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Morphological Changes of Follicular Cells in Hashimoto's disease: A Possible Cause of Overdiagnosis in Cytology

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Abstract

Morphological changes of benign follicular cells in Hashimoto's disease (HD) may mimic the changes seen in papillary thyroid carcinoma. This study analyzed the thyroid specimens obtained from a patient with HD, who underwent total thyroidectomy due to recent thyroid enlargement and indeterminate cytology. We observed two types of atypical cells, immature follicular cells in cord-like structures and solid basaloid cells, in the thyroid specimens. Both types of cells exhibited positive immunoreactivity for thyroid transcription factor 1 and possessed the nature of follicular cells. The solid basaloid cells also showed positive for p63 but not the immature follicular cells in the cord-like structures, indicating that the solid basaloid cells retained the stem cell nature. Traumatic injury or inflammation such as autoimmune inflammation of HD may cause cellular damage and lead to repair and regeneration of the follicular epithelium, thus increased stem/progenitor cells may appear in the thyroid as a part of the regeneration after injury. These cells are detectable under microscopy as immature atypical epithelial cells with pale chromatin and nuclear grooves. Presence of these immature follicular cells in the cytological smear samples from patients with HD may result in difficulty in differential diagnosis.

Keywords: Thyroiditis, cytology, false positive, repair cell, stem cell

Introduction

Hashimoto's disease (HD) was first described in 1912 and it is now the most common inflammatory disease of thyroid and the most common cause of hypothyroidism in adults (1-5). HD is an autoimmune disease characterized by elevated thyroid auto-antibodies in the serum and gradual thyroid failure with firm goiter. Nodular presentation of HD and concomitant malignant tumors may be found in the thyroid and some researchers have claimed that HD is a risk factor for papillary thyroid carcinoma (PTC) and malignant lymphoma (6-8). Therefore, it is important for clinicians to identify PTC or other types of thyroid neoplasms amidst a background of HD to ensure appropriate treatment. Unfortunately, there is a high rate of overdiagnosis for thyroid cytology in the HD setting (9-14). Cytological features suggestive of PTC and follicular neoplasms are often seen in fine needle aspiration cytology (FNA) from patients with HD. However, the mechanisms or explanations regarding why these atypical cells often appear in patients with HD have not been well documented in the literature. This paper presents a case of HD in which the thyroid specimen contained solid basaloid cells and immature epithelial cells with nuclear abnormalities suggestive of PTC. The underlying mechanisms for the origin of these atypical cells that suggest PTC in the cytological specimens from HD patients were further explored in this study.

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Case summary

A 62-year-old male patient visited a local hospital for a neck mass and he was then referred to Osaka Red Cross Hospital under a diagnosis of HD and suspicion of PTC. The patient complained of a tumor mass in his anterior neck for 3 years. Physical examination revealed a movable mass with a size of 25 mm in diameter in the midline of the patient's anterior neck. Computed tomography showed a mass lesion located in the isthmus and involved the left lobe of thyroid. FNA cytology was applied to the neck mass and cytological smears were performed with Papanicolaou staining. Laboratory tests for the thyroid function showed the following results (normal values in parentheses): TSH, 1.34 μU/ml (0.541-4.261); free-T3, 3.32 pg/ml (2.39-4.06); free-T4, 0.83 ng/dl (0.71-1.52); thyroglobulin, 0.4 ng/ml (0-32.7); anti-thyroglobulin antibody (TgAb), 865 U/ml (<27); and anti-thyroperoxidase antibody (TPOAb), 165 U/ml (<15). A clinical diagnosis of HD was made and the patient underwent total thyroidectomy based on the cytological diagnosis of atypia suspicious for PTC, recent enlargement of the thyroid mass, and patient's wishes.

