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Letter

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A Case of Multiple Myeloma Presenting with High-Output Heart Failure That Improved with Anti-angiogenesis Therapy

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Conflict of Interest
The authors have no financial conflicts of interest.

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INTRODUCTION

Heart failure (HF) patients usually have a low or normal cardiac output, but some patients complain of HF symptoms even with a high cardiac output. These patients are diagnosed with high-output heart failure (HOHF). HOHF has various etiologies including obesity, liver disease, arteriovenous fistula, lung disease, and myeloproliferative disease. Although its pathophysiology is not clearly understood, it is known that there is increased microvascular density, low systemic vascular resistance caused by an arteriovenous shunt, and increased cardiac output due to vasodilation and elevated oxygen consumption that is due to higher metabolism and body mass.[1)]

The proportion of myeloproliferative disorders among all HOHF is rare, but proper treatment is important because mortality is high if they go untreated.[1)2)] These cases do not respond to treatment of HF in general, but rather are improved by chemotherapy alone. Therefore, in HOHF patients, it is most important to understand the etiology of the disease. There have been few cases of HOHF caused by myeloproliferative diseases.

CASE

A 75-year-old Korean woman with history of a compression fracture presented with a chief complaint of dyspnea on exertion, which occurred six months ago. Her symptoms presented a week ago and were accompanied by worsening shortness of breath and upper respiratory infection symptoms. The patient was admitted to the emergency room. On examination, she was afebrile with a heart rate of 100 beats/minute and a blood pressure of 141/63 mmHg. Her oxygen saturation was 98% on room air. She had faint crackles at the base of her lungs bilaterally. Her abdominal examination was benign and her extremities were warm to the touch with 2+ bilateral lower extremity edema. Initial laboratory studies revealed a hemoglobin level of 9.7 g/dL, platelet count of 109,000 /μL, N-terminal pro-brain natriuretic peptide (NT-proBNP) of 5,615 pg/mL, blood urea nitrogen of 10.6 mg/dL, creatinine of 0.76 mg/dL, albumin of 4.1 g/dL, and calcium of 8.7 mg/dL. Her electrocardiogram demonstrated

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normal sinus rhythm and normal voltage. An echocardiogram with Doppler conveyed hyperdynamic left ventricular ejection fraction (LVEF) of 66%, no regional wall motion abnormalities, diastolic dysfunction, right atrium dilatation, right ventricle dilatation, and moderate tricuspid valve regurgitation (TR) with a right ventricular systolic pressure (RVSP) of 58 mmHg. Her initial diagnoses were heart failure with preserved ejection fraction (HFpEF), pulmonary hypertension, and anemia. No inducible myocardial ischemia was identified by methoxyisobutylisonitrile single photon emission computed tomography, and there were no specific findings by endoscopy or colonoscopy performed during her anemia workup. Bronchial wall thickening and luminal narrowing were confirmed by chest computed tomography (CT). However, no specific findings resulted from the pulmonary function test. Thyroid function test was confirmed in the normal range and hyperthyroidism could be excluded. There was no abnormality in the liver function profile, and there was no liver disease and large arteriovenous malformation in abdomen-pelvis CT performed by anemia workup. On day 11 of hospital treatment with 80 mg intravenous furosemide, the patient was moved to the intensive care unit due to dyspnea aggravation. Echocardiography was performed, revealing a LVEF of 55% and moderate TR (RVSP = 46 mmHg). Lab findings showed elevated serum kappa 6.23 mg/dL and lambda 110 mg/dL. We then identified a 3% elevation in reactive lymphocytes by a peripheral blood (PB) smear, decreased gamma globulin by serum protein electrophoresis (PEP), and albuminuria with proteinuria in the beta region by urine PEP. Daily administration of the oral diuretics furosemide (15 mg) and spironolactone (50 mg) was not sufficient to maintain euvolemia, resulting in re-aggravation of pulmonary edema. Follow-up laboratory studies revealed a hemoglobin of 8.9 g/dL, platelet count of 124,000 /μL, NT-proBNP of 2,305 pg/mL, blood urea nitrogen of 47.5 mg/dL, and creatinine of 1.37 mg/dL. A 4% increase in plasma cells, a serum kappa level of 285 mg/dL (reference range: 3–19 mg/dL), and a serum lambda level of 10.8 mg/dL (reference range: 5.71–26.3 mg/dL) were identified by a PB smear. A bone marrow biopsy was performed, and plasma cell myeloma was identified based on hypercellular marrow particles with 59.4% plasma cells. An echocardiogram with Doppler conveyed hyperdynamic left ventricular contraction and did not show left ventricular hypertrophy. One interesting finding was that the cardiac index measured by echocardiography was markedly high, with values as high as 9.58 L/min/m^2. Speckle-tracking longitudinal strain analysis was within the reference range (−21.9%), unlike the cardiac amyloidosis, and there was no apical-sparing pattern of the longitudinal strain (**Figure 1**). Global longitudinal strain patten and serum kappa, lambda level and bone marrow biopsy results were consistent with multiple myeloma. Therefore, heart biopsy was not performed to exclude amyloidosis.

