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Primary Neuroendocrine Carcinoma of the Esophagus

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A 79-year-old man was admitted to our hospital because of dysphagia and weight loss. Panendoscopy revealed a tumor mass with an irregular ulcer over the lower third portion of the esophagus. Histopathologic examination revealed small round blue cells with hyperchromatic nuclei and scant cytoplasm infiltrating the submucosal region. The tumor cells were immunohistochemically positive for neuron-specific enolase, chromogranin A and synaptophysin. Electron microscopy showed tightly aggregated neoplastic cells containing dense-core endocrine granules. A clinical survey included computed tomography of the chest and a whole-body bone scan, which revealed no evidence of other tumor lesions. All data indicated that this was a case of primary neuroendocrine carcinoma of the esophagus. The patient received palliative radiation therapy and died of aspiration pneumonia three months later.

Key words: neuroendocrine carcinoma, esophagus

INTRODUCTION

Most primary malignant neoplasms of the esophagus are squamous cell carcinoma and adenocarcinoma. Less common malignant neoplasms in this location include sarcoma, lymphoma, leiomyosarcoma, gastrointestinal stromal tumor and neuroendocrine carcinoma. Primary neuroendocrine carcinoma of the esophagus is very rare. A review of the current literature shows that neuroendocrine carcinomas represent 1-2.8% of esophageal cancer cases[1-9]. Here, we present a case of primary neuroendocrine carcinoma of the esophagus proven by clinical imaging and pathologic examination.

CASE REPORT

A 79-year-old male suffered from dysphagia and weight loss of about 10 kg within two weeks. He visited a local clinic and was referred to our hospital for further evaluation and treatment.

Physical examination showed a moderately developed and nourished male. Abdominal examination revealed tenderness over the epigastric region. Laboratory studies were conducted and the results were as follows: white blood cells: 6900/ μL; hemoglobin: 9.8 gm/dL; platelets: 222,000/μL; glucose: 109 mg/dL; blood urea nitrogen: 61 mg/dL; creatinine: 3.7 mg/dL; liver enzymes: AST, 30 U/L and ALT, 14 U/L; Na: 145 mmol/L; K: 4.7 mmol/L; uric acid: 13.2 mg/dL; and albumin: 3.7 g/dL. Carcinoembryonic antigen level was less than 1 ng/mL.

Panendoscopy revealed an ulcerative tumor mass with multiple irregular nodular formations in the esophagus about 30-40 cm below the incisor teeth (Fig. 1). A biopsy was taken. Computed tomography of the chest revealed asymmetric wall thickness in the lower third of the esophagus. A whole-body bone scan showed no significant abnormal findings. Histopathologic examination of the tumor mass revealed dense small round cells with hyperchromatic nuclei and scant cytoplasm. The tumor cells infiltrated the submucosal area and were immunohistochemically positive for neuron-specific enolase (Fig. 2A), chromogranin A (Fig. 2B) and synaptophysin (Fig. 2C). Electron microscopy revealed tightly aggregated neoplastic cells containing endocrine granules with an electron-dense core. There was no evidence of intercellular junctions (Fig. 2D). These findings indicated a case of primary neuroendocrine carcinoma of the esophagus. Because of impaired renal function and performance, the patient received palliative radiotherapy, percutaneous endoscopic gastrostomy and supportive care. He died from aspiration pneumonia three months after diagnosis.

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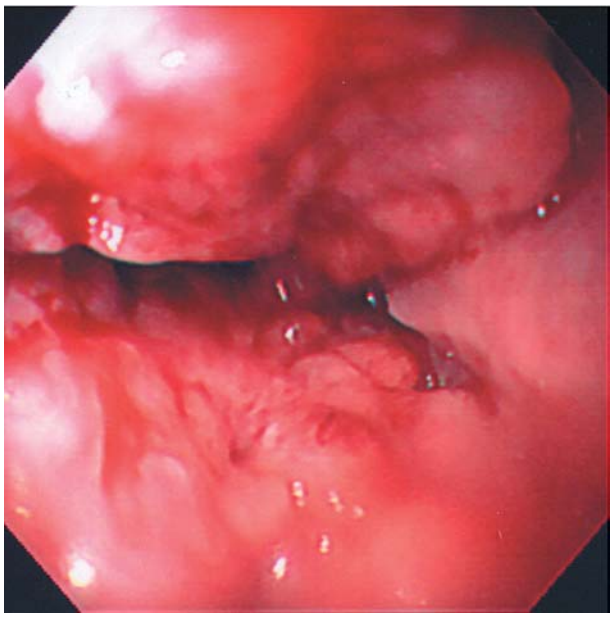

Fig. 1 Endoscope revealed a tumor mass with multiple nodules formation over low third of esophagus.

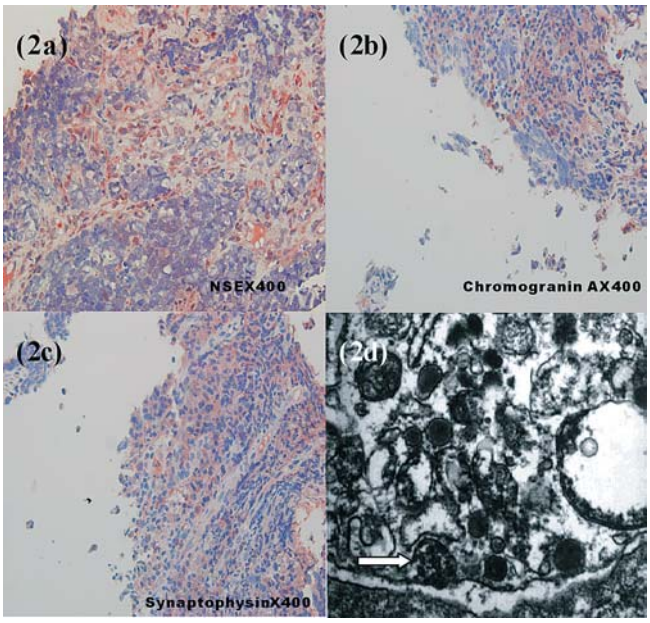

Fig. 2 Histopathologic examination showed a picture of dense small blue round cell tumor infiltrating in the submucosa. The tumor cells were immuno-histochemically positive for neuron-specific enolase(2a), chromogranin A(2b) and synaptophysin(2c). Electron microscope exhibited a picture of dense core endocrine granules in tumor cell (white arrow) (2d).

