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MEN 2A syndrome – Multiple endocrine neoplasia with autosomal dominant transmission

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ABSTRACT

INTRODUCTION: Multiple endocrine neoplasias (MEN) are rare inherited syndromes. MEN type 2 syndromes occur in 1:30000 individuals, and are reported in approximately 500–1000 families worldwide, the most frequent being MEN 2A (80%), followed by familial medullary thyroid carcinoma (15%) and MEN 2B (5%) (Marx and Wells, 2011; Dumitrache, 2012).

CASE: The patient, a 20-years old with MEN 2A syndrome, which has been manifested by bilateral pheochromocytoma and medullary thyroid carcinoma. It was a familial form, having first degree relatives (mother) with pheochromocytoma. The patient underwent laparoscopic adrenalectomy on her left in 2015, laparoscopic adrenalectomy on the right in 2019 and total thyroidectomy in 2020 year. The postoperative evolution of this patient is favorable. She is satisfied with the received treatment and is being supervised by an endocrinologist, undergoing hormone replacement therapy.

CONCLUSIONS: The case demonstrates the importance of the radical approach to MEN 2A syndrome from both a therapeutic and surgical point of view.

If a pheochromocytoma is detected, adrenalectomy should be performed before thyroidectomy or other surgery to avoid intraoperative catecholamine release.

Laparoscopy is the choice of approach in surgical treatment. Limitations only arise because of technical difficulties or tumor size.

1. Introduction

Multiple endocrine neoplasiass (MEN) are rare and complex autosomal dominant inherited syndromes caused by germline RET (Rearranged in Transfection) mutation and characterized by the association of tumors of two or more endocrine glands in the same patient. It was described by Erdheim in 1903 and classified in MEN type 1 (Wermer syndrome) and MEN type 2 with three subtypes - MEN 2A (Sipple syndrome), MEN 2B (Shimcke syndrome) and familial medullary thyroid carcinoma (FMTC) [1,2].

MEN type 2 syndrome occurs in 1:30000 individuals, and is reported in approximately 500–1000 families worldwide, the most frequent being MEN 2A (80%), followed by FMTC (15%) and MEN 2B (5%) [2,3].

Sipple syndrome is characterized by the association of medullary thyroid carcinoma (MTC) (in 80–100% of cases), uni- or bilateral pheochromocytoma (in over 50% of cases) and primary hyperparathyroidism (15%–30% of cases) in the same patient [3,4].

MEN 2A is an autosomal dominant disease caused by multiple mutations in the RET gene, located on chromosome 10q11.2, which leads to the damage of C cells derived from the neural crest. Hyperplasia of C cells appears early in life and can be considered as a precursor lesion for medullary thyroid carcinoma (MTC) [3].

The diagnosis can be confirmed before the appearance of macroscopic changes, by the increased value of calcitonin, considered a tumor specific marker for MTC (norm <10 pg. / mL) [5,6].

Imaging methods (ultrasound, CT, MRI) can be used to determine the extent of a tumor, and the possible existence of metastasis. Genetic confirmation is mandatory when the Sipple syndrome is suspected. The presence of RET gene mutation requires screening of first degree relatives [6,7].

The moment to perform prophylactic thyroidectomy for medullary thyroid carcinoma is a difficult decision due to clinical variability between different families with the same RET muta-

Abbreviations: ACTH, adrenocorticotropic hormone; CEA, carcinoembryonic antigen; FMTC, familial medullary thyroid carcinoma; MEN, multiple endocrine neoplasias; MTC, medullary thyroid carcinoma; PET, positive emission tomography.

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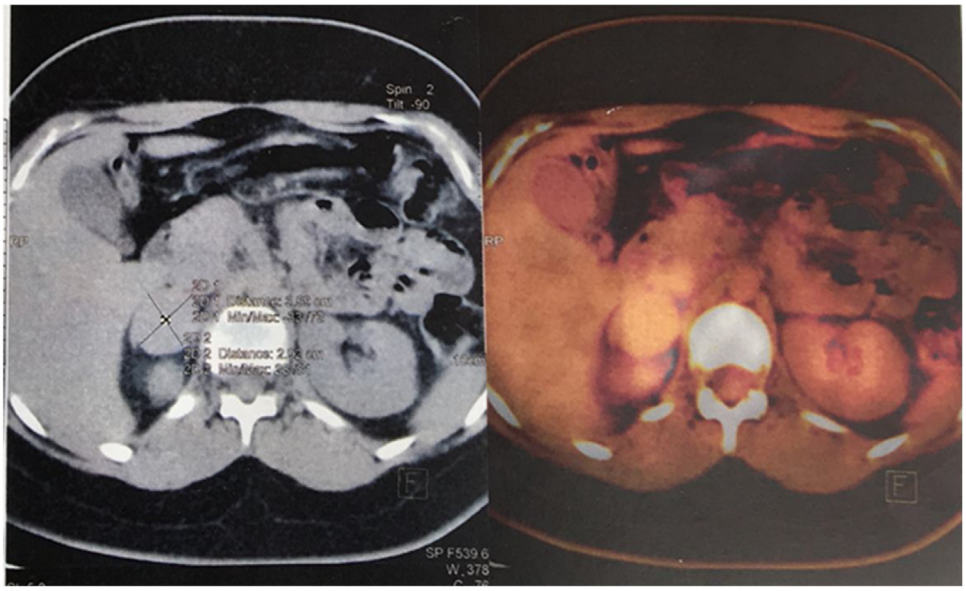

