

Human Papillomavirus–Associated Oropharyngeal High-Grade Neuroendocrine Carcinoma in an Adolescent: Case Report and Review of Literature

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ABSTRACT: Oropharyngeal small cell carcinomas (OPSmCC) are rare with only few case reports and case series published in the literature. More recently, an association of these tumors with human papillomavirus (HPV) infection has been detected. However, unlike oropharyngeal squamous cell carcinomas which have a better outcome when associated with HPV, OPSmCC exhibit an aggressive behavior. In this article, we report a case of tonsillar carcinoma arising in a 14-year-old boy that was associated with HPV infection. The tumor exhibited morphologic features of small cell carcinoma with no overt squamous differentiation. Yet, by immunohistochemistry, it showed diffuse and strong co-expression of both squamous and neuroendocrine markers. In addition, we present the clinicopathologic features of all the cases of OPSmCC reported in the literature for which p16 and/or HPV testing have been done.

KEYWORDS: Oropharynx, small cell carcinoma, squamous cell carcinoma, human papillomavirus, pediatric

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Introduction

In the head and neck region, the oropharynx is a preferential site for human papillomavirus (HPV) infection, persistence, and viral-induced tumorigenesis.¹ Human papillomavirus type 16 has been the causative agent in 22% of head and neck squamous cell carcinomas² and has been detected in 81% of oropharyngeal squamous cell carcinomas (OPSqCC).³ The association of HPV with OPSqCC has considerable clinical significance as these tumors have improved survival outcomes and better response to chemotherapy and radiation.⁴

Neuroendocrine carcinomas, on the contrary, are rarely encountered in the oropharynx with only few case reports and case series reported in the literature. In the last few years, an association of high-risk (HR) HPV with oropharyngeal small cell carcinomas (OPSmCC) has been documented,^{5,6} similar to that seen in small cell carcinomas of the uterine cervix.^{7,8}

In this article, we present the case of an HPV-related tonsillar carcinoma in a 14-year-old boy. This carcinoma, while having morphologic features of small cell carcinoma, exhibits an immunophenotype characteristic of both neuroendocrine and squamous differentiation. This case is highly unusual in the young age of the patient and in its immunohistochemical expression profile. In addition, we performed a literature review of all the cases of OPSmCC, for which p16 and/or HPV testing have been done.

Ethical Approval and Informed Consent

Written informed consent was obtained from the patient's guardian/legally authorized representative (father) for the

publication of this case report. Ethical approval is not required for case reports deemed not to constitute research.

Case Presentation

The patient, a 14-year-old Iraqi male, presented with “tonsillitis” and generalized lymphadenopathy. Tonsillectomy was performed and the pathology was interpreted in Iraq as rhabdomyosarcoma. Ultrasonography of the neck showed enlarged cervical lymph nodes. The patient received 6 cycles of chemotherapy (VAC regimen: Vincristine + Dactinomycin + Cyclophosphamide + Mesna) over 4 months. He showed good response to treatment as per his clinician. However, 6 months after discontinuing treatment, he presented again with generalized lymphadenopathy. Whole body positron emission tomography-computed tomography (PET-CT) showed fluorodeoxyglucose (FDG)-avid right cervical (level IIa; 1.9 cm in greatest dimension; SUVmax: 13.8), bilateral axillary (1.1 cm in greatest dimension; SUVmax: 7.83), and inguinal lymph nodes (1 cm in greatest dimension; SUVmax: 4.15). Excisional biopsy of an enlarged cervical lymph node followed by fine-needle aspiration biopsies of the bilateral axillary and inguinal lymph nodes (performed 16 months after his initial presentation) showed involvement by small round cell tumor. Three months later, the patient underwent right parotidectomy and cervical lymph node dissection. Histologic examination showed involvement of the parotid gland, adjacent muscle, and adipose tissue, along with levels II and IV cervical lymph nodes by the same tumor. Apart from the initial VAC chemotherapy regimen that he took upon diagnosis, the patient did



