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Case Report

A rare coexistence of parathyroid adenoma and medullary and papillary thyroid carcinoma

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Abstract: The combination of parathyroid adenoma, medullary thyroid carcinoma (MTC), and papillary thyroid carcinoma (PTC) has been reported occasionally, but it has now been recognized more often through effective evaluations. However, the etiology and risk factors remain unclear, so we discuss them in this article. Here, we report the case of a 64-year-old woman with parathyroid adenoma, MTC, and PTC diagnosed incidentally. This woman was admitted to the Xingtai People's Hospital affiliated to Hebei Medical University for an apparently aggravating symptom of hypodynamia. Her past medical history included diabetes and a left nephrolith. Upon admission, her bloodwork showed hypercalcemia, hypophosphatemia, and elevated serum parathyroid hormone. Subsequently, the sonographic findings revealed dominant nodules in both the right and left lobes with a left inferior suspected parathyroid adenoma. The patient underwent fine needle aspiration (FNA) of the bilateral thyroid lobes, the results of which were both thyroid carcinoma. Therefore, a thyroidectomy, a neck dissection, and the excision of a suspected parathyroid adenoma were performed. A histological examination revealed a combination of parathyroid adenoma, MTC, and PTC. Her serum calcium and parathyroid hormone levels returned to the normal range after the surgery. Our case highlighted the fact that even though the concurrent existence of parathyroid adenoma, MTC, and PTC is rare, the diagnosis of this coexistence should be considered in primary hyperparathyroidism (PHPT). To avoid repeat surgeries, patients with coexisting diseases should be screened cautiously. Therefore, we recommend a preoperative check of the calcium levels in patients with thyroid cancer and a preoperative thyroid check in all patients with PHPT.

Keywords: Parathyroid adenoma, primary hyperparathyroidism, medullary thyroid carcinoma, papillary thyroid carcinoma

Introduction

Primary hyperparathyroidism (PHPT) is present in up to 0.04-0.1% of the general population [1, 2], and parathyroid adenoma occurs in 75-85% of PHPT patients. Although the pathological relationship between parathyroid and thyroid diseases is common, the combination of parathyroid adenoma and thyroid cancer is rare, and there have been only sporadic reports of the combination of parathyroid adenoma and non-medullary thyroid carcinomas (NMTC) so far. The coexistence of parathyroid adenoma, PTC, and MTC is extremely rare. In spite of this, the diagnoses of these concurrent diseases also should be considered cautiously by clinicians because the coexistence of all these diseases can complicate patient management. We present here a case of a woman with coexisting parathyroid adenoma, MTC, and PTC, proven surgically and pathologically, so as to improve the quality of the management of this rare coexistence.

Case report

A 64-year-old woman presenting with hypodynamia and with an apparently aggravating manifestation for two weeks was admitted to our hospital for a work-up. The patient had a 20-year history of hypertension that was under control with extended release nifedipine, and a one-year history of diabetes mellitus. Her past medical history revealed a previously-diagnosed left nephrolith with abdominal pain through ultrasound ten months ago in another hospital. So, the patient received conservative treatment with pharmacotherapy only and experienced a remission of her symptoms. In the laboratory work done at our hospital, she

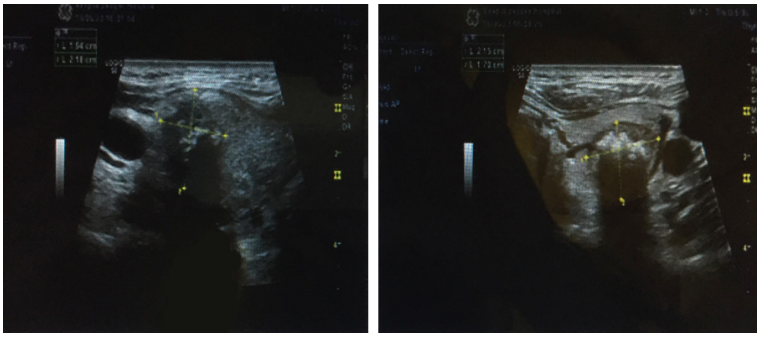

Figure 1. Ultrasound showed the dominant nodules in the bilateral right and left thyroid lobes: the diameter of the largest nodule was 1 cm in left lobe and 2 cm in right lobe.

