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Review - Study Group GIPaTeC

The papillomas of the sinonasal tract. A comprehensive review

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Key words

Schneiderian papilloma • Inverted papilloma • Exophytic papilloma • Oncocytic papilloma • Malignant transformation

Summary

Papillomas are uncommon tumors of the sinonasal tract histologically derived from the Schneiderian membrane. Three distinctive variants are described, the exophytic, the inverting and the oncocytic types. On physical examination, their appearance varies from exophytic-fungiform seen in the exophytic variant, to polypoid-papillary in both the inverting and oncocytic variant. The presence of an asymptomatic mass or epistaxis and unilateral nasal obstruction are the typical presenting symptoms. Clinically they tend to recur and, although benign, they may erode the bone laminas by pressure, especially the inverting type, causing proptosis and other co-morbidities. Malignant transformation is seen both synchronously, on a pre-existing papilloma, and metachronously after several recurrences of papilloma. Schneiderian papillomas are at a date a topic of controversy regarding their etiology, pathogenesis and biological behavior. Furthermore, histologic criteria to assess dysplasia and malignant transformation are ill-defined. The present study aims to comparatively review the histologic types of papillomas, their etiology, the currently available criteria for malignant transformation, their treatment and prognosis.

Schneiderian papillomas (SPs) accounts for the 0,5-4% of all the nasal tumors, usually affecting adults with a slight male predilection. They derive from the so-called Schneiderian membrane, an ectodermally derived ciliated respiratory mucosa that lines the sinonasal tract, which develops as an invagination of olfactory ectoderm during the fourth week of embrionic development [1]. So, transitional zone separates the endodermally derived respiratory epithelium of the nasopharynx and the keratinizing squamous epithelium of the nasal vestibulum [2]. This distinctive epithelium can give rise to three different histologic types of papillomas: the exophytic papilloma, the inverting papilloma and oncocytic papilloma [3]. Malignant transformation occurs uncommonly, in about 3% of SPs, with invasive squamous cell carcinoma being the most frequently reported tumor [4].

Exophytic papillomas (EPs), also known as fungiform or septal papillomas, account for 6-50% of all SPs. They are more commonly found in men between 20 and 50 years. They frequently arise from the anterior portion of the nasal septum, although the involvement of the lateral nasal wall is reported. In contrast with the other two variants, it rarely localizes in the paranasal sinuses [5]. Grossly, EP appears as a solitary discrete mass with a mushroom fashion and a wrinkled pinkish to grayish surface. It may be multifocal, but bilateral location is uncommon [6].

Inverted papillomas (IPs) are more commonly found in men between 40 and 70 years, accounting for 47-78% of all SPs. They characteristically arise from the lateral nasal wall, in the region of the middle turbinate or ethmoid recess, subsequently extending into the ethmoid and maxillary sinuses, being the frontal and sphenoidal sinuses less frequently involved [7]. The primary paranasal location is not infrequent [8]. About 8% of IPs arise from the nasal septum [9]. As in the exophytic type, IP is usually unilateral [10]. Grossly, IP appears as a polypoid tan to grayish mass with a warty surface and/or papillary projections [6] (Fig. 1). It has been suggested that ectopic migration of the Schneiderian membrane during embryogenesis could account for these aberrant papillomas in site contiguous with the sinonasal tract [5], such as middle ear and mastoid [11], pharynx [12], nasopharynx [13], lacrimal sac [14] and branchial cleft cyst [15].

The oncocytic type (OP) is rare and accounts for 2-26% of all SPs. It shares many features with IP, so that many authors consider OP as a microscopic variant of IP [1 16].

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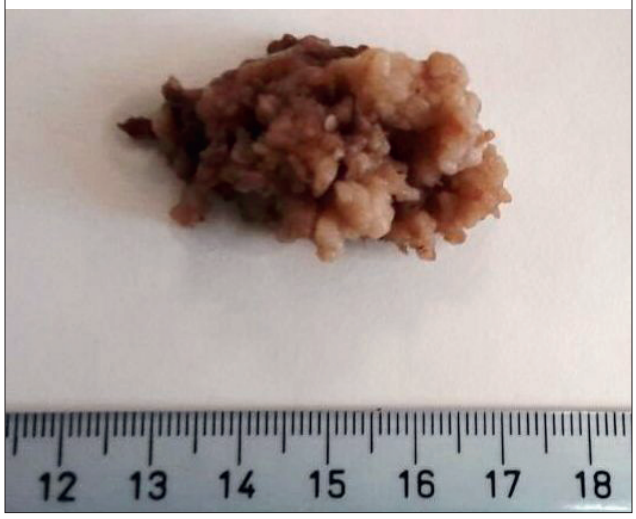
Fig. 1. IP of the lateral nasal wall.



