Review Article

Neuroendocrine tumor of larynx: A review of literature

ABSTRACT

Neuroendocrine neoplasms of the larynx are rare but are the most common nonsquamous tumors of this organ. There are 4 different types of laryngeal neuroendocrine tumors composed of paraganglioma, typical carcinoid, atypical carcinoid tumor, and small cell neuroendocrine carcinoma. Carcinoids and small cell neuroendocrine carcinomas are epithelial neoplasms, whereas paragangliomas are of neural origin. Diagnosis is based primarily on light microscopy and confirmed by immunohistochemistry and electron microscopy. Precise diagnosis is essential because the natural history, treatment, and prognosis vary widely for the different neoplastic categories. Typical carcinoids are very rare and are treated by wide local excision, usually partial laryngectomy, without elective neck dissection. Atypical carcinoid tumors are more common and more aggressive. They are treated by partial or total laryngectomy with elective or therapeutic neck dissection. Adjuvant chemo/radiotherapy may be of benefit in some cases. Small cell neuroendocrine carcinomas are highly aggressive and should be considered disseminated at initial diagnosis. The treatment is by irradiation and chemotherapy as surgery has proven to be of a little benefit. Paragangliomas are treated by local excision or partial laryngectomy.

Key words: Carcinoid tumor; larynx carcinoma; neuroendocrine tumor.

Introduction

Cancers of the larynx are usually squamous cell carcinomas. Neuroendocrine tumors are the most common nonsquamous types of neoplasms arising in larynx and represent <1% of all primary laryngeal tumors.[1] The first laryngeal neuroendocrine neoplasm (LNN) of neural type was identified in 1955 by Blanchard and Saunders,[2] whereas only recently laryngeal neuroendocrine carcinomas have been recognized.

In particular, the first atypical carcinoid tumor was reported in 1969 by Goldman *et al*.[3] The diagnosis is based on recognition of the characteristic neuroendocrine architecture and on the immunohistochemical confirmation of neuroendocrine differentiation. Diagnosis can be delayed as a result of the entity's rarity and tissue. Therapeutic options are various combination of surgery, chemotherapy, and radiation therapy based on histology.[4]

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Discussion

Extrapulmonary neuroendocrine small cell carcinoma is a relatively rare disease, with the larynx the most frequently affected organ in the head and neck. They can occur in any region of the larynx with the supraglottis the most commonly reported site.[5] LNN have been recognized as the most common nonsquamous types of neoplasms arising in this area. They account for <1% of all laryngeal neoplasms. To date, approximately 500 publications deal with this relatively

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uncommon yet intriguing family of laryngeal tumors.[6,7] The atypical carcinoid tumor is the most frequent of all LNN, followed by the small cell neuroendocrine carcinoma, paraganglioma, and the typical carcinoid. LNN are divided into two broad categories based on their tissue of origin: Epithelial and neural. The epithelial-derived tumors, neuroendocrine carcinomas, are subclassified into three subtypes: Typical carcinoid (well differentiated neuroendocrine carcinoma, Grade I), atypical carcinoid tumor (moderately differentiated neuroendocrine carcinoma, Grade II; large cell neuroendocrine carcinoma), and small cell neuroendocrine carcinoma (poorly differentiated neuroendocrine carcinoma, Grade III). Small cell neuroendocrine carcinoma includes oat cell, intermediate cell, and combined variants. Some authors consider the large cell neuroendocrine carcinoma of the larynx as a separate entity using the diagnostic criteria established for pulmonary neuroendocrine tumors.[8] However, in the most recent World Health Organization classification for tumors of the larynx, large cell neuroendocrine carcinoma is classified together with the atypical carcinoid tumor group.[9] In 2008, Wenig includes the large cell neuroendocrine carcinoma in the group of moderately differentiated neuroendocrine carcinoma (or atypical carcinoid tumor). The neural category consists only of paraganglioma.[10] LNN must be further divided into primary and secondary types, although the latter are extremely rare and only 5 cases of small cell neuroendocrine carcinoma have been reported in the literature.[11] A laryngeal metastasis from a primary small cell neuroendocrine carcinoma of the lung is distinguished from a primary LNN by imaging studies of the lung. However, in rare instances, a primary tumor (with laryngeal metastasis) may be situated in other organs.[12]

Pathology

Typical carcinoid, atypical carcinoid tumor, small cell neuroendocrine carcinoma, and paraganglioma are distinguished from nonneuroendocrine laryngeal neoplasms on light microscopy by their display of neuroendocrine morphology and on immunohistochemistry by reactivity with neuroendocrine markers and ultrastructural evidence of membrane-bound dense-core granules.

