

Case Report

A Possible New Multiple Endocrine Neoplasia Mutation in a Patient with a Prototypic Multiple Endocrine Neoplasia Presentation

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Key Words

Multiple endocrine neoplasia · Mutation and tumor · Hyperparathyroidism · Acromegaly

Abstract

Background: Multiple endocrine neoplasia (MEN) type 1 syndrome is an uncommon inherited disorder characterized by the occurrence of tumors involving two or more endocrine glands. These tumors include pheochromocytoma, adrenal cortical and neuroendocrine tumors including (bronchopulmonary, thymic, gastric), lipomas, angiofibromas, collagenomas, and meningiomas. MEN-4 is very rare and has been characterized by the occurrence of parathyroid and anterior pituitary tumors in association with tumors of the adrenals, kidneys, and reproductive organs. **Summary:** We report the case of a 40-year-old male without significant family history of endocrine disease who was found to have primary hyperparathyroidism, a pituitary tumor causing acromegaly, thyroid cancer, renal cell carcinoma, and pancreatic cysts. We posit that this represents a new version of MEN-4. While renal tumors (angiomyolipoma) have been reported as part of the MEN-4 phenotype, to our knowledge, this is the first case reported of the association of MEN-1 and/or MEN-4 phenotype with this unique constellation of tumors, including renal cell carcinoma. Interestingly, this patient tested negative (DNA sequencing/deletion) for MEN-1 (menin), MEN-4 (CDKN1B) and VHL genes. **Key Message:** Thus, while this case has clinical characteristics consistent with either MEN-1 or MEN-4, it may represent a unique genetic variant.

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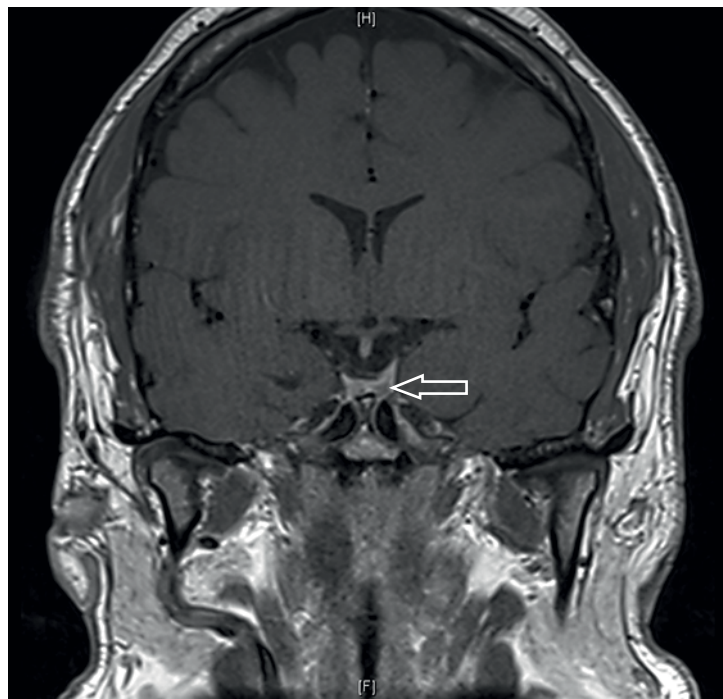


Fig. 1. Sagittal MRI of the pituitary showing an inhomogeneity consistent with microadenoma and measuring 6×3.5 mm.



Fig. 2. MRI of the abdomen delineating a mass lesion on the left renal inferior pole, which proved to be an RCC.

Case Presentation

A 40-year-old male with chronic diarrhea and elevated serum calcium and parathyroid hormone levels was referred to the endocrinology unit for evaluation of a possible primary hyperparathyroidism. He had a neck ultrasound for localization of a possible parathyroid adenoma, which showed a complex right mid thyroid lobe nodule that measured $18.7 \times 19.7 \times 19$ mm and a left inferior thyroid lobe nodule of $9 \times 7.5 \times 6.7$ mm. The patient's physical appearance was suggestive of acromegaly (prominent jaw, lower lip, tongue and deep voice). Initial workup revealed an elevated insulin-like growth factor (IGF-1) of 604 ng/ml with a confirmatory glucose suppression test [the growth hormone (GH) levels remained elevated]. Magnetic resonance imaging (MRI) showed a pituitary microadenoma measuring 6.0×3.5 mm (fig. 1). Prolactin and adrenocorticosteroid levels were normal, but testosterone levels were low without appropriately elevated luteinizing (LH) or follicle-stimulating hormone (FSH) levels. The history of diarrhea, primary hyperparathyroidism and possible acromegaly suggested the possibility of a multiple endocrine neoplasia (MEN) type 1 syndrome. However, serum gastrin, vasoactive intestinal polypeptide, glucagon, and chromogranin were all within the

