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SINE QUA NON RADIOLOGY-PATHOLOGY

Sine Qua Non: Sinonasal Inverted Papilloma

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Abstract
Inverted papilloma (IP) is a common proliferation of squamous epithelial cells of the sinonasal tract. Although considered benign, IP is known to cause local destruction, has a high rate of recurrence, and a low, but significant rate of malignant transformation. Differentiating an IP from its histologic mimickers is essential for appropriate risk stratification and long-term surveillance. A classic case of sinonasal inverted papilloma is discussed.

Keywords Sinonasal papilloma · Inverted papilloma · Schneiderian · Oncocytic papilloma · HPV · HPV-mediated squamous cell carcinoma

History

A 34 year-old female patient presented to her primary care physician with a history of left nasal congestion, sinus pressure and pain around her left eye. CT demonstrated an enhancing, heterogeneous soft tissue mass of the left maxillary sinus arising from the middle turbinate. The mass displayed a cerebriform appearance with an expansion of the infundibulum. In the absence of other significant paranasal sinus disease, an inverted papilloma was listed as the leading differential diagnosis and clinical correlation was recommended (Fig. 1). Physical examination at the Otolaryngology Clinic was unremarkable and no mass was visualized with an in-office endoscopy. The patient was consented for surgery and underwent a medial maxillectomy with a Caldwell-Luc surgical approach (Fig. 2). Histologic review confirmed the presence of an IP. During clinical surveillance, 9 months after her first surgery, recurrent disease was identified by CT scan. During her second surgery, the lesion was fully removed along with a bony site of attachment along the orbital floor. 12 months after the second procedure, the patient has recovered and has no radiographic or clinical evidence of a second recurrence.

Histologic Findings

Both the initial excision and recurrent disease were diagnosed as sinonasal inverted papilloma. Grossly, the specimens consisted of polypoid fragments of pink to tan tissue with a vaguely cerebriform appearance. Microscopic review revealed exophytic projections demonstrating a hyperplastic epithelium overlying well-encapsulated subepithelial nests (Fig. 3). The epithelium and subepithelial nests were composed of eosinophilic squamous epithelial cells. These cells matured from an organized, unremarkable layer of basal cells to squamous epithelial cells demonstrating mild pleomorphism, prominent cellular borders and cleared out cytoplasm. The nuclei demonstrated mild atypia with smooth, circular to oblong nuclear borders and scattered prominent nucleoli. The subepithelial nests were surrounded by an intact basement membrane in the background of a delicate fibrous stroma (Fig. 4). Scattered neutrophils and small microabscesses were interspersed throughout the proliferation and the stroma was admixed with a mild chronic inflammatory infiltrate composed of lymphocytes and scattered eosinophils. Rare mitotic figures were identified along the basal layers of the proliferation. No necrosis, desmoplasia,

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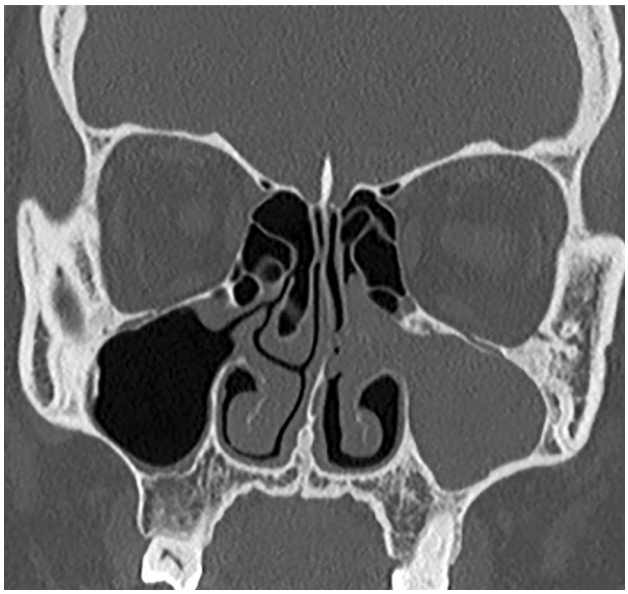

Fig. 1 Coronal CT of the sinus showing opacified left maxillary sinus with hyperostotic change along left inferior-medial orbital wall

