—Case Reports—

A Case of Immune Aplastic Anemia during Combined Treatment with Atezolizumab and Chemotherapy for Non-Small Cell Lung Cancer

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Immune check point inhibitors (ICIs) have durable antitumor effects. However, autoimmune toxicities, termed immune-related adverse events, occur in some patients. We report a case of severe immune aplastic anemia (AA) in a patient with non-small cell lung cancer who was receiving atezolizumab with bevacizumab/carboplatin/paclitaxel. Although the cancer has not recurred, his bone marrow is depleted and he did not respond to immunosuppressive therapy. He has survived for 1.5 years with blood transfusions and infection control. Immune AA associated with ICIs is rare, and a treatment has not yet been established. This case report provides information on the management and treatment response of patients with AA caused by ICIs. Further studies should investigate the mechanism and pathogenesis of immune AA caused by ICIs. (J Nippon Med Sch 2024; 91: 339–346)

Key words: atezolizumab, aplastic anemia, immune checkpoint inhibitor, immune-related adverse event, non-small cell lung cancer

Introduction

Atezolizumab, an immune check point inhibitor (ICI), is an antibody that blocks programmed cell death-ligand 1 (PD-L1). Cancer cells express PD-L1 on the cell surface to evade immune cells, and atezolizumab blocks this expression to induce an immune response against cancer cells. When PD-L1 molecules on the surface of cancer cells or stromal cells inhibit T lymphocytes from attacking and evading self-monitoring of the immune system, T lymphocytes are able to attack cancer cells if anti-PD-L1 antibodies have inhibited the mechanism[1]. Though ICIs are generally well tolerated, immune-related adverse events (irAE) may affect any organ or tissue. Among them, hematological irAE (hem-irAE) have received increasing attention[2–4].

Aplastic anemia (AA) has been reported in a few patients with hem-irAE, but the mechanism is unknown. Here, we report a case of immune AA in a patient with recurrent non-small cell lung cancer (NSCLC) who had received 2 cycles of treatment with atezolizumab plus bevacizumab plus carboplatin plus paclitaxel (ABCP).

All procedures followed were in accordance with the principles of the Helsinki Declaration of 1964 and later versions. Written informed consent was obtained from the patient for his inclusion in this report.

Case Presentation

A 67-year-old man with lung adenocarcinoma underwent right middle lobectomy. His medical history included ulcerative colitis that was well controlled with mesalazine, as well as hypertension and cured testicular seminoma. He had a smoking history of 47 pack-years.

For postoperative pathological Stage IIB (pT3N0M0) NSCLC (Union for International Cancer Control TNM

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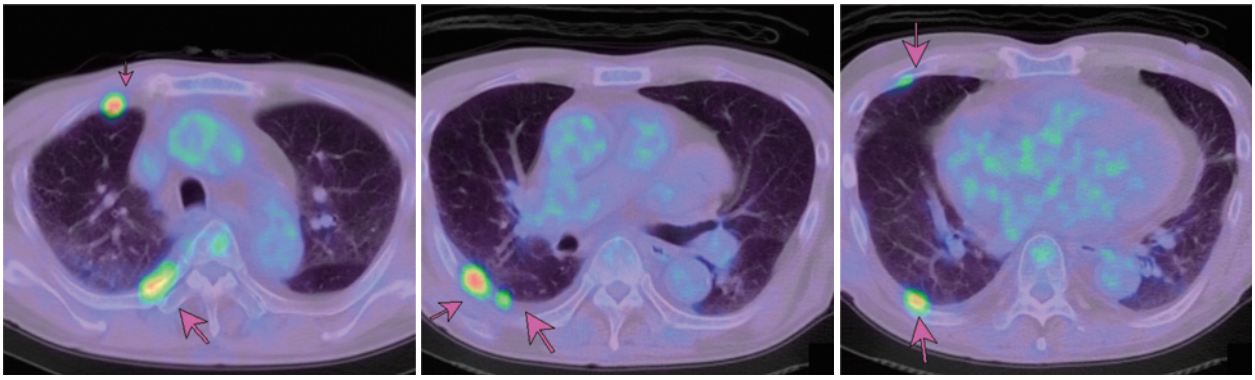


Fig. 1 Positron emission tomography-computed tomography (PET-CT) scans of the recurrent tumor.
PET-CT image shows strong uptake of FDG in multiple nodules on the right pleura. Lung adenocarcinoma recurred with right pleural metastasis 17 months after surgery.

