Clinical case

Unusual presentation of multiple endocrine neoplasia type 2A in a patient with the C634R mutation of the \textit{RET}-protooncogene

Présentation inhabituelle d’une néoplasie endocrinienne multiple type 2A chez une patiente porteuse de la mutation C634R du proto-oncogène \textit{RET}

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Résumé

Le but de ce travail est de rapporter une présentation atypique d’une NEM 2A, chez une patiente présentant une mutation C634R du proto-oncogène \textit{RET}. Il s’agit d’une femme, âgée de 41 ans, admise en raison d’une hyperglycémie récente. Elle avait, dans ses antécédents, une lithiase rénale bilatérale récidivante, opérée à deux reprises. L’examen physique a trouvé un nodule thyroïdien gauche dur de 1 cm. L’exploration biologique et l’imagerie ont confirmé le diagnostic d’hyperparathyroïdie primaire. La cervicotomie a retrouvé l’adénome parathyroïdien et le nodule thyroïdien était suspect. Une thyroïdectomie totale et un curage ganglionnaire approprié ont été réalisés. L’examen anatomopathologique a confirmé le diagnostic d’adénome parathyroïdien et a révélé un carcinome médullaire, bilatéral et multifocal. Ces constats ont conduit au diagnostic de néoplasie endocrinienne multiple type 2A. L’étude génétique a mis en évidence une mutation sur le codon 634 du proto-oncogène \textit{RET}. Au cours du suivi postopératoire, la pression artérielle ainsi que le taux des dérivés méthoxylés urinaires ont augmenté progressivement. Les données de l’imagerie étaient compatibles avec le diagnostic de phéochromocytome bilatéral. En conclusion, ce cas clinique de NEM2 lié à une mutation du codon 634 du gène \textit{RET} est particulier par son mode de révélation : (1) une hyperparathyroïdie, qui plus est, est liée à un adénome ; (2) un diabète dont les mécanismes sont probablement multifactoriels (héritéité familiale de diabète de type 2, hypercalcémie, excès de catécholamines).

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Abstract

The aim of this paper is to report an atypical presentation of MEN2A, in a patient carrying the C634R mutation of the \textit{RET}-protooncogene. A 41-year-old Tunisian woman was admitted to our department with newly diagnosed hyperglycemia. She had a history of bilateral urinary stone recurrence, managed successfully on two occasions. On physical examination a thyroid nodule of 1 cm on the left side was found. Laboratory evaluation and imaging findings confirmed the diagnosis of primary hyperparathyroidism. During cervicotomy, the parathyroid adenoma was resected and the thyroid node was suspected to be a carcinoma. Total thyroidectomy, with appropriate neck nodal resection, was performed. Histological examination confirmed the diagnosis of parathyroid adenoma and revealed a multifocal and bilateral medullary carcinoma. These findings led to the diagnosis of multiple endocrine neoplasia. DNA-analysis demonstrated a germline Cys634Arg mutation in the \textit{RET}-protooncogene. During the postoperative follow-up, blood pressure as well as the level of urinary methoxylated metabolites increased progressively. Imaging findings were compatible with the diagnosis of bilateral pheochromocytoma. In conclusion, this case report of MEN 2A linked to a 634 \textit{RET} mutation was peculiar by its revelation mode (1) hyperparathyroidism moreover linked to an adenoma and (2) associated with diabetes, mechanisms of which are probably multifactorial (familial type 2 diabetes, hypercalcemia, catecholamines excess).

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1. Introduction

Multiple endocrine neoplasia type 2A (MEN 2A) is an autosomal dominant inherited disease, which associates medullary thyroid carcinoma with pheochromocytoma and primary hyperparathyroidism. It is caused by activating germline mutation in the RET-protooncogene.

Medullary thyroid carcinoma is usually the first tumor diagnosed in almost all affected individuals; however pheochromocytoma occurs in about 20–50% and primary hyperparathyroidism in 5–20% of cases [1].

