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CASE REPORT

Long-term follow-up of a case of MEN1 and literature review

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Abstract

OBJECTIVE: To investigate the diagnosis and treatment of Multiple Endocrine Neoplasia Type 1 (MEN1), improve our understanding of the disease and highlight the importance of life-long follow-up of affected individuals.
METHODS: A retrospective analysis was performed on 1 MEN1 patient with long-term follow-up at the First Affiliated Hospital of Anhui Medical University.
RESULTS: A 51-year-old woman was diagnosed with MEN1 14 years ago, but exhibited a suspected disease course of at least 20 years. Prior to admission, the patient reported a cough lasting for two months. The patient's thyroid hormone, sex hormone, insulin, cortisol, parathyroid hormone, and ACTH circadian rhythm findings were within normal ranges. The patient exhibited elevated blood calcium levels. Examination led to the detection of thymoma and pancreatic neoplasms, whereas no obvious abnormalities were detected in her parathyroid gland or adrenal gland as determined via computed tomography (CT). Genetic analyses revealed a mutation in the MEN1 gene in this patient. As the patient had no relevant clinical symptoms, she refused surgical treatment, and follow-up was continued.
It was learned through follow-up that the patient underwent anterior mediastinal lesion resection and partial rib resection in June 2020 because she re-examined the chest CT showed that the anterior mediastinal mass was significantly larger than that in 2019. Pathology suggested neuroendocrine tumors. The patient is currently recovering well.
CONCLUSION: MEN1 is an uncommon condition in clinical settings, and it is important that clinicians be made aware of this disorder so that they can provide patients with appropriate and timely treatments.

INTRODUCTION

Multiple endocrine neoplasia (MEN) is a rare autosomal dominant heritable disease that is classified into MEN1 and MEN2 subtypes. Herein, we describe the case of a patient diagnosed with MEN1 with a 20-year disease course. Treating and diagnosing MEN1 is clinically challenging and thus warrants special consideration. When patients exhibit endocrine neoplasia, it is crucial that physicians establish whether or not these patients suffer from other adenomas so that these growths can be diagnosed and treated as quickly as possible in order to improve patient quality of life.

METHODS

Ethics

This study was approved by the Ethics Committee of The First Affiliated Hospital of Anhui Medical University (Quick-PJ 2020-03-30). Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Case report

Chief complaints

A 51-year-old woman presented to a local hospital due to a cough and sputum production without any obvious etiological basis.

History of present illness

The patient presented with a cough and sputum production without any obvious cause in June 2019. The patient underwent a chest computed tomography (CT) scan at Suzhou Municipal Hospital, revealing the presence of space-occupying lesions at the fourth rib and anterior mediastinum. The patient was then hospitalized in our hospital for detailed examination and treatment.

History of past illness

The patient married at the age of 24 and suffered from infertility for the following three years. At age 27, the patient experienced irregular menstruation (4-5 days / 3-4 months) and gained weight in her facial tissue. At age 28, the patient presented with galactorrhea, producing a white milky discharge. At that time, a local hospital measured her prolactin levels (180.0 ng/mL), and the patient was administered bromocriptine (2.5 mg, twice per day). After a 2-month treatment period, her prolactin levels were reduced to 40.0 ng/mL. Over the following three years, her prolactin levels repeatedly rose, and bromocriptine treatment was maintained without significant improvement. At age 32, the patient developed centripetal obesity and facial acne. A B ultrasound performed at a local hospital at that time detected a solid mass in the patient's left adrenal gland, and she was hospitalized in a Urology department. A pituitary coronary CT scan revealed the presence of a 1.0 cm-high pituitary neoplasia, while a 4.0 x 2.0 cm space-occupying lesion was detected in the left adrenal gland upon bilateral adrenal CT. Left adrenalectomy was then performed, and a 4.0 x 2.5 cm mass of irregular tissue was submitted for pathological evaluation, leading to a diagnosis of left adrenocortical neoplasia. At age 32, the patient underwent X-ray surgery to treat her pituitary tumors, and stopped bromocriptine treatment. Her prolactin levels were monitored and remained within the normal range for 2 years postoperatively. At age 37, the patient was sent to the emergency department of our hospital for the first time due to repeated episodes of syncope and coma accompanied by loss of consciousness. At that time, her blood glucose level was 0.5 mmol/L, and an abdominal examination led to a diagnosis of insulinoma. Surgery was then performed, and postoperative pathology suggested that the patient suffered from MEN. At the same time, her parathyroid hormone (PTH) levels were above 69 pg/mL. After surgery, the patient continued

