

Epidermal growth factor receptor, p16, cyclin D1, and p53 staining patterns for inverted papilloma

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Background: The aim of this study was better characterize the staining patterns of inverted papilloma (IP) with and without carcinoma by performing immunohistochemistry for p16, epidermal growth factor receptor (EGFR), p53, and cyclin D1 antibodies in a large patient cohort.

Methods: A total of 162 IP specimens were collected from 147 patients treated at the University of Michigan between 1996 and 2011. Twenty-two specimens contained carcinoma. Tumor was extracted for construction of 2 tissue microarrays and stained for p16, EGFR, p53, and cyclin D1. Tumor staining intensity and percentage staining were scored.

Results: Benign disease was positive for p16 in 64%, EGFR in 50%, p53 in 30%, and cyclin D1 in 76%. IP with carcinomatous degeneration was positive for p16 in 14%, EGFR in 71%, p53 in 62%, and cyclin D1 in 76%. The differences in staining positivity between benign and malignant disease reached significance for p16 and p53 only. Mean percentage staining by tumor surface area for IP and IP with carcinoma was 12%

vs 7% for p16 (no statistical significance [NS]), 20% vs 34% for EGFR (NS), 4% vs 24% for p53 ($p < 0.001$), and 17% vs 21% for cyclin D1 (NS).

Conclusion: Important characteristic staining pattern for IP with and without carcinoma are highlighted in this study. Unlike recent trends in human papilloma virus (HPV)-related head and neck malignancies, low expression of p16 is a marker for malignancy in this series. Positive staining for p53 correlates with the development of carcinoma in IP. © 2013 ARS-AAOA, LLC.

Key Words:

inverted papilloma; sinonasal carcinoma; p16; cyclin D1; EGFR; p53

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Inverted papillomas (IPs) of the sinonasal tract remain a topic of controversy among surgeons and pathologists with respect to etiology, pathogenesis, and biological behavior. Representing between 0.4% and 4.7% of all sinonasal neoplasms, the overall incidence of these tumors is between 0.74 and 1.5 cases per 100,000 persons per year.^{1,2} Risk factors for developing IP include outdoor and industrial occupation; smoking and other inflammatory diseases such as allergic rhinitis and sinusitis are not considered etiologic factors.³ These tumors are known

to degenerate into or simultaneously harbor carcinoma in some patients, oftentimes with aggressive growth patterns and intracranial or orbital extension that require radical resection. The current literature suggests a rate of malignancy of 5% to 27%,^{4,5} with an average of 10%.^{6,7} Surgery remains the mainstay for treatment of IP, and recurrence rates remains significant, with a literature reported rate of 5.7% to 32%.⁸⁻¹⁰

Perhaps secondary to its histologic appearance of hyperplastic Schneiderian mucosa enclosed in basement membrane that grows endophytically into the underlying stroma, the human papillomavirus (HPV) has been implicated in the development of IP.¹¹⁻¹⁵ However, definitive and objective data supporting this association remains sparse, and the true role of HPV in the pathogenesis of IP remains controversial. Detection rates for HPV vary widely in the literature, ranging from 0% to 72%, with an average of about 25%.^{1,11} Surrogate markers of HPV have been studied even less exhaustively, and no universally accepted immunohistochemical markers currently exist for this disease.

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The retinoblastoma protein (pRB)/p16^{INK4a} (p16) regulatory pathway is disrupted with HPV infection and is thus a good candidate for study in the pathogenesis of IP. The protein p16 functions as a cyclin-dependent kinase inhibitor that shuts down cyclin D1-dependent phosphorylation of the pRB, allowing dephosphorylation of pRb and cessation of cell cycle progression at the G1 to S checkpoint. The retinoblastoma protein in its dephosphorylated state binds to the E2F family of transcription factors that upregulate expression of proteins necessary for entry into the cell cycle. When a cell is infected with high-risk HPV, the viral E7 protein binds to and inactivates pRb, activating E2F independently of cyclin-dependent kinase. The functional inactivation of host pRb by the HPV E7 protein results in overexpression of p16, making p16 a reasonable surrogate marker for the presence of high-risk HPV.

