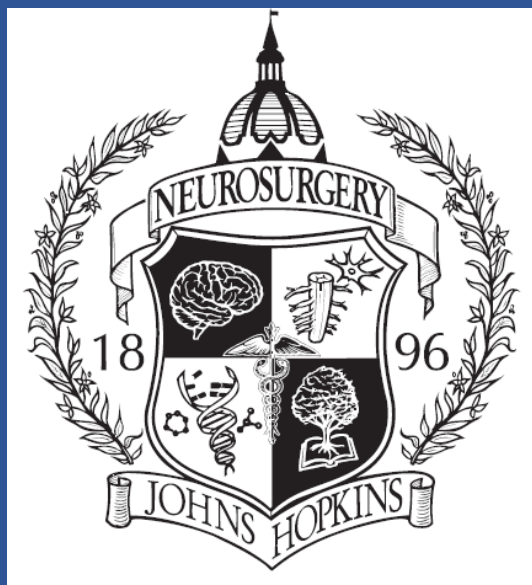


Human Papillomavirus is Not Associated with Olfactory Neuroblastoma Despite Expression of p16: Findings from a Single-Institution Study

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Introduction

Human papillomavirus (HPV) is a significant risk factor for head and neck cancers, particularly oropharyngeal squamous cell carcinoma, and is also associated with a subset of sinonasal cancers. It is unknown whether olfactory neuroblastoma (ONB) is associated with HPV. This study aimed to investigate if there is an association between ONB and HPV in a large single-institution series.

Materials and Methods

Cases/Tissue Microarray. A tissue microarray (TMA) was constructed from paraffin-embedded tissue blocks of 44 patients with ONB who underwent surgical resection at Johns Hopkins Hospital (JHH) between 1986 and 2011. Three 1-mm diameter punch cores of representative tumor were taken from each block, and fifteen normal tissues were included on the array as controls. Clinical data was obtained from the patient's medical records. Staging was according to modified Kadish¹ and histopathological grading was according to Hyams². This study was approved by the JHH Institutional Review Board.

Immunohistochemistry (IHC) for p16 expression. IHC for p16 expression was performed as previously described^{3,4}. Expression of p16 was scored positive if strong and diffuse nuclear and cytoplasmic staining was detected in $\geq 70\%$ of the tumor cells^{3,4}. Expression of p16 in less than $< 70\%$ of the tumor cells was defined as patchy.

HPV in situ hybridization. DNA and RNA *in situ* hybridization were performed as previously described⁵.

Statistical analysis. Statistical analyses were performed using Fisher's exact test for investigating differences in presentation, stages, and grades among p16 positive and negative cohorts. A p-value < 0.05 was considered statistically significant.

Results

A total of 44 cases were included in the construction of the TMA. Three cases on the array were subsequently further analyzed and determined to be olfactory carcinomas^{6,7} and one case was not an ONB, and thus these cases were excluded from this analysis. The clinical characteristics of the 40 patient ONB cohort is shown in Table 1.

Three cases (7.5%) were positive and had strong p16 expression (Figure 1), and 11 cases (27.5%) had patchy p16 expression (Figure 2).

High risk HPV was not detected in any of the 40 ONBs by DNA nor RNA *in situ* hybridization.

There were no significant associations between p16 positivity and presentation, stage, or grade.

Figure 1. Example of p16 positive ONB. Left panel (H & E), right panel (p16 IHC). Strong and diffuse staining is seen in a nuclear and cytoplasmic distribution.

