An Easily Misinterpreted Diagnosis of Laryngeal Tumor-atypical Carcinoid

Non-squamous cell carcinoma (SCC) is a rare cancer in the larynx. Although atypical carcinoid tumor is the most common one, it is frequently unrecognized. We present a 55-year-old man with laryngeal atypical carcinoid tumor in the supraglottic region with initial manifestation of neck metastases. Two diagnostic biopsies revealed malignancy of different cell origins. The final pathologic report confirmed this diagnosis after the patient received total laryngectomy and radical neck dissection later. He received post-operative radiotherapy and was disease-free after a 19-month follow-up. We discuss this tumor with particular reference to the difficulty in distinguishing this tumor from other tumors of the larynx. The accurate pathological identification of this tumor is essential for treatment and prognosis.

CASE REPORT

A 55-year-old man visited our clinic complaining of a sudden onset of a mass on his right neck for a week. He was a smoker and was relatively well except for having hypertension and prostate hypertrophy. Although gradual hoarseness developed about 4 months before his visit, he did not pay much attention to that. Physical examination revealed a 3 cm lymphadenopathy over his right upper jugular chain. The fiberoptic laryngoscopic examination showed a smooth surface tumor bulging over the right aryepiglottic (AE) fold, false vocal fold and ventricle with right vocal cord fixation (Fig. 1). A biopsy of the laryngeal lesion under flexible laryngovideoscopy at the clinic was done. However, the pathological report showed a picture of squamous mucosal tissue with infiltration of clusters of columnar and polygonal epithelial cells in subepithelial connective tissue; positive periodic acid and Schiff reagents (PAS) and a focal weakly positive mucin stain. A malignant salivary gland-type tumor was suspected, especially oncocytic adenocarcinoma. After admission, another biopsy was done via microlaryngoscopy under general anesthesia and the pathologic report at this time showed a positive cytokeratin and negative mucin stain to imply the epithelial origin of the tumor. Both biopsies showed pale eosinophilic cytoplasm and mild atypical nuclei with in-
filtration of cords of tumor cells in fibrotic connective tissue. A computed tomography (CT) scan showed a well-circumscribed right supraglottic 3 3 cm mass with extralaryngeal extension and right upper jugular lymphadenopathy (Fig. 2). Under the impression of laryngeal malignancy, we performed a total laryngectomy with right radical neck dissection (RND) for him, and the post-operative course was uneventful.

A permanent histopathology of the entire tumor specimen revealed nests of cuboidal to polyhedral tumor cells with eosinophilic granular cytoplasm infiltrating in subepithelial connective tissue (Fig. 3A); prominent nuclei with mild to moderate atypism, more than 2 mitoses and focal necrosis (Fig. 3B). The tumor cells were positive for Grimelius stain, focal positive for mucin stain but negative for phosphotungsin acid-hematoxylin stain (PTAH). Positive neuron-specific enolase (NSE), chromogranin-A and synaptophysin were noted in the immunohistochemical stain (Fig. 4). The sustentacular cells presented in paragangliomas were not identified with the immunohistochemical staining of S-100 protein. Therefore, the final pathologic diagnosis turned out to be atypi-
cal carcinoid tumor with lymphovascular permeation and perineural invasion. The neck specimen also showed metastatic lesions in 4 of 27 lymph nodes. There were no signs suggestive of carcinoid syndrome. His urinary 5-hydroxy-indole-acetic acid (5-HIAA) was 4.0 mg/day (normal range 0.7-8.2 mg/day) and blood calcitonin was 40.35 pg/mL (normal range < 90 pg/mL). The metastatic survey including chest radiograph, bone scan, and abdominal sonography showed negative findings. He received post-operative adjuvant radiotherapy 60Gy to the larynx and neck. After 19 months’ follow-up, the patient was alive and disease free.

DISCUSSION

Non-SCC of the larynx represents an extremely diverse group of diseases with different prognosis and rationales of management. Neuroendocrine tumors, particularly atypical carcinoid tumor, are often underdiagnosed and make up 0.2 to 0.6% of laryngeal malignancies. They usually form masses in the subsurface laryngeal stroma, and arise from a progenitor cell in the seromucous gland-duct apparatus of the larynx, that is from endodermal derivatives, with the capacity of neuroendocrine and true epithelial differentiation. The classification of neuroendocrine tumors proposed by World Health Organization was made according to epithelial or neural origin (Table 1).

