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PHAEOMOCYTOMA AND ACTH-DEPENDENT CUSHING’S SYNDROME: TUMOR CRF-SECRETION CAN MIMIC PITUITARY CUSHING’S DISEASE.

SHORT TITLE: CRF-secreting Phaeochromocytoma mimicking pituitary Cushing’s disease

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ABSTRACT

Introduction: 10% of corticotrophin (ACTH)-dependent Cushing’s syndrome arises from secretion by extra-pituitary tumors, with phaeochromocytoma implicated in a few cases. Ectopic secretion by phaeochromocytoma of corticotropin-releasing hormone (CRF), with secondary corticotroph hyperplasia, is even rarer, with only five cases in the literature hitherto. However, such cases may be classified as “ectopic ACTH” due to incomplete verification.

Clinical cases: We describe three patients with phaeochromocytoma and ACTH-dependent Cushing’s syndrome in whom biochemical cure was achieved following unilateral adrenalectomy. Although unable to access a validated CRF assay within the timeframe for sample storage, we nevertheless inferred CRF secretion in 2/3 cases by tumor-immunostaining (positive for CRF; negative for ACTH), supported in one case by pre-operative inferior petrosal sinus sampling (IPSS) indicative of pituitary ACTH source. Both cases were characterized by rapid post-operative wean off glucocorticoids, presumed to reflect the pituitary stimulatory-effect of CRF outweighing central negative feedback-inhibition by hypercortisolaemia. By contrast, the tumor excised in a third case exhibited positive immunostaining for ACTH -negative for CRF- and post-operative recovery of hypothalamo-pituitary-adrenal axis took significantly longer.

Discussion: Ectopic CRF production is biochemically indistinguishable from ectopic ACTH secretion, except that IPSS mimics pituitary Cushing’s disease and cortisol dynamics may normalize rapidly post-adrenalectomy. CRF secretion can be inferred through tumor-immunohistochemistry, even if no CRF assay is available. Unrecognized phaeochromocytoma ACTH-secretion may underpin some cases of cardiovascular collapse post-adrenalectomy through acute hypocortisolaemia. Despite advances in phaeochromocytoma genetics since previous reports, we were unable to identify somatic DNA defects associated with either ACTH- or CRF secretion.
INTRODUCTION

Cushing’s syndrome has an estimated prevalence of approximately 40 per million and incidence of about 1-2 cases per million population per year [1]. It is conveniently classified as either ACTH-dependent or ACTH-independent Cushing’s syndrome. ACTH-dependent hypercortisolism accounts for about 85-90% of Cushing’s syndrome and is typically characterized by chronic autonomous ACTH secretion [2]. Pituitary ACTH-secreting corticotroph cell adenomas exist in virtually all patients with pituitary ACTH hypersecretion (Cushing’s disease), whereas diffuse hyperplasia of anterior pituitary corticotroph cells, potentially resulting from hypersecretion of CRF, occurs only rarely.

Cushing’s syndrome has occasionally been attributed to concurrent ectopic secretion of both ACTH and CRF, but only rarely has it been unequivocally shown to be driven by autonomous ectopic CRF secretion, though incomplete biochemical and/or immunohistochemical characterization of published cases may partly explain this. Herein we present three patients with ACTH-dependent Cushing’s syndrome and pheochromocytoma; in one cases the tumor autonomously secreted ACTH while, in the other two, it appeared to secrete CRF (or related peptide), which in turn drove abnormal pituitary ACTH dynamics and endogenous hypercortisolemia. In the case of primary ectopic ACTH secretion, normal cortisol dynamics following successful removal of the tumor was only achieved after a period of suppressed hypothalamic-pituitary-adrenal (HPA) axis due to previous hypercortisolemia. This was not the case with the ectopic CRF-driven Cushing’s, where normal cortisol dynamics were rapidly restored following successful tumor resection, without noticeable HPA axis suppression, in the immediate postoperative period.