Tab. 1. Medical history and related laboratory data before admission

Project (Reference range	Prolactin (1.61-18.77 ng/ml)	Cortisol (138.00-690.00 nmol/L)	PTH (10.00-69.00 pg/ml)	Calcium (2.11-2.52 mmol/L)	FBG (3.90-6.10 mmol/L)
1996	180				
1998	244.8				
1999	75.8				
2000-07		1412.8			
2000-12	93.9	189.4			
2005-06		262	73.5		1.12
2007-04	22.7		80.9	2.91	0.35
2007-07		596	133	2.79	8.5
2008			96.7		

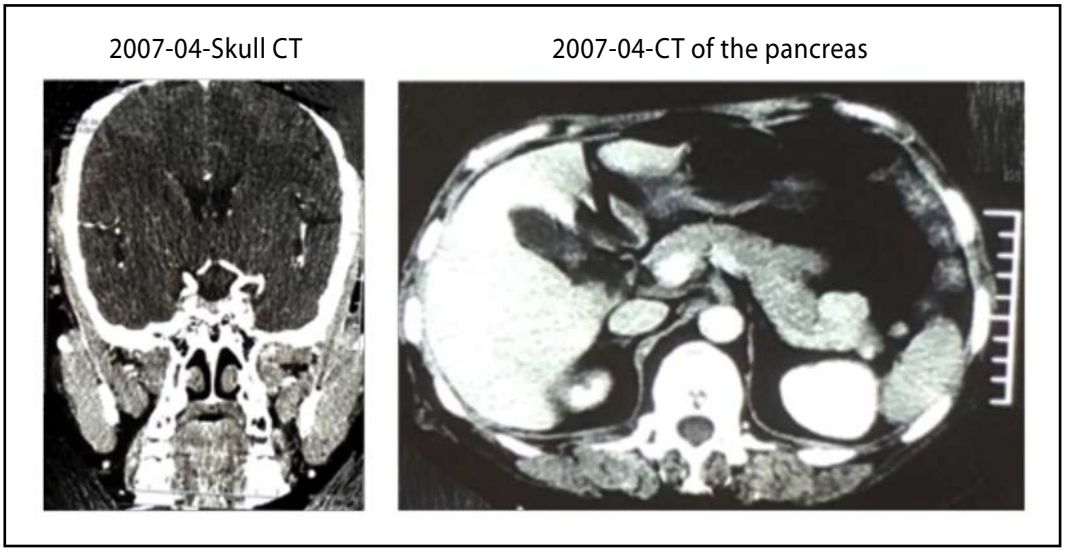


Fig. 1. Relevant imaging data before admission

to suffer from hypoglycemic comas. Two years later, the patient was again diagnosed with insulinoma at our hospital, and pathological evaluation revealed the presence of multiple insulinomas within her pancreas. Tumor cells were present in local blood vessels and were considered malignant. Immunohistochemical findings supported this diagnosis, and were as follows: NSE (+), Syn (+), cgA (+), S-100 (+), CEA (1), CK (1). No tumor cell residue was detected on the margin, nor was any tumor cell invasion of the spleen detected. The patient exhibited satisfactory postoperative recovery. Pre-admission laboratory findings for this patient are shown in Table 1. Relevant pre-admission imaging data for this patient are shown in Figure 1.

Family history

The parents died many years previously and their medical history was unknown. The patient has a daughter who is currently in good health, and none of her siblings have any history of tumor development at present.

Physical examination upon admission

Physical examination at the time of admission revealed that the patient had a blood pressure of 132/87 mmHg, a resting pulse of 82 bpm, and a body mass index of 20.8 kg/m^2. An inverted T-shaped surgical scar was seen on her mid-abdomen, and a 20 cm surgical scar was observed on her left lower back.

Laboratory examination

Laboratory tests conducted after admission revealed that the patient's thyroid hormone, cortisol, ACTH, circadian rhythm, insulin, sex hormone, and other test results were within normal ranges. Her blood calcium levels were found to be elevated at this time point. For

Tab. 2. Relevant laboratory data on admission and during hospitalization

Project	2019-08-20	2019-08-23	2019-08-28	Reference range
Cortisol		-	-	138.00-690.00 nmol/L
8am	391.19			
16pm	129.84			
12pm	75.78			
ACTH		-	-	<46 pg/ml
8am	22.60			
16pm	6.66			
12pm	7.59			
PTH	55	54.90	-	10.00-69.00 pg/ml
Calcium	2.75	2.94	2.62	2.11-2.52 mmol/L
FBG			5.6	3.90-6.10 mmol/L
HbA1c	4.90	-	-	4.00-6.00%

