CASE REPORT

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MALIGNANT MIXED TUMOR OF THE LARYNX

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Abstract: Background. Malignant mixed tumor of the larynx is a very rare neoplasm; only five cases have been reported, three in the English-language literature.

Methods. We report the case of a 69-year-old man with a 2-month history of hoarseness and a left laterocervical palpable mass.

Results. Total laryngectomy and bilateral radical neck dissection were performed. The tumor involved the glottic and subglottic regions and thyroid cartilage and extended to the anterior side of the larynx. Microscopically, the tumor was composed of three cellular types: epithelial cells, chondrocytes, and spindle cells. The epithelial cells resembled a moderately differentiated adenocarcinoma, the mesenchymal cells resembled a high-grade chondrosarcoma, and the spindle cells had immunohistochemical features of myoepithelial cells. The tumor metastasized to a cervical lymph node, with the three described components. The patient died 11 months after surgery.

Conclusions. The lesion in this case was considered to be a malignant mixed tumor. Differences between this tumor and that of laryngeal chondrosarcoma are discussed.

Keywords: malignant mixed tumor; larynx; carcinosarcoma; salivary gland tumor

Non-squamous carcinomas of the larynx are quite rare, and mesenchymal tumors and salivary gland–like tumors are included in this category. Mesenchymal tumors occur in 0.3% to 1% of all laryngeal neoplasms. Chondrosarcoma is the most common, whereas the others, including fibrosarcoma, rhabdomyosarcoma, malignant fibrous histiocytoma, osteosarcoma, synovial sarcoma, and liposarcoma, are infrequent. The most common salivary gland–like tumors with laryngeal involvement are pleomorphic adenomas (benign mixed tumors). Other salivary tumors described in the larynx are malignant mixed tumor, adenoid cystic carcinoma, mucopidermoid carcinoma, and acinous cell carcinoma. Malignant mixed tumor of the larynx is an extremely rare neoplasm with an ominous prognosis. To our knowledge, only five cases of laryngeal malignant mixed tumor have been reported, three of which are in the English-language literature. We present a new case of...
FIGURE 1. Macroscopic and histopathologic findings of a malignant mixed tumor of the larynx. (A) Sagittal section of larynx shows a solid, whitish tumor located in true and false folds and subglottic region. The tumor infiltrates the thyroid cartilage. Numbered scale, cm. (B) Photomicrograph shows the superficial areas of the tumor are composed of a malignant glandular proliferation (white star) associated with a chondromatous malignant proliferation (black star). No tumoral changes are observed in the superficial laryngeal epithelium (arrow) (hematoxylin-eosin stain; original magnification, ×100). (C, inset) Strong positive AE1/AE3 cytokeratin expression is seen in the malignant glands (anti-AE1/AE3 cytokeratin–hematoxylin stain; original magnification, ×400). (D) The extensive areas with a high degree of cartilaginous tumor infiltrate the perilaryngeal tissues (hematoxylin-eosin stain; original magnification, ×100). (E) An intense immunoreaction of S-100 protein is observed in the cytoplasm of malignant chondrocytes (anti-S-100–hematoxylin stain; original magnification, ×400). (F) Bundles of spindle cells with evident smooth muscle actin expression are intermixed with the glandular and chondromatous proliferations (anti-smooth muscle actin–hematoxylin stain; original magnification, ×100). (G) The lymph node metastasis is composed of epithelial (arrows) and cartilaginous malignant cells (hematoxylin-eosin stain; original magnification, ×400).
malignant mixed tumor of the larynx that developed early metastasis in the cervical lymph node.

CASE REPORT

The patient was a 69-year-old man with a 2-month history of hoarseness, dysphagia, odynophagia, and a left neck mass. He was a smoker for 30 years and had had a cough and expectoration for 4 years, as well as dyspnea with moderate efforts. He did not have anorexia or weight loss. There was no history of previous radiotherapy to the neck area. Physical examination revealed a large, fixed, rock-hard mass that moved during swallowing and that involved both sides of the thyroid cartilage, both true and false vocal folds, and the anterior and posterior commissures. The tumor extended to the subglottic region. Total laryngectomy and bilateral radical neck dissection, including both internal jugular veins, were performed. Two months after laryngectomy, the patient received 63 Gy to 68 Gy in the laryngeal region and 55 Gy in the supraclavicular and superior mediastinum. Six months after surgery, the patient had metastasis develop in two cervical lymph nodes. Fine-needle aspiration demonstrated malignant cells with intense myxoid induction of the stroma compatible with previous malignant mixed tumor. One month later, the patient had bilateral lung and vertebral metastases. Finally, 11 months after surgery, the patient died.

