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Case Report

Mesenchymal Stem Cell Treatment Improves Renal Failure and Multiple Episodes of Nephrolithiasis

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Abstract

It is difficult to regenerate or recover kidney function once it has been compromised. Once compromised this can lead to nephrolithiasis and renal failure. Mesenchymal stem cells (MSCs), are the prime candidate for regenerative medicine and cell therapy. This case report describes a 58-year-old male with a history of recurrent nephrolithiasis, decreased estimated glomerular filtration rate (eGFR), elevated blood urea nitrogen (BUN), and elevated serum creatinine with a concern for chronic kidney disease (CKD), stage 3 development who was treated with a total of four MSCs treatments of 5.0×10^8 MSCs per infusion over the course of two months. Post-treatment five years later revealed no recurrent nephrolithiasis and normal eGFR, serum BUN, and creatinine levels which suggest that MSCs can be a safe and effective modern treatment for CKD and nephrolithiasis.

INTRODUCTION

Chronic kidney disease occurs when the kidneys are damaged and unable to filter blood appropriately. CKD is diagnosed when a patient has a low estimated glomerular filtration rate (eGFR), and increased blood urea nitrogen (BUN), and serum creatinine levels for a minimum of three months [1]. If left untreated CKD progressively worsens and can lead to renal failure. Renal failure occurs when the kidneys lose their ability to excrete wastes, conserve electrolytes, maintain fluid balance, and concentrate urine [2]. This results in oliguria and azotemia, which are the decrease in urine and retention of nitrogenous waste products in the blood respectively. Creatinine in the blood also increases with a declining glomerular filtration rate [3,4]. Renal failure has accelerated rates of renal function decline and formation of fibrosis, along with decreased regenerative ability in the kidneys and reduced circulating progenitor cell (CPC), count [5,6]. These factors contribute to its high rates of morbidity and mortality. Current treatments for kidney failure are pharmaceutical, surgical therapies, and invasive solutions such as conventional dialysis, and kidney transplantation [7]. Due to the kidney's limited regenerative ability, there are no effective treatments, including pharmaceutical and surgical therapies, to prevent progression to end-stage kidney failure [8]. Therefore, therapeutic interventions that improve regeneration in the kidney should be explored.

Mesenchymal stem cells (MSCs), are the prime candidate for regenerative medicine and cell therapy. MSCs can be obtained and isolated from a variety of tissues such as the umbilical cord, the placenta, amniotic fluid, adipose tissue, etc [9,10]. Their regenerative and immunomodulatory properties can promote recovery in damaged tissues, making them a promising treatment for kidney failure [11]. This case report illustrates the results obtained from a patient with renal failure treated with high-cumulative-dose allogeneic MSCs.

CASE REPORT

A 58-year-old man with a history of hypertension controlled by losartan, chronic bilateral lower extremity pitting edema for 3 years, and recurrent nephrolithiasis every 3-4 months since 2013 presented with severe alternating left and right flank and back cramps that radiated to the groin and urethra. Studies have shown that medication used to treat hypertension affects kidney function [12,13]. This can be monitored using indicators of kidney function, such as estimated glomerular infiltration rate (eGFR), blood urea nitrogen (BUN), and creatinine.

The patient's renal function test on December 30, 2014 showed BUN of 26.0 mg/dL (normal value is 8.4-25.7 mg/dL), serum creatinine of 1.00 mg/dL (normal value is 0.6-1.3 mg/dL), and eGFR of 76 mL/min (stage 2 mild CKD, eGFR = 60-89

mL/min). The patient's renal function test on January 15, 2016 showed BUN of 29.0 mg/dL, serum creatinine of 1.44 mg/dL, and eGFR of 50 mL/Min (stage 3A moderate CKD, eGFR = 45-59 mL/min). The results of the renal function tests represented a decline in the patient's kidney function and concern for kidney damage.

