New issues in gastrointestinal stromal tumors of the stomach

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Abstract

Gastrointestinal stromal tumors (GISTs) constitute the majority of mesenchymal tumors of the gastrointestinal tract. The activating mutations in the receptor tyrosine kinases KIT and PDFRA are key molecular changes in the pathogenesis of these tumors and their recognition has led to the development of targeted therapies. Approximately 10% of GISTs, referred to as wild-type, lack such mutations and respond poorly to treatment with tyrosine kinase inhibitors. These GISTs are almost exclusive to the stomach and include primarily tumors that occur in children and tumors that are part of several tumor syndromes. Recent studies have shown that most wild-type GISTs are succinate dehydrogenase deficient. This review summarizes current advances in the molecular biology of GISTs and discusses the clinical and pathologic features associated with different genotypes.

Keywords gastrointestinal stromal tumor; immunohistochemistry; KIT; PDGFRA; SDHB; succinate dehydrogenase

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the GI tract with an annual incidence of 10–15 per 1,000,000. Once a group of poorly characterized spindle cell tumors with unpredictable clinical behavior, they have emerged as a well-defined, prognosticated entity and a model of targeted molecular therapy. Stomach (60%) and ileum/jejunum (30%) are the primary locations for the vast majority of GISTs. They are uncommonly encountered in the duodenum, colon, rectum, and esophagus. They are believed to have a common cell lineage with the interstitial pacemaker cells of Cajal. Morphologically and biologically, GISTs form a continuum from incidental minute benign spindle cell nodules to aggressive sarcomas. However, most GISTs, especially those in the stomach, are benign. About 30% of GISTs behave in malignant fashion. Their metastatic pattern is predominantly intra-abdominal with spread within the peritoneal cavity and to the liver. Metastases to lymph nodes are uncommon except in specific subsets of patients. Seventy per cent of GISTs are categorized as having spindle cell morphology, 20% are epithelioid, and the remaining 10% are mixed. The majority of GISTs are sporadic with the median age at diagnosis around 60. GISTs in children and young adults have unique clinicopathologic characteristics and are often part of familial syndromes.

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KIT and *PDGFR* mutations

Mutations in receptor tyrosine kinase (RTK) genes, *KIT* and the homologous *platelet-derived growth factor receptor α* (*PDGFRA*) are considered to be key events in GIST pathogenesis. This characteristic has been successfully exploited in the use of RTK inhibitors such as imatinib in the treatment of GISTs. Both KIT and PDGFRA belong to the type III receptor tyrosine kinase family and have similar structure with an extracellular ligand-binding domain, transmembrane domain, juxtamembrane domain, and a cytoplasmic kinase domain. Ligand binding results in receptor dimerization and phosphorylation-dependent signal transduction. Oncogenic mutations cause ligand-independent kinase activation. Eighty per cent of GISTs are mutant for *KIT* while 10% are mutant for *PDGFRA*, and the occurrence of these mutations is mutually exclusive. There are clinical and pathologic differences among GISTs with different types of *KIT* and *PDGFRA* mutations as well as differences in the relative frequencies of different mutations.[1]

The most common KIT mutation, present in 40–60% of GISTs, is in exon 11, which encodes part of the juxtamembrane domain. Exon 11 alterations are found in GISTs from all locations in the GI tract. These are varied in type and complexity and include deletions, insertions, and substitutions. Deletions are associated with worse clinical outcomes and malignant behavior. Another 10–20% of *KIT* mutations are in exon 9, which encodes the extracellular domain. Tumors with exon 9 mutations are less sensitive to imatinib treatment and occur in the small and large intestine with only rare examples in the stomach. Mutations in exon 17, which encodes the activation loop of the kinase domain, and exon 13, which encodes the ATP-binding region of the kinase domain, are rare. They tend to occur in the small intestine and have spindle cell morphology. Typically, untreated GISTs are heterozygous for a given mutation. It has been shown that the remaining wild-type *KIT* allele may be lost in some instances of tumor progression and malignant behavior.[2]

PDGFRA-mutant GISTs most often harbor mutations in exon 18, which encodes the activating loop. In particular, exon 18 D842V missense mutation has been identified as the most common *PDGFRA* mutation. Mutations in exons 12 and 14, affecting the juxtamembrane domain and the ATP-binding domain, are less common. As a group, *PDGFRA*-mutant GISTs are associated with a lower malignant potential than *KIT*-mutant GISTs, and no significant clinical differences have been detected among different *PDGFRA* mutations.

