Histopathological and immunohistochemical characteristics of gastrointestinal stromal tumor

Naglaa F. Abbas, Sonia L. El-Sharkawy, Wafaa E. Abdelaal

Department of Pathology, Medical Research and Clinical Studies Institute, National Research Centre, Giza, Egypt

Correspondence to Sonia L. El-Sharkawy, BSc, Department of Pathology, Medical Research and Clinical Studies Institute, National Research Centre, Dokki, Giza 12622, Egypt. Tel: 0233371615; e-mail: s.labib1960@gmail.com

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Gastrointestinal stromal tumor (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract with stomach being the commonest site. These mesenchymal neoplasms account for only about 1% of all primary malignant neoplasms of the gastrointestinal tract. These mesenchymal neoplasms belong to a group of tumors known as the connective tissue cancer group. GISTs are recognized to start from the interstitial cells of Cajal or their stem cell precursors. The natural evolution of these neoplasms is variable. Studies on GISTs have revealed molecular genetics and histopathological features that lead to molecular abnormality-based classification, diagnosis, and treatment. On the contrary, an increasing awareness of risk stratification is important to highlight the parameters that identify the biologic behavior based on recurrence or metastasis. This review aimed to study by histopathological and immunohistochemical tests for accurate diagnosis and differentiating GISTs from other tumors with the same location. In addition, molecular genetic understanding was necessary to determine the treatment approaches and identify patients who benefit from adjuvant therapy.

Keywords:
gastrointestinal stromal tumor, histopathology, immunohistochemistry, molecular genetics

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Introduction

Gastrointestinal stromal tumors (GISTs) are rare but proved to be the most common mesenchymal (nonepithelial) neoplasms of the gastrointestinal tract in both Egypt and worldwide [1]. Only ~1% of all primary malignant gastrointestinal neoplasms are these mesenchymal neoplasms [2]. According to reports, there are 7–15 incidences of GISTs per million people each year. Depending on the location, these tumors have a different occurrence across the globe. The prevalence of GISTs is estimated to be 10–15 cases per million in western countries and 15–20 cases per million in Asia annually [1]. A global estimate of disease incidence either in Egypt or in Africa has not been available.

These mesenchymal neoplasms belong to a group of tumors known as the connective tissue cancer group. GISTs are recognized to start from the interstitial cells of Cajal or their stem cell precursors. GISTs can develop in any part of the stomach (55.6) followed by small bowel (31.8). They can arise in other parts of gastrointestinal system such as esophagus and colorectum, and a small percentage are extragastrointestinal in the omentum, mesentry, retroperitoneum, and pleura [2].

The malignant risk of GISTs in the stomach accounts for 25% of gastric GISTs, whereas it is estimated to be 35–45% of small intestinal GISTs. They usually present sporadically with nonspecific symptoms such as abdominal pain, gastric ulcer, or gastrointestinal bleeding, or may be as incidental finding upon imaging examination. GISTs usually develop in adults over 40 years (50–70 years) with a slight male predominance, whereas up to 2% of GISTs develop in children with girls are more frequently affected [3]. In addition, GISTs were found to be associated with various syndromes, including familial GISTs, Carney Triade (CT), neurofibromatosis-1 (NF1), and Carney Stratakis Syndrome [3–6].

GISTs were described as biologically heterogenous tumors with variable tendencies of local recurrence or recurrent metastasis most commonly to liver and/or the peritoneum [7]. Although surgery is proved to be the proper curative management of localized GIST, many risk factors of local recurrence or metastasis were proposed, which may reach up to 50% even after complete surgical excision with intact capsule and free surgical resection margin [8,9].

Locally advanced or metastatic GISTs are notoriously tenacious to conventional radiation or chemotherapy. The discovery of the Kit tyrosine kinase receptor and the subsequent identification of alternative mutations in the platelet-derived growth factor receptor alpha (PDGFRA) gene showed that Kit and PDGFRA mutations are mutually exclusive [10]. This provided a model shift in the way of classification, diagnosis, and most importantly treatment of GISTs [10,11].

Imaging examinations as computed tomography (CT), endoscopy, abdominal ultrasound, MRI and positron emission tomography, can identify GISTs for tumor location, tumor size, invasion or metastasis to nearby structures [12].

Many risk stratification strategies were proposed for clinical application in the last decades to clarify tumor recurrence and prognosis. All of them were based on tumor size, its location, and mitotic figures to determine the relationship between malignant risk classification (according to Armed Forces Institute of Pathology criteria and the pathological and morphological features of GISTs) [13,14].

This challenging dilemma in the management of GISTs needs a collaborative team work to make a decision based on pathological and surgical prospective [15]. However, many reports showed some defective aspects in the present scheme and proposed newly prognostic factors as an adjuvant for the already approved schemes. Among these include a study of the inflammatory background of GIST and its possible role for the tumor prognosis [8].

Continuous research has helped further in clarifying genetic alteration of the disease and providing important prognostic data to permit the development of novel therapeutic options based on the underlying molecular testing strategies [16].

This review focuses on the molecular genetics of GISTs based on recent molecular profiles and highlights the histomorphological patterns and the immunohistochemical differential diagnosis of GISTs. Furthermore, it represents a thorough trial to understand the prognostic and therapeutic implications as guidelines helping clinical decision making in GISTs cases.

Molecular genetic profile

GISTs were first classified as smooth muscle tumors when they were first described in 1980, but the improvement of immunohistochemical and molecular diagnostic techniques has caused GISTs to be defined as a separate category [17] Regardless of genotype, the majority of GISTs (95%) are KIT positive by IHC [10], distinguishing them from other gastrointestinal spindle cell tumors such leiomyosarcomas and leiomyomas, which are CD117 negative [17].

