Review

Gastrointestinal Stromal Tumors: Clinicopathology and Advances in Molecular Pathogenesis

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Gastrointestinal stromal tumors (GISTs) are common mesenchymal neoplasms in the gastrointestinal (GI) tract that need to be differentiated from other GI mesenchymal tumors. They often present with heterogeneous features based on the anatomic locations, histomorphology and gene mutation status, which may lead to diagnostic and treatment challenges. Over the past decade, numerous studies revealed that KIT and PDGFRα tyrosine kinase pathways play key roles in the molecular pathogenesis of GISTs. Subsequently, specific biomarkers, such as CD117 and DOG1, have been developed and greatly improved the diagnostic accuracy. Moreover, advances in understanding the molecular nature of GISTs also provide valuable therapeutic targets. Two tyrosine kinase inhibitors, Imatinib and Sunitinib, have currently been approved for treating patients with advanced and metastatic GISTs.
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INTRODUCTION

Gastrointestinal stromal/mesenchymal neoplasms are often divided broadly into two major groups. The more common one consists of tumors that are referred to as gastrointestinal stromal tumors (GISTs). The less common group consists of a variety of GI tract stromal neoplasms that are histologically identical to their soft tissue counterparts, including smooth muscle cell tumor, schwannoma, fibromatosis, lipoma, hemanigoma, and peripheral nerve sheath tumors.

GISTs most occur in older individuals with no apparent gender predilection. Although GISTs do occur in children, their pathogenesis and clinical behavior are quite different, and are usually considered as a separated clinicopathological entity. Epidemiologic studies suggested that there are approximately 4000-6000 new GIST cases in United States annually. Most GISTs are sporadic, but about 5% of them are associated with tumor syndromes, such as Neurofibromatosis 1, Carney's triad and familial GISTs.

Over the past decade, significant advances have been made in the molecular pathogenesis of GISTs. These progresses not only greatly improved the diagnostic accuracy but also present specific therapeutic targets. Here we provide an overview of the key clinicopathologic and immunohistochemical features of GISTs and the differential diagnoses from other gastrointestinal mesenchymal tumors. In addition, we discuss the advances in the molecular pathogenesis of GISTs and the developments in targeted therapy.

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CLINICOPATHOLOGICAL FEATURES OF GISTS

Most GISTs are well circumscribed tumors within the gastrointestinal wall. Stomach is the most common location for GISTs (40-60%), followed by jejunum and ileum (25-30%), duodenum (5 %), colo-rectum (5-15%).[1-4] Rarely, tumors arise in esophagus, and other extra-gastrointestinal sites, such as retroperitoneum, mesentery and omentum, have been reported.[5-7]

Histologically, GISTs range from predominantly spindle cell to epithelioid cell type. A small subset GISTs have mixed cellular morphology. GISTs of the spindle cell type are composed of relatively uniform eosinophilic cells arranged in short fascicles or whorls (**Figure 1A**). Epithelioid cell type GISTs are composed of rounded cells with eosinophilic or clear cytoplasm (**Figure 1B**).[8] GISTs of the mixed type may have areas of abrupt transition between spindle and epithelioid areas or complex intermingling of both cell types throughout. In general, GISTs tend to have bland cytological features. However, the morphological feature alone cannot fully predict the clinical behavior. Typical malignant presentations include recurrent at the resection site, metastasizing to liver and/or abdominal cavity. Lymph node and extra-abdominal involvements are uncommon.[4]

Based on a long term follow up study, a current consensus was established which considers both tumor parameters (mitotic index, tumor size) and tumor anatomic location as risk predictors for malignant behavior (summarized in **Table 2**).[9] A revised NIH consensus criteria proposed inclusion of additional prognostic factors such as tumor rupture.[10] The 7th edition of cancer staging manual published a TNM staging system for GISTs developed by American Joint Committee on Cancer (AJCC) and International Union Against Cancer

(UICC).[11] However, the mitotic counting needs to be standardized. Moreover, whether to include GISTs with virtually no progression risk in the TNM system is still controversial.[12]

