Case report

Keywords: aldosterone-producing adenoma, adrenal myelolipoma, multiple lipomas, retinoblastoma gene (RB)

A rare combination consisting of aldosterone-producing adenoma and adrenal myelolipoma in a patient with heterozygosity for retinoblastoma (RB) gene

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Abstract

Various pathological disorders have been associated with primary aldosteronism, including glucagonoma, phaeochromocytoma and primary hyperparathyroidism.

In this report, a case of adrenal myelolipoma (a rare non-functioning tumour composed of mature adipose tissue and normal haematopoietic elements similar to bone marrow cells), aldosterone-producing adenoma and a pituitary microadenoma coexisting in a 62-year-old man with a 15-year history of arterial hypertension, previous ablation of an autonomously-functioning thyroid adenoma, multiple lipomas and an heterozygosity of the retinoblastoma (RB) susceptibility gene is reported.

We believe that this case probably represents another variant of the multiple neoplasia syndrome and we speculate that structural alteration of the RB gene may play a role in the tumorogenesis.

Introduction

The syndrome of hypertension due to a benign aldosterone-secreting adenoma of the glomerulosa of the adrenal cortex was first described by Jerome Conn in 1955. Since then, many case studies have been published[2-6] and the criteria for the biochemical and histopathological diagnosis have been extensively reported.

Various pathological conditions have been associated with primary aldosteronism, due to an aldosterone-secreting adenoma of the adrenal cortex, including glucagonoma,[7] phaeochromocytoma,[8] primary hyperparathyroidism[9,10] and a case of multiple endocrine neoplasia type 1 (MEN1).[11]

Adrenal myelolipomas are rare, benign mesenchymal tumours, composed of mature tissue and haematopoietic cells in varying proportions.[12] The simultaneous occurrence of adrenal myelolipomas has occasionally been found in patients with Conn's syndrome.[13,14]

In this report, a case of an aldosterone-producing adenoma and adrenal myelolipoma coexisting in a patient with a 15-year history of arterial hypertension, previous ablation of an autonomously-functioning thyroid nodule, multiple lipomas and an heterozygosity of the retinoblastoma (RB) susceptibility gene is reported.

We believe that this case may represent another variant of the MEN syndrome and we speculate that structural alteration of the RB gene may play a role in the tumorogenesis.

Case report

A 62-year-old man was referred to our Day-Hospital of Internal Medicine by his cardiologist with a 15-year history of poorly controlled arterial hypertension and recently hypokalaemia without diuretic therapy and monolateral gynaecomastia. There were no specific symptoms and, in particular, no muscle weakness. The patient was heterozygous for the RB tumour suppressor gene (the family secreting a splice site mutation in the RB gene: g73 868 A>6).[15] There were no endocrinopathies in other family members.

Previously, he had undergone thyroid lobectomy for a functionally autonomous adenoma at the age of 36 years. Moreover, his medical history included angina pectoris, hypercholesterolaemia and multiple lipomas. At initial assessment, his blood pressure (BP) was 170/105 mmHg, despite treatment with a calcium antagonist (amlodipine) and β-blocker (atenolol). Previously, treatment with an angiotensin-converting enzyme (ACE)-inhibitor (enalapril), calcium-antagonist (nifedipine) and diuretic (hydrochlorothiazide) had also failed to control his BP. Laboratory examination was remarkable apart from hypokalaemia (2.3 mmol/L) and a metabolic alkalosis (with a base excess of 6.5 mmol/L). Renal and liver function tests were normal. Twenty-four hours urine, on a normal salt diet (140–150 mmol/day) revealed: sodium excretion 103 mmol/24 hours, potassium excretion 75 mmol/24 hours and aldosterone excretion 44.2 μg/24 hours (normal value 2.8 to 25 μg/24 hours). Supine plasma renin activity (PRA) was suppressed to 0.1 ng/ml/hour (normal value 0.2 to 2.7 ng/ml/hour) and plasma aldosterone concentration (PAC) was raised at 74.2 ng/dl (normal value 0.75 to 15 ng/dl), giving a PAC/PRA ratio of 666 ng/dl: ng/ml/hour (greater than 40 suggests primary aldosteronism). Plasma cortisol (PC) level and the patient's response to an overnight dose of dexamethasone (1 mg/23 hours) was normal (4.2 μg/dl).

