Esophageal Carcinosarcoma that was Diagnosed as a Granulocyte-colony Stimulating Factor and Interleukin-6-producing Tumor with a Tumor Fever: A Case Report

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Abstract:
A 51-year-old man visited our hospital with a main complaint of precordial pain, difficulty swallowing, and pyrexia. The patient was diagnosed with esophageal carcinosarcoma, based on the characteristic morphology noted on upper gastrointestinal endoscopy and histology tests, and he underwent surgical treatment. His preoperative blood granulocyte-colony stimulating factor (G-CSF) and interleukin-6 (IL-6) levels were high, and the surgical specimens were positive in both immunohistochemical tests; therefore, he was diagnosed with a G-CSF- and IL-6-producing tumor. When pyrexia is seen as a paraneoplastic symptom, it is important to consider and investigate the possibility of a cytokine-producing tumor.

Key words: esophageal carcinosarcoma, granulocyte-colony stimulating factor, interleukin-6, tumor fever


Introduction
There are a number of reports on granulocyte-colony stimulating factor (G-CSF)-producing tumors in patients with malignant esophageal tumors; however, reports on tumors producing both G-CSF and interleukin-6 (IL-6) are rare. We herein report a rare case in which radical surgical therapy for esophageal carcinosarcoma with persistent pyrexia and inflammatory findings resulted in the resolution of a postoperative fever, and the carcinosarcoma was diagnosed as a G-CSF- and IL-6-producing tumor. We also discuss the pertinent literature.

Case Report
We evaluated the case of a 51-year-old man. His main complaints were precordial pain, difficulty swallowing, and a fever. At around 20 years old, he experienced a left leg fracture. He was not taking any oral medication. For the past 30 years, he had drunk 1,500 mL per day of beer and smoked 20 cigarettes per day.

The patient developed discomfort in the anterior chest and difficulty swallowing, beginning one month before presenting at the hospital. He developed a fever of around 38°C at 1 week before admission and became aware of precordial pain. Eating food became difficult, so he visited our department for consultation. An esophageal tumor was suspected, based on a simple computed tomography (CT) scan, and he was admitted on an emergency basis for a detailed examination and treatment.

On an examination, the patient was 182.5 cm tall, his weight was 58.4 kg, his body mass index was 17.5, his blood pressure was 129/85 mmHg, his pulse rate was 97 beats per min, and his body temperature was 38.0°C. The patient was conscious and lucid, with no jaundice of the...
bulbar conjunctiva and no anemia of the palpebral conjunctiva. The superficial lymph nodes were not palpable, and his abdomen was flat and soft, with no tenderness.

On admission, his blood test findings were as follows: the white blood cell (WBC) count was $12.8 \times 10^3 / \mu L$, and the platelet count was $414.0 \times 10^3 / \mu L$, both of which were elevated. Biochemical tests indicated a total protein level of $5.9 \, g/dL$ and albumin level of $2.4 \, g/dL$, and hypoproteinemia and hypoalbuminemia were present. The C-reactive protein (CRP) level was high, at $15.5 \, mg/dL$, indicating that an inflammatory response was present. The patient’s tumor markers were normal (Table 1).

Contrast CT revealed a tumorous lesion with internal heterogeneity, occupying approximately 10 cm of the lumen in a cranio-caudal direction in the upper and middle thoracic esophageal area. The right paratracheal lymph nodes were enlarged, and metastasis was suspected (Fig. 1). Simple magnetic resonance imaging (MRI) revealed an esophageal lesion part that exhibited high signals on both T2-weighted and diffusion-weighted images. The esophageal wall was intact, and there was no apparent infiltration of the airway or aorta (Fig. 2).

