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Case Report

A Novel and Rare Pathogenic Gene Variant in 2 Patients With Multiple Endocrine Neoplasia Type 1 (MEN-1) Syndrome

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Abstract

Multiple endocrine neoplasia type 1 (MEN-1) is a syndrome characterized by development of tumors including parathyroid adenomas, duodenopancreatic neuroendocrine tumors, and pituitary adenomas. We describe 1 patient with a novel and another with a rare pathogenic MEN-1 variant. Case 1 was a 61-year-old woman with recurrent hypercalcemia who ultimately required a subtotal parathyroidectomy, with a thymectomy revealing a thymoma. She then developed a gastrinoma requiring pancreatectomy and also had a biochemically nonfunctioning sellar mass. Genetic testing found a novel *MEN1:c.1192delC, p.(Gln398Argfs*47)* pathogenic variant. Case 2 was a 38-year-old woman with a family history of MEN-1, who had recurrent hypercalcemia and nephrolithiasis requiring a subtotal parathyroidectomy. She had a macroprolactinoma, but no pancreatic lesions. Genetic testing found a rare *MEN1:c.784-9G>A* pathogenic variant. MEN-1 syndrome should be considered in patients presenting with 1 or more classical MEN-1-associated tumors based on clinical suspicion.

Key Words: multiple endocrine neoplasia type 1 (MEN-1), novel pathogenic variant, pituitary adenoma, duodeno-pancreatic neuroendocrine tumor (NET), parathyroid adenoma, thymoma

Abbreviations: MEN-1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; NET, neuroendocrine tumor; NGS, next-generation sequencing; PHPT, primary hyperparathyroidism; RR, reference range.

Introduction

Multiple endocrine neoplasia type 1 (MEN-1) is classically characterized by tumors including parathyroid adenomas, duodenopancreatic neuroendocrine tumors (NETs), and anterior pituitary adenomas [1]. It is an autosomal dominant syndrome, caused by heterozygous pathogenic variants in the tumor suppresser *MEN-1* gene that encodes the menin protein [2]. More than 1200 inherited pathogenic variants in the *MEN-1* gene have been identified [3].

We report a novel and a rare pathogenic MEN-1 variant, including 1 associated with a thymoma. We describe the variable presentations, importance of genetic testing, and management considerations for patients with MEN-1.

Case Presentation

Case 1: Patient X, a 61-year-old woman, had no family history of MEN-1 and was hospitalized for PTH-dependent hypercalcemia.

Case 2: Patient Y was a 38-year-old woman whose mother had a clinical diagnosis of MEN-1 syndrome (insulinoma and primary hyperparathyroidism [PHPT]). She presented with recurrent episodes of nephrolithiasis with PTH-dependent hypercalcemia.

Diagnostic Assessment

Case 1: Patient X's initial corrected calcium was 12.42 mg/dL (3.10 mmol/L) (normal reference range [RR]: 8.82-10.22 mg/dL; 2.20-2.55 mmol/L) with a PTH of 169.7 pg/mL (18 pmol/L) (RR: 15.1-65.1 pg/mL; 1.6-6.9 pmol/L). Further workup revealed PHPT and a parathyroid scan showed evidence of a left inferior parathyroid adenoma. She later developed epigastric pain and diarrhea concerning for Zollinger-Ellison syndrome. Abdominal computed tomography scan showed a 1.5×2-cm pancreatic mass. A subsequent pancreatic magnetic resonance imaging (MRI) scan showed 2 lesions: a $2.2 \times 2.2 \times 1.8$-cm cyst and a 1.2×1.6-cm ovoid mass. Initial nonfasting gastrin

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was marginally elevated at 112 pg/mL (112 ng/L) (RR: <100 pg/mL; <100 ng/L). Endoscopic ultrasound-guided aspiration revealed a pancreatic NET, staining positive for cytokeratin, synaptophysin, and chromogranin A. Reassessment of her pancreas 1 year later revealed a new pancreatic head lesion measuring 1.7 × 1.5 cm and an increase in gastrin levels to 1400 pg/mL (1400 ng/L). Sellar MRI revealed a 4-mm sellar mass with biochemical investigations suggesting a nonfunctioning pituitary microadenoma.

