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CASE REPORT

Esophageal carcinosarcoma that disappeared pathologically by palliative radiotherapy alone

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Abstract

Only a few cases of esophageal granulocyte-colony-stimulating-factor (G-CSF)–producing esophageal carcinosarcoma are reported, and patients with G-CSF–producing tumors are typically considered to have poor prognosis. An 89-year-old man was examined for low-grade fever and dysphagia. Chest computed tomography revealed a huge 80-mm tumor on the thoracic esophagus without direct invasion to surrounding organs. Esophagogastroduodenoscopy (EGD) showed a huge mass occupying the esophageal lumen with a superficial flat lesion. Histopathological examination revealed that the tumor was composed of bizarre giant cells and pleomorphic spindle cells with hyperchromatic nuclei. Laboratory data showed aberrant elevation of leukocyte and neutrophil counts and G-CSF levels. The tumor was finally diagnosed as a G-CSF-producing esophageal carcinosarcoma, stage II (T2N0M0, Union for International Cancer Control-TNM Classification of Malignant Tumors, 8th edition). Considering his general condition, we performed palliative radiotherapy (45 Gy/15 fr) alone after consultation with surgeons and radiation oncologists. Follow-up EGD demonstrated the disappearance of the tumor, and the histological assessment of biopsy specimens confirmed no evidence of malignancy. The leukocyte count and G-CSF levels decreased within normal range. This is a very rare case of G-CSF-producing esophageal carcinosarcoma in which a pathologically complete response was achieved using palliative radiotherapy alone.

Keywords Esophageal carcinosarcoma · Palliative radiotherapy · Granulocyte-colony-stimulating factor

Introduction

Esophageal carcinosarcoma is a rare malignant neoplasm consisting of both carcinomatous and sarcomatous components. Esophageal carcinosarcoma reportedly accounts for 0.5–2.4% of all esophageal tumors [1, 2]. Although several treatments including endoscopic resection, chemotherapy, and chemoradiotherapy have been reported [3–5], standard strategies, except surgery, have not been established for treating esophageal carcinosarcoma. Unresectable esophageal carcinosarcoma is generally treated according to the protocols for esophageal cancers. However, the efficacy of radiotherapy alone has not been described until now.

In addition, there are a few reports of esophageal granulocyte-colony-stimulating-factor (G-CSF)-producing esophageal carcinosarcoma [6–10]. The G-CSF accelerates the clinical progression of the disease; therefore, patients with G-CSF-producing tumors are typically considered to have poor prognosis [6].

Here, we describe a case of G-CSF-producing esophageal carcinosarcoma in which a pathologically complete response was achieved by radiotherapy alone.

Case report

An 89-year-old man presented with low-grade fever and dysphagia comorbid with hypertension that was managed with oral medications. He drank alcohol (shochu: 400 mL daily) regularly and was a non-flusher. He never smoked. His Eastern Cooperative Oncology Group performance

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status was 1. Laboratory data indicated leukocytosis (leukocyte count 27,600/μL), neutrophilia (80.6% neutrophils), poor nutrition(Alb 2.8 g/dl), and an elevated serum level of C-reactive protein (5.1 mg/L). The serum G-CSF level was aberrantly elevated to 198 pg/mL (normal level < 39.0 pg/mL). The levels of tumor markers, such as carcinoembryonic antigen, cancer antigen 19-9, squamous cell carcinoma (SCC) antigen, neuron-specific enolase, and alpha-fetoprotein, were within normal limits. Computed tomography (CT) scans of the chest and abdomen demonstrated irregular thickening of the esophageal wall and narrowing of the lumen of the thoracic esophagus (Fig. 1a). There was no infiltration of other organs and no sign of locoregional lymph-node or distant metastasis. The 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET) examination showed only high FDG uptake in the thoracic esophagus with a standardized uptake value of 15.6 (Fig. 1b). Esophagogastroduodenoscopy (EGD) revealed a huge and relatively soft mass with an irregular surface occupying the esophageal lumen; it measured 8 cm and was located on the thoracic esophagus (Fig. 2a). The tumor was not stained by Lugol's iodine (Fig. 2b). There was a superficial flat lesion around the mass (Fig. 2c). Pathologic findings obtained from the biopsy specimens revealed that the tumor was composed of bizarre giant cells and pleomorphic spindle cells with hyperchromatic nuclei (Fig. 3a, b). There was a small focus of a sarcomatous component as well as moderately differentiated SCC in the same view. The immunohistochemical staining showed that the spindle cells were focally positive for CK5/6, p40, vimentin, and G-CSF (Fig. 3c–f).

