MEN 2A SYNDROME WITH LONG EVOLUTION – CASE REPORT

MIHAELA STANCIU[1], FLORINA POPA[2], MARIA ROTARU[3], NICOLETA CĂLUȚIU[4], IOAN GHEORGHE TOTOIAN[5]

[1,2,3]"Lucian Blaga" University of Sibiu, [4,5]County Clinical Emergency Hospital Sibiu

Keywords: *2A multiple endocrine neoplasia, long evolution*

Abstract: *Multiple endocrine neoplasia (MEN) are genetic syndromes characterized by the coexistence of two or more endocrine tumours in the same subject. They are classified in MEN type 1 and MEN type 2, which has three subtypes – MEN 2A, MEN 2B and familial medullary thyroid carcinoma (FMTC). Over 70 RET protooncogene mutations are incriminated in the pathogenesis of MEN type 2 syndrome. MEN type 2 syndrome occurs in 1:30000 individuals, the most frequent being MEN 2A (80%), followed by FMTC (15%) and MEN 2B (5%). Almost every patient with MEN 2A develops MTC, pheochromocytoma approximately 50% and 30% of them develop parathyroid tumours. We report a case with FMTC, operated and relapsed bilateral pheochromocytoma, having first degree relatives (brother and sister) with thyroid nodules and surgery for pheochromocytoma. RET mutation screening has not been investigated. Low compliance of the patient and his caregivers resulted in both therapeutic and preventive measures delay for the patient and his offspring.*

Cuvinte cheie: *neoplazii endocrine multiple 2A, evoluție îndelungată*

Rezumat: *Neoplaziile endocrine multiple (MEN) sunt sindroame genetice caracterizate prin coexistența unor tumori a două sau mai multe glande endocrine la același subiect. Sunt clasificate în MEN tip 1 și MEN tip 2 cu trei subclase – MEN 2A, MEN 2B și cancerul medular tiroidian familial (FMTC). În apariția sindromului MEN 2 sunt incriminate peste 70 mutații ale protooncogenei RET. Incidența este de 1:30000, cel mai frecvent întâlnit fiind MEN 2A (80%), urmat de FMTC (15%) și MEN 2B (5%). Aproape toți pacienții cu MEN 2A dezvoltă MTC, aproximativ 50% feocromocitom, iar 30% tumori paratiroidiene. Prezentăm cazul unui pacient cu FMTC și feocromocitom bilateral operat, recidivat, ce prezintă rude de gradul I (frate și soră) cu intervenții chirurgicale pentru noduli tiroidieni și feocromocitom. Screening-ul mutației genei RET nu a fost investigat. Complianța scăzută a pacientului și aparținătorilor săi a avut drept consecință atât întârzierea manevrelor terapeutice până la depășirea momentului chirurgical, cât și aplicarea măsurilor profilactice în cazul descendenților.*

INTRODUCTION

Multiple endocrine neoplasia – MEN are genetic syndromes with autosomal-dominant transmission, characterized by the coexistence of some tumours of two or more endocrine glands in the same subject.(1) They were first described in 1903 by Erdheim and are classified in MEN type 1 and MEN type 2 with three subclasses - MEN 2A, MEN 2B and familial medullary thyroid carcinoma (FMTC).(1,2)

In MEN 2 syndrome occurrence, there are incriminated over 70 RET protooncogene mutations (Rearranged during Transfection), affecting the C cells derived from the neural crest (which migrates into the adrenal medulla, sympathetic and parasympathetic ganglia and the upper portion of the thyroid lobes).(3,4) There is a great clinical variability between different families with the same RET mutation, making it difficult to decide upon the time of prophylactic thyroidectomy for the medullary thyroid carcinoma.(3)

MEN 2 syndromes occur in 1:30000 of individuals, the most common type being MEN 2A (80%), followed by FMTC (15%) and MEN 2B (5%). Almost all people with this condition develop medullary thyroid cancer (MTC), the most common cause of death in affected patients.(4) Approximately 50% of patients with MEN 2A develop pheochromocytoma, and 30% develop parathyroid tumours (hyperplasia or unique / multiple adenoma.(4) Rarely, patients with MEN 2A associate cutaneous lichen amyloidosis and the Hirschsprung disease.(2)

