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Case report

Outcomes of cell infusion for the treatment of neurological sequelae induced by spinal anesthesia-associated subdural hematoma: A case report

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ABSTRACT

Background: Subdural hematoma following spinal anesthesia for cesarean delivery is a rare complication. Surgical removal of the hematoma is the standard treatment. However, there are still many patients who suffer permanent nerve damage of varying degrees after surgery. Cell therapy has recently shown great potential for treating nerve damage.

Case presentation: This report described a case of paraplegia due to an epidural hematoma occurring after spinal anesthesia for cesarean section. The patient underwent surgery to remove the hematoma and rehabilitation afterward. However, no improvement was noted. Paralysis of the lower extremities associated with urinary retention and constipation persisted. The patient received three administrations of cell infusion: the first time with autologous bone marrow-derived mononuclear cells and the following two with autologous adipose mesenchymal/stromal cells. After three cell infusions, the patient was able to walk and could urinate and defecate voluntarily. Sensory and motor function were improved and MRI showed a decrease in adherence of the nerve roots and spinal cord.

Conclusions: Our results demonstrated that cell therapy may ameliorate paralysis of the lower extremities as well as fecal and urinary function following spinal hematoma associated with spinal anesthesia.

1. Introduction

Hematomas in the spinal cavity can be epidural, subdural, subarachnoid, and intramedullary [1]. Ruppen et al. showed that the incidence of epidural hematoma after epidural anesthesia for cesarean section was 1 in 168,000 [2].

Hematoma in the spinal canal compresses the spinal cord, leading to partial or complete paralysis of the lower extremities along with bowel and bladder dysfunction. Nerve damage may be reversed if early decompression surgery to remove the hematoma is performed. In contrast, nerve damage can be permanent if the surgery is delayed [3]. Although rehabilitation is the standard treatment

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for neurologic sequelae following intraspinal hematoma, positive outcomes are limited for cases with permanent nerve damage [1]. Recently, cell therapy has been applied to spinal cord injury (SCI) and intracranial lesions with promising results [4,5]. However, to our knowledge, there are no reports of using cell therapy to treat paralysis of the lower extremities due to hematoma following spinal anesthesia.

The aim of this report is to present the case of a woman experiencing paraplegia of the lower extremities associated with bowel and urinary dysfunction caused by a hematoma in the spinal cord after regional anesthesia who did not recover after rehabilitation. The patient underwent a comprehensive treatment approach involving a combination of cell therapy and rehabilitation. Due to their immediate availability after isolation and no need for a time-consuming cell culture, BMMMCs were infused first. Additionally, to expedite the delivery of cell therapy to the patient without performing an invasive procedure again, AD-MSCs cultured from adipose tissue, which were isolated during anesthesia for bone marrow aspiration, were employed for the second and third cell infusion. After the treatment, the patient's sensory and motor functions significantly improved, as well as voluntary control over walking, urination, and defecation, accompanied by positive changes observed in MRI scans. Together, our results indicate that the implementation of a comprehensive treatment approach combining cell therapy and rehabilitation yielded remarkable results for the patient, offering promising prospects for future applications in similar cases.

1.1. Cell preparation and characterization

A 300 ml bone marrow aspirate was harvested through the patient's anterior iliac crests under general anesthesia. After bone marrow aspiration, a 1 × 1 × 2 cm adipose mass was collected through a small incision in the right abdominal fold. For the first infusion, BMMNCs were isolated by gradient centrifugation using Ficoll-Paque (GE Healthcare, Sweden). The cell suspension was then washed with phosphate-buffered saline (PBS), analyzed for total mononuclear cells and $CD34^+$ cells by flow cytometry, and resuspended in 10 ml of 0.9% NaCl for administration. The adipose tissue was cut into small pieces and digested in 200 U/mL collagenase (Gibco, USA) for 1 hour at 37 °C. Isolated cells were cultured in culture flasks (Nunc; Thermo Fisher Scientific, USA) coated with CellStart substrate (Thermo Fisher Scientific) containing MSC culture medium supplemented with 50 U/mL penicillin/streptomycin (Life Technologies, USA) at 37 °C with 5% CO_2 for 7 days. The cells were cultured in fresh media without antibiotics and harvested when the cells reached 80% confluency. The cells were then stored in liquid nitrogen for further use. For the second and third cell infusions, the AD-MSCs at passage 1 were thawed and cultured to passage 3 to obtain a homogenous cell population. The cells were prepared in 10 ml of 0.9% NaCl (Braun, USA) at a dose of 1×10^6 cells/kg of body weight for injection.

