INTERNAL MEDICINE

□ CASE REPORT □

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

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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

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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 subsets 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-

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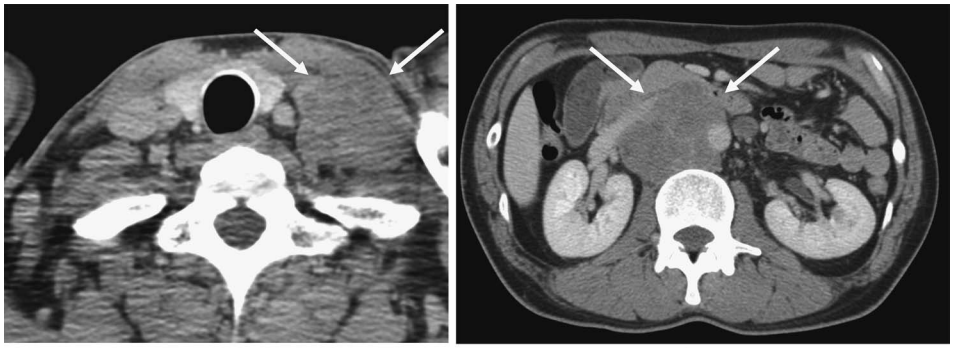
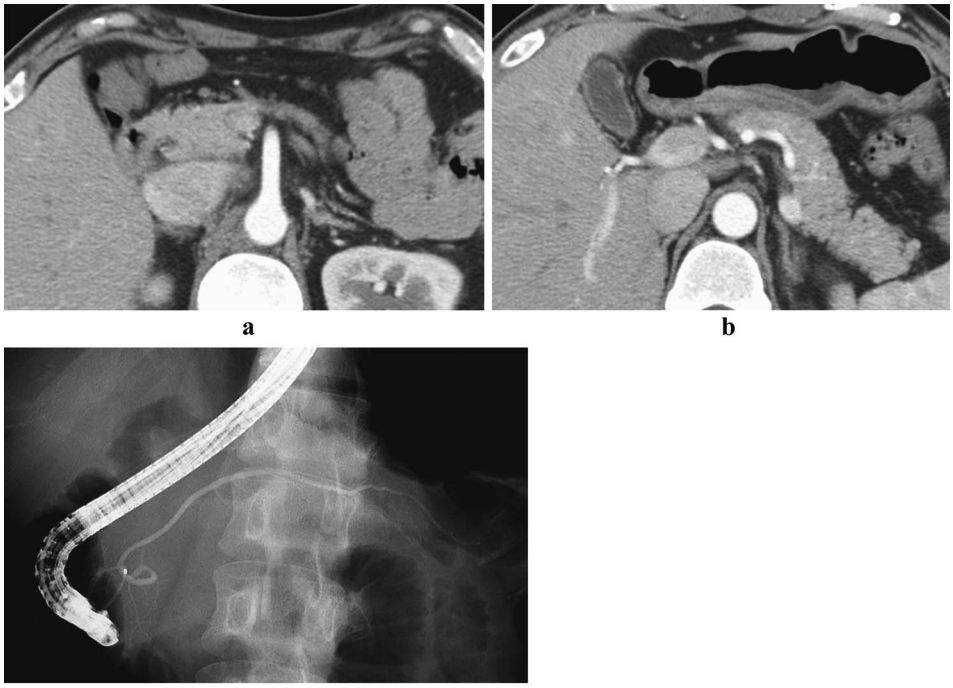


a b

Figure 1. **Enhanced computed tomography showing supraclavicular (a) and paraaortic (b) lymph node metastases (arrows) in March 2007.**



