Type 2 Cardiorenal Syndrome in Heart Failure with NSTEMI: A Case Report of 10 Months Follow Up

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Abstract. Cardiorenal syndrome (CRS) is a disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other. Chronic abnormality in cardiac function leading to kidney injury or dysfunction was a typical characteristic of CRS type 2. Renal dysfunction frequently coexists with chronic heart disease, which in this situation, it's often difficult to establish which of the 2 diseases is the primary one. We present the case of a 74-years old male was presented with chest pain, cough, dyspnee d'effort, and diaphoresis. He had a history of chronic heart failure, atrial fibrillation, and renal insufficiency. Chest radiography revealed pulmonary edema. The electrocardiogram showed Atrial Fibrillation (AF) with Left Bundle Branch Block (LBBB). On echocardiography we found RWMA (+), ejection fraction of 24%, TAPSE 12 mm. Initial laboratory result was a high concentration of urea and diminished renal function shown as a high concentration of creatinine with eGFR was 16.1 mL/min/1.73 m2 (MDRD) and Troponin I was 630 ng/L. He was transferred to ICU with NSTEMI, heart failure, renal insufficiency, and AF with LBBB. Patient was treated with Digoxin, intravenous Furosemide, Aspirin, Clopidogrel, Candesartan, Carvedilol, Rosuvastatin, Curcuma and Aminoral. On the next day, dopamine was given due to hypotension. Three days later, there's improvement in kidney condition and urine output. Patient felt neither chest pain nor dyspnea. On the 6th day, the patient was discharged. An adequate treatment of heart failure in cardiorenal syndrome can also improve renal condition.

Keywords: Cardiorenal Syndrome · Heart Failure · Chronic Kidney Disease · Hemodialysis

1 Introduction

As proposed by Acute Dialysis Quality Initiative, the broad definition of "Cardiorenal Syndrome" (CRS) was "disorders of the heart and kidneys whereby acute or chronic dysfunction of one organ may induce acute or chronic dysfunction of the other". Thus

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by this definition, CRS was classified into 5 subtypes based on the major cause and sequential organ involvement [1]. Description of the epidemiology of cardiorenal disease depends on heart-kidney interaction, predisposing and precipitating events, natural history, and outcome, thus each subtype has its epidemiological characteristic.

The classic explanation of the development of CRS was inability of the heart to generate forward flow, thus resulting in renal hypoperfusion, and leading to fluid retention, increased pre-load, and worsening renal failure. But the ADHERE registry claims that the incidence of rising creatinine serum was similar among patients with reduced and preserved ejection fraction heart failure, suggesting that hemodynamic adaptation of the kidney can be independent of cardiac hemodynamics [2]. It's hypothesized these four points integrate the connection of cardiorenal, Sympathetic Nervous System (SNS), Inflammation, Renin-angiotensin-aldosterone (RAA) system, and NO-ROS balance [3].

On heart failure, it is estimated that 64.3 million people worldwide have heart failure, with the prevalence approximately between 1% to 2% of the adult population [4]. In Asia, the prevalence was generally similar to global value (1–3%) and value reported from Europe and America study. The prevalence was reported as higher in men than women, a little bit younger than Europeans and Americans who have heart failure [5].

Renal function is extremely prevalent in patients with heart failure. Data from the Acute Decompensated Heart Failure National Registry of over 100.000 patients with heart failure, one-third of the patients have had renal dysfunction. Baseline renal function is an important adverse prognostic marker in heart failure. Elevated serum creatinine on admission and worsening renal function during hospital stay in ADHF, have both shown can predict prolonged hospitalization and increased mortality [6]. Furthermore, renal failure is also connected to the increased adverse cardiovascular outcome. Nearly 44% of patients with end-stage renal failure died from cardiovascular causes rather than from renal failure itself [7].

