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Clinical and Genetic Particularities in a Case with a Novel Mutation of MEN1 Gene

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Abstract

Primary hyperparathyroidism is a common endocrinological disorder. In rare circumstances, it is associated with familial syndromes, such as multiple endocrine neoplasia type 1. In this context, we report our case. The patient was a 48-year-old female with a hypocalcemia, which was discovered incidentally after total thyroidectomy. It was secondary to multiple parathyroid adenomas, which were mistakenly considered as nodular thyroid tissue both preoperatively, and peroperatively. This severe and symptomatic hypocalcemia was secondary to iatrogenic hypoparathyroidism and aggravated by Hungry Bone Syndrome. The family history of our patient led us to run a genetic study. It confirmed a MEN1 syndrome with a new mutation not previously described in the literature. The diagnosis of MEN1-associated PHPT should be confirmed by genetic testing. Early detection of the disease and correct treatment are therefore of great importance.

Keywords: Hypocalcemia; Primary hyperparathyroidism; Multiple endocrine neoplasia 1.

Introduction

Primary Hyperparathyroidism (PHPT) is a common endocrinologicaldisorder. In rare circumstances, it is associated with familial syndromes, such as Multiple Endocrine Neoplasia Type 1 (MEN1). This syndrome is caused by a germline mutation in the multiple endocrine neoplasia type 1 gene encoding the tumor-suppressor protein menin [1]. Usually, PHPT is the initial clinical expression in carriers of MEN 1 mutations, occurring in more than 90% of patients and appearing at a young age (20-25 years) [2]. MEN1/PHPT is generally accompanied by multiglandular disease, clinically manifesting with hypercalcemia, although it can remain asymptomatic for a long time and consequently not always be recognized early [3]. This leads to a delay in diagnosis and treatment. In this context, we report our case.

Case presentation

A 48-year-old female patient was admitted to our department in July 2016 for a post-thyroidectomy severe hypocalcemia, which was refractory to substitutive therapy. As for her family history, we noted a brother and a sister known and followed in our department for MEN1. The patient had hypothyroidism since 2011. During her follow-up, a right cervical tumefaction was noted. A neck ultrasound showed a suspicious right lobar nodule measuring 4 cm and a right jugulo-carotid adenopathy measuring 2 cm. Calcitonin was within normal range (<0.5 pg/ml). A right lobo-isthmectomy was first performed with an extemporaneous examination: a benign nodule but a lymphadenopathy suggesting a metastasis and leading to a totalization with a left recurrent curage. Surprisingly, the definitive

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anatomopathological study showed 5 parathyroid adenomas, the biggest one measured 6 cm. Paradoxically, there is no thyroid tissue. One week after the operation, the patient presented a severe and symptomatic hypocalcemia at 1.12 mmol/l associated with a hyperphosphatemia at 1.56 mmol/l. The evolution was marked by the persistence of hypocalcemia despite vitamin calcic substitution (Table n°1). The PTH measured on the 7th day after surgery was 10.9 pg/ml. Thus, the patient was referred tour department. Clinically and biologically, the patient had a favourable evolution with normalization of the calcium levels under oral and parenteral vitaminocalcic supplementation (Table n°1).Considering the surgical history of the patient (absence of thyroid tissue on the operative pieces) a complementary thyroid SPECT/CT was indicated in search of a thyroid ectopy or residual thyroid tissue. It showed minimal fixation projecting to the right paramedian thyroid cartilage that could correspond to thyroid tissue. Furthermore, the scan did not show any other visible thyroid location (Figure 1).

Owing to the young age of our patient and especially to the family background, a MEN1 was highly suspected. The screening for other endocrine tumors was negative. The genetic study confirmed the diagnosis by identifying a new missense mutation, not described in the literature, most likely pathogenic at exon 4 of the MEN1 gene in the heterozygous state. The analysis of the other exons did not show any defects (Figure 2).

Table 1: Postoperative biological assessment.

	D1 post-op	D2 post-op	D7 post-op	2 Months post op	In our departement
Calcium (mmol/l)	2.54	2.05	1.12	1.65	2.14
Phosphate (mmol/l)	---	---	1.56	1.5	1.6
PTH (pg/ml)	---	---	10.9	---	---
TSH (mU/l)	---	---	>100	88.66	---

