Brooke-Spiegler Syndrome With Associated Pegged Teeth

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GOAL

To understand Brooke-Spiegler syndrome (BSS) to better manage patients with the condition

LEARNING OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Recognize the classic triad of lesions in patients with BSS.
2. Describe the effect of gene mutations in BSS.
3. Propose treatments for BSS based on the malignant potential of lesions.

CME Test on page 328.

This article has been peer reviewed and approved by Ranon Ephraim Mann, MD, Assistant Professor, Department of Medicine (Dermatology), Montefiore Medical Center Medical Arts Pavilion. Review date: October 2008.

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Drs. Carlson, Haddad, and Pui report no conflict of interest. The authors report no discussion of off-label use. Dr. Mann reports no conflict of interest.

The occurrence of cylindromas, trichoepitheliomas, and spiradenomas completes the triad for Brooke-Spiegler syndrome (BSS). This combination represents a rare genetic syndrome with tumors expressing adnexal differentiation. Malignant transformation is rare but reported, and surgical excision is warranted to prevent turban tumor formation of the scalp. Genetic testing is encouraged, with mutations present on the cylindromatosis gene, CYLD, *locus. The occurrence of pegged teeth in our patient was most interesting, as it has not been reported in the literature in patients with BSS.*

Cutis. 2008;82:345-349.

Accepted for publication October 1, 2007.

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This case was presented in part at the American Osteopathic College of Dermatology Annual Meeting; September 30-October 4, 2007; San Diego, California; and at the Michigan Dermatological Society Meeting; April 4, 2007; Troy, Michigan.

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In the late 19th century, Brooke and Spiegler described the familial occurrence of multiple tumors of the skin appendages. Synonyms have included familial cylindromatosis, turban tumor syndrome, and Brooke-Spiegler syndrome (BSS).[1] In

this report, we describe a patient with pegged teeth and BSS. We discuss the pathogenesis, diagnosis, genetic testing, and treatment options for this interesting syndrome.

Case Report

A 40-year-old white woman presented in 1997 for evaluation of numerous flesh-colored papules on her face. One of the lesions was biopsied in 1999 and diagnosed as a trichoepithelioma (Figure 1). These particular lesions had been present since she was 13 years of age, increasing in size and number with time. Subsequently, in December 2003, she presented with a 0.8-cm pink papule in the left preauricular area; a biopsy was performed and a spiradenoma in association with a trichoepithelioma was diagnosed. In January 2006, she presented with enlarging "bumps" on her scalp. She denied any substantial pain, pruritus, or other symptoms, but was rather concerned about the recent growth of lesions, both in size and number. Her medical history was noncontributory. However, there was a family history of similar lesions on the face and scalp of a great-aunt and uncle. No workup or genetic testing was ever performed.

Physical examination revealed a healthy, well-nourished, middle-aged woman. There were numerous symmetrically distributed flesh-colored to off-white firm papules involving the bilateral nasolabial folds, coalescing in areas to form plaques (Figure 2). There were 3 pink, firm, smooth, well-circumscribed nodules with overlying telangiectases involving the vertex and crown of the scalp, measuring 0.7×0.7 cm, 1.4×1.1 cm, and 1.4×1.4 cm in size. There was mild tenderness to palpation of all 3 lesions. Most interestingly, examination of the oral cavity revealed pegged (conical) teeth (Figure 3). It was not clear if they were primary or secondary teeth. There was no history of incontinentia pigmenti or any other ectodermal dysplasia in the patient or family members. Further evaluation of the hair and nails revealed no additional abnormalities.

