RADIOGRAPHIC CHARACTERISTICS OF GASTROINTESTINAL STROMAL TUMOR (GIST)

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Key Words: Alpha-smooth muscle actin, CD34, c-kit, CT, gastrointestinal tract, GIMT (gastrointestinal mesenchymal tumor), GIST (gastrointestinal stromal tumor), ICC (interstitial cells of Cajal), immunohistochemistry, leiomyosarcoma, MRI, mesenchymal tumors, S-100 protein, single detector-row helical CT, stromal tumors.

Synopsis

Background: Recent advances in immunohistochemistry have revealed that the majority of the tumors originating from mesenchymal tissues of gastrointestinal tract (GI tract) are gastrointestinal stromal tumors (GISTs). The purpose of this study is to reevaluate the imaging findings of mesenchymal tumors of gastrointestinal tract pathologically proven as gastrointestinal stromal tumors.
Materials and Methods: Ten mesenchymal tumors of gastrointestinal tract were resected at our hospital from May 1993 till March 2001. These were examined immunohistochemically using antibodies against c-kit, CD34, alpha-smooth muscle actin, and S-100 protein. Their imaging findings in CT, MRI, and endoscopy and their clinical features were reviewed.

Results: A diagnosis of gastrointestinal stromal tumor was confirmed in all 10 cases by immunohistochemical studies. The imaging findings were similar in some respects to those of tumors that were conventionally diagnosed as leiomyosarcoma. However, gastrointestinal stromal tumors were less in vascularity than conventionally reported leiomyosarcomas. Moreover, the findings of necrosis or myxoid change in each small nodule of large multinodular tumor were characteristic of gastrointestinal stromal tumors.

Conclusions: The characteristic imaging findings of gastrointestinal stromal tumors in this study might be useful for their preoperative precise diagnosis.

Introduction

Although submucosal tumors of GI tract have been conventionally considered to originate from the smooth muscle layer, recent advances in immunohistochemistry has shown that many of them belong to tumors derived from various mesenchymal cells. All these tumors have been inclusively termed gastrointestinal mesenchymal tumors (GIMTs). In 1983, Mazur et al. introduced the concept of gastrointestinal stromal tumor (GIST) for a group of submucosal tumors of GI tract that are negative for muscle cell markers and nerve cell markers (Mazur, Clark et al. 1983), and currently 80% of GIMTs are considered to be GISTs, while 10% are myogenic tumors and 10% are neurogenic tumors (Miettinen, Sarlomo-Rikala et al. 1999), Nishida, Hirota et al. 2000). Generally, GISTs are considered to be positive for KIT and CD34, while tumors negative for these but positive for smooth muscle markers (alpha-smooth muscle actin, desmin, and caldesmon) are classified into myogenic tumors, and tumors positive for nerve markers (S-100 protein and neuron-specific enolase (NSE) are classified into neurogenic tumors (Nishida, Hirota et al.2000), Miettinen, Virolainen et al. 1995), Miettinen, Lasota et al.2001).

Accompanied with the establishment of the new classification of GIMTs, it is important to clarify the characteristics of their clinical pictures. We examined immunohistochemically GIMTs resected at our hospital and retrospectively reviewed their clinical features, especially the imaging findings of CT, MRI, and endoscopy.
Materials and Methods

Ten patients with submucosal mesenchymal tumors of GI tract were examined, who underwent surgical resection at our hospital from May 1993 till March 2001. Imaging studies such as CT, MRI, and endoscopy were performed in all 10 patients, and paraffin-embedded tissues of the resected specimens were available for immuno-histochemical study. The patients were 4 men and 6 women and their age ranged from 37 to 74 years old, with a mean of 60.7. Five of 10 tumors resected until 1997 did not undergo adequate immunohistochemical examination and their diagnosis at the time of operation was leiomyosarcoma in 2 cases and leiomyoma in 3. On the other hand, as for 5 tumors undergoing surgical resection since 1998, a diagnosis of GIST was made on 4 and leiomyosarcoma in 1.

