Case Report

Multiple, malignant, rapidly progressing mini gastrointestinal stromal tumors in the small intestine: a case report

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Abstract: Mini gastrointestinal stromal tumors (GISTs) in the small intestine are usually benign tumors. We report a rare case of rapidly progressive GIST in small intestinal in an elderly female patient who died shortly after surgery. This case is clinically important as it highlights the risk of mini GIST with malignant pathological features. Additionally, target therapy should be provided in the early postoperative period, and a higher chemotherapy dose may be considered (if necessary) to prevent recurrence and improve patient’s survival.

Keywords: Gastrointestinal stromal tumors (GIST), intestine, anastomotic recurrence, metastasis, death

Introduction

Gastrointestinal stromal tumors (GISTs) are distinct tumors that originate from mesenchyme in the gastrointestinal (GI) tract. GISTs are rare and comprise about 0.1%-0.3% of all GI malignancies [1]. Most commonly, GISTs occur in the stomach (60%), followed by the intestine (30%) [2].

Generally, the prognosis of GISTs depends on the degree of risk and the original position of the tumors [3]. Clinical manifestations of most GISTs are lack of specificity, such as ill-defined abdominal pain, nausea, repeated vomiting, dyspepsia, vomiting, obstruction, and GI hemorrhage. Sometimes the diagnosis of GISTs is difficult, and for mini GISTs it might be even more difficult and thus may be delayed because of the insufficient detail of imaging diagnostic methods.

With regards to risk for metastasis, intestinal GISTs > 5 cm (independent of mitotic rate) have at least moderate risk, and all tumors > 5 mitoses per 50 high-power fields (HPFs) under microscope have a high risk for metastasis [3]. Here, we report the case of a 70-year old female patient who died shortly after surgery because of multiple, malignant rapidly progressing GISTs in the small intestine.

Case report

A 70-year-old woman was admitted to Emergency Outpatient Unit complaining of persistent lower abdominal cramps. The pain suddenly started without any preceding events and last for approximately 10 hours. The patient did not take any medicine for her pain. Additionally, she had nausea and vomiting accompanied by constipation as well as iron deficiency anemia for 6 months’ duration for unknown cause. She had no radiating pain, fever, dizziness, headache, hematemesis, bloody purulent stools, or melena. Furthermore, she had no history of cardiac disease, hypertension, diabetes, or any chronic disease.

On physical examination, the patient was alert, conscious, and well oriented, and showed average vital signs with tenderness in the whole abdomen and rebounded pain. No obvious muscular tension or palpable masses were found. On auscultation, bowel sounds occurred twice per minute.

Laboratory tests included complete blood count and differential count, reticulocyte count,
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Iron metabolic tests, and coagulation profiles. Abnormal results (normal reference range) included hemoglobin 68 g/L (115-150 g/L), hematocrit 25.98% (35-52%), reticulocyte 26% (5-20%), serum iron 23 μg/dL (50-175 μg/dL) and a positive fecal occult-blood test.

CT abdomen revealed small intestinal obstruction, which was considered stercolith-induced (Figure 1A, 1B). No other notable abnormalities were found. Emergent bowel obstruction was diagnosed.

An exploratory laparotomy was performed immediately. Inside the lumen of the small intestine a stercolith was found blocking the middle section. On further exploration, a neoplasm (1.0/0.5/0.5 cm) located in the inner lumen of small intestine 50 cm from the Treitz ligament and another (1.0/1.0/1.0 cm) 110 cm from the Treitz ligament were found; each neoplasm was soft, polypus-like, and with an integral boundary. The exterior wall of the small intestine was intact, and hemorrhagic intestinal fluid could be seen in the involved lumen. No notable metastasis was seen on the greater omentum, mesentery, or enlarged lymph nodes. Wedge resections of the two neoplasms were performed separately.

