

Fine Needle Aspiration Cytology (FNAC) of Gastrointestinal Stromal Tumor : An Emphasis on Diagnostic Role of FNAC, Cell Block, and Immunohistochemistry

Recently the origin of gastrointestinal stromal tumors (GISTs) is thought to be the interstitial cells of Cajal or primitive stem cells. This study was performed to evaluate the roles of fine needle aspiration cytology (FNAC), cell block preparation, and immunohistochemistry in the diagnosis of GISTs. Nine cases of GIST in which FNAC was performed were included in this study. Cytologically, the tumor cells characteristically occurred in closely packed cohesive tissue fragments with high cellular density often in bloody background. The tumor cells often formed fascicles with parallel, side-by-side arrangements of the nuclei. Histologically, GISTs were highly cellular spindle or epithelioid tumor with basophilic appearance. Immunohistochemically, GISTs were c-kit positive in all of nine cases, CD34 positive in seven, focally SMA positive in two, and S-100 and GFAP negative in all. Both histologic and cell block sections showed the same histologic and immunohistochemical features. Cytomorphologically GISTs show a broad morphologic spectrum but rarely a significant nuclear pleomorphism and the assessment of malignant potential is difficult based on cytology alone. However, in the appropriate clinical and radiologic setting, a confident diagnosis of primary or metastatic GIST can be established by FNAC, cell block, and immunohistochemistry.

Key Words : *Gastrointestinal Neoplasms; Biopsy, Needle; Biopsy, Aspiration; Cytology; Immunohistochemistry*

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INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the most frequent mesenchymal tumor of the gastrointestinal tract (1, 2). GISTs typically present in older individuals and are most common in the stomach (60-70%), followed by small intestine (20-25%), colon and rectum (5%), and esophagus (<5%) (2). The confusion and controversy surrounding this tumor are related to its origin (1, 3, 4). Recently the origin of GISTs has been clarified and is thought to be the interstitial cells of Cajal (ICC) (2, 5, 6) or the primitive stem cells that can differentiate into both ICC and smooth muscle cells (7, 8). The former has been suggested because of the shared expression of c-kit and CD34 in GISTs and ICC and ultrastructural similarities between them. The latter is also supported by the common smooth muscle expression (2, 5, 9-13) in GISTs and the presence of GISTs arising in the peritoneum, mesentery, and omentum (3). GISTs are now defined as cellular spindle cell, epithelioid, or occasionally pleomorphic mesenchymal tumors of the gastrointestinal tract which express the KIT protein on immunohistochemistry (IHC) (11).

The cytologic findings of GISTs are not well documented

because recently the cell of origin for GIST has been clarified and most of the GISTs were diagnosed by surgical resection due to their submucosal or intramural location. Although there have been only a few case reports and series of cases published (14-19), every diagnosis was not supported by c-kit immunostain (18, 19), cytohistologic correlation (16), and histologic diagnoses (16, 18). Most of the cases were not correlated with follow-up data (14, 17, 18).

Until recently, GIST treatment consisted of a surgical resection followed by surveillance for metastatic disease. Chemotherapy and radiation have been ineffective (20). Recently, however, Joensuu et al. reported the effect of STI571 (Glivec, Novartis, Basel, Switzerland), an inhibitor of the tyrosine kinase activity of c-kit, in a patient with a metastatic GIST (21). A rapid and accurate cytologic diagnosis of primary, metastatic, or unresectable GISTs can help clinicians to decide and start a treatment. Thus, it is important for pathologists to be familiar with the cytologic features of GISTs.

In the present study, the clinical utility of fine needle aspiration cytology (FNAC) in the diagnosis of GISTs was evaluated with a focus on cytologic morphology and IHC. Cytohistologic correlation was also performed. We emphasized

the roles of FNAC, cell block preparation, and immunohistochemical stain for c-kit, CD34, S-100, GFAP, and SMA in reaching the correct diagnosis of GISTs.

