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# The Inverted Schneiderian Papilloma: a review and literature report of 43 new cases*

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SUMMARY

*Inverted Schneiderian Papilloma remains a controversial nasal disease. Although a benign pathology it is associated with aggressive local destruction, recurrence after removal and malignancy. New information regarding aetiology may aid management which at present consists of surgical resection. The best method of resection is still undetermined. This paper describes 43 cases of Inverted Schneiderian Papilloma presenting to a tertiary referral centre and discusses the present knowledge surrounding the pathology and its treatment.*

*Key words: Inverted Schneiderian Papilloma*

## INTRODUCTION

Inverted Schneiderian Papilloma remains a controversial nasal pathology.

Until recent times even its name was a subject for discussion and it has been known variously as papillary sinusitis, villous cancer and Ringertz tumour. Aetiological aspects are poorly understood and argument remains regarding any malignant potential and the appropriate method of management considering the destructive nature of the lesion and its tendency to recur. This paper reviews the recent literature concerning Inverted Schneiderian Papilloma and presents a series of patients with such pathology presenting at a tertiary referral centre.

Inverted Schneiderian Papilloma is a benign sinonasal tumour of ectodermal origin which is locally aggressive, destructive, tends to recur if incompletely removed and has significant malignant potential.

Ward in 1854 and Billroth a year later (Billroth, 1855) were the first to describe inverted papilloma as a defined lesion but it was not until 1935 that Kramer and Som distinguished the pathology from simple polyps. Ringertz (1938) revealed the tendency to invert into the underlying stroma but still felt the papilloma was in some way associated with simple nasal polyposis. We now know that Inverted Schneiderian Papilloma is a distinct pathology with a characteristic clinical process. Since the early 1980s research has attempted to resolve the question of deciding between conservative (endonasal) management and more radical treatment in the way of lateral rhinotomy with medial maxillectomy.

The incidence of inverted papilloma has been estimated at 0.74/100,000/year (Buchwald et al., 1995). There is a male predominance of 2-4 to 1 and whites are more likely to be affected than blacks (Seshul et al., 1995). Most patients present with this pathology in the sixth decade, the average age at presentation being 53. The tumour represents 0.5 to 4 % of all primary nasal neoplasms (Lawson et al., 1995).

Evidence is accumulating to implicate Human Papilloma Virus (HPV) in the aetiology of Inverting Schneiderian Papilloma. Environmental pollutants such as cigarette smoking, are also likely to be of significance. Respler et al., (1987), found an association between HPV11 and Inverted papilloma (IP) which was subsequently confirmed by Weber et al., (1988), who found HPV 6b/11 in 76% of cases of IP. Furuta et al., 1991 supported the theory of association with research, finding HPV11/16 in 19% of IP cases. In addition, there is a strong association between HPV 16 and IP with squamous cell carcinoma (Syrjanen et al., 1987; Brandwein et al., 1989; Furuta et al., 1991). More recent work reveals the finding of HPV 6/11 in IP is associated with a low risk of progression to SCC whilst HPV 16 / 18 found in IP is likely to give rise to a high risk of recurrence and progression to SCC. Smoking cigarettes increases the risk of progression to SCC in Inverted Schneiderian Papilloma (Beck et al., 1995). The cyclin-dependent kinase inhibitor p27Kip1 (p27) is hypothesised to contribute to tumorigenesis in some parts of the body and recent work indicates it may be important when expression is lost giving rise to increased cell proliferation. P27 may be a useful marker for dysregulation of cell kinetics in Inverted papilloma associated with HPV (Saegusa M et al., 1999)

The WHO Classification (1995) of intranasal papilloma describes three histopathological classes, that is, columnar cell

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papilloma, exophytic papilloma and inverted Schneiderian papilloma. Macroscopically, the latter is a firm, bulky, non-translucent polypoid mass with a pitted, corrugated surface and apparently more vascular than simple polyps.

