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Case Report

A Novel Mutation in a Family With Multiple Endocrine Neoplasia Type 1 and Aggressive Pancreatic Neuroendocrine Tumors

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ABSTRACT

Background: Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant disorder characterized by the occurrence of combined tumors in different glands, usually the parathyroid, pancreas and pituitary, as well as in other parts of the digestive tract. The present study describes the phenotype of a Brazilian family with MEN1 caused by a previously unreported *MEN1* gene mutation.
Case Report: We report the case of a 41-year-old male, the proband, who presented with angiofibromas, primary hyperparathyroidism, macroprolactinoma, and pancreatic neuroendocrine tumor. Next generation sequencing analysis of the *MEN1* gene in the patient's peripheral blood DNA sample revealed a deletion of 16 base pairs (c.1366-12_1369del;p) resulting in a framing error. Additional 5 members of the family (4 brothers and a first cousin) presented with clinical features of MEN1. All brothers underwent mutation screening and tested positive for the same genetic variant. Two of them were also diagnosed with papillary thyroid carcinoma.
Discussion: The c.1366-12_1369del;p mutation is located between the 10th and last exon of the *MEN 1* gene and it's preceding intron, encompassing the canonical sites in the splice junction. The 10th exon of *MEN1*, possibly lost with this variant, encodes the last 163 amino acids that compose the Menin protein's C-terminal region, which harbors nuclear localization signals essential for its internalization into the nuclear compartment and interaction with the nuclear matrix.
Conclusion: Our case reports add to the literature the description of a new pathogenic variant of the MEN 1 gene.

Introduction

Multiple endocrine neoplasia (MEN) is a rare autosomal dominant disorder marked by the development of tumors in specific endocrine glands. The first description of MEN type 1 (MEN1) was published in 1954, primarily associating it with tumors of the parathyroid glands, pituitary gland, and pancreas, though other endocrine organs may also be affected.[1] In approximately 85% of MEN1 cases, the initial clinical manifestation is primary hyperparathyroidism (PHPT), typically appearing in adulthood and persisting into the third decade of life.[2,3] The diagnosis of MEN 1 can be made clinically in a patient who has at least 2 out of 3 endocrine tumors (parathyroid, pituitary, and neuroendocrine tumor (NET) of gastro-entero-pancreatic tract) or a patient with 1 out of 3 endocrine tumors and a first-degree relative with MEN1 or it can be made based on the presence of having a germline MEN1 mutation.[3] Understanding the genetic mutations related to MEN1 is crucial for accurate diagnosis and genetic counseling.[4] More than 1300

Abbreviations: CT, computed tomography; MEN 1, multiple endocrine neoplasia type 1; NET, neuroendocrine tumor; NLS, nuclear localization signal; PHPT, primary hyperparathyroidism; PTC, papillary thyroid carcinoma.

Patient consent: Informed consent was obtained from all patients involved in this case report.

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mutations in the MEN1 gene have been documented, although a clear genotype-phenotype correlation remains elusive.[5] This case report details a novel pathogenic variant of the MEN1 gene (c.1366-12_1369del;p) and aggressive pancreatic NETs. Also, multiple family members presented with papillary thyroid carcinoma (PTC) (Fig. 1).

