Comparison of the clinical characteristics of primary thyroid lymphoma and diffuse sclerosing variant of papillary thyroid carcinoma

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Conflicts of interest

All authors declare no conflicts of interest.

Ethics approval

This was a retrospective analysis study. The study was approved by the Human Research Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.
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Abstract

Objective: Both primary thyroid lymphoma (PTL) and diffuse sclerosing variant of papillary thyroid carcinoma (DSVPTC) are two rare malignant tumours with different therapies and prognoses. This study compared their clinical features.

Methods: From a retrospective review of the pathologic database at our institute between January 2015 and August 2020, 52 PTL patients and 40 DSVPTC patients were included. Demographic, clinical, laboratory and ultrasound data were extracted from electronic medical records. Statistical analyses were performed using GraphPad Prism 5.0.

Results: Both PTL and DSVPTC were more likely to occur in women (83.7% and 67.5%), but DSVPTC patients were younger (median age: 36 vs 64.5), had fewer compressive symptoms, and more frequently had neck lymph node metastasis than PTL patients. The prevalence of Hashimoto’s thyroiditis (HT) and hypothyroidism was significantly higher in PTL patients than in DSVPTC patients (31% vs 17.5%). Hyperthyroidism could only be found in DSVPTC patients, which accounted for 7.5%. Heterogeneous echogenicity and irregular edges were frequently observed in both PTL and DSVPTC. However, compared with PTL, DSVPTC exhibited smaller lesion sizes, higher
frequencies of diffuse sonographic patterns and calcification, and lower
frequencies of hypoechoic features and internal blood flow signal. The overall
survival rate with PTL was 77.23%, which was lower than that with DSVPTC
(90.91%), but this difference was not significant (p=0.096).

Conclusion: Clinical characteristics such as - age, compression symptoms,
and sonographic features such as a large mass with heterogeneous
echogenicity, hypoechoic, irregular edges, and calcification are helpful for
impression diagnosis of PTL and DSVPTC before surgery.

Key words: Primary thyroid lymphoma; Diffuse sclerosing variant of papillary
thyroid carcinoma; Hashimoto’s thyroiditis; Ultrasound

Abbreviations:

CT=calcitonin;

DLBCL= diffuse large B-cell lymphoma;

DSVPTC = diffuse sclerosing variant of papillary thyroid carcinoma;

FISH= fluorescence in situ hybridization;

FT4=free thyroxine;

HT= Hashimoto's thyroiditis;

MALT=Mucosa-associated lymphoid tissue;

PTL = primary thyroid lymphoma;

TgAb = thyroid antithyroglobulin autoantibodies;

TC = thyroid cancer;

TPOAb = thyroid peroxidase antibody;
T4 = thyroxine;

FT3 = triiodothyronine;

T3 = triiodothyronine;

TRAb = TSH receptor antibody;

uTSH = ultrasensitive thyroid stimulating hormone;

US = ultrasound;

WHO = World Health Organization

Introduction

Primary thyroid lymphoma (PTL) is a rare malignant tumour that accounts for less than 5.0% of all malignant thyroid tumours and approximately 2.5% to 7.0% of all extra-nodal lymphomas (1, 2). The underlying pathogenesis of PTL remains unclear, but the major risk factor for PTL is the presence of Hashimoto’s thyroiditis (HT), which causes a 40- to 80-fold increase in the risk of PTL (3-6). Diffuse sclerosing variant of papillary thyroid carcinoma (DSVPTC) is also an uncommon tumour making up approximately 2% of all papillary thyroid carcinomas (PTCs) (7). DSVPTC has characteristic nuclear features of PTCs. In addition, carcinoma shows marked squamous metaplasia, numerous psammoma bodies, extensive interstitial fibrosis and heavy lymphocytic infiltration (8). The association of DSVPTC with HT has been reported because both present with goitre and with heavy infiltration of chronic inflammatory cells (9). The presence of co-existing HT can make the pre-operative diagnosis of DSVPTC difficult (10, 11).
Both PTL and DSVPTC are lymphocyte-rich thyroid lesions, but the therapeutic methods for these two diseases are different (12). PTL is a potentially curable thyroid malignancy, and the main treatment is multiple periodic chemotherapy (13), while initial radical surgery followed by radioiodine treatment is the common management strategy for DSVPTC (11). Therefore, a correct distinction between these tumours is quite important to avoid unnecessary surgery. To our knowledge, there have been no previous investigations comparing the clinical features between PTL and DSVPTC. Therefore, the aim of the present study was to compare these characteristics.

