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Case report

Febrile neutropenia in a patient with non-small-cell lung cancer treated with atezolizumab: A case report

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ABSTRACT

Hematological immune-related adverse events (hem-irAEs) related to immunotherapy have not been extensively characterized, and there is no report of neutropenia caused by atezolizumab administration. Herein, we report a case of febrile neutropenia caused by a hem-irAEs due to atezolizumab, which was treated with granulocyte-colony stimulating factor (G-CSF) and antibiotic prophylaxis. It is important that oncologists be aware of the hematological toxicities of immune checkpoint inhibitors (ICIs). Furthermore, antibiotics and G-CSF should be administered until absolute neutrophil count recovery in cases of febrile neutropenia complicated by atezolizumab. Systemic corticosteroids should not be administered because they can accentuate the risk of infection.

1. Introduction

Immune checkpoint inhibitors (ICIs) including programmed cell death-1/programmed cell death ligand-1 (PD-1/PD-L1) inhibitors provide positive survival benefits to patients with advanced non-small-cell lung cancer (NSCLC) [1]. However, these inhibitors can also result in a unique spectrum of toxicities known as immune-related adverse events (irAEs). Although irAEs mainly affect the skin, endocrine glands, digestive tract, joints, liver, and lungs, theoretically, all organs can be affected. The hematopoietic system can also be affected, and this condition is specifically called hematological irAEs (hem-irAEs) [2].

Hem-irAEs, including immune thrombocytopenia, pancytopenia, bicytopenia, pure red cell aplasia, immune aplastic anemia, hemolytic anemia, cytokine release syndrome with hemophagocytic syndrome, and neutropenia, could occur any time after ICI therapy [3]. Although the proportion of hem-irAEs is low, these are often clinically severe and life-threatening. In previous clinical trials, the frequency of hem-irAEs was estimated to be 4.7% for PD-L1 inhibitors [3]. Atezolizumab, a humanized, engineered monoclonal antibody of immunoglobulin G1, which targets PD-L1, has been widely used as a first-line treatment for metastatic non-squamous NSCLC [4]. However, hem-irAEs related to immunotherapy have not been extensively characterized, and there is no report of neutropenia caused by atezolizumab administration. Furthermore, no established evidence has been proposed regarding how clinicians should manage febrile neutropenia related to hem-irAEs.

Herein, we report a case of febrile neutropenia caused by atezolizumab therapy, which was successfully treated with granulocyte colony-stimulating factor (G-CSF) and antibiotic therapies.

2. Case report

A 79-year-old man presented to our clinic with progressive fatigue and fever (temperature, 40 °C), 120 days after the administration of bevacizumab and atezolizumab for recurrent NSCLC, in April 2020. Four years prior to this presentation, he was diagnosed with pulmonary adenocarcinoma classified as clinical T1bN2M0, stage IIIA. He was treated with concurrent neoadjuvant chemoradiotherapy with carboplatin (CBDCA) [Area under the curve (AUC) = 2; days 1, 8, 15, 22, 29, and 36] and paclitaxel (PTX) [40 mg/m^2; days 1, 8, 15, 22, 29, and 36], as well as radiation therapy with a total dose of 40 Gy. Subsequently, left upper lobectomy and hilar lymph node dissection were performed. After the surgery, the patient received two cycles of adjuvant chemotherapy with CBDCA (AUC = 5, day 1) and PTX (180 mg/m^2, day 1). After 27 months (i.e., 6 months prior to the admission), a follow-up chest computed tomography (CT) revealed several supraclavicular lymphadenopathies, and an open neck lymph node biopsy showed recurrence of pulmonary adenocarcinoma. PD-L1 expression in the tumor was negative. He then received four cycles of systemic therapy with CBDCA

