Clinical Journal of Gastroenterology (2019) 12:534–538
https://doi.org/10.1007/s12328-019-00995-7

CASE REPORT

Neuroendocrine carcinoma of the esophagus with an adenocarcinoma component

Yuki Kaneko[1] · Shin Saito[1] · Kazuya Takahashi[1] · Rihito Kanamaru[1] · Yoshinori Hosoya[1] · Hironori Yamaguchi[3] · Joji Kitayama[1] · Toshiro Niki[2] · Alan Kawarai Lefor[1] · Naohiro Sata[1]

Received: 20 February 2019 / Accepted: 21 May 2019 / Published online: 27 May 2019

Abstract

A 68-year-old male was referred with dysphagia. Endoscopic findings showed circular stenosis with a protruding mass in the lower esophagus. Biopsy showed adenocarcinoma and there was no evidence of distant metastases. A subtotal esophagectomy was performed. The resected specimen revealed a mixed neuroendocrine carcinoma with adenocarcinoma. The adenocarcinoma component was on the surface of the tumor and the neuroendocrine component invaded the deeper portion. Immunohistochemically, the neuroendocrine carcinoma component stained positive for cytokeratin 7 and cytokeratin 20, suggesting that the neuroendocrine carcinoma originated from the adenocarcinoma. The adenocarcinoma component stained positive for MUC2, which suggests that the adenocarcinoma component originated from Barrett's epithelium. Taken together, the neuroendocrine carcinoma may have originated from Barrett's epithelium. A metastasis to the liver was found 2 months after the surgical resection. Chemotherapy was administered, but there was no response. Most esophageal neuroendocrine carcinomas are accompanied by adenocarcinoma or squamous cell components, suggesting that these carcinomas originate from pluripotent cells in squamous or Barrett's epithelium. Appropriate chemotherapy for these lesions should be considered based on the cell of origin.

Keywords Esophageal neuroendocrine carcinoma · Mixed adenoneuroendocrine carcinoma · Barrett's esophagus · Origin of neuroendocrine carcinomas

Abbreviations

SCC Squamous cell carcinoma
CT Computed tomography

Introduction

Most esophageal carcinomas are squamous cell carcinomas (SCC) or adenocarcinomas arising in areas of Barrett's epithelium [1]. Neuroendocrine carcinomas rarely originate in the esophagus, accounting for only between 0.4 and 2% of all malignant esophageal tumors [2]. Esophageal neoplasms with neuroendocrine differentiation are classified into three categories, including well-differentiated neuroendocrine tumors, poorly differentiated neuroendocrine tumors and mixed adenoneuroendocrine carcinoma [3]. Neuroendocrine tumors categorized as low-grade (G1) or intermediate-grade (G2) neuroendocrine tumors according to the mitotic count and Ki-67 index [4]. Neuroendocrine carcinomas are defined as having a mitotic count of > 20/10 high power field and/or a Ki-67 index > 20% [3].

Histopathologically, neuroendocrine carcinomas display either large-cell or small-cell features and mixed adenoneuroendocrine carcinomas have both gland-forming epithelial areas and neuroendocrine carcinoma [3]. The latter phenotype is defined to have at least 30% of either component [5]. Esophageal neuroendocrine carcinomas are highly aggressive and generally have a dismal prognosis [2]. Optimum treatment of neuroendocrine carcinomas is undefined because of their rarity [4] and their management is based on studies of neuroendocrine tumors of the lung [6].

We report a patient with a mixed neuroendocrine carcinoma with adenocarcinoma of the esophagus who underwent

✉ Shin Saito
shin.s@jichi.ac.jp

[1] Department of Surgery, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan

[2] Department of Pathology, Jichi Medical University, Shimotsuke, Japan

[3] Department of Clinical Oncology, Jichi Medical University, Shimotsuke, Japan

subtotal esophagostomy and post-operative chemotherapy. We also describe the immunohistochemical studies to gain insight to the origin of the carcinoma.

