Tohoku J. Exp. Med., 2019, **249**, 255-263

Esophageal Carcinosarcoma with Basaloid Squamous Cell Carcinoma: A Case Report and Review of the Literature

Hirotaka Ishida,[1,2,3] Fumiyoshi Fujishima,[2] Yu Onodera,[1] Takuro Konno-Kumagai,[1] Shota Maruyama,[1] Hiroshi Okamoto,[1] Chiaki Sato,[1] Takahiro Heishi,[1] Tadashi Sakurai,[1] Yusuke Taniyama,[1] Takashi Kamei[1] and Hironobu Sasano[2]

[1]Department of Gastroenterological Surgery, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan
[2]Department of Pathology, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan
[3]School of Medicine, Griffith University, Gold Coast, Queensland, Australia

Esophageal carcinosarcoma is a rare tumor composed of neoplastic squamous epithelium and sarcomatous spindle cells. The origin of spindle cells remains unknown; however, the majority of sarcomatous components are currently considered to be derived from existing carcinomatous cells via epithelial-mesenchymal transition (EMT). We report a case of esophageal carcinosarcoma harboring basaloid squamous cell carcinoma successfully treated with preoperative chemotherapy. A 78-year-old man complaining dysphagia was diagnosed as esophageal carcinosarcoma. After two courses of preoperative chemotherapy with cisplatin and 5-fluorouracil, curative esophagectomy with lymph node dissection was performed thoracoscopically. Histopathological findings of the resected specimen revealed the mixture of basaloid squamous cell carcinoma and sarcomatous spindle cells. A transitional zone between both components was also detected. As fibrosis was identified around both two components, the findings indicated that both carcinomatous and sarcomatous neoplasms disappeared by preoperative chemotherapy. Final pathological diagnosis was esophageal carcinosarcoma with basaloid squamous cell carcinoma. No recurrent lesions have been detected for 25 months after the surgery. Sarcomatous spindle cells could be derived from the components of basaloid squamous cell carcinoma in our present case due to the presence of histological transition between two components. In addition, the marked immunoreactivity of vimentin (an EMT marker) detected in the tumor cells of basaloid squamous cell carcinoma could be consistent with the concept of monoclonal origin via EMT. The regimen targeting squamous cell carcinoma could also be effective in the treatment of sarcomatous components. Preoperative therapy might achieve the improvement of clinical outcome of patients with esophageal carcinosarcoma.

Keywords: basaloid squamous cell carcinoma; carcinosarcoma; esophagus; etiology; treatment
Tohoku J. Exp. Med., 2019 December, **249** (4), 255-263.

Introduction

Esophageal carcinosarcoma is a rare tumor composed of neoplastic squamous epithelium and sarcomatous spindle cells. Multiple diagnostic nomenclatures have been assigned to this particular neoplasm in terms of its histogenesis and biology, such as spindle cell squamous cell carcinoma, sarcomatoid carcinoma or pseudosarcomatous squamous cell carcinoma (Odze et al. 2019). The origin of sarcomatous components has remained unknown but sarcomatous components are considered to be derived from preexisting squamous cell carcinoma via epithelial-mesenchymal transition (EMT) or sarcomatous metaplasia (Sung et al. 2011, 2013). Basaloid squamous cell carcinoma is also a rare histological subtype of squamous cell carcinoma (Odze et al. 2019). Basaloid squamous cell carcinoma has various histological morphologies and multidirectional differentiations including basaloid cells, duct-like arrangement, amorphous hyaline substance in a tumor nest or coexisting conventional squamous cell carcinoma (Imamhasan et al. 2012; Odze et al. 2019).

Due to the low incidence of the neoplasm, it is difficult to establish the standard treatment strategies for esophageal carcinosarcoma. The surgical resection is considered one

Received November 5, 2019; revised and accepted December 4, 2019. Published online December 17, 2019; doi: 10.1620/tjem.249.255.
Correspondence: Hirotaka Ishida, M.D., Ph.D., Department of Gastroenterological Surgery, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan.
e-mail: h-ishida@surg.med.tohoku.ac.jp

of the most effective treatment options. However, preoperative/postoperative therapy could also improve patients' prognosis in a variety of cancer area. In fact, preoperative chemotherapy followed by radical surgery has demonstrated a favorable clinical outcome of patients with esophageal squamous cell carcinoma (Ando et al. 2012). Considering the low feasibility of a randomized prospective trial, it is pivotal to review previously published case reports or small case series in order to perform more accurate therapy for patients with the rare neoplasm.

Here, we present a rare case of esophageal carcinosarcoma harboring basaloid squamous cell carcinoma components to give some information about the mechanism of development in carcinosarcoma of the esophagus. In addition, we conducted a literature review that is relevant to the treatment strategies for esophageal carcinosarcoma.

Case Report

A 78-year-old man who manifested dysphagia was diagnosed as esophageal cancer by esophagogastroduodenoscopy (EGD) and presented to our hospital for the treatment. The patient had a history of relatively marked smoking (40 cigarettes per day for 15 years) and alcohol consumption (approximately 1,000 mL beer per day for 60 years). Esophagography revealed stenosis and wall irregularity in the esophageal cavity (Fig. 1a). An ulcerative- and infiltrative-type tumor was detected in the middle third of the thoracic esophagus (Fig. 1b). Computed tomography (CT) demonstrated the thickened esophageal wall and swelling of an anterior thoracic paraaortic lymph node without radiological evidence of invasion into adjacent structures or distant metastases. Positron emission tomography-CT (PET-CT) revealed an uptake of ^{18}F-2-fluoro-2-deoxy-D-glucose in the middle third of the thoracic esophagus [a maximum standardized uptake value (SUVmax) of 11.0] (Fig. 2a) and a thoracic paraaortic lymph node (SUVmax of 2.3). Pathological examination of biopsy specimens revealed components of both squamous cell carcinoma with immunoreactivity of AE1/AE3 (an epithelial marker for detection of carcinomatous cells) and p40 (a squamous-basal marker for detection of squamous cell carcinoma cells), and sarcomatous spindle cells with immunohistochemically positive for vimentin (a mesenchymal/EMT marker for detection of sarcomatous cells). Based on these findings, a clinical diagnosis before treatment was esophageal carcinosarcoma [cT3N1M0, cStage IIIB] according to the eighth edition of the Union for International Cancer Control tumor, node, and metastasis classification system (TNM classification 8th) (Brierley et al. 2017). As disease specific treatment strategies for patients with esophageal carcinosarcoma had not been established, therapeutic strategies of preoperative chemotherapy composed of cisplatin (CDDP) and 5-fluorouracil (5-FU) targeting squamous cell carcinoma components and subsequent radical surgery were planned. Preoperative chemotherapy with intravenous CDDP (80 mg/m^2/day on days 1 and 22) and continuously intravenous 5-FU (800 mg/m^2/day from days 1-5 and 22-26) were performed without any side effects. The evaluation via EGD, CT and PET-CT after the chemotherapy did reveal that the neoplasm was reduced (Figs. 1c and 2b). The clinical response of the preoperative therapy was partial response according to the Response Evaluation Criteria in Solid Tumours guideline (Eisenhauer et al. 2009). Curative esophagectomy with three-field lymph node dissection was performed thoracoscopically. The patient had favorable clinical courses following surgery and was discharged on postoperative day 17. Postoperative therapy was not performed, and no recurrent lesions have been detected for 25 months after the surgery.

