A CASE OF ESOPHAGEAL SMALL CELL CARCINOMA ASSOCIATED WITH HYPERCALCEMIA CAUSING SEvere ACUTE PANCREATITIS

KAORI KANNO¹, TAKUTO HIKICHI², KEIETSU SAITO¹, KENYA WATANABE¹, TADAYUKI TAKAGI¹, GORO SHIBUKAWA¹, TAKERU WAKATSUKI¹, HIDEMICHI IMAMURA¹, YUTA TAKAHASHI¹, AI SATO¹, MASAKI SATO¹, ATSUSHI IRISAWA¹, KATSUTOSHI OBARA², and HIROMASA OHIRA¹

¹Department of Internal Medicine II, Fukushima Medical University School of Medicine, Fukushima, 960-1295, Japan
²Department of Endoscopy, Fukushima Medical University Hospital, Fukushima, 960-1295, Japan

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Abstract: A 60-year-old woman was diagnosed with esophageal small cell carcinoma in October 2004 and received chemotherapy. However, the tumor grew gradually and multiple bone metastases occurred. Anorexia, nausea, emesis, numbness in both hands, and disturbed consciousness developed at the end of January 2006, and the patient was admitted to Fukushima Medical University Hospital. Abdominal pain, marked hypercalcemia and hyperamylasemia were noted and the patient was diagnosed with severe acute pancreatitis. Because the level of blood parathyroid hormone-related protein was elevated, we considered that esophageal small cell carcinoma caused human hypercalcemia and that metastatic bone tumors caused local osteolytic hypercalcemia, eventually leading to severe acute pancreatitis. This is an extremely rare case of esophageal small cell carcinoma associated with hypercalcemia causing severe acute pancreatitis.

Key words: esophageal carcinoma, small cell carcinoma, severe acute pancreatitis, hypercalcemia, EUS-FNA
INTRODUCTION

We report a case of esophageal small cell carcinoma in which human hypercalcemia of malignancy (HHM) was probably caused by primary tumor and metastatic tumors, and local osteolytic hypercalcemia (LOH) by metastatic bone tumors, eventually leading to severe acute pancreatitis. HHM is one of the paraneoplastic syndromes caused by parathyroid hormone–related protein (PTHrP)–producing tumor. The known sites of the primary foci of this tumor include the lungs, ovary, and esophagus, and its histological type is mainly squamous cell carcinoma\(^1\). Primary esophageal small cell carcinoma, which accounts for 1% to 4.7% of all esophageal tumors\(^2,3\), is rarer than esophageal squamous cell carcinoma. Thus, pancreatitis due to primary esophageal small cell carcinoma is extremely rare.

CASE REPORT

A 60-year-old woman experienced difficulty in swallowing solid food around September 2004. In October 2004, she presented to a clinic, where esophago–gastro–duodenoscopy (EGD) showed two tumors, a type-2 tumor, according to the Guidelines for Clinical and Pathologic Studies on Carcinoma established by the Japan Esophageal Society, 37 cm from the superior incisor teeth (Fig. 1A) and a submucosal tumor at the gastric cardia (Fig. 1B). Immediately she was referred to Fukushima Medical University Hospital. The esophageal tumor was diagnosed as small cell carcinoma by the histological examination of EGD biopsy specimens (Fig. 2); its depth of invasion was measured using endoscopic ultrasonography (EUS), which showed invasion into the adventitia (Fig. 3A). The submucosal tumor at the gastric cardia appeared as a tumor originating from the proper muscular layer on EUS (Fig. 3B). Endoscopic ultrasonography–guided fine-needle aspiration biopsy (EUS–FNA)

Fig. 1. Esophago–gastro–duodenoscopy. (A) A type-2 advanced tumor was found 37 cm away from the superior incisor teeth in the lower thoracic esophagus. (B) A submucosal tumor was found at the gastric cardia (arrow).
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Fig. 2. Histopathological findings. (A) HE staining: a confluence of many small agglomerations of small atypical cells with nuclear degeneration is observed. (B) Keratin staining and (C) CD56 staining were positive. The results were consistent with small cell carcinoma. (D) CEA staining was positive.

