



Ganglioneuromatous polyposis associated with type 2 B multiple endocrine neoplasia (MEN 2B) – case report

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Rycyk-Bojarzyńska A, Kasztelan-Szczerbińska B, Cichoż-Lach H, Jargieło A. Ganglioneuromatous polyposis associated with type 2 B multiple endocrine neoplasia (MEN 2B) – case report. *Ann Agric Environ Med.* 2024; 31(2): 302–305. doi: 10.26444/aaem/171736

Abstract

Multiple endocrine neoplasia type 2B (MEN 2B) is a rare autosomal dominant hereditary cancer syndrome which is characterized by the appearance of medullary thyroid carcinoma (MTC), pheochromocytoma, parathyroid adenomas, ganglioneuromas of the digestive tract, and musculoskeletal abnormalities. The case is presented of a 31-year-old male patient with numerous polyps in the colon described as ganglioneuromas which are ectodermal neoplasms emerging from a proliferation of ganglionic cells of the sympathetic nervous system. The results show elevated levels of normetanephrine, which is an endogenous catecholamine metabolite, and has high diagnostic sensitivity as well as specificity in pheochromocytoma detection. The patient underwent partial thyroidectomy due to a nodular goiter. He was admitted to the Department of Gastroenterology to lead a diagnostic pathway towards MEN 2B.

Key words

multiple endocrine neoplasia type 2 (MEN2), ganglioneuromatous polyposis, ganglioneuroma, pheochromocytoma, multiple endocrine neoplasia type 2B (MEN2B)

Abbreviations

MEN 2A – multiple endocrine neoplasia type 2A, **MEN 2B** – multiple endocrine neoplasia type 2B, **MTC** – medullary thyroid carcinoma, **CLA** – cutaneous lichen amyloidosis, **HD** – Hirschsprung's disease, **CT** – computed tomography, **MRI** – magnetic resonance imaging, **PET-CT** – positron emission tomography-computed tomography, **GP** – ganglioneuromatous polyposis, **DG** – diffuse ganglioneuromatosis, **NF1** – neurofibromatosis 1, **CS** – Cowden syndrome, **GI** – gastrointestinal

INTRODUCTION

Multiple endocrine neoplasia type 2 (MEN 2) is an autosomal dominant hereditary cancer syndrome caused by activating germline mutations of the *RET* protooncogene [1, 2]. Two clinical units can be distinguished: MEN 2A and MEN 2B. MEN 2 is further sub-divided into four subtypes:

- 1) classical MEN 2A, associated with medullary thyroid carcinoma (MTC), pheochromocytoma and primary hyperparathyroidism;
- 2) MEN 2A associated with cutaneous lichen amyloidosis (CLA);
- 3) MEN 2A associated with Hirschsprung's disease (HD) and familial MTC (FMTC) [3];

MEN 2B is a rare syndrome which occurs in the population of 1–2 in a million and is characterized by the appearance of medullary thyroid carcinoma, pheochromocytoma, parathyroid adenomas, ganglioneuromas of the digestive tract, and musculoskeletal abnormalities [1]. Catecholamine-producing pheochromocytoma occurs in about 50% of MEN 2B cases, while medullary thyroid carcinoma is typically the

first symptom of MEN 2B in 40% of all MEN 2B patients [3]. Pheochromocytoma is mostly benign, and in 50–80% of cases is bilateral and nearly always adrenal [4]. Ganglioneuromas are extremely rare ectodermal neoplasms of the sympathetic nervous system [5, 6]. In the histopathological image they can easily be differentiated from other types of polyps due to the presence of structures, such as nerve fibres, ganglion cells or Schwann's cells [5]. Less than 100 cases of ganglioneuromas are described in the medical literature [7].

CASE REPORT

The case is present of a 31-year-old male patient, with numerous polyps in the colon described as ganglioneuroma, treated with L-thyroxine after a partial strumectomy due to a nodular goiter. The patient had been taking levothyroxine every day, and was admitted to the Department of Gastroenterology to lead a diagnostic pathway towards multiple endocrine neoplasia type 2B (MEN 2B). He presented with periodic constipation, loss of appetite, and denied the appearance of diarrhea, vomits or blood in the stool. The patient's father had six colonic polyps removed in the past, and at the age of seven, the patient himself underwent colon polypectomy. In September 2018, a colonoscopy was performed which showed numerous polyps of different sizes throughout the course of

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the colon, and inflammatory foci in the mucous membrane of the caecum. Since then, no endoscopy procedures had been performed on the patient and he did not attend any gastroenterology appointments.

