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**Comprehensive treatment of rare multiple endocrine neoplasia type 1: A case report**

Ma CH *et al.* A rare case of MEN1

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**Abstract****BACKGROUND**

Multiple endocrine neoplasia type 1 (MEN1) is a rare hereditary disorder caused by mutations of the *MEN1* gene that is characterized by hyperparathyroidism and involves the pancreas, anterior pituitary, duodenum, and adrenal gland. Here we reported a 40-year-old male patient with MEN1 that first manifests as thymic carcinoid, then primary hyperparathyroidism and prolactinoma, followed by a pancreatic neuroendocrine tumor (NET) a decade later.

**CASE SUMMARY**

The patient underwent a thymectomy because of the thymic carcinoid ten years prior and a prolactinoma resection two years prior. His sister suffered from prolactinoma. His parents displayed a typical triad of amenorrhea, galactorrhea, and infertility. Computed tomography (CT) revealed a strong signal in the upper portion of the left lobes and posterior portion of the right lobes of the thyroid, and irregular soft tissue densities of the pancreatic body. Positron emission tomography/CT imaging further showed strong <sup>18</sup>F-FDG uptake in the tail of the pancreatic body and segment IV of the liver. The patient underwent pancreatic body tail resection, pancreatic head mass enucleation, and ultrasound-guided radio-frequency ablation for liver cancer. Pathology results reported NET grade 2. Whole exome sequencing revealed a verified pathogenic mutation c.378G>A (p.Trp126\*) in the *MEN1* gene. The diagnosis of MEN1

was confirmed. At the 1.5-year follow-up, the patient appeared healthy without any sign of reoccurrence.

## CONCLUSION

The present case may add some insight into the diagnosis and treatment of patients with MEN1.

## <sup>1</sup> INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1), a rare hereditary disorder caused by mutations in the tumor suppressor gene *MEN1*, refers to two or more simultaneous or sequential occurrences of parathyroid adenomas, anterior pituitary adenomas, or entero-pancreatic neuroendocrine tumors (NETs) in an individual<sup>[1]</sup>. <sup>2</sup> Hormone-secreting and hormone-nonsecreting tumors may occur among some 30 tissues in MEN1<sup>[2]</sup>. The most common clinical manifestations of MEN1 include parathyroid (> 90%) tumors, followed by pancreatic endocrine tumors (30%-70%) and pituitary tumors (30%-40%)<sup>[3]</sup>. MEN1 patients also present with other tumors, including adrenocortical tumor, carcinoids, pheochromocytoma, bronchopulmonary NET, thymic NET, gastric NET, lipomas, angiofibromas, collagenomas, and meningiomas<sup>[1, 3]</sup>. Herein, we reported a 40-year-old male patient with MEN1 that first manifests as thymic carcinoid, then primary hyperparathyroidism and prolactinoma eight years later, followed by a pancreatic NET grade 2, and insulinomas with intrahepatic metastases a decade later.

## CASE PRESENTATION

### *Chief complaints*

A 40-year-old male patient experiencing symptoms of hunger, such as fatigue and excessive sweating, for two years was admitted to the neurosurgery department at our hospital in August of 2018. The symptoms were relieved with food.

### *History of present illness and History of present illness*

The patient underwent a thymectomy because of the thymic carcinoid ten years ago

(July 2008). However, there were intermittent episodes of hypoglycemia symptoms in the following years. The minimum blood glucose level was 2.0 mmol/L. Hypoglycemia-like symptoms can be relieved with glucose infusions. Computed tomography (CT) and magnetic resonance imaging (MRI) findings of the head and neck showed signs of hyperparathyroidism and prolactinoma two years prior; thus, the patient underwent a prolactinoma resection (April 2016). Although the surgery was successful, the symptoms of dizziness and hypoglycemia remained unresolved. Therefore, he was readmitted to our department for further treatment and suspected MEN1.

### ***Personal and family history***

Family history showed that his sister suffered from prolactinoma and underwent gamma knife radiosurgery. His parents, five siblings (sisters), and two offspring displayed the typical triad of amenorrhea, galactorrhea, and infertility.

