Case Report

Establishing the First Diagnosis of Follicular Thyroid Carcinoma from the Femoral Metastatic Site in an 84-year-old Woman

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Follicular thyroid carcinoma (FTC) commonly presents as a solitary thyroid nodule, which is diagnosed by thorough examination of thyroidectomy/lobectomy specimen for capsular and vascular invasions. First diagnosis of FTC from femoral metastasis is very rare. Here, we report such a case in an 84-year-old woman who presented with increasing pain in her left thigh. A bone scan revealed multiple lesions in the bones including left femur. Four years ago, the patient suffered right humeral pathological fracture. The humeral lesion was positive for TTF-1 and was interpreted as "metastatic non-small cell carcinoma consistent with lung primary". However, subsequent bronchial washing and lung biopsy were negative for malignancy. Biopsy of left femoral lesion showed solid nests of cells with round to oval nuclei and abundant eosionophilic/granular cytoplasm. The nuclei of tumor cells contain one or more nucleoli and granular/vesicular chromatin. No typical nuclear morphology of papillary thyroid carcinoma (PTC) was noted. The tumor cells are positive for thyroglobulin and TTF-1, consistent with metastatic tumor from thyroid primary. Immunostains of HBME-1 and CK19 only mark scattered tumor cells, which do not support the differential diagnosis of metastatic PTC. CD56 and CK7 stains are both positive. Upon further communication, patient's remote history of "thyroid follicular adenoma", status post right lobectomy was obtained. The femoral lesion was negative for BRAF mutation. In conclusion, based on the overall morphological and immunohistochemical features as well as patient's history, the final diagnosis of metastatic FTC was made. We would like to raise the awareness that metastatic FTC should be included in the differential diagnoses for tumors metastasized to bone to avoid misdiagnosis.

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INTRODUCTION

Follicular thyroid carcinoma (FTC) is the second most common cancer of the thyroid gland after papillary thyroid carcinoma (PTC) and accounts for 10% of thyroid malignancy.[1] However, FTC is considered more aggressive than PTC because of a greater tendency to invade blood vessels and spread to distant organs, such as lung and bones.[2-5] There are two types of FTC, minimally invasive and widely invasive. FTC commonly presents as a solitary thyroid nodule. Grossly, minimally invasive FTC is indistinguishable from follicular adenomas. Thorough histological examination for capsular penetration and/or vascular invasion is the only criteria to differentiate theses two entities. Most cases of metastatic FTC occur after the diagnosis of the primary tumor. First diagnosis of FTC from metastatic sites is very rare. Here, we report such a case with discussion on differential diagnoses and potential pitfalls.

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CASE REPORT

The patient was an 84-year-old woman who presented with a pathologic fracture of the left femur. A whole body bone image study was performed. Patchy increased radionuclide accumulation was noted in bilateral shoulders, knees, spine, right humerus, bilateral parietal bones of the skull, right acetabulum, proximal left femur and left anterior iliac crest. A metastatic neoplasm involving multiple bones was suspected. Patient's pertinent medical history was significant for hypothyroidism and a pathologic fracture of right humerus four years ago. Biopsy of right humeral lesion then was done at an outside institute and tumor cells were positive for TTF-1 and CK7, negative for CK20, CDX2 and GCDFP. A diagnosis of "metastatic non-small cell carcinoma consistent with lung primary" was rendered. However, subsequent bronchial washing, bronchial brushing and lung biopsy were negative for malignancy. The patient was treated with radiation to her right humerus, Zometa and Tarceva for 1 year. She had been doing fairly well until suffered fracture of her left femur. To obtain a complete clinical history of the patient, multiple efforts were tried to reach the patient and her previous care providers. Neither the

slides nor the pathology report of the thyroid nodule were available for us to review. However, per her previous care provider, the thyroid nodule was a benign thyroid adenoma. Ten months after the left femur fracture, the patient suffered another pathologic fracture of the right humerus at previous fracture site. Histologically, both the femoral and the humeral lesions show similar histomorphology: Tumors were composed of solid nests of cells with round to oval nuclei and abundant eosionophilic/granular cytoplasm. No foci of necrosis or mitotic figures were noted (**Figure 1A**). The nuclei contain one or more nucleoli and granular/vesicular chromatin. Only rare nuclear grooves were found, but no intranuclear inclusion or nuclear clearing was noted (**Figure 1B**). Based on the morphological features, the differential diagnoses include FTC, PTC, medullary thyroid carcinoma, neuroendocrine carcinoma, paraganglioma and melanoma. A panel of immunohistochemical markers was performed. Tumor cells were immunoreactive for thyroglobulin (**Figure 2A**) and TTF-1 (**Figure 2B**), confirmed their thyroid origin. HBME-1 (**Figure 2C**) immunostain was negative and CK19 (**Figure 2D**) marked only scattered tumor cells, not compatible with the differential diagnosis of metastatic PTC. The negative staining results of synaptophysin, chromogranin, Congo Red and calcitonin (data not shown) exclude the possibilities of medullary thyroid carcinoma or neuroendocrine carcinoma. S100 and HMB45 immunohistochemical stains were both negative (data not shown), arguing against the differential diagnoses of melanoma or paraganglioma. In addition, the neoplastic cells are negative for mucicarmine and CK20 (data not shown), diffusely and strongly positive for CK7 (**Figure 2E**) and CD56 (**Figure 2F**). The overall morphology and immunophenotype of the femoral and humeral lesions, together with patient's history of thyroid nodule are most consistent with a diagnosis of metastatic FTC with Hurthle cell features. BRAF mutation test was performed and no mutation was detected, further supporting the diagnosis.

