

Human papilloma virus-associated metachronous squamous cell carcinoma of the larynx and uterine cervix: Case report and review of the literature

Semiramis Carbajal-Mamani^{a,1}, Neil Chheda^{b,2}, Ashwini Esnakula^{c,3},
Joel Cardenas-Goicoechea^{d,*}

^a University of Florida, Department of Medicine, United States

^b University of Florida, Department of Otolaryngology, United States

^c University of Florida, Department of Pathology, United States

^d University of Florida, Department of Obstetrics and Gynecology, Division: Gynecologic Oncology, United States

ARTICLE INFO

Keywords:

Human papilloma virus
Uterine cervical neoplasm
Laryngeal neoplasm

ABSTRACT

60 year old woman with a history of laryngeal carcinoma-HPV 16 positive, presents seven years later with an abnormal Pap smear. Cervical biopsy showed squamous cell carcinoma. Clinical stage was IB1. Patient underwent open radical hysterectomy and lymphadenectomy. Based on pathologic findings no adjuvant therapy was recommended. Uterine cervix carcinoma was also positive for HPV-16. There are no guidelines for cervical cancer screening in patients with laryngeal cancer and vice versa. Our recommendation is that patient with HPV-positive laryngeal cancer should be encouraged HPV vaccine as current guidelines, but more frequent screening, as recommended for women with specific co-morbid conditions, needs to be investigated. Research is needed to assess the role of screening for laryngeal cancer in women with cervical cancer and the effect of HPV vaccine on laryngeal cancer prevention.

1. Case

A 60 year old women presented with chief complaints of postmenopausal bleeding, and pelvic pain. Her recent cervical cytology at an outside institution revealed atypical squamous cells of undetermined significance. Human papilloma virus (HPV) testing on the cytology specimen was positive for high risk HPV. Subsequent colposcopy performed at the outside institution did not show any definitive mass lesion and colposcopy guided cervical biopsy showed moderate to severe cervical intraepithelial neoplasia, CIN 2–3. Patient underwent hysteroscopy and loop electrical excisional procedure (LEEP) at the outside institution. Hysteroscopy revealed cervical adhesions and a small endometrial polyp without definitive gross tumor in the cervix. Per outside pathology report, the fragmented LEEP specimen measured 1.7 × 1.6 × 1 cm in aggregate and showed an invasive squamous cell carcinoma, moderately differentiated with focal keratinization. The LEEP excision margins were positive for invasive carcinoma. Based on

these findings the patient was referred to our gynecologic oncology division for further management. On physical examination, the patient body mass index was 16.65 kg/m². Patient has long standing tracheostomy and Gastric tube related to her prior laryngeal cancer treatment. Pelvic exam revealed a small and mobile uterine cervix with post-surgical changes related to recent LEEP. No gross tumor was identified. Parametrium was free of disease. Remainder of physical exam was non-contributory. The patient past medical history was significant for invasive non keratinizing squamous cell carcinoma of larynx seven years ago (Fig. 1A). Pathologic stage was T3/N2c/M0. The tumor was diffusely and strongly positive for P16 by immunohistochemistry. The prior laryngeal biopsy was recently tested for HPV subtype. The tumor was positive for HPV 16 by DNA in situ hybridization (ISH) (Fig. 1B). Laryngeal cancer was treated with concurrent chemotherapy and radiation including 6 cycles of cisplatin and 70 Gy radiation and post treatment neck dissection. Patient has been married to a single husband for 40 years and had 2 spontaneous vaginal

* Corresponding author at: Division of Gynecologic Oncology Department of Obstetrics and Gynecology University of Florida College of Medicine, 1600 SW Archer RD, PO Box 100294, Gainesville, FL 32610, United States.

E-mail addresses: Semiramis.CarbajalMamani@medicine.ufl.edu (S. Carbajal-Mamani), Neil.Chheda@ent.ufl.edu (N. Chheda), esnakula@ufl.edu (A. Esnakula), Joelcardenas@ufl.edu (J. Cardenas-Goicoechea).

¹ Address: 1600 SW Archer RD. PO Box 100277, Gainesville, FL 32610, United States.

² Address: 1600 SW Archer RD. PO Box 100264, Gainesville, FL 32610, United States.

