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Case Report

Case report of durable responders to sintilimab plus second-line chemotherapy in relapsed/refractory angioimmunoblastic T-cell lymphoma

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Abstract: Angioimmunoblastic T-cell lymphoma (AITL) is a highly aggressive lymphoma characterized by complex and unique clinicopathological and biological features, as well as a generally poor prognosis. First-line treatment typically consists of anthracycline-based chemotherapy regimens, yet the long-term outcomes remains unsatisfactory, with most patients eventually experiencing disease progression. For patients with relapsed/refractory (R/R) AITL, standard treatment options are limited, and enrollment in clinical trials is often prioritized in practice. Here, we report two cases of R/R AITL patients who received sintilimab combined with second-line chemotherapy after prior chemotherapy failure and achieved sustained disease remission. As of now, one patient had a progression-free survival (PFS) of nearly 2 years before succumbing to a non-tumor-related cause. The other patient continues to survive well, with a PFS of over 4 years. These cases suggest that the combination of immune checkpoint inhibitor and chemotherapy may represent a promising treatment option for selected R/R AITL patients, offering notable efficacy and controllable safety.

Keywords: Angioimmunoblastic T-cell lymphoma, immune checkpoint inhibitor, sintilimab, chemotherapy, progression-free survival, case report

Introduction

Angioimmunoblastic T-cell lymphoma (AITL), a highly aggressive lymphoma originated from germinal-center T follicular helper (Tfh) cells, represents one of the most common subtypes of peripheral T-cell lymphoma (PTCL) [1]. It is more common in the elderly, with invasive courses, unique clinicopathological features and complex biological characteristics [2].

Anthracycline-containing regimens, including cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens, have been widely used as the frontline treatment for AITL. However, the 5-year overall survival (OS) remains poor at only 30-40%, with most patients experiencing disease progression after approximately 12 months of progression-free survival (PFS). For those relapsed/refractory (R/R) AITL, there is currently no well-established standard treatments, and clinical trials are usually considered the preferred option. The median PFS and OS of R/R AITL reported historically was 3.8 to 5.2 months and 6 to 12 months, respectively. These data urgently need to be improved.

Here, we report two R/R AITL patients who received immune checkpoint inhibitor (ICI) combined with second-line chemotherapy and achieved long-lasting disease control after the failure of previous CHOP chemotherapy. We present the cases in accordance with the CARE reporting checklist.

Cases presentation

Basic details of case one

A patient presented to the hospital with enlarged cervical lymph nodes in July 2020. Color Doppler ultrasound indicated multiple enlarged lymph nodes with diminished internal echoes and loss of corticomedullary differentiation in the IB, II, III, IV, V and VII draining regions

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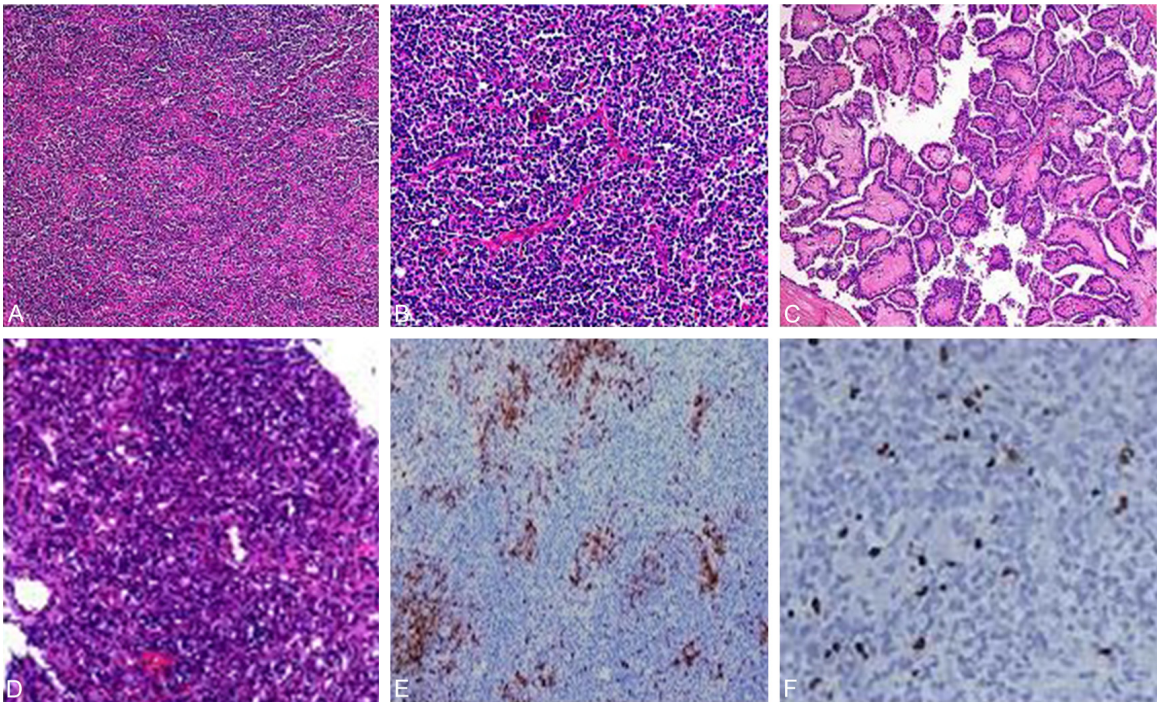

