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Case Report

MEN1 in a Patient With Nonsyndromic Familial Nonmedullary Thyroid Carcinoma

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Abstract

Clinical syndromes involving multiple endocrine glands have been well recognized for over a century. Multiple reports describing hereditary multiple endocrine neoplasia (MEN) syndromes involving pituitary, parathyroid, and pancreatic neuroendocrine tumors have been published. Differentiated (nonmedullary) thyroid cancer can also present as a hereditary syndrome with or without a specific genetic predisposition. We report the case of a man with nonsyndromic familial nonmedullary thyroid carcinoma, a pituitary adenoma, hyperparathyroidism, an adrenal adenoma, and pancreatic adenocarcinoma. Genetic testing did not reveal mutations in the commonly reported genes associated with MEN syndromes. MEN1 is characterized by endocrine neoplasia in at least 2 of the following glands: pituitary, parathyroid, and the gastro-entero-pancreatic (GEP) tract. Co-occurrence of MEN1 with familial nonmedullary thyroid carcinoma, however, has not been reported in the medical literature. This unique case of MEN1 co-existing in a patient with nonsyndromic familial thyroid carcinoma was not associated with any common MEN syndrome germline mutations.

Key Words: MEN1, acromegaly, familial thyroid cancer, Cushing syndrome

Abbreviations: GEP, gastro-entero-pancreatic; GH, growth hormone; IGF-1, insulin-like growth factor 1; MEN, multiple endocrine neoplasia; Tg, thyroglobulin; TSH, thyrotropin (thyroid-stimulating hormone).

Clinical syndromes involving multiple endocrine glands were recognized as early as 1900 by Erdheim. In 1953, Underdahl and colleagues from the Mayo Clinic reported a series of patients with tumors of the pituitary, the parathyroid glands, and the pancreatic islets [1]. Multiple reports over the next 10 years documented that many of these syndromes were hereditary [2]. The term *multiple endocrine neoplasia* (MEN) was suggested by Steiner in 1968. MEN1 is a syndrome characterized by endocrine neoplasia in at least 2 of the following: pituitary, parathyroid, and the gastro-entero-pancreatic (GEP) tract. Additional syndromes that may be related to the MEN syndromes have been identified as well [3]. We report the case of a man with familial nonmedullary thyroid carcinoma, a pancreatic adenocarcinoma, and MEN1 involving neoplasia in 3 additional endocrine glands.

Case Presentation

A 63-year-old man was referred to our medical center for evaluation of jaundice secondary to a pancreatic mass. The patient initially presented with painless jaundice. He was then sent for imaging and a laboratory workup, which revealed a pancreatic mass obstructing the biliary tree and an elevated total bilirubin of 1.3 mg/dL (22 µmol/L). He had a stent placed endoscopically to relieve the obstruction and was subsequently sent to our medical center for further evaluation. His history was significant for papillary thyroid carcinoma resected at age 26 followed by radioiodine remnant ablation. He subsequently developed acromegaly at age 51 (insulin-like growth factor 1 [IGF-1] = 776 ng/mL [101 nmol/L]; normal range: 46-219 ng/mL) and had trans-sphenoidal resection of a 13 mm adenoma which stained heavily for immunoreactive growth hormone (GH). From age 53 to 63 he was on various somatostatin analogs and/or pegvisomant for excessive GH production. These were discontinued 2 months prior to his hospitalization. Additionally, he was diagnosed with type 2 diabetes mellitus at 55 years of age. He also had a history of recurrent kidney stones.

His family history was significant for multiple family members with endocrine diseases. His mother had a thyroidectomy for differentiated thyroid carcinoma; one sister had a thyroidectomy for papillary thyroid carcinoma; another sister had parathyroid carcinoma; and a nephew had papillary thyroid cancer. His father had a tumor (uncertain histopathology) blocking the biliary tree with jaundice, and his daughter had a prolactinoma (Fig. 1).