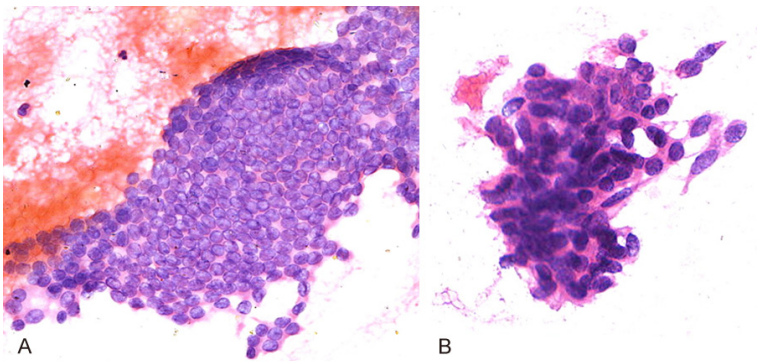

Figure 2. A. FIN of papillary thyroid carcinoma (magnification ×200). B. FIN of medullary carcinoma (magnification ×200).

had elevated serum calcium (2.95 mmol/l; normal range: 2.2-2.7 mmol/l), low serum phosphate (0.80 mmol/l; normal range: 1.0-1.6 mmol/l), and elevated parathyroid hormone (PTH: 573.0 pg/ml; normal range: 6-80 g/ml), indicating hypercalcemia, hypophosphatemia, and PHPT. The patient also was found to have osteoporosis through a measurement of her bone mineral density, and the T-score of the lumbar spines was minus 1.6. On a neck evaluation, the ultrasound showed dominant nodules in both the right and left thyroid lobes, and a nodule behind the lower pole of the left thyroid lobe was suspected to be parathyroid adenoma. The diameters of the largest nodules were 1 cm in the left lobe and 2 cm in the right lobe (**Figure 1**). Subsequently, the patient underwent FNA of the bilateral thyroid lobes, and the result of the right lobe was PTC (**Figure 2A**), and the result of the left lobe was suspected MTC (**Figure 2B**). Afterwards, the patient underwent a total thyroidectomy and an excision of the enlarged left inferior parathyroid. Her other parathyroid glands were normal and were saved. Meanwhile, all the excisional fresh specimens were sent to the pathology department for a rapid intraoperative diagnosis and a postoperative H&E staining diagnosis.

On gross inspection, the largest nodule of right thyroid lobe was 1.2 × 1 × 1 cm in diameter and appeared ill-defined and tan-white in color on a cut section. On microscopic examination, the intraoperative frozen section and postoperative H&E staining both confirmed it to be classical PTC (**Figure 3A**), and the immunohistochemical work also found that the PTC cells were positive for BRAF V600E (**Figure 3B**). The lesion was surrounded by a fibrous capsule, without any evidence of blood vessel or extra-thyroid extensions. The macroscopic character of the largest nodule of the left thyroid lobe was 2 × 1.5 × 1 cm in diameter and appeared well-defined and tan-yellow in color on a cut section. Calcification was also detected in this nodule. On microscopic examination, the intraoperative frozen section was positive for medullary carcinoma, and the postoperative H&E staining revealed MTC which was not encapsulated (**Figure 3C**) but was accompanied by microcalcifications. There was no evidence of vascular invasion, extra-thyroid extensions, or C-cell hyperplasia. Immunohistochemically, the tumor cells were positive for calcitonin (**Figure 3D**), chromogranin A (CgA) (**Figure 3E**), carcinoembryonic antigen (CEA), S100 and thyroid transcription factor-1 (TTF-1) (**Figure 3F**). Meanwhile, a frozen section of the left inferior parathyroid gland which measured 6 × 4 × 1.5 cm showed parathyroid adenoma, and the permanent pathology documented this as well (**Figure 3G**). Immunohistochemistry showed the tumor cells were positive for PTH (**Figure 3H**). So, the cervical lymph node specimens, including the prelaryngeal ones and the region VI ones of the bilateral neck, were sent to the pathology

