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Case Report

Development of angioimmunoblastic T-cell lymphoma after treatment of diffuse large B-cell lymphoma: a case report and review of literature

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Abstract: Cases of diffuse large B-cell lymphoma (DLBCL) arising after the initial diagnosis of angioimmunoblastic T-cell lymphoma (AITL) and DLBCL synchronous with AITL have been reported. To date, there is no report on the subsequent development of AITL in patients with DLBCL. Here we presented a rare case of AITL developing six months after the initial diagnosis of DLBCL. In order to investigate the clinical and molecular features of patients with AITL and DLBCL, we also reviewed the literature on AITL patients developing DLBCL, and patients with composite AITL and DLBCL.

Keywords: Angioimmunoblastic T-cell lymphoma, diffuse large B-cell lymphoma, composite lymphoma

Introduction

Second lymphoma different from the original lymphoma and composite lymphoma with distinct morphologic types of lymphoma have attracted interest of hematologists and hematopathologists since the diagnosis of either disease is often difficult to confirm and the prognosis varies among these patients. A few cases of diffuse large B-cell lymphoma (DLBCL) arising in patients with angioimmunoblastic T-cell lymphoma (AITL) have been reported [1-8], and a review of the literature showed a small number of patients with composite AITL and DLBCL [9-11]. So far, there is no report on the subsequent development of AITL in patients with DLBCL.

Development of second lymphoma might be caused by chronic antigenic stimulation such as virus infection and genetic changes resulted from chemotherapy [12]. It is well-known that patients with AITL suffer from immunodeficiencies that might lead to Epstein-Barr virus (EBV)-associated B-cells malignant transformation [9]. Likewise, it is proposed that composite lymphomas may arise from pluripotent cells with the ability to differentiate into B-cell and T-cell neoplasms simultaneously, due to either genetic predisposition or prior exposure to specific therapies or mutagens [13].

Here, we present a rare case of AITL arising six months after the initial diagnosis of DLBCL. We also summarize the clonal rearrangements of *immunoglobulin (IgH)* gene *and T-cell receptor (TCR)* genes, Epstein-Barr virus encoded RNAs (EBERs) analysis, and clinical outcome of AITL patients developing DLBCL and patients with composite AITL and DLBCL.

Case presentation

A 73-year-old man with multiple enlarged lymph nodes in the neck, mandible, and inguinal areas was admitted to our hospital in April 2012. He had received treatment for tuberculosis infection and was recovered in 2011. Positron emission tomography and computed tomography of the whole body disclosed generalized lymphadenopathy in the neck, mandible, axillae, chest, and inguinal areas with mild splenomegaly. Presenting complete blood count and chemistries including hemoglobin and total bilirubin

