Histopathologically TTF-1 and Calcitonin Positive Laryngeal Typical Carcinoid Tumor with Elevated Serum Calcitonin

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ABSTRACT

Even with 1% of the incidence, laryngeal neuroendocrine tumors are the second common tumors in larynx; as a subtype, typical carcinoid tumors are extremely rare. We presented a case of laryngeal typical carcinoid tumor and we discussed diagnostic criteria and treatment of these tumors. A 57-year-old male with a 3 months history of hoarseness was examined endoscopically and a laryngeal mass on left supraglottic area was seen. High levels of serum calcitonin were detected. The histopathological analysis of biopsy material was typical carcinoid tumor. Laryngeal tumor resection and left neck dissection were performed. The histopathologic result was TTF 1 and calcitonin positive primer laryngeal typical carcinoid tumor with cervical lymphoid metastasis. Serum calcitonin level returned to normal levels postoperatively. The distinction between laryngeal carcinoid tumors and metastasis of thyroid medullary carcinoma are difficult histopathologically. So, laryngeal carcinoid tumors should be kept in mind in these circumstances.

Keywords: Neuroendocrine, Typical carcinoid, Calcitonin, TTF-1, Medullary thyroid carcinoma, Larynx, Neck metastasis, Neck dissection

INTRODUCTION

Even neuroendocrine tumors are the most common non-squamous malignity of the larynx, their incidence is not more than 1% (1, 2). WHO (World Health Organization) classified neuroendocrine tumors histopathologically into 4 groups based on epithelial or neural origins. Epithelial tumors are classified into 3 subtypes: well differentiated neuroendocrine carcinomas (typical carcinoid tumors), moderately differentiated neuroendocrine carcinomas (atypical carcinoid tumors, large cell neuroendocrine carcinomas), poorly differentiated tumors (small cell neuroendocrine carcinomas) (1). Paraganglioma is the subtype of neuroendocrine tumors originated from the neural tissue (1). Histopathologically the distinction among these subtypes is not such easy that enough experiences and cooperation between the surgeon and the pathologist are needed. Typical carcinoid tumors are the least common subtype and most difficult one to be diagnosed among the subtypes and they have the best prognosis among other subtypes. Histopathologically, there must be no atypia, pleomorphism, necrosis and vascular invasion for diagnosis of a typical carcinoid tumor. These factors are some diagnostic factors for atypical carcinoid tumors. There are also some malignities such as metastasis of thyroid medullary carcinoma that are very challenging in differential diagnosis. It is such difficult that in literature there are some cases that had thyroidectomies with the certain diagnosis of the malignancy (8). In this study, we present a case of typical carcinoid tumor of the larynx and discuss the diagnostic criteria and treatment of these tumors.