OPs are equally distributed in both sexes, especially in patients after the fifth decade of life [17]. They are exclusively located in the lateral nasal wall or in the ethmoid and maxillary sinuses [7].

SPs may be asymptomatic. Common presenting symptoms, if any, are epistaxis and unilateral nasal obstruction. Nasal drainage, frontal headache, anosmia, are more frequently associated with IP. Pain is an uncommon complaint and, when present, it should always arise suspicion of secondary infection or malignant change [18]. Both SP and carcinoma ex-SP may cause orbital involvement by bone erosion or invasion, resulting in a locally invasive mass causing symptoms such as proptosis, visual loss, diplopia and increased morbidity [19].

Radiographic evaluation is not always necessary. When present, it shows a soft tissue density along the nasal septum or opacification and thickening of the paranasal sinuses. If bone erosion is present, it must be distinguished from the bone invasion associated to carcinoma arising in SP. Although the CT appearance of IP is variable and non specific, nonetheless IP is the most likely diagnosis when an unilateral nasal mass, producing benign bony changes, extends into the ethmoid or maxillary sinus and/or in the nasopharynx in an elderly patient with chronic nasal obstruction. In some instances, tomography may be useful to plan the surgical approach.

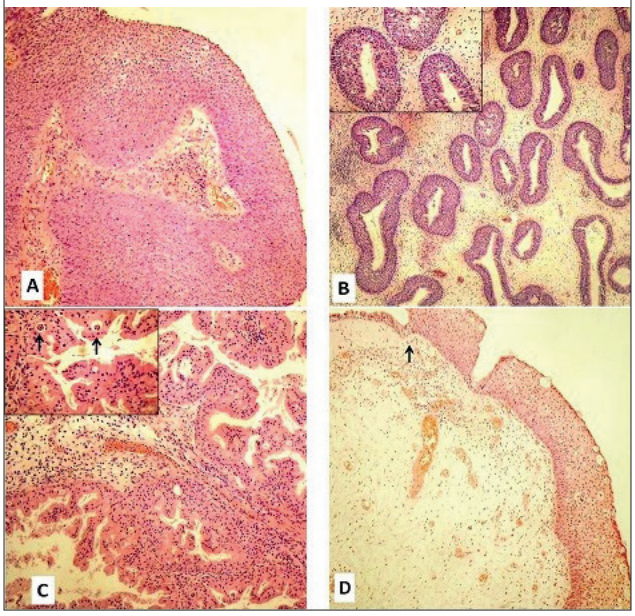
The pathogenesis of SP has not yet been delineated. Pre-existing chronic rhino-sinusitis was found to be a significant risk factor for both IP and OP of the paranasal sinuses. Other potential risk factors, including alcohol and tobacco use, or history of prior sinus surgery, failed to show a significant association with SP [3]. It has been suggested that both exophytic and inverted variant of SP may be etiologically related to human papillomavirus (HPV), most commonly to types 6, 11, 16 and 18. In contrast, OP in not related to HPV [7] A polymerase chain reaction (PCR) study by Macdonald and co-workers have found evidence of Epstein-Barr (EBV) DNA in IPs [20]. No evidence of EBV was found by others [2]. Further investigations are needed on this topic to better elucidate the relationship between IPs and EBV.

Microscopically, EPs are composed by delicate fibrovascular cores and covered by hyperplastic squamous transitional to ciliated pseudostratified columnar epithelium, with scattered mucin-secreting cells. Surface keratinization may be seen. Mitoses are usually rare. Malignant transformation is an uncommon event. IPs are characterized by a predominant endophytic growth pattern, with transitional to ciliated (respiratory type) epithelium nests totally enclosed in the basement membrane, growing with inward orientation in the underlying stroma. Mitoses may be seen, usually in the basal layer. Keratinization is not infrequent, sometimes with marked keratosis/parakeratosis in a verrucoid fashion. OPs may show both exophytic and endophytic growth pattern, characterized by multilayered tall columnar cells with small dark nuclei and finely granular (oncocytic) cytoplasm. The epithelial layer may have variable thickness, with scattered mucin-filled cysts and microabscesses. The underlying stroma is usually loose, with admixed inflammatory infiltration, mainly composed by lymphocytes, plasmacells and a variable number of eosinofils. If SP overlaps with polypoid chronic rhino-sinusitis, extensive stromal edema may be found (Fig. 2).

A mixed exophytic/inverting pattern or mixed oncocytic/inverting pattern may be observed. If any inverting pattern is seen, then the mixed lesion might be classified as IP [21].

