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## Multiple endocrine neoplasia type 1- presenting multiple lipomas and hypoglycemia onset

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### Summary

**Background:**

Multiple endocrine neoplasia type 1 (MEN1), also called Wermer syndrome, is an autosomal dominant disorder characterized by tumors of the parathyroid glands, the anterior pituitary, and the endocrine pancreas.

**Case Report:**

Here, we report a case of MEN1. Our patient was a 44-year-old woman who manifested typical features of MEN1, including insulinoma, pituitary tumors, and parathyroidoma, and exhibited multiple lipomas and a gastrinoma with duodenal ulcers. She was admitted to our hospital because of recurrent massive bleeding of the upper gastrointestinal tract and hypoglycemia. The first operation for pituitary tumors was performed when she was 40 years old. According to these examinations and her clinical course, the patient was diagnosed with insulinoma and gastrinoma. She subsequently underwent surgery for the pancreatic tumors. The majority of these tumor cells were immunohistochemically positive for insulin and negative for glucagon.

**Conclusions:**

This case suggests that multiple lipomas, insulinoma and gastrinoma may provide clues for a diagnosis of MEN1.

**key words:**

**multiple endocrine neoplasia type 1 • multiple lipomas • upper gastrointestinal bleeding • insulinoma • gastrinoma**

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## BACKGROUND

Multiple endocrine neoplasia type 1 (MEN1), also called Wermer syndrome, is an autosomal-dominant disorder caused by a mutation in the *menin* gene on chromosome 11q13 [1]. The protein encoded by this gene, MENIN, acts as a tumor suppressor by altering JunD-mediated transcription [2]. This syndrome is characterized by parathyroid adenoma (or hyperplasia), islet cell tumors of the pancreas, and pituitary tumors. MEN1 is an intractable disorder due to its clinical variability, which is caused by the complexity of the various hormones involved. Pancreatic tumors occur in about 30–80% of MEN1 patients and are the second most frequent clinical manifestation of MEN1 [3]. Most cases of multiple islet cell tumors are MEN1-related. Most of these tumors produce excessive amounts of hormones, such as gastrin, insulin, glucagon, somatostatin, neurotensin or vasoactive intestinal polypeptide, and are associated with distinct clinical syndromes [4]. In addition, massive bleeding from the gastrointestinal tract induced by gastrinoma or insulinoma is a major concern that occurs frequently in MEN1, despite the administration of proton pump inhibitors (PPIs) to reduce gastric acid secretion.

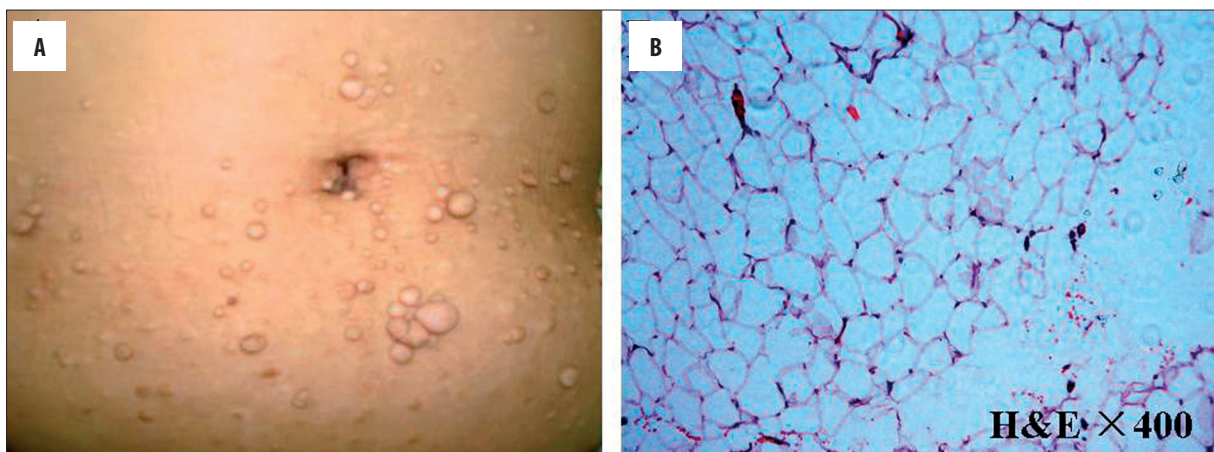
Although pancreatic tumors occur in approximately 30–80% of MEN1 patients [3], multiple lipomas, hypoglycemia and massive bleeding in the gastrointestinal tract are rarely documented. We report the case of a 44-year-old woman who presented with islet cell tumors, gastrinoma associated with massive bleeding of duodenal ulcers, pituitary tumor, supraparenoma, and parathyroidoma simultaneously, with upper gastrointestinal hemorrhage and hypoglycemia as initial symptoms.

