Cylindroma with malignant transformation in a patient with Brooke-Spiegler syndrome

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ABSTRACT

Introduction: Classic cylindromas are benign skin adnexal tumors of sweat duct origin that can be sporadic or arise multiply with other tumors in association with genetic syndromes such as Brooke-Spiegler syndrome. Malignant transformation is seldom seen, with less than 50 cases in literature. We report an extremely rare case of carcinoma ex-cylindroma in a genetic syndromic context.

Case Report: A woman with a history of Brooke-Spiegler syndrome presented with hemorrhagic and ulcerative change in a longstanding scalp lesion. After elective excision, gross description revealed a multinodular mass with a well-circumscribed smooth tan-pink component and a hemorrhagic, ulcerative component with yellow areas. Microscopy revealed both a residual benign cylindroma component with irregular solid nests of basaloid cells in a “jigsaw puzzle” architecture with surrounding hyaline sheath, and a malignant ulcerated component with loss of organization, cellular atypia, brisk mitoses, and necrosis. A diagnosis of malignant cylindroma, completely excised, was made. The patient will be seen in clinical follow-up.

Conclusion: This case represents a rare example of malignant transformation in a pre-existing cylindroma in a patient with Brooke-Spiegler syndrome. The scenario exemplifies the risk of genetic syndromes and role of follow-up of these so-called benign cylindromas, as malignant transformation needs to be identified for early management. Malignant cylindromas have potential for both locally aggressive recurrence and metastasis. Awareness and correct pathologic diagnosis is necessary preceding further future studies on natural history, prognosis, and treatment in this rare entity.

Keywords: Brooke-Spiegler syndrome, Malignant cylindroma

INTRODUCTION

Cylindromas are described in the WHO Classification System of Skin Tumours as benign skin adnexal tumors of apocrine/eccrine origin that can be associated with genetic syndromes such as Brooke-Spiegler syndrome. Patients with this genetic propensity can have multiple syndrome-associated tumors that grow throughout life [1]. Even in this context, malignant transformation in cylindromas is exceedingly rare; the total numbers of cases in English literature are in the double digits [2, 3]. We report a case of cylindroma with histologic evidence of malignant transformation in a woman with Brooke-Spiegler syndrome.

CASE REPORT

The case is received in consultation at our tertiary academic center. The patient, a woman in her seventh decade of life, initially presented with multiple tumor nodules over the face, scalp, and ears. Hemorrhage and ulceration were noted clinically, and the patient
elected for definitive excision of the largest symptomatic lesions. The only noted past history consisted of basal cell carcinoma and previous possible combination spiradenocylindromas. Genetic testing for CYLD germline mutations was positive, leading to a combined phenotypic-genotypic diagnosis of Brooke-Spiegler syndrome.

On gross examination at the referring laboratory, the excised right scalp lesion was a focally ulcerated multinodular mass. Cut section revealed heterogeneous areas. The majority of the mass was glistening and tan-pink with a smooth texture; however, a subcomponent directly underlying an ulcerated area was tan with hemorrhagic and diffusely yellow areas.

Light microscopic analysis of hematoxylin and eosin stained slides revealed a multinodular tumor of skin appendage origin. There were two juxtaposed parts (Figures 1 and 2). In the major component, bland lesional basaloid cells formed irregular angulated solid nests with occasional peripheral palisading. Each nest was surrounded by thick eosinophilic basement membrane material in the form of a hyaline sheath. The same eosinophilic material was also present as occasional globules within the solid nests. There was occasional duct formation. The overall low-power organization was exemplary of the so-called “jigsaw puzzle”-like architecture characteristic of cylindroma. This major component showed no mitoses, necrosis, or cellular atypia, in keeping with benignity. However, adjacent and juxtaposed to these benign areas was a second component with a more disorganized expansile loosely nested pattern containing atypical cells showing abundant central tumor necrosis and brisk mitoses including abnormal forms (Figures 1–3). This second component was intimately associated with the ulceration of the overlying skin that was seen grossly (Figure 4). Taking into account the adjacent classic cylindroma component, overall the lesion was diagnosed as a malignant cylindroma (sometimes called cylindrocarcinoma or carcinoma ex cylindroma) arising from a background of cylindroma or spiradenoma. Surgical margins were negative. The patient is to be seen with close clinical follow-up.

