Successful treatment of simultaneous malignant pleural mesothelioma and pulmonary adenocarcinoma: A case report

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Abstract. The present report described the case of a 74-year-old male patient with asbestos exposure whose chest computed tomography revealed a right lower lobe nodule and right pleural effusion. Pleural biopsy led to the diagnosis of epithelial malignant pleural mesothelioma (cT2N0M0, stage IB). Combination therapy with cisplatin + pemetrexed led to the complete remission of malignant pleural mesothelioma; however, the right lower lobe nodule grew in size over time. The patient was subsequently diagnosed with lung adenocarcinoma (cT1aN0M0, stage IA1) by computed tomography-guided biopsy performed 18 months after chemotherapy initiation and achieved remission of lung adenocarcinoma with stereotactic radiotherapy. The patient was alive without recurrence at the 12-month follow-up. The present case illustrated that multiple active regimens are currently available for malignant pleural mesothelioma and lung cancer that can aid in the treatment of complex cases.

Introduction

Malignant mesothelioma is a rare malignant tumor that occurs in the pleura, peritoneum, pericardium and testicular membrane, with most cases occurring in the pleura. Asbestos exposure is considered to be one of the main causes of the disease, as it has been reported that 78-88% of cases of malignant mesothelioma in men and 23-65% of cases in women are related to asbestos exposure (1,2). In addition, in the past few decades, lung cancer has become the leading cause of cancer death in men worldwide (3). Asbestos exposure is a common risk factor for malignant pleural mesothelioma and lung cancer (4); however, their coexistence is relatively rare (5-22). Combination therapy with cisplatin + pemetrexed is an active regimen for malignant pleural mesothelioma and non-squamous non-small cell lung cancer (23,24). However, there are few studies which have reported on patients with comorbid malignant pleural mesothelioma and lung cancer who were treated with a common chemotherapeutic regimen, such as cisplatin + pemetrexed (9,22). Therefore, the present report describes a patient with lung nodules that grew during the administration of cisplatin + pemetrexed therapy for malignant pleural mesothelioma, and they were subsequently diagnosed with invasive mucinous adenocarcinoma.

Case report

A 74-year-old male patient was referred to Gamagori City Hospital (Gamagori, Japan) for the evaluation of a blunted right costophrenic angle observed on a chest X-ray during a routine annual check-up (Fig. 1A) in November 2019. The patient had a smoking history of >30 years and a history of asbestos exposure related to their occupation for ~30 years. Chest computed tomography (CT) performed according to the standard setting revealed partial thickening of the right pleura (Fig. 1B), right pleural effusion and nodules along the right interlobar pleura (Fig. 1C). The initial diagnosis was lung cancer with carcinomatous pleurisy.

Cytological examination of the pleural effusion revealed numerous papillary and glandular masses with conspicuous nucleoli and partial multinucleation (Fig. 2A), suggesting malignant pleural mesothelioma. All staining was examined using an Olympus BX53 light microscope (Olympus Corporation). The cytological analysis of the pleural effusion cell block revealed atypical cells (Fig. 2B and C). Immunohistochemistry was performed on formalin-fixed and paraffin-embedded 3-4 μm tissue sections. For fixation, tissues were incubated with 10% formalin at room temperature for 24 h. Immunohistochemistry was performed automatically using BOND-III (Leica Microsystems, Inc.) and BOND Polymer Refine Detection Kit (cat. no. DS9800; Leica Microsystems, Inc.), according to the manufacturer's instructions. The following antibodies were used: Cytokeratin (CK)7 (clone OV-TL 12/30; cat. no. M7018;

