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Usefulness of Thyroglobulin Measurement in Fine-needle Aspiration Biopsy Specimens for Diagnosing Cervical Lymph Node Metastasis in Patients with Papillary Thyroid Cancer

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Abstract. The diagnosis of lymph node metastasis in patients with papillary thyroid cancer is an important factor when deciding to perform neck dissection at the initial surgery, as well as for evaluating the lymph node swelling after surgery. Ultrasound (US)-guided fine-needle aspiration biopsy cytology (FNAB-C) is the most useful technique for diagnosing lymph node metastasis. Recently, however, measurement of thyroglobulin in the wash-out of the needle (FNAB-Tg) has been proposed for early detection of neck lymph node metastasis in patients with differentiated thyroid cancer. The purpose of this study was to evaluate the usefulness of FNAB-Tg in detecting lymph node metastasis prior to initial or reoperative thyroid surgery. US-guided FNAB-C was performed on 129 enlarged lymph nodes of 111 patients before surgery. All of them were later histologically confirmed to contain metastasis. Immediately after obtaining an FNAB-C specimen, the needle was rinsed with 0.5 ml of normal saline solution, and the wash-out was subjected to measurement of the Tg level (FNAB-Tg). If the FNAB-Tg level was higher than the serum Tg of the patient, we diagnosed the lymph node as positive (metastatic lymph node). FNAB-Tg sensitivity was 81.4%, and FNAB-C sensitivity was 78.0%. Altogether, 4 (36.4%) of 11 cases judged "benign" and 6 (37.5%) of 16 cases judged "inadequate" by FNAB-C were positive by the FNAB-Tg measurement. Thyroglobulin measurement in fine-needle aspiration biopsy wash-out is thus a useful technique for diagnosing lymph node metastasis of papillary thyroid cancer.

Papillary thyroid cancer (PTC) is the most common malignancy of the thyroid gland, accounting for about 75% to 85% of thyroid malignancies in Western countries and for about 90% in Japan [1–4]. PTC has a good prognosis, especially among patients younger than 45 years of age. However, because of its frequent metastasis to the regional lymph nodes, recurrence of the tumor in cervical lymph nodes occurs in 5.4% to 13.0% of patients after initial surgery [5]. Thus removing lymph node metastasis by lymph node dissection during thyroid surgery is generally recommended [6, 7]. Accurate diagnosis of lymph node involvement is an important issue in patients with PTC, informing the decision to perform neck dissection at the initial surgery as well as during the follow-up after surgery. Ultrasound (US)-guided fine-needle aspiration biopsy cytology (FNAB-C) is the most useful technique for diagnosing node metastasis [8, 9]. Recently, measurement of thyroglobulin (Tg) in the wash-out of the needle used to perform FNAB on cervical lymph nodes (FNAB-Tg) has been proposed for early detection of neck lymph node metastasis in patients with differentiated thyroid cancer [10, 11]. However, the available information on the clinical results of this technique is limited. The purpose of this study was to evaluate the usefulness of FNAB-Tg for detecting lymph node metastasis.

Patients and Methods

Between October 2001 and March 2003, US guided-FNAB-C was performed on 129 enlarged lymph nodes (111 patients) before surgery. Altogether, 70 patients were evaluated before the initial surgery, and 41 were evaluated before reoperation for recurrence after the initial surgery. A total of 121 of 129 lymph nodes were located in the jugular chain (deep cervical nodes), 6 in the central component (paratracheal or pretracheal nodes) and 2 in other areas (subdermal or superficial cervical nodes); 96 lymph nodes were solid, and 33 were cystic or mixed solid and cystic. All of them were surgically removed later and histologically confirmed to contain PTC metastasis.

