International Journal of
Rheumatic Diseases

International Journal of Rheumatic Diseases 2018; **21:** 93–101

ORIGINAL ARTICLE

Clinical features and outcome of lymphoma patients with pre-existing autoimmune diseases

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Abstract

Aims: Previous epidemiological studies have shown that autoimmune diseases increase the risk of lymphoma development. However, whether autoimmune diseases deteriorate the outcomes for lymphoma patients remains unclear. This study aimed to identify the clinical features of lymphoma patients with pre-existing autoimmune diseases. Whether pre-existing autoimmune diseases impacted progression-free survival (PFS) and overall survival (OS) in lymphoma patients was further investigated.

Methods: We retrospectively reviewed medical records of 913 newly diagnosed lymphoma patients from January 2008 to November 2016. Thirty-four lymphoma patients with pre-existing autoimmune disorders were identified. Six of these 34 patients were lost to follow-up; their data was used to examine baseline clinical characteristics but not survival. Therefore, 28 lymphoma patients with autoimmune diseases were included in the autoimmune disease group for comparing the remission rate, PFS and OS to lymphoma patients without autoimmune diseases (control group; $n = 56$).

Results: Diffuse large B-cell lymphoma was the most common histological subtype (18/34; 52.94%). Complete remission rates in the autoimmune disease and control groups were 72.0% and 83.3%, respectively ($P = 0.178$). Patients with and without autoimmune diseases had similar PFS (45.4 ± 59.9 months *vs.* 51.5 ± 42.8 months; $P = 0.398$) and OS (46.4 ± 52.6 months *vs.* 50.1 ± 47.3 months; $P = 0.352$). By univariate analysis, pre-existing autoimmune diseases were not associated with inferior PFS ($P = 0.326$) or OS ($P = 0.627$).

Conclusions: Lymphoma patients with and without autoimmune disorders had comparable outcomes. Autoimmune diseases are not an obstacle to lymphoma treatment.

Key words: autoimmune disease, lymphoma, outcome, overall survival, progression-free survival.

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INTRODUCTION

Malignant lymphoma is the most common hematological malignancy, accounting for 3.37% of all cancers.[1] In 2016, around 13 600 malignant lymphomas were expected to be diagnosed in the USA.[2] Malignant lymphoma is histologically classified into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). The World Health Organization further categorizes both HL and NHL into various subtypes according to morphology, immunophenotype and molecular features.[3]

The precise pathophysiology of malignant lymphoma is not clear. Immunodeficiency has been shown to be partially responsible for lymphoma development. One example comes from solid organ transplant recipients. Liver transplant recipients have a higher incidence of NHL than the general population.[4] Infection is another possible etiology. The correlation between Epstein–Barr virus infection and Burkitt[5] or natural killer/T cell lymphoma[6] is well established. Moreover, *Helicobacter pylori* eradication is now the standard of care for *H. pylori*-positive gastric marginal zone lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma).[7] In addition to immunodeficiency and infection, autoimmune diseases are considered to be a risk factor for malignant lymphoma.

Compared to the general population, patients with Sjögren's syndrome (SS),[8] rheumatoid arthritis (RA)[9] and systemic lupus erythematosus (SLE)[10] have two- to five-fold increased risks of malignant lymphoma. Several hypotheses for this phenomenon have been proposed. Autoimmune diseases and lymphoma may share common risk factors. Additionally, T or B cell reactivation by longstanding chronic inflammation and antigen stimulation due to autoimmune diseases can be the major predisposing factors for lymphoma.[11] The clinical features of lymphoma patients with autoimmune diseases are rarely reported. Moreover, whether autoimmune diseases affect the outcome of patients with lymphoma is largely unknown. To approach these questions, we conducted this retrospective study.

The aim of this study was to identify the clinical characteristics of lymphoma patients who had pre-existing autoimmune diseases. This study also compared the remission rate, progression-free survival (PFS), and overall survival (OS) of lymphoma patients with and without autoimmune diseases. We further used a Cox regression model to investigate if the presence of autoimmune disease was associated with inferior outcome in lymphoma patients.

