

Role of Autologous Stem Cell Therapy in Relapsing Remitting Multiple Sclerosis: A Case Report

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Abstract: Multiple sclerosis is a progressive disease characterized by accumulating disability. Although advances in conventional treatment have been made to reduce the relapse rate, these modalities do little in terms of repair to the damaged CNS. Cellular therapy represents a promising approach in management of neurological conditions associated with morbid outcomes. Mesenchymal stem cells (MSC) foster repair of the CNS through tissue integration and differentiation into neural cells. Additionally, through mechanisms of neuroprotection and immunomodulation, MSCs may be effective in the treatment of multiple sclerosis. This report presents a case of relapsing remitting multiple sclerosis treated with autologous stem cells.

Keywords: Multiple sclerosis, Mesenchymal stem cells, Platelet rich plasma

I. Introduction

Multiple sclerosis (MS) is considered as an immune-mediated disease associated with immune activity directed against central nervous system antigens that frequently leads to severe physical and cognitive impairment. Structures within the nervous system damaged in MS include myelin, oligodendrocytes and underlying nerve fibers.

MS has been reported to affect more than 2 million people worldwide and is considered the most common non-traumatic cause of disability in young (<50 years) European adults [1]. MS has two distinct clinical phases corresponding to inter-related pathological processes: focal inflammation that drives activity during the relapse-remitting stage and neurodegeneration that underlies progressive disease characterized by accumulating fixed disability [2].

Histologically, active lesions are characterized by presence of macrophages containing fragments of myelin. Perivascular inflammatory infiltrate mostly composed of T-lymphocytes, reactive astrocytosis, and microglial cells are also seen. Oligodendrocytes are usually preserved or slightly reduced in newly demyelinating lesions. Chronic inactive plaques are associated with dense fibrillary gliosis, loss of oligodendrocytes, few microglial cells and marked reduction of axonal density [3].

MSCs may be effective in treatment of multiple sclerosis through mechanisms of neuroprotection, immunomodulation and neuroregeneration [4]. These properties may aid in reducing damage in the central nervous system of MS patients, which results from imbalance between the deleterious immune response and failure of the remyelinating mechanisms.

The following report describes autologous stem cell therapy along with platelet rich plasma administration in a patient with known history of multiple sclerosis unresponsive to standard therapy.

II. Case Report

A 19 year old male patient reported to StemRx Bioscience Solutions Pvt. Ltd. with the complaints of recurring gait disturbances and inability to perform daily activities effectively.

Medical history revealed that he first experienced loss of consciousness while playing on a ground before 4 years. He was unable to lift his leg thereafter and consulted a local physician for the same for which he was given medication for a brief period. Six months later, the patient was admitted to a hospital with the complaint of heaviness in his right leg and gait disturbance. Blood and radiological investigations were done and MRI revealed that the patient suffers from Multiple Sclerosis. He was under steroid medication for 3 months and the symptoms were brought under control. Over the course of the following year, the patient repeatedly had the previously mentioned complaints in addition to uncontrolled movements of the neck, inability to write, talk clearly and urine incontinence. Steroid therapy was advised which temporarily relieved the symptoms, however, the patient gradually stopped responding to the medications (in about 2 years after therapy was initiated). Thereafter, immuno-modulatory therapy with beta-interferon was given for 6 months followed by alternative

medicine modalities for 1-1.5 years, none providing any improvement of symptoms. In July 2014, the patient was bedridden following an episode of fever and general weakness.

On the patients' first visit, complete radiological and hematological investigations were done. Hematological assessment did not reveal any abnormalities with the exception of positive C-reactive protein level. The positive level indicates that CNS inflammatory response in MS is dependent on the peripheral immune compartment [5]. Fig. 1a & 1b show the MRI images taken before and after initiation of conventional treatment. Clinical assessment criteria have been presented in Table 1.

