

## Case Report

# Gut It Out: Laxative Abuse Mimicking Distal Renal Tubular Acidosis

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## Keywords

Distal renal tubular acidosis · Laxative abuse

## Abstract

**Background:** Distal renal tubular acidosis (dRTA) can be inherited or acquired. **Case Presentation:** Here, we describe the case of a 45-year-old female patient with non-anion gap metabolic acidosis, hypokalemia, and alkaline urine. She had a history of rheumatoid arthritis and kidney stones and failed to acidify urine upon the fludrocortisone and furosemide test. Therefore, the diagnosis of dRTA secondary to an autoimmune disease was made. A kidney biopsy was examined for markers of acid-secreting intercalated cells. Surprisingly, no obvious difference in the relative number of acid-secreting intercalated cells or in the distribution of major proteins involved in acid secretion was found. Furthermore, increasing doses of potassium citrate failed to correct the hypokalemia and acidosis. Since these findings were rather atypical for autoimmune dRTA, alternative causes of her hypokalemia and metabolic acidosis were sought. The patient was found to chronically consume laxatives, which can also cause kidney stones and may result in a false-positive urinary acidification test. **Conclusion:** Chronic laxative abuse may mimic dRTA and should therefore be considered in unexplained hypokalemia with non-anion gap metabolic acidosis.

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## Introduction

Distal renal tubular acidosis (dRTA), the inability to appropriately acidify urine in the face of metabolic acidosis or upon an acid challenge, can be inherited or acquired. The disease is characterized by non-anion gap metabolic acidosis and alkaline urine and is often accompanied by hypokalemia. Chronically, kidney stones or nephrocalcinosis are often found [1].

Inherited forms of dRTA are rare and caused by mutations in either the SLC4A1 (AE1) anion exchanger, the B1 (ATP6V1B1) or a4 (ATP6V0a4) subunits of the V-type H<sup>+</sup>-ATPase, or the transcription factor FOXI1 [2, 3]. These forms of dRTA are usually diagnosed during the first years of life and can be associated with sensorineural deafness with mutations in ATP6V1B1, ATP6V0a4, and FOXI1.

In contrast, acquired forms of dRTA are more common and can be caused by a variety of conditions including autoimmune diseases such as Sjögren's syndrome, rheumatoid arthritis, and systemic lupus erythematosus, by nephrocalcinosis and as a side effect of various drugs or toxins such as toluene, amphotericin B, or lithium [1, 4, 5].

Here, we describe the case of a patient with alkaline urine, hypokalemia, non-anion gap metabolic acidosis, and a positive urinary acidification test initially diagnosed as dRTA. However, her kidney biopsy did not reveal any obvious alterations in key proteins of the acid-secretory intercalated cells. Further investigation revealed chronic abuse of laxatives mimicking dRTA.

