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【 CASE REPORT 】

Malignant Pleural Mesothelioma with Bone Marrow Metastases

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Abstract:
A 64-year-old man with the bone marrow metastasis due to malignant pleural mesothelioma (MPM) was diagnosed with anemia, leukoerythroblastosis, thrombocytopenia, and lower back pain. A bone marrow biopsy demonstrated infiltrative malignant mesothelioma lesions in the bone marrow. The patient died within 15 days of the detection of the bone marrow involvement. Physicians should consider performing a bone marrow biopsy to diagnose bone marrow metastasis and treat patients with palliative chemotherapy at an earlier phase of the disease. To our knowledge, this is the first report of an MPM patient having bone marrow metastasis with anemia, leukoerythroblastosis, and thrombocytopenia.

Key words: bone marrow metastasis, malignant pleural mesothelioma, anemia, leukoerythroblastosis, thrombocytopenia

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Introduction

Malignant pleural mesothelioma (MPM) is a malignant tumor derived from the mesothelial cells of the serous membranes in the pleura (1-3). It is classified into the epithelial, biphasic, and sarcomatous types (4). MPM is an aggressive disease with a poor prognosis and limited treatment options; the median survival duration is approximately 1 year (1-3). Approximately 70% of MPM cases are associated with asbestos exposure, which is known as the primary risk factor for mesothelioma; asbestos is an environmental carcinogen (1-3, 5). The typically long latency period from asbestos exposure to the onset of MPM ranges from approximately 20-50 years (5). MPM generally spreads and invades locally to the chest wall, mediastinum, and diaphragm, and metastasizes to both the hilar and mediastinal lymph nodes. Although distant metastasis to the bone, contralateral lung, peritoneum, or liver is reported to occur in approximately 55% of MPM cases (6-8), bone marrow metastasis from MPM is extremely rare. Only 3 cases have been reported (9, 10). We herein report the fourth case of an MPM patient with bone marrow infiltration, anemia, leukoerythroblastosis, and thrombocytopenia.

Case Report

A 64-year-old man with MPM was referred to our hospital for chemotherapy. The patient had been immunohistopathologically diagnosed with MPM (epithelial type) at a previous hospital based on a surgical biopsy specimen of the right pleura. He had worked as a drug manufacturer and a manager of drug manufacturing in a pharmaceutical company, and may have experienced low-level exposure to chemical substances without asbestos. A histopathological examination revealed that the tumor cells contained eosinophilic granules and were positive for calretinin, podoplanin (D2-40), Wilms' tumour-1 (WT-1), mesothelin, cytokeratin 5/6 (CK5/6), and thrombomodulin, but negative for carcinoembryonic antigen (CEA), thyroid transcription factor-1

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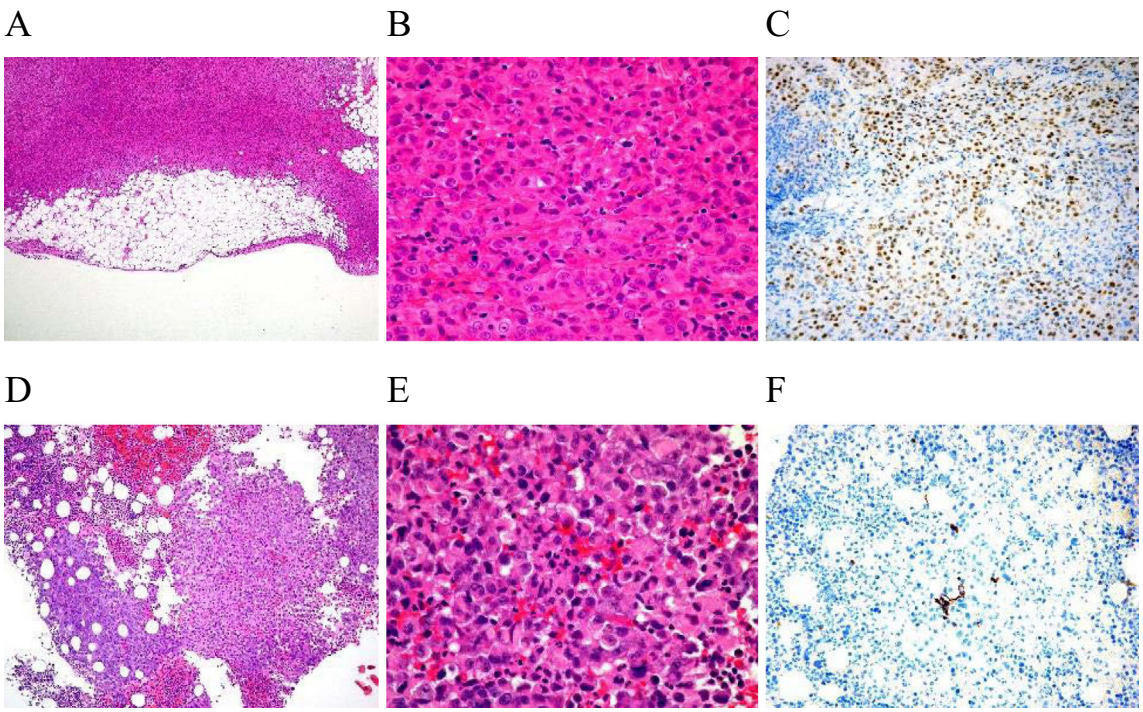

