

## Cutaneous Cylindromas of the Scalp and Frontal Region with Chronic Ulceration: A Case Report and Review of the Literature

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### ABSTRACT

Cutaneous cylindroma is an uncommon adnexal neoplasm of presumed follicular differentiation that characteristically involves the scalp and face. It may present as a solitary sporadic lesion or, less frequently, as multiple confluent tumors in the context of CYLD cutaneous syndrome, the unifying designation for Brooke–Spiegler syndrome, familial cylindromatosis and multiple familial trichoepitheliomas. Although histologically benign, multiple scalp cylindromas produce progressive disfigurement, cicatricial alopecia, ulceration and, in a minority of patients, malignant transformation to cylindrocarcinoma, an aggressive neoplasm with documented capacity for local destruction and metastasis. We report a 64-year-old woman with a lifelong history of multiple nodular lesions of the scalp, face and trunk that began in adolescence, in whom a chronically ulcerated frontal lesion raised clinical suspicion of malignant transformation. Wide surgical excision of the frontal and scalp lesions was performed with reconstruction by a full-thickness skin graft harvested from the abdominal region. Histopathological examination demonstrated ulcerated cylindromas with free surgical margins, and graft integration reached approximately 95%. Residual scalp tumors are being managed by planned staged excision in order to preserve as much hair-bearing scalp as possible. Using this case as a framework, we review the historical background, epidemiology, histopathological features, molecular pathogenesis and contemporary management of cutaneous cylindroma, with particular emphasis on the reconstructive decisions that confront the plastic surgeon. Recognition of the clinical warning signs of malignant change, appropriate genetic characterization of the patient and family, and the principle of tissue-preserving staged surgery remain central to the modern care of these patients.

**KEYWORDS:** Cylindroma; cylindrocarcinoma; CYLD cutaneous syndrome; Brooke–Spiegler syndrome; turban tumor; scalp reconstruction; full-thickness skin graft.

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### I. INTRODUCTION

Cutaneous cylindroma is a rare, slow-growing benign neoplasm of the skin appendages that shows a marked predilection for the scalp, face and neck. It accounts for approximately 0.7% of all adnexal neoplasms and is most often diagnosed in middle-aged and elderly patients [1,2]. The term cylindroma was introduced by Billroth in the mid-nineteenth century to describe an orbital tumor whose epithelial nests, viewed in cross-section, resembled hyaline cylinders; the name has persisted despite subsequent

recognition that the histogenesis of the lesion has little to do with its original description [1,3,4].

Two clinical presentations are classically recognized. The solitary form is sporadic, arises in mid to late adult life, and carries no familial implication. The multiple form is inherited in an autosomal dominant fashion and, when confluent tumors cover the vertex, produces the striking morphology historically described as a turban tumor [1,5]. The multiple form is now best understood under the unifying label of CYLD cutaneous syndrome (CCS), an

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inclusive designation proposed for the three overlapping phenotypes previously described as Brooke–Spiegler syndrome, familial cylindromatosis and multiple familial trichoepitheliomas, all of which arise from germline pathogenic variants in the tumor suppressor gene *CYLD* [3,6,7].

For the plastic surgeon, cylindroma is relevant for three reasons. First, the anatomical distribution of the tumors coincides with the aesthetic units of the scalp and face, so that oncological adequacy and reconstructive quality are inseparable objectives. Second, tumor burden in the hereditary form accumulates throughout adult life, which means that any single operation must be planned as one step within a lifetime surgical strategy rather than as a definitive event. Third, although cylindroma is a benign entity, malignant transformation to cylindrocarcinoma is a well-documented, aggressive and potentially lethal complication whose earliest manifestations — ulceration, rapid growth, bleeding and pain — are clinical rather than histological [5,8,9].

The present article reports a patient with extensive multiple cylindromas of the scalp and frontal region complicated by chronic ulceration of a previously biopsied lesion, and uses the case as a framework for a structured review of the current literature on the biology, diagnosis and surgical management of this tumor.

## II. CASE PRESENTATION

A 64-year-old female patient was referred with a history of multiple nodular cutaneous lesions showing chronic progression since adolescence. The earliest lesions were small and asymptomatic and were located on the nose and frontal region. Over the following decades she developed progressive enlargement of lesions on the scalp, together with the appearance of clinically similar lesions in other anatomical regions, including the back, the chest and the upper extremities. Some of the lesions located on the back subsequently acquired features similar to the larger lesions present on the scalp.

