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Case Report

A Case of Mediastinal Localized Malignant Pleural Mesothelioma Successfully Treated by Chemotherapy and Conversion Surgery

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Localized malignant mesothelioma is a rare disease and little is known about its treatment strategy. We herein report a case of localized malignant pleural mesothelioma that had infiltrated into the anterior mediastinum, which was successfully treated using chemotherapy and conversion surgery. A 63-year-old man with a mediastinal tumor was referred to our hospital. Pathologic analysis of the biopsy specimen showed malignant mesothelioma. Significant tumor shrinkage by cisplatin and pemetrexed was observed and he underwent radical surgery via a median sternotomy. The patient has been disease free for 12 months.

Key words: localized mesothelioma, mediastinum, cisplatin, pemetrexed, conversion surgery

Malignant mesothelioma (MM) is a rare disease arising from exposure to asbestos, a known carcinogen. Malignant pleural mesothelioma (MPM) is the most common form of MM and often spreads diffusely to both the parietal and visceral pleura and invasively into the chest wall and mediastinum. Despite the evolution of multimodality therapy, the prognosis of MPM remains dismal. According to the World Health Organization (WHO) classification, distinctly localized mesothelioma without diffuse spread has been distinguished from "diffuse malignant mesothelioma (DMM)" and has been newly termed "localized malignant mesothelioma (LMM)" [1]. Most cases of LMM develop from the pleura (localized malignant pleural mesothelioma [LMPM]) [2], and several reports have stated that curative intent surgery for LMPM has a better prognosis than that for diffuse MPM (DMPM) [3,4]. However, a standard therapy has not yet been established due to the paucity of evidence.

Herein, we report a case of LMPM that had infiltrated into the anterior mediastinum and that was successfully treated using chemotherapy and conversion surgery.

Case

A 63-year-old man with a productive cough was referred to our hospital for the treatment of a mediastinal tumor. He was a current smoker of 20 cigarettes per day (44 pack-year smoking history), and he had been working as an electrical engineer for 45 years, including in a shipyard during the first 5 years of his career, which suggests a history of exposure to asbestos. A chest X-ray demonstrated a superior mediastinal mass, and subsequent examinations using contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) revealed an 8.5 cm heterogeneous ante-

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rior mediastinal tumor. The tumor was adjacent to the aortic arch, innominate vein, and left main pulmonary artery (Fig. 1A). An 18-fluorodeoxyglucose positron-emission tomography (18F-FDG PET)/CT study showed a remarkably high uptake at the tumor site with a maximum standardized uptake value (SUVmax) of 9.3 (Fig. 1B). An invasive thymoma or thymic cancer was initially suspected, and a CT-guided biopsy was performed. However, the tumor consisted of tumor cells having enlarged nuclei with increased chromatin, inflammatory cells and necrotic area. Immunohistochemistry of the biopsy specimen revealed staining for keratin5/6, calretinin, Wilms' tumor suppressor gene (WT1: slightly positive in 10% of the tumor cells) and podoplanin (D2-40: slightly positive) in the tumor cells, suggesting an MPM (Fig. 2). On the other hand, the antibody tests for thymoma and/or thymic cancer (CD117, CD5, PAX8 and p40) were all negative. The antibody tests for lung cancer, carcinoembryonic antigen (CEA) and thyroid transcription factor-1 (TTF-1) were also negative. Consequently, the patient was diagnosed as having a localized MPM with a clinical International Mesothelioma Interest Group (IMIG) stage of IIIB (T4N1M0).

While no obvious contraindications for surgery were present, the patient was not a surgical candidate given the necessary surgical margin. He received four cycles of chemotherapy with cisplatin (CDDP) (75 mg/m^2) and pemetrexed (PEM) (500 mg/m^2) on day 1 every 3 weeks without experiencing any severe adverse events. A post-chemotherapy CT scan showed a marked reduction in the size of the tumor (Fig. 3A). An 18F-FDG PET/CT study also showed a significant metabolic response (SUVmax = 2.1) (Fig. 3B). No evidence of distant metastasis or infiltration into the aorta was seen, and the tumor was determined to be resectable.

