

Brooke-Spiegler Syndrome: A Case Report

Sarah Malerich, DO,* Danielle R. Lazzara, DO,** Alpesh Desai, DO***

*Dermatology Resident, 1st Year, Dermatology South Texas/University of North Texas Health Science Center, Houston, TX

**Rowan University School of Osteopathic Medicine, Stratford, NJ

***Program Director, Dermatology Residency, Dermatology South Texas/University of North Texas Health Science Center, Houston, TX

Disclosures: None

Correspondence: Sarah Malerich, DO; sarahmalerich@gmail.com

Abstract

Brooke-Spiegler syndrome (BSS) is a rare, inherited, autosomal-dominant genodermatosis characterized by the development of multiple adnexal cutaneous tumors including spiradenomas, cylindromas, spiradenocylindromas, trichoepitheliomas, epidermoid cysts, and milia. We present a case of Brooke-Spiegler syndrome with possible malignant transformation of a benign tumor.

Introduction

Brooke-Spiegler syndrome (BSS) is a rare, inherited, autosomal-dominant genodermatosis characterized by the development of multiple adnexal cutaneous tumors including spiradenomas, cylindromas, spiradenocylindromas, trichoepitheliomas, epidermoid cysts, and milia.¹⁻¹¹ Mutations identified in the cylindromatosis (CYLD) gene, mapped to chromosome 16q12-q13 via locus analysis, leads to aberrant regulation of putative stem cells of the follicular-sebaceous-apocrine unit, predisposing individuals to the gradual development of skin appendage neoplasms.^{3,4,10}

BSS has variable expressivity and incomplete penetrance; however, a high penetrance for adnexal tumors is observed in relation to increasing age of mutation carriers.^{3,7} A spectrum of phenotypic

presentations has been described in association with CYLD mutations, including familial cylindromatosis (FC) and multiple familial trichoepitheliomatosis (MFT), clinically defined by cutaneous cylindromas and trichoepitheliomas, respectively.^{3,4,7,9,10} Rarely, patients may present with solely cutaneous spiradenomas or spiradenocylindromas.¹⁰ Although FC, MFT, and BSS were classically considered distinct entities, BSS is now widely accepted to encompass all clinical variants, as the syndromes exhibit clinical, histological, and genetic overlaps consistent with phenotypic variations of the same disease.^{3,4,9,10} In fact, intrafamilial phenotypic variability amongst individuals with the same germline CYLD mutations has been frequently documented, further demonstrating the variability of BSS and a lack of genotype-phenotype correlation.⁷

Cutaneous tumors have a predilection for the face and neck and can range in number from 10 to several hundred, and thus can be physically disfiguring and psychologically distressing.^{7,10} Apart from cosmetic concerns, tumors in close proximity to the eyes and ears can impair the senses.^{1,9,10} Progressively growing cylindromas or spiradenomas overlying the external ear can occlude the external auditory canal, resulting in deafness.⁹ Benign adnexal tumors have the potential to undergo malignant transformation, which is notably more common in BSS than in the sporadic form.^{7,10} Extracutaneous, morphologically similar neoplasms can also arise in the salivary glands in association with BSS.^{1,2,4,7,9,10,12,13} It is highly recommended for patients presenting with multiple adnexal neoplasms to be referred for genetic testing and receive regular dermatologic examination to best manage therapy and monitor for malignant transformation of tumors.^{1,7,10}



Figure 1

Case Report

An 84-year-old female with a medical history of multiple firm, pink nodules with surface telangiectasias involving the forehead, external ears, and scalp presented to our clinic with the complaint of painful nodular growth (Figure 1). The patient had a family history of similar lesions in her brother, sister and mother.

A 1.6 cm x 0.5 cm biopsy was taken from the largest lesion. Histologic findings showed multiple nests of basaloid cells forming a jigsaw-like pattern with scant stroma surrounded by eosinophilic, hyaline-rich sheaths, consistent with cylindroma (Figures 2, 3 [p. 21]).

