CASE REPORT

Squamous Cell Malignancy Coexisting with Squamous Papilloma in the Larynx: Is This an Entity?

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Abstract

Background: Recurrent respiratory papillomatosis (RRP) is the most common benign mesenchymal neoplasm of the larynx caused by the human papillomavirus (HPV). This condition has a childhood-onset and adult-onset type, which historically has an inclination toward malignant transformation.

Case description: A detailed case discussion of two patients with two clinically distinct and dissimilar lesions on two different subsites of the larynx. Both patients were clinically diagnosed to have laryngeal papilloma, with a second malignant lesion.

In case 1, the final histopathology of the malignant lesion was found to have papillomatous fronds with evidence of severe dysplasia.

In case 2, histopathology of the malignant lesion revealed invasive squamous cell carcinoma with features of papilloma.

Both patients revealed "no type" in viral typing.

Conclusion: Malignant transformation in adult laryngeal papilloma may occur as a relatively acute phenomenon that may present at the first surgical intervention. It is often associated with the "no type" HPV entity. The presence of squamous papilloma and carcinoma of the larynx, even at two different subsites, should be histologically confirmed and considered a malignant transformation of the laryngeal papilloma.

Keywords: Adult-onset recurrent respiratory papillomatosis, Case report, Malignant transformation, No type recurrent respiratory papillomatosis, Recurrent respiratory papillomatosis, histopathology, Squamous papilloma.

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Introduction

Recurrent respiratory papillomatosis (RRP) is the most common benign mesenchymal neoplasm of the larynx, trachea, and bronchi caused by the human papillomavirus (HPV) and contributes to 84% of all benign neoplasms.[1] RRP presents at three median ages of 7, 35, and 64 years.[2] This condition has a childhood-onset type [juvenile-onset recurrent respiratory papillomatosis (JORRP)], which is more aggressive in nature, and an adult-onset recurrent respiratory papillomatosis (AORRP) type, which is less aggressive. However, some studies suggest that AORRP has an inclination toward malignant transformation.[3] The two primary HPV subtypes in RRP are HPV 6 and 11,[4] which are low-risk. Other subtypes include 16, 18, 31, 33, and 39 which are associated with lower prevalence.[4] Subtypes 16 and 18 are considered high-risk along with a "no type" identified when a specific DNA of HPV is nondemonstrable. This "no type" has proved to be an important predictor of the malignant transformation of the laryngeal papilloma.[5] Some studies report the incidence of high-grade dysplasia for laryngeal papilloma from as high as 50%[6] to as low as 10%.[7] Carcinoma ex-papillomatosis is believed to occur at the rate of 3–7% in AORRP.[5] Hall et al. concluded that the malignant transformation in RRP occurs *via* the integration of HPV into host cells which are susceptible to the malignant change and secondary to mutations in specific oncogenes including p53.[8] Studies have revealed that there is no correlation between the number of surgical procedures and the presence of dysplasia.[8] We recently managed two patients who had two distinct and dissimilar lesions on two different subsites of the larynx. In both these patients, one lesion appeared to be a classical papilloma identified for the first time and a second laryngeal lesion clinically appeared to be an infiltrative lesion entirely dissimilar from the primary papillomatous lesion. This raises the question if respiratory papillomatosis and laryngeal cancer can present independently of each other or if the presence of simultaneous laryngeal cancer and papilloma's should be presumed to be a malignant transformation of the squamous papilloma. Both these cases are discussed here briefly.

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Patient consent statement: The author(s) have obtained written informed consent from the patient for publication of the case report details and related images.

