

# Multiple Endocrine Neoplasia 2B Presenting with Pseudo-Hirschsprung's Disease

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Multiple endocrine neoplasia type 2B (MEN 2B) is a rare syndrome characterized by medullary thyroid carcinoma (MTC), pheochromocytoma and typical phenotypic features, such as marfanoid habitus, multiple mucosal ganglioneuromas and thickened corneal nerves. Individuals with MEN 2B may develop megacolon and pseudo-obstruction due to intestinal ganglioneuromatosis simulating Hirschsprung's (HSCR) disease. We hereby describe the clinical and genetic features of a 21-year-old male patient with MEN 2B associated with pseudo-HSCR disease. The patient had MTC, pheochromocytoma, marfanoid habitus, multiple mucosal ganglioneuromas, thickened corneal nerves and severe gastrointestinal involvement. Emergent laparotomy was performed when he was presented with acute bowel obstruction. The myenteric and submucosal nerve plexuses in the small and large intestines were composed of diffusely hyperplastic, disorganized, mature ganglion cells. Genetic testing revealed a *de novo* *ret* proto-oncogene germline mutation in codon 918 in exon 16. Megacolon and pseudo-obstruction similar to the HSCR disease may develop in patients with MEN 2B. However, the observed dysmotility is the result of an abnormal proliferation of intramural ganglion cells in contrast to the absence of enteric ganglia which were present in the HSCR disease. Attentiveness about the phenotypic characteristics and unusual findings might lead to early and correct diagnosis of the MEN 2B syndrome. This approach improves the survival rate and quality of life considerably.

**Key words:** multiple endocrine neoplasia type 2B ■ Hirschsprung's disease ■ intestinal obstruction ■ ganglioneuromas ■ medullary thyroid carcinoma ■ pheochromocytoma

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## INTRODUCTION

Multiple endocrine neoplasia type 2 (MEN 2) is an autosomal dominant inherited cancer syndrome that affects tissues derived from neural crest.<sup>1</sup> There are three hereditary variants of MEN 2 syndrome. MEN 2A is characterized by medullary thyroid carcinoma (MTC) in virtually 100% of the patients, pheochromocytoma in about 50% of the patients and primary hyperparathyroidism in about 20% of the patients. MEN 2B syndrome is a more complex phenotype consisting of MTC, pheochromocytoma, mucosal neuromas, marfanoid habitus, ganglioneuromatosis of the gut and corneal involvement. Familial MTC is the only MTC syndrome that is not associated with other endocrinopathies, and inherited predisposition to MTC is the only characteristic of the disease.<sup>2</sup>

Hirschsprung's (HSCR) disease is a common congenital malformation associated with the absence of enteric ganglia, which results in severe intestinal obstruction after birth. HSCR disease affects approximately 1/5,000 of neonates and may occur in either sporadic or heritable forms.<sup>3</sup> Association of MEN 2A and HSCR disease is well known.<sup>2</sup> Individuals with MEN 2B may also develop megacolon and pseudo-obstruction due to intestinal ganglioneuromatosis, simulating the HSCR disease.<sup>4,5</sup>

We hereby describe a MEN 2B patient presenting with severe gastrointestinal involvement simulating HSCR disease-like-phenotype.

## CASE REPORT

A 21-year-old male was admitted to our hospital mainly with the complaints of constipation since early childhood, the significance of which remained unrecognized for years by his local physicians. He also had a gradually enlarging swelling at the neck that has been present since 3 years of age. Patient's past medical history revealed a long-lasting chronic constipation and several operations due to intestinal obstructions. He had subtotal thyroidectomy in his local hospital with a diagnosis of euthyroid multin-

odular goiter three years ago. Thyroid histopathological specimens obtained from his local hospital showed multicentric microscopic lesions of MTC in both thyroid lobes.