The tumor was finally diagnosed as G-CSF–producing esophageal carcinosarcoma, clinical stage II (T2N0M0, Union for International Cancer Control-TNM Classification of Malignant Tumors, 8th edition). Considering

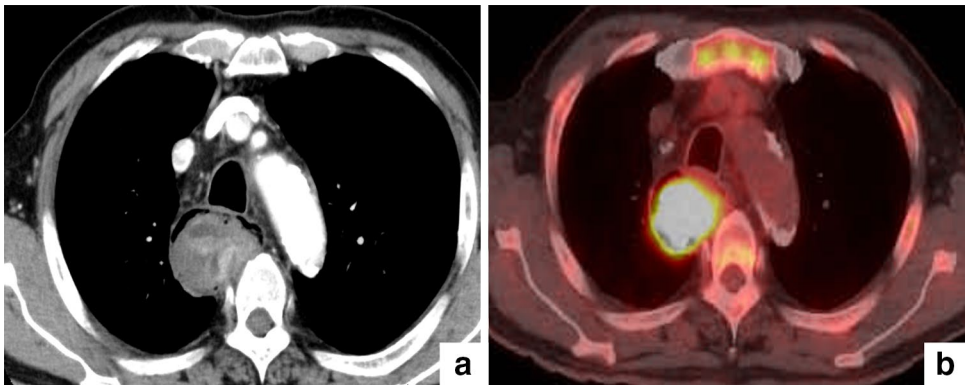

Fig. 1 Radiographic assessment of the tumor by computed tomography (CT) and 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET). **a** The CT scan demonstrates irregular thickening of the esophageal wall and narrowing of the lumen of the thoracic esophagus. **b** The FDG-PET scan shows high FDG uptake in the thoracic esophagus, with a standardized uptake value of 15.6

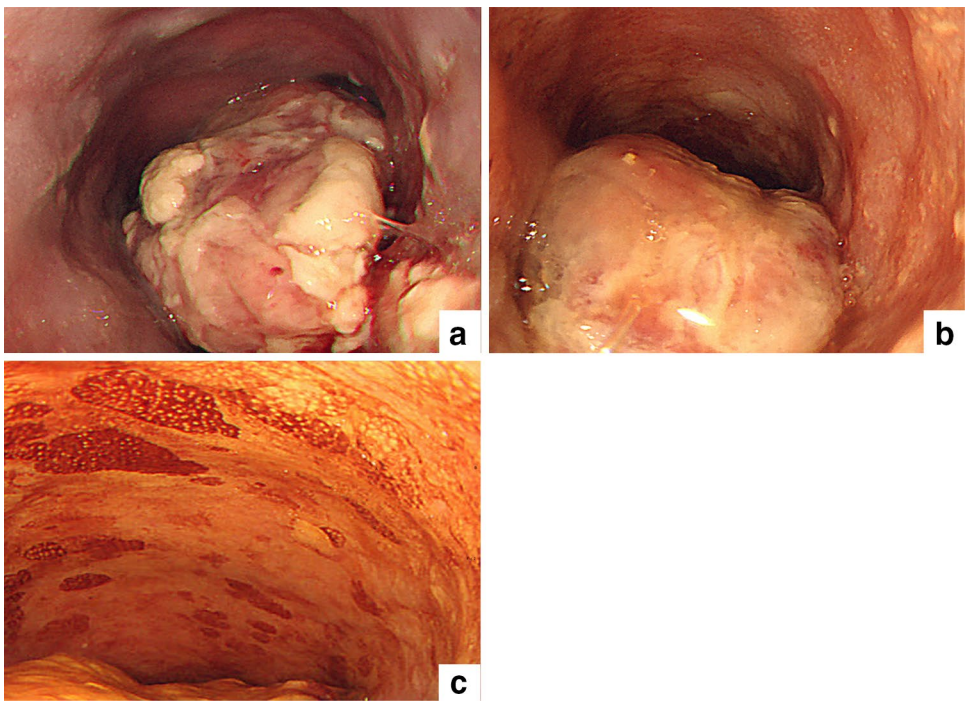

Fig. 2 Endoscopic appearance of the esophageal tumor. **a** Esophagogastroduodenoscopy reveals a huge mass with an irregular surface occupying the esophageal lumen of the thoracic esophagus. **b** The tumor is not stained by Lugol's iodine. **c** A superficial flat lesion is observed around the mass

