



## Case Report

# Granulocyte-Colony Stimulating Factor (G-CSF)-Producing Esophageal Squamous Cell Carcinoma: A Case Report

Takeshi Shimakawa, Shinichi Asaka, Atsuko Usuda, Kentaro Yamaguchi, Kazuhiko Yoshimatsu, Shunichi Shiozawa, Takao Katsube, Yoshihiko Naritaka

*Department of Surgery, Tokyo Women's Medical University Medical Center East, Tokyo, Japan*

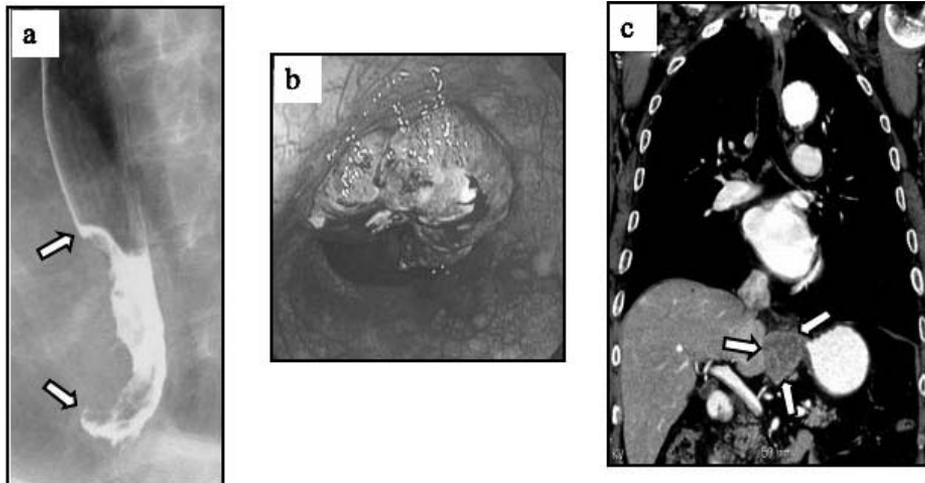
There are very few reports of esophageal G-CSF-producing cancer. This report describes a case of G-CSF-producing esophageal squamous cell carcinoma we recently encountered. A 70-year-old male patient had Stage III esophageal squamous cell carcinoma. The patient received preoperative chemotherapy, and therapeutic response for the primary lesion was rated as complete response and that of the lymph node metastasis as stable disease. A radical operation was then performed. A relapse to neutrophilia occurred as liver metastasis recurred postoperation, and serum G-CSF level was high. Immunohistochemical staining of the resected specimen with anti-G-CSF antibody was positive. The patient died about 1 year after the operation. According to our search of the literature, there are 22 cases of esophageal G-CSF-producing cancer. Carcinosarcoma was more frequent as compared to esophageal non-G-CSF-producing cancer. The prognosis was graver in those cases of G-CSF-producing squamous cell carcinoma, relative to cases of non-G-CSF-producing esophageal squamous cell carcinoma.

*Key words:* Granulocyte colony-stimulating factor – Esophageal cancer – Squamous cell carcinoma

The number of papers reporting cases of granulocyte colony-stimulating factor (G-CSF)-producing tumors has been increasing in recent years, but there are very few reports of G-CSF-producing esophageal tumor.<sup>1–6</sup> This report describes a case of G-CSF-producing esophageal squamous cell carcinoma that we recently encountered.

Corresponding author: Takeshi Shimakawa, Department of Surgery, Tokyo Women's Medical University Medical Center East, 2-1-10 Nishiogu Arakawa-ku, Tokyo 116-8567, Japan.

Tel.: +81 3 3810 1111; Fax: +81 3 3894 5493; E-mail: simakasu@dnh.twmu.ac.jp



**Fig. 1** (a) An esophagography revealed a type 3 esophageal cancer with a major axis of 12 cm. (b) An esophagoscopy also showed a type 3 esophageal cancer with a marked narrow lumen. (c) Abdominal CT: There was no infiltration of other organs. Lymph nodes Nos. 1, 3 and 7 were markedly enlarged *en bloc*, and were diagnosed as lymph node metastasis.

