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# Complexity of Giant GIST Case Series and Review of the Literature

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## Abstract

**Background:** Gastrointestinal stromal tumors are the most common type of mesenchymal tumors of the GI tract, most commonly found in the stomach and intestines. They are thought to grow from the interstitial cells of Cajal (ICCs) or precursors of these cells. They have an insidious onset and may grow to a very large size depending on the site of origin. **Material and method:** We present a case series of three patients who had very large GISTs that had different presentations and outcomes. Patients were from different backgrounds and all were above 50 years old. Each one had a palpable mass in the abdomen in the initial presentation with a multilobulated mass at imaging devoting malignant behavior and higher risk of the tumor. They are managed according to guidelines and treated with Imatinib, but none of them had genetic and molecular studies of the tumor due to non-availability of the test. **Conclusion:** As a conclusion, GISTs are not easy to diagnose especially in the early phase of the disease and it may take years for it to become clinically relevant. Thence a thorough medical history and physical exam with imaging and endoscopies are the main diagnostic modalities with the importance of molecular profiling that will guide therapy and predicting prognosis.

## Keywords

Gastrointestinal Stromal Tumor, GIST, GI Malignancy, Imatinib, Case Series

## 1. Introduction

Due to the development and advances in immune-histochemical staining techniques and improvements in microscopic structural imaging, gastrointestinal stromal tumors (GISTs) are becoming a noticeable tumor entity with its specific markers and characteristics. They were previously known to belong to neop-

lasms of the smooth muscles and it was believed that GISTs arose from the interstitial cells of Cajal, therefore they were called leiomyomas and leiomyosarcomas. But nowadays, it has been recognized that they arise from multipotent mesenchymal stem cells. [1] One key feature that differs with GISTs from these neoplasms is the expression of CD 117 antigen by nearly all GIST's (95%), whereas true leiomyosarcomas, leiomyomas, and other spindle cell tumors of the gastrointestinal tract are typically CD117 negative. [2]

They were viewed as one of the most treatment refractory tumors with conventional chemo-radiotherapy, but during the last decade, the pace with targeted therapy has accelerated due to the extensive work of research and the observations made in patients which led to a strategic management and plan in treating these patients. In other words, it was their origin that leads to the introduction of a chemotherapeutic regimen, imatinib mesylate, a tyrosine kinase inhibitor for c-kit. [3]

Early diagnosis is still challenging because signs and symptoms are not disease specific, they are related more to the site of the tumor. [4] Dysphagia in the esophagus, biliary blockage around the ampulla of Vater, and even small bowel intussusception are examples. GIST patients seldom develop lymph node metastases. GISTs of the peritoneum, omentum, mesentery, and liver are the most prevalent sites for distant metastases. GISTs have a strong proclivity for seeding, therefore intraperitoneal or even scar metastases are common. [5]

In this report we are going to present a series of 3 cases of giant gastrointestinal stromal tumors with different presentations and outcomes.

## 2. Case Series

We present a series of three cases of GIST's collected retrospectively from three different community hospitals in Beirut-Lebanon. All of the three cases were diagnosed after sending samples from the masses for pathology and immunohistochemistry. Biographical details are described in **Table 1**.

**Case 1**

Case of a 50 year old male patient who initially presented to the emergency department complaining about abdominal distention, unintentional weight loss and decreased appetite. His past medical history include hypertension and diabetes. He didn't mention any other associated fever, chills, gastrointestinal, urinary or respiratory symptoms. On physical exam he had moderate abdominal distention, soft abdomen, although a mass felt in the center of his abdomen, no lower limb edema and clear chest auscultation. His vital signs were within the normal range. Laboratory tests showed normal CBCD, creatinine, electrolytes and liver enzymes.

Ct scan chest abdomen and pelvis with iv contrast showed a very large multi-lobulated mass occupying the entire abdominal cavity showing heterogeneous density and enhancement measuring 27 (ML) - 15 (AP) - 24 (CC) cm. Superiorly the mass is abutting the anterior and inferior walls of the distal gastric body,

**Table 1.** Patient characteristics.

| | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| Age at diagnosis | 50 | 64 | 53 |
| Gender | Male | Female | Male |
| comorbidities | HTN, DM2 | HTN | HTN, DM2 |
| Signs and symptoms at presentation | Abdominal distention, weight loss, decreased appetite | Abdominal distention, weight loss, decreased appetite, abdominal pain | Abdominal distention, abdominal pain and high grade fever |
| Labs | Normal | Normocytic anemia, elevated LDH | ↑ wbc<br>↑ crp<br>↑ LDH |
| Imaging findings | Very large (27 * 13.5 * 24 cm) multi-lobulated mass, abutting distal part of the stomach. Peritoneal carcinomatosis | Very large mass (23 * 22 * 12) in the central abdominal cavity, with areas of necrosis. Liver metastasis. | Very large (12.5 * 10.2 * 10 cm) multilobulated necrotic mass occupying the left hypochondrium |
| Time from diagnosis to outcome (days) | Death after 2 months of diagnosis | Partial response after 6 months of treatment | 8 years |

antrum, pylorus and the first part of duodenum with no evidence of fat plane cleavage in between. It approaches the inferior border of the left hepatic lobe with preservation of a thin sheet of fat plane.

