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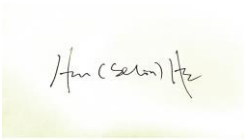

(Ms.) Hua (Selin) He

for *Medjaden*

Medjaden Bioscience Limited
General Office
Address: 11415 Ashford Willow, Sugar Land, Texas, 77478, USA
Email: medjaden@gmail.com
Website: www.medjaden.com

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Comprehensive treatment of rare multiple endocrine tumor type 1: a case report

Abstract

Multiple endocrine neoplasia type 1 (MEN1), a rare hereditary disorder characterized by hyperparathyroidism, involves the pancreas, anterior pituitary, duodenum, and adrenal gland. In this study, we have reported on a single patient who underwent pancreatic body tail resection, pancreatic head mass resection, segment IV liver tumor biopsy, and ultrasound-guided radio frequency ablation. Subsequent examinations revealed a mutation in the variant gene NM_001486.3 sequence. We recommend genetic screening for individuals with a family history of MEN1. While this gene may be a useful biomarker, the biological function of this mutation requires further exploration about their progression over time. If the patient was diagnosed with primary hyperparathyroidism with pituitary tumors and/or gastrointestinal neuroendocrine tumors, we should notice this disease. Thus we hope that this study will lead to improved strategies for the diagnosis and treatment of patients with MEN1.

Keywords: Multiple endocrine neoplasia type 1; MEN1; pancreas; tumor

1. Background

Multiple endocrine neoplasia type 1 (MEN1), previously known as Wermer syndrome, is a rare hereditary condition commonly associated with hyperparathyroidism, which is often accompanied by several non-specific symptoms. The MEN1 gene is on chromosome 11q13.1 and comprising 10 exons encoding a 610 amino acid protein named menin. MEN1 mutations are insufficient to develop MEN1 and loss of the unaffected MEN1 allele is important for tumorigenesis (1). MEN1 usually appeared in patients with age from 5 to 82 year old. The pancreas, anterior pituitary gland, duodenum, and adrenal gland are most susceptible to MEN1. The most common clinical manifestations of MEN1 include primary hyperparathyroidism (>90%), followed by pancreatic endocrine tumors (30-70%) (2). Insulin tumors in MEN1 patients account for about 10% to 30% of pancreatic tumors (the age of onset is less than 20 years old). The incidence of glucagonoma in patients with MEN1 is < 3%. The disease most commonly occurs in the tails of the pancreas. Pituitary tumors are seen in approximately 33% of patients with MEN1 (2, 3). This article reviewed a case who received MDT (Multiple Disciplinary Team) treatment. We also conducted a review of the relevant literature to summarize the status of this disease in hopes of increasing its awareness in the community.

2. Case report

2.1. Medical history

A 40-year-old male patient experiencing fatigue, excessive sweating, and increased hunger for two years was admitted to the neurosurgery department at our hospital in August, 2018.

The extreme hunger was relieved with food. After conducting a thorough medical history, the patient was found to have undergone a thymectomy 10 years before this incident. The minimum blood glucose level was 2.0 mmol/L. Computed tomography (CT) and magnetic resonance imaging (MRI) findings of the head and neck showed signs of hyperparathyroidism and prolactinoma two years prior, which resulted in the patient undergoing a prolactinoma resection. However, the hypoglycemia remained unresolved, and he was diagnosed with possible MEN1. During the family history examination, it was discovered that the patient's sister suffered from prolactinoma and underwent gamma knife radiosurgery. In addition, the patient's parents, five siblings (sisters), and two off-spring displayed typical amenorrhea-yellow-infertility triad symptoms.