Case Report

Proband History

In 2013, at the age of 32, the proband (III-6) presented at our outpatient clinic with complaints of headaches and galactorrhea. His significant family medical history included gastric ulcers in his deceased father and grandmother, but there was no known consanguinity. Initial lab results revealed markedly elevated prolactin levels exceeding 1000 ng/mL (normal range < 18 ng/mL). A magnetic resonance imaging scan identified a macroadenoma of the pituitary gland measuring 37 mm. The patient was initiated on cabergoline therapy, with the dosage adjusted to 2 mg per week. Over the course of 2 years, his prolactin levels normalized, and the size of the pituitary tumor decreased by approximately 60%. A clinical examination also revealed diffuse skin lesions characteristic of angiofibromas (Fig. 2), which raised suspicion for MEN1. Two years later, he was diagnosed with PHPT, showing an ionized calcium level of 1.5 mmol/L (reference range 1.1–1.35 mmol/L), a phosphorus of 3.2 mg/dL (reference range 2.5-4.5 mg/dL), and a parathyroid hormone level of 125 pmol/L (reference range 4–58 pmol/L). He presented with asymptomatic bilateral nephrolithiasis and low bone mass as evidenced by dual-energy x-ray absorptiometry (lumbar spine Z score of −2.9, femoral neck Z score of −1.7), despite no previous fragility fractures. An exploratory parathyroidectomy was performed, resecting only 2 glands due to localization challenges. Elevated ionized calcium (1.49 mmol/L) and parathyroid hormone (94 pmol/L) levels persisted. Further imaging studies (99mTc sestamibi scintigraphy, 4D cervical computed tomography [CT]) did not indicate parathyroid enlargement. Calcimimetic therapy was initiated, resulting in partial biochemical control after the patient declined reoperation.

Following the clinical diagnosis of MEN1, we conducted a comprehensive evaluation, including imaging studies to screen for asymptomatic NETs. A CT scan revealed 3 hypervascular hepatic lesions, while a Ga-68 DOTATOC-PET/CT study demonstrated significant uptake in these lesions as well as in the pancreas (neck, body, and tail). Serum gastrin and chromogranin-A levels remained within normal limits. Subsequently, the patient underwent pancreatectomy of the body and tail, along with partial hepatectomy. Histopathological and immunohistochemical findings confirmed well-differentiated pancreatic NET with a low mitotic index (<2%) and a Ki67 index < 1%, respectively. Somatostatin receptor ligand therapy was initiated after a new 14 mm liver nodule suggestive of metastatic NET was detected, yielding a favorable structural response. Next-generation sequencing of the MEN1 gene in the proband revealed c.1366-12_1369del mutation.

Highlights

- We describe a novel pathogenic variant of the multiple endocrine neoplasia type 1 (MEN1) gene: c.1366-12_1369del;p
- In addition to the classical features of MEN1 syndrome, 2 family members presented with papillary thyroid carcinoma, suggesting a unique phenotype for this variant
- This family case report emphasizes the importance of genetic screening in relatives of MEN patients

Clinical Relevance

When receiving a genetic test result for a suspected genetic disorder, clinicians should be aware that previously undescribed mutations may be classified as genetic variants of uncertain significance by commercial laboratories. However, when managing patients with classical clinical features and/or positive family history, genetic test results should be evaluated in accordance with updated guidelines for the interpretation of sequence variants.

Family History

All siblings of the proband underwent mutation screening, revealing MEN1 manifestations consistent with the proband. Genetic screening confirmed the same genetic variant among the brothers, while the 2 unaffected sisters tested negative. The family pedigree (Fig. 1) illustrates the hereditary pattern.

III-1

A 39-year-old male developed PHPT, low bone mass, and nephrolithiasis 3 years after the initial diagnosis. Imaging revealed a sellar lesion and thyroid nodules, leading to a diagnosis of multicentric PTC and parathyroid hyperplasia following surgical interventions. A pancreatic NET was confirmed, and subsequent

