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Primary Lymphoma of the Thyroid: Diagnostic and Therapeutic Considerations

Basro Sarinah and Abdullah Noor Hisham, Department of Breast and Endocrine Surgery, Hospital Putrajaya, Putrajaya, Malaysia.

BACKGROUND: Primary thyroid lymphoma is uncommon and accounts for less than 2–5% of all thyroid malignancies. The aim of the present study was to review our experience and management of primary thyroid lymphoma and to discuss the diagnostic and therapeutic considerations.

METHODS: Eleven women and six men with primary thyroid lymphoma were diagnosed and managed in our department between October 1998 and March 2006. The clinical course and pathological spectrum of this disorder affecting the thyroid gland were reviewed.

RESULTS: Twelve patients had a prior history of thyroid disease. Clinical symptoms included a rapidly enlarging neck mass (88%), dyspnoea (65%), dysphagia (53%) and hoarseness of voice (35%). Five patients were hypothyroid at the time of diagnosis. Fifteen patients underwent fine-needle aspiration cytology (FNAC). Six patients had an initial diagnosis of lymphocytic thyroiditis. FNAC results were highly suggestive of thyroid lymphoma in only five patients. In the remaining patients, FNAC results showed a follicular lesion in two patients and were inconclusive in the other two patients. A further incisional biopsy was performed in five patients, and a diagnosis of non-Hodgkin's lymphoma (NHL) was confirmed in four patients and inconclusive in one. Five patients had a core biopsy. Four revealed NHL and one had lymphocytic thyroiditis. Nine patients underwent surgery; three of whom had emergency debulking of the tumour for acute airway obstruction. A final diagnosis of thyroid lymphoma was confirmed in all these patients. Sixteen patients had B-cell and one had T-cell NHL. Fifteen patients received combination chemotherapy with or without irradiation. All tumours dramatically decreased in size soon after initiation of treatment. Overall survival was 82%, with a mean follow-up of 19 months.

CONCLUSION: The diagnosis of primary thyroid lymphoma should be considered when dealing with rapidly growing goitres. The role of FNAC in diagnosing thyroid lymphoma is limited but it is still useful in the initial work-up. Nevertheless, surgical intervention is often required to establish the diagnosis and relieve critical airway compression. A combination of chemotherapy and irradiation is the mainstay of management. [*Asian J Surg* 2010;33(1):20–24]

Key Words: lymphocytic thyroiditis, thyroid lymphoma

Introduction

Primary thyroid lymphoma is an uncommon malignancy. In most series, it comprises 0.6–5% of all thyroid cancers and < 2% of extranodal lymphomas.[1,2] Frequently, based on histology and fine-needle aspiration cytology (FNAC), it is difficult to distinguish between anaplastic carcinoma and thyroid lymphoma. In most instances, thyroid lymphoma

Address correspondence and reprint requests to Abdullah Hisham, Department of Breast and Endocrine Surgery, Hospital Putrajaya, Precinct 7, Putrajaya 62250, Malaysia.
E-mail: anhisham@pd.jaring.my • Date of acceptance: 10 November 2009

is diagnosed only after thyroid surgery for suspicious carcinoma has been performed.[3] The increased use of immunocytochemical lymphoid markers has improved the diagnosis and categorization of thyroid lymphoma.[4] It is now believed that cases previously diagnosed as anaplastic carcinoma could well be primary thyroid lymphoma. Recent onset of symptoms or a rapid change in size of a pre-existing thyroid mass are the hallmarks of both thyroid lymphoma and anaplastic carcinoma.[5,6] It is important to distinguish between these two tumours because anaplastic carcinoma has a much poorer prognosis, with few patients surviving beyond 2 years, whereas primary thyroid lymphoma has a favourable outcome with cyclophosphamide-based multimodality chemotherapy in combination with radiotherapy.[7–9]

Patients and methods

All patients diagnosed with primary thyroid lymphoma in our department from September 1998 to March 2006 were enrolled in this prospective study. The clinical course and pathological spectrum of this disorder as it affected the thyroid gland were reviewed.

A total of 17 patients, 11 women and 6 men, were managed over a period of 92 months. The mean age at presentation was 58 years, with a range of 31 to 82 years. Fifteen patients (88%) presented with a rapidly enlarging anterior neck mass; 12 of them had a history of pre-existing goitre (70%) with a mean duration of 7 years. Other associated symptoms included dyspnoea (65%), dysphagia (53%), hoarseness of voice (35%), and pain over the thyroid swelling (12%). Six patients also experienced associated constitutional symptoms such as loss of weight or appetite, and one patient had fever.

