

# A Novel *PRKAR1B-BRAF* Fusion in Gastrointestinal Stromal Tumor Guides Adjuvant Treatment Decision-Making During Pregnancy

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## Abstract

Gastrointestinal stromal tumors (GISTs) are rare in pregnancy, with only 11 reported cases. Adjuvant imatinib therapy, which targets the most common driver mutations in GIST (*KIT* and *PDGFRA*), is recommended for patients with high-risk GIST, but it has known teratogenicity in the first trimester. A 34-year-old G3P2 woman underwent exploratory laparotomy at 16 weeks' gestation for a presumed adnexal mass. Surgical findings included normal adnexa and a 14-cm solid small bowel mass. The mass was resected en bloc with a segment of jejunum followed by a primary anastomosis. Histopathology and genomic analyses demonstrated a GIST with high-risk features but lack of *KIT/PDG-FRA* mutations and identified the presence of a previously unreported, pathogenic *PRKAR1B-BRAF* gene fusion. Given her tumor profile, adjuvant therapy with imatinib was not recommended. GIST is rare in pregnancy, but can masquerade as an adnexal mass in women of childbearing age. Because neoadjuvant/adjuvant imatinib has risks of teratogenicity, tumor molecular profiling is critical as we identified a previously unreported gene fusion of *PRKAR1B* with *BRAF* that is predicted to be imatinib-resistant. In this case, testing provided the rationale for not offering adjuvant imatinib to avoid unnecessary toxicity to the patient and fetus.

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**G**astrointestinal stromal tumors (GISTs) are mesenchymal tumors arising in the wall of the gastrointestinal tract. They are rare, with an overall incidence of 6.8 cases per million persons in the United States each year.<sup>1</sup> However, in patients aged <40 years, there are only 2.6 cases per million persons annually.<sup>2</sup> Insertions, deletions, and missense mutations in the *KIT* and *PDGFRA* oncogenes cause approximately 85% of GISTs, whereas *BRAF* V600E missense mutations lead to approximately 1% of cases.<sup>3</sup> We and others recently reported that a small subset of GISTs also occur due to kinase fusions (eg, *ETV6-NTRK3*, *FGFR1-TACC1*,

*FGFR1-HOOK3*), a previously unappreciated mechanism for GIST tumorigenesis.<sup>4–7</sup>

GISTs amenable to resection are generally managed surgically, and patients with tumors harboring high-risk features are recommended to receive adjuvant therapy with imatinib, a tyrosine kinase inhibitor that targets the *KIT* and *PDGFRA* oncoproteins, but not *BRAF*, *NTRK3*, or *FGFR1*. Risk of recurrence is determined by tumor size, location, mitotic rate, and tumor rupture. Prediction tools, such as the modified NIH method,<sup>8</sup> the Armed Forces Institute of Pathology (AFIP; Miettinen criteria),<sup>9</sup> and the Memorial Sloan Kettering Cancer

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Center nomogram,<sup>10</sup> stratify risk and predict the likelihood of tumor recurrence after complete resection. If a tumor is considered high risk, adjuvant imatinib is typically recommended based on the ACOSOG Z9001<sup>11</sup> and SSG XVIII/AIO<sup>12</sup> trials, whose cumulative results demonstrated improved relapse-free survival and overall survival (OS) with at least 3 years of adjuvant imatinib. In the era of precision oncology, these recommendations should be provided in conjunction with genomic analyses that may predict imatinib sensitivity or resistance in order to maximize efficacy and minimize toxicity.

This case presentation reminds clinicians that GIST can occur in women of childbearing age and should remain in the differential diagnosis of an adnexal mass. We also review the genomics of GIST, and present a novel tumor mutation to highlight the emerging importance of molecular profiling in dictating personalized cancer treatment, especially during pregnancy.

## Case

A 34-year-old Hispanic G3P2 woman presented at 8 weeks gestation to a community hospital with abdominal pain, nausea, and vomiting. She reported that her symptoms had started 6 months earlier with the sensation of abdominal fullness. She had no prior medical or surgical history nor family history of malignancy. Transabdominal ultrasound evaluation was unremarkable except for the unexpected finding of a 13.9 x 6.2 x 9.2-cm complex right adnexal mass (Figure 1A). An MRI to further evaluate the mass confirmed a 14-cm complex mass, presumably arising from the right ovary (Figure 1B). Based on these results, the differential diagnosis included dermoid cyst, leiomyoma, and hemorrhagic cyst. Her serum CA125 level was mildly elevated at 81 U/mL (normal, 0–34). After consultation with a perinatologist, she was referred to gynecologic oncology for surgical management.

