

Brooke-Spiegler Syndrome and Phenotypic Variants: An Update

Dmitry V. Kazakov^{1,2}

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Abstract Brooke-Spiegler syndrome (BSS) is an inherited autosomal dominant disease characterized by the development of multiple adnexal cutaneous neoplasms most commonly spiradenoma, cylindroma, spiradenocylindroma, and trichoepithelioma. Multiple familial trichoepithelioma (MFT) is a phenotypic variant of the disease characterized by the development of numerous trichoepitheliomas (cribriform trichoblastoma) only. Malignant tumors arise in association with preexisting benign cutaneous neoplasms in about 5–10 % of the patients. Apart from the skin, major and minor salivary glands have been rarely involved in BSS patients. Extremely rare is the occurrence of breast tumors (cylindroma). The gene implicated in the pathogenesis of the disease is the *CYLD* gene, a tumor suppressor gene located on chromosome 16q12–q13. Germline *CYLD* mutations are detected in about 80–85 % of patients with the classical BSS phenotype and in about 40–50 % of the individuals with the MFT phenotype using a PCR based approach with analysis of exonic sequences and exon–intron junctions of the *CYLD* gene. There appears to be no genotype–phenotype correlations with respect to the severity of the disease, the possibility of malignant transformation, and development of extracutaneous lesions.

Keywords Brooke-Spiegler syndrome · Cylindroma · Spiradenoma · Trichoepithelioma · *CYLD* gene

Definition and Terminology

Brooke-Spiegler syndrome (BSS, OMIM 605041) is an inherited autosomal dominant disease characterized by the development of multiple adnexal cutaneous neoplasms most commonly spiradenoma, cylindroma, spiradenocylindroma, and trichoepithelioma (cribriform trichoblastoma) [1–3]. Multiple familial trichoepitheliomas (MFT, OMIM 601606) is a phenotypic variant of the disease characterized by the development of numerous trichoepitheliomas without accompanying cylindromas, spiradenomas, and spiradenocylindromas. Familial cylindromatosis (OMIM 132700) is traditionally held as an allelic disorder within BSS and MFT, but cases presenting with cylindromas only are so rare that the term is hardly valid. Moreover, rare patients present with only spiradenomas or spiradenocylindromas; all of these conditions are better to be considered phenotypic variations of BSS due to the overlap between them at the clinical, pathological, and genetic levels [1, 4]. Malignant tumors arise in association with preexisting benign cutaneous neoplasms in about 5–10 % of patients [5–7]. The gene implicated in the pathogenesis of the disease is the *CYLD* gene, a tumor suppressor gene located on chromosome 16q12–q13 [8–10]. Apart from the skin, morphologically similar neoplasms may rarely arise in the salivary glands [5, 11–13]. Extremely rare is the occurrence of mammary cylindroma [14].

Clinical Presentation

BSS patients present with multiple tumors mostly localized to the head and neck area (Figs. 1, 2). Most nodules are in the range of 0.5–3 cm, but larger lesions can also be encountered. The number of lesions varies from 10–30 to

✉ Dmitry V. Kazakov
kazakov@medima.cz

¹ Department of Pathology, Faculty of Medicine in Pilsen, Charles University in Prague, Prague, Czech Republic

² Sikl's Department of Pathology, Charles University Medical Faculty Hospital, Alej Svobody 80, 304 60 Pilsen, Czech Republic



Fig. 1 Multiple lesions on the scalp in the patient with Brooke-Spiegler syndrome. Histologically, the lesions were spiradenomas, cylindromas, and spiradenocylindromas

several hundreds. Involvement of the scalp with multiple confluent lesions led to the designation “turban tumor” (Fig. 1). Most tumors microscopically correspond to spiradenoma, cylindroma, or spiradenocylindroma. A considerable part of the integument can be involved in severe cases. The tumors mostly appear around puberty, usually show slow growth throughout life, and their number increases with age. Rapid enlargement associated with ulceration and bleeding should raise suspicion of malignant transformation, an event seen in about 5–10 % of cases (Fig. 2) [15]. In addition to the scalp lesions, patients with the classical BSS phenotype manifest as bilateral small (0.2–1 cm) discrete and/or confluent skin colored papules preferentially involving the nasolabial folds, morphologically representing trichoepithelioma.

