Inverted Papilloma: A Clinico-Pathological Dilemma with Special Reference to Recurrence and Malignant Transformation

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Abstract To study the clinicopathological profile, recurrence and malignant potential of the inverted papilloma of nose and paranasal sinuses in relation to the definitive diagnosis and the management undertaken. A total number of 52 cases of histologically proven inverted papilloma managed in our department of otolaryngology over a 10-year period (May 1998–April 2008) were followed up (until October 2009) and the results were analyzed retrospectively to find out any incidence of recurrence of these tumours. A total of 52 inverted papilloma cases were managed with different surgical interventions. Male:female ratio was found to be 10:1. The mean follow up period was 74 months (range 16 months–11 years). Recurrence was observed in 20 (38%) cases. 23% had recurrence without any specific histological pattern, 12% had recurrence with focal dysplasia and 4% had recurrence with malignant transformation into squamous

cell carcinoma (SCC). Post-operative radiotherapy was given to 8% (four cases) with malignant transformation. The management of inverted papilloma depends on its size and extension. Recurrence can be minimized by an appropriate surgical planning. Careful endoscopic assessment is essential to detect early recurrence. Recurrent inverted papilloma should be treated more aggressively. Malignant transformation in inverted papilloma should be managed like any aggressive sino-nasal malignancy.

Keywords Inverted papilloma · Recurrence · Malignant transformation · Management

Introduction

Inverted papilloma, one of the many variants of papillomatosis encountered in the nasal cavity and paranasal sinus region is a rare entity and has always remained a dilemma to the surgeons and pathologists because of its unpredictable recurrence and malignant transformation. Hyams [1] studied the biological features of the tumour and showed malignant transformation in 5–13% cases. Inverted papilloma is associated with squamous cell carcinoma (SCC) in approximately 10% of the cases. Malignancy may occur synchronously or metachronously [2]. Here is our experience with these lesions from clinical and pathological point of view in an attempt to find out its biological behaviour, particularly malignant transformation.

Materials and Methods

A total number of 52 cases of histologically proven inverted papilloma managed in our department of

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otolaryngology over a 10-year period (May 1998–April 2008) were retrospectively considered for this study.

Results

In this retrospective study, we analyzed 52 cases of inverted papilloma regarding its incidence, age–sex ratio, clinical behaviour, extent of disease, mode of management, recurrence rate and rate of malignant transformation.

During this period, 711 cases were operated for the management of nasal and sinonasal mass and among them 52 (7%) were found to be histologically proven cases of inverted papilloma.

In our series, most vulnerable age group belonged to the fifth decade (46%) (Table 1). Male:female ratio in this series was 10:1. Most of the patients presented with history of nasal obstruction (50 cases; 96%), rhinorrhoea (42 cases; 81%) and occasional epistaxis (29 cases; 56%) (Table 2). One case (2%) presented with skin ulceration and swelling over right maxilla with numbness over right cheek. History of previous operation was noted in 17 cases (33%) at the time of primary presentation. Clinical examination revealed nasal mass arising from lateral nasal wall in all the cases.

All the patients underwent radiological evaluation by CT scanning to assess the extent of disease. Most of the cases were found to involve the maxillary and ethmoid sinuses along with the nasal cavity (37 cases; 71%). Some of the cases were found to involve only the ethmoid sinuses along with the nasal cavity (12 cases; 23%). Some cases had only nasal masses without involvement of any of the sinuses (two cases; 4%). Erosion of antero-lateral wall of maxilla with extension into cheek was found in only one case (2%). Sphenoid and frontal sinus involvement was noticed in 4% of cases. Erosion of lamina papyracea and orbital involvement was found in 13% of cases. Pre-operative histopathological examination was done by multiple punch biopsies from the nasal mass in suspected cases to confirm the histopathological diagnosis. Few cases mimicked nasal polyp and were subjected to intranasal polypectomy without prior histopathological examination.

