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CASE REPORT

Esophageal combined carcinomas: Immunohoistochemical and molecular genetic studies

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Abstract

Primary esophageal combined carcinoma is very rare. The authors herein report 2 cases. Case 1 was a combined squamous cell carcinoma and small cell carcinoma, and case 2 was a combined squamous cell carcinoma, adenocarcinoma, and small cell carcinoma. Case 1 was a 67-year-old man with complaints of dysphagia. Endoscopic examination revealed an ulcerated tumor in the middle esophagus, and 6 biopsies were obtained. All 6 biopsies revealed a mixture of squamous cell carcinoma and small cell carcinoma. Both elements were positive for cytokeratin, epithelial membrane antigen, and p53 protein, and had high Ki-67 labeling. The small cell carcinoma element was positive for synaptophysin, CD56, KIT, and platelet-derived growth factor-α (PDGFRA), while the squamous cell carcinoma element was not. Genetically, no mutations of *KIT* and *PDGFRA* were recognized. The patient died of systemic carcinomatosis 15 mo after presentation. Case 2 was a 74-year-old man presenting with dysplasia. Endoscopy revealed a polypoid tumor in the distal esophagus. Seven biopsies were taken, and 6 showed a mixture of squamous cell carcinoma, small cell carcinoma, and adenocarcinoma. The 3 elements were positive for cytokeratins, epithelial membrane antigen, and p53 protein, and had high Ki-67 labeling. The adenocarcinoma element was positive for mucins. The small cell carcinoma element was positive for CD56, synaptophysin, KIT, and PDGFRA, but the other elements were not. Mutations of KIT and PDGFRA were not recognized. The patient died of systemic carcinomatosis 7 mo after presentation. These combined carcinomas may arise from enterochromaffin cells or totipotential stem cell in the esophagus or transdifferentiation of one element to another. A review of the literature was performed.

Key words: Esophagus; Combined carcinoma; Histopathology; Immunohistochemistry; Molecular genetics

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INTRODUCTION

Combined esophageal carcinomas are very rare and interesting tumors. A full review of the English literature revealed 24 reporting combined carcinoma of the esophagus[1-24]. Most were small cell carcinomas, and a few were non-small cell carcinomas[1-24]. The author herein reports 2 cases of combined carcinoma of the esophagus. One case is a combined squamous cell carcinoma and small cell carcinoma, and another case is a combined squamous cell carcinoma, adenocarcinoma, and small cell carcinoma

CASE REPORT

Case 1

A 67-year-old man was admitted to our hospital with dysphagia. An endoscopic examination revealed an ulcerated tumor (3 cm × 4 cm × 3 cm) in the middle esophagus (Figure 1A), and 6 biopsies were obtained. All 6 biopsies revealed a mixture of squamous cell carcinoma (Figure 1B) and small cell carcinoma (Figure 1C). The squamous element was composed of malignant cells arranged in a layer with focal keratinization (cancer pearls). The small cell carcinoma element consisted of malignant small cells with hyperchromatic nuclei, nuclear molding, absent nucleoli, and very scant cytoplasm. There was a gradual merging of the 2 elements.

The authors performed an immunohistochemical study using Dako Envision method, as previously described[25,26]. The immunohistochemical antibodies used were as follows: cytokeratins (AE1/3, Dako; CAM5.2 Bekton-Dickinson, CA, United States), epithelial membrane antigen (E29, Dako), neuron-specific enolase (BBS/NC/VI-H14, Dako), chromogranin (DAK-A3, Dako), synaptophysin (polyclonal, Dako), CD56 (UJ13A, Dako), p53 protein (DO-7, Dako), Ki-67 (MIB-1, Dako), KIT (polyclonal, Dako), and platelet derived growth factor receptor-α (PDGFRA) (polyclonal, Santa Cruz, CA, United States). The squamous cell carcinoma element was positive for cytokeratin, epithelial membrane antigen, p53 protein, and Ki-67 antigen (57% labeled), but negative for other antigens examined. The small cell carcinoma element was positive for cytokeratin (Figure 1D), p53 protein, Ki-67 (96% labeled), synaptophysin (Figure 1E), CD56, and chromogranin, KIT (Figure 1F), and PDGFRA (Figure 1G).