Figure 1. **A histopathological analysis of the right pleura (A, B and C) and bone marrow (D, E and F) biopsy specimens. The tumor cells infiltrated both the pleura and bone marrow (Hematoxylin and Eosin (H&E) staining, ×20) (A and D), (H&E staining ×200) (B and E). The cells were positive for Wilms' tumour-1 (WT-1) (WT-1 immunostaining, ×400) (C and F).**

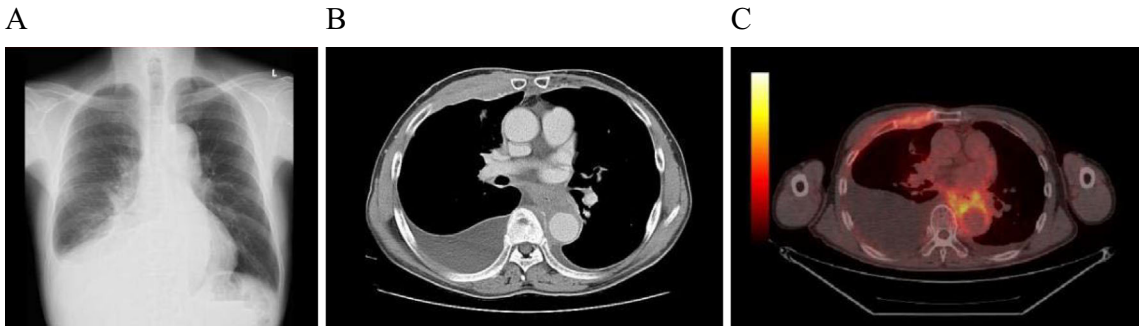

Figure 2. **Chest X-ray (A), Chest CT (B), and ^{18}F-FDG PET-CT (C) scans at the initial presentation. Right pleural effusion with thickening in the right front pleura is observed. The increased uptake of FDG in the right front pleura, mediastinal organs, and metastases in the mediastinal lymph nodes was observed.**

(TTF-1), and epithelial cell adhesion molecule (Ber-EP4) (Fig. 1A-C, and data not shown). Chest X-ray, chest computed tomography (CT), and the ^{18}F-Fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET)-CT showed the extension of the tumor to the mediastinal organs and metastases in the mediastinal lymph nodes (Fig. 2). The clinical stage was determined to be cT4N3M0 Stage IV (11). After talc pleurodesis, the patient received four cycles of chemotherapy with cisplatin plus pemetrexed, to which he showed a partial response. However, evidence of progressive disease was observed, with a new lesion in the right pleura at three months after his last treatment. Although he was given chemotherapy with the same drug regimen, he was admitted to our hospital because of general fatigue, dehydration, and right front chest pain after four days of chemotherapy. His general fatigue and dehydration were improved by supportive therapy with fluid replacement, and both nonsteroidal anti-inflammatory drugs (NSAIDs) and morphine reduced the intensity of his pain. He developed myelosuppression, including grade 3 leukopenia, anemia, and thrombocytopenia (Fig. 3). On days 7-11 of hospitalization, filgrastim (recombinant met-human granulocyte-colony stimulating factor) was administered. After the improvement of his myelosuppression, a prolonged fever developed, in spite of the administration of antibiotics. The laboratory data on day 17 of hospitalization showed the following: white

