Primary Carcinoid Tumor of the Larynx

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A case of laryngeal carcinoid in a 54-year-old Korean female is reported and discussed. This tumor is extremely rare in the larynx and there have been just over twenty cases reported in the literature to date. The case showed an initial histologic finding of epithelial dysplasia and was finally confirmed to be a carcinoid tumor. Laryngeal carcinoids are often atypical histologically and may be misdiagnosed as undifferentiated carcinoma. An electron microscopic study revealed neurosecretory-type granules. Although the patient underwent a total laryngectomy and radical neck dissection, multiple hepatic metastasis was noted postoperatively.

Key Words: Carcinoid tumor, larynx, neuroendocrine carcinoma.

The carcinoid was first recognized by Obendorfer (1907), who distinguished this from other types of carcinoma as a less aggressive entity. Carcinoid tumors are well known to occur in the respiratory tract, but a primary carcinoid tumor of the larynx is exceedingly rare. To the best of our knowledge, there are only 26 cases reported. It was first reported by Goldman et al. in 1969.

Histologically and electron microscopically, carcinoid tumors have characteristic findings that allow their distinction from other epithelial neoplasms. But the carcinoid tumor of the larynx often has atypical histologic findings, so it may be misdiagnosed as undifferentiated carcinoma. Clinically, nearly all laryngeal carcinoids are malignant pathologically. They infiltrate deeply and metastasize to the cervical lymph nodes. We report a carcinoid tumor of the larynx, which progressed more rapidly than the cases reported previously.

CASE REPORT

A 54 year-old female patient was admitted to Yongdong Severance Hospital on April 20, 1987 with a complaint of hoarseness, which persisted during the preceding month. She had smoked cigarettes for three years and had been taking anti-hypertensive drugs to control her hypertension. She had had no dyspnea, hemoptysis or dysphagia. Physical examination revealed a well developed woman in no acute distress. Indirect laryngoscopy showed diffuse edema on both true vocal folds without any limitation of motion. The mucous membrane of the cords looked smooth with no signs of erosion of the epithelium. There was no obvious mass on the supraglottis or glottis. There were no palpable lymph nodes. The first impression was that of typical Reinke's edema. So we performed microlaryngeal surgery with a sucking technique and a piece of redundant mucosa was removed with microlaryngeal forceps for biopsy, and the rest was vaporized with a carbon dioxide laser. The report of the histopathological examination was epithelial dysplasia. She was discharged with the advice of regular follow up.

One month later, she returned to our hospital with complaints of aggravated hoarseness. On indirect laryngoscopy, her right aryepiglottic fold and laryngeal surface of the epiglottis showed multiple fungating masses which was extended from the ventricular fold. One of the right superior jugular nodes was enlarged and palpable (3x2 cm). The node was firm but mobile. Biopsy was done from the aryepiglottic mass which was interpreted as carcinoma but there was doubt as to the type of carcinoma. Poorly differentiated carcinoid or adenosquamous carcinoma was suggested as most likely. Laryngeal CT scan showed a solid supraglottic mass shadow which was extended to the epiglottis and vallecular area and also revealed multiple jugular node metastasis of the right neck.
A total laryngectomy with right side radical neck dissection were performed on May 19th, 1987. All resection margins were free from tumor. The patient was discharged on June 10th, 1987 without any problems.

Four months later, she was admitted again to our hospital with complaint of abdominal pain accompanied by nausea and vomiting. Her wound was well without any evidence of recurrence in both the pharynx and neck. Her lungs were clear. Ultrasonography of the liver revealed multiple variable sized echogenic masses in the entire liver, and the liver scan showed similar multifocal cold lesions. The patient died at home five months following the discovery of her laryngeal lesion. An autopsy was not permitted.

PATHOLOGIC FINDINGS

**Gross Findings**

The laryngectomy specimen showed several exophytic nodules on the laryngeal surface of the right and left epiglottis and supraglottic areas. Each nodule was well circumscribed, but not encapsulated, covered by smooth, pink-gray mucosa and varied 0.3 to 1.8 cm in maximum dimension (Fig. 1). On section of the mass it was firm, yellow gray and localized to the submucosa. There was neither hemorrhage nor necrosis.