CLINICAL CASE REPORTS

Case 1

A 69 year-old female was admitted as a medical emergency with a two week history of oedema, uncontrolled hypertension and worsening hyperglycemia. Diabetes had been previously well-controlled with sub-maximal doses of metformin and gliclazide (HbA1c 6.6%), but in the previous 12 months glycemic control had deteriorated despite stable lifestyle. Over the same period she also reported onset of episodic sweating, tremor and palpitations. Medical history included dyslipidemia, hypertension and controlled cardiac failure. She was borderline obese (weight 80.9 kg; BMI 30 kg/m²). She had a plethoric face
and exhibited cardiac decompensation, with bilateral edema to mid-thigh and blood pressure 193/95 mmHg. ECG showed atrial fibrillation with fast ventricular response. Laboratory tests showed a markedly elevated plasma glucose 40.4 mmol/l, HbA1c 12.1% (NR <6.5%) and profound hypokalemia 1.9 mmol/l (NR 3.5-5.5).

She received intravenous potassium, magnesium and amiodarone, via central venous catheter, followed by oral beta-blockade for rate control, but hypokalaemia was refractory to treatment until the addition of spironolactone. Very large doses of intravenous insulin were required to control plasma glucose, indicating marked insulin-resistance, and Cushing’s syndrome was thus suspected. However, she remained hypertensive and continued to have persistent palpitations, and thus suspicion of phaeochromocytoma also emerged.

After eight days stabilization she was moved to the endocrine ward and investigated for evidence of cortisol and catecholamine excess. Overnight 1.5mg dexamethasone suppression test (ODST) showed an unsuppressed cortisol >2,000nmol/l (NR <50 nmol/l). Two 24 hour urine collections for urinary free cortisol (UFC) were also markedly elevated at 20,045 and 15,625 nmol/l, respectively (NR 0-320); plasma ACTH 516 ng/l (NR<47) confirmed ACTH-dependent hypercortisolism. ACTH precursors were elevated at 682 pmol/l [NR<40]. Phaeochromocytoma was also confirmed biochemically (Table 1), with fasting serum chromogranin A and pancreatic polypeptide both raised at 300 U/l [NR <30] and 710 ng/l [NR < 200]), respectively; urine 5-HIAA was normal.

MRI revealed no definite pituitary adenoma, but inferior petrosal sinus sampling (IPSS) nevertheless suggested pituitary Cushing’s disease without any clear lateralisation (Table 2). Cross-sectional imaging of the chest was normal, but the abdominal images showed a 3 cm right adrenal mass (with signal characteristics suggestive of phaeochromocytoma) and a bulky left adrenal gland consistent with chronically-raised ACTH drive (Figure 1). Meta-iodobenzylguanidine (MIBG) scintigraphy showed no abnormal focus of uptake.

Due to the severity of her illness she was started on Metyrapone for a total period of about 8 weeks; the dose was titrated after 48–72 h based on cortisol day curve to 750mg thrice daily fortunately with rapid clinical and biochemical response -near-undetectable 24hr urine free cortisol (UFC)- and so was given add-back Dexamethasone replacement. After incremental alpha-blockade she underwent right adrenalectomy, following which her symptoms subsided, glycemic control improved and she was taken off insulin. Over a period of 10 weeks following adrenalectomy she was weaned-off glucocorticoid replacement and appeared to be
cured of both Cushing’s disease and phaeochromocytoma (Table 1). Histology confirmed phaeochromocytoma; subsequent immune-staining showed no reactivity for ACTH, but did show significant cytoplasmic granular labelling for CRF among a scattering of peripheral tumor cells.