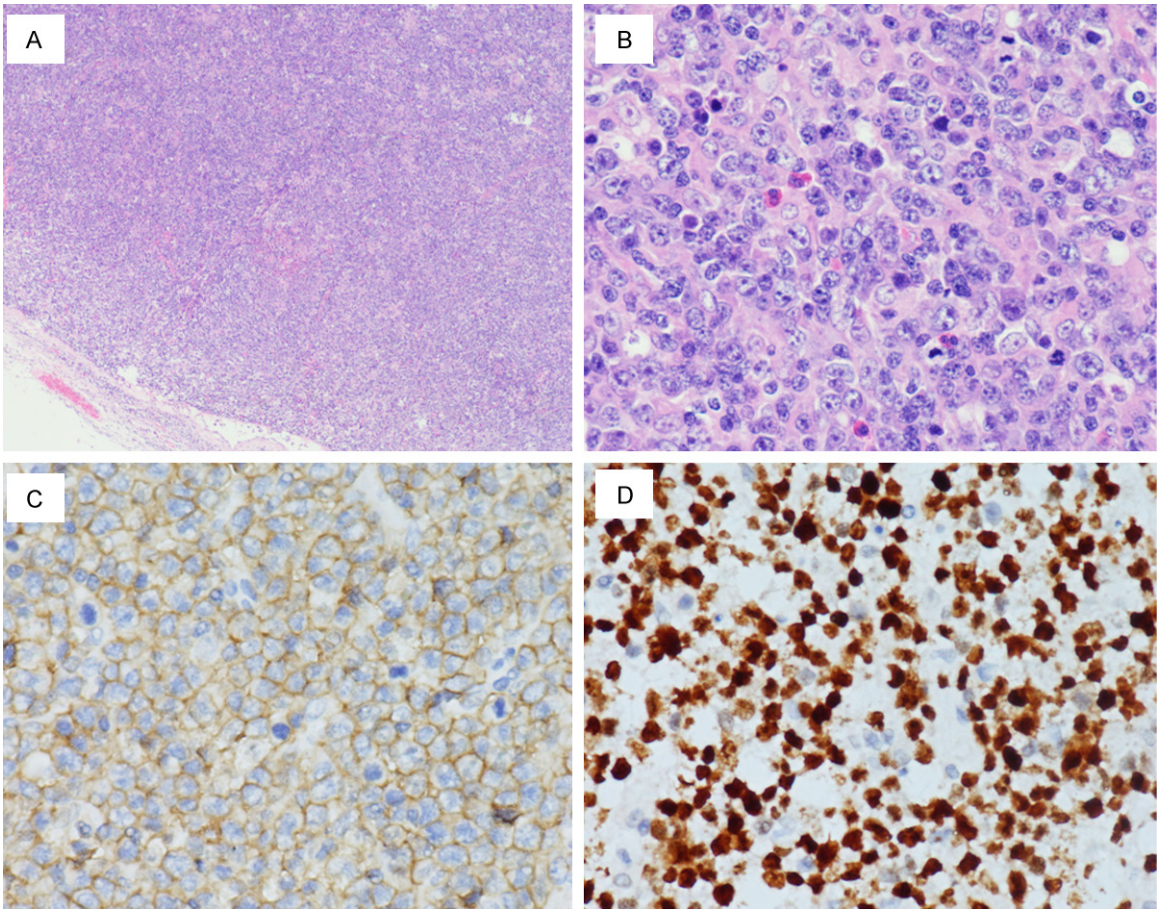

Figure 1. Lymph node biopsy showing morphological (A & B) and immunohistochemical findings with positivity for CD20 (C) and Ki67 (D).

were within normal limits. Biopsies of an enlarged right submandibular lymph node and one enlarged lymph node from inguinal areas revealed the same diagnosis consistent with DLBCL. The nodal architecture was partly effaced by a diffuse proliferation of large sized atypical lymphoid cells (**Figure 1A** and **1B**, H&E, hematoxylin and eosin). Immunohistochemical staining patterns demonstrated the atypical lymphoid cells expressed CD20 (**Figure 1C**) with a high proliferation rate measured by Ki67 (**Figure 1D**), but were negative for CD3, CD5, CD7, CD15, CD30, BCL-6, MuM1, TdT, ALK, TIA-1, cyclin D1, CD21, CD23, BCL-2, LCA, GrB, and CD56 (not shown). An in situ hybridization study for EBER and serological evaluation of EBV DNA were also negative. Polymerase chain reaction (PCR) analysis of *IgH* gene and *TCR* gene identified no clonal rearrangements (not shown).

After finishing one cycle of cyclophosphamide, pirarubicin, vindesine, and dexamethasone followed by five cycles of rituximab, cyclophosphamide, pirarubicin, vindesine and dexamethasone, the patient did not achieve complete remission and enlargement of the lymph nodes in the mediastinum demonstrated by computed tomography scan confirmed disease progression in September 2012. The patient failed to respond to the salvage regimen R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin). In October 2012, a biopsy of an enlarged left submandibular lymph node was performed, and to our surprise, it revealed AITL. The lymph node contained a prominent proliferation of high endothelial venules and diffuse infiltration of a mixed population of eosinophils, neutrophils, plasma cells, and medium to small sized atypical lymphoid cells (**Figure 2A** and **2B**, H&E). The atypical lymphoid cells were positive for CD2 (**Figure 2C**), CD3 (**Figure 2D**), and CD45RO (**Figure 2E**). CD23 staining indicated residual follicular dendritic cell (**Figure 2F**). A diagnosis of AITL was established. Clonal rear-

