DIAGNOSTIC PITFALLS OF FINE-NEEDLE ASPIRATION CYTOLOGY AND PROGNOSTIC IMPACT OF CHEMOTHERAPY IN THYROID LYMPHOMA

Jin-Ying Lu, Chung-Wu Lin,¹ Tien-Chun Chang, and Yao-Chan Chen

Lymphomas of the thyroid gland are very rare, constituting less than 5% of all thyroid malignancies and only about 2% of extranodal lymphomas [1–4]. The disease has a peak incidence in the seventh decade, a male to female ratio of 1:3 [1, 2], and a strong association with Hashimoto’s thyroiditis [1]. The most common histologic type is non-Hodgkin’s lymphoma of diffuse large B cell type [2–4].

Diagnosis of thyroid lymphoma remains difficult, because fine-needle aspiration cytology (FNAC), the most widely used method for the diagnosis of thyroid tumors in general, cannot reliably distinguish thyroid lymphoma from Hashimoto’s thyroiditis [5]. Since the accuracy of FNAC varies and depends on the experience of the performer, it is therefore of interest to determine the sensitivity of FNAC in all settings.
Combined modality therapy for thyroid lymphoma has achieved a nearly 100% survival rate in some series [6–9]. Since delayed diagnosis may adversely affect the effectiveness of chemotherapy [7, 8, 10], it is interesting not only to evaluate the effectiveness of chemotherapy in each setting, but also to determine whether the initial FNAC diagnosis affects the prognosis.

Perceiving a possible link between diagnostic accuracy and therapeutic outcome, we sought to determine the diagnostic accuracy of FNAC in patients with thyroid lymphoma, to highlight the prognostic impact of diagnostic pitfalls, and to confirm the effectiveness of chemotherapy. However, because of the small number of cases in our series, further large-scale studies are required to clarify these issues.

Materials and Methods

Thyroid lymphoma was diagnosed in 14 patients at National Taiwan University Hospital (NTUH) between 1981 and 2000. Nine cases had histopathologic evidence of diffuse large B cell lymphoma, one of follicular lymphoma, one of lymphoctic lymphoma, one of precursor B cell lymphoblastic lymphoma, one of MALToma, and one of Hodgkin’s disease. The clinical characteristics, diagnosis, treatment, and outcome of patients are shown in the Table. The mean age at diagnosis was 57 years (22–87 yr). The peak incidence was in the sixth decade of life.

Most patients were initially evaluated by high-resolution, real-time thyroid ultrasonographic scanning using an electric real-time linear array unit with a 7.5-MHz transducer (RT-2800, General Electric, Cordova, CA, USA). Sagittal and transverse images were recorded on Polaroid films. When the presence of thyroid lesions was suggested by ultrasonography, FNAC was performed using a 22-gauge needle without local anesthesia. The aspirates were expelled directly onto a glass slide, and then spread along the long axis with a second glass slide. For each needle pass, two air-dried glass slides were prepared, and stained using the Romanowsky-based Riu method [11]. An experienced attending physician in the Endocrinology Division interpreted all ultrasonographic and cytologic data. Biopsies from all patients were reviewed by a hematopathologist according to the REAL/World Health Organization (WHO) classification of lymphoid neoplasms [12].

Diagnosis of thyroid lymphoma was made in four patients before 1990, and these patients underwent either surgical resection (1 patient) or local radiotherapy (3 patients) as the mainstay of treatment. Thyroid lymphoma was diagnosed after 1991 in 10 patients. Anthracycline-based chemotherapy was administered as the major therapy in nine patients, with three patients receiving additional local radiotherapy. The remaining patient was treated conservatively because of poor general condition.

Results

All patients presented with a thyroid mass. Thyroid ultrasonography was performed in nine patients. Seven patients were found to have hypoechoic nodule(s) with posterior acoustic enhancement, consistent with the presence of a lymphoma (Fig. 1A–C). However, a diffuse pattern of heterogeneous hypoechochogenicity indistinguishable from Hashimoto’s thyroiditis was found in two patients (Fig. 1D). The identification of a nodule or an abnormal echoic pattern was considered an indication for FNAC.

