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De novo Multiple Endocrine Neoplasia Type 2B with Noncardiogenic Pulmonary Edema as the Presenting Symptom

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Abstract. Multiple endocrine neoplasia (MEN) type 2B is a rare hereditary disorder characterized by medullary thyroid carcinoma, pheochromocytoma, and neuroma. Early signs of MEN 2B are usually neuroma, gastrointestinal problems, and medullary thyroid carcinoma. Noncardiogenic pulmonary edema is rare as a presenting symptom. We report a 31-year-old male who was admitted to our hospital because of noncardiogenic pulmonary edema. He was 168 cm in height, weighed 55 kg, and had an arm span of 166 cm. No marfanoid habitus was evident, but thickened lips and tongue neuroma were present. Chronic constipation had been present since childhood, and the patient had a two-year history of untreated hypertension. Noncardiogenic pulmonary edema and toxic megacolon were noted, and abdominal computed tomography revealed bilateral adrenal tumors. Ultrasonography of the thyroid showed two mass lesions. Intubation and mechanical ventilation were performed because of severe hypoxemia. Endocrinological examinations showed high levels of serum and urinary fractionated catecholamines, serum calcitonin, serum carcinoembryonic antigen, and serum intact parathyroid hormone. It was suggested that the high level of catecholamine from pheochromocytoma had caused the pulmonary edema. RET gene analysis showed a codon 918 mutation in exon 16 resulting in an ATG (methionine) to ACG (threonine) substitution, but analysis of the patient's parents showed the wild type. Therefore, the patient was diagnosed as having *de novo* MEN 2B. He underwent laparoscopic bilateral adrenectomy and total thyroidectomy. However, the values of serum calcitonin and CEA did not decrease to the normal ranges. Patients with early-stage MEN 2B have distinct characteristics that can aid early detection of the disease, thus possibly allowing them to be saved.

Key words: *De novo*, Multiple endocrine neoplasia 2B, Noncardiogenic pulmonary edema

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MULTIPLE endocrine neoplasia (MEN) type 2 comprises three clinically related autosomal dominant cancer syndromes: MEN 2A, MEN 2B, and familial medullary thyroid carcinoma (FMTC), which share medullary thyroid carcinoma (MTC) as part of the disease spectrum. MEN 2B is characterized by combined occurrence of MTC, pheochromocytoma, and a distinct phenotype, including neuromas, bumpy lips, and a marfanoid habitus. All MEN 2 syndromes are caused by missense mutations in different areas of the RET gene. More than 95% of MEN 2B patients have a codon 918 mutation in exon 16, resulting in an ATG (methionine) to ACG (threonine) substitution (M918T) [1]. It is reported that about 50% of MEN 2B cases occur *de novo* [2]. In addition, the incidence of MEN 2B is very low, representing 5% of all MEN 2 cases. Thus, it is sometimes difficult to detect MEN 2B at an early stage. When the early signs, *i.e.*, neuroma and gastrointestinal problems, are not recognized, the diagnosis is usually made with discovery of MTC [3]. Therefore, Noncardiogenic pulmonary edema as the presenting symptom of MEN 2B is uncommon.

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In this report, we describe a 31-year-old man who presented at our hospital because of severe hypoxemia caused by noncardiogenic pulmonary edema, and was diagnosed as having *de novo* MEN 2B.

Case Report

A 31-year-old man was admitted to our hospital with a one-month history of worsening dyspnea. He had suffered chronic constipation since early childhood, and had a two-year history of untreated hypertension. Physical examination showed that he was 168 cm in height and 55 kg in weight, with an arm span of 166 cm. Therefore, he did not show the typical features of a marfanoid habitus. Blood pressure was 182/136 mmHg and sinus tachycardia was evident with a pulse rate of 150 beats/min. Body temperature was 37.0°C. Thickened lips and tongue neuromas were evident. On auscultation, coarse crackles were audible at the bilateral lung bases, but he had no gallop rhythm or heart murmur. The abdomen was distended and bowel sounds were decreased. There was no peripheral edema. Table 1 shows the results of laboratory examinations at admission. A complete blood cell count revealed an elevated white blood cell count (15500/μl). Blood chemistry examination showed some abnormal values as follows: serum albumin 3.9 g/dl, creatinine kinase (CK) 1286 IU/l, aspartate aminotransaminase (AST) 626 IU/l, alanine aminotransaminase (ALT) 787 IU/l, lactate dehydrogenase (LDH) 2169 IU/l, urea nitrogen 37 mg/dl, plasma glucose 172 mg/dl, total cholesterol 239 mg/dl, triglyceride 155 mg/dl, serum calcium 8.0 mg/dl, corrected serum calcium 8.1 mg/dl, and C-reactive protein (CRP) 3.74 mg/dl. The value of CK-MB fraction was 23 IU/l and normal. Gas analysis of arterial blood drawn while the patient was breathing room air revealed severe hypoxemia: PaO_2 42.0 Torr, $PaCO_2$ 31.6 Torr, arterial blood oxygen saturation (SaO_2) 59.6%, and pH 7.432.

