



CASE REPORT

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Dramatic regression and bleeding of a duodenal GIST during preoperative imatinib therapy: case report and review

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Abstract

Background: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the digestive tract. The majority of GISTs is located in the stomach. Only 3-5% of GISTs are located in the duodenum associated with an increased risk of gastrointestinal bleeding as primary manifestation. With response rates of up to 90%, but complications like bleeding due to tumor necrosis in 3%, imatinib mesylate dramatically altered the pre- and postoperative therapy for GIST patients.

Case presentation: A 58-year-old female patient presented with acute upper gastrointestinal bleeding 2 weeks after a giant GIST of the duodenum had been diagnosed. Neoadjuvant imatinib therapy had been initiated to achieve a tumor downsizing prior to surgery. During emergency laparotomy a partial duodenopancreatectomy was performed to achieve a complete resection of the mass. Histology revealed a high-malignancy GIST infiltrating the duodenal wall. Adjuvant imatinib therapy was initiated. At follow-up (19 months) the patient is still alive and healthy.

Conclusion: Giant GISTs of the duodenum are rare and - in contrast to other localizations - harbour a higher risk of serious bleeding as primary manifestation. Tumor necrosis and tumor bleeding are rare but typical adverse effects of imatinib therapy especially during treatment of high-malignancy GIST. In GIST patients with increased risk of tumor bleeding neoadjuvant imatinib therapy should thoroughly be performed during hospitalization. In cases of duodenal GIST primary surgery should be considered as treatment alternative.

Background

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal wall. Originating in the muscular wall of the viscera proliferating cells of a GIST show phenotypic similarities to the interstitial cells of Cajal, which coordinate the peristaltic movements of the gastrointestinal tract [1,2]. GISTs are defined as mesenchymal, spindle-shaped tumors, which can be distinguished from other soft tissue tumors like leiomyomas, myoblastomas etc. by c-kit protooncogen (CD117) expression [3]. With 33-63% the stomach is the most common site for a GIST, followed by the small intestine (23-38%) and the colorectal localiza-

tion (5-32%). In contrast GISTs of the duodenum, as presented in this case report, are very rare.

Clinical studies demonstrated that with imatinib (STI 571, Gleevec, Novartis Pharma) objective responses can be reached in more than 50% of patients with an advanced GIST. Unresectable locally advanced tumors, recurrent or metastatic GISTs showed longer progression-free survival under imatinib therapy [4-6]. All in all 80-90% of the patients with GISTs showed at least a partial tumor response [7]. After retrospective small-institutional reports and case series the neoadjuvant use of imatinib in GIST was first evaluated in the RTOG 0132/ACRIN 6665 study. Eisenberg recently published first results underlining the safety of imatinibmesylate in treatment of GISTs [8]. In another study 3% of the probands treated with imatinib developed complications caused by rupture of large tumor masses which became

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necrotic under pharmacotherapy [9]. These data correspond to complication rates described in the STI 571 study [9,10]. To the best of our knowledge these complication rates only referred to common tumor localizations, but not to uncommon GIST sites as duodenum, rectum or others [8].

We herein report a case of a patient with a giant GIST of the duodenum. After neoadjuvant imatinib therapy was initiated, a dramatic tumor regression led to an upper gastrointestinal bleeding and an emergency laparotomy.

Case Report

The 58-year-old female patient was hospitalized due to recurrent episodes of upper abdominal pain, anemia, weight loss, fatigue and fever attacks. Under suspicion of a duodenal perforation by a lymphoma or GIST, seen in an ultrasound examination, the patient was transferred to our clinic.

Physical examination of the patient with no history of preexisting diseases revealed a palpable mass in the right upper abdominal quadrant. Hemoglobin was 90 g/l.

