

CLINICAL CASE

MULTIPLE SURGERIES AND LONG-TERM ENDOCRINE FOLLOW-UP
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Abstract

MEN2A (Multiple Endocrine Neoplasia type 2) syndrome, an autosomal dominant condition, requires multiple surgeries in order to prevent or treat different tumours that are related to RET proto-oncogene mutations. Early intervention is most useful in cases with prior genetic confirmation. This is a case report presenting a long medical history of a female suffering of MEN2A syndrome. A 44-year-old woman, with a large family history of different endocrine cancers but no gene testing, is diagnosed at the age of 31 with a thyroid nodule of 1.7 centimeters (cm) which is removed by a partial thyroidectomy. Medullary thyroid cancer (MTC) is confirmed and calcitonin is found high. Total thyroidectomy is performed without consecutive normalization of calcitonin and secondary persistent post-operative hypoparathyroidism. 6 months later a right laparoscopic adrenalectomy is performed for a pheochromocytoma (Pheo) of 5.2 cm. Despite normal levels of metanephrines and normetanephrines, a left adrenal tumor of 1.5 cm is discovered one year later. One decade later, the blood calcitonin progressively increased and 41 lymph nodes from latero-cervical areas and central neck compartment were removed. 14 of them had MTC metastases. 8 months later, typical endocrine profile suggested a Pheo and laparoscopic left adrenalectomy is performed with chronic adrenal insufficiency needing lifelong hydrocortisone and fludrocortisone replacements. The MEN2A syndrome-related multiple surgeries are correlated with long-term endocrine follow-up in challenging cases such as ours requiring a multi-disciplinary approach. The lack of gene mutation identification during childhood or at close relatives delays the diagnosis and thus the potential curative surgical removal of the thyroid and adrenal tumours with a more severe prognosis.

Keywords: thyroidectomy, adrenalectomy, medullary thyroid carcinoma, pheochromocytoma**Introduction**

MEN2A (Multiple Endocrine Neoplasia type 2) syndrome represents a challenging autosomal dominant condition requiring multiple surgical

procedures in order to prevent or treat different endocrine tumours (and some of them are malignant) as medullary thyroid cancer, pheochromocytoma (mostly with bilateral pattern) and primary hyperparathyroidism

(which is actually the rarest event) [1,2,3]. The genetic background involves different mutations of RET proto-oncogene [1,2,3]. The condition associates together with MEN2B and familial thyroid medullary cancer more than 70 mutations [4]. The genotype correlates with the phenotype, thus the prevalence and aggressive profile regarding each component of the syndrome might be expected at different rates once the mutation is identified [4,5,6]. Unfortunately the family tree has to be identified in each family and needs gene mutations identifications of every family member. This is actually difficult to assess depending on the medical system of each country which offers the opportunity of genetic screening [7,8].

Early genetic diagnosis is essential for early intervention and close follow-up [3,7,8]. A specific mutation associates specific guideline recommendations in order to have the timing of prophylactic surgical remove of the thyroid (including during very early childhood for some mutations as those from the codon 918 or 634) [3,7,9]. The surgery in patients expected to have later in life a thyroid cancer or a catecholamines producing tumour needs a good cooperation with the patient, and clear ethical approach [10]. However every day practice of medicine brings a more complex panel of clinical presentations including the adult cases where the genetic confirmation is not obvious and it is not available from the very beginning. In these situations the surgery is recommended based on endocrine features, the patients' age, the comorbidities and close follow-up [11].

This is a case report presenting a long medical history of an adult female diagnosed with MEN2A syndrome who suffered multiple surgical interventions.

Case report

A 44-year-old female is admitted in 2015 for an endocrine check up, considering that the diagnosis of MEN2A syndrome has been established almost a decade ago and multiple surgeries were necessary for this matter (Graphic 1). She has been evaluated in different medical centers from Transylvania but also from Bucharest, Romania. The medical family

history is positive for papillary thyroid cancer (a sister), medullary thyroid cancer (another sister), medullary thyroid cancer together with bilaterally pheochromocytoma (a pattern cousin), and pheochromocytoma (another pattern cousin). Also, her father died at a young age of sudden cardiac arrest due to unknown causes (looking back to the family history we suspected a pheochromocytoma).

