International Journal of Surgery Case Reports 94 (2022) 107116

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.elsevier.com/locate/ijscr

Case report

Rapidly growing carcinosarcoma of the esophagus following definitive chemoradiotherapy: A case report and the literature review

Takuro Yamauchi [a], Yusuke Taniyama [a,*], Fumiyoshi Fujishima [b], Hironobu Sasano [b], Michiaki Unno [a], Takashi Kamei [a]

[a] Department of Surgery, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan
[b] Department of Pathology, Tohoku University Hospital, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan

ARTICLE INFO

Keywords:
Case report
Carcinosarcoma
Chemoradiotherapy
Esophagus
Salvage surgery
Spindle cell carcinoma

ABSTRACT

Introduction: Esophageal carcinosarcoma is a rare malignancy composed of both carcinoma and sarcoma-like spindle cells. This tumor is usually diagnosed before treatment due to its unique macroscopic appearance but accurate diagnose is difficult even via biopsy if the sarcomatous component is small. Herein, we report a rare case of esophageal carcinosarcoma showing rapid growth after definitive chemoradiotherapy.

Presentation of case: A 65-year-old man was diagnosed with locally advanced esophageal squamous cell carcinoma with lymph node metastasis. Following definitive chemoradiotherapy, the primary tumor and metastatic lymph nodes were markedly reduced. However, at 14 weeks after treatment, an ulcerative lesion appeared at the site of the primary tumor and was clinically interpreted as residual cancer. The tumor rapidly grew in a short period of time and new metastatic lesions were clinically detected in the supraclavicular lymph nodes. Salvage esophagectomy was immediately performed and histopathological examination of the resected specimen revealed that the tumor was largely composed of sarcomatous spindle cells harboring the histological transition from squamous cell carcinoma. The final diagnosis was esophageal carcinosarcoma.

Discussion: Due to its characteristics, esophageal carcinosarcoma may occasionally get diagnosed as squamous cell carcinoma by endoscopic biopsy and chemoradiotherapy be performed for latent sarcomatous components unintentionally. There are only a few reports of esophageal carcinosarcoma treated with chemoradiotherapy, with its safety and efficacy not fully verified.

Conclusion: In cases of rapidly growing tumors following chemoradiotherapy, carcinosarcoma should be considered as one of the differential diagnoses, warranting prompt surgical procedures.

1. Introduction

Esophageal carcinosarcoma is a rare composite tumor that constitutes less than 1% of all esophageal malignancies [1]. Esophageal carcinosarcoma is histologically composed of squamous cell carcinoma (SCC) and sarcomatous components. The origin of the sarcomatous cells remains unknown; however, these cells are thought to originate from the epithelial-mesenchymal transition of carcinomatous cells, which are interpreted as metaplastic changes to sarcomatous spindle cells [2,3]. Although the standard treatment strategy for esophageal carcinosarcoma has not been established, surgical resection is considered as the first option for radical treatment. The diagnosis of carcinosarcoma is usually not clinically difficult because of its unique appearance as a large polypoid lesion accompanied with early cancer lesion. However, its appearance could possibly change if the sarcomatous component is small, resulting that similar to usual carcinoma. In such a case, it is nearly clinically impossible to diagnose carcinosarcoma even by endoscopic biopsy. We report a rare case of carcinosarcoma demonstrating rapid growth after definitive chemoradiotherapy (dCRT) for esophageal SCC. In addition, we conducted a literature review on esophageal carcinosarcoma treated with CRT. This work has been reported in line with the SCARE Guidelines 2020 [4].

2. Presentation of case

A 65-year-old man presenting with dysphagia was diagnosed with

Abbreviations: CT, computed tomography; dCRT, definitive chemoradiotherapy; SCC, squamous cell carcinoma.

* Corresponding author at: Department of Surgery, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi 980-8574, Japan.
E-mail address: yusuketaniyama@med.tohoku.ac.jp (Y. Taniyama).

https://doi.org/10.1016/j.ijscr.2022.107116
Received 6 February 2022; Received in revised form 18 April 2022; Accepted 18 April 2022
Available online 21 April 2022

esophageal SCC by endoscopy and referred to our hospital. An esophagogram demonstrated stenosis and irregularity in the esophageal wall from the cervical to upper thoracic esophagus (Fig. 1a). An ulcerative and infiltrative tumor was confirmed by endoscopy (Fig. 1b). Pathological examination of the biopsy specimens revealed SCC without any evidence of sarcomatous elements. Computed tomography (CT) revealed thickening of the esophageal wall and swelling of the right recurrent nerve lymph nodes (Fig. 2a). The pretreatment clinical diagnosis was SCC, cT3N1M0, Stage IIIB, in accordance with the eighth edition of the Union for International Cancer Control classification [5].

