

Coexistence of the Hypersecretion of Catecholamine, Adrenal Cortical Nodular Hyperplasia, and Nephrotic-Range Proteinuria of Focal Segmental Scleronephrosis: Is It Fat-Induced Hypertension?

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ABSTRACT

Two patients had a long history of hypertension and one of them also had a nephrotic-range proteinuria secondary to focal segmental scleronephrosis which had been diagnosed by kidney biopsy. They presented with uncontrolled hypertension. Laboratory examination suggested hypersecretion of catecholamines by the left adrenal glands in both patients and primary aldosteronism in one of them. A computed tomography scan revealed small nodules on left adrenal gland in both patients. Patients underwent laparoscopic left adrenalectomy. After surgery, blood pressure was normalized and proteinuria was resolved. Most interestingly, prominent adipocytes infiltrated were detected in the adrenal cortex and were associated with the presence of lymphocytes, which suggested that adipocytes might have a role in the pathogenesis of these diseases in our patients.

Keywords: Pheochromocytoma, Aldosteronism, Adipocyte, Nephrotic Syndrome, Focal Segmental Scleronephrosis, Adrenal Cortical Hyperplasia

1. Introduction

Obesity is a known risk factor for both cardiovascular disease and mortality. Adipose tissue is a secretory organ that produces a variety of bio active substances (adipokines) and is involved in the regulation of various biological processes. Adipokines may interact with many organs in the body, such as blood vessels, adrenal glands, and kidneys. In literature, fatty infiltration has been noted in adrenal glands. Park *et al.* [1] reported a case of Cushing's syndrome with high basal plasma catecholamine levels. They found that lymphocytic infiltration and fatty metaplasia were prominent histological features within the nodules of the cortical adrenal gland. Boyanton *et al.* [2] also presented a man with an adrenal tumor and high catecholamine levels but the histopathologic examination revealed mature adipocytes and focal hematopoietic elements with normal com-

pressed adrenal tissue. Finally, Ajmi *et al.* [3] reported another patient with an adrenal mass and elevated cortisol and androgen levels; however, mixed components of fat and adrenal tissue were only seen on the pathological specimen.

In the present cases, we will discuss the possible role of adipocytes that may involve in the pathogenesis in our patients with hypersecretion of catecholamines, adrenal cortical nodular hyperplasia, and nephrotic-range proteinuria secondary to focal segmental sclerosis of the kidneys.

2. Case Presentation

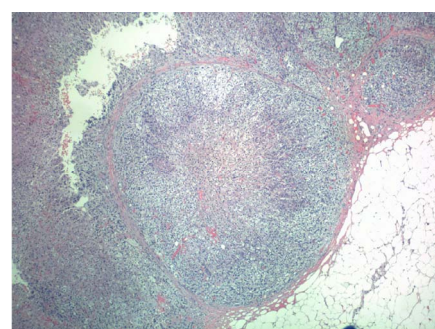
Patient A: A 56-year-old Vietnamese man with a 10-year history of hypertension was being treated with amlodipine 10 mg twice a day and amilorone 200 mg daily. His weight and height were 159 lbs. and 5 feet, respectively. He complained of more frequently palpitation,

anxiety, fatigue, and his blood pressure (BP) had been uncontrolled at home. Laboratory examination showed a serum potassium of 4.3 mmol/L (normal, 3.6 - 5.0), serum sodium of 141 mmol/L (normal, 135 - 145), serum chloride of 108 mmol/L (normal, 96 - 109), serum total carbon dioxide of 26.6 mmol/L (normal, 20 - 30), serum creatinine of 1.5 mg/dl (normal, 0.7 - 1.3), serum blood urea nitrogen (BUN) of 23 mg/dl (normal, 5 - 26), serum glucose of 87 mg/dl (normal, 65 - 99), and serum thyroid stimulating hormone (TSH) of 3.34 uIU/ml (normal, 0.5 - 1.5). Further blood tests revealed plasma renin of 4.9 ng/ml/hr (normal, 1.3 - 4), serum aldosterone of 3.5 ng/dl (normal, 1 - 15), serum cortisol 11.1 µg (normal, 3.1 - 22.4), 24-hours urine for metanephrine of 213 µg (normal, 35 - 350), 24-hours urine for vanillylmandelic acid (VMA) of 6.2 mg (normal, 0 - 6), plasma free normetanephrine of 1.19 nmol/L (normal, <0.9), plasma norepinephrine of 580 pg/ml (normal, <399), plasma epinephrine of 206 pg/ml (normal, <99), serum chromogranin A of 51/ml (normal, 0 - 50). A computed tomography (CT) scan of the adrenal gland showed a nodule 0.9 cm at the left adrenal limb.