The earliest thyroid abnormality present in the individuals with MEN 2A, MEN 2B and FMTC is C cell hyperplasia, which seems to represent carcinoma in situ that will progress to invasive carcinoma.(5) Changes are multicentric, with the frequent occurrence of several types of histological lesions in one or both thyroid lobes.(1) This multifocal aspect is present in FMTC, being absent in isolated MTC.(5) The cells have increased secretory activity, synthesizing calcitonin carcinoembryonic antigen (CEA), chromogranin A, dopa-carboxylase, histaminase, somatostatin, Thyrotropin-releasing hormone (TRH) and adrenocorticotropic hormone (ACTH).(4,6)

The diagnosis is confirmed by the increased value of basal calcitonin and after pentagastrin or calcium stimulation, even before the onset of macroscopic changes.(7) Whenever MTC is diagnosed, as well as in the case of the dual tumour association, the complete screening for MEN 2 is required. When the diagnosis is most probable, it must be confirmed genetically. The presence of RET gene mutations requires the screening of first-degree relatives.(1) The treatment of choice is thyroidectomy; only in those detected by genetic screening, surgery depends on age and specific RET mutation.(8)

[1]Corresponding author: Maria Rotaru, B-dul Mihai Viteazul, Nr. 25, Sibiu, România, E-mail: mrotaru07@gmail.com, Tel:+40269 235541
Article received on 10.06.2013 and accepted for publication on 02.09.2013
ACTA MEDICA TRANSILVANICA December 2013;2(4):276-280

Post-surgery follow-up is done by determining calcitonin and CEA. In patients with metastatic MTC, the administration of tyrosine-kinase inhibitors increases survival, and there is hope for effective therapies even in advanced disease.(9)

Pheochromocytoma in MEN 2 is rarely malignant, and the tumours tend to be multiple and bilateral.(4) All patients diagnosed with MTC should be investigated in order to exclude pheochromocytoma by determination of plasma and urinary free metanephrins and by imaging investigations (CT, MRI, scintigraphy Ci I^{131} - MIBG, PET).(10,11) The treatment is surgical, unilateral or bilateral suprarenalectomy being practiced according to the extent of disease upon diagnosis.(4)

Hyperparathyroidism occurs more frequently in MEN 2A, hyperplasia being observed more frequently than parathyroid adenoma. This can represent the beginning of MEN 2A before MTC.(1) The treatment consists of the resection of 3 ½ of gland or of all of the parathyroids with subcutaneous autograft of a portion of a gland.(12)

We present the case of a patient with MTC and bilateral pheochromocytoma, operated, relapsed, showing first degree relatives (brother and sister) with surgeries for thyroid nodules and pheochromocytoma.

CASE REPORT

We present the case of a patient aged 67 years old, residing in Sibiu, with MEN 2A syndrome, which has a history of insulin-required type 2 diabetes, right kidney stones, cholecystectomy for lithiasic phlegmonous acute cholecystitis (figure no. 1).

In 1974, he was investigated for the endocrine system, rising the suspicion of thyroid tumour formation (slow-growing thyroid nodule). In 1976, the patient was submitted to right subtotal lobectomy. The histopathological examination highlighted anaplastic thyroid carcinoma, subsequently irradiated with I^{131}.

Figure no. 1. Patient with MEN 2A syndrome

In 1986, there appeared a thyroid nodule in the left lobe (table no. 1.) and he was admitted at the "C.I. Parhon" Institute for radioiodotherapy (RIT). During hospitalization, he presented paroxysmal hypertensive crises, with elevated plasma and urinary metanephrines, both basal and during crises (table no. 2). Abdominal CT revealed a tumour in the right adrenal gland with a diameter of about 5 cm (table no. 3), the diagnosis being right adrenal pheochromocytoma.

