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Case report: Postoperative abdominal recurrence of pulmonary pleomorphic carcinoma showed a dramatic response to S-1 after pembrolizumab

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ABSTRACT

The patient was an 80-year-old woman with combined pulmonary fibrosis and emphysema. She was diagnosed with pulmonary pleomorphic carcinoma in the right upper lobe, which relapsed 18 months after the operation. Computed tomography showed a mass in contact with the posterior wall of the lower part of the stomach. The patient was treated with two cycles of pembrolizumab, but the disease progressed. She was treated with S-1 as second-line therapy, resulting in tumor-shrinking after two cycles. Progression was not observed over the next twelve months. We report a rare case involving S-1 after immune checkpoint inhibitor treatment.

1. Introduction

Pulmonary pleomorphic carcinoma (PPC) is a rare malignant tumor subtype of non-small cell lung cancer (comprising only 0.4% of all lung malignancies), characterized by an aggressive clinical course and poor prognosis [1,2]. In general, PPC is considered resistant to chemotherapy and radiotherapy, but reports have documented long-term survival benefits using cytotoxic anti-cancer agents [3] or immune checkpoint inhibitors (ICIs) [4–8]. Increased response rates to cytotoxic anti-cancer agents have been reported after ICI administration to patients with non-small cell lung cancer(9–11).

S-1 is an antimetabolite based on Tegafur, a prodrug of 5-fluorouracil. It effectively inhibits nucleic acid synthesis [12]. We report a PPC case that dramatically responded to S-1 as the second-line treatment after two courses of pembrolizumab, an anti-PD-1 antibody.

2. Case report

The patient was an 80-year-old woman with combined pulmonary fibrosis and emphysema (CPFE), atrial fibrillation, and chronic heart failure. She smoked 10 cigarettes per day from the age of 30–60 years. The patient visited our hospital in November because abnormal chest shadows were noted at her family hospital.

Blood tests revealed no abnormal findings, and the test results for tumor markers were negative. Chest computed tomography (CT) revealed a 21 × 23 mm nodule in the right upper lobe (Fig. 1A) with CPFE (Fig. 1B) and consolidation in the right lower lobe. Positron emission tomography (PET)-CT further revealed the accumulation of fluorodeoxyglucose in the nodule (maximum standardized uptake value: 18.8) (Fig. 2), but there were no findings suggestive of metastasis. She underwent bronchoscopy and was pathologically diagnosed with non-small cell lung carcinoma (NSCLC). Right upper lobectomy, lymph node dissection, and partial right lower lobectomy were performed. Histopathological investigation revealed the invasive growth of poorly differentiated PPC with spindle and polygonal cells. The tumor was diagnosed as PPC (pT1bN0M0 stageIA2). On immunohistochemical analysis, the tumor was ALK fusion gene-negative, CK7 positive, CK20 negative, TTF-1 negative, and vimentin-positive, and PD-L1 expression had a tumor proportion score of 40% (Fig. 3). Polymerase Chain Reaction invader assay showed EGFR mutation was negative. The focal infiltrative shadow of the partially resected right lower lobe was histologically associated with alveolar wall thickening, lymphocytic infiltration, and reactive changes in the alveolar epithelium, which is consistent with organizing pneumonia. Her performance status

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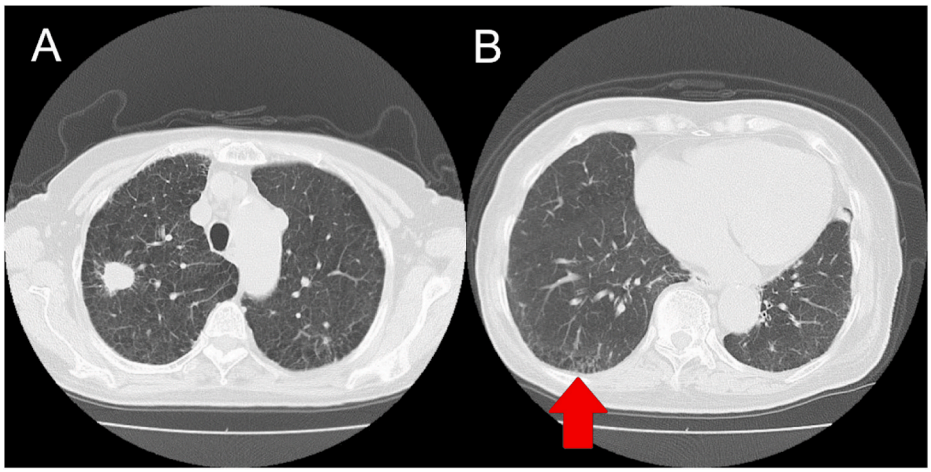

Fig. 1. Chest computed tomography at the first time of diagnosis. The image shows a 21 × 23 mm mass in the right upper lobe (A) and usual interstitial pneumonia pattern in the lung base (B, arrow).