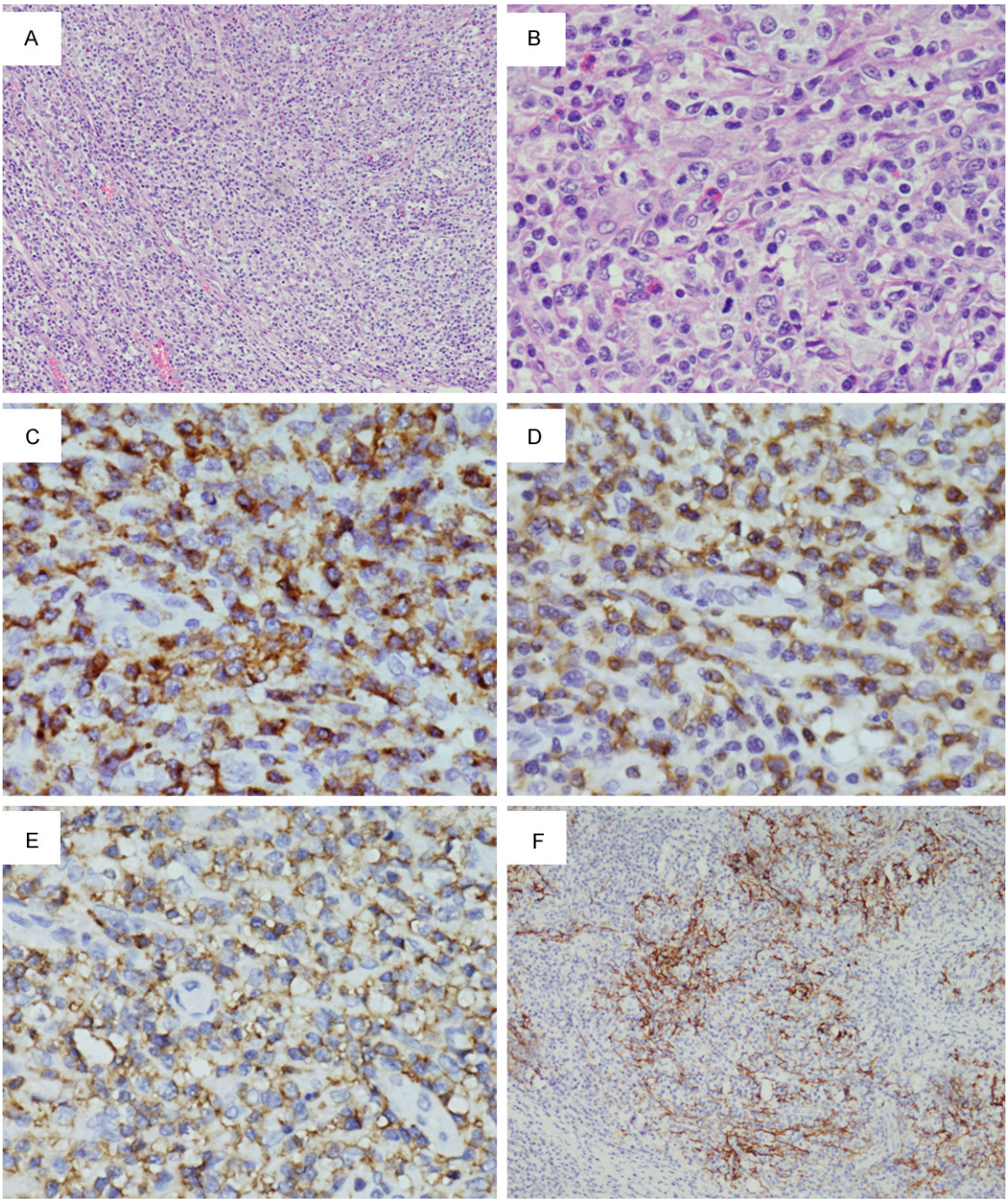

Figure 2. Lymph node biopsy showing morphological (A & B) and immunohistochemical findings with positivity for CD2 (C), CD3 (D), and CD45RO (E) and CD23 (F).

rangements of *IgH* gene and *TCR* gene were not found (not shown).

