Case Report
Primary aldosteronism complicated by hyperparathyroidism: report of one case and literature review

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Abstract: Primary aldosteronism (PA) is a category of secondary hypertension induced by inhibition of the renin-angiotensin system due to increased aldosterone secretion. Aldosterone-producing adenoma (APA) is the most common hypotype of PA. Primary hyperparathyroidism (PHPT) refers to the symptoms of increased bone resorption and increased calcium reabsorption of kidney tubules caused by parathyroid secretion and excessive synthesis of parathyroid hormone. APA, complicated with PHPT has been extremely rare in clinical practice. In this study, the diagnosis and treatment of one case of APA complicated by PHPT was reported. Relevant literature review was performed.

Keywords: Primary aldosteronism, primary hyperparathyroidism, multiple endocrine neoplasia

Introduction

PA is a secondary hypertension caused by increased aldosterone secretion, and after excision of adenoma, hypokalemia can be treated effectively. Most PA patients may be cured after operation [1]. Those with a long course of disease and severe complications may get partial relief postoperatively, and the serum potassium can recover to normal. MEN refers to a rare neuroendocrine neoplasm in which three or more endocrine tumors (or hyperplasia) occur successively or simultaneously [2]. Based on different etiologies and tumor combinations, MEN can be classified into MEN-1 and MEN-2. The most common MEN1 is primary hyperparathyroidism, pancreatic endocrine tumor, and hypophysoma, and the incidence rate of adrenal adenoma is 5-45%. In this study, the entire process of the diagnosis and treatment of one female patient diagnosed with aldosterone-producing adenoma (APA) complicated by PHPT was reported. The patient was followed up for postoperative evaluation of clinical efficacy and safey, aiming to provide evidence for the diagnosis and management of such complicated conditions.

Case report

The female patient was diagnosed with secondary hypertension, AP, and left adrenal adenoma, PHPT [3], pituitary microadenoma, and apoplexy linger effect. Spirolactone at a dose of 60-100 mg and salmon calcitonin acetate was administered twice. In December 2014, she received excision of the left adrenal adenoma in the Urologic Surgery Department of our hospital. Postoperative pathologic findings showed that the cortical adenoma grew in the left adrenal gland, consistent with the findings of immunohistochemical staining. Stain results included: Ki-67 (3-5%+), CYP11B2(+), P53 (weak individually +), vimentin (few cells 1+), CK high (-), and CK low (-). Postoperatively, the level of potassium was normal, PTH = 448.9 pg/ml and Cr = 76 umol/L. After discharge, the serum level of potassium reverted to normal. In May 2015, she was admitted to our hospital due to dizziness and muscular soreness for 1 month at postoperative 5 months. The serum level of potassium was 6.15 mmol/L. She received aldosterone at a dose of 26.98 ng/dl, renin = 6.78 pg/ml, and ARR = 3.97. Abdomen ultrasound showed multiple stones in the left kid-

Table 1. Renin-angiotensin-aldosterone examination results in her standing position for 2 h (2014-8)

	Aldosterone (ng/dl)	Renin (pg/ml)	Angiotensin II (pg/ml)	Aldosterone/(Renin)
Standing position 2 h	18.51 (4-31)	1.55 (4-38)	339.55 (49-252)	11.9

Table 2. Capoten test (Capoten 25 mg) (2014-8)

	Aldosterone (ng/dl) (1-16)	Renin (pg/ml) (4-24)	Angiotensin (pg/ml) (25-129)	Aldosterone/ renin
8:00 (Before taking medicine)	15.79	1.61	255.14	9.8
10:00 (After taking medicine)	303.73	4.87	45.20	6.24

Table 3. Parathyroid function test results

Test item (unit)	Test result (2014-8)	Test result (2017-2)
Ca (mmol/L)	2.99	2.85
P (mmol/L)	0.9	0.68
24-hour urinary ca (mmol/24 h)	10.2	0.8
24-hour urinary P (mmol/24 h)	10.0	14.3
VD3 (ng/ml)	3	4
ALP (U/L)	65	75
PTH (pg/ml)	289	610.1

