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Original Article

Increased Risk of Lymphoma in Men or the Elderly Infected with Tuberculosis

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Abstract. ***Purpose:*** **To identify factors associated with lymphoma in patients with prior *Mycobacterium tuberculosis* infection.**
Methods: **A retrospective case-control analysis was performed in a highly tuberculosis (TB)-endemic area. Patients with a history of TB before the diagnosis of lymphoma were retrospectively identified. Inpatients with lymphoma (n=1,057) and pathologically confirmed benign diseases (n=12,916) were consecutively enrolled at Xinjiang Medical University Cancer Hospital between January 2016 and December 2019.**
Results: **The proportion of TB infection in patients with lymphoma (n=148, 14.0%) was significantly higher than that in the control (benign diseases) group (n=175, 1.4%) (p<0.0001). The frequencies of TB infection in patients with Hodgkin lymphoma, B-cell non-Hodgkin lymphoma (NHL), and T/NK-cell NHL were 13.6%, 14.6%, and 11.9%, respectively. Relatively high proportions of TB infection were found in patients with chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL), marginal zone B-cell lymphoma (MZBL), and diffuse large B-cell lymphoma (DLBCL), at 20.6%, 18.6% and 15.3%, respectively, compared to other subtypes of B-cell NHL. For T/NK-cell NHL, the proportions of TB infection in patients with peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS), and anaplastic large cell lymphoma (ALCL) were 18.2% and 20%, respectively. The multivariate analysis revealed that male sex was an adverse risk factor for lymphoma after tubercular infection. In addition, male sex and older age (>60 years) were associated with B-cell NHL.**
Conclusion**: A high proportion of TB infection was found in patients with lymphoma. In TB-infected patients, older age and male sex were associated with susceptibility to lymphoma, suggesting that screening programmes might be useful for the early detection of lymphoma.**
Keywords Lymphoma; tuberculosis; Burkitt's lymphoma; diffuse large B lymphoma; Hodgkin's disease

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Introduction. There is an intricate and dangerous association between tuberculosis (TB) infection and cancer, especially lymphoma.[1-3] Tubercular infection may complicate the diagnosis of lymphoma.[1-3] Given its clinical and morphological similarities to TB, lymphoma diagnosis is often delayed in TB-infected individuals.[2,4-11] Approximately 10% of cancer patients may have active TB,[12] which may cause a delay in antitumour therapy. The toxicity of anti-TB treatment may lead to the administration of an insufficient dose in patients with lymphoma, increasing the risk for mortality due to a curable disease.[12] Additionally, some deaths in cancer patients are caused by TB flares and not the tumour *per se*.[13] However, the prevalence of TB among lymphoma patients remains unclear. Few studies have been performed in countries with a high TB burden.[14]

TB induces a chronic inflammatory state that which compromises the normal immune system and is a significant risk factor for the development of malignant haematological tumours.[5,15,14,16,17] TB may occur for decades before the onset of lymphoma.[15-18] A typical example of the association between TB infection and lymphoma is pyothorax-associated pleural lymphoma.[18-20] Therefore, the establishment of a lymphoma screening strategy targeting TB-infected patients may be an important strategy, particularly considering population ageing.

In this study, we analysed the proportion of TB infection in lymphoma patients and identified certain characteristics of lymphoma in TB-infected patients. A lymphoma screening strategy could help clinicians identify lymphoma early in the high-risk TB patient population.

Materials and Methods.

Case Selection Criteria. Between January 2016 and December 2019, a total of 1,120 patients with lymphoma were treated and followed in the Department of Lymphoma, Xinjiang Medical University Cancer Hospital, a tertiary care hospital in Xinjiang. Among this cohort, 42 patients with clinically suspected lymphoma but without pathological findings as well as 21 patients with comorbid lymphoma and TB after the initiation of lymphoma treatment were excluded. Finally, a total of 1,057 patients with lymphoma, with confirmed and clear pathological evidence according to the World Health Organization (WHO) classification, were enrolled in the case group. Patients with pathologically confirmed benign diseases (n=12,916) treated at Xinjiang Medical University Cancer Hospital between January 2016 and December 2018 were enrolled in the control group.