Fig. 1. PET-CT: Increased metabolic activity of FDG at the level of a tumor of the right adrenal gland (36 × 29 mm), possibly pheochromocytoma.

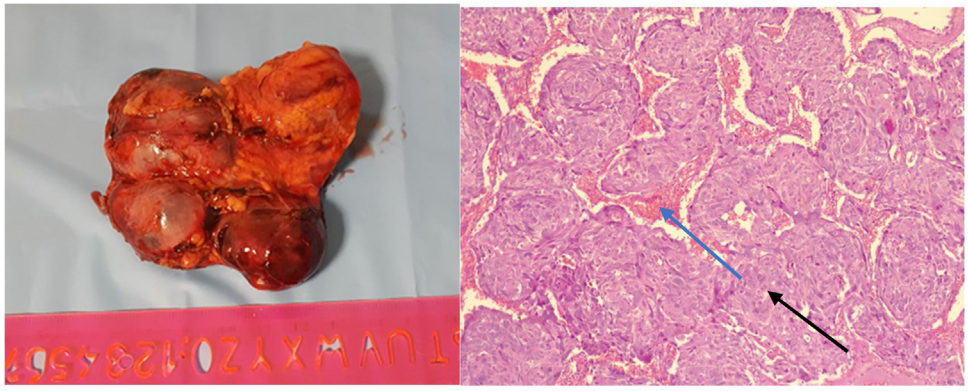

Fig. 2. (A, B) A - macroscopic view of multinodular solid adrenal tumor, the biggest was 41 × 32 mm. B - Photomicrograph (**original magnification**, **x10**; hematoxylin-eosin stain). Multifocal pheochromocytoma of adrenal medulla with alveolar pattern of growth (Zellballen architecture) (black arrow) and rich vascular network (blue arrow).

tion. The treatment of choice is thyroidectomy with postoperative follow-up by the assessment of calcitonin and CEA [8,9].

Thyroid cancer is the most common cause of death in the majority of patients with MEN 2A. Pheochromocytoma occurs in about 50% of patients with this pathology, and 15% of them develop parathyroid tumors (hyperplasia or adenoma) [3,4].

Pheochromocytoma is a catecholamine secreted tumor that is characterized by adrenal hyperplasia, but clinical symptoms and signs of the disease occur (biochemical tests and / or imaging methods) in only 50% of patients [10].

Pheochromocytomas in MEN2 are almost always benign but tend to be bilateral in 50–80% of cases and most frequently affects the age of 35–45 years, children under 10 can also be impacted [10,11].

In up to 25% of cases pheochromocytoma is the first manifestation of the disease, after MTC, which is reported to be the onset syndrome in 40% of patients, at the same time in 35% of cases MTC and pheochromocytoma are diagnosed simultaneously [10].

The most sensitive test in the diagnosis of pheochromocytoma is the concentration of the plasma and urinary metanephrines; CT, MRI, positive emission tomography (PET) are also indicated [12]. Surgical treatment (uni- or bilateral adrenalectomy) is being performed depending on the extent of the disease at the time of diagnosis. Laparoscopy is the choice of approach in surgical treatment. Limitations only arise because of technical difficulties or tumor size.

Hyperparathyroidism rarely occurs in MEN 2A, and manifests more frequently by hyperplasia than by parathyroid adenoma. Treatment consists in subtotal (3 1/2 gland) or total parathyroidectomy with a subcutaneous autograft of a portion of a gland [4].

We report the clinical case of a patient with MTC and bilateral pheochromocytoma, a familial form, having first degree relatives (mother) with pheochromocytoma. Genetic testing was not performed due to the death of the first degree relatives.

