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Presentation of Case

Dr. Jennifer L. Lyons (Medicine): A 75-year-old man was admitted to this hospital because of the recent onset of hypertension, hyperglycemia, and edema.

The patient had been in his usual state of health, with borderline hypertension and glucose intolerance, until 11 days earlier, when at a routine visit to his internist, the blood pressure was 171/75 mm Hg. The pulse was 73 beats per minute and the weight 101 kg. The physical examination was normal. The serum levels of total protein, albumin, globulin, bilirubin, alkaline phosphatase, cholesterol, lipids, creatine kinase, iron, iron-binding capacity, ferritin, vitamin B₁₂, free thyroxine (T₄), and total triiodothyronine (T₃) and tests of liver function were normal; other laboratory-test results are shown in Table 1. He was instructed to check his blood pressure and serum glucose levels at home, and a follow-up appointment was scheduled.

During the following week, the patient reported blood pressures from 160 to 186 mm Hg systolic and from 79 to 82 mm Hg diastolic, and a glucose level (according to finger-stick testing after an overnight fast) of 170 to 286 mg per deciliter (9.4 to 15.9 mmol per liter). He noted ankle swelling, weight gain of 4.5 kg, pain in both calves that made it difficult to walk, and intermittent double vision. Two episodes of left-sided epistaxis occurred, which resolved spontaneously. The night before admission, a frontal headache developed (rated 6 of 10 on a scale in which 10 is the most severe). He recorded a systolic blood pressure of 206 mm Hg. He came to the emergency department of this hospital at 1:30 a.m.

The patient reported noticing pedal edema intermittently for 1 month, which had increased during the previous week; one episode of hematuria had spontaneously resolved. He did not have shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, fevers, chills, nausea or vomiting, lower abdominal pain, or bowel or urinary symptoms. A diagnosis of hemochromatosis (homozygous C282Y mutation) had been made 8 years earlier, after routine laboratory tests showed elevated levels of serum iron and reduced iron-binding capacity, and was treated with regular phlebotomy. A diagnosis of prostate cancer had been made 22 years earlier and was treated with radical prostatectomy; pathological examination of the tissue
reportedly showed no evidence of lymph-node metastases, but the serum level of prostate-specific antigen (PSA) did not fall to 0 after the operation. Four years before admission, the serum level of PSA was 21.0 ng per milliliter, and administration of bicalutamide was begun. Six months later, the level of PSA was 2.3 ng per milliliter, and 8 months before admission it was 8.75 ng per milliliter. Bilateral adrenal nodules (2.1 cm by 1.8 cm on the left, and 2.3 cm by 1.1 cm on right) had been present and stable in size on multiple computed tomographic (CT) studies of the abdomen during the previous 6 years and were thought to represent adenomas.

Bilateral thyroid adenomas had been present for 15 years; 11 years before admission, a left thyroidectomy revealed a follicular adenoma. A nodule on the right thyroid had been stable; 2 years earlier, pathological examination of a specimen from a fine-needle aspiration biopsy showed benign follicular cells consistent with follicular adenoma. He had a history of colonic adenomas,
The remainder of the examination was normal. Dr. Graham T. McMahon: This 75-year-old man had a recent onset of hypertension, edema, hyperglycemia, and hypokalemic metabolic alkalosis; a rising level of PSA; and new liver lesions suggestive of metastatic tumor.

The acute onset of hypertension in an older patient warrants investigation. Acute, severe, or refractory blood-pressure elevation suggests secondary hypertension. Pheochromocytoma and hypothyroidism usually cause symptoms that this patient did not have, such as palpitations and constipation, respectively. Physical examination can provide clues that may suggest renovascular hypertension.

Differential Diagnosis

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disease, coarctation of the aorta, sleep apnea, and Cushing’s syndrome. A laboratory evaluation may be necessary to rule out primary hyperaldosteronism or primary hyperparathyroidism among others. In this case, mineralocorticoid excess and volume expansion are suggested by hypertension that is accompanied by edema, jugular venous distention, hypokalemia, and an elevated level of basic natriuretic peptide. Glucocorticoid excess is suggested by the presence of hyperglycemia and neutrophilia. In high concentrations, cortisol or its metabolites may induce volume retention by overwhelming 11β-hydroxysteroid dehydrogenase type 2 and activating the mineralocorticoid receptor.