The patient returned to our clinic two weeks later complaining of continued growth of the lesion with increased pain. An excision was performed, measuring 2.7 cm x 2.2 cm x 1.3 cm. The pathology report, discussed at dermatopathology consensus conference, was read as adnexal neoplasm, favoring cylindroma, with re-excision recommended to rule out malignant transformation of the benign tumor.

The patient was referred to facial plastic surgery for complete wide-margin excision and reconstruction. At the time of visit, three additional biopsies were taken from sites the patient deemed bothersome and were diagnosed as benign spiradenomas (2) and cylindroma (1). Histopathological examination revealed a lymphocytic cell population with basaloid cells arranged in rosettes, characteristic of spiradenomas, while the other tumor exhibited discrete nests in a jigsaw-puzzle pattern, representing a cylindroma. Given the patient's presentation of multiple adnexal cutaneous tumors,

along with family history and the autosomal-dominant inheritance pattern of Brooke-Spiegler syndrome, the patient was diagnosed with BSS.

Discussion

BSS, a rare, autosomal-dominant disorder, results from various mutations in the *CYLD* gene. *CYLD* normally encodes a deubiquitinating enzyme that negatively regulates nuclear factor-kappa-B, an adnexal proliferator inducer or tumor regulator protein.^{1,3,4,7,10,14} Via the two-hit hypothesis, loss of *CYLD* gene function results in tumorigenesis, clinically apparent in BSS. To date, an estimated 100 varied *CYLD* mutations have been identified, mainly frameshift and nonsense and the remainder missense or putative splice-site mutations, resulting in truncated proteins.^{9,10} Nonsense mutations are associated with the highest phenotypic variability and recurrence rate, while missense mutations often result in the MFT phenotype.⁶ Marked phenotypic variability between and within families with the same germline mutation is well documented.^{8,10} BSS encompasses all clinical variants, including FC and MFT, which were originally regarded as distinct clinical entities. Clinical variants are better represented as a phenotypic spectrum of BSS, accounting for overlap manifestations exhibited between described syndromes.^{6,10} Referral for genetic testing may be considered to confirm the diagnosis, as this will allow the clinician to educate the patient on inheritance pattern, which may impact family planning.

BSS patients often develop multiple cutaneous adnexal tumors favoring localization to the head and neck region. Cutaneous tumors associated with the syndrome typically present around puberty but can appear as late as the third or fourth decade, and gradually enlarge and proliferate in number throughout life.^{7,11} Tumors are generally asymptomatic; however, pain has been reported in up to 50% of patients and may be attributed to nerve compression.¹⁴ Trichoepitheliomas can present as the primary cutaneous manifestation of BSS and are defined as discrete or grouped, small, skin-toned, translucent papules frequently affecting the central face, particularly the nasolabial folds.^{6,10} Cylindromas are slow-growing eccrine sweat gland tumors that appear as firm, rubbery, pink-to-red, hemispherical nodules of variable size with surface telangiectasias most commonly involving the scalp and face.^{6,11,16} In BSS, cylindromas are often multiple in number and can become confluent on the scalp, a disfiguring presentation referred to as "turban-tumor."^{6,11,15} Spiradenomas are eccrine tumors, postulated to be differentiated from a common stem cell origin that gives rise to cylindromas, as evidenced by the hybrid spiradenocylindroma tumor described in BSS patients.^{6,10,16} Spiradenomas are blue-to-purple nodules, typically located on the ventral, upper portion of the body such as the upper extremities.⁶ Due to the tendency of these multiple skin appendage tumors to increase in size and number, affected individuals can suffer from extensive cosmetic deformation with immense psychological, social, and occupational impacts.⁸

In addition to cosmetic concerns, benign tumors have the potential to undergo transformation to their malignant counterparts. Malignant transformation is estimated to occur in 5% to 10% of BSS patients¹⁰ and should be suspected if lesions rapidly enlarge, change in color, bleed, or ulcerate.^{2,7,13,14,17-19}