FNAC was performed in 11 patients and revealed six lymphomas (Fig. 2A), one anaplastic thyroid cancer (Fig. 2B), three cases of Hashimoto’s thyroiditis (Fig. 2C) and one case of Riedel’s struma (Fig. 2D). The FNAC findings could be roughly classified into four patterns. Most commonly, a centroblastic pattern was seen in diffuse large cell lymphomas (Fig. 2A). The identification of a monomorphic pattern of abundant centroblasts in six patients led to a straightforward diagnosis of lymphoma. One patient had a diffuse large cell lymphoma that showed a large cell pattern and led to a misdiagnosis of anaplastic carcinoma (Fig. 2B). The large nuclei with prominent nucleoli mimicked a poorly differentiated carcinoma, leading to misdiagnosis by FNAC. A centrocytic pattern was noted in a case of MALToma (Fig. 2C). The finding of predominant centrocytes mixed with scattered centroblasts did not distinguish between Hashimoto’s thyroiditis and lymphoma, and was another pitfall in FNAC diagnosis. A fibroblastic pattern was found in one patient with nodular sclerosing Hodgkin’s disease (Fig. 2D). Many fibroblasts could be seen in the FNAC smear for this patient. The potential pitfalls of the fibroblastic pattern included Riedel’s struma and de Quervain’s thyroiditis with fibrous healing.

Because of these potential pitfalls, the final diagnoses of thyroid lymphoma was established by biopsy in all patients. Representative biopsy illustrations are shown in Fig. 2 (A–D, lower panel). The 80% sensitivity of ultrasonography and the 55% sensitivity of FNAC in this series indicate the importance of histologic study for a definite diagnosis of lymphoma.

Retrospectively, although biopsy provided the most definite diagnosis, the clinical manifestation of a grow-
### Table: Clinical features of patients with thyroid lymphoma

| No./Dx | Year (y/o) | Age | Thyroid Ab & Ultrasound Dx | Cytologic Dx | Pathology | LDH Stage | Treatment | Prognosis/
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1981</td>
<td>69/F</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Follicular lymphoma</td>
<td>NA</td>
<td>IIE</td>
<td>R/T 45 Gy</td>
</tr>
<tr>
<td>2/1985</td>
<td>57/F</td>
<td></td>
<td></td>
<td></td>
<td>L’t MNG</td>
<td>Lymphoma</td>
<td>DLBL &amp; Hashimoto’s thyroiditis</td>
<td>NA</td>
</tr>
<tr>
<td>3/1986</td>
<td>74/M</td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
<td>Anaplastic carcinoma</td>
<td>DLBL</td>
<td>1,109 IV</td>
</tr>
<tr>
<td>4/1986</td>
<td>87/F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bilateral cystic goiter</td>
<td>Small lymphocytic lymphoma</td>
<td>NA</td>
</tr>
<tr>
<td>5/1991</td>
<td>77/F</td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
<td>Hashimoto’s thyroiditis</td>
<td>DLBL</td>
<td>NA</td>
</tr>
<tr>
<td>6/1991</td>
<td>47/F</td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
<td>Lymphoma</td>
<td>DLBL</td>
<td>NA</td>
</tr>
<tr>
<td>7/1993</td>
<td>53/M</td>
<td>T3 95</td>
<td>NA</td>
<td>NA</td>
<td>Precursor B cell lympho-blastic lymphoma</td>
<td>NA</td>
<td>IIE</td>
<td>CHO x V</td>
</tr>
<tr>
<td>8/1993</td>
<td>53/F</td>
<td>T3 139</td>
<td></td>
<td></td>
<td></td>
<td>Bilateral goiter</td>
<td>Hashimoto’s thyroiditis</td>
<td>DLBL &amp; Hashimoto’s thyroiditis</td>
</tr>
<tr>
<td>9/1995</td>
<td>45/M</td>
<td>T4 4.4</td>
<td></td>
<td></td>
<td></td>
<td>Bilateral MNG</td>
<td>Hashimoto’s thyroiditis</td>
<td>MALToma</td>
</tr>
<tr>
<td>10/1995</td>
<td>51/F</td>
<td>T3 128</td>
<td></td>
<td></td>
<td></td>
<td>Diffuse goiter</td>
<td>Hashimoto’s thyroiditis</td>
<td>DLBL</td>
</tr>
<tr>
<td>11/1995</td>
<td>53/M</td>
<td>T3 97.6</td>
<td></td>
<td></td>
<td></td>
<td>Diffuse goiter</td>
<td>Lymphoma</td>
<td>DLBL</td>
</tr>
<tr>
<td>12/1996</td>
<td>40/F</td>
<td>T4 4.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>312 IE</td>
</tr>
<tr>
<td>13/1998</td>
<td>50/M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>428 IE</td>
</tr>
<tr>
<td>14/2000</td>
<td>79/M</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Under treatment at 2000 post-diagnosis</td>
</tr>
</tbody>
</table>