Case report

The patient is a 68-year-old male with dysphagia and weight loss. Endoscopic examination revealed a protruding mass with stenosis near the esophagogastric junction and Barrett's mucosa adjacent to the tumor (Fig. 1). Adenocarcinoma was diagnosed by biopsy of the protruding mass. Contrast-enhanced computed tomography (CT) scans of the chest and abdomen showed a tumor in the lower thoracic esophagus and cardiac lymph node enlargement consistent with metastases (Fig. 2). There was no evidence of distant metastases. A subtotal esophagectomy, with a two-field dissection and intrathoracic gastric tube reconstruction was performed. The proximal portion of the stomach was resected.

Macroscopic examination of the resected specimen showed a type1 tumor (6 × 2.5 cm) at the esophagogastric junction (Fig. 3). Histopathologically, the resected specimen showed two distinct components with an area of transition (Fig. 4a). The superficial portion of the tumor contained moderately to poorly differentiated adenocarcinoma (20%) (Fig. 4b), and the deep portion consisted of neuroendocrine carcinoma (80%), characterized by small cells proliferating with necrosis in a ribbon-like pattern, under the serous membrane (Fig. 4c). The lymph node metastases contained only neuroendocrine carcinoma. According to the TNM classification, the tumor was a stage IIIC (pT3, N3 (14/37) M0). Immunohistochemically, the neuroendocrine carcinoma component stained positive not only for chromogranin A and synaptophysin but also cytokeratin 7 and focal

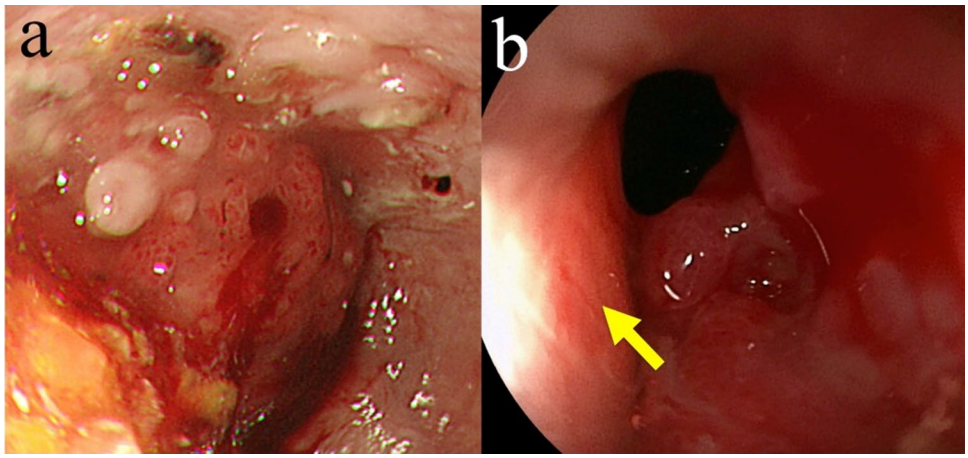

Fig. 1 Upper gastrointestinal endoscopy showed a type1 tumor with stenosis (**a**), and Barrett's mucosa (arrow) at the esophagogastric junction (**b**)