Histopathology of GISTs

GISTs vary greatly in size from a few millimeters to more than 30 cm, with the median size between 5 and 8 cm. The stomach is the commonest location, particularly the gastric body. In the small bowel, GISTs are most common in the jejunum. GISTs have exophytic growth, and small tumors confined to the submucosa and muscularis propria may protrude into the lumen while large ones project from the serosal surface into abdominal cavity displacing other organs. Some tumors are attached to the serosal surface by a narrow pedicle. GISTs are circumscribed

rather than infiltrative, even when they are malignant. Cut surfaces vary from firm and fibrous to fleshy and gelatinous. Large tumors may have hemorrhage and cystic degeneration with only a thin rim or viable tumor remaining. A rare subset of GISTs are extragastrointestinal and present as primary tumors in the omentum, mesentery, and retroperitoneum.

GISTs have two main morphologies, spindle cell and epithelioid. Spindle cell tumors are composed of fascicles of uniform bland spindle cells with fibrillar eosinophilic cytoplasm and indistinct cell borders. They have elongated nuclei with vesicular chromatin and inconspicuous nucleoli. Gastric spindle cell tumors have several characteristic histologic features. Many of them may have paranuclear vacuoles which are thought to be a diagnostically helpful fixation artifact. Gastric spindle cell GISTs also tend to form nuclear palisades. A unique feature of small bowel GISTs is skenoid fibers, which are collections of extracellular collagen present only in benign tumors. Nuclear atypia is uncommon in spindle cell tumors unless the tumor is frankly sarcomatous. Pure epithelioid morphology is found mostly in gastric tumors. Epithelioid GISTs have rounded nuclei with pale eosinophilic or clear cytoplasm. Some tumors have distinct cell borders while others have a syncytial pattern. Some epithelioid GISTs may have myxoid stroma and nuclear atypia. Both spindle cell and epithelioid tumors may be paucicellular with stromal sclerosis. Hypercellularity in both types correlates with malignant clinical behavior as does a frankly sarcomatous appearance. *KIT*-mutant gastric GISTs are predominantly spindle cell.[3]

Over 90% of GISTs, including virtually all *KIT*-mutant tumors, have KIT protein expression that can be detected by immunohistochemistry. The antibody labeling most often shows a diffuse cytoplasmic pattern. Other less common patterns are membranous and perinuclear dot-like (Golgi). Most of the small number of GISTs that do not stain with KIT antibodies have no detectable *KIT* mutations and instead harbor mutation in *PDFRA*. These tumors tend to be epithelioid and have stromal sclerosis. The remaining KIT-negative GISTs do not have mutations in either *KIT* or *PDFRA* and belong to the group of wild-type GISTs (see below). DOG1 is a newer highly specific GIST marker that is a chloride channel protein highly expressed in GISTs. DOG1 antibody has strong cytoplasmic and membranous staining in over 95% of GISTs. CD34 is commonly present in GISTs but is less specific than KIT or DOG1. Smooth muscle actin and muscle-specific actin can be variably expressed in GISTs, but desmin expression is rare.

GISTs that harbor mutations in *PDGFRA* differ from the majority of GISTs with *KIT* mutations. Nearly all *PDGFRA*-mutant GISTs arise in the stomach and have purely or predominantly epithelioid morphology. Other distinguishing morphologic features are prominent myxoid change, frequent rhabdoid forms, and binucleate and multinucleated tumor giant cells.[4,5] A quarter of *PDGFRA*-mutant GISTs are either negative or exhibit limited immunoreactivity for KIT. In contrast, *PDGFRA*-mutant GISTs are consistently immunoreactive with anti-PDGFRA antibody[6,7] (Figure 1). This feature may be useful in overcoming diagnostic uncertainty in GISTs with weak or absent KIT protein expression.

