

# Neuroendocrine carcinoma of the larynx with metastasis to the eyelid

Hussein A Assi, MD,<sup>1</sup> Raina Patel, MD,<sup>2</sup> and Syed Mehdi, MD<sup>3</sup>

<sup>1</sup>Department of Internal Medicine, Albany Medical Center, Albany, New York; and <sup>2</sup>Department of Pathology and <sup>3</sup>Division of Hematology/Oncology, Albany Stratton VA Medical Center, Albany, New York

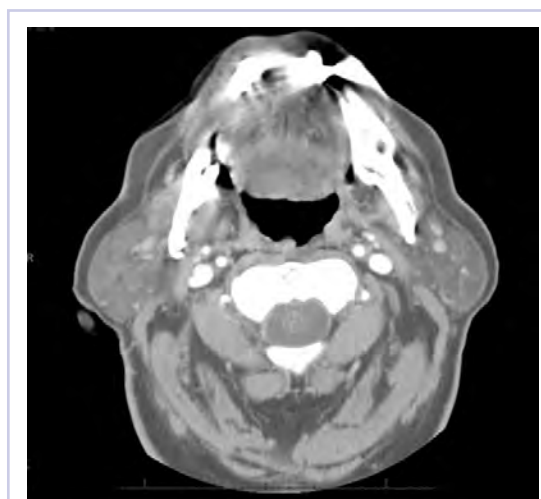
Neuroendocrine tumors are a rare type of neoplasms that comprise only 0.5% of all malignancies.<sup>1</sup> They usually arise from the gastrointestinal tract and the lung.<sup>1,2</sup> Neuroendocrine carcinoma of the head and neck is a relatively rare malignancy described in the literature. The larynx is the most commonly affected region of the head and neck.<sup>3,4</sup> Nevertheless, small-cell carcinoma comprises only 0.5% of all laryngeal cancers.<sup>5</sup> Neuroendocrine carcinoma of the larynx carries variable prognosis depending on the histological subtype.<sup>6</sup> Typical carcinoid rarely metastasizes, but atypical carcinoid and small-cell carcinoma have high rates of metastasis, usually in the lung and liver.<sup>2</sup> Cutaneous metastasis from neuroendocrine carcinoma is an extremely rare entity, with only few cases reported in the English literature.<sup>7,8</sup> We report the case of an elderly man with recurrent laryngeal neuroendocrine carcinoma with metastasis to the eyelid.

## Case presentation and summary

An 85-year-old man initially presented to the ear, nose, and throat clinic in September 2007 with a few months' history of hoarseness and foreign body sensation in the throat. He had an 80 pack-year smoking history, and he had quit 30 years prior to presentation. Flexible fiber-optic laryngoscopy revealed an erythematous polyp of 2-3 mm in the right posterior aspect of the supraglottic area. The results of a computerized-tomography (CT) scan of the neck showed a mucosal irregularity of less than 1 cm in the inferior posterior right false cord level near the arytenoid, with no evidence of adenopathy (Figure 1). A CT scan of the chest and abdomen did not show evidence of metastasis. Excisional biopsy of the polypoid lesion was performed, and histopathological examination of the specimen revealed moderately differentiated neuroendocrine carcinoma (Figure 2A). A wider excision of 1 cm was made,

but there was no malignant tissue. Based on those results, the tumor was put at stage I (T1N0M0). The patient did not receive adjuvant therapy. He was followed up with regular CT scans, which revealed stable examination.

Three and a half years later, in March 2011, the patient developed a skin lesion over his posterior scalp. Biopsy showed linear groups and nests of mitotically active atypical cells invading the dermis. The cells had fine chromatin and were positive for chromogranin and synaptophysin stains, confirming their neuroendocrine differentiation. S100 stain was negative, ruling out paraganglioma. The tumor cells were histologically similar to those seen in the patient's previous biopsy. Further evaluation for local recurrence of disease and distant metastasis was pursued. A CT scan of the chest and abdomen and magnetic-resonance imaging of the brain were negative. However, laryngoscopy showed biopsy-proven local recurrence in the right supraglottis.



**FIGURE 1** Computerized tomography (CT) scan of the neck showing a small polypoid mucosal lesion in the right posterior aspect of the supraglottic larynx.

Accepted for publication February 10, 2015. Correspondence: Hussein Assi, MD; [assih@mail.amc.edu](mailto:assih@mail.amc.edu). Disclosures: The authors have no disclosures. JCSO 2015;13:378-380. ©2015 Frontline Medical Communications. DOI 10.12788/jcso.0165.

