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Trichoepithelioma Multiplex: A Study of the Relationship between the Anatomical Location and the Histopathological Features

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Authors' contributions

This work was carried out in collaboration between the Department of Dermatology (Dr. D. Tenea) and Anatomical Pathology Unit (Dr. M. Louw). The author DT conceived and designed the study, collected data, interpreted the findings, reviewed the slides and clinical histories and wrote the manuscript. The author ML reviewed the histology slides and assisted in approving the final draft of the manuscript.

Research Article

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ABSTRACT

Trichoepithelioma multiplex is a rare, benign cutaneous genodermatosis of disputed histogenesis, consisting of tumors of trichogenic origin.
Aim: To explore the relationship between the anatomical location and the histopathological features of the trichoepitheliomas in a patient cohort with Trichoepitheliomamultiplex.
Methods: The study was conducted over the period 1995-2008 at the tertiary Dermatology and Anatomical Pathology referral centers of the University of Pretoria. The clinical and pathological features of confirmed cases were assessed. Sixty four H&E stained sections from skin lesions distributed over different body areas were examined with regard to 16 histopathological parameters for the evidence of follicular differentiation and features useful in distinguishing trichoepithelioma from basal cell carcinoma. Special stains were employed for the demonstration of mucin (PAS, Alcian blue) amyloid (Congo red) calcium (Von Kossa) and epithelial structures (AE1/AE3-CK antibodies).
Results: Trichoepithelioma multiplex was an uncommon diagnosis (20 patients). African patients were preponderant (16 vs.4 Caucasians) with slight male predominance (11 vs. 9

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females). Sporadic cases prevailed (15 vs. 5 familial cases).A wide variation in the severity of the clinical presentation was observed, young black males and familial cases being more severely affected. The face was involved in all cases (30 biopsies), followed by the scalp and back (13 biopsies each) and the neck (8 biopsies). There were variations in histopathological patterns with considerable overlap between them. Special stains differentiated between the tumours from different body areas with the exception of AE1/AE3-CK antibodies. Foreign body reactions were common in lesions showing many keratinous cysts and follicular damage. Trichoepithelioma was seen in relation to a benign pigmented intradermal nevus in one biopsy and adjacent to a basal cell carcinoma in two cases

Conclusion: A positive correlation could be established between the histopathological pattern of trichoepitheliomas and the body area from which the lesions were removed.

Keywords: Trichoepithelioma multiplex; familial multiple trichoepitheliomas; trichoblastoma; papillary mesenchymal bodies.

1. INTRODUCTION

Trichoepithelioma multiplex (TEM) is a rare, benign cutaneous genodermatosis, best classified as poorly differentiated hamartomas of the hair germ (trichogenichamartomas). In the latest WHO classification [4] trichoepithelioma is regarded as a variant of trichoblastoma.

Since the original description of multiple trichoepitheliomas in 1892 by Brooke and Fordyce, much controversy existed about its histogenesis and biological behaviour [1,2,7,9,24] The most accepted view is that multiple trichoepitheliomas develop from the undifferentiated germinative cells of folliculo-sebaceous-apocrine units that show varying degrees of follicular differentiation [10]. The genetic basis of TEM remains elusive. Half of the cases are sporadic. Familial cases show autosomal dominant inheritance with the onset of the disease around the puberty [3,9,24].

TEM shows a distinct clinical appearance consisting of multiple skin coloured papules and nodules with a predilection for the central face. The condition was reported mainly in Caucasians. There were few reports in Oriental and African patients [15,16,17].

The course is usually benign. Complications were seldom reported (ulceration, infection, malignant transformation). Despite being benign, multiple trichoepitheliomas pose cosmetic and sometimes functional problems.

Treatment modalities are limited, with inconsistent results and frequent recurrences.
The current study aims to demonstrate whether significant histological differences exist among the trichoepitheliomas located in different body areas.

To the best of our knowledge there are no comparable data in the medical literature, particularly in patients with dark skin.

2. MATERIALS AND METHODS

The study was conducted during the period 1995-2008 at two tertiary hospitals in Pretoria area.

Eight patients were seen prospectively, 12 were assessed retrospectively.

