

# Pure Red Cell Aplasia and Chromosomal Abnormality in a Patient With Lung Adenocarcinoma Receiving Immune Checkpoint Inhibitors: A Case Report

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**Abstract.** *Background/Aim: Immune checkpoint inhibitors can induce immune-related adverse events in various organs, thus careful observation is required. Case Report: A 69-year-old man was diagnosed with advanced lung adenocarcinoma and treated with combined therapy of carboplatin plus pemetrexed plus pembrolizumab. After two cycles of treatment, anemia was noted. Myelosuppression due to cytotoxic anticancer agents was suspected and the cytotoxic agents were discontinued, followed by three courses of pembrolizumab monotherapy. However, the anemia persisted, requiring red blood cell transfusions. A bone marrow biopsy revealed erythroblast hypoplasia and chromosomal abnormalities, resulting in a diagnosis of pure red cell aplasia. These adverse events were considered immune-related because of the treatment history with an immune checkpoint inhibitor, and 60 mg/day (1 mg/kg/day) of prednisolone was initiated. Anemia improved, and it did not recur during the tapering of prednisolone. Conclusion: Immune-related pure red cell aplasia should be considered*

*for patients presenting anemia during treatment with immune checkpoint inhibitors.*

Immune checkpoint inhibitors (ICIs) have improved the prognosis of patients with non-small cell lung cancer (NSCLC) without driver mutations (1). However, careful observation is required during treatment because ICIs can induce immune-related adverse events (irAEs) in various organs, and some patients have a fatal course. Herein, we report a case with NSCLC treated using an ICI-containing regimen, presenting pure red cell aplasia and chromosomal abnormality. Written informed consent was obtained from the patient for publication of this case report.

## Case Report

A 69-year-old man visited a hospital complaining of right back pain. He had a smoking history of 58 pack-years, and no past history. Magnetic resonance imaging revealed a tumor in the pelvis, and then he was referred to our hospital. Chest computed tomography detected a nodule in the left upper lobe, and a diagnosis of lung adenocarcinoma (cT1cN1M1c Stage IVb) was made by needle biopsy of a tumor in the pelvis. No driver mutation was detected using next-generation sequencing, and the tumor proportion score of programmed death ligand-1 expression was determined to be 30%-39% using the 22C3 antibody.

After radiotherapy (36 Gy) for bone metastasis, combined therapy with carboplatin plus pemetrexed plus pembrolizumab was initiated. Although the tumor response was good, normocytic and normochromic anemia (Hb: 6.1 g/dl) was noted after two cycles of the treatment. Cytotoxic agents were

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*Key Words:* Anemia, lung cancer, myelodysplasia syndrome, pembrolizumab.



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discontinued because they were suspected to cause myelosuppression. However, anemia persisted during the following three cycles of pembrolizumab monotherapy, requiring repeated red blood cell transfusion. There was no evidence of iron deficiency, folate or vitamin deficiency, hemolytic anemia, or parvovirus infection (parvovirus B19 IgM: negative). Chest computed tomography and upper gastrointestinal endoscopy revealed no findings, suggesting thymoma or gastrointestinal bleeding. Pembrolizumab was discontinued because immune-related anemia could not be excluded, and a bone marrow biopsy was performed. The bone marrow biopsy revealed erythroid blast hypoplasia with no obvious abnormalities in other blood cells, increased blast cells, and cancer cells (Figure 1). Based on these findings, a diagnosis of pure red cell aplasia was made, but myelodysplastic syndrome was also suspected because a chromosomal abnormality was detected by bone marrow biopsy (45, dic (15;18) (p11.2; p11.2) [15]/46, XY [5]).

We considered the efficacy of steroid therapy because pure red cell aplasia may have been induced by immune-related mechanisms based on the treatment history with an ICI-containing regimen. Treatment with 60 mg/day (1 mg/kg/day) of prednisolone was initiated, anemia improved, and no further red blood cell transfusions were required four days after the initiation of steroid therapy. Prednisolone was reduced to 25 mg/day, and no recurrence of anemia was observed. Although pembrolizumab therapy was not resumed considering the risk of irAEs, the progression of lung cancer was not observed.

## Discussion

We reported a case with lung adenocarcinoma, presenting with pure red cell aplasia and chromosomal abnormality during treatment with an ICI-containing regimen. It was necessary to discriminate this diagnosis from myelosuppression because the patient had received combined therapy with cytotoxic agents plus pembrolizumab. Furthermore, myelodysplasia syndrome was suspected owing to the chromosomal abnormality and treatment history of chemotherapy and radiation. A marked improvement was observed after the initiation of prednisolone (1 mg/kg/day).

The association between pure red cell aplasia and chromosomal abnormality is complicated. Although a case with idiopathic pure red cell aplasia presenting chromosomal abnormality was reported, pure red cell aplasia can onset as a prodrome of myelodysplastic syndrome (2), and cases with myelodysplastic syndrome with pure red cell aplasia have been reported (3). Myelodysplastic syndrome with pure red cell aplasia has two distinct phenotypes. One shows increased blasts in the bone marrow, and anemia may be caused by a defect of maturation and proliferation of erythroid precursors, as a part of myelodysplastic syndrome. The other shows no

