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Possible Pseudo-progression of Non-small Cell Lung Carcinoma in a Patient With Clinical Hyper-progression Associated With Trousseau Syndrome Who Was Treated With Pembrolizumab: A Case Report

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Abstract. *Background/Aim: Immune checkpoint inhibitors (ICIs), including nivolumab and pembrolizumab, have recently been shown to have clinical benefits in patients with advanced non-small cell lung cancer (NSCLC). The novel tumour responses to these agents are changing the management of patients with cancer. Pseudo-progression of disease (pseudo-PD), that is, an initial flare followed by shrinkage of the tumour, has been described as a distinctive response to ICIs. However, pseudo-PD manifest initial progression and is difficult to segregate with hyper progressive disease (HPD). We, therefore, analysed a case with pseudo-PD histologically. Patients and Methods: A 68-year-old Japanese man with stage IV non-small cell lung carcinoma (NSCLC) was treated by anti-PD-1 antibody (pembrolizumab). Four weeks later after second time treatment with pembrolizumab, the patient showed severe melena followed by Trousseau syndrome and died at day 174 after first treatment by pembrolizumab, suggesting HPD clinically. Primary lesion and metastatic lesions were analysed histologically. Results: Histological analysis revealed that NSCLC cells expressed PD-L1, and CD8+ tumor-infiltrated lymphocytes (TILs) were observed. CD8+ TILs showed higher rates of PD-1 indicating that lesions were of the inflamed type and the case was pseudo-PD. Furthermore, it was found that cancer cells expressed MUC1. Conclusion: The clinical appearance of the case was aggressive after treatment by pembrolizumab, and the case seemed to be HPD; however, histological analysis revealed that the case was likely pseudo-PD. Therefore, careful histological evaluation is important when investigating the clinical response to an ICI and mucin expression might be a predictive marker for Trousseau syndrome.*

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Key Words: Immune checkpoint inhibitors, non-small cell lung cancer, pembrolizumab, pseudo-progression, Trousseau syndrome.

Immune checkpoint inhibitors (ICIs) have been approved for the treatment of non-small cell lung cancer (NSCLC). If a tumour is diagnosed as NSCLC, the patient should be tested for driver gene mutations such as *EGFR, EML4-ALK*, and *ROS-1*. Patients found to have these mutations can be treated by molecular targeted therapy, including epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, anaplastic lymphoma kinase inhibitor, and ROS-1 inhibitor. ICIs are a new treatment paradigm for patients without driver gene mutations. Pembrolizumab, a PD-1 (programmed death-1) receptor antibody, is now used as first-line therapy for advanced NSCLC, whereas the second-line therapy consists of either pembrolizumab or nivolumab (1-3).

Some patients have responded to these immune-targeted therapies with tumour shrinkage or stable disease that would be consistent with the existing Response Evaluation Criteria in Solid Tumours (RECIST) criteria; however, distinct immune-related patterns of response have also been observed. There have been reports of patients with melanoma treated with ipilimumab, a monoclonal antibody against cytotoxic T-lymphocyte-associated antigen-4, showing an initial increase in tumour size, confirmed by biopsy of inflammatory cell infiltrates or necrosis, that is followed by a decrease in tumour burden. Furthermore, immune-related response patterns have been observed in

clinical trials of ipilimumab, including development of new lesions associated with oedema and infiltrates of immune cells as well as transient increases in baseline tumour markers. Delayed clinical responses have been also observed in studies of immunotherapeutic agents, namely, an increase in total tumour burden followed by tumour regression. This phenomenon is known as pseudo-progression of disease (pseudo-PD) (4). Although favourable in terms of prognosis, patients with pseudo-PD might be classified prematurely as having disease progression according to the World Health Organization or RECIST criteria. Accordingly, immune-related response criteria have been developed (2, 5).

In contrast, some patients treated with ICIs experience rapid paradoxical disease progression with worsening of their clinical status, which appears to have a negative impact on their survival. This phenomenon has been termed hyper-progressive disease (HPD), for which there are presently no known risk factors, except for older age (5, 6). The search for novel biomarkers for HPD is ongoing.

