Primary hyperaldosteronism and renal medullary nephrocalcinosis: 
A controversial association

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ABSTRACT
Primary hyperaldosteronism (PA) is a common disease with a prevalence of 5-10% in unselected patients with hypertension. Medullary nephrocalcinosis is a radiological diagnosis and refers to diffuse calcification in the renal parenchyma. The three commonest causes of nephrocalcinosis are PHPT, distal renal tubular acidosis and medullary sponge kidney. PA is not a recognized cause of nephrocalcinosis. In the literature there are few case reports linking PA with nephrocalcinosis. In this case series, we report three cases where PA was possibly associated with medullary nephrocalcinosis. In all three cases, the common causes of nephrocalcinosis were excluded by careful clinical history, biochemical evaluation and radiologic findings. We conclude and emphasize that PA as an etiology of medullary nephrocalcinosis should be sought after the common causes have been excluded, at least in those with hypertension that is difficult to control.
Keywords: Primary hyperaldosteronism; Nephrocalcinosis; Hypokalemia; Kaliopenic nephropathy

INTRODUCTION

Primary hyperaldosteronism (PA) is a common disease with a prevalence of 5-10% in unselected patients with hypertension. It is well known that PA leads to increased cardiovascular morbidity and mortality independent of hypertension. The typical manifestations of PA include hypertension, hypokalemia and metabolic alkalosis.

Nephrocalcinosis refers to diffuse calcification in the renal parenchyma and the term is more or less synonymous with the medullary nephrocalcinosis. While the term “nephrocalcinosis” was first coined in association with primary hyperparathyroidism (PHPT), a number of conditions have been linked to this condition. The three commonest causes of nephrocalcinosis are PHPT, distal renal tubular acidosis (dRTA) and medullary sponge kidney. The diagnosis is purely radiological and can be demonstrated on plain radiographs, ultrasound or computed tomography. The pathophysiology of nephrocalcinosis includes sustained hypercalcemia and hypercalciuria, tubular delivery of calcium to the interstitium and subsequent deposition based on local conditions including the pH and inhibitory ions.

PA is not a recognized cause of nephrocalcinosis and/or nephrolithiasis. In the literature there are few case reports linking PA with nephrocalcinosis and/or nephrolithiasis. We, hereby report three cases, where PA was possibly associated with medullary nephrocalcinosis. Postulated theories linking PA with nephrocalcinosis are also discussed.
CASE REPORT

Case 1

A 35-year-old woman who was having hypertension for five years was brought to our emergency room with sudden onset loss of consciousness following palpitations without abnormal body movements. On reception, her electrocardiogram showed ventricular tachycardia (VT) along with severe hypokalemia, metabolic alkalosis and hypernatremia (Table 1). She was initially treated for VT as per our institutional protocol along with intravenous potassium replacement. After stabilisation she was evaluated for cause of hypokalemia. Two similar episodes in the year prior to the present one were mistaken as seizure and evaluated with MRI brain and EEG that were unremarkable. Review of her records revealed hypokalemia and metabolic alkalosis during those episodes which was unfortunately overlooked by the treating physician. In view of her poorly controlled hypertension on three anti-hypertensive agents (Telmisartan 40mg, Amolodepine 10mg and Metoprolal 100 mg), recurrent unprovoked severe hypokalemia leading to VT along with metabolic alkalosis and high serum sodium, there was a strong clinical possibility of PA. She was taken off Telmisartan, Amolodepine and Metoprolal for 2 weeks and was prescribed tablet prazocin sustained release, verapamil and oral potassium replacement. After 2 weeks a morning sample (8:00 AM) was drawn for plasma aldosterone concentration (PAC) and plasma renin activity (PRA). PAC was exceedingly high and PRA was suppressed (Table1) with aldosterone renin ratio (ARR) highly suggestive of PA in the given clinical setting.
Table 1: Biochemical parameters of patients

