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CASE STUDY

Fluctuation of Heart Failure with Preserved Ejection Fraction During the Course of Cardiorenal Anemia Syndrome: A Case Report

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ABSTRACT

Heart failure (HF) with preserved ejection function (HFpEF) has a high prevalence in older adults. HF in the elderly tends to be complicated by renal failure and anemia, known as cardio-renal anemia syndrome (CRAS), with each pathology adversely affecting the other, leading to a negative spiral. The temporal evolution from the onset of HFpEF in CRAS is not well understood. We experienced an elderly case in which the initial onset of CRAS was followed by repeated exacerbations with HFpEF. Multiple medications, including a sodium-glucose cotransporter-2 inhibitor and an angiotensin receptor neprilysin inhibitor, were effective in conjunction with extensive cardiac rehabilitation. Our case highlights the difficulty of treating HFpEF with CRAS.

Keywords: Anemia, cardiorenal syndrome, elderly, iron deficiency.

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1. Introduction

With the aging of society, the prevalence of heart failure (HF) has increased and has been noted as a pandemic [1]. Among older adults, HF with preserved ejection function (HFpEF) predominates at a high rate [2]. The pathogenesis is complex with atrial fibrillation (AF), diabetes mellitus (DM), hypertension, chronic kidney disease (CKD), anemia, iron deficiency, etc. as risk factors [3]. As HF in the elderly tends to be complicated by renal failure (RF) and anemia, as cardio-renal anemia syndrome (CRAS), each pathology adversely affects the other and falls into a negative spiral [4]. Increased early diastolic mitral inflow velocity/early diastolic mitral annulus velocity rate (E/e′) [5], [6] is associated with increased risk of renal events and has been shown to be a new risk factor for CKD progression [7]. On the other hand, deterioration of renal function tends to lead to anemia by reducing the secretion of erythropoietin [8]. Hospitalized HF patients with CRAS had a significantly higher rate of primary outcome (cardiac death, non-fatal myocardial infarction, readmission due to HF) than those without CRAS during an average follow-up of 24 months follow-up period (27.5% vs. 10.7%) [9]. CRAS in chronic HF has increased sympathetic activity [10]. In addition, loop diuretics used in the presence of congestion worsen renal function and further enhance the sympathetic nervous system and the renin-aldosterone system [11], [12].

Meanwhile, the temporal evolution since the onset of HFpEF in CRAS is not well understood. In addition, the management of CRAS with HFpEF in the elderly is complex and a treatment method needs to be established. We experienced an elderly case in which the initial onset of CRAS was followed by repeated exacerbations with left ventricular diastolic dysfunction. The condition was stabilized by the use of multiple medications and comprehensive cardiac rehabilitation. Our case highlights the difficulty in the treatment of HFpEF with CRAS.

2. Case Report

The patient was a woman in her 80s (height 142.7 cm/weight 34.4 kg/body mass index 16.9 kg/m^2) (Fig. 1, Table I). She had gone to a nearby clinic for type 2 DM (T2DM) and hypertension. For cervical myelopathy due to spondylopathy with numbness and muscle weakness in the extremities, she underwent cervical laminoplasty. During this hospitalization, chronic inflammation and iron deficiency anemia of unknown cause were noted, but there were no abnormalities on gastroscopy. On day 0 (20 days after surgery; Fig. 1), she was transferred from

