Comparative cytology of stromal tumors of the gastrointestinal tract

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ABSTRACT

The cytologic features of four cases of stromal tumors arising in the gastrointestinal tract are presented here. Two benign schwannomas of the stomach showed characteristic findings of spindle cells within a background containing abundant mature lymphcytes. A benign gastrointestinal stromal tumor (GIST) of the duodenum demonstrated small clusters composed of spindle cells with uniform and cigar-shaped nuclei. A malignant GIST metastatic to the liver was composed of isolated plump spindle cells with hyperchromatic nuclei with multiple small nucleoli. The diagnosis and classification of a gastric or intestinal stromal tumor is possible based on the cytologic findings.

Key words : Cytology, Gastrointestinal stromal tumors, Soft tissue tumors, Immunohistochemistry

INTRODUCTION

Recent advances in diagnostic imaging, including endoscopic ultrasonography, have facilitated the detection of stromal tumors in the gastrointestinal tract. However, it is still difficult to identify the histological characteristics of the tumors by endoscopic biopsy prior to surgical resection. It is reasonable, therefore, to speculate that the diagnosis of these tumors by cytologic approaches may be more difficult (1). However, since they consist of heterogenous tumors differing in their clinical courses (2), the preoperative diagnosis of the tumors is clearly important. The cellular origin of a large number of the stromal tumors is still unknown and hence many pathologists prefer to tentatively designate them

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as gastrointestinal stromal tumors (GISTs)[3-7].

We describe the cytologic findings in four cases of stromal tumors arising in the gastrointestinal tract and discuss the cytologic diagnosis of subgroups of the tumors.

CASE REPORTS

Case 1

A 74-year-old female complained of a six month history of left flank pain. Abdominal ultrasound and endoscopic ultrasonography revealed a solid, 8.0 X 6.5 cm, intramural gastric mass protruding into the subserosa. She underwent a total gastrectomy.

Case 2

The patient was a 61-year-old female who had been diagnosed with Parkinson's disease. A routine endoscopic examination of the gastrointestinal tracts showed a intramural mass located at the cardiac region, measuring 5.8 cm in maximum diameter. She underwent a proximal gastrectomy.

Case 3

A 59-year-old male presented with a duodenal mass. Diagnostic imaging revealed that the mass measured 3.1 cm in maximum diameter and was situated within the muscularis propria of the third portion of the duodenum. Partial duodenectomy was performed.

Case 4

The patient was a 65-year-old male who had had a proximal gastrectomy three years previously for stromal tumor of the stomach. Abdominal ultrasound revealed three hepatic masses, which were considered to be metastatic tumors. He then underwent a partial hepatectomy.

MATERIALS AND METHODS

Four cases available for cytologic examination were identified in the files of the department of clinical pathology of Sapporo Medical University Hospital from among 53 stromal tumors in the gastrointestinal tract occurring between 1976 and 1997. All cytologic material were obtained by imprint preparation of the fresh specimen and immediately fixed in 95% ethanol for subsequent Papanicolaou staining. Formalin-fixed, paraffin-embedded tissues were used for histologic examination. The number of mitotic figures per 50 high-power fields (HPF) were counted in each case. Immunohistochemical study was performed

with the streptoavidin-biotin-peroxidase complex method. The antibodies used included vimentin, desmin, alfa-smooth muscle actin (SMA;DAKO), S-100 protein (polyclonal, Nichirei) and CD34 (clone HPCA-1, Becton Dickinson).

According to other recent studies on stromal tumors of the gastointestinal tract (8-11) and our immunohistochemical analysis of 53 tumors, it would seem that they can be histologically divided into four categories :

1) Leiomyomas : Tumors resembling smooth muscle cells, as evidenced by immunoreactivity with SMA and desmin.
2) Benign schwannomas, designated by Daimaru (9) : Tumors resembling schwann cells, as supported by immunoreactivity with S-100 protein, and characterized by the presence of peripheral lymphoid cuffs. These tumors differs from the conventional soft tissue schwannomas in that they lack distinct nuclear palisading.
3) GISTs, gastric type, benign or malignant : Tumors arising in the stomach and lacking differentiation towards either cell type. Occasionally, myxoid degeneration is prominent. Immunohistochemically, the tumors in this category are positive for CD34 and vimentin, and negative for desmin, SMA and S-100 protein.
4) GISTs, intestinal type, benign or malignant : Tumors arising in the intestine (the duodenum, jejunum and ileum) and lacking differentiation towards either cell type. Immunohistochemically, the majority of tumors in this category are positive for vimentin and SMA, whereas a minority of them also show focal and weak immunoreactivity for CD34. Desmin and S-100 protein are negative.