PATIENTS AND METHODS

Patients

The institutional review board of the Taichung Veterans General Hospital approved this study. Because of the retrospective study design, informed consent from the study subjects was waived by the institutional review board. We retrospectively reviewed the medical records of 913 newly diagnosed lymphoma patients from January 2008 to November 2016. Among these 913 patients, 34 (3.71%; 34/913) had autoimmune diseases prior to lymphoma diagnosis. Six of these patients were lost to follow-up; their data was used to examine baseline clinical characteristics but not survival. Therefore, a total of 28 lymphoma patients with autoimmune diseases were included in the autoimmune disease group for comparing the remission rate, PFS and OS to lymphoma patients without autoimmune diseases. For this comparison, we chose double the number of enrolled lymphoma patients without autoimmune diseases to be the control group after adjusting for age, gender and histological subtypes of malignant lymphoma ($n = 56$).

Outcome measurements

We categorized treatment response as complete remission (CR), partial response, stable disease, or progressive disease by using the revised response criteria proposed by Cheson *et al.*[12] We defined PFS as the time elapsed between treatment initiation and tumor progression confirmed by either imaging studies or clinical assessments or death from any cause. OS was defined as the time between lymphoma diagnosis and patient death due to any cause or end of follow-up.

Statistical analysis

Clinical characteristic comparisons among lymphoma patients with and without autoimmune diseases were analyzed by Mann–Whitney *U*-test or Chi-square test, where appropriate. We used non-parametric tests for the intergroup comparisons as indicated to present the data (median $\pm$ interquartile range). PFS and OS between the autoimmune disease and control groups were further compared using log-rank test. Prognostic factors associated with PFS and OS were evaluated by univariate analysis. Results were considered significant at $P < 0.05$. All statistical analyses were carried out using SPSS software, version 11.5 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics

Table 1 shows the comparison of clinical characteristics between the two groups of patients. Briefly, the ages of the lymphoma patients in the autoimmune disease group and the control group were 56.5 ± 17.3 and 58.0 ± 17.8 years, respectively (median ± interquartile range; $P = 0.547$). Twenty of the 28 patients (71.4%) in the autoimmune disease group and 40 of the 56 patients (71.4%) in the control group were women ($P = 1.000$). These two groups of patients did not differ significantly regarding lymphoma stage ($P = 0.910$), histological subtype ($P = 1.000$) or performance status ($P = 0.200$).

Clinical features of lymphoma patients with autoimmune diseases

Table 2 shows the clinical characteristics of the 34 lymphoma patients who had pre-existing autoimmune diseases in our study cohort. RA was the most common autoimmune disease in our patient cohort, accounting for 11 patients (32.35%), followed by SS (eight patients, 23.52%) and SLE (seven patients, 20.59%). The majority of patients were diagnosed with B-cell lymphoma. Diffuse large B-cell lymphoma (DLBCL) was the most common histological subtype (18/34; 52.94%). The second most common subtype was MALT lymphoma, identified in five patients (5/34; 14.71%). Two patients were diagnosed with HL, and four patients were diagnosed with T-cell lymphoma. Notably, the time from diagnosis of autoimmune diseases to confirmation of lymphoma was quite heterogeneous.

Lymphoma patients with and without autoimmune diseases had similar treatment response

Three patients in the autoimmune disease group and two patients in the control group died before treatment response assessment. The overall CR rate for all patients in this study cohort was 79.7% (63/79). The CR rate was 72.0% (18/25) for patients in the autoimmune disease group and 83.3% (45/54) for patients in the control group. The CR rate of lymphoma patients with and without autoimmune disease after intention-to-cure

Table 1 Demographic comparisons among lymphoma patients with and without autoimmune diseases

	Total ($n = 84$)	Autoimmune disease group ($n = 28$)	Control group ($n = 56$)	*P*-value
Age, years, median ± IQR	58.0 ± 17.5	56.5 ± 17.3	58.0 ± 17.8	0.547†
Sex, *n* (%)				
Male	24 (28.6)	8 (28.6)	16 (28.6)	1.000‡
Female	60 (71.4)	20 (71.4)	40 (71.4)	
Ann Arbor stage, *n* (%)				
1, 2	33 (39.8)	10 (37.0)	23 (41.1)	0.910‡
3, 4	50 (60.2)	17 (63.0)	33 (58.9)	
Histological subtype, *n* (%)				
HL	6 (7.1)	2 (7.1)	4 (7.1)	1.000‡
NHL	78 (92.9)	26 (92.9)	52 (92.9)	
B cell	72 (85.7)	24 (85.7)	48 (85.7)	1.000‡
T cell	6 (24.3)	2 (24.3)	4 (24.3)	
B symptom, *n* (%)				
No	55 (65.5)	21 (75.0)	34 (60.7)	0.292‡
Yes	29 (34.5)	7 (25.0)	22 (39.3)	
ECOG performance status, *n* (%)				
0, 1, 2	60 (71.4)	17 (60.7)	43 (76.8)	0.200‡
3, 4	24 (28.6)	11 (39.3)	13 (23.2)	
Extranodal involvement, *n* (%)				
No	26 (31.0)	9 (32.1)	17 (30.4)	1.000‡
Yes	58 (69.0)	19 (67.9)	39 (69.6)	
LDH (IU/L), median ± IQR	271.0 ± 266.3	237.5 ± 181.5	295.0 ± 273.0	0.627†