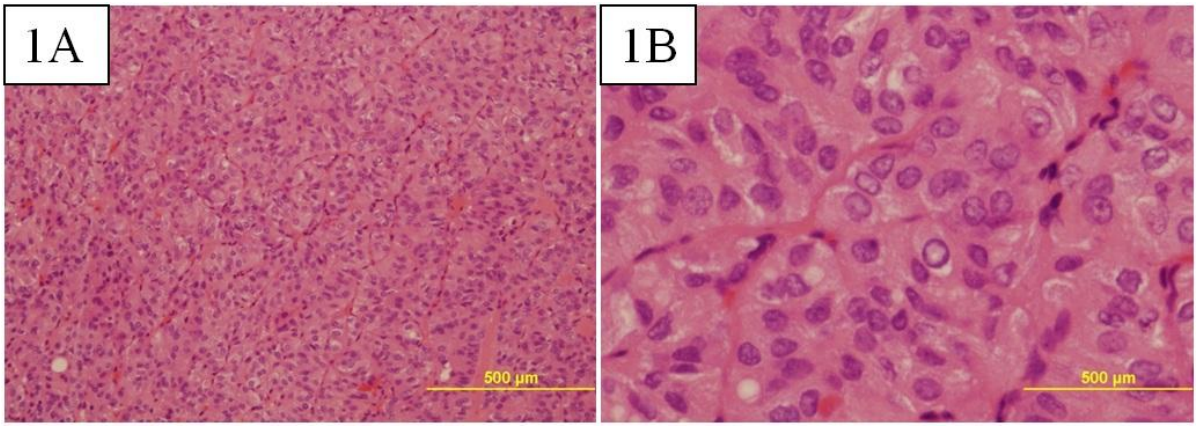

Figure 1. Morphological features of tumors. Tumors were composed of solid nests of cells with round to oval nuclei and abundant eosionophilic/granular cytoplasm. Necrosis or mitotic figures were not found (**1A**, 100x). The nuclei contain one or more nucleoli and granular/vesicular chromatin. Although rare nuclear grooves were present, no intranuclear inclusion or nuclear clearing can be found (**1B**, 400x).

DISCUSSION

Thyroid carcinoma is the most common endocrine cancer and its incidence is rising in the United States.[6] In WHO histological classification, there are several types of thyroid carcinoma, including PTC, FTC and medullary carcinoma. Among them, the most common ones are PTC and FTC, representing approximately 80% and 10% of thyroid carcinoma, respectively.[1] PTC affects all age groups and usually spread to regional lymph nodes. Unlike PTC, FTC occurs in older patients and disseminates by vascular system to the lung and bone. Data have shown that the bone is more commonly involved by metastatic breast cancer, prostate cancer, lung cancer and colon/rectum cancer.[7-8] However, our case demonstrates that metastatic thyroid cancer should be included in the differential diagnoses for work-up for metastatic tumors to bones.

TTF1 is one of the important immunohistochemical markers in the work up for tumor of unknown origin. However, it is not specific for carcinoma arising from lung.[9-11] It is also positive for thyroid carcinoma (nuclear stain)[9,12] and hepatocellular carcinoma (cytoplasmic stain).[13] Because thyroglobulin is specific for thyroid carcinoma, the combination of TTF1 and thyroglobulin can be used to differentiate lung carcinoma from thyroid carcinoma. The accepted criteria for diagnosis of PTC is the characteristic nuclear features. However, in some cases, identification of these nuclear features can be problematic. A flurry of studies has been done to examine the immunoprofiles of PTC and FTC. Strong and diffuse reactivity for CK19 is consistent with PTC.[14-15] The pitfall here is that CK19 can be focally positive in benign thyroid lesions or FTC, hence, the intensity and extend of CK19 reactivity is crucial for reaching the correct diagnosis. HBME-1 is well known for marking mesothelial cells. It is also very specific for PTC. The specificity of HBME-1 in detecting PTC ranges from 94% to 96%.[16-17] In conjunction with CK19, the specificity of these two markers for PTC can reach 100%.[16] In our case, tumor

cells are negative for HBME-1 and only focally positive for CK19, arguing against the diagnosis of metastatic PTC. Additional evidence favoring the diagnosis of metastatic FTC includes diffuse and strong reactivity of CD56 and negative BRAF mutation test in tumor cells. CD56 is a neural cell adhesion molecule and is also expressed by endocrine cells. Studies have shown that CD56 is negative in PTC, but positive in thyroid lesions other than PTC.[18] BRAF V600E mutation is the most common genetic alteration in PTC with 80% of PTC harboring this mutation.[19]

