Case Report

Histopathology of adenoid cystic carcinoma of the larynx and adenocarcinoma hybrid

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ABSTRACT

A 35-year-old Saudi female presented to the Ear, Nose and Throat clinic complaining of hoarseness of voice. Examination revealed subglottic mass, which proved to be adenoid cystic carcinoma of the larynx with adenocarcinoma hybrid. In this paper we discuss the pathological features and electron microscopy of adenoid cystic carcinoma in detail, including its differential diagnosis, prognosis and treatment.

Keywords: Adenoid cystic carcinoma, larynx, hybrid carcinoma, laryngeal carcinoma.

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Minor salivary gland tumors of the larynx are very rare. These account for less than 1% of epithelial malignancy of the larynx, arising in seromucinous minor salivary glands. The main histological types of malignant seromucinous glands are adenocarcinoma, adenoid cystic carcinoma (ACC), neuroendocrine carcinoma, and mucoepidermoid carcinoma.[1] These malignancies arise either from mucous secreting cells on the surface epithelium of the larynx, or from seromucinous glands that are distributed in the larynx in variable concentrations. We present a rare case of hybrid ACC and adenocarcinoma in a non-smoking Saudi female, with complete morphological examination, immunohistochemical results and electron microscopic (EM) findings. The patient underwent total laryngectomy with functional neck dissection. She was also treated by radiotherapy. Since then, namely 43 months after surgical treatment, the patient has been free of disease.

Case Report. A 35-year-old Saudi female presented to the Ear, Nose and Throat (ENT) clinic complaining of hoarseness of voice, irritant dry cough, and dyspnea increasing over the previous 4 months. The actual symptoms started over the previous 4 years. On examination, left vocal cord paralysis was seen with compensated right vocal cord, with a good glottic chinck. She was referred to a medical clinic to rule out bronchial asthma, with the preliminary diagnosis of vocal cord paralysis. She disappeared for several months and presented again with a progressive stridor, dysphagia and aspiration on swallowing.

On examination by direct laryngoscopy, a right subglottic horseshoe mass was seen. It extended from left to right vocal cords crossing the midline and extending inferiorly approximately 2 cms. A small biopsy was suggestive of mucoepidermoid carcinoma. She was then admitted for total laryngectomy with bilateral functional neck dissection in January 1996. Frozen section at the time of surgery confirmed ACC of the larynx involving both pyriform sinuses and ventricles. The inferior margin of the specimen showed microscopic infiltration at the level of 2nd tracheal ring. The right thyroid lobe, which was removed, was infiltrated by this tumor.

Pathological findings. The surgical specimen consisted of a larynx measuring 8.5 cm long x 4.5 cm

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in diameter that was opened from the posterior aspect. Anteriorly, there was an ulcerated nodular firm white mass measuring 4.5 x 2 cm in diameter. The mass involved the inferior half of the epiglottis with finger-like extension into the epiglottic fold on the right side. It also invaded the false and true vocal cords. The bulk of the tumor was present in the subglottic region. (Figure 1) Neck dissection and the right lobe of the thyroid were included. Microscopic examination revealed mucosa lined by ciliated, columnar and squamous epithelium. There were small-medium size cells infiltrating the submucosa, and perichondrial region of the epiglottic. The cells had variable patterns. A large portion of the tumor cells formed cribriform glands, lined by hyperchromatic uniform nuclei with pseudocyst formation containing amorphous eosinophilic material. Mitosis was sparse. Small compressed ductules were also noticed invading the perineural space. These glands stained positive with neutral mucin stain (PAS), as well as acid mucin (mucicarmin stain). Neutral mucin stain-Alcian blue stain for neutral and acidic mucin demonstrated that there were 2 types of mucin in pseudocysts of the cribriform glands as well as in the tubular glands. In addition, there were other glands exhibiting large to medium sized cells with rounded nuclei and prominent nucleoli. Pleomorphism and mitoses were abundant. The tumor cells invaded the cartilage to the outermost layer of the larynx and it extended to the resection margin microscopically. Normal thyroid tissue was seen in the substance of the larynx with scattered foci of tumor invasion. The diagnosis was ACC with adenocarcinoma hybrid. Few lymph nodes were identified without metastases. The tumor was stage T4NoMo. Immunohistochemical stains were performed on formalin fixed, paraffin embedded section containing tumor with both ACC and adenocarcinoma component. There was variable positivity in the 2 components with low and high molecular weight keratin (LMW keratin & HMW keratin), epithelial membrane antigen, Actin, S100, neuron specific enolase (NSE), oncoprotein, and proliferative marker Ki67. Carcinoembryonic antigen was positive in the adenocarcinoma component but was negative in the ACC. Tumor suppressor gene P53 was negative in both components. Fragments of the tumor were submitted in gluteraldehyde fixative for electron microscopic examination (EM). The blue section showed predominantly adenocarcinoma component and at the edge was ACC. Electron microscopy showed that in the adenocarcinoma component there were areas of clear glandular differentiation composed of epithelial and myoepithelial cells. (Figure 2) The epithelial cells showed short blunt microvilli formation on the lumenal surface of the cells, and joined by tight junctions. (Figure 4) It contained scattered thin filaments, with the lumenal border containing mucin. The myoepithelial differentiation showed basal lamina surrounding fusiform cells, which contained thin filaments. (Figure 3) In some cells there were electron dense membranes bound granules surrounded by clear hallow with features of neurosecretory granules. No pseudocyst formation is seen that contain basement membrane- like material.

