—Case Reports—

Efficacy of Cell-Free and Concentrated Ascites Reinfusion Therapy for Palliative Care in a Patient with Malignant Pleural Mesothelioma: A Case Report

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Cell-free and concentrated ascites reinfusion therapy (CART) is recognized as a useful treatment to improve the symptoms caused by refractory ascites. Recently, a few clinical studies have reported the effects of CART for malignant ascites, especially in gynecological and gastrointestinal cancers. We report the case of malignant ascites in a patient with malignant pleural mesothelioma (MPM) whose symptoms were relieved by CART. A 59-year-old Japanese male with MPM who had undergone pleural decortication had pleural and peritoneal recurrence. His general status deteriorated as he developed massive ascites due to peritoneal metastases. With the initiation of CART, he recovered well enough to receive cisplatin-based systemic chemotherapy. Repeated use of CART contributed to the maintenance of his good general condition and enabled him to undergo successive systemic chemotherapy, which might have lengthened his life. This is the first report that demonstrates the efficacy of CART for palliative care in a patient with MPM. Our experience indicates that CART should be considered as a treatment option to control refractory malignant ascites regardless of the type of cancer.

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Key words: cell-free and concentrated ascites reinfusion therapy, refractory malignant ascites, malignant pleural mesothelioma, chemotherapy, palliative care

Introduction

Cell-free and concentrated ascites reinfusion therapy (CART) is a type of apheresis therapy, which was first reported in 1960[1]. CART is carried out in four steps: 1) ascites paracentesis; 2) removal of cell components from the fluid, including cancer cells, by filtration with a plasma-separating filter; 3) concentration of the fluid by the removal of isotonic salt and water by filtration with a dialysis filter; and 4) intravenous reinfusion of the final fluid product[2]. CART has been applied to treat refractory ascites in patients with conditions such as liver cirrhosis, congestive heart failure, nephrotic syndrome, and malignancy.

The number of reports elucidating the effects of CART for malignant ascites has increased, especially in gynecological[3–5] and gastrointestinal cancers[5–8]. However, little is known about the importance of CART in other types of cancer. We report the case of a patient with malignant pleural mesothelioma (MPM) suffering from malignant ascites, whose symptoms were relieved by CART. Repeated use of CART, together with systemic chemotherapy, may have contributed to a longer survival.

Case

A 59-year-old Japanese male with MPM was admitted to our hospital because of massive ascites. He was a former smoker, and he had worked for fourteen years demolishing houses, with occupational exposure to asbestos. About 1.5 years prior to admission, he had initially been diagnosed with malignant epithelioid mesothelioma on cell block samples from a pleural effusion. He had undergone two cycles of neoadjuvant chemotherapy with cisplatin (CDDP) (75 mg/m^2 on day 1) and pemetrexed (PEM) (500 mg/m^2 on day 1), followed by pleural decortication of the right pleura. Immunohistochemical staining of surgically-resected pleural samples had shown that

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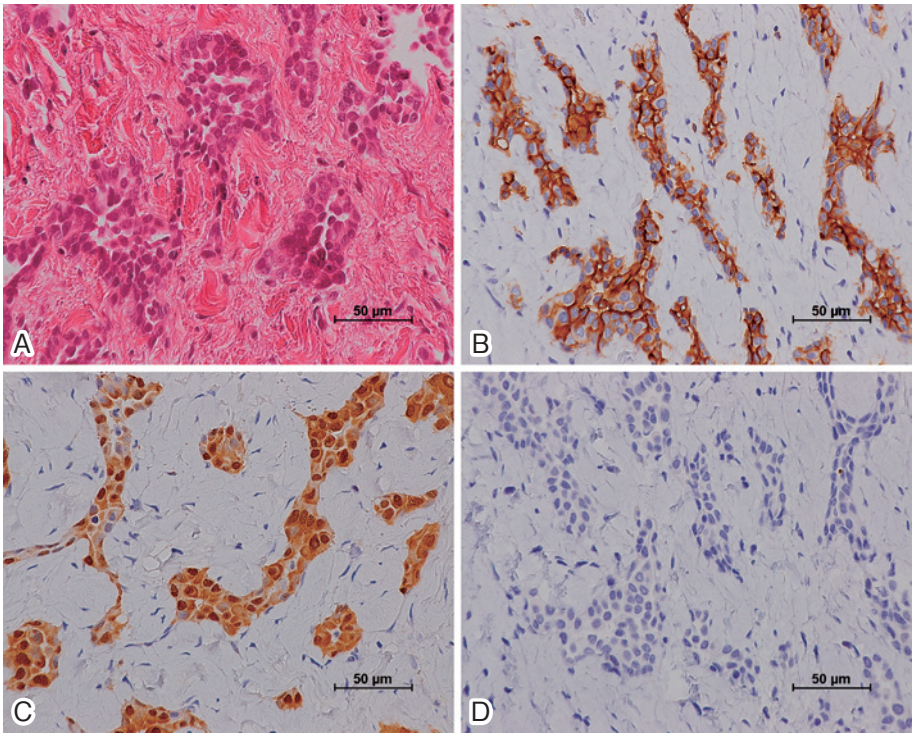

