Clinical Case Report

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Metastatic esophageal carcinosarcoma comprising neuroendocrine carcinoma, squamous cell carcinoma, and sarcoma

A case report

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Abstract

Rationale: Esophageal carcinosarcoma generally comprises 2 histological components: squamous cell carcinoma (SqCC) and sarcoma. Esophageal carcinosarcoma comprising 3 components is extremely rare and no reports have described therapeutic effects for this disease with metastasis.

Patient concerns: A 76-year-old man with dysphagia presented to a local clinic. Gastrointestinal endoscopy revealed a polypoid tumor in the middle esophagus and he was referred to our hospital.

Diagnosis and Interventions: Thoracoscopic esophagectomy with super-extended (D3) nodal dissection and gastric tube reconstitution was performed, which resulted in carcinosarcoma comprising neuroendocrine carcinoma (NEC), SqCC, and sarcoma. Pathological stage was T1bN1M0 stage IIB according to the TNM Classification of Malignant Tumors-7th edition. The NEC component was observed in lymph node. At 47 days after surgery, lymph nodes, liver, and bone metastasis appeared, and tumor markers such as ProGRP and NSE were elevated. Combination chemotherapy with cisplatin and etoposide (EP) adapted to NEC was performed.

Outcomes: The patient showed complete response within 4 cycles of chemotherapy. However, the disease recurred 5.5 months after the final course of EP chemotherapy.

Lessons: A therapeutic strategy based on assessment of which component caused metastasis might be important for metastatic carcinosarcoma comprising 3 components, although more accumulation of data about the efficacy of chemotherapy is necessary. Moreover, elucidation of the mechanisms underlying generation of carcinosarcoma is expected in the future.

Abbreviations: EP = cisplatin and etoposide, NEC = neuroendocrine carcinoma, NSE = neuron-specific enolase, ProGRP = pro-gastrin-releasing peptide, SqCC = squamous cell carcinoma.

Keywords: carcinosarcoma, esophagus, neuroendocrine, sarcoma, squamous

1. Introduction

Carcinosarcoma represents 0.5% to 2.8% of malignant esophageal tumors,[1] generally comprising 2 components: squamous cell carcinoma (SqCC) and sarcoma. Carcinosarcoma consisting of adenocarcinoma and sarcoma has been not usually observed.[2–4] The other histological components such as neuroendocrine carcinoma (NEC) in addition to SqCC and sarcoma are rarely observed. Previous reports have suggested that the sarcomatous component derives from SqCC,[5–7] but the precise mechanisms underlying the tumorigenesis of carcinosarcoma remain unclear. Esophageal carcinosarcoma commonly occurs in the middle thoracic esophagus. Given that such tumors often form polypoid lesions, dysphagia tends to appear in the early stage compared with esophageal SqCC.[1,8] However, 25% of esophageal carcinosarcomas show an ulcerative form. Standard treatment for resectable cases is surgery. Compared with esophageal SqCC, carcinosarcoma has a lower frequency of lymph node metastasis, but metastasis through blood vessels is observed more frequently.[8] Both carcinoma and sarcoma components reportedly cause metastasis.[9–11] The prognosis of carcinosarcoma compared with carcinoma differs between reports.[8,12] Whereas the general cause of death in carcinosarcoma is because of metastasis, no standard chemotherapy for metastatic esophageal carcinosarcoma has been defined and no reports have shown the efficacy of chemotherapy for metastatic esophageal carcinosarcoma.

This report describes a rare case of metastatic esophageal carcinosarcoma comprising NEC, SqCC, and sarcoma treated using systemic chemotherapy.

