Parasitic thyroid nodule with nodular hyperplasia supported by microRNA signature and molecular mutation study: a case report

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Abstract: Benign thyroid tissue has been reported in the lateral neck region other than thyroid glands and other parts of body without any malignant manifestation. When ectopic thyroid tissue forms a nodule, it is usually diagnosed as a parasitic thyroid nodule (or sequestered thyroid nodule). Parasitic thyroid nodules have been reported in the neck region without connection to the thyroid gland, mediastinum, and many other sites. Parasitic thyroid nodules can show nodular hyperplasia and exhibit similar histologic appearance as the main thyroid gland, and are often mistaken as metastatic thyroid carcinoma clinically and radiologically. An 82-year-old female with a history of left hemithyroidectomy for multinodular goiter developed a right chest wall mass, which was biopsied and showed thyroglobulin-positive follicular cells. The bone scan showed a right proximal humerus lytic lesion and L2 spine lytic lesion with iodine I131 uptake. Since the chest wall mass was suggestive of metastasis of occult primary thyroid carcinoma, the patient underwent a total thyroidectomy and chest wall mass excision. The pathology from both lesions showed identical appearance with nodular hyperplasia. The patient was then treated with I131 ablation and the disease was stable with no clinical symptoms. Molecular studies including microRNA (miRNA) analysis, NRAS mutation analysis and immunohistochemical staining for PTEN were performed on both thyroid and chest wall specimens. No abnormalities were identified. This is the first report demonstrating that a parasitic thyroid nodule can occur within the chest with extension into the chest wall and bones. This finding is supported by both histology and molecular studies. We conclude that molecular studies may serve as ancillary studies to confirm a diagnosis of parasitic thyroid nodule which can cause a serious dilemma when diagnosing metastatic thyroid carcinoma and has important therapeutic and prognostic implications.

Keywords: Parasitic thyroid nodule, thyroid cancer, microRNA, NRAS

Introduction

Certain benign neoplasms of connective tissue, such as leiomyoma and chondroma, are capable of spreading to other sites. The extension of an epithelial lesion to a distal site has been generally considered as a criterion of malignancy. Normal thyroid tissue and hyperplastic thyroid goiters have been reported to exist at other locations other than thyroid glands without any malignant manifestation. Such circumstances include ectopic thyroid tissue resulting from faulty embryogenesis (thyroglossal duct cyst and lingual thyroid), hyperplastic thyroid tissue outside the gland in Graves’ disease, mechanical implantation of thyroid tissue due to surgical intervention or trauma, thyroid tissue in cervical lymph nodes, thyroid tissue in struma ovarii, and sequestered thyroid nodule (parasitic thyroid nodule). Parasitic thyroid nodule has been reported in the neck region without connection to thyroid gland or in the mediastinum [1-3]. Parasitic thyroid nodules often show nodular hyperplasia and exhibit similar histologic appearance as the main thyroid gland [3].