The differential diagnoses for the scalp lesions included pilar cysts, basal or squamous cell carcinomas, spiradenomas, cylindromas, trichoblastomas, neurofibromas, and keloids or hypertrophic scars. The patient underwent an excisional biopsy of the smallest lesion in February 2006. Subsequently, excisional biopsies were performed on the other 2 lesions in April and July 2006. The first specimen revealed variably sized discrete aggregations of cuboidal epithelial cells with a rim of thickened eosinophilic basement membrane material surrounding tumor islands. There were 2 types of epithelial cells: cells with small, dark-staining nuclei present at the periphery in a palisading fashion, and light-staining nuclei lying in the center of the aggregations. Sweat duct lumina were appreciated within the tumor islands, and a diagnosis of cylindroma was made. The second biopsy showed a single, large, well-demarcated nodule of cuboidal epithelial cells arranged in interweaving cords present in the dermis. Again, there were 2 types of epithelial cells: smaller cells with dark nuclei lying at the periphery of the cords, and cells with larger pale nuclei in the center of the cords, associated with lumina. A diagnosis of spiradenoma was rendered. Based on the clinical findings and histopathologic diagnoses of trichoepithelioma, cylindroma, and spiradenoma, the patient received a diagnosis of BSS.

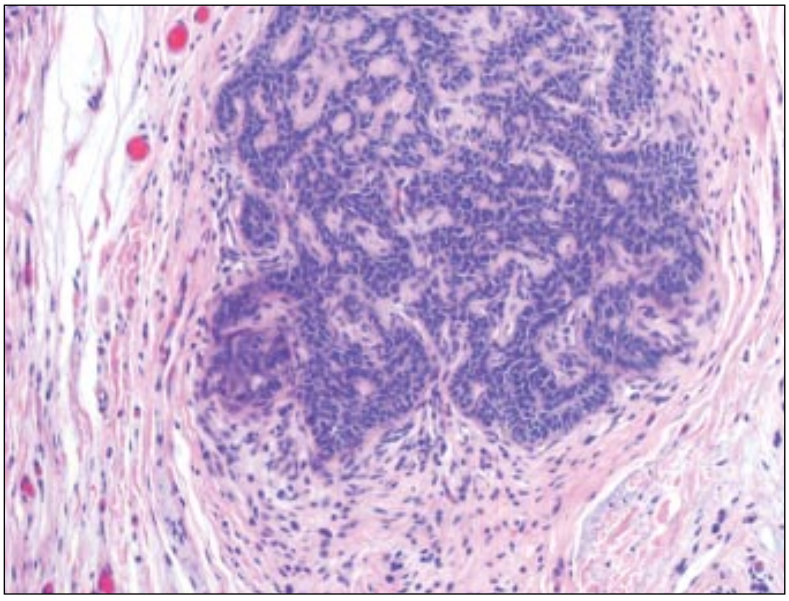

Figure 1. There are several well-circumscribed basaloid tumor islands arranged in a reticulated or cribriform pattern. Several areas of infundibular keratinization are present. Peripheral palisading of nuclei is apparent without retraction artifact. There is a loose collagenous stroma with many fibroblasts surrounding the basaloid tumor islands, with areas of papillary mesenchymal body formation (H&E, original magnification ×20).

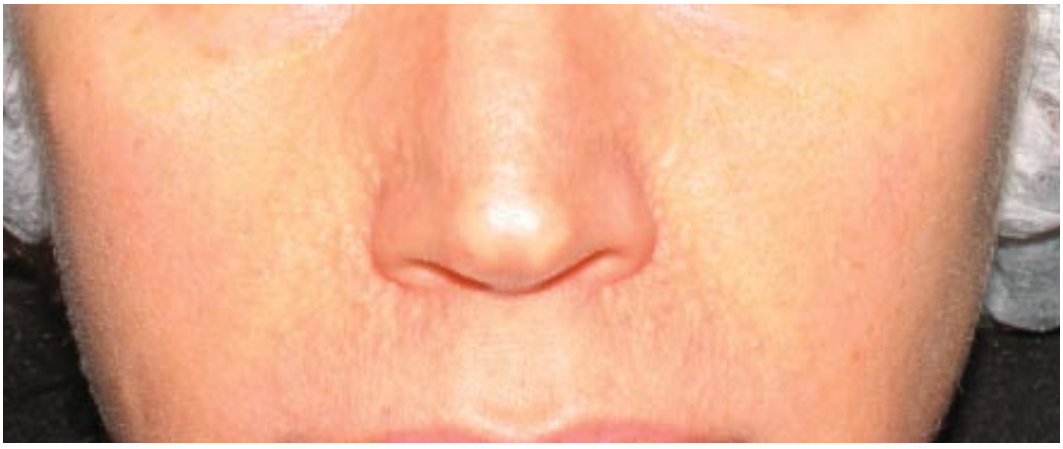

Figure 2. Numerous flesh-colored to off-white papules involving the bilateral nasolabial folds.