### ***Physical examination upon admission***

None.

### ***Laboratory examinations***

Laboratory examination findings are summarized in Table 1. The indexes for thyroid-stimulating hormone,  $\beta$ -collagen-specific sequence, total type I collagen amino-terminal extension peptide, fasting insulin, and insulin release, were abnormally elevated.

### ***Imaging examinations***

Parathyroid two-phase CT revealed a strong signal in the upper portion of the left lobes and posterior portion of the right lobes of the thyroid, in addition to the parathyroid glands (Figure 1A). Pancreatic perfusion CT imaging showed irregular soft tissue densities of the pancreatic body, which was closely associated with the adjacent stomach wall, with a small reduction in blood volume (BV) and a slight increase in flow extraction product (FEP); increased blood flow (BF), BV, mean transit

time and FEP in nodules of the posterior to the pancreatic body; increased BF and decreased BV in nodules of the pancreatic head; multiple circular low or slightly low-density shadows in liver parenchyma (Figure 1B). MRI of the liver and pancreas revealed multiple abnormal signals in the liver segment II, segment VIII, and the junction area of liver segments II and IV, as well as occupied lesions in the tail of the pancreatic body (Figure 2A). Enhanced MRI revealed occupied lesions in the body and tail of the pancreas (Figure 2B). Enhanced MRI revealed that liver segment IV was occupied, considering the possibility of angiomyolipoma. In addition, there were small cysts in segments II and VIII of the liver, and occupied lesions in the tail of the pancreatic body (Figure 2C).

Positron emission tomography (PET)/CT imaging (Figure 3) further showed strong  $^{18}\text{F}$ -FDG uptake in the tail of the pancreatic body and segment IV of the liver, indicating the presence of insulinomas with intrahepatic metastases. There were several circular nodules visible in the right and left lungs, showing there was partial increase signals in them. After undergoing complete surgical resection of the thymoma, ring-shaped hypermetabolism became visible around the aortic root, may result from fat intake.

### **FINAL DIAGNOSIS**

A multiple disciplinary team (MDT) consisting of an endocrinologist, oncologist, pathologist, radiologist, thoracic surgeon, and hepatobiliary surgeon was incorporated to manage this patient. MEN1 with thymic carcinoid, thymoma, parathyroid and insulinomas with intrahepatic metastases was initially diagnosed.

### **TREATMENT**

Since there were no obvious surgical contraindications, MDT recommended a radical excision of the lesions to alleviate hypoglycemia symptoms and improve the quality of life for the patient. The patient underwent a resection of the tail of the pancreatic body, enucleation of the pancreatic head mass, and ultrasound-guided radiofrequency ablation for liver cancer. During the operation, a nodule with a diameter of about 0.4-cm was observed in the diaphragmatic surface of the right liver

lobe. A mass of about 0.5 cm × 0.5 cm was palpable in the right posterior liver lobe, a tumor with about 2 cm × 2 cm in the falciform ligament about 4 cm from the hepatic margin, a mass of 1.5 cm × 1.0 cm on the pancreatic head, a mass of 5 cm × 3 cm × 3 cm on the pancreatic body, and a mass of 1.5 cm × 1 cm on the pancreatic tail. The intraoperative ultrasonography findings from the liver scan showed the right lobe nodules as cysts, and ultrasound-guided segment IV liver biopsy and radiofrequency ablation were performed.

