Case Report

Laryngeal Carcinoma in Nonsmokers: A New Challenge

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Abstract

Introduction: Laryngeal carcinoma represents a large percentage of the Head-and-Neck cancers diagnosed every year in the United States. In the past decade, an increase in the incidence of laryngeal carcinoma in nonsmokers has started to appear. This new patient is similar to the now common patient with HPV derived oropharyngeal carcinoma. To our best knowledge, there is few data available of this new laryngeal cancer patient in the Hispanic population including Puerto Rico. The aim of our study is to present one of the rare cases of advanced stage laryngeal squamous cell carcinoma with no previous history of smoking, drinking, or HPV and discuss the implications HPV may have in laryngeal carcinoma.

Methods: A case study of a patient with advanced laryngeal carcinoma without history of drinking and smoking was performed. Also, a review of literature using PubMed and Science Direct with the following keywords was done: laryngeal carcinoma, HPV, laryngeal cancer treatment, and nonsmoker. This study was IRB exempt.

Results: The literature has started to show an increase in the diagnosis of laryngeal carcinoma in patients without history of smoking. These patients have tested positive for HPV although this infection has not been proven to be the driving force as it is in some oropharyngeal carcinomas. Multiple recent studies have shown comparable results in advanced laryngeal carcinomas when comparing chemoradiation to the surgical standard in these cases.

Conclusion: The overall survivability and disease free survival in this new type of patient appears to be better to that of the smoker patient. There is still controversy regarding the treatment of these new patients with laryngeal carcinoma.

ABBREVIATIONS

HPV: Human Papilloma Virus; ER: Emergency Room; PCP: Primary Care Physician; LAD: Lymphadenopathy; FVC: False Vocal Cord; TVC: True Vocal Cord; CT: Computer Tomography; IHC: Immunohistochemistry

INTRODUCTION

Laryngeal carcinoma represents a large percentage of the Head-and-Neck cancers diagnosed every year in the United States. Over the past century, 90% of patients diagnosed with laryngeal carcinoma have been heavy smokers [1]. In the past decade, an increase in the incidence of laryngeal carcinoma in nonsmokers has started to appear [2]. The HPV-related squamous cell carcinoma has a varied, yet histologically distinct, morphologic phenotype. Most of these tumors are non-keratinizing squamous cell carcinomas and are sometimes described as having a basaloid phenotype [3].

Over expression of p16 can be identified by immunohistochemistry (IHC) in virtually all head and neck squamous cell carcinomas associated with HPV infection, making it a useful surrogate marker for the detection of HPV [3]. In these tumors, p16 is over expressed secondary to depletion of the retinoblastoma protein by the HPV-generated E7 oncoprotein [3].

The HPV patient tends to be younger, lower exposure to tobacco and alcohol and also have more advanced stages at presentation [4,5]. However, one study showed that HPV positive patients with laryngeal carcinoma did not have a statistical significant increase in survival rates, showing that it might not be a prognostic factor as it is in oropharyngeal carcinoma [4]. Although a growing number in reports of laryngeal cancer in patients without risk factors exists, literature examining this type of patient population is limited [6]. The aim of our study is to present one of the rare cases of advanced stage laryngeal squamous cell carcinoma with no previous history of smoking, drinking, or HPV and discuss the implications HPV may have in laryngeal carcinoma.
CASE PRESENTATION

A 63y/o male arrived to the Emergency Room (ER) with a chief complaint of shortness of breath and dyspnea upon exertion associated to a worsening hoarseness since 3 months ago. Tolerating regular diet by mouth but with difficulty upon deglutition. He reported only a past medical history remarkable for a mild hearing loss which had not been evaluated. He was then asked about his toxic habits, including tobacco, alcohol and illicit drug use, to which he denied all. His mother, daughter and son in law were later asked as well about this habits to which they all agreed that they did not exist.

