

CASE REPORT

Multidisciplinary therapy for granulocyte-colony-stimulating factor producing carcinosarcoma of the esophagus: report of a case

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Introduction

Carcinosarcoma is a rare malignant tumor that consists of both carcinomatous and sarcomatous elements. To make a definitive diagnosis, the histological identification of the coexistence of these elements in the tumor and an immunohistochemical analysis is needed [1–4].

Malignant tumors are sometimes accompanied by leukocytosis and other leukemoid symptoms due to the production of granulocyte-colony-stimulating factor (G-CSF), as in paraneoplastic syndromes [5, 6]. G-CSF belongs to a family of hemopoietic growth factors that regulate the production of granulocytes and macrophages. G-CSF-producing tumors have increasingly been noted to develop in a variety of organs, including the gingiva [7], lung [8], stomach [9], and pancreas [10].

We report an extremely rare case of a G-CSF-producing carcinosarcoma of the esophagus.

Key Clinical Message

The granulocyte-colony-stimulating factor (G-CSF)-producing esophageal carcinosarcoma is extremely rare in esophageal cancer. In the present case, multidisciplinary therapy, which is surgical resection with preoperative chemotherapy, has been effectively treatment to granulocyte-colony-stimulating factor producing esophageal carcinosarcoma of the esophagus.

Keywords

Esophageal carcinosarcoma, granulocyte-colony-stimulating factor, neutrophilia, preoperative chemotherapy.

Case Report

A 69-year-old Japanese man was referred to our hospital for a further examination of his hematological disorder. The patient presented with fatigue, swallowing disturbance, low-grade fever, and weight loss. There was no evidence of systemic infection or hematological disease. Laboratory data showed leukocytosis, neutrophilia (leukocyte count 12,200/ μ L, 88.6% neutrophils), and elevated serum levels of C-reactive protein reaching 3.0 mg/dL. The level of serum G-CSF was elevated by 86.4 pg/mL (normal level; <39.0 pg/mL). Both radiography and endoscopy of the upper gastrointestinal tract revealed a tumor, 6 cm in diameter, on the posterior wall of the cervical esophagus (Figs. 1 and 2). The histological findings of the biopsy specimens from the tumor suggested sarcomatoid squamous cell carcinoma, and a few cells were positive for antibodies against G-CSF (Fig. 3). Neither metastasis nor invasion to the adjacent organs was

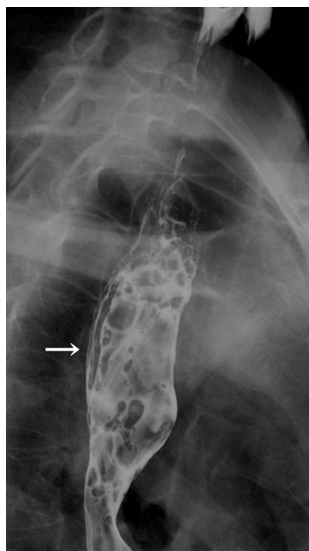


Figure 1. Radiography of the upper gastrointestinal tract. A polypoid tumor, 60 mm in size, was detected on the posterior wall of the cervical esophagus (arrow).

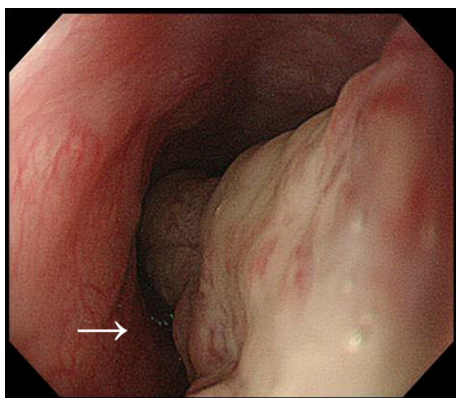


Figure 2. Endoscopy for the upper gastrointestinal tract. A polypoid and mobile tumor with an irregular surface was observed on the posterior wall of the cervical esophagus (arrow).