Six years post-adrenalectomy, she remains completely asymptomatic. In the intervening years she has undergone repair of an umbilical hernia and a second knee replacement; both of which were uneventful. Diabetes remains well controlled on just metformin 1 g twice daily and her blood pressure is maintained on perindopril 8 mg once daily. She remains under long term follow with the endocrine team. Although pre- and post-operative serum samples were stored for several years, we were unable to identify a laboratory with an “up-and-running” CRF assay during this period. Genetic analysis of lymphocyte DNA by UK national reference laboratory failed to show any coding sequence mutations in the \textit{PRKAR1A}, \textit{SDHB}, \textit{SDHC}, \textit{SDHD}, \textit{SDHAF2}, \textit{TMEM127}, \textit{VHL} and \textit{MAX}, or in exons 8, 10-11 and 13-16 of \textit{RET}. MPLA analysis did not detect any evidence of a pathogenic deletion or duplication within \textit{SDHB}, \textit{SDHC}, \textit{SDHD}, \textit{SDHAF2}, or \textit{VHL}.

**Case 2**

A 64-year old lady presented with abdominal pain and vomiting. She underwent an emergency laparotomy in which a metal wire impinging upon her small bowel (presumed from prior hysterectomy) was removed. Following this procedure her abdominal symptoms largely resolved, but review of the pre-operative CT of her abdomen also revealed an enhancing left adrenal mass and she was referred for endocrine assessment. She reported symptoms of non-specific tiredness and episodic sweating for the last 10 years, occasionally associated with palpitations. Her past medical history included treated hypertension and type 2 diabetes mellitus. She had also received symptomatic treatment for presumed idiopathic hyperhidrosis in the past. Medication included metformin, lisinopril and simvastatin. Blood pressure was 162/75 mmHg with pulse 86/min.

Initial investigations showed serum sodium 143 mmol/l (NR 135-145), potassium 4.5 mmol/l (NR 3.5-5.5) and HbA1c 6.5%. Cortisol was elevated at 9am (816 and 666 nmol/l) and midnight (175 nmol/l), as was ACTH (32 & 27 ng/l at 9am [NR<47] and 20 ng/l at midnight). Urine free cortisol was 47 nmols/24 hrs (NR <320), but 9am cortisol failed to suppress (<50 nmol/l) on dexamethasone suppression testing (DST): overnight 1mg (132 nmol/L), two-day low-dose 0.5mg qds (187 nmol/l) and two-day high-dose 2g qds (312

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nmol/l). Phaeochromocytoma was confirmed biochemically (Table 1), with raised catecholamine metabolites and chromogranin A (75 U/l [NR: <30]). MRI failed to demonstrate a pituitary lesion and MIBG scan showed uptake by the left adrenal gland.

Following incremental oral alpha blockade she underwent left laparoscopic adrenalectomy, with resolution of symptomatology and biochemical cure of both phaeochromocytoma (Table 1) and Cushing’s (Cortisol 102nmol/l at midnight and 33 nmol/l post-overnight 1mg DST). Blood pressure control improved, allowing antihypertensive drug doses to be halved. However, ACTH remained undetectable post-op and she required glucocorticoid replacement for six months thereafter.

Sections of the adrenal gland showed a medullary tumor with histologic features of a phaeochromocytoma, containing scattered cells peripherally showing strong cytoplasmic granular labelling for ACTH, without significant labelling for CRF. Genetic analysis of lymphocyte DNA by UK national reference laboratory failed to show any variants in the SDHB, SDHD and VHL genes apart from common polymorphisms of no clinical significance and MPLA analysis did not detect any evidence of a pathogenic deletion or duplication within SDHB, SDHC, or SDHD genes.

She remained under endocrine follow up for nearly 4 years, eventually dying of an unrelated cause.

Case 3

A 65 year old man with a history of benign prostatic hypertrophy presented to the emergency department of a private hospital in India with a history of vomiting, fever, rigors and anorexia. He was found to be febrile, dehydrated and emaciated, but was conscious and oriented with blood pressure 180/110mmHg.