At 16 weeks' gestational age, she underwent an exploratory laparotomy. Surgical findings were remarkable for normal bilateral adnexa, a gravid uterus, and a 14 x 10-cm solid mass arising from the mid-jejunum. There was no additional disease. The mass was resected en bloc with the jejunum, followed by a primary anastomosis. The patient did well postop-



**Figure 1.** Radiologic characterization of a gastrointestinal stroma tumor masquerading as an adnexal mass during pregnancy. (A) A 34-year-old G3P2 woman with abdominal pain was found to have a 13.9 x 6.2 x 9.2-cm complex right adnexal mass on transabdominal ultrasound. (B) MRI demonstrated a complex mass thought to arise from the right ovary.

eratively and reported resolution of her preoperative abdominal symptoms.

Histopathologic review showed a small bowel spindleoid GIST. Immunohistochemical studies of the tumor were positive for CD117 (eg, KIT, c-KIT) and DOG-1, characteristic markers of GIST. The tumor measured 14.0 x 10.0 x 7.0 cm (pT4), with a mitotic rate of 3 per 50 high-power fields. Due to its size, her tumor was predicted to have a high risk of recurrence,<sup>8–10</sup> and based on data from the ACOSOG Z9001<sup>11</sup> and SSG XVIII/AIO<sup>12</sup> trials, adjuvant imatinib should be offered.

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Thus, the patient was referred to gastrointestinal medical oncology for consideration of adjuvant therapy and to perinatology to review the teratogenic risks of imatinib during pregnancy, including an increased incidence of congenital anomalies when given in the first trimester, but a relatively low risk to the fetus in the second and third trimesters. Meanwhile, her tumor tissue was tested with the FoundationOne assay (Foundation Medicine, Inc., Cambridge, MA), a validated next-generation sequencing technology for the detection of genomic alterations in >300 cancer-related genes via simultaneous analysis of the extracted DNA for base substitutions, short insertions and deletions, amplifications and homozygous deletions, and gene rearrangements that are often altered in solid tumors. This comprehensive genomic profiling identified a previously unreported oncogenic *PRKAR1B-BRAF* fusion (Figure 2), but no evidence of other canonical drivers, including those in *KIT*, *PDGFRA*, *NF1*, *KRAS*, *SDHx* subunits, or other pathogenic alterations. Given the absence of *KIT* and *PDGFRA* mutations and a likely imatinib-resistant gene fusion, it was thought the patient would be unlikely to benefit from adjuvant imatinib, and that it would present potential unnecessary toxicity to her and the fetus. Thus, she elected for surveillance with periodic imaging. At 40 weeks 1 day, she presented for labor and delivered a healthy baby boy, weighing 3,634 g, via normal spontaneous vaginal delivery. At 20 months postoperatively, she remains without evidence of disease.

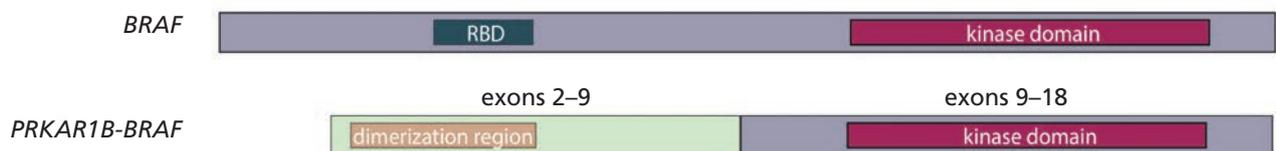
## Discussion

To date, there have been 11 reported cases of GIST diagnosed in pregnancy. More than half of these cases were thought to be adnexal or uterine masses prior to surgery, based on imaging and clinical presentation.<sup>13–21</sup> Thus, GISTs represent a diagnostic challenge during pregnancy and may be encountered

unexpectedly at the time of surgery for a presumed adnexal mass. As such, it is important for obstetricians and gynecologists to counsel women preoperatively that an “adnexal mass” may actually be arising from the gastrointestinal tract. With respect to GISTs, complete resection with the goal of negative margins and intact capsule offers the best chance for cure. After histopathologic review, these tumors should be assessed for risk of recurrence and categorized according to standard algorithms.<sup>8–10</sup>

If the risk of recurrence is high, at least 3 years of adjuvant imatinib is usually recommended. Imatinib is a small molecule tyrosine kinase inhibitor of *KIT* and *PDGFRA*, which are frequently mutated in GIST and drive unchecked downstream signaling that promotes tumor proliferation. Imatinib binds to the ATP-binding pocket of these mutated receptor tyrosine kinases and prevents tumor growth. This molecularly matched therapy has transformed the management of GIST and led to prolonged recurrence-free survival and OS when administered to high-risk patients in the adjuvant setting.<sup>11,12</sup> However, GISTs lacking mutations in *KIT* and *PDGFRA* are unlikely to benefit from imatinib.

