A Diagnostic and Therapeutic Approach to Paragangliomas of the Larynx

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**Background:** Differentiating paragangliomas from moderately differentiated neuroendocrine carcinoma in the larynx is a difficult management problem. As the biological behavior of these 2 entities is different, we developed an algorithm for the preoperative diagnosis and treatment of this disease.

**Design:** The sample case from which the algorithm was developed consisted of a 69-year-old man who was transferred to us after tracheostomy and an attempt at biopsy for airway obstruction secondary to a vascular mass. Biopsy resulted in substantial bleeding. Flexible laryngoscopy showed a vascular mass of the supraglottis. A computed tomographic scan showed 2 vascular masses at the carotid bifurcation and in the larynx. An arteriogram confirmed synchronous vascular tumors.

**Results:** The arteriogram showed the superior thyroid artery to be the major feeder vessel to this mass, a situation commonly seen in paragangliomas but not other neuroendocrine tumors. The presence of synchronous lesions and a vascular mass based on the superior thyroid artery helped differentiate paraganglioma from the other neuroendocrine tumors. As the biological behavior of paragangliomas is relatively benign, we performed a conservative supraglottic laryngectomy and excision of the carotid body tumor. Histologic diagnosis and immunohistochemical analysis confirmed the diagnosis of paraganglioma.

**Conclusions:** The vascular nature of neuroendocrine tumors prevents preoperative pathological diagnosis. Radiologic features demonstrating a vascular mass with a dominant feeder vessel by the superior or inferior thyroid artery may help in the clinical diagnosis of paragangliomas of the larynx. Since paragangliomas are rarely malignant, a conservative surgical procedure should suffice.


**NEUROENDOCRINE tumors of the larynx are the subject of much controversy in the recent literature. The major dispute centers on the pathological classification of these tumors. This is not a trivial debate because both treatment and prognosis are very different for the various types of lesions. Neuroendocrine neoplasms of the larynx are classified in several ways; however, the most accepted method starts by dividing them into epithelial vs neural origin. Paragangliomas are of neural origin. The epithelial group is subdivided into well-differentiated neuroendocrine carcinoma, moderately differentiated neuroendocrine carcinoma (MDNEC), and poorly differentiated neuroendocrine carcinoma. Well-differentiated neuroendocrine carcinoma is very rare, with only 12 cases reported in the larynx. Poorly differentiated neuroendocrine carcinoma of the larynx is somewhat more common, with about 150 cases in the literature.**

**REPORT OF A CASE**

**HISTORY AND PHYSICAL FINDINGS**

A 69-year-old man with a history of pneumonia and subsequent ventilator dependence thought to be secondary to poor pul-
monary function required a tracheotomy. His recovery was complicated by several episodes of bright-red hemoptysis both orally and via the tracheotomy tube. The blood was noted to come from the tracheostomy site only when the cuff was deflated.

After decannulation of the tracheostomy failed, direct and microscopic laryngoscopy was performed, which showed a vascular-appearing mass in the supraglottic larynx on the left side (Figure 1). Attempts at biopsy and laser phototherapy caused brisk bleeding and were aborted. The patient was transferred to our institution for definitive workup of this lesion. Flexible laryngoscopy confirmed the referring otolaryngologist’s findings.

RADIOLOGIC FINDINGS

Computed tomography of the neck with contrast medium demonstrated a large enhancing mass of approximately 4 cm that displaced the left carotid artery posterolaterally, as well as a supraglottic vascular mass that was not continuous with the neck lesion (Figure 2A). Magnetic resonance imaging with gadolinium contrast gave similar findings (Figure 2B). A presumptive diagnosis of carotid body and laryngeal paraganglioma was made. A 4-vessel arteriogram was performed (Figure 2C).