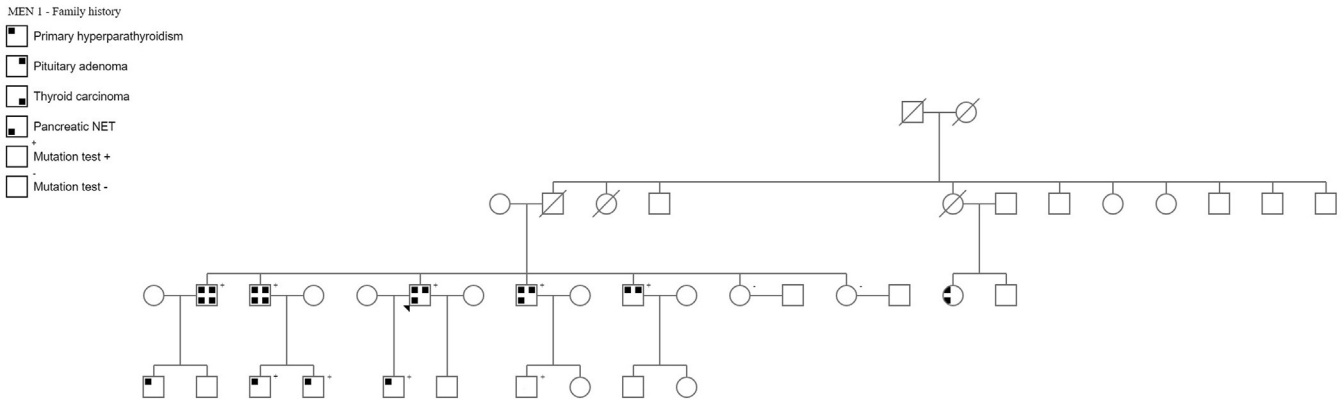

Fig. 1. Pedigree of the main clinical conditions and mutations in the family profile.

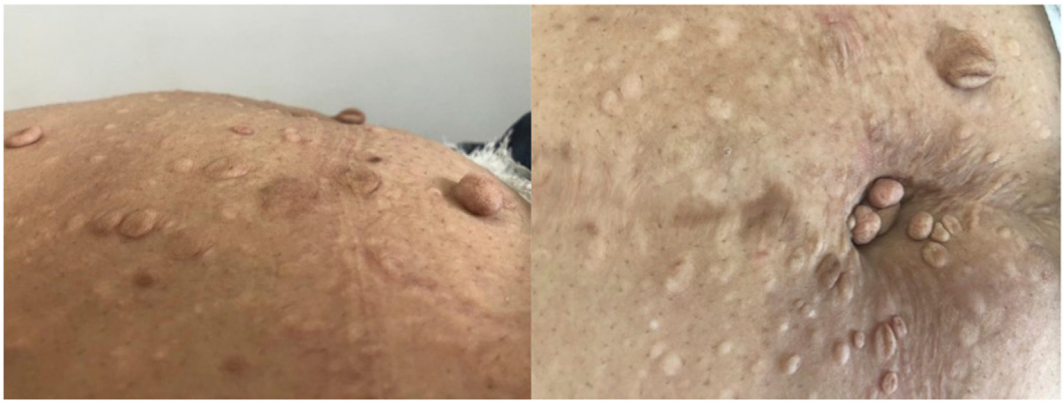

Fig. 2. Skin lesions suggestive of angiofibromas in the abdominal wall.

imaging indicated nonoperable lesions, prompting initiation of somatostatin receptor therapy and recommendations for radionuclide therapy with Lutetium-177.

III-3

A 37-year-old male presented with PHPT and a nonfunctioning pituitary microadenoma alongside small pancreatic lesions. Despite somatostatin receptor ligand therapy, control was poor, necessitating partial pancreatic resection. He was also diagnosed with microcarcinoma of the PTC, which is currently in remission.

III-8

A 31-year-old male diagnosed with PHPT and nephrolithiasis underwent parathyroidectomy. He later developed a nonfunctioning pituitary microadenoma and multiple pancreatic lesions, resulting in body and tail pancreatectomy.

III-10

A 34-year-old male with diffuse angiofibromas and PHPT underwent parathyroidectomy and prophylactic thymectomy. He later developed a nonfunctioning pituitary microadenoma, but no pancreatic lesions were identified.

III-16

A 39-year-old female cousin of the proband was diagnosed with PHPT and symptomatic nephrolithiasis. She exhibited elevated levels of chromogranin A and gastrin, and image identified a pancreatic nodule. Postsurgical histopathological analysis confirmed it as a NET.