Upper endoscopy revealed a large necrotic cavity in the inferior part of the duodenum. Multiple biopsies taken from the tumor mass confirmed the suspicion of a duodenal GIST. PET-CT scan showed a $9 \times 9 \times 15$ cm tumor mass arising from the duodenum with a maximal standard uptake value (SUV) of 15.5. The tumor had contact to the pancreatic caput and led to compression of the inferior caval vein and the inferior mesenteric vein. The portal vein as well as the common hepatic artery and the superior mesenteric artery showed no signs of infiltration or compression. Furthermore PET-CT did not reveal any signs of metastasis. According to a neoadjuvant approach preoperative therapy with imatinib (Gleevec, Novartis, Basel, Switzerland), 400 mg per day, was initiated immediately. Responder control by PET-CT scan was planned to be performed 4 weeks after initiation of the therapy. After 2 weeks under ambulatory pharmacological therapy the patient presented in the emergency room with an acute upper gastrointestinal bleeding. CT confirmed a dramatic bleeding from the upper GI tract necessitating mass blood transfusion (Fig. 1). Tumor size decreased to $7 \times 8 \times 12$ cm within only 2 weeks of imatinib treatment. An angiographic CT showed the diffuse tumor bleeding supplied by the gastroduodenal artery and some branches of the superior mesenteric artery. The diffuse bleeding forbade a coiling of the vessels. During the emergency laparotomy an encapsulated tumor mass could be identified, originating from the descendent part of the duodenum and reaching both the pancreatic caput and the right flexure of the colon. Obviously the giant tumor had led to a bleeding by arrosion of peripancreatic vessels. After ligation of the vessels supplying the mass a partial pancreaticoduodenectomy (Traverso-

Longmire) was performed to resect the tumor (Fig. 2). Additionally a resection of the right hemicolon was performed due to tumor infiltration of the right curvature of the colon. Continuity was reconstructed by gastrojejunostomy (Traverso-Longmire) on the one hand and an end-to-side-pancreaticojejunostomy on the other hand. An ileotransversostomy was performed to reconstruct the gastrointestinal passage.

Upon macroscopic examination the specimen showed a partially necrotic mesenchymal mass with a diameter of 9 cm, an infiltration of the duodenal wall leading to ulceration and perforation, an infiltration of the pancreas and two peripancreatic tumor islands (Fig. 2). There were no signs of metastases in locoregional lymphnodes. Histological examination of the tumour tissue revealed the typical appearance of a GIST composed of cells with spindle-shaped nuclei (Fig. 3D). Immunohistochemically the tumour cells showed an expression of Vimentin (Fig. 3C) and CD117 (Fig. 3E), a focal expression of CD34, smooth-muscle-actin (not shown) and a nuclear expression of the proliferation-associated Ki-67-antigen in approximately 5-10% of the tumour cells (Fig. 3F). The tumour was negative for S-100 and Keratin (not shown).

Two days after surgery the patient was weaned and successfully extubated. After an uneventful recovery the patient is alive and without any signs of tumor recurrence. Up to the follow-up of 19 months the patient permanently received an adjuvant imatinib therapy (400 mg per day).

Discussion

GISTs are defined as mesenchymal tumors arising from the gastrointestinal wall, mesentery, omentum or retroperitoneum. In contrast to leiomyosarcoma GIST cells express the c-kit proto-oncogene (CD117). Distribution of GIST in the gastrointestinal tract was analyzed in several studies. Tumors are mostly localized in the stomach (33-63%), small bowel (23-38%), whereas colon, rectum and esophagus are rare localizations. The female patient of this case report presented with a duodenal GIST as another rare GIST manifestation. Except for one large study on the histopathological pattern of duodenal GIST [11] only two studies with 8 and 15 patients respectively are published so far [12,13] analyzing the clinic and the outcome of duodenal GIST patients. Compared to other tumor localizations duodenal GISTs manifest with tumor-associated bleeding in 90 resp. 75% compared to 54% (stomach) [14] and 28% (ileo-jejunal) [15]. In contrast to other localizations duodenal GISTs are thus associated with a dramatically increased risk of an upper intestinal bleeding [11].