Another host regulatory pathway disrupted by HPV infection is cell-cycle control by the p53 tumor suppressor protein. E6 protein from the HPV DNA genome inactivates cellular regulatory protein p53 by associating with host E6-associated protein and ubiquitinating host p53, marking this cell-cycle regulatory protein for degradation.¹⁶ This process allows for unregulated cellular proliferation of epithelial cells and promotes oncogenesis. Epidermal growth factor receptor (EGFR) can be similarly be overexpressed in HPV-infected cells secondary to the viral E5 gene product.¹⁷

The purpose of this study was to better understand the biology of IP by analyzing the staining pattern for p16, EGFR, cyclin D1, and p53.

Materials and methods

The University of Michigan Institutional Review Board (IRB) approved this study. Patients were identified from the University of Michigan pathology archive, using the search target “inverted papilloma” for exact matches. This study required a stringent pathology review of all patient blocks by dedicated head and neck pathologist (J.M.). To ensure consistency of pathology and patient reporting, other Schneiderian papillomas such as fungiform papillomas and cylindrical/oncocytic papillomas were excluded for data analysis. We included any IP with or without dysplasia or carcinomatous degeneration treated at the University of Michigan between 1996 and 2011. A total of 162 IP specimens from 122 patients treated at the University of Michigan in the mentioned time period were studied. Charts were reviewed for demographic data, follow-up duration, recurrence, and presence of malignancy.

A tissue microarray (TMA) was constructed to facilitate the study of immunohistochemistry for p16, EGFR, p53, and cyclin D1. The technique for TMA construction has previously been methodically described,¹⁸ and the reader is referred to this reference for details of construction. Briefly, individual tumor blocks were cut and stained for hematoxylin and eosin if corresponding slides for the tumor block were not available from the pathology archives.

The area of tumor on each slide was marked, and the corresponding area of the tumor block was cored for TMA construction.

For immunohistochemistry, TMA slides were deparaffinized and rehydrated. The antigen retrieval method varied depending on the antibody used. For EGFR, pepsin was used (Life Technologies, Carlsbad, CA); 10 minutes at 37°C as per manufacture instructions. The standard citrate buffer was used for p53 and cyclin D1 (25 minutes at 92°C, cooled at room temperature for 25 minutes). For p16, CINtec p16^{INK4a} Histology kit (mtm laboratories, Westborough, MA); kit instructions were followed. For all slides, peroxidase was quenched with peroxidase block. All slides were also blocked with casein for 30 minutes at room temperature. Primary antibody, EGFR/31G7 (Life Technologies), p53/D01 and cyclin D1/Clone SP4 (Thermo Scientific, Fremont, CA), and p16 (CINtec p16^{INK4a} Histology kit; mtm laboratories, Westborough, MA) incubated for 1 hour and probed with EnVision+System-HRP (DAKO Carpinteria, CA) for p53, cyclin D1, and EGFR. For p16 the reagents from the manufacturer’s kit were used (mtm laboratories).

Antibody binding was scored on a scale of 1 to 4 for all antibodies: Grade 1 for less than 5% staining, grade 2 for 5% to 20%, grade 3 for 21% to 50%, and grade 4 for >50%. Intensity was scored as 1 for no staining, 2 for low intensity, 3 for moderate intensity, and 4 for high intensity. Proportion and intensity of staining were scored by a pathologist (J.B.M.) who was blinded to the clinical outcome.

SPSS (IBM, Armonk, NY) version 19 was used for all statistical calculation and analysis. The product limit method of Kaplan and Meier was used to calculate rates of local regional control, overall survival, and disease-specific survival.

Results

A total of 162 pathology blocks were available for study from 147 patients, and this formed our study group for immunohistochemical analysis. Twenty-two specimens (13.6%) contained carcinoma. Among this study group, 111 patients were male. The cohort consisted of 112 Caucasian patients, 27 Black patients, 7 Asian patients, and 1 Hispanic patient.

p16

Eight samples were unsatisfactory for study, resulting in 154 total specimens; 104 of 154 (67.5%) showed some degree of staining for p16, with an average stain area of 11.3% (Table 1). The staining pattern of p16 is nuclear and cytoplasmic (Fig. 1). Benign disease was positive for p16 in 64% vs 14% for IP with carcinoma ($p < 0.001$) (Table 2). Mean percentage staining for IP and IP with carcinoma was 12% vs 7% for p16 (no statistical significance [NS]) (Table 3).

