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Primary Thyroid Lymphoma: Can the Diagnosis Be Made Solely by Fine-Needle Aspiration?

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Background: Primary malignant lymphoma of the thyroid accounts for <5% of all thyroid malignancies and is primarily treated with chemotherapy and external beam radiation. With the advent of modern immunophenotypic analyses, fine-needle aspiration (FNA) can potentially obviate the need for surgical procedures.

Methods: To investigate the utility of FNA, data from 23 consecutive patients with primary malignant thyroid lymphoma evaluated at the Johns Hopkins Hospital from July 1985 to April 2000 were analyzed.

Results: Patients were categorized into two groups: those diagnosed before 1993 (group 1, n = 12) and those diagnosed after 1993 (group 2, n = 11). Although patients in group 1 were slightly older, there were no other differences between the groups with regard to sex, tumor grade, or tumor stage. Although no patient in group 1 was successfully diagnosed by FNA alone, seven patients (63%) in group 2 were diagnosed solely by FNA ($P = .019$, χ^2 analysis). Therefore, all 12 patients in group 1, but only 4 of 11 patients in group 2, required open surgical biopsy.

Conclusions: Primary thyroid lymphoma is an uncommon malignancy usually treated nonsurgically once the diagnosis is established. In most patients with malignant lymphoma of the thyroid, FNA, should obviate the need for open surgical biopsy.

Key Words: Thyroid lymphoma—Fine-needle aspiration—Diagnosis—Cytology.

Primary thyroid lymphoma is a relatively rare entity, accounting for only 2% to 5% of all thyroid malignancies.[1–3] The standard of care for treatment of these lymphomas has evolved significantly over the past 20 years from total surgical extirpation of the thyroid gland to a noninvasive therapy consisting of chemotherapy and external beam radiation once the diagnosis has been established.[2,4,5] By itself, the cytological appearance of the lymphoid cells is often not sufficient to establish a definite diagnosis of malignancy, necessitating open biopsy or thyroid lobectomy to establish the diagnosis of malignacy.[6] The advent of modern immunophenotypic analyses, including flow cytometry and immunohistochemistry, has greatly improved the accuracy of fine-needle aspiration (FNA) in diagnosing thyroid lymphoma and has obviated the need for more invasive surgical options.[[Fig. 1]]

The vast majority of primary thyroid lymphomas are B cell in origin and almost always arise in the background of chronic lymphocytic thyroiditis (Hashimoto's thyroiditis).[6–8] Some thyroid lymphomas arising in this background of lymphocytic thyroiditis are part of the mucosal-associated lymphoid tissue system (MALT). Indeed, up to 69% of thyroid lymphomas have been demonstrated to be of MALT origin,[9] and thyroid lymphomas are noted to occur in association with gastrointestinal MALTomas.[10,11] Difficulty in distinguishing malignant lymphoma cells from reactive lymphocytes on cytomorphological analysis has led some authors to suggest that FNA must always be followed up with open biopsy.[12,13]

Advances in immunophenotypic analysis, including immunohistochemistry and flow cytometry, have had a tremendous effect on the diagnosis of systemic lymphomas. Once considered a complement to open surgical biopsy, FNA alone has a reported accuracy rate of 80% to 100% in the diagnosis of systemic lymphomas be-

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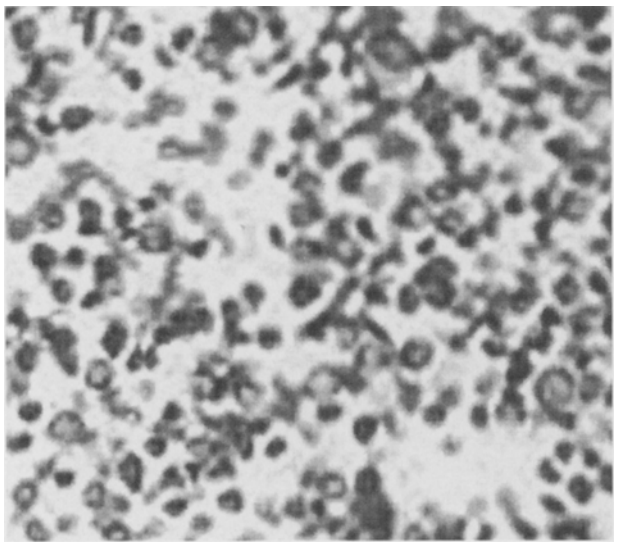

