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Case Report

Simultaneous medullary thyroid carcinoma and pheochromocytoma: a case report of MEN2A

Lei Zhao, Cheng Yang, Chao-Zhao Liang

Department of Urology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China

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Abstract: Multiple endocrine neoplasia type 2A (MEN2A) is a rare autosomal dominant inherited disease characterized by medullary thyroid carcinoma (MTC) and pheochromocytoma (PHEO). Simultaneous development of MTC and PHEO is very rare. Here we report a new case of 19-year-old male. Asynchronous surgical resection of right adrenal PHEO and MTC was successfully performed. MTC had been metastasis to the cervical lymph nodes. Therefore, early detection and timely intervention is pivotal to cure the disease.

Keywords: Multiple endocrine neoplasia type 2, Pheochromocytoma, medullary thyroid carcinoma, RET proto-oncogene

Introduction

Multiple endocrine neoplasia type 2 (MEN2) is a rare autosomal dominant inherited disease characterized by medullary thyroid carcinoma (MTC) and pheochromocytoma (PHEO) [1, 2]. MEN2A is the most common subtype of MEN2 (55% of all cases) [3]. Here, we report a case of nineteen years old man diagnosed MEN2A presenting with simultaneous MTC and PHEO. Furthermore, we review literature to discuss the updated knowledge in diagnosis and treatment of MEN2A.

Case presentation

A nineteen years old male who had suffered severe headache with nausea, vomiting, chest tightness for one year. Meanwhile, he presented intermittent palpitations, dizziness and sweating. Then, He was referred to our hospital in February of 2015. Physical examination revealed a 1.5 cm nodule at right lateral lobe of thyroid without palpable lymph nodes in the neck. No positive signs were found in other examinations. A history of MTC or PHEO or other hereditary familial disease is absent for this patient. Blood pressure monitoring revealed that the patient had severe hypertension, with systolic blood pressure of 180-250 mmHg and diastolic blood pressure of 95-110 mmHg. Ultrasonography showed a hypoechogenic mass with diameter of 1.3 cm×1.1 cm on right lobe of thyroid. Meanwhile, a giant hypervascular adrenal tumor between liver and right kidney was detected. Abdominal contrast-enhanced computed tomography (CT) showed a heterogeneously enhanced mass on the right side of adrenal gland with size of 7.0 cm×6.2 cm. No enhancement in part of the tumor with low density was identified. The left adrenal gland was normal. The diagnosis of CT was right adrenal PHEO (**Figure 1**). No positive finding was revealed from chest X-ray and electrocardiograph exams. Blood cell count, biochemical examination, urinalysis, stool routine, blood coagulation function test and serum calcium concentration were within normal range. Serum calcitonin level was apparently elevated with 327 pmol/l (normal range for male <18.2 pmol/l). 24 h urinary catecholamine was 1208 nmol/24 h (normal range <229.5 nmol/24 h). 24 h urinary vanillylmandelic acid (VMA) was weakly positive. Serum carcinoembryonic antigen (CEA) was also elevated with 12.58 ng/ml (normal range <5 ng/ml). Blood cortisol and aldosterone tests were normal. Thyroid function tests as well as serum parathyroid hormone were with normal range.