Fig. 1 Representative images of pathological specimen. (A) Hematoxylin and eosin staining. (B) Immunohistochemical (IHC) staining for D2-40. (C) IHC staining for Calretinin. (D) IHC staining for TTF-1.

the tumor cells were positive for D2-40, calretinin, EMA, WT-1, CK5/6, thrombomodulin and HBME-1, and negative for TTF-1, CEA, SP-A, BerEP4, MOC31 and desmin. The proportion of sarcomatoid component had been less than 10%. Hence, he had finally been diagnosed with epithelioid mesothelioma. The pathological findings are shown in **Figure 1A–D**. The pathological stage was stage III (T3N0M0 according to the IMIG classification). An additional 4 cycles of adjuvant chemotherapy with CDDP (75 mg/m^2 on day 1) and PEM (500 mg/m^2 on day 1) had been administered.

Ten months after the completion of chemotherapy, he visited our hospital with the complaint of abdominal distention and a 12-kg weight gain over 3 months. Computed tomography (CT) revealed right pleural thickening (**Fig. 2A**), pleural dissemination (**Fig. 2B**), peritoneal dissemination, and massive ascites (**Fig. 2C and D**). Although the result of the ascitic fluid cytology was recorded as class III by Papanicolaou classification, he was clinically diagnosed with recurrent MPM. His general status further deteriorated with worsening ascites. Administration of loop diuretics and repeated abdominal paracenteses did not improve his poor condition; therefore, he was hospitalized a few days later.

The clinical course after hospitalization is shown in **Figure 3**. He was in poor general condition with an Eastern Cooperative Oncology Group performance status (PS) of 2. His height and weight were 160 cm and 72.2 kg, respectively. Blood pressure and pulse rate were 128/94 mmHg and 113 beats/min, respectively. His abdomen was severely distended. Laboratory data were as follows: white blood cell count, 8,900/μL; hemoglobin, 13.1 g/dL; platelet count, 32.2×10^4/μL; serum total protein, 6.5 g/dL; serum albumin, 3.3 g/dL; blood urea nitrogen, 10.4 mg/dL; serum creatinine, 1.06 mg/dL; and C-reactive protein, 7.14 mg/dL. CART was performed to relieve his symptoms caused by massive ascites. The collected ascites was filtered through the columns of the AHF-MO model (Asahi Kasei Medical, Tokyo, Japan) and filtered ascites was then concentrated using the columns of the AHF-UP model (Asahi Kasei Medical). In the first CART, the amount of collected ascites was 4.5 L and the amount of concentrated ascites was 0.4 L. His body temperature was elevated to 39.6°C after reinfusion. As he regularly took nonsteroidal anti-inflammatory drugs (NSAIDs) against postoperative pain, a corticosteroid was administered at the onset of fever. After the first CART, his general condition improved and he was discharged a few days later. One more CART was performed in the outpatient department. In the second CART, the amount of collected as-

