

Synchronous medullar thyroid cancer and primary hyperparathyroidism on a female within the sixth decade of life with positive family history for type 2A MEN syndrome

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ABSTRACT

Medullar thyroid cancer (MTC) may be sporadic or familial, either linked with pheochromocytoma (PHEO) and primary hyperparathyroidism (PHP), as seen in type 2A MEN (Multiple Endocrine Neoplasia) syndrome, either isolated.

This is a 56-year old female known with mild arterial hypertension controlled under therapy, having a daughter with type 2A MEN syndrome (PHEO, MTC, PHP). Mild hypercalcemia and high parathormone were consistent for PHP, while calcitonin was 20 times above the upper normal limit for MTC. The PHEO tests were negative. Anterior cervical ultrasound confirmed a 2.7 cm thyroid nodule, local lymph nodes, and enlargement of inferior and superior left parathyroids. After total thyroidectomy with bilateral neck dissection and excision of the left inferior and superior parathyroid glands, MTC and parathyroid hyperplasia was confirmed. Calcitonin decreased to 5 times above the normal level. Further close follow-up and therapy of residual MTC is needed.

MEN 2A Syndrome may embrace various clinical presentations with more or less aggressive tumours, sometimes allowing a long time survival without neoplasia confirmation or incomplete phenotype until advanced age.

Keywords: medullar thyroid cancer, primary hyperparathyroidism, MEN syndrome

LIST OF ABBREVIATIONS

mm = millimetre; ACE = angiotensin-converting-enzyme; DXA = Dual-Energy X-Ray Absorptiometry; FT4 = free levothyroxine; MTC = Medullar Thyroid Cancer; MEN = Multiple Endocrine Neoplasia; PHEO = pheochromocytoma; PHP = primary hyperparathyroidism; PTH = parathyroid hormone; RET = REarranged during Transfection; TSH = Thyroid Stimulating Hormone; TPO = antithyroperoxidase antibodies; US = ultrasound

INTRODUCTION

Medullar thyroid cancer (MTC) may be sporadic or familial, either linked with pheochromocytoma (PHEO) and primary hyperparathyroidism (PHP) as seen in type 2A MEN (Multiple Endocrine Neoplasia) syndrome, or isolated (1,2). Once the RET (REarranged during Transfection) mutation is positive, there is a time-dependent pattern of tumours' onset, knowing that phenotype and age at diagnosis are tidily connected with the mutation itself (2,3,4). MTC

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and then PHEO are the most frequent neoplasia in MEN 2A syndrome, opposite to PHP (3,4). We aim to introduce an adult female case having a late recognition of the syndrome despite relevant family history and displaying a particular clinical presentation with positive HPT before PHEO confirmation.

CASE PRESENTATION

We report the case of a 56-year old non-smoking female who was admitted in the Department of Endocrinology in March 2016 for polyuria, polydipsia and intermittent headache. The patient had a history of grade I arterial hypertension, adequately controlled with ACE (angiotensin-converting-enzyme) inhibitors. The patient's daughter had been diagnosed with type 2A MEN syndrome based on PHEO, MTC plus PHP (no RET test was available, though).

On admission, the physical exam revealed grade I obesity, heart rate of 68 beats per minute, blood pressure 110/70 mmHg, without orthostatic hypotension. Laboratory tests found mild hypercalcemia and elevation of alkaline phosphatase levels (Table 1). The hormonal profile revealed high PTH (parathyroid hormone) consistent for PHP and extremely high circulating calcitonin levels (20 times above the upper normal limit), suggestive for MTC (Table 1). In association with family medical history, these data raised the question of a MEN 2A syndrome, so the adrenal tests seeking for PHEO were done (including chromogranin A, 24-hour urinary metanephrines and normetanephrines) (Table 1). No hormonal or imagery clue of the adrenal tumour was found.

Thyroid ultrasound (US) found multi-nodular goitre, a deeply hypoechoic nodule located in the left lobe, with irregular margins, predominantly peri-nodular vascularisation and intra-nodular coarse calcifications, measuring 17.7 by 18.9 by 27.5 mm (millimetre) (Figure 1). In addition, anterior cervical US described a left cervical lymph node of 9.9 by 11.2 mm in diameter, and two extra-capsular nodules of 14.8 by 10.8 mm, 11.6 by 7.6 mm respectively, possibly left inferior and left superior parathyroid glands and associated adenoma. Contrast-enhanced computer tomography scans of the neck, chest, abdomen and pelvis revealed a thyroid nodule of 20 by 18 by 20 mm with lymph nodes enlargement by the same side and, also, another nodule of 11 mm maximum diameter, located at the posterior part of the left thyroid lobe,

TABLE 1. The panel of investigations consistent with Medullar Thyroid Cancer and Primary Hyperparathyroidism on a 56-year old female having positive family history for type 2A MEN Syndrome. The data are displayed at first diagnosis and three months after cervical surgery which provided the pathological confirmation of both conditions.

