INTERNAL MEDICINE

□ CASE REPORT □

Improvement of Cardiac Function after Granulocyte-colony Stimulating Factor-mobilized Peripheral Blood Mononuclear Cell Implantation in a Patient with Non-ischemic Dilated Cardiomyopathy Associated with Thromboangiitis Obliterans

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Abstract

Cardiac involvement is a rare complication with thromboangiitis obliterans (TAO). We report a 29-year-old man with TAO accompanied with non-ischemic dilated cardiomyopathy. He had no history of heart disease, but echocardiogram demonstrated diffuse hypokinesis and dilated left ventricle. Coronary angiography revealed no organic stenotic lesion. For limb salvage, he was treated with granulocyte-colony stimulating factor (G-CSF)-mobilized peripheral blood mononuclear cell (PBMNC) implantation on his right leg. Not only ischemic leg symptoms, but also plasma level of BNP and ^{123}I-metaiodobenzylguanidine scintigraphic parameters improved after 24 weeks. G-CSF-mobilized PBMNC implantation could be an effective approach to treating non-ischemic cardiomyopathy.

Key words: peripheral blood mononuclear cell implantation, dilated cardiomyopathy, thromboangiitis obliterans, ^{123}I-metaiodobenzylguanidine, G-CSF

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Introduction

Recent experimental and clinical studies have shown that bone marrow-derived cell therapy directly into the heart for myocardial infarction improves cardiac function and neovascularization (1-3). Mobilization of bone marrow cells into the peripheral blood by certain cytokines, such as granulocyte-colony stimulating factor (G-CSF), offers a non-invasive therapeutic strategy for the regeneration of the myocardium after myocardial infarction (4, 5). In addition to mobilization, G-CSF has been reported to promote survival of cardiac myocyte and prevent left ventricular remodeling after myocardial infarction (3, 6-9). Cardiac myocyte death occurs in end-stage heart failure and may contribute to myocardial dysfunction both in ischemic and dilated cardiomyopathy (10), hence G-CSF is promising not only for the treatment of cardiac ischemia, but also for non-ischemic heart failure (11, 12).

Thromboangiitis obliterans (TAO), or Buerger's disease is a nonatherosclerotic, segmental vasculitis that most commonly affects the small and medium-sized vessels of the limb, but cardiac involvement is rare (13, 14). We report a case of non-ischemic dilated cardiomyopathy associated with TAO. G-CSF-mobilized peripheral blood mononuclear cell (PBMNC) implantation into the leg was performed for his critical limb ischemia with successful improvement of ischemic symptoms. Furthermore, the elevated plasma level of brain natriuretic peptides decreased after this treatment. Although echocardiography showed no remarkable improvement of left ventricle ejection fraction, fractional shortening or left ventricle diameter, both heart to mediastinum ratio and washout ratio of ^{123}I-metaiodobenzylguanidine improved after 24 weeks.

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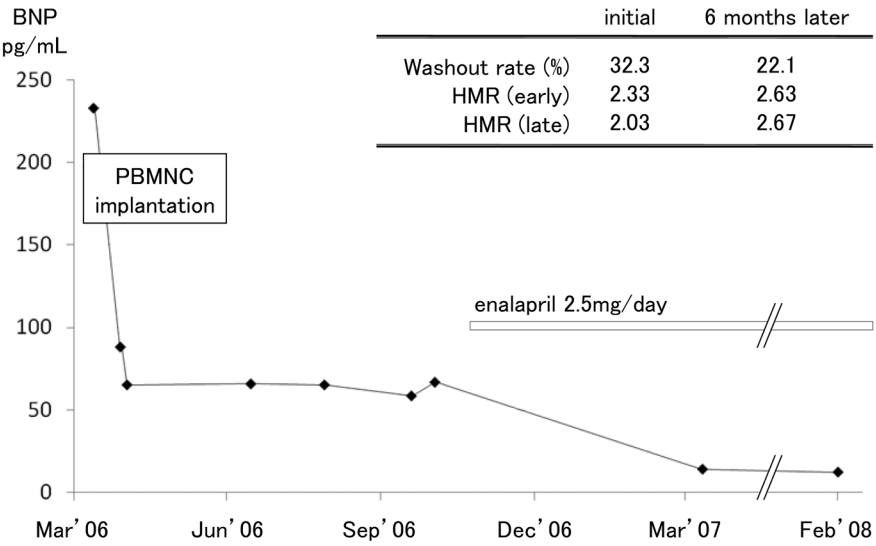

