



Heterogenous Intertumoral KIT Mutations in Long-term Stage 4 Gastrointestinal Stromal Tumor Survivor

Seiya Liu^{1*}

Irene Goo¹

Ty K. Subhawong²

Andrew E. Rosenberg³

Jonathan C Trent^{4,6}

Emily Jonczak⁴

Elizabeth Montgomery³

Alan Livingstone⁵

Gina D'Amato^{4,6}

¹University of Miami Miller School of Medicine, Miami, FL, USA

²Department of Radiology, University of Miami Miller School of Medicine, Miami, FL, USA

³Department of Pathology, University of Miami Miller School of Medicine, Miami, FL, USA

⁴Department of Medicine, Division of Medical Oncology, University of Miami Miller School of Medicine, Miami, FL, USA

⁵Department of Surgery, University of Miami Miller School of Medicine, Miami, FL, USA

⁶Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL, USA

Abstract

Gastrointestinal stromal tumors (GISTs) are mesenchymal neoplasms of the gastrointestinal tract, with a prevalence of 5% out of all sarcomas. We herein report the case of a 54-year-old man with metastatic GIST who initially presented to the emergency department with severe "anemia" CT examination revealed a 22 cm mass adherent to his small bowel and associated pelvic ascites and metastases. Surgical excision of the abdominal wall mass and partial omentectomy demonstrated extensive necrosis and a tumor mitotic rate of 17 per 5 mm². Molecular profiling of the primary mass showed a KIT exon 9 mutation. Despite eight years of sunitinib treatment, follow-up PET-CT evaluation showed three enlarging omental/peritoneal masses. Surgical excision and molecular profiling of each mass, opposed to the standard practice of profiling only one, demonstrated different KIT exon mutations between each mass, each with resistances to different tyrosine kinase inhibitor treatments.

Article Highlights

- Metastatic gastrointestinal stromal tumor can attain novel mutations
- Performance of therapies may decline in the setting of novel KIT mutations
- Molecular profiling of multiple metastatic nodules may aid in treating specific mutations

Keywords

Gastrointestinal stromal tumor, Tyrosine kinase inhibitor, Sarcoma, Next-generation sequencing, KIT exon mutation

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common type of mesenchymal neoplasm of the gastrointestinal tract [1]. KIT and PDGFRA mutations that characterize these tumors produce proteins that can be detected by immunohistochemistry in 85% of reported GISTs [2-5]. As such, CD117 (KIT) immunohistochemistry is a reliable diagnostic tool [6,7]. The development of next-generation sequencing (NGS) technology has also improved the detection of gene alterations in tumor-specific gene sequences, identifying new gene variations in KIT-expressing GISTs [8,9]. These identifiable and targetable mutations have led to the successful deployment of tyrosine kinase inhibitors (TKIs) such as imatinib, sunitinib, regorafenib, ripretinib and avapritinib for treatment of KIT-positive, KIT-mutant, or PDGFRA-positive GISTs [10-13]. In terms of clinical management, it is important to assess patient-specific and local tumor-specific GIST mutations for risk of resistance to existing therapies due to variations in molecular subsets [7,14,15]. Herein we report a case of recurrent, metastatic GIST with heterogenous intertumoral KIT mutations. To better understand this tumor and the associated treatments, we also reviewed relevant literature.

Article Information

DOI: 10.31021/IJCMC20225174

Article Type: Case Report

Journal Type: Open Access

Volume: 5 Issue: 1

Manuscript ID: IJCMC-5-174

Publisher: Boffin Access Limited

Received Date: 01 February 2022

Accepted Date: 25 February 2022

Published Date: 04 March 2022

*Corresponding author:

Seiya Liu

University of Miami Miller School of Medicine

1475 Northwest 12th Ave, Suite 3039

Miami, FL 33136

E-mail: seiyaliu@med.miami.edu

Citation: Liu S, Goo I, Subhawong T, Rosenberg AE, Trent JC, et al. Heterogenous Intertumoral KIT Mutations in Long-term Stage 4 Gastrointestinal Stromal Tumor Survivor; Case Report. Int J Clin Med Cases. 2022 Feb;5(1):174.

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Case Study

A 54-year-old male with no past medical history presented to the emergency room with complaints of chronic fatigue. Bloodwork showed a hemoglobin of 4.9 and he received further work-up with computed tomography (CT). CT evaluation demonstrated a large 22cm mass adherent to his small bowel with associated pelvic ascites and numerous tumor deposits. The patient underwent surgical resection of the abdominal wall mass and partial omentectomy. The primary site was determined to be small bowel. Pathological analysis of the samples revealed a high-grade GIST with extensive necrosis and a mitotic rate of 17 per 5mm². Subsequent molecular analysis showed that the primary tumor harbored a KIT exon 9 mutation.

