

Allogenic Mesenchymal Stem Cell Transplantation for Refractory Severe Pyoderma Gangrenosum

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Abstract

Background: Pyoderma Gangrenosum (PG) is a rare and an idiopathic, inflammatory ulcerative condition, and the treatment are empirical and based on small series or local experience. Mesenchymal stem cells (MSCs) have immunomodulatory and tissue-repairing effects in autoimmune diseases, thus may have a potential role in PG treatment.

Objectives: This study aimed to assess the efficacy of UC-MSC transplantation (UC-MSCT) for wounded skin in a refractory severe PG patient.

Methods: A 29-year-old male PG patient was recruited. UC-MSCs were prepared by the Stem Cell Center of Jiangsu Province (Beike Bio-Technology). The patient underwent two times of UC-MSCT on June 13th, 2012 and June 27th, 2012. The protocol was approved by our Ethics Committee and signed informed consent was obtained from the patient.

Results: The PG patient presented with pustules over the lower limbs and was refractory to oral prednisolone (initially 60 mg per day, tapered in 8 weekly steps to 5 mg per day), pulse intravenous cyclophosphamide (0.6 g per month for 6 months) and he also underwent two times unsuccessful of skin grafting for the lower extremity ulcers. There are no adverse events during the UC-MSCT treatment. After one week, he was free of intense pain and the exudation significantly reduced. Auto-skin grafting was given 4 weeks after UC-MSCT and the grafts came from his back and inner thigh. His ulcers significantly healed with complete resolution of pain 2 months after UC-MSCT. Maintenance therapy followed transplantation included prednisone 5 mg per day and intravenous cyclophosphamide 0.6 g per month.

Conclusions: This is the first reported case of successful allogenic UC-MSCT for refractory severe PG. Although additional studies are needed to confirm this finding, we believe that UC-MSCT may be considered a therapeutic option for PG patients unresponsive to conventional treatments.

Keywords: Pyoderma Gangrenosum; Mesenchymal stem cells; Transplantation

Case Report

Pyoderma Gangrenosum (PG) is a rare and an idiopathic, inflammatory ulcerative condition, often associated with systemic autoimmune disease such as inflammatory bowel disease, rheumatoid arthritis, monoclonal gammopathy or hematological malignancies. Immunological factors and neutrophil dysfunction can be considered to be involved in the etiopathogenesis of PG [1]. PG lacks specific clinical, histopathologic or laboratory findings and is a diagnosis of exclusion. The standard treatment is long-term immunosuppression, often with high doses of corticosteroids, which are empirical and based on small series or local experience [2]. Mesenchymal stem cells (MSCs) have immunomodulatory and tissue-repairing effects in autoimmune diseases [3,4]. Previous animal researches demonstrated that MSCs may contribute to wounded skin, via processes involving MSCs differentiation various cell components of the skin, or prolonging skin graft survival *in vivo* [5,6]. Recent clinical findings also showed that umbilical cord-derived mesenchymal stem cell transplantation (UC-MSCT) was safe and effective in skin repair in a patient with drug-induced Stevens-Johnson syndrome [7,8]. UC-MSCs have weak immunogenicity for lack of the expression of the major histocompatibility complex (MHC) class II (HLA-DR) antigens, which make them free from immune resonance and the possible risk of graft-versus-host disease (GVHD) in this therapy [9].

Here we report a successful treatment of refractory severe PG by UC-MSCT. Our patient, a 29-year-old man, presented with pustules over the lower limbs rapidly progressing to large, with central

necrosis and undermined erythematous edges, for 5 years. Laboratory investigations, clinical manifestations and the histopathologic results were indicative of PG. The patient was refractory to oral prednisolone (initially 60 mg per day, tapered in 8 weekly steps to 5 mg per day) and pulse intravenous cyclophosphamide (0.6 g per month for 6 months). He also underwent two times of skin grafting (both autografts, in 2007 and 2010, respectively) for the lower extremity ulcers. The results were disappointing, and the ulcer edge was still reddish, swollen, and oozing a pus-like discharge, measuring 20 cm×10 cm (left) and 15 cm×15 cm (right) (Figure 1A).

The patient underwent two times of UC-MSCT on June 13th, 2012 and June 27th, 2012. Preparation of UC-MSCs is as follows: Umbilical cords (UCs) were obtained from local maternity hospitals after normal deliveries under informed consents. After having been minced into 1-2 mm³ fragments, UCs were incubated with 0.075% type II collagenase for 30 min and then 0.125% trypsin for a further 30 min with gentle agitation at 37°C. The obtained cells were plated at a density of 1×10⁶/

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Figure 1A: Panel A Wound breakdown before UC-MSCT.



Figure 1B: Panel B Wound healing two months after UC-MSCT.

cm² in noncoated T-25 or T-75 cell culture flasks. Growth medium consisted of Dulbecco's modified eagle's medium with low glucose and 5% fetal bovine serum. After 3 days of culture, nonadherent cells were removed and the medium was changed twice-weekly thereafter. Once 60-80% confluence had been reached, adherent cells were replated at a density of 1×10^4 /cm² in UC growth medium for expansion. After two passages, cells were harvested to confirm the expression of CD106, CD105, CD44 and CD29, but not CD34, CD14, CD19, HLA-DR and CD45. The capacity of MSCs to differentiate along adipogenic and osteogenic lineages was also assayed. The protocol was approved by our Ethics Committee and informed consent was signed from the patient. All the infused MSC were derived from passage 2 to passage 5, and 1×10^6 cells/kg of body weight were given by intravenous infusion at each time, with no premedication such as steroids or antihistamines. He had no adverse events during treatment. After one week, he was free of intense pain and the exudation significantly reduced. Auto-skin grafting was given 4 weeks after UC-MSCT and the grafts came from his back and inner thigh. His ulcers significantly healed with complete resolution of pain 2 months after UC-MSCT (Figure 1B). Maintenance therapy followed transplantation included prednisone 5 mg per day and intravenous cyclophosphamide 0.6 g per month.

This is the first reported case of successful allogenic UC-MSCT for refractory severe Pyoderma Gangrenosum. Although additional studies are needed to confirm this finding, we believe that UC-MSCT

may be considered a therapeutic option in large area ulcerative PG patients unresponsive to conventional treatments.

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