The term of stromal tumor was introduced in 1983 by Mazur and Clark after revealing that these tumors are different from smooth muscle.[13] Up to mid 1990's, the immunophenotype of GISTs was not well characterized. Immunoreactivity for CD34 is positive in about 70% of the GISTs.[14] The discovery of CD117 (c-KIT) expression in GIST provide a specific and sensitive immunohistochemical marker in differentiating GISTs from other gastrointestinal (GI) mesenchymal tumors. CD117 is seen in about 95% of the GISTs and most demonstrate strong and diffuse cytoplasmic expression (**Figure 2B**).[15-16] Other expression patterns, such as perinuclear dot-like staining, or membranous staining, are also observed. In 30-40% of the cases, smooth muscle actin may also show positive staining. However, the entrapped smooth muscle cells from the gastrointestinal wall need to be excluded. In rare occasion, S100 and desmin may also show focal and weak immune reactivity (**Figures 2A-2D**).[8]

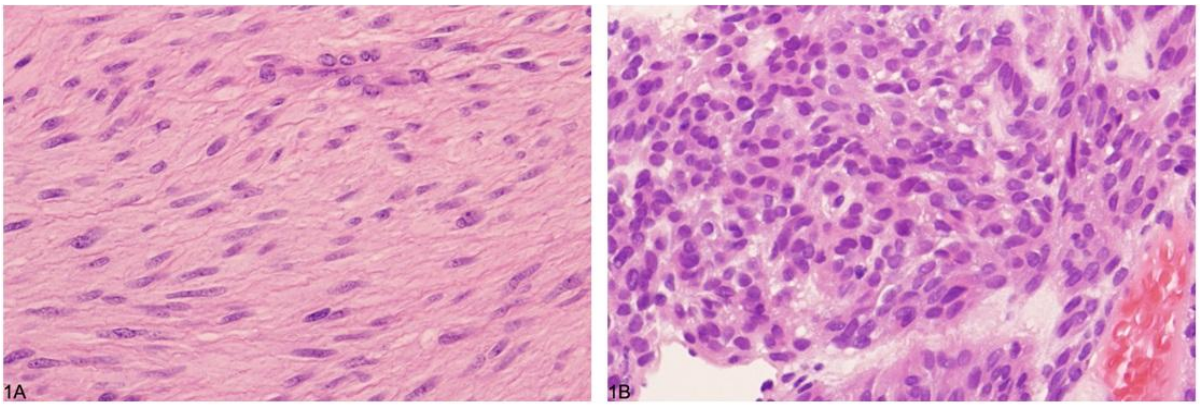

Figure 1. Histological features of GIST. 1A. spindle cell GIST with fascicles of uniform bland cells (40X). B. Epithelioid GIST. (40X)