Nowadays the dignity of resected tumors is classified in risk categories that are based on size and mitotic rate mainly: In a consensus approach Fletcher et al. came to

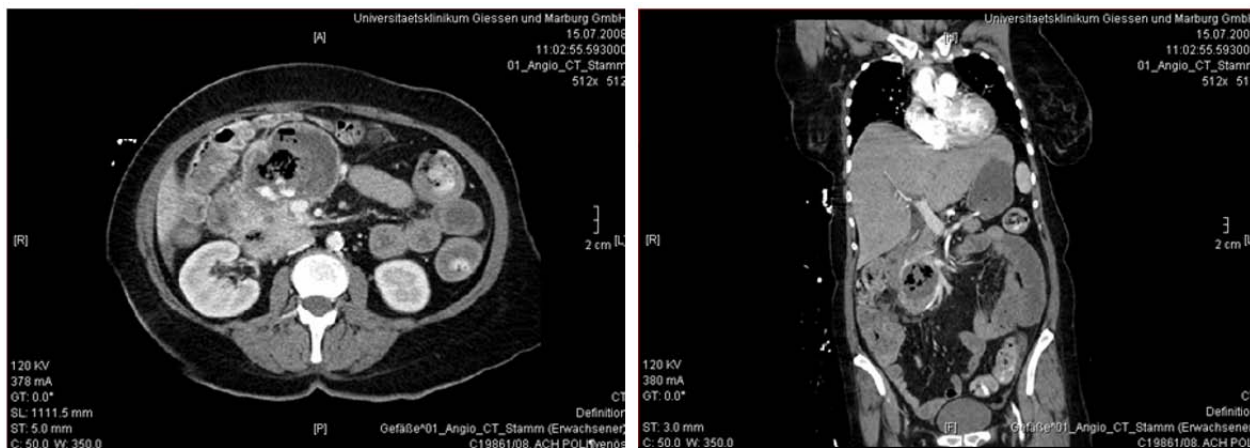


Figure 1 Transversal (left) and coronal (right) CT scans of the abdomen reveal a cystic and necrotic tumor cavity 2 weeks after initiation of imatinib therapy.

the result that tumor size (>5 cm) and mitotic activity (>5/50 high-power field) of the mesenchymal cells are the most important independent prognostic factors for tumor progression [3]. In our case postoperative examination of the specimen revealed a tumor mass of 9 × 15 cm in diameter. Ki67 was used as an immunohistochemical marker for cell proliferation. 5-10% of the tumor cells were Ki67+. Histopathological examination revealed a rate of 12 mitoses per 50 high power fields. Following the above-mentioned classification our patient fulfilled all criteria of a malignant tumor progress.

Surgical therapy of duodenal GIST depends on tumor localization and is either partial duodenectomy, or partial pancreaticoduodenectomy. Interestingly, a recent study revealed that duodenal GIST cells express a different pattern of immunohistochemical markers [16]. Additionally authors showed that duodenal GIST are associated with a more favorable prognosis compared to other tumor localizations. [16]. After review of recent literature the duodenal tumor localization in our case is thus associated with a better prognosis, but with an increased bleeding probability. These results are in line with the authors' opinion

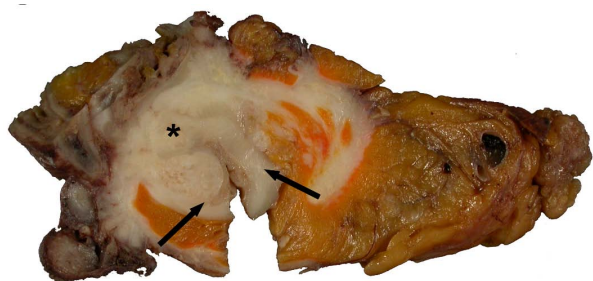


Figure 2 Cross-section of the surgical specimen showing the tumor (asterisk) infiltrating the duodenal wall (arrows).

that primary surgery could be the safest therapeutic option for a GIST of this localization. Beside the increased risk of tumor bleeding, caused by the localization, neoadjuvant imatinib therapy would additionally lead to a higher percentage of patients with a tumor bleeding.