Identification of TB Patients. TB cases were retrospectively identified as described in our previous report[21] according to the national guidelines for the diagnosis of tuberculosis in China.[22] In brief, TB cases were identified in inpatients by past medical history or radiologic findings, including chest X-ray and computed tomography (CT) scans. Both active and inactive TB cases before the diagnosis of lymphoma or benign diseases were included in the final analysis of the risk of lymphoma after TB infection. Among the cohort of 148 lymphoma patients with TB, most patients had inactive pulmonary TB according to clinical and radiological indicators, such as evidence of old pulmonary TB (n=133), while five patients had active pulmonary TB according to radiographic abnormalities consistent with active pulmonary TB or positive culture of *Mycobacterium tuberculosis* from sputum. Ten patients had extrapulmonary TB. In the control group, 167 patients had inactive pulmonary TB. Only two patients had radiographic abnormalities consistent with active pulmonary TB, while six patients had a past medical history of pulmonary TB diagnosed by a physician. For both groups, only the initial hospitalization was included in the analysis. In addition, nine TB patients had B-cell non-Hodgkin lymphoma (NHL), and three TB patients had T/NK-cell NHL, while none of the TB patients in the control group had immunodeficiency due to human immunodeficiency virus (HIV) infection.

Patient and Public Involvement. Since our study was a retrospective study, study participants and patient advisers were not involved in the recruitment or conduct of our study. Participants have the right to access the results of the study by contacting a member of the research team.

Statistical Analysis. Data were analysed using SPSS (version 24.0; SPSS, Chicago, IL). A two-tailed P value < 0.05 was considered statistically significant. Logistic regression analysis was used to assess odds ratios (ORs) and 95% confidence intervals (95% CIs).

Results. We identified 1,057 patients with lymphoma; the demographic characteristics are described in **Table 1**. Compared to that in control patients (1.4%), the proportions of TB infection were significantly higher in patients with Hodgkin lymphoma (13.6%), B-cell NHL (14.6%), and T/NK-cell NHL (11.9%). The results of the subgroup analysis of the proportion of TB infection among lymphoma patients are shown in **Table 2**. The proportions of TB infection were 19.1%, 9.5%, and 8.3% in patients with nodular sclerosis classical Hodgkin lymphoma (CHL), lymphocyte-rich CHL, and mixed cellularity CHL, respectively. Among B-cell NHL patients, patients with chronic lymphocytic leukaemia/small lymphocytic lymphoma had the highest

Table 1. Characteristics of patients with lymphomas or benign tumors.

Variable	Controls (N=12,916)	Lymphomas			
		Total (N=1057)	HL (N=154)	B-cell NHL (N=726)	T/NK-cell NHL (N=177)
Gender					
Male, n (%)	791 (6.1)	564 (53.4)	88 (57.1)	362 (49.9)	114 (64.4)
Female, n (%)	12,125 (93.9)	493 (46.6)	66 (42.9)	364 (50.1)	63 (35.6)
Age, median (range), yrs.	42 (86)	54 (86)	39.5 (76)	57 (85)	51 (76)
≤60 yrs., n (%)	12,251 (94.9)	660 (62.4)	129 (83.8)	413 (56.9)	118 (66.7)
>60 yrs., n (%)	665 (5.1)	397 (37.6)	25 (16.2)	313 (43.1)	59 (33.3)
Tuberculosis					
Yes, n (%)	175 (1.4)	148 (14.0)	21 (13.6)	106 (14.6)	21 (11.9)
No, n (%)	12,741 (98.7)	909 (86.0)	133 (86.4)	620 (85.4)	156 (88.1)

Notes: yrs., years. N/n, number; M, male; F, female; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma;

Table 2. Proportions of Tuberculosis (TB) in different subtypes of lymphoma.