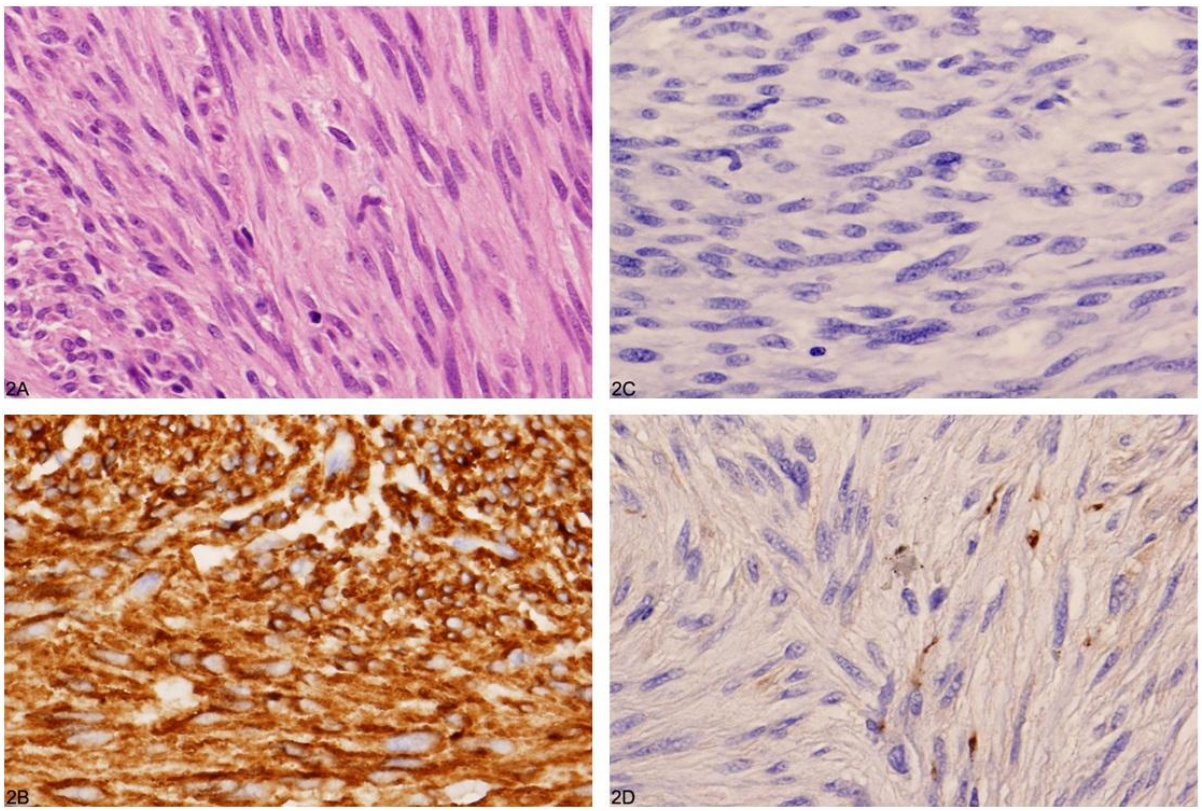

Figure 2. Typical morphological and immunohistochemical features of a gastric GIST (40X). A. H and E; B. CD117; C. Smooth muscle actin; D. S100.

About 5% KIT-negative GISTs may present as a diagnostic challenge. Several new markers discovered on tissue microarray were subsequently studied. The most well characterized one is Discovered on GIST-1 (DOG1).[17] DOG1 (also known as ANO1, TMEM16A) gene locates on chromosome 11 and encodes a calcium dependent chloride channel that has eight transmembrane domains.[18-20] DOG1 antibodies were developed and they are able to detect most KIT-positive GISTs as well as a subset of the KIT-negative GISTs, thus improves diagnostic accuracy, especially in KIT-negative GISTs. Other markers such as protein kinase C-theta (PKC-θ) and carbonic anhydrase II (CAII) have also been investigated for their utility as potential diagnosis and prognosis markers.[21-24]

Table 1. Immunohistochemical markers aid the differential diagnosis of GISTs and other gastrointestinal tract neoplasms. SMA: smooth muscle actin.

	GIST	Leiomyoma/ leimyosarcoma	Schwannoma	Fibromatosis	Melanoma
CD117	+	-	-	-	+
CD34	+	-	-	-	-
SMA	+/-	+	-	+/-	-
Desmin	-	+	-	-	-
S100	-	-	+	-	+
Other specific marker	DOG1			β-catenin (nuclear)	MelanA HMB45