2. Case report

We present the clinical case of patient M.S. 20 years old, with MEN 2A syndrome, which has been manifested by bilateral pheochromocytoma and medullary thyroid carcinoma.

In 2015, after a check-up, suspicion of an adrenal gland tumor was raised. The patient presented the following symptoms: hypertension with often crises, episodic headaches, palpitations, irritability, sweating, pallor.

The diagnosis was confirmed by biochemical tests (increased plasma and urinary metanephrines levels) and MRI, where an ovoid

Table 1
Laboratory tests 2014–2020 years.

Laboratory tests	29.12.2014	30.06.2018	08.10.2018	13.11.2018	15.01.2020
Cortisol	449,9 (171–536)	318,2 (171–536)			
ACTH	55,33 (7,2–63,3)				165,3
Aldosterone	21,2 (1,76–23,2) Supine (2,52–39,2) standing				
Vanilmandelic acid	26,45 (1–11) children (0,1–0,18) adults				
Phosphor	1,24 (1,09–2)				
PTH	308 (15–65)				42
Calcium ionic	1,06 (1,05–1,3)				
Calcium	2,39 (2,3–2,75)				
Sodium		136,8 (135–148)			
Potassium		4,81 (3,5–5,3)			
Anti-TPO	15 (up to 34)				
T3	2,4 (1,4–3,34)				5,7
T4	115,4 (76,1–170)				
TSH	2,52 (0,51–4,3)	2,14 (0,51–4,3)			3,06
FT4		13 (12,6–21)			
creatinine		59 (up to 88,4)			
urea		3,4 (up to la 8,3)			
metanephrines			571 (up to 375)		
normetanephrines			1197 (up to 550)		
3-metoxi-tiramina			75,7 (up to 460)		
Chromogranin A				263 (27–94)	
Calcitonin				121 (norm <10 pg/mL)	62,8

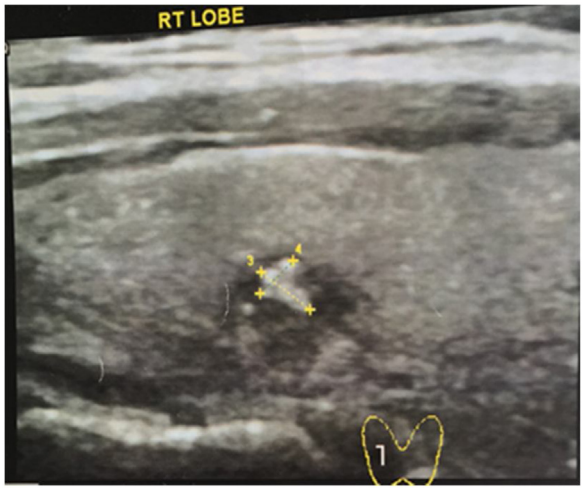

Fig. 3. USG of the thyroid gland: right lobe with one heterogeneous node 7 mm and multiple calcinates, intronodular vascularity.

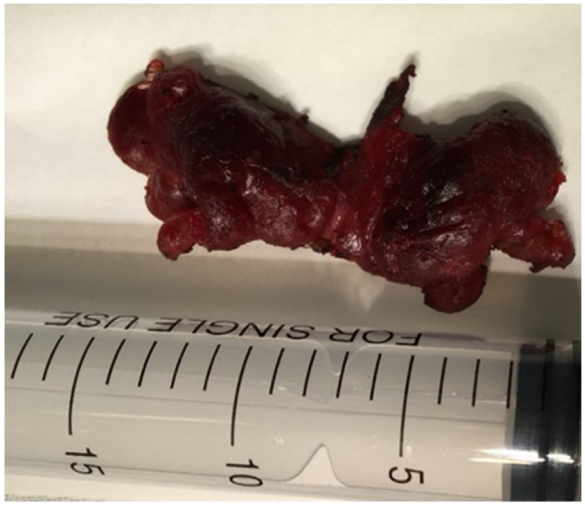

Fig. 4. Macroscopic view of the thyroid gland, 8 × 3 cm.

tumor (46 × 37 × 43 mm with regular contour, homogeneous structure) has been visualized.

According to the patient, her mother suffered from hypertension, episodic headache and palpitations during pregnancy. The diagnosis of eclampsia has been established. During birth she had a hypertonic crisis again and died within hours of the birth of profuse uterine bleeding. Necropsy revealed adrenal tumor on her left and histopathological examination confirmed multicentric, predominantly alveolar pheochromocytoma.

