OPEN ACCESS

GAVIN PUBLISHERS

Annals of Case Reports

Khan MM, et al. Ann Case Report 12: 281.

DOI: 10.29011/2574-7754/100281

Case Report

Massive Lower Gastro-Intestinal Bleed in Young Patient: A Rare Presentation of Gastro-Intestinal Stromal Tumor

Muzammil Muhammad Khan[*1], Mamoon Ur Rashid[2], Waqas Ullah[3], Yousaf Zafar[4], Hammad Zafar[2], Abu Hurairah[2]

[1]Internal Medicine Residency, Khyber Teaching Hospital, Peshawar, Pakistan

[2]Internal Medicine, AdventHealth, N. Orange Ave, Orlando, USA

[3]Internal Medicine Residency, Abington Hospital, PA, USA

[4]Internal Medicine Residency, UMKC Hospital, MO, USA

[*]**Corresponding author:** Muzammil Muhammad Khan, Internal Medicine Residency, Khyber Teaching Hospital, Peshawar, KPK, Pakistan. Email: drmuzammilk@gmail.com

Citation: Khan MM, Rashid MU, Ullah W, Zafar Y, Zafar M, et al. (2020) Massive Lower Gastro-Intestinal Bleed in Young Patient: A Rare Presentation of Gastro-Intestinal Stromal Tumor. Ann Case Report 12: 281. DOI: 10.29011/2574-7754/100281

Received Date: 07 December, 2019; **Accepted Date:** 06 January, 2020; **Published Date:** 10 January, 2020

Abstract

GIST although a rare cause gastric malignancy but one of the most common tumors arising from mesenchymal cells of the gastrointestinal cells. They arise most commonly from the stomach and intestine but can arise from anywhere in the GI tract. GIST can be benign or malignant. The commonest symptom in patients with GIST is vague abdominal pain and abdominal fullness. Mutations in one of the kit gene or PDGFRA gene are responsible for the development of the tumor. They have positive immunohistochemical reactivity for CD-117 antigen. This report presents a case of a 32-year-old male with no significant past medical history presenting with a life-threatening lower GI bleed from an ileal GIST.

Introduction

GIST is the malignant or potentially malignant tumors of the mesenchymal cells arising most commonly from the stomach and intestine but may also develop in the colorectum, esophagus, rarely in the mesentery, omentum or retroperitoneum (extra-intestinal GIST). They are comprised of spindle cells and epithelioid cells that stain positive for CD-117 (95 %) or CD-34 (70 %) on immunohistochemical reactivity. A gain of function mutation of KIT or PDGFRA is responsible which leads to uncontrolled activation of tyrosine kinase causing cellular proliferation and resistance to apoptosis [1]. Thus imatinib, an anti-tyrosine kinase inhibitor has been used in the treatment of the GIST. Mazur and Clark in 1983 were the first to describe stromal tumors as a separate entity [2]. Kindblom and associates in 1998 then explained that the actual cells of origin of these tumors are pluripotent mesenchymal stem cells destined to become interstitial cells of Cajal "Pacemaker Cells" the cells responsible for the communication of smooth muscle cells and autonomic nervous system hence regulating the GI motility [3].

Case Presentation

26-year-old male with no significant past medical history presented to the emergency room complaining of having 3-4 bloody bowel movements for the past few days. He stated having soft stool mixed with a large amount of bright red blood. Patient denied any previous episodes of GI bleed. Patient denied abdominal pain, nausea, vomiting, recent travel, sick contacts, loss of appetite, use of oral anticoagulants or weight loss. On presentation to the ED, patient was feeling dizzy and had low systolic blood pressure in the range of 70-80. Initially management was directed to stabilization of blood pressure. Patient was given IV boluses of normal saline and with continuous IV fluids. During hospitalization, patient dropped hemoglobin to 5.8 and was transfused 7 PRBC's in total over course of 2 days. CT abdomen w/contrast revealed a circumferential, lobulated proximal ileal small bowel mass measuring 2.3 x 2.2 x 2.9 cm. EGD and Colonoscopy were done initially which showed extensive amount of blood and clots throughout the colon with very limited views of underlying mucosa but terminal ileum was normal in appearance. No active bleeding was noted. The mass in the ileum was considered as likely source of bleeding. General surgery was consulted and resection of the tumor was planned. A 5 cm resection of segment of small bowel was done. Pathology report showed GIST tumor (Figure 1 and 2). Patient bleeding stopped subsequently after surgery. Patient was discharged home with no further episodes of GI Bleed.

