Recurrent Gastrointestinal Stromal Tumor of the Small Intestine with Malignant Features: A Case Report of Uncommon Tumor and Review of the Literature

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Abstract
Gastrointestinal (GI) stromal tumors (GISTs), although rare, are the most common mesenchymal tumor of the GI tract. They comprise approximately 80% of all GI mesenchymal tumors and most commonly occur in the stomach and small bowel. GISTs originate from interstitial cells of Cajal (ICCs), mesenchymal cells located within the muscular layer of the GI tract, which generate electrical pacemaker activity for gut motility. These cells express the KIT protein on their cell surface, and GIST almost universally stain positive for the KIT protein by immunohistochemical staining. We present a case of this uncommon tumor and review the literature.

Keywords: Stromal; Malignant; Recurrence; Necrosis; Imatinib

Introduction
Gastrointestinal [GI] stromal tumors [GISTs] are rare occurring tumors, however they comprise the most common mesenchymal neoplasm of the GI tract [1]. The majority of these tumors are incidental findings, therefore the true prevalence is unknown but estimated to be approximately 130 cases per million [3,4]. They originate from the submucosal of the gut and are thought to be derived from interstitial cells of cajal (ICCs) or ICC precursor cells [5]. GISTs are characterized and diagnosed by the presence of a gain-of-function mutation to the tyrosine kinase KIT proto-oncogene. The over-expression of c-KIT by gastric stromal tumors is responsible for the expression of KIT, PDGFR and ABL kinases [6]. Additional adjuvant therapies that are FDA-approved include sunitinib and regorafenib. In cases of unresectable tumors, neoadjuvant therapy followed by surgical resection if possible is the recommended course of treatment [3].

Case Presentation
A 52-year-old man with history of small intestine gastrointestinal stromal tumor presented with a large intraabdominal mass suspicious for recurrent tumor. The initial tumor was a high-grade GIST originating from the small bowel and infiltrating into the abdominal cavity measuring 19.5 cm. The histomorphology and the immunohistochemistry studies were diagnostic of GIST with malignant features. The tumor was surgically excised following neoadjuvant treatment utilizing the tyrosine kinase inhibitor Imatinib. Due to the large size of the tumor, surgical margins were involved by the tumor in multiple sites, so excision was followed by post-operative radiation treatment.

One year later, at a follow up imaging studies, a large intraabdominal mass was identified measuring 9 cm involving the small bowel, proximal colon and the mesentery. In addition, multiple masses were also identified in the abdominal and pelvic regions largest measuring 4.5 cm. CT with contrast of the current abdominal mass showed evidence of a heterogenous enhancing masses in the right lower abdominal quadrant. The clinical consideration was recurrent GIST with metastasis and malignant features. A CT guided core biopsy was obtained from the largest mass. Histomorphologically the tumor showed features of mixed

Abbreviation
GIST: Gastrointestinal stromal tumors; IHC: Immunohistochemistry; ICC: Interstitial cells of cajal; NNT: Number needed to treat

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highly atypical spindle and epithelioid cells with prominent malignant giant tumor cells and abundant mitosis (up to 40 mitosis/50 HPF) (Figure 1-A-B). Vascular invasion was easily identified. The excised tumor showed approximately 80% sclerosis and necrosis.

As the tumor was invasive, atypical, with high mitotic activity and extensively necrotic, it was classified as malignant. Immunohistochemistry studies showed that the tumor cells are positive for Vimentin (Figure 1C), CD34/QBEND-10 and CD117 (c-kit) (Figure 1D). The tumor cells were negative for Cytokeratin AE1/AE3, S-100, SMA, Desmin, CD31, Synaptophysin, and Chromogranin.

The histomorphology together with the IHC profile and the patient’s history was diagnostic of recurrent malignant gastrointestinal stromal tumor with multiple liver metastasis. The pathological characteristics of the recurrent tumor were compared with prior tumor and both showed similar features.

The patient received neoadjuvant treatment with tyrosine kinase inhibitor Imatinib, followed by debulking surgical removal of the retroperitoneal abdominal masses. Safe surgical margins were not possible due to the large size and infiltrative pattern of the tumor and multiple margins were involved by the tumor. The patient received post-operative radiation treatment, and there was no evidence of any additional metastatic sites.

The patient was followed up for 11 months with no evidence of metastasis or recurrence after which he expired due to extensive metastasis to the lung and liver and acute respiratory failure.

Discussion

GISTs, can be presented as a benign or as a malignant tumor, however, most investigators suggested that “benign” or “malignant” classification is not necessarily applied as they are not useful in patient’s management; instead, classification is focused on rate of recurrence and risk of metastasis.

