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【 CASE REPORT 】

The Association between Malignant Pleural Mesothelioma and Thoracic Radiation Therapy for Hodgkin's Lymphoma: The First Case Report in Japan

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Abstract:
Malignant pleural mesothelioma (MPM) is mostly observed in patients with a history of asbestos exposure. Although other causes are rare, there are several reports of MPM induced by therapeutic radiation, mainly in Europe and North America. However, no such case has been reported in Japan. We herein report a 50-year-old Japanese woman who developed MPM 25 years after thoracic radiation therapy for Hodgkin's lymphoma. The patient had no history of exposure to asbestos; therefore, her history of radiation therapy was considered to be the cause of MPM. Clinicians should consider secondary MPM in patients with a history of thoracic radiation therapy.

Key words: malignant pleural mesothelioma, radiation, thoracic radiation, Hodgkin's lymphoma, secondary malignancy

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Introduction

Malignant pleural mesothelioma (MPM) is a highly aggressive tumor, mainly caused by exposure to asbestos (1, 2). Previous studies (3-7) have suggested therapeutic radiation as another cause of MPM. Furthermore, several case reports (8-21) have suggested an association between thoracic radiation therapy and MPM, mainly in Europe and North America. However, no such case has been reported in Japan.

To our knowledge, this is the first report of a long-term survivor of a primary malignancy who had a history of thoracic radiation therapy and developed MPM in Japan. However, the number of patients with secondary MPM induced by thoracic radiation therapy may also increase in Japan, as the long-term survival after thoracic radiation therapy is expected due to technological improvements in radiation treatment, such as intensity-modulated radiation therapy (IMRT). Our findings suggest that long-term follow-up is needed after thoracic radiation therapy in order to check for the presence of secondary malignancies, including MPM.

Case Report

The patient provided her informed consent for the publication of the details concerning her case, including images.

A 50-year old Japanese woman without a history of exposure to asbestos or smoking had received chemotherapy with mechlorethamine, vincristine, procarbazine, and prednisolone and radiation therapy for Hodgkin's lymphoma when at 25 years old. The irradiated lesions were localized in the mediastinum (50 Gray/25 fractions) and abdomen (56 Gray/28 fractions) as the primary and recurrence sites, respectively (Fig. 1). Five years after the radiation therapy, chest computed tomography (CT) revealed a small amount of left pleural effusion. Since the effusion was too small to perform thoracentesis, follow-up with chest CT and X-ray was continued considering radiation pleuritis. The pleural effusion and thickness increased after 20 years of follow-up; there-

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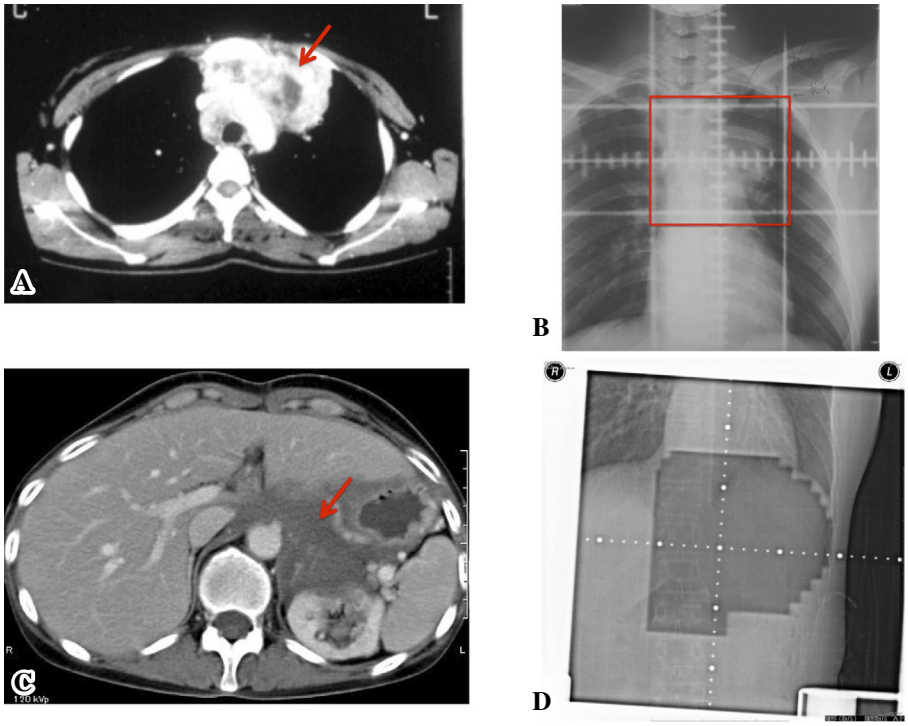

