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Case Report

Unusual presentation of a large GIST: a challenging diagnostic dilemma

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Abstract:

Introduction: *Gastrointestinal stromal tumors (GISTs) are rare neoplasms of the gastrointestinal tract associated with high rates of malignant transformation. Most GISTs present asymptomatically. They are best identified by computed tomography (CT) scan and most stain positive for CD 117 (C-Kit), CD34, and/ or DOG-1. There have been many risk stratification classifications systems which are calculated based on tumor size, mitotic rate, location and perforation.*

Case presentation: *A 42 years old man presented with dysphagia and weight loss for 2.5 months. On examination, he was severely anaemic having a huge intra-abdominal lump. He underwent laparotomy followed by removal of tumor mass with partial left lobectomy of the Liver.*

Conclusion: *We present a case of GIST of unusual location and presentation pattern. In general, only complete resection of tumor can lead to cure, although recurrence is common after surgery.*

Keywords: *Gastrointestinal stromal tumor (GIST); Tyrosine kinase receptor inhibitor (TKI); Oesophago- Gastro-Duodenoscopy (OGD); Endoscopic ultrasound (EUS); Fine needle aspiration biopsy (FNB); Immunohistochemistry (IHC); Imatinib; Venous thromboembolism (VTE).*

Introduction

Gastrointestinal stromal tumors (GISTs) were originally believed to have originated from the mesenchymal cells of the gastrointestinal tract (GIT).[1, 2] Kindblom and associates in 1998 found that these tumors actually originate from the intestinal cells of Cajal.[3] Hirota and colleagues discovered that these tumors express CD117 antigen (C-Kit), a gain of function mutation responsible for activating the growth of these tumors.[4] GISTs can occur anywhere in GI tract. The stomach (60%) is commonest site followed by small intestine (30%), duodenum (5%), colon/ rectum (5%) and esophagus (<1%). Primary mesenteric, omental and retroperitoneal GISTs have also been reported but they are very rare.[5] Extra intestinal GIST has been reported in gall bladder, pancreas, liver and urinary bladder.[6] The incidence across genders has been reported to be similar [7, 8] although some studies have found a higher predominance among men. [9, 10] Grossly, GISTs are usually unencapsulated but well circumscribed masses. The cut surface shows a whorled fibroid-like or more fleshy with variegated appearance. Large lesions show cystic degeneration or central necrosis. Ulceration of the overlying mucosa is common. Immune- histochemical markers are used to confirm the diagnosis.[11] Surgery remains the standard of care for the treatment of primary, resectable GIST. However, rates of recurrence and/ or metastasis are as high as 50%, even following R0 resection, moreover traditional chemotherapy and radiation are not effective on GIST.[12] With the discovery of mutations associated with these tumors, the treatment has changed dramatically. Imatinib mesylate, a selective tyrosine kinase receptor inhibitor (TKI), is used as an adjuvant or neoadjuvant therapy to improve the morbidity and mortality associated with GISTs. Due to growing resistance, sunitinib and regorafenib are effective second- line TKIs.[13- 19]

Case report

A 42 years old male patient working in Doha, Qatar presented to us with the history of dysphagia to solid and feeling of retro sternal food stuck with occasional regurgitation for 2.5 months and significant weight loss (around 8 kg) for same duration. The patient's relevant history included diabetes mellitus (controlled with oral hypoglycemic drugs) and hypothyroidism (Levothyroxine, 50 µgm, once daily). With this complaints he went to Hamad Medical Corporation, Doha, Qatar, where OGD, Barium swallow and meal, EUS with FNB, CT chest and abdomen were performed.

Oesophago- Gastro- Duodenoscopy (OGD) performed on 16/08/22 showed – "small amount of pooled saliva noted in lower esophagus, resistance felt while passing scope into stomach. Gastro esophageal junction mucosa looked normal but tight on the scope. Biopsies was taken from lower and mid esophagus. Bulkiness noted in the fundus with normal

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overlying mucosa, biopsies taken."

Barium swallow and meal performed on 22/08/22 showed – "delayed passage of contrast from the gastro-esophageal junction with smooth narrowed tapering, however no mucosal irregularity of obstruction, findings may suggest achalasia/ pseudo achalasia."

