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CASE REPORT

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Pseudoprogression during induction treatment with nivolumab plus ipilimumab combined with chemotherapy for metastatic lung adenocarcinoma: A case report

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Abstract

The incidence rate of pseudoprogression during immune checkpoint inhibitor monotherapy for non-small cell lung cancer is reportedly 3.6%–6.9%, while pseudoprogression during chemoimmunotherapy is rare. Reports on pseudoprogression during dual immunotherapy combined with chemotherapy are lacking. Herein, a 55-year-old male with invasive mucinous adenocarcinoma (cT2aN2M1c [OTH, PUL], stage IVB, and programmed death-ligand 1 expression <1%), renal dysfunction, and disseminated intravascular coagulation was treated with carboplatin, solvent-based paclitaxel, nivolumab, and ipilimumab. After treatment initiation, computed tomography (CT) on day 14 showed disease progression. The patient was diagnosed with pseudoprogression because of a lack of symptoms, improved platelet count, and decreased fibrin/fibrinogen degradation product levels. CT on day 36 showed a reduction in the primary lesion size, multiple lung metastases, and mesenteric metastases. Therefore, pseudoprogression should be considered during dual immunotherapy with chemotherapy.

KEYWORDS
dual immunotherapy, immune checkpoint inhibitor, ipilimumab, nivolumab, pseudoprogression

INTRODUCTION

Immune checkpoint inhibitors (ICI) have revolutionized the treatment of patients with non-small cell lung cancer (NSCLC). The nonconventional benefit or response, including "pseudoprogression," characterized by initial disease progression followed by tumor size reduction or no further progression during at least two tumor assessments, was first reported in phase III trials, CheckMate 017 and CheckMate 057, comparing nivolumab monotherapy versus docetaxel for previously treated squamous-cell NSCLC and non-squamous NSCLC, respectively. A pseudoprogression rate of 3.6%–6.9% has been reported in patients administered ICI monotherapy in phase III trials for NSCLC.[1] Chemoimmunotherapy with cytotoxic agents plus ICI is the standard first-line therapy for metastatic non-squamous NSCLC, which can prolong overall survival (OS), with a low rate of initial disease progression.[2] Dual immunotherapy, targeting programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), combined with chemotherapy, is another treatment strategy.[3] Reports on pseudoprogression during chemoimmunotherapy remain scarce, with only one case of treatment with carboplatin and pemetrexed combined with pembrolizumab.[4] Pseudoprogression during dual immunotherapy with chemotherapy remains unreported.

We present the case of pseudoprogression after the first cycle of dual immunotherapy with chemotherapy in a 55-year-old male with invasive mucinous adenocarcinoma.

CASE REPORT

A 55-year-old male with multiple pulmonary nodules observed on chest computed tomography (CT) was referred to our department. He was a past smoker

(20 pack-year) with chronic kidney disease due to retroperitoneal fibrosis. Blood assessment revealed renal dysfunction with increased serum creatinine level (1.77 mg/dL), disseminated intravascular coagulation (DIC) with thrombocytopenia (8.8 × 10^4/μL), and elevated levels of fibrin/fibrinogen degradation product (FDP; up to 30.6 μg/mL) and D-dimer (10.6 μg/mL), without bleeding or organ ischemia. Serum carcinoembryonic antigen (CEA) level was also elevated (16.3 ng/mL).

CT revealed multiple consolidations, masses, and nodules in bilateral lung fields (Figure 1A, D), with mesenteric masses and left hydronephrosis (Figure 2A). Percutaneous CT-guided lung biopsy at the right S^9a was performed. Histopathology showed columnar tumor cells with abundant intracytoplasmic mucin and nuclei at the basal side, characteristic of invasive mucinous lung adenocarcinoma, with a mixture of lepidic and papillary growth patterns. Tumor cell programmed death-ligand 1 (PD-L1) expression was <1%, determined using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies International Japan, Tokyo), and no driver oncogene was detected using next-generation sequencing (Oncomine Dx Target Test Multi-CDx system,