TABLE 1. Overall stain results of all samples based on intensity and percent staining

	p16	EGFR	p53	cyclin D1
Staining intensity^a				
No staining (I)	50	70	75	31
Weak staining (II)	0	13	0	33
Moderate staining (III)	14	39	1	27
Strong staining (IV)	90	34	80	66
Percent staining^b				
Staining (I)	67	72	98	37
Staining (II)	63	29	42	66
Staining (III)	19	29	13	48
Staining (IV)	5	26	3	6
Average staining %	11.3	21.7	7.5	17.3
Total satisfactory samples	154	156	156	157

^aStaining intensity (category I = no staining, category II = weak staining, category III = moderate staining, and category IV = strong staining).

^bPercent staining (category I = <5% staining, category II = 5% to 20% staining, category III = 21% to 50% staining, and category IV for >50% staining).
EGFR = epidermal growth factor receptor.

EGFR

Six samples were unsatisfactory for study, resulting in 156 total specimens; 86 of 156 (55%) showed some degree of staining for EGFR, with an average stain area of 21.7% (Table 1). The staining pattern of EGFR is membranous (Fig. 1). IP harboring malignancy stained positive for EGFR in a higher percentage of specimens (71% vs 50%), but this difference was not statistically significant (Table 2). The mean percentage staining for IP and IP with carcinoma was 20% vs 34% (NS) (Table 3).

p53

Six samples were unsatisfactory for study, resulting in 156 total specimens; 81 of 156 (52%) showed some degree of staining for p53, with an average stain area of 7.5% (Table 1). The staining pattern of p53 is nuclear (Fig. 1). Positive staining for p53 biomarker was found to be present in 30% of benign specimens vs 62% in specimens harboring malignancy ($p < 0.001$) (Table 2). Mean percentage staining for IP and IP with carcinoma was 4% vs 24% (NS) (Table 3).

Cyclin D1

Five samples were unsatisfactory for study, resulting in 157 total specimens; 126 of 157 (80%) showed some degree of

