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Advanced differentiation in trichoepithelioma and basal cell carcinoma investigated by immunohistochemistry against neurofilaments

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Abstract: Basal cell carcinoma (BCC) and trichoepithelioma (TE) are sometimes diagnostic challenges for the pathologist in terms of their differential diagnosis. Although literature is quite rich in information about histologic and immunohistochemical clues to distinguish the differences between both, no single finding must be completely reliable. Moreover, some consider that TE is a better differentiated follicular tumour, while BCC represents a less developed stage in differentiation. For instance, the latter opinion is supported by the evidence of follicular papillae in TE. The formation of a perifollicular nerve plexus happens later than the formation of the follicular papillae in the development of a normal follicle. The study of the presence of the perifollicular nerve plexus in both tumours which could then provide us with evidence on the stage of differentiation of both tumours. 5 cases of TE and 10 cases of BCC were randomly selected from our archives and an immunohistochemical study for neurofilaments was performed in all the cases. We found a peritumoural nerve plexus in all the cases (TEs and BCCs). Since this plexus is a late sign of differentiation and since both types of neoplasias share it, we conclude that TE and BCC are both terminally differentiated neoplasms. The ability of BCC to infiltrate would have more to do with the acquisition by the tumour of such a property, rather than with a stage of indifferentiation.

Keywords: neurofilament, trichoepithelioma, basal cell carcinoma

Introduction

Distinguishing between trichoepithelioma (TE) and basal cell carcinoma (BCC) is sometimes a very difficult task. Literature is full of reports that offer diagnostic clues, but the fact that many of those clues are immunohistochemical [1-11], ultrastructural [12] or even molecular [13], gives the idea that the subject is far from being simple.

Although most agree that TE and BCC show follicular differentiation, some consider that both entities represent different stages of differentiation: TE would represent a more developed stage of differentiation. The fact that TE shows papillary mesenchymal bodies while BCC does not, would support that hypothesis.

In this study, we focussed our attention on the existence of a peritumoural nerve plexus. In the normal development of the hair follicle, a perifollicular nerve plexus develops after the follicular papilla appears [14] (Fig. 1). This latter fact means that the evidence of the plexus is a finding indicative of later differentiation than the one that follicular papilla indicates. The evidence of such a plexus around TE and BCC, or its absence in any of those entities, might be then contributive in supporting or contradicting the hypothesis of TE as a better differentiated entity than BCC.

Materials and methods

We randomly selected 5 TE and 10 BCC from our archives and checked the slides in order to confirm the diagnosis. All the cases had been diagnosed with routine techniques (H+E), and classified according to the criteria that are described in the book of Lever´s histopathology of the skin [15]. We also tested the existence of a peritumoural nerve plexus with an immunohistochemical study for neurofilaments (Dakocytomation mouse anti-human antibody against neurofilament protein, clone 2F11; code M0762) in all the cases.

Results

In all the cases, the original diagnosis was confirmed (5 TE and 10 BCC). All TE were conventional. Seven

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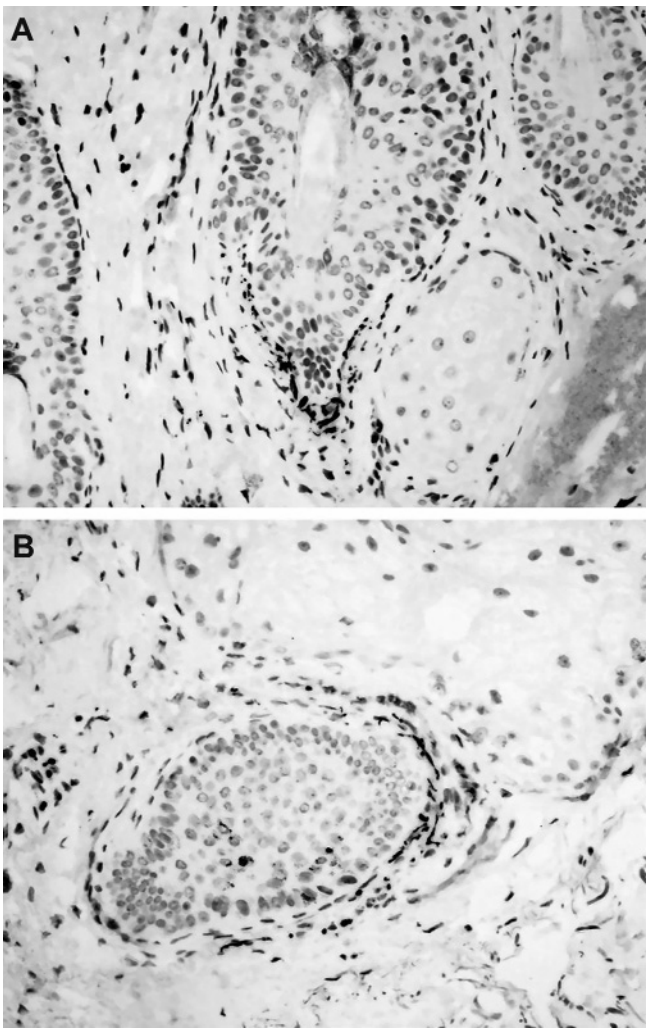

