Ultrasonographic Classification of the Metastases to the Thyroid Gland

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Background and Objectives: To classify the metastases to the thyroid gland arising from non-thyroidal malignancies on ultrasound (US).

Materials and Methods: We enrolled 45 consecutive patients with metastases to the thyroid gland from 2005 to 2012. We classified metastases into 4 types; type I: diffuse non-mass forming lesion, type II: a solitary suspicious nodule, type III: multiple suspicious nodules, and type IV: nodule(s) with no suspicion. We subcategorized type I into two subtypes; type IA: diffusely infiltrative lesion, type IB: diffuse micronodulation.

Results: The most frequent primary malignancy of thyroid metastases was lung cancer. The patients with thyroid metastases were 26 (57.8%) in type I; type IA: 16 (35.6%), type IB: 10 (22.2%), 14 (31.1%) in type II, 3 (6.7%) in type III and 2 (4.4%) in type IV. Type I metastasis included 18 of 25 patients with lung cancer and all 3 patients with stomach cancer. Thirty patients (73.3%) having type IA, II or III revealed malignant findings on US, in contrast, 12 (26.7%) patients having type IB or IV revealed no suspicious findings.

Conclusion: Type I (diffuse non-mass forming lesion) was the most common in thyroid metastases. A quarter of thyroid metastases revealed no suspicious findings on US. Thyroid metastases can be considered as a differential diagnosis, when diffuse non-mass forming lesions or nodules with no suspicion are revealed on thyroid US.

Key Words: Thyroid metastases, Ultrasound, Micronodulation

Introduction

Metastases to the thyroid gland occur infrequently in clinical practice. Several large clinical studies performed prior to 2000 revealed that clinically significant thyroid metastases was infrequent. In contrast, the incidence of thyroid metastases ranges from 2% to 24% in the patients affected by widespread malignant neoplasm according to autopsy studies. Some investigators have suggested that thyroid metastases were no longer considered rare. Thyroid metastases arising from non-thyroidal malignancies have been reported in 1.4–3% of patients who underwent surgery for thyroid cancer, however, the actual number of thyroid metastases may be greater because not all patients undergo surgery.

We analyzed two previous published reports regarding radiological findings on thyroid metastases. In the studies, the investigators enrolled a small population and analyzed thyroid metastases, representing only focal lesions on the images clinically.

In the present study, we classified thyroid metastases arising from non-thyroidal malignancies based on ultrasound (US) in a larger population and assessed the radiologic significance to differentiate thyroid metastases from other thyroid diseases.
Materials and Methods

This study was approved by the Institutional Review Board of Samsung Medical Center, and informed consent was waived. We retrospectively analyzed the clinical data and US findings of 45 patients with thyroid metastases arising from non-thyroidal malignancies in two institutions from 2005 to 2012. We evaluated patient age, gender, type of primary non-thyroidal malignancies, clinical presentation of thyroid metastases and the interval between initial diagnosis of primary malignancies and diagnosis of thyroid metastases. We excluded patients with lymphoma or with malignant tumors which invaded the thyroid gland directly from adjacent organs in the neck or upper mediastinum.