Activating mutations in the KIT gene, a transmembrane receptor with tyrosine kinase activity, were proven to be an oncogenic driving event of GISTs in 1998, according to a publication by Nakahara *et al.* [18]. KIT and PDGFRA mutations are mutually exclusive because it was established in 2003 that alternative mutations in the PDGFRA gene are the second most common driver mutation in GISTs [19]. Tyrosine kinase inhibitors (TKIs) as imatinib and sunitinib may be used for targeted treatment when the underlying genetic abnormalities are known [20–22].

The gain-of-function mutation of the KIT or PDGFRA gene is a key factor in the etiology of GIST. KIT and PDGFRA are receptor tyrosine kinases [23–25]. On chromosome 4q11–12 (the long (q) arm of chromosome 4 at location 12), both kits are found. They are activated by attaching to stem cell factor and PDGFRA, respectively. By a process known as phosphorylation, which involves combining oxygen and phosphorus at certain places, the activation of these genes triggers the activation of other intracellular proteins like MAP kinase and RAS, which play a crucial role in numerous signaling pathways. These signaling pathways, which the KIT protein activates, regulate a variety of crucial physiological functions, including cell division and growth. The exon 11 gain-of-function mutation in the c-Kit gene is the most frequently seen mutant location. The less frequent locations are exons 9 and 13. Exon 18 is the location of the PDGFRA gene mutation that is most frequently noticed. These mutations cause both genes to be overexpressed and autophosphorylated, which inhibits apoptosis and promotes unchecked cell growth [25,26].

It is generally known that the KIT or PDGFRA genes mutation are detected in about 80% of GIST [27,28]. On the contrary, ‘Wild-type’ (wt)-GISTs are those without KIT and PDGFRA mutations [29,30]. Regarding their clinical behavior and heterogeneous [29,30] profile, these tumors differ from KIT-mutant and PDGFRA-mutant GISTs. Recent developments in molecular pathology have aided in the elucidation of alternative molecular drivers in the so-called ‘wild type (wt)’-GIST group. This group has been shown to have alternative mutations, structural chromosomal modifications, and epigenetic changes, which complicates the molecular classification. Recent discoveries about the critical function of the SDH-complex, particularly in the pathobiology of pediatric GISTs, made it possible to distinguish between GISTs with succinate dehydrogenase B (SDHB)-retained and SDHB-deficient subgroups using immunohistochemistry [26].

The following are the mutations identified in GIST from a molecular perspective: KIT mutations are present in 75% of cases overall (often in exons 11 and 9 and infrequently in exons 13, 17, 14, and 18) [31].

(1) PDGFRA mutations (exon 18, exon 12, and infrequently exons 14 and 10 are mutated in 10% of cases) [32].
(2) Overall, 10–15% of individuals are KIT/PDGFRA wild-type [33]:
    (a) SDHx mutations or SDHC promoter hypermethylations account for 20–40% of cases of SDH deficiency [34].
    (b) BRAF (V600E) or NF1 mutations are present in about 13% of patients [34].
    (c) Less frequent occurrences include FGF4 duplication, FGFR1 fusions or point mutations, and ETV6-NTRK3 fusions [33,35].

Histopathology

Grossly, the diameter of GISTs can range from 1 to 2 cm to more than 20 cm. They are typically well defined and uncapsulated; however, occasionally, a pseudocapsule is visible. The tumors might be submucosal, intramural, or subserosal, with or without ulceration of the mucosa above them. The cut section may be homogenous, usually seen in small-sized tumors or heterogenous with areas of hemorrhage and necrosis in large-sized tumors. The tumors may be solid, cystic, or necrotic [36].

Microscopically, cellular features showed various morphological spectrum. But, the features can be divided into three principal histological patterns: a spindle cell type (70%), epithelial type (20%), or a combination of both, named mixed type (10%) (Fig. 1) [36,37].

Tumors composed mainly of spindle cells are generally compact and highly cellular with vesicular, storiform, whorled, or palisading architecture with ill-defined cell borders and minimal stroma. The cytoplasm is eosinophilic with somewhat fibrillar appearance. Within the epithelioid tumors, the cytoplasm is more abundant ranging from clear to amphophilic with clearly defined cellular borders, and cytoplasmic glycogen with a perinuclear distribution may be visible. Cells of epithelioid type are usually arranged in sheets and nests [38,39]. In general, the nuclear features of GISTs are variable, ranging from uniform and monotonous predominantly oval or spindle appearance to pleomorphic shaped nuclei, containing prominent nucleoli. Mitotic activity may be high or virtually absent. Hemorrhage and necrosis may be seen with inflammatory infiltrate composed mainly of plasma cells and lymphocytes may be present. Mixed type GISTs are neoplasms containing both types of cells, epithelioid and fusiform. The cellularity is variable and collagenous, and myxoid or sclerotic stromal change could be seen in each subtype [38,40].

Markers used in diagnosis, prognosis, and differential diagnosis of gastrointestinal stromal tumor

These are antibodies used immunohistochemical technique for D.D. of GISTs including Kit, DOG1, desmin, S100, α-smooth muscle actin (α-SMA), CD34, and β-catenin. Immunohistochemistry using SDHB is important for subtyping of GISTs. Ki-67 is important for predicting tumor recurrence.

