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CASE REPORT

Early detection of multiple endocrine neoplasia type 1: A case report

Jie-Hao Yuan, Su Luo, Ding-Guo Zhang, Li-Sheng Wang

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Jie-Hao Yuan, Su Luo, Ding-Guo Zhang, Li-Sheng Wang, Department of Gastroenterology, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University), Shenzhen 518020, Guangdong Province, China

Co-corresponding authors: Ding-Guo Zhang and Li-Sheng Wang.

Corresponding author: Ding-Guo Zhang, MD, Associate Professor, Department of Gastroenterology, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University), No. 1017 Dongmen North Road, Luohu District, Shenzhen 518020, Guangdong Province, China. zdg8012@sina.com

Abstract

BACKGROUND

Multiple endocrine neoplasias (MENs) are a group of hereditary diseases involving multiple endocrine glands, and their prevalence is low. MEN type 1 (MEN1) has diverse clinical manifestations, mainly involving the parathyroid glands, gastrointestinal tract, pancreas and pituitary gland, making it easy to miss the clinical diagnosis.

CASE SUMMARY

We present the case of a patient in whom MEN1 was detected early. A middle-aged male with recurrent abdominal pain and diarrhea was admitted to the hospital. Blood tests at admission revealed hypercalcemia and hypophosphatemia, and emission computed tomography of the parathyroid glands revealed a hyperfunctioning parathyroid lesion. Gastroscopy findings suggested a duodenal bulge and ulceration. Ultrasound endoscopy revealed a hypoechoic lesion in the duodenal bulb. Further blood tests revealed elevated levels of serum gastrin. Surgery was performed, and pathological analysis of the surgical specimens revealed a parathyroid adenoma after parathyroidectomy and a neuroendocrine tumor after duodenal bulbectomy. The time from onset to the definitive diagnosis of MEN1 was only approximately 1 year.

CONCLUSION

For patients who present with gastrointestinal symptoms accompanied by hypercalcemia and hypophosphatemia, clinicians need to be alert to the possibility of MEN1.

Key Words: Multiple endocrine neoplasia type 1; Gastrointestinal symptoms; Hypercalcemia; Early detection; Case report

Core Tip: Multiple endocrine neoplasia type 1 (MEN1) mainly affects the parathyroid glands, gastrointestinal tract, pancreas and pituitary gland and manifests as parathyroid adenomas, gastrinomas, insulinomas and pituitary tumors. As a rare disease, MEN1 is easily missed in clinical practice. We analyzed a case of MEN in a patient who had gastrointestinal symptoms as the main manifestation, and this report provides a reference for MEN1 clinical diagnosis and treatment.

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INTRODUCTION

As an autosomal dominant genetic disease, multiple endocrine neoplasia type 1 (MEN1) has a low incidence, diverse clinical manifestations, and a complex prognosis, and MEN1 is easily misdiagnosed; therefore, early diagnosis and treatment are very important[1,2]. In this case report, the diagnosis and treatment of a patient with MEN1 who manifested gastrointestinal symptoms as the initial symptom and parathyroid gland involvement are analyzed. For this patient, a definitive diagnosis was quickly reached. This case report provides a reference for the early diagnosis of MEN1 in clinical practice.

CASE PRESENTATION

Chief complaints

A 51-year-old male was admitted to the hospital on June 8, 2022, due to a 1-year history of subxiphoid pain and watery diarrhea.

History of present illness

One year prior, the patient developed subxiphoid pain accompanied by yellow watery stools 3-4 times per day without significant weight loss. No obvious abnormalities were found on gastrointestinal endoscopy at other hospitals. Symptoms improved after oral omeprazole, but discomfort recurred after withdrawal of the drug.

History of past illness

There was no specific past medical history.

Personal and family history

The patient denied a significant personal and family history.

Physical examination

There were no significant positive signs on physical examination.

