Common Head and Neck Cases in Our Consultation Referrals: Diagnostic Dilemmas in Inverted Papilloma

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Abstract Papillomas of the nose and paranasal sinuses comprise three morphologically distinct variants—everted papilloma, inverted papilloma and cylindric cell papilloma in descending order of frequency. Recurrence of everted papilloma is unusual and malignant change does not occur. However, inverted papilloma is associated with multiple recurrences and malignant change. The histology of low grade squamous cell carcinoma of the nose may mimic that of inverted papilloma and low grade squamous cell carcinoma may coexist with inverted papilloma and be present in the same biopsy material. There is a high index of suspicion of concomitant malignancy in the presence of severe atypia or hyperkeratosis. Columnar cell papillomas are also associated with an increased risk of malignancy but the rarity of these lesions makes accurate assessment of malignant potential difficult. The most common diagnostic dilemma for pathologists referring cases for second opinion is the recognition of low grade malignancy versus benign inverted papilloma at presentation and in lesions which recur. Recent studies have addressed the requirement for histological parameters to predict the clinical course of these lesions and new molecular markers are being applied to tissue diagnosis. The early recognition and treatment of malignancy associated with inverted papilloma is key to decreased morbidity and improved patient survival and forms the basis of this discussion.

Keywords Inverted papilloma · Associated squamous cell carcinoma · Carcinoma in situ · Diagnosis · Nose · Paranasal sinus

Introduction

Papillomas of the sinonasal tract comprise three histological types, exophytic or everted papilloma, columnar, cylindric cell or oncocytic papilloma and inverted papilloma. Everted papilloma originates mainly from the nasal septum whereas columnar cell papilloma and inverted papilloma arise from the lateral nasal wall or maxillary sinus [1]. Characteristic attributes of inverted papilloma are the tendency to recur (up to 60%), the locally aggressive behaviour and the doubt about the mechanism and frequency of the malignant change. While diagnosis of inverted papilloma is relatively unproblematic, the diagnostic challenge for the histopathologist is to predict clinical behaviour and prognosis.

The name inverted papilloma implies an endophytic growth pattern with downgrowth of epithelium into underlying stroma with preservation of the epithelial basement membrane. Histologically the nasal columnar epithelium and invaginating gland ducts and their branches undergo squamous metaplasia, which may range from a mild thickening of stratified squamous epithelium under the columnar epithelium to large epidermoid masses with marked glycogen secretion within the cells. Diagnosis is not difficult in the majority of cases, but a low grade squamous cell carcinoma can be mistaken for inverted papilloma [2]. The presence of any atypia or dysplasia in a lesion of this kind, in our experience, should raise the possibility of malignancy.

Although most unilateral nasal masses are non-neoplastic, inverted papilloma is the most common neoplastic cause [3]. These lesions comprise between 0.5% and 4% of all nasal tumours (2–3% of all nasal polyps) and are sited typically in the middle meatus, extending through the maxillary antrum [4]. Patients are usually in the 6th decade

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and males outnumber females by a ratio of 4:1. The most common presenting symptom is nasal obstruction, but other symptoms include nasal drip, facial pain, epistaxis, frontal headaches and epiphora. One study found that the association of unilateral epistaxis and unilateral nasal polyp was statistically significant for inverted papilloma [3]. The lesions are thought to arise from proliferating epithelium on the lateral nasal wall but they may take origin from many sites in the sinonasal tract.

Discussion

Squamous cell carcinoma associated with inverted papilloma may be synchronous (diagnosed at presentation) or metachronous (appearing at the same site as a previously excised inverted papilloma). A recent large series of inverted papillomas reported by Mirza et al. [5] described synchronous carcinomas in 7.1% (163/2,297 cases) and metachronous carcinoma in 75/2,047 cases implying a malignant transformation rate of 3.6%. In the same series atypia was associated with inverted papilloma in 9% of cases, dysplasia in 12% and carcinoma in situ in 3.4%. The cases in the atypia group showed a recurrence rate of 42% but only one case went on to develop carcinoma. No malignancy was reported in the dysplasia group and 3/11 cases in the carcinoma in situ group developed carcinoma. The time from presentation with inverted papilloma to malignant transformation was between 6 and 180 months (mean 52 months).

