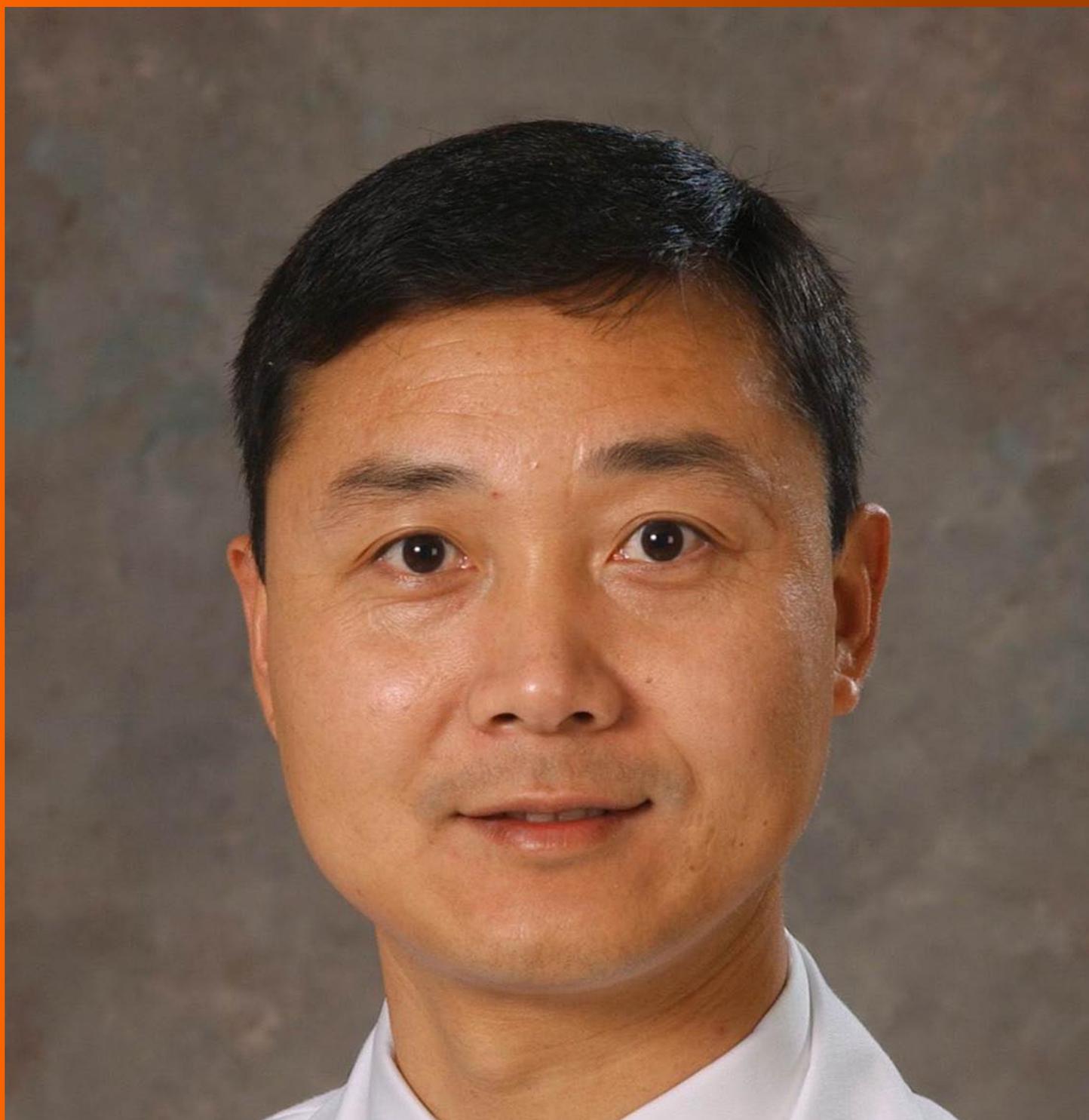


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*World Journal of Radiology (World J Radiol, WJR, online ISSN 1949-8470, DOI: 10.4329)* is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJR covers topics concerning diagnostic radiology, radiation oncology, radiologic physics, neuroradiology, nuclear radiology, pediatric radiology, vascular/interventional radiology, medical imaging achieved by various modalities and related methods analysis. The current columns of WJR include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (clinicopathological conference), and autobiography.

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**INDEXING/ABSTRACTING**

*World Journal of Radiology* is now indexed in PubMed, PubMed Central, and Emerging Sources Citation Index (Web of Science).