Since the patient no longer responded to the conventional regimens used in DLBCL and was diagnosed with AITL, he proceeded to the regimen of gemcitabine, lobaplatin, and L-asparaginase. Approximately one week after the completion of chemotherapy, the patient returned with enlarging lymph nodes, rash, and fever. In spite of various treatments including thalidomide and pemetrexed, the patient deteriorated rapidly with decreased hemoglobin and platelets. Creatinine was within normal lim-

Table 1. Summary of DLBCL developing after the initial diagnosis of AITL

Case No.	Diagnosis	Time to follow-up diagnosis (M)	Biopsy site	IgH	TCR	EBER-ISH	Treatment	Outcome	Ref
1	AITL		LN	ND	ND	ND	Observation	Spontaneous remission	[1]
	DLBCL	34	Soft tissue	+	-	+	Glucocorticoids	Died, 4 month	
2	AITL		LN	-	+	+	CC; BMT	CR	[1]
	DLBCL	29	LN	OC	-	+	CC; Radiation	CR	
	DLBCL	39	LN	NA	NA	NA	CC	Died, 3 month	
3	AITL		Left groin and left chest	-	+	-	NA	NA	[2]
	DLBCL	56		+	-	+	multi-CT	Respond temporily Died, 53 month	
4	AITL		NA	OC	+	+	CHOP/ESHAP/autoSCT	Remission, 1 month	[3]
	DLBCL	NA	NA	OC	NA	-	R	Remission 1 year	
5	AITL		LN	N/Amp	N/Amp	ND	CHOP	CR	[4]
	AITL	20	LN	-	+	ND	ESHAP/A-BMT	PR	
	AITL	22	BM	N/Amp	N/Amp	+	ESHAP	NR	
	DLBCL	24	BM	N/Amp	N/Amp	+	NA	NR	
6	AITL		LN	-	+	+	CHOP	CR	[4]
	AITL+DLBCL	8	LN	+	+	+	ECHOP	NR	
7	AITL		LN	NA	NA	NA	P	PR	[4]
	DLBCL	8	LN	+	+	+	Multi-CT	CR	
	AITL	15	LN	-	OC	NA	Multi-CT	PR, AWD 68 month	
8	AITL		LN	+	+	NA	NA	CR	[4]
	DLBCL	84	LN	+	-	+	NA	NA	
9	AITL		LN	NA	NA	NA	multi-CT-R	CR	[4]
	DLBCL	8	LN	NA	NA	-	Multi-CT-R	CR, A&W 24 month	
10	AITL		LN BM	-	NA	NA	Multi-CT-ALEM	CR,	[5]
	DLBCL	11	Mucosa of the duodenal	+	NA	NA	Supportive	Died, 2 week	
11	AITL		Left inguinal lymph node	-	+	-	THP-COP, CHASE	Symptoms improved	[6]
	DLBCL	23	Ileal	+	-	+	No	Died, 2 month	
12	AITL		Inguinal and cervical (Fine-needle aspiration cytology)	NA	NA	NA	FED, autoSCT	NA	[7]
	DLBCL	13	Cervical and supraclavicular	+	NA	NA	R-CHOP, alloSCT	CR	
13	AITL		Left inguinal	-	+	+	IHOP, radiotherapy	CRu	[8]
	DLBCL	47	Left neck	+	-	+	CHOP	NR	
	DLBCL+AITL	NA	BM	-	-	NA	RCHOP	PR, discharge	

AITL, angioimmunoblastic T-cell lymphoma; alloSCT, allogeneic stem cell transplantation; autoSCT, autologous stem cell transplantation; A-BMT, autologous bone marrow transplant; ALEM, alemtuzumab; A&W, alive and well; AWD, alive with disease; BM, bone marrow; CC, combination chemotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CHASE, cyclophosphamide, cytarabine, etoposide and dexamethasone; CR, complete remission; DLBCL, diffuse large B-cell lymphoma; EBER-ISH, Epstein-Barr virus encoded RNA in situ hybridization; ECHOP, etoposide, cyclophosphamide, doxorubicin, vincristine, and prednisone; ESHAP, etoposide, methyl prednisolone, cytarabine and cisplatin; FED, fludarabine, cyclophosphamide, dexamethasone; IHOP, ifosfamide, doxorubicin, vincristine, and prednisone; IgH, immunoglobulin heavy chain gene rearrangement; LN, lymph node; multi-CT, multiagent chemotherapy; NA, not available; N/Amp, not amplifiable; ND, not done; NR, no response; OC, oligoclonal; PR, partial response; R, rituximab; TCR, T-cell receptor rearrangement; THP-COP, pirarubicin, cyclophosphamide, vincristine, prednisolone.