ney and serum calcium was 2.98 mmol/L, PTH = 367.8 pg/ml and Cr = 116 umol/L. Sodium ibandronate and salmon calcitonin acetate and furosemide tablets were administered. After discharge, the serum potassium level was within the normal range. In July 2016, she was treated in the local hospital for acute pancreatitis, K = 4.48 mmol/L (oral administration of furosemide), Ca = 2.91 mmol/L and Cr = 230.1 umol/L. Subsequently, she was admitted to our hospital again. She occasionally felt uncomfortable in the precordium, had parched mouth, polydipsia, diuresis, headache, occasional osphyalgia, occasional bloating and sour regurgitation, without nausea, vomiting or diarrhea. Menstrual history: menopause at the age of 49. Family history: her grandfather was diagnosed with hypertension. Physical examination: BP = 160/110 mmHg; her mouth was skewed to the left, left upper eyelid was drooping, right eye couldn't be closed, the tongue protruded in the middle, cardiopulmonary resuscitation (-), she had lower limb varicosities and clubbed fingers and toes. She had muscle power of four limbs: class 4, bilateral biceps/triceps hyporeflexia, bilateral kee/achilles tendon hyporeflexia and positive bilateral Babinski.

Serum potassium = 2.13 mmol/L, 24-h urine potassium = 79.1 mmol/d, cortisol rhythm: cortisol = 205.95 nmol/L at 00:00 and 254.66 mmol/L at 08:00 a.m., ACTH = 23.41 pg/ml, and 45.52 nmol/L after overnight low-dose dexamethasone suppression test. After receiving 2-h RAAS (**Table 1**) and captopril test (**Table 2**) in a standing position, she did not achieve cortisol suppression. No abnormality was seen in sex hormones. No abnormality was seen in thyroid function including PRL, E2, FSH, LH and IGF-1. As illustrated in **Table 3**, parathyroid color ultrasound showed a solid mass in 8.4×7.7 mm in the rear of the lower pole of right lobe. 99mTc-Tetrofosmin image showed no hyperfunction of the parathyroid glands. Thyroid ultrasound revealed a 11.6×10.0×12.8 mm mixed mass near the posterior lower pole of right lobe, indicating a possible parathyroid adenoma. Parathyroid adenoma SPECT/CT: anomaly imaging agent showed gathering (99mTc-MIBI) on the right lobe of the thyroid in combination with CT scan. Hyperthyroidism or adenoma could occur in the posterior lower pole of right lobe of the thyroid. Thymus gland CT demonstrated no anomaly. Bone density showed signs of osteopenia. Routine examination of blood, urine, and stool and liver function, renal function, lipid profile, albumin, plasma glucose, myocardial enzyme, and tumor marker yielded normal results. ECG: sinus rhythm, wide lead ST-T change; echocardiography: left atrium was full, left ventricular wall was thickened, and left ventricular diastolic function was reduced. Abdomen ultrasound: liver damage, damage of both kidneys, cysts of both kidneys, and no abnormality discovered in liver, pancreas and spleen; coronal MRI: ischemic demyelination, softening lesion, and pontine lesion after haemonhage became softened. maxillary sinusitis on two sides, and no abnormality showed on coronal MRA. No abnormality was detected on renal artery color ultrasound.
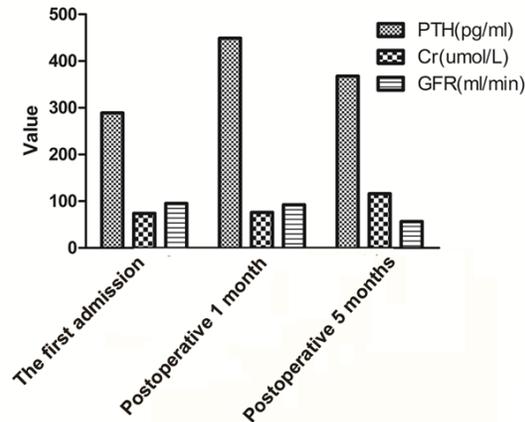
Figure 1. Comparision of the renal function and PTH level before, during and after operation.

In December 2014, the eGFR level was 73.7-99.4 ml/min and serum creatinine was 71-92 umol/L. In May 2015, the serum creatinine was increased and GRF was reduced, and the PTH was increased preoperatively, but was reduced postoperatively (**Figure 1**). The patient received parathyroid mass resection in our hospital, and postoperative pathology indicated parathyroid adenoma. At postoperative 3 days, the serum calcium level was 2.5 mmol/L and PTH was 14.87 pg/ml. After discharge, the patient was given with caltrate D at dose of 600 mg/day and calcitriol at a dose of 0.5 g/day. At 3 months after operation, the serum calcium was 2.6 mmol/L and PTH was 17 pg/ml.

The possibility of MEN1 type could not be excluded since she was diagnosed with adrenocortical adenoma, and parathyroidoma complicated with nonfunctional pituitary adenoma. Therefore, she received MEN1 gene detection in Shanghai Ruijin Hospital and demonstrated the A541 gene polymorphism variant (**Figure 2**).

