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Case Report

An Autopsy Case of Esophageal Squamous Cell Carcinoma Associated with Granulocyte Colony-Stimulating Factor Production

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ABSTRACT

A 54-year-old man who had been treated for hypertension visited our hospital because of abdominal pain. Abdominal ultrasonography suggested an abdominal tumor that had metastasized. Examination on admission revealed stage IV progressive esophageal cancer (squamous cell carcinoma) that could not be treated surgically. In addition, the tumor had metastasized to the liver. Because levels of granulocyte colony-stimulating factor (G-CSF) in serum were high, the esophageal cancer was suspected to produce G-CSF. After being admitted and discharged several times, the patient died of multiple organ failure. At autopsy, a superficial and distinctly depressed type tumor 40 mm in circumference was found in the lower esophagus. Histologic examination showed moderately differentiated squamous cell carcinoma with marked invasion of vessels. The infiltration reached the outer membrane through the muscularis propria. Metastasis to the liver and lymph nodes was found. Immunohistochemical studies confirmed G-CSF in the tumor cells of the primary and metastatic lesions. (Jikeikai Med J 2002 ; 49 : 191-5)

Key words : granulocyte colony-stimulating factor (G-CSF), esophagus, squamous cell carcinoma

INTRODUCTION

Since cancer associated with granulocyte colony-stimulating factor (G-CSF) production was first reported in 1977, many similar cancers have been reported in various organs. Although G-CSF production has been reported in esophageal cancer, G-CSF production in the primary and metastatic lesions has not been confirmed immunohistochemically.

We present a case of esophageal cancer in which associated G-CSF production was confirmed in the primary and metastatic lesions.

Clinical course

A 54-year-old man who had been treated for hypertension as an outpatient visited our hospital because of abdominal pain. Abdominal ultrasonography suggested a diffuse hepatic tumor. Examinations on admission revealed primary esophageal cancer (squamous cell carcinoma). The tumor was stage IV and was judged to be surgically untreatable. The white blood cell (WBC) count was increased ; although infectious diseases and leukemia were ruled out as causes, a G-CSF-producing tumor was suspect-

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ed because of high levels of G-CSF. After chemotherapy, the primary tumor shrank, the WBC count normalized, and G-CSF levels decreased. However, metastatic foci on imaging studies were unchanged. Although the patient was discharged from the hospital, he was readmitted because his condition deteriorated. He died of multiple organ failure. The period from the determination of diagnosis to death was only 3 months.

Autopsy findings

Autopsy was performed 100 minutes after death. The subject was 167 cm tall and weighed 60 kg. The autopsy findings are summarized in Table 1, and the main lesions were described below.

Esophagus: A superficial and distinctly depressed type tumor 40 mm in circumference was found in the esophagus (Fig. 1). Histologic examination showed moderately differentiated squamous cell carcinoma with poor keratinization (Fig. 2). The tumor had infiltrated through the muscularis propria to the outer membrane. Metastasis was found in veins and lymph nodes. Immunohistochemical staining of tumors cells was positive for G-CSF (Fig. 3). Parathyroid

Table 1. Autopsy diagnosis

I.	Esophageal cancer
1.	Primary lesion: A superficial and distinctly depressed type tumor
2.	Metastatic lesions: Liver, lung, and lymph nodes
II.	Disseminated intravascular coagulation
III.	Bilateral bronchopneumonia
IV.	Shock in the terminal phase
V.	Chronic esophagitis
VI.	A malnourished, middle-aged man of medium build

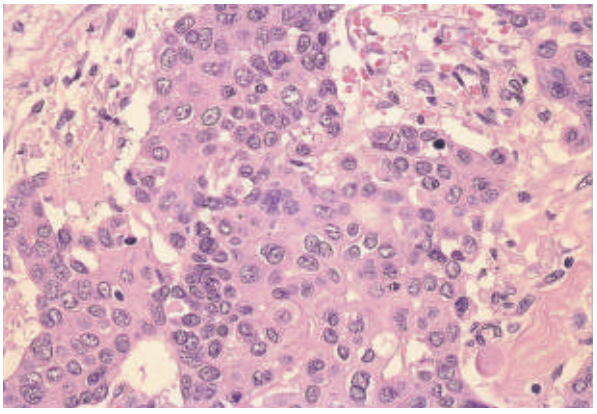

Fig. 2. Moderately differentiated squamous cell carcinoma (×100)