Research design and methods

Patients

From a retrospective review of the pathologic database at our institute between January 2015 and August 2020, 52 patients with PTL and 40 patients with DSVPTC were included in the present study. Demographic, clinical and laboratory data were extracted from the electronic medical records. This was a retrospective analysis. The study was approved by the Human Research Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. During the telephone follow-up, consent has been obtained from each patient or relative after full explanation of the purpose and nature of all data used.

Pathologic evaluation

All the pathologic specimens analysed in this study were reviewed by a
pathologist with plentiful experience in thyroid pathology. All diagnoses of thyroid lymphoma are based on the results of pathology and immunohistochemistry, and the diagnosis of some cases also combines genetic testing, such as fluorescence in situ hybridization (FISH). The specimens were classified according to the World Health Organization (WHO) classification of lymphomas in 2016(14). Fine needle aspiration (FNA) biopsy was defined as a biopsy performed with a needle gauge of 25G, and it was performed under ultrasound guidance. The diagnosis of DSVPTC was made according to the WHO classification, and the disease was characterized by extensive squamous metaplasia, diffuse fibrosis, calcification, abundant lymphocytic infiltration and psammoma bodies (15).

**Laboratory test**

The serum levels of triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3), free thyroxine (FT4), ultrasensitive thyroid stimulating hormone (uTSH), thyroid peroxidase antibody (TPOAb), thyroid antithyroglobulin autoantibody (TgAb) and parathyroid hormone (PTH) were detected by an immunochemical-automated analyser (Beckman Coulter UniCelDxI 800; Beckman Coulter, Inc., Brea, CA). TSH receptor antibody (TRAb) was detected by another immunochemical-automated analyser (Roche Cobas e601; Roche; Geneva, Switzerland).

**Thyroid ultrasonography**

Thyroid sonography was performed on an HD7 ultrasound system
(Philips, Shenyang, China) by experienced technicians who were blind to the design of this study. The ultrasonographic analysis was reviewed by radiologists (with more than 10 years of experience in thyroid imaging diagnosis) without any previous knowledge of the pathologic results. “Hypoechoic” was defined as having decreased echogenicity relative to adjacent thyroid tissue and “very hypoechoic” as decreased echogenicity relative to adjacent musculature.

**Definition of diseases**

PTL refers to lymphoma with thyroid as the first manifestation, involves the thyroid gland alone, with or without the local lymph nodes infiltration. Except for cases that have a history of lymphoma or other distant regions as a metastatic spread occurred at the time of the first diagnosis. (16). The diagnosis of hyperthyroidism was defined as either having a decreased TSH value<0.56 µIU/ml or being treated with anti-thyroid drugs. The presence of hypothyroidism was defined as either having an elevated TSH value>5.91 µIU/ml or being on levothyroxine replacement therapy at the time of diagnosis. The diagnosis of HT was suggested by a typical ultrasound pattern or by the presence of antithyroid antibodies (17).

**Statistical analysis**

Statistical analyses were performed using GraphPad Prism 5.0. Continuous variables with normal distributions are expressed as the mean ± standard deviation and were tested by Student’s t test; variables with
non-normal distributions are expressed as medians (interquartile range) and were tested by non-parametric testing (Mann-Whitney U test). Categorical variables are described as percentages (%) and were tested by the chi-square test or Fisher's test. The log-rank (Mantel-Cox) test was used to compare the survival curves. All statistical analyses were two-sided, and p<0.05 was considered statistically significant.

