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Case and Review

Imatinib-Resistant Gastrointestinal Stromal Tumor Presenting as a Large Abdominal Mass

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Abdominal mass · Gastrointestinal stromal tumor · Imatinib

Abstract
Gastrointestinal stromal tumors (GISTs) are the stromal or mesenchymal neoplasms affecting the gastrointestinal tract. Although they constitute 1% of primary gastrointestinal tumors, they are the most common nonepithelial tumors involving the gastrointestinal tract. They mostly present as overt or occult gastrointestinal bleeding. We present a case in which a 77-year-old female presented with a large abdominal mass. The origin of the mass was unclear on CT and MRI scan of the abdomen. Upper gastrointestinal endoscopic ultrasonography showed a cystic lesion in the perigastric region. A fine-needle biopsy of the lesion was performed, which was consistent with spindle type GIST. After the initial failure of imatinib therapy, the tumor was managed surgically.

Introduction

Stromal or mesenchymal neoplasms affecting the gastrointestinal tract typically present as subepithelial neoplasms, and they are divided broadly into 2 groups. The most common group consists of gastrointestinal stromal tumors (GISTs). These neoplasms are most often located in the stomach and proximal small intestine, but they can occur in any portion of the alimentary tract and occasionally in the omentum, mesentery, and peritoneum [1]. Within the gastrointestinal tract, GISTs are most common in the stomach (40–60%) and jejunum/ileum (25–30%). A far less common group of mesenchymal gastrointestinal tract neoplasms comprises a spectrum of tumors that are identical to those that might arise in the soft tissues throughout the rest

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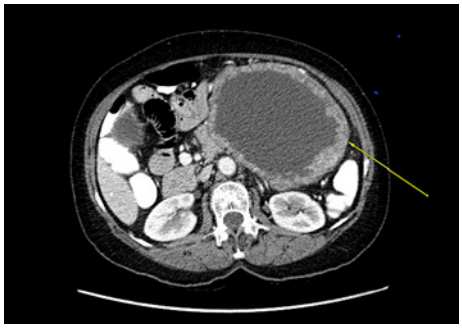

Fig. 1. CT scan of the abdomen with contrast material showing a large well-defined heterogeneous density mass in the left mid and upper abdomen. The mass has peripheral hyperdense thick wall and central hypodense cystic component (yellow arrow).

of the body. These include lipomas, liposarcomas, leiomyomas, true leiomyosarcomas, desmoid tumors, schwannomas, and peripheral nerve sheath tumors [2]. Even though GISTs are the most common nonepithelial neoplasms involving the gastrointestinal tract, mesenchymal tumors only constitute approximately 1% of primary gastrointestinal cancers [3]. GISTs occur predominantly in middle-aged and older individuals and rarely in those under the age of 40. GISTs are identified mainly by expression of the KIT protein and frequently harbor activating mutations in the KIT or platelet-derived growth factor receptor alpha (PDGFRA) genes [4]. These "gain of function" mutations in KIT are observed in both sporadic and hereditary cases, and the KIT proto-oncogene has been postulated to play an essential role in tumorigenesis.

Case Presentation

A 77-year-old female with a medical history significant for hypertension presented with left upper quadrant abdominal discomfort for 1 day accompanied by generalized weakness. She denied any fever, chills, night sweats, weight changes, chest pain, shortness of breath, palpitations, hematemesis, melena, hematochezia, diarrhea, or constipation. Her physical examination was unremarkable except for a large hard, nontender mass palpable in the abdomen's left upper quadrant. She underwent CT scan of the abdomen with contrast material which showed a 13.7 × 11.5 × 12.9 cm mass in the left mid and upper abdomen with an irregularly enhancing rim (Fig. 1). The mass was predominantly fluid in density. The origin of the mass was not clear on a CT scan of the abdomen. The initial impression was that the mass could be a large mesenteric cyst versus pancreatic pseudocyst. Subsequently, an MRI of the abdomen with contrast material re-demonstrated the large left upper quadrant mass lesion with predominant nonenhancing central fluid component and a peripheral rim of soft tissue (Fig. 2, 3). The origin of the mass was again not clear on an MRI of the abdomen. Upper gastrointestinal endoscopy was performed, which showed a submucosal lesion on the greater curvature of the gastric body (Fig. 4). The esophagus, duodenal bulb, first portion of the duodenum, and second portion of the duodenum were normal. Upper gastrointestinal endoscopic ultrasonography (EUS) showed an anechoic lesion suggestive of a cyst in the perigastric region. The outer wall of the lesion was thick. There was internal debris within the fluid-filled cavity (Fig. 5). A fine-needle biopsy of the thick wall was performed. His biopsy results were consistent with spindle cell type GIST. The patient was started on imatinib. A follow-up CT scan of the abdomen done 3 months later did not show any significant change in the tumor size. Because of inadequate response to imatinib, the patient was referred to surgery. She underwent exploratory laparotomy showing a 15 × 15 cm exophytic gastric wall tumor arising from the posterior wall of the body of the stomach. Gastric wedge resection was performed. The patient tolerated the procedure well. The pathology report of surgery specimens showed that all the surgical margins were free of tumor. The patient follows

