Pictorial Essay

Gastrointestinal Stromal Tumors: Clinical, Radiologic, and Pathologic Features

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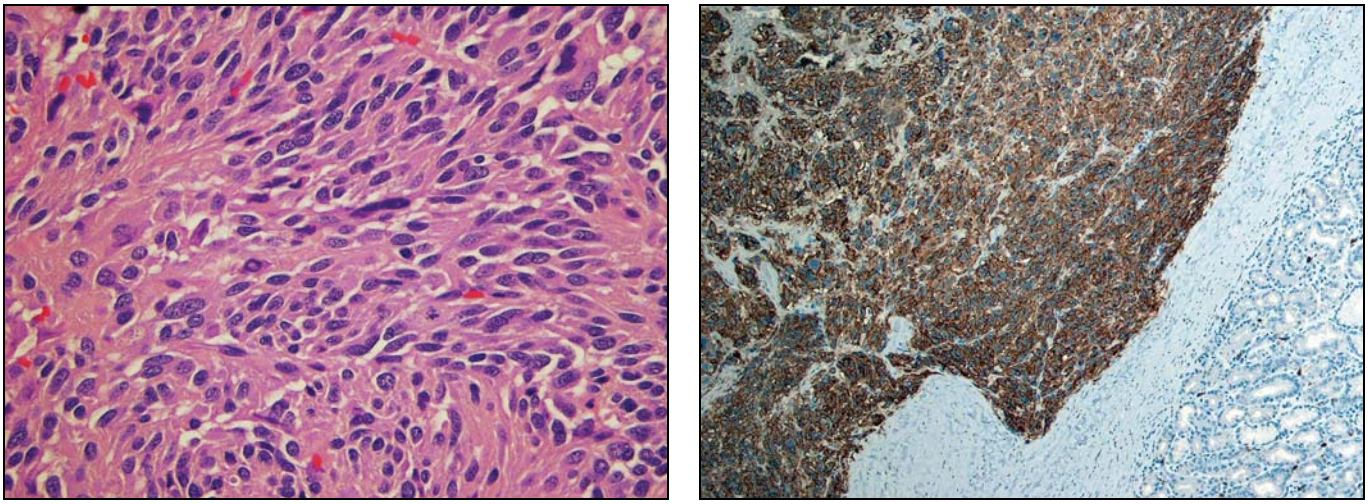
Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors to arise from the gastrointestinal tract. They are characterized by expression of a tyrosine kinase growth factor receptor, also called kit receptor or CD117. This expression allows unchecked growth of tumor and resistance to apoptosis. These tumors differ immunohistologically and behaviorally from other mesenchymal tumors such as leiomyosarcomas, which do not express kit antigen. In the



A **B**

Fig. 1.—50-year-old woman with small-bowel gastrointestinal stromal tumor (GIST).
A, Photomicrograph of histopathologic slide shows typical GIST composed of fascicles of nondescript spindle cells. Appearance on H and E stain is similar to that of smooth muscle tumor.
B, Photomicrograph of histopathologic slide shows that in appropriate clinicopathologic setting, c-kit positivity (brown staining) is diagnostic of gastrointestinal stromal tumor.

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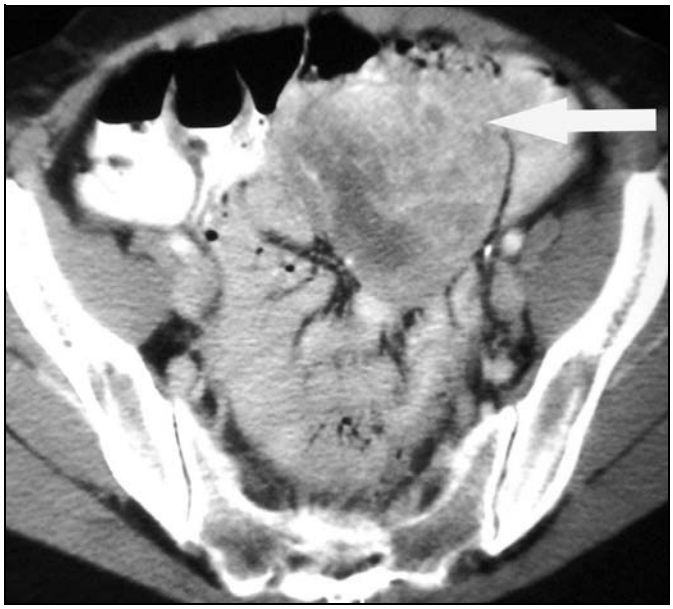


Fig. 2.—48-year-old woman with small-bowel gastrointestinal stromal tumor. Axial contrast-enhanced CT scan of pelvis shows exophytic heterogeneously enhancing mass (*arrow*).

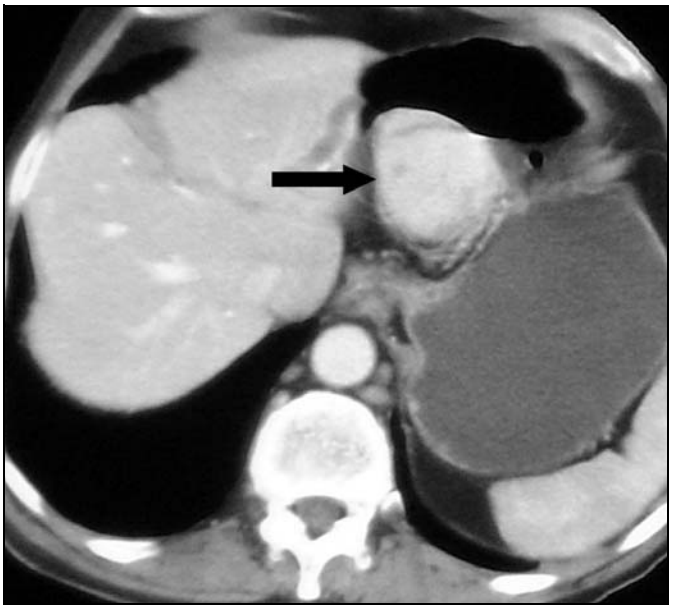


Fig. 3.—30-year-old man with gastric gastrointestinal stromal tumor. Axial contrast enhanced CT scan of upper abdomen shows intense homogenous enhancement of tumor arising from gastric wall (*arrow*).

