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Abstract

A 26-year-old female with Bartter's syndrome associated with Graves' disease is reported. This patient had a history of Graves' disease from the age of 22 and anti-thyroid drug (Methimazole) had been administered for 2 years. Thyroid function returned to normal but general fatigue and polyuria continued. Hypokalemia was diagnosed at 25 years of age and she was referred to our hospital for evaluation. Blood pressure was normal and laboratory data revealed normal thyroid function, hypokalemic alkalosis, high plasma renin activity and high plasma aldosterone concentration. She showed normal pressor sensitivity to norepinephrine infusion, grossly diminished pressor sensitivity to exogenous angiotensin II infusion compared with the normal. A renal biopsy specimen showed juxtaglomerular cell hyperplasia. Electron microscopy confirmed lacis cell (agranular cell) proliferation.

KEYWORDS: Bartter's syndrome, juxtaglomerular cell hyperplasia, secondary aldosteronism, plasma renin activity

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BARTTER'S SYNDROME

— CASE REPORT —

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Abstract. A 26-year-old female with Bartter's syndrome associated with Graves' disease is reported. This patient had a history of Graves' disease from the age of 22 and anti-thyroid drug (Methimazole) had been administered for 2 years. Thyroid function returned to normal but general fatigue and polyuria continued. Hypokalemia was diagnosed at 25 years of age and she was referred to our hospital for evaluation. Blood pressure was normal and laboratory data revealed normal thyroid function, hypokalemic alkalosis, high plasma renin activity and high plasma aldosterone concentration. She showed normal pressor sensitivity to norepinephrine infusion, grossly diminished pressor sensitivity to exogenous angiotensin II infusion compared with the normal. A renal biopsy specimen showed juxtaglomerular cell hyperplasia. Electron microscopy confirmed lacis cell (agranular cell) proliferation.

Key words: Bartter's syndrome, juxtaglomerular cell hyperplasia, secondary aldosteronism, plasma renin activity

In 1962 Bartter and his co-workers (1) described a syndrome of hypokalemic alkalosis, increased plasma renin activity (PRA) and plasma aldosterone concentration (PAC), juxtaglomerular cell hyperplasia, normal blood pressure and peripheral insensitivity to the pressor effects of angiotensin. Since then, many similar cases have been reported (2-6). All had renal lesions of varying severity with the characteristic feature of juxtaglomerular cell complex. The absence of hypertension and the response to infusion of angiotensin in these patient led Bartter and his associates to suggest that peripheral vascular insensitivity to angiotensin might result in juxtaglomerular stimulation, increased release of renin and secondary hyperaldosteronism. We report a case of Bartter's syndrome with euthyroid goiter who underwent renal biopsy and endocrinological examination.

CASE REPORT

Clinical history. A 26-year-old women admitted to our hospital because of hypokalemia.

She was well until 3 years before admission, at which time she complained of palpitations, sleep irregularities and excessive lacrimation. A physician diagnosed an enlarged thyroid gland and prescribed Methimazol 10–15 mg/day. Ten months later, the thyroid gland had decreased in size and symptoms had improved. Three months before admission, she complained of general fatigue and thyroid enlargement appeared again. She visited another physician and was found to have hypokalemia. Anti-thyroid medication was stopped because of slightly decreased thyroid function. At that time, the triosorb test was 28%, T₃ 80 ng/dl, T₄ 2.4 μg/dl; Hypokalemia and general fatigue, however, continued and she was referred to our hospital. A routine examination before admission, including urinalysis, was negative. The patient denied having any weakness of the extremities, or any previous renal or hepatic disease. She was taking no other medication. There was no family history of endocrinological or renal disorders.

Physical examination. Axillary temperature was 36.2°C, pulse rate 72/min, and respiration rate 14/min. Blood pressure was 102/60 mmHg. Her weight was 42 Kg and height, 153 cm. Eyes, skin, face and extremities were normal. There was no peripheral edema. A grade III, soft, diffuse and non tender thyroid swelling was noticed. There were no palpable lymph nodes. Lungs and heart were normal. The abdomen was flat and non tender: The liver was palpable 0.5 f.b. below the right costal margin. The spleen and kidneys were not palpable. Tendon reflexes were normal. Trousseau's and Chvostek's signs could not be elicited.