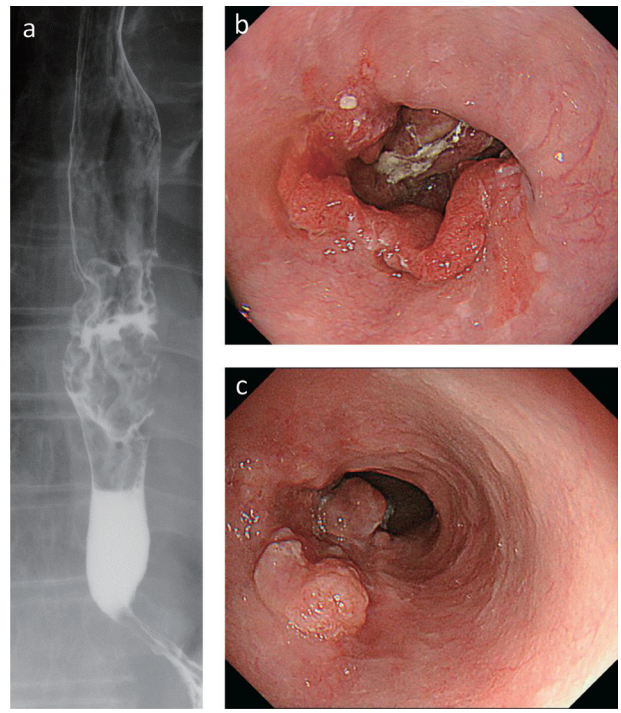

Fig. 1. Radiographic and endoscopic findings of the neoplasm.
a) Esophagography revealed stenosis and wall irregularity in the esophageal cavity. b) An ulcerative- and infiltrative-type tumor was detected in the middle third of the thoracic esophagus. c) The neoplasm was reduced after preoperative therapy.

Pathological Findings

Macroscopic analysis of the resected specimen revealed a 32 × 25 mm tumor in the middle third of the thoracic esophagus (Fig. 3a, b). Histopathological examination of the esophagus revealed both components of basaloid squamous cell carcinoma displaying basal cell morphology and sarcomatous spindle cells with high-grade of nuclear atypia (Figs. 3c and 4a, c, d). The detailed histological mappings in the resected specimens were illustrated in Fig. 3c. A transitional zone between both components was also detected (Fig. 4b). The component of basaloid squamous cell carcinoma invaded the muscularis propria. No lymph

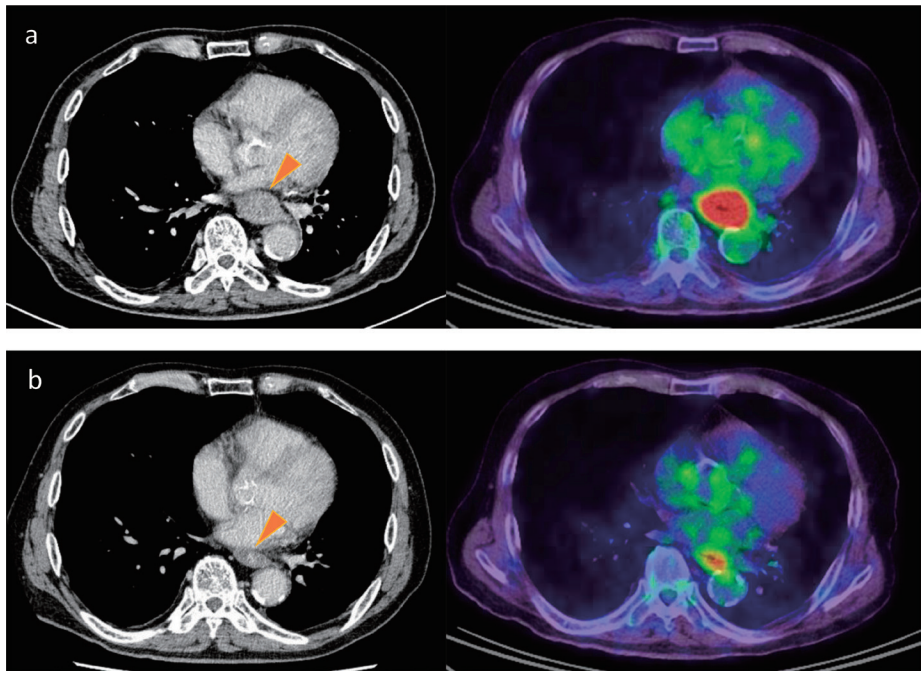

Fig. 2. Computed tomography (CT) and positron emission tomography-CT (PET-CT) findings.
a) CT scans demonstrated the thickness of esophageal wall (orange arrow) without evidence of invasion into adjacent structures or distant metastases. PET-CT showed an uptake of ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) in the middle third of the thoracic esophagus [a maximum standardized uptake value (SUVmax) of 11.0]. b) After preoperative chemotherapy, the tumor (orange arrow) was reduced and PET-CT showed less FDG uptake in the tumor [SUVmax of 5.0].