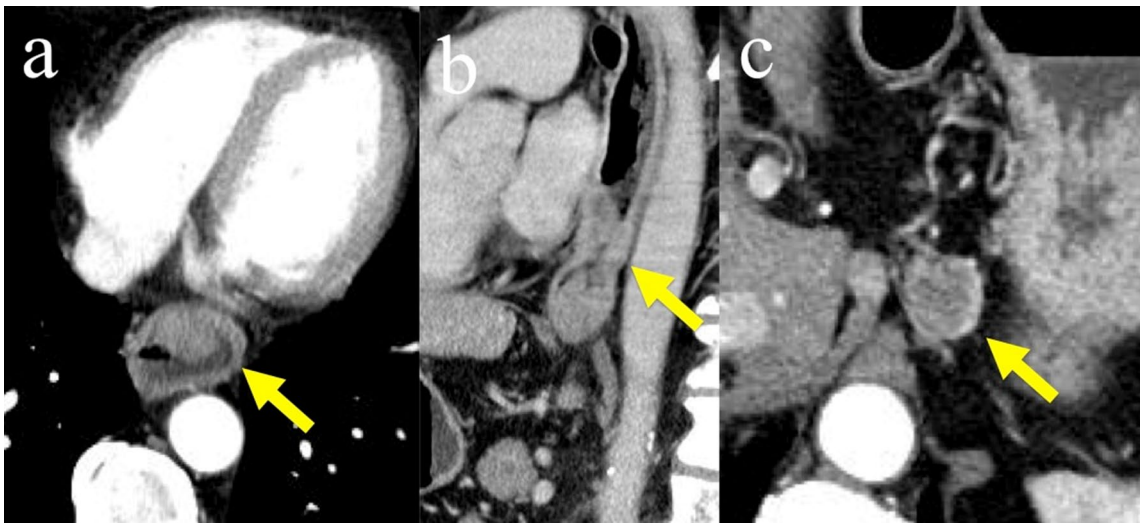

Fig. 2 Computed tomography (CT) scan showed a protruding tumor in lower thoracic esophagus (arrows) (**a**, horizontal view; **b**, axial view). Abdominal CT scan detected cardiac lymph node metastases (arrow) (**c**)

cytokeratin 20, suggesting that this component was derived from adenocarcinoma (Fig. 5). The adenocarcinoma component was diffusely positive for MUC2, suggesting that the adenocarcinoma component originated from Barrett's epithelium. Taken together, we concluded that the esophageal neuroendocrine carcinoma may have originated in Barrett's esophagus in this patient.

The patient was discharged uneventfully. However, 2 months later, contrast-enhanced CT scan revealed liver metastases. Irinotecan in combination with cisplatin [7] was administered but 3 months later there was evidence of disease progression which was followed by amrubicin chloride [8]. Amrubicin chloride also failed within 3 months and S-1 therapy was administered because the serum carcinoembryonic antigen level, which may be a marker for adenocarcinoma, became elevated (Fig. 6). Finally, the patient was treated with paclitaxel. Every chemotherapy regimen used was temporarily effective but was followed by disease progression within several months followed by a dramatic increase in serum tumor makers such as carcinoembryonic antigen, neuron-specific enolase and carbohydrate antigen 19-9 (Fig. 6). The patient died of disease 16 months after the initial resection.

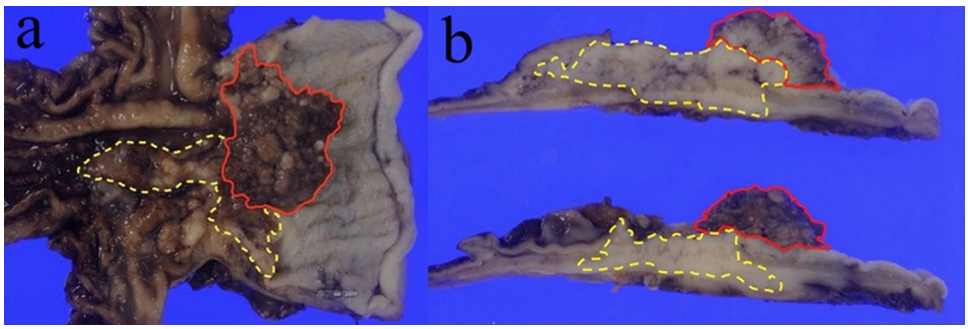

Fig. 3 Macroscopic examination showed a type1 tumor (6×2.5 cm) at the esophagogastric junction (**a**) and an invasive solid tumor continuous with that tumor (**b**). The protruding portion surrounded by the red line identifies the adenocarcinoma component and the deep area surrounded by the yellow dotted line is the neuroendocrine carcinoma component (**a**, **b**)