After surgery, all diabetes factors with abnormal serum levels were returned to normal levels (Table 1). The pathological findings are shown in Figure 4. The pancreatic tissues showed CKpan (+), synaptophysin (+), chromogranin A (+), partial CD56 (+), p53 (-), partial PGP9.5 (+), partial SSTR2 (+), CD10 (-), partial vimentin (+), a mitotic count of 6/10 high power fields (HPFs) and Ki-67 index of about 8%-20%, which confirmed the diagnosis of the pancreas NET grade 2. The liver tissues showed CKpan (+), synaptophysin (+), Chromogranin A (+), partial CD56 (+), p53 (-), PGP9.5 (+), a mitotic count of 4/10 HPFs and Ki-67 index of about 10%-20%, which confirmed the diagnosis of liver NET grade 2. Moreover, there were multiple tiny nodules around the pancreatic tissues, indicating that surgical resection could not completely remove the lesions. NET grade 2 was diagnosed according to the World Health Organization 2010 classifications for gastrointestinal and pancreatic NETs<sup>[4]</sup>. Furthermore, whole-exome sequencing revealed a verified pathogenic mutation c.378G>A (p.Trp126\*) in the *MEN1* gene (reference sequence NM\_130799.2). Therefore, the final diagnosis of MEN1 was confirmed.

### **OUTCOME AND FOLLOW-UP**

The patient was free of hunger symptoms. During the follow-up visit at six months, single-photon emission CT (SPECT)/CT revealed multiple small nodules in the lungs. After comparing the SPECT/CT scans with the PET/CT from four months prior, these nodules were suspected of being metastatic lesions. However, the nodules were too small to undergo needle biopsy, so the patient was placed under observation without additional treatment. At the last follow-up in January of 2020, the patient appeared healthy without any signs of disease reoccurrence.

## **DISCUSSION**

MEN1 is characterized by primary hyperparathyroidism caused by a parathyroid tumor, and involves the pancreas, anterior pituitary, duodenum, and adrenal gland. The annual incidence rate of MEN1 is about 1 in 30000<sup>[2]</sup>. Approximately 25% patients with thymic carcinoids are also diagnosed with MEN1<sup>[5, 6]</sup>, and in patients with MEN1, the incidence of thymic carcinoids is between 2% and 8%, with the disease most commonly occurring in patients 38 to 49 years of age<sup>[7, 8]</sup>. The patient in this study suffered from tumors of multiple organs, including the thymus, parathyroid, pituitary, pancreas, and liver. He first presented with thymic carcinoid, then primary hyperparathyroidism and prolactinoma, and later pancreatic NET with intrahepatic metastases. Moreover, the interval between thymic carcinoid and pancreatic NET was ten years. Since the diagnosis of the thymic carcinoid, the patient had been alive for more than 11 years. MEN1-insulinoma accounts for about 10% of pancreatic NET cases. The average age of onset is less than 40 years old, oftentimes less than 20 years old, while non-MEN1 insulinoma patients are more than 40 years old<sup>[9]</sup>. The symptoms of hypoglycemia often appear on an empty stomach or after physical activity, which can be relieved with food. The 72 h starvation test is the most reliable diagnostic method to demonstrate that the hypoglycemia is caused by high insulin<sup>[3]</sup>. Ultrasound, CT, MRI, and PET/CT are often used for preoperative localization of lesions, and intraoperative ultrasound can improve the success rate of surgery<sup>[3]</sup>. Endoscopic ultrasound (EUS) can be used to differentiate MEN1-related pancreas NET from sporadic pancreas NET<sup>[10, 11]</sup>. Moreover, preoperative biopsy through EUS/fine needle aspiration is useful for determining the differentiation status of pancreas NET<sup>[12-14]</sup>. A well-differentiated grade 1/2 tumor is one of the primary surgical indications for pancreas NET management<sup>[15]</sup>. However, the preoperative diagnosis of pancreas NET is relatively clear based on the patient's medical history, insulin level, Whipple's triad, CT, MRI, and PET/CT findings. Hence, EUS was not performed, which is a limitation of the present case.

Generally, patients with MEN1 should be managed by a MDT consisting of relevant specialists from endocrinology, radiology, oncology, pathology, and surgery<sup>[3]</sup>. For

this disease, intraoperative monitoring of the insulin release index is useful for determining whether the tumor is successfully removed. Chemotherapy is recommended for patients with metastatic insulinomas and may include streptomycin, 5-fluorouracil, doxorubicin, or hepatic artery embolization<sup>[16-18]</sup>. The patient in this study suffered from tumors of multiple organs, including the pancreas, parathyroid, and pituitary. The progression of MEN1 was successfully controlled by MDT in the current study.