In patients with the MFT phenotype, the trichoepitheliomas are usually confined to the face and sometimes manifest an X-like distribution, with confluence of the lesions in the nasolabial folds and also in the inner aspects of the eyebrow with apparent continuity between the two (Fig. 3) [16]. The severity of the phenotype in MFT is just as variable as in classical BSS, ranging from dozens of neoplasms to hundreds of confluent and disfiguring lesions [17]. Extensive involvement of eyelids and external auditory canal may lead to visual impairment and hearing loss, respectively [18]. Similar to other tumors, trichoepitheliomas in MFT develop at puberty or even earlier and



Fig. 2 Large ulcerated tumor in a patient with Brooke-Spiegler syndrome. Histology is depicted in Fig. 8. The patient died of multiple metastases



Fig. 3 Multiple familial trichoepitheliomas: small bilateral papules preferentially involving the nasolabial folds. (Courtesy of Dr. Bernhard Zelger, Innsbruck, Austria)

increase in size and numbers over years. Rapid enlargement of trichoepitheliomas may also herald their malignant transformation, usually as basal cell carcinoma (BCC).

The incidence of salivary gland involvement in BSS is unknown but appears to be very rare. Of 106 cases with BSS/MFT in the author's files, only two patients developed a salivary gland tumor in addition to skin lesions. Salivary gland involvement has so far been exclusively reported in patients with the classical BSS phenotype; it appears that MFT patients are spared. The parotid gland is involved in most cases, whereas submandibular glands are rarely affected, as are minor salivary glands, including intranasal minor salivary glands [15]. Multifocal presentation with simultaneous involvement of major and minor salivary glands is exceptional but multifocal unilateral involvement of the parotid gland as well as bilateral metachronous and synchronous parotid lesions have been documented [15]. In most reported cases, salivary gland involvement occurred after the age of 40 years.

Parotid tumors usually appear clinically as a freely movable mass generally measuring between 0.5 and 5 cm in diameter, with the largest reported neoplasm reaching 14 cm [11]. Facial nerve paralyzes or visual changes are rare. It appears that occurrence of a salivary gland neoplasm in a BSS family does not imply that other family members with cutaneous lesions will ultimately develop similar salivary gland tumors.

Histopathological Features

Tumors occurring in the setting of BSS/MFT are identical to their sporadic counterparts, however, multifocality, occurrence of several different neoplasm types in a single biopsy specimen, and presence of lesions with “hybrid” histopathological features (even focally) may be indicative of a syndromic association [3, 16]. Spiradenoma manifests as a single or several variably sized, well-demarcated nodules composed of small basaloid cells intermixed with paler cells and lymphocytes, which are an integral component of the neoplasm (Fig. 4). The basaloid epithelial cells are arranged in a trabecular, reticular, or solid fashion. In some tumors, larger nodules can coalesce to form a diffuse growth pattern. A few tubular structures are often present as are droplets of PAS-positive hyaline basal membrane material. Cylindroma manifests as a jigsaw puzzle arrangement of nodules of monomorphic basaloid cells containing and/or surrounded by eosinophilic basement membrane material. The peripheral cells often show palisading and are usually darker than the cells located in the central parts of the nodules. Intraepithelial lymphocytes are lacking or are very few in number (Fig. 5). Spiradenocylindroma manifests as areas typical of both cylindroma and spiradenoma, with spiradenomatous and cylindromatous elements being either closely intermingled within a given lesion or sharply segregated (Fig. 6). Focal

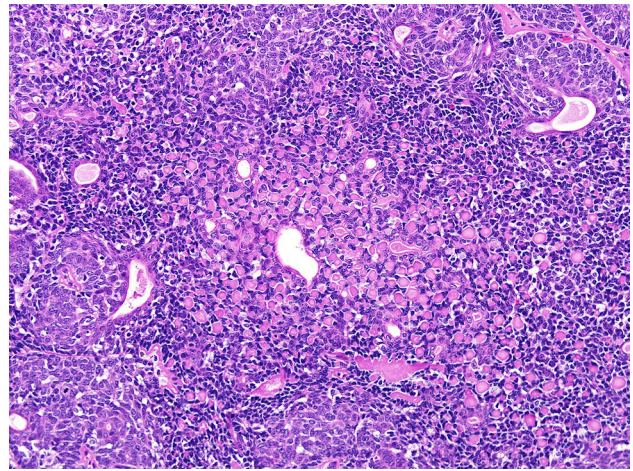


Fig. 4 Spiradenoma. Bland basaloid cells admixed with lymphocytes and droplets of basal membrane material. Focal ductal differentiation can be recognized