The patient's thyroid stimulating hormone (TSH) (2.1 μUI/ml), human growth hormone (HGH) (0.38 ng/ml), luteinising hormone (LH) (5.2 μUI/ml), follicle stimulating hormone (FSH)

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Figure 1 MRI scan of the abdomen showing the mass in the left suprarenal space

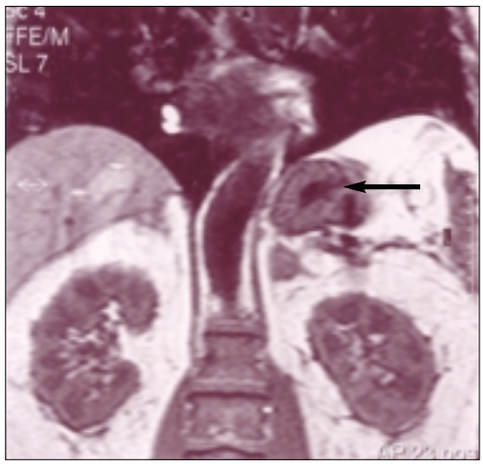
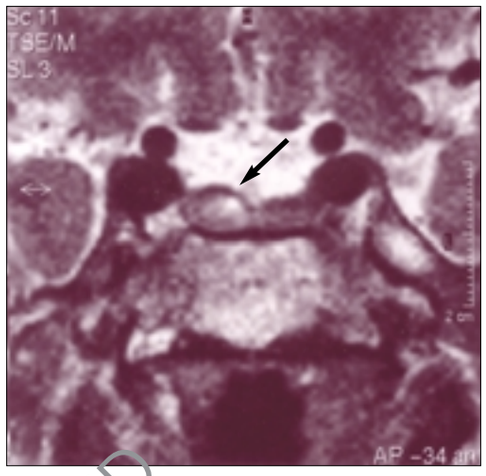
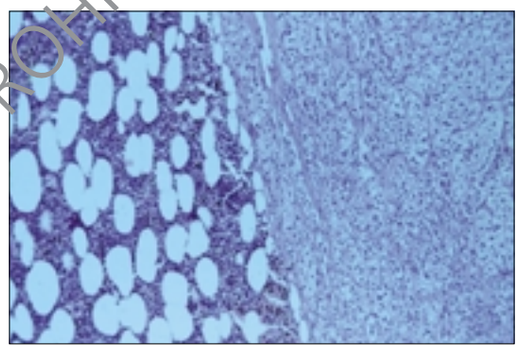


Figure 2 MRI scan of the pituitary showing the intrasellar microadenoma



(4.5 µUI/ml) levels were normal, while sequential prolactin (PRL) measurements revealed mild hyperprolactinaemia (30.6; 31.4; 30.2 ng/ml: normal value 2 to 14.5 ng/ml). Moreover, the evaluation of serum PRL levels before (27 ng/ml) and 20 minutes after the intravenous (i.v.) administration of 500 g of TRH as a bolus revealed an increase in PRL (105 ng/ml). Magnetic resonance imaging (MRI) of the abdomen revealed a mass in the left adrenal gland (Figure 1), and MRI of the pituitary gland showed an intrasellar lesion (7 mm) (Figure 2). In addition, an adrenal scan with 131-NP59 revealed exclusive uptake in the left adrenal gland concordant to MRI. The left adrenal gland was explored with laparotomic access. The resected adrenal gland revealed a well-encapsulated adrenal tumour, measuring 30 x 20 mm. The tumour was composed of granular clear cells in lobular arrangements and proliferating haematopoietic cells with areas of mature adipose tissue. The two tumours, aldosteronoma and myelolipoma, were merging into each other (Figure 3).

Figure 3 Myelolipoma (on the left side) and aldosteronoma (on the right side of the figure) are showed. Note the two tumours are merging into each other (HE x 125)



Left adrenalectomy normalised the serum electrolytes (sodium 143 mmol/L; potassium 4.1 mmol/L) blood gas analysis and hormonal data (PRA 1.1 ng/ml/hour; PAC 10.2 ng/dl; PAC/PRA 9.27 ng/ml/hour:ng/dl). The patient was normotensive (140/85 mmHg) on a single antihypertensive agent (nisoldipine, 10 mg/day). After one year, MRI of the pituitary gland showed an unmodified intrasellar lesion and the PRL value was 18.1 ng/ml. Follow-up at 36 months showed that the patient is still in good health, with normal BP, plasma electrolytes and renin-angiotensin-aldosterone system (RAAS) markers.

Discussion

Primary aldosteronism is characterised by the autonomous overproduction of adrenal aldosterone with suppression of PRA, sodium retention and consequent hypertension and hypokalaemia. Various primary adrenal pathological processes cause this syndrome: some of them are best treated by surgery (such as aldosterone-producing adenoma), and others by medical treatment (such as bilateral hyperplasia).

