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Original Article

Hashimoto's thyroiditis or/and thyroid cancer in patients with diffuse large B-cell lymphoma

Yuanfang Yue[1*], Jing Ma[1*], Qian Li[1], Tiantian She[2], Han Li[1], Su Liu[1], Lin Chen[1], Tinghui Yan[1], Shuang Gao[1], Zeng Cao[1], Yong Yu[1], Xiaofang Wang[1], Hongliang Yang[1], Haifeng Zhao[1], Yizhuo Zhang[1], Yafei Wang[1]

[1]Department of Hematology and Blood and Marrow Transplantation, Tianjin Medical University Cancer Institute and Hospital. National Clinical Research Center for Cancer; Tianjin Key Laboratory of Cancer Prevention and Therapy, Tianjin, China; [2]School of Medical Laboratory Science, Tianjin Medical University, Tianjin, China. [*]Equal contributors and co-first authors.

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Abstract: Objectives Diffuse large B-cell lymphoma (DLBCL) is an aggressive and highly heterogeneous malignancy. However, its pathogenesis remains not so clear, since other diseases like thyroid problems have recently been reported to accompany with DLBCL. Therefore, we evaluated the association between thyroid diseases and DLBCL, aiming to figure out their relationship and find valuable clues for the treatment of DLBCL. Method A total of 214 DLBCL patients who all had thyroid ultrasound examinations as part of the routine work-up were collected in this study from our hospital between 2010 and 2014. They were classified into three groups according to the results of thyroid ultrasound examination: Hashimoto's thyroiditis (HT), suspected thyroid cancer (TC) and thyroid nodules/normal groups. We comparatively analyzed the clinical characteristics, treatment response and prognosis among the three groups. Results Patients with HT, accounting for 18.7% (40/214) of all DLBCLs, were predominantly elderly females. They presented with the early-stage germinal center B cell-like (GCB) DLBCL and showed a better response to anti-DLBCL therapy than the other two groups. Patients with suspected TC accounted for 8.4% (18/214) of all DLBCLs, among which 4 patients were pathologically diagnosed with TC from the 6 patients who underwent thyroid biopsy. Additionally, there was no statistically significant difference in survival among the three groups, probably due to the short follow-up. Conclusion The high concurrency of DLBCL and thyroid diseases indicated an association between them. We thus propose that thyroid examination is necessary for DLBCL patients.

Keywords: Diffuse large B-cell lymphoma, Hashimoto's thyroiditis, thyroid cancer, association, prognosis

Introduction

Diffuse large B-cell lymphoma (DLBCL), the most common subtype of lymphoma, is an aggressive and highly heterogeneous malignancy. With the development of intensive chemotherapy and novel targeted agents such as rituximab, anti-DLBCL therapy could lead to prolonged lifespan in patients of DLBCL. However, the pathogenesis of DLBCL remains unknown. It was reported to be associated with immunodeficiency, autoimmune diseases or viral infections [1].

Hashimoto's thyroiditis (HT), an inflammatory autoimmune disorder that has affected 4% of all females, is the most common cause for hypothyroidism [2]. HT is usually diagnosed by measuring the serum levels of anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase antibodies (anti-TPO) [3, 4]. Thyroid ultrasound (US) examination is another assistant method for diagnosis of HT. It has a positive predictive value of 95% [4]. The extra-nodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT lymphoma) is another common subtype of lymphoma (especially extra-gastric lymphoma) that is closely associated with autoimmune diseases, such as thyroidal MALT lymphoma concomitant with HT, and salivary gland MALT lymphoma concomitant with Sjogren's syndrome (SS) [5-8]. Since thyroid gland is a non-mucosa-associated organ devoid of native lymphoid tissue, MALT lymphoma is supposed to develop beyond thyroid gland. However, the truth was that thyroidal

