CASE REPORT

Cancer of Unknown Primary Site in which Tumor Marker-Oriented Chemotherapy was Effective and Pancreatic Cancer was Finally Confirmed at Autopsy

Koushiro Ohtsubo¹, Hiroyuki Watanabe¹, Tadaaki Yamada¹, Tomoya Tsuchiyama¹, Hisatsugu Mouri¹, Kaname Yamashita², Kazuo Yasumoto², Hiroko Ikeda³, Yasuni Nakanuma³ and Seiji Yano¹

Abstract

We report a 47-year-old man with cancer of unknown primary site in whom pancreatic cancer was confirmed at autopsy. Although a primary lesion was not confirmed, we planned to perform tumor marker-oriented chemotherapy because pancreatic cancer was suspected as the primary lesion based on tumor markers and pathological findings from metastatic lymph node. Neither S-1 nor gemcitabine was effective. However, gemcitabine combined with low-dose cisplatin therapy resulted in a marked decrease in the size of tumors. Microscopic examination at autopsy revealed poorly differentiated adenocarcinoma in the pancreatic head, although a pancreatic mass was not clear macroscopically.

Key words: cancer of unknown primary site, pancreatic cancer, tumor marker, immunohistochemistry, chemotherapy

(Inter Med 48: 1651-1656, 2009)
(DOI: 10.2169/internalmedicine.48.2432)

Introduction

Cancer of unknown primary site (CUP) is a relatively rare entity, accounting for 2-10% of all solid malignancies (1, 2). Specific recommended treatment regimens in specific sub-sets of CUP have been reported (3). In contrast, although a standard chemotherapy regimen has not been reported, platinum combined with taxane or gemcitabine is often employed in the subgroups for which no specific therapy is available (4-10). The prognosis of CUP is generally poor with a median survival of 3 to 5 months after diagnosis (1, 2).

Here, we report a case of CUP in which tumor marker-oriented chemotherapy based on the results of tumor markers and pathological findings was effective, and microscopic findings at autopsy finally revealed pancreatic cancer (PCa).

Case Report

A 47-year-old man consulted a local hospital because of supraclavicular lymph node swelling in March 2007. He was referred to our hospital for closer examination and treatment. Computed tomography (CT) showed supraclavicular, paraaortic, and paraesophageal lymph node metastases, 42 mm, 69 mm, and 10 mm in diameter, respectively (Fig. 1). Positron emission tomography (PET) revealed accumulating spots in all 3 sites. However, the primary site could not be determined on whole-body CT, upper and lower gastrointestinal endoscopy, PET, or urological examination. The biopsy from the supraclavicular lymph node revealed poorly differentiated adenocarcinoma, positive for cytokeratin (CK) 7, and negative for CK20, TTF1, and SP-A on immunohistochemical examination. The results of biochemical examination were as follows (normal ranges are shown in parenthe-
Figure 1. Enhanced computed tomography showing supraclavicular (a) and paraaortic (b) lymph node metastases (arrows) in March 2007.

Figure 2. No definite abnormalities are shown in the pancreas on enhanced computed tomography (a, b) or endoscopic retrograde cholangiopancreatography (c).

Table: Serum biochemical parameters on March 16, 2007:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (Normal Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein</td>
<td>6.9 mg/dL (6.7-8.3 mg/dL)</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.1 mg/dL (4.0-5.0 mg/dL)</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>12 IU/L (10-48 IU/L)</td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>11 IU/L (3-50 IU/L)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>111 IU/L (108-324 IU/L)</td>
</tr>
<tr>
<td>γ-glutamyl transpeptidase [γ-GTP]</td>
<td>24 IU/L (11-48 IU/L)</td>
</tr>
<tr>
<td>Lactate dehydrogenase [LDH]</td>
<td>176 IU/L (120-214 IU/L)</td>
</tr>
<tr>
<td>Total bilirubin [T.Bil]</td>
<td>0.6 mg/dL (0.2-1.3 mg/dL)</td>
</tr>
<tr>
<td>Amylase [Amy]</td>
<td>81 IU/L (40-113 IU/L)</td>
</tr>
<tr>
<td>DUPAN-2</td>
<td>9,630 U/mL (&lt;150 U/mL)</td>
</tr>
<tr>
<td>Span-1</td>
<td>67 U/mL (&lt;30 U/mL)</td>
</tr>
<tr>
<td>Carcinoembryonic antigen (CEA)</td>
<td>within normal limits</td>
</tr>
<tr>
<td>Carbohydrate antigen 19-9 (CA19-9)</td>
<td>within normal limits</td>
</tr>
</tbody>
</table>

First, S-1 was administered at a dose of 120 mg/day for 2 weeks, followed by a 1-week rest beginning in April 2007. Thereafter, additional concurrent radiation therapy of the supraclavicular and paraaortic lymph nodes was performed with a total dose of 50 Gy (2 Gy × 25 fractions). Although the size of lymph nodes was decreased, multiple lung and liver metastases developed after 4 courses of S-1 chemotherapy. Therefore, the patient was treated with gemcitabine at a dose of 750 mg/m² (1,300 mg/body) biweekly beginning in July 2007. Subsequently, the dose of gemcitabine was gradually reduced to 350 mg/m² (600 mg/body). After 2
weeks, the maximal nodule of lung metastases decreased from 19 mm to 15 mm. The reduction rate was 21% in Response Evaluation Criteria in Solid Tumors (RECIST) (12). However, the size was enlarged after 1 month.

