Familial Gastrointestinal Stromal Tumor Syndrome: Report of 2 Cases With KIT Exon 11 Mutation

Derek H. Jones, MD, Jamie T. Caracciolo, MD, Pamela J. Hodul, MD, Jonathan R. Strosberg, MD, Domenico Coppola, MD, and Marilyn M. Bui, MD, PhD

Background: As with cases of sporadic gastrointestinal stromal tumor (GIST), familial GIST syndrome arises from mutations in KIT or PDGFRA. Only a few dozen such families have been described in the literature. Methods: Cases of 2 individuals from 2 different newly described kindreds with familial GIST syndrome were retrospectively reviewed. Pertinent immunohistochemical stains, including CD117, CD34, DOG1, desmin, and S100, were performed. Samples from each case were sent to outside facilities for molecular analysis. A review of the relevant literature was performed and the number of familial GIST syndrome cases reported was updated through July 2014.

Results: In case 1, a woman 40 years of age with a family history of GIST presented with abdominal pain and gastrointestinal bleeding. Biopsy of a gastric mass revealed spindle-cell type GIST. Molecular analysis revealed a heterozygous mutation of p.Asp579del in exon 11 of KIT. The patient was placed on imatinib therapy and an initial positive response was demonstrated by imaging. Disease regression was seen on computed tomography, and several GIST tumors were surgically resected. The patient has had stable disease since surgery. In case 2, an asymptomatic woman 29 years of age presented for screening due to a family history of GIST. One small nodule was noted in her stomach and another was noted in the duodenum; both were surgically resected. The patient recovered well following surgery. The GIST in this patient was noted to have similar histological, immunohistochemical, and molecular findings as case 1.

Conclusions: Imatinib has often been shown to be an effective therapy in both the familial and sporadic forms of GIST. There is no standard protocol for addressing the surveillance of patients with spindle-cell type GIST seen in the setting of familial GIST syndrome and with a p.Asp579del mutation of exon 11 on KIT.

Introduction

Although gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract, the incidence of familial GIST syndrome is rare, representing fewer than 5% of cases. Familial GIST syndrome is an autosomal dominant disease caused by germline mutations in KIT or PDGFRA, both of which are also involved in the initiation of most sporadic GIST cases. Other hereditary forms of GIST include deficiencies in the succinate dehydrogenase complex, Carney–Stratakis syndrome, and type 1 neurofibromatosis. In 2013, Neuhann et al summarized 24 cases of familial GIST syndrome arising from KIT. In addition to this publication, 5 other cases of familial GIST syndrome have been described that involve KIT and 3 reported cases of familial GIST syndrome arising from PDGFRA. The 2 additional kindreds described in this report raise the total number of reported familial GIST syndrome cases to 34.

Here we present clinical, gross, histological, immunological, and molecular findings of 2 cases of familial GIST involving the same mutation in exon 11 of KIT.

Materials and Methods

Clinical, radiological, and pathological data from the 2 patients were retrospectively reviewed following the research guidelines of the University of South Florida and the Moffitt Cancer Center in Tampa, Florida. The tissues were processed, sectioned,
and stained according to the guidelines from the College of American Pathologists. The hematoxylin and eosin stain and immunohistochemical studies were performed at the histology laboratory of the Moffitt Cancer Center. The immunohistochemical staining was carried out using the Discovery XT System (Ventana Medical Systems, Tucson, Arizona) per the manufacturer’s protocol. Samples from each case were subjected to genetic analysis. Case 1 was performed with Sanger sequencing by ARUP Laboratories (Salt Lake City, Utah), and case 2 was performed with Sanger sequencing by Knight Diagnostics Laboratories (Portland, Oregon).

Clinical and Radiological Information
Case 1
A 40-year-old woman presented with epigastric pain and recurrent gastrointestinal bleeding. Her family history was significant for GIST in her aunt and grandmother. The patient history included anemia and a small, spontaneously healing gastrointestinal perforation. Laboratory values, including liver aminotransferases and bilirubin, were within normal limits. Contrast-enhanced abdominal computed tomography (CT) with intravenous contrast demonstrated numerous hypervascular, exophytic, mural-based, soft-tissue masses arising from the stomach, duodenum, and jejunum (Fig 1A). No evidence of hepatic or intraperitoneal metastatic disease was seen.

