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Multiple endocrine neoplasia type 1 with refractory hypoglycemia and lung and liver metastases: a case report

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Abstract

Background: Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant genetic disease. MEN1 with multiple endocrine adenomatosis complicated by multiple endocrine tumors is often misdiagnosed or missed. Herein, we describe the first reported case of refractory hypoglycemia and liver and lung metastases in a patient with MEN1.

Case presentation: A 40-year-old man presented with a 3-month history of intermittent palpitations, fatigue, and sweating. The patient had a history of prolactinoma resection and refractory hypoglycemia 2 years earlier. Analyses of blood samples showed a decrease in random and fasting blood glucose and an increase in prolactin (PRL). Computed tomography (CT) and magnetic resonance imaging scans revealed two substantial masses in the pancreas and large masses in the liver and lung. Positron emission tomography-CT images showed hypermetabolic masses in the pancreatic body and tail. The liver and lung lesions were also hypermetabolic. The pancreatic lesion was surgically removed, and pathology confirmed that the mass was MEN1. The liver and lung masses were confirmed as metastatic tumors.

Conclusion: If clinicians better understand MEN1, they can obtain a detailed patient and family history during the initial visit, allowing earlier diagnosis and intervention and improved prognosis.

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Background

Multiple endocrine neoplasia (MEN) is a general term for a group of hereditary disorders in which multiple endocrine tissues develop tumors, with two or more endocrine gland lesions. It can be divided into types MEN1, MEN2, MEN3, and MEN4.[1] MEN1 is a rare autosomal dominant genetic disease, with a prevalence of 2 to 20 per 100,000 in the general population.[2] Clinically, patients with pancreatic masses complicated with refractory hypoglycemia are often diagnosed as having insulinoma. MEN1 multiple endocrine adenomatosis complicated with multiple endocrine tumors is more likely to be misdiagnosed or missed compared with insulinoma. Herein, we describe the first reported case of refractory hypoglycemia and liver and lung metastases with MEN1. If clinicians fully understand this disease, they can obtain a detailed family history during the initial visit to better detect and diagnose patients with MEN1 early, allowing interventions in the early stage of the disease and improving prognosis.

Case presentation

A 40-year-old man presented to the hospital with a 3-month history of intermittent palpitations, fatigue, and sweating. At that time, the patient had a random blood glucose of 2.0 mmol/L, and he was admitted to the hospital with hypoglycemia. His symptoms improved after glucose supplementation. The patient had a history of prolactinoma resection 2 years previously, and he complained of decreased sexual function, impotence, dizziness, and fatigue at the time of initial consultation 2 years ago. Laboratory examination at the initial presentation showed reduced sperm count and low blood glucose (random blood glucose: 3.1 mmol/L). Abdominal ultrasound examination showed no abnormality.

Thus, the patient's symptoms of dizziness, fatigue, and hypoglycemia did not attract the attention of clinicians, and only symptomatic treatment was given. Postoperative follow-up showed that the patient's symptoms of decreased sexual function, impotence, dizziness, and fatigue were obviously improved.

The patient's symptoms of dizziness and fatigue became gradually more frequent during the intervening 2 years. One year ago, the patient developed palpitations and his blood sugar gradually decreased. The patient's symptoms were relieved after self-feeding, and the attacks were irregular, occurring in the morning and afternoon. Because the attacks were irregular, it was very difficult to treat the patient's hypoglycemia for 3 months.

One day before the current presentation to our hospital, the patient developed delirium. At that time, analysis of blood samples indicated a fasting blood glucose of 2.34 mmol/L and fasting insulin of 55.29 µU/mL. In the pituitary gland, prolactin (PRL) was increased, and follicle-stimulating hormone, luteinizing hormone, estradiol, progesterone, and testosterone were normal. He was then admitted to the hospital for treatment. After admission, the results of magnetic resonance imaging (MRI) plain scan and enhancement of head, neck, and pancreas revealed changes in the sellar region that had occurred after the previous resection of the pituitary prolactinoma, parathyroid hyperplasia, and pancreatic body and tail tumors. A diagnosis of islet cell tumor was considered. Chest computed tomography (CT) showed multiple nodules in lung and liver, thought to be metastases. Because of the lung and liver metastases, clinicians did not initially plan to perform surgical resection of pancreatic tumor. However, because of the frequent and severe hypoglycemic symptoms of the patient, which did not improve significantly after symptomatic treatment, the pancreatic

tumor was resected. After surgical resection, some measures were used to control metastasis, mainly drug therapy, including streptozotocin combined with fluorouracil (5-FU). Because of the COVID-19 epidemic, the patient was unable to come to the hospital for monitoring of liver and lung metastases, and we could not determine the final effect of the above treatment measures. Postoperative follow-up showed that the patient's symptoms of dizziness, palpitation, and fatigue were improved, and a random blood glucose of 4.2 mmol/L was recorded.

