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Review

Cylindroma: an update

Clarice Jordão[1], MD, Taissa Canedo de Magalhães[1], MD, Tullia Cuzzi[2], MD, PhD, and Marcia Ramos-e-Silva[1], MD, PhD

[1]Sectors of Dermatology and
[2]Pathology, University Hospital and School of Medicine, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

Correspondence
Marcia Ramos-e-Silva, MD, PHD
Rua Dona Mariana 143/C-32,
Botafogo 22280-020
Rio de Janeiro
Brazil
E-mail: ramos.e.silva@dermato.med.br

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Abstract

This paper reviews the recent literature on cylindroma, a rare tumor originating from the cutaneous adnexal structures of the scalp and face. Benign cylindroma is more frequent in women, and there are solitary and multiple forms, which are autosomal. Malignant cylindroma can occur in the Brooke–Spiegler syndrome, and malignant transformation is more frequent in multiple variants than in solitary tumors. Its histopathological basis is controversial, and its origin is unknown, although it is known that there is a genetic basis for onset of these tumors in Brooke–Spiegler syndrome.

Introduction

Cutaneous cylindroma is a rare tumor originating from the scalp and face cutaneous adnexal structures.[1] Benign cylindromas are twice as common in women as in men. They can be found in both a single or in multiple form. The latter is usually inherited in autosomal dominant form.[1] There are controversies regarding its histopathological basis. Several theories have been proposed, although its real origin is still unknown.

In this article, the authors present a review regarding cylindromas in their clinical and histopathologic aspects and pathogenesis, besides discussing the Brooke–Spiegler syndrome, turban tumor, or familial cylindromatosis, and its hereditary aspects.

History

The term cylindroma was first used in 1856 by Billroth to describe an orbit tumor with hyaline appearance.[2] The term arose for its cylindrical shape seen in transversal section.[3] Presently, three forms of cylindromas are recognized: the benign cutaneous cylindroma, which may occur as isolated or multiple lesions; the malignant salivary cylindroma, also called cystic adenoid carcinoma; and the malignant cylindroma that occurs in the context of the Brooke–Spiegler syndrome.[4]

Despite the identical nomenclature for those lesions, both the clinical behavior and prognosis can vary drastically. Although the salivary form is usually primarily malignant, cancerous transformation is rare.

Clinical aspects

Clinical examination reveals firm, nodular, pink to reddish in color tumors, measuring about 2–6 mm, showing a slow growth[5,6] (Figs. 1 and 2).

Cutaneous cylindromas are in general benign but may become malignant on rare occasions. The first malignant cylindroma[7] was identified by Ancell in 1842.[4] Since then, only 30 cases were described. When these tumors appear in the context of multiple cylindromatosis, a condition seen in the Brooke–Spiegler syndrome,[3,8] the lesions present rapid growth from the beginning, with ulceration and pain, and proneness to a greater local growth exceeding 20 cm, as well as local recurrence and even the possibility of metastases.[1]

Histopathological aspects and pathogenesis

At histopathology, cylindromas demonstrate irregular isles comprising basaloid cells surrounded by a hyaline eosinophilic sheath. The tumoral isles typically present two groups of cells: peripheral cells in palisade with a small dark nucleus, which represent undifferentiated epithelial tumoral cells, and more differentiated centralized cells, with a big pale nucleus resembling ductal or secreting cells (Figs. 3 and 4).[9,10]