node involvement was detected and there was no evidence that cancer cells had existed in the lymph nodes before preoperative chemotherapy. Lymphvascular invasions were absent. Infiltration of lymphocytes/histiocytes/multinucleated giant cells and fibrosis/necrosis/granulomatous changes around both components of the neoplasm were identified. These findings indicated that both carcinomatous and sarcomatous components disappeared by preoperative chemotherapy, and the response to treatment was Grade 1b (approximately one-third to two-thirds of the neoplasm disappeared) according to the 11th Japanese Classification of Esophageal Cancer (The Japan Esophageal Society 2015). The osteogenic, myogenic and neurogenic differentiation were not detected. A small lesion of squamous cell carcinoma was detected in esophageal mucosa (carcinoma in situ, Fig. 3c). The subsequent immunohistochemical examination revealed that the tumor cells of basaloid squamous cell carcinoma were immunohistochemically positive for AE1/AE3, CAM5.2 (epithelial markers), p40 (a squamous-basal marker) and vimentin (a mesenchymal/EMT marker). In contrast, sarcomatous spindle cells demonstrated marked immunoreactivity of vimentin, whereas very weak immunoreactivity of AE1/AE3 and CAM 5.2 (Fig. 5). Final pathological diagnosis was esophageal carcinosarcoma with basaloid squamous cell carcinoma, ypT2N0cM0, fStage IIA (TNM classification 8th).

Discussion

Basaloid squamous cell carcinoma is a rare histological subtype of squamous cell carcinoma accounting for 0.07%-11.8% of all esophageal carcinomas (Bellizzi et al. 2009; Tachimori et al. 2017). Basaloid squamous cell carcinoma consists of basaloid-shaped cells harboring round-to-oval-shaped nuclei, dense hyperchromatic nuclei and basophilic scant cytoplasm presenting a high nucleus-cytoplasm ratio (Odze et al. 2019). The clinical outcome of patients with basaloid squamous cell carcinoma is well known to be significantly much worse than that of patients with conventional squamous cell carcinoma (Chen et al. 2012; Imamhasan et al. 2012; Ishida et al. 2019). Esophageal carcinosarcoma, known as spindle cell squamous cell carcinoma, is also a rare neoplasm that accounts for 0.1%-2.8% of all esophageal malignancies (Wang et al. 2013; Tachimori et al. 2017; Odze et al. 2019). Carcinosarcoma is composed of neoplastic squamous epithelium and sarcomatous spindle cells. Typical esophageal carcinosarcoma demonstrates a polypoid growth pattern and the neoplasm usually does not infiltrate deeply into the esophageal wall. Patients therefore have a symptom of dysphagia at the earlier stage and the survival outcome of patients with esophageal carcinosarcoma is generally better than that of patients with typical squamous cell carcinoma of the same size (Wang et al. 2013; Yoshimoto et al. 2018; Hashimoto et al. 2019). Although the etiology of sarcomatous spindle cells remains unclear, a concept of monoclonal origin from a single ancestor cell was proposed, in which sarcomatous components could be derived from carcinomatous components via EMT or sarcomatous metaplasia (Sung