Herein we report a patient with lung adenocarcinoma who was treated with pembrolizumab and showed marked disease progression suggestive of HPD; however, the histological findings in surgically resected specimens suggested pseudo-PD.

Case Report

The patient was a 68-year-old Japanese man with a 94 pack-year smoking history and diagnosis of primary lung adenocarcinoma. His clinical course is summarized in Figure 1. His tumour was diagnosed by endoscopic ultrasound-guided fine needle aspiration via the oesophagus and clinically staged as T4N2M0 IIIB (Figure 2A-D). The tumour was EGFR wild-type and negative for the EML4-ALK fusion gene. He received four cycles of carboplatin and pemetrexed and concurrent first-line irradiation (60 Gy/30 fractions). Computed tomography revealed a partial response according to the RECIST version 1.1 criteria and the sialyl Lewis^{x}-1 (SLX) level decreased to normal. However, approximately 4 months later, his lung cancer relapsed, with appearance of multiple metastatic lung lesions and a gradual increase in the sialyl Lewis^{x}-1 (SLX) level (Figure 1). Immunohistochemical (IHC) staining with anti-PD-L1 monoclonal antibody (clone 22C3) revealed an PD-L1 positivity rate of 70% in adenocarcinoma cells (Figure 2E). At this point, the patient opted for treatment with pembrolizumab, an anti-PD1 antibody. Four weeks later, having received two cycles of pembrolizumab, he noticed severe melaena. Contrast-enhanced computed tomography imaging of the abdomen revealed a metastatic lung tumour (Figure 2F), a small intestinal tumour (Figure 2G), and multiple metastases to the abdominal lymph nodes (Figure 2H). Gastrointestinal endoscopy revealed a small metastatic tumour in the stomach. The small intestinal tumour was surgically resected to treat the melaena. Tumours measuring 8×8×7 cm, 4×4×4 cm, and 3×3×3 cm were found elsewhere in the intestine (Figure 3A). Haematoxylin-eosin staining revealed that the morphological features of the adenocarcinoma cells in the lesion in the small intestine were similar to those of the adenocarcinoma cells in the primary lung lesion. IHC staining showed that the adenocarcinoma cells in the lesion in the small intestine were positive for thyroid transcription factor-1, which was compatible with metastatic adenocarcinoma (Figure 3B). The PD-L1 expression level in these cells was 100% (Figure 3B). The tumour had a necrosis area with bleeding site (Figure 3C). Two weeks after the operation, he reported good quality of life but was switched to docetaxel as third-line therapy because of a severe rash and growth of the tumour (Figure 1). One week later, he developed sudden-onset left-sided hemiplegia. Contrast-enhanced magnetic resonance images showed multiple cerebral infarctions (Figure 2I). The serum fibrin/fibrinogen degradation product (FDP) level was 207 mg/ml and the D-dimer level was 78 mg/ml (Figure 1). At this point, the patient was diagnosed as having Trousseau syndrome as a result of lung cancer and heparin was started. He developed dysarthria on the first day and became disorientated on the second day of treatment with heparin. His activated partial thromboplastin time and FDP and D-dimer levels were monitored during treatment. The dose of heparin was gradually increased to 25,000 units/day. There was a decrease in the levels of FDP and D-dimer when heparin was started (Figure 1); however, a week later, contrast-enhanced magnetic resonance images showed multiple infarctions. The hemiplegia did not resolve completely, and the dysarthria and disorientation gradually worsened, despite heparin therapy. Therefore, the patient was offered best supportive care. His general health status worsened and he died 174 days after receiving pembrolizumab.