Figure 1. **Clinical course. Plasma level of brain natriuretic peptide (BNP) decreased from 233 to 88 pg/mL at 14 days and 65 pg/mL at 18 days after G-CSF-mobilized PBMNC implantation. After administration of ACE inhibitor, plasma BNP levels further decreased to the normal range. PBMNC: peripheral blood mononuclear cells, HMR: heart to mediastinum count ratio**

Case Report

A healthy 29-year-old man was referred to our hospital because of 5 month history of intermittent claudication and 3 month history of non-healing ischemic ulcer of the 1st, 2nd, and 5th toes of right foot accompanied by rest pain despite conventional medical therapy and wound care. He had a history of tobacco smoking (0.5 pack per day) for 5 years, but he had stopped 2 months prior to admission. He had no history of hypertension, diabetes, dyslipidemia, or heart diseases. He had no family history of heart disease. On admission, his blood pressure was 120/60 mmHg, and pulse rate was 92 beats/min. Physical examination was unremarkable in the heart or respiratory sounds, but no palpable pulses of bilateral popliteal, posterior tibial or dorsal pedal arteries. Brachial and radial arterial pulses were palpable. Laboratory findings showed no abnormalities including inflammatory reactions, commonly measured autoantibodies, or coagulation tests, except for a marked increase of the plasma level of brain natriuretic peptide (BNP, 233 pg/mL), and an elevated plasma homocysteine level (13.2 mmol/L). Angiography showed total occlusion of the right superficial femoral artery and the distal area was filled with collateral small vessels. Although he had no history of heart disease and no antecedent symptoms suggesting myocarditis or congestive heart failure, an electrocardiogram showed inverted T wave in leads I, aV_L and $V_{4\text{-}6}$. Chest X-ray showed the cardiothoracic ratio of 40% with no evident pulmonary congestion. Transthoracic echocardiography demonstrated diffuse hypokinesis and dilatation of the left ventricular (LV); LV diastolic dimension 60 mm, LV systolic dimension 51 mm, with an ejection fraction (LVEF) of 33% and fractional shortening of 15%. Technetium ^{99}m-tetrofosmin myocardial perfusion scintigraphy on exercise revealed no ischemic lesion but a dilated left ventricle. Contrast-enhanced cardiac magnetic resonance examined at 7 weeks after G-CSF-mobilized PBMNC implantation showed no late gadolinium enhancement suggesting that myocardial inflammation observed in acute or chronic myocarditis is less likely.

His ischemic leg symptoms were severe, and he refused to have further cardiac examination or medical treatment such as angiotensin converting enzyme (ACE) inhibitor or β-blocker for his heart disease. Despite smoking cessation and conventional medical therapy, his skin ulcer and rest pain did not improve; hence, we performed G-CSF-mobilized PBMNC implantation on his right leg as we previously reported (15). Briefly, after administration of 10 $\mu g \cdot kg^{-1} \cdot day^{-1}$ G-CSF by subcutaneous injection for 5 days, PBMNC were harvested using an AS104 cell separator and concentrated PBMNC were injected into the right leg muscle at the 4th and 5th day in a total of 180 sites. Pain relief was observed 2 weeks after G-CSF-mobilized PBMNC implantation and bodily pain subscale rating on the short form-36 was improved from 10 to 22 at 2 weeks, and 74 at 48 weeks after G-CSF-mobilized PBMNC implantation. The ischemic ulcer had been covered with normal skin except for the 2nd toe. Because healing by granulation tissue could not be achieved over the exposed necrotic toe bone of the 2 nd toe, minor amputation through the distal phalanx was done at 16 weeks after G-CSF-mobilized PBMNC implantation. Maximum walking distance significantly increased from 0 m to 624 m at 12 weeks and more than 1,200 m at 48 weeks. No adverse events especially associated with LV dysfunction and cardiac arrhythmias occurred during and after G-CSF-mobilized PBMNC implantation. Rather, plasma level of BNP decreased from 233 to 88 pg/mL at 14 days and 65 pg/mL at 18 days after G-CSF-mobilized PBMNC

