Brooke–Spiegler Syndrome: Two Patients From a Turkish Family With Multiple Familial Trichoepithelioma

To the Editor:

Brooke–Spiegler syndrome (BSS) is a rare hereditary autosomal dominant disease. It is characterized by multiple benign skin appendageal tumors such as cylindromas, trichoepitheliomas, and spiradenomas. Familial cylindromatosis (FC) and multiple familial trichoepithelioma (MFT) are phenotypic variants of BSS. FC is characterized by cylindromas and MFT by trichoepitheliomas as the only tumor type. The cylindromatosis gene (*CYLD*) is the causative gene responsible for the development of BSS and its phenotypic variants. The *CYLD* is a tumor suppressor gene that plays a key role on regulation of NF-kB signaling pathway.[1] In this study, we present 2 cases in a Turkish family with MFT carrying the *CYLD* mutation and aim to discuss with the literature.

The case of 53-year-old male patient was referred to our clinic by the Plastic Surgery Department. The patient had a 25-year long history of multiple lesions on his face, which appeared in adolescence and slowly had been growing in sizes and numbers during the following years. Clinical examination showed the patient had numerous papules and nodules with ranging in size from 1 × 1 to 2 × 2 cm on the face mostly around the nose, periorbital area, and ears (Fig. 1). To date, results of all biopsies have supported the diagnosis of trichoepithelioma. In addition, basal cell carcinoma (BCC) has been determined in the last 2 histopathological examinations (Figs. 2 and 3).

The 19-year-old daughter of the proband also presented similar lesions but were fewer in number on her forehead, nasolabial, postauricular, and occipital regions. Her nodular and papular lesions began 8 years ago and most of them had been removed for esthetical

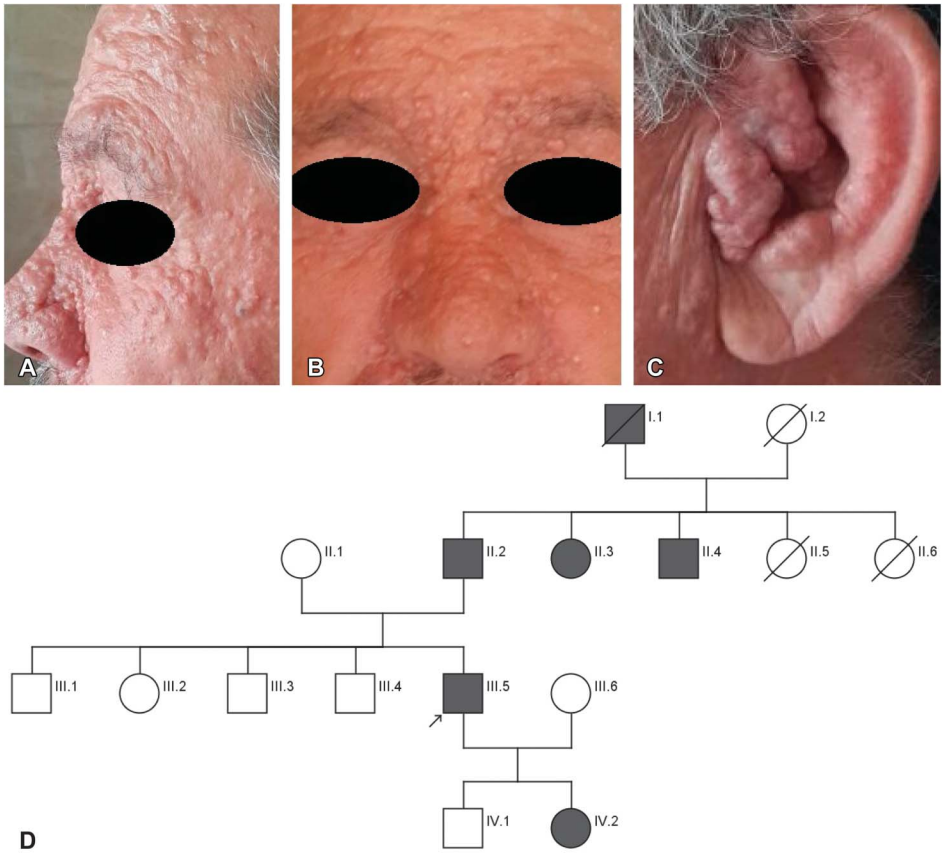

FIGURE 1. Clinical data of family with BSS. A–C, Multiple papules on the proband's face, mostly around the nose, periorbital area, and ears. D, Pedigree of the family.