Physical examination showed central obesity, enlarged supraclavicular fat pads, an interscapular "buffalo" hump, and nonpigmented axillary and abdominal striae. There were no lentigines or hyperpigmented lesions. He had no facial features suggestive of acromegaly and no masses or enlarged lymph nodes in the thyroid bed or cervical regions. Magnetic resonance imaging to characterize his pancreatic mass also revealed a 1.6-cm right adrenal mass.

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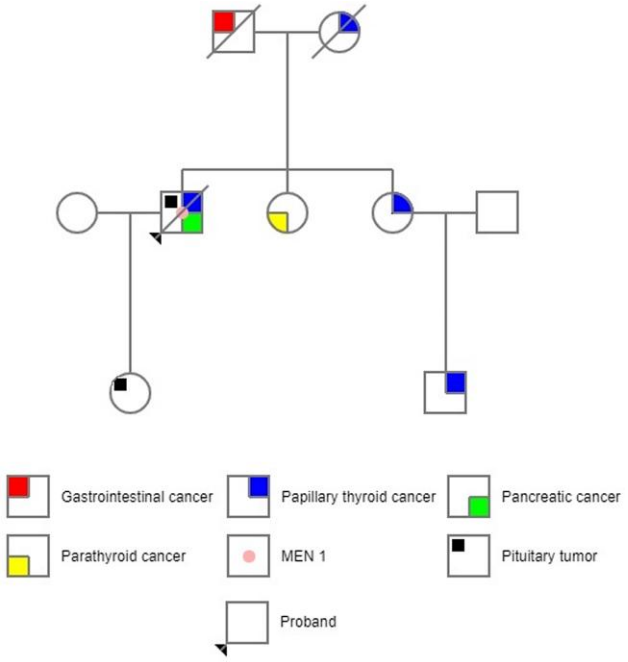

Figure 1. Available family pedigree for the patient (proband) who had MEN1 and familial nonmedullary thyroid carcinoma. Clinical entities are shown by color coding in the figure. Circles = females. Squares = males. Straight lines at 45 degrees through circles or boxes indicate family members who have expired.

Endocrinology was consulted for his uncontrolled diabetes mellitus, history of thyroid and pituitary tumors, hyperparathyroidism, concern for Cushing syndrome, and suspicion for MEN. He had a 24-hour urine free cortisol that was 120 mcg (324 nmol [normal range, 10-100 mcg/24 hours]) and an elevated 11 PM salivary cortisol at 2.9 ng/mL (8 nmol/L). Following a 1-mg overnight dexamethasone suppression test, his 8 AM cortisol remained at 11 mcg/dL (303 nmol/L) and his ACTH was suppressed at 2.5 pg/mL (0.55 pmol/L). These findings, along with the right adrenal mass seen on imaging, supported the diagnosis of adrenal Cushing syndrome. A neck ultrasound did not reveal residual thyroid tissue or any other abnormal masses. He had an elevated corrected calcium level of 11.6 mg/dL (2.9 mmol/L), a decreased phosphorus level of 2.2 mg/dL (6.8 mmol/L) and an elevated parathyroid hormone (PTH) of 135 pg/mL (14.3 pmol/L) upon admission. A SestaMIBI scan showed no evidence of a parathyroid adenoma. Despite this, he still had laboratory evidence of hyperparathyroidism as well as a history of recurrent kidney stones. Thus, 2 previously undiagnosed types of endocrine neoplasia were discovered upon this admission.

Further endocrine workup revealed normal levels of GH, IGF-1, follicle stimulating hormone, luteinizing hormone, testosterone, and prolactin. His thyrotropin (thyroid-stimulating hormone; TSH) was 2.8 mIU/L while on levothyroxine therapy; serum thyroglobulin (Tg) was detectable at 28.9 ng/mL with negative anti-Tg antibody. Serum calcitonin and carcinoembryonic antigen levels were within the normal reference ranges. Gastrin and glucagon levels were also normal. Screening for carcinoid tumor showed normal range levels of serotonin, urine 5-hydroxyindoleacetic acid, and chromogranin A. Screening tests for pheochromocytoma were also negative. Laboratory results are summarized in Table 1.

