

[CASE REPORT]

Development of Acute Adult T-cell Leukemia Following PD-1 Blockade Therapy for Lung Cancer

Kyohei Misawa¹, Hajime Yasuda², Hironari Matsuda³, Munechika Hara³, Tomonori Ochiai²,
Daisuke Koyama⁴, Hina Takano¹, Noriaki Iwao¹ and Michiaki Koike¹

Abstract:

Immune checkpoint inhibitors (ICIs) are widely used for the treatment of various cancers. However, paradoxical exacerbation of neoplasms, referred to as “hyperprogressive disease,” has been reported in a proportion of patients treated with anti-programmed cell death-1 (PD-1)/PD-1 ligand (PD-L1) blockade. We herein report a case of acute adult T-cell leukemia (ATL) that developed shortly after the administration of nivolumab, a PD-1 inhibitor, to treat non-small-cell lung cancer. There were no signs of ATL before the administration of nivolumab, and seropositivity for human T-cell leukemia virus type-1 (HTLV-1) was confirmed after the development of acute ATL. We speculate that nivolumab likely contributed to the development of acute ATL.

Key words: adult T cell leukemia/lymphoma, immune checkpoint inhibitors, nivolumab, hyperprogressive disease, human T-cell leukemia virus-1

(Intern Med 61: 3421-3424, 2022)

(DOI: 10.2169/internalmedicine.9405-22)

Introduction

Cancer is a leading cause of death worldwide. Treatment of cancer has evolved greatly, and T-cell immune checkpoint inhibitors (ICIs) targeting a wide range of cancers are a major recent breakthrough therapy (1, 2). In Japan, ICIs, including anti-programmed cell death-1 (PD-1)/PD-1 ligand (PD-L1) inhibitors and anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitors, are approved for treatment of a number of cancers, such as lung cancer, esophageal cancer, malignant melanoma and Hodgkin lymphoma. However, while impressive survival benefits have been reported with the use of ICIs, adverse effects due to excessive immune activation (3) and paradoxical acceleration of tumor growth have been reported by several groups (4-8). These adverse effects influence the treatment outcome, so the early recognition and appropriate management are extremely important.

T-cells are key players in tumor immunity. Cancer cells expressing PD-L1 can impair the T-cell function through

PD-1/PD-L1 interactions, which can lead to tumorigenesis; therefore, PD-1/PD-L1 blockade can be effective in a wide range of cancers. However, the effects of PD-1 blockade on T-cell malignancies may be complicated, as the targeted T-cells are the origin of the neoplasms. Clinical trials have demonstrated anti-tumor effects in a proportion of patients with T-cell lymphomas (9-11). Multiple clinical trials treating adult T-cell leukemia (ATL) with ICIs exist (8, 12), and three cases showing paradoxical exacerbation of ATL following PD-1 blockade therapy have been reported (8). Therefore, the efficacy and safety of ICIs for ATL remain unclear.

Nivolumab, a major PD-1 inhibitor, is an effective treatment option for refractory/relapsed classic Hodgkin lymphoma (13). We herein report a non-small-cell lung cancer (NSCLC) patient who developed acute ATL following administration of nivolumab.

¹Department of Hematology, Juntendo University Shizuoka Hospital, Japan, ²Department of Hematology, Juntendo University Graduate School of Medicine, Japan, ³Department of Respiratory Medicine, Juntendo University Shizuoka Hospital, Japan and ⁴Department of Hematology, Fukushima Medical University, Japan

Received for publication January 17, 2022; Accepted for publication March 1, 2022

