Case Report

The Healing Effect of Bone Marrow-Derived Stem Cells in Knee Osteoarthritis: A Case Report

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ABSTRACT

Osteoarthritis (OA) is a prevalent chronic disease impacting on quality of life and has societal and economical burden increasing with age. Yet, no confirmed pharmacological, biological or surgical therapy could prevent the progressive destruction of OA joint. Mesenchymal stem cells (MSCs) with immunosuppressive activities emerged a potential therapy. We describe a magnetic resonance images (MRI) approved 47 years old nomad female suffering from a severe right knee OA. After intra-articular injection of 36×10^6 passage 2 of bone marrow-derived stem cells (BMSCs), the patient's functional status of the knee, the number of stairs she could climb, the pain on visual analog scale (VAS) and walking distance improved after two months post-transplantation. MRI revealed an extension of the repaired tissue over subchondral bone. So as MSC transplantation is a simple technique, resulted into pain relief, minimized donor-site morbidity, provided a better quality of life, significantly improved cartilage quality with no need to hospitalization or surgery, cell transplantation can be considered as a reliable alternative treatment for chronic knee OA. Therefore these findings can be added to the literature on using BMSCs for treatment of OA.

KEYWORDS
Osteoarthritis; Knee; Bone Marrow; Mesenchymal Stem Cell; Transplantation

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INTRODUCTION

Lesions of articular cartilage are debilitating leading to fibrillation and subsequent degradation involving the subchondral bone resulting into development of osteoarthritis (OA).[1] The limiting factor in repair of articular lesions is the low intrinsic regeneration potential of cartilage tissue due to limitations of progenitor cells from the blood and bone marrow to enter the defect and the inability of resident articular chondrocytes to migrate into the lesion to secrete a reparative matrix.[2]

The disease affects the quality of life and has a striking impact

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on societal and economic cost and is considered as an important cause of premature death.[3] Knee OA has a high prevalence in Asian countries,[4] especially in Iran[5] while the causes of cartilage degeneration were shown to be trauma, aging process, overweight, overuse, inflammatory, autoimmune, metabolic, and infectious diseases, genetic predisposition, etc.[6]

Autologous chondrocyte implantation (ACI), matrix-induced autologous chondrocyte implantation (MACI), steroidal and non-steroidal anti-inflammatory drugs, visco-supplementation with injections of sodium hyaluronan, nutraceuticals including glucosamine, chondroitin sulphate, omega-3 fatty acids were reported as therapeutic measures to reverse the process, but with controversial findings.[7]

Mesenchymal stem cells (MSCs) are a powerful tool in repair of cartilage tissue as they are able to differentiate into many connective tissues such as fat, cartilage, bone, etc.[8] MSCs have immunomodulatory and anti-inflammatory effects,[9] self-renewal capacity, stemness maintenance, and plasticity allowing their application for allo- and xenotransplantation[10] while transplantation of MSCs is based on the capacity of these cells to home and engraft long-term into the appropriate target tissue[11] such as bone and cartilage in treatment of OA.[2]

Yet, no approved pharmacological intervention, biologic therapy or procedure has prevented the progressive destruction of the OA joint. Here, we describe a case report on the healing effect of bone marrow-derived stem cells in a female with confirmed MRI severe knee osteoarthritis.

CASE REPORT

The patient was a 47 years old nomad female with confirmed magnetic resonance images (MRI) severe right knee OA (classified as stage IV according to the Kellgren and Lawrence classification) (Figure 1). Her BMI was 25 kg/m^2. She did not respond to corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and glucosamine, chondroitin sulphate or omega-3 fatty acids, while she was asked to stop her medications one month prior and also after enrolling for cell transplantation.

The patient did not have any infection with hepatitis B, C, or HIV, any malignancy, any previous history of allergic reaction to any component of our therapeutic measure, any active cardiac, respiratory, neurologic or endocrine disease necessitating receipt of medication and was not pregnant or in lactating condition. An approval from the Ethics Committee of Shiraz University of Medical Sciences and informed written consent was provided from the patient.