## Case Report

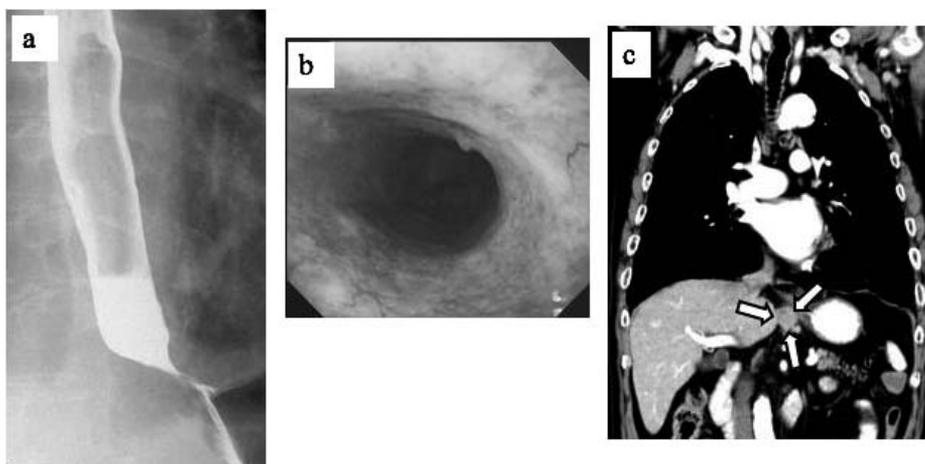
A 70-year-old male patient had a chief complaint of dysphagia. The patient was hypertensive and diabetic under management with oral medications. He had been smoking 40 cigarettes daily and drank alcohol (*shochu*; 1 L daily) for a period of 40 years.

The patient consulted a nearby clinic because he had been aware of choking on liquid/food when swallowing since September 2007. An upper gastrointestinal endoscopy led to a diagnosis of type 2 advanced esophageal cancer in the lower intratho-

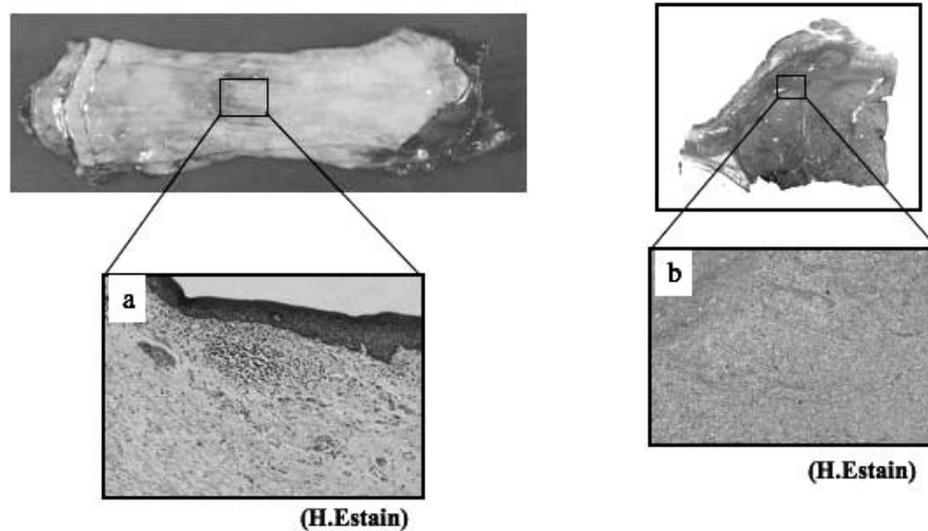
racic esophagus, and the patient was admitted to our hospital.

On admission, no anemia or jaundice was noted. No superficial lymph nodes were palpable. An esophagography and esophagoscopy revealed a type 2 cancer of the esophagus measuring approximately 5 cm in major axis on the anterior wall of the lower intrathoracic esophagus (Fig. 1 a, b).