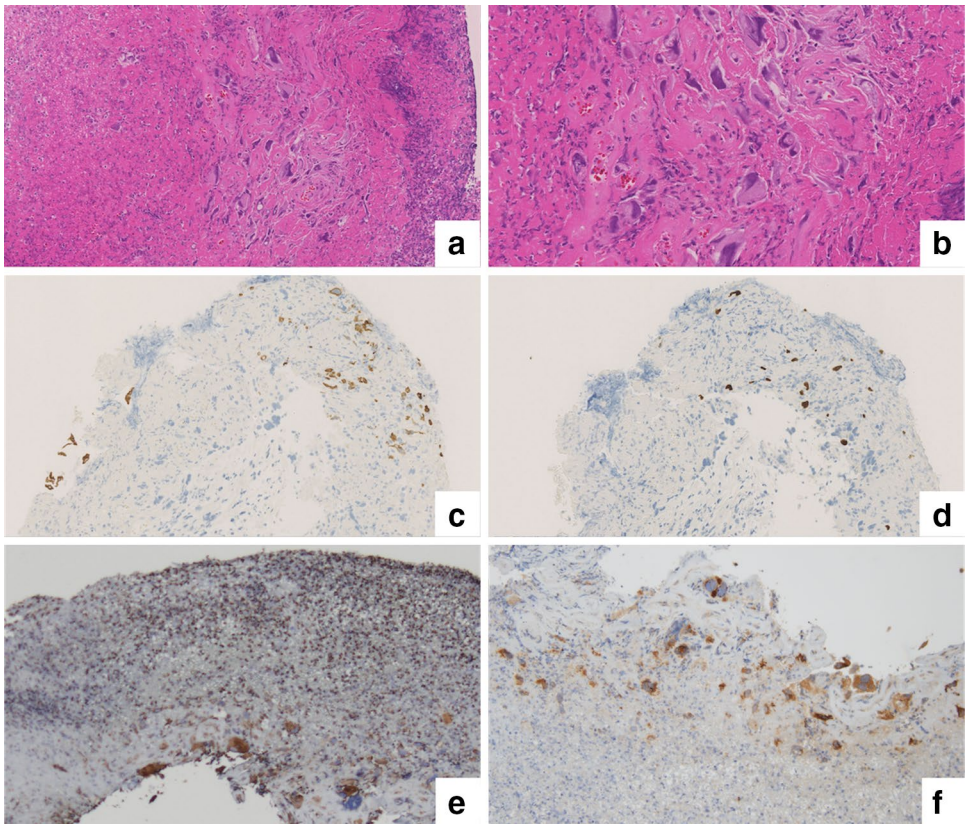

Fig. 3 Histopathologic evaluation of the esophageal tumor. **a, b** The tumor consists of bizarre giant cells and pleomorphic spindle cells with hyperchromatic nuclei (**a**; ×50, b; ×100). **c** Diffuse CK5/6 immunostaining of the sarcomatoid component (×50). **d** Diffuse p40 immunostaining of the sarcomatoid component (×50). **e** The immunohistochemical analysis showed that the tumor is positive for vimentin(×50). **f** The immunohistochemical analysis showed that the tumor is positive for G-CSF(×50)

his age, performance status, and poor nutrition, subtotal resection of the esophagus was invasive, and transhiatal esophagectomy was considered unsuitable because of the location and size of the tumor. Radical radiotherapy and definitive chemoradiotherapy were considered unsuitable because of its toxicity for him. Based on the evidence of radical radiotherapy and definitive chemoradiotherapy for esophageal carcinosarcoma, this case was thought not to achieve the complete response considering the characters of esophageal carcinosarcoma.