³ Address: 1600 SW Archer RD PO Box 100275, Gainesville, FL 32610, United States.

<https://doi.org/10.1016/j.gore.2020.100568>

Received 14 March 2020; Received in revised form 2 April 2020; Accepted 3 April 2020

Available online 07 April 2020

2352-5789/ © 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

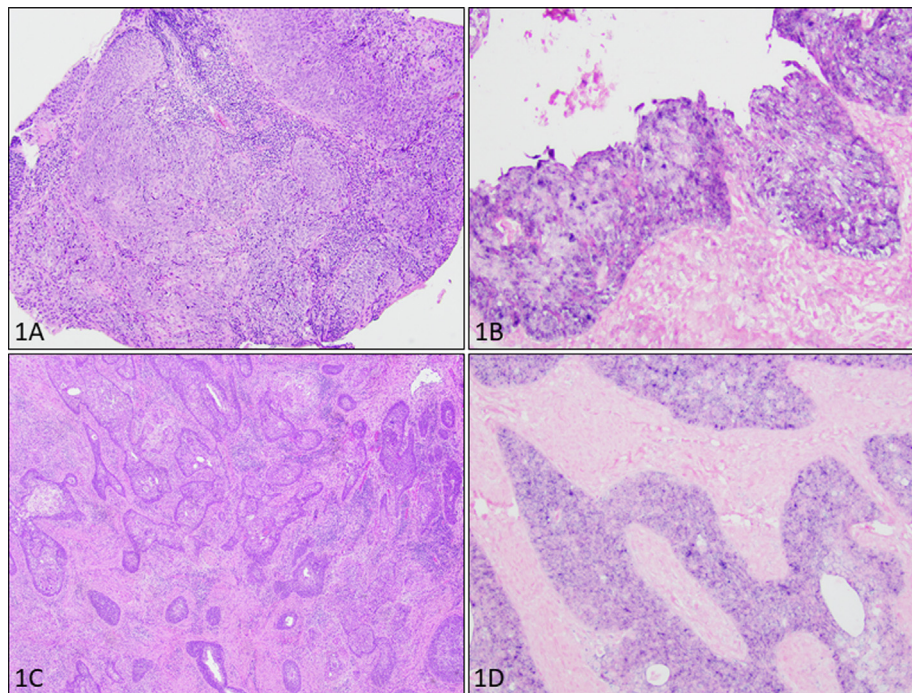


Fig. 1. Prior laryngeal mass biopsy showing non keratinizing squamous cell carcinoma (A) which is positive for HPV16 by DNA ISH (B). Subsequent radical hysterectomy specimen with invasive squamous cell carcinoma of the cervix (C). The cervical squamous cell carcinoma was positive for HPV 16 by DNA ISH (D).

delivery. The patient denies smoking, alcohol, or drug use. Family history was unremarkable.

1.1. Diagnostic work up

Cervical magnetic resonance imaging (MRI) performed at our institution showed an endocervical stromal lesion measuring 1.7×0.7 cm. There was no parametrial or vaginal invasion. Positron Emission Tomography – Computed Tomography (PET/CT) showed fluorodeoxyglucose (FDG) avidity near the cervix with a standardized uptake value (SUV) max of 3.59. There was no evidence of metastatic disease.

1.2. Treatment

Patient underwent open radical hysterectomy with bilateral pelvic lymphadenectomy. The hysterectomy specimen on gross examination showed an irregular defect in the endocervix consistent with prior LEEP excision without identifiable mass lesion. The entire cervix was submitted for histologic evaluation. Pathology showed residual moderately differentiated invasive squamous cell carcinoma involving the cervical stroma with areas of keratinization and basaloid features (Fig. 1C). The greatest dimension of the residual tumor was 0.7 cm, which was the depth of invasion into the cervical stroma. The tumor was positive for HPV 16 by DNA ISH (Fig. 1D). The tumor was limited to cervix. Lymphovascular invasion was identified. Parametrium and vagina were not involved by carcinoma. Pelvic lymph nodes were negative for metastatic carcinoma. The patient's prior pathology slides were not available for our review. We noted that the prior LEEP specimen was less than 2 cm in all dimensions and the current radical hysterectomy specimen showed only a microscopic tumor with greatest dimension of 0.7 cm invading into cervical stroma. Overall, based on all these findings the tumor was conferred a pathologic stage of pT1b1/N0; FIGO stage IB1.