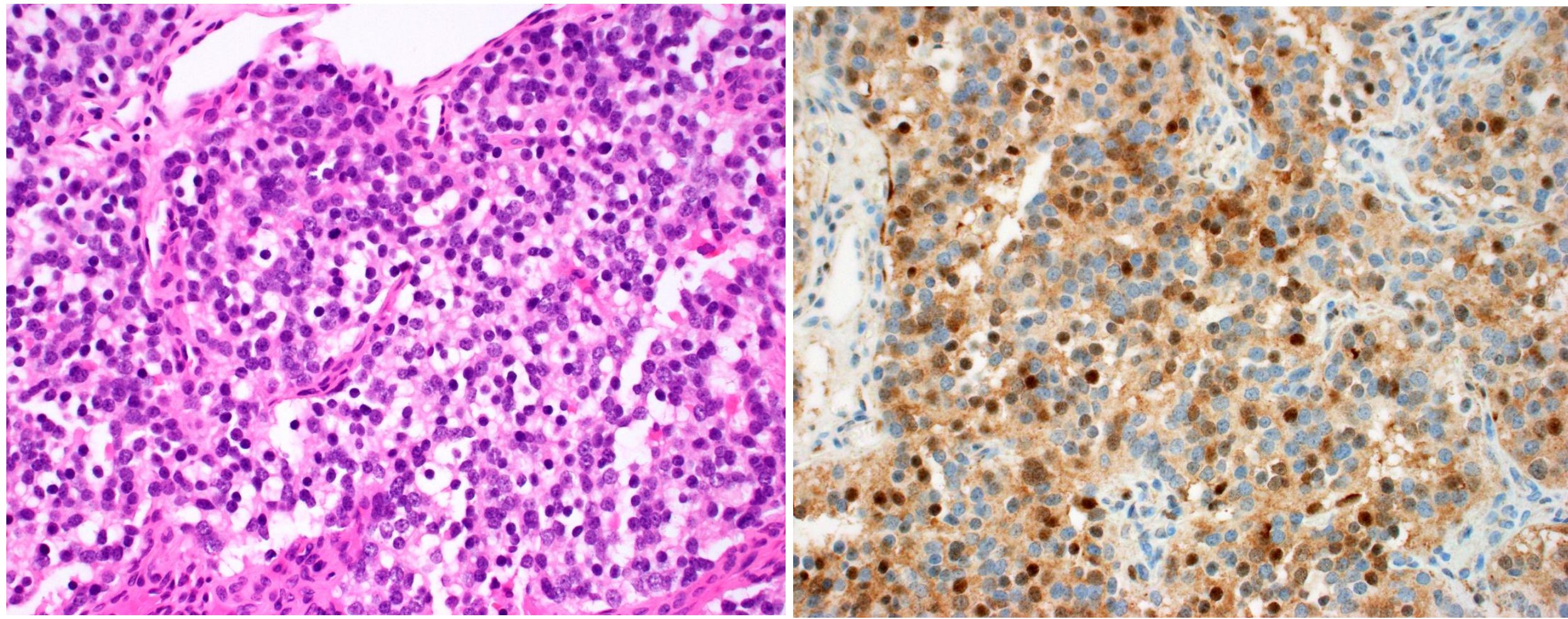


Figure 2. Example of ONB with patchy p16 staining. Left panel (H & E), right panel (p16 IHC).

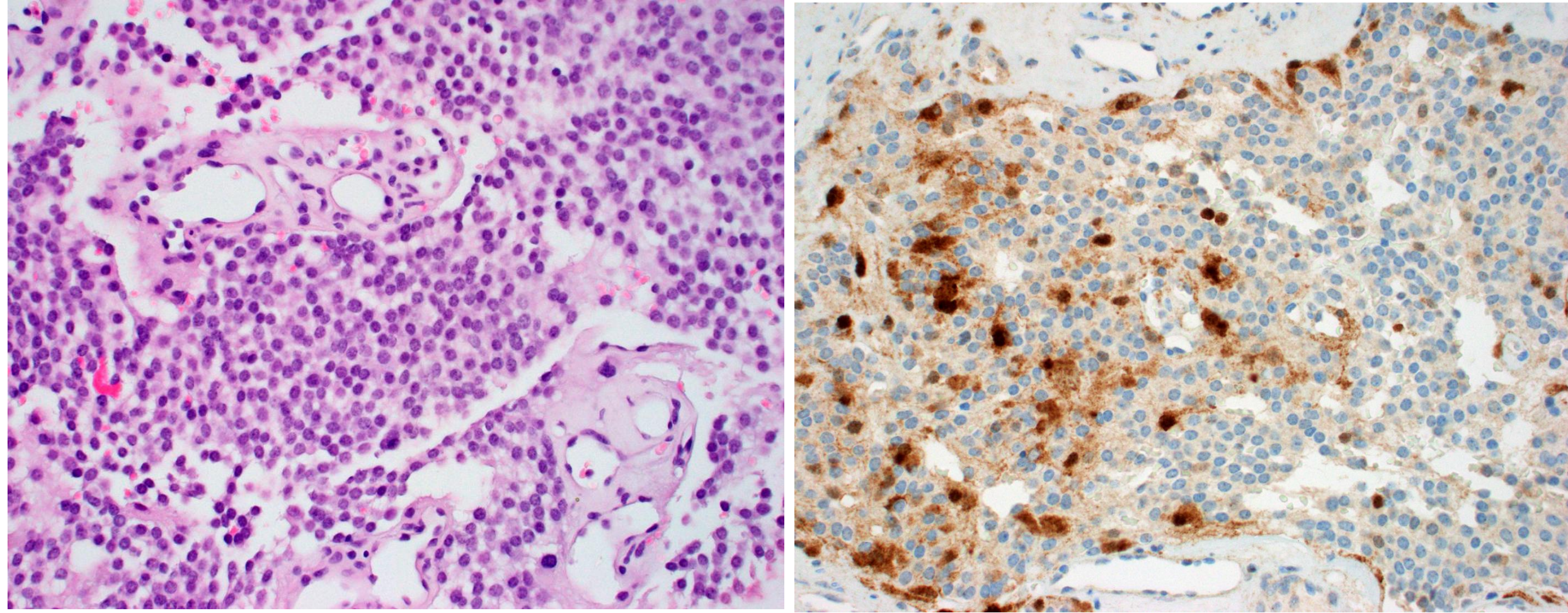


Table 1. Characteristics of ONB samples on the TMA

Mean age at dx (y)	52.6 (± 14.8)	New diagnosis	34 (85%)
Male gender	26 (65%)	Recurrence	6 (15%)
Kadish staging		Hyams grade	
A	3 (7.5%)	1	8 (20%)
B	4 (10.0%)	2	20 (50%)
C	28 (70.0%)	3	8 (20%)
D	5 (12.5%)	4	4 (10%)

Conclusions

Based on our data, although there is some expression of p16 in ONB, HPV is not associated with this sinonasal malignancy. Further investigation is needed to understand the significance of p16 expression in some ONB tumors.

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