detected by the computed tomography scan. Although the leukocytosis improved (leukocyte count 5700/ μ L, 72.4% neutrophils) after chemotherapy using cisplatin combined with 5-fluorouracil, the level of serum G-CSF was still abnormally high immediately prior to the operation (Fig. 4). Video-assisted thoracoscopic esophagectomy and total pharyngo-laryngo-esophagectomy were performed at the same time. The macroscopic findings of the resected specimens revealed a lobulated polypoid tumor in the cervical esophagus (Fig. 5). The histological findings revealed that the tumor consisted of a carcinomatous element of squamous cell carcinoma and a sarcomatous element of spindle-shaped and pleomorphic-shaped cells (Fig. 6). In the immunohistochemical analysis, the protein vimentin

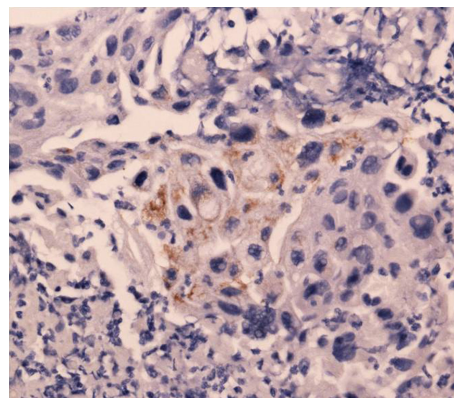


Figure 3. Immunohistochemical staining for the biopsy specimen was positive for granulocyte-colony-stimulating factor.

was diffusely positive, whereas that of AE1/AE3 was focally positive. The expressions of Desmin, S100, and α -smooth muscle actin were negative. The sarcomatous element was found in most of the proper mucosal layer. No tumor cells had invaded the submucosal layer and metastasized to the dissected lymph nodes. According to the TNM classification, the final stage of the tumor was defined as Stage I (T1N0M0) [11]. Though the tumor was mildly denatured after neoadjuvant chemotherapy, more than two-thirds of the tumor cells were viable. The serum level of G-CSF and the leukocyte count decreased to within the normal range after the resection (Fig. 4). The patient's recovery was uneventful, with neither tumor recurrence nor elevated serum levels of G-CSF occurring for 5 years after the surgery.

Discussion

Esophageal carcinosarcoma tends to assume a polypoid shape more frequently than does squamous cell carcinoma. The clinical symptoms and signs are similar to those of squamous cell carcinoma, including dysphagia, odynophagia, chest pain, and weight loss. The mean age of patients at diagnosis falls within their seventh decade, and a strong male preponderance exists [12]. Immunohistochemical analysis is the gold standard for the diagnosis of carcinosarcoma. CEA, EMA, pancreatin, chromogranin A, CD 56, and synaptophysin are highly specific markers for carcinomatous elements, whereas desmin, vimentin, and smooth muscle/sarcomeric actin signal sarcomatous elements [4, 13, 14].

There are two types of carcinosarcoma: the true carcinosarcoma and the so-called carcinosarcoma [15]. Three major theories have been proposed for the pathogenesis of carcinosarcoma. The first theory is that the spindle cell component develops in reaction to the carcinosarcoma. The second posits that two individual stem cells independently