May we review the imaging studies?

Dr. Michael A. Blake: CT of the abdomen obtained with the administration of intravenous contrast material on admission (Fig. 1A) shows multiple new, low-density lesions throughout the liver, which are highly suggestive of metastatic disease. The adrenal glands are enlarged, and the adrenal nodules (Fig. 1B) are bigger than they were on a scan obtained 2 years earlier. Examination of the pelvis was interpreted as showing no changes from previous examinations. Chest CT at the level of the thyroid gland shows evidence of the previous left hemithyroidectomy. There is heterogeneity of the remaining right lobe, which was stable in appearance and had been previously sampled, with no evidence of malignant conditions. Near the level of the hila, four new pulmonary nodules were noted, 5 mm or less in diameter, that were suggestive of metastatic disease (Fig. 1C).

Dr. McMahon: In endocrine disorders, the pace of the presentation can be an important indicator of the relative benignity of the underlying disease. In addition, pattern recognition is an important component of endocrinologic diagnosis, since most hormonal disorders present with diffuse metabolic and clinical derangements (Table 2), as in this case. The rapid onset of hypertension and metabolic changes and the presence of new liver lesions raise the specter of paraneoplastic Cushing’s syndrome, with severe hypercortisolism.

**CUSHING’S SYNDROME**

Cushing’s syndrome results from sustained hypercortisolism. The most common cause is administration of exogenous glucocorticoids. Secretion of corticotropin from the pituitary (Cushing’s disease) accounts for approximately 70% of endogenous cases; adrenal tumors and the ectopic production of corticotropin each account for ap-
proximately 15% of cases. The clinical and laboratory features of Cushing’s syndrome overlap with many other medical conditions, and very few patients fulfill the classic presentation of facial rounding, weight gain, striae, hirsutism, hypertension, and muscle weakness. The majority of patients have abnormal glucose tolerance, but edema and hypokalemic alkalosis, as seen in this patient, occur in only a minority. This patient had gynecomastia, which is not typical in Cushing’s syndrome but can be a manifestation of hypogonadism or a consequence of hyperestrogenemia from a hormonally active tumor. Gynecomastia occurs in approximately 10% of men treated with bicalutamide.

The diagnosis of Cushing’s syndrome requires the confirmation of hypercortisolism, generally with the measurement of 24-hour urinary cortisol excretion, measurement of midnight salivary cortisol levels, or both. Autonomous production of cortisol can be demonstrated with the use of a dexamethasone (1-mg) suppression test. Once hypercortisolism is established, a corticotropin level of more than 20 pg per milliliter (4.4 pmol per liter) suggests corticotropin dependency; a level below 5 pg per milliliter (1 pmol per liter) suggests an adrenal source. When corticotropin dependency is established, magnetic resonance imaging can identify pituitary tumors approximately 60% of the time.

The patient's left-sided facial droop and left-sided epistaxis are not readily attributable to a benign pituitary adenoma. Nevertheless, pituitary enlargement in response to a tumor that produces corticotropin-releasing hormone or a primary benign or malignant pituitary tumor could account for some of the patient’s visual symptoms.

The standard method for differentiating between Cushing’s disease and the ectopic production of corticotropin involves venous sampling from the inferior petrosal sinus. Cushing’s disease is the most likely diagnosis if the sinus-to-peripheral-vein ratio of plasma corticotropin is at least 2:1 before or at least 3:1 after injection of corticotropin-releasing hormone during sampling from the inferior petrosal sinus. Ectopic production of corticotropin is implicated if 8 mg of dexamethasone does not suppress the plasma cortisol level, although this test lacks sensitivity.

### Adrenal Nodules

The accelerated development of Cushing’s syndrome in a patient with known adrenal tumors introduces the differential diagnosis of adrenocortical carcinoma. Adrenal tumors, adrenal hyperplasia, and primary pigmented nodular adre-
necrotic and carcinomatous changes can lead to Cushing's syndrome, although the presentation of these conditions tends to be gradual.

