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ORIGINAL ARTICLE

Allogeneic transplantation of umbilical cord-derived mesenchymal stem cells for diffuse alveolar hemorrhage in systemic lupus erythematosus

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Abstract Umbilical cord-derived mesenchymal stem cell transplantation (UC-MSCT) has been proved to be effective in the treatment of systemic lupus erythematosus (SLE), based on animal experiments and clinical trials. Diffuse alveolar hemorrhage (DAH) is a rare complication of SLE with a high mortality usually over 50%. This study aimed to assess the efficacy of UC-MSCT in the treatment of SLE-associated DAH. Four SLE patients complicated with DAH, who underwent UC-MSCT, were included. Clinical changes before and after transplantation were assessed by measurements of hemoglobin, platelet level, oxygen saturation, and serological factors. High-resolution CT (HRCT) scans of the chest were performed to evaluate pulmonary manifestation. All the four patients showed dramatic improvements of their clinical manifestations. Hemoglobin was elevated after UC-MSCT and was sustained at a normal level 6 months after UC-MSCT in the four patients. Platelet level was upregulated in two patients who had thrombocytopenia at baseline. Oxygen saturation appeared to be normal at 1 month after UC-MSCT, and this result was confirmed by the HRCT scan of the chest. Serum albumin elevated to 3.5 g/dl 6 months after transplantation. Our findings suggest that UC-MSCT results in amelioration of oxygen saturation as well as hematological and serologic changes, which revealed that UC-MSCT could be applied as a salvage strategy for DAH patients.

Keywords Diffuse alveolar hemorrhage · Mesenchymal stem cells · Systemic lupus erythematosus · Transplantation

Introduction

Diffuse alveolar hemorrhage (DAH) is a rare pulmonary complication of systemic lupus erythematosus (SLE) with a frequency ranging from 0.52% to 5.7% [1–4]. Once the patients are diagnosed with DAH, it is usually life-threatening. The mortality rate is over 50% [1, 4, 5]. Though the pathogenesis of DAH is not very clear yet, Hughson MD et al. [6] suggested that it might be related to the immune complex deposition in alveolar wall and the induction of apoptosis in alveolar macrophages and other smaller cells.

DAH may be the initial manifestation of SLE [2, 5]. The most common symptoms include hypoxemia, dyspnea, cough, and fever, while hemoptysis is less frequent [1, 3, 5, 7]. Renal involvement is the most common extrapulmonary presentation. Renal failure is reported to be associated with the high mortality. Besides, thrombocytopenia, requirement for mechanical ventilation, infection, and high APACHE II (Acute Physiology, Age and Chronic Health Evaluation) also contribute to the high mortality [1, 3–5]. Immunosuppressive therapies including high-dose steroids and cyclophosphamide (CYC), which may decrease the high mortality, should be started immediately after diagnosis. Plasmapheresis may be useful for patients who are not responsive to the above regimens [8]. In recent years, SLE-associated DAH treated successfully with rituximab without CYC administration has been reported in some cases, but lacks larger-scale clinical studies [9–11].

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Mesenchymal stem cells (MSCs) are key components of bone marrow, which form a unique bone marrow niche with hematopoietic stem cells and possess immunomodulatory properties. They also have the ability to self-renew and differentiate into various cell lines. In the past two decades, MSCs have been shown to reside within the connective tissues of many organs [12]. Besides bone marrow, they can also be isolated from skeletal muscle [13], adipose tissue [14], umbilical cord [15], and so on. MSCs that especially derived from umbilical cord and bone marrow have been used as an effective treatment strategy for autoimmune diseases. We have reported the successful treatment of SLE-associated DAH by umbilical cord-derived mesenchymal stem cell transplantation (UC-MSCT) in a case which was followed up for 8 months [16]. In this study, we aimed to determine the clinical effects of UC-MSCT on SLE-associated DAH in four cases, including the one that previously reported and followed up for more than 2 years to get the safety profile.