The patient underwent surgical resection of recurrent supraglottic tumor as well as the solitary skin metastasis. He underwent radiation therapy to the skin lesion, but declined radiation therapy to his larynx. He received systemic chemotherapy with carboplatin and etoposide; however, he completed only 3 cycles owing to persistent thrombocytopenia. In 2012, he had recurrence of symptoms including hoarseness. Flexible fiber-optic laryngoscopy was performed and showed disease progression in the supraglottic area. He received palliative radiation to the larynx. During the next 2 years, the patient had more than 5 solitary skin biopsy-proven skin metastases, including the left upper eyelid (Figure 2B), all of which been managed by local excision.

## Discussion

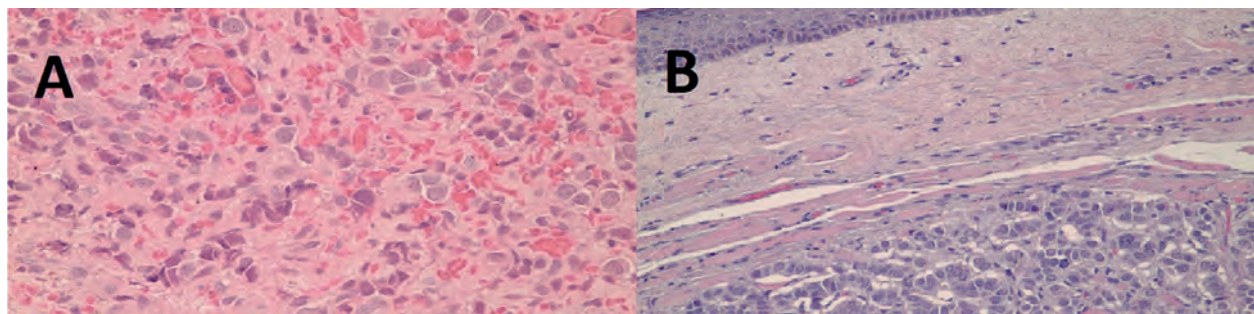
Neuroendocrine carcinoma is a pluriform group of rare tumors with increasing incidence over the past decade.<sup>1</sup> Although it is most common in the lung and gastrointestinal tract, it has been described in almost every organ system, including the head and neck.<sup>9</sup> According to a retrospective analysis of 1,618 cases of extrapulmonary small cell cancer, 11% arose from the head and neck region.<sup>10</sup> The larynx seems to be the most common region of the head and neck in which neuroendocrine carcinoma arises from,<sup>3,11</sup> although the latter makes up less than 1% of all laryngeal cancers.<sup>3</sup> More than 500 cases of primary laryngeal neuroendocrine tumors have been described in the literature.<sup>12</sup> Neuroendocrine carcinoma of the larynx was first reported in 1969 by Goldman and colleagues, who described a well-differentiated carcinoid tumor.<sup>13</sup> In 1983, Duvall and colleagues<sup>14</sup> were the first to report an atypical carcinoid tumor in the larynx. It wasn't until 1991 that a formal classification of the different histological subtypes was formalized by the World Health Organization.<sup>15</sup>

Neuroendocrine carcinoma of the larynx is categorized into 2 main groups: tumors of epithelial origin and tumors of neural origin (paragangliomas). The epithelial group is further subdivided into 3 subgroups according to

grade of differentiation: typical carcinoid (well-differentiated tumors), atypical carcinoid (moderately differentiated tumors), and small-cell carcinoma (poorly differentiated tumors). These different biological behaviors ultimately translate clinically into varying response to treatment and different prognoses between the subtypes.<sup>12</sup> Therefore, diagnostic accuracy is very important in guiding therapy as well as predicting clinical outcome.

In our case report, the patient had early stage, moderately differentiated neuroendocrine carcinoma, that is, atypical carcinoid tumor. Atypical carcinoid tumor is the most common subtype.<sup>16</sup> It carries a better prognosis compared with small-cell carcinoma, but a worse prognosis than typical carcinoid.<sup>6</sup> The literature on neuroendocrine carcinoma is derived mainly from case reports and case series, so there is little data on long-term survival and treatment strategies for the various histological subtypes. A meta-analysis of 436 reported cases of neuroendocrine carcinoma of the larynx was published in 2014,<sup>6</sup> with the aim of providing clinicians with more insight into the clinical and treatment outcome of affected patients. According the analysis, 30% of patients with atypical carcinoid tumor have distant metastasis at presentation. The recurrence rate was at 62.5%, with a 5-year disease-free survival and overall survival of 52.8% and 46%, respectively. In regard to the treatment modality, the study seems to emphasize the importance of radical surgical resection in improving disease-free survival, while showing no role for postoperative radiation therapy. This is in contrast to an editorial written by members of the International Head and Neck Scientific Group and published in 2011,<sup>17</sup> which offers local resection with or without neck dissection as reasonable options, in addition to postoperative radiotherapy in node-positive patients. This highlights the need for large multicenter retrospective studies to address these discrepancies.