Clinical features and the expression of this disease may be influenced by some factors, particularly the age and the nature of mutation [2].

MEN 2A, like other syndromes of familial endocrine neoplasia is still underdiagnosed, or late-diagnosed in many areas of the world.

Although register-based studies have already indicated that primary hyperparathyroidism may be the first component revealing a MEN2A [2], no case report on this topic has been published yet.

The aim of this paper is to report an atypical presentation of MEN2A in a patient carrying the C634R mutation of the RET-protooncogene.

2. Case report

A 41-year-old Tunisian woman was admitted to our department with newly diagnosed hyperglycemia. She had a history of bilateral urinary stone recurrence, which was managed successfully on two occasions. She complained of weight loss, polyuria and polydipsia. The patient’s family history was notable for the presence of type 2 diabetes in her mother and thyroid surgery in one sister.

On physical examination, blood pressure was 11/7 cmHg, BMI 17.2 kg/m² and a thyroid node (moving with deglutition) of 1 cm on the left side was found. Thyroid size was normal and no compression symptoms or abnormal cervical lymph nodes were noted. There were no features of Cushing’s syndrome or other endocrinopathies.

Laboratory tests revealed a hyperglycemia (> 4 g/l), hypercalcemia (from 110 to 118 mg/l) and hypophosphoremia (from 21 to 28 mg/l). Calcium was 250 mg/24 h and kaliemia 4.4 mmol/l. The diagnosis of primary hyperparathyroidism was confirmed regarding a PTH level of 2498 pg/ml and normal kidney function (creatinine 8 mg/l). Thyroid function tests were normal with a TSH level of 1.2 mUI/l, a FT4 level of 1.05 ng/dl and no anti antithyroperoxydase antibody detected. HbA1c level was 13.5% and the initial antidiabetic treatment prescribed was insulinotherapy.

Cervical ultrasound examination showed a normal thyroid size, with two nodes (9.5 and 5.5 mm) in the left side and a 29 mm solid mass in the inferior left parathyroid gland, which was confirmed by MIBI scintigraphy.

Needle aspiration biopsy was refused by the patient. Surgery was indicated and during the cervicotomy, the parathyroid adenoma was resected and the thyroid node was suspected to be a carcinoma. Total thyroidectomy, with appropriate neck nodal exploration and resection, was performed. The other parathyroid glands were normal.

Histological examination confirmed the diagnosis of parathyroid adenoma and revealed a multifocal and bilateral medullary carcinoma, with calcitonin positivity in the tumor cells and without lymph node metastases. These findings led to the diagnosis of multiple endocrine neoplasia. Calcitonin level, performed after thyroidectomy, using immunoradiometric assay (Nichols Institute, San Juan Capistrano, CA), was in the upper limit of the normal range (10 ng/l). Calcemia fell to a mean level of about 75 mg/l, without needing any treatment.

DNA-analysis demonstrated a germline Cys634Arg mutation in the RET-protooncogene on chromosome 10 q11.2.

During the postoperative follow-up, blood pressure increased progressively from a mean of 11/7 cmHg to 17/10 cmHg and the level of urinary methoxylated metabolites raised from 1.15 to 3.55 mg/24 h.

Abdominal tomodensitometry showed initially two large adrenal glands, confirmed by magnetic resonance imaging, performed some months later. There was no pancreatic mass revealed on the two examinations.

Finally, preoperative MIBG scintigraphy showed bilateral accumulation in both adrenal glands.

Subtotal adrenalectomy was followed by a decrease of blood pressure to the initial normal level. Blood glucose level reached 1.30 g/l and HbA1c 6.6%, without any medication, after having remained elevated (HbA1c between 7.3 and 9.2%) and being treated with oral agents after thyroidectomy.

The diagnosis of bilateral pheochromocytoma was confirmed by histological findings.