Initial laboratory tests showed hemoglobin 10.5 g/dl (NR 11-15), sodium 128 mmol/l (NR 135-145), potassium 4.0 mmol/l (NR 3.5-5), glucose 220 mg/dl (NR <200mg/dL), urea 37 mg/dl (NR 7-18) and creatinine 1.2 mg/dl (NR 0.6-1.2). 75g oral glucose tolerance test confirmed diabetes mellitus -fasting glucose 193 mg/dl (NR <126); two-hour value 420 (NR<200)- and he was started on intermediate acting insulin. The combination of new-onset diabetes mellitus, anorexia and gross emaciation, without features of ketoacidosis, prompted a search for underlying malignancy. Chest x-ray was normal, but a right supra-renal mass was detected on sonography and confirmed on CT scan. Urinary catecholamines and
metanephrines were both elevated at 818 mcg/24hr (NR: <275) and 3277 (NR: 25-312), respectively, and serum cortisol was elevated on two consecutive days at 650 & 690 mmol/l, with detectable ACTH at 29 and 22 ng/l, respectively. Midnight cortisol and ACTH were elevated at 422 nmol/l and 28 ng/l, respectively, and there was failure of suppression on both ODST and LDDST, with 9am Cortisol levels 126 and 111 mmol/l, respectively (NR <50); all in keeping with ectopic ACTH-dependent cortisol excess (Table 3). Pituitary MRI scan was inconclusive, but MIBG showed increased uptake by the right adrenal tumor.

After incremental alpha blockade he underwent laparotomy with intravenous hydrocortisone cover, and a 4 cm adrenal tumor was excised (histologically confirmed as phaeochromocytoma). Although he experienced significant hypotension post-excision, requiring inotropic support, thereafter he made a rapid post-operative recovery and was discharged on oral prednisolone 5mg daily. By 14 weeks post-operatively, he successfully passed the short synacthen test, with plasma cortisol physiologically suppressed <50 nmol/l on repeat ODST (Table 3); glycaemic control had greatly improved such that he no longer required insulin and he was clinically steroid-independent, having spontaneously discontinued Prednisolone just three weeks post-discharge. He was then lost to follow-up, as is typically the case for Indian patients perceiving themselves to be cured, but slides and paraffin-fixed blocks were retained and subsequently made available to the Newcastle Cellular Pathology department. Immunostaining was negative for ACTH, but 10-20% of tumor cells showed a strong positive reaction (cytoplasmic and granular) for CRF (Figure 2.B).

**Immunohistochemistry Methods**

Immunohistochemistry was performed on a Benchmark Ultra autostainer (Ventana, Tucson, AZ, USA) using polyclonal anti-corticotropin releasing factor (Sigma-Aldrich, St Louis, MO, USA) at dilutions of 1:2000 and 1:3000 and monoclonal anti-ACTH (BioGenex, Freemont, CA, USA) at a dilution of 1:100. Briefly, high pH heat induced epitope retrieval was performed for 32 and 8 minutes, respectively, at 100°C followed by 32-minute primary antibody incubation. Visualisation was achieved using a Ventana OptiView DAB polymer detection kit (Ventana, Tucson, AZ, USA). Positive demonstration of anti-CRF was confirmed in human placental tissue which produced strong cytoplasmic/ membranous staining in the trophoblastic cells, especially syncytiotrophoblast. Positive demonstration of
anti-ACTH was confirmed in human pituitary which produced strong cytoplasmic staining in the corticotrophs.

**DISCUSSION**

Ectopic ACTH syndrome is predominantly associated with bronchial carcinoid (25% of all cases), with phaeochromocytoma accounting for only 3% [3,4]. There are reports of tumors co-expressing ACTH and CRF, but ectopic CRF production alone is rarely reported (Table 4.A). To our knowledge there have been only 23 convincing reports of isolated ectopic CRF production [5-27], among which medullary thyroid cancer was the commonest cause, while phaeochromocytoma accounted for only five cases (Table 4.B). The diagnostic evaluation of ACTH-dependent Cushing’s syndrome has been extensively reviewed, but it is worth restating that the key investigations in differentiating ectopic secretion from Cushing's disease are pituitary MRI, IPSS-with-CRF-stimulation and high-resolution cross-sectional imaging of the chest and abdomen. Somatostatin analog scintigraphy may be also included as a diagnostic step in the workup of Cushing’s syndrome patients with a suspected ectopic ACTH production [34].