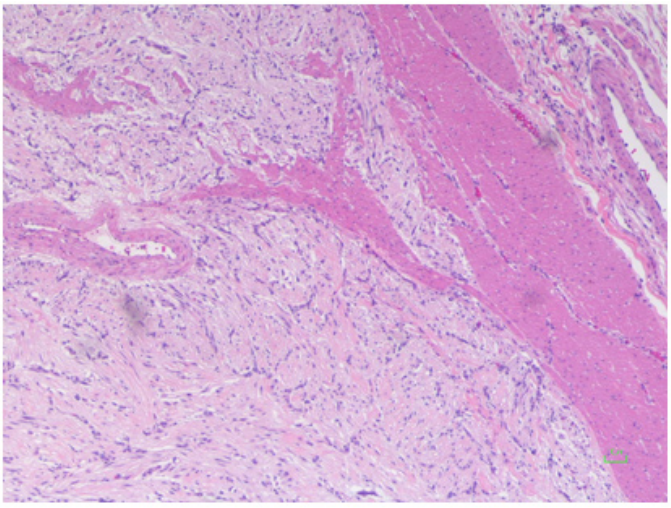

Figure 1: Biopsy of tumor demonstrating GIST invading muscular layer.

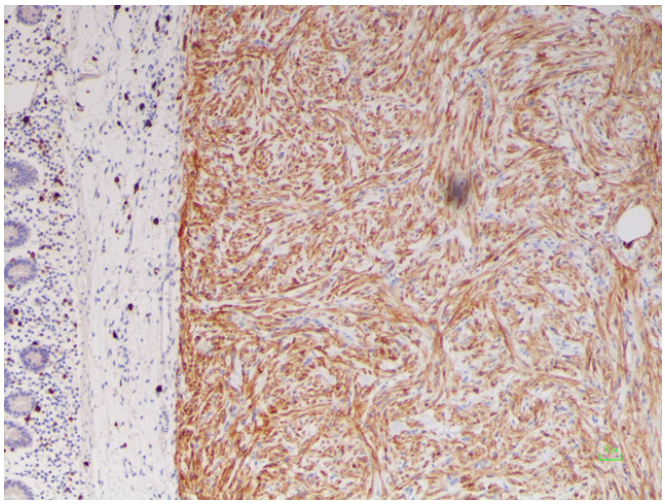

Figure 2: Biopsy demonstrating GIST with CD117 positive staining.

Investigations

Esophagogastroduodenoscopy and Colonoscopy: Important in GI bleeding management. In our case EGD and Colonoscopy were done initially which showed extensive amount of blood and clots throughout the colon with very limited views of underlying mucosa but terminal ileum was normal in appearance. No active bleeding was noted.

CT w/ Contrast: To determine pathology of GI bleed.

H and H: Important to monitor for GI bleed patient.

Differential Diagnosis

- Hemorrhoids
- Angiodysplasias
- Polyps
- Meckel's Diverticulum

Treatment

Surgical Resection is the cornerstone treatment for GIST with or without Tyrosine Kinase Inhibitors.

Discussion

There have been 3300 to 6000 cases reported per year in the United States. Several studies have shown that the median age of diagnosis is the 60s, however, it can occur at early stages as well. GIST has fairly equal incidence in men and women [4]. The predominant location of GIST is stomach (60%) and intestine (20-30%) but it can also be found in the colorectum, esophagus, mesentery, omentum, and retroperitoneum [1]. GIST can be familial or sporadic. The familial form is autosomal dominant [5]. GIST in children and young adults is fairly rare but can be present as a subset of GIST called Pediatric GIST and Syndromic GIST. GIST may also occur with Neurofibromatosis 1 (multiple small intestinal tumors) and Carney triad - gist, pulmonary chondroma and extra-adrenal paraganglioma (gastric epithelioid GISTs in young females).

