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Allogeneic mesenchymal stem cells transplantation in treatment of multiple sclerosis

J Liang¹, H Zhang¹, B Hua¹, H Wang¹, J Wang², Z Han² and L Sun¹

Multiple sclerosis (MS) is a chronic autoimmune disorder of the central nervous system. Umbilical cord derived mesenchymal stem cells are immunosuppressive. We transplanted mesenchymal stem cells in a patient with refractory progressive MS, and the disease course was stabilized after the transplantation. We postulate that mesenchymal stem cells have a potent immunosuppressive effect *in vivo*. *Multiple Sclerosis* 2009; 15: 644–646. <http://msj.sagepub.com>

Key words: multiple sclerosis; T2 lesions

Multiple sclerosis (MS) is considered an immune-mediated disease associated with immune activity directed against central nervous system antigens that frequently leads to severe physical and cognitive impairment. Based on this, many immunomodulatory or immunosuppressive strategies have been used for disease control, showing no or only partial effectiveness.

Mesenchymal stem cells (MSCs) are multipotential nonhemopoietic progenitor cells capable of differentiating into multiple lineages of cells such as nerve cells. They are able to escape alloantigen recognition because of their low immunogenicity. On the other hand, they can inhibit immune response both *in vitro* and *in vivo*. The inhibiting effect is related with the modulation of dendritic cells, T cells, and natural killer cells [1,2]. These properties make MSCs promising candidate cells in preventing rejection in organ transplantation and treatment of autoimmune disease. Furthermore, it has been shown that patients with MS have impaired MSC function compared with healthy donors, which inspired transplantation of MSCs in the treatment of MS [3]. In this article, we report for the first time the successful treatment of MS with umbilical cord-derived MSC transplantation (UC-MSCT).

At onset of disease, a 55-year-old woman experienced leg numbness. The symptom initially seemed trivial so that she did not seek medical attention. As the condition worsened, the numbness extended to

trunk and neck within six months. She then developed progressive weakness of all four limbs and became bed bound requiring hospitalization. Examination showed sensory loss, quadriparesis, and bilateral Babinski responses. CSF analysis showed a mononuclear cell pleocytosis (6 cells/uL). MRI study showed high-intensity large lesions on T2-weighted images in the bilateral frontal, occipital and parietal lobes, and a further lesion at the cervico-medullary junction. A diagnosis of *primary progressive* MS was made. Diseases such as SLE, perinuclear Anti-Neutrophil Cytoplasmic Antibody (p-ANCA) associated vasculitis, and mixed connective tissue disease were excluded. Following high-dose methylprednisolone (1000 mg/day for 3 days), she received prednisone 40 mg/day for more than 2 months but did not seem to obtain any clinical benefit. Immunosuppressants such as Cyclophosphamide (CTX) and Mitoxantrone were not used. Eight months after disease onset, she remained quadriplegic and was referred for UC-MSCT.

In August 2008, after informed consent and approval by the Ethics Committee at Drum Tower Hospital, she underwent UC-MSCT. This comprised the intrathecal injection of 1×10^7 cells and the intravenous injection of 2×10^7 cells, which followed preconditioning with CTX (600 mg daily for 3 days). She received no other immunosuppressive or immunomodulating therapy besides prednisone, 10 mg daily throughout the post-transplant period.

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There was no acute graft-versus-host disease (GVHD) or any toxicity after UC-MSCT. On day 3 after the transplantation, her sensory impairment significantly alleviated, and by day 9, her muscle strength increased and she could sit with assistance. On day 52, the patient showed objective improvement of neurological signs and she even could stagger along with the help of family. The Expanded Disability Status Scale (EDSS) score decreased at least 2 points from the baseline of 8.5, which was confirmed during 2 months after the evaluation on day 52. Follow-up MRI on day 56 showed a significant reduction in the T2 lesion load, especially in cervical cord which correlated with the clinical stabilization of MS after UC-MSCT (Figure 1). Consequently, the gadolinium-enhanced MR images were not performed. At the scheduled five-month review, she could walk slowly without assistance from others and the EDSS score was 5.5 down from 8.5 at study entry.