FIG. 1. Fine-needle aspiration illustrating thyroid lymphoma. Note the replacement of thyroid with neoplastic lymphocytes (Papanicolaou stain, ×250).

cause, in large part, of the addition of immunophenotyping studies.[14–18] We suspect that the addition of immunophenotyping has had a parallel effect on the FNA diagnosis of thyroid lymphomas. To investigate the utility of FNA in the diagnosis of primary thyroid lymphoma, we reviewed our experience with primary thyroid lymphoma over a 15-year period.

METHODS

Twenty-three consecutive patients diagnosed with primary thyroid lymphoma from July 1985 to April 2000 were identified from the Johns Hopkins Hospital pathology database, and their medical records were analyzed retrospectively. Pathology information, including cytopathologic diagnosis, histopathologic diagnosis, immunohistochemical profile, and flow cytometric analysis, was obtained from review of pathology reports. Statistical analysis was performed by using analysis of variance, χ^2 analysis, and the Mann-Whitney rank-sum test when appropriate (SPSS™ software, SPSS Inc., Chicago, IL). Significance was defined as a P value of $< .05$.

RESULTS

Patient Demographics

Patients with primary thyroid lymphomas were categorized into two groups: group 1 included those patients diagnosed before 1993 (n = 12), and group 2 included those patients diagnosed after 1993 (n = 11). Immunophenotypic analysis was routinely performed on FNA samples after 1993. The two groups were relatively evenly matched in terms of sex and stage: the female: male ratio was approximately 3:1 in both groups, and the majority of patients had stage I or II disease (Table 1). Patients in group 1 did tend to present at an older age. Associated symptoms on presentation included dysphagia (17%), dyspnea (30%), and hoarseness (9%).

Pathology

All 23 patients had a lymphoma of B-cell origin, and histological types consisted of 19 diffuse large-cell lymphomas, two small lymphocytic lymphomas, and two MALT lymphomas of the thyroid. These histological types were evenly distributed between groups 1 and 2 (Table 2).

Use of FNA

Four patients in group 1 (33%) had an FNA performed as part of their diagnostic work-up, whereas eight patients in group 2 (72%) had an FNA. Before 1993, immunohistochemical analysis and flow cytometric analysis was not routinely performed on FNAs, and therefore patients in group 1 who underwent FNA were at times evaluated by cytomorphological analysis only. All four FNAs in group 1 were nondiagnostic and required additional invasive procedures for diagnosis: two open biopsies, one lobectomy, and one core-needle biopsy.

Patients in group 2 had a diagnosis of thyroid lymphoma established by FNA nearly two thirds of the time; this was a statistically significant difference compared with group 1 (Table 2). More important, of the eight patients who had an FNA performed in group 2, seven (88%) were diagnosed with thyroid lymphoma on FNA alone, with no further invasive diagnostic testing necessary. In the only patient who had a nondiagnostic FNA, the result was found to be suggestive of lymphoma but

TABLE 1. *Patient demographics*

Variable	Group 1 (1985–1992)	Group 2 (1993–2000)	P value
n	12	11	–
Age (y)			
Median	72	55	.05
Range	47–86	37–79	
Sex			
Male	3 (25%)	4 (36%)	NS
Female	9 (75%)	7 (64%)	NS
Stage			
I	2	5	
II	8	2	NS
III	0	3	
IV	2	1	

NS, not significant. Significance at $P < .05$.

TABLE 2. *Lymphoma categories and fine-needle aspiration (FNA) results*

		REAL classification			FNA	
Variable	n	Diffuse large-cell	Small lymphocytic	MALT	Total	Diagnostic
Group 1 (1985–1992)	12	11	1	0	4 (33%)	0 (0%)
Group 2 (1993–2000)	11	8	1	2	8 (73%)	7 (63%)
P value			NS		.063	.019*

REAL, revised European-American classification system of lymphoid neoplasms, NS, not significant; MALT, mucosal-associated lymphoid tissue.
* $P < .05$.

needed confirmation by open biopsy, which demonstrated a low-grade MALT lymphoma.

