A Case of Malignant Peritoneal Mesothelioma Showed Complete Remission with Chemotherapy

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A 71-year-old woman presented with an abdominal mass and ascites and was subsequently admitted to our hospital in June 1995. Further examination revealed that the mass was malignant and, as a result, surgery was indicated. However, the mass demonstrated widespread peritoneal dissemination, which therefore could not be resected, and pathological findings suggested a malignant peritoneal mesothelioma. The patient showed a remarkable response to combined chemotherapy with an accompanying intraperitoneal injection of cisplatin and etoposide and an intravenous injection of caffeine. However, owing to side effects, this regimen was discontinued. The patient was administered a combination drug of uracil and tegafur (UFT) in addition to intraperitoneal injection of cisplatin as an outpatient. By the 223rd day after surgery, the tumor mass and ascites had completely disappeared according to the CT. Hence chemotherapy was judged to have resulted in complete remission. Such a marked response to chemotherapy is rare in an advanced malignant peritoneal mesothelioma such as the present case. Eight months later, the tumor recurred in the pleura. Another regimen of chemotherapy with cisplatin and CPT-11 was performed. However, this treatment proved ineffective. The patient subsequently died of respiratory failure in January 1997 due to the mesothelioma. This is a case report of complete remission of malignant peritoneal mesothelioma by combined chemotherapy.

Key words: malignant peritoneal mesothelioma

INTRODUCTION

Malignant peritoneal mesothelioma is a very rare form of intraperitoneal tumor. In many cases, malignant mesothelioma is not diagnosed until after surgery or autopsy (1-5). In general, by the time this condition is diagnosed clinically, the lesion has already spread widely in the peritoneum. As a result, malignant mesothelioma is generally treated by chemotherapy rather than surgically (2,5-7). Many reports (3,7,8) have suggested that combined chemotherapy with cisplatin may be effective for malignant mesothelioma of the pleura. However, the appropriate treatment regimen has not yet been clearly established. Similarly, several researchers have proposed combined chemotherapy with cisplatin as an effective treatment for malignant peritoneal mesothelioma (3,9-11). However, the complete remission rate associated with chemotherapy with cisplatin administration, either alone or in combination with other drugs, is reportedly low. Consequently, the long-term survival rate for such patients is low.

The present paper reports a rare case of malignant peritoneal mesothelioma that showed complete remission with combined chemotherapy.

CASE REPORT

A 71-year-old woman with no remarkable medical history noticed a mass on the left side of her abdomen in March 1995. She felt the mass grow gradually larger and decided to consult her family doctor in May 1995. An intraperitoneal mass as well as ascites were discovered on her abdominal CT and she was subsequently referred to our hospital. A poorly defined, firm, elastic, poorly mobilized tumor measuring 11 x 12 cm was observed on the left side of her navel. Although her abdomen was slightly distented, digital examination did not reveal any indurations. Laboratory data showed only a slight elevation in LDH and CRP. The tumor markers we examined were not elevated. Ultrasonography (US) of the abdomen revealed a heterogeneous solid tumor with an irregular rough shape (Fig. 1).
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Figure 1. Abdominal US reveals a solid heterogeneous tumor with an irregular rough shape.

Figure 2. Abdominal CT in June 1995 reveals a solid high-density tumor on left side of the mid-abdomen (arrows). Numerous ascites were recognized.

Abdominal CT revealed an intraperitoneal tumor with high density measuring 12 × 13 × 3 cm located primarily in the upper-left to middle-left region of the abdomen (Fig. 2). The tumor showed no invasion into the surrounding tissues or abdominal wall. Abdominal CT also revealed ascites. However, the other organs of the intraperitoneum including the liver, pancreas, bile duct and genital organs were intact, as was the upper digestive system. No swelling of the lymph nodes was evident. Barium enema revealed a narrow segment 5 cm in length in the transverse colon that appeared to be associated with the abdominal mass. However, endoscopic examination did not reveal any mucosal changes in this segment. Percutaneous aspiration cytological analysis revealed that the result was class V. However, the pathological type could not be determined.

Based on these findings, we judged carcinomatous peritonitis of the stomach or colon, resected a few nodules to diagnose and settled a reservoir tank for peritoneal injection. Microscopic examination of the nodules revealed infiltration of neoplastic cell nests with a small amount of fibrous tissue and small round cells. The individual cells demonstrated hyperchromatic anisonuclei with occasional vacuoles and eosinophilic or bright cytoplasm. The cells showed no distinctive glandular formation or squamous differentiation, but were arranged in a cord formation (Fig. 4). Immunohistochemical analysis was positive for keratin and epithelial membrane antigen (EMA). The cells were negative for CEA except for slightly positive staining in a few cell nests. The cells were also negative for vimentin, desmin and actin. The Alcian Blue digestive test with hyaluronidase was positive. Based on these findings, the tumor was strongly suggestive of malignant peritoneal mesothelioma.

