

Clinical Presentation and Treatment of Non-Hodgkin's Lymphoma of the Thyroid Gland

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Background: Non-Hodgkin's lymphoma (NHL) of the thyroid is a rare malignancy. The traditional approach to curative treatment of localized (stages I and II) NHL of the thyroid gland is surgical resection. The recent success of multimodality chemoradiotherapy suggests that surgery should be reserved for providing a tissue diagnosis or relief from acute airway obstruction. It is questionable whether this has made an impact on treatment approaches.

Methods: Retrospective chart review was conducted for all cases of localized NHL of the thyroid gland treated at Roswell Park Cancer Institute between January 1970 and January 1999.

Results: Ten patients (8 women, 2 men) with a mean age of 56.8 years were identified. Nine patients (90%) presented with a neck mass; seven patients (70%) had a history of Hashimoto's disease. Nine patients (90%) had extensive investigations to rule out extrathyroidal disease. All patients were treated with either a total thyroidectomy (eight patients) or a thyroid lobectomy (two patients). Nine (90%) were initially treated outside of Roswell Park Cancer Institute and referred secondarily for consideration of further therapy. Adjuvant therapy consisting of cyclophosphamide-based chemoradiotherapy was administered to nine patients. Overall survival was 80% at a mean follow-up of 8.6 years with a disease-specific survival rate of 100%.

Conclusions: A review of the literature suggests that fine needle aspiration (FNA) with flow cytometry and immunohistochemistry can be used to accurately diagnose NHL of the thyroid gland. Open biopsy should be reserved for cases where this technique is not available or where the diagnosis can not be confirmed by FNA alone. Extrathyroidal NHL should be ruled out by chest x-ray, CT scan of the abdomen, and bone marrow biopsy. Further review suggests that the most efficacious therapy is systemic chemotherapy in combination with radiation for local control. Debulking surgery should be used only to provide relief from acute airway obstruction.

Key Words: Thyroid lymphoma—Staging—Treatment.

Non-Hodgkin's lymphoma (NHL) of the thyroid gland is uncommon, accounting for only 1%–5% of all thyroid malignancies.^{1,2} Although NHL occurs as extranodal disease in 25%–50% of patients,^{3,4} less than 2% of cases originate in the thyroid gland.⁴ More commonly, in 10% of patients, it is seen as a manifestation of generalized disease with secondary involvement of the thyroid gland.⁵ Elderly women are most commonly affected, the

disease arising in association with chronic lymphocytic thyroiditis (Hashimoto's disease) in 40%–80% of cases.^{6,7} Histologically, NHL of the thyroid tends to present as a poorly differentiated lesion. However, there may be a subgroup of patients with characteristics of mucosa-associated lymphoid tissue (MALT).^{8,9,10} These lymphomas remain localized for an extended period of time. This accounts for the high prevalence of early disease, stages I_E (confined to the thyroid gland) and II_E (local lymph node involvement), at initial presentation.¹⁰

The treatment of localized NHL of the thyroid gland (stages I_E and II_E), regardless of histology, is controversial. The low incidence of the disease and the evolution of therapeutic approaches over the last several decades have led to inconsistent treatment recommendations. However, given the recent success of cyclophosphamide-

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based multimodality chemotherapy in combination with radiotherapy,¹¹ the role of surgery may be limited to providing tissue for diagnosis and for the relief of acute airway obstruction. Recognition of the thyroid as a component of the mucosa-associated lymphoid tissue (MALT) system warrants attempts at identification and eradication of antigenic stimulation of B-cell MALTomas.

METHODS

All cases of NHL of thyroid (stages I_E or II_E) treated at Roswell Park Cancer Institute between January 1970 and January 1999 were identified. The charts were retrospectively reviewed. Information related to clinical presentation, physical examination, diagnostic investigations, and therapeutic interventions was recorded. Pathology was reviewed for all cases.

RESULTS

There were 10 cases of stage I_E or II_E NHL of the thyroid treated at Roswell Park Cancer Institute between January 1970 and January 1999. Patients had a mean age of 56.8 years (range 23–76). There were eight females and two males (4:1 ratio).

The most common presenting symptom was a neck mass which was seen in nine (90%) patients (Table 1). Less frequently, patients presented with dysphagia (30%), hoarseness (20%), or dyspnea (10%). None of the patients had fevers, night sweats, or weight loss (B symptoms). Seven (70%) patients were either known to have preexistent Hashimoto's disease or were given this diagnosis at the time of surgery. Three (30%) patients were noted to have a history of goiter which was nonresponsive to suppressive therapy. Only one patient was known to have had previous low-dose radiotherapy to the head and neck.

