

## A Rare Case of Biphasic Malignant Peritoneal Mesothelioma with Refractory Ascites

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### Abstract

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An 81-year-old man was admitted to our hospital with abdominal distension due to refractory ascites of unknown origin. He subsequently died of aspiration pneumonia. Autopsy revealed a diagnosis of biphasic malignant peritoneal mesothelioma (MPM) containing both epithelioid and sarcomatous components. The diagnosis of MPM is often difficult because serum tumor markers, imaging studies, and the cytology of ascites may not provide enough information. Accordingly, peritoneal biopsy is necessary in order to diagnose MPM based on the histological and immunohistochemical findings.

**Key words:** refractory ascites, biphasic malignant peritoneal mesothelioma, peritoneal biopsy

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### Introduction

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Malignant mesothelioma is a tumor with a poor prognosis that arises from the mesothelial cells of the pleura, peritoneum, pericardium, or tunica vaginalis. The pleura is the most frequent site of origin, followed by the peritoneum. While malignant peritoneal mesothelioma (MPM) is a rare disease, we should consider it in the differential diagnosis of refractory ascites of unknown origin. Biopsy is required to establish a diagnosis of MPM and the results of other examinations tend to be unhelpful. Thus, MPM is often not diagnosed before death. We experienced a rare case of biphasic MPM that was complicated by refractory ascites. In the present study, we report the details and discuss the literature.

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### Case Report

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An 81-year-old man was admitted to our hospital with abdominal distension, lightheadedness, and bilateral leg edema. He had previously been independent, but lightheadedness had occurred two months previously, after which he required a crutch to walk. Bilateral leg edema had developed three weeks prior to his admission, but there was no dyspnea. Al-

though his appetite was good, he had noticed abdominal distension on the day before his hospitalization. The patient had a history of hypertension and had been diagnosed with type II diabetes mellitus 20 years previously. Furthermore, he had been admitted to hospital seven years previously for sudden deafness of the right ear. He had no occupational history of asbestos exposure, and he had worked as a bank employee between the 20 and 57 years of age. At presentation, his vital signs were as follows: blood pressure, 118/67 mmHg; pulse rate, 95 beats/minute; body temperature, 36.9°C, and oxygen saturation (measured by pulse oximetry) while breathing room air, 100%. On examination, he had pallor of the palpebral conjunctiva. While there were no abnormalities of the thorax, the patient's abdomen was distended and there was bilateral flank dullness without tenderness or abnormal bowel sounds. He also had bilateral leg edema. Laboratory tests showed that his renal and liver functions were normal, but he had microcytic anemia (hemoglobin, 8.6 g/dL; mean corpuscular volume, 78.9 fL), hypoalbuminemia (albumin, 1.9 g/dL), and his C-reactive protein level was elevated to 15.8 mg/dL.

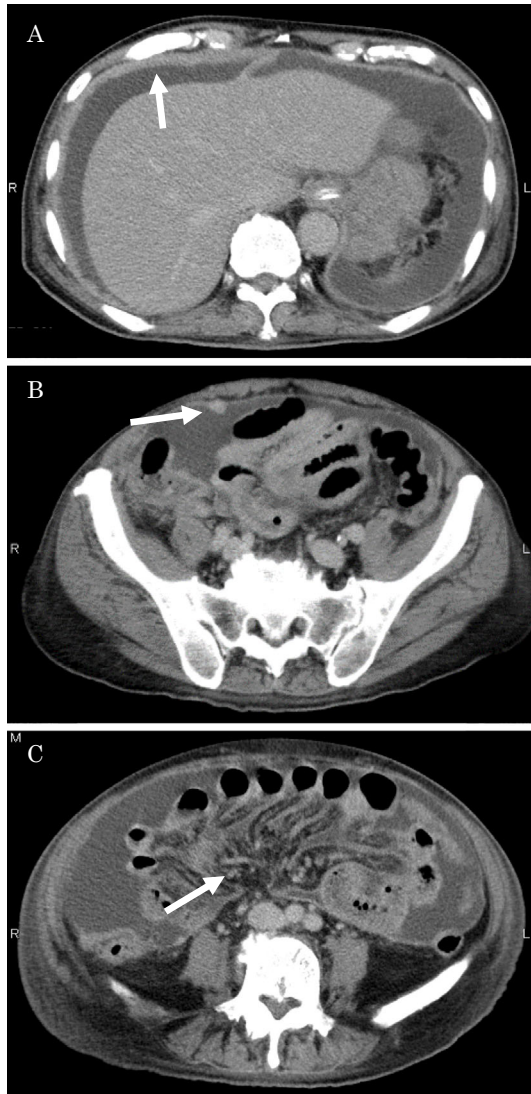
A chest radiograph showed cardiomegaly (cardiothoracic ratio: 50%) without pleural effusion or pulmonary congestion, while an abdominal radiograph showed air limited to

