Asymptomatic p16-Positive Oropharyngeal Squamous Cell Carcinoma
An Emerging Trend

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The rise in incidence of oropharyngeal squamous cell carcinoma (OPSCCa) in the United States is largely attributed to human papillomavirus (HPV).1 While the other types of head and neck cancers have decreased with the declining prevalence of tobacco use, the rapid increase of HPV–associated oropharyngeal cancer has demonstrated a need for new strategies in prevention, diagnosis, evaluation, and treatment.2 Despite patients frequently presenting with advanced disease and poorly differentiated histologic characteristics, HPV-related oropharyngeal cancer is typically associated with a favorable prognosis because it responds well to treatment.3

The epidemiology of HPV-associated oropharyngeal cancer is distinctly different than that of HPV-negative oropharyngeal cancer.4 The HPV-associated disease often afflicts younger cohorts with sexual behavior risk factors and minimal alcohol or tobacco use and is diagnosed at an early T stage with frequently advanced N stage.5 The epidemiologic differences in HPV-associated head and neck cancers may also lead to an emerging trend of incidentally noted asymptomatic early-stage HPV-associated oropharyngeal cancer, if detected prior to development of nodal metastasis. Early-stage tumors are typically associated with an excellent prognosis and are frequently treated with single modality therapy.6 For OPSCCa, p16 is now commonly used as a surrogate marker for HPV-associated disease. Herein, we describe 5 patients found to have completely asymptomatic primary site p16-positive squamous cell carcinoma during workup for other nonrelated medical problems. Four patients were found with early T-stage disease without nodal metastasis, and underwent surgical treatment as a single modality. One patient had advanced-stage disease and underwent chemoradiation. At a mean follow-up of 12.6 months, all patients remained disease free.

Methods
Patients incidentally diagnosed as having OPSCCa were identified based on clinical experience at a tertiary-care academic medical center from July 1, 2011, to July 1, 2013. Patients were selected only if they were diagnosed as having an asymptomatic primary site p16-positive tumors found during workup for other nonrelated medical problems. Four patients were found with early T-stage disease without nodal metastasis, and underwent surgical treatment as a single modality. One patient had advanced-stage disease and underwent chemoradiation. At a mean follow-up of 12.6 months, all patients remained disease free.

CONCLUSIONS AND RELEVANCE With the rise of p16-positive oropharyngeal squamous cell carcinoma and lack of screening technologies for early-stage disease, purely incidentally diagnosed disease might increase in incidence. These findings underscore the importance of a comprehensive physical examination on all patients. Although follow-up is too limited for definitive conclusions, early experience suggests that these patients can be treated with unimodality therapy when presenting with stage I or II disease.

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OBSERVATIONS A total of 134 patients with p16-positive oropharyngeal cancer were identified. Of these patients, 5 (3.7%) were identified as having completely asymptomatic primary site p16-positive tumors found during workup for other nonrelated medical problems. Four patients were found with early T-stage disease without nodal metastasis, and underwent surgical treatment as a single modality. One patient had advanced-stage disease and underwent chemoradiation. At a mean follow-up of 12.6 months, all patients remained disease free.

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head and neck incidentalomas using PubMed was performed. Medical records from the Washington University School of Medicine–Siteman Cancer Center head and neck multidisciplinary tumor board were used to obtain the total number of cases of p16-positive OPSCCa evaluated at our institution during the study period. All patients were noted to be p16 positive by immunohistochemical analysis of their pathologic specimens.

**Results**

A total of 134 patients, derived from multidisciplinary head and neck tumor board patient listings, were treated at the Washington University School of Medicine–Siteman Cancer Center with p16-positive OPSCCa during the time period included. Of these patients, 5 (3.7%) had their cancers identified incidentally and were asymptomatic. A summary of the patient characteristics is included in the Table. The median age of the 5 patients was 58 years (range, 56–73 years). Three of the 5 patients had their tumors discovered by physical examination either in the office or during an unrelated operative procedure. One patient’s tumor was identified in a pathology specimen from a tonsillectomy performed as part of an obstructive sleep apnea procedure. One patient’s tumor was identified based on a radiologic finding. Four of the 5 patients had stage T1 tumors without clinical nodal disease, and they were treated with transoral surgical resection and elective neck dissection. These patients were all found to have pT1N0M0 stage disease. These individuals did not receive any subsequent adjuvant therapy and were disease free after a median of 14 months of follow-up (range, 6–24 months). The fifth patient was referred for a large leukoplakic lesion on the right ventral aspect of the tongue but was found by physical examination to have an asymptomatic and previously unrecognized cT3N2b cancer of the left tonsil. This patient was treated with chemoradiation therapy and remained disease free 6 months after completion of therapy.