Sixty four H & E stained sections from lesions located in different body areas were examined according to 16 histological parameters for the evidence of follicular differentiation (follicular structures, keratinous cysts, papillary mesenchymal bodies) and features useful in distinguishing trichoepitheliomafrom BCC (stromal retraction, peripheral palisading, tumor necrosis, ulceration, brisk mitotic figures)(Adnexa1).

Special stains were employed in 17 of 20 cases for the demonstration of mucin (PAS, Alcian blue), amyloid (Congo red), calcium (Von Kossa) deposits and epithelial structures (AE1/AE3- CK antibodies). Because of the lack of adequate archival tissue blocks for 3 cases, special stains were not attempted.

3. RESULTS

The study showed that trichoepithelioma multiplex was an uncommon diagnosis (20 patients entered the study).

African patients were preponderant (16 vs. 4 Caucasians) with a slight male predominance (11 males / 9 females). There was a wide age range at the time of diagnosis (13 to 74 years) with a mean age of 33 years.

The majority of the patients reported the onset of lesions at puberty.

Most of the analysed cases were sporadic (15 patients). A positive family history was identified in 3 families (5 patients). African male patients and familial cases were more severally affected (Fig. 1; Fig. 2a-2b).Thirty skin specimens were collected from the face, 13 from the scalp, 13 from the back and 8 from the neck. The face was affected in all cases, followed by scalp, back, and neck.

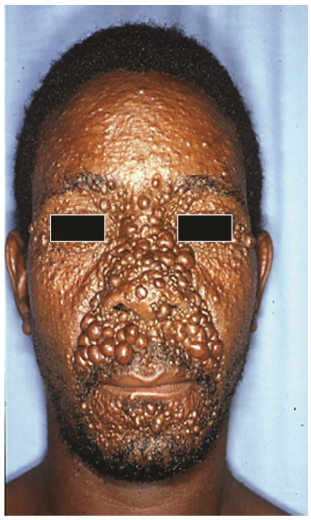

Fig.1. Young African man with severe disease (sporadic case)