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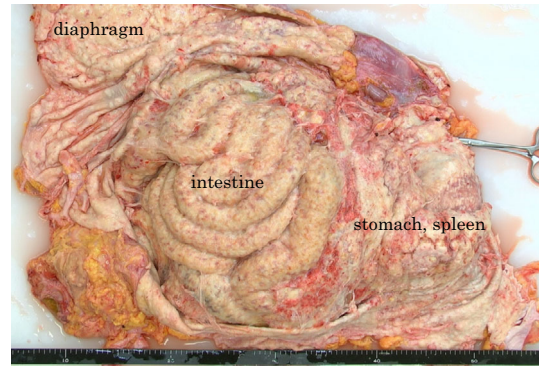
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**Figure 1.** Intravenous contrast-enhanced CT scans show massive ascites, thickening of the anterior peritoneum (white arrow in Panel A), and a nodule in the anterior peritoneum (white arrow in Panel B). The mesentery is shortened due to malignant infiltration (white arrow in Panel C).

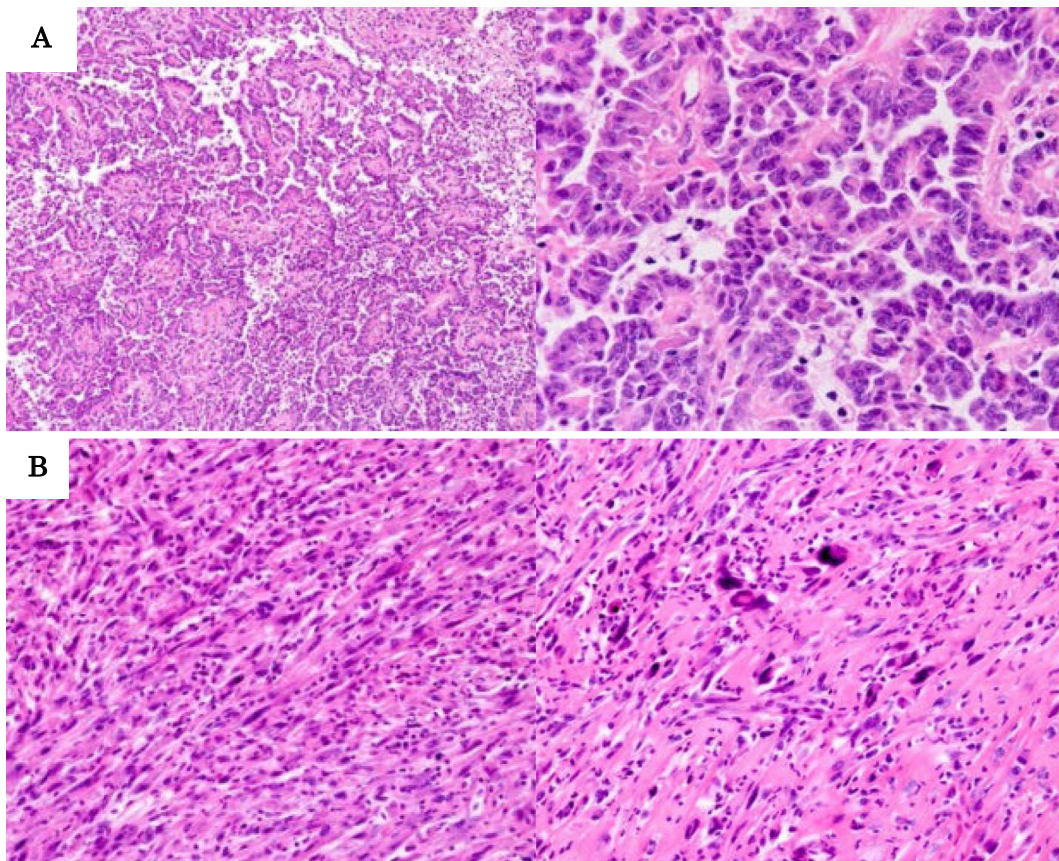
the epigastrium. He was admitted because of anemia, inflammation, and abdominal distension. His serum iron level was low (13  $\mu\text{g/dL}$ ) and his ferritin level was high (1,050 ng/mL), indicating disordered iron utilization and suggesting that his microcytic anemia had occurred secondarily to systemic inflammation. His urine was negative for protein, while his serum protein fractions showed a chronic inflammatory pattern that was characterized by a decrease in albumin and an increase in  $\alpha_1$ -globulin,  $\alpha_2$ -globulin, and  $\gamma$ -globulin (polyclonal gammopathy). We performed enhanced abdominal computed tomography (CT) to investigate the cause of abdominal distension, which revealed massive ascites, thickening of the anterior peritoneum, and shortening of the mesentery (Fig. 1). Neither abdominal lymphadenopathy nor abnormalities of the solid viscera were observed. Paracentesis revealed cloudy yellow ascites with a high total protein concentration of 3.0 g/dL, indicating that it was an