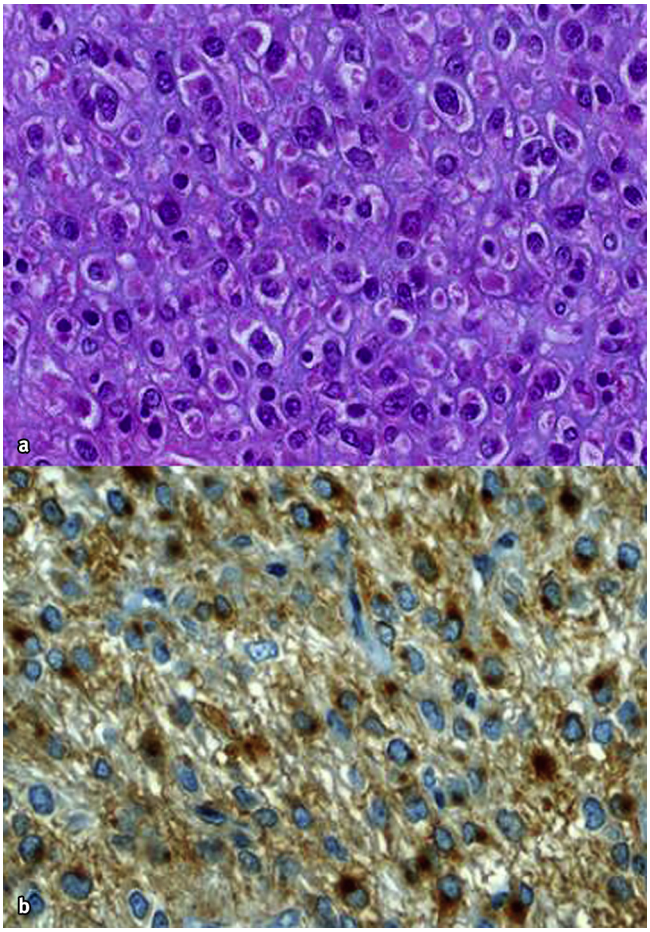

Figure 1 *PDGFRA*-mutant GIST. (**a**): Characteristic morphologic features of a *PDFRA*-mutant GIST tumor include epithelioid cells with cytoplasmic clearing and distinct cell borders. Binucleate forms are common. (**b**): Immunostain with anti-PDGFRA antibody has Golgi-type perinuclear dot pattern in addition to weaker cytoplasmic staining. Reproduced by kind permission from International Journal of Clinical and Experimental Pathology, "Value of epithelioid morphology and PDGFRA immunostaining pattern for prediction of PDGFRA mutated genotype in gastrointestinal stromal tumors (GISTs)" by Agaimy et al. 2013; 6(9):1839—1846.

Wild-type GISTs

Up to 15% of GISTs do not contain *KIT* or *PDGFRA* mutations and have been referred to as 'wild-type' GISTs. Interestingly, the proportion of such 'wild-type' GISTs is vastly greater in children and young adults, comprising 90 % of pediatric GISTs. Historically, these tumors have been characterized by poor response to imatinib treatment. They include both sporadic tumors and those arising in the setting of two hereditary syndromes, Carney—Stratakis dyad and neurofibromatosis type 1 (NF1), and the non-hereditary Carney triad. Recent studies have shown that a large subset of these so-called 'wild-type' GISTs are succinate dehydrogenase (SDH)-deficient, further discussed below. Rare BRAF-mutant GISTs also belong to the 'wild-type' category as do the remaining small proportion of GISTs without any known molecular defects.

Familial and syndromic GISTs

There is a hereditary predisposition to GISTs in families with a germline *KIT* or *PDGFRA* mutations but these families are rare. Less than 25 families have been identified in the published literature to date.[8,9] The pattern of in heritance is autosomal