2 Case Presenting

2.1 On Admission

A 74-years old male was presented in the emergency room (ER) with chest pain, cough, dyspnee d'effort, and diaphoresis since yesterday. The chest pain was induced by emotions and relieved by rest. He had a history of heart failure (3 years), atrial fibrillation, and renal insufficiency with routine hemodialysis since 3 months ago, but lack of compliance to visiting the doctor. On physical examination, the vital sign included a blood pressure of 138/93 mmHg, heart rate of 159 beats per minute, respiration rate of 35 breaths per minute, and SpO2 of 93% in room air. On cardiopulmonary examination, we found bibasal pulmonary crackles in both lungs, heart sound was normal with no additional sound nor murmur. Chest radiography revealed pulmonary edema and cardiomegaly. The electrocardiogram showed atrial fibrillation (AF) with Left Bundle Branch Block (LBBB). Initial laboratory result was a high concentration of urea and diminished renal function shown as a high concentration of creatinine (blood urea of 112 mg/dL, creatinine of 3.7 mg/dL) with eGFR was 16.1 mL/min/1.73 m2 (MDRD). Because the chest pain was typical with angina pectoris, Troponin I test was ordered and it's showing the result of 630 ng/L. Liver function was also declining as both liver enzymes were high

(AST 171 U/l, ALT 154 U/l). Lastly, we also found hemoglobin of 9.3 g/dL, leucocyte of 14900 /uL, normal value of electrolyte, and high concentration of leukocytes on urinalysis.

From this point, we can suspect several diagnoses from the initial examination in the ER. The initial diagnosis of this patient were NSTEMI, Chronic Heart Failure, Atrial Fibrillation-Rapid Ventricular Response with LBBB, Chronic Kidney Disease, and Urinary tract infection. Patient was treated in ER with 40 mg intravenous Furosemide due to fluid overload, 0.5 mg of Digoxin i.v, Heparin (3000 U) i.v, and perorally 160 mg of Aspirin, and 150 mg of Clopidogrel. After initial therapy, the patient was transferred to the Intensive Care Unit (ICU) for further observation.

In the ICU, the patient was still complaining about the dyspnea and chest pain but the vital sign was quite stable. On day two, echocardiography was performed. We found ejection fraction of 24%, TAPSE 12 mm, dilated left atrial and left ventricle, RWMA (+) dyskinetic in septal, severe hypokinetic anterior and apical, hypokinetic in other segments of the heart. We also found severe mitral regurgitation caused by ischemia. Since some data was collected, we can diagnose our patient with NSTEMI, Heart failure with reduced ejection fraction (HFrEF), type 2 Cardiorenal syndrome, Chronic kidney disease (CKD) grade 4, and severe mitral regurgitation. Based on the diagnosis, patients management plans on ICU were 40 mg twice daily intravenous Furosemide, intravenous Heparin 700 U/hour, intravenous daily 1 gr of Cefoperazone, perorally daily 80 mg of Aspirin,75 mg of Clopidogrel, 8 mg of Candesartan, 6.25 mg of Carvedilol BID, 10 mg of Rosuvastatin, Curcuma BID, Aminoral BID, and closely monitored fluid balance. On the second day, patient blood pressure was dropped to 59/33. Due to the unresponsiveness of fluid therapy, intravenous dopamine was initiated in 2 mcg/kg/min. Despite dopamine therapy, the blood pressure still did not hit the minimal target for hemodialysis therapy (70/43 mmHg), then norepinephrine was initiated in 0.2 mcg/Kg/min.

Three days later, there's improvement in kidney condition, whereas urea reduced from 112 mg/dL to 103 mg/dL and creatinine from 3.7 mg/dL to 2.5 mg/dL, urine output was increased from 0.8 ml/Kg/hr on the first day to 2.0 ml/Kg/hr on the 4th day, noted that this result was achieved without renal replacement therapy. Patient felt neither chest pain nor dyspnea, and hemodynamic was gradually stabilized. On the 6th day, the patient was discharged with urea reduced to 62 mg/dL, creatinine was 2.0 mg/dL and stable hemodynamic.

2.2 Previous History

Ten months prior to the last admission, the patient was presented in the emergency room (ER) with dyspnea and edema on the scrotum, both legs, and both arms. He also had chest pain that was precipitated by light activity. His past medical history was congestive heart failure but reluctant to visit the doctor regularly. He had no history of diabetes or kidney insufficiency before. On physical examination, the vital sign was stable, there were crackles on both lungs, distended abdomen might be due to ascites, pitting edema on both sides of legs and arms, and scrotal edema. On initial laboratory tests, urea and creatinine concentration was quite high (Urea of 92.6 mg/dL, creatinine of 2.0 mg/dL) with normal electrolyte status and albumin level. ECG showed atrial fibrillation with normal ventricular response with RBBB and right ventricle hypertrophy with right axis

deviation. Chest x-ray revealed cardiomegaly and pulmonary edema. Reflecting upon the signs and symptoms, the patient was diagnosed with CHF, AF NVR, and renal insufficiency, suspected for cardiorenal syndrome. Considering the "anasarca edema", the patient was treated with Furosemide drip 10 mg/hour, Spironolactone, Captopril, and HCT.

