A 42-year-old man attended his primary care physician complaining of fatigue. He had a medical history of Coxsackie B myocarditis in 2002 from which he had recovered fully as well as hypertension. His blood pressure had been well controlled on 3 agents (furosemide 40 mg daily, amlodipine 10 mg daily, and perindopril 8 mg daily). He had no notable family history.

Physical examination was unremarkable, but his blood pressure remained consistently elevated at 186/98 mmHg. Routine biochemical investigation revealed new onset of hypokalemia (serum potassium, 2.3 mmol/L).

Discussion of Differential Diagnosis

E.M. Freel: What would be the two most likely underlying differential diagnoses?

J.A. Staessen: What is the role of diuretic therapy in the hypokalemia? And the other question I have as a hypertension specialist? Why do you give furosemide?

E.M. Freel: Furosemide was discontinued. His potassium was rechecked, and it remained low. That is a very good point.

In our defense, he came to us as a tertiary referral. We would always use thiazide diuretics, particularly in someone with normal renal function. His diuretic was changed to a different agent to allow subsequent testing off diuretic, I think this alternative agent was an α-blocker.

G.L. Jennings: Perhaps the furosemide was a leftover from his myocarditis in the past.

E.M. Freel: Possibly. This gentleman has very intermittently attended his General Practitioner over the years, and it was a historical treatment.

J.P. Granger: Do you have any insight into the renal hemodynamics such as creatinine?

E.M. Freel: It was normal. The only abnormality on his routine biochemistry was hypokalemia which was new.

M. De Buyzere: What do we know about aldosterone?

E.M. Freel: Nothing yet, but we soon will.

E.L. Schiffrin: You asked for the 2 diagnoses, and nobody gave them yet. Primary hyperaldosteronism is one and the potential for renal artery stenosis that could also be associated with hyperaldosteronism and hypokalemia.

E.M. Freel: Yes.

G.L. Jennings: A third is other forms of secondary hyperaldosteronism such as liquorice?

E.M. Freel: Statistically, the most likely causes of this gentleman’s hypertension are primary aldosteronism or renal vascular disease.

Further Discussion of Differential Diagnosis

Thus, there was strong clinical suspicion of primary aldosteronism or renal artery stenosis as a cause for his worsening hypertension and hypokalemia. However, both plasma renin concentration and plasma aldosterone were suppressed which would effectively exclude both conditions.

Other causes of mineralocorticoid hypertension were considered and are outlined in the Table. There was no clinical evidence of Cushing syndrome, and screening tests were not in keeping with cortisol excess. The lack of family history of significant hypertension and previously normal serum potassium made a rare genetic disorder such as Liddle syndrome, in which constitutive opening of the renal epithelial sodium channel leads to chronic sodium retention and urinary potassium excretion leading to hypertension and hypokalemia less likely but not impossible.

Next Diagnostic Steps

E.M. Freel: I welcome some suggestions from the audience as to what investigation they would recommend now. Perhaps to exclude the unlikely but possible diagnoses: 11β-hydroxylase deficiency, 17α-hydroxylase deficiency, syndrome of apparent mineralocorticoid excess.

M. De Buyzere: Were there data on 24-hour urinary corticosteroids? Or was there imaging of the adrenals?

E.M. Freel: That is exactly right. It was very important that we performed a 24-hour urine collection to look at this gentleman’s multisteroid profile and look at his urinary corticosteroid biosynthetic pathway. So that is exactly what we did.

A 24-hour urine was performed for assessment of production of corticosteroids and their precursors by gas chromatography–mass spectrometry. Figure 1 illustrates the corticosteroid biosynthetic pathway in the adrenal cortex and demonstrates (yellow boxes) that this patient had elevated mineralocorticoid precursors deoxycorticosterone, deoxycorticosterone, and corticosterone.

The abnormal steroids were not in a pattern characteristic of rare genetic disorders in which enzyme deficiencies such as 11β-hydroxylase and 17α-hydroxylase results in
mineralocorticoid hypertension attributable to elevated mineralocorticoid precursors. Therefore, the only other explanation was that there was disordered adrenal architecture such as an adrenal tumor, and so a computed tomographic scan of the adrenal glands was requested.

**Confirmation of Diagnosis**

The adrenal computed tomographic scan (Figure 2) demonstrated a 7-cm heterogeneous left adrenal mass characteristic of adrenocortical carcinoma (ACC).

E.L. Schiffrin: So, when one has such an abnormal production of metabolites by the adrenals, should one think specifically of some type of tumor?

E.M. Freel: Essentially yes, unless the patient in question was a neonate, in which case an inborn or congenital abnormality listed above would be likely. But an adult patient presenting with this very odd pattern, it’s really only going to be an abnormality of architecture.

**Surgical Treatment**

The patient underwent left adrenalectomy and nephrectomy in May 2012. Histopathology confirmed ACC with clear excision margins, no involvement of excised lymph nodes, and an intact adrenal capsule. Hence, the tumor was staged as pT2 N0 M0. Malignancy was confirmed using the original Weiss criteria in which the presence of 3 positive features are required to confirm malignancy; this tumor had 6 positive features.