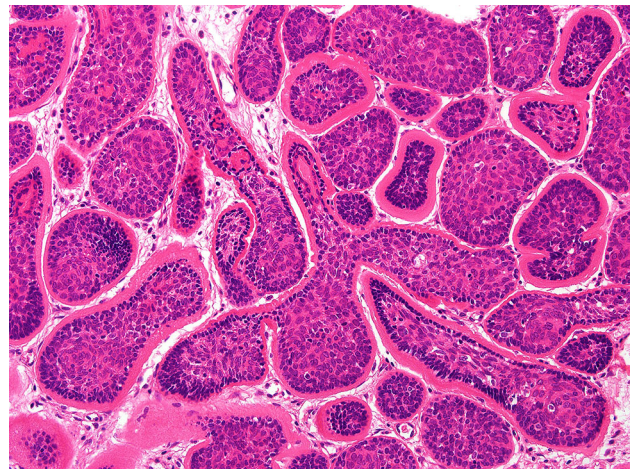


Fig. 5 Cylindroma. The neoplastic nodules are arranged in a jigsaw puzzle and are composed of monomorphic basaloid cells surrounded by eosinophilic basement membrane material. The cells at the periphery show palisading and are darker than the cells located in the central parts of the nodules

sebaceous and/or follicular differentiation has been reported [3].

Trichoepithelioma (cribriform trichoblastoma) is biphasic neoplasm with dual differentiation toward follicular germinative epithelium and specific follicular stroma. The epithelial component is composed of bland basaloid cells arranged in a cribriform pattern; the stroma resembles follicular papillae (papillary mesenchymal bodies) and the perifollicular sheath being composed of delicate fibrillary collagen bundles and numerous spindled fibroblasts (Fig. 7). Areas with ductal differentiation and intratumoral lymphocytes resembling a spiradenomatous moiety have been reported in MFT patients. Apart from trichoepithelioma, small nodular and large nodular trichoblastomas can rarely be seen [19].

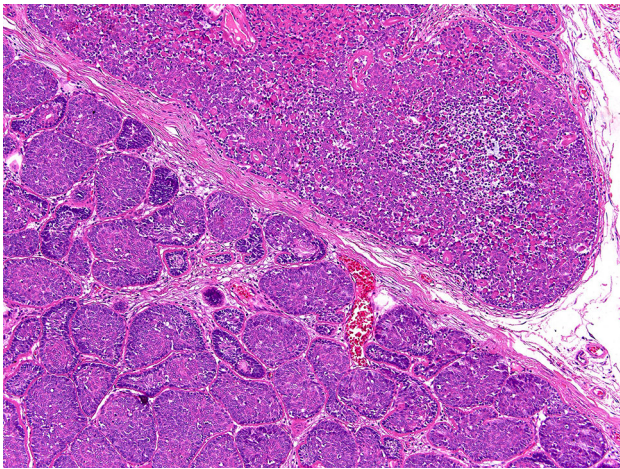


Fig. 6 Spiradenocylindroma. The lesion manifest in areas of typical cylindroma (*lower part*) as well as of spiradenoma (*upper part*)

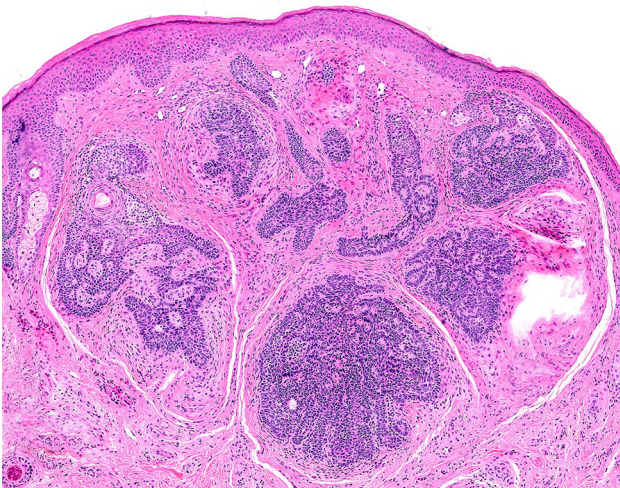


Fig. 7 Trichoepithelioma (cribriform trichoblastoma). The neoplasm has two components, namely the follicular germinative epithelium and the specific follicular stroma. The epithelial component is composed of bland basaloid cells arranged in a cribriform pattern, whereas the stroma resembles follicular papillae and the perifollicular sheath

