Severe hypertension secondary to renal artery stenosis and Cushing's syndrome

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ABSTRACT

We present an unusual patient who simultaneously had severe renal artery stenosis (RAS) and Cushing's syndrome. The case highlights the difficulty of reaching a specific diagnosis of Cushing's syndrome and the possible interaction between Cushing's syndrome and some other concurrent illnesses that this patient had. A 37-year old man presented with severe hypertension (HTN) and uncontrolled diabetes mellitus (DM) without clear physical signs of Cushing's syndrome. He was found to have severe osteoporosis, proximal myopathy, several cutaneous warts, tinea versicolor, and chronic viral hepatitis. Captopril-stimulated renal scan and renal artery angiogram revealed severe RAS. Partial balloon dilatation of RAS led to improvement in HTN. Unexpectedly, urine free cortisol (24 hour) was found extremely high. Serum adrenocorticotropic hormone (ACTH) was also elevated and high dose dexamethasone suppression tests were inconclusive. Several imaging studies failed to localize the source of ACTH. Despite normal MRI of the pituitary gland, bilateral inferior petrosal sinus sampling (IPSS) localized the source of ACTH secretion to the right side of the pituitary gland and right anterior hemihypophysectomy resulted in cure of Cushing's disease, HTN, DM, and tinea versicolor with significant improvement in cutaneous warts, osteoporosis, and chronic hepatitis. In conclusion, RAS and Cushing's syndrome may occur together. Significant hypercortisolemia can occur without clear signs of Cushing's syndrome. Controlling hypercortisolemia is of paramount importance when treating chronic infections in patients with Cushing's syndrome.

Saudi Med J 2005; Vol. 26 (4): 668-673

The majority of cases of hypertension (HTN) are of unknown etiology. This situation is referred to as essential hypertension and accounts for 90-95% of cases. Hypertension secondary to identifiable causes occurs in approximately 5% of cases. The importance of investigating the cause of HTN in this minority lies in the fact that many cases can be cured or effectively treated if the cause is identified. Renovascular HTN is the most common correctable cause of secondary HTN.[1] On the other hand, Cushing's syndrome is a rare cause of HTN accounting for <0.5% of cases, however, HTN is a common finding in Cushing's syndrome with a prevalence of approximately 60-80%.[2] We report here the clinical features, diagnostic work up, and management of an interesting case of severe HTN secondary to 2 rare causes, namely, renal artery stenosis (RAS) and Cushing's disease. In this report, our objectives are to draw the attention to this rare combination, to discuss the difficulties frequently encountered in identifying the source of excessive adrenocorticotropic hormone (ACTH) secretion in cases of ACTH-dependent Cushing's syndrome and the value of bilateral inferior petrosal sinus sampling (IPSS) in such a situation, and to highlight the interactions between severe hypercortisolemia of Cushing's syndrome with its accompanying immunosuppressive effects and some

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Received 21st October 2004. Accepted for publication in final form 16th January 2005.

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other concurrent illnesses that this patient had including hepatitis B virus chronic liver disease, extensive cutaneous warts, and tinea versicolor.