The patient was admitted in Chamran Hospital for physical exam and evaluation of the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, the Visual Analogue Scale (VAS) scoring of the pain intensity, walking ability (distance), the number of stairs to climb for the pain to appear, the time till the appearance of gelling, the knee flexion, and the patellar crepitus before and after cell transplantation. Before and after cell transplantation, MRI was undertaken for the affected knee in Faghihi Hospital. MRI of the affected knee was provided preoperatively, 3, 6 and 12 months after treatment on a Seimens 1.5 T MR system in the sagittal, coronal and axial planes.

For bone marrow aspiration, the patient was admitted in Nemazee Hospital. She was placed in prone position and was locally anesthetized with 1% lidocaine and about 60 ml of bone marrow was provided from iliac crest. Cell isolation was undertaken in the clean room of Mother

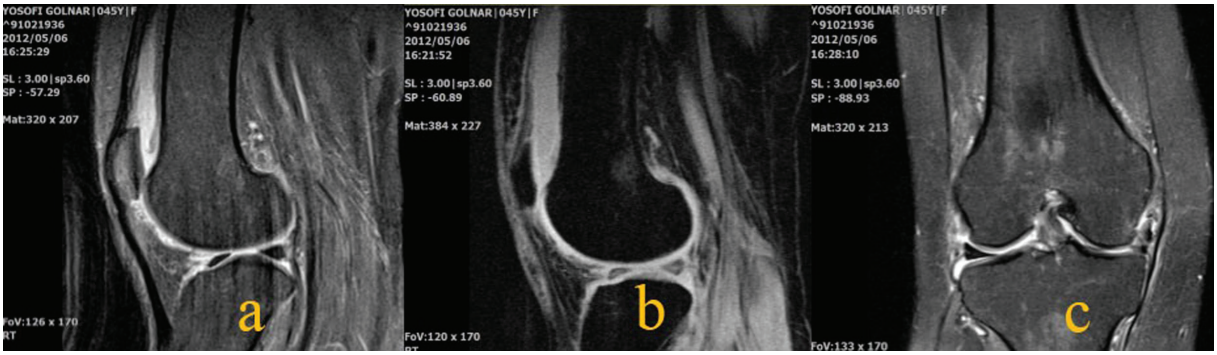

Fig. 1: MR images through the right knee joint before stem cell therapy. Proton density (**a,b**) and T1W gradient echo © sections.

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and Child Hospital. Fifty milliliter of phosphate buffer saline (PBS, Clinimax, Germany) was added to the sample, loaded onto a lymphodex (Inno-Train, Germany) and was centrifuged at 1500 g for 20 minutes to collect mononuclear cells. PBS was used to wash the mononuclear cells and they were plated into 150-cm^2 culture flasks containing 15 ml of alpha modified eagle medium (alpha MEM, Gibco, Germany) supplemented with 10% hyclon serum (Thermo Scientific, USA) and 100 IU penicillin and 100 IU streptomycin (Gibco, Germany).

A sample was provided to test for presence of any possible microbial contamination. Cell expansion was taken place by subcultures and passaged-2 cells were provided for cell injection. Four weeks after plating of cells and in passage-2, they were washed with PBS and trypsinized with 0.2% trypsin/EDTA and cell counting was performed using a nucleocounter (Chemometec, USA). A total of 36×10^6 cells were provided and under a controlled condition, they were transferred in 2 ml of the media to the operating room for cell transplantation into the knee joint.

Again a sample was provided to check any microbial contamination before injection into the knee. The adhered cells to the flasks were evaluated morphologically under inverted microscopy. Expression of surface markers in the patient's BM-MSCs was evaluated by flow cytometry to evaluate the positive surface biomarkers expression of CD44 and CD90 and absence of CD34 expression.