Before infusion, the viability of the cell product was measured by staining with Trypan blue and counted using a countess cell counter or by manual counting under a microscope. The cell viability of BMMNCs was 99.2%, and AD-MSCs for the second and third infusions were 96.3% and 98.6%, respectively. Flow cytometry analysis showed that the AD-MSCs exhibited normal MSC marker expression with 99.92% CD73, 99.95% CD90, 99.78% CD105, and 0% for negative markers (for the second infusion), 99.89% CD73, 99.71% CD90, 98.69% CD105, and 0.1% for negative markers (for the third infusion). The cells had normal karyotypes and were negative for mycoplasma, bacteria, and fungi.

1.2. Case presentation

The timeline of the case presentation is described in Fig. 1. A 35-year-old woman with an unremarkable health history underwent spinal anesthesia combined with a spinal epidural block for a second C-section on August 10th, 2020 (her first C-section for the first child on April 10, 2013). On postoperative day 2, the patient showed numbness, weakness in both legs, and urinary retention. Spinal MRI on August 18th, 2020, detected hypointensity due to hemosiderin deposits, heterogeneously hypointense cerebrospinal fluid at the lumbar region, thickening and adhesion of the cauda equina at L3, and adhesion of the cauda equina nerve roots (Fig. 2A).

A decompressive operation was performed to remove the hematoma at L1, L2, and L3 on August 19th, 2020. However, the patient still had paralysis of the 2 lower extremities, urinary retention, constipation, loss of sensation, and neuropathic pain in the lower extremities. Clean intermittent catheterization was carried out 4–6 times/day. Rehabilitation after the decompressive operation, including physical therapy (passive range-of-motion exercises), was applied for 36 days (from August 19th, 2020, to September 25th,

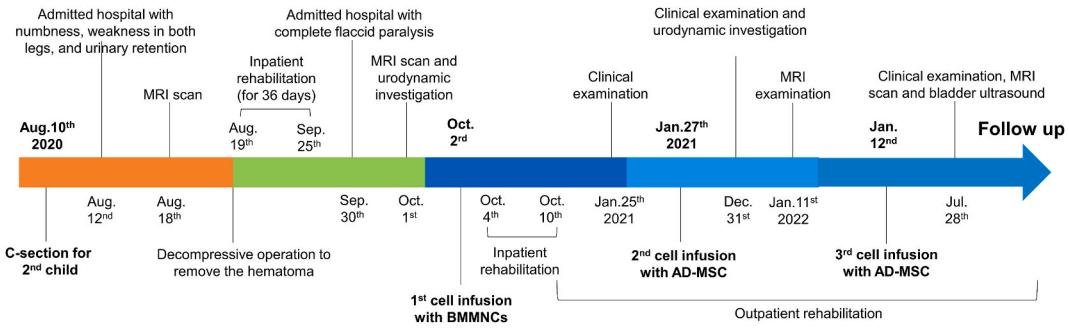

Fig. 1. Timeline of the case presentation description.

