



Review Article

Etiology of sinonasal inverted papilloma: A narrative review



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Abstract *Objective:* Sinonasal inverted papilloma (IP) is a benign and uncommon tumor of the nasal cavity and paranasal sinuses with a tendency for recurrence and even malignant transformation. Though the morphology and clinical behavior of this lesion has been well described, its etiology remains controversial.

Methods: Computerized searches were performed in PubMed, Scopus, and Google scholar through May 2015. In this review, etiologic factors including human papilloma virus (HPV), Epstein–Barr virus (EBV), cell cycle related proteins and angiogenic factors, occupational and environmental exposures, and chronic inflammation, will be discussed.

Results: Many studies indicate that HPV has been detected in a significant percentage of IP, while EBV has not been shown to be significantly associated. Certain cell cycle regulatory factors and angiogenic proteins contribute to the dysregulation of proliferation and apoptosis, and facilitate migration and tumor invasion. Occupational exposures, such as welding and organic solvents, have been implicated, and smoking seems more critical to recurrence and dysplasia rather than initial IP occurrence. Chronic inflammation may also have a causative relationship with inverted papilloma, but the mechanism is unclear.

Conclusions: Though etiology of sinonasal IP remains controversial, the studies reviewed here indicate a role for viral infection, cell cycle and angiogenic factors, environmental and

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occupational exposure, and chronic inflammation. Further study on etiologic factors is necessary for clinical guidance and therapeutic targets.

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Introduction

Sinonasal inverted papilloma (IP) is a benign and relatively rare tumor of the nasal cavity and paranasal sinuses, first described by Ward in 1854.¹ With an incidence between 0.2 and 1.5 cases per 100,000 persons per year, IPs account for 0.5%–4% of all sinonasal neoplasms.^{2–4} IP most commonly originates from the lateral nasal wall or maxillary sinus from the schneiderian sinonasal epithelium.⁵ There is a male predominance with a male-to-female ratio of 3.4:1.¹ While the morphological features and clinical characteristics of IP have been well described, its etiology and risk factors remain controversial.

Herein we summarize the current literature on the etiology of IP in an attempt to identify the primary characteristics associated with the development of this tumor. Associated factors, including human papillomavirus (HPV), Epstein–Barr virus (EBV), smoking, occupational, environmental and industrial exposures, cell cycle related proteins, angiogenic factors and chronic inflammation will be discussed and histopathologic features will be reviewed.

Histopathologic characteristics of IP

According to the World Health Organization (WHO), sinonasal papilloma is classified into three different histopathological groups⁶: exophytic papilloma (fungiform, septal, and squamous papilloma), inverted (inverting) papilloma, and oncocytic papilloma (cylindrical cell and columnar papilloma). IP is the most common among these groups, and generally appears as a large, polypoid mass with a grayish color and an uneven multinodular surface. Histologically, it is characterized by thickened neoplastic epithelium inverted into the underlying connective tissue with an intact basement membrane.¹ The tumor epithelium is composed of well differentiated columnar or ciliated respiratory epithelium with variable squamous differentiation.⁶

Transitional metaplasia of the respiratory epithelium is the first step in the histogenesis of a papilloma, and occurs as an intermediate stage between the pseudostratified columnar ciliated epithelium and stratified squamous epithelium.⁷ IP shows markedly thick inverted or endophytic growth of non-keratinizing transitional cells. The epithelium then undergoes squamous maturation and inverts into the stroma with a distinct basement membrane that separates the epithelium from the underlying connective tissue stroma. Surface keratinization and a granular cell layer have been described but are uncommon.⁷ The histopathologic characteristics of IP are closely related with the tumor's clinical behavior, with higher inflammatory infiltrates typically indicating benign, lower grade lesions.⁸