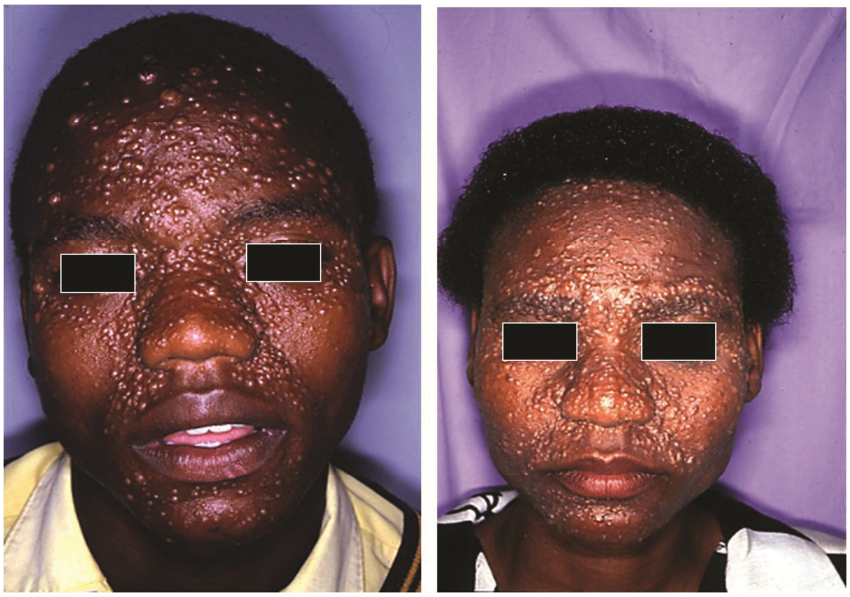

Fig. 2a. Multiple familial trichoepitheliomas: brother and sister

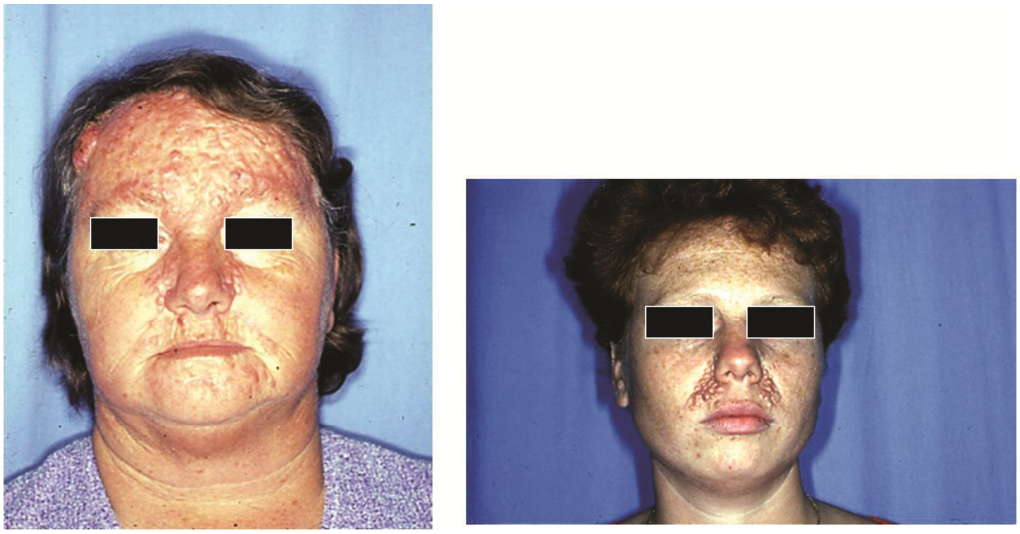

Fig. 2b. Multiple familial trichoepitheliomas: mother and daughter

Note the large nodule on the forehead with telangiectatic, erosive surface covered with crusts

The analysed skin specimens showed variable histopathological patterns ranging from a lace-like network or a cribriform pattern seen mainly on the face and scalp, to a solid pattern (islands and strands of monomorphousbasaloid cells seen chiefly on the neck and upper back [Fig. 3a]. Deeply sited tumors with a desmoplastic pattern were found in 3 cases [Fig. 3b].

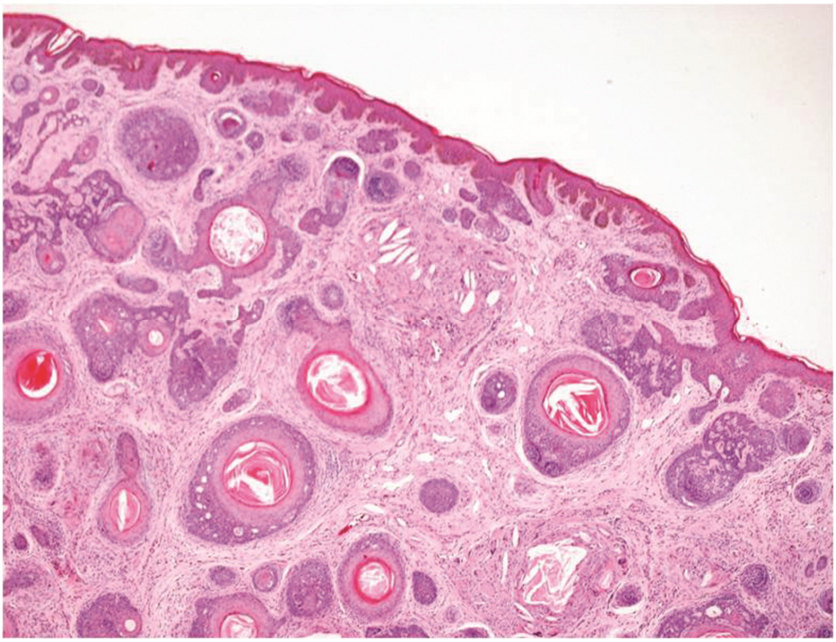

Fig. 3a. Low power view of a pattern characterized by the presence of many keratinized cysts and granulomatous foreign body reaction