Methods and materials

Patients

We retrospectively reviewed the medical records of four female SLE patients who were admitted between April 2009 and December 2010 to the Affiliated Drum Tower Hospital of Nanjing University Medical School and received UC-MSCT, ranging in age from 19 to 46 years. All patients met the American College of Rheumatology criteria for the classification of SLE [17]. The DAH inclusion criteria were defined as the presence of new infiltrates on chest radiographs, an acute drop of hemoglobin of at least 1.5 g/dl without evidence of an obvious bleeding, and one or more of the following symptoms and signs: dyspnea, hemoptysis, and hypoxemia. All patients received antibiotics and corticosteroids once DAH was diagnosed. Immunoglobulin at a dose of 10–20 g for at least 3 days and washed red blood cells were infused for supportive treatment. Platelet transfusion was performed if the patient had a thrombocytopenia.

UC-MSCT

None of the four patients responded to the traditional immunosuppressive therapy but underwent deteriorated physical conditions and laboratory index. We gave allogeneic UC-MSCT to each patient under their consent and the permission of the Ethics Committee of Drum Tower Hospital. Umbilical cord-derived mesenchymal stem cells (UC-MSCs) were prepared by the Stem Cell Center of Jiangsu Province as previously described [16]. One million cells per kilogram of bodyweight were infused intravenously. After transplantation, all the patients were followed up, and the doses of glucocorticoid as well as immunosuppressants were tapered if the patients' conditions were improved.

Laboratory tests

Hemoglobin (Hb), platelets, oxygen saturation, and serum albumin were detected. High-resolution CT (HRCT) scan of the chest was performed.

Statistical analysis

Statistical analysis was performed using GraphPad Prism software (version 5). The paired sample t test was used to detect the data for each patient before and after transplantation. $P<0.05$ was considered as statistically significant.

Results

Patient information

From April 2009 to December 2010, four female patients with SLE-associated DAH at a mean age of 32±15 years (19, 20, 44, and 46, respectively) were admitted and received UC-MSCT. Their disease durations were ranging from 15 days to 14 years (2 months, 2 months, 15 days, and 14 years, respectively) for SLE and from 15 days to 1 month (1 month, 11 days, 15 days, and 1 month, respectively) for DAH. Their mean length of follow-up was 15.75±6.65 months. As shown in Table 1, all the four patients demonstrated hemoptysis, and three of them had dyspnea. Patient 3 had obvious evidence of bleeding including gingival and vaginal bleeding. The management protocol for each patient before UC-MSCT was shown in Table 2.

Improvement of clinical symptoms

After UC-MSCT, all the four patients got free of hemoptysis and dyspnea within 1 week, and cough was ameliorated. Patient 2 with severe hypertension exhibited gradual down-regulation, from 180/100 mmHg to 125/61 mmHg 1 week following UC-MSCT. Gingival and vaginal bleeding were stopped in patient 3.

Changes in hematological status

All the four patients had severe anemia (Hb, 4.60±1.78 g/dl) at baseline, and Hb levels were dramatically elevated 1 week (7.55±1.25 g/dl, $n=4$, $P=0.035$) and 1 month (7.97±1.35 g/dl, $n=3$, $P=0.042$) after transplantation. Patients 1, 3, and 4 achieved a normal level of Hb (15.1 g/dl, 11.1 g/dl, and 12.1 g/dl, respectively) at 6 months and maintained Hb level above 11 g/dl at following visit times (Fig. 1a). Patient 3

Table 1 Demographic and clinical characteristics of patients with SLE-associated DAH

Patient no.	Sex	Age (years)	Disease duration[a]	Clinical manifestations	Length of follow up (months)
1	F	19	1 month	Hemoptysis, anemia, dyspnea, cough	24
2	F	20	2 months	Hemoptysis, anemia, dyspnea, severe hypertension	9
3	F	44	15 days	Hemoptysis, anemia, cough, gingival and vaginal bleeding, peliosis, melena	12
4	F	46	1 month	Hemoptysis, anemia, dyspnea, cough	18