Recently, we and others reported a handful of gene fusions in GIST<sup>4–7</sup> (Table 1). However, here we report a novel, previously unreported *PRKAR1B-BRAF* gene fusion in a patient with GIST (Figure 2). Mutations of *PRKAR1B*, which encodes a regulatory subunit of the cyclin AMP-dependent protein kinase A complex, have been implicated in neurodegenerative dementia<sup>22</sup> but are not well-associated with human cancer. According to several studies, approximately 1% of GISTs possess *BRAF* mutations, which are most often canonical V600E seen in other tumor types, including melanoma and colon cancer.<sup>3</sup> Constitutively activated *BRAF* potentiates the mitogen-activated protein kinase (MAPK) pathway, and hence facilitates tumor initiation and progression through promoting cell proliferation, migration,



**Figure 2.** *PRKAR1B-BRAF* kinase fusion identified in a gastrointestinal stromal tumor. A fusion involving the *N*-terminus of *BRAF* was identified. This fused exons 9–18 of *BRAF*, including the kinase domain, to exons 2–9 of *PRKAR1B*. The fusion resulted in loss of the Ras-binding domain (RBD) of *BRAF*, and gain of a dimerization region present within *PRKAR1B*. Note that exon 1 of *PRKAR1B* is noncoding and therefore excluded from the protein diagrams. The diagram is drawn to scale.

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Table 1. Reported Gene Fusions in Patients With GIST

Patient	Age, y	Sex	Primary Tumor Location	Tumor Stage	Gene Fusion
1 <sup>a</sup>	55	Male	Small bowel	T3N0M1	<i>ETV6-NTRK3</i>
2 <sup>a</sup>	54	Male	Colon	Unknown	<i>ETV6-NTRK3</i>
3 <sup>b</sup>	44	Male	Rectum	T2NxMx	<i>ETV6-NTRK3</i>
4 <sup>a</sup>	54	Male	Pelvic mass	Unknown	<i>FGFR1-TACC1</i>
5 <sup>a</sup>	54	Male	Stomach	T3N1M1	<i>FGFR1-TACC1</i>
6 <sup>a</sup>	38	Female	Small bowel	T3N1M1	<i>FGFR1-HOOK3</i>
7 <sup>b</sup>	Unknown	Female	Unknown	Unknown	<i>KIT-PDGFR A</i>
8 <sup>c</sup>	63	Female	Small bowel	T3N0M1	<i>MARK2-PPF1A1</i> <i>SPRED2-NELFCD</i>
9	34	Female	Small bowel	T4NxMx	<i>PRKAR1B-BRAF</i>
Summary	Average: 50 Median: 54	Male, 56% Female, 44%	44% small bowel, but spans stomach to rectum	22% nodal metastases 44% distant metastases	33% <i>ETV6-NTRK3</i> 33% <i>FGFR1</i> 33% Others

Abbreviation: GIST, gastrointestinal stromal tumor.

and survival.<sup>3</sup> Of note, *KIT*- and *PDGFRA*-mutated GISTs have a similar pattern of oncogenesis through upstream activation of this same RAS-RAF-MAPK axis. However, given that imatinib targets *KIT* and *PDGFRA* upstream of *BRAF*, it is unlikely to provide a therapeutic benefit in patients with downstream-activating *BRAF* genomic alterations. Potential treatments for GISTs with *BRAF* mutations include vemurafenib, dabrafenib, sorafenib, or other RAF multikinase inhibitors.<sup>23</sup> However, quality data on response rates to these agents in *BRAF*-mutated GIST are lacking.

Although limited studies have been performed, imatinib has been associated with fetal malformations and higher rates of spontaneous abortion in the first trimester,<sup>24</sup> whereas use in the second trimester appears relatively safe.<sup>25</sup> The largest study, examining 180 pregnancies, suggests an increased incidence of congenital anomalies, including exomphalos, renal and skeletal defects, and hypospadias, when fetuses are exposed in the first trimester.<sup>24</sup> Although no malformations have been noted when imatinib exposure

was limited to the second or third trimesters, the total number of patients with known timing of exposure limited to the second or third trimester is <10.<sup>25</sup>

## Conclusions

GISTs can be difficult to diagnose preoperatively and can be mistaken for adnexal masses on imaging in women of childbearing age. GISTs diagnosed during pregnancy provide further clinical challenges, and the current case highlights the importance of multidisciplinary care and the use comprehensive genomic profiling with next-generation sequencing to guide administration of, or contraindications to, adjuvant molecularly matched therapy. In this case, the identification of a previously unreported gene fusion of *PRKAR1B* with *BRAF* that would not be targeted by imatinib allowed us to avoid recommending likely ineffective treatment. Taken together, this personalized approach to precision oncology helped avoid unnecessary toxicity to the patient and fetus, and may lead to further studies of gene fusions in GIST.

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