Case Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
0(0) 1–7

DOI: 10.1177/0300060520962928
journals.sagepub.com/home/imr
SAGE

Metachronous double primary neuroendocrine tumors in larynx and lung: a case report

In Hye Song[1], Youn Soo Lee[1], Dong-Il Sun[2], Yong-Kil Hong[3] and Kyo-Young Lee[1]

Abstract

When a patient harbors two or more neuroendocrine tumors (NETs), it can be difficult to determine whether they are double primary tumors or metastases. A 60-year-old man complained of voice change lasting 1 month. On physical examination and imaging, a 1.8-cm mass was observed in his epiglottis, and a laser epiglottectomy was performed. Upon microscopic examination, the tumor consisted of medium-sized ovoid or short spindle cells. Immunohistochemical staining of the tumor cells was positive for synaptophysin, chromogranin, and calcitonin but negative for CD56; the Ki-67 proliferation index was approximately 5%. The patient was diagnosed with atypical carcinoid tumor. In 2015, a hypermetabolic endobronchial tumor was identified in the left lower lobe by positron emission tomography-computed tomography. Bronchoscopic biopsy revealed palisading large tumor cells with high nuclear-cytoplasmic ratio, frequent mitoses, and necrosis. The tumor cells were positive for CD56 and negative for cytokeratin-7, thyroid transcription factor-1, P40, synaptophysin, chromogranin, and calcitonin; the Ki-67 proliferation index was approximately 90%. Overall histologic findings were consistent with large cell neuroendocrine carcinoma rather than metastatic atypical carcinoid tumor. Detailed clinical and pathological review are essential to differentiate between metastatic NET and double primary NETs and, therefore, to provide the best management of the patient.

Keywords

Neuroendocrine tumor, carcinoma, neuroendocrine, neoplasm, second primary, lung, epiglottis

Date received: 3 April 2020; accepted: 10 September 2020

[1]Department of Hospital Pathology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[2]Department of Otorhinolaryngology-Head and Neck Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[3]Department of Neurosurgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea

Corresponding author:
Kyo-Young Lee, Department of Hospital Pathology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222, Banpo-daero, Seocho-gu, Seoul 06591, Republic of Korea.
Email: leekyoyo@catholic.ac.kr

Introduction

Neuroendocrine tumors (NETs) include a wide range of epithelial tumors that express neuroendocrine markers. NETs can arise from diverse organs such as the gastrointestinal tract, pancreas, liver, lung, and others, and they present with various histologic features and clinical behaviors.[1,2] Herein, we present a unique case of metachronous double primary NET occurring in larynx and lung.

Case report

A 60-year-old man presented to a local hospital with a complaint of voice change that had persisted for 1 month. He was a 20 pack-years smoker and on medication for hypertension. His sister had a history of gastric and breast cancers. Upon physical examination, an epiglottic mass was detected. He was referred to Seoul St. Mary's Hospital (Seoul, Republic of Korea) in December 2007 for further evaluation. On neck magnetic resonance imaging (MRI), a 1.8-cm, polypoid contrast-enhancing mass was observed, involving the epiglottis near the aryepiglottic fold (Figure 1A). No suspicious lymph node was identified. Complete blood count and serum electrolyte tests were within normal range, but serum calcitonin was not checked. In January 2008, laser epiglottectomy was performed under a diagnostic impression of hemangioma, carcinoid tumor, or squamous cell carcinoma.

On gross examination, the excised mass was well-defined, round, protruding, and 2.3 cm in diameter, with a dark brown cut surface. Microscopic examination revealed that the tumor was located in the subepithelial area. The overlying squamous mucosa was mostly intact with focal erosion. Multiple small cystic spaces filled with blood were observed in the tumor. The tumor consisted of medium-sized ovoid or short spindle cells with round to oval nuclei with salt-and-pepper patterned chromatin. Mitoses were rarely identified. On immunohistochemical staining, the tumor cells were positive for synaptophysin, chromogranin, neuron-specific enolase (NSE), and calcitonin, but negative for CD56 and S100 protein. The Ki-67 proliferation index was about 5% (Figure 2). Based on the overall findings, the patient was diagnosed with atypical carcinoid tumor, which is consistent with moderately differentiated neuroendocrine carcinoma according to the WHO Classification of Head and Neck Tumours (4th edition, 2017).[3] The patient did not suffer any complications after surgery, and received routine follow-up examination at 6-month intervals for 7 years without adjuvant therapy.