Laboratory findings. The urine volume was 2500–4500 ml/day and routine urinalysis revealed no protein or sugar, and 4 to 6 white blood cells in sediment per high power field. The hematocrit was 33.5%, hemoglobin 12.1 g/dl, and the white-cell count 4400/mm³ with a normal differential count. The erythrocyte sedimentation rate was 12 mm per hour. Blood urea nitrogen was 9 mg/dl, serum creatinine 0.8 mg/dl, fasting blood sugar 104 mg/dl, serum calcium 8.6 mg/dl, serum phosphorus 3.5 mg/dl, serum bilirubin 0.3 mg/dl and serum total protein 7.0 g/dl (albumin 4.1 g/dl and globulin 2.9 g/dl). With an ordinary diet, the serum sodium was 134 mEq/dl, serum potassium 2.4 mEq/dl, and serum chloride 96 mEq/dl. The measurement of urinary electrolytes showed sodium 100 mEq/l, potassium 23.6 mEq/l, calcium 8.5 mg/l, chloride 96 mEq/l, and phosphorus 13 mg/l. Potassium clearance was 27 ml/min with Na₂S₂O₃ loading. The glutamic oxalacetic transaminase (SGOT) was 14U/ml, lactic dehy-

drogenase (LDH) 260U/ml, creatine phosphokinase (CPK) 24U/ml, serum cholesterol 189 mg/dl, free fatty acids 540 μ Eq/l, phospholipids 157 mg/dl, β -lipoprotein 629 mg/dl, and triglycerids 67 mg/dl. Serologic tests for syphilis were negative and the antistreptolysin O titer was 80 Todd units. Antinuclear antibody was negative. Arterial blood gas results were pH 7.46, P_{CO_2} 41.9 mmHg, P_{O_2} 94.6 mmHg, HCO_3^- 29.4 mEq/l, and base excess 5.1 mEq/l. A 50 g glucose tolerance test showed a diabetic glucose tolerance curve with fasting blood sugar 104 mg, 30 min 152 mg, 60 min 188 mg, and 120 min 130 mg. The phenolsulphonphthalein (PSP) test was 15 min 35%, 30 min 48%, 60 min 68% and 120 min 86%. Endogeneous creatinine clearance was 83 ml/min. By para-aminohippurate (PAH) clearance, glomerular filtration rate (GFR) was 108 ml/min and renal plasma flow (RPF) was 607 ml/min. The maximum specific gravity of urine was 1014 by Fishberg's urine concentration test. By the urine acidification test (Wrong's method) with ammonium chloride loading 0.1 g/Kg, the pH of urine became 5.00 from 7.05 when metabolic acidosis was induced. An intravenous pyelogram was normal. Electrocardiography showed changes characteristic of hypokalemia.

Endocrinological examinations. T_3 resin uptake (Triosorb test) was 29%, T_3 153 ng/dl, T_4 7.1 μ g/dl, I^{131} thyroidal uptake 56%, and anti-thyroglobulin antibody was negative. After T_3 administration, I^{131} uptake was suppressed to 18%. Thyrotropin releasing hormone (TRH) test showed a normal response for thyroid stimulating hormone (TSH). Urinary excretion of 17-hydroxycorticosteroid was 7.1 mg/day, 17-ketosteroid 5.3 mg/day and catecholamine 98.6 μ g/day. ACTH (adrenocorticotrophic hormone) stimulation test showed normal response of plasma cortisol. With an ordinary diet, PRA was markedly increased (28.7 ng/ml/h with the patient supine) above normal (3.30 ± 1.25 ng/ml/h supine) (7). PAC was elevated above normal (5.81 ± 3.60 ng/dl supine) to 53.7 ng/dl with the patient supine. Angiotensin infusion test (Fig. 1): The normal response is a 15 to 20 mmHg increase in diastolic blood pressure with a 6 to 12 ng/Kg/min infusion of angiotensin. This patient showed marked resistance to the pressor effects of angiotensin, as did the patient described by Bartter. This patient required 60 ng/Kg/min for a 15 to 20 mmHg rise in diastolic blood pressure. She had normal pressor sensitivity to norepinephrine infusion compared with normal subjects.