Three principle considerations can be derived from this case report:

1. the association of an aldosterone-producing adenoma and myelolipoma;
2. the aldosterone-secreting adrenal adenoma at part of a MEN;
3. the involvement of RB tumour suppress gene in the pathogenesis of tumours.

As to the first point, myelolipomas are rare benign mesenchymal tumours or tumour-like lesions, composed of mature adipose tissue and haematopoietic cells in various proportions.[12] These lesions are most frequently located in the adrenal gland, but may also occur as isolated soft tissue masses in various sites, especially in the pelvic region.[16] Most cases occur in patients between 40 and 70 years; when the myelolipoma is large, the most common symptom is non-specific abdominal pain. However, in exceptional cases, adrenal myelolipomas have been diagnosed

because of their association with different endocrine adrenal disorders. These are usually the result of coexisting adrenal tumours or adrenal gland hyperplasia and include Cushing's syndrome, congenital 21-hydroxylase deficiency[17-22] and a case of pheochromocytoma.[23] This association led some authors to consider this tumour as a component of variant MEN.[24]

In the reported case, the myelolipoma was not discovered preoperatively and may represent an incidental finding at pathological examination. To our knowledge, the concomitant occurrence of primary aldosteronism and adrenal myelolipoma has been documented only in two previous cases with adrenal adenoma[13,14] and in one case with adrenocortical hyperplasia.[25]

Extra-adrenal endocrine dysfunction has been reported with myelolipomas, with rare cases of pituitary Cushing's disease,[20] adrenogenital syndrome associated with an interstitial tumour of the testis[26] and a case of hyperparathyroidism due to a parathyroid adenoma.[27] Moreover, myelolipomas are associated with extra-adrenal pathology, including different types of cancer such as oesophageal,[22] renal,[28] endometrial,[29] breast,[30] gastric[31] and small-cell lung cancer.[32]

The exact pathogenesis of adrenal myelolipoma is unknown, but it appears plausible that multiple factors, including hormonal stimulation are involved. A large number of theories have been proposed, including: ectopia of myeloid tissue, embolism of bone marrow elements, hamartosis, metaplasia, degeneration of cortical cells and haematopoietic proliferation of substances formed by tumour necrosis.[33] Some researchers[14] hypothesised that the association of adrenalcortical adenoma and myelolipoma in Conn's syndrome may be entirely coincidental and that corticotropin stimulation (since aldosterone-producing adenomas are partially corticotropin-dependent) may be involved in the pathogenesis of myelolipoma. This pathogenetic hypothesis is, in part, supported by experimental studies by Seyle and Stone,[34] who reported that crude anterior pituitary extracts, rich in corticotropin, caused marked myelopoiesis when injected into the adrenal cortex of rats.

As to the second point, aldosterone-secreting adrenal lesions are quite rarely associated with endocrinopathies[7-10,35] and some cases were diagnosed as MEN.[36-39] In particular, Beckers *et al*.[11] reported a female MEN1 patient with the exceptional association of hyperparathyroidism, elevated serum pancreatic polypeptide (PP) levels, hyperprolactinaemia, hyperthyroidism and hyperaldosteronism with loss of heterozygosity (LOH) for polymorphic chromosome 11 DNA markers, including those in the region of the MEN 1 locus (11q13 region).

A tumour lesion of an endocrine organ is sometimes associated with tumours in other endocrine organs and/or in non-endocrine organs. In particular, in MEN (type 1 and type 2A or 2B) and in familial occurrence of the two or more endocrine neoplastic disorders, neurofibromatosis type 1 or Von Hippel-Lindau disease, the pathogenesis has been intensively studied and the genetic defects have been revealed.[40]

In the present case, we reported a patient with an aldosterone-producing adenoma coexisting with myelolipoma, pituitary microadenoma, multiple lipomas and a previously resected thyroid adenoma. This case may be considered a variant form of MEN, since the patient presented with more than two endocrine tumours.

In addition, our patient presents a mutant RB allele that causes low-penetrance RB.[15] The RB gene is the protolyse for a class of recessive human cancer genes in which loss of activity of both normal alleles is thought to be associated with tumorogenesis.[41]

The two-step mechanism of RB gene inactivation in RB, proposed by Knudsen,[42] has been accorded almost universal acceptance as the general process by which tumour suppressor genes are affected in tumorogenesis. Functional inactivation of the RB gene, plays an important role in the pathogenesis of many malignant[43] and benign[44] tumours. Therefore, we speculate that structural alterations of the RB gene may have played a role in the tumorogenesis in this patient.

In conclusion, the association of an adrenal cortical aldosteronoma coexisting with myelolipoma, pituitary microadenoma, thyroid toxic adenoma and multiple lipomas is unique. We believe that this case probably represents another variant of the MEN syndrome.

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