Classification of Lung Cancer, 8th edition)[5], adjuvant chemotherapy was administered, namely, 4 courses of cisplatin plus pemetrexed. Genetic testing with the Oncomine Dx Target Test (ODxTT)[6] showed the driver mutations were all wild types. Immunohistochemical staining of the tumor tissue revealed that 20% of tumor cells expressed PD-L1.

Seventeen months after surgery, positron emission tomography-computed tomography (PET-CT) scans revealed marked uptake of fluorodeoxyglucose (FDG) in multiple nodules on the right pleura (**Fig. 1**), indicating that the cancer had recurred with pleural metastases of NSCLC. Consequently, the patient received his first infusion of ABCP. Three weeks later, baseline blood tests were normal, and the second cycle of ABCP was administered. Three weeks after that, his platelet count decreased to $5.3 \times 10^4/\mu L$, so the third cycle was discontinued. Thirty-eight days after the second cycle, he developed severe thrombocytopenia with fatigue and petechial bleeding of the lower extremities, resulting in emergency hospitalization.

Table 1 shows the laboratory findings at admission. Blood cell counts indicated severe thrombocytopenia ($1.1 \times 10^4/\mu L$); white and red blood cell (RBC) counts were preserved. There were no abnormalities of the coagulation system or signs of disseminated intravascular coagulation. Chest CT images indicated shrinkage of right pleural metastases after 2 cycles of ABCP therapy (**Fig. 2**).

Clinical course after hospitalization is shown in **Figure 3**. Repeated platelet transfusions were performed, but platelet count did not recover. As for the cause of thrombocytopenia, there was no history of radiotherapy, and the possibilities of infection and drug-induced or disseminated intravascular coagulation were excluded. Platelet-associated immunoglobulin G (PA-IgG) was elevated at 41.9 ng/10^7, suggesting idiopathic (or immune) thrombocytopenic purpura (ITP), and steroid therapy was started as diagnostic treatment. Dexamethasone 40 mg × 4 days was started and continued with 15 mg/day of prednisolone. His condition worsened and he developed anemia, leukopenia, and neutropenia. Administration of granulocyte-colony-stimulating factor and broad-spectrum antibacterial drugs for neutropenia was ineffective, and high fever persisted. For definitive diagnosis of pancytopenia, pathological evaluation by bone marrow aspirate clot was performed, which confirmed a diagnosis of AA. Pathological findings showed severe hypocellular fatty marrow with a rare residual erythroid island and lymphoid infiltrate, in the absence of features of morphologic dysplasia (**Fig. 4**). Cellularity of the bone marrow aspirate clot was 5-10%, and immunohistochemistry showed that hematopoiesis of myeloid and megakaryocytic lineage was significantly reduced. Infiltrating lymphocytes were CD8+ T cell dominant, as compared with CD41+ T cells and CD20+ B cells. Chromosome analysis showed no cytogenetic abnormalities. Highly sensitive paroxysmal nocturnal hemoglobinuria (PNH) RBC was within normal limits, at 0.002%, and plasma thrombopoietin levels (61.30 Fmol/mL) were high, confirming a diagnosis of immune AA. The severity grade under American Society of Clinical Oncology (ASCO) guidelines[7] was 3-4 because of the presence of hypocellular marrow <25%. Two months after the onset of thrombocytopenia, the patient developed respiratory failure and shock. A chest CT scan revealed a ground glass opacity (**Fig. 5**), which required admission to the intensive care unit (ICU) and use of a ventilator. Cultures were negative, and treatment with broad-spectrum antibacterial and antifungal drugs was ineffective. The pa-