In 2015 our patient underwent laparoscopic adrenalectomy on her left. Histopathological examination revealed multicentric, predominantly alveolar pheochromocytoma.

During the years 2015–2018, after the intervention, her well-being improved, with hypertonic crises only once a month. In July 2018 more intense, frequent hypertensive crises appeared with characteristic signs.

Thus, on 11.07.2018 a CT of the abdomen was performed, where a tumor (27 × 32 mm) of the right adrenal has been detected (benign origin according to the character of contrasting).

15.12.2018 PET-CT: Increased metabolic activity of FDG (mean SUV = 11.5) at the level of a tumor of the right adrenal gland (36 × 29 mm), possibly pheochromocytoma increased diffuse accumulation of radiopharmaceutical in the bone marrow, more evident in the thoracic segment of the spine and pelvic bones (Fig. 1).

All laboratory tests for the years 2014–2020 are presented in Table 1.

In April 2019, the patient underwent laparoscopic total adrenalectomy on the right. This intervention was done by head surgeon with thirty years' experience. Macroscopic examination revealed multinodular solid adrenal tumor, the biggest nodule being 41 × 32 mm. Histopathological examination described multicentric, predominantly alveolar pheochromocytoma (Fig. 2A, B).

In February 2020, the patient is hospitalized for scheduled total thyroidectomy, showing symptoms of a permanent lump in the throat, difficulty swallowing, feeling of suffocation in a supine position, general weakness, fatigue.

Total thyroidectomy is the recommended treatment for all medullary thyroid carcinoma in MEN 2A syndrome, confirmed by elevated calcitonin levels and imaging data.

USG of the thyroid gland 11.12.2014: right lobe - 19 × 12 × 32 mm, left lobe - 19 × 12 × 36 mm. Isthmus 3,3 mm, heterogeneous nodules 3 × 4 mm and 7 × 4 mm.

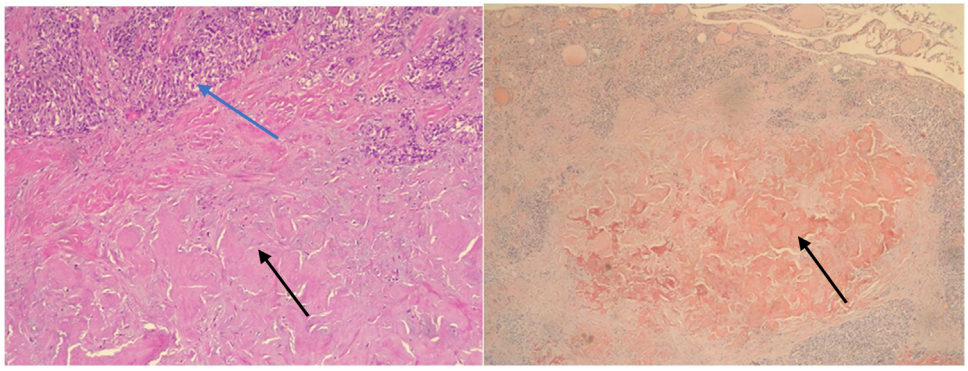

Fig. 5. (A, B). A - Photomicrograph (**original magnification**, **x10**; hematoxylin-eosin stain). Medullary thyroid carcinoma with trabecular pattern of growth. 1. Amyloidosis of the stroma (black arrow). 2. Plasmacytoid tumoral cells with round nuclei (blue arrow). B-Photomicrograph (**original magnification**, **x4**; (Congo red stain). Positive reaction for amyloid in tumoral stroma (black arrow).

USG of the thyroid gland 15.01.2020: right lobe - 14 × 14 × 31 mm, one heterogeneous node 7 mm with multiple calcinates, left lobe - 13 × 14 × 29 mm one heterogeneous node 8 × 6 mm with single calcined and irregular borders, pronounced peri- and intranodular vascularity), isthmus - 0.3 cm (Fig. 3).

CT of the thyroid gland with contrast 11.21.2018: areas with nodular lesions in both thyroid lobes with dimensions of 5 mm on the right and 12 × 9 mm on the left.

Total thyroidectomy was performed, macroscopic examination revealed multinodular thyroid gland with dimensions 8 × 3 cm (Fig. 4). This intervention was done by head surgeon with twenty years' experience. Given that regional lymphadenopathy was determined neither preoperatively nor intraoperatively, and thyroid gland with small nodules without invasion into a capsule, it was decided not to perform neck lymph nodes dissection.