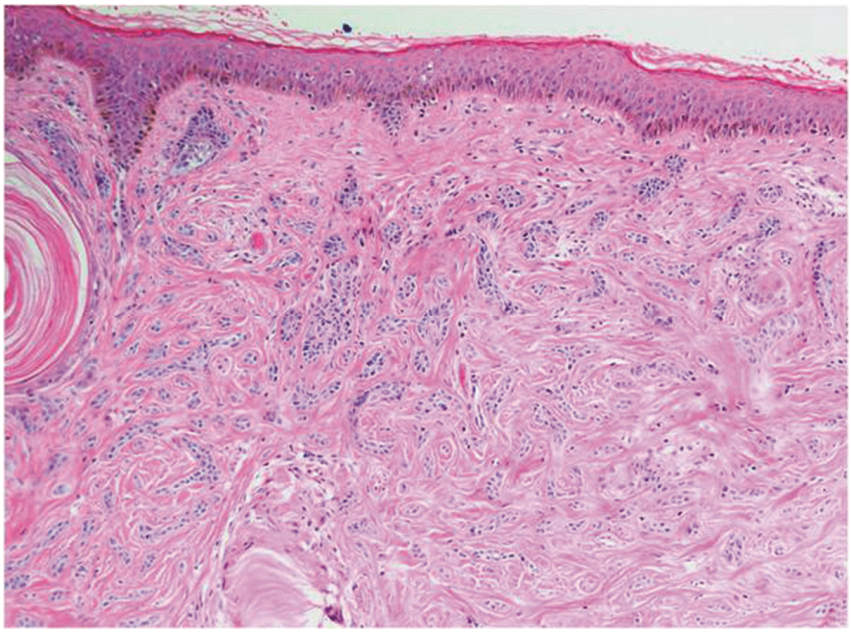

Fig. 3b.Desmoplastic trichoepithelioma

Considerable overlap between these patterns was seen resulting in a mixed histological picture.

Nearly all examined trichoepitheliomas (with the exception of 4 cases) regardless of their anatomical location, exhibited at least a hint of follicular differentiation, usually in the form of follicular germs and papillae (limited differentiation). In 28 of 64 examined specimens, the tumour aggregates assumed a more advanced degree of follicular differentiation especially lesions from the scalp and back.

Papillary mesenchymal bodies (PMB), usually common in trichoepitheliomas varied in size, shape and number. A striking difference was not found in relation to the anatomical location of the tumours [Table 1].

Keratinous cysts were present in a variable numbers and sizes in both lobules and stroma in 56 of 64 biopsies. Numerous small keratinous cysts were seen in all facial lesions (Fig. 3a). When present, large keratinous cysts were demonstrated on the upper back and neck. The scalp showed a variable number (few-to-many) and size (small-to-large) of keratinous cysts.

The vast majority of the tumour aggregates showed focal peripheral palisading of their basaloid cells (29/64); this was more evident in the lesions from face (17/30). A continuous pattern of palisading was demonstrated in deeper and larger tumours (21/64) mainly from the back (9/13).

A fibrotic stroma was demonstrated in 34 specimens (especially the lesions excised from the face (14/30) and back (13/13).

A predominantly fibromyxoidperitumoralstroma was seen on the scalp and neck (22 biopsies).

Stromal retraction from the tumour aggregates was lacking in 33 biopsies and was focally present in 27 biopsies, majority from the face (18/30).

A continuous artefactual clefting surrounding the tumour islands was seen in 4 cases, all from the face.

A sparse interstitial inflammatory infiltrate consisting predominantly of lymphocytes, with occasional plasma cells and histiocytes was seen in 28/64. Granulomatous foreign body reactions were identified in 27/64 biopsies. They were common in lesions showing many keratinous cysts in close proximity to ruptured cysts [Fig. 3a]. The reactions predominated on the face (13/30), followed by the scalp (9/13), back (4/13) and neck (1/8). However, they were more severe on the scalp.

Relevant histological findings regarding the deposition of mucin, calcium, amyloid within the tumour and/or in the stroma / foreign body granulomas are summarized in Table 1.

