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CASE REPORT

Combination of Diuretics in States of Resistant Nephrotic Edema: a Case Presentation

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ABSTRACT

While there remains no universally accepted definition for resistant edema, it is generally acknowledged as edema that fails to respond to maximally administered doses of diuretics. Nephrotic edema is characterized by high levels of proteinuria, notably urinary concentrations of serine proteases, which possess the ability to activate the epithelial sodium channel (ENaC), resulting in persistent fluid retention. Loop diuretics are typically preferred as first-line therapy for hypervolemia. However, the sustained activation of ENaC channels may lead to resistance to treatment. Consequently, the blockade of ENaC represents a potential therapeutic approach. We report the case of a 36-year-old man presenting with nephrotic edema managed with a combination of furosemide and human albumin. Despite an initially favorable response, the patient subsequently developed oliguria and progressive weight gain. On the third day, a regimen comprising amiloride (5 mg/day) and hydrochlorothiazide (50 mg/day) was initiated, resulting in complete resolution of edema after 11 days. No hyperkalemia was observed, with only a slight elevation in serum creatinine levels. Although clinical trials are limited, mounting evidence from human and animal studies supports the concept of nephrotic syndrome as an overfill phenomenon and underscores the potential benefits of ENaC blockers in the management of nephrotic edema.

Keywords: nephrotic syndrome, edema, diuretic resistance, ENaC channel, amiloride.

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INTRODUCTION

Nephrotic syndrome is a clinical syndrome defined by high levels of proteinuria, hypoalbuminemia, hyperlipidemia and fluid overload. In certain circumstances, fluid overload can lead to anasarca. Consequently, edema is typically the initial symptom observed by patients, prompting them to seek medical attention (1). Diuretic therapy is the mainstay treatment for excessive fluid. Loop diuretics are generally preferred as the initial treatment option by most of the clinicians, due to their high diuretic potential (2). However, patients frequently develop diuretic resistance.

While there is no precise definition for diuretic resistance, it is commonly accepted as a persistent fluid overload with no reduction in weight despite the administration of maximal doses of diuretics (2). Several factors contribute to diuretic resistance, including poor adherence to therapy, inadequate dosing, nephron remodeling induced by the workload associated with loop diuretics, or even misdiagnosis, as outlined in Table 1. These factors can manifest in hypervolemia of other etiologies such as heart failure or end-stage liver disease (3). A specific mechanism contributing to edema in nephrotic syndrome involves serine proteases present in the urine, which continuously activate the epithelial sodium (ENaC) channel, leading to sodium and water retention. Consequently, overcoming diuretic resistance often necessitates combining a loop diuretic with a secondary diuretic agent (4).

Given the activation of ENaC in nephrotic syndrome, an ENaC blocker appears to be the most suitable secondary option (5). In the present case report, we aimed to illustrate the pathophysiologic mechanisms and treatment options of diuretic resistance nephrotic edema. ❑

TABLE 1. Causes of diuretic resistance

1. Incorrect diagnosis: - chronic venous insufficiency - lymphedema
2. Non-adherence to: - treatment - low-sodium diet - fluid restriction
3. Reduced drug reaching the kidney - low doses - low frequency - gastrointestinal wall edema - concomitant administration with food - hypoalbuminemia
4. Reduced diuretic secretion - decreased kidney blood flow (hypovolemia) - decreased kidney mass - reduced tubular uptake of diuretic due to uremic toxins in acute/chronic kidney disease
5. Reduced kidney response - nephron remodeling - compensatory neurohormonal activation - urinary serine proteases - use of nonsteroidal anti-inflammatory drugs

CASE REPORT

Clinical history and initial laboratory data

A 36-year-old man with severe edema and a weight gain of 15 kg over a two-month period was referred to a tertiary Nephrology Clinic of a large hospital. He was previously treated in an outpatient clinic for nephrotic syndrome (serum albumin 1.8 g/dL; 24-hour proteinuria 13 g/dL), which was diagnosed three weeks prior to our examination. Serum creatinine levels were normal at that time. Tests results for serum anti-phospholipase A2 receptor antibodies (anti-PLA2Rs) were negative. Intravenous (iv) furosemide therapy with boluses of 40 mg every 12 hours was started, together with 50 mL/d human albumin. On the third day, the patient was seen in our department.