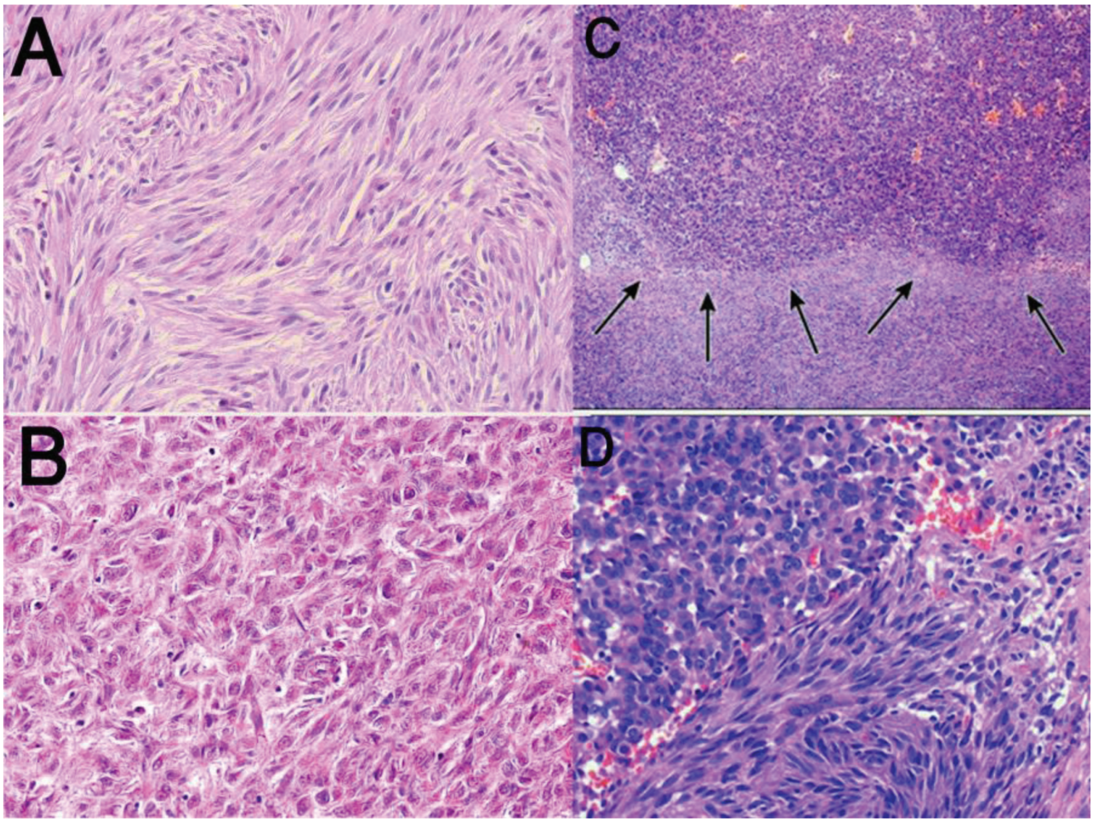
C-KIT/CD117

CD117, also known as c-kit, is a receptor tyrosine kinase that is expressed by erythroblast, germ cells, melanocytes, mast cells, and ICCs, and its tyrosine kinase activity is important for the development and proliferation of these cells. Given that ICCs are the precursor to GISTs, immunohistochemical analysis revealed that 95% of GISTs are robustly and diffusely KIT positive. GIST may show membranous, cytoplasmic, or paranuclear staining pattern for kit (Fig. 2, 4a). Tumors other than GISTs originating from gastrointestinal tract are usually negative for KIT, but some tumors such as perivascular epithelioid cell tumors might be positive for KIT [25,41–44]‘

DOG 1

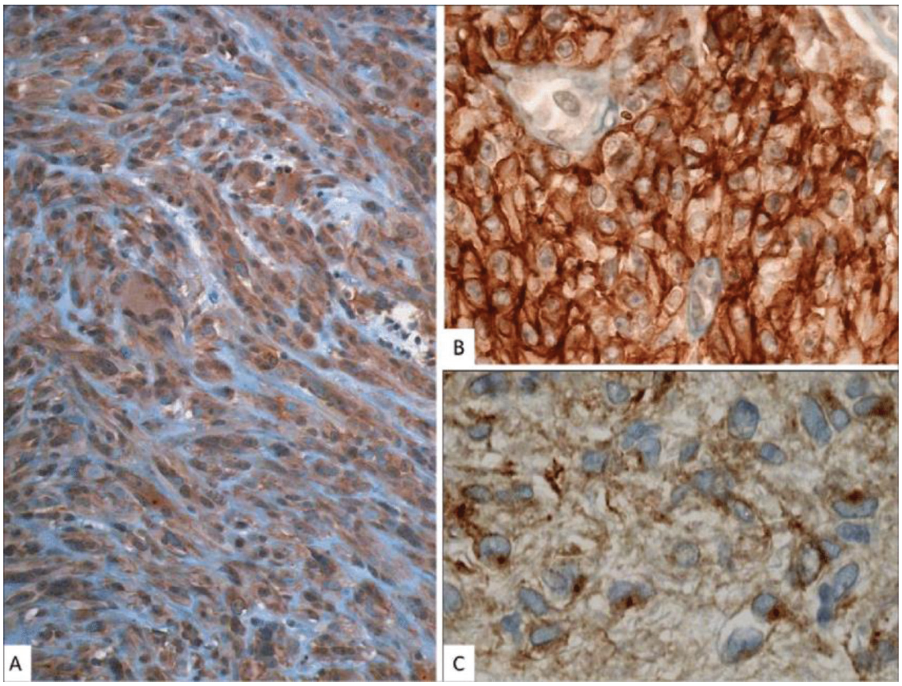
DOG 1 gene is a transmembrane calcium-activated chloride channel protein. The DOG1 function in ICCs is connected to slow waves that are present in the gastrointestinal system. ICCS, salivary glands, and pancreatic acinar cells generally express DOG1. Some tumors such as chondroblastomas, renal oncocytomas, and chromophobe renal carcinoma are shown to positively express DOG1 in more than 80% of these cases. DOG1 staining pattern in GIST may be