The authors declare no conflicts of interest.

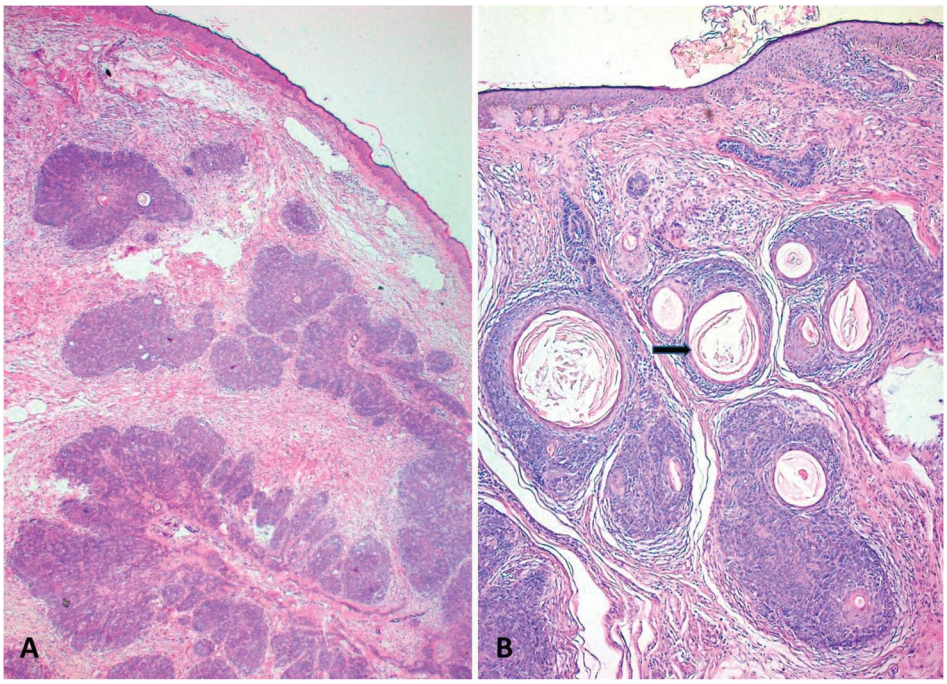

FIGURE 2. Trichoepithelioma. A, Hematoxylin eosin ×100. Nests of basaloid cells, some with abortive hair follicle differentiation. B, Hematoxylin eosin ×200. Another lesion of the same case. Basaloid lobules showing prominent keratocysts and infundibular keratinization (arrow) without epidermal continuity, retraction artifact, or stromal mucin.

reasons. Histopathological examinations of the lesions revealed trichoepithelioma. Pedigree analysis of the family is consistent and an autosomal dominant inheritance (Fig. 1).

The genetic investigations were conducted on the peripheral blood samples of the patients. From the blood sample, genomic DNA was isolated and the coding regions, and the flanking introns of the *CYLD* gene were amplified with specific primers. The polymerase chain reaction products were sequenced using ABI Prism 7000 sequencer.