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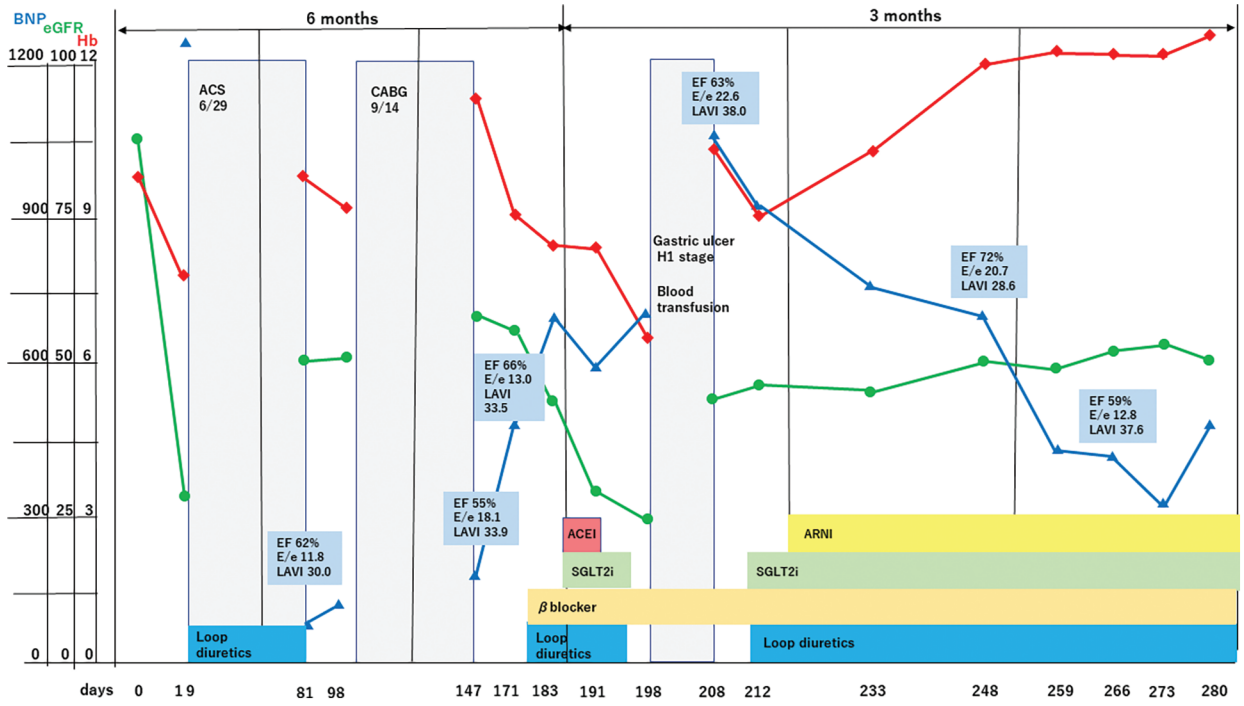

Fig. 1. Clinical course with serial changes in eGFR, Hb, BNP and LV diastolic function.

Patient was repeatedly transferred between acute care hospital (light blue backgrounds) and our convalescent hospital (white backgrounds) over a period of 280 days. Changes in BNP, cardiac function, eGFR, and Hb at our hospital and therapeutic drugs are shown.

At the time of first admission, only anemia was observed and renal function was normal. The first cardiorenal anemia syndrome (CRAS) occurred in association with ACS (day 0–19), and the second CRAS occurred on day 147–198 and were presumed to have occurred due to bleeding from gastric ulcer, and in both events patient was transferred to the acute care hospital for treatment. The third worsening of heart failure was observed at the time of the fourth hospitalization, although it had already started after CABG, but comprehensive cardiac rehabilitation of exercise, oral drug treatment and lifestyle guidance in our hospital improved the CRAS, and the patient was discharged (day 208–280). Hb and eGFR showed contrasting movements with BNP in the first, second and third waves of heart failure. E/e′ showed similar movement to BNP increase or decrease, but LAVI increased early on day 81 and the high level persisted even after treatment, showing poor association with BNP change.

Abbreviations: eGFR, estimated glomerular filtration rate; Hb, hemoglobin; BNP, brain natriuretic peptide; LV, left ventricular; NSTEMI, non-ST elevation myocardial infarction; EF, ejection fraction; E/e′, diastolic mitral inflow velocity/early diastolic mitral annular velocity rate; LAVI, left atrial volume index; CABG, coronary artery bypass grafting; ACEI, angiotensin converting enzyme inhibitor; SGLT2i, sodium glucose transporter 2 inhibitor; ARNI, angiotensin receptor neprilysin inhibitor.