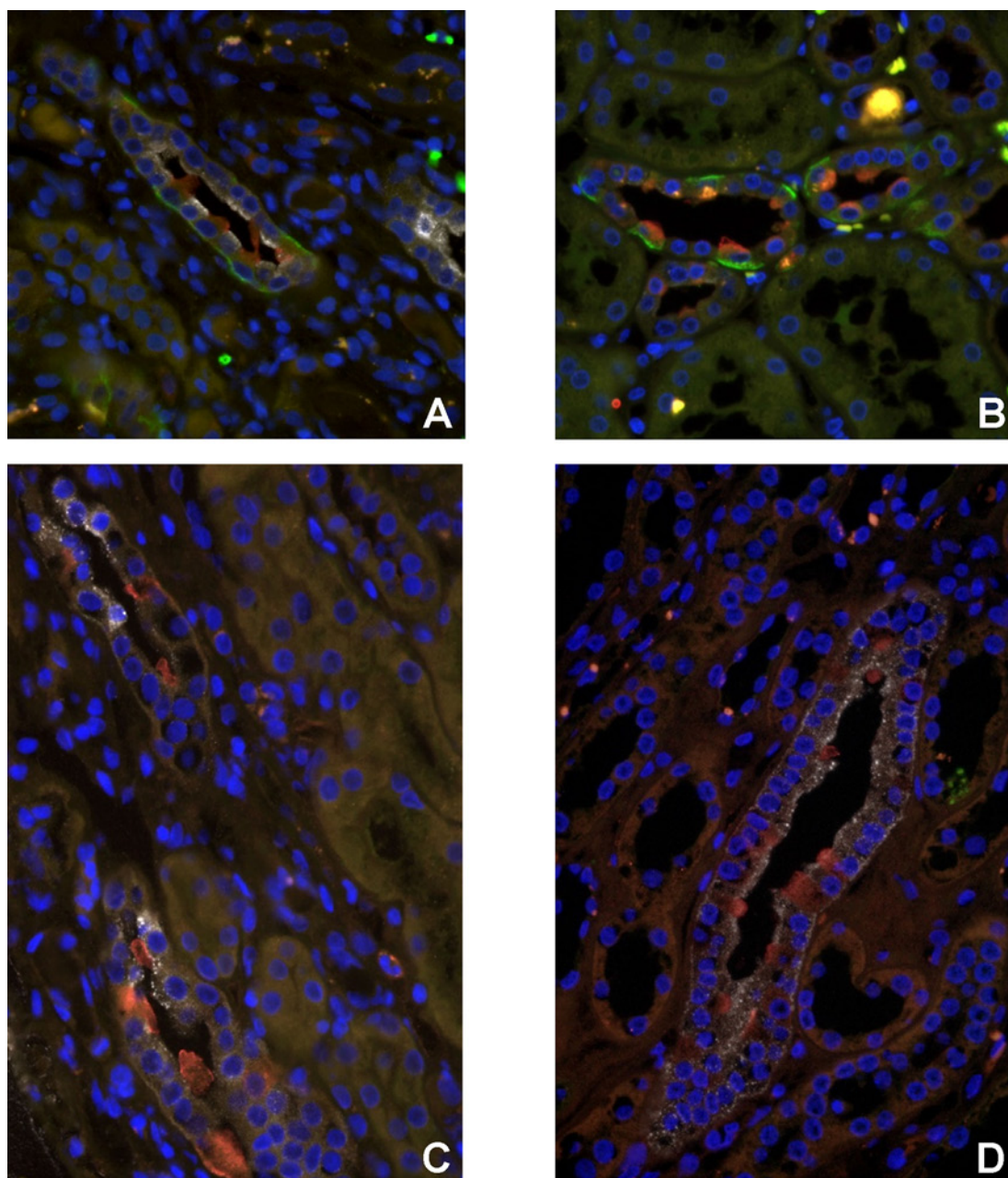
## Clinical Synopsis of the Case

A 45-year-old patient was referred from another hospital because of unexplained severe hypokalemia (plasma potassium frequently <2.5 mmol/L). She had a previous history of rheumatoid arthritis with autoantibodies against cyclic citrullinated peptides for which she had used hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine. At the time of referral, she was only using glucocorticoids (prednisone 5 mg once daily).

Her hypokalemia was characterized by renal potassium loss (urine potassium 29 mmol/L at the time of hypokalemia), normal blood pressure, and non-anion gap metabolic acidosis (plasma sodium 139 mmol/L, chloride 111 mmol/L, and bicarbonate 16 mmol/L) with a consistently high urine pH (7 or 8). She did not have nephrocalcinosis, but she did have recurrent kidney stones (stone composition unknown). Therefore, a presumptive diagnosis of dRTA was made, possibly secondary to rheumatoid arthritis [6].

A urinary acidification test was performed with fludrocortisone and furosemide, during which she failed to lower her urinary pH below 5.3 (urine pH at the start: 6.5; after 1 h: 6.0; after 4 h: 6.0; urine pH was measured immediately after collection). Treatment with potassium citrate was started (liquid potassium citrate containing 133 mmol potassium and 44 mmol citrate per day). Because she had a decrease in estimated glomerular filtration rate to 40 mL/min/1.73 m<sup>2</sup> with erythrocyturia and proteinuria (0.8 g/day), she underwent a kidney biopsy.