Subjective complaint of painful tumors is indication for excisional removal.⁹ Albeit rare, malignant adnexal neoplasms reported in the literature include cylindrocarcinoma, spiradenocarcinoma, and spiradenocylindrocarcinoma.^{3,5,6,12,13,19} Akgul et al. identified a total of 72 well-documented cases of cylindrocarcinoma via Pubmed database search, and of those cases, 10 patients developed lymph node and distant metastasis.¹⁸ Rare reports of trichoepithelioma degeneration to basal cell carcinoma have also been described.^{1,2,8,9,10} Extremely rare are reports of BSS associated with major and minor salivary gland tumors.^{1,2,4,7,10,12} Membranous basal cell adenoma is a dermal-analogue salivary gland tumor histologically identical to cutaneous cylindroma, which accounts for less than 2% of all salivary gland tumors. Basal cell adenocarcinoma, the malignant equivalent of membranous basal cell adenoma, can also manifest in BSS cases.^{4,12} Kazakov et al. reports an unusual case of a 68-year-old woman with a parotid gland tumor identical to cutaneous spiradenoma with partial transformation to basal cell adenocarcinoma.¹² Notably, the patient lacked features of BSS, and *CYLD* gene analysis displayed polymorphisms.¹² *CYLD* mutations have been identified in parotid-gland basal cell adenocarcinoma. Bowen et al. describes a BSS patient with a determined *CYLD*-6 mutation presenting with bilateral parotid-gland basal cell adenocarcinoma, evidencing syndrome association with germline *CYLD* mutations and the development of salivary gland malignancy.⁴ Cases of adenoid cystic carcinoma have also been reported.^{10,14} Despite undetermined patient risk factor, salivary gland tumors should be suspected in individuals with cutaneous tumors localized to the face in close proximity to salivary glands.^{7,12} BSS patients are particularly susceptible due to *CYLD* mutations and should be evaluated for salivary gland tumors, so close dermatology follow-up is highly recommended for individuals with BSS.^{1,7,10}

BSS tumors share histopathologic features with sporadic tumor forms.¹⁰ It is not unusual for a single biopsy specimen to exhibit multiple neoplastic morphologies or histologic evidence of hybrid tumors, such as the spiradenocylindroma, when associated with the syndrome as opposed to the sporadic form.^{5,10,12} In fact, cylindromas and spiradenomas are considered histologic extremes of the same neoplasm.⁹ Despite histological overlap, characteristic features distinguish these tumors. Cylindromas are well-circumscribed dermal nodules formed by monomorphic, basaloid cells arranged in a jigsaw-puzzle pattern and surrounded by eosinophilic basement membrane, hyaline material.^{6,10,11} Central cells are paler than palisading peripheral cells, creating dual epithelial cells.^{6,10} In contrast, spiradenomas are comprised of lymphocytes and lack the jigsaw arrangement typical of cylindromas.¹² Spiradenomas are dermal nodules composed of small, dark, basaloid epithelial cells arranged in a rosette pattern. The other prominent cell type is a large, pale-colored cell found at the center of the tumor nests.^{6,10,11} Trichoepitheliomas are characterized by basaloid palisading cells forming nests or cribriform patterns surrounded by fibroblast and collagen bundle-rich stroma.^{3,6,10,11} Multiple horn cysts are sometimes present.¹¹

Malignant transformation of cutaneous adnexal tumors is confirmed by histology and often requires a whole-tumor specimen to appreciate the overall architecture of the neoplasm, which displays