**Results**

The clinical characteristics of patients with PTL and DSVPTC are summarized in Table 1. This study retrospectively analysed 52 patients with PTL and 40 patients with DSVPTC confirmed by surgical pathology. Representative histological figures of PTL and DSVPTC were showed in Figure 1. The median age at presentation of patients with PTL was 64.5 years, while DSVPTC was more often seen in a younger age group, with a median age at presentation of 36. Both PTL and DSVPTC tended to occur more frequently in women; 83.7% were females among the 52 patients with PTL, and 67.5% were females among the 40 patients with DSVPTC. The median duration of PTL was 1 month (interquartile range: 0.42-2.5 months), while the median duration of DSVPTC was 3.3 months (interquartile range: 1.55-7.25 months). Compression symptoms such as a palpable neck mass, difficulty breathing, and dysphagia were more frequent in patients with PTL than in patients with DSVPTC. Symptoms such as neck pain, hoarseness, weight loss and fever were present in 2-4 patients with PTL, while these symptoms were
very rare in patients with DSVPTC. Compared to PTL, DSVPTC had a higher incidence of lymph node metastasis (82.5% vs 30.8%, p<0.001). There were no significant differences in radiation exposure history or thyroid cancer family history between the two groups (p>0.05).

In the laboratory findings, there were no significant differences in thyroid hormone levels (including TT3, TT4, FT3 and FT4) or ultrasensitive thyroid stimulating hormone (uTSH) levels between the two groups (p>0.05). There were also no significant differences in thyroid autoimmune antibodies (including Tg, TgAb and TPOAb) between the two groups (p>0.05); detailed data are shown in Table 2. When we defined HT as elevated thyroid autoimmune antibody or by the typical ultrasound pattern, we found that the prevalence of Hashimoto’s thyroiditis was much higher in the PTL group than in the DSVPTC group (65.4% vs 27.5%, p<0.05) (Fig 2A). Three patients (7.5%) presented with hyperthyroidism combined with DSVPTC, while none were diagnosed with hyperthyroidism and PTL. Hypothyroidism was defined as uTSH- or being on levothyroxine replacement therapy. We found that the prevalence of hypothyroidism in patients with PTL was higher than that in patients with DSVPTC (31% vs 17.5%) (Fig 2B).

The dominant sonographic findings are shown in Table 3. The dominant sonographic findings of PTL were large size (average 5.7±1.8 cm), nodular type (73.1%), heterogeneous echogenicity (86.5%), hypoechoic features (82.7%), irregular edges (90.4%), increased internal vascularity (84.6), and
calcifications (1.9%). DSVPTC cases mainly presented with diffuse type (85%), heterogeneous echogenicity (97.5%), irregular edges (87.5%), and calcifications (100%). Hypoechoic vascularity (22.5%) and increased internal vascularity (20%) were not commonly seen in patients with DSVPTC.

For analysis of the overall survival rate, data on patients who were alive at the last follow-up contact were censored. The overall survival rate of patients with PTL was 77.23% (95% confidence interval (CI), 53.15-89.98%), and that of patients with DSVPTC was 90.91% (95% CI, 50.79-98.77%) (Figure 3). There were no significant differences between survival rates in the two diseases (P=0.096). Six patients with PTL died during follow-up. Lymphoma progression was observed in 3 of the 52 patients due to abandonment therapy; one patient died of pneumonia, and one died of acute heart failure. Information regarding the cause of death was not available for the remaining patient. The only patient with DSVPTC died of thyroid cancer lung metastasis with infection and respiratory failure.

Discussion

PTL occurs preferentially in females, and the female-to-male ratio is approximately 3:1. The most common clinical presentation of PTL is a rapidly enlarging, painless goitre, which may cause dysphagia, dyspnoea, and hoarseness. In addition, B symptoms, including fever, night sweats, and weight loss, can be presented (18-20). The most frequent cases include non-Hodgkin lymphoma derived from B-cells, mainly diffuse large B cell lymphoma (DLBCL)
followed by mucosa-associated lymphoid tissue (MALT) lymphoma (21).