Case Description

Case I

A 69-year-old male visited our voice clinic with complaints of voice change for 1 year and no history of previous laryngeal surgery. Laryngoscopy revealed a large papillomatous cauliflower growth at the anterior commissure (Fig. 1A). On stroboscopy, the right vocal fold had an erythematous appearance with a markedly decreased mucosal wave. Narrow band imaging (NBI) revealed a squiggly-worm pattern of the blood vessels of the anterior commissure lesion suggestive of papilloma or malignancy and no obvious intrapapillary capillary loops were seen on the right vocal fold lesion (Fig. 1B). Histopathology following carbon dioxide laser excision of the anterior cauliflower lesion revealed carcinoma *in situ* with squamous papilloma. Viral typing of the papillomatous lesion revealed a "no type." A right type 1 cordectomy was performed for our patient with anterior commissure papilloma excision. Thus, the patient seemed to have two distinct lesions, one papillomatous anterior commissure lesion and another severe dysplasia of the right vocal fold with evidence of papilloma (Fig. 2) which was confirmed histopathologically.

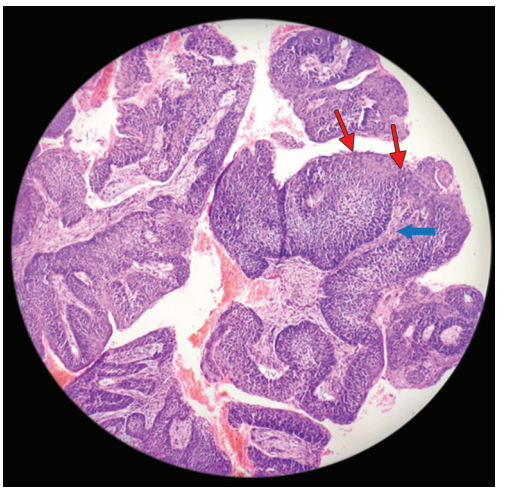


Fig. 2: Figure showing papillary fronds with fibrovascular core. Red arrows point toward thickened squamous epithelium showing moderate to severe dysplasia. The blue arrow depicts the papilloma with fibrovascular stroma on hematoxylin and eosin staining at 10× magnification

Case II

A 72-year-old male presented to our voice clinic with complaints of a gradually progressive change in voice for 4 months and no history of previous laryngeal surgery. Flexible laryngology revealed a large multilobed papillomatous lesion at the anterior commissure extending to the anterior infraglottis (Fig. 3). On stroboscopy, there was a bilateral decreased amplitude of the vocal folds' mucosal waves, possibly due to the large phonatory gap caused by the lesion. On NBI, a squiggly-worm pattern suggesting a 5b grade of the Ni et al. in 2011[9] classification was noted which can be found in malignancy as well as papilloma. Following the excision of this anterior lesion during surgery, another lesion was identified in the anterior infraglottis which had an infiltrative appearance (Fig. 4). Histopathology of the anterior commissure lesion revealed squamous papilloma and viral typing was reported as "no type." Histopathology of the anterior infraglottic lesion revealed invasive squamous cell carcinoma with features of papilloma (Fig. 5). Once again, though two distinct lesions were seen at two different subsites of the larynx, histopathology confirmed the presence of invasive squamous cell carcinoma with papilloma. Our patient was advised radiation therapy and regular follow-up.

