ENDOCRINE PATHOLOGY

Histological Evaluation of Thyroid Lesions by a Scanning Acoustic Microscope

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Background: Imaging by ultrasound (US) has been used in clinical diagnosis, but its resolution is not so high enough for accurate diagnosis. A scanning acoustic microscope (SAM), which uses US at 120 MHz with high resolution as a light microscope (LM), has been applied to evaluate thyroid histology including neoplastic and reactive lesions for its usefulness in clinical diagnosis. Methods: Paraffin sections in 10 μm thickness were observed by SAM with 120 MHz transducer (Honda Electronics, Toyohashi, Japan) and their images were compared with LM images. Results: Thyroid follicular structures were well visualized by SAM. Colloids in the follicles displayed greater speed-of-sound (SOS) according to the concentration. Higher concentrated colloids displayed greater SOS. Interstitial collagen fibers also showed greater SOS depending on the degree of fibrosis. Interstitial lymph follicles exhibited least SOS. Papillary carcinomas were visualized as papillary structure with fibrovascular cores. Papillary portions demonstrated less SOS compared to surrounding follicles. Psammoma bodies displayed as spots with greater SOS. Conclusions: SAM imaging has as high quality as that of LM and the following benefits over LM: 1) images were acquired in a few minutes without special staining; 2) images reflected the tissue elasticity of each lesion; 3) images reflected the follicular functions and structures; 4) digitized SOS data could be statistically comparable among lesions; 5) SAM images were comparable with other echographic images.

Key Words: Thyroid gland; Ultrasound; Microscope; Digital imaging; Elasticity

Three Cases of Adrenocortical Tumors Mistaken for a Hepatocellular Carcinoma/Diagnostic Pitfalls and Differential Diagnosis

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Adrenocortical adenoma and carcinoma in other parenchyma is extremely rare, and few cases are reported. Because of the rarity of these tumors, they sometimes cause a diagnostic problem. Adrenal cortical neoplasms in liver parenchyma could be presented as 3 fashions. Direct invasion or adhesion of adrenocortical tumors to liver parenchyma is one, maybe most common pattern. And adenoma or carcinoma arising in adrenohepatic fusion or tumor arising in ectopic adrenal tissue is the other possible scenarios which are rarely experienced. We report 3 cases of adrenal cortical tumors which are misdiagnosed as hepatocellular carcinoma at preoperative state. The first is an adrenocortical adenoma arising from adrenohepatic fusion tissue. The second and the third are adrenocortical carcinoma and adrenocortical oncocytoma arising in ectopic adrenal tissue in liver. We describe their clinical presentation, gross, microscopic findings, immunohistochemical findings with emphasis on differential diagnosis with hepatocellular carcinoma.

Key Words: Adrenals; Neoplasms; Carcinoma, hepatocellular

The Clinicopathological Significance of Multifocality in Papillary Thyroid Microcarcinoma

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Background: The papillary microcarcinoma (PMC) has been known a favorable prognosis than overt papillary thyroid carcinoma (PTC) (larger than 1 cm). Unlike multifocal overt PTC which is associated with aggressive behaviors, tumor behaviors and the definite guideline of treatment for multifocal PMC (mPMC) are not fully understood. Methods: We performed a retrospective study for conventional PMC to determine the relationship between tumor multifocality and clinicopathological characteristics. Results: In PMCs, tumor multifocality was identified in 103 of 383 cases (26.9%). PMC with multifocality was significantly correlated with lymph node metastasis (p=0.003) and higher stage of tumor, but not other clinicopathological parameters. The main tumor size of mPMC is significantly associated with BRAF V600E mutation and extrathyroidal extension, but not nodal metastasis. Of 103 mPMCs, 43 cases (41.7%) were suspicious for multifocal malignant tumor via pre-operative US. In 43 radiologically suspicious patients, four and eleven cases were confirmed as mPMC via pre-operative fine-needle aspiration biopsy and intra-operative frozen section, respectively. Twenty-eight of 43 radiologically suspicious for multifocality were confirmed post-operative pathologic examinations. Conclusions: These results suggest that multifocality in PMC is significantly associated with lymph node metastasis. Pre- or intra-operative evaluations for multifocality could be useful to decide the extent of thyroidectomy and lymphadenectomy at initial surgery.