Figure 1. Representative pathological images of case one (A-C) and case two (D-F). (A, B) HE staining of the lymph nodes in the left cervical IV region under light microscopy. IHC results: Tumor cells CD3 (+), CD10 (focal +), Bcl-6 (+), CXCL13 (focal +), PD-1 (+), Bcl-2 (+), CD5 (+), CD20 (-), CD21 (irregular FDC network +), CD23 (irregular FDC network +), Pax-5 (-), Cyclin-D1 (-), SOX-11 (-), IgD (-); Plasma cells MUM-1 (-); Ki67 LI: approximately 60%. In situ hybridization: EBER (individual cells +). (C) The right lobe and isthmus of the thyroid gland were classic papillary thyroid carcinoma. (D) HE staining of cervical lymph nodes observed under light microscopy indicated non-Hodgkin's lymphoma. IHC suggested AITL. IHC results: MUM-1 (-), CD20 (-), CD3 (+), Pax-5 (-), CD5 (+), CD23 (irregular hyperplasia of FDC), CD21 (irregular hyperplasia of FDC), CD15 (-), CD30 (-), PD-1 (+), Bcl-6 (-), Bcl-2 (+), CXCL13 (+); Ki67 (+, LI approximately 70%), Cyclin-D1 (-). (E) CD10 (partial +). (F) EBER in situ hybridization (+). AITL, angioimmunoblastic T-cell lymphoma; FDC, follicular dendritic cell; HE, hematoxylin-eosin; IHC, immunohistochemistry; LI, labeling index.

of the left neck. Then cervical lymph node dissection, total right thyroidectomy and partial left thyroidectomy were performed on October 9, 2020. The postoperative pathological results showed that the cervical lymph nodes were non-Hodgkin's T-cell lymphoma (**Figure 1A**, **1B**). Combined with the immunohistochemical (IHC) indicators (**Table 1**), it was consistent with AITL. The right lobe and isthmus of the thyroid gland were classic papillary thyroid carcinoma (**Figure 1C**).

From October 2020 to February 2021, the patient received 6 cycles of CHOP chemotherapy and maintained a no-evidence-of-disease (NED) status for a considerable period. A positron emission tomography-computed tomography (PETCT) performed on March 23, 2021 showed that the metabolic activity of lymphoma infiltrating foci had been completely inhibited after treatment. Subsequently, involved site radiation therapy was performed in 28 fractionations with a total dose of 50.4 Gy in clinical target volume from March 2021 to May 2021. In November 2021, follow-up computed tomography (CT) and PETCT images indicated the progression of the disease (**Figure 2A**). Then the patient received 6 cycles of GDP (gemcitabine, cisplatin, dexamethasone) chemotherapy combined with sintilimab from November 2021 to March 2022, with the best response of complete response (CR). Sintilimab continued to be used regularly as consolidation therapy, and the patient remained in a NED state with a good quality of life. Unfortunately, on October 30, 2023, the patient suffered an accidental trauma and passed away three days later. The entire clinical course was shown in **Figure 2B**.

Basic details of case two

A patient experienced unexplained fever and severe lower back pain, prompting the visit to hospital in May 2021. Ultrasound indicated

Table 1. Summary of the patient's baseline characteristics

Case	Sex	Age (year)	ECOG PS	Luganostage[a]	B symptoms[b]	IPI score[c]	LDH (U/L)	IHC											Prior treatment
								Bcl-2	Bcl-6	CD10	PD-1	CXCL13	Ki67	CD3	CD5	CD20	Pax-5	CD30	
1	Male	58	1	II	-	0	184	+	+	Focal +	+	Focal +	60%	+	+	-	-	-	CHOP +ISRT
2	Male	70	1	IIIS	+	3	452	+	-	Partial +	+	+	70%	+	+	-	-	-	CHOP

