



# Marked, Lasting Disease Regression and Concomitantly Induced Autoimmune Hemolytic Anemia and Hemophagocytic Lymphohistiocytosis in a Patient With Lung Adenocarcinoma and Autoantibodies Receiving Atezolizumab Plus Chemotherapy: A Case Report

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## ABSTRACT

Various immune-related adverse events can frequently occur, which may be life-threatening if programmed death 1 or its ligand is blocked. Here, we report a rare case of concomitant autoimmune hemolytic anemia and hemophagocytic lymphohistiocytosis caused by atezolizumab plus chemotherapy in a patient with lung adenocarcinoma and autoantibodies. Dramatic and lasting tumor regression in response to only one therapy cycle was achieved. Nevertheless, this case suggests that careful management is required when using immunotherapy in patients with autoantibodies.

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**Keywords:** Immune checkpoint inhibitors; Lung cancer; Autoimmune hemolytic anemia; Hemophagocytic lymphohistiocytosis; Case report

## Introduction

Immune-related adverse events (irAEs) caused by immune checkpoint inhibitors (ICIs) that target

programmed death 1 and its ligand (programmed death-ligand 1 [PD-L1]) have been widely reported in patients with cancer. Although there are few hematologic irAE reports owing to their rarity, these AEs can be lethal, and improving knowledge on the clinical course, treatment, and outcomes is warranted to improve patient management. Here, we report a rare case of combined autoimmune hemolytic anemia (AIHA) and hemophagocytic lymphohistiocytosis (HLH) in a patient with metastatic lung adenocarcinoma and positive blood test

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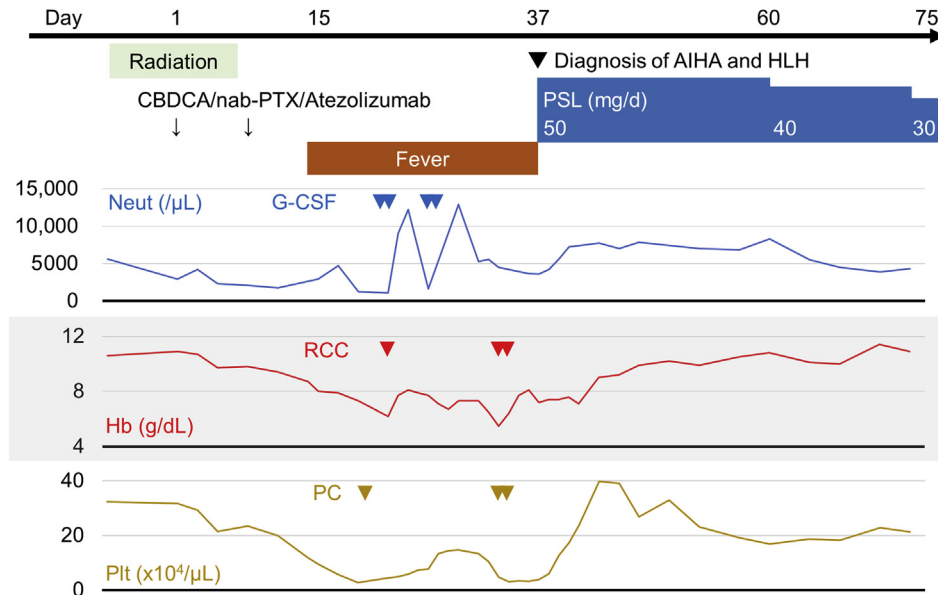
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**Figure 1.** Timeline of the clinical course of the patient. AIHA, autoimmune hemolytic anemia; CBDCA, carboplatin; G-CSF, granulocyte colony-stimulating factor; Hb, hemoglobin; HLH, hemophagocytic lymphohistiocytosis; nab-PTX, nab-paclitaxel; Neut, neutrophils; PC, platelet concentrates; Plt, platelet; PSL, prednisolone; RCC, red cell concentrates.

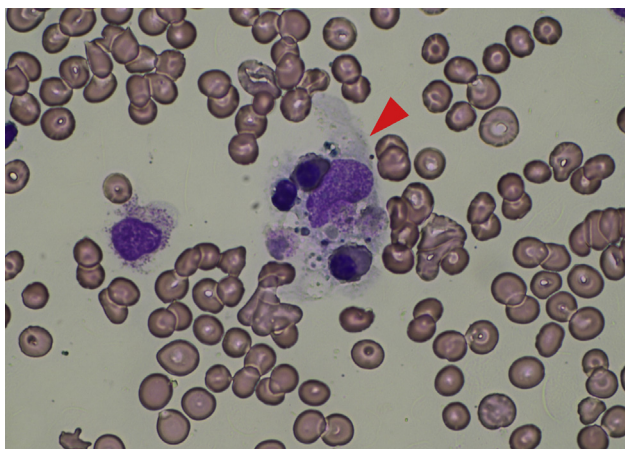
results for autoantibodies that emerged during treatment with anti-PD-L1 antibody, atezolizumab, plus chemotherapy. Despite the severe irAEs, a marked and lasting response was observed, although therapy was discontinued during the first cycle owing to the irAEs.

