

Megacolon as the presenting feature of multiple endocrine neoplasia type 2B: a case report

L Xu¹*, MB, BS, KW Shek¹, MB, BS, FHKAM (Radiology), KC Wong², MB, BS, KL Tong², MB, BS, FHKAM (Surgery), MN Hau³, MB, BS

¹ Department of Radiology and Imaging, ² Department of Surgery, ³ Department of Pathology, Queen Elizabeth Hospital, Jordan, Hong Kong

* Corresponding author: xl599@ha.org.hk

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Case report

A 29-year-old Chinese man with good past health presented in October 2018 with acute abdominal pain and distension. On admission, he was afebrile and normotensive (blood pressure 116/79, pulse 74). Physical examination revealed a grossly distended abdomen with sluggish bowel sounds and mild diffuse tenderness but no guarding or rigidity. Preliminary blood tests showed leucocytosis ($17.7 \times 10^9/L$) and metabolic acidosis (pH 7.29, base excess -4.3).

Markedly dilated large bowel loops were seen on radiograph. A flexible sigmoidoscopy performed to exclude sigmoid volvulus revealed no twisting point but was incomplete due to the presence of large amounts of stool. Urgent contrast computed tomography abdomen and pelvis showed that the entire length of the colon was grossly dilated up to 13 cm in diameter with loss of haustration and no obstructive mass, suggestive of megacolon. Several segments showed diminished mural enhancement. Bilateral avidly enhancing heterogeneous adrenal

masses were noted, measuring up to 3.1 cm on the left and 3.8 cm on the right. They had a density of about 52 HU pre-contrast and almost 150 HU in the arterial phase. In view of their intense arterial enhancement, bilateral pheochromocytoma was suspected (Fig 1).

Urgent laparotomy was deemed necessary. Due to the suspected pheochromocytomas, the patient was prescribed an alpha blocker to prevent catecholamine crisis and had intensive intra-operative and postoperative blood pressure monitoring.

Laparotomy revealed that the entire large bowel was grossly dilated with the caecum and ascending colon showing doubtful viability. The small bowel was only mildly dilated at the terminal ileum. Subtotal colectomy with ileostomy was therefore performed. Blood pressure remained stable intra-operatively.

The gross subtotal colectomy specimen was extremely dilated, up to 13 cm in diameter, with no tumour mass or perforation. Microscopic examination revealed diffuse expansion of the myenteric plexus in the muscularis propria, accompanied by many ganglion cells. There was extension of the myenteric plexus into the muscles, almost reaching the serosa, and many abnormally thick nerve bundles in the submucosa. The appendix and the terminal ileum were also involved, with thick nerve fibres in the lamina propria. Pathological findings were suggestive of diffuse ganglioneuromatosis (Fig 2).

Multiple 24-hour urine catecholamine tests were performed over weeks to avoid the confounding effects of stress in the immediate postoperative period. They confirmed the diagnosis of pheochromocytoma with persistently and markedly raised catecholamines: adrenaline up to 4371 nmol/d (ref <90), noradrenaline 4523 nmol/d (ref <610), normetanephrine 1286 nmol/d (ref <320), and free metanephrine 3341 nmol/d (ref <271).

Subsequent I-131 meta-iodobenzylguanidine (MIBG) whole-body scan showed markedly increased MIBG uptake at the left adrenal region and