EP must be distinguished from keratinizing cutaneous

Fig. 2. (A) EO composed by a multilayered transitional squamous epithelium with fungiform appearance (EE; x10 magnification); (B) endophytic growth of transitional epithelium nests in IP (EE; x10 magnification). Note the growing pattern with inward orientation (EE; x20 magnification); (C) oncocytic epithelium in OP (EE; x10 magnification). Note (*arrows*) the intraepithelial microabscesses (EE; x20 magnification); (D) chronic polypoid rhinosinusitis associated IP (EE; x10 magnification). Note (*arrow*) the abrupt transition between respiratory type and transitional type epithelium.



papillomas, such as the verruca vulgaris of the nasal vestibule, that lacks transitional epithelium and mucinous cells seen in EP. Surface keratinization is scanty in EP, in contrast with the extensive surface keratinization seen in verruca vulgaris. Moreover, the presence of the septal cartilage or minor salivary glands highlights the mucosal rather than cutaneous origin of the lesion.

The main entities that must be differentiated from IP are inverted ductal papilloma, nasal polyp with squamous metaplasia, and invasive carcinoma. Inverted ductal papilloma originates from the excretory duct of minor salivary glands and grows in the ductal lumen, remaining confined to it, and resulting in a well circumscribed lesion. Nasal polyps may have diffuse squamous metaplasia, but the presence of both thickened often hyalinized basement membrane and prominent minor salivary glands, as well as the absence of both multilayered transitional epithelium and inverting pattern of growth rule out IP.

Rhinosporidiosis may resembles the intraepithelial mucinous microcysts seen in OP, but organisms involve either the epithelial layer or the stroma in rhinosporidiosis, usually lacking the oncocytic epithelial features seen in OP. Low grade papillary adenocarcinoma may be confused in some instances with OP. There is no oncocytic pseudostratified epithelium in low grade papillary adenocarcinoma and, on the other hand, nuclear pleomorphism, invasive growth, and mitotic activity are usually absent in OP.

Malignant transformation is a crucial event affecting the clinical outcome in IP and OP. EP is not associated with an increased incidence of malignancies. The carcinoma can develop metachronously after SP resection in the site of surgical excision or can occur with a synchronous SP. Metachronous carcinoma are always preceded by SP recurrences.

On the other hand, carcinomas ex-SP are less common and may exhibit a broad range of behavior, from displasia to carcinoma in situ to frankly invasive carcinoma [22]. Malignancies most frequently associated with IPs are squamous cell carcinoma, verrucous carcinoma and adenocarcinoma. In contrast, mucoepidermoid carcinoma (MEC) and sinonasal undifferentiated carcinoma (SNUC) are predominantly associated with OP [3]. Malignant transformation should always been suspected when extensive bone destruction or pain are present.

Histologic criteria to define malignant transformation is not well developed. Dysplasia is quite difficult to define, because of the inverted growth pattern, the tangential sectioning and technical issues. Dyskeratosis, surface keratinization and increased epithelial pleomorphism suggest dysplasia, but the interobserver reproducibility is lacking on this topic. Surface keratinization alone does not qualify dysplasia.

Some features such as architectural disorder, increased epithelium to stroma ratio, high nuclear to cytoplasmic ratio, nuclear pleomorphism, increased mitotic count (> 25/10HPF) and atypical mitoses, decreased epithelial neutrophilic infiltration are associated with carcinoma ex-SP. Architectural disorder is identified by the lack of well developed maturation towards the surface and is associated with paradoxical maturation, the presence of abnormal keratinization or keratin pearls formation in the basal layer. A desmoplastic stromal response may be seen in areas of invasion, as well as cartilage or bone destruction. Perineural invasion, lymph-vascular invasion and tumor necrosis, qualified by ghost-cells within degenerated material, are others features of malignant transformation [22]. Demonstration of histologic continuum between carcinoma and dysplastic epithelium indicates the origin of carcinoma from SP [23]. Once a carcinoma is recognized, histologic type, degree of differentiation, adequacy of the resection margins and percentage of carcinoma with respect to the whole volume of the lesion should be assessed [7].

The neoplastic cells are immunoreactive to pan-keratin, EMA, p63, CK5/6 and high molecular weight (HMW) CK. Ki67 labeling is markedly increased in areas of malignant transformation and when it is greater than one half of the epithelial thickness, the diagnosis of dysplasia is likely. Moreover, a low expression of p16 and a positive stain for p53 correlates with the development of carcinoma in IPs [24].

The treatment of choice of SP is complete surgical excision, using both external and endoscopic approach, depending on the tumor location, the extent of disease, the available technology and the skill of the surgeon. Recurrences after surgical excision vary widely and usually suggest incomplete resection. Patient treated with a lateral rhinotomy and medial maxillectomy have shown a recurrence rate of 30%, in contrast with those treated with a less aggressive approach have shown a higher rate, accounting for 71%. Despite a trend of a more conservative sinonasal surgery, some authors advocate the lateral rhinotomy and medial maxillectomy as a treatment of choice in SP [25]. Radiation therapy is generally not recommended for SPs, unless associated to malignancy [18]. Long-term follow-up is recommended given that the recurrences can occur after prolonged periods of times [26].

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