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HIV Infection Itself may be a Cause of Hypokalemic Distal Renal Tubular Acidosis without Hypergammaglobulinemia

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Authors' contributions

This work was carried out in collaboration between all authors. Author GA led the conceptual design and wrote the manuscript including discussion and literature review. Author JAF assisted in obtaining the clinical data and case summary. Author NA was involved in literature review and case discussions. Author ST was involved in paper design. Authors GST and UB reviewed the manuscript. All authors read and approved the manuscript.

Case Study

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ABSTRACT

Distal renal tubular acidosis (dRTA) is seen in the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) population in the setting of hypergammaglobulinemia and antiretroviral agents, whereas isolated HIV infection is rarely reported to be associated with dRTA. We report a case of a young woman with a history of untreated HIV/AIDS who presented with profound generalized weakness and refractory hypokalemia along with non-anion gap metabolic acidosis and inappropriately high urine pH. Her serum gamma-globulin level was not significantly elevated and she was not on highly active antiretroviral therapy (HAART). No other cause of dRTA was evident. Subsequently, a diagnosis of dRTA secondary to isolated HIV/AIDS was made. Distal RTA can be acquired or inherited and is caused by defects in proton pumps or pH pressure gradients. In dRTA, the potassium level can be low, normal, or even high depending upon the pathophysiologic abnormality. Early recognition and prompt

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treatment is imperative to avoid the serious consequences of severe electrolyte and metabolic disturbances. Our case report is a reminder to clinicians to be mindful of this rare condition when evaluating unexplained dRTA and to include HIV/AIDS as part of the differential diagnosis of dRTA even in the absence of significant hypergammaglobulinemic (IgG level was slightly elevated) state or antiretroviral agents. We believe this is the second such case to be documented.

Keywords: Distal renal tubular acidosis; HIV; Hypergammaglobulinemia; non anion gap metabolic acidosis

1. CASE SUMMARY

A 37 year-old-female presented to the ER with profound progressive generalized weakness leading her to a bedridden state and inability to feed herself for one day. This was associated with constipation, bilateral leg pain, and intermittent abdominal pain, but no nausea or vomiting. She denied fever, chills, diarrhea, dysuria, cough, dyspnea, chest pain, headache or weakness of any part of body. There was no tingling or numbness. The patient was diagnosed with HIV/AIDS three years prior, but refused HAART. Past medical history includes pancreatitis, iron deficiency anemia, blood transfusion, chronic obstructive pulmonary disease (COPD) and depression. She has history of Cesarean section surgery. There is no family history of kidney disease. She admitted to smoking half a pack of cigarettes a day, occasionally drinks alcohol, but denied the use of illicit drugs. She has three children with no history of miscarriage or abortions. She has no known drug allergies. She has been taking dapsone for pneumocystis jiroveci pneumonia (PJP) prophylaxis, albuterol and tiotropium inhaler for COPD, and cyproheptadine for depression. She denied over the counter or herbal medications.

On examination, she was cachectic, lethargic, dehydrated and pale, but was not in respiratory distress. Vital signs included a temperature of 97.7℉, pulse rate 83 bpm, blood pressure 106/90 mmHg, and respiratory rate 14/minute. She had a tattoo on her body but no rash. There was no joint deformity, swelling or tenderness. Neurological examination was unremarkable except for generalized muscle weakness (power of 3/5) of all four limbs with intact sensation. The rest of the physical examination was unremarkable.

Laboratory studies (Table 1) revealed sodium 140 mmol/L (136-145), potassium 1.9 mmol/L (3.6-5.1), BUN 7 mg/dL (6-20), creatinine 0.8 mg/dL (0.5-0.9), chloride 118 mmol/L (90-110), CO2 10 mmol/L (22-28), albumin 4.2 g/dL (3.5-5.2), calcium 9.0 mg/dL (8.6-10.2), phosphate 2.7 mg/dL (2.7-4.5), magnesium 2.3 mg/dL (1.7-2.5), serum anion gap was 12 mmol/L (2.6-10.6). EKG showed normal sinus rhythm with the presence of U waves. The arterial blood gases showed a pH of 7.22 (7.350-7.450), PCO2 18 mmHg (35.0-45.0), PO2 130 mmHg (75.0-100.0), on nasal oxygen at 2L/min. Urine pH was 7.0 (5.0-8.5), with specific gravity of <1.005 (1.005-1.030), no glucose, trace protein, no cast, no RBC, few WBC's. The urine electrolytes revealed sodium 45 mmol/L, chloride 48 mmol/L, potassium 16 mmol/L. Her CD4 count was 162/uL two months prior to admission. Her HIV-1 RNA PCR was 5.1 log, HIV COPY 140,000 cpy/mL five months prior to admission. Her anti-nuclear antibody IgG was negative; gamma-globulin was 1.8g/dL (0.5 to 1.6). Renal ultrasound showed a right renal cyst, and no calculi were identified. Urine drug screen was negative.