A final diagnosis of Recurrent Relapsing Multiple Sclerosis was made. The relapsing-remitting subtype is characterized by unpredictable relapses followed by periods of months to years of relative remission with no new signs of disease activity.

III. Stem Cell Therapy

Three sessions of stem cell therapy with an interval of 15 days between each session was planned for the patient during his initial stay at the hospital. Follow up was done after 3 months during which two more sessions of cellular therapy was advised. Approximately 100 ml of bone marrow from the right iliac crest, 70-80 ml of adipose tissue from right gluteal region was aspirated under local anesthesia. 50 ml of peripheral blood was obtained from right cubital vein.

Stem cell transplantation was done by intrathecal, intravenous and intranasal routes. In addition, intravenous dose of PRP, which is a platelet concentrate and a reservoir of growth factors was administered. Physiotherapy exercises, neuromuscular stimulation, yoga, nutraceuticals and a balanced diet specific for the patients' condition were advised.

IV. Results

Clinically, positive effect of treatment was defined as a decrease in EDSS of 1.0 point or greater compared with baseline. The response to cellular therapy provided was seen during the first follow up period. The patient regained some of his abilities to perform routine activities with assistance. Graph 1 shows the improvement in functional system scores following cellular therapy. The improvement noticed in individual functional systems was gradual, but that was considered a positive effect on our part as the patient was bedridden when he first reported to the hospital.

Fig. 1c shows resolution of lesions in periventricular region in an MRI taken one year after cellular therapy. However, three tiny foci of restricted diffusion involving bilateral frontal subcortical white matter region and left perirolandic subcortical fronto-parietal white matter regions were observed. Nonetheless, this is considered an improvement in comparison to the previous extent of lesions and, periodic monitoring will be done to assess any further changes and plan treatment if needed at a later stage.

It was observed that the patient could walk on his own with occasional support. Significant improvement in gait was noticed. He is now able to perform daily living activities by himself which was not possible prior to treatment.

V. Discussion

Conventional therapies for multiple sclerosis using immunosuppressants, monoclonal antibodies etc. effectively reduce inflammation, but do little in terms of repair to the damaged central nervous system [6]. Treatment with beta-interferons were considered a major advance in the treatment of this disease, however, their effect is still limited [7].

The hypothesis of the use of autologous stem cell therapy is based on the theory that environmental factors play an important role in the pathogenesis of MS and that the therapy could be used to reset the autoimmune cell line thereby restoring self-tolerance [8]. BM-MS-C can promote neuroprotection by inhibiting gliosis, scar formation and apoptosis, and by stimulating local progenitor cells. It is also possible that these cells may differentiate into neural cells and contribute to cell replacement.

Stromal vascular fraction (SVF) derived from adipose tissue has been shown to contain mesenchymal stem cells (MSC), endothelial precursor cells, preadipocytes as well as anti-inflammatory M2 macrophages [9]. MSC compartment from SVF, inhibit innate immune activation by blocking dendritic cell maturation and subsequently suppress adaptive immunity by generating T regulatory (Treg) cells and blocking cytotoxic activities of CD8 cells.

In this report, we observed an improvement in clinical parameters, the results of which are being maintained. This is consistent with findings reported by Yamout et al. (2010) who stated that early signs of clinical improvement following BM-MS-C transplant are seen in most patients by 3 months and maintained up to 1 year [10]. Also, Liang et al. (2009) reported decrease in EDSS of at least 2 points from the baseline of 8.5, in a female patient diagnosed with primary progressive MS, which was confirmed during 2 months after transplantation of allogeneic mesenchymal stem cells [11]. These reports along with our findings support the effectiveness of stem cell therapy in multiple sclerosis. This could be attributed to the potential for migration of

mesenchymal stem cells into inflamed CNS tissue and differentiation into cells expressing neuronal and glial cell markers.

