EJCRIM
European Journal
of Case Reports
in Internal Medicine

TRANSVERSE MYELITIS SUCCESSFULLY TREATED WITH POSTERIOR DECOMPRESSION FOLLOWED BY SECRETOME AND MESENCHYMAL STEM CELL THERAPY

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Received: 02/04/2025
Accepted: 08/04/2025
Published: 16/05/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: The patient's parents provided written informed consent for the publication of his case.
Acknowledgments: We would like to thank all team that threated our patient in this report: Dr. Irwan Susanto Hermawan (director of Mayapada Hospital Bandung) and Dr. Deasy Sugesty (director of Mayapada Hospital Kuningan); Gatot Soebroto Army Hospital as our foster Hospital and Indonesia Stem Cell Committee. Ahmad Faried supported by the Grants-in-Aid (Center of Excellent) from Faculty of Medicine, Padjadjaran University Hospital, Jatinangor, West Java, Indonesia.
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How to cite this article: Faried A, Pribadi MA, Wibawa GA, Lazuardy MA, Farhan MR. Transverse myelitis successfully treated with posterior decompression followed by secretome and mesenchymal stem cell therapy. *EJCRIM* 2025;**12**:doi:10.12890/2025_005391

ABSTRACT

Introduction: Transverse myelitis (TM) is a rare spinal cord disorder caused by inflammation. Usually, this occurs as a complication of infection or autoimmune disease; however, idiopathic causes such as vaccinations have been reported. There have been no studies that include the use of stem cells for TM in an inpatient setting. We present a case demonstrating the efficacy of stem cell therapy in the treatment of TM.

Case presentation: A 5-month-old boy developed TM (he abruptly developed paraplegia, paraesthesia of both legs, urinary retention) 7 days after he received the pneumococcal conjugate vaccine (PCV). Laboratory tests were all negative except for evidence of recent PCV vaccination. A paediatric neurologist confirmed the diagnosis when the boy was 2.5 years old. Magnetic resonance imaging of thoracic spine showed hyperintense central and dorsal cord abnormalities beginning at the T2 level and extending into the thoracic cord at T6. The pattern was consistent with TM. Decompression laminectomy was performed. The patient was then given mesenchymal stem cell (MSC)-derived secretome and umbilical cord mesenchymal stem cell (UCMSC) administered intrathecally (3× within interval 4 weeks). After the first, treatment he began to show significant improvement in terms of motor function and the patient also showed increasing in autonomic function especially in erectile function. After the 2nd treatment there was adequate muscle response of the lower limbs, and his medical rehabilitation specialist trained him to do standing exercises. After the 3rd treatment there was adequate muscle response of the lower limbs, and his medical rehabilitation specialist trained him to walk.

To the best of our knowledge this is the first reported case of TM treated with stem cells in Indonesia. The pathophysiology of TM is an inflammatory disorder of the spinal cord that damages the myelin sheath of nerve fibres. Two primary therapies for TM are glucocorticoids and plasma exchange. Further, treatment options such as with secretome and UCMSCs promote both microenvironment correction and myelin regeneration.

To the best of our knowledge our case is the first reported case of TM in Indonesia treated with stem cells.

Conclusion: Our case demonstrates the potential of stem cell therapy as an alternative treatment modality in a case there was no other optional therapy for longitudinal extensive TM.

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

KEYWORDS

Transverse myelitis (TM), longitudinally extensive transverse myelitis (LETM), secretome and mesenchymal stem cells therapy

LEARNING POINTS

- Alternative therapy with mesenchymal cell-derived secretome and umbilical cord mesenchymal stem cells is very effective for longitudinally extensive transverse myelitis.

INTRODUCTION

Transverse myelitis (TM) is a rare inflammatory spinal cord injury caused by acute inflammation often presenting with rapid onset of weakness and sensory deficits; autonomic features of TM include urinary urgency, bowel/bladder incontinence, difficulty/inability to void, bowel constipation, or sexual dysfunction. Urinary retention may be the first myelitis sign and should warrant further study of myelopathy. A rare subtype of TM, longitudinally extensive transverse myelitis (LETM), refers to the inflammation of the spinal cord, involving three or more vertebral segments[1]. As TM progresses, it may cause severe disability. Usually, TM as a complication from infection or autoimmune disease; however, idiopathic causes such as vaccinations have been reported. TM generally occurs around the spinal cord at any level but most commonly affects the thoracic region. The disorder transverses the spinal cord, causing bilateral deficiencies. The duration of TM may be as little as 3 to 6 months or TM may become permanently debilitating[2].

One of the treatment options is promoting repair of the damaged myelin sheaths of the nerve fibres using stem cell derived therapy. It is widely believed that stem cells have the capacity for direct cell replacement and secrete neurotrophic substances, thereby boosting all the process of cells regeneration. Reported after transplantation of MSCs into the spinal cords of patients with TM, these cells will improve spinal cord oedema and severe inflammation caused by myelitis and promoting oligodendrocytes to produce myelin. Herewith, we present a case demonstrating the potential of MSC therapy in the treatment of TM.

