Multiple endocrine neoplasia type 2B (MEN2B) diagnosis: a case report

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Background: Multiple endocrine neoplasia type 2B (MEN2B) is a rare autosomal dominant syndrome characterized by medullary carcinoma of the early thyroid, pheochromocytoma, and non-endocrine manifestations, such as marfanoid habits and other skeletal abnormalities as well as mucosal neuromas and ganglioneuromatosis of the gastrointestinal tract.

Case Description: A 10-year-old male began follow-up at our service at 3 years of age through pediatric gastroenterology due to intestinal constipation. The mother also reported that the child had painless lesions on the tip of the tongue since birth with progressive worsening. The patient simultaneously began follow-up with pediatric endocrinology due to low gains in weight and height, between which only isolated low weight was found, and the onset of follow-up with the pediatric neurology team due to longstanding headache combined with vomiting, photophobia, and phonophobia as well as a specific reading and writing disorder. The patient was sent to clinical genetics. The child's karyotype was 46, XY (normal). Through a physical examination, the pediatric neurology team identified joint hypermobility, important muscle hypotrophy, gingival hypertrophy, and lipodystrophy. The patient was sent to neurogenetics, initiating a set of general laboratory exams for the investigation of the lipodystrophy and a panel of exams for lipodystrophy, neuropathy, and muscle hypotrophy as well as electroneuromyography. MEN2B due to genetic mutation was confirmed and the patient was sent to the pediatric endocrinology clinic for follow-up. Currently 10 years of age and again with the pediatric endocrinology team for the diagnosis of MEN2B, the investigation of pheochromocytoma and medullary thyroid cancer was initiated.

Conclusions: An additional mutation occurs in most cases of MEN2B. The diagnosis is only established when the child or, in most cases, adolescent presents with medullary thyroid cancer in an advanced and even metastatic stage. However, non-endocrine manifestations, can lead to an early diagnosis and timely intervention. The diagnosis of MEN2B is made with the confirmation of the autosomal dominant genetic mutation or a mutation of the *RET* gene. In the absence of these mutations, the majority of clinical

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manifestations should be present.

Keywords: Pediatrics; endocrinology; multiple endocrine neoplasia type 2B (MEN2B); genetics; case report

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Introduction

Multiple endocrine neoplasia type 2B (MEN2B) is a rare syndrome, the prevalence of which is 1/30,000–35,000. MEN2B is an autosomal dominant syndrome caused by mutations in the *RET* proto-oncogene and is associated with unfavorable outcomes. The condition is characterized by medullary carcinoma of the early thyroid (the main cause of death in affected patients), pheochromocytoma, and non-endocrine manifestations, such as marfanoid habits, other skeletal abnormalities as well as mucosal neuromas and ganglioneuromatosis of the gastrointestinal tract (1). Unlike multiple endocrine neoplasia type 2A (MEN2A), MEN2B does not involve hyperparathyroidism and has a worse prognosis (2).

In approximately 90% of cases, the mutation that gives rise to the syndrome is a new mutation. Thus, the diagnosis is only established when the child or, in most cases, adolescent presents with medullary thyroid cancer in an advanced and even metastatic stage (1). However, non-endocrine manifestations can lead to an early diagnosis and timely intervention.

Medullary thyroid carcinoma is a neuroendocrine neoplasm of parafollicular cells of the thyroid gland. As this is the main cause of death among patients with the syndrome and its penetrance is nearly 100% among affected individuals, adequate management of such patients involves prophylactic total thyroidectomy with the expectation to prevent the emergence of cancer and its dissemination throughout the organism (3).

Pheochromocytoma is found in approximately 50% of patients with multiple endocrine neoplasia type 2 (MEN2), as its occurrence depends specifically on the *RET* mutation; this condition is also more frequent in older patients (4,5). In patients with the syndrome, however, its occurrence is earlier in comparison to sporadic cases, emerging between 8 and 12 years of age; emergence prior to medullary thyroid cancer or as a first manifestation of the MEN2 syndrome is uncommon (6).