The authors performed a molecular genetic study for *KIT* (exons 9, 11, 13 and 17) and *PDGFRA* (exons 12 and 18) genes in paraffin sections using microdissection and the polymerase chain reaction-direct sequencing method, as previously described[27-30]. There were no mutations of the *KIT* (exons 9, 11, 13 and 17) and *PDGFRA* (exons 12 and 18) genes.

The patient was diagnosed with combined carcinoma of esophagus (stage Ⅱ, T2 N0 M0). Surgery was not considered because the tumor contained small cell carcinoma. The patient was treated with cisplatin-based chemotherapy and radiation, but died of systemic carcinomatosis 15 mo after presentation.

Case 2

A 74-year-old man presented with dysplasia, and attended our hospital. An endoscopy revealed a polypoid tumor (2 cm × 2 cm × 3 cm) in the middle esophagus (Figure 2A). Seven biopsies were taken, and 6 showed a mixture of squamous cell carcinoma (Figure 2B), small cell carcinoma (Figure 2C), and adenocarcinoma (Figure 2D). The squamous cell carcinoma element showed malignant cells in a layer with focal keratinization. The small cell carcinoma element was composed of small malignant cells with hyperchromatic nuclei, inconspicuous nucleoli, and scant cytoplasm. The adenocarcinoma element showed sheet-like tumor cells with focal acinar formations, in which mucins were identified. The 3 elements were positive for cytokeratins, epithelial membrane antigen, p53 protein, and Ki-67 (labeling: squamous cell carcinoma element, 34%; adenocarcinoma element, 29%; small cell carcinoma element 87%). The squamous cell carcinoma and adenocarcinoma elements were negative for CD56, chromogranin, synaptophysin, neuron-specific elolase, KIT and PDGFRA. In contrast, the small cell carcinoma element was positive for CD56 (Figure 2E), synaptophysin, KIT (Figure 2F), and PDGFRA (Figure 2G). Mutations of KIT and PDGFRA were not found.

The patient was diagnosed with combined carcinoma of the esophagus (stage Ⅱ, T2 N1 M0). Surgery was not considered because the tumor contained small cell carcinoma. The patient received chemoradiation, but died of systemic carcinomatosis 7 mo after presentation.

DISCUSSION

The present 2 cases of combined carcinoma of the esophagus were associated with small cell carcinoma. Small cell carcinoma is diagnosed with hematoxylin and eosin (HE) staining and is defined as an undifferentiated carcinoma consisting of small cells with characteristic cellular and nuclear features, such as small-sized cells, scant cytoplasm, hyperchromatic, finely granular, and molded nuclei, and inconspicuous nucleoli, according to the World Health Organization Blue Book[31]. Neuroendocrine features are recognized in more than 90% of small cell carcinoma[31]. Squamous cell carcinoma is characterized by a squamoid cell arrangement and the presence of intercellular bridges and keratinization. Adenocarcinoma is characterized by tubular formations and the presence of mucins. Case 1 in the present study fulfilled these criteria, and was definitely combined small cell carcinoma and squamous cell carcinoma. Likewise, Case 2 was an apparently combined small cell carcinoma, squamous cell carcinoma, and adenocarcinoma. The presence of p53 protein and high Ki-67 labeling supports the above diagnosis.

In the present study, there was gradual merging of the 2 elements in case 1 and of the 3 elements in case 2. These findings may indicate that each element is derived from transdifferentiation of other elements. Traditionally, small cell carcinoma of the esophagus is thought to be derived from enterochromaffin cells or APUD cells present in the normal esophagus. Otherwise, this esophageal tumor arises from totipotent stem cells of the esophagus, as suggested by Ho *et al*[2]. The present study could not determine the histogenesis of the combined carcinomas associated with small cell carcinomas.