One year before referral, an incisional biopsy of a larger frontal lesion had been performed at another center, with a reported diagnosis of “cylindroma”; the original histopathological report was not available for review. During subsequent follow-up, the biopsied lesion developed chronic ulceration together with local changes suggestive of possible malignant transformation.

On physical examination, multiple nodular and multilobulated lesions were identified, located predominantly on the scalp and frontal region. The lesions were violaceous, solid, alopecic and non-tender, measuring approximately 3–20 mm in diameter and projecting 5–18 mm above the surrounding skin surface. The previously biopsied frontal lesion measured 25 × 15 mm and presented with ulceration, haemorrhagic crusts, foul-smelling exudate

and a verrucous surface, with confluent adjacent lesions that showed no signs of ulceration. During the examination, toilet paper was observed adhered to the surface of the lesions, which the patient had been using as local coverage — an incidental finding that illustrates the functional and psychosocial burden imposed by this disease.



**Figure 1. Preoperative clinical view demonstrating multiple violaceous, alopecic, multilobulated nodules of the scalp and frontal region, with the ulcerated and crusted frontal lesion previously subjected to incisional biopsy.**

In view of the clinical suspicion of malignant transformation, a decision was made to perform wide surgical excision of the lesions located in the frontal region and scalp, with reconstruction using a full-thickness skin graft harvested from the abdominal region, and histopathological examination of the surgical specimen.

Histopathological examination of the resected tissue reported “ulcerated cylindromas”, with free surgical margins and no evidence of malignant transformation. Postoperatively, the graft achieved approximately 95% integration, with an area of partial loss of less than 2 cm at the graft edge. This area of graft loss was associated with a residual lesion that was itself prone to chronic ulceration, and the residual lesion was excised using electrocautery, after which the defect healed by secondary intention.



**Figure 2. Intraoperative appearance after wide excision of the frontal and scalp lesions and inset of the abdominal full-thickness skin graft.**

The remaining scalp lesions have been kept under close surveillance, with staged progressive excision planned in order to preserve as much hair-bearing scalp as possible. The patient was counselled regarding the hereditary nature of multiple cylindromatosis, the indication for family screening and the clinical warning signs that should prompt an unscheduled consultation.

### **III. DISCUSSION**

#### **A. Historical Perspective and Nomenclature**

The nomenclature surrounding cylindroma is a persistent source of confusion. Three distinct entities have historically shared the name: the benign cutaneous cylindroma, which may be solitary or multiple; the malignant salivary cylindroma, now correctly designated adenoid cystic carcinoma; and the malignant cylindroma, or cylindrocarcinoma, arising by transformation of a pre-existing cutaneous cylindroma [1]. Despite the shared designation, the clinical behavior and prognosis of these lesions differ dramatically, and the term cylindroma should be reserved for the cutaneous adnexal neoplasm.

The clinical description of multiple tumors of the scalp was made by Brooke in 1892 and by Spiegler in 1899, and the eponym Brooke–Spiegler syndrome subsequently came to designate the association of cylindromas,



trichoepitheliomas and, occasionally, spiradenomas on the head and neck, with onset in the second decade of life [1]. Because familial cylindromatosis and multiple familial trichoepithelioma share the same germline defect and represent phenotypic variants of the same disease, the contemporary literature increasingly favors the single term

CYLD cutaneous syndrome, a change in terminology that has practical value in genetic counselling and in trial recruitment [3,7].

#### **B. Epidemiology and Clinical Spectrum**

Sporadic cutaneous cylindroma presents as a firm, dome-shaped, smooth-surfaced pink to violaceous nodule, most often 2 mm to a few centimeters in diameter, growing slowly over years and typically located on the scalp, face or neck [1,2]. A striking female preponderance has been reported in the sporadic form, with figures approaching a nine-to-one ratio in some series [2]. In contrast, in genetically confirmed CCS penetrance is high and males and females are affected in approximately equal numbers, although the tumor burden is frequently greater in women [3].

In CCS the first tumors typically appear around puberty and accumulate progressively throughout adult life, a natural history that was reproduced faithfully in the present patient, whose lesions began in adolescence and continued to appear and enlarge over five decades [3,7]. Lesions arise preferentially on hair-bearing skin of the scalp and face but also involve the trunk, axillary and genital skin. When scalp tumors coalesce they may form a confluent mass that covers much of the vertex; this has been reported to affect up to one in four germline variant carriers and represents the clinical endpoint that pre-emptive staged surgery seeks to avoid [3].