Clinical symptoms of GIST vary from abdominal fullness or pain, early satiety, weight loss, upper or lower gastrointestinal bleeding leading to anemia, and sometimes abrupt spontaneous GI hemorrhage. Spontaneous hemorrhage may be due to erosion of the GI lumen, causing massive hemorrhage. Bleeding into the peritoneal cavity may lead to peritonitis and acute abdominal pain. Some specific symptoms due to local involvement of organs are also present such as Dysphagia due to esophagus involvement, biliary obstruction due to ampulla of Vater and intussusception [1]. It can metastasize to Liver and Peritoneum. GIST can sometimes be asymptomatic because the tumors are localized to the submucosa and their relatively non-aggressive nature as compared to carcinomas. Gastrointestinal exams, such as endoscopy may reveal these asymptomatic gists. Endoscopic submucosal resection is done in patients with tumors confined to mucosa and submucosa [6].

GIST may be benign or malignant. The malignant potential of GIST is determined by six factors which include size, mitosis, cellularity, necrosis, nuclear polymorphism, and c-kit mutation (Table 1) [7]. The pathological diagnosis of GIST depends on the morphology and immunohistochemical findings. The

morphological findings of GIST include spindle type (70%), epithelioid type (20%) or mixed type (10%) [8]. Almost 95% of the GIST tumors are positive for KIT (CD117) and/or discovered on GIST-1 (DOG1) and almost 70% are found positive on CD34 by immunohistochemistry. The diagnosis of GIST depends on KIT positivity along with positive morphological features compatible with GIST. When KIT is negative, then DOG1 staining followed by CD34 staining is considered diagnostic. The other diagnostic marker for GIST is mutation-positive for KIT and PDGFRA which is present in 5-10% of the patients.

	Benign	Malignant
Size	<5	>5
Mitosis	<2/50 HPF	>5/50 HPF
Cellularity	Low	High
Necrosis	Absent	Present
Nuclear polymorphism	Absent	Prominent
c-kit mutation	Absent	Frequently present

Table 1: Difference between benign and malignant GIST.

If it is negative, then immunostaining by Succinate Dehydrogenase by Iron-Sulfur Subunit B (SDHB) is recommended. The mitotic count is a prognostic factor and it is measured as a number of mitoses for a total area of 5mm2. So the pathologic diagnosis is based on microscopic features of GIST along with positive immunohistochemical markers (KIT, DOG1, PDGFRA mutations, SDH) which are necessary to make a diagnosis. However, the pathological report must include the risk assessment of the tumor e.g tumor size, location, number of mitosis on a total area of 5mm2 (Figure 3) [9]. Many classification and risk assessment criteria have introduced over the years but none is proven superior to others. In 2002, Fletcher and colleagues proposed the NIH classification, the first classification for this tumor, which classifies tumor in very low, low, intermediate and high-risk groups considering the size of the tumor and mitotic index. (Table 2) [10].

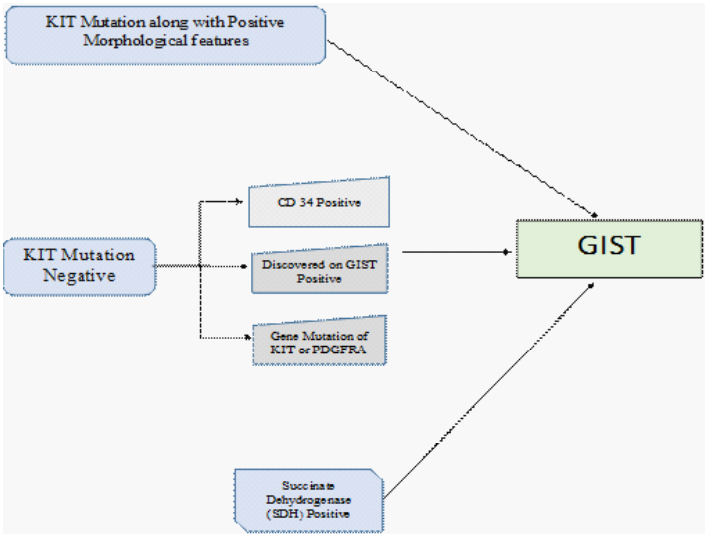

Figure 3: Differential diagnosis of GI tumor based on tumor markers.

Risk	Tumor size (cm)	Mitotic count (HPF)
Very low risk	<2	<5/50
Low risk	2.1 - 5	<5/50
Intermediate risk	<5	06-10-1950
	5 - 10	<5/50
High risk	>5	>5/50
	>10	Any mitotic count

Table 2: NIH risk of recurrence.