implantation. He finally agreed to have further cardiac evaluation, since his ischemic rest pain relieved. ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy examined at 4 weeks after G-CSF-mobilized PBMNC implantation showed diffusely reduced uptake of the myocardium and the heart to mediastinum count ratio (HMR>2.0) of 2.33 in the early phase and 2.03 in the delayed phase, and increased washout ratio (WR<22) of 32.4%. Coronary angiography which was done at 6 months after G-CSF-mobilized PBMNC implantation, showed no organic stenosis of the coronary arteries. Right ventricular catheterization was normal. Left ventriculography showed diffuse hypokinesis of LV and LVEF of 43%. Endomyocardial biopsy of LV revealed mild degeneration of cardiomyocyte and interstitial fibrosis without any obvious inflammation. These results were compatible with dilated cardiomyopathy (DCM). Plasma BNP level has been maintained at about 65 pg/mL for 24 weeks (Fig. 1). Despite the fact that the transthoracic echocardiographic parameters showed no significant change, ^{123}I-MIBG scintigraphic parameters improved 24 weeks later; there was an increase of HMR from 2.33 to 2.63 in the early phase and 2.03 to 2.67 in the delayed phase and a decrease of WR from 32 to 20. He accepted administration of ACE inhibitor (enalapril 2.5 mg/d); he was treated with ACE inhibitor from 24 weeks after G-CSF-mobilized PBMNC implantation. The level of plasma BNP further decreased from 66.3 pg/mL to 13.8 pg/mL, and the LVEF and the LV diameter in an echocardiogram normalized at 24 weeks after administration of ACE inhibitor; LVDd 52 mm, LVDs 40 mm, LVEF 46%, and FS 23%. Sustained improvements of ischemic limb symptoms such as rest pain and maximal walking distance continued up to 34 months in the follow-up period. The follow-up echocardiogram at 33 months after G-CSF-mobilized PBMNC implantation also showed sustained improvement, with LVDd 47 mm, LVDs 35 mm, LVEF 50%, and FS 26%.

Discussion

We reported a rare case of non-ischemic DCM in a patient with TAO. Not only his ischemic leg symptoms but also his cardiac functions monitored by the level of plasma BNP and MIBG scintigraphic parameters improved after G-CSF-mobilized PBMNC implantation on his ischemic leg.

This is the first report of a case of non-ischemic DCM associated with TAO. The etiology of TAO is still uncertain; tobacco smoking is critical to its onset, progression and recurrence (13). Although some epidemiological studies have shown that tobacco smoking increases the risk of idiopathic DCM (16), a recent multi-hospital case-control study in Japan showed that the odds ratio of tobacco smoking under 20 per day for DCM is 1.09 (17). Further, most TAO patients have a history of tobacco smoking, but cardiac complications, even coronary artery disease, are a rare complication of TAO (13, 14). Immunological abnormalities may involve both TAO and DCM but the precise mechanism is still unknown (18, 19).

The present patient could not walk well because of ischemic leg symptoms, so his bed rest level did not differ between before and 2 weeks after G-CSF-mobilized PBMNC implantation when pain relief started. His body weight and hematocrit level did not change during the treatments, suggesting that volume status did not affect plasma BNP level. Medical treatments were not changed during G-CSF-mobilized PBMNC implantation. Therefore, the reduction of plasma BNP level is mainly affected by G-CSF-mobilized PBMNC implantation. The decreased plasma BNP level sustained for 24 weeks after G-CSF mobilized PBMNC implantation. After administration of ACE inhibitor, plasma BNP levels further decreased to the level of normal range. Improvement of cardiac function detected by echocardiography such as reduced LV chamber size and increased LVEF was observed after ACE inhibitor administration.

