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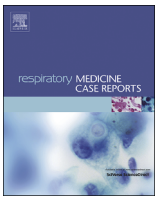

Case Report

Improvement in the clinical manifestations of interstitial lung disease following treatment with placental mesenchymal stromal cell extracellular vesicles in a patient with systemic sclerosis: A case report

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ABSTRACT

Background: Interstitial lung disease (ILD) is a severe systemic sclerosis (SSc) complication with no current approved or golden standard treatment. This report aims to investigate the effectiveness of treatment with placental mesenchymal stromal cell (MSC) extracellular vesicles (EVs) in a patient with ILD due to SSc.

Case presentation: The patient was a 55-year-old woman with a ten years history of SSc complicated by severe ILD. Over time, her lung disease progressed to interstitial fibrosis despite being treated with mycophenolate mofetil and monthly pulses of cyclophosphamide. Thus, she was treated with eight doses of placenta MSC-EVs. Four weeks after the third dose (Day 31 after the first dose), she reported marked improvement in her clinical symptoms, such as dyspnea and cough. Also, chest computed tomography (CT) scans demonstrated a significant reduction in ground glass consolidations and fibrotic changes. The patient was subsequently followed for twelve months, with findings showing significant improvement in exercise tolerance and reduced supplemental oxygen need.

Conclusion: In this single case, placental MSC-EVs were seen to provide a potentially efficient treatment for SSc-related ILD; however, further investigation and clinical trials are necessary.

1. Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease with different manifestations, including progressive skin, vessels, and internal organs fibrosis. Indeed, interstitial lung disease (ILD) and pulmonary artery hypertension (PAH) are the most common types of lung involvement in patients with SSc [1]. Lung fibrosis is irreversible in SSc patients. Current treatment options include cyclophosphamide, mycophenolate mofetil, rituximab, tocilizumab, and nintedanib, while slowing the progression to some extent, do not effectively inhibit the fibrosis process [2].

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All human cell types, including mesenchymal stromal cells (MSC), release extracellular vesicles (EVs). MSCs EVs contain proteins, lipids, mRNAs, microRNAs, DNAs, and organelles which may be transferred to damaged recipient cells, have an anti-inflammatory effect, and induce a reparative process. Growing evidence suggests that MSC EVs may have an exclusive role in immune tolerance-autoimmunity balance. Therefore, they could be involved in pathological immune responses. Previous studies on animal models of SSc have shown the benefits of MSC-EVs therapy in healing skin and lung fibrosis [3–7]. However, the therapeutic effectiveness of MSC-EVs on human subjects with SSc remains unknown. As far as we know, there has yet to be any previous report of treating SSc related ILD by MSC-EVs. The current report describes a case of intravenous infusion of allogenic MSC EVs in a patient diagnosed with ILD due to SSc, where the therapy was able to reduce lung complications and disease symptoms.

2. Case presentation

A 55-year-old woman with a 10-year history of SSc was referred to our clinic with a chief complaint of shortness of breath and dry cough worsening over five years. Her diagnosis as SSc was based on the American College of Rheumatology/European League Against Rheumatism classification [8]. At the early stages of her symptoms (five years ago), computed tomography (CT) scan of the chest showed fibrotic changes consistent with interstitial lung disease (ILD) related to SSc with pulmonary function tests (PFT), revealing a restrictive pattern; together these findings were suggestive of ILD secondary to SSc. At the time of presentation, she had a dry cough and chronic progressive dyspnea at rest (NYHA class 4). Also, she could not perform routine daily activities requiring supplemental oxygen therapy at home. Despite treatment with oral mycophenolate mofetil (2000 mg/day) and intravenous (IV) cyclophosphamide (1 gr monthly), her symptoms were progressive. Her other consuming medications at the visit included oral prednisolone (7.5 mg/day), bosentan (125 mg/day), dextromethorphan syrup (10 cc every 8 hours), diltiazem (60 mg/day), aspirin (80 mg/day), and a corticosteroid accompanied with long-acting beta-2 agonist spray (fluticasone + salmeterol; twice a day). Her family and social history were unremarkable. On examination, she had normal vital signs, was not cyanotic, and had a normal jugular venous pressure. Respiratory system examination revealed fine crackles in both lungs' lower half. Examination of the cardiovascular system and abdomen were within normal limits. Examination of the skin revealed diffuse skin thickness over the limbs, trunk, and face.