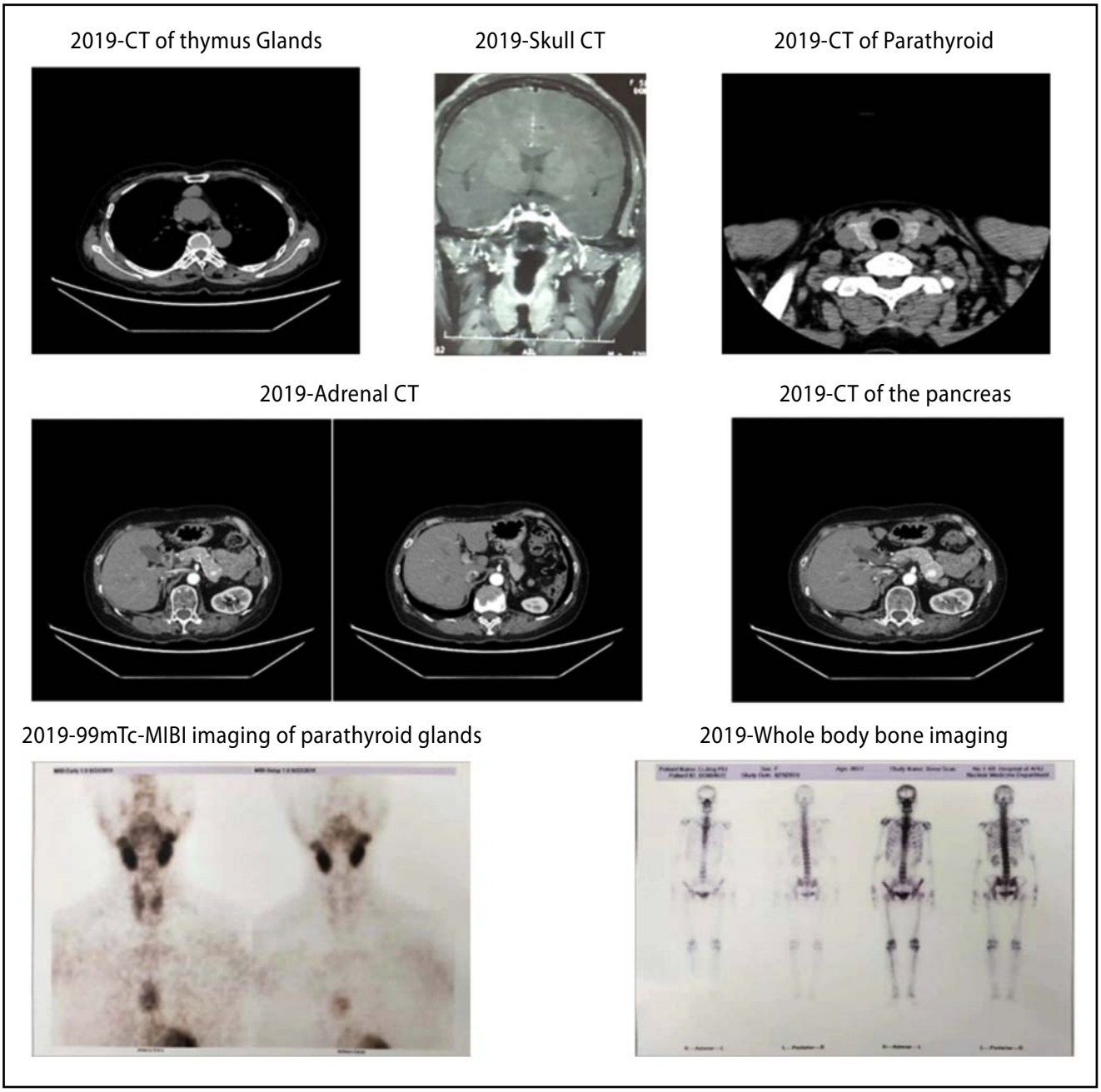


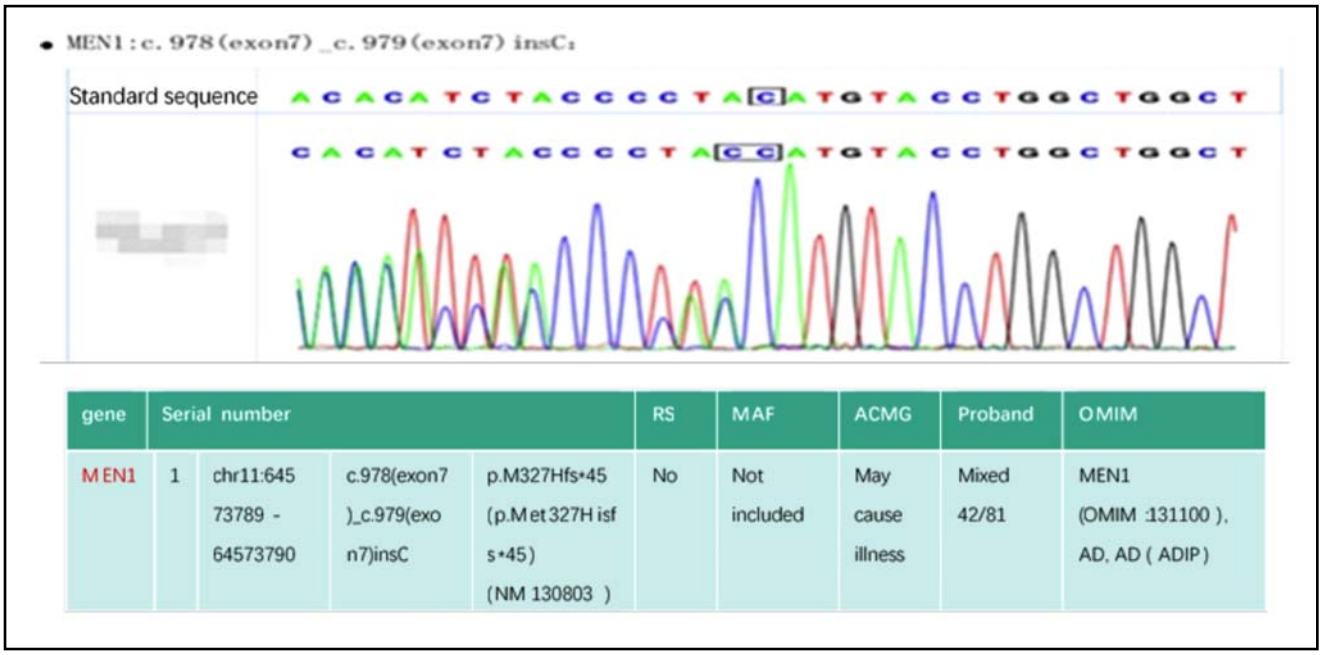
Fig. 2. Relevant examinations during hospitalization

full details regarding her laboratory findings at admission and during hospitalization, see Table 2.

Imaging examinations

Parathyroid nuclide scans revealed increased radioactive uptake in the bilateral submandibular glands and the inferior mediastinum, suggesting the potential for sarcoidosis or endocrine neoplasia. However, the patient exhibited parathyroid hormone levels within the normal range. Thoracic and abdominal pelvic CT scans revealed an anterior mediastinal mass that was identified as a suspected thymoma, a pancreatic tail mass that was identified as a suspected neuroendocrine neoplasia, a right anterior rib soft tissue mass with local bone destruction, a right middle lung nodule, and right middle lung fibrosis. Parathyroid and adrenal gland CT scans did not exhibit any obvious abnormalities, nor did whole-body bone scans. Magnetic resonance scans of the pituitary gland and skull revealed an empty sella, with multiple lymph nodes in the bilateral neck. Relevant imaging findings are shown in Figure 2.