[a]2014 Lugano stage standard; [c]the standard IPI, comprising: age ≥60 years, stages III to IV disease, LDH > normal (120-250 U/L), extranodal sites (ENSs) > one, and ECOG PS ≥2; [b]B symptoms comprising: unexplained fever (body temperature >38°C and lasting for more than 3 days), excessive night sweats (soaking clothes), and weight loss of more than 10% within 6 months. Bcl-2/-6, B-cell lymphoma-2/-6; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CXCL13, C-X-C motif chemokine ligand 13; ECOG PS, Eastern Cooperative Oncology Group performance status; GDP, gemcitabine/dexamethasone/cisplatin; ISRT, involved site radiation therapy; IHC, immunohistochemistry; IPI, international prognostic index; LDH, lactate dehydrogenase; Pax-5, paired box-5; PD-1, programmed cell death-1; S, splenic (infiltration).

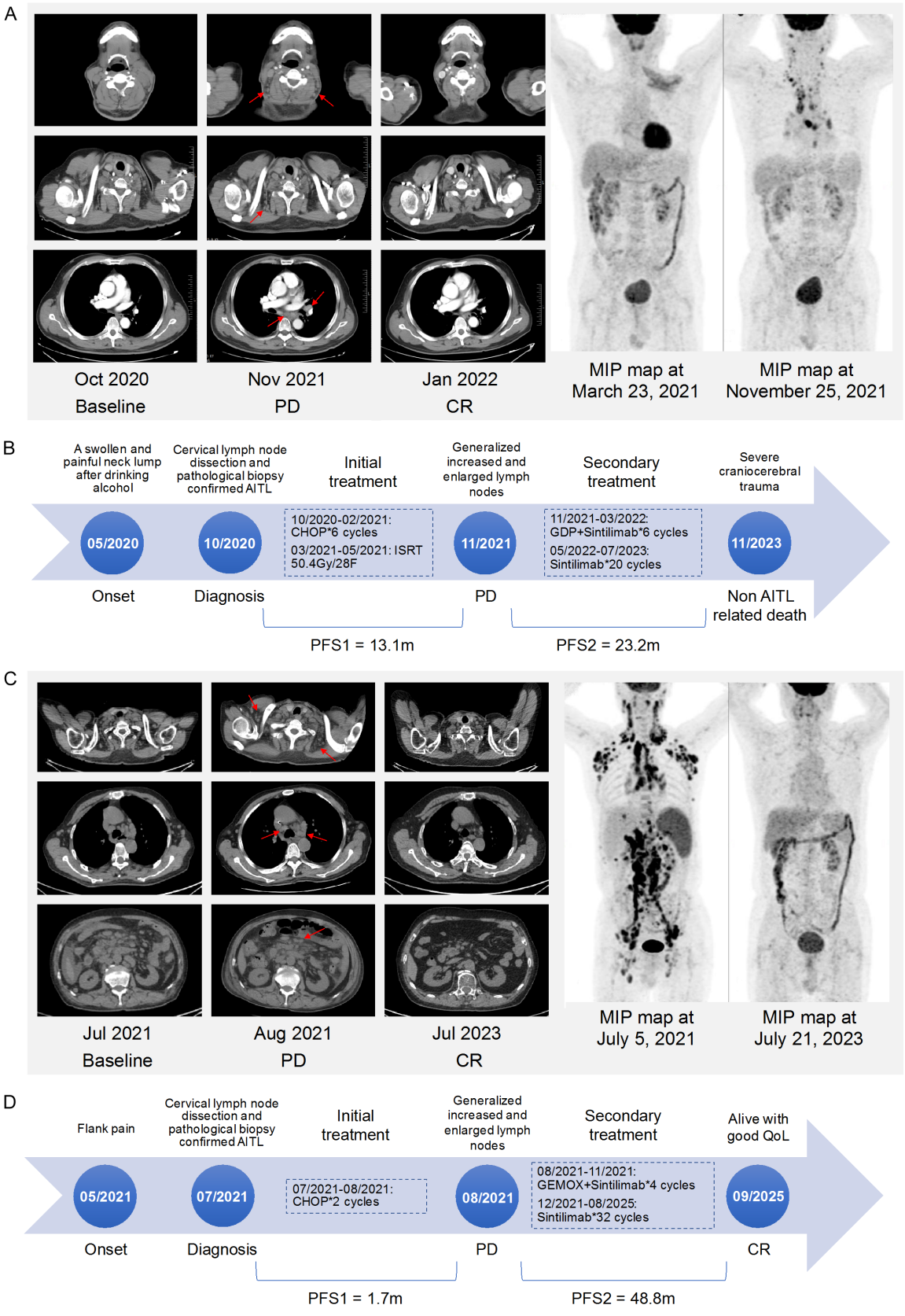

Figure 2. Representative images and timeline of case one (A, B) and case two (C, D). AITL, angioimmunoblastic T-cell lymphoma; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CR, complete response; CT, computed

tomography; GDP, gemcitabine/dexamethasone/cisplatin; GEMOX, gemcitabine/oxaliplatin; ISRT, involved site radiation therapy; MIP, maximum intensity projection; PETCT, positron emission tomography-computed tomography; PD, disease progression; PFS, progression-free survival; QoL, quality of life. The red arrows indicate the main recurrent and/or metastatic lesions. The CT images were shown on the left, and the PETCT images were on the right.

