

A 49-Year-Old Man With an Oral Lesion

Ronald N. Rubin, MD^{1,2}—*Series Editor*

A 49-year-old healthy man has been referred for evaluation from a dental office. During a routine cleaning visit, the dentist noted an irregular red lesion with a whitish central area near the man's left tonsil.

More detailed history reveals several weeks to months of mild discomfort with swallowing. He has had no earache, cough, dysphagia, or other local symptoms. He is a white-collar worker who works in sales. He had smoked casually when younger,

but he has not done so for the past 15 years. He consumes alcohol only socially, perhaps once a week.

Physical examination reveals normal vital signs. Focusing on the reason for referral, an irregular, round lesion measuring several centimeters is present where the left tonsil meets the palate. The lesion is mainly red but has white areas centrally. Results of a careful examination of the neck and supraclavicular and submandibular areas are negative for adenopathy.

Which one of the following is the most accurate and correct statement regarding this patient's case?

- A. Fine-needle aspiration (FNA) is the procedure of choice for initial biopsy of either the suspected primary lesion or any palpable lymph nodes.
- B. The more favorable prognosis and natural history of human papillomavirus (HPV)-associated tumors allows for less-intensive therapy regimens to be used with equivalent efficacy.
- C. The patient's prognosis can be further improved by administering the HPV vaccine.
- D. HPV-related head and neck cancers are now far more common than traditional alcohol- and tobacco-related forms in the United States.

Answer: D, HPV-related head and neck cancers are now far more common than traditional alcohol- and tobacco-related forms in the United States.

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This vignette illustrates the very striking changes in the spectrum of head and neck cancer. In the past several decades, substantive changes in human behavior have resulted in just as substantive and very marked alterations in the biology, pathophysiology, demographics, and prognosis of head and neck cancer (still essentially always squamous cell carcinomas) in the United States.

These statements allow me to invest a short paragraph or two with another vignette, historically accurate, to demonstrate this marked contrast of the "old" vs the "new" head and neck cancer. The case involved a 62-year-old retired Army officer who presented with persistent severe sore throat—more

TAKE-HOME MESSAGE

Head and neck cancer, almost always squamous cell carcinoma, still accounts for some 3% of new cancer diagnoses in the United States. A remarkable shift in demographics has occurred in recent decades, with the traditional older male-dominated, alcohol/tobacco-induced case mix being widely replaced by younger patients with HPV-induced lesions. The demographic shift is due to the simultaneous dramatic decrease in tobacco use coupled with changes in sexual practices over this period. Established practice guidelines for diagnosis (often FNA), HPV marker studies on the specimens, classical TNM staging, and aggressive combined modality therapies have resulted in improved prognosis, both functionally and in morbidity/mortality. HPV vaccination in younger people is expected to be significantly preventative over time to further diminish the incidence of these tumors.

specifically, painful swallowing when he ate. A social history revealed significant alcohol intake that was consistent with and not unusual for his line of work and the times. He also used tobacco very heavily. In addition, the man's lifelong sporadic pipe and cigar consumption radically increased when, following his significant military victories, photographs of him in national newspapers showed him with cigar in hand. A grateful public proceeded to send him more and more cigars—up to 10,000 boxes! This resulted in his becoming a cigar chain smoker at the rate of 20 per day for many years.

With this background, when his doctors examined him, not surprisingly, a large lesion was present on the right tonsillar pillar at the base of the tongue, precisely where the end of a cigar and its smoke jet might sit in a right-handed man. He succumbed to his tumor within 2 years. You may have recognized that this actual case was that of the great American general, hero of the Civil War, and president, Ulysses S. Grant.¹ And that had been the classic head and neck cancer risk profile and demographic, with the combination of heavy alcohol and tobacco use as the primary risk factors.²

But that was then, and this case is now, and very different demographics are in place.

The traditional epidemiology and demographics, as recently as the 1980s,² wherein typical patients had head and neck cancers induced by heavy tobacco and alcohol use, have been replaced in very large part by the major epidemiologic risk factor now being HPV infection related to oral sex exposure. In the 1980s, HPV-related tumors accounted for 16.3% of cases, whereas more recent data from the 2000s indicates that 72.7% of head and neck tumors are now HPV-related.^{3,4} These data make **Answer D** the correct choice here.

Some important facts and clinical sequelae follow this changing epidemiology. As a general rule, HPV-related head and neck cancers occur in a younger age group; anatomically are more prone to be found in the oral cavity, especially the tonsil area more so than the more clinically silent posterior pharynx and larynx; and have a patient population generally in better health than the alcohol- and tobacco-laden group of prior times.^{3,5} These facts likely explain why HPV populations, overall and stage-for-stage, have a more favorable prognosis than the chron-

ic alcohol and tobacco group.⁶ The oral cavity also makes effective cancer surgery resection procedures more possible, and such procedures are also associated with superior cure rates, which is additive to the better prognosis in HPV disease. It must be noted, however, that the favorable prognosis must not be an excuse for less-aggressive therapies to be tried in an attempt for diminished treatment morbidity and better cosmesis. In fact, stage-for-stage therapeutics, usually involving multimodality use of surgery and chemoradiotherapy, needs to be the same as for non-HPV disease, since studies have shown that less-intensive regimens are associated with worse outcomes.³ Such data make **Answer B** an incorrect choice.

Diagnosis involves thorough oropharyngeal endoscopy and imaging prior to biopsy. FNA is effective and frequently possible due to the oral cavity's dominant location of many HPV lesions. On those occasions when an obvious node is the most accessible site, FNA is not currently recommended, since tumor spillage can occur and complicate treatment, making **Answer A** incorrect. Any biopsy specimen needs to be tested by polymerase chain reaction (PCR) for HPV nucleic acid positivity or immunochemical stain for expression of p16, a protein that is a surrogate marker for HPV.⁷ Appropriate head and neck cancer tumor staging continues to be the traditional T (tumor size), N (presence, number, and location of involved nodes), M (presence of distant metastasis) system.

Therapeutics is quite complex and outside the domain of the generalist and the "What's the 'Take Home'?" column, but it involves varying combinations of surgery (when feasible), radiation, and combination chemotherapy. It is appropriate to mention the use of PD-1 and PD-L1 immune checkpoint inhibitors, which, similarly to the immunotherapy lung cancer drugs, have demonstrated very significant efficacy, albeit in a very small number of sensitive patients.³

Finally, regarding HPV vaccines and their role: HPV vaccination has already clearly shown to be prophylactic in two other HPV lesions—anogenital and cervical cancers. It can be assumed that there will be similar benefit in HPV head and neck cancer, but due to long latency, more time is required to document this.⁴ **Answer C** very much underestimates the time needed for any effect in a patient who already has a tumor and

overstates any acute benefit that might be expected, so—at least for now—it is an incorrect choice.

PATIENT FOLLOW-UP

Detailed oral endoscopy and examination of the neck demonstrated a suspicious lesion in the area of the left palatine tonsil. There was no palpable adenopathy anywhere in the neck. Imaging studies, including magnetic resonance imaging and positron emission tomography, showed only the presumed primary lesion measuring 3.1 cm. FNA was performed, the results of which confirmed moderately differentiated squamous cell carcinoma containing HPV DNA on real-time PCR. The patient's tumor stage was therefore T2N0M0, stage I disease. He will undergo combined therapy with surgery and adjuvant chemo-radiotherapy. ■

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