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Case Report

Pure Red Cell Aplasia Induced by Atezolizumab in a Patient with Small-Cell Lung Cancer Successfully Treated with Steroid Therapy: A Case Report

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Keywords
Pure red cell aplasia · Atezolizumab · Small-cell lung cancer

Abstract
Introduction: Combination therapy of atezolizumab and chemotherapy has become the standard treatment for small-cell lung cancer. Immune-related adverse events (irAEs) can occur during immune checkpoint inhibitor administration. A few reports exist on pure red cell aplasia (PRCA) as an irAE after atezolizumab treatment. PRCA is characterized by normocytic-normochromic anemia, a marked decrease in reticulocytes, and a decrease in bone marrow erythroblasts. Here, we report a case of atezolizumab-induced PRCA. ***Case Presentation:*** A 69-year-old male patient was brought to the emergency department with the chief complaint of seizures. Multiple metastatic brain tumors and a mass suspected to be the primary lesion in the right hilar region were observed. After a brain biopsy, he was diagnosed with small-cell lung cancer (cT1cN0M1c stage IVB). He received four courses of carboplatin, etoposide, and atezolizumab in combination with whole-brain irradiation, which led to a partial response. After six courses of atezolizumab maintenance therapy, severe anemia (hemoglobin, 3.4 g/dL) was observed. PRCA induced by atezolizumab was diagnosed using a bone marrow biopsy performed during red blood cell transfusion. Treatment was started with prednisolone 25 mg/day (0.5 mg/kg/day). Anemia improved, and the dose was gradually reduced to 5 mg/day. ***Conclusion:*** Reports of PRCA as an irAE are rare but important; hence, we reported this case.

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Introduction

Combination therapy of atezolizumab and chemotherapy has become the standard treatment for small-cell lung cancer [1]. Immune-related adverse events (irAEs) can occur during immune checkpoint inhibitor administration. Pure red cell aplasia (PRCA) is characterized by normocytic-normochromic anemia, a marked decrease in reticulocytes, and a decrease in bone marrow erythroblasts [2]. A few reports exist on PRCA as an irAE after atezolizumab treatment. Here, we report a case of atezolizumab-induced PRCA.

Case Presentation

We have completed the CARE Checklist for this case report and attached it as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000535468). A 69-year-old male patient was brought to the emergency department with the chief complaint of seizures. Multiple brain tumors were confirmed on cerebral contrast-enhanced magnetic resonance imaging, and he was urgently hospitalized. He had a smoking history, with 20 cigarettes daily, from the age of 20–55 years. A full-body contrast-enhanced computed tomography scan revealed a mass in the right hilum but no thymoma, and a brain biopsy was performed, leading to the diagnosis of small-cell lung cancer (cT1cN0M1c stage IVB). First, whole-brain irradiation was performed, followed by chemotherapy with carboplatin, etoposide, and atezolizumab every 3 weeks. A partial response was achieved after four courses of the chemotherapy regimen. Subsequently, six courses of atezolizumab maintenance therapy were administered every 3 weeks, and shrinkage of both the primary and metastatic brain tumors was maintained.

When he visited the hospital for the seventh course of atezolizumab, his hemoglobin level was 3.4 g/dL and severe anemia was confirmed. His vital signs were normal as follows: body temperature 36.5°C, heart rate 82/min, blood pressure 130/72 mm Hg, respiratory rate 16/min, and peripheral capillary oxygen saturation 97% (room air). His concomitant medications were levetiracetam and vonoprazan fumarate, and there was no history of drug changes from the start of chemotherapy until the onset of anemia. There was no decrease in other hematopoietic parameters (Table 1). Contrast-enhanced computed tomography and magnetic resonance imaging revealed no tumor progression (Fig. 1). There was no history of suspected antecedent infection or gastrointestinal bleeding. Four units of red blood cells were transfused, and the patient was referred to the hematology department for bone marrow biopsy. Biopsy revealed the presence of granulocytes and megakaryocytes and only a few erythroblasts (Fig. 2a, b). Based on these findings, the patient was diagnosed with PRCA, an irAE associated with atezolizumab. Treatment was initiated with prednisolone at 0.5 mg/kg/day (25 mg/day). Even after the start of treatment, the patient required two units of red blood cell transfusion once; however, an improvement was observed in the hemoglobin level 4 weeks after the start of treatment. Subsequently, the dose was gradually reduced by 5 mg every 2 weeks; even after the reduction to 5 mg, the hemoglobin level did not decrease again, and the same dose has been continued since then (Fig. 3).