His ischemic leg symptoms were so severe that he refused to have further cardiac examinations or medical treatment such as β-blocker or ACE inhibitor before G-CSF-mobilized PBMNC implantation; therefore, first MIBG scintigraphy was done at 1 month after G-CSF-mobilized PBMNC implantation. MIBG scintigraphy is now used as a useful tool for detecting abnormalities of the myocardial adrenergic nervous system in patients with heart failure (20, 21). MIBG abnormalities are correlated with LVEF, New York Heart Association functional class, and histopathological abnormalities (22, 23). Furthermore, MIBG abnormalities preceded deterioration in LVEF, and MIBG imaging reveals improvement before echocardiographic improvement, indicating that MIBG imaging is a more sensitive tool for monitoring cardiac functions (20, 24). Abnormalities in cardiac sympathetic activity contribute to the progression of heart failure, and recent studies reported a potential role of MIBG scintigraphy in predicting the therapeutic response to medical treatments such as β-blocker or ACE inhibitor in patients with heart failure (25, 26). In the present patient, improvement of MIBG parameters such as an increase of HMR and decrease in WR preceded that in echocardiographic changes, and responded well to ACE inhibitor. Most of the recent studies about the cell-based therapy for ischemic heart disease monitored cardiac function by LVEF, LV size, or LV scar size (2, 3, 5), which may prove difficult to truly reflect the effects of cell-based therapy. Our results indicate that MIBG scintigraphy may be a more sensitive tool for detecting the effects of cell-based therapy.

There are several possibilities concerning the serial change in cardiac function after G-CSF-mobilized PBMNC implantation. G-CSF per se has been reported to prevent LV remodeling and dysfunction after myocardial infarction. G-CSF mobilizes stem cells or progenitor cells from bone marrow into injured myocardium and accelerate myocardial or endothelial regeneration (3, 4, 7, 8). G-CSF also protects cardiomyocytes and endothelial cells from apoptotic cell death (9). In the clinical setting however, the efficacy of G-

CSF administration in patients with acute myocardial infarction is still controversial. A recent meta-analysis, which evaluated the effect of G-CSF on myocardial regeneration on the basis of the data generated by randomized, controlled trials of G-CSF after acute myocardial infarction showed that neither LVEF nor the infarct size were improved by G-CSF administration (5). In contrast, Abdel-Latif et al reported that bone marrow-derived cell transplantation in patients with acute myocardial infarction and chronic ischemic heart disease improved LVEF and decreased infarct scar size (2). These results suggest the possibility that the combination of G-CSF and PBMNC implantation improved the cardiac function in our patient.

Most of the cell-based therapies are done for ischemic heart disease, but Ogawa et al reported a case that showed the transient improvement of LV function after allogenic peripheral blood stem cell transplantation in a patient with myelodysplastic syndrome and DCM (27). Three months after cell therapy, LV volumes decreased and LVEF increased, however, 10 months later, the beneficial effects of cell therapy were lost (27). A recent clinical study showed that G-CSF administration improved physical performance not only for patients with ischemic cardiomyopathy but also for DCM (28). These results suggest that neovascularization is unlikely to be the mechanism of action of G-CSF-mobilized PBMNC implantation on cardiac function. Direct action on the cardiac adrenergic nervous system may be involved with the effect of G-CSF-mobilized PBMNC implantation.

There is still a possibility that the cause of cardiac dysfunction was acute myocarditis, and spontaneous improvement independent of the treatment may have occured in our patient, however, Agostini et al reported that no reversibility of MIBG uptake was obtained 6 months later in patients with acute myocarditis (29). Furthermore, experimental data showed that the transfer of endothelial progenitor cells improved in attenuating myocardial damage in rats with DCM induced following myocarditis (30).

Our report suggests that PBMNC implantation with G-CSF could be an effective approach to treating non-ischemic heart failure, though the exact mechanisms of the improved cardiac function are still unclear.

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