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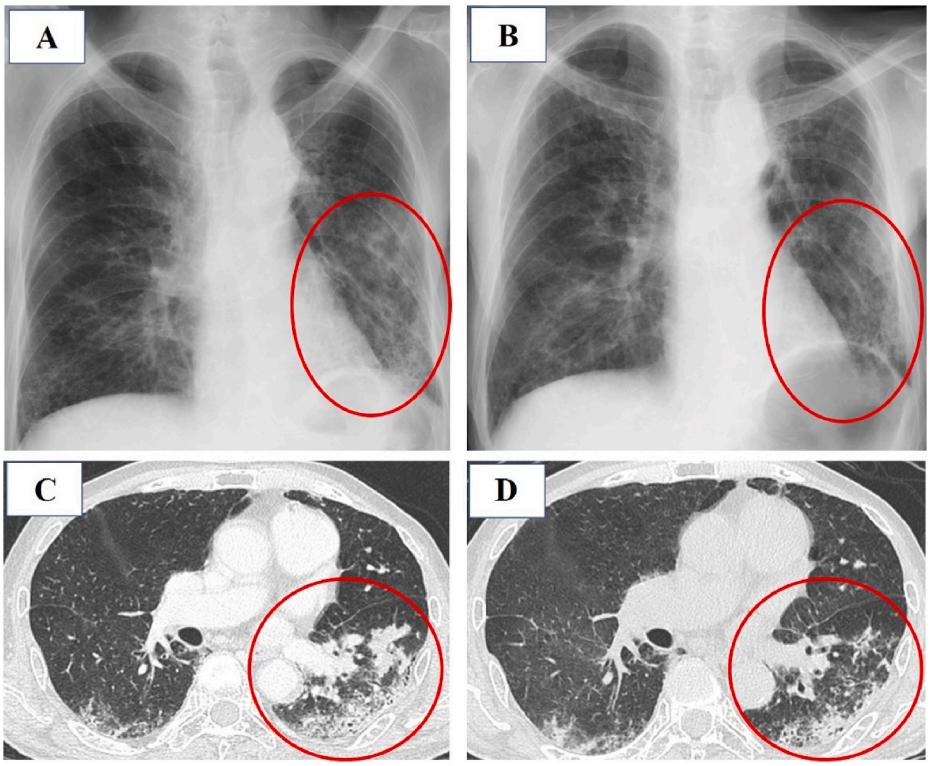

Fig. 1. Chest radiograph on admission, showing left lower lobe consolidation (A, C). Chest radiograph on day 15, showing improvement in bilateral consolidation (B, D).

(AUC = 6, day 1), PTX (175 mg/m^2, day 1), bevacizumab (15 mg/m^2, day 1), and atezolizumab (1200 mg, day 1) every 3 weeks, and maintenance therapy with bevacizumab (15 mg/m^2, day 1) and atezolizumab (1200 mg, day 1) was planned.

Thirty days after the first course of maintenance therapy (i.e., 14 days before admission), he visited the outpatient clinic to receive the second cycle of maintenance therapy, but as the blood test results showed leukopenia (white blood cell count of 2100/mm^3) and neutropenia (neutrophil count of 84/mm^3), systemic therapy with bevacizumab and atezolizumab was discontinued. The patient was afebrile, with no symptoms. As he lived close to our hospital, he was followed up without treatment. Five days after this visit (i.e., 9 days before admission), he visited our clinic for the follow-up of neutropenia. He was still afebrile, but laboratory tests showed deterioration of neutropenia, with an overall white blood cell count of 1600/mm^3 and a neutrophil count of 0/mm^3. He was prescribed 500 mg of levofloxacin, which he was advised to take if fever developed. Four days later, he developed a fever of over 40 °C and felt weak. He started taking levofloxacin and was admitted to our hospital the next day.

Upon admission, his vital signs were as follows: temperature, 40 °C; heart rate, 112 bpm; blood pressure, 145/68 mmHg; respiratory rate, 18 breaths/min; and oxygen saturation, 93% at room air. He was alert and conscious. Other than slight late inspiratory crackles in the left lower lobe, physical examination was unremarkable. No new medications were administered in the past 6 months, except for chemotherapy. Complete blood counts showed a hemoglobin level of 10.3 g/dL, white blood cell count of 600/mm^3, neutrophil count of 9/mm^3 (indicating severe neutropenia), and platelet count of 16.9 × 10^3/μL. Serum tests were negative for anti-neutrophil antibodies. In addition, viral infections such as parvovirus B19, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, and hepatitis B and C viruses were ruled out during the persistently severe neutropenia. His urinalysis was unremarkable. Chest radiography showed left lower lobe consolidation, suggesting acute pneumonia (Fig. 1A). Bone marrow (BM) aspiration revealed a decreased proportion of myeloid precursor cells and increased proportion of erythroid precursor cells and megakaryocytes, without any evidence of hematological disorders, such as acute leukemia, myelodysplastic syndrome, and aplastic anemia (Fig. 2). BM carcinomatosis or metastasis was not detected on BM biopsy. Chest CT showed bilateral dorsal infiltration (Fig. 1C). Based on these findings, we

