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CASE REPORT

동시화학방사선요법을 통해 내시경적으로 완전 관해된 식도 신경내분비종양 1예

김명희, 정현용, 성재규, 문희석, 강선형, 김덕기
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A Case of Endoscopically Complete Remission of Esophageal Neuroendocrine Tumors by Concurrent Chemoradiation Therapy

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Neuroendocrine tumors (NETs) of the esophagus are extremely rare, aggressive and have a poor prognosis. Combined therapy using chemotherapy, radiotherapy and/or surgery appear effective. Here, we present a patient with a complaint of dysphagia who was diagnosed with this rare tumor. Upper gastrointestinal endoscope of a 46-year-old female revealed a localized ulcerative lesion in the middle esophagus. Histologic exam of biopsy specimens indicated a neuroendocrine carcinoma. The tumor cells were arranged in microtubular structures, with small and round cells containing scanty cytoplasm. They were positive for synaptophysin and chromogranin A on immunohistochemical staining. A computed tomography scan showed an esophageal tumor with enlarged superior mediastinal lymph nodes and about 1.2 cm sized liver metastasis, similar to findings in PET-CT scanning. The patient was prescribed chemotherapy consisting of etoposide and cisplatin, which led to regression of disease on follow-up imaging study. She continues under clinical observation. We seek to increase awareness of this exceedingly rare but hazardous disease by sharing our unexpected finding. **(Korean J Gastroenterol 2016;68:265-269)**

Key Words: Neuroendocrine tumors; Endoscopy; Esophageal neoplasms

INTRODUCTION

Neuroendocrine tumors (NETs) of the esophagus are extremely rare but their incidence is sharply increasing.[1] In multicenter research conducted in Korea in 2012, 4,951 cases of gastroenteropancreatic NETs were analyzed. Of these, only 1.4% were reported to be esophageal NETs.[2]

Concrete data have not been published on its clinical features or prognosis because of its rarity. In addition, an optimal treatment strategy has not been established but various combinations of surgery, radiotherapy, and chemotherapy have been described. Moderate effectiveness has been achieved using chemotherapy to treat metastatic disease.[3,4]

The most common symptoms of esophageal NETs are progressive dysphagia and weight loss, as seen in the classical types of esophageal cancers.[1] We present a case of a patient who presented with common symptoms. She was successfully treated with a combination of chemotherapy and radiation therapy. The disease regressed when examined later by upper gastrointestinal endoscopy. This case highlights how

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seemingly ordinary patient symptoms can be indicative of a rare and interesting underlying disease process.

CASE REPORT

A 46-year-old woman presented with a one-month history of mild intermittent dysphagia, to solids only, with a few episodes of chest pain. Despite a decrease in her food intake, her appetite had not been affected. The patient had undergone upper gastrointestinal endoscopy two years prior, suggestive of gastritis only. Her medical history was significant for mild hyperlipidemia only. She denied a history of tobacco, alcohol, or drug use.

On presentation, her vital signs were stable and the phys-

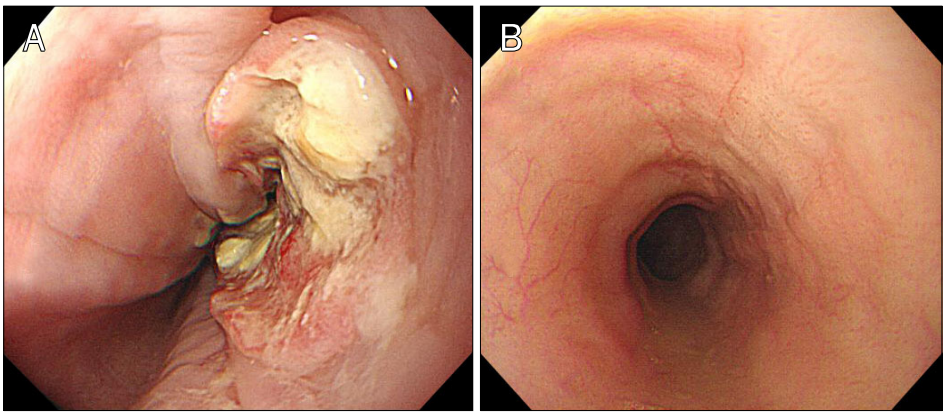

Fig. 1. (A) Upper gastrointestinal endoscopy revealed a localized ulcerative lesion in the esophagus. (B) The primary tumor of the esophagus diminished after chemotherapy and concurrent chemoradiation therapy.