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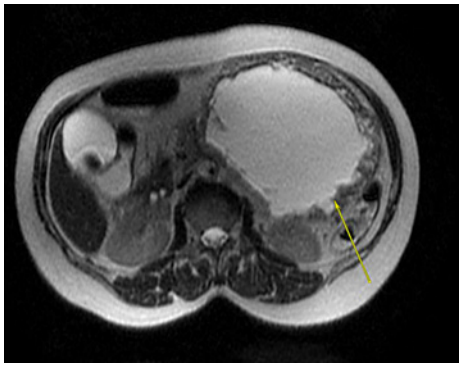

Fig. 2. MRI of the abdomen with contrast material showing an altered signal intensity large cystic mass lesion (yellow arrow).

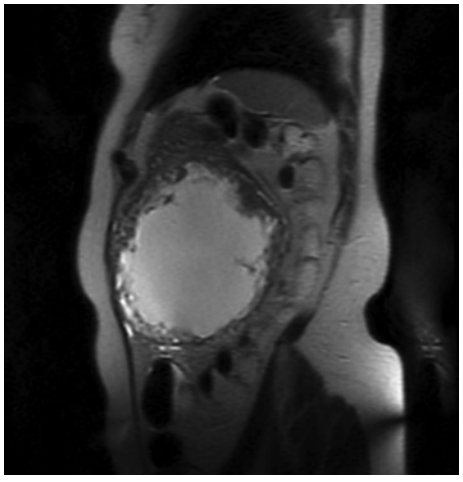

Fig. 3. MRI of the abdomen with contrast material (sagittal view) showing a large cystic mass with possible communication with the stomach.

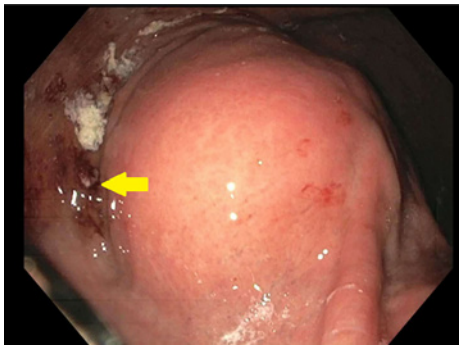

Fig. 4. Upper gastrointestinal endoscopy showing a submucosal lesion on the greater curvature of the gastric body (yellow arrow).

with oncology and gastroenterology services regularly and is slowly returning to her normal state of health.

Discussion

The clinical presentation of GISTs is variable and depends on the tumor location. In general, the distribution of clinical presentation is as follows: overt or occult gastrointestinal bleeding – 28% (small intestine) and 50% (gastric), incidental finding (asymptomatic) – 13–18%,

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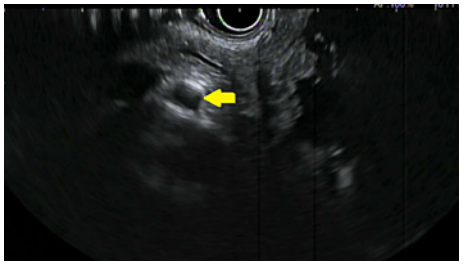

Fig. 5. Upper gastrointestinal ultrasound showing a lesion in the perigastric region suggestive of a cyst (yellow arrow).

abdominal pain/discomfort – 8–17%, acute abdomen – 2–14%, and asymptomatic abdominal mass – 5%. Paraneoplastic syndromes are rare in GISTs; however, potential paraneoplastic syndromes have been reported in a few patients, including consumptive hypothyroidism (caused by marked overexpression of the thyroid hormone-inactivating enzyme type 3 iodothyronine deiodinase within the tumor) and nonislet cell tumor hypoglycemia [5]. Some patients (particularly those with rare hereditary conditions) are affected by multiple primaries [6]. GISTs frequently metastasize to the liver and peritoneum and rarely to regional lymph nodes. They uncommonly metastasize to the lungs, the most common site of metastasis for most soft tissue sarcomas.