**Light Microscopic Findings**

The first laryngoscopic biopsy showed moderate epithelial dysplasia. The mass was well demarcated, largely confined within the submucosa, but had not true or pseudocapsule. The mucosa was not ulcerated, however, it was focally invaded by the tumor cells. The tumor was arranged in sheets, nests, acini, or trabecular patterns (Fig. 2). In some nests, its center underwent coagulation necrosis, in other nests, the tumor cells showed peripheral palisading and rosette-like features, and in another, a complex glandular pattern (Fig. 3). The tumor cells were uniform and had oval to round vesicular nuclei with clumped chromatin, one or two small nucleoli and a moderate amount of pinkish cytoplasm. There was focal squamoid differentiation; however, an in-

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**Fig. 1.** Multinodular mass is noted in the left epiglottis and both supraglottic areas, varying from 0.3 to 1.8 cm in diameter.

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**Fig. 2.** The tumor cells are arranged in nests with focal invasion of the mucosa (hematoxylin and eosin, x40).
tercellular bridge or cytoplasmic keratin was not found. Positive staining at the luminal border of the acini was demonstrated by periodic acid-Schiff stain with or without diastase treatment. Alcian blue stain was negative in these cells. Grimelius and Fontana-Masson stains were negative. Intravascular tumor thrombi or perineural invasion was not noted. Upper and lower resection margins were free from tumor. There was no tumor metastasis in the submandibular gland, submandibular lymph node and no tumor emboli in the internal jugular vein. One of sixteen lymph nodes along the internal jugular vein showed tumor metastasis, which was similar to the main lesion morphologically.

**Electron Microscopic Findings**

Electron microscopy was done using paraffin embedded blocks, so cytologic detail was moderately disrupted. However, many membrane bound electron dense granules of 100-330 nm were present, the distribution of which varied among cells (Fig. 4). In some cells there were no demonstrable granules, while others had many granules in random fashion or dense aggregates. These granules consisted of an electron dense core surrounded by a limiting mem-

Fig. 4. Membrane bound electron dense granules are noted in the cytoplasm, varying from 100 to 330 nm in size (uranyl acetate and lead citrate, ×8,000).
brane, characteristic of neurosecretory-type granules. A lumen like structure was noted, but was uncertain due to artifact.

**DISCUSSION**

Enterochromaffin or Kulchinsky-type cells are regarded as the presumed precursor of carcinoid tumor. To our knowledge, there are only 26 cases of laryngeal carcinoid reported in English literature, suggesting that these are very rare neoplasms. Bonikos and Bensch (1977) have demonstrated that enterochromaffin cells are present in the normal human larynx and trachea as well as bronchi. Therefore, it is an interesting feature that laryngeal carcinoids are extremely rare, when compared with the incidence in bronchi (Markel et al. 1980).

Williams and Sandler (1963) classified carcinoid tumors into three groups according to their site of origin: those of fore-gut, those arising from mid-gut and those arising from hind-gut. The larynx, trachea and bronchi are all fore-gut derivatives, and fore-gut carcinoids have different features from mid-gut carcinoids. Mid-gut carcinoids have argentaffin granules which are relatively large and pleomorphic. This granules contain serotonin which causes a positive argentaffin reaction. However, fore-gut carcinoids contain relatively small granules, they have a precursor of serotonin, and give a negative argentaffin reaction. Argyrophilia is commonly described in fore-gut carcinoids. We used Fontana-Masson stain for argentaffin reaction and Grimelius stain for argyrophil reaction. Our case showed neither argyrophilia nor argentaffin reaction. In cases of absence of argyrophilia, transmission electron microscopy is very helpful in confirming the diagnosis. Characteristic neurosecretory type granule can be seen in the cytoplasm of the tumor cells. The size of the granules of our case (100-330 nm in diameter) was larger than those of Tamai (90-230 nm) and Mills (75-250 nm) (Tamai et al. 1981; Mills and Johns 1984).