Adrenocortical carcinoma is very rare, with an annual incidence of approximately two cases per 1 million population. Of the 60% of adrenocortical carcinomas that are functional (i.e., hormone-secreting), 45% secrete both androgens and glucocorticoids; the rest secrete glucocorticoids alone (45%), androgens alone (10%), or, rarely, aldosterone (<1%). The clinical manifestations of hormone excess in adrenocortical carcinomas are rapidly progressive, as in this case.

Imaging can be helpful in differentiating benign from malignant adrenal masses. Low attenuation on a CT scan obtained without the administration of contrast material suggests a substantial lipid content that is most consistent with adrenal adenoma. Adrenal adenomas also tend to wash out at least 60% of the contrast material within 15 minutes after contrast administration. Adrenal cancers generally have an irregular appearance, high attenuation, and rapid growth. None of these are apparent in this case, and the relative stability of this patient's tumors in recent years makes a diagnosis of adrenocortical cancer unlikely. It is more likely that the recent bilateral adrenal enlargement in this case is due to either adrenal metastases or adrenal hyperplasia in response to corticotropin than to the development of hormonally active adrenal nodules.

**The Ectopic Corticotropin Syndrome**

Cushing's syndrome was first reported in 1928 in a patient with small-cell lung cancer; in the 1960s, corticotropin was shown to be the link between tumors (benign and malignant) and Cushing's syndrome. In patients with cancer, Cushing's syndrome generally develops quickly and is associated with extremely high levels of corticotropin and severe hypercortisolemia. Metabolic abnormalities tend to predominate in the clinical presentation, as in this case. Hypokalemia is present in approximately 70% of patients with Cushing's syndrome and is related to the degree of hypercortisolemia. The physical phenotype of Cushing's disease (i.e., facial fullness, a dorsocervical fat pad, and striae) may be absent in patients with ectopic corticotropin production, since these signs take weeks or months to develop. Pigmentation appears to be common in patients with small-cell lung cancer, and neuropsychiatric abnormalities have a particular association with neuroendocrine tumors.

Small-cell lung cancers, bronchial carcinoids, thymic tumors, islet-cell tumors of the pancreas, medullary thyroid carcinomas, and pheochromocytomas have all been associated with ectopic corticotropin secretion. The source of ectopic corticotropin remains unidentified in approximately 10% of patients with the syndrome, but that percentage has declined with improvements in imaging.

**Colon and Thyroid Carcinomas**

The patient had a colonic lesion with high-grade dysplasia. Although metastatic colonic adenocarcinoma has been associated with the ectopic corticotropin syndrome, these cases are rare. The patient also had follicular nodules of the thyroid. In contrast to medullary thyroid carcinomas, follicular adenomas and follicular carcinomas have not been associated with the ectopic corticotropin syndrome.

**Prostate Cancer**

This patient had a history of prostate cancer and progressive elevation in his serum PSA level, despite treatment with the androgen-receptor blocker bicalutamide. Small-cell neuroendocrine carcinoma accounts for only 1 to 2% of prostatic carcinomas, and prostatic tumors account for less than 2% of cases of the ectopic corticotropin syndrome. Neuroendocrine cells are found throughout the prostate and can secrete various active compounds including corticotropin, serotonin, chromogranin A, neuron-specific enolase, bombesin, calcitonin, and parathyroid-hormone-related protein. Neuroendocrine differentiation in prostate cancer has been reported to occur in patients treated with androgen ablation and carries a poor prognosis. Case reports of patients with ectopic corticotropin syndrome due to prostatic neuroendocrine carcinoma suggest that edema and hypokalemia are common and widely metastatic disease is present at diagnosis; the level of PSA is variably elevated.

**Summary**

Though the differential diagnosis remains broad, this patient's clinical picture, particularly the acute nature of the presentation, is most consis-
tent with a diagnosis of metastatic neuroendocrine cancer complicated by ectopic corticotropin syndrome. While awaiting the results of hormonal testing and medically stabilizing the patient, I would obtain a biopsy specimen of one of the liver lesions to confirm the diagnosis.