The mass is engulfing some of the jejunal loops. It is engulfing the mid to distal part of the superior mesenteric vein. It compresses the portal venous confluence and the right side of the splenic vein causing proximal engorgement of the portal and splenic veins with formation of significant collaterals (peri-splenic, mesenteric, and peri-hepatic). The superior mesenteric artery is drifted posteriorly with no signs of invasion. The celiac trunc, splenic and common hepatic arteries are spared.

Multiple peritoneal lesions are noted in the abdomen and pelvis (above the urinary bladder) showing heterogeneous density and enhancement consistent with seedings/carcinomatosis.

The liver is otherwise normal in size showing smooth contour and homogeneous density.

In the thoracic area, no signs of metastasis were noted (**Figure 1**).

Gastroscopy done and showed extrinsic compression on the stomach, mainly on the body of the stomach. Colonoscopy showed normal colonic mucosa with no lesions up to the terminal ileum.

Decision was made to do an ultrasound guided biopsy and to send it for pathology and histochemistry, which revealed a poorly differentiated cancer cells

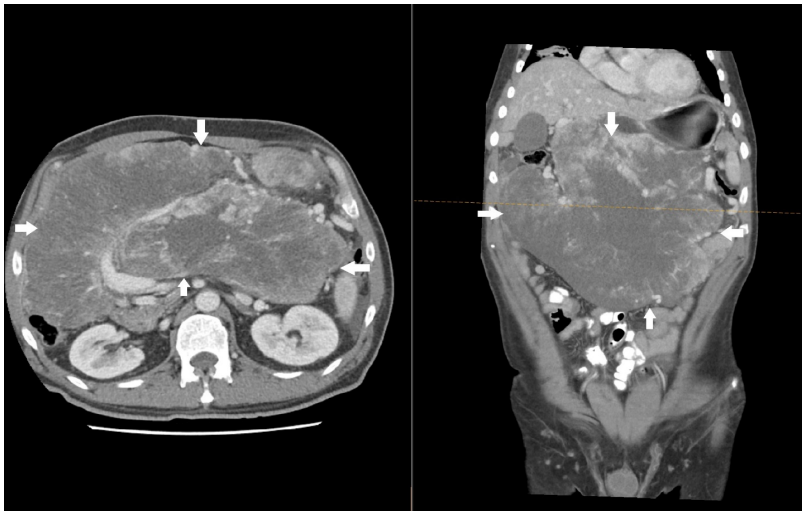


**Figure 1.** Axial section and coronal reformat from CECT Abdomen showing a large mass with heterogeneous contrast enhancement. White arrows pointing to the mass.

(**Figure 2**). Additional immunostains for CD117 and CD34 were performed to exclude the possibility of gastrointestinal stromal tumor (GIST) and showed strong positivity for DOG-1 and weak positivity for CD117. CD34 was negative. So the result was consistent with malignant gastrointestinal stromal tumor.

Immuno-stains are performed on formalin-fixed paraffin embedded sections of block 1A using a polymer detection system. All controls show appropriate reactivity.

Vimentin: positive, diffuse and strong.

MyoD1: negative.

Desmin: few cells positive.

TFE-3: negative.

CKAE1/3: negative.