PFT and chest CT scan were performed in which PFT showed a severe restrictive pattern (predicted FEV1 value = 49%, predicted FVC = 45%, FEV1/FVC = 113%). Chest CT scan (Fig. 1) showed diffuse ground-glass consolidations with sub-pleural reticulations and fibrotic changes. Also, the pulmonary artery trunk was dilated (33 mm), and other findings were not notable. Considering her past medical history and her current condition, the diagnosis was ILD caused by SSc.

Since following mentioned medications and a 6-month treatment by cyclophosphamide, no improvement was observed in her symptoms or paraclinical; it was decided to treat her with placenta MSCs EVs. The aim and method of the study were explained to the patient according to her level of knowledge, and she was freely asked to sign a consent form. The Medical Ethics Committee of Kermanshah University of Medical Sciences approved the study with the IRB number of IR.KUMS.REC.1400.794.

Following the admission, a routine blood test was requested (Table 1), which showed normal liver and kidney function. The MSC EVs have been prepared according to the methods we have explained before [9]. Three doses of placental MSC EVs (0.8–1.2 × 10^9 particles/kg) were administered intravenously through a peripheral access (cubital vein) on three consecutive days. The patient tolerated the treatment well, and no adverse effect such as chills, fever, immune-related reaction, liver and kidney dysfunction, or skin reaction was observed. Two similar injection was repeated 48 hours later for two consecutive days. Four weeks later, she received three doses of MSC EVs in three consecutive days. After being discharged in stable condition, she was followed in our rheumatology outpatient clinic for twelve months. She reported significant improvement in her clinical symptoms, with decreased dyspnea and dry cough. A chest CT scan was repeated about two months after first treatment course, and the results showed a marked reduction in ground glass consolidations and fibrotic changes (Fig. 2). However, PFTs did not show significant changes (predicted FEV1 value = 47%, predicted FVC = 44%, FEV1/FVC = 111%). Physical examination revealed a reduction in lung crackles. She is still

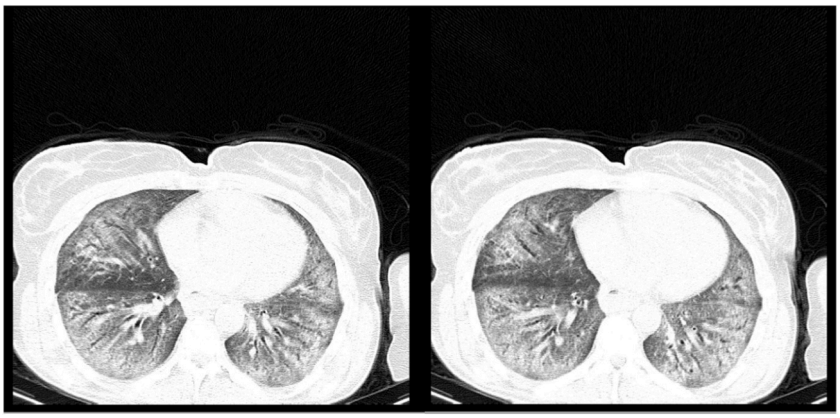

Fig. 1. Chest computed tomography (CT) scan before the intervention showed diffuse ground-glass consolidations with sub-pleural reticulations and fibrotic changes.

Table 1
Laboratory findings of the patient before and five days after the treatment.

Parameters (units)	Result on admission	Result after treatment
Hb (g/dl)	13.7	12.3
WBC (10^3/μl)	8.45	7.8
Platelet (10^3/μl)	237	284
PTT (second)	25	32
INR	1.1	1
Serum creatinine (mg/dl)	1	1.1
CRP (qualitative)	negative	negative
ESR (mm/1sthr)	24	17
LDH (IU/ml)	445	374
AST (IU/L)	39	35
ALT (IU/L)	27	30

Hb: hemoglobin, WBC: white blood cells, PTT: partial thromboplastin time, INR: International normalized Ratio, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, LDH: lactate dehydrogenase, AST: aspartate transaminase, ALT: alanine transaminase.