a b c

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

ses): total protein [TP; 6.9 mg/dL (6.7-8.3 mg/dL)], albumin [Alb; 4.1 mg/dL (4.0-5.0 mg/dL)], aspartate aminotransferase [AST; 12 IU/L (10-48 IU/L)], alanine aminotransferase [ALT; 11 IU/L (3-50 IU/L)], alkaline phosphatase [ALP; 111 IU/L (108-324 IU/L)], γ-glutamyl transpeptidase [γ-GTP; 24 IU/L (11-48 IU/L)], lactate dehydrogenase [LDH; 176 IU/L (120-214 IU/L)], total bilirubin [T.Bil; 0.6 mg/dL (0.2-1.3 mg/dL)], amylase [Amy; 81 IU/L (40-113 IU/L)]. Among the serum tumor markers, DUPAN-2 and Span-1 were elevated to 9,630 U/mL (normal range: <150 U/mL) and 67 U/mL (normal range: <30 U/mL), respectively, although carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were within the respective normal limits. Although no definite abnormalities were confirmed in the pancreas on magnetic resonance imaging (MRI) / magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP) or endoscopic ultrasonography (EUS) in addition to CT (Fig. 2), we planned to perform tumor marker-oriented chemotherapy because PCa was suspected as the primary lesion based on tumor markers and pathological findings (5, 10).

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 and radiation therapy in June 2007 (Fig. 3).

Therefore, the patient was treated with gemcitabine at a dose of 750 mg/m^2 (1,300 mg/body) biweekly beginning in July 2007 (Fig. 4). Subsequently, the dose of gemcitabine was gradually reduced to 350 mg/m^2 (600 mg/body). After 2

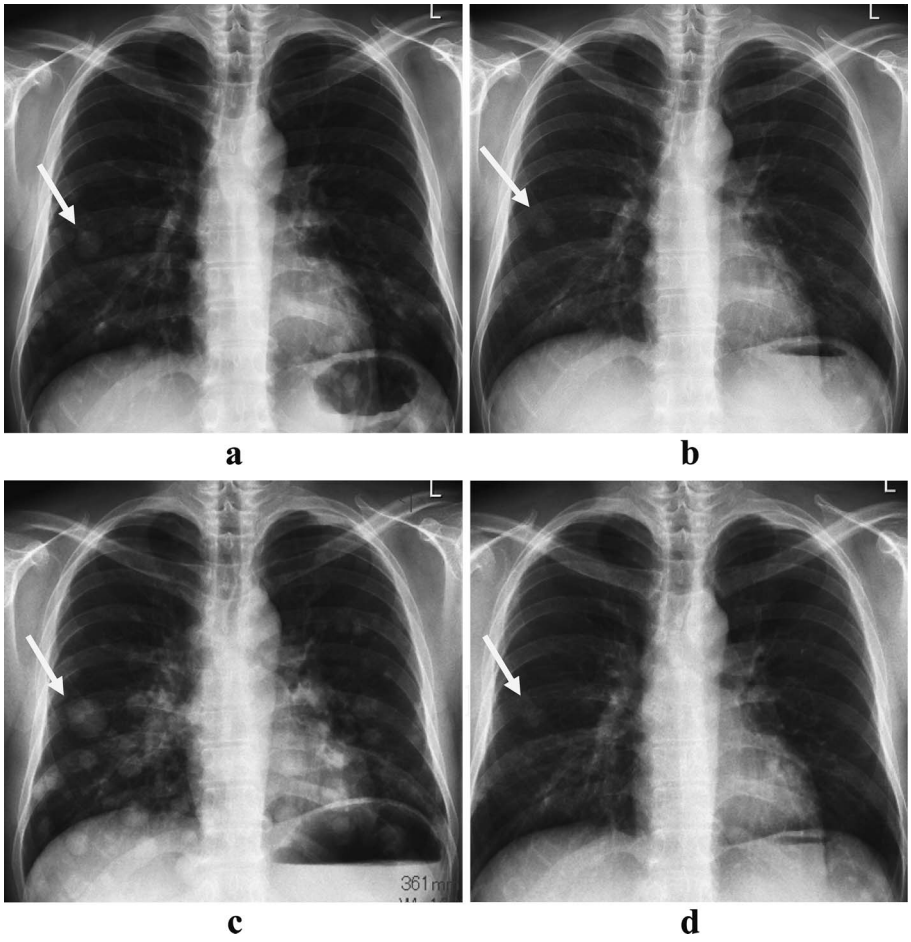


Figure 3. **Chest radiography: (a) lung metastases in July 2007; (b) reduction of lung metastases after administration of gemcitabine in August 2007; (c) exacerbation of lung metastases in October 2007; and (d) reduction of lung metastases after 4 weeks of administration of gemcitabine combined with cisplatin in December 2007. Arrows show the maximal nodule of each lung metastasis.**

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.