Treatment for the trichoepitheliomas consisted of several glycolic acid peels, and the patient was pleased with the results. Furthermore, complete excisional biopsies were performed for all tumors on the scalp. The patient considered genetic testing for herself and family members.

Comment

Brooke-Spiegler syndrome is inherited in an autosomal dominant fashion with complete penetrance and variable expression. Both interfamilial and intrafamilial phenotypic variability have been well-documented in BSS; thus, a correlation between genotype and phenotype is lacking.[2] Brooke-Spiegler syndrome is uncommon, with a female to male ratio of 2 to 1.[1] Characteristically, patients present with the classic triad of cylindromas, trichoepitheliomas, and spiradenomas. Often, other adnexal tumors are observed, including but not limited to trichoblastomas, basal cell carcinomas, milia, organoid nevi, and syringomas.[3] It was initially believed that cylindromas and spiradenomas showed sweat gland differentiation and trichoepitheliomas showed follicular differentiation.[4] This combination represents an unusual inherited tumor diathesis involving neoplasms derived from pluripotential basal cells with adnexal differentiation along both sweat gland and follicular lineages.[5-7] Typically, these tumors are located in the head and neck region, appear in puberty to early adulthood, and gradually increase in size and number throughout life.[8] Malignant transformation of cylindromas in particular is quite rare, but metastasis in the event of malignancy is not infrequent.[9-11] Malignancy is more frequent in patients with BSS rather than solitary cylindroma.[10-12] Patients also are at risk for developing benign and

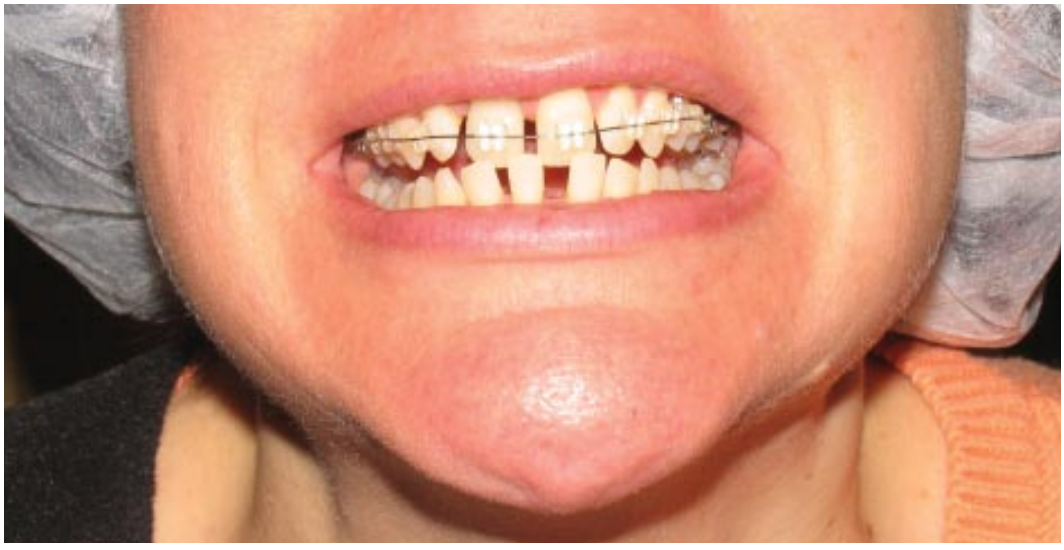

Figure 3. Clinically apparent pegged (conical) teeth.

malignant tumors of the salivary glands, particularly the parotid, including adenocarcinoma.[4,6,8,13]