Human papilloma virus

Several studies have attempted to clarify the correlation between human papilloma virus (HPV), IP, and subsequent malignant transformation. Kashima et al⁹ suggested HPV to be etiologically related to sinonasal papillomas, inverted papillomas and squamous cell carcinomas based on polymerase chain reaction (PCR) detection of HPV DNA in specimens of each pathology. Consistent with findings from previous studies, those with benign and malignant clinical courses were separable based on low and high-risk types of HPV, respectively. HPV-6 and -11 are regarded as low-grade risk types, and HPV-16 and -18 are regarded as high-grade risk types. Similarly, in an analysis of 22 lesions by McLachlin et al,¹⁰ HPV DNA was found to be present in IP as well as IP with associated squamous cell carcinoma (SCC), which suggested a role for HPV in both the pathogenesis and malignant transformation of papillomas. McKay et al,¹¹ in a retrospective study of 14 patients, reported that the viral genome of HPV had integrated into the specimens of 2 of 3 patients with sinonasal IP with SCC, again indicating that HPV played an active role in malignant transformation. However, based on the report of Cheung et al,¹² it was concluded that HPV infection might also represent the initiation or early promotional event in the multistep oncogenesis of IP. In support of this claim, a study of 57 Korean patients found HPV DNA in seven IP lesions, all of which were grades I and II (benign) IP. All other specimens of grade III and grade IV were negative for HPV DNA. Their HPV subtypes were 11/16, 31, 35/58, 52, and two specimens showed coinfection (HPV type 11/16 and HPV 33/58). High-risk HPV subtype DNA was detected in five specimens, suggesting that infection, particularly with high-risk HPV subtypes, was an early and inciting event in tumorigenesis.¹³ Finally, Hwang et al¹⁴ amplified HPV-16 in 2 of 5 cases of IP with SCC and in 2 of 3 cases of recurrent IP. Cohesively, these studies suggest a role for HPV not only in malignant transformation, but also in early lesion development and even recurrence.

Despite this wealth of data implicating HPV in the pathogenesis of IP, there are a number of studies presenting conflicting evidence. Kraft et al¹⁵ detected HPV-11 in only 1 of 29 IPs (3%), and in none of the four cases of IP with associated SCC. Furthermore, a study of 66 patients with IP and 5 patients with IP associated SCC did show HPV isolation (HPV-11, -19 (95%), HPV-6, -1(5%)) in 20 (30.3%) patients with IPs and in 3 patients (60%) with IP associated SCC (HPV-11, -3); however, subsequent analysis revealed that the presence of HPV DNA was not a statistically significant predictor of the recurrence of IPs ($p = 0.745$) nor was it a statistically significant risk factor for IP associated SCCs ($p = 0.32$).¹⁶ These results indicate that HPV infection may

represent incidental colonization rather than an important etiologic factor, and is not necessarily a reliable parameter to predict or malignancy or recurrence.

Cell cycle regulation

Several authors have attempted to elucidate potential mechanisms of HPV infection in the etiology of IP by investigating its effect on p53 and p21 expression. p53 acts as a tumor suppressor by starting a protective cell cycle arrest and an apoptotic response in DNA-damaged cells,¹⁷ and its gene mutations are well recognized as the most common genetic changes in head and neck cancer.^{17,18} E6 and E7, oncoproteins expressed by HPV genes, are involved in p53 down-regulation and consequently, disruption of the normal cell-cycle control.¹⁹ p21 can regulate cell-cycle arrest during the growth phase through p53-dependent or independent pathways, and its effects have also been shown to be abrogated by HPV oncoproteins.²⁰

Significant research has been conducted examining these proteins in IP, but the results are inconclusive. In a study conducted by Scheel, et al² HPV was detected in 11 of 90 (12%) patients, with HPV-11 being isolated in 9 of these samples. Differences in p53, p16 and cyclin D1 staining compared with controls were not significant, suggesting that dysregulation of these proteins is not an important mechanism in low-risk HPV-related IP. However, in another report of 37 patients, overexpression of p53 was found in carcinomas associated with IP but not in the benign lesions, supporting a role for p53 only in the carcinogenic process.¹⁷ Similarly, Blanchard et al¹⁸ demonstrated a clear inverse relationship between p53 expression and HPV presence in 28 patients with IP with SCC, wherein p53 overexpression was absent in the 4 HPV positive tumors and present in the HPV positive tumors. This also implies a correlation between p53 and malignant transformation, but must be weighed against the relatively low rate of HPV positivity in these lesions.

