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CASE REPORT

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A long-term survivor keeping in a complete response without treatment after pemetrexed maintenance therapy for advanced non-squamous non-small cell lung cancer

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Abstract

Pemetrexed has significant efficacy for some non-squamous non-small cell lung cancer cases, as demonstrated in the current case. For those patients, pemetrexed administration should be carefully considered.

KEYWORDS

complete response, cytotoxic drug, long-term survivor, non-squamous non-small cell lung cancer, pemetrexed maintenance therapy

1 | INTRODUCTION

Molecular targeted drugs and immune checkpoint blockades are not indicated for all advanced non-small cell lung cancer (NSCLC) cases. For such patients, cytotoxic drugs are the main treatment, and the prognosis remains poor. We present a valuable case of advanced NSCLC that was potentially permanent cured by pemetrexed maintenance chemotherapy.

Molecular targeted drugs and immune checkpoint blockades have remarkably improved outcomes for patients with advanced non-small cell lung cancer (NSCLC).[1,2] However, those drugs are not indicated for all advanced NSCLC cases. For such patients, cytotoxic drugs are the main treatment, and the prognosis remains poor.

Here, we report a patient with advanced non-squamous (non-Sq) NSCLC and malignant pleural effusion who was treated with cytotoxic drugs: cisplatin-based induction chemotherapy, followed by pemetrexed maintenance therapy (PMT), to which she achieved a durable complete response (CR) for six years to date, after discontinuing all drug treatments.

2 | CLINICAL CASE

A 46-year-old Japanese woman with a 12-pack/year smoking history with no asbestos exposure, presented with a chronic dry cough at a neighborhood hospital. Her chest images showed diffuse thickening of the right pleura with pleural effusion (Figure 1A-C). After excluding infectious diseases, she was suspected to have a malignant disease, because of the positive cytology of her right pleural effusion. A percutaneous right-pleural biopsy examination revealed stage IV (T4N2M1a) non-Sq NSCLC (Figure 2A,B) with immunostaining was positive for Ber-EP4 (Figure 2C) and slightly positive for CEA (data not shown) as carcinoma markers, and negative immunostaining for calretinin (Figure 2D) and D2-40 (data not shown) as mesothelioma markers. In that hospital, she was first treated with gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, as non-Sq NSCLC in a young Japanese woman might reasonably be expected to have an *EGFR* mutation. However, her tumor did not improve and was subsequently found to have no *EGFR* mutation. Gefitinib treatment was stopped after four weeks.

For her second-line treatment, she was referred to our hospital. On admission, drainage to her right pleural space was not feasible, as the prolonged pleural effusion had produced a sclerosing tumor. As systemic chemotherapy, cisplatin (75 mg/m^2) and pemetrexed (500 mg/m^2) were started, which led to a good partial response after the second cycle, as shown by computed tomography (Figure 3A,B). Bevacizumab was suggested but not added to this regimen, due to patient's refusal in consideration for its adverse effects (AEs). She received PMT (500 mg/m^2, every 21 or 28 days) followed by four cycles of the induction regimen of cisplatin and pemetrexed, and her pleural lesion continued to diminished, resulting in a CR at the 29th PMT cycle (Figure 3C,D). Her serum carcinoembryonic antigen (CEA) had been elevated (198 ng/mL at its zenith) during her second-line treatment, but had normalized with the success of PMT. She had not suffered any severe AE that would have required stopping chemotherapy, but did experience grade 2 hepatic dysfunction and grade 1 edema.

Although PMT was stopped at the 32th cycle at her insistence, she has retained a durable CR without recurrence for 73 months to date (Figure 4A-D). She has survived for eight-and-a-half years from the diagnosis of advanced non-Sq NSCLC and has remained disease-free without drug therapy for six years.

3 | DISCUSSION

This case required a differential diagnosis between primary lung cancer and malignant pleural mesothelioma, because of the diffuse right-side pleural thickening and effusion shown on her chest images. Immunostaining for at least two carcinoma markers (Ber-EP4: positive; CEA: slightly positive) and two mesothelial markers (calretinin and D2-40: both negative) was useful for this patient's diagnosis.[3] Elevated serum CEA (a negative tumor marker for mesothelioma) also helped rule out malignant pleural mesothelioma. She was diagnosed as non-Sq NSCLC for having no cytological cornification, in a difficult condition of determining exact histological type with artifact.