Case Report. A 37-year-old man presented with uncontrolled diabetes mellitus (DM) and severe HTN for 2 years. He discontinued all medications 2 months earlier "because they did not control DM and HTN". He gave history (hx) of significant weight gain 4 years ago but progressive weight loss of around 30 kg over the last 2 years without major changes in his appetite. He also complained of back pain and generalized weakness. He noticed an itchy rash over the trunk but no hx of thinning or easy bruising of the skin. Past medical hx was significant for chronic hepatitis B viral (HBV) infection since 1985, multiple warts over the hands for the last 2 years, and hx of renal stones. Family hx was negative for HTN or DM. He has a 20 pack-year hx of cigarette smoking but no hx of alcohol intake. Physical examination revealed a stable, thin, young man; weight 53 kg, height 168 cm, body mass index (BMI) 18.7. Blood pressure (BP) 200/120 in both arms without orthostatic changes. Pulses were regular and equal at a rate of 68/min. There were no somatic features of Cushing's syndrome; specifically there was no evidence of central obesity, moon facies, supraclavicular fullness, dorsocervical fat pad, skin bruises or striae. Abdomen: liver 4 cm palpable; the spleen and kidneys were nonpalpable; no abdominal bruits and no shifting dullness. Skin: macular hypo and hyperpigmented areas over the trunk consistent with tinea versicolor and several warts over the hands. Musculoskeletal system: severe proximal myopathy and significant tenderness over the lumbosacral spine. The rest of the physical examination was unremarkable. Initial laboratory investigations are shown in **Table 1**. Captopril-stimulated renal scan showed reduced fractional function of left kidney to 32% with diminished and delayed uptake of the tracer by the left kidney suggesting significant left RAS (**Figures 1a and 1b**). Renal angiogram confirmed the diagnosis of severe (>90%) left RAS (**Figure 2)**. Twenty-four hour urine free cortisol (UFC): 1353 µg/day (18-126.7), A.M. serum cortisol 1303.5 nmol/l (normal, 171-536), and P.M. serum cortisol 1207.25 nmol/l (normal, 64-340). Serum ACTH was measured twice: 84 and 90 ng/L (0-46). High dose (8 mg) overnight dexamethasone (Dex) suppression test: serum cortisol pre suppression 47.4 µg/dl and post suppression 35.2 µg/dl (26% reduction). High dose Dex suppression test (2 mg q 6h); UFC on day 1: 644 µg/day and on day 2: 376 µg/day (41.6% reduction). An MRI of the pituitary gland revealed normal pituitary gland without any suggestion of an adenoma (**Figures 3a and 3b**). Helical CT scans of the chest and abdomen were negative. A CT scan and MRI of the adrenal glands were normal. Flourine-18-Flourodeoxyglucose Positron Emission Tomography (FDG-PET) whole body scan and octreotide scan were negative. Bone mass density; T score - 4 at L2-L4 spine and - 4 at femoral neck. Liver Biopsy: chronic active viral hepatitis (HBV). Because of the inconclusive results of the non-invasive testing for localization of the source of ACTH secretion and the normal MRI of the pituitary gland, IPSS was performed (**Table 2**). The result showed that the source of ACTH secretion was the right side of the pituitary gland. The HTN was treated with a large combination of antihypertensive drugs including Enalapril 40 mg/day, Nifedipine LA 90 mg/day, Losartan 25 mg/day, Hydrochlorothiazide 50 mg/day, Prazosin 15 mg/day and Atenolol 100 mg/day. The BP remained elevated at 190-210/110-130. After the diagnosis of RAS was established, the patient underwent left renal artery balloon angioplasty, the stenosis was reduced to 50%, and blood pressure was much better controlled with only 3 drugs (Enalapril 40 mg/day, Losartan 25 mg/day, Nifedipine LA 90 mg/day). On the second-day post transsphenoidal surgery, the patient developed hypotension which necessitated discontinuation of all antihypertensive medications with excellent long-term BP control; 120-130/60-75 off any antihypertensive medications. The patient subsequently underwent uncomplicated transsphenoidal right anterior hemihypophysectomy. The histopathological examination showed a tiny microadenoma, and immunohistochemistry examination was strongly positive for ACTH. One month after surgery, UFC was 4.3 µg/day, serum cortisol 0.3 µg/dl and ACTH 14 ng/L. The patient was started on Dex 0.75 mg/day. Initially, the patient was on insulin at a total daily dose of 32 units/day. However, following hemihypophysectomy, blood sugar became and remained normal off any medications. Other laboratory investigations following surgery are shown in **Table 1**. The patient was started on calcium 1500 mg/day, Ergocalciferol 4000 units/day and Alendronate 10 mg/day. Four months after surgery, bone mass density improved significantly (T Score rose to -2.5). Hepatitis B infection was treated with Lamivudine, but liver function tests continued to deteriorate until after hemihypophysectomy when liver enzymes and bilirubin became normal. Tinea versicolor and cutaneous warts were initially observed without intervention. After surgery, tinea versicolor and most of the cutaneous warts disappeared.

Discussion. We described a case of a young man who presented with severe HTN, uncontrolled DM, and severe weight loss without the familiar stigmata of Cushing's syndrome. He was found, however, to have severe osteoporosis and significant

Table 1 - Laboratory investigations before and after transsphenoidal surgery.

Parameter	Before surgery	After surgery	Normal range
Fasting blood sugar (mmol/l)	9.1	4.3	3.4-6.1
Glycated hemoglobin (%)	16%	5.8%	<7%
Total Cholesterol (mmol/l)	8.6	4.8	3.0-5.2
High density lipoprotein (mmol/l)	0.83	1.61	0.80-2.20
Low density lipoprotein (mmol/l)	4.86	4.1	<2.6
Triglyceride (mmol/l)	3.96	1.8	0.4-1.8
Creatinine (mmol/l)	76	81	65-129
Serum sodium (mmol/l)	137	141	135-145
Serum potassium (mmol/l)	3.4	4.4	3.5-5.0
Serum calcium (mmol/l)	2.10	2.36	2.1-2.6
Serum phosphorous (mmol/l)	0.69	1.24	0.70-1.45
Serum albumin (g/l)	31	32	35-45
Serum parathyroid hormone (ng/l)	96	31	10-65
25 OH-vitamin D (nmol/l)	<13	71	22-116
Alkaline phosphatase (u/l)	625	242	25-125
Aspartate transaminase (u/l)	43	35	0-35
Alanine aminotransferase (u/l)	228	32	10-45
Bilirubin (µmol/l)	32	11	<21
24 h urine free cortisol (µg)	1353	4.3	18-126.7
Serum renin (u/ml)	81	-	5-47
Serum aldosterone (ng/dl)	28	-	6-22