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**NAME OF JOURNAL**  
*World Journal of Radiology*

**ISSN**  
 ISSN 1949-8470 (online)

**LAUNCH DATE**  
 January 31, 2009

**FREQUENCY**  
 Monthly

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**PUBLICATION DATE**  
 September 28, 2017

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## Imatinib response of gastrointestinal stromal tumor patients with germline mutation on *KIT* exon 13: A family report

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**Author contributions:** Engin G analysed data, designed and wrote the paper; Eraslan S performed molecular analysis and made the last revision of the report; Kayserili H performed genetic work-up and made the last revision of the report; Kapran Y performed the pathologic analyses; Akman H performed the computed tomography; Akyuz A performed surgical operations and Aykan NF collected the clinical data of patients, performed medical treatments and made the last revision of the report.

**Institutional review board statement:** This case report was approved by the Institutional Review Board of Istanbul University Oncology Institute in Istanbul.

**Informed consent statement:** The patients involved in this study gave their written informed consent authorizing use and disclosure of their protected health information.

**Conflict-of-interest statement:** All the authors have no conflicts of interests to declare.

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**Manuscript source:** Invited manuscript

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**Received:** January 27, 2017

**Peer-review started:** February 9, 2017

**First decision:** June 12, 2017

**Revised:** July 24, 2017

**Accepted:** August 2, 2017

**Article in press:** August 2, 2017

**Published online:** September 28, 2017

### Abstract

Familial gastrointestinal stromal tumor (GIST) is a rare autosomal dominant disorder associated with mutations in the *KIT* gene in the majority of cases. Although, exon 11 appears to be the hot spot region for approximately 95% of germline mutations, pathogenic variations have also been identified in exon 8, 13 and 17. Exon 13 germline mutations are extremely rare amongst familial GISTs and seven families with a germline mutation have been reported to date. Moreover, the role of imatinib mesylate in this rare familiar settings is not completely known so far. We describe here clinical, imaging, pathological and genetic findings of a family with four affected members; grandmother, his son and two grand-sons having a germline gain-of-function mutation of *KIT* in exon 13 and discuss the imatinib mesylate treatment surveillance outcomes towards

disease management.

**Key words:** Gastrointestinal stromal tumor; Familial; Germline mutation; Imatinib; Response

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**Core tip:** Familial gastrointestinal stromal tumor (GIST) with exon 13 germline mutations are extremely rare. Moreover, there are only a few reports describing the response to imatinib in familial GISTs. The data on the role of imatinib in familial GISTs is still limited. Understanding the role of imatinib is important for the appropriate management of mutation positive familial GISTs. It is also crucial to be able to determine the role of specific germline *KIT* mutations in. We hereby report our findings in consideration of up-to-date information.

Engin G, Eraslan S, Kayserili H, Kapran Y, Akman H, Akyuz A, Aykan NF. Imatinib response of gastrointestinal stromal tumor patients with germline mutation on *KIT* exon 13: A family report. *World J Radiol* 2017; 9(9): 365-370 Available from: URL: <http://www.wjgnet.com/1949-8470/full/v9/i9/365.htm> DOI: <http://dx.doi.org/10.4329/wjr.v9.i9.365>

## INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors originating in the gastrointestinal tract. GISTs constitute 1%-3% of all malignant gastrointestinal tumors and the majority of cases are sporadic<sup>[1]</sup>. Familial GIST is an extremely rare autosomal dominant condition which is predominantly due to germline gain-of-function mutations of *KIT* and to a lesser extent of *PDGFRA*<sup>[2]</sup>. Diffuse proliferation of interstitial cells of Cajal (ICCs) in the myenteric plexus layer of the intestine has been described in patients with familial GISTs<sup>[3]</sup>.

Familial GISTs, associated with germline gain-of-function mutations of *KIT* have been described in 35 families<sup>[2,4,5]</sup>. Somatic *KIT* mutations are reported in approximately 60% of all sporadic GISTs, and almost 95% of all mutations are located in exon 11<sup>[6]</sup>. In patients with familial GISTs, most germline mutations are also located in exon 11<sup>[4]</sup>. Familial GISTs with exon 13 mutations are extremely rare, the range of frequency of exon 13 mutations is between 0.8% to 4.1%. Seven families with a germline gain-of-function mutation of *KIT* in exon 13 have been reported to date<sup>[7-12]</sup>.

