

ORIGINAL ARTICLE

Immunophenotypic aspects of cylindroma and nodular hidradenoma

T Canedo,[†] MP de Almeida,[‡] T Cuzzi,[†] M Ramos-e-Silva^{†,*}

[†]School of Medicine and University Hospital, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

[‡]Sector of Dermatology, Biomedical Sciences Institute, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

*Correspondence: M Ramos-e-Silva. E-mail: ramos.e.silva@dermato.med.br

Abstract

Background Some adnexal tumours have many controversies about their histogenesis.

Objectives To evaluate the eccrine and/or apocrine differentiation phenotype in cases of cylindroma and clear cell hidradenoma with CD15 and p63 antibodies.

Methodology Slides and blocks of six cases of cylindroma and seven cases of nodular hidradenoma (clear cells) were analyzed by the technique of immunohistochemistry with CD15 and p63 antibodies.

Results In all cases of cylindroma we obtained negative results for CD15 antibody and positive for p63 antibody. In five of seven cases of nodular hidradenoma (clear cell), we could easily observe clear cells between 20% and 50% of tumour cells. In the two other cases, cystic lesions were present and occasional clear cells could be seen. The reaction with CD15 antibody was positive in granular and cytoplasmic pattern in six of seven cases, especially in cells with suggestive clear cytoplasm in lower proportion than this clear cells could be seen in haematoxylin and eosin. The positivity for p63 antibody, nuclear pattern, was observed in six of seven cases, in the major part of tumour cells. In only one case, the positivity was in 20% of cells.

Limitation Samples are in small number because these are relatively rare tumours.

Conclusions The present study suggests eccrine origin for both tumours: cylindroma and clear cell hidradenoma.

Received: 3 May 2009; Accepted 19 June 2009

Keywords

adenoid cystic, adenoma, carcinoma, cylindroma, hidradenoma, immunohistochemistry, neoplasms, sweat gland, sweat glands

Conflicts of interest

None declared.

Introduction

Adnexal neoplasias correspond to tumours of relatively uncommon occurrence. Some of these tumours, especially those of cutaneous origin, still have controversial histogenesis.

Cylindroma can occur in single or multiple forms. It affects the head, neck, and, with greater frequency, the scalp. It can also involve the skin of trunk and genitalia. When in multiple form, it coalesces and forms great plaques in mosaic pattern on the scalp, in which case they are called turban tumour.¹

In the solitary form, no familial history is present. The lesions appear in adult age on scalp and face. The multiple form is usually due to dominant heritage, and the Brooke–Spiegler syndrome should be considered, comprising an association of cylindroma and trichoepitheliomas.² The suppressor gene was identified in chromosome 16q and its loss is associated with the development of cylindromas.

Few cases of malignant transformation were described.^{3,4} Diagnosis is made by histopathology, in which the tumour is represented by cell groups of varied sizes of epithelioid cells that are usually surrounded by a periodic acid–Schiff (PAS)-positive hyaline sheath. There are two types of cells: a large type, with a moderate amount of cytoplasm, and a small one, with little cytoplasm and dark nucleus.⁵

Funding sources:

This study was supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.

Histochemical and immunohistochemical studies revealed the characteristics of both the eccrine glands and the apocrine glands.⁶ At the same time, the clear cell hidradenoma, also known, among other names, as eccrine acrospiroma, nodular acrospiroma and clear cell myoepithelioma, can be of eccrine or apocrine lineage.

Clear cell hidradenoma is considered a benign neoplasia, of slow growth, as solitary and firm nodule, with possible serous secretion, and some show tendency to ulcerate. Diagnosis is made by biopsy with histopathological examination,⁷ which reveals a well-delimited picture, comprising lobular masses with lumens of various sizes. In the solid portion of the clear cell hidradenoma, two types of cells are found: fusiform and polygonal.^{8,9} As suggested by some of its designations, the lesion would be composed of two types of cells: one with eosinophilic cytoplasm, usually more elongated, and another of a more polygonal format with a PAS-positive and clear cytoplasm. These two types of cells would be present in variable proportions in different cases, sometimes even with absence of clear cytoplasm cells.

More recently, it was proposed that the nodular clear cell hidradenoma would have an apocrine origin,^{10,11} so its name was therefore changed to apocrine hidradenoma. In the case where clear cytoplasm cells were absent, it would be considered of eccrine origin, being then called eccrine hidradenoma.