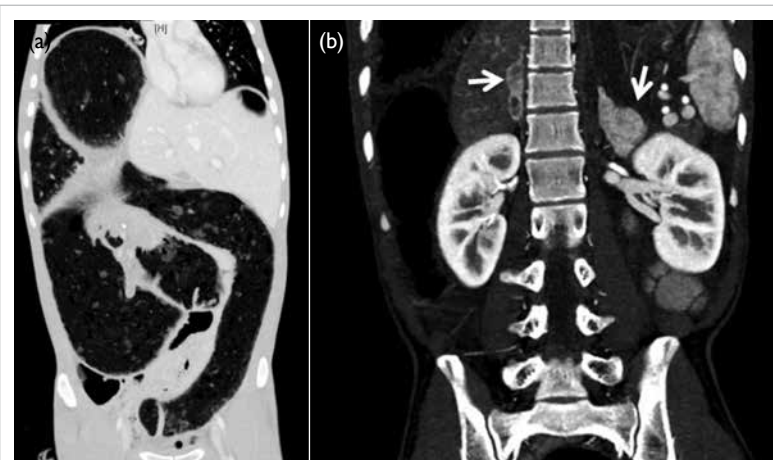


FIG 1. (a) Coronal contrast computed tomography of the abdomen and pelvis showing that the entire colon is grossly dilated up to 13 cm with loss of haustration and filled with faecal matter, suggestive of megacolon. (b) Coronal contrast computed tomography in arterial phase reveals bilateral avidly enhancing adrenal masses of about 150 HU, suspicious of pheochromocytoma (arrows)

moderately increased uptake at the right, in keeping with bilateral pheochromocytoma. There was no scintigraphic evidence of MIBG-avid metastasis.

Serum calcitonin level was also found to be elevated at 101 pmol/L (ref ≤ 2.8).

Given the elevated calcitonin and possibility of multiple endocrine neoplasia type 2B (MEN 2B), ultrasound of the thyroid was performed and revealed sub-centimetre, taller-than-wide hypoechoic nodules with internal echogenic foci in both thyroid lobes and multiple enlarged right cervical lymph nodes, also with echogenic foci (Fig 3). Ultrasound guided fine needle aspiration and cytology results determined both thyroid nodules to be medullary carcinoma, showing clusters of abnormal cells with immunostaining positive for calcitonin and chromogranin. A right level IV cervical lymph node was suggestive of metastatic medullary thyroid carcinoma (MTC).

The diagnosis of MEN 2B was made clinically and later confirmed by genetic testing that revealed a RET 918 mutation. This may have been a sporadic mutation since the patient had no positive family history. Staged surgeries for bilateral adrenalectomy followed by total thyroidectomy and neck dissection were subsequently performed.

Discussion

Megacolon is the abnormal, often irreversible, dilatation of the colon, greater than 12 cm in the caecum, 8 cm in the ascending colon and 6.5 cm in the rectosigmoid region.¹ The differential diagnoses for megacolon include congenital aganglionic megacolon in Hirschsprung's disease and toxic megacolon in inflammatory bowel disease and infections, in particular *Clostridium difficile* that can lead to pseudomembranous colitis. Other causes include Chagas', and Parkinson's disease, diabetic neuropathy, myotonic dystrophy, hypothyroidism, amyloidosis, and medications such as risperidone and loperamide.²