| Parameter              | Case 1   | Case 2   | Case3    | Normal range |
|------------------------|----------|----------|----------|--------------|
| Serum pH               | 7.48     | 7.50     | 7.46     | 7.35-7.45    |
| Serum bicarbonate (meq/L) | 29.8     | 27.7     | 28.1     | 18-22        |
| Serum potassium (meq/L) | 1.4      | 2.0      | 2.4      | 3.5-5.5      |
| Serum sodium (meq/L)   | 156      | 140      | 148      | 135-145      |
| Serum calcium (mg/dl)  | 9.1      | 9.0      | 8.7      | 8.8-10.5     |
| PAC (ng/dl)            | 37.3     | 36.4     | 14.99    | 1.76-23.2    |
| PRA (ng/ml/hr)         | 0.25     | 0.10     | 0.04     | 0.15-2.33    |
| ARR                    | 149.2 ng/dl per ng/ml per hour | 364 ng/dl per ng/ml per hour | 374.7 ng/dl per ng/ml per hour | Less than 30 |
| 24-hour urinary calcium (mg/kg/day) | 1.6 | 2.1 | 1.9 | 1.5-4 |

PAC = Plasma aldosterone concentration ; PRA = Plasma renin activity ; ARR = Adlosterone renin ratio.

CECT abdomen with adrenal protocol revealed right adrenal adenoma measuring 1.3×1.2 cm with non-contrast HU of 15 and absolute percentage washout of 86.7% and relative percentage washout of 61%. Both kidneys were normal without nephrocalcinosis or renal cysts. Laproscopic
right adrenalectomy was performed and the resected tissue was reported as adrenal adenoma on histopathological examination. Soon after surgery, hypokalemia got corrected and blood pressure declined. Over next several months antihypertensive medications were phased out. On follow up for five years, she is normokalemia and normotensive without treatment.

Three years after surgery, radiograph of abdomen done for abdominal pain revealed renal medullary nephrocalcinosis (Figure 1). A detailed work up was undertaken for the etiology of medullary nephrocalcinosis. She had normal serum pH (7.39, 7.36), calcium (9.2, 8.9 mg/dl), phosphate (3.78, 3.73 mg/dl) and normal 24-hour urinary calcium (79.8 mg). An ammonium chloride loading test was undertaken, the results of which showed adequate urinary acidification in response to the acid load. These results ruled out incomplete dRTA as the urine pH level declined below 5.5.
Case 2

A 38-year-old woman who had hypertension from 30 years of age with poor control on three medications, presented to our emergency room with acute pure motor quadriplegia of 24 hours duration. Her investigations revealed metabolic alkalosis with severe hypokalemia (Table 1). Her
quadripareisis resolved promptly within 6 hours with correction of hypokalemia. In view of her poorly controlled early onset hypertension along with unprovoked severe hypokalemia, PA was suspected. All offending drugs that could affect ARR measurements were stopped for 2 weeks. After 2 weeks a morning sample (8:00 AM) was drawn for PAC and PRA. PAC was exceedingly high and DRC was suppressed with ARR highly suggestive of PA (Table1). CECT adrenals revealed a right adrenal adenoma of size 2.3 ×1.3 cm with unenhanced attenuation of 4 HU. Her CT incidentally revealed bilateral medullary nephrocalcinosis without renal cysts. She underwent laparoscopic right adrenalectomy, which was followed by prompt reduction in requirement of anti-hypertensive medication and correction of hypokalemia. Like case 1 a detailed work up was undertaken for the etiology of medullary nephrocalcinosis and was negative. At one year follow up, she has well controlled BP on single anti-hypertensive medication without hypokalemia.

**Case 3**

A 28-year-old woman was referred to us for evaluation of resistant hypertension of 3 years duration. Her past medical history revealed intrauterine death attributed to uncontrolled hypertension. Her investigations revealed metabolic alkalosis with severe hypokalemia (Table 1). A morning sample (8:00 AM) was drawn for PAC and PRA. PAC was exceedingly high and PRA was suppressed with ARR highly suggestive of PA (Table1). CECT abdomen revealed a right adrenal adenoma. CECT incidentally revealed bilateral medullary nephrocalcinosis. She underwent laparoscopic right adrenalectomy, with histopathological examination of resected tissue reported as adrenal adenoma. On follow up for more than six years, she is normokalemia and off antihypertensive agents. Like the first two cases, work up for the etiology of medullary nephrocalcinosis was negative.
In all three cases, the common causes of medullary nephrocalcinosis were excluded by careful clinical history, biochemical evaluation and radiologic findings.