Malignant tumors evolving from the preexisting spiradenoma, cylindroma and spiradenocylindroma manifest in four main morphological patterns, occurring alone or in combination, namely (a) salivary gland type basal cell adenocarcinoma-like pattern, low-grade (BCAC-LG); (b) salivary gland type basal cell adenocarcinoma-like pattern, high-grade (BCAC-HG); (c) invasive adenocarcinoma, not otherwise specified (IAC-NOS); (d) sarcomatoid (metaplastic) carcinoma [6]. The proposed terminology for the first two patterns reflects the strong histopathological resemblance of these cutaneous tumors to basal cell adenoma/adenocarcinoma of salivary glands, neoplasms which closely resemble cutaneous cylindroma/spiradenoma (for

example, the membranous variety of basal cell adenoma of the salivary gland is morphologically identical to cutaneous cylindroma). The first two patterns appear to be more common in the setting of BSS in comparison with a sporadic disease. Microscopically, the transition between the benign preexisting tumor and the malignant neoplasm can be gradual or abrupt. The BCAC-LG pattern appears as small to medium-sized basaloid cells arranged in nodules or sheets of varying size and shape, sometimes with focal peripheral palisading, which have replaced the dual epithelial populations of the original benign neoplasm. Nuclear pleomorphism is mild to moderate, nucleoli are small or absent, and the cytoplasm is scant but the tumor manifests an infiltrative growth pattern. In case of malignant transformation of spiradenoma, lymphocytes are absent or sparse in the malignant areas.

Lesions with the BCAC-HG pattern are composed of medium-sized to large pleomorphic basaloid cells growing as confluent sheets and nodules in an infiltrative pattern, eliciting sometimes a desmoplastic stromal reaction. The cells usually have scant cytoplasm and vesicular nuclei containing conspicuous nucleoli. Atypical mitoses are plentiful. The typical dual cell population seen in the parent benign neoplasm is lost, as are usually intratumoral lymphocytes, which may surround the malignant islands (Fig. 8). With respect to MFT, small and large nodular variants of BCC have been reported [16, 19, 20].

As far as salivary glands are concerned, the most common benign tumor is the membranous type of basal cell adenoma. Distinctive lesions in patients with BSS, thought to represent precursor lesions to basal cell adenoma or its incipient variations have been reported. The appearances include hyperplasia of reserve cells in intercalated ducts with or without extension into the lumen, more advanced lesions seen as proliferative lobular buds sometimes with the formation of prominent hyaline material, and microadenomatous foci adjacent to intercalated ducts or acini [21, 22].

Malignant salivary gland tumors in patients with BSS appear to be extremely rare, are assumed to result from malignant transformation of a preexisting membranous basal cell adenoma, and are best classified as either low-grade or high-grade basal cell adenocarcinoma [23, 24]. Anaplastic epidermoid carcinoma and a basaloid lesion focally resembling adenoid cystic carcinoma have also been described [5, 22].

Molecular Biology

The *CYLD* gene contains 20 exons, of which the first three are untranslated, and extends over approximately 56 kb of genomic DNA. *CYLD* encodes a deubiquitinating enzyme that negatively regulates the nuclear factor-kappa B and

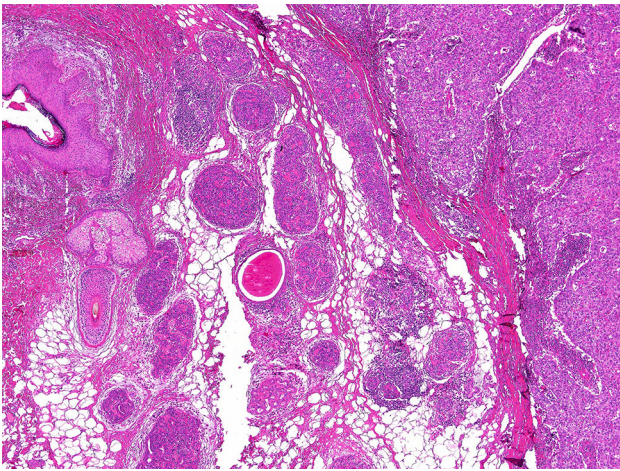


Fig. 8 High-grade malignant tumor composed of large basophilic cells evolving from a pre-existing spiradenoma, remnants of which can be recognized at the *left*. The malignant part can be likened to high-grade salivary gland basal cell adenocarcinoma