Upper gastrointestinal endoscopy was performed. An Ip-type lesion was found in the lumen at 27 to 37 cm from the incisors. The region of origin was suspected to be at 7 o’clock. The mucosa surrounding the lesion was normal, as seen on narrow-band imaging. Biopsy tissue imaging showed proliferation of spindle-shaped tumor cells, and these cells were S100 (focal+), c-kit (-), DOG1 (-), desmin (-), SMA (-), CK AE1/AE3 (-), and CD34 (-). Approximately 40% of the cells were positive for Ki67. The findings were HMB45 (-), Melan-A (-), and negative for malig-

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**Table 1. Laboratory Data on Admission.**

<table>
<thead>
<tr>
<th>[Peripheral blood]</th>
<th>[Blood chemistry]</th>
<th>[Serum markers]</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC 12.8×10^3 /μL</td>
<td>TP 5.9 g/dL</td>
<td>β-D-glucan 6 pg/mL</td>
</tr>
<tr>
<td>Neutro 76.9 %</td>
<td>Alb 2.4 g/dL</td>
<td>CMV antigenemia (-)</td>
</tr>
<tr>
<td>Lymph 9.6 %</td>
<td>T-bil 0.5 mg/dL</td>
<td>HBs Ag (-)</td>
</tr>
<tr>
<td>Mono 5.5 %</td>
<td>AST 9 IU/L</td>
<td>HCV Ab (-)</td>
</tr>
<tr>
<td>Eosino 7.3 %</td>
<td>ALT 9 IU/L</td>
<td>HIV Ag/Ab (-)</td>
</tr>
<tr>
<td>Baso 0.7 %</td>
<td>LDH 157 IU/L</td>
<td></td>
</tr>
<tr>
<td>RBC 3.26×10^6 /μ</td>
<td>ALP 151 IU/L</td>
<td></td>
</tr>
<tr>
<td>Hb 10.6 g/dL</td>
<td>γ-GTP 61 IU/L</td>
<td>CEA 2.69 ng/mL</td>
</tr>
<tr>
<td>Hct 32.7 %</td>
<td>BUN 6.9 mg/dL</td>
<td>CA19-9 16.9 U/mL</td>
</tr>
<tr>
<td>Plt 414.0×10^3 /μ</td>
<td>Cre 0.5 mg/dL</td>
<td>SCC 0.6 ng/mL</td>
</tr>
<tr>
<td>RBC 3.26×10^6 /μ</td>
<td>K 4.4 mEq/L</td>
<td></td>
</tr>
<tr>
<td>Hb 10.6 g/dL</td>
<td>HbA1c 6.1 %</td>
<td></td>
</tr>
<tr>
<td>Hct 32.7 %</td>
<td>CRP 15.8 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Plt 414.0×10^3 /μ</td>
<td>Fibrinogen 0.089 ng/mL</td>
<td></td>
</tr>
<tr>
<td>D-dimer 3.4 μg/mL</td>
<td>Procalcitonin 0.089 ng/mL</td>
<td></td>
</tr>
</tbody>
</table>

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**Figure 1.** Contrast-enhanced computed tomography scan. A tumorous lesion with internal heterogeneity, occupying approximately 10 cm of the lumen in the cranio-caudal direction in the upper and middle thoracic esophageal area. The right paratracheal lymph nodes were enlarged, and metastasis was suspected.
Figure 2. A simple MRI scan. Part of the lesion exhibited a high signal on a T2-weighted image. The esophageal wall was intact, and there was no apparent infiltration of the airway or aorta. MRI: magnetic resonance imaging

Figure 3. Upper gastrointestinal endoscopy. a) An Ip-type lesion was found in the lumen at 27 to 37 cm from the incisors. The region of origin was suspected to be at 7 o’clock. b) The mucosa surrounding the lesion was normal, as seen on narrow-band imaging. c) Pathology of the biopsy specimen showed the proliferation of spindle-shaped tumor cells, and these cells were S100 (focal+), c-kit (-), DOG1 (-), desmin (-), SMA (-), CK AE1/AE3 (-), and CD34 (-). Approximately 40% of the cells were positive for Ki67. The findings were HMB45 (-), Melan-A (-), and negative for malignant melanoma, indicating high-grade spindle cell sarcoma (Hematoxylin and Eosin staining ×100).