This patient had an extremely aggressive course after treatment with pembrolizumab. Even though he did not meet the criterion for HPD, namely, a tumour growth rate exceeding 50% (7), clinical progression of the disease accelerated after treatment with pembrolizumab. Therefore, we considered the disease state to be similar to that of HPD. We performed IHC staining of the tumour in the small intestine to investigate the disease at the histological level, revealing prominent infiltration of CD3^{+}, CD4^{+}, and CD8^{+} T-cells within the adenocarcinoma lesion (Figure 4A). The adenocarcinoma cells showed high human leukocyte antigen (HLA) class I expression levels on the cell surface and many cleaved caspase-3-positive cells in the tumour lesions, indicating that the tumour cells were being recognised by immune cells and undergoing apoptosis Figure 4A). Therefore, we concluded that the patient had pseudo-PD and not HPD at the histological level. We also investigated mucin expression in this patient, given its relationship with Trousseau syndrome. His cancer cells showed strong positive staining for MUC1 but not for MUC2, MUC5AC, or MUC6

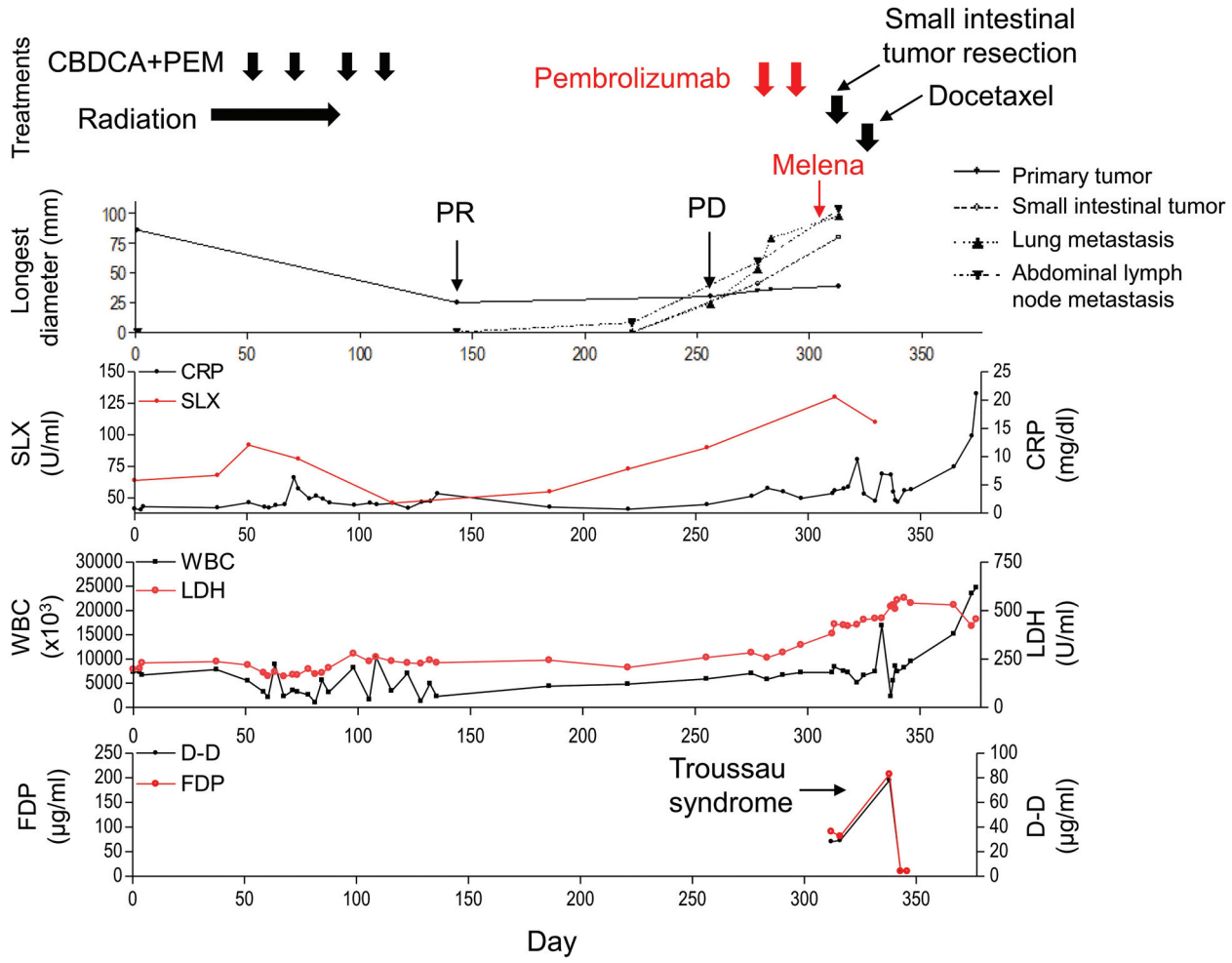

Figure 1. *Summary of the case report. The patient was initially treated with chemotherapy (carboplatin and pemetrexed) and radiotherapy. The tumour showed a partial response. However, metastatic lesions developed in the small intestine and lung with metastases to the abdominal lymph nodes. The patient was considered to have progressive disease and started on pembrolizumab. After two courses of pembrolizumab, the patient developed melaena, which prompted surgical