**DISCUSSION**

The 2018 WHO Classification of Skin Tumours defines classic cylindromas as essentially benign skin adnexal
tumors of apocrine or eccrine origin. Cylindromas can be sporadic or associated with genetic predisposition syndromes, and clinically appear as single to multiple small firm red-pink papules usually on the head and neck.

In this case, our patient had the eponymous Brooke-Spiegler syndrome, which was named after Henry Brooke and Eduard Spiegler, one of the first two authors to conclusively characterize the microscopic features of trichoepithelioma and cylindroma in 1892 and 1899, respectively [4].

The syndrome, part of the umbrella of CYLD cutaneous syndrome, is an autosomal dominant genetic disorder clinically recognized by the presence of numerous papulonodular adnexal cutaneous neoplasms first arising in the head and neck region of young adults in their second to third decades of life [1]. Histologically, these adnexal tumors are recognized as cylindromas, trichoepitheliomas, spiradenomas, and/or combination spiradenocylindromas, sometimes occupying the same space or with connection to adjacent follicular structures [4]. Basal cell carcinomas, epidermoid inclusion cysts, and even occasionally benign and malignant salivary gland basal cell neoplasms have also been reportedly associated with this syndrome [4, 5]. Later in life, these neoplasms continue to progress and accumulate in size and number. Multiple scalp cylindromas have in the past been referred to as turban tumors due to their unique coalescing nature. In terms of gender differences, females may have increased expressivity and make up a higher proportion of patients with cylindromas [6]. Our case fully exemplifies many of these features.

In review of the molecular genetics, the cylindromatosis gene, CYLD, has a tumor suppressor function and is located at 16q12 [7]. While the etiology and pathogenesis of cylindromas are technically unknown, as implied by the CYLD gene’s nomenclature, sporadic and syndrome-associated cylindromas both have CYLD gene mutations. Sporadic cylindromas and spiradenomas characteristically have loss of heterozygosity at 16q, and germline mutations are seen in up to 85% of patients with this typical clinical phenotype [5]. As with many other genetic predisposition syndromes, phenotypes are variable as is penetrance. Brooke-Spiegler syndrome, familial cylindromatosis, and multiple familial trichoepithelioma are all historically associated syndromes stemming from CYLD gene mutation and represent a clinical spectrum of disease, which some refer to as CYLD cutaneous syndrome [5, 8]. More specifically, Brooke-Spiegler syndrome refers to the clinical phenotype of multiple cylindromas, trichoepitheliomas, spiradenomas, and/or other basal cell neoplasms in combination, whereas familial cylindromatosis refers to a predisposition to only cylindromas, and multiple familial trichoepithelioma to only trichoepitheliomas [5]. In combination, the prevalence of CYLD cutaneous syndrome is still rare, estimated as just over 1/100,000 population [9]. In our case, the use of the terminology Brooke-Spiegler syndrome refers to the histologically defined phenotype of multiple tumor types, as well as the proven molecularly defined genotype of germline heterozygous mutation in the 16q12 locus.

Our case portrays the importance of recognizing clinical features suggestive of malignancy. Suspicious features, as detected by patients and/or clinicians, include pain, change in size or rapid growth, gross hemorrhage, ulcerative change, or frank necrosis [10]. In this case, ulceration and hemorrhage were noted by the patient. This is particularly important in CYLD cutaneous syndrome even though cylindromas, trichoepitheliomas, and spiradenomas are commonly thought to be benign. In review of the natural history of syndromic spiradenocylindromas, recent literature noted progressive annual growth in more than 90% of followed tumors, and it can be argued that in a genetic syndromic context, size progression should lead to consideration of early excision [11]. In our case, the tumor kinetics and growth rate were not available.

Overall, Brooke-Spiegler syndrome is a known risk factor for malignant transformation in its associated tumors especially if presenting multiply [12]. However, cases of malignant transformation are still seldom seen. There is scant literature describing malignant counterparts in pre-existing CYLD gene-associated tumors of the spiradenocylindroma spectrum. Malignant cylindromas are particularly rare. The first possible classic cylindroma-like entities were reported in 1842 by Ancell [13], with later characterization in 1899 by Spiegler, but malignant cylindromas were only first described in 1929/1930 by Wiedmann [14]. More recently, as of 2019, there were still less than 50 cases in English literature [10].