TABLE 1. Clinical presentation of localized (stages I_E and II_E) non-Hodgkin's lymphoma of the thyroid gland

| Presentation | Incidence (%) |
|----------------------------------|---------------|
| Neck mass | 9 (90) |
| Hashimoto's disease | 7 (70) |
| Dysphagia | 3 (30) |
| Goitre | 3 (30) |
| Hoarseness | 2 (20) |
| Dyspnea | 1 (10) |
| Fever, night sweats, weight loss | 0 |

Diagnosis

The diagnostic studies undertaken to stage the extent of disease are outlined in Table 2. Most patients were staged as either I_E or II_E after a series of investigations failed to show disease elsewhere. Bone marrow biopsy (50%) and gallium scanning (50%) were the most commonly used tests, the latter being more frequently used in the initial years of the study. Intra-abdominal disease was investigated through the use of either a CT scan (40%), liver scan (30%), ultrasound (10%), liver biopsy (10%), and/or intravenous pyelography (IVP) (10%). Intrathoracic disease was ruled out by either a CT scan (10%) or a chest x-ray alone (40%). Three patients had a negative lymphangiogram, which was used more frequently in the early years of the study.

Treatment

All patients underwent either a thyroid lobectomy (two patients) or total thyroidectomy (eight patients) (Table 3). Microscopic examination revealed a diffuse growth pattern in seven patients with a predominance of large cells in five cases and mixed large and small cells in two cases. Three patients had a follicular pattern with two composed of small cleaved cells and one of large cells. A diffuse large cell type was the most common (Fig. 1), representing 50% of the cases in this series. Two cases of large cell lymphoma were associated with Hashimoto's thyroiditis. In cases where immunotyping was done, the tumors were of B-cell origin.

Four patients were treated with postoperative adjuvant radiotherapy alone (3600–4300 rads), three with adjuvant cyclophosphamide-based chemotherapy, and two with a combination of chemoradiotherapy. Only one patient had no further therapy after total thyroidectomy. Overall survival was 80% (eight patients), with a mean follow-up of 8.6 years. Disease-specific survival was 100% with two people dead from other causes.

TABLE 2. Diagnostic investigations to rule out extrathyroidal disease

| Investigations | No. Pts. (%) |
|--------------------|--------------|
| Bone marrow biopsy | 5 (50) |
| Gallium scan | 5 (50) |
| CT abdomen | 4 (40) |
| Liver scan | 3 (30) |
| Ultrasound abdomen | 1 (10) |
| Liver biopsy | 1 (10) |
| IVP | 1 (10) |
| CXR | 4 (40) |
| CT Chest | 1 (10) |
| Lymphangiogram | 3 (30) |

TABLE 3. Demographics, treatment, and outcome in patients with localized non-Hodgkin's lymphoma of the thyroid gland

| Pt | Age | Gender | Surgery | Adjuvant | Stage | Histology | Outcome |
|----|-----|--------|-------------------------|------------------------------|------------------|-------------------------|------------------|
| 1 | 70 | F | Total thyroidectomy | 4000 rads | IA _E | Lymphocytic | FOD at 10 years* |
| 2 | 58 | F | Total thyroidectomy | 3600 rads | IA _E | Histiocytic (diffuse) | FOD at 15 years |
| 3 | 68 | F | Total thyroidectomy | 3600 rads M-COP ¹ | IIA _E | Histiocytic (diffuse) | FOD at 12 years |
| 4 | 52 | F | Total thyroidectomy | | IA _E | Small cell (cleaved) | FOD at 13 years |
| 5 | 33 | M | Total thyroidectomy | M-COP | IA _E | Large cell (noncleaved) | FOD at 8 years |
| 6 | 76 | M | Total thyroidectomy | 4000 rads | IA _E | Large cell (noncleaved) | FOD at 12 years |
| 7 | 59 | F | Total thyroidectomy | 3000 rads CHOP ² | IA _E | Mixed (diffuse) | FOD at 2 years* |
| 8 | 69 | F | Left thyroid lobectomy | 4300 rads | IIA _E | Mixed (diffuse) | FOD at 5 years |
| 9 | 60 | F | Total thyroidectomy | CHOP | IA _E | Large cell (diffuse) | FOD at 5 years |
| 10 | 23 | F | Right thyroid lobectomy | CHOP | IA _E | Large cell (diffuse) | FOD at 4 years |

FOD, free of disease.

¹ M-COP, methotrexate, cytoxan, vincristine, prednisone.

² CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone.

* Dead of other causes.

DISCUSSION

The present series is consistent with previously published reports that suggest that NHL of the thyroid gland tends to occur most commonly in women during the sixth and seventh decades of life. Eight of ten (80%) patients were women with a mean age of 56.8 years. Most patients presented with a neck mass alone; other symptoms were most commonly related to local compressive symptoms associated with acute thyroid enlargement. As expected, none of the patients had fevers, night sweats, or weight loss.

In most cases, the diagnosis can be suspected when the patient presents with an acutely enlarging thyroid mass, especially if there is a known or presumed history of chronic lymphocytic thyroiditis. The most important distinction is between thyroid lymphoma and anaplastic carcinoma, which has been traditionally established by open biopsy.¹² Until recently, there appeared to be no role for fine needle aspiration (FNA) in the diagnosis of thyroid lymphoma. This resulted from an inability to accurately make the diagnosis on the basis of cytology alone, especially against a background of Hashimoto's disease. The use of flow cytometry to characterize DNA aneuploidy¹³ and identification of B-cell lineage by immunohistochemistry for CD20¹⁴ has increased the diagnostic potential of FNA. Polymerase chain reaction (PCR)-based assay for immunoglobulin heavy chain rearrangements may also aid in the diagnosis by the identification of clonal populations of lymphocytes.¹⁵ Open biopsy should be reserved for patients for whom the diagnosis cannot be made by FNA alone or where the facilities are not adequate to provide a diagnosis using this technique.