Immunohistochemistry

Immunohistochemical examinations were carried out with formalin-fixed and paraffin-embedded sections using the EnVision system (Dako Cytomation, Tokyo, Japan) as per the manufacturer's instructions. The primary antibodies used for the examinations included pancytokeratin (AE1/AE3, Dako Cytomation), p53 (DO-7, Dako Cytomation), p63 (4A4, Nichirei Corporation, Tokyo, Japan), thyroid transcription factor 1 (TTF-1, also called Homeobox Protein NKX2-1) (SPT24, Nichirei Corporation), CEA (polyclonal, Dako Cytomation), and calcitonin (IR515, Dako Cytomation). Hematoxylin was used for nuclear counterstaining.

Results

Cytological findings

The cytological sample was moderately cellular against a background of a few lymphocytes (Fig. 1A and B). There were crowded groups of follicular cells with mild to moderate nuclear enlargement and nuclear overlapping (Fig. 1A and B). Moderate nuclear membrane irregularity was observed, which was accompanied with occasional nuclear grooves and molding (Fig. 1B). The nuclei were clear and exhibited a pale chromatin pattern (Fig. 1). There were no intranuclear pseudoinclusions. A few lymphocytes infiltrated into the follicular cell clusters (Fig. 1). Colloid substance, cyst fluid or tumor necrosis was absent. Benign follicular cells, showing round to oval monomorphic nuclei with finely granular or condensed chromatin, were absent. According to the Guidelines for Clinical Practice for the Management of Thyroid Nodules in Japan 2013 (15), our interpretation of this FNA specimen was as follows: Indeterminate: Atypical cell clusters suggestive of papillary thyroid carcinoma; and Recommendation: Repeat cytological examination. The cytological diagnosis of this case was probably classifiable as suspicious for malignancy by the recent Bethesda System for Reporting Thyroid Cytopathology and "Thy3a" by the United Kingdom Royal College of Pathologists Classification (16, 17).

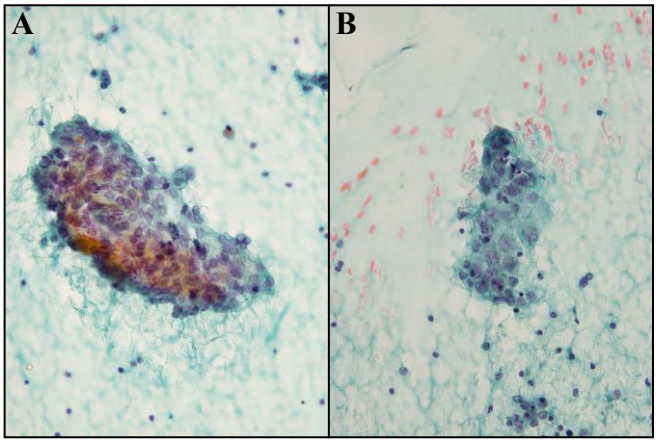

Figure 1. **A**: A large cluster of follicular epithelial cells in a background of a few lymphocytes. The nuclei of the epithelial cells are only mildly enlarged. However, moderately high cellularity and nuclear overlapping are noted. These cells have a clear opaque nucleus and a clear cyanophilic small cytoplasm with slightly increased nuclear/cytoplasmic ratio. No colloid lumen is noted in the cell cluster and no colloid substance is observed in the background. **B**: A small cluster composed of irregularly shaped follicular cells in a background of lymphocytes. These epithelial cells have a dense cyanophilic cytoplasm and an irregular large nucleus with prominent nuclear grooves. A few lymphocytes in the epithelial cluster can be observed (smear, Papanicolaou stain).