Buzzola et al.: A Possible New Multiple Endocrine Neoplasia Mutation in a Patient with a Prototypic Multiple Endocrine Neoplasia Presentation

Table 1. MEN-1 and -2 syndromes and their characteristic tumors

MEN-1 11q13	Parathyroid adenoma		Parathyroid adenoma	MEN-4 CDKN1B	
	Enteropancreatic tumor	Gastrinoma Insulinoma Nonfunctioning PPoma Glucagonoma VIPoma	Pituitary adenomas		
		Pituitary tumor	Prolactinoma Somatotropinoma Corticotropinoma Nonfunctioning		Reproduction organ tumors
		Associated tumors	Adrenal cortical Pheochromocytoma Bronchopulmonary NET Thymic NET Gastric NET Lipomas Angiofibromas Collagenomas Meningiomas		Adrenal renal tumors

normal range. MRI of the abdomen was performed as part of the workup for MEN, and revealed multiple small pancreatic cysts and a left renal mass (fig. 2). Endoscopic ultrasound confirmed simple multiple pancreatic cysts (which were not biopsied); colonoscopy revealed small benign polyps, which were endoscopically excised. The patient underwent a partial left nephrectomy yielding a clear cell renal carcinoma confined to the kidney, measuring 3.9 cm in the greatest dimension and classified as Fuhrman nuclear grade 2.

Subsequently, the patient underwent resection of 3.5 parathyroid glands at the time of near-total thyroidectomy for the cytologically suspicious nodule. Pathology confirmed a single focus 1.5-cm papillary thyroid carcinoma and hyperplastic parathyroid glands. Postoperatively, hypercalcemia persisted and he was started on cinacalcet therapy; levothyroxine was initiated for treatment of postoperative hypothyroidism. Transsphenoidal resection of the pituitary tumor yielded a microadenoma which immunostained positive for chromogranin. However, there was no staining for prolactin, GH, adrenocorticotrophic hormone, FSH, LH, thyroid-stimulating hormone or alpha subunits. Therefore, this would typically represent a null-cell adenoma. Despite the negative staining for GH, the serum IGF-1 levels remained elevated postoperatively.

Results

Due to the clinical features including primary hyperparathyroidism, a pituitary adenoma, thyroid cancer, renal cell carcinoma (RCC), and pancreatic cysts, we postulated that this represents a new variant of MEN-1 or -4. The MEN-1 syndrome is an uncommon inherited disorder characterized by the occurrence of tumors involving two or more endocrine glands (table 1) [1, 2]. These tumors include pheochromocytoma, adrenal cortical and neuroendocrine tumors including (bronchopulmonary, thymic, and gastric) lipomas, angiofibromas, collagenomas, and meningiomas. MEN-4 is very rare and has been characterized by the occurrence of parathyroid and anterior pituitary tumors in association with tumors of the adrenals, kidneys, and reproductive organs (table 2) [1–5].

Table 2. Germline changes in the *CDKN1B* gene and the clinical characteristics of the mutation-positive patients (with permission from Lee and Pellegata [4])

<i>CDKN1B</i> mutation	Parathyroid adenoma	Pituitary tumor	Other manifestations
<i>MEN-4 (MEN-1-like)</i>			
ATG-32-29del	PHPT		gastric carcinoid tumor
ATG-7G>C	PHPT		bilateral adrenal mass nonfunctioning uterine fibroid
K25fs	PHPT	ACTH-secreting	
A55T	PHPT (hepatic metastasis)		Zollinger-Ellison syndrome gastrinoma
P69L	PHPT	nonfunctioning	bronchial carcinoids, papillary thyroid carcinoma, multiple lung metastases
W76X	PHPT	GH-secreting (acromegaly)	
P95S	PHPT (2 parathyroid tumors)		Zollinger-Ellison syndrome mass in duodenum and tail of pancreas
Stop>Q	PHPT (3 parathyroid tumors)		
<i>MEN-4 (others)</i>			
G9R	PHPT		
K96Q		PRL-secreting	breast tumor
I119T		GH-secreting	
P133T	PHPT (1 parathyroid tumor)		

Mutations are numbered with reference to the cDNA sequence AY890407 (GenBank). ACTH = Adrenocorticotrophic hormone; GH = growth hormone; PHPT = primary hyperparathyroidism; PRL = prolactin.