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2. Case presentation

A 76-year-old man with dysphagia presented to a local clinic in March 2016. He had a medical history of duodenal ulcer and appendicitis. He drank alcohol every day and had smoked 1 pack of cigarettes a day for 50 years. Gastrointestinal endoscopy revealed a polypoid tumor in the middle esophagus (Fig. 1A) and he was referred to our hospital the following month. Upper gastrointestinal series showed an irregular elevated lesion spreading around 7 cm in the middle thoracic esophagus (Fig. 1B). Computed tomography (CT) showed a swollen lymph node at the back of the trachea in addition to the primary lesion. The pathological finding by biopsy of the primary site with gastrointestinal endoscopy showed well to poorly differentiated SqCC with focal neuroendocrine differentiation containing atypical cells with sarcomatous changes, resulting in the diagnosis of esophageal carcinoma cT1bN1M0 stage IIB according to the TNM Classification of Malignant Tumors-7th edition. In May 2016, thoracoscopic esophagectomy with super-extended (D3) nodal dissection and gastric tube reconstitution was performed. Pathological examination of the surgical specimen revealed NEC and sarcoma including cartilage in the body of the polypoid primary tumor, and SqCC and NEC at the base of the polypoid tumor, indicating that the primary site comprised 3 distinct histological components: NEC, SqCC, and sarcoma (Fig. 2). Immunohistochemical staining showed NEC, SqCC, and sarcoma stained positively for synaptophysin, p63, and vimentin, respectively (Fig. 3A–F). Lymphatic and blood vessels had been invaded by the NEC and sarcoma components, respectively. Furthermore, the NEC component had metastasized to lymph nodes (Fig. 3G, H). Before we initiated postoperative chemotherapy, CT and fluorodeoxyglucose-positron emission tomography (FDG-PET) CT revealed mediastinal and supraclavicular lymph nodes, liver and bone metastases 47 days after surgery. Blood examination showed elevated concentrations of tumor markers such as pro-gastrin-releasing peptide (ProGRP) (256.8 pg/mL) and neuron-specific enolase (NSE) (38.1 ng/mL). In contrast, tumor markers such as carcinoembryonic antigen (CEA) and squamous cell carcinoma antigen (SCC) were within normal ranges. Given that lymph node metastases were from the NEC component in addition to the elevation of tumor markers for NEC, we considered that metastases were mainly derived from the NEC component. Accordingly, we employed combined chemotherapy with cisplatin and etoposide (cisplatin at 60 mg/m^2 on day 1 and etoposide at 100 mg/m^2 on days 1–3: EP). After 4 cycles, CT and FDG-PET CT showed disappearance of all metastatic lesions, indicating complete response (Fig. 4). ProGRP and NSE concentrations improved within normal ranges. Five months after the final course of EP chemotherapy, bone and lung metastases were observed on FDG-PET CT. Furthermore, tumor markers such as ProGRP (924.4 pg/mL) and NSE (39.6 ng/mL) were again elevated. Amrubicin monotherapy was initiated, but disease progression was confirmed after 4 months and the patient was discharged to palliative care at another clinic. The patient died of primary disease in November 2017. Informed consent was obtained from the patient for the publication of the case details.

3. Discussion

Carcinosarcoma was first reported by Virchow in 1865, with esophageal carcinosarcoma subsequently described by Hanse-

