



Somatostatin Receptor Scintigraphy and Thyroid Follicular Epithelial-Derived Cancers

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Introduction

The incidental detection of nonmedullary thyroid carcinoma by somatostatin receptor scintigraphy is a known phenomenon (1, 2). Additionally, *in vitro* studies have demonstrated both the presence of somatostatin receptors and the growth-regulatory effects of somatostatin on tumoral thyroid cells (3, 4). The full meaning of these findings and their implications for the treatment of thyroid cancer are not well defined. Herein we report a case of a 73-yr-old man with appendiceal carcinoid and Hürthle cell-type follicular carcinoma of the thyroid, found during routine surveillance with Indium-111-pentetreotide scintigraphy. This interesting case highlights the potential use of somatostatin receptor scintigraphy in the diagnosis and evaluation of follicular cell-derived thyroid cancer and invites speculation about implications for therapy.

Case Description

A 73-yr-old man with appendiceal carcinoid underwent routine surveillance for metastases with somatostatin receptor scintigraphy that revealed a focus of avid Indium-111 activity in the right side of the neck (Fig. 1). Both ultrasonography and CT scan of the neck revealed a 2.8 × 1.8 × 3.5-cm lesion in the right thyroid lobe of a multinodular goiter (Fig. 2). Ultrasound-guided fine needle biopsy of the lesion was suggestive of a thyroid follicular neoplasm (Figs. 3 and 4). The patient was euthyroid and free of antithyroid antibodies. Total thyroidectomy was performed, and pathology revealed a 3-cm follicular, Hürthle cell carcinoma, with angio-

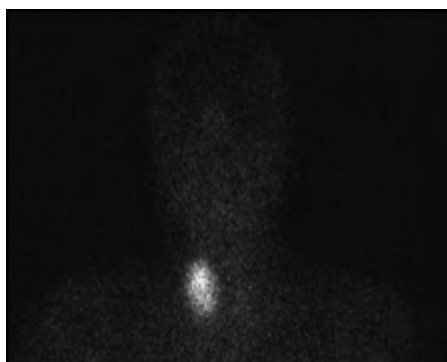


Figure 1. Preoperative octreoscan.

lymphatic invasion (Fig. 5). The tumor cells were positive on immunohistochemical staining for thyroglobulin, synaptophysin, and TTF-1 (Fig. 6), but negative for calcitonin and chromogranin. After total thyroidectomy was performed, somatostatin receptor scintigraphy, ultrasonography, ¹³¹I whole body scan, PET/CT, and stimulated thyroglobulin assay all revealed no evidence of cancer.

Discussion

Indium-111-pentetreotide is a radio-labeled somatostatin (SST) analog that binds to and images neuroendocrine tumors with SST receptors. The overall false positive rate of SST receptor scintigraphy using this particular agent is reportedly 3/508 (5). In the patient presented here, Indium-111-pentetreotide scintigraphy revealed a Hürthle cell, follicular thyroid cancer.

SST receptors are known to exist as five subtypes and are widely distributed throughout the body. The presence of SST receptors on thyroid cells in particular has been demonstrated *in vitro* (4) and are predominantly of subtypes 3 and 5. The presence of subtype 2, how-

ever, has been demonstrated on Hürthle cancer cells in one study (6). Indium-111-pentetreotide binds with high affinity to receptor subtype 2 and, to a lesser extent, subtypes 3 and 5.

SST ligand binding to the receptors present on thyroid cells has been observed in both normal thyroid and non-medullary thyroid cancer cell lines (4). Several studies have shown a positive thyroid cell growth response with SST analog administration, thereby proving the functionality of these receptors (4). With regards to mechanism of action, *in vitro* studies have demonstrated an inhibitory effect of SST on TSH-induced thyrocyte proliferation, incorporation of ³H-thymidine into RNA of follicular cells, and TSH-stimulated adenylate cyclase activity in tumoral thyroid tissue (3, 7, 8). An antiproliferative effect on nonmedullary thyroid cancer cells has also been observed (9).

Several small studies have produced evidence to suggest that SST receptor scintigraphy may be a useful imaging tool in thyroid cancer, especially in nonradioiodine-accumulating cancer of the Hürthle cell variety (10). One study reported results from 12 patients, 10 with Hürthle cell adenomas and 2 with Hürthle cell carcinomas, all producing positive Indium-111-pentetreotide scintigraphy results (11). A larger study looking at 29 patients with metastatic, Hürthle cell cancer was only successful in detecting disease in 79% of patients (23/29) but was positive in 95% of patients with thyroglobulin levels above 10 ng/ml (21/22) (10).

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LETTER FROM THE PRESIDENT

This issue of *EndoTrends* marks the end of a challenging but successful year for EFF. Although economic challenges have impacted all areas of education and health care, we are fortunate to be able to partner with others committed to training and education to provide many new initiatives in 2010.

The grant program in endocrinology, diabetes, and metabolism has been expanded. Grant awardees in 2009, as well as those close to but not awarded grant funding, will be invited to an educational/research presentation before the American Diabetes Association Scientific Sessions June 24, 2010, in Orlando, FL. A new, exciting preceptorship will begin in spring 2010 at the National Institutes of Health in diabetes and metabolism. Applications will soon be available online. Additionally, web-based endocrine grand rounds are currently being filmed and should be on our web site in January. The faculty is excellent, and we hope this opportunity to bring grand rounds to you online will be valuable. Our last initiative for 2010 will be case-based discussion groups online. We will be asking you to submit a mentor-reviewed case study and lead an online educational case discussion group. We wish to thank our corporate sponsors, specifically Amylin, Merck, Bristol-Meyers Squibb, and sanofi aventis, for making these projects feasible and so successful.

With progress comes change, and *EndoTrends* is no exception. The economy and its impact on traditional print publications make old means of communication no longer feasible. While the printed version of *EndoTrends* will still be sent to fellows, programs, and subscribers in our database, it will no longer be mailed to those not registered either on the mailing list or on MyEFF on the web page. However, all content will be available on our web site. In 2011, we will be an environmentally friendly PDF journal only. In the meantime, we hope you will enjoy our new formats, programming, and initiatives. We at EFF look forward to working for you and meeting you in the coming year. See you on Facebook!

Mark Stolar, M.D.
President

EndoTrends

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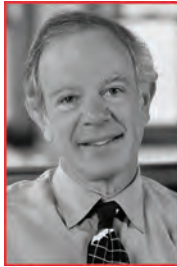
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Somatostatin Receptor Scintigraphy and Thyroid Follicular Epithelial-Derived Cancers

Hürthle cells are enlarged follicular cells with eosinophilic and granular cytoplasm that often exhibit nuclear pleomorphism. A possible explanation for the predilection of SST receptor scintigraphy to detect these unique cells may lie in their mitochondria-rich nature. SST is known to mediate several cellular functions, including apoptosis. One of the major pathways leading to apoptosis is mediated through the release

of apoptogenic factors from the mitochondria (12). The SST receptor subtype 2 has been shown to affect this pathway through the down-regulation of the mitochondrial Bcl-2 protein (12). Perhaps this explains why pentetreotide, an SST analog with high affinity for SST receptor subtype 2, may be attracted to mitochondria-rich Hürthle cells. Although thyroid cells predominantly contain SST receptor subtypes 3

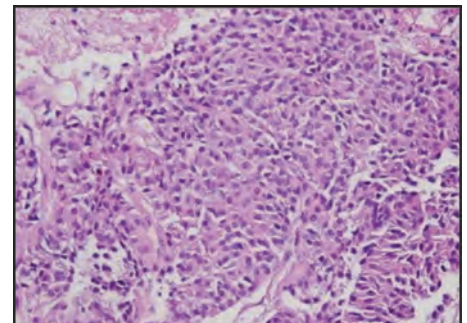


Figure 3. Cytopathology from FNA of thyroid nodule.

