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Case Report

Primary hepatic gastrointestinal stromal tumor showing remarkable myxoid change and hemangiopericytoma-like pattern

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Gastrointestinal stromal tumors (GISTs) in the liver are exceedingly rare. We report a case of hepatic GIST with myxoid changes and hemangiopericytoma-like patterns. A 69-year-old woman presented with epigastric discomfort, and underwent laparotomy for an extruded tumor in the liver. Five years later, recurrent tumor was excised. The primary tumor contained extensive necrotic and myxoid areas. Spindle and epithelioid cells plus a few giant cells with abundant myxoid matrix surrounded the necrotic areas. Immunohistochemically, the spindle cells were distinctly positive for KIT as well as vimentin and smooth muscle actin, leading to a diagnosis of hepatic GIST. The second excised tumor showed increased cellularity and nuclear atypia of epithelioid cells with hemangiopericytoma-like patterns. Although rare, we should consider GIST as a differential diagnosis for a hepatic mesenchymal tumor.

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most frequent non-epithelial tumors occurring in the gastrointestinal (GI) tract. Since Mazur and Clark first proposed the term GIST in 1983, numerous GIST cases and studies have been reported. Currently, GISTs are believed to originate from interstitial cells of Cajal (ICCs) or their stem cell-like precursors that can differentiate into both ICCs and smooth muscle cells.

GISTs primarily arising from the liver are extremely rare, although extragastrointestinal tumors (EGISTs), such as those in the mesentery, omentum and retroperitoneum, have been reported. Herein, we report a case of primary GIST in the liver that showed peculiar histological findings.

Materials and methods

The method of molecular analysis for KIT and platelet-derived growth factor receptor-α (PDGFRα) genes was described elsewhere.
Case Report

Clinical history

A 69-year-old menopausal female presented with epigastric discomfort for 3 weeks. Abdominal examination revealed a large firm hypochondrial mass. A computed tomography (CT) scan showed a large well-delineated cystic mass originating from the liver (Fig. 1). Laboratory tests showed slight elevation of the white blood cell count (8,720/mm$^3$) and serum $\beta$-GTP level (52 IU/l). All other values were within the normal ranges. Both hepatitis B virus surface antigen and hepatitis C virus antibodies were negative. A laparotomy was performed, which revealed a large extruded mass arising from segment 4 of the liver. Partial hepatic resection with complete excision of the mass was performed.

At 5 years after the operation, tumor was recurrent and a partial hepatic resection was undertaken again. The patient did not give her informed consent to the adjuvant therapy. The patient has remained disease-free for 4 years after the second operation.

Pathological findings

Gross examination of the first surgical specimen revealed a 9 $\times$ 5.3-cm extruded mass arising from the liver. On the cut surface, the mass was fleshy and solid, with grayish white and reddish colors (Fig. 2).

On microscopic examination, the tumor showed extensive necrotic and myxoid areas (Fig. 3a). Spindle cell proliferation in a fascicular pattern was observed at the periphery of the extensive necrosis (Fig. 3b). Skeinoid fibers were seen in the proliferated spindle cells (Fig. 3b, inset). In the vascular-rich myxoid area, small polygonal cells with occasional florid-type giant cells were observed (Fig. 3c, d), which resembled a myxoid lipoma. There were mitotic figures at 1-2 per 50 high-power fields (HPFs).

Immunohistochemically, the tumor cells were positive for vimentin, smooth muscle actin and desmin, but negative for DOG 1, CD34, S-100, CD31, factor VIII and D2-40. Since both AE1/AE3 and epithelial membrane antigen were negative, sarcomatoid carcinomas were excluded. Immunostaining for KIT protein revealed positivity in the spindle cells and weak positivity in the giant cells and epithelioid cells (Fig. 3e, f). The tumor cells showed positive immunostaining for neuron-specific enolase, but were negative for both chromogranin A and synaptophysin. We also performed ultrastructural analyses of the primary tumor. Neurosecretory granules were observed in the cytoplasm of the tumor cells (Fig. 4). The tumor was diagnosed as primary hepatic EGIST.

The recurrent tumor showed solid regions. In comparison with the primary tumor, the cellularity was increased, the nuclear/cytoplasm ratio was higher and there were prominent atypical nuclei (Fig. 5a). Hemangiopericytoma-like patterns were also conspicuous (Fig. 5b). There were significant mitotic figures at 87 per 50 HPFs. Numerous giant cells were markedly present. Immunostaining for KIT showed focal and weak positivity in the tumor cells (Fig. 5c).

Gene mutations in KIT or PDGFRA were not identified.
Figure 3. Microscopic features of the primary tumor. (a) The tumor shows spindle cell proliferation around a broad area of necrosis (hematoxylin and eosin). (b) Skeinoid fibers (inset) are present in the bundles of spindle cells (hematoxylin and eosin). (c) An abundant myxoid and epithelioid area with vascular proliferation is observed (hematoxylin and eosin). (d) Florid-type giant cells are present (hematoxylin and eosin). (e,f) Immunohistochemical staining for KIT in the spindle cell proliferation (e) and myxoid epithelioid pattern (f) areas.

Figure 4. Ultrastructure of the tumor cells. Small round neurosecretory granules are observed.
Discussion

GISTs occurring outside the GI tract are called EGISTs. EGISTs mostly arise from the mesentery and omentum, but are rarely found in the other organs. Although the origin of EGISTs remains controversial, it has been suggested that they may arise from pluripotent mesenchymal stem cells in the abdominal cavity.