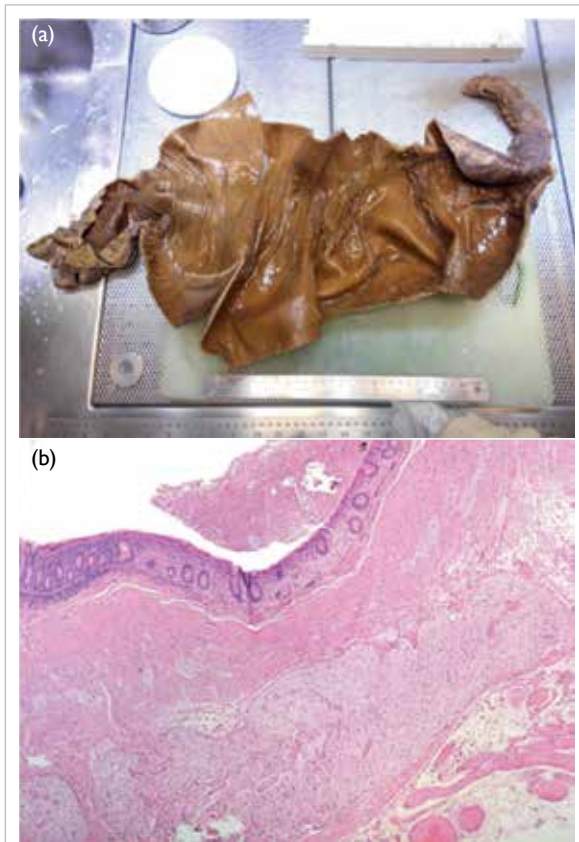


FIG 2. (a) Gross subtotal colectomy specimen: grossly dilated colon measuring up to 13 cm in diameter. (b) H&E section, 40x magnification, appendix: markedly expanded myenteric plexus consisting of mature Schwann cells and ganglion cells. Thick nerve fibres are also present in the lamina propria. Pathological findings suggest diffuse ganglioneuromatosis

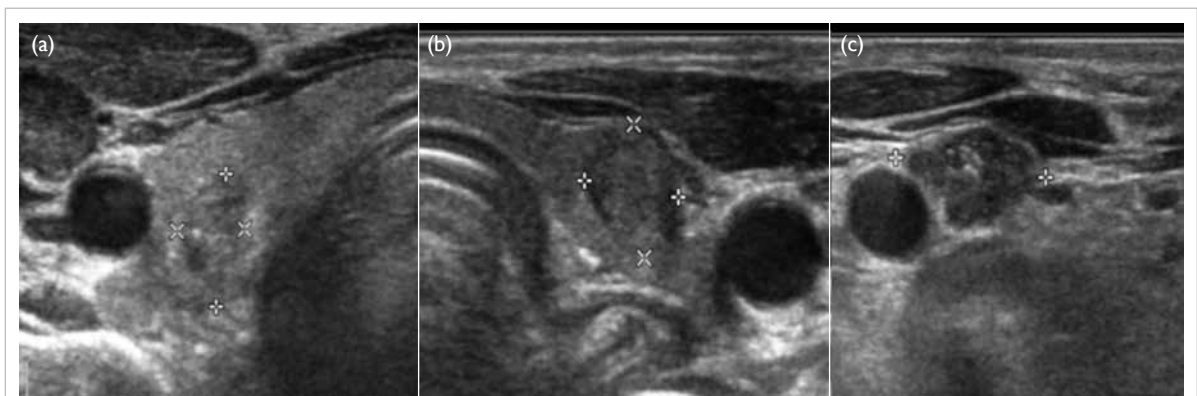


FIG 3. Ultrasonograph of the thyroid showing taller-than-wide slightly hypoechoic nodules (crosses) with internal echogenic foci measuring 0.5 cm x 0.5 cm x 0.8 cm in the right lobe (a), 0.6 cm x 0.8 cm x 0.7 cm in the left lobe (b), both confirmed by fine needle aspiration and cytology to be medullary thyroid carcinoma. Enlarged abnormal right cervical lymph nodes with echogenic foci up to 1.3 cm x 0.8 cm (c) are also confirmed to be metastatic medullary thyroid carcinoma

Although MEN 2B associated with ganglioneuromatosis and pheochromocytoma can also lead to megacolon, owing to its rarity, it is often not considered in the early diagnosis of megacolon.