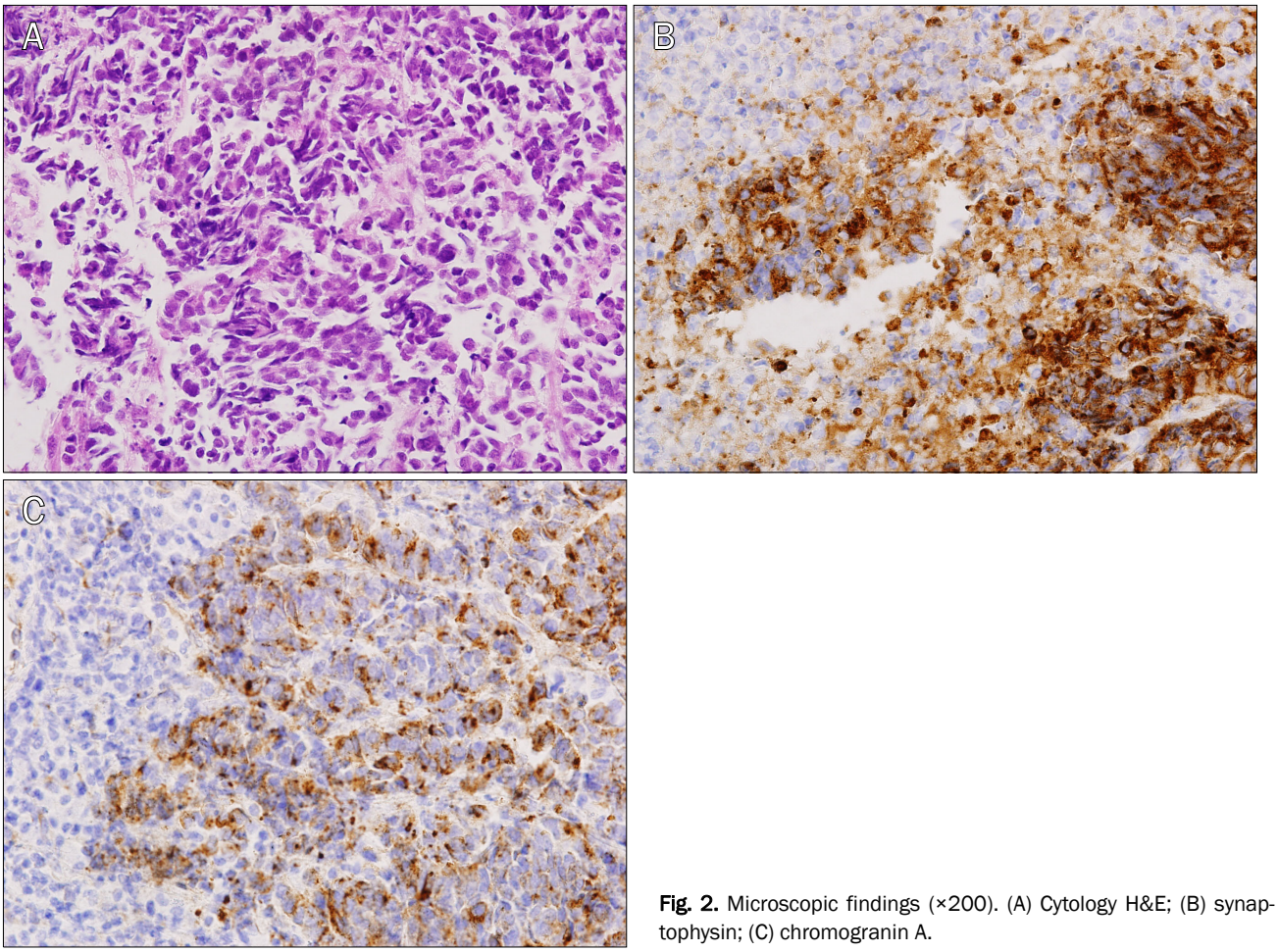

Fig. 2. Microscopic findings (×200). (A) Cytology H&E; (B) synaptophysin; (C) chromogranin A.

