Three Endocrine Neoplasms: 
An Unusual Combination of Pheochromocytoma, 
Pituitary Adenoma, and Papillary Thyroid Carcinoma

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Background: Three endocrine neoplasms—bilateral pheochromocytomas, somatotrophic pituitary adenoma inducing acromegaly, and papillary carcinoma of the thyroid—occurred concurrently in a patient. A genetic mutation was hypothesized. Possible previously described genetic mutations were explored.

Methods: Clinical assessments, laboratory data, images of tumors, histopathology, and immunohistochemistry of excised tissues documented the three neoplasms. Clinical assessment of the patient, family history, and a review of the literature sought a familial basis for the disorders.

Results: The methods confirmed the presence of three endocrine neoplasms. Each neoplasm was surgically excised and histologically verified. Surgical and 131I treatments reduced the papillary carcinoma, but eventually this tumor progressed to a lethal degree. History, including that of nine siblings, uncovered no familial neoplasms. No similar case was found in the literature, but possible associations with germline mutations were considered.

Conclusions: The concurrent development of pheochromocytomas, pituitary somatotrophic adenoma, and papillary thyroid carcinoma appears to be unique. Nevertheless, such tumors, particularly bilateral pheochromocytomas, strongly suggest a de novo germline mutation in a gene not previously associated with multiple endocrine neoplasia syndromes.

Introduction

Certain combinations of endocrine neoplasms, tumors that are generally functioning, have been shown to be familial. Multiple endocrine neoplasia type 1 (MEN-1), first described in 1954 (1), included hyperparathyroidism arising from multiple parathyroid adenomas, pituitary tumors of various types including prolactinomas and somatotropic adenomas, and neuroendocrine tumors arising in the pancreas including gastrinomas and insulinomas. Mutations of the MENIN gene were determined to be the source of the clinical manifestations of MEN-1 (2).

The features of MEN-2, medullary carcinoma of the thyroid (MTC), pheochromocytomas, and hyperparathyroidism derived from parathyroid gland hyperplasia, were first described in 1961 (3), but it soon became clear that a subset of patients exhibited MTC, pheochromocytomas, and pronounced facial features from ganglioneuromas, but not hyperparathyroidism (4). The former combination of familial tumors was designated MEN-2A and the latter, MEN-2B.

Germline mutations of the RET protooncogene underlie these multiple endocrine disorders (5). Variations in the specific mutations of oncogenes have generated diverse phenotypic appearances in affected individuals. However, none have exhibited the combination of the three endocrine neoplasias—bilateral pheochromocytomas, somatotrophic pituitary adenoma, and papillary carcinoma of the thyroid—manifested in our patient.

Case Presentation

When initially evaluated at the University of Michigan Health System in December 1996, the patient was a 29-year-old male carpenter. For about 2 years, he was afflicted by headaches and diaphoresis, both day and night. His elevated blood pressure was unmitigated by medications, including atenolol 25 mg/day. Yet, he continued to work regularly. In November 1996, a search for a cause of secondary hypertension included a CT that portrayed bilateral adrenal enlargements attributable to pheochromocytomas (Fig. 1A, B). He
had no visual symptoms. Libido and erectile function were reported to be normal.

He weighed 118 kg and stood 188 cm. Blood pressure was 170/116 and heart rate was 72 beats/min. Soft tissue swelling was prominent in his large hands and feet. His shoe size was 13 but was recently unchanged. Thickened skin was damp from perspiration. A number of small skin lesions were observed; one appeared to be a lipoma, but none were characteristic of a myxoma or a neurofibroma. Readily apparent were a large brow and an overbite in a prominent jaw. No abnormality was detected in either his visual fields or extraocular muscle movements. His tongue was expansive. Palpable enlargement of his left thyroid lobe was accompanied by two easily discerned lymph nodes in his left neck.

He was never married and had no children. Nine siblings were described: six sisters were 2–19 years older, and three brothers were 4–18 years older. None had developed the stigmata observed in the patient. Although one brother was said to be large, a family picture showed none of the siblings to be as tall as the patient. A sister died at age 45 years of a “heart problem.” The eldest sister had been diagnosed with heart disease. His father developed Hodgkin’s disease and prostate cancer; he died at age 72. His mother died of metastatic uterine cancer at age 69. Maternal and paternal grandparents, and uncles and aunts lived to old ages. Nieces and nephews were reported to be in good health. The family heritage was Polish, German, and Bahamian.

Analysis of urine showed elevated excretion rates of epinephrine (87 µg/24 hours; normal ≤20), norepinephrine (1090 µg/24 hours; normal ≤100), and vanillylmandelic acid (26 mg/24 hours; normal ≤10). The serum level of insulin-like growth factor (IGF-1) was elevated at 1048 ng/mL (normal ≤380), but the growth hormone (GH) concentration was normal. Concentrations of serum calcium, phosphorus, and parathormone were normal. Serum prolactin (PRL) was subnormal (2.0 ng/mL; normal 3.0–23.0), as was serum testosterone (2.0 ng/mL; normal 2.5–9.5).