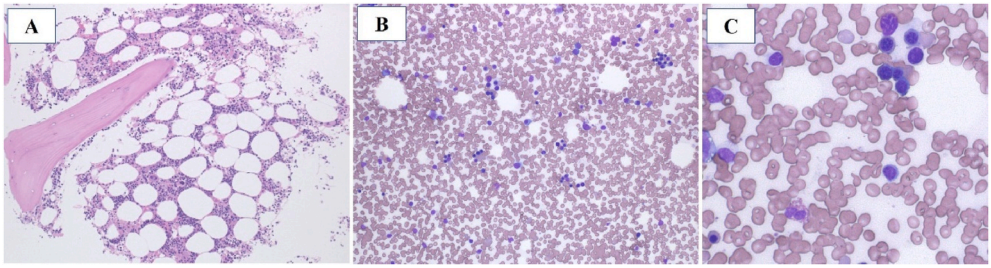

Fig. 2. Result of the histologic analysis of the bone marrow aspirate. (A) (original magnification × 200). Bone marrow smear showing decreased myeloid precursors and increased erythroid islands with normal morphology. (B, C) (original magnification × 400). Sample stained with hematoxylin and eosin showing normocellular marrow.

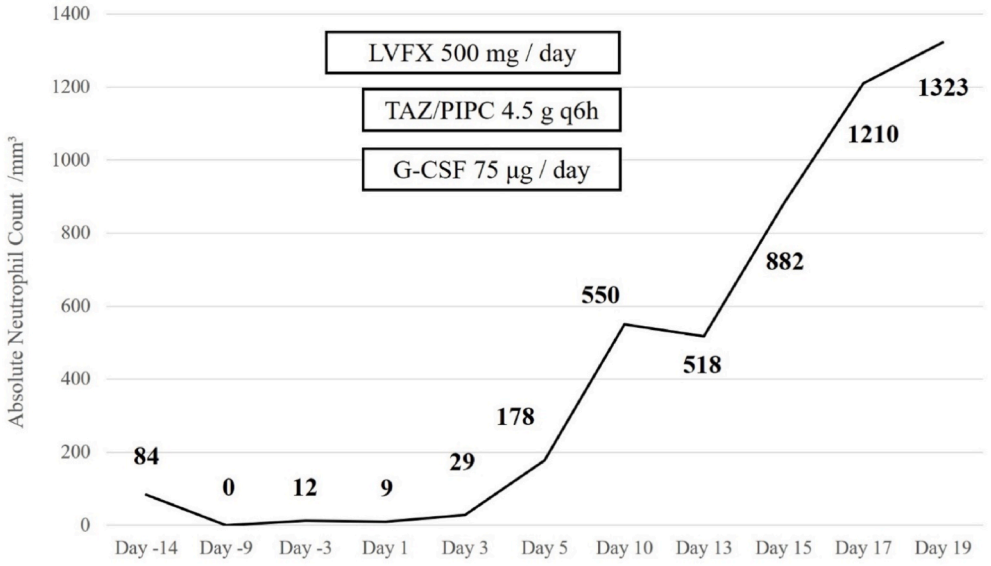

Fig. 3. A timeline illustrating the absolute neutrophil count since the beginning of atezolizumab-related toxicity. TAZ/PIPC: tazobactam/piperacillin; LVFX: levofloxacin; G-CSF: granulocyte colony-stimulating factor.

suspected febrile neutropenia caused by atezolizumab or bone marrow suppression caused by cytotoxic chemotherapy rather than bone marrow carcinomatosis secondary to adenocarcinoma of the lung. Given the clinical course, the patient developed acute severe neutropenia after two courses of maintenance therapy with bevacizumab and atezolizumab, which were less cytotoxic than other common chemotherapeutic agents. Therefore, we diagnosed him with pneumonia and febrile neutropenia, following hem-irAEs caused by atezolizumab.