There is a scarcity of studies regarding the differentiation of this group of tumours, and, therefore, there is no certainty about its source cell. For that reason this study used an immunohistochemical investigation with the following markers: antibody CD15 (Leu-M1) for apocrine glands,¹²⁻¹⁴ and antibody p63 for eccrine glands,¹⁵ in the attempt to help in the determination of the cell that leads to the tumour.

Objectives

General

Assess the phenotype for eccrine and/or apocrine differentiation in cases of cylindroma and nodular hidradenoma (clear cell hidradenoma), through immunohistochemistry techniques, employing CD15 and P63 markers.

Specific

1. Review the histopathological and diagnostic aspects in cases of cylindroma and nodular hidradenoma included in the study.
2. Assess the standard of positivity, when present, for the two referred antibodies, in those lesions.
3. Correlate the findings obtained by the immunohistochemical technique with some aspects of the histopathological examination, in the sections stained with haematoxylin and eosin (H&E).

Materials and methods

This study was approved by the Ethics Committee in Research of the University Hospital Clementino Fraga Filho (HUCFF/UFRJ).

Samples

The samples proceeded from the Sector of Pathology of the Clementino Fraga Filho University Hospital and also from the Sector of Pathology of Pedro Ernesto University Hospital, National Cancer Institute.

The original examined glass slides were evaluated for confirmation of diagnosis and consideration of some special microscopic features, as the circumscribed nodules located in the dermis, in case of cylindromas. Those nodules consist of basaloid cell nests in maze or in a jig-saw puzzle-like arrangement. The clear cell hidradenoma can be a solid cystic lesion, with a variable proportion of cells with clear cytoplasm and eosinophilic cytoplasm.

In addition to the glass slides, the paraffin blocks were also recovered and with them it was possible to carry out new investigations.

Six cases of cylindroma and seven cases of nodular hidradenoma (clear cells) obtained through this investigation were analyzed.

Immunohistochemical technique

The paraffin blocks were cut in a microtome and the slices of 5 microns thickness were stretched on slides previously washed with a sulfur–chromium solution, emulsified with a poly-L-lysine-based adhesive (Sigma Chemical, St Louis, MO, USA), at 10% and placed in oven at 60 °C during 12 h to improve their adhesion to the slides.

After identified for each antibody, the slides were returned to the oven at 60 °C for 20 min and then placed in three xylol baths (5 min each), and in three alcohol solutions in decreasing concentrations of 95%, 70% and 50% (5 min each), pursuant to the usual histotechnical procedure, at room temperature. According to the antibody, antigen recovery followed the procedures described by the respective manufacturer's instructions.

CD15 antibody slides (CD15 antibody, Dako North America Inc., Carpinteria, CA, USA; dilution 1 : 50), were immersed in an EDTA/TRIS tampon, pH 9.0, in a water bath chamber for 30 min at 96 °C for 40 min. Afterwards, the endogenous peroxidase activity was blocked with 3% hydrogen peroxide and methanol at 70% during 20 min.

After this stage, the slides were washed in distilled water and placed on a PBS tampon at pH 7.4 with Twin20 Sigma number P7949 to reduce the 'background' in three 5-min baths each. In sequence, the cuts were cycled with a hydrophobic Dako pen no. S2002 to avoid that they ran off, and incubated for 20 min with a blocker for unspecific proteins Dako no. X0909, to inhibit unspecific reactions. After that, the excess was drained and the previously diluted antibodies were applied in a PBS–Twin-20 solution.

The detection system employed was Advance HRP (Dako North America Inc.), a polymer used in detection of antigens present in low concentrations. This system is free of biotin.

Subsequently a diaminobenzidine chromogen (Dako North America Inc.) was added for a mean time of 30 s to 1 min. Afterwards the slides were washed in distilled water and counterstained

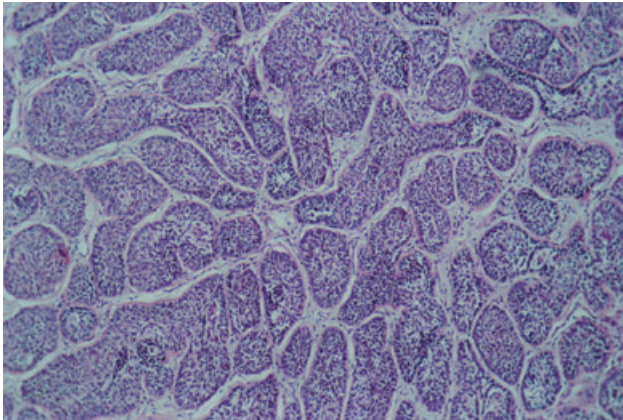


Figure 1 Cylindroma: juxtaped groups of tumoral cells with relatively scarce cytoplasm. (haematoxylin and eosin, obj. $\times 10$)

