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Case Report

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Appraising Treatment for Gastrointestinal Stromal Tumors of the Wild-Type Mutation in the Setting of NF1: A Case Report

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ABSTRACT

Gastrointestinal stromal tumors (GISTs) are rare mesenchymal neoplasms that can occur anywhere in the GI tract, but commonly present in the stomach and small bowel. Here we present a 39-year-old male with a suspected GIST in the setting of type I neurofibromatosis (NF1). Given the history of NF1 and presumable insensitivity to Imatinib, surgical oncology opted for resection of the mass after discussion with the multidisciplinary sarcoma tumor board. Instead of neoadjuvant therapeutic options for wild-type (WT) NF1-related GIST, surgical resection remains the most advantageous treatment. The efficacy of tyrosine kinase inhibition and other chemotherapies tailored for WT GIST is currently untenable and warrants increased clinical trials and exploration of WT pathogenesis concerning NF1 to support Imatinib-sensitive patients.

Keywords: Gastrointestinal stromal tumor; Chemotherapy; Neurofibromatosis (NF1); Next generation sequencing; Pathogenesis

INTRODUCTION

Gastrointestinal stromal tumors begin in Interstitial cells of Cajal (ICCs), a type of pacemaker stellate cells that communicate with the nervous system to induce contractions in the GI tract. Early-stage disease often lacks clinical manifestation, but eventual presentation of symptoms may include nausea, vomiting, melena, anemia, and fatigue [1]. Risk factors for Gastrointestinal stromal tumors (GISTs) include type I neurofibromatosis, being a male above 40 years of age, inherited syndromes (Carney-Stratakis syndrome), and a familial history of GISTs[2]. Diagnosis is generally confirmed by positive immunohistochemical staining of v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (*KIT, HGNC:6342)*, a receptor tyrosine kinase protein[3]. Mutations in the *KIT* and platelet-derived growth factor receptor alpha (*PDGFRα, HGNC:8803)* proto-oncogenes are the primary drivers of tumor pathogenesis, though a smaller percentage of cases involve separate genomic alterations [4]. In these wild-type mutations, which make up 10-15% of cases, patients are generally insensitive to Imatinib, the tyrosine kinase inhibitor used as the primary chemotherapeutic agent of choice in *KIT* and *PDGFRα* alterations[4]. Thus, the unique molecular drivers of the WT GIST demand consideration for separate treatment strategies. GISTs with WT mutations can be further classified by Succinate dehydrogenase (SDH) deficient or SDH-competent GISTs[5]. SDH, a mitochondrial enzyme previously thought to have sole metabolic purposes, has been implicated in tumorigenesis due to its malfunction placing oxidative stress on coenzyme Q: a complex in

the electron transport chain [6]. SDH-competent GISTs are related to neoplastic changes caused by germline mutations in the *NF1 (HGNC:7765)* and serine/threonine-protein kinase B-Raf (*BRAF, HGNC:1097)* genes, and Carney-Stratakis syndrome[5]. NF1 is the condition of interest in this case study.

Type I neurofibromatosis is an autosomal dominant inherited disorder that causes growth of benign tumors (neurofibromas) along nerves[7]. Afflicted patients are at a higher susceptibility to an assortment of neoplasms, including nerve sheath tumors and more uncommonly, sarcomas[8]. This can be ascribed to the tumor suppressor protein, neurofibromin that the *NF1* gene encodes. The role of the protein is to inactivate RAS (Rat Sarcoma), another protein involved in signal transduction of the mitogen-activated kinase (MAP) pathway-resulting in errors with cell proliferation[9]. There is a growing body of literature relating NF1 to GISTs. Corroborations of this idea include a 7% incidence of GISTs in the NF1 population, and a 150-fold risk in contrast to the general population[9]. In one 5-year study concerning patients with NF1 related GISTs, it was found that the tumors occurred in the small bowel 67% of the time, with 87% possessing spindle cell histology, a low mitotic rate, and a decade earlier median age of diagnosis in comparison to *KIT* & *PDGFRα* mutations[10]. The primary marker for diagnosis remained positive staining for *KIT*. Out of the 15 patients in the study, 6 were treated with tyrosine kinase inhibition therapy (Imatinib), which resulted in a single partial response which lasted <3 months. This finding lends credibility to the idea that NF1-related GISTs have unique sites of occurrence, demographics, and prognoses. It is also imperative to recognize Imatinib resistance as a primary concern for long-term outcomes. In consideration of the relative rarity of NF1 and GISTs, there exists a gap in clinical experience and the literature supporting alternative treatment, with a magnified risk in cases of unresectable metastatic cancer or tumors with arterial involvement. This case study will serve as an appraisal of the current and future treatment options for this condition, drawing on a rare case involving a young male for its basis.

