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A case report of spindle cell variant of medullary thyroid carcinoma in Hashimoto's thyroiditis

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Abstract

Background: Hashimoto's thyroiditis is a common autoimmune thyroid disease and often coexists with differentiated thyroid carcinomas, but the link between medullary thyroid carcinoma and Hashimoto's thyroiditis is not established, so the cases of these diseases occurring simultaneously are rare in the literature. Here we report a case of spindle cell variant of the medullary thyroid carcinoma in underlying Hashimoto's thyroiditis.

Case presentation: A 65-year old female was followed up in our Center because of hypothyroidism due to thyroid autoimmune disease. On neck ultrasound, an 11 X 7 X 9 mm hypoechoic nodule in the left thyroid lobe was found, and cytology was suggestive for spindle cell variant of medullary thyroid carcinoma. Calcitonin serum level was measured, and found elevated. After total thyroidectomy, pathology was compatible with spindle cell medullary thyroid carcinoma and Hashimoto's thyroiditis.

Conclusion: Medullary thyroid carcinoma in Hashimoto's thyroiditis is rare, but must not be taken out of consideration when thinking about routine ultrasound check-ups in patients with non-nodular autoimmune thyroid disorder.

Keywords: Medullary thyroid carcinoma; Hashimoto's thyroiditis; Thyroid neoplasm; Neck ultrasound.

Abbreviations: MTC: medullary thyroid carcinoma; CT: calcitonin; HT: Hashimoto's thyroiditis; FNAC: fine-needle aspiration cytology; CEA: carcinoembryonic antigen; NSE: neuron-specific enolase; PTC: papillary thyroid carcinoma; CCH: C-cell hyperplasia.

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Introduction

Medullary thyroid carcinoma (MTC) is a neuroendocrine tumor of parafollicular C-cells of the thyroid, which accounts for 5-10 % of all thyroid malignancies and is characterized by production of calcitonin (CT) [1]. It can be sporadic or inherited as a form of multiple endocrine neoplasia 2A or 2B syndrome or familial MTC. In 80 % of all cases, MTC develops sporadically and most of the patients have distant metastases upon diagnosis, so the prognosis depends highly on early detection of the disease [2].

On the other hand, Hashimoto's thyroiditis (HT) is a common autoimmune thyroid disease in which the gland is gradually destroyed by cell and antibody mediated immune processes, and is the leading cause of hypothyroidism in the world [3]. It is reported that HT often coexists with differentiated thyroid carcinomas [4], but cases of concurrent HT and MTC are rare in the literature [5-8]. In patients with thyroid nodules, with or without underlying HT, fine-needle aspiration cytology (FNAC) is used as an initial investigation for determining patients for nodule excision [9]. We present here an interesting case of MTC variant in HT diagnosed by cytology, serum CT level and pathology.

Case presentation

A 65-year old non-smoker Caucasian female patient with known arterial hypertension, diabetes type 2 on metformin therapy and oral carcinoma in remission has been followed up in our Center. There were no known cases of medullary thyroid carcinoma or multiple endocrine neoplasia in family history. On initial admission 18 years ago, she was diagnosed with HT and hypothyroidism and put on levothyroxine 75 µg/day. The first thyroid ultrasonography revealed normal sized gland with typical parenchyma findings for HT and no nodules present. After 18 years of follow up, a repeated ultrasonography found an 11 X 7 X 9 mm hypoechoic nodule in the left thyroid lobe, which was not palpable on neck examination. The nodule showed no ultrasonographic signs of intranodal calcification or hypervascularisation. There were no abnormal lymph nodes detected on the neck. FNAC of the left lobe nodule was performed using 23G needle, cytological smears were processed appropriately and stained by May Grünwald Giemsa technique. Thyroid aspirate showed destabilized clumps, traps and individual spindle cells with coarse chromatin structure and some intranuclear inclusions, few triangular cells with eccentrically placed nuclei and a discrete amphophilic cytoplasm, and some colloid. After the cytological suspicion of spindle cell variant of MTC, serum CT, carcinoembryonic antigen (CEA) and neuron-specific enolase (NSE) were measured. The upper limit for CT was 19 pg/mL, and the serum CT level measured in the patient was 165.4 pg/mL (ELCIA, Roche Diagnostics Ltd., Mannheim, Germany). Both CEA and NSE were within normal range. The preoperative chest X-ray and abdominal ultrasound were nonpathological, with no signs of adrenal hyperplasia. Calcium, phosphate and parathyroid hormone levels were also normal, ruling out multiple endocrine neoplasia type 2. The patient consequently underwent total thyroidectomy with pre- and paratracheal neck dissection in our Department for Otorinolargiology and Surgery of the Head and Neck. The pathology was compatible with 10 mm spindle cell MTC and HT (Figure 1A) corresponding to Stage I MTC (T1aN0M0). Cancer cell were spindle-like formed with round to oval small nuclei with coarsely clumped chromatin (Figure 1B). The pathological diagnosis of HT was made based on islets of epithelial eosinophilic cells and extensive lymphocytic infiltrate with germinal center formation around the tumor (Figure 1D). Immunohistochemical staining of the tumor tissue was positive for CT (Figure 1C), CEA, NSE, TTF-1, cytokeratin7, cytokeratin18 and cytokeratin19. One month after the surgery her CT serum level was undetectable (< 0.50 pg/mL). In the follow up of two years, the patient is still in remission.