Most of esophageal tumors with multiple differentiation (combined carcinoma) are associated with small cell carcinoma[1-15,17-24], although basaloid cell squamous cell carcinoma also shows multiple differentiation[16]. The cel-

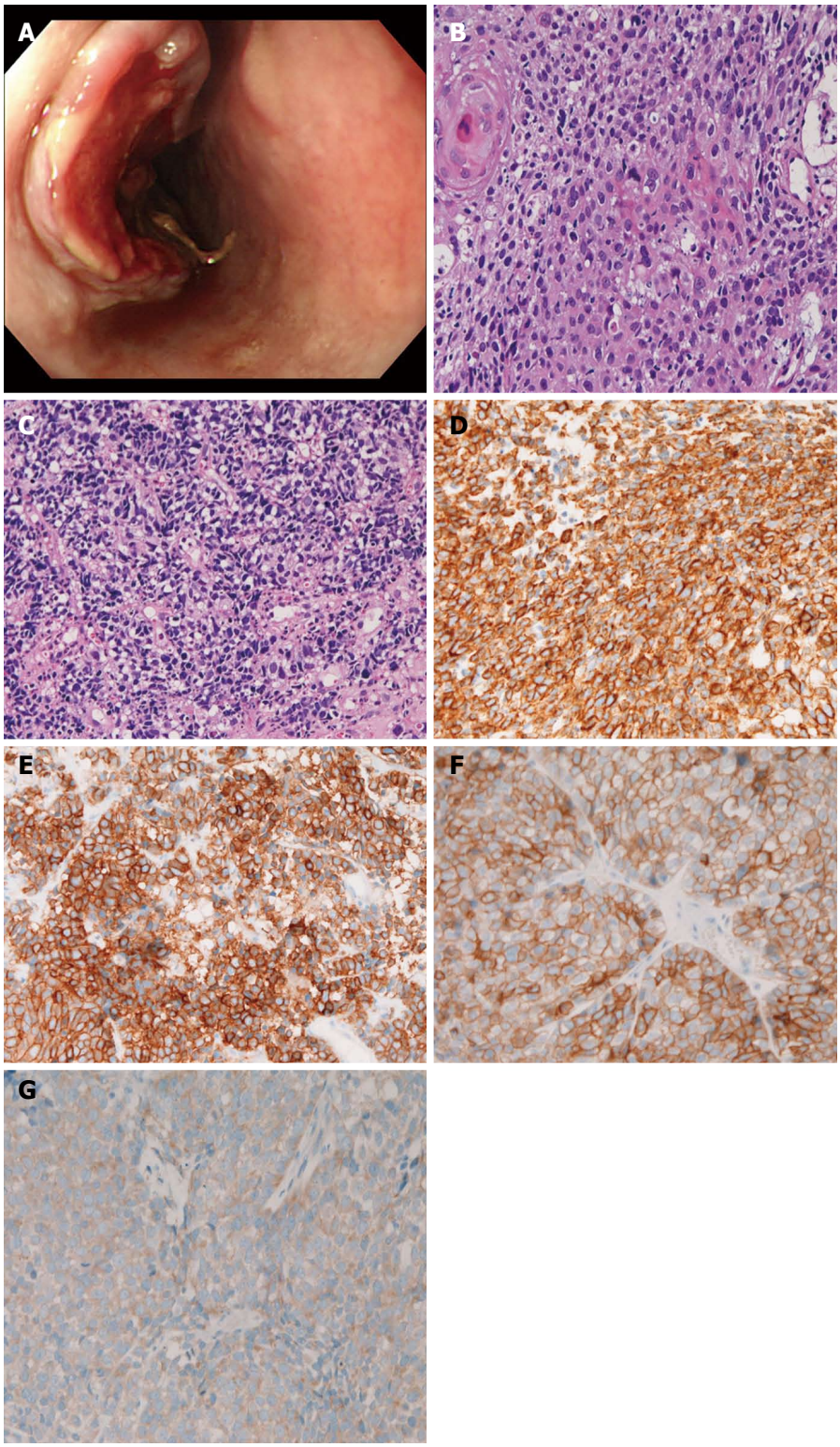

Figure 1 Case 1. A: Endoscopy. An ulcerated tumor is seen in the esophagus; B: Histology of the squamous cell carcinoma element of the esophageal tumor. Keratinization is seen [hematoxylin and eosin (HE), x 200]; C: Small cell carcinoma element of the esophageal carcinoma. The tumor cells show characteristic morphologies of small cell carcinoma (HE, x 200); D: Cytokeratins are expressed in the small cell carcinoma component (x 200); E: Synaptophysin is expressed in the small cell carcinoma component (x 200); F: KIT is expressed in the small cell carcinoma component (x 200); G: Platelet-derived growth factor-α is expressed in the small cell carcinoma component (x 200).