Fig 1: Patient on 7th POD in Surgery Ward

Endoscopic Ultrasound (EUS) performed on 13/09/22 revealed – "Linear EUS scope was used to examine in the lower esophagus as bulge was seen with normal overlying mucosa beyond which scope could not be passed. EUS examination showed a heterogenous isoechoic mass, near circumferential with hypoechoic areas (? Necrosis) with no clear borders from the liver- FNB taken with 22 G acquire needle and sent for 1. Cytology 2. Histology 3. AFB 4. Flow Cytometry."

EUS, FNB of lower esophagus shows atypical Spindle cell proliferation. Immuno Histochemistry (IHC) showed the following result-

- Dog-1: weak focally positive
- Vimentin: diffuse positive
- CD45: positive in lymphocytes and negative in the spindle cells.
- Ki67: high (positive in about 20-30% of the spindle cells)
- CD117, CD34, S-100, SMA, Desmin, Caldesmon, Actin, CKAE1/3, CK MMF-116, Synaptophysin, Chromogranin A, PAX-8, NKX-2, STAT-6, CK5/6, WT-1, and Calretinin – All controls show appropriate reactivity.

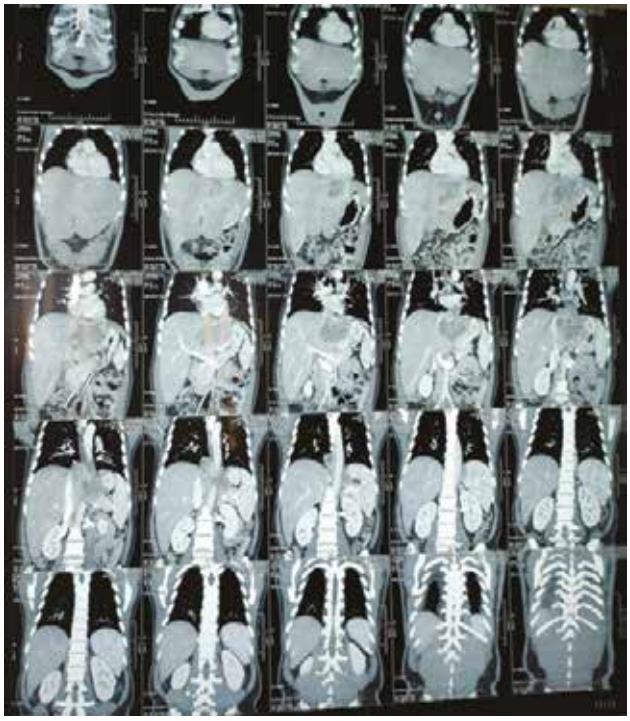

Fig 2: Pre operative CT Abdomen with contrast showing the extension of mass

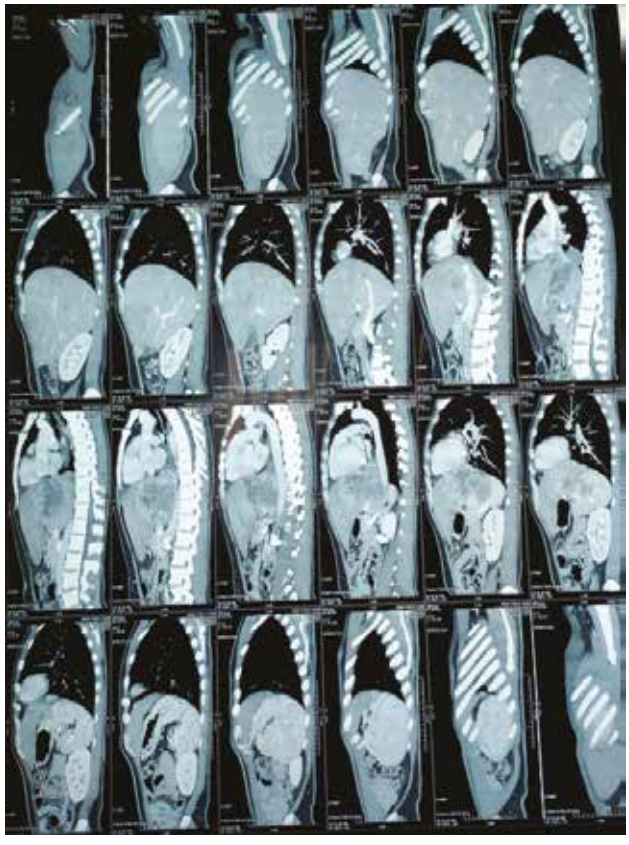

Fig 3: Mass involving esophagus and extending into mediastinum

Fig 4: CT showing local extension of the mass into the Liver

CT Abdomen and Chest performed on 01/09/22 showed – "There is a large irregular well- defined heterogenous predominantly hypodense mass lesion located at the lower esophageal/ epigastric region measuring 57×61×60 mm in TR, AP and CC dimensions respectively. The mass is indenting the superior-posterior border of liver with no clear fat plane and abutting left, middle hepatic vein as well as upper abdominal aorta. There is a suspicious large rounded lymph node located at epigastric region measuring 20 mm short axis noted and is not separated from the lower aspect of mass. This mass is suspicious for malignancy could be arising from the lower esophagus and growing exophytic with possibility of leiomyosarcoma the other D/D include neuroendocrine tumor."