Spindle to oval cells with nuclear pleomorphism and arranged in sheets

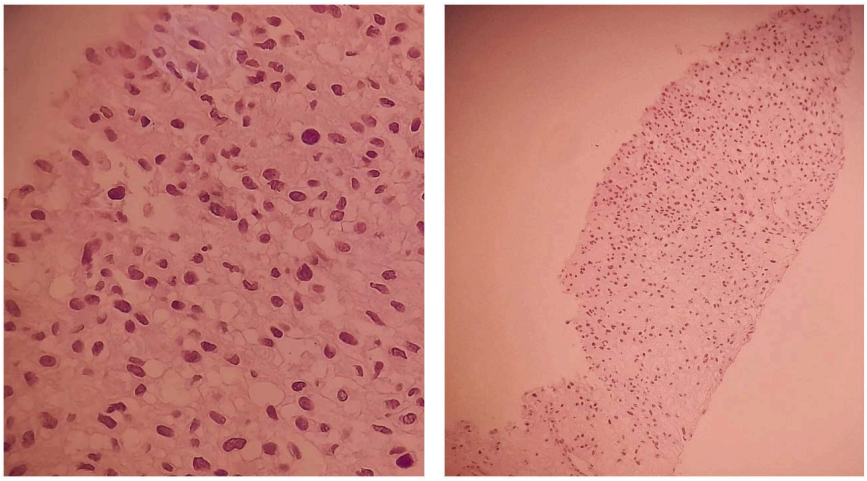
The patient started on Imatinib 400 mg po daily and discharged home.

He was admitted after two months for severe abdominal distention rapidly increasing from the last admission, abdominal pain, decreased oral intake and generalized fatigue. A repeated CT-SCAN showed that the mass has increased in size from (27 * 15 * 24 cm) LL * AP * CC to (30 * 19 * 32.7 cm), with increased amount of ascites and totally compressed stomach and more noticed mass effect to the bowel with no signs of intestinal obstruction (**Figure 3**).

He was started on total parenteral nutrition but his condition rapidly deteriorated due to sepsis and generalized edema mostly ascites and lower limbs, and he died due to cardiorespiratory failure.

**Case 2**

Case of a 64 years old female patient known to have hypertension, married and smoker presented for a recent weight loss, decreased satiety, abdominal distention and abdominal pain. On physical exam she was found to have distended soft abdomen, with ascites and a mass felt in the middle of the abdomen.



(a) (b)

**Figure 2.** Histopathological examination with hematoxylin and eosin staining of the mass ((a), ×200), ((b), ×100).

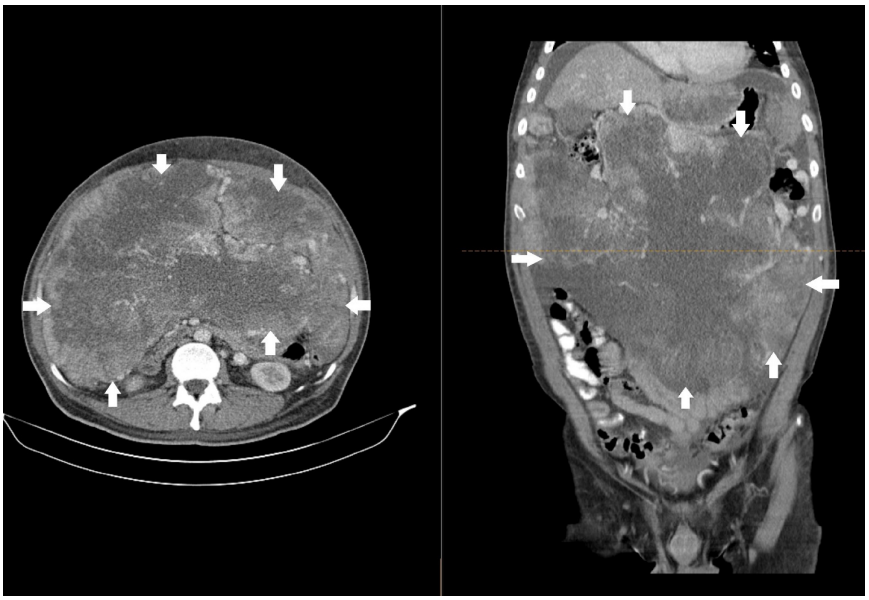


**Figure 3.** Showing the increase in size of the mass with compression of the adjacent structures. White arrows pointing to the mass.

Initial laboratory tests showed mild normocytic anemia with HGB 12 g/dl and MCV 88, normal WBC 5000 and normal platelet count 206,000. Creatinine, electrolytes and total serum protein were also in the normal range. LDH was elevated 349 U/L. Upper and lower gastrointestinal (GI) endoscopies done 5 months before presentation were negative.

CT scan of the chest abdomen and pelvis with intravenous contrast was done and showed a large lobulated mass occupying the central abdominal cavity measuring 23 * 22 * 12 cm, extending to upper pelvis, displacing bowel loops anteriorly and pancreas posteriorly, encasing the superior mesenteric artery. Showing heterogeneous enhancement with hypodense patch areas denoting ne-

crosis. Mild ascites is noted. Multiple hypodense lesions were seen in the liver, the largest is 3.3 cm in segment IV. No other abnormalities were seen, no retroperitoneal lymph nodes.

