Minireview Article

INVERTED SINONASAL PAPILLOMAS: UPDATE AND LITERATURE REVIEW

Abstract

Sinonasal inverted papilloma (IP) is a benign lesion that occurs in the nasal cavity and paranasal sinuses. Associated clinical problems include a tendency towards local destruction, recurrence and malignant transformation into squamous cell carcinoma. The most common nasal sites involved in order of descending prevalence are; lateral nasal wall, ethmoid cells, maxillary sinus, and, less often, the frontal and sphenoid sinuses and nasal septum. IP accounts for 0.5-4% of all nasal tumors. The annual incidence is approximately 0.6–1.5 cases per 100,000 per year. Most commonly, it affects patients in their fifth to sixth decades with a male to female ratio of 2-3:1. The entire Schneiderian membrane are at risk of developing inverted papilloma. Diagnosis is established through polyp biopsy and histological examination. Removal of all diseased mucosa and a meticulous histological examination of the entire specimen are necessary to ensure correct diagnosis. Treatment of sinonasal inverted papilloma aims to remove the disease completely at the first attempt, and to create post-operative anatomy which allows easy post-operative endoscopic surveillance.There are no pathognomonic histological features to predict the recurrence of inverted papilloma.There is an ongoing search for markers for inverted papilloma recurrence.There is evidence that the presence of HPV in inverted papilloma could be predictive of malignant transformation. The treatment of choice is complete surgical removal via an endoscopic approach, assisted with an external approach if complete resection is not possible endoscopically. Long-term follow up is indicated, although the majority of recurrent cases present within the first two to three years after initial treatment. The aim of this review is to give a comprehensive updated overview of the clinical presentation, diagnosis, management and prognosis of this unique lesion.

Key words: Sinonasal, squamous, inverted papilloma, schneiderian.

Introduction:

Inverted papilloma is a rare sinonasal tumor that mainly occurs in adults during the 5th decade. Three characteristics make this tumor very different from other sinonasal tumors: a relatively

strong potential for local destruction, high rate of recurrence, and a risk of carcinomatous evolution. The seriousness of this pathology lies in its association with carcinoma, which may be diagnosed at the outset or at recurrence during follow-up. It is important to diagnose recurrence to enable early treatment, especially in case of associated carcinoma or malignancy [32].

Definition and Historical perspective.

Sinonasal inverted papilloma (IP) is a benign lesion that occurs in the nasal cavity and paranasal sinuses.[1] Associated clinical problems include a tendency towards local destruction, recurrence and malignant transformation into squamous cell carcinoma.[1]In 1854, Ward was the first to document the occurrence of papilloma in the sinonasal cavity.[2]In 1991, the World Health Organization (WHO) classified sinonasal papilloma into 3 distinct histopathological subtypes: exophytic, inverted, and oncocytic.[3] The term inverted papilloma describes the histological appearance of the epithelium, i.e. inverting into the stroma, with a distinct and intact basement membrane that separates and defines the epithelial component from the underlying connective tissue stroma.[3]It was named as Schneiderian papilloma in honour of C. Victor Schneider, who in the 1660s identified the origin of the nasal mucosa from the ectoderm.[4] The aim of the review is to give an update on the clinical presentation, diagnosis, management and prognosis of this unique lesion.

Anatomical sites of presentation

The most common nasal sites involved by inverted papilloma, in order of descending prevalence, are: lateral nasal wall, ethmoid cells, maxillary sinus, and, less often, the frontal and sphenoid sinuses and nasal septum.[5]Controversy exists over whether septal papillomas are true inverted papillomas, or whether they represent the more commonplace squamous papillomas found in the upper respiratory tract.[2]Exceptionally, IPs may arise in other sites such as middle ear–mastoid, pharynx, nasopharynx, lacrimal sac, and possibly in the wall of a branchial cleft cyst.[5] It has been suggested that the ectopic migration of the Schneiderian membrane during embryogenesis could account for these aberrant papilloma in sites contiguous with the sinonasal tract.[5,6]

Incidence and demographics

IP accounts for 0.5-4% of all the nasal tumours.[3,4] The annual incidence is approximately 0.6–1.5 cases per 100,000 per year.[7] Most commonly it affects patients in their 5th–6th decades with a male to female ratio of 2–3:1.[8] They occur over a wide age group but in general are not common in children.[9]Inverted papilloma has occasionally been reported in the paediatric age group.[5]The three variants are defined by location, gross/endoscopic appearance and histologic features.[9] However, the clinical features and biologic behaviour are similar.[9] Symptoms vary and are dependent on location.[9]There is no side predilection, and bilateral cases are seen in 4.9% of patients.[2]The lesion's reported incidence is possibly overestimated due to selection bias, as reports are mostly from tertiary referral centres.[10] The true incidence of inverted papilloma is therefore difficult to determine. [2]