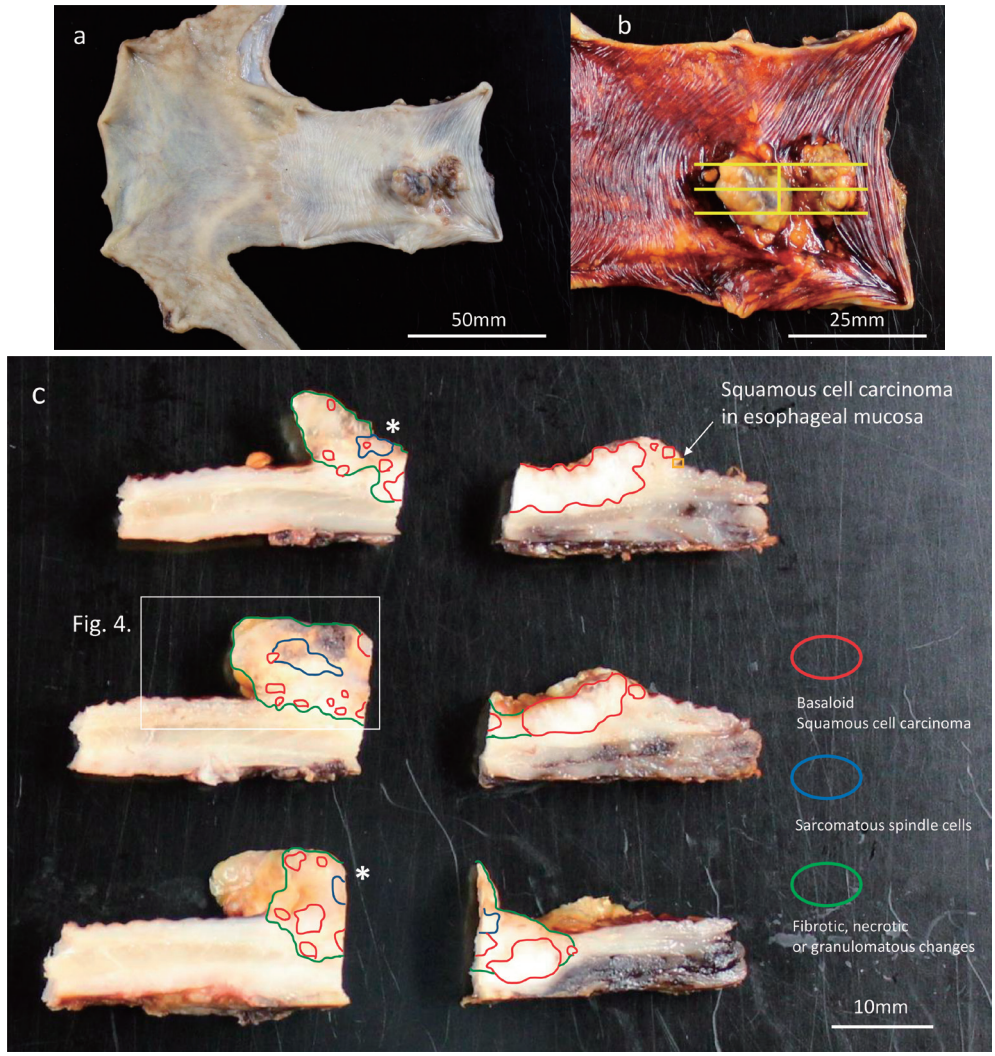

Fig. 3 Macroscopic findings of the resected specimen.
a) 32 × 25 mm of ulcerative- and localized-type tumor was observed in the middle third of the thoracic esophagus. b) The unstained area of iodine staining was not identified around the neoplasms. c) The histological mapping on the yellow lines in Figure 3b was illustrated. The area surrounded by red, blue and green lines included the components of basaloid squamous cell carcinoma, sarcomatous spindle cells and fibrosis/necrosis/granulomas changes, respectively. The potential locations of initial biopsy were demonstrated as asterisks. A relatively small lesion of squamous cell carcinoma was detected in esophageal mucosa (orange box).

et al. 2011, 2013). This hypothesis is based on the facts that the great majority of cases with carcinosarcoma contained a transitional zone between carcinomatous and sarcomatous components, and both elements shared the same genetic alterations (Kashiwabara et al. 2001; Amatya et al. 2004; Matsumoto et al. 2004).

Previously, three cases with esophageal carcinosarcoma having basaloid squamous cell carcinoma components were reported and are summarized in Table 1 (Ohtaka et al. 2002; Amatya et al. 2004; Hung et al. 2008). Ohtaka et al. (2002) reported a case with squamous cell carcinoma and basaloid squamous cell carcinoma having spindle cell components. Basaloid cell carcinoma demonstrated a gradual transition to chondrosarcomatous cells producing the matrix; thus, the authors concluded that carcinogenesis of the neoplasm might be associated with an undifferentiated stem cell of esophageal mucosa. Esophageal carcinosarcoma with basaloid squamous cell carcinoma sharing the similar point mutation of *TP53* was reported by Amatya et al. (2004). The similar mutation between carcinomatous and sarcomatous components indicated a high probability of a monoclonal origin for these components. Hung et al. (2008) reported a case of carcinosarcoma having basaloid squamous cell carcinoma and osteosarcoma components without a transitional zone. Each component might originate from two individual stem cells separately because no transitional zone was detected in the neoplasm. In addition, Schaefer et al. (2011) investigated the chromosomal aberrations in each basaloid squamous cell carcinoma and carcinosarcoma of the esophagus by using comparative genomic hybridization. As both basaloid squamous cell carcinoma and sarcomatous components displayed common copy

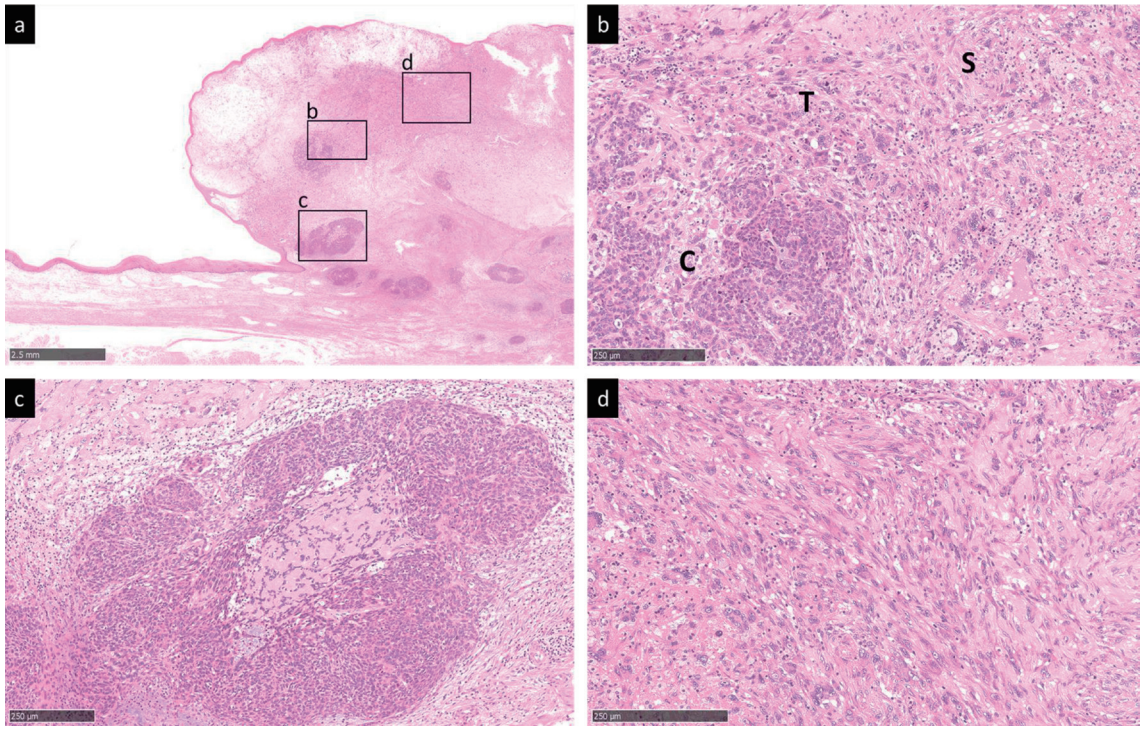

Fig. 4. Representative hematoxylin and eosin-stained histopathological illustrations of the neoplasm.
a) Low-pawer field of the tumor. Regenerative epithelium covered the lesion. b) A transitional zone (T) between carcinomatous (C) and sarcomatous (S) components. c) Basaloid squamous cell carcinoma displaying basaloid-shaped cells with dense hyperchromatic nuclei, a high nucleus-cytoplasm ratio, basophilic scant cytoplasm and basement membrane-like material. d) Sarcomatous spindle cells with high-grade of nuclear atypia.

