Review Article

Differential diagnosis of gastrointestinal stromal tumor by histopathology and immunohistochemistry

Seiichi Hirota

Department of Surgical Pathology, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan

Correspondence to: Seiichi Hirota, MD, PhD. Department of Surgical Pathology, Hyogo College of Medicine, Mukogawa-cho 1-1, Nishinomiya, Hyogo 663-8501, Japan. Email: hiros@hyo-med.ac.jp.

Abstract: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in the gastrointestinal (GI) tract. GISTs account for approximately 80% of the clinically relevant GI mesenchymal tumors. Although most GISTs show spindle cell morphology, 10–15% of GISTs show pure epithelioid configuration. Therefore, not only spindle cell tumors but also epithelioid cell ones developing in the GI tract are subject to the differential diagnoses of GISTs. GISTs are basically positive for KIT, a receptor tyrosine kinase (RTK) encoded by protooncogene c-*kit*, by immunohistochemistry, but approximately 5% of GISTs are only weakly or barely positive for KIT. Since almost all spindle cell type GISTs are strongly and diffusely positive for KIT regardless of different genetic subtypes, diagnosis of the spindle cell type GISTs is not difficult. On the other hand, epithelioid cell type GISTs show different staining patterns of KIT in different genetic backgrounds. Approximately half of the epithelioid cell type GISTs with platelet-derived growth factor receptor alpha (*PDGFRA*) gene mutation might show weak or undetectable staining of KIT. On the other hand, almost all GISTs are negative for desmin, which is a positive marker for mature smooth muscle cells, and S100 protein, which is a Schwann cell marker. Smooth muscle tumors such as leiomyomas and leiomyosarcomas, which usually show the spindle cell morphology, consist of approximately 10% of the clinically relevant GI mesenchymal tumors and are almost positive for desmin and negative for KIT and S100 protein. Schwannomas which nearly always show the spindle cell pattern, comprise up to 5% of the GI mesenchymal tumors, and almost all of them are positive for S100 protein and negative for KIT and desmin. Thus, most GI mesenchymal tumors are differentially diagnosed by immunohistochemistry (IHC) of KIT, desmin and S100 protein. However, mesenchymal tumors such as desmoids, solitary fibrous tumors (SFTs), inflammatory myofibroblastic tumors (IMTs), perivascular epithelioid cell tumors (PEComas), inflammatory fibroid polyps (IFPs), rarely develop in the GI tract, and have to be correctly diagnosed through detection of specific immunohistochemical markers and/or unique genetic aberrations.

Keywords: Gastrointestinal stromal tumor (GIST); pathological diagnosis; mesenchymal tumor; KIT

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the human gastrointestinal (GI) tract. They can develop anywhere in the GI tract from the esophagus to the rectum. Approximately 60% of them arise in the stomach and approximately 30% in the small intestine. Duodenal and rectal GISTs account for about 5% each among whole GIST cases, and esophageal GISTs are rarer and colonic GISTs are extremely unusual. GISTs are considered to be derived from interstitial cells of Cajal (ICCs), which are spindle-shaped mesenchymal cells (1). Thus, GISTs are also typically composed of spindle cells. However, a minor proportion (10–15%) of them have epithelioid feature, and some tumors show mixed cell type. Histological diagnosis of GISTs should be considered according to the

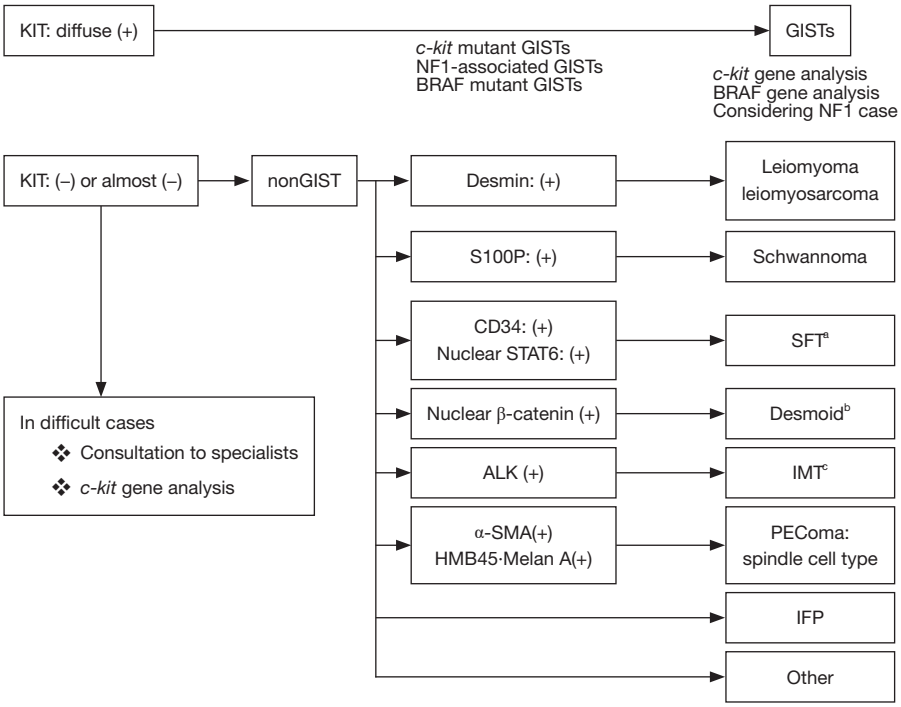

Figure 1 Flow chart of differential diagnoses of spindle cell mesenchymal tumors. [a], NAB2-STAT6 fusion gene analysis is useful; [b], β-catenin gene analysis is useful; [c], ALK FISH is useful. GIST, gastrointestinal stromal tumor; SFT, solitary fibrous tumor; IMT, inflammatory myofibroblastic tumor; IFP, inflammatory fibroid polyp; ALK, anaplastic lymphoma kinase; FISH, fluorescent in situ hybridization; STAT, signal transducer and activator of transcription; NAB2, NGFI-A binding protein-2; α-SMA, α-smooth muscle actin.

histological tumor cell type. For spindle cell type GISTs (*Figure 1*), spindle cell tumors such as desmoids, solitary fibrous tumors (SFTs), inflammatory myofibroblastic tumors (IMTs), perivascular epithelioid cell tumors (PEComas), inflammatory fibroid polyps (IFPs) are subject to the differential diagnoses. On the other hand, epithelioid cell tumors such as PEComas, carcinoids [or neuroendocrine tumors (NETs)] and adenocarcinomas should be distinguished from epithelioid type GISTs (*Figure 2*). Immunohistochemistry (IHC) is essential for the differential diagnoses of them. Antibodies used for IHC include those for KIT, desmin, S100 protein, α-smooth muscle actin (α-SMA), CD34, DOG1 (discovered on GIST-1), signal transducer and activator of transcription 6 (STAT6), β-catenin, and anaplastic lymphoma kinase (ALK). IHC for succinate dehydrogenase subunit B (SDHB) is needed for subtyping of GISTs, and Ki-67 IHC is useful for risk evaluation of GIST recurrence. Characteristics of these molecules used for IHC are described, and the above-mentioned tumors to be distinguished from GISTs are discussed here.