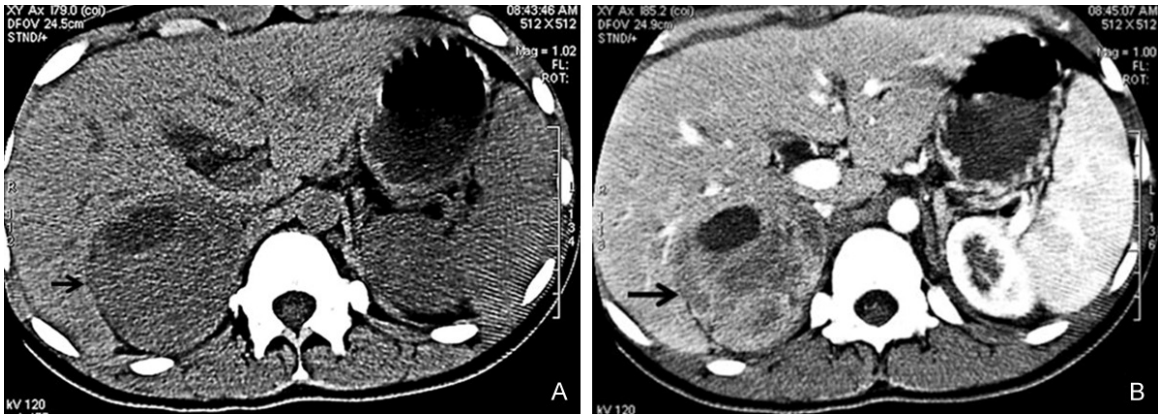

Figure 1. Computed tomography (CT) images of right adrenal mass. A: Unenhanced axial CT images shows a uneven mass (black arrow) about 8.5 cm×6.5 cm×6.5 cm with intact capsule located at the right adrenal gland. B: Enhanced axial CT images shows a round-like mass (black arrow) with cystic parts in addition to enhancing solid parts located at the right adrenal gland, consistent with adrenal pheochromocytoma.

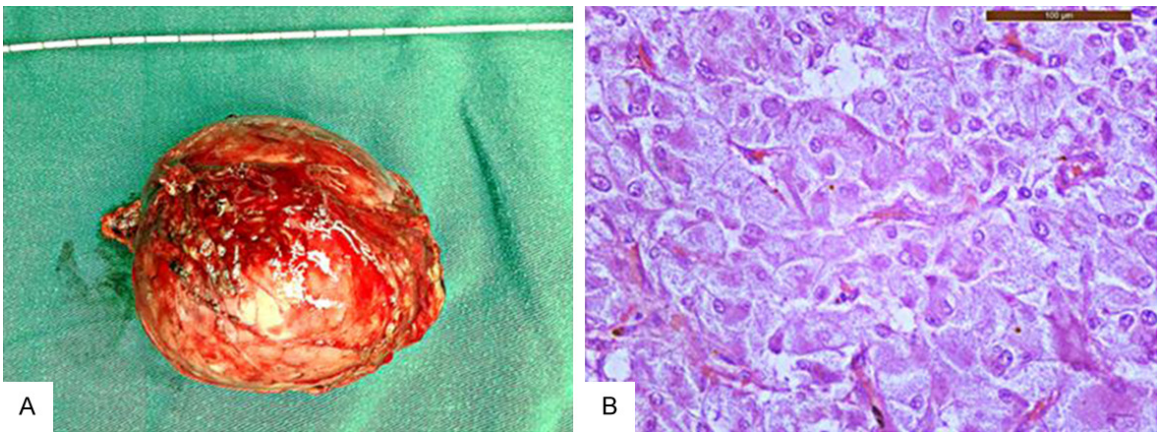

Figure 2. The adrenal specimen and its pathological image. A: The size of resected adrenal pheochromocytoma specimen is about 8.5 cm×6.5 cm. B: Pathological diagnosis of the right adrenal mass is pheochromocytoma (hematoxylin and eosin, 400× power).

According preoperative examination, right adrenal PHEO and thyroid tumor was first considered. Regarding that two endocrine gland tumors occurred simultaneously in one patient with young age, the diagnosis was consistent with MEN2. The patient didn't have mucosal neuromas of tongue, bumpy lips and Marfanoid body habitus, which are features of MEN2B. Due to absent of RET gene mutation detection, the diagnosis of MEN2A is considered. Hypertension was controlled by oral administration of prazosin before surgery. Preoperative fluid infusion was used to expand Blood volume about two weeks. In order to prevent the occurrence of hypertensive crisis, right adrenal pheochromocytoma was resected firstly. Subsequently, transperitoneal open adrenalectomy was successfully accomplished. Frequent blood pressure fluctuation was observed during the operation. The blood loss was minimal and blood transfusion not required. The resected specimen was yellowish and well-defined consistent with CT. The patient was uneventful and no complications occurred after operation. Postoperative pathological report was right adrenal pheochromocytoma (**Figure 2**). The patient's blood pressure returned to normal after operation.

