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Case Report

Combined intrathecal and intravenous exosome injection efficiency in a multiple sclerosis patient: a case report

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Abstract

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system with limited treatment efficacy for progressive forms. Mesenchymal stem cells (MSCs) and their secreted exosomes offer therapeutic potential via regenerative and immunomodulatory actions, including T-cell suppression and neurotrophic factor secretion. Exosomes, as cell-free alternatives, may mediate MSC effects by delivering cargo such as microRNAs, potentially promoting oligodendrocyte precursor cell differentiation and blood–brain barrier stabilization with reduced immunogenicity. Preclinical experimental autoimmune encephalomyelitis models and early MSC clinical trials demonstrate promise in reducing disease severity, although optimization of exosome sources, delivery routes (intrathecal versus intravenous), dosing, and standardization remains a challenge for clinical translation. Here, we describe a 44-year-old female with a 21-year history of progressive MS unresponsive to interferon beta-1a and Ocrelizumab, who presented with widespread neurological deficits, including sensory disturbances, weakness, and urge incontinence. Examination revealed ataxia, intention tremor, and hyperreflexia, with previous MRIs confirming MS plaques. In 2025, she received allogeneic umbilical cord-derived MSC exosomes (1 cc intrathecally; 1 cc intravenously at half dose) with adjunctive intravenous laser therapy. Within three weeks, she reported 70–80% symptomatic improvement, including resolution of Lhermitte's sign and enhanced muscle strength, vision, memory, and energy. Two-month follow-up MRIs showed persistent lesions without new contrast enhancement, indicating no active disease progression. This case highlights significant symptomatic improvement in long-standing progressive MS following combined intrathecal and intravenous allogeneic UC-MSC exosome administration. The rapid clinical benefits and absence of new MRI activity suggest a potential modulatory role for exosome therapy in MS, although these encouraging findings from a single case with adjunctive therapy necessitate larger, controlled clinical trials to validate efficacy, safety, and optimal protocols, and to elucidate underlying mechanisms.

Keywords: Multiple sclerosis, Mesenchymal stem cell, Umbilical cord-derived mesenchymal stem cells, Exosome, Mesenchymal stem cell-derived exosome.

1. Introduction

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system (CNS). Current treatments primarily target inflammation but have limited efficacy in progressive forms [1]. Mesenchymal stem cells (MSCs) and their exosomes have emerged as promising regenerative and immunomodulatory therapies [2, 3]. Below is a summary of key preclinical and clinical studies.

Mesenchymal stem cells exert their therapeutic effects in multiple sclerosis through immunomodulation by suppressing T-cell proliferation [4], reducing pro-inflammatory cytokines (IFN-γ, TNF-α, IL-17), and promoting regulatory T-cells (Tregs); neuroprotection via secretion of growth factors (BDNF, NGF, IGF-1) that enhance oligodendrocyte survival and remyelination; and anti-apoptotic effects that reduce neuronal and glial cell death [5, 6].

Exosomes derived from mesenchymal stem cells exert

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therapeutic effects in multiple sclerosis by delivering immunomodulatory miRNAs and proteins (e.g., miR-146a) to suppress inflammation, promoting remyelination through enhanced oligodendrocyte precursor cell (OPC) differentiation, and stabilizing the blood-brain barrier (BBB) to reduce disruption [7-10].

In preclinical studies using EAE models, both intravenous [11] and intrathecal [12] administration of mesenchymal stem cells (particularly bone marrow-derived MSCs) demonstrated reduced clinical severity, decreased demyelination and inflammation, delayed disease onset, and improved motor function, while adipose-derived MSCs [13] showed enhanced oligodendrocyte regeneration; similarly, MSC-derived exosomes [14] exhibited neuroprotective effects by reducing neuroinflammation, improving motor function through exosomal miR-219-mediated remyelination, and in vitro studies confirmed their ability to mitigate microglial activation and neuronal damage.

Clinical trials have demonstrated that mesenchymal stem cell therapy exhibits a favorable safety profile with no major adverse effects beyond transient fever or headaches, while showing modest but promising efficacy through improvements in expanded disability status scale (EDSS) scores, walking ability, and reduction of inflammatory markers [15-17].