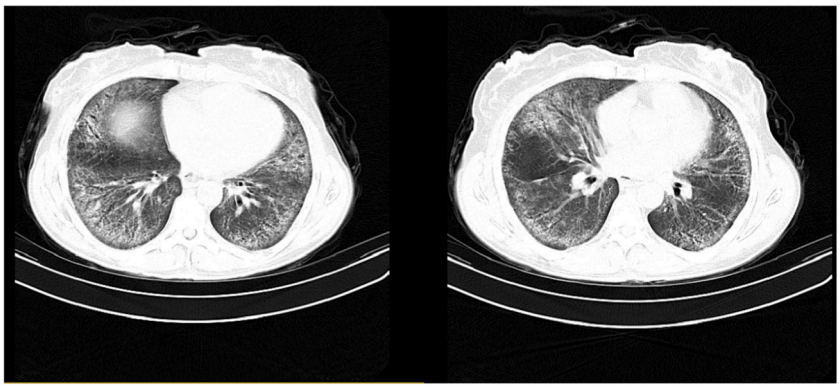

Fig. 2. Chest computed tomography (CT) scan after the intervention showed a significant reduction in ground glass consolidations and fibrotic changes.

under follow-up in our rheumatology clinic (so far 12 months). She claims that her clinical symptoms have notably improved after the MSC EV treatment, and she no longer needs supplemental oxygen.

3. Discussion

This report highlights the use of MSC-EVs in a patient with SSc with severe ILD whose condition was progressive despite conventional treatments. Although she was under different treatments, including cyclophosphamide and mycophenolate mofetil, her lung involvement progressed to severe ILD. As one of the last treatment choices, MSC EVs therapy was chosen. This treatment decreased the patient's respiratory-related signs and symptoms and significantly improved her chest CT scan. We selected the placenta as the source for allogeneic MSCs. Compared to other sources, including bone marrow, umbilical cord, and adipose tissue, the placenta is rich in stem cells and is more easily available [10].

So far, different studies have been conducted on SSc animal models investigating the treatment potential of MSC EVs. Rozier et al. has shown the efficacy of MSC EVs in HOCl-induced SSc models. Following this treatment, lung and skin involvement improved [5]. Yu et al. showed the anti-fibrotic and anti-inflammatory effects of human umbilical cord MSC-derived exosomes in a bleomycin-induced mouse model of scleroderma. Their data demonstrated an amelioration of extracellular matrix deposition and M2 macrophage polarization [7].

There has been growing evidence of the therapeutic role of the MSC EVs in several respiratory diseases, such as chronic obstructive pulmonary disease (COPD), asthma, coronavirus disease 2019 (COVID-19), acute respiratory distress syndrome (ARDS), idiopathic pulmonary fibrosis (IPF), and cystic fibrosis (CF). Suggested mechanisms of action of MSC EVs might be as follows: a decrease in lung cell apoptosis, a decrease of TNF-α levels, the polarization of macrophages to M2 anti-inflammatory phenotype, inhibition of group 2 innate lymphoid cells (ILC2s), inhibition of bone marrow morphogenetic protein receptor 2, increased proliferation and decreased apoptosis of alveolar epithelial cells [11]. The same mechanisms could be suggested for improving ILD due to SSc in our patients.

Autologous bone marrow transplantation has been performed in SSc patients with good effects in healing skin and lung complications, but this is an invasive therapeutic option with significant side effects. At the same time, MSC-EVs have not been shown to have significant side effects [12].

The strengths of the current study are that we performed a chest CT scan and PFT before and after the treatment with MSC EVs and compared them to evaluate response to the treatment. Also, we used the placenta as the source of MSC, which is available and rich in stem cells. There are some limitations to the study. For example, we tried this treatment just on one patient. Additional studies with

larger study groups are required to investigate the benefits and possible side effects of treatment with MSC EVs in SSc-related ILD. This study focused on treating lung fibrosis. The potential therapeutic effect of MSC EVs on other complications of SSc, like skin thickness and digital ulcers, should be investigated.

4. Conclusion

Herein, a severe case of ILD in a SSc patient who did not respond to standard treatments as described. Eventually, MSC EVs treatment resulted in significant improvement in the current patient's clinical symptoms and imaging findings. MSC EVs could be a potentially efficient treatment for SSc-related ILD. However, further clinical trials and research are needed.

5. Salient teaching points

- Interstitial lung disease (ILD) is among the severe complications of systemic sclerosis with the nature of inflammatory reactions.
- Mesenchymal stromal cells (MSCs) extracellular vesicles (EVs) are among the new anti-inflammatory agents recently used in different trials.
- MSCs EVs showed acceptable results in treatment of a patient with ILD caused by systemic sclerosis.
- Further clinical trials are necessary for testing this treatment option.

Ethical approval

The aim and method of the study were explained to the patient according to her level of knowledge, and she was freely asked to sign a consent form. The Medical Ethics Committee of Kermanshah University of Medical Sciences approved the study with the IRB number of IR.KUMS.REC.1400.794.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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