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CASE REPORT

Lung adenocarcinoma initially presenting as Trousseau's syndrome treated successfully with pembrolizumab: A case report

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Abstract

A 60-year-old woman was urgently admitted to our hospital because of vertigo and left hemiplegia. Laboratory examination showed thrombocytopenia, high levels of D-dimer and carcinoembryonic antigen. Brain magnetic resonance imaging (MRI) revealed multiple bilateral cerebral infarctions. Chest computed tomography (CT) showed an irregularly shaped tumor in the upper lobe of the left lung and mediastinal node swelling. The histopathological findings revealed adenocarcinoma negative for anaplastic lymphoma kinase fusion gene, sensitive epidermal growth factor receptor mutations. A diagnosis of lung adenocarcinoma initially presenting as arterial thromboembolism was made, and she was treated with direct oral anticoagulant (DOAC). Subsequently, pembrolizumab therapy was initiated because tumor cells were positive for programmed cell death protein 1 (PD-L1;60%), and resulted in reduction of the tumor with normalization of the platelet count and d-dimer. The treatment has been continued for over one year without any recurrence of the disease or thromboembolism.

Introduction

Trousseau's syndrome is characterized by unexpected cancer-related thromboembolic disorders in venous or arterial systems. Cerebral infarction due to arterial coagulation disorder has occasionally been observed as the initial clinical manifestation in patients with non-small cell lung cancer (NSCLC).[1,2] The prognosis in these NSCLC cases has been reported to be extremely poor[1–3] and the therapeutic approach is challenging. On the other hand, treatment with immune checkpoint inhibitors (ICIs) via antiprogrammed cell death protein 1 (PD-1) antibody has been the most important breakthrough in the treatment of advanced NSCLC over the past decade.[4]

We encountered a case of NSCLC initially presenting with multiple cerebral infarctions associated with thrombocytopenia and increased D-dimer. The patient was diagnosed with PD-ligand 1 (PD-L1) hyperexpression and treated with pembrolizumab supported by anticoagulation therapy. A partial response was observed and the patient was successfully treated without recurrence of the disease or thromboembolism for >one year. To our knowledge, this is the first report of a case of NSCLC initially presenting as arterial thromboembolism showing a good response to immune checkpoint inhibitor (ICI) therapy.

Case report

A 60-year-old woman was urgently admitted to our hospital because of vertigo and left hemiplegia. She had a smoking history of 20 pack-years over 30 years, but no remarkable disease history. Laboratory examination on admission showed thrombocytopenia ($4.0 \times 10^3/\mu L$) and high levels of D-dimer (37.6 μg/mL) and carcinoembryonic antigen (CEA; 45.1 ng/mL). Brain magnetic resonance imaging (MRI) showed multiple bilateral cerebral infarctions (Fig 1). Chest computed tomography (CT) revealed an irregularly shaped tumor in the upper lobe of the left

lung (Fig 2a) and swelling of the mediastinal nodes. Biopsy specimens taken from the lung tumor histopathologically demonstrated adenocarcinoma negative for anaplastic lymphoma kinase fusion gene and wild-type epidermal growth factor receptor (*EGFR*), and were positive for PD-L1 in 60% of tumor cells (IHC 22C3 pharmDx antibody). ECG showed no atrial fibrillation, and echocardiography showed neither atrial thrombi nor carotid artery stenosis. Cerebral infarctions and thrombocytopenia were treated immediately with 30 mg/day of edoxaban as a direct oral anticoagulant (DOAC). Although the patient had Eastern Cooperative Oncology Group performance status (PS) 4 on admission, rehabilitation by physical and occupational therapists improved PS to 3 and she was able to communicate well. Since she had a positive attitude for treatment, pembrolizumab monotherapy was initiated after receiving informed consent regarding the possible risks and benefits of therapy. Systemic chemotherapy or combination therapy was avoided because of her PS and thrombocytopenia. After two cycles of pembrolizumab therapy, the platelet count had increased to $16.0 \times 10^3/\mu L$, and D-dimer level decreased to 5 μg/mL. The tumor showed a partial response after pembrolizumab therapy (Fig 2b,c) and serum CEA level also decreased to 8.3 ng/mL. The patient had mild left hemiplegia but could live her daily life without care (PS 0). The therapy has been continued without any immune-related adverse events (irAE) or disease relapse.

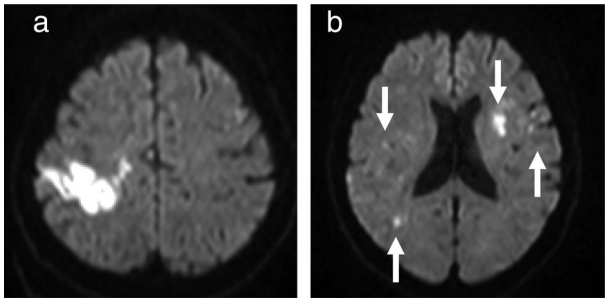

Figure 1 Magnetic resonance imaging (MRI) findings on admission. (**a**) Diffusion MRI showed a high intensity area in the right cerebral lobe. (**b**) Small multiple high-intensity areas were observed in the bilateral cerebral lobes (arrows).