Based on pathologic findings, no adjuvant therapy was recommended. Plan was to continue surveillance with physical exam, every 3–6 months for the first 2 years, followed by every 6 months for the next 3 years. Annual Pap smear and imaging will be based on

findings during follow up physical exams.

2. Discussion

Worldwide, cervical cancer is estimated 570,000 cases and 311,000 death in 2018, and ranks as the fourth leading cause of cancer death in women; however it is the most commonly diagnosed cancer in 28 countries and the leading cause of cancer death in 42 countries. Head and neck cancer accounts for more than 650,000 cases and 330,000 deaths annually (Bray et al., 2018).

There are over 205 different HPV genotypes. There are at least 15 types of HPV with oncogenic potential. The most common HPV associated to head and neck squamous cell carcinoma, and anogenital cancers is HPV-16. HPV-18 has also being associated with squamous intraepithelial lesions that can progress to squamous cell carcinoma in the head, neck and/or anogenital tract.

Human papilloma virus has been associated with uterine cervical cancer and head and neck cancer. Here we present patient with laryngeal cancer who later develop uterine cervical cancer. Both cancers showed the presence of HPV 16 by HPV DNA (ISH). It is well recognized that persistent infection of the uterine cervix with high-risk HPV is required for the development of invasive cervical cancer. The recommendation for cervical cancer screening has been well established. Women younger than 21 years do not need screening; women aged 21–29 years cytology alone every 3 years, women aged 30–65 years high risk HPV with cytology co-testing (preferred) every 5 years or cytology alone (acceptable) every 3 years (Committee on Practice B-G. Practice Bulletin No. 168, 2016).

Vaccination guidelines have been well established to reduce the incidence of anogenital cancer. HPV vaccines are recommended for girls and boys aged 11–12 years and can be given to females and males up to 26 years (Immunization Expert Work Group CoAHC, 2017). On October 5, 2018 the FDA approved the use of the 9-valent HPV vaccine (6, 11, 16, 18, 31, 33, 45, 52, and 58) in women and men aged 27 through 45 years. HPV vaccine is safe and highly effective against the most common types of HPV found in cervical and other anogenital cancers. The estimated vaccine effectiveness range from 80 to 91% in a US

community study after > 10 year after the 4-valent and 9-valent HPV vaccine introduction (Spinner et al., 2019). However, there are no guidelines for screening and vaccination to reduce the risk or prevent HPV-related oropharyngeal and laryngeal cancer. It is unclear whether HPV vaccine can also prevent HPV infections in the head and neck region. An analysis that included two phase 3 clinical trial (FUTURE II NCT00092534 and PATRICIA NCT 00122681) suggest that HPV vaccination may also prevent oropharyngeal cancer (Luostarinen et al., 2018). Furthermore, a population based study that included men and women from 18 to 33 years of age found that the prevalence of oral HPV 16/18/6/11 infection was significantly reduced in vaccinated versus unvaccinated individuals (0.11% v 1.61%;p = 0.08), corresponding to 88% reduction in prevalence (Chaturvedi et al., 2018).

Tobacco use, and alcohol consumption are important risk factors to laryngeal cancer. However, HPV infections has been associated in laryngeal squamous cell carcinoma from 3% to 85%. The wide range is related to variation in geographic region, study design, and in the sensitivity and specificity of the detection method (Wang et al., 2020).

The most common histological type of uterine cervical cancer and head and neck cancer is squamous cell carcinoma. A rise in the incidence of laryngeal carcinoma in patients with no history of alcohol or tobacco has been associated to HPV 16 infection and could be attributable to change in sexual norms. HPV integrates its DNA genome within the host cell nucleus, it dysregulates expression of the oncoproteins E6 and E7 affecting p53 and retinoblastoma tumor suppressor gene respectively. As a result there is an inhibition of apoptosis and malignant transformation (Marur et al., 2010).

The prognostic role of human papilloma virus status among patients with locally advanced hypopharyngeal and laryngeal cancer has been evaluated in 810 patients from the National Cancer Database. Patients with positive HPV appears to have better survival compared to patients with HPV negative (Bates et al., 2019).