past, GISTs were misdiagnosed as smooth muscle tumors because on light microscopy the two tumors share many features. We reviewed the imaging findings of 29 patients with GIST seen at our affiliated institutions. The tumors were predominantly of gastric (11 patients) or enteric (13 patients) origin. Two patients each had duodenal or rectal tumors, and one had a primary mesenteric tumor. In this essay, we discuss the imaging findings of these patients at presentation and after chemotherapy. We also describe the clinical and pathologic literature of this recently recognized tumor.

Clinical Features

The incidence of GIST is difficult to estimate because of previous diagnostic inconsistencies. There are probably 1,000–2,000 new cases per year in the United States [1, 2]. The average patient with GIST is 40–70 years old. Male to female incidence is now considered to be equal; some earlier articles purported a higher male incidence [2–6]. Despite being the most common mesenchymal tumor, GISTs only account for 1–3% of all gastrointestinal tumors and are dwarfed in numbers by the more common epithelial and lymphomatous tumors.

The clinical presentation depends on the size and site of tumor. Large series have shown the stomach to be the most common site, accounting for 60–70% [1, 4, 7–9]. Approximately one-third occur in the small bowel, with rare occurrence in the colon and rectum (5%), esophagus (< 2%), and appendix [10].

TABLE 1 **Immunohistochemical Properties of Gastrointestinal Mesenchymal Tumors**

Tumor Type	CD117	S-100 Protein	α–SMA	Vimentin
GIST	Positive	May be positive	Usually negative	Negative
GIGT	Negative	Positive	Negative	Negative
GILT	Negative	Negative	Positive	Negative
GIFT	Negative	Negative	Negative	Positive

Note.—GIST = gastrointestinal stromal tumor, GIGT = gastrointestinal glial tumor, GILT = gastrointestinal leiomyogenic tumor (includes leiomyosarcoma), GIFT = gastrointestinal fibrous tumor, CD117 = c-kit antigen, α-SMA = alpha–smooth muscle antigen.

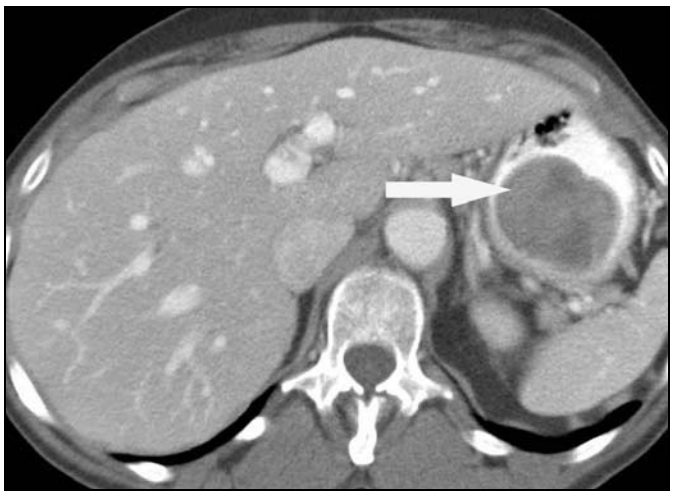


Fig. 4.—69-year-old woman with gastric gastrointestinal stromal tumor. Axial contrast-enhanced CT scan of upper abdomen shows large intraluminal component of tumor (*arrow*).

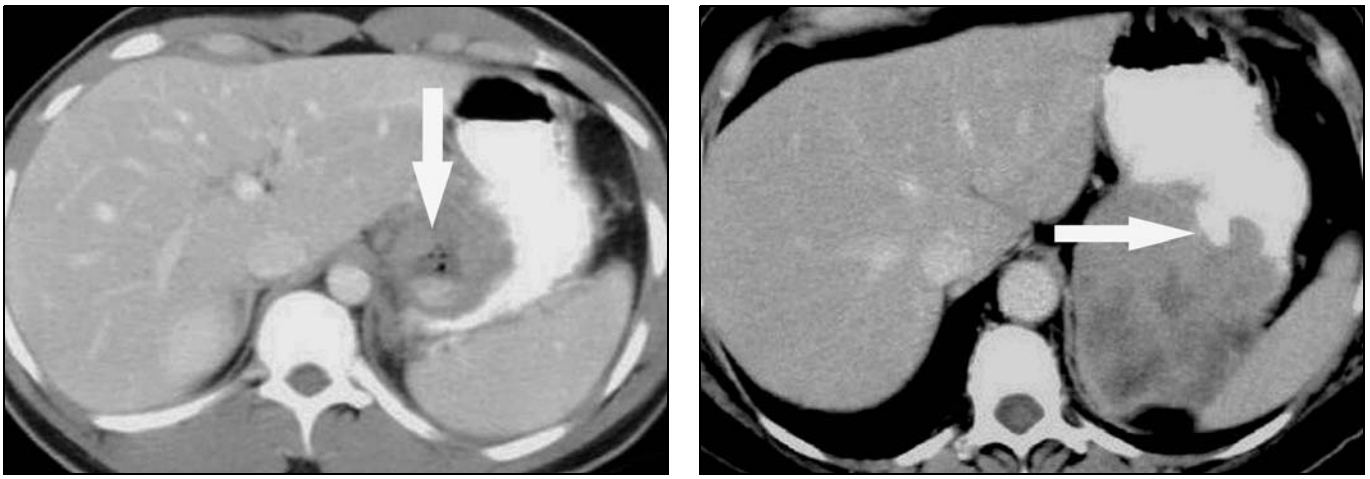


Fig. 5.—Gastric gastrointestinal stromal tumor (GIST).
A, Axial contrast-enhanced CT scan of upper abdomen of 69-year-old woman shows large intraluminal component of tumor with pocket of gas (*arrow*).
B, In 63-year-old woman with gastric GIST, axial contrast-enhanced CT scan of upper abdomen shows large heterogeneously enhancing tumor in stomach and ulcer filled with oral contrast agent (*arrow*).