In reviewing this available English literature on malignant cylindroma, locally aggressive invasion (including to underlying bone), multiple persistent
recurrences, and metastases by carcinoma have been noted, and rare deaths from metastatic disease have also been described [15]. In 1993, Gerretsen et al. reviewed 24 patients with malignant cylindroma, in which 9 developed local recurrence, 11 developed metastases to bone—in particular vertebral skeleton, as well as liver and lymph nodes, and 11 patients died from metastatic disease [16]. Clinically they may be painful and cause ulceration, as in our case. Greatest dimensions can exceed 20 cm [16]. Histomorphologically, the prototypical first case of malignant cylindroma in 1929 was depicted with loss of typical “jigsaw pattern” architecture, loss of peripheral palisading of basoid cells, and the presence of atypical polymorphous “clear” cells with prominent nucleoli [14, 17]. However, at present time, owing to a scarcity of documented cases, there are no defined criteria with which to delineate benign from malignant cylindroma. However, criteria for malignancy have been proposed drawing from previous case reports and historical generic indicators of malignant behavior common to many carcinomas—namely atypia, necrosis, and mitoses.

The histological features in our case show unequivocal malignant transformation and also clear demarcation between the benign and malignant components. The residual benign component is a classic cylindroma with basoid cells arranged in irregular solid nests with ductal structures and foci of hyaline basement membrane material. The same material surrounds the nests as a hyaline sheath. The malignant component is immediately adjacent and intermingled, and while still showing identifiable features of solid nests with basoid cells, architecturally the nests become expanded and disorganized with alteration to the peripheral palisading and nest size. The centrally located tumor necrosis, cellular pleomorphism, brisk mitotic rate, and ulceration give unambiguous indication of malignancy. The diagnosis is made entirely based on histomorphology on standard hematoxylin and eosin stain; immunohistochemistry is not helpful in discerning benign from malignant.

Although still not well-characterized microscopically due to the scarcity of cases, Kazakov et al. in 2009 sought to classify malignant transformation in spiradenocylindromas into four histologic patterns: salivary gland-type basal cell adenocarcinoma—like pattern either low or high grade, invasive adenocarcinoma not otherwise specified, and sarcomatoid carcinoma [15]. Our case shows some high grade features and similarities to salivary gland basal cell adenocarcinoma, but does not neatly fit. Overall, although these proposed patterns are helpful, these prognostic or therapeutic implications have not been discernibly confirmed, and there has yet to be widespread adoption of such classification.

As of recent years, the mainstay treatment for malignant cylindromas remains surgical management and clinical follow-up. In a literature review by Kim et al. in 2019, treatments ranged from wide local excision or Mohs micrographic surgery with or without adjuvant radiotherapy [10]. Their case attempted staged perimeter excision. The exact optimal clearance to obtain wide surgical margins is yet to be elucidated. The role of chemotherapy has not been explored. Unfortunately, while malignant cylindromas have a possibility of local recurrence and/or metastasis, optimal treatment options and robust recurrence rate statistics are still lacking.

Finally, as with many exceedingly rare malignant entities, awareness is tantamount to avoiding misdiagnoses with other benign or malignant skin adnexal tumors or metastases.

CONCLUSION

Cylindromas are usually considered benign skin adnexal neoplasms originating from the intradermal coiled duct area of sweat ducts. Malignant transformation in pre-existing cylindromas is possible but vanishingly rare, with less than 50 cases reported in English-speaking literature. This case report characterizes an example of malignant cylindroma in a patient with Brooke-Spiegler syndrome, contributing to the scarce existing literature on this rare entity. Patients with these CYLD cutaneous syndromes should be followed closely for sudden changes to existing tumors, followed by prompt tissue excision and accurate pathological diagnosis for early detection and management of malignant transformation. In this case, architectural distortion, cellular atypia, brisk mitoses, and necrosis were indicators of malignancy. Accurate diagnosis has prognostic and therapeutic implications, and follow-up of this case will also lead to progress and knowledge dissemination of the diagnostic characteristics, prognostics, and therapeutic interventions for this rare malignancy.

REFERENCES

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**Author Contributions**

Man Hymn Edwin Ho – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Salem Alowami – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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**Conflict of Interest**

Authors declare no conflict of interest.

**Data Availability**

All relevant data are within the paper and its Supporting Information files.

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