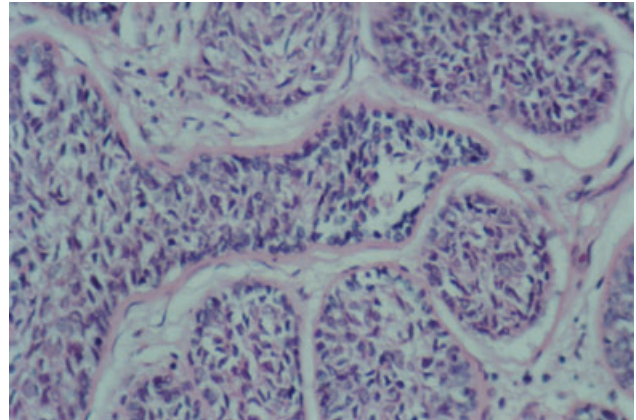


Figure 2 Cylindroma: eosinophilic hyaline band surrounding groups of tumoral cells. (haematoxylin and eosin, obj. $\times 40$)

in Harris' haematoxylin, turned blue in flowing water, dehydrated in alcohol with increasing concentrations and xylene, and mounted with Damar gum (Proquimios, Bangu, Rio de Janeiro, Brazil).

The positive reaction is detected by a brownish precipitate. Antibody CD15 has a cytoplasmic and membrane marking, while antibody p63 presents nuclear marking.

Histological sections from two cases of syringoma were used as positive control for antibody p63 and sections from two cases of apocrine hidrocystoma were used as positive control for antibody CD15. Each of these tumours reacted with both antibodies in order to also obtain negative-control reactions.

Results

The histological sections stained with H&E showed in the six cases of cylindroma a tumour comprising numerous nests of epithelial cells, of varied sizes and forms, separated by a hyaline sheath (Fig. 1). The nests are made of two types of cells: those with small hyperchromatic nucleus, located mainly in the periphery of the nests, in a palisade-like disposition; and cells with large nucleus, clearer, present in the middle of the nests. Tubular lumens were observed occasionally (Fig. 2).

In these six cases, there was negative reaction to antibody CD15 (Fig. 3), while the reaction was positive in all cases for antibody p63 (Fig. 4). Positivity was observed in nuclear pattern, comprising the majority of the tumour cells in each case (Fig. 5).

In five of seven cases of the nodular hidradenoma studied, in the histological sections stained with H&E, the presence of clear cells was easily observed, comprising between approximately 20% to 50% of the tumour cells (Figs 6 and 7). In two cases, the tumour was predominantly composed of cells with eosinophilic cytoplasm and only rare cells with clear cytoplasm were observed. In those two cases, the lesion was predominantly cystic (Fig. 8).

The reaction with antibody CD15 for that group was negative in one case and positive in the remainder, especially evidenced in

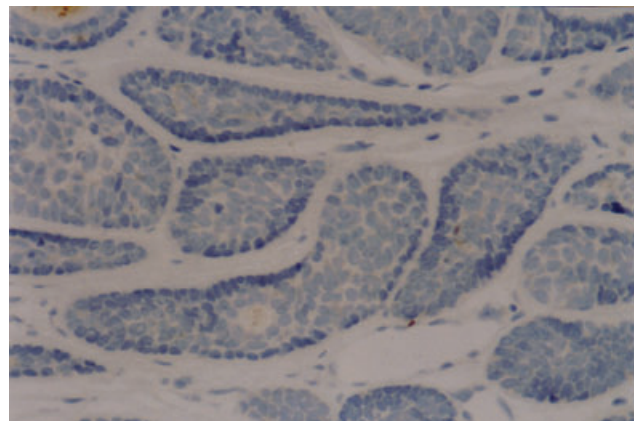


Figure 3 Cylindroma: negative reaction for antibody CD15. (immunoperoxidase, obj. $\times 40$)

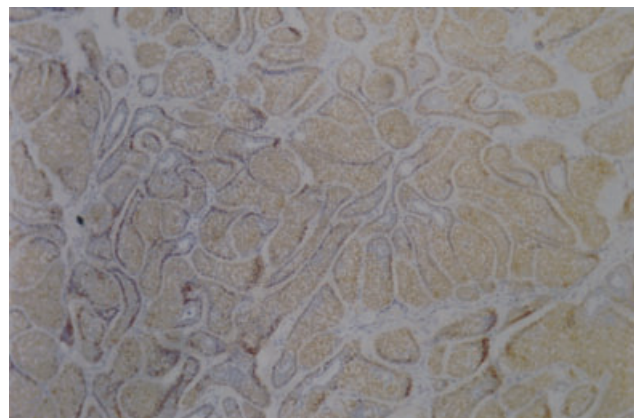


Figure 4 Cylindroma: positive reaction for antibody p63 in the majority of tumoral cells. (immunoperoxidase, obj. $\times 10$)