Correspondence to Kyohei Misawa, kmisawa@juntendo.ac.jp

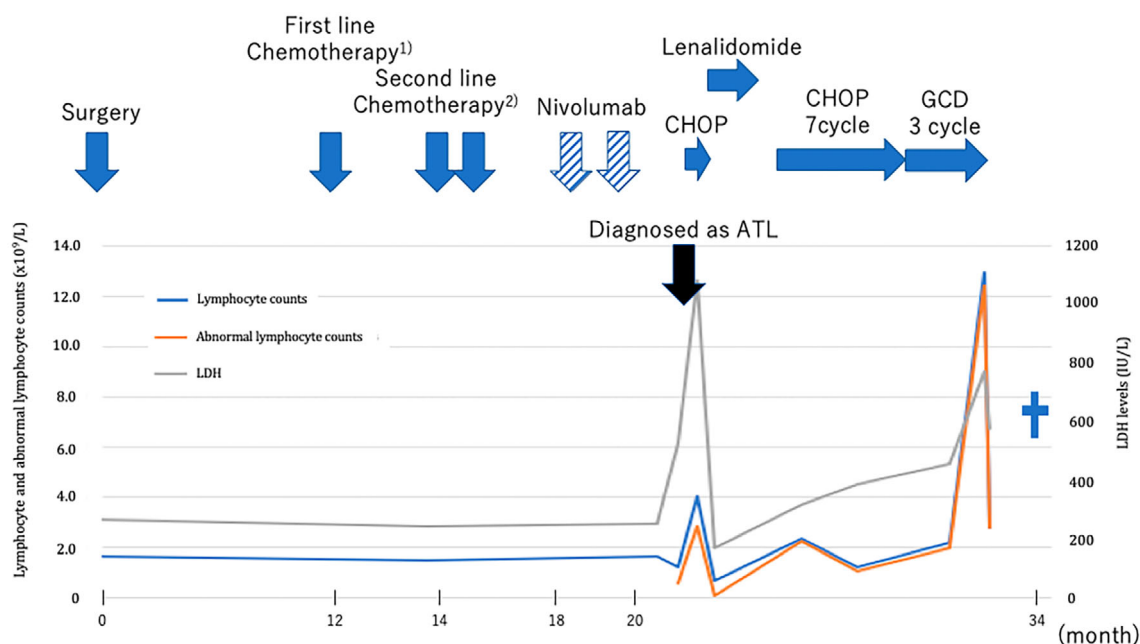


Figure. Clinical course of our patient who developed adult T-cell leukemia (ATL) following Nivolumab therapy. 1) Combination chemotherapy of carboplatin, tegafur, gimeracil, and oteracil potassium for non-small-cell lung cancer (NSCLC). 2) Combination chemotherapy of docetaxel and ramucirumab for NSCLC.

Case Report

A 65-year-old Japanese woman underwent upper lobectomy for stage I NSCLC, which showed weak expression of PD-L1. She had no history of medical illness or blood transfusions and no family history of leukemia. Before lobectomy, her white blood cell (WBC) count had been within the normal range with normal lymphocyte counts ($1.4 \times 10^9/L$).

One year after lobectomy, the lung cancer relapsed, and she received combination chemotherapy of carboplatin, tegafur, gimeracil, and oteracil potassium, but treatment could not be continued due to severe skin rash. Treatment was changed to combination chemotherapy containing docetaxel and ramucirumab. After two courses, she developed severe bacterial pneumonia, which led to treatment suspension. Transient thrombocytopenia was observed after each course of chemotherapy, but lymphocyte counts remained normal (1.0 - $2.0 \times 10^9/L$). Four months later, a progression of the lung cancer was observed, and nivolumab was chosen as the third-line treatment. After the second injection of nivolumab, an abrupt rise in lactate dehydrogenase (LDH) levels and abnormally large lymphocytes with convoluted nuclei and flower cells became apparent in the peripheral blood. The lung cancer showed no change, but the third injection was suspended because thrombocytopenia persisted.

Laboratory findings showed a WBC count of $3.8 \times 10^9/L$, and the WBC differential showed that the proportions of normal and abnormal lymphocytes were 27% and 26%, respectively. The hemoglobin level was 11.8 g/dL, the platelet

count was $5.6 \times 10^9/L$, the LDH level was 603 IU/L, and the soluble interleukin 2 (IL-2) receptor level was 13,962 IU/mL. Anti-human T-cell leukemia virus type-1 (HTLV-1) antibody analyzed by the particle agglutination method was positive, showing a high titer of over 8,192. A bone marrow evaluation revealed abnormal lymphocytes with an immunophenotype positive for CD4 and negative for CD8 with a dim expression of CD25 on flow cytometry. General lymphadenopathy, skin rash, hepatosplenomegaly, and hypercalcemia were absent. Although the demonstration of monoclonal integration of HTLV-1 proviral DNA through a Southern blot analysis was not carried out, acute ATL was diagnosed based on a constellation of the aforementioned clinical and pathological findings. CHOP therapy (cyclophosphamide, doxorubicin, vincristine and prednisone, 21-day cycle) was initiated, and a partial response was observed, but she opted for other treatment methods. The patient's ATL was positive for CC chemokine receptor 4 (CCR4), and treatment with mogamulizumab was proposed, but she refused due to personal reasons. Therefore, treatment was altered from CHOP to lenalidomide monotherapy. Two months later, she developed severe respiratory failure, and because lenalidomide could not be ruled out as the cause, CHOP therapy was resumed upon consent from the patient. An additional seven courses of CHOP therapy followed by three courses of GCD therapy (gemcitabine, carboplatin, dexamethasone) were carried out. However, the disease progressed, and she ultimately died of intracerebral hemorrhaging approximately one year after the diagnosis of ATL. The clinical course of the patient is summarized in Figure.