The patient had a paternal history of type 2 diabetes mellitus and a maternal history of hypertension. Despite his obesity, he had no other medical history.

On examination, the patient had severe periorbital and bilateral pitting edema and a weight of 115 kg but clear lungs, no respiratory distress, normal heart sounds, no abdominal pain, no organomegaly and no signs of ascites. His blood pressure was 110/80 mm Hg and his pulse rate 80 bpm. His urine output was less than 1 000 mL/d and he had clear urine and no hematuria. There were no signs of peripheral hypoperfusion or other findings such as arthralgia, rashes or purpura.

Both kidneys were normal in size and shape in an ultrasound examination. As shown in Tables 2 and 3, the patient had a normal kidney function with a serum creatinine concentration of 1.1 mg/dL, severe nephrotic syndrome with high cholesterol, triglyceride and fibrinogen levels, but no leukocytosis or inflammation. He

TABLE 2. Laboratory data

Parameter	Lab value	Reference range
Serum biochemistry		
Creatinine (mg/dL)	1.1	0.7-1.2
eGFR (mL/min/1.73 m^2)	89	>60
BUN (mg/dL)	18	19-49
Sodium (mEq/L)	136	132-146
Potassium (mEq/L)	4.1	3.5-5.5
Calcium (mg/dL)	9.5	8.7-10.4
Magnesium (mg/dL)	2.1	1.0-2.4
Albumin (g/dL)	2	3.2-5.2
Total cholesterol (mg/dL)	370	0-200
Triglycerides (mg/dL)	420	0-150
Glucose (mg/dL)	89	74-106
Bicarbonate (mmol/L)	21	20-26
Inflammatory markers		
C-reactive protein (mg/dL)	0.5	0-5
ESR (mm/h)	10	2-15
Fibrinogen (mg/dL)	350	200-400
WBC (10^3/uL)	9.2	4-9
Urine parameters		
24-hour proteinuria (g/24 h)	9.2	<0.03
24-hour sodium (mmol/L)	18	<20
24-hour potassium (mmol/L)	30	<20
Hematuria (el/uL)	5	0-20

BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; ESR=erythrocyte sedimentation rate; WBC=white blood cell count

TABLE 3. Immunological panel

Parameter	Lab value	Reference range
ANA (U/mL)	1.2	0-1
Anti-dsDNA Ab (U/mL)	2	0-5
Anti-SSA Ab (U/mL)	0.3	0-25
Anti-SSB Ab (U/mL)	2.6	0-25
ACTs (U/mL)	0.05	0-5
Anti-GBM Ab (U/mL)	0.02	0-5
RF (UI)	8	0-15
HbsAg (S/CO)	0.10	0-1
HCV Ab (S/CO)	0.03	0-0.8
HIV Ab (S/CO)	<0.05	0-1
C3 (mg/dL)	110	82-185
C4 (mg/dL)	45	15-53
IgA (mg/dL)	118	63-484
IgG (mg/dL)	980	540-1822
IgM (mg/dL)	157	22-240
Serum kappa free light chains (g/L)	2.23	1.7-3.7
Serum lambda free light chains (g/L)	1.08	0.9-2.1

Ab=antibodies; ACTs=antineutrophil cytoplasmic antibodies; ANA=antinuclear antibodies; dsDNA=double stranded deoxyribonucleic acid; GBM=glomerular basement membrane; SSA=Sjogren's syndrome-related antigen A; SSB=Sjogren's syndrome-related antigen B; HbsAg=hepatitis B surface antigen; HCV=hepatitis C; HIV=human immunodeficiency virus; IgA=immunoglobulin A; IgG=immunoglobulin G; IgM=immunoglobulin M; RF=rheumatoid factor

had normal levels of glucose and serum sodium, potassium, calcium and magnesium. No acid-base disorders were noted. Urine sediment was normal and the urine albumin/creatinine *ratio* was 10 g/g. An immunological panel was performed. No autoantibodies were detected. Test results for hepatitis B, C, HIV and serum kappa and lambda free light chains were negative. The levels of immunoglobulin A, G, M and complement were normal. Anti-PLA2R antibody tests were not repeated.