Patient was admitted to our hospital and intravenous fluid as normal saline with IV potassium was started. Despite 120 mEq potassium replacement over the first twelve hours via oral

and IV route, her potassium dropped further to 1.4mmol/L. Nephrology service was consulted. Although her magnesium level was within normal range, the possibility of normomagnesemic magnesium deficiency was considered as a probable cause of refractory hypokalemia [1]; thus magnesium was also given. After over 200mEq KCl supplementation, potassium level persistently remained below normal range. She was given sodium bicarbonate 650mg once a day and gradually increased to three times per day. Her potassium level started to rise up to normal over the next four days. Spironolactone was added. Patient began to show improvement and eventually attained her baseline physical activity. She was discharged on potassium supplementation, spironolactone and sodium bicarbonate.

Table 1. Laboratory data

Parameter	Reference range	Labs as out patient	Date of admission	After replacement
Sodium (mEq/L)	136-145		140	135
Potassium (mEq/L)	3.6-5.1		1.4	4.0
Bicarbonate (mEq/L)	22-28		10	23
Chloride (mmol/L)	90-110		118	105
Anion gap (mEq/L)	2.6-10.6		12	7
Serum urea nitrogen (mg/dL)	6-20		13	23
Serum creatinine (mg/dL)	0.5-0.9		1.1	0.6
Estimated glomerular filtration rate (mL/min/1.73 m^2)	>60		>60	>60
Calcium(mg/dL)	8.6-10.2		9.0	8.1
Magnesium (mEg/L)	1.7-2.5		2.3	1.8
Lactic Acid (mmol/L)	0.5-2.2		3.0	
Arterial blood gas				
pH	7.35-7.45		7.22	7.31
$PaCO_2$	35-45		18	19
Bicarbonate (mEg/L)	23-28		7.4	9.7
PaO_2	75-100		130	204
Urine				
pH			7	
Sodium (mmol/L)			45	
Potassium (mEq/L)			16	
Chloride (mmol/L)			48	
Cast			None Seen	
Absolute CD4	359 to 1519	162		
HIV-1 RNA by PCR (copies/mL)		370070		
log10 HIV-1 RNA (log10copy/mL)		5.568		
Gamma Globulin LCA (g/dL)	0.5 to 1.6		1.8	
Hepatitis				
Hepatitis A IgM	Negative	Negative		
Hepatitis B Core IgM	Negative	Negative		
Hepatitis C Ab	Negative	Negative		
Anti-nuclear IgG	Negative <1:80		1:80	

2. DISCUSSION

Renal tubular acidosis in patients with HIV/AIDS has been described in the context of antiretroviral therapy and hypergammaglobulinemia. Chakraborty et al. [2] reviewed records of 202 children with HIV/AIDS to investigate the prevalence of metabolic acidosis and found

a 9% incidence of dRTA. The authors observed that all of these children were taking anti-retroviral agents and most of them were also receiving co-trimoxazole for prophylaxis against Pneumocystis jirovecii pneumonia. Both of these therapies are well known to cause renal tubular dysfunction [2]. Antiretroviral agents known to cause tubular dysfunction include cidofovir, adefovir, tenofovir and indanivir [3]. In addition, Fanconi syndrome has been noted in HIV patients treated with cidofovir. Fanconi syndrome is a proximal tubular defect which results in impaired reabsorption and increased excretion of amino acids, bicarbonate glucose, urate and phosphate into the urine [4]. Foscarnet, an antiviral medication used in the treatment of cytomegalovirus infection, has a direct effect on renal tubular cells and has been reported to cause renal tubular acidosis, nephrogenic diabetes insipidus and acute tubular necrosis [5,6]. Table 2 lists the comprehensive list of renal conditions associated with HIV.

Table 2. Renal conditions associated with increased risk in HIV-infected patients

Tubulointerstitial
Acute tubular necrosis
RTA including Fanconi syndrome
Interstitial nephritis
Diffuse infiltrative lymphocytosis syndrome
Crystalluria with obstruction (especially with Indinavir)
Renal infection
Hydronephrosis
Renal tubular atrophy (associated with Indinavir)
Nephrogenic diabetes inspidus (with Foscarnet)
Glomerular Lesions
HIVAN (collapsing glomerulopathy)
FSGS
Minimal change disease
Immune complex–mediated glomerulonephritis
Lupus-like nephritis
IgA nephropathy
Membranoproliferative glomerulonephritis (associated with hepatitis C or B)
Membranous glomerulopathy (associated with hepatitis B or C, or neoplasia)
Acute postinfectious glomerulonephritis
Fibrillary and immunotactoid glomerulonephritis (often associated with hepatitis C)
Diabetic nephropathy
Amyloidosis, AA type (associated with intravenous drug use)
Thrombotic microangiopathy
Electrolyte disorders
Hypokalemia (dRTA like our case)
Hyperkalemia (due to TMP-SMX, Pentamidine)
Hyponatremia (SIADH due to PJP pneumonia)
Hypophosphatemia (with PI)
Hyperuricemia (with PI)
Hypomagnesemia
Hypocalcemia
Kidney neoplasms
Kaposi's sarcoma
Lymphoma

Abbreviations: HIVAN, HIV assoiated Nephropathy; FSGS, focal segmental glomerulosclerosis: PI, protease inhibitors

Laing et al. [7] in 2006 documented the first case of dRTA in HIV infection in the setting of hypergammaglobulinemia and acute kidney injury. Since hypergammaglobulinemia and anti-retrovial agents are well-documented reasons for dRTA, [8] it has remained a mystery whether the HIV virus has any cytopathic effect on renal tubules leading to dRTA. Our case is unique because dRTA was discovered in HIV/AIDS in the absence of antiretroviral therapy and hypergammaglobulinemia. Isa and Daud have recently described the first case of dRTA in an HIV/AIDS patient without hypergammaglobulinemia or anti-retroviral therapy [9].