Table 1. Serum laboratory evaluation & tumor markers

Analyte	Result	Normal ranges
Growth hormone	1.87 ng/mL	0.05-3.00 ng/mL
IGF-1	145 ng/mL	46-219 ng/mL
Follicle stimulating hormone	7.2 mIU/mL	1.5-12.4 mIU/mL
Luteinizing hormone	9.2 mIU/mL	1.7-8.6 mIU/mL
Testosterone	311 ng/dL	300-720 ng/dL
Prolactin	14 ng/mL	4-15 ng/mL
TSH	2.8 mIU/L	0.27-4.20 mIU/L
Thyroglobulin	28.9 ng/mL	1.3-31.8 ng/mL
Thyroglobulin auto-antibody	<0.9 IU/mL	0.0-4.0 IU/mL
Calcitonin	<2.0 pg/mL	0.0-7.5 pg/mL
Serotonin	140 ng/mL	50-220 ng/mL
Chromogranin A	45 ng/mL	0-103 ng/mL
Urine 5-HIAA	3 mg/gCR	0-14 mg/gCR
Gastrin	15 pg/mL	0-100 pg/mL
Dopamine	<20 pg/mL	0-20 pg/mL
Epinephrine	25 pg/mL	10-200 pg/mL
Norepinephrine	680 pg/mL	80-520 pg/mL
Metanephrine	<10 nmol/L	0.00-0.49 nmol/L
Normetanephrine	0.58 nmol/L	0.00-0.89 nmol/L
CEA	1.4 ng/mL	0.0-3.8 ng/mL
CA 19-9	48 U/mL	0-35 U/mL
Cortisol after DST	11 mcg/dL	6-18 mcg/dL
ACTH after DST	2.5 pg/mL	6-18 pg/mL
Calcium (corrected)	11.6 mg/dL	8.8-10.2 mg/dL
Parathyroid hormone	135 pg/mL	15-65 pg/mL
Phosphorus	2.2 mg/dL	2.4-4.5 mg/dL

Abbreviations: 5-HIAA, 5-hydroxyindoleacetic acid; ACTH, adrenocorticotropic hormone; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; DST, 1-mg dexamethasone overnight suppression test; IGF-1, insulin-like growth factor 1; TSH, thyrotropin (thyroid-stimulating hormone).

We performed genetic screening due to his significant family history of thyroid cancer and MEN. We tested his white blood cells for germline mutations in *APC, CHEK2, DICER1, MEN1, PRKAR1A, PTEN, RET, SDHB, SDHD, TP53*, and *WRN*. None of the common mutations were present in any of these genes.

Genetic testing was performed using a commercially available Invitae genetic panel. Identification and confirmation as needed, of significant known mutations and their locations, was carried out using methods established by Invitae [4].

A biopsy of the pancreatic lesion revealed adenocarcinoma. The patient then underwent a Whipple procedure, with resolution of biliary obstruction and right adrenalectomy with resolution of hypercortisolemia. Genetic testing of the pancreas cancer revealed mutations in *TP53, KRAS*, and *ERCC2*. The patient expired within 1 year due to progressive pancreas cancer.

Discussion

Our patient had 2 of the 3 most common tumors associated with MEN1: a GH-secreting pituitary tumor and hyperparathyroidism. Like approximately 10% of MEN1 patients,

our patient had no clear mutation in the *MEN1* gene. Compared with MEN1 patients who have an *MEN1* mutation, genotype-negative MEN1 patients are typically older and usually have hyperparathyroidism and a pituitary tumor (most commonly somatotroph adenomas) but rarely develop a neuroendocrine GEP tumor [5]. Our patient had no evidence of a neuroendocrine tumor of the GEP tract. His gastrin and glucagon levels were normal, and he never had hypoglycemia or a watery diarrhea syndrome. He also had no clinical features to suggest Carney complex or Cowden syndrome. Carney complex patients, who often have mutations in the *PRKAR1A* gene, present with myxomas and tumors of the pituitary, adrenal, and thyroid glands. Cowden syndrome patients have multiple hamartomas, and may develop cancers of the thyroid, breast, or uterus associated with mutations in the *PTEN* tumor suppressor gene. Our patient had a sister with parathyroid carcinoma; however, he likewise had no features of hyperparathyroidism-jaw tumor syndrome or McCune-Albright syndrome. Children with McCune-Albright syndrome (associated with *GNAS1* gene mutations) often have polyostotic fibrous dysplasia and café-au-lait pigmentation and rarely may have acromegaly, thyroid nodules, and adrenal Cushing syndrome. There were no other known cases of hyperparathyroidism in his family.