DSVPTC is characterized by diffuse enlargement of the thyroid gland and often lacks a specific mass (13). DSVPTC tends to occur more frequently in women, and the male-to-female ratio is approximately 1:5. Hyper-echogenicity, diffuse scattered micro-calcification and cervical lymph node metastasis are the characteristic ultrasonographic features of DSVPTC (9). On microscopic examination, DSVPTC has characteristic nuclear features of PTC. In addition, the carcinoma shows marked squamous metaplasia, numerous psammoma bodies, extensive interstitial fibrosis and heavy lymphocytic infiltration. Additionally, DSVPTC shows a higher prevalence of extra-thyroidal extension and cervical lymph node metastasis (10,12).

Typical DSVPTC shows different histological characteristics from PTL. For this reason, it is not difficult to diagnose these pathologies on microscopic examination. However, PTL and DSVPTC are both lymphocyte-rich thyroid lesions, and diagnostic challenges occur when these two types of malignancies associated in the context of Hashimoto's thyroiditis (HT)(22). Sometimes, PTL or DSVPTC can be mistaken clinically for thyroiditis because they share the same appearance of inflammatory background(23). The development of thyroidal MALT lymphoma has been described as an adverse event in patients suffering from long-standing HT(24). Differently, autoimmune thyroiditis is included among independent risk factors for papillary thyroid cancer development(25). It is important to differentiate PTL from DSVPTC, as
these diseases carry different prognoses and different treatment strategies. Both PTL and DSVPTC have generally good prognoses if diagnosed early and accurately and treated appropriately. Therefore, early preoperative diagnosis is helpful to develop a treatment strategy and improve the prognosis. The preoperative diagnosis of thyroid tumours depends on clinical symptoms and signs, laboratory examinations and ultrasound imaging examinations. When comparing the clinical features, we found that both PTL and DSVPTC were more likely to occur in women, but patients with DSVPTC were younger, had fewer compressive symptoms, and more frequently had neck lymph node metastasis than patients with PTL. This may be due to the fact that PTL is characterized by a rapidly growing mass in the neck, which may cause compression symptoms (18), while most DSVPTCs usually have indolent characteristics (26).

The laboratory findings did not show significant differences in thyroid hormone and autoimmune antibody levels between patients with PTL or DSVPTC. However, the prevalence of HT and hypothyroidism was significantly higher in patients with PTL than in those with DSVPTC (31% vs 17.5%). Hyperthyroidism could only be found in patients with DSVPTC, which accounted for 7.5%. HT is the most common form of autoimmune thyroiditis with heterogeneous clinical and pathological characteristics. In recent years, there have been case reports in the literature of PTL and DSVPTC occurring concurrently with HT. Some studies have indicated that both PTL and
DSVPTC are complications of HT (3, 27). The potential mechanism has generally been explained by aberrant follicular epithelial regeneration following chronic inflammatory damage or by the possibility that HT harbours potential precursor lesions of thyroid cancer (28). This evidence strongly supports a causal relation between thyroid cancer and pre-existing HT, and HT is considered a preneoplastic condition promoting thyroid carcinogenesis (29). In any case, in the context of HT, the risks of PTL and DSVPTC are significantly increased, and the difficulty of diagnosis is also significantly increased. Therefore, we should pay more attention to the differential diagnosis of PTL and DSVPTC when Hashimoto coexists.

Ultrasonography has been proven to be the most efficient method for the diagnosis of thyroid diseases and has the advantages of being non-invasive, involving real-time scanning, being easy to perform, and being widely available (13). When comparing the ultrasound features of PTL and DSVPTC, we found that both PTL and DSVPTC had heterogeneous echogenicity and irregular edges, but the lesion sizes of DSVPTC were smaller, diffuse sonographic patterns and calcifications were more frequently seen, and hypoechoic appearance and increased internal vascularity were rarer than those of PTL. The ultrasound features of PTL and DSVPTC were consistent with the findings of previous studies (13, 30).