US was performed using high-resolution US equipment (HDI 5000: Advanced Technology Laboratories, Bothell, WA, IU22: Philips Medical Systems, Bothell, WA, USA, and Ascendus: Hitachi Aloka, Tokyo, Japan) with 5–15 MHz linear array transducers. US guided fine needle aspiration (FNA) was performed using a 23 gauge syringe with free hand technique by one of board-certified radiologists with more than 2 years of experience. US guided core needle biopsy (CNB) was performed, using an 18 gauge, double action spring–activated, trucut–type needle (Acecut: TSK Laboratory, Tochigi–Ken, Japan). The US features of thyroid lesions were retrospectively reviewed by two radiologists experienced in thyroid imaging with the consensus. We classified thyroid metastases into four types based on US. Type I included diffuse non–mass forming lesion involving either unilateral or bilateral thyroid lobes, in which the volume of thyroid gland was variable, but the shape and contour of thyroid gland were relatively preserved. We subclassified type I into two sub–types: type IA: diffusely infiltrative lesion which revealed ill-defined or geographic hypoechogenicity, replacing normal thyroid parenchyma totally or near totally, type IB: diffuse micronodulation which revealed innumerable small hypoechogenic nodules involving either unilateral or bilateral thyroid lobes. Type II included a solitary suspicious malignant nodule with or without probable benign nodule(s) in the thyroid gland. Type II included multiple suspicious malignant nodules (more than two) in the thyroid gland. Type IV included thyroid nodule(s) with no suspicion in the thyroid gland. The inclusion criteria for suspicion of a malignant finding in a thyroid nodule on US were the presence of at least one of the following: the presence of macro- or microcalcification, a taller–than–wide shape, hypoechogenicity or marked hypoechogenicity, and a spiculated margin. Probable benign diagnosis based on US was made if thyroid nodules were negative for all malignant features.

Cytopathology was reviewed by one of seven experienced cytopathologists. Commercially available immunocytochemical and immunohistochemical studies for thyroglobulin antibody, thyroid transcription factor–1, carcinoembryonic antigen, cytokeratin, synaptophysin, and mucicarmine stains were applied case by case in patients who were not classified based on Hematoxylin and Eosin stain.

Results

Among 45 patients, thyroid metastases were confirmed by US guided FNA in 29 patients, CNB in 11 patients and surgery in the remaining five patients. Immunocytochemistry was used for five of the patients diagnosed by US guided FNA, and immunohistochemistry was performed for ten of the patients diagnosed by CNB and one of the patients who underwent surgery.

Patients with thyroid metastases included 30 males and 15 females (mean age, 62.6 years; range, 27–84 years). Primary non-thyroidal malignancies (n=45) included lung cancer (n=25), head and neck cancer (n=6), stomach cancer (n=3), renal cell carcinoma (RCC) (n=3), esophageal cancer (n=2), breast cancer (n=2), colorectal cancer (n=1), Merkel cell carcinoma (n=1), bladder cancer (n=1) and carcinoid tumor (n=1) (Table 1). Clinical presentation of thyroid metastases was as follows: palpable mass on the neck in 9 patients and incidentally detected lesions by imaging modalities in 36 patients: screening US in 4 patients, chest computed tomography (CT) in 12 patients and 18fluorodeoxyglucose positron emission/CT
Ultrasonographic Classification of the Metastases to the Thyroid Gland

Table 1. US classification and incidence of thyroid metastasis

| Primary malignancy       | No.     | Type IA | Type IB | Type II | Type III | Type IV |
|--------------------------|---------|---------|---------|---------|----------|---------|
| Lung cancer              | 25 (55.7%) | 9 (20%) | 9 (20%) | 3 (6.7%) | 3 (6.7%) | 1 (2.2%) |
| Head and neck cancer     | 6 (13.3%) | 2 (4.4%) |         |         |          |         |
| Stomach cancer           | 3 (6.7%) | 3 (6.7%) |         |         |          |         |
| Renal cell cancer        | 3 (6.7%) |         | 2 (4.4%) |         |          |         |
| Esophageal cancer        | 2 (4.4%) | 1 (2.2%) |         |         |          |         |
| Breast cancer            | 2 (4.4%) | 1 (2.2%) |         |         |          |         |
| Colorectal cancer        | 1 (2.2%) |         |         |         |          |         |
| Merkel cell carcinoma    | 1 (2.2%) |         |         |         |          |         |
| Bladder cancer           | 1 (2.2%) |         |         |         |          |         |
| Carcinoid tumor          | 1 (2.2%) |         |         |         |          |         |
| Total (n=37)             | 45 (100%) | 16 (35.6%) | 10 (22.2%) | 14 (31.1%) | 3 (6.7%) | 2 (4.4%) |

(18)FDG PET/CT) in 20 patients. The mean interval between the initial diagnosis of non-thyroidal malignancy and the detection of thyroid metastasis was 13.1 months (range, 0–101 months). Thyroid metastases were detected during the initial workup of primary non-thyroidal malignancies in 31 (68.9%) of 45 patients.