Discussion

Previous reports have shown that inhibition of the PD-1 pathway can accelerate malignant T-cell growth under certain conditions in a mouse model (14). The underlying mechanisms for paradoxical exacerbations of cancers after PD-1/PD-L1 blockade are unknown but are referred to by some authors as “hyperprogressive disease.”

Acute ATL developed immediately after nivolumab treatment for NSCLC in the present case. There were no signs of ATL before nivolumab treatment, and these findings along with reports from others suggest that nivolumab likely contributed to the development of acute ATL. Ramucirumab, a monoclonal antibody directed towards vascular endothelial cell growth factor receptor 2, is known to enhance the anti-tumor effects of PD-1 inhibitors (15). Therefore, the administration of ramucirumab sequentially to nivolumab may have further contributed to the development of acute ATL in the present case (16). A rheumatoid arthritis patient was previously reported to have developed a chronic type of ATL that diminished after cessation of methotrexate and infliximab, but no other drugs have been confirmed to evoke the onset of acute ATL thus far (17). The development of ATL following nivolumab administration may be an underrecognized event, as HTLV-1-positivity is restricted to certain regions of the world.

ATL is a subtype of T-cell lymphoma triggered by HTLV-1 infection. Only 2.5% to 4.0% of HTLV-1 asymptomatic carriers (ACs) progress to ATL, with most remaining ACs throughout their life (18). Although the virus-encoded Tax and HTLV-1 bZIP factor proteins are thought to play major roles in ATL pathogenesis, HTLV-1 infection alone is insufficient for oncogenesis. Additional genetic modifications are needed to cause progression to ATL, which typically occurs decades after the initial HTLV-1 infection. The role of PD-1 in the development of ATL is not fully elucidated. Although the significance is unknown, 26% of ATL patients have been reported to have *PDCD1* mutations (14). Other reports have shown a tendency toward a poor overall survival (OS) in patients with neoplastic PD-L1 expression, while PD-L1 expression in non-malignant stromal cells was reported to be associated with a better OS (19). PD-1/PD-L1 blockade may affect not only malignant but also non-malignant bystanders, so the decision to administer these drugs to ATL patients should be carefully considered.

The percentage of abnormal lymphocytes in the peripheral blood required to meet the criteria of smoldering ATL is a mere 5% (20). Therefore, distinguishing ACs from those with smoldering ATL among HTLV-1-infected populations is difficult, and overlapping cases may exist (21, 22). Furthermore, smoldering ATL patients may be underdiagnosed, as the automatic analyzers frequently used for the WBC differential analysis in real-world practice often fail to detect the small numbers of abnormal lymphocytes that can be found by microscopic examinations. An automatic analyzer was

also used to obtain WBC differentials in the present case, so the patient having had smoldering ATL before nivolumab administration cannot be ruled out. Therefore, whether this patient developed acute ATL from smoldering ATL or from being an AC is unclear. In a previous report, 67 NSCLC patients were tested for HTLV-1 antibodies, and 3 (4.5%) of these individuals were found to be HTLV-1 ACs. These three patients were treated with PD-1 inhibitors for lung cancer but did not show progression to ATL or development of other HTLV-1-associated diseases (23). In contrast, another report described a case of rapid progression of ATL after nivolumab administration in three patients, one of whom progressed from smoldering ATL to acute ATL (8). Though the detailed analysis of these cases revealed no unifying pathophysiology, the authors speculated that rapid expansion of the ATL cells reflected an unanticipated loss of ATL suppression triggered by PD-1 blockade (24). Similar to these cases, our patient likely progressed to acute ATL due to Nivolumab administration. However, because our study is a report of a single patient, the possibility that acute ATL developed coincidentally at the timing of nivolumab administration must also be considered.

Immunotherapy including PD-1 inhibition has shown remarkable efficacy in cancer patients. However, hyperprogressive disease may occur in a proportion of cases, and those with an HTLV-1 AC status or smoldering ATL may be at risk of developing acute ATL. Thus, screening for HTLV-1 before treatment with ICIs may be useful for identifying patients at risk of acute ATL development, and consultations with a hematologist beforehand are advised in patients who are seropositive for HTLV-1.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We thank the members of the Department of Hematology, Juntendo University School of Medicine, for encouraging this study.