While exosome clinical research remains in early stages with predominantly preclinical data, initial human case reports—including the presented case—demonstrate therapeutic potential through symptom improvement, and current investigations are actively evaluating optimal administration routes (intrathecal versus intravenous) and source material efficacy (umbilical cord versus bone marrow-derived exosomes) to advance translational applications [6].

Critical challenges in MSC and exosome therapy for MS include determining the optimal cellular source (umbilical cord versus bone marrow versus adipose-derived), establishing effective dosing regimens and delivery routes (with intrathecal administration showing potential CNS targeting advantages over intravenous), developing standardized protocols for exosome isolation and characterization, and evaluating the long-term durability of therapeutic benefits—all of which represent key priorities for future research to advance clinical translation [2, 3, 6].

Both MSCs and exosomes show potential in modifying MS progression by reducing inflammation and promoting repair. While MSC trials demonstrate safety and some efficacy, exosome therapy is still in early stages but offers a cell-free alternative with fewer risks [2, 3, 6, 16, 17]. Future research should focus on large-scale clinical trials, optimal delivery methods, and biomarker-based patient selection.

2. Case presentation

A 44-year-old female patient with a known history of MS presented to our hospital with complaints of progressive symptoms, including paresthesia, heaviness, and weakness confined to her left hand. Additional complaints included urge incontinence. Our patient reported worsened symptoms with heat and physical exertion.

Our patient had received a diagnosis of MS in 2003, which translates to a 21-year history of the disease at the time of presentation. Initial brain magnetic resonance imaging (MRI) in 2003 was positive for two MS plaques in the periventricular regions (left larger than right) and a small plaque in the right occipital lobe. No abnormalities were detected in other brain regions. Moreover, contrast-enhanced MRI of the cervical spine was initially (2003) conducted, which identified no pathologies in the region. Later in 2005, an MRI study of the thoracic spinal cord revealed a 15x6 mm MS plaque along T10 to T11. Our patient developed numerous neurological deficits, including numbness and heaviness in the face, tongue, right hand, and lower body below the T10 dermatome, reduced vibration sense, impaired fine motor movements of the right hand, and mood disturbances, throughout her 21-year course of MS.

The initial therapeutic regimen of our patient consisted of corticosteroid pulse therapy followed by weekly interferon beta-1a injection, which failed to induce clinical improvement. After 20 years of MS symptoms progression, the patient was started on ocrelizumab. Our patient received four ocrelizumab injections six months apart, without clinical improvement.

At the time of presentation, the clinical examination of our patient was positive for ataxia with a positive Romberg sign. Intention tremor observed during finger-to-nose testing bilaterally. Plantar reflexes were weak bilaterally, while hyperreflexia was observed in deep tendon reflexes. She subsequently agreed to the treatment plan and provided written informed consent. Previous MRI studies of the brain (Fig. 1 and 2), cervical spine (Fig. 3), and thoracic