Genetic testing of this patient was performed during hospitalization, revealing the presence of the MEN1 gene c.978_979insC mutation associated with MEN1 (OMIM 131100), which exhibits an autosomal dominant inheritance pattern (Figure 3). The variant was classified as potentially pathogenic according to the ACMG genetic variation classification criteria and



gene	Serial number				RS	MAF	ACMG	Proband	OMIM
MEN1	1	chr11:64573789 - 64573790	c.978(exon7)_c.979(exon7)insC	p.M327Hfs*45 (p.Met327Hisfs*45) (NM 130803)	No	Not included	May cause illness	Mixed 42/81	MEN1 (OMIM :131100), AD, AD (ADIP)

Fig. 3. Genetic test results

guidelines. Evidence was based on PVS1 (possible loss of gene function due to mutation) and PM2 (MAF < 0.0005; a low-frequency variation), indicating that this was a rare variant.

Final diagnosis

After a multi-disciplinary discussion, the patient was diagnosed with MEN1, thymoma, pancreatic tail tumor, thyroid nodules, pulmonary nodules, bilateral renal cysts, and kidney stones.

Treatment

As the nature of thymoma in this patient had not yet been established, follow-up monitoring was conducted as per the patient's wishes. Hepatopancreatobiliary surgery was scheduled in our hospital to remove the pancreatic tumor. However, as the patient's blood glucose levels remained normal over the course of repeated monitoring, the tumor was considered to be a non-functional neoplasia. The patient thus elected to not undergo surgery to remove this neoplasia.