Fig. 1. Nerve plexus around a normal follicle. **A**. vertical section. **B**. transversal section (original magnification ×20).

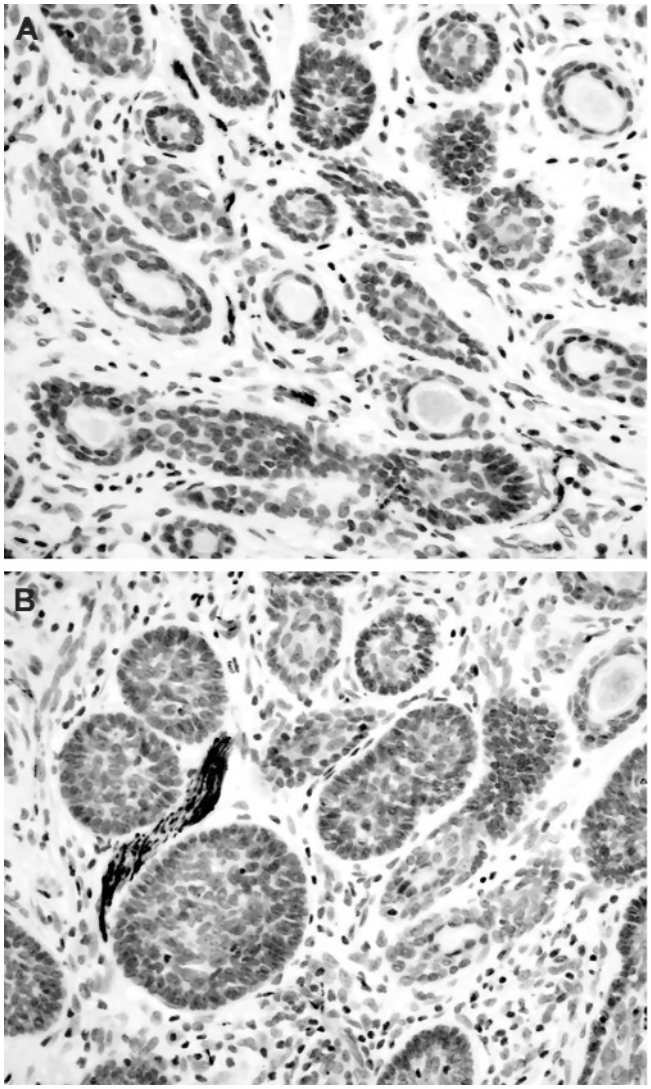

Fig. 2. Nerve plexus around two cases of trichoepithelioma. The fibres were scarce in some areas (**A**), while arranged in small groups in others (**B**) (original magnification ×20).

BCC belonged to the solid circumscribed variant; two of them were diagnosed as the solid infiltrative variant; one of them belonged to the morphea-like variant.

The details about the patients plus the location of the lesions are shown in Table 1. The immunostaining for neurofilaments showed a similar pattern in all the cases: a peritumoural nerve plexus was evident and was focally around tumoural islets, either of TE (Fig. 2) or of BCC (Fig. 3), mimicking the one evidenced in the normal follicle (Fig. 1). The plexus was either made of sparse fibres (Fig.3) or small groups of fibres (Fig. 1), and although its density slightly varied from case to case, the pattern was similar to the one observed around normal follicles.

Discussion

The distinction between basal cell carcinoma (BCC) and desmoplastic trichoepithelioma (TE) is not always easy. Literature is fully provided with many histological criteria in the differential diagnosis between both entities [16-20]. Nevertheless, the subject is far from being simple, taking into account the number of immunohistochemical studies [1-11], studies in molecular pathology [13], in immunofluorescence [21], or in ultrastructural pathology [12] that have focussed their attention on these different techniques for distinguishing both tumours from each other. The distinction is more important (although many times also very difficult) in small biopsies from delicate areas of the skin, such as the periocular tissues, owing to the different management of both tumours[22].