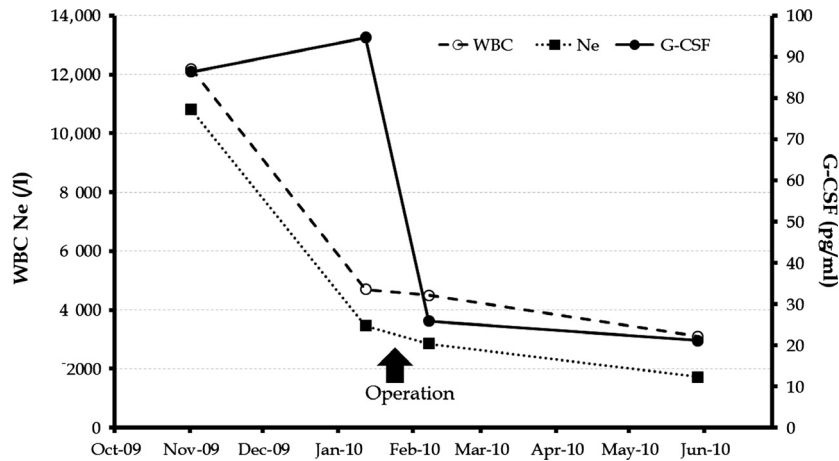


Figure 4. Changes in the serum levels of granulocyte-colony-stimulating factor (G-CSF) and in the counts of white blood cells (WBCs) and neutrophil WBCs (Ne).

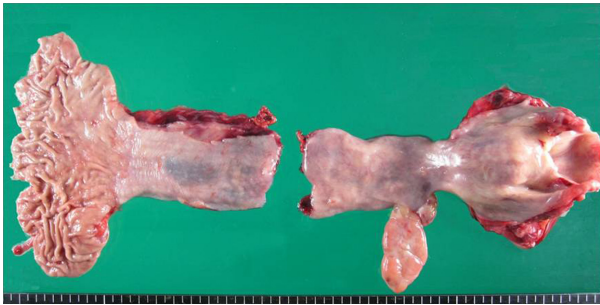


Figure 5. Macroscopic findings of the resected specimen showed a lobulated polypoid tumor that was 60 × 30 mm in diameter.

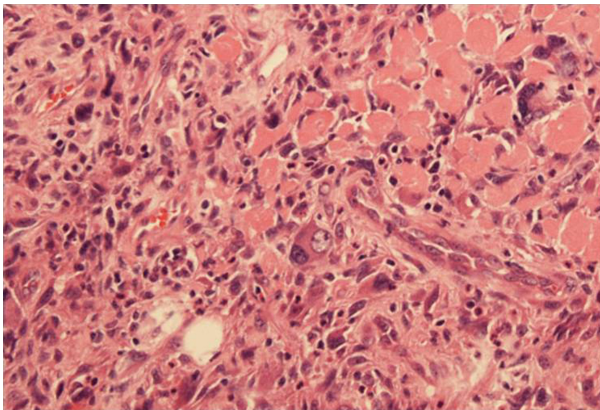


Figure 6. Histological findings after hematoxylin and eosin staining revealed a squamous cell carcinoma component and a sarcomatous component with spindle- and pleomorphic-shaped cells.

or simultaneously transform into malignant cells, progressing thereafter into separate tumors (true carcinosarcoma). The third theory suggests that the individual components are derived from the same malignant stem cell (so-called carcinosarcoma) [15]. This third theory has been genetically

demonstrated by the *TP53* mutation analysis of carcinosarcoma [16]. In the present case, the tumor was composed of both carcinomatous and sarcomatous elements. The transitional zone of those elements was observed, and no differentiated cells were detected in the sarcomatous elements, suggesting that both the carcinoma and sarcoma elements had the same origin. Thus, this case was diagnosed as a so-called carcinosarcoma of the esophagus.

Although several treatment modalities are available, including surgical resection, endoscopic resection, and chemoradiotherapy, no specific clinical management was recommended at the time [3, 5, 17, 18]. Iyomasa et al. reported that the prognosis of esophageal carcinosarcoma was poorer than that of squamous cell carcinoma in the esophagus due to the former's more frequent hematogenous metastasis [19]. Early detection and surgical resection may improve survival in a localized esophageal carcinosarcoma.

G-CSF-producing tumors have been reported in various organs since 1950 [20]. The diagnostic criteria for G-CSF-producing tumors include (1) marked leukocytosis, (2) a high serum concentration of G-CSF, (3) normalization of the leukocyte count after tumor resection, and (4) evidence of G-CSF production in tumor cells [8]. The present case contains a G-CSF-producing esophageal carcinosarcoma that meets all of these diagnostic criteria. To the best of our knowledge, five cases of G-CSF-producing esophageal carcinosarcomas, including the present case, have been reported in English (Table 1) [21–24]. All cases of the G-CSF-producing esophageal carcinosarcoma were reported in Japan. The serum levels of G-CSF in the six reported cases ranged from 48 to 286 pg/mL, and the tumor diameters ranged from 40 to 85 mm. Regarding to prognosis, the survival period was 4 months to more than 60 months.

