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Case report

Staged surgical approach for metastatic GIST, how far should we go? Case report

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ABSTRACT

Introduction: Gastrointestinal stromal tumor (GIST) is an uncommon mesenchymal neoplasm that commonly arises from the stomach and proximal small intestine but can develop in any part of the gastrointestinal tract. The disease can range from primary localized to an advanced metastatic unresectable disease in up to 30% of patients. Usually, metastasis involves the liver, peritoneum, and occasionally the lungs. The current standard treatment of localized resectable tumors is complete oncological resection, while advanced metastatic GISTs treatment remains contentious.

Case presentation: We report a case of a 34 years old pregnant female presenting with a 3 days history of multiple episodes of hematemesis and melena. Laboratory investigations were unremarkable except for severe anemia (Hgb 4.4 g/dL). After further investigations a diagnosis of duodenal GIST (DGIST) with liver metastasis was made. She received and showed good response to neoadjuvant Imatinib therapy, which was followed by a successful 2-stage surgery in the form of extended right hepatectomy and Whipple procedure with a good survival.

Clinical dissection: The evolution of Imatinib had a tremendous impact on surgery in metastatic GIST even in initially unresectable cases, thereby providing a better survival. However, the duration of neoadjuvant Imatinib course and the matter of resistance are still unclear those necessitating the use of different agents or the surgical approach.

Conclusion: Although with the advancements in surgical approaches and perioperative care, liver resection might be a curative option. The role of surgery in advanced GIST remains a controversial matter that needs critical selection of cases based on further future research.

1. Introduction

Gastrointestinal stromal tumor (GIST) is an uncommon mesenchymal neoplasm that most often arises from the stomach and proximal small intestine but also can develop at any part of the gastrointestinal tract (GIT) [1,2]. The clinical presentation is nonspecific and highly dependent on the location of the primary tumor. However early satiety and bloating are commonly associated with GIST of the upper GIT. The tumor tends to grow large in size and cause mechanical bowel obstruction, unless it is discovered earlier due to ulceration or bleeding [3,4]. The disease can range from primary localized to an advanced metastatic disease, and according to an appraisal done by The National Institute for Health and Care Excellence (NICE) 10–30% of patients with GIST do present with metastatic unresectable disease [5,6]. Usually, metastasis involves the liver, peritoneum, and occasionally lungs [7]. The current standard treatment of localized resectable tumors is complete oncological resection, while advanced metastatic GISTs treatment remains contentious [5]. This work has been reported in line with the SCARE 2020 criteria [8].

2. Case presentation

We report a case of 34 years old female, known case of G6PD deficiency, gravida 6 parity 2 with 3 previous abortions all of which were in

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the first trimester. She presented to our emergency department while she was pregnant in her 1st trimester, complaining of 3 episodes of vomiting fresh blood mixed with clots, as well as passing black, greasy, offensively smelling stool 8 times for 3 days prior to her presentation. The patient denied any history of passing any fresh blood per rectum, abdominal pain or distension, dysphagia, odynophagia, jaundice or itching. She had no history of bleeding from any other sites, nor recent unexplained bruising, and she had no family history of any coagulopathies nor malignancies. Upon presentation, physical examination showed that she was tachycardic and hypotensive, while her abdomen was soft, lax with no tenderness. Laboratory investigations showed severe anemia (Hgb 4.4 g/dL), with all other laboratory workup being unremarkable. She was resuscitated with transfusion of 4 units Packed Red Blood Cell (PRBC). After stabilization, an esophagogastroduodenoscopy (EGD) showed a bulge in the duodenum and antrum with no active bleeding. Biopsy of the duodenum showed that the mass is of GIST in origin. An abdominal ultrasound was done and showed a large solid mass in the mid abdomen close to the distal stomach and duodenum, measuring 6.8 × 6.1 × 8 cm with multiple liver lesions (Fig. 1). Abdominal Magnetic Resonance Imaging (MRI) showed that the mass was inferior to the head of the pancreas displacing the pancreas superiorly, and the second part of the duodenum laterally with heterogeneous intensity on T2-weighted images and some elements of hemorrhage and restriction diffusion. The distal Common bile duct was obliterated by the mass. There were multiple liver lesions with heterogeneous signal intensity, some of which showed restriction in diffusion T2-weighted images. The largest liver lesion was seen in segment VI measuring 5 cm, with other lesions present in segments V, VI, and VII measuring 3.2 cm, 1.4 cm, and 2.5 cm respectively (Fig. 2). A liver biopsy was consistent with metastatic GIST.

