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Treatment of Pulmonary Sarcoidosis Using Allogenic Bone Marrow-Derived Mesenchymal Stem Cell Therapy is Safe: A Case Report

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ABSTRACT

Mesenchymal stem cells have a proven potent immunomodulatory effect both in vitro and in vivo. We report a case of a 67-year-old male patient, first diagnosed with sarcoidosis in 2005, that responded well clinically and biologically to ImmunoART™ (developed by Educell Ltd.) allogenic, HLA-incompatible, and non-related bone marrow-derived MSCs in a dose of 10^6/kg. The patient presented to St. Catherine Specialty Hospital in 2021 with an exacerbation of respiratory symptoms. After a clinical and radiological examination with laboratory workup, radiological findings were consistent with pulmonary sarcoidosis, while laboratory work revealed increased leucocytes at 14.2 g/L, CRP at 51.2 mg/L, and lymphocytes at 4.25 g/L. The patient was then administered intravenous application of MSCs on three occasions in the out-patient clinic. MSC doses were prepared from a young, healthy donor who agreed to donate bone marrow for allogeneic treatment and who was negative for viral markers (HBs Ag, HBc Ab, HCV Ab, HIV 1-2 Ab, TPHA, HBV NAT, HCV NAT, HIV NAT) according to EU legislation. Cells were prepared in a controlled and verified laboratory for "Hospital exemption" cell preparation in the cleanroom facility in safety cabinet class A and expressed CD105, CD 73, and CD 90 but lacked the expression of CD45 and CD34. Before the treatment, standard print and detailed verbal information were provided to patients undergoing treatment. Immediately after the informed consent form (ICF) was signed by the patient. Throughout MSC therapy, the patient showed an improvement clinically and biologically with a decrease in inflammatory parameters. Laboratory values were assessed on days 2, 5, and 7. On day 7, leucocytes were 11.2 g/L, CRP 5.1 mg/L, and lymphocytes 4.0 g/L. In the follow-up period, the patient felt subjectively better, without any side effects of the MSC therapy. Unfortunately, the patient dropped out from follow-up, therefore, the prolonged effects of this therapy were not able to be assessed. Therefore, systemic MSC therapy presents an opportunity to treat sarcoidosis that needs to be further researched.

KEYWORDS: Mesenchymal stem cells, allogenic, sarcoidosis, bone marrow.

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INTRODUCTION

Sarcoidosis is a systemic disease that most often infects the lungs and lymph nodes (1). It is currently seen as an overzealous immune response to unknown stimuli. The response that follows triggers granuloma formation via stimulation of monocytes by Toll-like receptors 2 (TLR-2).

These stimulated monocytes differentiate into macrophages which subsequently form aggregates called granulomas. The granulomas become surrounded via T-cells which perpetuate the granuloma formation further (2). There is currently no cure for sarcoidosis with existent treatment only dampening the inflammatory responses and thus granuloma formation. This treatment remains flawed and can lead to relapses known as refractory sarcoidosis (3). Therefore, alternative methods such as the application of mesenchymal stem cells (MSCs) have recently gained attention. The early pioneering work done by Hayflick (4) has shown the potential of MSCs in vitro (4), however, clinical implementation of MSCs has only gained momentum in the last thirty years. The growing need for personalized medicine in outpatient and inpatient settings has emphasized the need for such therapeutic methods. As a result, the current options for such therapy are MSCs derived from bone marrow, (BM-MSC), adipose tissue (AD-MSC) and placenta. Restrictions in certain markets such as in America for placental and AD-MSCs have led to innovations in autologous BM-MSC therapy, a therapeutic option that has excellent outcomes and possesses immunomodulatory effects, making it an excellent tool in the treatment of anti-inflammatory diseases (2,5,6). Administration of MSCs for pulmonary use has two main methods, intra-tracheal and intra-venous, both of which have shown similar outcomes (7). In this paper, we present the case of a 67-year-old male diagnosed with previously untreated sarcoidosis who responded well clinically and biologically to IV administration of allogenic BM-MSCs.

