A 57-year-old man with a past medical history significant for hypertension and non-insulin-dependent diabetes mellitus presented for evaluation of chronic hypokalemia. Initially, the low potassium levels were attributed to his antihypertensive medication. However, hypokalemia persisted despite discontinuation of all potassium-wasting diuretics and supplementation with 80 mEq of oral potassium daily. A metabolic workup showed a plasma potassium level of 2.7 mEq/L (reference range, 3.5–4.7 mEq/L) and a plasma aldosterone level of 47 ng/dL (reference range, 4–31 ng/dL) (1.30 nmol/L; reference range, 0.11–0.86 nmol/L). The plasma renin activity was decreased, with a plasma aldosterone–plasma renin activity ratio of 47. The sodium level was mildly elevated at 148 mEq/L (reference range, 137–145 mEq/L). The magnesium, chloride, and bicarbonate levels, pH, white blood cell count, and cortisol levels were all within the reference ranges. The patient was given spironolactone therapy. A radiologic workup with abdominal computed tomography and magnetic resonance imaging demonstrated a left renal mass with solid and cystic components that was 3.2 cm in greatest dimension; the workup also revealed enlargement and prominence of the left adrenal gland.

The patient underwent left adrenalectomy and partial left nephrectomy. The 14-g left adrenal gland measured 4.8 × 3.0 × 2.0 cm and contained 4 golden yellow, well-circumscribed nodules scattered throughout the cortex that ranged from 0.3 to 0.8 cm in greatest dimension. The remaining normal adrenal cortex was unremarkable. The nodules did not invade the adrenal capsule or adrenal medulla. Within the parenchyma of the left partial nephrectomy specimen was an oval, well-circumscribed, centrally cystic, variegated yellow-gray to tan nodule that was 3.2 cm in greatest dimension.

Microscopically, the cells of the adrenal nodules ranged from large, pale, lipid-rich cells resembling the zona fasciculata to eosinophilic cells with a granular cytoplasm resembling the zona glomerulosa. There were areas of mild nuclear and cellular pleomorphism without anaplasia or necrosis. Focally, the cells of the nodules contained small eosinophilic intracytoplasmic inclusions with a laminated appearance surrounded by a clear halo (Figure 1). A Luxol fast blue stain of these inclusions was characteristic of the pathologic entity (Figure 2). The nodules were partially surrounded by a fibrous pseudocapsule. The renal mass showed cystic acini with a focal papillary architecture composed of clear cells with small uniform nuclei and occasional nucleoli (Figure 3).

**What is your diagnosis?**
Primary hyperaldosteronism refers to a group of disorders characterized by an autonomous overproduction of aldosterone. When this condition is caused by an aldosterone-secreting adrenocortical adenoma, it is termed Conn syndrome. Conn syndrome is the most common cause of primary hyperaldosteronism, occurs most frequently in adult middle age, and is more common in women than in men (2:1 male-female ratio). It is a rare but curable cause of hypertension.

Clinical symptoms are related to hypokalemia and hypertension, and may include weakness, paresthesias, cramps, tetany, fatigue, headache, and visual disturbances. Other signs may include electrocardiographic changes. Hypertension is usually moderate to severe. A few patients may be asymptomatic or have normal blood pressure.

The initial clinical workup is biochemical rather than radiologic, as imaging is not highly sensitive and may fail to demonstrate a tumor. In addition, there is a 2% to 10% incidence of nonfunctioning adrenal masses identified by computed tomography studies of the abdomen, referred to as incidentalomas. Plasma renin activity is suppressed in almost all patients with primary hyperaldosteronism, although it is also suppressed in 25% of patients with essential hypertension. A concomitant elevation of plasma aldosterone makes the diagnosis of primary hyperaldosteronism more likely. A plasma aldosterone–plasma renin activity ratio of greater than 25 is suggestive, and a ratio of greater than 50 is virtually diagnostic of primary hyperaldosteronism. The captopril test can also be used in diagnosis; during this test, administration of captopril fails to suppress aldosterone levels in affected patients. Many other biochemical tests are also used in evaluation. The imaging test of choice is computed tomography, which has a sensitivity of more than 80%. The differential diagnosis of primary hyperaldosteronism includes idiopathic hyperplasia, adrenocortical carcinoma, and glucocorticoid-responsive aldosteronism, in addition to Conn syndrome.

The treatment of choice for aldosterone-producing adenoma is adrenalectomy, and the laparoscopic technique is now widely used. These tumors can recur after adrenalectomy. Presurgical treatment with spironolactone for 3 to 4 weeks helps normalize potassium levels and minimize postoperative hypokaldosteronism. The outcome after adrenalectomy is good for the majority of patients, with marked reduction of hypertension.

Grossly, aldosterone-producing adrenocortical adenomas are typically small (<2 cm), unilateral, and solitary, although they have occasionally been reported to be bilateral or multiple. They are typically round to ovoid, golden yellow, and sharply demarcated, often by a pseudocapsule. The uninvolved adrenal cortex appears grossly normal, without atrophy. In contrast, adrenocortical carcinomas are typically bulky tumors averaging greater than 6 cm in maximum dimension at the time of diagnosis, with a weight of greater than 95 g.

Histologically, tumor cells of aldosterone-producing adrenocortical adenomas are typically arranged in small nests and cords. The majority of cells resemble the pale-staining, lipid-laden cells of the zona fasciculata, although they are larger. The morphology of individual cells may be heterogeneous, with cells resembling glomerulosa, fasciculata, or reticularis, or hybrid cells resembling both glomerulosa and fasciculata. Most tumor cells have small, round to oval vesicular nuclei, with small distinct nucleoli, although there may be some nuclear pleomorphism. Adenomas typically have fewer than 2 mitotic figures per 10 high-power fields and lack necrosis. An increased number of mitotic figures (>4 per 10 high-power fields), atypical mitoses, hemorrhage, and tumor necrosis suggest a diagnosis of carcinoma.

Treatment with spironolactone may result in spironolactone bodies in the aldosterone-producing tumor cells as well as in zona glomerulosa cells of the residual normal cortex. They appear as small, eosinophilic, lamellated intracytoplasmic inclusions, often demarcated from the surrounding cytoplasm by a clear halo. They are rich in phospholipid and stain medium blue with the Luxol fast blue stain.

The low-grade cystic renal cell carcinoma in this case was a coincidental finding. The tumor was entirely confined within the renal parenchyma, without evidence of capsular or vascular invasion. The partial nephrectomy margin of the resection specimen was free of tumor.

References