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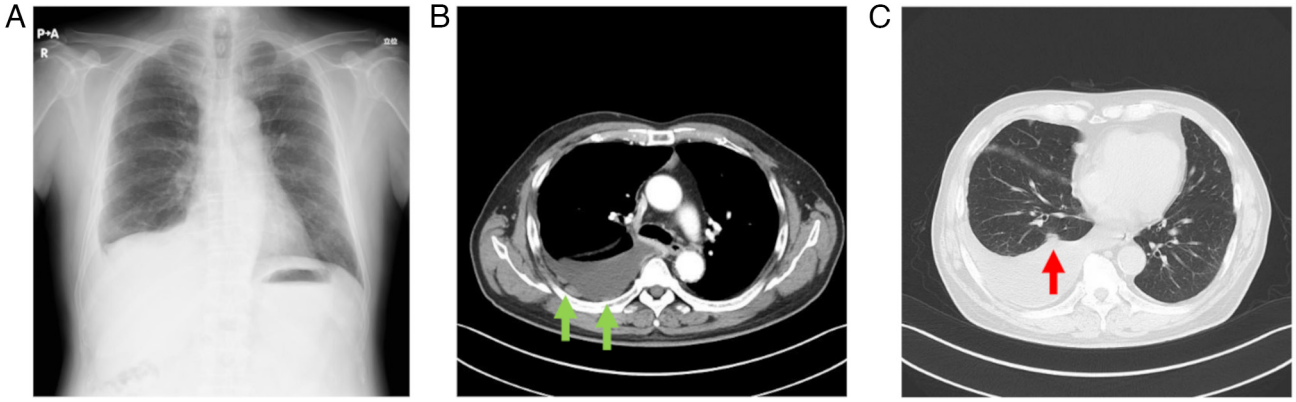

Figure 1. Initial imaging of the patient. (A) Chest X-ray showed blunting of the right costophrenic angle and computed tomography showed (B) partial thickening of the right pleura (green arrows) and (C) right pleural effusion and nodules along the right interlobar pleura (red arrow).