Key Words: Thyroid cancer, papillary; Multifocal; Papillary thyroid microcarcinoma; Lymph node metastasis

Clinical Significance of Minimal Extrathyroidal Extension in Solitary Papillary Thyroid Carcinomas

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Background: Because of the recent advances in diagnosis and treatment of thyroid cancer, the definition of minimal extrathyroidal extension (MTE) needs to be redefined. Methods: We performed a retrospective study for conventional papillary thyroid carcinomas (PTC) from 2000 to 2015. The main tumor size of MTE was significantly associated with BRAF V600E mutation and extrathyroidal extension, but not nodal metastasis.
Background: The definite diagnosis of minimal extrathyroid extension (ETE) is subjective because of lack of a well-defined true capsule in the thyroid gland. Any tumor with minimal ETE is categorized as T3 according to TNM stage system, regardless of tumor size. In this study, we analyzed the clinical significance of minimal ETE in the patients with solitary papillary thyroid carcinomas (PTCs). Methods: A total of 328 patients with solitary PTCs were retrospectively analyzed for recurrence free survival and presence of metastatic lymph nodes according to presence of minimal ETE and only tumor size classified by the TNM stage in Asan Medical Center from 1996 to 2003. Results: Forty-one patients (12.5%) revealed the recurrence. The recurrence free survival was significantly different according to only tumor size (p=0.001) regardless of presence of minimal ETE (p=0.110). The presence of metastatic lymph nodes was identified in 229 patients (69.8%), and significantly different according to only tumor size (p=0.001) regardless of presence of minimal ETE (p=0.057). In 43 patients (13%) with papillary microcarcinomas (T1a), the presence of metastatic lymph nodes was not significantly different according to presence of minimal ETE (p=0.746) in contrast to the patients with larger PTCs (p=0.053).

Conclusions: The presence of minimal ETE has no clinically significant impact on the recurrence free survival and the presence of metastatic lymph nodes. For patients with papillary microcarcinomas and minimal ETE, T3 categorization might cause an inappropriate overtreatment despite of absence of metastatic lymph nodes.

Key Words: Thyroid glands; Carcinoma, papillary

Coexistence of Hashimoto’s Thyroiditis with Papillary Thyroid Carcinoma: The Clinicopathological Features of P2X7 Receptor Expression

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Background: The purpose of the present study was to investigate the P2X7 receptor (P2X7R) expression with the clinicopathological features of coexistent Hashimoto thyroiditis (HT) with papillary thyroid carcinoma (PTC). Methods: A total 170 cases were examined, including 84 patients of PTC with HT and 86 patients of PTC without HT. P2X7 receptor expression was examined by immunohistochemical methods on formalin-fixed, paraffin-embedded thyroid tissues. Results: There were female patients, less extrathyroid extension, less lymph node metastasis, less lymphovascular invasion, and less frequent recurrence in the PTC with HT group compared to the PTC without HT. Patients with positive for P2X7R had significantly higher frequencies of lymphovascular invasion, extrathyroid extension, lymph node metastasis, and absence of the HT in the univariate analysis. In the multivariate analysis, the P2X7R expression was significantly higher if HT was absent and extrathyroid extension is present. In the group of PTC with HT, the final immunoreactive score was significantly higher in the patients with involvement of both lobes, tumor multifocality, lymphovascular invasion, and extrathyroid extension. However, there was no statistically significant relationship between the P2X7R expression and lymph node metastasis in the PTC with HT patients. Conclusions: Co-existing HT in patients with PTC has association with better prognostic factors, and P2X7R expression in PTC was correlated with poor prognostic factors. However, P2X7R expression may not predict lymph node metastasis in the PTC with HT patients.