SLE systemic lupus erythematosus, *DAH* diffuse alveolar hemorrhage

[a] From diagnosis of DAH to transplantation

appeared with gingival bleeding and peliosis as her initial manifestations. Laboratory tests showed a marked reduction of platelet with only 1×10^9/l. It was up to 4×10^9/l 1 day after UC-MSCT and kept increasing in the next days. Prednisone was tapered as the platelet level rose to 62×10^9/l 2 weeks later. It was sustained at a level of about 160×10^9/l after 6 months follow-up. Patient 4 also exhibited reduced platelet level with 30×10^9/l and reached 67×10^9/l 6 months after UC-MSCT. Though it is still lower than the normal level, it was sustained at a level of about 80×10^9/l in recent months (Fig. 1b).

Changes in serologic features

All the four patients had reduced serum albumin (3.01± 0.23 g/dl), and the levels gradually rose to normal 1 month after UC-MSCT (3.56±0.33 g/dl) and sustained in the subsequent visits (Fig. 2).

Amelioration of oxygen saturation

Three of the four patients who had dyspnea showed decreased oxygen saturation less than 90% (79±8%), and this measure improved significantly 1 week (95±1%, n=3, P=0.032) and 2 weeks (97±1%, n=3, P=0.022) after UC-MSCT. Patient 2 achieved a level of 99% since 2 weeks after transplantation. For patients 1 and 4, oxygen saturation was sustained at a level above 97% without oxygen aspiration 1 month later (Fig. 3).

Improvement of the infiltrates on chest radiographs

The initial chest HRCT scans showed bilateral, diffuse alveolar infiltrates, and no improvements were observed after the classical immunosuppressive therapy (Fig. 4a, d, g). About 1 week after UC-MSCT, complete resolution of the lung infiltrates was seen in the HRCT scan (Fig. 4b, e, h), and the results maintained stable along the follow-up periods (Fig. 4c, f, i).

Relapse and adverse event

Patient 1 had a relapse of DAH caused by a common cold 3 months after the first transplantation, with severe hemoptysis and dyspnea. HRCT scans showed diffuse infiltration on both lobes of the lung. She was given a second UC-MSCT after her unresponsiveness to 2 weeks conventional therapies. Clinical symptoms improved after the transplantation, and she went back to school to continue her studies after being followed up for more than 2 years. All the patients tolerated well, and no adverse event was observed during or after UC-MSCs infusion.

Table 2 Treatment before and after UC-MSCT for patients with SLE-associated DAH

Patient no.	Treatment before UC-MSCT	Treatment after UC-MSCT[a]
1	MP 40 mg/day, HCQ 0.4 g/day (×6 weeks); MP 500 mg/day (×6 days); IG 20 g/day (×3 days)	P 5 mg/day, HCQ 0.2 g/day
2	MP 60 mg/day (×6 weeks), 120 mg/day (×3 days), 240 mg/day (×3 days), 500 mg/day (×1 day), 1,000 mg/day (×2 days), IG 10 g/day (×10 days)	P 5 mg/day, CsA 100 mg/day
3	MP 250 mg/day (×3 days), 500 mg/day (×3 days), IG 10 g/day (×6 days), 20 g/day (×2 days), MP 40 mg/day (×5 days), CYC 0.4 g/biw (×5 times), vincristine 2 mg/week (×1 time)	P 10 mg/day, CYC 0.6 g/2 months
4	P 10 mg/day, HCQ 0.4 g/day, CYC 0.4 g/2 weeks	P 10 mg/day, HCQ 0.2 g/day

UC-MSCT umbilical cord-derived mesenchymal stem cell transplantation, *SLE* systemic lupus erythematosus, *DAH* diffuse alveolar hemorrhage, *MP* methylprednisolone, *IG* immunoglobulin, *P* prednisolone, *CsA* ciclosporin A, *CYC* cyclophosphamide, *HCQ* hydroxychloroquine, *biw* biweekly

