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Primary aldosteronism with concurrent primary hyperparathyroidism: clinical case load in a single centre

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Abstract. – OBJECTIVE: Primary aldosteronism (PA) represents the main cause of endocrine secondary arterial hypertension in which aldosterone production is inappropriately elevated. Primary hyperparathyroidism (PHPT) is an endocrine disease characterized by hypercalcemia due to overproduction of parathyroid hormone (PTH). Although these two endocrine pathologies are secondary to hypertension in middle aged population, the occurrence of the PHPT in PA patients has rarely reported in the literature. The aim of the study was to describe some PA patients with concurrent PHPT, referred in a tertiary center of arterial hypertension.

PATIENTS: We performed a retrospective study. In particular, the registry of 306 patients with PA seen in our center since 2004 was examined and revealed 8 patients (2.6%) with concurrent PHPT.

CONCLUSIONS: There are several possible explanations for the association of these two endocrine disorders, including the combination was a random finding that PA inheres PHPT or vice versa.

Key Words:
Primary aldosteronism, Primary hyperparathyroidism, Adrenal adenoma, Parathyroid adenoma.

Introduction

Primary aldosteronism (PA) represents the main cause of endocrine secondary arterial hypertension in which aldosterone production is inappropriately elevated and at least partially autonomous of the renin-angiotensin system[1]. PA is constituted mainly two subtypes, aldosterone-producing adenoma (APA), and bilateral idiopathic hyperplasia (IHA)[2], and is strongly associated with an excess of cardiovascular morbidity and mortality risk[3].

Primary hyperparathyroidism (PHPT) is an endocrine disease characterized by hypercalcemia due to overproduction of parathyroid hormone (PTH), dependent on single or double adenoma (80-85%), hyperplasia (15-30%), and parathyroid carcinoma (< 1%)[4]. Some studies have suggested that PHPT is associated with metabolic disorders such as glucose metabolism, metabolic syndrome, hypertension, and structural and functional alterations in cardiovascular system, whereas is uncertain the exact role of calcium and/or PTH in the development of cardiovascular disorders[5].

Recently, has been reported in patients with unequivocally confirmed PA due to an APA that was a highly significant increase of PTH[6]. This observation may be relevant since some studies have demonstrated a bidirectional interaction between renin-angiotensin-aldosterone system (RAS) and mineral metabolism[7], and severe hypertension. Although these two endocrine pathologies are secondary to hypertension in the middle aged population, the occurrence of the PHPT in PA patients has been rarely reported in the literature.

Aim of the study was to describe some PA patients with concurrent PHPT, referred in our Institution for study of secondary hypertension.

Patients and Methods

We performed a retrospective study at Specialized Center of Secondary Hypertension, Department of Internal Medicine and Medical Specialties, University of Rome "La Sapienza", Italy database.

Over the 9 years period (January 2004 to December 2012), 306 patients were diagnosed with PA. Of these 306 patients, only 8 had concurrent PA and PHPT. All medical records of these 8 patients were assessed, (Table I).

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Table I. Demographic, cardiovascular, metabolic and hormonal parameters in patients with concomitant primary aldosteronism and primary hyperparathyroidism (PA+PHPT).

PA+PHPT (n. 8)	Sex (M/F)	Age (yrs)	BMI (Kg/m²)	WC (cm)	SBP (mmHg)	DBP (mmHg)	HR (bpm)	K+ (mEq/l)	Creatinine (mg/dl)	Glycaemia (mg/dl)	Uric Acid (mg/dl)	CT (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)	TG (mg/dl)
1	F	25	26.77	89	120	70	160	1.8	0.7	80	5.9	188	61	106.6	102
2	M	55	34	110	150	100	65	2.9	1.22	108	8.9	259.7	45.1	187.8	133.9
3	F	77	19.5	78	150	100	80	3.7	1.06	112	7.2	191	53	118	100
4	F	66	30.3	96	145	85	54	3.1	0.93	102	7.9	212.2	67.6	119.54	125.3
5	F	52	23	85	150	90	79	3.75	0.78	95	7.3	206.2	44.6	124.36	186.2
6	F	60	30.11	98	150	110	65	4.07	1.14	97	6.5	283	51.4	198.04	167.8
7	F	64	32.6	104	150	80	64	3.1	0.7	94	8.9	225	48	164	65
8	M	61	31.3	103	185	80	53	3.2	1.3	101	9	241	31.5	168.8	201
Mean ± standard deviation	2M 6F	57.5 ± 15.14	28.44 ± 5	95.37 ± 10.72	150 ± 17.52	89.37 ± 13.21	77.5 ± 34.76	3.2 ± 0.69	0.97 ± 0.23	98.62 ± 9.76	7.7 ± 1.17	225.76 ± 33.51	50.27 ± 10.95	148.39 ± 35.37	135.15 ± 46.84