Some GISTs primarily arise in the omentum, mesentery, or retroperitoneum and are unrelated to the tubular gastrointestinal tract. Apart from their occurrence in the esophagus, GISTs are more prevalent in the gastrointestinal tract compared with true smooth muscle tumors such as leiomyosarcomas.

Clinical presentation is often vague. Abdominal pain or distention is the most common presentation of GISTs [2]. Gastrointestinal bleeding or unexplained anemia is the next most common presentation. Duodenal tumors present with obstructive jaundice and may be confused with pancreatic cancer. Surprisingly, despite the large size of duodenal tumors, bowel obstruction is rare. The exophytic and cavitary nature of the tumor may delay luminal constriction.

In the absence of metastatic disease, complete surgical excision is undertaken and offers the best hope of cure [3, 6]. Unlike carcinomas, resection of GISTs does not require wide bowel excision [8]. Lymphadenectomy is usually not required because these tumors do not show lymph node metastases [8, 11]. However, despite apparently complete resection with clear margins, the recurrence rate is high; hepatic or mesenteric recurrence occurs in 40–90% of patients undergoing apparently curative surgery [4, 12]. This may be partly due to tumor rupture leading to mesenteric implants; hence, the risk of recurrence emphasizes the importance of having meticulous surgical technique [11]. For this reason, percutaneous biopsy is best avoided [2].

Radiation therapy and standard chemotherapy have not been found to be successful in treating this disease [4, 13, 14]. Unlike more common breast, lung, and colon cancers, in

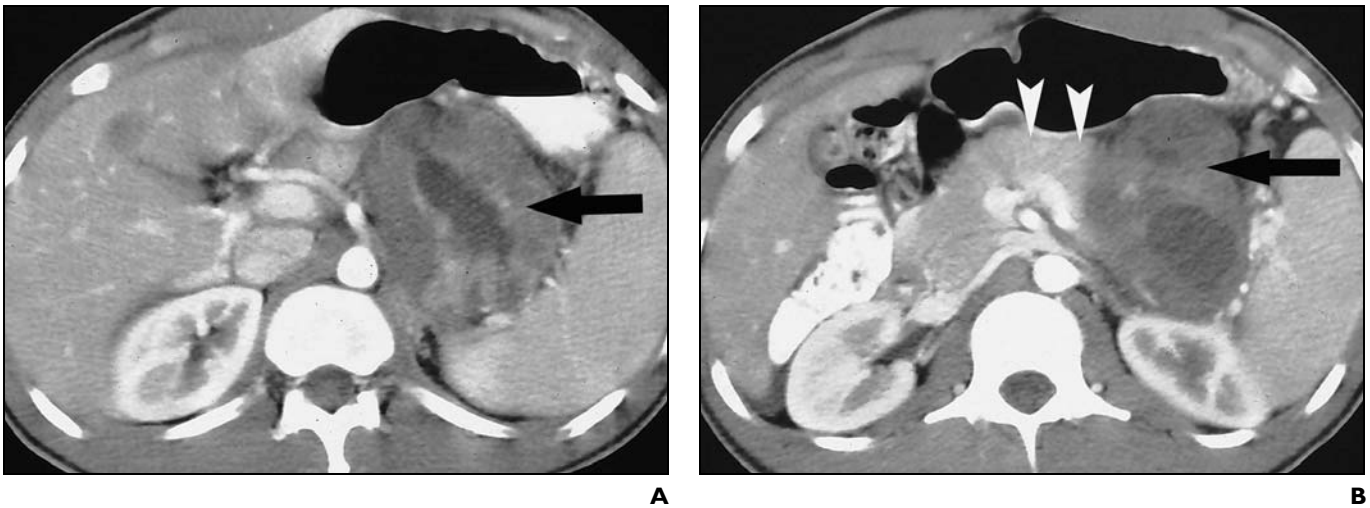


Fig. 6.—30-year-old man with gastric gastrointestinal stromal tumor.
A and **B**, Axial contrast-enhanced CT scan of upper abdomen shows large exophytic and necrotic tumor (*arrow*, **A** and **B**) in region of body and tail of pancreas (*arrowheads*, **B**). This tumor was originally mistaken for infected pancreatic pseudocyst.

