Malignant Peritoneal Mesothelioma with Production of G-CSF: Case Report and Review of the Literature

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Abstract

Background: This report presents the first case, to the authors’ knowledge, of tumor resection of a malignant deciduoid peritoneal mesothelioma producing granulocyte-colony stimulating factor (G-CSF).

Case Presentation: A 62-year-old man presented with a huge tumor located bilaterally over his entire abdominal cavity along with signs of fever and abdominal distension. Laboratory findings showed an increased white blood cell count and C-reactive protein level. The patient underwent surgical removal of the tumor along with tissue from the abdominal wall, and histopathological analysis led to a diagnosis of malignant peritoneal mesothelioma of the deciduoid type positive for G-CSF production based on serum level and immunohistochemical findings. Although the patient’s general condition quickly improved after surgery, local recurrence 7 months after the first chemotherapy treatment and 12 months after the first operation resulted in his death from the primary disease.

Conclusion: We report a very rare case of G-CSF-producing malignant peritoneal mesothelioma from the clinical course through to the valuable autopsy results.

Keywords: Malignant peritoneal mesothelioma; G-CSF

Background

Since Asano et al. first reported granulocyte-colony stimulating factor (G-CSF) production by a lung cancer patient [1], many cases of G-CSF-producing malignant tumors have been reported to the present day. However, malignant peritoneal mesothelioma is an uncommon disease, and production of G-CSF by a malignant peritoneal mesothelioma has not been reported to our knowledge. We report a very rare case of G-CSF-producing malignant peritoneal mesothelioma from the clinical course through to the valuable autopsy results.

Case Report

A 62-year-old man with abdominal distension and concomitant abdominal pain was admitted to the Department of Gastroenterology of Gifu University (Gifu, Japan). He had been exposed to asbestos over a 20-year period, and he was referred to a pulmonary specialist. Physical examination revealed a well-developed man with normal vital signs. Chest auscultation was normal.

Abdominal computed tomography (CT) scan revealed the presence of an abdominal tumor bilaterally occupying the entire abdominal cavity (Figure 1a, b). The tumor involved solid and superficial vascular structures and was about 40cm in size. Signal accumulation on a positron emission tomography-CT scan strongly indicated an abdominal tumor (Figure 2a, b). The patient had signs of a continuously elevated fever. His white blood cell (WBC) count was 21,310/mm³ with a differential count of 92.2% neutrophils, C-reactive protein level was 18.02mg/dL, IL-6 was 79.2pg/mL (normal level < 4pg/ml), and G-CSF serum level was 65.1pg/mL (normal level 5.78-27.5pg/mL). Endoscopic ultrasound/ﬁne needle aspiration examination of the obtained specimen resulted in a diagnosis compatible with malignant epithelial tumor. The patient was introduced to our department to determine whether the huge tumor could be resected from the abdominal cavity. Palpation revealed that the huge tumor could be moved separately from the abdominal wall. In April 2014, we performed surgery to resect the malignant peritoneal mesothelioma, remove major...
portions of the abdominal tumor, and restore the defective abdominal wall. The operative specimen was a huge tumor of 41 cm × 27 cm located in the abdominal cavity that had invaded the abdominal wall including the rectus abdominis and transversus abdominis (Figure 3). Operation time was 156 minutes, and blood loss was 900ml. Immunohistochemical staining revealed the following findings: AE1/AE3+, vimentin+, CK7+, and CK20- (Figure 4a); calretinin+, D2-40+, TTF-1, and WT1+; and hCG-, S100-, LCA+, and G-CSF+ (Figure 4b). The pathological diagnosis was malignant peritoneal mesothelioma with production of G-CSF. The postoperative course was stable and smooth, and the patient was discharged after the 16th postoperative day. Two months postoperatively, the patient was started on chemotherapy with pemetrexed (PEM) and cisplatin (CDDP). Each course consisted of the administration of single doses of PEM (500mg/m2) and CDDP (75 mg/m2) on day 1 with the course repeated every 3 weeks. The patient underwent 7 courses. Seven months after the first chemotherapy session, he presented with new signs of recurrence in the pelvic region of the abdominal wall and the superior spleen (Figure 5). The patient also had an elevated fever and abnormally high WBC count, and the tumor gradually continued to increase in size within the abdominal cavity. Therefore, we performed surgery to reduce the volume of the malignant peritoneal mesothelioma because of his strong chief complaints of increased fever and abdominal distension. A multidisciplinary committee in our hospital recommended the second surgery because of the patient’s strong symptoms.
Intraoperative findings of the second operation indicated that the tumor had invaded the sigmoid colon, from the ascending colon to around the hepatic flexure of the transverse colon. We selected the Hartmann method for tumor resection, right hemicolectomy, and sigmoidectomy. The operation time was 469 minutes, and blood loss was 2500ml. The pathological examination indicated malignant peritoneal mesothelioma. Unfortunately, the patient experienced drastic disease progression with peritoneal dissemination and liver metastasis over 2 months following the second operation, and he died of the primary disease 12 months after the first operation. At autopsy, malignant peritoneal mesothelioma was found in the lungs, liver, and many other organs (Figures 6a, b). The final diagnosis made on the basis of G-CSF staining was malignant peritoneal mesothelioma with the production of G-CSF.