Laboratory examinations

Laboratory investigations revealed no obvious abnormalities in routine blood work or examinations of liver, kidney, and thyroid function, tumor markers, and feces. The laboratory test results during hospitalization were as follows: Blood calcium, 2.63 mmol/L (reference value 2.05-2.55); blood phosphorus, 0.71 mmol/L (0.8-1.5); parathyroid hormone, 80.80 pg/mL (15-65); calcitonin, 21.7 pg/mL (< 18); 24-hour urinary calcium, 8.62 mmol/24 h (2.5-7.5); 25-hydroxytotal vitamin D, 48.4 nmol/L (75-250); gastrin, 281 pg/mL (13.00-15.00); and gastrin-17, 34.06 pmol/L (1.00-15.00). Human chromogranin A, anti-inner factor antibody immunoglobulin G, anti-parietal cell antibody immunoglobulin G, pituitary prolactin, human growth hormone, glycated hemoglobin, blood cortisol and adrenocorticotropic hormone at 8:00 am and 24-hour urinary vanillylmandelic acid were normal.

Imaging examinations

After admission, enhanced computed tomography (CT) of the abdomen showed marked enhancement of the mucosa of the stomach, duodenum and jejunum, and a nodule was observed on the medial wall of the duodenal bulb. Further gastroscopy revealed a bulge in the duodenal bulb with surface ulcer formation, and a deep biopsy was performed (Figure 1A). Ultrasound endoscopy revealed a hypoechoic lesion in the duodenal bulb, approximately 9.4 mm × 6.7 mm in cross-section, with inhomogeneous internal echogenicity (Figure 1B); the lesion protruded into the lumen and

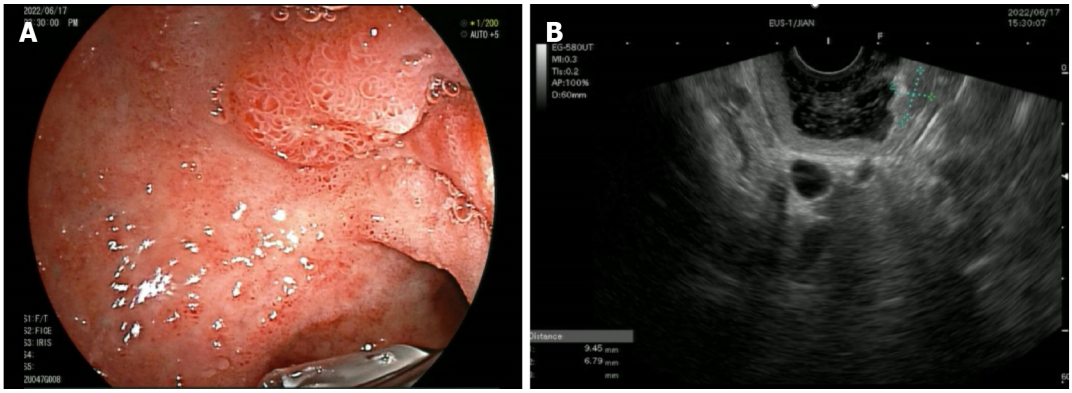

Figure 1 Imaging of lesions in the duodenal bulb *via* ultrasound endoscopy. A: Ultrasound endoscopy revealed a hypoechoic focus in the duodenal bulb that was irregularly shaped; B: The lesion originated from the submucosa.

originated from the submucosa. Endoscopic biopsy revealed atypical cell nests in the local mucosal layer and submucosal layer, which were considered to indicate micronodular hyperplasia of neuroendocrine cells. Immunohistochemistry results were as follows: CK (+), Syn (+), CD56 (-), CgA (+), Ki67 (approximately 2%+), and p53 (-). Urological ultrasound revealed a stone in the left kidney. Thyroid and parathyroid ultrasound revealed a hypoechoic lesion in the left thyroid gland, nearly 43 mm × 10 mm in size, for which origination from the parathyroid gland could not be excluded. Enhanced CT revealed a blood-rich nodule in the posterior left lobe of the thyroid gland and in the medial left common carotid artery, with a size of 17 mm × 11 mm (Figure 2A). Emission CT indicated a hyperfunctional lesion change (Figure 2B). A magnetic resonance imaging scan of the pituitary showed no abnormalities.