resection of the lesion in the small intestine. The patient subsequently developed signs of Trousseau syndrome. CBDCA, Carboplatin; CRP, C-reactive protein; D-D, D-dimer; FDP, fibrin degradation product; LDH, lactate dehydrogenase; PEM, pemetrexed; PD, progressive disease; PR, partial response; SLX, sialyl Lewisx-1; WBC, white blood cells.*

(Figure 4B). Therefore, it is possible that the Trousseau syndrome was caused by expression of MUC1.

Discussion

During treatment with an ICI, a tumour may increase in size initially and regress thereafter. This phenomenon is known as pseudo-PD and has been reported in 6.7–12.0% of patients with malignant melanoma treated with ICIs (4). There have been reports of pseudo-PD related to lung adenocarcinoma after treatment with nivolumab or pembrolizumab (8–10). Furthermore, histological analysis of tumour biopsy specimens showed high rates of tumour-infiltrating lymphocytes (10).

Although ICIs can achieve a profound tumour response in some cases, there is a subset of patients who appear to experience tumour flares while being treated with these agents. Champiat *et al*. first identified HPD as a possible clinical response to this treatment (6). In their study, HPD (defined as a 2-fold increase in TGR among patients with disease progression) was identified in 9% of evaluable patients who were treated with anti-PD-1 and PD-L1 monotherapy (6). Furthermore, Ferrara *et al*. found HPD in 14% of patients with NSCLC treated with anti-PD-1/PD-L1 monoclonal antibodies and that these cases had a poor prognosis (7). Although the mechanism by which immune checkpoint blockade induces HPD remains unclear, Kamada