Table 1 Laboratory findings

Hematology		γGTP	22 U/L	EBV VCA IgM	<10
WBC	6,580 /μL	CK	51 U/L	EBV EBNA	160
Neut	49.8 %	Na	142 mEq/L	Parvovirus B19 IgM	0.59
Lym	29 %	K	4.4 mEq/L	H pylori stool antigen	(–)
Mono	6.8 %	Cl	108 mEq/L	Other markers	
Eos	14.1 %	Ca	8.9 mg/dL	IgG	1,821 mg/dL
Baso	0.3 %	P	3.3 mg/dL	IgA	617 mg/dL
RBC	362×10^4 /μL	Fe	238 μg/dL	IgM	139 mg/dL
Hb	11.2 g/dL	T-Bil	0.65 mg/dL	CEA	4.26 ng/mL
Ht	32.5 %	TP	6.7 g/dL	KL-6	347 U/mL
MCV	89.8 fL	Alb	3.6 g/dL	ANA	40 ×
MCH	30.9 pg	BUN	23.2 mg/dL	homogeneous pattern	40 ×
MCHC	34.5 %	Cre	0.98 mg/dL	anti-dsDNA IgG antibody	1.6 IU/mL
RETIC	1 ‰	CRP	0.52 mg/dL	PA-IgG	41.9 ng/×10^7 cells
Plt	1.1×10^4 /μL	TSH	1.32 μU/mL	Thrombopoietin	61.3 Fmol/mL
Coagulation		FT3	3.09 pg/mL	PNH CD59/CD55	
PT (sec)	11.7 sec	FT4	1.15 ng/dL	R59+55+	99.2 %
PT (%)	84.9 %	ACTH	15.6 pg/mL	R59+55–	0.8 %
PT/INR	1.09	Cortisol	12.8 μg/dL	R59–55+	0 %
APTT	30.1 sec	Ferritin	743 ng/mL	R59–55–	0 %
Fibrinogen	368.6 mg/dL	TIBC	243 μg/dL	G59+55+	99.8 %
FDP	3.5 μg/dL	Vit B12	356 pg/mL	G59–55–	0 %
D-dimer	1.08 μg/mL	Folate	1.9 ng/mL	G59+55–	0.1 %
Blood biochemistry		Glucose	94 mg/dL	High-sensitive PNH cell count	
AST	12 U/L	HbA1c	6.3 %	PNH RBC	0.002 %
ALT	8 U/L	Infection biomarkers		PNH granulocytes	0.044 %
LD	123 U/L	CMV pp65⁺ cells	(–)	PNH monocyte	0.075 %
ALP	87 U/L	EBV VCA IgG	640		