The patient's family history meets the definition of familial nonmedullary thyroid carcinoma [6]. Medullary thyroid carcinoma was ruled out based on histopathology reports, and normal serum calcitonin and carcinoembryonic antigen levels. His measurable serum Tg could represent regrowth of a thyroid remnant 37 years after thyroidectomy without TSH suppression. His neck ultrasound did not reveal any thyroid bed masses or nodules and there was no lymphadenopathy. Of course, the measurable serum Tg could also be a result of occult thyroid cancer metastases, which were not detected by the multiple imaging studies which he underwent.

Acromegaly can be associated with other benign and malignant tumors. Although many patients with acromegaly have goiters and thyroid carcinoma, there is no well-described association between acromegaly and familial nonmedullary thyroid carcinoma. Acromegaly is also associated with functional and morphological abnormalities in the adrenal glands. In 2015, Ishikawa and colleagues reported a case with many features similar to our case, most notably that the patient had both acromegaly and adrenal Cushing syndrome [7]. Approximately 30% to 40% of MEN1 patients have functional and nonfunctional adrenal abnormalities.

The genetic basis of nonsyndromic familial nonmedullary thyroid carcinoma (NSFNMTC), which our patient fits, has been a topic of considerable interest in the past 5 years. The clinical features and secondary neoplasia in probands and family members have been described [8]. No cases of coexistence with MEN syndromes have been reported to data. However, the incidence of pancreas cancer, which occurred in our patient, seems higher in familial nonmedullary cases than in those with sporadic differentiated thyroid carcinoma [9]. Multiple susceptibility genes for nonsyndromic familial nonmedullary thyroid carcinoma have been identified by whole-exome sequencing in many unrelated families from China, Europe, and Japan [10].

Significant limitations in reporting this case include the inability to obtain pathological tissue from his thyroidectomy (performed 37 years prior) for genetic testing; and from his pituitary tumor which was removed 12 years prior. Reports of his family's history of endocrine neoplasia also often lack primary pathological evidence, being derived from interviewing multiple family members and old hospital records. Regarding the genetic testing, Invitae's deletion/duplication analysis determines copy number at a single exon resolution at virtually all targeted exons. However, in rare situations, single exon copy number events may not be analyzed due to inherent sequence properties or isolated reduction in data quality. Certain types of variants, such as structural rearrangements (eg, inversions, gene conversion events, translocations, etc.) or variants embedded in sequence with complex architecture (eg, short tandem repeats or segmental duplications), may not be detected.

In summary, genetic testing and clinical features in our MEN1 patient did not suggest a known syndrome (eg, Carney complex, Cowden syndrome, hyperparathyroidism-jaw tumor syndrome, or McCune-Albright syndrome). There are sporadic case reports in the medical literature of MEN1 with some features like our patient, but none with familial nonmedullary thyroid carcinoma. It is possible that features of MEN1 and nonsyndromic familial nonmedullary thyroid cancer in 1 individual occurred by chance alone; however, the presence of a single hereditary genetic predisposition in this family is also possible. Such a genetic basis may become evident if future similar cases are discovered.

Learning Points

- Take a careful family history to rule out hereditary endocrinopathies
- Review the features of genetic syndromes in familial endocrine cases
- Investigate the possibility of MEN in all patients with acromegaly
- Consider the possibility of functional adrenal tumors in MEN patients

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Author Contributions

All authors were involved in the care of this patient. All authors contributed to the collection of data and construction of the manuscript. All authors approved the final draft of the case report.

Disclosures

None of the authors have any conflicts of interest to declare.

Data Availability

The data that support the findings of this study are available on request from the corresponding author, RJR.

Consent Statement

Retrospective deidentified data review and reporting was approved by our Institutional Review Board.

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