J. Endocrinol. Invest. *25:* 53-57, 2002

CASE REPORT

Unusual clinical manifestation of pheochromocytoma in a MEN2A patient

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ABSTRACT. A case of unusual clinical manifestation of pheochromocytoma in a type 2A multiple endocrine neoplasia (MEN2A) patient is presented. A 27-year-old man affected by MEN2A syndrome, complaining of anxiety and depression, was admitted in our Division. Past medical history included a total thyroidectomy for medullary carcinoma in 1985, and left adrenalectomy for pheochromocytoma in 1994. Blood pressure was 130/85 mmHg without orthostatic hypotension and pulse rate was 72 beats/min. Laboratory data revealed thyroid hormones and carcinoembryonic antigen (CEA) in the normal range and high basal serum calcitonin levels (158 pg/ml). Plasma catecholamines and vanillylmandelic acid resulted in normal levels but epinephrine/norepinephrine ratio was elevated (0.65). The glucagon stimulation test showed positive clinical and biochemical response. Magnetic resonance imaging (MRI) and meta-iodobenzylguanidine (MIBG) scintiscan confirmed the presence of bilateral adrenal masses. Bilateral adrenalectomy by laparoscopic anterior approach was performed. Histology was consistent with adrenal pheochromocytomas. After surgical approach, psychiatric findings disappeared and did not recur at follow-up in spite of no medication for two years. In conclusion, bilateral pheochromocytoma is more frequent in MEN2A syndrome and probably understimated if the follow-up is not prolonged. In these cases clinical features are often aspecific and basal hormonal data may be normal in a great number of patients. Therefore long-term observation is justified in these patients. Pheochromocytoma was described as the "great mimic" for the numerous subjective manifestations. Differential diagnosis among typical features of neuropsychiatric disorders and pheochromocytoma must be considered.

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INTRODUCTION

Pheochromocytoma is a catecholamine secreting tumor, sporadic in 90% of cases and inherited in 10%. When it occurs in families, such as type 2A and 2B multiple endocrine neoplasia (MEN2A, 2B), Von Hippel-Lindau (VHL) syndrome, about 50% is bilateral and usually intra-adrenal (1).

Clinical features of pheochromocytoma are paroxysmal or sustained hypertension, headache, sweating, palpitations and skin pallor.

In this report, we describe a patient affected by MEN2A syndrome exhibiting a bilateral pheochromocytoma with unusual clinical manifestations and normal plasma and urinary catecholamines levels.

Key-words: Pheochromocytoma, MEN2A syndrome, psychiatric disease, laparoscopic adrenalectomy.

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Accepted February 14, 2001.

CASE REPORT

A 27-year-old man affected by MEN2A syndrome was first admitted to our Division in November 1996 complaining of state of anxiety and depression he had developed over the previous 10 months. This young patient showed persistent anxiety manifested by motor tension, vigilance, fidgeting, restlessne, sweating, dizziness; depression was accompanied by a constricting-type headache. In December 1995 he was already hospitalized in Neurological Division and discharged with diagnosis of psychotic persecution syndrome, subsequently he was treated with haloperidol (1 mg/day) for 9 months without improvement.

Table 1 - *Glucagon stimulation test before bilateral adrenalectomy.*

	Heart rate (beats/min)	Blood pressure (mmHg)	Plasma epinephrine (pg/ml)	Plasma norepinephrine (pg/ml)
Basal	68	120/80	50	118
3 min (peak)	100	190/100	1755	638

Normal basal levels: plasma epinephrine: 20-60 pg/ml; plasma norepinephrine: 135-300 pg/ml.

No psychiatric diseases were present in his relatives.

Past medical history included a total thyroidectomy for medullary carcinoma in 1985, and left adrenalectomy for pheochromocytoma in 1994. The patient, characteristically, complained of sweating, skin pallor and palpitations before adrenalectomy; laboratory data showed high levels of 24-h catecholamines and vanillylmandelic acid (VMA). Palpitations and sweating crisis were associated with elevated levels of plasma catecholamines.

Since 1985, the patient was taking 200 mg/day L-T_4 and 0.5 µg/day vitamin D_3 for hypothyrodism and iatrogenic hypocalcemia. No medical replacement therapy after left adrenalectomy was needed.

In 1996, during hospitalization in our Division the diagnosis of MEN2A syndrome by direct analysis of genomic DNA with restriction enzymes digestion was confirmed. This methodology showed the presence of RET proto-oncogene point mutation at codon 634 of exon 11 which results with substitution of cysteine to tyrosine.