Case presentation

A 39-year-old male with a reported history of neurofibromatosis (found after son's diagnosis) presented to urgent care with chief complaint of dark bowel movements and pale complexion. He was directed to emergency department (ED) for further evaluation but had a syncopal episode shortly after. Hemoglobin (Hgb) was 5.9 upon presentation. He received 4 units of packed red blood cells (PRBCs) and had a colonoscopy performed demonstrating no evidence of bleeding from any source. Staging computed tomography (CT) angiogram was performed and revealed a large mass in the left hemiabdomen emanating from the duodenum. This was followed by an upper endoscopy with identification of a friable ulcerated mucosal lesion with clip placement to control bleeding. However, bleeding persisted. The patient subsequently underwent an interventional radiology (IR) angiogram, showing a large tumor with arterial supply from the celiac, inferior mesenteric, and superior mesenteric origins. A successful embolization of the first jejunal branch supplying the tumor was performed. The patient was stabilized after embolization and transferred to a tertiary care oncology facility for further work up and treatment.

After transfer, the patient underwent endoscopic ultrasound, which revealed a single oval, hypoechoic, heterogeneous mass with well-defined margins in the fourth portion of the duodenum. A bleeding ulcer was also discovered and again clipped. Fine-needle aspiration (FNA) pathology showed a predominantly spindle cell proliferation consistent with GIST. Staging CT demonstrated the 10.6 x 9.1 x 9.7 cm mass with no evidence of metastatic disease in chest, abdomen, or pelvis. The mass was in close proximity to aorta, inferior vena cava, superior mesenteric artery and vein, as well as splenic artery and vein. There was no evidence of vascular encasement. The GIST had abutment of the pancreatic body as well as clear involvement of the left colonic mesentery with close proximity to the left renal vein (Figures 1-3).

The patient was clinically staged as IIIA (cT4, cN0, cM0, mitotic rate: low). Immunohistochemical stains were performed, exhibiting positive spindle cells for DOG-1, CD117, and CD34. SMA, S100, and AE1/AE3 were negative. The case was discussed at the institutional sarcoma multidisciplinary sarcoma tumor board, with recommendation of upfront surgical resection after molecular testing expectedly confirmed lack of KIT mutation. Surgery with curative intent was scheduled for 4/26/23.

