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Case Report

A Novel Pathogenic *MEN1* Gene Variant Identified in a Family With Multiple Pancreatic Neuroendocrine Tumors

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Abstract

Multiple endocrine neoplasia type 1 (MEN1) is a hereditary endocrine tumor syndrome caused by pathogenic variants in the *MEN1* gene, and most patients with this syndrome initially develop primary hyperparathyroidism (PHPT). Here, we report the case of a family wherein a germline *MEN1* variant was detected and multiple pancreatic neuroendocrine tumors (PanNETs) were observed at the initial evaluation. A 40-year-old woman presented with a complaint of abdominal discomfort, and a close examination revealed multiple pancreatic tumors. Distal pancreatectomy with splenectomy was performed, and the diagnosis was nonfunctional PanNETs. Five years later, her 76-year-old mother was referred to the hospital with multiple pancreatic tumors. A genetic test revealed that both patients harbored a previously unreported germline variant in the *MEN1* gene. Although it was classified as a variant of uncertain significance, we suspect that it may be associated with the pathogenesis of these lesions. This case report presents a new disease concept—familial isolated pancreatic neuroendocrine tumors, or FIPNETs—in patients harboring a pathogenic variant in the *MEN1* gene who experience only pancreatic lesions. We suggest that clinicians consider genetic testing for the *MEN1* gene in patients with multiple pancreatic lesions who show no signs of PHPT.

Key Words: multiple endocrine neoplasia type 1 (MEN1), multiple pancreatic neuroendocrine tumors (PanNETs), pathogenic missense variant

Abbreviations: EUS, endoscopic ultrasonography; FIHP, familial isolated hyperparathyroidism; FIPNET, familial isolated pancreatic neuroendocrine tumor; MEN1, multiple endocrine neoplasia type 1; NET, neuroendocrine tumor; PanNET, pancreatic neuroendocrine tumor; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant endocrine tumor syndrome affecting various organs. The three primary lesions of MEN1 are parathyroid gland hyperplasia or adenomas (primary hyperparathyroidism [PHPT]), duodenopancreatic neuroendocrine tumors (NETs), and anterior pituitary NETs [1]. The clinical picture of MEN1 is largely determined by the affected glands and the type of hormonal hypersecretion. PHPT is the most common abnormality identified in approximately 95% to 100% of patients with MEN1 [1, 2]. Moreover, PHPT is frequently the first manifestation of the disease at the mean age of 32 ± 13 years (range 11-68years), although up to one-third of patients with MEN1 do not present with PHPT as the first symptom [3]. Duodenopancreatic NETs are the second most frequent clinical manifestation of MEN1, with a lifetime prevalence of greater than 80% [2]. Most patients with MEN1 are diagnosed with duodenopancreatic NETs later in life, usually several years after being diagnosed with PHPT [3].

Pathogenic variants in the *MEN1* gene, which is located on chromosome 11q13.1 and encodes for the menin protein, are responsible for the development of MEN1 [1]. The *MEN1* gene was identified in 1997, and since then, more than 770 different germline and somatic pathogenic variants have been identified [4, 5]. Menin is involved in various biological processes, including transcriptional regulation; DNA damage repair; and cell signaling, division, proliferation, and migration [6]. The *MEN1* gene functions as a tumor suppressor, and loss-of-function variants lead to the development of MEN1. The extent of intrafamilial and interfamilial variability in the manifestation of the disease increases the difficulty of interpreting the identified *MEN1* allelic variants [2].

Herein, we report the case of a family with late-onset multiple pancreatic lesions. Notably, a germline variant of uncertain significance in the *MEN1* gene, which has not been previously reported, was identified in the family members. After repeated and detailed examinations, normocalcemic PHPT was recognized in one of the patients seven years after the onset of the first symptoms, and she was clinically diagnosed with MEN1. However, the manifestation was atypical for MEN1-related PHPT, which led us to suspect that this variant in the *MEN1* gene was relevant only to pancreatic lesions. The present case report expands on the phenotype of patients harboring a variant in the *MEN1* gene and provides information regarding the appropriate management of patients with multiple pancreatic tumors.