Histopathologic observation

The thyroid gland was diffusely enlarged and did not contain any mass lesions on gross examination. The mass lesion palpable in the patient's neck clinically was the prominent pyramidal lobe with no nodular lesions, calcification, or scar fibrosis that was suggestive of neoplastic change. Marked lymphocyte and plasma cell infiltration with occasional germinal follicles was noted diffusely throughout the thyroid gland. Follicular cells underwent degeneration, showing normofollicular and microfollicular structures with little colloid and minimal stromal fibrosis. The most striking findings in the thyroid were two types of atypical epithelial cells: solid basaloid cells (Fig. 2A and B) and immature epithelial cells in cord-like structures and lacking colloid (Fig. 3A and B). These cells differed from normal follicular and oxyphilic follicular epithelial cells often seen in HD. The solid basaloid cells surrounded the colloid follicles and lifted up the follicular cells as if they were basal cells of the thyroid follicles (Fig. 2A).They had a

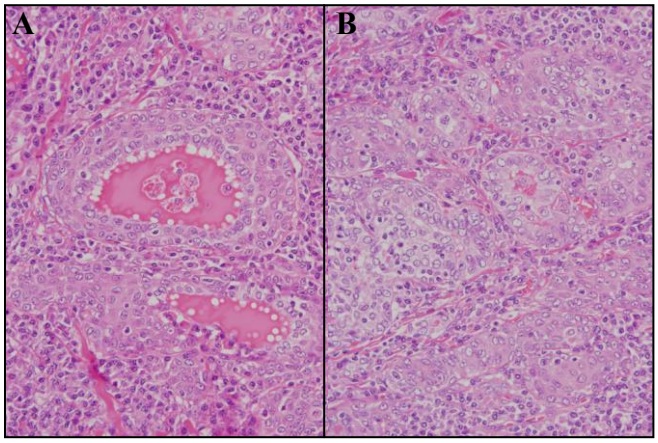

Figure 2. **A**: There are two colloid follicles in this field, containing pinkish colloid substance with small, clear vacuoles in the periphery. The colloid is surrounded with a single layer of follicular cells with a clear cytoplasm. Beneath the follicular cells, there are multiple layers of basaloid cells which are characterized by a dense eosinophilic cytoplasm and a large vesicular nucleus. Note the rich infiltration of lymphocytes and plasma cells in the stroma. **B**: Epithelial cells forming cord-like or trabecular structures. A few tubular structures are noted in the cord structure, but colloid substance is rarely seen. Note the clear nuclei in the epithelial cells in a tubular structure in the center field, and the dense eosinophilic cytoplasm of solid basaloid cells in the lower field (hematoxylin and eosin stain).

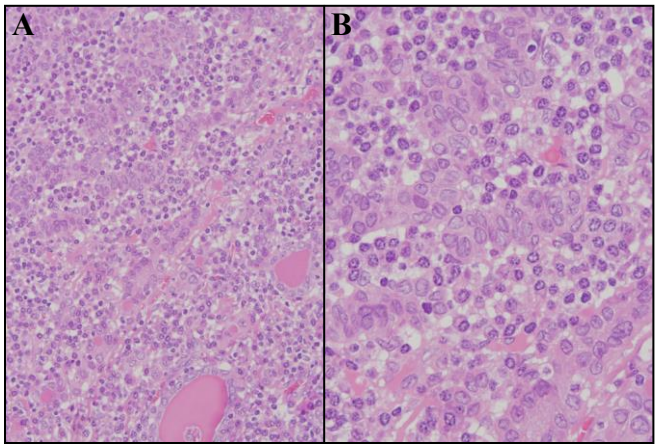

Figure 3. **A**: Immature follicular cells in cord-like arrangements in the upper right field and follicle-forming immature follicular cells with pink colloid substance in the lower left field. Note the rich infiltration of lymphocytes and plasma cells in the stroma.. **B**: Higher magnification of the Fig. 5. The immature cells have a basophilic cytoplasm and lack any cellular polarity to form colloid follicles. Note the numerous nuclear grooves in the immature cells of the cord-like structure. Also, note the rich infiltration of lymphocytes and plasma cells in the stroma (hematoxylin and eosin stain).

