Neuroendocrine tumors of the larynx

Lester D.R. Thompson, MD

Neuroendocrine neoplasms of the larynx encompass five separate tumors: paraganglioma, typical carcinoid, atypical carcinoid, small cell carcinoma, and large cell neuroendocrine carcinoma. Many synonyms are employed, with well-, moderately, and poorly differentiated neuroendocrine carcinoma commonly applied to the middle three tumors (World Health Organization preferred terminology). Paraganglioma is an exceedingly uncommon neuroendocrine tumor in the larynx, as is large cell neuroendocrine carcinoma, and therefore these will not be further discussed.

The most common laryngeal neuroendocrine tumor is the atypical carcinoid (moderately differentiated neuroendocrine carcinoma), which is a malignant epithelial tumor showing neuroendocrine histologic and immunohistochemical features. Small cell carcinoma is the next most common, while typical carcinoid (well-differentiated neuroendocrine carcinoma) is very uncommon. All of these tumors affect men more often than women, usually in the older decades of life (fifth to seventh decades), and with a strong association with heavy tobacco use.

Patients present with nonspecific clinical symptoms of hoarseness, dysphagia, and sore throat. In rare instances, aberrant hormone production by the tumor cells may result in a paraneoplastic syndrome. Outcome and management are different for each tumor type, but surgery is generally used for all, with chemotherapy added for the atypical carcinoid and small or large cell neuroendocrine carcinomas. Many patients present with advanced disease, and recurrences are common.

The vast majority of tumors affect the supraglottic larynx, usually as a submucosal nodule or polypoid mass, but sometimes below an ulcerated mucosa in higher-grade tumors.

Typical carcinoid grows in ribbons, nests, and festoons of relatively small to medium cells showing an intermediate nuclear-to-cytoplasmic ratio and round nuclei with delicate, salt-and-pepper nuclear chromatin distribution. Mitoses are inconspicuous.

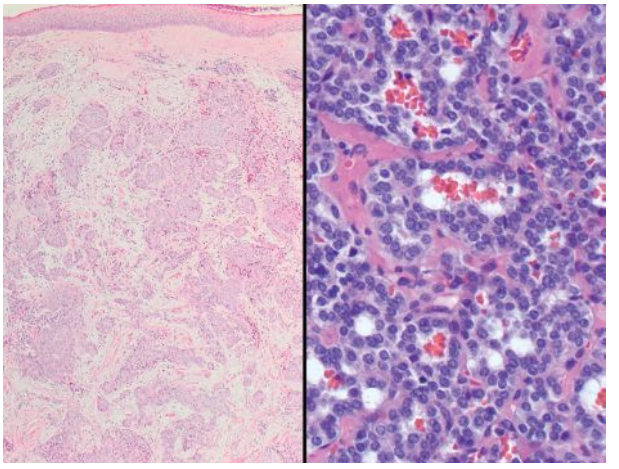

Figure 1. Atypical carcinoid. Left: There is an intact surface epithelium with numerous small glandular and ribbon-like nests in the stroma. Right: There is a relatively high nuclear-to-cytoplasmic ratio, delicate chromatin, and inconspicuous nucleoli.

Atypical carcinoid cells grow in nests, cords, sheets, and trabeculae (figure 1) of round to spindled cells with granular cytoplasm surrounding nuclei with stippled to coarsely distributed chromatin (figure 2). Gland-like structures or rosettes may be seen. Tumor necrosis and 2 to 10 mitoses per 10 high-power fields are used to define the tumors and separate them from typical carcinoid and small cell carcinoma.

Small cell carcinoma exhibits sheets, nests, and a trabecular arrangement of the neoplastic cells that are highly infiltrative, showing nuclei with granular chromatin and indistinct nucleoli. Nuclear molding, crush artifacts, necrosis, and high mitoses (>10 per 10 high-power fields) are easily identified (figure 3).

The neoplastic cells are positive for a variety of cytokeratins and will react with at least one neuroendocrine marker (synaptophysin [figure 2] > CD56 > chromogranin). TTF-1 is variably expressed, although

Continued on page 266

From the Department of Pathology, Southern California Permanente Medical Group, Woodland Hills Medical Center, Woodland Hills, Calif.

cation.[1] While the appearance is quite classic, pathology is needed to confirm diagnosis. Histology typically shows sheets of medium to large cells with abundant pink, granular cytoplasm and small, round nuclei with fine chromatin and small nucleoli; there is no evidence of Schwann cell origin, and the tumors are negative for S-100.[2] The lesion is typically covered by stratified squamous mucosa and may have some areas of ulceration or necrosis if it outgrows its blood supply.