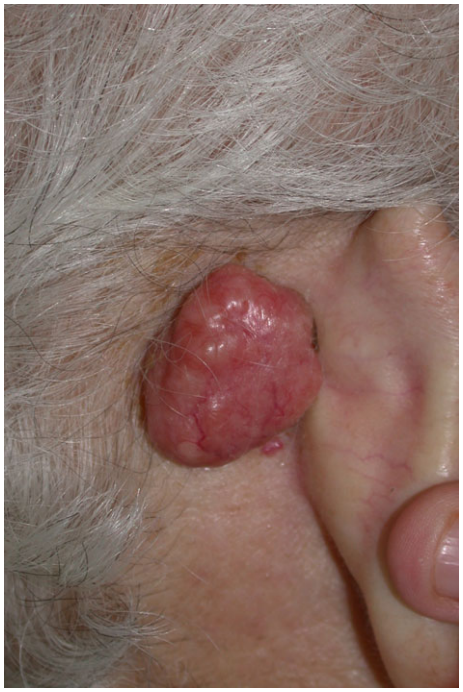

Figure 1 Cylindroma retroauricular region

Figure 2 Cylindroma on the scalp

The basal membrane of cylindromas is thickened and presents multiple alterations, such as absence of mature hemidesmosomes, defects in processing laminin 5, and reduction of the integrin a6b4 expression, in contrast to the increase of expression of integrin a2b1. The results of Tunggal *et al.*[11] show that in cylindromas, besides alteration of laminin 5 and its integrin receptors, there are multiple molecular defects contributing to structural abnormalities of basement membrane and other associated structures.

Abnormalities in the expression of the α11 and α5 chains of collagen IV were also observed.[12]

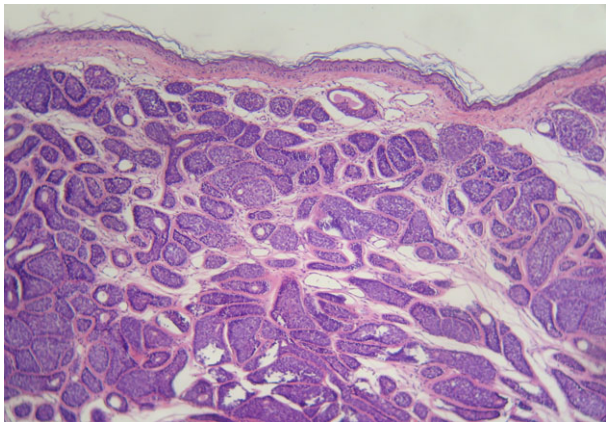

Figure 3 Histopathology of cylindroma: irregular isles of basaloid cells encircled by a hyaline eosinophilic sheath (hematoxylin and eosin, ×20)

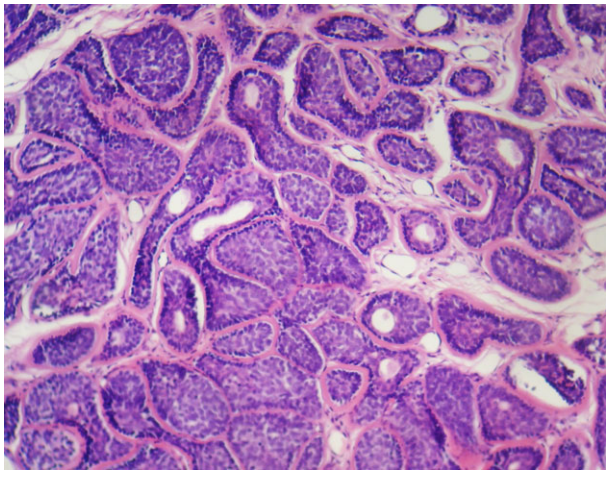

Figure 4 Histopathology of cylindroma: tumoral isles with two groups of cells: peripheral cells in palisade with a small dark nucleus, and more differentiated centralized cells, with a big pale nucleus (hematoxylin and eosin, ×100)

The histogenesis of cylindroma is not yet completely clarified. There are controversies whether its origin is in the eccrine or apocrine glands or even the follicular epithelium, as the tumor appears exclusively in hairy areas being absent in the palmoplantar region.[9,10]

Recently, it was demonstrated that the epithelial tumoral isles of cylindroma present reduced, or even absent, immunoreactivity to CYLD protein and that those cells would express specific follicular keratin.[13] Super-regulation of integrin ab1 in suprabasal keratinocytes is associated with an increase of proliferation,[14–16] supporting the hypothesis that the stem cells derived from follicular epithelium would be the specific cells responsible for cylindroma formation. These findings provide grounds

for the theory that the origin would be in the hair follicle, even if the tumors adopt several paths of differentiation presenting phenotypically different forms.[7] Assuming that stem cells from the follicular epithelium can be multipotent, they could differentiate into follicular, sebaceous, epidermal, and apocrine strains, according to the stimulus received.[17,18]