Pituitary ACTH-secreting corticotroph cell adenomas exist in virtually all patients with pituitary ACTH-hypersecretion (Cushing’s disease), though they may not always be visible on MRI, hence the value of IPSS, which in experienced hands has yielded a diagnostic accuracy approaching 100% in ACTH-dependent Cushing’s syndrome. However, false positive IPSS results have been reported, as has diffuse corticotroph hyperplasia following exploratory pituitary surgery, and both these findings are exactly what would be expected as a result of ectopic CRF secretion.

To distinguish between ectopic ACTH and CRF syndromes, plasma assay and immunostaining of tumor samples for both ACTH and CRF would ideally be available, but plasma CRF levels are rarely reported in the literature, because there is typically no clinical imperative to do so. We were able to identify only two cases of phaeochromocytoma-associated ACTH-driven Cushing’s syndrome, in which plasma CRF was either frankly elevated, or “inappropriately normal”; upper-end-of-normal in one case [12] and well-above the quoted reference range in the other [25]. Several reports of ectopic CRF secretion describe impaired cortisol-decrement following HDDST, but it is not commonly appreciated that this condition will necessarily result in false-positive localization of the primary tumor to the pituitary gland by IPSS. Herein we present three patients with phaeochromocytoma and
biochemical evidence of ACTH-dependent Cushing’s, among which tumor-ACTH secretion was only confirmed in one case; the remaining two secreting CRF -or a functionally and structurally closely-related peptide.

In case 1, long term clinical symptoms raised suspicion for the presence of phaeochromocytoma, which was confirmed by elevated overnight urinary normetanephrines and metanephrines and cross-sectional imaging. Further laboratory investigations revealed ACTH-dependent Cushing’s.—The presence of hypokalemia, older age, markedly-elevated circulating ACTH and the absence of definitive lesion in the pituitary MRI scan were in favor of ectopic ACTH; high-resolution CT chest, however, failed to show any potential culprit lung lesion. Therefore IPSS was undertaken, with the results suggesting a pituitary source of ACTH overproduction (initially interpreted as pituitary Cushing’s disease). However, as MRI had failed to show a convincing pituitary lesion and good medical control of Cushing’s had been rapidly achieved, the over-riding clinical priority was to excise the phaeochromocytoma.

Following resection of the right-sided phaeochromocytoma, ACTH levels fell and cortisol dynamics were rapidly restored to normal, allowing early discontinuation of post-operative steroids; in keeping with phaeochromocytoma-associated ectopic hormone secretion. Initial tumor-immunostaining for ACTH was negative (Figure 2A), increasing our suspicion that CRF might instead be the ectopically-secreted hormone. This we later confirmed by immunostaining for CRF. We speculate that the rapidity of postoperative recovery of the HPA axis may reside in the hypophysial corticotroph cells having been chronically-stimulated by the ectopic CRF, rather than being suppressed by endogenous hypercortisolaemia.

This index case prompted us to re-evaluate two other recent cases of phaeochromocytoma-associated ACTH-driven Cushing’s syndrome that had both been cured following unilateral adrenalectomy. Although case 2 manifest a similar biochemical cure of both the hormone excess syndromes following (left) adrenalectomy, the HPA axis remained suppressed for many months afterwards and tumor-immunostaining was positive for ACTH and not for CRF in keeping with direct ectopic ACTH secretion by the phaeochromocytoma. Case 3 presented with incidental adrenal mass in the context of cachexia and new-onset diabetes mellitus. However, as with the index case 1, there was rapid (definitely within 14 weeks post-op, but most likely within 3 weeks) normalization of cortisol dynamics post-operatively. Although pre-operative IPSS had not been performed, tumor staining for ACTH was likewise negative
and staining for CRP was significantly stronger than in case 1 (Figure 2B) -again consistent with ectopic CRF production by the phaeochromocytoma.