The patient was treated with dCRT. Radiation therapy (a total of 60 Gy in 30 fractions) was accompanied by two cycles of concurrent chemotherapy. The chemotherapy regimen included cisplatin (70 mg/m^2 on day 1) and 5-fluorouracil (700 mg/m^2 on days 1–5 per cycle). Post-treatment endoscopic and CT examinations revealed that the primary tumor was markedly reduced in size (Figs. 1c, 2b). In addition, the swollen lymph nodes were reduced to a normal size. Two additional cycles of the chemotherapy regimen described above were subsequently administered. An endoscopy performed at 14 weeks after the completion of dCRT revealed that an ulcerative lesion appeared at the same anatomical site as the primary SCC, suggesting the presence of residual cancer. Pathological examination of biopsy specimens revealed poorly differentiated SCC harboring highly atypical nuclei, which displayed a sarcoma-like morphology. Based on these findings, the clinical efficacy of the dCRT was determined as incomplete response/stable disease according to the Response Evaluation Criteria for esophageal cancer [6]. For radical treatment, salvage esophagectomy was planned; however, during the waiting period before surgery, the dysphagia increased dramatically. CT revealed a rapidly growing tumor, which filled the esophageal luminal space, and swelling of the supraclavicular lymph nodes in just 4 weeks (Fig. 2c, d). A thoracoscopic salvage esophagectomy was performed immediately.

An elevated tumor protruding into the esophageal cavity was detected in the cervical esophagus (Fig. 3a). Pathological examination revealed that the tumor was mainly composed of sarcomatous spindle cells harboring highly atypical nuclei (Fig. 3b, c). In addition, a small region of the SCC components was identified at the rising edge of the tumor margins and a transitional region with sarcomatous cells was confirmed (Fig. 3d, e). The sarcomatous cells invaded the muscularis propria. Metastatic sarcomatous components were also identified in the supraclavicular lymph nodes (Fig. 4a, b). Immunohistochemical examination revealed that the sarcomatous spindle cells were diffusely positive for vimentin and cytokeratin (using an AE1/AE3 antibody cocktail), whereas p40 was weakly positive (Fig. 5a, b, d, e, g, and h). In contrast, SCC cells were diffusely positive for AE1/AE3 and p40 and stained weakly for vimentin (Fig. 5c, f, and i). The muscularis propria was partially obscured by fibrosis and granulation tissue; these findings indicated the primary tumor had partially disappeared after dCRT. In addition, an extensive fibrosis was detected in the right recurrent nerve lymph node without any residual tumor cell (Fig. 4c, d). Finally, the pathological diagnosis was carcinosarcoma, ypT2N0M1 (non-regional lymph node), ypStage IVB.

The patient developed local recurrence and lung metastasis at 4 months after the surgery. Three cycles of chemotherapy with paclitaxel (80 mg/m^2 on days 1, 8, and 15 per cycle) were administered. However, there were no significant therapeutic effects, and the patient died at 12 months after surgery.

3. Discussion

Esophageal carcinosarcoma is a rare tumor, which consists of both sarcomatous and carcinomatous components. The origin of the sarcomatous spindle cell is virtually unknown; however, the metaplastic concept describing the generation of sarcomatous components monoclonally from a single ancestral cell has been widely accepted [2,3]. Specifically, the sarcomatous components may be caused by metaplastic changes during the epithelial-mesenchymal transition of the carcinomatous components of the tumor. This concept is supported by the observations that a transitional region is often identified between these two components and both components exhibit the same genetic variants [7,8]. This neoplasm usually displays intraluminal and polypoid growth, and clinical symptoms such as dysphagia appear at an early stage [9]. Carcinosarcoma develops rapidly, with a reported doubling time of approximately two months, whereas that of SCC being at least five months [10]. Despite this, carcinosarcoma is often detected at a relatively early stage and the prognosis is usually better than that of SCC [11–13]. However, compared with SCC, esophageal carcinosarcoma is more likely to recur because of hematogenous metastasis [14]; thus, the latent malignant potential of esophageal carcinosarcoma has remained controversial.