Figure 1



(a) GIST with spindle cell feature; the nuclei have typical blunt ends (HE stain ×200) [36]. (b) GIST with epithelioid feature; the tumor contain large and round cells arranged in nest or sheets (HE stain ×200) [36]. (c) GIST, mixed-cell type at low power (HE stain ×40); note the abrupt transition between spindle and epithelioid areas, as indicated by the arrows [37]. (d) Higher magnification of C (HE stain ×200); the tumor is composed of elongated spindle cells as well as rounded epithelioid cells [37]. GIST, gastrointestinal stromal tumor.

Figure 2



C-KIT/CD117 immunostaining of GIST. (a) Cytoplasmic pattern (×200). (b) Membrane and cytoplasmic pattern (×400). (c) Paranuclear (Golgi) pattern (×600) [43]. GIST, gastrointestinal stromal tumor.

cytoplasmic or dot-like paramembranous (Fig. 3). Some tumor types including glomus tumors, synovial sarcomas, and adenoid cystic carcinomas are also reported to be positive for DOG1. Therefore, positive immunostaining for DOG1 is not considered to be specific for GISTs [25,43,45].

Desmin

Desmin is a protein that is unique to muscles and is thought to be one of the intermediate filaments that make up the cytoskeleton. Desmin is present in normal stratified and smooth muscle cells. Therefore, leiomyomas are strongly positive for desmin, whereas leiomyosarcomas show variable positive staining for desmin, which may be partial, weak, or negative. On the contrary, neurogenic tumors and GISTs are negative for desmin [46].

S100 protein

The calcium-binding S100 protein family is typically found in melanocytes, Schwann cells, chondrocytes, myoepithelial cells, and other cell types. S100 protein has been shown to be positive in all Schwannomas but negative in all GISTs and smooth muscle cell tumors. (Fig. 4d) [44,47]

α-smooth muscle actin

A large part of the cytoskeletal structural network of smooth muscle cells, myofibroblasts, and myoepithelial cells is made up of SMA, one of the six actin isoforms. All benign and malignant smooth muscle tumors, the majority of glomus tumors, inflammatory myofibroblastic tumors, and inflammatory fibroid polyps are almost all positive (inflammatory fibroid polyps). However, a sizable portion of GISTs, particularly those of the small intestine, are also SMA positive (Fig. 4c) [25,44].

CD34

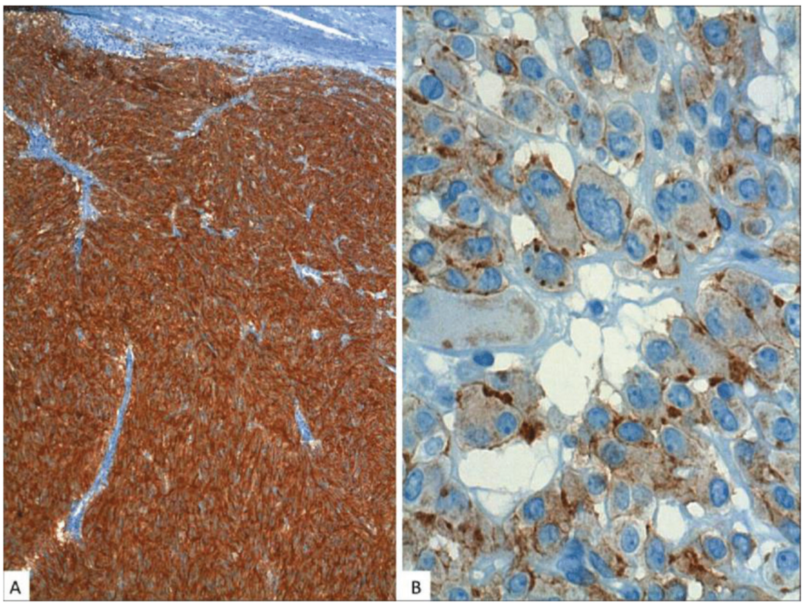
The majority of the time, CD34 is used as a marker for hematopoietic progenitor and stem cells. It is a glycoprotein found in cells that contribute to cell-cell adhesion. Hematopoietic, endothelial, and mesenchymal stem cells are all positive for CD34. Approximately half of GISTs other than gastric GISTs are CD34 negative, but more than 90% of gastric GISTs are CD34 positive. Leiomyomas and Schwannomas, two additional gastrointestinal mesenchymal cancers, may only partially or weakly stain for CD34 (Fig. 4b) [44,48].

B-catenin

B-catenin is a core component of the cadherin protein complex involved in regulation and coordination of cell–cell adhesion and gene transcription. It plays a key role in maintenance of tissue structure.