Microscopically, the lesion is a true endophytic epithelial neoplasm that arises from ciliated pseudostratified columnar epithelium derived from the ectodermal (Schneiderian) membrane. The epithelium is well differentiated, thickened, proliferative, hyperplastic with characteristic invaginations within which may be areas of squamous metaplasia. The underlying stroma comprises loose connective tissue and the basement membrane is intact and non-thickened with no hyalinisation (Michaels and Hyams, 1975).

Pathological behaviour may take two forms depending on whether the initial lesion lies medial or lateral to the lateral wall of the nose. Those on the medial side tend to have a well-defined localised attachment and present early whereas laterally placed lesions have a diffuse attachment and are usually advanced at presentation. Inverted papillomata infiltrate soft tissue compromising local structures and erode bone by pressure atrophy characterised by bone remodelling with high osteoclast activity. There is a significant recurrence rate following surgery and this may reflect persistent residual disease or the tendency to multicentricity in 12 to 30% of cases. Inverted Papilloma, carcinoma-in-situ and invasive SCC are found together in pathological samples suggesting progression from the benign to the malignant lesion (Vrabec, 1994a).

The majority of patients with inverted papilloma present with symptoms of nasal obstruction (71%). The next most common symptoms are epistaxis and headache (8%) with some patients complaining of nasal discharge, facial pain, chronic sinusitis, visual symptoms and epiphora (Bielamowicz et al., 1993). Examination reveals a bulky, firm, rubbery, non-translucent polypoid mass that is almost always unilateral. Ninety-six percent of tumours arise on the lateral wall in the region of the middle turbinate and meatus. The remainder present as lesions of the septum. Twelve to 30% of tumours are multicentric and clinical examination frequently under estimates the extent of the neoplasm.

Investigation should include histopathological confirmation of the diagnosis by biopsy and accurate assessment of the extent of the lesion by CT scanning. The changes on CT scanning are distinctive but not pathognomonic and include a unilateral polypoid mass enlarging the nasal fossa and usually displacing the nasal septum. Chronic sinusitis with adjacent sinus opacification occurs in up to 80% of patients. Calcification within the mass due to trapped bone is evident in 4% of such scans and may be associated with bone erosion due to pressure atrophy (not malignancy) in up to 50% of cases (Buchwald et al., 1995; Lawson et al., 1995). This bone erosion is probably the result of benign osteoclastic activity rather than the destructive effect by other mechanisms seen in malignant tumours. CT scanning remains the most useful method for assessing Inverting papilloma (Dammann et al., 1999). Recent literature however suggests the use of Magnetic Resonance Imaging (MRI) for determining the extent of disease particularly when the frontal sinus may be involved (Shohet and Duncavage, 1996) and there is associated sinus inflammation.

Surgical excision is the treatment of choice in the absence of contraindications. The main surgical options for excision include lateral rhinotomy with medial maxillectomy, a mid-facial degloving approach and the endonasal endoscopic method with subsequent simple excision or medial maxillectomy depending on the extent of the lesion.

Several factors influence the principles of selection of the surgical approach. Surgery for recurrent Inverted Papilloma is difficult as the disease tends to be more extensive than in the presenting situation, the anatomic boundaries are often distorted and implantation may have taken place in scattered areas such as the periorbita and dura that provide a challenge to clean excision. In addition, the disease may be multicentric in origin and there is a risk of malignant transformation. Clearly there-

Table 1. Recurrence rates after Lateral rhinotomy and medial maxillectomy (LRMM) and Endonasal resection (ER). Figures expressed as Percentage (Number of recurrences/Total number in operative group).

| Author | | LRMM | | ER | |
|---|---|---|---|---|---|
| Benninger, et al. | 1991 | 0 | (0/20) | 36 | (5/14) |
| Myers, et al. | 1990 | 5 | (1/22) | 0 | (0/4) |
| Pelausa and Fortier | 1992 | 7 | (1/14) | 77 | (37/48) |
| Outzen, et al. | 1991 | 7 | (3/44) | 27 | (3/11) |
| Lawson, et al. | 1989 | 9 | (7/77) | 10 | (1/10) |
| Segal, et al. | 1986 | 10 | (1/10) | 70 | (10/14) |
| Kristensen, et al. | 1985 | 12 | (7/57) | 38 | (8/21) |
| Phillips, et al. | 1990 | 13 | (9/72) | 44 | (16/36) |
| Smith and Gullane | 1987 | 27 | (3/11) | 57 | (4/7) |
| Dolgin, et al. | 1992 | 29 | (4/14) | 44 | (4/9) |
| Weissler, et al. | 1986 | 29 | (37/126) | 67 | (103/153) |
| Bielamowicz, et al. | 1993 | 30 | (6/20) | 74 | (17/23) |
| Waitz and Wigand | 1992 | | | 17 | (6/35) |
| Kamel | 1995 | | | 0 | (0/17) |
| Averages | | 16 | (79/487) | 56 | (226/402) |