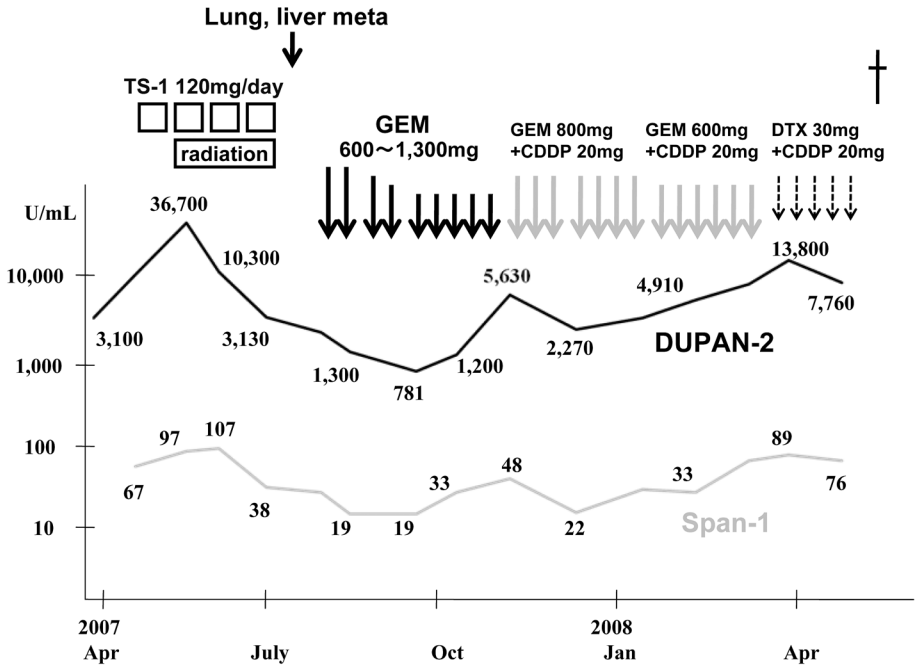


Figure 4. Clinical course in this case.

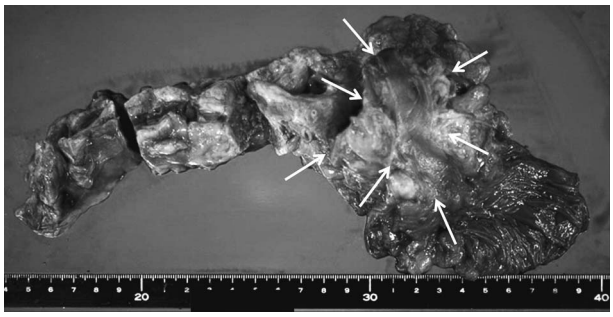


Figure 5. Macroscopic findings of the pancreas at autopsy. No definite pancreatic mass is observed. Arrows show pancreatic head cancer confirmed by microscopy.

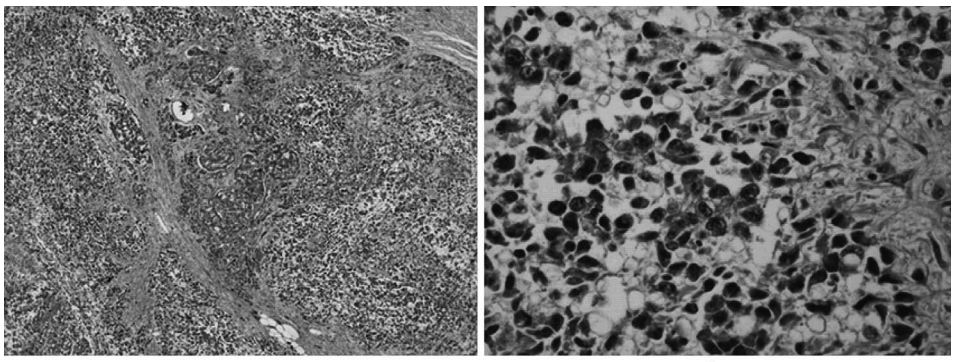


Figure 6. Microscopic findings of the pancreatic cancer at autopsy. Poorly differentiated adenocarcinoma is demonstrated in the pancreatic head (a, low-power field ×40; b, high-power field ×400).

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.

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