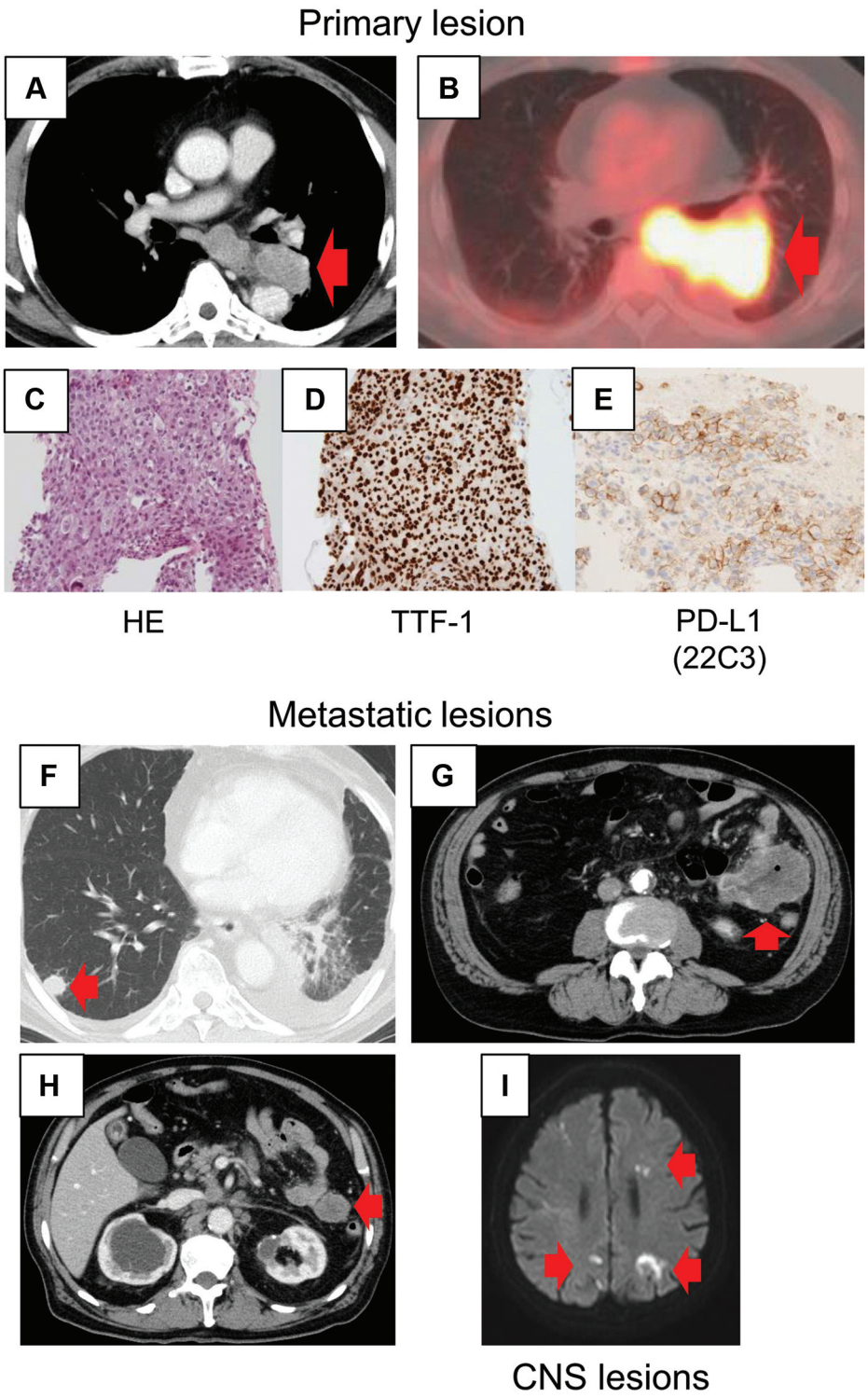

Figure 2. *Primary lung tumour, metastatic lesions, and lesions in the central nervous system. Contrast-enhanced computed tomography (A) and positron emission tomography/computed tomography (B) images of the primary lesion. Histology included immunostaining of a biopsy specimen from the primary lesion obtained by endoscopic ultrasound-guided fine needle aspiration via the oesophagus. Haematoxylin-eosin (C) and immunohistochemical (D) staining using anti-TTF-1 (clone 8G7G3/1) antibody (D) and anti-PD-L1 (clone 22C3) antibody (E). Contrast-enhanced computed tomography images of the lung metastasis (F), tumour in the small intestine (G), and abdominal lymph node metastasis (H) obtained just before resection of the tumour in the small intestine. Magnetic resonance imaging of the head after onset of neurological symptoms: a diffusion-weighted image showing multiple high-intensity areas (I). Arrows indicate lesions.*