## CASE REPORT

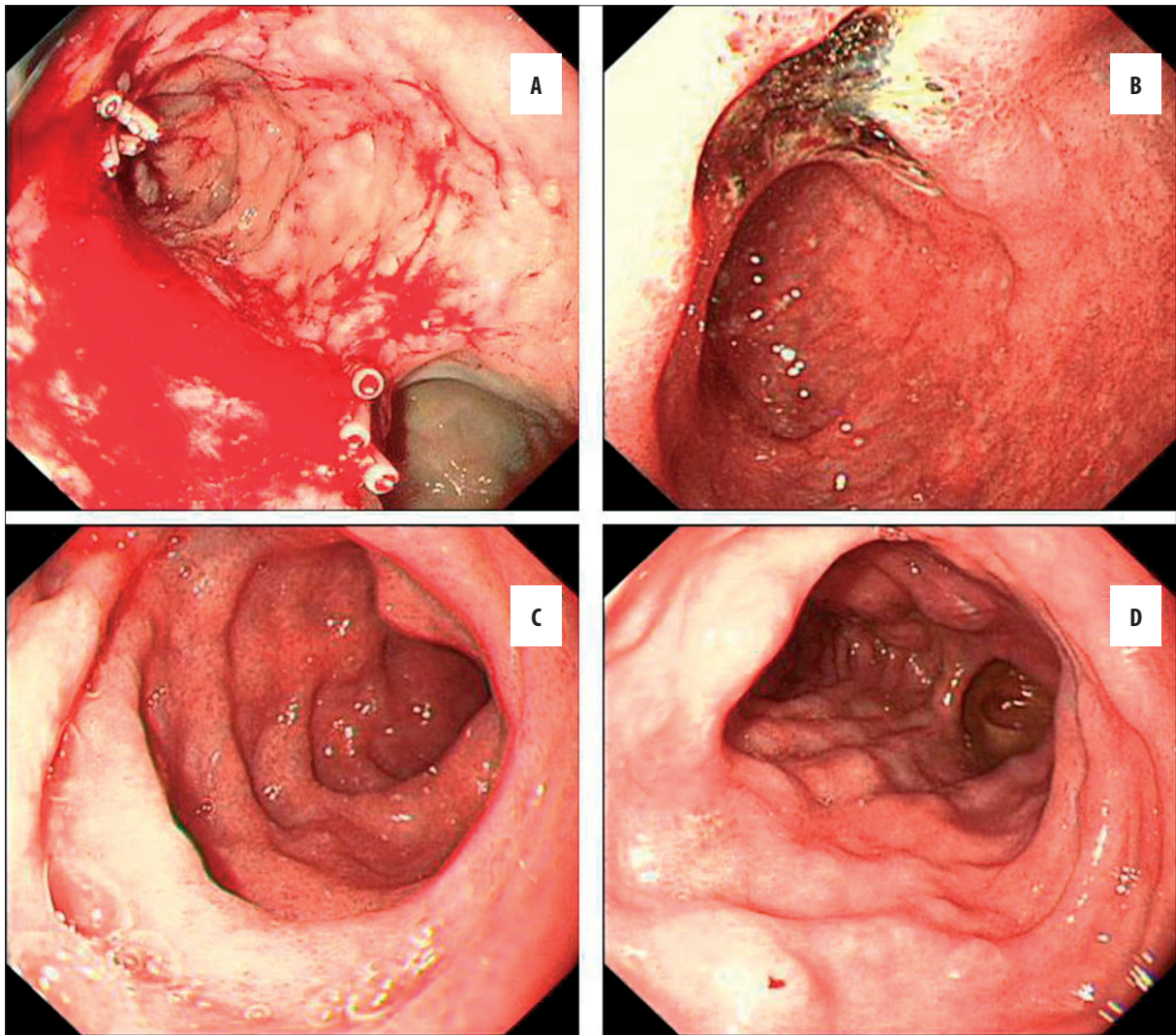
A 44-year-old woman with massive bleeding of the upper gastrointestinal tract, who presented with dark stool and anemia caused by duodenal ulcer, was admitted to our hospital. At the age of 40 (4 years ago) she was diagnosed with pituitary adenoma at another hospital and treated by surgical removal. At the age of 43 she underwent a second surgical treatment due to the recurrence of the pituitary adenoma. Pathological examinations showed adrenocorticotropic hormone (ACTH, +), prolactin (PRL –), follicle-stimulating hormone (FSH –),