Non-endocrine manifestations include mucosal neuromas, which typically involve the lips and tongue, gastrointestinal ganglioneuromas, abnormalities in the proportion of the upper and lower segments of the body, skeletal deformities, marfanoid habits, and myelinated corneal nerves. Functional disorders of the intestine, including chronic constipation and megacolon, are common (7).

The diagnostic suspicion of MEN2B should occur in all patients with a diagnosis of medullary thyroid cancer and/or pheochromocytoma, especially in those with a diagnosis of these neoplasms prior to 35 years of age or when more than one member of the family has the syndrome. The diagnosis of MEN2B is established with the confirmation of the autosomal dominant genetic mutation or a mutation

Highlight box

Key findings

- This report illustrates the difficulty in diagnosing a patient with multiple endocrine neoplasia type 2B (MEN2B).

What is known and what is new?

- MEN2B is an autosomal dominant syndrome caused by mutations in the *RET* proto-oncogene and is associated with unfavorable outcomes. The condition is characterized by medullary carcinoma of the early thyroid (the main cause of death in affected patients), pheochromocytoma, and non-endocrine manifestations, such as marfanoid habits, other skeletal abnormalities as well as mucosal neuromas and ganglioneuromatosis of the gastrointestinal tract.
- The diagnosis of MEN2B is delayed due to the rarity of the condition. Patients can have signs and symptoms that can diminish the diagnostic suspicion, but, when taken together, can lead to the suspicion of the syndrome. Fragmented care with different specialties and the coronavirus disease 2019 pandemic may have delayed the diagnosis.

What is the implication, and what should change now?

- An earlier establishment of the diagnosis improves the patient's chances, including the execution of prophylactic thyroidectomy prior to the emergence of medullary thyroid cancer. The present study also serves as a warning of the fragmentation of care among specialties. The sum of the signs and symptoms could have accelerated the diagnosis if seen as secondary to a common cause. Although rare, we must bear in mind that the syndrome occurs.

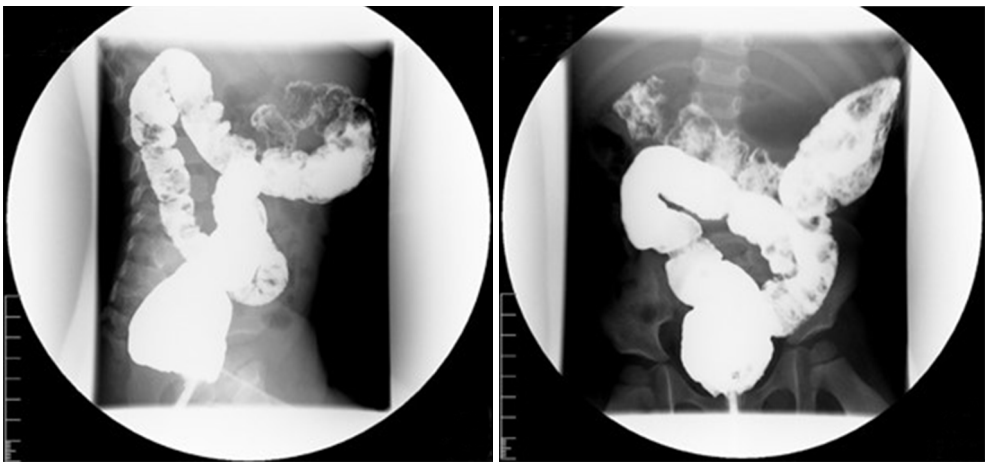

Figure 1 Opaque enema. Exam performed with barium sulfate injected through a tube through the rectal route. Exam showed no signs of congenital megacolon. Presacral space free.

of the *RET* gene; in the absence of mutations, the majority of the clinical manifestations should be present (8). We present this case in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-23-114/rc).