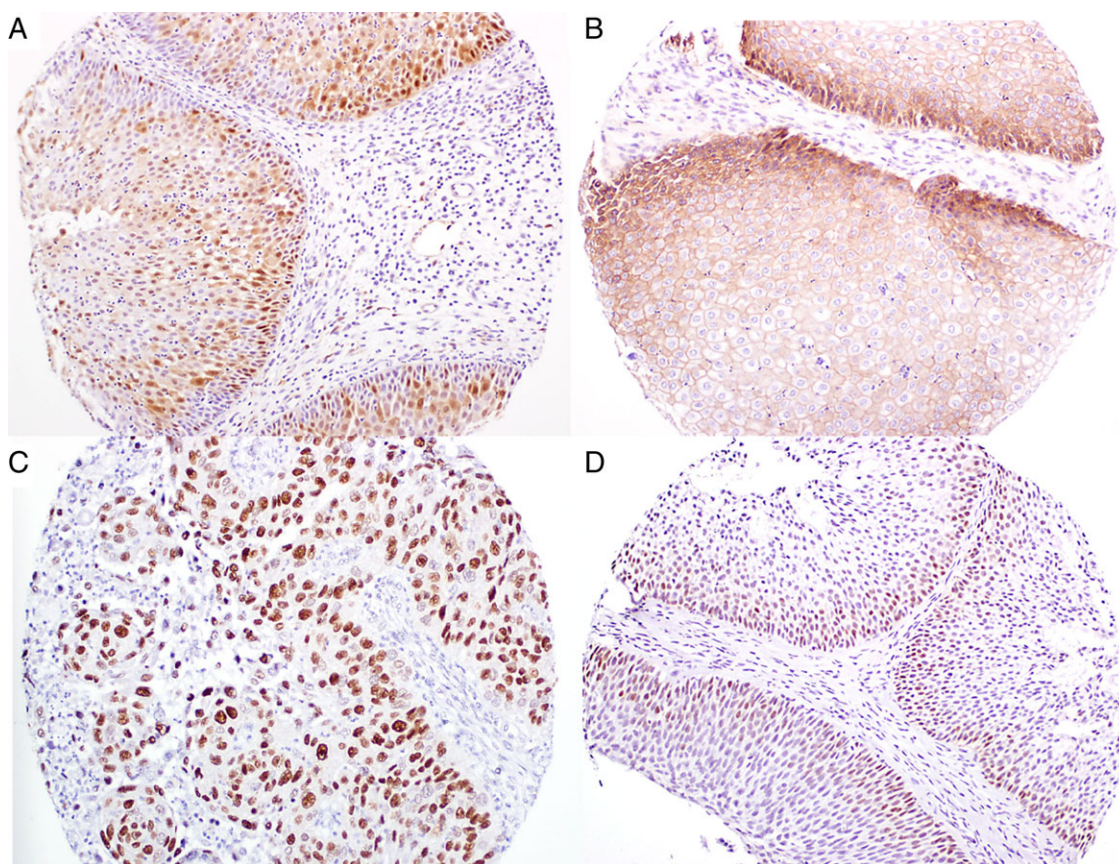


FIGURE 1. Stain patterns for biomarkers used. (A) p16 staining is cytoplasmic and nuclear; this IP specimen was graded 4 for intensity and 90% staining surface area. (B) EGFR staining is cytoplasmic; this IP specimen was graded 4 for intensity and 100% for staining surface area. (C) p53 staining nuclear; this IP specimen harbors squamous cell carcinoma and was graded 4 for intensity and 100% for staining surface area. (D) Cyclin D1 staining is also nuclear; this IP specimen was graded 3 for intensity and 30% for staining surface area. EGFR = epidermal growth factor receptor; IP = inverted papilloma.

TABLE 2. Number and percentage positive staining for p16, EGFR, p53, and cyclin D1 based on benign IP vs IP with carcinogenesis

	Benign IP	IP with carcinoma	Significance
p16+ (%)	85/133 (64%)	3/21 (14%)	$p < 0.001$
EGFR+ (%)	68/135 (50%)	15/21 (71%)	NS
p53+ (%)	45/135 (30%)	13/21 (62%)	$p < 0.001$
Cyclin D1+ (%)	104/136 (76%)	16/21 (76%)	NS

EGFR = epidermal growth factor receptor; IP = inverted papilloma; NS = not statistically significant.

TABLE 3. Average stain percentage for p16, EGFR, p53, and cyclin D1 for benign IP vs IP with carcinoma

	Benign IP (%)	IP with carcinoma (%)	Significance
p16	12	7	NS
EGFR	20	34	NS
p53	4	24	$p < 0.001$
Cyclin D1	17	21	NS

EGFR = epidermal growth factor receptor; IP = inverted papilloma; NS = not statistically significant.

staining for cyclin D1, with an average stain area of 17.3% (Table 1). Similar to p53 staining, cyclin D1 staining is nuclear (Fig. 1). Specimens with IP only and specimens with malignancy stained positive for cyclin D1 in 76% (NS) (Table 2). Whereas the stain intensity for p16, EGFR, and p53 for positive-stain specimens were almost all moderate to strong, the stain intensity for cyclin D1–positive samples varied widely. For cyclin D1, the mean percentage staining for IP and IP with carcinoma was 17% vs 21% (NS) (Table 3).

Discussion

Characteristic staining patterns and reactivity are demonstrated on a large cohort of patients in this study for p16, EGFR, p53, and cyclin D1. Overall, p16 staining was significantly more likely to be positive for benign disease, while p53 staining was more likely to be positive for IP with malignant degeneration. A higher percentage of IP specimens with malignancy showed some degree of staining for EGFR compared to benign IP, but this difference did not reach statistical difference. We did not find any difference in overall staining patterns between benign and malignant disease for cyclin D1. However, it is noted that a significant portion of both benign and malignant disease do demonstrate immunoreactivity to cyclin D1 antibodies.

The literature is sparse on studies using p16 as a surrogate marker for HPV detection for IP. Allende et al.¹⁹ and Shah et al.²⁰ have investigated the use of p16 as a marker for HPV presence in 2 separate studies, but these authors reported

contrasting results. Shah et al.²⁰ reported that that 87.5% of HPV-positive specimens by polymerase chain reaction (PCR) were positive for p16, while 90.9% of HPV-negative specimens also stained positive for p16. This study was limited by a small patient population ($n = 26$ patients) and used a combination of less sensitive PCR and biotinyl-tyramide–based chromogenic in situ hybridization for HPV detection. The high rate of p16 staining is opposite of the report by Allende et al.,¹⁹ in which 4 of 7 IP were focally positive for p16, 2 of 6 dysplastic lesions showed patchy staining for p16, and 2 of 7 carcinomas were positive for p16. Their study did not find HPV in any specimens.