Table 1.

Complete blood cell counts	
WBC	15500/μl
RBC	365×10^4/μl
Hemoglobin	12.3 g/dl
Hematocrit	34.7%
MCV	95.1 fl
MCH	33.7 pg
MCHC	35.4%
Platelets	17.4×10^4/μl
Blood chemistry	
Total protein	6.4 g/dl
Albumin	3.9 g/dl
Creatinine kinase	1286 IU/l
Creatinine kinase MB fraction	23 IU/l
Aspartate aminotransferase	626 IU/l
Alanine aminotransferase	787 IU/l
Lactate dehydrogenase	2169 IU/l
Creatinine	1.2 mg/dl
Urea nitrogen	37 mg/dl
Plasma glucose	172 mg/dl
Total cholesterol	239 mg/dl
Triglyceride	155 mg/dl
Sodium	142 mEq/l
Potassium	3.8 mEq/l
Chloride	101 mEq/l
Calcium	8.0 mg/dl
Phosphate	3.6 mg/dl
CRP	3.74 mg/dl
Arterial blood gas analysis	
pH	7.432
PaO_2	42.0 Torr
$PaCO_2$	31.6 Torr
SaO_2	59.6%

WBC: white blood cells, RBC: red blood cells, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, CRP: C-reactive protein

Chest X-ray examination showed bilateral fluffy infiltrates, suggesting pulmonary edema, but no cardiomegaly (cardiothoracic ratio 50%) (Fig. 1). Abdominal X-ray examination showed predominantly dilated ascending and transverse colons, compatible with toxic megacolon (Fig. 2). Abdominal computed tomography (CT) showed a 60-mm right adrenal tumor, a 30-mm left adrenal tumor and a dilated transverse colon with no free air (Fig. 3). Electrocardiography (ECG) revealed sinus tachycardia, but no evidence of ischemic heart disease. Echocardiography showed left ventricular diastolic dimension (LVDd) 54 mm, left ventricular systolic dimension (LVDs) 37 mm, ejection fraction (EF) 0.59, and normal wall motion.

Intubation and mechanical ventilation were performed because of severe hypoxemia due to pulmonary edema. Diltiazem hydrochloride to decrease blood pressure and imipenem cilastatin sodium 1 g a day were administered intravenously. Because impending rupture of the colon was suspected, transverse colonostomy to apply a stoma and biopsies of the colon and rectum were performed on the second hospital day. The sampled colorectal wall was thickened due to gan-

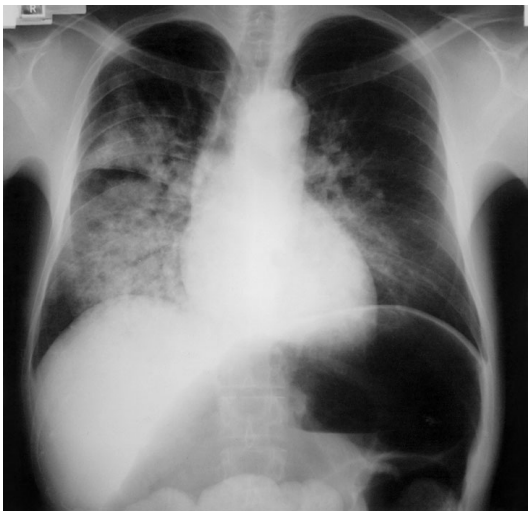

Fig. 1. Chest X-ray film showing bilateral pulmonary edema but no cardiomegaly, with a cardiothoracic ratio of 50%.