Renal biopsy specimen. Renal tissue obtained via percutaneous needle biopsy of the left kidney was fixed in 10% formalin solution and stained with hematoxylin and eosin, periodic acid-Schiff (PAS) and Bowie's stain. Material for electron microscopy was fixed in 5% glutaraldehyde solution, refixed in 1% OsO_4 , embedded in Epon and cut to ultrathin section on an ultramicrotome. In light microscopy, seventeen glomeruli were examined and showed almost nor-

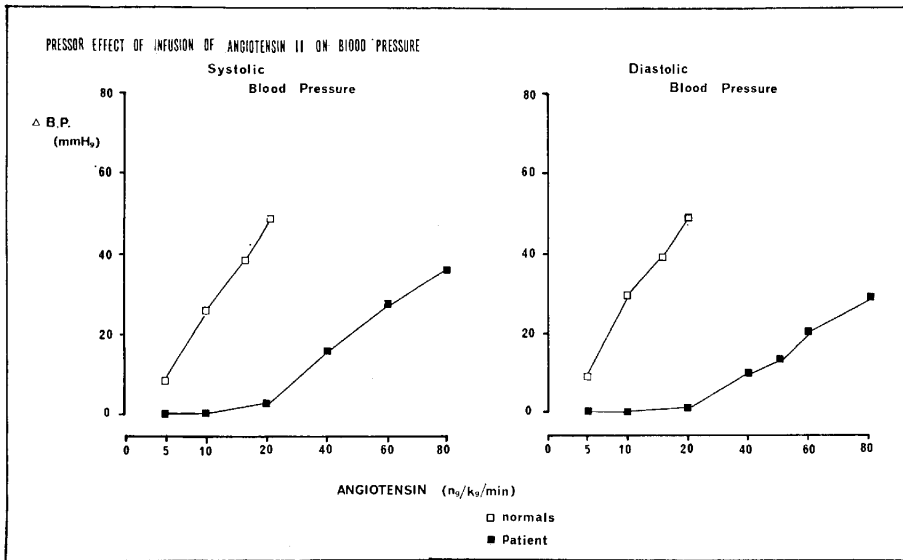


FIG. 1. ANGIOTENSIN INFUSION TEST

mal appearances (Fig. 2) except for one sclerotic glomerulus. There was no increase in mesangial cells or matrix. The proximal convoluted tubules were dilated and the distal convoluted tubules were locally degenerated. A few interstitial scars were present. The arterioles (particularly afferent arterioles) appeared slightly thickened; however, the arteries and vein appeared normal. The juxtaglomerular apparatus was markedly hyperplastic and hypertrophic in sections treated with PAS (Fig. 3) and Bowie's stain. An immunofluorescent technique was used to stain anti-human immunoglobulin G, A, M, complement and fibrinogen; however, positive immunofluorescences was not observed in any of the stains. By electron microscopy, there was no glomerular hypercellularity. The glomerular capillary basement membrane appeared to be uniform and of normal thickness. The epithelial cell foot-processes also appeared normal (Fig. 4). Juxtaglomerular cells without granules (lacis cells) were surrounded by increased amounts of basement membrane-like material and bundles of collagen (Fig. 5).

DISCUSSION

This case is similar in most respects to those first described by Bartter and his co-workers with clinical features which included hypokalemic alkalosis, secondary aldosteronism without hypertension, a marked elevation of PRA and a characteristic renal lesion. Subsequently, Greenberg and his associates (4), Schiffman (3) and Brackett *et al.* (5) added cases with similar characteristics.