Characteristics of markers for IHC used for differentiating GISTs from other tumors

KIT

KIT, a receptor tyrosine kinase (RTK), is encoded by the protooncogene c-*kit* which is the cellular homolog of the v-*kit* oncogene (2). KIT is expressed by erythroblasts, melanocytes, germ cells, mast cells and ICCs, and its tyrosine kinase activity is important for development and proliferation of these five lineage cells. Since GISTs are considered to originate from ICC (1), most GISTs diffusely and strongly express KIT. Tumors other than GISTs developing in the GI tract are usually negative for KIT, but some tumors such as PEComas and melanomas might be positive for KIT. Some mutations of the c-*kit* gene result in loss-of-function of KIT tyrosine kinase activity, while other mutations of the c-*kit* gene cause constitutive activation of KIT tyrosine kinase. These gain-of-function mutations of the c-*kit* gene are observed in GISTs (1), mastocytomas (3), seminomas (4) and melanomas (5).

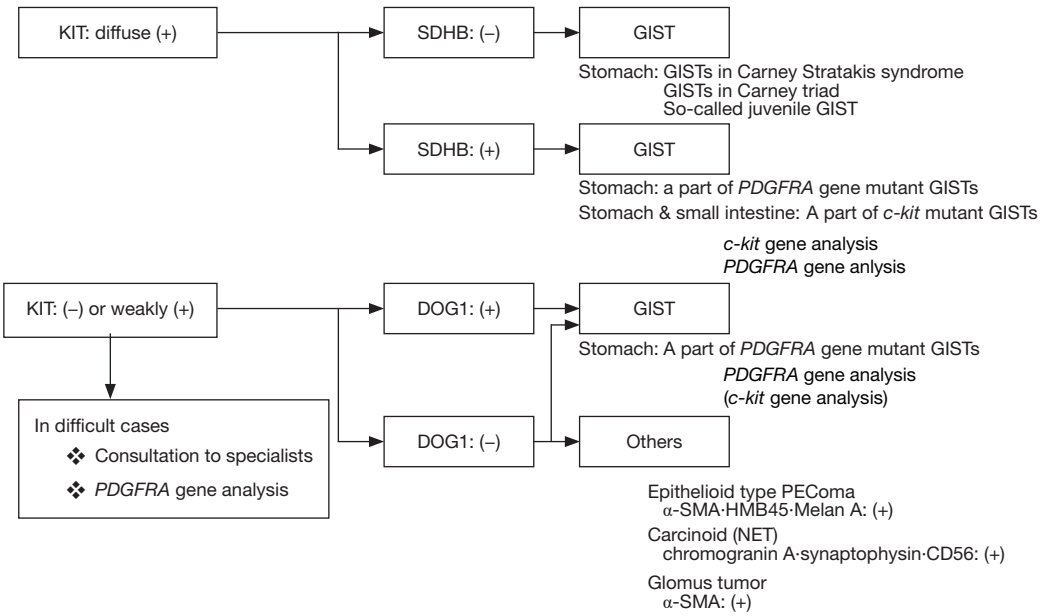

Figure 2 Flow chart of differential diagnosis of epithelioid cell mesenchymal tumors. SDHB, succinate dehydrogenase subunit B; GIST, gastrointestinal stromal tumor; PDGFRA, platelet-derived growth factor receptor alpha; NET, neuroendocrine tumor; α-SMA, α-smooth muscle actin; PEComa, perivascular epithelioid cell tumor.

Desmin

Desmin is a muscle-specific protein and is one of the intermediate filaments constituting the cytoskeleton. In normal tissue, not only smooth muscle cells but also striated muscle cells are positive for desmin. Therefore, leiomyomas are basically positive for desmin. Leiomyosarcomas which might not show sufficient differentiation to smooth muscle cells are variably positive for desmin. On the other hand, GISTs and neurogenic tumors are commonly negative for desmin.

S100 protein

S100 proteins are a family of the calcium-binding proteins, and commercially available antibodies against S100 proteins mainly detect S100A. In normal tissues, S100A is present in Schwann cells, melanocytes, chondrocytes, adipocytes, myoepithelial cells, and so on. Among the GI mesenchymal tumors, almost all Schwannomas are positive for S100 protein. In contrast, almost all GISTs and smooth muscle cell tumors are negative for S100 protein.

α-*SMA*

Polymer of actin forms actin filament, one of the microfilaments. α-SMA, one of the six actin isoforms, is a major cytoskeletal structural network of smooth muscle cells, myofibroblasts and myoepithelial cells. It is positive for almost all smooth muscle cell tumors such as leiomyomas and leiomyosarcomas, almost all glomus tumors, most of IMTs and IFPs among GI mesenchymal tumors. We should be careful that a considerable number of GISTs, especially small intestinal GISTs, are also positive for this marker.

CD34

CD34 is a cell surface glycoprotein which plays a role in cell-cell adhesion. Immunohistochemically, CD34 is positive for hematopoietic stem cells, mesenchymal stem cells, endothelial progenitor cells and endothelial cells. Over 90% of gastric GISTs are positive for CD34, but approximately half of GISTs other than gastric GISTs are negative for CD34. A considerable number of IFPs are positive for CD34, and some of other GI mesenchymal tumors such as Schwannomas and leiomyomas might show partial and/or weak staining for CD34.