	PAC (ng/dl)	PRA (ng/ml/h)	ARR (ng/ml: ng/ml/h)	AUR (µg/24h)	Subtype of PA	Calcium (mg/dl)	Ca^{++} (mmol/L)	Phosphorous (mg/dl)	Cl^- (mg/dl)	PTH (pg/ml)	Parathyroid adenoma localization
1	40.1	0.21	190.9	40	APA (left adrenal gland) ø 20 mm	11.7	1.55	2.5	95	148.4	Left superior and inferior parathyroid glands
2	36.59	0.44	83.15	33	IHA	11.5	1.37	2.8	103	70	Left inferior parathyroid gland
3	22.7	0.1	152	44.4	APA (left adrenal gland) ø 12 mm	10.8	1.34	2.6	97	105	Left inferior parathyroid gland
4	25.9	0.16	162.2	34	IHA	11	1.41	2.81	105.8	80	Right inferior parathyroid gland
5	13.45	0.25	53.8	36	IHA	13.6	1.38	2.4	102	98	Right inferior parathyroid gland
6	33.94	0.32	106	35.5	IHA	11	1.34	2.9	103	187	Right and left inferior parathyroid glands
7	19.53	0.24	79.04	30.6	APA (right adrenal gland) ø 11 mm	10.9	1.4	3	104	72.6	Right inferior parathyroid gland
8	38.1	0.1	389.3	32.8	IHA	10.3	1.35	2.5	104	76.5	Left inferior parathyroid gland
Mean ± standard deviation	28.78 ± 9.77	0.22 ± 0.11	152 ± 106.73	35.78 ± 4.4	3 APA 5 IHA	11.35 ± 1	1.39 ± 0.06	2.68 ± 0.21	101.72 ± 3.73	104.68 ± 42	

BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; K+: potassium; CT: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides PAC: plasma aldosterone; PRA plasma renin activity; ARR: plasma aldosterone/plasma renin activity ratio; AUR: urinary aldosterone; Ca^{++}: serum-ionized calcium; Cl: chloride; PTH: parathyroid hormone.

Case Reports

Patient 1

The first case, a 25 year-old woman was referred to our Institution with palpitations, abdominal pain and worsening dyspnea. A physical examination was completed with the following results: respiratory rate 35 breaths/min, heart rate 160 b/min and blood pressure 120/70 mmHg. The laboratory analysis showed severe hypokalemia (K+ 1.8 mEq/L; normal range 3.4-5.5), hypochloremia (95 mEq/l; normal range 98-105), hypercalcemia (ionized calcium 1.52 mmol/L; normal range 1.18-1.33), and metabolic alkalosis (pH 7.50; pCO_2 25 mmHg and HCO_3^- 35 mmol/L). The patient was given intravenous potassium chloride and amiodarone (a bolus of 300 mg and a 900 mg infusion in 5% glucose over 24 hrs) for an arterial flutter with 2:1 fixed AV conduction and a mean ventricular rate of 150 b/min. An endocrinological investigation revealed a suppressed plasma renin activity (PRA) (0.21 ng/ml/min; normal range 0.3-2.7), high plasma aldosterone concentration (PAC) (40.1 ng/dL; normal range 0.75-15) and high PAC/PRA ratio (ARR 190.9 ng/dL:ng/mL/h; normal range ≤ 30). In order to confirm the diagnosis of PA a captopril test was performed, and the ARR was elevated beyond the normal physiological limits. Magnetic resonance imaging (MRI) revealed the presence of a 2 cm nodule in the left cortical adrenal gland. Moreover, the PTH concentration was elevated to 148 pg/mL (normal range: 10-54 pg/ml) suggesting diagnosis of PHPT, confirmed by ultrasonography (US) and scintigraphy which revealed the presence of two parathyroid adenomas. On the basis of these results, we evaluated that she had PA with concurrent PHPT. She underwent in different time, left laparoscopic adrenalectomy and parathyroidectomy. A histopathological exam confirmed the presence of an adrenocortical adenoma and a parathyroid adenoma.

