Characteristics of chronic megacolon among patients diagnosed with multiple endocrine neoplasia type 2B

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Abstract

Background: Gastrointestinal symptoms are frequent in multiple endocrine neoplasia (MEN) 2B and may be related to megacolon.

Objective: The objective of this article is to review the clinical features of patients with MEN 2B, particularly megacolon.

Methods: We used natural language processing of electronic medical records of Mayo Clinic patients over 20 years: Eight patients with definite MEN 2B were identified; of these, four had megacolon. From these patients' records, three others with paper medical records were identified through familial association. We used a standard data sheet to identify features of the disease with particular emphasis on megacolon.

Results: Of the 11 patients identified with MEN 2B, seven (63%) had megacolon, typically presenting with constipation in infancy or megacolon in childhood. In addition, three patients had esophageal manifestations (two achalasia and one Zenker's diverticulum). Megacolon often required surgical intervention for intractable constipation, abdominal distension and discomfort. Histopathological features of resected colon revealed enteric and extrinsic nerve hyperplasia and ganglioneuromas of the submucosal and myenteric plexuses.

Conclusions: Among patients with MEN 2B, 63% had megacolon. Significant esophageal motor disorders in MEN 2B may affect ~25% of patients. Any presentation with megacolon should trigger a search for MEN 2B in order to identify the potentially fatal endocrine tumors.

Keywords

Achalasia, M918T mutation, Zenker's diverticulum

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Introduction

Multiple endocrine neoplasia (MEN) is an autosomal-dominant endocrine disorder that includes several subgroups: MEN 1, MEN 2A, MEN 2B, and familial medullary thyroid cancer (FMTTC). MEN 2A accounts for 80% of all MEN 2 cases,¹ whereas MEN 2B is the most aggressive variant and also the rarest, accounting for 5% of cases.²

MEN 2B is characterized by the presence of pheochromocytomas (40% of patients), skeletal abnormalities, in particular a Marfanoid habitus, medullary thyroid cancer (MTC, 100% of patients) and ganglioneuromas. Gastrointestinal involvement (GI) typically presents in infancy with constipation, abdominal discomfort and megacolon, which are caused by intestinal neuromuscular abnormalities, including neuromas.³ The presence of MEN 2B is also manifest with facial

abnormalities including “blubbery” lips, thickening of the tarsal plates, eversion of the upper eyelid, neuromas on the eyelids, conjunctiva, prominent corneal nerves and, particularly, ganglioneuromas of the gastrointestinal mucosa and tongue.

The prevalence of MEN 2 is estimated to be one in 35,000 people,⁴ while MEN 2B's prevalence is approximately one in 500,000.⁴ Previous studies at Mayo Clinic by Carney et al.⁵ in 1976 estimated the prevalence

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of chronic megacolon in patients with MEN 2B was 31%.⁵

Megacolon associated with MEN 2B is often misdiagnosed as Hirschsprung's disease, in which a short length of bowel can be aganglionic with increased cholinergic nerve fibers,⁶ and the colon proximal to this narrowed segment is distended. Ganglioneuromas associated with megacolon are characterized by an increased number of ganglion cells, supportive cells and nerve fibers in all layers of the bowel wall.⁶ The ganglioneuromas can lead to loss of bowel tone, distension, segmental dilation and, ultimately, megacolon. Megacolon is characterized on imaging studies by a permanently enlarged diameter greater than 6.5 cm at pelvic brim, greater than 8 cm in the ascending colon, or greater than 12 cm in the cecum.⁷ Infants with MEN 2B have gastrointestinal symptoms,⁸ with constipation and intermittent diarrhea being the most frequently reported.⁹ Elevated secretion of catecholamines may exacerbate reduced colonic tone, leading to toxic megacolon.¹⁰ This is important to consider, as pheochromocytomas (which produce catecholamines) occur in 40% of MEN 2B cases.

Our aim was to review the clinical features of patients with MEN 2B and megacolon by analysis of electronic medical records (EMRs) of patients diagnosed at Mayo Clinic between 1995 and 2015. From review of these EMRs, we identified three more patients with megacolon and MEN 2B evaluated before 1995, and retrieved their records, which were in paper form.