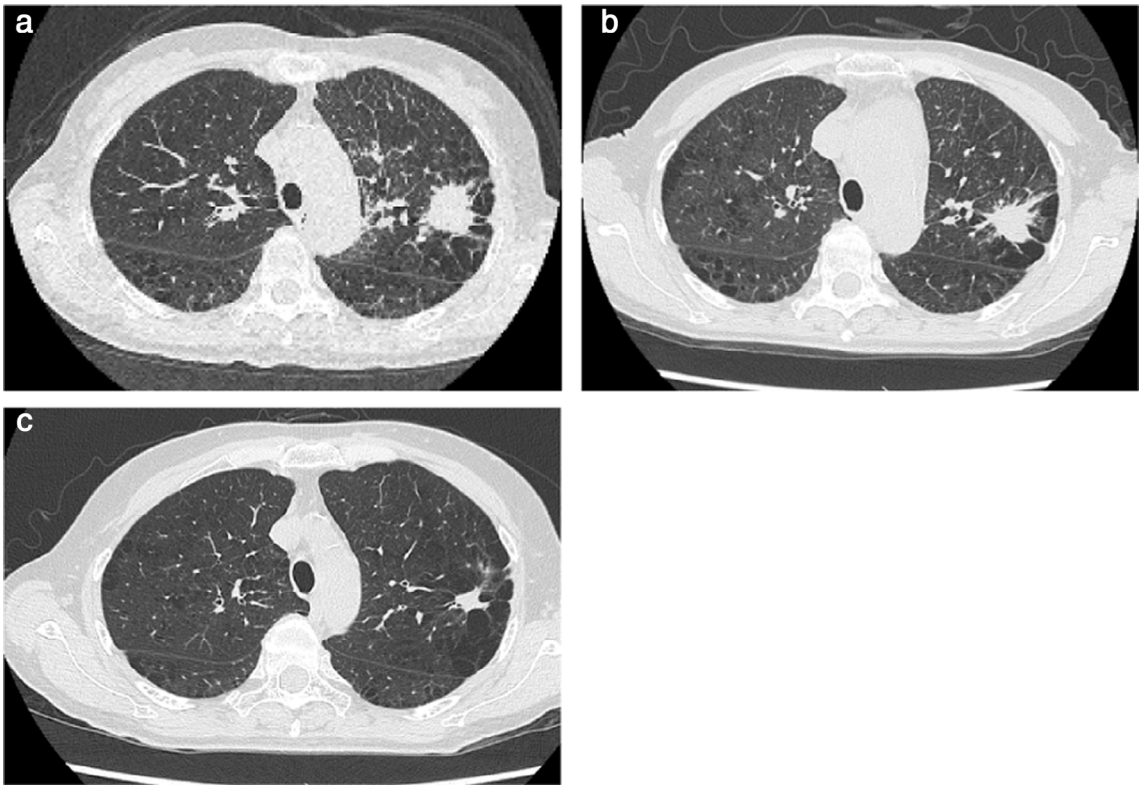

Figure 2 Serial chest computed tomography (CT) findings before and after pembrolizumab therapy. (**a**) Before pembrolizumab. (**b**) After three courses of pembrolizumab. (**c**) After nine courses of pembrolizumab.

Discussion

It has previously been reported that the median survival time after development of cerebral infarction in patients with NSCLC was 36 days, and overall survival was significantly shorter in NSCLC patients who developed cerebral infarction than in those without cerebral infarction.[1] A therapeutic approach in patients who initially present with cancer-associated cerebral infarction is challenging, and little information is available about an optimal chemotherapeutic regimen. In general, these patients may be not suitable for systemic chemotherapy.[1,3] In our case, pembrolizumab supported by anticoagulation therapy using DOAC was efficacious without disease relapse or recurrence of thrombosis. Targeting of specific biomarkers has improved outcomes in patients with advanced NSCLC. Several case reports have described success with anticoagulation treatment and molecular targeted agents for sensitive *EGFR* mutation in inhibiting repeated thrombosis due to Trousseau's syndrome and controlling lung tumors.[5,6] Thus, appropriate diagnosis for molecular targeted and/or clinical biomarkers is essential to avoid the loss of an opportunity for appropriate therapy even in NSCLC patients that initially developed cancer related arterial coagulation disorder.

However, several case reports have reported that ICI therapy could be a trigger for Trousseau's syndrome or disorders of the coagulation-fibrinolysis system.[7–11] Horio *et al.*[7] described a case of multiple cerebral infarcts and intratumoral hemorrhage in pre-existing brain metastasis four days after pembrolizumab in NSCLC. Sato *et al.*[8] retrospectively evaluated 83 NSCLC patients treated with ICIs and found that a total of 10 patients (12%) developed disorders of the coagulation-fibrinolysis system, such as acute coronary syndrome, multiple cerebral infarcts, pulmonary thromboembolism, bronchial hemorrhage, etc. Thus, coagulation disorders during treatment with ICIs may be an irAE. Since cancer is closely associated with a complex multifactorial hypercoagulation status, the mechanism underlying the beneficial outcome in our case remains unclear. In addition, the first-line efficacy of ICI administration for poor PS NSCLC patients remains to be elucidated in practice.[12,13] Further clinical experiences and studies of the underlying and switching mechanisms responsible for the onset of disorders or restoration during ICI therapy are needed.

Disclosure

The authors declare that there are no conflicts of interest.

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