

## Case Report

# Primary small cell carcinoma of the stomach: a case report with an immunohistochemical and molecular genetic analysis

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Received December 18, 2012; Accepted January 15, 2013; Epub February 15, 2013; Published March 1, 2013

**Abstract:** Small cell carcinoma (SCC) of the stomach is extremely rare; about 110 cases have been reported in the world literature. Immunohistochemical studies of various antigens and genetic studies of *KIT* and *platelet-derived growth factor- $\alpha$*  (*PDGFRA*) have not been performed in gastric SCC. An 84-year-old man consulted our hospital because of epigastralgia and weakness. Blood test showed anemia and increased CA19-9 (233 U/ml). Endoscopic examination revealed a large Borrmann type III tumor measuring 6x8 cm in the stomach. Biopsies from the tumor revealed typical small cell carcinoma with very scant cytoplasm, hyperchromatic nuclei, absent nucleoli, molded nuclei, and increased nucleocytoplasmic ratio. Immunohistochemically, the tumor cells were positive for pancytokeratin (PCK) WSS, PCK MNF-116, PCK AE1/3, PCK CAM5.2, cytokeratin (CK) 34BE12, CK 5/6, CK7, CK8, CK18, vimentin, EMA, KIT (CD117), CD56, synaptophysin, chromogranin, NSE, CA19-9, CEA, p53 protein, and Ki67 antigen (Ki-67 labeling = 60%). The tumor cells were negative for CK14, CK19, CK20, *PDGFRA*, CD45, CD45RO, CD3, CD20, CD30, and CD79a. A retrospective genetic analysis using PCR-direct sequencing method in paraffin sections identified no mutations of *KIT* (exons 9, 11, 13 and 17) and *PDGFRA* (exons 12 and 18) genes. Various imaging modalities including CT and MRI showed multiple small metastases in the liver, bilateral lungs, and perigastric lymph nodes. The patient was thus inoperable. The patient is now treated by cisplatin-based chemotherapy four months after the first manifestation.

**Keywords:** Stomach, small cell carcinoma, histopathology, immunohistochemistry, molecular biology of *KIT* and *PDGFRA*

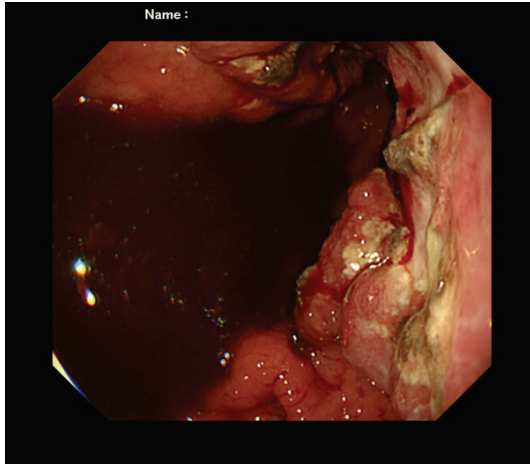
## Introduction

Small cell carcinoma (SCC) of the stomach is very rare. It was first reported in 1976 by Matsusaka et al [1]. Since then, about 110 cases have been reported in the world literature [2-5]. All are case reports, and there have been no studies of case series. In addition, there have been no immunohistochemical studies of gastric SCC. SCC of the lung is shown to express KIT and platelet-derived growth factor- $\alpha$  (*PDGFRA*), but has no mutations of these genes [6]. Several comprehensive studies of extra-gastric small cell carcinoma have been reported in the English literature [7-28]. However, there have been no reports of SCC of the stomach investigating protein expression and gene mutations of *KIT* and *PDGFRA*. The author reports herein a case of primary SCC of

the stomach with an examination of protein expressions of KIT and *PDGFRA* and gene status of *KIT* and *PDGFRA* genes. *KIT* and *PDGFRA* genes, both mapped to 4q12, encode receptor tyrosine kinase oncoproteins called KIT (CD117) and *PDGFRA*, respectively [29-34]. Both molecules are transmembranous oncoproteins, and play important roles in the carcinogenesis of several tumors such as gastrointestinal stromal tumor (GIST) [14-46]. The author also examined protein expression of various antigens by immunohistochemistry.