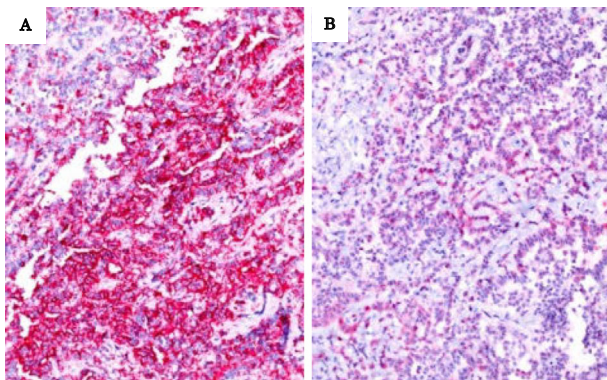
**Figure 2.** The macroscopic findings at autopsy; the digestive tract and the other abdominal organs have become a single mass.

exudate. The serum-to-ascites albumin gradient was 0.6 g/dL, demonstrating the absence of portal hypertension. The glucose concentration was 98 mg/dL and the cell count was 150/ $\mu\text{L}$  (mainly lymphocytes and histiocytes without neutrophils). A bacterial culture of the ascites was negative, which made bacterial peritonitis unlikely. Tuberculous peritonitis was excluded by the normal adenosine deaminase level (16.7 IU/L). Because his cytology was class III, malignant ascites was suspected. His serum tumor marker levels, including carcinoembryonic antigen and carbohydrate antigen 19-9, were normal. A gastrointestinal tract work-up revealed reflux esophagitis and chronic gastritis on endoscopy, but no malignant lesions were found. The patient vomited after endoscopy and developed chemical pneumonia due to the aspiration of gastric acid. The patient's respiratory insufficiency required ventilation, but he was subsequently weaned from the ventilator. However, he had recurrent vomiting and aspiration due to paralytic ileus. Cytological examinations of the ascitic fluid were repeated three times, but remained class II after the initial finding of class III. Because the patient's abdominal distension persisted, we performed the drainage of approximately 3 L of fluid; however, the re-accumulation was rapid and weekly drainage was required. The patient's hemoglobin level decreased to 6.9 g/dL and a transfusion of packed red cells was planned. A direct Coombs test was positive and warm antibody was detected in the blood examination before transfusion, despite the patient having no history of transfusion. We did not perform transfusion because agglutination occurred with all of the red cell products that were stored at our hospital. The patient died of aspiration pneumonia secondary to paralytic ileus on the 52nd day of hospitalization and an autopsy was performed with the consent of his family. The abdominal cavity contained 3,200 mL of clear yellowish ascites and the entire peritoneum was thickened with scattered small granules and nodules. Severe adhesion of the digestive tract was observed, which formed a cluster with the abdominal organs (Fig. 2). The entire peritoneum, gastrointestinal tract, and gallbladder showed prominent thickening, and there was also partial involvement of the liver and pancreas. A histological examination of the





**Figure 3.** Photomicrographs of Hematoxylin and Eosin (H&E) staining sections (left: H&E staining×40, right: H&E staining×400). Panel A shows the tubulopapillary pattern and Panel B shows the sarcomatous pattern.



**Figure 4.** Photomicrographs of immunohistochemical staining for HBME-1 (Panel A: ×100) and calretinin (Panel B: ×100). Both markers are positive.