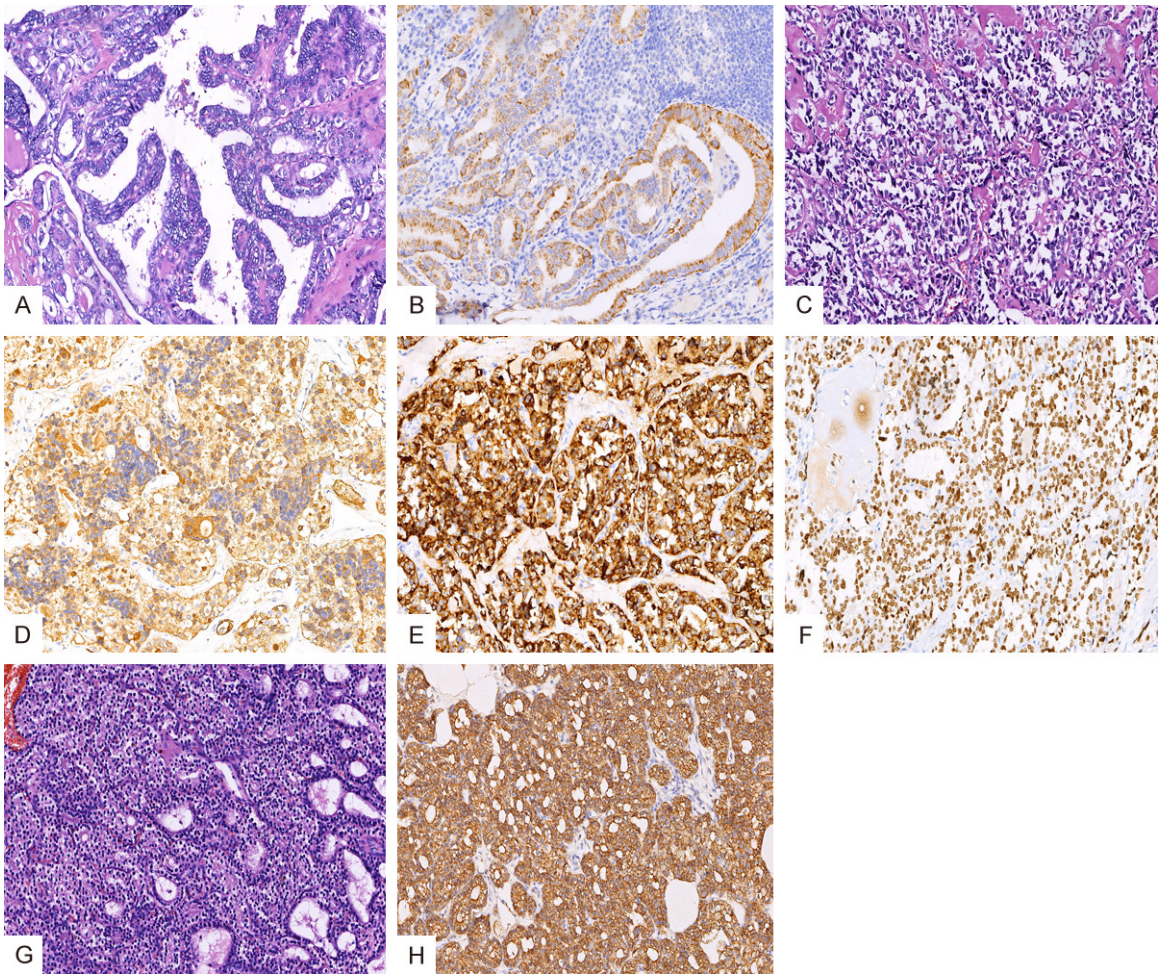

Figure 3. A. H&E of the papillary thyroid carcinoma (magnification ×200). B. Immunohistochemistry with anti-BRAF V600E (magnification ×200). C. H&E of medullary carcinoma (magnification ×200). D. Immunohistochemistry with anti-calcitonin (magnification ×200). E. Immunohistochemistry with CgA (magnification ×200). F. Immunohistochemistry with anti-TTF1 (magnification ×200). G. H&E of parathyroid adenoma (magnification ×200). H. Immunohistochemistry with anti-PTH (magnification ×200).

department for a postoperative H&E staining diagnosis, but the results showed that none of lymph nodes were involved by the tumor.