Discussion

Currently, adrenocortical adenoma is a common combination of MEN1. In this report, the patient suffered from parathyroid adenoma, and hypophysoma complicated adrenal adenoma. Hence, she was probably positive for MEN1, whereas her relatives had no medical history of endocrine tumors. Therefore, if this patient may have a sporadic case of MEN1.

MEN1 gene is located on chromosome 11q13, and 10 exons are included, in which exons 2-10 are the coding area, and 610 amino acids are included in encoded protein, and this protein is known as "menin". Menin is mainly a kind of nucleoprotein and plays a role in transcriptional control, genome stability, cell apoptosis, and cell cycle control by mutual interaction with other proteins. Over 600 mutation types of menin have been reported. This patient showed A541T gene polymorphism changes, and this gene was not a pathogenicity gene of MEN1. Therefore, this result was inadequate to validate the definite diagnosis of MEN. A previous study had demonstrated three mutations in the patient's gene sequencing. The first was homozygous change of nucleotide in the position of C.1818 of exon 9 from turn T into C, but the corresponding amino acid in the position 438 is histidine, which is a same sense mutation (rs540012). The second one is heterozygous change of nucleotide in the position of C2098 of exon 10 changing T into C, resulting in the mutation of amino acid in the position 527 from arginine to TGA (R527X, rs104894261). The third one is heterozygous change of the codon in the position C2140 of exon 10 turning A into G, causing the change of amino acid in the position 541 from alanine to threonine (A541T, rs2959656). Through inquiry of HGMD database and ensemble database, A541T may affect the protein function. A541T has a mutation rate of 1.4% in normal chromosome [4]. Ensemble database shows that the probability of basic group A in this locus in Asian population is 27%, and the mutation in this locus may reduce the sensitivity [5] to cell apoptosis. A541T is a potential pathogenic SNP. Type 1 parathyroid receptor is expressed in the cortical suprarenaloma with an increased production of aldosterone, and mineralocorticoid receptor is expressed in parathyroid cell nucleus [6]. In addition, PTH and PTH-RP play a vital role in promoting the secretion of human adrenal cortex in combination with adenylate cyclase and protein kinase C by PTH/PTH-RP receptor [7]. The increase of PTH level induces an increased calcium content in the urine and excrement, which may be weakened or eliminated by mineralocorticoid receptor antagonist [8]. Other studies have demonstrated that hyperparathyroidism is caused by PA and can improve with the treatment of primary aldosterone. In this case, when the patient was initially suspected to have parathyroid adenoma and aldosteronoma, the PTH value was 289 pg/ml. Preoperatively, the PTH value increased to 448.9 pg/ml. When she was admitted at 5

Sample NO: G17064

Name: Huang Yong'e

Test gene sequencing: MEN1

Comparison gene sequencing: NG-008929.1

Sequencing analysis

Exon	Sequencing direction	Coding amino acdi	Re-sequencing	Reason
1	F+R	1-58	pass	
2	F+R	52-111	pass	
3	F+R	105-148	pass	
4	F+R	154-218	pass	
5	F+R	219-261	pass	
6	F+R	266-304	pass	
7	F+R	305-350	pass	
8	F+R	351-395	pass	
9	F+R	396-450	pass	
10	F+R	451-563	PA541Taa CG1731AN	
12	F+R	560-610	pass	
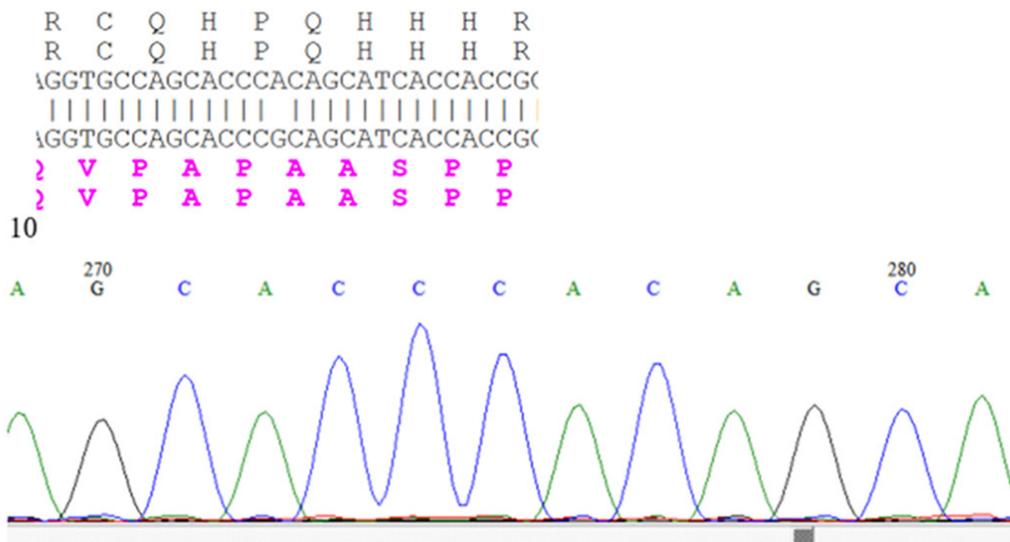
Figure 2. Diagram of MEN1 gene detection.

