

Rapid progression of a granulocyte colony-stimulating factor-producing liver tumor metastasized from esophagogastric junction cancer: A case report and literature review

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Abstract. The current study presents the case of a 72-year-old woman with a rapidly enlarged liver metastasis from esophagogastric junction (EGJ) cancer, accompanied by progressive leukocytosis (47,680/ μ l) and elevated serum granulocyte colony-stimulating factor (G-CSF; 779 pg/ml). The patient underwent right hemihepatectomy 26 months after a total gastrectomy. On the seventh post-operative day the patient's leukocyte count and serum G-CSF level decreased to 4,280/ μ l and \leq 19.5 pg/ml, respectively. Histologically, the lesion was a well to moderately differentiated adenocarcinoma similar to the primary lesion. Therefore, this tumor was clinically diagnosed as a G-CSF-producing liver metastasis from EGJ cancer, although immunohistochemical staining for G-CSF was negative. A right pulmonary nodule detected simultaneously with the hepatic mass was resected four months following the hepatectomy and was diagnosed as a pulmonary metastasis. The patient's leukocyte count was normal at the time of her initial surgery for EGJ cancer, and her clinical course varied for different metastatic sites. The liver metastasis was accompanied by progressive leukocytosis and elevated serum G-CSF and demonstrated rapid tumor growth during a six-month period, whereas the non-G-CSF-producing pulmonary metastasis grew slowly during the same period. In addition 21 reported cases of G-CSF-producing upper gastrointestinal tract cancer were reviewed to elucidate the clinicopathological features of this disease.

Introduction

Tumor-related leukocytosis, which is occasionally encountered in patients with malignant tumors, is a paraneoplastic syndrome involving high leukocyte counts without underlying infection, bone marrow metastasis, or corticosteroid administration (1,2). Tumor-related leukocytosis is observed in 10% of patients with solid tumors and is associated with poor clinical outcome (3). This condition is caused, in part, by granulocyte colony-stimulating factor (G-CSF) synthesized by neoplastic cells and has therefore been regarded as potentially indicative of the autocrine stimulation of tumor growth by G-CSF (4,5). However, little is known regarding the precise mechanisms of aggressive behavior and poor outcome in G-CSF-producing tumors. G-CSF production by tumors has been reported for various non-hematopoietic malignancies, predominantly lung or pancreatic cancer (6,7). On the other hand, G-CSF-producing cancer originated from upper gastrointestinal tract including esophagus, esophagogastric junction (EGJ), stomach is extremely rare, and the clinical characteristics and outcomes of this entity remain unclear.

Here, we present a patient with a rapidly enlarged liver metastasis from EGJ cancer accompanied by progressive leukocytosis and high levels of serum G-CSF, although her leukocyte count had been normal two years earlier at the first surgery for the primary lesion. Additionally, we review 21 cases of G-CSF-producing upper gastrointestinal tract cancer, including 20 previously published cases and the present case, to elucidate the clinicopathological features of this entity.

Case report

A 72-year-old woman had undergone laparoscopic total gastrectomy with regional lymph node dissection for EJC cancer [pT3N1M0, stage IIB according to the Union for International Cancer Control (UICC) TNM classification (8)]. Histopathological examination revealed well to moderately differentiated adenocarcinoma with a 3+ score for human epidermal growth factor receptor 2 (HER2) expression (9). Atrophic gastritis positive for *H. pylori* infection was identified in the pyloric gland area. The patient received adjuvant