The patient was imaged on a 3T MRI scanner with a dedicated 16-channel abdomen coil. The T2-weighted fat-suppressed images showed significant space occupation in the pancreatic tail (Figure 1a, b). In the arterial phase of enhanced CT scan, the lesion site showed slight enhancement relative to the adjacent tissue (Figure 1c, d). A chest CT showed multiple small nodules in the patient's lungs.

Positron emission tomography (PET)-CT of the pancreas showed a normal pancreatic body and a highly metabolic neoplasm in the pancreatic tail, with the largest standardized values taken (maximal standard uptake value, SUVmax) of increased metabolism of mass = 6.4 (pancreatic body) and 3.4 (pancreatic tail). The masses were approximately 4.9 cm × 4.1 cm × 3.1 cm (pancreatic body) and 1.5 cm × 1.3 cm × 1.2 cm (pancreatic tail) (Figure 1e, f). PET-CT also showed hyperplasia of the parathyroid gland.

After surgical resection (head, body, and tail of the pancreas), the tumor specimen was sent for pathology examination. The postoperative pathological results (Figure 1g) showed multiple endocrine neoplasia type 1 (MEN1), affecting the head, body, and tail of the pancreas and infiltrating the surrounding adipose tissue, without a clear endovascular tumor plug or nerve infiltration.

With respect to family history, the patient's older sister had surgery for a pituitary tumor when she was 32 years old, but the specific pathological results were unknown. Because the patient and his sister were the only family members to have the *MEN1* gene test, we could not prepare a complete family tree. Genetic analysis of the patient and his sister showed a heterozygous mutation, c.1636A>G (p. Thr546Ala), located in exon 10 of *MEN1*.

Discussion

The patient described herein had a pituitary prolactin tumor, most of which was excised 2 years previously; residual tumor resulted in the patient having an increased blood level of PRL. The patient's sustained decrease in blood glucose resulted in 3 months of intermittent palpitations, fatigue, and sweating. Refractory hypoglycemia was caused by the delayed detection of a pancreatic tumor. The identification of parathyroid hyperplasia further clarified the diagnosis of MEN1.