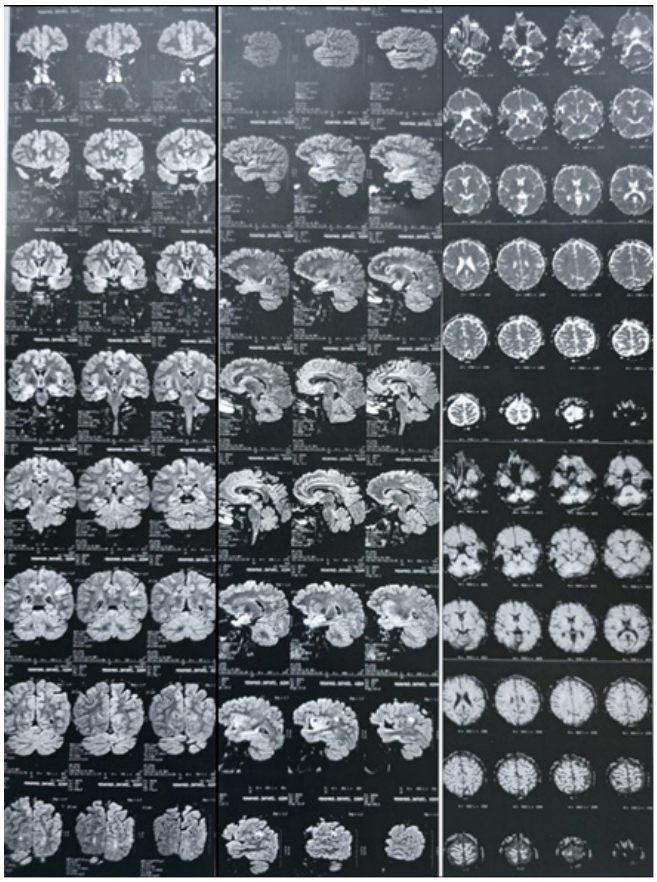

Fig. 1. Before exosome; Brain MRI without contrast was done. Technique was axial T1, T2, PD/W and sagittal T2/W and coronal T1W images. Findings are as follows: Evidence of multiple focal abnormal Signal intensity areas in periventricular & pericallosal white matter is seen, which are mostly suggestive of demyelinating plaques of multiple sclerosis.

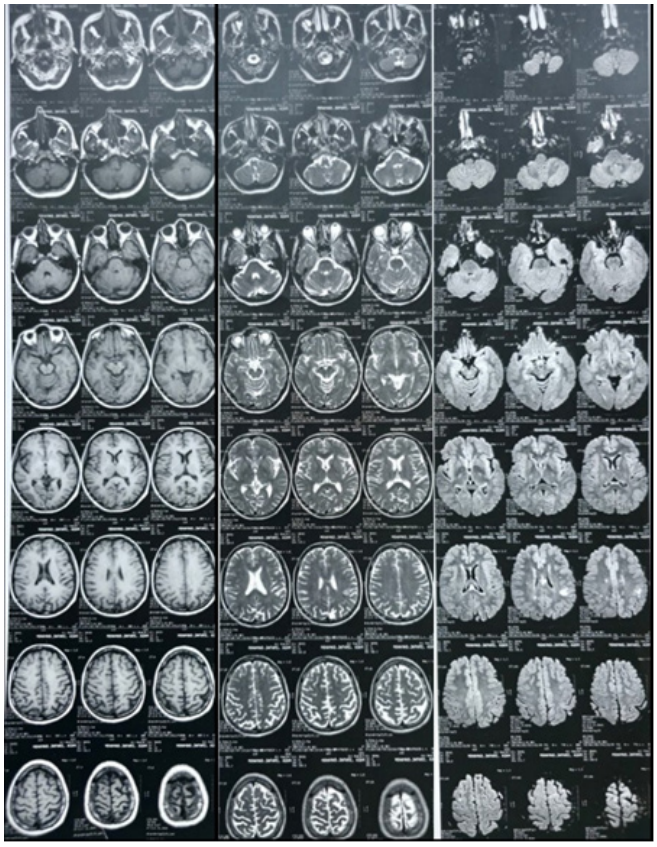

Fig. 2. Before exosome, Brain MRI with contrast was done. Technique was axial T1, T2, PD/W and sagittal T2/W and coronal T1W images. Findings are as follows: Evidence of multiple focal abnormal Signal intensity areas in periventricular & pericallosal white matter is seen, which are mostly suggestive of demyelinating plaques of multiple sclerosis.

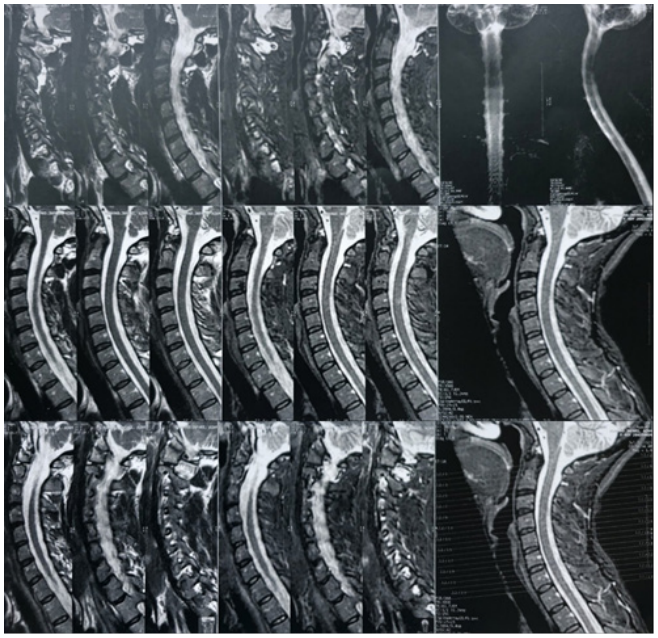

Fig. 3. Before exosome; Cervical spine MRI with contrast by technique of Sagittal T1, T2 and selected T2W images was done. Findings as follows: Single Small T2/STIR high signal Lesion in cervical cord at C4 level in favor of MS. Plaque without enhancement.