Physical examination did not show any alterations: blood pressure was 130/85 mmHg without orthostatic hypotension and pulse rate was 72 beats/min. Laboratory data revealed TSH, free T_4, free T_3 and carcinoembryonic antigen (CEA) in the normal range and high basal serum calcitonin levels (158 pg/ml). Plasma catecholamines and VMA resulted in normal levels (mean values: epinephrine 17.3 µg/day, norepinephrine 26 µg/day and VMA 1.5 mg/day) but epinephrine/ norepinephrine ratio was elevated (0.65) (2).

The glucagon stimulation test was performed in the morning after overnight fasting. Before glucagon injection the patient's heart rate was 68 beats/min and blood pressure was 120/80 mmHg. Three minutes after 1 mg glucagon iv administration as a bolus, blood pressure and heart rate were increased, 190/100 mmHg and 100 beats/min, respectively. Plasma norepinephrine increased 6-fold (118 to 638 pg/ml) while epinephrine rose 30-fold (50 to 1755 pg/ml) at the same time (Table 1).

Subsequently he underwent abdominal magnetic resonance imaging (MRI) which showed a nodule of 1.5 cm in right adrenal and another mass of 1.7 cm in the left adrenal gland (Fig. 1). Both lesions showed hyperintense signal on the T2 setting. ^{131}I meta-iodobenzylguanidine (MIBG) scintiscan confirmed bilateral pathological uptake.

Since serum calcitonin was increased, the patient underwent octreoscan which did not reveal any lesion; on the other hand ^{99}Tc dimercaptosuccinate acid (DMSA) scintiscan demonstrated abnormal trapping on the neck and in the upper left mediastin. Neck ultrasonography, cervical and thoracic

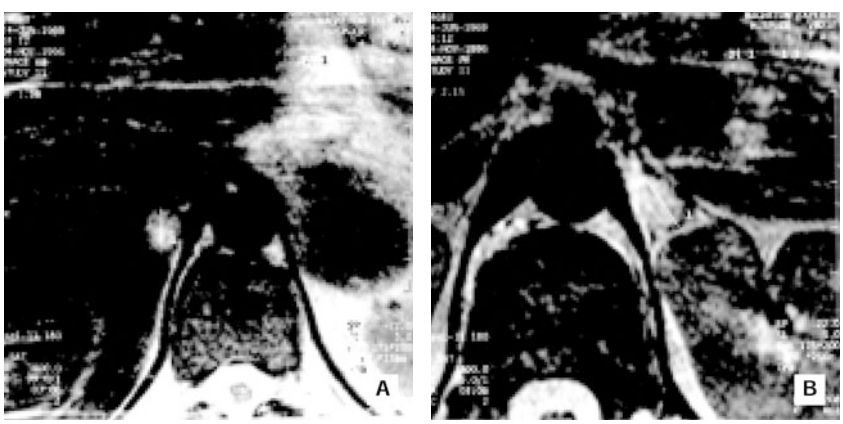

Fig. 1A, 1B - *Magnetic resonance images, demonstrating a nodule of 1.5 cm on the right adrenal gland and a mass of 1.7 cm on the left.*

computed tomography (CT) did not show pathological masses or lymph nodes enlargement. Hepatic ultrasonography, abdominal CT and traditional bone ^{99}Tc scintiscan excluded distant metastases.
In January 1997, after brief medical treatment with α blockers (doxazosin 2 mg/day), bilateral adrenalectomy by laparoscopic anterior approach was performed (3, 4). Histological studies were consistent with adrenal pheochromocytoma. Post-surgical recovery was uneventful and the patient was discharged in second post-operative day. One month after surgery, biochemical evaluations revealed normal excretion of catecholamines, VMA and CEA, with persistent high calcitonin levels.
After the removal of the adrenal glands psychiatric findings, consisting of anxiety and depression, disappeared; therefore the disorders were interpreted as being directly related to the tumor.
A second follow-up was performed in June 1998: physical state was good; blood pressure was 120/70 mmHg and pulse rate was 80 beats/min. Laboratory data revealed serum electrolytes, 24-h urinary catecholamines and VMA, TSH, free T_4, free T_3 and CEA in the normal range but persistent high basal serum calcitonin levels (434 pg/ml). Neck and abdominal ultrasonography did not show lymph nodes enlargement and excluded distant metastases. DMSA scintiscan total body and traditional bone Tc 99 scintiscan did not reveal pathological trapping. Thoracic and abdominal CT did not show pathological masses.
Psychiatric disorders did not recur and the patient did not need to take any drugs except substitution therapy (L-T_4, vitamin D_3, fluorohydrocortisone and cortisone acetate).