Upon flexible laryngoscopy, a large left supraglottic submucosal mass, without any ulceration or exophytic point, could be seen. The mass encompassed the entire aryepiglottic fold, false vocal cord (FVC) and arytenoid. The mass extended pass midline causing a mass effect on the right laryngeal structures. Even though the left true vocal cord (TVC) could not be visualized, there was no perceptible movement in the left side. The right TVC appeared to have the intention of movement, but due to the mass effect caused by the lesion, the cord could not mobilize. The mass appeared to have spared the epiglottis, anterior commissure, the right hemilarynx, and the pyriform sinuses. Due to the impending airway that the patient possessed, the decision for an awake tracheotomy followed by a panendoscopy (including direct laryngoscopy, bronchoscopy and esophagoscopy) with biopsy for diagnosis was taken.

The awake tracheotomy was performed without any complications and with the full cooperation of the patient. The panendoscopy procedure revealed a 1 cm ulcer at the posterior face of the left arytenoid. The mass extended to all of the previously mentioned areas with the addition of the petiole, the left TVC and the anterior commissure. There was no subglottic extension or invasion of the esophagus. Biopsy from the arytenoid ulcer was taken. The results came back positive for squamous cell carcinoma. The sample was then sent for p16 immunostain which return as strongly positive and diffused throughout the entire specimen (Figures 1, 2).

During his hospital stay, a neck and chest computer tomography (CT) with contrast enhancement was performed for staging purposes. The results showed a tumor located in the left hemilarynx with thyroid cartilage invasion and extension to the left strap muscles. Multiple small lymph nodes were seen that, even though were not positive by size criteria, did show heterogenous enhancement at level III and IV of the left neck (Figures 3,4). These results in addition to the results of the physical exam and panendoscopy, demonstrate an advanced carcinoma in our patient. Using the staging criteria from the National Cancer Institute, the patient was staged as a stage 4, T4aN2bM0 squamous cell carcinoma of the larynx.

A discussion about the different treatment modalities took place with the patient and his family members between a total laryngectomy and chemoradiation. Unfortunately, the patient decided for neither, and instead, decided to start a homeopathic remedy course back in his home country of the Dominican Republic.
DISCUSSION

Laryngeal carcinoma continues to represent a large percentage of the head and neck carcinomas diagnosed yearly. Recently, a trend of nonsmokers with advanced stage laryngeal carcinomas has started to present itself yet there is still controversy regarding the role of HPV as a prognostic factor and as a possible biomarker for higher success in organ-preservation treatments [2].

Various studies have been performed to assess the role of HPV as a prognostic factor in laryngeal carcinoma. Most of them are conducted in a diverse population of head and neck cancers including: oropharynx, larynx and hypopharynx. The patients in these studies range across the stages with the majority having stage 3 and 4 carcinomas.

Kanyilmaz, et al conducted a study to evaluate the impact of HPV in the response to therapy, overall and disease free survival [7]. The study showed that, like squamous cell carcinoma in the smoking patient, the TNM-stage and the N-stage were the main and only statistically significant (p=0.001) prognostic factor associated with disease free survival. p16 positive status, even though was found to be a prognostic factor in improved overall survival and disease free survival, was not statistically significant (p=0.2). Clayman, et al conducted a study with a small group of patients with laryngeal carcinoma (n= 59) in which nearly half (46%) of the patient population were HPV positive. In this study, HPV was found to be a negative prognostic factor for survival[4]. A retrospective study with 324 patients with laryngeal squamous cell carcinoma questioned the validity of p16 over expression as a marker of HPV in laryngeal squamous cell carcinoma [8]. They found that the over expression of p16 in this type of cancer was infrequent and active HPV transcription even lower [8]. Also, no statistically significant correlations were found with survival outcomes [8]. Another study conducted in 130 patients with laryngeal squamous cell carcinoma looking for an association between HPV status and the outcomes in patients found no significant correlations [9]. In contrast, a retrospective study conducted in patients with advanced staged carcinomas treated with surgery and post-operative radiotherapy showed that HPV positive status, as well as T category T1-T2, showed a significant difference in locoregional control (80% vs 54%) [7]. This study also showed that HPV status was a significant prognostic factor for overall survival and a non-statistically significant tendency towards metastasis free survival. A limitation of this study was that they grouped a large amount of primary tumor sites to their patient population selection, including oropharynx, which may have skewed their results.