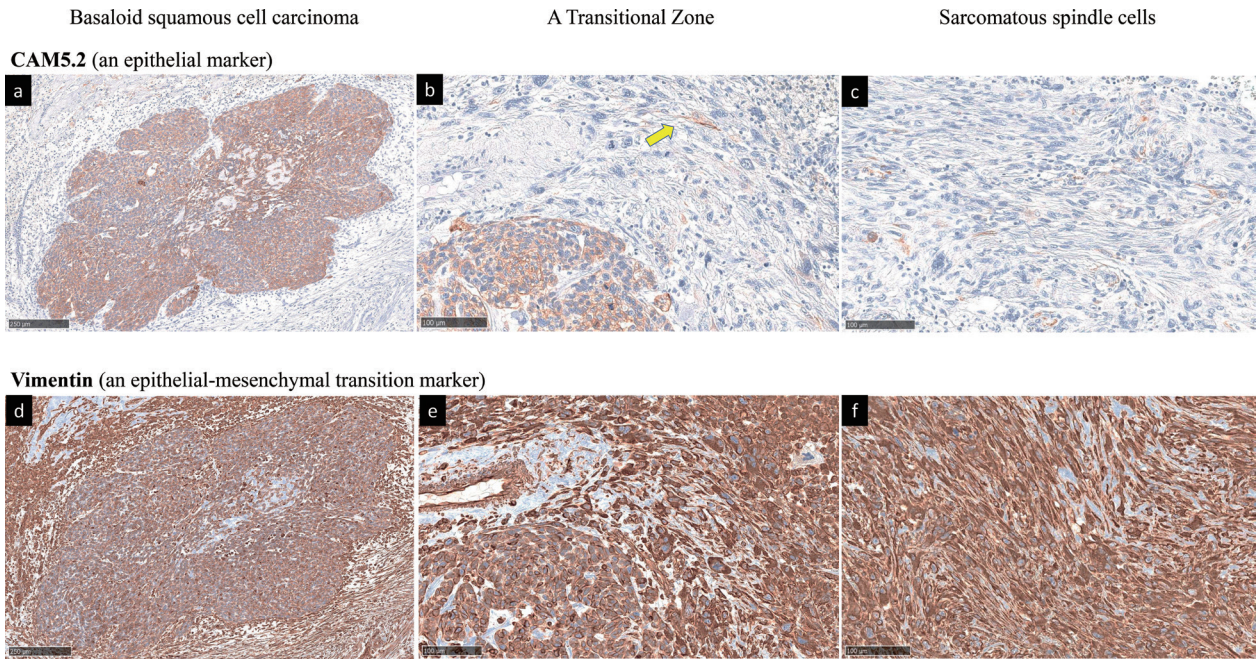

Fig. 5. Immunohistochemical features of esophageal carcinosarcoma with basaloid squamous cell carcinoma in our present case.
Marked CAM5.2 (an epithelial marker) immunoreactivity in a) basaloid squamous cell carcinoma, whereas very weak positive immunoreactivity of CAM5.2 detected in b) a transitional zone (yellow arrow) and c) sarcomatous spindle cells. Marked vimentin (a mesenchymal/epithelial-mesenchymal transition marker) immunoreactivity in d) basaloid squamous cell carcinoma, e) a transitional zone and f) sarcomatous spindle cells.

Table 1. Esophageal carcinosarcoma with basaloid squamous cell carcinoma.

Author	Year	Age	Sex	Endoscopic Finding	pT	pN	Basaloid squamous cell carcinoma Component	Sarcomatous Component	Transitional Zone	Genetic Alterations	Origin of Carcinosarcoma	Survival Outcome
Ohtaka	2002	61	M	1	T2	NX (c+s)	Cytokeratin ++ Vimentin –	Cytokeratin – Vimentin ++	**Present** Cytokeratin ± Vimentin –	NA	Undifferentiated stem cell	NA
Amatya	2004	64	M	1	T1b	N0	Cytokeratin ++ Vimentin +	Cytokeratin – Vimentin +++	NA	Similar *TP53* point mutation (missense mutation)	Monoclonal origin	12 months alive
Hung	2008	57	M	1	T2	N0	Cytokeratin ++	NA	**Absent**	NA	Two individual stem cells	30 months alive
Present case	2019	78	M	3	T2	N0	Cytokeratin +++ Vimentin +++	Cytokeratin ± Vimentin +++	**Present** Cytokeratin ± Vimentin +++	NP	Monoclonal origin (via EMT)	25 months alive

Endoscopic finding: 1, protruding type; 3, ulcerative and infiltrative type; c, carcinomatous lesion; s, sarcomatous lesion; Cytokeratin, an epithelial marker; Vimentin, an epithelial-mesenchymal transition marker; –, Negative; ±, less than 10% positive cells; +, 10-25% positive cells; ++, 25-50% positive cells; +++, more than 50% positive cells; NA, not available; NP, not performed; EMT, epithelial-mesenchymal transition.

number gains at the same chromosome, the result suggested a common genetic origin. In our present case, a transitional zone was detected between two components. Furthermore, the marked immunoreactivity of vimentin (an EMT marker) was detected in the tumor cells of basaloid squamous cell carcinoma. These findings indicated that sarcomatous cells might be derived from the components of basaloid squamous cell carcinoma via EMT. It was reported that the expression of vimentin was more frequently detected in basaloid squamous cell carcinoma, compared with typical squamous cell carcinoma (Zhang et al. 1998). Considering high proliferative activity and high incidence of distant metastases in patients with basaloid squamous cell carcinoma, EMT might tend to occur more frequently; thus, more cases with esophageal carcinosarcoma having basaloid squamous cell carcinoma components should have been reported. However, as only four cases with esophageal carcinosarcoma harboring basaloid squamous cell carcinoma have been reported so far including our present case, some different mechanisms might exist in development of the rare neoplasm. Further genomic sequencing may be required for molecular clues for the histogenesis of esophageal carcinosarcoma with basaloid squamous cell carcinoma. Sarcomatous spindle cells demonstrated very weak immunoreactivity of epithelial markers in our present case. However, Li et al. (2018) reported that AE1/AE3 were positive in sarcomatous components in only 23% of cases. Therefore, the absences of immunoreactivity of epithelial markers in sarcomatous components could not exclude the possibility of a concept of monoclonal origin.

