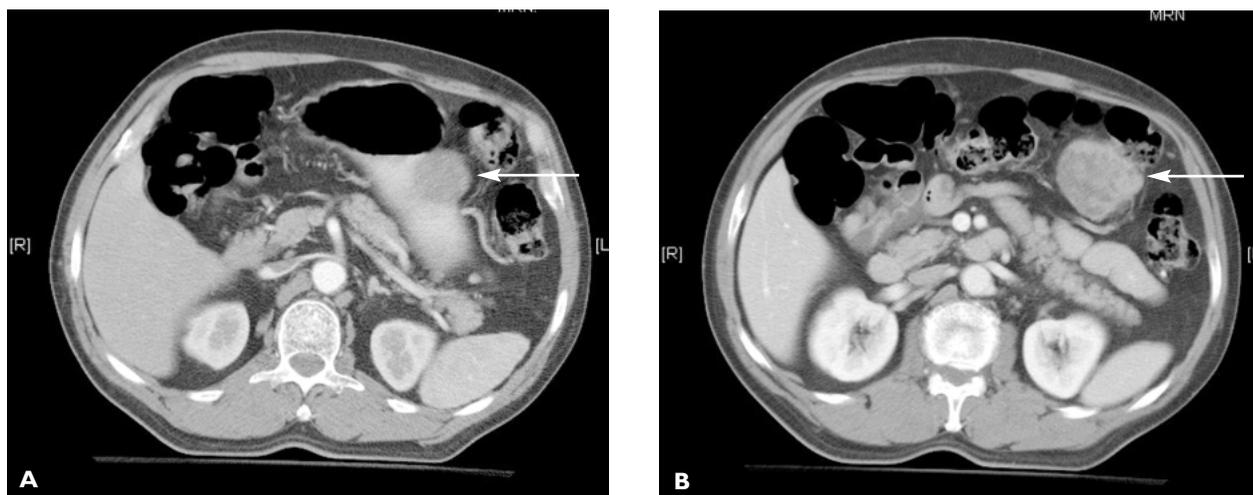*Dx***Ray**

A 70-Year-Old Man with an Abdominal Mass

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Figure 1. Contrast-enhanced computed tomography scans of the abdomen, showing a heterogeneous exophytic mass appearing to arise from the body of the stomach. The lesion measured 5.5 × 5.3 cm at its maximal dimensions. The scan on the left (**A**) shows the relationship of the mass to the stomach, and the scan on the right (**B**) shows the mass in its greatest dimension.

CASE PRESENTATION

A 70-year-old man is brought to the emergency department (ED) after falling from a ladder and landing on his right hip. The patient complains of severe pain with movement of the right lower extremity. He has no other complaints.

The patient's medical history is significant for hypertension, hypercholesterolemia, gastroesophageal reflux, and diverticulosis. The patient denies the use of tobacco or illicit drugs but admits to occasionally having a beer. His mother has congestive heart failure, and a brother has lung cancer.

Physical examination reveals a thin man appearing his stated age. Blood pressure is 123/74 mm Hg, heart rate is 74 bpm, respiratory rate is 18 breaths/min, and temperature is 98.7°F. The abdomen is nontender and not distended; bowel sounds are normal. There is no dullness to percussion, and palpation reveals no organomegaly or masses. Digital rectal examination is normal

and negative for fecal occult blood. There is significant pain with flexion and extension of the right hip. The remainder of the physical examination is unremarkable.

Laboratory studies (complete blood cell count with differential, electrolytes, glucose, and coagulation studies) are within normal limits.

A series of hip radiographs obtained in the ED reveal a right-sided hip fracture. Computed tomography (CT) scans of the abdomen reveal a 5.5 × 5.3 cm heterogeneous exophytic mass arising near the body of the stomach and extending inferiorly (**Figure 1**). The liver, gallbladder, spleen, pancreas, adrenal glands, and

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kidneys are unremarkable. There is no dilatation of the bowel or bowel wall thickening. Multiple diverticula are identified within the sigmoid colon, but there are no signs of secondary diverticulitis. The patient is admitted to the orthopaedic surgery service for an open reduction internal fixation of the right hip.