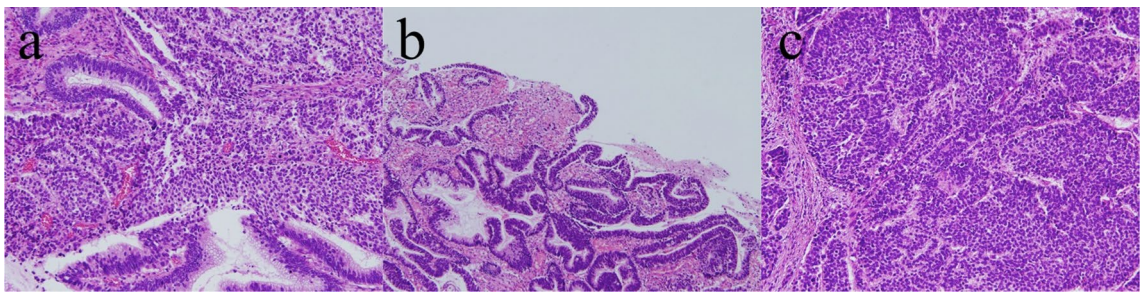

Fig. 4 Hematoxylin and eosin staining shows a transition from the adenocarcinoma component to the neuroendocrine carcinoma (**a**) (100×). The protruding part is moderately to poorly differentiated adenocarcinoma (**b**) (hematoxylin and eosin, 40×), and the deep part is the neuroendocrine carcinoma characterized by proliferating small cells with necrosis in a ribbon-like pattern (**c**) (hematoxylin and eosin, 100×)

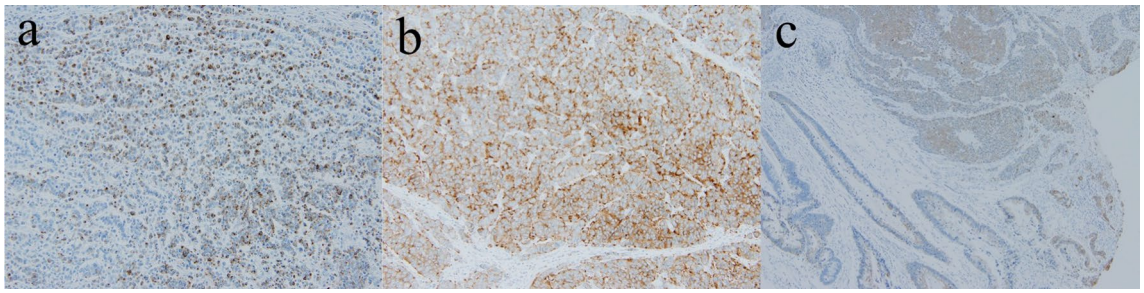

Fig. 5 Immunohistochemically, the neuroendocrine component stained positive for chromogranin A (**a**) (100×) and synaptophysin (**b**) (100×). This component showed diffuse positive staining for cytokeratin 7 (**c**) (40×) and focal positive staining for cytokeratin 20 (not shown)

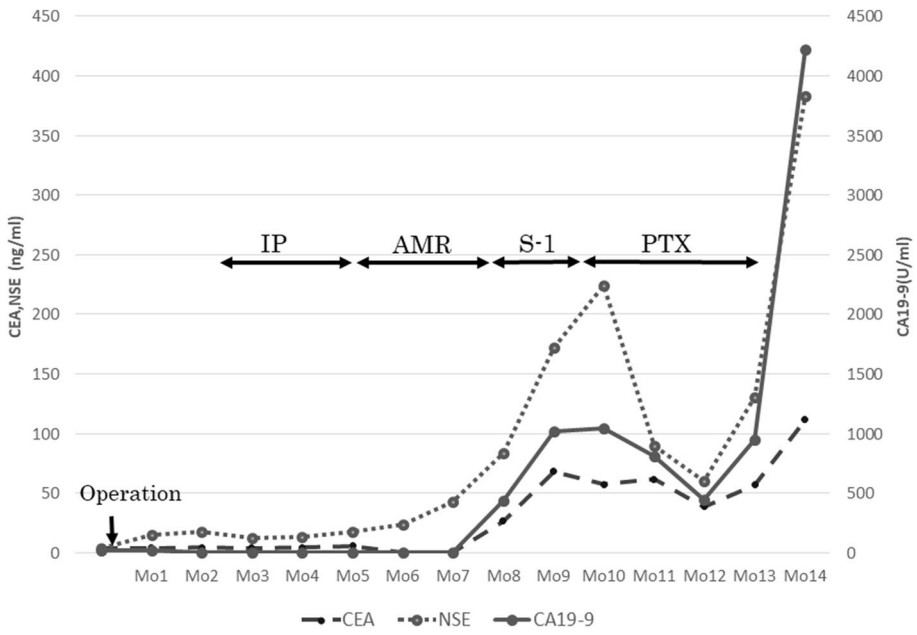

Fig. 6 Therapeutic course of chemotherapy and changes in specific tumor markers (*CEA* carcinoembryonic antigen, *NSE* neuron-specific enolase, *CA19-9* carbohydrate antigen 19-9, *AMR* amrubicin chloride, *PTX* paclitaxel, *IP* irinotecan in combination with cisplatin, *Mo* months after esophagectomy)