Results

All 17 patients had palpable goitre. Four patients had clinically palpable cervical lymph nodes. However, imaging studies showed the presence of cervical lymph nodes in 11 cases. Eleven of our patients were euthyroid (65%), five were hypothyroid (29%), and one presented with mild hyperthyroidism upon treatment (6%). Anti-microsomal and anti-thyroglobulin antibodies were only done in seven patients, and were found to be elevated in five of these patients.

Fifteen patients had FNAC performed, which revealed lymphocytic thyroiditis in six patients, and a high suspicion of thyroid lymphoma in five patients. In the remaining patients, FNAC results showed a follicular lesion in two patients, and were inconclusive in the other two patients. In one patient with an initial FNAC diagnosis of lymphocytic thyroiditis, repeat examination after 1 year was suggestive of either non-Hodgkin's lymphoma (NHL) or high-grade anaplastic carcinoma (Table 1).

Five of our patients had a core biopsy performed. Four were confirmed with NHL and one was confirmed with lymphocytic thyroiditis. Five patients had an open biopsy performed, and four were confirmed with. Nine patients underwent thyroidectomy; four of them were operated on in an emergency setting; tumour debulking was done for acute airway obstruction in three patients, and for severe pain in the other (Table 2).

In three patients who underwent thyroidectomy, the diagnosis of NHL was unsuspected preoperatively, and their initial FNAC result indicated lymphocytic thyroiditis. One patient underwent thyroidectomy for clinical suspicion of follicular malignancy. However, in one patient who was highly suspicious for lymphoma, all diagnostic investigations with FNAC, two repeated core biopsies, and a final open biopsy were inconclusive. It was only after thyroidectomy for significant pressure symptoms that a diagnosis of NHL was confirmed (Table 3).

Histologically, 16 of our patients had B-cell NHL and one had T-cell NHL. The latter was a 54-year-old Chinese woman who had a history of pre-existing goitre for 20 years, with sudden enlargement for 2 months. Subsequent staging and work-up of all these patients included computed tomography of the mediastinum and abdomen, and bone marrow aspiration. Six of our patients presented in stage IE (35%) and 11 patients in stage IIE (65%).

In 15 patients, treatment constituted of chemotherapy (CHOP regimen: cyclophosphamide, doxorubicin, vincristine and prednisolone) with or without radiotherapy. In all cases, a dramatic decrease in tumour size was noted after initiation of treatment. All patients except one are still alive without any relapse. Our overall survival was 82%, with a mean follow-up of 19 months (range: 2–30 months). One patient who underwent emergency tumour debulking for acute respiratory distress defaulted after two cycles of chemotherapy. Following this, the tumour reappeared and he succumbed 6 months after surgery, despite restarting chemotherapy.

The other two patients who underwent emergency debulking surgery for acute airway obstruction also died.

Table 1. Fine needle aspiration cytology (FNAC)

FNAC results	No. of patients (%)
Lymphocytic thyroiditis	6 (40)
Suggestive of lymphoid malignancy	5 (34)
Follicular lesion/neoplasm	2 (13)
Inconclusive	2 (13)
Total	15 (100)

Table 2. Diagnostic procedures

Diagnostic procedures	No. of patients (%)
Trucut biopsy	4 (23.5)
Open biopsy	4 (23.5)
Thyroidectomy	9 (53)
Hemithyroidectomy	1
Total thyroidectomy	4
Debulking of tumour	4

Table 3. Indication for surgery

Indication for surgery	No. of patients (%)
Unsuspected of NHL (FNAC: lymphocytic thyroiditis)	3
Clinical suspicion of follicular malignancy	1
Acute airway obstruction	3
Severe pain	1
Core and open biopsy were inconclusive	1
Total	9

NHL = non-Hodgkin's lymphoma; FNAC = fine-needle aspiration cytology.

One was an 81-year-old woman who was too fragile for postoperative chemotherapy, and recurrence was detected after 1 month. She was given radiotherapy but responded poorly and succumbed to the disease 4 months after surgery. The other patient died from aspiration pneumonia 5 days postoperatively.