ical examination was unremarkable. Her basic biochemical parameters were normal by a peripheral blood smear, including the tumor markers, carcinoembryonic antigen (1.6 ng/mL) and cancer antigen 19-9 (12 U/mL). An additional urinary 5-hydroxyindoleacetic acid measurement was not performed. Systemic hormone syndromes, such as flushing or diarrhea, were not identified.

Upper gastrointestinal endoscopy was performed and revealed a friable, non-obstructing lesion in the mid-esophagus, 28 cm from the incisors. A lesion with localized ulceration, white coating, and exudate was detected, measuring approximately 3×4 cm^2 in size (Fig. 1A).

It was concluded following histological analysis of the biopsies that the lesion was a neuroendocrine carcinoma of the small cell type because of the round- to spindle-shaped cells with scanty cytoplasm, granular nuclei, inconspicuous nucleoli, and immunohistochemical evidence of neuroendocrine differentiation. Many of the cells were reactive to synaptophysin and chromogranin A. In addition, staining for cytokeratin 5/6 was negative (Fig. 2). Unfortunately, the mitotic count and Ki-67 index were not evaluated during the histopathologic analysis.

A CT scan of the chest showed circumferential wall thickening, increased enhancement in the mid to lower esophagus, enlarged superior mediastinal lymph nodes, and a 1.2 cm hypoattenuating lesion in the S5 of the liver (Fig. 3). PET-CT was performed shortly after the chest CT scan and showed increased activity corresponding with the identification of the esophageal mass, the right upper paratracheal lymph node, and the right hepatic lobe (with respect to metastatic disease). The final staging of the lesions was T2N1M1.

Our patient was successfully treated with combined chemotherapy of etoposide (100 mg/m^2 on days 1, 2, and 3) and cisplatin (60 mg/m^2 on days 1 and 2) for four cycles, followed by concurrent chemoradiation therapy (10 cycles×300 cGy; a total of 3,000 cGy) with weekly cisplatin (30 mg/m^2 on day 1) for 6 cycles. Successful regression was observed on upper gastrointestinal endoscopy at the patient's later exams. The friable non-obstructing lesion, observed at the mid-esophagus, 28 cm below the incisors, disappeared. Only a scar could be detected at the site. Staining was not found after the application of Lugol's solution (Fig. 1B), indicating complete endoscopic remission. Lesions in the mid to lower levels of the esophagus were not detected on the follow-up chest CT (Fig. 4A, B). After six cycles of chemotherapy, the size of the metastatic lesion was reduced from 12 mm to 5 mm. However, tumor progression was found on a PET-CT performed after treatment. Radiofrequency ablation was conducted. There was no residual mass by abdominopelvic CT at three months (Fig. 4C).

The patient was observed for 17 months from the initial diagnosis to the final abdominopelvic CT.