## Case report

An 84-year-old man consulted our hospital because of epigastralgia, weight loss, and weakness. Physical examination revealed anemia and emaciation. A blood laboratory test



**Figure 1.** Endoscopic findings. A large Borrmann III gastric cancer is seen in the stomach.

showed anemia ( $343 \times 10^4/\mu\text{l}$ ; normal  $450\text{--}550 \times 10^4/\mu\text{l}$ ), increased liver and bile ductal enzymes (alkaline phosphatase 566 IU/l; normal 104–338; AST 99 IU/l, normal 8–38; ALT 59 IU/l; normal 4–44; LDH; 1787 IU/l, normal 106–211), increased creatine phosphokinase (500 IU/l; normal, 56–244), increased C-reactive protein (0.95 mg/dl; normal 0–0.30), decreased Fe ( $38\mu\text{g/dl}$ ; normal 54–200), and increased CA19-9 (233 U/ml). Serum CEA was within normal ranges (2.3 ng/ml). Endoscopic examination revealed a large Borrmann type III tumor measuring 6x8 cm in the stomach (**Figure 1**).

Biopsies were taken from the gastric tumor. They revealed typical SCC with very scant cytoplasm, hyperchromatic nuclei, absent nucleoli, molded nuclei, and increased nucleo-cytoplasmic ratio (**Figure 2A** and **2B**). Necrotic areas were scattered, and there were many mitotic figures.

An immunohistochemical analysis was performed by Dako Envision methods (Dako Corp, Glostrup, Denmark), as previously reported [47–54]. Immunohistochemically, the tumor cells were positive for pancytokeratin (PCK) WSS, PCK MNF-116, PCK AE1/3, PCK CAM5.2, cytokeratin (CK) 34BE12, CK 5/6, CK7, CK8 (**Figure 3A**), CK18, vimentin, EMA, KIT (CD117) (**Figure 3B**), CD56 (**Figure 3C**), synaptophysin, chromogranin (**Figure 3D**), NSE (**Figure 3E**), CA19-9 (**Figure 3F**), CEA, p53 protein, and Ki67 antigen (Ki-67 labeling = 60%). The tumor cells were negative for CK14, CK19, CK20, PDGFRA, CD45, CD45RO, CD3, CD20, CD30, and CD79a.

A molecular genetic analysis of *KIT* gene (exons 9, 11, 13, and 17) and *PDGFRA* (exons 12 and 18) gene were performed by the PCR direct sequencing method, as previously reported [14–28, 35–41]. The exons of both genes were selected because they are frequent mutation sites [14–44]. The primers are shown in **Table 1**. In brief, genomic DNA was extracted from paraffin blocks with proteinase K digestion and phenol/chloroform extraction, and subjected to PCR for 40 cycles ( $94^\circ\text{C}$  for one minute,  $52^\circ\text{C}$  for one minute,  $72^\circ\text{C}$  for one minute), using a thermal cycler (GeneAmp PCR system 9700, Applied Biosystems, ABI, CA). The annealing temperature was  $53^\circ\text{C}$ . PCR products were extracted, and subjected to a computed automatic DNA sequencer (ABI PRISM 3100 Genetic Analyzer, Applied Biosystems, ABI, CA).

The retrospective genetic analysis using PCR-direct sequencing method in paraffin sections identified no mutations of *KIT* (exons 9, 11, 13 and 17) and *PDGFRA* (exons 12 and 18) genes.

Various imaging modalities including CT and MRI showed multiple small metastases in the liver, bilateral lungs, and perigastric lymph nodes. The brain was free from metastasis. The patient was thus inoperative. The patient is now treated by cisplatin-based chemotherapy four months after the first manifestation.