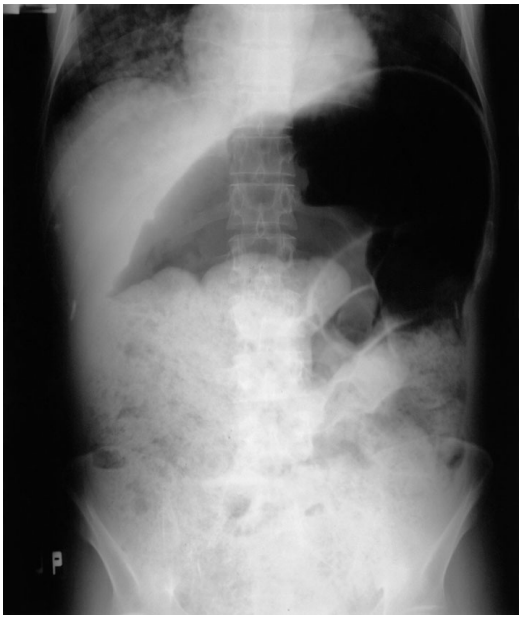

Fig. 2. Abdominal X-ray film showing predominant dilation of the ascending and transverse colon, compatible with toxic megacolon.

glioneuromatosis, which was characterized by hypertrophy of peripheral nerve bundles including ganglion cells (Fig. 4-a). The bundles involved the subserosal layer as well as the propria muscularis. Mechanical ventilation was continued for six days. After improvement of the hypoxemia due to pulmonary edema, the patient was extubated on the seventh hospital day.

Oral administration of doxazosine mesilate 2 mg a day was initially started, and the dose was gradually increased to 16 mg a day. Intravenous administration of diltiazem hydrochloride was switched to oral administration. Systolic blood pressure decreased to around 120 mmHg.

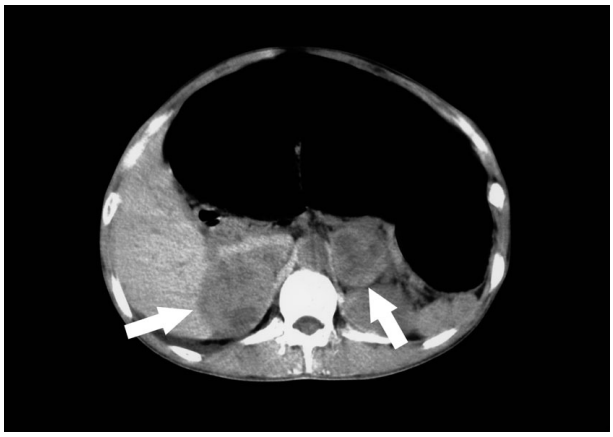

Fig. 3. Abdominal computed tomography (CT) showing a 60-mm right adrenal tumor, a 30-mm left adrenal tumor and a dilated transverse colon with no free air. White arrows indicate bilateral pheochromocytomas.

The results of endocrinological examinations are shown in Table 2. Elevated levels of serum and urinary fractionated catecholamines were revealed as follows: serum epinephrine 29314 pg/ml, serum norepinephrine 25508 pg/ml, serum dopamine 460 pg/ml, serum vanillylmandelic acid (VMA) 99.0 mg/l, urinary epinephrine 4610 μg/l, urinary norepinephrine 2920 μg/l, urinary dopamine 585 μg/l, urinary metanephrine 35.2 mg/l, urinary normetanephrine 12.0 mg/l, urinary epinephrine 2850 μg/day, urinary norepinephrine 2890 μg/day, urinary dopamine 595 μg/day, and urinary VMA 11.9 mg/day. Other endocrinological results included elevated values of serum calcitonin (5100 pg/ml) and intact parathyroid hormone (PTH; 287 pg/ml). An elevated level of CEA (24.0 ng/ml) was observed. Iodine 131-labeled metaiodobenzylguanidine (MIBG) scintigraphy confirmed involvement of the bilateral adrenal glands (Fig. 5). Ultrasonography of the thyroid showed two mass lesions, a 6-mm tumor in the right lobe and a 20-mm tumor in the left lobe. But ultrasonography did not detect parathyroid adenoma. Technetium 99m methoxyisobutylisonitrile (MIBI) scintigraphy did not show any abnormal uptake suggestive of parathyroid adenoma (data not shown).