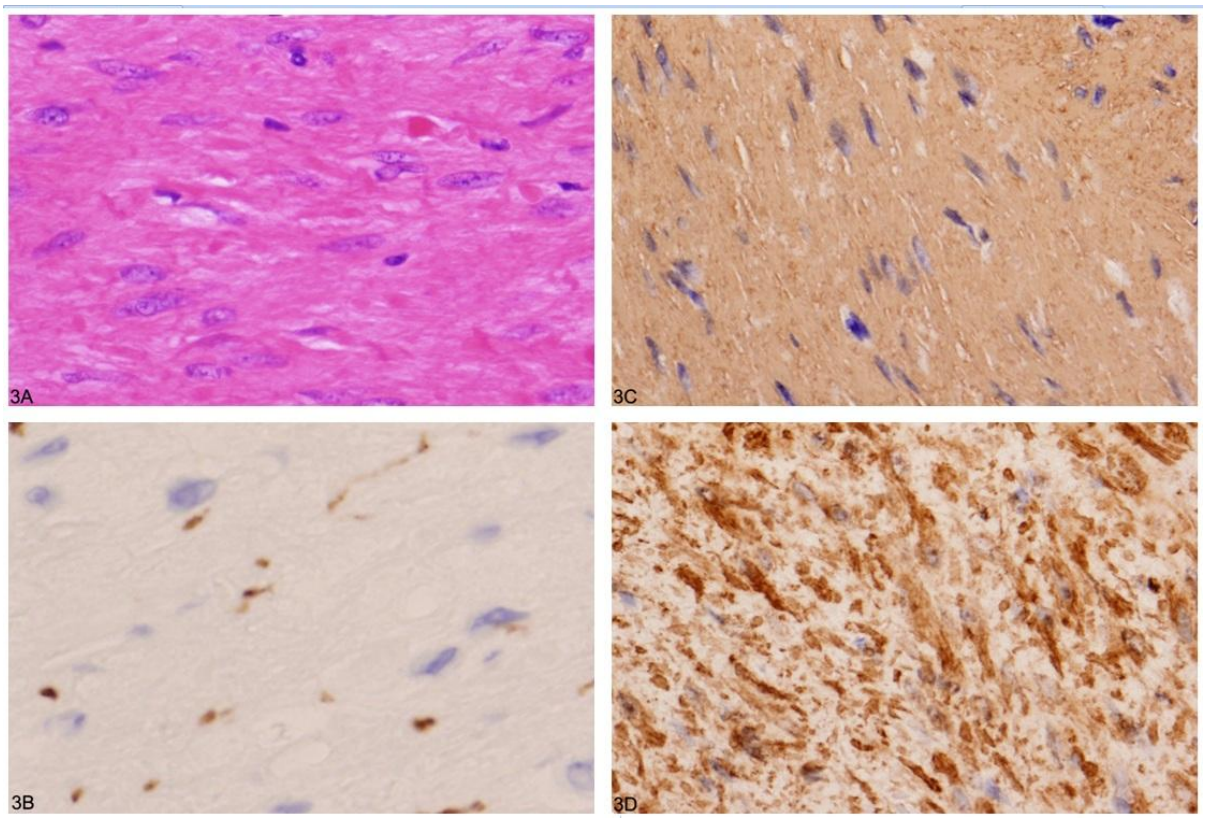

Figure 3. Morphological and immunohistochemical features of a gastric leiomyoma (40X). A. H and E; B. CD117; C. Smooth muscle actin; D. Desmin.

MORPHOLOGICAL MIMICKERS OF GISTS

GISTs have a spectrum of histological features and need to be distinguished from other GI mesenchymal tumors, such as leiomyoma, leiomyosarcoma, schwannoma, inflammatory myofibroblastic tumor, and fibromatosis. Occasionally, epithelioid GISTs may also mimic melanoma and sarcoma thus demanding differential diagnosis (**Table 1**). Leiomyomas in the GI tract commonly have a similar morphologic appearance as leiomyomas in other locations. They are usually small and well circumscribed and usually arise from the muscularis mucosae. Microscopically, leiomyomas are typically composed of fascicles of benign-appearing spindle cells with rare nuclear atypia and mitoses. The cellularity is usually low. Tumor cells often have cigar shaped nuclei and abundant, eosinophilic cytoplasm (**Figure 3A**). Leiomyosarcoma is a rare malignant smooth muscle cell tumor in the GI tract. The cells are mostly high grade with prominent nuclear atypia and mitoses.

Immunohistochemically, both leiomyomas and leimyosarcomas are positive for smooth muscle actin and desmin, and are negative (or show very weak non-specific focal staining) for CD117 (**Figures 3A-3D** and data not shown).[9,25] CD34 stain is negative for both leiomyomas and leimyosarcomas (data not shown).[9,25]

Gastrointestinal schwannomas are rare tumors that occur in stomach or colon in older adults.[9,26-27] They are relatively small intramural tumors that may be surrounded by peripheral lymphocytic cuff. The tumors are composed of bundles of spindle cells with low mitotic activity and focal atypia, and are often intermingled with fibrovascular septa. They often lack the nuclear palisading and Verocay bodies, which are typical of schwannoma in other locations. Tumor cells are S100 and GFAP positive, and SMA and CD117 negative (**Figures 4A-4D**).