At the beginning of this study, immunohistochemical examination using various antibodies was performed to make a differential diagnosis of GIST, myogenic tumor, and neurogenic tumor. From the paraffin-embedded tissues serial sections of about 1.5cm² in area and 4μm in thickness were obtained. As primary antibodies to identify GIST, mouse monoclonal antibody against human KIT (104D2; DAKO, Carpiteria, CA, USA) and mouse monoclonal antibody against human CD34 (NU-A41; Nichirei, Japan) were used, while mouse monoclonal antibody against human alpha-smooth muscle actin (1A4; DAKO, Carpiteria, CA, USA) and rabbit polyclonal antibody against human S-100 protein (H612; Nichirei, Japan) were used as primary antibodies to identify myogenic tumors and neurogenic tumors respectively. All the primary antibodies were used in a protein concentration of 2-5μg/ml. The sections were then reacted with biotinylated goat anti-mouse or rabbit antibody with streptavidin-peroxidase conjugates (LSAB² System; DAKO, Carpiteria, CA, USA). The localization of each antigen was visualized by the incubation with diaminobenzidine solution and then faint counterstaining was performed with Mayer's hematoxylin.

Next we defined the diagnostic criteria based on the previous reports on conventional leiomyosarcomas and reassessed the imaging findings of our cases.

Imaging characteristics of the tumor with CT and MRI were reviewed with regard to tumor lesion (single nodule or multinodular lesion), the direction of tumor growth
(whether the main direction of growth was intraluminal or extraluminal), mucosal ulceration, intratumoral necrosis or myxoid change, hemorrhage, invasion of surrounding tissues, peritoneal dissemination and metastasis to other organs. Vascularity of the tumor was assessed with arterial dominant phase of dynamic enhancement CT study or the volume and number of peritumoral drainage vein demonstrated in equilibrium phase.

In all patients, CT was performed with single detector-row helical CT (ProSeed, GEYMS, WI, USA) and MRI was performed with 0.5T machine (Vectra, GEYMS, WI, USA). All axial CT images were obtained with 10mm collimation and pitch of one. No retrospective reconstruction was performed. MRI was assessed with axial T1 weighted image (T1WI) and T2 weighted image (T2WI) and in some cases, sagittal or coronal T1WI and T2WI were added to obtain a clearer view of the lesion.

Ordinary contrast CT was performed after 150 seconds of bolus intra-venous administration of contrast material via antecubital vein to obtain equilibrium phase. In seven cases dynamic enhancement study was performed with same contrast material and administration route with injection rate of 3ml per second and pre-scan delay of 30 seconds for arterial dominant phase, 60 seconds for portal phase, and 150 seconds for equilibrium phase. We used 100ml of iodinated contrast material of 300mgI/ml (Iopamiron 300, Schering, Germany) for contrast CT. As for endoscopic findings, all ten tumors were reviewed with regard to tumor shape and ulceration.

Finally, to clarify whether imaging findings could provide prognostic information, we analyzed postoperative recurrence and the postoperative survival period. Informed consent for this study was obtained from all 10 patients.

Results

1. Immunohistochemical examination (Table I)

Both c-kit and CD34 were positive in all 10 patients, and S100 protein was negative in all of them. Alpha-smooth muscle actin was positive in 2 patients and negative in 8. Therefore a diagnosis of GIST was confirmed in all 10 cases.
Figure 1: (TOP) 74 year-old female with single nodular GIST. CT with IV enhancement shows 5 cm of single nodular tumor adjacent to posterior wall of gastric fornix. Low attenuation area representing necrosis is seen in the center of the tumor. Tumor parenchyma was enhanced in equilibrium phase.

Figure 2: (BOTTOM) 70 year-old female with GIST, consisted of multiple nodules. Giant ulcer is represented as protrusion of oral contrast medium to the tumor in pre-enhancement phase (A). Dynamic enhancement study shows less vascularity in the tumor and no prominent drainage veins are noted around the tumor (B) (C).
Figure 3: 37 year-old male with esophageal GIST. 3A: (TOP) Contrast enhancement CT shows huge mass adjacent to spine and thoracic aorta. Esophagus is stretched thin by tumor and its lumen is demonstrated as crescent air density area. Faint enhancement is seen peripherally, but non-enhanced areas are widely noted. Pathologically, they are not a necrosis but a fibromyxomatous loose interstitium. 3B: (BOTTOM) MRI of T2 weighted image(TR/TE/FA: 3000/85/90°) shows very high intensity area in the tumor representing fibromyxomatous change.
Figure 4: 61 year-old female with rectal GIST. Sagittal MRI image of T2WI (TR/TE/FA: 3000/85/90°) shows lobulated or multinodular huge homogeneous mass in the rectum. Low signal intensity of the tumor in T2WI represents that this tumor consists of rich fibrous tissue.