Computed tomography of the chest and abdomen demonstrated irregular thickening of the wall and narrowing of the lumen of the lower intrathoracic esophagus. An unhomogeneously visualized mass about 5 cm in diameter was noted at the



**Fig. 2** An esophagography (a) and esophagoscopy (b) revealed a type 2 cancer of the esophagus measuring approximately 5 cm in major axis on the anterior wall of the lower intrathoracic esophagus. (c) CT examination: An unhomogeneously visualized mass about 5 cm in diameter was noted at the esophago-gastric junction and was judged to be a lymph node metastasis.



**Fig. 3** Histopathologic findings: (a) Histopathologic examination of the resected esophagus revealed that the primary lesion, with no demonstrable cancer cells at all, was Grade 3 according to the histologic criteria for chemotherapy. (b) The mass at the esophago-gastric junction, which was finally diagnosed as gastric intramural metastasis rather than lymph node metastasis, so that the lesion was rated as Grade 1a.

esophago-gastric junction and was judged to be a lymph node metastasis (Fig. 1c). These findings led to a diagnosis of Lt, type 2, T3 N2 M0 cStage III, moderately differentiated squamous cell carcinoma.<sup>7</sup> The patient received 3 courses of preoperative FAP (5FU, ADM, and CDDP) chemotherapy, following which the therapeutic response of the primary lesion was rated as complete response (Fig. 2a, b) and that of the lymph node metastatic lesion as partial response (Fig. 2c). A radical operation was then performed. Middle-to-lower esophagectomy via right thoracotomy, two-area lymphadenectomy, and high intrathoracic gastroesophagostomy were performed. When the

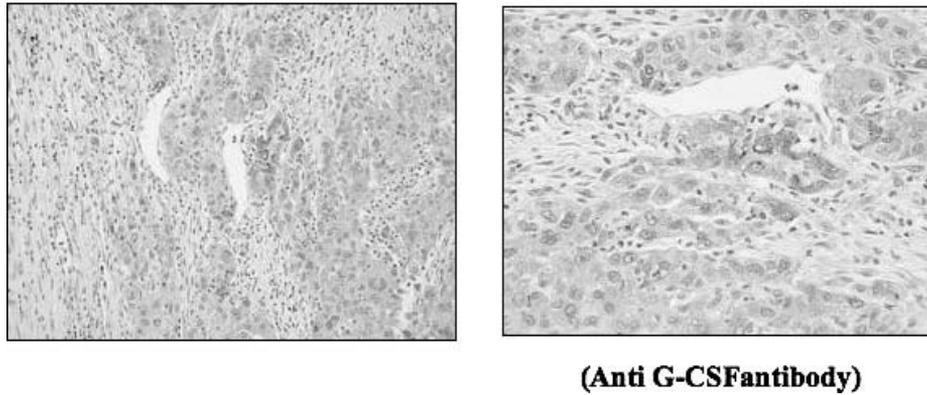
surgical intervention was undertaken, the mass at the cardia had further increased in size forming a lump with the gastric wall, and was resected *en bloc*.

Histopathologic examination of the resected specimens revealed that the primary lesion, with no demonstrable cancer cells at all, was Grade 3 according to the histologic criteria for chemotherapy (Fig. 3a). The mass at the esophago-gastric junction, which was judged to be a lymph node metastasis prior to the operation, was finally diagnosed as gastric intramural metastasis rather than lymph node metastasis, so that the lesion was rated as Grade 1a according to the criteria for chemotherapy (Fig. 3b).