Given his metastatic disease, the patient initially received imatinib 400 mg daily, which was increased to 800 mg once a KIT exon 9 mutation was identified. Due to progression of disease after 6 months, he was transitioned to sunitinib, initially with a 50 mg regimen daily for four weeks on and 2 weeks off, then to a 37.5 mg continuous regimen due to adverse effects. With sunitinib he developed a chronic hand-foot skin reaction and diarrhea, for which he took a three-day break per month to alleviate symptoms. Additionally, he used urea cream for his hands and feet, as well as loperamide and diphenoxylate-atropine for diarrhea relief. He was followed for elevated transaminases, elevated ferritin, and iron saturation, but with no established diagnosis of hemochromatosis due to his history of hepatic steatosis. His iron levels improved after ceasing alcohol intake. He received phlebotomies for symptom relief.

After eight years of sunitinib use with stable disease, a follow-up PET-CT scan showed three enlarging omental/peritoneal implants on the right side of his abdomen, with the largest measuring 3.4 x 2.3 cm compared to 1.4 x 1.2 cm on previous scan five months prior, with a SUV uptake value of 11.7, increased from 5.0 (Figure 1a). The patient underwent metastasectomy, with excision of residual metastatic GIST in the retroperic space (space of Retzius), omentum, as well as removal of a left upper quadrant implant and Trucut biopsy of the left liver lobe. Of note, molecular profiling (Caris Life Sciences TM) was conducted for each excised tumor rather than the standardized practice of only assessing one site. Two omental implants demonstrated different KIT mutation variants on exon 17, exon 9, and exon 1, shown to be sensitive to regorafenib but to have resistance to imatinib and sunitinib. One pelvic peritoneum implant demonstrated KIT exon 9 and 13 mutation variants, while another retroperitoneal implant showed KIT exon 9 mutation variants. Both peritoneal implants were thus interpreted as susceptible to imatinib, to sunitinib if imatinib-refractory, or to regorafenib if imatinib/sunitinib-refractory. Guardant 360®CDx liquid biopsy testing for comprehensive tumor mutation profiling revealed 0.2% cfDNA of TP53 R248W alteration but detected no KIT mutations. Four months after surgery, the patient developed ulcerative skin lesions on the heels of both feet, as well as elevated transaminases and testicular swelling. As such, sunitinib administration was withheld and other treatment modalities were considered.

Due to disease progression and worsening symptoms, the patient then received third-line treatment, namely regorafenib, at 160mg daily. During the first week of treatment, patient had poor tolerance of this regimen and therefore dose was decreased to 120 mg for one week. In the 18 days of regorafenib treatment, the patient reported complete loss of appetite, associated weight loss of five pounds, severe fatigue, one episode of unusual hemorrhage, bilateral upper extremity skin sensitivity and erythema, pain and swelling in the left knee, bilateral skin bullae in his heels, chills and shivering, and a fever of 104.8 Fahrenheit. Symptoms resolved after withholding treatment. Currently, the patient

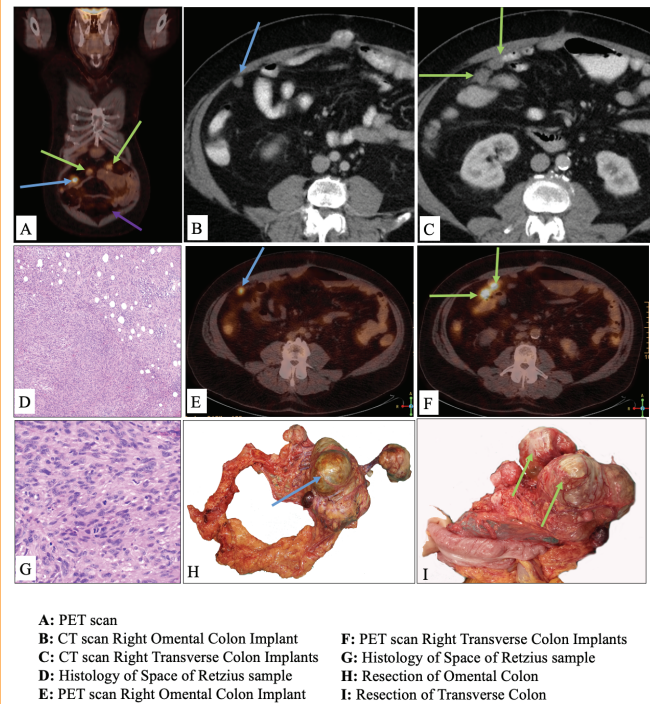


Figure 1: PET, CT, histology, and gross samples of patient tumor implants after eight years of sunitinib use with stable disease.

awaits initiation of a fourth-line therapy, namely ripretinib, for progressive disease despite regorafenib treatment (Figure 2).