Parameter	Value	Normal value	Units
At diagnosis			
Calcitonin	2000	< 10	pg/ml
TSH	0.54	0.4-4	μIU/mL
FT4	1.59	0.89-1.76	ng/dl
TPO	18.2	< 50	UI/ml
PTH	126.5	11-67	pg/ml
Total serum calcium	10.78	8.8-10.6	mg/dl
Ionized serum calcium	4.57	4.4-5.4	mg/dl
Serum phosphorus	2.64	2.5-4.5	mg/dl
Serum creatinine	0.58	0.51-0.95	mg/dl
Serum alkaline phosphatase	140	30-120	U/l
24-hours urinary metanephrines	86.8	< 375	μg/24 h
24-hours urinary normetanephrines	148	< 632	μg/24 h
Blood chromogranin A	34.06	< 76.3	ng/ml
Three months after total thyroidectomy and parathyroidectomy			
Calcitonin	112.4	< 10	pg/ml
TSH	31.4*	0.4-4	μIU/mL
FT4	0.95*	0.89-1.76	ng/dl
PTH	26.3	11-67	pg/ml
Total serum calcium	8.42	8.8-10.6	mg/dl
Ionized serum calcium	3.67	4.4-5.4	mg/dl
Serum alkaline phosphatase	101	30-120	U/l

TSH=Thyroid Stimulating Hormone; FT4=Free Levothyroxine; TPO=anti-thyroperoxidase antibodies; PTH=parathyroid hormone

*under daily oral 100 μg of levothyroxine

suggestive for a parathyroid adenoma. No other lesions of the liver, lungs or adrenal glands were detected. Central DXA (Dual-Energy X-Ray Absorptiometry) scan revealed osteoporosis (in correlation with menopausal status and PHP).

In April 2016, the patient underwent total thyroidectomy with bilateral neck dissection and excision of the left inferior and superior parathyroid glands. The pathological report confirmed MTC and double parathyroid hyperplasia lesions. Three months after surgery, blood calcitonin decreased, but remained elevated despite no evidence of loco-regional disease on US. The patient presented with mild hypocalcemia with normal PTH, requiring an increase in calcium and vitamin D supplementation, as well as high TSH (Thyroid Stimulating Hormone)

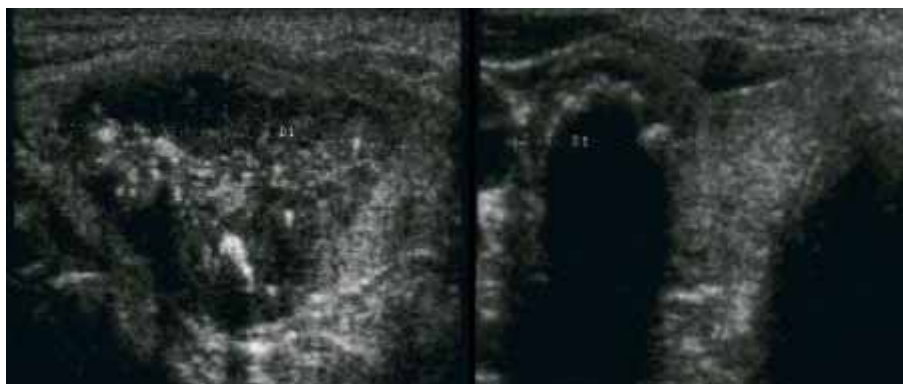


FIGURE 1. Preoperative anterior cervical ultrasound scan (different windows) of a 56-year-old patient with MEN 2A syndrome suggestive for an aggressive thyroid condition (confirmed as medullary thyroid cancer)

that required levothyroxine dose adjustments (Table 1). Further close follow-up and identification of residual MTC with adequate therapy is needed, as well as periodical check up for PHEO.

DISCUSSION

This case highlights a daily practice endocrine experience in a family with RET mutation (without the exact mutation on the proto-oncogene identified yet, but the clinical configuration is extremely suggestive). Type 2A MEN syndrome involves repeated surgeries and life-long follow-up (5-7). The presented case associates an atypical late diagnosis within the sixth decade of life (8,9). The history of high arterial blood pressure was not consistent with PHEO up to this moment, despite high frequency of the adrenal neoplasia in family with RET mutations and the fact that the patient's daughter had already been confirmed with PHEO (8). The headache the female accused was related to the blood pressure control, while the polyuria-polydipsia syndrome was associated with hypercalcemia. The phenotype was milder than seen at her younger relative, noting the fact that syndromic

genotype-phenotype correlation vary (6,9). We were not able to provide the entire pedigree consistent with tumours presence over the time in the family, despite its importance. We consider the most important clue of this case the lack of PHEO up to the age of 56 years (while PHP is already confirmed) which, apart from bilateral aspects in most cases, is expected to a 100% penetrance for some RET codons mutations (10). Unfortunately, after total thyroidectomy and careful bilateral neck dissection, calcitonin decreased, but did not normalise, which requires a large panel of serial imagery assessment to identify the source and provide, if possible, surgical resection (1,3,4,10).

CONCLUSION

Type 2 MEN Syndrome may embrace various clinical presentations with more or less aggressive tumours, sometimes allowing a long time survival without neoplasia confirmation or incomplete phenotype until advanced age.

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Conflict of interest: none

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