Replacement of calcium to normalize the serum calcium level decreased the value of intact PTH to 49 pg/

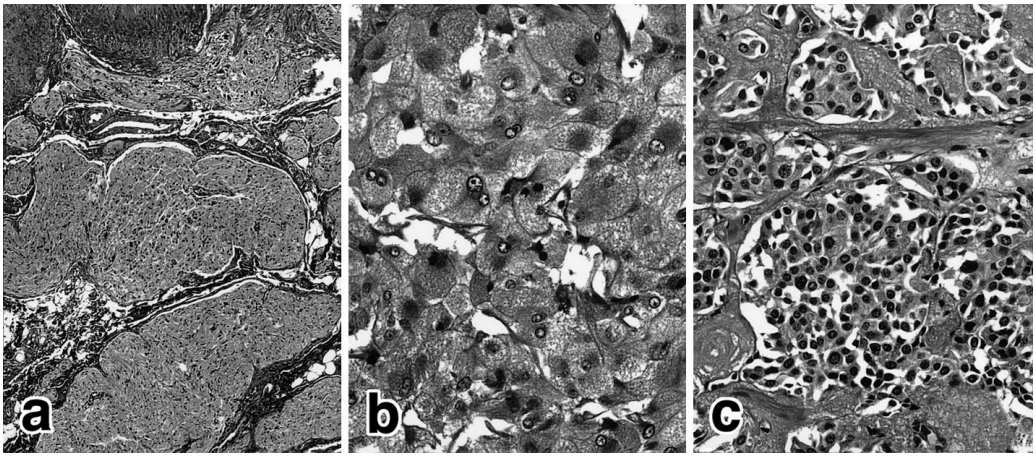

Fig. 4. a. Rectal biopsy (H & E: original magnification ×10). The rectal wall is thickened due to involvement of ganglioneuromatosis, especially around the subserosal layer. b. Adrenalectomy specimen (H & E: original magnification ×50). The left adrenal gland tumor is composed of cells possessing round nuclei and abundant eosinophilic cytoplasm, which are arranged in a Zellballen pattern. The right adrenal gland tumor showed the same constituents. c. Thyroidectomy specimen (H & E: original magnification ×50). Tumor cell nests, possessing hyperchromatic nuclei and relatively narrow cytoplasm, are separated by fibrotic stroma with amyloid deposition.

Table 2.

Endocrinological Tests	
Serum epinephrine	29314 pg/ml
Serum norepinephrine	25508 pg/ml
Serum dopamine	460 pg/ml
Serum vanillylmandelic acid	99.0 mg/l
Urinary epinephrine	4610 μg/l
Urinary norepinephrine	2920 μg/l
Urinary dopamine	585 μg/l
Urinary metanephrine	35.2 mg/l
Urinary normetanephrine	12.0 mg/l
Urinary epinephrine	2850 mg/day
Urinary norepinephrine	2890 mg/day
Urinary dopamine	595 mg/day
Urinary vanillylmandelic acid	11.9 mg/day
Calcitonin	5100 pg/ml
Intact PTH	287 pg/ml
CEA	24.0 ng/ml

ml (within the normal range) on the 49th hospital day. Elevated levels of the serum enzymes CK, AST, ALT and LDH also decreased to the normal ranges with stabilization of his general condition. Endocrinological evaluation and imaging studies were compatible with bilateral pheochromocytoma and MTC.

Because of suspected MEN 2B, we performed RET gene analysis after obtaining informed consent from the patient and his parents. All subjects gave their informed consent to participate in this study, and the investigation was performed in accordance with the principles of the Declaration of Helsinki. This study was approved by the institutional review board committee at Tokai University School of Medicine. Genomic DNA was extracted from blood cells and RET gene analyses were performed as described previously [4]. The analysis showed a heterozygous point mutation, ATG to ACG, resulting in substitution of methionine by threonine at codon 918 (M918T) in exon 16 of the RET gene (Fig. 6). However, the patient's parents showed the wild type (data not shown). Therefore, the patient was diagnosed as having *de novo* MEN 2B. After his general condition became stable, he was discharged on the 62nd hospital day.

