Clinical History

A 59-year-old male presented with a six-month history of intermittent weakness of his right foot, which had progressively worsened. Past medical history was positive for surgery for a left parotid gland basal cell carcinoma in 1994 and for removal of multiple benign cutaneous scalp lesions. Family history was positive for several family members who also had histologically similar, and multiple, benign skin lesions.

Clinical History

His intermittent weakness was initially felt to be ischemic in origin, but he subsequently had two additional episodes of expressive aphasia which prompted further workup. Magnetic resonance imaging studies revealed a large 4.0 x 3.9 cm, contrast enhancing, parasagittal mass suspicious for a bony-erosive meningioma (Case2-Figure 1).

Sagittal magnetic resonance imaging (MRI) scan, with gadolinium, shows invasion of the tumor deep into the left parietal lobe. Note the overlying scalp portion is nearly equal in volume to the intracranial parts of the tumor.

The intracranial lesion appeared to be in continuity with a bulging, fixed, cutaneous scalp lesion measuring 5 x 4 cm.

The patient was taken for neurosurgical resection of the mass. Intraoperatively, the tumor extended across dura but did not appear to invade the underlying brain; a near gross-total resection was achieved.

Low power photomicrograph shows the large and small basophilic nests of tumor cells invading through the skull, leaving only a few widely dispersed eosinophilic bone spicules and causing extensive fibrosis. Hematoxylin and eosin (H&E), 200X.
Low power photomicrograph of the tumor shows the characteristic islands of basaloid cells with peripheral palisading and surrounding hyaline bands. H&E, 200X.

High power photomicrograph best highlights the fact that histological features of malignancy, such as loss of the eosinophilic hyaline sheath at the perimeter of the nests, nuclear pleomorphism, and loss of peripheral palisading, are NOT present in this skull-invasive tumor. H&E, 600X.

High power photomicrograph of the spiradenoma areas illustrates the well-developed ducts that were focally present in the tumor. H&E, 600X.

1. What is the diagnosis?

The diagnosis is cylindroma; no malignant features were identified.

- Cylindromas are benign cutaneous adnexal neoplasms that usually occur sporadically and only rarely show transformation into cylindrocarcinoma.
- Sporadic cylindromas are most common in middle-aged to elderly women.
- Grossly, tumors occur as tan-pink nodules with a predilection for the head and neck.

Key microscopic features of benign cylindroma are illustrated in this case and include irregularly shaped islands of basaloid cells arranged in a "jigsaw puzzle" pattern, separated by a hyaline sheath.
The diagnosis is cylindroma; no malignant features were identified.

- Two cell types can be identified: a small cell with a dark nucleus that tends to palisade around the periphery of the islands, and a cell centrally located within the islands that shows a pale staining, vesicular nucleus.
- Malignant transformation of cylindromas is defined by anaplasia and pleomorphism of the nuclei with increased mitotic figures, loss of the hyaline sheath, loss of peripheral palisading, and stromal invasion.

Is it common for cutaneous tumors to invade the skull?!?

Definitely not; cutaneous tumors of the scalp, even highly malignant variants such as basal cell carcinoma or squamous cell carcinoma, seldom invade the underlying skull and dura and seldom enter diagnostic consideration for clinicians, pathologists, or especially neuropathologists!

- This is a very unusual case of a scalp cylindroma without features of malignancy invading through the skull and dura and producing massive intracranial extension.

Autosomal dominant tumor syndromes with cutaneous tumors

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Germline mutation of PTEN/ MMAC1 gene</th>
<th>Germline mutation of PTCH gene</th>
<th>Germline mutation of CYLD gene</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cowden syndrome</td>
<td>multiple trichilemmomas (85%), oral papillomatosis, cutaneous keratoses, gastrointestinal polyps (40%), thyroid tumors, benign breast tumors, breast cancers (30%)</td>
<td>Medulloblastoma Meningioma (5%)</td>
<td>Cylindromas, trichoepitheliomas, spiradenomas, and basal cell adenomas and adenocarcinomas of the parotid glands and minor salivary glands</td>
<td>Neurofibromatosis</td>
</tr>
<tr>
<td>Gorlin syndrome</td>
<td>multiple basal cell carcinomas and jaw keratocysts (both features found in 90% of patients by age of 40 years).</td>
<td>Dysplastic gangliocytoma of the cerebellum Meningioma (7%)</td>
<td>Note</td>
<td></td>
</tr>
<tr>
<td>familial cylindromatosis (Brooke-Spiegler syndrome)</td>
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4. This patient perhaps had some even rarer syndrome—what is it?
• Pt. had familial cylindromatosis (Brooke-Spiegler syndrome, OMIM 132700, 605041), a rare autosomal dominant tumor syndrome

• He had had removal of a salivary gland tumor 12 years previously and had undergone numerous previous surgical excisions of his scalp cylindromas over a 30-year time period

• In patients affected by familial cylindromatosis, the numerous cylindromas are typically on the head and neck and the trichoepitheliomas are generally located on the face, especially in the paranasal region

Scalp cylindromas may coalesce and become quite bulky, hence the name “turban tumor”

• Tumors generally begin to manifest during the first two decades of life, earlier than for sporadic cylindromas, and accumulate throughout life, often resulting in disfiguration,

• Paternal grandmother was severely affected, with his father and brother less severely afflicted; thus far, his 21-year-old daughter does not manifest the features.