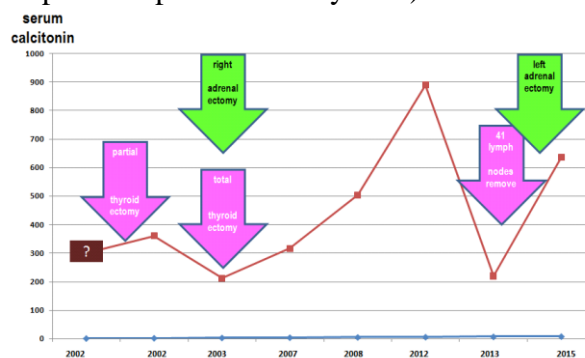


Figure 1 - The surgical and endocrine follow-up of an adult female patient with MEN2A syndrome: the levels of calcitonin over time and the timing of surgical procedures from 2002 to 2015. The normal levels of serum calcitonin are above 5 ng/mL.



Figure 2 - Computer tomography (CT): transversal plane, a left cervical lymph node (metastases of medullary thyroid cancer)

In 2002 a thyroid nodule of 1.7 centimeters was found and removed by a procedure of partial thyroidectomy with general anesthesia. The hospitalization was less than a week and no hypocalcemia was registered and no local edema was seen immediately after surgery. Levothyroxine substitution was necessary. The pathological report showed a medullary thyroid cancer. Before surgery no calcitonin assay was available but after the partial surgery the

calcitonin was as high as 359 pg/mL with normal levels of less than 5 pg/mL. Persistent hyper-calcitoninemia made necessary a second thyroid intervention; this time a total resection was assed together with lymph nodes neck dissection (Figure 2). Despite the radical intention of surgery the calcitonin did not normalize but decreased to 210 pg/mL. Persistent post-operative hypoparathyroidism was partially corrected with vitamin D and calcium supplements.

Six months later a right adrenal tumor of 5.2 by 2.8 centimeters was removed by a laparoscopic procedure of complete adrenalectomy because a pheochromocytoma was suspected (and confirmed after surgery by the pathological report). No cardiac event was presented despite the pathological confirmation of a pheochromocytoma remove. Later on the control tests for metanephrines and normetanephrines were normal but in 2003 a left adrenal tumor of 1.5 by 0.68 centimeters was discovered at computer tomography (CT) scan. A second pheochromocytoma was once more time suspected but the endocrine tests did not confirm it. At the same time the CT examination also revealed lymph nodes on the right and left side of the trachea of maximum 1 centimeter diameter, potentially related to the persistent high levels of calcitonin. Until 2007 the imagery aspects were stationary while the calcitonin increased to 313 pg/mL (Figure 3).



Figure 3 - Computer tomography (CT): transversal plane, a right cervical lymph node para-esophageal position (metastases of medullary thyroid cancer)

Then the left adrenal tumor increased to 2.4 by 1.45 centimeters and elevated levels of

catecholamines were consistent with the diagnosis of pheochromocytoma (plasma metanephrines of 124 pg/mL, normal levels between 10 and 45 pg/mL, plasma normetanephrines of 146 pg/mL, normal ranges between 15 and 90 pg/mL, blood chromogranin A of 339 ng/mL, with normal upper limit below 100 pg/mL). Left adrenalectomy was indicated but the patient delayed the procedure. Clinically she had rare episode of slightly elevated blood pressure. In the mean time calcitonin rose to 499 pg/mL in 2008 and arrived to 883 pg/mL in 2012.

The patient continued to refuse any type of surgical approach until 2013 on the base that, apart from inconstant mild hypertension, she had no major complaints. In 2013 another surgical intervention was performed removing 41 lymph nodes from bilaterally latero-cervical areas and central neck compartment. Among them 14 had metastases from medullary thyroid cancer (3 nodes located on the left cervical area and 11 of them were located on the central compartment). The Ki67 proliferation index was 3%. The recovery after surgery went well and the calcitonin decreased to 214 pg/mL but never re-entered within the normal ranges. No obvious metastases were found at thorax and abdominal CT scan. Eight months later the left adrenal tumor was removed by a laparoscopic procedure of adrenalectomy without any incidents (Figure 3,4). Chronic adrenal insufficiency needs lifelong hydrocortisone replacements.



Figure 3 - Computer tomography (CT): left pheochromocytoma (coronal plane)



Figure 4 - Computer tomography (CT): left pheochromocytoma (sagittal plane)

On admission, in 2015 the hormonal tests for pheochromocytoma were negative while calcitonin was considerable high (of 628.3 pg/mL). Chromogranin A was normal and low parathormone levels were consistent for surgery-associated tetania (a parathormone value of 12.25 pg/mL with normal level values between 15 and 65 pg/mL). A PET-CT (positron emission tomography) scan together with Indium 111 octreoscan were recommended in order to identify the patten of metastases from medullary thyroid cancer. Eventually in the case of carcinoid syndrome due to the same advanced condition somatostatin analogue is recommended as well as thyrosine kinase inhibitors in case of widely disease spreading.