- **What is the most likely diagnosis of this patient's gastric mass?**
  - (A) Leiomyoma
  - (B) Leiomyosarcoma
  - (C) Gastric schwannoma
  - (D) Gastrointestinal stromal tumor
  - (E) Lipoma

- **What is the best approach to evaluating the mass?**
  - (A) Surgical resection of the mass
  - (B) Video esophagogastroduodenoscopy and endoscopic ultrasonography with fine needle aspiration
  - (C) Small bowel radiography
  - (D) Repeat abdominal CT in 6 months
  - (E) Abdominal magnetic resonance imaging

ANSWERS

The correct answers are (D) gastrointestinal stromal tumor (GIST) and (B) esophagogastroduodenoscopy (EGD) and endoscopic ultrasonography (EUS) with fine needle aspiration (FNA).

Several elements of this patient's clinical presentation and initial workup point to GIST as the most likely diagnosis. The mass is asymptomatic, which is a very common clinical presentation for a GIST. Also, on CT scans the mass is highly heterogeneous and arises from what appears to be the gastric wall, a common appearance and location for a GIST. A leiomyoma or leiomyosarcoma is possible; however, these tumors are less frequently seen in the stomach than are GISTs. Gastric schwannomas, rather than being asymptomatic, often present with epigastric and/or abdominal pain. A lipoma is also possible but would likely appear much darker on CT scans due to its high fat content.

EGD and EUS with FNA would be the most appropriate next step in evaluating this patient's gastric mass. EUS allows endoscopic as well as ultrasonographic evaluation of the mass and its relation to the gastric wall, where GISTs frequently arise, and affords image acquisition that is superior to CT or magnetic resonance imaging (MRI). In addition, EUS-guided FNA allows definitive tissue acquisition from lesions below the mucosa, which are otherwise inaccessible endoscopically. Tissue diagnosis is always critical to guiding ther-

apy, regardless of the type of lesion identified. Surgical resection should be deferred until a tissue diagnosis has been obtained. Small bowel radiography would add little data beyond that obtained via CT and may provide suboptimal gastric views. Similarly, MRI likely would not afford additional useful information. Given the large size of the mass, repeating the CT in 6 months would be of little value because the lesion is likely to continue to grow.

OUTCOME OF CASE

The incidental finding of a gastric mass prompts a gastroenterology consultation following the patient's hip procedure, and it is recommended that the patient undergo EGD and EUS with FNA biopsy of the mass. Endoscopy reveals a normal-appearing esophagus and duodenum. Thickened folds are seen in the proximal gastric body, along the greater curvature, with apparent extrinsic compression. The pancreas appears normal. The mass is clearly seen, measures 5 cm in diameter, and has a heterogeneous echo texture, with well-defined borders. There is a small cystic space within otherwise solid-appearing tissue. Doppler ultrasonography reveals no evidence of vascularity or blood flow within the mass. The mass is noted to arise in the gastric wall from a distorted area of the muscularis propria (**Figure 2A**).

EUS-guided FNA biopsy is performed with a 22-gauge needle (**Figure 2B**). Initial cytologic evaluation reveals clumps of spindle cells (**Figure 3A**). Immunohistochemical staining and analysis reveals that the tumor is positive for CD117 (*c-kit*) as noted by the strong cytoplasmic reaction with membrane enhancement of the tumor cells (**Figure 3B**). The tumor is also positive for CD34, focally positive for smooth muscle actin (SMA), and negative for S-100, pan cytokeratin, and desmin.

Based on immunohistochemical and EUS findings, a diagnosis of GIST is made. Due to the tumor's size, endosonographic appearance, and presumed malignant potential, the patient is referred for surgical resection of the mass.