Eleven days after surgery, we started combined chemotherapy with supplementary administration of cisplatin, etoposide and caffeine using a reservoir tank. The procedure was explained in detail to both the patient and her family and informed consent was obtained. On the first day of therapy, 100 mg of cisplatin and 100 mg of etoposide were administered intraperitoneally. At the same time, 1500 mg/day of caffeine and sodium penzoate were injected intravenously for the first three days of therapy. Treatment was discontinued after the third day owing to mental duress. Twenty days after surgery (July 13), the patient was discharged. Abdominal CT on August 13 (the 41st day after surgery) showed a remarkable decrease in ascites and tumor size, which was 10 × 5 cm at the widest point. We recommended readmission in order to perform the combined treatment again. However, the patient did not want to accept the treatment as an in-patient. Therefore, we proposed another combination therapy to be performed on an out-patient basis. The patient was administered chemotherapy in combination with cisplatin and 5-fluorouracil (5-FU). UFT is a combination of uracil and tegafur in a 4:1 molar concentration ratio. The tumor levels of 5-FU achieved after the administration of UFT are higher than levels in the peripheral tissues. The 5-FU level in the tumor tissue is also sustained for a longer period (12). We consequently chose UFT instead of 5-FU. The patient
ingested 200 mg of UFT daily and 10 mg of cisplatin intraperitoneally every 2 weeks. This regimen was started on August 10. Fig. 5 shows the treatment history of the patient. CT on October 15 (the 103rd day after surgery) showed that the size of the tumor had been reduced to $5 \times 3$ cm (Fig. 6). On February 15, 1996 (the 223rd day after surgery), the ascites and tumor had completely disappeared according to CT (Fig. 7). At this point, the tumor was considered to be in complete remission as a result of chemotherapy, but this treatment including intraperitoneal injection was continued to avoid recurrence. However, 8 months later, on October 15, 1996, chest radiographs revealed a bilateral pleural fluid collection. Follow-up aspiration cytology of the fluid strongly suggested the recurrence of the malignant mesothelioma. Based on these findings, the patient was determined to be no longer in complete remission. At this point, the total dose of cisplatin administration was 370 mg. Informed consent was obtained and recurrent malignant mesothelioma was treated with another regimen of chemotherapy. On November 18, 80 mg of CPT-11 and 80 mg of cisplatin were injected intravenously. In spite of this treatment, pleural effusion persisted and increased gradually. The pleural effusion was occasionally drained using a chest tube. Her general status deteriorated and she died of respiratory failure on January 2, 1997.

DISCUSSION

Malignant mesothelioma is a relatively rare disease, that is found in only 0.01–0.1% of all autopsied cases (4,5). Peritoneal mesothelioma comprises only 20–30% of all malignant mesothelioma cases (2,4,5). Initial clinical symptoms include a sensation
of fullness and the presence of an abdominal mass caused by ascites, but no other remarkable symptomology has been observed (1). Furthermore, specific tests to reveal this type of malignancy have not yet been developed. As a result, many of these patients are misdiagnosed and discharged prematurely. Several months later when the symptoms worsen, the proper diagnosis is made (1). Ascites that result in abdominal distension appear in 90% of these patients (2,5). These ascites are comprised of hyaluronic acid secreted from tumor cells. Hyaluronic acid is contained in the cytoplasm of the tumor cells and is positive for the Alcian Blue digestive test with hyaluronidase. However, many researchers have suggested that open biopsy is necessary for accurate diagnosis (1,2,10). Corson and Pinkus (10) reported that immunohistochimically, malignant mesothelioma is positive for keratin and negative for CEA, which distinguishes mesothelioma from other malignant tumors. In the present case, the mesothelioma was diagnosed on the basis of positive results for the Alcian Blue digestive test and keratin.

Owing to the diffuse extension of this type of tumor, radical surgery is not usually an option. Chemotherapy is generally introduced instead of other treatments. In many cases, malignant peritoneal mesothelioma shows resistance or little response to treatment, resulting in a survival rate in the first year of only 64% (5). Alternatively, chemotherapy has been combined with cisplatin with some degree of success. Markman et al. (9) reported a positive effect in nine of 13 cases where patients received supplementary intraperitoneal cisplatin injection. Similarly, other researchers have reported (5,7,11) complete remission as a result of combined treatment with a regimen including cisplatin. However, the tumors examined in previous reports tended to be relatively local and non-invasive. Malignant peritoneal mesothelioma has been classified into two categories, solitary type and diffuse type. Many peritoneal mesotheliomas fall into the latter category (2,4,7,9). The effectiveness of chemotherapy for diffuse widespread disseminated tumors such as that in the present case has not previously been reported. Previous researchers have reported that combined chemotherapy with etoposide-cisplatin (EP) therapy is effective for disseminated malignant tumor of the peritoneum and malignant mesothelioma (13–17). To amplify the effect of cisplatin, caffeine was added to the regimen. Our previous reports (10,18) suggested that caffeine inhibits DNA repair through reduction of cisplatin-induced elongation of the G2 + M phase. Based on the present findings, simultaneous administration of cisplatin and caffeine appears to be effective. However, owing to the patient’s reluctance, this treatment regimen could not be repeated. Subsequently a combination of chemotherapy and supplementary administration of cisplatin was adopted and finally these treatments were effective. Some reports have suggested that 5-FU has a limited degree of effectiveness for malignant mesothelioma (7,19,20), but 5-FU administration in the present case seemed effective. In this case, it was difficult to discern which combinations of chemotherapy were effective. At the time of recurrence, an effective treatment regimen could not be established. Combined chemotherapy with CPT-11 and cisplatin administration had no effect on the recurrent malignant mesothelioma and the patient ultimately died as a result of respiratory failure.

In conclusion, we have reported a case of complete remission of malignant mesothelioma by combined chemotherapy. Intraperitoneal EP with caffeine and UFT administration with a low dose of cisplatin provided effective treatment for this patient.