Similar to the late presentation of supraglottic SCC, our patient noticed his supraglottic tumor when the tumor presented with neck metastasis. Neuroendocrine tumors produce a variety of biogenic amines or peptide hormones, but the majority of typical and atypical laryngeal carcinoid tumors reported have been non-functional. Elevated urinary levels of 5-HIAA may be the consequence of impaired tryptophan metabolism and is useful in detecting tumor relapse.

The differential diagnosis of 4 types of neuroendocrine tumors can be based on histological and immunohistochemical studies (Table 2). Apart from other neuroendocrine tumors, atypical carcinoid tumor should also be differentiated from other tumors such as poorly differentiated SCC, adenocarcinomas or medullary carcinomas of the thyroid. Atypical carcinoid tumor may appear “undifferentiated” by light microscopy and might be misinterpreted if its neuroendocrine characteristics remain unrecognized. The first biopsy specimen of our patient revealed malignant salivary gland tumor based upon the findings of mucosal tissue infiltrating with tumor cells and positive PAS and mucin stain. The second one showed epithelial tumor due to positive cytokeratin and negative mucin stain. The characteristics of their

Table 1. Classification of neuroendocrine tumors of the larynx

<table>
<thead>
<tr>
<th>A. Tumors of epithelial origin</th>
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<tbody>
<tr>
<td>1. Well differentiated: typical carcinoid tumors (TCT)</td>
</tr>
<tr>
<td>2. Moderately differentiated: atypical carcinoid tumors (ACT)</td>
</tr>
<tr>
<td>3. Poorly differentiated: small cell neuroendocrine carcinomas (SCNC)</td>
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<table>
<thead>
<tr>
<th>B. Tumors of neural origin</th>
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<tbody>
<tr>
<td>Paraganglioma</td>
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</table>


Fig. 4. The tumor cells are positive for immunohistochemical staining of chromogranin (chromogranin, 100X).
neuroendocrine and epithelial differentiation were the causes for misinterpretation, especially in small and distorted specimens. Some cases of laryngeal atypical carcinoid tumor in the literature were diagnosed by the specimens of salvage laryngectomy after their treatment with primary radiotherapy failed.6,11

Atypical carcinoid tumor presents not only early neck metastasis (43%) but also a high rate of distant metastasis (45%) mainly to the skin, lung and liver.3,5 Mainstay of treatment includes surgical excision with a wide tumor-free margin, neck dissection and surveillance for metastasis. The effectiveness of radiotherapy or chemotherapy has not been demonstrated. Primary radiation therapy with adjuvant chemotherapy is not indicated, either.5 The survival rate was 48% in five years and 30% in 10 years from the study of 127 published cases. Poor prognosis was found among patients with tumor size larger than 1 cm, and involvement of the skin and subcutaneous tissues.6 Recent research in nuclear medicine has developed two compounds, iodinated metaiodobenzylguanide (MIBG) and radiolabelled somatostatin, useful for scintigraphical detection and delineation of carcinoid.12 An somatostatin analog, Octrotide, shows a growth inhibitory effect upon some neuroendocrine tumors with positive somatostatin receptors.12

In conclusion, atypical carcinoid tumor is an under-diagnosed laryngeal malignancy. It differential diagnosis requires histological features together with a panel of immunohistochemical staining. Accurate diagnosis is important because of its varied clinical behavior and response to treatment.

### Table 2. Comparison of Laryngeal Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Histologic findings</th>
<th>TC</th>
<th>ATC</th>
<th>SCNC</th>
<th>Paraganglioma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plemorphism/Ulceration</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>N/C ratio</td>
<td>Low</td>
<td>Variable</td>
<td>High</td>
<td>Variable</td>
</tr>
<tr>
<td>Mitosis (per 2 mm², ten HPF)</td>
<td>&lt; 2</td>
<td>2-10</td>
<td>&gt; 11</td>
<td>-</td>
</tr>
<tr>
<td>Epithelial mucin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Argyrophilic granule</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Vascular/perineural invasion</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Immunohistochemical stain</td>
<td>NSE/Chromogranin/synaptophysin</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CEA/Cytokeratin/EMA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
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Usual management

- Conservative surgery
- Wide excision and neck dissection
- Chemotherapy and radiotherapy
- Conservative surgery

5-year survival rate, %

- TC: ~100
- ATC: 48
- SCNC: 5
- Paraganglioma: ~100

TC = typical carcinoid; ATC = atypical carcinoid; SCNC = small cell neuroendocrine carcinoma; N/C = nucleus-cytoplasm; HPF = high power field; NSE = neuron-specific enolase; CEA = carcinoembryonic antigen; EMA = epithelial membrane antigen.

Modified from Ferlito et al.,2,9 Woodruff and Seniel,4 Dier R and Dammrich J,7 Soga J et al.10

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