CASE REPORT

A 57-year-old male referred to the ENT clinic with a 3 months history of hoarseness. His history revealed that 20 years ago he had stopped smoking although he had had a 10 packet/ year prior history. He and his family had no malignancy history. As a chronic disease, he had only diabetes mellitus. On endoscopic laryngeal examination a 0,7x1,7cm sized, hemorrhagic, polypoid laryngeal mass on left supraglottic area was seen. Under general anesthesia the laryngeal mass was excised totally (Figure 1.). The histopathological analysis of the total excisional biopsy was consistent with typical carcinoid tumor (pancytokeratin, synaptofizin, chromogranin, CD 56 were positive and S-100 was negative. Ki-67 proliferation index was %5-10, having no necrosis, mitotic activity is low -2 per 10 high power field). But according to the analysis, the tumor cells were in close proximity to the surgical margins. Cervical USG was performed a 16,7x12,4mm sized pathologic lymph node in left submandibular region and a 5,2x2,7 mm sized pathologic lymph node in left supraclavicular region were seen. There was also a 32x15 mm sized heterogeneous doubtful nodule with central degeneration in right thyroid gland. Cervical MRI showed that...
there was a 19x14 mm pathologic lymph node in the left level 2A region. And in right thyroid lobe a 21x22 mm sized doubtful node that had a central degeneration was seen. Fine-needle aspiration biopsies were performed from the pathologic cervical lymph node and also twice time from doubtful thyroid nodule to exclude medullary thyroid carcinoma. Pathologic evaluation of the thyroid nodule had a benign cytology. Histopathological examination of the submandibular lymph node revealed that the same morphologic properties with the laryngeal mass (pleomorphism, strongly marked nucleolus and chromatin forms with the view of ‘salt and pepper’). The biopsy material of laryngeal mass was reanalyzed by additional staining methods. TTF-1 showed strong nuclear positivity, calcitonin showed strong cytoplasmic positivity and thyroglobulin showed cytoplasmic negativity (Figure 2.). TTF-1 positivity primarily seen in metastasis of medullar thyroid carcinoma, but, neuroendocrine tumors could barely show TTF-1 positivity. The material showed characteristics of typical carcinoid tumor. Whole body PET CT was performed. There was only a hypermetabolic metastatic lymph node in the left jugulodigastric area. No other focus was established in whole body scan. The thyroid function tests (TSH: 3.48 uIU/mL, FT3: 0.77pg/mL, FT4: 0.29ng/dL), tumor markers (CA 125: 20U/mL, CEA: 2.5 ng/mL, CA15-3: 16U/mL), 24-hour urine 5-HIAA levels (6.36 mg/day), and chromogranin A (:23 ng/mL) were all normal. Serum calcitonin level (:16.5 pg/mL) was borderline elevated. Because of possible surgical margin positivity, wide resection to the laryngeal tumor area was performed. There was no tumor positivity at the margins according to the histopathologic analyses. Then left neck dissection was performed. The histopathologic analyses showed that there was a pathologic lymph node that was consistent with metastasis of typical carcinoid tumor. Immunohistochemical analysis revealed that, the metastatic lymph node showed strongly diffuse positive immunoreactivity for CD-56, chromogranin, synaptophysin, diffuse positivity for calcitonin, negative immunoreactivity for thyroglobulin and interestingly TTF-1. The final pathologic diagnosis of the case was “primer laryngeal typical carcinoid tumor with left cervical metastasis”. 6 months after surgery, the wholebody PET CT was re-performed and there was no hypermetabolic reactivity. In his postoperative endoscopic examinations, there is no regional recurrence sign.

Figure 1: Macroscopic view of the tumor

Figure 2: Positive TTF-1 immunoreactivity of the typical carcinoid tumor

CASE REPORT

The first neuroendocrine tumor in larynx was diagnosed in 1969 by Goldman with the similarity of appendix carcinoid tumors (6). In 1983 Duvall made the classification between typical and atypical carcinoid tumors. The classification that was made in 1991 by WHO (6). The classification was made according to epithelial differential grade. Cellular atypia, pleomorphism, high mitosis rates, necrosis are the qualifications that are used for classification. In this classification, typical carcinoid tumors are in well differentiated group, atypical carcinoid tumors and large cell carcinomas are in moderately differentiated group, small cell carcinomas are in poorly differentiated group. Some authors confirmed large cell carcinomas in poorly differentiated group (6).

Neuroendocrine tumors originate from the enterochromaffin (Kulchitsky) cells, part of the APUD system (amine precursor uptake and decarboxylation) (3). The enterochromaffin cells dominantly found in gastrointestinal system (%70) and respiratory system (%25) (3). So that it can be said that neuroendocrine tumors dominantly found in gastrointestinal and respiratory systems. In thymus, ovaries, urinary system, tympanic cavity, paranasal sinuses and larynx, rarely these cells can be found.

In head and neck region neuroendocrine tumors mostly found in larynx. 90% of larynx malignities are squamous cell carcinomas. Even neuroendocrine tumors are the second most common tumor type in larynx, their incidence is not much more than %1. In larynx, the enterochromaffin cells are dominantly found at supraglottic region. That’s why the neuroendocrine tumors of larynx usually originate from supraglottic region (mostly arytenoids, aryepiglottic fold) (3).