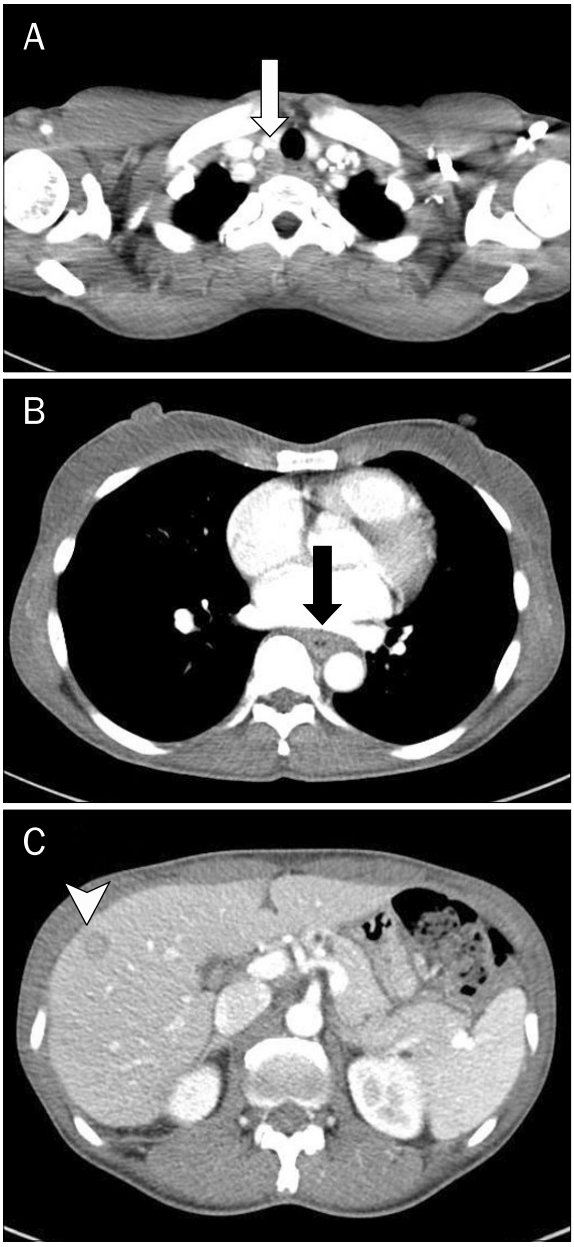

Fig. 3. A computed tomography scan showed (A) enlarged superior mediastinal lymph nodes (white arrow) of (B) an esophageal tumor (black arrow) with (C) a ~1.2-cm-sized hypoattenuated lesion (arrowhead) in S5 of the liver.

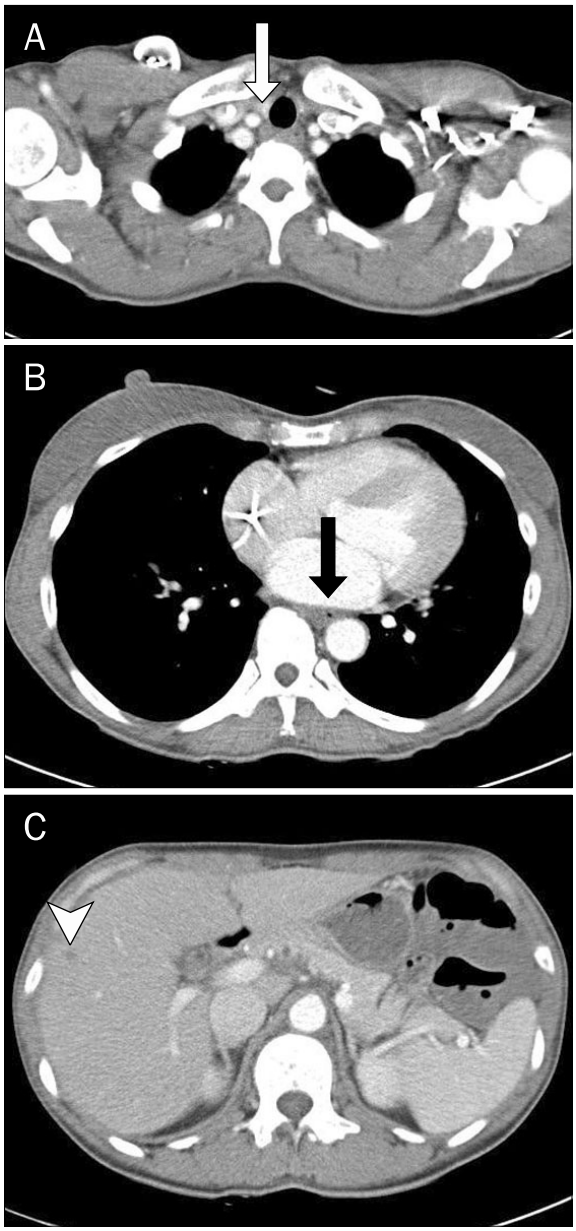

Fig. 4. A computed tomography scan showed (A) the primary tumor (white arrow) at the esophagus, (B) a metastatic tumor (black arrow) in the lymph node, and (C) S5 of the liver diminished in size (arrowhead) after chemotherapy and concurrent chemoradiation therapy.