At the level of the chest no abnormalities were seen.

Pet Scan confirmed the presence of a 26 * 18.4 * 30 cm (TR * AP * CC dimensions) large mass in the upper abdomen, invading the liver with two subcapsular hepatic lesions (Figure 4).

Decision was made to do an ultrasound guided peritoneocentesis and ultrasound guided biopsy of the mass.

Histology revealed a neoplastic proliferation consisting of spindle cells with big elongated hyper-chromic nuclei arranged in fascicles with moderate nuclear atypia. The intervening stroma is fibrotic and moderately inflamed. Moderate mitosis is seen. Mild necrosis is seen.

Immuno-histochemical study revealed proliferative cells strongly positive for CD 34, CD117 and BCL2. S100 and smooth muscle actin are negative (Figure 5).

The overall pattern is consisting with gastrointestinal stromal tumor.

Patient started on Imatinib, and a PET CT SCAN was done after 6 months, which showed a decrease in the size of the mass to become 23 * 20 * 16 cm in size with decreased FDG uptake of the mass. Also and a decrease in the size and near resolution of activity of the FDG-avid lesions in the liver. Findings consistent with partial response to treatment (Figure 6).

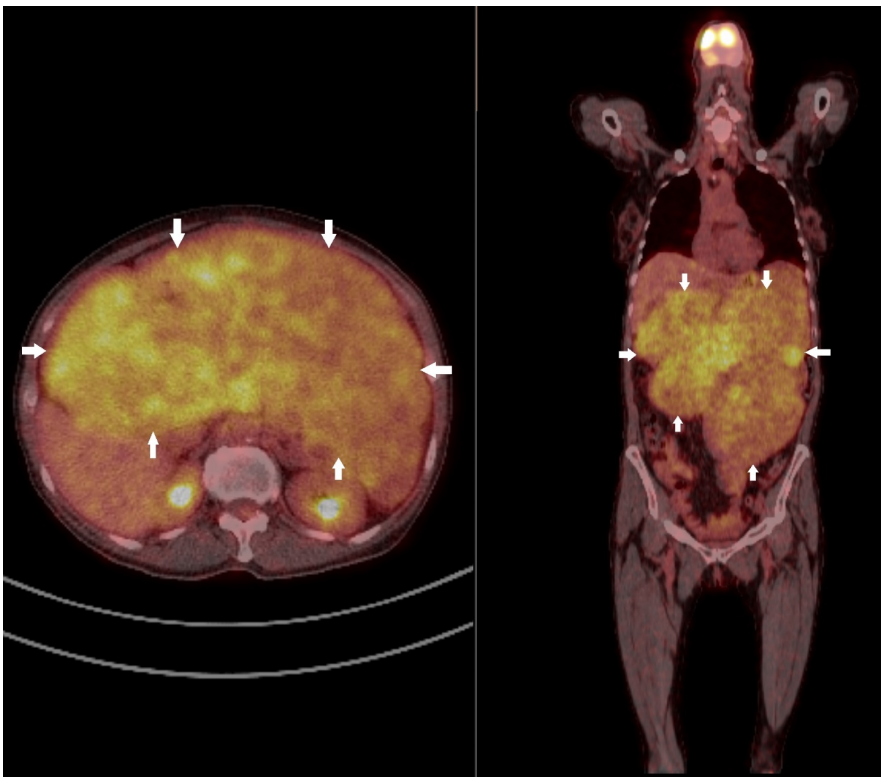


Figure 4. Axial and coronal view of the PET CT showing the large lobulated mass occupying the central abdominal cavity. White arrows pointing to the mass.