Several studies have attempted to define histological parameters which could predict multiple recurrence and malignant transformation. Eggers et al. [6] reported a retrospective analysis of 93 cases and Katori et al. [7] analysed a series of 39 cases of inverted papilloma to establish histological parameters to predict recurrence and malignant transformation. Multiple recurrences without malignancy were related to frontal sinus site, increased hyperkeratosis, presence of squamous epithelial hyperplasia, and increased mitotic index. Malignancy was associated with the presence of bone invasion, absence of inflammatory polyps, high ratio of neoplastic epithelium to stroma, increased hyperkeratosis and decreased eosinophils. Clinically benign behaviour was related to the presence of inflammatory polyp and absence of hyperkeratosis [7] (Fig. 1).

The mechanisms of growth and malignant transformation in inverted papilloma remain obscure. Increased expression of matrix metalloproteinase 9, an enzyme with the capacity to cleave collagen and elastin, has been demonstrated in inflammatory cells adjacent to the hyperplastic epithelium in patients with inverted papilloma [2, 4].

Increased expression of hepatocyte growth factor and its receptor c-met has also been observed in patients with

inverted papilloma suggesting these molecules have a role in proliferation [4].

The rarity of the lesions has hampered the development of molecular prognostic markers. An immunohistochemical study has shown increased expression of p21 and p53 in inverted papillomas associated with dysplasia and squamous cell carcinoma [8]. HPV family 6/11 and 16/18 DNA has been observed in inverted papilloma associated with severe dysplasia and squamous cell carcinoma and HPV infection may be an early step in the process of malignant transformation [9]. An increased incidence of dysplasia has been observed in inverted papillomas positive for HPV family 6/11 and 16/18 DNA while decreased expression of p21 and p53 has been observed in HPV 16/18 positive inverted papillomas compared with those which are HPV 16/18 negative [8].

Increased expression of EGFR and TGF α has been observed on immunostaining in benign inverted papilloma and those associated with dysplasia and carcinoma in situ [10]. HPV infection has been shown to elevate EGFR levels by post translational mechanisms in keratinocytes and laryngeal papilloma cells [9]. Recently the muscle segment homeobox gene *Msx2*, implicated in the regulation of craniofacial bone metabolism, organ development and tumourigenesis has been demonstrated in inverted papillomas but not in normal tissue or inflammatory polyps. The protein expression level was directly and significantly associated with tumour recurrence [11].

Glycolytic activity has been shown to be increased in inverted papilloma and low grade squamous cell carcinoma on Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) imaging [12].

Recommended treatment of inverted papilloma is complete surgical excision based on the premise that recurrence results from residual disease left at surgery and that complete surgical excision reduces the risk of malignant transformation (metachronous disease). External surgical approaches such as lateral rhinotomy and midfacial degloving have largely been replaced by a combination of endoscopic techniques, image guidance and powered instrumentation. It has become acceptable to avoid en bloc resection, even in the presence of malignant disease, as long as total removal is achieved and confirmed at frozen section, which may involve multiple biopsies. Histological examination requires careful examination of all the tissue submitted.

Adjuvant radiotherapy with or without chemotherapy is advocated and chemoradiotherapy may be the treatment modality of choice for extensive lesions not amenable to surgery [13].

Inverted papilloma can recur after an apparent remission. Most recurrences occur within the first 2 years but late recurrences up to 10 years have been described. Long-

Fig. 1 H and E stained sections showing tissue from a recurrent nasal tumour in a 28 year old male. At presentation there were features of inverted papilloma and synchronous squamous cell carcinoma (**a** and **b**). The recurrent tumour (**c** and **d**) resembled inverted papilloma but showed cytological atypia and increased mitotic figures

term follow up is recommended, of at least 5 years, but given the risk of late recurrence and the mean time to development of carcinoma at 52 months (range 6–180 months) lifelong follow-up may be appropriate [13].

Conclusion

Low grade squamous malignancies can mimic inverted papilloma and surgical pathologists should be aware of this diagnostic dilemma. Distinction between benign, locally aggressive and malignant lesions is still based on morphology. Recent developments in imaging technology and the application of immunohistochemical and molecular markers to tissue diagnosis may help predict biological behaviour of these lesions in the future.

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