

Intestinal Ganglioneuromatosis: an unusual presenting feature in MEN2B syndrome as acute toxic megacolon

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Introduction

Multiple endocrine neoplasia 2B syndrome is rare tumour syndrome characterized by early-onset medullary thyroid carcinoma, pheochromocytoma, Marfanoid body habitus, oral mucosal neuromas, intestinal ganglioneuromatosis, and medullated corneal nerve fibers. Although gastrointestinal symptoms are common among patients with MEN 2B syndrome, acute toxic megacolon as the first presentation of the syndrome is rare. On the other hand, intestinal ganglioneuromatosis is a rare condition among the various causes of intestinal dysmotility. Apart from MEN2B syndrome, it can be associated with neurofibromatosis, and with Cowden syndrome in the form of polyposis. Here we present a case of acute toxic megacolon due to intestinal ganglioneuromatosis in a previously healthy adult man, raising the suspicion for MEN2B syndrome, which was eventually confirmed by the identification of pheochromocytoma and medullary thyroid carcinoma, and genetic studies.

Case report

A previously healthy 29-year-old Chinese man presented with acute abdominal pain and distension. He was afebrile and normotensive on admission. Physical examination showed markedly distended abdomen with sluggish bowel sounds. Blood test showed elevated white cell count ($17.7 \times 10^9 / L$) and metabolic acidosis (pH 7.29, base excess -4.3). Urgent contrast computed tomography of 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. Bilateral adrenal masses measuring up to 3.1 cm on the left and 3.8 cm on the right were noted. Both showed arterial enhancement, suggestive of bilateral pheochromocytoma.

Urgent laparotomy revealed that the entire large bowel was grossly dilated with doubtful viability at the cecum and ascending colon. The small bowel was only mildly dilated at the terminal ileum. Subtotal colectomy with ileostomy was then performed.

Pathological findings

Grossly, the specimen comprised large bowel measuring 101 cm in length, terminal ileum measuring 8 cm in length, and appendix measuring 6 cm in length. The large bowel was markedly dilated, measuring up to 13 cm in diameter, and was distended by fecal material. The distal 20-cm of the specimen was non-dilated, and it measured 3 cm in diameter. The terminal ileum and the appendix were also similarly distended by fecal material, measuring 4 cm and 0.5 cm in diameter respectively. Examination of the entire specimen showed no evidence of mechanical obstruction.

Microscopic examination showed large bowel with diffuse expansion of the myenteric plexus in the muscularis propria, comprising bundles of mature schwannian cells and numerous ganglion cells. The myenteric plexus appears almost continuous in the plane between the inner circular and outer longitudinal smooth muscle layers. Furthermore, there is extension of the plexus into the muscles, and almost reaching the serosa. Many abnormally thick nerve bundles are also readily seen in the submucosa. The terminal ileum and appendix are similarly involved, with thick nerve fibers seen in the lamina propria of the appendix as well. Abundant lipofuscin-laden macrophages are seen in the lamina propria of the large bowel.

Clinical outcome

Multiple 24-hour urine catecholamine tests showed persistent and marked elevation of catecholamines, while MIBG whole body scan showed increased uptake at bilateral adrenal glands, confirming the diagnosis of pheochromocytoma.

Serum calcitonin level was also found to be elevated. Ultrasound of the thyroid revealed sub-centimeter nodules in both lobes and multiple enlarged cervical lymph nodes. Subsequent fine needle aspiration of the thyroid nodules showed medullary thyroid carcinoma, and the cervical lymph node is suggestive of metastasis.

The diagnosis of MEN2B syndrome was made clinically, and subsequently confirmed by genetic testing that revealed germline RET 918 mutation. Sporadic mutation is suspected, since the patient had no positive family history. Bilateral adrenalectomy and total thyroidectomy and neck dissection were then performed.

The patient is alive with disease at three years since there is radiological suspicion of loco-regional relapse of medullary thyroid carcinoma, pending further investigations.