CASE DESCRIPTION

In January 2022, a 5-month-old boy was referred by his general practitioner to a major hospital in a regional Bandung city. The infant boy had suddenly developed apparent weakness of both legs, abruptly developed



Figure 1. A 5-month-old boy developed transverse myelitis (TM) 7 days after PCV vaccination. A paediatric neurologist confirmed the diagnosis of TM when the boy was 2.5 years old. Clinical findings were paraplegia, paraesthesia of both legs and autonomic nerves deficits. He had difficulty rolling over, always using his hands to move his legs and feet. He was unable to stand and even had to crawl instead of walk.

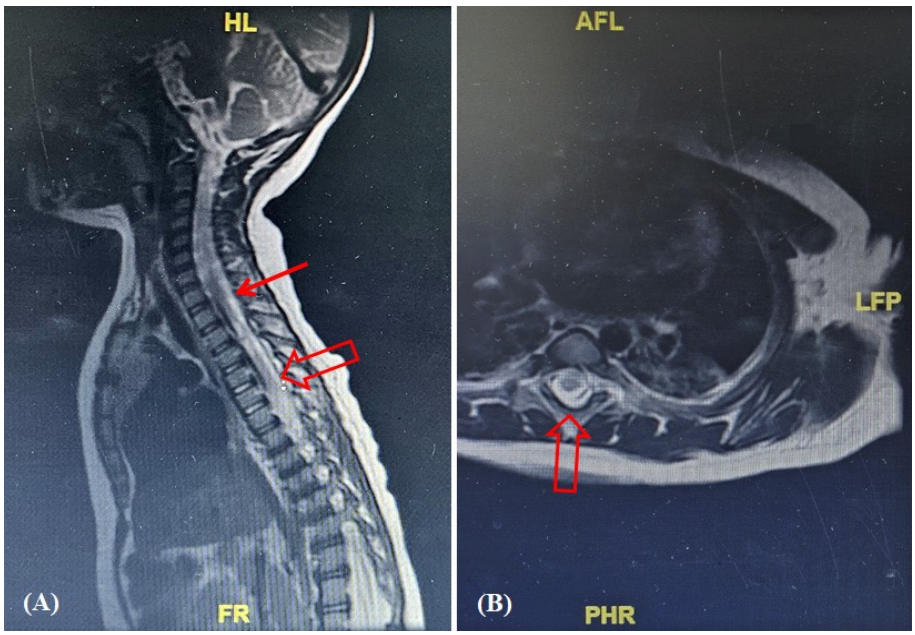


Figure 2. T2-weighted thoracic spine magnetic resonance imaging. A) A T2-weighted sagittal image shows multi-segmental longitudinal, high-signal-intensity lesions with the cord swelling at T2- (thin red arrow) down to T6 (thick red arrow; B) Axial view of a T2-weighted image showing a centrally located lesion occupying more than half of the cord at T6 (thick red arrow).

paraplegia, paraesthesia of both legs and urinary retention. He had had a normal vaginal delivery and had been reviewed by maternal and child health nurses who had noted normal development, including the commencement of crawling, prior to the onset of this episode. He had received his first scheduled vaccinations in December 2021, at the age of 4 months. Seven days prior to the onset of symptoms he had received his scheduled vaccinations, which were conjugated pneumococcal vaccine and rotavirus. The child was reviewed by physiotherapists in Bandung in which he had been hospitalized and at the age of 8 months, was referred to Jakarta Paediatric Rehabilitation Center, because of continuing problems with autonomic nerves include urinary urgency, bowel/bladder incontinence, difficulty/inability to void, bowel constipation and erectile dysfunction. Paediatric assessment confirmed reduced saddle and rectal sensation. Severe weakness of both lower limbs was also observed, and the patient had not been able to stand-up and to walk *(Fig. 1)*. The diagnosis of TM was confirmed at the age of 2.5 years old, based on the presenting symptoms, laboratory results, the subsequent evolution of symptoms and examination findings at the time. The diagnosis was consistent with the criteria proposed in 2002 by the Transverse Myelitis Consortium Working Group[3].

Magnetic resonance imaging (MRI) revealed multisegmented longitudinal lesions, relatively firm boundaries, irregular edges at the level of thoracic vertebral bodies 3-4 (VT3-4) that provided isointense signal changes on T1W1 and hyperintense changes on T2W1 and T2FS. Thickening of the thecal sac on the left lateral aspect at the level of VT2-6 indicated that there was an intramedullary mass that provided isointense signal changes on T1W1 and hypointense changes on T2W1 and T2FS. A sagittal view showed swelling fromVT2 down to VT6 *(Fig. 2A)*. An axial view of a T2-weighted image showing a centrally located lesion occupying more than half of the spinal cord at VT6 *(Fig. 2B)*. These findings are consisted with the diagnosis of compressive LETM. Subsequently, we decided to perform decompression laminectomy followed by intramuscular administration of mesenchymal stem cell-derived secretome along with allogeneic umbilical cord mesenchymal stem cells (UCMSCs) intrathecally 3× within 4 weeks *(Fig. 3)*. Secretome and UCMSCs were provided by Regenic authorized by the Indonesian Food and Drug Authority (BPOM). After the first administration, the patient began to show a significant improvement in terms of motor function and also showed increasing improvement in autonomic function especially in erectile function. After the second administration there was adequate muscle response of the lower limbs, and his medical rehabilitation specialist trained him to do standing exercises. After the third administration of UCMSCs there was adequate muscle response of the lower limbs, and his medical rehabilitation specialist trained him to walk *(Fig. 4)*.