[a] At the last follow-up

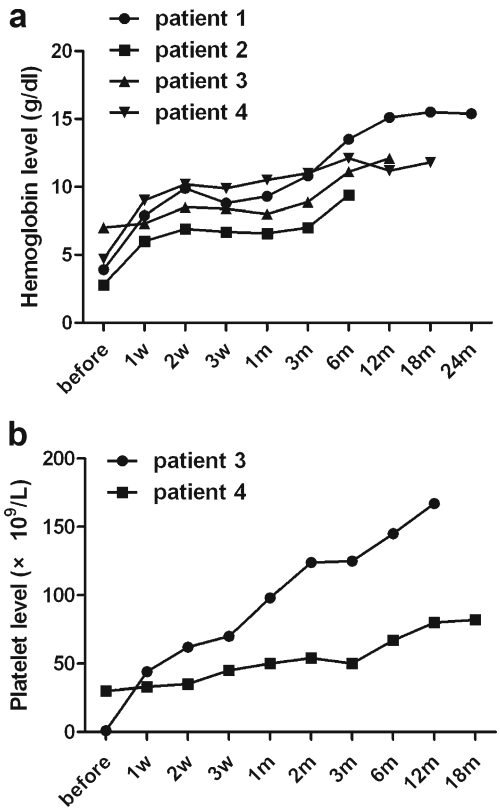

Fig. 1 **a** Hemoglobin levels before and after mesenchymal stem cell transplantation (MSCT) in each patient. **b** Levels of platelet before and after MSCT in patients 3 and 4. *w* week, *m* month

Discussion

Recent studies have suggested that MSCs may have therapeutic applications in several clinical disorders. For SLE, both animal experiments and clinical trials have shown a significant amelioration of the disease activity by mesenchymal stem cell transplantation (MSCT) [18–22]. Besides, more and more data indicate that MSCT attenuates acute lung injury (ALI) in mice [23–25]. Lee JW et al. [26] further

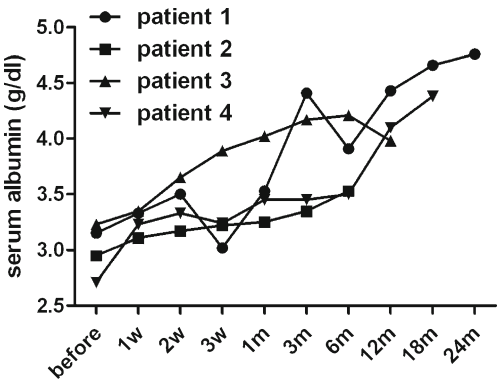

Fig. 2 Serum albumin levels in each patient before and after umbilical cord-derived mesenchymal stem cell transplantation (UC-MSCT). *w* week, *m* month

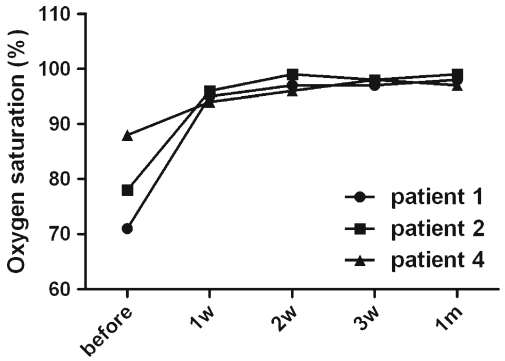

Fig. 3 Levels of oxygen saturation before and after umbilical cord-derived mesenchymal stem cell transplantation (UC-MSCT) in three patients. *w* week, *m* month

defined the therapeutic potential of MSCs in *Escherichia coli* endotoxin-induced ALI in the ex vivo-perfused human lung. These results indicated that MSCT might be useful in the treatment of SLE-associated DAH. However, Carrion F and colleagues [27] performed autologous MSCT in two SLE patients, and no effect on disease activity was seen. We have previously shown that BM-MSCs from SLE patients demonstrate early signs of senescence and have abnormal functions [28], which may make allogeneic MSCT effective in the treatment of SLE and may explain the inefficacy of autologous MSCT.