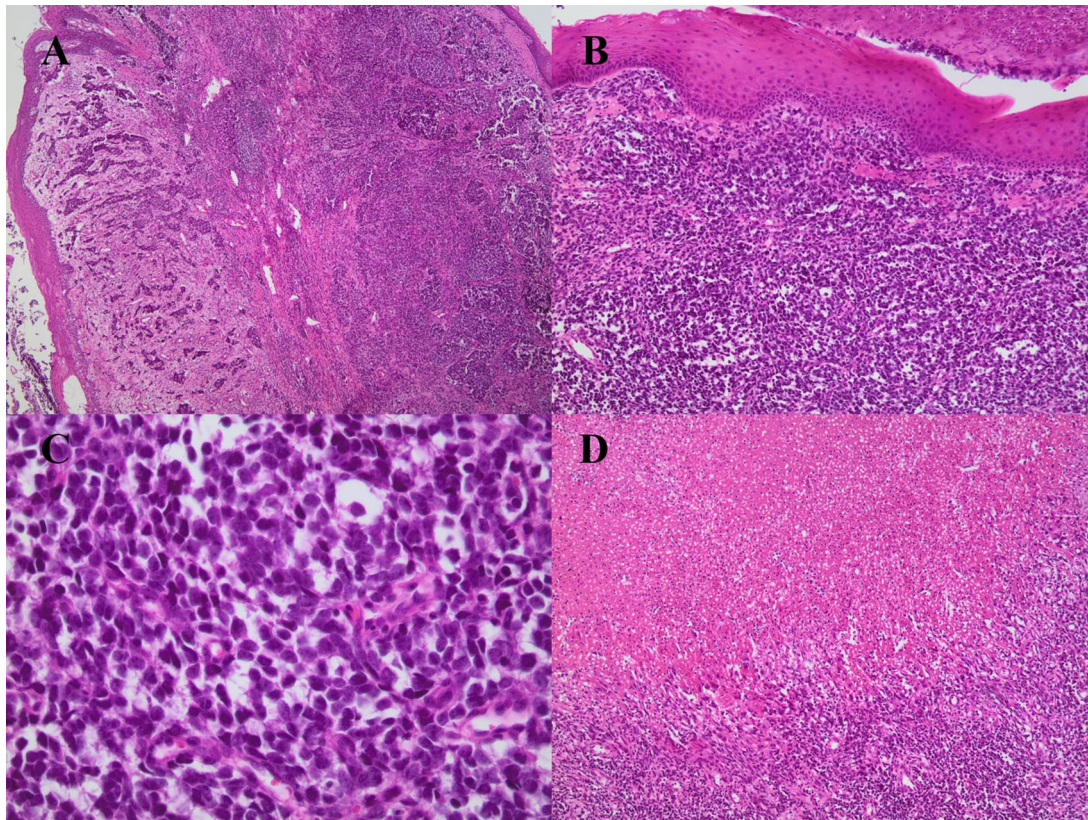


Figure 1. (A) Low power view of the tonsillar mass showing tumor cells arranged in cords, nests, and solid sheets (hematoxylin and eosin stain, 40 \times). (B) The tumor cells are arranged in solid sheets with no dysplasia in the overlying squamous epithelium (hematoxylin and eosin stain, 100 \times). (C) The tumor cells have scant cytoplasm and enlarged, evenly hyperchromatic nuclei that exhibit prominent molding (hematoxylin and eosin stain, 400 \times). (D) Abundant areas of necrosis are identified (hematoxylin and eosin stain, 100 \times).

not receive any additional chemotherapy. At last follow-up (at the time the article was written; 19 months after diagnosis), the patient was alive with disease present. The paraffin blocks and slides of the tonsillar mass were sent to the American University of Beirut–Medical Center (AUB-MC) for review (Note: The patient was managed in Iraq and not at AUB-MC).

Microscopic Findings and Ancillary Studies

Histologic examination of the tonsillar mass revealed an invasive neoplasm with focal ulceration of the overlying squamous epithelium. The tumor cells are arranged in cords, nests, and solid sheets (Figure 1A and B). The cells have minimal cytoplasm and enlarged, evenly hyperchromatic nuclei (Figure 1C). Nucleoli are inconspicuous. Prominent nuclear molding and crush artifact are present. Areas of necrosis are identified (Figure 1D). No obvious squamous differentiation is seen, and there is no dysplasia of the surface squamous epithelium.