Biopsies of an exophytic gastric mass and a peripancreatic duodenal mass were performed with the guidance of endoscopic ultrasonography. Both tumors were diagnosed as GIST. Molecular analysis revealed a mutation of exon 11 on KIT, and imatinib therapy was initiated. The patient underwent follow-up CT with oral and intravenous contrast 6 months following the initiation of imatinib therapy that demonstrated the decreased size of disease sites consistent with a partial response to therapy (Fig 1B). However, within 9 months of initiating imatinib, the patient presented with increased abdominal pain. Abdominal CT was repeated and demonstrated an increase in size of several lesions, including the duodenal mass (Fig 1C). Given the relatively limited extent of her multifocal disease and the absence of metastatic disease, surgical debulking was recommended. She underwent partial gastrectomy, pancreas-sparing duodenectomy, proximal jejunal resection, and cholecystectomy. The patient recovered well from surgery and reports that she is feeling better. CT was obtained 4 months following surgery, and the imaging demonstrated no evidence of recurrence or distant metastatic disease.

Case 2
A woman 29 years of age who was asymptomatic presented for screening secondary to a family history of familial GIST in her mother and grandmother. After an initial evaluation, the patient exhibited mild epigastric discomfort and subsequently presented with a mildly elevated level of alanine transaminase, possibly due to hepatic steatosis. The patient did not exhibit anemia and other laboratory values were not abnormal. Endoscopic ultrasonography performed with esophagogastroduodenoscopy had demonstrated subcentimeter, mural-based, hypoechoic, gastric, and duodenal soft-tissue nodules (Fig 2). These small, submucosal, intramural nodules were isodense and isoenhancing to the gastric and duodenal walls; therefore, they were not readily evident with CT imaging. Abdominopelvic CT did not demonstrate evidence of hepatic metastatic disease or peritoneal carcinomatosis. Both lesions...

Fig 1A–C. — Serial CT scans at a similar level over time from case 1. (A) Axial contrast-enhanced abdominal CT demonstrates a 3.9-cm exophytic, mural-based, hypervascular duodenal mass (white arrow) and a similarly appearing jejunal mass (yellow arrow). The red asterisk denotes the duodenum. (B) Six months after CT shown in Fig 1A, both masses demonstrated decreased size on imatinib therapy consistent with tumor response. The duodenal mass measured 2.9 cm. No new lesions or interval development of metastatic disease was seen. (C) Six months after CT shown in Fig 1B, the duodenal mass increased in size and measured 3.3 cm, which was consistent with resistance to imatinib therapy. CT = computed tomography.
were subsequently surgically resected. The patient is not on imatinib therapy and was recovering well 1 month following surgery.

**Gross, Histological, and Immunohistochemical Findings**

**Case 1**

Histologically, cells from both the gastric and duodenal mass biopsies were of spindle-cell morphology and largely uniform in appearance. The cells had cigar-shaped nuclei and pale eosinophilic cytoplasm. Skeinoid fibers were present in the interstitium. Necrosis was not identified. Mitotic rate could not be accurately determined due to the small sample size. The tumor was immunohistochemically positive for CD117 and DOG1, while negative for CD34, desmin, actin, S-100, and pan-keratin (AE1/AE3/CAM 5.2). Findings were consistent with the diagnosis of spindle-cell type GIST.

The surgical resection specimens consisted of a 3.0 × 1.3 × 0.8-cm section of the lesser gastric curvature, a 2.8 × 1.0 × 0.5-cm section of the posterior stomach wall, a 5.4 × 2.4 × 1.8-cm wedge of an anterior gastric wall mass, a 3.8 × 1.0 × 0.8-cm wedge of a posterior gastric wall mass, and a section of duodenum and proximal jejunum approximately 44.0 cm in length with attached adipose tissue yellow-tan in color on the serosal aspect (Fig 3). In the gastric sections, various nodules up to 1.0 cm extending to the serosa that ranged from tan-pink, tan-white, to white in color were observed. In the duodenal and proximal jejunal resections, approximately 6 tan-white to pink-tan nodules ranging from 0.6 to 4.0 cm in size were observed; some extended to the serosa.

Histologically, the resected tumor specimens were of similar morphology as the gastric and duodenal biopsies (Fig 4A–C). The mitotic rate was 3 per 5 mm². Minimal tumor necrosis was observed (approximately 5% of total tumor volume), corresponding to a minimal treatment effect. The viability rate of the tumor cells observed was 90% to 95%. Tumors were diagnosed as spindle-cell type GIST and staged as T2M0N0.

**Case 2**

Macroscopically, a 1.5 × 0.6 × 0.4-cm section of the anterior gastric mucosa was resected. It contained a circumscribed nodule that was tan-white in color and measured 1.1 × 0.9 × 0.6 cm in size. In addition, a 0.9 × 0.6 × 0.5-cm section of duodenum containing a small nodule was resected. It consisted of cauterized fibrotic tissue brown-tan in color.

Histologically, findings were also consistent with spindle-cell type GIST. The mitotic rate was 0 per 5 mm². The tumor was immunohistochemically positive for CD117 (Fig 5A), strongly positive for DOG1 (Fig 5B), and negative for S100, actin, and desmin. The Ki-67 labeling index was between 1% and 2%. Cell necrosis was not identified.