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chemotherapy with S-1 for a year and did not experience tumor recurrence or metastasis prior to the events described here. Before gastrectomy, her leukocyte count was $7,770/\mu\text{l}$, with 68.8% neutrophils. During follow-up, the leukocyte count increased to $27,150/\mu\text{l}$ with 87.0% neutrophils at the 21st month after gastrectomy, but the serum C-reactive protein concentration was within a normal range (0.07 mg/dl). Bone marrow aspiration biopsy revealed a hypercellular marrow with predominantly granulocytic mature cells. Molecular analyses revealed neither a BCR/ABL fusion gene nor the JAK2-V617F mutation. The patient's serum G-CSF level was significantly elevated (779 pg/ml; normal, <39 pg/ml). Contrast-enhanced computed tomography (CT) during the 24th postoperative month revealed a low-density mass measuring approximately 80 mm in diameter in the right lobe of the liver, with irregular and peripheral enhancement of the lesion in the arterial phase and wash-out in the portal and delayed phases (Fig. 1). Furthermore, a small nodule with a size of 6 mm was identified in the right lower lobe of the lung. The hepatic mass had not been detected on abdominal CT performed 6 months previously, suggesting rapid tumor growth. Although the patient did not exhibit symptoms, her leukocyte count continued to increase, reaching $47,680/\mu\text{l}$ during the 26th postoperative month. As other potential causes of leukocytosis were excluded, we hypothesized that this condition was a paraneoplastic manifestation induced by G-CSF production by the liver tumor. Based on appropriate radiological findings for hepatocellular carcinoma, the lesion was diagnosed as G-CSF-producing hepatocellular carcinoma, with liver metastasis from EGJ cancer included as a differential diagnosis, and the patient underwent right hemihepatectomy 26 months after gastrectomy. The resected specimen included a hard, solid, whitish tumor measuring $99 \times 79 \times 63$ mm in size in the right lobe of the liver (Fig. 2A). Histopathological examination revealed a well to moderately differentiated adenocarcinoma (Fig. 2B). The tumor in the liver and the primary lesion had similar histology and identical immunohistochemical (IHC) patterns, including reactivity to cytokeratin (CK)7, CK19, CK20, and carcinoembryonic antigen (CEA). The HER2 expression score (9) of the liver tumor was 3+, as was that of the primary lesion (Fig. 2C). IHC examination using an anti-G-CSF monoclonal antibody revealed negative G-CSF expression (Fig. 2D). However, the patient's leukocyte count and serum G-CSF level had dramatically decreased to $4,280/\mu\text{l}$ and ≤ 19.5 pg/ml, respectively, on the seventh postoperative day. Therefore, clinically, the tumor was diagnosed as G-CSF-producing liver metastasis from EGJ cancer, although IHC staining for G-CSF was negative. The right pulmonary mass had slightly expanded to 8 mm on chest CT performed during the 28th postoperative month (Fig. 1B). However, the patient's leukocyte count ($3,650/\mu\text{l}$) and serum G-CSF level (32.0 pg/ml) were in the normal range. Thoracoscopic partial pulmonary resection was performed four months after hepatectomy. Histological examination of the pulmonary mass revealed similar findings to those obtained for the primary lesion and the liver metastasis, and the HER2 expression score (9) of the pulmonary tumor was 3+. Thus, this mass was diagnosed as pulmonary metastasis. We decided not to proceed with adjuvant chemotherapy after pulmonary resection because no other obvious recurrence was identified. The patient's leukocyte count and serum G-CSF have continued

to remain at normal levels during follow-up (Fig. 3). She has experienced no tumor recurrence and has survived 38 and 12 months after gastrectomy and hepatectomy, respectively.

Discussion

In general, the following criteria are used as the diagnostic standard for detecting a G-CSF-producing tumor: (1) an increased number of leukocytes, primarily mature neutrophils, with no other explanatory factors; (2) elevated serum G-CSF; (3) a reduction in the leukocyte count following tumor resection; and (4) confirmation of G-CSF production via immunostaining (10). However, clinically, positive immunostaining is not a definitive finding for the diagnosis of G-CSF-producing tumors (11). It has been suggested that the rapid secretion of G-CSF without intracellular retention is the reason why such tumors may exhibit negative staining with an anti-G-CSF monoclonal antibody (12). In fact, Yokoyama *et al* (13), reported a case involving G-CSF-producing gastric cancer that exhibited negative IHC staining for G-CSF but highly increased G-CSF mRNA levels detected using real-time reverse transcription polymerase chain reaction. In the present case, postoperative observations indicated that criteria (1) to (3) were fulfilled, and the lesion satisfied the criteria for a G-CSF-producing tumor.