lular origin of small cell carcinoma is unknown. In the full review of the English literature on combined carcinomas of esophageal cancers, Rosen *et al*[1] reported an epidermoid carcinoma simulating oat cell carcinoma. Ho *et al*[2] reported that 2 of 4 cases of esophageal small cell carcinoma contained foci of squamous cell carcinoma. Reid *et al*[3] described a case of esophageal small cell carcinoma with foci of squamous cell carcinoma. Reyes *et al*[4] reported that foci of squamous cell carcinoma were seen in 4/16 esophageal small cell carcinoma. Sarma[5] mentioned that there were oat cell carcinomas with squamous cell carcinoma foci and adenocarcinoma foci. Doherty *et al*[6] reported that there were oat cell carcinomas with squamous cell carcinoma *in situ*, with squamous cell carcinoma, with adenocarcinoma, and with carcinoid. Sato *et al*[7] reported a case of small cell carcinoma with invasive squamous cell carcinoma. Sasajima *et al*[8] demonstrated one case of esophageal carcinoma showing multiple differentiations into oat

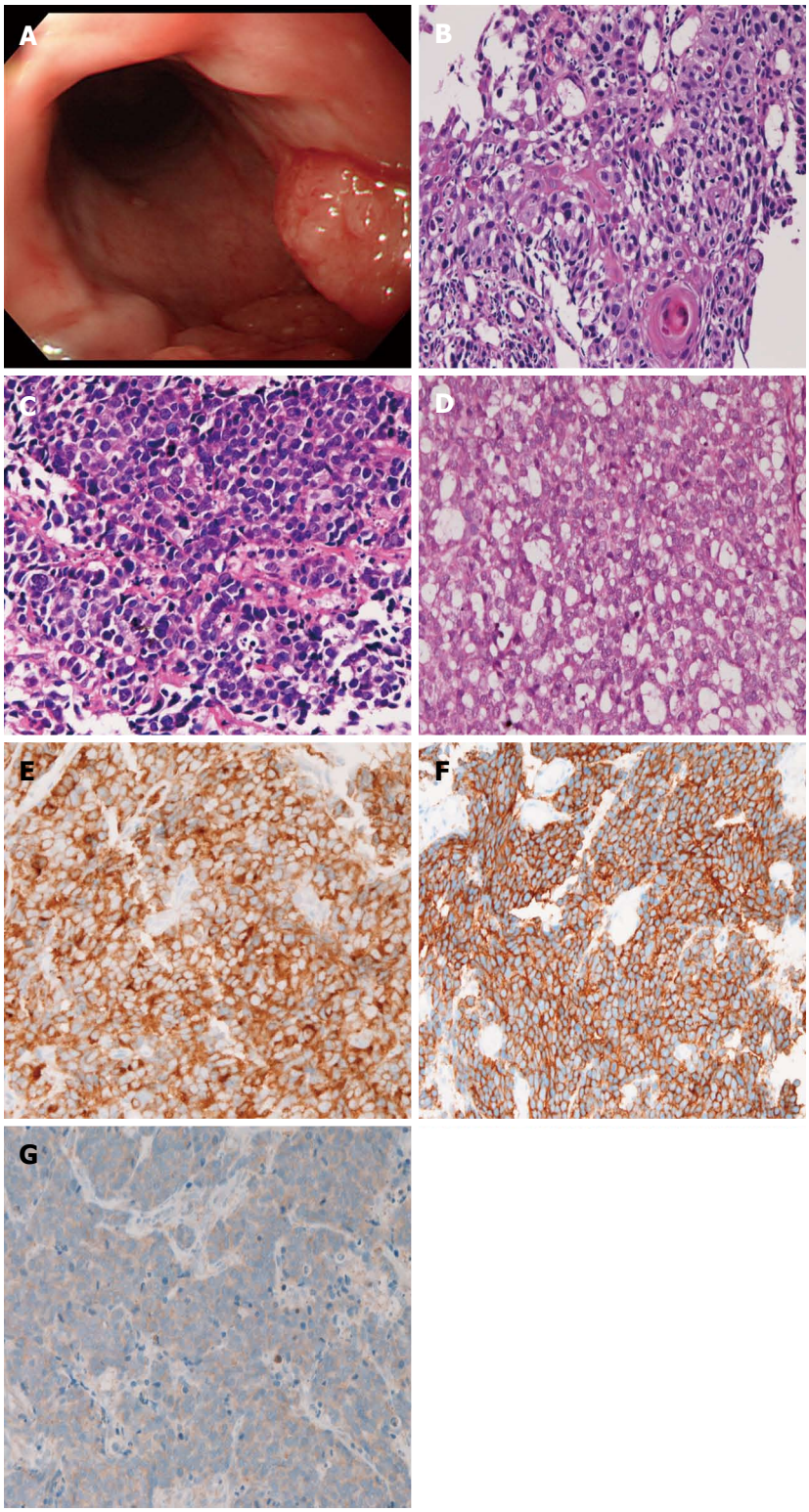

Figure 2 Case 2. A: Endoscopy. An elevated tumor is seen in the esophagus; B: Histology of the squamous cell carcinoma element of the esophageal tumor. A cancer pearl is seen [hematoxylin and eosin (HE), x 200]; C: Small cell carcinoma element of the esophageal carcinoma. The tumor cells show characteristic morphologies of small cell carcinoma (HE, x 200); D: Adenocarcinomatous element shows focal tubular formations (HE, x 200); E: CD56 is expressed in the small cell carcinoma component (x 200); F: KIT is expressed in the small cell carcinoma component (x 200); G: Platelet-derived growth factor-α is expressed in the small cell carcinoma component (x 200).

cell carcinoma, adenoid cystic carcinoma, adenocarcinoma, and squamous cell carcinoma. Mori *et al*[9] reported that 7 squamous cell foci and 2 adenocarcinoma foci were recognized in 10 small cell carcinomas. Attar *et al*[10] showed concomitant squamous cell carcinoma in small cell carcinoma. Beyer *et al*[11] mentioned that there was considerable histological heterogeneity in small cell carcinoma. Fujiwara *et al*[13] reported