By immunohistochemistry, the tumor cells show positivity for 3 neuroendocrine markers, albeit in varying intensities and extent: synaptophysin (diffuse and strong) (Figure 2A), chromogranin (focal and weak), and CD56 (focal). In addition, the tumor cells show expression of squamous markers: p40 (diffuse) (Figure 2B), p63 (diffuse), and cytokeratin (CK) 5/6 (focal) (Figure 2C). CK AE1/AE3 is diffusely positive in the cells. P16 (clone E6H4) shows diffuse nuclear and cytoplasmic positivity

in more than 70% of the cells (Figure 2D). CD99 shows weak positivity in the majority of the tumor cells. All muscle markers (desmin, myogenin, MyoD1, and muscle-specific actin antibody) are negative. The tumor cells are also negative for thyroid transcription factor-1 (TTF-1), nuclear protein in testis (NUT) protein, and CD34. INI1 (SMARCB1) expression is retained, and p53 shows a wild-type pattern of expression.

In situ hybridization (ISH) for HR HPV E6/E7 mRNA was performed at a reference laboratory (Mayo Medical Laboratories, Rochester, MN, USA; Testing done using the RNAscope HPV kit [Advanced Cell Diagnostics, Inc, Hayward, CA, USA] which detects HPV genotypes: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82). The tonsillar mass was positive for high-risk HPV infection as evidenced by ISH positivity for HR HPV E6/E7 mRNA (Figure 3).

The overall findings are consistent with an HPV-positive, oropharyngeal carcinoma that shows morphologic features of small cell carcinoma and immunohistochemical evidence of both squamous and neuroendocrine differentiation.

Discussion

The case presented herein is peculiar in several respects. The young age of the patient (14 years old) is unusual. To our knowledge, no case of OPSmCC has been reported in the pediatric age group. The youngest age reported was 35 years