Surgery is the primary treatment for localized GISTs. Imatinib mesylate, which is a tyrosine kinase inhibitor, is administered as adjuvant therapy for high-risk groups after the operation or as neoadjuvant therapy for the management of advanced GISTs which are not candidates for surgery at initial diagnosis<sup>[13,14]</sup>. There are only a few reports describing the response to

imatinib in familial GISTs confirming it as a promising therapeutic option<sup>[4,5,10]</sup>.

We here describe clinical, imaging, pathological and genetic findings of a family with four affected members, grandmother, his son and two grandsons having a germline gain-of-function mutation of *KIT* in exon 13 and discuss the imatinib treatment surveillance outcomes towards disease management.

## CASE REPORT

We describe a family, father and two sons, with multiple GISTs. Grandmother was reported as being operated at the age of 62 and staged as advanced GIST. Genetic analysis was carried out on DNA obtained from peripheral blood samples from three affected individuals, and there was no DNA available from the grandmother (Figure 1). Sequence analysis of *KIT* gene (RefSeq ID: NM\_000222.2; NP\_000213.1) revealed a heterozygous exon 13 c.1924A>G (p.Lys642Glu; p.K642E) gain-of-function mutation in all three cases (Figure 2). This result was in concordance with the familial GIST diagnosis.

All three had been operated and found to have low risk, grade 1 multiple GISTs (T2N0M0). Immunohistochemical studies of the tumors showed strong positivity for CD117 (c-kit) (Figure 3). The father and older sibling were treated with imatinib for rest tumors after resection and showed a partial response to treatment.

### Patient 1 (III-1; 36 years)

The patient has been hospitalized due to massive GIS bleeding at the age of 20 and was operated at the age of 27 after an intensive rectal bleeding. Mesenteric angiography showed bleeding from proximal jejunal branches and tumoral staining. The bleeding branches embolized. Abdominal computed tomography (CT) revealed proximal jejunal wall thickening and nodular solid lesions with 2.5 cm in diameter. Laparoscopic jejunal resection was made and histopathological examination showed low risk grade 1 GIST with strong positivity for CD117(c-kit) (pT2N0M0). Postoperative follow-up PET-CT demonstrated normal findings. He was, thereafter, treated with imatinib (400 mg/d) for five years due to residual multiple, milimetric GISTs and annual follow-up PET-CT showed no recurrence during that period. Imatinib treatment was terminated upon patient's request, end of five years treatment, in 2012. A recent follow-up PET-CT scan identified two nodular lesions in jejunum, 2 cm (SUVmax: 4.69) and 1.5 cm (SUVmax: 1.68) in diameters, which were consistent with GIST recurrence (Figure 4). Abdominal CT revealed multiple duodenal, jejunal and ileal contrast enhanced solid, nodular lesions with maximum 3 cm in diameter. The patient rejected the operation and preferred the re-treatment of imatinib (400 mg/d). A partial response was obtained again in the following 3 mo (Figure 5). The proband had multiple nevi on palms and soles which showed

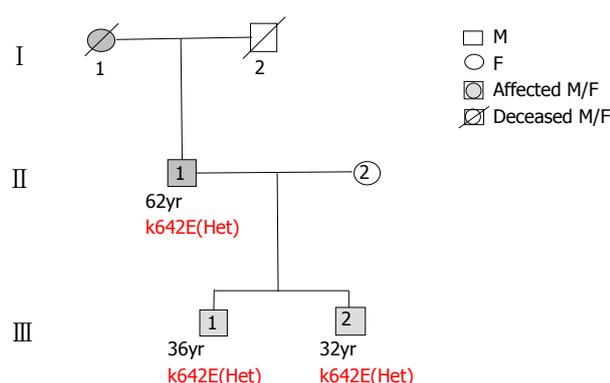


Figure 1 Pedigree of the family shows vertical transmission of *KIT* exon 13 c.1924A>G (p.Lys642Glu; p.K642E) mutation. Het: Heterozygous.

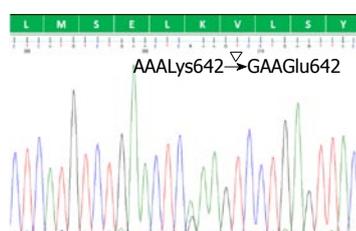


Figure 2 Electropherogram shows exon 13 c.1924A>G missense mutation leading to a change of lysine at position 642 to glutamine (p.Lys642Glu; p.K642E) (dbSNP: 121913512) of *KIT* gene at heterozygote state in three affected family members.

regression after the initiation of the treatment and had hypopigmentation of skin in general.