The mainstay of treatment is surgical resection of the lesion with clear surgical margins. However, many cases present with metastasis and even following surgical resection with clear margins nearly half of patients still see recurrence of disease [8]. Therefore, adjuvant and neoadjuvant pharmacotherapy has been of increasing use in treating patients and prolonging time to disease progression [6].

When surgical resection of GIST is inadequate, either because metastasis has occurred, disease has reoccurred, or surgical removal of the tumor is not appropriate, pharmacologic agents are used to specifically target overactivated proteins displayed on tumor cells.

GIST are characterized by c-kit activating mutations which leads to an over-expression of the tyrosine kinase receptor KIT [8]. The constitutively activated kinase then activates a cascade of signaling pathways which results in the inhibition of apoptosis [4]. Interestingly, the most common mutation of the KIT gene, occurring in 65% of cases, is a deletion within the exon 11.
domain that alters a key region of the protein which regulates the kinase activation loop. This commonly deleted or disrupted area is responsible for inhibiting the activation of the kinase in the absence of a bound ligand [4]. Therefore, in the presence of this mutation, continuous activation can proceed in the absence of a molecular stimulus.

GIST recurrence is determined based on classification systems developed by the National Institute of Health (NIH) consensus criteria and the Armed Forces Institute of Pathology criteria, which are based on mitotic count, tumor size, primary tumor site, and tumor rupture. The recurrent tumor in our case was classified as malignant with high potential for recurrence and metastasis.

First line of treatment for metastatic or recurrent disease is Imatinib mesylate, known by the brand name Gleevec [6]. Imatinib was the first tyrosine kinase inhibitor to receive approval by the Food and Drug Administration (FDA) in 2001 for the treatment of metastatic and unresectable GISTs [6,9]. A once daily oral dose of Imatinib is the recommended dose for all KIT mutations, however if an exon 9 KIT mutation is present than 400mg Imatinib twice daily can be considered [4]. After 1-3 months of treatment with imatinib mesylate, it is appropriate to obtain repeat imaging to assess for response to therapy. If stable disease is present at this time, surgery can be considered or continuation of pharmacotherapy if unresectable. In the case of progressive disease following trial of imatinib, surgery can be considered with unifocal lesions or an increase in imatinib to 400mg twice daily in the setting of multifocal lesions.

Imatinib is the first-line treatment for metastatic and unresectable GISTs, however studies have also demonstrated the effectiveness of Imatinib for adjuvant therapy following surgical resection. A randomized, placebo-controlled, double-blinded study has demonstrated the decreased risk of disease reoccurrence with 1 year of imatinib adjuvant therapy versus surgery alone. Additionally, 3 years of adjuvant therapy versus 1 year of treatment was associated with decreased disease reoccurrence [10]. The number needed to treat (NNT) after 1 year of Imatinib adjuvant therapy was seven patients, and the NNT fell to 4 patients with 3 years of Imatinib adjuvant treatment [10]. Although the side effects most commonly seen with one year of treatment are relatively mild- namely dermatitis, diarrhea and abdominal pain, more severe adverse events are associated with 3 years of treatment [10,11].

In the setting of poor response to imatinib or intolerance to the medication, alternative drugs including Sunitinib, known by the brand name Sutent, and Regorafenib, known as Stirvarga, can be used or added to the therapy [4]. Between 10% and 15% of all GISTs are intrinsically resistant to imatinib therapy and approximately 50% of tumors develop secondary resistance to the drug within 2 years [12].

Sunitinib is a tyrosine kinase inhibitor with anti-tumor and anti-angiogenic effects and is considered the second-line treatment after imatinib intolerance or resistance occurs [12]. In a randomized, blinded study, patients with imatinib-resistance GISTs treated with Sunitinib therapy averaged 27.3 weeks until disease progression, compared to 6.4 weeks until reoccurrence of disease in the placebo group [13]. Due to the significant improvement in those receiving Sunitinib versus the control group, the study was unblinded early. Therapy was well-tolerated with the most commonly seen adverse events being fatigue, diarrhea, skin discoloration and nausea [13].

We present a case of GIST with high malignant features to highlight the variability, diagnostic and treatment challenges in patients with this tumor. The diagnosis of GIST can be challenging, and the use of Immunohistochemistry studies is essential to avoid diagnostic errors. Hopefully, continued investigation drives further development of efficacious diagnosis and safe treatments for improving patient outcomes.

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Placebo-Controlled