was performed, and the tumor was also diagnosed as small cell carcinoma (Fig. 4A; Fig. 4B). Because no sign of small cell carcinoma was found in the neighboring regions including the lungs, we considered that esophageal carcinoma was the primary focus, and that it metastasized to the gastric cardia. Since she was diagnosed with Stage IV primary esophageal small cell carcinoma, she was treated by chemotherapy according to the treatment regimen for small cell carcinoma of the lung in the absence of an established standard treatment for that of the esophagus. From December 2004, 5 cycles of Irinotecan (CPT-11)/Cisplatin (CDDP) were administered, reducing both the primary focus and the gastric metastasis for a while. However, because they grew slowly again, the therapy was changed to 4 cycles of Etoposide (VP-16)/CDDP and 3 cycles of Docetaxel, but in vain; the primary tumor still grew, and the number of metastatic mediastinal lymph nodes increased, and so from November 2005, 2 cycles of TS-1 were given. Nevertheless, anorexia, backache, nausea, and emesis occurred in late January 2006. Bone scintigraphy revealed an abnormal accumulation of radioactivity in the lumbar vertebrae (Fig. 5), and magnetic resonance imaging (MRI) showed multiple metastatic lesions in the lumbar vertebrae and pelvis. On January 30, 2006, numbness in both hands and abnormal behavior also occurred. Thus, on February 2, 2006, the patient was admitted to
Fig. 3. Endoscopic ultrasonography. (A) Hypoechoic mass was observed in the lower thoracic esophagus and invasion into the adventitia was observed (arrow). (B) The tumor at the gastric cardia, 25 mm in diameter, was in the 4th layer, i.e. the proper muscular layer. It was not contiguous with the tumor in the esophagus (arrow).

Fukushima Medical University Hospital. On admission, there was tenderness in the epigastric area. Laboratory findings were as follows: Ca, 17.5 mg/dl; amylase (AMY), 949 IU/l; BUN, 79 mg/dl; and Crea, 1.9 mg/dl, indicating hypercalcemia,
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Fig. 4. EUS-FNA. (A) Image of puncture needle (dotted arrow) into the gastric submucosal tumor under EUS (arrow). (B) Many cell agglomerations with an extremely high N/C ratio and increased chromatin were observed using Papanicolaou staining. The finding was consistent with small cell carcinoma.

hyperamylasemia, and renal dysfunction. The levels of tumor markers, carcinoembryonic antigen (CEA) (13,164.8 ng/ml, normal < 4.9 ng/ml), carbohydrate antigen 19–9 (CA19–9) (45.4 U/ml, normal < 37 U/ml), and neuron specific enolase (NSE) (27.8 ng/ml, normal < 10.0 ng/ml) were elevated, and the level of bone metastasis marker pyridinoline cross-linked carboxyterminal telopeptide of type 1 collagen (ICTP) (18.2 ng/ml, normal < 4.5 ng/ml) was also elevated. Intact PTH was markedly decreased to 2.0 pg/ml (normal 6.5–59.7 pg/ml), whereas PTHrP was increased to 16.1 pmol/l (normal < 1.1 pmol/l). Because numbness in both hands, disturbed consciousness, and anorexia were considered to be attributed to hypercalcemia, massive
Fig. 5. Bone scintigraphy. Abnormal accumulation of radioactivity was observed in the skull and lumbar vertebrae (arrow).

Fig. 6. Plain MRI of the brain. No metastatic lesions were found in the brain. Irregular tumors were observed in the left temporal and occipital cortical bone and bone marrow (arrow).
fluid replacement was performed, and diuretic, bisphosphonate, and calcitonin were administered. However, disturbed consciousness persisted, raising suspicion of brain metastasis. Plain MRI of the brain (Fig. 6) revealed irregular tumors in the temporal and occipital cortical bone and bone marrow, but no tumor suspicious of metastasis in the brain parenchyma. Acute pancreatitis was also suspected because of abdominal pain and hyperamylasemia. Therefore, abdominal computed tomography (CT) was performed without contrast medium; renal dysfunction was noted, and there was a history of allergy to contrast medium (Fig. 7). It showed diffuse swelling of the pancreas, a low absorbance area in the pancreatic head, and effusion extending from the retroperitoneal space to the inferior poles of both kidneys. It also showed pleural effusion, ascites, multiple metastatic tumors in the liver, metastatic bone tumors in the spine, and multiple swollen lymph nodes around the aorta. These findings led to the diagnosis of severe acute pancreatitis with a score of 3, which was treated conservatively with gabexate mesilate, urinastatin, and antibiotics without success. Renal dysfunction and acidosis worsened, and disseminated intravascular coagulation (DIC) developed. The patient died on February 8, 2006.

