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Inverted Sinonasal Papilloma: Update and Literature Review

Babatope Lanre Awosusi [a++*] and Adam Tolulope Rahman [b++]

[a] King Khalid Hospital, Almajma'ah, Saudi Arabia.
[b] King Salman Medical City Medina, Saudi Arabia.

Authors' contributions

This work was carried out in collaboration between both authors. Author BLA conceptualized the idea of this review article and wrote the initial draft. Both authors read and approved the final manuscript.

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ABSTRACT

Inverted sinonasal papilloma is a benign neoplasm that usually affects the intra-nasal cavity and adjacent paranasal sinuses. Inverted papillomas have three unique features that distinguishes them from other sinonasal tumors including; a propensity for local destructive growth, a high rate of recurrence and risk of malignant transformation. The reported yearly incidence is about 0.6 to 1.5 cases per 100,000 people per year and they usually account for 0.5% to 4% of all nasal tumors. They occur at the following locations; both lateral nasal walls, ethmoidal cells, maxillary sinus, the frontal sinus, sphenoid sinuses and the nasal septum in decreasing order. It occurs most commonly in the fifth and sixth decades of life with a male-to-female ratio of 2-3:1. Inverted papilloma can arise from the entire Schneiderian membrane and molecular genetics have confirmed that it is an actual neoplasm that arises from a single progenitor cell. Most cases are diagnosed from clinical history and thorough physical examination. However, complete removal of all affected tissue with thorough histopathological evaluation is recommended to ensure a correct diagnosis. While there is yet no established pathognomonic histopathological feature to predict recurrence with all certainty,

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[++] *Anatomic Pathologist;*
**Corresponding author: E-mail: awosusilanre2@gmail.com, Awosusilanre2@yahoo.com;*

there is ongoing investigation for predictive markers of recurrence. Smoking seems to be a recognized risk factor for developing multiple recurrences and there is evidence that the presence of HPV serotypes 16 and 18 could be predictive of malignant transformation. The main aim of treatment is to achieve compete surgical resection and to prevent recurrence and malignant transformation. A period of clinical follow up is recommended after treatment. The aim of this review is to provide a comprehensive and updated overview of the clinical presentation, diagnosis, management and prognosis of this unique lesion.

Keywords: Inverted papilloma; sinonasal; squamous; schneiderian.

1. INTRODUCTION

Inverted sinonasal papilloma is an uncommon sinonasal neoplasm that affects adults usually in the fifth decade [1]. Inverted papilloma have three unique features that distinguishes them from other sinonasal tumors including a propensity for local destruction, recurrence and a risk of malignant transformation [1]. After making a diagnosis of inverted papilloma, a period of follow-up is important to recognize recurrence early and to prevent malignant transformation [1]. It is worthy of note that malignant transformation can occur synchronously or metachronously at recurrence or during follow-up [2].

Inverted Sinonasal papilloma is a benign neoplasm that occurs in the nasal cavity and paranasal sinuses [1]. There are some associated unique characteristics including destruction of adjacent local tissue, high rate of recurrence and risk of malignant transformation [1]. Ward was the first to discover and describe a case of inverted papilloma occurring in the sinonasal cavity in 1854 [2]. The World Health Organization first classified sinonasal papilloma into three different histopathological subtypes in 1991 [3]. These histologic subtypes still stand till date with some additional variants included; exophytic (fungiform, septal, and squamous papilloma), inverted (inverting), and oncocytic (cylindrical cell and columnar papilloma) [3]. The term “inverted papilloma” actually refers to the inverting histologic appearance of the epithelium with an intact underlying basement membrane that separates the epithelium from the underlying connective tissue stroma [3]. It was initially named Schneiderian papilloma in honour of late C.V Schneider who first discovered the ectodermal origin of the nasal mucosa in the 1660s [4]. The aim of this review is to give an update on the clinical presentation, diagnosis, management and prognosis of this very unique lesion.

2. ANATOMICAL SITES OF PRESENTATION

Inverted papilloma can affect the following sites; lateral nasal wall, ethmoid cells, maxillary sinus, the frontal sinus, sphenoid sinuses and the nasal septum in a decreasing order of prevalence [5]. There is still some controversy on the true nature of septal papilloma, whether they are inverted papilloma or they actually represent other upper respiratory tract squamous papillomas [2]. Rarely, inverted papilloma may arise from the middle ear mastoid, the lacrimal sac, pharynx, nasopharynx, and even in the wall of a branchial cleft cyst [5]. Some theories have been proposed to explain these aberrant papilloma in sites contiguous with the sinonasal tract, one of these theories is that the Schneiderian membrane undergoes ectopic migration during embryogenesis [5,6].