In this paper, we use the term "GIST" in a restricted sense that excluded leiomyomas and schwannomas. Leiomyomas and benign schwannomas have a benign behavior, whereas the biological behavior of GISTs is difficult to predict regardless of the type of the tumors. The distinction between benign and malignant GIST was based on multiple factors, including tumor size, mitotic activity, cellularity, histological grade and invasion according to previously published criteria (8).

CYTOLOGIC FINDINGS

The imprint smears from case 1 and 2 shared a number of common cytologic features. They demonstrated cellular smears composed of isolated spindle cells within a background containing abundant mature lymphcytes (Fig. 1A). The spindle cells had long hair-like cytoplasmic processes and solitary elongated or tapered nuclei, and occasionally formed loose aggregates (Fig. 1B). There was mild nuclear pleomorphism.

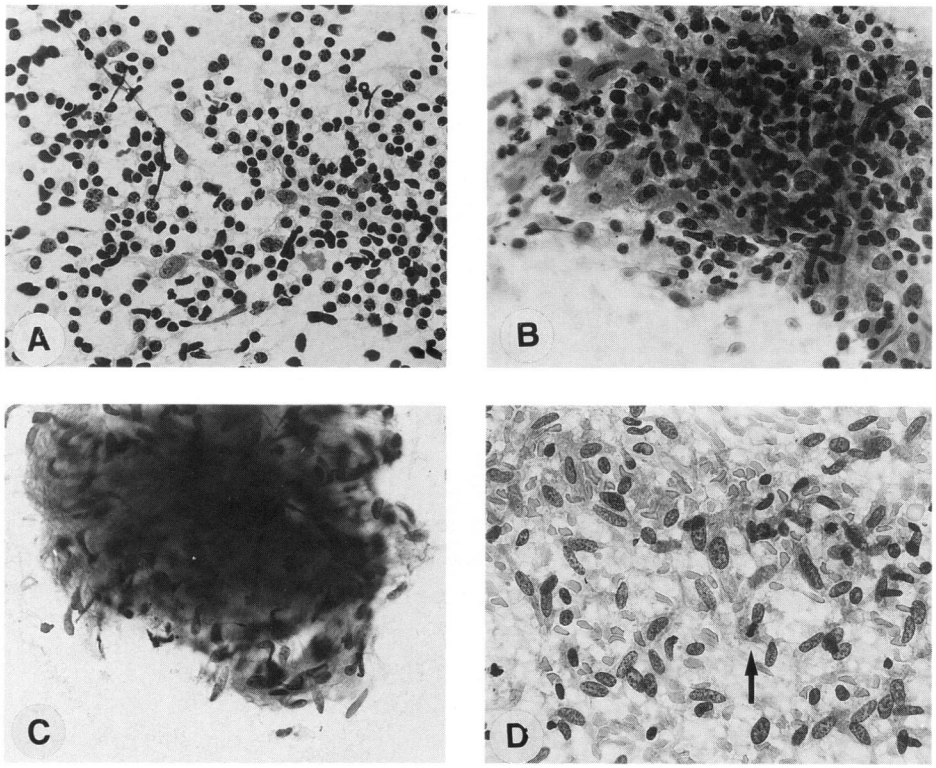

Fig. 1 Cytologic findings (Papanicolau stain). (A) Case 1. The imprint smear shows isolated spindle cells within the background containing abundant mature lymphcytes (X 200). (B) Case 2. Cellular aggregate composed of spindle cells with elongated or tapered nuclei and lymphocytes (X 400). (C) Case 3. Small cluster of spindle cells with uniform and cigar-shaped nuclei (X 400). (D) Case 4. Isolated and noncohesive plump spindle cells. Nuclei are hyperchromatic, with discernible nucleoli. A mitotic figure is seen (arrow) (X 400).