Discussion

Here, we report a case of PRCA, an irAE, caused by atezolizumab treatment with steroids. PRCA is classified as congenital or acquired, and the known causes include tumors, infectious diseases, autoimmune diseases, and blood diseases [1, 3]. In some cases of primary and

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Table 1. Laboratory findings before atezolizumab maintenance therapy and after six courses of atezolizumab

Item	Before atezolizumab maintenance therapy	After six courses of atezolizumab	Unit
White blood cell	10,030	5,290	/μL
Red blood cell	304	115	$\times 10^4$/μL
Hemoglobin	10.1	3.4	g/dL
Platelet	23.4	35.5	$\times 10^4$/μL
C-reactive protein	0.28	0.25	mg/dL
Total protein	6.8	6.5	g/dL
Albumin	3.9	4.2	g/dL
Total bilirubin	0.3	0.3	mg/dL
Aspartate aminotransferase	18	12	U/L
Alanine aminotransferase	9	10	U/L
Sodium	138.6	140	mEq/L
Potassium	4.1	3.3	mEq/L
Chlorine	101.6	103	mEq/L
Blood urea nitrogen	14.8	15.8	mg/dL
Creatinine	0.76	0.73	mg/dL
Iron	–	181	μg/dL
Ferritin	–	561	ng/mL
Total iron-binding capacity	–	200	μg/dL
Vitamin B12	–	218	pg/mL
Folic acid	–	8	ng/mL

Significant decrease in the hemoglobin level after six courses of atezolizumab administration.

secondary PRCA associated with large granular lymphocytic leukemia or thymoma, cellular immunity is thought to be involved in the pathogenesis through direct or indirect injury of erythroblasts by T cells or natural killer cells [4]. Lung cancer is also known to be a cause of PRCA; however, limited reports exist on this phenomenon. Known treatments for PRCA include the addition of immunosuppressants, such as cyclosporine and steroids, or monotherapy with cyclosporine [5]. Additionally, a previous study reported that PRCA developed after pembrolizumab treatment for Hodgkin's lymphoma. Steroid treatment was unsuccessful; however, intravenous immunoglobulin therapy was successful [6]. PRCA was also reported to occur when nivolumab was used for treating a melanoma [7]. In a study by Isoda et al. [6], the maintenance dose of prednisolone was 10 mg. The report by Yuki et al. [7] only stated that the prednisolone dosage was gradually tapered.

In this case, a rapid decrease in hemoglobin levels occurred during atezolizumab maintenance therapy, leading to the diagnosis of PRCA based on bone marrow biopsy results. No antecedent infections, findings suggestive of gastrointestinal bleeding, tumor exacerbation, or new drugs suspected of being drug-related were prescribed. Treatment with prednisolone was started, and the condition improved to the point where blood transfusions were not required after 4 weeks. Subsequently, prednisolone was gradually reduced to 5 mg; however, nemia did not progress, and the effect of treatment was considered beneficial. In our case, considering the favorable course of anemia and the prognosis of patients with small-cell lung cancer, we decided to use 5 mg as the