Therefore, after consultation with surgeons and radiation oncologists, we performed palliative radiotherapy (45 Gy/15 fr) alone for local control to prevent obstruction of the esophagus by the huge mass (Fig. 4a, b). As for adverse events of radiotherapy, only radiation pneumonitis

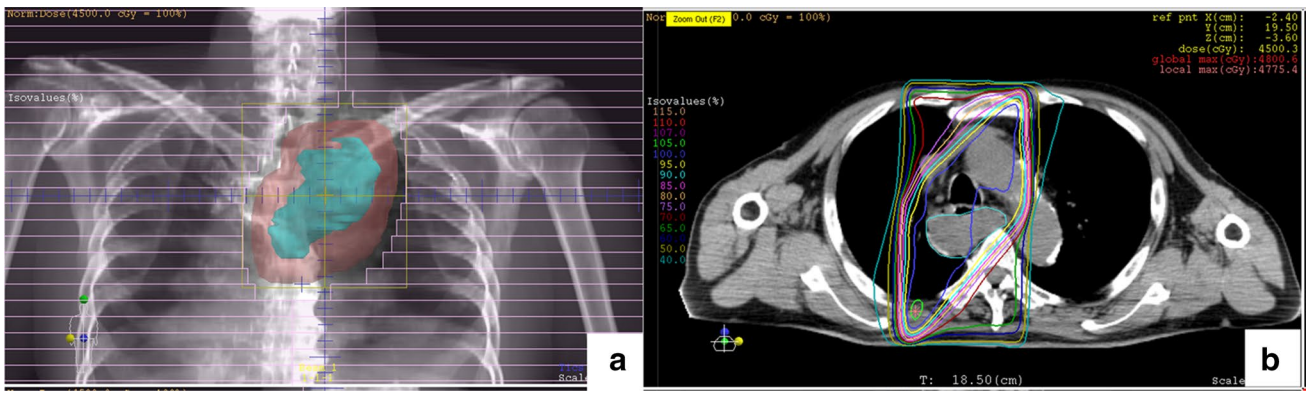

Fig. 4 Outline of radiotherapy. **a** The macroscopic tumor shown on computed tomography is delineated as a gross target volume, and the same volume is defined as the clinical target volume (shown in cyan). We added a 2-cm margin for the planning target volume (shown in red). Three-dimensional conformal radiotherapy (10 MV) was delivered using four ports. (b) Dose distribution of the radiotherapy. The isodose line of 95% is indicated by the yellow line

was detected on CT (grade 1 according to the Common Terminology Criteria for Adverse Events, version 4.0).

One month after radiotherapy, EGD revealed a remarkable reduction of the mass, which was visualized as a small polypoid lesion (Fig. 5a–c). Histologically, there was no evidence of malignancy in the biopsy specimens. Follow-up CT showed no residual tumor (Fig. 6). The leukocyte count and G-CSF levels decreased within normal range (Fig. 7). He remained free of disease for 25 months after radiotherapy.

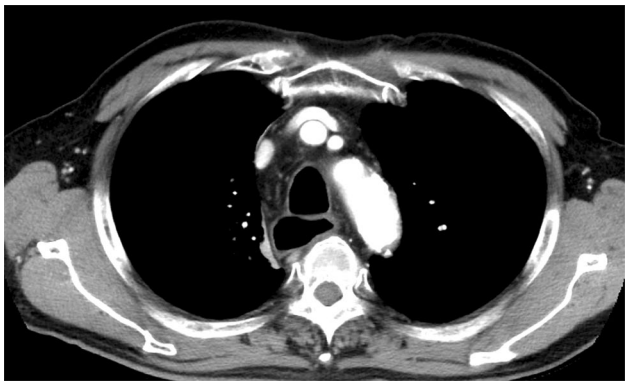

Fig. 6 Follow-up computed tomography showing no residual tumor

Discussion

Similar to SCC of the esophagus, esophageal carcinosarcoma occurs most often in middle-aged men with a history of smoking or drinking or both [11]. The clinical presentation of esophageal carcinosarcoma is similar to that of SCC with dysphagia. The lesion typically has as a polypoid shape that spreads superficially [12]. Because of intraluminal growth, esophageal carcinosarcoma manifests symptoms relatively early [13]. Clinically, esophageal carcinosarcoma is characterized by rapid growth [2]. Akagi et al. [14] reported that the doubling time of esophageal carcinosarcoma is about 2.2 months, whereas that of esophageal carcinoma is at least twice as long (about 5 months).