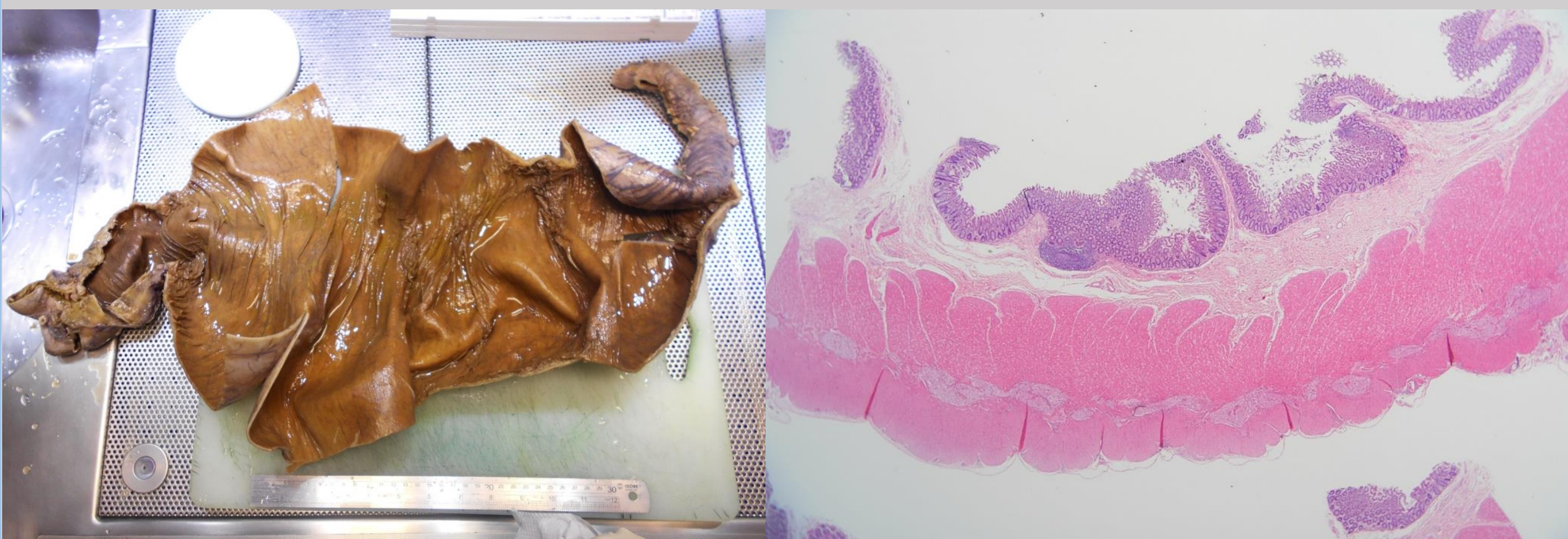


Fig 1.: Gross subtotal colectomy specimen: grossly dilated colon measuring up to 13 cm in diameter

Fig 2. H&E section, 10x magnification, large intestinal wall: There is diffuse expansion of the myenteric plexus, forming an almost continuous layer within the muscularis propria.