The patient underwent laparoscopic left adrenalectomy at the second admission and right adrenalectomy at the third admission. On the latter occasion, total thyroidectomy was combined with the adrenalectomy. The left adrenal gland tumor measured 30 mm, and that on the right measured 60 mm. The tumors were solid and well demarcated by encapsulation, and showed a homogeneously brown-yellow cut surface. Microscopically, the tumor cell nests had a characteristic Zellballen structure supported by delicate stromal cells (Fig. 4-b). The cells were immunohistochemically positive for chromogranin-A. The nuclei were round and small, and the cytoplasm was abundant and finely granular with an accentuated eosinophilic appearance. These findings were characteristic of pheochromocytoma. The total thyroidectomy specimen consisted of

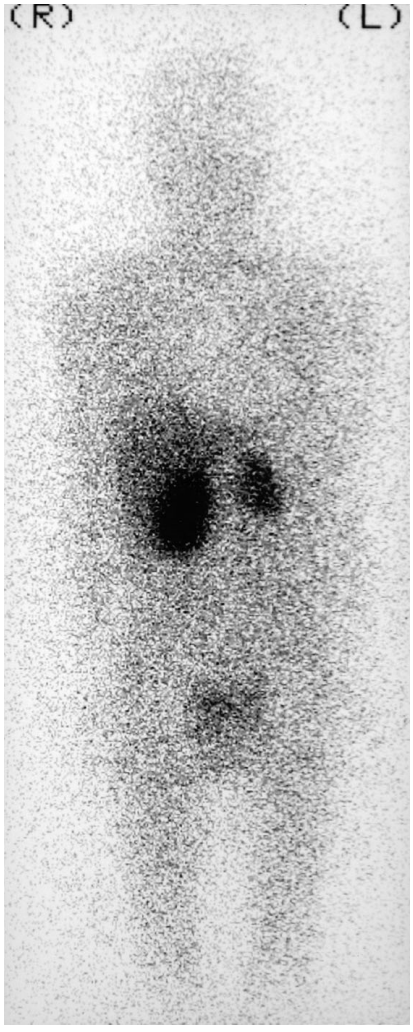

Fig. 5. Iodine 131-labeled metaiodobenzylguanidine scintigraphy confirms bilateral involvement.

atypical cells arranged in variable-sized solid nests (Fig. 4-c). The cells possessed round hyperchromatic nuclei and narrow eosinophilic cytoplasm. Calcitonin production by the tumor cells was demonstrated immunohistochemically. The fibrotic stroma intersecting the tumor nests was characterized by amyloid deposition and immunohistochemical expression of CEA. This evidence confirmed the diagnosis of medullary carcinoma. Metastatic disease was noted in the regional lymph nodes.

After bilateral adrenalectomy and total thyroidectomy, the patient was given hormone replacement therapy comprising hydrocortisone 30 mg a day, fludrocortisone acetate 0.1 mg a day, and levothyroxine sodium 125 μg a day. He was discharged on the 53rd hospital day.

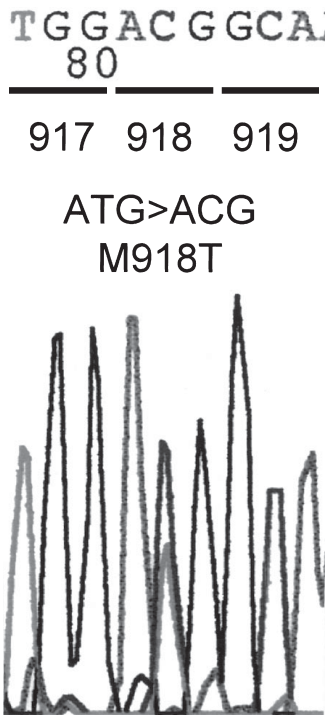

Fig. 6. Sequence analysis of the RET gene. This patient had a heterozygous point mutation of ATG to ACG, resulting in substitution of methionine by threonine at codon 918 in exon 16 of the RET gene.

Distant metastasis was not apparent in any imaging studies. However, calcitonin and CEA levels did not return to normal after total thyroidectomy, suggesting that the patient had micrometastases from the MTC. Radiation therapy with a total dose of 58 gray was delivered using a linear accelerator, but the latest values of calcitonin and CEA were 850 pg/ml and 9.0 ng/ml, respectively. The patient has been doing well as an outpatient for the last three years.