Our patient had severe non-anion gap hyperchloremic metabolic acidosis with compensated respiratory alkalosis, hypokalemia, alkalotic urine and positive urine anion gap. The inherited or familial forms were very unlikely since she had no chronic features of RTA such as short stature, kidney stones, nephrocalcinosis and lack of a positive family history. She had no sign of Fanconi syndrome [4]. She was not taking any medication such as ifosfamide, amphotericin, lithium, amiloride, trimethoprim, pentamidine [2,6] which can possibly lead to dRTA. There was no clinical or laboratory evidence to suggest autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, Sjogren syndrome, chronic active hepatitis, primary biliary cirrhosis, or thyroiditis. Renal ultrasound did not show any structural kidney disease or obstructive lesions. Our literature review found no link between dapsone or cyproheptadine and dRTA. Her kidney function was normal and there was no proteinuria. Her calcium level was normal excluding calcium disorders like primary hyperparathyroidism or vitamin D intoxication. Her urinary calcium level was not checked. There was no evidence of liver disease. We came to the conclusion that HIV infection was the sole cause of dRTA and to the best of our knowledge; this is the second case to be reported in literature where HIV infection caused dRTA in the absence of significant hypergammaglobulinemia and HAART. This raises the probability of a direct toxic effect of the Human Immunodeficiency virus on renal tubular cells and a possible link between dRTA and isolated HIV/AIDS.

Distal RTA is characterized by an inability of the kidney to excrete hydrogen ions along the distal nephron resulting in progressive hydrogen ion retention manifesting as metabolic acidosis (normal anion gap). Urine pH of >5.5 in the presence of systemic acidosis is the hallmark feature of dRTA. With an incomplete dRTA, urine is persistently alkalotic (urine pH >5.5) with normal serum bicarbonate level. Distal RTA can be acquired or familial. The inherited or familial form is characterized by growth retardation, bone disease and kidney stones [10].

Urinary acidification process is primarily mediated by the intercalated cells and to some extent by the principal cells in the cortical and medullary collecting tubules by secreting protons into renal tubular lumen with different transporters. Two basic mechanisms responsible for impaired proton secretion and resultant dRTA include: 1) defects in proton transporters 2) pH gradient defect across the distal nephron resulting in leaky luminal membranes [11].

Distal RTA is divided into hypokalemic, normokalemic and hyperkalemic forms, hypokalemic being the most common and classic form. Hypokalemic form is due to a defect in the transporters such as H-K-ATPase, anion exchanger 1 (AE1), and the cytosolic carbonic anhydrase II (CA II), whereas an isolated defect in H-ATPase activity (with normal H-K-ATPase and the Na-K-ATPase activity) in the collecting tubule will cause normokalemic type dRTA especially in advanced kidney disease and chronic transplant rejection. The term distal “voltage-dependent” RTA is used for hyperkalemic dRTA owing to impaired sodium reabsorption by principal cells across the cortical collecting tubule with characteristically

normal or elevated aldosterone level differentiating it from type IV RTA. A pH gradient defect has been observed in amphotericin-induced dRTA [12].

Due to insufficient data, the effect of HAART on HIV-related dRTA is still unknown. Treatment of dRTA is directed towards correction of metabolic and electrolyte disturbances to prevent complications like life-threatening hypokalemia, skeletal defects, nephrocalcinosis and nephrolithiasis. Alkali therapy should be aimed to achieve relatively normal serum bicarbonate concentration (22 to 24 meq/L). Adults are given 1 to 2 meq/kg of sodium bicarbonate or sodium citrate. Children often need 4 to 8 meq/kg per day due to higher bicarbonate losses and larger acid production in growing skeletons. Potassium supplementation is also required in the majority of patients with hypokalemic dRTA [10,12]. Potassium-sparing diuretics like amiloride or spironolactone may conserve potassium, reducing potassium requirement, although large prospective studies are needed to establish this. Our patient was started on spironolactone and did well.

3. CONCLUSION

In conclusion, our case demonstrates the severity of electrolyte and metabolic abnormalities of dRTA in untreated HIV/AIDS patients in the absence of significant hypergammaglobulinemia and HAART. Early recognition and appropriate treatment is essential to avoid potential complications. This case implies that prospective studies are needed to determine the effect of HAART on renal tubular acidosis in patients with HIV/AIDS, and whether HAART can alter the incidence of RTA.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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