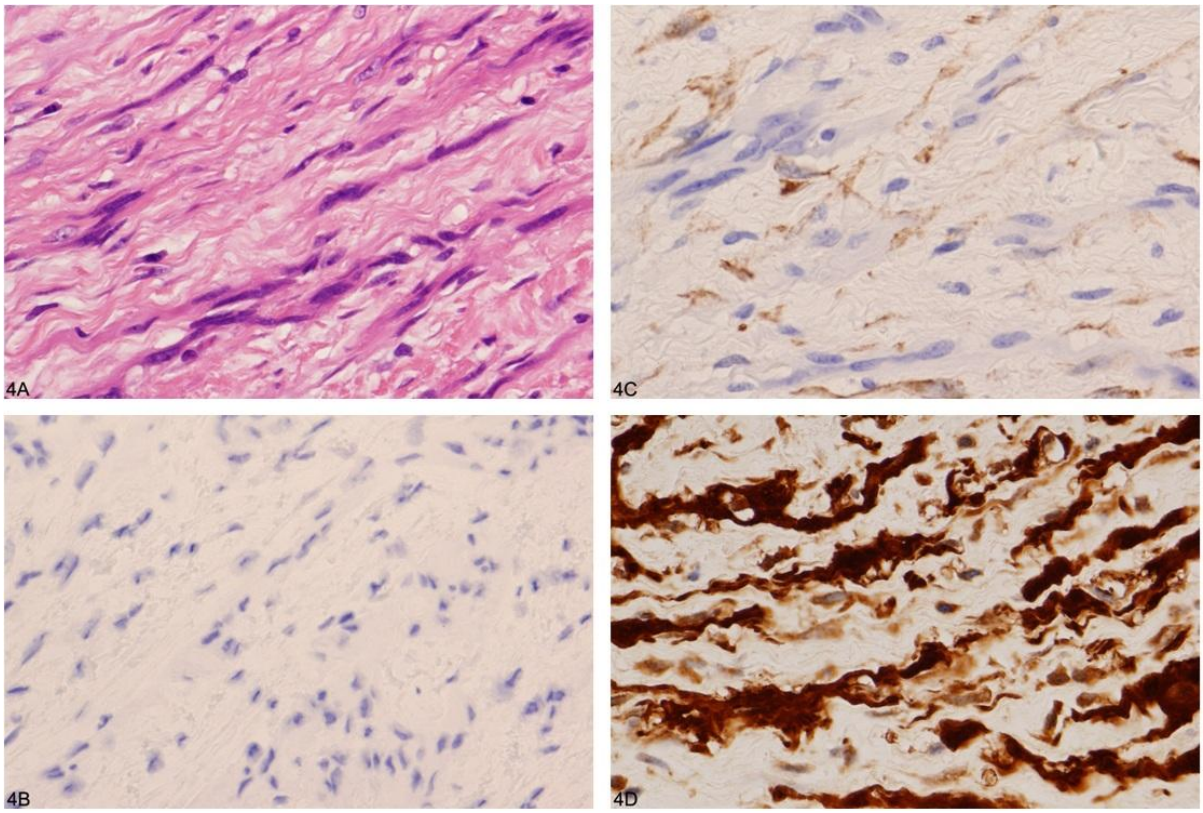

Figure 4. Morphological and immunohistochemical features of a gastric schwannoma (40X). A. H and E; B. CD117; C. Smooth muscle actin; D. S100.

Intra-abdominal inflammatory myofibroblastic tumors are often present as mesenteric masses in children and young adults. Histologically, these tumors are composed of spindled cells intermingled with lymphoplasmacytic infiltration and fibrotic streaks. The tumor cells are negative for CD117 and CD34, but can be positive for smooth muscle actin. Translocation involving ALK gene in chromosome 2p23 that activating the anaplastic lymphoma kinase (ALK) expression is the main pathogenetic event. Positive cytoplasmic ALK staining is regarded as an important diagnostic marker.[28]

Fibromatosis in the GI tract occurs sporadically or in connection with Gardner syndrome. Histologically, the tumor is rich in collagen with mildly dilated prominent vessels. Immunohistochemical demonstration of nuclear beta-catenin positivity may be helpful in diagnosis.[29]

Hemangiopericytomas are intermediate sarcoma that primarily occurs in deep soft tissue particularly at pelvic retroperitoneum, but also in the limb as well as head and neck. Tumors consist of numerous vascular channels with plump endothelial nuclei and surrounding oval and spindled cells that resemble the cellular area of solitary fibrous tumor. They are usually immunoreactive for CD99 and CD34, and negative for CD117, smooth muscle actin and desmin (**Figures 5A-5D**).

Melanoma in the GI tract is uncommon. They may exhibit spectrum of morphology and can be confused with high grade GISTs. The differential diagnosis is further complicated by positive CD117 staining in melanoma cells and rare S100 positivity in GIST cells. Thus, specific melanoma markers, such as HMB45 and Melan-A, are very important tools to aid in the differential diagnosis.