Table 1. Clinical characteristics of DLBCL patients among three groups

Group	HT	Suspected TC	Nodule or normal thyroid	*p*-value
No. n (%)	40 (18.7)	18 (11.5)	156 (72.9)	
Gander, n (%)				<0.01
Female	30 (75.0)	11 (61.1)	74 (47.4)	
Male	10 (25.0)	7 (38.9)	82 (52.6)	
Age, n (%)				<0.01
<60	13 (32.5)	10 (55.6)	97 (62.2)	
≥60	27 (67.5)	8 (44.4)	59 (37.8)	
B symptoms, n (%)				>0.05
Yes	10 (25.0)	3 (16.7)	32 (20.5)	
No	30 (75.0)	15 (63.3)	124 (79.5)	
Extranodal sites number, n (%)				>0.05
0	11 (27.5)	7 (38.9)	37 (23.7)	
≤1	22 (55.0)	7 (38.9)	59 (37.8)	
>1	7 (17.5)	4 (22.2)	54 (34.6)	
Unknown	0	0	6 (3.8)	
Immunophenotype, n (%)				<0.05
GCB	23 (57.5)	7 (38.9)	52 (33.3)	
Non-GCB	16 (40.0)	11 (61.1)	91 (58.3)	
Unknown	1 (2.5)	0	13 (8.3)	
Ki-67, n (%)				>0.05
<50%	5 (12.5)	4 (22.2)	11 (7.1)	
≥50%	33 (82.5)	14 (77.8)	120 (76.9)	
Unknown	2 (5.0)	0	25 (16.0)	
LDH (ug/l), n (%)				>0.05
≤240	23 (57.5)	11 (61.1)	84 (53.8)	
>240	17 (42.5)	7 (38.9)	71 (45.5)	
Unknown	0	0	1 (0.6)	
β2MG (mg/l), n (%)				>0.05
≤2.6	24 (60.0)	15 (83.3)	102 (65.4)	
>2.6	16 (40.0)	3 (16.7)	53 (34.0)	
Unknown	0	0	1 (0.6)	
DLBCL Treatment, n (%)				>0.05
Chemptherapy	18 (45.0)	7 (38.9)	46 (18.0)	
R+chemotherapy	18 (45.0)	9 (50.0)	101 (64.7)	
No treatment	4 (10.0)	2 (11.1)	9 (5.8)	
Cycles of chemotherapy, n (%)				>0.05
≤4	16 (40.0)	5 (27.8)	52 (33.3)	
>4	24 (60.0)	13 (72.2)	104 (66.7)	
Ann arbor Stage, n (%)				<0.05
I-II	27 (67.5)	12 (66.7)	73 (46.8)	
III-IV	13 (32.5)	6 (33.3)	82 (52.6)	
Unknown	0	0	1 (0.6)	
IPI, n (%)				>0.05
0-1	24 (60.0)	11 (61.1)	77 (49.4)	
2	11 (27.5)	2 (11.1)	35 (22.4)	

MALT lymphoma arose from pre-existing HT, or, HT-induced lymphocytic infiltration of thyroid gland. Additionally, salivary gland MALT lymphoma was also found to coexist with SS [9]. Furthermore, Troch et al. demonstrated that HT was not only associated with thyroidal MALT lymphoma, but also with non-thyroidal MALT lymphoma [10]. All these indicated a possible association between HT and lymphoma. However, whether DLBCL co-exists with HT and how they are mutually associated has not been assessed so far.

In addition, we fortuitously found a few cases of DLBCL concomitant with thyroid cancer (TC). It's also uncertain whether DLBCL is directly associated with TC, or HT acts as a bridge between them. Therefore, the objective of this study is to analyze the clinical characteristics and prognosis of all the cases of DLBCL concomitant with HT/TC and assess the relationship between DLBCL and HT/TC, thus providing a better guidance for clinical practice.