Differential diagnosis

Nephrotic syndrome was confirmed. The absence of an active urinary sediment, negative serology and the lack of systemic clinical features have rendered focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD) or PLA2R-negative membranous nephropathy as possible etiologies for the nephrotic syndrome. PLA2R membranous nephropathy constitutes over 70% of primary membranous nephropathy cases. Additionally, given the patient's age, absence of other comorbidities and drug usage, as well as negative serology for systemic lupus erythematosus (SLE) and other autoimmune diseases, we have excluded secondary membranous nephropathy stemming from cancer, autoimmune diseases, drugs, or infections. The abrupt onset of the nephrotic syndrome points towards MCD as the more likely diagnosis.

Clinical follow-up

The patient was started on continuous intravenous furosemide at 5 mg/h in combination with a low-salt diet. The clinical and biological evolution was favorable during the first two days, with an improvement in urine output (diuresis up to 2 500 mL/d), a weight loss of 3 kg and a reduction in hypervolemia from 8.1 L to 5.8 L, as measured by bioimpedance. However, on the third day, he began to have a low urine output of less than 1 000 mL/d, weight gain and a bioimpedance measurement of 11.4 L. Although we ensured that the patient followed our medical advice of a low-salt diet and restriction of fluid to 1 500 mL/d, the patient still gained weight. We determined that he had diuretic resistant nephrotic edema and decided to use different classes of diuretics. Thus, we started the patient on a fixed combination of hydrochlorothiazide and amiloride (50/5 mg, 1 tb/d). We also treated the patient with immunosuppressive therapy,

TABLE 4. Laboratory data after 11 days of diuretic treatment

Parameter	Lab value	Reference range
Serum biochemistry		
Creatinine (mg/dL)	1.39	0.7-1.2
BUN (mg/dL)	60	19-49
Sodium (mEq/L)	138	132-146
Potassium (mEq/L)	4.5	3.5-5.5
Calcium (mg/dL)	9.0	8.7-10.4
Magnesium (mg/dL)	2.06	1.0-2.4
Albumin (g/dL)	2.5	3.2-5.2
Bicarbonate (mmol/L)	32	20-26
Urine parameters		
24-hour proteinuria (g/24 h)	7.3	<0.03
24-hour sodium (mmol/L)	96.47	<20
24-hour potassium (mmol/L)	26.16	<20

BUN=blood urea nitrogen

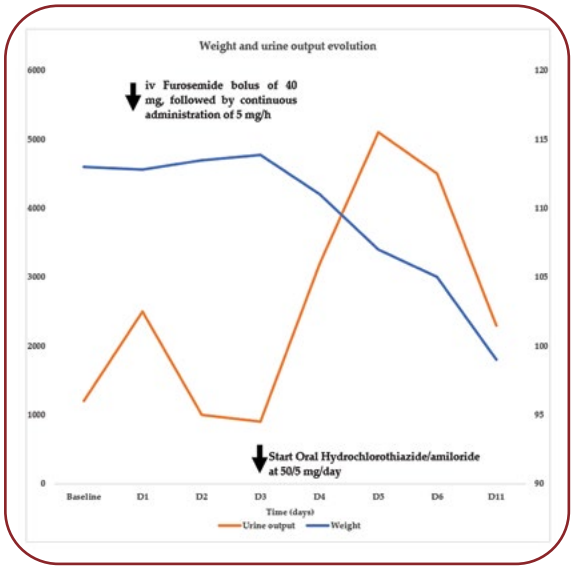

FIGURE 1. Patient's evolution in terms of body weight and urine output during admission. Treatment periods with diuretics are indicated. IV=intravenous

administering oral corticosteroids at 1 mg/kg *per* day, along with rituximab (500 mg).

After 11 days, diuretic treatment resulted in effective resolution of edema and a concomitant weight loss of 18 kg (Figure 1). The patient had no electrolyte imbalances, no episodes of hypotension and only a slightly increased serum creatinine level (1.39 mg/dL) and bicarbonate level (32 mmol/L), which returned to normal within a week. Serum albumin levels increased to 2.5 g/dL. However, proteinuria remained largely unchanged, staying within the nephrotic range, with protein excretion at 7.3 g/24 h (Table 4).