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Case Presentation

A 40-year-old woman with a history of uterine fibroids presented to a local clinic with a complaint of abdominal discomfort. She had undergone a laparoscopic myomectomy eight years ago. She was otherwise in good health and did not require any medication. Her family members had not been diagnosed with any particular inherited disorders.

Diagnostic Assessment

The patient's vital signs were all within normal limits, and physical examination findings were unremarkable. Biochemical tests revealed no abnormalities. Subsequently, contrast-enhanced abdominal computed tomography was performed, which revealed a multilocular tumor mass measuring 21 × 19 mm in the pancreatic tail (Fig 1A). She was referred to our hospital for a thorough pancreatic examination, including magnetic resonance imaging. The majority of the pancreatic tumor showed low signal intensity on T1-weighted magnetic resonance images, and the lesion margins showed high heterogeneous signal intensity (Fig 1B). Doppler endoscopic ultrasonography (EUS) revealed increased blood flow in the lesion (Fig 1C). Furthermore, EUS revealed tumors in other pancreatic regions, including three tumors in the pancreatic body and one in the uncinate process. Subsequently, EUS-guided fine-needle aspiration of the tumor through the pancreatic body was performed, which revealed it to be a neuroendocrine tumor. This finding prompted us to evaluate hormone secretion, especially the levels of gastrin, glucagon, and insulin (Table 1). However, endocrinological tests revealed no abnormalities. Based on these findings, the patient was diagnosed with nonfunctional multiple pancreatic neuroendocrine tumors (PanNETs).

Treatment

After multidisciplinary team discussions, distal pancreatectomy with splenectomy and enucleation of the tumor at the uncinate process was performed. The histopathological evaluation of the specimen revealed 13 pancreatic tumors consistent with PanNETs, the largest measuring 26 × 18 mm (Fig 2A and 2B). Lymphovascular and perineural invasions were not observed and the pathological tumor stage was T1N0Mx. Based on the 2022 World Health Organization classification of neuroendocrine neoplasms, the tumors were classified as NET G1 according to the mitotic count (<2 mitoses/2 mm^2) and Ki-67 labeling index (<3%; Fig 2C).

Outcome and Follow-up

The postoperative course was uneventful. Five years after the surgery, the 76-year-old mother of our patient underwent a routine examination that revealed multiple pancreatic tumors (Fig 1D). EUS-guided fine-needle aspiration showed that these tumors were consistent with PanNETs, thus indicating that the multiple pancreatic tumors in this family may have been caused by an inherited genetic condition. After appropriate genetic counseling, both patients underwent a genetic test, which revealed a missense variant in exon 3 of the *MEN1* gene (c.632T > A; p. Val 211 Asp). This variant had not been previously reported and the significance of this single-nucleotide variation was categorized as uncertain. However, based on the family history in the present case, we hypothesized that this variant is pathogenic.

We began a regular and detailed examination of the MEN1-related manifestations in both patients. They showed no other MEN1-related manifestations for at least two years. However, seven years after the daughter's initial visit, a biochemical test revealed calcium levels at the upper limit of the