Fig. 4. Before exosome; Thoracic spine MRI with contrast, the following results were obtained. Technique was sagittal T1, T2 and selected axial T_1W images. Single T2/STIR high signal Lesion in thoracic cord at T10-T11 level is in favor of M.S plaque without enhancement. Bony structures, including vertebral bodies and posterior elements, are intact with normal signal.

spine (Fig. 4) conducted in July 2023 were reviewed as control imaging.

Regarding the failure of previous treatments, the potential benefits and hazards of allogeneic umbilical cord-derived mesenchymal stem cell (UC-MCS) exosome therapy were explained to our patients. Allogeneic UC-MSCs were isolated from full-term umbilical cords after maternal consent and infectious disease screening. MSC identity was confirmed by flow cytometry (CD73+, CD90+, CD105+, CD34–, CD45–, HLA-DR–). Exosomes were harvested from conditioned medium using tangential flow filtration and size-exclusion chromatography, concentrated in sterile PBS, and stored at –80 °C. Nanoparticle tracking analysis showed a modal diameter of 104 ± 18 nm, with a concentration of 2.4 × 10^10 particles/μL. The intrathecal dose (1 mL) contained ~2.4 × 10^13 particles (120 μg protein), while the intravenous dose was half strength (~1.2 × 10^13 particles). Western blot confirmed CD63, CD81, and TSG101 expression, with calnexin negative. Sterility, mycoplasma, and endotoxin tests were negative. Allogeneic UC-MSC exosome was injected intrathecally (1 cc) under aseptic conditions through a 25G spinal needle at the L4-L5 space, and intravenously (1cc, half strength). Additionally, our patient received intravenous laser blood irradiation (630nm, 780nm, 808nm) every other day for one week as adjunctive therapy. Within three weeks of treatment, the patient reported a 70-80% improvement in symptoms, including resolution of heaviness, numbness, and Lhermitte's sign, along with notable gains in muscle strength, vision, memory, and energy levels. While follow-up MRI revealed no active disease progression two months after the allogeneic US-MSC exosome treatment, persistent demyelinating lesions in the periventricular, centrum semiovale, and corona radiata white matter were observed (Figs 5, 6, and 7).

Contrast-enhanced thoracic spinal MRI (Fig. 8 and 9) was negative for disease activity.

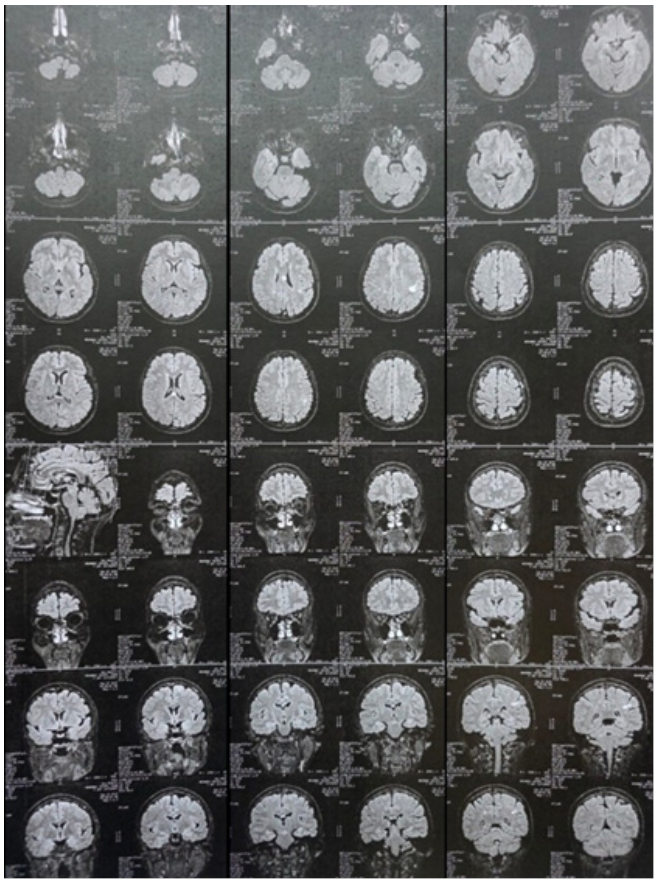

Fig. 5. After exosome, Brain MRI without contrast 2 months after injection of exosome was done. Technique was axial T1, T2, PD/W and sagittal T2/W were performed. Findings are as follows: Multiple signal change Lesions in white matter in peri and para-ventricles are seen due to demyelinating Lesions. Some of these plaques are located in semi-Centrum ovalis and corona radiata. Large tumefactive plaque in subcortex of left parietal lobe is seen with a 18x14mm dimension.