Discussion

We have reported a 31-year-old man with *de novo* MEN 2B in whom pulmonary edema was the presenting symptom. This patient had bilateral fluffy infiltrates demonstrable on chest X-ray film and severe hypoxemia, suggesting pulmonary edema. Cardiothoracic ratio was 50% and normal. ECG had no ischemic change. The value of CK was elevated at the admission, but the fraction of CK-MB was normal, suggesting no myocardial injury. Moreover, neither left ventricular enlargement nor wall motion abnormality

was detected on echocardiography. Thus, we considered the pulmonary edema in the patient to be noncardiogenic in origin.

Pulmonary edema as the first sign of MEN 2B is uncommon, although some reports have suggested a relationship between pulmonary edema and pheochromocytoma. Pulmonary edema as the first presentation of pheochromocytoma is rare and usually rapidly fatal [5, 6]. In most pheochromocytoma patients, pulmonary edema is cardiogenic in origin, because marked catecholamine release from the tumor may cause cardiovascular emergencies, such as hypertensive crisis, myocarditis, cardiomyopathy, and myocardial ischemia [7, 8]. However, noncardiogenic pulmonary edema may also occur. Pathogenesis of noncardiogenic pulmonary edema in patients with pheochromocytoma includes some theories. It was suggested that a rise in the pulmonary-capillary hydrostatic pressure result from postcapillary venoconstriction secondary to local effects of catecholamines and cause upstream transudation of fluid in the alveoli of interstitial space in animal study [9]. Increased permeability of the alveolocapillary membrane secondary to an elevation in catecholamines has been invoked [5]. It was shown that catecholamines dramatically increase after a variety of central nervous system insults [10]. And massive alpha-adrenergic stimulation is thought to have an important role in the initial phase of neurogenic pulmonary edema [11].

The most distinguishing characteristic of MEN 2B is the distinct phenotype. Many studies have indicated the early occurrence of clinical gastrointestinal symptoms in MEN 2B patients [3]. Of these symptoms, chronic constipation and diarrhea are most commonly observed. Our patient had a long history of chronic constipation, and biopsy of his intestinal mucosa showed ganglioneuromatosis, indicating that alimentary tract manifestations had been present since an early age. Toxic megacolon observed at admission was caused by ganglioneuromatosis. Elevated secretion of catecholamine from pheochromocytoma has been suggested to aggravate toxic megacolon [12].

This patient with MEN 2B showed an elevated level of intact PTH as well as an elevated calcitonin level. However, imaging studies did not show parathyroid adenoma. Transient hypocalcemia of unknown origin might have caused the patient's initial high PTH level. Although the physiologic role of calcitonin in humans remains obscure, its acute administration decreases the tubular reabsorption of calcium and directly impairs osteoclast-mediated bone resorption [13, 14]. Therefore it is suggested that calcitonin elevation and hypocalcemia induced secondary elevation of intact PTH. The serum CK level was elevated on admission. Transient elevation of the CK level has been reported in cases of pheochromocytoma and is probably related to catecholamine-induced myositis [15]. Elevations in the levels of other enzymes, such as AST, ALT and LDH, are nonspecific but have been reported in association with pheochromocytoma [16].

In MEN 2B, MTC is the most serious and potentially lethal complication. MTC in MEN 2B is known to run an aggressive course, as compared with MTC in MEN 2A and FMTC. Metastatic MTC may be found in children younger than 5 years old, and it has been suggested that thyroidectomy should be performed before the age of 6 months in MEN 2B [17]. After total thyroidectomy and radiation therapy, values of serum calcitonin and CEA did not decrease to the normal ranges, suggesting the presence of micrometastasis.

Unfortunately, postsurgical serum calcitonin levels do not become normalized in most patients with MTC [18]. Kebebew *et al.* analyzed 58 patients with sporadic MTC, 23 patients with FMTC, 16 patients with MEN 2A, and 7 patients with MEN 2B and revealed that 38% of the patients had postsurgical persistent hypercalcitoninemia and no clinical or radiographic evidence of residual tumor, surviving for an average of 3.6 years (ranging from one month to 23.7 years) [19]. A nationwide survey on the treatment policy for MTC and well differentiated thyroid carcinoma (papillary carcinoma and follicular carcinoma) [20, 21] indicated that clinicians should be prepared to offer individualized options for inherited MTC screening and risk-reducing surgery. Thus, early detection of MEN 2B may save patients, particularly from MTC.

In conclusion, we have reported a patient with *de novo* MEN 2B in whom noncardiogenic pulmonary edema was the presenting symptom. It is important to be aware of possible presenting symptoms compatible with the features of MEN 2B.

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