MATERIALS AND METHODS

Nine cases of GIST in which FNAC was performed were collected from the files of the Department of Pathology, Korea Cancer Center Hospital, Seoul, Korea, from 1985 to 2000. The FNAC smears were obtained from five primary tumors and four metastases. The sites of aspiration biopsies included stomach (n=3), small intestine (n=2), liver (n=3), and omentum (n=1). FNAC was performed under the guidance of ultrasound or computed tomography; a 23-gauge needle was used. The aspirated material was smeared on glass slides, and then fixed in 95% ethanol and stained with Papanicolaou stain for cytologic evaluation. The remaining aspirated material was fixed in 7.5% buffered formalin and made into a clot with the addition of agar. The clot was then processed for paraffin embedding. Sections cut from the cell block were stained

with hematoxylin and eosin. Aspirate preparations were carefully evaluated for various cytomorphologic features and cytologic patterns of GISTs.

Immunohistochemical stain for c-kit (polyclonal antiserum, 1:40 dilution, Santa Cruz Biotechnology, Santa Cruz, CA, U.S.A.), CD34 (QBEnd/10, 1:40 dilution, NeoMarkers, Fremont, CA, U.S.A.), S-100 (polyclonal antiserum, 1:40 dilution, Zymed, San Francisco, CA, U.S.A.), GFAP (G-A-5, 1:80 dilution, Immunon, Pittsburgh, PA, U.S.A.), and SMA (1A4, 1:40 dilution, NeoMarkers) was also performed on all surgical sections and five available cell blocks. The sections of the block, 4 μ m in thickness, were deparaffinized in xylene, hydrated with 100% ethanol and 95% ethanol, and rinsed in distilled water. For pretreatment of c-kit and CD34, microwave antigen retrieval (10 mM citrate buffer; pH 6.0) was done. Endogenous peroxidase was blocked with 0.1% H₂O₂. Slides were incubated with serum blocking solution (Zymed, San Francisco, CA, U.S.A.), primary antibodies, biotinylated secondary antibody (Zymed), and Streptavidin-Horseradish Peroxidase (Zymed). Diaminobenzidine solution was used as chromogen. The slides were counterstained with hema-