3. Discussion

The peculiarities of our observation are mainly linked to the discovery of the MEN 2A syndrome as in actual fact, newly diagnosed diabetes with high hyperglycemia was the reason for admission in our department.

Although symptomatic kidney stone had been identified several years earlier, the diagnosis of hyperparathyroidism was delayed. It seems that this disease is still underdiagnosed in such conditions, particularly in young patients, probably because isolated primary hyperparathyroidism is usually discovered in the sixth decade [3]. Clinical features vary according to patient characteristics and the risk of kidney stone is increased in males and young patients [4].

The relationship between diabetes and hyperparathyroidism is a matter of debate; in fact, endogenous calcium may be involved in the development of diabetes and this effect is mediated mainly through effects on insulin sensitivity rather than on insulin secretion [5,6]. Chronic pancreatitis due to hyperparathyroidism may lead to diabetes [7] but this hypothesis seems to be unlikely in our case, considering the absence of clinical and biological manifestations. In the context of our patient, diabetes may be type 2 considering the family history, or secondary to catecholamine hypersecretion [8], related...
to adrenal medullary hyperplasia, although blood pressure was normal without any specific symptoms [9]. Weight loss may be related to insulinopenia, induced by type 1 diabetes but more probably to neoplasia, hypercalcemia and catecholamine hypersecretion. Only longer-term follow-up of this patient, who did not require insulin after surgical intervention, will clarify the type of diabetes, which may be a result of the interaction of more than one mechanism. Improvement of blood glucose level is expected and observed after suppression of catecholamine secretion, even when diabetes is linked to autoimmune insulinopenia [10,11].

In MEN 2A, hyperparathyroidism is rarely the presenting feature and it is characterized by a mild hypercalcemia, which is usually asymptomatic [12]. However, in our case study, primary hyperparathyroidism was associated with a complication, namely a kidney stone, which was present in about 15% of patients with MEN 2A-related hyperparathyroidism in a European study [12]. As MEN is a general disease, it is expected that all parathyroid glands may be involved. However, the disease may be cured by simple resection of an enlarged parathyroid gland in some cases [12]. Our patient had only one adenoma, but the possibility of total parathyroidectomy could not be excluded, considering the extensive surgery undertaken. When hyperparathyroidism is the revealing feature of MEN, as in our reported case, the risk of surgery complications may be increased by the presence of undiagnosed pheochromocytoma.

Although pheochromocytoma or primary hyperparathyroidism may reveal the disease, they are nearly always systematically associated with undiagnosed medullary carcinoma [1].

Germline mutations in MEN 2A syndromes have been described in seven exons [8,10,11,13–16] of the RET protooncogene [13]. Mutation of codon 634 (exon 11) constitutes 80–90% of causes of MEN 2A, and it is the most common mutation associated with pheochromocytoma [14,15].

Despite the absence of a significant association between a particular mutation and the familial risk for hyperparathyroidism, the prevalence among families with a C634R mutation was slightly higher than in families with other mutations of codon 634 [16]. However, in patients with C634R, the penetrance of hyperparathyroidism is significantly related to age, increasing more than in patients carrying other mutations. In fact, the risk increases from 14% by age 30 to 48% by age 60 [2].

Medullary thyroid carcinoma in patients with MEN may have different presentations, from C-cell hyperplasia to multiple and bilateral carcinoma. Despite the presence of a thyroid node, our patient did not complain of any specific symptom.

Follow-up of our patient revealed the spontaneous progression of asymptomatic adrenal medullary hyperplasia to concomitant bilateral pheochromocytoma, which develops in less than 10% of patients with C634R mutation [17].

Our case illustrates the complete expression of MEN 2A syndrome and underlines the severity of C634R mutation, with a high penetrance of hyperparathyroidism and pheochromocytoma. Although primary hyperparathyroidism is rarely a component of type 2 multiple endocrine neoplasia, the discovery of a thyroid node in a young patient should lead to calcitonin and urinary methoxyflurane metabolite assessments.

References