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Case Report

Malignant Gastrointestinal Stromal Tumor: Case Report with Uncommon Presentation and Review of the Literature

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Abstract

Gastrointestinal stromal tumors (GISTs) are rare, making up less than 1% of all gastrointestinal tumors. Each year, approximately 4,000 to 6,000 adults in the United States will be diagnosed with a GIST. However, they are common mesenchymal tumors accounting for 80% of gastrointestinal mesenchymal tumors, as well as comprising 3-5% of all sarcomas and 1% of all gastrointestinal neoplasms. GISTs can occur along any location in the GI tract, but most GISTs are found in the stomach (60%), as well as the jejunum and ileum of the small intestine (20-30%). This case describes a 49-year-old male who presents with a malignant recurrent GIST two years after resection of a primary GIST. GISTs represent a problematic subset of gastrointestinal neoplasms due to the variability of immunohistochemistry and cytogenetics of the tumors across patients. GISTs should always be included in the differential diagnosis of presentation of a gastrointestinal mass. Early detection combined with complete resection of the mass, administration of tyrosine kinase inhibitors, as well as observation for possible recurrence is considered the current standard of care in patients with GIST.

KEYWORDS: Gastrointestinal, Malignant, immunohistochemistry, Imatinib, Mutation

ABBREVIATION

GIST: Gastrointestinal stromal tumors, **EGIST**: Extra-gastrointestinal gastrointestinal stromal tumors, **IHC**: Immunohistochemistry, **FNA**: Fina needle aspiration, **EUS-FNA**: Endoscopic ultrasonography-guided fine-needle aspiration

INTRODUCTION

Gastrointestinal stromal tumors (GIST) account for 80% of gastrointestinal mesenchymal tumors, and 1-3% of all gastrointestinal neoplasms [1,2]. GISTs can occur along any location in the GI tract, but most GISTs are found in the stomach (60%), as well as the jejunum and ileum of the small intestine (20-30%) [3]. However, GISTs are not limited to the GI tract; some have been discovered in the pancreas and gallbladder and are known as extra-gastrointestinal GIST (EGIST), though these are considered exceptional or metastasis from malignant GIST tumors located in the GI tract [4]. GISTs were considered rare tumors until 2000, often being misclassified as leiomyomas, leiomyoblastomas, or leiomyosarcomas [1]. Advances in immunohistochemical studies and the discovery of the activating mutation of the C-kit tyrosine kinase allowed diagnosing GISTs commonplace. The current understanding of GISTs is that they arise from interstitial cells of Cajal, which are derived from mesoderm and serve as the pacemaker cells for the gastrointestinal tract [5,6].

Although GISTs are the most common mesenchymal tumors of the GI tract, mesenchymal tumors only constitute 1% of all primary gastrointestinal cancers [7]. GISTs are predominantly found in middle-aged or older individuals, with the mean age of diagnosis being at 64 years of age [8]. Although the majority of GISTs are sporadic, 5% of patients diagnosed with primary familial GIST syndrome, neurofibromatosis type 1, and Carney-Stratakis syndrome carry a predisposition [9]. GISTs are rare in pediatric patients, but are linked to mutations in succinate dehydrogenase, as well as Carney-Stratakis syndrome [10]. Interestingly, the majority of pediatric GISTs have distinct characteristics from adult GISTs, including the absence of a mutation in C-kit tyrosine kinase in 85% of cases [11]. GISTs, can be presented as a benign or as a malignant tumor, however, some investigators suggested that "benign" or "malignant" classification is not necessarily applied as they are not useful in patient management; instead, classification is focused on rate of recurrence and risk of metastasis [12-14].

GISTs represent a problematic subset of gastrointestinal neoplasms due to diagnostic challenges they present. Most GISTs (70%) show spindle-cell morphology, although a significant amount of GISTs show pure epithelioid morphology (20%) or mixed cellularity (10%) [2,12]. Therefore, spindle cell tumors, epithelioid cell tumors and mixed cell tumors are subject to differential diagnoses of GIST. In contrast to spindle-cell type GISTs that stain strongly for C-kit, epithelioid-cell type GISTs

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have different staining patterns of C-kit. Pediatric GISTs share different characteristics and mutations than familial and adult GISTs, making the differential even more broad [9-11].