thyroid-stimulating hormone (TSH –), growth hormone (GH –), and luteinizing hormone (LH –). Physical examination at this time showed acromegaly, anemia and abdominal lipoma, confirmed by hematoxylin-eosin staining (Figure 1). Laboratory examinations showed the following indexes (normal range in parentheses): hemoglobin, 51 g/L; peripheral white cell count, 7840/L (3500–8500); peripheral red cell count, 2220/L (3500–5500); total bilirubin, 6.3  $\mu$ mol/L (4–23.9); alkaline phosphatase, 38 U/L (35–125); c-glutamyl transpeptidase, 12 U/L (7–50); aspartate aminotransferase, 15 U/L (14–40); alanine aminotransferase, 21 U/L (5–35); and prothrombin time, 13.8 s (11.0–14.5). Hepatitis B and C markers were negative. Fecal occult blood test was positive. Serum hydrocortisone levels at 0 pm and 8 am were 155.1 nmol/L and 271.5 nmol/L (138.0–690.0), respectively. The fasting gastrin level was 216 pg/ml (<100 pg/ml), and the secretin test showed a significant gastrin level increase to 678 pg/ml (increase of <200 pg/ml after secretin).

Endoscopic examination of the upper gastrointestinal tract indicated erosive gastritis and multiple duodenal ulcers with bleeding (Figure 2). Massive bleeding from the upper gastrointestinal tract was relieved after pharmacological treatment with a proton pump inhibitor (PPI). However, a second endoscopic examination revealed that the ulcer remained intractable (Figure 2). Moreover, the patient exhibited hypoglycemia with dizziness and hypodynamia every morning, and blood glucose fluctuated between 0.80 and 1.40 mmol/l. The endocrine functions were as follows (normal range in parentheses): growth hormone, 11.2 mIU/L (<26 mIU/L); prolactin, 59 ng/ml (5–27 ng/ml); parathyroid hormone, 178.23 pg/ml (10–55 pg/ml); serum hydrocortisone levels at 12 am, 8 am and 4 pm were 84.88, 246.15 and 121.50 nmol/L, respectively; fasting blood glucose, 1.39 mmol/L; postprandial 2-hour blood glucose, 8.34 mmol/L; fructosamine, 93.2  $\mu$ mol/L (122–236); glycosylated hemoglobin, 4.9% (<6%); fasting serum C-peptide, 0.77 nmol/L (0.17–0.66 nmol/L); fasting serum insulin, 0.31 U/ml (2–20 U/ml); postprandial 2-hour serum C-peptide, 2.08 nmol/L; serum insulin, 51.52 U/ml; calcitonin, 198.0 ng/L (0–18.2 ng/L); and mandelic acid, 20.08 mg/24 hs (<13.6 mg/24 hs). Abdominal computed tomography (CT) showed a mass 5 cm in diameter in the corpus pancreas, which was confirmed by endoscopic ultrasonography (Figure 3). A parathyroidoma and 2 nodules 1 cm in



**Figure 1.** The patient showed multiple lipomas. (A) Abdominal multiple tumors. (B) Histology of the abdominal tumor biopsies confirmed that the tumors were multiple lipomas (H&E staining).