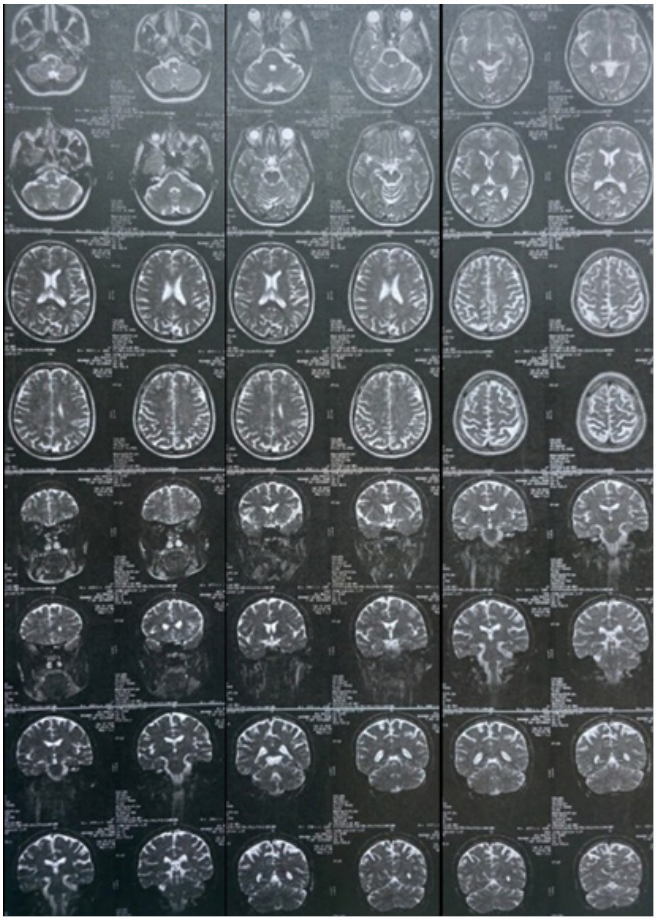

Fig. 6. Before exosome, Brain MRI with contrast was done. Technique was axial T1, T2, PD/W and sagittal T2/W and coronal T1W images. Findings are as follows: Evidence of multiple focal abnormal Signal intensity areas in periventricular & pericallosal white matter is seen, which are mostly suggestive of demyelinating plaques of multiple sclerosis.

3. Discussion

The present case report details the combined intrathecal and intravenous administration of allogeneic UC-MSC exosomes to a 44-year-old female patient with a 21-year history of progressive MS, who had previously shown limited response to conventional disease-modifying therapies. The patient exhibited a notable 70–80% symptomatic improvement within three weeks of receiving combined intrathecal and intravenous exosome administration, with follow-up MRI indicating no active disease progression. These findings, while from a single case, contribute to the growing interest in cell-free therapies, particularly exosome-based approaches, for neuroinflammatory and neurodegenerative conditions like MS.

The rationale for exploring exosome therapy in MS stems from the well-documented immunomodulatory and regenerative capacities of their parent MSCs [6]. MSCs have demonstrated therapeutic potential in preclinical MS models (EAE) and early phase clinical trials, attributed to their ability to suppress detrimental immune responses, protect neurons, and potentially promote myelin repair [6, 12]. Exosomes, as nanoscale vesicles secreted by MSCs, are believed to carry much of the therapeutic cargo—including proteins, lipids, and miRNAs—that mediates these beneficial effects [18, 19]. The use of exosomes offers several potential advantages over direct cell transplantation, such as a lower risk of immunogenicity, no risk of ectopic differentiation or malignant transformation, and the ability to cross biological barriers like the BBB more readily due to their small size [18-20]. Barabadi et al., in a systematic review and meta-analysis of preclinical studies, concluded that stem cell-derived extracellular vesicles (EVs), including exosomes, significantly reduced disease severity and neuroinflammation in animal models of MS, supporting their therapeutic investigation [21].