Typical carcinoid tumors are the most uncommon subtype of neuroendocrine tumors. Patients are dominantly male (m/f: 1/3) generally for neuroendocrine tumors; but there is no association in typical carcinoid tumors about gender (6). The patients are usually at fifth and sixth decades of their life (3). Typical carcinoid tumors are unrelated to smoking, whereas other neuroendocrine tumors have a distinctive association (4). The common symptoms are dysphagia, odynophagia, otalgia and hemoptysis.
In some cases of neuroendocrine tumors, ectopic hormone production was described. These are mostly calcitonin, serotonin, ADH, ACTH, somatostatin and CEA (6). Some neuroendocrine tumors can cause paraneoplastic syndromes, because of the neurosecretory components (3). Also, there can be also elevated serum neutriopeptide levels (serotonin and other vasoactive amine metabolites, 5-HIAA) rarely (3-5). But in typical carcinoid tumors these situations are very rare. In our case serum chromogranin-A levels and 24-hour urine 5-HIAA levels were normal.

There will be no systemic signs until any paraneoplastic syndrome occurs. Elevated serum ADH can cause Bartter Syndrome; elevated serotonin and other vasoactive amine metabolites can cause carcinoid syndrome; as a Myasthenic Syndrome, Eaton Lambert Syndrome and Ectopic ACTH Syndromes are some of the paraneoplastic syndromes that can be seen with neuroendocrine tumors. But paraneoplastic syndromes are extremely rare in typical carcinoid tumors.

It can be said that typical carcinoid tumors have benign character (5 years survival rates are 100%) (3). In literature, there are some manuscripts that point lower survival rates for typical carcinoid tumors. Currently this situation is associated with the ‘unspecified carcinoids’ (6). For the differential diagnosis between typical and atypical carcinoid tumors, some histopathological criteria must be determined such as atypia, pleomorphism and necrosis. Inadequate analyses and questionable diagnosis are risky for the prognosis of the case.

In spite of the comparatively ‘benign’ character of typical carcinoid tumors, there can be metastatic activities (%33) (7). Metastasis can be in lymph nodes, liver, bone and skin, heart, brain and pleura.

In microscopic examination, a tumoral proliferation with trabecular and ‘ribbon-like’ nests of small uniform cells that have round-oval nucleuses and chromatins in the form of ‘salt and pepper’ is seen. There is no necrosis, atypia and increased mitotic activity and these are the main differences from atypical carcinoid tumors (4). Mitotic activity is low which is 2 per 10 high power field (HPF). On immunohistochemistry; Ki-67 proliferation index is %5-10, synaptophysin, pancytokeratin, chromogranin, CD-56 are diffuse positive and S-100 is negative in these tumors as it was seen in our case (2).

Medullary thyroid carcinoma is very similar to typical carcinoid tumor histopathologically. In immunohistochemical analyses, calcitonin immunoreactivity is important for diagnosis of medullary thyroid carcinoma but it is not a useful marker for distinction that it can be identified in both medullary thyroid carcinoma and laryngeal neuroendocrine tumors at high rates (8). TTF-1 is a transcription factor that regulates thyroid carcinoma and laryngeal neuroendocrine tumors at marker for distinction that it can be identified in both medullary thyroid carcinoma but it is not a useful test in these cases. In our case wide resection to the tumor area and left neck dissection were performed. Because as the histopathologic analysis of the first surgery -excisional biopsy of the laryngeal mass- was consistent with possible tumor positivity at surgical margins, wide resection to the tumor area was performed. And the histopathologic analysis of the second operation was tumor free. So, we did not think about an extended surgery.

In conclusion, primer laryngeal typical carcinoid tumors are extremely rare tumors and pathologically difficult to distinguish from metastasis of thyroid medullary carcinomas. For differential diagnosis, serum calcitonin levels are most useful tests but typical carcinoid tumor can rarely cause elevated serum calcitonin levels as seen in our case.

REFERENCES