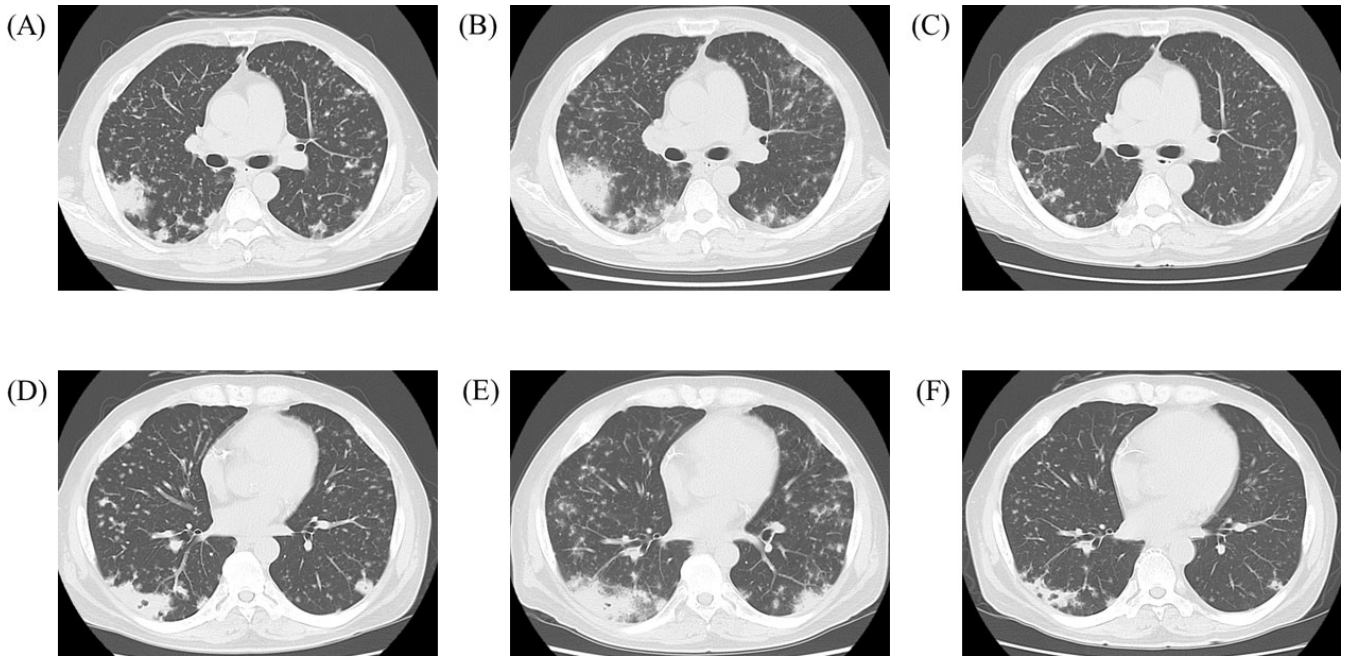

FIGURE 1 Pre-treatment chest CT images showing the primary lesion accompanied by ground glass opacities at right S^2a (A) and multiple lung metastases in all lung lobes (A, D). Chest CT images obtained on day 14 of the first cycle showing disease progression in the primary lesion (B) and multiple lung metastases (B, E). Chest CT images obtained on day 36 after the treatment initiation showing reduction in primary lesion size and multiple lung metastases (C, F). CT, computed tomography

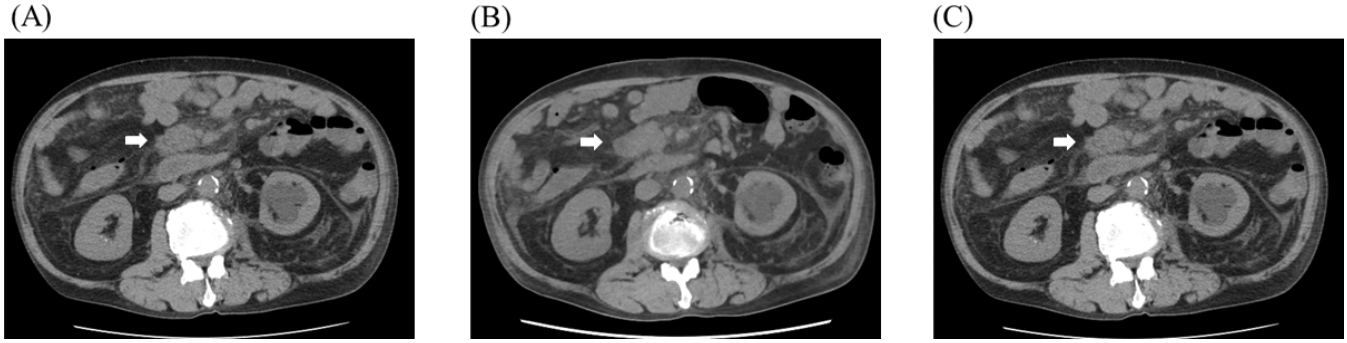

FIGURE 2 Abdominal CT image showing mesenteric metastasis (arrow; A): note that the representative metastasis is shown, and the other metastases to the mesentery are not shown. The abdominal CT image obtained on day 14 showing an enlargement of the mesenteric metastasis (arrow; B), which shrank on day 36 after the treatment initiation (arrow; C). CT, computed tomography

Life Technologies Corporation Japan, Tokyo). Systemic cancer staging revealed no distant metastases other than multiple lung and mesenteric metastases, establishing clinical T2aN2M1c [OTH, PUL] stage IVB.