Endoscopies were performed for supervision of colon and stomach. Colonoscopy revealed sections of low intensity chronic inflammation of the large intestine mucosa, with the presence of lymphatic nodules, xanthomas, features of pseudopolyps and multiple ganglioneuroma foci. Endoscopy of the upper digestive tract showed chronic gastritis with focal foveolar hyperplasia.

During gastroscopy performed during the patient's stay in the Gastroenterology Department, numerous, small polyps were found in the descending and bulbous part of the duodenum. A few were taken for histological examination. Six polyps were also detected in the pyloric part of the duodenum, of which the largest was removed with a diathermic loop. Body mucosa showed regular folds and was abundant with Elster-type polyps (max. 10 mm diameter). Thyrological assessment was also carried out which confirmed the correct hormonal balance, and further blood tests were commissioned in order to increase the diagnostics towards one of the components of the MEN 2B syndrome (medullary thyroid cancer).

The results showed elevated levels of normetanephrine, an endogenous catecholamine metabolite which has a high diagnostic sensitivity as well as specificity in pheochromocytoma detection. Other test results, such as calcitonin, chromogranin A, 5-hydroxyindoleacetic acid (5-HIAA), normetanephrine, and 3-methoxytyramine, were within normal limits. Table 1 shows the main results of laboratory investigations on the patient.

The patient was discharged from the hospital with a recommendation to undergo genetic testing to exclude the presence of germline mutation in the *RET* gene.

Table 1. Main results of laboratory investigations on the patient

LABORATORY TEST RESULTS			
Variable	Unit	Reference range	On admission
Chromogranin A	ng/ml	<94.0	49.4
5-HIAA	mg/24 h	2.0-9.0	4.3
Metanephrine	pg/24 h	43.0-260.0	297.7
Normetanephrine	pg/24 h	128.0-484.0	323.3
3-methoxytyramine	pg/24 h	55.0-247.0	221.6
TSH	mIU/L	0.55-4.78	0.45
FT4	ng/dl	0.89-1.76	1.42
Calcitonin	pg/ml	<18.2	8.71
CEA	ng/ml	<5.0	<0.5
PTH	pg/ml	18.4-80.1	33.0
Ca	mg/dl	8.7-10.4	9.6

*5-HIAA - 5-hydroxyindoleacetic acid, TSH -Thyroid stimulating hormone, FT4 - Free tetraiodothyronine, CEA - Carcinoembryonic antigen, PTH - Parathyroid hormone

DISCUSSION

MEN syndromes include MEN 1, MEN 2 (or MEN 2A), MEN3 (or MEN 2B), and the recently identified MEN 4 associated with *CDKN1B* mutation [8, 9]. Most patients, i.e. 75% of MEN 2 cases, present with symptoms of MEN 2A.

MEN 2B, first identified in 1975, is the most aggressive of the MEN 2 variants. MEN 2B is an autosomal dominant syndrome which appears rarely (1:35 000). The average age of patients diagnosed with MEN2B is 14 years while the patient in the presented case was a man aged 30 when diagnosis was made [10].

All variants of MEN 2 show a high penetrance for MTC [11]. MEN 2B is characterized by MTC and pheochromocytoma, plus decreased upper/lower body ratio, a marfanoid habitus, and the presence of mucosal neuromas and intestinal ganglioneuromatosis [12, 13]. In the PubMed database, there are more than 900 articles related to MEN 2B, among which mucosal neuroma and Marfan-like habitus were observed in 99% of MEN 2B patients, 95% had MTC, and 50% of patients had pheochromocytoma [10].

MTC is the major cause of death among patients with MEN 2, and there are specific guidelines recommending the proper management of MTC in patients with MEN 2B. If possible, even prophylactic thyroidectomy should be performed [1, 14]. Unfortunately, there are no recommendations for the management of ganglioneuromatous polyposis [15]. The clinical characteristics of MEN 2B are summarized in Table 2) [13].