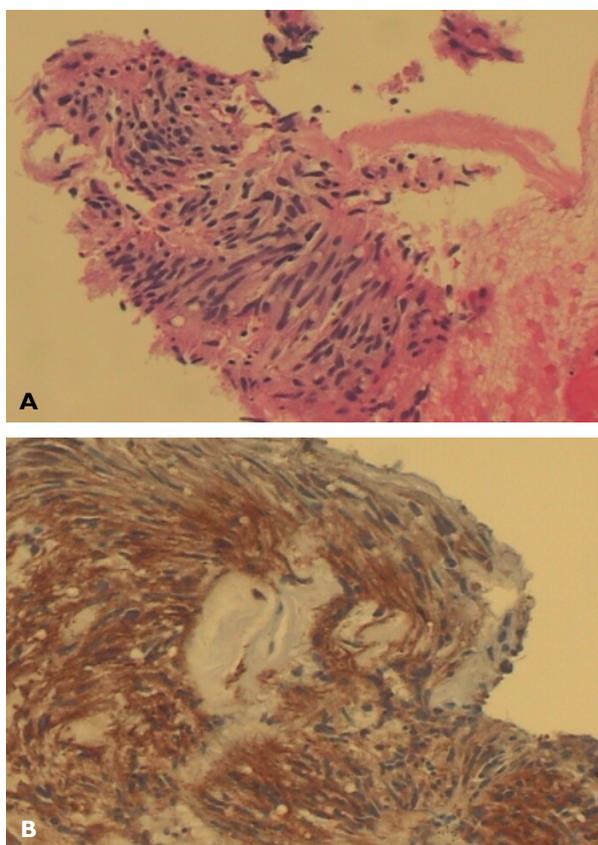## DISCUSSION: GASTROINTESTINAL STROMAL TUMORS

Although they represent only 0.1% to 3% of all gastrointestinal (GI) neoplasms, GISTs are the most common mesenchymal tumors of the GI tract and may arise from the GI wall, mesentery, omentum, or retroperitoneum.[1] They can occur throughout the GI tract and are most commonly located in the stomach (50%–60%), followed by the small intestine (20%–30%), colon and rectum (5%–10%), and esophagus (< 5%).[2]
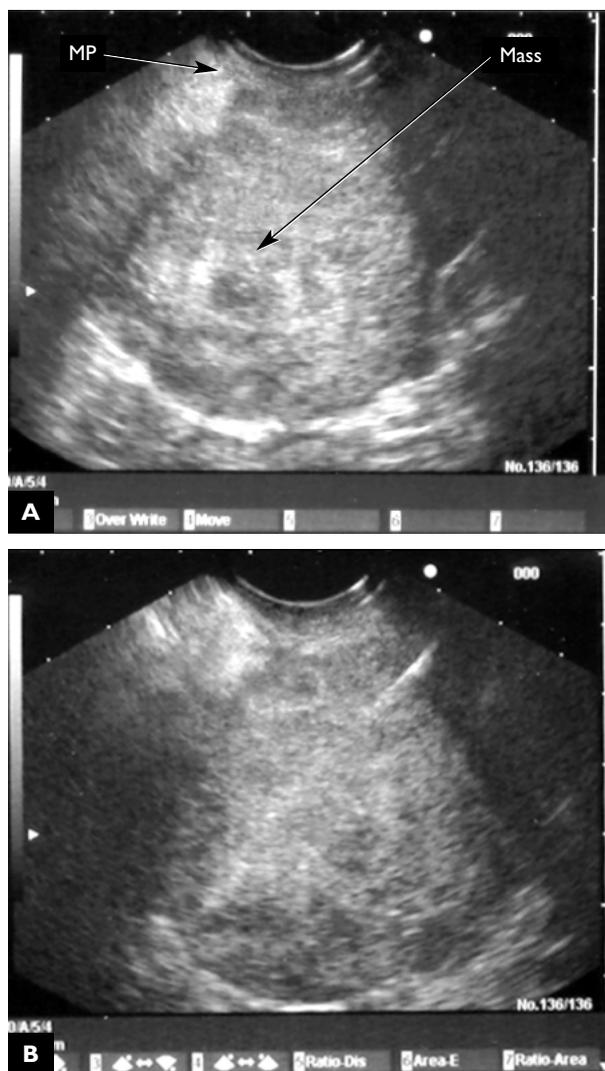
Figure 2. (A) Curvilinear array 7.5-MHz endoscopic ultrasonography (EUS) scan of the gastric mass showing the tumor originating from the muscularis propria (MP; fourth hypoechoic layer of the gastric wall). **(B)** EUS-guided fine needle aspiration of the mass with a 22-gauge needle.