DISCUSSION

NETs of the esophagus are very rare. Only a few cases have been reported.[1] In a 2014 study, 2,037 pathology reports of gastroenteropancreatic NETs were reviewed. Of these, 26 cases (1.3%) were located in the esophagus. Slightly higher rates are reported in the data from Korea, compared with those in Western countries. It is possible that this could be attributed to the development and widespread use of endoscopy screening in Korea.[1] The reported prevalence of neoplasms ranges from 0.05% to 2.40% as a proportion of all esophageal cancers.[5]

Most esophageal NETs are large (4-10 cm in diameter), present as ulcerated or fungating masses, and deeply infiltrate the esophageal wall. Typically, esophageal NETs are a single lesion on endoscopic findings and commonly develop along the lower third of the esophagus. The neuroendocrine cells are mainly distributed on the mucosal glands of the distal esophagus.[6]

Although the risk factors are not well defined for esophageal NETs, they seem to be similar to those for squamous cell esophageal cancer (a history of alcohol consumption and smoking). Common presenting symptoms include dysphagia, abdominal discomfort, weight loss, and melena.[1] Systemic syndromes, with an inappropriate production of hormones, such as excessive secretion of the antidiuretic hormone, watery diarrhea with hypokalemia, and achlorhydria, have been reported.[7] A low rate of carcinoid syndrome is found in esophageal NETs in particular, and they present as silent or nonspecific symptoms. Therefore, an early diagnosis of an esophageal NET is difficult and is often preceded by initial detection. Thus, the use of endoscopy is advised for the early detection of tumors.[8]

Microscopically, small cell NET may present as a round or oval shape, with dark nuclei and scanty cytoplasm that form solid sheets and nests. The immunohistochemistry results for chromogranin A, synaptophysin, neural cell adhesion molecule/CD56, galactosylgalactosylxylosylprotein 3-beta-glucuronosyltransferase 1/Leu7, and neuron-specific enolase are usually positive. Synaptophysin is the most sensitive diagnostic marker.[9]

Results are inconsistent on whether synaptophysin or chromogranin expression is associated with a better prognosis. One Korean multicenter study reported that synaptophysin and chromogranin expression were not significant prognostic factors.[2]

Our patient presented with dysphagia, the most commonly reported symptom. In addition, she had a localized ulcerative lesion (of 3 cm in diameter) in the middle third of the esophagus, a regional lymph node that is susceptible to tumor spread, and liver metastasis. Esophageal NETs are staged according to the TNM classification of malignant tumours for

esophageal carcinomas for practical purposes.

The patient was treated with chemotherapy, consisting of etoposide and cisplatin, which are usually used for small cell carcinoma of the lung. Partial response to the chemotherapy was achieved. On the follow-up chest CT scan, performed after four cycles of chemotherapy (etoposide and cisplatin), a significant change was not observed. After concurrent chemoradiation therapy that focused on the esophageal lesion, the patient was assessed by upper gastrointestinal endoscopy at the next visit and was in a disease-free state.

The treatment of a primary NET depends on the clinical staging. However, a specific treatment algorithm for esophageal NET has not been established. Esophagectomy and/or radiotherapy, combined with chemotherapy, is indicated for the treatment of locoregional disease with curative intent. Cisplatin, etoposide, cyclophosphamide, and doxorubicin are the "gold" standard of most combined chemotherapy regimens since chemotherapy for esophageal NET is similar to that for small cell lung cancer, with which it shares clinicopathological similarities.[10] Endoscopic treatment has been performed only on patients with tumors measuring $\leq$ 10 mm (with a range of 2-8 mm) and no regional lymph node metastasis.[2]

In conclusion, esophageal NETs are rare and aggressive, with a poor prognosis. However, the survival period seems to be longer in patients with locoregional disease. It is important to have case knowledge of multimodal therapies when treating this rare disease. A good prognosis is essential for NETs involving the gastrointestinal tract. The treatment and prognosis of NETs is different from that of squamous cell carcinoma. Therefore, early upper gastrointestinal endoscopy, in conjunction with a histopathological review, is required for an accurate diagnosis of NETs.

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