MRI images of the sella turcica depicted a pituitary adenoma without extension into the suprasellar space or the cavernous sinus (Fig. 2); the floor of the sella was not optimally visualized.

During phenoxybenzamine therapy on January 22, 1997, the pheochromocytomas were excised by bilateral total adrenalectomies. The surgeon reported that “there did not appear to be any normal adrenal gland remaining” on the right side. The pathologist recorded complete adrenalectomies; the right adrenal gland was the larger and contained two pheochromocytomas, while the left gland contained a pheochromocytoma as well as nodular medullary hyperplasia (Fig. 3A, B). Bilateral pheochromocytomas with medullary hyperplasia are typical of those observed in familial cases.
A prior ultrasound-guided fine needle biopsy enabled aspiration of papillary carcinoma cells from the left thyroid nodule, and, thus, under the same anesthesia, a total thyroidectomy removed a nodular left lobe and normal-appearing right lobe, isthmus, and pyramidal lobe. Multiple enlarged nodes were dissected free from the left neck. Histologic examinations displayed extensive primary papillary carcinoma that replaced most of the left lobe and also involved the right lobe. The majority of the tumor displayed a follicular growth pattern, but areas of papillary architecture were present (Fig. 4A, B). The tumor was invasive and extended into extrathyroidal tissues. Numerous cervical lymph nodes contained metastatic papillary carcinoma. Postoperative daily maintenance therapy consisted of hydrocortisone in divided doses, 15, 10, and 5 mg; fludrocortisone 0.1 mg; and thyroxine 0.2 mg.

In March 1997, thyroxine therapy was temporarily withheld, and serum thyrotropin (TSH) rose to 51 mU/mL (normal 0.3–5.0), and thyroglobulin was 74 ng/mL. He was treated with 7.4 GBq (200 mCi) of $^{131}$I, and 2 days later whole body scintiscans revealed 3 foci of radioactivity in his left neck, and smaller foci in his right neck (Fig. 5A). Over the subsequent years his thyroxine dose was changed in efforts, not always successful, to suppress his TSH below 0.1 mU/L.

On March 21, 1997, a transphenoidal resection appeared to have completely removed his pituitary adenoma. The tumor was strongly positive for chromogranin A and focally positive for growth hormone (Fig. 6). The postoperative value for IGF-1 was lower but still elevated at 506 ng/mL. Medications were unchanged at this discharge from the hospital. Re-evaluation on April 30, 1997, recorded his blood pressure as 150/80 sitting and standing, and he weighed 120 kg.

On April 1, 1998, a scintiscan displayed foci of radioactive iodine in his neck that were less intense than in 1997, but his hypothyroid-stimulated thyroglobulin concentration was higher (191 ng/mL). A second treatment with $^{131}$I, 7.4 GBq, was administered. Subsequent care was complicated by miscommunications between patient and physicians.
While hypothyroid in June 2005, imaging with single-photon tomography of diagnostic \(^{131}\)I combined with CT showed lung nodules and hilar nodes containing radioactivity. He received his third treatment, another 7.4 GBq of \(^{131}\)I; images of this radioactivity prominently displayed the metastases (Fig. 5B).

In September and December of 2005, he felt well and was working regularly. Under thyroxine suppression, his thyroglobulin had declined to 22 ng/mL. During the latter evaluation, a CT with contrast medium demonstrated a large hilar node, but no change in small lung metastases; also portrayed was adrenal gland tissue not dissimilar from the original normal gland (Fig. 7).

He returned on July 5, 2007, feeling well and working regularly. However, his prescriptions for hydrocortisone and fludrocortisone had expired 2 months previously, and he was without these medications thereafter. Thyroxine was continued at 0.2 mg/day. His weight was unchanged from the previous visit; his blood pressure was 137/85 and his heart rate, in beats/min, was 40 while sitting and 54 standing. There was no increased pigmentation of his skin or oral mucus membranes. Assessments of adrenal cortex function gave plasma levels of adrenocorticotropic hormone (ACTH), 36 pg/mL (normal 9–52), and cortisol 0.15 mg/L (normal 0.07–0.32). It was apparent that he harbored accessory adrenal cortical tissue, and hydrocortisone and fludrocortisone were not re-prescribed. While his TSH remained suppressed, his serum thyroglobulin had risen to 112 ng/mL. His IGF-1 level was then normal.

The patient was last seen on December 9, 2008. His weight was unchanged; his blood pressure was 127/67 and heart rate...
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Discussion

Our patient manifested a unique combination of endocrine
tumors: bilateral pheochromocytomas within a background of
medullary hyperplasia, pituitary adenoma secreting
growth hormone and associated with acromegaly and possi-
bly gigantism, and papillary carcinoma of the thyroid. No

No known syndrome or conceivable interrelationships among
the tumors explained the combination. The family history was

unrevealing. Nevertheless, a de novo germline mutation
seemed likely.

