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Cytopathologic Herpes Simplex Virus Features in Laryngeal Squamous Cell Carcinoma

Laryngeal SCCA usually presents with hoarseness when the glottis is involved, dysphagia if the supraglottis is involved, and difficulty of breathing and stridor in subglottic involvement. A neck mass as an initial presentation of laryngeal carcinoma is commonly linked to the involvement of the supraglottis due to its rich lymphatic drainage. About 70% of supraglottic tumours present with advanced disease (stages III-IV),¹ while 75% of glottic tumours present with localized disease (stages I-II).¹

Smoking and alcohol consumption are considered highly significant etiologic factors but evidence has suggested a possible role for *human papilloma virus* (HPV) infection, *ras* oncogene activation, and gastroesophageal reflux as well.² To the best of our knowledge, laryngeal squamous cell carcinoma has not been associated with *herpes simplex virus* (HSV).

We report a case of laryngeal squamous cell carcinoma with an unusual presentation and peculiar histopathology, and discuss its potential association with *herpes simplex virus*.

CASE REPORT

A 67-year-old man consulted for a right lateral neck mass that gradually started enlarging eight months prior to consult. There was no fever, cough, nasal discharge or congestion, hoarseness, dysphagia, difficulty of breathing, weight loss, oral ulcers, difficulty opening and closing the mouth, or facial asymmetry, and he did not consult a health professional or take any medication. He was a smoker but did not drink alcoholic beverages. He finally consulted due to the gradual increase in size of the neck mass.

Physical examination revealed a 6 x 7 cm hard, fixed, right neck mass involving levels II, and III. Flexible endoscopy showed an enlarged right arytenoid with normal-looking mucosa. (Figure 1 A, B). A CT scan of the neck revealed a 2.8 x 3.8 x 6.3 cm supraglottic/glottic soft tissue mass and right-sided cervical lymphadenopathies suggestive of metastasis. (Figure 2 A, B) Direct laryngoscopy with biopsy of the (arytenoid) supraglottic mass and panendoscopy surprisingly revealed only an enlarged right arytenoid and no lesions in the false and true vocal folds or oral, nasopharyngeal, oropharyngeal, tracheal, and esophageal mucosa. Histopathology showed focal moderate dysplasia with cytopathic changes probably *Herpes Simplex virus* infection with probable involvement of the submucosal layer requiring deeper bites for further diagnosis.

At this point, although the working impression was a benign lesion, we still considered the possibility that this was a malignancy because of the dysplastic changes noted on the histopathology report. A repeat laryngoscopy with biopsy of

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the supraglottic mass and fine needle aspiration biopsy of the neck mass yielded a histopathologic diagnosis of moderately differentiated squamous cell carcinoma and level II lymph node metastatic SCCA. With a diagnosis of laryngeal SCCA stage IVA (T3 N2b M0), a total laryngectomy with bilateral neck dissection (radical on the right and modified radical on the left) and total thyroidectomy was performed. There was a submucosal lesion confined to the supra and glottic area on the right side of the posterior aspect of the cut larynx. (Figure 3) Final histopathology showed moderately differentiated, keratinizing invasive squamous cell carcinoma with viral cytopathic changes. (Figure 4)

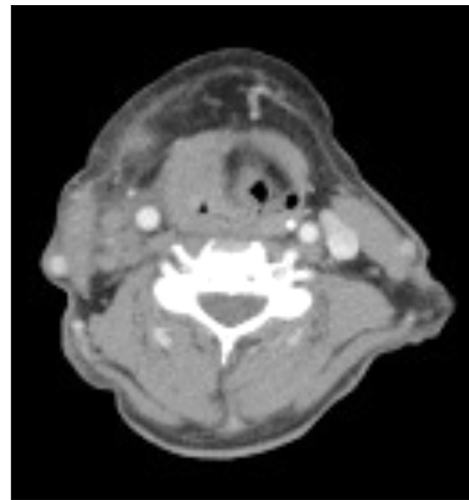


Figure 2A. Contrast CT scan of the neck, A, axial view and

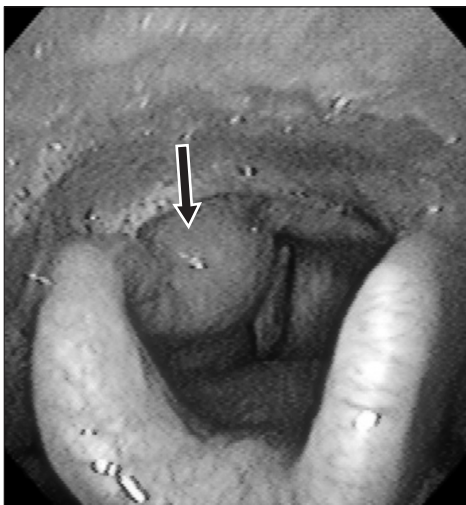


Figure 1A. Hypopharyngeal examination showing an enlarged right arytenoid (black arrow) with no apparent mucosal involvement.



Figure 2B. B, coronal view, showing almost complete obliteration of the paralaryngeal space with thickening of the right false and true vocal folds.



Figure 1B. Laryngoscopy revealed slightly edematous vocal folds, with no visualized masses.



Figure 3. Posterior view of cut larynx showing submucosal and paraglottic space involvement.