The condition is most probably under-diagnosed, as it may coexist or develop alongside simple inflammatory polyps.[2] It is possible to miss an inverted papilloma coexisting with simple inflammatory polyps, if biopsy samples collect inflammatory polyps only.[2] For this reason, some surgeons collect all polyps for histological diagnosis, to reduce the chance of missing a concurrent inverted papilloma.[2] It is also possible to miss an inverted papilloma developing later in the course of an inflammatory nasal polyp, if the initial histological diagnosis found the polyp to be inflammatory and no histological examination of subsequent polypectomy specimens was performed.[2] Therefore, serial biopsies of recurrent inflammatory polyps may reduce the risk of missing a developing inverted papilloma.[2]

Histopathology

Inverted papilloma is derived from the sinonasal (SN) Schneiderian membrane which is derived from both the neuroectoderm of the olfactory placode and the nasopharyngeal mucosa of endodermal origin.[11] Such a diverse origin probably explains the very different histological appearance of benign papilloma at its site.[11] This multipotent epithelial neoplasm can differentiate into respiratory, transitional, or squamous cell lines.[12] The histological feature that distinguishes IP from other mucosal lesions is the propensity of the neoplasm to invert, proliferating into the underlying stroma with an intact basement membrane.[12]

Aetiology

The entire Schneiderian membrane (the embryological origin of the mucous membranes of the sinonasal cavity) is at risk of developing inverted papilloma.[13] Molecular genetic investigations have shown that inverted papilloma is a neoplasm arising from a single progenitor cell.[1]

The exact aetiology till today remains unclear.[14] Many have associated the occurrence of IP with chronic inflammation, Human Papilloma Virus (HPV) infection, Epstein- Barr virus (EBV), smoking, occupational, environmental exposures, cell cycle related proteins and angiogenic factors.[12,14]The presence of HPV DNA subtypes 6, 11, 16, and 18 has been found to be associated with a higher chance of recurrence and malignant transformation.[15] HPV serotypes 6 and 11 are less associated with IP.[15] HPV 16 and 18 were found to be related to the malignant transformation.[16]With regards to EBV, the recent available literature does not support a role for this virus in the aetiology of IP.[17]

Diagnosis

The diagnosis of sinonasal inverted papilloma is suspected from the clinical history, physical examination (including endoscopic nasal examination) and imaging (i.e. CT and magnetic resonance imaging (MRI).[2] Macroscopically, inverted papilloma has a mulberry-like, uneven surface and a livid grey colour.[1] Diagnosis is established through polyp biopsy and histological examination. Thorough removal of all diseased mucosa and a meticulous histological examination of the entire specimen are necessary to ensure correct diagnosis.[2]

Treatment

Treatment of sinonasal inverted papilloma aims to remove the disease completely at the first attempt, and also to create post-operative anatomy which allows easy post-operative endoscopic surveillance.[1] It is very important to identify the site of attachment of the tumour pedicle in order to ensure full resection.[18]Current surgical approaches are generally divided into the endoscopic and the external.[2] The method of choice depends on the extent of the disease, the skill of the surgeon and the technology available.[2]Although some authors have used radiotherapy in cases in which the tumour was inoperable or complete resection impossible,

generally this modality is used as an adjunct when inverted papilloma is associated with malignancy.[1,19]

Recurrence

Most recurrence occurs early within the first two to three years after initial treatment (mean, 30 months; range, 14-48 months), although a small percentage of cases have been seen five to six years post-operatively.[20] Most recurrence occurs at the site of the original tumour, strongly suggesting incomplete local resection (i.e. residual disease) as the main cause of recurrence.[10]

The likelihood of local recurrence after inverted papilloma resection varies. It can be as high as 100 per cent for non-endoscopic, endonasal approaches; however, on average it ranges from 5 to 50 per cent, depending on the extent of the disease and the resection.[20] The average recurrence rate is 13 per cent for endoscopic procedures, as high as 34-58 per cent for limited endonasal procedures, and 14-17 per cent for lateral rhinotomy with medial maxillectomy.[10]