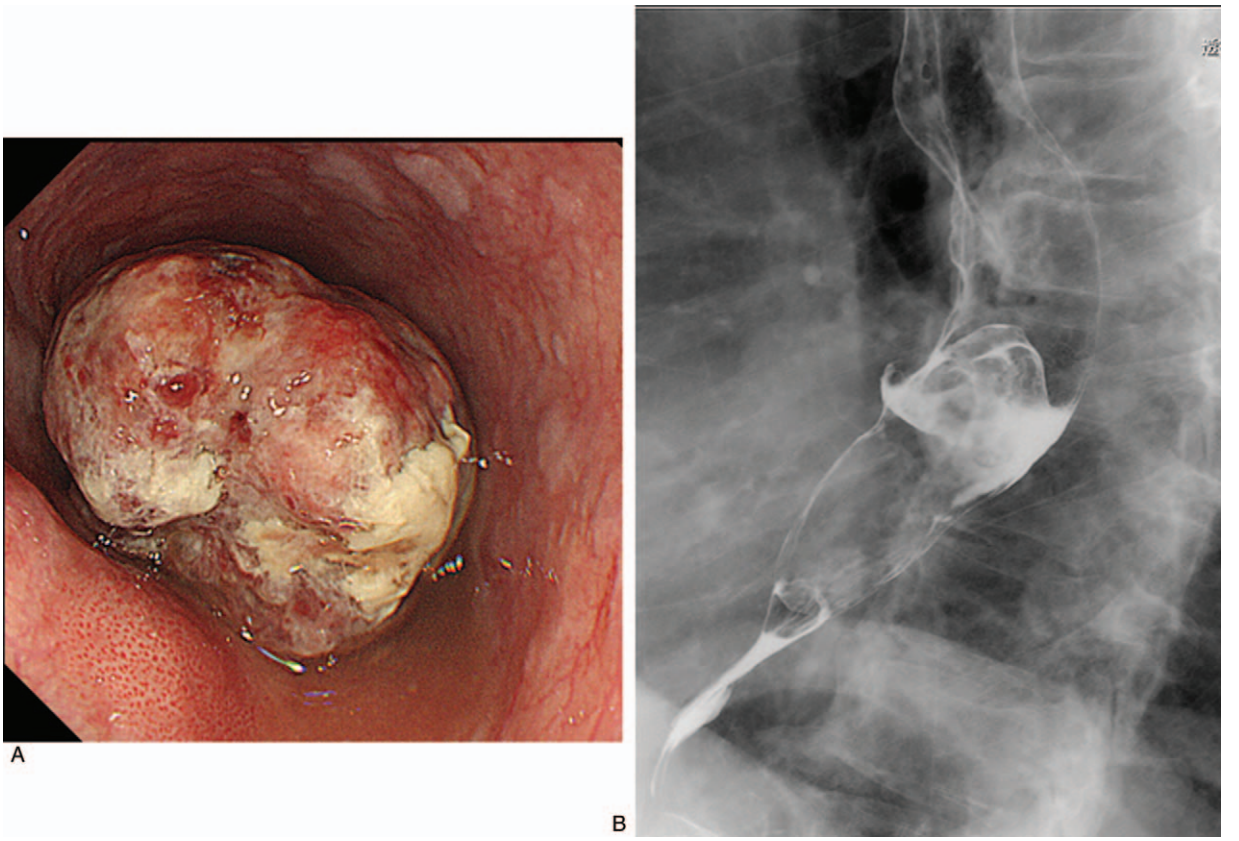

Figure 1. Gastrointestinal endoscopy shows a polypoid tumor in the middle esophagus (A). Upper gastrointestinal series reveals an irregular, elevated lesion spreading around 7 cm in the middle thoracic esophagus (B).

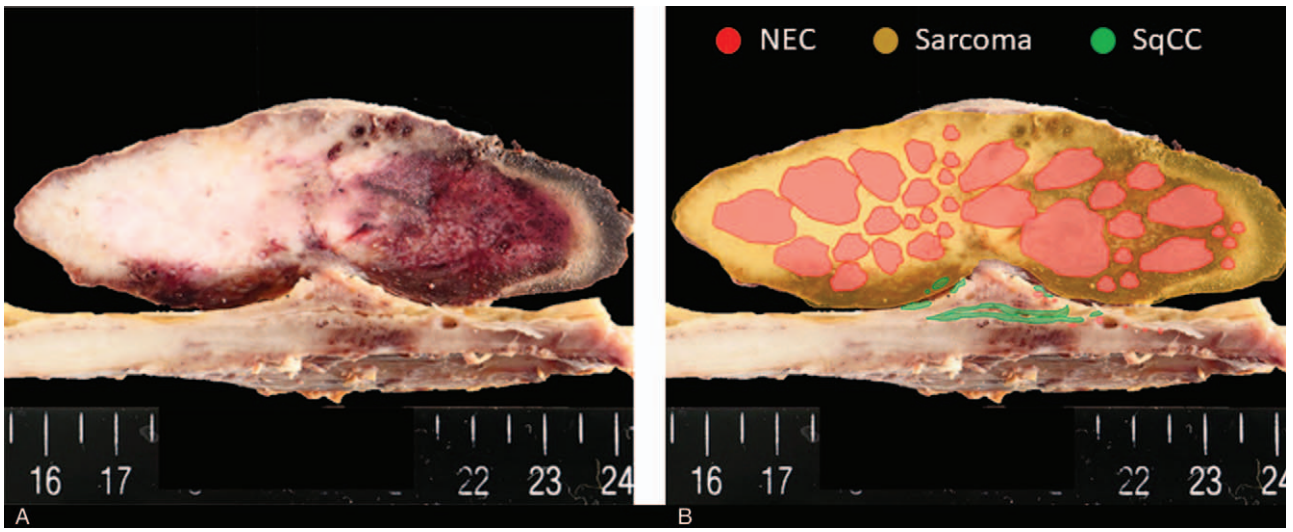

Figure 2. Gross findings of the resected specimen (A). Resected specimen reveals NEC and sarcoma in the body of the polypoid primary tumor, and SqCC and NEC at the base of the polypoid tumor (B). NEC = neuroendocrine carcinoma, SqCC = squamous cell carcinoma.