In general, carcinosarcoma is a mixed tumor with carcinomatous and sarcomatous components, both of which could exist in mixed forms or separately in each region. In the latter case, SCC could be present on the luminal side of the esophagus and the sarcomatous components in the deeper side. Therefore, even though the first biopsy specimen is diagnosed as SCC, the resected specimens may be diagnosed as carcinosarcoma, especially in a case in which the sarcomatous component is small. In our case, the initial endoscopy revealed an ulcerative and infiltrative tumor, which were not consistent with the morphological features of carcinosarcoma, suggesting that the sarcomatous component was not considerably large. The sarcomatous components that were originally present might have been retained and rapidly increased after CRT.

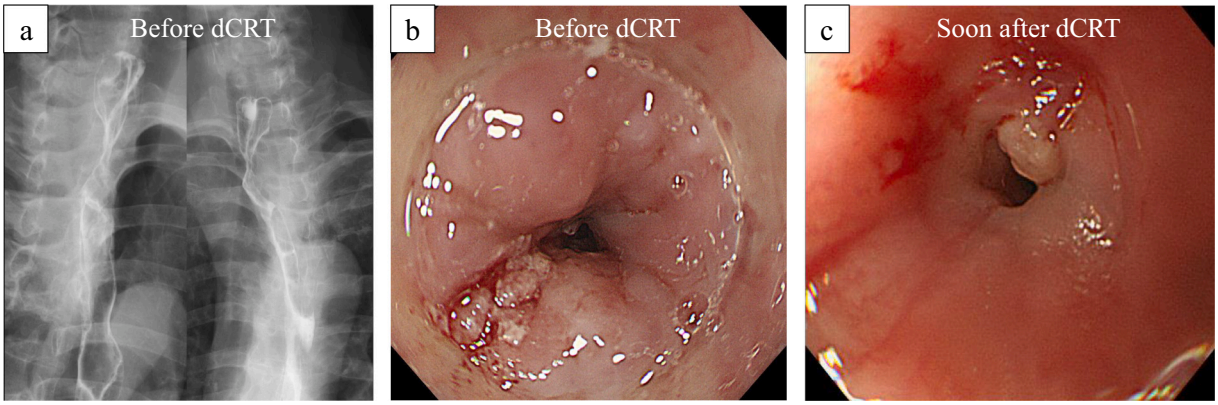

Fig. 1. Radiographic and endoscopic findings of the tumor
a) The esophagogram shows stenosis and irregularity in the esophageal wall from the cervical to upper thoracic esophagus. b) An ulcerative and infiltrative type of tumor confirmed by endoscopy. c) A markedly reduced tumor after definitive chemoradiotherapy (dCRT).