Cell morphology revealed fibroblastic like adherent cells in all culture flasks (Figure 2). No contamination was visible in the cell transplantation sample. Flow cytometric findings denoted to expression of CD44 and expression of CD90 (mesenchymal stem cell markers) and negative expression for CD34 (hematopoietic cell marker) (Figure 3). During the follow-up, no local or systemic adverse events were observed and the patient was satisfied with the therapy after two months with an increasing trend by passing time.

Twelve months after cell transplantation, the WOMAC changed from 3 to 2, and the VAS from 80 mm to 11 mm. This modification for walking ability was 170 m before and 700 m after treatment and for the number of stairs to climb for the pain to appear was 5 stairs before and 50 stairs after therapy. The time till the appearance of gelling was 8 min and reached to 30 min and the knee flexion was 100° and improved to 120° twelve months after cell transplantation.

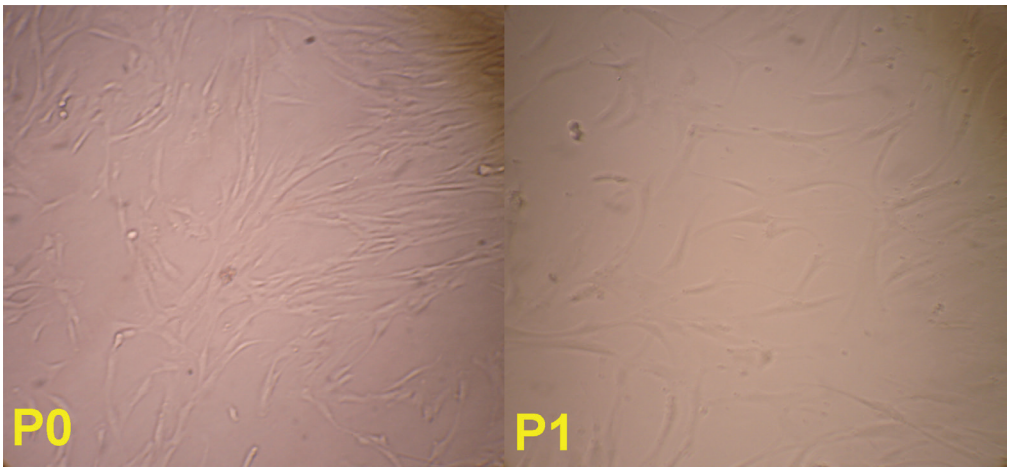

Fig. 2: Emerging of adherent cells with fibroblastic morphology 3 days after culture initiation of the patient's BM-MSCs (P0=primary culture and P1=first passage).

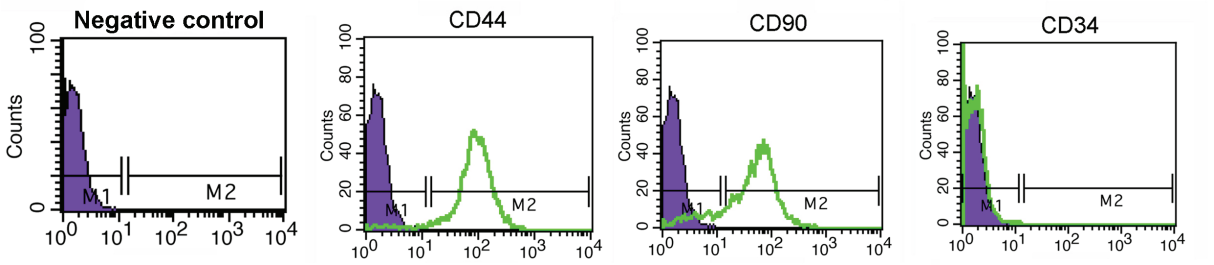

Fig. 3: Expression of surface markers in patient's BM-MSCs. There were positive surface biomarkers expression of CD44 and CD90 and lack of CD34 expression.

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The patellar crepitus was 3 before and 2 after therapy. After 6 months, the MRI of the right knee revealed an increase in thickness of the covering cartilage in distal condyle of the femur and the proximal part of the tibia (Figure 4A-C). These changes were much more significant after 12 months follow up (Figure 4D-F).