Therefore, the patient was treated with gemcitabine at a dose of 450 mg/m\(^2\) (800 mg/body) combined with cisplatin at a dose of 10 mg/m\(^2\) (20 mg/body) biweekly beginning in November 2007. Subsequently, the dose of gemcitabine was reduced to 350 mg/m\(^2\) (600 mg/body). The maximal nodule of lung metastases decreased in size from 28 mm to 16 mm after 4 weeks. The reduction rate was 43% in RECIST. Although tumor markers were gradually elevated, the lung metastases showed no enlargement for 4 months. Therefore, the efficacy in this case was judged as partial response (PR). Although neutropenia (grade 3) was observed in Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (13), the toxicity was tolerable.

However, lung metastases and carcinomatous lymphangitis developed in March 2008. Thereafter, he received docetaxel at a dose of 15 mg/m\(^2\) (30 mg/body) combined with cisplatin at a dose of 10 mg/m\(^2\) (20 mg/body) weekly beginning in March 2008. However, the patient’s general condition worsened, and he died of respiratory failure in May 2008.

At autopsy, distant metastases were detected in the lungs, pleura, pericardium, diaphragm, esophagus, liver, and adrenal glands, and peripancreatic, paraaortic, mediastinal, and left supraclavicular lymph node metastases were found. Although a pancreatic mass was not recognized macroscopically, microscopic findings revealed poorly differentiated adenocarcinoma 65×50×45 mm in diameter in the pancreatic head (Figs. 5, 6). On immunohistochemical staining, the lesion was positive for CK7, CEA, CA19-9, and negative for CK20, TTF1, and SP-A; these findings were the same as those of the biopsy from the supraclavicular lymph node. We retrospectively reevaluated the pancreas in the previous CT. However, a pancreatic head mass was not detected throughout the whole clinical course.

The primary lesion was determined to be pancreatic cancer and not lung cancer for several reasons, as follows. First, the immunohistochemical findings supported a diagnosis of pancreatic cancer rather than lung cancer. Second, the diagnosis of pancreatic cancer with multiple lung metastases would be more reasonable than that of lung cancer with pancreatic metastasis, although the possibility of the latter was not completely excluded.
Discussion

CUP is a relatively rare entity, accounting for 2-10% of all solid malignancies (1, 2). Among autopsy cases, the two most commonly identified primary sites are the pancreas (20%) and lung (18%) (14). Adenocarcinoma is the most common histological diagnosis on light microscopy (approximately 55%). Although favorable prognosis and specific recommended treatment regimens have been reported...
in patients with specific subsets of CUP, these subgroups represent a minority (about 15%) of the population of patients with CUP (3). In contrast, although a standard chemotherapy regimen has not been reported, platinum is the mainstay of treatment regimens, and combination therapy with taxane or gemcitabine has often been employed in subgroups for which no specific therapy is available (4-10). The prognosis of CUP is generally poor with a median survival period of 3 to 5 months after diagnosis (1, 2).

In the present case, the biopsy from the supraclavicular lymph node revealed poorly differentiated adenocarcinoma, positive for CK7, and negative for CK20, TTF1, and SP-A on immunohistochemical examination. Furthermore, both DUPAN-2 and Span-1 were elevated in serum. These findings were compatible with pancreaticobiliary cancer. Therefore, we planned to perform tumor marker-oriented chemotherapy for PCa (5, 11), although a pancreatic mass was not detected.

Currently, S-1 is administered for gastric, colorectal, lung, laryngeal, pancreatic, and biliary cancers in Japan. Four (21.1%) of 19 patients achieved PR in metastatic PCa in an early Phase II study (15). There have been few reports of CUP in which S-1 was effective (16). First, S-1 was administered, followed by radiation therapy for supraclavicular and paraaortic lymph nodes. Although the supraclavicular and paraaortic lymph nodes were decreased in size, multiple lung and liver metastases developed. Therefore, this regimen was judged to show no clinical efficacy.

Gemcitabine was administered for lung, pancreatic, and biliary cancers. Clinical benefit response was observed in 14.3-23.8% in advanced PCa (17, 18). Subsequently, gemcitabine was administered. Although the lung metastases decreased in size temporarily, they were again enlarged after 1 month.