Materials and methods

Mayo Clinic Institutional Review Board approved the study for patients who had consented to the use of their medical records for research.

The Advanced Cohort Explorer search tool, which was developed at Mayo Clinic, was used to identify patients who had been treated for MEN at Mayo Clinic (Figure 1). Initially the terms "MEN 2B," "Multiple Endocrine Neoplasia 2B," and "Multiple Endocrine Neoplasia Type 2B" were searched in the EMRs at Mayo Clinic between 1995 and 2015. Prior to 1995, patient medical records were documented on paper. This Advanced Cohort Explorer search tool identified 105 patients. Once duplicates were removed, 25 patients were left. Based on the EMRs, 17 of these patients were excluded: One patient had Hirschsprung's disease, 10 patients had MEN 2A, four patients mentioned that MEN had been excluded (mentioned in differential diagnoses), and two patients had metastatic carcinoid tumors. The remaining eight patients had all been diagnosed with MEN 2B, and four had documentation of megacolon. Using these patients' medical records, a further three patients with MEN 2B and megacolon were identified as members of the family of one of the first group of patients.

The data extraction for this study was performed using a standard data sheet and included demographic data, gene mutation identified, family history, manifestations of the disease including signs and symptoms in

Figure 1. Search strategy for identification of patients with megacolon associated with multiple endocrine neoplasia (MEN) 2B.

the eyes, lips, tongue, thyroid, adrenal glands, esophagus, colon, anorectal, and skeletal manifestations.

Results

Patient demographics and non-gastrointestinal manifestations

We identified a total of seven patients with MEN 2B and megacolon. Table 1 shows the demographic data including age at diagnosis both of MEN 2B and megacolon. The youngest age at diagnosis of MEN 2B was 3 years and the oldest was 51 years. Megacolon was diagnosed on autopsy performed on Patient G, who was the father of Patients C, E, and F. The remaining three patients (A, B, and D) had no recorded family history of diagnosed MEN 2B. As expected, all patients had suffered from MTC; one had pheochromocytoma and one had Cushing's disease.

Sixty percent of patients were described as having prominent lips and 100% of patients had neurofibromas on their tongue, particularly the anterior two-thirds of the tongue. Sixty percent of the patients also had neck dissections to remove metastatic lymph nodes from the MTC.

Megacolon

Seven of 11 (63%) patients with MEN 2B had megacolon (Table 2); four underwent colectomy with ileosigmoidostomy, one had total colectomy with ileorectal anastomosis. The colon in one patient (Figure 2) was recorded as 20 cm in diameter, including the cecum (20 cm). On histopathology, the commonly encountered changes were hypertrophy, hyperplasia and dysplasia of ganglion cells (Figure 2), and enteric or subserosal nerve hypertrophy (Figure 2).

Anorectal symptoms

Two patients (Patients A and C) developed symptoms of rectal evacuation disorder after they had undergone

colectomy (Table 2). One of the patients had undergone colectomy elsewhere and it is therefore unclear whether the evacuation disorder was also present prior to the colectomy (Patient A); the second patient underwent colectomy at Mayo Clinic, and there was no evidence of rectal evacuation disorder prior to the colectomy. The clinical impression (both evaluated clinically by the senior author) was confirmed by anorectal manometry and balloon expulsion (weight required to expel the balloon was >470 g in Patient A) or by electromyography (EMG) measurement of anal sphincter contraction (baseline EMG recording 0.5–5.1 microvolt (Mv) (normal <1.0 mv) in Patient C). Both patients underwent pelvic floor retraining; Patient A achieved complete relief only after undergoing ileostomy.

Esophageal involvement

Two of the patients with megacolon had achalasia confirmed on esophageal manometry (Patients C and G who were a father and son), and one had a Zenker's diverticulum (Patient D) (Table 2).

Discussion

In addition to the classical manifestations of MEN 2B syndrome, this case series illustrates two important and novel findings. First, there are patients with MEN 2B and megacolon who also experience significant esophageal motility problems that likely reflect neuromuscular incoordination, that is, achalasia and Zenker's diverticulum. Second, constipation after colectomy was associated with an evacuation disorder that requires separate treatment.