On echocardiography, ejection fraction was reduced to 23%, TAPSE 10 mm, global hypokinetic, dilatation of cardiac chambers, and moderate mitral regurgitation possibly due to ischemia. On the 4th day of admission, edema was reduced. On the 7th day, edema was resolved, and i.v furosemide dose was tapered until 10 mg qDay. Creatinine rose to 2.3 mg/dL, sodium and potassium depleted might be due to aggressive furosemide usage (Na+ 132 mmol/L, K+ 2.88 mmol/L). KSR was given three times daily to compensate for potassium loss. Patient was discharged on day 10th in stable condition.

Two months before the last admission. Patient came to the ER with a bloated feeling for one week, nausea, and loss of appetite. Laboratory tests revealed the level of urea was 230 mg/dL, creatinine of 12.8 mg/dL, and potassium of 8.40 mmol/L. ECG showed tall T, reflecting hyperkalemia state as shown in the laboratory test. After trying to stabilize the heart membrane with calcium gluconates, taking into consideration the severe hyperkalemia and acute kidney injury state, emergency dialysis was performed. Afterward, he routinely undergoes dialysis every month but discontinues the heart failure drugs.

2.3 Follow-Up

One day, the patient suddenly stopped coming for his routine dialysis. We contacted the family and it was confirmed that the patient died in his home just three days after his last dialysis or 1 month after the last admission.

3 Result and Discussion

Cardiorenal syndrome (CRS), defined as "disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other". There are five subtypes, divided based on pathological mechanism and major cause [1]:

1. Acute cardiorenal syndrome (type 1)

Acute kidney injury (AKI) and/or dysfunction as the result of acute worsening of heart function, like acute heart failure (AHF) and/or acute coronary syndrome (ACS) complicated by worsening renal function (WRF). Acute kidney damage (AKI) appears to develop in between 27 and 40% of patients hospitalized for acute decompensated heart failure (ADHF) and falls into this clinical category.

2. Chronic cardiorenal syndrome (type 2)

Kidney injury and/or dysfunction as the result of chronic abnormalities of heart function is used to describe chronic HF leading to renal failure. It's a common syndrome which is reported in 63% of patients hospitalized with congestive heart failure (CHF).

3. Acute reno-cardiac syndrome (type 3)

Heart injury, disease, and/or dysfunction (like uremic cardiomyopathy, arrhythmia due to hyperkalemia) as the result of acute worsening of the kidney, where cardiac function is secondary to AKI.

4. Chronic reno-cardiac syndrome (type 4)

Heart injury, disease, and/ or dysfunction as the result of Chronic Kidney Disease (CKD). This subtype refers to disease or dysfunction of the heart occurring secondary to CKD [1]. In a current meta-analysis, an exponential relationship was found between the severity of renal failure and the likelihood of all-cause mortality, with excess cardiovascular fatalities accounting for more than half of all deaths [7].

5. Secondary cardio-renal syndrome (type 5)

Heart and kidney damage and/or dysfunction are caused by systemic diseases. There is no primary or secondary organ dysfunction, but systemic disease, whether acute or chronic, affects both organs. Sepsis, systemic lupus erythematosus, amyloidosis, and other chronic inflammatory diseases are examples [1].

The traditional explanation for CRS in the presence of a cardiocentric primum movens relies on the failing heart's inability to produce forward flow, resulting in prerenal hypoperfusion. Fluid retention, increasing preload, and worsening pump failure result from insufficient renal afferent flow, which stimulates the RAA system axis, the sympathetic nervous system, and arginine vasopressin production [2].

3.1 Type 2 Cardiorenal

In our patient, he had a clinical picture of CHF with reduced left ventricular ejection fraction on echocardiography, along with biochemical indications of renal impairment, the onset or progression of which is plausibly due to congestive HF, thus the diagnosis of CRS type 2 should be considered. Increased creatinine with low eGFR values (16.1 mL/min/1.73 m2) which we calculated using the Modified Diet in Renal Diseases study (MDRD) method as evidence of renal dysfunction in the context of a CRS type 2.