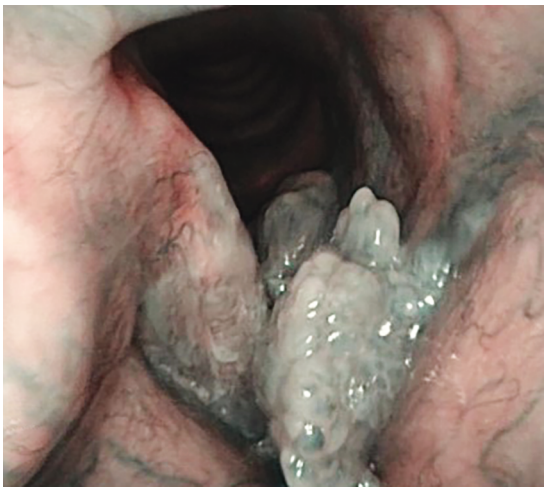
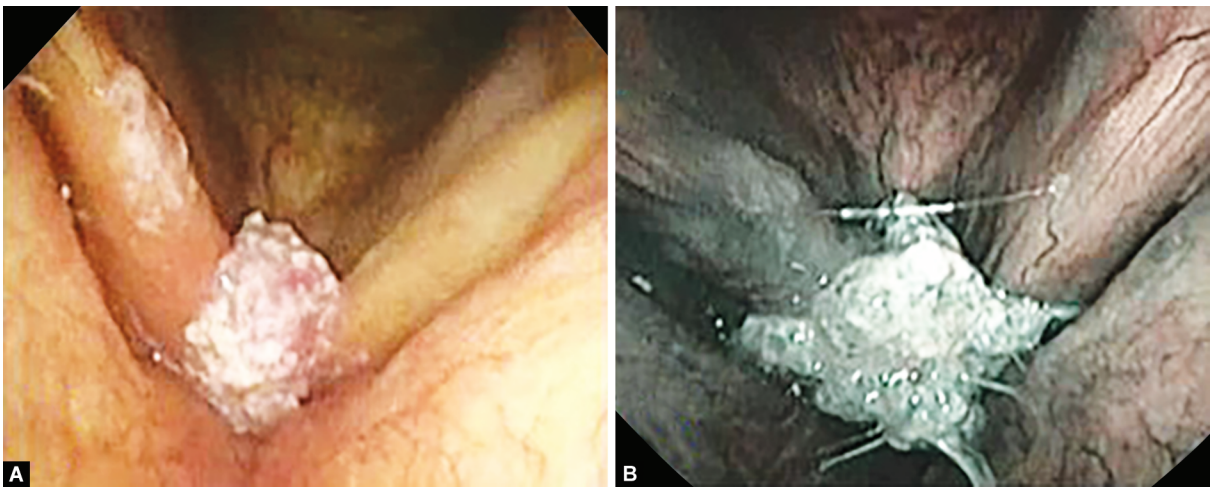


Fig. 3: Flexible laryngology along with NBI revealed a large multilobed papillomatous lesion at the anterior commissure extending to the anterior infraglottis along with a squiggly-worm pattern of the blood vessels



Figs 1A and B: (A) Clinical stroboscopic picture depicting a large papillomatous cauliflower growth at the anterior commissure along with an erythematous right vocal fold; (B) NBI revealed a squiggly-worm pattern of the blood vessels of the anterior commissure lesion suggestive of papilloma or malignancy

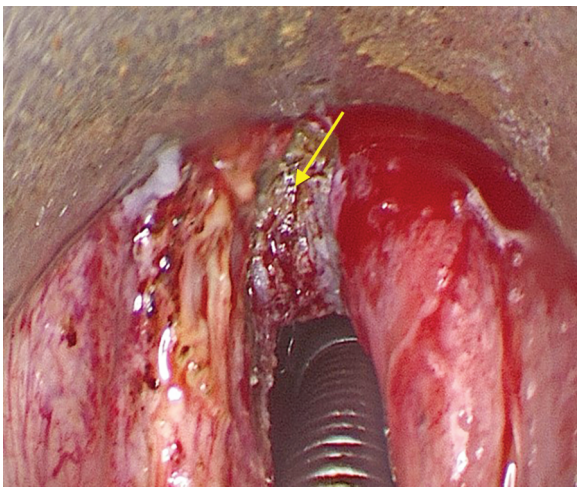


Fig. 4: Once the papillomatous lesion was excised, another distinct lesion was seen in the anterior wall of the subglottis (arrow)

