นิพนธ์ต้นฉบับ

# Fine- needle aspiration cytology improved sensitivity in differential diagnosis of non - toxic diffuse goiter.

Vitaya Sridama*
Sumalee Tantivirasuth* Sasinee Pokto*

**Sridama V, Tantivirasuth S, Pokto S. Fine- needle aspiration cytology improved sensitivity in differential diagnosis of non - toxic diffuse goiter. Chula Med J 1994 May;38(5): 263-270**

*One hundred twenty-five patients with non-toxic sporadic diffuse goiter were investigated by means of fine - needle aspiration cytology and the measurement of thyroid antibody level. One hundred and eleven patients had adequate cytology. The results could be classified into three patterns, including lymphocytic thyroiditis, colloid gioter, and normal or hypercellularity of thyroid epithelial cells. The percentage of each pattern was 29.7, 57.7 and 12.6 respectively. Sensitivity of the tests for diagnosis of Hashimoto's thyroiditis was 0.87 and 0.89 for thyroid antibody level and thyroid cytology respectively. The specificity of positive thyroid antibody for the diagnosis of Hashimoto's thyroiditis is 0.94.*

*In conclusion, fine - needle aspiration cytology has sensitivity comparable to thyroid antibody determination in the differential diagnosis of non-toxic diffuse goiter. Using both thyroid antibody assay and cytology could probaly increase sensitivity and specificity for the diagnosis of Hashimoto's thyroiditis.*

**Key word** : *Diffuse gioter, Fine needle aspiration, Cytology.*

Reprint request : Sridama V, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Received for publication. May 1,1994.

*Department of Medicine, Faculty of Medicine, Chulalongkorn University.

วิทยา ศรีดามา, สุมาลี ตันติวีระสุทธิ์, ศันสนีย์ โภคโต. การตรวจ ไฟนด์ - นีดดัล แอซพิเรชั่น ไซโตโลยี่ เพิ่มความไวในการวินิจฉัยแยกโรคต่อมธัยรอยด์โตทั่วไปแบบไม่เป็นพิษ. จุฬาลงกรณ์-เวชสาร 2537 พฤษภาคม;38(5): 263-270

*ผู้ป่วยต่อมธัยรอยด์โตทั่วไปแบบไม่เป็นพิษ จำนวน 125 คน ได้รับการตรวจวินิจฉัยโดยการใช้ fine needle aspiration cytology และ การวัดระดับ thyroid antibody ในผู้ป่วยที่การตรวจทาง cytology ดีพอที่จะอ่านผลได้ จำนวน 111 คน แบ่งออกเป็น 3 แบบ คือ Lymphocytic thyroiditis, colloid goiter และ normal หรือ hypercellularity ของ thyroid epithelial cells พบ 29.7 57.7 และ 12.6% ตามลำดับ ความไว (sensitivity) ของการวัดระดับ thyroid antibody และการตรวจ thyroid cytology สำหรับการวินิจฉัยโรค Hashimoto's thyroiditis เท่ากับ 0.87 และ 0.89 ตามลำดับ*

*สรุปว่า fine - needle aspiration cytology มี sensitivity เท่าเทียมกับการวัดระดับ thyroid antibody ในการวินิจฉัยแยกโรค non-toxic diffuse goiter การใช้ทั้ง thyroid antibody และ cytology น่าจะช่วยเพิ่ม sensitivity และ specificity ในการวินิจฉัยโรค Hashimoto's Thyroiditis.*

Non-toxic diffuse enlargement of thyroid gland is a common disorder.[1] Known causes include iodine deficiency,[2] goitrogens[3] enzymatic defects in thyroid homone synthesis,[4] physiologic hyperplasia,[5] Hashimoto's thyroiditis,[6] and idiopathic.[7] The measurement of thyroid hemagglutination anibodies (thyroglobulin and microsomal) allows differential diagnosis of Hashimoto's thyroiditis from other causes of non-toxic diffuse goiter.[8] Fine - needle aspiration biopsy cytology is now widely used for the selection of patients with solitary thyroid nodules for operation.[9-10] This techinique may also be helpful in the differential diagnosis of non-toxic diffuse goiter. However, fine - needle aspiration biopsy cytology has not been extensively investigated in patients with non - toxic diffuse goiter. It is the purpose of this study to evaluate the sensitivity and specificity of fine needle biopsy cytology in differential diagnosis of non - toxic difuse goiter.