Case 2: Patient Y had PHPT with an initial corrected calcium of 10.62 mg/dL (2.65 mmol/L) and a PTH of 128.3 pg/mL (13.6 pmol/L). A parathyroid scan showed increased uptake in multiple parathyroid glands. She also had a macroprolactinoma (prolactin: 172 ng/mL (172 µg/L) (RR: 3-29 ng/mL; 3-29 µg/L) with an 18-mm sellar mass in the largest diameter on MRI) but no pancreatic lesions.

Treatment

Case 1: Before her MEN-1 diagnosis, patient X underwent a left inferior parathyroidectomy (pathology showed parathyroid hyperplasia) with initial normalization of hypercalcemia. Initial management of her pancreatic NET with proton pump inhibitor therapy relieved her symptoms, but given radiographic and biochemical progression, she received a total pancreatectomy and prophylactic cholecystectomy. Her pathology showed multiple adenomatosis and low-grade (G1) NETs with the greatest dimension being 2.5 cm, Congo Red stain positive for amyloid, mitotic rate <2 per 2 mm^2, and Ki-67 index <3%. Her gastrin levels subsequently normalized and she developed postpancreatectomy diabetes requiring insulin. After developing recurrent PHPT, she underwent a subtotal parathyroidectomy with concomitant thymectomy. Her pathology showed parathyroid hyperplasia of multiple glands and a 0.5-mm thymoma, with no significant mitotic activity or necrosis, positive for p63 and pancytokeratin, and rarely positive for terminal deoxynucleotidyl transferase.

Case 2: Given patient Y's family history and PHPT, she was treated with a subtotal parathyroidectomy (pathology showed parathyroid hyperplasia of multiple glands), which kept her hypercalcemia and nephrolithiasis in remission for >10 years. She received cabergoline treatment for 1 year, which led to normalization of prolactin and shrinkage of the sellar mass to 8 mm in its largest diameter.

Outcome and Follow-up

Case 1: Patient X was referred for genetic testing by next-generation sequencing (NGS), which revealed a novel frameshift variant, *MEN1:c.1192delC, p.(Gln398Argfs*47)*, predicted to cause premature termination of the gene and nonsense-mediated decay of the mRNA. On serial assessments, her calcium levels remain normal, her sellar mass is stable, and her pancreatic NET remains in remission without symptoms and normal gastrin levels.

Case 2: Patient Y had reported negative genetic testing for MEN-1 previously (results not available to us). We re-referred her for genetic testing by NGS, which revealed a rare intronic variant, *MEN1:c.784-9G > A*; known to introduce a premature termination codon through activation of a cryptic splice site, which leads to an inactive menin protein [4, 5]. Although it is a rare pathogenic variant and absent from databases including the Genome Aggregation Database, it has been associated with MEN-1 [5-9]. Nearly a decade after her subtotal parathyroidectomy, she developed recurrent nephrolithiasis, PHPT, and a parathyroid scan demonstrated increased uptake in a left-sided gland. She is currently awaiting repeat surgical resection with a prophylactic thymectomy. Her sellar mass has been stable for 8 years after previous cabergoline treatment and there is no evidence of pancreatic NETs.