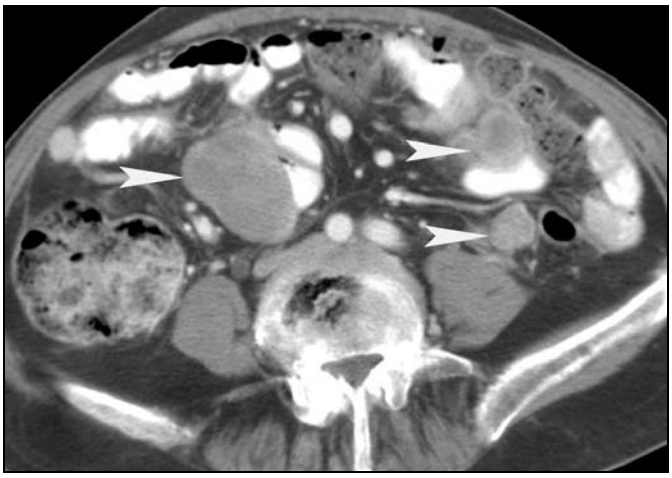


Fig. 7.—76-year-old man with small-bowel gastrointestinal stromal tumor. Axial contrast-enhanced CT scan of pelvis shows smooth mesenteric metastasis (*arrowheads*) at presentation. There is no indrawing or spiculation of mesentery.

which tumor development requires multiple mutations of several genes, GIST occurs because of gain-of-function mutation of a single kit gene found on chromosome 4. The resultant increase in tyrosine kinase activity allows the tumor to grow unchecked. In 1999, a new agent was found to be effective against GIST by selectively inhibiting tyrosine kinase enzyme. This agent was recently approved for clinical use in United States as imatinib mesylate (Gleevec, Novartis) [15]. It is a new breed of targeted molecular therapy that has minimal toxicity. Recent studies report a median disease-free survival rate in malignant nonmetastatic GIST of about 5 years and only 10–20 months if metastases are present [3, 4, 12, 14, 16]. In our experience, nearly all patients with metastatic disease show good response to imatinib therapy, with most being in remission at 24 months.

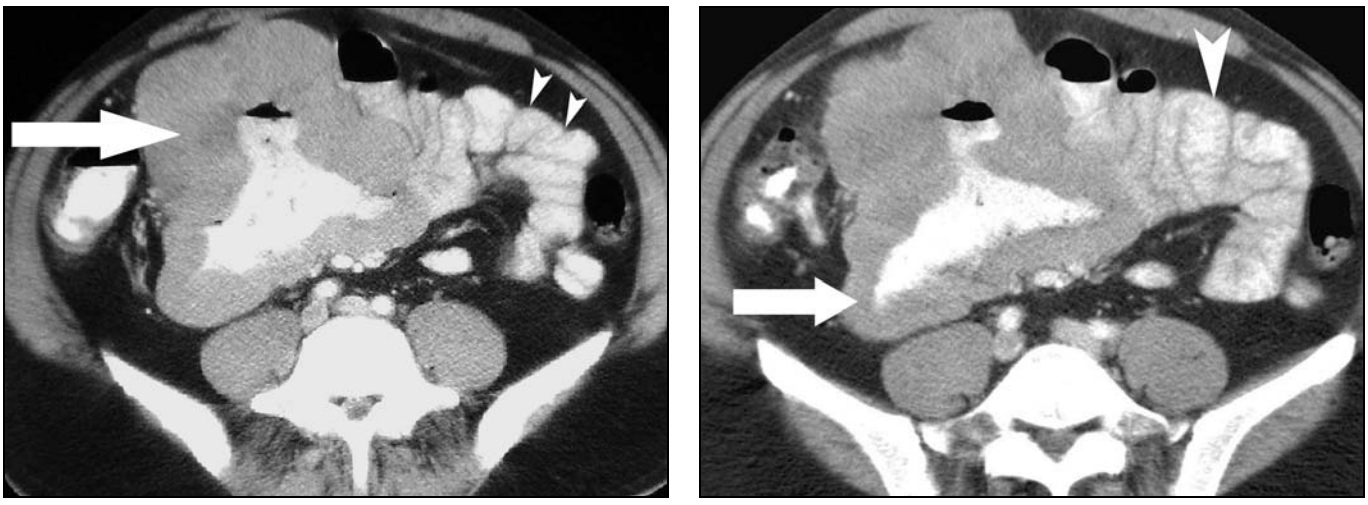
Pathologic Features

Histology

GISTs have a tendency to exophytic growth. They commonly involve the muscularis propria and, in 50% of cases, may show mucosal ulceration [17]. On light microscopy, GIST can simulate leiomyosarcoma, and hence in the past, it was labeled as such. However, the two tumors have different origins; GISTs are thought to originate from a stem cell that normally expresses CD117.

The histologic classification is based on the predominant cell type, either spindle or epithelioid cell [1, 18] (Fig. 1). The former accounts for about 75% of gastric GISTs [19] and is also the most common type of GIST at other sites. Gastric GISTs in the greater curvature have a low malignant potential despite reaching a large size [8]. In general, 20–30% of GISTs are malignant at presentation [1, 20].

It is difficult to predict malignant potential. Features associated with worse prognosis include distal bowel location, tumor size, and high mitotic activity [7]. Tumor necrosis, cystic change, nuclear atypia, tumor vascularity, and degree of staining for CD117 do not reliably indicate the malignant potential of GISTs [8]. Tumor size is the single most predictive factor of metastatic potential [4, 12]; thus, the radiologist has a role in predicting



A **B**

Fig. 8.—45-year-old man with small-bowel gastrointestinal stromal tumor.
A and **B**, Axial contrast-enhanced CT scans of mid abdomen show large mass (*arrow*) arising from small bowel, causing aneurysmal dilatation of bowel. Proximal (*arrowheads*) and distal segments of small bowel were of normal caliber.