Accurate staging of non-Hodgkin's lymphoma provides prognostic information and can guide therapeutic management.^{11,16,17} Most patients in the present series

had at least one test, and in most cases a series of tests, to rule out extrathyroidal disease. There was only one patient who had no further investigations undertaken after a total thyroidectomy which provided the diagnosis.

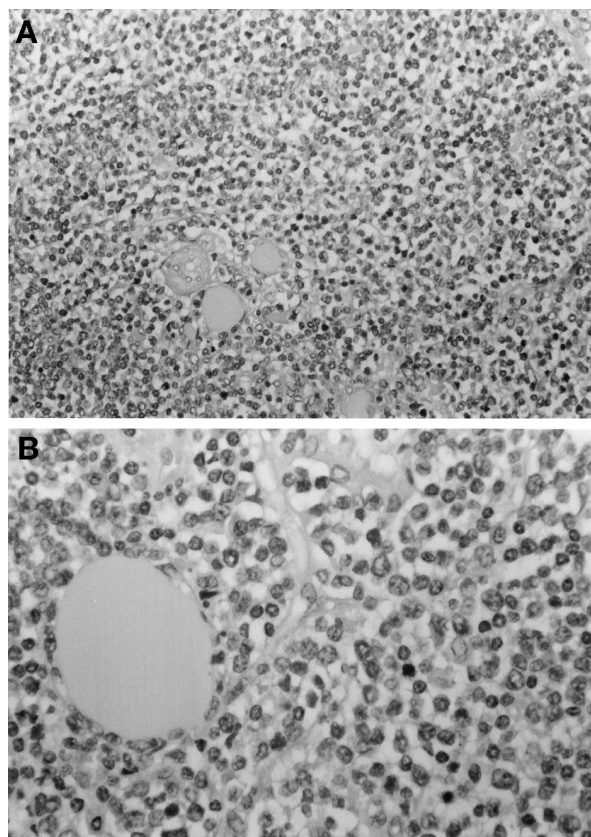


FIG. 1. Malignant lymphoma, diffuse large cell type. (A) The tumor diffusely infiltrates the thyroid gland with foci of residual entrapped non-neoplastic thyroid follicles (Hematoxylin and Eosin, 200x), and (B) higher magnification showing large non-cleaved cells with round to oval nuclei, clumped chromatin and nucleoli. An entrapped thyroid follicle is present (Hematoxylin and Eosin, 400x).

Importantly, 50% of the patients had a bone marrow biopsy to rule out marrow involvement. However, bone marrow biopsy has not been a universally accepted staging procedure. Five-year survival rates of 30%–40% after local therapy for presumed stage I disease^{8,18} suggest that understaging of patients may result in less than optimal treatment for disease which has extended beyond the thyroid gland or the regional lymphatics. Investigations aimed at ruling out extrathyroidal disease are important because they may have an impact on definitive therapy. Presently, a chest x-ray, CT scan of the abdomen, and bone marrow biopsy are the most important investigations in ruling out disseminated disease.

Although all patients in the present study had either a thyroid lobectomy (two patients) or a total thyroidectomy (eight patients), radiotherapy alone or in conjunction with chemotherapy is warranted in early stage disease.^{11,17} A review of 211 patients with NHL localized to the thyroid gland¹⁷ 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%, respectively). The advantage of using radiotherapy to provide local control is that surgical injury to the recurrent laryngeal nerves and the parathyroid glands can be avoided while providing equally effective local control.¹¹

The association between Hashimoto's disease (chronic lymphocytic thyroiditis) and non-Hodgkin's lymphoma has been widely debated. It is sometimes difficult to distinguish the two entities histologically,⁷ and it is presumed that the chronic inflammatory response elicited in Hashimoto's disease will eventually lead to malignant degeneration. Progression can be identified by monoclonal antibody identification of light chain restriction.¹⁹ The transformation may require chronic antigenic stimulation similar to that seen with *H. pylori* and B-cell associated MALToma of the stomach.^{8,9,10} In fact, several authors consider non-Hodgkin's lymphoma of the thyroid to represent lymphomatous transformation of mucosa-associated lymphoid tissue.^{8,9,10} Arising within the stomach, thyroid, lung, and salivary glands, these tumors enjoy a prolonged period of localized disease. A common antigenic stimulus is suggested by the observation that late recurrences tend to arise in other mucosa-associated lymphoid tissues. Further studies examining

the role of *H. pylori* and other potential stimulants of chronic lymphocytic thyroiditis may define a subset of patients who are potential candidates for either eradication of the inciting stimulus or more directed therapy of B-cell mucosa-associated lymphomas.

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