In July 2015, the patient presented to the Seoul St. Mary's Hospital with a complaint of bilateral cheek masses. On contrast computed tomography (CT) of the neck, three enhancing masses, up to 2.4 cm, were identified in both parotid glands (Figure 1B). Upon needle biopsy, the tumor was confirmed to be NET, and it showed similar histologic and immunohistochemical features to the previously excised epiglottic mass. Therefore, the parotid gland tumors were considered metastatic NET from the epiglottis. The patient received a thorough examination, including positron emission tomography (PET)-CT and chest CT in August 2015. In addition to the metastatic tumors in both parotid glands with a maximum standardized uptake value (SUVmax) of 3.9, a hypermetabolic endobronchial tumor was identified in the superior segmental bronchus of the left lower lobe, with a SUVmax of 10.3 (Figure 1C). A bronchoscopic biopsy revealed palisading large tumor cells, which showed high nuclear-cytoplasmic ratio and frequent mitoses (15–20/high-power field). Necrosis was also observed. On immunohistochemical staining, the tumor cells were positive

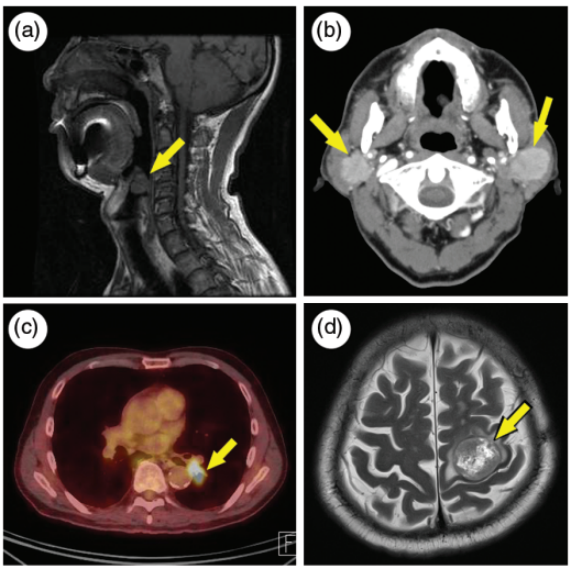

Figure 1. Imaging studies of the patient over time. (a) In December 2007, a 1.8-cm polypoid mass was observed in the epiglottis on magnetic resonance imaging (MRI) T2 weighted image. (b) In July 2015, neck contrast computed tomography (CT) revealed several enhancing masses, up to 2.4 cm, in both parotid glands. (c) In August 2015, a hypermetabolic endobronchial tumor with maximum standardized uptake value (SUVmax) of 10.3 was identified in the superior segmental bronchus of the left lower lobe on positron emission tomography (PET)-CT. (D) In November 2015, brain MRI revealed a 3.1-cm enhancing mass in the left frontal lobe on T2 weighted image.

for CD56, but negative for cytokeratin-7, thyroid transcription factor (TTF)-1, P40, synaptophysin, chromogranin, and calcitonin. The Ki-67 proliferation index was about 90% (Figure 3). Overall histologic findings were consistent with large cell neuroendocrine carcinoma. Two cycles of chemotherapy based on etoposide and cisplatin were instituted. In November 2015, however, the patient complained of nausea and vomiting. A 3.1-cm enhancing mass was identified in the left frontal lobe of the brain by magnetic resonance imaging (Figure 1D). The tumor was removed via craniotomy and showed similar histologic and immunohistochemical findings to the lung mass, consistent with metastatic large cell neuroendocrine carcinoma from lung. The patient was treated with chemotherapy and radiation therapy after brain surgery, but died due to the growing lung mass and subsequent pneumonia in September 2016 at the age of 68.

After de-identification of patient information, exemption from informed consent was approved by the Institutional Review Board of Seoul St. Mary's Hospital.