Multiple endocrine neoplasia is an autosomal dominant endocrine disorder comprised of MEN type 1 and the rarer MEN type 2, and caused by familial or sporadic germline mutations in the RET protooncogene. Multiple endocrine neoplasia 2A accounts for 80% of all MEN type 2 cases, whereas MEN 2B, the most aggressive and rarest variant, accounts for 5%.³ The prevalence of MEN 2 is estimated to be one in 35 000 population, while that of MEN 2B is approximately one in 500 000 population.⁴

Multiple endocrine neoplasia type 2B is characterised by the presence of medullary thyroid cancer (100% of cases), pheochromocytomas (40%–50% of cases), multiple neuromas and/or diffuse gastrointestinal ganglioneuromatosis (40% of cases) as well as facial and skeletal abnormalities, including mucosal neuromas of the lips and tongue, medullated corneal nerve fibres, distinctive facies with enlarged lips and in particular Marfanoid habitus.³

Gastrointestinal ganglioneuromatosis is the predominant aetiology of gastrointestinal symptoms in MEN 2B, and results in thickening of the myenteric plexi with hypertrophy and increased ganglion cells, supportive cells and nerve fibres in all layers of the bowel wall,² as demonstrated in our case. This leads to loss of normal bowel tone, segmental dilatation, and megacolon, with symptoms often presenting in infancy or early childhood.

It is also important to note that sustained high catecholamine levels secreted by pheochromocytomas can decrease intestinal peristalsis and tone that on its own can precipitate ileus, leading to megacolon and bowel ischaemia.⁵ The bilateral pheochromocytomas in our patient may have also contributed to the development of megacolon. Pheochromocytoma classically presents with hypertension, palpitations, headache, and diaphoresis, although not in our patient. It can be diagnosed clinically by elevated 24-hour urinary excretion of catecholamines and their metabolites. On computed tomography, pheochromocytoma is usually evident as a heterogeneous mass with areas of necrosis and cystic change, typically enhancing avidly (attenuation ≥ 110 HU on arterial phase).⁶ Due to the presence of these features, pheochromocytoma was suspected early on in this case, allowing for prompt diagnosis and treatment to prevent catecholamine crises. On magnetic resonance imaging, which is considered the most sensitive modality with a sensitivity of 98%, pheochromocytoma is slightly hypointense on T1-weighted and markedly hyperintense (lightbulb

sign) on T2-weighted imaging with prolonged contrast enhancement.⁶ Meta-iodobenzylguanidine scintigraphy may be helpful in multifocal or extra-adrenal pheochromocytoma.

The definitive treatment is adrenalectomy and should ideally be performed before thyroidectomy or other surgical intervention. Adequate preoperative alpha-adrenergic receptor blockade before beta blockade is crucial to control blood pressure and avoid intra-operative catecholamine crisis that may lead to haemodynamic instability and end-organ damage or dysfunction.³

Medullary thyroid carcinoma, originating from the parafollicular calcitonin-producing cells, occurs in all MEN 2 patients. It is the first clinical manifestation in most cases, appearing between the age of 5 and 25 years in MEN 2A patients and is more aggressive, developing a decade earlier in MEN 2B patients.¹ Individuals with MEN 2B who do not undergo thyroidectomy by age 1 year are prone to metastatic disease and have an average life expectancy of 21 years. Surprisingly, our patient again presented late.

Medullary thyroid carcinoma correlates with increased serum levels of calcitonin. On ultrasound, primary thyroid lesions and metastatic lymph nodes show punctate high echogenic foci, as seen in our case. About 30% of MTCs show uptake in MIBG scan. Fluorodeoxyglucose–positron emission tomography may be used for metastatic disease and is about 75% sensitive.⁷

The MEN 2B is a rare but important disease complex. Early diagnosis is necessary due to the risk of endocrine malignancies, particularly MTC, and prophylactic thyroidectomy is advised. As demonstrated in this case, although the patient had a rather late presentation and no family history, earlier diagnosis of MEN 2B can be achieved by recognising its phenotypical features and understanding that gastrointestinal ganglioneuromatosis as well as associated pheochromocytoma, which often have characteristic clinical and radiological features, may lead to loss of bowel tone, causing bowel dilatation and even megacolon.

Author contributions

All authors contributed to the concept of study, acquisition and analysis of data, drafting of the article, and critical revision for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

The patient was treated in accordance with the Declaration of Helsinki. The patient provided informed consent for all procedures.

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