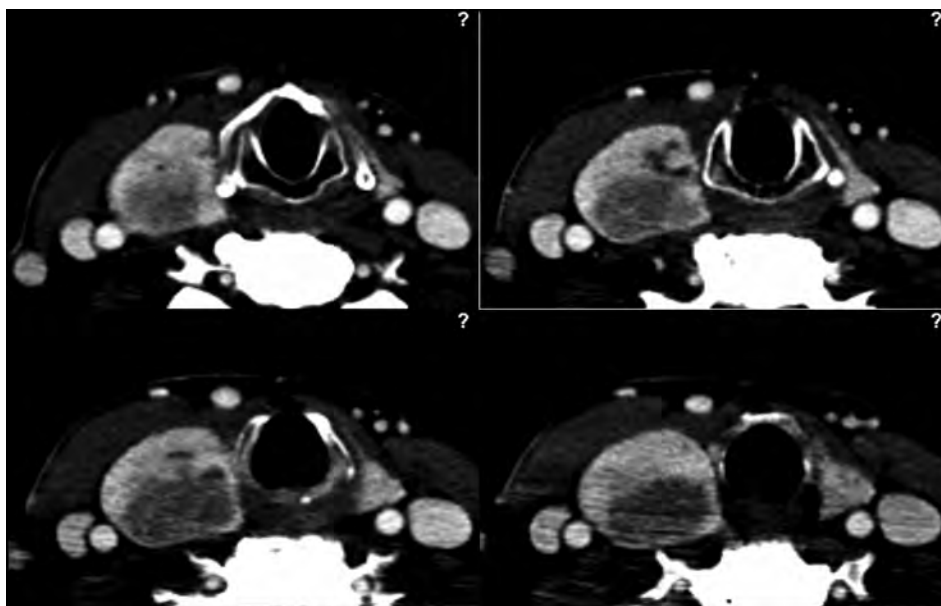


Figure 2. Preoperative CT scan of the neck.

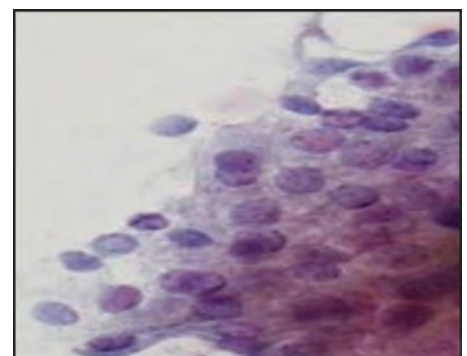


Figure 4. Cytopathology showing round nuclei with smooth contour and granular nucleoli.

and 5, the presence of subtype 2 has been demonstrated on Hürthle cancer cells (6).

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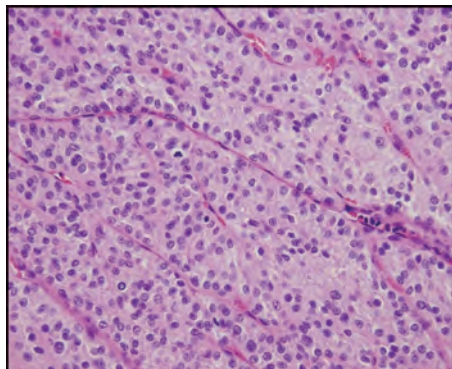


Figure 5. Surgical specimen, thyroid.

Despite evidence that SST receptor scintigraphy may be a useful imaging modality, its utility is not well enough established to warrant routine use in thyroid cancer. It has been proposed that conflicting results may be due to the variable density and expression of SST receptor subtypes on the surface of thyroid tumor cells. As mentioned previously, pentetreotide is an analog with great affinity for SST receptor subtype 2 and this is very useful in the imaging of tumors of neuroendocrine origin, such as carcinoid. Some have proposed the use of other radiolabeled SST analogs, such as depreotide or DOTA-1-Na13-octreotide, which may demonstrate a more favorable receptor affinity profile for the detection of thyroid cancer (4, 13).

With regards to therapeutic implications, *in vitro* studies looking at the use of available SST analogs have showed an antiproliferative effect on thyroid

cancer cells (6). Clinical trials have so far failed to show a remarkable therapeutic benefit and results are widely variable (4, 10, 14). In addition to the use of commercially available SST analogs (Eg, Sandostatin LAR), radiolabeled analogs have been proposed. A pilot study of eight patients with radioiodine-resistant, differentiated thyroid cancer were treated with Yttrium-90-labeled octreotide (DOTATOC). Thirty-five percent of the patients demonstrated stable disease, and 65% had progression (15). A recent publication using the same agent with a different dosing protocol looked at 24 patients with differentiated thyroid cancer resistant to radioiodine therapy. Seven patients (29.2%) demonstrated a decrease in thyroglobulin levels (median reduction 48.9%). Median follow-up was 14.9 months, and an increased survival time from diagnosis was described (16). These and other findings do suggest a role for somatostatin analogs as treatment for thyroid cancer. The current commercially available analogs act mainly on SST receptor subtype 2. Perhaps investigational SST analogs targeting different receptor subtypes, such as SOM-230 and DOTATOC, may present more effective results.

It is our hope that this case will encourage new studies to evaluate this novel use for SST receptor scintigraphy as a diagnostic tool. It also raises interesting concepts with regards to therapy and

may offer a fresh opportunity to revisit the treatment of nonradioiodine avid, differentiated thyroid cancer, especially of the Hürthle cell variety.

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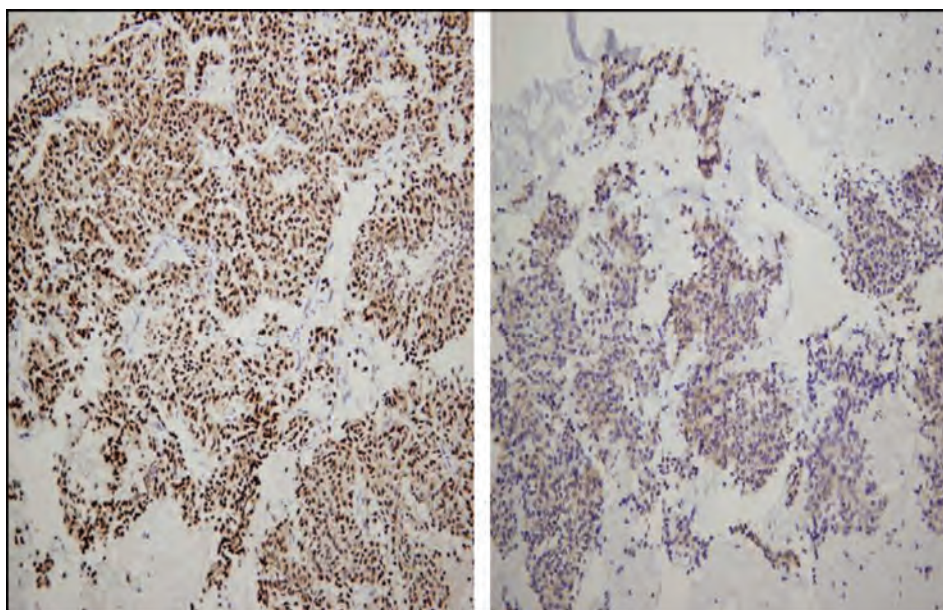


Figure 6. a, TTF-1 stain. b, Synaptophysin stain.

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Case Report

Donor-Transmitted Paraganglioma in Recipient of Liver Transplant

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Introduction

Transmission of malignancies from organ donors to their recipients has been well described in the literature. We describe the first case of donor-transmitted paraganglioma in a recipient of a liver transplant.

Case

This is a case of a 78-yr-old female with a history of hepatitis B and cirrhosis due steatohepatitis who underwent orthotopic liver transplantation in 2002. She did well shortly after transplantation, staying free of graft rejection and opportunistic infections. Approximately 5 yr after her transplantation, however, she began experiencing postprandial abdominal pain. This pain was attributed to a ventral incisional hernia that developed as a result of her initial operation. She sought a surgical evaluation and was tentatively planned for a hernia repair. Before this could be achieved, however, she suffered an acute episode abdominal pain, nausea, vomiting, and diarrhea, which prompted hospitalization in late 2008.