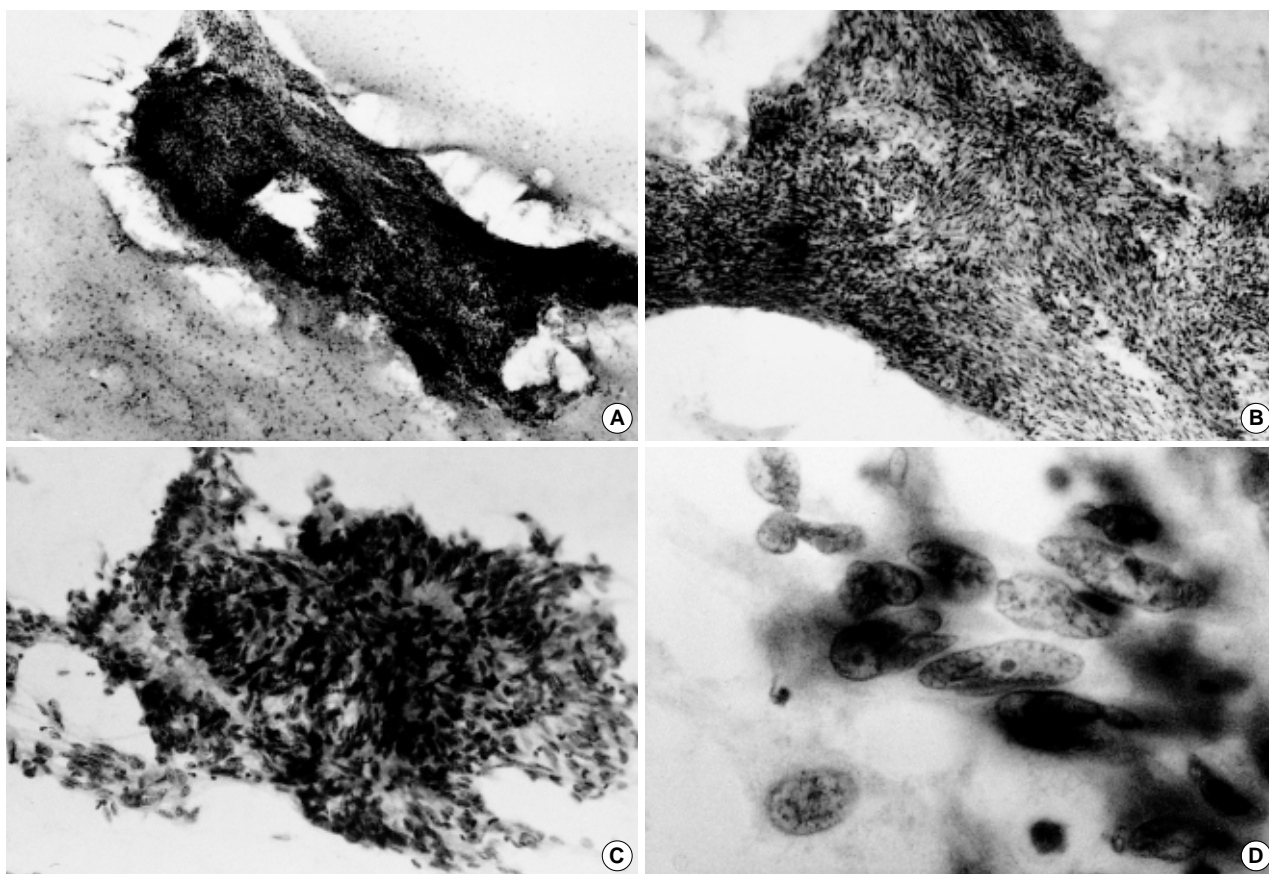


Fig. 1. FNAC of GIST. **A:** At low-power magnification, the tumor cells occur in closely packed cohesive tissue fragments with some loose groupings and single cells (Papanicolaou, $\times 40$). **B:** The tumor cells often form fascicles with parallel, side-by-side arrangements of nuclei with scant cytoplasm (Papanicolaou, $\times 100$). **C:** Nuclear palisading is occasionally observed (Papanicolaou, $\times 200$). **D:** Some tumor cells show elongated, ovoid, or irregular-shaped nuclei with mildly coarse chromatin and small nucleoli (Papanicolaou, $\times 1,000$).

toxylin solution. Immunostaining results of the cell block sections were compared with those of the surgical sections.

The histologic sections of GISTs were divided into three groups according to the criteria of Lewin et al. (22). The guidelines for the diagnosis of malignancy or potential aggressiveness in GISTs were composed of two unequivocal factors (histologically confirmed metastases and invasion of adjacent organs) and seven high-risk factors [size (>5.5 cm in stomach, >4 cm in small or large intestine), mitoses ($>5/50$ high-power fields in stomach, any in small or large intestine), tumor necrosis, nuclear pleomorphism, dense cellularity, microscopic invasion of the lamina propria or blood vessels, and pattern; alveolar or cell balls in the epithelioid variant]. Malignant GIST was given when one unequivocal or two or more high-risk factors were present, GIST of uncertain malignant potential (UMP) when only one high-risk factor was present, and benign GIST when there was no high-risk factors. In this study, spindle cell and epithelioid tumors were not separated because epithelioid tumors had areas of spindle cells or vice versa (22) and a previous study showed similar antigen expression (9). The follow-up information was reviewed from the hospital records, tumor registries, and database of the clinical research institute.

RESULTS

Cytologic Findings

Cytological features of the GISTs are summarized in Table 1. They demonstrated low to moderate overall cellularity usually in bloody background. All tumor cells occurred characteristically in closely packed cohesive tissue fragments with a high cellular density. Some tumor cells occurred singly and in loose groupings (Fig. 1A). The tumor cells often formed fascicles with parallel, side-by-side arrangements of nuclei (Fig. 1B). Nuclear palisading was found in three cases (Fig. 1C). They had spindle-shaped, elongated, ovoid, round, or irregular-shaped nuclei. Four had predominantly spindle nuclei and five predominantly oval nuclei. Multinucleate tumor cells were encountered occasionally. There was a mild to moderate nuclear pleomorphism (Fig. 1D). The chromatin was finely to moderately coarsely granular. In three of the nine cases mitotic figures were rarely observed. The nucleoli were indistinct or noticeable. The neoplastic cell cytoplasm was scant to moderate and some of the tumor cells appeared as stripped nuclei. The cell membranes were inconspicuous. In two of the nine cases perinuclear cytoplasmic vacuoles