DISCUSSION

To the best of our knowledge our case is the first reported case of TM in Indonesia treated with stem cells. Clinically, the hallmark of TM is inflammatory spinal cord injury caused by acute inflammation often presenting with rapid onset of weakness, sensory deficits and autonomic nerves deficits. Imaging studies that used frequently for diagnosing TM is MRI. In this report, an MRI of the thoracic spine revealed hyperintense central and dorsal cord abnormalities beginning at the T2 level and extending into the thoracic cord at the T6. The pattern was consistent with TM. The primary approach to managing TM involves addressing the issues associated with both intravenous glucocorticoids and plasma exchange therapy[4]. As currently, there is a lack of therapeutic options specifically designed for TM.

Mesenchymal stem cells (MSCs) have potential to treat TM. This disease is caused by inflammation in the spinal cord, which can lead to partial or total paralysis[1]. Inflammation is a way for our body to protect itself; since the spinal cord is tightly wrapped in bonny vertebrae, there is no room



Figure 3. We performed a A) decompression thoracic laminectomy at thoracic Vertebrae T3 to T5, and B) intramuscular administration of secretome with allogeneic UCMSCs intrathecally 3 times within 4 weeks.

for swelling or oedema caused by inflammation. Even a minor inflammation applies significant pressure and thus could damage the spinal cord. Among a variety of cell candidates for allogeneic transplantation, human UCMSCs are an attractive choice for treating intractable spinal cord injury because they are easy to obtain, there is no ethical controversy, they proliferate rapidly, and they have an immune and paracrine effect[5]. Human UCMSCs have been shown to modulate microglia and their pro-inflammatory status through secreted factors. When exposed to LPS-activated astrocyte-conditioned medium, human UCMSCs expressed the anti-inflammatory protein TSG-6 messenger ribonucleic acid seven fold more than when exposed to a saline solution[6].

The immunomodulatory effects of the MSC secretome have been studied in the murine experimental autoimmune encephalomyelitis (EAE) models of demyelinating diseases. Zhang et al., showed hBM-MSC treatment increased both axonal density in the white matter of EAE mouse brains and numbers of nerve growth factor (NGF)-reactive brain parenchymal cells[7]. MSC-based therapies for immune disorders, i.e. autoimmune diseases, have been shown to



Figure 4. After the first administration, A) the patient began to show significant improvement in terms of motor function and also increasing improvement in autonomic function especially in erectile function; B) After the second administration of UCMSCs there was adequate muscle response of the lower limbs, and his medical rehabilitation specialist trained him to do standing exercises; C) After the third administration of UCMSCs there was adequate muscle response of the lower limbs, and his medical rehabilitation specialist trained him to walk.

be promising mainly due to their immunomodulatory and anti-inflammatory activity. MSCs have been tested in many animal models of demyelinating diseases, such as EAE, either alone or in combination with other agents, as genetically modified cells, or as culture medium from MSCs[8]. Further, an overview of emerging therapies demonstrated that intrathecal delivery of MSCs, to bypass the blood brain barrier, led to functional improvement in patient with demyelinating diseases[9].

The first administration of subarachnoid stem cells for spinal cord injury was in 2008. This convenient, minimally invasive technique has been considered the safest and most effective approach for cell delivery because of less retention in other organs, reduced host immune response, more cell engraftment and better tissue sparing in the injured spinal cord[10]. Previous studies have suggested that transplanting a greater number of cells is advisable because stem cell therapy has a dose-dependent effect. Thus, repeated cell administrations, which are facilitated by the ease of repeatability, in our case 3 times, from intrathecal transplantation delivery, seem to be more beneficial for patients with spinal cord diseases[10].

In the absence of treatment guidelines for patients suffering from inflammatory caused spinal cord injury, especially for the Asian population, Yang et al., presented a protocol that demonstrates that intrathecal administration of allogeneic human UCMSCs at a dose of 10^6 cells/kg once a month for 4 months is safe and effective and leads to significant improvement in neurological dysfunction and recovery of quality of life[11]. This report demonstrated that the administration of secretome and human UCMSCs is believed to have the ability to release paracrine factors, modulating microglia (inflammation) activation, thereby augmenting spinal cord repair; resulted in notable improvements in motor and functional outcomes. Consequently, this therapy is efficacious for cases of longitudinally extensive transverse myelitis (LETM).

CONCLUSION

TM is a rare progressive case that if not promptly addressed, can result in severe disability. Stem cell therapy along with additional secretome is a promising treatment modality for promoting both microenvironment correction and myelin regeneration, thereby improving both motor and functional outcomes. Our case demonstrates the potential of stem cell therapy as an alternative treatment modality for LETM.

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