CASE REPORT

The patient presented to the Center for precision and preventative medicine at St. Catherine Specialty Hospital due to an exacerbation of respiratory symptoms. He was diagnosed with sarcoidosis in 2005 for which he denied taking any medication. Subsequent laboratory tests revealed increased leucocytes at 14.2 g/L, CRP at 51.2 mg/L, lymphocytes at 4.25 g/L, and IL-6 was increased to 28.6 ng/L while blood gas analysis showed a decreased partial oxygen pressure of 6.8 kPa and O_2 saturation at 89%. CT imaging a day later showed bilateral interstitial thickening of the broncho-vasculature and interlobular septi with milk cloud/glass appearance, highly in favor of pulmonary sarcoidosis. Immediately after the patient was started on an IV therapy of allogenic, HLA-incompatible, and non-related bone marrow-derived MSCs at a dose of 10^6/kg.

Laboratory workup on day 2 revealed a decrease in inflammatory markers with leucocytes at 11.0 g/L, CRP 18.7 mg/L, lymphocytes at 2.11 g/L, IL-6 dropped to 9.07 ng/L and blood gas analysis revealed an increase in partial oxygen to 7.9 kPa and O2 saturation at 92%. Day 5 laboratory workup showed normalization of leukocytes at 9.7 g/L, CRP at 13.5 mg/L, lymphocytes at 2.22 g/L, and IL-6 was 2.51 ng/L further blood gas analysis showed partial oxygen pressure at 8.0 kPa and O2 saturation of 93%. On day 7 of outpatient treatment leukocytes were slightly elevated at 11.2 g/L, CRP 5.1 mg/L, lymphocytes at 4.0 g/L, and IL-6 fell to 2.74 ng/L. Additional blood gas analysis revealed partial oxygen pressure was slightly increased (8.5 kPa) and normalization of O2 saturation to 94%. After day 7 the patient stopped coming to follow-up appointments and the clinic lost all contact with him.

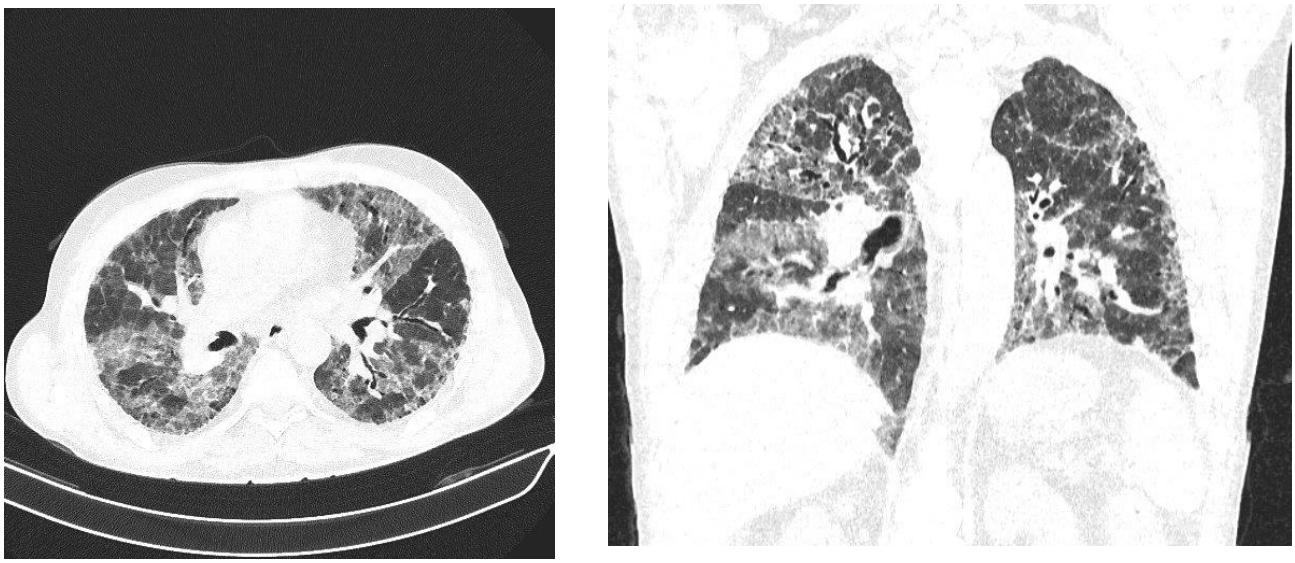

Figure 1: Computed tomography (Left) -axial plane, (Right)-coronal plane

CT features of pulmonary sarcoidosis: small, rounded, multiple nodules in peribronchovascular interstitium and subpleural location, interlobular septal thickening, nodular irregular thickening of peribronchovascular interstitium,

ground-glass opacities.