c-Jun N-terminal kinase pathways by removing lysine 63-linked polyubiquitin chains from several specific substrates. Germline *CYLD* mutations are detected in about 80–85 % of patients with the classical BSS phenotype and in about 40–50 % of the individuals with the MFT phenotype using a PCR based approach with analysis of exonic sequences and exon–intron junctions of the *CYLD* gene [16, 25, 26]. Most mutations (~50 %) are frameshift (~25 %), nonsense (~15 %), missense, and (~10 %) putative splice-site, and the vast majority of the mutations are predicted to result in truncated proteins. There is no hotspot but most mutations have been detected in exons 9–20, whereas exons 4–8 are spared [27]. Reasons for the absence of a demonstrable *CYLD* mutation are being intensively investigated; large deletions in *CYLD* and mutations in intronic sequences leading to intronic exonization have been detected in a subset of those patients [28–30]. There appears to be no genotype-phenotype correlations with respect to the severity of the disease, the possibility of malignant transformation, and development of extracutaneous lesions. Variability of phenotypic expression between and within families with the same germline *CYLD* mutation has been documented [8, 26, 27].

Cutaneous neoplasms associated with BSS harbor a large spectrum of somatic mutations representing both loss of heterozygosity (LOH) and sequence alterations. Somatic alterations may differ among multiple neoplasms even of the same histopathological type, occurring in the same patient [26].

Compliance with Ethical Standards

Conflict of interest The author has nothing to disclose to the editor any direct or indirect financial implication that publication of this paper may have for them, their relatives, or their institution.

References

1. Clarke J, Ioffreda M, Helm KF. Multiple familial trichoepitheliomas: a folliculosebaceous-apocrine genodermatosis. *Am J Dermatopathol*. 2002;24:402–5.
2. Bignell GR, Warren W, Seal S, et al. Identification of the familial cylindromatosis tumour-suppressor gene. *Nat Genet*. 2000;25:160–5.
3. Kazakov DV, Soukup R, Mukensnabl P, et al. Brooke-Spiegler syndrome: report of a case with combined lesions containing cylindromatous, spiradenomatous, trichoblastomatous, and sebaceous differentiation. *Am J Dermatopathol*. 2005;27:27–33.
4. Puig L, Nadal C, Fernandez-Figueras MT, et al. Brooke-Spiegler syndrome variant: segregation of tumor types with mixed differentiation in two generations. *Am J Dermatopathol*. 1998;20:56–60.
5. Antonescu CR, Terzakis JA. Multiple malignant cylindromas of skin in association with basal cell adenocarcinoma with adenoid cystic features of minor salivary gland. *J Cutan Pathol*. 1997;24:449–53.
6. Kazakov DV, Zelger B, Rutten A, et al. Morphologic diversity of malignant neoplasms arising in preexisting spiradenoma, cylindroma, and spiradenocylindroma based on the study of 24 cases, sporadic or occurring in the setting of Brooke-Spiegler syndrome. *Am J Surg Pathol*. 2009;33:705–19.
7. Tantcheva-Poór I, Vanecek T, Lurati MC, et al. Report of three novel germline *CYLD* mutations in unrelated patients with Brooke-Spiegler syndrome, including classic phenotype, multiple familial trichoepitheliomas and malignant transformation. *Dermatology* 2016;232(1):30–7. doi:10.1159/000437303.
8. Bowen S, Gill M, Lee DA, et al. Mutations in the *CYLD* gene in Brooke-Spiegler syndrome, familial cylindromatosis, and multiple familial trichoepithelioma: lack of genotype-phenotype correlation. *J Invest Dermatol*. 2005;124:919–20.
9. Young AL, Kellermayer R, Szigeti R, et al. *CYLD* mutations underlie Brooke-Spiegler, familial cylindromatosis, and multiple familial trichoepithelioma syndromes. *Clin Genet*. 2006;70:246–9.
10. Saggat S, Chernoff KA, Lodha S, et al. *CYLD* mutations in familial skin appendage tumours. *J Med Genet*. 2008;45:298–302.
11. Pingitore R, Campani D. Salivary gland involvement in a case of dermal eccrine cylindroma of the scalp (turban tumor). Report of a case with lung metastases. *Tumori*. 1984;70:385–8.
12. Rockerbie N, Solomon AR, Woo TY, et al. Malignant dermal cylindroma in a patient with multiple dermal cylindromas, trichoepitheliomas, and bilateral dermal analogue tumors of the parotid gland. *Am J Dermatopathol*. 1989;11:353–9.
13. Scott AR, Faquin WC, Deschler DG. Parotid mass in a woman with multiple cutaneous cylindromas. *Head Neck*. 2010;32:684–7.
14. Nonaka D, Rosai J, Spagnolo D, et al. Cylindroma of the breast of skin adnexal type: a study of 4 cases. *Am J Surg Pathol*. 2004;28:1070–5.
15. Zarbo RJ, Ricci A Jr, Kowalczyk PD, et al. Intranasal dermal analogue tumor (membranous basal cell adenoma). Ultrastructure and immunohistochemistry. *Arch Otolaryngol*. 1985;111:333–7.
16. Kazakov DV, Michal M, Kacerovska D, et al. Cutaneous adnexal tumors. Philadelphia: LWW; 2012. p. 814.
17. Linos K, Schwartz J, Kazakov DV, et al. Recurrent *CYLD* nonsense mutation associated with a severe, disfiguring phenotype in an African American family with multiple familial trichoepithelioma. *Am J Dermatopathol*. 2011;33:640–2.
18. Hester CC, Moscato EE, Kazakov DV, et al. A new cylindromatosis (*CYLD*) gene mutation in a case of Brooke-Spiegler syndrome masquerading as basal cell carcinoma of the eyelids. *Ophthalmic Plast Reconstr Surg*. 2013;29:e10–1.