Discussions

This case report is highly suggestive for some issues that clinicians (both surgeons and endocrinologists) need to face in front of a patient with MEN2A syndrome.

This case highlights the importance of an early diagnosis and associated curative surgery if this is possible in cases with MEN2A syndrome. The main conduct was based on the endocrine anomalies as thyroid nodules or adrenal tumours at CT scans associated with increased levels of calcitonin and/or metanephrines/normetanephrines. Despite the fact that guidelines recommend thyroidectomy during the first two decades of life depending on

gene mutations, the real life medicine brings cases as this one having the first moment of diagnosis at adult age (in this situation at age of 31) [11].

After the first two procedures of thyroidectomy with the medullary thyroid carcinoma confirmation and the right adrenal tumour remove, the hormonal tests were not clearly consistent for a second contra-laterally pheochromocytoma. In the majority of cases there is an adrenal medullary hyperplasia prior to the tumour itself based on genetic persistent stimulus [12]. The term of micro-pheochromocytoma has been proposed by some authors for imagery lesions of almost 1 centimetre [12].

In our complex case there have been consecutive interventions at the thyroid and adrenals. Despite the increased levels of medullary adrenal hormones, there was no cardiac event during the anaesthetic management of the two surgeries for pheochromocytoma. Generally, if the medullary thyroid cancer is synchronously diagnosed with a uni or bilateral pheochromocytoma, the first recommended surgery is for the adrenal tumour/tumours due to the catecholamine potential related cardiovascular risks [13,14]. In our case, the right adrenalectomy was performed 6 months after total thyroidectomy because the endocrine tests were not conclusive and the gene testing was not possible. Knowing the rarity of the MEN2A syndrome and the costs of gene mutations identifications, it is generally recommended to also perform surgery in cases without genetic confirmation but with highly endocrine suggestive tests, since surgery is the only method with curative potential of the disorders [15].

The total thyroidectomy and adequate lymph nodes dissections is essential in medullary thyroid cancer representing the only option if the target is to cure the patient [16]. The main aspect is essentially simple: the sooner the intervention, the better the outcome [3,16]. Unfortunately this was not our case. The endocrine diagnosis prior to the first procedure of thyroidectomy was missed and afterwards the blood calcitonin levels (which represents the best prognosis tool) were never found normal again. (See Graph1) The lymph nodes dissection is particularly important in this type of cancer

since the first metastases are seen locally in most of the cases. The routine dissections involve the lymph nodes from cervical areas next to the thyroid but also the extended lateral cervical and central neck compartment dissection if the diagnosis is already established at the moment of surgery and spreading of the disease is suggested by the imagery and endocrine assays [17]. Others difficulties are related to persistent high levels of calcitonin after neck surgery and no localisation of the disease. Advanced imagery methods as Gallium-68 or fluorine-18-fluorodeoxyglucose (18F-FDG) PET/CT might help the data achieved by CT or magnetic resonance imaging (MRI) [18].

The approach of medullary adrenal tumours may be done by an open procedure or by laparoscopy which lately has been preferred in most cases [3,19,20]. Generally the decision is made by the surgical team. Special attention is necessary to the cardiac arrhythmia or cardiac arrest and / or blood pressure disturbances caused by adrenaline and noradrenaline while the tumour is manipulated during intervention or soon after its removal [3,19,20]. Special drugs are necessary before and during adrenalectomy in order to obtain an alpha/beta receptors blocking and to have an adequate fluid replacement level which requires special attention by the anaesthesia team [19]. Adrenal sparing surgery is the third option in the pheochromocytoma approach. It is recommended in special surgical centres with experience in this particular matter in cases when bilateral adrenalectomy is necessary and consecutive adrenal insufficiency should be avoided. In fact, primary adrenal insufficiency may be seen even after a partial procedure because of the fact that devascularisation during adrenalectomy damages the residual adrenal parenchyma. Some other studies did not find that glucocorticoid replacement was necessary after adrenal sparing technique [20,21]. If bilateral synchronous adrenal tumours are identified, their simultaneous removal is useful [20,21].

As limits of our case we mention the lack of family tree with specific gene tests for each member since the patient was refractory to inform and to bring to control all the relatives. However this is a very frequent situation in our

country due to difficulties of gene mutation identifications in public hospitals.

Conclusions

This adult female case with MEN2A syndrome-related multiple surgeries is important for long-term follow-up in challenging cases requiring a multi-disciplinary approach. The lack of gene mutation identification during childhood or at close relatives postpones the diagnosis and thus the surgeries as the only curative options are also delayed and a poorer prognosis is registered.

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