DISCUSSION

In this case report, we present the clinical and biological amelioration of a patient with long-standing sarcoidosis with pulmonary involvement by the administration of IV BMSC. This is not the first time that MSCs were used in the treatment of pulmonary diseases. Previous research has shown that SARS-CoV-2 can be successfully treated with MSCs (8). Furthermore, MSCs have been shown to be a potential therapeutic tool in the treatment of sarcoidosis (9)**.** MSCs act via three mechanisms to exert their trophic effects. These mechanisms are anti-apoptotic, anti-scarring, angiogenic, as well as antimicrobial. The mechanisms relate to an innate response to inflammation, as is the case in sarcoidosis. Therefore, modulating this response in the disease can lead to a decrease in symptoms and is the rationale for this treatment method. It is possible that these MSCs act via these mechanisms in order lessen fibrotic changes created from chronic inflammation in the lungs while simultaneously reducing the inflammatory response. Demonstrating an anti-apoptotic function, the reduced cytoprotective ability in hepatocyte growth factor (HGF)-knockdown BM-MSCs indicates that sustained production of HGF may play an important role in anti-apoptotic cytoprotection lungs that are exposed to elastase (10). Meanwhile in BM-MSC and separately genetically modified MSCs overexpressing hepatocyte growth factor (MSC-HGF) the rate of apoptosis was reduced in an induced lung irradiation model. Apoptosis rates reached a peak 7 days after lung radiation but significantly decreased in MSC-HGF and MSC mice from day 1 to day 28 compared to the control group. Elaboration further on the anti-scarring effects, the MSCs-HGF had significantly reduced serum TGF- β levels and the mRNA expression levels of profibrotic factors TGF-β, Col1A1, and Col3A1 in mouse lung tissue compared with the radiation and MSC-Null groups (11). Finally, in vitro examination revealed that paracrine effects of BM-MSC-secreted stanniocalcin-1 (STC1) mediate anti-apoptotic effects in both UV irradiated fibroblasts and hypoxia-induced low pH injury of lung cancer epithelial cells (12). Concerning the anti-scarring effects, a separate study has found that early administration of BM-MSCs protects against pulmonary fibrosis (13). A study found that BM-MSCs secrete secreted frizzled-related protein 2 (Sfrp2), which in turn induces macrophages to secrete stromal cell-derived factor 1 (SDF1) and plasminogen activator inhibitor-1 (PAI-1). Both SDF1 and PAI-1 promote endothelial cells to differentiate into blood vessels (14). Additionally, MSCs have been shown to promote change of M1 macrophage phenotype to anti-inflammatory M2 phenotype macrophage, potentially further reducing systemic inflammation (15). The monitoring of interleukin 6 (IL-6) was done to follow the progression of the disease as IL-6 is a potent immunomodulator. In its paracrine mechanism of action through upregulation of Th17 cells (16). These cells then function to inhibit anti-inflammatory regulatory T cells (Tregs) resulting in increased inflammation. Furthermore, increased levels of IL-6 have been shown in sarcoidosis patients (17)**.** Il-6 has been linked to increased levels of serum amyloid A protein (18), responsible for the pathogenesis of sarcoidosis (19). The anti-inflammatory properties of BM-MSC have been shown in animal models to reduce IL-6 levels and increase the number of Tregs in the blood and lungs (20). Furthermore, the antimicrobial effect of both BM-MSC and AD-MSC was shown in vitro by a reduction in the CFUs formed in culture dishes (21). In contrast, a high reduction in CFUs has been demonstrated in in-vitro simulated osteomyelitis conditions where excellent tissue penetration is necessary. The antimicrobial effect is mainly caused by LL-37-human cathelicidin antimicrobial peptide (22).

CONCLUSION

Based on our recent experience treating COVID-19 patients, reported uses of MSCs for several health conditions/diagnoses by other clinicians, and our results with the patient with sarcoidosis we believe that IV administration of BM-MSCs is a viable therapeutic option in treating pulmonary diseases. However, more data is needed on bigger sample sizes to draw concrete conclusions regarding the long-term efficacy of such therapy for a like sarcoidosis.

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