The choice of UC-MSCs as the exosome source in this case is of significant gravity. UC-MSCs are considered an attractive cell source due to their ease of collection via non-invasive methods, high proliferative capacity, and potent immunomodulatory properties, which may surpass those of bone marrow or adipose-derived MSCs [6]. Alanazi et al. (2022) highlight that UC-MSCs exhibit lower immunogenicity, making allogeneic transplantation, as in our case, more feasible.

The route of administration is a critical factor in delivering therapeutics to the CNS. This patient received both intrathecal and intravenous exosomes. Intrathecal administration aims to deliver exosomes directly into the CSF, thereby bypassing the BBB and potentially achieving higher therapeutic concentrations at target sites within the CNS [12, 18]. This route was recently explored by Akhlaghpasand et al. in a phase I clinical trial for complete subacute spinal cord injury (SCI), where intrathecal administration of allogeneic UC-MSC-derived exosomes was found to be

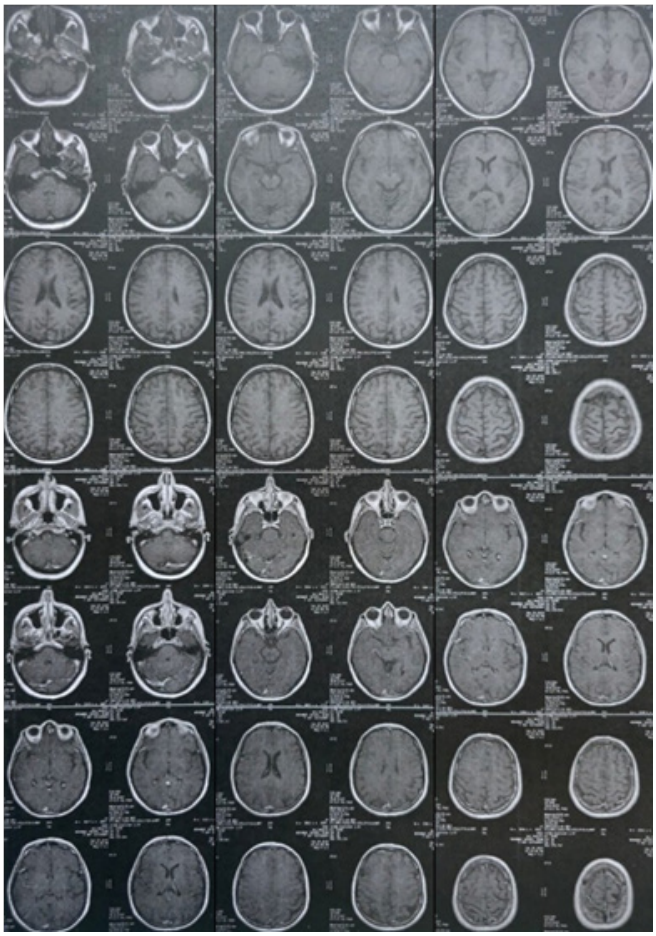

Fig. 7. After exosome, Brain MRI without contrast 2 months after injection of exosome was done. Technique was axial T1, T2, PD/W and sagittal T2/W were performed. Findings are as follows: Multiple signal change Lesions in white matter in peri and para ventricles are seen due to demyelinating Lesions. Some of these plaques are located in semi-Centrum ovalis and corona radiata. Large tumefactive plaque in subcortex of left parietal lobe is seen with 18x14mm dimension.