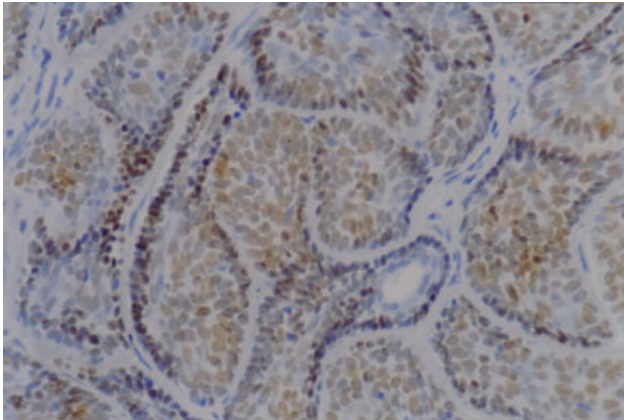


Figure 5 Cylindroma: positive reaction for antibody p63 in nuclear pattern in the majority of tumoral cells. (immunoperoxidase, obj. $\times 40$)

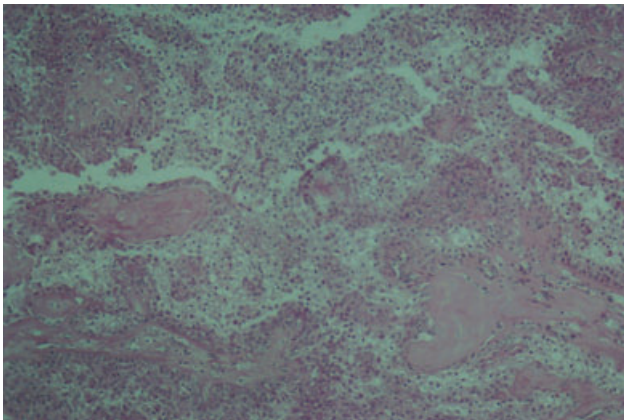


Figure 6 Clear cell hidradenoma: note clear cells and non-clear cells, and the typical hyaline stroma. (haematoxylin and eosin, obj. $\times 10$)

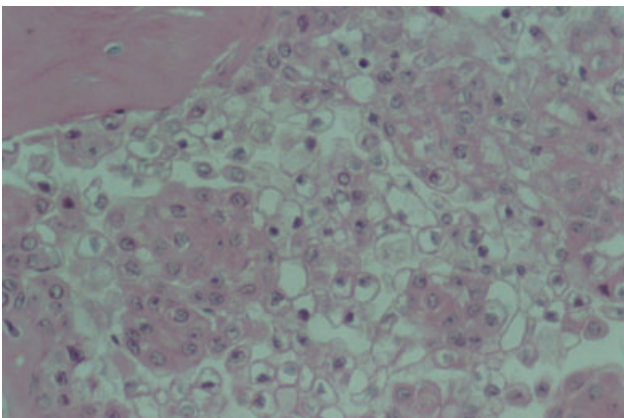


Figure 7 Detail of the previous figure as evidence of clear cells and non-clear cells. (haematoxylin and eosin, obj. $\times 40$)

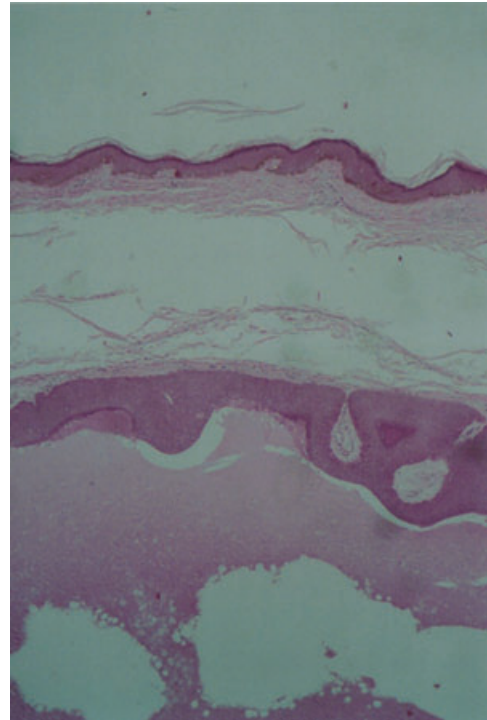


Figure 8 Clear cell hidradenoma: predominantly cystic lesion. (haematoxylin and eosin, obj. $\times 4$)