**Figure 2.** Multiple duodenal ulcers were observed using gastroscopy. (A) Multiple duodenal ulcers with massive bleeding. (B) Multiple duodenal ulcers were ameliorated 2 months after surgical removal of pancreatic endocrine neoplasia. (C,D) Duodenal ulcers healed well 1 year after surgical removal of pancreatic endocrine neoplasia.

diameter in the bilateral side adrenal glands were observed in the CT scan (data not shown). Endoscopic examination of the upper gastrointestinal tract revealed erosive gastritis and multiple duodenal ulcers after treatment with PPI, and a histopathological examination showed moderate inflammation with lymphoplasmacytic and neutrophil infiltration (data not shown).

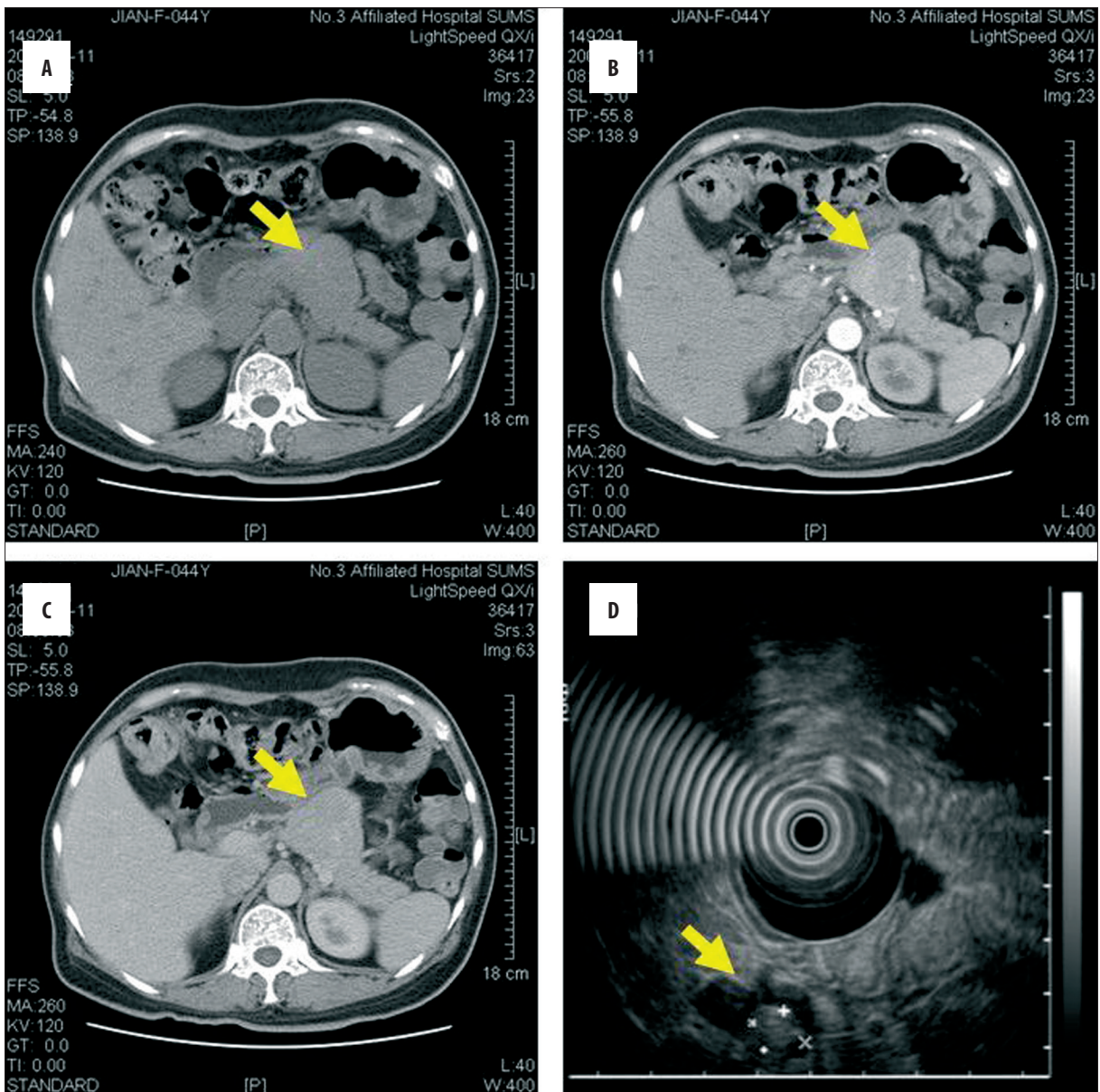
The patient was diagnosed with MEN1 with associated pituitary tumors, parathyroidoma, insulinoma, and gastrinoma with duodenal ulcers based on the data above. Therefore, a laparotomy was performed to extirpate the pancreatic tumor. After surgical operation, pathological examination and immunohistochemistry confirmed the tumor character. H&E staining revealed an endocrine neoplasia in the tumor, and immunohistochemistry demonstrated synaptophysin (Syn +), chromogranin (CgA +), neuron-specific enolase (NSE +), CD56 (+), somatostatin (+), progesterone (PR +), insulin (+), glucagon (–) and cytokeratin (CK +) (Figure 4). These tumor cells were immunohistochemically positive for insulin and negative for glucagon. After surgical operation, the patient was subsequently treated with a PPI for 3 months,