Discussion

These cases collectively present common and unique clinical features associated with MEN-1 syndrome. Parathyroid adenomas/hyperplasia characterized the initial presentation for both patients, a common finding seen in ∼95% of patients with MEN-1 [1, 10]. Screening/monitoring includes measuring calcium and PTH at the time of MEN-1 diagnosis and annually thereafter [1, 10]. Recommended treatment is subtotal parathyroidectomy (removal of three-and-a-half glands) with a concomitant prophylactic thymectomy (given risk of thymic carcinoid) [1, 10]. Patient X received a left inferior parathyroidectomy initially per PHPT guidelines before her MEN-1 diagnosis, whereas patient Y's PHPT was treated per MEN-1 guidelines with a subtotal parathyroidectomy given her family history of MEN-1 [1, 10-12]. Both patients had recurrent PHPT following initial surgical intervention, highlighting the importance of long-term monitoring given higher risk of recurrence in those with, compared to those without, MEN-1 syndrome [10, 12].

Pituitary adenomas were initially asymptomatic for both patients and highlight the importance of pituitary screening in patients with MEN-1. Pituitary adenomas are the least common of the classical MEN-1 triad, with a lifetime prevalence of ∼50% in MEN-1 [1]. Suggested screening/monitoring includes assessment of prolactin, IGF-1, and pituitary MRI at the time of diagnosis with repeat biochemical testing annually and pituitary MRI every 3 to 5 years [1, 10]. Treatment of pituitary adenomas in patients with MEN-1 is the same as sporadic pituitary adenomas [1, 10]. Treatment includes surveillance, medical management (eg, dopamine agonists for prolactinoma), transsphenoidal surgery, and radiation therapy [1, 4]. Both patients' pituitary adenomas were treated as per guidelines [10, 12, 13].

Duodenopancreatic NETs are seen in >80% of patients with MEN-1 by age 80 years [1]. Patient X developed a gastrinoma, the most common functioning-NET in MEN-1 [14]. Developing dyspepsia and diarrhea highlights the importance of considering MEN-1 in those with other classical MEN-1 triad tumors. Suggested screening/monitoring includes pancreatic imaging, fasting glucose, and gastrin levels at the time of diagnosis with repeat biochemical testing annually and imaging every 2 to 3 years thereafter [1, 10]. More recently, screening with chromogranin A, pancreatic polypeptide, or glucagon has been questioned [1]. Treatment varies based on the type and staging of the NET. For instance, surgical resection is standard of care for insulinomas, whereas nonfunctioning NETs or gastrinomas may be treated medically vs surgically depending on size, progression of tumor, local spread, symptoms, surgical risks, and comorbidities [1, 4]. Patient X's gastrinoma was treated with proton pump inhibitor initially, but she required a pancreatectomy because of disease progression per guideline recommendations, which are less clear given paucity of research [1, 10, 12].

Nonclassical triad MEN-1 tumors include angiofibromas, lipomas, collagenomas, and meningiomas as well as thymic, thyroid, bronchopulmonary, adrenal, and breast tumors [1, 10]. The only nonclassical tumor for our patients was a

thymoma, revealed from patient X's MEN-1 guideline-based prophylactic thymectomy during subtotal parathyroidectomy [1, 10, 12]. The majority of thymic tumors in MEN-1 are carcinoids, found in 1% to 5% of patients. Thymomas, however, are extremely rare, with a recent systematic review finding only 11 cases of thymomas reported in patients with MEN-1 [15, 16]. Screening/monitoring for these other tumors after diagnosis includes: (1) thoracic imaging (for thymic and bronchopulmonary tumors) every 1 to 2 years; (2) abdominal imaging (for adrenal tumors) every 3 years; and (3) breast cancer screening starting at age 40 years [1, 10]. Treatment varies based on the tumor and is discussed elsewhere [1, 10].