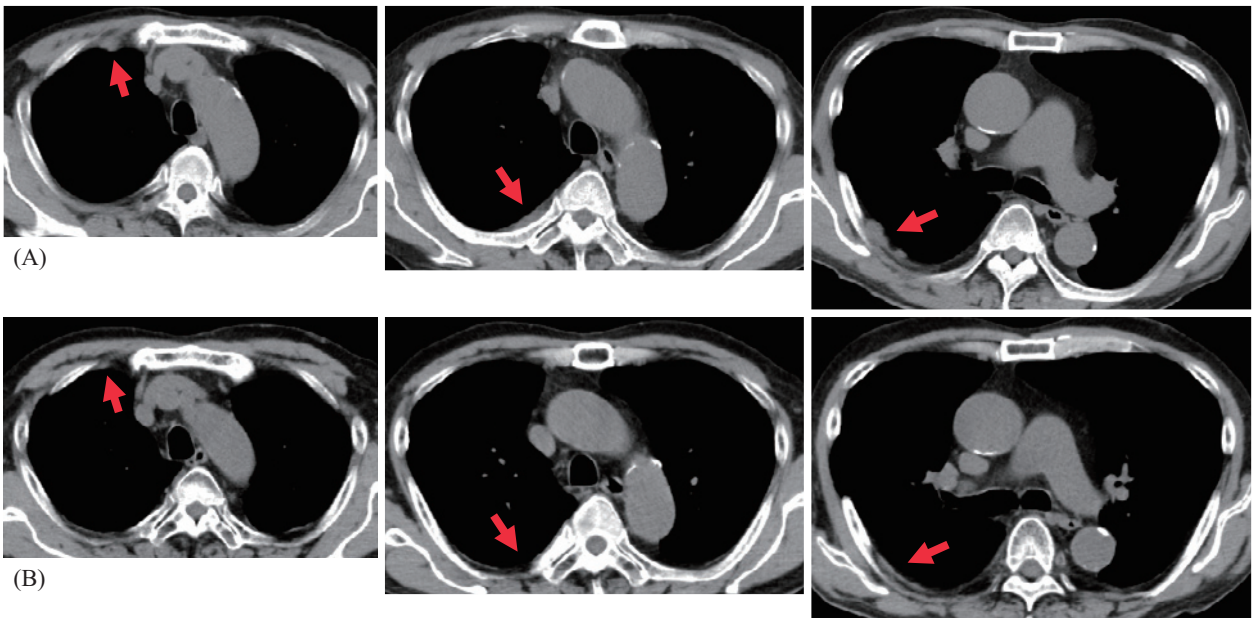


Fig. 2 Chest computed tomography scans before (A) and after (B) two cycles of treatment with atezolizumab/bevacizumab/CBDCA/PTX (ABCP therapy).
(A) CT image 2.5 months before admission. Multiple nodules and irregular pleural thickening are detected on the right pleura, indicating recurrence of pleural dissemination after a right middle lobectomy for lung adenocarcinoma. (B) At admission, pleural metastases had shrunk after two cycles of ABCP.

