No need to hesitate: immune-related neutropenia and thrombocytopenia that improved by corticosteroids
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Keywords
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Abstract
Unlike cytotoxicity, haematological toxicity is a rare immune-related adverse event that is occasionally irreversible and refractory. A 67-year-old man was diagnosed with advanced lung squamous cell carcinoma. After 41 cycles of nivolumab as third-line chemotherapy, the patient developed severe neutropenia and thrombocytopenia. The bone marrow biopsy and serum immunological tests indicated no evidence of bone marrow failure and suggested autoimmune mature blood cell destruction. After initiating treatment with prednisolone 50 mg orally and filgrastim 75 μg subcutaneously once daily, neutropenia and thrombocytopenia recovered within four and nine days, respectively. The filgrastim was discontinued four days later, and the corticosteroid was discontinued three months later; there has been no haemocytopenia recurrence since then. The patient has remained untreated for more than two years without progression of lung cancer. In conclusion, corticosteroids should be considered for the treatment of autoimmune haemocytopenia if refractory bone marrow dysplasia can be ruled out.

Introduction
Although immune checkpoint inhibitors have drastically improved the outcome of patients with non-small cell lung cancer (NSCLC), they cause a unique series of adverse events called immune-related adverse events (irAEs) [1]. The most common irAEs include endocrine dysfunction (such as hypothyroidism and adrenal dysfunction), colitis, and interstitial pneumonia [2]. Unlike cytotoxicity, haematological toxicity is a rare irAE that is occasionally irreversible and refractory [3]. Here, we have reported a case of NSCLC in which the patient developed severe neutropenia and thrombocytopenia 1.5 years after initiating treatment with nivolumab.

Case Report
A 67-year-old man with a history of smoking presented with cough and fatigue. Chest computed tomography (CT) showed a mass in the left lower lobe of the lung along with partial atelectasis, swelling of the left hilar lymph node, and pleural effusion (Fig. 1A). Tissue samples obtained by bronchoscopy confirmed the diagnosis of pulmonary squamous cell carcinoma. According to the eighth edition of the Union for International Cancer Control TNM classification, the carcinoma was classified as stage IVa (cT3N0M1a).

The patient was administered two cycles 50 mg/m² of nedaplatin on day 1 and 50 mg of S-1 twice daily on days 1–14 every three weeks, which resulted in enlargement of atelectasis by tumour progression. Subsequently, the patient was administered nine cycles of 100 mg/m² of nanoparticle albumin-bound paclitaxel (nab-paclitaxel) on days 1, 8, and 15 every four weeks. Treatment with nab-paclitaxel stabilized the disease; however, chest CT performed after the ninth cycle showed an increase in the left pleural effusion, confirming disease progression (Fig. 1B). Nivolumab treatment (3 mg/kg on day 1 every two weeks) administered as third-line therapy resulted in tumour shrinkage. The general condition of the patient gradually improved without any adverse events. After the 35th cycle of nivolumab, the patient’s neutrophil and thrombocyte counts in the peripheral blood gradually decreased. The
Patient was admitted to our institute for investigating the cause of neutropenia and thrombocytopenia; the neutrophil and thrombocyte counts had decreased to 200 and 60,000/mm³, respectively, after the 41st cycle of nivolumab.

Peripheral blood investigation on admission revealed the following: lymphocyte count, 800/mm³; monocyte count, 400/mm³; and haemoglobin level, 12.9 g/dL. Furthermore, there were no blast cells in the peripheral blood. Blood and serum immunological tests were positive for direct and indirect Coombs tests, weakly positive for -platelet-associated immunoglobulin G, and negative for antinuclear antibodies and antineutrophil cytoplasmic antibody. Bone marrow biopsy performed on the day of admission revealed hypoplastic bone marrow, but there was no evidence of dysplastic cells, fibrosis of the bone marrow, or increased adipose tissue (Fig. 2). Based on these findings, myelopathy, myelodysplastic syndrome, myelofibrosis, and leukaemia were considered unlikely causes of neutropenia and thrombocytopenia. Owing to the suspicion of blood cell destruction by autoimmune mechanisms, treatment with prednisolone 50 mg orally and filgrastim 75 μg subcutaneously once daily was initiated.

Four days after the initiation of the corticosteroid and filgrastim, the patient’s neutrophil count in the peripheral blood increased to 8900/mm³ and the administration of filgrastim was discontinued. Nine days after the initiation of the corticosteroid, the patient’s platelet count in the peripheral blood had normalized (211,000/mm³) and the patient was discharged. The corticosteroid was tapered down and discontinued three months later. The neutropenia and thrombocytopenia have not recurred since then. The patient has remained untreated for more than two years without progression of lung cancer.

Discussion

In our case of severe neutropenia and thrombocytopenia caused by nivolumab, initiated for the treatment of NSCLC, the patient responded to corticosteroid treatment. In our case, we investigated the cause of neutropenia and thrombocytopenia using blood and serum immunological tests and bone marrow biopsy. These intensive investigations revealed that haemocytopenia was due to autoimmune mechanisms.
destruction of mature peripheral blood cells. Furthermore, these investigations also distinguished the autoimmune destruction of mature peripheral blood cells from bone marrow failure, which is refractory to corticosteroid therapy, intravenous immunoglobulin (IVIG) therapy, and granulocyte colony-stimulating factor (G-CSF) therapy [3]. Similar to our case, the patient with Hodgkin’s lymphoma in another case developed neutropenia and thrombocytopenia 15 months after initiating nivolumab, which was treated with corticosteroid and IVIG therapy [4]. In the other case as well, serum immunological tests and bone marrow biopsy were used to diagnose autoimmune neutropenia. Hence, an aggressive causal investigation including bone marrow biopsy should be performed when haemocytopenia as an irAE is detected.

In our patient, a corticosteroid was administered for three months and a G-CSF was administered for four days to treat neutropenia and thrombocytopenia. The effect of the corticosteroid was noted within 10 days without any adverse events including infectious diseases. However, given the risk of infection, there are concerns about the use of corticosteroids as a systemic immunosuppressant for severe neutropenia. IVIG therapy alone without corticosteroid therapy has been reported to be effective for nivolumab-induced severe autoimmune neutropenia [5]. Considering the simplicity of oral administration of corticosteroids, corticosteroids can be used for autoimmune neutropenia if the possibility of refractory bone marrow dysplasia can be ruled out.

In conclusion, the aetiology of haemocytopenia as an irAE should be thoroughly investigated for providing adequate treatment. When haemocytopenia occurs due to mature cell destruction and not because of bone marrow failure, corticosteroids should be considered for the treatment of autoimmune haemocytopenia.

Disclosure Statements

Appropriate written informed consent was obtained for publication of this case report and accompanying images. KF has received honoraria from Boehringer Ingelheim. TM has received honoraria from Bristol Myers Squibb, Chugai Pharmaceutical, AstraZeneca, Novartis, and Boehringer Ingelheim. The other authors have no conflicts of interest to declare.

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Author Contribution Statement

Osamu Kanai wrote the draft and revised the manuscript. Koichi Nakatani prepared images and provided the informed consent to the patient. Koichi Nakatani, Kohei Fujita, Misato Okamura, and Tadashi Mio revised the manuscript. Koichi Nakatani and Tadashi Mio constructed the design of this work.

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