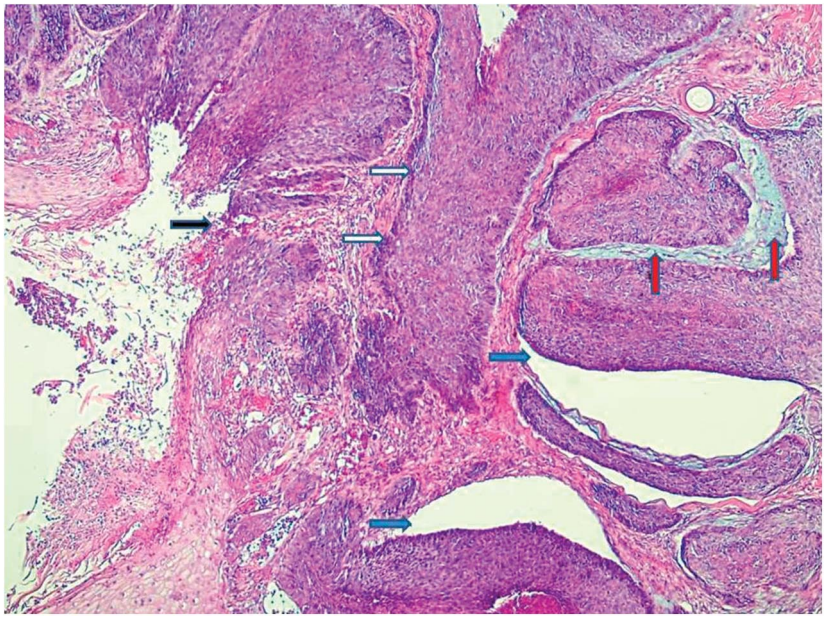

FIGURE 3. Hematoxylin eosin ×200. Basal cell carcinoma. Basaloid lobules showing peripheral palisading (white arrows) and retraction artifact (blue arrows) accompanied with stromal mucin (red arrows) and epidermal ulceration (black arrow).

Our investigations have been identified a heterozygous nonsense mutation (c.2104delA, p.Ile702X) in the 15th exon of the *CYLD* gene in 2 patients. The presence of the mutation leads to the formation of premature stop codon and thus to the synthesis of a truncated *CYLD* protein.

Until now, more than 90 mutations have been identified for the *CYLD* gene in individuals presented with the phenotypic characteristics of BSS, FC, and/or MFT in the literature. The most of reported *CYLD* mutations cause premature protein truncations. First, a germline *CYLD* mutation is inherited, and second, noninherited *CYLD* mutation or loss of heterozygosity occurs in cells for tumor formation in BSS.[2,3]

The c.2104delA, p.Ile702X mutation has been described only once in the mother and daughter by Sima et al.[4] Our patients had clinically and histopathologically diagnosed MFT, whereas their patients had multiple scalp tumors and histopathologically diagnosed cylindromas.[4] The comparisons of mutations and clinical variations have revealed that

the nonsense mutations are associated with the highest phenotypic diversity and recurrence rate, whereas missense mutations are associated with trichoepitheliomas and a milder phenotype. But, a clear genotype–phenotype correlation is currently unknown.[5,6]

Also BCC has been determined in our patient. As far as we know, the BCC has been reported for the first time with c.2104delA, p.Ile702X mutation. Trichoepitheliomas are typically benign but rarely develops BCC in patients affected with MFT. However, *CYLD* is important in more common cancers such as colorectal, hepatocellular carcinoma, and melanoma.[7]

Consequently, our report supports the view that there is a lack of genotype–phenotype correlation. In addition, the inability to establish genotype–phenotype correlation suggests different changes such as secondary epigenetic events downstream besides the *CYLD* mutations. Further studies to confirm these arguments will be helpful in elucidating the mechanism leading to phenotypic differences observed in patients carrying the same mutations. Better understanding of the molecular mechanisms of *CYLD* and BSS may help to identify new treatment options. Furthermore, physicians should be aware of the potential for the development of BCC despite commonly benign clinical presentation. Long-term follow-up of the patients will be crucial to the early diagnosis of malignancies.

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REFERENCES

1. Verhoeft KR, Ngan HL, Lui VWY. The cylindromatosis (CYLD) gene and head and neck tumorigenesis. *Cancers Head Neck.* 2016;1:10. Review.
2. Lee DA, Grossman ME, Schneiderman P, et al. Genetics of skin appendage neoplasms and related syndromes. *J Med Genet.* 2005;42:811–819.
3. Bignell GR, Warren W, Seal S, et al. Identification of the familial cylindromatosis tumour-suppressor gene. *Nat Genet.* 2000;25:160–165.
4. Sima R, Vanecek T, Kacerovska D, et al. Brooke-Spiegler syndrome: report of 10 patients from 8 families with novel germline mutations: evidence of diverse somatic mutations in the same patient regardless of tumor type. *Diagn Mol Pathol.* 2010;19:83–91.
5. Blake PW, Toro JR. Update of cylindromatosis gene (CYLD) mutations in Brooke-Spiegler syndrome: novel insights into the role of deubiquitination in cell signaling. *Hum Mutat.* 2009;30:1025–1036. Review.
6. Nagy N, Farkas K, Kemény L et al. Phenotype-genotype correlations for clinical variants caused by CYLD mutations. *Eur J Med Genet.* 2015;58:271–278. Review.
7. Kazakov DV, Schaller J, Vanecek T, et al. Brooke-Spiegler syndrome: report of a case with a novel mutation in the CYLD gene and different types of somatic mutations in benign and malignant tumors. *J Cutan Pathol.* 2010;37:886–890.