**Molecular Analysis**

**Case 1**

The core biopsy of the gastric mass guided by endoscopic ultrasonography was found to have a mutation on exon 11 of KIT. A deletion of GAT was present in positions 1735 to 1737 (c.1735_1737delGAT), which
resulted in the loss of aspartic acid at position 579 (p.Asp579del). The mutation was heterozygous. Exon 9 from KIT was intact.

**Case 2**
Molecular studies were performed from a peripheral blood sample. Similar to the results from case 1, a heterozygous p.Asp579del mutation was detected in exon 11 of KIT.

**Discussion**
Mutations in familial GIST syndrome involve KIT and PDGFRA, which are the same genes mutated in 80% to 88% of cases of sporadic GIST. Wild-type GIST arising from other molecular pathways may comprise up 15% of GIST cases, and they are typically negative for KIT and PDGFRA mutations but positive for mutations of BRAF V600E, the RAS family, and the succinate dehydrogenase complex. However, it is possible that cases of wild-type GIST might be less common than previously thought. For example, one study suggests that 1% to 2% of GIST previously regarded as the wild-type form may actually harbor mutations in exon 8 of KIT.

The Table demonstrates similarities and differences between the molecular basis of familial and sporadic GIST caused by KIT mutations. In familial GIST syndrome, KIT mutations in exon 9 have not been reported as they have with sporadic GIST. The reasons for a lack of exon 9 mutations in familial GIST syndrome remain unclear, but reasons may become elucidated as more information is gained on familial GIST. Six cases have been reported of familial GIST syndrome due to mutations in KIT exon 13 and 4 cases have been reported due to mutations in exon 17. By comparison, exon 9 mutations account for 15% of KIT mutations in the setting of sporadic GIST, whereas exons 13 and 17 account for 2% and 1%, respectively. Although pure insertions involving KIT are documented in sporadic GIST, none have been documented in
familial GIST syndrome (see Table).15,16 Our literature review demonstrates that, as a whole, mutations of exon 11 of KIT are more common among sporadic GIST than familial GIST syndrome. However, given the small number of familial GIST syndrome cases to compare with the much larger number of sporadic GIST cases, these differences must be thoroughly examined. In the future, reports of additional cases of familial GIST will help achieve a better analysis of these underlying similarities and differences.

Twenty families with familial GIST have arisen from exon 11 of KIT as described by Neuhann et al,4 Nakai et al,5 Adela et al,7 and the cases presented here. KIT and PDGFRA are members of the family of class 3 tyrosine kinase receptors. The juxtamembrane domain of this family is highly conserved and has been demonstrated to have an inhibitory effect on the kinase domain of the tyrosine kinase receptor.17 The juxtamembrane domain of KIT is encoded by exon 11.13 A mutation in this region has been molecularly modeled to disrupt the usual autoinhibitory state of KIT, leading an activated gain-of-function state.18 Because of this gain-of-function type mutation, individuals are typically heterozygous for these mutations. The current report describes 2 additional cases of a mutation of p.Asp579del in exon 11 of KIT, adding 2 kindreds to the 3 previously reported families with familial GIST syndrome demonstrating this mutation.18,20 Mutations causing familial GIST syndrome have no clear differentiating factors from mutations causing sporadic GIST, and the mutation of p.Asp579del has also been documented in sporadic GIST.21 The p.Asp579del mutation is not within the region of high-frequency mutations noted at positions 556 to 560 in exon 11 of KIT in patients with GIST.18 However, 11 of the 20 cases of familial GIST syndrome with a mutation in exon 11 of KIT are located in this high-frequency region. Of these 11 cases, 7 are from the most common mutation in familial GIST syndrome, p.Val559Ala. The KIT exon 11 mutation p.Val559Ala is also a common missense mutation in GIST.22 A large study found that patients with deletions in exon 11 of KIT from positions 562 to 579 have significantly higher risk for metastatic disease than patients with mutations at positions 550 and 561, suggesting that patients with the mutation of p.Asp579del, such as the patients in this report, may be at high risk for metastatic disease.23

These 2 cases also contribute to the body of evidence suggesting that phenotypic features cannot reliably indicate the presence of familial GIST syndrome. As with sporadic GIST, nonspecific signs and symptoms in familial GIST syndrome include gastrointestinal bleeding, abdominal pain, ulcer-type symptoms, and a variety of other gastrointestinal complaints. No specific serum markers are currently used to routinely screen or diagnose GIST. Familial GIST syndrome has classically been associated with hyperpigmentation, urticaria pigmentosa, and dysphagia. However, a growing number of cases do not demonstrate these symptoms, including our 2 patients. Notably, patient age can be a guiding feature as patients with familial GIST syndrome typically present at least 10 years prior to patients with sporadic GIST, presenting at a median age of 60 to 65 years.1,2

