Gastrointestinal Stromal Tumors

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KEYWORDS

• GIST • Leiomyoma • Leiomyosarcoma • Leiomyoblastoma
• Stromal tumors mesenchymal neoplasm

KEY POINTS

- What is now known as gastrointestinal stromal tumor (GIST) used to be called as gastrointestinal (GI) smooth muscle tumor: leiomyoma if benign, leiomyosarcoma if malignant, and leiomyoblastoma if with epithelioid histology.
- GISTs typically occur in older adults, and the median patient age in the major series has varied between 60 and 65 years although are rarely seen in children and young adults.
- Most GISTs, approximately 85% to –90%, contain oncogenic KIT or platelet-derived growth factor receptor alpha mutations. However, loss of function of succinate dehydrogenase complex has been identified as alternative pathogenesis, especially in GISTs in young patients.
- Most common clinical symptoms of GIST are GI bleeding and gastric discomfort or ulcer-like symptoms.
- Wedge resection is the most common surgery for a small-sized to medium-sized gastric GIST, and sufficient margins can usually be obtained.

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the gastrointestinal (GI) tract. Soon after GIST was recognized as a tumor driven by a KIT or platelet-derived growth factor receptor alpha (PDGFRA) mutation, it became the first solid tumor target for tyrosine kinase inhibitor therapies. More recently, alternative molecular mechanisms for GIST pathogenesis have been discovered. These are related to deficiencies in the succinate dehydrogenase (SDH) complex, neurofibromatosis type 1 (NF1) gene alterations in connection with NF1 tumor syndrome, and mutational activation of the BRAF oncogene in very rare cases.

Clinically GISTs are diverse. They can involve almost any segment of the GI tract, from distal esophagus to anus, although the stomach is the most common site. From an oncologic perspective, GIST varies from a small, harmless tumor nodule to a metastasizing and life-threatening sarcoma. This article presents the clinical, pathologic, prognostic, and to some degree, oncological aspects of GISTs with attention to their clinicopathologic variants related to tumor site and pathogenesis.

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HISTORY OF GIST AND TERMINOLOGY

What is now known as GIST, used to be called GI smooth muscle tumor: leiomyoma if benign, leiomyosarcoma if malignant, and leiomyoblastoma if with epithelioid histology. Tumors previously classified as GI autonomic nerve tumors have also turned out to be GISTs, as have many tumors historically classified as GI schwannomas or other nerve sheath tumors.

Electron microscopic studies from the late 1960s and on demonstrated that most of the "GI smooth muscle tumors" differed from typical smooth muscle tumors by their lack of smooth muscle–specific ultrastructure.[1] Immunohistochemically they lacked smooth muscle antigens, especially desmin.[2] As they also lacked Schwann cell features, GIST was then proposed as a histogenetically noncommittal term for these tumors.[3] The discovery of KIT expression and gain-of-function KIT mutations in GIST in 1998 was the basis of the modern concept of GIST – a generally KIT positive and KIT mutation-driven mesenchymal neoplasm specific to the GI tract.[4,5]

EPIDEMIOLOGY OF GIST

GIST, once considered an obscure tumor, is now known to occur with an incidence of at least 14 to 20 per million, by population-based studies from northern Europe.[6,7] These estimates represent the minimum incidence, as subclinical GISTs are much more common. In an US study, 10% of well-studied resection specimens of gastro-esophageal cancer harbored a small incidental GIST in the proximal stomach.[8] An autopsy study from Germany also found a 25% incidence of small gastric GISTs.[9]

GISTs typically occur in older adults, and the median patient age in the major series has varied between 60 and 65 years. GISTs are relatively rare under the age of 40 years, and only less than 1% occurs below age 21. Some series have shown a mild male predominance. Over half of the GISTs occur in the stomach. Approximately 30% of GISTs are detected in the jejunum or ileum, 5% in the duodenum, 5% in the rectum, and less than 1% in the esophagus. Based on our review of Armed Forces Institute of Pathology (AFIP) cases, as many as 10% of all GISTs are detected as advanced, disseminated abdominal tumors whose exact origin is difficult to determine.

Despite occasional reports to the contrary, the authors do not believe that GISTs primarily occur in parenchymal organs outside the GI tract at sites such as the pancreas, liver, and gallbladder. At the 2 first mentioned organs, GISTs are metastatic or direct extensions from gastric or duodenal or other intestinal primary tumors. The authors are skeptical about primary GISTs in the gallbladder and note that the reported evidence for this diagnosis is tenuous and that molecular genetic documentation is absent.[10,11] Furthermore, review of all gallbladder sarcomas in the AFIP failed to find any GISTs.[12] Similarly, GISTs diagnosed in prostate biopsies are of rectal or other GI and not prostatic origin.[13]

GIST IS PHENOTYPICALLY RELATED TO GI CAJAL CELLS

Almost all GISTs express the KIT receptor tyrosine kinase, similar to the GI Cajal cells that regulate the GI autonomic nerve system and peristalsis.[14] These cells have a stem cell–like character, as demonstrated by their ability to transdifferentiate into smooth muscle.[15] KIT-deficient mice lack GI Cajal cells and those with introduced KIT-activating mutations develop Cajal cell hyperplasia and GISTs, supporting the role of Cajal cells in GIST oncogenesis.[16]