## Subjects and methods

### Subjects

The study group included 125 patients with non-toxic diffuse goiter, 30 controls who have other thyroid diseases, (14 patients with subacute thyroiditis and 16 patients with solitary thyroid nodules) and 16 normal healthy volunteers without any thyroid disease. These patients included all new patients with diagnosis of non-toxic diffuse goiter attended thyroid clinics, Chulalongkorn Hospital during 12 months period. The non-toxic diffuse goiter group was diagnosed on the basis of generalized enlargement of the thyroid gland (more than 20 grams or 1.5 times normal size) without definite nodules. Thyroid hormone levels were normal in 122 patients. Three patients had low thyroid hormone levels with elevated TSH (thyroid stimulating hormone) level. The group of patients had a mean age group of 29 (range 15-51 years). All except 2 patients were female. Their average gland size by palpation was 32 ± 12 grams (range 25-100 grams).

Subacute thyroiditis was diagnosed by the presence of a painful thyroid gland, a low 131I uptake, and elevated erythrocyte sedimentation rate. Patients with solitary thyroid nodule who had cytology and surgical pathological findings other than lymphocytic thyroiditis were included as thyroid disease controls.

## Methods

Fine - needle aspiration biopsy cytology was performed in all subjects except the normal controls. A 22 gauge needle was used for aspiration. The needle was attached to twenty ml syring with a pistol grip holder. Specimens were immediately smeared on slides. At least two slides were fixed in 95% alcohol and two slides were air - dired. Fixed slides were stained by the Papaniocolaou method. Air-dry slides were prepared using Wright-Giemsa stain.

Five milliliters of blood was drawn from each subject. Thyroglobulin (TGHA) and microsomal hemagglutination antibody (MCHA) assay were performed using a commercial kit (Wellcome, Dartford, England).

Sensitivity of assays was calculated by using the formula (true positives)/(true positives + false negatives). Specificity was calculated by using the formula (true negative)/(true negatives + false positive).

Cytological examinations were performed without knowledge of clinical data and the results of thyroid antibody titer.

## Results

Among 125 patients with non-toxic diffuse goiter, 111 patients (88.8%) had adequate cytology for interpretation. The percentage of each

cytology finding was 29.7, 57.7 and 12.6 for lymphocytic thyroiditis, colloid goiter and normal or hypercellularity of thyroid epithelial cells, respectively (Table 1). Thyroid antibody assay was performed in all but 2 patients in the lymphocytic thyroiditis group. A titer of 1:100 or more was considered a positive titer. Thyroglobulin hemagglutination antibody assay was positive in 51.6% of patients with cytological proven lymphocytic thyroiditis and in 2.6% of patients with other types of non-toxic diffuse goiter. No positive thyroglobulin hemagglutination antibody assay was found in the thyroid controls and normal controls (Table 2). Microsomal hemagglutination antibody assay was positive in 74.2% of patients with cytologically proven lymphocytic thyroiditis, and in 7.7% of other types of non-toxic diffuse goiter. There were 6.3% and 7.1% positive microsomal antibody assays in patients with solitary thyroid nodules and subacute thyroidits, respectively (Table 2). The specificity of each test for the diagnosis of lymphocytic thyroiditis was then 0.98, 0.94, and 0.94 for TGHA, MCHA and TGHA and/or MCHA, respectively. The specificity of thyroid cytology could not be evaluated since these patients were not operated. The sensitivity of thyroid antibody assay in diagnosis of lymphocytic thyroiditis was 0.71, 0.74 and 0.87 for TGHA, MCHA and TGHA and/or MCHA. The sensitivity of thyroid cytological diagnosis, calculated on an assumption that the proportion of lymphocytic thyroiditis is the same in patients with adequate cytology and inadequate cytology,is 0.89. In patients with inadepuate cytology, 35.7% had positive thyroid antibodies.

**Table 1.** Cytological findings in 125 patients with non-toxic diffuse enlargement of thyroid gland.

| Cytological diagnosis | Number of patients | % of total | % of patient with adequate specimens |
|---|---|---|---|
| Lymphocytic thyroiditis | 33 | | 29.7 |
| Colloid goiter | 64 | 88.8 | 57.7 |
| Normal of hypercelularity of thyroid epithelial cells | 14 | | 12.6 |
| Inadequate specimen | 14 | 11.2 | |
| Total | 125 cases | | |

**Table 2.** Prevalence of thyroid antibodies (thyroglobulin and microsomal) in non-toxic diffuse goiter, other thyroid disease, and normal controls.