Discussion

NHL of the thyroid tends to have a female predominance. In our series, it was a 1.8:1 female to male ratio but others have reported it to be as high as 4:1.[10,11] Clinically, it can mimic anaplastic thyroid carcinoma in that both have similar clinical characteristics of rapid growth, which might be associated with dyspnoea, dysphagia, pain and hoarseness of voice. NHL of the thyroid usually presents in the 5th to 7th decades of life. A large number of these cases had a prior history of Hashimoto's thyroiditis (range: 40–80%).[2,12]

It is accepted widely that patients with Hashimoto's thyroiditis have a greater risk of subsequently developing thyroid lymphoma, with an overall 60–80-fold higher risk than in the general population.[13] It is estimated that 1 in 200 cases of Hashimoto's disease goes on to develop primary thyroid lymphoma. There is also evidence that large-cell lymphoma probably evolves from persistent low-grade mucosa-associated lymphoid tissue (MALT) malignant lymphoma, suggesting a morphological progression from chronic lymphocytic thyroiditis to low-grade MALT lymphoma, and subsequently, to high-grade large-cell lymphoma.[1] The time interval between the diagnosis of Hashimoto's thyroiditis and the subsequent development of malignant lymphoma of the thyroid is approximately 9–10 years.[14]

FNAC has an established role in the management of thyroid nodules and goitres. However, its role in diagnosing thyroid lymphoma is limited because the small yield from FNAC makes the cytological differentiation of thyroid lymphoma from lymphocytic thyroiditis and anaplastic carcinoma difficult.[15] Furthermore, the yield from FNAC may not be representative. Therefore, although FNAC is usually used in the initial work-up of all thyroid patients, a core needle or open biopsy is often required to diagnose thyroid NHL. Occasionally, even thyroidectomy is required.

FNAC frequently reveals lymphocytes that are often interpreted as evidence for the presence of thyroiditis. The histological differentiation between pre-existing thyroiditis and thyroid lymphoma is often difficult and can lead to an underestimate in the reporting of the association.[2,16] Scholefield et al[16] have concluded that serial autoantibody assays in patients with Hashimoto's thyroiditis might be necessary to help predict the onset of lymphomatous change in this condition.

Cases of high-grade lymphoma can be confused with anaplastic carcinoma, but this distinction can be made easily on immunohistochemical grounds using antibodies to cytokeratins and leukocyte common antigens. The essential difference between a reactive and a neoplastic lymphoid infiltrate is the presence of light chain restriction in the latter.[17] Lymphoma tumours usually have a diffuse growth pattern; residual follicles are often seen within the

tumour at the border. It is of particular interest that tumour cells might also be present in these follicles (Figure 1).

Similar to the findings of the present study, most thyroid lymphomas are of B-cell origin and predominantly of diffuse large-cell type.[1,2,11,18] The second most common histological type is MALT lymphoma.[11,18] Other less frequently encountered types include Hodgkin's disease, Burkitt's lymphoma and plasmacytoma. T-cell lymphoma is extremely rare, with only a few cases reported in the literature. Most of the T-cell lymphomas reported have been in Asia. In general, T-cell lymphoma is associated with a worse prognosis than is B-cell lymphoma.[19,20]

The choice of treatment in primary thyroid lymphoma is based on the histological subtype of the neoplasm, its stage, and the tumour bulk, as well as the other associated comorbid factors. Similar to previous studies,[11,21–23] the majority of patients with thyroid lymphoma in the current study presented with stage I and II disease (about 80%). The staging is adopted from the Ann Arbor system for Hodgkin's disease. The overall survival ranges from 35% to 79%.[11,23–26] The 5-year survival for each stage is 80% for stage IE, 50% stage for IIE and < 36% for stage IIIE and IVE.[26]

Several prospective randomized trials have shown an advantage in combining chemotherapy with radiotherapy for patients with stage I and II intermediate- and high-grade NHL.[23,27] A review of 211 patients with NHL localized to the thyroid gland has revealed that overall and distant recurrence rates were significantly reduced in patients who were treated with a combination of systemic chemotherapy and radiation, in contrast to those who were treated with radiotherapy alone (overall recurrence: 7.7% *vs*. 37%; distant recurrence: 5.1% *vs*. 30.8%).[8] A similar relapse rate of 30% has been reported by DiBiase et al.[23] Most centres advocate the CHOP chemotherapy regimen.

Pedersen and Pedersen[24] have reported that histological grade is not a statistically significant factor in survival; however, it is significant in stage IIIE and IVE disease. In contrast, Laing et al[25] have reported that the presence of histopathological features of MALT is a statistically significant factor in patient survival and also a favourable prognostic factor for high-grade lymphoma. Lymphoma of non-MALT origin has a poorer prognosis. The overall cause-specific survival at 5 years for patients with NHL of MALT origin was 90% compared with 55% for those without evidence of MALT origin.