Table 1. The site of the lesions

Histopathological Parameters		Face	Scalp / Behind the Ear	Neck	Upper Back
1	*Epidermal continuity*	Present: 20/30 Focally present: 8/30 Absent: 2/30	Focally present: 4/13 Absent: 9/13	Absent: 8/8	Absent: 13/13
2	*Follicular structure formation*	Present: 8/30; Attempts:18/30 Absent: 4/30	Present: 12/13 Attempts: 1/13	Present:2/8 Attempts: 6/8	Present: 6/13 Attempts: 7/13
3	*Horn cysts*	Present in all ; variable sizes (S→L) ; small cysts predominate	Variable size (S→L) and number (few →many)	Variable size (S→L) ; large cysts predominate; few	Absent: 9/13 Present: 4/13 (large cysts predominate)
4	*PMBs*	Variable: absent to many	Attempts predominate 1-2 PMB present in each specimen	Attempts of PMB formation > well- formed PMBs	PMB: absent Majority: occasional attempts
5	*Peritumoral stroma*	Fibrotic : 14/30 Fibromyxoid : 11/30 Myxoid : 5/30	Fibrotic : 5/13 Fibromyxoid : 6/13 Myxoid : 2/13	Fibrotic : 2/8 Fibromyxoid : 5/8 Myxoid : 1/8	Fibrotic stroma : 13/13)
6	*Stromal retraction*	Absent : 8/30 Poorly formed : 18/30 Continuous : 4/30	Absent : 9/13 Poorly formed : 4/13	Absent : 5/8 Poorly formed : 3/8	Absent : 11/13 Focally present : 2/13
7	*Tumor pattern*	Mixed (nests, strands, cribriform, small solid aggregates)	Considerable variation (lace-like / cribriform pattern to strands/ solid pattern	Solid pattern > lace-like	Solid pattern > lace-like (small islands/nests in a desmoplastic stroma
8	*Palisading of basaloid cells*	Focally present : 17/30 Continuous : 8/30 Absent : 5/30	Discontinuous : 7/13 Well formed : 4/13 Absent : 2/13	Focally formed : 3/8 Absent : 5/8 Continuous : not seen	Partially formed : 2/13 Well formed : 9/13 Absent : 2/13
9	*Mucin deposition*	PAS+ T > S : 17/23 Alcian blue + S > T : 6/23 Lacking stains: 7 Bx.	PAS+ T > S : 8/12 Alcian blue + S > T : 4/12 Lacking stains: 1 Bx	PAS+ T > S : 4/6 Alcian blue + S > T : 2/6 Lacking stain: 2 Bx	PAS + S >T : 9/11 Alcian blue T > S : 2/11 Lacking stains : 2 Bx
10	*Calcifications*	Focal deposits: 10/23 Absent : 13/23 Not performed : 7/23	Large cyst contents : 7/12 Absent : 5/12 Not performed : 1 case	Absent : 5/6 Focally present : 1/6 Not performed in 2 cases	Present : 6/11 Absent : 5/11 Not performed: 2 cases
11	*Amyloid deposition*	Absent	Stromal deposition: 1/13	Absent	Absent

Table 1 continues …

12	*AE1/AE3 antibodies*	Highlighted all epithelial structures, tumor islands and PMB regardless of the anatomical location (Fig. 5)			
13	*Tumor necrosis*	Absent	Absent	Absent	Absent
14	*Inflammatory infiltrate*	Present : 10/30 Minimal : 12/30 Absent : 8/30	Present-mild : 5/13 Present-moderate : 7/13 Absent : 1/13	Present-minimal : 4/8 Present - moderate : 1/8 Absent : 3/8	Present-minimal: 7/13 Heavy : 3/13 Absent : 3/13
15	*Foreign body reaction*	Lack of FBR in 20/30 Present : 10/30 Heavy FBR : 3/10	Absent: 8/13 Present : 5/13 Heavy FBR : 4/5	Absent : 7/8 Present - mild : 1/8	Absent : 9/13 Present – mild : 4/13
16	*Mitoses*	Absent : 14/30 Rare : 12/30 Common : 4/30	Absent : 5/13 Scattered : 6/13 Common : 2/13	Absent : 5/8 Rare : 2/8 Common : 1/8	Many : 6/13 Rare : 3/13 Absent : 4/13

Abbreviations: T = tumour; S = stroma; FBR = foreign body reaction; Bx = biopsy

No tumor necrosis, cytological atypia or significant mitotic activity could be demonstrated in this study. Trichoepithelioma was seen in close relation to a benign pigmented intradermal nevus in one specimen [Fig. 4a and 4b] and in two elderly Caucasians, trichoepithelioma was found adjacent to a BCC.

