Familial and Multiple Gastrointestinal Stromal Tumors with Fair Response to a Half-dose of Imatinib

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Since our first report in 1998, approximately 30 families with multiple GISTs due to a germline gain-of-function mutation of c-kit have been reported. We herein present a case of a family with multiple GISTs that have a germline c-kit mutation in exon 11 (Del-Val560) in two siblings. One of the patients showed a fair response to treatment with a half-dose of imatinib (200 mg/day). There are few reports describing the response to imatinib in familial GISTs and this drug appears to be a promising therapeutic option.

Key words: gastrointestinal stromal tumor, germline mutation, c-kit, imatinib

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Introduction

Gastrointestinal stromal tumors (GISTs) are one of the most common mesenchymal tumors originating from the gastrointestinal (GI) tract. Previously, most mesenchymal tumors in the GI tract were believed to originate from smooth muscle. However, with the progress in immunohistochemical analysis, it was noted that most GI mesenchymal tumors were different from true leiomyomas and lacked smooth muscle differentiation. In 1998, we first identified that GISTs appear to originate from interstitial cells of Cajal (ICCs) and that most GISTs have gain-of-function mutations of c-kit (1).

Familial GIST is an extremely rare autosomal dominant disorder based on a hereditary predisposition to develop multiple GISTs due to a germline gain-of-function mutation of c-kit (2). Diffuse proliferation of ICCs in the myenteric plexus layer of the intestine has been described in patients with familial GISTs. We have also shown the polyclonal nature of diffuse ICC proliferation using inactivation at the human androgen receptor (HUMARA) locus as well as the monoclonality of GIST tissues (3).

The somatic c-kit gene mutation is reported in approximately 90% of all sporadic GISTs (4), and it is frequently located in exon 11. In patients with familial GISTs, most of the germline mutations are also located in exon 11.

We herein describe a family having a germline gain-of-function mutation of c-kit in exon 11 (Del-Val560). Notably, one of the patients showed a fair response to imatinib. To our knowledge, there are few reports describing the response to imatinib in familial GISTs, and we report them here together with a review of the pertinent literature.

Case Report

A 43-year-old woman (Fig. 1; case 1) with a 3-year history of rheumatoid arthritis treated with infliximab complained of a dull right lower abdominal pain and underwent contrast-enhanced abdominal computed tomography (CT). Abdominal CT revealed a large mass lesion (50x30 mm in size) in the small intestine (Fig. 2). The patient was admit-
ted to our hospital for further examination. Laboratory findings such as common blood cell count and blood biochemistry were normal. Esophagogastroduodenoscopy (EGD) revealed multiple gastric submucosal tumors. Single balloon enteroscopy showed a jejunal protruding submucosal tumor with ulceration on the surface (Fig. 2). Surgical resection of the jejunum was performed. The tumor was maximum 40 mm in size. Immunohistochemical analysis revealed that the tumor was positive for KIT and negative for CD34 (Fig. 3), and it was diagnosed as GIST. Hyperplasia of ICC was not observed in the resected specimen. The mitotic count was less than 5/50 high power field (HPF); therefore, the tumor...
was classified as low risk group in the Miettinen classification (5). The infliximab treatment was stopped for this patient and no adjuvant chemotherapy was performed. There are two main reasons for choosing strict follow-up: (1) the resected tumor was low risk, and (2) the cost of taking imatinib is expensive. However, imatinib should be started if the tumor progression is faster than expected.

The father of this patient, a 79-year-old man (Fig. 1; case 2), had a previous history of small bowel surgery for small bowel perforation due to mass lesion at a local hospital when he was 76 years old. Upon request, the medical records of the father were obtained, which revealed that abdominal CT showed multiple mass lesions (maximum 80 mm in size) at the small intestine and the histology of the operated sample was confirmed as GIST. We suspected the possibility of familial GISTs and had the patient undergo contrast-enhanced abdominal CT. CT findings revealed multiple mass lesions located at the duodenum and the small intestine (Table). EGD and endoscopic ultrasonography (EUS) revealed a hypoechoic submucosal tumor originating from the 4th layer (Fig. 4). EUS-guided fine needle aspiration biopsy (EUS-FNAB) was performed. The tumor was positive for KIT and negative for CD34 and diagnosed as GIST (Fig. 4).