**Discussion**

Malignant mesothelioma is a malignant tumor that occurs in mesothelial cells, which widely cover the abdominal cavity. Malignant mesothelioma can occur in the pleura, peritoneum, pericardium, and tunica vaginalis of the testis [1-3]. There are many cases of occurrence in the pleura and peritoneal region, with 80% of all cases reported in the pleural region, 10-20% of cases in the peritoneal region, 0.8% of cases in the pericardial region, and 0.5% of cases in the tunica vaginalis of the testis [4-5]. A national survey of malignant mesothelioma in Japan reported rates of 26% in females [7]. Malignant peritoneal mesothelioma is considered to present a wide range of pathological findings and is classified into four histological types: 1) epithelial, 2) sarcomatoid, 3) desmoplastic, and 4) biphasic. The sarcomatoid type presents the most aggressive disease. Although there are no sarcomatoid types in the Australian mesothelioma registry, the biphasic type comprises about 14% of tumors, but most cases are of the epithelial type [6]. Yan et al. reported rates of 92% for the epithelial type, 8% for the biphasic type, and 0% for the sarcomatoid type [7]. The rates of malignant peritoneal mesothelioma in Japan from 2003 to 2005 were reported to be 17% for the epithelial type, 12% for the sarcomatoid type, and 12% for the biphasic type [5]. We diagnosed the present patient as having epithelioid mesothelioma with deciduoid change. Deciduoid mesothelioma is a rare variant of mesothelioma. Initially, deciduoid mesothelioma was considered to occur in the peritoneum of young female adults on the basis of the reports by Talerman [8] and Nascimento et al [9]. However, it is now known that deciduoid mesothelioma is not confined only to young women and to the peritoneal cavity; it also occurs in adult men and women in the pleural cavity. In 30 cases of deciduoid mesothelioma reported by Maeda et al., 13 (43.3%) were located in the peritoneal cavity and 15 (50%) in the pleural cavity. The reason for the high incidence of deciduoid mesothelioma in the peritoneal cavity compared with conventional mesothelioma requires further study [10]. In general, asbestos exposure is said to be related to the main cause of malignant pleural mesothelioma, but the ratio of malignant peritoneal mesothelioma to asbestos exposure is less than that for malignant pleural mesothelioma [11].

Patients with mesotheliomas do not present with distinctive symptoms, and this causes difficulties in diagnosis and treatment. Two types of symptoms are generally reported in patients with peritoneal mesotheliomas: 1) abdominal pain, which is usually localized and related to a dominant tumor mass with little or no ascites, and 2) abdominal distention without abdominal pain. Patients with mesotheliomas generally present with one of these two types of symptoms and signs. Imaging is mandatory in the diagnosis, and ultrasonography and CT scans of the abdomen are useful. However, pathological examination of biopsy or resection specimens is essential to confirm a definitive diagnosis. Prognosis is determined by the clinical presentation, the completeness of cytoreduction, and the sex of the patient [12-14].

Women have been reported to survive with this condition longer than men. The prognosis of malignant mesothelioma is very poor, and the 1- and 2-year survival rates are 21.3% and 3.51%, respectively. Deciduoid mesothelioma is also considered to have a poor prognosis [15]. Prognosis appears to be improved with the use of intraperitoneal chemotherapy. Over the past decade, the management of these patients has evolved similarly to ovarian cancer treatment. Currently, cytoreductive surgery, heated intraoperative intraperitoneal chemotherapy with CDDP and doxorubicin, and early postoperative intraperitoneal paclitaxel are used. Adjunct intraperitoneal paclitaxel and second-look cytoreduction are recommended after these perioperative treatments depending on the patient’s performance status and the decision of the hospital’s multidisciplinary committee.