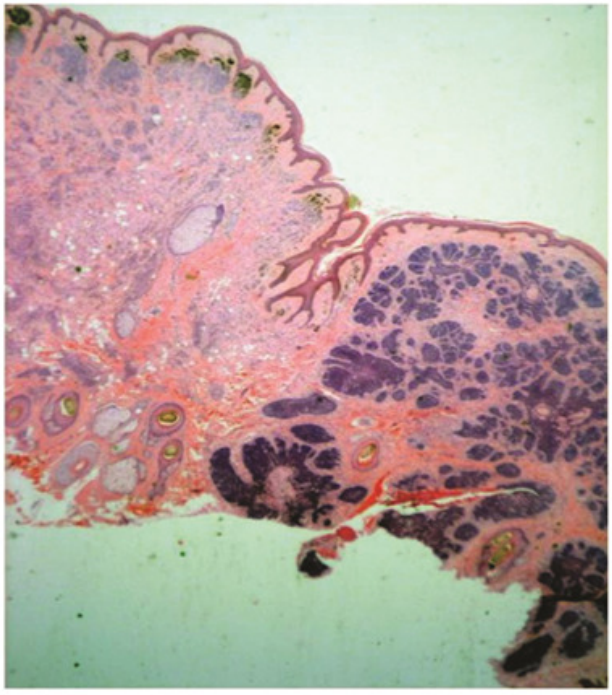

Fig. 4a. Combined trichoepithelioma and a pigmented intradermal naevus in a patient with TEM

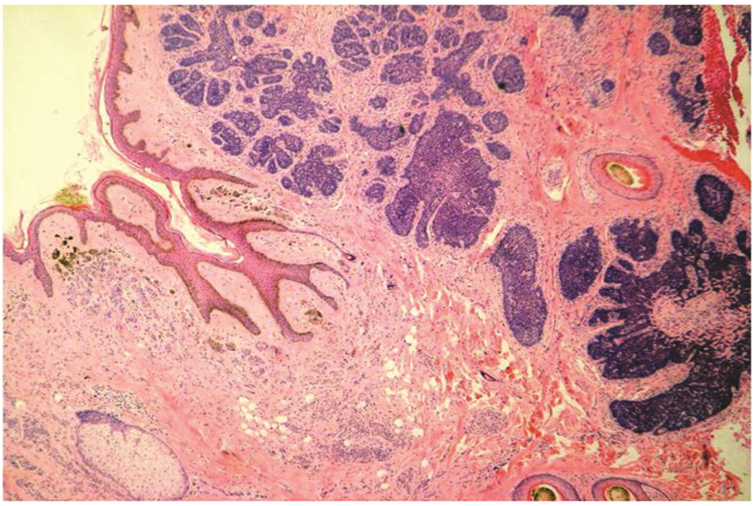

Fig. 4b. Higher magnification of figure 4a

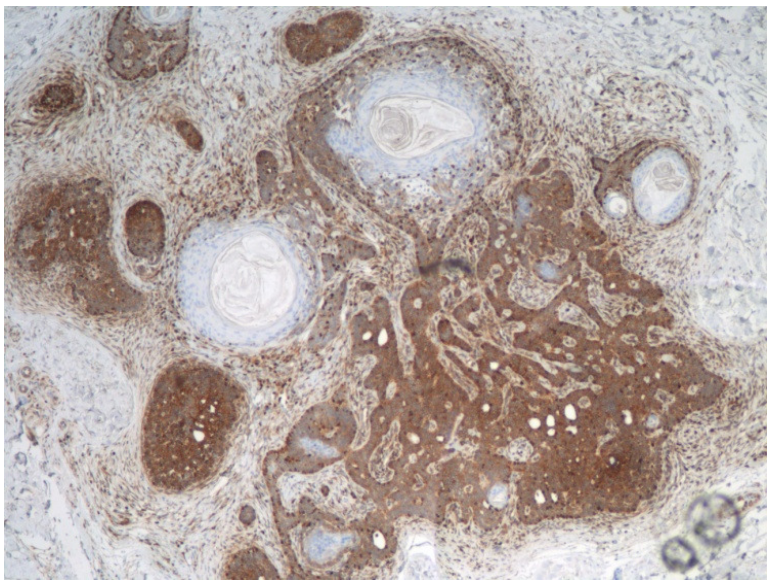

Fig. 5. AE1/AE3 antibodies highlighting epithelial structures, tumor islands and papillary mesenchymal bodies