Patient 2

The second case, a 55 yr-old-man with resistant arterial hypertension (treated with β-blockers; ATI- receptor blockers and diuretic) was referred in our Institution. At admission blood pressure was 150/100 mmHg, heart rate 75 bpm.

Biochemical data showed hypokalemia (2.9 mEq/L) hypercalcemia (11.5 mg/L total calcium; 1.37 mmol/L ionized calcium), high PAC (36.59 ng/dl) and suppressed PRA (< 0.5 ng/ml/h) with ARR 83.15 ng/dL:ng/mL/h. 24 h-ABPM revealed moderate systolic and diastolic hypertension with "non-dipper" pattern. The confirmator test with saline infusion demonstrated not suppression of PAC (8.2 ng/dl; normal value < 7 ng/dl). Abdominal computed tomography (CT) images revealed a 10 mm nodule in the adrenal gland. Moreover, PTH level was increased (70 pg/ml) and US parathyroid scan showed a nodule in the left inferior parathyroid gland, confirmed with ^{99m}Tc-sestamibi scintigraphy. PA with concurrent PHPT was diagnosed.

The patient was submitted to parathyroidectomy and the neoplasia was removed, with histopathological diagnosis of parathyroid adenoma. After parathyroidectomy PTH and calcium returned to normal values (13.6 pg/ml and 8.5 ng/dl, respectively). The patient refused the adrenalectomy unilateral and aldosterone antagonist, beta-blockers, and ACE-inhibitors (ACE-I) was started with good blood pressure control.

Patient 3

The third case, a 77 yr-old hypertensive woman was referred with resistant hypertension (treated with ACE-I, Ca-A, diuretics), chronic atrial fibrillation (FA) (treated with warfarin) and multinodular toxic goiter (treated with methimazole). At admission blood pressure was 150/100 mmHg, heart rate 80 b/min body mass index (BMI) 19.5 kg/m^2. Biochemical analysis showed impaired fasting glucose (glycaemia 112 mg/die), high serum total and ionized calcium (10.8 mg/dl and 1.34 mmol/l, respectively) and high plasma PTH level (105 pg/ml). Moreover, PAC was high (22.7 ng/dL) associated to suppressed PRA (0.1 ng/dL/h) with ARR 152 ng/dL: ng/mL/h. CT imaging showed a nodule, diameter 12 mm, in the left adrenal gland, and parathyroid US scan revealed a nodule in the left inferior parathyroid gland. The diagnosis was PHPT with concurrent PA, but the coexistence of chronic atrial fibrillation and the age of the patient not indicated the surgery therapy. The patient was treated with aldosterone antagonist, ACE-I and bisphosphonates with controlled blood pressure and mineral metabolism.

Patient 4

The fourth case was a 66-yr-old woman referred to for resistant hypertension (ACE-I, Ca-A, β-blockers and diuretics) and osteoporosis (BMD 0.687 g/m^2 and T-score -3.8 at lumbar spine).

Past medical history revealed a nodular benign thyroid disease and dyslipidemia. At the admission she showed hypokalemia (K^+ 3.1 mEq/L) associated to hypercalcemia (Ca^+ 11 mg/dl and Ca^{++} 1.41 mmol/L). The hormonal study revealed PAC 25.95 ng/dL, PRA 0.16 ng/mL/h (ARR 162.2 ng/dL: ng/ml/h) without suppression PAC (10 ng/dL) at the saline infusion; and high PTH values (112 pg/ml). Abdominal CT scan showed enlargement of both adrenal glands and adreal venous sampling (AVS) did not reveal lateralization of PAC secretion. Diagnosis of IHA with concurrent PHPT was posed. US parathyroid scan and scintigraphy showed a lesion on the inferior right parathyroid gland and histologic examination after parathyroidectomy reveal an adenoma. After parathyroidectomy calcium (8.3 mg/dl) and PTH (32 pg/ml) returned to normal values. ACE-I, Ca-A, β-clockers and spironolactone (50 mg/die) was started with good control of electrolytes and blood pressure.