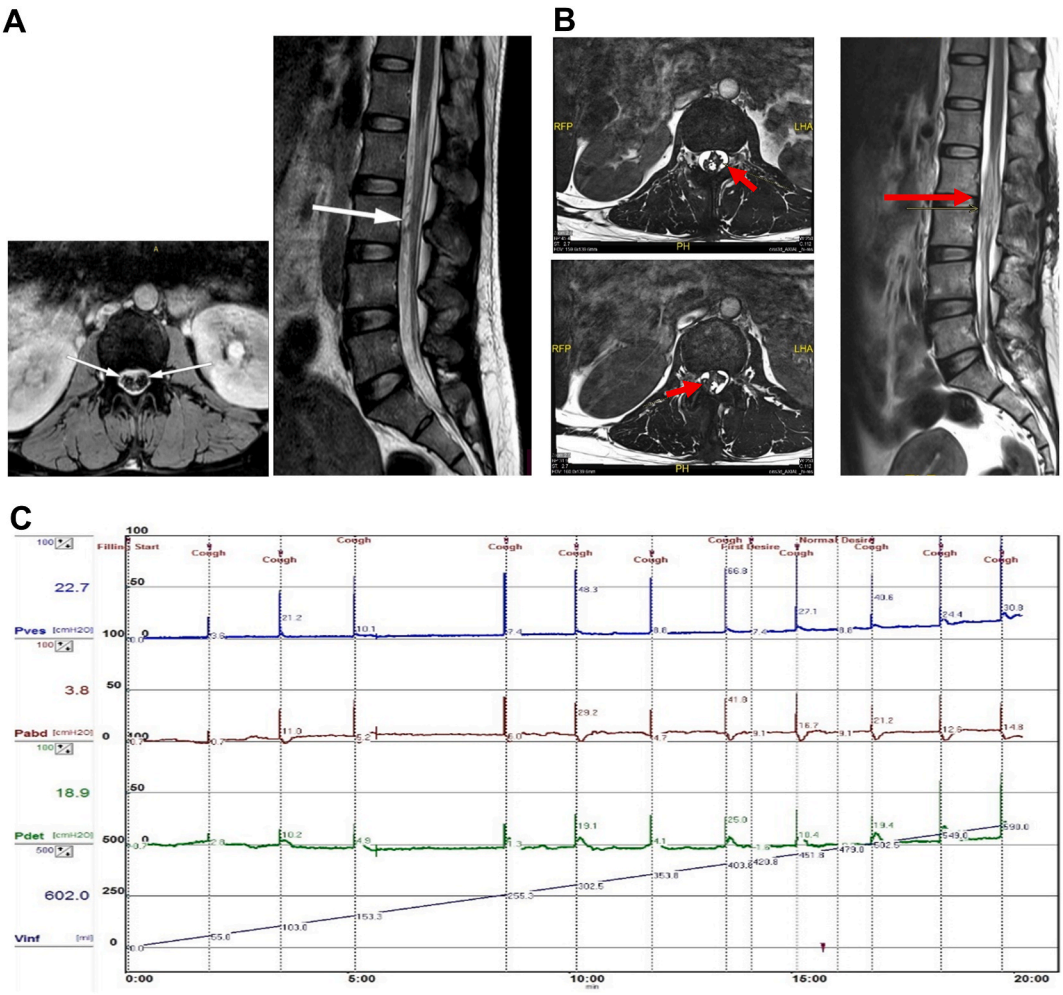

Fig. 2. MRI scan and urodynamic investigation of the patient before cell infusion. (A) Preoperative MRI scan of the patient on August 18th, 2020 with a representative axial T2W FFE 3D (left panel) and a representative sagittal T2W image (right panel). (B) Postoperative MRI (T2-tse-sag) conducted before administration of cell therapy to the patient on October 1st, 2020 with a representative axial CISS image at the level of vertebra L2 (left upper panel), a representative axial CISS image at the level of vertebra L3 (left lower panel), and a representative sagittal T2W image (right panel). (C) Urodynamic investigation of the patient before cell infusion.

2020) at the Rehabilitation Center, Bach Mai Hospital, but no improvement was shown.

Clinical examination on September 30, 2020, revealed complete flaccid paralysis of the lower extremities. Sensation was lost on the left leg from L1 to L5 and on the right leg from L2 to S1. Anal examination showed that superficial and deep sensation still existed, but voluntary anal sphincter contraction was not present. The patient felt severe neuralgia in her two lower extremities, and she could not defecate and urinate voluntarily.

Spinal MRI on October 1, 2020, revealed that the nerve roots of the cauda equina at the L2 and L3 vertebral bodies were distortional and adhered together without clear margins. These nerve roots were stuck to the anterior, posterior and lateral walls of the spinal canal (Fig. 2B).

Urodynamic investigation showed that the bladder capacity was 590 ml, and Pdet max was lower than 10 cmH2O. The patient could not void, and the postvoid residual urine volume was 590 ml (Fig. 2C and Table 1). Motor subscores in the lower extremities were 5/50 points. The light touch sensory subscores were 82/112 points, with 41 points for each side.