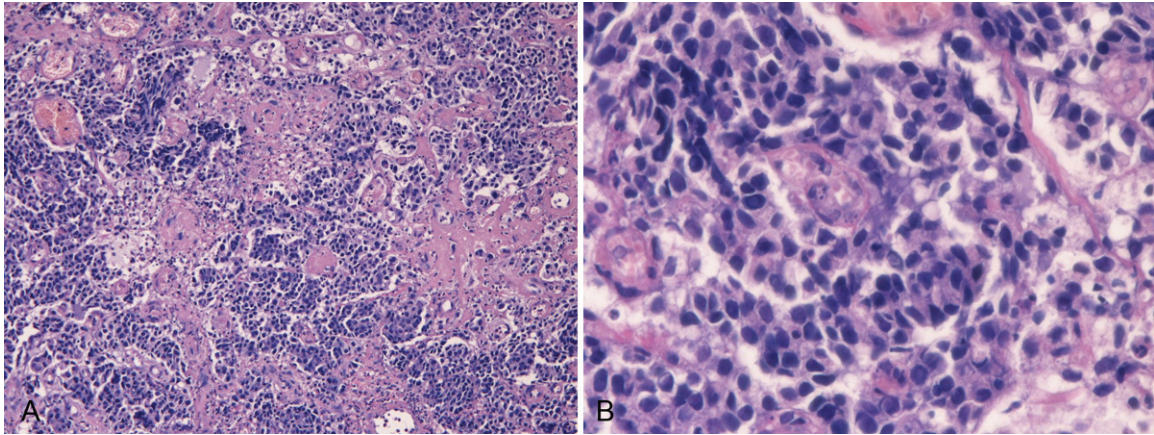
## Discussion

In the current case, tumor formations were seen in the stomach, liver, bilateral lungs, and perigastric lymph nodes. The largest tumor was that of the stomach, and the gastric tumor was primary in shape by endoscopy. Thus, the current case is primary gastric malignant neoplasm.

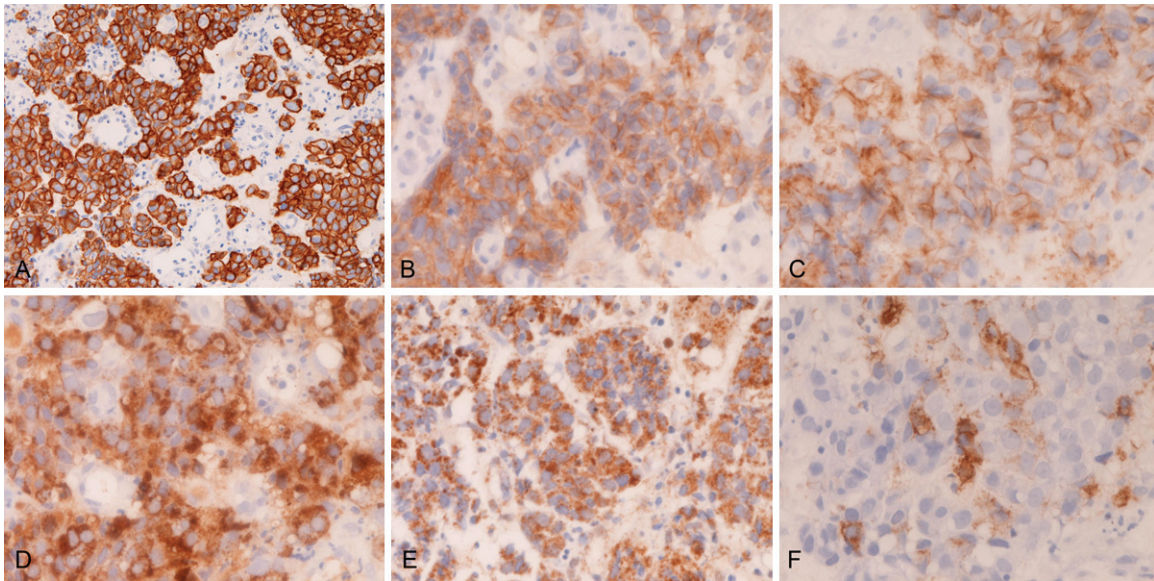
Histologically, the tumor was composed of small cells with very scant cytoplasm, hyperchromatic nuclei, absent nucleoli, molded nuclei, and increased nucleo-cytoplasmic ratio. Necrotic areas were scattered, and there were many mitotic figures. SCC is defined by only HE histology [55]. According to WHO criteria [55], it is defined as a malignant epithelial tumor consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli. The tumor cells are round, oval and spindle-shaped. Nuclear molding is prominent. Necrosis



## Gastric small cell carcinoma



**Figure 2.** HE histology of small cell carcinoma of the stomach. A: The biopsy showed malignant cells with hypercellularity. Necrotic areas are scattered. Low power view. HE, x50 HE, x100. B: Higher power view. The tumor are composed of malignant epithelioid tumor cells characterized by small cells, scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli. The tumor cells are round, oval and spindle-shaped. Nuclear molding is prominent. These features are typical for small cell carcinoma. HE, x200.



