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Multiple papulonodular lesions on central area of the face: what is your diagnosis?

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Abstract

A healthy 31-year-old woman presented with a 20-year history of asymptomatic skin-colored papules and nodules on the central area of the face. Her maternal grandmother, aunts, mother, and sister also had similar lesions. Clinical, histopathological, and genetic features allowed the diagnosis of multiple familial trichoepithelioma. The patient and family were referred to the genetic department for genetic counselling. Close follow-up for the possibility of secondary basal cell carcinoma is warranted.

Keywords: neoplasms; adnexal and skin appendage; genes; tumor suppressor; mutation

Case Synopsis

A healthy 31-year-old woman presented with a history of multiple asymptomatic skin lesions on her face, which had developed since puberty and increased in number and size over the years. Her maternal grandmother, three aunts, mother, and sister also had similar papules on the face. Dermatological examination revealed multiple skin-colored papules and nodules located on the scalp, forehead, nose, nasolabial folds, and perioral region (Figures 1-3).

Skin biopsies of two lesions showed small horn cysts, islands of basaloid cells with palisading periphery (**Figure 4**).

Genetic study showed a pathogenic heterozygotic mutation in exon 9 of the cylindromatosis gene

[c.1112C>A(p.Ser371*)], supporting the clinical diagnosis of multiple familial trichoepithelioma. Surgical excision was performed in a few lesions greater than 10 mm, whereas others were treated with CO₂ LASER, cryotherapy, and electrosurgery. The patient and family were referred to the genetics department.

Case Discussion

Multiple familial trichoepithelioma (MFT; OMIM 601606) is an autosomal-dominant genodermatosis characterized by multiple facial skin-colored papules



Figure 1. Multiple dome-shaped papules and nodules on the central area of the face.



Figure 2. Right lateral view highlighting the central area of the face as the preferential location of the lesions.



Figure 3. Forehead lesions in detail.

and nodules predominantly located on the central area of the face – nasolabial folds, nose, forehead, and upper lip – and occasionally on the scalp, neck, and upper trunk [1, 2]. The first locus had been previously mapped to chromosome 9p21, but no susceptibility gene had been identified [3]. Latter,

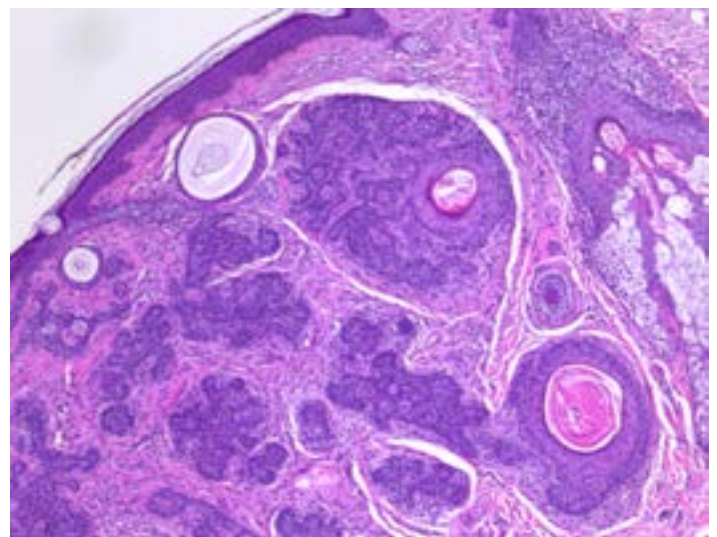


Figure 4. Trichoepithelioma. Histopathologic examination of a frontal lesion revealed islands of basaloid cells with palisading periphery, small horn cysts and clefts between stromal elements or between stroma and adjacent dermis (H&E, 40x).

Zhang et al. [4] identified for the first time mutations in the cylindromatosis gene (CYLD) on chromosome 16q12-q13, as the genetic defect of this skin disorder. The CYLD gene acts as a tumor suppressor, whereas CYLD protein is a deubiquitinating enzyme implicated in modulation of the nuclear factor (NF)- κ B pathway [1, 2, 4]. There are more than 20 germline CYLD gene mutations reported in MFT [2]. It still remains unclear whether abnormal function of other genes could also be the cause of MFT, such as reported loci in chromosome 9p21. Mutations in the CYLD gene on chromosome 16q12-q13 are also the cause of familial cylindromatosis (multiple cylindromas) and Brooke-Spigler syndrome (multiple trichoepitheliomas, cylindromas and spiradenomas), [1, 2, 5]. These various manifestations have been regarded as different expressions of a folliculosebaceous-apocrine genodermatosis [1, 5].

Trichoepithelioma is regarded as a poorly differentiated hamartoma of the hair germ and occurs either as a sporadic non-familial or a multiple-familial type [1, 2, 4]. The onset of the lesions is usually in childhood or at the time of puberty [1]. Association of multiple trichoepitheliomas with malignancy is rare and most of the cases described are basal cell carcinomas [6]. Histopathologically, trichoepitheliomas contain branching nests of basaloid cells, horn cysts, and abortive hair papillae [2, 7].

Many other genetic syndromes presenting with multiple facial lesions like Cowden syndrome, Birt-Hogg-Dubé, Muir-Torre, and Gorlin syndromes should be considered in differential diagnosis and require histological differentiation.

Multiple facial trichoepitheliomas can be cosmetically and psychologically disabling, resulting in low self-esteem. Various treatment modalities have been suggested, including CO₂ and argon LASER [8], cryotherapy, electrosurgery, and surgical excision [9]. Topical 5% imiquimod cream has also been advocated as a useful treatment [11]. Very gradual improvement has been reported following the use of acetylsalicylic acid and subcutaneous adalimumab to block TNF activation of NF- κ B at two levels of the pathway [11].

This case report illustrates the importance of recognizing this genodermatosis for subsequent genetic counselling. Such cases should be kept under long-term observation because of the risk, although rare, of malignant transformation of the lesions.

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