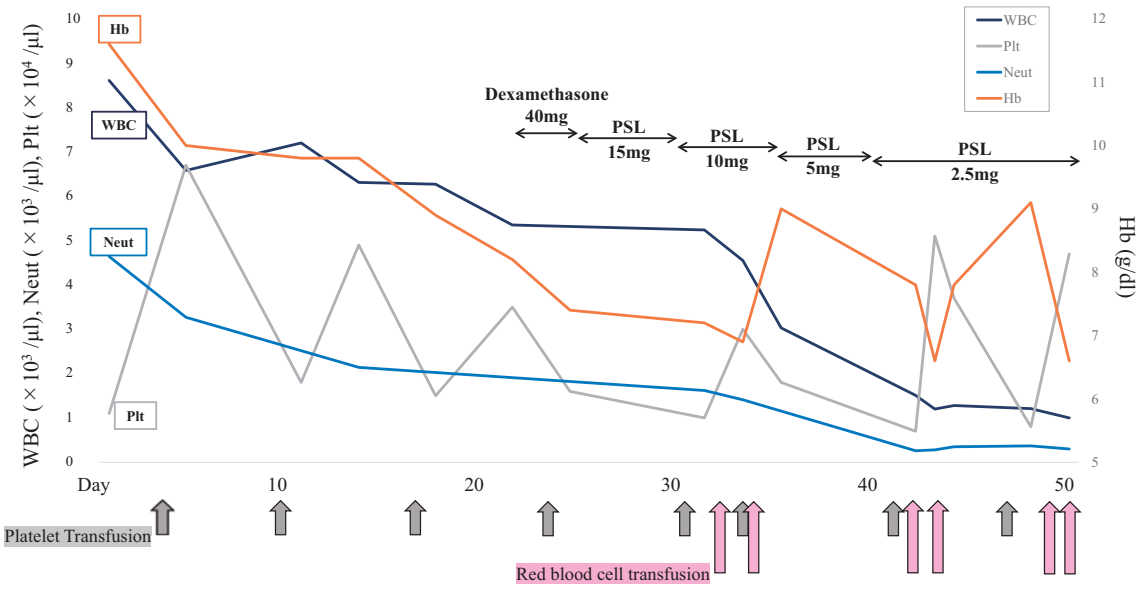


Fig. 3 Clinical course after hospitalization.
Blood testing on admission showed severe thrombocytopenia (platelet count, 1.1 × 10^4 /μL) and normal white and red blood cell counts. Platelet count did not recover after repeated platelet transfusions. Platelet-associated immunoglobulin G (PA-IgG) was elevated, suggesting idiopathic (or immune) thrombocytopenic purpura, and steroid therapy was started as diagnostic treatment. The patient was started on 40 mg × 4 days of dexamethasone and continued on 15 mg/day of prednisolone, but his condition worsened and he developed anemia, leukopenia, and neutropenia.

tient presented with acute respiratory distress syndrome of unknown cause. He was treated with steroid pulse therapy (methylprednisolone 1 g for 3 days) for acute circulatory failure, acute lung injury, or severe irAE, which was very effective. Because the patient had received frequent blood transfusions, it was later suggested that transfusion-related acute lung injury was a possible cause. Treatment with 1 mg/kg/day prednisolone was continued, and he was extubated and discharged from the ICU. However, bone marrow function did not recover, and he required regular platelet and RBC transfusions. Pathological findings on follow-up bone marrow aspiration and biopsy remained unchanged, with hypoplastic bone marrow (MF 0-1), and we determined that steroids would not be as effective. Prednisolone was thus tapered off, and treatment was switched to intravenous immunoglobulin (IVIG) and cyclosporine A (CyA). After 2 months of treatment with CyA, bone marrow function had not recovered, and CyA was discontinued.

At 1.5 years after onset of AA, the patient takes prednisolone 1 mg/day as a maintenance dose and undergoes weekly platelet and RBC transfusions. His lung cancer has not recurred and he maintains a clinical complete response.

Discussion

In the IMpower150 study, ABCP therapy significantly improved progression-free survival and overall survival among patients with progressive non-squamous NSCLC. The most common irAEs were rash, hepatitis, hypothyroidism, hyperthyroidism, pneumonitis, and colitis[8,9]. In the present case, 1 month after administration of 2 cycles of ABCP, a patient with postoperative recurrent NSCLC developed thrombocytopenia, which subsequently progressed to pancytopenia. His clinical course was distinctly different from the myelosuppression associated with common cytotoxic drugs, and hematopoietic function was never restored.

Several reviews reported that AA developed as a hem-irAE. A review of large clinical trials of ICIs estimated that the frequency of hem-irAEs was 3.6% for all grades and 0.7% for grades 3-4. The frequency of hem-irAEs was higher with anti-programmed cell death-1 (PD-1) (4.1%) and anti-PD-L1 (4.7%) than with anti-cytotoxic T-lymphocyte-associated protein 4 (0.5%). The mean time to onset was 10 weeks after ICI initiation. The large ranges for time to onset (1-84 weeks) and incidence suggest that hem-irAEs can develop at any time after ICI therapy. Among 63 patients with hem-irAEs, 12 (19%) had pancytopenia or immune AA. Moreover, hem-irAEs were severe adverse reactions and the mortality rate was