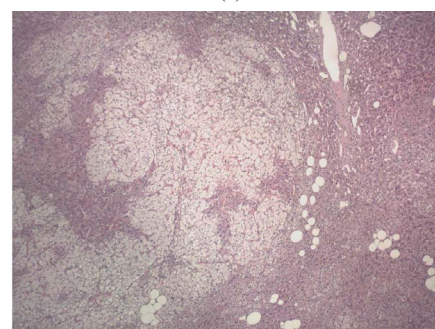
He then underwent laparoscopic left adrenalectomy. The specimen consisted of two pieces of adrenal gland measuring 6 × 4.5 × 0.7 cm in aggregate. The adrenal is covered with multilobular adipose tissue. Pathological examination reported a cortical nodular hyperplasia of the adrenal gland (**Figure 1(a)**). Most interestingly, there were abundant adipocytes in the adrenal cortex in association with the presence of lymphocytic infiltration (**Figures 2(a)** and **3(a)**).

After surgery, his BP has been stable (110/70), and subsequent levels of serum catecholamine and urinary VMA decreased to normal values.

Patient B: A 56-year-old Vietnamese man with a 20-year history of hypertension was being treated with valsartan 320 mg, amlodipine 10 mg, and benazepril 20 mg daily. His weight and height were 161 lbs. and 5 feet ¼ inches, respectively. He complained of cramping in his extremities and his BP had been uncontrolled at home. Laboratory examination showed a serum potassium of 3.1 mmol/L (normal, 3.6 - 5.0), serum sodium of 139 mmol/L (normal, 135 - 145), serum chloride of 99 mmol/L (normal, 96 - 109), serum total carbon dioxide of 25 mmol/L (normal, 20 - 30), serum creatinine of 1.5 mg/dl (normal, 0.7 - 1.3), serum blood urea nitrogen (BUN) of 25 mg/dl (normal, 5 - 26), serum glucose of 103 mg/dl (normal, 65 - 99), serum thyroxine (T4) of 6.8 µg/dl (normal, 4.5 - 12), serum thyronine uptake of 34% (normal, 24 - 39), and serum thyroid stimulating hormone (TSH) of 1.6 uIU/ml (normal, 0.5 - 1.5). Further blood tests revealed plasma renin of <0.1 ng/ml/hr

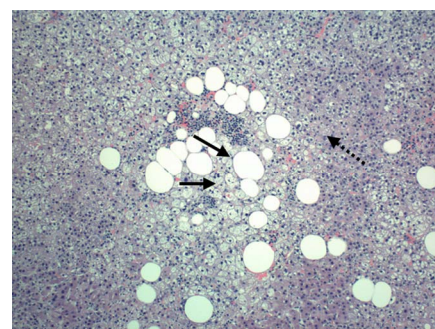


(a)

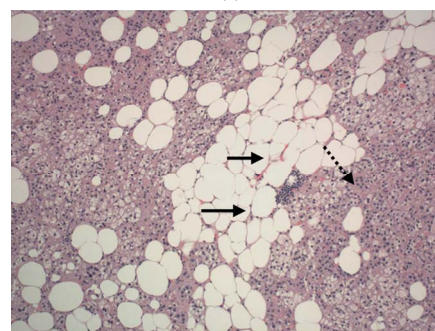


(b)

Figure 1. Photomicrograph (10×) showing nodular hyperplasia of the adrenal cortex. The nodule in the left field is composed of mostly large clear cells.



(a)



(b)

Figure 2. Photomicrograph (10×) showing infiltrates of numerous adipocytes (→) and adjacent lymphocytes (····→) in the adrenal cortex.