**DISCUSSION**

Esophageal small cell carcinoma was first reported in 1952 by McKeown as oat-cell carcinoma. In Japan, approximately 200 cases have been recorded in *Japanese Central Review Medicine* since 1983. In addition, primary esophageal small cell carcinoma is so rare that it accounts for only 1% to 4.7% of all esophageal tumors. This carcinoma spreads widely lymphatically or hematogenously from early stages; it is often advanced when detected. Bayer et al. reported that in the 134 cases of esophageal small cell carcinoma they saw or found in the literature, the average life...
expectancy after diagnosis was 5.3 months, and that the one-year survival rate was 10%. Thus, the prognosis of esophageal small cell carcinoma is extremely poor, and no standard treatment has been established. Our patient was treated by chemotherapy according to the treatment scheme for small cell carcinoma of the lung, but died 16 months after diagnosis.

Acute pancreatitis was the direct cause of death in this patient. Although acute pancreatitis is known to result from alcohol consumption and gallstones, it may also be caused by hypercalcemia. A well-known disease that causes hypercalcemia is primary hyperparathyroidism whose major clinical symptoms are produced by nephrolithiasis and bone lesions. Acute pancreatitis associated with primary hyperparathyroidism was first reported in 1957 by Cope et al., and the frequency of the association has been reported to be 1% or less. On the other hand, acute pancreatitis associated with pseudohyperparathyroidism caused by esophageal carcinoma is extremely rare. We were able to find no case in *Japana Centra Revuo Medicina* or MEDLINE during the period of 1983 to 2006. Since our patient had no history of alcohol consumption, no gallstones revealed on imaging study and no increase in hepatic and biliary enzymes, alcohol and gallstones were excluded as possible causes of acute pancreatitis. However, her blood test showed marked hypercalcemia. These findings led us to consider that hypercalcemia was the cause of acute pancreatitis.

Several possible mechanisms have been proposed for the development of acute pancreatitis in patients with hyperparathyroidism, including the following four: 1) pancreatitis is prone to occur because hypercalcemia raises the serum trypsin level; 2) pancreatitis occurs because hypercalcemia causes calcification and stenosis in the pancreatic parenchyma and duct; 3) pancreatitis occurs because blood flow is reduced by PTH-induced microembolization or by damage to the pancreas by PTH itself; and 4) pancreatic necrosis occurs because both protein that should be secreted into the pancreas and protein catabolic enzyme accumulate owing to the impairment of pancreatic exocrine function with increase in intracellular calcium. Although none of these mechanisms have been fully understood, they may also be involved in the development of acute pancreatitis in patients with hypercalcemia associated with small cell carcinoma.

Hypercalcemia is often seen in malignant tumors, especially esophageal carcinoma. Tachimori et al., examining 382 cases of esophageal carcinoma, reported that hypercalcemia was present in 38% of recurrent nonexcision cases. Malignancy-associated hypercalcemia is presumed to be caused by cytokines produced by tumor cells or the immune cells activated by tumor cells. It is roughly divided into two syndromes, HHM and LOH. HHM is caused by excessive production of PTHrP, a PTH-like hormone, by tumors and is considered to account for 80% or more of the cases of malignancy-associated hypercalcemia. LOH is presumed to be caused by bone metastasis of tumor cells and multiple myeloma, because tumor cells in bones produce local factors including cytokines. In this patient, because
examination on admission showed multiple bone metastases and a high level of blood PTHrP, the hypercalcemia was considered to be HHM, although the possibility of LOH contributing to it could not be ruled out. It is noteworthy that there are papers reporting that HHM is caused by squamous cell carcinomas of the esophagus, lung, skin, head, neck and kidney, but, as for small cell carcinomas, there are very few papers reporting that HHM is caused by those of the ovary\textsuperscript{15–17} and prostate\textsuperscript{18}. Fereidooni\textsuperscript{19} reports a 63-year-old woman who developed esophageal carcinoma associated with hypercalcemia. The carcinoma consisted of two components, squamous cell carcinoma and pleomorphic small cells. The hypercalcemia was assumed to be due to PTHrP, and immunohistochemistry showed that it was caused not by squamous cell carcinoma, but by pleomorphic small cells alone. We have found reports of acute pancreatitis caused by hypercalcemia in small cell carcinomas of the ovary\textsuperscript{20} and lung\textsuperscript{21}, but not of the esophagus in \textit{Japana Centra Revuo Medicina} or MEDLINE during the period between 1983 and 2006.

Thus, this is an extremely rare case of esophageal small cell carcinoma associated with hypercalcemia causing severe acute pancreatitis.

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