Without any pre- or postoperative pharmacotherapy complete surgical resection can lead to a 5 year survival of up to 45% [17]. The introduction of imatinib mesylate, a tyrosine kinase inhibitor targeting KIT has provided a much needed chemotherapeutical option for patients

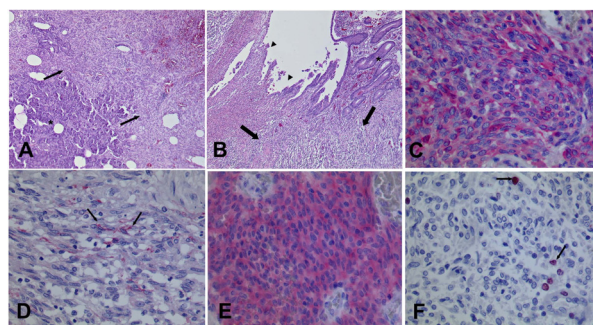


Figure 3 A) GIST infiltrating adjacent Pancreas; asterisk = pancreatic glands and ducts, arrows = GIST [hematoxylin-eosin staining, Original magnification 50x]. B) GIST perforating into the lumen of the duodenum; asterisk = mucosa of the duodenum, arrowheads = ulceration, arrows = GIST [hematoxylin-eosin staining, Original magnification 50x] C) Immunohistochemical staining for Vimentin showing positive reaction in almost all cells (red colour) [Original magnification 400x] D) Cells of the GIST with spindle-shaped nuclei (arrows) and mixed lymphocytes and granulocytes [hematoxylin-eosin staining, Original magnification 400x] E) Immunohistochemical staining for CD117 (c-kit) showing positive reaction in almost all cells (red colour) [Original magnification 400x] F) Immunohistochemical staining for Ki-67 showing proliferation in approximately 5-10% of cells (red nuclear signal, arrows) [Original magnification 400x].

with both resectable and irresectable GISTs. Despite the noted success of imatinib surgical resection is the main treatment modality for primary GIST of any localization. Imatinib treatment of GISTs is a dynamic process with the permanent risk of pharmacoresistance [4,18] and a maximal response within the first 6 months of therapy [4]. Nevertheless the benefit of adjuvant imatinib for primary GIST has been underlined by several trials completed recently. As a consequence surgeons started to use imatinib in a neoadjuvant therapy to reach tumor-downsizing and thus increased rates of complete tumor resection.

As mentioned above complications like tumor necrosis and tumor bleeding occur in 3% of patients under imatinib therapy. These data are in line with results of the STI 571 study. In the prospective RTOG study Eisenberg reports on a minimal rate of toxicity or of intraoperative complications under neoadjuvant imatinib therapy in 30 cases [8]. Nevertheless only 1 of 30 patients with imatinib therapy prior to surgery had a duodenal GIST [8]. It thus remains unclear, if the high safety of imatinib can be transferred to patients with GISTs at rare tumor localizations. Alternatively primary surgery should be seen as an alternative therapeutic approach. In cases of duodenal GIST primary surgery could be supported by a preoperative transarterial embolization as published previously [19].

Conclusions

(1) The review of literature reveals a higher rate of tumor bleeding as primary tumor manifestation in cases of duodenal GIST. (2) Beside the rare and uncommon localization we describe the case of a giant GIST of highest malignancy according to the classification of Fletcher et al. (3). Imatinib led to revolutionary changes in therapy of primary and metastatic GIST, but is associated with rapid tumor regression, necrosis and tumor bleeding in 3%. For the case presented a higher complication rate is to be expected.

In GIST patients with these localizations and thus an increased risk of tumor bleeding neoadjuvant imatinib therapy should thoroughly be performed during hospitalization. In cases of duodenal GIST primary surgery should be considered as treatment alternative.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AH and BH equally contributed to this study and were responsible for data collection and analysis of the patient's case. Furthermore they wrote the manuscript. BB performed the histopathological examination of the resected specimen. TS is the corresponding author of this study. He is responsible for the paper format and submission. MH and HJ were surgeons treating the patient. They helped to draft the manuscript. WP is the director of the department. He designed the study. All authors read and approved the final manuscript.

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