Multiple Familial Trichoepitheliomas

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Abstract
Trichoepithelioma is a benign hamartomatous tumor of the pilosebaceous follicle that may occur either as a nonhereditary solitary lesion or as multiple lesions that are often dominantly inherited. The gene for multiple trichoepitheliomas (MTs) has been mapped to a locus 9p21. MTs may represent a syndrome in which tumors develop from undifferentiated germinative cells of the pilosebaceous-apocrine unit.

The exact prevalence is unknown. MTs appear to be rather uncommon. They most commonly appear in early childhood or at puberty. They appear as multiple, skin-colored to pink, firm, papulonodular lesions, which are located mainly on the face or, occasionally, on the scalp, the neck and the upper trunk. Trichoepitheliomas gradually increase in number and in size, producing significant cosmetic disfigurement. Malignant transformation to basal cell carcinoma (BCC) is rare and occurs late in the course of the disease. However, BCC associated with MTs is commonly reported.

Diagnosis is based on history, clinical examination and it is confirmed by skin biopsy. Treatment is difficult. Surgical excision and various destructive modalities have been tried with occasionally good results. All methods carry significant risk of side-effects, most importantly scarring. Recurrences are common. Long-term vigilance and follow up for BCC development is warranted.

Keywords
Hamartoma of pilosebaceous follicle, skin tumor, locus 9p21, locus 16q12-13, epithelioma adenoids cysticum, basal cell carcinoma, Brooke-Spiegler syndrome

Synonyms
Multiple benign cystic epithelioma

Definition
Trichoepithelioma is a benign hamartomatous tumor of the pilosebaceous follicle that usually appears in childhood or early adolescence and occurs on the face or, less often, on the scalp, neck and trunk. In 1892, Brooke originally described it as epithelioma adenoids cysticum and Fordye as multiple benign cystic epithelioma.

Epidemiology
The exact prevalence is unknown. Multiple trichoepitheliomas (MTs) appear to be rather uncommon. They most commonly appear in early childhood or at puberty. Both sexes are equally affected. There is no racial predisposition.
Etiology
MTs are often dominantly inherited. The gene for MTs has been mapped to a locus on chromosome 9p21 (Harada H et al, 1996). The Brooke-Spiegler syndrome, which is characterized by the development of multiple trichoepitheliomas, cylindromas and, occasionally, spiradenomas, is also inherited as an autosomal dominant trait. The responsible gene has been mapped to chromosome 16q12-13 (Hu G et al, 2003). It is possible that these two separate genes influence each other to develop different tumors. Current data suggest that a defective tumor suppressor gene may be involved. MTs may represent a syndrome in which tumors develop from undifferentiated germinative cells of the pilosebaceous-apocrine unit (Clarke J, 2002). Mutations in genes regulating proliferation and differentiation of putative stem cells of the pilosebaceous-apocrine unit would give rise to different combinations of adnexal skin tumors, as well as to other neoplasms. Consequently, on histological examination some of the lesions of MTs show features either of pilosebaceous differentiation (trichoepithelioma or basal cell carcinoma BCC) or apocrine differentiation (spiradenoma or spiradenocylindroma).

Clinical description
MTs begin to develop during childhood or puberty. They appear as multiple, skin-colored to pink, firm, rounded, translucent, shiny, well-demarcated, papulonodular lesions. They are located mainly on the face, particularly on the nasolabial folds, nose, upper lip, forehead and eyelids. Occasionally, the scalp, the neck and the upper trunk may be affected as well. The lesions are grouped but discrete. On the face, they are often symmetrical. The center may be slightly depressed or umbilicated. Trichoepitheliomas gradually increase in number and in size, producing significant cosmetic disfigurement. They are usually 2-5 mm in diameter; however, lesions may enlarge up to 5mm on face and ears and up to 2-3 cm in other sites.

The patient is otherwise asymptomatic. Telangiectatic vessels may be observed on the surface of the larger lesions, mimicking BCC. In contrast to BCC, ulceration occurs very rarely. Malignant transformation to BCC is rare and occurs late in the course of the disease. Although, BCC associated with MTs is not uncommonly reported (Misago N et al, 2001), some authors believe that this does not represent a true association (Wallace ML et al, 1997).

Diagnostic methods
Diagnosis is based on history, clinical examination and it is confirmed by skin biopsy. If necessary, genetic studies may be used to detect the abnormalities in band 9p21. Horn cysts are the characteristic histologic feature of trichoepithelioma. They consist of a fully keratinized inner shell surrounded by strands and solid nests of flattened basophilic cells resembling the cells of BCC. Adenoid structures may be present and calcification of cystic material and foreign body reaction to it may be seen. Occasionally, primitive hair papillae and even hair shaft-like structures may be observed, indicating a high degree of differentiation. A fibrous stroma surrounds the horny cysts. Histological differentiation from keratotic BCC may be difficult (Odom RB et al, 2000).

Differential diagnosis
Differential diagnosis includes BCC, other appendageal tumors, syringoma and angiofibroma.

Treatment
Treatment is difficult and often unrewarding (Sindu SK, 1997). Preventive measures are unknown. Surgical excision and various destructive modalities, including cryotherapy, dermabrasion, electrodessication and curettage, have been tried with occasionally good results. Multiple treatments may be needed in several occasions. All methods carry significant risk of side-effects, most importantly scarring. Recurrences are common. Recently, satisfactory clinical results have been reported with high energy pulsed CO2 laser, with no recurrences in the treated area for 12 months (Rosenbach A and Alster TS, 2001).

With the time, lesions of MTs may become less obvious; therefore a wait-and-see strategy may be advisable (Crotty K et al, 2003). Nevertheless, long-term vigilance and follow up for BCC development is warranted (Pariser RJ, 1986).

References


Hu G, Onder M, Gill M et al. A novel missense mutation in CYLD in a family with Brooke-