In 2006, Miettinen and colleagues added that along with tumor size and mitotic count, tumor location is also of significant prognostic indicator for risk assessment. Miettinen was also the first who described the total area for mitotic counting [11]. In 2008, a modified NIH classification was created by Joensuu and associates. They determined that tumor rupture during surgery had a significant negative prognosis (Table 3) [12]. Radiological diagnosis of GIST is made with Endoscopic Ultrasound (EUS), Contrast-Enhanced Computed Tomography (CECT), Magnetic Resonance Imaging

(MRI) and PET/CT combination. Initial imaging that is always performed in all of the gastrointestinal diseases is the abdominal ultrasound, however, it's only helpful if the tumor size is greater than 5cm [13]. Ultrasound cannot delineate the location of the tumor origin. Endoscopic Ultrasound has been used as it helps in the sampling of the tissue as well as can tell us about the depth of invasion. The accuracy of EUS-FNA is reported to be 80-85% [14]. Despite different diagnostic techniques, contrast-enhanced CT (CECT) remains the diagnostic test of choice.

Risk	Tumor Size (cm)	Mitotic Count (HPF)	Tumor Site
Very low risk	<2	<5/50	Any
Low risk	2.1 – 5	<5/50	Any
Intermediate risk	<5	06-10-1950	Gastric
	5.1 – 10	<5/50	Gastric
High risk	Any	Any	Perforated tumor
	>5	>5/50	Any
	>10	Any	Any
	Any	>10/50	Any
	2.1 – 5	>5/50	Non-gastric
	5.1 – 10	<5/50	Non-gastric

Table 3: Modified NIH risk of recurrence.

CECT can characterize the lesion, tell us about the size and extent of the lesion, and detect metastasis during initial staging workup. It can also be used to monitor the treatment efficacy and surveillance follow up of recurrence. CT guided biopsy can help in the definitive diagnosis of the tumor. Response to therapy is assessed by Response Evaluation Criteria in Solid Tumors (RECIST) or Choi criteria. Choi criteria are more effective than RECIST criteria in assessing the tumor response to tyrosine kinase inhibitor therapy (imatinib). Responsive tumors show a decrease of size >10 % and a decrease of density >15 % on CECT [15]. MRI like CT can also provide information about tumor size, perforation, metastasis, and invasion into surrounding structures but MRI is more useful for diagnosing rectal GISTs, liver metastasis, hemorrhage and necrosis of tumors. PET/CT can provide useful information about the staging of the tumor. PET/CT can also differentiate between benign and malignant GIST tumors. Additionally, PET/CT is more accurate in providing information about liver metastasis than CT alone (Table 4) [16].

Imaging modality	Advantages	Disadvantages
CT enterography	Identifies location of tumors, local invasion, metastasis and definitive diagnosis (CT guided biopsy). Determines response to adjuvant treatment	
Abdominal ultrasound	Useful for visualization of tumor > 5cm	Inconsistent reliability in presence of necrosis, ulceration and air in the bowel.
Magnetic resonance imaging	Identifies location of tumors, perforation, local invasion and metastasis.	Does not display full thickness of small bowel and mesentery.
PET/CT combination imaging	GIST tumor staging, identifying areas of necrosis, differentiating benign vs malignant tumors, determining sensitivity to adjuvant therapy. Better for imaging liver metastasis than CT alone.	

Table 4: Role of Imaging in GIST management.

The gold standard treatment for GIST is surgical resection by laparoscopy or laparotomy. Laparoscopic surgery is recommended when the tumor is in the stomach or small intestine and tumor size is less than 5 cm. Laparoscopic surgery also has the advantage of short hospital stay, resumes normal diet sooner and decreases the need for pain medication [16]. Wu and colleagues reviewed retrospectively patients from 1995 to 2002 and determined that complete surgical resection with negative margins is the curative treatment of the GIST. However, if there is metastatic disease then adjuvant therapy with Imatinib/Sunitinib is recommended along with surgery [17]. Imatinib is a tyrosine kinase inhibitor that blocks ATP binding sites on CD117 and PDGFRA and inhibits signal transduction. CD117 and PDGFRA positive tumors can benefit from this therapy. However, in Imatinib/Sunitinib resistant metastatic GIST, a new drug Regorafenib has been approved by the FDA [18].