**Table 1** Results of the laboratory tests on admission

Blood cell count			Biochemical test		
WBC	16700	/ $\mu$ L	BUN	9.2	mg/dL
RBC	$402 \times 10^4$	/ $\mu$ L	Cr	0.68	mg/dL
Hb	12.7	g/dL	Na	125	mEq/L
Plt	$31.7 \times 10^4$	/ $\mu$ L	K	4.3	mEq/L
	Biochemical test		Cl	97	mEq/L
TP	7.5	g/dL	CRP	5.18	mg/dL
Alb	3.8	g/d	HbA1c	6.3	%
GOT	18	IU/L		Tumor marker	
GPT	15	IU/L	SCC	6.8	ng/mL
T.Bil	0.7	mg/dL	CYFRA	0.9	ng/mL
$\gamma$ -GTP	152	IU/L			

Alb, albumin; GOT, glutamic-oxaloacetic transaminase; GPT, glutamate pyruvate transaminase; Hb, hemoglobin; Plt, platelet; RBC, red blood cell; SCC, squamous cell carcinoma; T.Bil, total bilirubin; TP, total protein; WBC, white blood cell;  $\gamma$ -GTP,  $\gamma$ -glutamyltransferase.



**Fig. 4** Immunohistochemical staining of the resected tissue specimen with anti-G-CSF antibody was positive, and the condition was diagnosed as G-CSF-producing esophageal cancer.

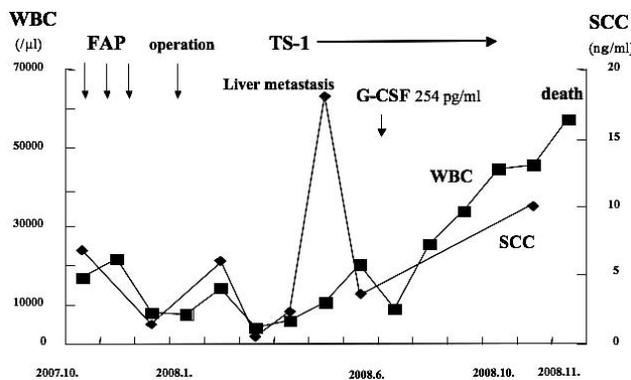
The patient had been noted to have neutrophilia without signs of infection prior to the chemotherapy and showed improvement in this respect in harmony with his favorable therapeutic response (Table 1). Nevertheless, a relapse to neutrophilia occurred as liver metastasis recurred 3 months post operation; therefore, a G-CSF producing tumor was suspected and laboratory tests revealed a serum G-CSF level as high as 254 pg/mL using ELISA (the reference value:  $\leq 39.0$  pg/mL). Immunohistochemical staining of the resected tissue specimen with anti-G-CSF antibody was positive, and the condition was diagnosed as G-CSF-producing esophageal cancer (Fig. 4). The patient died of the primary disease about 1 year after the operation despite subsequent chemotherapy (Fig. 5).

**Discussion**

In healthy individuals, G-CSF is produced mainly in vascular endothelial cells, fibroblasts, monocytes, and macrophages. G-CSF-producing tumors give

rise to clinical manifestations due to neutrophilia etc. caused by excessive production of G-CSF. This concept was elaborated by Fahey<sup>8</sup> in 1951 who pointed out the possibility that tumor *per se* produces myelostimulant substances. In 1974, Robinson<sup>9</sup> reported elevated plasma and urine G-CSF levels in patients with malignant tumor presenting with neutrophilia, and Asano *et al*<sup>10</sup> demonstrated G-CSF production in lung cancer patients. Subsequently, there have been increasing reports documenting G-CSF production in lung cancer,<sup>10–13</sup> gastric cancer,<sup>14–16</sup> and liver cancer,<sup>17</sup> but there are few reports on this condition in cases of esophageal cancer.<sup>1–6,18–32</sup>

Diagnostic criteria for G-CSF-producing tumors include: (1) a marked increase in leukocyte count, (2) elevated G-CSF activity, (3) a decrease in leukocyte count following tumor resection, and (4) verification of G-CSF production in tumor.<sup>10</sup> This case fulfilled all 4 criteria for G-CSF-producing tumors. According to our search of the literature, there have been 22 cases of G-CSF-producing esophageal cancer reported in Japan, including the 2 herein described cases; hence it is remarkably uncommon (Table 2).<sup>1–6,18–32</sup> Characteristic features of those documented cases lie in the age range of 53–80 years, all males, with a higher percentage of a histologic type of carcinosarcoma (12/22 patients, 54.5%) as compared to usual malignant neoplasma of the esophagus. Of 10 cases of squamous cell carcinoma, the lesions were all moderately to poorly differentiated cancers, except 1 case unknown in this respect, while there was no case of well differentiated cancer. The prognosis was graver in those cases of G-CSF-producing squamous cell carcinoma, relative to cases of non-G-CSF-producing esophageal squamous cell carcinoma, in