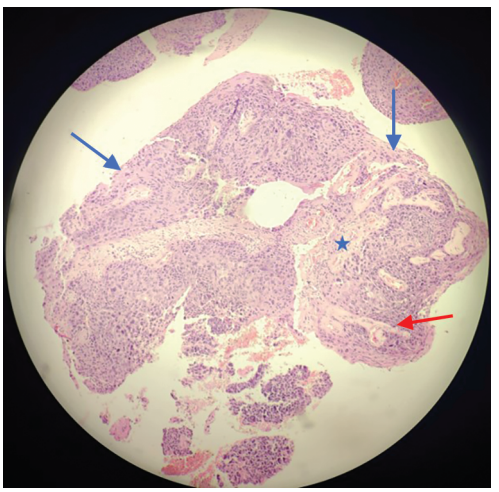


Fig. 5: Figure of hematoxylin and eosin staining at 10× magnification showing papillary frond with a fibrovascular core marked by a red arrow. Blue arrows point to squamous epithelium showing severe dysplasia and carcinoma *in situ*. The asterisk is present over the collagenous stoma which shows irregular nests of invasive squamous cell carcinoma

Discussion

The rate of malignant transformation in RRP is <1% in children and 3–7% in adults.[10] The aggressive clinical course of benign papilloma can lead to malignant transformation and even death if it extends through the lower respiratory tract.[7] However, our patients did not have an aggressive course and presented for the first time with papilloma and carcinoma of the larynx. HPV subtypes 16 and 18 have a high-risk potential for malignant transformation, especially squamous cell carcinoma.[4] The spontaneous transformation of RRP to squamous cell carcinoma is not characterized by a histologic progression through dysplasia over time but can result from the loss of HPV expression.[11] This is probably why "no type" is often associated with malignant transformation in RRP, as was the situation in both of our patients. "No type" RRP is a specific type of HPV where DNA is not demonstrable. This "no type" situation was the only significant risk factor for malignant transformation in a study published by Lee et al. (*p*-value of 0.05).[5] The cumulative risk of malignant transformation in patients without demonstrable HPV DNA was found to be significantly higher than that in HPV-positive patients (relative risk 8.0; 95% confidence interval 1.1–60.3; and *p*-value of 0.05).[5] Omland et al. reported that HPV-negative is a rare finding, which is more frequently seen with adult-onset RRP and was associated with a relatively high-risk of laryngeal neoplasia or carcinoma in the respiratory tract.[12]

An HPV-negative or a no-type biopsy was associated with more than a twofold increase in the risk of developing high-grade laryngeal neoplasm and almost a 50-fold increase in the risk of squamous cell carcinoma in the respiratory tract when compared to patients with HPV-positive biopsy.[12] Both our patients of papilloma with malignancy had a "no type" RRP. Ribeiro El-Achkar et al. in 2018 described a case similar to our two patients, who had a 4-month history with a malignant lesion diagnosed alongside a papillomatous lesion, which was attributed to the presence of HPV 16.[7] They attributed this to malignant transformation and pointed toward the rarity of cases where malignant transformation follows a rapid course.[8] In a study by Go et al. in 2003 at least two patients showed benign papilloma adjacent to the carcinoma which confirmed that malignant transformation occurred amid RRP.[11] Multiple recurrences, alcohol consumption, smoking, immunosuppression, irradiation, and chemotherapy have all been cited as risk factors in the development of squamous cell carcinoma, the only malignancy directly associated with this disease[13,3,14–17] although, this transformation may also occur in absence of any of these above factors.[18] Like in our patients where there was no history of any predisposing factors, and it was a completely nonenvironmental impacted virgin papilloma. To conclude, our adult-onset patients presented to us for the first time with a relatively short history and were a "no type" on immunohistochemistry.

Conclusion

Malignant transformation in adult laryngeal papilloma may occur as a relatively acute phenomenon that may present at the first surgical intervention. Malignant transformation of laryngeal papilloma is often associated with the "no type" HPV entity. The presence of squamous papilloma and carcinoma of the larynx, even at two different subsites, should be histologically confirmed and considered a malignant transformation of the laryngeal papilloma.

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