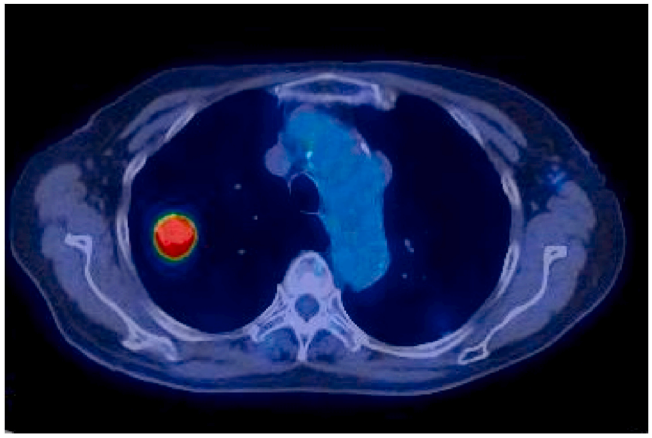

Fig. 2. Positron emission tomography-computed tomography image. Fluorodeoxyglucose accumulation was observed in the tumor in the right upper lobe.

temporarily decreased to 2 after the surgery, and postoperative chemotherapy was not administered because of advanced age.

In December of the following year, her interstitial pneumonia worsened. Prednisolone was initiated at 25 mg/day, and then reduced to 7 mg/day as the patient improved. In June, two years after the surgery, abdominal CT showed a 121 × 71 mm large irregular mass extending caudally to the lower stomach's posterior wall (Fig. 4). The patient was diagnosed with a metastatic abdominal recurrence of PPC using ultrasound endoscopic puncture aspiration. Histopathological investigation showed poorly differentiated cancer cells. On immunohistochemistry, the tumor was positive for CK7 and negative for CK20 and TTF-1.

Although PPC is generally drug-resistant, we administered pembrolizumab as a single-agent therapy since her performance status was 1 and there were some reports that ICI was effective. However, there was a risk of exacerbating interstitial pneumonia. Nevertheless, after sufficient explanation, the patient wanted to proceed with the treatment. She received two cycles of pembrolizumab therapy in July, but the disease progressed one month later. Abdominal CT showed a 126 × 97 mm enlarged mass without any new lesion. She complained shortness of breath, but there are no change with performance status.

The patient was treated with S-1 (100 mg/day for four consecutive weeks, followed by a two-week rest period, in a six-week cycle) as second-line therapy in August. Surprisingly, the tumor dramatically shrunk at four months after two cycles of S-1 therapy (Fig. 5). Exacerbation of interstitial pneumonitis or recurrence was not observed after twelve months of treatment. The patient is under careful observation for recurrence.

3. Discussion

There are a few reports of long-term survival with S-1 [13,14]. One case received S-1 as second-line therapy following cisplatin and docetaxel [13]. The other patient, who had metastatic recurrence after postoperative chemotherapy with uracil-tegafur, was unresponsive to carboplatin, paclitaxel, and radiotherapy [14]. However, PPC is generally resistant to treatment, and single-agent cytotoxic anti-cancer agents are less effective.

In some case reports, long-term survival was achieved with ICI treatment [4–8]. In a cohort study [15] of 125 patients with PPC, about 90% of the patients were positive for PD-L1 (≥1%), but the response rate among those who used ICI monotherapy as first-line treatment was 49%. The median progression-free survival (PFS) was 7.2 months.

ICI is reportedly effective in patients with high PD-L1 expression [4–7]. However, there were cases wherein nivolumab was effective against PPC with few PD-L1 positive cells [8].

In this case, the expression of PD-L1 was 30%–40%, and first-line pembrolizumab treatment showed significant progress. However, S-1 as a second-line treatment was effective. The effectiveness of S-1 monotherapy was unexpected. Since pseudoprogression has been reported with nivolumab [16], the effect of prior pembrolizumab treatment may be significant.