In October 1986, the right pheochromocytoma was removed. The intraoperative exploration of the left adrenal gland found a calcified tumour formation that could not be excised; at the same time, the patient was diagnosed with type 2 diabetes. Because after the removal of the right pheochromocytoma, the values of plasma catecholamine were at the lower limit of the normal values and the hypertensive paroxysms disappeared, the left adrenal tumour was interpreted as unclassified.

Table no. 1. Thyroid imaging examinations

Year	Thyroid ultrasound	Thyroid scintigraphy	Cervical region and thorax CT
1986	Cold nodule in the isthmus, LST normal		
1988	Small isthmic hypoechogenic nodule	LST moderately enlarged, right thyroid remaining. Normal RIC at 2 hours and 24 hours	
1997		Cold isthimic nodul.nodular LST	
2006	LST has a relatively well-defined nodular formation of 1,38 / 2,15 cm, non-homogeneous contents and hypoechogenic and hyperechoic areas with peri and intranodular vascularity. Left lateral - cervical ganglion of 1/1 cm.	LDT cannot be viewed, LST heterogeneous capture in the 1/3 average, a nodular formation with relatively homogeneous fixation	
2009	Post-thyroidectomy right lobe status, LTS presented a hypoechoic formation with macrocalcifications, Doppler signal of 2.2 / 2/1, 5 cm. In the left latero-cervical part, on average 1/3, fusiform adenopathy of 16.5/3,1 mm, in the right latero-cervical part, on average, similar lymphadenopathy of 16/4, 8 mm.	Right post-thyroidectomy status, right thyroid remaining, left lobe with a large volume, showing 2 cold nodules with the rest of the lobe normocapturing, lower isthmic cold nodule	
2011			Subtotal ablation of LDT with thyroid tissue present, right paratracheally in the thyroid lodge of 17/08/15 mm. LST with a iodophilic tumour process with eccentric calcification towards left, of 23/17 mm. Latero-cervical lymph nodes, lower and upper mediastinally calcified. CT lung parenchyma aspect normal, no lesions with secondary character.
03.2012			Subtotal ablation of the LDT. LST with a tumour process, partially calcified of 22/19 mm. Para- and pretracheal tumour nodules of 19/13 mm, 16 mm and 17 mm. Right lower jugular-carotid

			adenopathy of 12 mm. Mediastinally: tumour process located at the level of pericardium insertion on the great vessels, caudally to the pulmonary vein, partially necrotic, of 45/25 mm.
11.2012			Homogenous thyroid tissue in the right lodge. LST has a macronodule with calcification in the upper pole, of 24/18 mm. Right partially calcified paratracheal tumour nodules of 18/13 mm. Other two pretracheal nodules with intranodular calcifications of 15 and 14 mm. At the level of the pericardium insertion into the great vessels, a iodophilic non-homogeneous nodule of 40/30/32 mm. bordering the pulmonary artery trunk.
2013	Right lobectomy, small hypodense areas in the right lodge; LST- 4.92 / 2.3 / 3cm with a macronodule of 2.6 / 1.75 / 2.2 cm located posteriorly, with peripheral microcalcifications, circulation present peri- and intranodularly; isthmus - 0.5 cm, without adenopathies.		

Table no. 2. Plasma and urinary catecholamines and metanephrines in the evolution of pheochromocytoma

Year			NA ser	A ser	NA urine	A urine	MN plasm	NMN plasm	MN urine	NMN urine	AVM	Cg A
Normal values			**1,5–2,5 µg/l**	**0,3–0,5 µg/l**	**10–50 µg/24h**	**4–9 µg/24h**	**<45 pg/ml**	**<90 pg/ml**	**<350 µg/24h**	**<600 µg/24h**	**1,7 mg/24h**	**VN=43 ng/ml**
1986	**Basic**	day 1	6	1	510	195					8,4	
		day 15			750	283					16,4	
		day 23	6,26	0,70	800	384			960			
	HTA crisis (zi 1)		38	8								
1987			3,50	0,45	48	13					2,88	
1988			4,07	0,58	35	14					1,76	
1990			2,50	0,75	57,6	22						
1997									300		3,45	
2009							125	818	870	2819		241
2011							164	1167	1005	2418		286
2012							207	737				293

