Trichoepithelioma: A Comprehensive Review

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ABSTRACT Trichoepithelioma is an uncommon benign adnexal neoplasm. It can present as a solitary non-familial or multiple familial form. Trichoepithelioma usually develops in early childhood or puberty. Females are more affected. It is attributed to two genetic mutations on chromosomes 9p21 and 16q12-q13. Multiple familial trichoepithelioma is an autosomal-dominant disorder, characterized by numerous nodules and papules, predominantly on the face and occasionally on the scalp, neck, or upper trunk, positive family history, and histopathological findings. The lesions gradually increase in both size and number over time; however, they remain mostly asymptomatic. Although it is rare, trichoepithelioma lesions can undergo malignant transformation to trichoblastic carcinoma or basal cell carcinoma. Patients mainly seek treatment because the lesions are usually disfiguring and can lead to psycho-social issues. Non-pharmacologic approaches (e.g., excisional surgery, laser resurfacing), as the current mainstay of management, suffer from several drawbacks. New treatment techniques such as pharmacotherapy with potentially effective agents deserve more attention and investigation.

KEY WORDS: trichoepithelioma, epidemiology, clinical presentations, management

INTRODUCTION

Trichoepithelioma is a rare, benign tumor of the pilosebaceous unit that originates from the hair follicles (1,2). It was first described almost simultaneously in 1892 in England by Brooke (3) as "epithelioma adenoids cysticum" and in the United States by Fordyce (4) as "multiple benign cystic epithelioma". Trichoepithelioma can be divided into 3 subgroups including multiple familial trichoepithelioma (MFT), solitary non-hereditary trichoepithelioma, and desmoplastic trichoepithelioma (5). MFT can also be present in Brooke-Spiegler syndrome (BSS) characterized by different combinations of inherited adnexal neoplasms including multiple trichoepitheliomas, cylindromas and occasional spiradenomas (6). Furthermore, other rare syndromes such as the Rombo syndrome (vermicular atrophoderma, milia, hypotrichosis,basal cell carcinomas, trichoepitheliomas and peripheral vasodilatationwith cyanosis) and Basex syndrome (follicular atrophoderma, hypotrichosis, trichoepitheliomas, basal cell carcinomas, andhypohidrosis) can be associated with MFT (7). Although the term trichoepithelioma is still used in the literature, it is currently considered as a variant of tricoblastoma, a term that was coined in 1970, in the dermatopathology lexicon (8).

Epidemiology

Trichoepithelioma is a rare cutaneous condition. Its exact prevalence is unknown. A dermatopathology laboratory in the USA reported about 2.14 and 2.75 cases of trichoepitheliomas in 9000 specimens per year (9). To the best of our knowledge, there is no official data about the frequency of trichoepitheliomas in Iran. Mapar *et al.* recently reported MFT in 6 members in the family of an Arabian descent in three generations (10). Mohammadi and SeyedJafari also described a large family of Iranian origin with 15 individuals affected with MFT in four generations (11). Although its pattern of inheritance is autosomal dominant and both sexes receive equal genes, MFT seems to affect females more, probably due to smaller expressivity and chromosomal penetration in males (12). Cases of MFT typically arise in young to aging adults (9). However, MFT can first present in younger individuals aged between 10 and 20 years (13). Interestingly, Carter *et al.* in 2007 reported the first case of congenital desmoplastic trichoepithelioma, presenting with widespread erythematous plaques with milia-like lesions over the right scalp, face and neck in a girl born at term to a healthy mother (14). There is no racial predisposition to MFT (15).

ETIOLOGY

Two genetic mutations have been identified to be associated with MFT. The first one discovered is located on the chromosomes 9p21 (16). Later, another mutation in the cylindromatosis tumor suppressor gene (CYLD) was found on the chromosome 16q12-q13. The CYLD gene consists of 20 exons, of which three are un-translated, suggesting genetic heterogeneity of MFT. However, the MFT phenotype related to 9p21 is indistinguishable from that related to CYLD (17). BSS is also linked to the CYLD gene (6). Solitary trichoepithelioma has been linked to a gene at chromosome 9q22.3 (2). As in BSS and familial cylindromatosis, individuals with CYLD-related MFT are born with one mutated copy of the CYLD gene in each cell (first hit). The second mutation or deletion of genetic material involving the other copy of the CYLD gene occurs in hair follicle cells, rather than in eccrine-apocrine cells observed in multiple cylindromas, during a person's lifetime (second hit) (18). While this is not conclusive, some researchers believe that familial cylindromatosis, BSS, and MFT are different phenotypic variables of a single entity (19).