Given that no improvement was observed after rehabilitation, the patient was indicated for cell therapy in combination with rehabilitation. After explaining the benefits and risks of cell administration to the patient and receiving approval from the hospital's board of directors, cell therapy was indicated. The patient was intrathecally infused with 1240×10^6 autologous BMMNCs (52.9×10^6 CD34 cells and 0.61×10^6 MSCs) on October 2nd, 2020; 52×10^6 autologous AD-MSCs (1×10^6 cells/kg body weight) on January 27th, 2021 and 49×10^6 autologous AD-MSCs (1×10^6/kg of body weight) on January 12th, 2022, in 10 ml of 0.9% NaCl. Forty-eight hours after the first cell infusion, the patient started physical therapy, including practicing passive range of motion exercises, muscle strengthening exercises, gait training, and walking with aids for 10 days (from October 4th, 2020, to October 14th, 2020) at Vinmec

Table 1
Urodynamic investigation of the patient before and after cell infusion.

Criteria	Before 1st cell infusion	After 2nd cell infusion
First desire (ml)	420.8	259
Strong desire (ml)	479	380
Bladder capacity (ml)	590	430
Pdet	Under 10 cmH20	26 cmH20
Leaking	No	No
Voiding (ml)	Can not	151
Postvoid residual urine volume (ml)	590	280

International Hospital (2 hours per day). The patient was then moved to Hanoi Rehabilitation Hospital to continue physical therapy until November 10, 2020. Physical therapy was continued in the outpatient clinic throughout the years (1 hour per day). There were no serious adverse events during or after the therapy. The adverse events after cell therapy, including pain at the site of bone marrow aspiration and adipose tissue collection, disappeared within 30 hours and 58 hours, respectively. Although the patients slept poorly 24 hours after the 1st cell infusion, this was not related to the cell therapy because it occurred before cell infusion. Neck and shoulder pain that presented 8 hours after the 3rd cell infusion was controlled by pain killers within 21 hours. Motor function and sensation were scored by American Spinal-Cord Injury Association (ASIA) scores [6,7], and muscle strength was assessed by manual muscle testing (MMT) [8]. Urinary function was investigated by clinical examination and cystometry. Bowel function was assessed by clinical examination. In addition, spinal cord MRIs were performed to assess the spinal cord condition before and after cell infusion.

After the 1st administration, sensation was recovered for the left leg from L1 to L3. The patient could flex the hip and extend the knee in the full range of movement in the left extremity. The patient was able to walk for short distances with a knee ankle foot orthosis (KAFO) brace on both sides, along with a walking frame after the 2nd administration and without KAFO after the 3rd administration. Numbness and neuropathic pain were reduced after the 1st administration, and neuropathic pain relievers were no longer required after the 2nd administration (Table 2).

Spinal MRI on October 10, 2020 (1 week after the first cell infusion), showed no changes when compared to before the cell infusion (data not shown). An MRI on January 11, 2022 (15 months and 9 days after the first cell infusion), showed that adherence of the nerve roots and spinal cord had decreased compared with that on a previous MRI scan before cell infusion. No inflammatory manifestation was observed (Fig. 3A). The motor subscores in the lower extremities increased from 5/50 before cell infusion to 8/50 points after the 1st administration, 16/50 points after the 2nd administration and 21/50 points after the 3rd administration (Fig. 2B, upper panel). The light touch sensory subscores increased from 82/112 points before cell infusion to 85/112 points after the 1st administration, 88/112 points after the 2nd administration and 91/112 points after the 3rd administration (Fig. 3B lower panel) (Table 2).

Urodynamic investigation after the 2nd administration showed that the bladder capacity was 430 ml, Pdet max was 26 cmH2O and the postvoid residual urine volume was 280 ml (Fig. 3C and Table 1). Bladder ultrasound after the 3rd administration showed that the residual urine volume was 3–5 ml, and the first desire occurred at 200 ml. After 3 injections, the patient could urinate and defecate voluntarily without stool leakage. Anal examination presented strong sphincter contraction (Table 2).