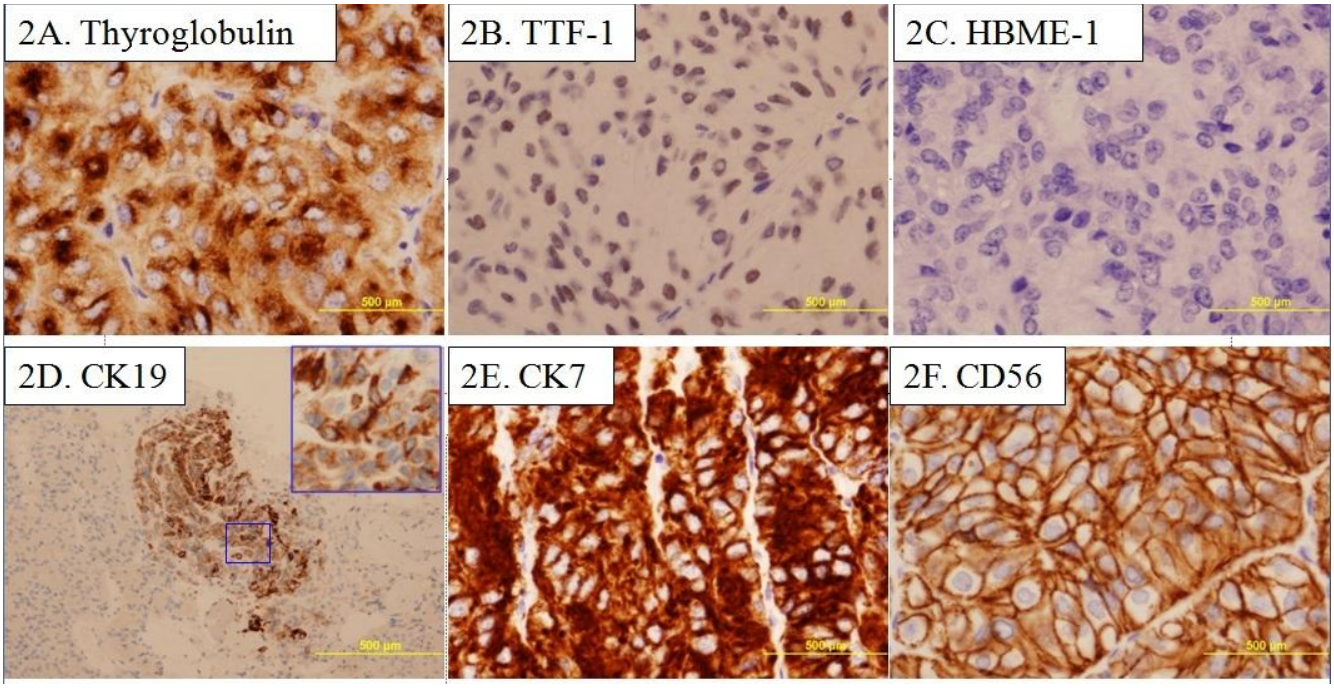

Figure 2. Immunohistochemical features of tumor. Tumor cells (400x) were positive for thyroglobulin (**2A**) and TTF-1 (**2B**), and negative for HBME-1 (**2C**). Focal immunoreactive for CK19 (**2D**) was present. CK7 (**2E**) and CD56 (**2F**) stains were both positive.

In conclusion, patient's clinical history of thyroidectomy for a thyroid nodule, multiple bone lesions with immunohistochemistry positive for TTF1, thyroglobulin, and CD56, and negative for HBME1 and CK19, as well as lack of BRAF mutation are most consistent with a diagnosis of metastatic FTC. This case is extremely rare and difficult due to previous misdiagnosis of the humeral lesion as "metastatic non-small cell carcinoma consistent with lung primary" along with the patient's ambiguous clinical history. Our case demonstrates the importance of investigating clinical history and developing correct differential diagnoses. In addition, our case emphasizes the necessity of accessory studies, such as the application of a panel of immunohistochemical markers and genetic testing in making a correct diagnosis.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

ABBREVIATIONS

FTC: follicular thyroid carcinoma; PTC: papillary thyroid carcinoma

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