2. CT, MRI and endoscopic findings (Figures 1, 2, 3, 4, Table I, II, III)

The primary lesion of GIST was located in the esophagus, stomach, and rectum in 1, 8, and 1 of the patients, respectively. The gastric lesion was localized in the fornix or the upper body in seven of the eight patients and in the pyloric region in 1. Tumor sizes ranged from 3cm to 17cm in diameter, with a mean size of 8.0cm (Table I). The tumor consisted of a single nodule in 5 patients and multinodular lesion in 5. Among 8 large tumors more than 5cm in diameter (case2-9), five were multinodular. The main direction of tumor growth was extraluminal in 7 patients and intraluminal in 3. CT and MRI observed mucosal ulceration in 2 tumors. Low-attenuation area in each small nodule of multinodular tumor and similar area in single nodule tumor, smaller in size, were observed
# TABLE I

Immuno-histochimical analysis of GIMTs

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Organ</th>
<th>Site</th>
<th>Size (cm)</th>
<th>CD34</th>
<th>c-kit</th>
<th>SMA</th>
<th>S100</th>
<th>Confirmed DFS (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 53m</td>
<td>Stomach</td>
<td>Pyloric region (lesser curvature)</td>
<td>3x2.9x2.8</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>36</td>
</tr>
<tr>
<td>2 66f</td>
<td>Stomach</td>
<td>Anterior wall of the upper body (greater curvature)</td>
<td>17x16x12</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>84</td>
</tr>
<tr>
<td>3 73f</td>
<td>Remnant stomach</td>
<td>Upper body (lesser curvature)</td>
<td>5x4.8x4.5</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>6</td>
</tr>
<tr>
<td>4 74f</td>
<td>Stomach</td>
<td>Fornix (posterior wall)</td>
<td>5x4.9x4.6</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>39</td>
</tr>
<tr>
<td>5 52m</td>
<td>Stomach</td>
<td>Fornix (posterior wall)</td>
<td>5x5x4.5</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>6</td>
</tr>
<tr>
<td>6 37m</td>
<td>Esophagus</td>
<td>Left wall of lower esophagus</td>
<td>12x11x10.8</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>38</td>
</tr>
<tr>
<td>7 70f</td>
<td>Stomach</td>
<td>Posterior wall of the upper body</td>
<td>9x5x9</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>Recurred at 8 months</td>
</tr>
<tr>
<td>8 61f</td>
<td>Rectum</td>
<td></td>
<td>10.5x9x7</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>Hepatic metastasis at 17 months</td>
</tr>
<tr>
<td>9 58f</td>
<td>Stomach</td>
<td>Upper body (greater curvature)</td>
<td>10.4x6.5x6.1</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>16</td>
</tr>
<tr>
<td>10 63m</td>
<td>Stomach</td>
<td>Fornix-posterior wall of the upper body</td>
<td>4x3.8x3</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>30</td>
</tr>
<tr>
<td>Direction of growth</td>
<td>Nodule</td>
<td>Ulceration</td>
<td>Necrosis or mixed change</td>
<td>Hemorrhage</td>
<td>Early enhancement</td>
<td>Enhanced in the equilibrium phase</td>
<td>Tumor stain</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>--------</td>
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<td>--------------------------</td>
<td>------------</td>
<td>------------------</td>
<td>----------------------------------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>Intraluminal</td>
<td>Single</td>
<td>(+)</td>
<td>(-)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(c)</td>
<td></td>
</tr>
<tr>
<td>Extraluminal</td>
<td>Single</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(c)</td>
<td></td>
</tr>
<tr>
<td>Intraluminal</td>
<td>Multiple</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(c)</td>
<td></td>
</tr>
<tr>
<td>Extraluminal</td>
<td>Multiple</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(c)</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE II**

CT and MRI findings of GISTs
in seven of 10 tumors. These areas consisted of necrosis or myxoid change. Hemorrhage was not observed in any patient. No tumors showed invasion of surrounding tissues, peritoneal dissemination, or metastasis to other organs at the time of diagnosis.

Contrast enhancement in the equilibrium phase was observed in all 10 patients. It was weak, and no peritumoral angiogenesis was detected in any patient. Only one of 7 patients undergoing a dynamic study showed early enhancement. These findings of contrast enhancement suggested that GISTs were hypovascular tumors compared with leiomyosarcoma (Table II).

As for the endoscopic findings, a shape of submucosal tumor was observed in 7 patients and extraluminal compression was observed in 3. Ulceration was observed in three of 7 submucosal tumors (Table III).