Patient Y, but not patient X, had a family history of MEN-1 syndrome, hinting at the possibility of inherited vs de novo pathogenic variants, respectively [10]. De novo pathogenic variants are less common (8%-14%) in MEN-1 compared with inherited ones (86%-92%) [10]. Patient Y had negative genetic testing initially, but a positive test on repeat testing. Without access to the previous genetic testing, we hypothesize it is because of availability of NGS for repeat testing that was not likely used earlier. Briefly, our clinically validated NGS-target panel tests for the *MEN-1* and *CDKN1B* genes, associated with MEN-1 and -4, respectively. The panel includes all exonic regions and 20 base pairs of flanking intronic regions, using the SeqCap EZ Choice Library system (Roche NimbleGen) and the Illumina MiSeq sequencer, and can detect single nucleotide variants, indels, and copy number variants [17]. Although some earlier genetic testing methodologies, such as Sanger sequencing, did not include the analysis of intronic regions, this NGS panel successfully identified the pathogenic intronic variant for patient Y. Patients with a clinical diagnosis of MEN-1 deemed pathogenic variant-negative with older genetic testing methods should be offered repeat genetic testing with NGS panels or whole-genome sequencing, given advancements in genetic testing and its implications on patients and their family members.

Although difficult to demonstrate, reports have shown that there may be correlations between MEN-1 genotypes and phenotypes [18]. The rare pathogenic variant (*MEN1:c.784-9G > A*) has not been shown to have any specific genotype-phenotype correlation [5]. The genotype-phenotype correlations for the novel pathogenic variant (*MEN1:c.1192delC, p.(Gln398Argfs*47)*) will be determined as more patients are discovered.

Further research to increase our knowledge of pathogenic MEN-1 variants is needed and has several benefits. First, confirmation of the diagnosis impacts treatment. For example, a subtotal parathyroidectomy with concomitant prophylactic thymectomy is recommended for the management of PHPT in patients with MEN-1 but not usually for other patients with PHPT. Second, patients testing positive for pathogenic variants in MEN-1 gene (~70%-95% of all patients with MEN-1) have worse outcomes compared to those with a clinical diagnosis with negative genetic testing; including earlier onset, more aggressive disease, and increased likelihood of developing a third tumor [1, 12, 19].Third, genetic screening for family members of patients with pathogenic variant-positive MEN-1, if positive, can lead to early diagnosis, treatment, and improved outcomes [1, 10, 12]. Finally, as genetic testing becomes more cost effective and more pathogenic MEN-1 variants are discovered, routine genetic screening of patients with only 1 of the classical MEN-1 tumors may become more common practice Currently, genetic testing is recommended only in patients with 2 or more classical MEN-1 tumors, first-degree relatives of those with MEN-1 syndrome, and in patients with only 1 classical MEN-1 tumor with 1 of the following: (1) PHPT diagnosed before age 30, (2) multigland parathyroid disease, (3) gastrinoma, (4) multiple pancreatic NET, (5) family history of MEN-1, or (6) 2 or more MEN-1-associated tumors that are not part of the classical triad for diagnosis [1, 10].

In conclusion, we report patients with novel and rare MEN-1 pathogenic variants, as well as just the twelfth patient reported to have a rare thymoma in MEN-1. Further research identifying new pathogenic MEN-1 variants will provide a larger genetic pool for the screening and diagnosis of MEN-1, which is valuable information that could improve outcomes for these patients.

Learning Points

- For patients presenting with 1 of the classical MEN-1-associated tumors, MEN-1 syndrome should be considered based on clinical suspicion (eg, developing Zollinger-Ellison syndrome in patient X with an existing parathyroid adenoma).
- Given the high risk of recurrence and new tumor development, it is important to perform clinical, biochemical, and radiographic surveillance in patients with MEN-1.
- Repeating genetic testing with NGS for patients with clinical MEN-1 who have previously tested negative for pathogenic variants (with older testing) may be beneficial.

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Contributors

J.C.L. provided primary authorship/revisions of the manuscript. H.R. and T.S.K. were involved in diagnosis, patient care, and authorship/revisions of the manuscript. K.K.C., S.V.U., and L.C.S. were involved with authorship/revisions of the manuscript. All authors reviewed and approved the final draft.

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Informed Patient Consent for Publication

Signed informed consent was obtained directly from the two patients.

Data Availability Statement

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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