Extracutaneous manifestations deserve mention. Salivary gland tumors, in particular membranous basal cell adenoma of the parotid, occur in a minority of patients, and pulmonary cylindromas of the large airways have been described and may compromise ventilation [3]. Reported associations with parotid adenoma and carcinoma, sebaceous naevus, basal cell carcinoma, milia and multiple fibromas underline the need for a systemic rather than a purely dermatological follow-up [1].

The functional and psychosocial burden of the disease is considerable and is frequently underestimated. Progressive alopecia, malodor from ulcerated lesions, recurrent bleeding and the need for improvised dressings — as observed in our patient — combine to produce social withdrawal. These factors should be recorded in the preoperative assessment and are legitimate components of the indication for surgery even in the absence of suspected malignancy.

#### **C. Histopathological Features and Differential Diagnosis**

Cylindroma is a well-demarcated, unencapsulated dermal tumor composed of irregular islands and nests of basaloid cells fitted together in the characteristic jigsaw-puzzle configuration and surrounded by a thick, eosinophilic, periodic acid–Schiff–positive basement-membrane-like hyaline sheath [1,2]. The epithelial islands display a biphasic cell population: small peripheral cells with dark, hyperchromatic nuclei arranged in palisade, representing the undifferentiated compartment, and larger, more

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differentiated central cells with pale vesicular nuclei that morphologically resemble ductal or secretory cells [1,2]. Small ductal structures and intercellular hyaline droplets are frequently identified. In benign lesions there is no necrosis and no nuclear atypia, and mitotic activity is minimal [2].

The basement membrane of cylindroma is structurally abnormal, with absence of mature hemidesmosomes, defective processing of laminin 5, reduction of integrin  $\alpha 6\beta 4$  and increased expression of integrin  $\alpha 2\beta 1$ , together with altered expression of the  $\alpha 1(IV)$  and  $\alpha 5(IV)$  collagen chains [1,10]. Immunohistochemically, cylindromas are typically CD15-negative and p63-positive, a profile that assists in their distinction from nodular hidradenoma [1,11].

The principal differential diagnoses are eccrine spiradenoma and the solid variant of adenoid cystic carcinoma. Spiradenoma is distinguished by the absence of the thick pink basement-membrane material, a more vascular stroma and prominent intratumoural lymphocytic infiltration; the two lesions may coexist as spiradenocylindroma, a hybrid tumor particularly characteristic of CCS [2,12]. Adenoid cystic carcinoma is distinguished by its infiltrative growth pattern, atypical nuclear features and readily identified mitoses [2,13]. Basal cell carcinoma, trichoepithelioma and dermal analogue tumors of the salivary glands complete the differential list [2,14]. A summary is given in Table I.

**Table I. Principal Differential Diagnoses of Dermal Cylindroma**

| Entity                                   | Distinguishing features                                                     |
|------------------------------------------|-----------------------------------------------------------------------------|
| Eccrine spiradenoma                      | Absent thick hyaline sheath; vascular stroma; intratumoural lymphocytes     |
| Adenoid cystic carcinoma (solid variant) | Infiltrative pattern; nuclear atypia; frequent mitoses; perineural invasion |
| Trichoepithelioma                        | Follicular germinative differentiation; papillary mesenchymal bodies        |
| Basal cell carcinoma                     | Epidermal connection; peritumoural clefting; mucinous stroma                |
| Nodular hidradenoma                      | CD15-positive; solid-cystic architecture; clear cell component              |

## D. Molecular Pathogenesis: CYLD, NF- $\kappa$ B and MYB

The histogenesis of cylindroma remained contentious for decades, with successive arguments favoring an eccrine, an apocrine and a follicular origin. The distribution of the tumor exclusively in hair-bearing skin, its absence from palmo-plantar surfaces, the expression of follicular keratins

and the demonstration of reduced or absent CYLD immunoreactivity in the epithelial islands together support derivation from follicular epithelial stem cells, which under different stimuli may differentiate along follicular, sebaceous, epidermal or apocrine lines [1,15].