The case was discussed in our multidisciplinary oncology board and the decision was to perform a therapeutic abortion followed by systemic chemotherapy (Imatinib) then to reassess the response later. After 12 cycles of Imatinib, the patient was re-evaluated and showed a good response in form of stable primary tumor and regression of the multiple hepatic lesions with no other distant metastasis on MRI. A liver MRI showed lesion's regression of segments V, VI, and VII to 2.8 cm, 1.1 cm, and 2.1 cm respectively (Fig. 3). The case was discussed again in our multidisciplinary oncology board, and in light of her response to the Imatinib the discussion was to go for two staged surgeries.

The patient underwent extended right hepatectomy of the 3 hepatic lesions. Pathology report came as the largest nodule showed metastatic GIST with extensive myxoid changes (degenerative changes) with residual viable tumor being around 3%. There were no viable tumor cells in the other three nodules. All surgical margins were clear of any malignancy (Fig. 4A). The patient had a smooth postoperative course and was discharged home in a good condition. After 2 months, the patient underwent a Whipple procedure for the primary tumor. Pathology report came as residual gastrointestinal stromal tumor/spindle cell type (positive immunohistochemistry staining for both CD-17 and DOG-1) with treatment effect grade I, with no mitotic figures identified and negative margins (Fig. 4B, C, D). The final pathological stage was: yPT2 PN0 PM1. The patient had a smooth postoperative course and was discharged home in a good condition. After discharge the patient was kept on maintenance Imatinib. The last follow-up was 52 months postoperatively, where the patient was in a good condition with no signs of recurrence.

3. Discussion

GIST is considered a relatively rare entity, accounting for only 1% of all primary gastrointestinal tumors with the incidence being 10–13 per million population per year [5,9]. Furthermore, the duodenum is considered to be among the rare locations for this tumor to arise, accounting for less than 4% of all GISTs [10]. The management of duodenal GIST (DGIST) varies depending on the stage of the disease, where the standard line of treatment for a localized DGIST is surgical resection with negative margins without the need for lymphadenectomy, as submucosal and the subsequent lymph node involvement are rarely present. Localized DGIST usually carries a good prognosis [10,11]. Nonetheless, even a localized DGIST may represent a surgical challenge due to the complexity of the anatomy involved and the close proximity to vital organs. This in turn, would influence the type of operation performed to resect such tumor, i.e. Whipple or limited resection. On the other hand, advanced disease, especially involving the liver, may elevate the challenge and raise controversy regarding the best course of action in such cases [11,12].

Understanding the pathogenesis of GISTs drastically improved its management, especially pertaining to advanced metastatic disease. The pathogenesis arises from activating mutations in KIT and platelet-derived growth factor receptor alpha (PDGFRA) gene and identified by immunohistochemically C-KIT protein (CD 117 antigen) expression [13]. The evolution of Imatinib, which is a tyrosine kinase inhibitor (TKI) that inhibits both KIT and PDGFRA, has dramatically changed the management of both localized and metastatic GISTs. It was first used in the early 2000s in Finland, for patient with advanced GIST who showed disease progression despite multiple surgeries and chemotherapy [14].