Case presentation

A 10-year-old (currently) male began follow-up at our service at 3 years of age through pediatric gastroenterology due to intestinal constipation. The radiographic exam with opaque enema revealed no signs of congenital megacolon, with an appearance of functional constipation, frequent abdominal pain, the absence of bowel movements for 2 to 3 days, anal pain due to the evacuation effort and large, hardened stools (*Figure 1*). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient and his guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

In a follow-up appointment with the gastroenterology team, the mother also reported that the child had painless lesions on the tip of the tongue since birth with progressive worsening. The patient was sent to the pediatric otolaryngology team for the assessment of the lesions on the tongue. Upon the first appointment with the team, the child (now 5 years of age) reported a progressive increase in the lesions, pain only when biting the lesions and reported no bleeding. Other findings were weight loss and satellite lesions in other locations. During the physical examination, the lesions were described as verrucose on the tip of the tongue of approximately 2 mm × 2 mm, numerous, without cystic content, without active bleeding, without associated ulcers and painless upon palpation. Resection at a surgical center was proposed, with a subsequent anatomopathological study, but was not performed due to the loss of contact with the team.

The patient simultaneously began follow-up with pediatric endocrinology due to low gains in weight and height, between which only isolated low weight was verified, and the onset of follow-up with the pediatric neurology team due to longstanding headache combined with vomiting, photophobia, and phonophobia as well as a specific reading and writing disorder. Due to the possibility of the prescription of imipramine, the patient was sent for cardiological assessment to permit the use of the medication. The echocardiogram revealed dysplasia of the tricuspid and mitral valves without dysfunction.

In follow-up with the pediatric gastroenterology team, the patient continued having constipation. Anorectal manometry revealed that the rectoanal inhibitory reflex was absent, suggesting diseases that affect this reflex, such as Hirschsprung disease, although the biopsy was negative for this diagnosis. During the physical examination, a triangular face with a protruding chin and protruding ears were noted and the patient was sent for the assessment of the clinical genetics team.

Table 1 Results of laboratory exams after genetic diagnosis of MEN2B

Exams	Result	Reference value
Calcitonin (pg/mL)	384.0	Less than or equal to 7
Total calcium (mg/dL)	8.5	8.8–10.2
Ionized calcium (mmol/L)	1.3	1.10–1.40
Phosphorus (mg/dL)	5.9	2.7–4.5
Alkaline phosphatase (U/L)	229	142–335
TSH (mIU/L)	1.85	0.6–4.84
Free T4 (ng/dL)	1.73	0.93–1.7
PTH (pg/mL)	14.86	15–57
Antithyroglobulin antibody (IU/mL)	15.30	Less than 37
Antimicrosomal antibody (IU/mL)	9.70	Less than 18
Adrenalin (mcg)	5	Up to 27
Noradrenalin (mcg)	12.6	Up to 97
Dopamine (mcg)	302	Up to 540

MEN2B, multiple endocrine neoplasia type 2B; TSH, thyroid stimulating hormone; T4, thyroxine; PTH, parathormone.

At 5 years and 11 months of age, the patient was submitted to the first assessment of the genetics team, which reported the following findings: scoliosis, high-arched palate, thick lips, facial asymmetry, long eyelashes, abnormal dental arch, protruding ears, discrete clinodactyly in the fifth finger of the hands, salient lingual papillae, myopia, prognathism, accentuated distance between the hallux and second toe with a deep plantar fold and joint hyperextensibility. The mother reported having two other children and reported no consanguinity between the parents. At the end of the examination, a karyotype exam was requested to discard chromosome diseases. The child's karyotype was 46, XY (normal). The patient was sent to the physiotherapy team for the assessment of the joint hypermobility, which confirmed the condition and initiated weekly follow-up.

Patient and family had a new complaint of urinary incontinency. The investigation was conducted by the pediatric surgery team. Ultrasound of the kidney and urinary tract revealed high postmicturition residue, with no other abnormalities. Normal magnetic resonance (MR) was performed of the spleen and neural axis. The urodynamic study revealed high detrusor pressure during attempts to urinate, which may suggest obstruction, but may also be an involuntary contraction of the detrusor muscle. Doxazosin was initiated, with an improvement in abdominal pain and no urinary complaints after 15 days of use of the medication.

In follow-up with the pediatric endocrinology team, besides the low weight, the patient began to exhibit a deceleration of growth. At an appointment 3 months later, however, the patient had adequate growth velocity for his age and was between the 25th and 50th percentiles. The decision was made to only observe growth velocity in clinical follow-up.