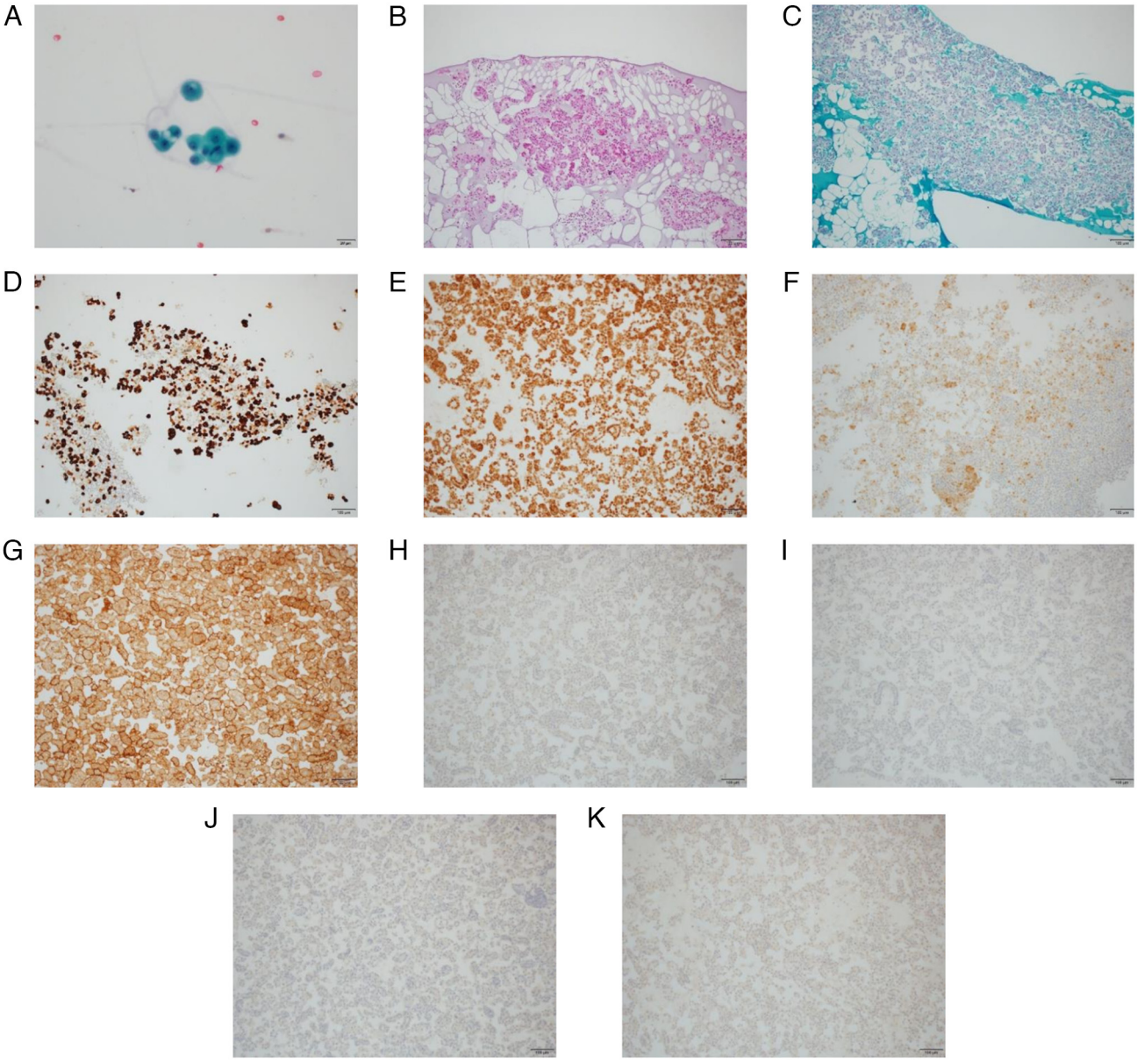

Figure 2. Pleural fluid cytology. (A) Papillary and glandular mass with prominent nucleoli and partial multinucleation on Papanicolaou stain (magnification, x40). (B) Hematoxylin and eosin staining of cell block (magnification, x10). (C) Periodic acid Schiff staining of cell block (magnification, x10). Evaluation of the cell block by immunohistochemistry revealed atypical cells, which were positive for (D) CK7 (magnification, x10), (E) CK5/6 (magnification, x10), (F) calretinin (magnification, x10) and (G) mesothelin (magnification, x10), and negative for (H) CK20 (magnification, x10), (I) CDX2 (magnification, x10), (J) napsin A (magnification, x10) and (K) p40 (magnification, x10). CK, cytokeratin.