After admission, the patient had a persistent fever higher than 38°C without shivering, but we were unable to locate

nant melanoma, indicating high-grade spindle cell sarcoma (Fig. 3).
an infection. Various culture tests, including blood cultures, were performed multiple times, but they were all negative. Antibiotics were ineffective, and the fever was diagnosed as a tumor fever.

Based on each of the aforementioned tests after admission, and on the characteristic morphology and biopsy findings, esophageal carcinosarcoma was the primary consideration. Although the diagnosis based on the biopsy was spindle cell sarcoma, the characteristic morphology of the tumor excluded the possibility of esophageal gastrointestinal stromal tumor (GIST), which takes the form of a submucosal tumor (SMT). On day 30 of hospitalization, the patient underwent thoracoscopic-assisted esophagectomy and gastric tube reconstruction. On a resected specimen, a pedunculated tumor measuring 10×5×2.5 cm growing extramurally into the esophageal lumen was found (Fig. 4).

On histopathology, the tumor image consisted of spindle-shaped, atypical, multi-rhombic cells proliferating to form a solid mass in some areas. Some areas had intermixed areas of poorly differentiated to moderately differentiated squamous cell carcinomas, which had infiltrated near the muscularis propria. The condition was diagnosed as a carcinosarcoma that was mainly comprised of undifferentiated sarcoma components. A slightly depressed lesion measuring 2.0×1.5 cm was found in the area of the esophagus surrounding the tumor, and histologically squamous cell carcinoma was found within the mucosal membrane. Diffuse neutrophil infiltration was noted on the tumor surface layer with bleeding and necrosis. The resection stump was negative, but metastasis of a poorly differentiated squamous cell carcinoma was found in part of the lymph node. The ultimate diagnosis was esophageal carcinosarcoma pT1b-SM3, pN1, M0, med, INFa, l1, v1, Stage II (Fig. 5).

Immunostaining with anti-G-CSF antibodies and anti-IL-6 antibodies both revealed positive cells only in the sarcoma component. G-CSF- and IL-6-positive cells were found in proportions of approximately 13% and 20%, respectively, with moderate or greater positivity.

Postoperatively, the patient’s fever abated, beginning on postoperative day 2. On day 7, the WBC count was 5.5×10^3/μL, the platelet count was 313×10^3/μL, and the CRP level was 3.57 mg/dL. Four weeks after surgery, the WBC count was 5.8×10^3/μL, the platelet count was 313×10^3/μL, and the CRP level was 0.15 mg/dL, indicating an improvement in inflammatory findings and thrombocytosis. The patient’s entire clinical course is shown in Fig. 6.

Both blood G-CSF and IL-6 in the serum were elevated the day before surgery, with a G-CSF of 66.8 pg/mL (reference value: 10.5-57.5 pg/mL) and IL-6 of 26.6 pg/mL (reference value: ≤2.41 pg/mL); the IL-6 levels were particularly high.

The patient’s postoperative progress was good; therefore, he was discharged on day 17. His progress has been monitored on an outpatient basis since discharge. Postoperative chemotherapy was considered, but the patient did not agree with the suggestion. At 5 months after surgery, the blood G-CSF level was 25.8 pg/mL, and the IL-6 level was 0.834 pg/mL, confirming that both had fallen to within the reference ranges. However, seven months after surgery, recurrence was found in the left supraclavicular fossa and mediastinal lymph nodes. Under the patient’s agreement, chemoradiotherapy (radiation: 2 Gy×30 times, total 60 Gy, chemotherapy: 5-fluorouracil 800 mg/m² day 1-5, cisplatin 80 mg/m² day 1; 2 courses) was started.