References

1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* **12**: 252-264, 2012.
2. Sharma P, Allison JP. The future of immune checkpoint therapy. *Science* **348**: 56-61, 2015.
3. Zhong L, Wu Q, Chen F, Liu J, Xie X. Immune-related adverse events: promising predictors for efficacy of immune checkpoint inhibitors. *Cancer Immunol Immunother* **70**: 2559-2576, 2021.
4. Karabajakian A, Garrivier T, Crozes C, et al. Hyperprogression and impact of tumor growth kinetics after PD1/PDL1 inhibition in head and neck squamous cell carcinoma. *Oncotarget* **11**: 1618-1628, 2020.
5. Kobari Y, Kondo T, Takagi T, Omae K, Nakazawa H, Tanabe K. Rapid progressive disease after nivolumab therapy in three patients with metastatic renal cell carcinoma. *In Vivo* **31**: 769-771, 2017.
6. Sama S, Hadfield MJ, Lopetegui Lia N, Vredenburg J. Hyperprogression in PDL1 expressive, recurrent gastroesophageal-junction adenocarcinoma after pembrolizumab. *Cureus* **11**: e4862, 2019.
7. Yamaguchi K, Tsuchihashi K, Tsuji K, et al. Prominent PD-L1-

- positive M2 macrophage infiltration in gastric cancer with hyperprogression after anti-PD-1 therapy: a case report. *Medicine (Baltimore)* **100**: e25773, 2021.
8. Ratner L, Waldmann TA, Janakiram M, Brammer JE. Rapid progression of adult T-cell leukemia-lymphoma after PD-1 inhibitor therapy. *N Engl J Med* **378**: 1947-1948, 2018.
 9. Lesokhin AM, Ansell SM, Armand P, et al. Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. *J Clin Oncol* **34**: 2698-2704, 2016.
 10. Barta SK, Zain J, MacFarlane AW 4th, et al. Phase II study of the PD-1 inhibitor pembrolizumab for the treatment of relapsed or refractory mature T-cell lymphoma. *Clin Lymphoma Myeloma Leuk* **19**: 356-364 e3, 2019.
 11. Bennani NN, Pederson LD, Atherton P, et al. A phase II study of nivolumab in patients with relapsed or refractory peripheral T-cell lymphoma. *Blood* **134**: 467, 2019.
 12. Ishitsuka K, Utsunomiya A, Ishida T. PD-1 inhibitor therapy in adult T-cell leukemia-lymphoma. *N Engl J Med* **379**: 695, 2018.
 13. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med* **372**: 311-319, 2015.
 14. Wartewig T, Kurgys Z, Keppler S, et al. PD-1 is a haploinsufficient suppressor of T cell lymphomagenesis. *Nature* **552**: 121-125, 2017.
 15. Yasuda S, Sho M, Yamato I, et al. Simultaneous blockade of programmed death 1 and vascular endothelial growth factor receptor 2 (VEGFR2) induces synergistic anti-tumour effect *in vivo*. *Clin Exp Immunol* **172**: 500-506, 2013.
 16. Molife C, Hess LM, Cui ZL, et al. Sequential therapy with ramucirumab and/or checkpoint inhibitors for non-small-cell lung cancer in routine practice. *Future Oncol* **15**: 2915-2931, 2019.
 17. Hashiba Y, Hidaka T, Umekita K, et al. Remission of chronic type ATL in a patient with rheumatoid arthritis after withdrawing methotrexate and infliximab combination therapy: a case report. *Mod Rheumatol Case Rep* **2**: 9-13, 2018.
 18. Gessain A, Cassar O. Epidemiological aspects and world distribution of HTLV-1 infection. *Front Microbiol* **3**: 388, 2012.
 19. Miyoshi H, Kiyasu J, Kato T, et al. PD-L1 expression on neoplastic or stromal cells is respectively a poor or good prognostic factor for adult T-cell leukemia/lymphoma. *Blood* **128**: 1374-1381, 2016.
 20. Ishitsuka K, Tamura K. Human T-cell leukaemia virus type I and adult T-cell leukaemia-lymphoma. *Lancet Oncol* **15**: e517-e526, 2014.
 21. Kobayashi S, Watanabe E, Ishigaki T, et al. Advanced human T-cell leukemia virus type 1 carriers and early-stage indolent adult T-cell leukemia-lymphoma are indistinguishable based on CADM1 positivity in flow cytometry. *Cancer Sci* **106**: 598-603, 2015.
 22. Kamihira S, Iwanaga M, Doi Y, et al. Heterogeneity in clonal nature in the smoldering subtype of adult T-cell leukemia: continuity from carrier status to smoldering ATL. *Int J Hematol* **95**: 399-408, 2012.
 23. Yoneshima Y, Kato K, Minami H, et al. HTLV-1 seropositive patients with lung cancer treated with PD-1 inhibitors. *Cancer Sci* **111**: 3395-3396, 2020.
 24. Rauch DA, Conlon KC, Janakiram M, et al. Rapid progression of adult T-cell leukemia/lymphoma as tumor-infiltrating Tregs after PD-1 blockade. *Blood* **134**: 1406-1414, 2019.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).