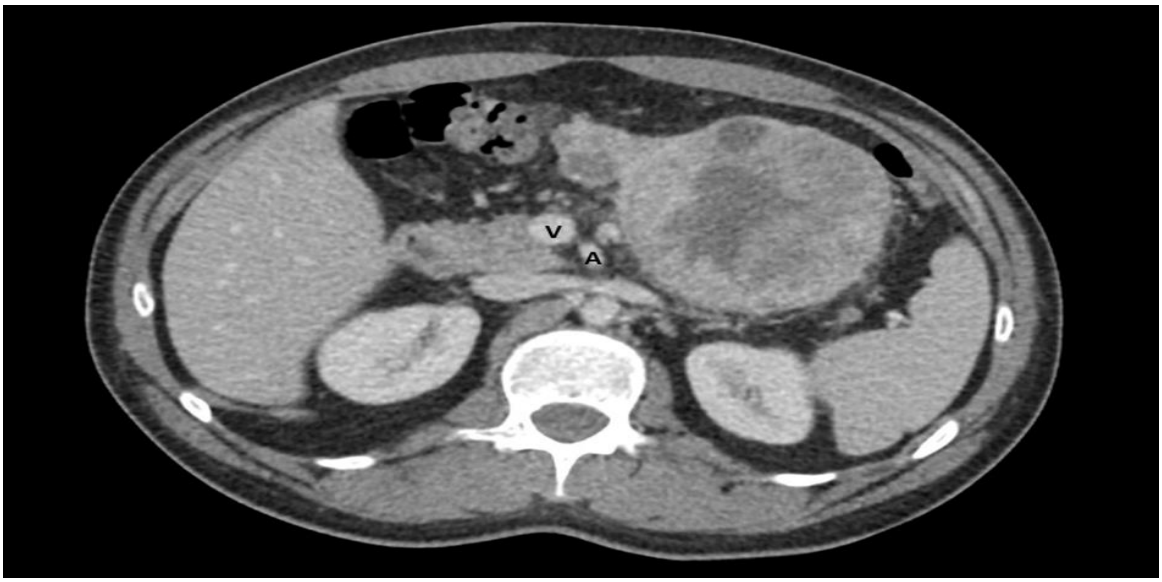

Figure 1. The Superior Mesenteric Vein [SMV(V)] and Superior Mesenteric Artery [SMA(A)] are labeled accordingly in relation to the large left upper quadrant mass.

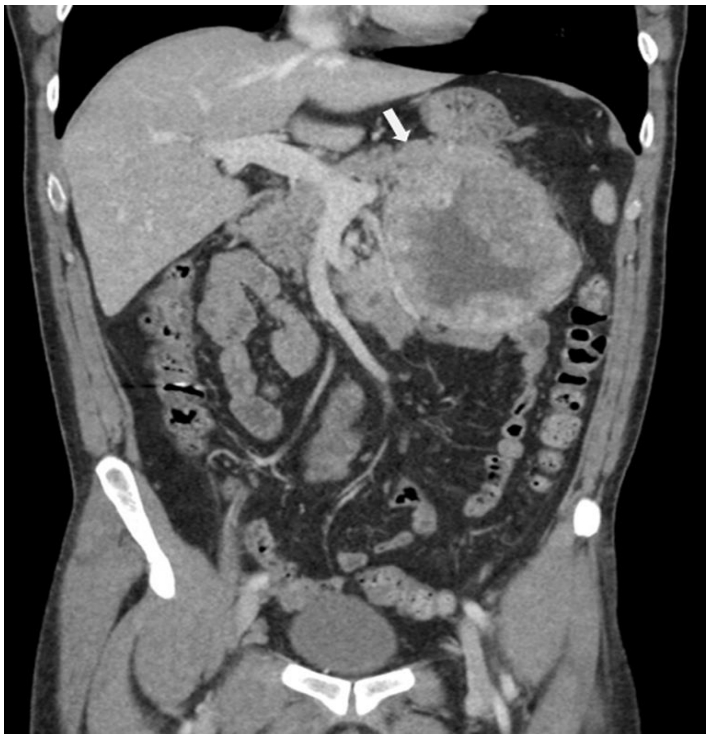

Figure 2. An arrow is provided in this figure of the patient's pancreas.