At 9 years of age, the patient was still in follow-up with the teams, but irregularly due to the coronavirus disease 2019 (COVID-19) pandemic, which, according to the mother, had negative repercussions for the patient's quality of life.

In another assessment with the pediatric neurology team, the physical examination revealed joint hypermobility, important muscle hypotrophy, elongation of the face, voluminous lips, gingival hypertrophy, and lipodystrophy.

The patient was sent to neurogenetics, initiating a set of general laboratory exams for the investigation of the lipodystrophy and a panel of exams for lipodystrophy, neuropathy, and muscle hypotrophy as well as electroneuromyography. MEN2B due to genetic mutation was confirmed (mutation of *RET* gene Met 918 Thr—exam conducted on March 25th, 2022). Now 10 years of age, a new investigation was conducted by the pediatric endocrinology team for the diagnosis of MEN2B and the investigation of pheochromocytoma and medullary thyroid cancer began (*Table 1*). Ultrasound of the thyroid and neck revealed Thyroid Imaging Reporting and Data System (TI-RADS) 5 thyroidal nodules (*Figure 2*).

The otolaryngology team performed total thyroidectomy with cervical clearance, guided by intraoperative frozen exam of the margin of the recurrent laryngeal nerve in which typical cell proliferation was identified amidst fibrosis. Laboratory exams were performed on the 10th day of the postoperative period (*Table 2*). The patient is currently in outpatient follow-up with the teams and pediatric oncology.

Discussion

MEN2B is characterized by early medullary thyroid cancer (the main cause of death among affected individuals), pheochromocytoma, and non-endocrine manifestations, such as marfanoid habits and other skeletal abnormalities as well as mucosal neuromas and ganglioneuromatosis of the gastrointestinal tract. Unlike the 2A form, MEN2B does not involve hyperparathyroidism and has a worse prognosis.

