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# Bartter Syndrome-Induced Kaliopenic Nephropathy- A Case With Unique Pathological Findings

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## Abstract

Hypokalemia is universally present in patients with Bartter syndrome. The case presented here with Bartter syndrome and persistent severe hypokalemia revealed unique pathological findings on renal biopsy. Prolonged hypokalemia is related to renal injury, but cause may differ. These findings included: mesangial sclerosis, patchy tubular atrophy, interstitial fibrosis, mononuclear infiltration, as well as thickening of tubular basement membrane. Tubular epithelium revealed focal loss of apical brush border. Typically observed tubular cell vacuolization or presence of renal cysts that are frequently reported, were absent in the case. Kaleopenic nephropathy is associated with eating disorders and laxative abuse among other causes of chronic hypokalemia in patients. Severe renal function impairment requiring dialysis has been previously reported. Juxtaglomerular apparatus hyperplasia noted in our case has been reported in Bartter syndrome, renal ischemia, and cyclosporin use. Despite the fact that Keleopenic nephropathy has disappeared from literature in the past 20 years, we believe the condition still exists.

**Key Words**: Bartter syndrome; Kaleopenic nephropathy; Hypokalemia

## Introduction

Hypokalemia-induced renal changes, or kaliopenic nephropathy, was first mentioned in 1956 by JW Conn to describe structural and physiological changes found in renal tubules due to a significant drop in serum potassium, induced by hypermineralcorticoidism [1]. If potassium depletion is prolonged enough, as seen in Bartter syndrome, characteristic lesions can be noted, Table 1 [2,3]. Most pronounced changes in our case were the presence of mesangial sclerosis along with interstitial fibrosis and tubular atrophy, but typical association of tubular vacuolization or cyst formation were absent, thus it is understandable these findings were brought upon by hypokalemia rather than Bartter syndrome. Other typical findings observed include ammoniagenesis [4], increased bicarbonate reabsorption [5] leading to metabolic alkalosis, as well as an impaired ability to concentrate urine [6].

Bartter syndrome is a rare disorder of the nephron that can occur sporadically or can be inherited in an autosomal recessive pattern. The most striking primary defect seems to be in the reabsorption of chloride in the loop of Henle (thick ascending limb) even though the primary defect has been debated thru the years ever since FC Bartter had first described the syndrome in 1962 [2]. The defect in chloride reabsorption can impair passive reabsorption of potassium as well as sodium at the same site [7]. Classic signs and symptoms of this syndrome include polydipsia, polyuria, and decreased urine concentrating ability [8]. Features of this syndrome are hypokalemia, hypochloremic metabolic alkalosis, hyperreninemia, hyperaldosteronism, normal to mildly reduced serum magnesium, and normal to low blood pressure. The most distinguishing and consistent pathological finding in Bartter syndrome is the hyperplasia of the juxtaglomerular apparatus, irreversible even if given a potassium-sparing diuretic [9]. Current treatments include potassium supplementation and potassium-sparing diuretics. Renin inhibitors and angiotensin converting enzyme-inhibitors have also been utilized in the treatment of this particular syndrome [10].

## Case Study

A 37 year old female with history of Bartter syndrome presented with severe persistent hypokalemia. Physical examination was unremarkable. Laboratory findings revealed potassium 2.3 mEq/L, chloride 87 mEq/L, CO2 38 mmol/L, renin 13.6, aldosterone 11.6, magnesium 2.2 mg/dL, and GFR 41 ml/min. This patient's blood pressure has been consistently normal with the systolic ranging from 100 to 115 mmHg and the diastolic

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| Bartter Syndrome | Kaliopenic Nephropathy | In our case |
|---|---|---|
| Juxtaglomerular apparatus hyperplasia/ hypertrophy | Mesangial Sclerosis | Present |
| | Increase in interstitial surface area | Present |
| | Interstitial fibrosis | Present |
| | Tubular atrophy | Present |
| | Cyst formation | Not present |
| | Tubular vacuolization | Not present |