There are no effective preventative measures for GIST, as it is linked with advanced age and certain inherited conditions. Early detection combined with complete resection of the mass, administration of tyrosine kinase inhibitors, as well as observation for possible recurrence is considered the current standard of care in patients with GIST [15].

CASE PRESENTATION

A 49-year-old man with history of pre-gastric Gastrointestinal Stromal Tumor (GIST) presented two years later with a large abdominal mass. The earlier tumor was surgically removed with clear surgical margins and no post-operative treatment was administered. Additional details of the original tumor were not available for review.

CT with contrast of the current abdominal mass showed evidence of a heterogenous enhancing masses in the left upper abdominal quadrant. Additionally, there were multiple intrahepatic low attenuation lesions. Imaging interpretation suggested recurrent gastrointestinal stromal tumor with liver metastasis, and it was recommended for tissue confirmation. The largest mass in the liver measured 4 X 3 cm and the largest abdominal mass measured 6 x 5 cm, which was located at the pancreatic tail and spleen.

The pathological differential diagnosis was a recurrent gastrointestinal stromal tumor versus pancreatic neuroendocrine tumor or other types of mesenchymal tumors. A final needle aspiration biopsy (FNA) with adequate cellblock preparation from one of the liver masses was obtained and the diagnosis was compatible with a metastatic high grade gastrointestinal stromal tumor.

The patient received neoadjuvant treatment utilizing the tyrosine kinase inhibitor Imatinib, followed by debulking surgical removal of the retroperitoneal abdominal masses. Surgical removal included the tumor masses, left adrenal gland, spleen, and portions of the pancreas and stomach. (**Figure-1A**). There was no attempt to remove liver masses. Microscopic examination showed histomorphologic features of mixed highly atypical spindle and epithelioid cells with prominent malignant giant tumor cells and abundant mitosis (more than 12 mitosis/10 HPF) (**Figure 1-B-C**). Vascular invasion was easily identified (**Figure 1D**).

Immunohistochemistry (IHC) studies were utilized for evaluation. The tumor cells were positive for Vimentin, CD34/QBEND-10 and CD117 (c-Kit) (**Figure 1E**). The tumor cells were negative for Cytokeratin AE1/AE3, S-100, SMA, Desmin, CD31, Pan Melanoma, CD-56, Synaptophysin, Chromogranin, and CDX-2.

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 excised tumor mass showed more than 75% non-viable post-chemotherapy necrosis and fibrosis. Surgical margins were not free in multiple sites. Patient received another round of post-operative chemotherapy plus radiation and was free of recurrence of tumor for 9 months follow up, after which he expired due to massive metastatic diseases and multiple organ failure.