In the present case, considering the diagnosis of squamous cell carcinoma and sarcomatous spindle cells before neo-adjuvant chemotherapy demonstrated in biopsy specimens, we postulate that the tumor harbored squamous cell carcinoma components in addition to those of basaloid squamous cell carcinoma and sarcomatous spindle cells, which might represent the dominant component before preoperative therapy. The endoscopic findings, an ulcerative/infiltrative type, which were not necessarily characteristic of those of carcinosarcoma, the efficacy of neo-adjuvant chemotherapy and the pathological findings, the presence of a relatively small component of squamous cell carcinoma in esophageal mucosa in the surgically resected specimens could support this possibility above. The potential location of initial biopsy might be around the components of both sarcomatous spindle cells and fibrosis/necrosis/granulomas in which squamous cell carcinoma could be present before neo-adjuvant treatment (asterisks in Fig. 3c). Therefore, the tumor might disappear as a result of preoperative chemotherapy and it was relatively difficult to conclude that this particular neoplasm consisted mainly of basaloid squamous cell carcinoma before the therapy.

There is no doubt that curative surgical resection is the most effective method to cure esophageal carcinosarcoma completely. However, the treatment strategies of esophageal carcinosarcoma before/after surgery, known as neo-adjuvant/adjuvant therapy, have not been established due to the rather limited number of cases and the difficulty of implementation of a prospective trial. The aim of neo-adjuvant therapy is to reduce the tumor volume, make the curative resection possible and improve patients' survival outcome. Conventional squamous cell carcinoma could benefit from preoperative therapy composed of 5-FU/CDDP (FP, 2 courses), especially in patients with localized advanced tumor (Ando et al. 2012). In contrast, there are only a few case reports or small case series regarding the neo-adjuvant/adjuvant therapy for patients with esophageal carcinosarcoma. We searched for English articles via PubMed published since 2000 containing the key terms "esophagus", "carcinosarcoma" and/or "spindle cell carcinoma". Fourteen cases were identified in which preoperative therapy were performed and are summarized in Table 2 (Zuiki et al. 2009; Kobayashi et al. 2010, 2015; Kuo et al. 2010; Katsuya et al. 2017; Yoshimoto et al. 2018). Five patients underwent chemoradiotherapy in which the dose of radiation ranged from 38 to 62Gy, and chemotherapy were per-

Table 2. Esophageal carcinosarcoma treated with preoperative therapy.

Author	Year	Age	Sex	Endoscopic Finding	Preoperative Treatment	pT	pN	Pathological Response	Residual Tumor	Survival Outcome
Zuiki	2009	50	M	1	FP+62Gy	T1b	N1 (c)	NA	c	36 months alive
Zuiki	2009	66	M	1	FP+40.8Gy	T1b	N0	NA	s	19 months alive
Kobayashi	2010	68	M	2	S-1/cisplatin	Tis	N0	2	c	60 months alive
Kobayashi	2010	64	M	0-1p	FP+38Gy	T1a	N1	2	c+s	11 months dead
Kuo	2010	68	M	1	NA	T3	N1	NA	NA	27 months alive
Kuo	2010	45	M	3	NA	T4	N1	NA	NA	6 months alive
Kobayashi	2015	69	M	0-1p	FP	T1a	N0	1	c+s	60 months alive
Katsuya	2017	60	M	0-1	FP	T1b	N3 (c)	0	c+s	4.5 months dead
Katsuya	2017	57	M	1	FP	T1b	N1 (c+s)	0	c+s	6.8 months dead
Katsuya	2017	64	M	1	FP	T1b	N0	1	c+s	28 months dead
Katsuya	2017	65	M	5	FP	T1b	N0	1	s	40.9 months alive
Katsuya	2017	67	F	1	FP+50.4Gy	T1b	N0	1	s	10.9 months dead
Katsuya	2017	73	F	1	FP+41.4Gy	T1b	N0	2	s	47 months alive
Yoshimoto	2018	73	M	1+3	DCF	Tis	N0	2	c	12 months alive
Present case	2019	78	M	3	FP	T2	N0	1	c+s	25 months alive

Endoscopic finding: 0-1, superficial and protruding type; 0-1p, pedunculated type; 1, protruding type; 2, ulcerative and localized type; 3, ulcerative and infiltrative type; 5, unclassified type; FP, cisplatin+5-fluorouracil; S-1, oral tegafur/gimeracil/oteracil; DCF, docetaxel + cisplatin + 5-fluorouracil; c, carcinomatous lesion; s, sarcomatous lesion.
Pathological response: 0, No evidence of effect; 1, Viable tumor cells occupy more than 1/3 of the tumorous area; 2, Viable tumor cells remain in less than 1/3 of the tumorous area; NA, not available.

formed in the other cases. The major regimens of chemotherapy were FP, oral tegafur/gimeracil/oteracil (S-1)/CDDP or docetaxel/FP (DCF), and these regimens targeted carcinomatous components. More than two-thirds of the neoplasm disappeared in four cases by preoperative therapy. Of particular interest, the sarcomatous components were not detected in the resected specimen in three cases. The findings indicated that the regimens targeting squamous cell carcinoma components could also be effective in the treatment of sarcomatous components. This fact would be rational because the chemotherapy could be effective if the two components share the same origin or the same genetic abnormalities each other (a concept of monoclonal origin). In the fifteen cases, the origin of sarcomatous spindle cells was considered in only three cases including our present case (the same origin in all the three cases). Molecular genetic analyses for detection of genetic alterations were not performed in any cases. Further investigations are therefore required for clarification. Docetaxel is a semisynthetic member of the taxoid class of antineoplastic agents. Docetaxel-based chemotherapy targeting sarcomatous components is currently used in several areas, such as bone, soft tissue or gynecological sarcomas, and showed favorable response rates (Hensley et al. 2008; Takahashi et al. 2017; Choi et al. 2018). Thus, DCF that could be effective for both carcinomatous and sarcomatous components may be a rational option of preoperative chemotherapy for patients with esophageal carcinosarcoma. 21%-42% of patients with esophageal carcinosarcoma underwent adjuvant therapy after surgery (Zhang et al. 2016; Schizas et al. 2018; Hashimoto et al. 2019). However, no survival improvements have been reported so far because patients in more advanced stage received postoperative therapy. Considering low feasibility of a randomized prospective trial because of the limited number of cases of esophageal carcinosarcoma, it is needed to assess experts experience and evidence from case reports or small case series in order to find out the appropriate candidates who could benefit from neo-adjuvant/adjuvant therapy.