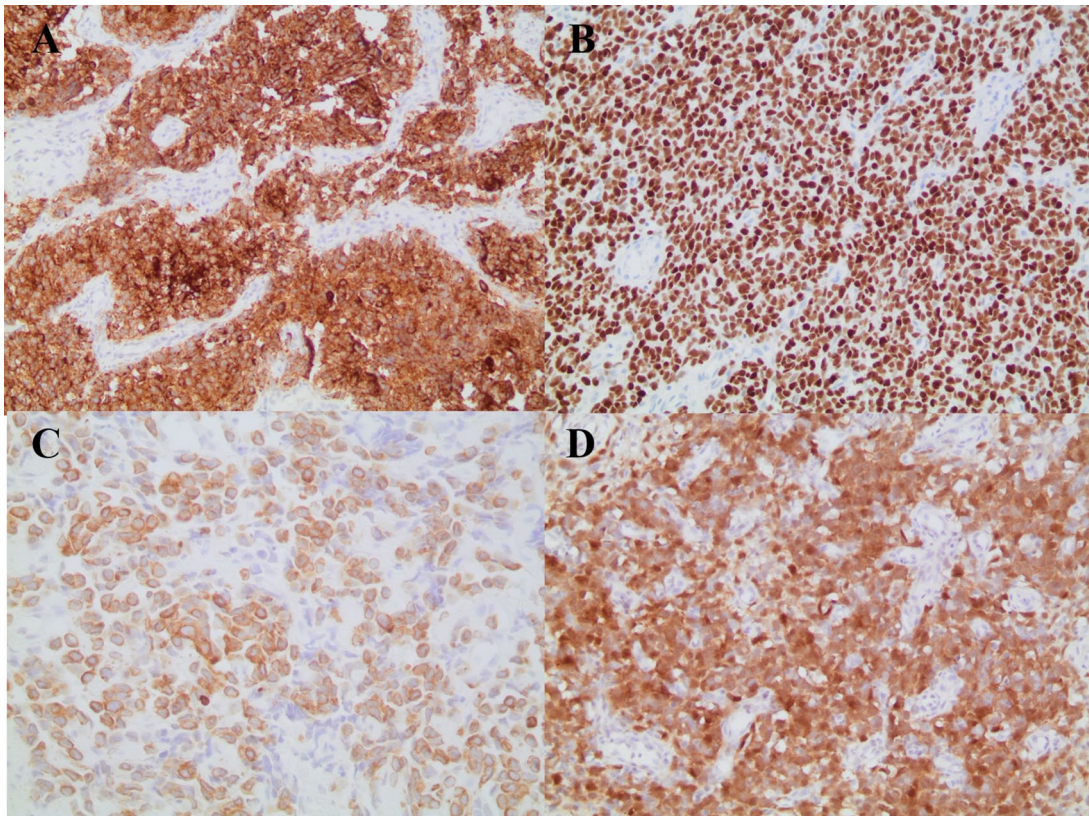


Figure 2. The tumor cells show diffuse positivity for synaptophysin (A) and p40 (B) (200×). (C) Cytokeratin 5/6 is focally positive (400×). (D) p16 shows diffuse nuclear and cytoplasmic positivity (200×).

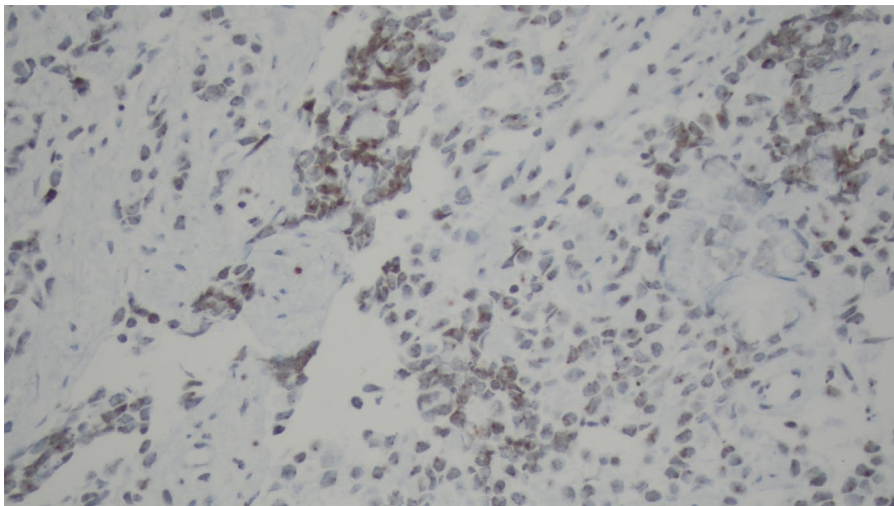


Figure 3. The tumor cells are positive for high-risk HPV E6/E7 RNA chromogenic ISH. HPV indicates human papillomavirus; ISH, in situ hybridization.

old.⁶ This raises some questions about the method of acquisition of HPV in this patient and about the time frame between infection and the development of carcinoma.

The role of high-risk HPV infection in tumorigenesis is well established. Human papillomavirus has a predilection to infect certain mucosal sites such as the genital (cervical, vaginal, and vulvar) and oropharyngeal (particularly tonsillar) mucosa.⁹ Multiple theories have tried to explain why HPV preferentially infects these sites. This tendency may be related to the specific

microenvironment at these sites which makes them more vulnerable to HPV infection. For instance, programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) signaling pathway is selectively activated in the tonsillar crypt epithelium which leads to a decreased T-cell cytotoxic response, thereby facilitating HPV tumorigenesis.¹

Human papillomavirus-related OPSqCC are characterized by a distinct microscopic appearance that is typically non-keratinizing.¹ The tumor cells invade the lymphoid stroma as

Table 1. List of cases of oropharyngeal small cell carcinomas for which p16 and/or HPV testing have been done.