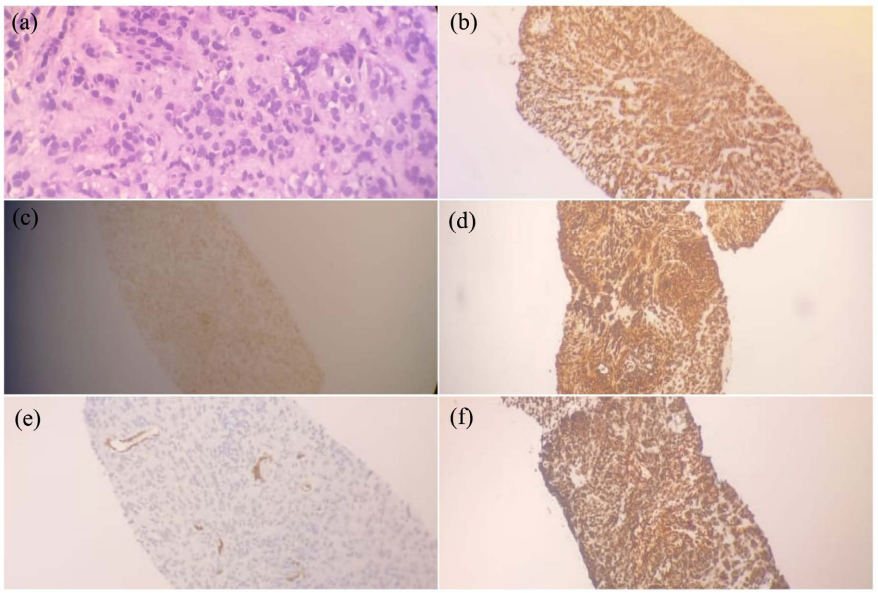



**Figure 5.** Histopathological examination with hematoxylin and eosin staining of the mass ((a), ×40) in addition to immunohistochemical staining patterns. The GIST was positive for CD 117 (b), CD 34 (d) and BCL2 (f), but negative for S-100 (c) and SMA (e).

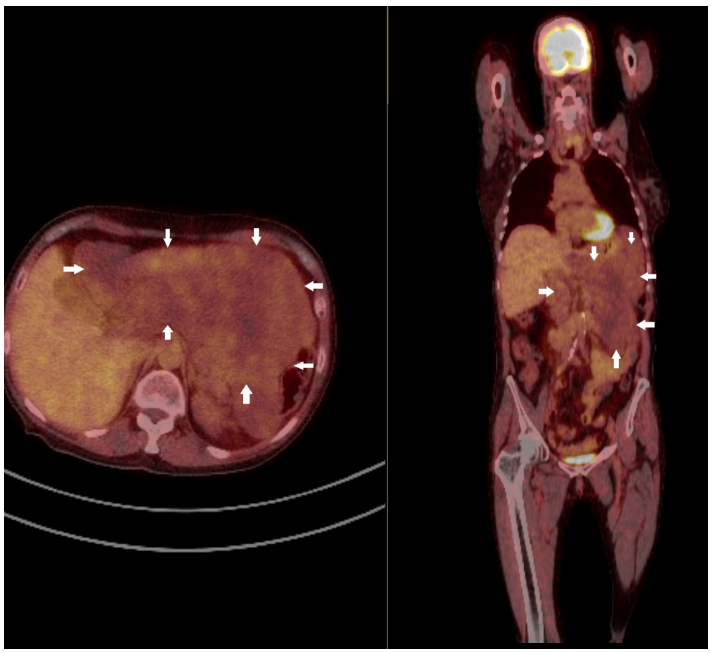


**Figure 6.** Repeated PET SCAN showing partial response to treatment and decreased size and FDG uptake of the mass. White arrows pointing to the mass.

Patient was advised to stay on the same regimen with a follow-up imaging at 6 months to assess stability and further response to treatment.

**Case 3**

A 53 year old male hypertensive, diabetic, nonsmoker presented in 2014 to the emergency department for abdominal pain and high grade fever. Routine laboratory tests showed elevated inflammatory markers. Patient reported being treated

with antibiotics since 8 months in another hospital for a perigastric lesion thought to be an abscess and didn't follow up for it. So decision was made to do a CT-SCAN abdomen and pelvis with IV contrast. It showed a 12.5 * 10.2 * 10 cm multilobulated necrotic mass occupying the left hypochondrium that probably originates from the gastric wall, inseparable from the splenic hilum and encompassing the splenic vein. No picture of metastatic lesions seen (**Figure 7**).

Endoscopy done and showed the presence of a fungating mucosal hard lesion, 7 cm in diameter at the level of the great curvature, 3 to 4 cm below the cardia.

Patient underwent surgery that ended with partial gastrectomy, splenectomy and removal of the mass.

Histopathology showed stromal tumor compatible with GIST, DOG 1 and CD 117 positive, S 100 negative, free surgical margins and negative lymph nodes (0/5).

After surgery, patient did not receive any treatment and in October 2015 his abdominal pain recurred.

CT abdomen showed 18 * 14 * 14 cm mass with necrotic center localized to the lesser curvature pushing the left hepatic lobe and hilum where invasion of liver cannot be ruled out. Multiple lesions having the same characteristics at the level of the greater omentum, the largest measuring 6.9 (AP) × 9.3 (ML) × 9.4 (ML) cm, with carcinomatosis and moderate ascites (**Figure 8**).