Our study is the first to statistically analyze and demonstrate a significantly higher degree of staining for p16 in IP only compared to IP with malignancy. Our results suggest that p16 expression is usually not lost during the development of IP. In the process of carcinogenesis, the p16 gene is more likely to be inactivated. This finding parallels non-HPV-related head and neck cancer, in which loss of p16 expression is 1 of the most common oncogene alterations secondary to loss of chromosomal region 9p21.^{21,22} The progression to malignancy in IP may share similar pathways or gene alterations seen in the development of other head and neck malignancies, but the exact mechanisms require further study.

Because inactivation of retinoblastoma protein by high-risk HPV E7 protein leads to p16 overexpression, p16 positivity is considered a useful surrogate marker for the presence of high-risk HPV in head and neck cancer.^{23–25} The validity of p16 staining as evidence for HPV has not been shown in IP. Although our current study does not specifically address HPV presence directly via in situ hybridization in PCR studies, the low average staining by surface area for all IPs in this study (12% for benign disease and 7% for IP with carcinoma) is significantly less than the diffuse positive staining seen in HPV-related head and neck cancer.^{23,24,26–28} One study by Lewis et al.²⁶ suggests 75% staining as a suitable cutoff for defining HPV positivity, and few of our specimens would meet this criteria. At this time, it is not possible to delineate whether the p16 staining detected in IP seen in the current study is a HPV-related phenomenon or not. Because other factors such as abnormalities of the retinoblastoma protein or deletion and methylation of the p16 locus can also lead to p16 overexpression, p16 staining can be nonspecific.


EGFR is studied in our analysis because it can also be altered by HPV infection. The E5 gene protein from HPV DNA is a small hydrophobic protein consisting of 83 amino acids that localizes to the cell membrane, Golgi apparatus, and endosome. E5 enhances the activation of EGFR and its downstream signal transduction pathways, leading to increased mitogenic activity.¹⁷ Proposed mechanisms for HPV E5 upregulation of EGFR include the EGFR-E5 protein complex, which affects EGFR activity, E5 inhibition of endosome acidification, which inhibits degradation of endocytic EGFR, and E5 inhibition of trafficking from early to late endosomes to delay EGFR degradation.

Abnormal activation is seen in many epithelial malignancies such as head and neck cancer, and is associated with poorer outcomes.^{29–31} For IP, we found a trend for higher EGFR staining for IP with malignant degeneration. The difference in EGFR staining between IP with carcinoma and IP alone parallels what is seen in the development of epithelial malignancies but did not reach statistical significance. Chao et al.³² also reported a high percentage of EGFR staining in IP specimens and low staining in polyp and inferior turbinate tissue, but the study did not perform statistical calculation to assess these differences.

Last, this study suggests that p53 alteration is important in the progression of IP to malignant disease. IP with carcinoma stains positive for p53 at more than twice the frequency of IP alone (62% vs 30%). Compared to the low average percent stain by surface area in IP alone (4%), samples with malignancy showed significantly higher percentage area of positive staining (24%). In a study of 30 patients with Schneiderian papillomas, including 3 patients with either dysplasia or carcinoma, Mirza et al.¹³ found 30% of samples to be p53 positive by immunohistochem-

istry. Positive staining for p53 in this study correlated to a 19% increase in the likelihood of malignancy at surgery. The difference in p53 staining between benign and malignant disease is higher in our cohort of patients. Franzmann et al.³³ also reported an overexpression of p53 in carcinomas occurring in sinonasal papillomas but not in the benign tumors of the sinonasal mucosa. Staining for p53 is also low for benign IP in a recent report by Sham et al.³⁴ Our study is congruent with these reports with respect to the close relationship between p53 staining and malignancy.

Conclusion

Important characteristic staining patterns for IP with and without carcinoma are highlighted in this study. The majority of inverted papilloma without malignancy contain areas of positive staining p16, and complete loss of expression of this tumor suppressor protein is a marker for malignancy in this series. This study also indicates that mutations in p53 likely play an important role in the process of malignant degeneration. 

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