Patients and methods

A total of 214 DLBCL cases all having thyroid ultrasound examinations were collected in this study from 2010 to 2014 at our institution. Thyroid ultrasound examinations were taken as part of routine work-up for all of them. According to their ultrasound results they were divided into three groups, i.e. HT, suspected TC and thyroid nodules/normal gr-

3	5 (12.5)	5 (27.8)	31 (19.9)	
4-5	0	0	13 (8.3)	
Response, n (%)				<0.05
PD	6 (15.0)	6 (33.3)	50 (32.1)	
SD	3 (7.5)	1 (5.6)	5 (3.2)	
PR	3 (7.5)	0	24 (15.4)	
CR/CRu	18 (45.0)	8 (44.4)	62 (39.7)	
Relapse	10 (25.0)	3 (16.7)	7 (4.5)	
Unknown	0	0	8 (5.1)	
Follow-up, n (%)				
Alive	21 (52.5)	7 (38.9)	79 (50.6)	
Death	12 (30.0)	6 (33.3)	58 (37.2)	
Unknown	7 (17.5)	5 (27.8)	20 (12.8)	

Abbreviations: DLBCL, diffuse large B-cell lymphoma; HT, Hashimoto's thyroiditis; TC, thyroid cancer; GCB, germinal center B-cell origin; IPI, International Prognostic Index; PD, progress disease; SD, steady disease; PR, partial response; CR, complete remission; CRu, uncertified complete remission.

oups. The clinical characteristics, treatment response and prognosis among the three groups were comparatively analyzed. For detailed information, see **Table 1**.

The diagnostic criteria for DLBCL are based on the 2008 WHO classification for DLBCL [1]. HT can be diagnosed (defined by Colin et al.) by such indicators as markedly elevated levels of serum anti-thyroglobulin antibodies (anti-TG) or/and anti-thyroid peroxidase (anti-TPO) antibodies, a hypoechogenetic appearance on thyroid ultrasound and histopathology of thyroid fine-needle biopsies or surgical specimen [5]. As for TC, thyroid imaging reporting and data system (TI-RADS) score ≥4 implied high risk of malignancy and its diagnosis was based on the 2004 WHO classification for thyroid tumors [11, 12]. The systemic examinations for all patients included serological checkup and imaging examinations such as thyroid ultrasound, Computed Tomography (CT), X-radiation, Magnetic Resonance Imaging (MRI), and Positron Emission Tomography-computed Tomography (PET-CT).

Statistical analysis

All data was processed using SPSS 19.0, and categorical variables were analyzed using Chi-square test. Over survival (OS) was defined as the length of time from the date of diagnosis to the date of death or the end of follow-up. Kaplan-Meier method was used for survival analysis, with the differences between groups analyzed by the log-rank test. A $P<0.05$ was considered to be statistically significant.

Results

HT group

There were a total of 40 cases of DLBCL concomitant with HT (n=214, 18.7%), whose majority were females (30 female versus 10 male) and whose median age was 66 years (range 42-83 years). 18 cases suffered from primary thyroidal lymphoma, 2 out of them pathologically diagnosed with transformed DLBCL (one derived from stage III follicular lymphoma (FL) and the other from MALT lymphoma). The remaining 22 cases, however, suffered from non-thyroidal lymphoma, with only one case of transformed DLBCL (from stage III FL). There were 12 cases of nodal lymphoma and 10 cases of extra-nodal lymphomas, the latter comprised of 4 cases of HP-positive gastric lymphoma, 1 case of pulmonary lymphoma, 1 case of mediastinal lymphoma, 1 case of intestinal lymphoma, 1 case of omentum majus lymphoma, 1 case of parotid and submandibular glands lymphoma and 1 case of tonsil lymphoma.

4 cases (n=40, 10.0%) had a history of HT prior to the diagnosis of DLBCL while the other 36 cases were diagnosed with HT in addition during DLBCL staging. 9 cases took levothyroxine orally due to low serum fF4 levels. 7 cases (n=40, 17.5%) had other immune-or infection-related diseases, 3 with a history of drug allergy, 1 with SS, 1 with a 10-year history of both SS and rheumatoid arthritis and 2 with chronic hepatitis B.