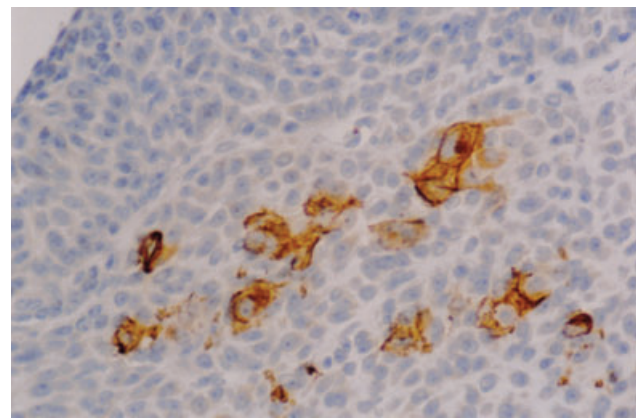


Figure 9 Clear cell hidradenoma: positivity for antibody CD15, granular pattern in cytoplasm with membrane accentuation, involving polygonal cells, with large cytoplasm. (immunoperoxidase, obj. $\times 10$)

cells with an aspect suggestive of clear cytoplasm. This positive reaction in the cells with apparently clear cytoplasm compromised a smaller proportion of the cells with clear cytoplasm components of the tumour, as observed in those with H&E stain (Fig. 9). Thus for instance, in one of the cases (case 4), the H&E stain evidenced 50% of clear cells, and CD15 was positive in less than 10% of the tumour mass.

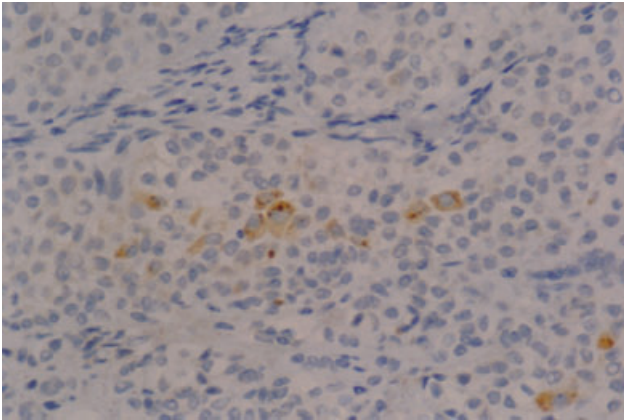


Figure 10 Clear cell hidradenoma: positive reaction for antibody CD15 in cells of suggestive clear cytoplasm in the cystic tumoral luminal space. (immunoperoxidase, obj. $\times 40$)

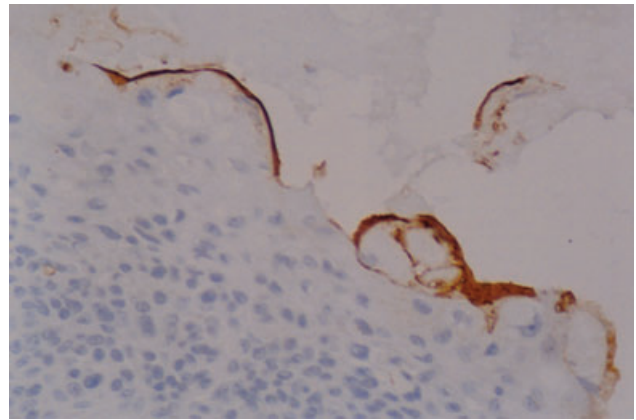


Figure 12 Nodular hidradenoma: positivity for antibody CD15 in cytoplasmic pattern. Note adjacent negative cytoplasm cells. (immunoperoxidase, obj. $\times 40$)