Standard treatment for esophageal carcinosarcoma, except operation, has not been established because of the small number of reports. Outcomes of esophageal carcinosarcoma treatments, such as radiation alone and chemoradiotherapy, have been reported in case reports, a single-center analysis, and multi-center-analysis, but we could not find

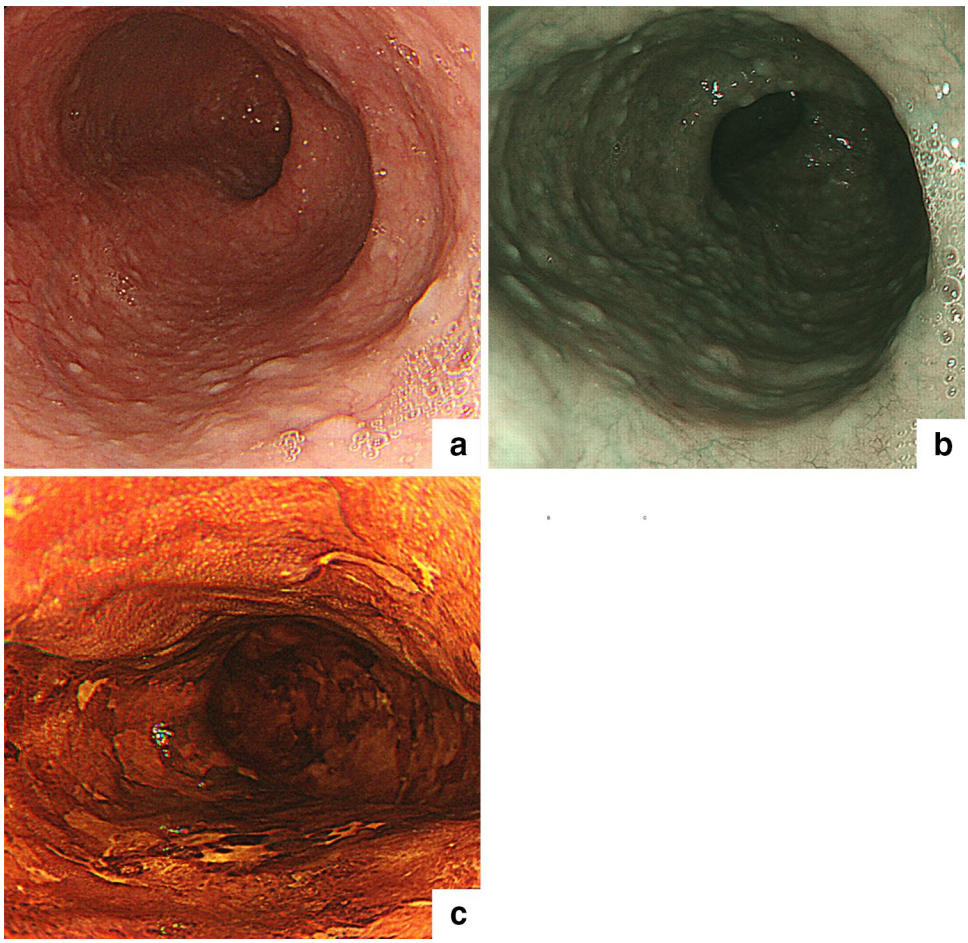

Fig. 5 Esophagogastroduodenoscopy 1 month after radiotherapy reveals a remarkable reduction of the mass, which was visualized as a small polypoid lesion (**a** white-light imaging, **b** narrow-band imaging, and **c** Lugol's iodine staining)