Six (75%) of eight patients in group 2 who had an FNA underwent further analysis of the aspirate by flow cytometry or immunohistochemical staining. Two patients did not have further analysis because of an insufficient amount of tissue. It is interesting to note that both FNAs were diagnostic of thyroid lymphoma solely on the basis of cytomorphological characteristics. All seven patients diagnosed with thyroid lymphoma by FNA had a clinical course consistent with the diagnosis and received treatment based solely on the FNA results. Of the three patients in group 2 who did not have an FNA performed and required more invasive procedures for diagnosis, one had an open biopsy, one had a lobectomy, and one had a total thyroidectomy. For those patients undergoing operative procedures, eight had an open biopsy, four had thyroid lobectomies, one had a total thyroidectomy, one had a subtotal thyroidectomy, and one had a core-needle biopsy.

DISCUSSION

Primary thyroid lymphoma is an uncommon malignancy; it accounts for <2% of all extranodal lymphomas and <5% of all thyroid malignancies.[1–3] The great majority of thyroid lymphomas are non-Hodgkin's and are of B-cell lineage, although rare reports of T-cell lymphomas and Hodgkin's disease have been described in the literature.[1,19–21] The relationship between Hashimoto's thyroiditis and primary thyroid lymphoma has been controversial. A hypothesis that chronic stimulation of lymphocytes by thyroiditis, causing the development of malignant clones, has been proposed but is not yet clearly defined.[22,23]

The role of the surgeon in the management of thyroid lymphoma is diminishing. Less than 25 years ago, the standard of care for thyroid lymphoma was radical resection, because the disease was thought to be a form of anaplastic thyroid carcinoma. Thyroid lymphomas would often present quite dramatically, with a rapidly growing neck mass and symptoms of dysphagia, dysphonia, dyspnea, and even tracheal compression/obstruction in a manner similar to anaplastic carcinoma.[1] In the past, surgeons would perform radical thyroidectomies,[24] the treatment of choice at that time for anaplastic carcinoma.[6,25] As the benefit of chemotherapy and radiotherapy over surgery in thyroid lymphoma became evident,[9,12,19,26–31] the need for surgical intervention diminished, although invasive procedures were still necessary to establish the diagnosis.[23,32] With the eventual introduction of FNA in the diagnosis of systemic lymphomas, several authors began to discuss whether the technique could be used for thyroid lymphomas and obviate the need for any surgical intervention.[19,28,33,34] In this report, our data demonstrate that the majority of patients with thyroid lymphoma can be diagnosed by FNA alone, especially when it is combined with flow cytometry and immunohistochemical analysis.

The advances in FNA diagnosis of primary thyroid lymphoma have mirrored those of systemic lymphoma. As cytopathologists gained experience making the diagnosis of nodal lymphoma on FNA, that expertise translated into diagnosing lymphoma on FNA aspirates obtained from thyroid masses. Additionally, part of the improved comfort level of pathologists to make the diagnosis of lymphoma is due to the ever-evolving lymphoma classification system. In its latest adaptation, the revised European-American classification of lymphoid neoplasms, there is a marked de-emphasis of tissue architecture and an increased value placed on individual cell morphology in conjunction with immunophenotyping—ideal for diagnostic cytopathology.[14,35] Already, large retrospective studies have confirmed the ability of the revised European-American classification of lymphoid neoplasms classification system to identify major types of lymphoma with a high reproducibility rate.[36,37]

Therefore, part of the improvement in the ability to diagnose thyroid lymphoma on FNA aspirates after 1993 is due to the improved comfort level of cytopathologists in making the diagnosis; this is reflected by the fact that the two patients in group 2 who did not receive addi-

tional immunophenotyping analysis nevertheless were diagnosed with thyroid lymphoma on FNA alone, whereas none of the four patients in group 1 who had an FNA could be diagnosed conclusively. Seven of eight patients in group 2 were correctly diagnosed with thyroid lymphoma by FNA without the need for additional tissue acquisition by more invasive techniques. This 88% sensitivity rate matches the 80% to 90% rates reported for FNA in systemic lymphoma.[14–18] The only nondiagnostic FNA in group 2 occurred in a patient with a low-grade MALT tumor, which can be a difficult diagnosis even on an open surgical biopsy specimen. The FNA result was suggestive of lymphoma, and the MALT tumor was confirmed by open biopsy. It is interesting to note that low-grade lymphoma was diagnosed by FNA in group 2 on two other occasions, including one MALT tumor, suggesting that low-grade lymphomas can be diagnosed by FNA alone, although with less consistency.