Upon arrival to the hospital, the patient's vital signs were notable for a blood pressure of 175/75 mmHg with a pulse rate of 52 beats/min. She was ill-appearing and her abdominal exam was significant for a tender ventral hernia. A computed tomography scan of the patient's abdomen was promptly performed, and it demonstrated the presence of two ventral hernias as well as three intrahepatic lesions that were not present at the time of transplantation. She had multiple lesions in the left lobe of the liver, the largest measuring 39 mm and a solitary lesion in

the right lobe measuring 36 mm. The lesions were described as hypodense on noncontrast images and hyperenhancing with retention of contrast on delayed images. Given her particular risk factors, these lesions were most suspicious for posttransplant lymphoproliferative disease *vs.* metastasis of an unknown primary malignancy. She therefore underwent ultrasound-guided fine-needle biopsy of the left sided, 39-mm lesion under conscious sedation, and she tolerated it well, without hemodynamic instability. The findings of this biopsy unexpectedly confirmed the presence of a paraganglioma. It was recalled that the patient's donor had a known paraganglioma at the aortic bifurcation that was incidentally found at the time of organ harvesting. The donor's tumor was 3 cm in size and was largely necrotic. The viable sections of this tumor showed a cellular pattern consistent with paraganglioma and immunohistochemistry staining was positive for synaptophysin and chromogranin, negative for S100. Immunohistochemical staining of the patient's liver lesion was also positive for synaptophysin and chromogranin and negative for S100.

The patient was discharged after the liver biopsy and referred to our endocrine clinic for further evaluation. Upon more careful review of her medical history, the patient has been hypertensive for several years with documented systolic blood pressures ranging from 150–180. She had recently been placed on an angiotensin receptor blocker and β blocker with some improvement. She had also sought medical care 1 yr prior for nonexertional, episodic shortness of breath and palpitations. She underwent an extensive cardiopulmonary evaluation and was found to

have no obvious pathology. She denied headaches, anxiety, or postural dizziness. Her past medical, family, and social histories were otherwise unremarkable. Her medications included tacrolimus, mycophenolate mofetil, epivir, metformin, pantoprazole, valsartan 80 mg daily, and metoprolol 25 mg BID, which was added during her last hospitalization. Her physical exam was notable for a blood pressure of 150/80 mmHg and a regular pulse with a rate of 59.

The patient had completed two collections of 24 urinary catecholamines and metanephrines at the time of our initial evaluation, the results of which are shown in Table 1.

Other pertinent labs included normal liver function tests, basic metabolic panel and complete blood count, chromogranin-A of 105.3 ng/ml (<36.4) and neuron-specific enolase of 8.1 μ /liter (<8.6). Plasma catecholamines were also checked and confirmed excess production of norepinephrine (Table 2). A metaiodobenzylguanidine (MIBG) scan was also performed but did not show any positive findings.

We initiated α -blockade with phenoxybenzamine 10 mg twice a day and instructed her to continue her ARB and β blocker. After discussion of her case at liver tumor board, it was decided that the best course of action would include percutaneous radiofrequency ablation (RFA) of the right-sided mass followed by left partial hepatic lobectomy and intraoperative repeat RFA of the right-sided mass. The patient has very recently undergone both procedures. Her follow up catecholamine measurements are pending.

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	Norepinephrine (15–80 µg/24 h)	Epinephrine (0–20 µg/24 h)	Dopamine (65–400 µg/24 h)	Metanephrine (<400 µg/24 h)*	Normetanephrine (<900 µg/24 h)*
Collection 1	122	0.9	143	19	935
Collection 2	109	0.9	105	37	2496
Normotensive ranges are: Metanephrine 30–180 µg/24 h and Normetanephrine 148–560 µg/24 h. *Normal values pertain to hypertensive subjects.					

Discussion

Donor-transmitted malignancies

The incidence of donor transmitted malignancies is estimated to be quite small. Data from the Organ Procurement and Transplantation Network/United Network for Organ Sharing estimate that 0.04% of organ donors have some type of malignancy and are transmitted at a rate of 0.017% (1). Based on the Israel Penn Transplant Tumor Registry that has collected data from the U.S. and internationally for over 4 decades, the rate of transmission of any known malignancy from donor to recipient is 42% (2). Among the reported and confirmed cases of donor-transmitted malignancies, the risk of transmission appears highest in lung (60%), similar among kidney, liver, and heart recipients (45%, 37%, and 30% respectively) and smaller in pancreatic (25%). The rate of transmission also varies by the type of malignancy, choriocarcinoma being the highest (93%), followed by melanoma (74%), kidney (61%), lung (43%), and breast (29%), and CNS (23%). Rarely have endocrine tumors been reported to be transmitted in this fashion. There are three cases of small-cell neuroendocrine carcinoma transmitted via kidney and liver grafts (3). Additionally, there are two reported cases of Merkel cell carcinoma transmitted to kidney and heart recipients from distinct donors (4). To our knowledge, there have been no reported cases of pheochromocytomas or paragangliomas transmitted through organ transplantation in the literature. There is one reported case of a cadaveric kidney donor

who was found to have an ipsilateral pheochromocytoma with capsular invasion at the time of organ harvesting. The recipient immunosuppression with cyclosporine, prednisolone and eventually azathioprine. Two years after transplant, her MIBG scan and urinary catecholamines did not suggest the presence of pheochromocytoma (5).

Paragangliomas

Paragangliomas and extra-adrenal pheochromocytomas are chromaffin cell tumors of the neuroectoderm, derived from cells that ultimately form the autonomic nervous system. These tumors can arise from anywhere within the sympathetic or parasympathetic nervous system, including the adrenal medulla (in the case of pheochromocytomas) and autonomic ganglia (in the case of paragangliomas). Paragangliomas of the sympathetic nervous system may or may not have the ability to secrete catecholamines, whereas those from the parasympathetic nervous system are universally biochemically silent.

The genetics of paragangliomas have become an area of interest in the past decade. Although pheochromocytomas and paragangliomas were once believed to be familial in only 10% of cases, recent studies have found this percentage is closer to 25% (6). Most relevant to the genetics of paragangliomas are the mutations involving succinate dehydrogenase, a mitochondrial enzyme involved in the oxidation-phosphorylation pathway. Mutations in SDHB, C, and D are implicated in familial paragangliomas (PGL4, PGL3,

PGL1, respectively). SDHB mutations tend to be associated with extraadrenal sympathetic PGs located in the abdominal or thoracic cavity, whereas SDHC and SDHD mutations tend to generate head and neck lesions (7–9). Genetic testing of the patient’s resected lesion has yet to be performed.

Determining the origin of malignancy in transplant recipients

Although it is rather convincing that this patient’s paragangliomas were transmitted from her donor, the question of tumor origin in transplant recipients is not always clear. In the situation of nonsex-matched donors, the number of X and Y chromosomes can be used to make this distinction. In sex-matched recipients, modalities such as microsatellite allelic analysis and comparative genomic hybridization can be utilized (3).

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Norepinephrine (70–750 pg/ml)	Epinephrine (0–110 pg/ml)	Dopamine (0–29 pg/ml)
30199	<10	122

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V, Niccoli-Sire P, Pasiëka JL, Rohmer V, Tucker K, Jeunemaitre X, Marsh DJ, Plouin PF, Robinson BG. Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. *J Clin Endocrinol Metab*. 2006; 91:827–836.