fore a procedure should be selected that will provide least incidence of recurrence as the best opportunity of cure is at the primary procedure.

The lateral rhinotomy approach provides good exposure, allows for total excision, minimal deformity, easy postoperative examination and importantly low rates of recurrence. The procedure is however prone to early potential complications of epiphora, dacryocystitis, diplopia, CSF leak, transitory blepharitis and lid oedema. Later in the postoperative period the patient may present persistent crusting in the cavity, pain, a nasocutaneous fistula, mucocoele, vestibular stenosis, a poor scar or nasal collapse.

Mid-facial degloving is ideal for the lateral nasal wall and midfacial structures with the considerable advantage of no evident scar. Unfortunately, the approach allows poor access to the supraorbital ethmoid cells, lacrimal sac and frontal sinuses that may require separate incisions (Phillips et al., 1990; Myers et al., 1990; Vrabec, 1975b; Suh et al., 1977; Eavey, 1985).

The transnasal endoscopic approach that may include a medial maxillectomy gives good exposure, post-operative examination conditions and a good cosmetic and functional result. There is no skin or sub-labial incision and the nasolacrimal duct and medial palpebral ligaments remain intact. In addition, the orbital floor is preserved avoiding the production of a potential gateway into the extranasal tissues (Kamel, 1992; Waitz and Wigand, 1992).

Recurrence rates are related to completeness of removal and the appropriate careful selection of cases for each procedure. Table 1 presents figures for recurrence from 12 research teams. The crude average overall rates of recurrence are 16% for the external approach and 60% for endonasal procedures. The overall average time to recurrence has been reported as 56 months (Vrabec, 1994a). The overall incidence of malignancy in 19 series over varying follow-up periods is 10.8% (Table 2). The rates of reported malignancy are prone to sampling error by pathologists however and most series are submitted from a tertiary referral population. It has been calculated that the mean time from a diagnosis of Inverted Schneiderian Papilloma to the presentation of squamous cell carcinoma is 63 months (Lesperance and Esclamado, 1995).

Table 2. Incidence of malignancy. Figures expressed as Percentage (Number of malignancies/Total number of patients in group)

| Author | | Synchronous | Metachronous | Totals |
|---|---|---|---|---|
| Outzen, et al. | 1991 | 2 (1) | 0 (0) | 2 (1/55) |
| Weissler, et al. | 1986 | 4 (8) | 1 (3) | 5 (11/223) |
| Lawson, et al. | 1989 | 5 (4) | 1 (1) | 6 (5/87) |
| Smith and Gullane | 1987 | 4 (2) | 2 (1) | 6 (3/48) |
| Phillips, et al. | 1990 | | | 7 (8/112) |
| Kristensen, et al. | 1985 | 5 (4) | 4 (3) | 9 (7/83) |
| Segal, et al. | 1986 | | | 10 (3/30) |
| Dolgin, et al. | 1992 | 10 (4) | 2 (1) | 12 (5/41) |
| Bielamowicz, et al. | 1993 | 8 (5) | 8 (5) | 16 (10/61) |
| Myers, et al. | 1990 | 21 (7) | 0 (0) | 21 (7/33) |
| Benninger, et al. | 1991 | 22 (10) | 4 (2) | 26 (12/46) |
| Average | | 6.7 (45/677) | 2.5 (17/677) | 9.2(62/677) |
| Osborn, et al. | 1956 | | | 5 (9/168) |
| Calcattero, et al. | 1980 | | | 9 (3/34) |
| Hyams, et al. | 1971 | | | 13 (19/149) |
| Ridolfi, et al. | 1977 | | | 13 (19/149) |
| Christensen & Smith | 1986 | | | 18 (7/39) |
| Yamaguchi, et al. | 1979 | | | 53 (8/15) |
| Vrabec, et al. | 1975 | | | 12 (3/29) |
| Lesperance, et al. | 1995 | | | 27 (14/51) |
| Average | | | | 10.8 (129/1192) |