The diagnosis of carcinoid is made on the histological characteristics of the carcinoids and demonstration of the neurosecretory granules even though argentaffin or argyrophil reaction was positive. Mills reported several histologic features of the laryngeal carcinoids: 1. presence of nests, cords, trabeculae, or ribbon of uniform to mildly pleomorphic cells, 2. glandular or rosette-like structures may be present, 3. overlying mucosa is frequently intact without tumor invasion, 4. frequent perineural and perivascular invasion, and 5. high mitotic rate and anaplasia associated with poorly differentiated squamous cells or adenocarcinoma are absent (Mills 1984). The present case showed typical nests, and a trabecula and rosette-like pattern of small uniform polygonal cells. But perineural invasion was not noted in the present case. We found central necrosis surrounded by tumor cells which have squamoid features and had never been noted in the other cases described before. Therefore, carcinoids arising in this region have a wide variety of histologic findings. These atypical features may make carcinoids difficult to recognize and a diagnosis as undifferentiated carcinoma is easy to make.

Including the present case, there have been twenty men and seven women with a laryngeal carcinoid tumor whose ages ranged from 43 to 76 years, and our case was in the younger group. Laryngeal carcinoids have their origin from the supraglottis and glottis in most cases, only one case has originated from the subglottis. So the initial symptoms were not different from those of supraglottic tumor, such as hoarseness and sore throat. The first symptom of the present case was also hoarseness. Her indirect laryngoscopic finding of Reinke's edema made it difficult to diagnose appropriately. Likewise, only a few cases were confirmed as carcinoid tumor prior to examining the laryngectomy specimen. Suggested impressions of pathological findings were undifferentiated carcinoma, poorly differentiated carcinoma and adenocarcinoma. This difficulty is caused by the rarity of this entity, submucosal nature of the tumor, and atypical histologic findings. Differentiation of this carcinoid from undifferentiated carcinoma is important especially in early cases, because the carcinoid tumor does not respond to radiation therapy. Four of eight cases received irradiation prior to surgery, but its effect was not satisfactory in all cases (Goldman et al. 1969; Tamai et al. 1981; Mills 1984; Gapany-Gapanavičius and Kenan 1981). Carcinoid tumor may produce various biogenic amines either singley or in combination. Reported laryngeal carcinoids have been clinically nonfunctional as in our case (Baugh et al. 1987).

Carcinoid tumors of the larynx showed a high degree of malignancy in all cases, and this was clearly demonstrated in our cases. These tumors infiltrate locally and spread via lymphatics to the cervical lymph nodes. Forty four percent of cases showed regional neck node metastasis and their histological findings were indistinguishable from those of the primary tumor. Carcinoid tumors may metastasize distantly via a hematogenous route in various organs such as skin, subcutaneous tissue, lung and liver. In our case, four months after total laryngectomy and ipsilateral neck
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dissection, multiple hepatic masses, which were considered to be a metastasis, developed in disregard of the lack of evidence of regional recurrence. In the two reported cases of laryngeal carcinoid, one by Goldman (1969) and the other by Ferlito (1976), distant metastasis were noted in the skin and bone, and both cases died with tumors two years after diagnosis.

In contrast to the bronchial carcinoid, the laryngeal carcinoid has more aggressive clinical behavior (Briselli et al. 1978). In our case, distant metastasis was noted even in a very short period of time despite the good primary site. This may be caused by its infiltrative growth, perineural and perivascular invasion, and we suggest that the necrosis finding might be associated with its aggressive clinical course.

Four patients who received radiation therapy, even in the full dose, have failed to control their disease. Laryngeal carcinoid should be treated with wide excision. Mills (1984) said that sometimes perineural invasion was discontinuous within the tumor. It is, therefore, reasonable to say that the treatment of choice is wide surgical excision beyond the resectable margin with the aid of a frozen section.

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