### TABLE III

<table>
<thead>
<tr>
<th>Endoscopic findings</th>
<th>ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Submucosal tumor</td>
<td>(-)</td>
</tr>
<tr>
<td>2 Extraluminal compression</td>
<td></td>
</tr>
<tr>
<td>3 Submucosal tumor</td>
<td>(-)</td>
</tr>
<tr>
<td>4 Submucosal tumor</td>
<td>(-)</td>
</tr>
<tr>
<td>5 Submucosal tumor</td>
<td>(-)</td>
</tr>
<tr>
<td>6 Extraluminal compression</td>
<td></td>
</tr>
<tr>
<td>7 Submucosal tumor</td>
<td>(+)</td>
</tr>
<tr>
<td>8 Submucosal tumor</td>
<td>(+)</td>
</tr>
<tr>
<td>9 Extraluminal compression</td>
<td></td>
</tr>
<tr>
<td>10 Submucosal tumor</td>
<td>(+)</td>
</tr>
</tbody>
</table>

3. Analysis of prognosis

Eight of the 10 patients had no recurrence after a mean follow-up period of 28.1 months (range: 6 months to 84 months), while in 2 patients the tumor re-occurred at 8 and 17 months after operation (Table I). One patient with recurrence had a large multinodular
tumor, measuring 9 cm in diameter. The tumor located in the upper gastric body, showed extraluminal growth and had dirty ulceration and necrosis. The other patient with recurrence had a rectal multinodular tumor measuring 10 cm in diameter which had ulceration and showed intraluminal growth.

Discussion

Recently, submucosal tumors of GI tract are inclusively termed GIMTs, including GISTs, myogenic tumors, and neurogenic tumors that are classified with immunohistochemical examination. GIMTs may occur in all parts of GI tract from the esophagus to the rectum. The distribution of GIMTs is 60-70% in the stomach and 20% in the small intestine, with the remainder in the esophagus, large intestine, and rectum (Miettinen, Sarlomo-Rikala et al. 1999), Nishida, Hirota et al. 2000), while the greater and lesser omentum are also occasionally affected (Miettinen, Monihan et al. 1999), Takahashi, Kuwano et al. 1998). These tumors have similar biological features regardless of their site or origin. Among clinical features, a size of 5 cm or greater, invasion of surrounding tissues or distant metastasis, bleeding, and necrosis are suggestive of malignancy, and tumors of the small and large intestine have a poorer prognosis than those of the stomach (Miettinen, Sarlomo-Rikala et al. 1999), Nishida, Hirota et al. 2000), Ng, Pollock et al. 1992), DeMatteo, Lewis et al. 2000), Chou, Eng et al. 1996).

GIST is morphologically similar to the interstitial cells of Cajal (ICC) present in the GI tract. In addition, ICC express KIT protein and CD34, those markers are also expressed on GISTs, and so GISTs are considered to derive from ICC or from mesenchymal cells which can differentiate toward ICC (Nishida, Hirota et al. 2000), Kindblom, Remotti et al. 1998), Sircar, Hewlett et al. 1999).

ICC may originate in mesenchymal cells and are found in the intermuscular plexus (Auerbach’s plexus), in the submucosal plexus (Meisner’s plexus), and between the muscles of the intestinal wall. KIT protein expressed on ICC is involved in intestinal peristalsis, and ICC may be a pacemaker cell for peristalsis of GI tract. This concept is supported by the occurrence of paralytic ileus secondary to reduced peristalsis in mice and rats with a loss-of-function mutation of the c-kit gene, and by the abnormality of ICC that
has been reported in Hirschsprung’s disease and congenital pyloric stenosis, those are associated with impaired gastrointestinal motility (Vanderwinden, Rumessen et al. 1996), Yamataka, Kato et al. 1995), Vanderwinden, Liu et al. 1996).

Gain-of-function mutations have been reported to occur mainly in exon 11 of the c-kit gene in GISTs (Nishida, Hirota et al. 2000, Hirota, Isozaki et al. 2000), Hirota, Nishida et al. 2001), and familial GISTs with multiple tumors in the stomach and small intestine have this type of mutation (Nishida, Hirota et al. 1998). Also, a point mutation (codon 559 of exon 11) of this gene has been reported to occur in 2 sisters who had multiple GISTs of GI tract associated with pigmentation of the skin (Maeyama, Hidaka et al. 2001). These facts suggested that abnormality of the c-kit gene may be one of the causes of GISTs. In addition, gain-of-function mutation of the c-kit gene has also been reported to be related to the clinical picture, that is, 57% of GISTs show this mutation, and these tumors are large and highly malignant histopathologically, tend to show marked invasion and metastasis, and have a poor prognosis (Taniguchi, Nishida et al. 1999), Nishida, Nakamura et al. 2000).