Administering PMT after an induction combination of cisplatin and pemetrexed reportedly has a survival benefit for patients with advanced non-Sq NSCLC,[4] and so PMT has become a standard chemotherapy for those patients. In the above-mentioned phase III trial, the median number of maintenance cycles in the PMT arm was 7.9; 28% in the PMT arm received > 10 cycles of maintenance therapy, 10%

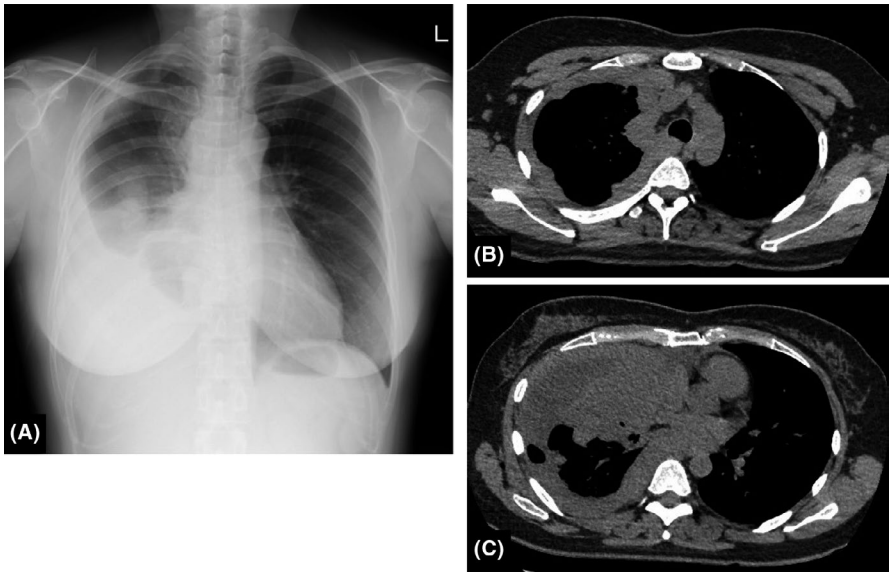

FIGURE 1 Radiological findings at admission to our hospital. Chest X-ray showed decreased radiolucency in the right upper-peripheral, middle, and lower lung fields with dullness at the right costophrenic angle (A). Chest computed tomography shows diffuse thickening of the right pleura with effusion (B, C)