Chemotherapy with atezolizumab and bevacizumab was discontinued. Empirical antibiotic therapy with 500 mg of levofloxacin and 4.5 g of piperacillin/tazobactam and G-CSF therapy were initiated. We simultaneously started oxygen flow at 1L/min with a nasal cannula. After the initial therapy, his body temperature dropped to 36 °C on the third day of hospitalization. Culture of the sputum on admission revealed only an alpha-hemolytic streptococcus infection. On the 10th day, his neutrophil count recovered to over 500/mm^3 (Fig. 3), and both antibiotic therapy and G-CSF therapy were discontinued. Oxygen therapy was also discontinued because his oxygen saturation reached 98% at room air on the 11th day. Follow-up chest radiography and chest CT demonstrated improvement of left lower lobe consolidation (Fig. 1B, D). After completing these treatments, his general appearance remained satisfactory and neutrophil counts remained within normal limits. He was discharged on the 19th day.

3. Discussion

Our study showed that antibiotic and G-CSF therapies were effective in the treatment of febrile neutropenia caused by atezolizumab administration. We did not use systemic corticosteroids because of the risk of additional infection. The clinical course of this patient provided two important clinical suggestions.

First, atezolizumab could have caused a hem-irAE in the form of neutropenia. To the best of our knowledge, this is the first report of a case with hem-irAE-related neutropenia associated with atezolizumab. In previous studies, 20 cases of hem-irAE-related neutropenia have been reported, including five cases associated with pembrolizumab, four with ipilimumab, and 11 with nivolumab [3,5]. In most of these cases, the neutropenia was profound and severe, with an absolute neutrophil count close to 0/mm^3, and severe infection occurred during neutropenia in 12 cases. A large study by Nicolas and colleagues assessed three French pharmacovigilance databases of hem-irAEs induced by anti-PD-1 or anti-PD-L1 immunotherapy in 948 patients; they found 35 (3.7%) patients with hem-irAEs [5], of which nine had neutropenia (26%), nine had autoimmune hemolytic anemia (26%), and nine had immune thrombocytopenia (26%). Six (67%) of the nine patients with neutropenia developed fever; one patient (11%) died of septic shock during the episode of febrile neutropenia [5]. Little is known about the mechanism of neutropenia development after atezolizumab initiation. However, several data suggest that the PD-1/PD-L1 axis is crucial for preventing immune-mediated damage of the hematopoietic niche [6] Importantly, ICIs are associated with the development of anti-neutrophil autoantibodies in the serum of some patients [7,8]. Additionally, neutropenia might be associated with abnormal large granular lymphocytes, such as T lymphocytes or natural killer lymphocytes, which should be screened using blood and bone marrow smears [3].

Second, the administration of antibiotics and G-CSF is crucial for the clinical management of febrile neutropenia caused by atezolizumab. Based on the guidelines for the management of immune toxicities by the European Society for Medical Oncology and American Society of Clinical Oncology, most patients with grade II or higher irAEs should be treated

Learning points

1. Atezolizumab could induce neutropenia as hem-irAEs.
2. Antibiotics and G-CSF should be administered until absolute neutrophil count recovery. Systemic corticosteroids are not essential as they increase the infection risk.

with steroids. ICI therapy should be discontinued when hematologic toxicities occur, even if the toxicity level is grade I [9,10]. From a pharmacological perspective, dose adjustment for readministration of ICIs is not recommended because irAEs related to anti-PD1 or anti-PD-L1 are not dose-dependent [11]. Neutropenia is one of the most frequent hem-irAEs and the risk of mortality is generally associated with bacterial and fungal infection [12]. In cases of febrile neutropenia, antibiotics and G-CSF should be administered until absolute neutrophil count recovery. In a previous study, six out of nine patients with neutropenia caused by ICIs were treated without corticosteroids; five of them survived [3,5]. Given the risk of worsening of infection and adverse events due to steroids, corticosteroids should not be administered systemically in this context [12].

4. Conclusion

In conclusion, antibiotics and G-CSF should be administered until absolute neutrophil count recovery in cases of febrile neutropenia complicated by atezolizumab. Systemic corticosteroids should not be administered because they can accentuate the risk of infection.

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Declaration of competing interest

The authors state that they have no conflicts of interest.

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