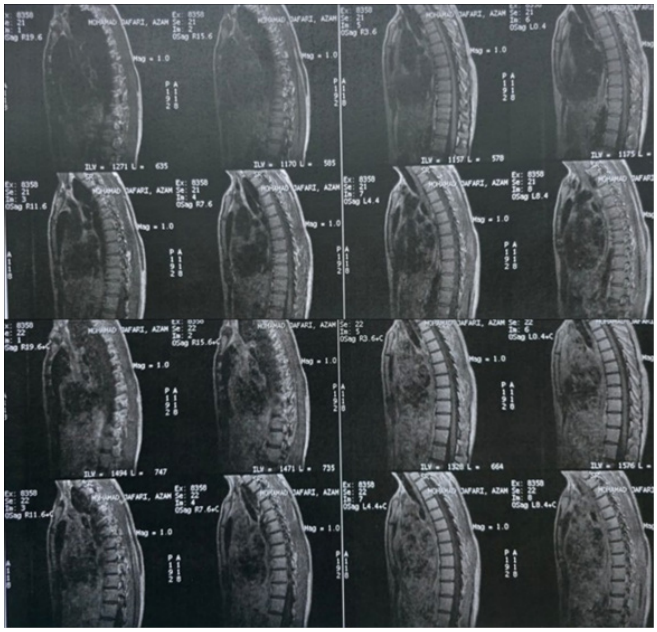

Fig. 8. After exosome, Thoracic spine MRI without contrast was done as well. Technique was sagittal T1, T2/W and selected axial T1/W images were performed. Reveal no CSF block or extrinsic pressure in thoracic region. Vertebral bodies, disc spaces, bone marrow signal, posterior elements, dural sac and nerve root canals appear normal. In post-Gd-DTPA injection images, no abnormal enhancement is seen.

Fig. 9. After exosome, Thoracic spine MRI with contrast was done as well. Technique was sagittal T1, T2/W and selected axial T1/W images were performed. Reveal no CSF block or extrinsic pressure in thoracic region. Vertebral bodies, disc spaces, bone marrow signal, posterior elements, dural sac and nerve root canals appear normal. In post-Gd-DTPA injection images, no abnormal enhancement is seen.

safe and associated with potential clinical improvements [22]. While systemic (intravenous) administration is less invasive, the efficiency of exosome transit across the BBB remains a subject of investigation [18, 20]. Morando et al. noted that even with systemic MSC administration in EAE models, therapeutic effects were observed both peripherally and centrally, despite limited CNS engraftment, suggesting that peripherally administered exosomes might also exert central effects, possibly through both direct CNS penetration and modulation of peripheral immune cells that subsequently traffic to the CNS [12]. The dual-route approach used here may thus combine the benefits of direct CNS targeting with systemic immunomodulation.

The observed rapid and substantial clinical improvement (70-80% within three weeks) in this patient, who had a long-standing progressive disease, is striking. Symptoms such as heaviness, numbness, Lhermitte's sign, muscle strength, vision, memory, and energy levels all reportedly improved. Such broad improvements suggest effects on both inflammatory and neurodegenerative aspects of MS. Preclinical studies consistently demonstrate that MSC-derived exosomes can reduce neuroinflammation, promote OPC differentiation into mature oligodendrocytes, and enhance remyelination [19, 23]. Zhang et al. showed that exosomes from rhesus monkey MSCs improved neurological outcomes in EAE mice by increasing mature oligodendrocytes and MBP levels, decreasing amyloid-β precursor protein (APP) density (a marker of axonal injury), and shifting microglia from a pro-inflammatory M1 to an anti-inflammatory M2 phenotype, partly by inhibiting the TLR2/IRAK1/NFκB pathway [23]. The neuroprotective effects observed in EAE models [12] and the promotion of

cognitive function in various neurological condition models by exosome therapy [19] further support the diverse benefits reported in this case.

The MRI finding of "no active disease progression" two months post-treatment, characterized by the absence of new contrast-enhancing lesions, is a positive sign, indicating a halt in new inflammatory activity. However, the persistence of demyelinating lesions is expected over this short follow-up period. True remyelination and structural repair are longer-term processes. The large tumefactive plaque noted in the post-exosome brain MRI, lacking contrast enhancement, was likely a chronic, inactive lesion. Longer-term imaging follow-up would be necessary to ascertain any changes in lesion volume or evidence of remyelination.

The mechanisms underlying the therapeutic effects of exosomes are multifaceted. Their cargo, rich in miRNAs, proteins, and lipids, can modulate various cellular pathways in recipient cells [18]. Immunomodulation is a key aspect, involving the suppression of pathogenic T-cell responses, induction of regulatory T-cells, and modulation of macrophage/microglia activity towards an anti-inflammatory, pro-regenerative state [6, 23]. For example, Li et al. demonstrated that MOG-peptide modified exosomes derived from anti-inflammatory macrophages could induce antigen-specific immune tolerance in an EAE model by promoting tolerogenic dendritic cells and regulatory T cells [24]. Neurotrophic factors and anti-apoptotic molecules delivered by exosomes may directly support neuronal survival and function [19]. Furthermore, specific miRNAs within exosomes, such as miR-219 (implicated in oligodendrocyte differentiation and remyelination) or those discussed by Mosora et al. in the context of MS progression, may play crucial roles [25]. The adjunctive intravenous laser therapy also warrants consideration as a potential contributor to the observed effects, although its specific impact cannot be disentangled in this case report.