Table 3. Percentage of patients presenting with symptoms of:

| | |
|---|---|
| Nasal obstruction | 88.4 |
| Bloody rhinorrhoea | 23.3 |
| Facial pain | 21.0 |
| Clear rhinorrhoea | 16.3 |
| Post-nasal drip | 11.6 |
| Hyposmia | 7.0 |

## METHOD

A retrospective review of medical records of patients with a histological diagnosis of Inverting Schneiderian Papilloma presenting to the Radcliffe Infirmary between November 1980 and November 1998. The data was collected on an Access database by a single author (NM).

## RESULTS

The number of patients presenting was 43. Men represented 67% of the total with a mean age of presentation of 51.5 years. Thirty-three percent of the patients were women and their mean age of presentation was 53 years.

The recorded symptoms at presentation included nasal obstruction, bloody rhinorrhoea, clear rhinorrhoea, facial pain, post nasal drip and hyposmia (see Table 3). The mean length of history for these symptoms was 10 months. Fourteen percent of patients were smoking at the time of presentation and 25.6% had smoked in the past.

Disease location was recorded on the basis of initial recorded clinic examination, CT scan (performed in 67% of cases) and operative findings in order to provide the most accurate reflection of the true pathology. All cases presented unilateral pathology. The most commonly affected sites in the nasal cavity and paranasal sinuses were the middle meatus, maxillary sinus and ethmoid sinuses (see Table 4). All 3 cases involving the sphenoid sinus had associated involvement of the ethmoid sinuses and middle meatus. 2 of the 3 also had maxillary sinus involvement. Inverted papilloma involving the nasal septum and inferior turbinate was found to be isolated disease in all such cases.

Associated sinusitis indicated by pus evident at the time of resection occurred in 34% of patients and simple nasal polyps were found in 12%. Of the 43 patients presenting with Inverting Schneiderian Papilloma 10 were lost to follow-up prematurely. Reasons for this included patients leaving the region (two), there was one known coincidental death prior to a planned lateral rhinotomy for recurrence, a refusal of further treatment

Table 4. Percentage of sites affected by pathology.

| | |
|---|---|
| Middle meatus (MM) | 77.0 |
| Maxillary sinus (MS) | 56.0 |
| Ethmoid sinus (ES) | 34.9 |
| Middle turbinate | 14.0 |
| Inferior turbinate | 9.3 |
| Nasal septum | 9.3 |
| Sphenoid sinus | 7.0 |
| Nasal vestibule | 2.3 |
| | |
| MM + MS | 51.2 |
| MM + ES | 30.0 |
| MM + MS + ES | 16.3 |

and subsequent discharge, and in 5 cases no cause for the lack of follow-up was apparent. The two methods of approach for excision of Inverting papilloma in the nasal cavity and sinuses employed over the period of study were endoscopic removal for limited disease and formal lateral rhinotomy for extensive disease at the first presentation or difficult recurrences. At presentation, definitive treatment was by endoscopic approach in 72.1% of patients and by lateral rhinotomy in 27.9%. Seventeen patients treated using the endoscope remained free of disease with a mean follow-up of 4.1 years. The average time to recurrence for those treated endoscopically was 2.4 years. Fifteen patients underwent lateral rhinotomy for either primary disease (eight) or recurrence following endoscopic procedures. The average time of follow-up clear of disease was 4.4 years. Two patients presented recurrence following lateral rhinotomy. One patient developed recurrent Inverted papilloma 10 years after the original procedure. This was treated endoscopically with no evidence of pathology 5 years later. The second case developed recurrence 1.3 years after lateral rhinotomy and after endoscopic excision has been clear of disease for a further 3.5 years. There were no recorded complications following endoscopic excision but in the lateral rhinotomy group was a post-operative CSF leak, a frontal mucocoele and a post-operative cerebro-vascular accident which the patient survived.