G-CSF-producing tumors are considered to have a poor prognosis because the autocrine and paracrine

Table 1. Clinicopathological findings of granulocyte– colony-stimulating factor producing esophageal carcinosarcoma.

Author	Year	Age (year)	Sex	G-CSF (pg/ml)	Size (mm)	Type	Depth	LN metastasis	Surgery	Chemotherapy	Prognosis
Ota [21]	1998	62	Male	286	40	0-I	sm	Unknown	Resection	Unknown	Unknown
Maejima [22]	2007	80	Male	111	60	1	U	Unknown	No resection	None	Dead in 4 months
Sasaki [23]	2007	62	Male	108	85	1	mp	Positive	Resection	Performed	Dead in 5 months
Miyamoto [24]	2008	51	Male	48	80	1	Ad	Positive	Resection	Performed	23 months alive
Our case	2014	69	Male	86.4	50	0-Ip	mm	Negative	Resection	Performed ¹	60 months alive

LN, lymph node; sm, submucosa; mp, muscularis propria; Ad, adventitia; mm, muscularis mucosa.

¹Neoadjuvant chemotherapy.

mechanisms of G-CSF via the JAK2/STAT3 pathway contribute to the migration and proliferation of cancer cells [25–28]. G-CSF, therefore, accelerates the clinical progression of the disease [7, 29].

In experiments on G-CSF-expressing tumor cells both in vitro and in vivo, G-CSF dose-dependently stimulated the proliferation and migration of tumor cells. These cells also demonstrated increases in angiogenesis and the recruitment of neutrophils and macrophages [28]. Strong neovascularization causes rapid tumor growth and leads to the recruitment of many inflammatory cells [26–28]. In addition, reactive oxygen species (ROS) and nitric oxide (NO), which is produced by infiltrated neutrophils, caused DNA damage and genomic alterations in the epithelial cells [30–32]. Moreover, the invasive progression of the tumor and remodeling of the extracellular matrix are associated with the infiltration of inflammatory cells [32].

There is no feasible evidence of using neoadjuvant chemotherapy for esophageal carcinosarcoma. In the present case, neoadjuvant chemotherapy with 5-fluorouracil plus cisplatin was performed because the Japan Clinical Oncology Group (JCOG) 9907 study recommended neoadjuvant chemotherapy followed by surgery as a standard treatment for localized advanced squamous cell carcinomas of the thoracic esophagus [33, 34]. In addition, G-CSF-producing tumors have an aggressive clinical course [7, 9, 10, 35]. Chemotherapy with 5-fluorouracil plus cisplatin seemed to be partially effective in the present case, as the leukocytosis was improved, though the serum level of G-CSF was not decreased. Laryngo-pharyngo-esophagectomy was performed in a good condition. Moreover, the pathological findings of the resected specimen revealed that the tumor was mildly denatured. Generally, the prognosis of the G-CSF-producing tumors is poor. Therefore, early detection and multidisciplinary therapy are important for curing G-CSF-producing esophageal carcinosarcomas, due to the current lack of a specific approach. Recently, an in vitro study showed that expressing the JAK2/STAT3 pathway of G-CSF tumors contributed to chemo-resistance against cisplatin and paclitaxel [27]. Targeted therapies to inhibit the JAK2/STAT3

pathway are expected to increase the sensitivity of chemotherapy to G-CSF-expressing tumors in the future.

In conclusion, the present report summarizes our experience in treating a patient with an extremely rare G-CSF-producing esophageal carcinosarcoma. In such cases, it is important to make an early diagnosis and determination of a therapeutic strategy, especially to improve the prognosis of a patient with such a tumor.

Conflict of Interest

None declared.

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