IQR, interquartile range; HL, Hodgkin lymphoma; NHL, Non-Hodgkin lymphoma; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.
†Mann–Whitney *U*-test.
‡Chi-square test.

Table 2 Clinical features of lymphoma patients with autoimmune disease (n = 34)

Number	Age	Sex	AD	Lymphoma subtype	Stage	Initial treatment	Best response after initial treatment	Time from AD to lymphoma, years	Survival, days	Current status
1	33	M	AS	Hodgkin lymphoma	4	ABVD	CR	6	1218	Alive
2	48	M	RA	Hodgkin lymphoma	2	ABVD	CR	6	895	Alive
3	64	F	SS	Burkitt lymphoma	4	R-HyperCVAD	CR	Nil.	3094	Dead
4	49	F	RA	DLBCL	3	CHOP	PR	Nil.	230	Dead
5	71	F	RA	DLBCL	4	R-CVP	CR	4	2829	Alive
6	44	F	RA	MALT lymphoma	1	CEOP	CR	Nil.	2673	Alive
7	77	F	SS	DLBCL	4	No treatment	Not assessable	< 1	1	Dead
8	51	F	SLE	DLBCL	3	R-CHOP	CR	22	2339	Alive
9	61	M	Vasculitis	DLBCL	3	R-CNOP	CR	5	2484	Alive
10	67	F	RA	DLBCL	2	R-CHOP	CR	Nil.	1016	Dead
11	62	F	SS	MALT lymphoma	2	Surgery	CR	10	2189	Alive
12	63	F	Polyarthritis	DLBCL	2	R-CHOP	CR	Nil.	2044	Alive
13	51	M	Graves' disease	Low grade B-cell lymphoma	1	Radiotherapy	SD	17	2011	Alive
14	57	F	AIHA	Burkitt lymphoma	4	R+HyperCVAD	CR	< 1	1831	Alive
15	47	F	SS	MALT lymphoma	2	CVP	CR	< 1	2021	Alive
16	78	M	RA	DLBCL	3	R-CVP	SD	20	151	Dead
17	67	F	Polyarthritis	DLBCL	4	R-CHOEP	PD	Nil.	296	Dead
18	49	M	RA	Follicular lymphoma	3	R-CHOP	CR	4	1478	Alive
19	64	F	SLE	DLBCL	4	R-CEOP	PR	22	1461	Alive
20	56	F	SLE	DLBCL	2	R-CHOP	CR	35	1492	Alive
21	51	F	RA	DLBCL	4	R-CHOP	CR	9	1323	Alive
22	53	M	RA	DLBCL	4	R-CHOP	PR	6	1246	Alive
23	35	F	SLE	DLBCL	1	R-CHOP	CR	10	692	Alive
24	68	F	Dermatomyositis	DLBCL	4	R-CHOP	CR	2	774	Alive
25	58	M	Dermatomyositis	DLBCL	4	No treatment	Not assessable	9	14	Dead
26	52	F	SS	MALT lymphoma	4	Radiotherapy	PR	10	537	Alive
27	61	F	RA	DLBCL	3	R-CEOP	Lost to follow-up	Nil.	Nil.	Unknown
28	70	F	SS	DLBCL	4	R-CEOP	Lost to follow-up	Nil.	Nil.	Unknown
29	66	F	RA	Follicular lymphoma	Unknown	Nil.	Lost to follow-up	21	Nil.	Unknown
30	28	M	SS	MALT lymphoma	Unknown	Surgery	Lost to follow-up	3	Nil.	Unknown
31	45	F	SLE	Panniculitis-like T cell lymphoma	2	CVP	CR	20	2596	Alive
32	68	F	SS	Peripheral T cell lymphoma	Unknown	Surgery	Not assessable	6	0	Dead

Table 2 (continued)