Postoperative histopathological examination for the two neoplasms revealed a spindle cell tumor (small intestine) (Figure 1A), with necrosis and hemorrhage, and invasion of the serosa; the mitotic index (number of mitoses per 50 high-power fields) was > 50/50 HPF (Figure 1B). Immunohistochemistry indicated strong staining for c-Kit/CD117 (Figure 1C) and CD34 (Figure 1D), and with negative staining for Dog-1. According to the National Institutes of Health (NIH) risk classification, the tumor was GIST with high malignancy potential.

The patient recovered well postoperatively, and was discharged from hospital. Imatinib was suggested as her further treatment, but for some unknown reason she refused it.

Three weeks later, the patient was admitted to hospital again complaining of progressively aggravating abdominal distension and continuous hematochezia, accompanied by vomiting. Abdominal enhanced CT revealed an irregular enhanced mass in the small intestine; GIST recurrence was suspected. CT scan also indicated metastasis in the mesenteric lymph nodes.

Continuous hematochezia was considered. One month after the first operation, the patient was scheduled for a second surgery. Intraoperatively, a recurrent tumor in the small intestine at the first anastomosis (50 cm from Treitz ligament) was detected. It had blocked the lumen with serous invasion, had burst, and was bleeding. In the corresponding mesentery and left greater omentum, palpable enlarged lymph nodes were detected.

Palliative surgery was performed to relieve the obstruction. The tumor could not be resected but a part small bowel resection and anastomosis were performed, and all the corresponding and mesenteric lymph nodes were also excised. The histopathological and immunohis-

Figure 1. Histopathological characteristics of the intestinal neoplasms. A. Spindle cell tumor - small intestine (hematoxylin and eosin [H & E] staining, ×10); B. The mitotic index > 50/50 HPF (H & E staining, ×100); C. GIST-c-Kit/CD 117 positive (×4); D. GIST-CD 34 positive (×4).
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Figure 2. Original and postoperative artery phase computed tomography (CT). A and B. Arrows show stercobilith-induced small intestinal obstruction. C. Arrow shows tumor recurrence (cross section).

Figure 3. Postoperative artery phase CT of the abdomen in coronal plane. Arrow: recurrent tumor.

Tochemistry diagnoses were the same as the primary tumor. The cutting edges were clean without tumors, and metastatic tumors in 6 out of 12 mesenteric lymph nodes were found. The tumor was graded as GIST T1N1M0/G2 with high potential for malignancy. The gene diagnosis was wild-type GIST given that no target gene mutations in the 9th, 11th, 13th, 17th exons of C-Kit gene or the 17th, 12th exons of PDGFRα gene were detected.

Seven days after the surgery, the patient presented with abdominal distension, nausea, and vomiting. A CT scan indicated a large mass (11.4/8.3/12.1 cm) suggestive of tumor recurrence (Figures 2C-4). The patient started taking imatinib 400 mg/day intermittently, but with obvious side effects (nausea and vomiting). A week later, the symptoms worsened and recurrent hemorrhage was a feature. Aunitinib was considered as the replacement therapy, but the patient died one week later.

Discussion

Gastrointestinal stromal tumors are common mesenchymal tumors in digestive-tract [4]. Indeed, clinical autopsy results confirm that their incidence is far higher than official clinical statistics [5]. As the anatomical position of the small intestine is in the middle part of the digestive tract, direct and effective routine inspection is difficult, hence this may explain the low detection rate of small intestine GISTs. In clinics, small intestinal GISTs are often not found until the tumors reach a certain size, cause obstruction, or are associated with complications such as bleeding or tumor rupture [6]. Nevertheless it is difficult to detect small intestinal GISTs in the early stage because these symptoms are unspecific for prediction, consequently delaying the time for early diagnosis and treatment.

With the development of histopathological assays (especially molecular pathology and the landmark success of molecular target medicine imatinib mesylate for the treatment of GISTs), diagnosis and treatment tend to be standardized. In 2007, National Comprehensive Cancer Network (NCCN) released guidelines (updated every year) regarding malignant tumors. The application of pathological tests, target therapy, and these guidelines benefit many patients [8].