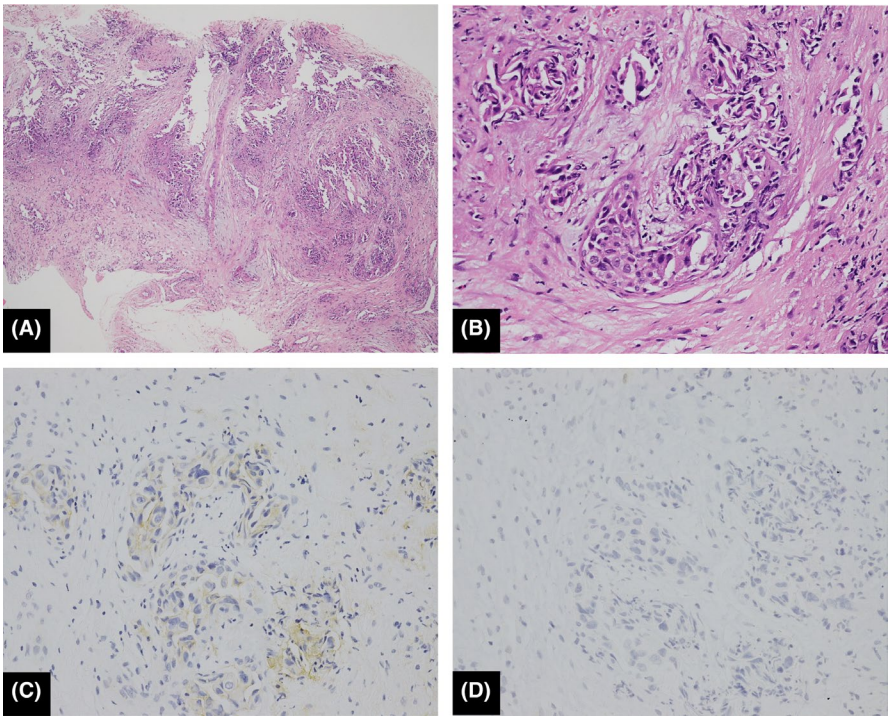

FIGURE 2 Percutaneous pleural biopsy specimen shows (A, B) no cornification in non-Sq NSCLC; (C), positive staining for Ber-EP4 (carcinoma marker); (D) negative staining for calretinin (mesothelioma marker). (A: hematoxylin/eosin staining, 4 × original magnification; B–D: 20 × original magnification.)

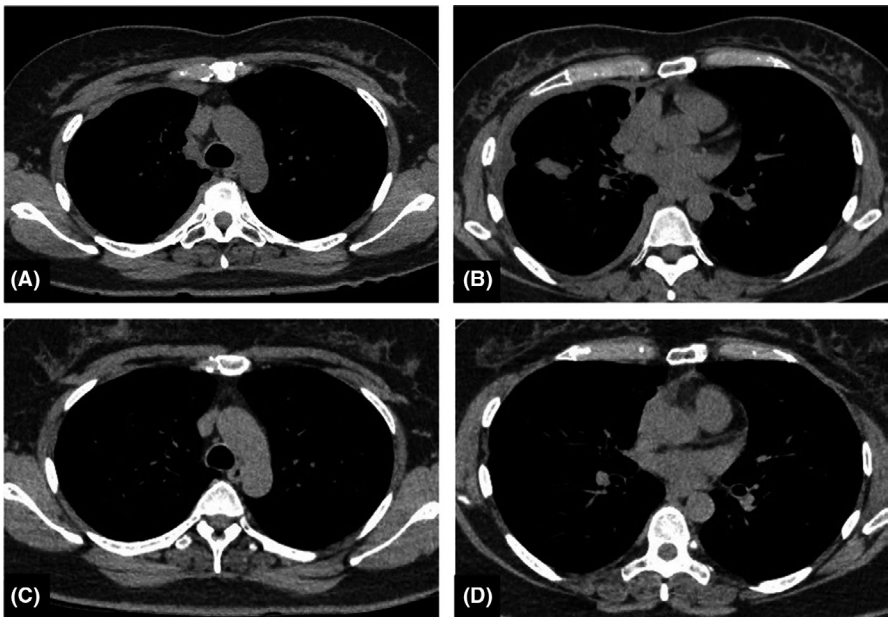

FIGURE 3 Chest computed tomography shows improved pleural disease after cytotoxic chemotherapy (A, B: after two cycles of cisplatin and pemetrexed) (C, D: after 29 cycles of maintenance pemetrexed, leading to a complete response)

received > 20 cycles, and 4% received > 30 cycles. Median overall survival (from the start of maintenance treatment) in the PMT arm was 13.9 months.[4,5] In the present case, the patient could have received the 32 cycles of PMT after the induction chemotherapy of cisplatin and pemetrexed for four cycles. She had mild AEs—grade 2 hepatic dysfunction and grade 1 edema—which were in line with previous reports of PMT.[4,5] Considering the absence of severe AEs, the high effectiveness of PMT, and her strong motivation for the therapy, she could have received PMT for a longer period.

As pemetrexed has been shown to be effective against non-Sq NSCLC[6,7] and malignant pleural mesothelioma,[8] and is therefore often used to treat these diseases. CR outcomes have been attributed to pemetrexed in some reports of non-Sq NSCLC and malignant pleural mesothelioma.[9,10] In this case, the patient reached in a CR, with the disappearance of pleural malignancy, by PMT use, in addition to keeping a longer CR than in previous reports—73 months after discontinuing PMT. This case implies the possibility of a permanent cure of non-Sq NSCLC through the cytotoxic chemotherapy; PMT. To our speculation, the