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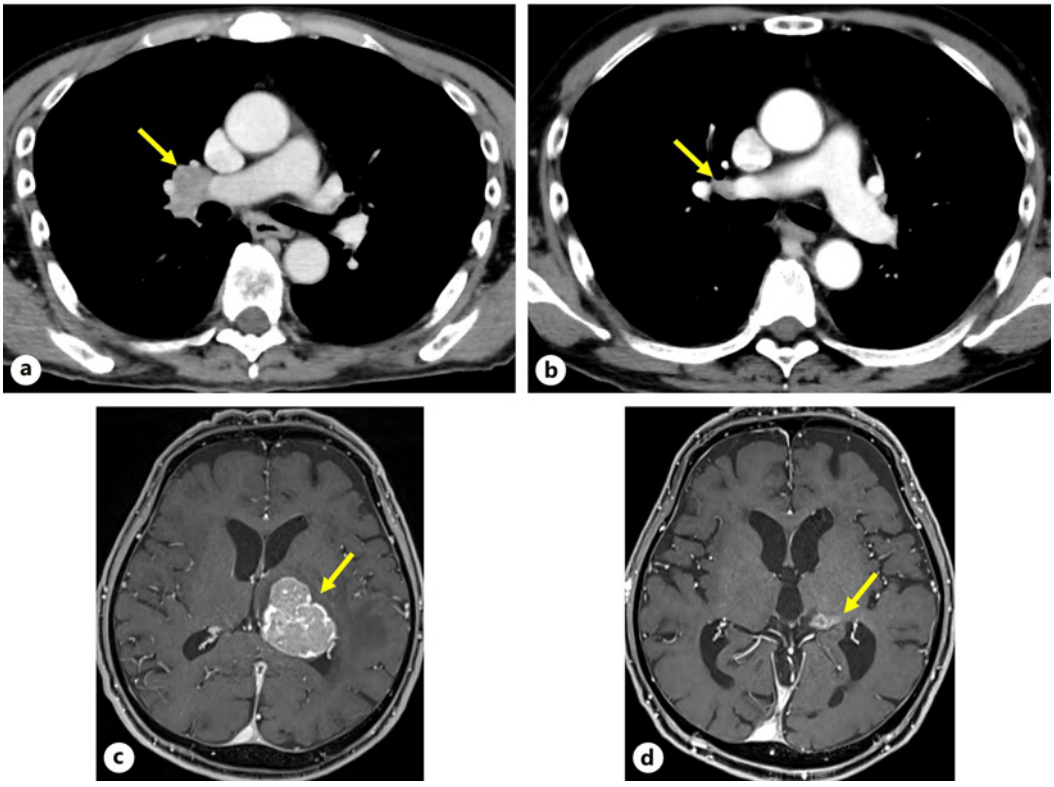

Fig. 1. Comparison of images during the initial diagnosis and the appearance of anemia. **a** Primary tumor at initial diagnosis on contrast-enhanced CT. **b** Primary tumor during anemia on contrast-enhanced CT. **c** Brain metastases at initial diagnosis on head MRI. **d** Brain metastases during anemia on head MRI. MRI, magnetic resonance imaging; CT, computed tomography.

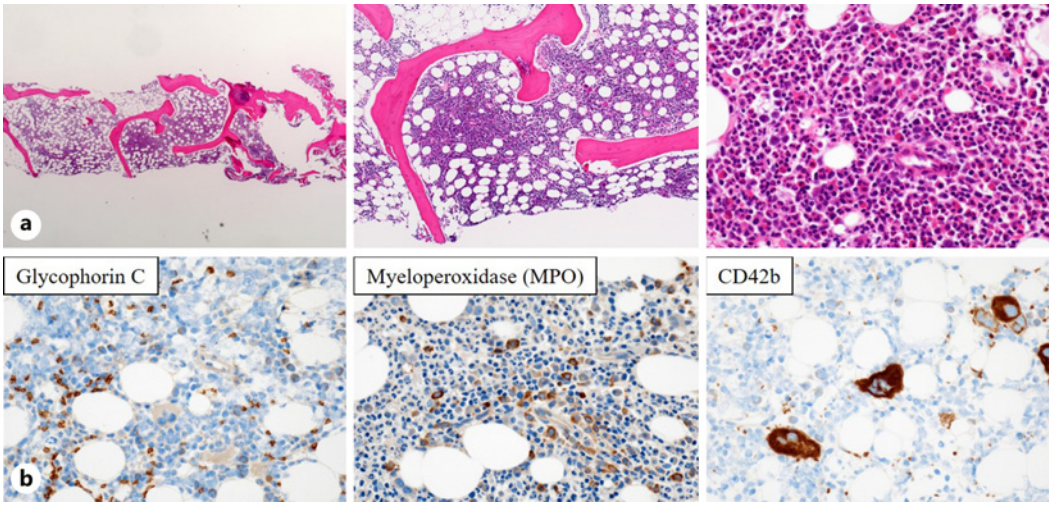

Fig. 2. a Hematoxylin and eosin staining findings of bone marrow specimens. No erythroblast islands were observed. **b** Immunohistochemical staining findings of bone marrow specimens. Granulocytic cells (myeloperoxidase [MPO]-positive) and megakaryocytes (CD42b-positive) were observed; however, erythroblasts (glycophorin C-positive) were absent. These findings were consistent with PRCA.