In this study, all the four patients received intravenous high dose of steroids once they were diagnosed with DAH. Furthermore, transfusion of washed red blood cells and immunoglobulin was added. None of them responded to the management protocol with a continuing drop of Hb. In order to explore a new way to improve the disease, we first considered the possibility of UC-MSCT. All the four patients stopped hemoptysis, and the intractable dropping of Hb was reversed after UC-MSCT. Severe high blood pressure was downregulated in patient 2, and platelet level rose up in patients 3 and 4. Normal oxygen saturation and daily activities without dyspnea suggested an improved pulmonary function. To confirm this, HRCT scan of the chest was performed and showed a consistent result. What is most important, during 9 to 24 months follow-up after transplantation, the doses of steroid as well as immunosuppressive drugs were tapered and combined with sustained disease improvements. Two of the four patients discontinued immunosuppressive agents since 14 and 6 months after MSCT (patients 1 and 4, respectively). Furthermore, a second MSCT was given to patient 1 to overcome the relapsed severe hemoptysis and dyspnea, and the patient still tolerated well and received complete response. No side effect occurred in any of them. All of these lines of evidence supported that UC-MSCT may explore a more extensive usage in the treatment of SLE-associated DAH.

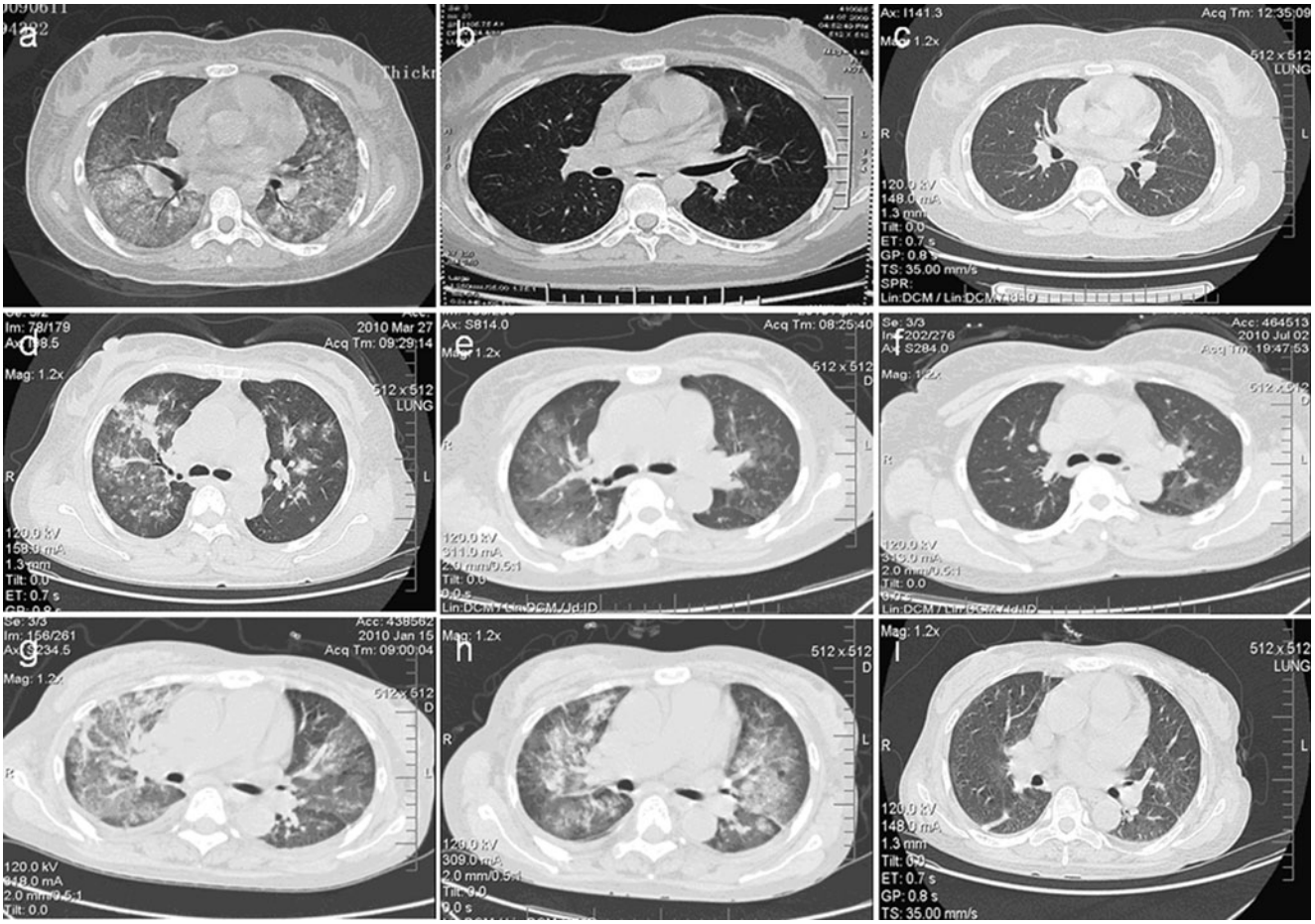

Fig. 4 Chest HRCT scans before and after UC-MSCT. **a**, **d**, **g** An initial HRCT scan of the chest shows bilateral, diffuse alveolar infiltrates for patients 1, 3, and 4, respectively. **b**, **e**, **h**, One week after UC-MSCT, a repeat HRCT scan of the chest shows amelioration of the lung infiltrates for patients 1, 3, and 4. **c**, **f**, **i** Chest HRCT scans at the last visit show complete resolution of the lung infiltrates for patients 1, 3, and 4. *HRCT* high-resolution CT, *UC-MSCT* umbilical cord-derived mesenchymal stem cell transplantation