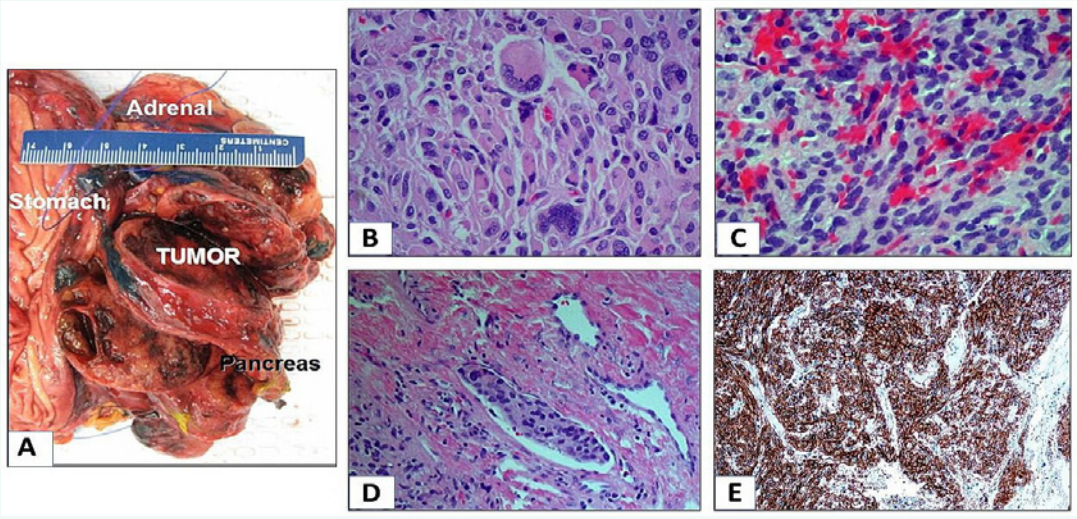

Figure 1 Pathological examination of the tumor
1A: Excised surgical mass including left adrenal, tumor, spleen, and portions of stomach and pancreas
1B: Epithelioid tumor cells with frequent multinucleation and increased mitosis cells (H&E stain X60)
1C: Spindle tumor cells with moderate atypia (H&E stain X40)
1D: Positive CD117

DISCUSSION

GISTs represent 80% of all gastrointestinal mesenchymal tumors. 60% of GISTs are found in the stomach and 20-30% are found in the small intestine, thought they can be found outside of the gastrointestinal tract via metastasis from a primary neoplasm [3,4]. GISTs arising outside of the gastrointestinal tract are thought to arise from interstitial cells of Cajal that were accidentally dispersed during the development of the embryo.[16] Recently, investigators are suggesting that all GISTs are considered potentially malignant and are therefore classified based on rate of recurrence and risk of metastasis [12-14].

Clinically, most GISTs are asymptomatic and are discovered incidentally during an endoscopic procedure or on an imaging analysis done for another purpose. More often, they are associated with vague symptoms such as bloating, abdominal pain or discomfort, and early satiety; some may ulcerate, bleed, or grow large enough to cause gastrointestinal obstruction [17]. Consumptive hypothyroidism and non-islet cell tumor hypoglycemia are paraneoplastic syndromes associated with GISTs, though these are rare occurrences [18]. GISTs frequently metastasize to the peritoneum and liver, though rarely to regional lymph nodes or lungs, the most common site for soft tissue sarcoma metastasis [12]. 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 [19]. The recurrent tumor in our case was classified as malignant with high potential for recurrence and metastasis.

Radiologically, GIST usually appears as solid, smoothly contoured masses that enhance brightly with IV contrast [12]. Tumors larger than 15 cm may appear more compound due to hemorrhage, degeneration, and necrosis. Leiomyomas and GISTs may appear as submucosal masses with smooth margins, with an overlying mucosa and central ulceration.

Standard endoscopic biopsy techniques do not obtain sufficient tissue for diagnosis [20]. Snare biopsies are generally avoided for GISTs, as they can result in bowel perforation. Preoperative biopsy is not recommended for a resectable lesion in which there is a high degree of suspicion and radiological evidence of a GIST. However, biopsy is preferred to confirm metastatic disease or if preoperative tyrosine kinase inhibitors are considered prior to attempting resection in patients who have a large lesion considered to be GIST. The use of immunohistochemistry for KIT protein expression, polymerase chain reaction (PCR) for KIT mutations, and cytologic analysis may be used in diagnosing these lesions by endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA). In our case, diagnosis was confirmed by EUS-FNA of one of the metastatic liver lesions.

GISTs were considered rare tumors until 2000, often being misclassified as leiomyomas, leiomyoblastomas, or leiomyosarcomas [1]. The current understanding of GISTs is that they arise from interstitial cells of Cajal, which are derived from mesoderm and serve as the pacemaker cells for the gastrointestinal tract [5,6]. Cajal cells characteristically stain positive for CD117, CD34, DOG-1 and protein kinase C theta [21-23]. The discovery of CD117 expression by GISTs was a scientific breakthrough in differentiating GISTs from leiomyosarcomas, leiomyomas, and other spindle cell tumors of the GI tract, which are CD117 negative [24]. CD117 antigen is compatible with the c-KIT receptor tyrosine kinase, a product of the KIT protooncogene. In normal cells, KIT receptor tyrosine kinase activity is regulated by binding of the KIT ligand or stem cell factor (SCF) to the endogenous ligand [25]. Mutations in KIT lead to constitutive activation of KIT, resulting in stimulation of cell survival, growth, and proliferation [26]. Numerous studies have indicated that approximately 80% of GISTs can carry a mutation for the KIT gene, allowing a structural variant of the KIT protein to be formed, which can be abnormally activated to enable oncogenic signaling [24]. KIT mutations in GIST can occur in different exons of the gene, with 70% affecting exon 11, which codes for the intracellular juxtamembrane domain of the receptor, and 12-15% affecting exon 9, which codes for the extracellular ligand-binding domain [24,26]. Activating mutations in the KIT gene are associated with GISTs, testicular seminomas, mast cell disease, melanoma, and acute myeloid leukemia [27]. Approximately 15% of GISTs lack mutations in KIT. A set of GISTs lacking KIT mutations have activating mutations in platelet-derived growth factor receptor alpha (PDGFRA) receptor tyrosine kinase [28-30].

