Abstract

We report a woman with ascites, hydrothorax, pancreatic tumor, left cystic ovarian tumor, and an elevated serum cancer antigen 125 level. Exploratory laparotomy was performed to determine peritoneal disseminated carcinoma of unknown origin. Immunohistochemical analysis demonstrated positive staining for carcinoembryonic antigen, trypsin, and progesterone receptor and nonspecific or negative reaction for calretinin, estrogen receptor, amylase, lipase, Wilms tumor gene 1 protein, and inhibin or chromogranin A. These results together with the morphology of tubular structure suggested the pathological diagnosis of adenocarcinoma with pancreatic characteristics and contradicted ovarian cancer or mesothelioma. Immunohistochemistry is an adjunct tool to differentiate the primary site of carcinomatous peritonitis.

Key words: carcinomatous peritonitis, pancreas, ovary, ascites, hydrothorax

Introduction

We often encounter patients with ascites with hydrothorax. It is well known that Meigs’ syndrome is characterized with solid, benign ovarian tumors, ascites, and hydrothorax with resolution of these complications after surgical resection. As a result of recent application to atypical cases associated with myomatous uterus (pseudo-Meigs’ syndrome) or malignant diseases of the ovary and uterus (1), it was suggested that gynecological malignancies such as ovarian or uterine cancers are likely responsible for the malignant etiologies of ascites with hydrothorax. However, pancreatic cancer is another disease that produces ascites and hydrothorax. It is necessary to differentiate these diseases because of the differences in prognosis and response to the therapy. In general, the survival and the tumor responses to chemotherapy in advanced ovarian cancer are superior to those of pancreatic cancer (2, 3).

We herein report a woman having ascites, hydrothorax and pancreatic tumor identified with abdominal CT, and cystic lesion of the left ovary on MRI. Exploratory laparotomy revealed the existence of peritoneal disseminated carcinoma of unknown origin. Since it was difficult to differentiate the origin of the tumor solely by histological examination with hematoxylin-eosin (HE) stain, specimens were subjected to immunohistochemistry analyses.

Case Report

A 72-year-old woman noticed brown-colored vaginal discharge six months previously and felt distension of the pelvic region. Then, it progressed in an upward direction with onset of shortness of breath two months previously. Obstetric history revealed that she gave birth at the age of 24 and 31. Past medical history revealed myoma of uterus at the age of 35, in which the patient underwent simple hysterectomy. There was no occupational history of exposure to silica, asbestos etc. Physical examination revealed no palpable mass of breast and no swelling of superficial lymph nodes. Multiple solid masses greater than 1 cm in diameter were detected at the abdominal wall or peritoneum through the surface of the distended abdomen with ascites. Her chest radiograph revealed massive pleural effusion at the right lung (Fig. 1A). Thoracic CT revealed massive pleural effusion at the right side and a small amount of effusion at the left lung. There was no tracheal obstruction, nodular shadow or enlargement of the mediastinal lymph node suggesting the presence of...
lung cancer. Abdominal CT revealed massive ascites and diffuse nodular irregularity of the peritoneum (Fig. 1B). A mass in the mid-section of the body of the pancreas was detected (Fig. 1C). Pelvic MRI revealed cystic swelling of the left ovary (Fig. 1D), supported by transvaginal echogram. However, abnormal findings of the liver and biliary ducts were not identified in abdominal CT and echogram. Repeated aspirations of pleural and ascitic fluid were performed to indicate exudative (effusion) in nature but without cytological evidence of malignant cells. The level of hyaluronic acid was within normal limits (32.5 μg/dl). The levels of cancer antigen 125 (CA-125) in serum and pleural effusion were elevated to as high as 1,408 U/ml (normal <35) and 2,410 U/ml, respectively. Serum levels of other tumor markers were as follows: cytokeratin 19 fragment (CYFRA) 4.0 ng/ml (normal <3.5), carbohydrate antigen 19-9 (CA19-9) 10 U/ml (normal <37), carcinoembryonic antigen (CEA) 1.9 ng/ml (normal <3.0), DuPan2 25 U/ml (normal <150), SPan-1 8.8 U/ml (normal <30). After obtaining informed consent, exploratory laparotomy was performed to clarify the pathology of the disease. Due to peritoneum coalescing into a mass with diffusely disseminated nodular lesions (omental cake), it was not possible to palpate or resect either the pancreas or ovary. Several peritoneal nodules were resected and subjected to pathological examination and diagnosed as origin-unknown carcinoma with tubular formation and stroma with HE stain (Fig. 2A, B). Malignant mesothelioma, adenocarcinoma or neuroendocrine tumor of pancreas, and epithelial ovarian cancer and/or sex cord-stromal neoplasms of the ovary were listed as probable candidates for pathological diagnosis. Immunohistochemistry was positive for CEA, trypsin and progesterone receptor (PR) in the tubular components (Fig. 2C, D, E), nonspecific reaction for calretinin (Fig. 2F), estrogen receptor (ER),...
Figure 2. Histological examination of the peritoneal nodular tissues obtained from exploratory laparotomy. HE staining was performed (A: ×40, B: ×200). Note the variation in the size of the ductal structures with stroma. Immunohistochemical staining for CEA (C: ×200), trypsin (D: ×200), progesterone receptor (PR) (E: ×200), and calretinin (F: ×200) are demonstrated. Inset figure in F indicates positive nuclear staining of normal mesothelial cells as a control.
negative for pancreatic amylase, lipase, Wilms tumor gene 1 (WT1) protein, alpha-subunit of inhibin, chromogranin A. Together with HE staining and these immunohistochemical findings, we diagnosed this case as adenocarcinoma with pancreatic characteristics. After the surgery, we obtained informed consent to manage the patient on gemcitabine-based chemotherapy, which was thought to be effective against major pancreatic cancers. Ascites was reduced and the serum level of CA 125 was decreased to 164 U/ml after three courses of chemotherapy with gemcitabine (800 mg/ body at day 1 and 8) and docetaxel (70 mg/ body at day 8) administered in intervals of 4 weeks. Although the sizes of the pancreatic and ovarian tumor were not significantly reduced, her performance status was improving after repeated chemotherapy.