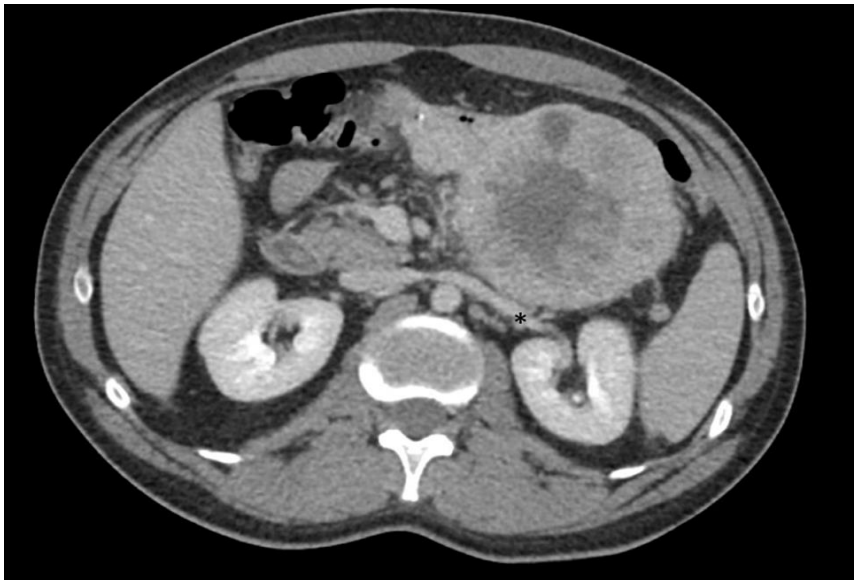

Figure 3. The left renal vein is highlighted in this figure with a star.

Surgical Procedure

The procedure was performed with the initial aim of a duodenal resection, with possible left colon resection, possible subtotal pancreatectomy, and possible left nephrectomy. The operation began with a full mobilization of the transverse colon, entering the lesser space below the gastrocolic ligament. It was clear that the mass was involving the duodenum just distal to the Ligament of Treitz. It was also identified that the mass invaded the neck, body, and tail of the pancreas, and could not be dissected off without compromising the integrity of the GIST. The pancreatic neck was subsequently transected, and the splenic artery, and vein were controlled and sequentially transected. The retroperitoneal attachments to the spleen, colon, and kidney were circumferentially dissected out. A resection of two-thirds of the adrenal gland followed, with gross involvement identified. Mesenteric blood supply to the involved portion of the duodenum was clipped and tied off, with significant blood supply directly from the superior mesenteric artery to the tumor noted. The tumor also involved a significant portion of the left mesocolon requiring en bloc left colon resection. The specimen was meticulously dissected free from its remaining attachments and blood supply and sent to pathology confirming clear gross margins. The reconstruction was performed utilizing a hand sewn side to side duodenojejunostomy and followed by a standard stapled colocolonic anastomosis.

Pathology

Final pathology demonstrated proximal and distal duodenal margins free of tumor involvement. Invasion into the adjacent pancreatic parenchyma was not identified. The remaining pancreas, colon, and left adrenal gland were without diagnostic abnormality. Twenty lymph nodes were negative for the tumor. There was confirmed multifocality of the tumor, with greater than 10 tumor nodules with sizes ranging from 0.5-13.2 cm. The mitotic rate was identified to be 2 mitoses per 5 mm2, and a high-risk classification was assigned to the GIST. Next generation sequencing (NGS) of the primary tumor confirmed Imatinib insensitivity with a lack of mutations in *KIT* and *PDGFRα*. *BRAF*, *NF2 (HGNC:7773)*, *SDHA (HGNC:10680)*, *SDHB (HGNC:10681)*, *SDHC (HGNC:10682)* were also found to be negative for mutation. NGS results demonstrated coverage of *NF1* (exons 31,52) and SDHD (exon 4) were below the quality minimum, although no pathogenic mutations were identified. The pathologist noted that additional testing may be

warranted. Further communication with genomic pathology has revealed a trend of low coverage in exons 31, 52 for NF1 cases. The coverage of the exons at 300x was deemed sufficient by bioinformatics, and variants were ruled out. Without confirmatory germline testing of the patient's child, possible complex mutations in this case cannot be affirmed.

The patient tolerated the procedure well and was discharged home on postoperative day 7. CT on 7/18/23 was unremarkable, with surveillance imaging planned for 3-month intervals.

DISCUSSION

NF1-related GISTs

Neurofibromatosis is classified as a tumor susceptibility syndrome within which there is an increased risk in the formation of several tumor types, with a reported cumulative cancer risk of 38% in NF1 carriers by age 50, and a 59.6% lifetime risk in comparison to 3.9% and 30.8%, respectively, within the general population[11]. Moreover, one commonality that has been identified between NF1-related GIST and sporadic GIST is the loss of function in neurofibromin. This results in the activation of the RAS-MAPK cascade, which can also be affected by *KIT* mutations-ending in tumorigenesis [11].