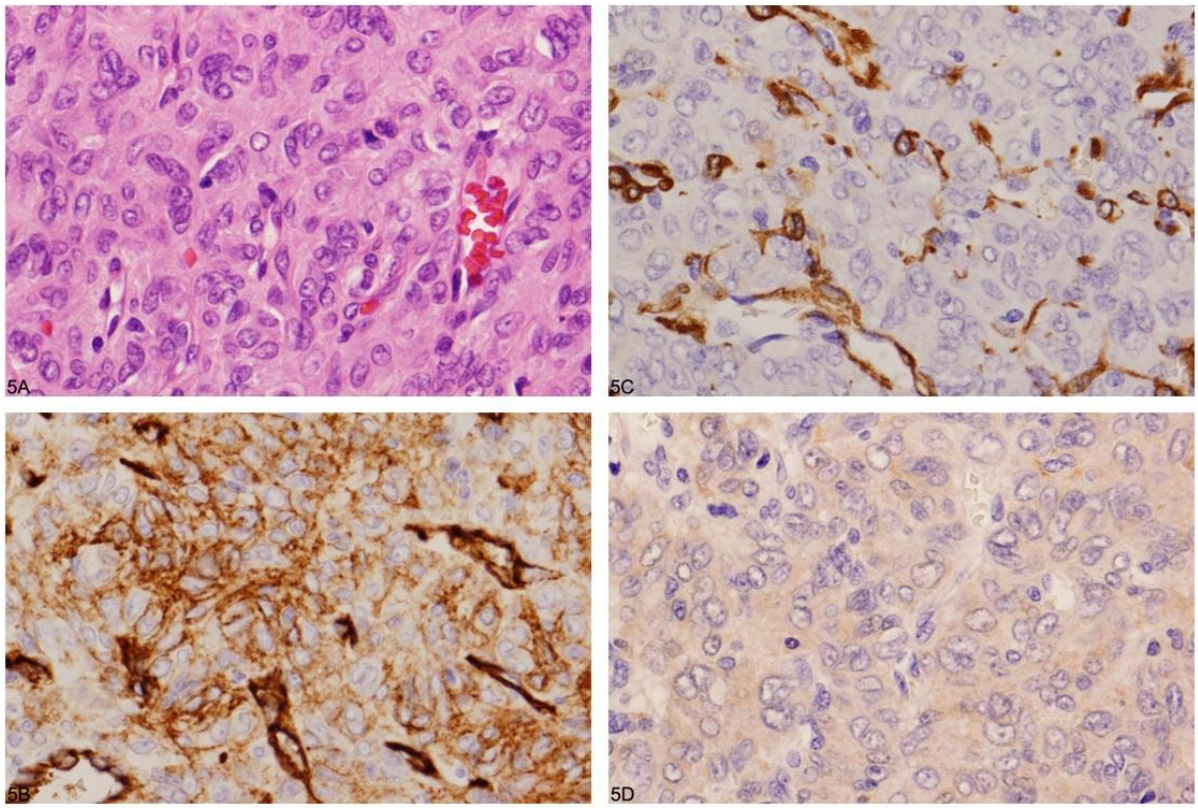

Figure 5. Morphological and immunohistochemical features of a gastric hemangiopericytoma (40X). A. H and E; B. CD34; C. Smooth muscle actin; D. Desmin.

MOLECULAR PATHOGENESIS OF GISTS

GISTs are believed to be derived from the interstitial cells of Cajal or their progenitors. The interstitial cells of Cajal serve as pacemaker cells connecting myenteric plexus and smooth muscle of the GI tract and regulating GI peristalsis. Studies have shown that they express KIT and KIT ligand, stem-cell factor (SCF). KIT signaling pathway is essential for their differentiation and survival.[30-31] c-KIT is a proto-oncogene which encodes a 145 KD membrane receptor tyrosine kinase. The KIT receptor can be detected by staining for CD117, a cell surface antigen on the extracellular domain of the KIT receptor. The ligand-receptor binding results in receptor homodimerization, which leads to activation of signal transduction pathways that regulate cellular proliferation and differentiation.[32] In 1998, Hirota and colleagues first reported gain-of-function KIT mutations in human GISTs.[15] Transgenic animal models showed that constitutively active Kit signal stimulate interstitial cell proliferation and resulting in GISTs development.[33-34] Subsequently, numerous studies showed that over 80% GISTs have mutations in the KIT gene. Most common mutations are identified in the juxtamembrane domain encoded by exon 11 (about 65%). Other less common mutations are found in exon 9, 13, or 17, encoding extracellular domain and the two intracellular kinase domains, respectively.[35-38]