The stomach is the most common location for GIST, followed by the small intestine and colon-rectum [9], and a correct diagnosis depends on morphological pathology and immunohistochemistry. Usually, immunohistochemistry st-
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...aining shows c-Kit/CD117-positive (95%), CD-34-positive (40-50%), SMA (smooth muscle actin)-positive (20-30%) and S100 desmin-positive (about 10%). Ki67 as a marker of cell proliferation is necessary in order to make a precise diagnosis of GIST [5].

Pathological reports have revealed that the mitotic index (number of mitoses per 50 high-power fields) is more than 50/50 HPF. According to the NCCN soft-tissue sarcoma guideline published in 2013 [3], assessment of malignant potential for intestine GISTs is based on tumor size and mitotic index. However, in predicting the biological behaviors of GISTs, there was no clear guide when tumor size is below 2 cm with mitotic index higher than 50/50 HPF.

Due to the difficulty and inadequacy in predicting GIST malignant potential by tumor size and mitotic index alone, updated NCCN soft-tissue sarcoma guidelines were published in 2015 [8]; these required the tumor location as an indicator in assessing tumor risk. The latest NCCN guideline suggests that small GIST tumors (< 2 cm) in the small intestine are more aggressive than in the stomach. Accordingly, tumors are classified as high malignant potential GISTs with possible metastasis or tumor-related mortality rates of 50%-90% [5].

For high-risk small intestine GISTs, postoperative recurrence and metastasis are not uncommon, and recurrence or metastasis may occur after 6 months [10]. Cancer recurrence was seen 3 weeks after primary surgery in our patient. In the first surgery, wedge resection was performed with a 5-cm safety edge distance from the tumor; there was no tumor infiltration. In the second operation, removal of the recurrent tumor as well as the corresponding mesangial tissues was done with a guided cutting edge distance. Besides, block dissection including metastatic lymph nodes and mesenteric lymph nodes was attempted as not only had the tumor burst and was bleeding, but tumor cells had implanted and metastasis in the lymph nodes had started.

Considering the high malignancy potential immediately after tumor resection, the patient was recommended c-Kit and PDGFRA gene mutation tests before undergoing further target therapy. The discovered gene mutation was a wild type with a predicted effect at about 0-40% [5, 9]. In order to get a better effect, the dosage of the medicine and the selection were taken into account.

Other clinical studies found that the GISTs with different genotypes and testing points showed a big range of sensitivity to different drugs, as shown by the wild type (c-Kit and PDGFRA mutation was not detected) in this case. Furthermore, proper imatinib administration is also necessary for effective treatment. For ineffective cases receiving a standard dose of imatinib, a higher dose or replacement with second-line drugs could be considered, but our patient deteriorated too fast for the clinical effect of target therapy to be observed.

This report describes a case of mini GIST originating from the small intestine, with a high mitotic index according to the pathology along with a wild type (in c-Kit and PDGFRA gene) mutation. Imatinib in normal doses lacks sensitivity, but before adjusting the target therapy,
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tumors can recur quickly with mesangial lymph nodes metastasis. Usually, for malignant and potentially malignant GIST tumors, postoperative adjuvant therapy is needed to prolong survival. Additionally, major surgery may affect the immune system thus leading to such progression of malignancy.

Although the NCCN for soft-tissue sarcoma provided a whole protocol for benefitting most patients with GISTs, this is controversial as it deals with mini GISTs below 2 cm in size, and there is insufficient clinical data to provide a unified guide. According to the NCCN soft-tissue sarcoma guideline published in 2013, wild-type GIST may require a succinate dehydrogenase (SDH) gene test as the primary assessment. In 2015, NCCN released the latest guideline for soft-tissue sarcoma; this guideline clearly suggests genotyping before drug therapy [8]. Although some GISTs may progress rapidly after surgery [8], mini GIST tumors are rare.

By reporting this case, we hope to remind clinicians that for patients with high-risk mini GIST tumors which have malignant pathological features (especially tumor location of intestine which is considered as high risk with aggressive biological behavior and potentially metastatic risk), proper postoperative target therapy should be provided, and urgent administration of a higher dose may be necessary to prevent recurrence and to postpone survival for such patients.

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Disclosure of conflict of interest

None.

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