The overall survival rate of PTL patients was 77.23%, which was lower than that of patients with DSVPTC (90.91%). Although the survival rate
between the two groups was not significantly different due to the small sample size, the mortality rate of PTL was still slightly higher. The high mortality of patients with PTL might be related to their malignant histological types, advanced age, many complications, and failure to receive active treatments (20). In contrast, although most patients with DSVPTC have cervical lymph node metastasis at the beginning of diagnosis, surgery and radiation therapy are very effective, and the patients are relatively young and generally have a better prognosis (13).

There are some limitations to this study. First, we had a small population size for PTL and DSVPTC because both were rare diseases, and it was difficult to obtain many cases for analysis. Second, we only retrospectively analysed patients with medical records in our hospital for the past 5 years, and the data are not broadly representative. Third, this is a retrospective study. Although both PTL and DSVPTC are related to HT, they cannot explain the causal relationship between HT and these two diseases. Further multi-centre, large-sample, prospective research studies are needed to explore the relationship between HT and these thyroid tumours. Both PTL and DSVPTC are lymphocyte-rich thyroid lesions, and sometimes it is difficult to differentially diagnose such patients with HT before surgery. In this retrospective study, we found certain clinical features, such as age, duration, compression symptoms; sonographic features such as size of thyroid or mass, echogenicity, irregular edges, calcification were helpful for initial impression
diagnosis of PTL and DSVPTC before surgery. Further differential diagnosis and confirmation will depend on the combination of cytology, histology, and even genetics.
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Figure Legends

**Figure 1** Representative histological figures of DSVPTC and thyroid diffuse large B-cell lymphoma (DLBCL).

(A). Histopathology of DSVPTC showing the carcinoma had numerous psammoma bodies, papillary structures and fibrous stroma. (Haematoxylin and eosin × 100).

(B). Higher magnification showing many tumour cells have squamoid differentiation and nuclear characteristic of papillary thyroid carcinoma. Psammoma bodies were in the red circle. (Haematoxylin and eosin × 400).

(C). Representative case with thyroid diffuse large B-cell lymphoma (DLBCL). Thyroid follicles were in the red circle. (Haematoxylin and eosin × 400).

(D). Representative immunostaining for B cell-derived lymphoma with monoclonal antibody against cell surface marker CD20 (× 200). Thyroid follicles were in the red circle.

**Figure 2** Comparison of the percentage of Hashimoto’s thyroiditis cases and the proportion of different thyroid functions in patients with PTL and DSVPTC.

(A). The diagnosis of HT is suggested by a typical ultrasound pattern or by the presence of antithyroid antibodies.

(B). Hyperthyroidism was defined as either an uTSH value < 0.56 µIU/ml or treatment with antithyroid drugs. Hypothyroidism was defined as uTSH > 5.91 µIU/ml or being on levothyroxine replacement therapy.

**Figure 3** Comparison of the survival rate of patients with PTL (black line) and DSVPTC (red line). The overall survival rate of PTL patients was 77.23% (95% confidence interval (CI), 53.15-89.98%), and that of DSVPTC patients was 90.91% (95% CI, 50.79-98.77%).
Figure 1 Representative histological figures of DSVPTC and DLBCL

217x162mm (96 x 96 DPI)
Figure 2 Compare the percentage of Hashimoto

(A) Proportion of Hashimoto’s Thyroids

PTL: 65.4%  
DSV: 27.5%

(B) 100%

PTL: 66%  
DSV: 75%

- Normal
- Hypothyroidism
- Hyperthyroidism

157x70mm (96 x 96 DPI)
Figure 3 Comparison of the survival rate

$P=0.0228$
Table 1. Clinical characteristics of patients with PTL and DSVPTC.