To exclude cardiac origin and pulmonary hypertension, coronary angiogram and cardiac catheterization were subsequently performed. Her cardiac output (9.47 L/min; normal range: 4–8 L/min) and cardiac index (6.68 L/min/m^2; normal range: 2.5–4.0 L/min/m^2) were increased, while her systemic vascular resistance (422.43 dsc^{-5}; normal range: 800–1,200 dsc^{-5}) and pulmonary vascular resistance (212.57 dsc^{-5}; normal range: <250 dsc^{-5}) were decreased. The pulmonary capillary wedge pressure (PCWP) was found to be 17 mmHg and the left ventricular end-diastolic pressure (LVEDP) to 19 mmHg. She was diagnosed with HF due to high cardiac output, which is sometimes accompanied by myeloproliferative disorders like multiple myeloma. She was treated with bortezomib (1.36 mg), melphalan (8 mg), and prednisolone (60 mg) combination therapy for the next four weeks, along with oral dexamethasone. Two weeks after the initiation of therapy, she no longer had pulmonary edema according to a chest X-ray and peripheral edema. The bortezomib, melphalan, and prednisolone combination therapy was continued because she remained euvolemic, and she was taken for a repeat echocardiography test. One month after chemotherapy,

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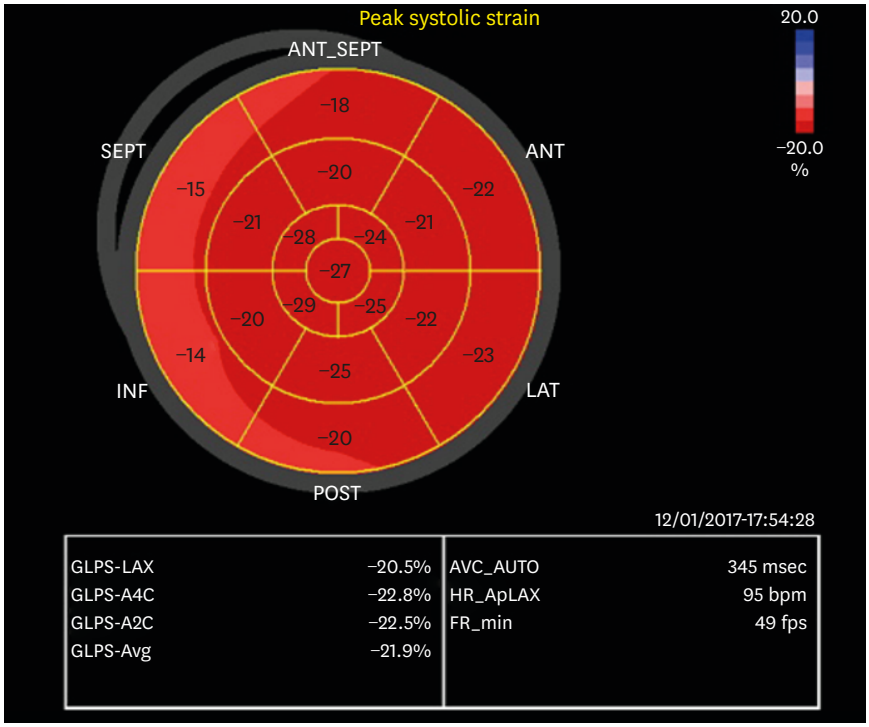