a case of small cell carcinoma with concomitant squamous cell carcinoma. Takubo *et al*[14] found a combination of small cell carcinoma and squamous cell carcinoma in 11 of 21 cases, and a combination of small cell carcinoma and mucoepidermid carcinoma in 1 of 21 cases. Medgyesy *et al*[15] found a combination of small cell carcinoma and adenocarcinoma in 1 of 8 cases, and a combination of small cell carcinoma and squamous cell carcinoma in 1 of 8 cases. Cho *et al*[16] identified a combination of basaloid squamous cell carcinoma and squamous cell carcinoma in 8 of 18 cases, a

combination of basaloid squamous cell carcinoma and adenocarcinoma in 3 of 18 cases, a combination of basaloid squamous cell carcinoma and small cell carcinoma in 2 of 18 cases. Uğraş *et al*[18] reported a combined carcinoma composed of small cell carcinoma and squamous cell carcinoma. Ishihara *et al*[19] found an esophageal combined carcinoma consisting of Pagetoid squamous cell carcinoma, choriocarcinoma, and mucoepidermoid carcinoma. Yamamoto *et al*[20] reported *in situ* and invasive squamous cell carcinomas were present in 3 of 6 cases of small cell carcinoma. Wu *et al*[21] reported that small cell carcinoma with squamous cell carcinoma was found in 3 of 9 cases. Yun *et al*[22] identified squamous differentiation in small cell carcinoma in 2 of 21 cases. Bilbeau *et al*[23] reported a case of small cell carcinoma with adenocarcinoma in a Barrett's esophagus. Maru *et al*[24] reported that a combination of small cell carcinoma and adenocarcinoma was seen in 15 of 40 cases, and a combination of small cell carcinoma and squamous cell carcinoma in 1 of 40 cases. Therefore, this literature review showed that combined carcinoma of the esophagus is not so rare among small cell esophageal carcinomas, and that the majority of combined carcinoma is associated with small cell carcinoma. The review also confirmed that esophageal combined carcinoma composed of small cell carcinoma and squamous cell carcinoma is the most common, followed by a combination of small cell carcinoma and adenocarcinoma. The present 2 cases also are the common type of combined esophageal carcinoma.