Table 1. Cytological features of nine cases GISTs

Case No.	1	2	3	4	5	6	7	8	9
Aspiration site	stomach	stomach	liver	liver	liver	stomach	omentum	small intestine	small intestine
Background	bloody	bloody	bloody	clear	bloody	bloody	bloody	bloody	clear
Overall cellularity	low	low	moderate	low	low	moderate	moderate	moderate	moderate
Cellular density in tissue fragments	high	very high	very high	very high	moderate to high	high	very high	high	high
Cellular arrangement	closely packed with parallel arrangement, loose groupings, single cells	closely packed with parallel arrangement, a few single cells	closely packed with focal parallel arrangement and nuclear palisading, loose groupings, single cells	closely packed, numerous single cells	closely packed with parallel arrangement, loose groupings, single cells	closely packed with parallel arrangement and focal nuclear palisading, loose groupings, single cells	closely packed with parallel arrangement, numerous single cells	closely packed with focal parallel arrangement, loose groupings, single cells	closely packed with nuclear palisading, loose groupings, single cells
Nuclear shape	spindle, oval	spindle, oval	oval, spindle	oval, round	spindle	spindle	oval, spindle	oval	oval, spindle, round
Nuclear pleomorphism	moderate	moderate	moderate	moderate	moderate	mild	moderate	mild	moderate
Chromatin	mildly coarse	mildly coarse	mildly coarse	moderately coarse	mildly coarse	fine	moderately coarse	mildly coarse	moderately coarse
Nucleoli	indistinct	indistinct	indistinct	noticeable	indistinct	indistinct	noticeable	noticeable	noticeable
			focally noticeable						
Mitosis	-	-	+	-	-	-	+	-	+
Cytoplasmic border	indistinct	indistinct	indistinct	indistinct	indistinct	indistinct	indistinct	focally distinct	indistinct
Amount of cytoplasm	scant to moderate	scant	scant	scant	scant to moderate	scant to moderate	scant to moderate	scant to moderate	scant to moderate
Cytoplasmic vacuoles	-	-	-	-	-	-	+	+	-
Vascularity	+	-	+	+	-	-	-	+	+
Necrotic debris	-	-	+	-	-	-	+	-	-

GISTs, gastrointestinal stromal tumors.

were found. In five of the nine cases blood vessels were seen within the periphery of the tumor fragments or cell clusters. In two cases, necrotic debris was found.

Clinicopathologic Findings

Clinical features of the study cases are summarized in Table 2. Grossly the tumors were firm to soft or fish flesh-like yellow-white, tan, gray-pink, or variegated. Most had areas of hemorrhage and some had areas of necrosis, myxoid change, ulceration, or cavitation (Fig. 2). Histologic features of the study cases are summarized in Table 3. Histologically, most of the tumors showed an overall basophilic appearance with a high cellularity (Fig. 3A). Five cases showed some areas of palisading. Nuclear pleomorphism was mild to moderate (Fig. 3B). Mitotic counts varied from 1 to 76 per 50 high-power fields (mean, 30.8). The nucleoli were indistinct or noticeable. The cell membranes were inconspicuous except

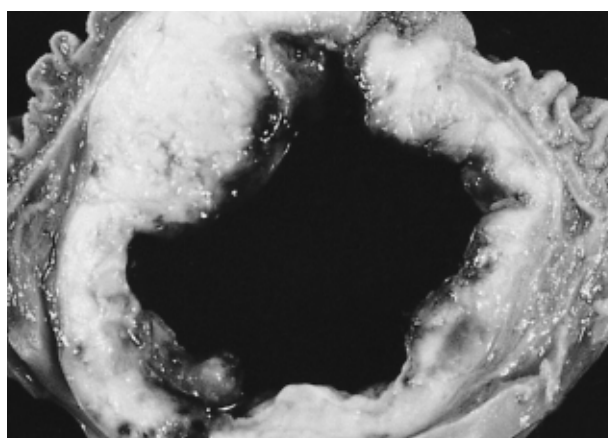


Fig. 2. Excised surgical specimen shows soft, fish-flesh tan, gray-pink cut surface with central necrosis and cystic change.

one case. The cytoplasmic vacuoles were found in most of the cases. All tumors showed hemorrhage. Coagulation necrosis not associated with overlying superficial ulceration was observed in five tumors. The cell blocks (Fig. 4) prepared from