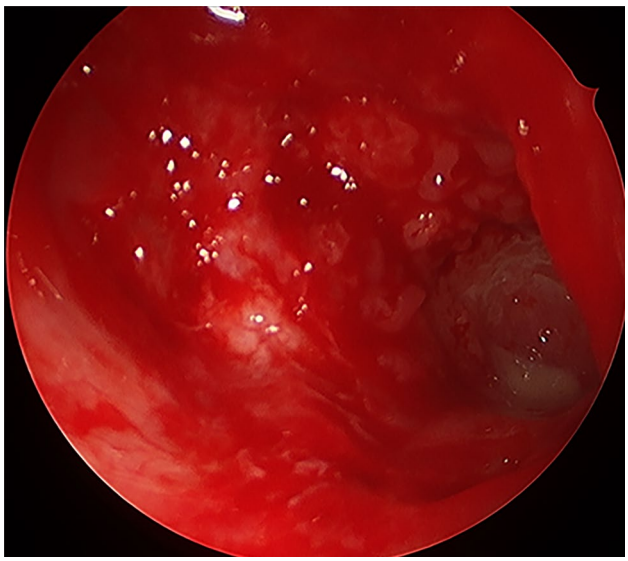

Fig. 2 Papilloma along left orbital floor

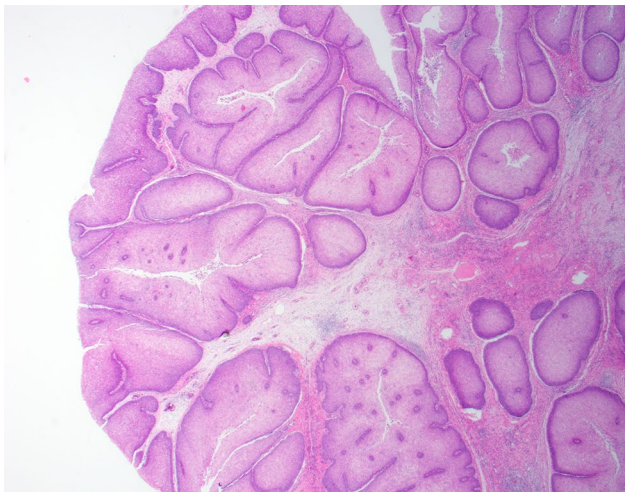

Fig. 3 An exophytic proliferation with pronounced endophytic downward growth composed interconnected nests or islands of epithelial cells

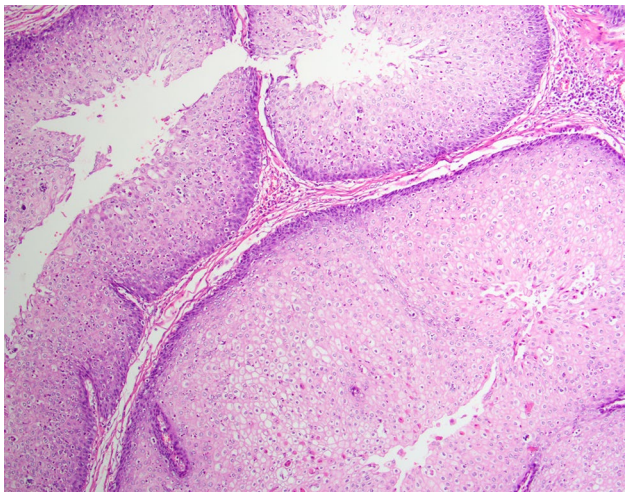

Fig. 4 The lesional cells demonstrated maturation from a peripheral basal layer of small purple cells to larger eosinophilic cells with mild pleomorphism, distinct cellular borders and cleared out cytoplasm

invasive features, atypical mitotic figures or keratinization were identified.

Discussion

Sinonasal inverted papillomas, also termed Schneiderian papillomas, are common epithelial neoplasms of the head and neck, that comprise upwards of 4% of all sinonasal tumors [1–3]. IP may be found in patients of any age, but are predominately identified in patients in their 5th to 6th decades of life with a 2–3:1 male to female ratio [4]. Patients may present asymptomatically or with nonspecific symptoms such as epistaxis, airway obstruction and pain. IP are characterized by their cerebriform appearance with a hyperplastic epithelial surface which demonstrates a downward, endophytic growth pattern composed of interconnected subepithelial nests. Although considered benign, appropriate risk stratification and surveillance of patients is essential, as approximately 5–15% of IP undergo malignant transformation [5–7]. Rare cases of IP have transformed into mucoepidermoid carcinoma, but

the majority of malignancies associated with an IP are nonkeratinizing squamous cell carcinoma (SCC) [8–10].