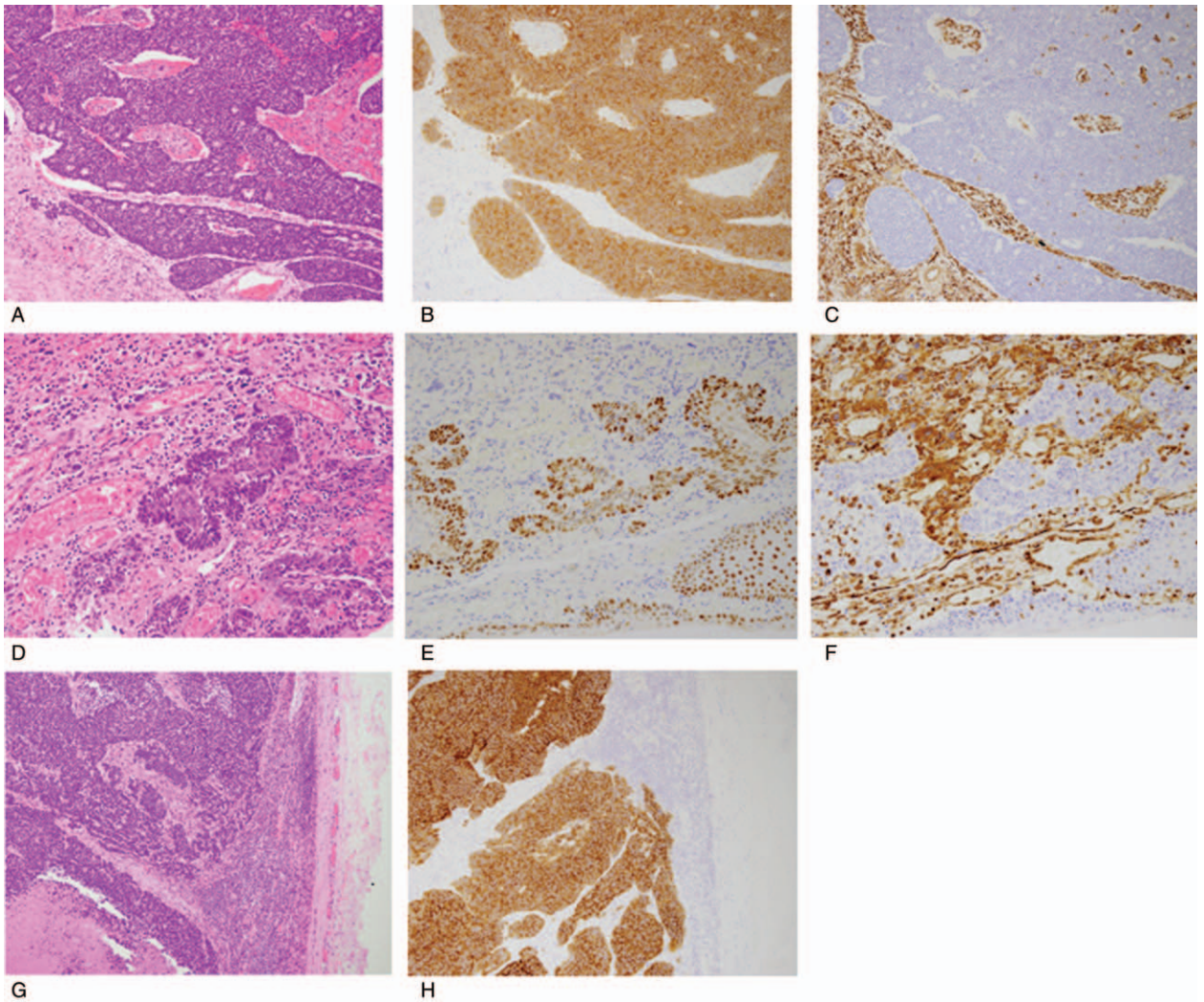

Figure 3. Hematoxylin and eosin (HE) and immunohistochemical staining of primary tumor (A–F) and lymph node metastasis (G, H). HE staining of the neuroendocrine carcinoma (NEC) and sarcoma component in primary tumor (A). NEC and sarcoma are positive for synaptophysin (B) and vimentin (C), respectively. HE staining of squamous cell carcinoma (SqCC) and the sarcoma part in the primary tumor (D). SqCC and sarcoma component are positive for p63 (E) and vimentin (F), respectively. HE and synaptophysin staining of lymph node metastasis (G, H).