CYLD, a tumor suppressor gene, encodes a deubiquitinating enzyme that negatively regulates the activation of the nuclear factor κβ (NF-κβ) and c-Jun N-terminal kinase pathways (20). NF-κβ is a prominent transcription factor involved in inflammation, immune response, oncogenesis, and apoptosis (21). Missense mutation in CYLD gene results in amino acid substitution within the ubiquitin-specific protease domain of CYLD protein, consequently dysregulating the proliferation and differentiation of putative stem cells of the pilosebaceous-apocrine unit (5).

During the recent decades, several novel mutations in CYLD gene have been reported in either MFT or BSS within families of Algerian (17), Turkish (19), Israeli (22), Spanish (18), Taiwanese (23), or Chinese descents (24). According to the Genetics Home Reference database last reviewed in June 2012, at least 20 CYLD germline mutations have been identified in individuals with BSS, more than 30 in subjects with familial cylindromatosis, and at least 22 in individuals with MFT (25).

CLINICAL MANIFESTATIONS

MFT usually presents as multiple skin colored, pink, or bluish firm, rounded, translucent, shiny, well-demarcated papules or nodules. The lesions locate

Figure 1. Numerous skin-colored or pinkish, asymptomatic papules and nodules on the face (particularly in the peri-nasal and chin areas) in two 17- and 25-year-old brothers. Their father and grandmother had similar lesions except for an ulcerated nodule in the peri-nasal area and an ulcerated, severely pruritic lesion on the forehead of the grandmother. Due to unbecoming appearance caused by facial skin lesions, the two brothers abandoned education and became shepherd. Details of multiple familial trichoepithelioma in this family have been recently published (10).

Table 1. Details of pharmacologic agents used for the management of trichoepitheliomas in 4 clinical studies

Reference	Clinical setting	Pharmacologic agents	Dose, Route and Duration of administration	Efficacy
Van Voorst Vader *et al*, 1986 (51)	Multiple trichoepitheliomas and cystic acne	13-cis-retinoic acid	1 mg/kg/day orally for 12 weeks	Ineffective
Urquhart and Weston, 2005 (50)	Multiple trichoepitheliomas	Imiquimod cream in combination with tretinoin gel 1%	3 times a week and then, twice daily topically (Imiquimod) along with once a day topically (tretinoin) for 3 years	About 80% improvement
Fisher and Geronemus, 2006 (53)	Recurrent multiple familial trichoepitheliomas	Aspirin in combination with adalimumab	325 mg twice a day orally (aspirin) along with 40 mg every other week for the first 2 months and thereafter, 40 mg every week as subcutaneous injection (adalimumab) for 8 months	Remarkable degree of improvement
Alessi*et al*, 2009 (52)	Trichoepitheliomas as a part of Brooke-Spiegler syndrome	Imiquimod cream 5%	5 to 7 times per week topically for 32 weeks	Partial clinical response

dominantly on the face, particularly around the nasolabial folds, nose, forehead, and eyelids. They are often symmetric on the face. Occasionally, the scalp, neck, and upper trunk can also be involved (2,15,20). The lesions are usually 2-5 mm in diameter (Figure 1). However, they may increase in size to up to 5 cm and 2-3 cm on the face or ears and other sites, respectively (15). Trichoepithelioma lesions may also gradually increase in number over years (2). The center of the lesions can be slightly depressed or umbilicated (15). There can be dilated (telangiectatic) blood vessels over the surface of large lesions (2,15).