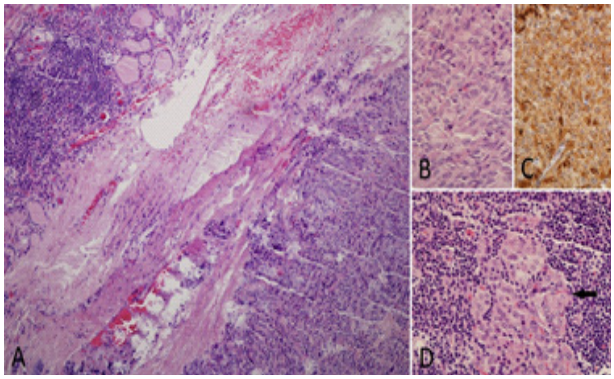

Figure 1: Spindle cell variant of medullary thyroid carcinoma in Hashimoto's thyroiditis. (A) The spindle cell variant of the medullary thyroid carcinoma is shown in the bottom right corner and lymphocytic infiltration in Hashimoto's thyroiditis in upper left corner (staining: hematoxylin and eosin, magnification: x100). (B) Carcinoma cells (staining: hematoxylin and eosin, magnification: x400). (C) Positive immunohistochemistry for calcitonin in carcinoma cells (magnification: x400). (D) Islets of epithelial eosinophilic cells (arrow) and extensive lymphocytic infiltrate in Hashimoto's thyroiditis (staining: hematoxylin and eosin, magnification: x400).

Discussion and conclusion

The link between chronic inflammatory disease and cancer development has been established many years before [10]. In the case of HT, it is hypothesized that papillary thyroid carcinoma (PTC) and HT share the same platform of molecular pathogenesis, as HT sometimes exhibits RET/PTC rearrangements, and thyroid cells expressing both RET/PTC and BRAF mutation may induce genes encoding molecules involved in the immune response [11]. An association between C-cell hyperplasia (CCH) and HT has also been described in the literature [12]. The pathophysiological link may involve an immunopathological mechanism, or an effect of cytokines, inflammatory mediators secreted or a C-cell growth factor [12]. However, a distinguishment between physiologic or neoplastic HT-associated CCH has not been made.

In MTC, early diagnosis and management clearly improve the prognosis. Schuetz et al. reported an overall prevalence of MTC and CCH in HT patients of 0.35 %, which was even lower than in patients with nodular disease [13]. Another study suggested that the autoimmune inflammatory process retards the growth and dissemination of thyroid carcinoma [4], which would be a favorable outcome for the patients. Regarding CT levels, serum CT can be elevated in patients with HT, but some studies determined CT cut off point for the diagnosis of MTC as > 60 pg/mL [14]. Cytological smears of MTC usually contain plasmacytoid, epitheloid, small, spindle or mixed cells, with

cytoplasmic granularity staining bright red with MGG, "neuroendocrine" nuclear appearance with granular chromatin [9], as seen here. Pure spindle cell MTC is rare, and can resemble spindle cell melanoma, fibroblastic tumor, low-grade soft tissue tumors or anaplastic carcinoma [9], which must be taken in account in differential diagnosis and can be resolved with serum CT measurement. In a study by Bugalho et al., it was found that serum CT measurement was superior to FNAC in MTC diagnosis [15]. In doubt, CT in FNAC washout fluid or immunocytochemistry for CT can be performed, which was also successfully done before in out institute, but in this case was unnecessary.

The diagnostic value of CT screening in non-nodular HT can be discussed, as prognosis of MTC is mainly related to the stage of the disease. Meta-analysis of Trimboli et al. demonstrates that FNAC is able to detect only approximately one-half of histologically proven MTC lesions [16], but the diagnostic value of routine serum CT measurement in patients with HT is debatable in the literature [13], especially in patients with mildly elevated serum CT, when the result does not succeed in distinguishing between CCH and MTC.

Considering the economic side of CT screening in patients with HT given its frequency, a routine ultrasound check-up in patients with non-nodular autoimmune thyroid disease must not be taken out of consideration.

Declarations

Ethics approval and consent to participate: The patient described in this Case report has given his/her consent for using his/her data to write this Case report.

Consent for publication: Written consent to publish this information was obtained from the patient described in this Case report.

Conflict of interest: The authors declare no conflict of interest.

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