We chose UC-MSCs because they share most of the characteristics with bone marrow-derived MSCs and have distinct advantages of higher proliferation, accessibility, and lower risk of viral contamination [4]. Umbilical cords were obtained from local maternity hospitals after normal deliveries. After having been minced to 1–2 mm³ fragments, UC were incubated with 0.075% collagenase type II (Sigma, St Louis, Missouri, USA) for 30 min and

then 0.125% trypsin (Gibco, Grand Island, New York, USA) for 30 min with gentle agitation at 37°C. The obtained cells were plated at a density of $1 \times 10^6/\text{cm}^2$ in non-coated T-25 or T-75 cell culture flasks (Becton Dickinson, San José, California, USA). Growth medium consisted of Dulbecco's modified Eagle's medium with low glucose (DMEM-LG, Gibco) and 5% fetal bovine serum (FBS; Hyclone, Logan, Utah, USA). After 3 days of culture, non-adherent cells were removed and the medium was changed weekly twice thereafter. Once 60–80% confluence had been reached, adherent cells were replated at a density of $1 \times 10^4/\text{cm}^2$. After two passages, the cells expressing CD106, CD105, CD44, and CD29 were harvested but not CD34 or CD45. 1×10^6 cells/kg of the patient weight were given.

Several studies have indicated that MSCs possess an array of immunosuppressive capabilities. A recent case report has suggested that systemic infusion of MSCs resulted in suppression of severe treatment-resistant acute GVHD after allogeneic bone marrow transplantation [5]. Our team has successfully used UC-MSCT in the treatment of several autoimmune diseases such as systemic lupus erythematosus, Sjogren's syndrome accompanies autoimmune hemolytic anemia, progressive systemic sclerosis, and polymyositis. In this case, the UC-MSCT resulted in disease stabilization and improved

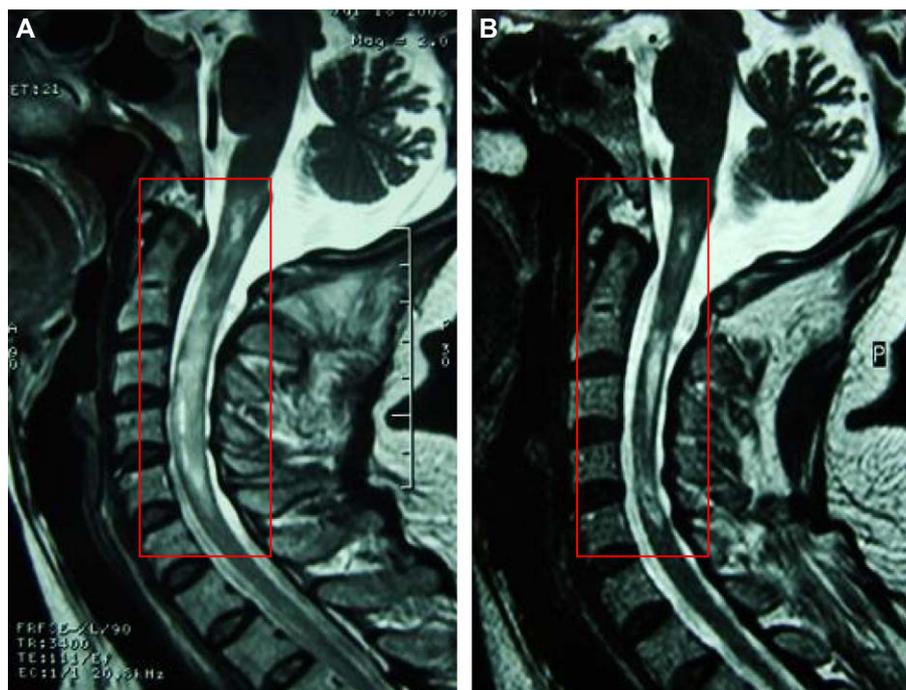


Figure 1 MRI study. Comparison of T2-weighted images in the cervical cord. (A) pre UC-MSCT; (B) on day 56 after UC-MSCT. Lesion size and cord swelling have decreased considerably after UC-MSCT.

quality of life. Considering the considerable improvement of disease disability and the low-dose of CTX used, we consider that the MSCs exerted a potent therapeutic effect either alone or in concert with the CTX.

The effect of MSCs may be via one or more mechanisms. These include 1) as immunomodulators by producing soluble factors induced upon stimulation; 2) direct cell replacement by differentiating into neural and glial cells in the CNS. Our findings show that UC-MSCT could be considered as a viable therapeutic approach for patients with MS with a progressive incapacitating disease course unresponsive to conventional treatment regimens.

Acknowledgments

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