Despite the lack of exposure to the common risks factors known to cause laryngeal carcinoma, especially tobacco, the nonsmoker patient still has an increased risk of second primaries in the head and neck region (28% in the study population), particularly in the oral cavity [6]. This could mean that, just as tobacco, a “field cancerization” can be produced by the malignant strains of HPV [6].

Another controversy surrounding the nonsmoking laryngeal cancer patient is related to its treatment. It has been suggested that the oncoproteins involved in HPV-positive oropharyngeal cancers, specially E6-I, which play a role in the enhanced radiosensitivity may also be present in laryngeal cancers [10, 11]. If we consider the oncogenesis of HPV derived oropharyngeal carcinoma to be the same one that occurs in the larynx, then the same principle could be applied to treatment of HPV-positive laryngeal squamous cell carcinoma. Several studies, have shown that patients with HPV-associated squamous cell carcinomas have better outcomes than those with nonviral-related tumors.

A study conducted by Shaughnessy, et al. in 155 patients with laryngeal and hypopharyngeal tumors, showed that HPV status, when treated with chemoradiation, had a tendency for patients with HPV-HPV positive tumors to have significant improvements in 2-year disease free survival (100% vs 68%, p=0.04) and local recurrence-free survival (100% vs 72%, p=0.05), although no difference was found in overall survival. When compared with surgery in patients with HPV-positive tumors, the same study showed a significant increase in the 2-year disease free survival (100% vs 60%, p=0.03) and a trend towards improved 2-year local recurrence-free survival (100% vs 80%, p=0.08) [12]. This study was hindered by their patient population, since all except for two of the patients in the study had a history of heavy tobacco use at some point in their lives which has been shown to be an important independent prognostic factor even in the setting of HPV-positive tumors in the oropharynx [13].

Another study that looked to improve on the findings of the Veterans Affairs Laryngeal Cancer Study Group of 1991, demonstrated that chemosensitivity and radiosensitivity of a laryngeal tumor could be assessed by giving one cycle of chemotherapy, consisting of 5-fluorouracil and a platinum agent, followed by radiotherapy [14]. In this study, complete response or partial response was achieved in 100% of patients with T2 disease and 75% of those with T3/T4 disease following the induction protocol and continuation of the chemoradiation in those patients that were found to be responding to the treatment. The complete response rate for patients that completed the induction and later chemoradiation was of 97.7% in patients with...
T2 disease and 100% in those with T3/T4 disease. In patients with advanced disease (T3/T4), a great number of the tumors were located in the supraglottis as it is with the patient in our presented case.

Future clinical trials will be aimed at deintensifying treatment regimens for these tumors. Currently, patients are typically treated with a variety of options including: induction chemotherapy, followed by surgery, surgery followed by adjuvant therapy if required, or chemoradiation. Patients with HPV-associated tumors are more likely to demonstrate substantial response to induction chemotherapy and, thus, are more likely to be eligible for chemoradiation and organ preservation, although some patients may still require surgery. In addition, new methods of treatment are being devised that use novel therapeutic vaccines. Published data regarding the utility of vaccine prevention for HPV oral lesions are currently lacking, but, hopefully, the advent of a preventative vaccination will affect head and neck cancers incidence [15].

Unfortunately, studies demonstrating a direct relationship between HPV infection and development of laryngeal carcinoma are still needed. HPV status in laryngeal carcinoma continues to be controversial with its presence as the oncogenic driving force being called into question. The observations from the literature review demonstrate that the disease of laryngeal carcinoma is one that is changing with patients presenting the disease but none of the common risks factors. Larger studies are required to establish a direct relationship of HPV and laryngeal cancer in nonsmoking patients and determine if they also would benefit from organ preserving treatment modalities as it is in oropharyngeal carcinoma.

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REFERENCES