Key Words: Thyroid cancer, papillary; Thyroid neoplasms; Hashimoto disease; Receptors, purinergic P2X7; P2X7

Monophasic Synovial Sarcoma of the Thyroid Gland

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Synovial sarcoma is rare soft tissue tumor, commonly arising in para-articular areas of extremities but also occurring in head and neck. However, primary synovial sarcoma of the thyroid gland is extremely rare tumor which has been reported only three times in the English literatures previously. Herein, we report a 47-year-old woman who had an incidentally detected thyroid mass on routine health check-up. The tumor shaved 7.8 mm-sized anechoic lesion in the isthmus of thyroid gland on ultrasonography, which was suspected malignancy. After fine needle aspiration, total thyroidectomy and lymph node dissection were performed. Macroscopically, the mass was white, irregular shaped and elastic solid tumor. Microscopically and immnohistochemically, the tumor was compatible with monophasic synovial sarcoma. In addition, result of SYT/SSX fusion transcript study confirmed the diagnosis of synovial sarcoma. One year post-surgery, no new lesion or recurrence in the other sites are identified.

Key Words: Thyroid glands; Sarcoma, synovial; SYT/SSX fusion protein

A Testing Algorithm for Detection of the BRAFV600E Mutation Using Immunohistochemistry in Papillary Thyroid Carcinoma

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Background: BRAF mutation in papillary thyroid carcinoma (PTC) is useful diagnostic marker that is most frequent alteration in that tumor. We tried to develop a testing algorithm for BRAFV600E mutation in papillary thyroid carcinoma, using immunohistochemical staining (IHC). Methods: Formalin-fixed paraffin-embedded PTC tissues of 91 patients were immunostained with BRAFV600E mutation-specific Ab. The BRAF V600E IHC results were interpreted by semi-quantitative scoring system that sums the scores of proportion of positive cells (score, 0 to 5) and staining intensity (score, 0 to 3). To confirm mutation, four methods of direct-sequencing, pyrosequencing, peptide nucleic acid
clamping polymerase chain reaction (PCR), and real-time PCR were used. When two or more methods showed positive detection, it was determined to be mutation-positive. 

**Results:** By the receiver operating characteristic (ROC) curve, the cutoff value of IHC was 5.5 to detect mutation (area under the ROC curve, 78.9%; sensitivity, 88.4%; specificity, 68.2%). In 10 cases of score <4, none revealed positive BRAF mutation by the present definition. In 68 cases of score ≥ 6, 89.7% revealed BRAF mutation in 2 or more methods, and 97.1% revealed in one or more molecular methods. By the result, we could suggest that BRAF IHC score ≥ 6 predict BRAF mutation, and BRAF IHC score <4 exclude possibility of BRAF mutation. Therefore, such scores in BRAF IHC may not need further molecular study. BRAF IHC score of 4 or 5, however, may need additional molecular study to confirm BRAF mutation. 

**Conclusions:** We developed the immunohistochemical staining system for screening test of BRAF V600E mutation which is helpful to judge whether molecular study are required or not.

**Key Words:** Thyroid cancer, papillary; BRAF V600E mutation; BRAF V600E; mutation-specific antibody; Immunohistochemical staining; Screening test

**AP06-PP-0011**

**Correlation Between BRAFV600E Mutation and Clinicopathologic Factors in Papillary Thyroid Cancer**

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**Background:** The BRAF V600E mutation is the most common genetic alteration in papillary thyroid carcinoma (PTC) and several studies have shown that it is associated with aggressive clinicopathologic characteristics of the tumor. The aim of this study was to investigate the correlation between BRAF V600E mutation and clinicopathologic factors of PTC. 

**Methods:** Five hundred ninety patients with PTC who had undergone BRAF V600E mutation analysis were enrolled in this study. Each patient’s clinical information including age, sex, tumor histology, size, extrathyroid extension (ETE), lymph node metastasis (LNM), multiplicity, coexistence of chronic lymphocytic thyroiditis (CLT) and BRAF V600E mutation status were obtained from our database. 