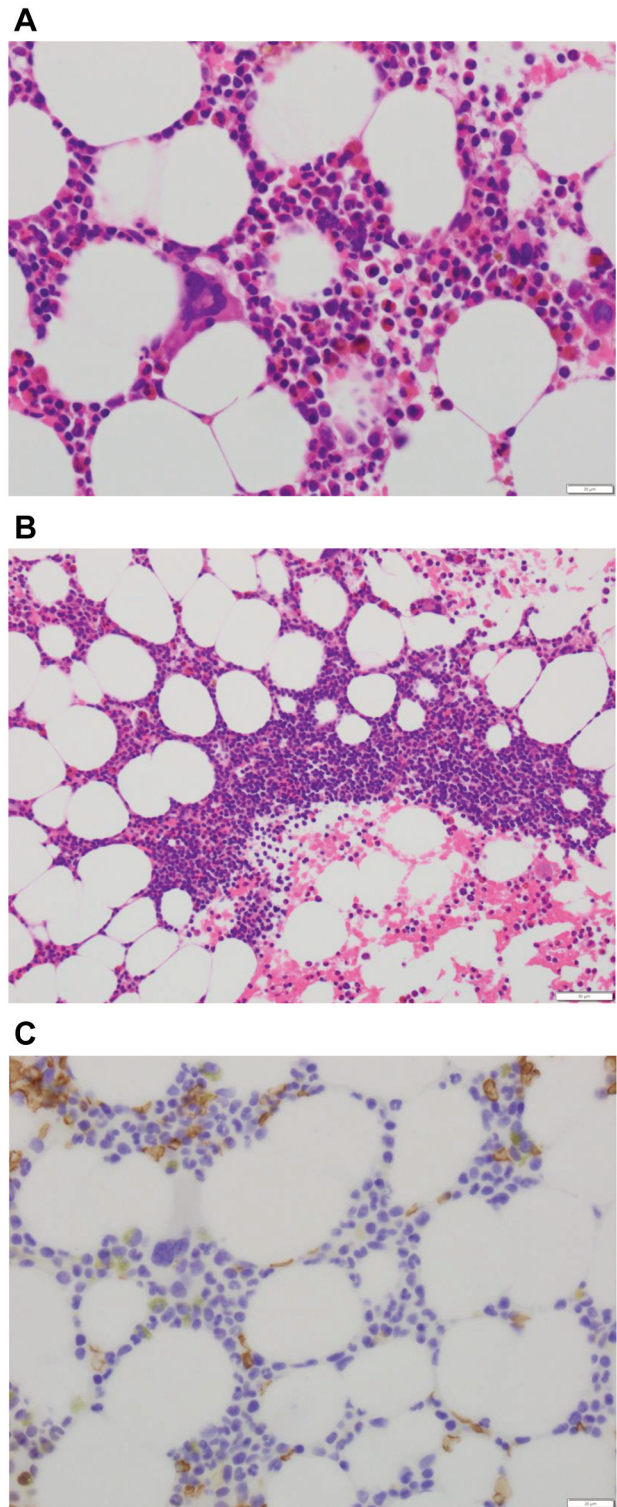


Figure 1. Micrographs of the bone marrow trephine biopsy. A) Normoplastic bone marrow. Erythroblasts are severely reduced, erythroblast islands are absent, and hematopoietic foci are dominated by granulocytes. B) A cluster of lymphocytes can be seen, suggesting an immunological mechanism. C) Few erythroblasts are found to be positive for glycophorin A. Most of the glycophorin A-positive cells are red blood cells.

blastic changes in the bone marrow, and an immunogenic mechanism is proposed because of the good response to immune suppressive therapy (3). In the present case, an immunogenic mechanism was likely associated with the onset of pure red cell aplasia, given the good response to steroid therapy, and we believe that ICI therapy induced the pathology of anemia. However, the possibility that chromosomal abnormality resulted from chemotherapy or radiation therapy cannot be excluded.

It has been reported that anemia of all grades and grades 3-4 were observed in 11% and 5.4% of patients treated with ICIs, respectively (4). Additionally, pure red cell aplasia was reported in 4 of the 118 patients who showed hematologic irAEs (5), which suggests that ICI-induced pure red cell aplasia is rare. However, pure red cell aplasia is considered an important adverse event of ICI therapy because it can result in severe anemia and affect the prognosis of patients.

Although steroids are commonly used for the treatment of patients showing hematologic irAEs, including hemolytic anemia, aplastic anemia, or thrombocytopenia, resistance to steroid therapy has been reported in 20% of the patients (5). Pure red cell aplasia induced by ICI therapy was reported in three patients with melanoma (5-7) and one patient with Hodgkin lymphoma (8). Among these four patients, three patients showed favorable responses to steroid therapy but one patient required additional intravenous immunoglobulin therapy because the anemia was not improved by steroid therapy. Furthermore, of the three patients showing an initial response to steroids, two patients required additional intravenous immunoglobulin therapy due to the recurrence of anemia. These previous reports suggest the efficacy of immunoglobulin therapy for pure red aplasia induced by ICI therapy.

## Conclusion

Combined therapy with platinum doublet plus ICIs has improved the overall survival of patients with NSCLC (1) and is considered a major therapeutic option. However, combined therapies can increase the risk of adverse events. It is not always easy to identify the cause of anemia because a variety of conditions, including myelosuppression, chronic inflammation, or tumor-related bleeding, may be associated with anemia and observed during the combined therapy. Although hematologic irAEs can worsen the prognosis, a response to steroid therapy may be expected. Overall, careful evaluation and appropriate treatment are required for managing anemia observed during ICI therapy.

## Conflicts of Interest

The Authors declare no competing financial interests or personal relationships in relation to this report.

## Authors' Contributions

TH, MI, SM, MH, NT, KH, ZS, KT, CT, SO, KK, SI, TM, and RH contributed to the treatment of the patient with NSCLC. TS contributed to the diagnosis and treatment of pure red cell aplasia. ST and AN contributed to the pathological diagnosis. TH and MI wrote the original draft of the manuscript, and all Authors contributed to reviewing and editing the manuscript.

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*Received February 8, 2024*

*Revised March 7, 2024*

*Accepted March 8, 2024*