The genetic basis of the hereditary form was established with the identification of CYLD, a tumor suppressor gene located on chromosome 16q12–q13 [16]. More than one hundred pathogenic single nucleotide variants and small insertions or deletions have been reported in coding exons, most predicted to result in protein truncation, together with a minority of large deletions, splice-affecting intronic variants and inversions [3]. Mutations cluster in exons 16 to 20, which together account for a substantial proportion of known variants [1]. Importantly, mosaic presentations occur and may result in parent-to-child transmission, a nuance with direct implications for genetic counselling [3].

CYLD encodes a deubiquitinating enzyme that removes polyubiquitin chains from substrate proteins and thereby restrains the activity of nuclear factor kappa B (NF- $\kappa$ B). Loss of CYLD function results in constitutive NF- $\kappa$ B signaling and inhibition of apoptosis, providing a coherent mechanism for the accumulation of tumors in mutation carriers [17]. Subsequent work has extended this picture considerably. Sporadic dermal cylindromas frequently express the MYB–NFIB fusion transcript, the same rearrangement found in approximately half of adenoid cystic carcinomas, providing a molecular explanation for the long-recognized histological similarity between the two tumors [18,19]. In CYLD-defective familial tumors, by contrast, the fusion transcript is absent, yet strong nuclear expression of wild-type MYB is demonstrable, and RNA interference against MYB markedly reduces proliferation of patient-derived cylindroma cells [18,20]. Activation of MYB, whether as a fusion product or in its wild-type form, therefore appears to be a convergent feature of both sporadic and hereditary cylindroma and constitutes a potentially actionable therapeutic target [18].

Whole-genome analyses have further identified recurrent somatic mutation of the epigenetic modifiers DNMT3A and BCOR in CCS tumors, indicating that additional cooperating events shape tumor development beyond biallelic CYLD inactivation [21]. Transcriptomic profiling has also highlighted dysregulated tropomyosin receptor kinase (TRK) signaling as a candidate dependency, which provided the rationale for the first pharmacological intervention trial in this disease [22].

## E. Malignant Transformation and Its Clinical Recognition

Malignant transformation of a cutaneous cylindroma is rare but well documented. Fewer than fifty cases of cylindrocarcinoma have been reported in the English-language literature, and the natural history of the entity is therefore derived largely from case reports and small pooled

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series [2,8]. In the largest classical review, malignant transformation occurred in 37.5% of reported cases arising in solitary tumors and in 62.5% arising in the multiple form; since the solitary form is at least as common as the multiple form in the general population, the multiple hereditary variant carries the greater relative risk of transformation [5].

The clinical signs that should raise suspicion are consistent across series and are summarized in Table II: ulceration, rapid growth, bleeding, blue or pink discoloration, pain, a change to a soft or fluctuant consistency, and tethering of the tumor to underlying bone [3,5]. It must be emphasized that each of these features may also occur in a benign lesion, particularly where cystic degeneration has supervened, so that the clinical signs are indications for biopsy or excision rather than diagnostic criteria in themselves [5]. Conversely, none of the individual features is sufficiently sensitive to be relied upon alone, and a persistently ulcerated lesion — as in our patient — warrants excision with histopathological assessment of the entire specimen rather than repeat incisional sampling.

**Table II. Clinical Warning Signs of Malignant Transformation in Cutaneous Cyndroma**

| Clinical feature                | Reported frequency |
|---------------------------------|--------------------|
| Ulceration                      | 62.5%              |
| Rapid growth                    | 50.0%              |
| Bleeding                        | 33.3%              |
| Blue or pink discoloration      | 16.7%              |
| Pain                            | 16.7%              |
| Weak consistency or fluctuation | 12.5%              |
| Fixation to deeper planes       | 12.5%              |

Frequencies derived from the pooled analysis of 24 published cases of malignant cutaneous cyndroma reported by Gerretsen et al. [5].

The histopathological diagnosis of malignancy rests on loss of the architectural and cytological hallmarks of the benign tumor. Disturbance or loss of the jigsaw pattern, loss of the hyaline sheaths, loss of peripheral palisading and loss of the biphasic cell composition, combined with marked cellular pleomorphism, a high mitotic index and necrosis, constitute the accepted criteria (Table III) [1,5]. Perineural extension and lymphatic dissemination may be present. The malignant component may be undifferentiated, or may retain moderately to well-differentiated cyndromatous areas, sometimes admixed with spindle cell and squamous elements or with glandular formations resembling those of spiradenoma, and this morphological heterogeneity accounts for much of the diagnostic difficulty reported in the literature [5].