**Results:** Among 590 patients, 505 (85.6%) had BRAF V600E mutation and 85 (14.4%) did not. Overall, the BRAF V600E mutation was significantly associated with conventional subtype (p<0.001), LNM (p=0.019), multiplicity (p=0.020) and absence of CLT (p=0.030). In conventional PTC cases, absence of CLT (p=0.023) was significantly associated with BRAF V600E mutation. In follicular variant PTC cases, older age (>45 years, p=0.005) was significantly associated with BRAF V600E mutation. Although BRAF V600E mutation did not show significant correlation with tumor size, consistent positive correlation between conventional type and BRAF V600E mutation was noted regardless of tumor size. 

**Conclusions:** Conventional subtype and aggressive factors including ETE, LNM, and multiplicity were associated with BRAF V600E mutation. In addition, absence of CLT was significantly associated with BRAF V600E mutation. As BRAF V600E mutation is associated with aggressive clinicopathologic factors, it could be used as potential predictor for poor clinical outcome.

**Key Words:** Thyroid cancer, papillary; BRAF mutation; Hashimoto disease

**AP06-PP-0012**

**A Thyroid Nodular Hyperplasia with Adipose Metaplasia: A Case Report**

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Thyroid nodular lesions with fat component are very rare. Very few cases were reported in the literature. A 48-year-old female patient was admitted into Inha University Hospital with an incidentally found neck mass. Ultrasound image showed an isoechoic solid nodule with hypoechogenic rim at left lower portion of left thyroid. The nodule measured 2.4×1.5×3.7 cm. Ultrasound-guided fine needle aspiration was done. The lesion was diagnosed as atypical cells of undetermined significance on aspiration cytology. The smear revealed several small clusters of atypical follicular cells showing pale nuclei and irregular nuclear membrane in a background of blood and small amount of colloid. The patient underwent lobectomy of left thyroid. Microscopically, the nodule was confined to the thyroid parenchyma. The nodule revealed admixed benign thyroid follicles and mature adipose tissue. There was no evidence of malignancy, such as papillary carcinoma or follicular carcinoma. Also, we excluded the possibility of follicular adenoma because there was no definite capsule. The admixed adipose tissue did not have continuity with perithyroid soft tissue. The nodule was positive for CD56, but negative for galectin-3, cytokeratin 19, and cyclin D1. We diagnosed this lesion as nodular hyperplasia with adipose metaplasia. The pathogenesis of mature adipose tissue in thyroid nodule is unclear. It may originate from metaplasia of stromal fibroblast due to tissue hypoxia or entrapment of adipose tissue during embryogenesis.

**Key Words:** Thyroid glands; Adipose tissue; Thyroid nodule; Metaplasia

**AP06-PP-0013**

**Impact of RAS Mutation Analysis on the Management of Cytologically Indeterminate Nodules**

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**Background:** Follicular variant of papillary carcinoma (FVPTC) and follicular neoplasm often cause a diagnostic dilemma in fine needle aspiration (FNA) and are often interpreted as “indeterminate” in FNA. RAS mutations are found in 40-50% of follicular carcinomas, 20-40%
The Modified Bethesda System for Reporting Thyroid Core Needle Biopsy Offers the Comparable Efficiency for Predicting Malignancy Risk Compared with Fine Needle Aspiration Cytology: Two-Year Retrospective Review of Single Institution