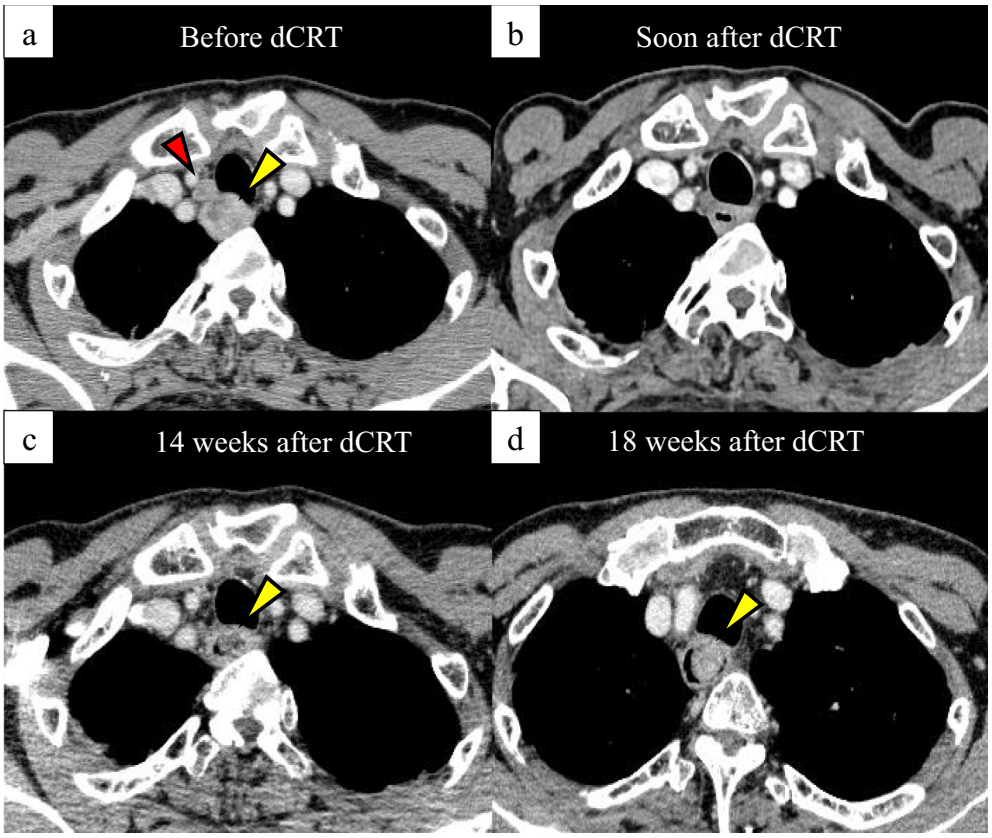

Fig. 2. Computed tomography findings
a) Computed tomography reveals thickening of the esophageal wall (yellow arrow) and swelling of the right recurrent nerve lymph nodes (red arrow). b) After definitive CRT (dCRT), the primary tumor and swollen lymph nodes are both markedly reduced. c) After additional chemotherapy, a regrowth of the primary lesion is noted 14 weeks after completion of dCRT (yellow arrow). d) Four weeks later at 18 weeks post-dCRT, the primary tumor shows a dramatic increase in growth (yellow arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

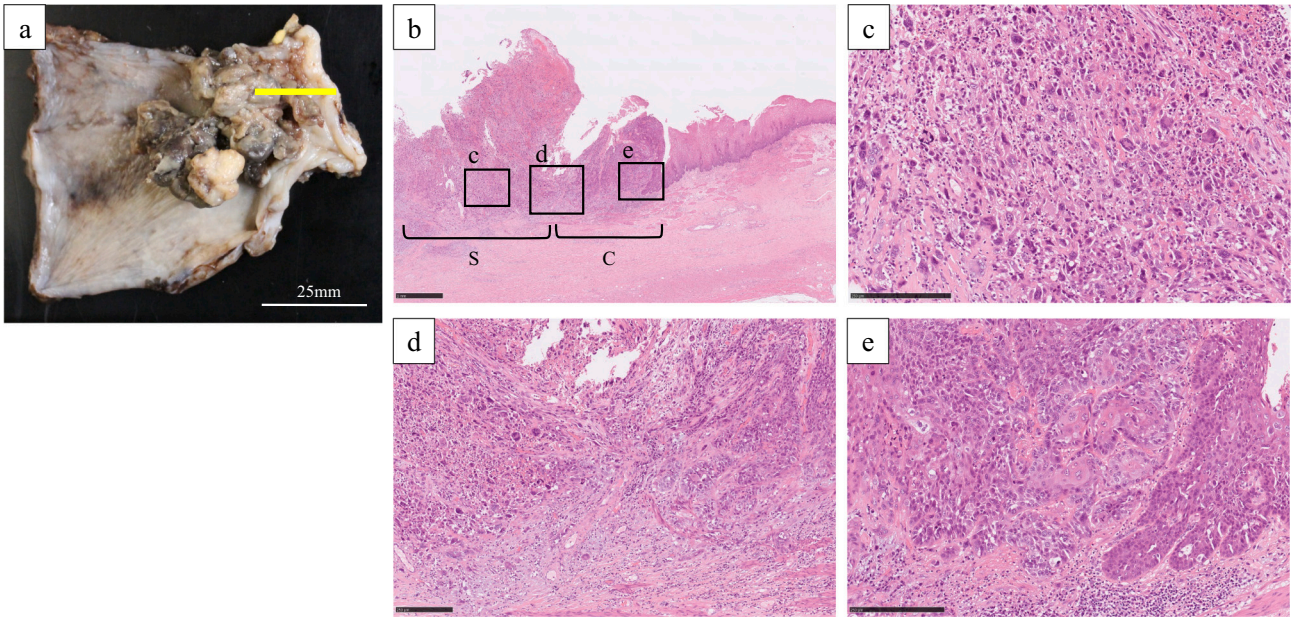

Fig. 3. Macroscopic and microscopic findings of resected specimens
a) An elevated tumor protruding into the esophageal cavity is observed in the cervical esophagus. The yellow line indicates the cutting line. b) Low power field of the tumor containing both sarcomatous (S) and carcinomatous (C) components. c) Sarcomatous spindle cells with highly atypical nuclei. d) A transitional region between the sarcomatous and carcinomatous components. e) Squamous cell carcinoma with keratinization is observed at the rising edge of the tumor margin. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

However, it is slightly perplexing that the tumor had grown so rapidly in such a short period of time, despite the fact that it had temporarily reduced markedly with CRT. This may be due to the difference in the response to CRT between the two components. In other words, CRT may have been effective only for SCC but not for the sarcomatous components. Pathological examination demonstrated both fibrosis and granulation tissue at the sites of primary lesion and lymph nodes, suggesting the disappearance of the tumor; in contrast, the residual sarcomatous