Discussion

Most esophageal neuroendocrine carcinomas are accompanied by SCC or adenocarcinoma components [2, 4, 6, 9]. Mixed adenoneuroendocrine carcinoma is defined as having both a neuroendocrine carcinoma component and an adenocarcinoma component representing at least 30% of the tumor [3]. Esophageal mixed adenoneuroendocrine carcinomas are also associated with adenocarcinoma in areas of Barrett's esophagus [10]. Since in the present patient, the adenocarcinoma component represented about 20% of the tumor, this patient was diagnosed with a mixed neuroendocrine carcinoma with adenocarcinoma of the esophagus. Maru et al., reviewed 40 patients with esophageal neuroendocrine carcinoma. 15 patients out of 40 had mixed neuroendocrine carcinoma with adenocarcinoma (37.5%) and Barrett esophagus was identified in 11 patients (27.5%) in their study [9].

Neuroendocrine carcinoma of the esophagus is often diagnosed at an advanced stage, resulting in an overall poor prognosis [2]. In addition, it is difficult to make an accurate diagnosis from a biopsy specimen when the surface of the lesion is covered with epithelial carcinoma components. The protruding proximal part of the tumor in the present patient was adenocarcinoma and the biopsy specimen was obtained from this portion, resulting in an initial diagnosis of adenocarcinoma of the esophagus. Therefore, we decided to perform a curative esophagectomy. The resected specimen revealed that the adenocarcinoma component was on the surface of the lesion and the neuroendocrine carcinoma component which represented 80% of the overall tumor was present in the most distal portion of the lesion in the deeper layer (Fig. 3b). Metastases from neuroendocrine carcinoma were found in multiple lymph nodes, suggesting that the neuroendocrine carcinoma component may be more biologically aggressive than adenocarcinoma.

The World Health Organization defines that neuroendocrine carcinomas are positive for endocrine markers such as chromogranin A, synaptophysin and CD56 [2]. Immunohistochemically, the neuroendocrine carcinoma component stained positive for cytokeratin 7 and cytokeratin 20 in the present patient, suggesting that this component maintains epithelial features and might be derived from adenocarcinoma. MUC2 is an intestinal-type mucin which is commonly found in goblet cells of areas of Barrett's esophagus mucosa [11, 12] and the adenocarcinoma component was diffusely positive for MUC2, suggesting that the adenocarcinoma component originated from Barrett's epithelium. We also identified a transition zone from adenocarcinoma to the neuroendocrine carcinoma component (Fig. 4a) and macroscopic Barrett's mucosa adjacent to the tumor (Fig. 1). Taken together, the esophageal neuroendocrine carcinoma in the present patient may have arisen from Barrett's esophagus [10, 13]. Finally, this patient was diagnosed with a mixed neuroendocrine carcinoma with adenocarcinoma of the esophagus arising from Barrett's epithelium.

Esophageal neuroendocrine tumors are very rare [6] and there is no established standard treatment at this time [4]. The role of surgery in the treatment of patients with esophageal neuroendocrine carcinomas remains controversial [4]. Patients with gastrointestinal neuroendocrine carcinomas are usually treated with the same chemotherapy protocols as patients with small cell lung carcinoma [14]. Since esophageal neuroendocrine carcinomas may originate from pluripotent cells present in squamous epithelium or

ducts in Barrett's epithelium [3], suitable chemotherapy for patients with these lesions depends on the cellular origin of the tumor.

The present patient developed liver metastases 2 months after undergoing a curative esophagectomy and chemotherapy including irinotecan in combination with cisplatin, amrubicin chloride, S-1 and paclitaxel were given. Despite this aggressive treatment, the disease progressed in a few months. Neoadjuvant chemotherapy is considered to be the standard approach for treating patients with stage II or III esophageal squamous cell carcinoma [15]. Since the present patient was pre-operatively diagnosed with adenocarcinoma of the esophagus and suffered from severe dysphagia, neoadjuvant chemotherapy was not given. Mixed neuroendocrine carcinomas may have a better prognosis than pure neuroendocrine carcinomas [9], but multidisciplinary therapy is recommended [4, 16]. Making an accurate diagnosis before deciding the treatment strategy is important for treating patients with esophageal neuroendocrine carcinoma. Development of an optimal treatment strategy will require evaluating the outcomes of individual patients since it is difficult to accumulate a large series of patients with these rare lesions.