In summary, we present a rare case of esophageal carcinosarcoma harboring basaloid squamous cell carcinoma components, in which sarcomatous cells might be derived from the components of basaloid squamous cell carcinoma via EMT. In addition, preoperative therapy targeting squamous cell carcinoma components could also be effective in the treatment of sarcomatous components; thus, treatment before surgery might be considered for improvement of patients' clinical outcome. As the obvious criteria of neo-adjuvant/adjuvant therapy for patients with esophageal carcinosarcoma have not been established, the potential factors need to be clarified in patients who could benefit from pre-/post-operative therapy.

Conflict of Interest

The authors declare no conflict of interest.

References

Amatya, V.J., Takeshima, Y., Kaneko, M. & Inai, K. (2004) Esophageal carcinosarcoma with basaloid squamous carcinoma and rhabdomyosarcoma components with TP53 mutation. *Pathol. Int.*, **54**, 803-809.

Ando, N., Kato, H., Igaki, H., Shinoda, M., Ozawa, S., Shimizu,

H., Nakamura, T., Yabusaki, H., Aoyama, N., Kurita, A., Ikeda, K., Kanda, T., Tsujinaka, T., Nakamura, K. & Fukuda, H. (2012) A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Ann. Surg. Oncol.*, **19**, 68-74.

Bellizzi, A.M., Woodford, R.L., Moskaluk, C.A., Jones, D.R., Kozower, B.D. & Stelow, E.B. (2009) Basaloid squamous cell carcinoma of the esophagus: assessment for high-risk human papillomavirus and related molecular markers. *Am. J. Surg. Pathol.*, **33**, 1608-1614.

Brierley, J.D., Gospodarowicz, M.K. & Wittekind, C. (2017) Oesophagus and Oesophagogastric Junction. In *TNM Classification of Malignant Tumours*, 8th ed., edited by Union for International Cancer Control. John Wiley & Sons, Ltd, NewYork, NY, pp. 57-62.

Chen, S.B., Weng, H.R., Wang, G., Yang, J.S., Yang, W.P., Li, H., Liu, D.T. & Chen, Y.P. (2012) Basaloid squamous cell carcinoma of the esophagus. *J. Cancer Res. Clin. Oncol.*, **138**, 1165-1171.

Choi, Y., Yun, M.S., Lim, S.H., Lee, J., Ahn, J.H., Kim, Y.J., Park, K.H., Park, Y.S., Lim, H.Y., An, H., Suh, D.C. & Kim, Y.H. (2018) Gemcitabine and docetaxel combination for advanced soft tissue sarcoma: a nationwide retrospective study. *Cancer Res. Treat.*, **50**, 175-182.

Eisenhauer, E.A., Therasse, P., Bogaerts, J., Schwartz, L.H., Sargent, D., Ford, R., Dancey, J., Arbuck, S., Gwyther, S., Mooney, M., Rubinstein, L., Shankar, L., Dodd, L., Kaplan, R., Lacombe, D., et al. (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur. J. Cancer*, **45**, 228-247.

Hashimoto, M., Kitagami, H., Niwa, H., Kikkawa, T., Ohuchi, T., Takenouchi, T. & Hosokawa, M. (2019) Prognosis and prognostic factors of esophageal spindle cell carcinoma treated by esophagectomy: a retrospective single-institution analysis. *Esophagus*, **16**, 292-299.

Hensley, M.L., Blessing, J.A., Mannel, R. & Rose, P.G. (2008) Fixed-dose rate gemcitabine plus docetaxel as first-line therapy for metastatic uterine leiomyosarcoma: a Gynecologic Oncology Group phase II trial. *Gynecol. Oncol.*, **109**, 329-334.

Hung, J.J., Li, A.F., Liu, J.S., Lin, Y.S. & Hsu, W.H. (2008) Esophageal carcinosarcoma with basaloid squamous cell carcinoma and osteosarcoma. *Ann. Thorac. Surg.*, **85**, 1102-1104.

Imamhasan, A., Mitomi, H., Saito, T., Hayashi, T., Takahashi, M., Kajiyama, Y. & Yao, T. (2012) Immunohistochemical and oncogenetic analyses of the esophageal basaloid squamous cell carcinoma in comparison with conventional squamous cell carcinomas. *Hum. Pathol.*, **43**, 2012-2023.

Ishida, H., Kasajima, A., Onodera, Y., Konno, T., Maruyama, S., Okamoto, H., Sato, C., Heishi, T., Sakurai, T., Taniyama, Y., Takahashi, M., Fujishima, F., Jingu, K., Ishioka, C., Sasano, H., et al. (2019) A comparative analysis of clinicopathological factors between esophageal small cell and basaloid squamous cell carcinoma. *Medicine* (*Baltimore*), **98**, e14363.

Kashiwabara, K., Sano, T., Oyama, T., Najahima, T., Makita, F., Hashimoto, N., Iwanami, K., Kawashima, O., Matsumoto, T. & Matsuzaki, Y. (2001) A case of esophageal sarcomatoid carcinoma with molecular evidence of a monoclonal origin. *Pathol. Res. Pract.*, **197**, 41-46.

Katsuya, Y., Honma, Y., Taniguchi, H., Kato, K., Okita, N., Takashima, A., Iwasa, S., Hamaguchi, T., Boku, N., Umezawa, R., Inaba, K., Ito, Y., Itami, J., Koyanagi, K., Igaki, H., et al. (2017) Clinicopathological features and pathological evaluation of preoperative treatment of patients with resectable esophageal carcinosarcoma. *Esophagus*, **14**, 317-323.