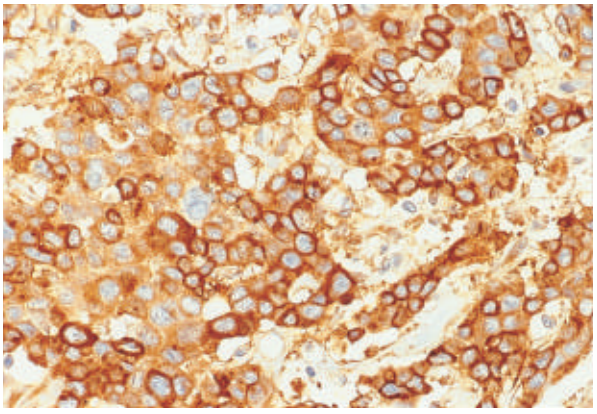

Fig. 3. G-CSF was positive in the cytoplasm of tumor cells (×100)

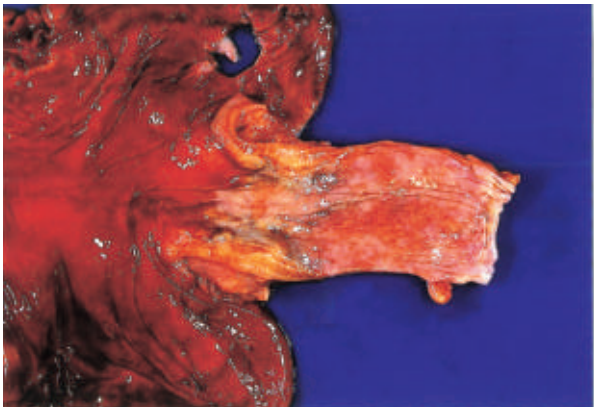

Fig. 1. A superficial and distinctly depressed type tumor

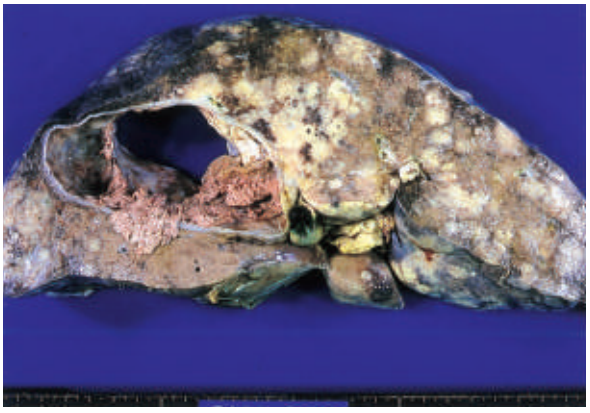

Fig. 4. Large and small metastatic nodules

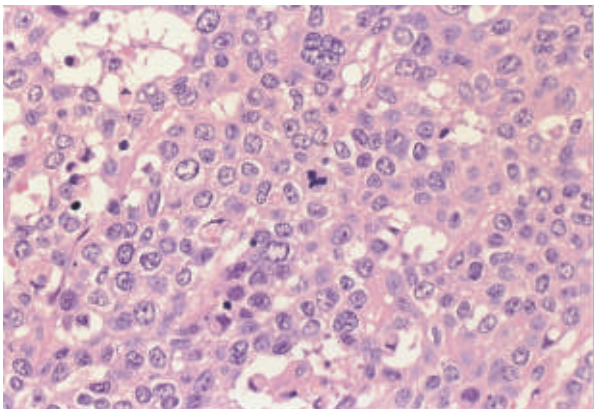

Fig. 5. Metastatic lesions of squamous cell carcinoma (×100)

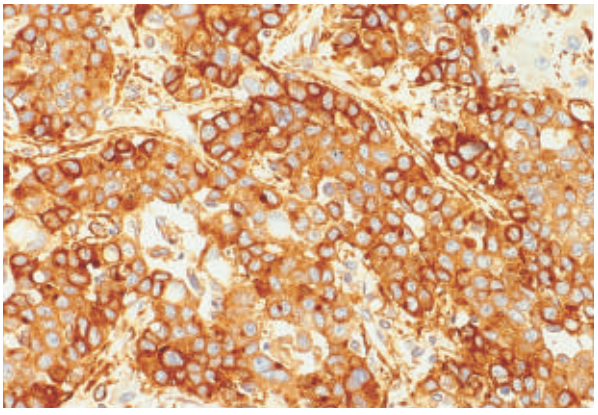

Fig. 6. G-CSF was positive in the cytoplasm of squamous cell carcinoma (×100)

hormone-related protein (PTH-rP) was weakly positive.