DOG1

DOG1 gene was found as a specific transcript in GISTs by

using cDNA microarrays (6). DOG1 is a transmembrane calcium-activated chloride channel protein. Slow waves developing in the GI tract are considered to be associated with function of DOG1 in ICCs. DOG1 is normally expressed not only by ICCs but also by other cell types including acinar cells of the pancreas and salivary glands. Tumors such as renal oncocytomas, chondroblastomas, acinic cell carcinomas, chromophobe renal cell carcinomas are reported to be immunohistochemically positive for DOG1 in over 80% of those cases. Some other tumor types including adenoid cystic carcinomas, glomus tumors, synovial sarcomas also might show positive result for DOG1 IHC. Thus, DOG1 immunopositivity is not considered to be specific for GISTs (7).

STAT6

STAT6 is one of seven STAT family proteins. STAT6 is expressed in many tissues, especially in the immune system. Cytokine binding to the receptor induces the Janus kinase (JAK) activation, and subsequent STAT6 activation and homodimerization result in nuclear transfer of the protein. The nuclear STAT6 regulates (activates) the translation of the target proteins. In SFTs, NGFI-A binding protein-2 (NAB2)-STAT6 fusion protein is specifically detected in the nucleus (8,9).

β-*catenin*

Intracellular domain of the cadherins which play an important role in cell-cell adhesion binds to β-catenin, and the β-catenin can link cadherins with actin filaments. Thus, the β-catenin is important for maintenance of tissue structure. On the other hand, the β-catenin also plays a role as a factor for regulation of transcription. When Wnt signaling cascade is activated, stabilized non-phosphorylated β-catenin is transferred to nucleus to activate transcription of target genes. Mutations of the β-catenin gene also result in abundant accumulation of nuclear β-catenin and induce abnormal cell proliferation. As observed in colorectal cancers and malignant melanomas, most desmoids have β-catenin gene mutations (10) and nuclear accumulation of abundant β-catenin protein.

ALK

ALK is a RTK which has a transmembrane domain and an extracellular domain. ALK tyrosine kinase activity plays an important role in the development of the central nervous system. ALK can function as an oncogenic molecule by formation of fusion genes with some other genes. Nucleophosmin (*NPM*) gene is a main partner in anaplastic large-cell lymphomas, EML-4 in adenocarcinomas of the lung, and TMP3/4 in IMTs (11).

SDHB

Succinate dehydrogenase (SDH) is composed of several components including subunit A (SDHA), SDHB, subunit C (SDHC) and subunit D (SDHD). SDH complex is fixed at the inner membrane of the mitochondria and plays an important role in both tricarboxylic acid (TCA) cycle and electron transport system. In the TCA cycle, SDH complex oxidizes succinate to fumarate. Mutations of every subunit of SDH result in unstable condition of SDH complex, and the degradation and inactivation of SDH complex induce accumulation of succinate. High concentration of succinate results in decreased hypoxia induced factor 1 (HIF-1) degradation, and the resultant high level of HIF-1 induce proliferation of tumor cells via vascular channel formation.

Ki-67

Ki-67 is a nuclear protein which is present in proliferating cells during G1, S, G2 and M phases. Ki-67 is used as a cell proliferation marker and is regarded as a predictor of tumor recurrence. High Ki-67 labelling index usually means high recurrence rate of the tumor. In clinical practice in GIST, Ki-67 IHC may be used for both the direct prediction of recurrence and the determination of hot spot (high mitotic area) for mitotic counting.

Histology, IHC and gene abnormalities in GIST subtypes and tumors to be distinguished from GISTs

GISTs, spindle cell type

Basically, almost all spindle cell type GISTs express KIT strongly and diffusely (*Figure 3A*,*B*). Thus, the diagnosis of spindle cell type GISTs is not difficult. DOG1 is also expressed by almost all spindle cell type GISTs (*Figure 3C*). CD34 shows over 90 % of gastric spindle cell type GISTs (*Figure 3D*), but about half of GISTs other than gastric

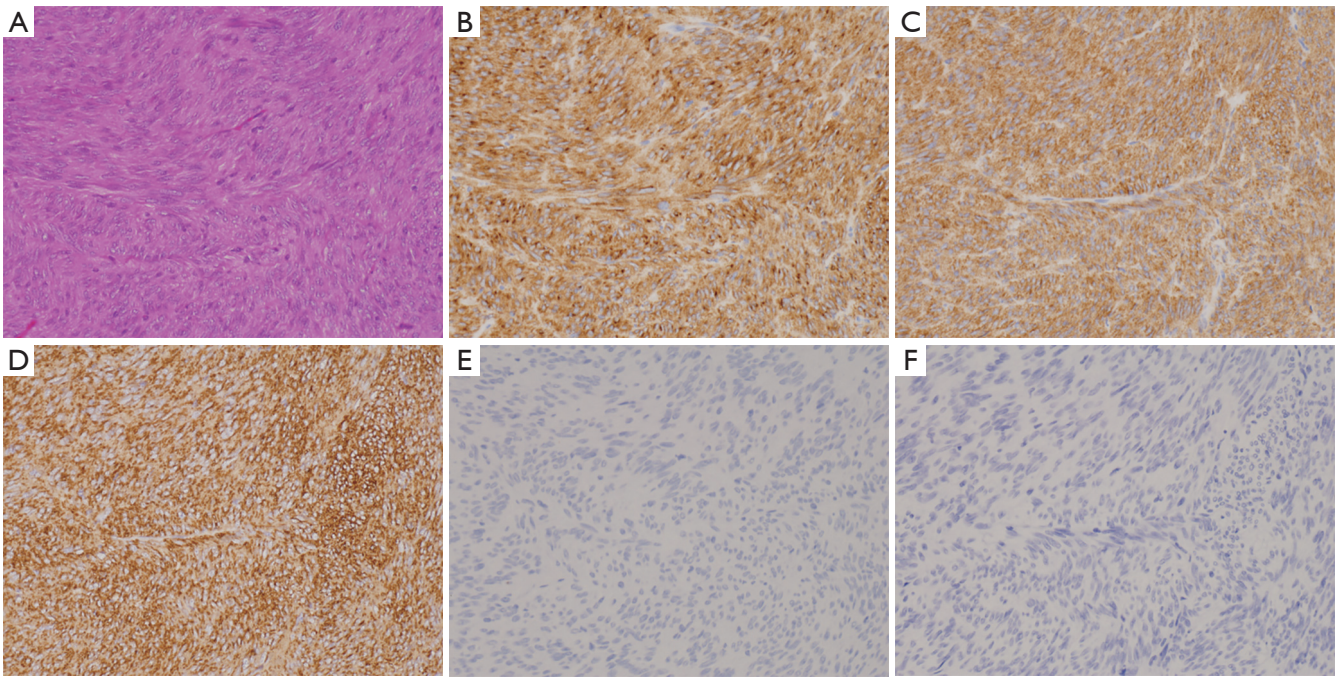

Figure 3 Spindle cell type GIST (c-kit mutant case, stomach; ×200). (A) HE staining; (B) KIT (IHC); (C) DOG1 (IHC); (D) CD34 (IHC); (E) desmin (IHC); (F) S100P (IHC). GIST, gastrointestinal stromal tumor; IHC, immunohistochemistry.