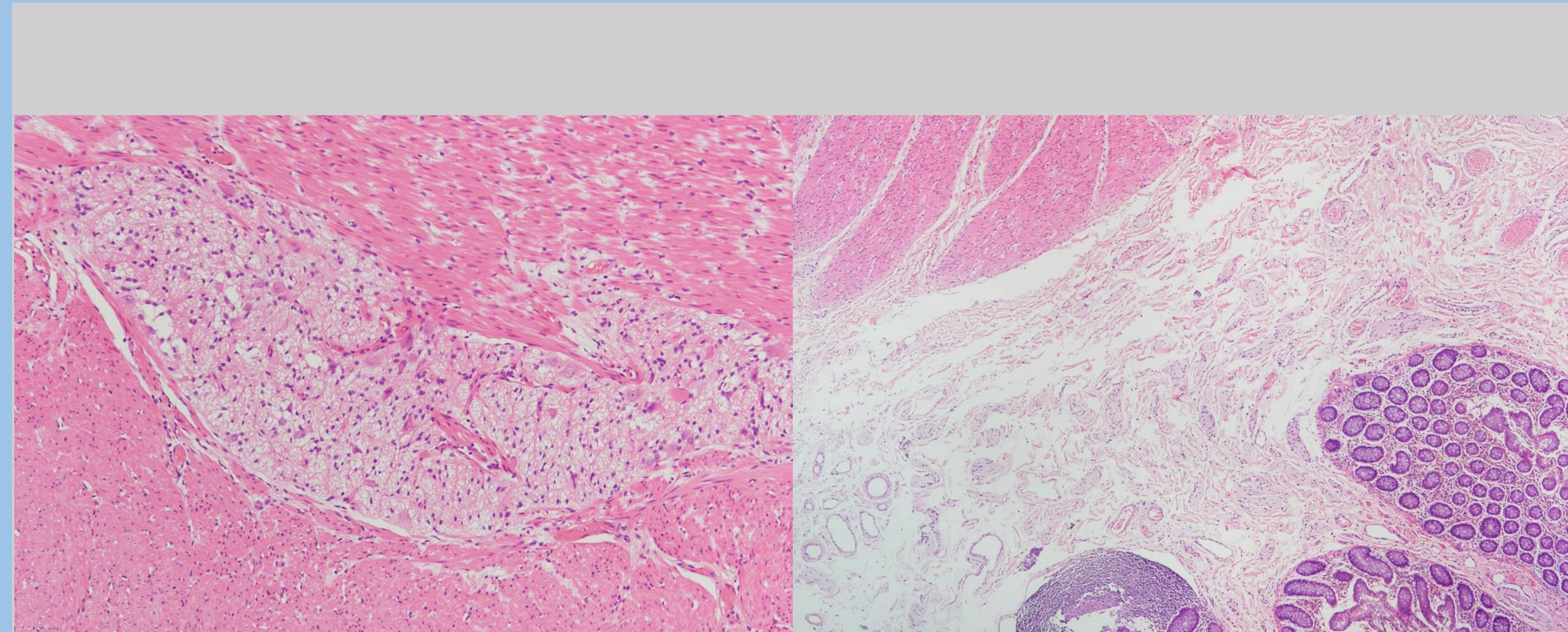


Fig 3. 100x magnification of Fig 2: The expanded plexus comprises bundles of mature schwannian cells and ganglion cells.

Fig 4. H&E section, 40x magnification, large intestine: Thick nerve bundles are also seen in the submucosa.