5. Have other cases of intracranial invasion been reported for cutaneous cylindromas?

Yes: while an uncommon occurrence, both benign and malignant cylindromas have rarely been reported to invade bone. A literature review revealed several examples of malignant transformation with invasion of underlying skull/dura and intracranial extension, some of which were also definitely in patients with familial cylindromatosis (with two more examples in the older German-language literature cited by reference).

We were able to identify only one other case in the literature of a benign cylindroma invading the underlying skull and producing intracranial extension and this patient also suffered from familial cylindromatosis.

6. What is known about the genetics and biology of familial cylindromatosis?

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We were able to identify only one other case in the literature of a benign cylindroma invading the underlying skull and producing intracranial extension and this patient also suffered from familial cylindromatosis.
• Syndrome autosomal dominant with complete penetrance, but expression is variable, as is illustrated in this patient's family history
• CYLD gene involved with the syndrome mapped to 16q12-q13
• Clinically similar, but apparently distinct disorder, multiple familial trichoepitheliomas (MFT), mapped to 9p21 - Recently, however, a family presenting predominantly with trichoepitheliomas (and resembling the MFT phenotype) was found to have a novel missense mutation in the CYLD gene and was recognized to be a variant of the Brooke-Spiegler syndrome
• Phenotypic range of expression in Brooke-Spiegler syndrome is broad, with considerable inter- and intra-familial heterogeneity

Loss of heterozygosity at cylindromatosis gene locus, CYLD, in sporadic skin adnexal tumours

• CYLD gene important in sporadic skin adnexal tumors, not just syndromic ones
• Loss of heterozygosity identified in sporadic skin adnexal tumors such as apocrine hydrocystomas, eccrine spiradenomas, and sebaceous adenoma
• Cylindromas and spiradenomas are tumors of sweat gland origin, whereas trichoepithelioma is a tumor of hair follicle origin
• Observation has lead many to believe that CYLD gene mutations result in dysregulation of the folliculosebaceous-apocrine stem cells

7. If this tumor was so benign, why did it invade his skull?

7. Possible reasons for skull invasion
• Cylindromas in familial cylindromatosis tumor syndrome may have a propensity to invade underlying skull due to their long-standing nature and multiplicity
• May be an element of “patient neglect” in these few patients where the tumor has been skull invasive
• Multiple previous surgical resections down to the level of the pericranium may weaken nearby bone
8. Are there biological markers present in these tumors that might explain the aggressive behavior, other than mitotic rate?

9. This is a pretty rare case—Are there other types of cutaneous or head and neck tumors that the pathologist is more likely to see invading the skull?

Skin tumors (usually basal cell and squamous cell carcinoma of face and ear invading the skull base)....
Cutaneous tumors seldom are skull-invasive and invasion is especially uncommon over the skull convexity. Tendency for bony invasiveness in some, but not all, tumor types can be related to histological subtype, differentiation, depth of invasion, patient neglect, and/or perineural invasion.

Take home bullet point:

1. Cutaneous tumors seldom are skull-invasive and invasion is especially uncommon over the skull convexity.
**Some notable SKULL INVADERS**

*from the surgical pathology world:*

- paragangliomas of head and neck
- olfactory neuroblastomas
- nasopharyngeal carcinomas
- sinonasal undifferentiated carcinomas of the frontal sinuses
- mucoepidermoid carcinomas
- adenocarcinomas
- adenoid cystic carcinomas of parotid or minor salivary gland

**Take home bullet point:**

2. Adenoid cystic carcinomas of major and minor salivary glands show relatively frequent intracranial involvement and are the most important “skull invader” for pathologists to know about.

**Adenoid cystic carcinomas**

Although ACC constitutes only about 1% of head and neck malignancies, the reported incidence of cranial base invasion is 4-22%.

Skull-invasive ACCs most commonly involve the infratemporal fossa, cavernous sinus, and middle fossa.

**When do ACCs invade skull?**

Many (69%) of patients with skull-base invasive ACCs already have evidence of their cranial base invasion by the time they first come to medical attention. **EARLY**

Remaining patients later develop skull-base involvement months after the head and neck primary was diagnosed and treated with surgery, radiation, chemotherapy. **LATE**

**Clinical features of skull-invasive ACCs mimic primary intracranial tumors!**

Patients with involvement of the skull base by their ACC manifest with neurological symptoms including trigeminal neuralgia, diplopia, visual deficits, nasal symptoms, hearing alterations, and swallowing difficulties.

**Rare patients show intracranial ACCs without a known extracranial primary.**
Intracranial involvement by ACC may be due to either direct extension or hematogenous spread, although skull-base invasive tendency in ACCs is perhaps best linked to histological finding of perineural invasion.

Take home bullet point:

3. Patients with ACC may manifest neurological symptoms at the time of initial presentation, reflecting the ability of these tumors to develop skull-base invasion early in the clinical course. Rare patients show intracranial ACC without a documentable extracranial primary.

Case 2 was a benign cylindroma invading the convexity of the skull, in a patient with an uncommon familial autosomal dominant syndrome, due to mutation in the CYLD gene mapped to 16q12-q13.