| | Number | TGHA Number Positive (%) | MCHA Number Positive (%) | TGHA and/or MCHA Number Positive (%) |
|---|---|---|---|---|
| Non-toxic diffuse goiter | | | | |
| Lymphocytic thyroiditis | 31 | 16 (51.6) | 23 (74.2) | 27 (87.1) |
| Colloid goiter | 64 | 2 ( 3.1) | 6 (9.4) | 6 (9.4) |
| Normal or hypercellularity of thyroid epithelial cells | 14 | 0 (0) | 1 (7.1) | 1 (7.1) |
| Other thyroid disease (thyroid controls) | | | | |
| Thyroid nodules | 16 | 0 (0) | 1 (6.3) | 1 (6.3) |
| Subacute thyroiditis | 14 | 0 (0) | 1 (7.1) | 1 (7.1) |
| Normal controls | 19 | 0 (0) | 0 (0) | 0 (0) |

**Table 3.** Specificity and sensitivity of thyroid antibodies and thyroid cytology for diagnosis of lymphocytic thyroiditis.

| | Specificity | Sensitivity |
|---|---|---|
| TGHA | 0.98 | 0.71 |
| MCHA | 0.94 | 0.74 |
| TGHA and/or MCHA | 0.94 | 0.87 |
| Thyroid cytology | UC | 0.89 |

UC = Unable to calcalute

## DISCUSSION

The cause of non-toxic diffuse goiter can be diagnosed on the basis of a history of low iodine intake, goitrogen consumption, pregnancy, puberty, and family history of goiter with associate abnormalities eg. neurosensory deafness.[4] Laboratory diagnosis of these conditions may require urinary iodine levels,and $^{131}I$ uptake with special tests (eg. perchorate discharge test). However, in most patients with sporadic goiter, no definite cause can be found.[7] Thyroid growth stimulating immunoglobulins may be present in some of these patients.[11] This immunoglobulin is reported to stimulate thyroid growth more than thyroid cell function. Hashimoto's thyroiditis is also a common cause of sporadic euthyroid diffuse goiter.[1] A common laboratory test for differential diagnosis of non-toxic diffuse goiter is thyroid hemagglutination antibody assay.[8]

Fine - needle aspiration biospy is now a common procedure for differential diagnosis of thyroid nodules. The technique can be easily performed without serious complications. No local anesthesia is required.[9] Using this technique in non-toxic diffuse goiter, we can classify the cytological finding into three patterns: lymphocytic thyroiditis, colloid goiter, and normal or hypercellularity of thyroid epithelial cells. The cytologic findings of lymphocytic thyroiditis includes infiltration of normal, immature lymphocytes and plasma cells.[12] Thyroid epithelial cells and colloid are rarely found. Cytological findings of colloid goiter and normal or hypercellularity of thyroid epithelial cells are probably associated with other causes of non-toxic diffuse goiter. These cytological finding are the pathological finding in colloid nodular goiters, which contain giant follicles filled with large amount of colloid bordered by a flat thyroid epithelium and clusters of hyperplastic thyroid epithelial cells.[13] Most of these cytological findings probably represent patients with idiopathic non-toxic diffuse goiters since no definite cause was found from history in these patients. The prevalence of lymphocytic thyroiditis in this group of patients (30%) is comparable to previous reports.[14]

The sensivity of thyroglobulin and microsomal antibody assay for diagnosis of Hashimoto's thyroiditis is 0.71, and 0.74. Measuring both types of thyroid antibodies increase sensitivity to 0.87. Sensitivity of fine needle aspiration biopsy cytology for diagnosis of Hashimoto's thyroiditis is 0.89. The sensitivity is less than 1.0 because there were some patients whom adequate cytology was not obtained. The proportion of patients with inadequate cytology (11.2%) is more than that found by us and by others when using this technique in patients with thyroid nodules (approximately 3-5%).[9-10] This can be explained by the fact that non-toxic diffuse goiter of any cause might have some degree of fibrosis[7] which makes it difficult to obtain adequate cytology in a proportion of patients.

The specificity of combined thyroglobulin and/or microsomal antibody for diagnosis of Hashimoto's thyroiditis is 0.94. Specificity of fine needle aspiration cytology cannot be calculated since these patients were not operated upon. A similar pattern of cytology can be found in patients with lymphoma of thyroid gland[15] and transient painless thyroiditis.[16] However, patients with lymphoma usually present with a solitary thyroid nodule rather than diffuse goiter. The history of subacute course, association with post partum period and low $^{131}I$ uptake can be used to differential diagnosis of post partum thyroiditis. When using cytology, in the light of history of patients with diffuse non-toxic goiter, the specifity of the cytology in diagnosis of Hashimoto's thyroiditis is probably close to one.

