Multiple familial trichoepitheliomas with a novel frameshift mutation in *CYLD gene*: a case report

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ABSTRACT:

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Trichoepithelioma is a rare benign adnexal tumor. There are three clinical variants which are: solitary, multiple, and desmoplastic. Trichoepitheliomas affect middle-aged adults with a female predilection. Multiple trichoepitheliomas usually present as multiple small papules on the face, often involving the nasolabial folds. We report the case of a 70-year-old Thai woman presented with multiple skin-colored papules and nodules on scalp, forehead, nose, and both knees since she was 20 years old. Her family members also have similar skin lesions in the autosomal dominant pattern of inheritance. Genetic testing revealed novel heterozygous mutation in *CYLD gene.* Histopathology showed a well-circumscribed, dermal tumor composed of basaloid germinative epithelial cells arranged in a cribriform pattern within concentric fibroblast-rich stroma with papillary mesenchymal bodies. There are several keratin horn cysts embedded in the fibrotic stroma. She was diagnosed with Multiple familial trichoepitheliomas and subsequently treated with surgical excisions.

Key words: Trichoepithelioma, multiple familial trichoepitheliomas, *CYLD* gene

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Trichoepithelioma is an adnexal neoplasm derived from basal cells in hair follicles. There are three clinical variants: solitary, desmoplastic and multiple[1,2]. It is considered the cribriform variant of trichoblastoma with infundibulocystic differentiation. The diagnosis requires both clinical and histological features. Multiple familial trichoepitheliomas affect young adults predominantly in female due to smaller expressivity and chromosomal penetration in males[2]. Genetic mutation in *CYLD* gene on chromosome 16 has been identified to be associated with multiple familial trichoepitheliomas, similar to Brooke-Spiegler syndrome that is phenotypic variant of the disease[3].

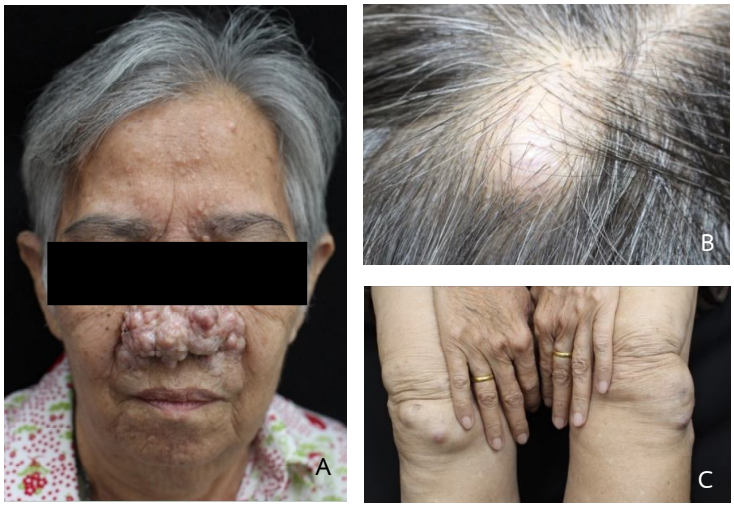

Figure 1 Multiple skin-colored papules and nodules predominantly on the nose, forehead (A), scalp (B) and both knees (C)

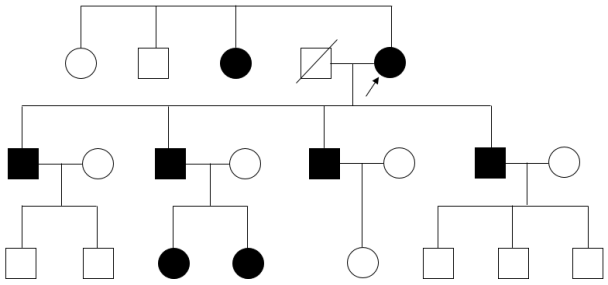

Figure 2 Pedigree of family. Female and male family members are depicted as circles and squares, respectively. Affected family members are represented by black symbols. The proband is indicated by the arrow.