Perioperative Management in Graves' Disease and Conn's Syndrome

Wai Ping A. Li, Andreea O. Lungu, Steven K. Libutti, Chenwi M. Ambe, Maria Merino, Richard Chang, Craig Cochran, and Francesco S. Celi
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Introduction

The risk of iodine overload-induced thyrotoxicosis, potentially leading to life-threatening complications such as thyroid storm in patients with poorly controlled Graves' disease and toxic multinodular goiter, is substantial. Here, we describe the challenges associated with the diagnosis, localization studies, and the perioperative management of a case of primary hyperaldosteronism in a patient with thionamide-resistant Graves' disease.

Clinical Case

A 36-yr-old African American female with a 2-yr history of poorly controlled Graves' disease who initially presented with fatigue, insomnia, mild dysphagia and a 20-lb weight loss despite an increased appetite. She was initially treated with thionamides and β -blockers and referred to our institution for further evaluation and management. The physical examination was remarkable for bilateral exophthalmos and a large, diffuse, nontender goiter. Laboratory studies revealed a TSH level of 0.08 μ IU/ml (reference range 0.4–4 μ IU/ml), free T_4 4 ng/dl (reference range 0.8–1.9 ng/dl), T_3 794 ng/dl (reference range 90–215 ng/dl). She had a positive thyroid-stimulating Ig at 2.4 (normal value \leq 1.3 TSI index) and a high TSH receptor antibodies titer at 87% (normal value $<$ 16%). A thyroid uptake scan showed the thyroid gland was enlarged with diffuse uptake of 87.4% at 24 h. These studies were consistent with a diagnosis of hyperthyroidism secondary to Graves' disease. Ultrasound of the thyroid revealed a moderate heterogenous thyroid with a right lobe measuring $3.4 \times 3.4 \times 6.5$

cm, left lobe measuring $3.4 \times 3 \times 5.5$ cm. There was a $1.4 \times 0.8 \times 1.2$ cm well-defined echogenic nodule in right upper thyroid. Fine needle aspiration revealed a benign thyroid nodule. A decision of performing a total thyroidectomy was made on the basis of poor response to thionamide therapy, exophthalmos, compressive symptoms, and patient preference.

During the thyroid evaluation, hypertension (systolic values ranging between 150 and 160 mmHg, and diastolic values ranging between 100 and 105 mmHg), severe hypokalemia 1.6 mmol/liter (reference range 3.3–5.1 mmol/liter) and metabolic alkalosis 40 mmol/liter (reference range 21–31 mmol/liter) were noted. A follow-up set of laboratory tests confirmed the hypokalemia and urine electrolytes showed low urine sodium, elevated potassium, and low chloride. Upon further questioning, the patient reported symptoms of nocturia, polydipsia, and polyuria for at least 1 yr. She denied abuse of liquorice. She had no palpitations, muscle weakness, or cramping. An electrocardiography (EKG) revealed normal sinus rhythm without EKG characteristic changes associated with hypokalemia. However, the EKG pattern suggested left ventricular hypertrophy and left atrial enlargement. The evaluation for secondary hypertension was significant for an elevated serum aldosterone 49 ng/dl (reference $<$ 21 ng/dl) and suppressed plasma renin ($<$ 0.6 ng/ml-h). The aldosterone to renin ratio was 81.6, and it was strongly indicative of hyperaldosteronism. The diagnosis of hyperaldosteronism was confirmed with a saline infusion test with serum aldosterone

values above 10 ng/dl throughout the 4-h saline infusion.

The biochemical diagnosis of hyperaldosteronism would require further localizing modalities such as imaging and adrenal sampling studies with iodinated radiocontrast medium. The timing and logistics of these studies posed a major dilemma due to the risk of iodine-induced thyrotoxicosis. This patient planned to undergo thyroidectomy, and it was likely that she might be requiring adrenalectomy for hyperaldosteronism. A big challenge arose in coordinating the diagnostics studies and planning for two potential surgeries.

Localization studies and preoperative management were performed while the patient was admitted to provide close monitoring. A contrast computed tomography of the adrenals revealed a left 1.2 cm adrenal nodule. Adrenal vein sampling was performed on the next day. The data clearly revealed a lateralization corresponding to the side of the lesion (Table 1).

To avoid the risk of worsening hyperthyroidism after exposure to contrast medium from the adrenal vein sampling and the CT study, the patient was treated throughout the hospitalization with high-dose thionamides, SSKI, calcium channel blockers, and aggressive potassium replacement. Spironolactone was added after the results of the venous sampling became available. A total thyroidectomy was performed on hospital d 4. Histopathologic examination of the thyroid glands revealed hyperplastic thyroid tissue, consistent with

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Table 1
Results of Adrenal Vein Sampling of a 37-yr-old Female with Hyperaldosteronism and a 1.2-cm Left Adrenal Nodule Detected in Abdominal CT Scan

	Aldosterone (ng/dl)			Cortisol (μg/dl)		
	Right	Left	Peripheral	Right	Left	Peripheral
-5 min	15	220	18	10.4	5.2	2.4
0 min	17	238	18	12.3	5.8	2.6
10 min	92	9200	62	322	153	9.0
15 min	116	8010	67	316	157	10.4

Graves' disease and one small 0.3 cm focus of papillary carcinoma on the left thyroid. A laparoscopic left adrenalectomy was then performed 12 d after the thyroidectomy. Interestingly, the histology indicated diffuse adrenal hyperplasia. The patient had an excellent postoperative course and both potassium and antihypertensive medications were discontinued over 1 month. At the 3-month postoperative follow up, serum aldosterone level was 2 ng/dl, and serum renin was less than 6 ng/ml·h. Currently, her only medication is L-T₄ 112 μg daily.

Discussion

Graves' disease is the most common cause of hyperthyroidism, accounting for 50–80% of the cases in the U.S. Among patients with Graves' disease, the female to male ratio is between 5:1 and 10:1 (1). Common available treatment modalities include pharmacological treatment with antithyroid drugs that inhibit thyroid hormone synthesis and/or release, radioiodine therapy, and thyroidectomy. Surgery is the least often used treatment option but is used in patients for whom radio-ablation is contraindicated; patients who have complications with antithyroid drugs, large goiters, or nodules suspicious for malignancy; and patients with desire for definitive treatment.

In 1955, hyperaldosteronism was first described by Dr. Jerome Conn in a patient with adrenocortical tumor and was cured with adrenal tumor resection (2). The estimated prevalence has a range of 1.4% to 32% (3). For unilateral aldosterone-secreting adenoma or hyperplasia, surgical resection is still the treatment of choice.

Concomitant Graves' hyperthyroidism and primary hyperaldosteronism are extremely rare events. To the best of our knowledge, there is first case report of surgical management of Conn's syndrome associated with Graves' disease. A previous report describes the association of Conn' syndrome to thyrotoxicosis-associated hypokalemic periodic paralysis, but in this the management of hyperthyroidism was achieved by means of thionamides (4). Interestingly, our patient did not present with the classic symptoms even with severe hypokalemia.

Our patient had undiagnosed hypertension and hypokalemia secondary to primary hyperaldosteronism. Her recent echocardiogram revealed mild concentric left ventricular hypertrophy, a finding consistent with prolonged exposure to hyperaldosteronism. Since the diagnosis of hyperthyroidism, she was treated with a β blocker that might have partially masked the hypertension. Interestingly, upon further questioning, the patient stated that she was found to have hypokalemia during a routine physical examination several years before the diagnosis. While in a chronic hypokalemic state, she developed polyuria, polydipsia, and nocturia. It is nonetheless surprising that despite such a severely low serum potassium level, she did not have any hypokalemia-related muscle weakness EKG changes or cardiac arrhythmia.

This case illustrates the challenges posted in evaluation and treatment of primary hyperaldosteronism in a patient with known Graves' hyperthyroidism and severe hypokalemia. Localization of aldosterone secreting adenoma requires diagnostic modalities

with iodinated radiocontrast medium. Iodine may exacerbate thyrotoxicosis in Graves' disease, known as the Jod-Basedow phenomenon (5). It is crucial to treat this patient with high-dose thionamides and SSKI during the work up for primary hyperaldosteronism. The patient was treated with Spironolactone and potassium supplement before thyroidectomy to minimize the electrolytes abnormalities and hypertension perioperatively. Thyroidectomy in patients with poorly controlled thyrotoxicosis has been associated with increased postoperative death caused by thyroid storm (6). Furthermore, because hyperthyroidism represents a risk factor for perioperative complications, we decided to perform total thyroidectomy before the adrenalectomy.