Discussion

Gastrointestinal stromal tumors (GISTs) are common gastrointestinal mesenchymal tumors that present with variable immunophenotypes [7,13,15]. The discovery of a host of KIT mutations in various exons has led to the development of effective targeted therapies using tyrosine kinase inhibitors (TKIs). While imatinib has been established as an effective first-line therapy for GIST, about 15% of GIST patients have tumors that are resistant to imatinib due to variant KIT mutations, notably in exons 9, 13, and 17 [5,7,14,16]. The emergence of sunitinib and other TKIs as treatment options in imatinib-resistant patients has provided other viable treatment options in the face of singular resistance to imatinib [5,10,17].

This 54-year-old male patient with metastatic GIST originating from the small bowel demonstrates the importance of conducting next-generation sequencing (NGS) on multiple metastatic sites. Given the heterogenous mutations at each tumor location, clinical management would be dramatically different without the relevant knowledge of exon-specific resistances. The sudden development of disease progression and metastatic implants despite multiple years of stable disease with sunitinib treatment demonstrates the importance of follow-up, imaging, and next-generation sequencing of resected tumors. Previous studies have also described the development of multiple TKI-resistant KIT mutations after initial imatinib and subsequent sunitinib treatment [17]. If metastatic implants have heterogenous KIT mutations, as is the case for this patient, the clinical approach must change appropriately to effectively control further disease progression.

Of particular interest, the omental implants with KIT exon 17, exon 9, and exon 1 mutations, respectively, grew the most aggressively compared to the other pelvic, peritoneal, and

Space of Retzius Exon 9 Variant: p.A502_Y503dup Exon 13 Variant: p.N655S, c.1964A>G	Omental Colon Exon 9 Variant: p.A502_Y503dup Exon 17 Variant: p.S821_N822insl	Transverse Colon Exon 9 Variant: p.A502_Y503dup Exon 13 Variant: p.K642E, c.1924A>G
Benefit Sunitinib Lack of Benefit Imatinib Regorafenib	Benefit Regorafenib Lack of Benefit Imatinib Sunitinib	Benefit Sunitinib Lack of Benefit Imatinib Regorafenib

Figure 2: Exon variants of each excised tumor with potential benefits and lack of benefits to treatments.

retroperitoneal implants with KIT exon 9 and 13 mutations. Exon 17 mutations are most common in small intestinal GIST with no discernible difference in clinical prognosis compared to non-KIT-mutated, wild-type GISTs [18]. Given the patient's clinical presentation, one of the omental implants with an exon 17 mutation likely resulted from tumor implantation of the primary site. However, the largest omental implant with KIT exon 17 and 9 mutations is consistent with previous studies that outlined the aggressiveness of non-gastric exon 9 mutated tumors [5,18]. KIT exon 13 mutations are more common in secondary imatinib resistance, and associated with aggressive behavior for gastric GISTs, but not for small intestinal GISTs, which are intrinsically more aggressive than gastric GISTs [19]. The KIT exon mutations present in the implants are consistent with expected growth patterns of non-gastric GISTs. The omental GISTs harboring KIT exon 9 mutations demonstrate the most explosive growth and the retroperitoneal and pelvic peritoneum implants with KIT exon 9 and 13 mutations demonstrated lower levels of growth and smaller size compared to the omental implants (Figure 2).

Localized GISTs are commonly treated with surgical excision. Metastatic disease in the context of GIST is less likely to be resolved with surgical excision, but rather require more targeted approaches [8]. The development of NGS has opened the door to identifying targetable mutations. While standard practice of use for NGS has been limited to assessing only one site of disease for mutations, as opposed to multiple tumor locations, this case of intertumoral heterogeneous mutations demonstrates the need to analyze multiple sites in the setting of metastatic disease [5]. Although GIST has a relatively high 5-year survival rate across all stages, long-term survival (>10+ years) dramatically decreases despite standard TKI treatment, potentially due to the rise of novel TKI-resistant mutations [20].

Conclusion

Improved understanding of KIT mutations will lead to improved outcomes. Assessing patient-specific and local tumor-specific GIST mutations for variations in resistance is crucial for clinical management of treatment-resistant GISTs. Discovering agents that will target the current TKI resistant mutations and implementing multi-tumor analysis is therefore of the utmost importance.

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