origin do not apparently express CD34. Expression of CD34 appears to be inversely related to that of α-SMA. Thus, positive rate of α-SMA is not so high in gastric GISTs, but it is high in GISTs other than gastric GISTs. Expression of desmin (*Figure 3E*), S100 protein (*Figure 3F*), ALK, nuclear β-catenin and nuclear STAT6 is not usually detected. Ki-67 labelling index is variable from tumor to tumor. High Ki-67 labelling index and high mitotic counts predict high recurrence rate of GISTs. Representative genotypes of spindle cell type GISTs include c-*kit* gene mutants, NF1 mutants and BRAF mutants (*Figure 1*).

GISTs, epithelioid cell type

Representative genotypes of epithelioid cell type GISTs are c-*kit* gene mutants, Platelet-derived growth factor receptor alpha (*PDGFRA*) gene mutants and *SDH* gene abnormal types. About half of epithelioid cell type GISTs have c-*kit* gene mutations or *SDH* gene abnormalities. In these cases, KIT is expressed strongly and diffusely (*Figure 4A-D*). However, in residual half of epithelioid cell type GISTs such as *PDGFRA* gene mutants, expression of KIT is variable. Diagnosis of GISTs with low or almost no KIT expression may be difficult. As described above, KIT and DOG1 show very similar expression pattern. However, DOG1 may be more clearly positive in some *PDGFRA* mutant GISTs (*Figure 4E-G*), and KIT may be more clearly positive than DOG1 in other *PDGFRA* mutant GISTs. Thus, DOG1 IHC may be useful for the diagnosis of GISTs with low or almost no KIT expression. SDHB is positive in c-*kit* mutant GISTs (*Figure 4H*) and *PDGFRA* mutant GISTs (*Figure 4I*), while it is immunohistochemically negative in the SDH gene abnormal GISTs including those in Carney Stratakis syndrome (12), those in Carney triad and so-called juvenile (or pediatric) GISTs (*Figure 4J*) (13). About half of epithelioid type GISTs express CD34. Expression of desmin, S100 protein, ALK, nuclear β-catenin and nuclear STAT6 is not usually detected. Ki-67 labelling index is variable from tumor to tumor. High Ki-67 labelling index and high mitotic counts might predict high recurrence rate of the tumor as in the case of spindle cell type GISTs.

Leiomyomas

Leiomyomas are hypocellular tumors composed of spindle cells (*Figure 5A*). Almost all tumors are diffusely and

