Baltic Journal of CLINICAL MEDICINE and RESEARCH • 2025/01 • 009-012
https://doi.org/10.25143/rsu-bjcmr.2025.01.009-012
BJCMR

Familial MEN2A Syndrome with Hereditary Medullary Thyroid Cancer

Rebeka Dragūne[1], **Natalja Kapļa**[2]

Affiliation: [1] University of Latvia, Faculty of Medicine;
[2] Pauls Stradins Clinical University Hospital, Latvia

E-mail: rebekadrag@gmail.com

Summary

This case reports MEN 2A syndrome with familial medullary cell carcinoma of the thyroid gland with inheritance in 3 generations. Four of the five tested family members were asymptomatic but with suspicious changes in thyroid ultrasound. Therefore, this case represents the importance of testing family members before they develop any symptoms.

Keywords: MEN2A syndrome, Familial medullary thyroid carcinoma, RET gene.

Introduction

Multiple endocrine neoplasia (MEN) syndromes are infrequent inherited disorders in which more than one endocrine gland develops benign or malignant tumours or grow excessively without forming tumours. There are 3 well-known forms of MEN syndromes – MEN1 (Wermer syndrome), MEN2A (Sipple syndrome), and MEN2B and a newly documented one – MEN4. All these types have autosomal dominant predispositions. The *MEN1* gene is responsible for MEN1 disease, *RET proto-oncogene* for MEN2 and *CDNK1B* for MEN4 syndrome (Yasir et al., 2023; Wijewardene et al., 2017).

MEN1 syndrome is rare, with and incidence of 1 in 30,000 people. Patients with MEN1 syndrome are characterized by the co-occurrence of primary hyperparathyroidism affecting 95% of patients, neuroendocrine tissue tumour (NET's) of gastro-entero-pancreatic organ systems in 30–80% of patients where gastrinoma is most common and insulinoma is the second most common tumour and/or pituitary adenomas in 15–50% of patients where prolactinoma is most common tumour (Singh et al., 2024).

MEN2 syndromes are less common than MEN1. MEN2A phenotype represents approximately 95% of all cases of MEN2 syndrome and are in high risk (95%) of developing medullary thyroid carcinoma (MTC), pheochromocytomas develop in 50% of patients and hyperparathyroidism in 20-30% of patients. MEN2B syndrome, like MEN2A, is characterized by MTC as initial feature in 95% of patients and pheochromocytoma in 50% of patients but differs in that a marfanoid body type and mucosal neuromas may develop (Brandi et al., 2021; Eng et al., 2023).

MEN4 syndrome is the rarest and patients develop anterior pituitary tumours, parathyroid tumours, which may occur in association with tumours of the kidneys, adrenals and reproductive organs (Brock et al., 2023).

This case describes a familial medullary cell carcinoma of the thyroid gland (FMTC) with inheritance in 3 generations with 5 family members affected.

Case report

73-year-old men was admitted to emergency department in serious condition – diarrhoea, weight loss, skin flushing and lower extremity weakness. Objectively – dehydration, massive neck

lymphadenopathy, large nodular goiter. Thyroid ultrasound showed – a large nodule with multiple small calcifications in the right lobe and a similar nodule in the left lobe (TIRADS 5) (Fig.1). Radiologically – metastatic process in the lungs, liver, bones, neck and mediastinal lymph nodes. Thyroid CORE biopsy and laboratory evaluation showed ACTH-secreting MTC (Table 1). The patient died one month after the diagnosis established. Because of severe MTC, the relatives of the patient underwent preventive testing for MEN2A syndrome. All patients underwent fine needle aspiration and were tested for *carcinoembryonic antigen* (CEA), serum fasting calcitonin and RET gene mutation, calcium, parathyroid hormone (PTH), vitamin D (Table 2). Also, all patients underwent 24-hour urinary catecholamine testing to exclude the presence of pheochromocytoma. Two of the patients' sons showed high catecholamines, so they underwent ^{123}I-MIBG testing, but no pheochromocytoma was identified.

Patients' son is 49 years old and asymptomatic. USG showed – colloidal nodose thyroid gland and nodule in the right lobe (TIRADS 4a) (Fig.2). His daughter is 26-year-old and asymptomatic. USG showed – thyroid gland nodule (TIRADS 4a) (Fig.3).

Table 1. Laboratory findings in 73-year-old-patient

Laboratory tests		Reference intervals
Calcitonin level	97756 pg/ml	< 8.4 pg/ml
CEA	2052.22 ng/ml	0–5 ng/ml
24-hour urine cortisol	802.60 ug/24h	20.0–292.3 ug/24h
ACTH	80.70 pg/ml	0–46 pg/ml

Table 2. Laboratory findings in patients' relatives

Patient	CEA (ng/ml)	Calcitonin level (pg/ml)	RET gene mutation	Vitamin D (ng/ml)	PTH (pg/ml)	Calcium (mmol/l)
Reference intervals	0-5	< 8.4		> 30	18.5–88	2.1–2.6
Patients 49-year-old son	18.3	440.75	+	N	N	N
His 26-year-old daughter	8.82	115	+	N	N	N
His 21-year-old son	N	N	-	N	N	N
Patients 44-year-old son	10.6	706.60	+	N	N	N
His 16-year-old daughter	0.7	67.63	+	N	N	N