One month later, the patient was readmitted to general surgery ward of our hospital. Intraoperative frozen sections revealed that cancer focuses in bilateral thyroids were verified, therefore total thyroidectomy was performed. Simultaneously central cervical lymph nodes

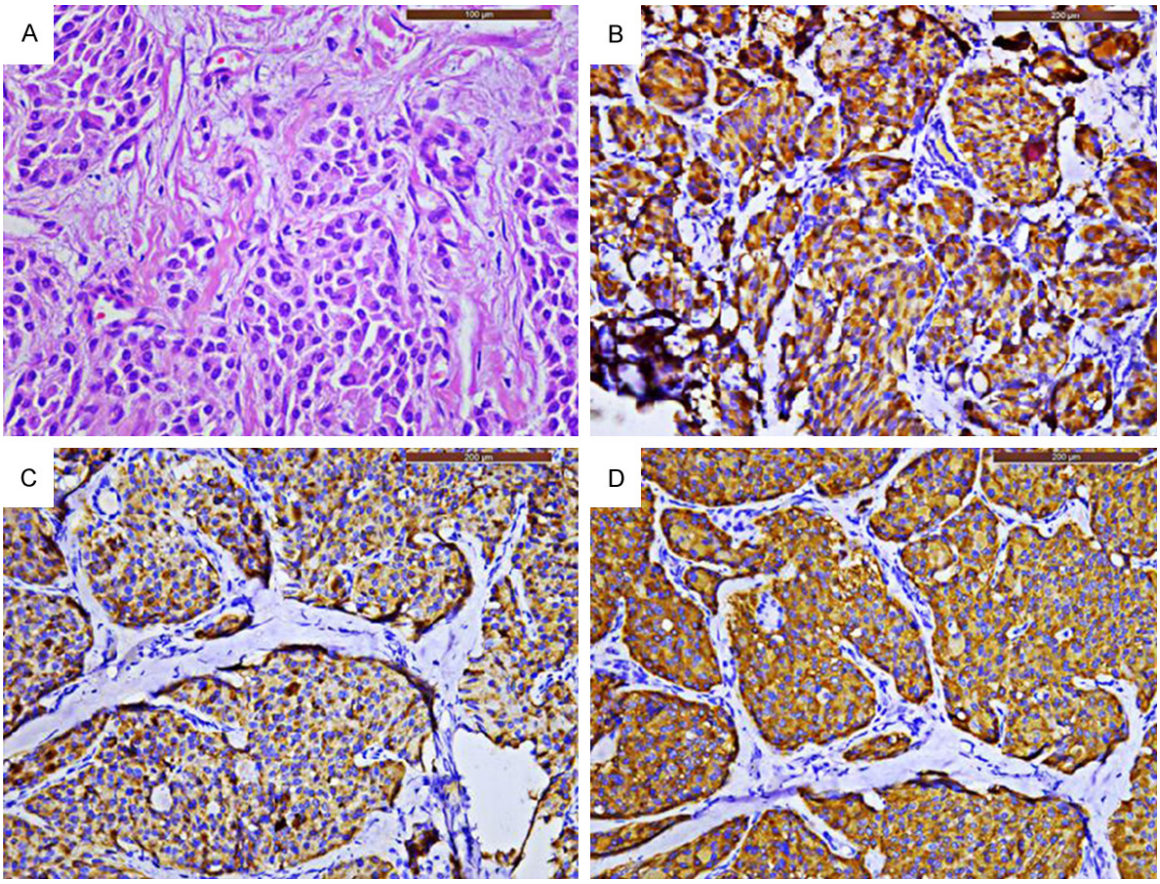

Figure 3. Pathological Images of the thyroid lesion. A: Pathological diagnosis of the thyroid nodule is Medullary thyroid carcinoma (hematoxylin and eosin. 400× power). B: Calcitonin is positive in MTC (400× power). C: Chromogranin is positive in MTC (400× power). D: Synaptophysin is positive in MTC (400× power).