27 cases were clinically diagnosed as stage I-II DLBCL and 13 diagnosed as stage III-IV DLBCL. 18 cases were treated with rituximab in combination with chemotherapy and another 18 cases were treated with traditional chemotherapy, altogether leading to 18 cases (n=40, 45%) of complete remission/uncertified complete remission (CR/CRu). 4 cases rejected treatment. At the end of follow-up (median peri-

Table 2. Clinical characteristics of DLBCL patients with TC

N	Gender	Age	Disease sites	The time of diagnosing TC	TC type	HT	Stage	Treatment	Response to treatment	Relapse	Survival (months)	Alive	Death reason
1	Female	67	Thyroid (bilateral) +cervical lymph nodues	At initial review	PTC (left lobe)	Yes	II	Thyroidectomy+R-CHOP (6 cycles)	CR	No	10	No	-
2	Female	42	General superficial lymph nodes+mediastinal/retroperitoneal lymph nodues	During treatment	PTC (right lobe)	No	III	R-CHOP (6 cycles)+ESHAP (2 cycles)+of R (2 cycles) for DLBCL; Thyroidectomy for TC	CR	Yes	32	Yes	Lung fection
3	Male	59	Cecum and right colon	After treatment	MTC (right lobe)	No	I	Enterotomy+chemotheray (8 cycles)	CRu	Yes	24	No	-
4	Female	60	Breast; thyroid (new site at relaspe)	After treatment	PTC (right lobe)	Yes	IV	Mastectomy+CHOP (4 cycles)+DNCE (6 cycles)	CRu	Yes	45	Yes	Lymphoma progression

Abbreviations: DLBCL, diffuse large B-cell lymphoma; HT, Hashimoto's thyroiditis; TC, thyroid cancer; PTC, papillary thyroid carcinoma; MTC, medullary thyroid carcinoma; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; ESHAP, etoposide, cisplatin, cytarabine and methylprednisolone; DNCE, dexamethasone, navelbine, cisplatin and etoposide; CR, complete remission; CRu, uncertified complete remission.

od: 12 months), there were 12 deaths (n=40, 30%) and the mean survival time was 38 months.

Suspected TC group

18 cases (n=214, 8.4%) of DLBCL were diagnosed as TI-RADS 4, indicating high risk for TC. Therefore, these 18 cases were classified as suspected TC group. They were 11 females and 7 males, with the median age of 59 years (range 42-76 years). Only 6 cases (n=18, 33.3%) underwent thyroidal biopsy, among which 3 cases was pathologically diagnosed with papillary thyroid carcinoma (PTC) and 1 diagnosed with medullary thyroid carcinoma (MTC). One case of confirmed TC was a 67-year-old female who was initially diagnosed with PTC, HT and thyroid DLBCL. She achieved CR after thyroidectomy and 6 cycles of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone). However, she died of lung infection eventually, with survival time up to 10 months. Another case of confirmed TC was a 42-year-old female diagnosed with nodal DLBCL. She suffered from a gradual enlargement of thyroid gland after the lymphoma treatment and later on was definitely diagnosed with PTC. After the thyroidectomy she reached CR. A third case of confirmed TC was a 59-year-old male. He received an 8-month chemotherapy regimen due to the lymphoma of the cecum and right hemicolon, and reached CRu. Two months later, however, he was diagnosed with MTC. He died of lymphoma relapse ultimately, with the survival time up to 24 months. The last case of confirmed TC was a 60-year-old female with breast DLBCL. After the treatment of mastectomy and 4 cycles of CHOP regimen, she reached CR. Nonetheless, DLBCL relapsed in new locations (thyroid and systemic lymph nodes) within half a year. Results of histopathological analysis after thyroidectomy showed a complicated pathological type: HT and MALT lymphoma in the left lobe of thyroid gland, with local lymphoma cells transforming into large cells, and PTC in the right lobe of thyroid gland. Following the treatment of 6 cycles of DECN (dexamethasone, navelbine, cisplatin and etoposide), she returned to CR. Two above live cases of confirmed TC kept alive throughout the follow-up period, with no sign of disease progression. The detailed information can be seen in **Table 2**.