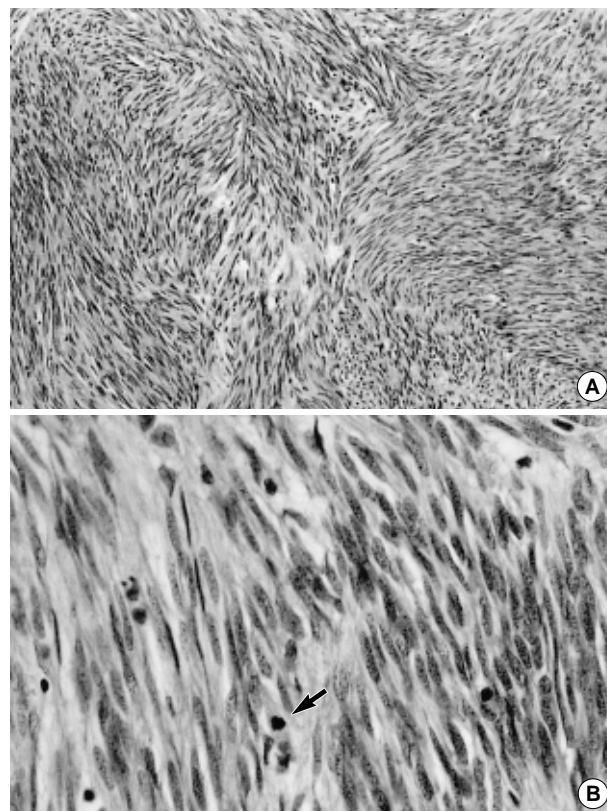


Fig. 3. Histologic section of GIST. **A:** Low magnification of the tumor shows a high cellularity with an overall basophilic appearance. The tumor consists of interlacing fascicles of spindle cells (H&E, $\times 100$). **B:** The tumor shows elongate nuclei with mildly coarse chromatin and a mitotic figure (arrow) (H&E, $\times 400$).

Table 2. Clinical features of nine cases who underwent FNAC of GISTs

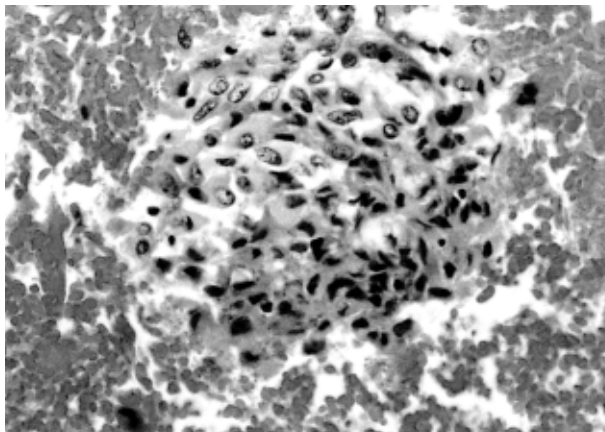
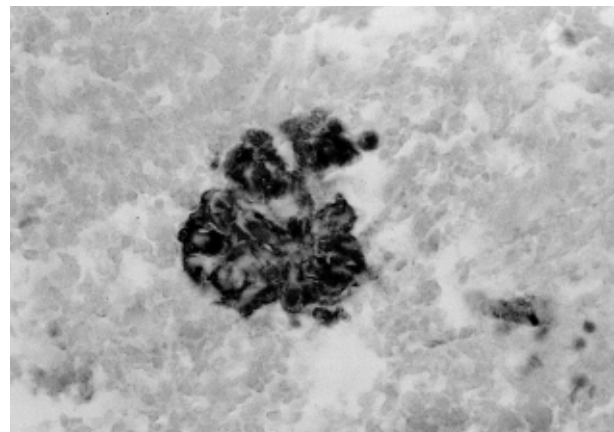
Case No.	Sex/Age (yr)	Diagnosis	Treatment	Primary location	Size (cm)	Adjacent organ invasion	Associated disease	Follow-up period (mo)	Clinical course
1	M/52	malignant GIST	STG	stomach	25	present	absent	2	Dead
2	F/59	malignant GIST	TG	stomach	30	absent	absent	23	Hepatic metastasis & recurrence (8 mo), Dead
3	F/35	malignant GIST	TG	stomach	17	absent	absent	24	Hepatic metastasis (16 mo), Dead
4	F/47	malignant GIST	TG	stomach	7	absent	gastric carcinoma	51	Hepatic metastasis (31 mo), Dead
5	M/62	malignant GIST	TG	stomach	12	present	absent	63	Hepatic metastasis (54 mo), Dead
6	F/48	GIST of UMP	EX	stomach	5	absent	chronic hepatitis, HBV	66	Alive without the disease
7	F/45	malignant GIST	SR	small intestine	15	absent	absent	24	Omental metastasis (24 mo), Alive with the disease
8	F/60	malignant GIST	EX	small intestine	12	absent	absent	36	Hepatic metastasis (35 mo), Alive with the disease
9	M/55	malignant GIST	SR	small intestine	20	absent	absent	2	Alive without the disease

FNAC, fine needle aspiration cytology; GISTs, gastrointestinal stromal tumors; STG, subtotal gastrectomy; TG, total gastrectomy; EX, excision; SR, segmental resection; UMP, uncertain malignant potential.