TREATMENT AND OUTCOME

The decision was made to perform a supraglottic laryngectomy and resection of the carotid body tumor. The operation was performed without incident, and the patient did well postoperatively with no further hemoptysis. Light microscopy showed the tumor to be composed of round to polygonal epithelioid cells arranged in nests of varying sizes (Zellballen pattern). The cells had eosinophilic cytoplasm. Blood vessels were interspersed through the tumor (Figure 3A). Immunohistochemical stains for neuron-specific enolase and chromogranin showed immunoreactivity of the tumor cells (Figure 3B-C). The S100 protein stained the sustentacular cells (Figure 3D). Calcitonin and cytokeratin did not stain the tumor cells (Figure 3E-F). These findings support our diagnosis of paraganglioma of the larynx. Two months postoperatively, the patient shows no evidence of disease.

COMMENT

Paragangliomas are of neural origin, specifically the paraganglion cells of the parasympathetic nervous system. It is the only neuroendocrine tumor that is more common in women (3:1), and it has been seen in almost all decades of life. Only 65 adequately studied laryngeal paragangliomas have been reported, and most of these were located in the supraglottis. They usually present in the same way as other laryngeal tumors, with voice changes, airway compromise, and hemoptysis. Only 1 case of a functional laryngeal paraganglioma has been reported.

Some investigators believe paragangliomas of the larynx are almost exclusively benign and should be treated as such, with local conservative resection and no further regional nodal dissection. Historically, the litera-
ture has reported a 25% malignancy rate; however, it is apparent that this rate included neuroendocrine carcinomas. Ferlito et al used immunohistochemical techniques to prove that most of these neoplasms were actually MDNEC.

One must not rely on the classic histologic finding known as the Zellballen pattern, which is described as chief cells that are clustered into round nests of cells. This well-known cellular arrangement can be found in the carcinoid tumors, melanomas, and medullary carcinomas of the thyroid. There is a fibrovascular stroma surrounding these cell nests, which contain at their periphery the sustentacular cells that are difficult to see on routine stains but are easily apparent on special immunostaining. Other characteristic microscopic findings include an eosinophilic cytoplasm and large nuclei.

Figure 3. A, “Nesting” of cells and blood vessels (hematoxylin-eosin, original magnification ×20). B, Reactivity of tumor cells (neuron-specific enolase, original magnification ×20). C, Reactivity of tumor cells (chromogranin, original magnification ×20). D, Staining of sustentacular cells (brown, spindle cells at edge of nest) (S100 protein, original magnification ×40). E, Negative immunoreaction (calcitonin, original magnification ×20). F, Negative immunoreaction (cytokeratin, original magnification ×20).
of about 30 to 80 years. They are also most commonly hormonally active, resulting in the carcinoid syndrome. This tumor, unlike the paraganglioma, has a high likelihood for metastasis and behaves in an aggressive manner, as shown by the low (48%) 5-year survival. A particularly distressing feature of these tumors is the 22% incidence of metastasis to skin, which can occur as the presenting sign without lymph node involvement.

Microscopically, these tumors can mimic paraganglioma with a Zellballen pattern. The cells have an eosinophilic cytoplasm with hyperchromatic nuclei that contain large nucleoli. Frequent mitotic figures are seen. Invasion is a feature that aids in distinguishing paragangliomas from neuroendocrine carcinomas. The diagnosis should be confirmed by immunohistochemical and electron microscopic studies. These tumors should also be positive for the neuroendocrine and, more important, the epithelial markers as listed previously. They can stain positive for calcitonin and bombesin. Only about 20% of MDNECs are S100 protein positive.

There have been no reports, to our knowledge, of angiographic studies of carcinoids of the head and neck. However, angiographic studies of small-intestine carcinoids have shown “poor to moderate accumulation of contrast medium in the tumor and no filling of the veins.”

This controversy may be provoking but does nothing to help the otolaryngologist diagnose these lesions preoperatively, when it would benefit the patient most. In addition, frozen-section diagnosis is not helpful, as immunohistochemical stains are required to differentiate these 2 entities. With the potential dangers of performing a biopsy on such a vascular tumor, a safe and predictable management decision tree is needed.