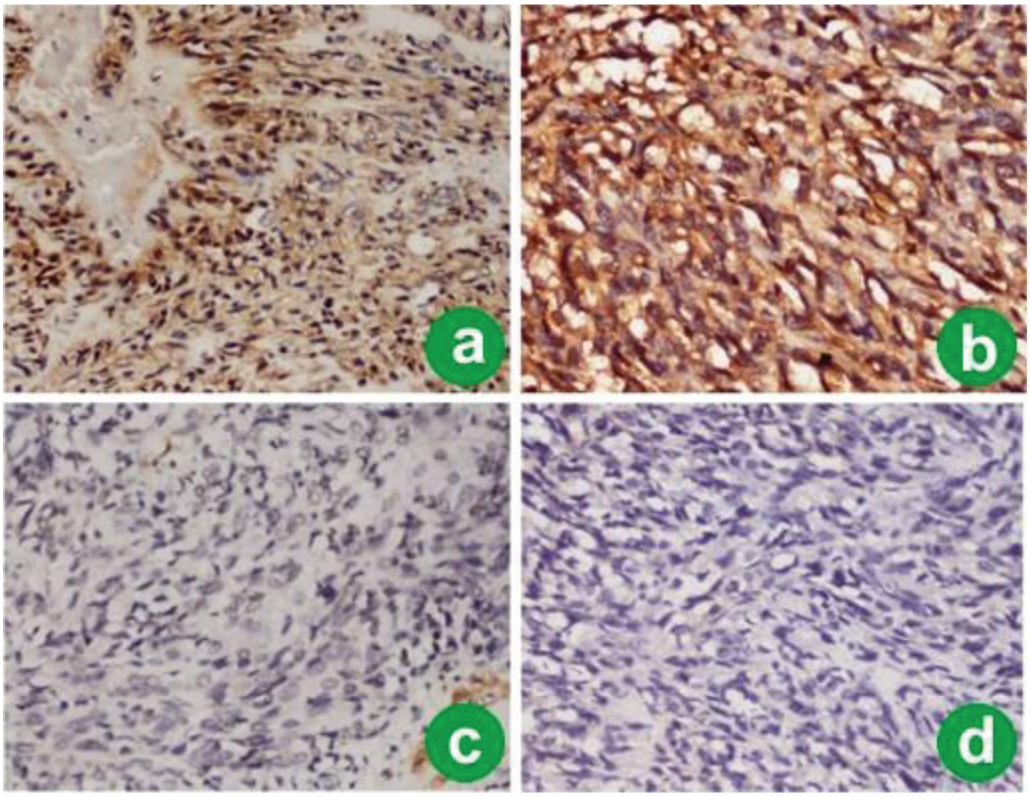
The Wnt system is one of the potent pathways that activate nuclear B-catenin. Mutation of B-catenin gene leads to abundant accumulation of the nuclear B-catenin, resulting in abnormal cell proliferation. Most desmoid colorectal cancers and malignant

Figure 3



DOG1 immunostaining of GIST. (a) Intense cytoplasmic and membrane immunostaining (×100). (b) Epithelioid GIST showing membrane and dot-like paramembrane staining (×600) [43]. GIST, gastrointestinal stromal tumor.

Figure 4



Immunohistochemistry findings of GIST. (a) C-KIT/CD117 positive in tumor cells (×40). (b) CD34 positive in tumor cells (×100). c. Smooth muscle actin negative in tumor cells (×40). d. S-100 negative in tumor cells (×40) [44]. GIST, gastrointestinal stromal tumor.

melanoma have mutations of the B- catenin gene with abundant nuclear accumulation of B-catenin [45].

Ki-67

Ki-67 is a well-known cell proliferation marker that is present in all active phases of cell cycle (G1, S, G2, and M) but absent in resting cells. Ki-67 has a predictive role for tumor recurrence, where high Ki-67 labeling index usually present in tumors shows high recurrence rate. In GISTs, Ki-67 is a reliable marker for prognosis and prediction of recurrence [49]

Differential diagnosis

Gastrointestinal stromal tumors, spindle cell type

Diagnosis of spindle cell-type GISTs is not difficult. Almost all GISTs with spindle cell morphology show diffuse and strong expression of Kit. More than 90% of gastric spindle-type GISTs show CD34 expression, but half of spindle cell-type GISTs other than gastric show weak or negative expression of CD34. Immunohistochemical expression of S100 protein, desmin, and nuclear B-catenin is not detected in GISTs. Expression of α-SMA is high in GISTs other than gastric. Ki-67 is variable from tumor to tumor. However, both high mitotic count and high Ki-67 labelling index are prognostic parameters that predict the high rate of recurrence in GISTs [41].

Gastrointestinal stromal tumors, epithelial cell type

The c-kit gene mutations, PDGFRA gene mutations, and SDH gene abnormal type are the genotypes of epithelioid cell-type GISTs. About 50% of GISTs have anomalies in the SDH or c-kit genes in epithelioid cells. KIT is shown to be diffusely and strongly expressed in these cases. However, PDGFRA gene mutants show variable KIT expression. GISTs of low or no KIT expression may be a diagnostic problem.

DOG1 which show similar pattern of expression as KIT may be more clearly positive in some PDGFRA mutant GISTs of epithelioid cell type. SDHB is positively expressed in both C- kit mutant GISTs and PDGFRA mutant GISTs, but it shows negative expression in familial cases of GISTs [50,51]. GISTs of epithelioid cell type is negative for S100 protein desmin and nuclear B-catenin, and half of these tumors express CD-34. High Ki-67 labelling index together with high mitotic count usually predicts high rate of recurrence of epithelioid type of GIST [41].

Leiomyomas

These are spindle cell tumors that are usually hypocellular. Almost all leiomyomas show strong and diffuse expression for α-SMA and desmin but not for KIT, DOG1, Nuclear B-catenin, and S 100 proteins.