Many of the studies mentioned above have mainly focussed on the phenotype of the tumoural cells [2,3,5,6,9-11] including their proliferation rate [9]. Nevertheless, some other groups have also evaluated the expression of certain immunohistochemical mark-

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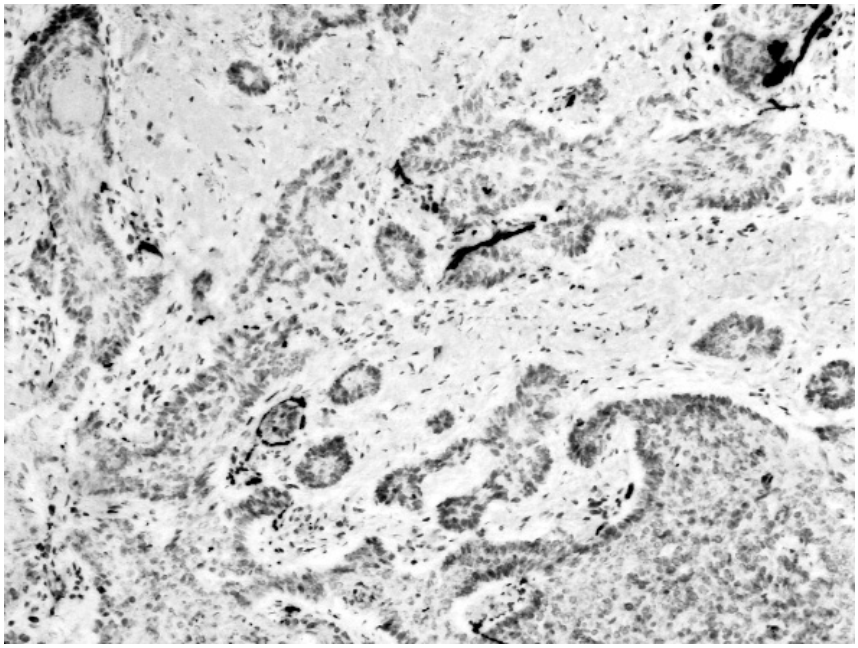

Fig. 3. Nerve plexus in a case of BCC, in which the fibres can be seen surrounding many of the tumour islets, with a spare distribution (original magnification ×10).

Table 1. Cases in which the peritumoral plexus were investigated with immunohistochemistry.

Case	Gender	Age	Tumor	Location
1	Male	88	BCC, nodular	Right paranasal area
2	Female	80	BCC, infiltrating	Upper lip
3	Male	74	BCC, nodular	Infra-auricular area
4	Male	80	BCC, nodular	Pre-auricular area
5	Female	78	BCC, nodular	Left Nasogenian fold
6	Male	80	BCC, nodular	Face
7	Male	75	BCC, infiltrating	Right nasogenian fold
8	Female	90	BCC, nodular	Left nasogenian fold
9	Male	77	BCC, morpheiphorm	Dorsal aspect of the nose
10	Male	74	BCC, nodular	Dorsal aspect of the nose
11	Female	45	Trichoepithelioma	Forehead
12	Male	69	Trichoepithelioma	Nose
13	Female	80	Trichoepithelioma	Left parietal side of the head
14	Male	82	Trichoepithelioma	Lower eyelid of the right eye
15	Female	69	Trichoepithelioma	Back

ers in the tissues surrounding the tumoural cells, like the stroma [1,3,4,11,21] or the basal membrane [21].

In our study, we focussed on a well known fact in normal histology, that nerve endings form a rich plexus around normal hair bulbs[23].

Some embryology studies have demonstrated that although some scattered nerve fibres appear before any morphological evidence of hair follicle development exists [24], a proper perifollicular nerve plexus appears ontologically after the development of the follicular papilla [14].

Many authors have remarked that TE and BCC probably have a common origin from pluripotential cells that develop towards hair structures [19,25-29]. According to some, both neoplasms would differ in their degree of differentiation, since TE would present a higher degree of differentiation, plus a more abundant peri-tumoural stroma [28]. One of the well recognized histological

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clues in the recognition of trichoepithelioma is the presence of papillary mesenchymal bodies [17]. The latter finding is only occasionally found in BCC [17]. The hair bulb formation appears to be even more exclusive, which seems to be a "privilege" of TE over BCC [17]. All these findings would agree with the argument that TE is a more differentiated expression of a follicular tumour. Nevertheless, the finding of a peritumoural nerve plexus in TE as well as in BCC seems to indicate that the stage of differentiation of both types of tumours is quite advanced. According to this, the main difference between the two tumours will be the malignant invasive potential of BCC. Although that might not necessarily be related to its degree of differentiation, but to changes in the phenotype of its cells with the acquisition of such an invasive potential.

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