With this above findings he came to Bangladesh and presented to us at United Hospital on 17/10/22 for definitive management. On examination, he was severely anemic (Hb: 6.6 gm/dl) with very poor nutritional status (wt.: 58 kg, BMI 19, S. Albumin 25 gm/L), other biochemical parameters were within normal limit. On local examination he had an ill-defined firm lump mainly occupying Epigastric area and partly into right and left Hypochondriac area. Three units of fresh blood transfused pre operatively before we go for definitive procedure.

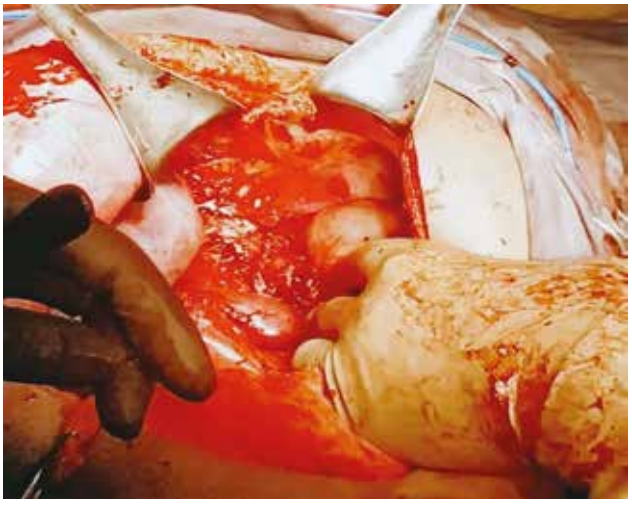

Fig 5: Laparotomy with midline incision showing GIST arising from esophagus and with extension to stomach and left lobe of liver

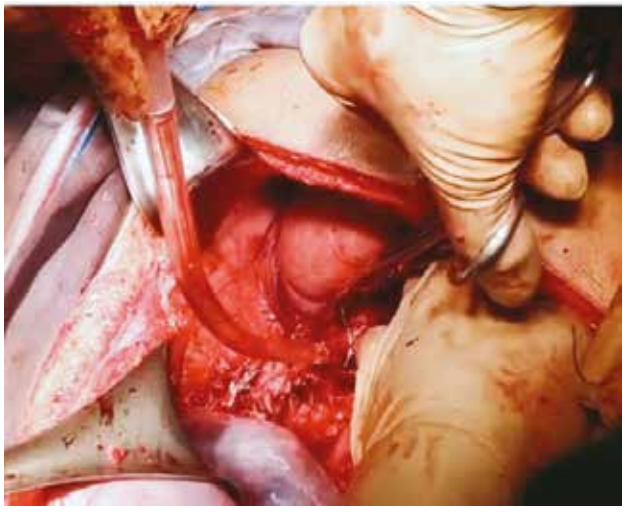

Fig 6: Operative view after partial left hepatectomy

The patient underwent Laparotomy exploration under General anesthesia on 23/10/22 with CV line and Epidural line in situ. Abdomen opened with Makuuchi incision. A mass encompassing the posterior surface of the left lobe of liver, lesser curvature of the stomach, anterior and lateral surface of Aorta and Inferior vena cava, encircling lower end of the esophagus. Debulking done, mass excised in piece, left lateral sectionectomy (partial hepatectomy) done along with the mass. Parts of the mass cleared from lateral surface of the aorta, vena cava, lesser curvature of Stomach. Lower part of esophagus obstruction released. Two drains placed, left sided drain over lower end of esophagus and another right sided drain close to the cut surface of the liver. Patient received four units of fresh blood and two units of fresh frozen plasma per operatively. He was on Noradrenaline support on 1st POD (post operative day) . He received another three units of fresh blood on 1st, 3rd and 4th POD respectively. He was on TPN (total parenteral nutrition) up to 6th POD when he was gradually started oral feeding. He was discharged in stable

condition with right sided drain in situ on 7th POD. This drain was removed on 15th POD.