Table 1 Age and sex distribution

Age group (years)	No. of patients	Percentage
20–30	6	11.5
31–40	12	23
41–50	24	46
51–60	8	15.5
>60	2	4

Table 2 Symptoms and signs

Symptomatology	No.	Percentage
Nasal obstruction	50	96
Rhinorrhoea	42	81
Epistaxis	29	56
Proptosis	10	19
Skin ulceration	1	2
Swelling over cheek	1	2
Numbness over cheek	1	2

Table 3 Surgical approaches

Treatment modality	No.	Percentage
Intranasal polypectomy	10	19
Lateral rhinotomy and medial maxillectomy	31	60
Endoscopic debrider assisted medial maxillectomy	7	13
Total maxillectomy	4	8

Table 4 Recurrence pattern with histopathological evaluation

Recurrence	No.	Percentage
Recurrence (nonspecific)	12	23
Recurrence with focal dysplasia	6	12
Malignant transformation	2	4

Thirty-one cases (60%) including the cases presenting with recurrent inverted papilloma underwent lateral rhinotomy and medial maxillectomy. Ten previously undiagnosed cases (19%) underwent intranasal polypectomy and post-operative histopathological examination. Four (8%) cases (two initial presentations as SCC in inverted papilloma cases and two malignant transformation from inverted papilloma to SCC) underwent total maxillectomy. Seven cases (13%) were treated by endoscopic microdebrider assisted mass removal and endoscopic medial maxillectomy (Table 3). Post-operative radiotherapy was given to the four cases with malignant changes. The mean follow up period was 74 months (range 16 months–11 years).

Among the 52 cases of inverted papilloma managed in our series, 12 (23%) had recurrence without any specific histological pattern, six (12%) had recurrence with focal dysplasia and two (4%) had recurrence with malignant transformation (Table 4).

Discussion

The earliest description of the nasal papilloma was by Billroth (1855). Inverted papilloma has unique histological

appearance and must be distinguished from other papillomas and polyps of nose. Since identification of this tumour, a considerable variety of synonyms have been applied to the it like fibromyxoid papilloma, transitional cells papilloma, Ewing papilloma, Schneiderian papilloma or Ringertz's papilloma [3]. It was called 'inverted papilloma' by Norris [4] and later by Hyams [1]. Vrabec [5] suggested the term 'inverted schneiderian papilloma' as these tumours originated from schneiderian membrane, which was derived from the ectoderm of nasal placodes.

The term 'inverted papilloma' is derived from the histological appearance. The neoplastic epithelium inverts into the underlying stroma and the lesion is endophytic rather than exophytic from a microscopic viewpoint [6]. Inverted papilloma (just like nasal polyps in general) is more frequently originated from the middle meatus region. By extension, the tumour may involve the adjacent paranasal sinuses, usually involving the ethmoidal labyrinth and the maxillary antrum; however, it can reach the frontal sinus, sphenoid and even the orbit in more advanced cases. Inverted papilloma is a rare tumour accounting for 0.4–4.7% of all nasal and sinus neoplasms [1]. But the incidence of inverted papilloma according to our study was 7%. Our study indicates that the tumour was more common in the fifth decade. Similar age incidence was reported by different authors [7].

There is a male preponderance of this tumour [6] and we observed a 10:1 male:female ratio in our series. Clinical examination alone is insufficient to know the exact extent of the disease.

X-ray of paranasal sinuses does not differentiate inverted papilloma from other common sino-nasal masses accurately. Inverted papilloma usually presents as an enhancing mass originating in the middle meatus region with associated obstruction of osteomeatal unit. Coronal CT scan usually reveals sinus opacification secondary to osteomeatal complex obstruction. Small inverted papillomas show no bony changes, making identification of the tumour difficult in the early stages of the disease. Large inverted papillomas show bone remodelling and mass effect in middle meatal region. CECT shows a characteristic lobulated tumour with cerebriform pattern in the maxillary sinus lumen. Ten percent of inverted papillomas show tumour calcification and 40% show entrapped bone [8]. Although benign, inverted papillomas have a locally invasive behaviour, with about 70% of the cases showing areas of erosion in the CT scan. However, such finding is usually secondary to bone remodelling because of tumour pressure and not because of bone invasion itself [9]. In MR imaging, T1 weighted MR shows an enhancing mass in the middle meatus with extension into maxillary or ethmoid sinus. On T2 image, it shows obstructed mucus containing sinuses which do not enhance and high signal intensity

from the tumour. Current imaging recommendation in inverted papilloma is coronal CT for tumour identification and T2 weighted enhanced MR for tumour mapping. High recurrence and propensity for metachronous malignancy makes radiologic follow up imperative for inverted papilloma [8].