On physical examination, he was identified as normotensive with a blood pressure of 110/70 mmHg, and found to have marfanoid habitus, multiple mucosal neuromas in oral mucosa, lips and tongues. On slit-lamp examination, thickened corneal nerves and Lisch nodules were detected.

On admission to our general surgery department, a commercially available radioimmunoassay revealed elevated serum calcitonin (706 pg/mL, normal range 0–10 pg/mL). Ultrasonography-guided, fine-needle aspiration biopsy of the suspected lymph node confirmed MTC. Then, he had a completion thyroidectomy and regional lymph node dissection in our center with a positive tumor histopathology in thyroid and lymph nodes. Tumor staging was performed according to the International Union against Cancer tumor–node–metastasis (TNM) classification, which was T2 N1b M0.<sup>6</sup> Gastrointestinal radiological examination with barium and computed tomography has shown severely dilated intestinal segments at the level of both small and large intestines at the follow-up (Figure 1). Emergent laparotomy was performed when he presented with abdominal pain, fever, chills, nausea, vomiting and constipation, because of the patient's intestinal dysmotility and marked colon dilatation caused by acute bowel obstruction.

During laparotomy, diffusely enlarged and thickened distal transverse and proximal descending colon was observed. Obstruction at this level required partial resection of a 31-cm-long segment

of colon. An end-to-end colonic anastomosis was performed to bypass the obstructed bowel. Enterotomy enabled multiple full-thickness biopsies, which were obtained from bead-like thickenings, both in the small and large intestines. Histopathological examination showed diffuse intestinal ganglioneuromatosis with abundant neural tissue in both the myenteric and submucosal nerve plexus involving the resected colon segment and biopsies from the remaining colon and small intestine. There were diffuse hyperplastic and disorganized mature ganglion cells and nerve fibers. Aganglionosis was not detected. The diagnosis was severe intestinal ganglioneuromatosis. Soft-tissue mass on the buccal mucosa was resected, and its histopathological examination confirmed a neuroma.

The clinical presentation and laboratory work-up best fit the diagnosis of MEN 2B syndrome, which necessitated a search for pheochromocytoma. On admission, the 24-hour excretion levels of urinary catecholamine metabolites were normal with vanillylmandelic acid of 4.9 mg/24 hr (normal range, 1.9–9.8 mg/24 hr) and metanephrine of 0.76 mg/24 hr (normal range, 0.01–1 mg/24 hr). However, screening for pheochromocytoma with magnetic resonance imaging detected a mass lesion of 4 cm in the left adrenal gland. The patient underwent unilateral open transabdominal adrenalectomy and the histopathological examination confirmed the presence of a pheochromocytoma.

The family history was unremarkable. The parents of the patient and four brothers were reported to be in good states of health. Genetic testing revealed a germline mutation of the *ret* proto-oncogene in codon 918 in exon 16. A further genetic analysis of the first-degree relatives revealed no affected family members. Therefore, it was concluded that the patient had a de novo MEN 2B mutation.

At 24 months' follow-up, basal (16 pg/mL) and pentagastrin-stimulated calcitonin levels (64 pg/mL) remained slightly elevated with no evidence of recurrence or metastasis of MTC. The patient was normotensive, with the levels of 24 hours' urinary vanillylmandelic acid and metanephrine being within normal ranges and with normal magnetic resonance imaging of the other adrenal gland. The patient had been having occasional abdominal cramps with intermittent episodes of diarrhea and constipation with no evidence of recurrent bowel obstruction.