Literature review revealed 61 papers and 72 cases of phaeochromocytoma-associated Cushing’s syndrome (Supplementary data). In most cases pathology documented ACTH-positive chromaffin tumor along with adrenocortical hyperplasia, while in three cases pathology confirmed the presence of a mixed cortico-medullary tumor in which corticosteroid production by the tumor per se appeared a more likely etiology than ectopic ACTH production [35-37]; in three other cases [38-40] the co-presence of adrenocortical adenoma and a phaeochromocytoma was demonstrated. IPSS was undertaken in only five cases and, all cases, confirmed ectopic ACTH secretion [6,41-44].

We acknowledge the limitations of immunostaining as a surrogate for tumorous hormone secretion. Positive staining indicates the presence within the cells of the epitope to which the antibody has been raised, and it cannot be 100% inferred that the same cells had been secreting functionally active hormone. Indeed, Liddle, et al. demonstrated ACTH-immunoreactivity in 8% of tumor tissue extracts from patients without the ectopic ACTH syndrome [28]. Conversely negative immunostaining means that the epitope has not been identified, which does not necessarily prove that the cells had not been secreting functionally active hormone. Liddle, et al. thus suggested the five criteria for confirming ectopic ACTH production: (1) clinical and laboratory evidence of endogenous hypercortisolemia; (2) positive immunostaining for ACTH in tumor extracts; (3) elevated or inappropriately normal plasma ACTH in the presence of hypercortisolemia; (4) evident elevated ACTH levels in the venous effluent from the tumor site; (5) ACTH activity fall after removal of the tumor. Only case 2 discussed in this paper fulfilled 4/5 criteria based on pre- and post-operative biochemical studies as well as pathologic confirmation.

CONCLUSION

We report three cases of phaeochromocytoma-associated ACTH-dependent Cushing’s syndrome, where both hormone excess syndromes resolved following unilateral adrenalectomy. In all three cases the source of abnormal ACTH drive was uncertain, but the over-riding clinical priority was to remove the phaeochromocytoma, following which Cushing's was demonstrably cured in all three cases. Hence, phaeochromocytoma was initially inferred to be the ultimate source of ACTH. However, this was confirmed only in case 2, where there was positive tumor-immunostaining for ACTH (negative for CRF). Cases
1 and 3 were similarly characterized by post-operative cure, but also exhibited relatively rapid restoration of normal cortisol dynamics and negative immunostaining for ACTH (positive for CRF). Although lack of tumour staining for ACTH in cases 1 and 3 cannot entirely exclude ACTH co-secretion, these cases nevertheless do appear to represent an extremely rare cause of ACTH-dependent Cushing’s syndrome, with ectopic CRF production by phaeochromocytoma driving secondary corticotroph hyperplasia. To our knowledge these are potentially only the 6th and 7th such reported cases. Moreover, Case 1 is the first such report where secondary pituitary ACTH-hypersecretion was unequivocally demonstrated with IPSS, initially leading to false-positive diagnosis of pituitary Cushing’s disease.

We speculate that unusually-rapid restoration of normal cortisol dynamics post-adrenalectomy [45] for a tumor presumed to be ectopically-secreting ACTH, might instead indicate unrecognized ectopic CRF production. It is also conceivable that acute hypocortisolaemia, in relation to unrecognized co-secretion of ACTH, may underpin some cases of cardiovascular collapse following adrenalectomy for phaeochromocytoma. Despite advances in our knowledge of phaeochromocytoma genetics since the publication of previous reports, we were not able to identify any somatic DNA defect that might be associated with either ACTH- or CRF secreting phaeochromocytoma.