Patients with familial GIST syndrome or other GIST-related syndromes, such as type 1 neurofibromatosis, typically present with multifocal disease, whereas most patients with sporadic GIST usually present with solitary primary tumors.24 Sporadic GIST may present with multiple gastrointestinal masses in the setting of metastatic disease or from independent mutations. Metastatic disease may be diagnosed in the setting of peritoneal sarcomatosis, the second most common pattern of metastatic disease following hepatic metastatic disease. Approximately 11% of patients presenting with GIST have metastatic disease identified at the time of initial diagnosis.25 Several studies indicate that a substantial portion of patients with multifocal disease may arise from independent mutational events. Two large studies, one by Agaimy et al26 and the other by Gasparotto et al,27 indicate the presence of multiple molecular origins in multifocal GIST in 7 of 11 and 6 of 10 cases, respectively. The presence of multiple mutations could be explained by premutational epigenetic changes.26 Current guidelines from the National Comprehensive Cancer Network recommend mutational testing for KIT and PDGFRA in the primary evaluation of GIST, but they make no recommendations for further analysis in the case of multifocal disease.28 Due to the variety of possible etiologies in patients presenting with multifocal disease, genetic screening for familial GIST syndrome may be a prudent step in the initial evaluation of multifocal disease. In addition, genetic counseling for individuals with familial GIST syndrome should be considered to identify other family members at risk.

In general, histological and immunohistochemical features do not differentiate cases of familial GIST syndrome from cases of sporadic GIST. Both feature

<table>
<thead>
<tr>
<th>Genetic Finding</th>
<th>Sporadic GIST</th>
<th>Familial GIST Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Involved KIT exons</td>
<td>8, 9, 11, 13, 17</td>
<td>8, 11, 13, 17</td>
</tr>
<tr>
<td>Type of mutation</td>
<td>Substitution Duplication Deletion Insertion Deletion–insertion</td>
<td>Substitution Duplication Deletion Deletion–insertion</td>
</tr>
<tr>
<td>KIT mutations involving exon 11, %</td>
<td>70–90</td>
<td>65</td>
</tr>
</tbody>
</table>

GIST = gastrointestinal stromal tumor.
spindle cell or, less frequently, epithelioid histologies. Both are usually positive for CD117 and DOG1 and negative for desmin, keratin, and S100. Similar to sporadic GIST, CD34 variability has also been noted in familial GIST syndrome. A high rate of response to imatinib has been well documented in cases of sporadic GIST, and familial GIST may also be sensitive to imatinib treatment. Typically, patients with mutations of exon 11 of KIT have an especially strong response to imatinib. Tarn et al reported that the mutations of exon 11 on KIT may not affect the nucleotide-binding site, thereby lowering the probability of imatinib resistance. However, recent data demonstrate that changes to the juxtamembrane domain can affect the structure of the kinase domain, thus resulting in imatinib resistance, such as the case with p.Val559Ile. Kleinbaum et al noted a strong response to imatinib in patients with familial GIST syndrome who had a KIT exon 11 p.Asp579del mutation. Nine of the 11 family members who did not receive imatinib eventually died from metastatic GIST, whereas all 4 patients receiving imatinib achieved stable disease for more than 4 years. Typically, sunitinib is a second-line therapy following treatment failure with imatinib. Currently, several reports have focused on the general topic of familial GIST syndrome. Burgoyne et al provided a review of nonsporadic GIST, and Corless et al provided a comprehensive review of the molecular basis of GIST. No guidelines currently exist for screening patients with familial GIST, nor do any clear indications exist for the role or extent of surgery in the setting of multifocal disease. The patient in case 1 had symptomatic multifocal tumors and achieved palliation with neoadjuvant imatinib followed by surgical resection, whereas the patient in case 2 was asymptomatic and chose to undergo surgery for her identifiable sites of disease. It is unclear whether the removal of small, low-grade tumors will ultimately improve her long-term prognosis, particularly because additional tumors are likely to develop over her lifetime.

The role of imatinib as a chemopreventive agent in familial GIST is also unclear. Although it is possible that imatinib can prevent or delay growth of multifocal GIST in this population, it is uncertain to what extent imatinib therapy improves long-term prognoses among patients with nonmetastatic, low-grade tumors.

Conclusions

Familial gastrointestinal stromal tumor syndrome is a rare disease, but the number of associated families identified continues to expand. The 2 cases identified in this report add to the growing body of evidence that will better help researchers and clinicians understand the epidemiology, characteristics, and optimal treatment of familial gastrointestinal stromal tumor syndrome.

References