**Figure 3.** Immunohistochemical findings of the tumor cells. The tumor cells are positive for cytokeratin 18 (A), KIT (CD117) (B), CD56 (C), chromogranin (D), NSE (E) and CA19-9 (F). The expression of KIT is membranous. A: x200. B, C, D, E, F: x400.

is typically extensive and mitotic count is high [55]. More than 90 % of small cell carcinoma has neuroendocrine features [55]. The present case fulfills the criteria of SCC. Therefore, the current case is a typical primary gastric SCC.

The present case of gastric SCC is the first with an immunohistochemical examination in the gastric SCC. The tumor cells of the current gastric SCC cells were immunohistochemically positive for PCK WSS, PCK MNF-116, PCK AE1/3,

PCK CAM5.2, CK34BE12, CK 5/6, CK7, CK8, CK18, vimentin, EMA, KIT, CD56, synaptophysin, chromogranin, NSE, CA19-9, CEA, p53 protein, and Ki67 antigen (Ki-67 labeling = 60%). The tumor cells were negative for CK14, CK19, CK20, PDGFRA, CD45, CD45RO, CD3, CD20, CD30, and CD79a. The CK profile of pulmonary and extrapulmonary SCC is not restricted but shows various expression patterns [6-28], and there is SCC without CK expression [54]. The positive reaction of the current tumor cells for

**Table 1.** Primer sequence

Forward	Reverse
<i>KIT</i> exon 9 5'-TCC TAG AGT AAG CCA GGG CTT-3'	5'-TGG TAG ACA GAG CCT AAA CAT CC-3'
<i>KIT</i> exon11 5'-GAT CTA TTT TTC CCT TTC TC-3'	5'-AGC CCC TGT TTC ATA CTG AC-3'
<i>KIT</i> exon 13 5'-GCT TGA CAT CAG TTT GCC AG -3'	5'-AAA GGC AGC TTG GAC ACG GCT TTA-3'
<i>KIT</i> exon 17 5'-CTC CTC CAA CCT AAT AGT GT-3'	5'-GTC AAG CAG AGA ATG GGT AC-3'
<i>PDGFRA</i> exon12 5'-TTG GAT ATT CAC CAG TTA CCT GTC-3'	5'-CAA GGG AAA AGC TCT TGG-3'
<i>PDGFRA</i> exon 18 5'-ACC ATG GAT CAG CCA GTC TT-3'	5'-TGA AGG AGG ATG AGC CTG ACC-3'

chromogranin, CD56, synaptophysin and NSE, all of which are neuroendocrine antigens, indicates that the current SCC has apparent neuroendocrine features. Thus, the present case may be properly designated as "small cell neuroendocrine carcinoma" [55]. The positive CA19-9 and CEA suggests that the current gastric SCC shows focal adenocarcinomatous differentiation. The serum CA19-9 was high in the present case, which is consistent with presence of immunoreactive CA19-9 in tissue specimens. Positive p53 indicates p53 gene mutations. The high Ki-67 labeling suggests high cell proliferative activity and high malignant potential. SCC is occasionally similar to malignant lymphoma on HE-stained sections. Positive EMA, an epithelial antigen, indicates that the current tumor is an epithelial tumor. Although vimentin is an antigen of mesenchymal cells, it is well known that vimentin is occasionally expressed in epithelial tumor, as was the case of the current SCC. The negative reaction of CD45, CD45RO, CD3, CD20, CD30 and CD79a means that the current tumor is not malignant lymphoma. The positive KIT may suggest KIT gene mutations, while the negative PDGFRA may suggest no PDGFRA gene mutations.

The current gastric SCC showed distant metastases to multiple organs and lymph nodes. The patient is now treated by cisplatin-based chemotherapy. These findings imply that primary gastric SCC has poor prognosis. The pathogenesis of the current SCC of the stomach is unclear. It has been considered that SCC may arise from totipotent stem cell present in the mucosal epithelium [43]. In the present case, the gastric SCC may arise from such totipotent stem cells.