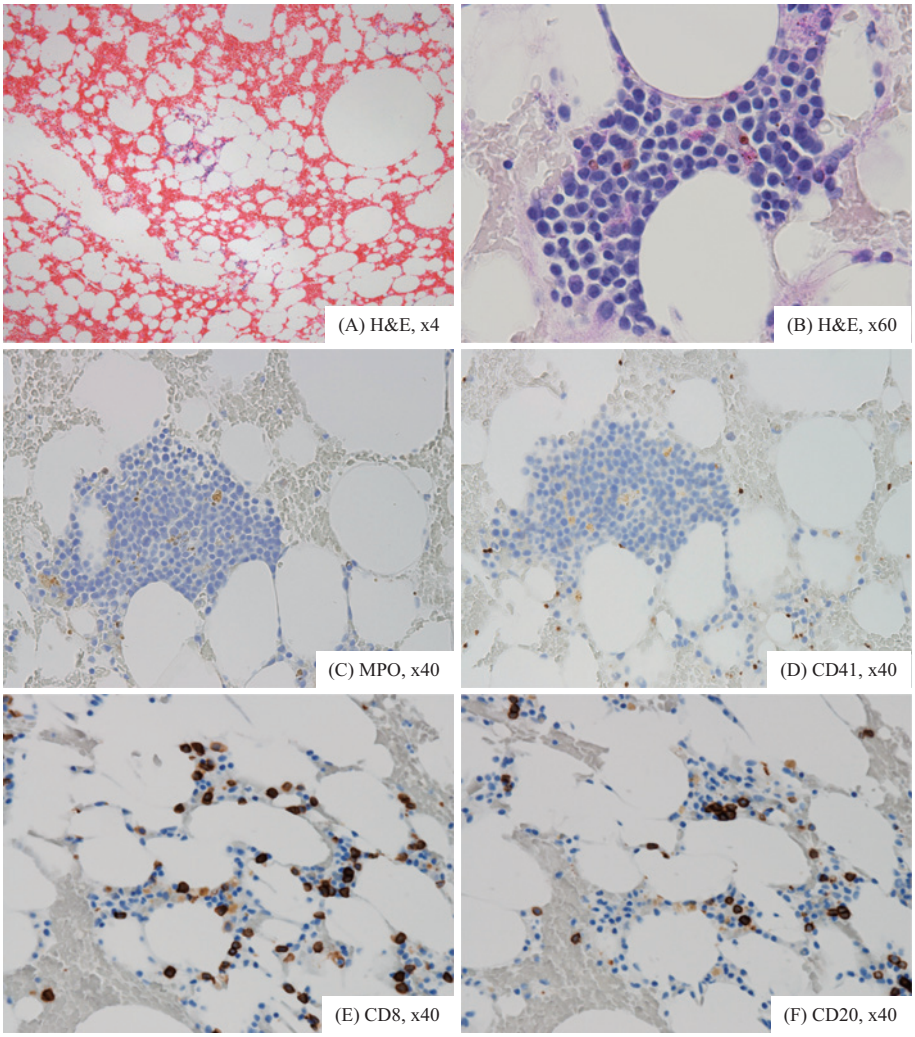
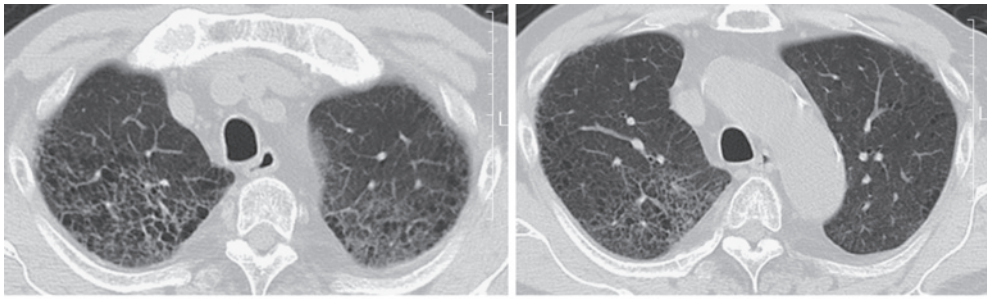


Fig. 4 Pathological features in bone marrow aspiration clot.
(A) Bone marrow clot showed severe hypocellular fatty marrow with contamination of peripheral blood, consistent with aplastic anemia (hematoxylin and eosin [H&E] stain, original magnification ×4).
(B) A few erythroid islands without dysplastic change were preserved (H&E, ×60).
(C, D) Neither a myeloid nor a megakaryocytic lineage was identified by immunohistochemistry for MPO and CD41 (×40).
(E, F) CD8+ T cells (E) but not CD20+ B cells infiltrated bone marrow (F) (×40).