Discussion

The image information of this case suggested that pancreas and ovary were candidate primary sites to disseminate into the peritoneum. Although several studies have demonstrated that elevated CA125 levels in serum and ascitic fluid only reflected the amount of ascites (4), CA125 is still a well-established tumor marker for epithelial ovarian cancer (5). On the other hand, it was demonstrated that CA19-9 of over 74 U/ml was diagnostically important for pancreatic cancer (6). High levels of CA125 in serum and pleural fluid, a low serum level of CA19-9, and clinical symptoms indicated high preference to the ovary as the primary site for this case. We did not perform magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP). But we chose surgery, since we considered it important to obtain the specimens from the pancreas and ovary. However, we were able to obtain the specimen only from peritoneal nodules due to peritoneal coalescence.

Calretinin, a 29 kDa calcium binding protein, known as a marker of mesothelioma (60 of 60 epithelioid mesothelioma cases, 100%) (7) is also strongly expressed among sex cord-stromal neoplasms (sensitivity 100%, specificity 85%) and fibrous neoplasms (sensitivity 89%, specificity 85%) of the ovary (8). Ovarian sex cord-stromal neoplasms are heterogeneous including granulosa cell tumors (GCTs), Sertoli-Leydig cell tumors, thecomas, and fibrothecomas, representing approximately 8% of ovarian neoplasms. Characteristic positive staining pattern was nuclear and cytoplasmic staining with “fried egg” appearance (9). Nonspecific cytoplasmic staining without nuclear staining as observed in the present case has also been recognized in lung and breast adenocarcinomas which metastasized to the pleural space (9).

Immunoreactivity for WT1 was detected in 86% of ovarian cancer cells which metastasized into the body fluid (10) and in 74% of sex cord-stromal neoplasms (11). Positive immunostaining for alpha-subunit of inhibin was observed in 92% of sex cord-stromal neoplasms but only in 2% of epithelial ovarian cancer (8). Inhibin has 71% sensitivity and 99% specificity for the diagnosis of sex cord-stromal and fibrous neoplasms of the ovary (8). Negative results of immunohistochemistry for WT1 protein or inhibin decreased the possibility of epithelial ovarian cancer and sex cord-stromal neoplasm of the ovary. Although trypsin/ trypsinogen expression has been documented in cholangiocarcinomas (26 in 27 cases, 70%) (12), CT and echographic studies denied its possibility as the primary site.

Expression of ER and PR was studied in various adenocarcinomas. It has been demonstrated that either ER or PR were positive in the malignant pleural cells which metastasized from the ovary (86% for ER, 50% for PR), breast (72% for ER, 52% for PR) (10). According to Yeh’s analyses, PR but not ER was expressed in all examined solid pseudopapillary tumors of the pancreas (13). In contrast, none of the 20 examined pancreatic ductal adenocarcinoma expressed ER or PR (13). Although the morphology of ductal structure was obvious in this case, positive immunoreactivity for PR and negative staining for amylase or lipase was atypical for pancreatic ductal adenocarcinoma. Therefore, histological typing was obscure.

To clarify the primary site of cancer is important to select chemotherapeutic agents. Gemcitabine-based chemotherapy is of choice for pancreatic cancer (14). We also administered docetaxel as a partner agent with gemcitabine because of its wide efficacy for advanced pancreatic cancer and advanced ovarian cancer (15, 16). Although the prognosis of advanced pancreatic cancer is extremely poor (2), the introduction of proper chemotherapy could improve the performance status of the patient. It is worthy to mention in this report that immunohistochemistry is helpful in differentiating the primary site of origin-unknown carcinomatous peritonitis.

Acknowledgements: The authors appreciate Professor K. Suda (Department of Pathology, Juntendo University School of Medicine) for his advice. We also appreciate Y. Takemura, and S. Motoyoshi for their expert technical support and discussion.

References

6) Nazli O, Bozdag AD, Tansug T, Kir R, Kaynak E. The diagnostic importance of CEA and CA 19–9 for the early diagnosis of pancreatic