As mentioned above, small cell carcinoma is diagnosed by HE staining[31]. About 90% of small cell carcinoma has neuroendocrine features[31]. The neuroendocrine features can be demonstrated by immunohistochemical demonstration of neuroendocrine antigens such as chromogranin, synaptophysin, CD56, and neuron-specific enolase or by ultrastructural demonstration of neuroendocrine secretory vesicles[32]. Yamamoto *et al*[20] described that CD56, neuron-specific enolase, and chromogranin were positive in a small cell carcinoma component while they were negative in the squamous cell carcinoma component in 3 cases of combined esophageal carcinoma. They also demonstrated that both components were positive for cytokeratins and epithelial membrane antigen. Wu *et al*[21] described that esophageal small cell carcinomas were positive for neuron-specific enolase, chromogranin A, and synaptophysin in all 9 cases investigated. Yun *et al*[22] described that the percentage of endocrine markers in 21 esophageal small cell carcinomas was as follows: synaptophysin, 95%; CD56, 76%; chromogranin A, 62%, neuron-specific enolase, 62%, TTF-1, 71%; epithelial membrane antigen, 62%; cytokeratins, 57%; S100 protein, 19%. Maru *et al*[24] described that chromogranin was positive in 31 of 40 and synaptophysin in all 40 esophageal neoroendocrine carcinomas. In the present case, synaptophysin, CD56 and chromogranin were positive in the small cell carcinoma component in case 1, and CD56 and synaptophysin were positive in the small cell carcinoma component in case 2. In both cases in the present study, all the elements were positive for cytokeratin and epithelial membrane antigen. The non-small cell carcinoma components were negative for the neuroendocrine carcinoma. These findings are compatible with those of previous studies.

The present study has new findings: it showed positive expression of *KIT* and *PDGFRA* in the small cell carcinoma element of the 2 combined esophageal carcinomas. The present study also revealed that the squamous cell carcinoma and adenocarcinoma components were negative for KIT and PDGFRA protein and were negative for *KIT* and *PDGFRA* mutations in the esophageal combined carcinoma. KIT and PDGFRA are transmembranous receptor tyrosine kinase oncoproteins involved in carcinogenesis[33-35]. The vast majority of small cell carcinoma develops in the lung. In small cell lung carcinoma, KIT is frequently expressed, but no mutations of *KIT* gene have been recognized[36-46]. In small cell lung carcinoma, protein expression and mutations of PDGFRA are unknown. In extrapulmonary small cell carcinoma, KIT and PDGFRA proteins are frequently expressed, but there have been no mutations of *KIT* and *PDGFRA* genes found[46-48]. Many more studies of the *KIT* and *PDGFRA* gene status in esophageal combined carcinomas are necessary to elucidate the molecular mechanism of the carcinogenesis.

The biological behavior of these combined carcinomas of the esophagus is not known. However, it is thought that these combined carcinomas behave like small cell carcinoma, because the great majority of these combined carcinomas contain a small cell carcinoma element[1-24]. The option for treatment is not surgery but chemotherapy and radiation as in pulmonary small cell carcinoma[1-24]. The chemotherapy employed was cisplatin and etoposide[1-24]. Adjuvant radiation therapy may be effective. The combined carcinomas of the esophagus have a higher propensity for systemic metastases[1-24]. The survival rate is not clear because of a limited number of cases. However, survival was thought to be similar to that of pulmonary small cell carcinoma[1-24].

In summary, the authors presented 2 rare cases of esophageal combined carcinoma with double (squamous cell carcinoma and small cell carcinoma) and triplicate differentiation (squamous cell carcinoma, small cell carcinoma, and adenocarcinoma). The authors speculates that the combined carcinomas are basically small cell carcinomas with squamous and/or adenocarcinomatous differentiation. The present esophageal combined carcinomas may arise from enterochromaffin or totipotent stem cell of the esophagus. It is also possible that each element of the esophageal combined carcinomas may be derived from transdifferentiation of other elements. There were expressions of KIT and PDGFRA in the small cell carcinoma component of the esophageal combined carcinomas, but were negative for mutations of *KIT* and *PDGFRA*.

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