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REFERENCES


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LEGENDS TO FIGURES AND TABLES

Figure 1
Case 1: Contrast-enhanced axial CT image showing poorly-enhancing, low-attenuation 3cm right adrenal mass (thin blue arrow) and a bulky left adrenal gland (bold blue arrow).

Figure 2
ACTH and CRF immunostaining:
(A) Case 1: Negative tumor ACTH-staining, with some positivity in the adjacent adrenal cortex
(B) Case 3: CRF-positive cells in peripheral areas of the tumour

Table 1
Cases 1 and 2:
Catecholamine dynamics pre- and post- adrenalectomy

Table 2
Case 1:
Inferior petrosal sinus sampling with CRF infusion

Table 3
Case 3:
Cortisol and catecholamine dynamics pre- and (14 weeks) post-right adrenalectomy
Table 4

(A) Tumors causing ectopic ACTH Cushing syndrome
(B) Phaeochromocytoma as source of ectopic CRF production

_Supplementary data:_

Cushing syndrome associated with Phaeochromocytoma

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Cases 1 and 2:</th>
<th>Catecholamine dynamics pre- and post- adrenalectomy</th>
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<td><strong>Overnight urine</strong></td>
<td><strong>Metanephrine/Creatinine ratio</strong></td>
<td><strong>Normetanephrine/Creatinine ratio</strong></td>
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<tr>
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Table 2 (Case 1):

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<th>low IVC</th>
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IPS = inferior petrosal sinus
IVC = inferior vena cava

Table 3

Case 3: Endocrine lab results pre- and (14 weeks) post-right adrenalectomy

<table>
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<th>Pre-op</th>
<th>Post-op</th>
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<td><strong>Cortisol nmol/l</strong></td>
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</tr>
<tr>
<td>9am</td>
<td>650 &amp; 690</td>
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<tr>
<td>1mg overnight DST</td>
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<td>Low-dose DST</td>
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<tr>
<td>Catecholamines</td>
<td>818</td>
<td>-</td>
<td>&lt;275</td>
</tr>
<tr>
<td>Metanephrines</td>
<td>3277</td>
<td>-</td>
<td>&lt;312</td>
</tr>
</tbody>
</table>
Table 4

A. Tumors causing ectopic ACTH Cushing syndrome

<table>
<thead>
<tr>
<th>ACTH-secreting [28-33]</th>
<th>CRF-secreting [5-27]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell carcinoma (esp. lung)</td>
<td></td>
</tr>
<tr>
<td>Pancreatic islet cell tumor</td>
<td></td>
</tr>
<tr>
<td>Neuroendocrine tumor (lung, thymus, gut, pancreas, ovary)</td>
<td></td>
</tr>
<tr>
<td>Medullary thyroid cancer</td>
<td></td>
</tr>
<tr>
<td>Phaeochromocytoma</td>
<td></td>
</tr>
</tbody>
</table>

B. Phaeochromocytoma as source of ectopic CRF production

<table>
<thead>
<tr>
<th>Investigators:</th>
<th>tumor staining for:</th>
<th>serum level:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lois, et al. [Cases 1 and 3 in this mss]</td>
<td>negative</td>
<td>positive</td>
</tr>
<tr>
<td>Bayraktar, et al. [10]</td>
<td>negative</td>
<td>positive</td>
</tr>
<tr>
<td>Eng, et al. [7]</td>
<td>negative</td>
<td>positive</td>
</tr>
<tr>
<td>Jessop, et al. 13</td>
<td>negative</td>
<td>positive</td>
</tr>
<tr>
<td>Mondello, et al. [20]</td>
<td>-</td>
<td>positive</td>
</tr>
<tr>
<td>Ruggeri, et al. [8]</td>
<td>negative</td>
<td>positive</td>
</tr>
</tbody>
</table>