Trichoepithelioma lesions are without ulceration and there is no pruritus, so they are considered asymptomatic (15). However, they can undergo the transformation into malignant neoplasms, such as trichoblastic carcinoma or basal cell carcinoma (BCC). Lee *et al*. briefly reviewed demographic and clinical characteristics of 12 cases of trichoblastic carcinomas arising from trichoepithelioma (26). According to a study by Pincus *et al*. (27), 6 reports describing 11 patients that evolved BCCs from MFT have been identified in the English language literature from 1959 to 2008. Interestingly, cases of sporadic TEs associated with BCCs have also been reported. In 4 of the above reports, patients noticed the bleeding and/or ulceration at the site of the lesions (27). Mapar *et al*. (10) recently reported on a case of a 55-year-old woman presenting with slowly progressive, asymptomatic papules and nodules on her face for the last 37 years. She sought medical attention because one of her skin lesions became pruritic and ulcerated. The ulcerated skin lesion was diagnosed as BCC derived from

the trichoepithelioma, based on her history, physical examination, histopathological, and immunohistochemistry findings (10). It has been advocated that clinicians should examine patients with MFT carefully and be much more vigilant about any rapid growth or ulceration in the pre-existing lesions as they are probably worrisome features of malignant transformation. Moreover, implementing preventive measures, such as optimal sunlight protection, are crucial in this regards (27,28).

There are also occasional reports of MFT association with other systemic disorders such as cerebellar infarction secondary to occlusion of the right posterior inferior cerebellar artery in a 63-year old woman (29). Magnetic resonance imaging and angiography demonstrated a cerebellar aneurysm arising from the bifurcation of the middle cerebral artery along with right-subclavian pulmonary collateral vessels. Both her mother and uncle had died from subarachnoid hemorrhage (29). Other systemic abnormalities with MFT reported in the literature are as follows: malignant lymphoepithelial lesion of the parotid gland (30), cheilognathopalatoschisis, jaw cysts, epilepsy, oligophrenia, bradykinesia, labyrinthine deafness, adipopositas, Dupuytren contracture, and micturition disturbance (29). Clinical relevance of these diseases/disorders with MFT is unknown (31).

PATHOLOGY

Two major histopathological characteristics of MFT are horn cysts and tumor islands of basaloid cells. Horn cysts consist of fully keratinized centre surrounded by basophilic cells. These cells lack atypia

and mitosis. In contrast to the squamous cell carcinoma, keratinization in horn pearls is abrupt and complete in MFT (5). Occasionally, primitive hair papillae, as well as hair shaft-like structures, can be observed in these central areas (2,20). The tumor islands are with peripheral palisading and increase in surrounding fibrous stroma (5). Tiny collections of mature sebocytes, as well as ductal differentiation may also be observed (20).

In small biopsies particularly, differentiating MFT vs. solitary trichoepithelioma from BCC can be very difficult (32). Histopathological findings in favor of trichoepithelioma over BCC are as follows: 1) symmetry of the lesion and circumscription, 2) aggregations with smooth borders, 3) clefts between stroma (rather than between epithelium and stroma), 4) absence of artifactual retraction between tumor cells and the surrounding stroma, 5) fibrocytic (rather than mucinous) stroma, 6) low mitotic activity, and 7) presence of mature' follicular differentiation including well-formed cornified cysts and papillary mesenchymal bodies (2,33,34).

Immunohistochemical staining technique might also distinguish between BCC and MFT. Antibodies against a number of immunomarkers such as CD34, bcl-2, androgen receptor, transforming growth factor-β (TGF-β), and CD10 can be exploited in this regard (32). Furthermore, more recent studies have demonstrated p75 neurotrophin receptor (p75NTR) (35) and pleckstrin homology-like domain, family A, member 1 (PHLDA1) (36)as useful and practical adjuncts in differential diagnosis of MFT from BCC even in problematic cases (e.g. small skin biopsies). The diffuse pattern of bcl-2 staining in BCC lesions has been reported by at least 3 independent study groups (10,32,37). However, the reliability of bcl-2 in distinguishing MFT from BCC has been questioned by other studies (38,39). CD10 demonstrated different staining patterns between MFT and BCC, basaloid versus stromal cells, respectively, and therefore may be a favorable immunohistochemical marker in differentiating MFT from BCC (40). However, in a case reported recently, only periphery of basaloid cells in the BCC lesion showed strong CD10 immunoreactivity and it was entirely undetectable in trichoepithelioma lesions (10). Kirchmann *et al.* (41) and Illueca *et al.* (42) implicated CD34 expression in MFT rather than BCC lesions. This is in contrast to Mapar *et al.* findings of the lack of CD34 staining in both trichoepitheliomas and BCC lesions. Altogether, the immunomarkers bcl-2, CD10, and CD34 appears not to be helpful in differentiating BCC from MFT. However, evaluating the accuracy of relatively novel markers, such as androgen receptors, TGF-β, p75NTR, and PHLDA1, seems necessary in this matter (10).