slightly more dense and eosinophilic cytoplasm than follicular cells, and showed some similarity to the embryonic remnant of the third branchial pouch, so-called solid cell nests of the thyroid (18-21). The immature epithelial cells formed immature cord-like or trabecular structures, but did not form tubular or colloid substance-containing follicular lumen, showing some similarity to the embryonic developing thyroid or trabecular/embryonal variant of follicular adenoma. Different from the solid basaloid cells, the immature epithelial cells had a basophilic cytoplasm. Cells with intermediate characteristics between the two types of cells were also noted as shown in Fig. 2B. The nuclei of the basaloid cells were vesicular with small nucleoli, and the immature cells in a cord-like structure (Fig. 3A) had a clear, pale chromatin pattern, while the intermediate cells arranged in a colloid-lacking follicular pattern (Fig. 2B). Interestingly, the immature epithelial cells in cord-like arrangements displayed numerous nuclear grooves (Fig. 3B). These two types of abnormal epithelial cells were diffusely distributed in the thyroid without forming any mass lesions that were suggestive of neoplastic growth.

Immunohistochemical results and interpretation

The immunohistochemical results for the solid basaloid cells and immature epithelial cells in cord-like structures were comparatively analyzed using serial sections stained for TTF1, calcitonin, AE1/AE3, and p63. The nuclei of the solid basaloid cells were positively stained for TTF1 (Fig. 4A), while the nuclei in the peripheral (basal) layer were positively stained for p63 (Fig. 4B). The epithelial cells in the innermost layer of the colloid follicles were negatively stained for p63 (Fig. 4B). Majority of the solid basaloid cells were judged as positive for both TTF1 and p63. These results differed from those reported for the solid cell nests of the thyroid, the latter were positive for p63 and negative for TTF1 (20-23). Immunohistochemical examination of the immature epithelial cells in the cord-like structures showed positive staining for pan-cytokeratin (AE1/AE3) (Fig. 5A) and TTF1 (Fig. 5B), but negative staining for p63. These results suggested that the immature epithelial cells in cord-like structures possessed the follicular cell nature. Similar cord-like structures have been described in embryonic developing thyroid (24). Both types of epithelial cells were negatively stained for calcitonin. Increased C cells, and p53- and/or CEA-positive cells were not found in the thyroid.

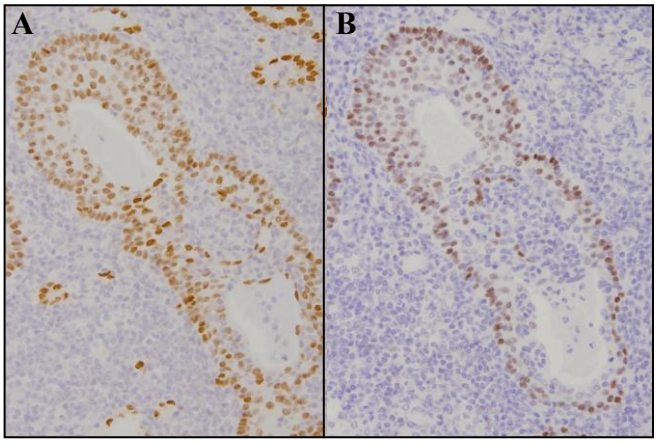

Figure 4. Two colloid follicles surrounded by multiple layers of epithelial cells (solid basaloid cells). The nuclei of the cells are positively stained for TTF1 (4A), and the nuclei of the peripheral (basal) layer cells are positively stained for p63 (4B). Note that the epithelial cells in the innermost layer of the colloid follicle are negatively stained for p63 (4B). Majority of the solid basaloid cells are judged as positive for both TTF1 and p63 (A: immunoperoxidase stain for TTF1 and B: immunoperoxidase stain for p63, hematoxylin nuclear counterstain).