There were no reports on the radiographic characteristics of tumors confirmed as GIST immunohistologically as far as we searched the literature. According to the reviews of the CT findings of conventional leiomyosarcomas of GI tract, as for the stomach, 90% of leiomyosarcomas occurred in the fornix and body, commonly measured 5 cm or more, grew extraluminally, and were usually heterogenous tumors associated with necrosis. Calcification was often observed, and metastatic lesions, especially hepatic metastases, frequently showed central necrosis (Levine, Megibow et al. 2000), Otto 1993), Champman 1998), Robert, David et al. 1998), Harpreet, Ralph et al. 1999), Robert, Elizabeth 1982), John, Elliot et al. 1985), Levine, Buck et al. 1996), Alan, Jesus et al. 1984). There are not so many reports mentioning the vascularity of leiomyosarcoma, but they are generally considered to have rich vascularity (Levine, Megibow et al. 2000), Otto1993), Robert, and Elizabeth 1982), Alan, Jesus et al. 1984).

As for smooth muscle-derived tumors of the large intestine and rectum, intraluminal growth was less common, but extraluminal growth or a mixed pattern were often shown Seung, Hyun et al. 2000).
Endoscopic findings of GIMTs and leiomyosarcomas have been also reported. According to them, GIMTs and leiomyosarcomas are often observed as submucosal tumors with or without ulceration. In some cases, only ulceration or extraluminal compression is observed (Mihssin, Moorthy et al. 2000, Shyr-Ming, and Sheen-Chen et al. 1994). Leiomyoma of GI tract is considered to be a small and homogenous tumor without degeneration or necrosis.

We reconsidered our 10 cases of GIST comparing with these reported imaging findings of leiomyosarcoma or leiomyoma of GI tract.

1. Distribution of the origin in GI tract, direction of growth, localization in the stomach, endoscopic findings of GISTS

These factors are similar to those of conventional leiomyosarcoma, because many tumors currently classified as GIMT used to be diagnosed as leiomyosarcoma previously, and many of GIMTs proved to be GISTS immunohistochemically. In most of our cases tumors grew extraluminally and were frequent in the fornix of the stomach. The former is compatible with the fact that ICC are abundant in Auerbach’s plexus lying between the longitudinal and circular muscle layers in muscularis propria, as well as inside the circular muscle itself, both of those exist in the serosal side of GI tract (Cecilia 1999). The latter is also compatible with the fact that ICC are more abundant in the fornix than in the pyloric region of the stomach (Cecilia 1999). In case 1, the tumor was originated from inside the circular muscle of the pyloric region and this is compatible with the fact that ICC in the pyloric region exists in the circular muscle (Cecilia 1999).

2. Morphology and vascularity of GISTS

In our 10 cases, large GISTS were multinodular tumors and necrosis or myxoid changes were seen in each small nodule. Conventionally, large tumors were often diagnosed as leiomyosarcoma, but these findings in our GISTS have not been reported in leiomyosarcoma. Therefore, it is possible that these findings are characteristic of GIST. But we can not rush to conclusion because many GISTS might be included in conventional leiomyosarcoma. So we reviewed some reports on leiomyosarcomas of other organs. Leiomyosarcomas originate from uterus, retroperitoneum, soft tissues of extremities other than GI tract and they are large hypervascular tumors those consist of single nodule and
have central necrosis or hemorrhage regardless of primary lesion (Eric, Kim et al. 1999), Seynaeve, Mortelmans et al. 2001). These reports also suggested that the new findings reported in this study are characteristic of GISTs. In addition, one of 10 patients has a small tumor with internal myxoid change. Small tumors were conventionally diagnosed as leiomyoma, but this finding differs from those of leiomyoma. Therefore it might be also characteristic of GISTs.

As for vascularity, GISTs were hypovascular tumors compared with conventional leiomyosarcomas.

3 Imaging findings as prognostic factors

Only two of ten patients had postoperative recurrence, who had large tumors in size. This is in agreement with conventional reports that large tumors have poor prognosis.

In this study, we analyzed imaging findings of 10 GISTs. Generally,

- Large GISTs consisted of multiple small nodules, while GISTs smaller in size appeared as single nodular. The former have low-attenuation area in each small nodule of multinodular tumor representative of necrosis or myxoid change, and the latter also have similar area in single nodule tumor.
- GISTs were hypovascular compared with leiomyosarcoma and tended to grow extraluminally.

These characteristic imaging findings of GISTs might be useful for precise preoperative diagnosis.

Acknowledgments

We are grateful to Dr. H. Iri, department of pathology, Tachikawa Hospital, for suggesting immunohistological diagnosis of GISTs and also to Mr. T. Usuda and Mr. S. Sasai for expert technical assistance.

References