This case report, while highly encouraging, has limitations inherent to a single-patient study without a control group. The observed benefits could represent an exceptional individual response or be influenced by the placebo effect. The contribution of the adjunctive laser therapy cannot be excluded. Standardized, quantitative outcome measures beyond subjective symptom reporting would strengthen future investigations. Nevertheless, the report aligns with the therapeutic promise shown in preclinical models [12, 21, 23, 24] and early human studies in related conditions [22].

Future research must focus on conducting rigorous, placebo-controlled, multicenter clinical trials to definitively establish the safety and efficacy of exosome therapy in MS. Key areas include the optimization of exosome sourcing, isolation, characterization, dosing, and administration routes [18, 20]. The development of exosome engineering strategies to enhance targeting or enrich therapeutic cargo [18, 20] also holds promise. Identifying biomarkers, potentially including specific exosomal miRNAs [25], to predict treatment response and monitor efficacy will be crucial for personalizing therapy. Long-term follow-up is essential to determine the durability of the observed effects and to monitor for any late adverse events.

4. Conclusion

This case report describes marked symptomatic improvement in a patient with progressive multiple sclerosis following combined intrathecal and intravenous administration of allogeneic UC-MSC exosomes, accompanied by adjunctive intravenous laser therapy. The short-term absence of new MRI activity and the rapid clinical changes are intriguing, but given the inherent limitations of a single uncontrolled case and the presence of a confounding co-intervention, these observations should be considered preliminary and hypothesis-generating. Larger, controlled clinical trials are required to determine whether exosome therapy is safe, reproducible, and truly effective in modifying the course of multiple sclerosis.

Abbreviation

MS (Multiple Sclerosis), CNS (Central Nervous System), MSCs (Mesenchymal Stem Cells), EAE (Experimental Autoimmune Encephalomyelitis), OPC (Oligodendrocyte Precursor Cell), BBB (Blood-Brain Barrier), EDSS (Expanded Disability Status Scale), UC-MSC (Umbilical Cord-derived Mesenchymal Stem Cell), MRI (Magnetic Resonance Imaging), IFN-γ (Interferon-gamma), TNF-α (Tumor Necrosis Factor-alpha), IL-17 (Interleukin-17), BDNF (Brain-Derived Neurotrophic Factor), NGF (Nerve Growth Factor), IGF-1 (Insulin-like Growth Factor-1), miRNA (MicroRNA), Tregs (Regulatory T-cells), APP (Amyloid-β Precursor Protein), TLR2 (Toll-like Receptor 2), IRAK1 (Interleukin-1 Receptor-Associated Kinase 1), NFκB (Nuclear Factor Kappa B), EVs (Extracellular Vesicles), SCI (Spinal Cord Injury), MBP (Myelin Basic Protein)

Conflict of interest

The authors declare that they have no conflict of interest.

Consent for publications

All authors confirm that they have read and approved the final version of the manuscript for publication.

Ethics approval and consent to participate

This case report was conducted in accordance with the ethical standards of the institutional and national research committees and with the principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethical Committee of the University of Ardebil.

Informed consent

Written informed consent was obtained from the patient for participation in this study after a detailed explanation of the treatment plan, potential risks, and anticipated benefits. The patient reviewed the manuscript and provided written consent for the publication of clinical details and any potentially identifiable images, with the understanding that anonymity would be preserved to the greatest extent possible.

Availability of data and materials

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Authors' contributions

A.M.J. and K.S. conceived and designed the study. A.M.J., K.S., and M.K. collected clinical data and managed the patient's treatment. Y.Z.M., M.W., and H.M.W. contributed to the development and optimization of the exosome and

laser therapy protocols. S.A.G. performed and interpreted the radiological assessments. F.H., N.T.H., and M.A. contributed to clinical evaluation, patient follow-up, and data interpretation. A.M.J. drafted the initial manuscript. All authors read and approved the final version of the manuscript.

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