The patient recovered well after the operation. Her calcium, phosphorus, and parathyroid hormone levels returned to normal rapidly after the surgical intervention. This patient has been followed-up regularly and has remained asymptomatic for two and a half years subsequent to the surgery. Her serum thyroxin and calcium levels have remained normal.

Discussion

The coexistence of thyroid carcinoma and PHPT have been reported and have gained recognition by more and more clinicians. Parathyroid adenoma occurs in 75-85% of PHPT patients, and coexistent MTC and PHPT is the most common combination in view of the fact that both cell types originate from parafollicular cells. In contrast, concomitant non-medullary thyroid cancer and PHPT is very rare (2-18%), with only a few interrelated case reports [1, 3-6], and the distinct embryologic origin of parathyroid cells and thyroid follicular cells is a feasible reason [7]. Therefore, concomitant parathyroid adenoma, MTC, and PTC is fairly uncommon, with only a few cases reported.

The overall incidence of PHPT coexisting with thyroid carcinoma is uncertain because only a few studies have addressed this question, and the results showed different frequencies. In addition, the reasons for the coexistence of

PHPT and thyroid carcinoma are controversial. Some researchers have shown their coexistence as coincidental [8]. Some researchers have suggested that previous, low-dose head and neck radiation therapy is a risk factor for inducing the two diseases [9]. In addition, others have assumed that increased endogenous calcium levels or probable growth factors such as epithelial growth factors or insulin-like growth factors, such as goitrogenic factors, are the cause. So far, the exact pathogenesis has not been established [10], so further studies with larger sample sizes need to be conducted to confirm the mechanism.

The co-occurrence of thyroid carcinoma along with PHPT has gained recognition by more and more clinicians. In most of the case reports, the patients presented with or without symptomatic hyperparathyroidism preoperatively. Thyroid carcinoma was usually diagnosed incidentally through the intraoperative or postoperative pathology findings [11]. Also, another retrospective study found that thyroid carcinoma was also found in 2% to 6% of patients with PHPT through postoperative pathological examinations [12]. Because the simultaneous involvement of the bilateral glands and the clinical manifestations are complicated, the disease frequently goes unrecognized. In spite of the fact that concurrent thyroid cancer and parathyroid adenoma is rare, special care should be required for the diagnosis of this coexistence in order to prevent repeated surgeries.

The preoperative evaluation of patients with PHPT and concomitant thyroid cancers is important for determining the therapeutic strategy and the therapeutic schedule. Ultrasonography (US), fine needle aspiration (FNA), and 99mTc-MIBI scans are the recommended diagnostic tools for PHPT and concomitant thyroid cancers. It has been reported that ultrasound has the high positive predictive sensitivity of 83.5% in the diagnosis of parathyroid adenoma [13], and Tc99 scanning helped us confirm the final diagnosis of parathyroid adenoma and examine the ectopic glands in the preoperative assessment. Moreover, US can improve the localization of the thyroid nodules, and an accurate diagnosis of the thyroid nodules is performed by combining FNA with a sensitivity of 89%, a specificity of 91%, and an accuracy of 90% [14]. It is especially important to pay attention to the solitary thyroid nodule found using US. Therefore, the combination of 99mTc-MIBI, US, and US-FNA (if needed) are recommended as the best diagnostic tools for the parathyroid localization of PHPT and concomitant thyroid cancers. It is worth noting that the concurrence of PTC and PHPT may culminate in a discrepancy between the clinical features and the FNA cytology that may result in a false-positive diagnosis [15]. So, the operation was recommended to cure thyroid and parathyroid diseases. Also, the histopathology of the resected specimen remains the gold standard for diagnosing these rare, co-occurring diseases. The resected specimen must always be subjected to the rapid intra and postoperative hematoxylin and eosin staining to confirm the final diagnosis.

To date, this case demonstrates the need for clinical alertness to comorbidities and the importance of a preoperative diagnosis of the diseases described here. Therefore, we recommend a preoperative serum calcium level check in all patients with thyroid cancer and a preoperative thyroid check using the recommended diagnostic tools in all patients with PHPT. These checks can be easily performed using the serum calcium measurement. In addition, it is recommended to remove any relevant thyroid nodules during the parathyroid surgery.