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Background: Thyroid core needle biopsy (CNB) is increasingly used as a complementary tool for diagnosing thyroid nodules. However, reporting system for thyroid CNB is not established. Here we evaluate the applicability of Bethesda system for reporting CNB of thyroid. Methods: A total of 1,844 thyroid nodules underwent CNB at our institution between January 2010 and September 2011. All CNB results were classified into 6 categories similar to the Bethesda system: unsatisfactory, benign, indeterminate, follicular neoplasm (FN), suspicious for malignancy (SM) and malignancy. Malignancy rate of each category was estimated in resected specimens. Results: The distribution of 6 categories from 1884 cases of CNB was as follows: 3.8% unsatisfactory, 50.7% benign, 13.6% indeterminate, 7.8% FN, 3.8% SM, and 20.3% malignancy. Of the total 1,884 CNB cases, 485 (26.5%) were followed by surgical resection. The overall surgical yield of malignancy was 23.8%. The malignancy rate for the 6 categories was as follows: 80% for unsatisfactory, 32.4% for benign, 33.9% for indeterminate, 48.5% for FN, 97.9% for SM, and 99.2% for malignancy. Relatively high malignancy rates were noted in unsatisfactory and benign categories which might be resulted from false negative result of clinically suspicious nodules. The false-positive rate was 0.97%. The specificity for diagnosing malignant thyroid nodules and all neoplasms were 97% and 64% respectively, which were comparable to those of reported fine needle aspiration cytology of thyroid nodules. Conclusions: The modified Bethesda system is efficient for reporting thyroid CNB and may offers guideline for patient management.

Key Words: Thyroid glands; Biopsy, large-core needle; Bethesda system; Malignancy rate

Expression of CXCL12 in Papillary Carcinoma of Thyroid and Its Diagnostic Usefulness

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Results: The distribution of 6 categories from 1884 cases of CNB was as follows: 3.8% unsatisfactory, 50.7% benign, 13.6% indeterminate, 7.8% FN, 3.8% SM, and 20.3% malignancy. Of the total 1,884 CNB cases, 485 (26.5%) were followed by surgical resection. The overall surgical yield of malignancy was 23.8%. The malignancy rate for the 6 categories was as follows: 80% for unsatisfactory, 32.4% for benign, 33.9% for indeterminate, 48.5% for FN, 97.9% for SM, and 99.2% for malignancy. Relatively high malignancy rates were noted in unsatisfactory and benign categories which might be resulted from false negative result of clinically suspicious nodules. The false-positive rate was 0.97%. The specificity for diagnosing malignant thyroid nodules and all neoplasms were 97% and 64% respectively, which were comparable to those of reported fine needle aspiration cytology of thyroid nodules.
Background: CXCL12 and CXCR4 play an important role in tumor growth, proliferation, vascularization, immunosuppression, and metastasis. Both tumor cells and stromal cells elaborate chemokines to sustain tumor cell growth and induce angiogenesis. Methods: Tissue specimens including 30 papillary carcinoma, 10 follicular carcinoma, 3 poorly differentiated carcinoma, 20 follicular adenoma, and 20 nodular hyperplasia were stained for immunohistochemistry of CXCL12, CD34, α-smooth muscle actin, and CD31 and liquid-based cytology slides from sixteen additional cases including 10 papillary carcinoma, 4 follicular adenoma, and 2 nodular hyperplasia were prepared for immunocytochemistry of CXCL12 to examine whether the CXCL12 expression between thyroid neoplasms is different and the difference can be useful for diagnosis of thyroid neoplasms. Results: In tissue sections 28 out of 30 cases of papillary carcinoma showed CXCL12 expression in 25% or more of the follicular tumor cells. Fifty-one out of 53 cases of other thyroid neoplasms including nodular hyperplasia, follicular adenoma, follicular carcinoma, and poorly differentiated carcinoma showed CXCL12 expression in less than 3% of follicular tumor cells. In liquid-based cytology all ten cases of papillary carcinoma showed CXCL12 expression in most of the follicular tumor cells but the tumor cells in four cases of follicular adenoma and two cases of nodular hyperplasia did not show CXCL12 expression. Conclusions: The CXCL12 expression of papillary carcinoma might be related with different biological behaviors including lymph node metastasis and stroma producing behavior of papillary carcinoma and CXCL12 can be useful for improving diagnostic accuracy of papillary carcinoma in liquid-based cytology. Key Words: CXCL12; Thyroid cancer, papillary; Cytopathology