If a patient cannot undergo complete surgical resection of GIST, neoadjuvant treatment with Imatinib is effective to reduce the size of GIST so a complete resection with clear margins is

possible. A baseline CECT is performed to measure the preoperative size and then followed with Imatinib. Imatinib should be stopped just before the surgery and continued after the surgery regardless of surgical margins [18]. The three agents approved for the treatment of GISTs are Imatinib, sunitinib, and ponatinib. Several studies have recommended that recurrence-free rates with Imatinib are far superior to without imatinib. The SSG XVIII trials described that high-risk GISTs have better 5-year recurrence-free rates with the treatment of 3 years (66%) as compared to 1 year (48%) of Imatinib therapy. Many patients with GISTs due to mutations in CD117 exons 9, 11, 13, 14 and 17 were found resistant to imatinib therapy [19]. Later in 2014, it was reported that patients with mutations in exons 11 mutations have better survival with Imatinib as compared to patients with exons 9 mutations.

Ramaswamy reported that patients with mutations in exon 9 have 38 months of overall survival as compared to patients with exon 11 who had an overall survival of 66 months. Sunitinib was then later suggested for resistant GISTs with mutations of exon 9, 13, 14 and wild type GISTs (no CD117 or PDGFRA mutations). Ponatinib is the recommended treatment for patients with a mutation with exon 17 [20]. New therapies are being studied for the treatment of resistant GISTs. Heinrich also proposed Pronatinib for the treatment of patients with imatinib and sunitinib resistant CD 117 exon 11 mutations. They found that median survival was 7 months with Pronatinib therapy but side effects needed to be studied further. In an ongoing study, patients with resistant TKIs and unresectable GISTs have been treated with immunotherapeutic drugs nivolumab and Ipilimumab. We have compiled a table of ongoing and completed studies for innovative treatments of GIST. A great deal of research is still in process to get a better understanding of the resistant, unresectable and metastatic GIST (Table 5).

	Clinical Study	Type of Study	Mechanism of Action	Indication
1	Avapritinib vs Regorafenib	Randomized Clinical Trial	Avapritinib also known as BLU 285 is a potent inihibitor of KIT and PDGFRα.	Metastatic GIST previously treated with Tyrosine Kinase Inhibitors
			Regorafenib is a multikinase inhibitor that act against RET, VEGFR, KIT, PDGFR.	
2	Pazopanib	Interventional Clinical Trial	VEGFR, PDGFR, c KIT and FGFR inhibitor	Metastatic and Locally advanced unresectble GIST resistant to Imatinib and Sunitinib
3	Ripretinib (DCC-2618)	Expanded Access Single Arm Study	KIT and PDGFRα inhibitor	Locally advanced unresectable and metastatic GIST that have received prior treatment with FDA approved medications
4	Ponatinib	Non Randomized Clinical Trial	BCR-ABL, VEGFR, KIT and PDGFR inhibitor.	Locally advanced unresectable and metastatic GIST that has KIT Exon 11 mutation GIST and failed prior Tyrosine kinase inhibitor treatment.
5	Vandetanib	Interventional Clinical Trial	Inhibits EGFR-dependent cell survival and EGF-stimulated and VEGF stimulated tyrosine kinase phosphorylation	Wild type GIST in patients with deficiency of Succinate Dehyrogenase (SDH).
6	Imatinib Alternating With Regorafenib Compared to Imatinib Alone	Randomized Interventional Clinical Trial	Regorafenib is a multikinase inhibitor that act against RET, VEGFR, KIT, PDGFR.	Metastatic GIST
7	Nilotinib Versus Imatinib	Randomized Interventional Clinical Trial	Nilotinib is a transduction inhibitor that targets BCR-ABL, c-kit and PDGFR.	Unresectable or Metastatic GIST.
8	Safety and Efficacy of AT13387, Alone or in Combination With Imatinib	Interventional Clinical Trial	AT13387 is a small molecule inhibitor of HSP90 that binds to the ATP site on the N-terminal domain of HSP90 with high affinity inhibiting proliferation and survival of different cell lines.	GIST resistant to other treatments.

Table 5: Latest Clinical Trials and Treatment of GIST.

Conclusion

We have reported a case of a patient with Ileal GIST who had symptoms of life-threatening bright red bleeding causing hemodynamic instability. The patient was diagnosed with Biopsy. Although mild GI bleeding or melena is common in GIST, gross bleeding leading to hemodynamic instability is uncommon. It is diagnosed by CT scan but endoscopic U/S, MRI and PET scan can be done as well. FDA approved treatments are Imatinib, sunitinib and regorafenib. Laparoscopic resection of the tumor along with adjuvant Imatinib is the gold standard treatment. When the surgical resection is not amenable, then neoadjuvant treatment with Imatinib followed by surgery is recommended.