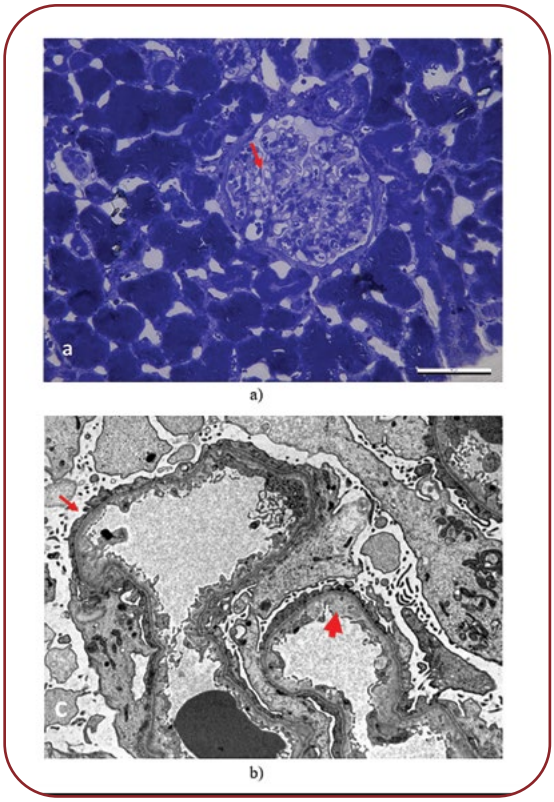

FIGURE 2. Kidney biopsy: minimal change disease; light microscopy: toluidine blue, normal glomerulus shows open capillary loops with no evidence of proliferative lesions (arrow), no segmental sclerosis (a); electron microscopic examination: podocyte foot process effacement (small arrow), no dense deposits present (big arrow) (b).

Diagnosis

Once the patient entered clinical remission, we performed a kidney biopsy, and an analysis of the biopsy sample confirmed that the patient had minimal change disease (Figure 2).❑

DISCUSSION

The presented case highlights that fluid overload primarily stems from excessive ENaC activity. Subsequently, when treatment was directed towards inhibiting ENaC channels, the patient demonstrated a noteworthy reduction in weight, as assessed by bioimpedance.

Despite an initially favorable response within the first two days, on the third day, urinary output decreased to less than 1 000 mL/24 h, along with a weight gain of 2 kg. Intravenous human albumin in combination with furosemide was not administered, as there were no indications of hypovolemia. Furthermore, initial treatment with

albumin and furosemide yielded no response. Additionally, titration of furosemide doses was not attempted due to serum potassium levels reaching 3.1 mEq/L. Consequently, an ENaC blocker was deemed a more suitable option. Although amiloride as monotherapy was unavailable, a fixed combination with hydrochlorothiazide/amiloride (50/5 mg/day) was utilized. Following treatment initiation, the patient exhibited a significant reduction in weight over the subsequent eleven days, totaling 18 kg, with no electrolyte imbalances. Upon discharge, the patient presented without edema, with a bioimpedance of +0.5 L and within normal blood pressure parameters.

Unilateral animal models of nephrotic edema have provided evidence indicating that sodium and water retention result from specific intrarenal factors, thereby challenging the "underfill" hypothesis (6). The "underfill" hypothesis refers to hypoalbuminemia which determines low oncotic pressure, leading to fluid extravasation from the intravascular space into the interstitial space, consequently inducing hypovolemia. This process triggers neurohormonal activation, including the renin-angiotensin-aldosterone system, sympathetic nervous system and vasopressin secretion, ultimately resulting in secondary sodium and water retention (2).

Conversely, the "overfill" hypothesis suggests primary sodium and water retention. Subsequent research conducted over the past two decades on the structure and function of ENaC has revealed that the regulation of ENaC channels involves not only channel density, but also open channel probability. Proteinuria, characterized by the presence of certain serine proteases, has been identified as capable of inducing a high open probability of ENaC channels and activating them through proteolysis. Among these proteases, plasmin, derived from plasminogen through the action of urokinase plasminogen activator (UPA), is the most prevalent (7).

Amiloride offers multiple advantages as it acts as an ENaC blocker and also has the potential to inhibit UPA (5). It is widely acknowledged that urokinase plasminogen activator receptor (uPAR) is intricately involved in the detachment of podocytes from the glomerulus, consequently leading to proteinuria (8). Thereby, amiloride could be considered a potential diuretic for management of nephrotic edema, by reducing ENaC activity, but also plasmin levels and proteinuria (5).