As these tumors are usually present at birth and can be quite large, they typically present with difficulty taking oral feeding and quite possibly airway obstruction. As a result, removal is typically undertaken quite quickly, usually between 2 days and 6 weeks of life.[3] Typically, no additional comorbidities are found; our case was slightly complicated by the presence of tetralogy of Fallot, which necessitated the use of cardiac anesthesia and a preoperative cardiac evaluation. The vast majority of these patients do well postoperatively with no sequalae. While these lesions are rare, it is important to keep them in the differential of neonatal head and neck masses.

References

1. Pathak M, Narula D. Case series of gingival granular cell tumor—a revelation in neonates. J Oral Maxillofac Surg Med Pathol 2016. DOI: 10.1016/j.ajoms.2016.02.004
2. Childers EL, Fanburg-Smith JC. Congenital epulis of the newborn: 10 new cases of a rare oral tumor. Ann Diagn Pathol 2011;15(3):157-61.
3. Messina M, Severi FM, Buonocore G, et al. Prenatal diagnosis and multidisciplinary approach to the congenital gingival granular cell tumor. J Pediatr Surg 2006;41(10):E35-8.

Continued from page 262

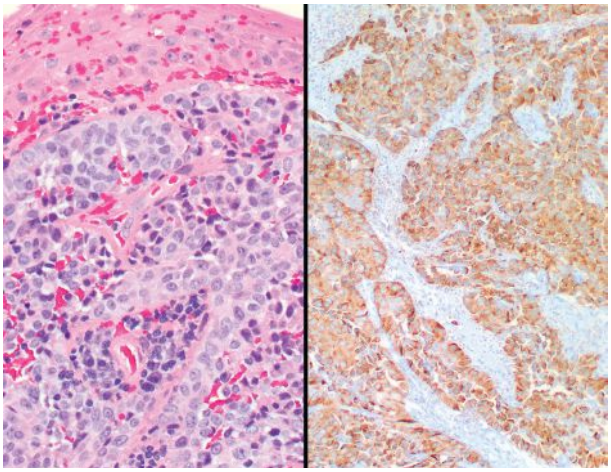

Figure 2. Atypical carcinoid. Left: There is a ribbon to festoon-like arrangement of the neoplastic cells, which show limited pleomorphism. The surface epithelium is uninvolved. Right: A strong and diffuse reaction with synaptophysin in all of the neoplastic cells is characteristic.

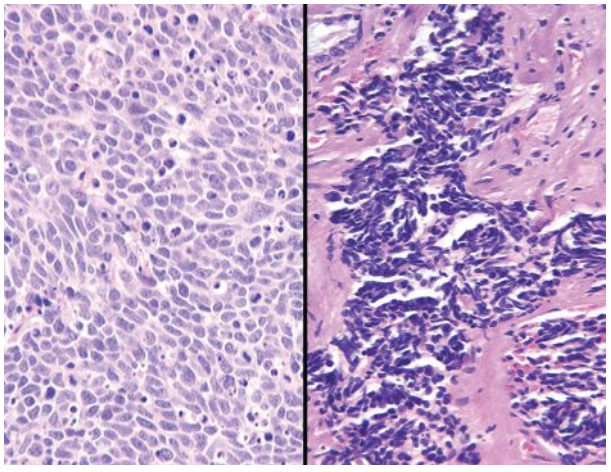

Figure 3. Small cell carcinoma. Left: There is a syncytial architecture of slightly spindled cells that show a high nuclear-to-cytoplasmic ratio, high mitotic rate, and apoptotic cells. Right: Crushed tumor is common in small cell carcinoma, with nuclear molding and overlapping frequently seen.

more often in higher-grade tumors. Curiously, atypical carcinoids are often positive with calcitonin, a marker usually found in medullary thyroid carcinoma. Ki-67 immunostaining can be employed to determine a proliferation index, but it is not used in grading of tumors as it is in other organs.

Suggested reading

Ferlito A, Rinaldo A, Bishop JA, et al. Paraneoplastic syndromes in patients with laryngeal neuroendocrine carcinomas: Clinical manifestations and prognostic significance. Eur Arch Otorhinolaryngol 2016;273(3):533-6.

van der Laan TP, Plaat BE, van der Laan BF, Halmos GB. Clinical recommendations on the treatment of neuroendocrine carcinoma of the larynx: A meta-analysis of 436 reported cases. Head Neck 2015;37(5):707-15.