In summary, even if Graves' disease and primary hyperaldosteronism are not uncommon diseases, the concomitant presence of Graves' and Conn disease requiring surgical treatment has not been previously reported. Optimization of perioperative management in these patients should be sought to improve the outcome.

Acknowledgments

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Case Report

Subcutaneous Recombinant Human Parathyroid Hormone (PTH) Injection Provides a Diagnostic Tool for Identification of Non-Phenotypically Evident Pseudohypoparathyroidism by Unmasking PTH Resistance

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Introduction

Hypocalcemia and hyperphosphatemia in the setting of elevated intact PTH and normal vitamin D metabolites, raises the possibility of PTH resistance or pseudohypoparathyroidism.

Case Presentation

Here we present the case of a 50-yr-old man seen in our endocrine clinic July 2008 with a chief complaint of chronic intermittent numbness and tingling in the legs, arms, neck, and face. He had noticed no other abnormalities—specifically, no headaches, visual changes, diplopia, motor disturbances, or changes in sexual function, or bowel or bladder function.

In December 2007 he was admitted to a local emergency department for a near syncopal episode and seizure like activity. Work up was negative for seizure disorder. Head computed tomography scan showed nonspecific extensive, dense, bilateral basal ganglia calcifications, along with scattered other cerebral calcifications and moderate bilateral cerebellar calcifications. Laboratory studies revealed a low serum calcium level of 6.2 mg/dl, with normal albumin of 4.4 g/dl, high serum phosphorus of 5.6 mg/dl, high intact PTH of 222 pg/ml, low 25(OH)D less than 6.0 ng/ml. Thyroid function tests were normal with TSH of 1.43 μ U/ml and free T₄ of 1.19 ng/dl. The patient was treated with iv calcium, which corrected his hypocalcemia and led to resolution of the symptoms. He was discharged home on oral calcium and vitamin D supplementation.

When we saw him in July 2008, he was on oral calcium 500 mg four times per day and Calcitriol 0.5 μ g three times

per week. He still complained of chronic intermittent numbness but had not had any further episodes of syncope or seizures since December of 2007. His past medical history was significant for depression, bicycle accident in 1990s, and left cataract surgery. He had a family history of hypocalcemia in mother, sister, sister's daughter, and brother. Physical exam revealed a well-developed man with normal stature, intact visual fields, and normal findings on neurological examination. None of his metacarpals were shortened. Chvostek's and Trousseau's signs were negative. He had no thyromegaly either. Results of laboratory studies revealed serum calcium of 9.0 mg/dl, PTH 161.1 pg/ml, PO₄ 3.8 mg/dl, creatinine 1.0 mg/dl, 25(OH)D 61 ng/ml; 24 h urinary calcium was 103 mg, and urinary phosphorus was low at 0.2 g.

Lack of availability of iv PTH in the U.S. and Canada led us to contemplate the possibility of testing for PTH resistance by using available sc formulation for osteoporosis treatment. Hence, we asked the patient for permission to perform a test designed by us; we named sc PTH resistance challenge (scPTHrc). Patient agreed and subsequently underwent the scPTHrc. Twenty micrograms of sc recombinant human PTH (1–34) were injected in the abdominal flank area. Baseline urinary cAMP, serum calcium and intact PTH were measured before and 2 h after the administration of recombinant hPTH(1–34). Urinary cAMP was measured also 4 h after the PTH challenge. Results are summarized in Table 1.

Based on the small interval change in the urinary cAMP from 0.166 nmol/mg

to 0.187 nmol/mg 2 h after the administration of hPTH (1–34), our patient had resistance to PTH action or pseudohypoparathyroidism. In addition to these results, patient had a significant family history of hypocalcemia but no features of Albright's hereditary osteodystrophy. The constellation of signs and symptoms as well as the laboratory data in response to the scPTHrc test led us to conclude that our patient had pseudohypoparathyroidism type 1b.

Discussion

The idiopathic and inherited forms of PTH resistance are referred to as pseudohypoparathyroidism (PHP). They are due to lack of cellular response to PTH.

The first cases of documented PTH resistance were described by Albright in 1942.

Biochemically, PHP mimics hypoparathyroidism with hypocalcemia and hyperphosphatemia, but the PTH level is elevated and there is a markedly blunted response to the administration of PTH. There are several types of PHP 1a, pseudopseudohypoparathyroidism (PPHP), 1b, 1c, and 2 (Table 2).

Patients with PHP type 1a have a characteristic somatic phenotype known as Albright's hereditary osteodystrophy (AHO), in addition to the biochemical features of hypocalcemia, hyperphosphatemia, and secondary hyperparathyroidism (1). This phenotype includes short stature, round face, short neck, brachydactyly, shortened metacarpals (4th and 5th), sc ossifications, and impaired mentation. PTH type 1a is caused by autosomal dominant inheri-

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Table 1
Results of PTH Challenge

Laboratory test	Baseline	2 h after PTH challenge	4 h after PTH challenge
Urinary cAMP/Cr (nmol/mg)	0.166	0.187 (<2.4-fold increase)	0.241
Serum calcium (md/dl)	9.2 (albumin 4.5)	8.8	
iPTH (pg/ml)	97.1	138.8	

tance loss of function of one allele of the gene (*GNAS1*) encoding the stimulatory G protein α -subunit ($Gs\alpha$). This produces only 50% of normal level of the $Gs\alpha$ -subunit, which couples the PTH receptor to adenylate cyclase. Because $Gs\alpha$ also couples many other receptors to adenylate cyclase, the expected result of this mutation would be a generalized disorder of hormonal unresponsiveness. The presence of primary hypothyroidism and primary hypogonadism in these patients indicates resistance to TSH, LH, and FSH, and this occurs fairly commonly. Responsiveness to other hormones, such as ACTH, glucagon is fairly normal (2).

PPHP refers to phenotypical AHO with normal responsiveness to PTH. Patients with PPHP often are found in the same kindreds as those with PHP1a, and they invariably inherit the same abnormal $Gs\alpha$ gene found in their PTH-resistant relatives. When patients inherit the mutant $Gs\alpha$ gene from their fathers, they exhibit PPHP; when they inherit the mutant $Gs\alpha$ gene from their mothers, they exhibit PHP. This pattern, in which the phenotype depends on the parent of origin, is termed genetic imprinting. Renal expression of *GNAS1* gene appears to be determined only by the maternal allele so that a defect only in the maternal allele of *GNAS1* will result in unresponsiveness of the renal tubule to PTH binding. Patients with PPHP will have the normal maternal allele for *GNAS1* and therefore their kidneys respond normally to PTH.

PHP type 1b is defined by renal resistance to PTH without clinical features of AHO and with normal $Gs\alpha$ levels in fibroblasts. It has been suggested that PTH resistance is confined to the kidney in this disorder leading to only hypocalcemia, hyperphosphatemia, and secondary hyperparathyroidism without any other endocrinopathies. PTH type 1b is also linked to the *GNAS1* locus, but does not involve mutations in the coding region of the *GNAS1*. It is a result of abnormal methylation of $Gs\alpha$ promoter region leading to a tissue specific $Gs\alpha$ abnormality. The locus responsible for PHP1b has been found to reside on chromosome 20q13.3, the same region that contains the *GNAS1* gene, encoding $Gs\alpha$. The disease is inherited with the imprinting characteristic of PHP1a, but mapping studies suggest that the disease-causing mutations are close to but distinct from the $Gs\alpha$ coding region. Approximately half of the cases of PHP type 1b have a 3-kb deletion of DNA sequences located approximately 220 κ B centromeric of the *GNAS1* locus. This deletion removes several exons of the STX16 locus (Fig. 1), which encodes syntaxin-16, a protein that plays a role in intracellular trafficking. Although the development of PHP1b correlates with maternal inheritance of this gene defect, STX16 itself is not imprinted. However, deletions in this locus result in a loss of methylation at the distant A/B locus that contains an alternative promoter that competes with the normal *GNAS1* promoter. Transcription directed by this unmethylated promoter does not produce appropriate levels of $Gs\alpha$ pro-

tein in the renal cortex. Deletions in the region of DNA encoding NESP55, a chromogranin-like neurosecretory peptide, have also been found in PHP1b. These deletions also cause abnormal imprinting of exon A/B and presumably define a distinct imprint control region within *GNAS1*.