Discussion

NETs show substantial clinical and histologic heterogeneity. They express a variety of neuroendocrine markers, including synaptophysin, chromogranin, CD56, NSE, serotonin, calcitonin, somatostatin, and calcitonin.[1,2] The histologic grading system of NETs generally depends on mitotic count and Ki-67 index, but the nomenclature of NETs differs between organs.[4] For example, gastroenteropancreatic NETs are

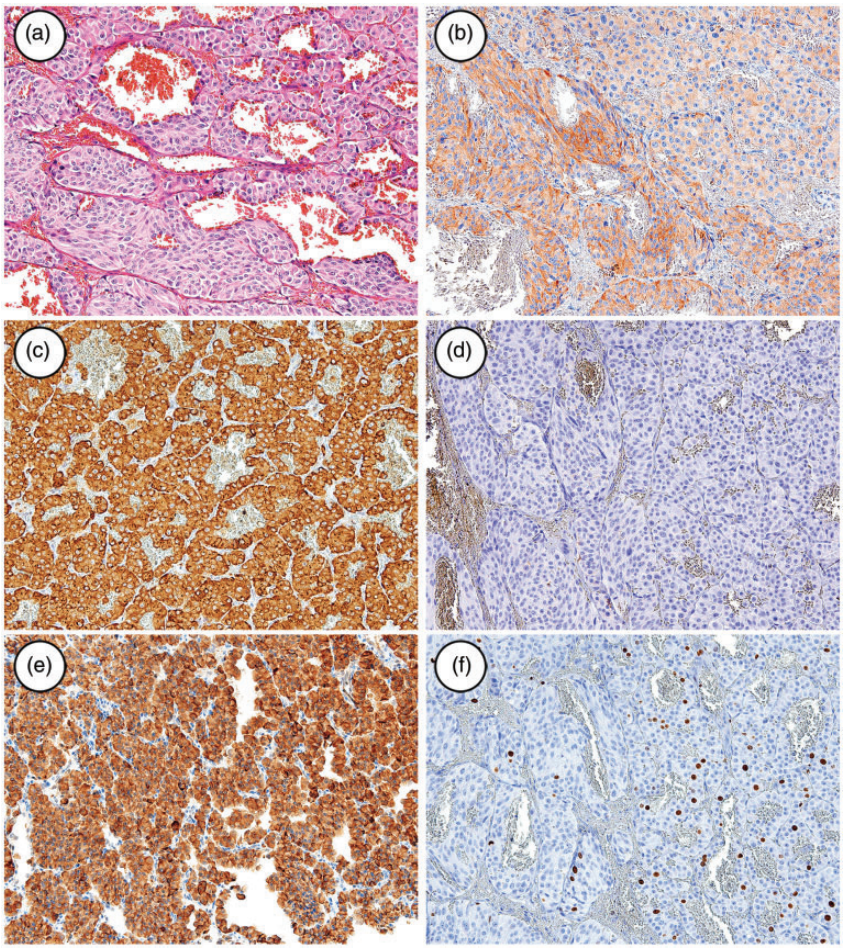

Figure 2. Micrographs of the epiglottic mass. (a) The tumor consisted of nests of medium-sized ovoid or short spindle cells, which showed amphophilic or oncocytic cytoplasm and round to oval nuclei with distinct nucleoli and salt-and-pepper patterned chromatin (hematoxylin and eosin, 200×). (b–f) On immunohistochemical staining, the tumor cells were positive for synaptophysin (b, 200×), chromogranin (c, 200×), and calcitonin (e, 200×) but negative for CD56 (d, 200×). The Ki-67 proliferation index was about 5% (f, 200×).

classified into NET grade 1, NET grade 2, and neuroendocrine carcinoma.[5] However, NETs of the lung are classified into carcinoid, atypical carcinoid, small cell carcinoma, and large cell neuroendocrine carcinoma; and NETs of the hypopharynx and larynx are classified into well, moderately, and poorly differentiated neuroendocrine carcinoma.[3,6] NETs show diverse recurrence and survival rates, which are closely associated with histologic grade.[3–6]

Usually, surgical resection is the treatment of choice for primary NETs, except in small cell carcinoma or advanced cases, whereas cytotoxic agents, somatostatin analogs, everolimus, sunitinib, bevacizumab, interferon-α, peptide receptor radionuclide therapy, or palliative resection can be used