To improve the evaluation of the differentiation of cylindroma from hidradenoma in eccrine/apocrine, studies with antibodies CD15 and p63 were carried out. The immunohistochemical technique was employed, resulting in negative CD15 and positive p63 for all cylindromas. The limitation found in the study was due to the small sample, although dealing with a rare tumor.[19]

Malignant cylindromas differ from benign lesions by the loss of the saw-like pattern, loss of the hyaline sheath, and loss of the biphase cellular distribution. There is strong cellular pleomorphism with increased mitotic index.[7]

Brooke–Spiegler syndrome

The observation of multiple cylindromas was first made by Brooke in 1892 and later by Spiegler in 1899.[20] Nowadays, the presence of multiple cylindromas is known as the Brooke–Spiegler syndrome, turban tumor, or familial cylindromatosis.[5]

The Brooke–Spiegler syndrome is classified by the presence of cylindromas, trichoepitheliomas, and occasionally, spiradenomas, on the head and neck, beginning in the second decade of life.[5,21]

The syndrome is characterized by lesions located on the scalp, face, and neck. Cylindroma occurs typically in a sporadic form in mid-age and elderly patients, while multiple tumors are found in hereditary disorders. In those patients, the presentation occurs early and progressive growth occurs during the lifespan requiring repeated surgical interventions.[22] Despite growth being slow, compressive and cosmetic symptoms are remarkable. The nodules can coalesce on the scalp resulting in a turban-like aspect.[1] Association with this syndrome and adenoma and carcinoma of the parotids, sebaceous nevus, basocellular carcinomas, milium, xeroderma pigmentosus, hypo- and hyperchromia, polycystosis of the lungs, kidneys, breast, and multiple fibromas were identified.[23] There are reports of malignant transformation of dermal cylindromas and the possibility of metastases to the lymph nodes, thyroid, liver, lungs, and bones.[23] They may even infiltrate the skull, causing hemorrhage and meningitis. Therefore, a systemic follow-up of these patients is important.[1,24] Patients with this syndrome are prone to the development of multiple adnexal tumors, such as cylindromas, trichoepitheliomas, and spiradenomas.

Genetic aspects

Benign sporadic, dermal cylindromas express the MYB-NFIB gene fusion. These findings by Fehr *et al.* broaden the spectrum of neoplasms associated with MYB oncogene activation and reveal a novel genetic link between adenoid cystic carcinoma and dermal cylindroma. These results further strengthen the indication that there may be important common molecular pathways for the development of benign and malignant breast, salivary, and adnexal tumors.[25]

It is proposed that the mutation responsible for the Brooke–Spiegler syndrome is in the *CYLD* gene located in chromosome 16, with varied expression and absolute penetration.[21] The cylindromatosis gene (*CYLD*) was described as the only suppressive tumoral gene responsible for the syndrome. Mutations were identified in this gene, and they occur mainly at the end of the codification of the 03/02 portion of the gene (exons 80–20). These mutations are found in patients with phenotypic characteristics of the Brooke–Spiegler syndrome, familial cylindromatosis, and multiple familial trichoepithelioma. All those conditions share the same genetic basis but would represent phenotypical variations of the same disease. The mutations in the exons more commonly involved are in 16–18 and 20. Together they represent 60% of known mutations in the *CYLD* gene.[1,26,27]

Patients with this syndrome have mutations in the *CYLD* gene, which is a tumor suppressor gene situated on chromosome 16q. The major clinical features of Brooke–Spiegler syndrome are the presence of heterogeneous skin tumors and wide inter- and intrafamilial phenotypic variability. Until now, 68 distinctive *CYLD* mutations have been recognized.[28]

Conclusion

Despite being rare, it is necessary to recognize these scalp and face tumors, so physicians, in general practice, dermatology, and other specialties, can make early diagnoses and see those patients regularly for detection of a possible dominant multiple hereditary form. More studies are required to elucidate its pathogenesis, genetics, histopathologic basis, and origin.

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