MSCs were prepared as described in the previous study [14]. A biopsy of gingival connective tissue from a healthy donor was minced into small pieces and cultured in αMEM (ThermoFisher Scientific, Grand Island, NY, USA), supplemented with 10% AB serum (Sigma-Aldrich, St Louis, MO, USA). Antibiotics, 100 U/ml penicillin, 100 µg/ml streptomycin, and 0.25 µg/ml Amphotericin B (ThermoFisher), were added to the culture. The medium was replaced every other day, and the cells were passaged at 85% confluence [14]. The patient received a dose of 5.0×10^8 MSCs per treatment twice a month for two months for a total of four treatments. During and after each treatment, the patient was closely monitored for any adverse reactions including, but not limited to, fever, chills, nausea, vomiting, headache, rash, pruritis, and shortness of breath, etc. No adverse reactions were observed and the patient denied all positive symptoms. The patient was routinely monitored for five years post-treatment with no recurrence of nephrolithiasis and resolution of bilateral lower extremity pitting edema. The patient denied making any dietary, lifestyle or medicinal modifications during this period. The patient's renal function test on December 16, 2016 showed marked improvement with a BUN of 22.0 mg/dL, serum creatinine of 0.88 mg/dL, and eGFR of 87 mL/Min. These results illustrate an improvement in renal function from baseline after MSCs treatment.

DISCUSSION

This in-human case shows that the primordial stem cell improved kidney function and decreased the recurrence of nephrolithiasis. MSCs provided a multifactorial treatment that helped the patient's kidney function return to normal. It shows the potential safety and therapeutic use for high-cumulative-dose MSCs for CKD. MSCs' immunomodulatory effects have anti-inflammatory effects [15,16] and promoted tissue regeneration by modulating capillary permeability, renal blood flow, and immunological responses [7,8,17,18]. MSCs' ability to self-renewing abilities can contribute to kidney repair by lowering tubular epithelial cells (TECs), apoptosis, increasing TEC proliferation, thus helping the kidney regenerate [19,20]. MSCs produce extracellular vesicles (EVs), that promote proangiogenic effects that help the renal microvasculature [21-23] and reduce renal fibrosis [24-26]. All these effects help promote the repair and recovery of damaged renal tissues, and preserve and improve renal function. MSC treatment also decreased the rate of mortality and relapse rate of malignant conditions, thus improving long-term survival [27].

Animal studies support this in-human case. Mice and canines with kidney injury treated with MSCs had significantly decreased levels of serum creatinine, decreased BUN, and demonstrated morphological and functional recovery of renal tubular epithelial cells, thus improving kidney injury [28-30]. The MSCs had promoted a switch in the macrophage phenotype that suppressed inflammatory response while simultaneously promoted kidney function [28]. Renal histology comparison between mice treated with MSCs compared to untreated mice showed MSCs treatment improved and repaired glomerular and tubular damage in the kidney [30]. In swine with hypertension, treatment of MSCs attenuated stenotic kidney injury by improving eGFR, improving renal blood flow, decreasing inflammation, decreasing oxidative stress, decreasing the number of apoptotic cells, and decreasing endoplasmic reticulum stress [31]. Interestingly, MSC treatment in swine with renovascular disease improved both cardiac function and structure as well as reversed renovascular hypertension four weeks after revascularization. It was also observed that the MSC treatment reduced oxidative stress, reduced inflammation, and preserved stenotic-kidney function [32]. In another swine study, MSCs improved kidney vascularization, tubular function, reduced fibrosis, and inflammation [33]. Studies with rats also revealed improved renal function after MSC treatment as well as the safety of the treatments [8,34].

In contrast to the cases discussed above, some studies have found that MSC therapy might cause kidney harm, including structural and functional abnormalities that vary based on the patient's features such as hypertension [35]. However, it's important to note that these patients are most likely suffering from other underlying illnesses including cancer, sickle cell disease, and/or immunological weaknesses [35]. Nonetheless, more recent data suggest that kidney injury after stem cell treatment has been decreasing due to lower myeloablative regimens, reduced exposure to amphotericin B, and decreased risks of sinusoidal obstruction [27].

In conclusion, this in-human case demonstrates that early diagnosis and treatment with MSC therapy has the potential to improve renal failure and could be the gold standard to prevent future hemodialysis or kidney transplantation. There are challenges, such as the necessity for standardization of MSC treatment methodology and limited funding available. More research is needed to validate MSCs as a successful treatment strategy for treating renal failure. The practicality and efficacy of MSC treatment, as well as the best dosing regimen and associated risks and benefits, should all be investigated.

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