Figure 3. (A) Photomicrograph of tissue sample obtained by fine needle aspiration (FNA) showing cytologic atypia and copious spindle cells (hematoxylin and eosin stain, × 200). **(B)** Photomicrograph of tissue sample obtained by FNA showing a strongly positive reaction to immunohistochemical stain for CD117, or *c-kit* (× 200).

GISTs of the gallbladder and appendix also have been reported.[3,4]

Recent advances in the understanding of the molecular, histologic, and clinical characteristics of GISTs have helped to clarify some of the long-standing confusion regarding the classification and prognostication of these tumors. Previously thought to be neoplasms of smooth muscle origin that are typically benign, GISTs are now regarded as a heterogeneous group of nonepithelial (mesenchymal) tumors of the GI tract with variable cells of origin and a clinical course not easily predicted by standard pathologic means.[3,5,6] The clinical spectrum of these tumors varies widely, from benign to highly malignant. Historically, malignant tumors have had a poor response to conventional cytotoxic therapy. However, the recent availability of an effective systemic therapy has dramatically influenced the management of patients with advanced GIST.

Incidence

GISTs are most often diagnosed in the fifth to the seventh decade of life, being uncommon in adults younger than 40 years and extremely rare in children. There appears to be a slight male predominance. The true incidence of GIST is unknown; however, unconfirmed estimates of new cases of GIST in the United States have been calculated to be as high as 5000 to 6000 per year.[5–7]

GISTs comprise less than 1% of malignancies of the esophagus, stomach, colon, and rectum; in the small bowel, however, GISTs account for 20% of malignancies

if lymphomas are excluded.[2] About 50% of GISTs are metastatic at presentation, with the most common sites of metastases being the peritoneum and the liver.[3,8]

Histopathology

GISTs have some common phenotypic features with interstitial cells of Cajal, the cells that regulate peristalsis, and GISTs are thought to possibly originate from these cells or their progenitors.[9] Histopathologically, GISTs may be predominately spindle cell type (70%–80%) or epithelioid type (20%–30%) or of mixed histology (< 10%). The spindle cell type consists of eosinophilic cells in short fascicles or whorls with uniform ovoid nuclei and indistinct cell margins. The epithelioid type consists of round cells with variable eosinophilic to clear cytoplasm and uniform nuclei that are round to ovoid.[5,6]

GISTs are differentiated from other mesenchymal tumors of the GI tract (eg, leiomyomas, leiomyosarcomas, schwannomas, and lipomas) by their characteristic expression of a growth factor receptor with tyrosine kinase activity, termed KIT. KIT is defined by the CD117 antigen and is a product of the *c-kit* proto-oncogene. More than 80% of GISTs have somatic mutations that lead to activation of the KIT tyrosine kinase and are considered to be caused by these mutations.[8–10]

Clinical Presentation

Up to one third of GISTs are asymptomatic, with tumors typically discovered incidentally at surgery, during radiologic studies performed for another reason (as in the case presented), on physical examination, or during surveillance endoscopic studies. Symptomatic lesions present with manifestations that depend on tumor size, growth pattern, and location. Overall, the most common presenting features are a palpable abdominal mass followed by GI bleeding (occult more common than overt), and abdominal pain.

