The gastrointestinal stromal tumor is the most common mesenchymal neoplasm of the gastrointestinal tract. The gastrointestinal stromal tumor universally expresses KIT and DOG-1 and frequently harbors oncogenic mutations in the KIT gene. While the gastrointestinal stromal tumor usually arises in the alimentary tract, it is rarely found in the extragastrointestinal area. When it is, it is called an extragastrointestinal stromal tumor. Although the pathogenesis, prognostic factors and outcomes of gastrointestinal stromal tumors are well known, those of extragastrointestinal stromal tumors have not been fully studied. We report, herein, a unique primary extragastrointestinal stromal tumor from the pleura in a 73-year-old woman who presented with pleural mass. The extragastrointestinal stromal tumor was surgically resected and confirmed by means of an immunohistochemical study and molecular analysis.

Key words: gastrointestinal stromal tumor – pleural cavity – KIT – DOG-1 – Thoracic-Mediastinum – pleura

INTRODUCTION

The gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract (GIT), although it constitutes only 1% of primary GI malignancy (1). This neoplasm is thought to originate from the interstitial cells of Cajal (ICC), which is the pacemaker for the peristaltic movement of the GIT (2). The median age of patients is around 60, and there is no gender predilection (3,4). More than 95% of GISTs have an expression of KIT protein, and recently discovered on GIST (DOG-1) has also been suggested as a useful diagnostic marker. These two markers are considered as the most specific and sensitive markers for GISTs (1,5,6). Regarding the genetic aberrancy, ~80% have a KIT mutation and 8–10% have mutations in the platelet-derived growth factor receptor, alpha polypeptide (PDGFRα). Both genes are located on the long arm of chromosome 4, and the gain-of-function mutations of the genes are considered to be a major driving force in the pathogenesis of GIST (7).

Thus, imatinib, a selective inhibitor of KIT and PDGFRα, is an effective agent in both adjuvant and palliative settings (8). GIST most often arises in the stomach (60–70%), which has the most favorable prognosis, and from ileum to jejunum (25–30%), but also occurs in the colorectum (5–15%), duodenum (5%) and esophagus (<2%) (9,10). Some GISTs develop outside the alimentary canal, such as omentum, mesentery and retroperitoneum. These types are called extra-GISTs (EGISTs) (11,12). Other unusual anatomical locations have been reported as primary sites of GIST, such as liver (13), mediastinum (14), pharynx (15) and gall bladder (16). While the clinicopathologic parameters and outcomes of GISTs are widely known, those of EGISTs have not been completely defined yet, owing to their sparsity.

Here, we present a unique primary GIST arising from the right pleural cavity in a 73-year-old woman confirmed by means of an immunohistochemical study and molecular analysis.
CASE SUMMARY

A 73-year-old female was admitted to our institute presenting with right flank pain that occurred 3 days ago. The patient had been taking anti-hypertensive medications for 10 years and had undergone a small bowel resection due to mesenteric hematoma 4 years prior. A chest X-ray was taken and a large mass was noted on the right lower lung field (Fig. 1A). A chest computed tomography (CT) revealed that there was a well-demarcated, homogeneous, 11 × 6.5 cm-sized mass abutting the pleura and diaphragm at the right lower lobe (Fig. 1B). To find out the potential primary site, an upper and lower GI endoscopy was done, which was negative for malignancy. An abdominopelvic CT showed that there was no evidence of primary malignancy originating from the abdominopelvic cavity. Tumor markers, including CEA, CA19-9, aFP and CA125, were all within the normal limit.

A curative resection of the mass was performed and on a surgical field, a large mass was noted at the lower field of the right lung, which was stocked to the tendinous diaphragm. On laparoscopic examination, tumor infiltration was not noted on the abdominal cavity. The resected tumor was round to ovoid mass with an expansile growth feature encapsulated by a thin fibrous tissue. The tumor measured 11 × 9.5 cm in size. The cut surface revealed a homogeneous gray whitefish-flesh appearance. Microscopically, the tumor was composed of spindle or ovoid cells with scanty eosinophilic cytoplasm. The tumor cells had uniform, large pleomorphic nuclei with conspicuous nucleoli. Mitotic figures were frequently observed up to 8 per 50 high power fields. Immunohistochemical stains of the tumor cells revealed strong positivity for CD117 (c-Kit) (Fig. 2A), DOG-1 (Fig. 2B), Bcl-2 and vimentin. The Ki-67 labeling index for the tumor proliferative activity was ≈10%.

The immunohistochemical markers for the solitary fibrous tumor of the pleura or malignant mesothelioma, including CD34, WT-1, calretinin, D2-40 and cytokeratin, were all negative. As a primary GIST arising from the pleura is extremely rare, we thereby reexamined the surgical specimen regimen taken from the ‘hematoma surgery’ that the patient had undergone at other hospitals 4 years ago. The specimen was proved to be a simple hematoma (Fig. 3) without any evidence of GIST. Finally, molecular analysis was carried out, and the tumor harbored deletion in exon 11 of KIT. The patient is on adjuvant treatment of imatinib (400 mg/day) and alive without any evidence of disease recurrence.

DISCUSSION

In the current article, we described a case of a 73-year-old female with GIST at the right pleural cavity confirmed by an immunohistochemical study (KIT and DOG-1) and molecular
analysis (KIT exon 11 mutation). This report is the second after Long et al. (17) to describe a case of primary pleural GIST harboring a mutation in exon 11 of the KIT gene. Similar to their report, our case of GIST showed a high mitotic number, large size and strong positivity for both KIT and DOG-1. There is also a unique case of pleural GIST reported by Kitano et al. (18). In that case, a 58-year-old male patient had undergone surgical resection of gastric GIST, and 11 years later, the patient had a GIST in the left pleural cavity. The authors concluded that it was a recurring GIST originating from prior gastric GIST, owing to the same genetic feature (KIT exon 11 mutation). However, it could be suspected as another primary GIST developed in the pleural cavity, because of an 11-year time interval and an unusual spreading pattern. A review of these cases is summarized in Table 1.