Table 2. Summary of composite AITL and DLBCL

Case No.	Biopsy site	IgH	TCR	EBER-ISH	Treatment	Outcome	Ref
1	left side of the neck	-	+	+	6 cycle CHOP	CR, relapsed a few month later	[9]
					ESHAP, autoSCT	NA	
2	left cervical	-	+	+	No	Sudden death	[10]
3	LN	-	+	-	Thal	CR AWD 12 month	[4]
4	LN	+	+	+	ECHOP	NR	[4]
5	LN	ND	ND	-	R-THP-COP	CR, alive 13 month	[11]
6	LN	S*+	S+	+	CHOP	CR, alive 3 month	[11]
7	LN	ND	ND	ND	NA	NA	[11]
8	LN	S+	S+	+	NA	Dead 2 month	[11]
9	LN	S+	S+	+	NA	Dead 3 month	[11]
10	LN	S+	S-	+	R-THP-COP	CR, alive 1 month	[11]
11	LN	S+	S+	+	R-THP-COP	PR, dead 2 month	[11]
12	LN	S-	S+	+	CHOP+Ra	CR, alive 12 month	[11]
13	LN	+	+	+	NA	Dead 2 month	[11]
14	LN	+	+	-	R-CHOP	CR, alive 2 month	[11]
15	LN	+	ND	+	NA	NA	[11]
16	LN	-	+	-	NA	NA	[11]
17	LN	S+	S+	+	NA	NA	[11]
18	LN	S+	S+	+	R-CHOP	NR, dead 4 month	[11]
19	LN	S+	S+	+	NA	NA	[11]
20	LN	S+	S+	ND	NA	NA	[11]

*S indicated using southern blotting analysis, while others using PCR. AITL, angioimmunoblastic T-cell lymphoma; autoSCT, autologous stem cell transplantation; AWD, alive with disease; CR, complete remission; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; DLBCL, diffuse large B-cell lymphoma; EBER-ISH, Epstein-Barr virus encoded RNA in situ hybridization; ECHOP, etoposide, cyclophosphamide, doxorubicin, vincristine, and prednisone; ESHAP, etoposide, methyl prednisolone, cytarabine and cisplatin; IgH, immunoglobulin heavy chain gene rearrangement; LN, lymph node; ND, not done; NR, no response; PR, partial response; R, rituximab; TCR, T-cell receptor rearrangement; Thal, thalidomide; THP-COP, pirarubicin, cyclophosphamide, vincristine, prednisolone.

its, total bilirubin and indirect bilirubin were increased, and Coombs' test was positive. Eventually, the patient was complicated by hemolytic anemia and pneumonia and succumbed to his disease two months after the diagnosis of AITL at the end of December 2012.

Discussion

We described a unique case of AITL arising six months after the initial diagnosis of DLBCL. The histological features of DLBCL and AITL in the initial and follow-up biopsies were examined by hematopathologists in our hospital and other hospital. PCR analysis of *TCR gene* rearrangements performed on the initial specimen was negative, suggesting AITL is unlikely to occur synchronously with DLBCL. We postulated that immune dysregulation might impair immune surveillance in our patient, leading to the expansion of B-cell neoplasms followed by T-cell neoplasms.

So far, there is no report of second AITL arising in patients after the initial diagnosis of DLBCL, although a few patients with the initial diagnosis of AITL have been found to develop DLBCL [1-8], which is summarized in **Table 1**. Among thirteen patients documented, the time interval from the initial diagnosis of AITL to the development of DLBCL ranged from eight months to eighty-four months. Clonal (monoclonal and oligoclonal) *IgH* or *TCR* gene rearrangements was detected at the time of diagnosing DLBCL or AITL respectively, supporting the histological findings. Noticeably, case 6 and 13 developed composite AITL and DLBCL after treatment of AITL. Clonal *IgH* gene and *TCR* gene rearrangements were both positive in case 6, whereas they were both negative in case 13. As seen in **Table 1**, treatment outcome varied among these patients. Although five patients achieved complete remission (CR) after receiving treatment of second DLBCL, two cases (case 2 and

case 7) relapsed in less than ten months. However, case 4 achieved remission for one year with rituximab and two cases (case 7 and case 9) were alive after multiagent chemotherapy for over two years. During the follow-up, five patients did not survive, among which three patients died within four months after development of DLBCL.