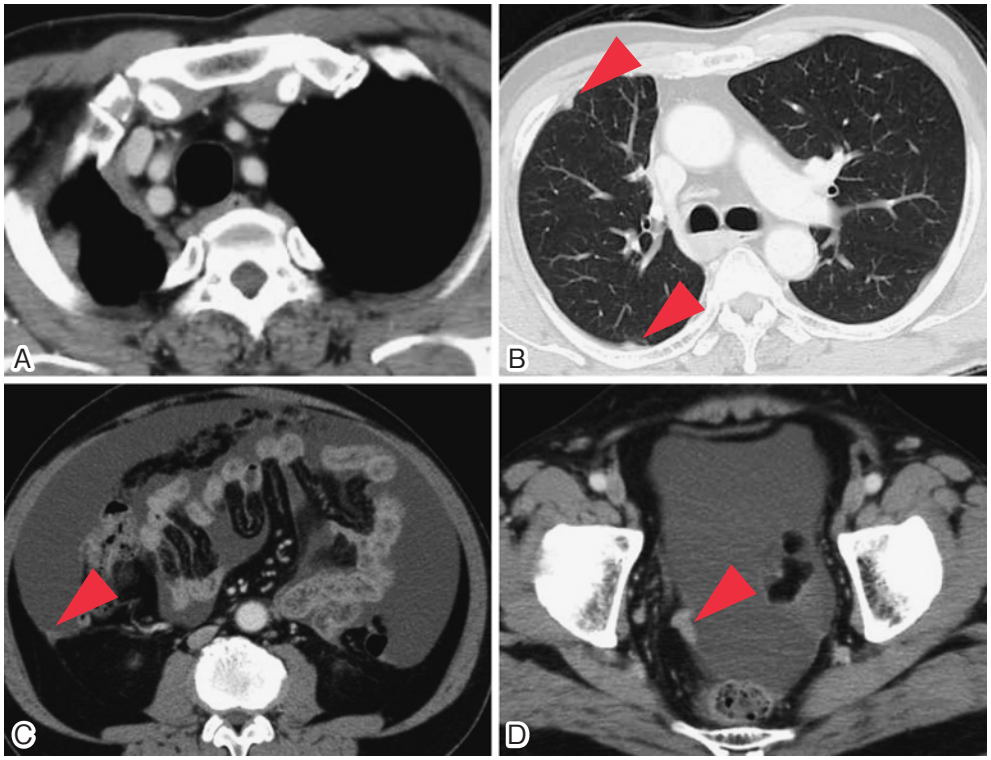

Fig. 2 Computed tomography just before the first hospitalization after recurrence. (A) Pleural thickening. (B) Pleural dissemination (**arrow head**). (C–D) Peritoneal dissemination (**arrow head**) and massive ascites.