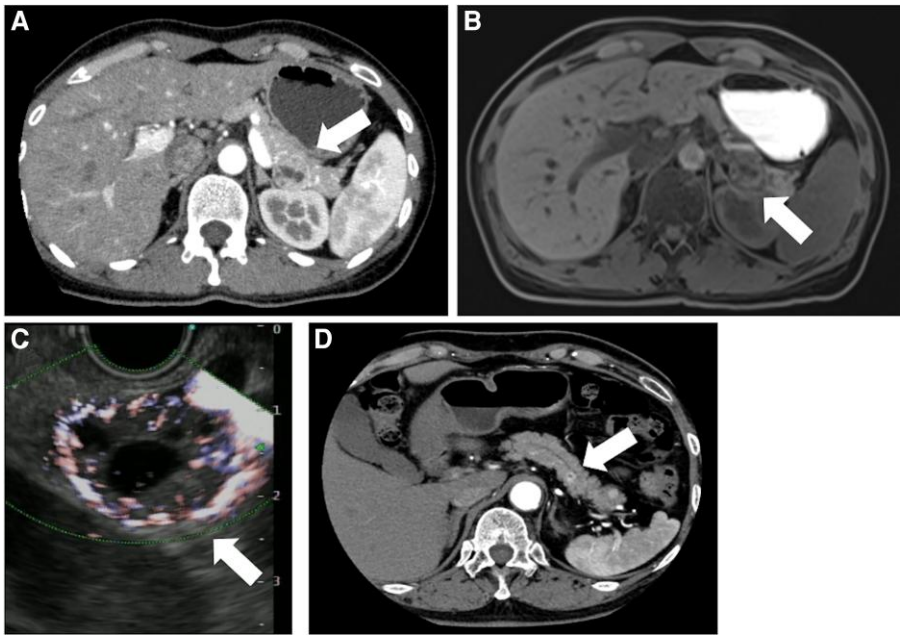

Figure 1. Multiple pancreatic tumors. A to C, Clinical images of the patient in the present case report and D, from her mother. A, Contrast-enhanced abdominal computed tomography (CT) scan shows the tumor with rim staining (white arrow) in the pancreatic tail. B, Magnetic resonance imaging; the major part of the tumor shows low signal intensity (white arrow) on T1-weighted images. C, Doppler endoscopic ultrasonography reveals increased blood flow around the tumor area (white arrow). D, The contrast-enhanced abdominal CT scan shows solid nodules and cystic lesions (white arrow) in the pancreatic body.

Table 1. Laboratory values

Test	Result	Reference range
Glucose	4.8 mmol/L (86 mg/dL)	4.1-6.1 mmol/L (73-109 mg/dL)
HbA_{1c}	5.6%	4.9-6.0%
IRI	57.4 pmol/L (8 μU/mL)	7.2-78.9 pmol/L (1-11 μU/mL)
Gastrin	129 ng/L (pg/mL)	42-200 ng/L (pg/mL)
Glucagon	174 ng/L (pg/mL)	71-174 ng/L (pg/mL)
Albumin	42 g/L (4.2 g/dL)	41-51 g/L (4.1-5.1 g/dL)
Ca	2.4 mmol/L (9.5 mg/dL)	2.2-2.5 mmol/L (8.8-10.1 mg/dL)
IP	0.87 mmol/L (2.7 mg/dL)	0.87-1.5 mmol/L (2.7-4.6 mg/dL)
Intact PTH	5.5 pmol/L (52 pg/mL)	1.6-6.9 pmol/L (15-65 pg/mL)
FSH	7.6 IU/L (mIU/mL)	3.01-14.72 IU/L (mIU/mL)[a]
LH	8.8 IU/L (mIU/mL)	1.76-10.24 IU/L (mIU/mL)[a]
Estradiol	423.3 pmol/L (115.3 pg/mL)	106-722.5 pmol/L (28.8-196.8 pg/mL)[a]
GH	0.31 μg/L (ng/mL)	0.13-9.88 μg/L (ng/mL)
IGF-1	95 μg/L (ng/mL)	46-282 μg/L (ng/mL)
Prolactin	20 μg/L (ng/mL)	0-30 μg/L (ng/mL)
ACTH	8.273 pmol/L (37.57 pg/mL)	1.6-13.9 pmol/L (7.2-63.3 pg/mL)
Cortisol 8 AM	510 nmol/L (18.5 μg/dL)	120-582 nmol/L (4.5-21.1 μg/dL)
PAC	3.49 pmol/L (126 pg/mL)	1.0-6.7 pmol/L (36-240 pg/mL)
PRA	3.6 μg/L/h (ng/mL/h)	0.2-2.7 μg/L/h (ng/mL/h)
DHEA-S	3.68 μmol/L (106 μg/dL)	1.4-7.56 μmol/L (41-218 μg/dL)
$1,25\text{-}(OH)_2$Vit-D	165.6 pmol/L (69 pg/mL)	48-144 pmol/L (20-60 pg/mL)
25-(OH)Vit-D	34.4 nmol/L (13.8 ng/mL)	50-125 nmol/L (20-50 ng/mL)

Abbreviations: ACTH, adrenocorticotropin; Ca, calcium; DHEA-S, dehydroepiandrosterone sulfate; FSH, follicle-stimulating hormone; GH, growth hormone; HbA_{1c}, glycated hemoglobin A_{1c}; IGF-1, insulin-like growth factor 1; IP, inorganic phosphorus; IRI, immunoreactive insulin; LH, luteinizing hormone; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PTH, parathyroid hormone.