2.2. Laboratory examination

Laboratory tests showed that the parathyroid hormone was 7.96 pmol/L (range 1.6-6.9 pmol/L), thyroid stimulating hormone was 7.36 μIU/L, prolactin level was 17.13 ng/ml, total T4 (TT4) was 64.68 nmol/L, thyrotropin hormone (TSH) was 7.54 μIU/L, alpha-fetoprotein was 3.83 ng/mL, carcinoembryonic antigen was 3.51 ng/mL, carbohydrate antigen 19-9 (CA 19-9) was 15.17 U/mL, β-collagen-specific sequence was 1.21 ng/mL, total type I collagen amino-terminal extension peptide was 204.4 ng/mL, fasting insulin level was 55.29 μU/mL (range 1.6-6.9μU/mL), fasting C-peptide was 5.06 ng/mL, and gastrin (GAS) elevation 183.66 pg/ml (range 28.10-106.50). The blood cortisol levels were recorded as 5.28 μg/dL at 0 h, 4.91 μg/dL at 8 h, and 2.49 μg/dL at 16 h, while the 24 h urinary cortisol was 368.82 μg/24 h.

2.3. Imaging examination

Parathyroid gland dual-phase imaging and organ tomography (Fig. 1) 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.

Pancreatic perfusion CT imaging (Fig. 3) showed irregular soft tissue densities of the pancreas, which was closely associated with the adjacent stomach wall. There was a small reduction in blood volume (BV), while flow extraction product (FEP) was slightly increased. The blood flow (BF), blood volume (BV), mean transit time (MTT), and FEP of the little nodules in the posterior portion of the pancreas were elevated, with BF and FEP showing the highest levels. Despite an increase in BF and reduction in BV, there were no significant changes in the MTT or FEP of the small nodules in front of the head of the pancreas. Multiple round low-density shadows were visible in the liver parenchyma.

Using PET/CT imaging (Fig. 4), a strong signal of ^{18}F-FDG uptake was visible in the tail of the pancreatic body and segment IV of the liver, which was indicative of intrahepatic metastases or metastatic insulinomas. 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. The diffuse metabolism of the stomach was elevated, which was consistent with the diagnosis of gastritis obtained through gastroscopy. The shape of the left adrenal gland was pleins and indicative of the left adrenal hyperplasia.

2.4. Surgery and pathology

The MDT suggested that the patient undergo radical resection of the lesion to relieve hypoglycemia and improve his overall quality of life. The patient agreed and provided written informed consent for the procedure. The patient was scheduled to undergo a pancreatic body/tail resection, pancreatic head mass resectionpancreaticoduodenectomy (Whipple operation), segment IV liver tumor biopsy, and ultrasound-guided radiofrequency ablation.

The intraoperative ultrasonography findings from the liver scan showed the right lobe nodules as cysts, and the pathological results revealed the presence of several neuroendocrine tumors (NET, G2) on the pancreatic head, pancreatic body and pancreatic tail. In addition, there was infiltration of the peripheral adipose tissue with no clear intravascular tumor thrombus or nerve infiltration. The surgical margins were clean at the cutting edge of the pancreatic body and tail, and the pathological findings are shown in Fig. 5. The operation was considered successful.

2.5. After MDT

Based on the 2017 World Health Organization (WHO) classification for pancreatic neuroendocrine neoplasms (PanNEN) (10), Ki-67 expression in the pancreatic tissues was about 8%-20%, and multiple neuroendocrine tumors (NET, G2) were diagnosed clearly. In the liver, Ki-67 expression ranged from 10 to 20%, and multiple endocrine neoplasia (NET, G2) were found. The pathological findings indicated that surgical resection could not

completely remove the lesion, which may be attributed to the high recurrence rates of malignant insulinoma. After surgery, the fasting insulin was 9.95 μU/mL (range 2.6-24.9), fasting C-peptide was 1.81 ng/mL (range 1.6-6.9), and fasting blood glucose was 3.98 mmol/L (range 3.9-6.1). Thyroid stimulating hormone was 2.24 μIU/L, while prolactin was 25.67 ng/ml. High-throughput sequencing of the gene chip revealed a pathogenic variation in the NM_130799.2 sequence of the MEN1 gene, along with a pathogenic mutation in the NM_001486.3 sequence of the GCKR gene. The diagnosis of MEN1 was definite, and the GCKR gene was closely related to type 2 diabetes mellitus (T2DM). The sequence of the variant gene NM_001486.3 was used first, yet its biological function required further exploration. The patient's first-degree relatives were recommended to undergo genetic screening.