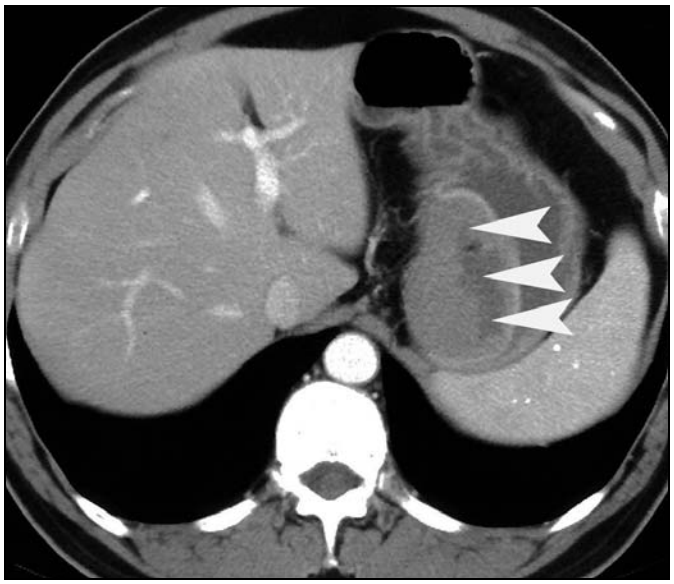


Fig. 9.—54-year-old man with gastric gastrointestinal stromal tumor. Axial contrast-enhanced CT scan of upper abdomen shows area of crescent-shaped necrosis (*arrowheads*) in tumor, "Toricelli-Bernouilli" sign.

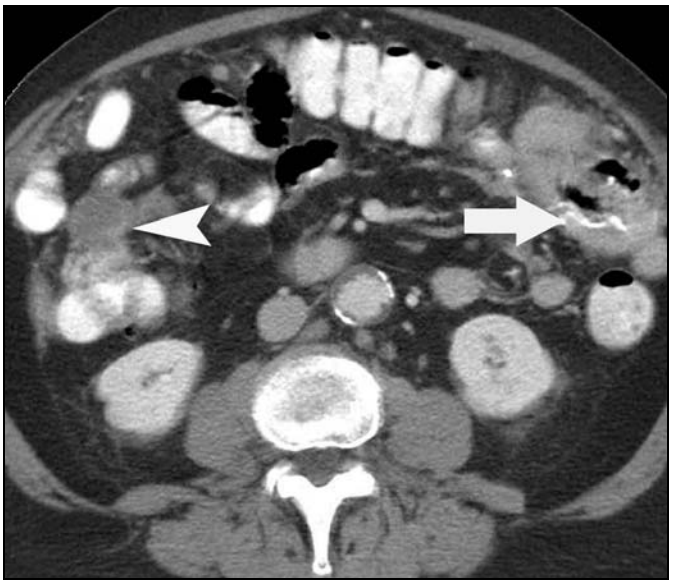


Fig. 10.—76-year-old man with small-bowel gastrointestinal stromal tumor. Axial contrast-enhanced CT scan of mid abdomen shows rounded nodule (*arrowhead*) in mesentery in keeping with metastases. Metastasis is far from site of resected tumor (*arrow*). Note that differentiation from unopacified bowel is difficult and requires meticulous attention.

malignancy. Tumors of less than 2 cm are usually benign, whereas those over 5 cm are usually malignant [11]. However, many pathologists believe that all GISTs will eventually become malignant, and smaller tumors should be classified as at lower risk for malignancy rather than as benign [20].

Immunohistochemistry

Mesenchymal tumors are currently classified not only from their light microscopic appearance but also using immunochemistry. Table 1 shows a simplified version of the current classification. Specific markers for glial tumors include S-100 protein and glial fibrillary acidic protein. For smooth muscle tumors, specific markers include α–smooth muscle antigen and desmin; for fibrous tumors, the specific marker is vimentin. In the future, molecular genetics may help to determine which GISTs will become malignant. In general, certain mutations, such as the gain-of-function mutation in exon 11 of c-kit antigen and an increased number of mutations are associated with malignant potential [7, 8].

Radiologic Features

Tumor at Presentation

At presentation, most GISTs are large, usually between 3 and 10 cm. The predominant pattern seen in our cohort of patients and reported in another radiologic series [21] was a heterogeneously enhancing exophytic mass (Fig. 2). Small gastric GISTs may show intense enhancement with IV contrast administration (Fig. 3); this is a less common finding in the small bowel, probably because enteric tumors are larger and more malignant at presentation [22]. Hemorrhage can be seen in

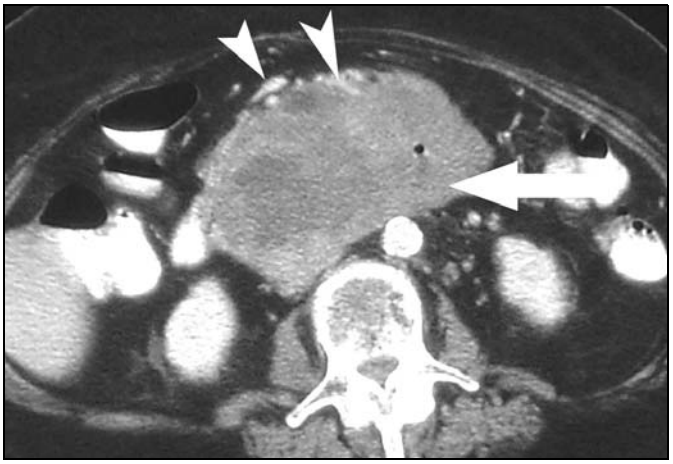


Fig. 11.—75-year-old woman with small-bowel gastrointestinal stromal tumor. Axial contrast-enhanced CT scan of mid abdomen shows large mesenteric mass (*arrow*) growing around mesenteric vessels (*arrowheads*). There is no thrombosis of mesenteric vessels.