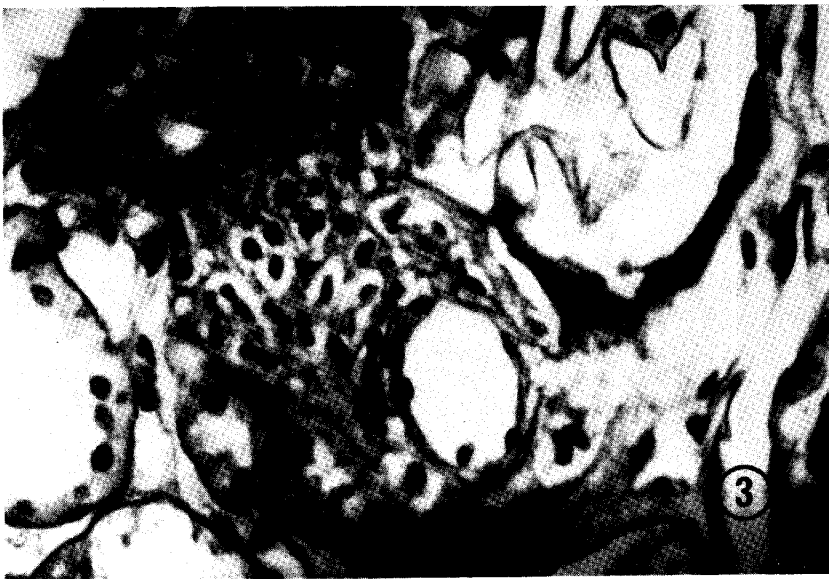


Fig. 2. Renal biopsy specimen showing hyperplasia of the juxtaglomerular cells. PAS stain, $\times 200$

Fig. 3. A thickened afferent arteriole with juxtaglomerular cells including prominent nuclei. H-E stain, $\times 400$

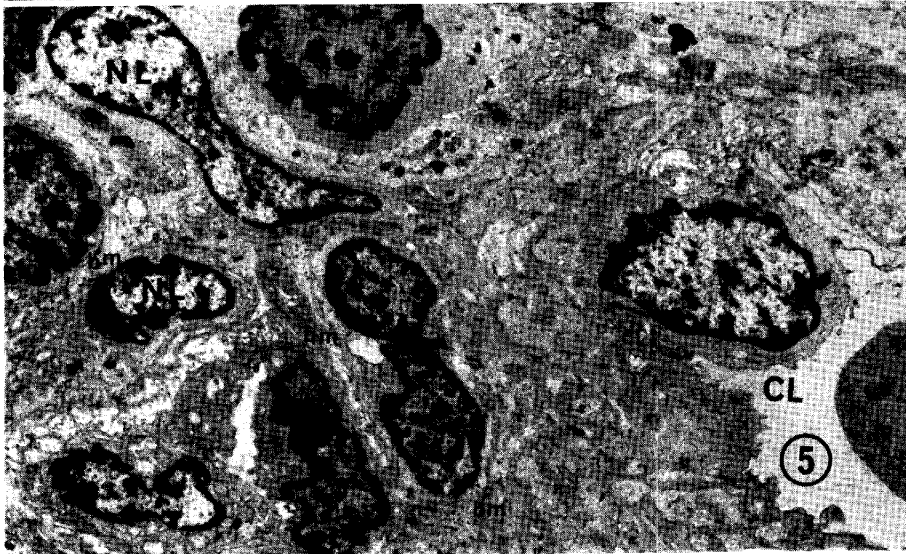
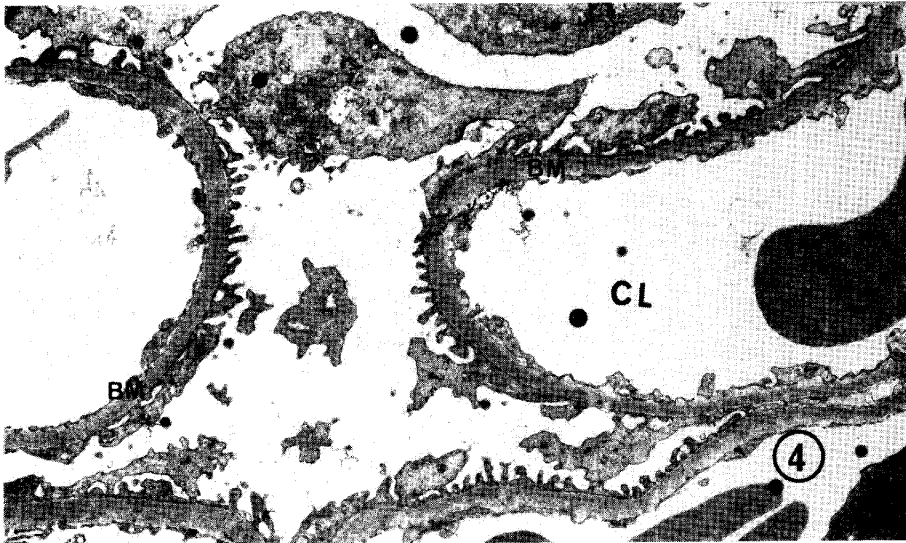