In the present case, a normal leukocyte count was initially detected at the first surgery for the primary EGJ cancer, and the clinical course varied for different metastatic sites. Interestingly, the liver metastasis, which was accompanied by progressive leukocytosis and elevated serum G-CSF, showed rapid tumor growth during a six-month period, whereas the subsequent pulmonary metastasis, which was associated with a normal leukocyte count and normal serum G-CSF, grew slowly during the same time period. These findings indicate the existence of tumor cell heterogeneity in different metastatic sites or a subset of cancer cells acquiring the ability to produce G-CSF that could respond to G-CSF with enhanced proliferation, a phenomenon suggestive of autocrine mechanisms and of more aggressive biological activities for such cells compared with that of cancer cells that do not produce G-CSF.

In a PubMed search, 14 case reports (13-26) and 6 cited publications (11,27-31) regarding G-CSF-producing upper gastrointestinal tract cancers, including esophageal cancer (12 cases), EGJ cancer (1 case), and gastric cancer (7 cases), were retrieved from the English-language literature. Demographic and clinical characteristics for all of the described cases of such cancers, including the present case, are summarized in Table I. A male predominance was identified in these 21 cases (90% vs. 10%). Interestingly, male predilection was also observed in G-CSF-producing pancreatic cancer (85% vs. 15%) (7). However, the association of sex predominance with G-CSF production in cancer tissue is unclear. Pyrexia was observed in 7 of these 21 cases, although the patient described here remained asymptomatic despite her large tumor burden. Two cases and one case of G-CSF-producing gastric cancer were histologically diagnosed as adenosquamous carcinoma and undifferentiated carcinoma, respectively. Among the 21 described cases, neutrophil infiltration in the tumor was observed in only two cases of G-CSF-producing esophageal

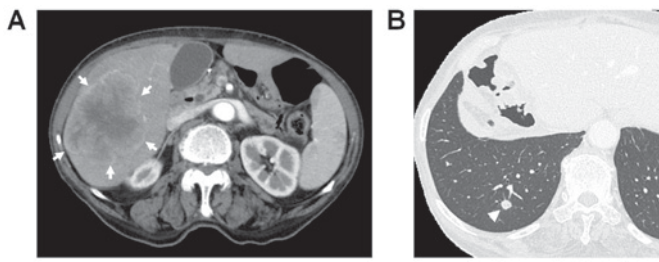


Figure 1. Imaging studies. (A) Abdominal CT revealed a low-density tumor measuring ~80 mm in diameter in the right lobe of the liver with irregular and peripheral enhancement of the lesion in the arterial phase and wash-out in the portal and delayed phases (white arrows). (B) A Chest CT revealed a right pulmonary tumor that slowly increased from 6 to 8 mm during a six-month period (white arrow head). CT, computed tomography.

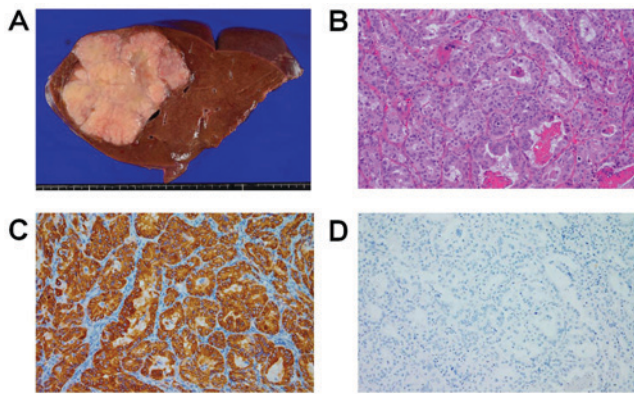


Figure 2. Pathology of the liver tumor. (A) Macroscopic appearance of the resected specimen. The tumor was a well-defined, whitish mass lesion with a diameter of 99 mm. (B) Microscopic evaluation following hematoxylin-eosin staining of the tumor tissue revealed a well- to moderately differentiated adenocarcinoma (magnification, x200). (C) IHC examination revealed human epidermal growth factor receptor 2 expression scores of 3+ for the liver tumor (magnification, x200). (D) IHC examination revealed negative granulocyte colony-stimulating factor expression (magnification, x200). IHC, immunohistochemical.