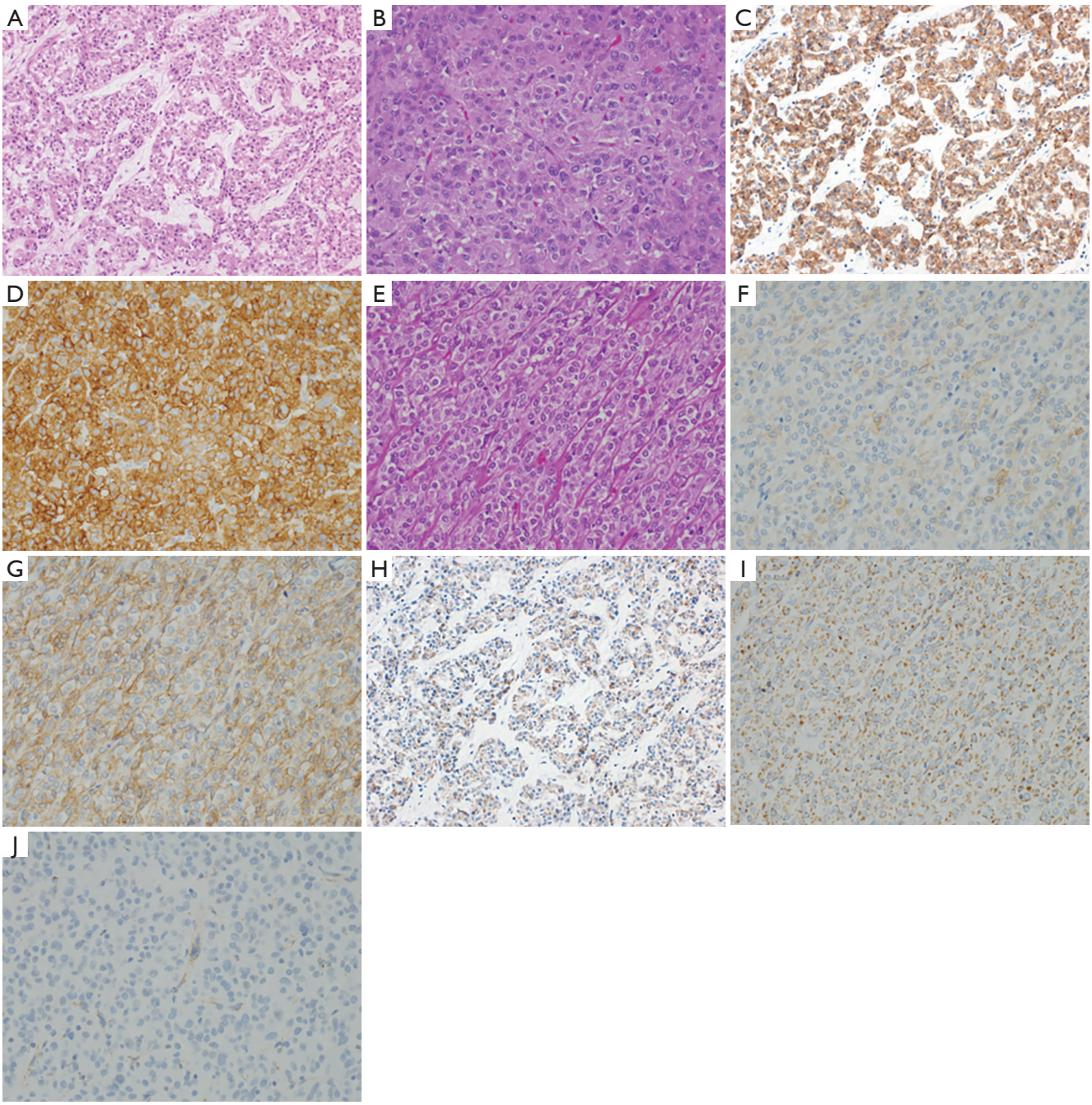

Figure 4 Epithelioid cell type GISTs (×200). (A, C, H) c-kit mutant case; (B, D, J) SDH abnormality case; (E-G, I) PDGFRA mutant case; (A, B, E) HE staining; (C, D, F) KIT IHC; (H-J) SDHB IHC; (G), DOG1 IHC. GIST, gastrointestinal stromal tumor; SDHB, succinate dehydrogenase subunit B; PDGFRA, platelet-derived growth factor receptor alpha; IHC, immunohistochemistry.

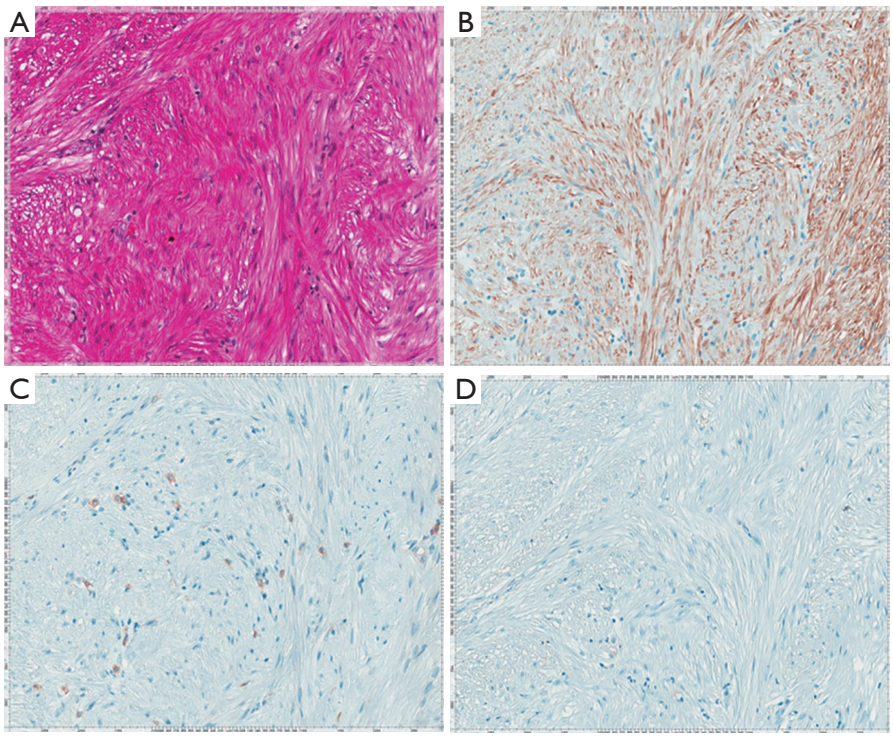

Figure 5 Leiomyoma (×200). (A) HE staining; (B) desmin IHC; (C) KIT IHC; (D) S100P IHC. IHC, immunohistochemistry.

strongly positive for α-SMA and desmin (*Figure 5B*) but not for KIT (*Figure 5C*), DOG1, S100 protein (*Figure 5D*), ALK, nuclear β-catenin and STAT6. CD34 is sometimes positive in leiomyomas. Although tumor cells themselves are not positive for KIT, many KIT-positive mast cells are often scattered within the tumor (*Figure 5C*). Similarly, leiomyomas often contain many ICCs that are positive for both KIT and DOG1. Thus, we should take care of evaluation of the IHC result of KIT and DOG1 in leiomyomas.

Leiomyosarcoma

Leiomyosarcomas are hypercellular tumors composed of spindle cells (*Figure 6A*). The tumor cells of them are often more pleomorphic than those of GISTs, but the differential diagnosis between leiomyosarcomas and GISTs is not always easy only by histology on hematoxylin and eosin staining. Almost all tumors are diffusely and strongly positive for α-SMA (*Figure 6B*). Desmin might be also diffusely and strongly positive, but some tumors show partial and/or weak staining (*Figure 6C*). No apparent staining of desmin might be shown in some cases. Basically, they are negative for KIT (*Figure 6D*), DOG1, S100 protein, ALK, nuclear β-catenin and STAT6. CD34 is sometimes positive in leiomyosarcomas. Similarly, in leiomyomas, some leiomyosarcomas contain KIT-positive mast cells (*Figure 6D*) and KIT and DOG1-positive ICCs within the tumors.

Schwannomas

Schwannomas are a spindle cell tumor. Density of the tumor cells (nuclei) may be high in parts, and that may be sparse in other parts (*Figure 7A*). Schwannomas of the GI tracts are often surrounded by foci of lymphocyte aggregation (*Figure 7A*). Almost all tumors are diffusely and strongly positive for S100 protein (*Figure 7B*). KIT (*Figure 7C*), DOG1, desmin (*Figure 7D*), α-SMA, ALK, nuclear β-catenin and STAT6 are basically negative. CD34 might be positive in some Schwannomas.