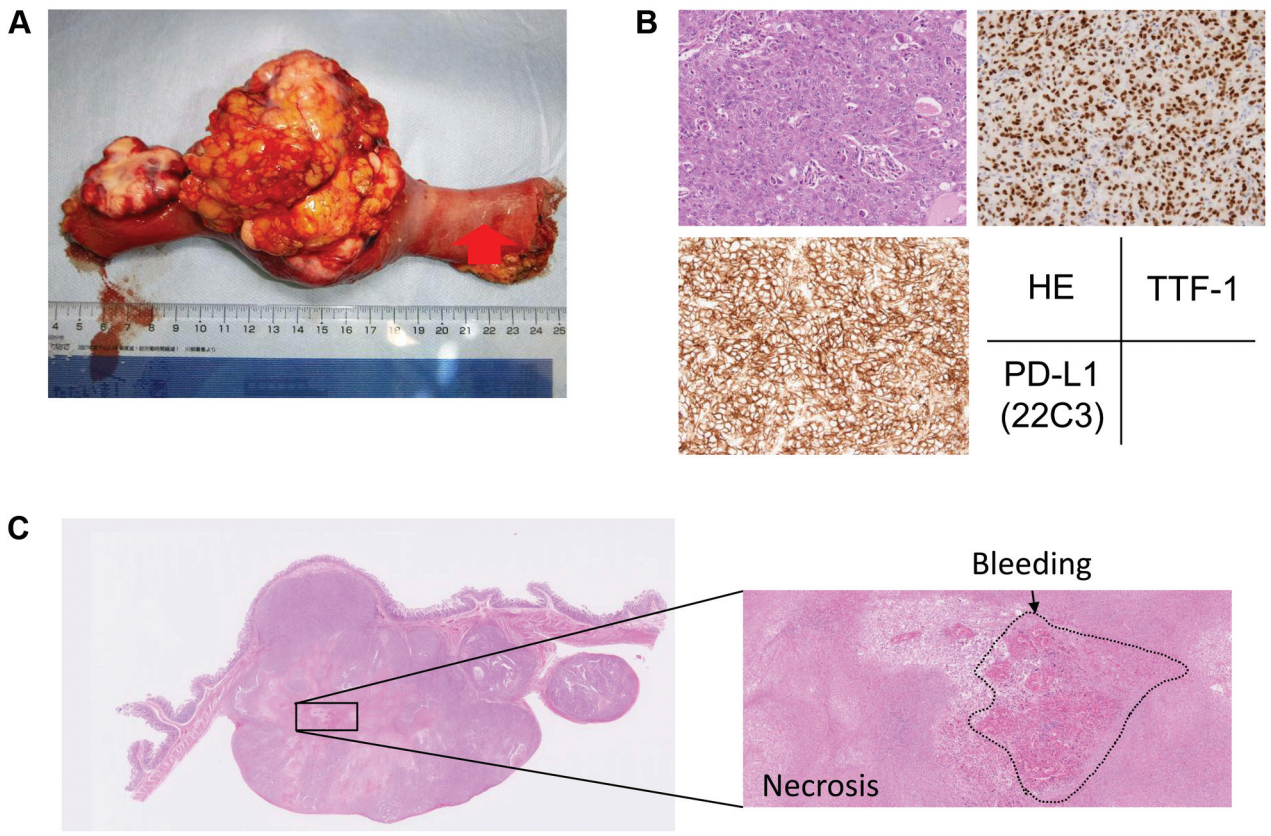

Figure 3. *Metastatic tumour in the small intestine. (A) Macroscopic image of the metastatic lesion in the small intestine. (B) Histological images of the lesion. Haematoxylin-eosin and immunohistochemical staining using anti-TTF-1 (clone 8G7G3/1) and PD-L1 (clone 22C3) antibody. (C) Histology showed necrosis and bleeding from the lesion.*

et al. have postulated that it involves activation of tumour-infiltrating effector regulatory T-cells (Tregs) (11). In an analysis of patients who developed HPD after PD-1 blockade, it was found that PD-1+ effector regulatory T-cells from tumour-infiltrating lymphocytes enhanced the immune suppressive activity of PD-1 blockade, which might explain the tumour progression. Our patient showed aggressive disease progression after treatment with pembrolizumab. However, his aggressive clinical course might have been related to melaena and Trousseau syndrome, and histological evaluation showed that the case was not HPD.