NA=norepinephrine, A=epinephrine, MN=metanephrines, NMN=normetanephrines, AVM= Vanillyl mandelic acid, Cg A=chromogranin A

Table no. 3. CT examinations of the adrenal glands

Year	Abdominal CT	
	Right SR	**Right SR**
1986	Tumour formation of about 5 cm	
1997	tumour nodule of 1.3 cm, located cranially to the right upper renal pole; right upper calyces tumour mass extended in the pelvis of 4,7 / 2,7 cm	homogeneous, dense, iodophilic tumour of 2,75 / 2 cm
2009	voluminous heterogeneous tumour mass with agglutinated central calcification (on approx 2.4 cm), with a size of 5.9 / 4,8 cm. This formation marks the visceral hepatic part and comes in direct contact with the right kidney, compressing the pelvis. It exerts a mass effect on the right renal vein.	macronodular formation (30/22 mm), with iodophilic non-homogeneous structure with central necrosis aspect
2011	Tumour mass extended in the right kidney up to the renal sinus; it is iodophilic, non-homogenous and a diameter of 48/45 mm axially and of 58 mm vertically.	Iodophilic tumour mass with central necrosis, axial diameters of 24/26 mm and 36 mm vertically. Hepatic microcalcifications in segments V, II and VI
03.2012	Tumour mass extended in the renal sinus, with axial diameters of 67/45 mm.	Tumour mass in the left SR of 26/25 mm.
11.2012	Tumour mass extended at the level of the right renal sinus, marks the pelvis and disorganizes the upper and middle urinary tract, of 61/49 mm.	Iodophilic tumour mass, partially necrosed, with diameters of 29/25 mm axially

In 1988, the patient was readmitted at the "C.I. Parhon" Institute, where a hypodense thyroid nodule was highlighted at the thyroid level, as well as the enlarged left lobe volume, non-homogenous with central hot area, also presenting slightly elevated catecholamine levels (table no. 2), for which the periodical check up was recommended.

The patient did not come to the check-up until 1997, when the abdominal CT (table no. 3) showed a left adrenal tumour of 2.75 / 2 cm and right adrenal tumour recurrence, as well as right urothelial tumour. Urinary catecholamine values were within normal limits (table no. 2).

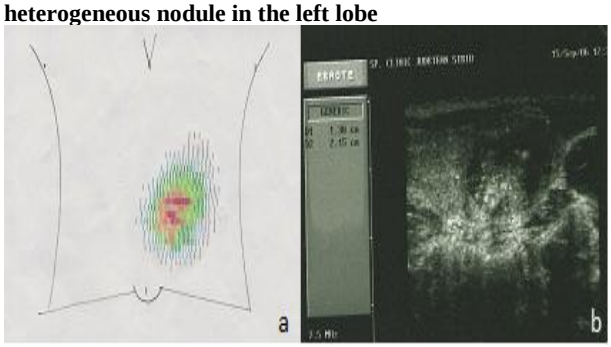
Following the puncture of the isthmic thyroid nodule, an old bleeding calcified in a meso-follicular nodule has been observed. Again, the periodical medical check-up was suggested. Between 1997-2002, diabetes seemed to be unbalanced, reason for which insulin therapy was started.

In 2006, during a hospitalization in the Endocrinology Clinic of Cluj-Napoca, thyroid scintigraphy was performed (table no. 1.) that showed a hot nodule in the third part of the left thyroid lobe (figure no. 2a), and by ultrasound (table no. 1), a nodule of 1.38 / 2.15 cm was noticed, with non-homogeneous

and hypoecogenice and hyperechoic areas, peri and intranodularly Doppler vascularity (figure no. 2b).

Calcitonin value was 82 times higher above the normal value (1068 pg / ml). In conjunction with the family history (sister and brother, both operated for pheochromocytoma and thyroid nodules), the patient was diagnosed with MEN 2A, the genetic screening not being possible.

