Case Report

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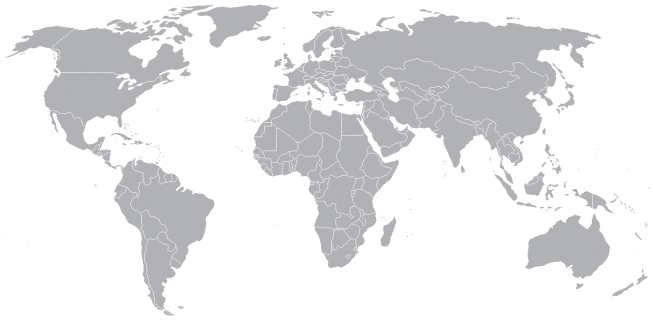

Histopathologically TTF-1 and Calcitonin Positive Laryngeal Typical Carcinoid Tumor with Elevated Serum Calcitonin

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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 pocket/ 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 excisonal 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 heterogenous doubtful nodule with central degeneration in right thyroid gland. Cervical MRI showed that

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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 rarely 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.

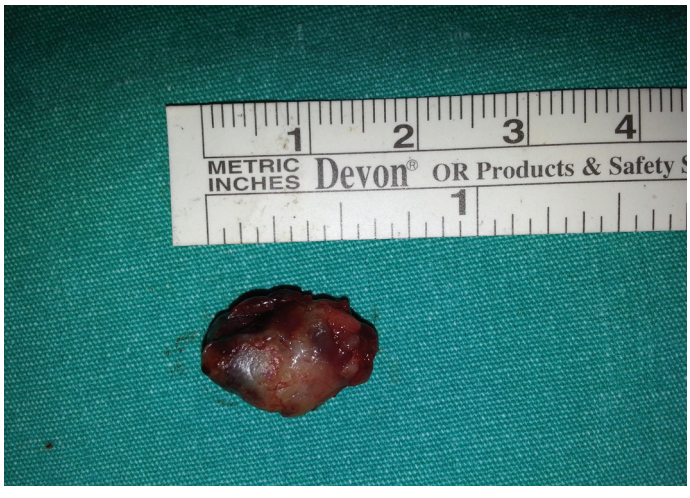

Figure 1: *Macroscopic view of the tumor*

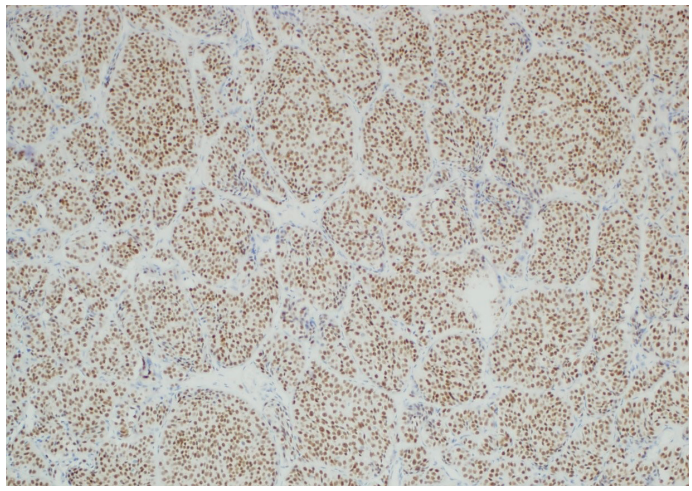

Figure 2: *Positive TTF-1 immunreactivity of the typical carcinoid tumor*

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 neuropeptide 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 all normal.

There will be no systemic signs until any paraneoplastic syndrome occurs. Elevated serum ADH can cause Bartter Syndrome; elevated serotonin and other vasoactive amin 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 the gene expression of thyroid specific proteins (8). Many studies showed that TTF-1 immunoreactivity could be seen in neuroendocrine or non-neuroendocrine tumors of thyroid, lungs, ovaries etc. (8). In our literature review we found very few researches about TTF-1 immunoreactivity of laryngeal neuroendocrine tumors and medullary thyroid carcinomas. Thyroid malignity such as medullary carcinomas show %80-100 positivity for TTF-1 (8). In contrast typical carcinoid tumors of lungs show %35 positivity, atypical carcinoid tumors and small cell carcinomas show more than %90 positivity for TTF-1 (8). Hirsch et al. reported that TTF-1 immunoreactivity found in only %13 of moderately differentiated neuroendocrine tumors in larynx while %90 in medullary thyroid cancers in their series (8). In our literature review, we could not find any statistical data about the TTF-1 positivity ratios of laryngeal typical carcinoid tumors .

