

Case Report

Distinguishing between HPV-Associated Metastatic Anal Squamous Cell Cancer and HPV-Associated Oropharyngeal Cancer

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The histology and immunohistochemistry (IHC) of primary and metastatic diseases from a human papilloma virus- (HPV-) related anal squamous carcinoma (ASCC) would typically demonstrate the same histology as an HPV-related oropharyngeal squamous carcinoma (OPSCC). However, determining whether a site of squamous cell carcinoma represents distant metastatic ASCC versus a metastatic HPV-related metastasis from an OPSCC to a regional lymph node carries profound prognostic and therapeutic implications. A patient with a history of locally advanced ASCC treated with standard concurrent radiation therapy and chemotherapy in 2015 is described. In 2018, an enlarged supraclavicular lymph node was excised demonstrating squamous cell carcinoma and radiographic staging revealed no other areas suspicious for malignancy. Direct laryngoscopy with operating telescope and biopsies demonstrated squamous cell carcinoma at the tongue base. Described here are assays that might be considered in distinguishing between whether a focus distant from a previously identified ASCC represents metastatic disease or instead a separate primary HPV-related cancer.

1. Introduction

The incidence of HPV-related ASCC and that of HPV-related OPSCC are rising [1]. By histology and IHC evaluation, HPV-related separate ASCC and OPSCC primaries would typically be similar or identical. Promising assays and currently available tests to help distinguish the likely origin of the squamous cell carcinoma in the supraclavicular lymph node and at the tongue base are reviewed as well as clinical considerations. Distinguishing between a focus of metastatic disease from a known HPV-related primary carcinoma versus metastatic disease from a different HPV-related primary carcinoma remains challenging.

2. Case Presentation

A 54-year-old woman underwent an anal canal/rectal mass biopsy on 6-6-2015 which showed invasive moderately differentiated squamous cell carcinoma with basaloid features. Computerized tomography (CT) of the chest/abdomen/pel-

vis suggested involvement of the regional, but not distant lymph nodes. She completed concurrent radiation and chemotherapy (5-fluorouracil (5-FU) and mitomycin C) on 8-12-2015. On 12-14-2018, a CT scan chest/abdomen/pelvis showed no evidence of metastatic disease.

After discovery on routine examination by her primary physician, she underwent excision on 12-26-2018 of an asymptomatic left enlarged supraclavicular lymph node which showed “metastatic squamous cell carcinoma, largest focus measuring 17 mm”. Immunohistochemical (IHC) staining was p16 positive in both the anal canal biopsy and the supraclavicular lymph node. HPV HR type 16 PCR testing of the supraclavicular lymph node was positive. On 1-7-2019, she received FOLFOX chemotherapy (5-FU/leucovorin/oxaliplatin) for presumed metastatic ASCC.

On 2-12-2019, positron emission tomography/CT scan showed no FDG avid masses and only “low level increased fluorodeoxyglucose (FDG) uptake in the supraclavicular lymph node resection bed, consistent with granulation tissue.” On 3-1-2019, a repeat CT chest/abdomen/pelvis again

showed no evidence of metastatic disease. On 3-14-2019, the patient underwent a direct laryngoscopy with operating telescope and biopsies. Findings included “normal appearing tongue, vallecular, and epiglottis.” Random tongue biopsies revealed “left tongue base biopsy: p16 positive basaloid squamous cell carcinoma.” Additional staging followed by concurrent radiation and chemotherapy was planned for an apparent carcinoma of the tongue base, metastatic to a left supraclavicular lymph node.

The uncertainty of the diagnosis (supraclavicular lymph node involvement by ASCC versus involvement by OPSCC), the standard therapies, and expected outcomes for each of the possibilities were explained to the patient and she elected to proceed with standard therapy for OPSCC. On 4-2-2019, radiation (66 Gy in 33 fractions) with concurrent cisplatin (100 mg/m² every 28 days) was initiated for OPSCC metastatic to a supraclavicular lymph node. She had received two cycles of cisplatin and completed radiation on 5-17-2019. Follow-up scanning is planned.

3. Discussion and Conclusions

Both ASCC and OPSCC are commonly related to human papillomavirus mucosal infection and malignant transformation. In the case described, because of the histologic similarity between the primary ASCC (2015), the excised supraclavicular lymph node (2018), and the tongue base biopsy (2019), there would appear to be three most likely possibilities. It is possible that the patient has metastatic ASCC to a supraclavicular lymph node and tongue base. Standard first-line therapy for this possibility would be systemic platinum-based combination chemotherapy. Alternatively, the patient could have metastatic ASCC to the supraclavicular lymph node or, although rare, HPV-related skin cancer or other cancer metastatic to the lymph node and, in addition a separate OPSCC (primary tongue base cancer). For this possibility, one could consider systemic platinum-based chemotherapy for the metastatic ASCC preceded or followed by definitive radiation or resection of the primary tongue base cancer with or without ipsilateral or bilateral neck dissection (with curative intent for the tongue base cancer). The third possibility is that the patient has a tongue base OPSCC metastatic to the supraclavicular lymph node which would be initially treated with curative-intent concurrent radiation and chemotherapy, as described above for the patient in this report. As can be seen, the treatment and outcomes expected for each of these possibilities would be very different.