Chronic abnormality in cardiac function leading to kidney injury or dysfunction was a typical characteristic of CRS type 2. Renal dysfunction frequently coexists with chronic heart disease, which in this situation, it's often difficult to establish which of the 2 diseases is the primary one [3]. CKD has been observed in 45% to 63% of chronic heart failure patients [9], but it is unclear how to classify these patients as often some patients may have had preceding CRS-1, or to differentiate these patients from (CRS-4) [3].

Renal congestion and hypoperfusion, as well as elevated right atrial pressure, are part of the pathophysiology of CRS-2. Other factors such as neurohormonal activation, inflammation, and oxidative stress also play a role in renal dysfunction in chronic heart failure patients. Aside from specific mechanisms, it's proposed that multiple episodes of acute decompensation of the heart or kidney may contribute to the progression of HF and CKD. This is supported by evidence indicating that, after adjusting for all known risk factors for HF survival, the number of prior hospitalizations for HF was a significant predictor of death [10]. Our patient was admitted to the hospital 2 times prior, the first one was due to a decompensated condition of heart failure and the next one was deteriorated renal function leading to hyperkalemia and renal replacement therapy, showing the progression of cardiorenal syndrome.

Between each admission, the patient was reluctant for routine control of the outpatient clinic and only eagerly visited the hospital when he felt his condition was worsening, so medical therapy was suboptimal. Although recurrent hospitalizations may be a sign of disease severity, inadequate treatment, or poor patient compliance, may result in heart structural modification, increased fibrosis, and LV modeling. Furthermore, the frequency of HF hospitalizations was independently related to the development of CKD in a long-term study of 70 patients with dilated cardiomyopathy [11]. Acute kidney injury episodes have also been shown in animal models and epidemiologic studies to have a negative impact on the development and progression of CKD [12]. Hesitancy to visit the doctor to get medical therapy may be the reason for the worsening condition of the heart (from ischemic heart disease on the first admission to NTSEMI, and from acute kidney injury to chronic renal failure).

We ordered troponin I (TnI) examination to make sure acute coronary syndrome condition, but high concentration of troponin might be also due to the chronic kidney disease. The pathophysiology of higher TnI levels in CKD patients compared to non-CKD patients is unknown. Although decreased renal clearance has been proposed as a cause of TnI increase in CKD, the evidence for this theory is mixed. Another explanation is that there is a simultaneous chronic myocardial injury in certain cardiorenal disorders that are driven by underlying inflammatory processes. Troponin levels may rise as a result of the severity of epicardial coronary artery disease (CAD), which may be accompanied by subendocardial ischemia and potential microinfarctions. Additionally, higher levels of Troponin I may be due to left ventricular hypertrophy and cardiac fibrosis in CKD, indicative of underlying structural abnormalities that are independent of CAD. The association between troponin I and death in patients with CKD was stronger for patients without obstructive CAD than obstructive CAD. Troponin I was a strong predictor of all causes of death, cardiovascular death, and MACE in those with CKD, it became even stronger as eGFR declined [13].

3.2 Patients Management

Treatment for one organ may aggravate the condition of the other, making management of cardiorenal syndrome difficult. Therapy of CHF with concomitant renal impairment is still not evidence-based, as these patients are generally excluded from CHF trials. Typically, these patients are hypervolemic, and more intensive diuretic treatment is needed. In our patient, we use furosemide to treat the congestive condition rather than renal replacement therapy. Furosemide use in cardiorenal syndrome may still be debatable. Some research found that diuretic use in heart failure may relieve the symptoms but no benefit in short or long-term mortality or rehospitalization [14].

In both HF and renal failure, diuretics are the first line of defense against fluid overload. Despite deteriorating renal function, aggressive diuresis enhances patient survival [15], and it's especially useful for CRS 1, 2, and 4 treatment. Diuretic resistance, which is a sign of poor prognosis in patients with CHF, is a key challenge that clinicians must deal with when treating patients with CRS. It is a well-known diuretic side effect that is described as a reduction in the maximal diuretic impact, which eventually decreases salt and chloride excretion [2]. In refractory congestive cases, Renal Replacement Therapy (RRT) may be required [1].