<table>
<thead>
<tr>
<th>Patient No./Age, y</th>
<th>Presenting Medical Problem</th>
<th>Method of Identification of OPSCCa</th>
<th>Tumor Location and Clinical Stage</th>
<th>Treatment</th>
<th>Outcome Following Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/57</td>
<td>Left cerumen impaction</td>
<td>Physical examination</td>
<td>Right tonsil, T1N0M0</td>
<td>Transoral resection + neck dissection</td>
<td>No evidence of disease at 24 mo</td>
</tr>
<tr>
<td>2/56</td>
<td>Obstructive sleep apnea treated with tonsillectomy and UPPP</td>
<td>Pathologic characteristics of tonsil specimen</td>
<td>Right tonsil, T1N0M0</td>
<td>Transoral resection + neck dissection</td>
<td>No evidence of disease at 6 mo</td>
</tr>
<tr>
<td>3/73</td>
<td>Lung nodule</td>
<td>Radiology</td>
<td>Right tonsil, T1N0M0</td>
<td>Transoral resection + neck dissection</td>
<td>No evidence of disease at 10 mo</td>
</tr>
<tr>
<td>4/58</td>
<td>Vocal fold paralysis following spine surgery</td>
<td>Physical examination</td>
<td>Left tonsil, T1N0M0</td>
<td>Transoral resection + neck dissection</td>
<td>No evidence of disease at 17 mo</td>
</tr>
<tr>
<td>5/73</td>
<td>Right oral tongue leukoplakia</td>
<td>Physical examination</td>
<td>Left tonsil, T3N2bM0</td>
<td>Chemoradiotherapy</td>
<td>No evidence of disease at 6 mo</td>
</tr>
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</table>

Abbreviation: UPPP, uvulopalatopharyngoplasty.

**Discussion**

With the rise of p16-positive oropharyngeal cancer presenting with advanced-stage disease, there is a significant need for new technologies for early detection. As secondary prevention by HPV detection and cervical cytologic detection lead to a decline in cervical cancer incidence, a similar strategy has been suggested in HPV-associated oropharyngeal cancer. However, a Papanicolaou test equivalent used in high-risk individuals likely will have limited utility as a screening modality. Part of this difficulty is that an HPV-induced oropharyngeal premalignant lesion has not yet been identified. In addition, these cancers are thought to initiate in the deep crypts of the tonsils that are not accessible to surface cytologic collection methods. Thus, primary prevention with prophylactic HPV vaccination has been highlighted as the most likely opportunity for decreasing the future incidence of this disease, although studies addressing the efficacy of HPV vaccination and subsequent prevention of HPV-associated OPSCCa have not been performed.

Incidently identified lesions found during routine physical examination or imaging can lead to the discovery of early-stage malignant neoplasms. During head and neck physical examinations, incidentally noted tonsil asymmetry is a frequently encountered clinical dilemma. Pathologic study of surgically removed asymmetric tonsil specimens has identified an occult malignancy rate of approximately 5%. These data produce a clinically difficult situation because 20 patients with asymmetric tonsils would need to undergo surgery to identify a single malignant neoplasm. Furthermore, incidental malignant disease identified during microscopic pathologic evaluation of grossly normal tonsillectomy specimens is even smaller, with some studies demonstrating an occult malignancy rate of just 0.5%. This has produced an argument that the use of microscopic pathological analysis for normal tonsillectomy specimens may result in unnecessary cost and use of resources. However, surgical removal of asymmetric tonsils or microscopic analysis of grossly normal tonsil speci-
mencens may be indicated in patients with various risk factors or high clinical suspicion.

In the current era of high-definition imaging, head and neck incidental findings are frequently noted in patients undergoing radiography for various nonotolaryngologic indications. In addition, the prevalence of positron emission tomographic (PET) scanning use has greatly risen in the workup of various malignant neoplasms, leading to numerous incidental findings of unclear importance. One study evaluated incidentally identified lesions of the head and neck during PET scanning for known or suspected malignant neoplasms in nonhead and neck areas. The investigators identified a 2.4% prevalence of incidentally discovered lesions with high standardized uptake values in the head and neck. Further diagnostic testing of these patients ultimately revealed an otolaryngologic malignant neoplasm in 21%. Identification of incidental thyroid nodules by computed tomographic imaging, magnetic resonance imaging, or PET is another frequently described event. The malignancy rate for incidentally discovered thyroid nodules on imaging has been reported as high as 34.8%, confirming the need to carefully work up this finding.

We present 5 patients who were identified as having asymptomatic p16-positive oropharyngeal carcinoma discovered by a variety of methods: clinical examination, radiologic studies, and pathologic examination. Four of these patients were found to have early-stage disease. One patient was identified as having advanced-stage disease and had been evaluated by several previous clinicians for tongue leukoplakia. His asymptomatic contralateral p16-positive cT3 tonsil cancer, however, was not noted until his appointment with the head and neck surgeon. The emergence during the past few years at our institution of incidentally identified p16-positive OPSCCa is likely the result of the evolving landscape in oropharyngeal carcinoma.

Conclusions

The epidemiology of OPSCCa is changing which has led to an increase in the incidence of p16-positive OPSCCa. There are currently no available screening technologies to detect early primary site disease. Resultantly, purely incidentally diagnosed HPV-associated OPSCCa may increase in incidence. During the past 2 years at our institution, this phenomenon has accounted for 3.7% of all patients (5 of 134) evaluated for p16-positive OPSCCa. These data will be used as a baseline for tracking the incidence of this condition in the upcoming years. While experience with these patients is very limited, initial observations suggest that patients with incidentally identified disease can present at an early stage and have a favorable prognosis, potentially with unimodality therapy.