P. O’Dwyer: You may wonder why we took out this gentleman’s kidney. The computed tomographic scan didn’t show you that his vascular pedicle is involved with this tumor. He also has a premalignant lesion in his kidney. So, he had 2 good reasons for a laparoscopic adrenalectomy and nephrectomy. The tumor is 12 × 8 cm.

E.M. Freel: Would it be worth commenting on laparoscopic versus open adrenalectomy in this situation with a big tumor and a malignancy?

P. O’Dwyer: We attempt laparoscopic adrenalectomy on everybody and the reason for that is both the view you get, particularly on the right side you can operate much better on the right-hand side than doing an open. A very large one on the right-hand side required thoracoabdominal incision to get you the same access to a large right adrenal tumor. But laparoscopically, we can mobilize it and put it up over the right lobe of the liver. The cava is the key thing. If you are doing that in open surgery, you are using your hand and these are necrotic tumors and it is quite easy to perforate these tumors. I don’t think we have perforated any tumor laparoscopically because dissection is so much more gentle. More than 400

Table. Disorders Associated With Hypertension and Hypokalemia and the Corresponding Effects on Plasma Renin and Aldosterone Production

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Plasma Renin</th>
<th>Plasma Aldosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary aldosteronism</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Renin-secreting tumor</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Liddle syndrome</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>11β-Hydroxylase deficiency</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>17α-Hydroxylase deficiency</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Syndrome of apparent mineralocorticoid excess</td>
<td>↓</td>
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</tr>
</tbody>
</table>

E.L. Schiffrin: What you mean by that is that it is not a benign tumor.

E.M. Freel: That is entirely true. And that is confirmed by the radiological appearance of this tumor which by size alone would suggest malignancy. Benign tumors tend to be <4 cm.

11β-Hydroxylase deficiency indicates 11β-hydroxylase; 17β-Hydroxysteroid dehydrogenase; 3β-HSD, 3-beta-hydroxysteroid dehydrogenase; P-450, 17α-hydroxylase; and P-450, 21-hydroxylase.

**Figure 1. Corticosteroid biosynthetic pathway.** Elevated mineralocorticoid precursors highlighted in yellow. 3β-HSD indicates 3-beta-hydroxysteroid dehydrogenase; 17β-HSD, 17-beta-hydroxysteroid dehydrogenase; 11βOH, 11-beta-hydroxylase; DHEA, dehydroepiandrosterone; P-450, 17α-hydroxylase; and P-450, 21-hydroxylase.
adrenalectomies and we haven’t seen a local recurrence yet. And 40% of the tumors are >6 cm.

Postoperative Outcome

Within 1 month of surgery, his blood pressure normalized on dual therapy (amlodipine 10 mg daily and perindopril 8 mg daily) and his plasma potassium also returned to within the normal range. A subsequent 24-hour urine steroid profile was also normal. He was commenced on the adrenolytic drug, Mitotane (Lysodren, o,p′-DDD, a congener of the pesticide dichlorodiphenyltrichloroethane) which was well tolerated. However, 2 years later, the patient developed an isolated liver metastasis which was detected on routine surveillance imaging and resected in early 2014. He remains well and free from radiological or biochemical evidence of recurrence.

Adrenocortical Carcinoma

ACC is rare with an incidence of 1 to 2 cases/million per year and is more common in women than men (female: male: 1.5–2.5:1). Typically, there is a bimodal age distribution, with disease peaks before the age of 5 and in the fourth to fifth decade of life; the disease is usually more aggressive in adults than in children.3 Approximately 60% of ACC are hormone secreting and so may present with a clinical syndrome consistent with corticosteroid hormone excess.3 In 45% of cases, the clinical presentation can be consistent with Cushings syndrome (attributable to cortisol excess) or, in 25%, a combination of Cushings syndrome and androgen excess (leading to virilization). Less than 10% present with androgen excess alone and ≈1% present with aldosterone excess.5 Excess production of 17-deoxysteroids of the zona glomerulosa (deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone) as a manifestation of ACC is rare. There are only a few case reports in the literature, and so the exact prevalence is difficult to estimate but certainly accounts for <1% of all ACC.5

ACC carries a poor prognosis. Five-year survival is ≈45% to 60% for early-stage disease (stage I–II) and 10% to 25% for advanced stage disease (stage III–IV). Complete surgical resection is the only means of cure but is only possible in stage I to III disease.6 However, resection is not curative for many, probably attributable to the presence of occult micrometastases at the time of initial presentation, even with stage I disease. For example, in a single-center report of 202 consecutive cases of ACC, 40% of patients with stage I to III disease had developed distant metastasis 2 years after diagnosis (27%, 46%, and 63% of patients with stage I, II, and III disease, respectively).7

Given the aggressiveness of this disease and relatively disappointing surgical outcomes, use of adjuvant therapy is often required. In this setting, the most commonly used drug is the adrenolytic agent, mitotane (Lysodren, o,p′-DDD, a congener of the pesticide dichlorodiphenyltrichloroethane) which was used in the case outlined above. Although there is no prospective randomized controlled trial of adjuvant mitotane treatment in ACC, a retrospective observational study led by Terzolo et al6 provides the best evidence of clinical benefit.