enlarged lymph nodes in the supraclavicular, axillary, and inguinal regions. Subsequent CT and PETCT suggested that these lymph nodes may be malignant lymphoma (**Figure 2C**). The pathology and IHC of cervical lymph node puncture confirmed AITL (**Figure 1D-F** and **Table 1**). The patient received CHOP chemotherapy in July 2021. After two cycles of chemotherapy, the CT imaging indicated an increase and enlargement of multiple lymph nodes throughout the body. Disease progression was evaluated in August 2021 (**Figure 2C**). Thereafter, the patient received 4 cycles of GEMOX (gemcitabine, oxaliplatin) chemotherapy combined with sintilimab, with the best response of CR. Since December 2021, 32 cycles of sintilimab monotherapy have been continuously administered as consolidation treatment. The entire treatment timeline was shown in **Figure 2D**. During the second-line treatment, no unexpected adverse events (AEs) occurred. The patient tolerated the treatment well and had no serious AEs.

Discussion

The introduction of ICI has significantly improved the clinical efficacy of many solid tumors, such as lung cancer and hepatocellular carcinoma [3, 4]. However, the application of ICI in hematologic malignancies is still mostly at exploratory stage [5].

Data on ICI in AITL was also limited, and the reported outcomes varied considerably. A small-sample exploratory study showed favorable efficacy in 9 patients with R/R AITL treated with 5-azacytidine combined with nivolumab, with an overall response rate (ORR) of 78% [6]. A phase Ib study reported an ORR of 40% using nivolumab in 5 R/R PTCL patients [7]. While, another study observed modest clinical activity of nivolumab in 12 patients with R/R PTCL, including 6 AITL [8]. Additionally, due to the hyperprogression and short duration of response in one-third of the cases (mainly AITL), the researcher halted the study. These disparate research results may be related to the complexity and heterogeneity of the tumor microenvironment (TME) of AITL.

One point that has gradually been recognized is that AITL is both a neoplastic disease and an inflammatory disease, characterized by an intricate TME, primarily composed of diverse immune cells, stromal components and cytokines [9]. It is reported that 80% to 90% of neoplastic Tfh cells in AITL express programmed cell death-1 (PD-1) [2]. Additionally, immunoblasts infected with epstein-barr virus (EBV) upregulate the expression of programmed death ligand-1 (PD-L1). The extensive expression of PD-1 and PD-L1 contributes to a powerful immunosuppressive TME, which dampens the activity of effector T cells and shields neoplastic Tfh cells from immune surveillance. Therefore, blocking the PD-1/PD-L1 axis may be a potential therapeutic option for AITL.

Here, we report our experience in two cases of R/R AITL. After the combination of ICI and second-line chemotherapy, both patients achieved durable disease control, with PFS ranging from 24 to 48 months. However, PD-1 monotherapy often demonstrates limited efficacy in an immunosuppressive TME. The survival benefits observed in these two patients may therefore be attributed to the synergistic anti-tumor effect of ICI and chemotherapy. In addition to the cytotoxic effects of directly inducing apoptosis of tumor cells, chemotherapy has also been reported to enhance immune response by up-regulating the expression of major histocompatibility complex class I (MHC-I) molecules and promoting the maturation of antigen-presenting cells [10]. Obviously, more in-depth exploration is necessary.

The study has certain limitations. The unavailability of patients' tumor tissues and peripheral blood - including genetic and immune cell profiling, as well as the expression of PD-L1 - prevented us from exploring potential correlations between gene mutations or changes in immune cell components and the response to ICI-based therapy. Although our results indicate that ICI combined with chemotherapy has potential feasibility in R/R AITL, it is important to note that these findings are based on two separate cases. Therefore, these outcomes should be interpreted with caution until further supported by more robust evidence.

Conclusions

This study identified that ICI combined with chemotherapy may be a valuable treatment option for some R/R AITL patients after front-line chemotherapy failure. More studies are needed to verify these findings.

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Disclosure of conflict of interest

None.

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