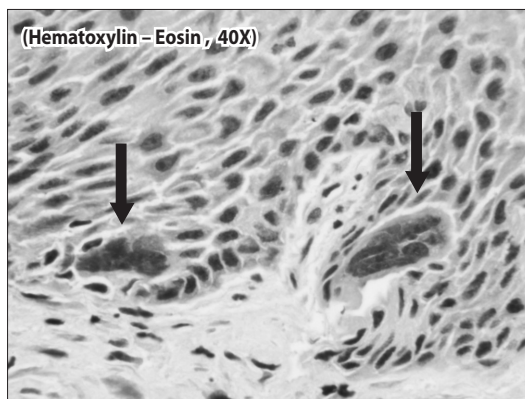


Figure 4. Histopathologic Section of laryngeal specimen, (Hematoxylin and Eosin high power magnification 40x) showing multinucleated giant cells that result from fusion of cell membranes bearing viral glycoproteins.

DISCUSSION

In this case, the patient initially presented with a lateral neck mass without associated signs and symptoms. This made it more difficult to diagnose, since neck masses can have varying etiologies involving a large number of different structures of the head and neck. Squamous cell carcinoma on physical examination usually presents with an ulcerative, exophytic, or polypoid lesion.² This patient initially showed an enlarged right arytenoid with normal-looking mucosa and no involvement of the false and true vocal folds, consistent with the absence of symptoms of hoarseness or dysphagia. Considering the patient's age and the history of smoking, a malignant neoplasm was still the most plausible explanation for the lateral neck mass and supraglottic bulge. Imaging was important to evaluate deeper structures that might be involved. Computed tomography is an indispensable tool for evaluating submucosal laryngeal masses or otherwise unexplainable symptoms (usually hoarseness) that might herald such a mass.³ CT scans showed involvement of the supraglottis and glottis, inconsistent with the patient's history and physical examination findings.

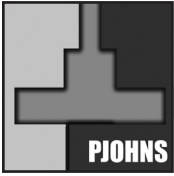
Our patient was diagnosed to have transglottic SCCA with paraglottic space (PGS) involvement. Paraglottic space involvement in either a glottic or supraglottic tumor is staged as T3 and is significant because the extent of the PGS means that tumors in this space may spread to involve any or all of the three regions of the larynx.² The PGS lies lateral to the true and false vocal folds and extends laterally to the thyroid cartilage.² Anteriorly, each PGS is continuous with the paraepiglottic space, and tumors may spread along this pathway.²

Transglottic tumors are an important subset of laryngeal tumors with aggressive behavior and high risk of lymphatic

metastasis. The term *transglottic* was first used by McGavran and associates in 1961.⁴ It is not used in the American Joint Commission and associates for Cancer (AJCC) staging system and is defined by Kirchner and colleagues as a tumor that crosses the ventricle in a vertical direction.⁴ Tumors can become transglottic in four ways: by crossing the ventricle directly; by crossing at the anterior commissure; by spreading through the paraglottic space; and by spreading along the arytenoid cartilage posterior to the ventricle. The latter form of spread does not predict deep invasion: in Kirchner's series of 50 transglottic tumors studied in whole organ preparations, none of the 8 tumors with transglottic spread along the arytenoid demonstrated laryngeal cartilage invasion.⁴ In the same series, invasion of the laryngeal framework was seen in over half of transglottic tumors over 2 cm. Cervical metastases were seen in 30% of cases; and in primary tumors greater than 4 cm in dimension, 55% of tumors had nodal metastases.⁴

The biopsy showed moderate dysplasia with viral cytopathic changes suggestive of submucosal rather than mucosal involvement, and this was consistent with our intraoperative findings. In general, squamous cell carcinomas histologically involve the epithelial layer of a certain structure. However, in a specific type of laryngeal carcinoma -- ventriculosaccular squamous cell carcinoma -- epithelial lesions are not visibly apparent.² Our case may have been similar to ventriculosaccular SCCA in this regard.

The histopathologic slides of our patient revealed multinucleated giant cells, which resulted from fusion of cell membranes bearing viral glycoproteins. (Figure 4) Alterations in the cell nuclei and cytoplasmic tails between the cells were seen. These cytopathic effects (CPE) are seen in HSV-infected cells. This is another issue because *Herpes* viruses are less likely linked to laryngeal malignancies. *Herpes simplex virus* (HSV) is less strongly correlated with the development of oral carcinomas than EBV or HPV.⁵ On the other hand, serologic studies have shown that patients with head and neck cancer have higher levels of IgM antibody to HSV type one than control subjects.^{6,7} HSV can transform cells in vitro to a malignant phenotype. This may be due to an HSV-encoded peptide that increases mutagenicity of infected cells. In one series of 31 young adults with head and neck cancer, antipeptide antibody levels were significantly higher in the patients than in control subjects.⁸ However, most of the studies generalized the association of viruses with malignancies of the oral cavity in general, not with laryngeal carcinoma alone. The question regarding which caused which is left; did the



Herpes virus cause the laryngeal SCCA or was it a superimposed infection due to the patient's immunocompromised state?

Head and neck carcinomas are closely linked to Epstein-Barr and Human Papilloma viruses, particularly carcinoma of the nasopharynx and the oral cavity respectively. At present, accepted causal associations between viruses and human cancer include HPV and cervical cancer; human T-lymphotrophic virus type-1 (HTLV-1) and adult T-cell leukemia and lymphoma; hepatitis B and C and liver cancer, Epstein-Barr virus (EBV) and nasopharyngeal cancer, Burkitt's and Hodgkin's lymphomas, and some non-Hodgkin's lymphomas; and human herpes virus 8 (HHV-8) and Kaposi's sarcoma.⁹

There may or may not be an association between *herpes simplex* virus and laryngeal SCCA, but our experience suggests that the matter is worth investigating. The clinical history and physical examination findings may not always reveal the true extent of disease, and imaging modalities may mislead, but the complementary nature of all these should be considered *vis-à-vis* intraoperative findings and final histopathologic results.

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