Type of Lymphoma	No. of TB /Total No. (%)	No. of TB /Total No. (%)					
		Age, y			Sex		
		≤60	>60	*P*	Male	Female	*P*
Hodgkin lymphoma (total N=154)							
Nodular Lymphocyte-predominant	0/4 (0)	0/4 (0)	0/0 (0)	-	0/3 (0)	0/1 (0)	-
Classical Hodgkin lymphoma							
Lymphocyte-rich	6/46 (13.0)	4/38 (9.5)	2/8 (25.0)	0.28	6/33 (18.1)	0/13 (0)	0.16
Nodular Sclerosis	13/68 (19.1)	12/61 (19.7)	1/7 (14.3)	1.00	6/28 (21.4)	7/40 (17.5)	0.76
Mixed Cellularity	2/34 (5.9)	2/24 (8.3)	0/10 (0)	1.00	1/23 (4.3)	1/11 (9.1)	1.00
Lymphocyte-depleted	0/2 (0)	0/2 (0)	0/0 (0)	-	0/1 (0)	0/1(0)	-
B-cell NHL (total N=726)							
DLBCL	66/431 (15.3)	26/233 (11.2)	40/198 (20.2)	0.01	39/193 (20.2)	27/238 (11.3)	0.02
FL	9/83 (10.8)	7/60 (11.7)	2/23 (8.7)	1.00	4/42 (9.5)	5/41 (12.2)	0.74
MZBL	11/59 (18.6)	3/35 (8.6)	8/24 (33.3)	0.04	8/33 (24.2)	3/26 (11.5)	0.32
MCL	2/28 (7.1)	0/9 (0)	2/19 (10.5)	1.00	2/22 (9.1)	0/6 (0)	1.00
Burkitt lymophma	3/22 (13.6)	0/17 (0)	3/5 (60.0)	0.01	0/15 (0)	3/7 (42.9)	0.03
SLL/CLL	7/34 (20.6)	3/16 (18.8)	4/18 (22.2)	1.00	3/21 (14.3)	4/13 (30.8)	0.39
Other	8/69 (11.6)	3/43 (7.0)	5/26 (19.2)	0.14	6/36 (16.7)	2/33 (6.1)	0.26
T/NK-cell NHL (total N=177)							
NK/T	5/59 (8.5)	4/46 (8.7)	1/13 (7.7)	1.00	4/42 (9.5)	1/17 (5.9)	1.00
PTCL, NOS	6/33 (18.2)	2/12 (16.7)	4/11 (36.4)	0.64	3/14 (21.4)	3/9 (33.3)	0.64
TLBL	3/24 (12.5)	3/20 (15.0)	0/4 (0)	1.00	2/15 (13.3)	1/9 (11.1)	1.00
ALCL	3/15 (20.0)	2/10 (20.0)	1/5 (20.0)	1.00	3/9 (33.3)	0/6 (0)	0.23
AITL	0/11 (0)	0/5 (0)	0/6 (0)	-	0/6 (0)	0/5 (0)	-
Other	4/45 (8.9)	1/25 (4.0)	3/20 (15.0)	0.31	3/28 (10.7)	1/17 (5.9)	1.00

Note: HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; MZBL, marginal zone B-cell lymphoma; DLBCL, Diffuse large B-cell lymphoma; FL, Follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; PTCL, NOS, peripheral T-cell lymphoma, non-specified; TLBL, T-lymphoblastic lymphoma; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma.

proportion of TB infection (20.6%), followed by patients with marginal zone B-cell lymphoma (18.6%), diffuse large B-cell lymphoma (DLBCL) (15.3%), and Burkitt lymphoma (13.6%). Among the T/NK-cell NHL patients, the highest proportion of TB infection was found in patients with anaplastic large cell lymphoma (20.0%), followed by peripheral T-cell lymphoma, nonspecified lymphoma (18.2%), and T-lymphoblastic lymphoma (12.5%). Notably, none of the patients with angioimmunoblastic T-cell lymphoma had previous TB

infection.

Although there was no significant impact in HL and T/NK lymphoma patients, age was a notable effect modifier in the association between TB infection and some subtypes of B-cell NHL. The odds of DLBCL in patients with TB aged more than 60 years was 1.99 (95% CI, 1.16–3.42) (p=0.012) times higher than that in patients aged less than or equal to 60 years. Patients with TB who were older than 60 years also had an increased risk of MZBL compared to patients in the younger age group (adjusted OR, 5.39; 95% CI, 1.23–23.58) (p=0.025). Notably, in contrast to that in younger patients, the proportion of TB infection in patients with Burkitt lymphoma aged over 60 years was 60% (p=0.006). Similarly, a significant change in the effect was observed for the association between TB and some B-cell NHL subtypes in all sex subgroups. For example, the adjusted OR for the association between TB and DLBCL was higher in males than in females (OR, 1.96; 95% CI, 1.14–3.35) (p=0.014). In contrast, the proportion of TB infection was higher in female (42.9%, 3/7) than male (0.0%, 0/15) Burkitt lymphoma patients (p=0.023).

To identify individuals at risk of lymphoma among the TB-infected population, unconditional multivariate logistic regression analysis was carried out. As shown in **Table 3**, TB-infected men had higher risks of all types of lymphoma than TB-infected women. Additionally, elderly patients (>60 years) were susceptible to B-cell NHL, including DLBCL, but were protected against HL.