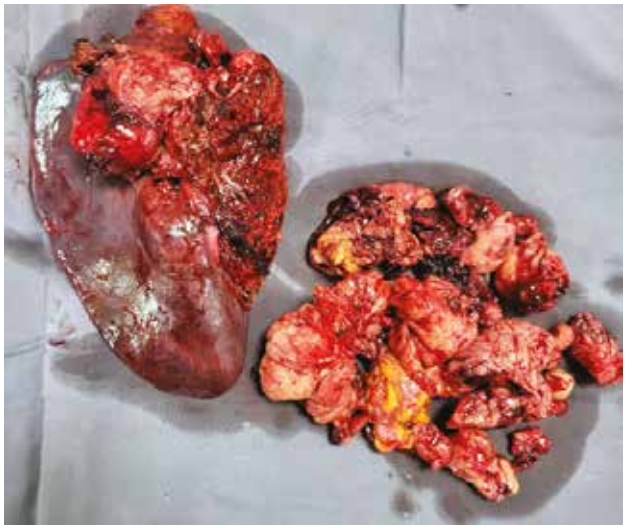

Fig 7: Specimen showing excised left lobe of liver (left) and piece meal excised tumor from esophagus and stomach (right)

Final histopathology report reveals- Gastrointestinal stromal tumor (GIST), High grade with tumor size > 10 cm and Mitotic count: 5-7 per 50 HPF. Resected part of the liver shows: Metastatic GIST.

On 41st POD (03.12.2022), patient was readmitted in hospital under Oncology department with complaints of generalized weakness, anorexia, abdominal swelling and bilateral pedal oedema. He was being treated conservatively and tablet Imatinib 400mg 12 hourly started. During his hospital stay USG of W/A and chest CT and abdominal CT done. CT findings showed large mediastinal mass compressing aorta and IVC. Ultra sonogram report revealed inferior vena cava thrombus.