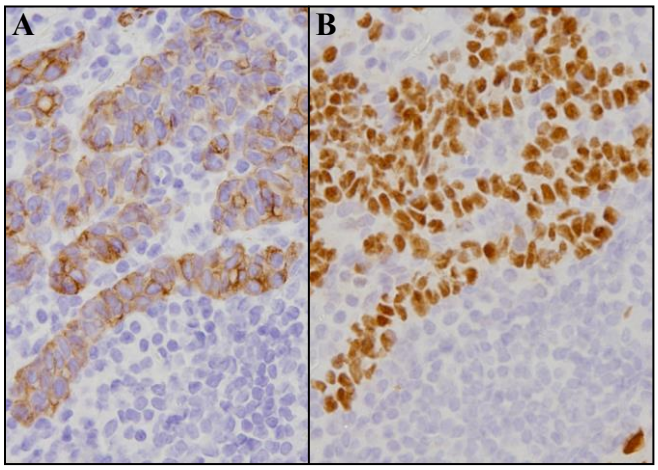

Figure 5. Immunohistochemistry of the immature follicular cells in cord-like arrangements for AE1/AE3 (5A) and TTF1 (5B). The cell cytoplasms are positively stained for AE1/AE3 (8A) and the cell nuclei are positively stained for TTF1 (5B), suggesting that they are immature follicular cells resembling the embryonic thyroid epithelium. Note the irregular nuclear contour, although the nuclear grooves are not discernible (A: immunoperoxidase stain for AE1/AE3 and B: immunoperoxidase stain for TTF1, hematoxylin nuclear counterstain, X20).

Discussion

Diagnosis of HD is made clinically and the diagnostic criteria in most clinical guidelines include: 1) diffuse and non-tender goiter, 2) exclusion of Graves' disease, and 3) presence of auto-antibodies (TgAb, TPOAb) in the serum. Nodular presentation of HD may create serious concern on coexisting malignant neoplasms. This is because PTC and other types of neoplasms can exist in the thyroid with or without HD and some researchers have claimed a higher incidence of PTC and malignant lymphoma in patients with HD than in those without HD (6-8). When nodular lesions are found in patients with HD, FNA may be employed to the index nodule to rule out coexisting malignancy. Unfortunately, it is well known that overdiagnosis in thyroid cytology may occur in the HD setting (9-14). Cytological features suggestive of PTC and follicular neoplasms are often seen in the thyroid FNAs from HD patients. Harvey et al. found that the features most commonly leading to overdiagnosis of PTC in HD were pale, powdery or clear chromatin, occasional nuclear grooves or nuclear vacuoles, high cellularity with a microfollicular pattern, and a paucity of background lymphocytes (14). Most of these features were observed in our patient (Fig. 1A and B) and we had to advise this patient to undergo surgical treatment because of indeterminate cytological diagnosis (atypical cell clusters suggestive of PTC) together with recent enlargement of thyroid mass.

The present study clearly illustrated abnormal epithelial cells observed in the surgical specimens of a patient with HD, which corresponded well to those in the cytological smears. These cells had follicular cell nature as well as immature stem/progenitor cell characteristics. These observations explained well why cytological smear samples from HD patients often contain immature atypical follicular cells with PTC-type nuclear abnormality. This is the first

report in the literature to demonstrate the immature stem/progenitor cell-type follicular cells in a patient with HD, which may lead to misdiagnosis of suspicious for malignancy in the cytological examination.

Squamous cells and solid basaloid cells can appear in a variety of conditions including benign nodules, malignant neoplasms, inflammatory diseases, and embryonic remnants of thyroid. Solid cell nests of the thyroid have been considered to be the embryonic remnants derived from the third branchial pouch and can be found in thyroid glands in the cases of HD (18-22). Li et al. identified solid cell nests in 12 out of 105 patients with HD when one representative section from each patient was examined (19). Reis-Filho et al. and Burstein et al. have shown that the main cells of solid cell nests are strongly positive for p63, a p53 homologue that is consistently expressed in basal/stem cells of stratified epithelia, and they have concluded that the p63 positivity represents the stem cell nature of these cells (20,21). Similar features were observed for the solid basaloid cells in our patient, thus the solid basaloid cells in our patient might possess stem cell nature. However, the solid basaloid cells also exhibited follicular cell differentiation evidenced by TTF1 positivity, which differed from the solid cell nests of the thyroid. Bai et al. reported an encapsulated thyroid neoplasm with squamous cell differentiation and with cells exhibiting intermediate features between follicular and squamous cells (25). This transformation phenomenon observed in their case indicates that the basaloid squamous cell differentiation may occur in follicular cell neoplasm and present the multipotential/stem cell nature of tumor cells (25).