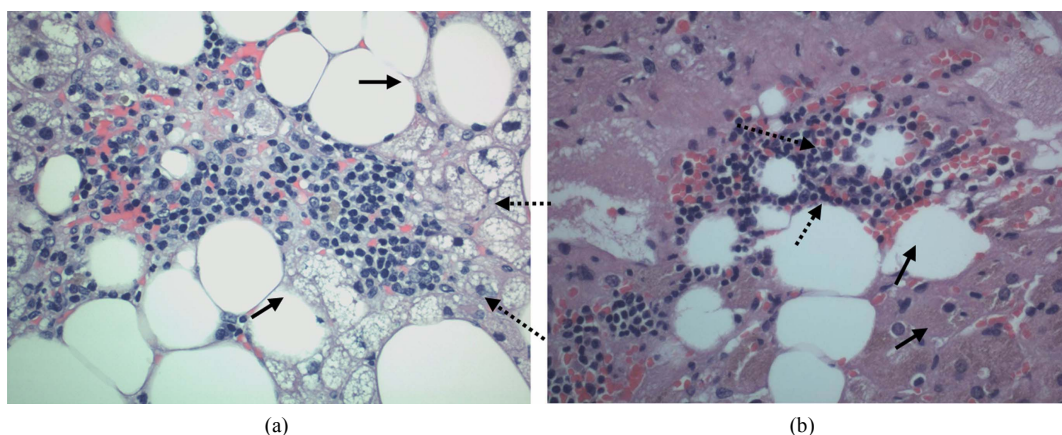


Figure 3. Photomicrograph (40×) showing infiltrates of adipocytes (→) and adjacent lymphocytes (····→) in the adrenal cortex.

(normal, 1.3 - 4), serum aldosterone of 17.1 ng/dl (normal, 1 - 15), serum cortisol 11.8 µg (normal, 3.1 - 22.4), 24-hours urine for metanephrine of 503 µg (normal, 35 - 350), 24-hours urine for vanillylmandelic acid (VMA) of 17 mg (normal, 0 - 6), plasma free normetanephrine of 0.96 nmol/L (normal, <0.9), plasma free metanephrine of 0.35 nmol/L (normal, <0.5), serum chromogranin A of 109/ml (normal, 0 - 50). A computed tomography (CT) scan of the adrenal gland showed the left adrenal limb at 1.8 × 0.9 cm compared to the right adrenal limb at 1.7 × 0.2 cm. An adrenal vein sample found plasma free metanephrine of 24.9 nmol/L in the left adrenal vein and <0.2 nmol/L in the right adrenal vein. Also, plasma free normetanephrine was 4.95 nmol/L in the left adrenal vein and 0.44 nmol/L in the right adrenal vein.

He also has had a history of more than 30 years of proteinuria, ranging from 2000 - 4000 mg/day with mild chronic renal failure and serum creatinine of 1.4 to 1.7 mg/dl. He had a kidney biopsy, suggestive of focal segmental sclerosis (FSS) of the kidney. Before surgery, his 24-hours urine collection for protein and serum creatinine was 2851.6 mg and 1.9 mg/dl, respectively.

He was started on spironolactone 25 mg twice a day orally with good blood pressure controlled (120/70). His serum potassium was 5.2 mmol/dl. Also, valsartan, amlodipine, and benazepril were discontinued.

He then underwent laparoscopic left adrenalectomy. The specimen consisted of fibroadipose tissue measuring 11.5 × 3 × 3 cm with the left adrenal gland measuring 7 × 1 × 1 cm. The entire specimen weighed 42 g. Pathological examination reported a section in a longitudinal orientation but none in transverse section. Unfortunately, the specimen did not show the medullary portion of the adrenal gland. However, pheochromocytoma could not be entirely excluded based on the available sections. Still, changes in the adrenal cortex were suggestive of nodular

hyperplasia (**Figure 1(b)**). Most interestingly, there were abundant adipocytes in the adrenal cortex in association with the presence of lymphocytic infiltration (**Figures 2(b) and 3(b)**).

After surgery, spironolactone was discontinued and his BP has been stable (110/70). The laboratory examination revealed serum creatinine of 1.53 mg/dl, serum glucose of 80 mg/dl, serum BUN of 17 mg/dl, serum sodium of 136 mmol/L, serum chloride of 100 mmol/L, serum total carbon dioxide of 22 mmol/L, and urine protein of 320 mg/24hrs. Subsequent levels of serum catecholamine, renin, aldosterone, and urinary VMA decreased to normal values.

3. Discussion

Pheochromocytoma, a catecholamine-secreting tumor, arises from chromaffin cells of the adrenal medulla that is rare. The simultaneous occurrence of adrenomedullary and adrenocortical tumors is extremely rare. There are only five reported cases in the literature [4]. We have suggested that a local interaction between the adrenocortical and medullary areas may be involved.