3. INCIDENCE AND DEMOGRAPHICS

Out of all the nasal neoplasms, inverted papilloma alone accounts for about 0.5 to 4% with an annual incidence of 0.6 to 1.5 cases per 100,000 persons per year [3,4,7]. Though the tumors occur over a wide age range, they are not commonly seen in children [8]. However, some cases have been reported in the paediatric age group [5]. It usually affects individuals in their fifth to sixth decades with a male-to-female ratio of 2-3:1[8,9]. The three subtypes of inverted papilloma are defined by their radiologic features, specific location, gross appearance and distinct histopathologic features [9]. However, the overall clinical characteristics and biologic behaviour of the neoplasms are somewhat similar [9]. The presenting symptoms of patients vary depending on the location of the tumours [9]. The tumours have been reported to be bilateral in about 4.9% of cases with no particular side predeliction [2]. The overall reported incidence may probably be overstated because of a bias in selection of cases, as most reported cases are from tertiary

centres [10]. Therefore, it is difficult to ascertain the actual incidence of inverted papilloma [2].

There is also a possibility that Inverted papilloma cases are under-reported because some cases may be misdiagnosed as an inflammatory polyp if both cases co-exist, this will be an example of a sampling bias [2]. It is therefore advisable to biopsy and submit all nasal polyps for histopathological analysis to reduce the chance of missing a co-existing inverted papilloma [2]. Careful histologic evaluation of recurrent inflammatory polyps is also recommended to reduce the risk of missing an evolving inverting papilloma or malignant transformation in an already established inverted papilloma [2].

4. HISTOPATHOLOGIC FEATURES

Inverted papilloma usually arises from a structure that has been described as the “Schneiderian membrane” which is actually a membrane in the sinonasal tract that developed from two different germ cell layers namely; the nasopharyngeal mucosa of endodermal origin and the neuroectoderm of the olfactory placode [11]. This type of embryology is the reason why some cases have different histological appearances and can differentiate along squamous, respiratory and transitional cell lines [11,12]. The unique features of inverted papilloma includes the capacity for inversion into the underlying fibrous stroma with an intact basement membrane and the high propensity for recurrence [12].

5. ETIOLOGY

Inverted papilloma can arise from the entire Schneiderian membrane (as described above) and molecular genetics have confirmed that inverted papilloma is an actual neoplasm developing from a single progenitor cell [1,13]. However, the exact etiology still remains unclear [14]. Some investigators have associated the development of inverted sino-nasal papilloma with cigarette smoking, persistent chronic inflammation, Human Papilloma Virus (HPV) infection, Epstein-Barr virus (EBV) infection, occupational and environmental exposures, while some have associated it with mutations in cell cycle proteins and angiogenic factors [12,14]. A higher rate of recurrence and malignant transformation has been associated with the presence of some HPV DNA subtypes including; HPV 6, 11, 16, and 18 [15]. While HPV serotypes 6 and 11 have recently been found to be less associated with the pathogenesis of inverted papilloma, HPV 16 and 18 have been further implicated in the risk of malignant transformation [16]. No specific causal relationship between EBV infection and inverted papilloma has been ascterteined [17].

6. CLINICAL PRESENTATION

Most individuals present with nonspecific symptoms like nasal discharge, epistaxis, nasal congestion, and nasal obstruction [8].

7. DIAGNOSIS

Most cases are usually diagnosed from clinical history and thorough physical examination, which usually includes an endoscopic nasal examination. However, some cases may require radiologic imaging including a computed tomography scan and magnetic resonance imaging [2]. Histopathologic evaluation after surgical resection still remains the gold standard for confirmation of diagnosis [1,2]. Surgical pathologic examination of an inverted papilloma usually reveals uneven mulberry-like, grey-white cut surfaces [1]. A complete excision of all affected mucosa is necessary to prevent a recurrence and a meticulous histopathological examination of the entire specimen is recommended to rule out atypia and malignant transformation [2].

8. TREATMENT MODALITIES

The main aim of treatment is usually to achieve a compete surgical resection of the lesion, to prevent a recurrence and to follow-up post-operatively with regular nasal endoscopic examinations [1]. It is imperative to identify and excise the site of attachment of the tumour pedicle to as to achieve a complete resection [18]. The current surgical methods used are broadly classified into two, namely; endoscopic and external approaches [2]. The method of choice will definitely depend on the anatomical location of the lesion, the extent of the disease, the available equipment and the experience of the surgeon [2]. Some authors have advocated for the use of radiotherapy if the tumour cannot be operated or if complete resection is not achievable, or as an adjunct if there is associated malignancy [1,19].

9. RECURRENCE

Most cases of recurrence usually occur within the first two to three years with a mean duration of 30 months, although some cases have been

reported to occur five to six years post-operatively [20]. Most cases of recurrence occur at the same initial site, most probably due to incomplete surgical resection, therefore implicating residual disease as the leading cause of recurrence [10]. The chances of recurrence varies from as high as 100 percent to as low as 5 percent depending on the extent of disease and the surgical resection approach used [20]. The average recurrence rate that has been reported in literature varies by surgical method used and includes; 13% for endoscopic methods, 14 to 17% for lateral rhinotomy with medial maxillectomy and 34 to 58% for limited endonasal techniques [10].