Gemcitabine and cisplatin have synergistic interactions in vitro (19, 20). The addition of cisplatin to gemcitabine significantly improves the median time to progression and overall response compared with gemcitabine alone in PCa (21). Furthermore, median overall survival is more favorable in combination with cisplatin as compared with gemcitabine alone in PCa, although the difference in clinical benefit response between them was not statistically significant (21, 22). In patients with CUP, chemotherapy regimens of gemcitabine combined with platinum have been reported with a response rate of 30.5-55% (9, 10). Surprisingly, gemcitabine combined with low-dose cisplatin therapy (23) resulted in a marked decrease in the size of lung metastases, and no increase in size was observed for 4 months. Therefore, gemcitabine combined with cisplatin therapy as tumor marker-oriented chemotherapy contributed to the prolongation of survival in the present case.

Microscopic examination at autopsy revealed poorly differentiated adenocarcinoma in the pancreatic head. The primary site was determined to be pancreatic cancer based on the results of immunohistochemical examination and the distribution of the tumors. Surprisingly, a pancreatic mass was not clear macroscopically. The reasons for the discrepancy between the macroscopic and microscopic findings are supposed as follows. First, the volume of the fibrous tissues in the tumor was less than that in the normal pancreatic tissues. Therefore, the tumor could not be recognized as the hard mass. Second, the main pancreatic duct was not involved by the tumor. Therefore, the dilatation of the main pancreatic duct or obstructive pancreatitis was not developed.

The main points of this case were as follows. First, we planned to perform tumor marker-oriented chemotherapy based on the results of tumor marker analysis, as well as pathological and immunohistochemical findings, and sequential chemotherapies were effective. Therefore, although the primary site cannot be demonstrated in CUP, tumor markers and pathological findings would help in both detection of the primary site and in the choice of chemotherapeutic agents. Second, the addition of cisplatin enhanced the effects of gemcitabine. Therefore, if gemcitabine alone shows no efficacy, the addition of cisplatin would be recommended. Third, the primary site was confirmed only on microscopic examination. Therefore, autopsy would be significant in CUP.

In conclusion, we reported a rare case of CUP in which gemcitabine combined with cisplatin as tumor marker-oriented chemotherapy was effective and microscopic findings at autopsy showed PCa.

References

9. Pittman KB, Oolver IN, Koczvarl B, et al. Gemcitabine and car-
boplatin in carcinoma of unknown primary site: a phase 2 Adela-

die Cancer Trials and Education Collaborative study. Br J Can-


tion with either gemcitabine or irinotecan in carcinomas of un-

known primary site: results of a randomized phase II study—trial for the

French Study Group on Carcinomas of Unknown Primary (GEF-


of adenocarcinoma of unknown primary site successfully treated

with gemcitabine monotherapy. Gan To Kagaku Ryoho 33: 1489-


evaluate the response to treatment in solid tumors. European Or-

ganization for Research and Treatment of Cancer, National Cancer

Institute of the United States, National Cancer Institute of Canada.


13. Trott A, Colevas AD, Sezer A, et al. CTCAE v3.0: development

of a comprehensive grading system for the adverse effects of can-


14. Nystrom IS, Weiner JM, Heffelfinger-Juttner J, Irwin LE, Bute-

man JR, Wolf RM. Metastatic and histologic presentations in un-


15. Ueno H, Okusaka T, Ikeda M, Takezako Y, Morizane C. An early

phase II study of S-1 in patients with metastatic pancreatic cancer.


mary cancer responding to TS-1. Gan To Kagaku Ryoho 33:


17. Casper ES, Green MR, Kelsen DP, et al. Phase II trial of gemcit-

abine (2,2′-difluorodeoxycytidine) in patients with adenocarci-


survival and clinical benefit with gemcitabine as first-line therapy

for patients with advanced pancreas cancer: a randomized trial. J


19. Crul M, van Waardenburg RC, Bocxe S, et al. DNA repair mecha-

nisms involved in gemcitabine cytotoxicity and in the interaction

between gemcitabine and cisplatin. Biochem Pharmacol 65:


20. Padrón JM, van Moorsel CJ, Bergman AM, Snitskamp-Wilms E,

van der Wilt CL, Peters GJ. Selective cell kill of the combination

of gemcitabine and cisplatin in multilayered postconfluent tumor


cisplatin for the treatment of patients with locally advanced and/or

metastatic pancreatic carcinoma: a prospective, randomized phase

III study of the Gruppo Oncologia dell’Italia Meridionale. Cancer


22. Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase

III trial of gemcitabine plus cisplatin compared with gemcitabine

alone in advanced pancreatic cancer. J Clin Oncol 24: 3946-3952,

2006.

23. Ko AH, Dito E, Schillinger B, Venook AP, Bergsland EK, Tem-

pero MA. Phase II study of fixed dose rate gemcitabine with cis-

platin for metastatic adenocarcinoma of the pancreas. J Clin Oncol