Researchers have stated that myelin repair can happen without induction, probably due to activation of progenitor oligodendrocytes, causing spontaneous remyelination. It has also been found that PDGF plays an important role in multiplication and growth of these progenitor cells [12]. The administration of PRP in this patient ensured that an increased number of growth factors such as, PDGF, VEGF, TGF-beta, EGF, FGF, IGF-1, was delivered to the surgical area. PRP secrete 70% of the stored growth factors within 10 minutes and close to 100% within the first hour. Thereafter additional amounts of growth factors are synthesized upto 8 days following which the platelets die [13].

Additionally, Brain Derived Neurotrophic Factor (BDNF), which is a member of the neurotrophin family of growthfactors, has been shown to enhance CNSmyelination during development. BDNF also exerts neuroprotectiveroles following demyelination in animal models of MS [14]. Deficient BDNF in T-cells resulted in progressive disability and enhanced axonal loss while, overexpression of BDNF presented with less severe disease and axonal protection [15]. We administered BDNF drops orally as a supportive modality to enhance myelination.

The goal of diet modifications and neuromuscular rehabilitation in multiple sclerosis is to reduce the oxidative stress and aid in strength maintenance. For this purpose, a gluten free diet was advised with adequate intake of protein rich foods, cruciferous vegetables and citrus fruits. Antioxidant supplements were prescribed to further achieve improved outcomes following treatment. A gradual improvement in strength and endurance of muscle groups was noticed 4-5 months after the above protocol was initiated.

VI. Conclusion

The purpose of cellular therapy done for MS is to slow the progression of the disease, minimize symptoms during exacerbations and to improve physical and mental functions. The injection of MSC was not associated with any adverse reaction in this patient, and resulted in improvement of clinical parameters along with limiting disease progression. Nevertheless, further long term follow up is essential to assess the maintenance of results. Also, further trials are necessary to determine the required cellular dose, number of injections, timing of injections, determining the best cell subtypes (among stem cell population) to achieve optimum results in patients with multiple sclerosis as well as other autoimmune conditions.

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FIGURES, GRAPHS and TABLES

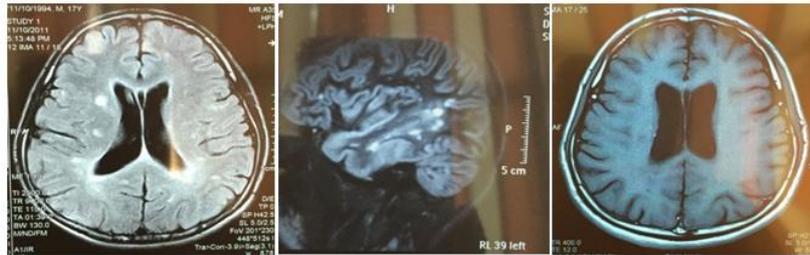
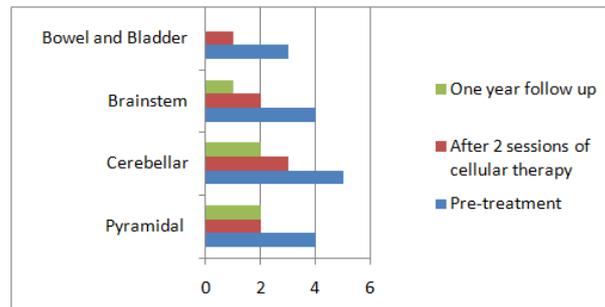


Fig. 1 a-c: 1a and b: Multifocal areas of signal abnormality noticed in periventricular area before and after conventional treatment, c: Resolution of periventricular lesions one year after cellular therapy

Index	Pre-treatment	Post-treatment (One year follow up)
Expanded Disability Status Scale (EDSS)	9.0 (Helpless bed patient; can communicate and eat).	3.0 (Mild disability in three or four functional systems though fully ambulatory)
Hauser Ambulation Index	9 (Restricted to wheelchair; unable to transfer self independently)	3 (Walks independently; able to walk 25 feet in 20 seconds or less).

Table 1: Clinical assessment criteria before and after cellular therapy



Graph 1: Kurtz functional system score changes