Inverted papillomas grow in two architectural patterns: (a) papillary or exophytic and (b) inverted with an inward invaginating epithelial growth in underlying stroma. Histologically the papillomas shows intramucosal projection of basaloid cells with occasional squamous differentiation. Lining is most frequently formed by intermediate epithelium or transitional epithelium. In areas where squamous maturation is present, koilocytosis may be noted in the superficial layers. These cells are characterised by abundant clear cytoplasm, distinct cell borders, and wrinkled, sometimes binucleated nuclei. A distinctive feature is the consistent findings of microscopic mucous cysts interspersed through out the epithelium of the papilloma [6]. Cytologic atypia of varying degree and mitotic figures are more common in recurrent diseases. Keratinisation in an inverted papilloma is atypical and if present, should alert the pathologist of other diagnosis like malignancy.

The major clinical problem of inverted papilloma is recurrence [6]. The abnormal epithelium of papilloma not only extends into secretory ducts but also probably has ability to spread laterally into adjacent nasal mucosa and into the paranasal sinuses, gradually replacing the normal respiratory epithelium. In inverted papilloma this lateral extension probably explains the high rate of local recurrence after excision of clinically evident lesion. Batsakis believed that recurrence is an expression of disease persistence after inadequate removal. Another probable explanation of recurrence is multicentric origin, which Batsakis advocated as a misconception [6]. This is because most of the recurrences are found near the original lesion and they are most likely extension of disease via metaplasia of adjacent mucosa. Since 1998, we were evaluating the post operative cases of all histologically proven inverted papilloma endoscopically at regular intervals to detect early recurrence. In our series the recurrence rate was 38%. This higher rate of recurrence was most probably due to inadequate primary surgery, mostly intranasal polypectomy and leaving the disease at its origin itself. Blind intranasal mass removal without prior histopathological diagnosis commonly leaves behind residual tumour mass and this is one the causes of recurrence. Other important cause of recurrence are tumour involvement of difficult areas of nose and paranasal sinuses like frontal recess and frontal sinus, sphenoid sinus and sphenoethmoidal recess and in the vicinity of lamina papyracea. Lawson et al. [10] reported 12% recurrence rate in endoscopic removal of inverted papilloma and a comparable 18% recurrence rate

in more aggressive technique. Pasquini et al. [11] reported lower recurrence rate of 3% with endoscopic procedure and 24% with traditional approaches. Endoscopic approaches have low recurrence rate as also evidenced by other studies [11–13]. If inverted papilloma involves inferomedial wall of frontal sinus, modified Lothrop procedure should be done, whereas in cases of lateral or more superior involvement of the frontal sinus, an osteoplastic flap may be additionally needed to gain adequate exposure [7]. Complications of endoscopic procedure are about 0–19.6% which range from epistaxis, epiphora, temporary infra-orbital hypoaesthesia, minimal orbital fat exposure, peri-orbital ecchymosis. CSF leak is seen in less than 6% of cases [12]. Recurrence rate usually increases with duration of follow up. Most recurrences are seen within the first 5 years after diagnosis, but some lesions recur even after 10 years. Prediction of recurrence cannot be made by microscopic examination [6]. Nuclear atypia, short of carcinoma can be expected in approximately 10% of inverted papilloma. However, Batsakis didn't believe in higher recurrence rates in inverted papilloma with cellular atypia and he commented that prediction of biological activity of any inverted papilloma cannot be made solely on the basis of histological appearance [6]. Analysing a recent series Mirza et al. [14] observed that the recurrence rates were 12.8% for endoscopic procedures, 17% for lateral rhinotomy with medial maxillectomy, and 34.2% for limited resections such as nasal polypectomy and Caldwell-Luc approaches. They estimated that the malignant potential for recurrent disease was up to 11%. In another series of thirteen inverted papilloma, eleven (85%) had recurrence in the ethmoid sinus, particularly at the lamina papyracea ($n = 8$; 62%) [15]. Recurrence over lamina papyracea can be minimized by its removal during medial maxillectomy or thinning by diamond or cutting burr during endoscopic procedure. If the disease is found to involve fovea ethmoidales careful endoscopic curettage should be performed for complete disease removal as well as to prevent CSF leak [7]. Endoscopic resections are recommended for lesions of lateral nasal wall extending into ethmoids, sphenoid and medial wall of maxillary sinus [10]. Involvement of lateral recess and floor of maxillary sinus need an additional sublabial exposure.