The patient presented with typical pituitary prolactinoma, insulinoma, and parathyroid hyperplasia. We believe that the imaging characteristics of these tumors are crucial for the diagnosis of MEN1. The imaging features of pancreatic lesions in MEN1 are as follows: (1) CT scans show that most tumors are small, do not change the shape and contour of pancreas, and have a similar density to normal pancreas. Only a few tumors are larger, with localized masses.[3] Most insulinomas with enhanced CT are blood-rich, the arterial phase enhancement is significantly higher than that of normal pancreas, and the density of the venous phase is similar to that of normal pancreas. Dynamic contrast-enhanced CT is helpful to identify this feature. Moreover, metastases of liver and peripancreatic lymph nodes can be found in malignant pancreatic endocrine tumors.
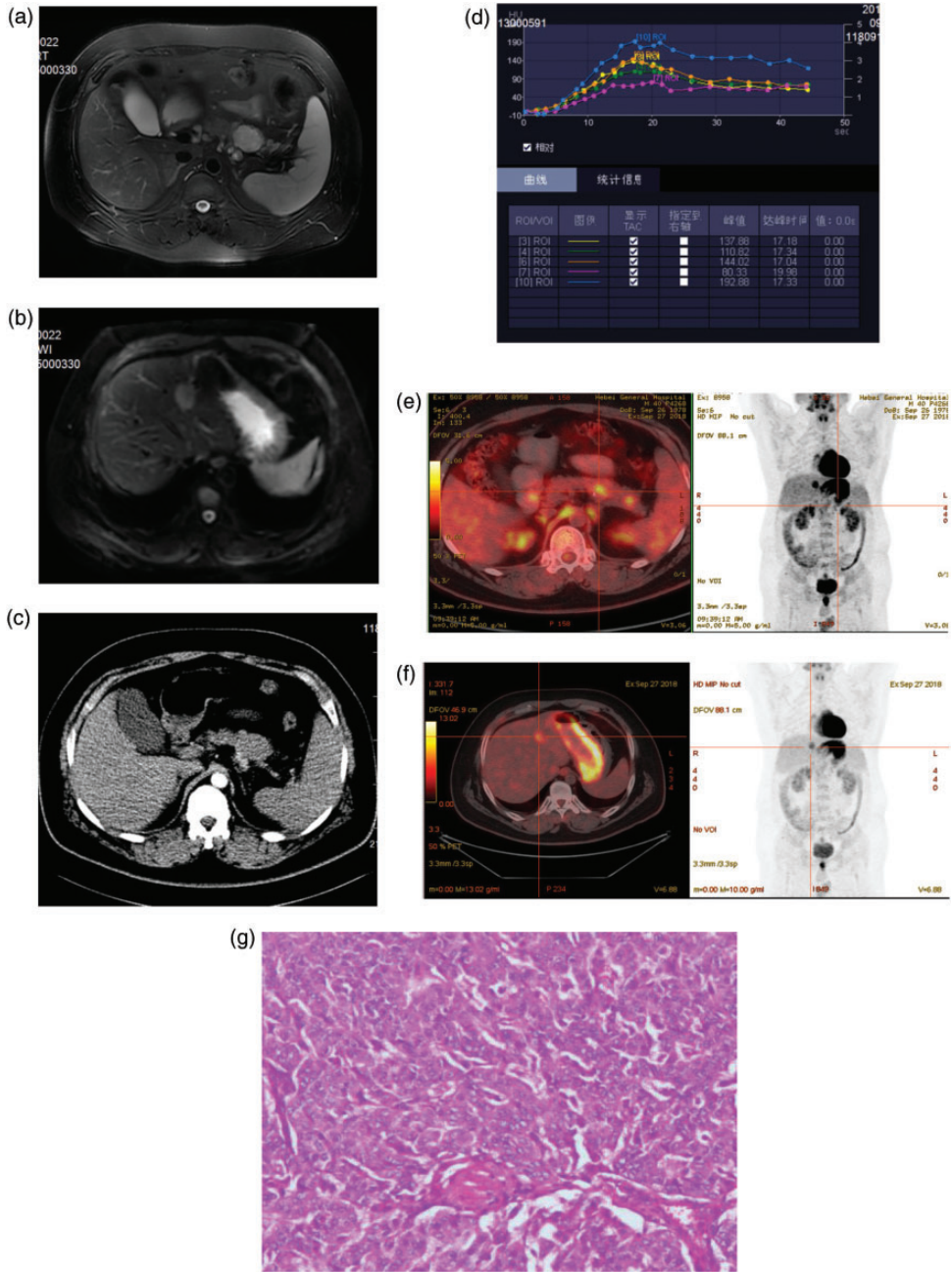
Figure 1. (a) Plain scan of pancreatic magnetic resonance imaging (MRI) T2 fat-suppressed sequence: the pancreatic tail was significantly occupied. (b) Diffusion-weighted imaging (DWI) showing abnormal high-intensity imaging of the liver II, IV segment junction. (c) Computed tomography (CT) enhanced arterial phase was similar to that of adjacent tissues and showed mild enhancement. (d) Dynamic contrast-enhanced (DCE)-CT: blood flow (BF), blood volume (BV), mean transit time (MTT), and time to peak in the posterior tubercle of the pancreas increased, with BF, FEP as the main factor, and BF increased and BV decreased in the

The patient described here had liver and lung metastases, a typical manifestation of malignant insulinoma. (2) By MRI, pancreatic lesions are typically round, oval, or irregular, with clear boundaries, low signal on T1-weighted imaging (T1WI), high signal on T2WI, edge enhancement on enhancement scan, uneven internal enhancement, and obvious appearance of hyperglycemic tumor if accompanied by liver metastasis. In metastatic lesions, T1WI shows low signal intensity, T2WI shows high signal intensity, diffusion-weighted imaging (DWI) shows high signal intensity, the arterial phase is obviously enhanced, and the venous phase and delayed phase enhancements are significantly decreased, showing "fast in and out."[4] (3) CT scan can show the metabolism of lesions and metastases, which is very important for the differential diagnosis of benign and malignant lesions. The metabolism of the pancreatic mass was obviously increased in our patient, with $SUVmax = 6.4$ (pancreatic body). Multiple round nodules could be seen in the lung and liver. We observed no abnormal metabolism and a slight increase of delayed metabolism in the early stage of pulmonary lesions. The metabolism of liver lesions increased in the early stage and decreased with delay, $SUVmax = 5.1$ (delayed). The use of PET-CT as a functional examination for benign and malignant lesions that are unclear by CT and MRI greatly improves the diagnostic accuracy.