The biopsy contained 27 glomeruli, of which none showed global sclerosis. The glomerular capillaries, glomerular basement membrane, and mesangium all appeared normal. Immunofluorescence did not show any deposits for IgG, IgA, IgM, C3c, C1q, kappa, or lambda. Electron microscopy showed a normal aspect of the podocytes, endothelial cells, and glomerular basement membrane and did not identify any electron-dense deposits. In the tubulointerstitium, no inflammatory cell infiltrate was observed. To further investigate a possible autoimmune origin of dRTA, markers for principal and intercalated cells and acid-base transporters were analyzed by immunofluorescence, showing normal expression of AE1, AQP2, and the H<sup>+</sup>-ATPase subunits B1 and a4 (Fig. 1; online suppl. methods; for all online suppl. material, see [www.karger.com/doi/10.1159/000501855](http://www.karger.com/doi/10.1159/000501855)).



**Fig. 1.** Kidney biopsies from the patient (**A, C**) and control biopsies from 4 different healthy kidneys (**B, D**) were stained with antibodies against the B1  $H^+$ -ATPase subunit (red), the anion exchanger AE1 (green), and AQP2 (white) (**A, B**) or against the  $\alpha 4$   $H^+$ -ATPase subunit (red) and AQP2 (white) (**C, D**). The nuclei were stained blue with DAPI. A similar relative number of cells stained for the B1 subunit and for the AE1 exchanger in the patients' and the controls' kidney biopsies. Similarly, the  $\alpha 4$  subunit was stained similarly in the patients' and controls' kidney biopsies. Original magnification,  $\times 400$ .

In the subsequent course in the outpatient clinic, the patient repeatedly presented with hypokalemia and acidosis despite increasing doses of potassium citrate. This forced us to reanalyze the case. The biochemical picture during one of these episodes (plasma potassium 2.9 mmol/L and bicarbonate 16.9 mmol/L) now showed lower urinary potassium (17 mmol/L) with a slightly negative urine anion gap (urine sodium + potas-

sium – chloride =  $66 + 17 - 89 = -6$  mEq), a normal estimated  $\text{NH}_4^+$  level (54 mmol/L by calculation of the urinary osmol gap), and a urine sodium-to-chloride ratio  $<1$ . This suggested a self-induced cause of hypokalemic metabolic acidosis, e.g., due to laxative abuse. Indeed, her urine test resulted positive for emodin, bisacodyl, and rhein. A urinary screen for diuretics was negative.

## Discussion

We reported a case of non-anion gap metabolic acidosis with hypokalemia and impaired urinary acidification during a fludrocortisone and furosemide test. The differential diagnosis of non-anion gap metabolic acidosis includes renal and extrarenal causes [1, 4]. Renal causes are impaired kidney function as well as classic dRTA (type I dRTA). Abnormal aldosterone levels or signaling would be associated with the hyperkalemic variant of type IV RTA. However, our patient was clearly and repetitively hypokalemic. The patient's history of rheumatoid arthritis suggested a possible renal involvement. dRTA is observed in a substantial percentage of patients with autoimmune diseases such as lupus erythematosus, Sjögren's syndrome, or rheumatoid arthritis, presumably due to autoantibodies directed also against structures of acid-secreting intercalated cells [5–9]. Indeed, a urinary acidification test (fludrocortisone and furosemide) [10] demonstrated a reduced ability to acidify urine, which is consistent with dRTA. However, a kidney biopsy stained for markers of acid-secreting intercalated cells and principal cells showed a normal relative abundance of acid-secreting cells and no obvious alteration in the distribution of proton pumps in these cells. This is in contrast to previous reports where kidney biopsies from patients with dRTA due to autoimmune disease had shown an absence of markers of acid-secreting intercalated cells [5, 11]. Furthermore, the kidney biopsy did not show tubulointerstitial nephritis, which is typically found in patients with autoimmune dRTA.