CD 34 is sometimes positively expressed in leiomyomas. Although KIT is not detected in tumor cells, but some leiomyomas contain mast cells that are positive for KIT. Some other tumors may contain many interstitial cells of Cajal, which are positive for both KIT and DOG1 [52].

Leiomyosarcomas

These are hypercellular neoplasms that are composed spindle cells. The tumor cells are pleomorphic more than those of GISTs. Almost all tumors are strongly and diffusely positive for α-SMA. Desmin might be diffusely and strongly expressed but some tumors show weak or negative staining. Leiomyosarcomas are negative for KIT, DOG1, nuclear B-catenin, and S 100 protein, with some cases positive for CD34 (Fig. 5) [25,53].

Schwannomas

Schwannomas are spindle cell tumors that show high density of tumor cells in parts of the tumor and sparse cells in other parts and arranged in trabecular or fascicular pattern in other parts. Gastrointestinal schwannomas are usually surrounded by lymphocytic aggregates. Almost all tumors show strong and diffuse positivity for S 100 protein and glial fibrillary acidic protein. KIT, desmin, and nuclear B- catenin are usually negative, whereas some schwannomas are positive for CD 34 (Fig. 6) [25].

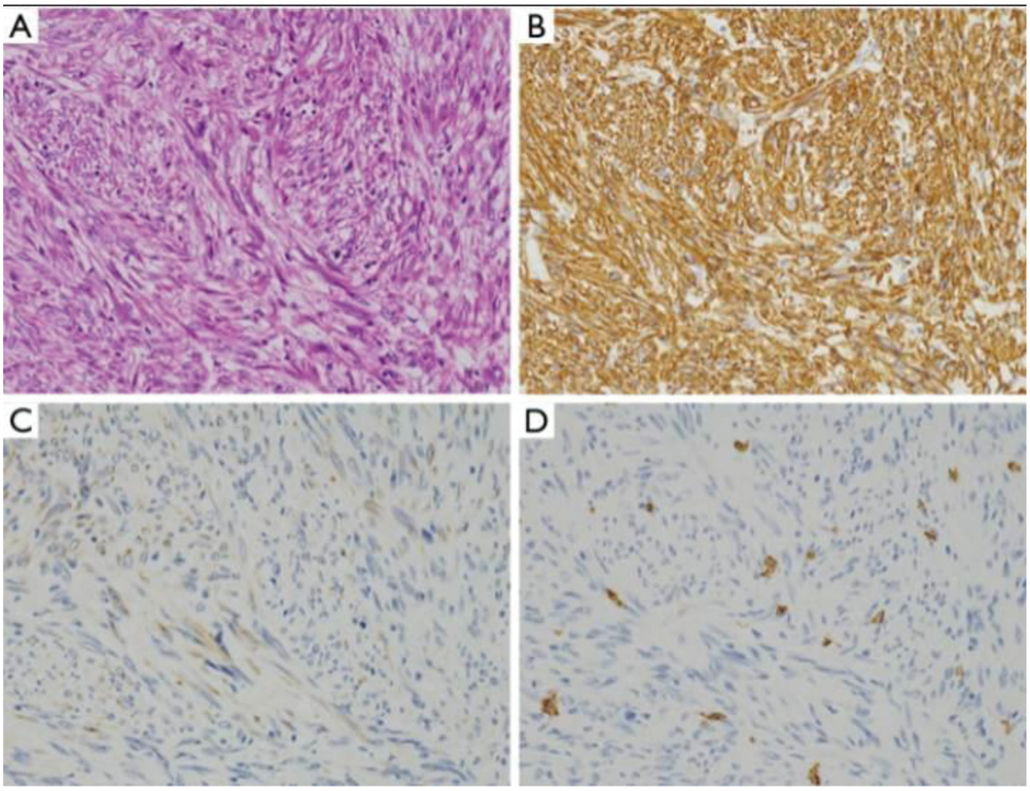
Desmoids

Desmoids are hypocellular tumors that are composed of stellate or spindle cells. Most tumors have mutation in B-catenin gene, so show immunohistochemical staining of B-catenin. Thus desmoids are usually accurately diagnosed by B-catenin; however, desmoids are basically negative for KIT, DOG 1 and S 100 proteins [54]