Prior to the era of Imatinib, all conventional cytotoxic

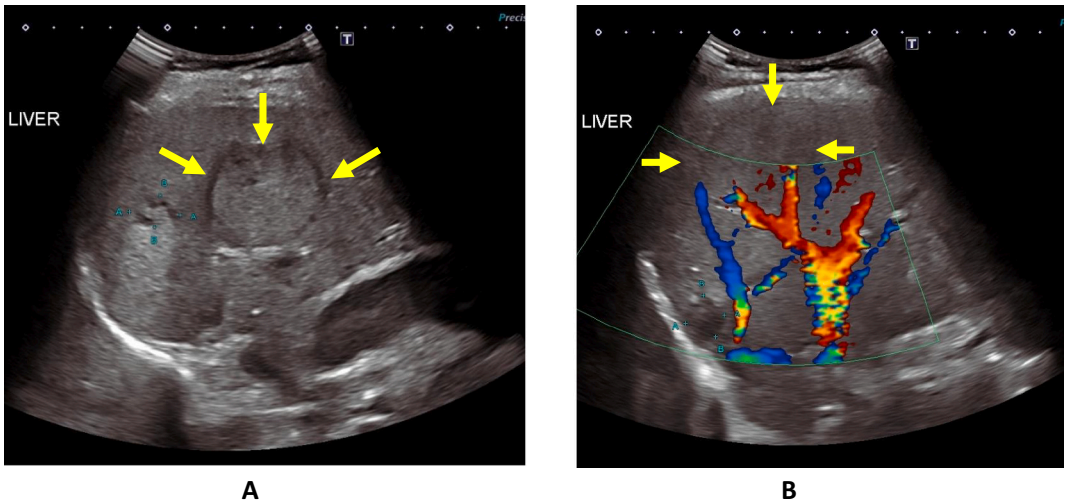

Fig. 1. (A&B) Ultrasound liver showing multiple solid lesions,the largest is demonstrating a complete halo sign (bull's eye lesion).