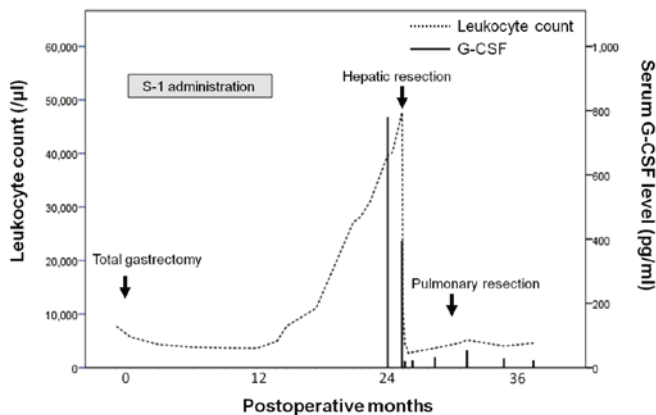


Figure 3. Clinical course and changes in leukocyte count and the level of serum G-CSF. G-CSF, granulocyte colony-stimulating factor.

cancer (16,25). However, no specific morphological features were found. In addition, this is the first reported case of G-CSF-producing upper gastrointestinal tract cancer with HER2 expression. However, to the best of our knowledge, no

studies have demonstrated correlations or interactions between HER2 and G-CSF. Among the 21 described cases, 14 cases involved surgical resection, whereas the remaining 7 cases involved chemo- and/or radiation therapy or the best supportive care due to advanced disease or deterioration of the patient's general condition. Overall survival in these 21 cases ranged from 2 to 24 months. For the 13 cases involving resection, excluding a case of gastric cancer that exhibited G-CSF production only after recurrence, resection of the G-CSF-producing tumor was followed by a decrease in leukocyte count, with normal leukocyte levels reached in 10 of these 13 cases. However, in 8 of 13 cases, an increase in leukocyte count and recurrence were observed during the early postoperative period, and 6 patients died of their disease within 2 years after surgical resection. In addition, chemotherapy and/or radiotherapy decreased the leukocyte counts and serum G-CSF levels in accordance with the remission of tumors in five cases (15,21,28,30,31). These findings suggest that leukocyte count or serum G-CSF level would be useful for monitoring disease in cases involving G-CSF-producing tumors, even if conventional biomarkers are negative. The patient described here is the first reported case of G-CSF-producing upper gastrointestinal tract cancer that underwent surgical resection of distant organ metastasis. The patient has survived for 38 months and 12 months after surgical resection of the non-G-CSF-producing primary lesion and the G-CSF-producing liver metastasis, respectively. Little is known about surgical indications for patients with EGJ cancer who undergo surgery for the primary lesion and experience recurrence. Depypere *et al* (32), analyzed 1754 patients surgically treated with curative resection for esophageal cancer and EGJ cancer and reported a 49.9% 5-year overall survival rate in patients who underwent surgical resection of isolated local recurrence or solitary solid organ metastasis with or without systemic therapy. However, a multidisciplinary team is needed for the optimal management of the recurrence of EGJ cancer, and surgery should be limited to selected patients, especially when considering the surgical indication for patients with G-CSF-producing EGJ cancer given its rapid progression and unfavorable prognosis. In the present case, hepatectomy was planned because the liver tumor was initially diagnosed as G-CSF-producing hepatocellular carcinoma based on radiological findings. In addition, pulmonary resection was performed because the lung tumor grew slowly without leukocytosis, unlike the liver tumor, and primary lung cancer was included as a differential diagnosis.