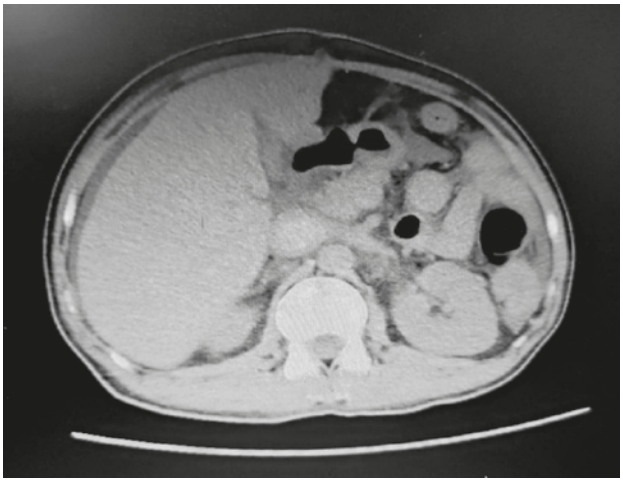

Fig 8: Post operative CT Abdomen on 35 th POD showing IVC thrombus and ascites

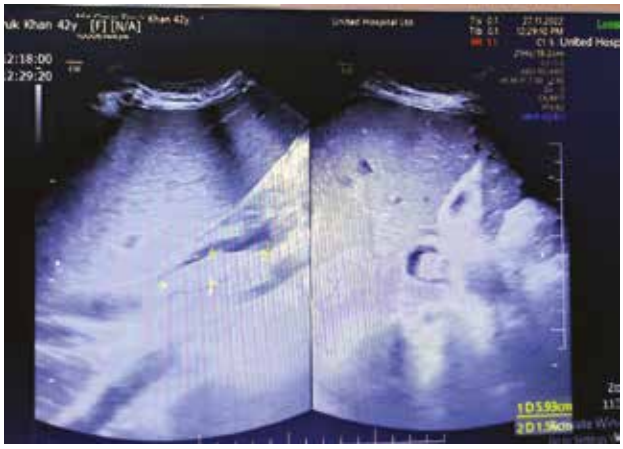

Fig 9: USG of Abdomen, yellow pointer showing Inferior Vena Cava Thrombus

He was being treated accordingly but hemodynamically became unstable with persistent low blood pressure (60/40 mm of Hg) and tachycardia (low volume). On 06.12.2022 he underwent endoscopic guided naso gastric tube insertion. But the patient condition deteriorate and his oxygen demand increased. He developed sudden respiratory arrest and on 45th POD (07.12.2022) he was declared death due to suspected pulmonary embolism from inferior vena cava thrombus.

Discussions

GIST's occurs throughout the tubular GI-tract from the lower esophagus to the anus. GIST's have a wide variety of clinical presentation depending on the site of involvement. Esophageal GIST's may present with dysphagia[20], and stomach or small intestinal GIST's may present with perforation, pain or obstruction[22]. Large tumors may present as an abdominal mass or symptoms of paraneoplastic syndrome. Consumptive hypothyroidism caused by marked over expression of the thyroid hormone- inactivating enzyme type 3 iodothyronine deiodinase (D3) within GIST's has been reported[23]. Malignant GIST's may present with metastasis most commonly to the liver and peritoneum. In our case, the patient presented with dysphagia, severe anaemia, abdominal lump, weight loss and hypothyroidism.

The diagnosis of GIST is often suspected on contrast-enhanced CT or magnetic resonance imaging (MRI) showing an abdominal mass. Imaging can also evaluate the extent of the tumor and assess for the presence of metastasis[24]. Endoscopy can be done to evaluate a luminal involvement by the mass. In our case the patient was first diagnosed with GIST with the help of FNA biopsy under EUS guidance. Usually GIST's are well-demarcated, hypoechoic lesions arising from the fourth layer of the gastrointestinal tract (muscularis propria), although small lesions may arise from the second layer (muscularis mucosae)[25, 26] .

Pathologically, the diagnosis of GIST can be confirmed by morphology and immunohistochemistry. The majority of GIST's (approximately 70%) are composed of Spindle cells, about 20% are composed of epitheloid cells, while remaining

10% of mixed spindle epitheloid morphology[27,28]. GIST's have a characteristic immunohistochemical profile useful for diagnosis[29]. GIST's originate from CD34-positive stem cells residing within the wall of the gut, which can then differentiate incompletely toward the interstitial cells of Cajal (ICC) phenotype. More than 95% of GIST's exhibit KIT (CD117). Expression of CD34 is not specific for GIST's but is noted to be a prognostic indicator as most cases of malignant GIST are CD34 positive. Five percent of GIST cells are not caused through activation and aberrant signaling of the KIT receptor, but rather through mutational activation of the structurally related kinase known as the platelet-derived growth factor-alpha (PDGFRA). Definitive diagnostic criteria for CD117-negative true GIST are currently obscure. The DOG1 gene, which encodes for chloride channel protein actin 1 (independent of KIT and PDGFRA), was discovered in 2004 and is specific for GIST in appropriate clinical and pathological context. Approximately 3% of GI tract are negative for both DOG1 and KIT. Approximately 50% of KIT negative GIST are positive for DOG1 and 50% DOG1 negative GIST's are positive for KIT. Although DOG1 is highly specific for GIST, it can be positive also in uterine type retroperitoneal leiomyomas, peritoneal leiomyomatosis, synovial sarcomous and esophageal squamous cells and gastric carcinoma[30,31,32]. Our patient histopathology showed tumor mostly composed of spindle to round shaped cells and was positive for both DOG1 and Vimentin on FNA biopsy.