FINAL DIAGNOSIS

Sequencing of the *MEN1* gene showed detection of heterozygous variants. MLPA technology to detect large segment deletions/insertions in the *MEN1* gene did not detect mutations.

TREATMENT

The patient underwent left inferior parathyroidectomy on June 23, 2022, with a postoperative pathological diagnosis consistent with parathyroid adenoma. Watery diarrhea persisted after surgery. Then, combined laparoscopic and gastroscopic duodenal bulb resection of the mass was performed.

OUTCOME AND FOLLOW-UP

Postoperative pathological analysis revealed a neuroendocrine tumor, G1, located in the mucosal and submucosal layers, with a maximum diameter of approximately 0.6 cm, and no tumor was observed at the margins of the incision or basal incision (Figure 3). Immunohistochemistry results were as follows: CK (+), CD56 (+), Syn (+), CgA (+), SSTR2 (2+), and Ki-67 (approximately 2%+). No tumor metastasis was detected in the lymph nodes of the gastric wall (0/1). After discharge following the procedure, the patient's symptoms of abdominal pain or diarrhea were significantly improved compared with before the procedure.

DISCUSSION

MENs are a group of hereditary diseases involving multiple endocrine glands. MEN can be divided into MEN1 and MEN2[1]. MEN1 mainly affects the parathyroid glands, gastrointestinal tract, pancreas and pituitary gland and manifests as parathyroid adenomas, gastrinomas, insulinomas and pituitary tumors. As a rare disease, MEN1 is easily missed in clinical practice[2]. In this case, we analyzed the diagnosis of MEN1 in a patient with gastrointestinal symptoms as the main manifestation, and this report provides a reference for the clinical diagnosis and treatment of MEN1.

The characteristics of this patient were as follows: (1) A middle-aged male with a chronic course; (2) Recurrent abdominal pain, diarrhea, and symptoms relieved by oral proton pump inhibitors (PPIs). Symptoms recurred after the discontinuation of PPIs, and gastrointestinal endoscopy in the hospital did not reveal obvious pathological changes; (3) Admission examination findings suggested hypercalcemia and hypophosphatemia. Further examination revealed elevated parathyroid hormone, calcitonin and urinary calcium levels. Parathyroid enhanced CT revealed blood-rich