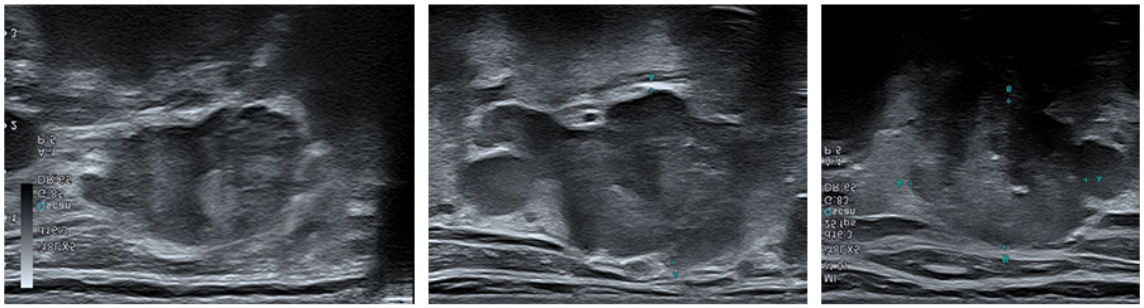

Figure 1. 73 year-old patient. TIRADS 5.

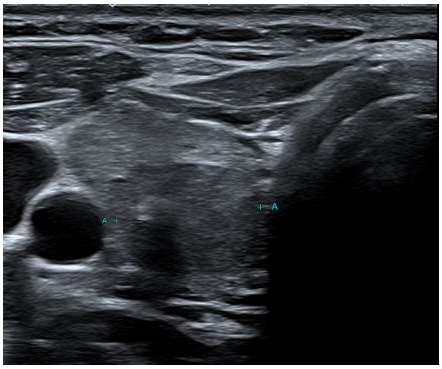

Figure 2. 49-year-old patient. TIRADS 4a.

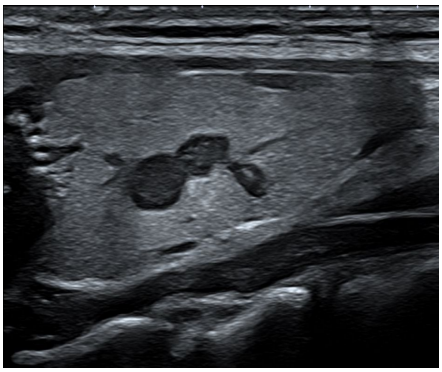

Figure 3. 26-year-old patient. TIRADS 4a.

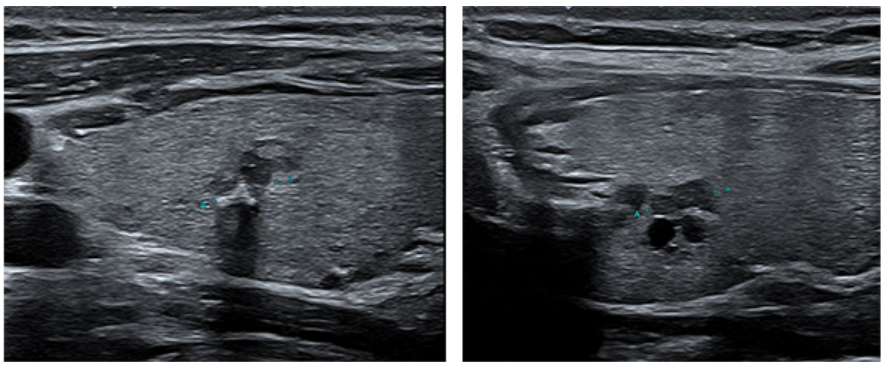

Figure 4. 44-year-old patient. TIRADS 4a.

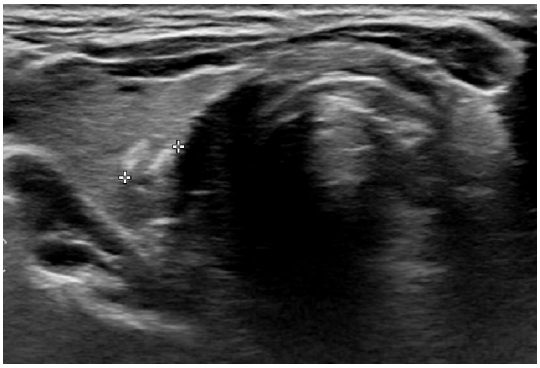

Figure 5. 16-year-old patient. TIRADS 5.

Patients another son is 44 years old and asymptomatic. USG showed – nodules in both lobes (TIRADS 4a) (Fig.4). His daughter is 16-year-old and asymptomatic. USG showed – a small nodule with microcalcifications in the right lobe (TIRADS 5) (Fig.5). Among the five family members, four were diagnosed with medullary thyroid carcinoma in both thyroid lobes, while one had MTC diagnosed in a single lobe. Genetic analysis identified heterozygous variant in the RET gene c. 1832G>A, p. (Cys611Tyr). All patients underwent total thyroidectomy with central/lateral lymph node dissection.

Conclusions

The most common MTC presentation is a solitary thyroid nodule without any symptoms. It is important to detect the risk factors for familial MEN syndrome, such as high fasting calcitonin and a family history of MTC. After the diagnosis of MTC is made, other family members must be evaluated for fasting calcitonin, CEA, PTH, thyroid ultrasound, and RET gene mutation.

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