months after operation, the PTH value was 367.8 pg/ml, suggesting that the patient's parathyroid hormone level reduction was possibly caused by excision of the aldosteronoma.

This patient had hyperkalemia in 5 months after excision of aldosteronoma, and also she had an increased serum creatinine level and reduced GFR in 5 months after operation. This is not a unique report that patients with primary aldosteronism have hadhyperkalemia after operation. This has also been reported in the foreign literature [9]: one case of patient with aldosteronoma had hyperkalemia after operation. This patient's PRA wass low after operation, and PAC was in the normal range, and so the postoperative hyperkalaemia may have been related to a relative aldosterone reduction. It is reported by other studies [10] that aldosterone may be independent of hypertension and cause direct damage to kidney, and the patients with PA have a higher prevalence rate of renal damage than the patients with primary hypertension. Excess aldosterone secretion can increase the pressure on glomeruli, and further cause renal damage. Aldosterone may cause direct and quick renal artery vasoconstriction, or it may adjust vascular remodeling by oxidative stress [11].

Fischer *et al.* found that 16% of APA patients had hyperkalemia after operation, and 5% had long-term hyperkalemia and 11% had one-time record of hyperkalemia. Postoperatively, plasma aldosterone was not detected in 14 patients and 4 cases had a lower aldosterone level. Over 90% of these patients with hyperkalemia had serious hypokalemia before operation, indicating that they had a stronger suppression on adrenal glomerular zones bilaterally than those with mild hypokalemia. Preoperative decrease of eGFR, the increase of serum creatinine before and after operation and microalbuminuria were all important predictive factors [12] of postoperative hyperkalemia. In primary hyperparathyroidism patients, excessive PTH may be combined with kidney cell surface receptor. The kidney tubules will have an increased capability of Ca reabsorption. When serum calcium exceeds normal level, more Ca will be filtered by glomeruli and urinary calcium discharge will increase, resulting in the formation of kidney stones, renal calcification and renal function damage due to the deposition of calcium phosphate and calcium oxalate. Glomerular filtration rate will be reduced [13]. In this case, the eGFR was 73.7-99.4 ml/min and serum creatinine was 71-92 umol/L before operation in critical conditions, probably related to

the long-term renal damage due to high aldosterone and excessive PTH. Postoperatively, the serum creatinine was increased and the eGFR was decreased. At postoperative 5 months, the patient suffered from hyperkalemia. The renin and aldosterone levels were normal after operation. Postoperative hyperkalaemia could be caused by the renal damage and aldosterone reduction.

Parathyroid color ultrasound indicated a solid mass, 8.4×7.7 mm in the rear of lower pole of the right lobe, possibly derived from the parathyroid. However, MIBI showed no parathyroid adenoma upon the initial admission, possibly related to the change of photographic developer in our hospital. Previously, we used a 99mTc-MIBI photographic developer; subsequently, we gradually changed to use of a 99mTc-Tetrofosmin photographic developer instead of 99mTc-MIBI photographic developer. After use of tetrofosmin photographic developer, tetrofosmin yielded a blurring image with lower sensitivity than MIBI. Consequently, we changed to use of a 99mTc-MIBI photographic developer again. For this patient, tetrofosmin photographic developer was used. As the replaced radionuclide was not sensitive, a false negative result was obtained while radiograph reading. Secondly, this could be caused by the extremely small tumor.

Taken together, the kidney damage may be caused by aldosterone and PTH. Patients with PA-complicated PHPT should be treated as early as possible to avoid affecting the postoperative effect due to the aggravated renal damage. PA and PHPT can mutually interact, which provides a novel thinking for the clinical treatment of this complicated condition.

Disclosure of conflict of interest

None.

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