Figure 1. **Chest contrast-enhanced CT finding of primary Hodgkin's lymphoma (A: arrow). Chest X-ray and irradiated lesion of the primary tumor (B: red line). Abdominal contrast-enhanced CT finding of tumor recurrence that developed two years after the first radiation therapy session for the primary tumor (C: arrow). X-ray of the irradiated lesion for tumor recurrence (D). CT: computed tomography**

fore, she visited our hospital for an evaluation (Fig. 2). There were no pleural calcifications. Positron emission tomography also revealed the uptake of ^{18}F-fluorodeoxyglucosea in the thickening pleura (Fig. 3). We performed a full-thickness pleural biopsy. The specimen showed tubule-papillary components in the pleura (Fig. 4A). Immunohistochemistry showed positive staining for calretinin (Fig. 4B), D2-40 (Fig. 4C), and CK5/6 (Fig. 4D) and negative staining for CEA (Fig. 4E) and p40 (Fig. 4F). These findings led to the diagnosis of epithelial type of MPM. There were no asbestos bodies.

Chemotherapy with carboplatin and pemetrexed was administered and maintenance therapy with pemetrexed is currently ongoing.

Discussion

Most cases of MPM are attributable to asbestos (1, 2). Although previous reports (3-7) have suggested an association between thoracic radiation therapy and MPM, such cases are rare. Several cases (8-21) of MPM induced by thoracic radiation therapy have been reported. However, there have been no reports of MPM associated with thoracic radiation therapy in Japan, although two case reports (22, 23) of malignant "peritoneal" mesothelioma after abdominal radiation therapy have been published. In our case, previous thoracic radiation therapy was considered a risk factor for the development MPM based on the clinical history.

However, it is difficult to conclude that thoracic radiation therapy was the only cause of MPM in present case, for several reasons as follows; First, there may be a possibility of non-occupational asbestos exposure from the environmental exposure. Non-occupational exposure is also associated with MPM (24). Furthermore, Alessandro et al (25) have shown that relevant role of non-occupational asbestos exposures accounts for almost 30% of cases of MPM in women. However, the radiological and pathological findings indicated that asbestos exposure was unlikely to be involved in the development of MPM in our case. Second, there have been several putative causes of MPM, such as via exposure to carbon nanotubes, thorium dioxide, simian virus 40 and exposure to metals that cause chronic serosal inflammation (26). It is difficult to exclude the association with these causes completely. Third, several studies have reported that chemotherapy also increases the risk of subsequent malignant neoplasms (27, 28). In a study by Vandenbos et al. (8), the risk of subsequent MPM was higher in patients who underwent radiotherapy only than in those who underwent chemoradiotherapy. Chemotherapy may be a factor associated with the development of MPM in the present case. Fourth, the pathological findings indicated the usual epithelial type of MPM in the present case. Chirieac et al. (7) have reported that about 80% of radiation-associated MPM cases were of the epithelial type, and about 20% of radiation-associated MPM cases were of the biphasic type. Among these previously reported cases, two had unusual