IP may cause local destruction and invasion of the vital structures and surfaces of the sinonasal cavity, and are known to have a recurrence rate of up to 20% [11, 12]. Recurrence typically occur within the first year post-operatively [13, 14], but may recur as late as 6 years, supporting prolonged surveillance typically by in-office endoscopy [15, 16]. There may be a higher recurrence risk in the younger population [17, 18]. Although these tumors are typically excised due to their symptomatic nature and potential for malignant degeneration, observation may be possible in poor surgical candidates or in cases where surgical violation of periorbita or dura risks intra-orbital or intracranial spread, respectively.

Radiologic correlation is important in the diagnosis of an IP as location specific and radiographic features are supportive of the diagnosis. The majority of IP arise from the lateral nasal side wall, and on MRI, IP demonstrate the same septate striations and cerebriform features frequently found on endoscopic exam. Other radiologic findings, such as bony site attachment, known as hypertrophic osteitis, further support the diagnosis of IP and have been detected in 95% of cases [19]. The combination of these findings allow for a greater than 95% specificity and positive predictive value in the radiologic diagnosis of an IP [20]. Other papilloma and inflammatory polyps of the sinonasal tract may occur synchronously and decrease the specificity of MR imaging. However, subsequent histologic evaluation is frequently sufficient in differentiating an IP from other lesions of the sinonasal tract.

Histologically similar sinonasal lesions, such as exophytic papilloma (EP), resemble IP grossly, and are similarly described as mushroom shaped lesions with exophytic projections. Like IP, location specific features can be supportive of the diagnosis, as EP occur almost exclusively on the nasal septum [20, 21]. Microscopically, EP may also demonstrate similar papillary structures composed of hyperplastic layers of epithelial cells around fibrovascular cores. True to their name, EP lack the endophytic growth patterns of IP and the hyperplastic epithelial layers of an EP should be confined to the surface of the papilloma. The endophytic growth pattern of an IP may be challenging to differentiate from a fragmented epithelial projection of an EP in a morcellated specimen. However, even in a fragmented specimen, the presence of epithelial nests surrounded by a well-defined basement membrane in the background of a delicate fibrous stroma, is highly suggestive of an endophytic growth pattern and consistent with an IP.

Oncocytic papilloma (OP), or cylindrical papilloma, represent the least common variant of sinonasal papilloma and may demonstrate both exophytic and endophytic growth patterns. In contrast to the epithelioid cells of an IP or EP, OP demonstrate tall, stratified, columnar cells with ovoid nuclei. The cells have eosinophilic and granular cytoplasm. OP are also frequently interspersed with intraepithelial microabscesses containing both neutrophils and mucin [22]. As this case demonstrates, scattered intraepithelial neutrophilic microabscesses may be a shared feature of OP and IP, but the markedly different mucosal linings should allow for definitive diagnosis.

Other entities in the differential diagnosis include sinonasal hamartomas, particularly the respiratory epithelial adenomatoid hamartomas (REAH). REAH are glandular proliferations arising from the epithelium of the sinonasal tract. Grossly, REAH may appear similar to an inverted papilloma. However, while IP has an intact, well-defined membrane, REAH, demonstrate a dense, pink, hyalinized basement membrane, that is generally readily identifiable on low power. Importantly, while inverted papilloma may reveal occasional mucocytes, REAH is a glandular proliferation, and will lack the squamous or columnar differentiation that is characteristic of a sinonasal papilloma [23].

Inflammatory polyps, another common entity of the sinonasal tract, may also endoscopically appear similar to IP. However, inflammatory polyps consist of thin layers of ciliated epithelium overlying an edematous and vascularized stroma. The lack of epithelial hyperplasia and the presence of ciliated respiratory epithelium and the edematous stroma should allow for differentiation between an inflammatory polyp and a sinonasal papilloma.