4. ADNEXA I

Relevant features analysed in this histopathological review were as follows:

1. Epidermal continuity: assessed as present / absent
2. Follicular structure formation: present / absent
3. Keratinized cysts: variation in size, number; present / absent in stroma or in tumour
4. Papillary mesenchymal bodies (PMB): present / absent
5. Quality of peritumoralstroma: fibrous, myxoid, fibromyxoid
6. Stromal retraction defined as the presence of clefts between the aggregates of neoplastic cells and stroma: graded as absent, focal or common
7. Tumour pattern assessed as: lace-like or retiform, solid nests/islands, strands, cribriform
8. Palisading of peripheral basaloid cells: present/absent
9. Mucin deposition: present / absent, within the tumour islands or within the stroma (highlighted by PAS and Alcian blue stains.
10. Calcification: present / absent (in the tumour, in stroma, in the foreign body reaction). Calcium deposits were highlighted by Von Kossa stain)
11. Amyloid deposits: present / absent (highlighted by Congo red stains)
12. Anti-CK AE1/AE3 antibodies used as a pan-specific cocktail of antibodies for tumour keratins to highlight the epithelial origin of trichoepithelioma as an aid to conventional histopathology
13. Tumour necrosis and ulceration: present / absent
14. Inflammatory response: present / absent
15. Foreign body giant cell reaction: present / absent
16. Mitotic figures graded semi-quantitatively as rare or common and qualitatively as cytological atypia: present / absent

5. DISCUSSION

Trichoepitheliomas are benign cutaneous adnexal neoplasms showing poor differentiation toward follicular germinative cells and specific follicular stroma [3,7].

A family history with an autosomal dominant inheritance is usually evident in 50%-60% of the patients [8,9,24].

In our study however, the majority of the cases were sporadic (15 patients) with only 3 families being affected.

Whereas some early studies of patients with multiple familial trichoepitheliomas [5] suggested a role of the PTCH gene, recent studies [6,7] identified mutations in CYLD gene on chromosome 16, a gene responsible for 3 clinically distinctive genodermatoses: Familial Cylindromas, Brooke–Spiegler Syndrome, Multiple Familial Trichoepitheliomas, suggesting that these syndromes not only share a common genetic basis, but may represent phenotypic variations of the same disease [8].

Trichoepitheliomas may be also part of a constellation of rare syndromes such as: Rombo syndrome, Bazex syndrome, Rassmussen syndrome [9,11,12,13].

A review of familial cases of TEM indicated no consistent associated systemic anomalies such as those described in the above mentioned syndromes [14].
In our study, only one case presented Tuberous Sclerosis as a relevant medical history.

A male predominance in this study, contrasts with the general view of decreased male penetrance and expressivity [9,14].

Similar to other studies [9,10,14] the majority of the patients, reported the onset of the lesions during the childhood, with a peak at puberty. Our youngest patient was a 13 year-old African boy with the onset of the lesions at the age of 9 years.

The patients presented a wide variation of clinical involvement, but unusual configuration such as linear, dermatomal, hemifacial or in the lines of Blaschko was not seen.

Half of the patients, all of African origin presented grossly disfiguring lesions affecting most of the face.

Similar findings were reported by W K Jacyk in an African patient in 1980 [15].

There are only a few isolated reports of TEM with such a gross disfigurement, especially from Africa [16,17]. The surface of the lesions appeared unremarkable in all patients with the exception of 2 patients, both Caucasians in whom ulceration was present (Fig. 2b - mother).