Typical and atypical carcinoid tumors

These tumors display a variety of features. The cells may be arranged in cords, nests, trabeculae, or glandular patterns. The typical carcinoid is composed of uniform and small polygonal cells with regular round or oval centrally placed nuclei and granular eosinophilic cytoplasm. The cells are separated by a fibrovascular or hyalinized stroma. Mitoses, cellular pleomorphism, and necrosis are usually absent in the typical carcinoid. Oncocytic, oncocytoid, mucinous and amyloid changes, focal "Zellballen," and rosettes may be seen in typical and atypical carcinoids. In contrast to the typical carcinoid, the neoplastic cells are larger and the nuclei are often vesicular and contains prominent nucleoli in the atypical carcinoid tumor. Typical carcinoid has fewer than 2 mitoses per mm^2 (10 high-power fields) without necrosis, whereas atypical carcinoid tumor has 2–10 mitoses per mm^2 and/or necrosis.

Small cell neuroendocrine carcinoma

These are oat cell, intermediate, and combined. The oat cell type is composed of sheets of small cell with hyperchromatic nuclei and scant cytoplasm. Occasionally, the cells form interconnecting the ribbons. Cell necrosis and mitotic activities are frequent. Rosette formation may be seen. In the intermediate cell type, the growth pattern is similar, but the cells are slightly larger, more polygonal, spindle shaped, or fusiform. The cytoplasm is more prominent than in the oat cell type. In the combined type (the rarest of the three types), the tumor is a mixture of small cell neuroendocrine carcinoma with another tumor, usually squamous cell carcinoma or adenocarcinoma. Small cell neuroendocrine carcinoma may be immunoreactive with cytokeratins, epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), and with general neuroendocrine markers, including chromogranin, CD56, CD57, synapthophysin, neuropeptides, including calcitonin, somatostatin, adrenocorticotropic hormone, bombesin, and serotonin. In addition, small cell neuroendocrine carcinoma may be positive for thyroid transcription factor-1.[13,14]

Immunohistochemically, the chief cells are positive for all the general neuroendocrine markers such as chomogranin, synaptophysin, CD57, and neuropeptide markers, including galanin and somatostatin). They do not stain with epithelial markers (cytokeratin, CEA, and EMA) or with calcitonin and bombesin and this supports the diagnosis. Sustentacular cells are stained by antibodies to S-100 protein and glial fibrillary acidic protein. The chief cells are S-100 protein and glial fibrillar acid protein negative.[15]

Treatment

Typical carcinoid tumor

Surgical excision is the treatment of choice for typical carcinoid of the larynx.[16,17] Conservation surgery, particularly supraglottic subtotal laryngectomy, may be suitable but large tumors require total laryngectomy. Neck dissection is not indicated in view of the usual absence of lymph node metastases.[18] Moreover, irradiation and chemotherapy have been found to be ineffective.[14]

Atypical carcinoid tumor

The mainstay of treatment for atypical carcinoid tumor of the larynx is surgical excision. Partial or total laryngectomy may be performed depending on the site and extent of the primary tumor. As most tumors are supraglottic in location, supraglottic laryngectomy is often the procedure of choice. Elective neck dissection appears to be warranted in view of the high incidence of both early cervical metastasis and subsequent involvement of cervical nodes.[18] Bilateral selective neck dissection should also be used therapeutically for mobile metastatic disease. Although earlier literature indicated that radiation and chemotherapy employed preoperatively, postoperatively, or as a primary modality were ineffective in the management of this malignancy.[19,20] Gillenwater *et al*., in a retrospective review of patients treated at The University of Texas M.D. Anderson Cancer Center, reported that a few patients with atypical carcinoid tumors responded to these modalities, suggesting that a combined approach may be beneficial, at least for some patients.[21]

Small cell neuroendocrine carcinoma

It is generally agreed that surgery alone or in combination with radiation does not improve local tumor control and is not the initial treatment of choice.[16,22]