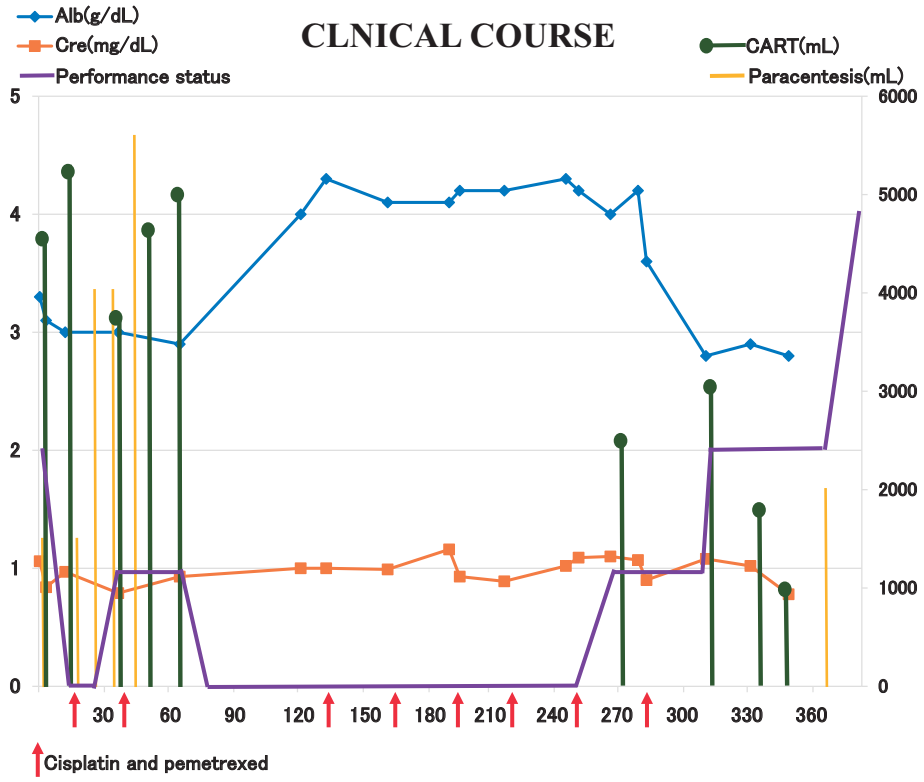

Fig. 3 The levels of serum albumin and creatinine, the amounts of ascites drained either by concentrated ascites reinfusion therapy or conventional abdominal paracentesis, and the alteration of performance status during the patient's clinical course.

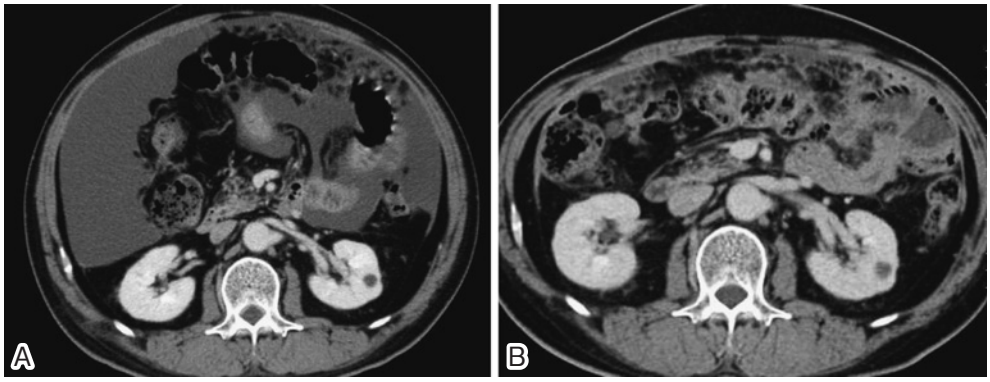

Fig. 4 (A) Massive ascites in another section of the same computed tomography (CT) shown in Figure 1. (B) CT 2 months after the fifth concentrated ascites reinfusion therapy, in a section at almost the same level as that shown in Figure 4A. Ascites has completely disappeared.

cites was 5.3 L and the amount of concentrated ascites was 0.65 L. A corticosteroid was used as a prophylaxis just prior to the reinfusion of his ascitic fluid. His symptoms, including abdominal distention, appetite loss, and fatigue, were significantly improved. Since his PS remained good (PS, 0–1), he succeeded in receiving systemic chemotherapy with CDDP (75 mg/m^2 on day 1) and PEM (500 mg/m^2 on day 1). Both CART and conventional abdominal paracentesis were frequently needed to control massive re-accumulation of ascites for the first 2 months after starting chemotherapy. As his serum albumin levels and renal function did not deteriorate during chemotherapy and he remained well with a PS of 1, he was safely able to receive two cycles of chemotherapy with CDDP (75 mg/m^2 on day 1) and PEM (500 mg/m^2 on day 1). His ascites did not continue to accumulate.

Three months after the second cycle of chemotherapy, CT revealed that pleural dissemination had slightly increased, but the ascites had disappeared (**Fig. 4A and B**). The serum albumin level had returned to normal. He was determined to restart treatment. Although the disease progression had arrested to some extent by continuing chemotherapy, his ascites gradually increased again. CART was reintroduced for palliative care, but after administration of an additional 6 cycles of chemotherapy, we continued to provide best supportive care. CART was repeated for symptom relief, and he was able to spend the rest of his life mostly at home. He died at home 3 months after the last course of chemotherapy.