Imatinib 400 mg once daily was started and a decision was made for a debulking surgery with subtotal colectomy and ileocolic anastomosis. Large heterogeneous mass 20 * 20 cm arising from transverse colon and multiple intraabdominal masses in the left sub-diaphragmatic (arising from the posterior wall of stomach) and sub-hepatic areas were resected.

Patient had a stable disease until June 2018 when the CT SCAN showed an increase in the size of the previously seen hepatic lesion from 2.8 cm to 3.5 cm, so he was shifted to sunitinib and a follow up CT abdomen done in January 2019 showed a stable disease with no masses but retroperitoneal lymph nodes.

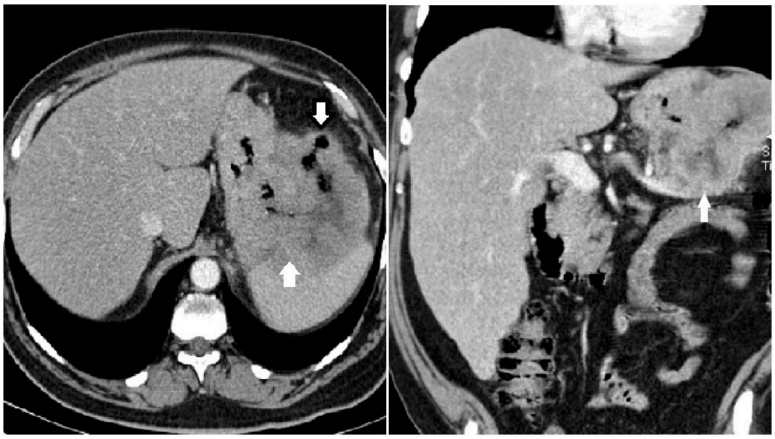


**Figure 7.** Axial and coronal view from CT abdomen showing the multilobulated necrotic mass occupying the left hypochondrium originating from the gastric wall, inseparable from the splenic hilum as shown by white arrows.

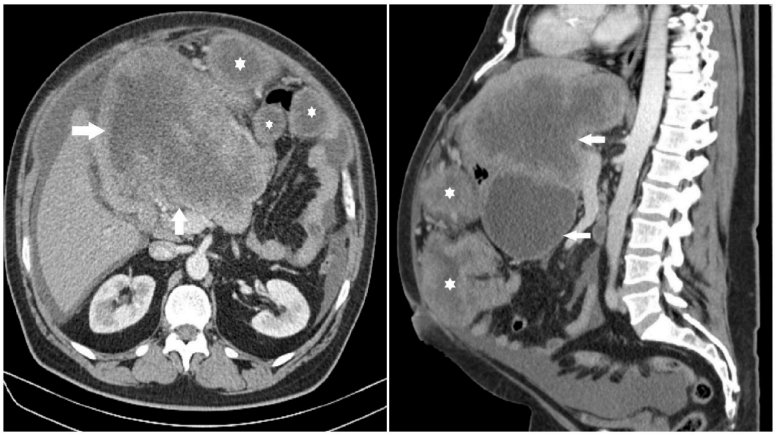


**Figure 8.** Axial and sagittal views from CECT abdomen showing the recurrence of the disease with 16.8 (AP) × 17.8 (ML) × 19 (CC) cm mass with necrotic center localized to the lesser curvature, infiltrating/compressing the liver as shown by the white arrows. Black stars: Two large lesions are noted at a lower level in the anterior abdominal cavity measuring 11.8 (AP) × 15.1 (ML) × 10.7 (CC) cm [the left one] and 9.3 (AP) × 15.2 (ML) × 12.3 (CC) cm [the right one]. White stars: Multiple small lesions are noted, mainly in the left upper abdominal cavity, the largest is located in the left paramedian aspect measuring 6.9 (AP) × 9.3 (ML) × 9.4 (ML) cm.

In April 2020 the patient had progression of the disease evidenced by thickening of the pylorus with a mass like lesion on both sides of the gastric lumen showing irregular borders, enhancing wall and hypodense areas of necrosis, with probable liver invasion. Gastroscopy done and showed hypertrophic fundic and gastric folds, but biopsy result was negative for malignancy, though it could be superficial. So decision was made to start regorafinib.

In April 2021 a follow up CT abdomen showed progression of the disease with a 54 * 46 mm mass in the gastric antrum and 59 * 56 mm in the liver.

At that time surgery team declared that lesions are not resectable and Ripretinib (4th line) was prescribed by oncology team. Medication was not available and patient was taking symptomatic treatment only.