For the immature epithelial cells, they may originate from the regeneration of the follicular cells and stem cells in thyroid due to traumatic injury and repair of the thyroid gland following FNA. Ozaki et al. have demonstrated that the numbers of cells with bromodeoxyuridine-positivity and cells with clear or faintly eosinophilic cytoplasm are markedly increased in the central area of the thyroid gland two weeks after partial thyroidectomy in a mouse model to produce thyroid regeneration (26). Microarray followed by pathway analysis revealed that the expressions of genes involved in embryonic development and oncogenesis were altered by partial thyroidectomy. These results suggest that both C cells and follicular cells could be affected by partial thyroidectomy and the immature cells may be derived from stem/progenitor cells on their way to differentiate into C cells or follicular cells (26). As a conclusion, we think that the stem/progenitor cells may participate in the repair and/or regeneration of the thyroid and these cells may result in the difficulty in cytological diagnosis. Such immature stem/progenitor cells may appear during regeneration following severe inflammation in HD or traumatic injury following FNA procedure. FNA might have played a role in our HD patient for the atypical follicular cells suggestive of PTC because the FNA examination at our hospital was carried out only 3 weeks after the previous FNA done in another hospital. Layfield et al. recommended a 3-month interval between FNA to prevent false-positive interpretations due to reactive changes (16, 27). However, this was unlikely in our patient because those abnormal cells were distributed diffusely throughout the thyroid gland and were not accumulated in any places where the fine needle might have reached. The immature follicular cells in cord-like structures and the solid basaloid cells in our patient might be immature stem/progenitor cells induced by injury and regeneration, thereby those atypical cells appeared in the cytological smear.

Some researchers reported that the cells in some lesions in HD exhibited PTC-type nuclear features and they interpreted these lesions as multiple submicroscopic foci of PTC in HD thyroid because HD almost always harbors genetic rearrangements that are strongly associated with PTC (12). However, some other researchers reported that the genetic changes might be a passenger mutation rather than a driver mutation because follicular cells in HD share only low-level recombination events with a subset of PTC (28), and BRAF and RET/PTC rearrangements are absent in the dominant nodules of HD in some reports (29). The genetic changes may explain the PTC-type nuclear features observed in the immature follicular cells because RET/PTC rearrangements are often associated with borderline PTC-type nuclear features (12, 30, 31).

On reviewing the cytological samples of our case, we think that the cytological features that could provide helpful information in differential diagnosis and avoid misdiagnosis include: 1) no nuclear pseudo-inclusions in the abnormal follicular cells, 2) a few lymphocytes in the background, and 3) a few lymphocytes in the follicular cell clusters (32).