**Table III. Histopathological Criteria of Malignant Transformation**

| Histological criterion            | Present in reported cases |
|-----------------------------------|---------------------------|
| Cellular pleomorphism             | 87.5%                     |
| Disturbance of the jigsaw pattern | 79.2%                     |
| Loss of hyaline sheaths           | 58.3%                     |
| Frequent mitoses                  | 54.1%                     |
| Loss of peripheral palisading     | 45.8%                     |
| Large cell predominance           | 25.0%                     |

Adapted from the pooled series of Gerretsen et al. [5]; percentages refer to cases in which the criterion was recorded as present.

Cylindrocarcinoma behaves as a locally aggressive tumor. Extensive local infiltrative growth or distant metastases were documented in two-thirds of pooled cases, with infiltration of the galea in half of scalp tumors and occasional intracranial or intracerebral extension; metastases were reported in 46% of patients, most frequently to regional lymph nodes, liver and spinal bone, but also to lung, rib, femur, stomach and thyroid [5]. Local recurrence occurred in 41% of surgically treated patients and a substantial proportion of patients died as a direct result of the tumour [5]. These figures justify a low threshold for definitive excision and for structured long-term follow-up in patients with multiple lesions.

## F. Surgical Management and Reconstruction of the Scalp

Complete surgical excision remains the treatment of choice for both benign and malignant cyndroma. For solitary benign lesions, simple excision with a narrow margin is curative in most instances, although recurrence rates of up to 40% have been reported and mandate follow-up [2,5]. For cylindrocarcinoma, wide local excision with histologically confirmed clear margins is the established standard, and there is a growing body of evidence supporting margin-controlled techniques. A recent systematic review of published cylindrocarcinoma cases treated by Mohs micrographic surgery or conventional excision reported a lower recurrence rate with Mohs surgery and concluded that margin-controlled excision should be considered a valid and effective option where the technique is available [23]. Staged perimeter excision has been described as a practical alternative for large scalp tumors when Mohs surgery is not accessible, allowing histological confirmation of clearance before definitive reconstruction [4].

The management of the patient with multiple hereditary tumors poses a different problem, in which the surgical objective is not a single curative resection but the lifelong preservation of scalp integrity and hair-bearing tissue. Total scalp excision with skin grafting remains the historical last

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resort for severely affected patients in whom tumors have coalesced into a confluent mass, and early, pre-emptive removal of individual tumors is thought to reduce the likelihood of ever reaching that endpoint [3]. This informed the approach adopted in our patient, in whom the ulcerated frontal lesion and the largest adjacent scalp tumors were removed in a single procedure while the remaining lesions were left for planned staged excision, thereby maximizing the amount of hair-bearing scalp retained.

Reconstructive choice follows the general principles that govern scalp resurfacing, in which defect size and depth, availability of adjacent laxity, the state of the periosteum and the anticipated need for further surgery determine the technique selected. Reported reconstructive options after resection of scalp malignancy span primary closure, local flaps, dermal substitutes, split- and full-thickness skin grafting, tissue expansion and free tissue transfer, and no single method is universally superior [24]. In large contemporary series of scalp malignancy, skin grafting and primary closure account for the majority of reconstructions, with flaps and microvascular transfer reserved for full-thickness or bone-involving defects [24]. One-stage reconstruction combining a dermal regeneration template with a skin graft has been described as a means of achieving durable coverage while reducing operative time in patients unsuitable for extensive procedures [25].

In the multiply affected patient, however, the calculus differs in an important respect: because further excisions are anticipated, local flaps that consume adjacent scalp laxity and rotate potentially tumor-bearing tissue should be used sparingly. Skin grafting, although it produces a permanently alopecic and often depressed area, preserves the surrounding scalp for future procedures and permits straightforward clinical surveillance of the wound bed. A full-thickness graft, as used in the present case, provides better contour, less secondary contraction and a more durable surface than a split-thickness graft, at the cost of a donor site requiring primary closure; the abdominal donor site is well tolerated and provides ample tissue for large defects. Graft take of approximately 95% in our patient is consistent with expectations for a well-vascularized subgaleal recipient bed, and the small area of edge loss was attributable to an adjacent residual tumor rather than to a technical failure of the graft.

Two practical points arise from this case. First, incisional biopsy of a large scalp cylindroma should be undertaken with the recognition that the biopsy site itself may become a locus of chronic ulceration and infection; where the lesion is already suspicious, excisional biopsy is preferable. Second, residual lesions adjacent to a graft margin should be addressed at the time of the primary procedure whenever oncologically and technically feasible, since a chronically ulcerated tumour lying at the graft edge is a predictable cause of partial graft loss.