In the remaining 12 cases not undergoing thyroid pathological examination, 6 had nodal DLBCL and 6 had extra-nodal DLBCL (1 at the skin of right lower limb, 1 at thyroid, 1 at mediastinum, 1 at ilium and 2 at tonsil). In terms of other immune-or infection-related diseases, 1 case had suffered from systemic lupus erythematosus (SLE) for 20 years, with a history of allergy to antibiotics, 2 had both TC and HT and 1 had hepatitis B.

8 cases (n=18, 44.4%) were diagnosed at high risk for TC during the treatment of DLBCL and 3 out of them were eventually pathologically confirmed with TC through thyroid biopsy. For therapeutic methods for DLBCL, 7 cases underwent R-CHOP chemotherapy, either alone or in combination with DNCE or RESHAP, and only 1 case received radiotherapy and 4 cycles of rituximab.

In respect to thyroid-related treatments, 4 cases underwent total thyroidectomy rather than chemotherapy or radiotherapy when they had been pathologically confirmed with TC by the frozen section technique. 12 cases received routine thyroid examination only. At the end of the follow-up (median period: 12 months), there were 6 deaths (n=18, 33%), with the mean survival time up to 31 months.

Thyroid nodules/normal thyroid group

There were 74 females and 82 males in thyroid nodules/normal thyroid group, with the median age of 57 years (range 3-92 years). 109 cases (n=156, 69.8%) had thyroid nodules, 101 out of which were diagnosed with TI-RADS 1-2 and the rest diagnosed with TI-RADS 3. 14 cases had hepatitis B, 2 cases with family history of cancer, 1 with a history of syphilis infection, 8 with a history of drug allergy, 1 with ankylosing spondylitis, 1 with rheumatoid arthritis and 1 having liver transplantation due to severe hepatitis A. 2 cases also had bladder cancer and liver cancer while 1 case had suffered from breast cancer 5 years before the diagnosis of DLBCL.

Out of the 156 cases, 73 cases were clinically diagnosed with stage I-II DLBCL, 82 with stage III-IV DLBCL. At the end of the follow-up (median period: 22 months), there were 58 deaths (n=156, 39%) and the mean survival time was 51 months.

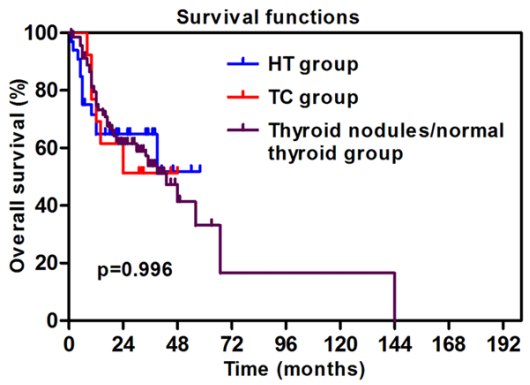

Figure 1. Kaplan-Meier estimates for the OS rates among HT, suspected TC and thyroid nodules/normal thyroid group.

By analyzing many clinical and prognostic parameters, we found that there was statistically significant difference in gender, age, immunophenotype, staging and treatment response among the three groups. In contrast with the other two groups, DLBCL concomitant with HT were likely to affect elderly females. Additionally, they mostly presented with early-stage DLBCL and showed better response to treatment. In spite of no significant difference in survival time among the three groups, thyroid nodules/normal thyroid group was the best group while suspected TC group was the worst in terms of mean survival time (**Figure 1**).