The number of patients with thyroid metastases was as follows: type IA (n=16, 35.6%), type IB (n=10, 22.2%), type II (n=14, 31.1%), type III (n=3, 6.7%) and type IV (n=2, 4.4%) (Table 1). Type I was most common in thyroid metastasis (26/45, 57.8%). Type IA included 9 (20%) of the patients with lung cancer and all 3 (6.7%) patients with stomach cancer. Type IB included 9 (20%) of patients with lung cancer and one (2.2%) of patients with breast cancer. Type II included 4 (8.9%) of patients with head and neck cancer and 2 (4.4%) of patients with RCC. Type III included 3 (6.7%) of patients with lung cancer. Type IV included one (2.2%) of patients with lung cancer and one (2.2%) of patients with RCC (Figs. 1–5).

Five patients underwent surgeries due to indeterminate cytology (n=1), gradual growth of tumor during follow-up (n=3) and patient’s demand (n=1). In a patient with indeterminate cytology who had RCC, the initial US guided FNA revealed indeterminate cytological results (a few follicular cells with mild nuclear atypia), and the following four US guided FNAs showed consecutive non-diagnostic results due to blood in the samples. The diameter of the lesion increased from 2.8 cm to 5.6 cm based on US over 18 months. Thyroid metastasis was confirmed by right lobectomy under the impression of growing benign nodule.

Discussion

In the present study, the most frequent primary origin of thyroid metastases was lung cancer. Thyroid metastases were detected by 18)FDG PET/CT or chest CT in the majority of patients. The most frequent type of thyroid metastases was type I, which revealed diffuse non-mass forming lesion on US. Our results were opposite against the previous studies, which were focused on only focal lesions on thyroid gland.5,8)

In numerous large cohort autopsy studies, the most common primary non-thyroidal origin of thyroid metastases was lung or breast.1,10–12) These thyroid metastases detected on autopsy tended to be clinically occult. Conversely, many clinical studies have showed that the most frequent primary non-thyroidal malignancy resulting in symptomatic or clinically evident thyroid metastases was RCC.3,13,14) In the present study, the lung was the most frequent origin of thyroid metastases, corresponded with autopsy studies. We supposed that the subclinical manifestation of thyroid metastases was detected more frequently than the past, because the clinical application of CT and 18)FDG PET–CT has gradually been increasing in the patients with malignancies.

Recently, the incidence of thyroid metastases has been reported to be relatively higher than that prior to
Many non–palpable thyroid nodules were increasingly detected by various imaging modalities. In our clinical situation, $^{18}$FDG PET/CT is routinely applied for certain patients with malignancies to evaluate staging of the primary malignancy and detect distant metastasis. In the present study, thyroid metastases were detected by imaging modalities in the majority of population. Only 9 (20%) patients had clinical symptom, representing palpable mass on the neck. We consented that thyroid metastases were no longer considered rare. The detection of thyroid metastases may increase in this clinical situation, as the clinical use of CT and $^{18}$FDG PET/CT gradually increases.

To date, the information to regard US findings of thyroid metastases has been lacking and the most clinicians and radiologists have assumed that metastases are similar to usual primary thyroid carcinomas, especially papillary thyroid cancer, in terms of US features. In a previous report, Chung et al. classified thyroid metastases based on US and focused on focal lesions of the thyroid gland, in which they evaluated malignant findings of thyroid nodules and a number of suspicious nodules. In the other previous report, the investigators also focused on focal lesions and didn’t evaluate US classification.