**Fig. 5** Clinical course.

Table 2 G-CSF-producing esophageal cancer

Case	Author	Year	Age	Sex	Pathologic findings	G-CSF (pg/mL)	Size(cm)	Depth	LN metastasis	Treatment	Prognosis
1	Fukushima	1992	54	M	SCC	782	?	?	?	chemoradiotherapy	5M dead
2	Taguchi	1993	62	M	poorly diff. SCC	positive	?	?	positive	resection	24M alive
3	Takahashi	1994	53	M	poorly diff. SCC	201	?	?	?	chemoradiotherapy	3M dead
4	Fujimori	1997	63	M	carcinoma	286	3.5	sm	negative	resection	8W alive
5	Akutsu	1998	62	M	carcinoma	26	8	mp	positive	resection	11M dead
6	Ota	1998	63	M	carcinoma	286	4	?	?	resection	?
7	Egawa	1998	76	M	moderately diff. SCC	183	2.5	S0	positive	resection	12M dead
8	Oshiro	1999	56	M	carcinoma	109	6	mp	positive	resection	8W alive
9	Matsumoto	2000	66	M	moderately diff. SCC	154	4.5	T3	positive	resection	15M dead
10	Kato	2000	54	M	moderately diff. SCC	150	4	a	positive	chemotherapy	3M dead
11	Ichiishi	2000	66	M	carcinoma	?	?	?	?	BSC	2M dead
12	Asai	2001	60	M	carcinoma	120	12	sm	positive	resection	8W alive
13	Shibasaki	2002	79	M	carcinoma	231	8	?	negative	resection	2M alive
14	Fujimori	2003	76	M	carcinoma	101	11	sm	negative	?	12M dead
15	Ito	2004	70	M	carcinoma	64	11	T2	negative	resection	57M alive
16	Sasaki	2007	62	M	carcinoma	108	8.5	mp	positive	resection	5M dead
17	Maejima	2007	80	M	carcinoma	111	6	?	?	(-)	4M dead
18	Miyamoto	2008	51	M	carcinoma	48	8	T3	positive	resection	23M alive
19	Mimatsu	2008	69	M	poorly diff. SCC	113	12	T3	positive	radiation	7M dead
20	Tanabe	2009	76	M	moderately diff. SCC	134	11.8	T2	positive	chemoradiotherapy	10M dead
21	Our case	1998	73	M	moderately diff. SCC	41	12	a	positive	chemtherapy	2M dead
22	This case	2007	70	M	moderately diff. SCC	254	5	T2	positive	resection	12M dead

SCC, squamous cell carcinoma.

that there was only 1 patient who survived for 2 years after treatment whereas the remaining 9 patients did not survive for 2 years or longer and were not alive when reported. Of 12 patients with carcinoma, in contrast, 6 patients were still alive when reported and the longest duration of survival reported was 57 months,<sup>32</sup> the prognosis being relatively more favorable as compared with that of squamous cell carcinoma.

As for G-CSF-producing tumors of other organs, one report stated that squamous cell carcinomas were rather common among lung cancers while relatively undifferentiated or poorly differentiated tumors were frequent among cancers of the gastrointestinal system and that the prognosis was unfavorable in most cases;<sup>25</sup> hence seeming similar to esophageal cancer.

As a reason thereof, G-CSF has been suggested to have a bearing as an autocrine growth factor upon tumor growth and metastasis.<sup>14</sup> Therefore, it is considered that due caution should be exercised regarding the possibility that administration of G-CSF preparations for the control of neutropenia may favor tumor growth.

In conclusion, we encountered an extremely rare case of G-CSF-producing squamous cell carcinoma of the esophagus. The condition was

refractory to chemotherapy and the prognosis was unfavorable.