After obtaining informed consent, blood samples from cases 1 and 2 were used to analyze the sequence of the c-kit gene. In case 1 and 2, a germline c-kit mutation was identified in exon 11, resulting in the deletion of codon 560 coding for valine (Fig. 5), and they were diagnosed as having familial GIST. No c-kit mutation was found in the analyzed blood sample of the brother of case 1 (Fig. 1; case 3).

Imatinib treatment for GISTs was considered for case 2. Due to his age, case 2 received a half-dose of imatinib (200 mg/day). The size of all GISTs markedly reduced after one year (duodenal GISTs are shown in Fig. 6).

### Discussion

Multiple GISTs are more frequently observed in patients with type 1 neurofibromatosis (NF-1) than in familial GISTs. Patients who have multiple GISTs without classical symptoms of NF-1 may be familial GIST cases. A detailed familial history and physical examination may determine the diagnosis.

The mechanism of tumor initiation in familial GISTs remains unclear. We investigated the resected specimen of case 1 using sequence analysis. However, the tumor had a heterozygous c-kit mutation. We cannot exclude a second hit in other genes that would be responsible for tumor initiation.

Including our previous reports, germline c-kit mutations have been identified in approximately 30 families (6) at the extracellular domain (exon 8) (7), the juxtamembrane domain (exon 11) (8-15), the tyrosine kinase I domain (exon 13) (16), and the tyrosine kinase II domain (exon 17) (2, 17). Previous reports present hyperpigmentation of the skin (7, 9-12, 15), mastocytosis (7, 11, 12, 15), and dysphagia (2, 7, 9, 12, 17) in addition to multiple GISTs. The valine deletion in exon 11 identified here in this family at the juxtamembrane domain of c-kit has been reported in another family by Nishida et al. (14). Unlike Nishida’s case, neither case 1 nor case 2 had hyperpigmentation. Although mastocytosis and dysphagia are sometimes observed in fa-
Figure 4. Endoscopic findings of SMT in the first portion of the duodenum. The conventional view (a) and EUS image using convex probe 7.5 MHz (b) are shown. Microscopic findings of the samples obtained from EUS-FNAB are also depicted using Hematoxylin and Eosin staining (c) and immunohistochemistry for KIT (d) and CD34 (e) [original magnification: (a), (b), and (c), 80×].

Case 1: daughter

Case 2: father

Figure 5. Germline c-kit mutation in exon 11 in case 1 and 2. Sequence analysis of c-kit exon 11 showed a heterozygous deletion of 3 base pairs resulting in the loss of codon 560 coding for valine. DNA was extracted from whole blood.

milial GIST patients, our patients and Nishida’s case did not have those symptoms.

According to the clinical practice guidelines for GIST in Japan, surgical treatment is the first choice for sporadic GISTs (18). Unlike sporadic GISTs, multiple tumors are usually observed in familial GISTs leading to a higher proportion of unresectable tumors. With at least three tumors in the duodenum, we provided case 2 with three options: (1) surgical resection using pancreatoduodenectomy, which we did not recommend; (2) imatinib treatment; and (3) monitoring every 3 months. He decided to be treated with imatinib. The clinical response for his tumors would also suggest positive drug response in his daughter who carries the same genetic mutation.

Heinrich et al. reported that the partial response rate of imatinib was 83.5% in patients with sporadic GISTs harboring exon 11 c-kit mutations, whereas patients with tumors with exon 9 c-kit mutation, or no detectable mutation of c-kit or PDGFRA, had a partial response rate of 47.8% and 0.0%, respectively (19). In patients with familial GISTs, imatinib may become a potential therapeutic option such as in our case where a half-dose of imatinib was effective. The long-term prognosis for patients with familial GISTs is not yet known. However, the growing speed of intestinal GISTs is relatively slow in case 2. Initiating drug therapy should be decided depending on the clinical status in each individual case.
The authors state that they have no Conflict of Interest (COI).

References