### Patient 2 (III-2; 32 years)

He was referred due to abdominal distension and dysphagia at the age of 32. Gastroduodenal endoscopic examination and endoscopic ultrasonography (EUS) showed a gastric submucosal 1.4 cm tumor in diameter on the small curvature of prepyloric antrum. Colonoscopy showed normal findings.  $^{18}\text{F}$ -FDG PET-CT revealed two lesions, one at the prepyloric antrum 1.5 cm in diameter with a SUVmax: 5.0 and another at jejunum 2.2 cm in diameter with a SUVmax: 5.39. Abdominal CT showed multiple solid, contrast enhanced mass lesions maximum 3.5 cm in diameter located at the jejunum in addition to the prepyloric antral mass. Partial jejunal resection, multiple wedge resection of stomach and jejunum was performed. Histopathological examination showed low risk grade 1, multifocal masses, two, in stomach at 2.5 cm in diameter and multiple in jejunum, more than 20 with a maximum diameter of 4 cm). Tumors showed strong positivity for CD117 (c-kit) (pT2N0M0). The patient opted for no adjuvant therapy and decided to be followed up by routine annual PET-CT.

### Patient 3 (III-3; 62 years)

The father had been treated for gastrointestinal bleeding at the age of 18 and preoperatively diagnosed

as GIST at the age of 25. He had Billroth operation at the age of 28 and had bleeding episodes thereafter and is on imatinib for the past eight years. At the age of 53, abdominal CT revealed multiple solid lesions with heterogenous contrast enhancement at the distal duodenum, max 5.2 cm in diameter, proximal and middle jejunum, max 5.0 cm in diameter. Three similar solid lesions were further identified at the esophageal wall of the esophago-gastric junction level (2.0 cm in diameter), at the colonic wall of the splenic flexura level (1.2 cm in diameter) and of the rectosigmoid junction level (1.0 cm in diameter), respectively. There was no additional pathologic finding in the liver, peritoneal or retroperitoneal areas. Partial jejunal resection and multiple wedge resections from the esophagus, colon and rectum were performed. Histopathological examination showed low risk grade 1 multifocal GIST with strong positive CD117 (c-kit) (pT2N0M0). After the operation, the patient has been treated with imatinib (400 mg/d) for 8 years due to residual multiple, milimetric GISTs without recurrence on annual follow-up PET-CT.

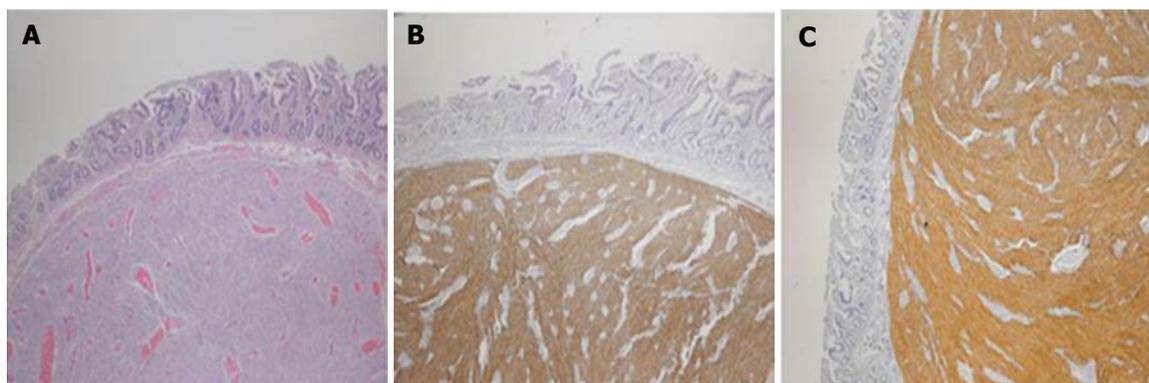
## DISCUSSION

We present an extremely rare condition of autosomal dominant familial GIST with heterozygous c.1924A>G (p.Lys642Glu; p.K642E) germline *KIT* mutation in exon 13 (K642E). All three patients had been operated and two of them were treated with imatinib due to residual multiple, milimetric GISTs to which they all showed partial response.

