	TC	M	79	Right arm	2	0.7	KA	Nodule	no
88	TC	M	83	Left cheekbone	0.8	IN SITU	BCC	Ulcerated nodule	yes
89	TC	F	84	Left eyebrown	0.8	3	BCC	Nodule	no
90	TC	M	85	Scalp	NA	2	UD Nodule	Ulcerated nodule	yes
91	TC	F	87	Thorax	2	1.1	SCC	Ulcerated nodule	yes

FIGURE LEGENDS

Figure 1 – A (PAS Diastase staining, 10x): tricolemmal carcinomas showing negativity of PAS-diastase staining; B (Cytokeratin 14, 10x): tricolemmal carcinomas showing diffuse intense positivity; C (p53, 10x): tricolemmal carcinomas showing diffuse intense positivity.

Figure 2 – Differences in growth patterns from squamous cell carcinoma (upper microphotographs), which exhibits a predominant "radial" proliferation and tricholemmal carcinoma (lower microphotographs), which shows a predominant "vertical" extension (H&E, 4x).

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AUTHORS' CONTRIBUTION

ADG, FB and MB drafted the manuscript; RG and AC analyzed histological data; EG provided clinical data; LV performed immunohistochemistry; EB and SF supervised the work. All authors read and approved the final version of the manuscriptâ€• .