In a study of Hong Kong patients, Tong et al found that p21 overexpression was universally present in all IP lesions, while only 3 of 73 (4%) of these tumors were HPV positive. Katori et al²⁰ found p21 and p53 expression in 13/29 (45%) and 11/29 (38%) of IP, respectively. Increased staining of p21 and p53 was shown in the nuclei of specimens with IP with severe dysplasia and IP with SCC, and higher rates of dysplasia were seen in IP lesions with HPV. However, a significant decrease in expression of p21 and p53 was observed in the HPV positive IPs as compared with the HPV negative tumors. Altavilla et al²¹ also showed that tumors harboring dysplastic epithelium were strongly positive for p21 and p53 in transitional and metaplastic cells, but conversely found that the HPV associated IPs also highly expressed p21. Overall, these studies suggest a complex relationship between HPV, p53, and p21, which may dependently or independently influence the development and malignant transformation of IP.

To summarize, while many studies have detected HPV DNA in IP specimens, HPV infection as the inciting event in papilloma development or the transformation to malignancy has not yet been proven.⁸ In fact, it is widely accepted that squamous metaplasia of the respiratory

epithelium must occur before HPV involvement, as a squamocolumnar junction is a prerequisite for HPV to gain access to its target cells.⁸ Furthermore, the interactions between HPV and cell cycle regulatory factors in tumorigenesis and the progression of dysplasia are intricate and incompletely understood.

Epstein–Barr virus

In regard to Epstein–Barr virus, the recent available literature does not support a role for this virus in the etiology of IP. In a previous review of sinonasal papilloma, it was reported that EBV was no longer considered to be a significant factor in the development of IP.²² This claim was upheld in a study of 73 Hong Kong patients with IP, wherein EBV DNA was not detected in any of the biopsy specimens.²³ Another review of 25 surgically resected IPs failed to detect EBV infection by *in situ* hybridization.²⁴

Environmental factors

Smoking is considered to be the most important risk factor in the development and the recurrence of neoplasms occurring in the head and neck. In IP specifically,²⁵ the analytic data does not support a function for smoking in its development, but may be contributory to recurrence and carcinogenesis. A case-controlled trial comparing 47 patients with IP and 47 control subjects showed there was no significant difference between smokers and nonsmokers in the incidence of IP.²⁶ Similarly, Sham et al²⁷ concluded in their case-controlled study that heavy smoking was not substantiated as a risk factor in conditional logistic regression analysis (odds ratio, 2.62; 95% CI = 0.64–10.66, $p = 0.18$). However, smoking has been shown to be associated with recurrence and malignant transformation of IP. In a study of 132 patients, 39 (29.5%) of whom were smokers, IP recurred in 21 of 132 (15.9%) patients. 11 of 39 smokers (28.2%) compared with only 10 of 93 nonsmokers (10.7%) had recurrent disease, demonstrating a significantly higher recurrence rate among smokers ($p = 0.012$).²⁸ Another study by Hong et al²⁵ found that in 162 patients with IP, 14 of 53 (26.4%) smokers underwent malignant transformation, while only 3 of 109 (2.8%) nonsmokers developed associated carcinoma ($p < 0.001$). The results strongly suggest smoking history to be correlated with recurrence and malignant transformation of IP, but not necessarily in the initial development of papilloma.

It has also been speculated that occupational and industrial exposures are contributory factors in the etiology of IP. Sham et al²⁷ found that 10 of 50 (20%) IP patients had industrial exposure in the construction, textile, printing, paper making, and electronic industries, while only 8 of 150 (5.3%) in the control group reported the same exposures (odds ratio, 8.69; 95% CI = 2.53–29.86; $p = 0.001$). This study also revealed that an outdoor occupation was a statistically significant factor associated with IP (odds ratio, 3.49; 95% CI = 1.18–10.36; $p = 0.02$).

A retrospective study conducted in Italy²⁹ examining the relationship between occupational exposure and the incidence of IP showed that the risk of IP was significantly increased for those reporting exposure to welding fumes

and organic solvents, with a dose–response relationship observed in organic solvents. In general, the literature supports a causative role for smoking, occupational, and industrial exposures in the development of IP.