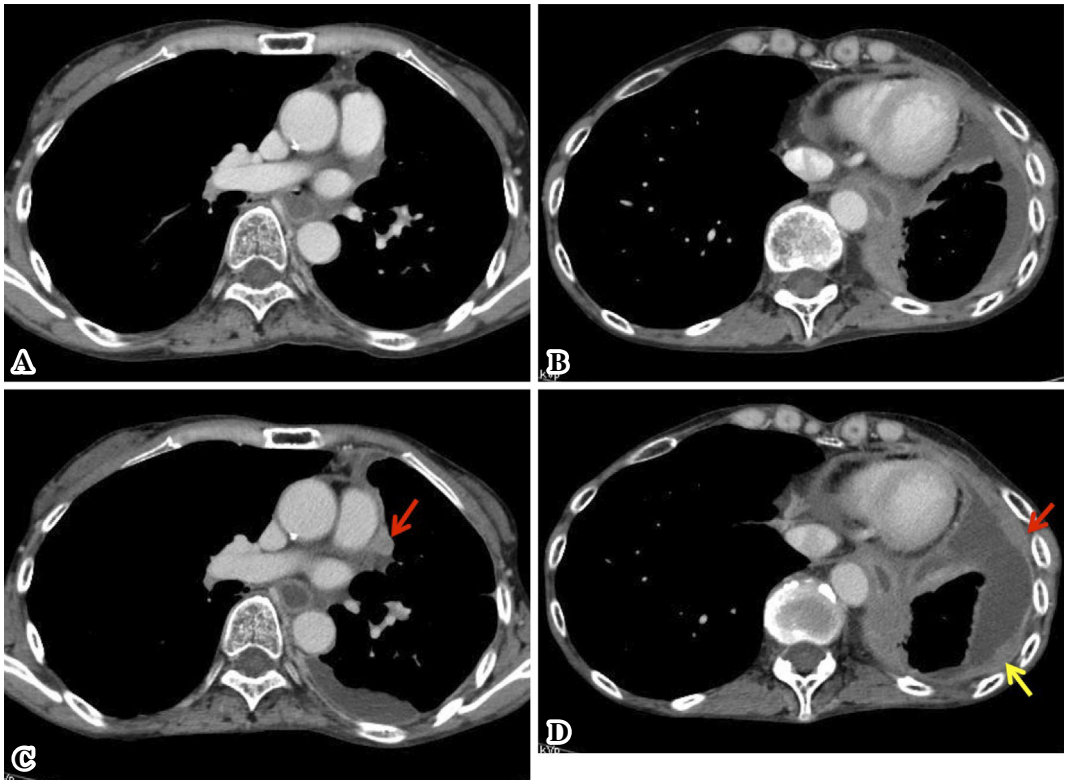

Figure 2. **Chest contrast-enhanced CT a year before the first visit to our hospital revealed a small amount of pleural effusion (A, B). Chest contrast-enhanced CT finding at the first visit to our hospital revealed an increase in pleural effusion and thickness [C, D; arrow (yellow arrow showing the full-thickness pleural biopsy lesion)]. CT: computed tomography**

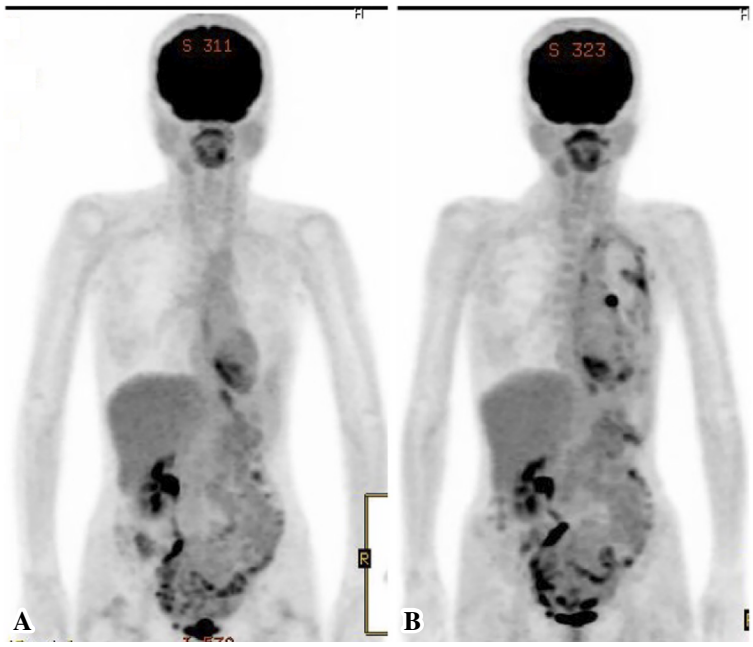

Figure 3. **FDG-PET a year before the first visit to our hospital revealed no FDG uptake (A). FDG-PET at the first visit to our hospital revealed an FDG uptake in the left pleural cavity (B). FDG: ^{18}F-fluorodeoxyglucose, PET: positron emission tomography**

histological patterns, such high-grade cytology with pleomorphic rhabdoid cells and myxoid features. These unusual patterns may be features of radiation-associated MPM, since unusual histological features in MPM are extremely uncommon and rarely reported. However, there were no such pathological findings in our case.