In affected families, mutations have been demonstrated in the cylindromatosis gene, *CYLD,* located on band 16q12-13.[14] This gene consists of 20 exons and reveals the characteristic attributes of a tumor suppressor gene with loss of heterozygosity.[1,15,16] *CYLD* plays a role in governing cell cycle and apoptosis.[9] Mutational changes in the *CYLD* gene could affect the normal regulation of the stem cell population of the folliculosebaceousapocrine unit. In turn, mutations in the genes that regulate proliferation and differentiation of the putative stem cells, possibly located in the bulge region of the hair follicle,[3] could give rise to different combinations of adnexal skin tumors.[1,2,17-19] More recently, spiradenomas have been proposed to be apocrine tumors on the basis of adnexal morphogenesis and their close association with follicular and apocrine tumors in BSS.[10] The morphogenesis of both apocrine and sebaceous glands is dependent on the hair follicle because the glands develop from epithelial buds arising directly above the isthmus. However, eccrine glands develop from the base of the interfollicular rete ridges of embryonic skin. Cylindromas and spiradenomas are not eccrine tumors but neoplasms of the folliculosebaceousapocrine unit, as demonstrated by the occurrence of sebaceous and trichoblastic differentiation in spiradenocylindromas. It is hypothesized that cylindromas and spiradenomas may be polar extremes of a spectrum of adnexal neoplasms with apocrine differentiation.[13] Since the initial observation of mutations in the *CYLD1* gene as cause for BSS,[15] a host of different mutations have been reported, including frameshift mutations,[1,20] splice site mutations,[1] small deletions and insertions,[1,15,21] and novel missense mutations.[8] Most mutations lead to a premature translational stop, which disrupts the protein function.[21]

The *CYLD* gene interacts with several members of the nuclear factor-κB signaling pathway, which play important roles in inflammation, immune response, and oncogenesis. Inhibition of the *CYLD* gene enhances activation of the transcription factor nuclear factor-κB and leads to increased resistance to apoptosis and advanced carcinogenesis,[21] which also results in compromise of the early steps in the development of epidermal appendages, including hair follicles and sweat glands.[22] The exact mechanisms of *CYLD*-dependent tumorigenesis in the skin remain to be established.

Cylindromas located on the head and neck region may eventually cover the entire scalp, resulting in so-called turban tumors.[8] Mutational screening for the *CYLD* gene is beneficial to patients with multiple cylindromas and/or trichoepitheliomas as well as their family members. Physicians caring for patients and family members affected with BSS should contact the medical genetics department of their respective local medical school or academic medical center. Early identification of mutation carriers and appropriate genetic counseling may improve the therapeutic management to avoid complications such as disfigurement (turban tumor) or malignant transformation.[21] Excision of all cylindromas and spiradenomas is recommended due to the low risk for malignant potential (cylindrocarcinoma and spiradenocarcinoma).[8]

If untreated, BSS can cause considerable disfigurement and discomfort, and severely neglected cases may require scalp surgery and reconstruction.[23] Additionally, laser treatments, such as CO_2 and erbium:YAG lasers, have been used for surgical destruction of several of the adnexal tumors (cylindromas and trichoepitheliomas), though the former ideally should be excised for histology because of the low risk for malignant transformation.[5,9] Dermabrasion, chemical peels, electrodesiccation, and cryotherapy also may be considered as alternative treatment modalities.[9] Brummelkamp et al[24] demonstrated that inhibitory effects caused by *CYLD* gene mutations potentially can be reversed by application of salicylates or prostaglandin A. This discovery may give hope for novel therapeutic approaches in the future.

The presence of pegged (conical) teeth in our patient is unusual, as this finding has not been described in BSS. The question remains, are these truly pegged teeth, and if so, is it merely an incidental (idiopathic) finding or rather part of an altogether new syndrome? As a result, genetic testing is extremely inviting.

Conclusion

Brooke-Spiegler syndrome consists of the classic triad of cylindromas, trichoepitheliomas, and spiradenomas. Mutations occur in the *CYLD* gene on band 16q12-13. Brooke-Spiegler syndrome is theorized as reflecting genetic dysfunction in the regulation of the folliculosebaceousapocrine unit. Early diagnosis is important with confirmatory genetic testing of the patient and family members. Further studies including genetic testing will need to be conducted to determine the relationship between pegged (conical) teeth and BSS.

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