DISCUSSION

Consistent with our findings, positive therapeutic effects of MSCs in human models were previously shown in different studies. In Jo et al.'s study, patients with knee OA of the knee were transplanted with 1.0×10^7, 5.0×10^7 and 1.0×10^8 adipose-derived stem cells (AdSCs) into the knee. There was no adverse event and the WOMAC score improved at 6 months after injection and thick, hyaline-like cartilage regeneration was visible.[12] Orozco et al. in patients with knee OA treated with intra-articular injection of 40×10 autologous bone marrow-derived stem cells (BM-SCs) observed that the patients demonstrated rapid and progressive improvement of algofunctional indices by 1 year and also showed a highly significant decrease of poor cartilage areas with improvement of cartilage quality.[13]

Injection of BM-SCs in knee OA was shown to improve pain, functional status of the knee, and walking distance without any adverse events. An increase in cartilage thickness and a considerable decrease in the size of edematous subchondral bone were noticed.[14] Davatchi et al. performed single intra-articular BM-SCs injection in OA knees and described a marked clinical improvement in subjective parameters, although physical parameters improved much less.[15] Kasemkijwattana et al. showed a good defect filling and repair of tissue with BM-SCs in patients with knee OA and a significant clinical improvement.[16] Gigante et al. reported that BMSCs in patients with medial femoral condyle lesions, could result into normal arthroscopic appearance.[17]

Nejadnik et al. compared the first-generation ACI technique with implantation of BM-SCs and showed a similar pattern of clinical and subjective improvement up to 2 years postoperatively.[18] Haalem et al. used BM-SCs for treatment of articular knee cartilage defects and showed that