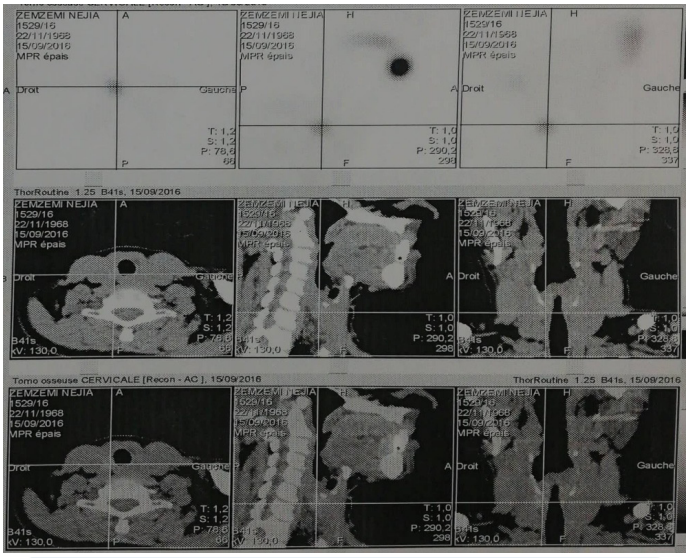

Figure 1: ThyroidSPECT/CT.

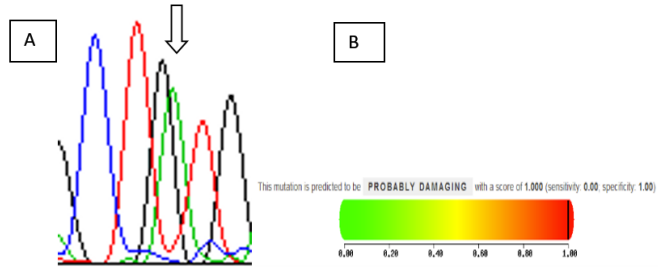

Figure 2: The electrophoretic profile of the identified mutation **(A)** and the prediction profile of its pathogenicity **(B)**.

Discussion

PHPT is a condition caused by hyperfunction of the parathyroid tissue, usually involving only one gland. However, it is often multiglandular when expressed within complex hereditary syndromes, such as MEN1 [4]. PHPT in MEN1 is the most common form of endocrinopathy. It represents 2-4% of all forms of PHPT. It is amoung the first endocrine manifestation in most patients. All individuals are affected by the age of 50 [5]. Our patient had a late diagnosis. The occurrence of hyperparathyroidism at a young age carries a high suspicion of MEN1 syndrome, supported by family history, as in our patient's case, and an association with other endocrinopathies typical of MEN1 syndrome [6]. Preclinical diagnosis of MEN1 gene mutations should be offered to all patients with suspected genetic disease [7]. More than 700 different germline and somatic mutations in the MEN1 gene locus have been reported since its cloning in 1997 [8,9]. The majority of MEN1 mutations lead to a truncated protein lacking the nuclear localization signals. Whereas, some mutations (missense mutations) affect the function of critical amino acid residues in menin, reduce its stability, or enhance its degradation [10]. The genetic study of our patient confirmed the diagnosis by identifying a new missense mutation, not described in the literature, most likely pathogenic at exon 4 of the MEN1 gene in the heterozygous state.

Generally, a multiglandular disease causes PHPT and the parathyroid glands can become hyperplastic or develop adenomas. The growth of the glands is asynchronous and asymmetric [11]. As each gland is considered to be a monoclonal lesion in which the germline mutation in the MEN1 gene confers on the parathyroid tissue a high susceptibility for the development of a tumor after the second somatic mutation [12,13]. Morphologically, parathyroid glands in MEN1 may appear macroscopically normal, also because they can differ in terms of volume, weight, and size [11]. Our patient had multiple parathyroid adenomas, which were mistakenly considered as nodular thyroid tissue both preoperatively and preoperatively. The diagnosis was ajusted by the anatomopathological examination. Regarding the management of PHPT, surgery is the recommended treatment as it reduces the risk of kidney stones, fractures, improves bone mineral density, and potential cardiovascular morbidity. It also improves quality of life and reduces gastrin production in MEN1 patients who have a gastrinoma [14,15]. The optimal surgical approach in PHPT in MEN1 is still under discussion. The choice being between: subtotal parathyroidectomy with removal of at least three to three and a half glands; and total parathyroidectomy with removal of all parathyroid glands and autologous parathyroid tissue graft [16].

Conclusion

This is a case of hypocalcemia discovered incidentally after total thyroidectomy, secondary to multiple parathyroid adenomas, which were mistakenly considered as nodular thyroid tissue both preoperatively, and peroperatively. This severe and symptomatic hypocalcemia was secondary to iatrogenic hypoparathyroidism and aggravated by Hungry Bone Syndrome. The family history of our patient led us to run a genetic study confirming MEN1 syndrome with a new mutation not previously described in the literature. The diagnosis of MEN1-associated PHPT should be confirmed by genetic testing. Early detection of the disease and correct treatment are therefore of great importance.

Consent

Written informed consent was obtained from the patient andis available for review.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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