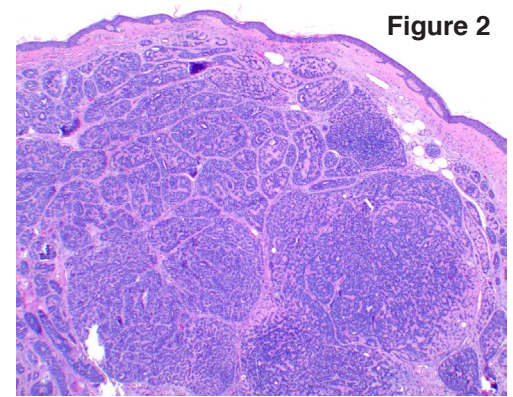


Figure 2

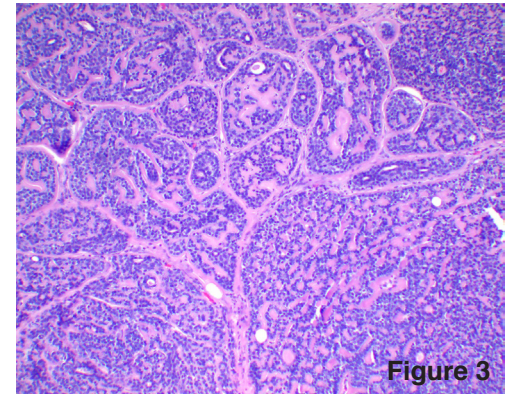


Figure 3

heterogeneity, with benign portions accounting for 5% to 40% of the tumor.^{3,13} Transition from benign preexisting tumor to malignant pathology can be gradual or abrupt.¹⁰ Four main patterns of malignant cutaneous neoplasms are recognized: low-grade salivary gland-type basal cell adenocarcinoma-like pattern; high-grade salivary gland-type basal cell adenocarcinoma-like pattern; sarcomatoid (metaplastic) carcinoma; and invasive adenocarcinoma, not otherwise specified.^{10,12,13} In low-grade salivary gland-type basal cell adenocarcinoma, small-to-medium basaloid cells form nodules varying in shape and size, with peripheral palisading occasionally present.¹⁰ Cell nucleoli are small or absent, cytoplasm is scant and an infiltrative growth pattern is appreciated. High-grade pattern malignant tumors display medium-to-large pleomorphic basaloid cells forming an infiltrative pattern of confluent sheets and nodules. The cells have vesicular nuclei, scant cytoplasm, and high mitotic count. Loss of dual epithelial cells and lymphocytes characteristic of the precursor benign tumor are other distinguishing features.^{9,10}

Treatment of BSS is mainly aimed to improve cosmesis and includes resurfacing modalities such as thermal electrodesiccation, cryotherapy, dermabrasion, trichloroacetic acid, retinoic acid, and erbium-YAG/carbon dioxide (CO₂) laser.^{3,8,9,17,19} Resurfacing therapy is most appropriate and effective for trichoepitheliomas; however, patients will need repeat treatments due to recurrence of lesions.^{9,17} Surgical excision of tumors with wide local excision or Mohs micrographic surgery is most effective and preferred due to potential malignant transformation of benign neoplasms.^{3,17,19} Tumors are quite vascular and require a substantial blood supply to support growth, posing a challenge to the excision of large, confluent neoplasms.^{9,19} Jatan et al. reports use of pre-operative radiological embolization to minimize bleeding and maximize extent of tumor excision.¹⁹ Radiotherapy has been

used for large field treatment of cylindromas and spiradenomas but may invoke further DNA damage and promotion of tumor development in adjacent cells.^{3,9,17,19} Malignant cutaneous tumors must be diagnosed in a timely fashion in order to promptly begin treatment.¹⁴ Current literature indicates wide surgical excision with a minimum of 2 cm lateral margins and 1 cm basal margins, wound closure using flap techniques and/or partial thickness skin grafts, and subsequent radiotherapy to decrease risk of tumor recurrence.^{5,14,15,18} In rare cases of adnexal tumor malignancy with lymph node involvement, favorable patient outcome status-post excision is significantly reduced, and patients often succumb to disease.¹³ Patients should receive early treatment to minimize disfigurement secondary to tumor development and regular dermatologic evaluation to monitor lesions and detect potential malignancies.^{8,7}

Causative therapy for BSS remains under investigation.⁶ Recent studies have revealed impaired tropomyosin kinase (TRK) signaling associated with CYLD mutations, as well as overexpression of TRK in cylindroma cells.^{6,9} Utilization of a TRK inhibitor molecule, lestaurtinib, may serve as a novel causative treatment option for BSS patients.^{6,9} Continued genetic studies are necessary to further develop effective, causative therapies that significantly improve patient outcomes beyond the symptomatic relief provided by current treatment modalities.⁶

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