### *G. Adjuvant and Emerging Non-Surgical Options*

Non-surgical treatments have a limited but defined role. Carbon dioxide laser ablation has been used to treat small lesions and to reduce recurrence in multiple cylindromatosis, principally as an adjunct to resection rather than as a substitute for it [2]. Radiotherapy has traditionally been reserved for unresectable tumors or as an adjuvant after incomplete excision of cylindrocarcinoma [4,18]; whole-scalp radiation therapy has been described for recurrent benign cylindromas in patients whose tumor burden makes repeated surgery impractical [26]. It should be borne in mind, however, that radiotherapy has itself been implicated as a possible trigger of malignant transformation in a small number of historical cases, and this must be weighed in patients with a lifelong disease and a long expected survival [5].

The first targeted intervention to reach clinical trial in this disease was pegcantratinib, a topical TRK inhibitor evaluated in the TRAC randomized trial in patients with CCS. Although the trial demonstrated safety and confirmed cutaneous drug penetration, treated tumors did not achieve the primary response endpoint, and the concentrations attained were judged inadequate to abrogate TRK signaling; dose escalation was proposed for future study [22]. The identification of MYB activation as a convergent oncogenic event, together with the availability of small-molecule MYB inhibitors in preclinical development, offers a further avenue that may eventually reduce dependence on repeated surgery [18,20]. For the present, however, surgery remains the only intervention of proven benefit, and patients should be counselled accordingly.

### *H. Genetic Testing, Counselling and Follow-Up*

Confirmation of a germline CYLD pathogenic variant establishes the diagnosis of CCS, permits cascade testing of at-risk relatives, informs reproductive decision-making including preimplantation genetic diagnosis, and identifies patients who may be eligible for trials of pre-emptive medical therapy [3]. In a patient such as ours, with lesions beginning in adolescence and a distribution encompassing the scalp, face and trunk, the clinical diagnosis of CCS is strongly suggested, and genetic characterization should be offered. Absence of a family history does not exclude the diagnosis, since de novo and mosaic presentations are recognized [3,27].

Long-term follow-up should be structured rather than opportunistic. Patients should be reviewed at defined intervals, with photographic documentation of tumor distribution and size to permit objective assessment of growth kinetics, and should be explicitly instructed to report ulceration, rapid enlargement, pain, bleeding, color change or fixation of any lesion [3]. Given the reported association with salivary gland and, rarely, pulmonary tumors, symptoms referable to the parotid region or the airway

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warrant specific evaluation [1,3]. Surveillance for cutaneous malignancy in general is prudent, since apparently de novo skin malignancies may also arise in these patients [3].

## IV. CONCLUSIONS

Cutaneous cylindroma is an uncommon adnexal neoplasm which, in its multiple hereditary form, constitutes a lifelong surgical problem rather than a single operative event. The case presented illustrates the characteristic natural history of CYLD cutaneous syndrome: onset in adolescence, progressive accumulation of tumors on the scalp, face and trunk over five decades, and eventual ulceration of a dominant lesion raising legitimate concern for malignant transformation.

Three principles emerge for contemporary practice. First, clinical vigilance is the primary defense against cylindrocarcinoma: ulceration, rapid growth, bleeding, pain and fixation are the signals that mandate definitive excision with full histopathological assessment, because no imaging or clinical feature reliably distinguishes benign from malignant disease preoperatively. Second, reconstruction in the multiply affected patient should be selected with the next operation in mind; skin grafting, and specifically full-thickness grafting, preserves adjacent scalp laxity for future staged excisions and facilitates surveillance, whereas extensive local flaps may compromise both. Third, these patients require genetic characterization, family counselling and structured long-term follow-up, and benefit from management within a multidisciplinary framework that includes plastic surgery, dermatology, pathology and clinical genetics.

Although surgery remains the only treatment of proven efficacy, the elucidation of the CYLD–NF- $\kappa$ B axis and of MYB activation as a convergent oncogenic mechanism has opened credible avenues for targeted medical therapy. Until such treatments mature, careful, tissue-preserving, staged surgical management with early intervention on suspicious lesions offers these patients the best combination of oncological safety and functional and aesthetic outcome.

## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest relevant to the content of this article, and that no financial support was received for the submitted work.

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