blood cell count, 41,500/mm^3; hemoglobin, 7.9 g/dL; alkaline phosphatase, 513 U/L; and lactate dehydrogenase, 1,981 U/L. Moreover, leukoerythroblastic changes were observed in the peripheral blood. A bone marrow biopsy on day 19 revealed the replacement of the marrow by a diffuse neoplastic infiltrate containing eosinophilic granules, granulocytes with an altered nuclear morphology, the absence of megakaryocytes, dyserythropoisis, and poor cellularity (Fig. 1D and E). The neoplastic cells were accompanied by nuclear deviation and multinuclear cells, and were diffusely positive for cytokeratin (AE1/AE3) and vimentin, focally positive for D2-40, WT-1, and mesothelin, and negative for calretinin, CEA, and TTF-1 (Fig. 1D-F and data not shown). Based on these results, the patient was diagnosed with MPM with bone marrow infiltration. During his prolonged fever, despite the continued administration of NSAIDs and morphine, severe lower back pain also developed on day 14 of hospitalization. Spine magnetic resonance imaging (MRI) on days 16 and 18 of hospitalization revealed metastatic lesions at multiple bone sites, including the thoracic spine, lumbar spine, and sacral vertebra, and spinal cord compression was found in the eleventh and twelfth thoracic vertebra (Th11/Th 12) (Fig. 4). Palliative radiotherapy was administered with irradiation of the thoracic part of the spinal cord (Th11/Th 12) at a dose of 24 Gy divided into six fractions (one fraction per day) on days 22-27 of hospitalization. However, paraplegia of the lower extremities and neurogenic bladder and bowel dysfunction due to metastatic invasion of the spinal cord developed on day 23. On day 31 of hospitalization, the patient developed persistent severe back pain, anemia, and thrombocytopenia, and later died suddenly on day 32 of hospitalization.

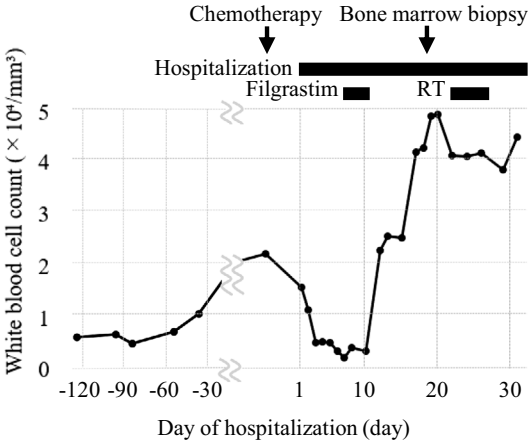

Figure 3. A schematic illustration of the clinical course and the changes in the white blood cell counts.

Discussion

The postmortem records of 318 patients with MPM demonstrated that extrathoracic metastasis of MPM was observed in the liver (31.9%), peritoneum (24.4%), and bone (13.8%) (8). In these records, metastasis was found in many