The smears from case 3 were poorly cellular, containing a dissociated population of small clusters composed of spindle cells with ill-preserved cytoplasms (Fig. 1C). The nuclei were uniform and cigar-shaped with blunded ends. The background was necrotic and lymphocytes were scant. No mitotic figures were seen.

In case 4, the imprint smears contained slender or plump spindle cells in single form in a bloody and myxoid background (Fig. 1D). The tumor cells showed hyperchromatic, well-outlined slender to oval nuclei with mutiple small nucleoli. Some cells preserved abundant, cyanophilic cytoplasm with long cytoplasmic processes. There was thickening of the nuclear membrane and moderate nuclear pleomorphism. Mitotic figures were occasionally seen.

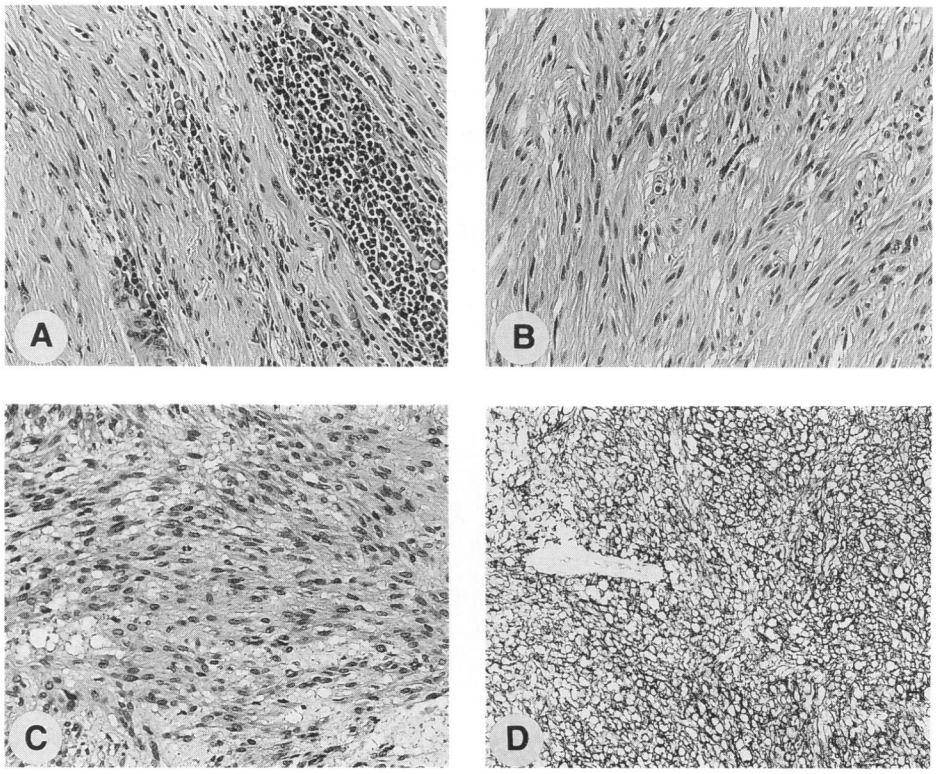

Fig. 2 Histologic findings. (A) Case 1. Woven nests of spindle cells with the infiltration of mature lympncytes. (B) Case 3. Uniform spindle cells are arranged in fascicles. (C) Case 4. Round to short spindle cells are arranged in ill-defined fascicles with intercellular myxoid matrix (A-C ; hematoxylin and eosin, X 200). (D) Case 4. All tumor cells are positive for CD34 (immunoperoxidase stain, X 200).