The definition of composite lymphoma is two or more different types of non-Hodgkin's and/or Hodgkin's lymphoma that may or may not originated from the same clone and that are discovered in a single organ or tissue [14, 15]. Clonal studies and clinical outcome of twenty patients with confirmed diagnosis of composite AITL and DLBCL documented from 2002 to 2012 are summarized in **Table 2** [9-11]. Among eighteen cases with available clonal *IgH* gene rearrangements results, *IgH* was negative in 28% of cases (5/18). Among seventeen cases with available clonal *TCR* gene rearrangements results, TCR was negative in 6% of cases (1/17). As can be seen from **Table 2**, ten patients received treatment, resulting in a 70% complete response rate and a 10% partial response rate. However, the prognosis of these patients is generally poor. One patient (case 1) who achieved complete remission after six cycles of CHOP relapsed a few months later. Two patients (case 4 and case 18) did not respond to CHOP-based therapy. Among eleven patients with available treatment outcome, six patients died within four months during follow-up including one patient (case 11) who achieved partial response and one patients (case 18) who failed to respond to R-CHOP.

EBV infection is considered to play a vital role in contributing to the development of DLBCL in AITL patients because of immunodeficiency [9]. However, EBER and serological evaluation of EBV DNA were both negative in the present case, suggesting EBV infection might not be involved in the DLBCL development in our patient. EBV-negative DLBCL is documented in a few cases [5, 11, 16]. As summarized in **Table 1**, in eleven cases of second DLBCL after initial diagnosis of AITL with available EBER results, EBV-negative DLBCL was found in 18% of cases (2/11). As for composite AITL and DLBCL with available EBER results summarized in **Table 2**, EBER was not detected in 19% of cases (3/16). Further studies are needed to find out the possible underlying infection in our case.

Indeed, in the present case, it is possible that both diagnostic lymph nodes from the neck and inguinal areas obtained at the initial diagnosis happened to be the lesion of DLBCL. Other biopsy sites such as spleen might show typical AITL. Nevertheless, it is clinically impractical to biopsy all the enlarged lymph nodes to confirm the diagnosis.

Of note, it was only after the treatment of gemcitabine and pemetrexed did the patient develop hemolytic anemia with positive Coombs' test. At that time, drug-induced hemolytic anemia was suspected. Although cytarabine, cisplatin, and gemcitabine have been reported to cause drug-induced hemolytic anemia, the Coombs' test should be negative [17], which is not in accordance with our patient. Pemetrexed has been reported to cause immune hemolytic anemia with positive Coombs' test in lung cancer [18, 19]. Anti-pemetrexed antibody in patient's serum is considered to be cause of the patient's immune hemolytic anemia [18, 19]. Unfortunately, due to the sudden death of the patient, we are unable to find out whether the patient developed drug-induced hemolytic anemia or hemolytic anemia with positive Coombs' test caused by AITL.

In conclusion, we presented a rare event of AITL developing six months after the initial diagnosis of DLBCL in a patient who responded poorly to conventional treatment. The present case put emphasis on second biopsy and clonal *IgH* gene and *TCR* gene rearrangements analysis if DLBCL patients relapsed with enlarged lymph nodes to investigate the histological and molecular features of second lymphoma. It also indicated that PCR clonal analysis might fail to distinguish T cell lymphoma from B cell lymphoma in some cases, urging the need to develop other techniques to analyze the B-cell or T-cell clone. A review of the literature on patients developing DLBCL after the initial diagnosis of AITL or synchronously with AITL suggested the adverse prognosis of these patients and that novel regimens are needed to improve the clinical outcome for these patients.

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Disclosure of conflict of interest

None.

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