Table 3. Histological features of nine cases who underwent FNAC of GISTs

Case No.	Cellularity	Cellular shape	NP	Mitoses/50 HPF	Chromatin	Nucleoli	Cytoplasmic border	CV	Amount of cytoplasm	Nuclear atypia	H	N	U	MI
1	high	spindle	-	19	mildly coarse	rare	indistinct	+	scant to moderate	moderate	+	+	+	-
2	high	spindle, epithelioid	-	51	mildly coarse	indistinct	indistinct	+	scant to moderate	moderate	+	+	+	+
3	high	spindle	+	76	mildly coarse	indistinct	indistinct	+	scant to moderate	moderate	+	+	+	-
4	high	spindle, epithelioid	-	25	moderately coarse	noticeable	distinct	+	moderate	moderate	+	+	+	-
5	high	spindle	+	54	mildly coarse	indistinct	indistinct	-	scant to moderate	moderate	+	-	+	+
6	moderate	spindle	+	6	fine	indistinct	focally distinct	+	moderate	mild	+	-	-	-
7	high	spindle	-	2	moderately coarse	indistinct	indistinct	+	scant to moderate	moderate	+	+	+	+
8	high	spindle	+	1	mildly coarse	noticeable	focally distinct	+	scant to moderate	moderate	+	-	-	-
9	moderate	spindle	+	43	moderately coarse	noticeable	indistinct	+	moderate	moderate	+	-	+	+

FNAC, fine needle aspiration cytology; GISTs, gastrointestinal stromal tumors; NP, nuclear palisading; CV, cytoplasmic vacuole; H, hemorrhage; N, necrosis; U, ulcer; MI, mucosal invasion.

**Fig. 4.** Cell block of GIST. Syncytial aggregates of spindle or oval cells are shown (H&E, ×400).**Fig. 5.** The tumor cells show a diffuse strong immunoreactivity to c-kit (c-kit immunostain, ×400).**Table 4.** Immunohistochemical features of nine cases of gastrointestinal stromal tumors

Case	Cell blocks					Surgical sections				
	c-kit	CD34	S-100	GFAP	SMA	c-kit	CD34	S-100	GFAP	SMA
1	+	+	-	-	-	+	+	-	-	-
2						+	-	-	-	-
3						+	+	-	-	+
4						+	+	-	-	-
5	+	+	-	-	-	+	+	-	-	+
6						+	+	-	-	-
7	+	+	-	-	-	+	+	-	-	-
8	+	+	-	-	-	+	+	-	-	-
9	+	-	-	-	-	+	-	-	-	-

GFAP, glial fibrillary acidic protein; SMA, smooth muscle actin.

the FNAC showed the similar histological features to surgical sections.

Immunohistochemical Findings

The immunohistochemical features of the GIST cases in both histologic and cell block sections are summarized in Table 4. All cases were diffusely and strongly c-kit positive (Fig. 5) and S-100 and GFAP negative. Four of the five cell block sections and seven of nine histologic sections were CD34 positive. Two of the nine histologic sections were focally SMA positive.

DISCUSSION

Cytologically, GISTs occurred characteristically in closely packed cohesive tissue fragments with a high cellular density often in bloody background and often formed fascicles with parallel, side-by-side arrangements of nuclei. These findings were supported by the histologic sections in which GISTs consisted of broad bundles, interlacing fascicles, or occasionally whorls of spindle or oval cells with a high cellular density and overall basophilic appearance at low magnification. In Li et al. study (17) in which histologic analysis was not performed in about 1/3 of cases, benign and borderline GISTs tended to have cells arranged in tightly cohesive clusters. Malignant GISTs were more likely to exhibit loosely cohesive groups with many single cells, but in the present study all GISTs including eight malignant and one UMP occurred characteristically in closely packed cohesive tissue fragments with a high cellular density. Histologically, GISTs are a highly cellular tumor (10) compared with moderately cellular schwannomas (23) and paucicellular leiomyomas (11, 24) and at least cellular density of GISTs in tissue fragments, whether tightly or loosely cohesive, is thought to be relatively higher than that of schwannomas and leiomyomas.