Desmoids

Desmoids are composed of spindle or stellate cells

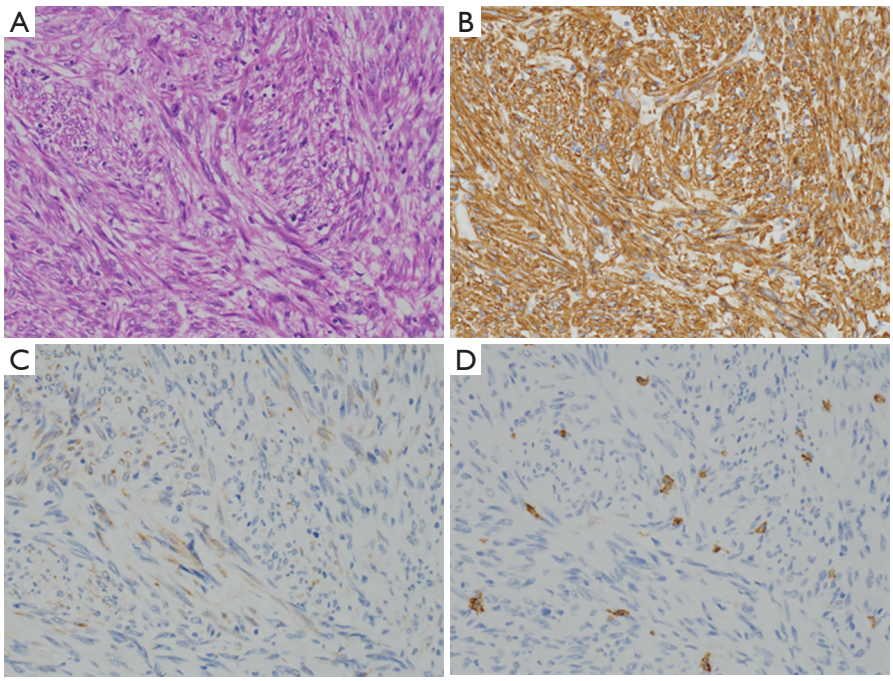

Figure 6 Leiomyosarcoma (×200). (A) HE staining; (B) α-SMA IHC; (C) desmin IHC; (D) KIT IHC. IHC, immunohistochemistry; α-SMA, α-smooth muscle actin.

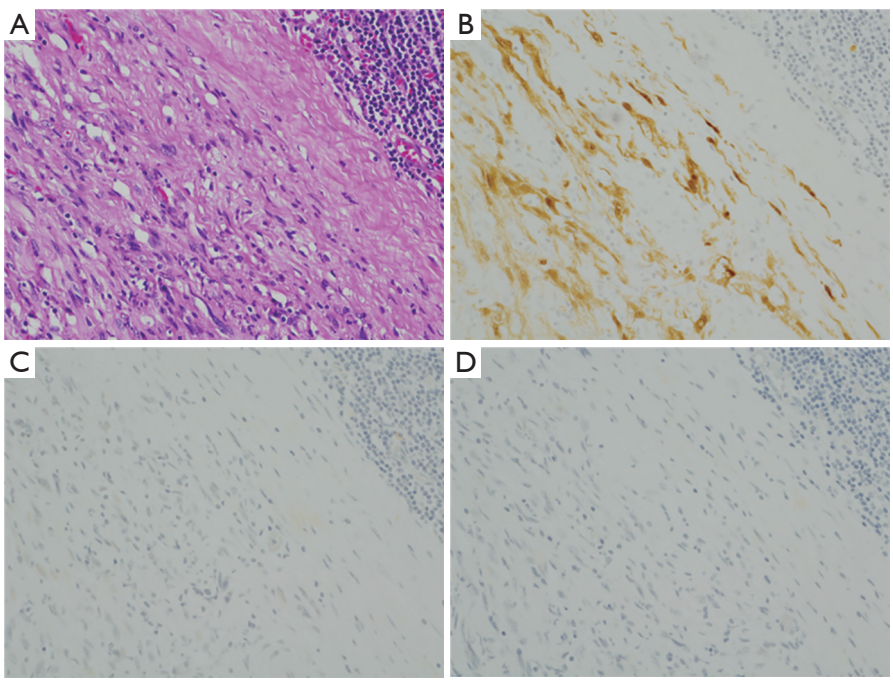

Figure 7 Schwannoma (×200). (A) HE staining; (B) S100P IHC; (C) KIT IHC; (D) desmin IHC. IHC, immunohistochemistry.

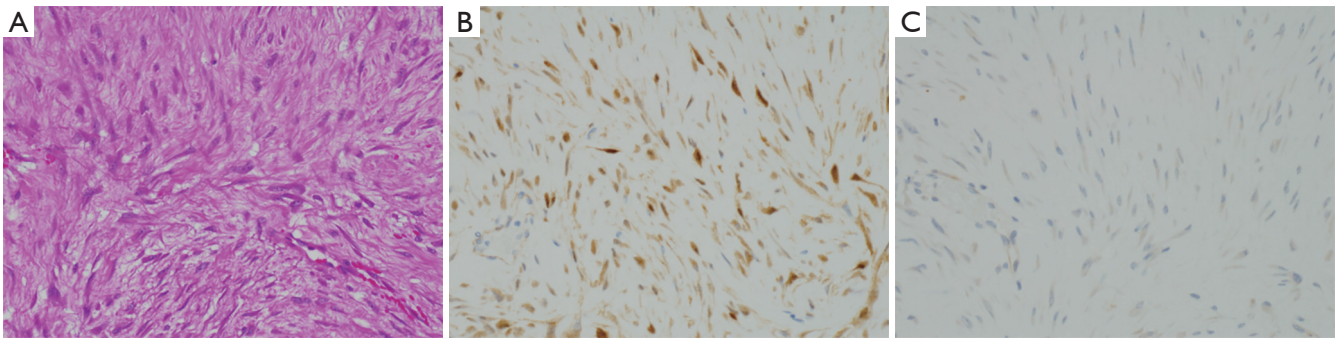

Figure 8 Desmoid (×200). (A) HE staining; (B) β-catenin IHC; (C) KIT IHC. IHC, immunohistochemistry. IHC, immunohistochemistry.

(*Figure 8A*). Tumors are usually paucicellular (*Figure 8A*). Most of them have mutations at exon 3 of the β-catenin gene. As described above, the mutations result in inhibition of degradation and subsequent accumulation of the protein. The increased protein is transferred to nuclei, and functions as transcription activator for the target proteins. Nuclear staining of β-catenin by IHC is observed in most of desmoids (*Figure 8B*). Basically, they are negative for KIT (*Figure 8C*), DOG1, S100 protein, ALK and STAT6. Desmoids might show non-specific weak staining by certain types of KIT antibodies using inappropriate staining procedure, but we can not observe diffuse and strong staining of KIT in desmoids as observed in GISTs. Thus, the β-catenin IHC is useful to diagnose desmoids accurately. Analysis of β-catenin gene mutation is a more direct method for β-catenin abnormality on diagnosis of desmoids (10).