The lack of improvement of hypokalemia and metabolic acidosis with  $\text{K}^+$  citrate supplements led to a reevaluation of the patient, which revealed a chronic abuse of laxatives. Also, the urinary ammonium excretion estimated from the urine osmol gap now suggested an extrarenal cause of the metabolic acidosis and hypokalemia due to intestinal loss of  $\text{K}^+$  and  $\text{HCO}_3^-$ . Chronic use of laxatives is known to cause wasting of both ions [12]. Hypokalemia per se is expected to rather stimulate renal acid excretion and bicarbonate synthesis, leading to metabolic alkalosis [13–15].

In our patient, intestinal losses of  $\text{HCO}_3^-$  may have exceeded the renal capacity to compensate these losses. The renal losses of  $\text{K}^+$  observed during the earlier visits may in part be explained by glucocorticoid treatment [16], secondary aldosteronism due to hypovolemia or vomiting, or surreptitious use of diuretics (her urine was only screened once for diuretic use). The reason for the abnormal urinary acidification test results remains elusive, but false-positive results have previously been reported for the furosemide and fludrocortisone test [8, 17]. In general, the following causes can lead to a false-positive urinary acidification test. First, concurrent hypovolemia may increase sodium reabsorption in the proximal tubule and therefore blunt the response to furosemide and fludrocortisone in the distal nephron. Second, bacteriuria may artifactually increase the urine pH (some bacteria can split urea into ammonia). Third, the urine pH can increase if carbon dioxide diffuses, and the urine pH should therefore be measured immediately or the urine should be collected under mineral oil. Therefore, if available, urine titratable acidity and ammonium are superior to urine pH in the evaluation of dRTA [18–20].

Regarding our patient, one possible explanation is that hypovolemia increased reabsorption by the proximal tubule and blunted the response of furosemide and fludrocortisone



**Table 1.** Similarities and differences between distal renal tubular acidosis and laxative abuse

	Distal renal tubular acidosis	Chronic laxative abuse
Non-anion gap metabolic acidosis	Yes	Yes
Hypokalemia	Yes	Yes
Kidney stones	Yes	Possible
Nephrocalcinosis	Yes	No
Impaired urinary acidification	Yes	Possible
Urinary ammonium excretion	Reduced	Increased
Urinary sodium-to-chloride ratio	Normal (1)	Reduced (<1)

in the distal nephron. Chronic laxative abuse can also cause kidney stones, including calcium oxalate or ammonium urate stones [21]. Thus, chronic laxative abuse may mimic dRTA (Table 1). Recently, the urinary sodium-to-chloride ratio was reported as a useful parameter to differentiate the various causes of chronic hypokalemia, including dRTA and laxative abuse [12]. In dRTA, the urinary sodium-to-chloride ratio is typically close to 1, whereas laxative abuse will reduce this ratio due to volume depletion (lower urinary sodium excretion) and metabolic acidosis (higher urinary chloride excretion).

In summary, chronic abuse of laxatives causes intestinal losses of  $K^+$  and  $HCO_3^-$  and should be considered as a differential diagnosis in patients with non-anion gap metabolic acidosis even in the presence of apparently impaired urinary acidification. Urinary ammonium excretion (estimated or measured) and the urinary sodium-to-chloride ratio may help to differentiate dRTA from chronic laxative abuse.

### Statement of Ethics

The patient gave written informed consent for the biopsy, the examination, and the publication of her case report. Control biopsies were obtained and examined under a protocol approved by the Ethics Committee of the canton of Zurich (No. KEK-Zh-Nr. 2012-0312).

### Disclosure Statement

All authors declare no conflicts of interest.

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### Author Contributions

M.S. and C.A.W. performed experiments; E.J.H. saw the patient and collected clinical information; N.M., E.J.H., and C.A.W. planned and analyzed experiments and clinical data; M.S., E.J.H., and C.A.W. wrote the manuscript; and all authors read and approved the manuscript.

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