## DISCUSSION

MEN 2B is characterized by typical phenotypic features, such as mucosal and intestinal ganglioneuromatosis, decreased upper/lower body ratio, a marfanoid habitus, thickened corneal nerves, MTC and pheochromocytoma.<sup>1</sup> MEN 2B patients show a more

**Figure 1. Gastrointestinal radiological examination with barium showing severely dilated large intestine**



aggressive form of MTC and have the worst prognosis among hereditary MTC patients. Early diagnosis and management are crucial for long-term survival. MEN 2B is associated with a point mutation in exon 16 (codon 918) of the *ret* proto-oncogene in more than 95% of the cases.<sup>2</sup> Our case was found to have a mutation in the *ret* proto-oncogene in codon 918 in exon 16. The parents and four brothers were found to be negative for the *ret* proto-oncogene mutation. Unlike MEN 2A and FMTC mutations, de novo mutations are responsible for approximately 50% of all MEN 2B patients.<sup>2</sup>

Transmural ganglioneuromatosis may occur anywhere along the gastrointestinal tract and lead to loss of normal bowel tone, distention, segmental dilation and megacolon. Intestinal symptoms may vary with the area of the involved alimentary tract. The most frequently reported symptoms in previous studies were constipation and intermittent diarrhea.<sup>4,5</sup> Chronic constipation may be attributed to hypomotility as a result of hyperplasia of the intrinsic autonomic ganglia in the intestinal wall and abnormal sphincter function at various levels. Gastrointestinal symptoms usually manifest in infancy and childhood and present before symptoms of extraintestinal endocrine abnormalities. Abdominal pain, obstruction, ileus, appendicitis, failure to thrive and weight loss were other manifestations of intestinal disease. Gastrointestinal symptoms should be managed initially with conservative measures, such as laxatives and conventional enemas, because less than a third of patients will develop symptoms requiring surgery, and most gastrointestinal symptoms can be managed with conservative techniques on a long-term basis.<sup>4,5,7-15</sup>

MEN 2B mutations cause hyperplasia of the RET expressing cells, predisposing them to tumor formation through a gain of function, whereas HSCR mutations cause colonic aganglionosis through a loss of function mechanism.<sup>16</sup> In patients with MEN 2B, megacolon and pseudo-obstruction similar to HSCR disease might develop; however, the observed dysmotility is a result of an abnormal proliferation of intramural ganglion cells and thickening of the myenteric plexus in contrast to the absence of enteric ganglia found in HSCR disease.<sup>7,15</sup> This is an example of two different genetic alterations resulting in similar gastrointestinal clinical pictures, but the underlying histopathological features are entirely different. Accordingly, the intestinal ganglioneuromatosis seen in MEN 2B is named as HSCR-like or pseudo-HSCR disease.<sup>10-15</sup>

In many cases, other extraintestinal stigmata of MEN 2B, such as mucosal neuromas of the lips and tongue, marfanoid habitus, thickened corneal nerve fibers and even MTC, are already present. Despite

the well-characterized phenotypic expression of MEN 2B, the diagnosis of MEN 2B is often missed or delayed, especially when the cases are sporadic, similar to the patient presented here.<sup>4,5</sup> In our case, MEN 2B was diagnosed after MTC was clinically evident. We thought that delay in diagnosis was due to inexperienced physicians in his local hospital. Unfortunately, diagnostic delays result in grave prognosis, since effective treatment and cure of MTC relies on early diagnosis.<sup>2</sup> Previous studies suggested that 93% of the patients with MEN 2B had gastrointestinal symptoms 1–24 years before the diagnosis of MEN 2B.<sup>4</sup> The correct diagnosis was frequently overlooked in MEN 2B patients. Presence of the characteristic features, such as multiple mucosal neuromas, marfanoid habitus and bowel dysfunction, should alert physicians to the possibility of this syndrome.

Pheochromocytoma may be unilateral or bilateral, and it has been reported to occur in 50% of all *ret* mutation carriers of MEN 2B. These patients usually have minimal complaints of intermittent headaches and palpitations. Extensive efforts should be undertaken to exclude the presence of pheochromocytoma. Potential hypertensive crises resulting from unexpected pheochromocytoma, which occur especially during operations such as thyroidectomy or acute abdominal obstruction, may result in severe problems or even sudden death.<sup>17,18</sup>

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