Systemic investigation revealed that advanced lung cancer caused DIC. Low PD-L1 expression (<1%) predicted limited chemoimmunotherapeutic efficacy, with renal dysfunction hampering pemetrexed administration; hence, dual immunotherapy with platinum doublet chemotherapy was used: carboplatin (AUC 5), solvent-based paclitaxel (175 mg/m^2), nivolumab (360 mg/body), and ipilimumab (1 mg/kg). Grade 2 rash on day 7 and grade 4 neutropenia on day 9, determined using common terminology criteria for adverse events ver5, were treated with subcutaneous filgrastim (75 μg for 2 days). Chest radiography on day 14 showed exacerbated lung metastases. CT revealed disease progression in the primary lesion (Figure 1B), multiple lung metastases (Figure 1B, E), and mesenteric metastases (Figure 2B). The patient was asymptomatic, with improved platelet count (10.3 × 10^4/μL) and decreased FDP level (10.1 μg/mL), suggesting disease stabilization. Serum CEA was 17.3 ng/mL at this timepoint, which was partly due to renal dysfunction and did not suggest the disease progression. Exacerbated metastases were considered pseudoprogression; the second cycle of induction therapy was performed on day 22. CT on day 36 revealed a reduction in primary lesion size (Figure 1C), multiple lung metastases (Figure 1C, F), and mesenteric metastases (Figure 2C), when serum CEA was elevated to 18.9 ng/mL. Continuation maintenance therapy with nivolumab every 3 weeks plus ipilimumab every 6 weeks was administered for five cycles every 3 weeks with an ongoing regimen.

DISCUSSION

ICI response evaluation is challenging in patients with disease progression, given the absence of criteria to distinguish pseudoprogression from true disease progression. Pseudoprogression is attributed to a transient influx of activated cytotoxic CD8-positive T lymphocytes, that is, effector T cells, in the tumor bed, substantially increasing tumor size.[1] As pseudoprogression is rare, most patients exhibiting disease progression are categorized as true disease progression.[1] Hence, discriminating between pseudoprogression and true progression is crucial.

The incidence of pseudoprogression with chemoimmunotherapy for NSCLC is markedly lower than that with ICI monotherapy, with only one case reported.[4] This low rate could be partly explained by the additive effect of cytotoxic agents, inducing tumor shrinkage and maintaining a low initial progressive disease rate (∼8.8%) in the KEYNOTE-189 trial.[2] However, effector T cell influx theoretically occurs during chemoimmunotherapy. Hence, pseudoprogression during chemoimmunotherapy should be considered.

Dual immunotherapy combined with chemotherapy causes synergistic anti-CTLA-4 and anti-PD-1 antibody effects, improving OS irrespective of PD-L1 expression status, confirmed in the CkeckMate 9LA trial.[3]

Activation of the priming phase in the cancer-immunity cycle is a notable difference with dual immunotherapy. Anti-PD-1 antibody acts on the effector phase by activating effector T cells to eliminate tumor cells. Anti-CTLA-4 antibody plays a pivotal role in the priming phase, guiding and activating naïve effector T cells into tumor-specific effector T cells, as well as in the effector phase via appropriate signals allowing activated tumor-specific effector T cells to eliminate tumor cells.[5] The former process includes the trafficking of effector T cells into the tumor bed; the latter induces inflammatory cell infiltration into the tumor bed, along with the burden of killed tumor cells. This could explain pseudoprogression during induction treatment with nivolumab plus ipilimumab combined with platinum doublet chemotherapy.

To our knowledge, this is the first report on pseudoprogression during nivolumab plus ipilimumab combined with platinum doublet chemotherapy. Pseudoprogression should be considered during dual immunotherapy combined with chemotherapy.

AUTHOR CONTRIBUTIONS

Yusuke Kunimatsu designed and wrote the manuscript. Yukari Kano and Takayuki Takeda were the treating physicians. Rei Tsutsumi, Mai Tanimura, and Keiko Tanimura collected the data. Izumi Sato and Keiko Tanimura analysed and assessed the clinical course. All authors participated in the interpretation and discussion of the observed findings. Takayuki Takeda supervised the entire work and revised the final manuscript.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study is available on request from the corresponding author. The data are not publicly available due to privacy restriction.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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