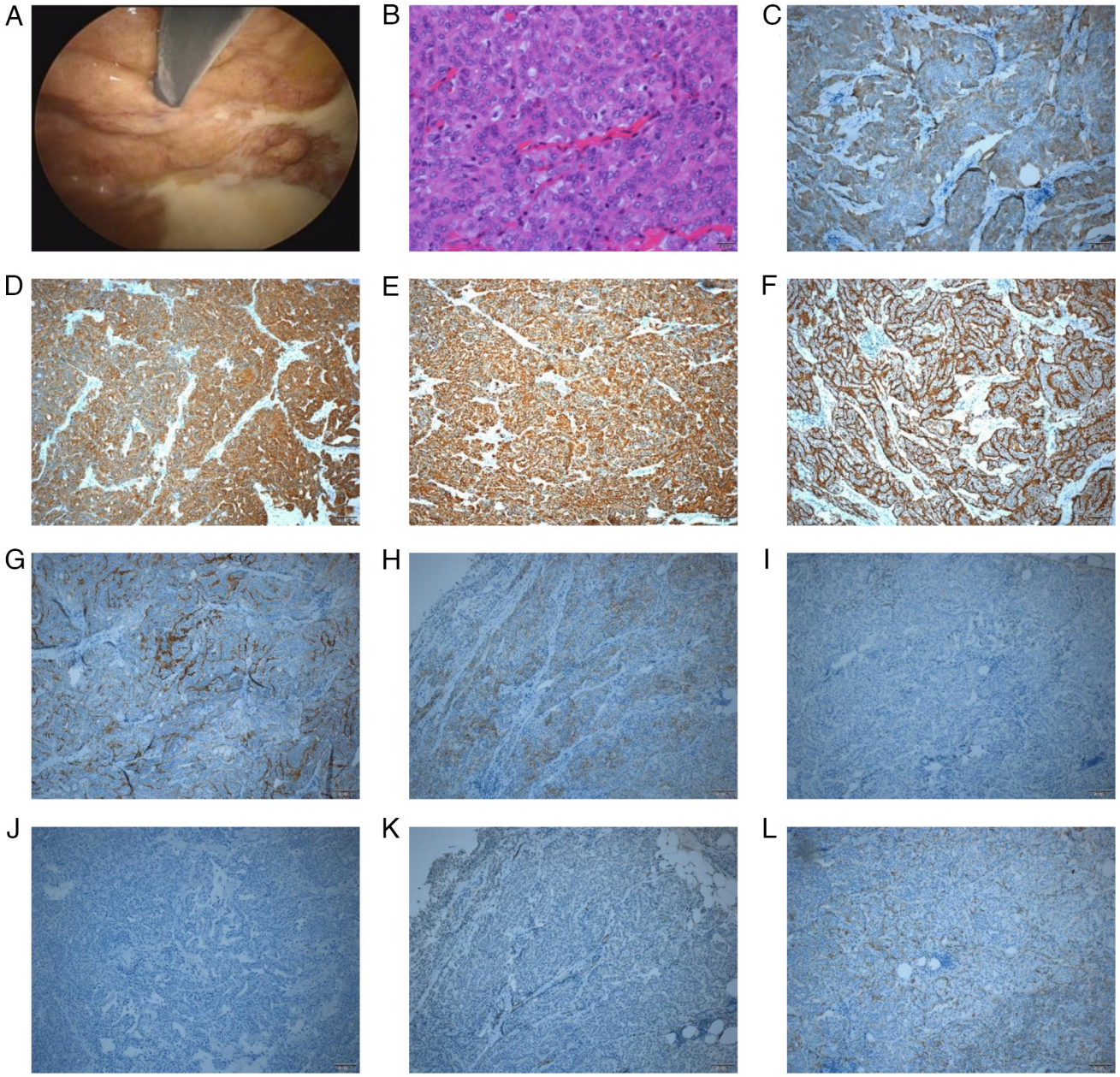

Figure 3. Findings from the thoracoscopic biopsy. (A) Thoracoscopy revealed a nodule in the right dorsolateral pleura, and at a magnification of (B) x40, epithelioid malignant mesothelioma was observed in the resected specimen stained with hematoxylin and eosin. Immunostaining demonstrated that the specimen was positive for (C) calretinin, (D) keratin AE1/AE3, (E) CAM 5.2, (F) podoplanin (D2-40) and (G) epithelial membrane antigen; however, the basal surface was only mildly positive for (H) epithelial cell adhesion molecule/MOC-31. The specimen was negative for (I) thyroid transcription factor-1 and (J) carcinoembryonic antigen and mildly positive for (K) Wilms tumor protein 1. The specimen was also mildly positive for (L) sialyated heart development protein with EGF like domains 1 on the basal surface (magnification for all, x10).

1:100; Dako; Agilent Technologies, Inc.), CK5/6 (clone D5/16 B4; cat. no. M7237; 1:50; Dako; Agilent Technologies, Inc.), calretinin (clone SP13; cat. no. 413561; ready to use; Nichirei Corporation), mesothelin (clone 5B2; cat no. NCL-MESO; 1:50; Leica Microsystems, Inc.), CK20 (clone Ks.20.8; cat. no. M7019; 1:50; Dako; Agilent Technologies, Inc.), CDX2 (clone DAK-CDX2; cat. no. M3636; 1:50; Dako; Agilent Technologies, Inc.), napsin A (polyclonal; cat. no. 418061; ready to use; Nichirei Corporation) and p40 (clone BA28; cat. no. PA0163; ready to use; Leica Microsystems, Inc.). The cell block was positive for CK7 (Fig. 2D), CK5/6 (Fig. 2E), calretinin (Fig. 2F) and mesothelin (Fig. 2G), and negative for CK20 (Fig. 2H), CDX2 (Fig. 2I), napsin A (Fig. 2J) and p40 (Fig. 2K) according to immunohistochemistry. Therefore, the atypical cells were identified as mesothelial cells. However, determining whether these were reactive mesothelial or pleural mesothelioma cells was difficult because the mesothelioma cells in body cavity fluid are generally very diverse.

The pleural biopsy specimen obtained by thoracoscopy (Fig. 3A) at Toyokawa City Hospital (Toyokawa, Japan) was partially solid and histopathology revealed medium-sized epithelioid cells with mild/moderate atypia (Fig. 3B). Infiltration into adipose tissue was also noted. The specimen