Hematoxylin and Eosin (H&E) staining sections revealed neoplastic cells with a tubulopapillary appearance (Fig. 3A), as well as tightly packed spindle cells (Fig. 3B), which represented epithelioid and sarcomatous tumor components, respectively. The tumor cells were negative for carcinoembryonic antigen (a marker of adenocarcinoma), but were positive for HBME-1 (Fig. 4A), calretinin (Fig. 4B), cytokeratin, CAM 5.2, and cytokeratin 5/6 (markers of mesothelioma) on immunohistochemical staining. Biphasic MPM was diagnosed based on these findings.

## Discussion

Malignant mesothelioma is a lethal tumor that arises from the serosa of the pleura, peritoneum, pericardium, or tunica vaginalis of the testis. The peritoneum is the second most frequent site after the pleura, with MPM accounting for approximately 10-15% of all mesotheliomas. In Japan, the Ministry of Health, Labour and Welfare reported that MPM accounts for approximately 100 of the 1,400 deaths due to mesothelioma each year. MPM is classified into three histological subtypes: epithelioid, sarcomatoid, and biphasic. A biphasic tumor has both epithelioid and sarcomatous components, each of which contributes to more than 10% of the overall histology. MPM with a sarcomatoid component is associated with a worse prognosis; the median survival time of patients with epithelioid MPM is reported to be 55 months, while that of patients with the combination of the sarcomatoid and biphasic subtypes is only 13 months (1). The present case suggests that physicians should make the following considerations. First, in patients with abdominal ascites of unknown etiology, we should consider a peritoneal lesion and MPM in the differential diagnosis. Wang et al. studied 153 patients with ascites of unknown etiology and found that all of them showed abnormalities of the peritoneum or greater omentum on ultrasonography (2). Although

our patient did not work with asbestos and despite the fact that asbestos bodies were not detected in his lungs at autopsy, the chief known risk factor for mesothelioma is asbestos. Asbestos was used as fire-resistant covering material in Japan, mainly from the 1960s to 1970s, and it is said that the estimated average latent period between exposure and the development of the tumor is approximately 30 years. Our patient was spontaneously exposed to asbestos from the surrounding environment, and the tumor may have developed through the latent period. Accordingly, the possibility of the development of MPM in aged patients may increase in the near future, and we must take it into consideration. Second, it is difficult to make a definite diagnosis of MPM. Although elevated serum levels of hyaluronan, carbohydrate antigen 125, alpha fetoprotein, carcinoembryonic antigen, and mesothelin are found in some patients, the specificity of these markers is not high enough to make a diagnosis (3, 4). Computed tomography may also reveal various findings in MPM patients, including moderate to massive ascites, omental thickening, irregular/nodular sheet-like thickening of the peritoneum (5), but there are no specific imaging features. The cytological examination of the ascitic fluid is also of limited diagnostic utility because it is difficult to distinguish whether the cells found in the ascites are reactive mesothelial cells or malignant cells. Accordingly, peritoneal biopsy, with histological and immunohistochemical examinations, is required to make a definite diagnosis because the differential diagnoses of MPM include metastatic adenocarcinoma, peritoneal serous carcinoma, and soft tissue sarcoma, each of which can have a similar histological appearance. Immunohistochemical staining for several markers can assist in excluding these other diseases (5-8). The biopsy methods that are available include CT-guided, ultrasound-guided, and laparoscopic biopsy. Among these options, ultrasound-guided biopsy can be recommended because it is no more complicated than CT-guided biopsy and anesthesia is not necessary (unlike laparoscopic biopsy). Finally, Coombs-positive hemolytic anemia is known to be one of the paraneoplastic phenomena that are associated with MPM. A direct Coombs test was positive and warm antibodies were detected in our patient, despite the patient having no history of transfusion, but there was no obvious hemolysis because his serum haptoglobin level (461 mg/dL) did not decrease, and no evidence of splenomegaly on CT. These findings suggest that MPM may cause abnormalities of the immune system. Selleslag et al. reported that steroid therapy improved hemolytic anemia in patients with MPM (9).

## Conclusion

MPM is a rare malignancy and it is often difficult to diagnose based on the cytology of ascitic fluid. We should consider MPM in the differential diagnosis of unidentified ascites, even if the patient has no obvious history of asbestos exposure. There is a strong possibility of peritoneal disease in patients with unidentified ascites; thus, a peritoneal biopsy is necessary to investigate the cause. Ultrasound-guided percutaneous peritoneal biopsy can be recommended for the diagnosis of MPM.

**The authors state that they have no Conflict of Interest (COI).**

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