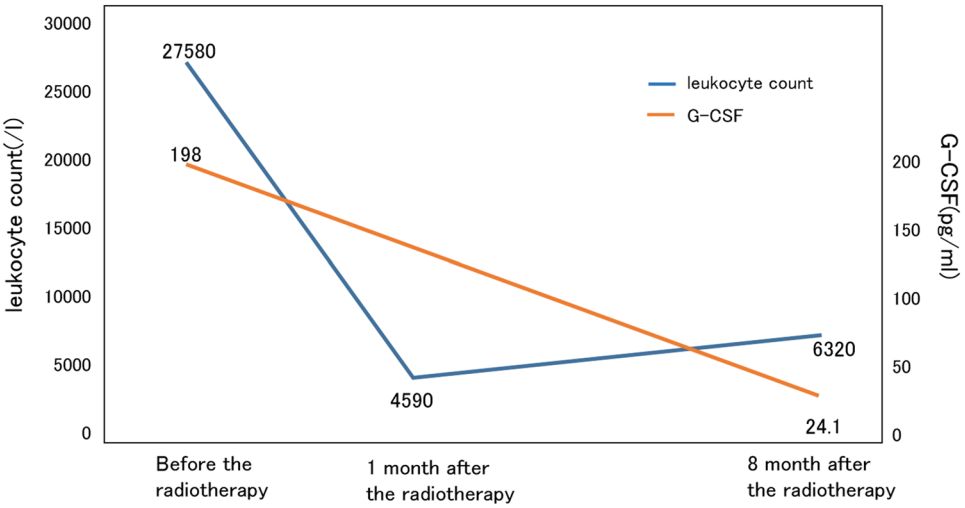

Fig. 7 Change in the serum leukocyte count and granulocyte-colony-stimulating-factor (G-CSF) levels during the course of radiotherapy

any systemic review or meta-analysis [3–5, 15–17]. Regarding esophageal cancer, Penniment et al. [18] reported that a short course of radiotherapy alone should be considered as a safe and well-tolerated treatment for dysphagia in patients with advanced or metastatic esophageal cancer. They concluded that palliative chemoradiotherapy showed a modest, but not statistically significant, increase in dysphagia relief compared with radiotherapy alone. Radiotherapy is a locally effective treatment for esophageal tumor. Radiotherapy alone might be useful for reducing the tumor volume in esophageal carcinosarcoma; however, it is unknown whether it can cure the malignancy. We could not find the reports of patients with esophageal carcinosarcoma who were cured by radiotherapy alone, so the indication for radiotherapy in the management of esophageal carcinosarcoma should be considered carefully. Ogasawara et al. [3] described a case of esophageal carcinosarcoma in which the tumor was reduced by neoadjuvant radiotherapy. In this case, carcinosarcoma was diagnosed as stage I (T1bN0M0) and treated with neoadjuvant radiotherapy (40 Gy). After radiotherapy, the patient underwent total esophagectomy with regional lymph-node dissection, and the tumor was finally diagnosed as pStage 0 (pT1aN0M0). However, the patient developed lung metastasis 14 months later and died 16 months postoperatively [3]. In our case, radiotherapy resulted in unexpected disappearance of the tumor, and we have carefully monitored the patient for signs of local recurrence or distant metastasis over several years. We were astonished by the complete regression of the huge mass, for which radical radiotherapy of 60 Gy or more is considered to be required accompanied by chemotherapy. We never thought that complete regression of the huge mass could be achieved with a dose of 45 Gy/15 fr. Recently, there was another surprising report that a lower irradiation dose contributed to a better outcome; in the clinical trial of Radiation Therapy Oncology Group 0617, concurrent chemoradiotherapy at a dose of 60 Gy for inoperable non-small cell lung cancer resulted in a better outcome than that at a dose of 74 Gy [19]. The outcome with a dose of 74 Gy was worse in overall survival and local control. Hence, this might suggest that the additional 14 Gy of the dose resulted in the local tumor becoming more refractory. There might be an unknown treatment parameter to explain this discrepancy. The effect of radiotherapy is known to be boosted by tumor-immunity reaction. After the emergence of immune checkpoint inhibitors, this boosting effect attracted attention by shrinking the tumor mass outside irradiation fields. This is called the abscopal effect, and it is sometimes reported with the use of immune checkpoint inhibitors [20]; nevertheless, it has been already reported before the development of immune checkpoint inhibitors [21]. Actually, we did not expect such a good response in our case. If we would like to gain the radical efficacy, we chose the definitive chemoradiotherapy or surgical treatment. We considered the palliative dose, 45 Gy/15 fr, which might result in improvement of symptoms, but could not prolong survival. Thus, the reason why 45 Gy/15 fr radiation brought the complete response remains unknown. Therefore, this case report is considered valuable. We do not know exactly why radiation had such a good response, but we made some speculations. One possible mechanism is immunological effect by irradiation, as stated previously. Recent development of immunoradiology revealed that irradiation activates and increases the immune reaction against neoantigen. Recently, Bruton Joe et al. reported a case of adenocarcinoma of the esophagus [22]. In this report, after palliative radiation therapy to the primary tumor and adjacent lymph nodes, a complete response was observed not only in the irradiated tissues, but also in non-irradiated metastatic lymph nodes. This is thought to be the result of boosting effect by tumor-immunity reaction in this report. In the same way as this report, we guessed that abscopal effect results in shrinking the tumor mass in our case. Experimental attempts to induce the abscopal effect