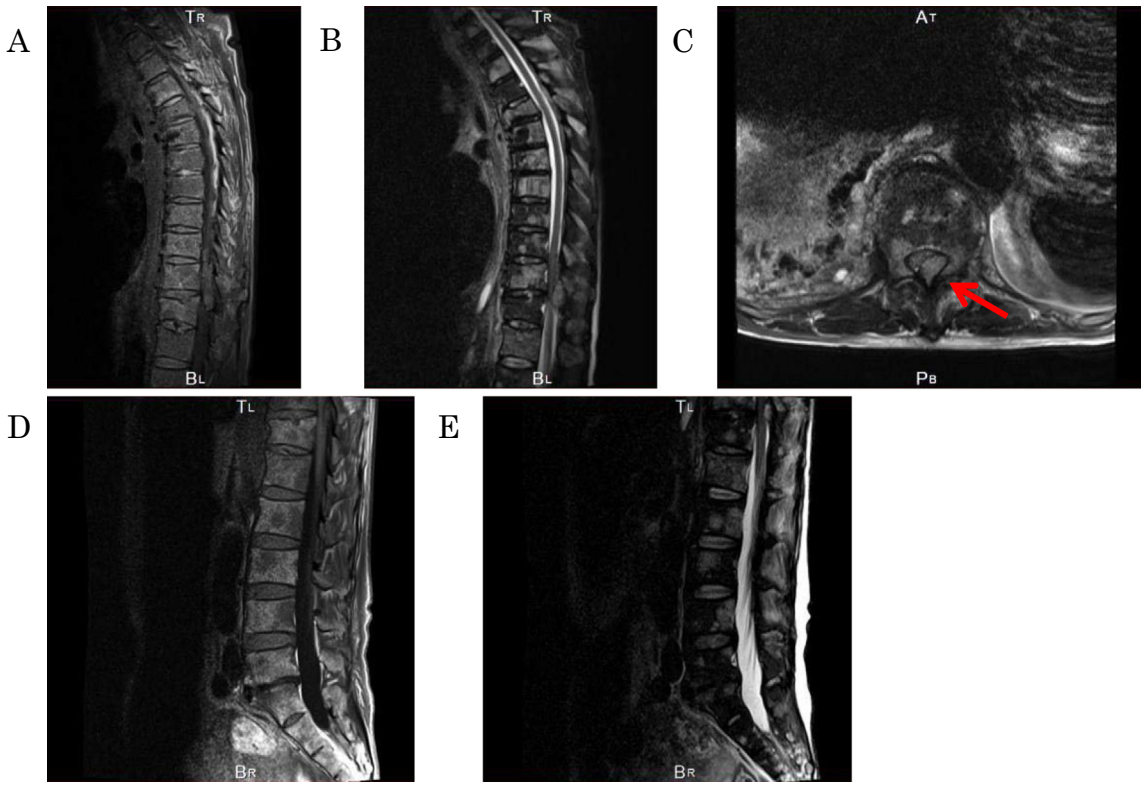

Figure 4. Spine MRI. Multiple bone metastases were of low intensity on T1-weighted imaging (A and D) and were of high intensity on fat suppressed imaging (B and E). A vertebral metastasis in Th11/Th12 showed spinal cord compression on axial T2-weighted imaging (C).

organs that are not usually regarded as sites of MPM metastasis, including the adrenals (10.2%), spleen (10.8%), and brain (3.0%) (8). There are only 3 reports of MPM patients with bone marrow metastasis (9, 10). To the best of our knowledge, this study represents the first report of a MPM patient with bone marrow metastasis and anemia, leukoerythroblastosis, and thrombocytopenia.

Bone metastasis from solid malignant tumors rarely develops into bone marrow metastasis, which is associated with a poor prognosis. Bone marrow metastasis is associated with hematological disorders, including anemia, leukoerythroblastosis, and disseminated intravascular coagulation (DIC). This condition is called disseminated carcinomatosis of the bone marrow (DCBM) (12-21). Previously published reports have shown that DCBM is associated with gastric cancer and includes 3 major symptoms: anemia, lower back pain, and bleeding tendency. The patient in the present case developed anemia, leukoerythroblastosis, thrombocytopenia, and severe lower back pain as characteristics of DCBM, and a bone marrow biopsy revealed infiltrative malignant mesothelioma in the bone marrow. Based on reports of solid malignant tumors, the prognosis of patients with DCBM is considered to be extremely poor (14-17). These previous reports demonstrated that the median survival of DCBM from gastric cancer after the detection of bone marrow metastases was significantly shorter in patients who were given the best supportive care (BSC) than in the patients who were given palliative chemotherapy (14-17). The three previous studies by Kim et al., Rhee et al., and Kwon et al. reported that the median overall survival from the time of the detection of bone marrow involvement in BSC was 20 days, 16 days, and 11 days, respectively (14, 16, 17). Conversely, they showed that the median overall survival in the patients who received palliative chemotherapy was 67 days, 99 days, and 121 days, respectively (14, 16, 17). Thus, they suggested that palliative chemotherapy should be considered for gastric cancer patients with DCBM (14, 16, 17). It was also reported that an early diagnosis and prompt chemotherapy could contribute to improved survival of a few months in colon cancer patients with DCBM (22). The patient in the present case was given the best supportive care before the detection of bone marrow metastasis; however, his clinical course was extremely rapid, and he died within 15 days of the detection of bone marrow involvement.

Although the present case showed different pathological findings between the pleura and bone marrow, other malignancies were not detected by PET-CT imaging at the initial presentation or by CT and MRI imaging during treatment. Thus, we determined that the diagnosis in the present case was MPM with bone marrow infiltration. Differences in staining methods and the handling of specimens may have led to the discrepant pathological findings between the pleura and bone marrow. It is acknowledged that the present case was limited by these discrepant findings.

Although mesothelioma is strongly associated with asbestos exposure, approximately 20% of patients with mesothelioma have no demonstrable asbestos exposure, even after a detailed assessment (23-26). It has been reported that other mineral fibers, such as erionite, nanotubes, and irradiation are possible risk factors for the development of mesothelioma (24). This patient worked in a pharmaceutical company and may not have been exposed asbestos or another mineral fiber.

In conclusion, to the best of our knowledge, this is the first report of an MPM patient with bone marrow metastasis, anemia, leukoerythroblastosis, and thrombocytopenia. The prognosis of MPM with bone marrow metastasis with or without palliative chemotherapy is uncertain, because the previous reports only evaluated the prognosis of gastric cancers with DCBM. Although it may be of minimal value to the patients to diagnose such a severe and rapidly progressive case, the accumulation of cases would reveal the true significance of palliative chemotherapy for MPM with bone marrow metastasis. Thus, a bone marrow biopsy should be considered in order to facilitate the diagnosis of MPM and treatment with palliative chemotherapy at an earlier phase of the disease.

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

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