PHP type 1c includes patients with AHO and PTH resistance who have been found to have normal $Gs\alpha$ activity.

In PHP2, PTH infusions increase urinary cAMP normally; however, PTH does not elicit a phosphaturic response. This syndrome, like PHP1b, lacks signs of AHO or resistance to other hormones, but unlike PHP1b, it is nonfamilial in origin. A similar biochemical phenotype can also be observed in vitamin D deficiency, and some authors have suggested that PHP2 is a manifestation of vitamin D deficiency rather than a distinct clinical entity.

To confirm that resistance to PTH is present, patients can be challenged with iv PTH (Ellsworth-Howard test). For this purpose, synthetic human PTH (1–34) (teriparatide acetate, 3 IU/kg body weight) is infused iv over 10 min, and urine is collected during the hour preceding the infusion, during the half-hour following the infusion, 30–60 min after the infusion, and 1–2 h after the infusion and assayed for cAMP and creatinine. Data are expressed as nanomoles of cAMP per liter of glomerular filtrate, based on creatinine measurements. Normally, there is an increase in urinary cAMP of more than 300 nmol/liter glomerular filtrate after administration of 3 IU/kg iv synthetic hPTH (1–34). However, iv synthetic human PTH (1–34) is not available in the U.S. or Canada. The recombinant hPTH (1–34) that is available in the U.S. can be used only for sc administration in the treatment of osteoporosis. Therefore, we designed a sc recombinant hPTH (1–34) resistance challenge (scPTHrc) test to prove for resistance to PTH in our patient. Based on the study of Lindsay *et al.* 1993 (3), we first determined the possible kinetics and biochemical response to sc recombinant hPTH (1–34). In that

Table 2
Types of Pseudohypoparathyroidism

Disorder	Urinary cAMP response to PTH	Urinary PO4 response to PTH	Other hormonal resistance	AHO
PHP 1A	Decreased	Decreased	Yes	Yes
Pseudo-PHP	Normal	Normal	No	Yes
PHP 1B	Decreased	Decreased	No	No
PHP 1C	Decreased	Decreased	Yes	Yes
PHP 2	Normal	Decreased	No	No

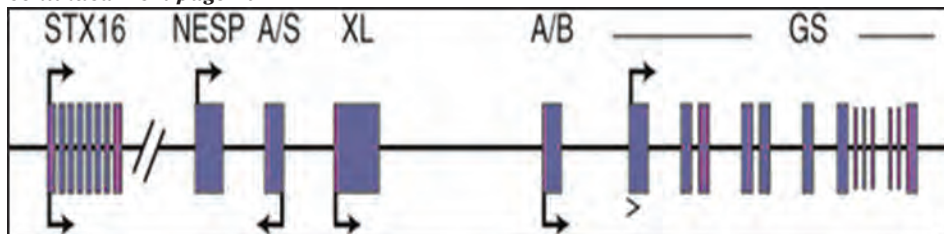


Figure 1. GNAS1 locus.

study, a standard dose (400 U or 25 μ g) of recombinant hPTH (1–34) was administered sc to estrogenized osteoporotic patients without resistance to PTH. Administration of sc recombinant hPTH (1–34) led to 3-fold increase in the urinary cAMP 2 h after the administration (3). If 20 μ g were to be injected, we assumed 2.4-fold increase in the urinary cAMP 2 h after the administration should be expected. In our patient,

however, the administration of 20 micrograms of recombinant hPTH (1–34) led to a blunted increase in the urinary cAMP from 0.166 nmol/mg (before the PTH administration) to 0.187 nmol/mg 2 h after the administration. This confirmed the resistance to PTH.

Conclusions

We concluded our scPTHrc test was practical, sensitive and specific for con-

firming the diagnosis of PHP and/or PTH resistance in other syndromes. However, larger populations should be tested before implementation of such a test is made a standard of care.

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Familial Paraganglioma Syndrome with SDHB Mutation

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Introduction

Catecholamine-secreting tumors are rare, occurring in less than 0.2% of patients with hypertension (1, 2). They can present as paroxysmal “spells” with symptoms such as palpitations, tremor, pallor, sweating, or headaches, or they may be detected incidentally on biochemical or imaging work-up for hypertension (3). The majority of these tumors are sporadic, but 15–20% of pheochromocytomas (adrenal) or paragangliomas (extraadrenal) are hereditary. The following case report demonstrates the presentation, work-up, and treatment of a patient with a hereditary paraganglioma syndrome.

Case Presentation

The patient is a 20-yr-old Caucasian gentleman who presented to a student health clinic in February of 2008 for symptoms of an upper respiratory tract infection. He was found to be hypertensive at this visit, and remained so during

subsequent visits with his primary care physician, with systolic blood pressures as high as the 170s. He had no symptoms at that time, and specifically denied chest pain, palpitations, headaches, blurred vision, or diaphoresis.

A work-up for secondary causes of hypertension was initiated. During a renal ultrasound, a 4-cm hypoechoic mass was noted in the left upper quadrant; follow-up computed tomography (CT) scan of the abdomen showed a left retroperitoneal mass which was suspicious for a pheochromocytoma. Twenty-four-hour urine for metanephrines and catecholamines revealed an elevated norepinephrine of 1520 μ g/d (normal 30–350 μ g/d), and an elevated normetanephrine of 3861 μ g/d (normal 50–650 μ g/d). Plasma normetanephrine was also elevated at 10.8 nmol/liter (normal 0.00–0.89 nmol/liter). The patient was started on phenoxybenzamine in preparation for surgery, and underwent resection of the mass. Pathology was consistent with a

pheochromocytoma or paraganglioma. Genetic screening for the RET proto-oncogene mutation was negative.

The patient was doing well postoperatively but continued to have persistent mildly elevated blood pressure (systolic blood pressure in the 140s). His plasma normetanephrines also remained persistently elevated. A CT of the neck and abdomen was performed looking for other masses that may correspond to possible extraadrenal paraganglioma. A lower thoracic left paravertebral mass was noted on the abdominal CT (Fig. 1); upon further review of his original CT, this mass was noted as well. Magnetic resonance imaging (MRI) of the thoracic spine also showed the paravertebral mass (Fig. 2). An iodine-131-metaiodobenzylguanidine (MIBG) scan with single photon emission CT (SPECT) was performed, and was positive for focal paraspinal activity in the left inferior chest corresponding to the area seen

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Figure 1. Thoracic CT scan with paraspinal paraganglioma (arrow).

on CT and MRI (Fig. 3). No other increased activity was seen on the MIBG scan.

The patient was therefore taken back to the operating room and the paraspinal mass was removed. Pathology was consistent with pheochromocytoma or paraganglioma. A sample of the patient's blood was sent to the Baylor College of Medicine laboratory for mutation analysis of the succinate dehydrogenase gene. The sample tested positive for a heterozygous unclassified familial missense variant (c.380T>G) in succinate dehydrogenase subunit B. This resulted in a substitution of serine for isoleucine at position 127 of the SDHB gene (I127S). The original tumor was also tested and found to be positive for this same variant, with loss of heterozygosity.



Figure 2. MRI of thoracic spine, demonstrating paraspinal paraganglioma.