Fine needle aspiration biopsy cytology has a sensitivity comparable to thyroid antibody assay in the differential diagnosis of non-toxic diffuse goiter. This technique can be used instead of thyroid antibody assay. Using both thyroid antibody and cytology probably increase the sensitivity and specifity for diagnosis of Hashimoto's thyroiditis. Cytology increases sensitivity by detection of Hashimoto's patients with negative antibody. Thyroid antibody increases sensitivity by detection of these patients with inadequate specimen for cytology. Specificity of cytology is also helpful in diffential diagnosis of patients with borgerline thyroid antibody titer.

This study was supported in part by FERNOR project, Chulalongkorn University.

## References

1. Turnbridge WMG, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Evans JG, Young E, Bird T, Smith PA. The spectrum of thyroid disease in a community: The Whickham Survey. Clin Endocrinol 1977 Dec;7(6): 481-93
2. Thilly CH, Delange F, Ermans AM. Further investigations of iodine deficiency in the etiology of endemic goiter. Am J Clin Nutr 1972 Jan;25(1): 30-40
3. Delange F, Thilly CH, Ermans AM. Iodine deficiency, a permissive condition in the development of endemic goiter. J Clin Endocrinol Metab 1968 Jan; 28(1):114-6
4. Stanbury JB : Inherited metabolic disorders of the thyroid system. In: Ingbar SH, Braverman LE, eds. Werner's the Thyroid. A Fundamental and Clinical Text. 5 th ed. Philadelphia:J.B.Lippincott, 1986: 687-95
5. Aboul-khair SA, Crooks J, Turnbull AC, Hytten FE. The physiological changes in thyroid function during pregnancy. Clin Sci 1974; 27: 195-207
6. Doniach D, Bottazzo GF, Russel RCG. Goitrous autoimmune thyroiditis (Hashimoto's disease). Clin Endocrinol Metab 1979 Mar;8(1): 63-80
7. Studer H, Gebel F. Simple and nodular sporadic goiter. In: Ingbar SH, Braverman LE,eds. Werner's the Thyroid. A Fundamental and Clinical Text.5th ed. Philadelphia: J.B. Lippincott, 1986: 687-95
8. Amino N, Hagen SR, Yamada N, Refetoff S. Measurement of circulating thyroid microsomal antibodies by the tanned red cell hemagglutination technique: its usefulness in the diagnosis of autoimmune thyroid diseases. Clin Endocrinol 1976 Mar; 5(2): 115-25
9. Lowhagen T, Granberg PO, Lundell G, Skinnari P, Sundlad R, Willems JS. Aspiration biopsy cytology (ABC) in nodules of the thyroid gland suspected to be malignancy. Surg Clin North Am 1979 Feb;59(1):3-18
10. Herle JV, Rich P, Ljung BME, Asharaft MW, Solomon DH, Keeler EB. The thyroid nodule. Ann Intern Med 1982 Feb; 96(2): 221-32
11. Drexhage HA, Bottazzo GF, Doniach D, Bitensky L, Chayen J. Evidence for thyroid-growth-stimulating immunoglobulin in some goitrous thyroid diseases. Lancet 1980 Aug 9;2(8189): 287-91
12. Schnurer LB, Widstrom A. Fine-needle biopsy of the thyroid gland: A cytohistological comparison in 303 cases of goiter. Ann Oto Rhinol Laryngol 1978 Mar-Apr; 87(2): 224-7

13. DeVisscher M, Beckers C, De Cronbrugghe B, Herveg JP. Is there any fundamental difference between endemic and sporadic non-toxic goitre? Acta Endocrinol 1964; 45: 365-9

14. Doniach D, Hudson RV, Roitt IM. Human autoimmune thyroidits: clinical studies. Br Med J 1960 Feb 6; I(5170): 365-73

15. Compagno J, Oertel JE. Malignant lymphoma and other lymphoproliferative disorders of the thyroid gland. A clinicopathologic study of 245 cases. Am J Clin Pathol 1980 Jul; 74(1): 1-11

16. Woolf PD. Transient painless thyroiditis with hyperthyroidism: a variant of lymphocytic thyroiditis? Endocr Rev 1980 Fall; 1(4): 411-20