Figure no. 2. MTC recurrence: a - thyroid scintigraphy b - heterogeneous nodule in the left lobe



In 2009, the patient was hospitalized for glycemic imbalance under insulin therapy, being diagnosed with ventricular extrasystolic arrhythmia, complicated type 2 diabetes, difficult to balance, hypertension. Chest Rx revealed a calcareous radiopaque image projected paratracheally right at the level of the upper mediastinum along the sternoclavicular joint, as well as calcareous radio-opaque image projected in the soft parts, laterocervically and bilaterally.

He was transferred to the Department of Endocrinology of Sibiu for reinvestigation. Thyroid ultrasound (table no. 1.) highlighted at that moment, right thyroid lobectomy. LTS presented of a hypoechoic formation with macrocalcifications, with Doppler signal of 2,2 / 2/1, 5 cm. Left adrenal gland ultrasound highlighted an enlarged adrenal gland of 5/2/4, 3 cm, and the adrenal CT (table no. 3) highlighted post right operated pheochromocytoma, with a large local recurrence, left adrenal tumour formation.

Thyroid hormone dosages were within the normal limits without outpatient substitution treatment (TSH = 2.67 μUI / ml, FT4 = 1.1 ng / ml, PTH = 27.10 pg / ml). Plasma and urinary catecholamine values were markedly increased (table no. 2), suggesting residual hypersecretion and CEA = 229.97 ng / ml suggested the secondary determination of MTC.

In 2010, the patient was admitted at the Fundeni Institute, with a view to suprarenalectomy, but the patient was noncompliant to the cardiac treatment, so it was decided to transfer him to the Parhon Institute. Adrenal surgery was not performed.

Upon the revaluation in July 2011, plasma and urinary hormone dosages (table no. 2.) conformed the relapse of pheochromocytoma and MTC, suboptimal status of vitamin D (25-OH-vit. D = 22.10 ng / ml), Osteocalcin = 17.37 ng / ml, CrossLaps = 0.29 ng / ml (slightly decreased bone turnover). On CT scan (tables no. 1, 3), adrenal masses were distinguished, right adrenal tumour extended to the right renal sinus; hepatic microcalcifications, subtotal thyroidectomy, left thyroid tumour nodule, lower laterocervical lymph nodes and upper mediastinally, as well.

In October 2011, surgery was performed with a view to suprarenalectomy; intraoperatively liver metastases were highlighted in both lobes, viscerolisis was performed, exploratory laparotomy, liver metastases biopsy. The histopathological examination highlighted a tumour nodule with middle-sized epithelial cells arranged in a tubuloacinar structure and alveolarly with frequent stromal calcifications, developed liver parenchyma - endocrine tumour morphology.

In March 2012, the patient was re-evaluated at the Parhon Institute, hormone dosages were consistent with the diagnosis of pheochromocytoma and metastatic MTC (table no. 2). The CT examination highlighted the occurrence of mediastinal masses at the level of the insertion of the pericardium on the great vessels, of 45/25 mm (table no. 3). Due to the major risk of hypoglycaemia in inducing a catecholamine crisis in a patient with pheochromocytoma and the lack of benefits in maintaining a proper glycemic control in this patient, it was decided to change the insulin therapy scheme with 2 doses of retard Levemir insulin. Upon the revaluation of November 2012, there was a slight increase in the size of all tumours, deciding upon a conservative treatment, with periodic reassessment.

In May 2013, the patient was re-admitted at the Parhon Institute, CEA value being increased (210.05 ng / ml). It was concluded that he was a patient with MEN 2A syndrome with MTC with residual disease and mediastinal and hepatic secondary metastases, recurrent pheochromocytoma with bilateral adrenal tumours, in which it was considered inappropriate to perform suprarenalectomy in the presence of liver metastases. The antihypertensive treatment will continue, as well as the periodical check-up.

DISCUSSIONS

Although thyroid neoplasia was the first manifested pathology, histopathologically, anaplastic thyroid carcinoma (1976) was described. The right lobectomy was subsequently complemented by RIT without surgical reintervention for completing thyroidectomy.