and all symptoms were relieved. Endoscopic examination of the upper gastrointestinal tract demonstrated that the erosive gastritis and multiple duodenal ulcers had healed after 1 year of PPI treatment (Figure 3).

## DISCUSSION

MEN is characterized by the occurrence of tumors in 2 or more endocrine glands in a single patient. Two major forms of MEN – type 1 and type 2 – can be distinguished. MEN1 syndrome appears as a hyperplasia of the parathyroid gland and is accompanied by islet cell tumors and pituitary adenoma. MEN2 syndrome has 2 clinical presentations. MEN2a presents as a medullary thyroid carcinoma with bilateral pheochromocytoma and hyperplasia of the parathyroid gland, and MEN2b is characterized by the additional appearance of neurocutaneous manifestations without primary hyperparathyroidism. In addition to these tumors, adrenal cortical carcinoid and lipomatous tumors have also been described in patients with MEN1. Carcinoid tumors occur more frequently in MEN1 patients and may be inherited as an autosomal dominant condition with MEN1 [5]. Our patient presented





**Figure 3.** Computed tomography (CT) scan and endoscopic ultrasonography (EUS) examination indicated a tumor (yellow arrow) in the corpus pancreas. (A) Plain CT scan image. (B) CT image in the arterial phase of contrast enhancement. (C) CT image in the parenchymal phase of contrast enhancement. (D) EUS image.