IFP

IFPs usually show a polyp-like finding protruding into the GI tract lumen. They are composed of sparse fibroblast-like spindle cells and often contain inflammatory cells especially eosinophils (*Figure 9A*). The fibroblastic spindle cells are often arranged concentrically around vessels (so-called onion-skin lesion) (*Figure 9A*). CD34 (*Figure 9B*) and α-SMA might be positive for the fibroblastic spindle cells in the tumors, but negative cases are also present. Basically, the spindle cells are negative for KIT (*Figure 9C*), DOG1, S100 protein, ALK, nuclear β-catenin and STAT6. Since mutations of *PDGFRA* gene mostly observed at exon 12 and rarely at exon 18 are detected in almost all IFP cases, IFPs are considered to be a genuine neoplasm (14).

PEComas

PEComas might show epithelioid cell type morphology or spindle cell type one (*Figure 10A*). They are usually positive for both smooth muscle markers such as α-SMA (*Figure 10B*) and melanoma markers such as HMB45 (*Figure 10C*), Melan A (*Figure 10D*) and MITF. KIT is apparently stained in some cases (*Figure 10E*). Basically, tumor cells are negative for DOG1, S100 protein, ALK, nuclear β-catenin and nuclear STAT6. TFE3 is positive in some cases by IHC, and rearrangement of TFE3 by fluorescent *in situ* hybridization (FISH) might be detected in those cases (15,16).

SFTs

SFTs are basically spindle cell tumors and have thick collagen bands and vessels with staghorn-like configuration (*Figure 11A*). Almost all tumors are positive for CD34 (*Figure 11B*) and nuclear STAT6 (*Figure 11C*). Basically, tumor cells are negative for KIT (*Figure 11D*), DOG1, S100 protein, ALK and nuclear β-catenin. They have NAB2-STAT6 fusion genes in most cases (8,9).

IMTs

IMTs often contain many inflammatory cells especially lymphocytes and plasma cells within the tumors (*Figure 12A*). Immunohistochemically, half of them are positive for ALK (*Figure 12B*). Rearrangement of ALK

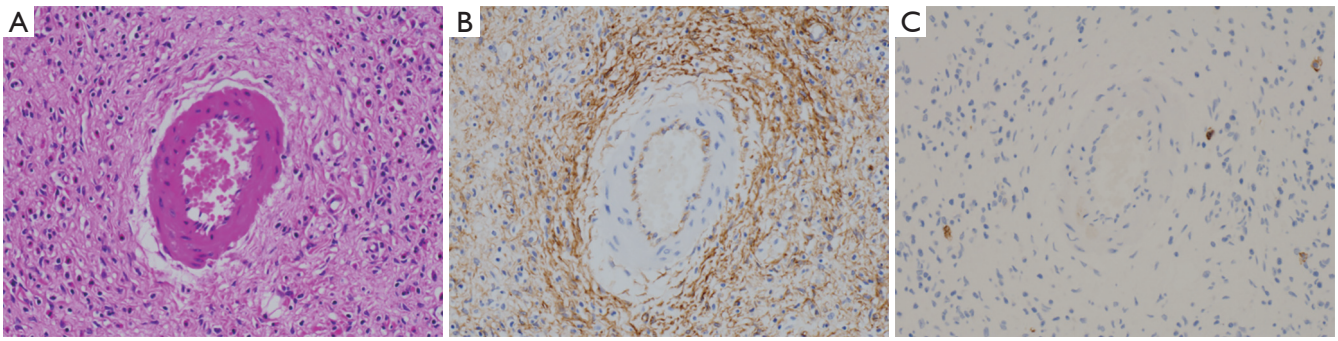

Figure 9 IFP (×200). (A) HE staining; (B) CD34 IHC; (C) KIT IHC. IFP, inflammatory fibroid polyp; IHC, immunohistochemistry.

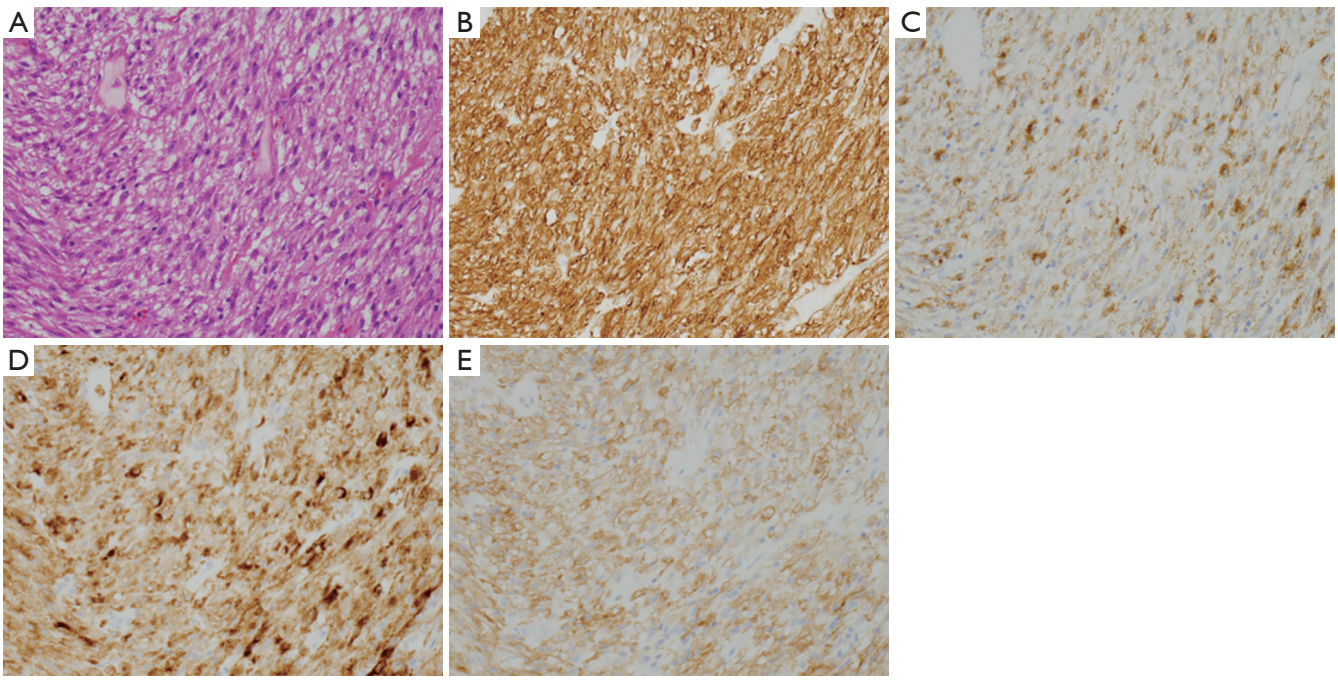

Figure 10 PEComa (×200). (A) HE staining; (B) α-SMA IHC; (C) HMB45 IHC; (D) Melan A IHC; (E) KIT IHC. PEComa, perivascular epithelioid cell tumor; α-SMA, α-smooth muscle actin; IHC, immunohistochemistry.

gene is detected by FISH in half of the cases (11). α-SMA is usually positive in IMTs (*Figure 12C*), but the tumor cells are basically negative for KIT (*Figure 12D*), DOG1, S100 protein, nuclear β-catenin and nuclear STAT6.