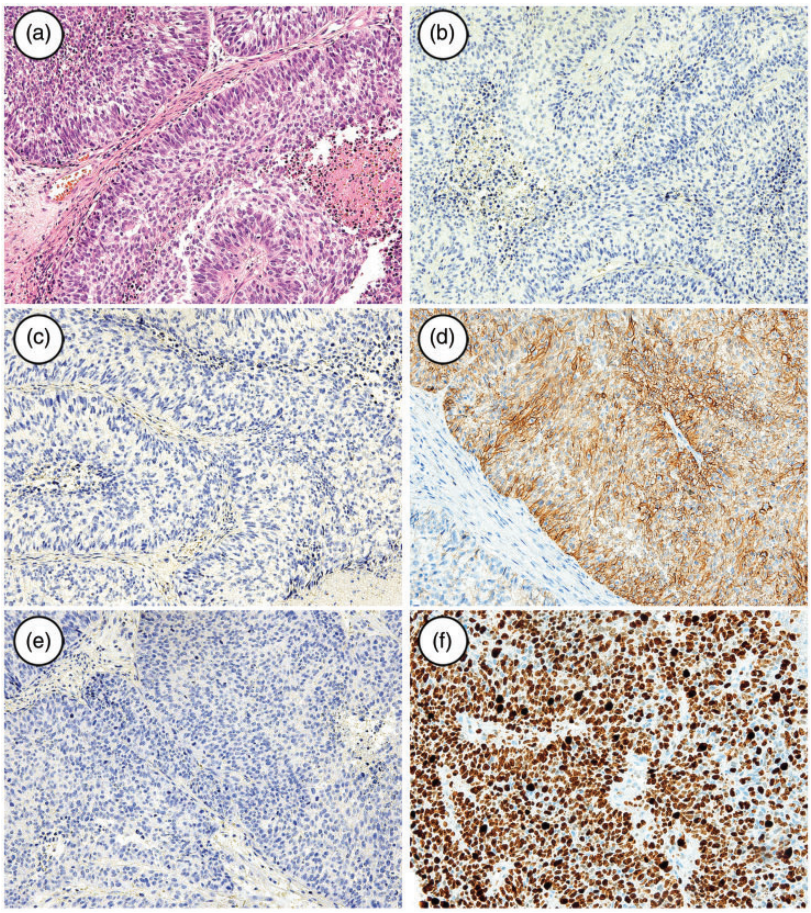

Figure 3. Micrographs of the endobronchial mass. (a) The tumor cells were large and arranged in a palisading pattern with frequent mitoses and geographic necrosis (hematoxylin and eosin, 200×). (b–f) On immunohistochemical staining, the tumor cells were positive for CD56 (d, 200×) but negative for synaptophysin (b, 200×), chromogranin (c, 200×), and calcitonin (e, 200×). The Ki-67 proliferation index was about 90% (f, 200×).

for metastatic NETs.[7,8] Therefore, it is important for clinicians and pathologists to differentiate between double primary NETs and metastatic NETs. However, because NETs can occur in many organs, it can be difficult to distinguish double primary from metastatic tumors when NETs are identified in two or more organs in a patient, and to determine which organ is the primary site. In some well-differentiated NETs, immunohistochemistry can be helpful in making a differential diagnosis.[9] In the medical literature, we found several case reports of double or multiple primary NETs involving the pancreas and uterine cervix; pituitary gland; stomach and duodenum; and pancreas and ileum (Table 1).[10–13] Clear differences in histologic or immunophenotypic features between tumors should be considered when a diagnosis of double or multiple primary NETs is made. We considered the present case to be a double primary NET because

Table 1. Clinicopathological features of double or multiple primary NETs reported in the literature