We could not find another similar case to our case presentation with a laryngeal cancer who subsequently presented with cervical cancer. This case raises the question of whether HPV+ oropharyngeal or laryngeal carcinoma represent an additional risk factor for cervical cancer development. This may prompt the clinician to perform more frequent screening. Additional studies and analysis would be needed for the development of formal guidelines. More frequent and prolonged cervical screening is recommended for women infected with HIV, immunocompromised (such as those who have received solid organ transplant), exposed to diethylstilbestrol in utero, and previously treated HSIL (CIN 2, 3) or cancer (Committee on Practice B-G. Practice Bulletin No. 168, 2016). This also raises additional questions such as; should patients with uterine cervical cancer be screened for laryngeal cancer? Is oral gargle sample a good strategy for screening? (Martin-Gomez et al., 2019). What is the effectiveness of HPV vaccination

against oral HPV infection? Hence, strategies for primary and secondary prevention for HPV-related head and neck cancers should be considered and explored, and this may include use of HPV vaccination, and screening. Currently there are no indications for screening for symptomatic oral HPV infections because the natural history is incompletely understood.

Conclusion: Laryngeal and uterine cervical cancer is associated to HPV 16. Laryngeal carcinoma patients should receive HPV vaccine and may need more frequent and longer screening for cervical cancer with co-testing Pap smear and HPV. Research is needed to assess the role of HPV vaccine in prevention of laryngeal cancer.

CRediT authorship contribution statement

Semiramis Carbajal-Mamani: Conceptualization, Writing - original draft. **Neil Chheda:** Writing - review & editing. **Ashwini Eshnakula:** Visualization, Writing - review & editing. **Joel Cardenas-Goicoechea:** Conceptualization, Writing - review & editing.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

References

- Bates, J.E., Morris, C.G., Hitchcock, K.E., Dziegielewska, P.T., Mendenhall, W.M., Amdur, R.J., 2019. Locally advanced hypopharyngeal and laryngeal cancer: Influence of HPV status. *Radiother. Oncol.* 140, 6–9.
- Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., Jemal, A., 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 68 (6), 394–424.
- Chaturvedi, A.K., Graubard, B.I., Broutian, T., Pickard, R.K.L., Tong, Z.Y., Xiao, W., et al., 2018. Effect of prophylactic human papillomavirus (HPV) vaccination on oral HPV infections among young adults in the United States. *J. Clin. Oncol.* 36 (3), 262–267.
- Committee on Practice B-G. Practice Bulletin No. 168, 2016. Cervical cancer screening and prevention. *Obstet. Gynecol.* 128 (4), e111–e130.
- Immunization Expert Work Group CoAHC, 2017. Committee opinion no. 704: Human papillomavirus vaccination. *Obstet. Gynecol.* 129 (6), e173–e178.
- Luostarinen, T., Apter, D., Dillner, J., Eriksson, T., Harjula, K., Natunen, K., et al., 2018. Vaccination protects against invasive HPV-associated cancers. *Int. J. Cancer* 142 (10), 2186–2187.
- Martin-Gomez, L., Giuliano, A.R., Fulp, W.J., Caudell, J., Echevarria, M., Sirak, B., et al., 2019. Human papillomavirus genotype detection in oral gargle samples among men with newly diagnosed oropharyngeal squamous cell carcinoma. *JAMA Otolaryngol. Head Neck Surg.* 145 (5), 460–466.
- Marur, S., D'Souza, G., Westra, W.H., Forastiere, A.A., 2010. HPV-associated head and neck cancer: a virus-related cancer epidemic. *Lancet Oncol.* 11 (8), 781–789.
- Spinner, C., Ding, L., Bernstein, D.I., Brown, D.R., Franco, E.L., Covert, C., et al., 2019. Human papillomavirus vaccine effectiveness and herd protection in young women. *Pediatrics* 143 (2).
- Wang, H., Wei, J., Wang, B., Meng, L., Xin, Y., Dong, L., et al., 2020. Role of human papillomavirus in laryngeal squamous cell carcinoma: A meta-analysis of cohort study. *Cancer Med.* 9 (1), 204–214.