The imaging features of pituitary lesions in MEN1 are as follows: (1) CT requires coronal thin slice scanning, in which 40% to 80% of the pituitary height is increased. However, values above the normal height of pituitary are not absolute, with about 60% of the sellar floor bone showing thinning, depression, or erosion. Plain scan is mostly isodense, or it could be slightly high density, low density, or show cystic changes. Tumors are scanned for low density immediately after rapid injection of contrast agent, or scanned after delay for equal or high density. Primarily homogeneous enhancement is observed, with a

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Figure 1. Continued.
anterior small nodule of the pancreas. MTT and FEP did not change significantly. (e) Positron-emission tomography (PET)-CT showed a hypermetabolic mass in the pancreatic body and tail in the normal position of the pancreas, with an increase in metabolism of the mass of the pancreatic body: maximal standard uptake value ($SUVmax$) = 6.4 (pancreatic body) and 3.4 (pancreatic tail), and the size was $4.9 \times 4.1 \times 3.1$ cm (pancreatic body) and $1.5 \times 1.3 \times 1.2$ cm (pancreatic tail). The mass density and metabolic distribution was even, which could be seen in a calcification point. The lesion boundary was clear, with some protrusion outside the normal pancreatic contour. The pancreatic duct was not dilated, and the peripancreatic fat gap was clear. Several round unmetabolized lymph nodes ranging in diameter from 1.3 to 2.1 cm can be seen in the anterior and posterior pancreas. The lymph node shape was regular, and the boundary was clear. (f) PET-CT showing liver morphology, with a normal location, smooth edge, and normal liver lobe ratio. A class of circular hypermetabolic and low density lesions were found in segment IV of the liver parenchyma; $SUVmax$ = 6.9 (early stage), 5.1 (delayed), and the size of the liver tumor was 3.0×2.2 cm. The lesion boundary was clear and the distribution of internal density metabolism was even. In the left and right lobes of the liver, there was a saccular low-density shadow without metabolism. (g) Hematoxylin-and-eosin-stained pathology image (200× magnification). Pathological results showed multiple endocrine neoplasia (MEN1), including the head, body, and tail of pancreas, with 6 mitoses per 10 high-power fields, infiltrating surrounding adipose tissue, no intravascular tumor thrombus, and nerve invasion. Immunohistochemical staining showed pan cytokeratin (CKpan) (+), Syncytia (Syn) (+), chromogranin A (CgA) (+), CD56 (part+), protein 53 (P53) (−), protein gene product 9.5 (PGP9.5) (part+), somatostatin receptor 2 (SSTR2) (part+), CD10 (−), vimentin (part+), Ki-67 (~8% positive), gastrin (−), and insulin (partial cell+).

few uneven masses. Few show circular enhancement or necrosis. The liquefaction area is not enhanced, and calcification is rarely seen as a scattered dot or block.[5] (2) MRI is generally used in coronal and sagittal thin layers (<3 mm). Pituitary tumor shows low signal on T1WI, but a mixed high/low signal in tumor with hemorrhage. T2WI shows equal or high signal. In early stages, the tumor signal is lower than that of pituitary gland in a contrast-enhanced scan. Delayed enhancement tumor signal can be slightly lower than, equal to, or higher than that of pituitary gland. Combining imaging with the clinical and biochemical indices, a PRL tumor was easily diagnosed.

Ultrasound and PET-CT scans in this patient showed an obviously hyperplastic parathyroid gland. The differential diagnosis should include single pituitary adenoma, parathyroid hyperplasia or adenoma, pancreatic neuroendocrine neoplasms, and other types of multiple endocrine adenomatosis.[6–8]

The World Health Organization 2010 classification provides a valuable tool to stratify MEN in three prognostic subgroups based on the proliferation index. The Ki-67 value was selected as the proliferation index, and Ki-67 in the patient was 8% and classified as G1. Tumor morphology and further subdivision of grading substantially improve prognostic stratification of these patients.[9]

MEN1 is a rare hereditary syndrome that affects endocrine tissues of the pituitary, parathyroid, and pancreas. It must be carefully managed when it involves different disorders in individuals or families; careful management can improve the patient's prognosis.[10,11] Although the clinical manifestations of MEN1 are complex and variable, the pathological changes and imaging signs of the pituitary, parathyroid, and pancreas have certain commonalities and their incidence is clearly familial.

These factors are very helpful for the early diagnosis and treatment of the disease.[12–14]

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Authors' contributions

YW designed the report and wrote the paper; HZ collected the patient's clinical data and information; both authors read and approved the final manuscript.

Ethical approval

Ethical approval was deemed unnecessary. The patient gave written consent for publication of this case report.

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