2. Discussion

Hematoma in the spinal cavity associated with epidural or spinal anesthesia can cause paralysis of the lower extremities and bladder and bowel disorders. Surgery to remove the hematoma is considered the standard treatment. Regardless of the cause, the prognosis depends on the time from onset to surgery. A previous study showed that paraplegia of the lower extremities was improved better when surgery was conducted $\leq$12 hours after symptoms arose [3]. In our report, the patient underwent a decompressive operation at a very late stage (on the 9th day after onset). The neurological sequelae did not improve after 36 days of rehabilitation, so they may be considered permanent damage.

Herein, we used BMMNCs because they can be infused immediately after bone marrow processing without cell culture/expansion. AD-MSCs were also used because the procedure was less invasive for the patient. After cell therapy, the patient showed a remarkable recovery. Sensation of the lower extremities was recovered. She could walk independently and fully control her defecation and urination. Spinal MRI showed a decrease in nerve root adhesions and the disappearance of any inflammatory manifestations. Similar results were observed in previous studies using BMMNCs [9,10] and AD-MSCs [11] for patients with SCI.

Several possible mechanisms have been suggested for the treatment outcomes. BMMNCs have been reported to induce angiogenesis [12], inhibit inflammatory cytokines (IL-6, TNF-a, and IL-1b), increase VEGF and hepatocyte growth factor (HGF) levels, improve neuropathic pain in mice with SCI [13], provide neuroprotective effects, suppress cavity formation, and increase the Basso-Beattie-Bresnahan locomotor score [14]. Previous studies showed that AD-MSCs reduced inflammatory cytokines, decreased oxidant metabolite levels, increased the expression of neuronal markers [15], induced various growth factors (HGF and VEGF), which might mediate regeneration of injured spinal cord [16], and released proteases, immunomodulatory factors, and cellular matrix molecules to promote regeneration of neural tissue [17], neuronal survival, fueled axonal repair, and regeneration of peripheral nerves [18].

Our results are encouraging. However, our study has several limitations. The first limitation of our study is that despite the recommended cell infusion at 3-month intervals, the patient was unable to adhere to the prescribed regimen. The late 3rd cell infusion (1 year after the 2nd cell infusion) might have limited the effectiveness of the therapy. Another limitation is that this is only one case

Table 2
Outcomes of cell therapy for the patient.

Evaluation methods	Before cell infusion	1st injection (October 2nd, 2020)	2nd injection (January 27th, 2021)	3rd injection (January 12th, 2022)
Clinical examination	**September 30th, 2020:** - The patient showed no sign of movement of lower extremities, except for hip flexible muscles, and ankle flexible muscles in right side with light palpable contraction. Neuropathic pain in both lower extremities was recorded. - Motor subscores: 5/50 points. - Light touch sensory subscores: 82/112 points - Anal examination: voluntary anal sphincter contraction was not present. The patient felt severe neuralgia in her two lower extremities, and could not defecate and urinate voluntarily	**January 25th, 2021:** - In left extremity, patient could flex the hip and extend the knee in full range of movement with gravity eliminated. In the right, the contraction in ankle plantar flexible muscles was palpable. Numbness and neuropathic pain were reduced. - Motor subscores: 8/50 points. - Light touch sensory subscores: 85/112 points. - Anal examination: No improvement in anal sensation, anal sphincter contraction and urinary function	**December 31st, 2021:** - The patient was able to walk for short distances with KAFO brace on both sides, along with a walking frame - Motor subscores: 16/50 points. - Light touch sensory subscores: 88/112 points - Anal examination: The patient was able to feel urges for urination and defecation and could urinate and defecate voluntarily	**July 28th, 2022** - Great improvement in sensation and movement in both legs. The patient was able to walk for short distances without KAFO - Motor subscore: 21/50 points. - Light touch sensory subscore: 91/112 points - Anal examination presented strong sphincter contraction
MRI examination	**October 1st, 2020:** The nerve roots of the cauda equina at L2 and L3 vertebral bodies were distortional and adhered together without clear margins. These nerve roots were stuck to the anterior, posterior and lateral walls of the spinal canal	NA	**January 11th, 2022:** Adherence of the nerve roots and spinal cord had decreased compared with that before cell infusion	**July 28th, 2022** Spinal MRI scan indicated no significant changes compared to the last examination
Urodynamic investigation	**September 30th, 2020:** - The bladder capacity: 590 ml - Pdet max: Under 10 cmH2O - Postvoid residual urine volume: 590 ml	NA	**December 31st, 2021:** - Bladder capacity: 430 ml, - Pdet max: 26 cmH20 - Postvoid residual urine volume: 280 ml	NA
Bladder ultrasound	NA	NA	NA	**July 28th, 2022** The residual urine volume was 3–5 ml, and the first desire occurred at 200 ml.