RESULTS

Gross Pathology. The surgical specimen was a total laryngectomy and bilateral radical neck dissection. We observed a mass that measured $7 \times 6 \times 4$ cm and involved both sides of the thyroid cartilage. The cut surface showed a well-circumscribed and exophytic mass, whitish in color, with necrotic and ulcerated areas that involved both true and false vocal folds and anterior and posterior commissures and extended along the anterior side of the larynx and subglottic region to 4 cm from the inferior surgical edge. Cross-sections revealed that the tumor had invaded the thyroid cartilage and was very close to the surgical edges, although it did not reach them (Figure 1A).

Light Microscopy. The tumor was composed of the following three cellular types: (1) epithelial cells, situated at the periphery (Figure 1B,C); (2) chondrocytes, situated in the central area (Figure 1B,D,E); and (3) spindle cells (Figure 1B,F). The spindle cells were frequently intermixed with the other tumoral cells. The malignant epithelial component was formed by glandular structures. The epithelial cells had an eosinophilic cytoplasm, a large irregular hyperchromatic nuclei, coarsely granular chromatin, and prominent nucleoli (Figure 1B). The epithelial component showed intensely positive reactivity for anti-AE1/AE3 cytokeratin antibody (DAKO, Glostrup, Denmark, at 1:100 dilution) (Figure 1C), and anti-EMA antibody (DAKO, at 1:100 dilution). A desmoplastic stroma was seen in areas of epithelial proliferation, with strong positive expression of anti-vimentin antibody (DAKO, at 1:100 dilution). The cartilaginous component was composed of binucleated and multinucleated chondrocytes with pleomorphic nuclei and numerous mitoses (Figure 1D). Intracytoplasmic expression of anti-S-100 antibody (DAKO, at 1:800 dilution) (Figure 1E) and vimentin was evident in the malignant chondrocytic proliferation. The spindle cells had the benign aspect of myoepithelial cells, as confirmed by the intense expression of anti–smooth muscle actin antibody (DAKO, at 1:100 dilution) (Figure 1F). The tumor was not related to surface epithelium, which showed neither metaplasia nor dysplasia. There was no evidence of any pre-existing benign mixed tumor. The thyroid cartilage and prelaryngeal tissues had been invaded by the tumor. One of 13 lymph nodes in both sides of the neck had been invaded by a metastatic tumor (Figure 1G), which included the three cellular components described previously.

DISCUSSION

The three proliferating components—glandular, cartilaginous, and spindle—observed in this tumor determine the diagnosis of malignant mixed tumors, similar to those described in the salivary glands.

In the larynx and salivary glands, the terms “malignant mixed tumor” and “carcinosarcoma” have been used without distinction, although this is controversial. Carcinosarcoma of the larynx is a biphasic neoplasm in which both the epithelial and stromal components fulfill the histologic criteria for malignancy. However, our case presented a similar pattern in a primary laryngeal tumor and in the lymph node, characterized by the intimate association of a malignant glandular
tumor, a chondrosarcoma, and a spindle cell proliferation of myoepithelial cells. These findings are consistent with the diagnosis of malignant mixed tumor of the larynx.

Several hypotheses have been advanced concerning the histogenesis of nonsquamous malignant laryngeal tumors. With respect to carcinosarcoma, four etiologic hypotheses have been proposed. The first considered carcinosarcoma to be a squamous carcinoma with reactive mesenchymal proliferation. This theory is no longer favored, because the spindle cell component could metastasize independently of the carcinoma. The second hypothesis proposes that the carcinosarcoma is a collision tumor, in which carcinoma and sarcoma developed simultaneously but independently. The third regards the carcinosarcoma as a malignant tumor arising in a mesenchymal and epithelial embryonic rest. The fourth hypothesis is based on the occurrence of the double differentiation of a totipotent malignant cell into carcinomatous and sarcomatous components. The fourth hypothesis is probably the most acceptable, based on evidence from immunohistochemical and ultrastructural studies.

The histologic and immunohistochemical data in our case confirm that the malignant mixed tumor is probably the consequence of a glandular, myoepithelial, and chondromatous transformation of the same precursor malignant cell. The existence of adenocarcinomatous and chondrosarcomatous areas in the lymph node metastasis indicates that this laryngeal malignant mixed tumor originated in the seromucous glands of the larynx. Moreover, this hypothesis is consistent in part with the origin of the malignant mixed tumor in the salivary gland, because some malignant mixed tumors of the salivary gland also arose in a previously pleomorphic adenoma (a so-called benign mixed tumor). The histogenesis of malignant mixed tumor of the larynx is not well established; however, in the major salivary glands, the origin of this tumor has been related to a proliferation of myoepithelial cells, which have been considered as totipotent precursor cells. In our case, the immunohistochemical data confirmed the presence of abundant smooth muscle actin–positive myoepithelial cells intermixed with adenocarcinomatous and chondrosarcomatous components.

The clinical presentation of the laryngeal malignant mixed tumor was not different from other laryngeal carcinomas; however, a more equal distribution between men and women was observed. The prognosis of the malignant mixed tumors of the larynx is worse than that of patients with squamous laryngeal carcinomas.

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