There is an indisputable relation of carcinomas with inverted papillomas. Initially, the nasal columnar epithelium changes into a transitional epithelium, followed by the occurrence of squamous metaplasia. Once epithelial dysplasia is established, carcinoma in situ and invasive SCC may follow [1]. Combined lesions of papilloma and carcinoma fall into three histological categories. In first group the carcinoma and the inverted papilloma occupy the same anatomical region but there is no evidence that the papilloma has given rise to the cancer. Papillomas with a focus

Fig. 1 CT scan (coronal cut) showing a heterogenous mass attached with lamina papyracea in a case of recurrent inverted papilloma

Fig. 2 CT scan (axial cut) showing a heterogenous mass in the right nasal cavity invading the orbit in a case of transitional cell carcinoma arising in a pre-existing case of inverted papilloma

of invasive carcinoma form the second group. The third category is represented by the patients who after treatment for an inverted papilloma develop invasive cancer without exhibiting further evidence of papillomas [6]. In a series of 15 cases, Batsakis observed that all the carcinoma were of squamous cell variety and fell into the categories of the first and the second group [6]. There are no criteria to predict which papillomas will develop carcinomas. The frequency with which papillomas recur as well as the length of time between recurrences does not correlate with the risk of subsequent carcinomas. Several mechanism of malignant transformation has been proposed recently. Fan et al. [12]

Fig. 3 Photomicrograph of an inverted papilloma showing papillomatous proliferation of squamous epithelium growing inward. Normal pseudostratified columnar epithelial lining is seen on the *left side*

Fig. 4 Photomicrograph of an inverted papilloma with features of atypia: increased layering with nuclear atypia, nuclear overcrowding and nuclear hyperchromasia. Few cells show mitotic figures but the basement membrane is intact

Fig. 5 Photomicrograph of transitional cell carcinoma showing islands of epithelial cells with scanty cytoplasm and nuclear polymorphism with nuclear hyperchromia infiltrating into the stroma with break in the basement membrane

proposed programmed cell death theory in the causation of malignant transformation and they concluded that inhibition of apoptosis could be an early sign of inverted papilloma undergoing malignant transformation. A high proliferative rate was a characteristic of inverted papilloma-associated malignant diseases [16]. A group of Chinese investigator investigated the role of fascin which may play a role in the formation of inverted papilloma. Pre-cancerous lesions of inverted papilloma exhibit elevated levels of fascin that may be associated with carcinogenesis of inverted papilloma [17].

Treatment of malignant transformation was always surgical. In a series of seven malignant inverted papilloma, neoadjuvant chemotherapy was given to four patients following surgical excision of the tumour and post operative radiation therapy was delivered in five patients [18] (Figs. 1, 2, 3, 4, 5).

Conclusion

After a 10-year period retrospective study involving 52 cases of histologically proven inverted papilloma we conclude that endoscopic nasal biopsy and confirmation of histological pattern is mandatory in males over 35 years before the definitive surgery for any nasal and sinonasal mass. Suspicion of inverted papilloma should arise when the mass is firm and more extensive than expected, originating from the lateral wall, there is more intra-operative bleeding and cannot be removed in toto with an elongated stalk. Preoperative diagnosis can be obtained from multiple

deep biopsies from different sites. Complete removal is essential during surgery. Inadequate tumour removal, multifocal origin, paranasal sinus involvement and histological epithelial atypia or dysplasia, are the lesions which are likely to recur. In this series, 12 (23%) had recurrence without any specific histological pattern, six (12%) had recurrence with focal dysplasia and two (4%) had recurrence with malignant transformation. Radical treatment like endoscopic medial maxillectomy, lateral rhinotomy and medial maxillectomy or total maxillectomy is mandatory in cases with recurrence and malignant transformation. Regular endoscopic follow up is necessary up to 5 years post-operatively. Radiotherapy may be necessary for the malignant cases and also for some of the recurrent cases.

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