CASE REPORT

Efficacy of extracorporeal ultrafiltration in patients with diuretic-resistant heart failure

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SUMMARY

Renal congestion contributes to the cardiorenal syndrome. There are some heart failure cases that are refractory to diuretic therapy. If the dose of diuretics is titrated, it leads to irreversible renal dysfunction. Early administration of tolvaptan is effective in treating fluid retention and congestion. However, in case of tolvaptan resistance, starting extracorporeal ultrafiltration (ECUM) at an early stage should be considered. Tolvaptan has been proven efficient, and we believe it should be incorporated with the classical method, ECUM. Herein, we present a case of successful application of ECUM to a heart failure patient refractory to any diuretics and tolvaptan.

BACKGROUND

Fluid retention and congestion are responsible for 90% of cases of heart failure requiring hospitalisation,^{1 2} and greater severity of congestion is associated with worse outcomes.³ Loop diuretics remain the first-line therapy for acute decompensated heart failure (ADHF) and are currently prescribed for ~90% of hospitalised patients with ADHF.² Tolvaptan, a vasopressin type-2 receptor antagonist, is expected to resolve patients' congestion refractory to loop diuretics. However, there are cases refractory to tolvaptan treatment that was intended to resolve fluid

retention and congestion. This diuretic resistance is associated with high morbidity and mortality.⁴ Extracorporeal filtration has emerged as a potentially promising alternative to diuretic therapy in ADHF.^{5 6} We herein describe the successful application of extracorporeal ultrafiltration (ECUM) in a case of heart failure refractory to any diuretic, including tolvaptan.

CASE PRESENTATION

A 59-year-old man with a medical history of atrial septal defect patch closure was presented at our institution. He had no medical history and hospitalisation after patch closure, which was performed in his teens. His typical diet included outside foods or home-packed meals purchased from convenience stores, which have a high salt content. He had dyspnoea and pedal oedema for 2 months prior to hospitalisation. His symptoms were exacerbated thereafter, and it became difficult for him to stand up. His heart rate was 120 bpm, and his blood pressure was 90/70 mm Hg. He had advanced abdominal distension and leg oedema. There were bilateral coarse crackles in the base of both lungs. ECG revealed sinus rhythm, a heart rate of 121 bpm, incomplete right bundle branch block, and low voltage in the limb leads (figure 1). A chest radiography revealed cardiomegaly, pleural fluid

Figure 1 An ECG reveals sinus rhythm, heart rate of 121 bpm, incomplete right bundle branch block and low voltage in the limb leads.

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Figure 2 Left column: the chest radiogram obtained on admission revealing cardiomegaly, pleural fluid and congestion. Right column: the chest radiogram obtained after treatment revealing minimal pleural fluid and resolution of congestion.

and congestion (figure 2). Transthoracic echocardiogram revealed severe diffuse hypokinesis of the left ventricle, paradoxical septal motion, cardiac dilation of all chambers, no shunt flow, dilated inferior vena cava and 27 mm Hg of peak gradient of tricuspid regurgitation. However, the echocardiogram also showed expansion of the right atrium and ventricle, which suggested pulmonary hypertension. As it became apparent, there was a residual shunt through an atrial septal defect, and Qp/Qs was 1.27. This implies that the residual shunt may not influence haemodynamics. We did not obtain a histological diagnosis.

There was considerable fluid retention, so we started treatment with non-invasive positive pressure ventilation and intravenous injection of furosemide 40 mg/day, supported by dobutamine (3γ). Since urinary osmolality was 586 mOsm/kg, we assumed that he might be responsive to tolvaptan and, thus, administered tolvaptan 7.5 mg/day. The patient responded well to treatment up until the 5th day with a urine volume over 2000 mL. Volume retention persisted; the urine volume decreased from the 7th day onwards and renal function worsened. Creatinine level increased from 0.82 to 1.48 mg/dL. We increased the total dose of furosemide up to a maximum of 200 mg; however, the response to this treatment was poor. We considered one of the reasons for the resistance to the diuretics might be the renal congestion. Therefore, we performed ECUM to resolve the renal congestion directly and mechanically, and

removed over 4000 mL of water over 2 days. The urine volume then dramatically increased (figure 3), despite decreasing the dose of furosemide. We speculate that coactive removal of water reduced the central venous pressure (CVP), which increased the glomerular pressure gradient and the glomerular filtration rate.

DIFFERENTIAL DIAGNOSIS

- ▶ Liver cirrhosis
- ▶ Nephrotic syndrome
- ▶ Renal failure
- ▶ Hypothyroidism
- ▶ Malnutrition

OUTCOME AND FOLLOW-UP

The patient had a good clinical course following the removal of renal congestion by a short duration of ECUM. He was discharged from our hospital after 40 days with normal renal function with instructions on salt restriction and oral medication use. He was not rehospitalised thereafter.