The novel findings in the present gastric SCC are that immunoreactive KIT was positive, but immunoreactive PDGFRA was negative. In SCC of other organs, both KIT and PDGFRA tend to be positive [6, 14-29]. The present is the first report of gastric SCC that examined KIT and PDGFRA proteins and *KIT* and *PDGFRA* genes. KIT and PDGFRA proteins and *KIT* and *PDGFRA* genes have rarely been investigated in extrapulmonary small cell carcinoma [14-29], while several comprehensive reports are present in small cell lung carcinoma. KIT has been reported to be expressed in 30-80% of the small cell lung carcinoma [6, 44, 45]. The present case shows that gastric SCC also expresses KIT protein. Only one study of PDGFRA protein has been reported in small cell lung carcinoma [6], and this study [6] showed frequent expression of PDGFRA in small cell lung carcinoma. Many studies showed positive protein expression of KIT and PDGFRA in extrapulmonary SCC of other organs [14-29]. The present case of gastric SCC did not show PDGFRA expression, suggesting that the present oral SCC does not express this oncoprotein.

The present cases did not identify mutations of *KIT* and *PDGFRA* genes. Most reports of small cell lung carcinoma have shown no mutations in *KIT* genes [6, 43], except for Boldrini et al. [44] who found five mutations in 60 small cell lung carcinomas. On the other hand, Terada [6] and Sihto et al. [43] identified no *KIT* mutations in many cases of small cell lung carcinomas. More studies of *KIT* mutations remain to be performed in the SCC. With regard to *PDGFRA* mutations, Terada [6] and Sihto et al. [43] found no mutations in many cases of small cell lung carcinomas. Sihto et al. [43] insisted that KIT

expression in small cell lung carcinoma is due not to *KIT* gene mutations but to *KIT* gene amplification. With regard to extrapulmonary SCC, Terada [6, 14-28] showed that there are no mutations of *KIT* and *PDGFRA* in the extrapulmonary SCC.

Among many *KIT*-positive tumors, GIST and extra-GIST are representative [10-15, 37, 39-41]. It is thought that GIST arises from interstitial cell of Cajal, a pacemaker neuronal cell that normally expresses *KIT* protein [29-37]. In contrast, SCC is an undifferentiated carcinoma with neuroendocrine phenotypes. The original cell of SCC is unknown. Recently, Blumming et al. [45] found that GIST expresses synaptic vesicle proteins, and suggested that GIST has endocrine features. Therefore, it is suggested that there may be an association between GIST and SCC in that the both entities have neuroendocrine features.

Several studies of GIST have revealed that there are minute subclinical microGISTs or "GIST tumorlets" in the gastrointestinal tract [56, 57]. The incidence of these is about 20%, and these are considered as GIST precursors. Frequent *KIT* mutations (about 46%) and occasional *PDGFRA* mutations (about 4%) are present in these "GIST tumorlets" [56, 57]. However, these "GIST tumorlets" do not always develop into clinical GIST. Other genetic events are necessary for the development of clinical GIST. In contrast, little is known about the precursor lesions in SCC.

Recently, the phosphorylation (activation) status of *KIT* and *PDGFRA* has been studied [58, 59]. This is particularly important in *KIT* mutation-negative tumors as in the present case. *KIT* kinase activation and downstream signaling proteins leading to tumorigenesis have been studied, but little is known as yet. Protein kinase C- $\theta$  and PI3-kinase/AKT are activated in imatinib-resistant GIST [58, 59], and analyses of these *KIT* signaling molecules may be important in the treatment of GIST. Such studies are not performed in SCC. In the present case, the author could not investigate these molecules, because no relevant antibodies were available. *KIT* tyrosine kinase activity and *KIT* signaling abnormalities in SCC remain to be elucidated.

In summary, the author reported an extremely rare case of primary gastric SCC. An extensive

immunohistochemical study was performed. The gastric SCC expressed *KIT* protein, but not *PDGFRA* protein. No *KIT* and *PDGFRA* mutations were recognized.

## Conflict of interest statement

The author has no conflict of interest.

## Acknowledgements

This work was approved by Ethics Committee of our hospital.

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