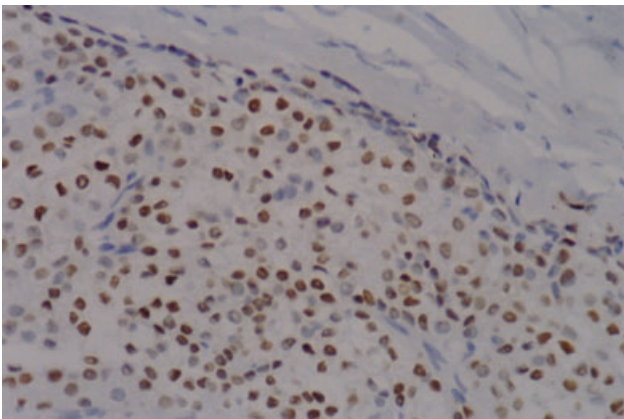


Figure 11 Nodular hidradenoma: positive reaction in nuclear pattern for antibody p63 in the majority of tumoral cells. (immunoperoxidase, obj. $\times 40$)

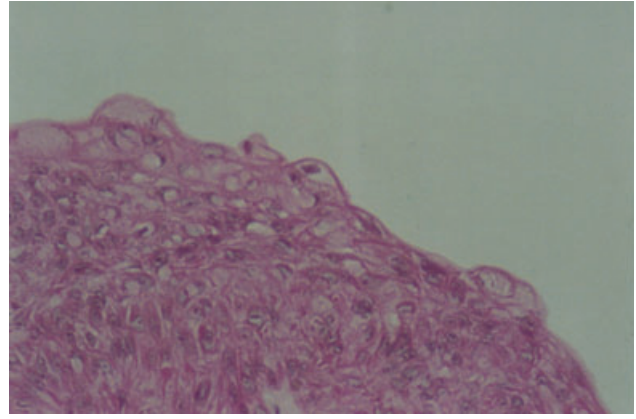


Figure 13 Clear cell hidradenoma: tumoral epithelium of the cystic space covering with clear cytoplasm cells in the luminal border. (haematoxylin and eosin, obj. $\times 40$)

In the two cases of nodular hidradenoma where the clear cell population was scarce and where the tumour was predominantly cystic, a positive reaction for antibody CD15 was noted in a few cells lining the cystic space (Fig. 10). A new assessment of the histological sections stained with H&E showed presence of clear cytoplasm cells in that same location (Fig. 11).

The positivity observed with that antibody showed a fine granular form, with prominence in membrane (Fig. 10), and with a cytoplasmic pattern (Fig. 12).

Still in this group of tumours, positivity for antibody p63 was noted in all cases, comprising the majority of the tumour cells, in a nuclear pattern (Fig. 13), with exception of a single case, where positivity was noted in about 20% of the proliferating cells.

The histological syringoma sections (positive eccrine control) that reacted with antibody p63 evidenced positive reaction in the

tumoral cells in a nuclear pattern (Fig. 14). The use of antibody CD15 resulted in negative reaction in that lesion. The histological sections of apocrine hidrocystoma (positive apocrine control) which reacted with antibody CD15 evidenced a positive reaction in the tumour cells, in a granular cytoplasmic pattern, with accentuation of membrane (Figs 15 and 16). In this situation, linear cytoplasmic positivity was also observed in short cuboidal cells lining the luminal spaces (Fig. 17). The use of antibody p63 resulted in a negative reaction in this lesion.

The details of the markings are given in Tables 1 and 2.

Discussion

Some cutaneous adenomas have a controversial histogenesis.

Eccrine and apocrine glands show different antigenicity and antigen expression of their descendent cells. This is often retained

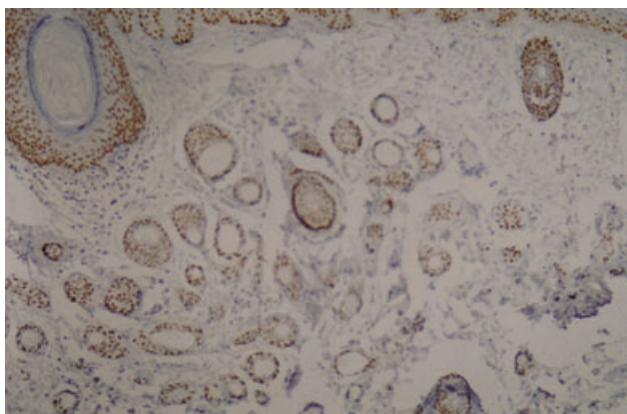


Figure 14 Syringoma. Histological syringoma section with positive reaction for antibody p63, in nuclear pattern – positive control. (immunoperoxidase, obj. $\times 10$)