Patient 5

The fifth case was a 52-year-old woman referred for hypertension and high levels of serum alkaline phosphatase (394 U/L; normal range 35-104 U/L) and hypercalcemia (13.6 mg/dl). Her past medical history reported oophorectomy for right ovarian cyst and appendectomy.

Biochemical analysis confirmed hypercalcemia (ionized calcium 1.38 mmol/L), high serum alkaline phosphatase (415 U/L) and revealed PTH values (98 pg/ml). Bone mineral density (BMD) showed osteopenia (T-score -2.2 of lumbar spine and femoral neck, respectively). Subsequent investigation for arterial hypertension revealed high ARR (53.8 ng/ml:ng/ml/h) and not suppression of PAC level (9 ng/dl) after saline infusion. US and scintigraphy parathyroid scan and abdominal MRI revealed a nodule in the right inferior parathyroid gland and enlargement of bilateral adrenal gland, without nodules. AVS did not reveal PAC lateralization. Based on these data PHPT and IHA was diagnosed. AT-1 blocker and spironolactone (100 mg/day) was started and the patient underwent to parathyroidectomy (parathyroid adenoma). After surgery serum calcium (8.9 mg/dl), serum alkaline phosphatase (99 U/L) and PTH (30 pg/ml) returned into normal values.

Patient 6

The sixth case was a 60-year-old woman referred for bilateral adrenal lesions, incidentally discovered, and arterial hypertension. Past medical history reported gastroesophageal reflux disease and diverticulosis of the colon. The screening tests of the adrenal incidentalomas revealed normal value of 24-h urinary free cortisol excretion (UFC 99 μg/24h; normal value 2,8-30 μg/24h), 24-h urinary total metanephrines (120 μg/24h; normal value 74-297 μg/24h), dexametasone overnight test (plasma cortisol 1.1 μg/dl; normal value ≤ 1.8 μg/dL), plasma ACTH (80 pg/ml), and high ARR (106.1 ng/dL:ng/mL/h) and 24-h urinary aldosterone excretion (35.5 μg/24h). PAC level was not suppressed (10 ng/dl) after saline infusion. Moreover, blood test showed hypercalcemia (11 mg/dL) associated to high PTH values (187 pg/mL). The patient refused AVS, whereas US parathyroid scan and ^{99m}Tc-sestamibi scan revealed a nodule in the left and right inferior parathyroid glands. The patient refused other investigations and surgery treatment. The therapy with aldosterone antagonist, bisphosphonates and AT-1 blockers was started.

Patient 7

The seventh case was a 64-year-old woman for referred resistant hypertension, treated with ACE-I, CA-A, α-blockers and diuretics. Past medical history reported hysterectomy for adenomyomatosis. At admission biochemical data showed hypokalemia (K+ 3.1 mEq/L), hypercalcemia (total calcium 10.9 mg/dl; ionized calcium 1.4 mmol/l) and high plasma PTH levels (72.6 pg/ml). Moreover, several crystals of calcium oxalate were detected at urinary-analysis. ARR (79.04 ng/dL:ng/mL/h) was higher and captopril test (captopril 50 mg per os) was performed, because the blood pressure values were very high (PAS 190 and PAD 120 mmHg), without reduction of ARR. MRI showed a nodule (diameter 11 mm) in the right adrenal gland, and US parathyroid scan revealed a hypoaechoic nodule under the right thyroid lobe (diameter 1.8 × 11 mm). Based on these data PHPT with concurrent PA was diagnosed. The patient started pharmacological therapy with spironolactone (100 mg/day) and in different moment laparoscopic right adrenalectomy and parathyroidectomy was performed. Histologic examination revealed adrenal adenoma and parathyroid adenoma.