Another large factor in the ability to diagnose thyroid lymphomas by FNA is the advances in ancillary techniques, immunophenotyping in particular, in the cytopathologic diagnosis. In the systemic lymphoma literature, a series by Kaleem et al.[38] reported that with use of cytomorphological analysis alone, a definitive diagnosis of lymphoma was made in only 18% of cases, but once the results of immunophenotyping were factored in, a definitive diagnosis was possible in 88% of cases; only 12% remained less than definitive.[35] In primary thyroid lymphoma, initial series looking at FNA in thyroid lymphoma had less than spectacular results. Matsuda et al.[39] reported a series of 119 patients with thyroid lymphoma and found that FNA was suggestive of lymphoma in 78% of the cases but could not be confirmed without open biopsy. Skarsgard et al.[12] reported that FNA was suggestive but not diagnostic 56% of the time in their series of 27 patients. Several other series have had similar results,[25,32,34] and it is important to note that none of these series incorporated any additional immunophenotyping studies, such as flow cytometry or immunohistochemistry on FNA samples.

This series is one of the first in which FNA in combination with immunophenotyping has been successfully demonstrated to diagnose thyroid lymphoma, confirming the diagnosis 88% of the time without the need for further invasive procedures. The diagnosis was made with a combination of cytomorphogenic analysis demonstrating monomorphic lymphoid cells and immunophenotyping analysis indicating B-cell lineage of lymphocytes with characteristic tumor clonality. The diagnosis was confirmed with immunohistochemical staining with CD20, restricted expression of λ or κ light chains, immunoglobulin gene rearrangements, or a combination of these.[9,13,40,41] Additionally, DNA aneuploidy and increased proliferated activity on FNA are characteristic findings in thyroid lymphoma.[40,42]

The benefits of diagnosing thyroid lymphoma with FNA are obvious, including the ease, safety, rapidity, and potential cost-effectiveness of the procedure compared with those of open biopsy or thyroidectomy. Additionally, most patients with a thyroid mass will have an FNA performed as part of their standard work-up. There are several potential difficulties, however. The technique is extremely operator dependent—inadequate sampling leads to false negatives and insufficient material for flow cytometry. Therefore, we recommend three or four separate needle passes until the specimen is cloudy, making multiple passes from different areas of the lesion, and performing a repeat FNA when necessary before proceeding with an open biopsy. Fortunately, the technique of FNA is one that many physicians are comfortable with. The proficiency of pathologists at confirming a diagnosis of thyroid lymphoma on FNAs, however, will also depend on their level of expertise in performing complex immunophenotyping procedures on FNA aspirates—a capability that many pathology laboratories may not have. FNA, even in the best of hands, is limited by potential sampling error and artifact. In such cases, and in any instance in which a diagnosis is equivocal on FNA, open biopsy is recommended. Open biopsy is a technique that surgeons are comfortable with, and when it is performed under local anesthesia, it poses minimal morbidity to the patient. Therefore, FNA should not be considered a replacement for open biopsy but rather an additional diagnostic test in the work-up of thyroid lymphoma that can be performed in the office, before the need for an open surgical biopsy.

Once considered a surgical disease, the current management of thyroid lymphoma has evolved to the point where an invasive procedure is required only for diagnosis or palliation. The ability to use fine-needle biopsy for diagnosis obviates the need for open biopsy or lobectomy and allows for early treatment, which can improve survival.[13] The success of our pathologists in diagnosing primary thyroid lymphoma on FNA has rendered it an essentially nonsurgical disease; it minimizes patient discomfort, maximizes safety to the patient, and avoids a delay in the initiation of therapy.

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