**Table 1:** Classic distinct changes seen on renal biopsy

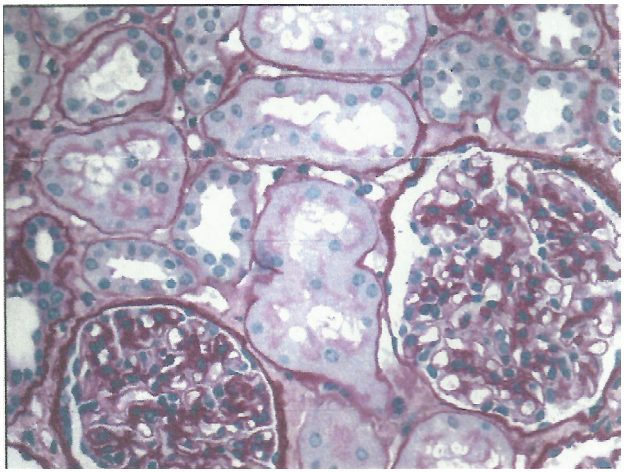

**Figure 1(A):** Demonstration of a glomerulus with mesangial sclerosis [H&E stain]

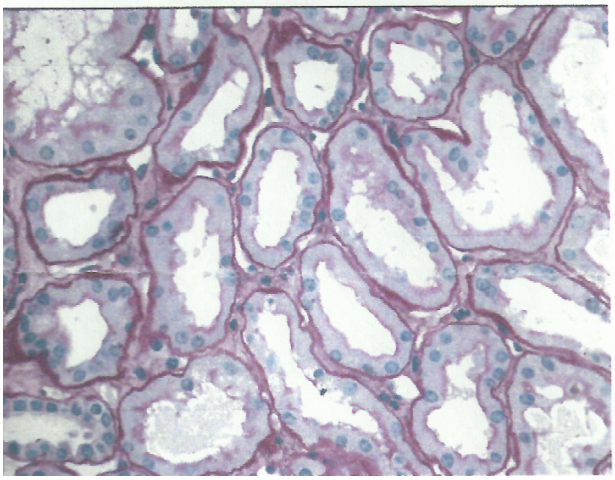

**Figure 1(B):** Tubules exhibiting basement membrane thickening and atrophy of tubular cells [H&E stain]

pressure ranging from 50 to 70 mmHg. Urinalysis was performed and revealed normal results. Her medications included Spironolactone and potassium chloride. Despite treatment with a potassium-sparing diuretic and potassium supplementation, patient's serum potassium level remained depressed.

A renal ultrasound revealed bilaterally normal sized kidneys with thin cortices.

A renal biopsy was performed and revealed the following (read

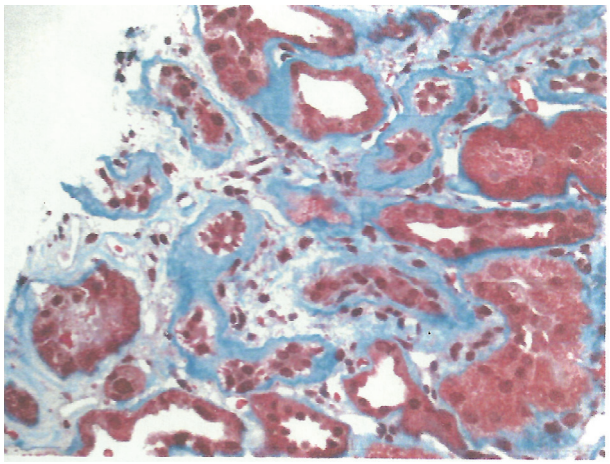

**Figure 2:** Interstitial fibrosis as observed in blue [Trichrome stain]

by Dr. M. Barry Stokes of NY Presbyterian/Columbia University Irving Medical Center, NYC):

## Renal biopsy

Upon staining with hematoxylin & eosin (H&E), periodic acid-Schiff (PAS), trichrome, and Jones methenamine silver (JMS), there was an observation of hyperplasia of the juxtaglomerular apparatus. Patchy tubular atrophy and interstitial fibrosis with mononuclear inflammatory infiltrates were noted. There was absence of tubular vacuolization and cyst formation. Biopsy also revealed tubular epithelium with focal loss of apical brush border.