Fig. 4. Electron photograph from renal biopsy specimen. Glomerular capillary basement membrane is normal thickness. The epithelial cell foot-processes appear normal. $\times 2000$

Fig. 5. Juxtaglomerular cell hyperplasia near the hilar area of a glomerulus without granules is increased in number and surrounded by basement membrane like material. $\times 4000$
NL; nucleus of lacis cell bm; basement membrane like material CL; capillary lumen BM; basement membrane

Our case had normal renal function as estimated by PSP, PAH and endogenous creatinine clearance, although a urinary concentration defect presumably related to chronic potassium depletion was observed. Urinary acidification was normal during ammonium chloride loading. With sodium restriction and potassium supplements, the administration of spironolactone resulted in correction of the alkalosis and return of the plasma potassium level to lower normal. As in previously reported cases, hypertension was not present in our case and the response to infusions of angiotensin II was suppressed. It is of interest that the dose of angiotensin II required to produce a rise of 20 mmHg in diastolic pressure in patients with the syndrome of juxtaglomerular cell hyperplasia without hypertension is ten to twenty times more than that required in normal subjects (8). In our case, about ten times was required. Norepinephrine infusions, as in other patients with this syndrome, produced a near normal rise in blood pressure during infusions. In the renal biopsy specimen, hyperplasia of the juxtaglomerular cells was striking and the afferent glomerular vessels were characterized by thickening of the vessels walls and narrowing of the lumens. As Brackett *et al.* (5) observed, electron microscopy confirmed the presence of a few juxtaglomerular cells containing an increased number of renin granules, and juxtaglomerular cells without granules (lacis cells) were increased in number and surrounded by basement membrane-like material.

In hyperthyroidism, the renin-angiotensin-aldosterone system is activated. PRA and PAC are above normal, but are not as high as in Bartter's syndrome. Fukuchi *et al.* (9) showed that, in hyperthyroidism, PRA was 2.22 ± 1.62 ng/ml/h (normal 1.07 ± 3.20). The cause of high level PRA and PAC in hyperthyroidism is that thyroxine has a sodium losing effect and sympathomimetic stimulation. Sodium and water losing induce renal blood flow reduction and PRA rises. Sympathomimetic stimulation activates the renin-angiotensin-aldosterone system. This patient was diagnosed as hyperthyroidism at 22 years of age and an anti-thyroid drug was administered. At admission to our hospital, she had diffuse goiter; however, her thyroid function was normal. Hyperthyroidism seemed to be in remission because her thyroidal I^{131} uptake was normally suppressed by T_3 administration and then the antithyroid drug was stopped. In Japan, the incidence of thyrotoxicosis with hypokalemia and periodic paralysis is high in male patients (10). The exchangeable pool of potassium may be reduced in hyperthyroidism (11). This occurs regularly in males and infrequently in females. The fat stores in women may defer the breakdown of protein and the release of cell potassium. In 1965, Staffurth *et al.* (12) confirmed that serum potassium concentrations become normal in thyrotoxicosis when the thyroid function is ameliorated. In our case, hypokalemia continued after remission. This is suggestive of Bartter's syndrome. Examinations revealed high

PRA, PAC and juxtaglomerular cell hyperplasia.