Case report

A 70-year-old Thai woman presented with multiple skin-colored papules and nodules on scalp, forehead, nose and both knees since she was 20 years old (Figure 1). She noticed that her lesions gradually have been increasing in numbers and sizes. The surrounded area showed no signs of inflammation. She denied any constitutional or systemic symptoms. Moreover, all of her sons have similar papules and nodules on their faces, and some granddaughters have less severe papules and nodules on their face (Figure 2). Her medical history is hypertension and she has taken 10 mg of amlodipine daily. Her blood pressure is well controlled.

On physical examination, multiple skin-colored papules and nodules predominantly on the nose, scalp, forehead and also both knees. Histopathology from nodules of face and knee showed well-circumscribed, dermal tumor composed of basaloid germinative epithelial cells arranged in a cribriform pattern within concentric fibroblast-rich stroma with papillary mesenchymal bodies. There are several keratin horn cysts embedded in fibrotic stroma (Figure 3). Genomic DNA was isolated from peripheral blood leukocytes, by using Gentra Puregene Blood Kit®, Qiagen. The samples were prepared according to an Agilent SureSelect Target Enrichment Kit preparation guide. The libraries were sequenced with Illumina platform sequencer. Mapping reference was used hg19 from UCSC (University of California Santa Cruz) genome browser (original GRCh37 from NCBI, Feb. 2009). A novel heterozygous two deleted nucleotides (c.1052_1053delGA) was identified in *CYLD* gene (NM_015247.2), which creates a frameshift and resulting in a prematurely truncated protein (p. Arg351Ilefs*2). This mutation was confirmed by Sanger sequencing (figure 4). Germ-line mutations in *CYLD* are found in patients with familial skin appendage tumors such as Brooke–Spiegler syndrome, familial cylindromatosis, and multiple familial trichoepitheliomas[4]. Our patient's clinical and histopathology had only multiple trichoepitheliomas. Also, all her sons and granddaughters had similar lesions without histological results and genetic testings. Thus, the patient was diagnosed with multiple familial trichoepitheliomas, and she was treated with several surgical excisions because of cosmetic issues. In addition, we plan to follow up the patient after elective surgeries and we did counseling for family members about the disease, clinical course and prognosis.

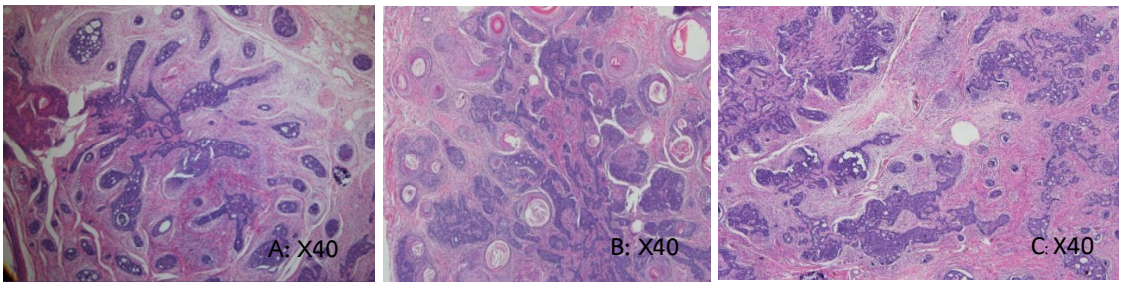

Figure 3 Skin biopsies stained with hematoxyline eosin (H&E, 40X) show dermal tumor composed of basaloid germinative epithelial cells arranged in a cribriform pattern within concentric fibroblast-rich stroma with papillary mesenchymal bodies. There are several keratin horn cysts embedded in fibrotic stroma. A (scalp), B (nose), C (knee)