T Hospital, an acute care hospital, to our hospital, a convalescent hospital, for rehabilitation. On day 19, she developed acute HF due to non-ST elevation myocardial infarction (NSTEMI) and was transferred to T Hospital. Severe anemia and worsening renal dysfunction were also observed at the time of transfer. Coronary angiography revealed 3-vessel disease as one of the causes of HF. Initially, conservative treatment was prioritized for acute HF. Loop diuretics were used extensively, and transient deterioration of renal function and anemia were noted. After the HF improved, she was readmitted to our hospital on day 81. On day 107, coronary artery bypass graft (CABG) (LITA-LAD; SVG-4PD; free RITA-HL) was successfully performed. The patency of 3 grafts were determined by angiography 20 days after operation. She was readmitted to our hospital on day 147 for rehabilitation of post-CABG disuse syndrome. During this hospitalization, HF, RF and anemia gradually progressed, so she was transferred to T hospital on day 198, and gastric ulcer (H1 stage) was found on gastroscope, which was suspected to be the source of bleeding. Two units of red blood cell concentrate were transfused and proton pump inhibitor (PPI: vonoprazan fumarate 20 mg/day) was started. She was readmitted to our hospital on day 208. At the time of transfer, she had no symptoms of HF at rest, but brain natriuretic peptide (BNP) was markedly elevated. In the course of hospitalization, shortness of breath on exertion appeared, and gradual cardiac enlargement on chest radiographs, increased BNP level, and deterioration of E/e′ [5], [6] and left atrial volume index (LAVI) on echocardiography [13] were observed. Combined use of a loop diuretic (trasemide 4 mg/day) plus a sodium glucose cotransporter 2 inhibitor (SGLT2i) (empagliflozin 10 mg/day) and an angiotensin receptor neprilysin inhibitor (ARNI; sacubitril-valsartan sodium hydrate 100 mg/day) gradually improved BNP and cardiac enlargement on chest radiograph. Blood pressure also increased, but the addition of amlodipine 5 mg and ARNI 100 mg was effective in lowering blood pressure. Continued administration of oral iron supplements improved anemia. BNP did not normalize but improved, and E/e′ and LAVI showed different transitions, with E/e′ indicating improvement in HF, although the decrease was in tandem, while the improvement of LAVI was poor until the

TABLE I: Serial Body Weight, Laboratory Data at 1st, 3rd and 4th Admissions

	1st admission (day 0)	3rd admission (day 147)	4th admission (day 208)
Body weight (kg)	34.4	32.8	40.5
TP (g/dL)	6.5	7.3	6.7
Alb (g/dL)	2.9	3.5	2.9
AST (IU/L)	19	23	46
ALT (IU/L)	9	19	31
γGTP (IU/L)	19	16	165
BUN (mg/dL)	14	27	28
Cre (mg/dL)	0.51	0.73	0.93
eGFR (mL/min/1m^2)	85.5	57.5	44.1
Na (mEq/L)	135	132	134
K (mEq/L)	3.2	5.1	4.4
Cl (mEq/L)	96	98	101
CRP (mg/dL)	1.0	0.4	0.8
BNP (pg/mL)	–	183.6	1055.4
WBC (/μL)	7500	8600	7900
RBC ($\times 10^4$/μL)	365	358	319
Hb (g/dL)	9.7	11.2	10.2
Ht (%)	29.7	33.1	30.1
Plt ($\times 10^4$/μL)	33.4	33.5	21.6

end. Renal function and anemia stabilized, with clinical symptoms allowing 3Mets of exercise. The patient was discharged with independent activities of daily living. Oral iron preparations (sodium ferrous citrate) were administered at 100 mg/day until day 19 and at 200 mg/day from day 198. Intravenous iron infusion was not used. Serum iron (μg/dL), TIBC (μg/dL), and ferritin (ng/mL) were 27, 158, 293.4 on day 259, and 32, 165, 362.4 on day 280, respectively. The anemia improved and cardiac function remained unchanged 3 weeks after discharge (EF 58.3%; LAVI 30.5; E/e′ 21.4; NT pro BNP 2781; eGFR 59).