Dx = diagnosis; LDH = lactate dehydrogenase, mg/dL; stage = Ann-Arbor staging system; NA = Not available; Ab = antibody; AMA = anti-thyroid microsomal antibody; DLBL = diffuse large B cell lymphoma; MNG = multiple nodular goiter; HD = Hodgkin’s disease; NS = nodular sclerosing type; MALToma = mucosa-associated lymphoid tissue lymphoma; R/T = radiotherapy; CR = complete remission; CR1 = 1st complete remission; CR2 = 2nd complete remission; T3 = triiodothyronine, ng/dL (normal range 80–200); T4 = thyroxine, μg/dL (normal range 4.5–12); TSH = thyroid-stimulating hormone, μIU/ml (normal range 0.4–4.0); c/w = compatible with; AAD = against advice discharge; CHF = congestive heart failure; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; COP = cyclophosphamide, vincristine and prednisolone; COPP-B = cyclophosphamide, vincristine, prednisolone, cyclophosphamide, doxorubicin, etoposide, prednisolone, cyclophosphamide, doxorubicin, bleomycin, vinblastine and dacarbazine; EPOCH = etoposide, etoposide, vincristine, cyclophosphamide, doxorubicin, Bleomycin, vinblastine and dacarbazine; ProMACE-CytaBOM = cyclophosphamide, doxorubicin, etoposide, prednisolone, cyclophosphamide, doxorubicin, bleomycin, vinblastine and dacarbazine; ESHAP = etoposide, methylprednisolone, high-dose cytarabine, bleomycin, vincristine, methotrexate, folinic acid; ESHAP = etoposide, methylprednisolone, high-dose cytarabine, bleomycin, vincristine, methotrexate, folinic acid.
ing thyroid mass was usually the first clue to thyroid lymphoma. In nine of the 14 patients, the thyroid tumor was a rapidly growing painless mass that had developed from 1 to 3 months prior to diagnosis. In the remaining five patients, the thyroid mass was a slow-growing mass that had developed over a period of 6 to 12 months. On physical examination, the thyroid lump felt like a hard or rubbery mass, and was bilateral in four patients and unilateral in 10 patients.

In addition to the local finding of a thyroid mass, five patients also had extrathyroid involvement. Endoscopic examination and biopsy in two patients showed gastrointestinal involvement of lymphoma presenting as severe gastrointestinal bleeding. The stomach was the most common site of involvement. Bone marrow examination was included in the staging of thyroid lymphoma in 11 cases in this series. Interestingly, only one of these patients, who had a low-grade MALToma, had evidence of bone marrow involvement. The breast, axillary lymph nodes, pericardium, esophagus, retroperitoneum, pancreas, and spinal cord were each involved in one patient only.