## Case Presentation

A 65-year-old woman with a 40 pack-year smoking history was diagnosed with having poorly differentiated lung adenocarcinoma metastasizing in the right axillary lymph nodes, thyroid, liver, left adrenal gland, lumbar vertebra, and left iliac bone (T1bN0M1c, stage IVB) on the basis of histologic examinations of the right axillary lymph node and thyroid biopsy samples. The OncoPrint Dx Target Test identified no targetable oncogenic driver mutations. The PD-L1 tumor proportion score was 1% to 10% (PD-L1 22C3 immunohistochemistry assay). With palliative radiation therapy targeting the lumbar metastasis (total dose, 30 Gy), treatment with atezolizumab plus carboplatin and nab-paclitaxel was initiated. Although a routinely performed blood test before treatment to comprehensively identify autoantibodies detected an antinuclear antibody (titers of 1:160 with homogeneous pattern; 1:160 with speckled pattern; and 1:80 with nucleolar pattern) and an antidouble-strand DNA antibody at 17 IU/mL, there was no evidence of connective tissue disease, which allowed the careful use of atezolizumab. As illustrated in [Figure 1](#), persisting pancytopenia (grade 3 decreased neutrophil count, grade 3 anemia, and grade 3 decreased platelet count, in

accordance with the Common Terminology Criteria for Adverse Events version 5.0) accompanied by fever occurred, and nab-paclitaxel administration was interrupted on day 15. Although a granulocyte colony-stimulating factor and antibiotics were administered, the neutrophil counts of the patient increased only temporarily, and her fever did not resolve. Furthermore, 2 U of red blood cell concentrate was infused on days 22, 33, and 34 and 10 U of platelet concentrate was infused on days 20, 33, and 34, with little effect. AIHA was diagnosed on the basis of a positive direct antiglobulin test result with immunoglobulin G and C3d along with a low haptoglobin value ( $<10$  mg/dL).

In addition, a bone marrow aspiration test was performed on day 29 to evaluate the cause of persistent neutropenia and thrombocytopenia, which revealed hemophagocytosis ([Fig. 2](#)). The laboratory data revealed a low fibrinogen value (185 mg/dL) and high values of triglyceride (225 mg/dL), ferritin (14,101 ng/mL), aspartate aminotransferase (334 IU/L), and soluble interleukin-2 receptor (2147 U/mL). The test results for Epstein-Barr virus and cytomegalovirus were negative. On the basis of these data, the prolonged fever, and splenomegaly, the patient was also diagnosed with having HLH with a HScore of 284 indicating the probability of HLH greater than 99%.<sup>1</sup> Treatment with prednisolone 1 mg/kg/d was initiated on day 37. The fever and the general condition of the patient rapidly improved, and the blood cell counts gradually increased. The prednisolone dose was incrementally decreased, and the patient was discharged on day 75. Although no



**Figure 2.** Bone marrow smear using May-Giemsa stain. A hemophagocytic macrophage is indicated by the arrowhead. Original magnification  $\times 1000$ .

additional immunotherapy or chemotherapy against lung adenocarcinoma was administered, the primary and metastatic tumors exhibited marked and durable responses lasting for 8 months after starting the therapy (Fig. 3A and B).