**Discussion**

The concept of carcinosarcoma was first advocated by Virchow in 1864 and is a general term for a tumor with tumorous proliferation of both epithelial and non-epithelial components within a single tumor (1). Esophageal carcinosarcoma was first reported by Von Hansemann (2) in 1904 and was first reported in Japan by Mizukake (3) in 1929. Akutsu et al. (4) reported that the incidence of this tumor accounts for approximately 0.56% of all malignant esophageal tumors, and the male-to-female ratio is approximately 7:2, with more men developing the condition than women. People in their 50s and 60s (mean age: 61.8) are the most susceptible, and there is a high incidence of pedunculated morphology, accounting for 72% of all tumors. The tumors commonly develop in the middle section of the esophagus, and patients with tumors with large diameters and those
positive for vascular invasion are said to have a poor prognosis (5). Based on the morphological characteristics, the onset of symptoms such as dysphagia is thought to occur earlier than in patients with normal esophageal cancer (6), but the depth of invasion tends to be shallower than that for rapid-growth cancer. Almost all polypoid lesions have a sarcomatoid component, while the carcinoma components in the stem and base are often superficial carcinomas. Therefore, it is thought that sarcomatoid metaplasia occurs on the original, superficial carcinoma, and only this sarcomatoid component grows rapidly into a polyp towards the lumen (7).

The present patient had persistent pyrexia prior to surgery as well as an elevated WBC and thrombocyte count and CRP level. Infection was ruled out using various culturing and imaging tests, so we investigated the possibility of a tumor fever that was caused by a cytokine-producing tumor. The results of our investigation showed that the preoperative blood G-CSF and IL-6 levels were both elevated, and the resected specimens were positive for both stains. Postoperatively, the patient’s fever abated, and the WBC count, CRP, blood G-CSF and IL-6 levels, all normalized after surgery.

A tumor fever is a sign of paraneoplastic syndrome is characterized by a lack of shivering. In a report by Baicus et al. (8) in 2003, 41 of 164 (25%) patients with a fever of an undetermined etiology had malignant tumors, and Klastersky et al. (9) reported that a fever was seen in 47 of 6,608
Table 2. Japanese Case Reports of G-CSF and IL-6-producing Carcinosarcoma of the Esophagus.

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Site</th>
<th>Macrotumor type</th>
<th>Tumor diameter (cm)</th>
<th>Stage</th>
<th>Treatment</th>
<th>Temp (°C)</th>
<th>Blood G-CSF (pg/mL)</th>
<th>Blood IL-6 (pg/mL)</th>
<th>Pathological G-CSF-producing cells</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujimori&lt;sup&gt;10&lt;/sup&gt; (2003)</td>
<td>76</td>
<td>M</td>
<td>Mt</td>
<td>0-Ip</td>
<td>11.0</td>
<td>I</td>
<td>Surgery</td>
<td>&gt;38.0</td>
<td>101</td>
<td>77.1</td>
<td>Sarcoma cells</td>
<td>Died at 12 months</td>
</tr>
<tr>
<td>Tamura&lt;sup&gt;7&lt;/sup&gt; (2011)</td>
<td>47</td>
<td>M</td>
<td>Mt-Lt</td>
<td>I</td>
<td>6.0±2.6</td>
<td>II</td>
<td>Surgery</td>
<td>39.8</td>
<td>Unknown</td>
<td>-</td>
<td>Sarcoma cells</td>
<td>Died at 16 months</td>
</tr>
</tbody>
</table>

G-CSF: granulocyte colony-stimulating factor, IL-6: interleukin-6

We experienced a rare case in which radical surgery was performed for a patient with esophageal carcinosarcoma accompanied by a high fever who was diagnosed with a G-CSF- and IL-6-producing tumor. When pyrexia is seen as a paraneoplastic symptom, it is necessary to consider that a cytokine-producing tumor may be present.

The authors state that they have no Conflict of Interest (COI).

References

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