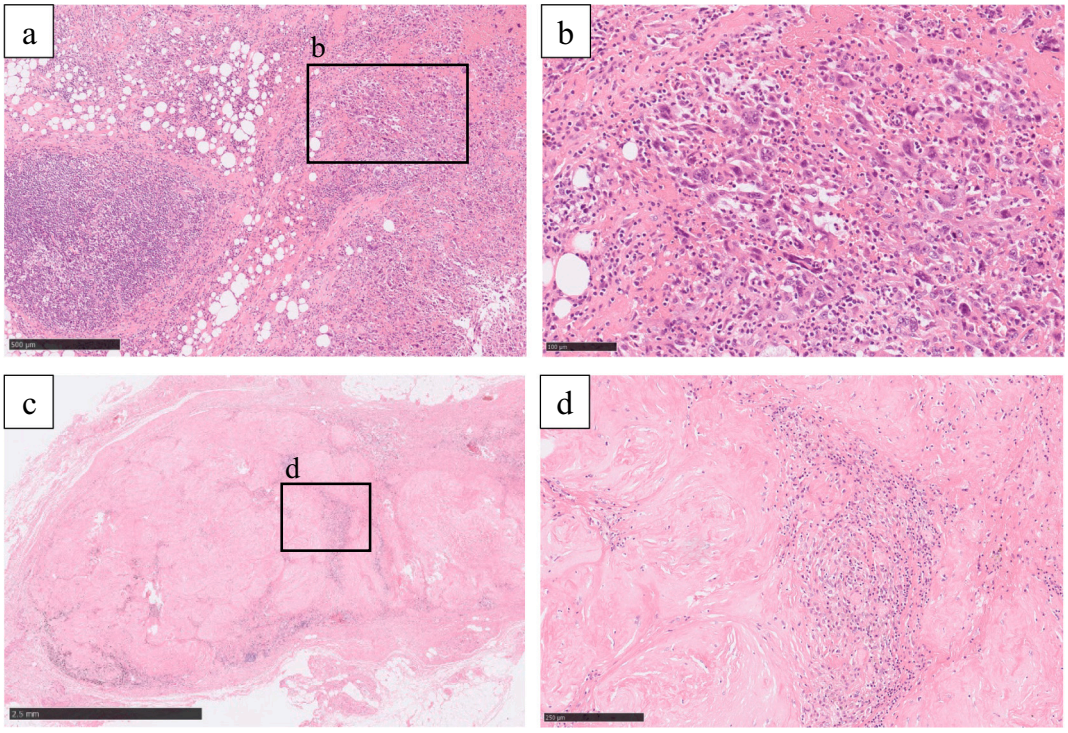

Fig. 4. Microscopic images of the dissected lymph nodes
(a) The supraclavicular lymph nodes containing the metastatic components of the neoplasm. (b) The metastatic lesion is mainly composed of sarcomatous spindle cells with highly atypical nuclei. (c) An extensive fibrosis is observed in the right recurrent nerve lymph node. (d) No viable tumor cells are observed here.

spindle cells showed massive proliferation.

The standard treatment strategy for esophageal carcinosarcoma has not yet been established, however surgical resection is considered one of the most reliable curative options. Although the efficacy of preoperative/postoperative adjuvant therapies has been demonstrated in various cancers, their safety and efficacy in carcinosarcoma remains to be elucidated. A prospective trial is impractical due to the small number of cases, and it is important to accumulate case reports in order to develop more accurate treatment strategies for carcinosarcoma. Using Pubmed and Scopus, we searched the literature for carcinosarcoma treated with CRT, and found nine cases identified since 2000 (summarized in Table 1) [15–19]. In these cases, the initial biopsy diagnosis was carcinosarcoma in six and SCC in three. Two patients achieved complete response with CRT alone, one of whom relapsed within three months. Seven patients underwent radical surgery. Long-term survival was achieved in six, and three patients died of distant metastasis. Although these cases are not enough to draw a definitive conclusion, CRT might not be the ideal treatment for carcinosarcoma. In our case, the residual sites were mainly composed of sarcomatous components, and squamous cell carcinoma was observed only in limited areas. Moreover, the newly appeared metastatic lesion on the supraclavicular lymph node consisted only of sarcomatous components. These findings suggested that the therapeutic effects on the sarcomatous components were not enough compared to that in SCC. Therefore, surgical resection with regional lymph node dissection should be performed for curative treatment when sarcomatous components are detected.