Discussion. As we know the larynx is initially lined by ciliated columnar epithelium, except for the true vocal cord, which is lined by, stratified squamous epithelium. The lingual or the anterior surface of the epiglottis is invariably covered by stratified squamous epithelium. The posterior laryngeal surface of the epiglottis is covered by stratified squamous epithelium in its upper portion but this merges with respiratory type epithelium inferiorly.[2] Seromucinous glands are present throughout most of the larynx and communicate with the surface epithelium by ducts that are lined by either squamous cells, columnar epithelium or a mixture of the 2. The glands are most abundant in the false cords and saccule; there are also extensive groups of these seromucinous glands just below the anterior commissure. Immediately superior to the anterior commissure, there is a narrow zone devoid of glands.[2] The estimated concentration of seromucinous glands in the false vocal cord is 128 glands/cm^2. However, its concentration on the vocal cord is 13 gland/cm^2. The greatest concentration of the gland is in the saccule at 139 gland/cm^2. There is low density of the glands in the extrinsic laryngeal regions. A typical intraepithelial gland is made up of 15-30 mucus secreting cells with a structure like that of goblet cells. Intraepithelial glands are numerous in the supraglottis and least numerous in the subglottis.[3] The external surface of the larynx contains a microscopic island of normal thyroid tissue within the fibrous capsule of the larynx and trachea. The thyroid follicles are small and appear normal. Continuity with the main thyroid gland is not usually demonstrated. Less commonly thyroid tissue is found internal to the cartilage of the larynx and tracheal rings. These foci of extrathyroid tissue are lost on connection to the main thyroid gland during embryogenesis.[2]

Laryngeal carcinoma is classified into squamous cell carcinoma (95%) and adenocarcinoma (1%). The former arises from the surface epithelium of the larynx. The adenocarcinoma arises from seromucinous salivary glands present in the surface epithelium and submucosa. It includes ACC, mucoepidermoid carcinoma,[4,5,6] and adenocarcinoma, either of neuroendocrine features or a pure form of adenocarcinoma, poorly differentiated. A few cases of laryngeal acini cell carcinoma have been reported in the literature. Epithelial-myoepithelial carcinoma and myoepithelial carcinoma rarely occurs in the

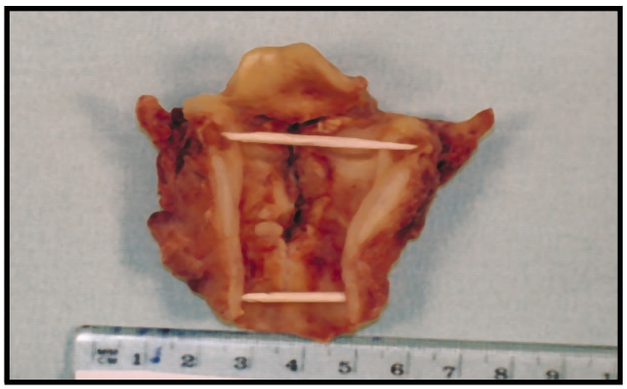

Figure 1 - Portion of the larynx showing ulceration of the mucosa, with nodular white firm mass.