**Dr. Nancy Lee Harris (Pathology): Dr. Lyons, would you tell us what the clinical thinking was?**

**Dr. Lyons:** Our suspicion was high for Cushing’s syndrome due to carcinoma metastatic to the liver. The initial workup included diagnostic testing for Cushing’s syndrome, including measurement of urinary free cortisol and salivary cortisol levels, and then we arranged for a liver biopsy.

**CLINICAL DIAGNOSIS**

Metastatic neuroendocrine carcinoma (most likely of prostatic origin), with the ectopic corticotropin syndrome.

**DR. GRAHAM T. MCMAHON’S DIAGNOSIS**

Metastatic neuroendocrine carcinoma (most likely of prostatic origin), with the ectopic corticotropin syndrome.

**PATHOLOGICAL DISCUSSION**

**Dr. Chin-Lee Wu:** A fine-needle aspiration of the liver was performed (Fig. 2). On the cores of liver tissue, small groups of malignant tumor cells were seen in lymphatic channels. The tumor cells are small and round with scant cytoplasm, indistinct cell borders, hyperchromatic nuclei with finely granular chromatin, nuclear molding, and inconspicuous nucleoli. On immunohistochemical staining, the tumor cells expressed the epithelial marker cytokeratin, thyroid transcription factor 1 (TTF-1), and the neuroendocrine marker chromogranin A; many cells expressed corticotropin, evidence that they are the source of ectopic corticotropin hormone. The tumor cells were negative for PSA.

Small-cell carcinoma is an aggressive neuroendocrine cancer most commonly seen in the lung, but it can also arise in extrapulmonary organs, including the prostate. In some patients who have had a conventional adenocarcinoma of the prostate, the disease may recur as a small-cell carcinoma after hormonal therapy and present with a paraneoplastic syndrome. Approximately half the cases of small-cell carcinoma of the prostate express TTF-1, a protein that is frequently expressed in thyroid and pulmonary tumors, including non–small-cell carcinomas. Prostate markers such as PSA are usually not expressed in the small-cell carcinoma of the prostate.

In summary, the pathological diagnosis is metastatic small-cell carcinoma. The origin of the tumor cannot be determined on the basis of the pathological findings alone. However, evaluation did not reveal pulmonary or other extrapulmonary cancers. Thus, the combined pathological and clinical features are most consistent with small-cell carcinoma of prostatic origin.

**Dr. Blake:** CT scans of the pelvis performed 1 month after admission show a mass in the region of the pelvis that is consistent with recurrent prostatic cancer (Fig. 3A). Although the pelvic CT scan on admission was initially reported as showing no change from previous studies, in retrospect, this mass was present but was partially obscured by streak artifact from surgical clips. An 18F-fluorodeoxyglucose (FDG) positron-emission tomographic scan (Fig. 3B) obtained 1 month later showed intense uptake of FDG in the liver metastases; there was also intense uptake in bone metastases that was not apparent on the initial CT scan. The adrenal masses showed only mild FDG uptake, suggesting that the increase in their size may have been due to the influence of corticotropin, as proposed by Dr. McMahon.

**DISCUSSION OF MANAGEMENT**

**Dr. McMahon:** Medical management of hypercortisolism is often necessary in preparation for surgery or for palliation. The principal treatments are metyrapone and ketoconazole. Metyrapone would need to be used cautiously in this case, since inhibition of 11β-hydroxylase may increase androgen levels in the presence of an elevated corticosterone level. Ketoconazole may be especially appropriate for a patient with prostate cancer, since it should reduce androgen production in the adrenal gland. Other drugs include aminoglutethimide, mitotane, mifepristone, and somatostatin analogues. Surgical adrenalectomy is occasionally necessary if excision of the corticotropin-producing tumor is either impossible or not curative.
Dr. Harris: I would like to ask Dr. Geoffrey Walford from Endocrinology and Dr. Atish Choudhury from Medical Oncology to discuss their management of this patient's disease.