## References

1. Shimakawa T, Naritaka Y, Wagatsuma Y, Haga S, Ogawa K, Kajiwara T *et al.* Granulocyte-colony stimulating factor-producing esophageal carcinoma: a case report. *Operation* 2001;55(11):1842-1844
2. Sasaki K, Natsugoe S, Higashi M, Okumura H, Matsumoto M, Hanazono K *et al.* Esophageal carcinoma with granulocyte colony-stimulating factor: a case report. *Esophagus* 2007; 4(3):129-134
3. Maejima K, Watanabe M, Komine O, Mizutani S, Bou H, Tokunaga A *et al.* Granulocyte-colony stimulating factor-producing esophageal carcinoma: a case report. *Esophagus* 2007;4(3):117-120
4. Miyamoto K, Shibata S, Kawasaki H. Carcinoma of the esophagus producing granulocyte-colony stimulating factor: report of a case. *Esophagus* 2008;5(3):171-175
5. Mimatsu K, Oida T, Kano H, Kaawasaki A, Amano S. Aggressive progression of granulocyte colony-stimulating factor producing squamous cell carcinoma of the esophagus: case report and literature review. *Esophagus* 2008;5(4):205-209
6. Tanabe T, Kanda T, Ishihara N, Kosugi S, Matsuki A, Watanabe G *et al.* An esophageal squamous cell carcinoma patient with high serum granulocyte-colony stimulating factor level: report of a case. *Esophagus* 2009;6(4):253-258