We propose an algorithm (Figure 4) that begins with computed tomography with contrast enhancement to better define a vascular-appearing, submucosal tumor of the larynx. When no enhancement is noted, one may plan on endoscopy with biopsy as with any aerodigestive tract neoplasm. If the mass does indeed enhance, we recommend proceeding to 4-vessel angiography. This would identify whether any major feeding arteries to the tumor are present, as well as screen for synchronous lesions. These findings would be more consistent with a paraganglioma. An arteriogram is also important preoperatively to determine the status of the circle of Willis and prepare the surgeon for the unlikely event of carotid resection. When a named feeding vessel is identified, such as the inferior or superior thyroid artery, we prepare the patient for a conservative resection, since this leads us to believe the mass is indeed a paraganglioma.

In our case, we opted for a supraglottic laryngectomy. In our case, we consider embolization of the mass, which has been shown to decrease operative time and aids in preparing the patient for a conservative resection, since this leads us to believe the mass is indeed a paraganglioma.

The angiographic findings consistent with a paraganglioma are “profuse vascularity, well-defined nutrient vessels, and a dense, nonhomogeneous tumor blush in the capillary phase.” The immunohistochemical findings most indicative of a paraganglioma are positivity with regard to neuroendocrine markers such as chromogranin, neurofilament, synaptophysin, and neuron-specific enolase. They should be negative for all epithelial markers, such as cytokeratin, epithelial membrane antigen, and carcinoembryonic antigen (CEA). The sustentacular cells should be positive for S100 protein. Neither calcitonin nor bombesin is present in paragangliomas. However, immunoreactivity to calcitonin can be found in about two thirds of the MDNECs.

The MDNEC tumors of the larynx are uncommon, with only about 300 cases reported to date. It is, however, the most common neuroendocrine tumor of the larynx. It has a male-female ratio of 3:1 and an age range of about 30 to 80 years. They are also most commonly seen in the supraglottis. In addition to the symptoms one would expect with a supraglottic mass, neuropathic pain syndromes via unnamed vasculature. If no major vessel is identified, such as the inferior or superior thyroid artery, we prepare the patient for a conservative resection, since this leads us to believe the mass is indeed a paraganglioma. In our case, we opted for a supraglottic laryngectomy. Also, at this point we consider embolization of the mass, which has been shown to decrease operative time and overall blood loss.

Other factors that favor the neoplasm being a paraganglioma are synchronous lesions in the head and neck and the profuse tumor blush mentioned above. Neuroendocrine carcinomas usually do not produce such massive filling with contrast medium. This suggests that a relatively small volume of blood is delivered to carcinoids via unnamed vasculature. If no major vessel is identified or if there is any evidence of metastasis, the lesion is thought to be an MDNEC and a more radical procedure is suggested, such as a total laryngectomy. Elective neck dissection in a clinically negative neck (ie, one with no obvious clinical evidence of nodal metastasis) would be in order, with further dissection for any positive lymph nodes.

Figure 4. Algorithm for differentiation of laryngeal paraganglioma and moderately differentiated neuroendocrine carcinoma (MDNEC). CT indicates computed tomography; MR, magnetic resonance; and Dx, diagnosis.
nodes. The MDNEC is not radiosensitive, although radiotherapy has been used for palliation after a biopsy was performed.22

CONCLUSIONS

Laryngeal paragangliomas have been difficult to distinguish from MDNECs of the same site. The inability to examine these vascular tumors by biopsy has hindered preoperative diagnosis in the past. We believe that one can obtain a presumptive diagnosis before tissue retrieval, as outlined in Figure 4. This, along with precise pathological studies including light microscopy and immunohistochemical methods, should help otolaryngologists reach the correct diagnosis and offer intervention that is appropriate. Further investigation into this matter is warranted, with prospective studies involving special attention to arteriography of laryngeal neuroendocrine carcinomas.

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