Some studies have reported that exposure to ICIs enhanced cytotoxic chemotherapy administered after ICI treatment [9–11]. A retrospective study investigated the efficacy of S-1 or docetaxel therapy after nivolumab in NSCLC [17]. Due to the small number of cases, they were not able to show a statistically significant difference. The RR to S-1 immediately after nivolumab was 30%, and the median PFS was 3.8 months. The RR to S-1 without ICIs was 17.6%, and median PFS was 2.6 months. S-1 immediately after nivolumab treatment was more efficacious than regimens without ICI pretreatment. The mechanism likely involves promoting T-cell proliferation and cytokine production [18], suppressing immunosuppressive cell proliferation, and enhancing leukocyte transport to the tumor [19]. In this case, the proposed mechanism may have been involved, and cytotoxic anti-cancer agents were more effective.

The histological specificity for the effectiveness of chemotherapy is unclear. Increased expression of vascular endothelial growth factor 2, and decreased expression of glucose-regulated protein and 78 kDa/ binding immunoglobulin protein were associated with a poor prognosis

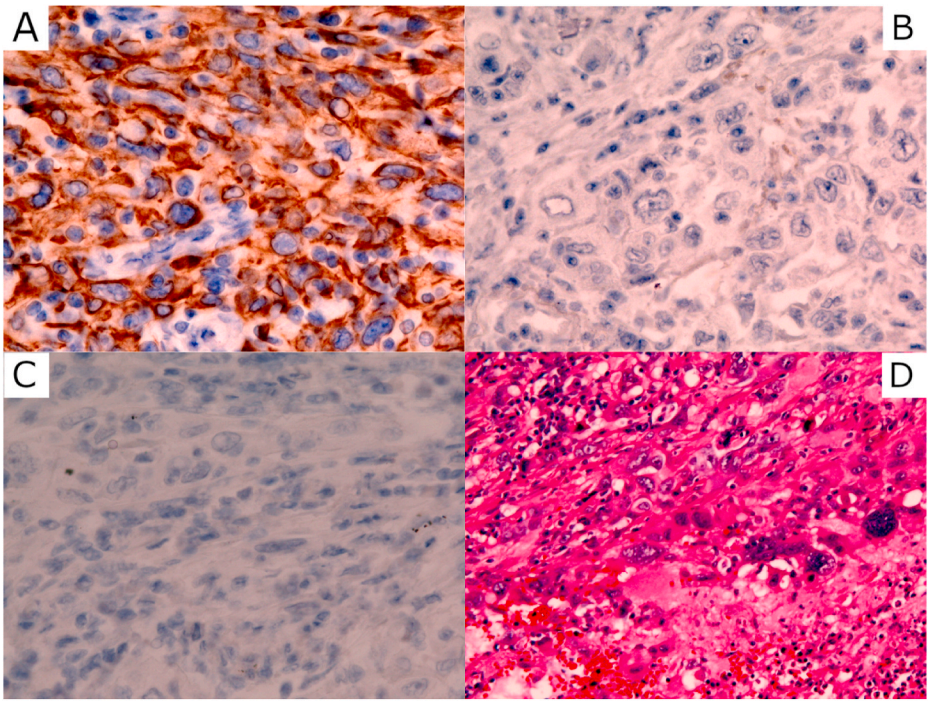

Fig. 3. Histopathological findings. The nodule stained for CK7 (A, × 40), CK20(B, × 40), TTF-1 (C, × 40), HE(D, × 20). The tumor consisted of necrotic and granulation tissue, with infiltration of inflammatory cells. Invasive growth of poorly differentiated pleomorphic carcinoma with spindle cells was observed.