Case (reference)	Age (y) and sex	Number of tumors	Location of tumors	Histologic diagnosis	Note	Prognosis
1[10]	50 F	2	Entero-pancreas	NEC, WD	Ki-67: 2%	Disease-free
			Uterine cervix	Small cell NEC	Ki-67: almost 100% Mainly in situ with microinvasion	
2[12]	53 F	Multiple	Stomach	NET, grade 1		Disease-free
			Duodenum	NET, grade 1	Gastrin+	
3[13]	72 F	2	Ileum	NET, grade 1	Serotonin+	Disease-free (follow-up: 20 months)
			Pancreas	NET, grade 1	Pancreatic polypeptide+	
Current case	67 M	Multiple	Epiglottis	NEC, MD	Calcitonin+ Ki-67: about 5%	Deceased after 1 year
			Lung	Large cell NEC	Calcitonin− Ki-67: about 90%	

IHC, immunohistochemistry; MD, moderately differentiated; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; WD, well differentiated.

the microscopic morphology and immunohistochemical features of the laryngeal NET were clearly different from those of the lung NET.

In summary, we report a rare case of metachronous double primary neuroendocrine tumors in the larynx and lung. Our report suggests that when a patient presents with two or more NETs, detailed clinical and pathological review should be carried out to differentiate between metastatic NET and double primary NETs and, therefore, to institute the best management for the patient.

Acknowledgments

The authors would like to thank Enago (http://www.enago.co.kr) for the English language review.

Declaration of conflicting interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

In Hye Song https://orcid.org/0000-0001-6325-3548

References

1. Plockinger U, Rindi G, Arnold R, et al. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). *Neuroendocrinology* 2004; 80: 394–424. DOI: 10.1159/000085237.
2. Williams ED and Sandler M. The classification of carcinoid tumours. *Lancet* 1963; 1: 238–239.
3. El-Naggar AK, World Health Organization and International Agency for Research on Cancer. *WHO classification of head and neck tumours*. 4th ed. Lyon: International Agency for Research on Cancer 2017; 95–98.
4. Kim JY, Hong SM and Ro JY. Recent updates on grading and classification of neuroendocrine tumors. *Ann Diagn Pathol* 2017; 29: 11–16. DOI: 10.1016/j.anndiagpath.2017.04.005.
5. Bosman FT, World Health Organization and International Agency for Research on Cancer. *WHO classification of tumours of*

the digestive system. 4th ed. Lyon: International Agency for Research on Cancer, 2010; 13–14.
6. Travis WD, World Health Organization and International Agency for Research on Cancer. *WHO classification of tumours of the lung, pleura, thymus and heart*. 4th ed. Lyon: International Agency for Research on Cancer, 2015; 63–77.
7. Liu T, Liao J, Dang J, et al. Treatments for patients with advanced neuroendocrine tumors: a network meta-analysis. *Ther Adv Med Oncol* 2019; 11: 1758835919853673. DOI: 10.1177/1758835919853673.
8. Ye H, Xu HL, Shen Q, et al. Palliative resection of primary tumor in metastatic nonfunctioning pancreatic neuroendocrine tumors. *J Surg Res* 2019; 243: 578–587. DOI: 10.1016/j.jss.2019.04.002.
9. Yang Z, Klimstra DS, Hruban RH, et al. Immunohistochemical characterization of the origins of metastatic well-differentiated neuroendocrine tumors to the liver. *Am J Surg Pathol* 2017; 41: 915–922. DOI: 10.1097/pas.0000000000000876.
10. Sisti G, Buccoliero AM, Novelli L, et al. A case of metachronous double primary neuroendocrine cancer in pancreas/ileum and uterine cervix. *Ups J Med Sci* 2012; 117: 453–456. DOI: 10.3109/03009734.2012.707254.
11. Mete O, Alshaikh OM, Cintosun A, et al. Synchronous multiple pituitary neuroendocrine tumors of different cell lineages. *Endocr Pathol* 2018; 29: 332–338. DOI: 10.1007/s12022-018-9545-4.
12. Chen WC, Warner RRP, Harpaz N, et al. Gastric neuroendocrine tumor and duodenal gastrinoma with chronic autoimmune atrophic gastritis. *Pancreas* 2019; 48: 131–134. DOI: 10.1097/mpa.0000000000001204.
13. Tsunenari T, Aosasa S, Ogata S, et al. Synchronous neuroendocrine tumors in both the pancreas and ileum: a case report. *Int J Surg Case Rep* 2016; 22: 47–50. DOI: 10.1016/j.ijscr.2016.03.028.