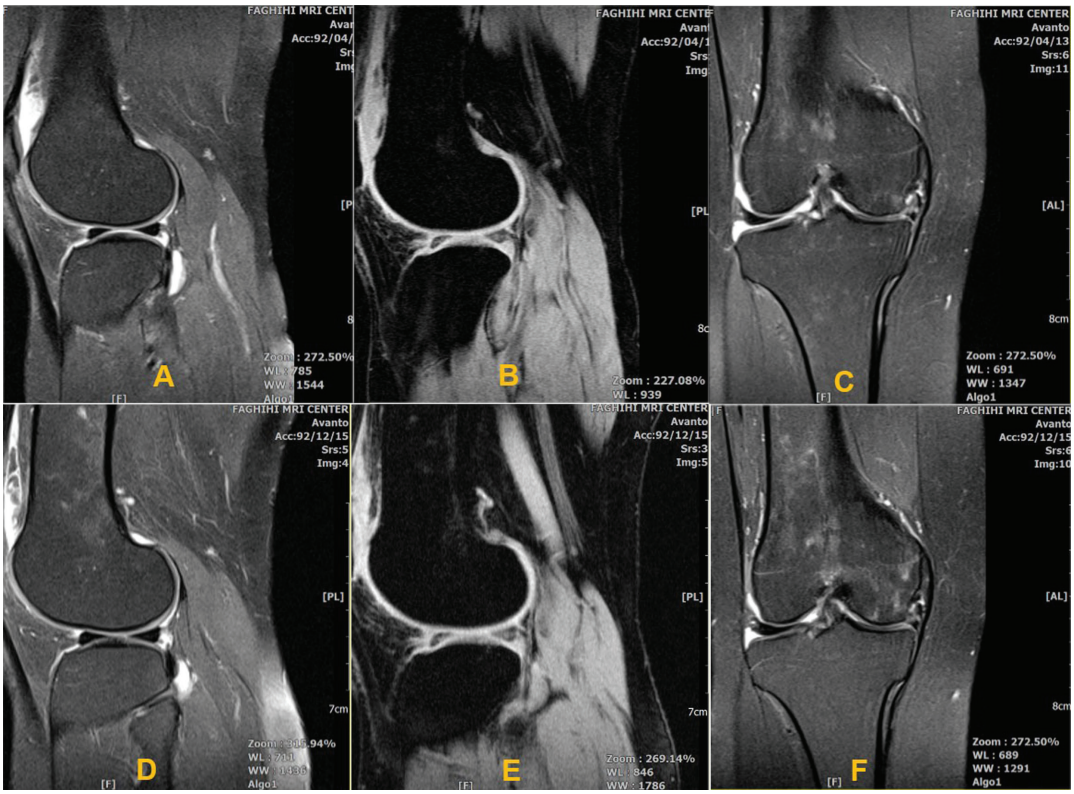

Fig. 4: MR images through the right knee joint six months after stem cell therapy. Proton density (**A&C**) and T1W gradient echo (**B**) sections revealed thickness of covering cartilage in distal condyle of femur and proximal part of tibia. MR images through the right knee joint twelve months after stem cell therapy. Proton density (**D&F**) and T1W gradient echo (**E**) sections revealed thickness of covering cartilage in distal condyle of femur and proximal part of tibia.

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symptoms improved after 12 months, and MRI revealed complete defect filling and complete surface congruity with cartilage tissue.[19]

Centeno et al. showed encouraging results after treating a knee cartilage lesion by intra-articular injection of BM-SCs with an increase in cartilage and meniscus volume, and an improvement in range of motion and pain score.[20] Wakitani et al. described results after the treatment of patello-femoral cartilage defects with BM-SCs and improvement in clinical symptoms at 6 months, which was maintained over 17–27 months.[21] Adachi et al. in a large osteochondral knee defect treated with cultured BM-SCs noted a good cartilage and bone regeneration.[22]

Wakitani et al. described the use of BM-SCs in knee OA reported clinical improvement by arthroscopic and histological scoring.[23] They found clinical improvement in patients with full-thickness knee cartilage defects treated with BM-SCs after 6 months, which remained stable 5 years after treatment.[24] Buda et al. showed good subchondral bone and cartilage tissue regeneration after arthroscopic implantation of BMSCs in osteochondral knee defects.[25] Giannini et al. in patients with OA found that one-step BMSC transplantation could lead to a good restoration of the cartilaginous layer.[26]

Varma et al. reported an improvement in symptoms, with shortened hospital stay and better quality of life after BMSCs injection in patients with knee OA.[27] Giannini et al. in treatment of osteochondral talar dome lesions with BMSCs showed newly formed tissue that were well integrated with the surrounding tissue with an improvement in clinical scores.[28]

The immunomodulatory properties of AdSCs in patients with OA was previously shown[29] which explain the healing effect of the cells in affected joint. These cells in knee cartilage defects were shown to improve pain and the quality-of-life.[30] Kim et al. evaluated clinical and MRI outcomes after mesenchymal stem cell implantation in patients with knee osteoarthritis and showed encouraging clinical and MRI outcomes and repairing cartilage lesions in OA knees.[31] Emadedin et al. in their long-term follow-up of intra-articular injection of autologous mesenchymal stem cells in patients with knee, ankle, or hip osteoarthritis revealed that in affected joints, they are safe and therapeutically beneficial.[32] Davatchi et al. in their 5 years follow-up of mesenchymal stem cell therapy for knee osteoarthritis reported that transplant knees were all in a rather advanced stage of OA. Earlier transplantation may give better results in long-term follow-up.[33]

Similar to above-mentioned studies, in our patient with severe knee OA and one year follow up after cell transplantation, the findings were satisfactory. The functional status of the knee, the number of stairs they could climb, the pain on visual analog scale and walking distance improved in our patient two months post-injection. Magnetic resonance images (MRI) at baseline, and post-stem cell injection revealed an extension of the repair tissue over subchondral bone. So as MSC transplantation is a simple technique, resulted into pain relief, minimized donor-site morbidity, provided a better quality of life, significantly improved cartilage quality with no need to hospitalization or surgery, cell transplantation can be considered as a reliable alternative treatment for chronic knee OA. These findings can be added to the literature on using MSCs for treatment of OA while we have compared our results completely with previous available studies chronologically.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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