Number	Age	Sex	AD	Lymphoma subtype	Stage	Initial treatment	Best response after initial treatment	Time from AD to lymphoma, years	Survival, days	Current status
33	18	M	SLE	T cell lymphoma/leukemia	4	HyperCVAD	PD	7	Nil.	Unknown
34	61	F	SLE	Peripheral T cell lymphoma	4	CVP	Lost to follow-up	15	Nil.	Unknown

M, male; F, female; AD, autoimmune disease; AS, ankylosing spondylitis; RA, rheumatoid arthritis; SS, Sjögren's syndrome; SLE, systemic lupus erythematosus; AIHA, autoimmune hemolytic anemia; DLBCL, diffuse large B cell lymphoma; MALT lymphoma, extranodal marginal zone lymphoma of the mucosa-associated lymphoid tissue; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; R, rituximab; HyperCVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate, cytarabine; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CVP, cyclophosphamide, vincristine, prednisolone; CEOP, cyclophosphamide, epirubicin, vincristine, prednisolone, CNOP, cyclophosphamide, mitoxantrone, vincristine, prednisolone; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, prednisolone; CR, complete remission; PD, progressive disease; PR, partial response; SD, stable disease.

therapies was not significantly different ($P = 0.178$) (Table 3).

Comparisons of PFS and OS among lymphoma patients with and without autoimmune diseases

The PFS of patients in the autoimmune disease group and the control group were 45.4 ± 59.9 and 51.5 ± 42.8 months, respectively (median $\pm$ interquartile range; $P = 0.398$) (Fig. 1a; $P = 0.332$ by log-rank test). The OS (presented as median $\pm$ interquartile range) of patients in the autoimmune disease group was 46.4 ± 52.6 months. The OS was 50.1 ± 47.3 months in the control group. The OS of the two groups of patients was not significantly different ($P = 0.352$) (Fig. 1b; $P = 0.626$ by log-rank test).

The presence of autoimmune disease was not associated with inferior outcome in lymphoma patients

Prognostic factors in lymphoma patients in our study cohort were investigated by Cox regression analysis. Regarding PFS, univariate analysis showed that lactate dehydrogenase $\geq$ 240 IU/L ($P = 0.018$), presence of B symptoms ($P = 0.046$), poor performance status ($P < 0.001$), and not responding to first-line chemotherapy ($P < 0.001$) were associated with shorter PFS. However, the presence of a pre-existing autoimmune disease was not associated with inferior PFS ($P = 0.326$) (Table 4).

In terms of risk factors associated with OS, older age ($P = 0.025$), lactate dehydrogenase $\geq$ 240 IU/L ($P = 0.020$), presence of B symptoms ($P = 0.040$), poor performance status ($P < 0.001$) and refractoriness to chemotherapy ($P < 0.001$) were significantly associated with worse OS in lymphoma patients. However, the presence of a pre-existing autoimmune disease was not associated with worse OS in lymphoma patients ($P = 0.627$) (Table 4).

DISCUSSION

Although autoimmune diseases are considered to be risk factors for developing malignant lymphoma,[11] whether the presence of autoimmune diseases has an impact on the outcome of malignant lymphoma remains largely unknown. Our results demonstrated that neither the PFS nor the OS was inferior in lymphoma patients with pre-existing autoimmune diseases than those without underlying autoimmune disorders. The findings of the current study are partially supported

Table 3 Best treatment response after first line therapy†

	Total (n = 79)	Autoimmune disease group (n = 25)	Control group (n = 54)	P-value‡
Best treatment response after first-line therapy, n (%)				
CR	63 (79.7)	18 (72.0)	45 (83.3)	0.178
PR	6 (7.6)	4 (16.0)	2 (3.7)	
SD	4 (5.1)	2 (8.0)	2 (3.7)	
PD	6 (7.6)	1 (4.0)	5 (9.3)	

CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease.
†Three patients in the autoimmune disease group and two patients in the control group died before treatment response assessment.
‡Chi-square test.

by a case-control study from a Swedish group, which demonstrated that the 5-year OS rate of 16 NHL patients with SLE was 50%. This 5-year OS rate is comparable to that of NHL patients in the general population.[13] Similar results have been observed in patients with SS. The OS of 46 lymphoma patients identified from 1300 primary SS patients in a Spanish cohort had a similar result.[14]