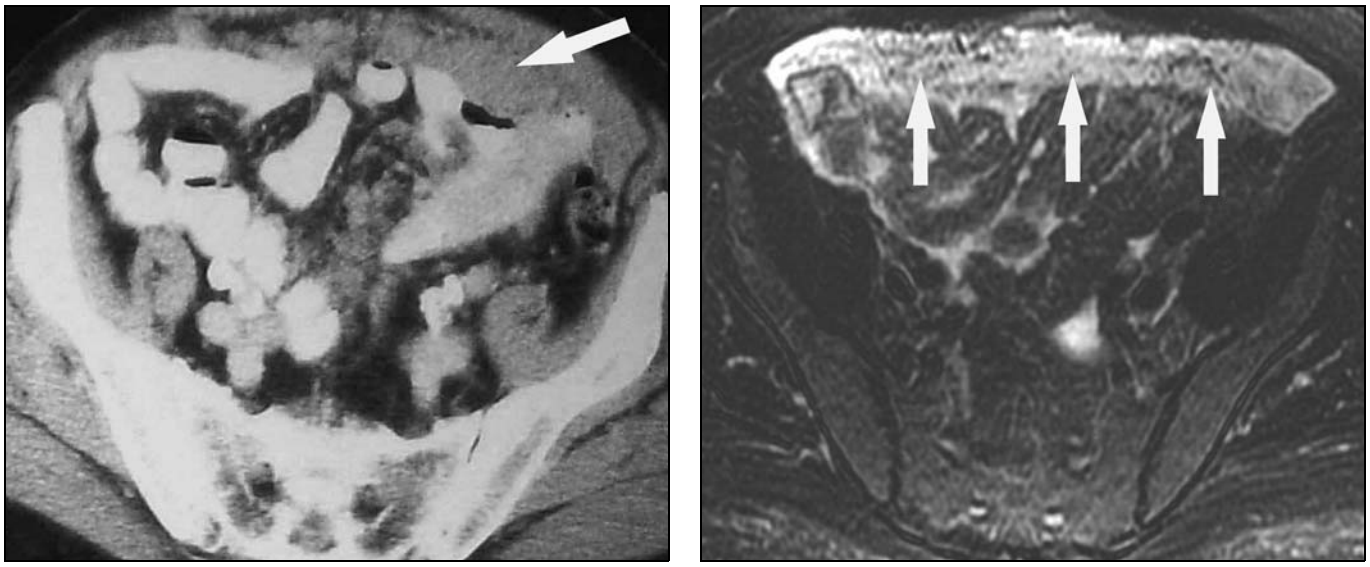


Fig. 12.—76-year-old man with small-bowel gastrointestinal stromal tumor.
A and **B**, Axial contrast-enhanced CT scan (**A**) and axial T2-weighted fat-suppressed fast spin-echo MRI (**B**) of pelvis show omental caking (*arrows*).

larger tumors on unenhanced images. An intraluminal component can occasionally be seen on CT (Fig. 4). Mucosal ulceration occurs in 50% of gastric tumors (Fig. 5) shown by the presence of air or oral contrast material within the mass. Many cases of exophytic gastric GISTs in our series were initially misdiagnosed as a pancreatic mucinous tumor or pseudocyst (Fig. 6).

Unlike adenocarcinoma, GIST does not involve the bowel wall concentrically. As a result bowel obstruction is rare, despite the large size of the GIST. The intraluminal component accounts for a small proportion of tumors. Unlike carcinoid tumors, the primary lesion is large and is the predominant finding. Mesenteric masses at presentation are usually well defined with a smooth surface and do not show spiculation or indrawing of mesentery (Fig. 7). Like lymphoma, GIST can also show aneurysmal dilation of the bowel (Fig. 8). This may be partly because the cavitary nature of these fast-growing tumors allows enlargement of the apparent lumen. The tumors may also damage the myenteric plexus, allowing dilatation of lumen. The cavitation may allow air to collect in the nondependent

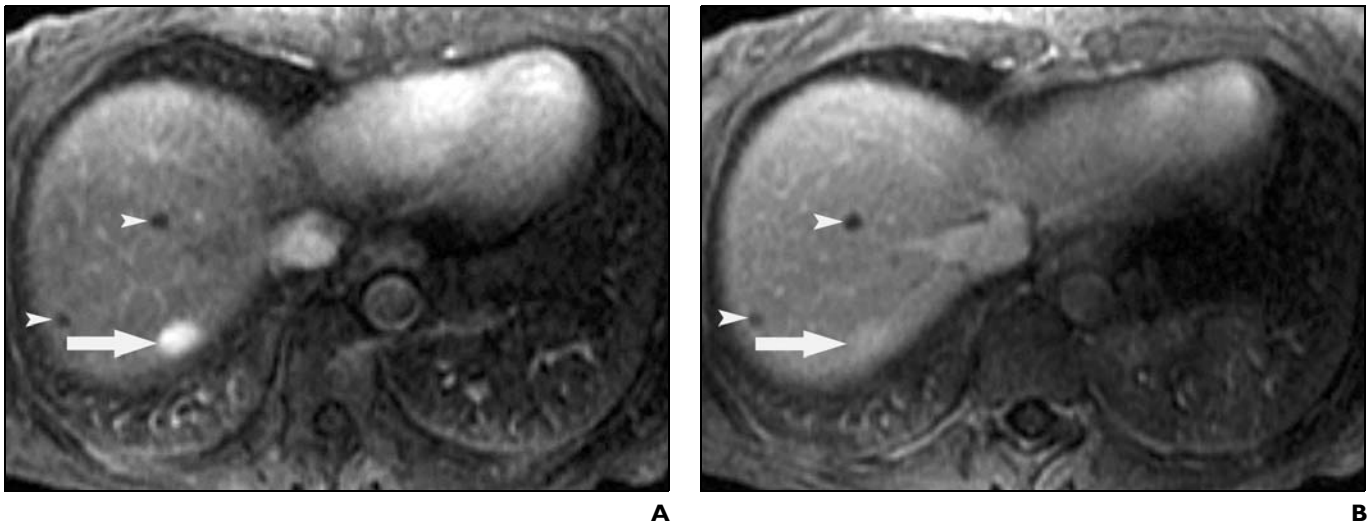


Fig. 13.—78-year-old woman with small-bowel gastrointestinal stromal tumor.
A, Axial breath-hold 3D fat-suppressed gradient-echo MRI of liver with gadolinium shows bright homogenous enhancement of metastasis (*arrow*) in late arterial phase. Smaller hypovascular metastases are also evident (*arrowheads*).
B, In venous phase, MRI of large metastasis shows complete washout of contrast material (*arrow*). Smaller hypovascular metastases are also evident (*arrowheads*).