dissection was done. Intraoperative exploration found that the parathyroid glands were normal and preserved. Serum calcium and parathyroid hormone levels were normal postoperatively. The patient received thyroid hormone replacement therapy postoperative and recovered well with no complications. Postoperative pathological report revealed bilateral MTC with metastasis of cervical lymph nodes. Immunohistochemistry results were as follows (**Figure 3**): calcitonin(+), synaptophysin(+), chromogranin(+), CyclinD1(+), PTH(-), TG(-).

The patient was followed up every 3 months postoperatively. Eight months later, the level of serum calcitonin and CEA was normal. No evidence of tumor recurrence was detected by imaging examinations.

Discussion

MEN2A is an autosomal dominantly inherited disease which is a subtype of MEN2. In addition, MEN2 also included MEN2B and familial medullary thyroid carcinoma (FMTC) [1, 2]. The prevalence rate of MEN2 is 1/35000 [1]. MEN2A is characterized by developing MTC, PHEO and primary hyperparathyroidism (PHPT), represents of 70-100%, 50% and 20-30% in MEN2A patients, respectively [2]. Simultaneous development of MTC and PHEO in a patient is very rare. The main disease to be distinguished from MEN2A is MEN2B. In addition to the occurrence of MTC and PHEO, there are other special features for MEN2B, such as multiple mucosal neuromas in the tongue, lips or eyelids, intestinal ganglioneuromatosis, a marfanoid habitus, medullated corneal nerve fibers and musculoskeletal abnormalities [2]. Unlike MEN2A, PHPT does not occur in patients with MEN2B [4]. Patients with MEN2B indicate earlier onset and more aggressive type of MTC [4]. Most patients with MEN2B develop metastatic MTC in childhood or adolescence [5]. Our patient didn't have the characteristic features of MEN2B.

The pathogenesis of MEN2 is the mutations of the RET proto-oncogene. RET gene is located on chromosome 10q11.2 [4]. Mutations of the RET proto-oncogene lead to autophosphorylation of the tyrosine kinase domain and activation of downstream signaling pathways. MEN2 have a strong genotype-phenotype correlation [6, 7]. The American Thyroid Association (ATA) guidelines categorized the RET mutations into four levels of risk [6]. About 98% patients with MEN2A reveal a germline RET mutation in exon 10 or 11 [1]. Mutations at codon 634 is the most frequently found in MEN2A patients [1]. The specific RET mutation correlates with the age of onset and aggressiveness of MTC [8]. Patients with codon 918 mutation and MEN2B are at high risk of aggressive MTC occurring at a young age [8]. Therefore, genotype-phenotype correlation has important clinical implications for its treatment. Unfortunately, due to absence of RET gene mutation test, we don't know exactly the type of mutation of the patient. 80% of MEN2A cases are caused by genetic inheritance, so there are a part of patients due to de novo mutations [9]. This is consistent with our patient, he hasn't family history.