Discussion

The existence of different phenotypes among patients with the MEN-1 and -4 syndrome, even between members of the same affected family, is well known. However, the presentation of endocrine and malignant tumors as well as the postsurgical persistence of hormonal abnormalities in this patient without family history makes the clinical diagnosis of MEN likely. To our knowledge, this is the first described case with concurrent primary hyperparathyroidism, papillary thyroid cancer, acromegaly, and RCC. It is quite possible that this case represents a unique variant of a MEN gene mutation that has not been currently identified.

A recognized MEN-1 mutation is identifiable in approximately 70% of familial cases of multiple endocrine tumors [6], but among patients with the MEN-1 phenotype, 10–30% may not have an identifiable mutation of the MEN-1 gene [6]. Two studies reported that 5–10% of MEN-1 kindred have the occurrence of phenocopies – a term that refers to the development of disease manifestations linked with a specific genotype – but instead are attributable to another cause [7]. In one instance, a patient with two MEN-1 associated tumors did not have a ‘classic’ *menin* mutation, but was found to have a mutation of the gene encoding parafibromin, previously linked to the hyperparathyroidism-jaw tumor syndrome [7]. The apparent lack of a genotype/phenotype correlation as well as the wide diversity of mutations in the 1,830-bp coding region of the MEN-1 gene makes mutational analysis for definitive diagnosis of the MEN-1 syndrome more difficult [3]. Patients with truncating mutations in the N- or C-terminal region (exons 2, 9, or 10) of the MEN-1 gene have a significantly higher rate of

malignant tumors (55 vs. 10%; $p < 0.05$) than those with other mutations [8]. However, in two prospective studies [8, 9], none of the patients with germline mutation for MEN-1 developed RCC or thyroid cancer, as seen in the current case.

Renal manifestations of MEN are rare except for renal stones associated with hyperparathyroidism as seen in MEN-1 and -2. Renal tumors are very rare with MEN. Approximately 5–8% of RCC is hereditary [10]. Very few cases of renal cell tumors associated with MEN have been reported in the literature. The first case of hypernephroma (RCC) associated with MEN-1 was reported in 1986 by Dekker et al. [11]. In 1990, there was a report of an MRI of a patient with MEN-1 syndrome showing adrenal enlargement due to a nonfunctioning adenoma and an RCC next to a simple renal cortical cyst [12]. An unusual association of bilateral renal tumors and Wermer's syndrome (MEN-1) was described by Jeddi et al. [13] in 1996. In 2014, Cavalli et al. [14] reported a sarcomatoid carcinoma of the kidney in a patient with MEN-1. Therefore, our patient represents a very rare and unique case of MEN.

The presence of a renal tumor is consistent with the MEN-4 phenotype even though the patient did not have an identifiable mutation of the MEN-4 gene. The fact that no mutation was detected in the MEN-1 gene could be caused by mutations lying outside the region tested, large deletions involving complete exons (which can be found in up to 33% of affected patients), or single nucleotide polymorphisms of yet undetermined significance. The possibility of other, yet unrecognized genes producing the MEN-1 or MEN-4 phenotype cannot be entirely excluded [3, 5, 6]. The clinical course of the rarer MEN-4 patients is not well characterized, but it is likely that they will also have a similar course as persons with MEN-1.

However, on genetic testing no mutation was detected in the MEN-1 gene by Athena Diagnostic. Further, genotyping was negative for deletion or duplication variants within the genomic region encompassing the MEN-1, VHL and CDKN1B genes, by prevention genetics analysis. The patient also tested negative for sequencing and deletion for the MEN-4 gene (CDKN1B). Further, full exome sequencing, bioinformatics, variant filtering, as well as gene and variant medical review by ExomeNext did not reveal any somatic or mitochondrial alterations.

Conclusion

The currently reported case likely represents a unique and novel variant of MEN-1 or -4. The persistent primary hyperparathyroidism and hypercalcemia after surgery is being managed with cinacalcet. The patient has been started on Pegvisomant (GH receptor blocker) for treatment of persistently elevated IGF-1 levels after transphenoidal resection of a null-cell pituitary adenoma. In addition to the close follow-up of this patient, all family members are undergoing genetic testing for MEN-1 and -4. Family members with genetic abnormalities consistent with MEN-1 or -4 will undergo screening for tumor detection and early treatment [1]. Indeed, mutational analysis can identify family members who do not have the MEN mutation and can therefore mitigate the burden of screening and anxiety regarding potential disease [7].

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