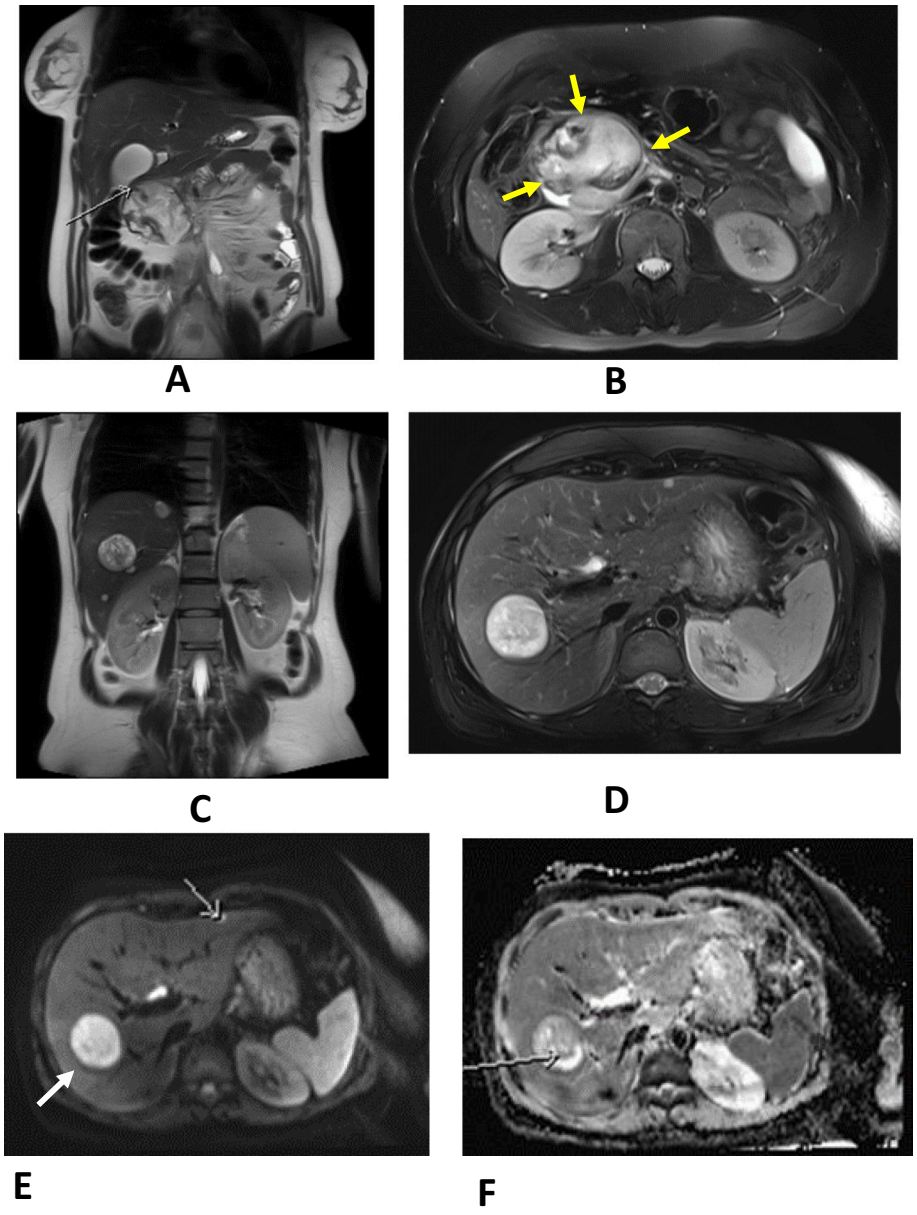

Fig. 2. MRI abdomen pre-neoadjuvant imatinib showing: A) on coronal, B) Axial views, a mass with a heterogeneous intensity on T2-weighted images with element of hemorrhage, located inferior to the head of the pancreas pushing it superiorly & pushing the 2nd part of the duodenum laterally. C) on coronal D) axial views, multiple liver lesions with heterogeneous signal intensity on T2-weighted images. (E&F) MRI abdomen pre-neoadjuvant imatinib showing: on axial view, liver lesions showing signs of restriction on diffusion and ADC MAP images respectively.

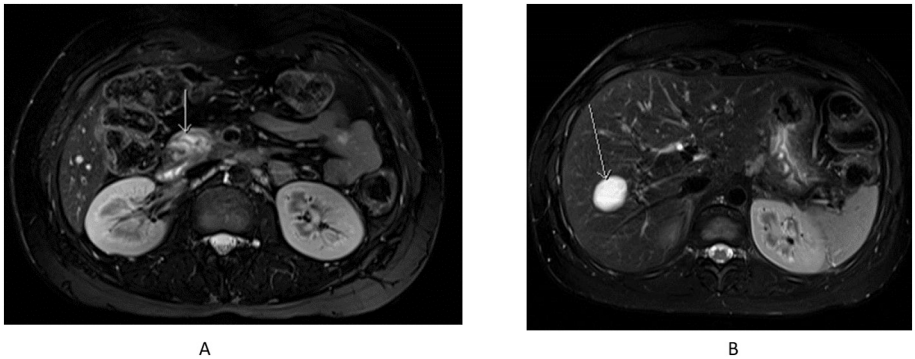

Fig. 3. MRI abdomen post-neoadjvent imatinib on axial showing marked regression of both (A) primary tumor (B) liver lesions on T2-weighted images.

chemotherapies, radiotherapy, and/or resection were used with a low response rate [13]. After the evolution of Imatinib 80% of patients showed either stable disease or partial response ranging from 50 to 96%. This discovery shifted the practice towards medical therapy for advanced GISTs [5,13,15]. Unfortunately, resistance to Imatinib commonly develops in advanced GISTs, necessitating the use of different