Inflammatory fibroid polyps

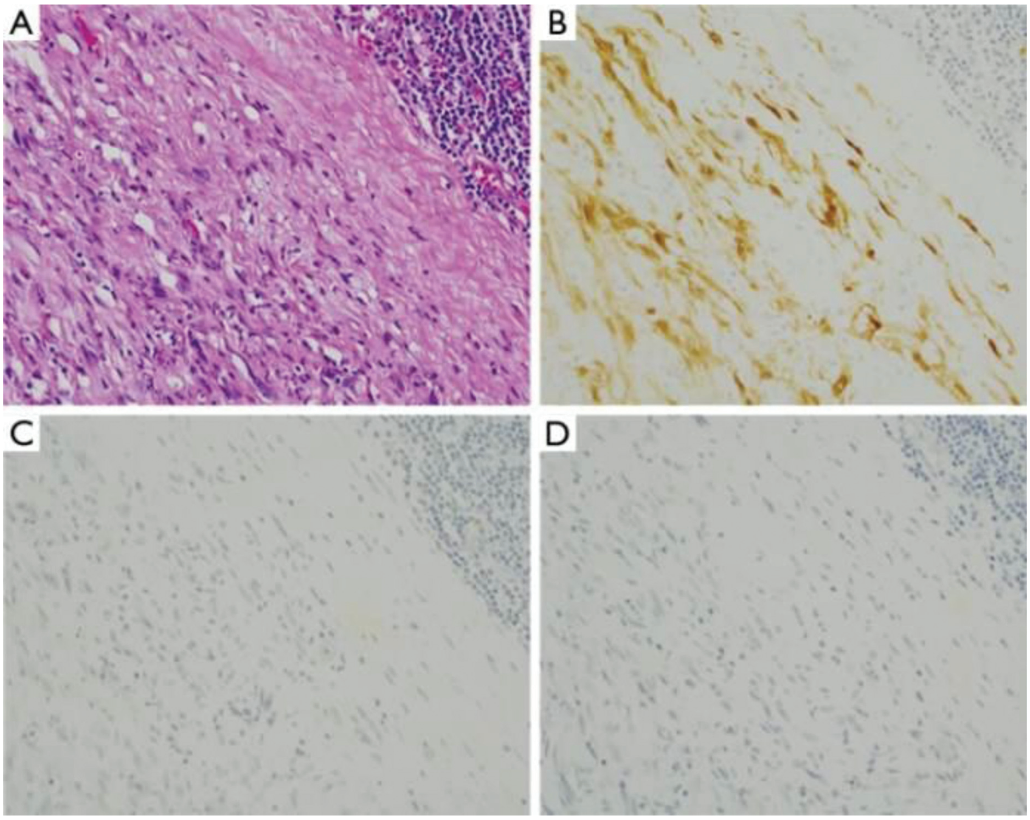
These are polyps that are seen protruding in the lumen of GIST. They are composed of sparse fibroblastic cells, which are often arranged concentrically around blood vessels giving onion-like appearance. They are basically negative for KIT, DOG1, nuclear B-catenin, and S 100 protein, with some cases that may be positive for CD 34 and α-SMA [55].

Figure 5



Liomyosarcoma (×200). (a) HE staining; (b) Positive for α-SMA; IHC (c) Negative for desmin; IHC (d) Negative for KIT IHC. IHC, immunohistochemistry [25].

Figure 6



Schwannoma (×200). (a) HE staining; (b) positive for S100, IHC (c) negative for KIT, IHC (d) negative for desmin. IHC, immunohistochemistry [44].

Solitary fibrous tumors

These are spindle cell tumors that show thick collagen bands and blood vessels with staghorn-like configuration. CD 34 is almost positive in all tumors; however, KIT, DOG 1, nuclear B-catenin, and S 100 protein are negative [56].

Inflammatory myofibroblastic tumors

These tumors contain many inflammatory cells, especially plasma cells and lymphocytes. Inflammatory myofibroblastic tumors usually show positive staining for α-SMA but the tumor cells are negative for KIT, DOG1, nuclear B-catenin, and S 100 protein [57].

Perivascular epithelial cell tumors

These tumors might show either epithelioid or spindle cell-type morphology. They are usually positive for markers of melanoma (HMB 45) and for α-SMA. However, the tumors are negative for DOG 1, nuclear B-catenin, and S 100 protein [58].

Glomus tumors

These tumors are composed of epithelioid cells and are very rare in the GIT, and all of them are positive for α-SMA. However, glomus tumors are negative for KIT, DOG 1, S 100, nuclear B-catenin, and CD 34 [59].

Diagnosis

(1) Endoscopic examination is crucial for making a conclusive diagnosis as it enables direct tumor imaging and offers the chance for biopsies for pathological analysis.
(2) Endoscopic ultrasonography enables evaluation of the gastrointestinal invasion and identification of the digestive tract layer as the origin of the GIST [60].
(3) Contrast-enhanced CT is the preferred imaging technique for determining the nature and extent of neoplasms as well as the presence of metastases [61].
(4) Abdominal ultrasonography, MRI, and positron emission tomography are additional tools for evaluating GISTs and exploring metastases [62].
(5) Histopathology provides conclusive diagnosis. Biological samples can be collected during laparoscopic excision, laparotomy, or endoscopic exploration. When there are metastases, a biopsy of the metastases can also be obtained for histological diagnosis [63]. Three morphological

types – spindle cell type, epithelioid type, and mixed type – have been identified based on how tumor cells appear after hematoxylin and eosin staining [63,64].

(6) Immunohistochemistry is essential for the diagnosis of GISTs. GISTs are positive for CD117/c-Kit in more than 95% of cases. DOG1, CD34, S-100 protein, SMA, and Ki67 are additional indicators for the identification of GISTs [23,65].

Histopathological prognostic factors and risk assessment

GISTs have a wide range of biological behaviors from benign to malignant and to malignant cases that metastasis to the liver and/or peritoneum [10]. Additionally, GISTs exhibit a highly complex evolutionary pattern, which makes it extremely challenging to anticipate their propensity for malignancy. Multiple consensus methods have been created to allow for the categorization of GISTs based on the risk of metastasis or recurrence because all GISTs might be categorized as being malignant [1].

Some criteria such as tumor size or location, mitotic count, failure to have clean margins during operation, rupture of the tumor before or during surgery, and deletion in kit axon 11 are known to be factors that help to predict the malignant potential of GISTs [1].