There have been a few reported cases of G-CSF-producing gastric cancer similar to the present case in that metastatic disease or local recurrence was present when paraneoplastic leukocytosis was detected. Kawaguchi *et al* (17), reported a case of gastric cancer with an aggressive course after recurrence in the liver and lymph nodes as a G-CSF-producing tumor, despite the fact that the primary lesion did not exhibit G-CSF production; the patient in question died of the disease only two months after surgery. Moreover, Yamano *et al* (26), reported a case of G-CSF-producing gastric cancer in which rapid progression of the residual tumor was observed after endoscopic mucosal resection. In that case, histological analysis of the tumor resected via endoscopic mucosal resection revealed a well-differentiated adenocarcinoma with negative immunoreactivity for G-CSF, whereas the residual

Table I. Characteristics of reported cases of G-CSF-producing upper gastrointestinal cancer.

Cancer Location	First author	Age (yrs)	Sex	Pyrexia	Histology		IHC staining for G-CSF	Leukocyte count at diagnosis (per μ l)	G-CSF level at diagnosis (pg/ml)	Treatment	Postoperative leukocyte count (per μ l)	Postoperative G-CSF level (pg/ml)	OS (mos)	Status	(Refs.)
					Type	Grade									
Esophagus	Ichiishi	66	M	-	SCC	G2-G3	Positive	33,900	NM	BSC	NA	NA	2	DE	(16)
	Matsumoto	66	M	-	SCC	G2	Positive	41,500	154	Resection	15,300	52.0	16	DE	(27)
	Kato	54	M	-	SCC	G2	Positive	16,900	150	CT	NA	NA	3	DE	(28)
	Nakata	56	M	+	SCC	G2	Positive	24,300	78	Resection	9,400	6.5	18	Alive	(29)
	Mimatsu	69	M	+	SCC	G3	Positive	19,600	113	RT	NA	NA	7	DE	(30)
	Tanabe	76	M	-	SCC	G2	Focally positive	24,260	134	Resection	10,450	NM	10	DE	(31)
	Mayanagi	30	M	+	SCC	G1	Positive	19,020	53.7	Resection following CRT	6,130	21.4	3	Recurrent	(20)
EGJ	Shimakawa	70	M	-	SCC	G2	Positive	16,700	NM	Resection following CT	Normalized	NM	12	DE	(24)
	Oshikiri	65	M	+	SCC	G1	Focally positive	15,900	140	Resection	Normalized	19.0	3	Alive	(11)
	Kitani	92	F	-	SCC	G2	Positive	23,500	131	Resection	5,000	<19.5	18	Alive	(18)
Stomach	Fukuda	50	M	-	SCC	G3	Positive	27,100	60.2	CRT	NA	NA	3	DE	(15)
	Yamaguchi	60s	M	-	SCC	G3	Positive	25,100	292	BSC	NA	NA	3	DE	(25)
	Komatsu	73	M	-	SCC	G2	Positive	45,710	231	Resection	6,870	12.0	19	Alive	(19)
	Present case	72	F	-	AC	G1-G2	Negative	47,680 ^a	779 ^a	Resection	4,280	<19.5	12 (38 ^b)	Alive	
	Obara	78	M	-	AC	G3	NM	58,200	NM	Resection	Normalized	NM	8	DE	(23)
	Endo	55	M	+	ASC	NM	Positive	35,000	105	Resection	Normalized	11.0	24	DE	(14)
	Yokoyama	57	M	+	UND	G4	Negative	34,000	107	Resection	13,000	35.6	4	DE	(13)
	Yamano	77	M	+	AC	G3	Positive	38,590	NM	BSC	NA	NA	3	DE	(26)
	Kawaguchi	62	M	-	AC	G3	Negative	54,300 ^a	28 ^a	Resection	NA	NA	2	DE	(17)
	Mori	72	M	-	AC	G2	Positive	34,900	293	CT	NA	NA	23	DE	(21)
Moro	66	M	-	ASC	NM	Focally positive	12,900	NM	Resection	Normalized	NM	8	Recurrent	(22)	