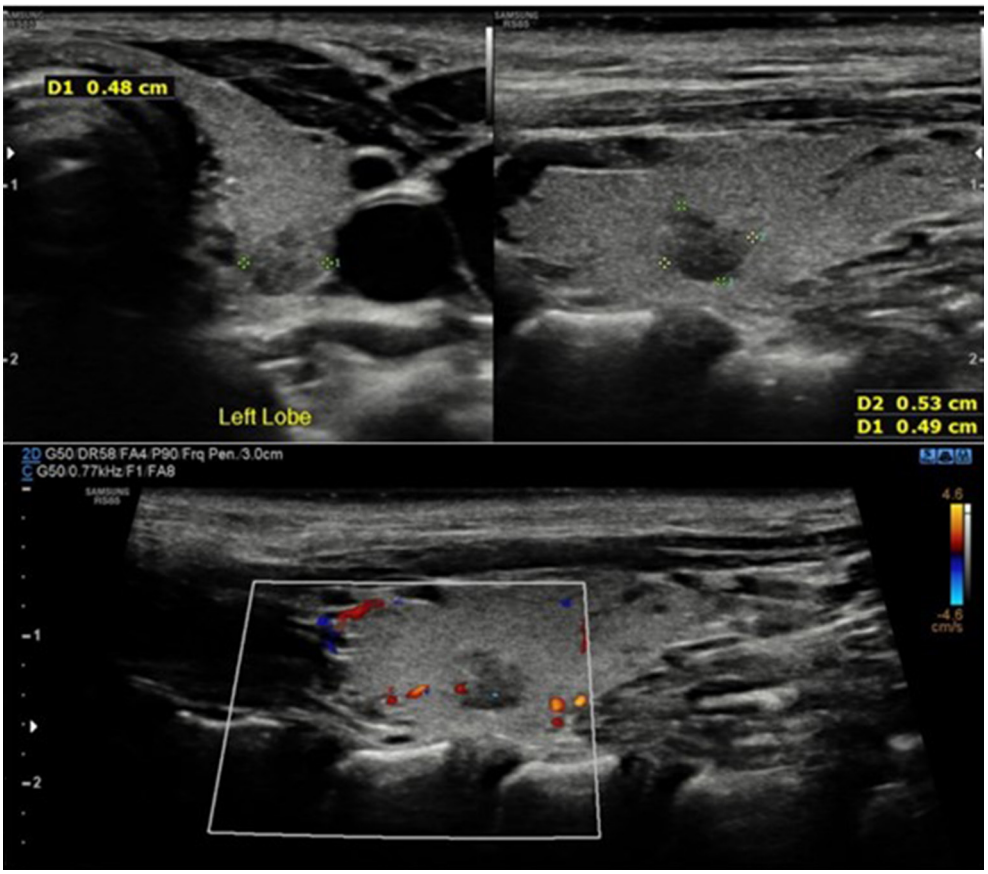

Figure 2 Ultrasound of thyroid gland with regular contour and normal dimensions, presenting solid, heterogeneous echotexture due to nodular images described below. Nodule in right lobe measured 2.4 cm × 0.9 cm × 0.3 cm on the largest axes (V: 1.0 cm^3). Nodule in isthmus measured 1.3 cm × 0.1 cm × 1.1 cm on the largest axes (V: 0.07 cm^3). Nodule in left lobe measured 2.4 cm × 0.9 cm × 0.9 cm on the largest axes (V: 1.0 cm^3). Total volume approximately 2.0 cm^3. Solid nodular image, predominantly hypoechoic, poorly defined margins, taller than wide, located in middle-posterior third of right lobe, measuring approximately 1.0×0.5×0.3. TI-RADS 5. Solid nodular image, predominantly hypoechoic, poorly defined margins, taller than wide, located in middle-posterior third of left lobe, measuring approximately 0.5×0.5×0.5. TI-RADS 5. The white box is marking the nodules' area. V, volume; TI-RADS, Thyroid Imaging Reporting and Data System.

Table 2 Laboratory exams performed on the 10th day of the postoperative period

Exams	Result	Reference value
Calcitonin (pg/mL)	353	Less than or equal to 7
Total calcium (mg/dL)	9.1	8.8–10.2
Ionized calcium (mmol/L)	1.3	1.10–1.40
Phosphorus (mg/dL)	5.9	2.7–4.5
TSH (mU/L)	35.17	0.6–4.84
Free T4 (ng/dL)	1.10	0.93–1.7
Carcinoembryonic antigen (ng/mL)	49.67	<3.8

TSH, thyroid stimulating hormone; T4, thyroxine.

This is a rare syndrome, the prevalence of which is one in every 30 thousand people.

Our patient presented with functional intestinal constipation and mucosal lesions at 3 years of age, which had not been previously investigated. Such data could suggest the possibility of MEN2B, along with scoliosis and joint hypermobility, which are non-endocrine manifestations of the syndrome. However, due to the low prevalence of MEN2B, the high prevalence of isolated constipation and high prevalence of joint hypermobility at our service, which is a reference service for the latter condition, the diagnostic hypothesis of MEN2B was not raised based merely on the combination of these findings.

After the genetic investigation at 10 years of age due to important muscle hypotonia and lipodystrophy, the mutation was encountered and the diagnosis of MEN2B was established, at which point the investigation of medullary thyroid carcinoma and pheochromocytoma was initiated.

During the investigation of medullary thyroid carcinoma, high calcitonin levels were found, which is one of the markers of neoplasia, and highly suspicious nodules were found in the gland bilaterally, along with abnormal cell proliferation during the frozen exam of the periphery of the recurrent laryngeal nerve during surgery.

The diagnosis was made when the patient was 10 years of age. This is in line with the mean age (10.6±3.9 years) found by Makri and collaborators (1) in a retrospective analysis of 38 patients with a diagnosis of MEN2B under care at the US National Institutes of Health between July 2007 and February 2018. Among these 38 patients, 35 were sporadic cases, 22 were only diagnosed after an endocrinological manifestation and 13 were diagnosed due to a non-endocrinological manifestation. Thus, the diagnosis comes late and the majority of patients have a new mutation, as occurred with the patient described in this report. Even in the presence of non-endocrinological manifestations, the diagnosis is made due to an endocrinological manifestation in most cases.

Twenty-four-hour urinary metanephrine exams were within the limits of normality and there were no clinical signs or symptoms that would cause an increase in catecholamines, that is, the presence of functioning pheochromocytoma.