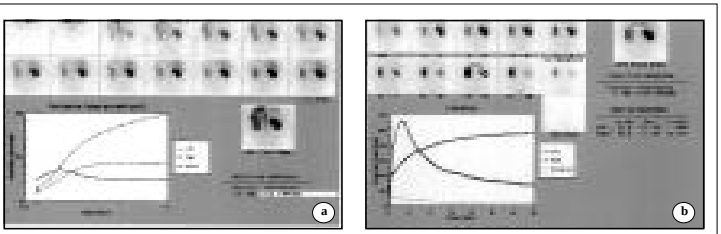

Figure 1 - Captopril-enhanced iodine-123 hippuran renal scan showing **a)** perfusion and **b)** functional images of delayed and diminished uptake of the tracer by the left kidney, a picture consistent with significant stenosis of left renal artery.

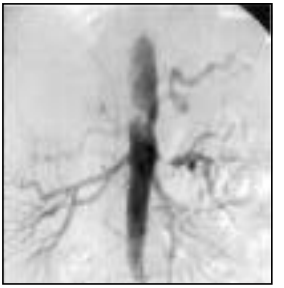

Figure 2 - An anterior view of renal artery angiogram shows a very tight stenosis at the origin of the left renal artery.

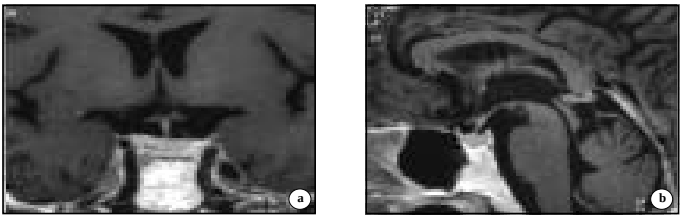

Figure 3 - Gadolinium-enhanced **a)** coronal and **b)** sagittal sections of MRI of the sella turcica showing normally looking pituitary gland without evidence of pituitary adenoma.

Table 3 - Results of bilateral inferior petrosal sinus sampling.

Sites	Basal		Post-CRF				
Time (minutes)	-30'	-5'	+2'	+5'	+10'	+15'	+30'
Left antecubital vein (ACTH)*	26	31	35	37	58	69	49
Left inferior petrosal sinus (ACTH)	33	35	48	59	70	66	80
Right inferior petrosal sinus (ACTH)	355	359	1994	1153	1269	942	566

*ACTH normal range (0-46) ng/l, ACTH - adrenocorticotropic hormone, CRF - corticotropin releasing factor

proximal myopathy. As part of his work-up for secondary HTN, UFC was measured and unexpectedly was found extremely elevated confirming the diagnosis of Cushing's syndrome. At the same time, he was found to have severe RAS. Partial balloon dilatation of the RAS improved his BP control but did not completely correct it. The HTN, however, was cured after he underwent transsphenoidal anterior hemihypophysectomy for Cushing's disease. This scenario is highly suggestive that HTN in this case is secondary to both RAS and Cushing's disease.

The RAS results in diminished renal perfusion of the affected kidney. This leads to stimulation of the renin-angiotensin-aldosterone system with consequent vasoconstriction and sodium and fluid retention.[1] Fibromuscular dysplasia accounts for approximately 10% of cases.[1] It usually affects young women and frequently involves the distal 2 thirds of the renal artery.[1] Atherosclerotic RAS accounts for 90% of cases and usually affects old men with multiple risk factors for atherosclerosis. The site of stenosis is usually at the ostium and proximal one third of renal artery.[1] Our patient probably had the atherosclerotic type of RAS since he is a male smoker with hyperlipidemia and DM and the stenosis involved the proximal part of the left main renal artery.