Learning Points/Take Home Messages

- Role of EDG and colonoscopy in GI bleeding is inevitable.
- Surgical Resection is the cornerstone treatment for GIST with or without Tyrosine Kinase Inhibitors.
- CT w/ contrast proves to be beneficial in patients in determining cause of GI bleed.

References

1. Miettinen M and Lasota J (2003) Gastrointestinal stromal tumors (GISTs): definition, occurrence, pathology, differential diagnosis and molecular genetics. Pol J Pathol 54: 3-24.
2. Mazur MT and Clark HB (1983) Gastric stromal tumors. Reappraisal of histogenesis. The American journal of surgical pathology 7: 507-519.
3. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM (1998) Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. The American journal of pathology 152: 1259-1269.
4. Corless CL and Heinrich MC (2008) Molecular pathobiology of gastrointestinal stromal sarcomas. Annu Rev pathmechdis Mech Dis 3: 557-586.
5. Isozaki K, Terris B, Belghiti J, Schiffmann S, Hirota S, et al. (2000) Germline-activating mutation in the kinase domain of the KIT gene in familial gastrointestinal stromal tumors. Am J Pathol 157: 1581-1585.
6. Cantor MJ, Davila RE, Faigel DO (2006) Yield of tissue sampling for subepithelial lesions evaluated by EUS: a comparison between forceps biopsies and endoscopic submucosal resection. Gastrointestinal endoscopy 64: 29-34.
7. Nowain A, Bhakta H, Pais S, Kanel G, Verma S (2005) Gastrointestinal stromal tumors: clinical profile, pathogenesis, treatment strategies and prognosis. Journal of gastroenterology and hepatology 20: 818-824.
8. van Roggen JG, Van Velthuysen ML, Hogendoorn PC (2001) The histopathological differential diagnosis of gastrointestinal stromal tumours. Journal of clinical pathology 54: 96-102.
9. Akahoshi K, Oya M, Koga T, Shiratsuchi Y (2018) Current clinical management of gastrointestinal stromal tumor. World J Gastroenterol 24: 2806-2817.
10. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, et al. (2002) Diagnosis of gastrointestinal stromal tumors: a consensus approach. International journal of surgical pathology 10: 81-89.
11. Miettinen M and Lasota J (2006) Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Archives of pathology & laboratory medicine 130: 1466-1478.
12. Joensuu H (2008) Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Human pathology 39: 1411-1419.
13. Vernuccio F, Taibbi A, Picone D, La Grutta L, Midiri M, et al. (2016) Imaging of gastrointestinal stromal tumors: From diagnosis to evaluation of therapeutic response. Anticancer research 36: 2639-2648.
14. Akahoshi K, Sumida Y, Matsui N, Oya M, Akinaga R, et al. (2007) Preoperative diagnosis of gastrointestinal stromal tumor by endoscopic ultrasound-guided fine needle aspiration. World journal of gastroenterology 13: 2077-2082.
15. Rammohan A, Sathyanesan J, Rajendran K, Pitchaimuthu A, Perumal SK, et al. (2013) A gist of gastrointestinal stromal tumors: A review. World journal of gastrointestinal oncology 5: 102-112.
16. Parab TM, DeRogatis MJ, Boaz AM, Grasso SA, Issack PS, et al. (2019) Gastrointestinal stromal tumors: a comprehensive review. Journal of gastrointestinal oncology 10: 144-154.
17. Wu PC, Langerman A, Ryan CW, Hart J, Swiger S, et al. (2003) Surgical treatment of gastrointestinal stromal tumors in the imatinib (STI-571) era. Surgery 134: 656-665.
18. Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, et al. (2013) Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. The Lancet 381: 295-302.
19. Oppelt PJ, Hirbe AC, Van Tine BA (2017) Gastrointestinal stromal tumors (GISTs): point mutations matter in management, a review. Journal of gastrointestinal oncology 8: 466-473.
20. Ramaswamy A, Bal M, Swami R, Shetty O, Bose S, et al. (2017) Early outcomes of exon 11 mutants in GIST treated with standard dose Imatinib. Annals of translational medicine 5.