GISTs represent a problematic subset of gastrointestinal neoplasms due to the variability of immunohistochemistry and cytogenetics of the tumors across patients. GISTs are mainly identified by expression of the KIT protein and activating mutations in the KIT or platelet-derived growth factor receptor alpha (PDGFRA) genes. Although the majority of GISTs are sporadic, 5% of patients diagnosed with primary familial GIST syndrome, neurofibromatosis type 1, and Carney-Stratakis syndrome carry a predisposition [9]. Individuals with neurofibromatosis I have a high incidence of GISTs in the small intestine and primarily do not carry somatic mutations in the KIT or PDGFRA genes. GISTs are rare in pediatric patients, but are linked to mutations in succinate dehydrogenase, as well as Carney-Stratakis syndrome [10,31]. Interestingly, the majority of pediatric GISTs have distinct characteristics from adult GISTs, including the absence of a mutation in C-kit tyrosine kinase or PDGFRA in 85% of cases as well as high incidence of lymph node metastases [10,11,32]. Moreover, most adult GISTs occur sporadically, while pediatric GISTs arise due to defined syndromes.

GISTs range in their cellular morphology, with the majority being spindle-cell type and the minority belonging to either the epithelioid-cell type or mixed type. Spindle-cell type GISTs are composed of uniform eosinophilic cells arranged in whorls or short fascicles [33]. When compared with leiomyomas, spindle-cell GISTs have paler eosinophilic cytoplasm and a fibrillary appearance. Epithelioid-type GISTs are composed of rounded cells with variably eosinophilic or clear cytoplasm with round to oval nuclei, vesicular, and nested architecture; possibly causing confusion with a melanocytic or epithelial neoplasm

[34]. However, epithelioid-type GISTs are often KIT-expression negative and have platelet derived growth factor receptor alpha (PDGFRA) mutations. Consequently, caution should be exercised when typing these neoplasms. The tumor in our case was of mixed morphology with strong positivity for CD-117 and CD34

There are no effective preventative measures for GIST, as it is linked with advanced age and certain inherited conditions. Early detection combined with complete resection of the mass, administration of tyrosine kinase inhibitors, as well as observation for possible recurrence is considered the current standard of care in patients with GIST [15]. Our presented case shows evidence of recurrence 2 years after initial GIST.

Prior to 2000, there was no effective therapy for metastatic or unresectable GISTs. Studies have shown that sarcomas of the GI tract have a low response rate to chemotherapy, proving that GISTs have a higher rate of primary resistance to chemotherapy [35-37]. The discovery of mutational activation of PDGFRA or KIT revolutionized treatments of GISTs, leading to the development of receptor tyrosine kinase inhibitors. Receptor tyrosine kinase inhibitors block signaling of PDGFRA or KIT by binding the ATP-binding pocket needed for phosphorylation to activate the receptor [38].

This case and literature review seeks to shed light on the variability, diagnostic and treatment challenges in patients who have GIST. Early detection combined with complete resection of the mass, administration of tyrosine kinase inhibitors, as well as observation for possible recurrence is considered the current standard of care in patients with GIST, however, most GISTs are found incidentally [15]. This delay in early detection poses an additional hurdle due to the potential malignancy and metastatic spread of most GISTs. The definitive diagnosis is made through immunohistochemical and radiological findings, which aids in the correct diagnosis of these neoplasms.

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