Specimens for FNAB-C were obtained with a 22-gauge needle connected to a 10 ml syringe under US guidance. Immediately after the aspiration, samples were smeared onto glass slides for cytologic examination. The same needle and syringe were rinsed with 0.5 ml of normal saline, and the wash-out was subjected to thyroglobulin measurement (FNAB-Tg). When the aspirates were serous fluid, Tg was measured without dilution. The measured values were evaluated without considering the dilution. If

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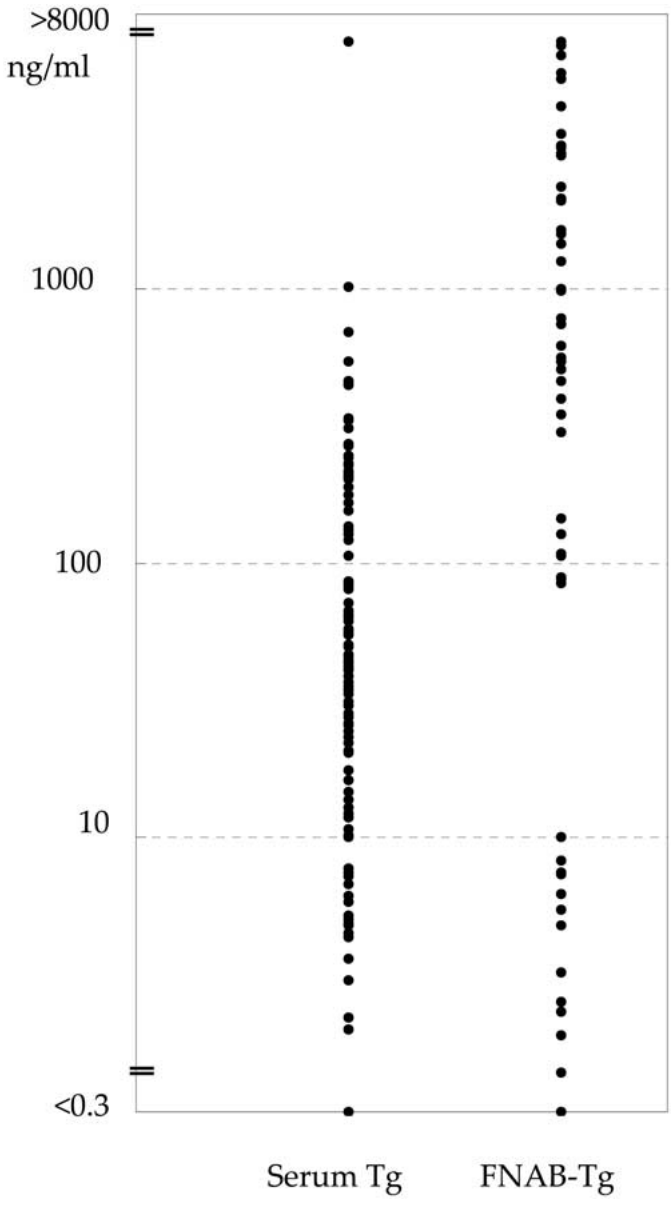

Fig. 1. Fine-needle aspiration biopsy thyroglobulin (FNAB-Tg) and serum thyroglobulin (Tg) levels.

the FNAB-Tg level was higher than the serum Tg of the patient, we assumed that the lymph node was positive (metastatic lymph node).

Results

The levels of FNAB-Tg and serum Tg are shown in Fig. 1. In sum, 105 lymph nodes were positive by FNAB-Tg (range 6.2–8000 ng/ml) and 24 lymph nodes were negative (range 0.6–88.8 ng/ml). All lymph nodes that had a cystic component (cystic or mixed lymph nodes, 33 lymph nodes) were positive and 72 of 96 (75.0%) solid lymph nodes were positive by FNAB-Tg (Table 1). FNAB-Tg sensitivity was 81.4%, and FNAB-C sensitivity was 78.0% (Table 2). Altogether, 4 (36.4%) of 11 (37.5%) cases judged "benign" and 6 of 16 cases judged "inadequate" by FNAB-C were positive by the FNAB-Tg measurement. However, 7 of 96 lymph nodes that were positive by FNAB-C were negative by FNAB-Tg. FNAB-Tg and FNAB-C made up for the loss of each other in 13.8% of 123 nodes that were subjected to both FNAB-Tg and FNAB-C (Table 3).

Table 1. US findings of lymph nodes and the diagnostic results of FNAB-Tg and FNAB-C.