LITERATURE REVIEW	CASE NUMBER	AGE, GENDER	SMOKING	EXTENT OF DISEASE AT PRESENTATION/ PRESENTING SYMPTOMS	FOLLOW-UP (MONTHS)	P16	HPV STATUS (TYPE, IF AVAILABLE)	ASSOCIATED SQUAMOUS COMPONENT
Bishop and Westra ⁵	1	65, F	+	Lung metastases	DWD (6)	+	+(HPV 16)	Present in 4 of the 5 HPV-positive cases (was synchronous in 3 of the 4 cases)
	2	67, M	+	Neck metastases	DWD (15)	+	+(HPV 16)	
	3	67, M	+	Epistaxis	NED (20)	+	+	
	4	55, M	-	Neck metastases	DWD (9)	+	+(HPV 16)	
	5	49, M	-	Neck metastases	NED (5)	+	+(HPV 16)	
	6	72, M	+	Odynophagia	DWD (12)	+	-	
	7	66, M	+	Neck metastases	DWD (12)	-	-	
	8	63, M	N/A	Odynophagia	DWD (9)	+	-	
	9	83, M	N/A	Oropharyngeal mass	DWD (2)	-	-	
Kraft et al ⁶	10	63, M	N/A	N/A	N/A	+	+(HPV 18)	+
	11	67, M	+	Neck metastases	NED (25)	+	+(HPV 16)	-
	12	48, M	+	Local	Neck and distant metastases (14)	+	+(HPV 33)	-
	13	65, M	+	Brain metastases	Distant metastases (10)	+	+	-
	14	35, F	N/A	Neck metastases	NED (150)	+	-	-
	15	57, M	+	Neck metastases, lung metastases	Recurrence and distant metastases (9)	+	+	-
	16	56, M	+	Neck metastases	N/A	+	+	-
	17	82, F	+	Neck metastases	Distant metastases (7)	-	N/A	-
Hojilla et al ¹³	18	50, M	+	Neck metastases	NED (8)	+	+(HPV 16)	-
Kaka et al ¹⁴	19	78, F	+	Oropharyngeal mass	Distant metastases (12). DWD.	+	- By ISH	+(Metachronous; history of oral cavity squamous cell carcinoma)
	20	58, M	+	Neck metastases	Distant metastases, found 6 months after treatment. DWD.	+	+	+
Bates et al ¹⁵	21	64, F	+	Neck metastases	DWD (15)	+	+(HPV 18)	-
	22	59, M	N/A	Neck metastases	DWD (26)	+	+(HPV 16)	-
Alos et al ¹⁶	23	59, M	+	Stage IV	DWD (14)	+	-	-
Misawa et al ¹⁷	24	81, F	-	Neck metastases	DWD (22)	+	+(HPV 16)	-
	25	54, M	+	Neck metastases	DWD (10)	+	+(HPV 18)	-

(Continued)

Table 1. (Continued)

LITERATURE REVIEW	CASE NUMBER	AGE, GENDER	SMOKING	EXTENT OF DISEASE AT PRESENTATION/ PRESENTING SYMPTOMS	FOLLOW-UP (MONTHS)	P16	HPV STATUS (TYPE, IF AVAILABLE)	ASSOCIATED SQUAMOUS COMPONENT
Nakano et al ¹⁸	26	59, M	+	Neck metastases	Distant metastases. DWD (12)	+	N/A	+
Bonomi et al ¹⁹	27	56, M	-	Neck metastases	NED (3 months after therapy)	+	+(HPV 16)	-
Takasugi et al ²⁰	28	78, M	+	Enlarged lymph nodes in the neck and mediastinum (clinical stage IV A)	NED (16)	+	N/A	-
Fecher et al ²¹	29	64, F	-	Neck metastases	Distant metastases (6)	+	N/A	+ (Cervical lymph node: both small cell and squamous carcinomas. Primary tonsillar tumor: pure small cell carcinoma)
Ho et al ²²	30	69, M	+	Neck metastases. pT1N2bM0	Distant metastases. DWD (26)	+	+	- (Not very clear)
Current case	31	13, M	-	Tonsillitis. Probable multiple lymph node metastases	Metastases to cervical, axillary, and inguinal lymph nodes. Involvement of parotid gland (19)	+	+	No obvious squamous features on morphology but positive for squamous markers by IHC

Abbreviations: DWD, died with disease; F, female; HPV, human papillomavirus; IHC, immunohistochemistry; ISH, in-situ hybridization; M, male; N/A, not available; NED, no evidence of disease.