TREATMENT

Although MFT is asymptomatic, affected patients mainly seek treatment for cosmetic concerns because the lesions are usually dense as well as disfiguring, and can lead to social isolation (15,28,43). Currently, no preventive measures are known (15). Excisional surgery is considered as the primary treatment approach (9). Other non-pharmacological treatment modalities that have been also tried include laser resurfacing (44-46), electro-surgery (43), cryosurgery (47), and dermabrasion (9). Regarding laser resurfacing, Rallan and Harland demonstrated that the treatment of trichoepitheliomas with erbium:Yag and CO_2 laser was associated with less scarrins and recurrence after 2 years compared to conventional treatments (48). Similarly, acceptable clinical response without considerable pain, bleeding, and postsurgical edema was also reported by CO_2 laser treatment in two patients with multiple trichoepitheliomas on the face (49).

Plausible complications of non-pharmacological treatments include recurrence of the skin lesions, pain requiring local anesthetic injection, bleeding, scarring, and secondary skin cancer. Besides these pitfalls, some of the above approaches are time-consuming, costly, and inconvenient for patients (50). Based on the fact that MFT lesions may regress and become less obvious over time, and due to the complications of non-pharmacological measures, some experts suggest a wait-and-watch approach along with assurance strategy (15,31).

Due to the drawbacks of non-pharmacological therapies, pharmacotherapy has been also investigated for MFT management. In a primary report, a 12-week treatment with 1 mg/kg/day oral 13-*cis*-retinoic acid was found ineffective in a patient with multiple trichoepitheliomas and non-inflammatory cystic acne lesions on the face and neck (51). A Brazilian study of several types of cutaneous tumors reported that a 32-week treatment with topical 5% imiquimod cream (5 to 7 times per week) in 2 cases of trichoepitheliomas as part of BSS was associated with only partial clinical response with the median follow up of 10 months (52). In another survey, about 80% of the lesions of an 11-year-old girl with multiple trichoepitheliomas were reversed by topical imiquimod cream (first 3 times a week and then twice daily) and tretinoin gel 1% (once daily) combination after 3 years, without scarring. The clinical superiority of the mentioned combination rather than imiquimod alone is justified by tretinoin's ability to normalize epidermal turnover and therefore flattening of the thickness of the trichoepithelioma and enhancing imiquimod absorption.

(50). The therapeutic actions of imiquimod are attributed to promoting the maturation and secretion of tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ) and consequently, development of a Th1 lymphocyte-mediated immune response (50,52). Pharmacological agents with inhibitory effects on NF-κβ functions, such as corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) might be also potentially effective in the treatment of MFT (28). In this regards, Fisher and Geronemus reported a case of MFT recurrence in a 41-year-old white woman in spite of numerous laser resurfacing procedures for 15 years (53). The patient achieved remarkable degree of improvement with a combination of oral aspirin (325 mg twice daily) and subcutaneous adalimumab (for the first 2 months, 40 mg every other week and thereafter, 40 mg every week) for 8 months. This combination can block TNF-α-induced NF-κβactivation at 2 levels (53). Table 1 summarizes the studied pharmacologic agents for the management of MFT.

CONCLUSION

Trichoepithelioma can manifest as a solitary non-familial or multiple familial type. MFT is a relatively rare, heritable, disfiguring, benign adnexal neoplasm that can be diagnosed by the centro-facial distribution pattern of papules and nodules, positive family history, and related histopathological findings. Although very uncommon, MFT in a patient may develop and turn into BCC. Therefore, close clinical monitoring of affected patients for possible BCC transformation is crucial. Differentiating between MFT and BCCs is usually challenging and current immunohistochemical staining techniques appear to be of little value. Treatment of MFT lesions only by the current non-pharmacological modalities, such as excisional surgery, is usually difficult and can be associated with complications. Pharmacotherapy option with potentially effective topical and systemic agents such as corticosteroids, NSAIDs, and anti-TNF-α (e.g., pentoxifylline, infliximab, etanercept) has been largely ignored and clinical studies are warranted in this area.

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