

## Case Report

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## A Rare Case of Quadruple Negative GIST with an Unusual Presentation in a Young Female

Srijan Valasapalli<sup>1\*</sup>, Sanjivani Sathe<sup>2</sup>, Joseph A Policarpio<sup>3</sup> and Suparna Mantha<sup>4</sup>

<sup>1</sup>Internal Medicine Residency Program, Carle Foundation Hospital, IL, USA

<sup>2</sup>Internal Medicine, Carle Urbana, USA

<sup>3</sup>Carle Illinois College of Medicine, Carle Foundation Hospital Champaign, USA

<sup>4</sup>Hematology, Internal Medicine, Hematology/Oncology and Medical Oncology, USA

### ABSTRACT

Gastrointestinal stromal tumors (GISTs) are an uncommon malignancy, with origin in the interstitial cells of Cajal located in the myenteric plexus. The incidence is 5000 new cases every year in the US. It is important to determine genetic alterations in GIST. Approximately 90% of GISTs have a gain of function mutation in either the c-KIT protooncogene (which encodes for the receptor tyrosine kinase KIT) accounting for 75%, or the platelet derived growth factor receptor alpha (PDGFRA) protooncogene which accounts for 15%. Only 5-10% constitute Wild Type (WT) GISTs with mutations observed in BRAF, NF1, & SDH. While Imatinib, a Tyrosine Kinase Inhibitor (TKI), is used as adjuvant therapy for most KIT-positive tumors, it cannot be used in TKI-resistant tumors that harbor alternative genetic mutations. We present a rare case of quadruple negative (negative for all aforementioned genes) GIST with a mutation identified as ETV6-NTRK3 fusion. This mutation was first described in a case of rectal quadruple negative WT GIST.

### \*Corresponding author

Srijan Valasapalli, Internal Medicine Residency Program, Carle Foundation Hospital, IL, USA. E-mail: srijan.valasapalli@carle.com

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### Introduction

90% of Gastrointestinal Stromal Tumors (GISTs) have a gain of mutations in c-KIT (75%) or PDGFRA (15%). Only 5-10% constitute WT GISTs with mutations observed in PDGFRA, BRAF, NF1, & SDH [1]. We present a rare case of quadruple negative (negative for all aforementioned genes) GIST with a mutation identified as ETV6-NTRK3 fusion, a translocation first described in a case of rectal quadruple-negative WT GIST and rarely reported [2,3].

### Case Presentation

A 23-year old female with no prior medical history was admitted two times in three months for fatigue and hematochezia, with a hemoglobin of 7 g/dL. Colonoscopy and esophagogastroduodenoscopy showed normal findings. During video capsule endoscopy, the capsule failed to exit the small bowel, and an ulcerated lesion was identified in the distal jejunum. She then underwent antegrade double-balloon enteroscopy that revealed a non-bleeding jejunal ulcer which was resected and sent to pathology.

Parallely, she underwent a pelvic ultrasound for menstrual irregularities, which showed a 5 x 5 cm right adnexal mass. A series of neoplastic markers were negative. Follow-up Computed tomography (CT) of the abdomen and pelvis showed a heterogeneous mass in the pelvis, likely representing a GIST

arising from the adjacent small bowel loop or an exophytic right ovarian mass. With the conundrum of identifying the mass's origin, she underwent explorative laparotomy which revealed a malignant-appearing small bowel mass of 6.5 cm x 5 cm growing from the proximal small intestine wall was identified and resected. Both resected specimens were identified as GIST with a mitotic index >5 mm/m<sup>2</sup>, and the patient was referred to Oncology. Germline genetic testing for c-KIT, PDGFRA, BRAF, NF1 & SDH were all negative. There was no role for tyrosine kinase inhibitors (TKIs) as the tumor was KIT-negative. Subsequently, Comprehensive Genomic Profiling (CGP) of the tumor showed an ETV6-NTRK3 fusion. Currently, the patient remains on active surveillance.

### Discussion

RNA sequencing on WT tumors can assess the possible involvement of fusion proteins such as ETV6-NTRK3 fusion. This assay is indicated for all quadruple-WT (qWT) GISTs, as recommended by a report from the DUTCH GIST registry. The ETV6-NTRK3 fusion protein activates IGF-1 downstream signaling, causing cell growth by IRS1 activation, and is therefore amenable to be targeted by IGF1 and ALK inhibitors [1, 2]. Additionally, LOXO-101 is a selective tyrosine receptor kinase inhibitor, currently in phase 1 clinical trial, for NTRK mutations [4]. Routinely used TKIs do not have a role in KIT negative GISTs. This case demonstrates the importance of identifying additional gene mutations in this rare

subset of tumors for which targeted therapies exist [4]. Consulting an expert geneticist and pathologist when WT GIST is suspected may help to reveal non-obvious findings that will ultimately result in efficacious therapy [1].

### Conclusions

The increasing application of comprehensive genomic profiling continues to advance personalized medicine in oncology. Further analysis of demographic and pathological data, and genomic profiling of qWT GISTs, can help to further clarify the largely undefined pathobiology of this GIST subtype. Additionally, this next-generation sequencing may reveal genomic alterations that are potentially targetable and therefore clinically relevant [5].

### References

1. Wada R, Arai H, Kure S, Peng WX, Naito Z (2016) “Wild type” GIST: Clinicopathological features and clinical practice. *Pathol Int. Aug.* 66: 431-7.
2. Brenca M, Rossi S, Polano M, Gasparotto D, Zanatta L, et al. (2016) Transcriptome sequencing identifies ETV6-NTRK3 as a gene fusion involved in GIST. *J Pathol. Mar.* 238: 543-9.
3. Nannini M, Urbini M, Astolfi A, Biasco G, Pantaleo MA (2017) The progressive fragmentation of the KIT/PDGFRA wild-type (WT) gastrointestinal stromal tumors (GIST). *J Transl Med.* 5: 113.
4. Shi E, Chmielecki J, Tang CM, Wang K, Heinrich MC, et al. (2016) FGFR1 and NTRK3 actionable alterations in “Wild-Type” gastrointestinal stromal tumors. *J Transl Med.* 12:339.
5. Cho WC, Shin YK, Na YS, Ryu MH, Ku JL, et al. (2020) The role of novel fusion genes in human GIST cell lines derived from imatinib-resistant GIST patients: A therapeutic potential of fusion gene. *Biochemical and Biophysical Research Communications.* 529: 699-706.

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