sheets and lobules, with central necrosis often present within the lobules.¹ The cells have an immature basaloid appearance with high nuclear to cytoplasmic ratio and syncytial cytoplasm.¹ Unlike non-HPV-associated OPSqCC, surface dysplasia and a strong desmoplastic stromal reaction are typically absent.¹ These morphologic features may overlap with small cell carcinoma which is rarely encountered in the oropharynx and has, also, been found to be associated with HPV infection.^{5,6} However, OPSmCC exhibit an aggressive behavior and have a much more dismal outcome when compared with OPSqCC.^{5,6}

There are several possible modes of transmission of HPV. Sexual contact is believed to be the most common mode in both children and adults.¹⁰ Other modes include non-sexual contact and maternal transmission.^{10,11} Maternal transmission can occur in various ways, prenatally or perinatally, including via the amniotic fluid and through direct exposure during delivery.¹⁰⁻¹² Most neonatally acquired HPV occurs through vertical transmission.¹² No information is available about the HPV status of the patient's mother in this case.

The accurate estimation of the time between HPV infection and the development of carcinoma remains difficult to determine. This is due to many reasons including the difficulty in

determining the time of infection and in determining the incubation period of HPV which can produce latent infections that can reactivate after many years.¹¹

Review of the literature revealed 30 patients with OPSmCC for which p16 and/or HPV testing (by ISH and/or polymerase chain reaction [PCR]) have been done (Table 1).^{5,6,13-22} The ages of the patients ranged from 35 to 83 years with a mean age of 63 years. There is a male predominance with a 3.3:1 male to female ratio. Of 25 patients (80%), 20 were either current or former smokers; 60% of patients (18 of 30 patients) had cervical lymph node metastases at presentation (with no evidence of distant metastases), 17% (5 patients) had distant metastases, and at least 3 patients had localized disease (10%). The extent of disease at presentation was not clear in 4 patients. These findings indicate that it is common for patients with OPSmCC to have nodal metastases and distant hematogenous metastases (such as to the lungs and brain) at initial presentation. It is, therefore, important to consider this entity in the workup of patients presenting with metastases, especially cervical nodal metastases, with an unknown primary tumor.

P16 was positive in 90% of OPSmCC (27 of 30 cases). Human papillomavirus was detected, by ISH and/or PCR, in 19 of 26 cases (73%). Of the 13 cases in which HPV genotyping

was performed, HPV 16 was the most common subtype (9 cases; 69%), followed by HPV 18 (3 cases; 23%) and HPV 33 (1 case; 8%). The percentage of detection of HPV in OPSmCC (73%) approaches that seen in OPSqCC where HPV 16 was detected in 81% of OPSqCC.³ These findings are in contrast with small cell carcinomas of the lung which were found not to be associated with high-risk HPV infection.²³ On the contrary, small cell carcinomas of the uterine cervix have been shown to be associated with high-risk HPV infection, with HPV 18 being the most prevalent subtype.^{7,8} Five of the 24 cases (21%) that were positive for p16 (and HPV testing was performed) were negative for HPV by ISH and/or PCR. In a study done by Alos et al, 14 of 19 cases (73.7%) of high-grade neuroendocrine carcinomas of the head and neck, one of which was an oropharyngeal carcinoma, showed strong and diffuse positivity for p16 but were negative for HPV by ISH and PCR.¹⁶ These findings indicate that while p16 is a good surrogate marker for HPV infection in OPSqCC,^{24,25} it may not be as good a surrogate marker in high-grade neuroendocrine carcinomas of the head and neck.¹⁶ The expression of p16 in HPV-negative, high-grade neuroendocrine carcinomas of the head and neck may be attributed to the dysregulation of the p16/RB/cyclin D1 pathway through the loss or inactivation of RB1.¹⁶

Of the 17 patients in whom HPV was detected and follow-up data were available, 53% (9 patients) died of their disease, 6 to 26 months after diagnosis (mean: 16 months); 29% (5 patients) had no evidence of disease at last follow-up (3–25 months); and 35% (6 patients) developed distant metastases during the course of their disease. The presence of HPV does not appear to confer a prognostic advantage in OPSmCC, as is seen in squamous cell carcinomas in which HPV detection is associated with a much better overall survival.^{5,6} This aggressive behavior is similar to that seen in small cell carcinomas of the uterine cervix which are associated with early distant metastases and low survival rates.^{5,8} The patient presented in this article was alive at last follow-up (19 months after diagnosis), despite not receiving additional chemotherapy (apart from the 6 cycles of VAC regimen that he initially took). He had, however, evidence of locoregional disease with metastases to cervical, axillary, and inguinal lymph nodes.