Glomus tumors

Most of glomus tumors composed of epithelioid tumor cells. In the GI tract, glomus tumors are very rare. Almost all glomus tumors are positive for α-SMA. However, they are usually negative for KIT, DOG1, CD34, desmin, S100 protein, nuclear β-catenin and nuclear STAT6.

Conclusions

GISTs, leiomyomas and Schwannomas are main GI mesenchymal tumors, but many other types of soft tissue tumors might develop in the GI tract. We have to be careful for the differential diagnoses of these GI mesenchymal tumors. Since we have expensive but very

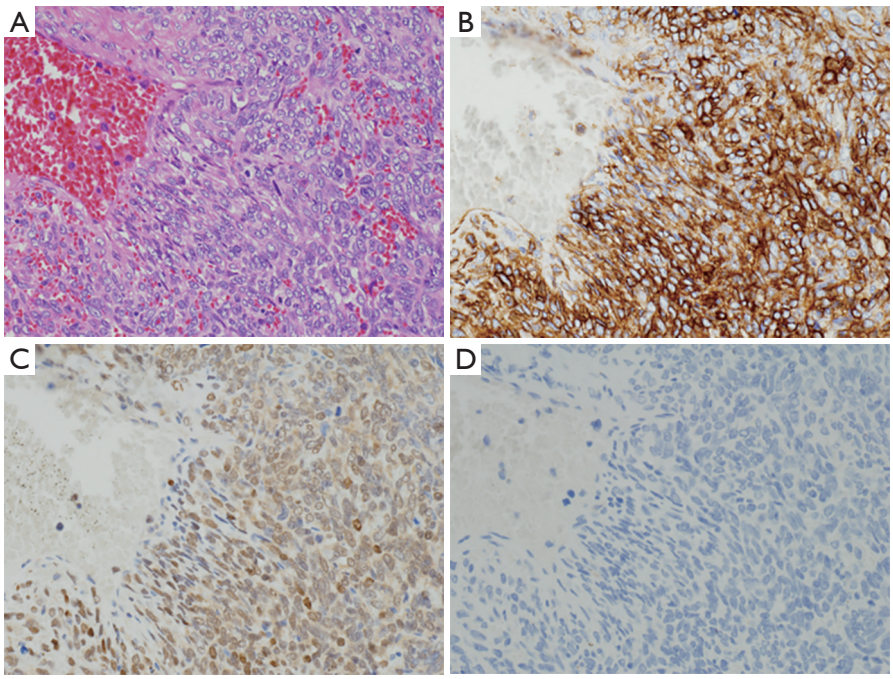

Figure 11 SFT (×200). (A) HE staining; (B) CD34 IHC; (C) STAT6 IHC; (D) KIT IHC. SFT, solitary fibrous tumor; STAT, signal transducer and activator of transcription; IHC, immunohistochemistry.

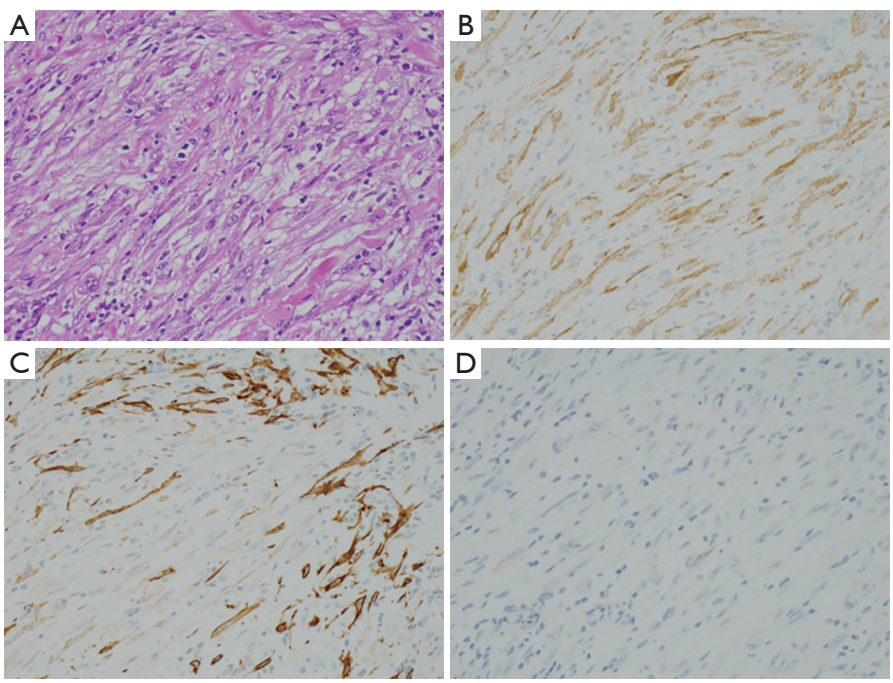

Figure 12 IMT (×200). (A) HE staining; (B) ALK IHC; (C) α-SMA IHC; (D) KIT IHC. IMT, inflammatory myofibroblastic tumor; α-SMA, α-smooth muscle actin; IHC, immunohistochemistry; ALK, anaplastic lymphoma kinase.

effective molecular target drugs such as imatinib, sunitinib and regorafenib for GIST treatment, not only incorrect diagnosis of GIST in nonGIST cases but also incorrect diagnosis of nonGIST in GIST ones give disadvantage to those patients. For correct diagnosis of GISTs, IHC and/or unique genetic analyses for differential diagnoses are necessary.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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