## **CONCLUSION**

In conclusion, we presented a case of MEN1 that appeared sequentially as thymic carcinoid, primary hyperparathyroidism and prolactinoma, and pancreatic NET with intrahepatic metastases. Through the consultation of MDT for complete preoperative diagnosis and postoperative treatment and management, the patient was successfully treated in our clinic. If a patient is diagnosed with primary hyperparathyroidism with pituitary tumors or gastrointestinal NET, and the family history shows similar symptoms, MEN1 should be considered, and genetic testing is recommended. We hope that this study will add new insight into the diagnosis and treatment of patients with MEN1.

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### **Figure Legends**

**Figure 1 Computed tomography examination.** A: Parathyroid two-phase computed tomography (CT) revealed a strong signal in the upper part of the left lobes and posterior part of the right lobes of the thyroid; B: Pancreatic perfusion CT imaging revealed irregular soft tissue densities of the pancreas body, which were localized around the stomach wall.

**Figure 2 Magnetic resonance imaging examination.** A: Liver and pancreas magnetic resonance imaging (MRI) examination revealed multiple abnormal signals in the liver segment II, segment VIII and the junction area of liver segment II and IV, as well as occupied lesions in the tail of the pancreatic body; B: Enhanced MRI revealed occupied lesions in the body and tail of the pancreas; C: Enhanced MRI revealed that the liver segment IV was occupied, considering the possibility of angiomyolipoma. There were also small cysts in segments II and VIII of the liver, and occupied lesions in the tail of the pancreatic body.

**Figure 3 Positron emission tomography/computed tomography examination.** A, B, D and E: Hypermetabolic lesions in the lungs (A), intrahepatic segment IV (B), and the body (D) and tail (E) of the pancreas; C: No metabolic round nodules in the anterior pancreas; F: Diffusely increased metabolism in the stomach wall.

**Figure 4 Pathological examination.** H&E staining showed (magnification, 40 ×; 100 ×) multiple nodules next to the pancreatic tumor, in the pancreatic tissue around the pancreatic body, and next to the pancreatic tail. Immunohistochemistry showed (magnification, 40 ×; 100 ×) CKpan (+), synaptophysin (Syn) (+), Chromogranin A (CgA) (+), partial CD56 (+), p53 (-), partial PGP9.5 (+), partial SSTR2 (+), CD10 (-), partial vimentin (+) in pancreas tissues, and CKpan (+), Syn (+), CgA (+), partial CD56 (+), p53 (-), and PGP9.5 (+) in liver tissues. Bar, 100 μm. Syn: Synaptophysin; CgA: Chromogranin A.

**Table 1 Laboratory examination findings from the patient with multiple endocrine neoplasia type 1 before and after treatment**

Items	Factors	Values at admission	Postoperative values	Reference range
Thyroid function	Parathyroid hormone	7.96 pmol/L	7.11 pmol/L	1.6-6.9
	Thyroid-stimulating hormone	7.36 $\mu$ IU/L	2.24 $\mu$ IU/L	0.27-4.2
	Total T4	64.68 nmol/L	79.12 nmol/L	78.38-157.4
Pituitary hormone	Prolactin	17.13 ng/mL	25.67 ng/mL	1.61-18.77
Tumor biomarkers	Alpha-fetoprotein	3.83 ng/mL	-	0-25
	Carbohydrate antigen 19-9	15.17 U/mL	-	< 37
	Carcinoembryonic antigen	3.51 ng/mL	-	< 5
Bone metabolism	B-collagen-specific sequence	1.21 ng/mL	-	0.3-0.6
	Total type I collagen amino-terminal extension peptide	204.4 ng/mL	-	20.25-76.31
Diabetes	Fasting insulin	55.29 $\mu$ U/mL	9.95 $\mu$ U/mL	2.6-24.9
	Fasting blood glucose	1.79 mmol/L	3.98 mmol/L	3.9-6.1
	Fasting C-peptide	5.06 ng/mL	1.81 ng/mL	1.6-6.9
	Insulin release index	1.31	0.2	<0.3

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