Disclosure of conflict of interest

None.

Abbreviations

MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma; FNA, fine needle aspiration; PHPT, primary hyperparathyroidism; NMTC, non-medullary thyroid carcinomas; PTH, parathyroid hormone; CgA, chromogranin A; CEA, carcinoembryonic antigen; TTF-1, thyroid transcription factor-1; US, ultrasonography.

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References

[1] Arciero CA, Shiue ZS, Gates JD, Peoples GE, Dackiw AP, Tufano RP, Libutti SK, Zeiger MA and Stojadinovic A. Preoperative thyroid ultrasound is indicated in patients undergoing

parathyroidectomy for primary hyperparathyroidism. J Cancer 2012; 3: 1-6.
[2] Bilezikian JP and Silverberg SJ. Clinical practice. Asymptomatic primary hyperparathyroidism. N Engl J Med 2004; 350: 1746-1751.
[3] Montenegro FLM, Smith RB, Castro IV, Tavares MR, Cordeiro AC and Ferraz AR. Association of papillary thyroid carcinoma and hyperparathyroidism. Rev Col Bras Cir 2005; 32: 115-119.
[4] Wilson SD, Doffek KM, Wang TS, Krzywda EA, Evans DB and Yen TW. Primary hyperparathyroidism with a history of head and neck irradiation: the consequences of associated thyroid tumors. Surgery 2011; 150: 869-877.
[5] Onkendi EO, Richards ML, Thompson GB, Farley DR, Peller PJ and Grant CS. Thyroid cancer detection with dual-isotope parathyroid scintigraphy in primary hyperparathyroidism. Ann Surg Oncol 2012; 19: 1446-1452.
[6] Lehwald N, Cupisti K, Krausch M, Ahrazoglu M, Raffel A and Knoefel WT. Coincidence of primary hyperparathyroidism and nonmedullary thyroid carcinoma. Horm Metab Res 2013; 45: 660-663.
[7] Sabetkish N and Tavangar SM. An unusual combination of parathyroid adenoma, medullary and papillary thyroid carcinoma. Acta Medica Iranica 2013; 51: 337-340.
[8] Xiao H, Yu B, Wang S and Chen G. Concomitant Graves' disease and primary hyperparathyroidism: the first case report in mainland of China and literature review. Chin Med J (Engl) 2002; 115: 939-941.
[9] Stephen AE, Chen KT, Milas M and Siperstein AE. The coming of age of radiation-induced hyperparathyroidism: evolving patterns of thyroid and parathyroid disease after head and neck irradiation. Surgery 2004; 136: 1143-1153.
[10] McCarty MF. Parathyroid hormone may be a cancer promoter-an explanation for the decrease in cancer risk associated with ultraviolet light, calcium, and vitamin D. Med Hypotheses 2000; 54: 475-482.
[11] He Y, Liu S, Guo H and Shi B. Incidental finding of papillary thyroid carcinoma with BRAFV600E mutation in a patient with coexistent primary hyperparathyroidism and Graves' hyperthyroidism. BMJ Case Rep 2014; 2014: bcr2013-203436.
[12] Erba L, Baldari S, Borsato N, Bruno G, Calò-Gabrieli G, Carletto M, Ciampolillo A, Dondi M, Erba P, Gerundini P, Lastoria S, Marinelli P, Santoro M, Scarano B, Zagni P, Bagnasco M and Mariani G. Retrospective analysis of the association of nodular goiter with primary and secondary hyperparathyroidism. Eur J Endocrinol 2001; 145: 429-434.
[13] Nasiri S, Soroush A, Hashemi AP, Hedayat A, Donboli K and Mehrkhani F. Parathyroid adenoma localization. Med J Islam Repub Iran 2012; 26: 103-109.
[14] Koike E, Yamashita H, Noguchi S, Murakami T, Ohshima A, Maruta J, Kawamoto H and Yamashita H. Effect of combining ultrasonography and ultrasound-guided fine-needle aspiration biopsy findings for the diagnosis of thyroid nodules. Eur J Surg 2001; 167: 656-661.
[15] Beecham JE. Coexistent disease as a complicating factor in the fine needle aspiration diagnosis of papillary carcinoma of the thyroid. Acta Cytol 1986; 30: 435-438.