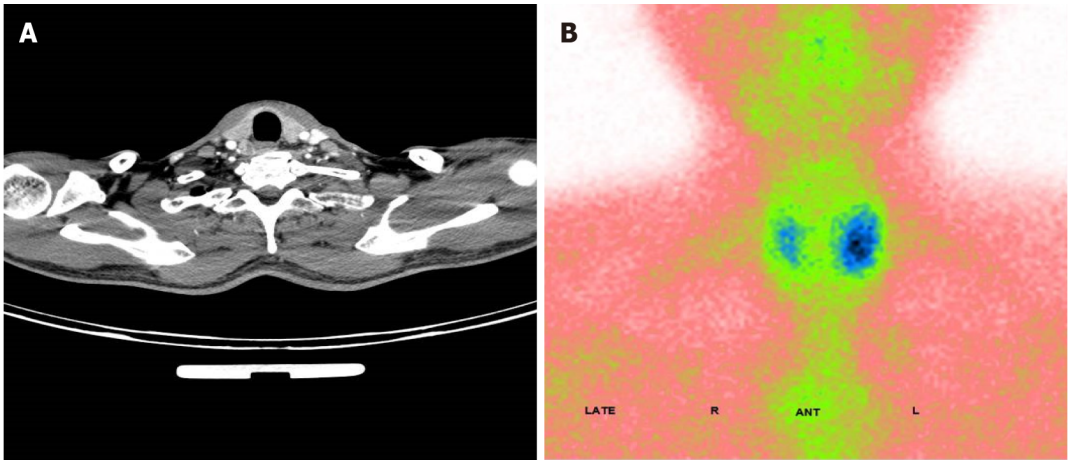

Figure 2 Imaging of lesions of the thyroid and parathyroid glands. A: Enhanced computerized tomography image showing a blood-rich nodule in the posterior left lobe of the thyroid gland; B: Emission computed tomography revealed a hyperfunctional lesion change in the left lobe of the thyroid gland.

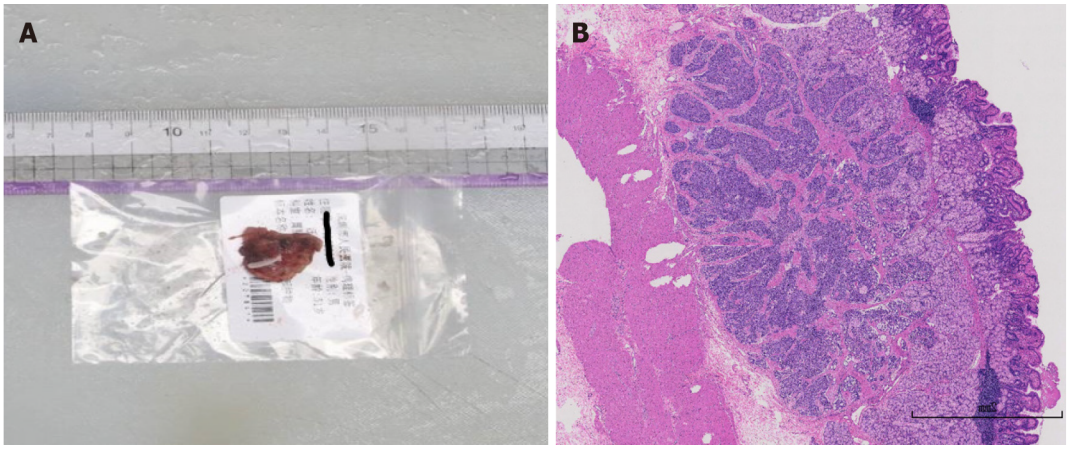

Figure 3 Postoperative pathological analysis of the duodenal bulbous lesion. A: The postoperative duodenal bulb mass specimen measured approximately 2 cm × 2 cm × 0.7 cm; B: Histopathological analysis findings suggested that the lesion was a neuroendocrine tumor, stage G1.

nodules, and the findings of emission CT of the parathyroid glands suggested hyperfunctioning parathyroid lesions; (4) Gastroscopy at our hospital revealed duodenal bulging and ulceration. Ultrasonographic endoscopy revealed submucosal hypoechoic foci and elevated serum gastrin levels; (5) Pathological analysis findings after the resection of the left lower parathyroid gland and the duodenal bulb suggested parathyroid adenomas and neuroendocrine tumors; and (6) Heterozygous variants in the *MEN1* gene were detected. Combined with the medical history, imaging, endoscopic and pathological data, this case is consistent with MEN1.