IV-1, IV-3, IV-4, IV-5

These family members have been diagnosed with PHPT and have varying histories of parathyroid surgery and genetic mutation confirmation, with some awaiting further procedures.

IV-7

Genetic mutation confirmation was obtained, but there is currently no clinical or biochemical evidence of disease.

Table presents a summary of the clinical presentations, associated tumors, and genetic testing results for each family member.

Discussion

MEN1 Gene Mutation Analysis

Next-generation sequencing of the MEN1 gene in the proband revealed a deletion of 16 base pairs, resulting in a frameshift mutation. The c.1366-12_1369del mutation occurs at the boundary of the 10th exon and its preceding intron, likely leading to the loss of the region encoded by exon 10.

Interestingly, although genotype-phenotype correlations in pancreatic NETs remain unvalidated, previous studies suggest that mutations in MEN1 exons 2, 9, and 10 may be associated with an increased risk of malignant pancreatic NETs.[6] While pancreatic

Table
Summary of clinical features and genetic testing of the family members

Family member	Clinical presentation and relative tumors				Genetic testing
III-1	PHPT Low bone mass Nephrolithiasis	Nonfunctioning microadenoma	PTC	Pancreatic NET	Positive
III-3	PHPT	Nonfunctioning microadenoma	Microcarcinoma PTC	Pancreatic NET	Positive
III-8	PHPT Nephrolithiasis	Nonfunctioning microadenoma	-	Pancreatic NET	Positive
III-10	PHPT	Nonfunctioning microadenoma	-	-	Positive
III-16	PHPT Nephrolithiasis	-	-	Pancreatic NET	Not tested
IV-1	PHPT	-	-	-	Not tested
IV-3	PHPT	-	-	-	Positive
IV-4	PHPT	-	-	-	Positive
IV-5	PHPT	-	-	-	Positive

Abbreviations: NET = neuroendocrine tumor; PHPT = primary hyperparathyroidism; PTC = papillary thyroid carcinoma.

NETs arise in less than 10% of cases within familial syndromes, they are present in 30% to 80% of MEN1 patients.[7,8] Moreover, studies indicate that the incidence of PTC in patients with MEN1 is relatively low, with one study reporting that only 4.52% of MEN1 patients are affected by PTC.[9] Although thyroid neoplasms, including adenomas and carcinomas, may occur in over 25% of individuals with MEN1, their occurrence is often incidental due to the high prevalence of thyroid disorders in the general population.[8] Additionally, similar to this family, approximately 24 cases of PTC have been documented in MEN1 patients.[8-17] Notably, the expression of the Menin protein is generally preserved in human thyroid carcinomas.[18]

Specifically to the c.1366-12_1369del mutation, the American College of Medical Genetics classified this mutation as “Likely Pathogenic” based on its impact on transcription and absence in global databases like gnomAD and ABraOM, indicating an extremely low allele frequency.[19]

Cloned in 1997, the MEN1 gene encodes the Menin protein, a critical tumor suppressor involved in various cellular processes, including DNA damage response. Patients with germline mutations in MEN1 typically exhibit endocrine tumors characterized by loss of heterozygosity at MEN1 alleles.[20] The c.1366-12_1369del variant likely results in the loss of the 10th exon of the MEN1 gene, which encodes the last 163 amino acids of the C-terminal region of Menin.[20] This region contains crucial nuclear localization signals (NLS1, NLS2, and NLSa) that facilitate Menin's transport into the nucleus and its interaction with the nuclear matrix. The deletion would impair Menin's mobilization to the nucleus, compromising its function. Notably, 70% of pathogenic MEN1 mutations disrupt the C-terminal, further underscoring this effect.[21] Additionally, the variant results in the loss of 2 phosphorylation sites (Ser543 and Ser583), which are vital for recruiting Menin to the nucleus in response to DNA damage, thereby affecting its tumor suppressor role.[22]

Structural modeling of the wild-type Menin protein compared to the variant underscores the significant impact of the deletion on its architecture, reinforcing its pathogenicity (Fig. 3).