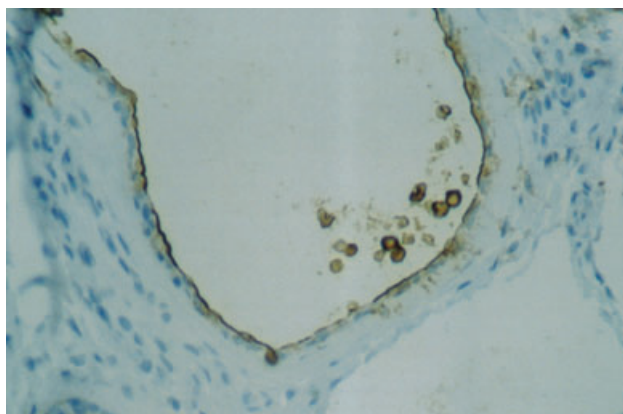


Figure 17 Apocrine hidrocystoma. Positive reaction for antibody CD15 in granular pattern with accentuation of membrane in product from glandular secretion and in luminal cover cells of the tumour. (immunoperoxidase, obj. $\times 10$)

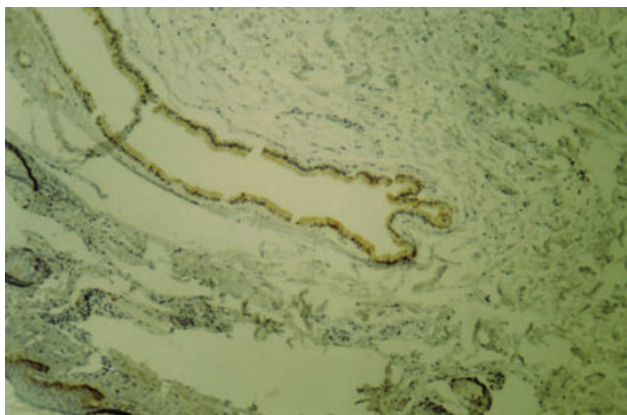


Figure 15 Apocrine hidrocystoma: positive reaction for antibody CD15 in granular cytoplasmic pattern. (immunoperoxidase, obj. $\times 10$)

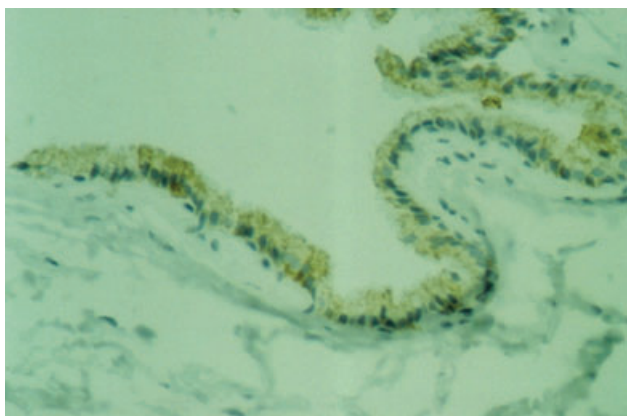


Figure 16 Detail of the foregoing figure. (immunoperoxidase, obj. $\times 40$)

Table 1 Cylindroma: immunohistochemical marking by CD15 and p63

	CD15	P63
Case 1	–	+
Case 2	–	+
Case 3	–	+
Case 4	–	+
Case 5	–	+
Case 6	–	+

in the generated neoplasia so the immunohistochemical method would be a good way to classify the tumours of the sweat glands.¹⁶

Some markers have been used for apocrine differentiation, as GCDFP-15,^{17,18} lysozyme,¹² TAG-72,¹⁹ and for eccrine differentiation, as PRP²⁰ and CEA.²¹ In the present study, PRP was initially chosen to be used as marker for eccrine glands; however, results were unsatisfactory (data not shown).

According to Bumgardner *et al.*, the association of cylindromas and trichoepitheliomas in a same patient, or combined in a single lesion, suggests a cell with a common source. The coexistence of those two tumours suggests that cylindroma has an apocrine origin. However, the occurrence of eccrine spiradenomas in patients with the Brooke–Spiegler syndrome and its coexistence with cylindromas, in the so-called spiradenocylindroma, questions the eccrine origin of the cylindroma.²²

Meybehm and Fisher, in histochemical analyses, suggest that cylindromas and spiradenomas may originate from both eccrine and apocrine glands, originating from a multipotential stem cell, similar to that associated with trichoepitheliomas, supporting therefore the theory of apocrine follicle sebaceous unit, which would explain the association of the three tumour types.²³

Table 2 Clear cells hidradenoma: immunohistochemical marking by CD15 and p63 and comparison of the percentage of clear cells present with haematoxylin and eosin (H&E) stain