4. Conclusion

We presented a rare but clinically important case of carcinosarcoma showing rapid growth after dCRT. There are few reports of esophageal carcinosarcoma treated with CRT, and its safety and efficacy have not been fully verified. Carcinosarcoma may be diagnosed as SCC on endoscopic biopsy. Therefore, CRT may be unintentionally given for patients with latent carcinosarcoma. In cases of rapidly growing tumors after CRT, as in our present case, prompt surgical procedures should be considered with suspicion of sarcoma exacerbation.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Sources of funding

None declared.

Ethical approval

Ethical approval has been exempted from our institution for this case report.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Registration of research studies

None declared.

Guarantor

Yusuke Taniyama and Takashi Kamei.

CRediT authorship contribution statement

TY drafted the manuscript, and YT, FF, and HS supervised the writing of the manuscript. FF and HS contributed to pathological methodology and evaluation. YT and TK performed perioperative management of the patient. HS, MU, and TK supervised the entire process. All authors read

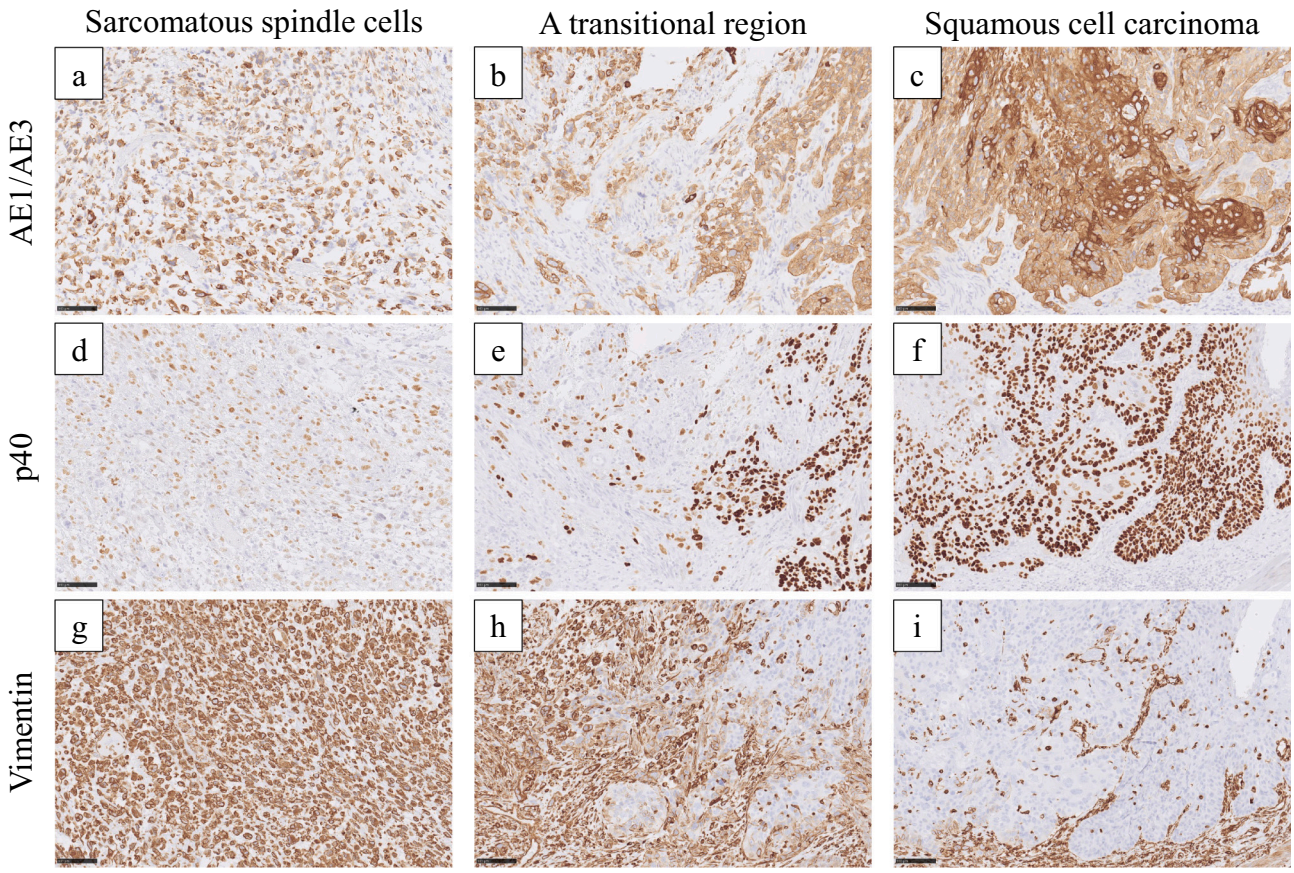

Fig. 5. Immunohistochemical findings of the tumors
Diffuse staining for cytokeratin (epithelial cell marker) is observed using an AE1/AE3 antibody cocktail in a) sarcomatous spindle cells, b) the transitional region, and c) squamous cell carcinoma. Weakly positive staining for p40 (a squamous-basal cell marker) is observed in d) sarcomatous spindle cells and e) the transitional region, whereas strong positive staining is observed in f) squamous cell carcinoma. Diffuse staining for vimentin (a mesenchymal cell marker) is observed in g) sarcomatous spindle cells and h) the transitional region, and very weak staining is observed in f) squamous cell carcinoma.

Table 1
Esophageal carcinosarcoma treated with chemoradiotherapy.

Author	Year	Age	Sex	Biopsy	Clinical Findings	CT	RT	Response	Surgical Resection	Pathological Findings	Outcome	Recurrence
Sanada	2006	58	M	C + S	cT4bN0	DTX + CDDP	66Gy	Non-CR	Bypass	–	8 months dead	Liver
Nakagawa	2009	71	M	C	cT1bN0	FP	60Gy	CR[a]	+	pT2N0	45 months alive	–
Zuiki	2009	50	M	C + S	cT3-4 N1	FP	62Gy	Non-CR	+	pT1bN1	36 months alive	–