In 2001, Deschenes demonstrated that amiloride reduced sodium reabsorption in the collecting duct in puromycin aminonucleoside nephrosis (PAN) in rats (9). Later, in 2015, Staehr *et al* conducted a study on both humans and experimentally induced PAN in rats, showing that amiloride, an ENaC blocker and an off-target inhibitor of uPA, caused reduced plasminogen activation and decreased sodium retention (10).

In 2016, Patel-Chamberlin demonstrated that amiloride causes significant diuresis in Na^+Cl^- cotransporter (NCC) knockout mice and in those pretreated with acetazolamide. Inhibition of pendrin with acetazolamide in the context of NCC inactivation leads to upregulation of ENaC. Therefore, future consideration should be given to a diuretic combination of acetazolamide, thiazide and amiloride for a favorable outcome (11).

Although large-scale trials on amiloride in nephrotic edema are lacking, early data indicate the benefits of adding an ENaC blocker to other diuretics for a favorable clinical response. In 1967, Singh *et al* conducted a study on a sample of 11 patients with nephrotic syndrome and treatment-resistant volume expansion, of which seven patients received treatment with amiloride and hydrochlorothiazide, and five patients with amiloride and ethacrynic acid. In both treatment groups, the addition of amiloride resulted in a significant increase in natriuresis, from 91.6 mEq/day to 188 mEq/day in the case of the combination with hydrochlorothiazide, and from 94.9 mEq/day to 159 mEq/day in the case of the combination with ethacrynic acid. Better control of fluid balance and volume expansion was observed with the combination treatment involving amiloride. The study authors concluded that amiloride is effective in treatment-resistant nephrotic edema and may be superior to spironolactone or triamterene, another ENaC channel antagonist (12).

In another factorial 24 study, the efficacy of amiloride, chlorothiazide, ethacrynic acid and furosemide administered in various combinations was investigated in patients with treatment-resistant hypervolemia. The study included eight patients, of which five had nephrotic syndrome. The results showed that patients treated with chlorothiazide, ethacrynic acid and

furosemide experienced a significant increase in diuresis and natriuresis, while those treated with amiloride showed an increase in diuresis that was half the effect of the other diuretics. The study authors concluded that amiloride demonstrated moderate efficacy but had an additive effect when used in combination with other diuretics. Furthermore, it was noted that one patient with nephrotic syndrome continued to exhibit treatment-resistant hypervolemia with all three administered diuretics, but with the addition of amiloride, a significant increase in natriuresis was observed, though this phenomenon could not be explained at the time (13).

Studies conducted on populations of patients with diabetic nephropathy or other renal diseases manifested with proteinuria, which had secondary objectives of assessing weight curve changes under amiloride treatment, did not show statistically significant differences compared to baseline weight or the control treatment group. The varying results of these studies can be explained by the small number of patients, indicating the need for large scale trials to reach a definitive conclusion. Additionally, the patient profiles were different. The studies included patients without hypervolemic status, and the majority had subnephrotic proteinuria and medically controlled hypertension, which might explain the absence of benefits from amiloride treatment (14, 15).

Two more recent case reports of resistant nephrotic edema have demonstrated significant weight reduction following the administration of an ENaC blocker (amiloride, triamterene) (16, 17). Additionally, a recent randomized trial involving 22 patients with nephrotic edema revealed a significant reduction in weight with the oral combination of diuretics (amiloride/hydrochlorothiazide/furosemide) compared to monotherapy with intravenous furosemide (18).

While acknowledging the potential antiproteinuric role of immunosuppressive therapy in the presented case (19), it is noteworthy that the patient experienced a favorable clinical course immediately after amiloride was added on day 3. ❑

CONCLUSION

In summary, we presented a case of nephrotic edema that demonstrated resolution of edema following diuretic treatment with a combination of intravenous furosemide and oral amiloride and hydrochlorothiazide, with no severe complications. The use of ENaC blockers in nephrotic edema management represents a targeted approach to addressing the underlying sodium retention issue, leading to significant weight loss and edema resolution. The most common adverse event associated with its usage is hyperkalemia or acute kidney injury, particularly when administered concurrently with other diuretics (20). Nonetheless, our patient exhibited normokalemia throughout the entirety of the admission period. Furthermore, despite a marginal elevation in serum creatinine at the time of discharge, it normalized within one week thereafter. ❑

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