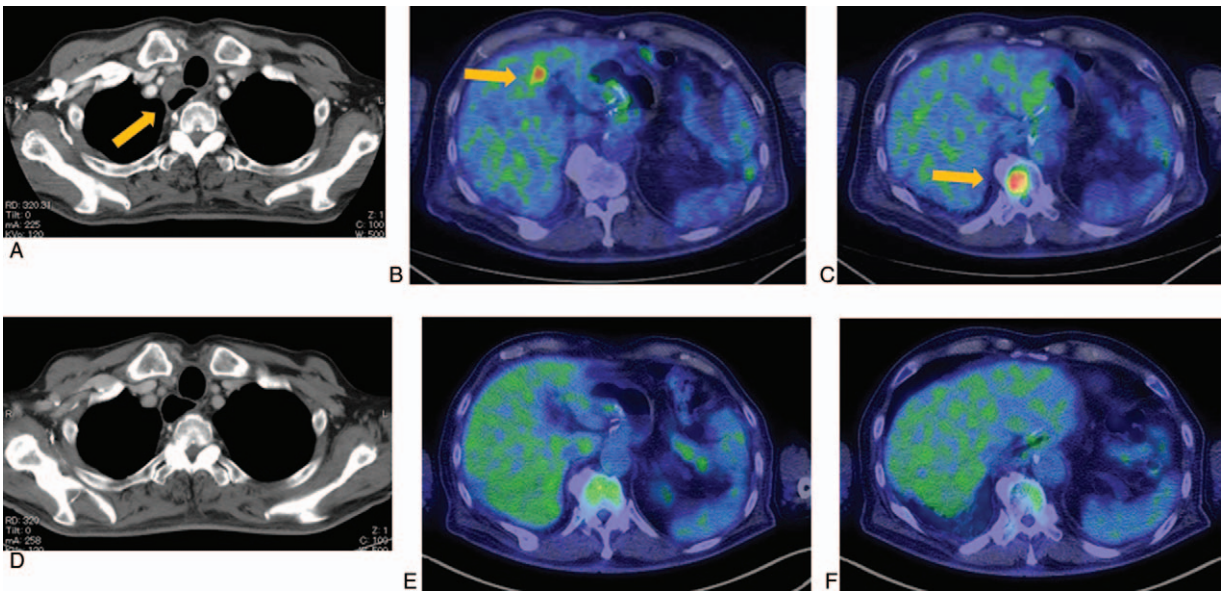

Figure 4. Computed tomography and fluorodeoxyglucose-positron emission tomography reveal mediastinal and supraclavicular lymph node (A), liver and bone metastases (B, C). Following 4 cycles of chemotherapy, supraclavicular lymph node (D), liver and bone metastases (E, F) disappeared.

mann in 1904.[13] Carcinosarcoma generally consists of 2 components: carcinoma and sarcoma. Carcinosarcoma has been variously termed pseudosarcoma, sarcomatoid carcinoma, polypoid carcinoma, true carcinosarcoma, and so-called carcinoma, among others.[8] The term carcinosarcoma was used by Lane et al in 1957.[14] However, whether the sarcomatous component had malignant potential or was only reactive benign tissue accompanying a malignant carcinoma component was not clarified. Later studies showed the malignant potential of the sarcomatous component.[9–11] Furthermore, Iascone and Barreca reviewed previous reports of carcinosarcoma and pseudosarcoma and showed similar prognoses, suggesting that the 2 tumors represent a single pathological entity.[1]

