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), while 75% of glottic tumours present with localized disease (stages I-II).

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. 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 cytopathologic 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...
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)
Our patient was diagnosed to have transglottic SCCA in this regard. 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. 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. 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. 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. 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. 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.

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.

acknowledgements

We thank Dr. Ronaldo G. Soriano for providing case details and intraoperative photos; Dr. Ann Margaret V. Chang for interpreting the slides and raising the possible association between laryngeal scca and herpes simplex virus; and Dr. Cecilia Gretchen Navarro-Locsin for help with the literature review and final editing. We also thank Dr. Christian Neil F. Romero for help with editing, and our chairs Dr. Ray Casile (QC) and Dr. William Lim (BGC) and Residency Training Officers Dr. Joseph Arañas (QC), and Dr. Keith Agullera (BGC) for their continued support.

References