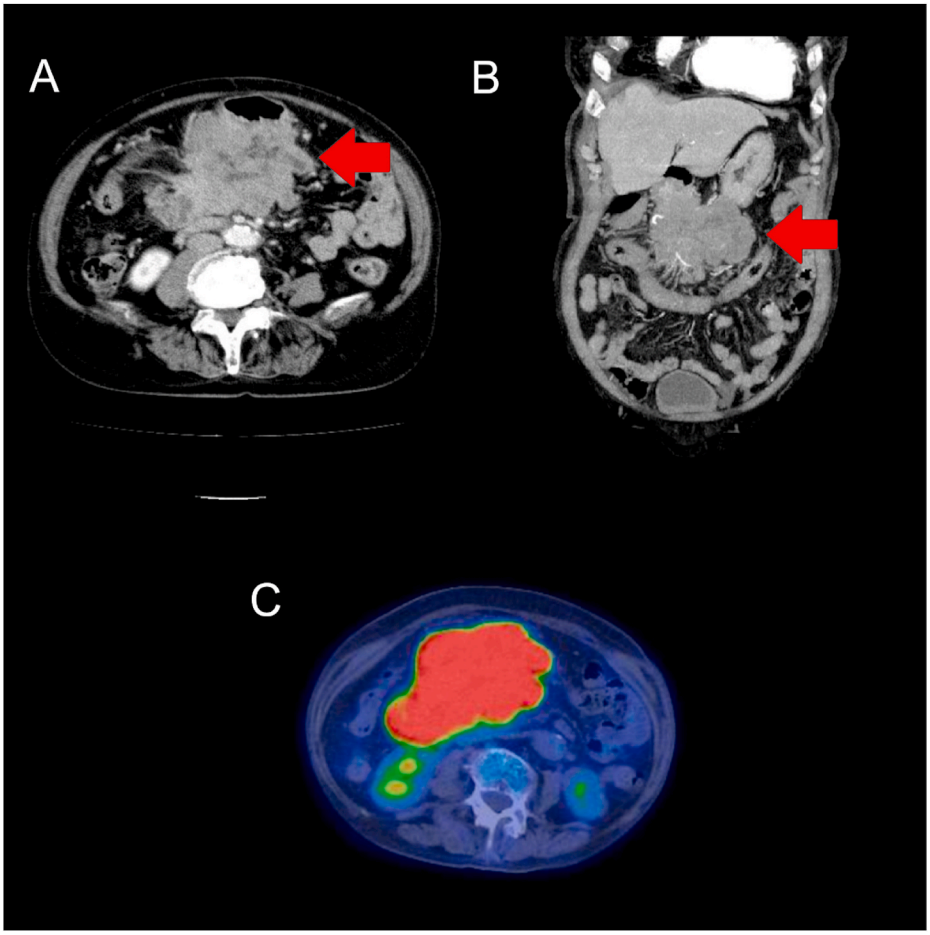

Fig. 4. Abdominal computed tomography at the time of recurrence. A is an axial section, B is a coronal section and C is a positron emission tomography-computed tomography image. A 121 × 71 mm large irregular mass extending caudal to the posterior wall of the lower stomach was seen (arrow).

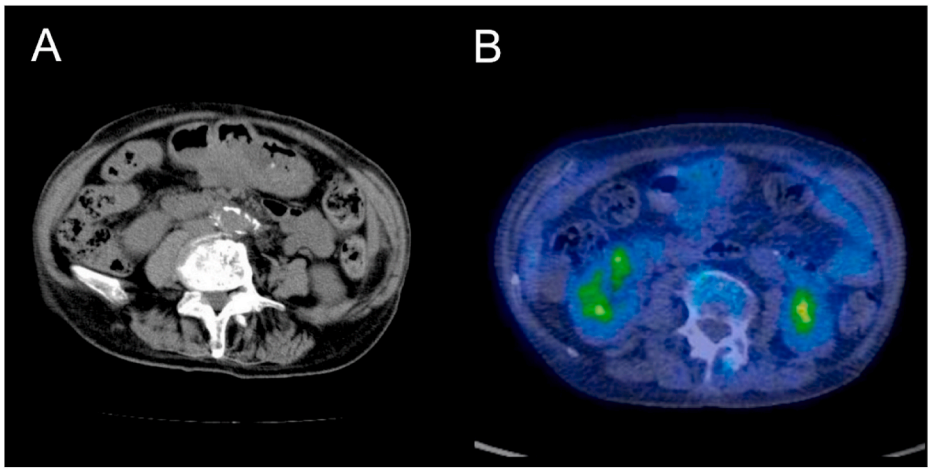

Fig. 5. Abdominal computed tomography (CT) (A) and positron emission tomography-CT (B) after two cycles of S-1 treatment.

among PPC patients who underwent surgical resection [20]. These results suggested that the stain was significant, but it was difficult to obtain at our institution.

PPC is rare, and there is no established therapy. In this case, ICI therapy was unsuccessful as the first-line treatment, but S-1, which was used as second-line therapy, elicited a significant response. The utility of salvage chemotherapy, including its long-term prognosis, needs to be carefully evaluated.

4. Conclusion

We encountered a case of abdominal recurrence after surgery for PPC, which was unresponsive to the first-line pembrolizumab, but significantly responsive to second-line S-1. The long-term prognosis and future recurrence should be carefully monitored.

Declaration of competing interest

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

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