Table 3. Multivariate analysis of risk factors to lymphoma in patients with tuberculosis.

Subtype of Lymphoma	Adjusted OR (95%CI)			
	Male		Age>60 yrs.	
Hodgkin's lymphoma	5.324 (2.056-13.788)	p=0.001	0.139 (0.039-0.504)	p=0.003
B-cell NHL*	3.387 (1.836-5.106)	p=0.000	2.596 (1.571-4.291)	p=0.000
DLBCL*	2.788 (1.566-4.963)	p=0.000	2.196 (1.23-3.92)	p=0.008
T/NK-cell NHL	5.773 (2.097-15.892)	p=0.000	0.691 (0.269-1.777)	p=0.444

Notes: OR, odds ratio; 95% CI, 95% confidence interval. NHL, non-Hodgkin's lymphoma; DLBCL, Diffuse large B-cell lymphoma. *Adjusting with Hepatitis B surface antigen (HBsAg).

Discussion. People infected with TB develop malignant lymphoma more frequently than the general population.[14,17,25,15] In this study, we found that the proportion of TB infection in lymphoma patients, ranging from 11.9% to 14.6%, was significantly higher than that in control individuals (1.4%). Importantly, TB infection can have a substantial impact on the older male population, predisposing them to certain subtypes of lymphoma, particularly B-cell NHL. Screening for lymphomas in men and/or older patients with a history of TB can prompt timely diagnosis and treatment.

In the present study, we confirmed a positive association between HL and TB infection. This result corroborates observations by Vineis P. *et al*., Kou *et al*., and Everatt *et al*.[23-25] However, over the past two decades, the association between NHL and TB has been controversial. Here, we suggest that TB infection is positively related to NHL. Similarly, a systematic review showed that TB infection was associated with haematological malignancies, including HL, NHL, and leukaemia.[26] Ageing is a risk factor for NHL transformation, particularly DLBCL, MZBL, and Burkitt lymphoma, in TB patients. Case-control studies support the indication that TB infection is a risk factor for the incidence of DLBCL.[27] Therefore, TB may be a pathogenic factor for DLBCL. This theory is extremely important in the association between TB infection and pyothorax-associated pleural lymphoma, a prototype of DLBCL-CI, which predominately occurs in older male patients with DLBCL after a long history of TB infection.[28] With ageing of the population, NHL lymphoma in individuals with prior TB infection is becoming an increasingly important public health issue. In this study, TB infection was particularly associated with Burkitt lymphoma in older females. To the best of our knowledge, this may be the first study to show that TB is a risk factor for Burkitt lymphoma in older females.

We found a higher risk for B-cell NHL history in older men with a history of TB infection than in women. Indeed, many more males than females are infected with TB in low- and middle-income countries.[29] Moreover, the incidence of NHL among males is significantly higher than that among females.[30] Several critical roles of oestrogens in the regulation of haematopoietic stem cells and immune cells[31,32] may partly explain the lower risk of NHL in TB-infected females. Costas et al. observed a significantly higher risk of B-cell NHL in women who underwent hysterectomy and bilateral oophorectomy than in women who did not, supporting the role of oestrogens.[33] In addition, more TB-infected men present clinical symptoms than women.[34] However, a large sample prospective cohort study is warranted.

A definitive causal conclusion cannot be reached due to the small sample size and the inherent nature of retrospective studies. In our study, we adjusted for age and sex but did not examine the role of immunodeficiency due to HIV infection, hereditary immunodeficiency syndromes, immunosuppressive

treatments, or other confounding factors associated with both TB and lymphomas. In addition, without confirmation of Epstein-Barr virus (EBV) infection, pathologists sometimes could not determine if NHL belonged to the Burkitt lymphoma or DLBCL subclassification due to extensive necrosis.[2] Whether older women with TB have an increased risk of Burkitt lymphoma warrants future research. Since we did not perform the HIV test in the patients with Tuberculosis and Lymphoma, we cannot exclude a role of this virus.

Conclusions. The present study indicated that approximately 10%-20% of lymphoma patients in a highly TB-endemic area in China had prior TB infection. Male patients with previous TB infection are more likely to develop lymphoma, especially elderly male patients.

Ethical Approval. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was reviewed and approved by the Xinjiang Medical University Institutional Review Board (number K-2021003). Informed consent was obtained from all individual participants included in the study.

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