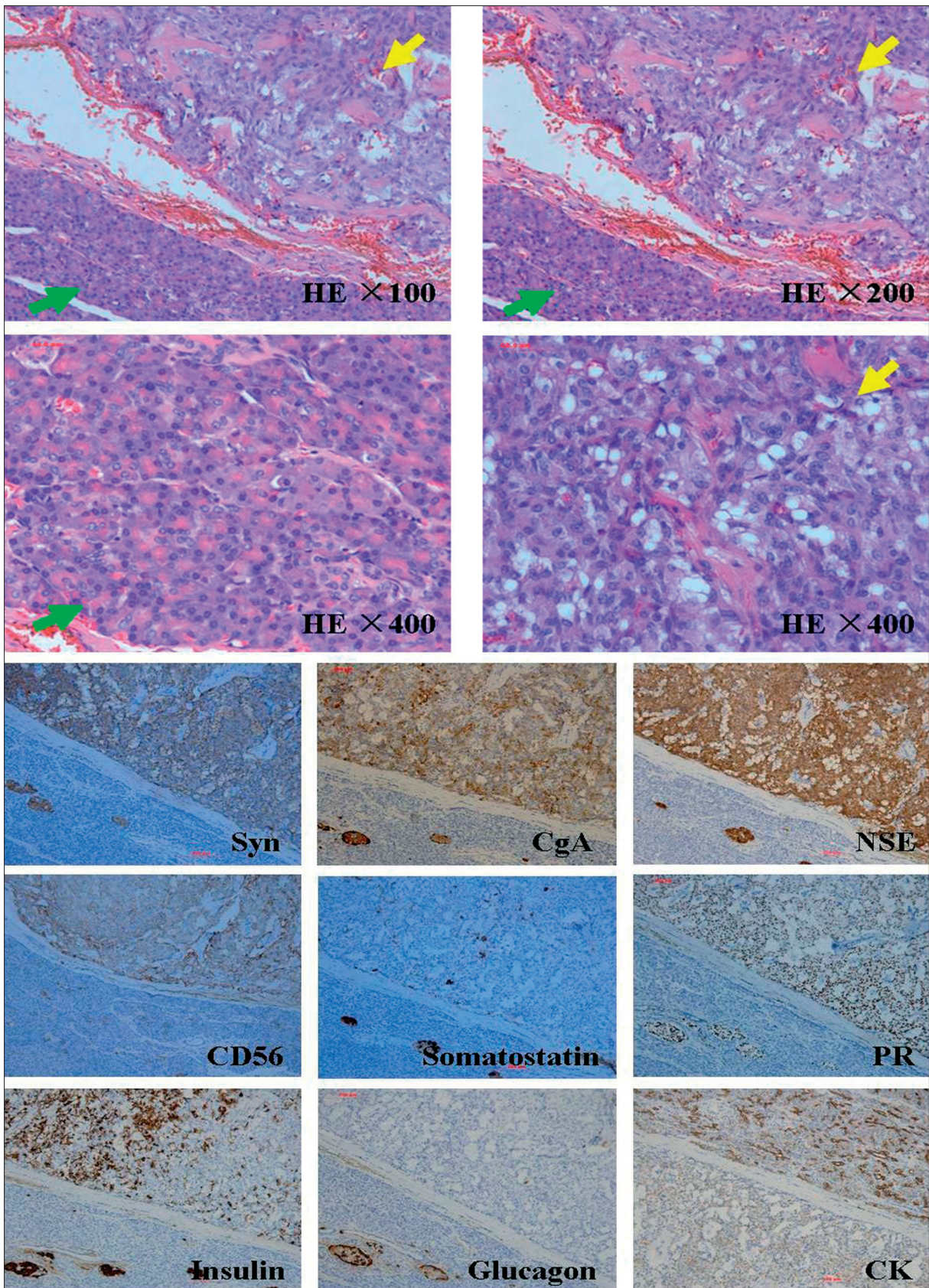
frequent upper gastrointestinal tract bleeding and hypoglycemia as the principal symptoms; multiple lipomas, gastrinoma, insulinoma, pituitary tumors, suprarenoma, and parathyroidoma were simultaneously observed in this patient.

MEN1 is an autosomal dominant disease, and its etiology is currently regarded as a genetic defect in chromosome 11 (11q13) [1]. Clinical diagnostic criteria for MEN1 syndrome include the presence of 2 endocrine tumors that are parathyroid, pituitary, or GEP (gastro-entero-pancreatic) tract tumors. In these cases, biochemical testing detects an increase in serum concentrations of parathyroid hormone and calcium in primary hyperparathyroidism, an increase in the serum concentration of prolactin from a prolactinoma, and an increase in serum concentrations of gastrin, insulin, and VIP from tumors of the GEP tract. Prolactinomas are imaged using MRI. Neuroendocrine tumors (NETs) are detected using

somatostatin receptor scintigraphy, and pancreatic endocrine tumors are detected with endoscopic ultrasound and CT. Molecular genetic testing for MEN1, which is the only gene associated with MEN1 syndrome, detects MEN1 mutations in approximately 80–90% of probands with familial MEN1 syndrome, and approximately 65% of simplex cases. The combination of clinical and genetic investigations and a deepened understanding of molecular genetics has aided in the clinical management of patients [6]. Although the diagnosis of MEN1 is relatively easy because of improved hormonal assays, radiological equipment and genetic analyses, the most appropriate treatments and early diagnoses of insulinoma, Zollinger-Ellison syndrome, and hyperparathyroidism remain controversial.

Gastrinoma and insulinoma are the 2 most common functional pancreatic neuroendocrine tumors in patients with MEN1 [7]. In MEN1 patients affected by pancreatic





**Figure 4.** Histopathology and immunohistochemical staining demonstrated that the pancreatic tumor was an endocrine neoplasia. In the upper images, yellow arrows point to the tumor tissue, and green arrows point to non-tumor tissue. In the lower images, immunohistochemical staining showed that the pancreatic tumor was an endocrine neoplasia, Syn (+), CgA (+), NSE (+), CD56 (+), Somatostatin (+), PR (+), Insulin (+), Glucagon (-), and CK (+); original magnification ×100.



endocrine neoplasias, hypoglycemia has a prevalence of approximately 20% with 1 or more macroscopic (>0.5 cm) localizations [8]. MEN1 patients with insulinoma are usually admitted to the hospital for a relapse of hypoglycemia. Although insulinomas are benign tumors, the development of pancreatic nodules often makes pancreatic resection inevitable [9]. There are 2 surgical approaches — open and laparoscopic. The goals of each approach are similar and include tumor enucleation or resection with part of pancreatic parenchyma, usually within the body and tail [10].