| Characteristic                  | PTL (n=52)          | DSV (n=40)          | P value       |
|--------------------------------|---------------------|---------------------|---------------|
| Age (years)                    | 64.5(55.25-71.75)   | 36(31-46.75)        | <0.001*       |
| Female, n, (%)                 | 43(83.7)            | 27(67.5)            | 0.14          |
| Duration of disease (months)   | 1(0.42-2.5)         | 3.3(1.55-7.25)      | 0.23          |
| Radiation exposure History, n, (%) | 1(1.9)       | 2(5)                | 0.58          |
| Family history of thyroid cancer, n, (%) | 2(3.8)       | 3(7.5)              | 0.65          |
| Palpable mass, n, (%)          | 19(36.5)            | 6(15)               | 0.03*         |
| Dyspnea, n, (%)                | 8 (15.4)            | 2 (5)               | 0.18          |
| Dysphagia, n, (%)              | 5(9.6)              | 1(2.5)              | 0.23          |
| Neck pain, n, (%)              | 3 (5.8)             | 0                   |               |
| Hoarseness, n, (%)             | 3 (5.8)             | 0                   |               |
| Weight Loss, n, (%)            | 4 (7.7)             | 0                   |               |
| Fever, n, (%)                  | 2 (3.8)             | 0                   |               |
| Metastases, n, (%)             | 16(30.8)            | 33(82.5)            | <0.001*       |

*P<0.05, difference was statistically significant. PTL, primary thyroid lymphoma; PTC, papillary thyroid carcinoma.

The duration of disease comes from the time between the appearance of the chief complaint in the medical history record and the confirmation of pathological diagnosis.
Table 2. Laboratory findings of patients with PTL and DSVPTC.

| Variable               | PTL (n=52)         | DSV (n=40)         | P value |
|------------------------|--------------------|--------------------|---------|
| TT3 (0.66-1.61ng/ml)   | 0.89±0.20          | 0.87±0.19          | 0.79    |
| TT4 (5.44-11.85ug/dl)  | 8.40±1.51          | 6.99±2.21          | 0.28    |
| FT3 (2.01-4.82pg/ml)   | 2.93±0.72          | 2.89±0.66          | 0.62    |
| FT4 (0.59-1.25ng/dl)   | 0.61±0.36          | 0.86±0.23          | 0.71    |
| uTSH (0.56-5.91ulU/ml) | 4.91(2.57-48.8)    | 2.29(1.64-12.48)   | 0.54    |
| Tg (0-50.03ng/ml)      | 12.3(4.18-81.12)   | 18.4(3.16-88.56)   | 0.94    |
| TgAb 0-4 (lu/ml)       | 25(6.55-1322)      | 8.5(2.5-1002)      | 0.11    |
| TPOAb (0-9Iu/ml)       | 56.9(25.3-668.1)   | 23.2(1.6-316.6)    | 0.13    |
| TRAb (0.3-1.8IU/l)     | 0.4(0.3-1.4)       | 1.5(0.6-2.2)       | 0.58    |

*P<0.05, difference was statistically significant. PTL, primary thyroid lymphoma; PTC, papillary thyroid carcinoma. TT3, total triiodothyronine; TT4, total thyroxine; FT3, free triiodothyronine; FT4, free thyroxine; uTSH, highly sensitive thyrotropin; TgAb, antithyroglobulin autoantibodies; TPOAb, antithyroperoxidase autoantibodies; TRAb, TSH receptor autoantibodies.
Table 3. Ultrasound features of PTL and DSVPTC.

| Variable                                      | PTL (n=52) | DSV (n=40) | P value |
|-----------------------------------------------|------------|------------|---------|
| Size (maximum diameter of lesion, cm)         | 5.7±1.8    | 4.2±0.6    | 0.007*  |
| Sonographic pattern, n (%)                    |            |            |         |
| Diffuse, n (%)                                | 14(26.9)   | 34 (85)    | <0.001* |
| Nodular, n (%)                                | 38(73.1)   | 6 (15)     |         |
| Heterogeneous echogenicity, n (%)             | 45(86.5)   | 39(97.5)   | 0.06    |
| Hypoechoic, n (%)                             | 43(82.7)   | 9(22.5)    | <0.001* |
| Irregular edge, n (%)                         | 47(90.4)   | 35(87.5)   | 0.19    |
| Increased internal vascularity, n (%)         | 44(84.6)   | 8(20)      | <0.001* |
| Calcifications, n (%)                         | 1(1.9)     | 40(100)    | <0.001* |

*P<0.05, difference was statistically significant. PTL, primary thyroid lymphoma; PTC, papillary thyroid carcinoma.