DISCUSSION

MEN2A is an autosomal dominant genetic syndrome characterized by the presence of medullary thyroid carcinoma in 100%, pheochromocytoma in 50% and hyperparathyroidism in 30% of cases. Bilateral adrenal medullary involvement is present in about 50% of MEN2A patients, but it is probably understimated; the discovery is more frequent when the follow-up is prolonged (5, 6).
Two years after the first left adrenalectomy, our patient showed a pheochromocytoma on the right adrenal and a relapse on the left side. During the last year he complained of psychotic persecution attacks without the characteristic symptoms of pheochromocytoma such as hypertension, palpitations, skin pallor. During his recovery in Neurological Division the urinary catecholamines levels resulted in normal range; no functional tests neither radiological examinations were performed in search of an adrenomedullary tumor.
After 10 months, when the patient was admitted to our Division, he complained only anxiety and depression. Three subsequent 24-h measurements of urinary catecholamines and VMA levels resulted again in the normal range while epinephrine/norepinephrine ratio resulted elevated (2). The latter pattern is very commonly seen in MEN2-associated pheochromocytoma; therefore the patient did undergo dynamic biochemical evaluations. A stimulation glucagon test was performed: in spite of high specificity but low sensitivity of this test in pheochromocytoma (respectively 100% and 81%) (7), in our patient, positive clinical and biochemical response permitted diagnosis of secreting tumor. MRI and MIBG scintiscan confirmed the presence of bilateral adrenal masses.
In this case the anxiety, the depression and probably the previous psychotic attacks were the only manifestations of pheochromocytoma. These symptoms remitted after surgery and did not recur (in spite of no medication for two years), suggesting the relationship between the tumor and the psychiatric manifestations. The psychiatric disorders, in fact, did not improve when the patient assumed haloperidol.
The mechanism of psychiatric disturbances is not clearly understood; it is presumed that mental changes observed in patients with pheochromocytoma resulted either from a direct action of catecholamines on cerebral tissue or from the changes secondary to blood pressure variations (8). The similarities between the anxiety state observed in patients with pheochromocytoma and those with "pseudo-pheochromocytoma" were noted by several Authors (9-12).
Pheochromocytoma was described as the "great mimic" for the numerous subjective manifestations. Differential diagnosis among typical features of neuropsychiatric disorders and pheochromocytoma, especially in patients affected by familiar disease, must be considered (13).
Personality, psychiatric aspects, psychologic adaptation in cancer patients were extensively studied. Some authors reported a comparable frequency of depression, anxiety, psychosis, delirium in cancer and medical patients (14, 15). In breast cancer patients adaptation to illness depends on several parameters: psychologic adjustment that the patient had before illness, the social support, the spouse, the extent of spread, surgical operability, the doctor-patient relationship etc. An optimal readapta-

tion and psychologic well-being despite illness is in relation to each variable (16).
In spite of the frequent biochemical and radiological evaluations, after surgical adrenalectomy, our patient did not show psychiatric symptomatology anymore. The absence of psychiatric aspects in the relatives of this patient affected by MEN2A, and moreover the disappearance and the absence of recurrence of psychotic attacks after surgery, strongly suggest that psychiatric symptoms were unusual clinical manifestation of pheochromocytoma instead of a psychological pattern of MEN2A families.
Laparoscopic bilateral adrenalectomy was a safe and minimally invasive approach without perioperative complications (17).
The persistence of hypercalcitoninemia up to 11 years after total thyroidectomy for medullary carcinoma, remained an open clinical problem. In 2 follow-up observations, radiological exams were negative (18, 19), so, in absence of overt clinical disease, a periodic follow-up has been considered as mandatory (20, 21).
In conclusion, bilateral pheochromocytoma is more frequent in MEN2A syndrome and probably understimated if the follow-up is not prolonged. In these cases clinical features are often aspecific and basal hormonal evaluation (plasma and urinary catecholamines) may be normal in the great number of patients. Recently some authors demonstrated that measurements of plasma normetanephrine and metanephrine are useful in screening for detecting pheochromocytoma (22). Therefore long-term observation is justified in these patients: epinephrine/norepinephrine ratio in 24-h collection and eventually glucagon test should be taken into account.
Therefore, this report reminds the clinicians that a pheochromocytoma can be confused with neuropsychiatric disorders in adults as well as in children (23-25) and that it should be considered in the differential diagnosis of such illnesses.

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