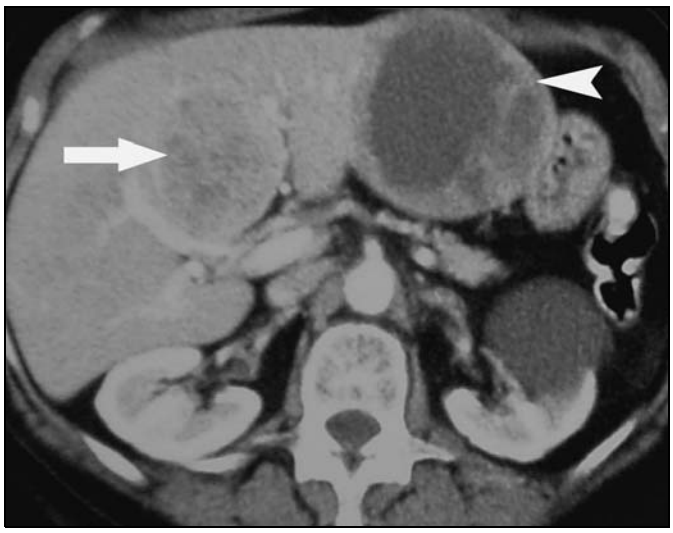


Fig. 14.—50-year-old woman with gastric gastrointestinal stromal tumor. Axial contrast-enhanced CT scan of liver reveals hypovascular (*arrow*) and hypervascular (*arrowhead*) metastases.

aspect of larger tumors, described as the "Toricelli-Bernouilli" crescentic necrosis sign (Fig. 9). Calcification was not seen in any tumor at presentation but was occasionally seen in metastases after specific chemotherapy.

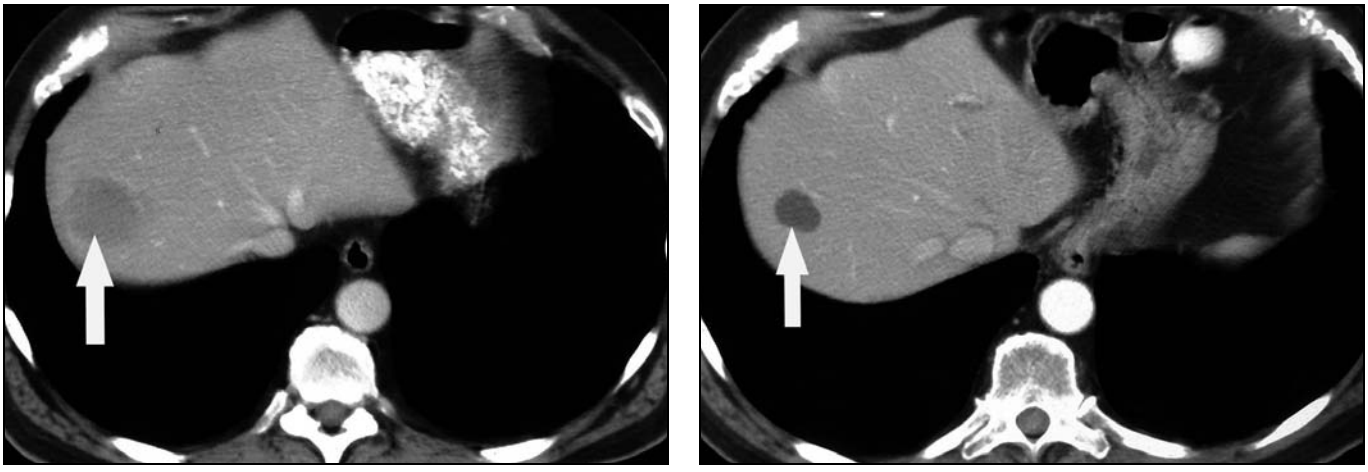
We did not see vascular invasion or venous thrombosis associated with GIST, even if a large tumor was close to mesenteric or splenic veins.

Metastatic Disease

Lymphadenopathy.—Lymph node metastases were not seen in any of our patients; unlike adenocarcinoma or lymphoma, the lymphatic route does not appear to be a common mode of tumor spread. The presence of significant adenopathy should raise the possibility of an alternative diagnosis.

Mesenteric–omental disease.—Mesenteric metastases are common at relapse. These may be related to peritoneal spill of tumor content at surgery. However, they can also be found at presentation in large enteric tumors and, much less commonly, in gastric tumors. Many mesenteric masses have a low-density center, even when the primary tumor is hypervascular. Our experience is that these metastases are missed because they may be small and distant from primary tumor (Fig. 10). Differentiation from unopacified bowel may be difficult, and a meticulous attention to all parts of the mesentery is required. CT is better at depicting mesenteric metastases than MRI. This may partly be due to bowel motion artifact and partly because we did not use oral contrast agents for MRI examinations. Large mesenteric masses may grow around the mesenteric vessels but do not tend to cause distal venous thrombosis (Fig. 11).

Omental disease is seen less frequently than mesenteric disease. Omental masses are usually small (< 2 cm) and homogeneously enhancing. Omental caking was seen in only one of 29 patients (Fig. 12). Because of the mobility of the omentum, some masses may appear in different positions on subsequent



A **B**

Fig. 15.—78-year-old woman with small-bowel gastrointestinal stromal tumor.
A, Axial contrast-enhanced CT scan of liver obtained before treatment shows predominantly low-attenuation metastasis (*arrow*) with hyperdense foci.
B, Axial contrast-enhanced CT scan obtained after treatment with imatinib mesylate (Gleevec, Novartis) shows cystic change in metastasis (*arrow*).