Comparing diuretic with renal replacement therapy has been a clinical trial subject for some research to find the optimal mode of decongestion in heart failure. Some randomized controlled trial, Ultrafiltration versus Intravenous Diuretics for Patient Hospitalised for Acute Decompensated Congestive Heart Failure (UNLOAD), Relief for Acutely Fluid-Overloaded Patient With Decompensated Congestive Heart Failure (RAPIDCHF), Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF) have compared diuretic therapy in patient with acute decompensated HF. In RAPIDCHF and UNLOAD trial, ultrafiltration had a better effect on fluid loss than diuretic, but there's no significant difference in effect on renal function [16, 17]. In the CARESS-HF trial, which focuses on CRS type 1, no significant difference in fluid loss between ultrafiltration and diuretic, but the ultrafiltration group had significant higher creatinine and adverse events than the other one [18] The same result was also founded in Continuous Ultrafiltration for Congestive Heart Failure (CUORE) study [19]. Improved renal function in our patient despite using furosemide as decongestive therapy may be coherent with some trials. Optimal cardiogenic therapy may also play an important role in renal function in a cardiorenal setting.

Falling cardiac output and underfilling of the renal arterial tree activate both SNS and RAA system in the presence of substantial cardiac failure [9]. The kidneys of patient with HF produce significant amounts of renin into the circulation [14], which leads to the synthesis of angiotensin II, a potent vasoconstrictor that increases systemic vascular resistance, venous tone, and congestion, as well as activating the SNS. Angiotensin II also stimulates tubular sodium reabsorption, which has a considerable effect on the kidneys [10]. Thus RAA system activation in the kidney causes sodium and water retention, systemic vasoconstriction, and even lower glomerular filtration, as well as ventricular remodeling. We employ candesartan as an angiotensin receptor blocker to block the RAA system. Subgroup analyses of clinical trials of RAA system antagonism in HF have demonstrated that the beneficial effects on morbidity are not reduced by concurrent CKD. Angiotensin-converting enzyme inhibition and angiotensin receptor blockers are known to worsen renal function prompting reluctance to prescribe and a low threshold for stopping. They should not be stopped since, despite a drop in GFR, patients had a lower mortality rate [20]. Renal function degradation is more common in patients with CKD or renal artery stenosis, even if it is usually brief and reversible. But these drugs can cause hyperkalemia, which may necessitate dietary restrictions [1].

Carvedilol is a β -blocker that we use in our patient. Beta-blockers are not utilized in the treatment of acute HF, however, they are used in the treatment of chronic HF. MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Chronic HF), a randomized study of approximately 4,000 patient with symptomatic HF and EF 40%, demonstrated that metoprolol was at least as effective in lowering death and hospitalization in the advanced CKD group [21]. Study of Cardiac Insufficiency Bisoprolol Study II (CIBIS II) conducted a similar analysis and found no evidence of a decline in bisoprolol efficacy with lower renal function [22]. It was, however, linked to an increase in bradycardia and hypotension. They should be used with caution in patients with acute decompensated HF because they can limit forward flow and worsen renal failure [20].

Considering the pathophysiology of cardiorenal syndrome, we use dopamine as neurohormonal modulation and inotropic therapy. When patient blood pressure was reduced,

dopamine was used to increase the blood pressure and in the hope of taking the renal protective effect. Dopamine is a catecholamine with effects on the β-and α-adrenergic receptors, as well as the renal dopaminergic receptors, resulting in cardiac inotropy, systemic vasoconstriction, and improved renal blood flow [23]. Recent research, on the other hand, has shown mixed results. In the ROSE-HF trial, dopamine administration did not affect cumulative urine volume or renal function in patients with AHF when compared to placebo [24]. According to meta-analysis data, improved urine output was associated with no significant differences in creatinine, rehospitalization, or mortality [25]. Indeed, patient urine output was gradually increasing, followed by decreasing creatinine in serum.

To conclude, another therapy was recommended by The European Society of Cardiology (ESC) for patient with Heart failure, that include ACE inhibition/ARB and β-blockers as first-line therapy, with the addition of a mineralocorticoid receptor antagonist (MRA) for those who remain symptomatic. All this therapy is in conjunction with diuretics, which are used for symptoms or signs of volume overload and congestion. This may be followed by substitution of an angiotensin receptor neprilysin inhibitor (ARNI) for ACE inhibition in selected patients and consideration of RRT in appropriate candidates [1].

4 Conclusion

Early recognition of the cardiorenal syndrome case should be addressed in every patient with cardiac and/or renal disease to prevent the worst progression. Optimal treatment of the heart in cardiorenal syndrome type 2 may also help to improve the renal condition. Whereas inadequate treatment of one organ may lead to the deterioration of the other. Thus balanced, comprehensive, multidisciplinary management should be considered to ensure the patient's long life outcome.

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