Liver : The liver weighed 3500 g. Most of the parenchyma had been replaced by large and small metastatic nodules with a maximum diameter of 150 mm (Fig. 4). Cut sections of the tumor were yellow or white. Necrosis was extensive, and the tumor had infiltrated the portal vein (Fig. 5). G-CSF production was confirmed through immunohistochemical staining (Fig. 6). PTH-rP was weakly positive.

Bone marrow : The bone marrow was hyperplastic with decreased fatty casts. Granulocytes at various stages of maturation showed diffuse proliferation and marked hypermorphosis. Islets of erythroblasts were decreased in size, and the density of blood megakaryocytes was mildly decreased.

Spleen : The spleen weighed 168 g and was mildly

Table 2. Reported cases

	1991 Tujinaka	1992 Fukushima	1993 Taguchi	1994 Takahashi	1998 Egawa	2000 Kato
Age (years) sex	58, male	54, male	62, male	53, male	76, male	54, male
Histologic diagnosis	Poorly differentiated squamous cell carcinoma	not mentioned	Poorly differenthated squamous cell carcinoma	Poorly differentiated squamous cell carcinoma	Moderately differentiated squamous cell carcinoma	Moderately differentiated squamous cell carcinoma
Treatment	Total gastrectomy Radiotherapy, Chemotherapy	Radiotherapy Chemotherapy	Partial esophagectomy Radiotherapy	not mentioned	Partial esophagectomy Total gastrectomy	Chemotherapy
WBC	30,000/mm	50,000/mm	35,400/mm	91,400/mm	78,000/mm	16,900/mm
G-CSF	low sensitivity	782 pg/ml	4,821 pg/ml	8,400 pg/ml	183 pg/m	150 pg/g
Platelets	230,000/ul	not mentioned	510,000/ul	490,000/ul	108,000/ul	250,000/ul
Ca	5.7 mEg/l	not mentioned	4.9 mEq/l	not mentioned	not mentioned	upper normal limit
Interleukin	not mentioned	not mentioned	not mentioned	IL-1α250< IL-1β59, 2 IL-6 3750 IL-8 38300	IL-6 709 pg/ml	IL-1α 10.6 pg/ml IL-6 23.1 pg/ml
Outcome	Death 55 days after surgery	Unknown	Unknown	Unknown	Death 13 months after diagnosis	Death 3 months after diagnosis

swollen. Congestion was severe, and extramedullary erythropoiesis of granulocytes was scattered throughout the red pulp.

DISCUSSION

Since Asano et al.[1] reported G-CSF production in squamous cell carcinoma of the lung in 1977, G-CSF production has been reported in various organs including lung[2-6], middle ear[7], oral cavity[8], tongue[9], head and neck[10], thymus[11], bladder[12,13], ureter[14] and uterine cervix[15]. Esophageal cancer associated with G-CSF production has also been reported[16-20].

In the present case, we concluded that the increase in the WBC count was not due to infectious disease or leukemia but to G-CSF production by the tumor. That G-CSF levels decreased and the WBC count normalized when the tumor shrank with chemotherapy supports this conclusion. Production of G-CSF in the primary and metastatic lesions was immunohistologically confirmed at autopsy. In addition, levels in serum of PTH-rp, interleukin (IL)-1, IL-4, and tumor necrosis factor α (TNF-α) were high.

Previous studies suggest that G-CSF-producing tumors are related to high levels of various interleukins[19,20]. The tumor in our patient was weakly positive for PTH-rP. Although we did not examine autopsy specimens for expression of IL-1, IL-6, or tumor necrosis factor α (TNF-α), we speculate they were produced by the tumor.

Tumors that produce G-CSF progress extremely rapidly and have a poor prognosis. Our patient died only 3 months after diagnosis.

Table 2 is reported cases of esophageal cancer in which associated G-CSF production.

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