Trousseau syndrome was first described by Armand Trousseau in 1865 as affecting "patients with internal organ cancer with significant ambiguous phlebothrombosis" (12). Trousseau syndrome is a type of paraneoplastic syndrome associated with latent malignant tumours that produce neurological symptoms. This condition is recognized as causing systemic thrombosis as well as brain infarction due to enhancement of the coagulation system by the tumour and has been reported in patients with gastric, lung, pancreatic, and ovarian cancers (13). In lung cancer, Trousseau syndrome has been associated with molecular targeted therapy and current immunotherapy (13, 14). This syndrome is better considered as a spectrum of disorders, ranging from thrombosis induced primarily as a result of production of tissue factors by tumour cells through to a platelet-rich microthrombotic process triggered by carcinoma mucins and involving P-selectin and L-selectin. Other mechanisms proposed include hypoxia and oncogene activation, which can also fit in this spectrum of pathways and result in generation of thrombin and deposition of fibrin. A further possibility that has yet to be explored is activation of the endothelium by tumour-derived inflammatory cytokines, which could induce expression of various adhesion molecules, including V-CAM and E-selectin (15). Our patient's cancer cells were positive for MUC1, and to our knowledge, this is the first case of lung cancer associated with Trousseau syndrome after immunotherapy in which expression of mucin was confirmed. Therefore, mucin released from tumour cells destroyed by cytotoxic T-cells might cause Trousseau syndrome, and