A thyroid nodule is very common and can be caused by benign lesions including inflammation, nodular hyperplasia (adenomatoid goiter),
fOLLICULAR ADENOMA, OR BY MALIGNANT LESIONS INCLUDING PAPILLARY THYROID CARCINOMA (PTC), FOLLICULAR CARCINOMA, ANAPLASTIC CARCINOMA, MEDULLARY CARCINOMA OR LYMPHOMA. MOLECULAR MARKERS HAVE BEEN EXTENSIVELY INVESTIGATED IN THYROID CANCERS. BRAF (V600E) ACTIVATING MUTATION, RET REARRANGEMENTS (RET/PTC) AND NTRK1 REARRANGEMENTS HAVE BEEN IDENTIFIED IN PAPILLARY THYROID CARCINOMA [4-10]. A CHROMOSOMAL TRANSLOCATION (t(2;3) [q13;p25]) RESULTING IN FUSION OF PAX8 GENE AND THE PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA 1 (PPAR-gamma-1) GENE HAS BEEN IDENTIFIED IN FOLLICULAR CANCERS AND MAY DISTINGUISH FOLLICULAR CARCINOMAS FROM PAPILLARY CANCERS [11]. HOWEVER, THIS TRANSLOCATION CANNOT DIFFERENTIATE FOLLICULAR CARCINOMA FROM FOLLICULAR ADENOMA [12]. MUTATIONS OF RAS GENES INCLUDING HRAS, NRAS AND KRAS PROTO-ONCOGENES HAVE BEEN IDENTIFIED IN ABOUT 30% OF FOLLICULAR CANCERS WITH THE NRAS MUTATIONS BEING MORE COMMON THAN HRAS AND KRAS [13]. HOWEVER, HRAS, KRAS, AND NRAS MUTATIONS HAVE ALSO BEEN IDENTIFIED IN FOLLICULAR ADENOMAS, ALTHOUGH NRAS MUTATIONS APPEAR MORE COMMON IN FOLLICULAR CARCINOMA THAN IN FOLLICULAR ADENOMA OR HYPERPLASIA [14-17]. COWDEN SYNDROME IS ONE OF THE BEST-DESCRIBED SYNDROMES WITH PTEN MUTATION. PATIENTS WITH COWDEN SYNDROME HAVE APPROXIMATELY A 70-FOOD INCREASED INCIDENCE OF THYROID CANCER COMPARED TO THE GENERAL POPULATION [18]. SIMILARLY, APPROXIMATELY ONE-QUARTER OF SPORADIC FOLLICULAR ADENOMAS HAVE A HEMIZYGOUS DELETION OF A CHROMOSOME REGION CONTAINING PTEN. MiRNAs REGULATE GENE EXPRESSION BY BINDING TO SPECIFIC TARGETS IN THEIR 3’ UNTRANSLATED REGIONS (UTRs) AND ARE INVOLVED IN THE PATHOGENESIS OF A VARIETY OF TUMORS. SEVERAL miRNAs HAVE BEEN REPORTED TO BE UPREGULATED IN THYROID CANCERS [19]. FURTHERMORE, OUR RECENT RESULTS HAVE DEMONSTRATED AN EXPRESSION LEVEL OF FOUR miRNAs (miR-146b, miR-221, miR-187 AND miR-30d) IN THYROID FINE NEEDLE ASPIRATION MATERIAL. THIS IS ABLE TO CLASSIFY THYROID LESIONS AS BENIGN OR MALIGNANT LESIONS WITH A SENSITIVITY OF 93% AND A SPECIFICITY OF 94% [20].

Figure 1. Radiological findings of humerus and L2 spine. A. MRI of right proximal humerus shows an intramedullary lytic lesion. B. MRI of L2 spine shows a lytic lesion.
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Case presentation

Clinical findings

An 82-year-old female with a history of left hemithyroidectomy for multinodular goiter developed a right chest wall mass. CT scan showed a 4-cm mass beneath the intercostal muscle within the chest with extension into the chest wall. Subsequently, the patient had a chest wall mass biopsy that showed thyroglobulin-positive follicular cells. The bone scan performed at that time showed a right proximal humerus lytic lesion and a L2 spine lytic lesion, which was re-demonstrated on MRI (Figure 1A and 1B). A Radioactive iodine I131 scan showed uptake in the thyroid, chest wall mass, right proximal humerus, and L2 spine. The patient then underwent a total thyroidectomy to remove the remaining thyroid gland and chest wall mass excision. The pathology from both lesions showed identical appearance with nodular hyperplasia and was confirmed by a well-known pathologist. The patient was treated with radioactive I131 ablation twice. After the I131 treatment, MRI showed persistent but stable lesions in the humerus and spine. Clinically, the patient was doing well without any clinical symptoms related to these lesions although her thyroglobulin level was elevated up to 2,100. The patient was followed up routinely, and, fourteen years later after initial diagnosis of nodular hyperplasia of thyroid, she passed away at age of 93 years due to cardiovascular modalities.