larynx. Adenoid cystic carcinoma of the larynx accounts only for 0.25% of laryngeal carcinoma. The age of occurrence is variable, found mostly in the 4th-6th decade of life. The sex incidence is approximately equal. This tumor occurs predominantly in the subglottic region, however a few cases are found in the supraglottic region.[7] Glottic origin of the tumor is extremely rare. Adenoid cystic carcinoma of the larynx has similar morphology and histogenesis as that of other ACC of minor salivary glands, which is derived from epithelial or myoepithelial cells of intercalated or terminal duct elements of the seromucinous glands in the submucosa of the larynx.[8,9] The typical histological appearance is proliferation of small uniform cells with small dark nuclei and scant cytoplasm, with no nuclear atypia or mitotic activity. Hyperchromasia is prominent with even distribution of chromatin in the nuclei. The tumor cells are present in cribriform, tubular or solid pattern. Distinction between these different patterns has no great input on prognosis, however, solid variant seems to have the worst prognosis.[10] The majority of ACC develop in the pseudocytic area, they contain material that is PAS positive, diastase resistant and mucicarmine positive.[8] Although treatment of ACC is variable according to institution, the primary modality of therapy is surgical excision with lymph node dissection. Postoperative radiotherapy has improved the overall survival rate of ACC. Long term survival in ACC must be viewed after 10 or 20 years due to the insidious nature of this neoplasm. This case showed typical morphology of ACC intermingled with tubules lined by typical adenocarcinoma cells. In this case, we prefer to use the term hybrid carcinoma because the tumor arises at a single site (larynx) and is composed of 2 distinct morphology, adenoid cystic and adenocarcinoma.[11] Hybrid carcinoma is different from Collision tumor. The later represents a meeting of 2 malignancies arising at independent topographic sites. Collision tumor commonly represents carcinoma with sarcoma or lymphoma and rarely between 2 types of carcinoma.[11] In hybrid carcinoma, 2 malignancies

Figure 2 - This power shows 2 populations of cells. Oval cells with rounded nuclei and small nucleoli. In between fusiform cells with dark staining nuclei. Basement lamina surrounded these 2 cells (2500x).

Figure 3 - Myoepithelial cells show basal lamina, and fine cytoplasmic filaments (3975x).

Figure 4 - Epithelial cells with glandular differentiation. Short microvilli tight junctions and luminal secretions (3975x).

are present in one topographic site, and one tumor morphology may be over looked if the tumor is not adequately sampled. On the other hand, treatment strategy depends on the behavior of the aggressive component of the hybrid neoplasm.[11]

In this case the tumor cells morphology and immunohistochemistry reaction showed an epithelial origin, with neuroendocrine differentiation (positive NSE & S100) as well as myoepithelial cells differentiation (actin and S100 positivity).[12] These findings are confirmed by EM which showed epithelial differentiation with glandular formation, (Figure 4) myoepithelial differentiation and epithelial with neuroendocrine differentiation.[13] Our electron microscopic findings are in agreement with other EM findings of ACC of the salivary gland in a child that was reported by Tsuyoshi Murao.[14] He found that ACC exhibit features of myoepithelial differentiation as well as short microvilli projection into glandular lumina. However, his case shows the presence of pseudocyst formation, which contain basal lumina-like material and numerous crystalline spicules. On the other hand, our case shows sparse neurosecretory granules by EM and positive neuronal markers by immunohistochemistry. All these findings suggest that the histogenesis of this tumor is myoepithelial cells of intercalated ducts of the minor salivary gland in the submucosa of larynx that is capable of differentiation towards ACC, adenocarcinoma, with neuroendocrine features. The follow-up period for this patient is not long enough to determine cure. Furthermore presence of adenocarcinoma in addition to ACC will worsen the prognosis and it is expected that our patient will develop recurrence or die from the adenocarcinoma component.

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