Abstract
Brooke–Spiegler Syndrome (BSS) is a rare genodermatosis characterized by the progressive formation of adnexal skin tumors in the scalp and face, mainly trichoepitheliomas, cylindromas, and spiradenomas. It has also been associated with salivary glands neoplasms. It is due to mutations in the tumor suppressor gene cylindromatosis (CYLD gene) localized on chromosome 16q12–q13. Around 93 mutations have been described. The study of CYLD gene in patients and their relatives is of vital importance to establish the molecular diagnosis and offer appropriate genetic counseling. There is a low risk of malignancy and patients require long‑term follow‑up. A case of BSS in a family is described. The existence of the genetic mutation at the CYLD gene c. 1628_1629delCT in three of the women affected was demonstrated. This mutation has only been described once in a previous study.

Key Words: Brooke–Spiegler syndrome, cylindromatosis protein, familial cylindromatosis, genodermatosis, trichoepithelioma multiple familial

Introduction
Brooke–Spiegler Syndrome (BSS) is a rare genodermatosis characterized by the progressive formation of adnexal skin tumors in the scalp and face, mainly trichoepitheliomas, cylindromas, and spiradenomas. It has also been associated with salivary glands neoplasms. It is due to mutations in the tumor suppressor gene CYLD (Cylindromatosis gene) on chromosome 16q12–q13. It is characterized by the progressive formation of multiple adnexal skin tumors since puberty. It has also been associated with salivary glands neoplasms. There is a low risk of malignancy and patients require long-term follow-up.

Case Report
A 71-year-old woman was evaluated due to the progressive development of asymptomatic lesions in her head during the last 4 years. Her medical history was unremarkable. The physical examination showed multiple rounded skin-colored or erythematous papules, 2–8 mm in diameter, located in scalp and forehead [Figure 1]. We performed several excisional biopsies and the histopathological diagnosis was spiradenoma in all of the lesions, except for one cylindroma.

Regarding her family history, she referred the presence of lesions at the scalp and forehead in her mother, her mother’s brother, and two of her three daughters, some of them very similar to our patient’s. Next, we performed a physical examination of her two affected daughters showing multiple papules and nodules of 1–3 cm, some of them painful [Figures 2 and 3]. The most symptomatic lesions were excised and its dermatopathological study was reported as cylindromas. We could not examine the rest family members that she referred as affected. Once all the information was collected, we elaborated the family pedigree, which suggested an autosomal dominant inheritance pattern of the disease [Figure 4a].

Suspecting a genetic syndrome, we requested the study of the CYLD gene in our patient and her two affected offsprings. The exon 8 sequencing of the CYLD gene revealed the heterozygous mutation c. 1628_1629delCT in a family with brook-spiegler syndrome.
Aguilera, et al.: CYLD mutation in a family with Brook-Spiegler syndrome

It consists of a two base-pair deletion that originates a new frameshift, the first codon is now the stop codon p.Ser543Xfs*1.

Therefore, to complete the familiar study, we performed the genetic test on our patient’s daughter presenting no signs or symptoms suggesting BSS. The result was negative, showing the wild-type genotype [Figure 4b]. Her 11 and 5-year-old children did not present any clinical data either.

Finally, we offered genetic counseling to her first-grade relatives. We provided concise information about the main characteristics of SBS and the 50% probability of the descendants to develop this syndrome, due to its autosomal dominant inheritance.

Discussion

BSS is a rare entity with more than fifty cases published internationally to date. It is characterized by the progressive development of adnexal skin tumors in scalp and face. Clinical manifestations start since puberty and its incidence is higher in females without distinction of race. BSS has also been associated with increased risk of salivary glands neoplasms and other tumors although with very little evidence.

Trichoepitheliomas are numerous and appear progressively covering the face. Cylindromas appear at the scalp reaching a considerable size, often forming the “turban tumor.” Spiradenomas are also multiple and appear in extremities, trunk and less frequently in the scalp (this is a rare location of single sporadic spiradenomas).

Recent studies demonstrate a common apocrine origin of spiradenomas and cylindromas, with an expression of hair follicle stem cells specific markers, mainly CD200 and cytokeratin. Thus, we prefer to avoid the adjective “eccrine” traditionally applied to spiradenomas.

This syndrome is due to mutations in the tumor suppressor gene CYLD localized on chromosome 16q12−q13. It is a tumor suppressor gene that codifies a protein of the deubiquitinating enzymes family. It negatively regulates activation of factors such as nuclear factor-kappa-B, JNK, and Wnt, involved in inflammation and cellular division. The loss of deubiquitinating activity of CYLD correlates with tumorigenesis (apoptosis resistance, uncontrolled cell division). It presents an autosomal dominant inheritance pattern with variable penetrance of 66–100%. Germ-line mutations predispose to the disease, and sometimes, a second acquired somatic mutation determines the final phenotype. Around 93 different mutations have been registered. No correlation between location or type of mutation and its phenotypic expression has been found so far. The genetic study in our case revealed the existence of the heterozygotic mutation c. 1628_1629delCT. There is only one report of this mutation in 2008 found in a family with multiple trichoepitheliomas; therefore, our case confirm the association of this genetic mutation with BSS.

Two entities have been recognized as phenotypic variations of BSS (MIM#605041) due to mutations in the CYLD gene. Multiple Familial Trichoepithelioma,
also known as trichoepithelioma adenoides cystica (MIM#601606), presents with numerous trichoepitheliomas since puberty predominantly located in the face. In familial CYLD (MIM#132700), multiple cylindromas appear in face and scalp of the patients. On the other hand, there have been described some cases of multiple familial spiradenomas, predominantly located in the scalp.\(^\text{8-10}\) No genetic study was performed in these cases; therefore, it could not be confirmed the existence of BRSS or one phenotypic variation.

The risk of malignancy is low and it occurs in longstanding lesions.\(^\text{1,9}\) Alarm signs are ulceration, bleeding, fast growth, blue nodules, or pain.\(^\text{5}\) Malignant spiradenoma is a very aggressive neoplasm with a risk of metastasis around 50% and a mortality of 39% if left untreated.\(^\text{8,9}\)

There are no standard guidelines regarding management of BSS. First-line treatment is surgical removal of the lesions whenever possible.\(^\text{5,6}\) Other options include cryotherapy, laser therapies, and radiotherapy.\(^\text{5}\)

**Conclusion**

We present a new case of BSS in a family due to the heterozygous CYLD mutation c.1628_1629delCT. Particularities of this case were the late onset in our patient and the relatively low number of cylindromas and trichoepitheliomas found in comparison with the cases found in the literature. Thus, our case may support the hypothesis about the relationship between the germline mutation, variable presence of somatic mutation and the final phenotype.\(^\text{9}\)

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**What is new?**

We describe a new case of BSS due to the rare heterozygous CYLD gene mutation c.1628_1629delCT in three women of the same family. The particularities of the clinical manifestations (late onset, relatively low number of tumors) may support the hypothesis about the relationship between the germline mutation, variable presence of somatic mutation and the final phenotype.

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