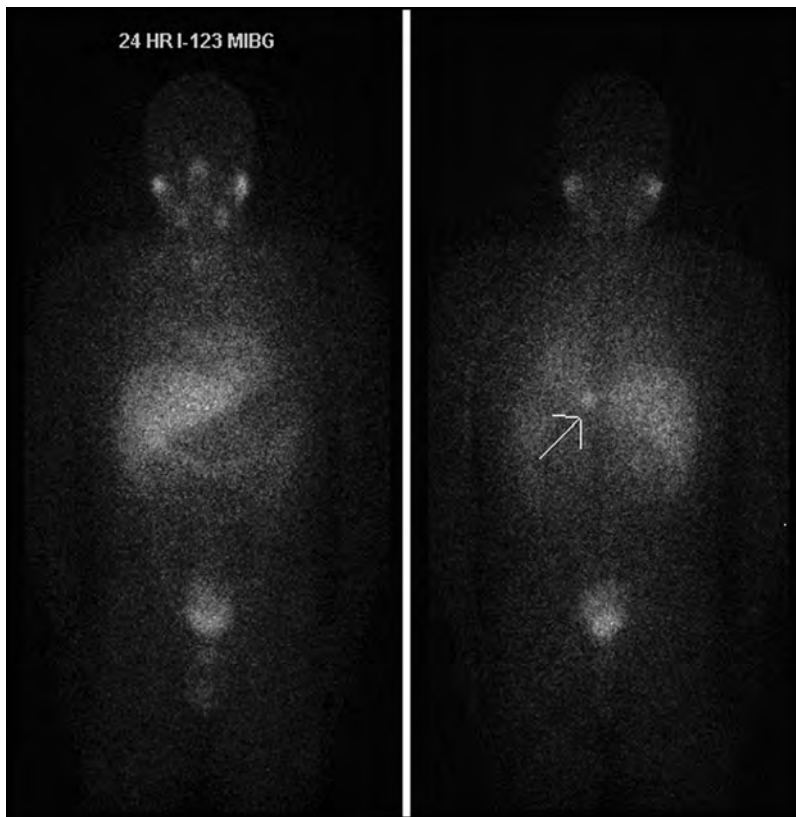


Figure 3. MIBG scan, showing increased paraspinal uptake corresponding to mass on CT.

The patient's family underwent testing for this mutation. His mother is positive and has a history of hypertension, but workup for pheochromocytoma or paraganglioma has been negative to this point. His sister is also positive for the mutation, with negative work-up. His maternal grandfather was tested and is positive for the mutation as well.

The patient was seen in clinic for follow-up. His blood pressure had normalized (systolic blood pressure in the 110s), and he had recovered from his surgery well. Urine catecholamines/metanephrines and plasma metanephrines were repeated. These were all found to be in the normal range, supporting complete surgical resection of his disease. He will continue to have periodic screening to assess for recurrence of his disease.

Discussion

This case illustrates several key points regarding the work-up and treatment of catecholamine-secreting tumors. First, it demonstrates the importance of postoperative biochemical evaluation to assess surgical cure. This patient had a paraganglioma at

an additional site, and without post-surgical monitoring, may have had his therapy delayed, leading to other potential health issues. Second, it reinforces the importance of genetic testing in patients who present with catecholamine-secreting tumors, even in those with no family history of pheochromocytomas or paraganglioma. In this case, screening found an abnormality in the SDHB complex; characterizing the mutation can help predict the most likely areas of disease involvement and will allow counseling about the increased risk of malignant paragangliomas associated with SDHB mutations. Detection of the mutation in the index case made it possible to identify other carriers of this mutation within the family so that they could have appropriate work-up and surveillance. It also allows screening of future generations to identify at-risk individuals.

Finally, the case illustrates the most common presentation of hereditary paraganglioma resulting from a mutation in the SDHB subunit. Extraadrenal

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abdominal and thoracic tumors are the most common, whereas head and neck paragangliomas are rarer. Also, although carriers of the mutation are at increased risk for development of paraganglioma, there is not 100% penetrance, because 31% of carriers will still be disease free at the age of 60 (4).



Case Report

A Case of Hyperandrogenism in a Postmenopausal Female

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Introduction

Hyperandrogenism is a common clinical presentation in women seen in an endocrine clinic. However, hyperandrogenemia in postmenopausal women is less frequently seen, especially that from an ovarian source. Herein, we present a patient initially referred to our clinic for evaluation of acromegaly and subsequently found to have hyperandrogenism, secondary to hyperthecosis.

Case Presentation

A 60-yr-old female with multiple medical issues, including hypothyroidism and hyperlipidemia, presented to our clinic for evaluation of acromegaly. The patient noted that over the past 2 yr she had developed symptoms that were concerning for acromegaly. She had increased wrist and ankle size. Her shoe size increased from size 10 medium to 11.5 wide. She noted increased ring size from 6 3/4 to 9, as well as neck size. She noted increased prominence of her shoulders and increased size of her abdominal flank area. She had a total 40-lb weight gain in the past 6 months, most of it occurring in a 2-month period just before her visit with us. She noted a fuller facial appearance, wider nose, and increased fine facial hair growth. Lastly, she had been frequently biting her tongue the last 6 months, but denied having developed acne or skin tags.

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The patient has an extensive past medical history which includes hypothyroidism, hyperlipidemia, TIA, seizures, factor XIII deficiency and atrial fibrillation. She had a hysterectomy at age 25, and has no natural children. Both ovaries were conserved. She had seven miscarriages thought secondary to problems with her uterine lining and factor XIII deficiency. She developed menopausal symptoms around age 50. Her medications included L-T₄, atorvastatin, furosemide, and digoxin. She does not smoke and rarely consumes alcohol. There is no family history of endocrine disorder, except for hypothyroidism in her mother.

The patient's physical exam showed a blood pressure of 116/72 and pulse of 84. Her height was 68" and she weighed 202 lb. A picture from her driver's license was used for comparison, which was taken from 3 yr before her office visit. There was no noticeable enlargement of the frontal bones or the jaw. On exam, the tongue was normal size, and her teeth were not widely spaced. A left thyroid nodule was palpated. There was no dorsal or supraclavicular fat pad. The patient had mildly prominent abdominal flanks; however, there were no abdominal striae. There was soft tissue enlargement around her ankles and the dorsum of her foot bilaterally. Although she had some enlargement of her fingers proximally, her fingers appeared to taper normally in size toward the distal aspect. Her

strength was intact, and her neurologic exam normal, including her reflexes. She did not show signs of hirsutism.

The patient was initially evaluated for acromegaly, which was negative. She had a normal random IGF-I level of 95 ng/ml. Her 2 h oral glucose tolerance test/GH challenge test was normal with peak GH levels of 0.64 ng/ml at 30 min.

The patient's androgen levels were evaluated, given her clinical manifestations of hyperandrogenism. Her total testosterone was elevated at 79 ng/dl (2–45 ng/dl), free testosterone level of 6.6 pg/dl (0.1–6.4 pg/dl), and % free testosterone of 0.83 (0.5–2.0%). DHEAS, 17(OH)progesterone, and androstenedione levels were normal. FSH, LH, and estradiol were consistent with menopause. Thyroid function tests and PRL levels were also normal. Fasting glucose and insulin levels were obtained, and were 95 mg/dl and 42 μIU/ml, respectively, and indicative of hyperinsulinemia.

Further evaluation of her hyperandrogenism included a 1 mg dexamethasone suppression test, which showed a normal suppressed cortisol level of 0.9 μg/dl. Transvaginal ovarian ultrasound showed an echogenic focus measuring 1.5 × 0.5 × 0.5 cm immediately adjacent to her right ovary. The right ovary measured 2.1 × 1.6 × 1.8 cm and the left ovary measured 3.4 × 1.7 × 1.5 cm;

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both larger than expected for a postmenopausal female. Computed tomography of the abdomen and pelvis with contrast did not show any abnormality of the adrenals or ovaries.