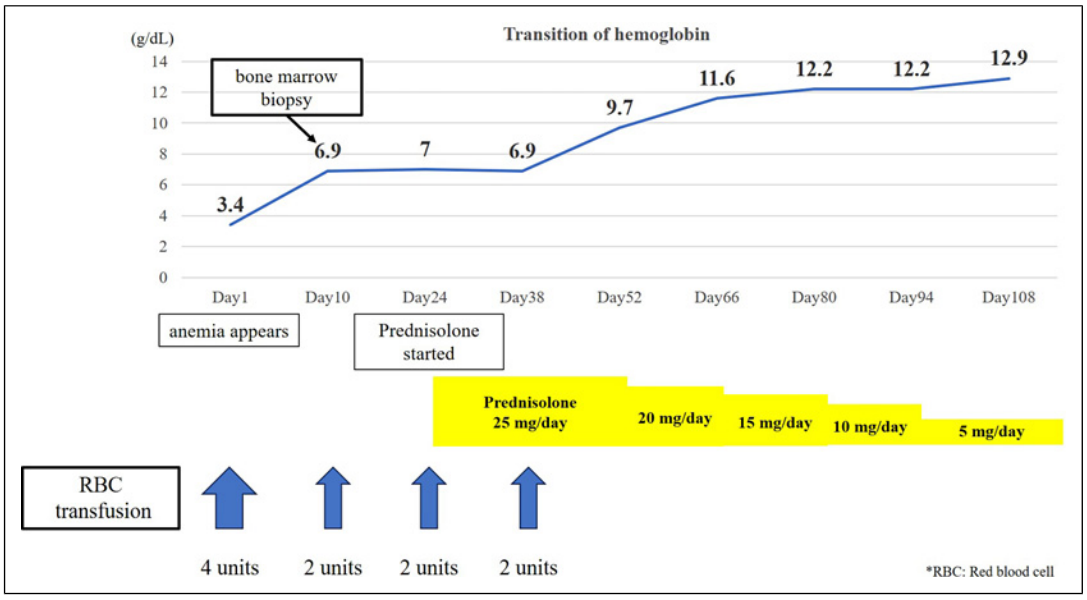

Fig. 3. Transition of the hemoglobin level and course of treatment.

maintenance dose as recurrence of PRCA would have been a challenge. Few case reports have showed that combined chemotherapy and radiotherapy resulted in a good prognosis [8]. Additionally, some studies have indicated that the use of immune checkpoint inhibitors may increase the complete response rates in solid tumors [9]. Furthermore, in this case, the progression of the small-cell carcinoma was favorable after chemotherapy and radiation therapy for metastatic brain tumors, and it was believed that the prognosis could be prolonged by appropriate management of the side effects. To the best of our knowledge, no reports exist on PRCA associated with lung cancer or as an irAE, and our patient's case is considered rare since PRCA due to immune checkpoint inhibitors is a rare occurrence. In conclusion, we report a case of PRCA, an irAE caused by atezolizumab, which was successfully treated with steroids.

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Statement of Ethics

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images. Ethical approval is not required for this study in accordance with local guidelines.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest to declare.

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Author Contributions

Keita Kawakado wrote this case report. Keita Kawakado, Shunsuke Ito, Kento Kono, Yuki Mitarai, and Takashi Yanagawa treated this patient. Makoto Nagasaki performed a pathological diagnosis. All authors discussed the results of this case report, made comments on the manuscript, and finally approved this version to be published.

Data Availability Statement

All data from this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding authors.

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