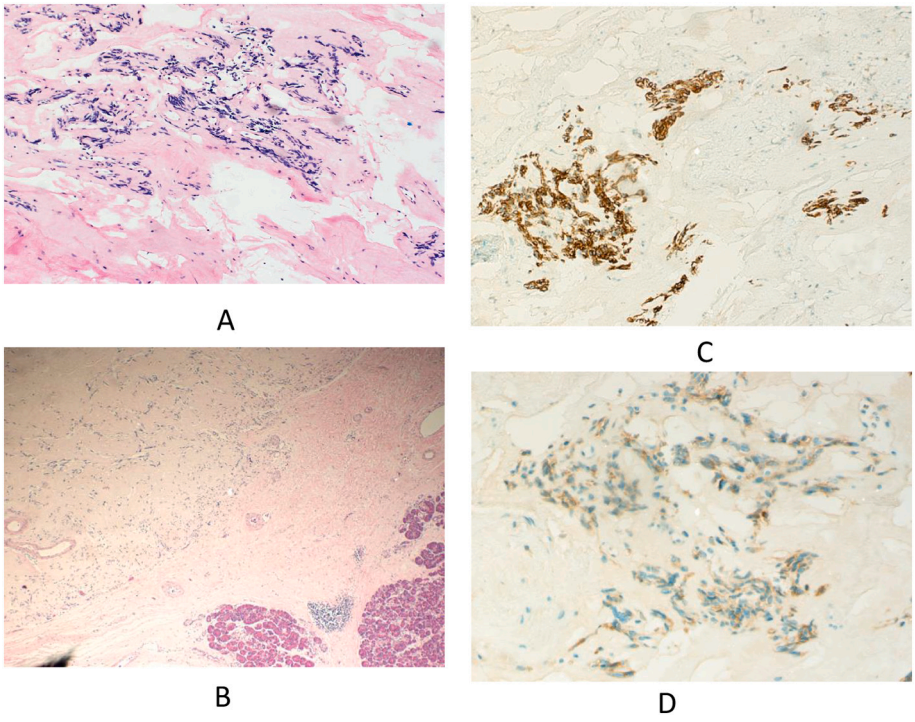

Fig. 4. Histopathological examination A: H & E staining of the resected liver metastatic nodule using with a magnification power of X10, demonstrating an extensive myxoid changes (degenerative changes) with residual viable tumor. B: H & E staining of the primary tumor in the duodenum adjacent to the head of pancreas demonstrating a residual spindle cells with treatment effect grade I. C: Immunohistochemistry staining showing CD17 positive uptake in the primary tumor in the duodenum adjacent to the head of pancreas. D: Immunohistochemistry staining showing DOG1 positive uptake in the primary tumor in the duodenum adjacent to the head of pancreas.

agents or the surgical approach [16]. The role of surgery in advanced GIST remains controversial and needs critical case selection [17].

.Until recently advanced GIST used to carry poor outcomes where the 5-years survival was reported to be less than 10%, particularly in patients with liver metastasis and/or peritoneal dissemination. As this tumor was highly resistant to both chemotherapy and radiation, surgery was considered the foundation of managing GISTs. As such, even when liver metastasis was resectable, recurrence was frequent, and the overall 5-year-survival was around 34% at best [5,18]. Additionally, around one third of patients present with unresectable metastatic disease, where surgical management alone yields a poor prognosis of a median survival ranging from 6 to 18 months [18].

Currently, with the advancements in surgical approaches and perioperative care, liver resection might be a curative option when complete surgical excision is possible. Moreover, the utilization of neoadjuvant TKIs – like Imatinib – have facilitated the role of surgery, particularly in patients with unresectable liver metastasis, and even reduced the need for extensive resection in difficult anatomical locations like the duodenum, where pancreaticoduodenectomy can be avoided by limited duodenal resection [10,11,12].

Unfortunately, in cases of initially unresectable liver metastasis, the literature is still unclear on the timing and duration of using neoadjuvant imatinib in relation to surgical management. To avoid the issue of developing TKI resistance, it is crucial to identify a suitable duration for the use of neoadjuvant Imatinib. However, resection is recommended within 6 months to avoid acquired secondary mutations causing TKIs resistance, which can be radiologically identified as "stagnation of tumor shrinkage" [12,19,20,21].

4. Conclusion

The evolution of TKIs had a tremendous impact on surgery in metastatic GIST, where previously the role of surgery in an unresectable metastatic disease was minimal, it now has the potential to be curative, thus resulting in increased survival. However, the duration of a neoadjuvant TKI course and the matter of TKI resistance remain areas of contention, making the role of surgery in advanced GISTs controversial and in dire need of critical case selection.

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Ethical approval

IRB approval is not needed for Case reports in our center.

Consent

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Author contribution

All authors contributed equally in literature review, written the manuscript, reviewing and editing.

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