In the most current report, NGS results returned with a lack of a variants on exons 31, 52. Without genetic testing of the patient's child, the nature of this mutation cannot be positively affirmed to be germline or somatic. Clinical features point to GIST in the setting of an *NF1* germline mutation, however. As aforementioned, a 5-year study found that NF1-GIST tumors had 67% occurrence in the small bowel, 87% spindle cell histology, low mitotic rate, and a decade earlier median age of diagnosis in comparison to KIT & PDGFRα mutations [10]. In a study relating age to GIST prognosis, three-quarters of GISTs were diagnosed in patients above 50, with a median age of 58 [12]. Together, the low mitotic rate, spindle cell histology, history of NF1, and young age of the patient fit the profile of NF1 related GISTs. In addition, NF1-GISTs have a propensity to be multifocal in contrast to sporadic GISTs[10].

The decision to proceed with curative intent surgery was made in accordance with a review of the GIST features matching NF1, and the incidence of Imatinib sensitivity in the NF1 population. Surgical therapy remains the mainstay in GIST treatment and palliation, as it represents the only chance for cure[13].

MEK Inhibition

Experience with WT GIST demonstrates no improvement in event-free survival with extensive or serial resections, suggesting that surgical therapy should be relegated to the initial resection[13]. Moreover, MEK inhibition is referenced in its propensity for reducing the size of NF1-GISTs, in the presence of Imatinib resistance. In one report assessing the efficacy of MEK inhibitors for plexiform neurofibromas, the oral inhibitor selumetinib resulted in >20% volumetric tumor shrinkage in 70% of pediatric NF1 patients[14]. Other MEK inhibitors such as mirdametinib and trametinib have shown an objective response of >20% tumor shrinkage in 42% of patients, and >20% plexiform volume reduction in 50% of patients, respectively. The therapy is generally well-tolerated but has toxicities to consider. Frequent toxicities of these inhibitors include GI complications, creatinine kinase elevation, and skin toxicity[14]. A growing body of literature on MEK inhibition supports the application of the novel therapy in GISTs in the setting of a clinical trial. Inhibition of the signaling pathway components RAF and MEK have shown improved outcomes in patients in contrast to conventional chemotherapy or treatment with B-RAF inhibitors[14]. Inhibition of RAF and MEK, as components of the MAPK signaling cascade, may be able to reproduce similar results as seen in B-RAF mutated melanoma considering the similar pathogenesis in WT GISTs.

Clinicopathologic features of WT GISTs are typically indolent, even in relapses, with a median event-free survival (EFS) of 2.5 years[15]. EFS post-surgery was linked to presence of metastatic disease and high mitotic rates[15]. This feature of WT tumors is useful when considered alongside the lack of curative therapy outside of surgery. In the future, the unique molecular drivers responsible for WT GISTs, including those in the setting of NF1, must be examined to develop appropriate therapies. Moreover, the ambiguity of the mutation source in this case lends

importance to NGS and confirmatory germline testing in WT GISTs.

CONCLUSION

NF1 is a disorder which encompasses a wide range of complications, including acting as a molecular driver for malignant GISTs. As of now, surgical resection of GISTs is the mainstay treatment option. Clinicians should be aware of the unique pathogenesis and phenotypes of NF1-related GISTs and proceed with curative intent surgical treatment when possible. Genetic testing for patients with familial history of NF1 is key in determining tumor susceptibility and determining treatment strategy. Additional clinical trials for MEK inhibitors are warranted to better understand if this therapeutic modality is valuable in WT GISTs.

CONFLICT OF INTEREST

The persons involved in the writing of this paper do not have any financial, academic, or political affiliations that may affect the interpretation of the case.

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Data Sharing Statement

The authors encourage that all the data from this case report be used in support of clinical methodologies and the creation of further literature. https://pubmed.ncbi.nlm.nih.gov/

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