Int Surg 2015;**100:**249–253
DOI: 10.9738/INTSURG-D-13-00209.1

The Reliability of Fine-Needle Aspiration Biopsy in Terms of Malignancy in Patients With Hashimoto Thyroiditis

Murat Kapan[1], Akin Onder[1], Sadullah Girgin[1], Burak Veli Ulger[1], Ugur Firat[2], Omer Uslukaya[1], Abdullah Oguz[1]

[1]*Department of General Surgery, Dicle University Medical Faculty, Diyarbakır, Turkey*

[2]*Department of Pathology, Dicle University Medical Faculty, Diyarbakır, Turkey*

The aim of this study was to analyze the presence of malignancy in patients with Hashimoto's thyroiditis and to investigate the reliability of preoperative fine-needle aspiration biopsy (FNAB). The retrospective study included 44 patients who were operated on for nodular goiter between December 2010 and October 2011. The patients underwent thyroidectomy following a cytologic analysis plus FNAB. Hashimoto's thyroiditis was confirmed on histopathology in all patients. FNAB results were defined as benign in 14 (31.8%), suspicion for malignancy in 17 (38.6%), malignant in 9 (20.5%), and inadequate in 4 (9.1%). Following the thyroidectomy, presence of papillary thyroid carcinoma and follicular variant of papillary thyroid carcinoma were detected in 10 patients (22.7%) and 1 (2.3%) patient, respectively. The FNAB results were interpreted in terms of malignancy, which revealed the sensitivity as 80%; specificity, 40%; false positives, 69.2%; false negatives, 14.3%; positive predictive value, 31.8%; negative predictive value, 85.7%; and diagnostic accuracy, 50%. The coexistence of Hashimoto's thyroiditis with papillary thyroid carcinoma is quite common. The FNAB results for such cases are hard to evaluate, and they are likely to increase the number of false positives.

Key words: Hashimoto's thyroiditis – Papillary thyroid carcinoma – Fine needle aspiration biopsy

Corresponding author: Murat Kapan, Associate Professor, Dicle University Medical Faculty, Department of General Surgery, 21280 Diyarbakır, Turkey.
Tel.: +90 412 248 8001; Fax: +90 412 248 8523; E-mail: drmuratkapan@gmail.com

Hashimoto's thyroiditis (HT) is also known as chronic lymphocytic thyroiditis, with an incidence rate of 1% to 4% and incidence of 3 to 6 per 10,000 individuals per year.[1] It is the second most common thyroid lesion next to endemic goiter, and it is more frequent in women.[2] It generally presents as diffuse goiter, while its presentation as 1 or 2 predominant nodules is quite rare. In the preoperative stage, it is quite difficult to determine whether these nodules are caused by HT or by an HT-related malignancy. There are numerous studies suggesting that there is a strong relation between HT and thyroid neoplasms and that HT leads to a higher incidence rate for thyroid malignancy.[3] However, Pradeep *et al*[4] have reported that they did not observe any associated malignancy in HT in their series.

Fine-needle aspiration biopsy (FNAB) is a safe procedure, which is well defined for the primary diagnosis of thyroid patients.[5] The initial aim in performing FNAB is to identify the thyroid nodules that require surgery and decrease the overall incidences of thyroidectomy in patients with benign diseases.[6,7] FNAB is reported as a superior and cost-effective procedure for the diagnosis of HT, as compared with antibody testing.[8] Nevertheless, the false positives and false negatives in FNAB lead to a diagnostic pitfall.[6]

The aim of this study was to analyze the presence of malignancy in HT patients and to investigate the reliability of FNAB through a comparison between pre- and postoperative histopathologic results.

Materials and Methods

The retrospective study included 44 patients who were operated on for nodular goiter and then diagnosed with HT between December 2010 and October 2011. The patients underwent thyroidectomy following FNAB. Indication for surgery was suspicion of the presence of malignancy and malignant nodules; the detection of suspicious nodules on ultrasonography (Usg); and the presentation of several symptoms and for some cosmetic reasons. Histopathology confirmed Hashimoto's thyroiditis in all of the patients. FNAB was performed under the guidance of Usg once the patients were diagnosed with a thyroid nodule larger than 1 cm in diameter and suspicious for malignancy. Sonographic features such as microcalcification in the nodule, ill-defined margin, and marked hypoechogenicity were determined to be suspicious for malignancy, as well. Cytologic analysis included cell population, pleomorphism, nucleocytoplasmic ratio, nuclear features including nuclear grooving and intranuclear cytoplasmic inclusion, cytoplasmic features, necrosis, and lymphocytic infiltration. On the basis of aspiration specimens, the cases were classified as benign, suspicious for malignancy, malignant, and inadequate. An adequate FNAB specimen was defined as one containing at least 10 fragments of follicular epithelium on at least 5 to 6 slides. Bilateral total thyroidectomy was performed for a number of reasons including prevalence of suspicion for malignancy and malignant FNAB, presence of suspicious nodules on Usg, presentation of several symptoms, and cosmetic reasons. In the pathologic examination of thyroidectomy specimens, the presence of lymphocytic infiltration at the germinal center, which destroys the normal follicular structure in nontumoral areas, and/or the presence of fibrotic areas were accepted as chronic lymphocytic thyroiditis (i.e., HT). Also, other benign or malignant lesions on the thyroid tissue were recorded. While measuring the FNAB values of specificity, sensitivity, positive predictive value, and negative predictive value, the cases of suspicion for malignancy were added to the malignant group, and the inadequate ones were excluded in the measurement.