Fletcher *et al.* [66] have recommended the combination of tumor size and mitotic activity to predict GIST behavior. Subsequently, risk stratification using in addition to tumor size and mitotic count, the primary tumor location as being modified grading system that assess the aggressive behavior of the tumor. This system demonstrated that gastric localization of GIST shows a better prognosis compared with GIST of small intestine or rectum [67]. Some studies proposed that rupture of the tumor is strongly correlated with risk of peritoneal metastasis [33,34] Other reports showed that blood vessel invasion is a strong indicator of liver metastasis [35]. However, clinically, the most widely accepted classification that depends on tumor size and mitotic count for predicting aggressive behavior of GIST is as follow:

(1) Very low risk: tumoral size less than 2 cm; mitotic count less than 5/50 high-power field (HPF).
(2) Low risk: tumoral size 2–5 cm; mitotic count less than 5/50 HPF.
(3) Intermediate risk: tumoral size less than 5 cm and mitotic count 6–10/50 HPF, or tumoral size 5–10 cm and mitotic count less than 5/50 HPF.
(4) High risk: tumoral size more than 5 cm and mitotic count more than 5/50 HPF, or tumoral size more than 10 cm and any mitotic rate, or any tumoral size and mitotic rate more than 10/50 HPF [35].

Treatment

Surgery is the recommended treatment for localized GISTs. The goal in treating primary GISTs is full removal; hence, the tumor and its pseudocapsule should both be removed with an adequate surgical margin (R0). Regional lymph node excision is not necessary as GISTs seldom spread to lymph nodes. Surgery is not prohibited in the presence of metastases. Approximately 85% of GISTs have mutations in KIT or PDGFRA receptors, which explains the favorable response to TKIs [68].

KIT or PDGFRA receptor mutations account for ~85% of GISTs, which explains the good response of GISTs to TKIs [68].

However, KIT/PDGFRA wild-type patients make up 10–15% of the population with GISTs [66]. SDH deficiency or BRAF/RAS/NF1 mutations have been found in half of them, whereas the other half, which are quadruple WT GISTs, exhibit more molecular heterogeneity. The therapy options for this population of patients are very limited because they frequently exhibit TKI resistance [33,69]. SDH-deficient tumors, which have a high rate of primary resistance to TKIs but a sluggish progression, fall into a distinct category. These patients' therapeutic therapy is not yet well established. They frequently do not respond to imatinib therapy, but they might respond to sunitinib or regorafenib, and they might be eligible for a number of clinical trials [70,71].

Patients with large tumors in whom rapid resection is not possible (e.g. total gastrectomy) should be given neoadjuvant imatinib [57–59]. Patients with KIT mutations and the majority of PDGFRA mutations can currently use imatinib [72,73].

Additionally, several research studies contend that the actual proportion of patients with KIT/PDGFRA wild-type is lower than previously thought. These studies attribute this to mistakes in genetic testing and a lack of KIT/PDGFRA mutations. These authors concluded that imatinib may be helpful even in patients with the KIT/PDGFRA wild-type group [69].

Over the past 20 years, a growing body of evidence has shown that the mutational status of GIST is a good predictor of therapy response. A number of TK, including KIT, PDGFR, ABL, and BCR-ABL, are selectively inhibited by imatinib mesylate, an oral medication. Since the year 2000, it has been used in GIST therapy for patients with metastatic/advanced disease, and it has altered the solid tumor treatment program with targeted therapy, modifying the survival of these patients [74]. Numerous TKIs, including sunitinib, regorafenib, and most recently ripretinib and avapritinib, were licensed when imatinib treatment was found to be ineffective. These TKIs are mostly used in advanced (recurrent and metastatic) disease [16,72,75,76].

Studies showed the prognostic importance of particular types of mutations found in GIST and the ability to predict therapy response. Common KIT exon 11 mutations in tumors are linked to aggressive behavior, increased risk of disease recurrence, and metastasis. This is especially true if the tumor is in the stomach [77–79]. Therefore, it would appear relevant to take into account this molecular knowledge while making decisions, particularly if neoadjuvant therapy was indicated. Imatinib has been proven to be effective against tumors with KIT exon 9 mutations, but these GIST need a double dose (800 mg daily) [21]. Imatinib and sunitinib resistance is primarily found in exon 18 of PDGFRA-mutated cancers [19,21].

Imatinib, on the contrary, is effective for GISTs with PDGFRA gene exon 14 mutations [19]. Avapritinib, however, was just recently authorized for the treatment of advanced PDGFRA-mutant GIST [16]. As disease progression in the pediatric GIST group has been observed to occur later with sunitinib therapy than with imatinib, it has been determined that sunitinib therapy should be used as the first line of treatment for these children [22,79].

GIST morphology may be affected by TKI therapy. There can be a sharp decline in tumor cellularity as well as noticeable stromal abnormalities, such as pronounced sclerosis and myxoid transformation. The cytomorphology is still generally comparable to the initial tumor in most instances. However, significant modifications to the tumor's morphology have been reported. The so-called dedifferentiated GIST is extremely uncommon but well described, typically displaying an abrupt shift from a 'standard' GIST morphology in a dedifferentiated component [39,80].

Although dedifferentiation in GIST is frequently linked to long-term TKI therapy, it can also happen spontaneously [39,81]. The dedifferentiated component has a necrotic look, strong nuclear atypia, and an anaplastic/pleomorphic appearance. Dedifferentiation typically does not involve new mutations of the primary driving oncogene. These cancers, however, exhibit genetic instability [39].

Conclusion

GISTs are a category of GISTs having a distinctive and heterogenous group of neoplasms with respective to their histologic origin, molecular genetic feature, cellular difference, and biologic behavior. For proper diagnosis and differentiating GISTs from other tumors sharing the same localization, histopathological and immunohistochemical studies are necessary. In addition, the molecular genetic awareness of GISTs helps to determine the proper treatment and improve the prognosis of the patients.

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Conflicts of interest

There are no conflicts of interest.

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