Review of the literature showed that malignant degeneration of the tumors is a rare event [18,19,20] and the presence of ulceration does not necessarily mean a malignant lesion. In one review [24] none of 192 examined lesions had microscopic features suggestive of malignant transformation.

Differential diagnosis between BCC and trichoepitelioma is usually made on the basis of the degree of the follicular differentiation (advanced in trichoepithelioma, less pronounced in

BCC), the presence (in TEM) or absence (in BCC) of Merkel cells (CK20), the expression of AR-androgenic receptors in BCC as opposed to lack of their expression in TEM and bcl-2 expression (patchy and peripheral in TEM, diffuse in BCC [7,20,22,23].

We employed these markers only in 3 difficult cases in which a close resemblance between TE and BCC with follicular differentiation was found. The quality of the stroma is another defining discriminant between trichoepithelioma and BCC (fibromyxoid with plump fibroblasts in trichoepithelioma, scarce with a few fibroblasts in BCC).

Previous studies [7,14,25] demonstrated that trichoepithelioma presented two distinctive stromal patterns. The bulk of stroma consists of spindle-shape fibroblasts associated with abundant collagen. In present study, the fibroblasts in the stroma are tightly associated with the islands of basaloid cells, encircling them, but they lack the retraction artefact typical of BCC. The other type of stroma is represented by aggregations of plump fibroblasts, which produce minimal amount of collagen, named papillary mesenchymal bodies or follicular papillae [7,25].

In our study, there were mainly attempts of hair bulb formation and only 1-2 well differentiated primitive hair bulbs with “ball and claw” configuration.

Three male cases presented features of a desmoplastic trichoepithelioma: narrow epithelial strands, rims of compact collagen around the aggregates of basaloid cells, small keratinous cysts, sparse inflammatory infiltrate and granulomatous inflammation around ruptured cysts (Fig.3b).

Desmoplastic trichoepithelioma is associated with an intradermal / compound melanocytic nevus at a frequency of 10% [27,28,29,30]. It remains unclear why this particular combination should occur repeatedly. That might represent an example of epithelial induction by melanocytic nevi [30], proliferations of components of the nevus regarded as a benign tumour [32] or as Keen suggested, the local paracrine effect of cytokine / growth factors secreted by the nevus cells accounts for the epithelial proliferations [33,34].

In our study, a single specimen revealed a trichoepithelioma in close relation to a benign pigmented intradermal nevus [Fig. 4a and 4b]. The two components were closely intermingled and not only placed side by side. The close apposition between melanocytes and epithelial cells suggests that melanocytes might play a role in controlling epidermal growth apart from just supplying it with melanin.

Localized cutaneous amyloidosis in trichoepitheliomas is poorly documented.

It is a rare, secondary phenomenon in contrast to common amyloid deposition in BCC. Amyloid is believed to be derived from the degenerated (apoptotic) tumour cells producing excessive amounts of tonofilaments which are discharged into extracellular milieu [35,36]. We were able to demonstrate amyloid deposition in a single patient (lesion from the scalp).

Foreign body giant cell reactions and focal calcification occur not uncommonly in relation to benign neoplasms and nevi. In our study, foreign body granulomas and focal ossification were seen adjacent to ruptured cysts implying folliculitis or follicular damage due to trauma [37].

6. CONCLUSIONS

Trichoepithelioma multiplex was an uncommon diagnosis particularly in African patients, with a low prevalence of familial cases.

A positive correlation could be established between the histopathological pattern of trichoepitheliomas and the body areas from which the lesions were removed.

In cases of diagnostic difficulties, one has to consider the usual presentations of uncommon disease (TEM) as well as the unusual presentation of common disease (BCC). In this regard, the study brings an added value in making a more accurate histopathologic diagnosis in problematic cases.

CONSENT AND ETHICAL APPROVAL

The patients were recruited according to South African lows governing participation in a biomedical research. The majority of the cases included in this study were retrospective (12). The authors declare that written informed consent was obtained for prospective cases (8). The patient data protection and confidentiality were ensured.

The protocol for this research project has been approved by the Ethics Committee of the University of Pretoria in conformity to the provisions of the revised Declaration of Helsinki (Tokio 2004).

DECLARATION

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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