### Table 1: Review of the literature on granulocyte colony-stimulating factor (G-CSF)-producing malignant mesothelioma.

<table>
<thead>
<tr>
<th>Age/Gender</th>
<th>Exposure to Asbestos</th>
<th>Primary Lesion</th>
<th>WBC</th>
<th>Neutrophil</th>
<th>GCSF (serum level) (pg/ml)</th>
<th>IHC</th>
<th>Subtype</th>
<th>Treatment</th>
<th>Survival</th>
<th>Reference/Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>45/M</td>
<td>Yes</td>
<td>PI</td>
<td>51000</td>
<td>93</td>
<td>49.7</td>
<td>P</td>
<td>Sarcomatoid</td>
<td>Chemotherapy</td>
<td>4wk</td>
<td>This Study</td>
</tr>
<tr>
<td>76/M</td>
<td>Unknown</td>
<td>RP</td>
<td>24000</td>
<td>71</td>
<td>50</td>
<td>P</td>
<td>Biphasic</td>
<td>BSC</td>
<td>5mo</td>
<td>Masuda et al. [23]</td>
</tr>
<tr>
<td>61/M</td>
<td>No</td>
<td>PI</td>
<td>21300</td>
<td>93</td>
<td>67.2</td>
<td>P</td>
<td>Biphasic</td>
<td>BSC</td>
<td>7mo</td>
<td>Ohybayashi et al. [27]</td>
</tr>
<tr>
<td>54/M</td>
<td>Unknown</td>
<td>PC</td>
<td>57200</td>
<td>93</td>
<td>88</td>
<td>P</td>
<td>Biphasic</td>
<td>Surgery</td>
<td>10d</td>
<td>Hario et al. [19]</td>
</tr>
<tr>
<td>48/M</td>
<td>Yes</td>
<td>PI</td>
<td>33100</td>
<td>85</td>
<td>138</td>
<td>P</td>
<td>Desmoplastic</td>
<td>Chemotherapy</td>
<td>4mo</td>
<td>kasuga et al. [24]</td>
</tr>
<tr>
<td>65/M</td>
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<td>PI</td>
<td>53600</td>
<td>93</td>
<td>36</td>
<td>P</td>
<td>Sarcomatoid</td>
<td>Chemotherapy</td>
<td>19m</td>
<td>Yoshiimoto et al.[21]</td>
</tr>
<tr>
<td>70/M</td>
<td>Unknown</td>
<td>Per</td>
<td>46300</td>
<td>96</td>
<td>147</td>
<td>P</td>
<td>Deciduous</td>
<td>BSC</td>
<td>12mo</td>
<td>kimura et al. [28]</td>
</tr>
<tr>
<td>59/M</td>
<td>Yes</td>
<td>PI</td>
<td>147000</td>
<td>96.2</td>
<td>77</td>
<td>P</td>
<td>Sarcomatoid</td>
<td>Surgery</td>
<td>2mo</td>
<td>Nishimura et al. [26]</td>
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<tr>
<td>68/M</td>
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<td>PI</td>
<td>34950</td>
<td>217</td>
<td>N</td>
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<td>BSC</td>
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<tr>
<td>49/M</td>
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<td>50000</td>
<td>89.4</td>
<td>130</td>
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<td>Surgery</td>
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<tr>
<td>54/M</td>
<td>Yes</td>
<td>PI</td>
<td>64200</td>
<td>96</td>
<td>136</td>
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<td>Oka et al. [1]</td>
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<tr>
<td>76/M</td>
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<td>64600</td>
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<td>71.8</td>
<td>P</td>
<td>Sarcomatoid</td>
<td>Surgery/Chemotherapy</td>
<td>28wk</td>
<td>Fujimura et al. [5]</td>
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<tr>
<td>62/M</td>
<td>Yes</td>
<td>Per</td>
<td>21310</td>
<td>92.2</td>
<td>65.1</td>
<td>P</td>
<td>Epithelial</td>
<td>Surgery/Chemotherapy</td>
<td>12mo</td>
<td>This Study</td>
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</table>

Presently, the National Comprehensive Cancer Network Guidelines Version 1.2013 recommends PEM-based chemotherapy as first-line therapy for malignant pleural mesothelioma. Therefore, we selected chemotherapy with PEM and CDDP [16-17] and considered this to be effective as adjuvant chemotherapy for our patient. Leukocytosis is sometimes accompanies malignant neoplasms in the absence of infection, and relatively few cases are accompanied by a high G-CSF level. Although previous studies showed no correlation between neutrophil count and G-CSF level [18-20], Shimasaki et al. reported that G-CSF may contribute at least in part to the unknown leukocytosis observed in malignant neoplasms, especially in patients with lung cancer [21]. Katoh et al. reported that the production of G-CSF is the most potent and common cause of tumor-induced leukocytosis [22]. Nevertheless, Rikimaru et al. reported the first clinical case of malignant pleural mesothelioma producing G-CSF in the English language literature [23]. Presently, a review of malignant mesothelioma producing G-CSF in the English literature shows 12 rare cases, but almost all of these cases are of malignant pleural mesothelioma [24-30]. Our case is the second reported clinical case of malignant peritoneal mesothelioma producing G-CSF in the English language literature. However, it is the first reported case in English in which surgery and chemotherapy were performed to treat this condition. The other such case was treated with best supportive care and chemotherapy (Table 1). We also investigated this malignant peritoneal mesothelioma producing G-CSF by autopsy. Immunohistochemical staining with anti-human G-CSF monoclonal antibody at autopsy revealed that the liver, lung, and other specimens were producing G-CSF. Our case was proved on the basis of the clinical course and the pathological findings.

Conclusion

This case shows the importance of considering the rare clinical course such as that of peritoneal mesotheliomas in patients. Especially, cases of malignant deciduoid-peritoneal mesothelioma are rare, and this is first surgically treated case that was diagnosed on the basis of the clinical course and confirmed by the pathological findings at autopsy.

Abbreviations

CDDP: cisplatin; CRP: C-reactive protein; CT: computed tomography; G-CSF: granulocyte colony-stimulating factor; PEM: pemetrexed; WBC: white blood cell.

References

16. NCCN Guidelines Version 1.2013:
24. Kasuga I, Ishizuka S, Minemura K, Utsumi K, Serizawa H and Ohyashiki

Nobuhisa Matsuhashi, et al._
Annals of Pharmacology and Pharmaceutics

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