The etiology of Bartter's syndrome is not clear. Bartter *et al.* first suggested that the primary defect was vascular insensitivity to the pressor action of angiotensin. This would lead to compensatory overproduction of renin, secondary hyperaldosteronism and hypokalemia. However, it is known that insensitivity to angiotensin is not specific for Bartter's syndrome and is observed whenever PRA is elevated as in renovascular hypertension or liver cirrhosis. On the other hand, Cannon *et al.* (6) suggested that primary renal salt wasting, either at proximal tubules or ascending limb level or as a result glomerulo-distal tubular shunts, led to sodium depletion with secondary activation of the renin-angiotensin system with hyperaldosteronism. They postulated that pressor insensitivity to angiotensin was secondary to volume depletion. However, the primary site of the tubular sodium reabsorptive defect in this syndrome has not been established. Chaimovitz *et al.* (13) indicated that free water formation was markedly reduced at all rates of distal tubular delivery, and suggested that salt wasting is mainly a consequence of a defect of sodium transport at the ascending Henle's loop. Sodium reabsorption defects at this site impair the ability of the kidney to develop medullary hyperosmolarity and lead to hypoosmotic urine in the patient. In the studies of White (14) and Fujita *et al.* (15), rapid infusions of albumin or saline solution resulted in correction of angiotensin insensitivity, and they suggested that the overproduction of renin and aldosterone was physiologic rather than autonomous. Modlinger *et al.* (16) showed that the blood volume tended to increase concomitantly with the decrease in PRA, by the administration of large doses of propranolol to a patient with Bartter's syndrome. These results suggest that the decreased blood volume was a result and not a cause of the hyperreninemia. Thus, it is sure that renal salt wasting exists in this syndrome, however, the relation between renal salt wasting and hyperreninemia remains to be clarified.

In our case, histologic findings by electron microscopy demonstrated that agranular cells (lacis cells) increased in number, occupying almost all of the juxtaglomerular cells. These cells were surrounded by basement membrane like material and prominent collections of collagen bundles, and were morphologically similar to mesangial cells. These findings are consistent with the proposal of Hatt (17) that an increase in the number of juxtaglomerular cells occurs through metaplasia of the smooth muscle cells of the media of the afferent arterioles. Brackett *et al.* (5) suggested that the renal arteriolar lesion resulted in decreased circulation through afferent arterioles which set renin release at high levels. A similar arteriolar lesion occurs in chronic diarrhea or chronic volume depletion, and renin injections can cause vascular change. Thus, the prolonged excessive release of endogenous renin might elaborate the vascular lesion of the

afferent arterioles in this syndrome.

Until recently there was no effective treatment for Bartter's syndrome except potassium supplements and anti-aldosterone agents. However, in 1976 Verberckmoes *et al.* (18) observed hyperplasia of the renomedullary interstitial cells in Bartter's syndrome. In view of the suggested association of these cells with prostaglandin production (Muirhead *et al.* 1972) (19), a known inhibitor of prostaglandin synthetase (indomethacin) was administered to a patient with this syndrome. The initial results were excellent and this finding has been confirmed by Fichman *et al.* and Gill *et al.* (20, 21). Littlewood *et al.* (22) reported that, in their therapy, indomethacin was changed into ketoprofen, a known prostaglandin inhibitor, with fewer side effects, because of the long-term use of indomethacin caused side effects of gastric erosion, headache or hallucinations. They expect that many patients will be spared the serious consequences of their metabolic disturbance and survive when prostaglandin synthetase inhibitors *i.e.* ketoprofen come into use.

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