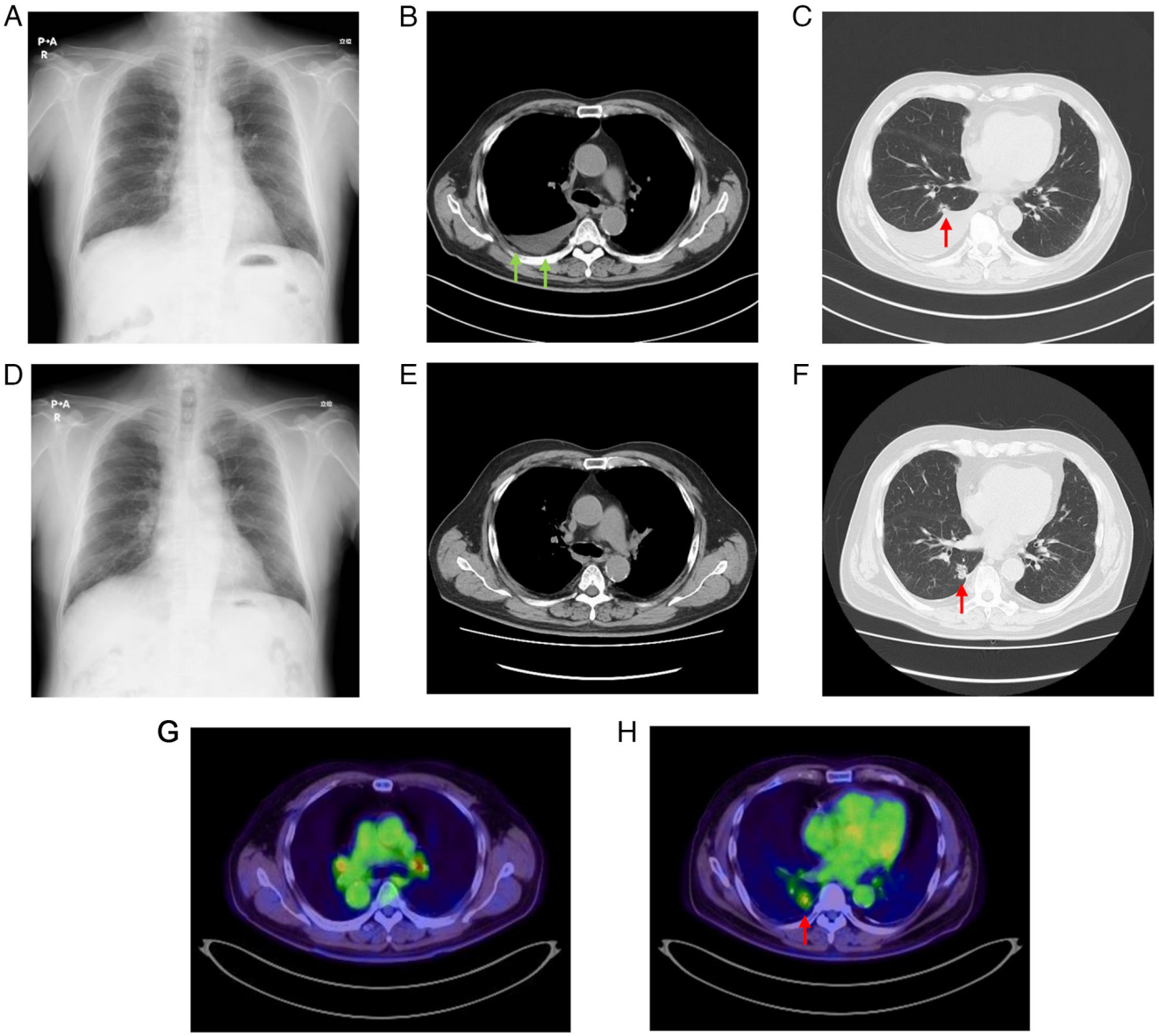

Figure 4. Imaging from the start of combination therapy with cisplatin + pemetrexed until after the discontinuation of pemetrexed. (A) Follow-up chest X-ray after four courses of combination therapy with cisplatin + pemetrexed revealed improvement in the right pleural effusion. (B) Follow-up computed tomography after four courses of combination therapy with cisplatin and pemetrexed revealed reduction of the pleural masses diagnosed as malignant pleural mesothelioma (green arrows); (C) however, the nodule in the S10 segment of the right lower lobe appears to have slowly grown (red arrow). At 18 months after chemotherapy initiation, (D) chest X-ray showed that the right pleural effusion remained improved. (E) Computed tomography showed disappearance of the right pleural nodule and right pleural effusion; (F) however, a continuation of the enlargement of nodules nodule in the S10 segment of the right lower lobe was observed (red arrow). (G) ^{18}F-fluorodeoxyglucose positron emission tomography showed no evidence of distant metastasis of the lung cancer or recurrence of malignant mesothelioma. (H) ^{18}F-fluorodeoxyglucose positron emission tomography at the same time showed the nodule with abnormal uptake (red arrow).