During the follow-up visit at 6 months, SPECT/CT (GE Discovery NM/CT 670, Chicago, IL, USA) showed multiple small nodules in the lungs. After comparing the SPECT/CT scans with the PET/CT from 4 months prior, these nodules were suspected of being metastatic lesions.

3. Discussion

multiple endocrine tumor(MEN) refer to two or more simultaneous or sequential occurrence instances of endocrine gland hyperplasia or carcinogenesis. The disease results from a heterozygous mutation of the tumor suppressor gene. Once normal allele is deleted or mutated, normal cells would progress to tumor cells (4). The most common type of MEN1

lesion is primary hyperparathyroidism induced by parathyroid tumors, which accounts for approximately 95% of the cases (2). The annual incidence rate of MEN1 is 0.2/100,000, and approximately 25% patients with thymic carcinoid tumors are also diagnosed with MEN1 (6). In patients with MEN1, the incidence of thymic carcinoid tumors is between 2 and 8% with the disease most commonly occurring in patients 38 to 49 years of age (7-8).

In a previous study, insulinomas were found to account for 10-30% of pancreatic tumors in patients with MEN1. Ten percent of these patients had insulinoma as the initial symptom, and 4% of insulinomas were caused by MEN1 mutation. In our study, we found a pathogenic mutation in the NM_001486.3 sequence of the GCKR gene, which could be a potential target for diagnosing MEN1 in the future.. Usually, the disease was single, and the age of onset was less than 40 years old, even less than 20 years old, while non-MEN1 insulinoma patients were more than 40 years old at the disease onset (3).

While insulinomas display slow grow characteristics, they are potentially malignant. Although the five-year survival rates in patients after surgical resection of insulinomas is well, the disease still has a high recurrence rate. It remains difficult to excise the tumor completely. Therefore, some microscopic nodules remain after the surgery and attribute high recurrence rates, and may also be a significant feature of malignant insulinomas.

For this disease, a high-carbohydrate diet, diazoxide or octreotide treatments can be used. However, surgery is often the best therapy, which may include simple pancreatic tumor

removal, pancreatic body and tail resection, partial pancreatectomy, or other surgical strategies. 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.

4. Conclusions

We displayed a typical MEN1 syndrome characterized by multiple endocrine tumors, including prolactinomas, thymic carcinoids, and pancreatic and liver neuroendocrine tumors. From our findings, we recommend genetic screening for individuals with a family history of MEN1. In this case, a mutation was discovered in the variant gene NM_001486.3 sequence, which may be an excellent target for future diagnostics and therapies. Based on these above, if the patient was diagnosed with primary hyperparathyroidism with pituitary tumors and/or gastrointestinal neuroendocrine tumors, we should notice this disease. We hope that this study will lead to improved strategies for the diagnosis and treatment of patients with MEN1.

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Figure Legends

Figure 1. Parathyroid gland dual-phase imaging and organ tomography revealed a strong signal in the upper part of the left lobes and posterior part of the right lobes of the thyroid.

Figure 2. Ultrasonography showed hypoechoic nodules in the dorsal lobe of the left and right lobe of the parathyroid gland. There were no apparent abnormalities in the thyroid gland, and no enlarged lymph nodes in the bilateral neck.

Figure 3. CT imaging revealed irregular soft tissue densities in the pancreas, which were localized around the stomach wall.

Figure 4. PET/CT examination. a. Multiple round nodules in both lungs with slightly increased metabolism. b. Hypermetabolic lesions in the intrahepatic segment IV. c. No metabolic round nodules in the anterior pancreas. d. High metabolic mass in the body of the pancreas. e. High metabolic nodules in the tail of the pancreas. f. Diffusely increased metabolism in the stomach wall.

Figure 5. Pathological examination. a. Multiple nodules next to the pancreatic tumor. b. Multiple nodules in the pancreatic tissue around the pancreatic body. c. Multiple nodules next to the

pancreatic tail.