![Figure 3. Hematoma, previously resected. (magnification ×40).](image_url)

While the annual incidence of GIST is estimated at 7–14 per 1 million in the general population (19), the incidence of a tumor arising outside of the GIT, that is, EGIST, is reported to be ~10% of GIST. In a report by Du et al., 15 out of 141 (10.6%) cases were found to be positive for EGIST (20). Cho et al. (4) also reported similar incidences of the disease (10.1%), with the most common site being mesentery (45.1%) followed by intra-abdominal (34.3%), pelvis (9.8%), retroperitoneum (3.9%) and abdominal wall (3.9%). In a SEER data analysis, 323 out of 2812 (11.5%) cases were reported as EGIST (21). However, after reassessing the surgical report, clinical history and pathologic findings, Agaimy et al. claimed that most cases of EGIST should have been categorized as either an extension of GIST outside the muscle layer or metastasis (22).

There are several hypotheses for the development of EGIST. This tumor is identical to the GIST in terms of its histological and immunohistochemical features (11,12,23). As the presence of the so-called interstitial Cajal-like cells (ICLCs) has been reported in many organs, such as the urinary bladder, gall bladder, omentum, uterus, prostate and myocardium (24), it is reasonable to assume that EGIST originates from common precursor cells that differentiate into the ICC-derived neoplasm outside of the GIT during their development. An alternative explanation is that this tumor might originate from the pluripotent mesenchymal stem cells located outside of the GIT. However, some suspect that previously reported cases of EGIST have been misdiagnosed by over-interpretation of the KIT immunostains in fibroblastic and other mesenchymal tumors (10).

Unlike GIST, the clinical implications of EGIST are not fully understood. However, compared with GIST, EGIST is thought to have a worse prognosis (4,12,21). This is because

### Table 1. Case comparison of the primary EGIST of the pleural cavity

<table>
<thead>
<tr>
<th></th>
<th>Long et al. (17)</th>
<th>Kitano et al.* (18)</th>
<th>The current report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/gender</td>
<td>62/Male</td>
<td>58/Male</td>
<td>73/Female</td>
</tr>
<tr>
<td>Size (cm)</td>
<td>14 × 8.5 × 5</td>
<td>18.5</td>
<td>11 × 9.5</td>
</tr>
<tr>
<td>Location</td>
<td>Left</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>Pattern</td>
<td>Spindle</td>
<td>Spindle</td>
<td>Spindle</td>
</tr>
<tr>
<td>Mitosis (No./50 HPF)</td>
<td>10</td>
<td>NA</td>
<td>8</td>
</tr>
<tr>
<td>Ki-67 index (%)</td>
<td>NA</td>
<td>NA</td>
<td>10</td>
</tr>
<tr>
<td>Immunohistochemistry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIT</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>DOG-1</td>
<td>Positive</td>
<td>NA</td>
<td>Positive</td>
</tr>
<tr>
<td>Molecular features</td>
<td>KIT exon 11 mutation</td>
<td>KIT exon 11 mutation</td>
<td>KIT exon 11 mutation</td>
</tr>
<tr>
<td>Imatinib treatment</td>
<td>Yes, as adjuvant</td>
<td>Yes, as palliative</td>
<td>Yes, as adjuvant</td>
</tr>
<tr>
<td>Outcome</td>
<td>No evidence of recurrence</td>
<td>Alive with disease (8 months)</td>
<td>No evidence of recurrence</td>
</tr>
</tbody>
</table>

EGIST, extragastrointestinal stromal tumor; NA, not available; DOG-1, discovered on GIST.

*This case may be a metastasized one.
EGIST is frequently accompanied by adverse prognostic factors, such as high proliferative indices, large size, lymph node involvement and distant metastasis. A mutational analysis of EGIST revealed that this neoplasm harbors a less frequent KIT mutation at exon 11 (41.4%) (23), which implies a good response to imatinib. Given that development outside the GIT may result in the delay of presentation of clinical symptoms, a substantial portion of cases of EGIST are diagnosed at late stage, which can make it difficult to manage surgically and thereby result in a worse prognosis.

As with GIST, complete surgical resection has been carried out as the primary treatment of EGIST (13–17,25,26). Regarding the prognostic factors, Yamamoto et al. suggested that in the case of EGIST, a high mitotic rate (>5/50 HPF) and a high Ki-67 labeling index (>10%) were associated with adverse outcomes (23). Of note, tumor size, which is a major factor in both the National Institute of Health (NIH) and the Armed Forces Institutes of Pathology criteria (27), was not associated with an adverse outcome, because most EGISTs were >5 cm. An analysis by Guye et al. also demonstrated that tumor size was not an adverse prognostic factor in multivariate survival analysis of a large GIST cohort composed of 2489 patients (88.5%) with GIST and 323 patients (11.5%) with EGIST (21). Thus, a more stratified strategy is needed for managing this disease entity including incorporation of molecular features.

CONCLUSION
We reported a rare case of GIST arising from the pleural cavity that shares identical histologic, immunohistochemical and molecular characteristics with typical cases of GIST. A complete surgical resection was carried out and adjuvant treatment of imatinib was performed following the NIH risk stratification. Considering the unique features of EGIST, risk stratification, including the anatomical sites and molecular characteristics, should be re-defined for this rare disease entity.

Conflict of interest statement
None declared.

References

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