Microscopic examination may also identify dysplasia and precursor lesions within sinonasal papilloma. Like elsewhere in the body, full thickness atypia, the lack of maturation, suprabasal mitosis and atypical mitotic figures are features of epithelial dysplasia that may be identified in a dysplastic IP. Subtle features of dysplasia may be difficult to identify in tangentially cut nests where the superficial epithelium is obscured by an involuting, endophytic growth pattern. Immunohistochemical staining may serve as an adjunct in such cases. P16, TP53 and Ki-67 (MIB-1) immunohistochemical stains may be helpful in highlighting areas of increased mitotic activity or atypia that require more investigation. Similar to other forms of dysplasia, hematoxylin and eosin stained slides remain the gold standard when determining the final diagnosis.

Although rare, sinonasal squamous cell carcinoma (SNCC) is the most common malignancy of the sinonasal tract and may demonstrate significant histopathologic overlap with IP [8]. Histologically, SNCC may present as keratinizing or nonkeratinizing subtypes and appears morphologically similar to SCC located in other parts of the body. From a low power magnification, SNCC may appear similar to an IP. Both entities may reveal islands of tumor cells with an endophytic growth pattern. However, at a higher magnification, the islands of SNCC will lack the intact basement

membrane identified in IP, and will invade the surrounding stroma. Importantly, carcinoma is composed of atypical and pleomorphic epithelial cells and a desmoplastic stroma may be identified. The lack of cellular maturation, presence of central necrosis and prominent mitotic figures are other features that should raise the suspicion for SNCC [9, 10].

Definitive diagnosis is essential to appropriately risk stratify patients with sinonasal papilloma. IP have a rate of malignant transformation of 5–15% and accurately identifying an IP will aid the clinician in determining suitable clinical surveillance [8, 9, 11]. Whereas EP, although histologically similar, have virtually no rates of malignant transformation and postoperative surveillance may be decreased. In contrast to EP, OP have similar rates of transformation to an IP and should be followed in a similar fashion [23]. Although inflammatory polyps and REAH may occur in conjunction with an IP, no rates of malignant transformation have been reported in these entities [24].

The underlying mechanism of malignant transformation in an inverted papilloma remains unclear. Studies have both demonstrated a positive and negative association of high-risk HPV infections with malignant transformation [25]. These contradictory claims question whether the relationship of HPV and the malignant transformation of IP is causative or merely associative. EP may also share an association with HPV infections, but gene sequencing has linked EP predominately to lower risk HPV serotypes [26]. OP have no proven association with HPV infections, and a hypothesized separate neoplastic process may be the underlying cause of the distinctly different epithelial linings [27–29].

Successful removal of IP have included both external and endoscopic surgical approaches. Although an endoscopic approach may provide the patient with an improved cosmetic outcome, lower postoperative pain and a lower risk of trigeminal nerve damage, external or open procedures provide the surgeon with a wider surgical field [30]. As this case demonstrates, the wider surgical field of the Caldwell-Luc approach allowed the surgeon to remove the bony attachments and bur away the underlying bone in hopes of achieving definitive care and preventing recurrence. However, recent review articles and meta-analysis have demonstrated that new endoscopic approaches were able to obtain statistically similar or even improved rates of disease recurrence, and suggest that in the future, minimally invasive endoscopic procedures may supplant open surgical procedures as the gold standard for the removal of sinonasal papilloma [31].

In summary, inverted papilloma are common sinonasal neoplasms that are characterized by endophytic growth of epithelial nests. These lesions are considered benign, but have a significant malignant transformation potential. IP are also known to cause local destruction and their treatment relies on surgical procedures to remove the tumor, and as this case demonstrates, recurrence is common. Although radiologic interpretation is highly supportive of the diagnosis, pathologic review is essential to differentiate IP from their histologically similar counterparts. And finally, although the diagnosis of IP may be challenging, definitive diagnosis can relay critical prognostic information to the clinician which will be used to determine the appropriate level of long-term surveillance for the patient.

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Compliance with Ethical Standards

Conflict of interest Frederic C. Jewett declares that he has no conflict of interest. Michael Coulter declares that he has no conflict of interest. Brenda L. Nelson declares that he has no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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