References

1. Hashimoto H. Zur Kenntnis der lymphomatosen Veranderung der Schiddruse (Struma lymphomatosa). Achiv fur klinische, Berlin. 1912:97:219-48.
2. Pearce EN, Farwell AP, Braverman LE. Thyroiditis. N Engl J Med, 2003:348:2646-55.
3. Lloyd RV, Douglas BR, Young WF. Endocrine Diseases. Washington, DC, American Registry of Pathology, 2002
4. Kakudo K, Li Y, Hirokawa M, Ozaki T. Diagnosis of Hashimoto's thyroiditis and IgG4-related sclerosing disease. Pathol Int 2011:61:175-83.
5. Kakudo K, Li Y, Taniguchi E, Mori I, Ozaki T, Nishihara E, Matsuzuka F, Miyauchi A. IgG4-related disease of the thyroid glands. Endocr J 2011:59:273-81.
6. Kato I, Tajima K, Suchi T, Aozasa K, Matsuzuka F, Kuma K, Tominaga S. Chronic thyroiditis as a risk factor of B-cell lymphoma in the thyroid gland. Jpn J Cancer Res 1985:76:1085-90.
7. Okayasu, Fujiwara M, Hara Y, Tanaka Y, Rose NR. Association of chronic lymphocytic thyroiditis and thyroid papillary carcinoma. A study of surgical cases among Japanese, and white and African American. Cancer 1995:76:2312-8.
8. Repplinger D, Bargren A, Zhang YW, Adler JT, Haymart M, Chen H. Is Hashimoto's thyroiditis a risk factor for papillary cancer? J Surg Res 2007:150:49-52.
9. Carson HJ, Castelli MJ, Gattuso P. Incidence of neoplasia in Hashimoto's thyroiditis: A fine-needle aspiration study. Diagn Cytopathol 1996:14:38-42.
10. Kumarasinghe MP and De Silva S. Pitfalls in cytological diagnosis of autoimmune thyroiditis. Pathol 1999:31:1-7.
11. MacDonald L and Yazdi HM. Fine needle aspiration biopsy of Hashimoto's thyroiditis. Sources of diagnostic error. Acta Cytol 1999:43:400-6.
12. Arif S, Blanes A, Diaz-Cano SJ. Hashimoto's thyroiditis shares features with early papillary thyroid carcinoma. Histopathol 2002:41:357-62.
13. Haberal AN, Toru S, Ozen O Arat Z, Bilezikçi B. Diagnostic pitfalls in the evaluation of fine needle aspiration cytology of the thyroid: correlation with histopathology in 260 cases. Cytopathol 2009:20:103-8.
14. Harvey AM, Truong LD, Mody DR. Diagnostic pitfalls of Hashimoto's/lymphocytic thyroiditis on fine-needle aspirations and strategies to avoid overdiagnosis. Acta Cytol 2012:56:352-60.
15. Nakamura H. Guidelines for clinical practice for the