Given her symptoms of hirsutism and hyperinsulinemia, she was started on metformin and aldactone. After initiating treatment, the patient's total testosterone declined to 30 ng/dl, free testosterone of 3.4 pg/ml, and % free testosterone of 1.12. Because of the concern about the possible enlarged right ovary/right ovarian mass, and given her menopausal status and age, the patient underwent a laparoscopic bilateral oophorectomy. Pathology reports revealed both ovaries to have physiologic changes and stromal hyperplasia that was consistent with hyperthecosis. Repeat androgen levels after the oophorectomy revealed that total testosterone had fallen to normal limits at 9 ng/dl, a free testosterone level of 1.4 pg/ml, and a % free testosterone of 1.56. Since the surgery, the patient has noted no further symptoms of hirsutism, and clinically significantly better.

Discussion

Hyperandrogenism in a postmenopausal woman is uncommon. However, when it is noted, hyperthecosis is an important etiology to consider. Hyperthecosis can occur in either pre- or postmenopausal women. Although the etiology of hyperthecosis in postmenopausal women is unclear, it is thought that it may be secondary to abnormal gonadotropic regulation of postmenopausal ovarian function leading to stromal hyperplasia and luteinization of the ovarian stroma (1).

The rate of testosterone production normally decreases in postmenopausal women mostly because of a decline in the peripheral production of testosterone from androstenedione. The postmeno-

pausal ovary is a hormonally active endocrine gland. During menopause, ovarian testosterone production remains relatively constant, whereas there is a decline in estrogen production. Thus, the ovaries become primarily androgen-producing glands. In hyperthecosis, the relatively high rate of androgen production is secondary to an increase in gonadotropin secretion that stimulates steroidogenesis in ovarian hilar cells or luteinized stromal cells (2).

Clinical features of hyperthecosis can include obesity and amenorrhea or irregular menstrual cycles. Patients can experience symptoms of hyperandrogenism that includes hirsutism, clitoral enlargement, temporal balding, and deepening of the voice. Severe hirsutism and virilization in postmenopausal women are more often due to hyperthecosis than virilizing ovarian tumors. Patients with hyperthecosis likely have an increased risk of endometrial hyperplasia and perhaps endometrial carcinoma. A correlation exists between the severity of hyperthecosis and degree of insulin resistance. Familial occurrences of hyperthecosis have been reported as well.

Biochemical findings can include elevated testosterone levels, with serum total testosterone levels above 200 ng/dl. DHEAS levels tend to be normal. As with our patient, hyperinsulinemia is commonly seen (3). The diagnosis of hyperthecosis can only be definitely made by histological analysis of tissue sample with the presence of nests of luteinized cells in the ovarian stroma. Other findings that raise the suspicion of hyperthecosis include marked bilateral ovarian enlargement, with average ovarian volume above 10 cm³. The normal postmenopausal ovary has mean volume of 2.5–3.7 cm³ (2).

Definitive treatment of hyperthecosis is bilateral oophorectomy. Other modalities that can be used to treat the symp-

toms of hyperthecosis include oral contraceptive pills in premenstrual women, aldosterone antagonists (e.g. spironolactone), and GnRH agonists (e.g. leuprolide) (4). The testosterone level of our patient decreased with initiation of aldactone. For patients found to have insulin resistance, metformin and thiazolidinediones can be used (5).

Ovarian hyperthecosis is an infrequent cause of hyperandrogenism in postmenopausal women, is rarely described in the literature, and often only in the form of case reports. This case highlights the potential for the ovaries in a postmenopausal female to cause hyperandrogenism. One key point from our patient was the findings on ovarian ultrasound, in which the patient's ovaries were reported to be normal size by radiology. However, when the patient's postmenopausal status was taken into account, the ovaries were in fact enlarged. As mentioned above, marked bilateral ovarian enlargement is a key finding in hyperthecosis and will help in determining the etiology of hyperandrogenism in the postmenopausal female.

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FOUNDATION NEWS

EFF Is Now on Facebook!

EFF has joined the social networking world and has a group page on Facebook. When you logon to Facebook, search for “Endocrine Fellows Foundation” (not EFF). Several endocrine Fellows are already on this page, so join them and network with your colleagues.

Grant Award Recipients for the 2009 Fall Cycle

FELLOWS DEVELOPMENT RESEARCH GRANT PROGRAM IN DIABETES, OBESITY, AND FAT CELL BIOLOGY

This research grant is supported by an unconditional educational grant from Amylin Pharmaceuticals, Inc. and provides for clinical grants in the area of cardiometabolic disorders in obesity and diabetes. Four grants have been awarded for the 2009 Fall Cycle in the amount of \$20,000.00 each.

Anna Milanesi, M.D.—Cedars Sinai Medical Center

“Bone Marrow Derived Stem Cell for Type 1 Diabetes”
Program Director, Jane Weinreb, M.D.

Jennifer Park, M.D.—University of California, San Francisco

“The Role of the Calcium-Sensing Receptor (CaR) in the Hypothalamic Regulation of Appetite and Energy Homeostasis”

Program Director, Michael German, M.D.

Paul Piper, M.D.—University of Texas Southwestern Medical Center

“Investigating Ghrelin Secretion in Primary Cell Culture”

Program Director, William Kovacs, M.D.

Carolina Solis, M.D.—University of Texas Health Sciences Center San Antonio

“Effect of Plasma Glucose Reduction by Selective SGLT2 Inhibition on Mitochondrial Dysfunction and Impaired Insulin Sensitivity and β Cell Dysfunction in T2DM”

Program Director, Ralph DeFronzo, M.D.

MARILYN FISHMAN GRANT FOR DIABETES RESEARCH

This research grant, named in honor of EFF’s long-time executive director, is funded through an unconditional education grant from the partnership of Bristol-Myers Squibb and AstraZeneca International and is limited to studies involving type 2 diabetes. Four grants have been awarded for the 2009 Fall Cycle in the amount of \$15,000.00 each.

Caroline Messer, M.D.—Mount Sinai Medical Center

“Pancreatic β -Cell Dysfunction in PCOS Patients: The Role of Metformin”
Program Director, Robert Yanagisawa, M.D.

Joanna Mitri, M.D.—Tufts Medical Center

“The Effects of Vitamin D Supplementation on Systemic Inflammation, Lipid Profile and Endothelial Dysfunction in Pre-Diabetes”

Program Director, Ronald Lechan, M.D., Ph.D.

Sadaka Shahani, M.D.—Baylor College of Medicine

“Effect of Bariatric Surgery on Vascular Inflammation and Insulin Resistance in Patients with Metabolic Syndrome”

Program Director, Ashok Balasubramanyam, M.D.

Jeanie Tryggestad, M.D.—University of Oklahoma Health Sciences Center

“Vascular Compliance and Endothelial Function in Children with Obesity and Type 2 Diabetes”

Program Director, Steven Chernausek, M.D.

THE EFF ENDOCRINE RESEARCH GRANT

This grant is for general endocrine topics, including, but not limited to, thyroid, bone, adrenal, pituitary, growth, and reproductive disorders. Two grants have been awarded for the 2009 Fall Cycle in the amount of \$7,500.00 each.

David Howard, M.D.—University of Colorado Denver

“Circulating Triglyceride Saturation, Not Concentration, Predicts Insulin Resistance and Cardiovascular Disease in Humans”

Program Director, Daniel Bessesen, M.D.

Natalie Shaw, M.D.—Massachusetts General Hospital

“Effect of Sleep Apnea on Nocturnal GnRH/LH Pulsatile Secretion in Children in Early Puberty”

Program Director, Joseph A. Majzoub, M.D.

Cycle 1, Spring 2010 Research Grant Applications

The on-line research grant application process will be available at the end of January 2010 for Cycle 1, Spring 2010 grant applications. Please see the EFF web site, www.endocrinefellows.org, for more information.