Zuiki	2009	66	M	C	NA	FP	40.8Gy	Non-CR	+	pT1bN0	19 months alive	–
Kobayashi	2010	68	M	C + S	cT3N1	S-1 + CDDP	40Gy	Non-CR	+	pTisN0	60 months alive	–
Kobayashi	2010	72	M	C + S	cT3N1	FP	64Gy	CR	–	–	29 months alive	–
Kobayashi	2010	64	M	C + S	cT2N1	FP	38Gy	Non-CR	+	pT1aN1	11 months dead	Liver and bone
Katsuya	2017	67	F	C	cT1bN1	FP	50.4Gy	Non-CR	+	pT1bN0	10.9 months dead	Skin
Katsuya	2017	73	F	C + S	cT2N1	FP	41.4Gy	Non-CR	+	pT1bN0	47 months alive	–
Present case	2021	65	M	C	cT3N1	FP	60Gy	Non-CR	+	pT2N0M1[b]	12 months dead	Lung

C, carcinomatous lesion; S, sarcomatous lesion; CT, chemotherapy; FP, cisplatin+5-fluorouracil; S-1, oral tegafur/gimeracil/oteracil; CDDP, cisplatin; RT, radiotherapy; CR, complete response; NA, not available.
[a] Relapse after 3 months.
[b] Metastasis to non-regional lymph nodes.

and approved the final manuscript.

Declaration of competing interest

All authors declare no conflict of interest.

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.

References

[1] Y. Tachimori, S. Ozawa, H. Numasaki, R. Ishihara, H. Matsubara, K. Muro, T. Oyama, Y. Toh, H. Udagawa, T. Uno, Comprehensive registry of esophageal cancer in Japan, Esophagus 14 (2017) (2010) 189–214, https://doi.org/10.1007/s10388-017-0578-4.

[2] C.O. Sung, H. Choi, K.W. Lee, S.H. Kim, Sarcomatoid carcinoma represents a complete phenotype with various pathways of epithelial mesenchymal transition, J. Clin. Pathol. 66 (2013) 601–606, https://doi.org/10.1136/jclinpath-2012-201271.

[3] C.O. Sung, C.K. Park, S.H. Kim, Classification of epithelial–mesenchymal transition phenotypes in esophageal squamous cell carcinoma is strongly associated with patient prognosis, Mod. Pathol. 24 (2011) 1060–1068, https://doi.org/10.1038/modpathol.2011.59.

[4] R.A. Agha, T. Franchi, C. Sohrabi, G. Mathew, for the SCARE Group, The SCARE 2020 guideline: updating consensus Surgical CAse REport (SCARE) guidelines, Int. J. Surg. 84 (2020) 226–230.

[5] J.D. Brierley, M.K. Gospodarowicz, C. Wittekind, UICC TNM classification of malignant tumours, in: Oesophagus and Oesophagogastric Junction, 8th ed., Wiley-Blackwell, Oxford, 2017, pp. 57–62.

[6] Japanese Classification of Esophageal Cancer, 11th Edition: part II and III, Esophagus 14 (2017) 37–65, https://doi.org/10.1007/s10388-016-0556-2.

