Multiple gastrointestinal stromal tumors caused by a novel germline *KIT* gene mutation (Asp820Gly): a case report and literature review

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract; most of them have gain-of-function mutations of the *KIT* gene. There have been rare cases of families with multiple GISTs, that had autosomal dominant germline *KIT* mutations. Here, we present a case of multiple GISTs caused by a novel germline *KIT* mutation. Intraoperatively, the main tumor was present in the body of the stomach, and multiple small nodules were detected mainly in the upper and middle part of the gastric wall; several nodules were also present in the small bowel wall. The main tumor and surrounding nodules were resected. DNA sequencing of the tumor tissue, adjacent normal mucosal tissue, and peripheral blood leukocytes revealed that the patient had germline Asp820Gly mutation in exon 17 of the *KIT* gene. This is the first case with germline Asp820Gly mutation in exon 17 of the *KIT* gene.

Keywords Gastrointestinal stromal tumor · GIST · Exon 17

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract [1]. GISTs are derived from the interstitial cells of Cajal (ICCs) or their precursors owing to gain-of-function mutations in either the *KIT* gene that encodes the KIT receptor tyrosine kinase (CD117), or the platelet-derived growth factor receptor alpha gene [2]. Most GISTs are sporadic, and often have mutations in exons 11 or 9 of the *KIT* gene. In contrast, familial and multiple GISTs with germline *KIT* mutations occur as a rare autosomal dominant disorder. Approximately

40 cases of familial GIST have been reported to date [3]. Mutations in exon 11 of the *KIT* gene were detected in 25 families, while mutations in exon 17 were detected in only four families. The previously observed mutations in exon 17 are Asp820Tyr and Asn822Tyr [4–7]. Herein, we present the case of a patient with multiple GISTs with a novel germline *KIT* gene mutation (Asp820Gly) in exon 17.

Case presentation

In 2009, a 73-year-old female patient was admitted to the Department of Gastrointestinal Medicine at our hospital due to epigastric pain. She had no symptoms on the skin such as neurofibromas and café-au-lait spots, reminiscent of type 1 neurofibromatosis. Upon endoscopic examination, multiple gastric submucosal tumors (SMTs) were found in the lesser curvature of the stomach (Fig. 1a). The patient was followed up as an outpatient as she did not have severe symptoms, and her SMTs were of a moderate size (diameter < 2 cm). Gastric endoscopic examinations were performed in 2009, 2010, and 2012. In 2010, the patient started experiencing heartburn, and the maximum diameter of the SMTs on computed tomography (CT) scan was approximately 2 cm (Fig. 1b). However, in 2015,

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Fig. 1 Representative images obtained on endoscopic examination and computed tomography (CT) scan. **a** Endoscopic image showing multiple SMTs in 2009 (white arrowheads). **b** A CT image of the main tumor in 2010. The maximum diameter was approximately 2 cm (red arrowheads). Scale bar: 5 cm. **c** An endoscopic image of the main tumor in 2015 (white arrowheads). **d** A CT image of the main tumor in 2015. The maximum diameter was greater than 5 cm (red arrowheads). Scale bar: 5 cm

surgical treatment was required owing to enlargement of the tumors to > 5 cm in diameter (Fig. 1c, d).

Intraoperatively, the main tumor was found in the body of the stomach (Fig. 2a). Multiple small nodules were also detected, mainly in the upper and middle part of the gastric wall (Fig. 2b), and several nodules were observed in the small bowel (Fig. 2c). Considering the treatment burden related to surgery, only the main tumor and the nodules around the main tumor were resected.

Results

The operative specimens revealed that the main tumor had a diameter of 8 cm (Fig. 3a, b). Histopathological examination showed that multiple small nodules were present around the main tumor, which along with the small surrounding nodules were composed of spindle shaped cells (Fig. 3c). The tumor cells tested positive for both, KIT and CD34 on immunohistochemical examination (Fig. 3d, e), and the mitotic rate was less than 5 per 50 high-power fields. The risk stratification of the main tumor was intermediate, according to the modified

Fig. 2 Representative images obtained intraoperatively. **a** The main tumor of the stomach (white arrowhead). **b** Small nodules were detected on the serous surface of the stomach (white arrowheads). **c** Small nodules were also detected on the surface of the small bowel (white arrowhead)

Fig. 3 Macroscopic and histological images of operative specimens. **a** A macroscopic image of the resected main tumor. **b** The cut surface of the tumor. The maximum diameter of the main tumor was 8 cm, including the necrotic tissue. **c** Specimens stained with hematoxylin and eosin showed that the tumor was composed of proliferation of

spindle shaped cells (original magnification: $\times 200$). **d** Immunostaining for KIT showed positive findings (original magnification: $\times 40$). **e** Immunostaining for CD34 also showed positive findings (original magnification: $\times 40$)

Fletcher classification. Sequence analysis of the genomic DNA revealed that the main tumor had an Asp820Gly mutation in exon 17 of the *KIT* gene (Fig. 4). The mutation was also detected in the adjacent normal mucosal tissue of the stomach, indicating that it was a germline mutation (Fig. 4). Sequence analysis using genomic DNA derived from peripheral leukocytes confirmed the germline Asp820Gly mutation (Fig. 4).