These insulin-secreting tumors arise in approximately 10% of MEN1 patients and are often associated with gastrinomas, which appear approximately 1 decade earlier than sporadic insulinomas [11]. Pancreatic insulinoma is characterized by a rapidly developing hypoglycemia. Biochemical analysis has revealed that an increase in plasma or serum insulin concentrations (reference values are 2–20 U/ml, or 14.35–143.5 pmol/L, respectively) appears with high plasma or serum concentrations of C-peptide (reference values are 0.5–2.0 ng/ml or 0.17–0.66 nmol/L, respectively) [12]. A resection of the affected pancreatic tissue and enucleation of macroscopic nodules in the residual pancreas is curative [13]. Chemotherapy with streptozotocin or octreotide is used for metastatic diseases.

These gastrin-secreting tumors represent more than 50% of all pancreatic tumors in MEN1. Approximately 40% of MEN1 patients have gastrinoma that manifests as Zollinger-Ellison syndrome before age 40, which is approximately 1 decade earlier than sporadic gastrinomas [11]. Zollinger-Ellison syndrome may lead to upper abdominal pain, diarrhea, esophageal reflux, vomiting, acid-peptic or duodenal ulcers, and, more rarely, heartburn and weight loss. Gastrinomas represent the major cause of morbidity and mortality in MEN1 patients, principally due to the perforation of severe multiple peptic ulcers. Biochemical diagnosis is confirmed by an increase in basal gastric acid secretion [14], and gastrinoma is defined by elevated basal serum concentration of gastrin (normal range <100 ng/l) [15].

The treatment for non-metastatic gastrinoma is surgical resection. The treatment for multiple and disseminate gastrinomas consists of therapy with a human somatostatin analogue, the administration of a PPI or H2-receptor blockers to reduce gastric acid secretion, chemotherapy with streptozotocin, and surgical excision of all resectable tumors. Gastrinomas in MEN1 syndrome are frequently multiple and usually include a malignant component. In approximately 50% of patients, gastrinomas have already metastasized before diagnosis, which results in the death of 30% of patients. Pancreatic gastrinomas are more aggressive than duodenal gastrinomas due to their larger size and greater risk for hepatic metastases [9].

Patients with MEN1 have gastroduodenal ulcers that are mostly induced by Zollinger-Ellison syndrome [9]. Although our patient did not present gastric ulcers, she had erosive gastritis and multiple duodenal ulcers, which are rarely associated with MEN1. The massive bleeding from the upper gastrointestinal tract was relieved by treatment with an inhibitor of gastric acid secretion (a PPI), but the ulcer remained intractable. Moreover, abdominal computed tomography (CT) showed a mass in the corpus pancreas, and removal of the pancreatic tumor is preferable. Therefore, a laparotomy was performed to extirpate the pancreatic tumor

in the pancreatic head. Fortunately, immunohistochemistry staining suggested that the islet cell tumor was benign.

## CONCLUSIONS

The clinical manifestations of ulcers associated with MEN1 are different from peptic ulcers in the stomach and duodenum. Severe clinical signs have been observed, including massive bleeding and resistance to the usual treatments for peptic ulcer. In our patient, a PPI did not have a curative effect on the duodenal ulcers. Therefore, abdominal and/or cervical CT or endocrine function examinations should be performed to prevent a missed diagnosis of MEN1 in patients with intractable duodenal ulcers and hypoglycemia. Early diagnosis by familial screening and hormonal assays related to MEN1 is essential to improve the mortality rate of patients with MEN1, and the need for a careful analysis of pancreatic tumors in patients with MEN1. This case suggests that multiple lipomas, insulinoma and gastrinoma may provide clues for a diagnosis of MEN1

## Statement

The authors state that they have no conflicts of interest (COI).

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