was positive for calretinin (Fig. 3C), cytokeratin AE1/AE3 (clone AE1/3; cat. no. IR053; ready to use; Dako; Agilent Technologies, Inc.; Fig. 3D), CAM 5.2 (clone CAM 5.2; cat. no. 349205; ready to use; BD Biosciences; Fig. 3E), podoplanin (clone D2-40; cat. no. 413451; ready to use; Nichirei Corporation; Fig. 3F) and epithelial membrane antigen (clone E29; cat. no. 790-4463; ready to use; Roche Diagnostics; Fig. 3G); however, the basal surface was only mildly positive for epithelial cell adhesion molecule (MOC-31; clone MOC-31; cat. no. 790-4561; ready to use; Roche Diagnostics; Fig. 3H). The specimen was negative for thyroid transcription factor-1 (clone SP141; cat. no. 790-4756; 1:3; Roche Diagnostics; Fig. 3I) and carcinoembryonic antigen (clone TF3H8-1; cat. no. 760-2507; ready to use; Roche Diagnostics; Fig. 3J), and mildly positive for Wilms tumor protein 1 (clone 6F-H2; cat. no. 413861; ready to use; Nichirei Corporation; Fig. 3K). The specimen was also mildly positive for sialyated heart development protein with EGF like domains 1 on the basal surface (clone SKM9-2; cat. no. 418231; ready to use; Nichirei Corporation; Fig. 3L). Despite the mild positivity for MOC-31 in most areas, the histologic diagnosis was epithelioid mesothelioma based on the overall immunostaining results. Bone scintigraphy and brain-enhanced magnetic resonance imaging (MRI) performed according to the standard settings showed no overt findings of distant metastases. Therefore, the patient was diagnosed with malignant pleural mesothelioma (cT2N0M0, stage IB), according to