Although radiation alone did not improve survival, it was successful in controlling the tumor at the primary site. Adjuvant chemotherapy appeared to prolong the median survival among patients from 11 to 19 months. The combination of primary radiation therapy and adjuvant chemotherapy resulted in median patient survival of 55 months, representing significantly longer survival than with any other treatment regimen. The commonly used chemotherapeutic agents are cyclophosphamide, doxorubicin, vincristine, methotrexate, and lomustine. A 9–18 months period of treatment is usually suggested.[23] Resistance to chemotherapy represents an important indicator of poor prognosis. The recurrence is usually generalized and the results of any therapy are poor. Nevertheless, palliative chemotherapy may be warranted even under these circumstances, as some improvement in the quality and length of life may be achieved. As the chemotherapeutic agents commonly employed do not penetrate the blood-brain barrier, prophylactic cranial irradiation has been suggested as part of the management of this cancer.[24] However, Ferlito and Rinaldo have pointed out that central nervous system metastasis occurs in only 7.7% of patients with laryngeal small cell neuroendocrine carcinoma, and this occurs usually as a preterminal event. Therefore, such elective treatment is not indicated.[11]

Paraganglioma

Laryngeal paragangliomas are almost invariably benign and should be treated as such. Surgery is preferable to radiation for paragangliomas arising in the larynx as cure can be easily achieved without loss of laryngeal function. Partial laryngectomy remains the mainstay of treatment. With appropriate clinical suspicion and the use of modern imaging techniques, laryngeal paragangliomas can be routinely diagnosed and treated with the preservation of laryngeal function.[25]

Prognosis

The clinical course of laryngeal typical carcinoid is not indolent, as was believed in the past, and distant metastases, which involve the liver and cause death, have occurred. Soga *et al*.[26] observed that 33.3% of 42 patients with typical carcinoid of the larynx also developed metastases. The 5-year survival rate for typical carcinoid of the larynx was 48.7% in a large series as recently reported.

The clinical behavior of an atypical carcinoid tumor is aggressive and is more aggressive when the metastatic index is high. An unfavorable course is observed when there are lymphatic emboli or when the Ki-67 index is higher than 5%. 28 Soga *et al*.[26] described finding metastases in 66.7% of 199 cases of atypical carcinoid tumor of the larynx. Cervical lymph node metastases are often present. Other sites of metastases include bone, skin, subcutaneous tissues, distant lymph nodes, lung, etc., Death has usually resulted from distant metastases and not from local or regional recurrence. The 3-, 5-, and 10-year survival rates of the patients were 58.5%, 36.5%, and 12.2%, respectively. Thus, the survival rate decreased slowly with the passage of time.[27]

In the cases like we reported small cell neuroendocrine carcinoma of the larynx prognosis is very poor, and the clinical course is rapidly fatal. It is the most lethal tumor of the larynx. More than 90% of patients with this tumor develop metastatic disease.[28] The most common sites of metastatic spread of this very aggressive neoplasm are the cervical lymph nodes, liver, lung, bones, and bone marrow. As with small cell lung cancer, small cell neuroendocrine carcinoma of the larynx should be regarded as a systemic disease. A 2008 publication, using the National Cancer Institute's Surveillance and End Results database, found 5-year survival rates for glottic and supraglottic small cell carcinoma of 15% and 24.1%, respectively.[7]

The biological behavior of laryngeal paraganglioma is almost exclusively benign. Malignant behavior has been reported in several cases, but critical reviews of the literature have accepted only 1 case of metastatic paraganglioma of the larynx. No paraneoplastic syndromes have been reported in association with paraganglioma.[27]

Conclusion

LNN constitute a variety of rare neoplasms of the larynx that have had numerous names and classification in the past, but are currently classified as typical carcinoid, atypical carcinoid tumor, small cell neuroendocrine carcinoma, and paraganglioma. It is most important to classify each case correctly as the clinical course, treatment, and prognosis varies greatly according to the diagnosis. Typical carcinoids are more aggressive than previously believed and metastasize in about 1/3 of cases. They are treated by partial or total laryngectomy without neck dissection. Atypical carcinoid tumors metastasize to regional nodes as well as distantly. They are treated surgically by partial or total laryngectomy with elective or therapeutic neck dissection. Small cell neuroendocrine carcinomas are highly aggressive. Treatment is by irradiation and chemotherapy. The survival rates are similar to those for small cell lung cancer. Laryngeal paragangliomas should be treated by local excision or partial laryngectomy.

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Conflicts of interest

There are no conflicts of interest.

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