Table 1 Granulocyte-colony-stimulating-factor (G-CSF)-producing esophageal carcinosarcoma

Author	Age (year)	Sex	G-CSF (pg/ml)	Size (mm)	Depth	LN metastasis	Treatment	Prognosis
Ota	63	Male	286	40	T1	Negative	Surgery	Unknown
Maejima	80	Male	111	60	Unknown	Unknown	Best supportive care	Dead in 4 months
Sasaki	62	Male	108	85	T2	Positive	Surgery + chemotherapy	Dead in 5 months
Miyamoto	51	Male	48	80	T3	Positive	Surgery + chemotherapy	23 Months alive
Kobayashi	69	Male	86	50	T1	Negative	Chemotherapy + surgery	60 Months alive
Our case	89	Male	198	80	T2	Negative	Palliative radiotherapy	25 Months alive

also confirmed the boosting effect on irradiated tumors in a sarcoma model of mice [23]. Our clinical case may also be merited by this immunologic response; the short treatment period of 3 weeks and avoidance of systemic chemotherapy might have contributed to maintaining favorable immune reactions. If this hypothesis is expected to have a high probability, prophylactic nodal irradiation can be replaced by the systemic immune response, which we did not intend for so much in this case. Another speculation was that the necrosis inside the tumor had occurred in some degree. Then, even a low dosage, 45 Gy/15 fr, caused a good response.

The diagnostic criteria for G-CSF–producing tumors include marked leukocytosis, a high serum concentration of G-CSF, normalization of the leukocyte count after tumor resection, and evidence of G-CSF production in the tumor cells. The G-CSF accelerates the clinical progression of the disease, and G-CSF–producing tumors are typically considered to have poor prognosis [6]. To the best of our knowledge, five cases of G-CSF–producing esophageal carcinosarcomas have been reported (Table 1) [6–10]. Among them, four were treated by surgical resection and three were treated by chemotherapy; however, we could not find any report of a patient who was completely cured with radiotherapy alone. In our case, high FDG uptake was shown in the sternum. We consider that this high FGP uptake was due to the reactivity; perhaps, G-CSF produced by carcinosarcoma stimulated the sternum marrow. Diffuse FDG uptake in bone marrow induced by G-CSF producing carcinosarcoma must be taken into consideration. After radiotherapy (45 Gy/15 fr), the serum leukocyte count and G-CSF levels decreased within normal range.

Considering his general condition, radical radiotherapy and definitive chemoradiotherapy were thought to be too toxic. In addition, because limited evidence was available for esophageal carcinosarcoma, we decided to perform palliative radiotherapy (45 Gy/15 fr) alone for local control to prevent obstruction of the esophagus by the huge mass. Accordingly, radiotherapy alone led to complete response and improved the patient's symptoms, such as dysphagia. If this case did not achieve complete response, we did not plan the additional treatment such as radiotherapy or mild chemotherapy. In conclusion, we experienced a case of G-CSF-producing esophageal carcinosarcoma, which was achieved a pathologically complete response by palliative radiotherapy alone.

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Compliance with ethical standards

Conflict of interest Keiichi Kimura, Yoshito Hayashi, Keisuke Otani, Yoshiki Tsujii, Hideki Iijima, Fumiaki Isohashi, Kazuhiko Ogawa, and Tetsuo Takehara declare that they have no conflict of interest.

Human rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from patient for being included in the study.

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