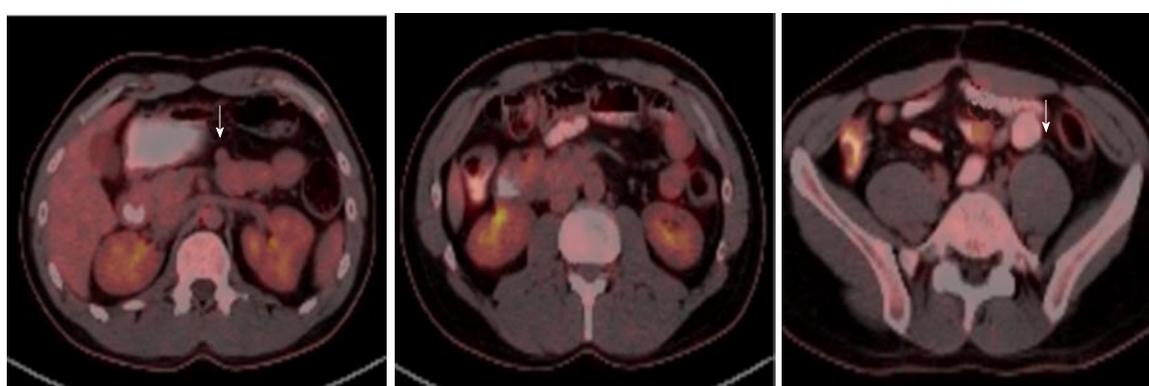
Surgery is the initial treatment for primary and localized GISTs, targeting complete resection with macroscopic and microscopic negative margins and functional preservation by wedge resection, whenever applicable. The management of a positive microscopic margin after macroscopic complete resection is not well defined, and options may include re-excision, watchful waiting, and adjuvant imatinib therapy. Imatinib mesylate is a first-line standard therapy for inoperable, metastatic, or recurrent GISTs. It is also indicated as adjuvant treatment for intermediate or high risk group of GISTs<sup>[14]</sup>.

Only about half of the patients with sporadic GIST respond to imatinib treatment; 12%-14% show primary resistance to imatinib, and 40%-50% experience secondary resistance and disease progression within 2-3 years from the beginning of therapy<sup>[5]</sup>. With regard to familial GISTs, there are only 12 reports on the use of imatinib in 24 patients with *KIT* germline mutations<sup>[8,10,15-24]</sup>.

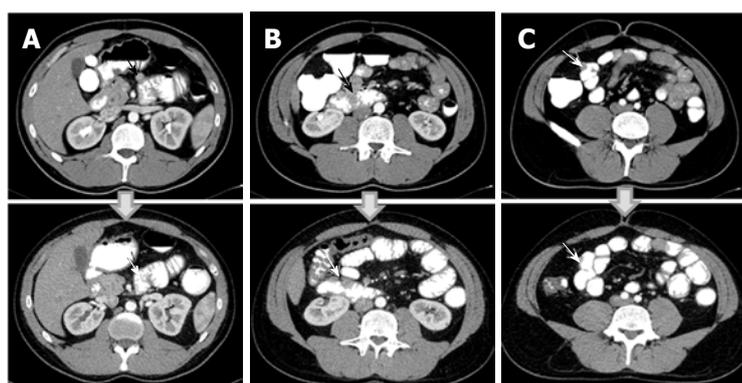
The effect of imatinib on the inhibition of *KIT* activation is dependent on the site of the mutation within the *KIT* gene<sup>[5,25]</sup>. Previous studies described that the best responses were obtained in GISTs with exon 11 mutations with a daily dose of 400 mg while a daily double dose of 800 mg is required in cases with exon 9 mutation<sup>[5,26,27]</sup>. Clinical data on the effect of imatinib against sporadic GISTs with exon 13



**Figure 3** Microscopic findings of gastrointestinal stromal tumor located in the proximal jejunum. Hematoxylin and Eosin staining revealed spindle cells in small bowel submucosa and wall (A). Immunohistochemistry for DOG1 (B) and c-KIT (C) showed immun activity in the tumor cell (original magnification: A, B and C, 40 ×).



**Figure 4** <sup>18</sup>F-fluorodeoxyglucose positron emission tomography-computerized tomography scans of the gastrointestinal stromal tumors recurrence. Serial <sup>18</sup>F-FDG PET-CT scans showed submucosal, solid lesions in jejunum (SUVmax: 1.68-1.50) (A, B) and ileum (SUVmax: 4.69) (C) with maximum 2 cm in diameter, consisted with GIST recurrence on the follow-up (arrows). <sup>18</sup>F-FDG: <sup>18</sup>F-fluorodeoxyglucose; PET-CT: Positron emission tomography-computerized tomography; GIST: Gastrointestinal stromal tumors.