19. Kazakov DV, Vanecek T, Nemcova J, et al. Spectrum of tumors with follicular differentiation in a patient with the clinical phenotype of multiple familial trichoepitheliomas: a clinicopathological and molecular biological study, including analysis of the *CYLD* and *PTCH* genes. *Am J Dermatopathol*. 2009;31:819–27.
20. Pincus LB, McCalmont TH, Neuhaus IM, et al. Basal cell carcinomas arising within multiple trichoepitheliomas. *J Cutan Pathol*. 2008;35(Suppl 1):59–64.
21. Headington JT, Batsakis JG, Beals TF, et al. Membranous basal cell adenoma of parotid gland, dermal cylindromas, and trichoepitheliomas. Comparative histochemistry and ultrastructure. *Cancer*. 1977;39:2460–9.
22. Reingold IM, Keasbey LE, Graham JH. Multicentric dermal-type cylindromas of the parotid glands in a patient with florid turban tumor. *Cancer*. 1977;40:1702–10.
23. Ellis GL, Wiscovitch JG. Basal cell adenocarcinomas of the major salivary glands. *Oral Surg Oral Med Oral Pathol*. 1990;69:461–9.
24. Hyman BA, Scheithauer BW, Weiland LH, et al. Membranous basal cell adenoma of the parotid gland. Malignant transformation in a patient with multiple dermal cylindromas. *Arch Pathol Lab Med*. 1988;112:209–11.
25. 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;37:886–90.
26. 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.
27. Grossmann P, Vanecek T, Steiner P, et al. Novel and recurrent germline and somatic mutations in a cohort of 67 patients from 48 families with Brooke-Spiegler syndrome including the phenotypic variant of multiple familial trichoepitheliomas and correlation with the histopathologic findings in 379 biopsy specimens. *Am J Dermatopathol*. 2013;35:34–44.
28. Kazakov DV, Thoma-Uszynski S, Vanecek T, et al. A case of Brooke-Spiegler syndrome with a novel germline deep intronic mutation in the *CYLD* gene leading to intronic exonization, diverse somatic mutations, and unusual histology. *Am J Dermatopathol*. 2009;31:664–73.
29. van den Ouweland AM, Elfferich P, Lamping R, et al. Identification of a large rearrangement in *CYLD* as a cause of familial cylindromatosis. *Fam Cancer*. 2011;10:127–32.
30. Vanecek T, Halbhuber Z, Kacerovska D, et al. Large germline deletions of the *CYLD* gene in patients with Brooke-Spiegler syndrome and multiple familial trichoepithelioma. *Am J Dermatopathol*. 2014;36:868–74.