Acknowledgements The authors declare no conflicts of interests and no funds regarding the publication of this paper.

Compliance with ethical standards

Conflict of interest Yuki Kaneko, Shin Saito, Kazuya Takahashi, Rihito Kanamaru, Shiro Matsumoto, Yoshinori Hosoya, Hirofumi Fujii, Joji Kitayama, Toshiro Niki, Alan Kawarai Lefor and Naohiro Sata declare that they have no conflict of interest.

Human rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Ethical approval The need for ethical approval for this paper was waived by the committee of Jichi Medical University Hospital.

References

1. Kitajima T, Kaida S, Lee S, et al. Mixed adeno (neuro) endocrine carcinoma arising from the ectopic gastric mucosa of the upper thoracic esophagus. World J Surg Oncol. 2013;11:218.
2. Egashira A, Morita M, Kumagai R, et al. Neuroendocrine carcinoma of the esophagus: clinicopathological and immunohistochemical features of 14 cases. PLoS One. 2017;12:e0173501.
3. Bosman FT, Carneiro F, Hruban RH, et al. WHO classification of tumours of the digestive system. 4th ed. International Agency for Research on Cancer. Lyon: IARC Press; 2010.
4. Deng HY, Ni PZ, Wang YC, et al. Neuroendocrine carcinoma of the esophagus: clinical characteristics and prognostic evaluation of 49 cases with surgical resection. J Thorac Dis. 2016;8:1250–6.
5. Kadhim MM, Jespersen ML, Pilegaard HK, et al. Mixed adenoneuroendocrine carcinoma is a rare but important tumour found in the oesophagus. Case Rep Gastrointest Med. 2016;2016:9542687.
6. Tustumi F, Takeda FR, Uema RH, et al. Primary neuroendocrine neoplasm of the esophagus—report of 14 cases from a single institute and review of the literature. Arq Gastroenterol. 2017;54:4–10.
7. Xiao X, Wang S, Xia S, et al. Retrospective study of irinotecan/cisplatin followed by etoposide/cisplatin or the reverse sequence in extensive-stage small cell lung tumor. OncoTargets Therapy. 2015;8:2209–14.
8. Asayama M, Fuse N, Yoshino T, et al. Amrubicin for the treatment of neuroendocrine carcinoma of the gastrointestinal tract: a retrospective analysis of five cases. Cancer Chemother Pharmacol. 2011;68:1325–30.
9. Maru DM, Khurana H, Rashid A, et al. Retrospective study of clinicopathologic features and prognosis of high-grade neuroendocrine carcinoma of the esophagus. Am J Surg Pathol. 2008;32:1404–11.
10. Cary NR, Barron DJ, McGoldrick JP, et al. Combined oesophageal adenocarcinoma and carcinoid in Barrett's oesophagitis: potential role of enterochromaffin-like cells in oesophageal malignancy. Thorax. 1993;48:404–5.
11. McIntire MG, Soucy G, Vaughan TL, et al. MUC2 is a highly specific marker of goblet cell metaplasia in the distal esophagus and gastroesophageal junction. Am J Surg Pathol. 2011;35:1007–13.
12. Turkmen IC, Bassullu N, Uraz S, et al. CDX2, COX2 and MUC2 expressions in Barrett's esophagus: can they be useful in determination of the dysplasia? Turk patoloji dergisi. 2012;28:251–8.
13. Saint Martin MC, Chejfec G. Barrett esophagus-associated small cell carcinoma. Arch Pathol Lab Med. 1999;123:1123.
14. Okuma HS, Iwasa S, Shoji H, et al. Irinotecan plus cisplatin in patients with extensive-disease poorly differentiated neuroendocrine carcinoma of the esophagus. Anticancer Res. 2014;34:5037–41.
15. Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol. 2012;19:68–74.
16. Saif MW, Vethody C. Poorly differentiated neuroendocrine tumor of the esophagus with hypertrophic osteoarthropathy and brain metastasis: a success story. Cureus. 2016;8:646.