Figure 1. Global longitudinal strain: Bull's Eye Plot. Global longitudinal strain and regional longitudinal strain at the initial echocardiography.
ANT = anterior; GLPS = global longitudinal systolic peak strain; INF = inferior; LAT = lateral; POST = posterior; SEPT = septum; GLPS-LAX = GLPS of apical long axis view; GLPS-A4C = GLPS of apical four chamber view; GLPS-A2C = GLPS of apical two chamber view; GLPS-Avg = generating the average GLPS; AVC_AUTO = aortic valve closure detected automatically; HR_ApLAX = heart rate during the acquisition of the apical long axis view; FR_min = minimum flow rate.

echocardiography showed a LVEF of 59%, mild TR, and a RVSP of 33 mmHg. After 2 months of chemotherapy, NT-proBNP decreased from 2,305 to 1,713 pg/mL. After checmotherapy, the kappa/lambda ratio was markedly reduced (**Figure 2**).

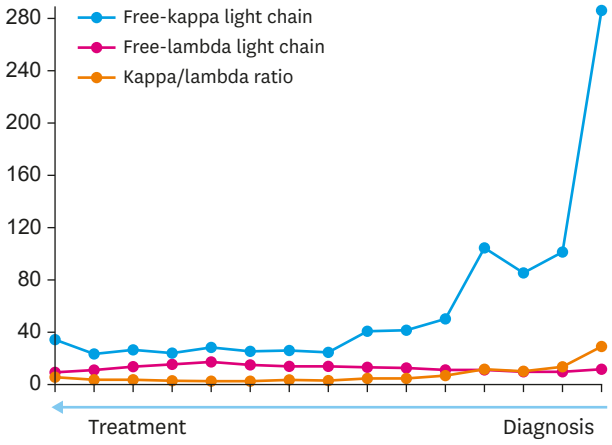

Figure 2. Serum free-kappa light chain (mg/dL), free-lambda light chain (mg/dL), and the kappa/lambda ratio. The rightmost point is the serum free-kappa light chain, free-lambda light chain, and the kappa/lambda ratio at the time of plasma cell myeloma diagnosis. The trends from the right to the left of the graph reflect the decreased kappa/lambda ratio after chemotherapy.

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DISCUSSION

HOHF is an important cause of cardiac failure and is associated with increased mortality.[1-4] Right heart catheterization was performed in Mayo Clinics for 15 years in patients with HF, and the medical records of 120 HOHF patients were obtained, most of which had obesity and liver disease. Myeloproliferative disease patients accounted for 8% of the HOHF patients.[1] Multiple myeloma patients with overloading such as our case do not respond to traditional HF treatment. The main pathophysiology is low systemic vascular resistance,[3][4] which may be associated with increased metabolic demand for tissue perfusion.[5] For example, obesity requires an excess quantity of tissue to perfuse. In cases of myeloproliferative disease diagnosed as extramedullary hematopoiesis, arterial resistance is lower and metabolic demand is higher, resulting in congestion. Traditional HF treatment without diagnosing myeloproliferative diseases may result in worse clinical outcomes and increase mortality. In our case, the patient's dyspnea was poorly controlled by diuretics treatment.

Treating these diseases with traditional HF therapy is not effective. Effective treatments that have been utilized include transcatheter embolization for an intramedullary arteriovenous fistula[6][7] and systemic chemotherapy.[8] Our case was treated with systemic steroids, bortezomib, and mephalan. It is thought that these pharmacologic agents act by various mechanisms such as cytokine suppression, increased host immune response, and inhibition of angiogenesis.[1-5][8] For HOHF, it is important to perform differential diagnosis in patients with clinical HF and normal ejection fraction. In our case, cardiac catheterization, serum kappa levels, and serum lambda levels were confirmed. After bone marrow biopsy was performed, the patient was ultimately diagnosed with plasma cell myeloma.

CONCLUSION

Clinical HF includes not only pump failure, but also functional impairment and abnormalities external to the heart that affect vascular load and metabolism. HOHF must be considered in the differential diagnosis of patients presenting with HFpEF. HOHF may be under-diagnosed in patients with myeloproliferative disease like multiple myeloma.

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