In contrast, thyroid metastases manifested variable US classifications in the present study. Notably, the most frequent type was diffuse non–mass forming lesion involving either unilateral or bilateral thyroid lobes (type IA and IB). Type IA thyroid metastasis tended to reveal heterogeneously hypoechoic infiltrative lesion to replace normal thyroid parenchyma entirely or near

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**Fig. 1.** Type IA thyroid metastases in a 61-year-old male with lung cancer. Diffuse infiltrative hypoechoic lesion is demonstrated in the entire thyroid gland with multiple microcalcifications (white arrowhead). Diffuse infiltrative lesion reveals mild hypervascularity on color Doppler examination. Normal thyroid parenchyma is entirely replaced by the infiltrative lesion. On histology, obtained by core needle biopsy, malignant cells of metastatic adenocarcinoma with stromal fibrosis replace normal follicular structures entirely on the biopsy specimen (A: transverse plane, B: color Doppler examination, C: Hematoxylin & Eosin stain, ×40, D: cytokeratin stain, ×100).
entirely (Fig. 1). The volume of thyroid gland frequently increased in variable ranges due to the infiltrative tumor. However, the shape and contour of the thyroid gland were relatively preserved. Type IB thyroid metastasis revealed diffuse micronodulation, which represented innumerable linear or curvilinear hypoechoic lesions with longest diameter of less than 1 cm in either one thyroid lobe or both lobes (Fig. 2). Yeh et al. reported micronodulation on thyroid US at first, as an US sign of Hashimoto thyroiditis. Micronodulation in Hashimoto thyroiditis tended to reveal round to oval or nodular shape, surrounded by echogenic rims as well as small, hypoechoic on US. However, diffuse micronodulation in type IB thyroid metastasis revealed linear or curvilinear (slit-like) shape without the presence of surrounding echogenic rim. On histology, obtained by CNB, metastatic cells were demonstrated to infiltrate partially into follicular and parafollicular structures occupying small portion of the biopsy specimen and preserve the considerable portion of thyroid gland. We supposed that the partial infiltration of metastatic cells might affect linear or curvilinear micronodulation on US in type IB thyroid metastasis. When a diffusely infiltrative lesion or micronodulation of the thyroid gland is revealed on US in the patients with malignancies, thyroid metastases should be considered as a differential diagnosis.

Ten (22.2%) patients with type IB thyroid metastasis revealed micronodulation on US, mimicking Hashimoto thyroiditis. Additionally, two (4.4%) patients with type IV thyroid metastasis showed thyroid nodule(s) without suspicion. In the present study, thyroid metastases demonstrated no suspicious malignant findings on US in a quarter of the patients. Therefore, the detection of thyroid metastases on US could be underestimated clinically, because thyroid metastases were mis-
regarded as Hashimoto thyroiditis or a benign thyroid nodule.

FNA is a safe and efficient diagnostic tool for thyroid nodules. However, several authors have reported that the incorrect result was 24% (40 of 167 cases) to diagnose thyroid metastases on preoperative FNA.\(^2\) However, all US guided FNAs revealed correct cytological results of thyroid metastases, except for a patient with RCC in the present study. It was known that immunocytochemistry helped to decrease incorrect
FNA result of thyroid metastases, which could differentiate secondary malignancy from primary malignancy in thyroid gland.\(^9\)

The present study has several limitations. First, this study was a retrospective analysis. The selection bias of the patients might occur. Second, not all suspicious malignant thyroid nodules in type III were evaluated by US guided FNA or CNB. Third, surgery was not performed for all thyroid metastases. False positive results of thyroid metastases diagnosed by US guided FNA or CNB was not considered. Fourth, the correlation with US image and pathology was not performed in all patients. Fifth, US criteria of malignant findings to evaluate thyroid metastases were based on the guideline, in which only nodular thyroid diseases were analyzed.\(^9\) Because type I thyroid metastasis was not a nodular diseases, there might be a limitation to apply the guideline.

## Conclusion

To conclude, thyroid metastases reveal variable features on US, representing diffuse non-mass forming lesion as well as nodular thyroid disease. Thyroid metastases can be considered as a differential diagnosis, when the patients with non-thyroidal malignancies reveal diffuse non-mass forming lesions or nodules without suspicion on thyroid US.

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