Histopathological examination of the thyroid tissue revealed non-encapsulated medullary carcinoma with trabecular pattern, amyloidosis of the tumor stroma, low degree of pleomorphism and minimal mitotic activity, without LVI-0 and 0 lymphovascular invasion, surgical resection margins negative to tumor (R0), no invasion into thyroid capsule, pT1aNxMx LVI-0 Pn-0 R0. Histochemical investigation with Congo red for detecting amyloid deposits in the tumor stroma was positive (Fig. 5A, B).

The postoperative evolution of this patient is favorable. She is satisfied with the received treatment and is being supervised by an endocrinologist, undergoing hormone replacement therapy. Currently the patient receives 25 mg of cortisone in the morning and the fourth part at noon, prednisolone tablets 2.5 mg in the morning, under the monitoring of the arterial pressure, and L-thyroxin tablets 50 mg.

Recent laboratory tests (25.05.20): PTH - 19,3 pg/mL, calcitonin – 18,7 pg/mL, TSH- 0,2ul/mL, ionic calcium – 1,09 mmol/l. The decrease in calcitonin from 121 to 18.7 pg/mL reflects the effectiveness and radicality of the surgical treatment applied.

3. Discussions

Sipple syndrome is the most common type of multiple endocrine neoplasias MEN 2 (80% of cases). It is characterized by the presence of medullary thyroid carcinoma (MTC), uni- or bilateral pheochromocytoma (in over 50% of cases) and primary hyperparathyroidism resulting from parathyroid cells hyperplasia or adenoma (15–30% of cases) [3,4].

The case emphasizes the importance of the radical approach to MEN 2A syndrome from both a therapeutic and surgical point of view. It is necessary a strong collaboration with the physician and endocrinologist for the evaluation of family members of patients with multiple endocrine neoplasia in the absence of the possibility of their genetic testing.

Imaging check-up in combination with annual monitoring of calcitonin, chromogranin A, and metanephrines in a patient with MEN 2A syndrome is a practical way to supervize the case and make timely decisions for surgical intervention and to prevent complications.

Prior to surgery, the presence of a functional pheochromocytoma should be ruled out by appropriate biochemical analysis in all MEN 2A and MEN 2B patients. If a pheochromocytoma is detected, adrenalectomy should be performed before thyroidectomy or other surgery to avoid intraoperative catecholamine release. Laparoscopic adrenalectomy is the gold standard in the treatment of pheochromocytoma. Limitations only arise because of technical difficulties or tumor size. Long-term treatment with alpha and beta blockers should only be used in patients with unresectable tumors.

Pheochromocytoma occurs in about 50% of patients MEN 2A, is almost always benign but tends to be bilateral in 50–80% of cases and most frequently affects the age of 35–45 years, children under 10 can also be impacted. In up to 25% of cases pheochromocytoma is the first manifestation of the disease, after MTC, which is reported to be the onset syndrome in 40% of patients, at the same time in 35% of cases MTC and pheochromocytoma are diagnosed simultaneously [9].

In our case we had the bilateral, benign pheochromocytoma, which appeared almost at the same time as the medullary thyroid carcinoma. In cases when the pheochromocytoma is the first manifestation of the disease we must be careful about the development of MTC which is an aggressive tumor with rapid metastasis.

4. Conclusions

The radical approach to MEN 2A syndrome is very important from both a therapeutic and surgical point of view. Imaging check-up in combination with annual monitoring of calcitonin, chromogranin A, and metanephrines in a patient with MEN 2A syndrome is a practical way to supervise the case and make timely decisions for surgical intervention and to prevent complications.

If a pheochromocytoma is detected, adrenalectomy should be performed before thyroidectomy or other surgery to avoid intraoperative catecholamine release.

Laparoscopy is the choice of approach in surgical treatment. Limitations only arise because of technical difficulties or tumor size.

Declaration of Competing Interest

No conflict of interest.

The work has been reported in line with the SCARE 2018 criteria [13].

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Ethical approval

The case report is exempt from ethnical approval in our institution.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

S.U. – designed the model and proposed the concept with the help of N.Ş.,M.B.,Z.A.

N.Ş. – wrote the manuscript with support from S.U. and R.R was in charge of overall direction and planning.

Z.A. – data collection and performed the final revision of the manuscript.

V.G. – data analysis and performed the numerical calculations for the table.

M.B. – formulating the conclusion of the case.

M.P. – analysis and interpretation of histological samples.

R.R. – assisted with correction of the data, planned and helped shape the case.

All authors discussed the results and commented on the manuscript.

Registration of research studies

The case report is not a research.

Guarantor

The Guarantor is Mrs. Natalia Şipitco, PhD, associate professor.

Provenance and peer review

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