The evolutional mechanism underlying carcinosarcoma is thought to involve each component of carcinoma and sarcoma deriving from a common origin cell. Chino et al[15] reported a case of carcinosarcoma with a diameter of 4 mm, suggesting that both carcinoma and sarcoma components exist even at the early stage. Typically, the body of the polypoid tumor comprises sarcoma, whereas the base was the SqCC component of our case. From the perspective of the pathology, carcinosarcoma cells possessing the characteristics of a transition state from SqCC to sarcoma were observed in both components. Electron microscopy also showed the presence of tonofilaments and desmosomes (characteristic of epithelial cells) in the sarcoma cells.[5,16] Furthermore, both mesenchymal and epithelial markers are also positive in both carcinoma and sarcoma components according to immunohistochemistry. Analysis of the expression pattern of p53 mutation revealed a common mutational pattern in both carcinoma and sarcoma.[17] Another study that investigated expression of MDM2 and CDK4 also showed the same expression patterns between carcinoma and sarcoma.[6] Finally, loss of heterozygosity analysis revealed the sarcomatous component as genetically derived from the squamous cell component.[7] These studies indicated that SqCC and sarcoma are derived from a common origin. Probably, SqCC with potential to change into sarcoma might initially emerge and subsequently became carcinosarcoma. In the present case, the carcinoma comprised 3 components: NEC, SqCC, and sarcoma. A single case in Japanese literature reported to possess 3 components.[18] Robertson et al[4] reported a case of carcinosarcoma comprising 4 components; NEC, SqCC, adenocarcinoma, and sarcoma. Whereas no previous reports have described NEC mixed with sarcoma, NEC mixed with SqCC was reported.[19] Accordingly, we hypothesized that in the present case, the mixture of NEC and SqCC arose first, followed by the emergence of sarcoma from SqCC. However, the origin cell of this carcinosarcoma and the mechanisms underlying conversion of SqCC to sarcoma remain to be elucidated.

The treatment for resectable carcinosarcoma is esophagectomy and lymph node dissection, as in esophageal carcinoma. Although the regimen of preoperative chemotherapy is not determined because of the rarity, the efficacy of chemoradiotherapy or the combination of docetaxel, cisplatin, and 5-fluorouracil is reported.[20–24] The prognosis of esophageal carcinosarcoma compared with esophageal carcinoma is still not consistent. Talbert et al[12] reported better prognosis for carcinosarcoma than for carcinoma, and reasoned that carcinosarcoma is more easily found in the early stage because of the growth pattern of protrusion into the lumen, resulting in a lower frequency of lymph node metastasis. In contrast, Iyomasa et al[8] reported similar prognosis between them. In their report, whereas the 3-year survival rate was better for carcinosarcoma (62.8%) than for carcinoma (28.1%), the 5-year survival rate was comparable (26.7% vs. 22.4%, respectively). The optimal treatment for unresectable or metastatic esophageal carcinosarcoma has still not been established. Few reports have shown the treatment of unresectable esophageal carcinosarcoma, and no reports have provided useful treatments for metastatic cases. Kawano et al[25] showed complete response in a case of local unresectable esophageal carcinosarcoma by chemoradiotherapy (radiation, 5-fluorouracil, and cisplatin). Nakao et al[26] reported the effect of chemoradiotherapy comprising radiation and S-1 for local unresectable esophageal carcinosarcoma.

Given that no reports have presented the effects of chemotherapy on metastatic carcinosarcoma, systemic chemotherapy in the present case was chosen based on the clinical and histological characteristics of the patient. The present case showed regional lymph node metastasis of NEC and prominent elevation of tumor markers for NEC, suggesting NEC as the dominant component for metastasis. For the treatment of advanced gastrointestinal NEC including esophageal NEC, systemic chemotherapy based on the standard regimen for small cell lung cancer (SCLC) is generally used. The response rate to cisplatin combined with etoposide or irinotecan as the standard regimen for SCLC is reportedly around 31% to 75% for gastrointestinal NEC.[27,28] EP chemotherapy was performed, resulting in complete response after 4 cycles. This result suggests that precise evaluation of the component of carcinosarcoma causing metastasis is important for determining chemotherapy against carcinosarcoma comprising 3 components, although more data about the efficacy of treatment are necessary to be accumulated and it is also still not known whether the sensitivity of each component of carcinosarcoma for certain chemotherapy is different.

4. Conclusion

We have reported a rare case of metastatic esophageal carcinosarcoma comprising NEC, SqCC, and sarcoma. A therapeutic strategy based on assessment of which component caused metastasis is important for metastatic carcinosarcoma comprising 3 components. Moreover, elucidation of the mechanisms underlying generation of carcinosarcoma is expected in the future.

Author contributions

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