Primary hepatic GIST is extremely rare. To our knowledge, only five previous cases have been reported. In the total of six cases, including the present case, the age range was broad at 17-79 years (mean age: 48 years) and the ratio of males and females was 4:2 (Table 1). Case 4 was diagnosed as low-grade malignant GIST in their report. The other four cases were judged to be high risk due to risk classification by Fletcher et al. based on the tumor size and mitotic activity. The present case corresponded to intermediate risk, while the recurrent tumor was clearly defined as high risk. In the current case, since the recurrent tumor appeared in the remaining liver, it was considered a local recurrence.

Histologically, the morphologies of GISTs are spindle cells, epithelioid cells and, rarely, pleomorphic cells. In our case, the primary tumor showed somewhat scattered epithelioid cell proliferation with florid-type giant cells in an abundant myxoid matrix, which resembled a myxoid lipoma. However, as a result of more detailed observations, spindle cell proliferation and skeinoid fibers, which are not unique but characteristically found in GISTs, could be observed for making the diagnosis. On the other hand, the recurrent tumor showed prominent hemangiopericytoma-like patterns, as previously reported by Takahashi et al. Immunohistochemistry for KIT revealed strong positive staining in the spindle cells, with only weak staining in the epithelial and giant cells. These peculiar histologic features and the unexpected primary hepatic GIST led to difficulty in reaching the correct diagnosis.

Ultrastructurally, the tumor cells in the present case had neurosecretory granules in their cytoplasms. Therefore, our case may have some characteristics of a gastrointestinal autonomic nerve tumor, which is now classified as a variant of GIST.

It has been reported that epithelioid-type GISTs often show weak or negative immunostaining for KIT. Sakurai et al. reported that GISTs with a myxoid stroma show weak or negative staining for KIT, and these cases frequently show PDGFRα gene mutations, but not KIT gene mutations. However, in a few cases, no KIT or PDGFRα gene mutations were identified. Likewise, no KIT or PDGFRα gene

Figure 5. Microscopic features of the recurrent tumor. (a) The tumor cells are composed of highly pleomorphic epithelioid cells (hematoxylin and eosin). (b) The hemangiopericytoma-like pattern area shows branching vessels with a staghorn configuration (hematoxylin and eosin). (c) Immunostaining for KIT.
mutations were detected in the present case.

Immunohistochemically, KIT positivity is a major defining feature for GIST and also a constitutional feature, whileDOG1 which was negative in the current case is useful and a rather sensitive marker in GIST. Other tumors that show KIT-positive are mastocytoma, seminoma, pulmonary small cell carcinoma, and blastic extramedullary myeloid tumor. However, by their overall clinicopathologic features, these tumors can hardly be confused with GISTs. Therefore, the present case was consistently diagnosed as EGIST.

Some GISTs arising in the gallbladder have already been reported, and it is likely that ICCs are seen in the wall of the gallbladder as a normal cellular component. GISTs of the liver may originate from similar ICC-like cells in the Glisson capsule of the liver.

Mesenchymal tumors arising in the liver are generally rare. In particular, GISTs showing histologic features resembling those in the present case need to be distinguished from angiomylolipoma, solitary fibrous tumor, malignant epithelioid hemangioendothelioma, myxoid lipoma, myxoid liposarcoma or myxoid leiomyoma. These tumors show distinctive immunohistochemical profiles and the diagnosis should not be difficult. However, if pathologists do not consider the possibility of GIST arising in the liver without immunohistochemistry of KIT and analysis of gene mutations, the correct diagnosis cannot be made. It is therefore important that variations of the histologic patterns of GISTs and their appearance in unexpected regions should be well recognized.

In conclusion, we experienced a rare case of EGIST arising in the liver that showed unique histologic patterns, including myxoid lipoma-like and hemangiopericytoma-like patterns. The epithelioid cells in GISTs tend to show weak or negative immunostaining for KIT, and pathologists need to diagnose these tumors with caution, especially in cases arising in a rare region.

Table 1. Clinicopathological data for cases with gastrointestinal stromal tumor of the liver

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Site</th>
<th>Size (cm)</th>
<th>Histology</th>
<th>Mitoses</th>
<th>Immunohistochemistry</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>79</td>
<td>F</td>
<td>Right lobe</td>
<td>15±12-9.5</td>
<td>Spindle</td>
<td>4 per 10 HPFs</td>
<td>+, focal</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>M</td>
<td>Left lobe</td>
<td>18±14-10</td>
<td>Spindle</td>
<td>20 per 50 HPFs</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>M</td>
<td>Left lobe</td>
<td>Not noted</td>
<td>Mixed</td>
<td>75 per 50 HPFs</td>
<td>+</td>
<td>Not identified</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>M</td>
<td>Right lobe</td>
<td>5.1±3.8-4.6</td>
<td>Spindle</td>
<td>No mitoses (needle biopsy)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>70</td>
<td>M</td>
<td>Left lobe</td>
<td>20±20</td>
<td>Epithelioid</td>
<td>1 per 50 HPFs</td>
<td>-</td>
<td>PDGFRA</td>
</tr>
<tr>
<td>Present case</td>
<td>69</td>
<td>F</td>
<td>Right lobe</td>
<td>9±5.3</td>
<td>Mixed</td>
<td>1-2 per 50 HPFs (primary tumor)</td>
<td>+, focal and weak</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: PDGFRA, platelet-derived growth factor receptor-α; HPFs, high-power fields.

References