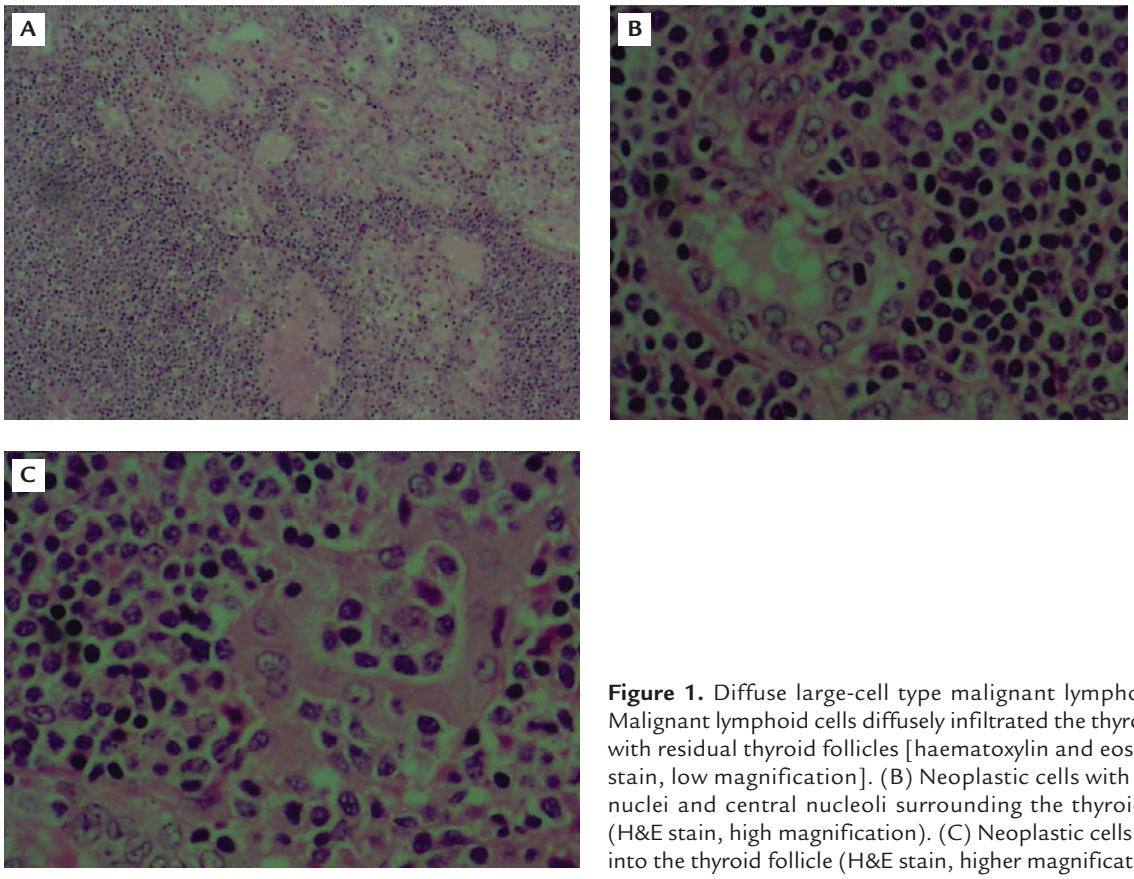

Figure 1. Diffuse large-cell type malignant lymphoma. (A) Malignant lymphoid cells diffusely infiltrated the thyroid gland with residual thyroid follicles [haematoxylin and eosin (H&E) stain, low magnification]. (B) Neoplastic cells with rounded nuclei and central nucleoli surrounding the thyroid follicle (H&E stain, high magnification). (C) Neoplastic cells plugging into the thyroid follicle (H&E stain, higher magnification).

The role of the surgeon in the treatment and diagnosis of thyroid lymphoma has evolved from surgical debulking to open biopsy. With the use of irradiation and chemotherapy, the need for surgery has nearly disappeared, except in those patients who present with significant airway compromise. A study by Rebecca et al[28] on 27 patients with thyroid lymphoma and significant airway obstruction who underwent palliative surgery showed good long-term palliation (overall 5-year survival of 77%) and low operative morbidity.

The diagnosis of primary thyroid lymphoma should be considered when dealing with rapidly growing goitres. FNAC is a useful first step in diagnosing thyroid cancers; surgical intervention is confined mainly to critical airway compression with resection of the thyroid mass and to some extend incisional biopsy for a confirmatory diagnosis. A combined modality of treatment with chemotherapy and irradiation is the mainstay of management of thyroid lymphoma.

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