GISTs of the esophagus most commonly cause dysphagia and weight loss. GISTs of the stomach usually are associated with GI bleeding (20%–50% of cases), abdominal pain (40%–50%), or a palpable mass (25%–40%).[3,4] GISTs of the small bowel are more frequent in the jejunum, followed by the ileum and duodenum. Presenting symptoms may include GI bleeding, abdominal pain, or a palpable mass. Cases of duodenal lesions presenting as jaundice have been reported.[11] Partial or complete intestinal obstruction and intussusception can also occur. Ileal tumors presenting with pain or a palpable mass can often be mistaken for gynecologic disease in women.[3,4] GISTs of the colon are associated with GI bleeding, abdominal pain, a palpable mass, or change in bowel habits. Rectal GISTs usually cause hematochezia or rectal pain or fullness; alternatively, asymptomatic lesions may be found during routine prostate or gynecologic examination.

GISTs can perforate, causing acute peritonitis, abscesses, or ascites. Although rare, primary GISTs of the mesentery, omentum, or retroperitoneum can occur. They usually present as solitary intra-abdominal masses instead of multiple, scattered nodular lesions seen in the metastatic spread of primary GISTs. Symptoms include abdominal pain or a palpable mass.[3,4]

Diagnostic Evaluation

EGD is a widely accepted procedure for the evaluation of gastric masses.[12] However, an accurate diagnosis of GIST and differentiation from other submucosal lesions cannot be achieved by endoscopy alone. Thus, EUS, which allows transmural examination of the lesions as well as tissue acquisition, is becoming the standard for investigating GISTs.

On routine endoscopic evaluation, GISTs commonly appear as a bulge located in the GI tract, with normal overlying mucosa and a smooth, regular appearance without major mucosal irregularities. Occasionally, an area of umbilication or mucosal ulceration may be seen. Tumors can vary considerably in size from lesions less than a centimeter to overt masses greater than 30 cm in diameter. On EUS, GISTs are typically hypoechoic lesions with well-defined margins, although they can occasionally have irregular margins and ulcerations. Most GISTs originate from within the muscularis propria (fourth hypoechoic layer of the GI wall), although some may originate from the muscularis mucosa or submucosa.[13]

The diagnosis of GIST should not be based on endosonographic images and anatomic location alone. Tissue sampling of suspected GISTs is essential for establishing a diagnosis and determining malignancy. EUS-guided FNA has been found to be useful and important in the diagnosis of GI submucosal tumors. Combining EUS findings with immunohistochemical studies has been reported to have a sensitivity and specificity of 100% for the diagnosis of malignant GISTs.[14,15] Immunohistochemical studies include staining tissue samples for CD117, CD34, S-100, and SMA. Tumors positive for SMA indicate differentiation toward smooth muscle cells (leiomyomas and leiomyosarcomas), and tumors with a positive reaction for S-100 indicate differentiation toward neural elements (schwannomas).[14] Lipomas are rarely sampled via EUS because they can be diagnosed by their hyperechoic appearance, which is pathognomonic. However, a biopsy of such a lesion would reveal copious benign adipose tissue.

Factors Determining Malignant Potential

The highly variable clinical behavior of GISTs has created great interest in identifying factors that predict malignant potential. Many prognostic factors have been proposed; however, the criteria for malignancy differ greatly among the various published studies.