Table 2. Criteria of MEN 2B diagnosis

MEN 2B	Medullary thyroid carcinoma (MTC)
	Adrenal medulla (pheochromocytoma)
	Intestinal and mucosal ganglioneuromatosis
	Characteristic habitus, marfanoid

Medullary thyroid carcinoma (mtc). MTC is presented as a solitary thyroid nodule or a multinodular goiter [3]. Typical manifestations of MEN 2B are MTC and intestinal ganglioneuromatosis [11, 16], two conditions that lead to dysmotility and have a high impact on a quality of MEN 2B patients life. MTC can be asymptomatic for many years among MEN 2B patients. The product of MTC is calcitonin which is also used as a very good diagnostic marker of this type of cancer. MTC associated with MEN 2B is very aggressive and the prognosis is poor [11]. The patient in this case report presented with a nodular goiter, typical for MTC, and underwent a partial thyroidectomy.

Adrenal medulla (pheochromocytoma). As a result of improved management, both pheochromocytoma and MEN 2A and MEN 2B have been eliminated as a major cause of death [11]. Screening for pheochromocytoma is possible by measuring plasma or 24-hour urine normetanephrine and metanephrine levels [17, 18]. However, there is still a lack of consensus about which test should be performed, although according to recommendations, either one can be used as the first test [11, 19].

When plasma or urinary catecholamine values are increased, or in the case of suspicion of a pheochromocytoma, the next step should be performing abdominal magnetic resonance imaginig (MRI), computed tomography (CT) imaginig, or positron emission tomography-computed tomography (PET-CT) imaging [19]. Among the imaging methods, CT has a high sensitivity (around 100%) for the screening of adrenal tumours, while MRI seems to be more useful for detecting a pheochromocytoma than computed

tomography [20, 21]. According to the guidelines by the European Association of Nuclear Medicine, the most sensitive imaging method is PET-CT, with a sensitivity of 94%-100% [20].

Ganglioneuromatous polyposis. Ganglioneuromas are mostly benign and uncommonly encountered in the gastrointestinal tract. They can be classified into major: polypoid ganglioneuromas (most common), ganglioneuromatous polyposis (GP), and diffuse ganglioneuromatosis (DG) [22, 23, 24]. They can be associated with neurofibromatosis 1 (NF 1), juvenile polyposis, MEN 2B, non-familial adenomatous polyposis, tuberous sclerosis, Cowden syndrome (CS), and Ruvalcaba-Myhre-Smith syndrome [5, 22, 23, 24]. Ganglioneuromas in the gastrointestinal (GI) tract can be manifestations of various syndromes, for example, Mauro et al. (2021) presented the case of a 9-year-old boy with DG [25]. However, Nguyen et al. (2006) described the case of a 13-year-old patient who had intestinal ganglioneuromatosis only [26]. In these two dissertations [25, 26], in order to explain the alimentary tract ganglioneuromatosis, further examinations towards different syndromes and symptoms were carried out which were crucial for the diagnose of ganglioneuromas.

MEN 2B patients may be asymptomatic or may present with mostly GI symptoms, such as abdominal pain, constipation or diarrhea, and may include ganglioneuromatosis [22]. A few cases of toxic megacolon have also been observed [10, 27, 28, 29]. O'Riordain et al. performed a study involving patients with MEN 2B syndrome in which 90% of participants had colonic disturbances, mostly constipation, and all of them had MTC [29]. Ganglioneuromas, especially in the colon, is rare among adults [30, 31, 32, 33]. The diagnosis of ganglioneuromas is based on histopathological analysis, such as a biopsy stained with haematoxylin and eosin, which would show spindle and ganglion cells [23, 30].

Characteristic habitus, marfanoid. Patients with MEN 2B can develop a characteristic appearance called Marfan-like habitus [34], but this did not occur in the patient in the presented case report. Patients with Marfan-like habitus present with pectus carinatum, reduced elbow extension, hindfoot deformity, gothic palate, downslanting palpebral fissures, and lens subluxation [35]. One of the most common descriptions of MEN 2B with Marfan-like habitus is the biological mother of President Abraham Lincoln, Nancy Hanks Lincoln, who died at the age of 34 [36].

CONCLUSIONS

The management of MEN 2 can be referred to as the '5P' strategy: to prevent, predict, personalize, offer psychological support, and participate [37]. The strategy aims to improve the clinical outcomes for individuals with MEN 2 who present with a worse health-related quality of life in many domains, including anxiety, depression, fatigue, pain interference, physical functioning, and sleep disturbance. The patient in the presented case report was representative of this group, and remains under hospital supervision because he requires treatment tailored specially for his needs. He has also been scheduled for surveillance colonoscopy in a year's time.

Ganglioneuromatous polyposis as a part of MEN 2B is rarely described in the medical literature; hence, there is still lack of consensus of opinion concerning all aspects of MEN 2B, which requires further investigation.

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