SPSS 11.5 (SPSS Inc, Chicago, Illinois) was used for analysis of the data. Quantitative data were expressed as mean ± SD, and descriptive analyses were performed. Chi-square test was used to compare qualitative data. A P value of <0.05 was considered significant.

Results

The patients comprised 39 (88.6%) women and 5 (11.4%) men, with a mean age of 45.1 ± 12.9 years (range, 21–78 years). Of these, 2 (4.5%) presented with hypothyroidism, 1 (2.3%) with hyperthyroidism, and the remaining 40 (93.2%) with euthyroidism. Following FNAB, the nodules had a mean diameter of 26.5 ± 17.9 mm (range, 12–82 mm). FNAB results were defined as benign in 14 (31.8%), suspicion for malignancy in 17 (38.6%), malignant in 9 (20.5%), and inadequate in 4 (9.1%). Bilateral total thyroidectomy was performed in 26 patients (59.1%) because of the presence of suspicion for malignancy and malignant nodules; in 8 patients (18.2%), because of the detection of suspicious nodules on Usg; and in the remaining 10 patients (22.7%), because of the presentation of several symptoms and for some cosmetic reasons. On the basis of

Table 1 Correlation of FNAB results and histopathologic diagnosis in 44 cases

	Histopathologic Diagnosis		
FNAB	Benign n (%)	Malignant n (%)	Total n (%)
Benign	12 (27.3)	2 (4.5)	14 (31.8)
Suspicious for malignancy	14 (31.8)	3 (6.8)	17 (38.6)
Malignant	4 (9.1)	5 (11.4)	9 (20.5)
Inadequate	3 (6.8)	1 (2.3)	4 (9.1)
Total	33 (75.0)	11 (25.0)	44 (100)

thyroidectomy specimens, HT was confirmed in all patients, while 10 (22.7%) of them were concurrent with papillary thyroid carcinoma, 1 (2.3%) with follicular variant of papillary thyroid carcinoma, 5 (11.4%) with follicular adenoma, and 1 (2.3%) with Hürthle cell adenoma. The statistics revealed a significant difference between the histopathologic analysis of thyroidectomy specimens and FNAB results ($P = 0.05$) (Table 1). The FNAB results were interpreted in terms of malignancy at HT background, which revealed the sensitivity as 80% and specificity at 40%. Also, the rate for false positive was revealed as 69.2%; false negative, 14.3%; positive predictive value, 31.8%; negative predictive value, 85.7%; and diagnostic accuracy, 50%.

Discussion

HT is a kind of autoimmune thyroiditis that mainly affects females in the fourth decade.[1] It can also result in hypothyroidism, which requires lifelong thyroid hormone replacement.[2] The patients in our series had a mean age of 45.1 years, and the female to male ratio was 7.8:1. Most of our patients had euthyroidism, and they did not receive any medication. Only 2 patients (4.5%) had hypothyroidism. In the study by Pradeep *et al*,[4] the incidence of hypothyroidism was 14.3%, and most of the patients were euthyroid, as in our series. This can be due to the focal thyroiditis.

The studies report that the antithyroglobulin and antimicrosomal antibodies are positive in 60% to 80% of the cases and that thyroiditis may not exist in 10% to 15% of antibody-positive patients.[2] The incidence rate for HT is higher than the incidence rate assessed by only using serologic tests. Thus, the diagnosis of HT should be supported by cytologic tests.[2]

The coexistence of HT with papillary thyroid carcinoma (PTC) is a noteworthy and debated issue, with the possibility of occurrence being reported between 0.3% and 58.0%.[10–12] The question as to which one triggers the other has not yet been determined.[10] Various hypotheses have been proposed in the studies related to this question. Okayasu[13] maintained that the thyroid-stimulating hormone, which is increased by hypothyroidism as a result of thyroiditis, may lead to PTC as it promotes the proliferative activity in follicular epithelioid cells; however, Bagnasco *et al*[14] argued that lymphocytic infiltration and the development of thyroiditis are triggered by the antigenic materials that are secreted by the tumor. HT is commonly held responsible for the presence of lymphocytes and antibodies in the thyroid patterns of local units in concurrent eosinophils as well, and the eosinophils are reported as a possible chemotactic factor for the aggregation of lymphocytes.[15] Yoon *et al*[16] and Ersoy *et al*[10] reported the incidence rate for HT in PTC patients as 28.7% and 27.3%, respectively. Indeed, Loh *et al*[17] and Sclafani *et al*[18] reported this rate as 17.0% and 20.3%, respectively. Yet, Anil *et al*[19] reported that in HT patients, the incidence rate for malignancy was 1% following the FNAB and 2.7% in the control group; indeed, they support that the presentation of HT does not increase the incidence rate for malignancy. In our series, the results revealed that the incidence rate for the coexistence of HT with PTC was 25.0%; among these patients, 10 had PTC and 1 had a follicular variant of PTC.