		FNAB-Tg	
US finding	No. of nodes	Positive	Negative
FNAB-Tg			
Cystic or mixed	33	33 (100%)	0
Solid lymph node	96	72 (75.0%)	24
FNAB-C			
Cystic or mixed	31	29 (93.5%)	2
Solid lymph node	92	67 (72.8%)	25

US: Ultrasonography; FNAB-Tg: fine-needle aspiration biopsy thyroglobulin; FNAB-C: fine-needle aspiration biopsy cytology.

Table 2. Diagnostic results of FNAB-Tg and FNAB-C.

Measurement	Positive	Negative	Sensitivity (%)
FNAB-Tg	105[a]	24[b]	81.4
FNAB-C	96[c]	27[d]	78.0

[a]Range 6.2–8000 ng/ml; mean SD 5663.4 3235.5 ng/ml.
[b]Range < 0.5–88.8 ng/ml; mean SD 6.0 3.7 ng/ml.
[c]Malignancy or suggestive of malignancy.
[d]Benign or inadequate materials.

Table 3. Relations between FNAB-C and FNAB-Tg.

	FNAB-Tg	
FNAB-C	Positive	Negative
Positive	89 (72.4%)	7 (5.7%)
Negative	10 (8.1%)	17 (13.8%)

Except six patients who were subjected to only FNAB-Tg.

Discussion

Measurement of Tg in the wash-out of the aspiration biopsy needle has been proposed for early detection of neck lymph node metastasis in patients with differentiated thyroid cancer. Frasoldati et al. reported that for the 69 lymph nodes examined FNAB-Tg sensitivity and specificity were 84.0% and 95.4%, respectively [10]. They also reported that the cutoff level was 39.3 ng/ml in patients awaiting thyroid surgery and 1.1 ng/ml in patients after thyroid ablation. Taking their cutoff levels in our present study and adjusting the dilution rate, which were 78.6 ng/ml in the patients awaiting thyroid surgery and 2.2 ng/ml in the patients after total thyroidectomy, 107 nodes were positive for FNAB-Tg and 22 nodes were negative (sensitivity 82.9%). In their study, patients in the negative control group had normal thyroid glands and may have had normal serum Tg levels.

However, we often see patients who have high levels of serum Tg because they have thyroid disease-like thyroid nodules or metastatic thyroid carcinoma. If the aspirates were contaminated with blood with high Tg levels, FNAB-Tg values may be high even if the lymph nodes did not contain metastasis. Al-

though Frasoldati et al. reported that the specificity of FNAB-Tg was 100% [11], false-positive results for FNAB-Tg are possible in patients with high serum Tg, causing patients to undergo an unnecessary operation. Thus in our study we did not define a cutoff level; and if the FNAB-Tg was higher than the serum Tg of the patient, we assumed that the lymph node was positive.

However, as the samples for FNAB-Tg had already been diluted with 0.5 ml of normal saline, even if they were contaminated with blood that contained a high level of serum Tg the FNAB-Tg values for a negative node would be markedly lower than that of a positive node. The dilution rate may vary because the volume of residual sample in the washout of the needle varies. Our preliminary experiment on Tg measurement of washouts containing a high level of Tg suggested that dilution rates varied from 50- to 200-fold.

In the present study, we did not evaluate the effects of antithyroglobulin antibody (TgAb). In the presence of TgAb, Tg levels might be erroneously reported to be lower than true values in most assay systems. Regardless, high FNAB-Tg levels indicate abnormal Tg levels in the aspirates, suggesting the presence of metastatic differentiated thyroid cancer or thyroid tissue. However, more study is certainly needed. Unfortunately, in the present study, we could not discuss the specificity or negative predictive value because patients with negative lymph nodes by FNAB-Tg and FNAB-C did not undergo node dissection.

Another caution is that if the needle passes through the thyroid gland, FNAB-Tg values are high irrespective of node pathology. In short, this method cannot be used for lymph nodes near the thyroid gland (e.g., paratracheal, pretracheal, and prelaryngeal nodes) before thyroidectomy. In our study, all paratracheal nodes had a recurrence after thyroidectomy, and the needle could not pass through the thyroid gland.

Conclusions

Thyroglobulin measurement in fine-needle aspiration biopsy wash-out is a useful technique for aiding in the diagnosis of lymph node metastasis of papillary thyroid cancer.

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