Adequate management of these patients includes prophylactic total thyroidectomy with the expectation of preventing the emergence of medullary thyroid carcinoma and its dissemination throughout the organism. Surgery performed on the patient described herein was total thyroidectomy with cervical clearance after anatomopathological findings compatible with medullary thyroid carcinoma. The patient was sent to pediatric oncology for treatment.

The occurrence of pheochromocytoma prior to the emergence of medullary thyroid carcinoma or as an initial manifestation of MEN2 is uncommon. The present case is in line with this, as the patient presented with thyroidal abnormalities but had no signs, symptoms, or laboratory findings suggestive of pheochromocytoma.

Mucosal neuromas were found in our patients since early childhood. However, the resection proposed by the otolaryngology team was not performed due to the absence of pain and warning signs as well as the occurrence of the COVID-19 pandemic.

We found an abnormality in the proportion of the upper and lower segments of the body in the patient, along with skeletal deformities, such as scoliosis found by the clinical genetics team and marfanoid habits. Functional disorders of the intestine are common and the patient had chronic intestinal constipation.

The diagnosis of MEN2B is established when there is confirmation of the autosomal dominant genetic mutation or a mutation of the *RET* gene, as occurred in the patient. In the absence of the mutation or genetic testing, the majority of clinical manifestations should be present. The patient had a set of non-endocrinological manifestations, but no investigation of endocrine neoplasms was performed due to the absence of a diagnostic suspicion.

Conclusions

After diagnosis, the clinical signs and symptoms appeared too obvious not to have raised the possibility of MEN2B earlier. Some criticisms can be posed here, such as the follow-up of the patient by each specialty and each investigating only what matched the specialty in a fragmented way from the whole. This is a criticism not only of our service, but of current fragmented medicine.

Moreover, we are an essentially public service with resources above the national average but with frailties with regards to the request for genetic tests. Thus, in many cases, such as this one, the diagnosis is compromised due to the need for proof of the mutation or the need for numerous signs and symptoms of the syndrome in order to arrive at the diagnosis without the genetic test.

The occurrence of the pandemic also caused delays in the follow-up of the patient, which contributed to the delayed diagnosis. The low prevalence of the syndrome is another factor that contributed to the delay. Despite the delay, the patient will be followed up by a multidisciplinary team addressing the occurrence of the syndrome in a timely manner with the expectation of improving his quality of life and life expectancy.

This is a learning experience for working with other patients: common diseases are common, but rare diseases, although rare, also exist.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-23-114/rc

Peer Review File: Available at https://acr.amegroups.com/article/view/10.21037/acr-23-114/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-23-114/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient and his guardian for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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References

1. Makri A, Akshintala S, Derse-Anthony C, et al. Multiple Endocrine Neoplasia Type 2B Presents Early in Childhood but Often Is Undiagnosed for Years. J Pediatr 2018;203:447-9.
2. O'Riordain DS, O'Brien T, Grant CS, et al. Surgical management of primary hyperparathyroidism in multiple endocrine neoplasia types 1 and 2. Surgery 1993;114:1031-7; discussion 1037-9.
3. Bussières V, Roy S, Deladoey J, et al. Prophylactic thyroidectomies in MEN2 syndrome: Management and outcomes. J Pediatr Surg 2018;53:283-5.
4. Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 2015;25:567-610.
5. Siqueira DR, Ceolin L, Ferreira CV, et al. Role of RET genetic variants in MEN2-associated pheochromocytoma. Eur J Endocrinol 2014;170:821-8.
6. Imai T, Uchino S, Okamoto T, et al. High penetrance of pheochromocytoma in multiple endocrine neoplasia 2 caused by germ line RET codon 634 mutation in Japanese patients. Eur J Endocrinol 2013;168:683-7.
7. O'Riordain DS, O'Brien T, Crotty TB, et al. Multiple endocrine neoplasia type 2B: more than an endocrine disorder. Surgery 1995;118:936-42.
8. American Thyroid Association Guidelines Task Force; Kloos RT, Eng C, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009;19:565-612.