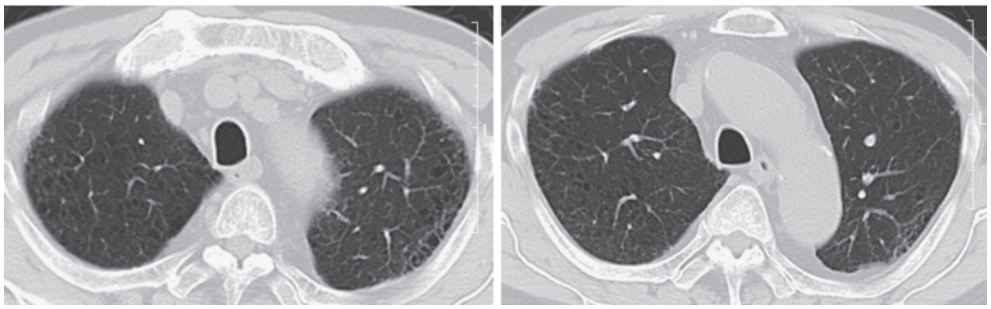
14%[4]. Omar et al. conducted a systematic review of hem-irAEs. Of 118 cases, most patients had melanoma (57.6%) and 26.3% had lung cancer; only 7 had pancytopenia or AA, which was treated with nivolumab (n = 1), ipilimumab (n = 3), pembrolizumab (n = 1), and combined ipilimumab and nivolumab (n = 2)[10]. In an observational study of 948 patients, 5 patients developed AA among 35 cases of hem-irAEs. Of these 35 patients, 21 (60%) showed improvement of hem-irAEs[11].

In a multicenter cohort study of 623 patients with NSCLC who received anti-PD (L) 1 therapy, 206 (33.1%) developed irAEs; 186 (29.9%) were treated with anti-PD (L) 1 monotherapy, 20 (3.2%) with combination therapy, and 3 of the 33 patients treated with a combination including cytotoxic chemotherapy developed irAEs[12]. Randomized controlled trials of treatments for advanced NSCLC suggested that the incidence of grade 3-4 adverse events may not differ between single/combined ICIs and platinum-based chemotherapy with or without bevacizumab[13]. Although no studies have directly compared immune hematological adverse events for ICI monotherapy and combination therapy, adverse effects on bone marrow might be more severe with combination therapy, including ABCP.

The relationship between the incidence of irAEs and treatment response to ICIs is controversial. A previous



(A)



(B)

Fig. 5 Chest computed tomography scans before (A) and after (B) treatment for lung injury.
(A) At onset of clinical acute respiratory distress syndrome, ground glass opacity is present in both lung fields. Background emphysema resulted in a Swiss cheese appearance of lung tissue.
(B) At the time of recovery from lung injury, the ground glass opacity has disappeared. There has been no recurrence of lung cancer.

study reported a higher response rate to ICI therapy and increased overall survival in patients who developed irAEs such as liver injury, interstitial pneumonia, hypothyroidism, and rash[14]. In contrast, a summary of 17 patients with severe AA as an irAE reported a low response rate (20-30%) and a higher mortality rate (5 of 17)[15]. Our systematic review of the literature in PubMed identified fewer than 30 cases of pancytopenia or AA as hem-irAE of ICIs for all malignancies; none involved atezolizumab as the causative drug. Thus, to our knowledge, this is the first case of atezolizumab-related AA and is thus a valuable report of recurrence-free NSCLC and long-term survival without recovery of bone marrow function.