MTC is usually the first manifestation of MEN2A between 20-30 years old [10]. Unlike sporadic MTC, MEN2A related MTC is often bilateral, multicentric and aggressive with possible metastasis to the cervical lymph nodes [1]. These were consistent with our patient. Thyroid and neck ultrasonography should be routinely performed. Serum calcitonin and CEA in patients with MTC is often elevated. Importantly, the patients with probable diagnosis of MEN2 should be offered germline RET mutation analysis if feasible. The most effective method for early stage MTC is to perform total thyroidectomy with central neck lymph nodes dissection [6]. Recently, lymph nodes dissection to both laterocervical compartments and the upper mediastinum had been suggested [11]. All patients should receive L-Thyroxine replacement therapy after operation. Prophylactic thyroidectomy was believed to be effective treatment for patients with RET mutation carriers [8]. Recommendations for the time point of prophylactic thyroidectomy are based on genotype-phenotype correlations [8]. Radiotherapy and chemotherapy have limited, transient activity in patients with unresectable or metastatic MTC [12]. Molecular therapeutics targeting RET pathway is a promising approach [1]. Vandetanib is a multiple tyrosine kinase inhibitor (multi-TKI) of RET, vascular endothelial growth factor receptor 2 (VEGFR-2), VEGF-3, epidermal growth factor receptor (EGFR). A large, multicenter, randomized controlled Phase III clinical trial reported that the patients treated with vandetanib had a significantly longer progression-free survival (PFS) (30.5 months) than placebo group (19.3 months) [13]. Cabozantinib is another multi-TKI of RET, VEGFR2 and c-MET. A trial compared cabozantinib with placebo in 330 patients with metastatic MTC. Cabozantinib achieved a statistically significant improvement of PFS, with 11.2 months for cabozantinib versus 4.0 months for placebo [14].

The presentations of MEN2A related PHEO are similar to sporadic counterparts, including diaphoresis, headache, palpitations, hypertension and tachycardia. PHEO frequently become evident about 10 years later after occurrence of MTC in MEN2A patients [8]. In contrast, adrenal PHEO is the first manifestation in 13-27% of MEN2A patients [15]. Young patients with PHEO should be evaluated for possible MTC. Levels of plasma normetanephrine and metanephrine have been shown to be more sensitive and specific for detecting PHEO [16]. CT, MRI and metaiodobenzylguanidine (MIBG) scintigraphy are frequently used to evaluate PHEO. Bilateral adrenal glands are frequently involved simultaneously or subsequently in PHEO patients with MEN2 [17]. Therefore, the patient detected after initial diagnosis should be managed long term follow-up. All patients with PHEO should be adequately prepared before surgery, including the application of alpha-receptor blockers to control blood pressure and expand the blood volume. If the contralateral adrenal gland is normal, unilateral total adrenalectomy can be performed. If bilateral adrenal glands are involved, adrenal cortical-sparing adrenalectomy should be performed to reduce the occurrence rate of postoperative adrenal insufficiency or steroid dependency [11]. For patients with MEN2A, PHEO should be removed before thyroidectomy, because an undetected PHEO could cause fatal hypertensive crisis intraoperatively. Laparoscopic surgery is a preferred technique and has the good cosmetic effect [18]. A study comparing robotic versus laparoscopic resection of PHEO show that the robotic approach is similar to the laparoscopic regarding

safety and efficacy. The lower morbidity, less postoperative pain and shorter hospital stay were observed in the robotic approach [19].

PHPT occurs in 20-30% of patients with MEN2A and can result from a single adenoma or hyperplasia of the parathyroid glands [2]. The patient present here didn't have PHPT. The clinical manifestations of MEN2A related PHPT are similar to sporadic cases, including: nephrolithiasis, osteopenia or osteoporosis, and so on [17]. The treatment for MEN2A patients with PHPT is to excise the enlarged glands and keep at least one apparently normal parathyroid gland. If normal parathyroid glands are inadvertently removed during thyroidectomy, they should be autografted into the forearm [1].

Because MTC is malignant, the prognosis of patients with MEN2A was closely related to the early detection and treatment of MTC. The case present had simultaneous development of MTC and PHEO. The patient had metastatic MTC and his prognosis need long time follow-up to evaluate. The surgery for MTC was delayed after adrenalectomy about one month. The safety and effectiveness of homochromous MTC and PHEO surgery needs to be further studied. Young patients with early onset of MTC or PHEO should be suggested RET gene mutation analysis to exclude MEN2.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Chao-Zhao Liang, Department of Urology, The First Affiliated Hospital of Anhui Medical University, Jixi Road No. 218, Hefei 230022, Anhui, China. Tel: 0086-551-629-23861; Fax: 0086-55162923861; E-mail: Liang_chaozhao@163.com

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