In September 2021 patient presented with severe jaundice involving the whole body, pruritus and elevated liver enzymes and bilirubin with cholestatic pattern predominance: GGT 200 U/L Alkaline phosphatase 196 IU/L Bilirubin Total 12 mg/dL/Direct 11.3 mg/dL SGPT 108 U/L SGOT 148 U/L. CT abdomen with contrast showed an increase in the extent of perigastric seedings seen around cardia, lesser curvature, and antro-pyloric, the latter being the largest measuring 100 * 71 mm, invading the body of pancreas and compressing the proximal and the mid portion of common bile duct. There is increase in liver lesions size with largest at segment 5 measuring 66 * 54 mm in intimate contact with gallbladder with possible invasion. Moderate intrahepatic biliary ductal dilatation with a mass effect on the left intrahepatic bile duct. Multiple perigastric and peritoneal lymph nodes (**Figure 9**). Patient's condition was eventually managed with permanent percutaneous biliary drainage and antibiotics then discharged home on palliative treatment with pain killers.

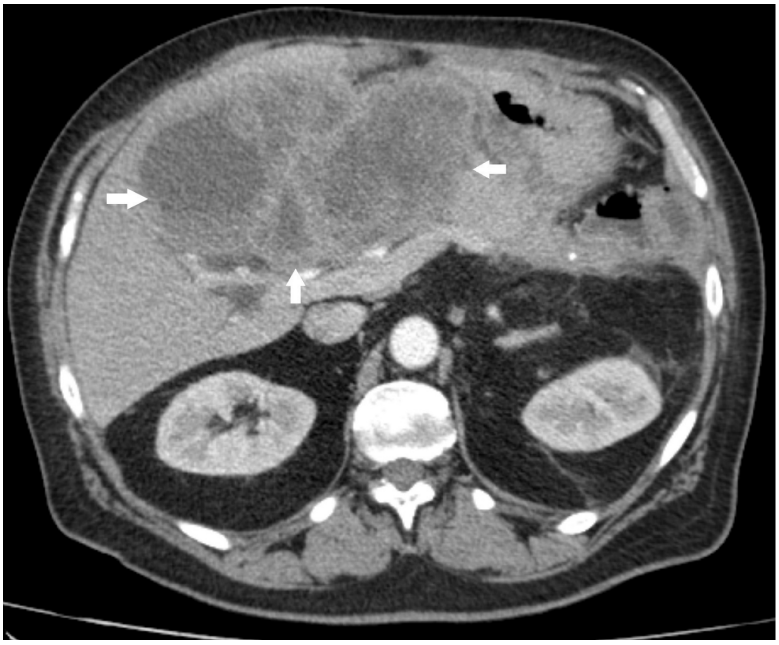


**Figure 9.** Showing the extension of the mass with invasion of the pancreas (right white arrow), compression of the proximal and the mid portion of common bile duct (lower middle white arrow). Increased liver lesions size with largest at segment 5 measuring 66 * 54 mm in intimate contact with gallbladder with possible invasion and moderate intrahepatic biliary ductal dilatation (left white arrow).

## 3. Discussion

In front of a large abdominal mass one must consider a gastrointestinal stromal tumor, since they are the most common mesenchymal tumors but only account for 0.1% to 3% of all gastrointestinal tumors [1]. They have a relatively low incidence rate since only a few microscopic tumors grow to a relevant size with malignant potential hence, most of the GISTs are discovered incidentally [5]. They occur at older age groups with a median age between 65 - 69 years with rare cases under the age of 40 [6]. When diagnosed at a younger age it is important to consider familial or genetic disorders associated with the disease for which they account around 5% of all cases of GISTs [7]. If familial gist is suspected, genetic testing must be conducted to evaluate for certain heritable mutations in the KIT or platelet-derived growth factor receptor alpha (PDGFRA) genes [8] [9] [10] [11].

GISTs most commonly occur in the stomach 40% - 60% [12], but can occur anywhere along the gastrointestinal tract, and rarely occur outside of the gastrointestinal tract where they are called extra-gastrointestinal stromal tumors and account only 5% of all GISTs. They occur in the retroperitoneum, mesentery and omentum [13] [14]. So they are basically submucosal lesions that may grow in an endoluminal, exophytic, or mixed (dumbbell-shaped) pattern. [15]

Patients usually present with different signs and symptoms depending on the tumor size and location [15], for example tumors involving the stomach manifest with bleeding (acute hematemesis, melena, or chronic microcytic anemia)

and abdominal pain, while tumors of the small intestines present with intestinal obstruction [16] [17] [18] as a result of the growth of the tumor and direct obstruction of the lumen, intussusception or volvulus around the tumor in the case of extra-luminal tumors [19]. All of our cases presented with nonspecific symptoms of abdominal discomfort, weight loss and abdominal pain. Considering colonic and rectal GISTs, and due to their rarity, there's no estimation or clear definition of their presentation, but in most cases they are found incidentally during digital rectal examination or gynecological controls. Bigger tumors may present with a palpable pelvic mass, intestinal obstruction, abdominal pain or perforation [17] [20] [21]. This might be attributed due to the fact that GISTs grow transmurally, so they can gain an extraordinary size before being recognized [21].