Surgical resection remains the treatment of choice for all resectable tumors since it is the only chance for cure[33,34]. Treatment for GIST depends on the tumor size and location. Esophageal GIST's greater than 2 centimeters need to be excised[35], however for those smaller than 2 centimeters different guidelines recommend different management; there is a conservative approach with follow up with repeat esophagogastroduodenoscopy (EGD) and removal if there is an increase in size. Another approach recommends removal of the tumor for fear of the risk of metastasis[36]. For gastric GIST's, submucosal lesions < 1 cm with EUS findings suggestive of benign tumor may be followed conservatively. Management of gastric lesions between 1 and 2 cm remains controversial[37]. For duodenal GIST's, excision is advised whether endoscopically or surgically with pancreaticoduodenectomy[38]. For GIST's in the colon and rectum, excision of the tumor is advised, however sometimes it is challenging especially in the rectum so preoperative Imatinib is advised to downsize the tumor and achieve better surgical outcomes[39]. The goal of surgery is complete resection of gross disease avoiding tumor rupture and achieving negative margins. Intraoperative tumor rupture is associated with intra-abdominal dissemination of tumor cells and subsequent high risk of local recurrence[40]. Incomplete resection should be performed only for palliation of emergency symptoms e.g. bleeding, pain or mass effect[41]. Thus the tumor size, mitotic count per 50 high-power fields (HPFs) and tumor location are considered the three most important prognostic factors for prediction of GIST recurrence. Tumors with low mitotic activity, five or fewer mitoses per 50 HPF, usually have a benign behavior as compared to those with more than five per 50 HPF are described as malignant. Tumors with more than 50 mitoses per 50 HPF are described as high- grade malignant[42]. In our patient mitoses count was 5-7 mitotic count per 50 HPF.

Regarding medical treatment, the approaches to treating GISTs are to resect primary low – risk tumors, resect high risk primary or metastatic tumors with Imatinib 400mg daily for 12 months, or if the tumor is unresectable, neoadjuvant Imatinib 400mg daily followed by surgical resection is recommended[1] . Neoadjuvant Imatinib should be considered for patients with: 1) marginally resectable tumors or resectable GIST's, who have a risk of significant morbidity; or 2) primary localized GIST, whose tumors are deemed unresectable[43]. When neoadjuvant treatment is considered, progression and response of tumors before and during the treatment should be assessed by the MDT (multi disciplinary team) using CT (with optional MRI) and / or PET scans.

Beside all this our patient presented late and his tumor was very large in size with infiltration to left lobe of Liver, part of inferior vena cava (IVC) and aorta. For total curative purpose we had to perform left hepatectomy with reconstruction of inferior vena cava with the help of hepatobiliary surgeon in the same sitting. Inferior vena cava resection and reconstruction with concomitant liver resection sometimes represent the only chance for patients with liver tumors (whether primary or metastatic) involving the IVC to get cured, and it is shown to be safe and effective[44, 45]. IVC resection and reconstruction can be completed using a range of surgical techniques and in all instances, there is a perceived risk of thrombus formation because of venous stasis, which is usually an indication for intraoperative systemic heparinization[46]. In contrast, the indications of post operative systemic anti coagulation after IVC resection or reconstruction are less clear; no formal guidelines exist on this topic.Our patient did not received any anti-coagulation in peri-operative period. Some studies[47] do not recommend routine anticoagulation to prevent VTE associated morbidity following IVC repair and reconstruction. IVC thrombosis is associated with significant acute and chronic morbidity. It presents a diagnostic challenge to the clinician and requires a high index of suspicion. Pain and swelling of both lower limbs, lower back pain, dilatation of superficial abdominal veins and a concurrent rise in inflammatory markers and pyrexia are diagnostic indicators[48]. Our patient got re-admitted on 41st POD (03.12.2022) in Oncology department with abdominal swelling and bilateral pedal oedema. He underwent ultra sonogram of whole abdomen which confirmed inferior vena cava thrombosis. The immediate risk of IVC thrombosis is pulmonary embolism (PE), which occurs in over 30% of cases[49]. Our patient died on 07.12.2022 (45th POD) due to suspected pulmonary embolism. Before death he received tablet Imatinib 400mg 12 hourly for only 4 days.

Conclusion

For many years, the understanding of GIST's, which are the most common mesenchymal tumors of the gastrointestinal tract, has been very limited. However, it is now possible to

provide a more precise definition through the use of pathology classification and molecular techniques. Coupled with the advancement of clinical practice, especially the development of targeted therapy, there is now a much better insight into its treatment. Our patient presented with dysphagia, weight loss and abdominal pain, which is common symptom of many pathologic conditions. It is important to consider GIST's as one of the differential diagnosis when patients presents with similar symptoms, as early stage diagnosis improves outcome and long-term prognosis.

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