Outcome and follow-up

Through follow-up, it was learned that the patient went to a hospital in Shanghai in June 2020. The patient rechecked some examinations: 1) The patient's pancreatic magnetic resonance showed nodules in the tail of the pancreas, but because the patient's blood glucose and insulin levels are basically normal, there is no indication for surgery. Continue follow-up. 2) The patient's blood calcium levels were 2.6-2.7 mmol/L, PTH levels were 70-80 pg/ml, and ultrasound showed nodules in the right parathyroid area. Because the patient had no obvious clinical symptoms and the blood calcium levels were only slightly elevated, which can be followed up for observation. 3) The patient re-examined the chest CT showed that the anterior mediastinal mass (3.7*2.3cm), which was significantly larger than in 2019. She underwent anterior mediastinal lesion resection and partial rib resection in June 2020. Pathology revealed neuroendocrine tumors. Postoperatively Recovery is good.

DISCUSSION

MEN1 is an autosomal dominant condition characterized by the simultaneous or successive development of multiple endocrine neoplasias or hyperplasias (Norton *et al.* 2015; Thakker *et al.* 2012), often manifesting in the form of parathyroid neoplasias, gastrointestinal pancreatic neoplasias, insulinomas, and anterior pituitary neoplasias (often prolactinomas) (Sadowski *et al.* 2015). In rarer cases, related adenomas can also develop in the form of foregut carcinoids, lipomas, angiofibromas, thyroid neoplasias, adrenocortical neoplasias, angioleiomyomas, and spinal ependymal neoplasias (Ye *et al.* 2017). With the exception of gastrinomas, the majority of these neoplasias are not metastatic but can cause significant symptoms owing to the secretion of hormones including gastrin, insulin, parathyroid hormone, prolactin, growth hormone, glucagon, or adrenocorticotropic hormone (Hurtado-Pardo *et al.* 2017). In the present case, abnormal lactation was the first manifestation of MEN1 in the affected patient, at which time the patient was diagnosed with pituitary adenoma. After 9 years, the patient experienced recurrent hypoglycemia and was diagnosed with MEN1. It is important to note that pancreatic endocrine neoplasias often do not occur in isolation, and special

attention must be paid to ensure that complete resection of such masses is achieved during surgical treatment (Zhu *et al.* 2019). The patient in this report also developed a thymoma and a pancreatic tail tumor, but the latter was found to be a non-functional neoplasia and was not surgically resected or treated in any way. There are many factors that must be considered when diagnosing and treating a patient with MEN1. At the time of adrenocortical neoplasia diagnosis in a patient with a history of prolactinoma, a detailed evaluation for a potential MEN1 diagnosis ought to have been made (Ito *et al.* 2017). When this patient was diagnosed with an insulinoma, she had already exhibited hyperparathyroidism, thus supporting a more definitive MEN1 diagnosis. Such patients often exhibit multiple pancreatic neuroendocrine tumors, and as such it would have been possible to avoid the need for reoperation if insulin-secreting tumor localization had been confirmed prior to the initial operation (Takeda *et al.* 2017).

MEN can exhibit a variety of clinical manifestations in affected patients depending on the specific combination of neoplasias that develop. As symptoms associated with particular affected glands may be noted multiple years apart, they can easily be diagnostically separated from one another. After MEN diagnosis, symptomatic neoplasias must be treated as quickly as possible, with surgical resection being the preferred treatment for hyperparathyroidism (Lairmore *et al.* 2014). As gastrin responds well to drugs including proton pump inhibitors, treatment of such abnormal secretion is generally drug-based (Cavalcoli *et al.* 2015). However, surgical resection is the preferred treatment option for patients suffering from insulinomas. The present MEN1 patient also exhibited elevated serum calcium levels and PTH 14 years previously. Over a decade later, she was diagnosed with thymoma and pancreatic neoplasias, the latter of which were found to be nonfunctional. This patient has not exhibited any evidence of parathyroid neoplasia to date, and careful long-term follow-up is essential to preserve quality of life for this patient.

CONCLUSION

In cases where patients present with one or more endocrine tumors, it is important that clinicians remain vigilant and take a detailed medical history. Special attention must be paid to endocrine hormone levels to detect any lesions affecting endocrine tissues to avoid the potential for misdiagnosis and to expedite patient treatment. The present case also highlights the importance of lifelong follow-up for patients diagnosed with MEN1. Regular physical examinations of relative os MEN patients should also be conducted as appropriate. Overall, we hope that this case report will advance current understanding and diagnosis of MEN1.

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The article is original, is not under consideration or has not been previously published in another journal.

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