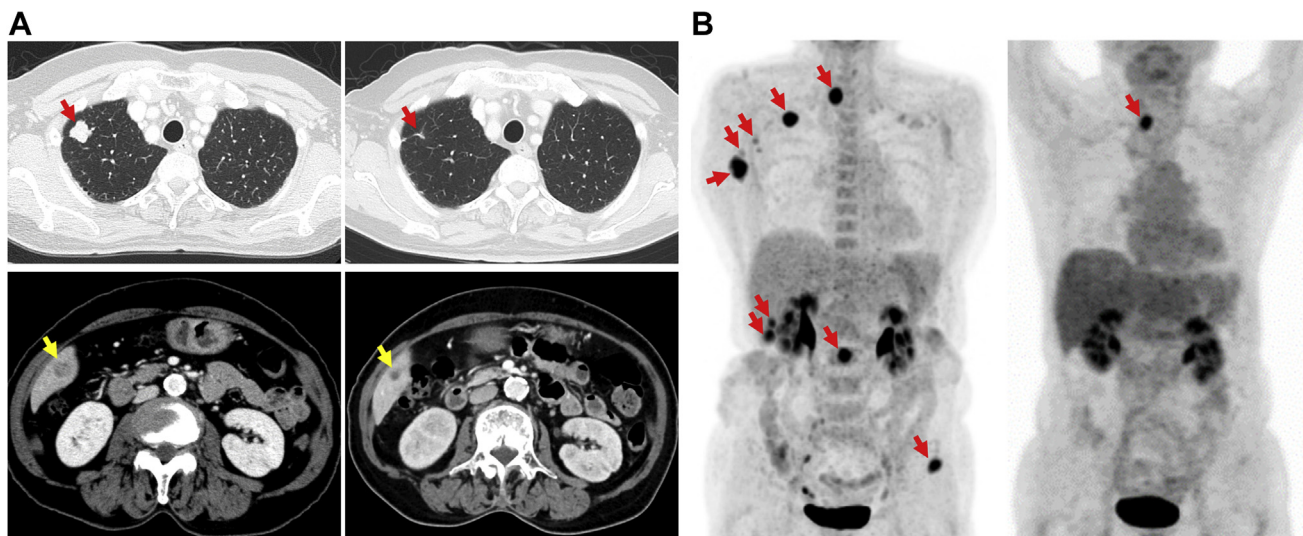
## Discussion

Here, we present a rare case of combined AIHA and HLH that emerged during treatment for metastatic lung adenocarcinoma using atezolizumab plus platinum-

doublet chemotherapy. To the best of our knowledge, there are no published reports of cytotoxic chemotherapy-induced combined AIHA and HLH; there is only one such reported case that was caused by programmed death 1 blockade.<sup>2</sup> In addition, AIHA<sup>3</sup> and HLH<sup>4</sup> have been separately reported as irAEs of ICIs. Therefore, the hematologic irAEs that were observed in the present case were likely to be attributed to atezolizumab.

HLH as an irAE is lethal; 23% of patients with this irAE die, even if they receive treatment.<sup>4</sup> In addition, HLH can worsen rapidly. Therefore, early diagnosis and treatment are desirable. Nevertheless, recent combined therapies using cytotoxic chemotherapy and immunotherapy may delay the diagnosis, highlighting the importance of careful and active surveillance of patients who are treated with ICIs when rare but lethal irAEs along with common AEs are taken into account.

Autoantibody presence might be associated with a higher rate of irAEs and possibly better survival outcomes in patients with NSCLC and solid-organ cancers who are treated with ICIs.<sup>5,6</sup> This is consistent with the severe irAEs and marked, durable response that we observed in our patient after only one cycle of atezolizumab. Nevertheless, the autoantibody type and levels that are associated with ICI safety and efficacy remain unknown. This unmet clinical need should be addressed in future studies.



**Figure 3.** Tumor responses to one cycle of atezolizumab plus chemotherapy. (A) Computed tomography revealing the primary lung lesion in the right upper lobe (indicated by red arrows) and a metastatic lesion in the liver (indicated by yellow arrows) before (left) and 2 months after (right) administration of atezolizumab plus chemotherapy, which was terminated during the first treatment cycle. (B) Coronal FDG PET image at the time of diagnosis revealing increased tumor uptake at the thyroid, right lung, right axillary lymph node, liver, lumbar vertebra, and left iliac bone (red arrows; left). Follow-up FDG PET 7 months after initiation of atezolizumab plus chemotherapy revealing remarkable reduction of FDG uptake in the primary and metastatic lesions (right). Only FDG uptake at the thyroid metastasis remains highly detectable (red arrow). FDG, fluorodeoxyglucose; PET, positron emission tomography.

## Conclusion

ICI-induced hematologic toxicity is rare, and additional clinical data are needed. ICI use in patients with autoantibodies should be carefully considered after evaluating the risks and benefits, and careful management is needed to improve care for patients who are treated with ICIs.

## CRedit Authorship Contribution Statement

**Yoshinari Endo:** Conceptualization, Data curation, Visualization, Writing—original draft preparation.

**Yusuke Inoue:** Conceptualization, Visualization, Writing—original draft preparation, Writing—review and editing, Supervision.

**Masato Karayama, Yasuyuki Nagata, Hironao Hozumi, Yuzo Suzuki, Kazuki Furuhashi, Noriyuki Enomoto, Tomoyuki Fujisawa, Yutaro Nakamura, Naoki Inui, Takafumi Suda:** Validation, Writing—review and editing, Supervision.

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