Imaging and endoscopy are the two main diagnostic modalities used in the diagnosis of GISTs, except in some cases of small < 2 cm submucosal gastroduodenal lesions when endoscopic biopsies may be difficult, so the laparoscopic excision may be the only way to obtain a proper sample for histological diagnosis [22]. CT SCAN with IV contrast is recommended as the initial evaluation as it can better visualize small intestinal thickness and the presence of bowel perforation when compared with MRI [23] [24]. It is reasonably replaced with MRI in patients with contraindication to CT [25]. Moreover, endorectal ultrasound and pelvic MRI play an important role in case of rectal lesions [23]. The ESMO also recommends excision of abdominal masses not amenable to endoscopic assessment, except for patients with metastatic disease or those eligible for neoadjuvant imatinib, they should undergo CT/ultrasound guidance for multiple core needle biopsies in the context of a large mass where surgery is likely to be a multivisceral resection [22]. When evaluating for a metastatic disease, CT SCAN provides an accurate detection of peritoneal and mesenteric metastasis, but liver metastasis are better evaluated using MRI or PET-CT because they may appear isodense on contrast enhanced CT [26].

When biopsy is done it should be sent for histological and immune-histochemical studies in addition to the identifications of specific mutations that guides therapy [9]. GISTs fall into one of three categories depending on morphological and histochemical features: spindle cell type (70%), epithelioid type (20%) and mixed type (10%). IHC comes to distinguish GISTs from other subepithelial tumors that may arise in the gastrointestinal tract, usually with the expression of the KIT protein or CD 117 that is expressed by nearly all GISTs, DOG-1, CD34, smooth muscle actin, and to a lesser extent S-100 protein, desmin or keratin [27] [28] [29] [30].

Testing for molecular alterations and mutations yield a very important prognostic factor and guide therapy, for example some mutations are associated with a more favorable prognosis or in the contrary are associated with higher rates of relapse [31] [32]. Some tumors that stain for KIT are negative for KIT mutations therefore they have a poor response to imatinib [33]. However, some categories do not need molecular testing, in small (<2 cm) especially gastric lesions who

undergone complete resection, and in whose tumor histology and immunohistochemistry are consistent with either a KIT or PDGFRA mutation.

Our three cases had many features suggesting aggressive disease and risk for disease recurrence at presentation. These include tumor size, metastasis at presentation and imaging features of lobulated mass with heterogeneous enhancements [34] [35] [36] [37] according to the National Institute of Health (NIH) consensus criteria, the modified NIH consensus criteria and the Armed Forces Institute of Pathology criteria [38] [39]. Therefore it was mandatory to start imatinib, since Chemotherapy for GIST has been reported to be ineffective and its efficacy remains controversial [40], and all the guidelines recommend adjuvant therapy with imatinib for 3 years, which improves not only relapse-free survival but also the overall survival of high-risk patients [24], except in the 3rd case when the patient lost follow up after his first surgery, and eventually presented with disease relapse after one year despite clear surgical margins. It was also evident in the three cases that none of them had distant metastasis which is well known for GISTs that they tend to metastasize to remote organs [24] including liver and abdominal cavity [41] [42] [43][44]. Our third case was also shifted to 2nd and 3rd line therapy after losing control of the disease and having many relapses [45] [46].

In our second case and in the metastatic GIST imatinib should be continued indefinitely until clinically relevant disease progression or intolerance, because treatment interruption is generally followed by relatively rapid tumour progression [47]. Surgical decision is individualized and discussed with the patient, and follow up should be based on risk assessment and usually with CT SCAN or MRI of the abdomen and pelvis every 3 - 6 months for the high risk group [48].

## 4. Conclusion

The importance of our study resides in the early detection and critical management of GISTs as symptoms may be present for a relatively long period before disease being clinically relevant. So it is crucial for physicians to screen for submucosal lesions by EUS, and to do imaging as appropriate if endoscopy was negative and patient is still complaining about symptoms. And since there's not yet a test to screen for GISTs nor true population at risk except in familial and genetic disorders, GISTs will remain a silent disease and a tricky diagnosis.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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