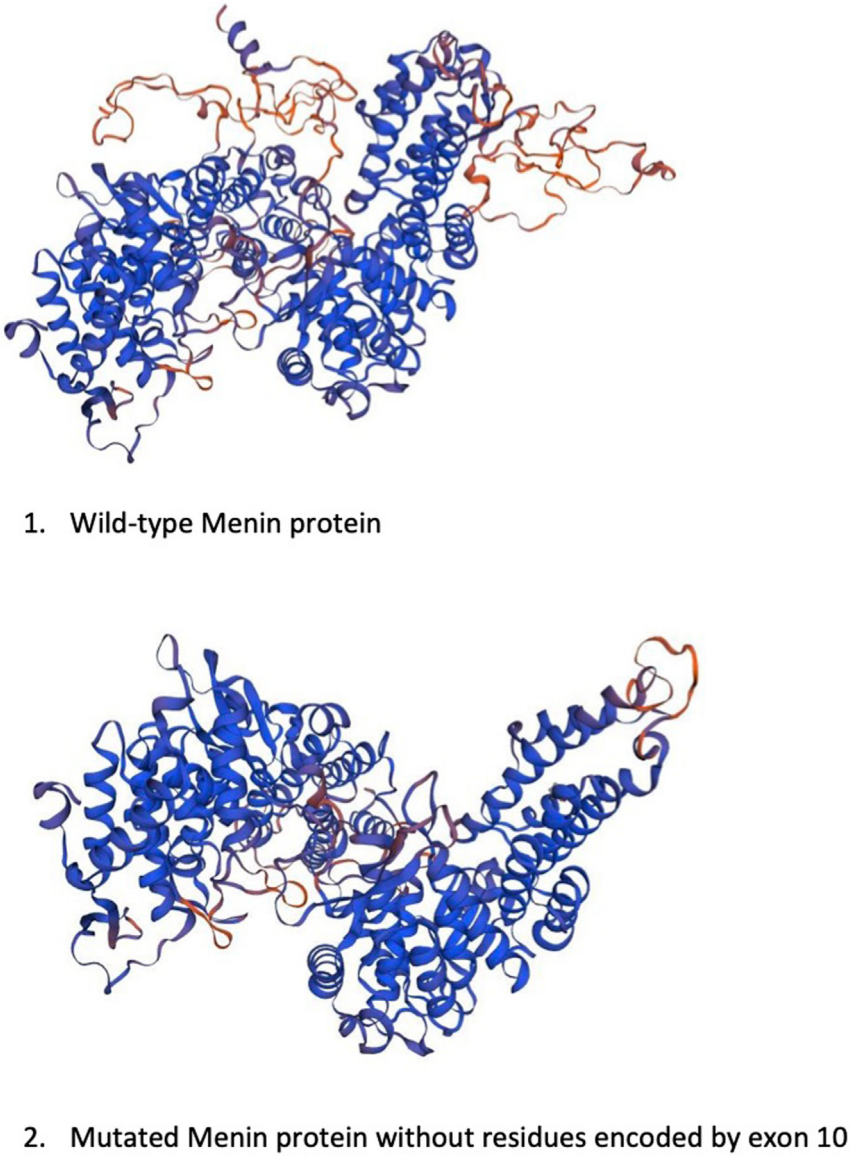

Fig. 3. Three-dimensional predicted tridimensional structure of the Menin mutated protein.

Conclusion

The investigation of genetic mutations in the context of MEN1 has proven invaluable in this case, facilitating early diagnosis and potentially preventing unnecessary follow-up procedures. This case enriches the literature on MEN1 by detailing a novel mutation and highlighting the phenotypic variability even among affected family members carrying the same genetic variant. Understanding these variations is crucial for the development of tailored management strategies and improving patient outcomes in MEN1.

Disclosure

The authors have no conflicts of interest to disclose.

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