10. CLINICAL PREDICTORS OF RECURRENCE

There is limited data on predisposing factors for developing recurrent inverted sinonasal papillomas [10]. However, smoking seems to be a recognized risk factor for developing multiple recurrences [21]. Anatomical location of the tumour in the frontal sinus have also been shown to favour recurrences, this may be as a result of the difficulties associated with achieving a total resection [2,22].

11. HISTOLOGICAL PREDICTORS OF RECURRENCE

Till date, there is no established pathognomonic histopathological feature to predict recurrence of inverted papilloma with all certainty [2]. However, some histologic parameters raise suspicion of recurrence including; squamous epithelial hyperplasia, hyperkeratosis, an increase in mitotic index to more than two mitoses per high power field and absence of inflammatory polyps [2].

12. PREDICTIVE MARKERS OF RECURRENCE

There is still ongoing investigation to determine valuable predictive markers of recurrence in inverted papilloma. However, some markers have been proposed to be of benefit in predicting recurrence, these includes; increased proliferative activity (as determined by high Ki67 levels and high proliferating cell nuclear antigen) and loss of basal cell keratin 14 expression [23]. Also, high serum levels of squamous cell carcinoma (SCC) antigen can be used as a marker for recurrence because the serum level should normally decrease after surgical removal [24]. Another marker that has been suggested to be of value is Fascin which is usually expressed at low levels in normal epithelium, but becomes significantly increased in cases of inverted papilloma. Serial measurement of the serum level of Fascin can be thus be used as a marker to predict recurrence in cases of inverted pappiloma [25].

13. MALIGNANT TRANSFORMATION

Malignant transformation into squamous cell carcinoma (both keratinizing and non-keratinizing subtypes) is commonly seen, accounting for approximately 10% of cases. The other less frequent cases of malignant transformation that has been reported in literature includes adenocarcinoma, verrucous carcinoma and mucoepidermoid carcinoma [26]. HPV serotypes 16 and 18 has been implicated to be associated with severe dysplasia and malignant transformation, therefore HPV infection may be an early stage in carcinogenesis of inverted papilloma [27]. The association between inverted papilloma and malignancy can be metachronous or synchronous, with an incidence rate that varies from 2 to 27% and a median rate of 9% [28,29].

The histologic features that should raise suspicion of malignancy in inverted papilloma includes; evidence of bone invasion, marked squamous epithelial hyperplasia with hyperkeratosis, a high mitotic index, the absence of inflammatory polyps, an elevated ratio of neoplastic epithelium compared to stroma, absent or scant eosinophils and an abundance of plasma cells [90].

14. PREDICTIVE MARKERS FOR MALIGNANCY

A already stated above, there is significant evidence that the presence of HPV in inverted papilloma could be predictive of recurrence and possible subsequent malignant transformation [2,31]. However, the available data from regions with low prevalence of high-risk HPV on the association between HPV infection and sinonasal neoplasms is still somewhat limited [32]. Also, the usefulness of p16 as a surrogate marker of HPV infection and definite prediction of malignant transformation in inverted papilloma cases also needs more investigation [32]. So despite

repeated detection of HPV in inverted papilloma cases, a definitive causal association still remains at best controversial [33]. Furthermore, a new unique histological tumor type has been described as HPV-related multi-phenotypic sinonasal carcinoma [33]. Studies have also reported that HPV related sino-nasal malignancies have a decreased mortality rate as compared to HPV-negative tumors, just like what has already been seen and described in other head and neck carcinomas [33]. Over expression of p53 may also serve as a marker for malignant transformation in cases of inverted papilloma [2]. Serum levels of Fascin can also be markedly increased in cases of malignant transformation, so serial measurement of this marker can be also used as a predictive marker for malignancy [2,26].

15. FOLLOW UP

After making a diagnosis of inverted papilloma, a period of long-term follow up is advised to detect recurrence and metachronous carcinoma very early before it becomes advanced [2]. Some authors have also advocated life-long follow up of cases, though this may actually not be possible in routine clinical practice [34]. Surgical pathology still remains the gold standard for the diagnosis and classification of sinonasal tumors including inverted sinonasal papilloma, so recurrent cases should be completely excised for thorough histopathologic examination to rule out atypia and malignancy [35]. Magnetic resonance imaging with contrast can be very useful pre-operatively to differentiate actual neoplastic transformation from reactive post-operative changes and non-neoplastic inflammatory polyps it can also help the surgeon to determine the choice of surgical approach and to choose the best sites to biopsy [1].

16. CONCLUSION

Inverted Sinonasal papilloma is a benign neoplasm that most often presents with symptoms and signs due to unilateral nasal polyposis. It has a propensity to recur with attendant risk of malignant transformation. Diagnosis is confirmed by histopathologic evaluation of excised polyps, but some cases may require radiologic assessment pre-operatively to determine the extent of the disease. Complete surgical removal through an endoscopic approach remains the treatment of choice. However, if total resection cannot be achieved via endoscopic approach, an external surgical approach can be adopted. Presently no histological or biological markers can accurately and reliably predict the risk of recurrence or malignant transformation. Most recurrent cases present within the first two to three years after initial treatment, so a period of clinical and radiologic follow up is recommended after treatment.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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