In our patient, the early stage tumor was initially managed with local resection, yielding a disease-free survival of 3.5 years. The patient had both local recurrences, treated with further resection, chemotherapy and radiation ther-



**FIGURE 2** A, Photomicrograph showing moderately differentiated neuroendocrine carcinoma in the right arytenoid (hematoxylin-eosin, x40). B, Photomicrograph of the cutaneous tumor showing neuroendocrine carcinoma similar to the original tumor (hematoxylin-eosin, x20).

apy, and recurrent distant metastases, all of which were solitary skin metastases. The usual sites of metastasis originating from neuroendocrine carcinoma include the lung and liver,<sup>2</sup> with cutaneous metastasis being very uncommon.

As far as we know, we report the first case of a recurrent neuroendocrine carcinoma of the larynx with metastasis to the eyelid. Laryngeal neuroendocrine malignancy is a rare entity, and subsequent cutaneous metastasis is even more unusual. Histopathological examination of the specimen is of paramount importance to distinguish between different subtypes. This, in return, has a significant impact on the patient's treatment modalities and prognosis.

## References

1. Taal BG, Visser O. Epidemiology of neuroendocrine tumours. *Neuroendocrinology*. 2004;80 Suppl 1:3-7.
2. Hong S, Li L, Liu X, Tu C. Neuroendocrine carcinoma of the larynx with subcutaneous and intramuscular metastases: a case report. *Int J Clin Exp Pathol*. 2014;7:8217-8222.
3. Subedi N, Prestwich R, Chowdhury F, Patel C, Scarsbrook A. Neuroendocrine tumours of the head and neck: anatomical, functional and molecular imaging and contemporary management. *Cancer imaging*. 2013;13:407-422.
4. Singla A, Singla A, Gallagher R. A rare case and literature review of primary neuroendocrine carcinoma of the tongue. *J Surg Case Rep*. doi:10.1093/jscr/rju084. Published online August 22, 2014. Accessed September 1, 2015.
5. Gnepp DR. Small cell neuroendocrine carcinoma of the larynx. A critical review of the literature. *ORL J Otorhinolaryngol Relat Spec*. 1991;53:210-219.
6. Van der Laan TP, Plaat BEC, Van der Laan BFAM, Halmos GB. Clinical recommendations on the treatment of neuroendocrine carcinoma of the larynx: A meta-analysis of 436 reported cases. *Head Neck*. 2015;37:707-715.
7. Wick MR, Millns JL, Sibley RK, Pittelkow MR, Winkelmann RK. Secondary neuroendocrine carcinomas of the skin. An immunohistochemical comparison with primary neuroendocrine carcinoma of the skin ("Merkel cell" carcinoma). *J Am Acad Dermatol*. 1985;13:134-142.
8. Ottinetti A, Colombo E, Dardano F, et al. Cutaneous metastasis of neuroendocrine carcinoma of the larynx: report of a case. *J Cutan Pathol*. 2003;30:512-515.
9. Berniker AV, Abdulrahman AA, Teytelboym OM, Galindo LM, Mackey JE. Extrapulmonary small cell carcinoma: imaging features with radiologic-pathologic correlation. *Radiographics*. 2015;35:152-163.
10. Wong YNS, Jack RH, Mak V, Henrik M, Davies EA. The epidemiology and survival of extrapulmonary small cell carcinoma in South East England, 1970-2004. *BMC Cancer*. 2009;9:209.
11. Nakahara S, Takemoto N, Inohara H. Small cell carcinoma of the larynx treated by concurrent chemoradiotherapy: a case report. *Case Rep Otolaryngol*. <http://www.hindawi.com/journals/cr-ot/2012/316165/cta/>. Published online 2012. Accessed September 1, 2015.
12. Ferlito A, Barnes L, Rinaldo A, Gnepp DR, Milroy CM. A review of neuroendocrine neoplasms of the larynx: update on diagnosis and treatment. *J Laryngol Otol*. 1998;112:827-834.
13. Goldman NC, Hood CI, Singleton GT. Carcinoid of the larynx. *Arch Otolaryngol*. 1969;90:64-67.
14. Duvall E, Johnston A, McLay K, Piris J. Carcinoid tumour of the larynx. A report of two cases. *J Laryngol Otol*. 1983;97:1073-1080.
15. Barnes L. Neuroendocrine tumours. In: *Pathology and genetics of head and neck tumours (IARC WHO Classification of tumours)*. Eds, Barnes L, Eveson J, Reichart P, Sidransky D. Lyon, France: IARC Press; 2005:135-139.
16. Ferlito A, Silver CE, Bradford CR, Rinaldo A. Neuroendocrine neoplasms of the larynx: an overview. *Head Neck*. 2009;31:1634-1646.
17. Ferlito A, Lewis JS, Rinaldo A. The evolving management of laryngeal neuroendocrine carcinomas. *Eur Arch Otorhinolaryngol*. 2011;268:1247-1248.