Patient 8

The eight case was a 61-year-old man referred in our Institution for severe arterial hypertension treated with ACE-I, α-blockers, Ca-A and diuret-

ics. Past medical history reported dyslipidemia and impaired fasting glucose (IFG). At admission the patient reported headache, asthenia and muscular weakness for about six months.

Blood analysis showed glycaemia (101 mg/dL), hypokaliemia (K^+ 3.2 mEq/L) and hypercalcemia (total calcium 10.3 mg/dl and ionized calcium 1.35 mmol/L), associated to high PTH level (76.5 pg/mL). Subsequent hormonal analysis showed suppressed PRA (0.1 ng/mL/h), high PAC (38.93 ng/dL), and high ARR (389.3). After saline infusion PAC levels were not suppressed (14.2 ng/dL).

Abdominal MRI revealed enlargement of right adrenal gland, without nodules, and parathyroid US scan showed a hypoecoic nodule under the left thyroid lobe (diameter 8 mm) confirmed the ^{99m}Tc-sestamibi scintigraphy that revealed increased uptake in that area. The AVS was not diagnostic, the right adrenal vein cannulation was not possible and the patient refused other investigations.

We started antihypertensive treatment with spironolactone (50 mg/day) and he underwent to parathyroidectomy. Histological examination showed a parathyroid adenoma.

Discussion

Hypertension is one of the most common disease in modern society, and most patients will have no identifiable cause for their hypertension (essential or primary). However, a minority of patients will be diagnosed with secondary hypertension, having a clearly identifiable cause for the increased blood arterial pressure[1].

PA is an endocrine secondary cause of hypertension characterized by autonomous overproduction of adrenal aldosterone with suppression of PRA, sodium retention, and consequent hypertension. Various primary adrenal pathological processes cause this syndrome: some of them are best treated by surgery and others by medical[2]. The APA is the most important cause of PA and represents one of the few curable cause of secondary arterial hypertension.

Various pathological conditions have associated with PA, including glucagonoma[8], pheochromocytoma[9], multiple endocrine neoplasia type 1 (MEN 1)[10], and PHPT. In particular, the presence of both PA and PHPT in the same subject has been reported in only few patients[6]. The PHPT, the third most common endocrine disorder, is characterized by excess of PTH secretion, inappropriate with respect to circulating ionized calcium concentration[11].

Taking into account a relatively prevalence of both PA and PHPT in the general population, these findings may be explained a coincidence of both these endocrine disorders.

The first case was described in 1980 by Fertig et al[12] that described a 51-year-old female patient affected by PA due to multiple adenomas of the adrenal glands, which developed ten years after bilateral adrenalectomy PHPT caused by inferior left parathyroid adenoma. Successively, another case reports were reported in the English literature[13].

In this paper we report our cases load in the association of PA and PHPT. In particular, the registry of all patients with PA seen in our center since 2004 (306 patients) was examined and revealed 8 patients (2.6%) with concurrent PHPT.

There are several possible explanations for the association of these two endocrine disorders, including the combination was a random finding that PA inheres PHPT or "vice versa". Recently, in a relative cohort of patients with unequivocally confirmed PA due to APA, Maniero et al[6], showed a highly significant increase (31%) in the number of cases of PHPT. Thus, suggesting that there a bi-directional functional link between the adrenocortical zona glomerulosa and the parathyroid gland. Pilz at al[7] showed that patients with PA are prone to secondary hyperparathyroidism that can be successfully treated with either mineralcorticoid receptor (MR)-antagonists or adrenal surgery.

Recently, Rossi et al[14] impressively demonstrated the expression of the MR in both PTH-secreting adenoma and in normal parathyroid gland tissue. Interestingly, the MR was predominantly located in the nucleus of the parathyroid cells, indicating that aldosterone (and cortisol) participate in a "tonic" regulation of PTH synthesis and secretion. Tomaschitz at al[15] documented that the efficacy of the MR eplerenone to reduce PTH secretion in patients with parathyroid hormone excess. Finally, several studies in humans demonstrated that in PHPT, aldosterone concentrations are elevated and decrease after parathyroidectomy[16].

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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