Dr. Geoffrey A. Walford (Endocrinology): The diagnosis of corticotropin-dependent Cushing's syndrome was confirmed by markedly elevated urinary free cortisol, late-night salivary cortisol, and serum corticotropin levels. Insulin, spironolactone, and antihypertensive medications were used to manage hyperglycemia, hypokalemia, and hypertension, respectively. Treatment with
Ketoconazole and, later, metyrapone was begun to reduce the synthesis of cortisol. The patient had a good response to this regimen. Cortisol levels fell to values at the low end of the normal range, and prednisone was begun to prevent the expected hypoadrenalism. Edema of the lower extremities was treated with diuretics.

Figure 3. Follow-up Imaging Studies.
An axial image from a pelvic CT scan obtained after the administration of intravenous contrast material shows a mass (Panel A, arrow) in the region of the prostate that is highly suggestive of a prostatic tumor. The lesion was present on admission but was not recognized because of streak artifact from the surgical clips. An axial image from a positron-emission tomographic scan after the administration of $^{18}$F-fluorodeoxyglucose (FDG) shows intense uptake of FDG in the liver metastases (Panel B, arrows) and in a bony metastasis in the spine (arrowhead). Neither of the adrenal masses show significant uptake, suggesting that their increase in size may have been due to the influence of corticotropin. Coronal images from a technetium-99m–labeled methylene diphosphonate bone scan (posterior view) (Panel C) and a CT scan displayed on bone windows (Panel D), both obtained 3 months later while the patient was receiving chemotherapy, show multiple abnormal foci of radiotracer uptake (arrows) in the bones corresponding to sclerotic lesions (arrows) on the CT scan, features consistent with bony metastases.
extremities resolved, and he was able to discontinue insulin, spironolactone, and antihypertensive agents.

Dr. Atish Choudhury (Oncology): The standard first-line palliative chemotherapy regimen for small-cell carcinoma is carboplatin and etoposide, which was initiated while the patient was in the hospital. Soon after the initiation of chemotherapy, the corticotropin level decreased to normal levels. The patient's blood pressure, edema, and levels of blood sugars and electrolytes all improved toward normal.

Approximately 3 months later, after four cycles of chemotherapy, restaging by means of CT scans showed that the liver metastases and pulmonary nodules had decreased in size. Ketoconazole and metyrapone were discontinued. Despite resolution of visceral disease, the bony disease progressed.

Dr. Blake: A bone scan with technetium-99m-labeled methylene diphosphonate (Fig. 3C) and a CT scan displayed on bone windows (Fig. 3D) were obtained after the patient had received the four cycles of chemotherapy. Multiple abnormal foci of radiotracer uptake in the bones correspond to newly seen sclerotic lesions on the CT scan, features consistent with bony metastases.

Dr. Choudhury: We suspected that the visceral disease and the bony disease may represent two different processes, with the bony disease representing progression of his original prostatic adenocarcinoma in the bone. Although his PSA level had been rising while he was taking bicalutamide at initial presentation, we thought that the progression of his prostatic adenocarcinoma while his corticotropin levels were high could have been related to excessive adrenal production of androgens, which would have overwhelmed the ability of bicalutamide to inhibit their action. After the corticotropin level normalized, we restarted bicalutamide and initiated treatment with a gonadotropin-releasing hormone agonist (leuproide); the PSA level decreased from 17 to 2 ng per milliliter.

Unfortunately, despite an excellent initial response to chemotherapy, the small-cell cancer recurred within 2 months after completion of six cycles of therapy; also, levels of corticotropin and cortisol rose and symptoms recurred. At this time, the patient elected not to pursue further therapy, and he died in the hospital in the company of family members, approximately 7 months after the diagnosis.

Dr. Richard J. Lee (Medical Oncology): The patient expressed gratitude before his death that he was to be the subject of a case history, so that others could learn from his experience.

ANATOMICAL DIAGNOSIS

Secondary Cushing's syndrome due to metastatic small-cell carcinoma of prostatic origin.

Presented at the Medicine Case Conference, February 27, 2009.

Dr. Wu reports being listed as a coinventor on patents related to the diagnosis of prostate cancer; as of publication, these patents have not been licensed. No other potential conflict of interest relevant to this article was reported.

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