^aData when G-CSF production manifested, which occurred only after recurrence. ^bSurvival time from the first surgery for the primary lesion. AC, adenocarcinoma; ASC, adenosquamous carcinoma; BSC, best supportive care; CRT, chemoradiation therapy; EGJ, esophagogastric junction; G-CSF, granulocyte-colony stimulating factor; IHC, immunohistochemical; NM, not mentioned; OS, overall survival; RT, radiation therapy; SCC, squamous cell carcinoma; UND, undifferentiated carcinoma; M, male; F, female; DE, deceased.

tumor, which showed rapid tumor growth, presented as a poorly differentiated adenocarcinoma with positive immunoreactivity for G-CSF; this finding suggested that histological change in the tumor may have influenced G-CSF production and induced rapid progression. However, in the present case, histological evaluation of the liver metastasis revealed a well to moderately differentiated adenocarcinoma similar to the primary lesion, and there was no evidence of dedifferentiation or anaplastic transformation. In addition, we assessed the tumor proliferative ability of each lesion by immunostaining for Ki-67, as previously described (33). Notably, the Ki-67 index of the liver metastasis (58.4%) was similar to the Ki-67 indices of the primary lesion and the pulmonary metastasis (65.0 and 73.6%, respectively). In addition, the presence of tumor-infiltrating lymphocytes in liver and lung metastasis was similar, whereas abundant stromal myofibroblasts with elevated expression of α -smooth muscle actin was observed in only liver metastasis. No differences in CD3+ lymphocyte and CD20+ lymphocyte counts were noted between normal liver and lung tissue surrounding the tumor. These findings suggest that morphological and biological characteristics remained unchanged throughout the clinical course of the described case, even though rapid tumor growth and elevated G-CSF were only observed during the course of the liver metastasis.

G-CSF has been reported to promote tumor progression in different tumor models. A prior study demonstrated that G-CSF could promote the survival and activation of myeloid-derived suppressor cells via the signal transducer and activator of transcription 3 (STAT3) signaling pathway, resulting in the induction of immune suppression (34). Furthermore, G-CSF is known to regulate epithelial to mesenchymal transition (EMT) via recruitment of the *c-jun* proto-oncogene. Moreover, in previous studies, G-CSF increased the proliferation and migration of tumor cells in a manner dependent on ERK1/2 and RSK1 phosphorylation (4) and stimulated tumor angiogenesis (35,36). However, the precise mechanisms of G-CSF-dependent autocrine growth and proliferation are not well known.

Clinically, a more aggressive course is sometimes observed in the metastatic site than in the primary lesion. The case described here suggests that one of the mechanisms of this biological change might be due to tumor cell heterogeneity in different metastatic sites or to a subset of cancer cells acquiring the ability to produce G-CSF. The present case involved successful treatment with radical surgery for a G-CSF-producing liver metastasis and was distinct from previously described cases in that the patient exhibited long-term survival. Given the unfavorable prognosis and relatively high probability of treatment failure associated with G-CSF-producing tumors, optimal diagnostic and therapeutic approaches and careful monitoring for the early detection of recurrence should be considered for patients with such tumors.

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Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Authors' contributions

SoH and NH designed the report. MT, TF, HS, IO, ShH and YO treated the patient and contributed to the collection of the clinical data. SoH analyzed the data and wrote the manuscript. NH, ShH and IO reviewed and edited the manuscript. NH, SW, SaH and KH reviewed the pathological findings, performed immunohistochemical staining and prepared the pathological images.

Ethics approval and consent to participate

Not applicable.

Consent for publication

The patients provided written informed consent for the publication of their clinical data and images.

Competing interests

The authors declare that they have no competing interests.

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