Clinical predictors of recurrence

There are no robust clinical prognostic factors determining who is at risk of developing recurrent inverting papilloma.[10] However, Jardine et al. found that patients who smoked showed a trend towards multiple recurrences.[21] In addition, patients with a frontal sinus inverted papilloma have been shown to be more prone to multiple recurrences.[22] This might be due to the technical difficulties of undertaking complete endoscopic resection in this anatomical area.[2]

Histological predictors of recurrence

There are no pathognomonic histological features to predict the recurrence of inverted papilloma.[2] However, there are certain histopathological parameters that raise suspicion of recurrence.[2] Multiple recurrences (without malignancy) are related to an increase in hyperkeratosis, the presence of squamous epithelial hyperplasia, an increase in mitotic index (i.e. to more than two mitoses per high power field) and an absence of inflammatory polyps.[2]

Markers for recurrence

There is an ongoing search for markers for inverted papilloma recurrence. Although no definite and reliable marker has yet been found, increased proliferative activity (reflected by Ki67 levels), loss of basal cell keratin 14 expression and high levels of proliferating cell nuclear antigen on immunohistochemical staining of an inverted papilloma specimen can be suggestive of recurrence.[23] Serum squamous cell carcinoma (SCC) antigen levels can be used as a marker for recurrence; the marker level decreases after surgical resection of inverted papilloma.[24] Fascin is usually expressed at a low level in normal epithelium, but it is significantly increased in benign inverted papilloma. Serial measuring of this protein can be used as a marker for inverted papilloma recurrence.[25]

Malignant transformation

Malignant transformation can occur as keratinizing and non-keratinizing squamous cell carcinoma (by far the most common, seen in approximately 10% of cases) and other less frequent histology such as mucoepidermoid carcinoma, verrucous carcinoma, and adenocarcinoma.[26]HPV family 6/11 and 16/18 has been observed in IP associated with severe dysplasia and squamous cell carcinoma and HPV infection may be an early step in the process of malignant transformation.[27]The association between IP and malignancy can be metachronous or synchronous.[28] The reported incidence of metachronous or synchronous malignancies with IP varies from 2 to 27%; the median rate being 9%.[29]

Histological predictors of malignancy

Certain histopathological parameters raise suspicion of the development of SCC in inverted papilloma.[2] Malignancy is related to the presence of bone invasion, absence of inflammatory polyps, increased ratio of neoplastic epithelium to stroma, increased hyperkeratosis, presence of squamous epithelial hyperplasia, high mitotic index, low number of eosinophils and the presence of plasma cells.[30]

Predictor markers for malignancy

There is evidence that the presence of HPV in inverted papilloma could be predictive of malignant transformation.[2,31] Over-expression of p53 may serve as a marker for malignant transformation of inverted papilloma.[2] Fascin, an actin-binding protein, is usually expressed at a low level in normal epithelium, but its expression is significantly increased in benign inverted papilloma, and greatly increased in associated malignancy. Serial measurement of this marker can be used as a marker for malignancy.[2,26.]

Follow up

Recurrent inverted papilloma and metachronous carcinoma can develop after a prolonged period of time.[2] Long-term follow up is recommended to detect recurrence, as disease can become extensive before it becomes symptomatic.[2] Some authors advocate life-long follow up of inverted papilloma patients.[32]Hyperkeratosis, squamous epithelial hyperplasia and a high mitotic index are negative prognostic indicators which may be useful in the future follow up of patients with inverted papilloma.[2]If recurrence is suspected, biopsy of the polyps and/or cross-sectional imaging is required.[2] Magnetic resonance imaging with contrast is used to differentiate tumour from post-operative changes and inflammatory polyps; it can also guide the surgeon to the optimum sites for biopsy.[1]

Conclusion

Sinonasal inverted papilloma is a benign tumour which mostly presents with symptoms owing to unilateral nasal polyposis. It has a tendency to recur, and also carries the risk of malignant transformation. Diagnosis is confirmed by histology but may require CT or MRI to assess accurately the extent of the disease. The treatment of choice is complete surgical removal via an endoscopic approach, assisted with an external approach if complete resection is not possible endoscopically. Currently, no histological or biological markers can accurately and reliably predict the risk of recurrence or malignant transformation. Long-term follow up is

indicated, although the majority of recurrent cases present within the first two to three years after initial treatment.

Declaration

Ethical approval and consent to participate.

Not applicable.

Consent for publication.

Not applicable.

Availability of data and material

Not applicable.

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