Within 10 years (1986), the patient was diagnosed with right adrenal pheochromocytoma, operated, simultaneously with the presence of a left adrenal unclassified tumour. At the same time, it was shown the presence of a thyroid nodule in the isthmus. 10 years (1997) later, imagistically, there was a right adrenal pheochromocytoma recurrence, but the patient refused the surgical reintervention.

30 years after thyroidectomy (2006), the diagnosis of recurrent MTC, relapsed right pheochromocytoma was established. The patient underwent cholecystectomy for phlegmonous acute cholecystitis, delaying the reintervention for pheochromocytoma.

Although biologically, hyperparathyroidism has not been demonstrated in 2009, the patient had a history of gallstones and kidney lithiasis diagnosed in 2006.

In the absence of marfanoid habitus and mucosal multiple neurinomas, associated with the presence of thyroid nodules and pheochromocytoma in the first degree relatives, the diagnosis of MEN 2A syndrome was set up. Type 2 diabetes was associated to endocrine neoplasia, two brothers and a sister of the patient being diagnosed with this condition.

Due to the low compliance of both the patient and his family for RET mutation screening, this has not been investigated.

CONCLUSIONS

The case supports the importance of radically addressing MTC from the surgical point of view, excising the central nodule to avoid the dissemination of lesions.

In the absence of the genetic evaluation of family members, a better collaboration with the family physician is required for an endocrine assessment (thyroid and adrenal) of the family members of a patient with multiple endocrine neoplasia.

Monitoring calcitonin, metanephrines and chromogranin annually in a patient with MEN 2A syndrome, completed by the imaging investigations represent a practical manner to follow-up the case and prevent complications.

REFERENCES

1. Brănișteanu DD. Neoplaziile endocrine multiple. În Zbranca E. Endocrinologie, ghid de diagnostic și tratament. Iași: Ed. Polirom; 2008. p 429-438.
2. Dumitrache C. Sindroamele de neoplazie endocrină multipla (MEN). În Endocrinologie clinică, mic tratat de endocrinologie. București: ed. Național; 2012. p. 521-532.
3. Wells SA Jr, Pacini F, Robinson BG, Santoro M. Multiple Endocrine Neoplasia Type 2 and Familial Medullary Thyroid Carcinoma: An Update. J Clin Endocrinol Metab. 2013 Jun 6. [Epub ahead of print].
4. Marx SJ, Wells SA Jr. Multiple endocrine neoplasia. In Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, editors. Williams textbook of endocrinology, 12th edition. Elsevier Sounders; 2011. p. 1728-1767.
5. Gómez K, Varghese J, Jiménez C. Medullary thyroid carcinoma: molecular signaling pathways and emerging therapies. J Thyroid Res. 2011:815826. doi: 10.4061/2011/815826.
6. Sevarino KA, Wu P, Jackson IM, et al. Biosynthesis of thyrotropin-releasing hormone by a rat medullary thyroid carcinoma cell line. J Biol Chem 1988;263:620-623.
7. [7] Skinner MA, Moley JA, Dilley WG, Owzar K, Debenedetti MK, Wells SA Jr. Prophylactic thyroidectomy in multiple endocrine neoplasia type 2A. N Engl J Med 2005;353(11):1105-1113.
8. Ferreira CV, Siqueira DR, Ceolin L, Maia AL. Advanced medullary thyroid cancer: pathophysiology and management. Cancer Manag Res 2013;5:57-66.
9. Wells SA, Gosnell JE, Gagel RF, et al. Vandetanib for the treatment of patients with locally advanced of metastatic hereditary medullary thyroid cancer. J Clin Oncol 2010;28:767-772.
10. Lenders JW, Pacak K, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA 2002;287:1427-1434.
11. Ilias I, Pacak K. Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. J Clin Endocrinol Metab 2004;89:479-491.
12. Alevizaki M. Management of hyperparathyroidism (PHP) in MEN2 syndromes in Europe. Thyroid Res. 2013;6(1):S10. doi: 10.1186/1756-6614-6-S1-S10.