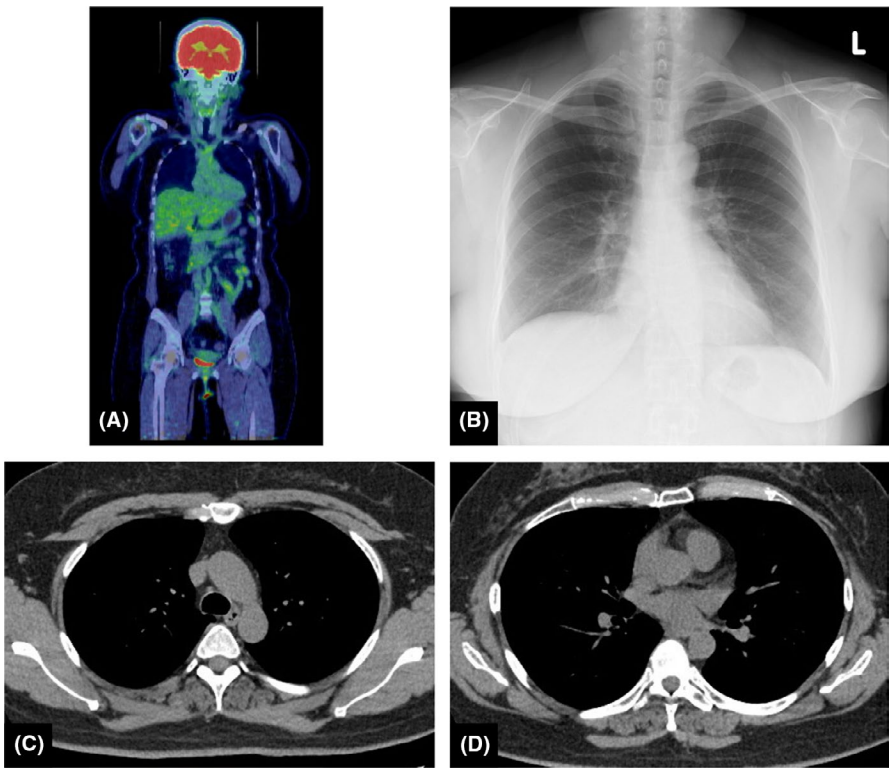

FIGURE 4 Proton emission tomography, two months after discontinuing maintenance pemetrexed, shows no enhanced signal throughout the body (A). Chest X-ray after 51 mo (B) and chest computed tomography at 54 mo after discontinuing PMT show no recurrence (C, D)

combination of the relationship of their cancer stem cells combined with the extreme inherent sensitivity to induction of apoptosis from deoxyribonucleic acid (DNA) damaging agents might play a key role in a long-term CR of this case, as the chemotherapy curable malignancies have previously postulated.[11]

Pemetrexed is a multitargeted antifolate that inhibits multiple enzymes, such as thymidylate synthase (TS) and dihydrofolate reductase (DHFR). TS and DHFR expressions negatively correlate with the treatment efficacy of pemetrexed in NSCLC patients; non-Sq NSCLC patients with low TS and DHFR expression levels tend to have high responsiveness.[10,12,13] In addition, up-regulated *TS* gene expression has a function in acquired pemetrexed resistance in NSCLC.[10,14] In contrast, NSCLC that harbors translocation of the anaplastic lymphoma kinase (*ALK*) gene has been shown to be highly responsive to pemetrexed,[15] which suggests that this patient's tumor is likely to have a *ALK* translocation, although the lack of an appropriate specimen precludes testing for *ALK* translocation. If the patient ever has a disease recurrence, she might undergo rebiopsy to ascertain *ALK* translocation, and TS and DHFR expression.

4 | CONCLUSION

We present a valuable case of advanced non-Sq NSCLC, treated with pemetrexed which led to a CR and long-term survival without recurrence for six years so far, after discontinuing all the drug treatments. Pemetrexed has significant efficacy for some non-Sq NSCLC cases, as demonstrated in the current case. For the patients with advanced non-Sq NSCLC, pemetrexed administration should be carefully considered.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTIONS

MF: involved in primary author and correspondence author. DS, TK, WK, KM, SH, TK, and JF: involved in manuscript analysis.HM and NY: involved in pathological analysis.

ETHICAL APPROVAL

Written informed consent was obtained from the patient for the publication of this case report.

DATA AVAILABILITY STATEMENT

The data that support the findings of this report are available from the corresponding author, MF, upon reasonable request.

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