The HTN is a common clinical finding in Cushing's syndrome with a reported prevalence of 60-80%.[2] In a study of 130 cases of Cushing's syndrome, HTN was present in 64% of cases of Cushing's disease, 70% in patients with adrenal adenoma and in all patients with adrenal cancer and ectopic ACTH production.[2] Exogenous glucocorticoids also cause HTN but with a lower prevalence of 4-25%.[3] The severity of HTN in Cushing's syndrome is variable. Most cases are of moderate severity.[4] However, in a study by Ross and Linch, 14% of patients with Cushing's syndrome had blood pressure >200/120 mm Hg. End organ damage was common; 55% had abnormal echocardiographic changes and 28% had cardiomegaly.[4]

Several mechanisms operate in the pathogenesis of HTN in Cushing's syndrome.[5] Normally, cortisol is converted to cortisone, a weak mineralocorticoid, by the enzyme 11-ß hydroxysteroid dehydrogenase

type II. The marked hypercortisolemia in severe cases of Cushing's syndrome probably overwhelms this enzyme leading to accumulation of cortisol, which binds to the renal mineralocorticoid receptors and causes an increase in sodium and fluid retention and extracellular fluid volume expansion. In addition, glucocorticoids cause shift of fluid from intracellular to extracellular compartment resulting in further increase in plasma volume. Other mechanisms include augmented activity of the sympathetic nervous system and increased peripheral vascular sensitivity to catecholamine. Hypercortisolemia also increases the hepatic production of the renin substrate, angiotensinogen; renin-angiotensin system activity is increased among patients with Cushing's syndrome.

Cure from Cushing's syndrome does not always result in cure of HTN; up to a third of patients may continue to have persistent hypertension.[6]

Apart from HTN, this case showed the high diagnostic value of IPSS even in cases like our patient where imaging studies are negative. Previous work has established the high accuracy of this procedure.[7] On the other hand, in our patient, the results of the noninvasive biochemical testing, both the overnight high dose (8 mg) and the 2-day high dose (2 mg q6h) Dex suppression tests were inconclusive and misleading. Previous studies reported that the 2-day high dose Dex suppression test has a high specificity of 100% but relatively low sensitivity of approximately 70% for the diagnosis of Cushing's disease when a criterion of suppression of UFC to >90% was applied.[8] The sensitivity improved (72-83%) when either suppression of UFC> 90% or urinary 17-hydroxycorticosteroid > 64% were taken as an indication of the presence of Cushing's disease.[8] When the level of suppression is less than these limits, significant overlap between cases of Cushing's disease and ectopic-ACTH secretion occurs.[8] Our patient's result fell in this range (46% suppression) and thus were inconclusive. The high dose (8 mg) overnight Dex suppression test has been shown to be comparable to the conventional 2-day high dose Dex suppression test. A suppression of serum cortisol to >50% of baseline suggests Cushing's disease. In our patient, serum cortisol was suppressed only to 26%, which was also inconclusive.

Another interesting aspect of this case is the possible interplay between Cushing's disease and other concurrent diseases that this patient had. For example, it is probable that the chronic immunosuppression induced by hypercortisolism led to activation of hepatitis B viral infection and worsening of liver function. Similarly, it is likely that immunosuppression also contributed to the appearance and severity of cutaneous warts and tinea versicolor. Glucocorticoids have significant effects on the immune system and predisposition to infections.[9] In cases of chronic hypercortisolemia, circulating CD4 cells and natural killer-cell activity are depressed.[9] Glucocorticoids also induce synthesis of I Kappa B alpha, a protein that normally inactivates a nuclear factor Kappa B.[9] Kappa B normally activates the synthesis of a number of cytokines. Thus, the inhibition of Kappa B leads to generalized inhibition of cytokine synthesis and release. The susceptibility to opportunistic infections correlates with the severity of hypercortisolemia.[9] In our patient, there was a prompt improvement in the liver function tests and disappearance of tinea versicolor and most of the cutaneous warts after the transsphenoidal surgery indicating recovery of the immune system.

Our patient also had severe osteoporosis and vitamin D deficiency. Cushing's syndrome causes osteoporosis through a number of mechanisms. Glucocorticoids inhibit bone formation and increase bone resorption.[10] They probably have a direct inhibitory effect on osteoblasts.[10] In addition, glucocorticoids inhibit the production of insulin-like growth factor-1, an important stimulator of bone formation and decrease the level of testosterone.[10] Glucocorticoids also increase bone resorption directly by stimulation of osteoclast-like cells and indirectly by decreasing gonadotropin level leading to secondary hypogonadism.[10] Furthermore, glucocorticoids directly inhibit gastrointestinal calcium absorption and increase calcium renal excretion. This negative calcium balance combined with direct stimulatory effect of glucocorticoids on PTH secretion lead to secondary hyperparathyroidism, which further increases bone resorption.

In conclusion, we described an interesting case who presented with an unusual combination of 2 rare causes of a common disease, namely, HTN. In addition to being rare, the case illustrates many facets of Cushing's syndrome including the difficulty of reaching a specific diagnosis of Cushing's disease especially when the radiological studies are negative and the non-invasive biochemical testing is inconclusive, the great diagnostic value of IPSS in such a situation, the impact of severe immunosuppression induced by hypercortisolemia on multiple chronic infections that this patient had and finally the rewarding outcome when Cushing's syndrome was cured.

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