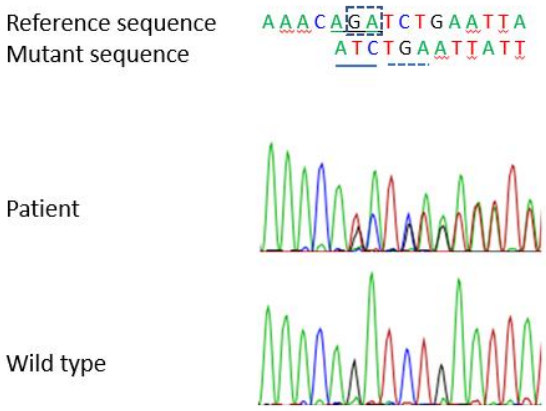

Figure 4 Heterozygous frameshift mutation, C.1052_1053delGA comparing with reference sequence (wild type) of this segment in exon 9 of *CYLD* gene

Discussion

Trichoepithelioma is a rare benign skin lesion that originates from hair follicles. There are three clinical variants: solitary, desmoplastic and multiple. It is considered the cribriform variant of trichoblastoma with infundibulocystic differentiation.

Solitary trichoepithelioma usually affects middle-aged adults with female predilection while solitary giant trichoepithelioma generally appears in elderly individuals and both sexes are affected equally[5]. The lesion presents as a single, flesh-colored papule. The most common site is the face, and it is often located on the nose,

cheek, upper lip. Also, it can be located on the scalp, and neck area. Desmoplastic trichoepithelioma usually affects middle-aged adults with female predominance. Lesions present as a single, white to yellow, firm papule or plaque with a central depression[6]. The most common locations are cheek and nose. It is also known as the columnar variant of trichoblastoma. Multiple trichoepitheliomas present as multiple small papules on the nose, forehead, scalp, neck, upper trunk, and perianal region[7]. It typically affects a younger patient population and predominantly in females[2]. Multiple trichoepitheliomas are observed with an autosomal dominant inheritance pattern and are associated with *CYLD* gene mutation on chromosome 16, similar to Brooke-Spiegler syndrome. The cylindromatosis gene (*CYLD*), which protein product functions as a tumor suppressor, underlies Brooke disease. *CYLD* encodes a deubiquitinating enzyme that impedes NF-KB (nuclear factor kappa-light-chain-enhancer of activated B cells) and JNK (c-Jun N-terminal kinase) pathways. The key role of NF-KB transcription factor is immune response, inflammation, oncogenesis and protection against apoptosis. Thus, *CYLD* inhibition raises resistance to apoptosis that lead to tumorigenesis[8]. Associated diseases of multiple familial trichoepitheliomas are Brooke–Spiegler syndrome, Rombo syndrome[2], and Bazex-Dupre Christol syndrome[9].

Brooke-Spiegler syndrome is an inherited autosomal dominant genodermatosis characterized by the development of multiple adnexal cutaneous tumors including spiradenomas, trichoepitheliomas, cylindromas, spiradenocylindromas, epidermoid cysts, and milia. It is more frequent in females, typically in the second and third decades of life. Mutations identified in the *CYLD* gene on chromosome 16q12-13 via locus analysis[3,10]. The nonsense mutations are associated with the highest phenotypic diversity and recurrence rate, whereas missense mutations are associated with trichoepitheliomas and milder phenotype.

Histopathology of trichoepitheliomas are well-circumscribed, dermal tumor composed of basaloid germinative epithelial cells arranged in a cribriform pattern within concentric fibroblast-rich stroma with papillary mesenchymal bodies. There are several keratin horn cysts embedded in fibrotic stroma.

Malignant transformation of trichoepithelioma is a rare condition. However, there are several reported cases that multiple trichoepitheliomas have transformed into basal cell carcinoma[11]. The main histological features that distinguish basal cell carcinoma from trichoepithelioma are higher frequency of apoptotic cells and mitotic figures[12]

and the absence of papillary mesenchymal bodies.

Moreover, there are few trichoepithelioma cases transformed to trichoblastic carcinoma, malignant hair matrix tumor[13] and squamous cell carcinoma[14]. There are some clues for cutaneous malignancy, for example, ulceration, sharply growing tumors, distinction from surrounding lesions, and bleeding.