DISCUSSION

Neuroendocrine carcinoma has been described as malignant carcinoid, anaplastic carcinoma, undifferentiated carcinoma, small-cell carcinoma, oat-cell carcinoma and amine precursor uptake and decarboxylation cell carcinoma. The most common name reported previously is small-cell carcinoma. Neuroendocrine carcinoma is a distinct pathologic entity that was first described in the lung. It accounts for about 20% of bronchogenic carcinomas. Primary extrapulmonary tumors have been described in other organs, including the nasal cavity, paranasal sinus, larynx, hypopharynx, salivary glands, thymus, esophagus, stomach, pancreas, small and large intestines, cervix, prostate, bladder and breast[10-13]. About 5% of small-cell carcinomas are of extrapulmonary origin. Primary neuroendocrine carcinoma of the esophagus was first described by McKeown in 1953[14] and about 300 cases have been reported in the literature. However, neuroendocrine carcinoma represents only 1-2.8% of esophageal cancer cases. According to the WHO histological classification, esophageal tumors can be divided into epithelial and nonepithelial tumors. Epithelial tumors can be divided into squamous cell papilloma, intraepithelial neoplasia, carcinoma and carcinoid tumors. Neuroendocrine carcinoma is a rare subtype of the carcinoma group of esophageal tumors.

The most common presenting symptoms of neuroendocrine carcinoma of the esophagus are dysphagia, weight loss, retrosternal and epigastric pain[15-16]. Other clinical symptoms related to the extent of the disease include dyspnea, odynophagia, dysphonia and gastrointestinal tract bleeding.

The most important conclusive histological diagnosis involves immunohistochemical staining and electron microscopy. Neuroendocrine carcinoma is thought to be derived from the diffuse endocrine system in the epithelial tissues of the gastrointestinal tract. Endocrine cells usually occur singly in the gastrointestinal tract, less often in groups of two to five cells, and are unevenly distributed among the basal cells of the mucosa. Attar et al. noted a predominant distribution of neuroendocrine carcinoma in the middle- and lower-third of the esophagus that was related to the abundance of endocrine cells in this region[17]. Immunohistochemical markers for neuroendocrine cells, such as neuron-specific enolase, chromogranin A and synaptophysin, are commonly used to identify neuroendocrine tumors[18]. Electron microscopy can detect dense-core granules contained in neuroendocrine cells within these tumors[19]. In our patient, tumor cells were positive for neuron-

specific enolase, chromogranin A and synaptophysin, and electron microscopy revealed some tightly aggregated neoplastic cells with electron-dense core granules. Clinical surveys, including computed tomography of the chest and a whole-body bone scan revealed no evidence of other tumor lesions. Thus, primary neuroendocrine carcinoma of the esophagus was diagnosed.

The treatment of primary neuroendocrine carcinoma of the esophagus depends on clinical staging. Currently, no specific staging system for neuroendocrine carcinoma of the esophagus has been established. Some clinicians use the tumor-node-metastasis (TNM) system[20]; however, most clinicians have adopted the system used by the Veteran's Administration Lung Study Group[21]. This latter system consists of two categories: limited disease (LD), defined as a tumor contained within a localized anatomic region, with or without involved regional lymphadenopathy; and extensive disease (ED), defined as a tumor outside locoregional boundaries. Treatment for LD is potentially curative, whereas treatment of ED is palliative[22]. Like most solid tumors, initial therapy represents the best and probably the only chance to cure LD. Because no single treatment modality has been associated with a significant survival advantage in LD, it seems reasonable to combine them during primary treatment[23]. Chemotherapy can induce major regression of localized disease and can concurrently treat occult metastasis. Surgery may represent the best option to control the primary tumor. In ED, the use of surgery, chemotherapy or radiotherapy is restricted. However, symptoms may be treated by various methods, such as percutaneous endoscopic gastrostomy, esophageal dilatation or stent implant. Percutaneous endoscopic gastrostomy is a safe technique that is easy to perform and should be considered in all patients referred for a gastrostomy and in patients requiring prolonged enteral feeding. Our patient presented with impaired renal function and performance status; thus, he received palliative radiotherapy and percutaneous endoscopic gastrostomy. His dysphagia improved under these treatments.

The prognosis of patients with ED is usually dismal; most patients present with regional or overt distant metastasis. Casas et al. described that clinical staging, tumor size and administration of chemotherapy influence patient outcomes[24]. Our patient presented with an ulcerative tumor mass, did not receive chemotherapy and survived for three months after diagnosis.

In conclusion, primary neuroendocrine carcinoma of the esophagus is a rare anatomically microscopic clinical disease. The present case is a reminder to clinical physicians that histological differentiation with immunohistochemical staining and electron microscopy may be important for accurate diagnosis. Early diagnosis and treatment was suggested for our patient because of the aggressive nature of the disease and distant metastasis. Even if the clinical staging is advanced, percutaneous endoscopic gastrostomy can still be conducted to improve the patient's quality of life.

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