management of thyroid nodules in Japan. The Japan Thyroid Association, Nankodo Co. Ltd, Tokyo, 2013 (in Japanese).
16. Ali CZ and Cibas ES. The Bethesda system for reporting thyroid cytopathology. Springer, New York, 2010.
17. Lobo C, McQueen A, Beale T, Kocjan G. The UK royal college of pathologists thyroid fine-needle aspiration diagnostic classification is a robust tool for the clinical management of abnormal thyroid nodules. Acta Cytol 2011:55:499-506.
18. Kakudo K, Bai Y, Ozaki T, Homma K, Ito Y, Miyauchi A. Intrathyroid epithelial thymoma (ITET) and carcinoma showing thymus-like differentiation (CASTLE): CD5-positive neoplasms mimicking squamous cell carcinoma of the thyroid. Histol Histopathol 2013 [Epub ahead of print].
19. Li Y, Zhou G, Ozaki T, Nishihara E, Matsuzuka F, Bai Y, Liu Z, Taniguchi E, Miyauchi A, Kakudo K. Distinct histopathological features of Hashimoto's thyroiditis with respect to IgG4-related disease. Mod Pathol 2012:25:1086-97.
20. Reis-Filho JS, Preto A, Soares P. Ricardo S, Cameselle-Teijeiro J, Sobrinho-Simões M. p63 expression in solid cell nests of the thyroid: further evidence for a stem cell origin. Mod Pathol 2003:16:43-8.
21. Burstein DE, Nagi C, Wang BY, Unger P. Immunohistochemical detection of p53 homolog p63 in solid cell nests, papillary thyroid carcinoma, and Hashimoto's thyroiditis: a stem cell hypothesis of papillary carcinoma oncogenesis. Hum Pathol 2004:35:465-73.
22. Cameselle-Teijeiro J, Abdulkader I, Pérez-Becerra R, Vázquez-Boquete A, Alberte-Lista L, Ruiz-Ponte C, Forteza J, Sobrinho-Simões M. BRAF mutation in solid cell nest hyperplasia associated with papillary thyroid carcinoma. A precursor lesion? Hum Pathol 2009:40:1029-35.
23. Ozaki T, Nagashima K, Kusakabe T, Kakudo K, Kimura S. Development of thyroid gland and ultimobranchial body cyst is independent of p63. Lab Invest 2011:91:138-46.
24. Katoh R, Kawaoi A, Miyagi E, Li X, Suzuki K, Nakamura Y, Kakudo K. Thyroid transcription factor-1 in normal, hyperplastic, and neoplastic follicular thyroid cells examined by immunohistochemistry and nonradioactive in situ hybridization. Mod Pathol 2000:13:570-6.
25. Bai Y, Mori I, liu Z, Li Y, Ozaki T, Taniguchi E, Asai M, Naito A, Kakudo K. Squamous cell components in a thyroid follicular adenoma: significant evidence of follicular cell origin by histomorphological, immunohistochemical and molecular analysis. Pathol Int 2011:61:577-81.
26. Ozaki T, Matsubara T, Seo D, Okamoto M, Nagashima K, Sasaki Y, Hayase S, Murata T, Liao XH, Hanson J, Rodriguez-Canales J, Thorgeirsson SS, Kakudo K, Refetoff S, Kimura S. Thyroid regeneration: characterization of clear cells after partial thyroidectomy. Endocrinol 2012:153:2514-25.
27. Layfield LJ, Abrams J, Cochand-Priollet B, Evans D, Gharib H, Greenspan F, Henry M, LiVolsi V, Merino M, Michael CW, Wang H, Wells SA. Post-thyroid FNA testing and treatment options: a synopsis of the National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference. Diagn Cytopathol 2008:36:442-8.
28. Rhoden KJ, Unger K, Salvatore G, Yilmaz Y, Vovk V, Chiappetta G, Qumsiyeh MB, Rothstein JL, Fusco A, Santoro M, Zitzelsberger H, Tallini G. RET/Papillary thyroid cancer rearrangement in nonneoplastic thyrocytes: follicular cells of Hashimoto's thyroiditis share low-level recombination events with a subset of papillary carcinoma. J Clin Endocrinol Metab 2006:91:2414-23.
29. Sadow PM, Heinrich MC, Corless CL, Fletcher JA, Nosé V. Absence of BRAF, NRAS, KRAS, HRAS mutations, and RET/PTC gene rearrangements distinguishes dominant nodules in Hashimoto thyroiditis from papillary thyroid carcinomas. Endcr Pathol 2010:21:73-9.
30. Arora N, Scognamiglio T, Lubitz CC, Moo TA, Kato MA, Zhu B, Zarnegar R, Chen YT, Fahey TJ 3rd. Identification of borderline thyroid tumors by gene expression array analysis. Cancer 2009:115:5421-31.
31. Fusco A, Chiappetta G, Hui P, Garcia-Rostan G, Golden L, Kinder BK, Dillon DA, Giuliano A, Cirafici AM, Santoro M, Rosai J, Tallini G. Assessment of RET/PTC oncogene activation and clonality in thyroid nodules with incomplete morphological evidence of papillary carcinoma. A search for the early precursors of papillary cancer. Am J Pathol 2002:160:2157-67.
32. Nishigami E, Liu Z, Taniguchi E, Koike E, Ozaki T, Mori I, Kakudo K. Cytological features of well-differentiated tumors of uncertain malignant potential: indeterminate cytology and WDT-UMP. Endocr J 2012:59:483-7.