Cytologic and histologic tests remain the gold standard for the diagnosis of HT.[9] Hence, FNAB is the initial method of choice for the evaluation of thyroid lesions.[7] Cytologic features of HT include a mixed population of follicular and Hürthle cells, low to moderate colloid and lymphocytic infiltration of epithelial cell clusters.[1]

Various difficulties exist with the FNAB diagnosis of HT. Diagnosis of HT is likely to be overlooked in smears showing cytologic evidence of hyperplasia or abundant colloid.[1] In addition, a nodule with a diameter of 3 cm and greater decreases the sensitivity of FNAB.[20] The presence of atypical results in HT, such as enlargement, aggregation, and nuclear inclusions and grooves, are likely to be confused with PTC, which may lead to a misdiagnosis (Fig. 1).[21,22] It is quite difficult to use the FNAB for the diagnosis of follicular neoplasms in HT background since HT is likely to allow cytologic changes including the metaplastic oncocytic epithelium and hyperplastic follicular lesions that occur in follicular neoplasms.

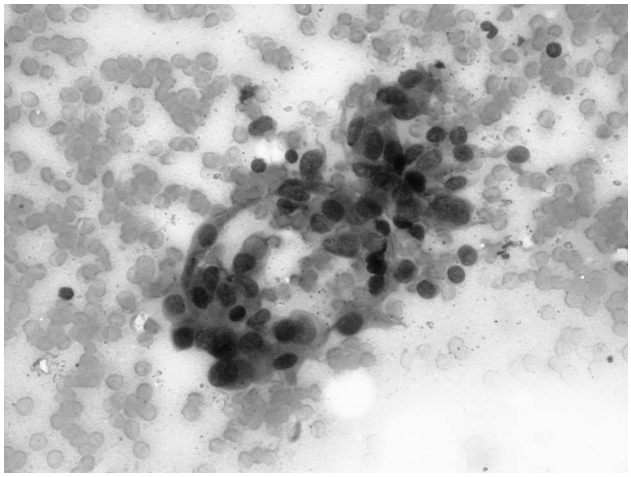

Fig. 1 FNAB from the thyroid nodule of the patient diagnosed with HT, but PTC was detected histopathologically, after the resection, in the postoperative period. A cluster of the cells, some of which have abundant eosinophilic granular cytoplasm and some changes similar to "nuclear cleaving" but no clear evidence of malignancy (Giemsa stain, ×400).

Reported sensitivity, specificity, and diagnostic accuracy for FNAB in diagnosis of thyroid lesions are 65% to 99%, 72% to 100%, and 53% to 98%, respectively.[24–27] Some studies hold that FNAB yields an accuracy rate of 92% for the diagnosis of HT.[2,9] Nasser *et al*[28] reported a sensitivity of 92% and a specificity of 97% for the use of FNAB in diagnosis of PTC. Cap *et al*[5] revealed the FNAB results for the diagnosis of thyroid malignancies: sensitivity, 86.0%; specificity, 74.0%; diagnostic accuracy, 75.0%; positive predictive value, 34.0%; and negative predictive value, 97.0%. In the study by Haberal *et al*,[21] sensitivity was 92.6%; specificity, 91.6%; diagnostic accuracy, 91.9%; positive predictive value, 83.3%; and negative predictive value, 96.5%. Burch *et al*[29] have reported that the rate of false negatives in FNAB is 10.3%.[29] Unlike the literature, the present study was aimed to analyze the diagnostic accuracy of FNAB in the PTC cases occurring on HT background or coexisting with HT. The FNAB results in our study yielded the sensitivity as 80.0%; specificity, 40.0%; false positives, 69.2%; false negatives, 14.3%; positive predictive value, 31.8%; negative predictive value, 85.7%; and diagnostic accuracy, 50%. The differences between these results and the ones that are assessed for the benign and malignant thyroid lesions were believed to be the result of the atypical cytologic changes in HT. These changes may lead the FNAB results to be misevaluated or to be mistaken as suspicious for malignancy. Also, the false positives may lead to unnecessary surgery. The cases that were considered suspicious for malignancy constituted 38.6% of our series. Accordingly, in the cases that are serologically diagnosed with HT, the solitary use of FNAB may reveal a lower rate for malignancy owing to the challenges of cytologic analyses.

Conclusion

The coexistence of HT with PTC is quite common. The evaluation of FNAB results for such cases are challenged by lymphocytic infiltration and atypical cytologic changes, which are likely to increase the number of false positives.

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