Of the KIT negative GISTs, a subset harbor mutations in another receptor tyrosine kinase protein, platelet derived growth factor receptor α (PDGFRα). PDGFRα shares structure similarity with KIT and activates overlapping downstream targets.[39-40] The mutations found in PDGFRα also correspond to the mutation hotspots in KIT, namely the juxtamembrane domain and kinase domains.[41] DOG1 and PKCθ immune markers are positive in both types of GISTs.[17, 23] Consistent with the functional overlap, KIT and PDGFRα

mutations are mutually exclusive[40, 42] In spite of molecular similarities, KIT and PDGFRα mutated GISTs present with some distinctive clinical and pathological features, including anatomic location, gene expression profile, malignant potential and responses to therapy. PDGFRα-mutant GISTs often display predilection for stomach site, epithelioid morphology, and variable CD117 expression.[41-43]

Familial GISTs have also been reported.[44] They harbor KIT or PDGFRα mutations which are inherited in an autosomal dominant pattern. Patients often develop multiple GISTs, and usually at younger age than patients with sporadic tumor. Tumor behavior varies from indolent to aggressive. Additional manifestations, such as cutaneous hyperpigmentation and mastocytosis, are often present.[45-46]

About 10% GISTs have no detectable of either KIT or PDGFRα mutation. They are clinically indistinguishable from KIT- or PDGFRα-mutant GISTs. Many of them show positive KIT expression although the underlying mechanisms of KIT activation are unclear. Recent studies have revealed that these so called wild-type GISTs display various oncogenic mutations. The BRAF V600E mutation, which is common in papillary thyroid carcinoma and melanoma,[47-48] is present in up to 13% of wild-type GISTs.[49] Mutations in the succinate dehydrogenase (SDH) complex of respiratory chain complex II have also been identified in wild-type GISTs. Germline mutations in SDH subunits (SDHB, SDHC or SDHD) related to Carney-Stratakis syndrome, which increase the risk of GIST as well as paraganglioma and pheochromocytoma.[50] Multiple signaling molecules, including hypoxia-inducible factor 1α (HIF1α), vascular endothelial growth factor (VEGF), MAPK and PI3K-AKT pathways may be implicated; however, the tumorigenic mechanisms of SDH loss-of-function in GISTs remain obscure.

Individuals with neurofibromatosis type I (NF1) have much higher risk to develop one or more GISTs.[66–70] The syndrome results from germline mutation of NF1 gene, which encodes Neurofinromin, a GTPase-activating protein. NF1-associated GISTs are often multi focal and most arise in the small intestine. Most of the tumors do not harbor KIT or PDGFRα mutations, however, majority show positive CD117 immunoreactivity.

Approximately 1–2% of all GISTs arise in pediatric population. Unlike GISTs in adults, they are rarely positive for KIT or PDGFRα mutations and display a different gene expression signature from adult-type GISTs.[51-52] In addition, Carney's triad, a non-heritable syndrome presents with coexistence of pediatric-type GISTs with pulmonary chondromas and/or paragangliomas.[53] However, the gene(s) for this rare syndrome remain elusive.

Table 2. Risk assessment of primary GISTs based on tumor parameters and tumor location. Adapted from Miettinen and Lasota.[9] HPF: high power field. * denotes small case numbers.

Tumor parameters		Disease progression risk based on tumor location	
Mitotic index	Tumor size	Stomach	Non-stomach
≤5/50 HPF	≤2 cm	None	None
	2-5 cm	Very low	Low
	5-10 cm	Low	Moderate
	>10 cm	Moderate	High
>5/50 HPF	≤2 cm	None *	High*
	2-5 cm	Moderate	High
	5-10 cm	High	High
	>10 cm	High	High