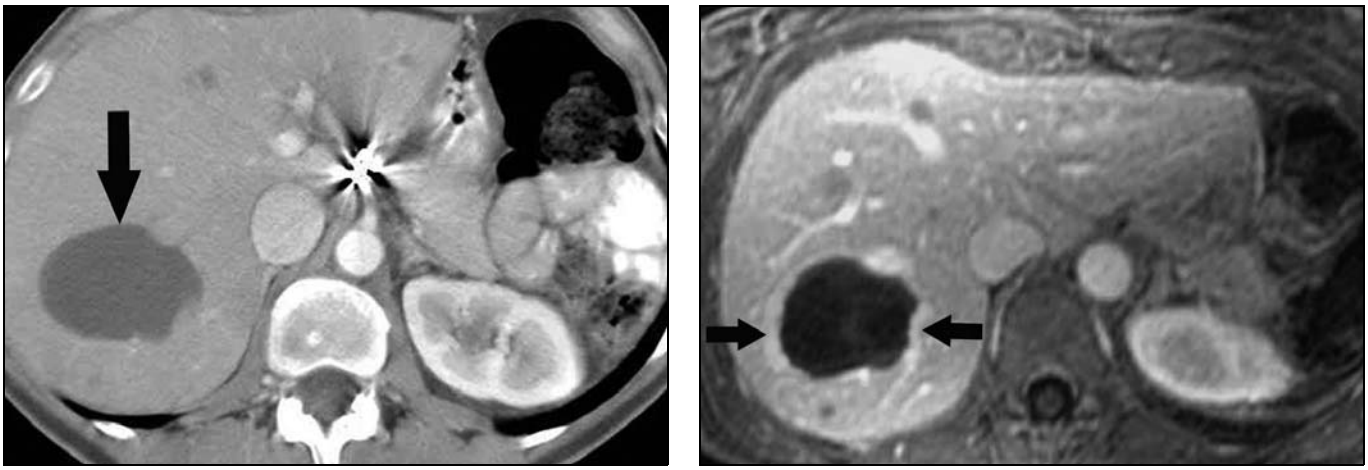


Fig. 16.—50-year-old woman with small-bowel gastrointestinal stromal tumor
A, Axial contrast-enhanced single-phase CT scan of liver shows low-density well-defined cystic mass (*arrow*), which was treated metastasis, simulating simple cyst.
B, Gadolinium-enhanced T1-weighted fat-suppressed gradient-echo image, obtained at same level as **A**, shows peripheral and nodular enhancement (*arrows*) in metastasis. MRI was performed 1 month before CT (**A**). Patient relapsed 2 months later while still on imatinib mesylate (Gleevec, Novartis) therapy.

scans. Despite a high risk of solid mesenteric metastases, ascites is rare and is more likely to be a result of chemotherapy [15].

Liver metastases.—Small liver metastases are usually hypervascular on CT and MRI before chemotherapy. Dual-phase CT or MRI with gadolinium may show bright homogeneous enhancement in the late arterial (portal venous inflow) phase and almost complete washout on the hepatic venous phase (Fig. 13). Consequently, untreated liver metastasis may be missed on a single venous phase CT study. However, not all metastases have similar vascularity. In the same liver, there may be hypo- and hypervascular masses (Fig. 14), possibly indicating different generations of metastases. On MRI, the masses are usually of low or intermediate signal on T1-weighted sequences and marginally bright on T2-weighted sequences. When MRI is used to assess liver metastases, we routinely perform a multiphasic volumetric fat-suppressed gadolinium-enhanced series. Necrosis is common in larger masses. Hemorrhage is rare within the liver metastases but may manifest as increased signal on T1-weighted sequence. Purely cystic metastases are rare before therapy but are a common finding on CT after specific chemotherapy.

Other metastases.—Lung metastases are extremely rare in GIST, even in the presence of extensive liver and peritoneal metastases. This is a major difference in the metastatic pattern between GIST and leiomyosarcoma. It appears that GISTs, unlike leiomyosarcomas [13, 16], preferentially spread via the portal vein. We have not come across brain or bone metastases and are not aware of confirmed reports of these.

Appearance After Therapy

Mesenteric and liver metastatic diseases become hypovascular and, in some cases, completely cystic on CT, even after 1 month of targeted chemotherapy (Fig. 15). This finding has also been reported by others [23]. We have noted that a few patients with apparently completely cystic masses on CT showed subsequent relapse with increase in the size of metastases. Some of these metastases showed enhancement on MRI (Fig. 16). Overall, MRI is likely to be better than single-phase CT in assessing the viability of metastases.

Conclusion

GIST is a new classification for a group of mesenchymal tumors that predominantly exhibit an altered oncogene, kit (CD 117). These tumors are different in behavior and immunology from the better known smooth muscle tumors of the gastrointestinal tract. Specific molecular therapy, with imatinib mesylate, is now available. Radiologists can often predict the correct diagnosis at presentation by the appearances of a large exophytic bowel mass, which may show necrosis or hemorrhage. Hypervascular liver metastases and smooth low-density mesenteric masses suggest metastatic disease. Adenopathy, concentric bowel involvement, large-volume ascites, and spiculated mesenteric masses suggest an alternative diagnosis. The radiologic appearances can change drastically after therapy. Previously solid hypervascular masses may become completely cystic on CT even within 1 month of treatment. MRI can better evaluate liver metastases than CT. However, CT is superior in detecting mesenteric metastases.

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