Gastrinoma manifests as excessive gastric acid secretion and thus recurrent peptic ulcers, epigastric pain and diarrhea and is known as Zollinger-Ellison syndrome. Hereditary gastrinoma is associated with MEN1[3]. Research has shown that 20%-30% of cases of Zollinger-Ellison syndrome are caused by MEN1, while approximately 60% of MEN-1 patients will develop gastrinoma[4]. Gastrinoma also manifests as gastroesophageal reflux disease, such as acid reflux and heartburn. Due to atypical early symptoms, gastrinoma can easily be missed and misdiagnosed[5]. Studies have shown the time from the appearance of gastrointestinal symptoms to the final diagnosis of gastrinoma usually takes more than 5 years[6]. Diagnosis is based on the clinical manifestations of hypergastrinemia, elevated serum gastrin, endoscopic findings, imaging evidence and pathological analysis findings. In this patient, symptoms improved after the use of PPIs and recurred after their discontinuation, which indicates the possibility of gastrinoma. Postoperative pathological analysis findings suggested a neuroendocrine tumor. Serum gastrin was elevated more than 10-fold, so the possibility of gastrinoma was high. The patient was diagnosed with MEN1 only 1 year after the onset of symptoms in this case, and timely treatment prevented further progression.

A greater percentage of parathyroid tumors than gastrinomas occur in MEN1. Studies have shown that nearly 90% of MEN1 patients have parathyroid gland involvement, resulting in primary hyperparathyroidism[7]. Generally, MEN1 causes mild symptoms of hypercalcemia, and affected individuals can even be asymptomatic, while the incidence of hypercalcemic crisis is low[8]. Sometimes, hypercalcemia is found only during laboratory tests, which is an obstacle to early detection. In this case, the patient's blood biochemistry results suggested hypercalcemia. Further examination revealed a renal stone and parathyroid gland nodules, which are key for the diagnosis of a parathyroid adenoma. For patients with gastrinoma combined with hypercalcemia or a parathyroid tumor, we need to consider whether MEN1 is

possible. The mechanism by which gastrinoma develops in MEN1 has still not been elucidated. Hackeng *et al*[9] proposed the hypothesis of a parathyroid-intestinal axis and suggested that the hypercalcemia induced by parathyroid tumor may promote gastrinoma development by affecting calcium-sensing receptors, which promote the proliferation of gastrinocytes and thus promote the development of tumors[9].

MEN1 is an autosomal dominant disorder linked to the *MEN1* gene on chromosome 11q13. Deletions or mutations in the *MEN1* gene result in a shortening of the encoded protein Menin. Altered length Menin cannot be transferred to the nucleus, resulting in a loss of function[10]. It has been reported that a proportion of patients diagnosed with MEN1 do not present with mutations in the *MEN1* gene, and their diagnosis is mainly based on clinical criteria[11]. de Laat *et al*[12] showed that the clinical manifestations of patients with mutation-positive *vs* mutation-negative MEN1 differed. Patients with mutation-negative MEN1 later developed MEN1-related clinical symptoms, with a better MEN1 prognosis. In this case, heterozygous variants of unknown significance were detected in the whole exon by gene sequencing, which indicated a high probability of MEN1 when combined with the clinical manifestations. However, attention should be given to identifying MEN1-like syndrome or sporadic coincidence of two neuroendocrine tumors.

CONCLUSION

In this case, the patient presented with nonspecific gastrointestinal symptoms, hypercalcemia and elevated serum gastrin and was ultimately diagnosed with MEN1. The time from symptom onset to definitive diagnosis of MEN1 was only 1 year. MEN1 can manifest different clinical symptoms and is easily misdiagnosed. Therefore, for patients with gastrointestinal symptoms, especially the recurrence of symptoms after PPI discontinuation, it is necessary to be alert to the possibility of MEN1 to achieve early diagnosis and early treatment and to improve the outcomes.

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FOOTNOTES

Author contributions: Yuan JH collected the data and drafted the manuscript; Luo S performed the electronic gastroscopy and ultrasound gastroscopy; Zhang DG and Wang LS diagnosed and clarified the final treatment plan for the patient and revised the manuscript, they are the co-corresponding authors of this manuscript; and all the authors read and approved the final manuscript.

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ORCID number: Jie-Hao Yuan 0009-0008-4850-9996; Su Luo 0000-0001-7459-4743; Ding-Guo Zhang 0000-0001-7728-9672; Li-Sheng Wang 0000-0002-7418-6114.

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