Angiogenic factors

A number of cellular factors associated with angiogenesis have also been implicated in IP growth. Osteopontin (OPN) is a secreted phosphoprotein critical to the formation, migration, and invasion of various tumor cells. Vascular endothelial growth factor (VEGF) plays an essential role in mediating neoangiogenesis during tumor progression by promoting endothelial cell mitogenesis and migration, increasing vascular permeability, and forming blood vessels. Liu et al³⁰ reported that staining levels, mRNA expression, and protein levels for OPN and VEGF were higher in IP tissues as compared with control tissues, and that the correlation between expression level and disease severity was significant. These results suggest that the OPN-VEGF relationship contributes to tumor progression by enhancing angiogenesis and may drive the clinical progression of IP. Angiomotin is another protein modulating angiogenesis via down-regulation of angiostatin, a circulating inhibitor of angiogenesis. Byun et al⁴ reported that, based on PCR and Western blot analysis, angiomotin was significantly overexpressed in IP tissues versus normal sinus mucosa, suggesting association with progression and growth of IP via angiogenesis.

Influence of chronic inflammation

IP typically originates from the lateral nasal wall where chronic inflammatory changes are common, as in the ostiomeatal complex and middle meatus.⁵ On histopathologic examination, these changes can often be seen at the periphery of IP tissues, a finding that has prompted research into association with chronic inflammatory states.^{8,31} A recent study of IP in Chinese patients revealed elevated quantities of neutrophils, macrophages, eosinophils, CD8+ T cells and T-reg cells, with neutrophils representing the predominant inflammatory cell type.³¹ Furthermore, coexistent nasal polyposis was present in 28% and concomitant chronic rhinosinusitis present in 100%. These results indicate that active cell-mediated innate and acquired immune responses played an important role in the development of IP. Yoon et al³² reported that 21.9% of IP specimens were bordered by inflammatory nasal polyps, suggesting that chronic inflammation may have been a precursor to IP. Orlandi et al³³ found that the Lund–Mackay Score in the contralateral sinus tended to be higher in patients with IP than with other sinonasal tumors. The relationship between inflammation and IP was also studied by Roh et al,⁸ who demonstrated that the inflammatory cell population was significantly greater in IP as compared with other sinonasal papillomas (exophytic and oncocytic papilloma) and that this cell population was more significant in lower grade lesions, suggesting an early role for inflammation in the development of IP. It has been postulated that chronic inflammation creates an environment for viral

replication and stimulates the production of cell mediators that alter apoptotic pathways leading to tumor growth.³³

Attempts have been made to identify the specific factors at play in the influence of chronic inflammation in the sinonasal cavity on IP. Yoon et al³⁴ reported that COX-2 expression was positively correlated with histopathologic grade, with higher expression in advanced grades, suggesting that COX-2–mediated inflammatory signals may contribute to promoting the proliferation of the advanced sinonasal IP.

The expression of proliferation and apoptotic markers including PCNA, bax, cytochrome C and caspase-8 in IP and nasal polyps, has also been studied.³⁵ While PCNA, a proliferation marker, was more frequently observed in IP than nasal polyps, apoptotic markers caspase-8 and bax were less frequently observed in IP compared with nasal polyps. These results indicate that dysregulation of cell proliferation and apoptotic factors are likely involved in IP development. Finally, matrix metalloproteinases (MMPs), recognized as key enzymes in tissue remodeling, have been shown in high concentrations in inflammatory cells adjacent to hyperplastic IP epithelium. Papon et al³⁶ reported that a significantly increased number of MMP-9 positive inflammatory cells were found abutting the hyperplastic epithelium compared with non-hyperplastic epithelium, indicating that MMP-9 expressing inflammatory cells may be involved in the transition from chronic inflammation to papilloma.

While inflammatory cells are identified as a significant cell population in IP, the mechanistic relationship between chronic inflammation and IP is complex and dependent on a number of cellular factors that are incompletely understood.

Conclusion

Sinonasal IP is a rare and benign tumor occurring in the sinonasal cavity, and is an important clinical entity due to its marked tendency for recurrence and malignant transformation. Though its etiology remains controversial, the studies reviewed here indicate a role for viral infection, cell cycle and angiogenic factors, environmental and occupational exposure, and chronic inflammation. Further study regarding risk factors and the relationships of these various mediators of inflammation, proliferation, and apoptosis in this disease process is warranted to guide clinical decision-making and identify therapeutic targets.

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