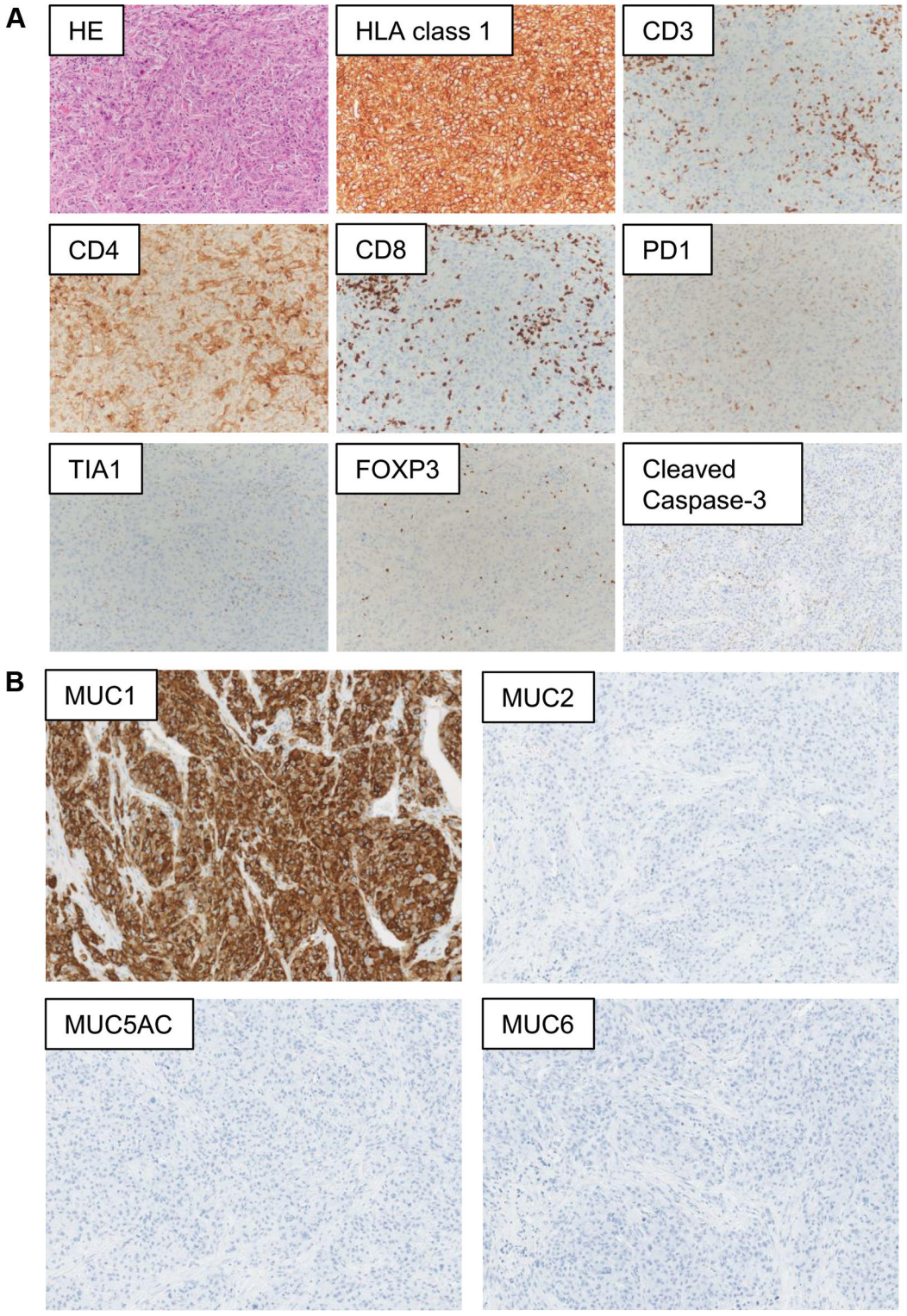

Figure 4. *Immunohistochemical analysis of the small intestine metastatic tumour. (A) Immunological evaluation of the tumour by immunohistochemical staining. The metastatic tumour in the small intestine was subjected to immunohistochemical staining with anti-HLA-class 1 (clone EMR8-5), CD3 (polyclonal), CD4 (clone 1F6), CD8 (clone C8/144B), PD-1 (clone EH33), TIA-1 (clone TIA-1), FOXP3 (clone 236A/E7), and cleaved caspase-3 (clone 5A1E) antibodies. (B) Expression of mucin. Results of immunohistochemical staining of the metastatic tumour in the small intestine using anti-MUC1 (clone Ma695), MUC2 (clone Ccp58), MUC5AC (clone CLH2), and MUC6 (clone CLH5) antibodies.*

evaluation of mucin expression in the tumour might be important for prediction of this syndrome.

In a previous article, Flala *et al*. summarized the relation of immune related adverse effect (irAE) and objective responsive rate (ORR) by treatment using ICIs (16). Most of the studies suggested that irAE was related to better ORRs. Although, Trousseau syndrome is not an irAE, Trousseau syndrome caused by cancer cell lysis that express mucin is a sign of immune reactivity to cancer cells. Thus, irAE and Trousseau syndrome caused by ICIs might manifest good immunological response and might be related to good ORR. Another point is how to predict irAR or Trousseau syndrome and how can they be controlled. This case suggests that mucin expression might be a biological marker for prediction of Trousseau syndrome. To conclude the hypothesis, further accumulation of analysis is needed.

In summary, we encountered a case of NSCLC with probable pseudo-PD after ICI therapy. Histological evaluation revealed a vigorous immune reaction and mucin expression in the tumour. Mucin expression might be related to Trousseau syndrome in such patients. These observations highlight the importance of histological evaluation for prediction of pseudo-PD and Trousseau syndrome.

Conflicts of Interest

The Authors declare that they have no conflicts of interest to disclose.

Authors' Contributions

Conception and design: Yosuke Shionoya, Yoshihiko Hirohashi, Munehide Nakatsugawa, Toshihiko Torigoe. Data collection: Yosuke Shionoya, Yoshihiko Hirohashi, Haruka Takahashi, Midori Hashimoto, Kaoru Nishiyama, Yasunari Takakuwa, Terufumi Kubo. Data analysis and interpretation: Yosuke Shionoya, Yoshihiko Hirohashi, Toshihiko Torigoe. Manuscript writing: Yosuke Shionoya, Yoshihiko Hirohashi, Toshihiko Torigoe. Final approval of the manuscript: Yosuke Shionoya, Yoshihiko Hirohashi, Munehide Nakatsugawa, Terufumi Kubo, Takayuki Kanaseki, Omohide Tsukahara, Toshihiko Torigoe.

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