[7] H. Ishida, F. Fujishima, Y. Onodera, T. Konno-Kumagai, S. Maruyama, H. Okamoto, C. Sato, T. Heishi, T. Sakurai, Y. Taniyama, T. Kamei, H. Sasano, Esophageal carcinosarcoma with basaloid squamous cell carcinoma: a case report and review of the literature, Tohoku J. Exp. Med. 249 (2019) 255–263, https://doi.org/10.1620/tjem.249.255.

[8] R.R. Cha, W.T. Jung, H.W. Oh, H.J. Kim, C.Y. Ha, H.J. Kim, T.H. Kim, G.H. Ko, A case of metachronous development of esophageal squamous cell carcinoma in the patient with esophageal carcinosarcoma, Korean J. Gastroenterol. 64 (2014) 364, https://doi.org/10.4166/kjg.2014.64.6.364.

[9] A.K. Madan, A.E. Long, C.B. Weldon, B.M. Jaffe, Esophageal carcinosarcoma, J. Gastrointest. Surg. 5 (2001) 414–417, https://doi.org/10.1016/s1091-255x(01)80071-8.

[10] I. Akagi, M. Miyashita, H. Makino, T. Nomura, K. Ohkawa, T. Tajiri, So-called carcinosarcoma of the esophagus: report of a case, J. Nippon Med. Sch. 75 (2008) 171–174, https://doi.org/10.1272/jnms.75.171.

[11] L. Wang, Y. Lin, H. Long, H. Liu, H. Rao, Y. He, T. Rong, Y. Liang, Esophageal carcinosarcoma: a unique entity with better prognosis, Ann. Surg. Oncol. 20 (2013) 997–1004, https://doi.org/10.1245/s10434-012-2658-y.

[12] T. Yoshimoto, S. Kobayashi, K. Kanetaka, K. Kobayashi, Y. Nagata, M. Morita, Y. Isagawa, N. Kinoshita, M. Takatsuki, S. Eguchi, 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 (2018), https://doi.org/10.1186/s40792-018-0425-4.

[13] M. Hashimoto, H. Kitagami, H. Niwa, T. Kikkawa, T. Ohuchi, T. Takenouchi, M. Hosokawa, Prognosis and prognostic factors of esophageal spindle cell carcinoma treated by esophagectomy: a retrospective single-institution analysis, Esophagus 16 (2019) 292–299, https://doi.org/10.1007/s10388-019-00667-y.

[14] S. Iyomasa, H. Kato, Y. Tachimori, H. Watanabe, H. Yamaguchi, M. Itabashi, Carcinosarcoma of the esophagus: a twenty-case study, Jpn. J. Clin. Oncol. 20 (1990) 99–106.

[15] Y. Sanada, J. Hihara, K. Yoshida, Y. Yamaguchi, Esophageal carcinosarcoma with intramural metastasis, Dis. Esophagus 19 (2006) 119–131, https://doi.org/10.1111/j.1442-2050.2006.00551.x.

[16] S. Nakagawa, H. Yabusaki, O. Tanaka, Rapid-growth carcinosarcoma of the esophagus arising from 0-IIc squamous cell carcinoma after definitive chemoradiotherapy: a case report, Esophagus 6 (2009) 123–126, https://doi.org/10.1007/s10388-008-0181-9.

[17] T. Zuiki, Y. Hosoya, T. Ui, H. Haruta, K. Kurashina, S. Saito, A. Lefor, T. Niki, M. Nakazawa, Y. Yasuda, Therapeutic effectiveness of chemoradiotherapy for carcinosarcoma of the esophagus: two case reports and a review of the literature, Esophagus 6 (2009) 189–195, https://doi.org/10.1007/s10388-009-0187-y.

[18] D. Kobayashi, M. Koike, Y. Kodera, M. Fujiwara, G. Nakayama, A. Nakao, Carcinosarcoma of the esophagus treated with chemoradiotherapy: report of four cases, Esophagus 7 (2010) 119–125, https://doi.org/10.1007/s10388-010-0233-9.

[19] Y. Katsuya, Y. Honma, H. Taniguchi, K. Kato, N. Okita, A. Takashima, S. Iwasa, T. Hamaguchi, N. Boku, R. Umezawa, K. Inaba, Y. Ito, J. Itami, K. Koyanagi, H. Igaki, Y. Tachimori, Clinicopathological features and pathological evaluation of preoperative treatment of patients with resectable esophageal carcinosarcoma, Esophagus 14 (2017) 317–323, https://doi.org/10.1007/s10388-017-0579-3.