[a]Follicular phase.

normal range and nonsuppressed parathyroid hormone (PTH) levels without renal impairment or vitamin D deficiency. Subsequent thyroid ultrasonography revealed an enlargement of one of parathyroid glands (16 mm), leading to a diagnosis of normocalcemic PHPT. The results of 99 mTc-sestamibi multiplexed ion beam imaging scintigraphy and bone mineral density measured with dual-energy x-ray absorptiometry were not significant, and abdominal ultrasonography did not reveal nephrocalcinosis. Although these findings are inconsistent with the typical features of PHPT, we assumed a slight autonomous hypersecretion of PTH, which did not result in major complications. Other than PHPT, no other MEN-1 related abnormalities (eg, pituitary or adrenal tumors) were identified. Based on these findings, we diagnosed both patients with MEN1. According to the current practice guidelines for MEN1-related PanNETs, a tumor should be surgically resected if it is larger than 20 mm in diameter or if it is growing rapidly during surveillance [7]. Because the largest tumor in the mother was 15 mm in diameter and did not meet the criteria for surgery, we decided to observe her PanNETs without surgery. To date, the mother has not shown any other MEN1-related symptoms.

Discussion

Here, we report on a family wherein the mother and daughter developed multiple PanNETs and harbored a missense variant in the *MEN1* gene. The daughter was later diagnosed with normocalcemic PHPT, one of the main manifestations of MEN1. We suspected that only multiple PanNETs were associated with the variant in the *MEN1* gene and that the normocalcemic PHPT was incidentally found independent of the variant.

In the present case, the patients exhibited multiple PanNETs, which is atypical of sporadic PanNETs. In contrast, multifocal PanNETs are characteristic of MEN1. Current guidelines recommend genetic testing to screen for any variant in the *MEN1* gene in patients suspected of MEN1, for example, patients developing multiple PanNETs at any age [1]. In addition to MEN1, other pancreatic hereditary diseases, including von Hippel-Lindau disease, neurofibromatosis type 1, and tuberous sclerosis complex have been reported. We considered the possibility of these diseases even though the characteristic manifestations thereof had not been identified in the patients. Because there are several differential diagnoses of hereditary PanNETs in this case, it is important to remain alert to the emergence of additional manifestations.

To date, many studies regarding pathogenic variants in the *MEN1* gene have been published [4, 5]. According to several protein–protein interaction studies, pathogenic variants in the *MEN1* gene may affect the interaction between menin and related proteins [6]. Approximately 25% of pathogenic variants in the *MEN1* gene are missense variants whose effects on the protein's structure and function have not yet been determined [8]. The patients in this case harbored a missense variant, c.632T > A (p. Val 211 Asp) in exon 3 of the *MEN1* gene. The variant is located in a region that mediates interactions with surrounding proteins, such as JunD, Smad3, NM23H1, NMHC II-A, and HDAC1 [4]. On searching the NCBI PubMed literature database and free online databases for articles and/or reports June 7, 2023, we found that this missense variant had not been previously reported. A similar variant, c.632T > G (p. Val 211 Gly), was submitted in the ClinVar database (www.ncbi.nlm.nih.gov/clinvar, accession No. VCV000566175), but it was categorized as "uncertain." Based on the family history of multiple PanNETs, we speculate that the missense variant found in these patients may affect menin function. Further genealogical and molecular studies are required to unequivocally determine how this variant is involved in the pathophysiology of PanNETs.

MEN1 variants have been involved in the pathogenesis of familial isolated hyperparathyroidism (FIHP), an endocrinopathy that affects only the parathyroid gland [9]. *MEN1* variants have been found in 42 families with FIHP, and 38% of these nucleotide variants were missense variants [4]. This finding suggests an association between missense variants and milder manifestations, as missense variants are expected to be less severe than nonsense and frameshift variants. In