7. The Japan Esophageal Society. *Guide line for the clinical and pathological studies on carcinoma of the esophagus*. 10<sup>th</sup> ed. Tokyo: Kanehara Press, 2007
8. Fahey RJ. Unusual leukocyte responses in primary carcinoma of lung. *Cancer* 1951;**4**(5):930–935
9. Robinson, WA. Granulocytosis in neoplasia. *Ann N.Y. Acad Sci* 1974;**230**(1):212–218
10. Asano S, Urabe A, Okabe T, Sato N, Kondo Y, Ueyama Y *et al*. Demonstration of granulopoietic factor(s) in the plasma of nude mice transplanted with a human lung cancer and in the tumor tissue. *Blood* 1977;**49**(5):845–852
11. Abe Y, Nakamura M, Katoh Y, Ogawa J, Inoue H, Tada N. A case report of lung cancer producing granulocyte colony-stimulating factor that induced leukocytosis (in Japanese with English abstract). *Jpn J Lung Cancer* 1992;**32**(2):279–284
12. Nakamura M, Oshika Y, Abe Y, Ozeki Y, Katoh Y, Yamazaki H *et al*. Gene expression of granulocyte colony stimulating factor (G-CSF) in non-small cell lung cancer. *Anticancer Res* 1997;**17**(1b):573–576
13. Hasegawa S, Suda T, Negi K, Hattori Y. Lung large cell carcinoma producing granulocyte-colony-stimulating factor. *Ann Thorac Surg* 2007;**83**(1):308–310
14. Aimoto T, Yoshida H, Koyama N, Nihei M, Sakonji M, Ohda M. A case of a granulocyte-stimulating factor producing gastric carcinoma. *Jpn J Gastroenterol Surg* 1997;**30**(10):2004–2008
15. Endo K, Kohnoe S, Okamura T, Haraguchi M, Adachi E, Toh Y *et al*. Gastric adenocarcinoma producing granulocyte-colony stimulating factor. *Gastric Cancer* 2005;**8**(3):173–177
16. Sunami T, Hushitani H, Kimura K, Yukimoto K, Sawada R, Sakamoto K *et al*. Granulocyte-stimulating factor producing gastric carcinoma: case report and literature review. *Jpn J Gastroenterol Surg* 2010;**43**(4):370–377
17. Aita K, Seki K. Carcinosarcoma of the liver producing granulocyte-colony stimulating factor. *Pathol Int* 2006;**56**(7):413–419
18. Fukushima Y, Takeda H, Tazaki S, Anzai K, Funatomi H, Onuki M *et al*. A case of esophageal carcinoma with an elevated serum level of granulocyte-colony stimulating factor. *Jpn J Gastroenterol* 1992;**89**(Suppl.):784
19. Taguchi J, Kobayashi S, Yang S, Hirano T, Komada T, Sato N *et al*. Granulocyte-colony stimulating factor producing esophageal cancer: report of a case report and review of the literature. *Jpn J Clin Immun* 1993;**16**(5):383–387
20. Takahashi T, Matsushita A, Ishikawa T. Granulocyte-colony stimulating factor and IL-8 producing tumor. *Rinsho Ketsueki* 1994;**35**(10):1179
21. Fujimori M, Kuroshima S, Sekishita Y, Shiono T, Honma K, Yamaguchi Z. Granulocyte-colony stimulating factor producing esophageal carcinosarcoma: a case report. *Jpn J Surg Assoc* 1997;**58**(3):586–590
22. Akutsu Y, Koide Y, Okazumi S, Arima M, Kubozawa H, Isono K. A case of granulocyte-colony stimulating factor-producing polypoid carcinosarcoma of the esophagus. *Jpn J Cancer Clin* 1998;**44**(1):96–101
23. Ota S, Kato A, Kobayashi H, Yonezumi M, Yamaguchi J, Musashi M *et al*. Monoclonal origin of an esophageal carcinosarcoma producing granulocyte-colony stimulating factor: a case report. *Cancer* 1998;**82**(11):2102–2111
24. Egawa M, Ota U, Ito N, Oikawa M, Tachibana F, Akaike Y. Granulocyte-colony stimulating factor-producing esophageal squamous cell carcinoma: a case report. *Fukushima J Rural Medicine* 1998;**40**(1): 29–32
25. Oshiro T, Yahata H, Haruta N, Tanji H, Shinozaki K, Uchida K *et al*. A case report of granulocyte-colony stimulating factor producing so-called carcinosarcoma of esophagus. *Jpn J Gastroenterol Surg* 1999;**32**(10):2350–2354
26. Matsumoto G, Ise H, Kimura Y, Inoue H, Suzuki N, Ohtani H *et al*. Granulocyte-colony stimulating factor-producing esophageal carcinoma: serum level as a marker for monitoring the effects of treatment. *Int J Clin Oncol* 2000;**5**(5):328–333
27. Kato M, Osawa H, Usui N, Hano H. An autopsy case of esophageal squamous cell carcinoma associated with granulocyte colony-stimulating factor production. *Jikeikai Med J* 2002;**49**(4):191–195
28. Ichiishi E, Yoshikawa T, Kogawa T, Yoshida N, Kondo M. Possible paracrine growth of adenocarcinoma of the stomach induced by granulocyte colony stimulating factor produced by squamous cell carcinoma of the oesophagus. *Gut* 2000;**46**(3):432–434
29. Asai K, Igarashi S, Shimizu H, Miyata H, Horiguchi Z. A case of rapidly enlarged G-CSF producing esophageal so-called carcinosarcoma showing a variety of lesions. *Jpn J Gastroenterol Surg* 2003;**36**(6):464–469
30. Shibasaki H, Hirai I, Kawaguchi K, Moritani T, Kamiga M, Kimura W. Polypoid carcinosarcoma of the esophagus producing granulocyte-colony stimulating factor: a case report. *Jpn J Surg Assoc* 2002;**63**(12):2920–2925
31. Fujimori M, Ono K, Manase H, Yanagi S, Suzuki A, Shiono T. A case of G-CSF producing esophageal carcinosarcoma with strong inflammatory reaction. *Jpn J Surg Assoc* 2003;**64**(5):1094–1097
32. Ito H, Harada A, Deguchi T, Konishi S, Sueoka S, Sonohara F *et al*. A case of surgery for a granulocyte-colony stimulating factor-producing esophageal carcinosarcoma which resulted in a long-term survival. *Jpn J Gastroenterol Surg* 2010;**43**(9):900–905