Our study results revealed that the presence of autoimmune disease was not associated with differences in either PFS (P = 0.326) or OS (P = 0.627) in lymphoma patients. We also analyzed other possible prognostic factors for both PFS and OS. Results showed that lactate dehydrogenase ≥ 240 IU/L, B symptoms, poor performance status and refractoriness to front-line chemotherapy, were associated with both inferior PFS and OS. This result is consistent with the recommendation of poor prognostic parameters in the revised International Prognostic Index.[15]

Regarding the clinical features of lymphoma patients with autoimmune diseases, DLBCL was the most common histological subtype in our cohort, accounting for 52.94% (18/34) of lymphoma patients. This histological distribution was similar to that reported by Varoczy *et al.*,[16] who found that DLBCL was diagnosed in 13 of 30 (43.3%) lymphoma patients who had autoimmune disease. A multi-center cohort study conducted by Bernatsky *et al.*[17] also supported this finding. Among 18 DLBCL patients, RA and SLE were the leading underlying autoimmune disorders, accounting for seven and four patients, respectively. Although the underlying mechanism is not entirely understood, a strong correlation between RA and DLBCL has been well established.[18] A proliferation-inducing ligand (APRIL) might be a factor. Compared to other lymphoma subtypes, DLBCL cells have

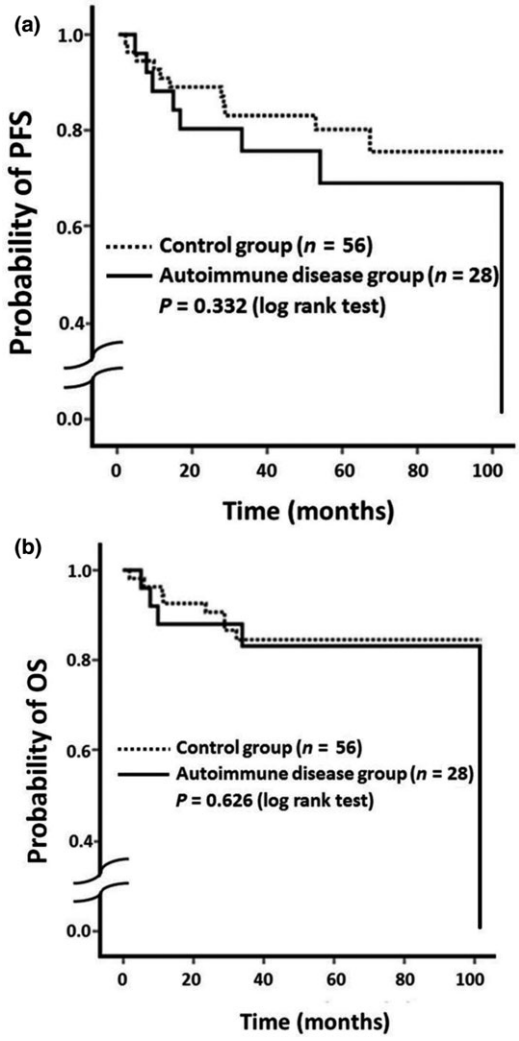

Figure 1 (a) Progression-free survival (PFS) and (b) overall survival (OS) comparison among lymphoma patients with and without autoimmune diseases. (a) The PFS (presented as median ± interquartile range) of patients in the autoimmune disease group and the control group were 45.4 ± 59.9 and 51.5 ± 42.8 months, respectively. The PFS was not significantly different between these two groups of patients (P = 0.332 by log-rank test). (b) The OS (presented as median ± interquartile range) of patients in the autoimmune disease group was 46.4 ± 52.6 months. It was 50.1 ± 47.3 months in the control group. This difference was not statistically significant (P = 0.626 by log-rank test)

higher APRIL expression.[19] Furthermore, a high concentration of APRIL has been reported to be associated with both RA and SLE development.[20] However, the elevated odds ratio for high expression of APRIL has only been observed in SLE, but not RA, patients.[19] Further studies are required to clarify the underlying

Table 4 Prognostic factors of PFS and OS in lymphoma patients with autoimmune disease