Tumor size and mitotic activity. At present, size of the primary tumor and level of mitotic activity are regarded as the most important features in predicting malignant behavior.[16] Generally, tumors less than 5 cm in the largest diameter are commonly accepted as most likely benign, whereas tumors equal to or greater than 5 cm are considered most likely malignant. However, this is not an entirely reliable rule as some tumors less than 5 cm in size have been known to metastasize.[17–19] The number of mitoses counted in 10, 30, or 50 adjacent high-power fields (HPF) has been shown to be useful for distinguishing malignant from benign tumors. A mitotic count greater than 5 mitoses per 50 HPF is considered to be associated with malignant behavior.[2,20]

Metastasis and recurrence. Malignant behavior is defined by omental, mesenteric, or peritoneal seeding; invasion to adjacent organs; or metastasis to extraintestinal organs or the abdominal wall. The most common sites of extraintestinal spread are the liver (50%), lung (10%), and bone (< 10%). Tumor recurrence after surgical resection also is considered indicative of malignancy.[16]

Gain-of-function mutations. Gain-of-function mutations in the *c-kit* gene occur in up to 90% of GISTs and lead to constitutional activation (phosphorylation) of the receptor. The activating mutation perpetuates the KIT signal and the downstream phosphorylation cascade in the signal transduction pathway, ultimately leading to activation of cellular proliferation.[21,22] Studies have shown that mutations of exon 11 on the *c-kit* gene encoding the juxtamembrane domain were associated with larger tumor size and more frequent invasion of adjacent tissues.[23] Mutation-positive GISTs showed higher mitotic figures and more significant necrosis and hemorrhage. Patients with mutation-positive GISTs also experienced more frequent recurrences and had higher mortality.[23] Mutations in exon 9 and 13 have also been described but are rare. These tumors are associated with large tumor size and extragastric location, appear clinically aggressive, and carry a poor prognosis.[22]

Genetic markers. DNA sequence copy number changes (gains and losses of genetic material) are found in all GISTs. Benign GISTs appear to have significantly fewer DNA copy number changes and fewer gains than malignant primary and metastatic GISTs.[24]

Imaging characteristics. EUS studies have identified prognostic factors for malignancy for GISTs, including large size, presence of cystic spaces within the tumor, and ulceration or irregular contour. The presence of at least 1 of these features had a sensitivity of 91%, specificity of 88%, and positive predictive value of 93% in the diagnosis of malignant GIST; the presence of 2 of these features had a positive predictive value of 100% for malignant or borderline malignant tumors; if all 3 EUS features are absent and the diameter of the tumor is less that 4 cm, there is a high likelihood of the tumor being benign.[16] EUS features associated with malignant potential were almost exclusively seen in tumors positive for CD117 (*c-kit* protein).[7] These features can all be useful in selecting candidates for resection.[13,25]

Treatment

Surgery. Surgery continues to be the primary treatment for GIST, with 5-year overall survival rates ranging from 40% to 55% after complete resection.[26] Surgery is indicated for all GISTs that cause symptoms as well as for tumors suspected of being malignant or potentially malignant. The main goal of resection is to remove all apparent gross disease. However, wide margins of resection do not appear to be necessary. Similarly, lymphadenectomy is not typically indicated, as lymph node metastases are rare. Asymptomatic small lesions (< 3 cm) with benign echo features can be followed expectantly with endoscopic and endosonographic surveillance.[26]

Imatinib. KIT mutations, which are found in most GISTs, are thought to promote tumor growth or prevent apoptosis (programmed cell death). These findings have led to the application of the orally bioactive tyrosine kinase inhibitor, imatinib mesylate (STI-571), as targeted therapy for GIST. The safety and efficacy of imatinib treatment for metastatic GIST was confirmed by the results of 2 phase I/II trials.[27,28] The response of GISTs to imatinib mesylate may be dependent on the KIT mutational status of tumors. Patients with exon 11 mutations had a significantly higher partial response rate to treatment than patients with exon 9 mutations or those with no detectable KIT mutation. The time to treatment failure was significantly prolonged for patients with exon 11 mutations.[28] Imatinib mesylate was approved by the U.S. Food and Drug Administration for the treatment of unresectable metastatic GISTs in May 2002. The potential role of imatinib in metastatic GISTs and as adjuvant or neoadjuvant therapy remains to be determined.[26–29] **HP**

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