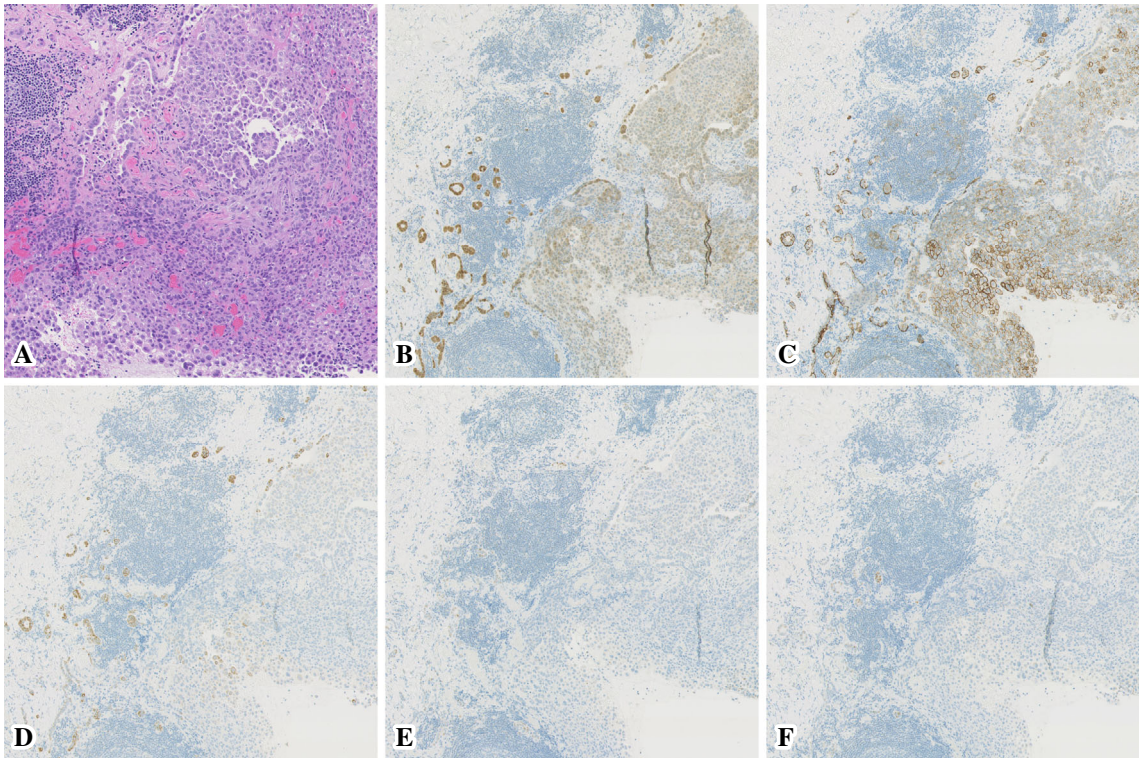

Figure 4. **Pathological findings of a full-thickness pleural biopsy specimen revealed epithelioid-type MPM (A). IHC showed positive staining for calretinin (B), D2-40 (C), and CK5/6 (D) and negative staining for CEA (E) and p40 (F). MPM: malignant pleural mesothelioma, IHC: immunohistochemistry, CK: cytokeratin, CEA: carcinoembryonic antigen**

Thoracic radiation therapy was considered a cause of MPM in the present case for several reasons. First, the tumor lesion was limited to the area of the irradiated lesions. Second, there was no evidence of exposure to asbestos in her medical history, nor were there any relevant radiological findings, such as pleural plaques or pleural calcifications, or pathological findings, such as asbestos bodies. In a previous study (7), the frequency of asbestos bodies was significantly lower in cases of radiation-associated MPM than in those of asbestos-associated MPM. Third, the patient was relatively young for MPM. A previous study (7) also showed that patients with radiation-associated MPM were significantly younger than those with asbestos-associated MPM.

Recently, several techniques for radiation therapy have been developed, such as IMRT. Chun et al. (29) reported that IMRT was associated with lower rates of severe pneumonitis than three-dimensional conformal external beam radiation therapy for locally advanced non-small-cell lung cancer treated with chemoradiotherapy. An improvement in the prognosis of patients treated with thoracic radiation therapy is expected through these technical developments. However, these may also cause an increase in the incidence of secondary malignancies, including MPM, among long-term survivors after thoracic radiation therapy in Japan.

The present and previous case reports (8-21) suggest that MPM tends to develop from 9 to 41 years after thoracic radiation therapy. Thus, long-term follow-up is needed in order to check for the presence of secondary malignancies, including MPM, and physicians should consider performing pathological examinations if necessary.

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

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