	PFS		OS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.03 (0.99–1.08)	0.105	1.06 (1.01–1.12)	0.025
LDH (IU/L)				
< 240	1.00		1.00	
≥ 240	3.81 (1.25–11.60)	0.018	11.28 (1.46–87.45)	0.020
B-symptom				
No	1.00		1.00	
Yes	2.56 (1.02–6.47)	0.046	3.34 (1.06–10.55)	0.040
ECOG performance status				
0, 1, 2	1.00		1.00	
3, 4	12.42 (3.79–40.70)	< 0.001	17.01 (4.88–59.28)	< 0.001
Best treatment response after first-line therapy				
CR, PR, SD	1.00		1.00	
PD	10.52 (3.51–31.53)	< 0.001	13.63 (4.15–44.77)	< 0.001
Autoimmune disease				
No	1.00		1.00	
Yes	1.58 (0.63–3.95)	0.326	1.32 (0.43–4.07)	0.627
Sex				
Male	1.00		1.00	
Female	1.31 (0.43–3.97)	0.638	1.90 (0.42–8.68)	0.407
Histological subtypes				
NHL	1.00		1.00	
HL	0.04 (0.00–118.74)	0.438	0.04 (0.00–417.27)	0.503
Ann Arbor stage				
Stage 1, 2	1.00		1.00	
Stage 3, 4	1.75 (0.67–4.62)	0.255	1.81 (0.56–5.87)	0.326
Extranodal involvement				
No	1.00		1.00	
Yes	0.79 (0.31–2.01)	0.615	0.54 (0.18–1.62)	0.273

PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma.

pathogenesis for the association between DLBCL and RA.

In addition to 13 patients with DLBCL, five patients in this study cohort had MALT lymphoma. SS was the underlying autoimmune disorder in four of these five patients. MALT lymphoma constitutes the majority of lymphomas in SS patients.[21]. By promoting the hyperactivity and lymphoproliferation of B cells, B-lymphocyte stimulator[22] and FMS-like tyrosine kinase 3 ligand[23] are considered to be the essential factors for MALT lymphoma development in SS patients. The protein A20-associated nuclear factor-κB pathway, driven by *TNFAIP3* mutations, is another possible mechanism for the transformation of SS into MALT lymphoma.[11] However, the interactions among various pathways contributing to MALT lymphoma development in patients with SS remain largely unexamined.

Not only B-cell lymphomas but also HL and T-cell lymphomas were identified in our study cohort. In our analysis, two HL patients were identified in the autoimmune disease group. RA was found in one of the two HL patients. Epstein–Barr virus replication-related chronic inflammation could be the reason for RA development in HL patients.[24] The HL patient who had RA in our study was positive for Epstein–Barr virus immunoglobulin G (IgG) to viral capsid antigen. Ankylosing spondylitis was another underlying autoimmune disorder. Aksu *et al.*[25] reported an HL patient diagnosed six months after anti-tissue necrosis factor (TNF) treatment to ankylosing spondylitis. Notably, the HL patient with ankylosing spondylitis in our study had also been treated by an anti-TNF regimen, suggesting that anti-TNF could increase the risk of HL development in patients with autoimmune disorders. Fortunately,

conventional chemotherapy with anthracycline, bleomycin, vinblastine, and dacarbazine successfully cured these two HL patients (Table 1).

Compared to the HL patients, the outcome of patients with autoimmune diseases and T-cell lymphoma was relatively dismal in the current study. Several possible pathophysiologies have been proposed. The upregulation of genes for either immunosuppression or autoimmunity is one hypothesis for this phenomenon.[26] Another possible pathophysiology is the NOTCH pathway. NOTCH1 and NOTCH3 receptors have been reported to play a role in T-cell lymphoma development in patients with celiac disease.[27] Because only a few T-cell lymphomas have been found in patients with autoimmune diseases,[28] more cases are needed to understand the epidemiology, clinical and immunophenotypic features, and underlying mechanisms of T-cell lymphoma development in patients with autoimmune disorders.

The retrospective nature and limited patient numbers are the major limitations of the current study. Additionally, our study cohorts had various histological lymphoma subtypes and heterogeneous autoimmune diseases. Future studies with a prospective study design and focusing on the association between certain histological lymphoma subtypes and specific autoimmune disorders are needed to understand the impact of autoimmune diseases on the outcome of malignant lymphoma. In conclusion, our study demonstrated that lymphoma patients who have pre-existing autoimmune disorders have a comparable outcome to patients without autoimmune diseases. The presence of autoimmune diseases should not be an obstacle to lymphoma treatment.

ACKNOWLEDGEMENTS

This work was supported by the Taichung Veterans General Hospital under Grant TCVGH-1053702C and TCVGH-1043703D.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

YHS collected the data and wrote the paper. YY collected and analyzed the data. KHC analyzed the data. YHC designed the study and critically reviewed the manuscript. CLJT designed the study, analyzed the data and wrote the paper. All authors approved the final version.

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