Four weeks after the chemotherapy, the patient underwent radical surgery via a median sternotomy. No signs of invasion into the aortic arch, innominate vein, or left main pulmonary artery were seen, and the tumor was resected. The left phrenic nerve was preserved, and an intraoperative frozen section of the dorsal margin was negative for tumor cells. A diffuse, thickened parietal pleura was observed, and a partial biopsy was performed on the left third rib. The patient was discharged 15 days after surgery without any complications. Pathological examination of the resected specimen revealed residual malignant cells, 4 mm in diameter, in a lymph node, but the other areas of the tumor showed only tumor scars without viable malignant cells. Immunohistochemistry showed the tumor cells in the lymph node to be positive for keratin5/6, calretinin and heart development protein with epidermal growth factor-like domains 1 (HEG-1) and negative for BRCA1-associated protein 1 (BAP1), CEA, and TTF-1, suggesting a metastasis from the MPM (Fig. 4). The tumor cells contained epithelioid and spindle-shaped cells, suggesting biphasic MPM. The parietal pleura tissue consisted of collagenous fibrous tissue and had been infiltrated by lymphocytes and plasma cells, but no tumor cells were present. The patient has been followed for 12 months and has shown no signs of recurrence.

Discussion

LMM is a relatively newly recognized mesothelial tumor that has often been confused with solitary fibrous tumor (SFT). Crotty *et al.* reported a series of 6 LMPM cases with clinicopathological features in 1994 [5]; since then, about 170 cases of LMM have been reported [6]. LMM has been distinguished from DMM in the WHO classification since 2004 [1]. Although the microscopic and immunohistochemical findings of LMM are the same as those for DMM, LMM typically does not exhibit either wide serosal spread or dissemination. Allen *et al.* reported that 21 of 23 LMM cases were plural mesothelioma (LMPM) [2], and several reports of abdominal LMM have been published [2,6]. Only 0.5% to 1.6% of diagnosed mesotheliomas are classifiable as LMM, and literature on its epidemiology remains scant [6]. The median patient age is around 62 to 66 years, and the male to female ratio ranges from 3:2 to 3:1 [2,3,6]. The percentage of cases with a reported history of occupational or environmental asbestos exposure varies from 17.4% to 90% [2-4,6]. This percentage appears to be relatively low, since about 80% of MM cases have a history of asbestos exposure; nevertheless, the incidence of LMM does seem to be related to asbestos exposure [7,8]. The incidence of MM is increasing worldwide because of the history of asbestos use and a latency period of about 40 years until clinical presentation [7]. This background suggests that the prevalence of LMM may increase.

MM is pathologically divided into three subtypes: epithelioid, sarcomatoid, and biphasic mesothelioma. The most common subtype of LMM is epithelioid, rep-

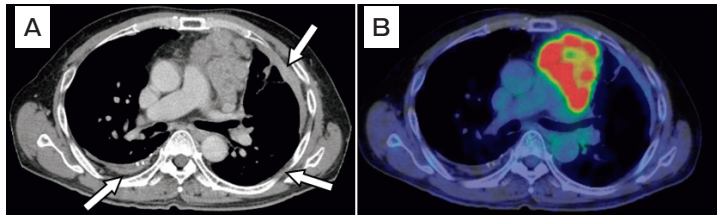

Fig. 1 (A) A contrast-enhanced chest CT image shows a heterogeneous, enhanced anterior mediastinal mass. The white arrowheads indicate bilateral pleural thickening and plaques. (B) 18F-FDG PET/CT shows an intense uptake in the tumor (SUVmax = 9.3)

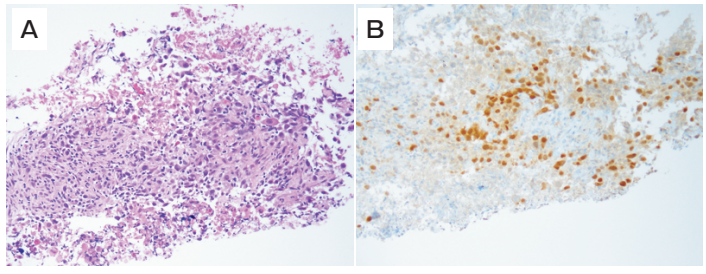

Fig. 2 Pathological examination of the biopsy specimen. (A) The tumor cells had eosinophilic cytoplasm with large irregular nuclei. (B) Immunohistochemistry showed positive staining for calretinin.