**DISCUSSION**

Medullary nephrocalcinosis is a type of metastatic calcification that usually arises due to conditions that either increase serum calcium or urinary calcium excretion. Commonest causes of medullary nephrocalcinosis include PHPT, dRTA and medullary sponge kidney. The uncommon causes include Bartter’s disease, Sarcoidosis, Dent’s disease, Vitamin D toxicity, Oculocerebral syndrome, Milk alkali syndrome, Idiopathic hypercalciuria, Liddle’s syndrome, Lowe’s syndrome, Primary hyperoxaluria, X-linked hypophosphatemia, Williams’ syndrome, Wilson’s disease and prolonged use of diuretics.²

PA is not a recognized cause of nephrocalcinosis and/or nephrolithiasis. In the literature there are few case reports linking hyperaldosteronism with nephrocalcinosis and/or nephrolithiasis.²,⁵–¹⁰ The first case of PA associated with nephrocalcinosis was reported by Oghihara et al., the patient was normokalemic.⁵ In 1994 Yang et al., reported nephrocalcinosis associated with PA in a 45-year-old woman and implicated chronic hypokalemia in the pathogenesis of nephrocalcinosis.⁸ In 2015 Mittal et al., reported a series of five patients, two with PA and three with secondary hyperaldosteronism associated with nephrocalcinosis.² In this series, all five patients had severe chronic hypokalemia. In our series, the three cases had severe chronic hypokalemia.

Various pathogenic mechanisms relating hyperaldosteronism with medullary nephrocalcinosis have been proposed. The earliest proposed mechanism is that chronic
hypokalemia secondary to hyperaldosteronism can cause a tubular interstitial injury. This is associated with elevated ammoniagenesis and subsequent renal damage through ammonia activated alternate complement pathway. The renal cyst formation, interstitial inflammation and medullary nephrocalcinosis may all be related to the ammonia mediated nephropathy.\textsuperscript{8,11} This has been aptly described as “chronic kaliopenic nephropathy”. A careful look at all the previously published cases reveals severe chronic hypokalemia in all cases with normokalemia in a single case. We believe this was the likely mechanism in our three cases as well, as all three had severe chronic hypokalemia.

Hypercalciuria occurring in hyperaldosteronism is one of the well-recognised mechanisms by which PA can cause nephrocalcinosis. Urinary calcium correlates with sodium excretion; each 100 mEq/dL increment in sodium excretion promotes an increase of 40 mg/dL in calcium excretion.\textsuperscript{12} Increased urinary calcium excretion in PA could be due to the reduced reabsorption of sodium in aldosterone-insensitive tubular sites.\textsuperscript{13} Hypercalciuria was the unlikely mechanism in our three cases as we documented normal 24-hour urinary calcium excretion in all cases. Other proposed mechanisms include metabolic alkalosis associated with hypokalemic states causing decreased calcium phosphate or oxalate solubility in the alkaline urine and thus predisposing to nephrocalcinosis.\textsuperscript{14} Another mechanism involves PA induced hypocitraturia.\textsuperscript{10} It is possible that through multiple ways, PA creates a milieu favourable for nephrocalcinosis.

Though we have not proven direct causal association between PA and nephrocalcinosis in our three cases, we arrived at this possibility after ruling out the common etiologies of nephrocalcinosis. The detection of nephrocalcinosis six months after curative resection of
adrenal adenoma in our first case casts doubts on the causal association between the two conditions. On the other hand, it may indicate progression of microscopic to macroscopic nephrocalcinosis.

CONCLUSION

We conclude and emphasize that medullary nephrocalcinosis could be a manifestation of PA. PA as an etiology of medullary nephrocalcinosis should be sought after the common causes have been excluded, at least in those with hypertension that is difficult to control.

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Conflicts of interest

There are no conflicts of interest.

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