Discussion

To date, there has been no report studying the link between HT and DLBCL with large samples, except 3 reports of rare cases [13-15]. Our data revealed that the incidence of HT in DLBCL patients was 18.7%, higher than those in general population (5-6%) [4] and MALT patients (16%) [10]. In the HT group, 18 cases had thyroidal DLBCL and 22 had non-thyroidal DLBCL. Our data suggested that HT might be a high risk factor for DLBCL, no matter whether lymphoma was localized within the thyroid gland or not. Catarina Dias et al. summarized from large data that in patients with autoimmune rheumatic diseases over-expression of regulatory cytokine BAFF (B-cell activating factor) could lead to B cell dysregulation and hyperactivity and Wang et at demonstrated that immune conditions were in coordination with immune-regulatory genes (TNF G308A and IL10 T3575A) polymorphisms which reported as risk factors for non-Hodgkin lymphoma (NHL), both contributing to the formation of lymphoma [16, 17]. Therefore, immune system dysfunction plays an important role in the development of DLBCL. However, whether DLBCL shares similar pathogenesis with HT requires further investigation.

TC, the most common endocrine malignancy, was reported to be the fastest growing cancer in the United State in the last decade [18]. In China, the morbidity of TC increased gradually from year to year, especially in females [19]. Despite being a relatively indolent malignancy, TC relapsed frequently, thus leading to increased mortality [18-20]. Most scholars insisted that thyroid nodules and HT were inclined to develop into TC, but it was still controversial whether HT was a high risk factor for TC [21-23]. According to a Meta-analysis, 20% of thyroid nodules were diagnosed as TC [24]. To improve the accuracy of thyroid ultrasound for TC diagnosis, thyroid imaging reporting and data system (TI-RADS) was introduced by Kwak et al. It had a sensitivity of 93% and a negative predictive value of 100% for TC diagnosis [11]. In our study, 18 cases were suspected as TC, 4 cases out of which were pathologically confirmed as TC through thyroid biopsy. However, we didn't get the accurate incidence of TC in DLBCL patients. There have been only two reports describing one mere case of thyroid MALT concomitant with both TC and HT so far, without elucidation of its pathogenesis however [25, 26]. In this study, we reported 4 cases of DLBCL concomitant with both TC and HT (n=18, 22.2%). However, we still couldn't deduce HT as the bridge linking DLBCL and TC due to a small sample. Katoh et al. observed an over-expression of Forkhead-box (FOX) family which involved in transcription regulation and DNA repair in multiple cancers including TC and DLBCL [27] and maybe FOX overexpression possibly underlay the co-existence of TC and DLBCL.

There were a few limitations in our study. Firstly, as a few DLBCL patients were diagnosed concomitantly with TC during or after the treatment of DLBCL, it was possible that treatment-related factors contributed to TC, which, however, needed to be explored. Secondly, there was a lack of detailed and complete information regarding genetic aberrations in DLBCL

patients, such as BCL-2, C-MYC and EBV. As a result, this part of data was not shown.

In conclusion, DLBCL may be associated with HT/TC. It was necessary for clinicians to include thyroid examination in DLBCL diagnosis, in case of missed diagnosis of thyroid malignancy. Additionally, patients with HT should undergo thyroid examination regularly as well, in case of the development of DLBCL (thyroidal or non-thyroidal) or/and TC. On the other hand, we should go on with this follow-up to figure out whether HT or TC influences the survival time of DLBCL patients. Meanwhile, the common pathogenesis of the three diseases requires to be investigated, for it will provide new insights for the identification of effective therapeutic targets.

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Disclosure of conflict of interest

None.

Address correspondence to: Yafei Wang, Tianjin Medical University Cancer Institute and Hospital, 1 Huanhuxi Road, Hexi District, Tianjin 30060, China. Tel: 0086-18622221250; E-mail: Drwang2005@163.com

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