Disturbance in thyroid function might accompany the finding of a thyroid lymphoma. Coexisting autoimmune thyroiditis was diagnosed based on serologic results in four cases. Another four cases exhibited subclinical hypothyroidism, which was probably due to autoimmune thyroiditis, too, but serologic results were not available to establish a diagnosis. Overt hypothyroidism was not present in any of the patients. Other constitutional symptoms such as weight loss, fever, and night sweats were uncommon, appearing in only one patient, who had human immunodeficiency virus infection.

Four patients with thyroid lymphoma were treated with total thyroidectomy or local radiotherapy at our hospital before 1990. One patient had local recurrence soon after local radiotherapy at a dose of 4,500 cGy. Another patient died suddenly after total thyroidectomy. Two patients had good response after local radiotherapy at doses of 5,000 and 4,000 cGy, but developed severe gastrointestinal bleeding 1 and 3 months later. Both these patients had endoscopically proven gastric lymphoma and died of gastrointestinal bleeding. Thus, among the four patients in whom thyroid lymphoma was diagnosed before 1990, one had recurrence and three died soon after the diagnosis. The mean survival time after diagnosis for these patients was 60 days (range, 6–124 d).

Thyroid lymphoma was diagnosed in 10 patients at NTUH during the period from 1991 through 2000. Except for one patient lost to follow-up after the diag-
agnosis, nine of the 10 patients underwent anthracycline-based systemic chemotherapy tailored to the pathologic classification. These regimens were CHOP (cyclophosphamide, adriamycin, vincristine, prednisolone) for six patients with diffuse large B cell lymphomas, CHO (cyclophosphamide, adriamycin, vincristine) for one patient with lymphoblastic lymphoma, ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) for one patient with Hodgkin’s disease, and ProMACE-CytaBOM (cyclophosphamide, doxorubicin, etoposide, prednisolone, cytarabine, bleomycin, vincristine, methotrexate, folinic acid) for one patient with MALToma. Seven of the nine patients achieved complete remission promptly and remained disease free and alive at a mean follow-up of 68 months. The mean disease-free survival was 60 months with follow-up ranging from 3 to 92 months.

Only two of the nine patients treated after 1990 died. These were the first patient treated with chemotherapy, and the only MALToma patient. Systemic chemotherapy was first applied in our hospital in the treatment of a patient with thyroid lymphoma in 1991. She received one course of CHOP, three courses of COP, and five courses of COPPB (cyclophosphamide, vincristine, prednisolone, cisplatin, bleomycin) combined with local radiotherapy 3,000 cGy to the thyroid. She achieved complete remission after this regimen and remained cured until she died of congestive heart failure in 1999.
The patient with MALToma was treated initially with three courses of EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin), and achieved complete remission. However, recurrence developed 1 month later. Four courses of COPP, EPOCH, ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin) with peripheral blood stem cell harvest led to a second remission. He was maintained on oral steroids and interferon and remained in complete remission, but developed myelodysplastic syndrome and pancytopenia and died of intracranial hemorrhage 2 years later.

In summary, patients treated before and after 1990 had significantly different mean disease-free survival times (60 d vs 60 mo, $p = 0.005$ by Student’s $t$-test). The mean values of other prognostic factors including age (72 yr vs 54 yr, $p = 0.2053$), lactate dehydrogenase (LDH) concentration (1,109 mg/dL vs 473 mg/dL, $p = 0.1432$), and staging (stage 3 vs stage 2, $p = 0.3056$) were not significantly different between the two groups based on Mann-Whitney test.

**Discussion**

Most patients in this series presented with a thyroid mass that grew rapidly during the 1 to 3 months prior to diagnosis, a feature of thyroid lymphoma already reported by Matsuzuka et al [9]. Signs of a thyroid mass are common to lymphoma of the thyroid and undifferentiated thyroid carcinoma. Nevertheless, in elderly patients with a past history of Hashimoto’s thyroiditis and a rapidly enlarged neck mass, a diagnosis of thyroid lymphoma is highly likely [8, 9].