Kobayashi, D., Koike, M., Kodera, Y., Fujiwara, M., Nakayama, G. & Nakao, A. (2010) Carcinosarcoma of the esophagus treated with chemoradiotherapy: report of four cases. *Esophagus*., **7**, 119-125.

Kobayashi, S., Nagata, Y., Tokai, H., Ito, M. & Fujioka, H. (2015) Multidisciplinary therapy for granulocyte-colony-stimulating factor producing carcinosarcoma of the esophagus: report of a case. *Clin. Case Rep.*, **3**, 681-685.

Kuo, C.J., Lin, T.N., Lin, C.J., Wu, R.C., Chang, H.K., Chu, Y.Y., Lien, J.M., Su, M.Y. & Chiu, C.T. (2010) Clinical manifestation of esophageal carcinosarcoma: a Taiwan experience. *Dis. Esophagus*, **23**, 122-127.

Li, X.M., Song, X., Zhao, X.K., Hu, S.J., Cheng, R., Lv, S., Du, D.F., Zhang, X.Y., Lu, J.L., Ku, J.W., Zhang, D.Y., Zhang, Y., Fan, Z.M. & Wang, L.D. (2018) The alterations of cytokeratin and vimentin protein expressions in primary esophageal spindle cell carcinoma. *BMC Cancer*, **18**, 356.

Matsumoto, T., Fujii, H., Arakawa, A., Yamasaki, S., Sonoue, H., Hattori, K., Kajiyama, Y., Hirose, S. & Tsurumaru, M. (2004) Loss of heterozygosity analysis shows monoclonal evolution with frequent genetic progression and divergence in esophageal carcinosarcoma. *Hum. Pathol.*, **35**, 322-327.

Odze, R.D., Lam, A.K., Ochiai, A. & Washington, M.K. (2019) Tumours of the oesophagus. In *WHO classification of tumours. Digestive system tumours*, 5th ed., edited by the WHO classification of timours editorial board. International agency for research on cancer, Lyon, France, pp. 23-58.

Ohtaka, M., Kumasaka, T., Nobukawa, B., Hirai, S., Suda, K., Ohno, Y., Iwazaki, R., Ikegami, Y. & Fukasawa, M. (2002) Carcinosarcoma of the esophagus characterized by myoepithelial and ductal differentiations. *Pathol. Int.*, **52**, 657-663.

Schaefer, I.M., Enders, C., Polten, A., Haller, F., Frolich, A.M., Cameron, S., Schuler, P., Schweiger, P., Gunawan, B., Beham, A. & Fuzesi, L. (2011) Common genomic aberrations in basaloid squamous cell carcinoma and carcinosarcoma of the esophagus detected by CGH and array CGH. *Am. J. Clin. Pathol.*, **135**, 579-586.

Schizas, D., Mastoraki, A., Bagias, G., Ioannidi, M., Kanavidis, P., Moris, D., Tsilimigras, D.I., Spartalis, E., Arkadopoulos, N. & Liakakos, T. (2018) Carcinosarcomas of the esophagus: systematic review of a rare nosologic entity. *J. BUON*, **23**, 1432-1438.

Sung, C.O., Choi, H., Lee, K.W. & Kim, S.H. (2013) Sarcomatoid carcinoma represents a complete phenotype with various pathways of epithelial mesenchymal transition. *J. Clin. Pathol.*, **66**, 601-606.

Sung, C.O., Park, C.K. & Kim, S.H. (2011) Classification of epithelial-mesenchymal transition phenotypes in esophageal squamous cell carcinoma is strongly associated with patient prognosis. *Mod. Pathol.*, **24**, 1060-1068.

Tachimori, Y., Ozawa, S., Numasaki, H., Ishihara, R., Matsubara, H., Muro, K., Oyama, T., Toh, Y., Udagawa, H. & Uno, T.; Registration Committee for Esophageal Cancer of the Japan Esophageal Society (2017) Comprehensive registry of esophageal cancer in Japan, 2010. *Esophagus*, **14**, 189-214.

Takahashi, M., Komine, K., Imai, H., Okada, Y., Saijo, K., Takahashi, M., Shirota, H., Ohori, H., Takahashi, S., Chiba, N., Mori, T., Shimodaira, H. & Ishioka, C. (2017) Efficacy and safety of gemcitabine plus docetaxel in Japanese patients with unresectable or recurrent bone and soft tissue sarcoma: results from a single-institutional analysis. *PLoS One*, **12**, e0176972.

The Japan Esophageal Society (2015) *The 11th Japanese Classification of Esophageal Cancer*, KANEHARA & CO., LTD, Japan (in Japanese).

Wang, L., Lin, Y., Long, H., Liu, H., Rao, H., He, Y., Rong, T. & Liang, Y. (2013) Esophageal carcinosarcoma: a unique entity with better prognosis. *Ann. Surg. Oncol.*, **20**, 997-1004.

Yoshimoto, T., Kobayashi, S., Kanetaka, K., Kobayashi, K., Nagata, Y., Morita, M., Isagawa, Y., Kinoshita, N., Takatsuki, M. & Eguchi, S. (2018) Preoperative chemotherapy with docetaxel, cisplatin, and 5-fluorouracil for locally advanced esophageal carcinosarcoma: a case report and review of the

literature. *Surg. Case Rep.*, **4**, 18.
Zhang, B., Xiao, Q., Yang, D., Li, X., Hu, J., Wang, Y. & Wang, W. (2016) Spindle cell carcinoma of the esophagus: a multicenter analysis in comparison with typical squamous cell carcinoma. *Medicine* (*Baltimore*), **95**, e4768.
Zhang, X.H., Sun, G.Q., Zhou, X.J., Guo, H.F. & Zhang, T.H. (1998) Basaloid squamous carcinoma of esophagus: a clinicopathological, immunohistochemical and electron microscopic study of sixteen cases. *World J. Gastroenterol.*, **4**, 397-403.
Zuiki, T., Hosoya, Y., Ui, T., Haruta, H., Kurashina, K., Saito, S., Lefor, A., Niki, T., Nakazawa, M. & Yasuda, Y. (2009) Therapeutic effectiveness of chemoradiotherapy for carcinosarcoma of the esophagus: two case reports and a review of the literature. *Esophagus*, **6**, 189-195.