HISTOLOGIC FINDINGS

In case 1, the tumor existed in the subserous layer of the gastic wall and appeared to be contiguous with the muscularis propria. The overlying mucosal layer was intact. The tumor was composed of woven nests of compact bundles of spindle cells admixed with an infiltration of mature lymphocytes (Fig. 2A). Of paticular note was a peripheral cuff of lymphoid aggregates around the tumor mass. The nuclei varied in shape and size, displaying mild pleomorphism. Immunohistochemically, the tumor cells were positive for S-100 protein and vimentin, and negative for desmin, SMA and CD34. A diagnosis of benign schwannoma of the gastrointestinal tract was made according to the criteria proposed by Daimaru et al. Case 2 also demonstrated approximately the same histological and immunohistochemical features as those of case 1, which were

consistent with the criteria of benign schwannomas.

The duodenal tumor in case 3 was composed of spindle cells with cigar shaped nuclei and fine cell processes that were arranged in fascicles or focally striform patterns (Fig. 2B). Necrosis was not present and mitotic figures were rare (0.14 mitoses per 50 HPF). Immunohistochemical stainings revealed that the tumor cells were positive for SMA and vimentin, and negative for desmin, S-100 protein and CD34. The tumor was classified as a benign GIST, intestinal type.

In case 4, the metastatic liver tumor was composed of round to spindle cells arranged in ill-defined fascicles with an intercellular myxoid matrix (Fig. 2C). The spindle cells contained round to oval nuclei with abundant eosinophilic cytoplasm. In some areas, epithelioid cells showing round or polygonal shapes with perinuclear vacuoles were prominent. The mitotic count was five mitoses per 50 HPF. Immunohistochemically, the tumor cells were positive for CD34 (Fig. 2D) and vimentin, and negative for desmin, SMA and S-100 protein. On retrospective examination, this tumor showed the same basic features as the original gastric tumor, which was resected three years previously, and measured 3.5 cm in maximum diameter. This tumor was a malignant GIST, gastric type.

DISCUSSION

Primary stromal cell neoplasms arising in the wall of the stomach and intestines form a set of heterogenous tumors with differing clinical and pathological findings (3-7). Historically, the stromal cell tumors have been believed to be myogenic, probably because most of them contain long spindled shaped cells and arise from the muscularis propria. However, many studies have demonstrated that a large number of them show non-myogenic phenotypes, immunohistochemically and ultrastructurally (12-16). It has recently been accepted that the group of the stromal cell tumors which cannot be assigned to any specific cellular lineage tentatively be termed gastrointestinal stromal tumors (GISTs). We also believe that the term "GIST" should be used in a restricted sense that excluded leiomyomas and schwannomas.

Recently, it has been reported that a subset of GISTs expresses CD34 antigen, which is well known as a marker of hematopoietic stem cells (13, 17). In normal tissue, CD34 antigen is expressed by not only hematopoietic cells but also by endothelial cells, perineural stromal cells and dendritic cells within the dermis (18). In our immunohistochemical observations, only gastric type GISTs demonstrated diffuse immunoreactivity for CD34 (data not shown). This finding is consistent with the idea that different types of stromal tumors occur in different sites, as emphasized by Appelman (2).

In the present report we show that benign schwannomas have distinctive

cytologic features, which are spindle cells with long hair-like cytoplasmic processes in a lymphocyte-rich background. In addition, the malignant GIST metastatic to the liver in case 4 was composed of plump spindle cells with nuclear atypia and mitotic activity, which were not observed in the benign GIST in case 3. The cytological findings of GISTs were consistent with those described by King et al (1). Since a benign schwannoma shows a uniformly indolent behavior whereas it is widely believed that the biologic behavior of GISTs is less predictable (9, 11), it is important to distinguish between them. Therefore, we suggest that cytologic preparations with the aid of clinical information and immunohistochemical techniques, could be useful for the detection of cell populations that have the potential to progress to malignancy

The tumors showing differentiation toward neural cells in the autonomic myenteric plexus are designated as gastrointestinal autonomic nerve tumors (GANs), which are clinically aggressive and mostly defined by their ultrastructural features (19, 20). Since these tumors are not histologically and immunohistochemically distinctive, we cannot exclude the possibility that the gastric tumor in case 4 belongs to GANs.

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