The classical paper by Carney et al.⁵ documented alimentary tract manifestations of MEN 2B and identified five of 16 patients (31%) with megacolon. Four of the patients (from the same family, Patients C, E, F, and G) in our current series were included in the report from Carney et al. Among these patients, two had passed away, one as a result of post-surgical infection

Table 1. Patient demographics

	Patient A	Patient B	Patient C	Patient D	Patient E	Patient F	Patient G
Age (years) at diagnosis of MEN 2B	8	20	Not known	3	31	18	51
Age (years) at diagnosis of Megacolon	Infancy	25	60	3	24	18	70 from autopsy
Gender	M	M	M	F	M	F	M
RET mutation	ND	M918T	M918T	M918T	ND	ND	ND
Family history of MEN	–	–	+	–	+	+	+

MEN: multiple endocrine neoplasia; RET: rearranged during transfection proto-oncogene; ND: no information available; M: male; F: female. Patients C, E, F (siblings) and G (father) are members of the same family.

Table 2. Manifestations of multiple endocrine neoplasia (MEN) 2B syndrome in seven patients with megacolon

PATIENT		A	B	C	D	E	F	G
Eye signs	Ganglioneuromas	✓	✓	✓	x	✓	✓	✓
	Corneal fibrous nerve	x	x	✓	x	✓	✓	✓
	Eyelid eversion	x	x	x	✓	x	x	x
Lips/tongue signs	Prominent lips	✓	✓	✓	✓	✓	✓	✓
	Ganglioneuromas	✓	✓	✓	✓	✓	✓	✓
Thyroid problems	MTC	✓	✓	✓	✓	✓	✓	✓
	Total thyroidectomy	✓	✓	✓	✓	✓	x	✓
	Partial thyroidectomy	x	x	x	x	x	✓	x
	Neck dissection	✓	✓	✓	x	x	✓	x
Esophageal problems		x	x	Achalasia	Zenker's diverticulum	x	x	Achalasia
Adrenal involvement		x	Cushing's syndrome	x	Bilateral pheochromocytomas	x	x	x
Colon	Megacolon	✓	✓	✓	✓	✓	✓	✓
	Colectomy	✓	x	✓	✓	x	x	x
	Ileosigmoidostomy	✓	x	x	✓	✓	x	x
Anorectal symptoms		✓	x	✓	x	x	x	x
Skeletal	Marfanoid habitus	✓	✓	✓	✓	✓	✓	✓
	Joint laxity	x	x	x	x	✓	✓	x
	Scoliosis	x	x	✓	x	x	✓	x
	Pes cavus	x	x	x	x	x	x	✓

✓: present; x: absent; MTC: medullary thyroid cancer.

related to the MTC and the second in 1989 whose autopsy results were available, demonstrating proliferation of nerves and nerve plexuses in several digestive tract organs including the esophagus, pancreas, and colon.

Megacolon is caused by loss of normal bowel tone, leading to segmental distension and dilation (as shown in Figure 2a). This study found that of the 11 patients who were diagnosed with MEN 2B, seven (63%) had megacolon. Among the patients in the Carney et al. study,⁵ five had megacolon and four (80%) had surgical procedures. Demos et al.⁹ reported that megacolon was the most common radiographic finding of young patients with MEN 2B, and Cope and Schleinitz¹¹ recommended the need for vigilance by radiologists to identify diverticula in children and megacolon in adults. Patient D, similarly to Patient A, had constipation and gastrointestinal symptoms from infancy. Initially, Patient D was diagnosed as having Hirschsprung disease but, subsequently, the megacolon from MEN 2B was recognized. The patient was treated with colostomy, underwent a revision of colostomy at age 9, and finally, at age 14, an ileostomy. This patient still has the ileostomy in place, with no significant problems.