PROGNOSIS AND TYROSINE KINASE INHIBITOR THERAPY

Long term clinical follow-up studies indicated that virtually all GISTs have malignant potential and a guideline for assessing progressing risk was proposed.[52, 54] These criteria are recommended by National Comprehensive Cancer Network (NCCN) and College of American Pathologist.[55] The recent advances in dissecting the molecular natures of the GISTs also revealed correlation of specific mutations and tumor behavior. For example, several mutations in exon 9 have been associated with aggressive phenotype.[56-59]

Prior to the tyrosine kinase inhibitor (TKI) therapy era, surgical resection was the main treatment modality for localized tumors while conventional chemotherapy was the management option for tumors of advanced stage. The response rate to conventional chemotherapy was low and the typical median survival length for tumors of advanced stage was 18-24 months.[4] The Imatinib treatment was first conducted on a patient with metastatic tumor in 2000 with dramatic response.[60] This successful outcome led to multicenter clinical trials. A phase II clinical trial on 147 patients with unresectable or metastatic GISTs had 54% patients with partial response and 28% patients with stable disease.[61] Long term follow up revealed that median overall survival was 58 months, greatly improved from that in the pre-TKI therapy period.[62] Currently, Imatinib and Sunitinib are FDA approved first and second line treatment of advanced or metastatic disease. They are small molecules which competitively bind to the ATP-binding pocket of KIT and PDGFRα, inhibiting autophosphorylation and activation, resulting in inhibition of downstream signaling transduction.

Imatinib binds to amino acid residues within the ATP-binding pocket as well as the activation loop, whereas Sunitinib interacts with different amino acid residues in the ATP-binding pocket.[63] In addition, Sunitinib also possesses activity against vascular endothelial growth factor receptors (VEGF) and thus has anti-angiogenic properties.[64]

Surgery remains to be the standard management for resectable GISTs with no evidence of metastasis. For patients with localized GISTs but are at intermediate to high risk of relapse, adjuvant Imatinib treatment can delay recurrence. In early 2012, FDA approved the adjuvant use of Imatinib in light of positive results from clinical trials.[65] Preoperative Imatinib neoadjuvant treatment is also an emerging management option.[66] Two phase III trials assessed the efficacy and side effects of Imatinib at daily dosage of 400 mg or 800 mg and showed that both dosage achieved similar responses. However, the 800 mg dose was associated with more side effects. Thus the 400 mg is the suggested initial therapeutic dose. It can be increased to 800 mg if the tumor progresses. GISTs with exon 11 mutations demonstrated the most favorable response to 400 mg Imatinib treatment, compared with tumors with exon 9 mutations or tumors lacking KIT and PDGFRα mutations.[67-69] One phase III clinical trial showed that tumors harbor exon 9 mutation may benefit from initial 800 mg treatment.[70] KIT exon 9 mutation and wild-type GISTs display better Sunitinib responses than tumors harbor KIT exon 11 mutations. However, the most common PDGFRα mutant, exon 18 D842V, is highly resistant to both Imatinib and Sunitinib.[71] Thus, in addition to tumor size, location and mitotic index, incorporating the mutational analysis will enhance the accurate assessment of prognosis.

Despite the initial responses, nearly 50% of GISTs treated with Imatinib therapy develop resistance in the first 2 years. Resistance is categorized as either primary resistance or secondary resistance. Primary resistance to Imatinib is defined as lack of therapeutic responses within the first 6 months of treatment and is commonly associated with patients with KIT exon 9, PDGFRα exon 18, and wild-type KIT genotypes. Secondary resistance is defined by initial responses for a period of 6 months on Imatinib followed by disease progression. New mutations developed in KIT or PDGFRα are considered as the underlying mechanisms.[64,72] A group of second-generation tyrosine kinase inhibitors, such as Sorafenib, Dasatinib and Nilotinib, are currently in phase II and phase III clinical trials. Drugs against other targets are also in development.[44]

SUMMARY

Great advances have been made in understanding the molecular pathogenesis of GISTs. Current NCCN guideline recommend KIT mutational analysis on metastatic and advanced diseases, but only on selected primary cases, such as KIT-negative GISTs.[73] The mutational status of GISTs may present as another useful factor in assessing tumor prognosis. Challenges remain for elucidating the molecular nature of the wild type and syndrome associated GISTs. Moreover, the high percentage drug resistance rate demand development in new generation of tyrosine-kinase inhibitors. Researches on investigating other molecular mechanisms that lead to tumor progression may provide alternative therapeutic targets and modalities.

CONFLICT OF INTEREST
None.

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