Pathology and molecular studies

Fine needle aspirations (FNA) smears from both thyroid and chest wall lesions showed colloid and benign follicular cells on both Diff-Quik
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stain and Papanicolaou stain (Figure 2A, 2B and 2D, 2E). Histologic sections of both thyroid and chest wall lesion showed variable sized follicles lined by flatten epithelial cells and filled with colloid. This is a typical appearance of nodular hyperplasia of the thyroid (adenomatoid goiter) (Figure 2C and 2F).

The paraffin embedded tissue blocks from the total thyroidectomy and chest wall lesion excision were obtained and a total RNA was extracted. MiRNA expression was measured by real-time reverse transcriptase-polymerase chain reaction (RT-PCR) according to a previous study protocol [20] and the results showed no overexpression of four miRNAs (miR-146b, miR-221, miR-187 and miR-30d). NRAS mutation analysis by sequencing was also performed on both specimens and no NRAS mutation was identified. Immunohistochemical staining for PTEN protein was performed on histological sections of both specimens and no loss of PTEN protein was found.

In summary, morphologic findings and molecular study results support the benign nature of both thyroid and chest wall lesions.

Discussion

Parasitic thyroid nodule is a nodule of non-neoplastic thyroid tissue separated from the main thyroid glands and usually shows nodular hyperplasia. These nodules develop either by hyperplasia of ectopic thyroid tissue or by separation of a portion of thyroid tissue from the main gland. Separation of a portion of thyroid tissue can be caused by a mechanical action of neck muscles, surgery or trauma. Ectopic thyroid tissue is caused by a failure of migration of the thyroid during the embryonic period and can be present anywhere in the body. This has been reported in the head and neck including the anterior tongue, submandibular region, larynx, trachea, parotid gland, and posterolateral neck. It has also been reported in the chest including esophagus, mediastinum, pericardium, lateral wall of heart, lungs, axilla, and in the abdomen including liver, gallbladder, pancreas, duodenum and adrenal gland [21-32]. Parasitic thyroid nodule developed from ectopic thyroid tissue is more common in females than in males and can be encountered in any age group. Most cases of so called “benign metastasizing goiter” reported in earlier literatures actually showed thyroid cancer in the main thyroid glands [33-36]. Later, benign ectopic thyroid tissues were demonstrated by different reports which concluded that not all ectopic thyroid tissues are metastatic thyroid cancers [36]. Ectopic thyroid tissues or parasitic thyroid nodules may present as a functional gland with thyroglobulin production, and they usually show a similar histological appearance to that of the main thyroid gland. This includes nodular hyperplasia and inflammatory changes. Follicular adenoma and carcinoma have been found in the ectopic tissues as well [37-41].

As with abnormally located thyroid tissues, the main differential diagnosis of parasitic nodule is metastatic thyroid carcinoma. Clinically and radiologically, parasitic thyroid nodules are often mistaken as metastatic thyroid carcinoma. Morphologic criteria favoring a diagnosis of parasitic thyroid nodule include an absence of cytologic and architectural features of thyroid carcinoma, absence of lymphoid tissue, lack of primary thyroid carcinoma in the main thyroid gland, and similar morphology between parasitic thyroid nodules and the main thyroid gland (nodular hyperplasia, chronic lymphocytic thyroiditis, etc).

We believe this is the first report demonstrating that parasitic thyroid nodule can occur in the chest with extension into the chest wall and bones. In our study, the benign nature of parasitic thyroid nodule was not only supported by histologic morphology, but also supported by molecular studies including miRNA analysis and mutation analysis. Therefore, molecular studies may serve as ancillary studies to confirm a diagnosis of parasitic thyroid nodule which can cause a serious dilemma when diagnosing metastatic thyroid carcinoma and has important therapeutic and prognostic implications.

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Disclosure of conflict of interest

None.
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Authors’ contribution

ZL and RS designed the study and drafted the manuscript. HH, WL, SL and AC carried out the molecular genetic studies. All authors read and approved the final manuscript.

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