Interestingly, 30% (9 of 30 cases) of OPSmCC occurred in association with squamous cell carcinomas.^{5,6,14,18,21} In 7 cases, both the small cell and squamous components were present next to each other. In the other 2 cases, the small cell component occurred at the site where a previous squamous cell carcinoma was present.^{5,14} In the case reported by Fecher et al, the cervical nodal metastasis was composed of both small cell and squamous components, whereas the tonsillar mass was composed of pure small cell carcinoma.²¹ In all those cases, however, the small cell carcinoma was morphologically and immunohistochemically distinct from the squamous cell carcinoma, with the small cell component being positive for neuroendocrine markers and negative for squamous markers and

the squamous component exhibiting an opposite phenotype. Both components were positive for p16 (when tested). Human papillomavirus was detected in both components in 6 cases^{5,6,14} and was negative by ISH in 1 case.¹⁴ In 2 cases, HPV testing was not performed.^{18,21}

The oropharyngeal carcinoma presented in this article showed immunohistochemical expression of both neuroendocrine and squamous markers, though no 2 distinct components were evident by morphology. It showed strong and diffuse positivity for synaptophysin and focal staining with chromogranin and CD56. It, also, showed strong and diffuse positivity for p63 and p40, and focal positivity with CK5/6. In all of the reported cases of OPSmCC, none showed such strong co-expression of squamous markers. Even in the cases where a squamous cell carcinoma occurred next to the small cell carcinoma, both tumors (squamous cell and small cell carcinomas) had distinct morphology and expression profiles. In a study done by Bishop and Westra, 4 of 8 cases of OPSmCC were positive for p63, while none was positive for CK5/6.⁵ In another study by Serrano et al, 17 of 19 (89%) high-grade neuroendocrine carcinomas of the head and neck were positive for p63, while 4 of 19 cases (21%) showed positivity for CK5/6.²⁶ P63, while being a useful marker in the distinction between lung squamous cell and small cell carcinomas, is not useful in the distinction in head and neck carcinomas.^{5,26} High molecular weight cytokeratins, including CK5/6, however, are more useful in the distinction.^{5,24} The strong and diffuse p63 and p40 and focal CK5/6 expression seen in the present case argue for the presence of squamous differentiation in this high-grade neuroendocrine carcinoma, even though the tumor had a morphologic appearance of small cell carcinoma with no obvious squamous features seen.

The differential diagnosis in the presented case includes small, round, blue cell tumors that occur in the pediatric age group. These include rhabdomyosarcoma which is excluded by the negative staining for muscle markers (myogenin, MyoD1, desmin, and muscle-specific actin antibody). The diffuse, but weak, positivity for CD99, seen in this case, can be a potential pitfall for the diagnosis of Ewing sarcoma, which is another entity in the differential diagnosis. CD99 is a non-specific stain for which positivity, when present, should be interpreted with great caution. The diffuse positivity for squamous and neuroendocrine markers in this case excludes Ewing sarcoma. NUT midline carcinoma and INI1-deleted carcinomas are also in the differential diagnosis. They were ruled out by the absence of expression of the NUT protein by immunohistochemistry and retention of INI1.

The distinction between HPV-related oropharyngeal small cell and squamous cell carcinomas, though difficult, is important to make. This is mainly due to the aggressive behavior associated with small cell carcinoma, as opposed to its squamous counterpart, in whom HPV infection imparts a significantly better outcome.⁶ In this article, we presented the case of an HPV-related tonsillar carcinoma, arising in an adolescent

male, which exhibited features of both small cell and squamous cell carcinomas. Although the prognosis of such tumors is dismal, the patient presented herein was doing relatively well despite being off chemotherapy.

Author Contributions

All authors contributed to the preparation and critical revision of the manuscript. All authors approved the manuscript for submission.

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