In this study, 3 cohorts of patients from separate centers with stage I to III disease underwent surgery with curative intent. One cohort was given adjuvant mitotane, and the other two were not. Mitotane treatment was associated with a significantly longer recurrence-free survival as compared with either control group (median recurrence-free survival, 42 versus 10 and 25 months in the Italian and German control groups, respectively). Therefore, use of mitotane for ≤2 years after apparently curative surgery for ACC is now standard practice although the question of its use in patients with apparently low-risk disease is currently being explored in the ADIUVO (Efficacy of Adjuvant Mitotane Treatment in Prolonging Recurrence-Free Survival in Patients with Adrenocortical Carcinoma at Low-Intermediate Risk of Recurrence) study.

There is no curative therapy for recurrent or metastatic ACC; however, resection of locally recurrent or distant disease may prolong survival in some patients.5–11 This is particularly true if the disease-free interval is >12 months as was the case with the patient outlined above. It is in the setting of recurrent disease that the largest prospective randomized trial of ACC to date was undertaken. The First International Randomized trial in locally advanced and Metastatic Adrenocortical Carcinoma Treatment (FIRM-ACT) trial randomly assigned 304 patients with advanced ACC not amenable to radical surgery to mitotane plus either combination chemotherapy (etoposide, doxorubicin, and cisplatin; EDP) or streptozotocin.12 There was a significantly prolonged progression-free survival in the mitotane–combination chemotherapy group; however, this was just 5 versus 2 months in the streptozotocin-treated group. Overall, survival was not significantly different (14.8 months in mitotane–combination chemotherapy, 12 months in mitotane–streptozotocin; P=0.07) suggesting that, although mitotane–combination chemotherapy was the best chemotherapy regime to be offered in advanced/recurrent ACC, the prognosis in this setting is dismal.

In summary, hypertension with hypokalemia is statistically most likely to be attributable to primary aldosteronism or renal artery stenosis. In this case, assessment of a baseline aldosterone-to-renin ratio should help begin to differentiate between these 2 disorders. Suppression of renin and aldosterone, as was the situation in this case, should result in a search for more obscure underlying causes of this clinical phenotype.
Final Discussion of Hot Topics in Adrenal Tumors

M. De Buyzere: Two questions. First question is are you aware of markers of very bad, a very poor prognosis? I am aware of a publication microRNA-210 would be predictive of a very poor prognosis. And the second question, there is a European network (European Network for the Study of Adrenal Tumours [ENSAT]) when you are faced with an adrenal mass. What do you think about these recommendations?

E.M. Freel: In Glasgow, we are members of ENSAT and we find this organization to be very useful, particularly in the management of incidental adrenocortical masses which we see lots of now on routine imaging. They comprise a large number of referrals to the endocrine clinic. And again I think you point out a very important point, that before we let P. O’Dwyer with his laparoscope go near any adrenal mass we always exclude catecholamine excess first. Irrespective of the imaging phenotype, some sort of assessment of catecholamine production always has to be done. In terms of criteria to try and predict a bad outcome, obviously ENSAT staging it at presentation will help do that. MicroRNA-210 is obviously very new, and it is not something we do routinely in analysis of our adrenal tumors although it is something we could be looking to do as part of the ENSAT network. But certainly the briskness of the tumor, the KI-67 index, is one indicator which we tend to use and just the number of positive Weiss criteria and the size of the tumor are all useful markers of prognosis.

E.L. Schiffrin: Perhaps going back to primary aldosteronism, would you like to comment on some of the mutations that occur in channels that may have a bearing on the development of adrenal adenomas/aldosteronomas?

E.M. Freel: Thank you. That has been a hugely burgeoning area in the last couple of years since the article in Science from Rick Lifton’s laboratory that showed there were somatic mutations in a potassium channel in about one third of patients with adnomatous primary aldosteronism and these were also identified in the germline of a small number of patients with a very rare syndrome (of familial hyperaldosteronism type III). Since the original article by Rick Lifton, with the help of ENSAT and other European adrenal tumor associations, there has been a lot of work looking at channels and looking at the genetics underlying adena-matous primary aldosteronism. There have been mutations now identified in roughly 40% of tumors. KCNJ5, which was the original mutation discovered in Rick Lifton’s laboratory, is the most predominant one and it results in the loss of selectivity of the potassium filter. As a result of this mutation, the adrenocortical cell is constantly activated and hypertrophies and proliferates and produces aldosterone.

There have also been mutations identified in calcium channels and in ATP channels, a huge growth area during the past 2 to 3 years.14,15

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None.

References

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