Between thyroid medullar carcinoma and typical carcinoid tumor, the most definitive parameter is serum calcitonin level (8). In medullary thyroid carcinomas serum calcitonin level is highly elevated such as a tumor marker. However, in literature there are 6 exceptions as neuroendocrine tumors that had elevated serum calcitonin levels (6, 9-14). In most of these cases, thyroidectomies were also performed. After all, the neuroendocrine tumors were diagnosed (8). In our case serum calcitonin level is also elevated (16.5 pg/mL, N<15 pg/mL). Interestingly six months after the surgery our patient's serum calcitonin level is 8.76 pg/mL. So that it can be said that as like our patient some typical carcinoid tumors can cause elevated serum calcitonin levels. Our case is the 7th laryngeal neuroendocrine tumor with elevated serum calcitonin level. In English literature review, we did not find any other primer laryngeal typical carcinoid tumor case with elevated serum calcitonin level.

The treatment of laryngeal typical carcinoid tumor is conservative surgery such as wide local excision or partial laryngectomy (15, 16). If necessary neck dissections can be added to the procedure (1). Chemotherapy and radiotherapy is useless for typical carcinoid tumors (1). Conversely, other types of neuroendocrine tumors are more aggressive tumors. They must be treated by extended surgeries (1). Radiotherapy and chemotherapy can be added to the procedure (1). 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

1. Ferlito A, Silver CE, Bradford CR, Rinaldo A. Neuroendocrine neoplasms of the larynx: an overview. Head Neck. 2009 Dec;31(12):1634-46.
2. Ferlito A, Devaney KO, Rinaldo A. Neuroendocrine neoplasms of the larynx: advances in identification, understanding, and management. Oral Oncol. 2006 Sep;42(8):770-88.
3. McBride LC, Righi PD, Krakovitz PR. Case study of well-differentiated carcinoid tumor of the larynx and review of laryngeal neuroendocrine tumors. Otolaryngol Head Neck Surg. 1999 Apr;120(4):536-9.
4. Mills SE. Neuroectodermal neoplasms of the head and neck with emphasis on neuroendocrine carcinomas. Mod Pathol. 2002 Mar;15(3):264-78.
5. Overholt SM, Donovan DT, Schwartz MR, Laucirica R, Green LK, Alford BR. Neuroendocrine neoplasms of the larynx. Laryngoscope. 1995 Aug;105(8 Pt 1):789-94. PubMed PMID: 7630288.
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 May;37(5):707-15.
7. Sato S, Kuratomi Y, Yamasaki F, Inokuchi A. A case of typical carcinoid of the larynx. Case Rep Otolaryngol. 2012;2012:717251. doi: 10.1155/2012/717251. Epub 2012 Apr 23. PubMed PMID: 22953121; PubMed Central PMCID:

PMC3420405.
8. Hirsch MS, Faquin WC, Krane JF. Thyroid transcription factor-1, but not p53,is helpful in distinguishing moderately differentiated neuroendocrine carcinoma of the larynx from medullary carcinoma of the thyroid. Mod Pathol. 2004 Jun;17(6):631-6.
9. Smets G, Warson F, Dehou MF, Storme G, Sacré R, Van Belle S, Somers G, Gepts W, Klöppel G. Metastasizing neuroendocrine carcinoma of the larynx with calcitonin and somatostatin secretion and CEA production, resembling medullary thyroid carcinoma. Virchows Arch A Pathol Anat Histopathol. 1990;416(6):539-43.
10. Guerzider P, Fiche M, Beauvillain C, Le Bodic MF. [Neuroendocrine tumor of the larynx. Report of a case]. Ann Pathol. 1991;11(4):253-6.
11. Insabato L, De Rosa G, Terracciano LM, Lupoli G, Montedoro D, Ravetto C. A calcitonin-producing neuroendocrine tumor of the larynx: a case report. Tumori. 1993 Jun 30;79(3):227-30.
12. Morales C, Tomás Bezos J, Alvarez-Quiñones Sanz M, García Mantilla J, Carrera F. [Calcitonin-producing neuroendocrine carcinoma of the larynx: atypical carcinoid tumor]. Acta Otorrinolaringol Esp. 1996 Jul-Aug;47(4):333-5.
13. Vildé F, Arkwright S, Paoli C, Périchon I, Le Charpentier Y, Le Bodic MF. [Neuroendocrine carcinoma of the larynx with secretion of calcitonin: primary tumor or metastasis of the medullary thyroid carcinoma?]. Ann Pathol. 1996;16(2):104-7.
14. Machens A, Holzhausen HJ, Dralle H. Minimally invasive surgery for recurrent neuroendocrine carcinoma of the supraglottic larynx. Eur Arch Otorhinolaryngol. 1999;256(5):242-6.
15. Mhawej R, Farah C, Haddad A, Tabchy B. Primary neuroendocrine tumors of the ear, nose and throat: A report of three cases and a review of the literature. Oncol Lett. 2015 Oct;10(4):2533-2536. Epub 2015 Aug 13. PubMed PMID: 26622884; PubMed Central PMCID: PMC4580071.
16. Wang Q, Chen H, Zhou S. Typical laryngeal carcinoid tumor with recurrence and lymph node metastasis: a case report and review of the literature. Int J Clin Exp Pathol. 2014 Dec 1;7(12):9028-31. eCollection 2014. Review. PubMed PMID: 25674282; PubMed Central PMCID: PMC4314005.