DISCUSSION

This case highlighted two important issues. First, the resistance to diuretics in patients with heart failure has several aetiologies, with renal congestion as one possibility. Second, the treatment of renal congestion using ECUM can be useful in patients

Figure 3 A summary of the clinical course. The 2-day extracorporeal ultrafiltration method (ECUM) removes 4000 mL of water mechanically. It leads to an increase in urine output, despite the decreasing diuretic dose.

resistant to diuretics including tolvaptan. There are some reports on the efficacy of ultrafiltration as an alternative treatment for patients resistant to traditional diuretic therapy. However, we could not find such reports since tolvaptan has been widely used.

We diagnosed our patient with acute decompensated heart failure based on several physical findings and examinations; however, we considered the differential diagnosis of volume retention such as liver cirrhosis, nephrotic syndrome, renal failure, hypothyroidism and malnutrition. There were no significant findings on blood examination or abdominal ultrasound scan. The criteria for nephrotic syndrome were not met. Thyroid hormone level was normal. Though malnutrition might be one factor related to exacerbation, 3.2 g/dL of serum albumin suggested heart failure was more suitable as this patient's main aetiology.

The patient's volume retention was not resolved fully with intravenous catecholamine and diuretics, including tolvaptan. Worsening renal function during heart failure treatment, or type 1 cardiorenal syndrome, is associated with poor outcome. Fluid volume control with diuretics or extracorporeal ultrafiltration is crucial, as fluid overload is one of the important mechanisms for both acute decompensated heart failure and acute kidney dysfunction in cardiorenal syndrome.^{7 8}

We considered the differential diagnosis of diuretic resistance in heart failure patients such as renal congestion, renin-angiotensin-aldosterone system (RAAS) activation, dehydration, low blood pressure and direct pressure of renal interstitium by ascites.

First, in heart failure, increasing CVP may cause renal congestion. Transmission of venous congestion to renal veins impairs the glomerular filtration rate.⁹ Second, treatment with loop diuretics causes a negative sodium and water balance and inhibition of the macula densa, that is, loop diuretics may worsen RAAS activation. Therefore, we administered from 25 up to 75 mg of spironolactone, considering the RAAS activation. This was based on a previous study reporting that aldosterone antagonists used at natriuretic doses might be one approach to overcome diuretic resistance.¹⁰ However, the dose of spironolactone used in our study may be insufficient. Third, dehydration or low blood pressure shows diuretic resistance. Since extracellular fluid challenge, vasopressor and the maximal dose of furosemide were not effective in our case, it is unlikely that the reason for diuretic resistance was dehydration or low blood pressure. Finally, increased intra-abdominal pressure caused by ascites may contribute to diuretic resistance.¹¹ The patient's abdomen was distended due to ascites. An option that was considered was to puncture the ascites, had ECUM failed.

In this case, we performed ultrafiltration to remove the renal congestion mechanically, not indirectly. Even though we reduced the amount of diuretics, a large volume of urine was passed after performing ECUM. We speculate that the removal of water reduced the CVP, which increased the glomerular pressure gradient and the glomerular filtration rate. Assuming renal congestion was the main aetiology of diuretic resistance, CVP and resistance to diuretics might be the highest on admission. Therefore, we considered that the initial volume reduction would not reduce the CVP fully, and might lead to RAAS activation. As a result, urine volume might decrease after the initial response. Furthermore, fluid returned from third space into blood vessel. It could affect the CVP. We believed the main

aetiology of diuretic resistance to be renal congestion. The fractional excretion of urea nitrogen was 11% when renal function worsened, which supported this notion.

Hence, we should consider the ECUM for patients who have a large volume overload and high CVP after diuretic therapy. However, if patients have diuretic resistance but not high CVP, ECUM may not be effective.

Learning points

- ▶ Tolvaptan is effective in treating fluid retention and congestion for heart failure patients refractory to loop diuretics.
- ▶ Some cases involve patients that were refractory to diuretics and novel treatment with tolvaptan.
- ▶ Renal congestion is one of the important aetiologies of diuretic resistance.
- ▶ We experienced the successful application of extracorporeal ultrafiltration method (ECUM) in the case of resistance to loop diuretics and tolvaptan.
- ▶ We should consider ECUM for patients who have a large volume overload and high central venous pressure after diuretic therapy.

Contributors NN and KN mainly designed and wrote this manuscript. TO supervised and revised it.

Competing interests None declared.

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