**Figure 5** Imatinib response evaluation of the gastrointestinal stromal tumors using contrast-enhanced abdominal computerized tomography. Pre- and post-treatment CT images are shown on upper and lower series respectively. A partial response is seen in jejunal (A, B) and ileal (C) GISTs in the following 3 mo after imatinib therapy (arrows). CT: Computerized tomography; GIST: Gastrointestinal stromal tumors.

mutations are limited. However, it has been proven that imatinib is effective in controlling the progression of sporadic GISTs in patients with K642E mutation. *In vitro* assays also showed that activation of K642E is inhibited by imatinib<sup>[26,27]</sup>.

Several research and follow-up studies has shown that twelve exon 11 positive patients on 400 mg/d

imatinib had stable outcome, lasting from 12 to 58 mo<sup>[10,19-21,23]</sup>. Three out of four exon 17 mutated patients<sup>[22,24]</sup>, two out of three exon 13 mutated patients<sup>[8,10]</sup> and one exon 8 mutated patient<sup>[15]</sup> also reported to be stable after imatinib treatment initiation.

In our family, the father and the older son were treated with imatinib (400 mg/d) without recurrence.

There were no signs of recurrence in the father. However, the older son showed recurrence four years after the cessation of imatinib treatment upon patient's request. Imatinib was re-administered with a daily dose of 400 mg and CT scan showed a significant decrease in the tumor size, after three months of the treatment.

We conclude that, *KIT* mutation analysis is advisable prior to initiation of imatinib treatment, as it can help predicting the tumor response. However, data on the role of imatinib in familial GISTs is still limited. We believe that case studies will contribute to our understanding the significance of mutation analysis in regard to the drug dosage, duration of treatment, drug response and follow-up studies of imatinib therapy in familial GISTs. The prognostic comparison of the outcome of imatinib treatment in sporadic GISTs and familial GISTs may play a role in defining the underlying mechanisms and pathways.

## COMMENTS

### Case characteristics

A family, a father (62-year-old) and two sons (32 and 36 years old) having multiple gastrointestinal stromal tumor (GIST) are described.

### Clinical diagnosis

Massive GIS hemorrhage in the father and his older son, abdominal distension and dysphagia in the younger son.

### Differential diagnosis

Gastric varices, Mallory-Weiss tear, neoplasm and hemorrhagic gastritis in upper GIS; bleeding, diverticulosis, angiodysplasia, colitis (infectious or ischemic), inflammatory bowel disease, colon cancer in lower GIS bleeding. Dysphagia can be seen in mechanical obstruction or neuromuscular motility disorders.

### Laboratory diagnosis

All labs were within normal limits.

### Imaging diagnosis

Imaging computed tomography showed multiple, submucosal, solid masses in 2-5 cm sizes in the upper and lower gastrointestinal tract. <sup>18</sup>F-FDG PET-CT revealed high FDG activity (SUVmax 5.0-5.4) in the solid lesions.

### Pathological diagnosis

Immunohistochemistry for DOG1 and c-kit showed immun activity in the tumor cell. Sequence analysis of *KIT* gene revealed a heterozygous exon 13 c.1924A>G gain-of-function mutation in all three cases in concordance with the familial GIST diagnosis.

### Related reports

Exon 13 germline mutations are extremely rare amongst familial GISTs and seven families with a germline mutation have been reported to date. Moreover, there are only a few reports describing the response to imatinib in familial GISTs confirming it as a promising therapeutic option.

### Term explanation

Familial gastrointestinal stromal tumor (GIST) is a rare autosomal dominant disorder associated with mutations in the *KIT* gene in the majority of cases presents multiple GIST. Although surgery is the primary treatment for localized GISTs, imatinib mesylate is used as adjuvant or neoadjuvant therapy in high risk or advanced GIST groups.

### Experiences and lessons

We conclude that *KIT* mutation analysis is advisable prior to initiation of imatinib

treatment in familial GIST, as it can help predicting the tumor response. We believe that case studies will contribute to our understanding the significance of mutation analysis in regard to the drug dosage, duration of treatment, drug response and follow-up studies of imatinib therapy in familial GISTs.

### Peer-review

The authors describe three members of a family treated with surgery and imatinib due to a familiar GIST with a rare mutation. The role of imatinib in this rare familiar settings is not completely known so far. The paper is interesting, addresses a novel topic and adds further knowledge to literature.

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