The diagnosis of GISTs could be challenging, especially in asymptomatic cases. Contrast-enhanced CT is the imaging method of choice to characterize an abdominal mass, evaluate its extent, and assess the presence or absence of metastatic disease. Oral as well as intravenous contrast should be administered to define the bowel margins. Although MRI has a comparable diagnostic yield and lacks radiation exposure, CT is a preferred initial imaging study for screening and staging, except perhaps in a patient who cannot receive intravenous contrast [7]. The usual CT appearance of a GIST is that of a solid, smoothly contoured mass that enhances brightly with intravenous contrast. Very large tumors (>15 cm) may appear more complex due to necrosis, hemorrhage, or degenerating components. It may be challenging to identify the origin of a large mass because of exophytic growth.

Endoscopy may be useful to characterize the lesion further if a gastric mass is identified. Both GISTs and leiomyomas may appear as a submucosal mass with smooth margins, normal overlying mucosa, and bulging into the gastric lumen. Endoscopy alone cannot accurately distinguish between intramural and extramural tumors. By contrast, EUS has provided a breakthrough for characterizing such masses by identifying the layer of origin and enabling guided-tissue acquisition for diagnostic studies, including immunohistochemistry. Endosonographically, GISTs are typically hypoechoic, homogeneous lesions with well-defined margins, although they can rarely have irregular margins and ulcerations. Endoscopic biopsies using standard techniques usually do not obtain sufficient tissue for a definite diagnosis [8]. EUS-guided fine-needle biopsy forceps may not yield enough tissue, but the main utility is excluding other lesions that arise submucosally. Snare biopsies (in which a polypectomy snare is used to remove a large piece of tissue) can result in perforation and generally should be avoided, except in carefully selected cases [8].

The preoperative biopsy is not generally recommended for a resectable lesion in which there is a high suspicion for GIST, and the patient is otherwise operable. However, a biopsy is preferred to confirm the diagnosis if metastatic disease is suspected or if preoperative imatinib is considered before attempted resection in a patient who has a large locally advanced lesion thought to represent a GIST. If a preoperative biopsy is undertaken, a EUS-guided biopsy is preferred over a percutaneous biopsy. Image-guided percutaneous biopsy carries the theoretical risk of the tumor capsule's rupture with the peritoneal spread of

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disease. The combined use of cytologic analysis, immunohistochemistry for KIT protein expression, and polymerase chain reaction for KIT mutations (if needed) may permit the diagnosis of most of these lesions by EUS-guided fine-needle aspiration. Watson et al. [9] reported a sensitivity of 82% and a specificity of 100% for EUS-guided fine-needle aspiration in the diagnosis of GISTs.

The biologic behavior of GISTs is variable. All the GISTs should be considered to have a malignant potential, even those 2 cm or less with bland histologic features [1]. All GISTs ≥2 cm in size should be resected. However, there is no consensus on the management of smaller GISTs. The natural history of GISTs <2 cm, including their growth rate and metastatic potential, remains unknown. Although these small GISTs may be followed endoscopically until they grow or become symptomatic, the optimal frequency of follow-up and specific risks of this strategy is uncertain [10]. Before the year 2000, there was no known effective therapy for unresectable or metastatic GISTs. Treatment of GISTs was revolutionized by the finding that mutational activation of KIT or PDGFRA stimulated the growth of these cancer cells. Molecularly targeted therapy with imatinib induced dramatic, rapid, and sustained clinical benefit in GISTs. The radiographic response is often indicated by an early decrease in tumor density on contrast-enhanced CT scan, followed by slow tumor regression after the initiation of imatinib therapy. Clear-cut evidence of progression at the time of the first formal disease re-evaluation (typically 2 to 3 months after starting therapy) is considered initial (primary) resistance, while progression or relapse after a period of stable or responding disease is referred to as late (secondary) resistance [11].

Our patient had some clinical and laboratory features which are not typical of a usual case of GIST. First, the presentation of GIST as an abdominal mass is a rare occurrence (5%). The presentation as an abdominal mass of unknown origin made the diagnosis challenging. Second, GIST usually presents as a solid and smoothly contoured mass on a contrast-enhanced CT scan, whereas the mass in our case was cystic with irregular margins. Last, GISTs usually respond very well to imatinib therapy leading to a decrease in size, whereas the tumor in our case was imatinib resistant despite being KIT positive.

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Statement of Ethics

This manuscript is a case report and, in presence of the patient's written consent, does not need the review from IRB at BronxCare Hospital Center. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors of this manuscript do not have any conflicts of interest to declare.

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Author Contributions

All authors certify that he or she has participated sufficiently in the intellectual content and the analysis of data. Each author has reviewed the final version of the manuscript and approves it for publication.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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