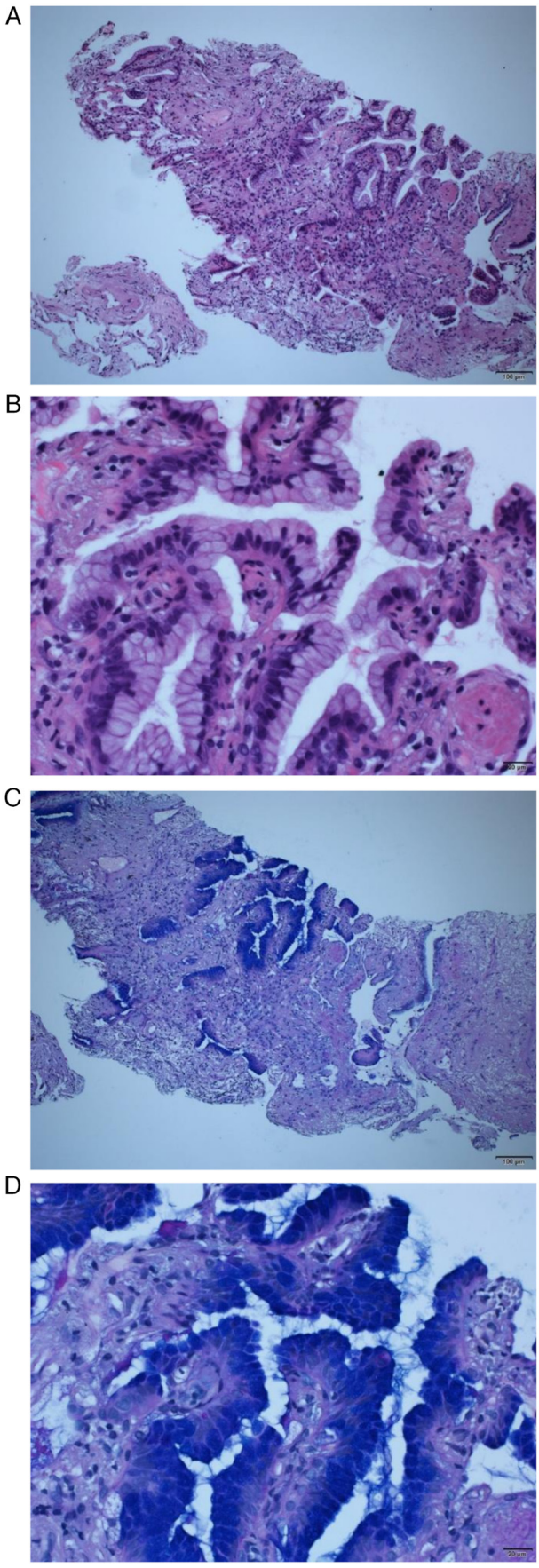

Figure 5. Pathological findings of the computed tomography-guided biopsy. Histopathologic examination of the biopsy specimen obtained from the lesion in the S10 segment of the right lower lobe indicates adenocarcinoma. Hematoxylin and eosin staining at a magnification of (A) x10 and (B) x40. Periodic acid-Schiff staining at a magnification of (C) x10 and (D) x40.

the 8th edition of the Union for International Cancer Control Tumor-Node-Metastasis classification (25).

The patient refused surgery, which is the standard treatment for stage IB pleural mesothelioma, especially epithelial mesothelioma (23), due to their relatively advanced age. Therefore, 2 months after the first visit, four courses of combination therapy with cisplatin + pemetrexed (cisplatin supplied by Nichi-Iko Pharmaceutical Co., Ltd. administered intravenously at 75 mg/m^2 on the first day + pemetrexed supplied by Eli Lilly Japan K.K. administered intravenously at 500 mg/m^{2}on the first day, one cycle in 21 days) were administered. Follow-up chest radiography performed during this time revealed an improvement in the right pleural effusion (Fig. 4A), and follow-up CT revealed the reduction of the pleural masses (Fig. 4B). However, the nodule in the S10 segment of the right lower lobe appeared to have slowly grown during the four courses (Fig. 4C). Primary lung cancer was suspected based on the follow-up CT findings; however, the nodule had slightly increased in size. After four courses, the patient was switched from combination therapy with cisplatin + pemetrexed to maintenance therapy with pemetrexed (administered intravenously at 500 mg/m^2 on the first day, one cycle in 21 days), which was discontinued after three courses due to drug-induced pneumonia.

Follow-up revealed that the pneumonia was resolved and the pleural mass disappeared (Fig. 4D and E); however, the nodule in the S10 segment of the right lower lobe had grown ~5 mm in the 18 months since initial diagnosis (Fig. 4F). ^{18}F-fluorodeoxyglucose positron emission tomography (Fig. 4G and H) and brain-enhanced MRI performed according to the standard settings revealed no evidence of distant metastasis of primary lung tumor or recurrence of mesothelioma. Therefore, at 20 months after the first visit, CT-guided biopsy was performed. Pathological examination of the specimen, performed with hematoxylin and eosin staining with Carazzi's hematoxylin for 25 min and eosin for 7 min at room temperature (Fig. 5A and B), and periodic acid Schiff staining with 1% periodic acid for 10 min, Schiff's solution for 15 min and Mayer's hematoxylin for 4 min at room temperature (Fig. 5C and D), revealed that the alveolar air space was replaced by papillary-like, highly cylindrical epithelium, suggesting invasive mucinous adenocarcinoma.

No pleural invasion of adenocarcinoma was observed in the biopsy specimen. Thus, the patient was diagnosed with lung adenocarcinoma (cT1aN0M0, stage IA1) in the right lower lobe (25). The patient was provided with a full explanation that the standard treatment for stage IA1 non-small cell lung cancer is resection of >1 lung lobe. The patient refused surgery and underwent stereotactic radiotherapy (3 days, maximum total dose 58.9 Gy), which resulted in the nodule shrinking and subsequent control of enlargement. At 12 months after radiotherapy, there was no recurrence of mesothelioma or lung cancer. Follow-up is presently ongoing to monitor for recurrences every 3 months and the patient is not undergoing any further treatments.