Treatment of multiple familial trichoepitheliomas is focused on cosmetic aspect[12]. Currently, there are several modalities of treatment. The surgical interventions include CO2 laser and electrocautery, curettage, dermabrasion and surgical excision. In addition, non surgical treatments are topical imiquimod cream, topical retinoid, and the tumor necrosis factor inhibitor (adalimumab)[1]. Fisher and Geronemus reported a case of multiple familial trichoepitheliomas recurrence in a 41 years old female that was treated with a combination of subcutaneous adalimumab (for the first 2 months, 40 mg every other week and then, 40 mg every week) and oral aspirin 325 mg twice a day for 8 months. This combination can block TNF-α-induced NF-Kβ activation at 2 levels[2,15]. Finally, the limitation of this study includes no histological features and genetic testing of all her sons and her granddaughters.

References

1. du Toit JP, Schneider JW, Visser WI, Jordaan HF. The clinicopathological spectrum of trichoepitheliomas: a retrospective descriptive study. Int J Dermatol 2016;55:270-7.
2. Karimzadeh I, Namazi MR, Karimzadeh A. Trichoepithelioma: A Comprehensive Review. Acta Dermatovenerol Croat. 2018;26:162-5.
3. Sarah Malerich D DRL, DO, Alpesh Desai, DO. Brooke-Spiegler Syndrome: A Case Report. JAOCD. 2017;38:19-21.
4. Nagy N, Farkas K, Kemény L, Széll M. Phenotype-genotype correlations for clinical variants caused by CYLD mutations. Eur J Med Genet 2015;58:271-8.
5. Teli B, Thrishuli PB, Santhosh R, Amar DN, Rajpurohit S. Giant solitary trichoepithelioma. South Asian J Cancer 2015;4:41-4.
6. Mamelak AJ, Goldberg LH, Katz TM, Graves JJ, Arnon O, Kimyai-Asadi A. Desmoplastic trichoepithelioma. J Am Acad Dermatol. 2010;62:102-6.
7. Heller J, Roche N, Hameed M. Trichoepithelioma of the vulva: report of a case and review of the literature. J Low Genit Tract Dis 2009;13:186-7.
8. Yiltok SJ, Echejoh GO, Mohammad AM, Ituen AM, Igoche MI, Dades OT. Multiple familial trichoepithelioma: a case report and review of literature. Niger J Clin Pract 2010;13:230-2.
9. Centurión SA, Schwartz RA, Lambert WC. Trichoepithelioma papulosum multiplex. J Dermatol 2000;27:137-43.
10. Mirjana Paravina JK VK, Gordana Sav i, Mirjana Milinkovi, Mirjana Milosavljevi. Brooke spiegler

syndrome-a case report. J Dermat Cosmetol. 2018;2:16-8.

11. Kallam AR, Satyanarayana MA, Aryasomayajula S, Krishna BA. Basal Cell Carcinoma Developing from Trichoepithelioma: Review of Three Cases. J Clin Diagn Res 2016;10:PD17-9.
12. Mohammadi AA, Seyed Jafari SM. Trichoepithelioma: a rare but crucial dermatologic issue. World J Plast Surg 2014;3:142-5.
13. Lee KH, Kim JE, Cho BK, Kim YC, Park CJ. Malignant transformation of multiple familial trichoepithelioma: case report and literature review. Acta Derm Venereol 2008;88:43-6.
14. Ganguly S, Jaykar KC, Banerjee PK, Ahmed N. Multiple familial trichoepitheliomas in association with squamous cell carcinoma. Indian Dermatol Online J 2012;3:151-3.
15. Fisher GH, Geronemus RG. Treatment of multiple familial trichoepitheliomas with a combination of aspirin and a neutralizing antibody to tumor necrosis factor alpha: A case report and hypothesis of mechanism. Arch Dermatol 2006;146:782-3.