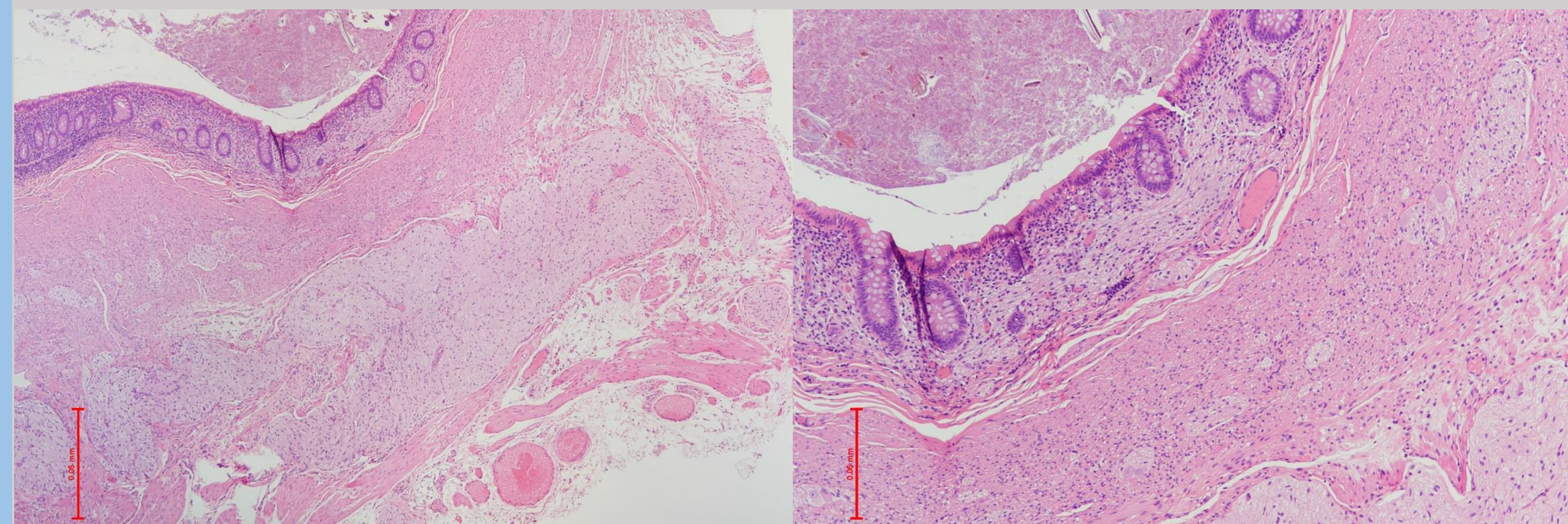


Fig 5. H&E section, 40x magnification, appendix: Markedly expanded myenteric plexus.

Fig 6. H&E section, 100x magnification, appendix: The lamina propria also shows thick nerve bundles.

Discussion

Multiple endocrine neoplasia type 2B is an autosomal dominant tumor syndrome characterized by early-onset medullary thyroid carcinoma, pheochromocytoma, and a pathognomonic physical appearance that includes a Marfanoid body habitus, oral mucosal neuromas, intestinal ganglioneuromatosis, and medullated corneal nerve fibers [1].

It is a rare tumor syndrome with estimated annual incidence of 1 in 38,750,000 and prevalence of 1 in 500,000 [2]. It is caused by activating germline mutation in the RET proto-oncogene, with M918T mutation being the most common (95-97%). Although the syndrome is heritable, the vast majority (>90%) of index cases of MEN2B are due to de novo mutations [1].

Gastrointestinal symptoms are common among MEN2B patients, reaching an incidence of 61-90% [3]. The presentation is usually during infancy (52%) or before adulthood (86.9%). [3] Constipation is the most common gastrointestinal symptom (73%), followed by colonic dilatation on X-ray (29%) and diarrhea (29%) [3]. Toxic megacolon or enterocolitis are relatively rare (5.4 %).

Intestinal ganglioneuromatosis is reported in approximately 40-90% of MEN2B patients [3]. The lower end of the spectrum may be an underestimation due to the lack of surgical intervention (biopsy/ resection) for their gastrointestinal problems. Histologically, it is characterized by diffuse expansion of submucosal and myenteric plexus [4]. Extension of the nerve plexus through the muscularis propria and presence of thick nerve fibers in the mucosa can also be observed [5]. This leads to loss of normal bowel tone, hypomotility, bowel distension, and may rarely cause megacolon

Although intestinal ganglioneuromatosis is the predominant etiology of gastrointestinal symptoms in MEN2B, pheochromocytoma can also contribute to decreased intestinal peristalsis, while high-level of calcitonin secreted by medullary thyroid carcinoma can lead to diarrhea .

Intestinal ganglioneuromatosis has also been described in neurofibromatosis, Cowden syndrome (in the form of polyposis), and in the ganglionic segment of Hirschsprung's disease, although the most frequent association is still MEN2B.

Conclusion

We present a case of toxic megacolon due to intestinal ganglioneuromatosis in a previously healthy adult man, raising the suspicion for MEN2B syndrome, which was eventually confirmed by the identification of pheochromocytoma and medullary thyroid carcinoma, and genetic studies. Unfortunately, our patient had a rather late presentation where medullary thyroid carcinoma with cervical lymph node metastasis has already been developed. Nevertheless, it is important for pathologists to recognize intestinal ganglioneuromatosis in surgical specimens, especially from young patients who have presented with constipation, bowel dilatation or megacolon. This is because of the relative frequent association with MEN2B, in which early diagnosis can potentially reduce the morbidity or mortality from other endocrine neoplasms, for instance by performing prophylactic thyroidectomy for medullary thyroid carcinoma in patients with confirmed germline mutation.

Reference:

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