Patients with bilateral pheochromocytomas have familial
and/or germline mutations in 59 (6) and 76 (7) percent
of cases, respectively. The bilateral tumors are most frequently
observed in Von Hippel-Lindau (VHL) disease, MEN types
2A and 2B, and neurofibromatosis type 1 (NF1) (6,7). Bi-
lateral pheochromocytomas are occasionally seen in patients
with a succinate dehydrogenase D (SDHD) mutation (7), but
have not been described in those carrying the SDHB gene.

Unfortunately, blood was not obtained for genetic analyses
before his demise.

Thyroid

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have not been described in those carrying the SDHB gene.

Although mutations of SDHB and SDHD are frequently
associated with pheochromocytomas, paragangliomas are also
common; the latter manifestation was not present in our
patient.

The literature offers little evidence from which to construct
further associations. Major components of VHL disease—
hemangioblastoma of the central nervous system, renal cell
carcinoma, pancreatic cysts, retinal angioma, and epididymal
cysts (8)—were absent in our patient, but possibly the latter
two features could have been overlooked. In contrast to
pheochromocytomas developing in the MEN-2 syndromes,
the tumors arising as part of VHL disease usually do not
secrete epinephrine (9), a product which was excreted at an
elevated rate in our patient.

In addition, the almost invariable component of MEN-2,
MTC, was absent in our patient although a very small focus
could have been overlooked. A careful examination had
revealed none of the common lesions of NF1: neurofibro-
mas, café-au-lait spots, axillary freckling, and abnormality
of the iris (10).

Growth hormone–secreting pituitary adenomas have been
associated with MEN type 1 (11) and the mutation of aryl
hydrocarbon receptor–interacting protein gene (11–13).
A possible association within our patient appears in the report
demonstrating that the frequency of papillary carcinoma of
the thyroid was increased in patients with acromegaly. In 125
patients with acromegaly, 7 developed papillary carcinoma of
the thyroid, 2 of which were the follicular variant; a carcino-
genic role for IGF-1 was proposed (14).

Papillary carcinomas of the thyroid are components of the
syndrome of phosphatase and tensin PTEN homolog muta-
tion (15,16), Cowden syndrome, and familial adenomatous
polyposis (17). However, neither pheochromocytomas nor
pituitary adenomas were included in these familial associa-
tions. Nevertheless, familial non-MTCs of the papillary type
were found relatively frequently to metastasize to bilateral
cervical nodes and lead to a dire prognosis (18), as in our
patient.

Another combination has been reported; papillary carci-
noma of the thyroid was developed in a patient with bilateral
pheochromocytomas associated with a paraganglioma but
no mutation was found to indict VHL, MEN, SDHB, or
SDHD (19).

Accessory adrenal cortical tissue has been reported fol-
lowing adrenalectomies (20) and has sustained Cushing’s
syndrome in other patients (21,22). The frequency of this
anomaly is unknown, and, being nonneoplastic, the accessory
adrenal cortex maybe unrelated to the three endocrine neo-
plasms in our patient.

We could not find a link that would associate the three
endocrine tumors in our patient. Nonetheless, novel muta-
tions are frequently reported, for example, in the MEN-1 (23)
and MEN-2 (24) syndromes. It is reasonable to consider that
one or more of the germline mutations discussed previously
were at the base of our patient’s three endocrine disorders.
Unfortunately, blood was not obtained for genetic analyses
before his demise.

Addendum

Since acceptance of this manuscript by the editors of
Thyroid, the authors were made aware of a publication (25)
describing a 37-year-old man who exhibited multiple para-
gangliomas, bilateral pheochromocytomas and a growth
hormone–secreting pituitary adenoma associated with a novel
SDHD mutation; family members displayed paragangliomas.

Referenced was an article we had overlooked (26). This
study cited a previously described (27) 52-year-old woman
who manifested: a right adrenal pheochromocytoma that was
invasive, a chromophobe pituitary adenoma, and papillary
carcinoma of the thyroid.

Conclusion

We present a patient with three concurrent endocrine
neoplasms: bilateral pheochromocytomas, somatotrophic
adenoma inducing acromegaly, and metastatic papillary
carcinoma of the thyroid. Accessory adrenal cortical tissue
was also found but maybe unrelated. Family history uncov-
ered no relative with a comparable phenotype. Any one of a
number of mutations is possible, but unfortunately blood for
genetic analysis was not obtained before the patient died of
progressive thyroid carcinoma. As technology to perform
whole genome sequencing using paraffin-embedded tissue
advances, this case will be revisited in an attempt to identify a
novel gene mutation.

Acknowledgment

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Author Disclosure Statement

All authors declare that no competing financial interests exist.

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