However, the potential mechanisms of how MSCs act on DAH are not very clear yet. Several theories have been developed to describe the effects of MSCs on the lungs in ALI models. Immunomodulatory property is a major characteristic of MSCs. Gupta N et al. [23] found that coculture of alveolar macrophages and MSCs reduced level of macrophage stimulation. In addition, Th1 cells were downregulated, and CD4+CD25+Foxp3+ Treg cells were elevated by MSCT in ALI mice [24]. Animal experiments exhibited that recruitment of macrophages and neutrophils preceded the hemorrhage by several days in DAH [29]. Thus, MSCs may also play an important role in the macrophage- and neutrophil-infiltrated lungs in SLE-associated DAH, which might explain the amelioration of the lung exudations. However, disputes still existed whether MSCs prevent neutrophil chemotaxis to the alveolus. Despite the above effect, MSCs may improve the lung injury by balancing anti- and pro-inflammatory factors. MSC instillation decreased levels of tumor necrosis factor alpha, interferon-γ, and macrophage inflammatory protein-2, while increased IL-10 level in ALI models [23–25]. Koh H et al. [30] have found elevated serum levels of Th2 cytokines as well as Th1 cytokines in DAH following hematopoietic stem cell transplantation which might also be a target for MSCs. Although MSCs were proved to differentiate into bone, fat, and cartilage, researches in the late 1990s found that they could also develop a nonmesodermal phenotype [31, 32]. Kotton et al. showed that injected MSCs following bleomycin-induced lung injury developed morphologic and molecular characteristics of type I pneumocytes [33]. The histological appearance of SLE-associated DAH includes diffuse alveolar damage, organizing pneumonia, and nonspecific cellular pneumonitis [34]. The differentiation of MSCs into pneumocytes may repair the damage of alveolar wall. However, the exact mechanism needs further confirmation.

In conclusion, we suggested that allogeneic UC-MSCT might be a new salvage treatment option for SLE-associated DAH. All the four patients showed clinical and hematological improvements after UC-MSCT with no obvious side effect for at least 6 months. However, further clinical trials

with more patients and longer periods of follow-up are needed to determine the efficacy and safety of UC-MSCT.

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Disclosures None.

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