If the patient in fact has metastatic ASCC to either or both the supraclavicular lymph node and tongue base, her disease would be considered incurable, with palliative chemotherapy or immunotherapies being endorsed based on modest response rates [2]. If the cancer was instead a primary OPSCC metastatic to the supraclavicular lymph node, then the cancer would be considered potentially curable with multimodality therapy [3].

Harlé et al. very recently reported applying capture-based next-generation sequencing (NGS) (CaptHPV) to the ASCC of a patient who was later found to have squamous cell cancer involving his tongue. CaptHPV assay allows for the identifi-

cation of the physical state, viral load, insertion site, and presence of genomic alterations in the specimen evaluated for 245 different HPV genotypes. Based on the HPV insertional signature, the authors concluded that “We show that the identity of these two cartographies in the two tumors unambiguously demonstrates that the lingual tumor derived from the anal carcinoma” [4]. Based on their work, if the CaptHPV assay was applied to the tissues from our patient described above and the tumors showed identical cartographies, it would seem reasonable to conclude that our patient has metastatic ASCC to a supraclavicular lymph node and tongue base. In spite of their conclusion, a solitary metastases to the tongue (as described by Harlé et al.) would be a remarkably unusual diagnosis. Therefore, it also seems reasonable to consider the possibility that in a particular patient with separate HPV-related primary cancers, the insertional cartographies could be the same.

Roth et al. also used molecular profiling to help determine whether a patient more likely had metastatic ASCC to the lung versus a primary squamous cell carcinoma of the lung. Both tumors were histologically similar. In spite of both tumors being HPV16 positive (which suggests a nonlung origin of the pulmonary lesion), the authors performed allelotyping for loss of heterozygosity (LOH) on the two tumors for a “broad panel of LOH cancer-associated markers.” Based on the concordance seen, they concluded that these results taken together “confirmed the histopathological impression of anal SCC” [5].

On the other hand, if the molecular profiles are different in the ASCC compared to the tongue and supraclavicular tumors, can one conclude that the tumors are clearly from separate tissues of origin? Gao and Smith reported that the molecular profile (using NGS) for “OPSCC appears distinct from cervical cancer” [6]. However, Koncar et al. used immunohistochemistry and molecular profiling to study 743 p53 wild-type HPV-related cancers (including anal, OPSCC, cervical, and vulvar cancers) and concluded that “no gene had a statistically significant difference in mutation frequency or copy number between the four different types of squamous cell carcinoma. The only significant differences between cohorts were frequency of ERCC1 and SPARC loss as determined by IHC” [7].

Also, there are no reports regarding whether there are frequent changes in the molecular profiles of HPV-derived anal or OPSCC cancer when comparing metastatic to primary disease [4]. As a result, finding a difference in NGS from possible metastatic disease might imply different tissues of origin but could alternatively imply a change in the profile between metastatic and primary disease.

In summary, determining whether a focus of HPV-related squamous cell carcinoma represents metastatic spread from an ASCC primary or a second HPV-related primary carcinoma can be challenging. Currently, the likelihood of recurrence after definitive treatment for an ASCC, the time since definitive treatment of the ASCC, and the radiographic sites of apparent recurrence are used to distinguish whether a radiographically or clinically identified site of disease distant from the primary ASCC likely represents metastatic ASCC versus metastatic disease from an HPV-related OPSCC. A

conventional search for a non-ASCC primary should be initiated once the possibility that a non-ASCC HPV-related cancer is suggested, and biopsies of normal-appearing oral pharyngeal mucosa—including diagnostic tonsillar biopsies—should be strongly considered or even mandatory when the possibility of OPSCC is raised.

The case presented illustrates how evaluating for an occult OPSCC primary and—as the assay becomes more widely available—how the use of CaptHPV NGS might aid in distinguishing whether a site of squamous cell malignancy represents metastatic ASCC or instead metastatic OPSCC in a patient with a history of ASCC. If clinically and radiographically the disease appears to metastatic then, particularly if the molecular profiling is identical or very similar, it seems reasonable to conclude that the new focus represents metastatic disease. Findings from future studies comparing the molecular profiles of different HPV-related cancers and comparing the molecular profiles of primary and metastatic diseases from patients with known metastatic HPV-related cancer might be useful in planning strategies to distinguish whether a distant focus of squamous cell carcinoma represents metastatic ASCC or is instead derived from a second HPV-related primary.

Ethical Approval

Approval is waived by the institution where this patient was evaluated and treated.

Consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflicts of Interest

The author declares that there are no conflicts of interest regarding the publication of this article.

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