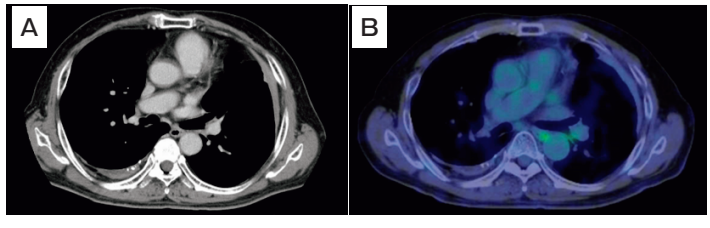

Fig. 3 Post-chemotherapy radiological examinations. (A) A contrast-enhanced chest CT image showed significant tumor shrinkage. (B) 18F-FDG PET/CT revealed a metabolic response in the tumor (SUVmax = 2.1)

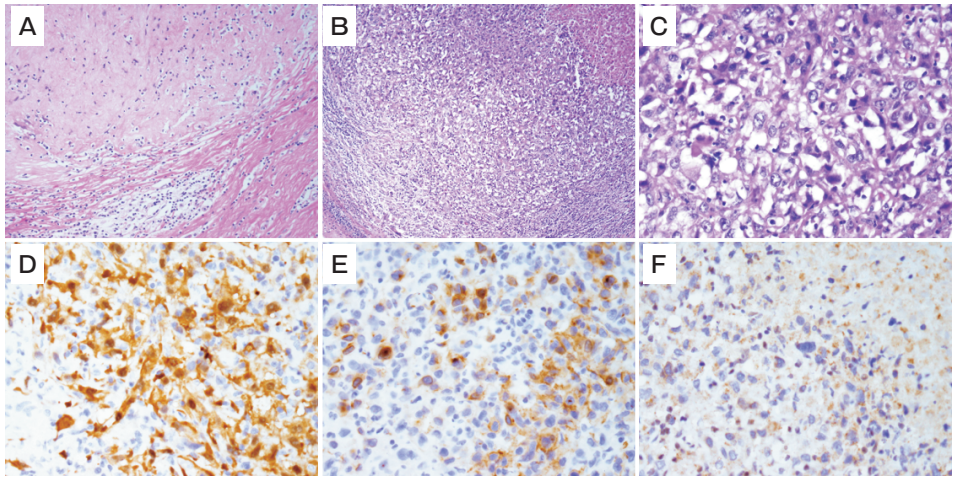

Fig. 4 Pathological examination of the resected specimen. (A) Histological examination of the tumor showed fibrosis and no active tumor cells. (B) Low-magnification image and (C) high-magnification image of the metastatic lymph node. Immunohistochemistry of the lymph node was positive for (D) calretinin and (E) HEG1 and negative for (F) BAP1.

resenting 40% to 70% of LMM cases [2-4,6]. Usually, sarcomatoid mesothelioma is a lethal disease, but long-term survivors with sarcomatoid LMM have been reported [2,3,6].

Little is known about the treatment strategy for LMPM, but the most commonly reported treatment has been surgical resection [6], and the median survival period after surgery is 56 to 58 months [2,4]. However, LMPM is often diagnosed postoperatively, and adjuvant chemotherapy has been conducted in several cases. Nakano *et al.* reported that 11 of 13 LMPM cases at their institution originated in the parietal pleura [3]. In such cases, a tumor resection that includes the adjacent chest wall is technically possible. In the present case, however, the tumor was adjacent to the ascending aorta, and an initial surgery was thought to be difficult considering the safety margin; consequently, we decided to treat the patient with chemotherapy. Hino *et al.* also reported a case of mediastinal LMPM that was treated with neoadjuvant chemoradiotherapy followed by surgery [9]. However, Hino's patient was initially diagnosed as having thymic adenocarcinoma and was treated with carboplatin (CBDCA), paclitaxel and concurrent radiation, and a significant volume reduction was not observed. The diagnosis of LMPM was made based on immunohistochemical analysis of the resected specimen, and a local recurrence was detected 12 months after the surgery. Chemotherapy with PEM and CDDP has been reported to confer an increased survival benefit in cases of unresectable MPM, compared with CDDP alone [10], and international guidelines also recommend chemotherapy regimens containing PEM plus platinum [11,12]. Neoadjuvant PEM plus CDDP followed by surgery has also been reported as a component of multimodality therapy [13,14]. We observed a significant tumor volume reduction after PEM and CDDP chemotherapy; pathologically, an almost complete remission was obtained, except at a lymph node site. Because LMPM recurrences are usually local or metastatic, but progression to DMPM is atypical, local control is critical [2-4]. Adjuvant radiation therapy after the surgery may be useful. Indeed, adjuvant radiotherapy after surgical treatment was reported to improve overall survival in a series of patients with MPM [15]. The radiation field for the present case would be the mediastinum and the risk of radiation pneumonitis would be low.

In conclusion, clinicians should keep LMPM in mind as a possible differential diagnosis for atypical mediastinal tumors. This case suggests that neoadjuvant chemotherapy with PEM and a platinum doublet followed by surgery could be an alternative treatment allowing a subsequent R0 resection. Further studies are required to establish a standard therapy for mediastinal LMPM.

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