Discussion

CART is increasingly being applied for the treatment of refractory malignant ascites. This patient's course points to two important clinical issues. First, CART can effectively relieve the symptoms of massive ascites, even in a patient with MPM. In gynecological[3,5] and gastrointestinal[5,6] cancers, investigators have reported that CART contributes to the improvement of various symptoms caused by malignant ascites. The most common treatment for massive, symptomatic malignant ascites is abdominal paracentesis. Therapeutic paracentesis yields temporary relief in up to 90% of patients with refractory ascites[9]. The mean amount of ascitic fluid that must be removed to yield significant improvement of the symptoms of abdominal pressure is reportedly 5.3 L[10]. However, frequent paracenteses may be needed in a short period of time[11] because the amount of fluid that can safely be drained each time is limited[12–14]. Repeated paracenteses may lead to loss of protein[15,16]. Furthermore, a decrease in circulating plasma volume due to draining large amounts of ascitic fluid may cause renal dysfunction[12,14]. Therefore, the administration of albumin is often required. In CART, cellular components are removed from the original ascites, the collected fluid is concentrated by removing water, and it is then reinfused intravenously into the patient. Hence, large amounts of ascites can be safely drained each time[4] and the amount of intravenous protein and renal function can be maintained[3,4,8]. These contribute to keeping patients in a good condition. In our case, several of the patient's manifestations improved with CART due to aspiration of the massive ascites without a reduction in protein levels or impairment of renal function.

Second, repeated use of CART together with systemic chemotherapy may have prolonged the patient's life. Ueda et al.[3] reported that administration of anti-cancer agents following CART, in patients with refractory ascites caused by advanced gynecological cancer, prolonged

overall survival. Had he not undergone CART, it is quite unlikely that our patient could have tolerated as much chemotherapy as he did. The present standard of care for first-line treatment of MPM patients who are not candidates for curative surgery is CDDP and PEM[17]. However, CDDP-based chemotherapy should generally be avoided for patients with a poor PS, renal dysfunction, or uncontrollable fluid retention. In this case, CDDP-based chemotherapy was impracticable due to the contraindications noted above, until we began using CART. As mentioned above, CART is considered to be superior to conventional abdominal paracentesis in maintaining renal function and serum protein levels, which can improve PS, allowing administration of CDDP-based chemotherapy. In this case, CDDP and PEM were effective. Four weeks after the second cycle of chemotherapy, additional abdominal puncture was not needed for approximately 7 months. Moreover, after chemotherapy was restarted, pleural dissemination was partially reduced in size and any other intrathoracic lesions also remained stable thereafter. Repeated use of CART to support systemic chemotherapy with CDDP and PEM probably resulted in longer survival than would have been the case without the use of CART.

Fever is reported to be the most frequent adverse event of CART. Steroids or NSAIDs are often administered as a prophylaxis before the reinfusion of ascites[3,6–8]. In this case, grade 2 fever was observed in the first CART in spite of his regular use of NSAIDs. After the additional administration of a corticosteroid, it was successfully managed. No other clinically significant adverse events were observed.

In thoracic neoplasms, pleural effusion is a common finding. A malignant pleural effusion that causes symptoms may require pleurodesis, a procedure in which the visceral pleura covering the lung is made to adhere to the parietal pleural lining of the chest cavity, preventing re-accumulation of fluid and collapsing of the lung. While this is a useful treatment option to control malignant pleural effusion, adhesion therapy is not done for ascites. It is relatively rare for thoracic neoplasms to cause ascites; accordingly, little is known about CART in the field of thoracic oncology. It is important for this procedure, which can be performed on an outpatient basis or even at home, to be considered for patients with thoracic neoplasms suffering from ascites.

In conclusion, CART effectively relieved symptoms due to massive ascites in a patient with MPM and repeated use of CART, together with systemic chemotherapy, may contribute to prolonged survival in such patients. This is the first report demonstrating the efficacy of CART for palliative care in a patient with MPM. Our experience indicates that CART should be considered as a very effective treatment option to control malignant refractory ascites, regardless of the type of cancer.

Conflict of Interest: The authors have no conflicts of interest to disclose.

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