Granulocyte-colony-stimulating factor producing esophageal squamous cell carcinoma: a report of 3 cases

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Abstract Although different types of granulocyte-colony-stimulating factor (G-CSF)-producing carcinomas have been reported, G-CSF-producing esophageal squamous cell carcinoma (SCC) is extremely rare. The prognosis of G-CSF-producing esophageal cancer has generally been reported to be very poor. Here, we report three cases of G-CSF-producing SCC who were successfully treated by use of multimodal therapy.

Keywords G-CSF-producing tumor · Squamous cell carcinoma · Multimodal treatment

Introduction

Different types of granulocyte-colony-stimulating factor (G-CSF)-producing carcinomas have been reported. These tumors are characterized by aggressive growth resulting in very poor prognosis [1]. Increased levels of serum G-CSF in patients with these tumors cause elevated neutrophil

production in the bone marrow and peripheral leukocytosis. G-CSF-producing esophageal squamous cell carcinoma (ESCC) is extremely rare, and very poor prognosis has been reported. We report herein 3 cases of patients with G-CSF-producing ESCC who were successfully treated by use of multimodal treatment.

Case 1

A 59-year-old Japanese man presented with nausea, vomiting, and bloody stools. Upper gastrointestinal endoscopy revealed a tumor protruding into the lower esophagus, and the pathological diagnosis of the biopsy specimen was squamous cell carcinoma (SCC) (Fig. 1a). Computerized tomography (CT) revealed a tumor without obvious metastases located in the lower esophagus (Fig. 1b). Although the white blood cell count (WBC) was significantly elevated to 38,780/ μ l and C-reactive protein (CRP) was 0.35 mg/dl, there were no other abnormal data from biochemical analysis and a coagulation study. Because a G-CSF-producing tumor was suspected, the serum G-CSF concentration was measured, and found to be 241 pg/ml (normal range <2 pg/ml), and the patient was diagnosed with a G-CSF-producing ESCC. He underwent esophagectomy, and the WBC and G-CSF concentration decreased to normal ranges by postoperative day 7. Histological examination revealed moderately differentiated SCC (Fig. 1c) with a pathological stage of T3N1M0 (stage III). Seven months after surgery, the patients WBC increased to more than 20,000/ μ l, and an increased serum G-CSF (180 pg/ml) was also observed. CT revealed a lung metastasis. He was treated by chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (DCF), and remains alive 13 months after surgery.

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Fig. 1 **a** Upper gastrointestinal endoscopy revealed a type 1 tumor in the lower esophagus. **b** CT scan revealed a tumor located in the lower esophagus without definite invasion of adjacent organs and lymph nodes, or distant metastasis. **c** Histopathological findings of the primary tumor. The tumor was composed of moderately differentiated squamous cell carcinoma ($\times 40$)

Case 2

A 58-year-old Japanese man presented with dysphagia. Upper gastrointestinal endoscopy revealed an ulcerated tumor in the lower esophagus which was diagnosed as SCC by biopsy (Fig. 2a). CT revealed a tumor in the lower esophagus with metastasis in the right cardiac lymph node (Fig. 2b). His WBC was 52,000/ μ l and CRP was 0.22 mg/dl. There were no other abnormal laboratory findings. The serum G-CSF concentration was 197 pg/ml, suggesting a G-CSF-producing ESCC. Two courses of neoadjuvant chemotherapy using DCF were performed, with subsequent decrease of the WBC and G-CSF concentrations to normal ranges. He underwent esophagectomy and histopathological examination revealed a pathological complete response (pCR) (Fig. 2c). He remains alive without recurrence 17 months after diagnosis.

Case 3

A 75-year-old Japanese man presented with nausea as his chief complaint. Upper gastrointestinal endoscopy revealed

a protruding tumor at the esophagogastric junction which was diagnosed as SCC by biopsy (Fig. 3a). 18 F-fluorodeoxyglucose positron emission tomography (FDG/PET) revealed a tumor located at the esophagogastric junction with multiple lymph node metastases (Fig. 3b). The WBC was 26,200/ μ l and CRP was 8.44 mg/dl. There were no other abnormal laboratory findings. His serum G-CSF concentration was 239 pg/ml, and he was diagnosed with a G-CSF-producing ESCC. He underwent systemic chemotherapy with the DCF regimen, for unresectable advanced ESCC with distant metastasis. After 2 courses of chemotherapy, repeat FDG/PET revealed a marked decrease in FDG accumulation both in the primary and in the metastatic lesions (Fig. 3c), and the WBC and G-CSF concentrations decreased to normal ranges. The patient is still undergoing chemotherapy and remains alive 3 months after diagnosis.