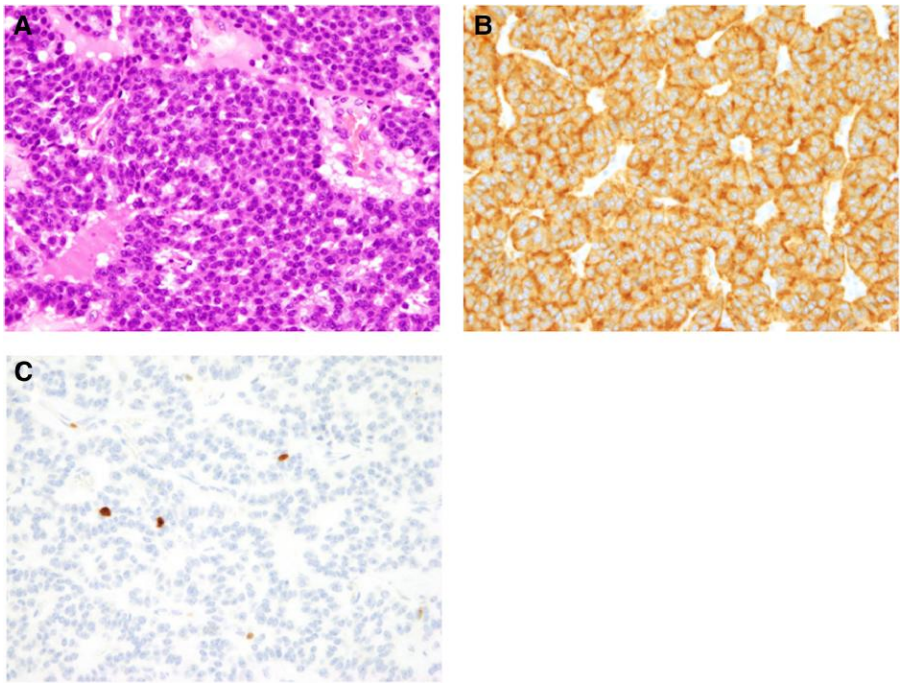

Figure 2. Immunohistochemical staining of pancreatic resected tumors. A, Hematoxylin and eosin staining was used to observe tumor cells. B, The synaptophysin stain shows neuroendocrine differentiation. C, The Ki67 stain shows a proliferation index of less than 3%. Images acquired at 400× magnification.

contrast to FIHP, it is remarkable that the patients in the present case showed only multiple PanNETs at the initial evaluation. This observation suggests a new disease concept that is comparable to FIHP—familial isolated pancreatic neuroendocrine tumors (FIPNETs)—in patients with a pathogenic variant in the *MEN1* gene who develop only pancreatic lesions among MEN1 manifestations. In the present case, the affected lesions were not confined to the pancreas as the daughter later developed normocalcemic PHPT. Nevertheless, the enlarged parathyroid gland was found in only one of the glands, which is inconsistent with the typical feature of MEN1-related PHPT wherein all parathyroid glands are likely to be affected. In this regard, we considered the possibility that the variant found in this family only caused multiple PanNETs, with the daughter developing normocalcemic PHPT independent of the variant. If this is correct, both patients should be diagnosed with FIPNETs rather than MEN1. This assumption would be helpful to explain why the mother did not develop PHPT even in her 70s. Although PanNETs have an earlier onset in patients with MEN1 [10], in the present case, pancreatic lesions in the daughter and mother were not identified until they were aged 40 and 76 years, respectively. This observation might indicate that the missense variant found in this family has a minor effect on tumorigenesis, resulting in less severe manifestations, namely, late-onset multiple PanNETs.

In conclusion, we herein reported on a family wherein the members developed multiple PanNETs. The family history led us to consider inherited disorders, and we found a germline variant in the *MEN1* gene that has not been previously reported. Thus, clinicians should consider genetic testing of the *MEN1* gene when identifying multiple PanNETs, even in patients without signs of PHPT.

Learning Points

- Clinicians should consider genetic testing of the *MEN1* gene in patients presenting with multiple PanNETs.
- Even in patients without PHPT, it is important to consider the probable presence of a variant in the *MEN1* gene.
- As a new disease concept, FIPNETs may underlie clinical features in patients harboring pathogenic variants in the *MEN1* gene who develop only pancreatic lesions among MEN1 manifestations.

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Contributors

All authors made individual contributions to authorship. J.A. and N.M. were involved in the diagnosis and management of this patient; J.A. and K.H. were responsible for the patient's surgery; and H.H. and N.M. wrote and edited the manuscript. All authors reviewed and approved the final draft.

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Disclosures

None declared.

Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient.

Data Availability Statement

Some or all data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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