To our knowledge, coexistence of the the hypersecretion of the catecholamine, adrenal cortical nodular hyperplasia, and nephrotic-range proteinuria secondary to focal segmental scleronephrosis (FSS) has not been reported in the literature. Most interestingly, a prominent adipocyte infiltrate in the adrenal cortex was seen in association with the presence of lymphocytes, which suggested that adipocyte might have a role in the pathogenesis of these concomitant diseases in our patients.

Obesity has been associated with increased macrophage infiltration of adipose tissue, and these macrophages may be an important component of the chronic inflammatory response involved in the development of obesity-associated disease. In obese patients, Weisberg *et*

al. [5] showed that adipose tissue contains an increased number of macrophages. Drastic weight loss resulted in both a significant decrease in macrophage number and changes in chemoattractant gene expression in adipose tissue [6]. The mechanism of macrophage recruitment to adipose tissue presumably involves increased secretion of chemotactic molecules by adipocytes, such as the C-C motif chemokine ligand 2 (CCL2 or monocyte chemoattractant protein-1) [7-8].

A link between adipose tissue and the cortical adrenal gland, particularly via the mineralocorticoid aldosterone, has already been demonstrated. Gene expression in the renin-angiotensin-aldosterone system (RAAS) was increased in the adipose tissue from obese animal models and human subjects [9,10]. There are reports of high levels of circulating angiotensinogen (AGT), rennin and aldosterone; and high levels of activity of angiotensin-converting enzyme (ACE) in obese patients [11,12]. Weight loss is also associated with a decrease in serum aldosterone, plasma renin activity, angiotensinogen and ACE levels [13,14]. Ehrhart-Bornstein *et al.* [15] incubated fat cells in a conditioned medium from primary mammary gland adipocyte cultures—with NCI-H295R adrenocortical cells for 24 hours. They found that adipocyte secretory products directly stimulate aldosterone secretion 7-fold in human adrenocortical cells (NCI-H295R). This effect is independent of adipose angiotensin II. Possible molecular mechanisms involved in this aldosterone secretion include acidity by either an oxidized derivative of linoleic acid [16] or by a potent mineralocorticoid-releasing factor [15] contained in a medium conditioned by human adipocytes. Furthermore, Schinner *et al.* [17] suggested that the Wnt-signaling pathway is one of the mechanisms mediating the effects of fat cells on adrenal steroidogenic acute regulatory (StAR) transcription as well as cortisol and aldosterone secretion.

The interaction of the sympatho-adrenomedullary system with adipose tissue has been reported in the literature. Resting plasma norepinephrine was found to be a positive predictor of changes in body mass index [18]. Leptin is an adipostatic hormone synthesized and secreted by fat tissues [19]. Plasma leptin concentrations are elevated in obese subjects [20]. Glasow *et al.* [21] investigated a functional leptin receptor in human adrenal tissue and, they showed a differential action of leptin on human adrenocortical and chromaffin cell hormone production. Leptin directly stimulates catecholamine secretion and synthesis in cultured porcine adrenal medullary chromaffin cells [22].

The association between obesity and nephrotic-range proteinuria was first reported in 1974 [23]. Since then,

FSS has been linked to massive obesity [24,25]. Obesity-related FSS is distinctive from idiopathic FSS as it is associated with lower incidence of nephrotic syndrome and has a more indolent course [26]. However, drastic weight reduction is associated with a resolution of this nephrotic syndrome [27]. Plasma adrenomedullin (AM) has been isolated from human pheochromocytomas and adipose tissue [28,29]. High levels of plasma AM have been reported in obese subjects [30]. Plasma AM decreased significantly after weight loss from gastric bypass surgery [31]. That plasma AM directly related to the level of proteinuria [32] and changes in AM levels may be the result of heavy proteinuria [33].

In summary, our patients presented with hypersecretion of catecholamine, cortical nodular hyperplasia of the adrenal gland. After surgery, their blood pressures were normalized. Nephrotic-range proteinuria was resolved in one patient. Most interestingly, prominent adipocytes infiltrated were seen in the adrenal cortex in association with the presence of lymphocytes, which suggested that adipocytes might have a role in the pathogenesis of these diseases in our patient. However, a coincidence of these diseases cannot be excluded.

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