Discussion

The present report described the successful treatment of a patient with simultaneous malignant pleural mesothelioma

and pulmonary adenocarcinoma. In a database analysis of ~3,800 patients with malignant mesothelioma, lung cancer as a complication was only reported in 18 (0.5%) patients (26). To the best of our knowledge, 27 such cases have been previously reported in the literature (5-22), but none of the reports described the lung cancer as invasive mucinous adenocarcinoma. Distinguishing between malignant pleural mesothelioma and advanced-stage lung cancer is challenging (27), which may be a reason for the low frequency of reported cases.

The treatment of malignant pleural mesothelioma requires a multidisciplinary approach and includes surgery, chemotherapy and radiotherapy. A review by Bou-Samra *et al* (28), which analyzed the 2022 National Cancer Database in the US, found no notable changes in the proportion of patients who underwent surgery, including extrapleural lung resection, extended pleurectomy, corticectomy, pleural corticectomy and partial pleurectomy, for malignant pleural mesothelioma from 2004 to 2020. The authors concluded that the observed lack of increase in surgical treatment rates may be due to the lack of a clear evidence-based consensus on surgical approaches for mesothelioma.

Randomized controlled studies to determine the best treatment options for malignant pleural mesothelioma are lacking due to the relative rarity of this diagnosis. The current management of pleural mesothelioma involves a multidisciplinary team and expert consensus based on stage and histologic subtype. Specifically, surgery with neoadjuvant chemotherapy or adjuvant chemotherapy is recommended for stage I-IIIa and epithelial histology, whereas systemic therapy and/or supportive care are the current recommendations for stage III-IV or unresectable mesothelioma (29). The recently developed grading system for epithelioid mesothelioma, which is based on the nuclear atypia, mitotic count and necrosis scores, is recommended as a prognostic tool by the 2021 World Health Organization Classification of Thoracic Tumors guidelines (30). However, it remains unclear whether this grading system can predict prognosis better than clinical staging and how it can be implemented during treatment decision-making (31).

Conversely, surgical resection of >1 lung lobe is the standard treatment for stage I-II non-small cell lung cancer. In cases where surgery is not feasible for medical reasons, radical radiotherapy is the first choice (32). Although several recent retrospective studies were performed using pooled analyses or propensity scores to evaluate treatment options in cases where resection was possible (33-36), no randomized controlled trials to date have reported the comparison of outcomes between surgery and radical radiotherapy, to the best of our knowledge. In the present case, radiation therapy was successful in suppressing the progression of adenocarcinoma. However, this does not mean that surgery can be avoided or radiotherapy may be preferred in certain cases.

Combination therapy with cisplatin + pemetrexed, a commonly used regimen for unresectable malignant pleural mesothelioma, is also currently used for non-squamous non-small cell lung cancer. The reported response rate to combination therapy with cisplatin + pemetrexed is 41.3% for all malignant pleural mesotheliomas (37) and 44.0% for all lung adenocarcinomas (38). In the present case, combination therapy with cisplatin + pemetrexed was successful for the treatment of mesothelioma; however, the nodule in the right lower lobe, which was later diagnosed as adenocarcinoma, continued to grow, indicating a lack of response to treatment. A literature search found no articles discussing the use of percutaneous lung needle biopsy in patients with pleural mesothelioma in remission. Therefore, whether the biopsy method that allows communication between the thoracic cavity and pleura poses a risk of worsening the depth of invasion in the event of recurrence is an issue to be assessed in future research. In such cases, immune checkpoint inhibitor(s) therapy, such as nivolumab, which has been approved for non-small cell lung cancer and malignant pleural mesothelioma, may be considered.

In conclusion, currently available multiple active regimens for malignant pleural mesothelioma and lung cancer should aid the treatment of complex cases such as that presented in the current case report. The long-term impact of these approaches on recurrence should be evaluated in future studies.

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Availability of data and materials

The datasets used and/or generated in the current study are available from the corresponding author on reasonable request.

Authors' contributions

YA conceived and designed the study, and prepared the draft of the manuscript. YH and TO treated the patient, analyzed and interpreted the results. YA, TS, MT and TO performed data collection. YA, TS, YH, MT and TO confirm the authenticity of all the raw data. All authors reviewed the results, and read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient signed an informed consent form that included the acquisition of clinical data and images in an anonymous form for publication.

Competing interests

The authors declare that they have no competing interests.

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