Mesangial sclerosis and thickening of tubular basement membranes were seen (Figure 1 A). Tubules exhibiting basement membrane thickening and atrophy of tubular cells (Figure 1B). Interstitial collagen and rare interstitial mononuclear inflammatory cells were also noted (Figure 2). Immunofluorescence examination was negative.

## Discussion

There are many more etiologies of hypokalemia and since a significant drop in potassium can be life threatening and the most noteworthy lab value to a physician, it is important to be able to identify and assess any potential causes in a timely fashion.

As seen in this case, the patient has a history of Bartter syndrome with chronic severe hypokalemia that was difficult to control at times despite treatment. Chronic and significant hypokalemia may result in irreversible renal changes. In this unique case, tubular cell vacuolization or renal cysts were not reported, often reported in kaleopenic nephropathy [11]. Juxtaglomerular hyperplasia was discovered upon the examination of this patient's biopsy, commonly seen in Bartter syndrome. However, the most unusual findings were the presence of mesangial sclerosis and tubular basement membrane thickening. Segmental mesangial sclerosis has been described in certain diseases such as diabetic glomerulosclerosis [12], focal segmental glomerulosclerosis [13], as well as an early marker for end stage renal disease [14]. This was not the case in this specific patient due to absence of diabetes mellitus. Tubular basement membrane thickening has also been reported in the diabetic glomerulosclerosis [15]. Saban Elitok et al described a patient in 2016 with GFR 15ml/min with severe hypokalemia caused by diuretic abuse [16]. In that particular case, renal pathology revealed normal glomeruli, interstitial edema, and round cell infiltrate, tubules were filled with hyaline casts and small vessel fibrosis was also observed [16]. However, invariable and striking feature was vacuolization of the renal tubular epithelium both in proximal and distal renal tubular epithelium [16]. Serum potassium of less than 3.6 is associated with more pronounced progression of chronic kidney disease in all races. Hypokalemia was

associated with loss of kidney function independently of the race: a 1 mEq/L lower potassium was associated with an adjusted difference in slope of GFR of 0.13 ml/min/1.73m$^2$/year [17].

In our patient renal ultrasound showed bilateral thinning of renal cortex consistent with chronicity of kidney disease. The absence of any other cause of kidney disease in this patient, leads us to believe the renal insufficiency is secondary to kaleopenic nephropathy. Vacuolization of proximal convoluted tubule accompanying chronic hypokalemia has indeed been described half a century ago [1]. The proposed mechanism underlying the deleterious effects of lower potassium on kidney function includes direct tubulointerstitial injury via modulation of renal inflammation [18], local activation of renin angiotensin system [19], increased expression of angiotensin II receptors [20] or indirect effects through worsening hypertension. Another possible mechanism entails generation of excess ammonia in the proximal convoluted tubules in response to hypokalemia [21]. As mentioned, hypokalemic kidney injury can present in many ways, the appropriate method of diagnosis and management should depend on biopsy findings.

## Conclusion

Although certain pathological findings are to be expected with some renal injuries, one should not assume the same associations to occur. The absence of tubular vacuolization and renal cysts should not be a reason to rule out hypokalemia induced renal injury. Also, atypical findings (i.e. mesangial sclerosis, tubular basement membrane thickening, minimal juxtaglomerular apparatus hyperplasia) should not dismiss certain etiologies, but should broaden the search for the particular cause of pathology. The reason as to why these anomalous pathologies can occur in this distinct setting has yet to be explored.

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