This study documented that there was a relatively high prevalence of esophageal dysfunctions (42%,

three of seven patients) in MEN 2B, suggesting neuromuscular dysfunction in MEN 2B. There are two prior single cases reported of achalasia in patients with MEN 2B.^{12,13} There are no reports of Zenker's diverticulum in patients with MEN 2B, although cases of familial Zenker's diverticulum have been reported, possibly with autosomal dominant transmission^{14,15} in the absence of any evidence of MEN 2B manifestations. Carney et al.⁵ documented that none of the 16 patients had esophageal symptoms, although three of the autopsies revealed diffuse ganglioneuromatosis of the esophagus and stomach enteric plexuses. Given the observation of ganglioneuromas in the esophagus, we hypothesize that the achalasia and pharyngo-esophageal incoordination that led to Zenker's diverticulum formation in our patients resulted from similar neural complications of the MEN 2B. We do not have any esophageal tissue to assess whether there were features of ganglioneuromatosis in the patients in our series. In a study reported by Cohen et al. in 2002,¹⁶ 39% (11/28) of patients had difficulty swallowing and two of 28 patients with MEN 2B had abnormal barium swallow, while 14% experienced vomiting before their diagnosis of MEN 2B. The precise cause of the dysphagia is unclear from the report, and there was no specific mention of objective evidence of the

Figure 2. Composite figure showing radiological and histopathological features of megacolon in multiple endocrine neoplasia (MEN) 2B. (a) Megacolon on x-ray; (b) gangliocytic nerve cell dysplasia; (c) increased number of ganglion cells; and (d) subserosal nerve hypertrophy.

motility disorders documented in our series of patients at Mayo Clinic.

Two of our patients presented with constipation following colectomy; both were evaluated clinically by the senior author. One of the patients had undergone colectomy elsewhere and it is therefore unclear whether the evacuation disorder was also present prior to the colectomy; the second patient underwent colectomy at Mayo Clinic, and there was no evidence of rectal evacuation disorder prior to the colectomy. When these patients demonstrated evidence of rectal evacuation disorder, they underwent intense pelvic floor retraining. Unfortunately, this was not sufficient to reverse the constipation and marked abdominal distension in the patient in whom the status of rectal evacuation was uncertain prior to the colectomy, and this patient ultimately required defunctioning ileostomy.¹⁷ It is unclear whether the choice of the surgical operation may have been responsible for the development of postoperative constipation due to rectal evacuation disorder in this patient. However, it is relevant to note that ~30% of >1400 patients presenting to a specialty motility clinic with the chief complaint of constipation had evidence of a rectal evacuation disorder.¹⁸ It is unclear whether the MEN 2B actually caused the rectal evacuation

disorder, but given the prevalence in constipation without MEN 2B, it may be a coincidental finding.

Gastrointestinal manifestations such as constipation and diarrhea are common in infancy and childhood, but megacolon can develop in infancy in patients with MEN 2B¹⁹ and can potentially serve as a good marker to aid the early diagnosis of MEN 2B and, thus, improve survival from the ubiquitous MTC. MTC in MEN 2B is often identified after it has metastasized. Vasen et al.² found that 11 of 15 patients had a thyroid nodule as a first sign of disease. MTC can develop at a younger age in MEN 2B than in MEN 2A,²⁰ and screening should begin around 4 years of age in patients with MEN 2B.

Ganglioneuromatosis was found in all cases in this study (see Figure 2b and 2c), and mirrors results in the literature.^{5,9} Gastrointestinal ganglioneuromatosis is the main cause of most alimentary tract symptoms in patients with MEN 2B¹⁶ and can be found from mouth to anus.⁹ Constipation is often the most common early symptom.⁹ Constipation is caused by enteric neural dysfunction, leading to hypomotility and abnormal sphincter function, particularly in the colon.⁹ When examined histologically, ganglioneuromatosis shows irregular thickening of the myenteric plexus (see Figure 2d).¹¹

Limitations and strengths

As MEN 2B is a rare disease, one of the limitations to this study is the small number of patients available for study. Moreover, as genetic testing for this disease became available only in the 1990s, patients who died before that date did not have the proto-oncogene (*RET*) mutation recorded. This was a retrospective study, which could be advantageous in a rare disease, especially with the availability of EMR and natural language processing to identify the rare disease and its manifestations.

Conclusions

Megacolon is a relatively common manifestation of MEN 2B in patients who were identified and treated at the Mayo Clinic. Approximately a quarter of our 11 patients had significant esophageal motor abnormalities, which was rarely recognized previously. It is conceivable that this results from the same neural mechanism that results in megacolon.

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Conflict of interest

None declared.

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