GISTs had spindle-shaped, elongated, ovoid, round, irregular-shaped nuclei with mild to moderate nuclear pleomorphism and scant cytoplasm. The correspondence between the cytologic and histologic features was observed also at high magnification. However, it was difficult to find mitoses, a criterion to diagnose malignant GISTs, in the cytologic smears because most of the tumor cells occurred in closely packed cohesive thick tissue fragments. Li et al. (17) also found that mitoses in the resected malignant GISTs were seldom seen in FNAC smear. Besides, in the present and previous (14, 15, 19) studies malignant GISTs had no significant pleomorphism in the cytologic smears. The assessment of malignant potential is difficult based on cytomorphologic features alone and predictions about potential aggressiveness should be best reserved for gross and histologic examination of the resected specimen.

Malignant counterparts of gastrointestinal schwannomas have not been documented (11). True leiomyosarcomas are very rare in the gastrointestinal tract (11). The important differential diagnoses of GISTs without significant nuclear pleomorphism include leiomyomas and schwannomas. The separation of GIST from schwannoma or leiomyoma is clinically important because the former group has a high risk of malignant behavior (1, 3, 4, 24) and the latter pursues a benign course (11, 23, 25-27). GISTs differ clinicopathologically from leiomyomas and schwannomas (5, 8, 11, 28-30). Most gastrointestinal mesenchymal tumors belong to the group of GISTs (11). Schwannomas are rare in the gastrointestinal tract and mainly occur in the stomach, rarely in the colon or esophagus (23, 25-27), and they have never been reported in the small intestine, mesentery, or retroperitoneum.

Similar to GISTs, schwannomas predominantly occur in older middle age (23, 25). Leiomyomas occur in the esophagus, colon, and rectum, but are very rare elsewhere in the gastrointestinal tract. They are the most common mesenchymal tumor of the esophagus (11, 24). The esophageal leiomyomas occur more often in males (2:1) and at a younger age than GISTs with a median age of 30-35 yr (11). Immunohistochemically, schwannian differentiation is typical of schwannomas, which are positive for S-100 (6, 9, 11, 12, 23, 25-28), GFAP (23, 25, 26, 28), and vimentin (6, 7) and negative for SMA (9, 25, 26, 28), c-kit (6, 10, 12, 28), and CD34 (6, 9, 25, 26, 28). Smooth muscle differentiation is typical of leiomyomas, which are usually positive for smooth muscle actin (2, 9-12, 28). Nonreactivity, however, is the rule with S-100 (6, 9, 10), vimentin (6), CD34 (6, 9-12, 28), and c-kit (5, 6, 10-12, 28).

We believe that most of the cases of smooth muscle tumors of the gastrointestinal tract reported in the literature probably belong to the GIST category; Park et al. (31) reported FNAC cytology of a case of gastric epithelioid leiomyosarcoma metastasized to the liver, which stained positively for vimentin and CD34 and showed no reactivity to desmin, alpha-smooth muscle actin, and S-100 protein. Its clinical and immunohistochemical features were consistent with GIST; Wee and Nilsson (32) reported FNAC biopsy of five cases of metastatic leiomyosarcoma. Among these tumors, a gastric primary epithelioid leiomyosarcoma demonstrated vimentin immunoreactivity and was negative for SMA, pan actin, desmin, myosin, and S-100. Its clinicopathologic and immunohistochemical features were also consistent with GIST.

Cytomorphologically GISTs show a broad morphologic spectrum but rarely a significant nuclear pleomorphism, and thus it is difficult to diagnose GISTs with a high risk of malignant behavior based on cytology alone. However, in an appropriate clinical and radiologic setting the presence of closely packed spindle or oval cells forming fascicles with parallel side-by-side arrangements of nuclei suggests GIST and its immunohistochemical features in the cell block sections are sufficient to distinguish GIST from leiomyoma or schwannoma. In conclusion, a confident diagnosis of primary or metastatic GIST can be established by FNAC cytology, cell block, and IHC for c-kit, CD34, S-100, GFAP, and SMA.

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