	H&E	CD15	P63
Case 1	30% clear cells	> 30% clear cells	+ nuclear pattern
Case 2	50% clear cells	–	+ 70%
Case 3	40% clear cells	+ focal	+ 50%
Case 4	> 50% clear cells	< 10%, cytoplasmatic and focal of membrane	+ 50% nuclear pattern
Case 5	Few clear cells in border (cystic)	Linearity of membrane surrounding cystic area (> half)	< 50%
Case 6	Few clear cells in border (cystic)	Linearity of membrane surrounding cystic area (focal)	+ 50%
Case 7	50% clear cells	Focal, cytoplasmatic and focal of membrane. 20% stained = H&E	+ 80%

There is a report of a case of malignant cylindroma of the external ear canal and, in that topography, there are no eccrine glands. The sebaceous glands of the ear in the external auditory canal, in embryology, develop in association⁴ with the growth of the hair follicle and represent a modified apocrine sweat gland.

Requena and collaborators reported association of cylindroma with some benign tumours of the parotid, and consider their histopathological findings similar to those of cylindromas, suggesting a relation between them and the apocrine origin for cylindromas.²⁴

Immunohistochemical studies showed that the differentiation in cylindromas includes apocrine and eccrine gland elements and strongly suggests the possibility of a common progenitor capable of the eccrine or apocrine differentiation.

In the present study, the six cases of cylindroma were positive for antibody p63 and negative for antibody CD15. These findings favour the eccrine histogenesis for this group of tumours.

In case of the nodular hidradenoma neoplasias (clear cells), many controversies about their histogenesis also exist. Ohnishi and collaborators, in a study on the histogenesis of that tumour, observed eccrine differentiation, and assumed that eccrine poroma and hidradenomas would be in the same spectrum, whose main difference would be the presence of clear cells and the degree of differentiation in the cells of the eccrine ducts.^{25,26} Others, as Ângulo and collaborators¹¹ and Knoedler and collaborators,²⁷ are in favour of apocrine differentiation, for presence of secretion by decapitation.

According to Requena and collaborators, the hidradenoma presents apocrine differentiation for the following reasons: the clear cells can be found in neoplasia of eccrine, apocrine, follicular and sebaceous nature; enzymatic studies are not subject to replication and unreliable regarding a differentiation for eccrine or apocrine origin; ultrastructural studies are not reliable in detecting the tissue source or its differentiation, because the findings vary according to the portion of the gland and its activity; apocrine secretion has to be well defined to differentiate the eccrine glands; small cells present in apocrine neoplasia are different from those found in eccrine poroma; polygonal cells present in neoplasia also appear in other apocrine neoplasia, such as mixed apocrine cutaneous tumours; mucinous cells present are also found in

other apocrine tumours; connections between tubular structures and the infundibulus suggest apocrine nature.

Hidradenomas have been classified into two groups: one with eccrine differentiation (poroid hidradenoma), and the other with apocrine differentiation.^{8,26}

In the cases of nodular hidradenoma (clear cells) analysed, p63 was positive in all samples, and in six of seven cases, it was positive in at least 50% of the tumour cells, for each case. On the other hand, positive CD15 cells were seen in a quite focal manner. These positively stained elements were interpreted as corresponding to a smaller proportion of cells with clear cytoplasm. In two of the cases, the positively stained cells delimited the luminal tumour space. The close morphological parallel between the pattern of positivity found for CD15 in these tumours and that observed in control group corroborates the indication of this marker as a signal for apocrine differentiation and corroborates also the opinion of some authors^{10,11,27,28} that the presence of clear cytoplasm cells in clear cell hidradenoma would be indicative of apocrine differentiation.

We found also interesting, however, that CD15 positive reaction was seen in a smaller proportion of the cells as compared with those with a clear cytoplasm seen in H&E stained slides as we showed in cases 1, 3, 4 and 7.

In case 2 approximately 50% of tumour cells had clear cytoplasm in H&E, while CD15 antibody resulted negative.

In addition, an eccrine phenotype was demonstrated, albeit not exclusive, but widely predominant. The focal positive reaction for the CD15 antibody was a most unexpected and point out to two questions: one related to the correspondence of clear cytoplasm to apocrine differentiation, and the other related to the specificity and sensibility of the applied antibodies, for which a few references could be found.

Conclusion

The positive marking for p63 antibody observed in cylindroma and the absence of positive reaction for the CD15 antibody in this group of tumours favour an eccrine histogenesis for such lesions.

The positive marking for antibody p63 observed in most nodular hidradenomas together with focal positive reaction to CD15

antibody may indicate a predominantly eccrine differentiation with focal apocrine phenotype.

These results give another view on a subject that is still controversial.

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