Overall, the risk of recurrence following endoscopic clearance was 44.4% and 14.3% following lateral rhinotomy.

In this study none of the histological samples at initial presentation (n=43) or at the time of recurrence (n=22) revealed evidence of malignant change.

## DISCUSSION

This series represents the largest published in the UK in recent years. The epidemiological findings in this study agree with those previously published. The male to female ratio was found to be 2 to 1 and the mean age at presentation of 53 years described in the literature was similar to our findings.

Nasal obstruction is the predominant presenting symptom in all previous series and 88.4% of our patients suffered this complaint. Other authors have found additional symptoms to be less common than in our series. Over 20% of our patients presented with epistaxis and facial pain whereas in other reports only around 8% have provided similar symptoms.

Two patients or 4.7% of our patients were suffering from septal Inverting papilloma which is the usually quoted incidence of non-lateral wall pathology.

The figures in this series relating to the incidence of recurrence following surgery are somewhat better than the overall average rates in the previous literature. In this series the recurrence rate following endoscopic excision was 44.4%, and 14.3% after a lateral rhinotomy approach. The figures in the literature are 56% and 16% respectively. Although these figures may be considered a broad guide they should be interpreted with caution in view of the inherent variables such as the differing presenting pathology, difficulty in assessing completeness of removal at the primary procedure and the bias in selecting cases for preferred or more appropriate procedures. No valid comparison between the recurrence rate for each technique can be easily made therefore.

Table 2 indicates the average incidence of associated malignancy in 19 reported studies as around 10%. We found no invasive carcinoma or carcinoma-in-situ in our total of 65 tissue samples of Inverting papilloma sent for histopathological examination. It is suggested that the average time from a diagnosis of Inverted papilloma to Invasive carcinoma is 5.3 years. Our follow-up period has extended only to 4.1 years in the endoscopic group and 4.4 years in the lateral rhinotomy group however and this may be an explanation for the absence of malignancy in our samples. The literature clearly provides some evidence for the association of Inverted papilloma with carcinoma. Vrabec (1994a) has found Inverting papilloma adjacent to carcinoma-in-situ and invasive carcinoma suggesting progression from the benign to the malignant disease. Some suggest however that the evident malignancies at recurrence were present at presentation and merely represent sampling error by the histopathologist. This fact should not divert our attention from the clear association between Inverting papilloma and carcinoma and the need for prolonged follow-up in cases treated endoscopically where recurrence rates are high and the incidence of malignant change after longterm review is significant.

Endoscopic nasal surgery is now beyond its infant stage and many ENT surgeons are skilled in its performance. As time goes on it becomes more reasonable to treat limited Inverted papilloma of the nasal cavity by endoscopic means. The potential complications are few in expert hands with little morbidity, and assuming efficient recurrence free follow-up for a period of 10 years this will provide optimal management. For more extensive nasal cavity lesions, and particularly cases involving the paranasal sinuses where endoscopic access may not be optimal, the lateral rhinotomy approach is to be preferred. The recurrence rates are less and subsequent examination to ensure freedom from disease is aided by the large cavity which is easily viewed with the endoscope. The disadvantage of this procedure relates to the potential complications which were evident in our series. One patient developed a CSF leak, a second a frontal mucocoele and a third suffered a stroke in the immediate postoperative period. The average age of presentation of this pathology is 53

years and often the potential disadvantage of a facial scar with a lateral rhinotomy approach is not a significant consideration in management.

In conclusion, the management of Inverting Schneiderian Papilloma remains problematic chiefly due to the risk of recurrence and the association with malignancy. With increasing knowledge with regard to the aetio-pathology of this benign tumour and its tendency for malignant transformation we may more fully understand its natural history and be able to perhaps prevent or more efficiently manage both primary and recurrent disease. Present literature should encourage us to attempt full clearance at the first operative procedure and long follow-up to detect subsequent malignancy.

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