Discussion

G-CSF-producing carcinomas have been reported for lung, renal, gynecologic, pancreatic, hepatobiliary, gastric, and colorectal cancers [2–9]. Although G-CSF production has

Fig. 2 **a** Upper gastrointestinal endoscopy revealed a type 2 tumor in the lower esophagus. **b** CT revealed a tumor located in the lower esophagus and right cardia lymph node metastasis without definite invasion of adjacent organs, or distant metastasis. **c** High accumulation was observed in both the primary lesion and the lymph node metastasis by PET. Abnormal accumulation of SUV max10.8 was observed in the primary lesion. **d** No viable cancer cells were observed. Histopathological examination revealed a pathological complete response ($\times 40$)

been observed, irrespective of the involved organs or histologic types, the actual frequency of G-CSF-producing tumors is unknown, because there have been no autopsy studies. Although only 4 cases of G-CSF-producing ESCCs have been reported in the literature [10–13], we treated 3 cases within a relatively short period of time, indicating that the true incidence of this type of tumor of the esophagus may be higher than previously believed.

G-CSF-producing tumors are diagnosed on the basis of four criteria:

1. extreme leukocytosis;
2. increased serum G-CSF levels;
3. improvement of leukocytosis after tumor resection; and
4. positive G-CSF immunohistochemical staining [2].

However if the first 3 criteria are satisfied, immunohistochemical staining can be omitted. In our 3 patients, both extreme leukocytosis and increased serum G-CSF concentrations were found. The leukocytosis improved after surgery in the first case and after chemotherapy in other cases. In addition, we confirmed normalization of serum G-CSF levels for all patients after their treatment.

The common features of G-CSF-producing ESCCs have previously been reported. All the affected patient were men, and all tumors were located in the lower esophagus. All tumors appeared grossly as protruding types with or without ulceration. The clinical features of our cases were similar.

G-CSF-producing tumors are believed to have high malignant potential and poor prognosis. G-CSF promotes proliferation, differentiation, and maturation of progenitor cells in the neutrophil lineage, and mobilizes hematopoietic stem cells from the bone marrow to the peripheral blood. It also activates and prolongs the survival of mature neutrophils [14]. It has been reported that G-CSF stimulates the in-vitro growth of a non-hematopoietic malignant cell line [15]. Tachibana et al. [5] reported that G-CSF production and G-CSF receptor expression by cancer cells are crucially important in mediating the malignant progression of non-haematopoietic cancer cells. It is thus possible that an autocrine growth mechanism mediated by G-CSF may lead to tumor progression. We confirmed expression of the G-CSF receptor on the cell surfaces of the specimens from our cases. This finding is indicative of

Fig. 3 **a** Upper gastrointestinal endoscopy revealed a type 1 tumor from the lower esophagus to the cardiac part of the stomach. **b** PET revealed a tumor located in the lower esophagus, and many swelling surrounding lymph nodes. **c** High accumulation was observed in both the primary lesion and lymph node metastasis by PET. Abnormal accumulation of SUV max18.4 was observed in the primary lesion

an autocrine growth mechanism mediated by G-CSF (results not shown).

Prolonged survival has been achieved for patients treated with chemotherapy or for patients treated with surgery plus neoadjuvant [16, 17] or adjuvant chemotherapy [18, 19]. Early recurrence and poor prognosis is common for patients treated with local therapy alone, for example surgery or radiotherapy [20, 21]. Therefore, systemic chemotherapy is the first choice of treatment for G-CSF-producing tumors, and surgery should be considered only when neoadjuvant chemotherapy has been effective. Leukocytosis can be a good marker for response or recurrence of these tumors.

We have reported 3 cases of patients with G-CSF-producing ESCC who were successfully treated by use of multimodal therapy. Although G-CSF-producing tumors are thought have a poor prognosis, it is possible that multimodal treatment may achieve long-term survival of patients with G-CSF-producing ESCC.

Conflict of interest The authors declare that they have no conflict of interest.

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