Discussion

In familial and multiple GISTs, various types of germline mutations have been detected in exons 8, 11, 13, and 17. Approximately 40 cases of familial and multiple GIST with germline *KIT* mutation have been reported to date [3], among which 25, 9, and 4 families had mutations of exons 11, 13, and 17, respectively. Only one case each has been reported with familial and multiple GIST with mutations in exons 8 or 9. The present case is the fifth report of a case involving multiple GISTs having an exon 17 *KIT* mutation. Notably, this is the first case of an Asp820Gly germline mutation, since previously detected exon 17 mutations included only Asp820Tyr and Asn822Tyr (Table 1) [4–7].

Some concomitant symptoms of familial GISTs have been reported. Since the function of the KIT receptor tyrosine kinase is essential for the development of both, ICCs and

Fig. 4 The results of the DNA sequence analysis of the *KIT* gene in exon 17. Adenine has been replaced by guanine heterozygously at codon 820 of exon 17, resulting in the exchange of aspartic acid (Asp) for glycine (Gly), Asp820Gly, in the patient's samples. The upper, middle, and lower DNA sequences indicate the main tumor, normal mucosal tissue, and peripheral leukocytes, respectively

Table 1 Details of the cases involving familial GIST with a mutation in exon 17 of the *KIT* gene

Family	First author (year)	Mutated protein	Sex	Age, (years)	Tumor location	Modified Fletcher classification	Surgery	Imatinib	Survival
Family 1	Hirota et al. (2002)	Asp820Tyr	Male	71	Gastric, small bowel	Unknown	+	–	Survived
			Female	Unknown	Unknown	Unknown	–	–	Died
			Female	57	Gastric, small bowel	Unknown	+	–	Survived
			Female	70	Gastric	Unknown	–	–	Survived
			Female	65	Gastric	Unknown	–	–	Survived
			Male	36	Gastric	Unknown	–	–	Survived
Family 2	O’Riain et al. (2005)	Asp820Tyr	Male	38	Gastric, duodenum, small bowel, liver	High risk	+	–	Unknown
			Female	54	Gastric, small bowel	Intermediate risk	+	–	Unknown
			Female	63	Small bowel	Unknown	+	–	Unknown
			Female	30	Small bowel	Unknown	–	–	Survived for decades after surgery
			Male	70	Ileocecal	Unknown	+	–	Unknown
Family 3	Thalheimer et al. (2008)	Asn822Tyr	Female	42	Small bowel, omentum, mesentery	Low risk	+	Adjuvant	Survived (complete remission)
			Female	44	Small bowel	Low risk	+	–	Survived
			Male	49	Small bowel, pararectal tumor	Unknown	+	Adjuvant	Survived
			Male	Unknown	Gastric, small bowel	Unknown	+	–	Survived to the age of 80 years
Family 4	Veiga et al. (2010)	Asp820Tyr	Male	56	Gastric, small bowel, rectal	High risk	+	Neoadjuvant + + adjuvant	Survived (stabilized)
			Female	62	Gastric, greater omentum	High risk	+	Adjuvant	Died
Our patient ^a	Our case (2019)	Asp820Gly	Female	73	Gastric, small bowel	Intermediate risk	+	–	Survived

^aThe family history of the present patient is as yet unknown

melanocytes and mast cells, gain-of-function mutations of the *KIT* gene may induce diffuse ICC hyperplasia, hyperpigmentation, and mastocytoma. ICC hyperplasia at the gastroesophageal junction may be associated with achalasia-like dysphagia. Heartburn, a symptom observed in the present case, may be related to the dysphagia caused by ICC hyperplasia at the gastroesophageal junction [5].

We experienced a case of multiple GISTs caused by a novel germline *KIT* gene mutation (Asp820Gly); this patient was probably a proband with the novel mutation. The diagnostic criteria for familial GISTs have not been formally defined yet. The detection of germline *KIT* gene

mutations in both, tumor tissues and adjacent normal tissue or blood samples (peripheral leukocytes) is usually necessary for a positive diagnosis. In the present case, although we demonstrated the presence of mutations in the all the samples, i.e., tumor tissues, adjacent normal mucosal tissue, and peripheral leukocytes (Fig. 4), further investigations into detailed family history, including germline mutations, are needed to prove familial GIST.

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Compliance with ethical standards

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

Ethics approval Not applicable.

Patient anonymity and informed consent Written informed consent was obtained from the patient for publication of this report and the accompanying images, and the patient's anonymity was upheld.

Availability of data and materials All data supporting the conclusions of this study are included in this published article.

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