When thyroid lymphoma is suspected, ultrasonography is the most commonly used diagnostic tool in our hospital. Ultrasonography reliably assists in identifying a representative area of the lymphoma for biopsy [13]. Although not diagnostic for thyroid lymphoma, certain ultrasonographic features are unique and provide strong evidence to support such a diagnosis. These include a hypoechoic or almost anechoic nodular appearance intermingled with varying degrees of echogenic structures and posterior acoustic enhancement [9, 13, 14]. However, in two of our patients, the thyroid lymphoma had the unusual appearance of diffuse hypoechoogenicity indistinguishable from Hashimoto’s thyroiditis. In a case of suspected thyroid lymphoma, the finding of diffuse hypoechoogenicity suggested that the malignant lymphoma may have arisen from pre-existing Hashimoto’s thyroiditis.

In our hospital, FNAC is usually the next step following ultrasonography. A cytologic diagnosis of thyroid lymphoma can usually be established based on the finding of a monomorphic poorly differentiated lymphoid infiltrate [5, 15–17]. Occasionally, as in our series, thyroid lymphomas are misdiagnosed as thyroiditis or anaplastic carcinoma. These errors arise because low-grade lymphomas are composed of predominantly small lymphocytes mimicking Hashimoto’s thyroiditis [17], and high-grade non-Hodgkin’s lymphomas are composed of pleomorphic cells indistinguishable from anaplastic thyroid cancer. Due to these potential pitfalls, FNAC alone cannot be used for the diagnosis of thyroid lymphoma. Previous reports have also emphasized that a definitive diagnosis of lymphoma and its specific classification must involve surgical biopsy or core needle biopsy with light microscopic examination and immunohistochemical studies [5, 18].

Exceptionally, in one of our patients with a typical ultrasonographic picture of thyroid lymphoma, FNAC showed the unusual finding of abundant fibroblasts suggestive of Riedel’s struma. This patient turned out to have Hodgkin’s disease of the nodular sclerosing type by surgical pathology after left subtotal thyroidectomy. Retrospectively, the presence of fibroblasts in the thyroid gland is consistent with Riedel’s struma, fibrosing autoimmune thyroiditis, fibrosing peritumor thyroiditis, de Quervain’s thyroiditis with fibrous healing, and Hodgkin’s disease [19, 20]. Cyto logic evidence of chronic fibrosing thyroiditis is thus an indication for incisional biopsy to exclude the possibility of nodular sclerosing Hodgkin’s disease [17], and FNAC may be valuable in avoiding unnecessary advanced surgical intervention in such cases [21].

The treatment of thyroid lymphoma has evolved considerably in the last 20 years [22, 23]. Thyroid lymphoma may initially appear as a local problem, but it is a systemic disease process and systemic chemotherapy such as CHOP combined with radiation therapy should be used initially as part of the combined therapy. Surgical resection and involved-field radiation therapy alone are no longer recommended because of the high relapse rate in aggressive lymphoma [24–26]. These extrathyroid relapses may involve the gastrointestinal tract, retroperitoneal nodes, axilla, liver, spleen, and other sites [4, 24, 25, 27, 28] and may be effectively treated by the use of combined treatment modalities [24, 25, 28]. The only indication for local treatment is MALToma, a low-grade lymphoma, which, if confined to the thyroid gland, can be optimally treated with regional therapy alone [29, 30].

The cases of thyroid lymphoma diagnosed before 1990 in this series had a very poor prognosis compared with the excellent prognosis after 1990. Because there was no significant difference in other prognostic factors, such as age, elevated LDH, performance status, extranodal involvement, and Ann Arbor stage [31], the worse prognosis before 1990 was most likely the result of the treatment modalities used (local radiotherapy or resection alone in cases of potentially systemic disease).
We conclude that thyroid lymphoma is potentially curable if diagnosed early. The prompt detection of this disease, based on typical clinical manifestations and distinct ultrasonographic pictures, complemented with FNAC and confirmation with core needle or surgical biopsy, is essential to achieve an optimal outcome of treatment with chemotherapy.

References