3. Discussion

In this case, HF developed twice during the course of approximately 8 months of transfers between acute care hospital and convalescent hospital. In addition to the ischemic event, the first time HF was associated with anemia and RF, and the second time HF was triggered by anemia associated with gastrointestinal bleeding and worsening of RF. Both are based on multiple risk factors: T2DM, hypertension, old age and female, and hyperactivity of sympathetic nervous system and renin-aldosterone system associated with diuretic use. Iron deficiency may have been one of the causes of myocardial dysfunction [14], [15].

3.1. Mechanism of HF (potential link between CRAS and HFpEF)

Treatment of HF with high doses of diuretics without improvement of anemia resulted in a significant decline in renal function in this case. In patients with STEMI, complications of acute HF and anemia at presentation are associated with worse short- and long-term outcomes than in the presence of either alone due to their interaction [16]. This case was NSTEMI rather than STEMI, but the pathological condition was similar to STEMI and it can be said that it is the same case. The cause of anemia in the first admission was chronic inflammation [17], and the cause of anemia in the second admission was inferred to be bleeding from a gastric ulcer. Both were associated with worsening of RF and HF. Iron supplementation and blood transfusion improved anemia and stabilized RF and HF. The cause of chronic inflammation was not identified, so the course of anemia needs to be monitored. The involvement of coronary microvascular endothelial inflammation has been suggested as a cause of HFpEF, and the association with the inflammatory response in this case cannot be ruled out [18]. Iron deficiency causes HF independent of hemoglobin levels [19] and may have been involved as a causative factor in HFpEF in this case.

3.2. Treatments

In the second HF, the dose of diuretics could be reduced by concomitant administration of iron supplements, SGLT2i [20], ARNI [11], [21], [22] which improved HFpEF and stabilized CRAS. ARNI (101 $\pm$ 62 mg/day at baseline and 126 $\pm$ 59 mg/day at study end) for 3 months has been shown to improve anemia and reduce its prevalence in patients with HFrEF [23]. Telmisartan has been reported to improve myocardial fibrosis and diastolic function in cardiorenal syndrome with HFpEF [24], and a similar mechanism may have worked in ARNI. Iron deficiency is not only a cause of anemia, but also causes heart failure, and iron supplementation improves the severity of HF even if without anemia [25]. In our case, iron deficiency (Fe/TIBC $<$ 20%) [26] was detected even when oral iron supplements were administered at 200 mg/day. Ferritin was higher than 200, but was unreliable as an assessment of iron deficiency due to the influence of chronic inflammation. Although the anemia improved, it is possible that the use of intravenous iron infusion may have further improved cardiac function [17].

3.3. Limitations

In our case, there are several imitations as follows. First, data on cardiac function and BNP before the onset of the first HF event were not obtained. Second, temporal data on serum iron, transferrin, and ferritin were not obtained. Third, long-term follow-up data was lacking. Fourth, E/e′ was measured only on the septal side.

4. Conclusions

We experienced a case of CRAS with repeated HF events during an 8-month hospital stay for rehabilitation after orthopedic surgery. In both HF events, it was concluded that anemia, worsening RF and HFpEF were related, and the third exacerbation improved with treatments. In our case, HFpEF appeared as a form of HF in association with CRAS and iron deficiency, and E/e′ [5], [6] and LAVI [13] showed different trends. In CRAS, it is important to continuously assess not only HF but also renal function, anemia and iron deficiency during treatment.

Competing Interests

Authors have declared that no competing interests exist.

The patient gave a written informed consent that permitted to use her data for publication in this journal.

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