Because pancytopenia has several factors, and AA itself is an exclusive diagnosis, other factors, such as infections and drugs, should be analyzed[16]. Hematopoietic stem cell (HSC) damage is believed to be caused by abnormalities in HSCs or their microenvironment and immunologic mechanisms. The pathophysiology is immune mediated in most cases and is associated with activated type 1 cytotoxic T cells[17]. PD-1 is expressed on activated CD4+ and CD8+ T lymphocytes (including regulatory T lymphocytes [Treg]), B lymphocytes, and macrophages. PD-L1 is a ligand for PD-1 expressed on antigen presenting cells and tumor cells. PD-L1 binding to PD-1 on effector T cells induces a negative regulatory signal and decreases the immune suppressive function of follicular Tregs while stimulating the immune suppressive function of blood Tregs. This suggests that these ICIs enhance autoantibody production in germinal centers[18]. Clinically, lymphocytes, especially T lymphocytes, are strongly involved in the pathogenesis of AA, as the disease is improved by drugs that selectively injure T cells, such as cyclosporine and anti-thymocyte globulin[17]. ICIs activate CD8+ T cells, eliciting both anti-cancer activity and irAEs[19]. In our patient, infiltrating lymphocytes were CD8+ T cell dominant in the hypocellular fatty marrow. Because activated CD8+ T cells and the mechanisms associated with them damage HSCs, the pathological findings may be linked to development of immune AA.

There is no established treatment for AA that develops as a hem-irAE[10]; patients are handled on a case-by-case basis, in accordance with general treatment for AA. Thus, ASCO proposed clinical practice guidelines for management of irAE in patients treated with ICIs in 2018 and revised them in 2021[7]. The management strategy for grade 3-4 AA according to the ASCO guidelines is as follows: i) Hold ICI and provide growth factor support and close clinical laboratory evaluations daily; discontinue treatment until AE has reverted to grade 1. ii) Administer

horse anti-thymocyte globulin (ATG) plus cyclosporine, if no response; repeat immunosuppression with rabbit ATG plus cyclosporine and cyclophosphamide. iii) Supportive transfusions as per local guidelines. iv) Human leukocyte antigen (HLA) typing and evaluation for bone marrow transplantation if patient is a candidate. v) For refractory AA, consider eltrombopag plus supportive care. However, the section on hematologic toxicity states that hematologic toxicities associated with ICIs are poorly described, in part because of low incidence and, possibly, because of lack of recognition. The guidelines further state that the situation is complicated by the increasing use of combinations of ICIs with myelosuppressive cytotoxic chemotherapy. Optimal treatment of AA associated with irAEs remains unclear because of this infrequency and complexity. ATG plus cyclosporine, cyclophosphamide, and eltrombopag is indicated for patients with severe AA who are not candidates for HSC transplantation, but caution is warranted because of severe long-term immunodeficiency. In our patient, treatment options for AA were evaluated after considering the patient's history of recurrent NSCLC with metastasis. The patient declined potent immunosuppressive therapies because of his age (67 years), general condition, and the risk of fatal complications, such as infection. ASCO guidelines state that most patients respond after pausing ICI treatment and are managed successfully with corticosteroids, IVIG, growth factor, and transfusion support, as required. In our patient, severe AA was treated with high-dose corticosteroids, cyclosporine, and IVIG, but he did not respond to treatment. An association between elevated plasma thrombopoietin levels and sensitivity to immunosuppressive therapy has been reported[20], and the fact that erythropoietin was only mildly elevated in our patient may have been a contributing factor to his poor treatment response. Elucidation of the pathogenesis of AA and the effects of ICIs on immune cells and bone marrow might help us understand why the decrease in HSCs was refractory to therapy and irreversible.

Conclusion

This is the first case report of a patient with NSCLC treated with atezolizumab plus cytotoxic agents who developed AA and did not recover bone marrow function. Further studies should investigate the mechanism and pathogenesis of immune AA caused by ICIs.

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