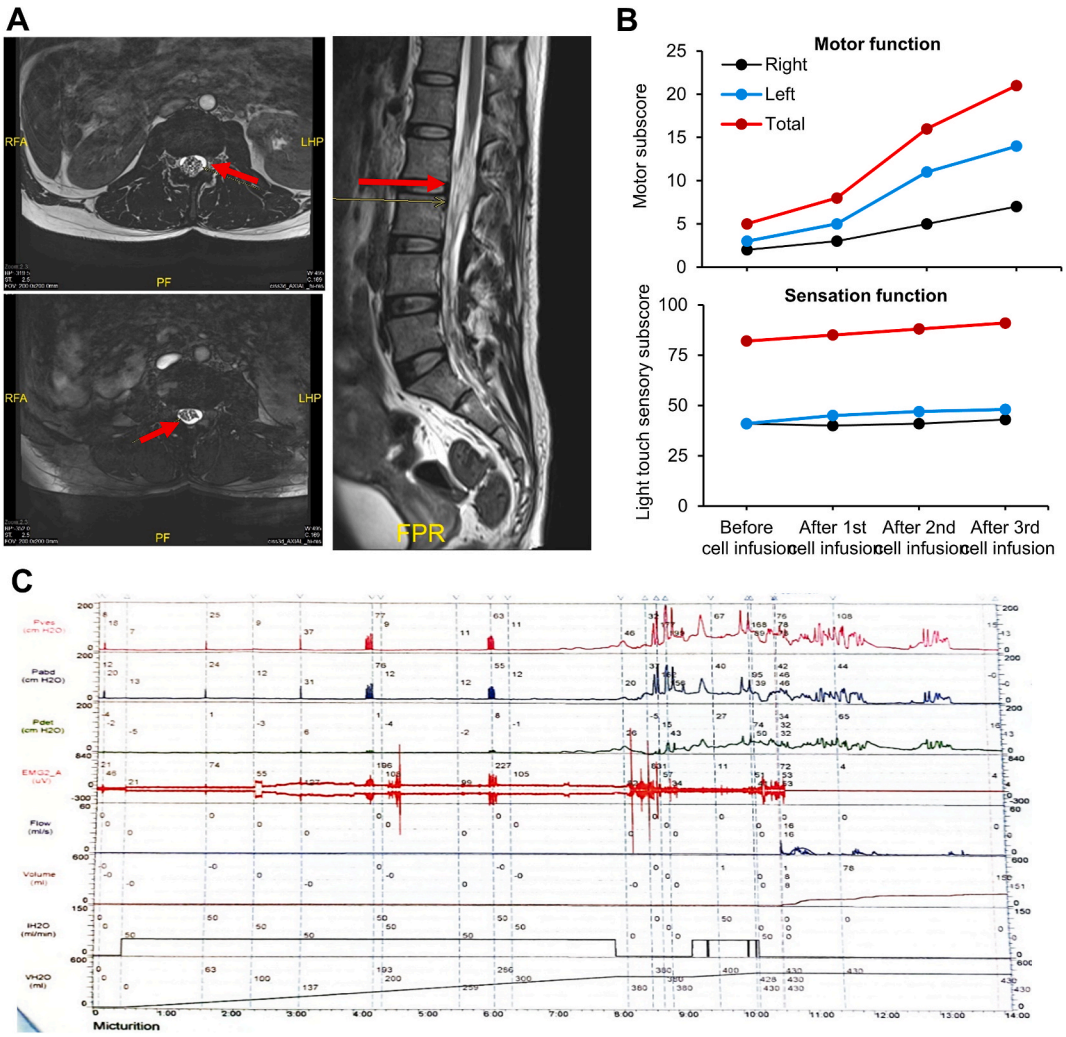

Fig. 3. MRI scan, urodynamic investigation, and motor and sensory function of the patient after cell treatment. (A) Spinal MRI scan of the patient after the 2nd cell infusion on January ^{11th,} 2022 with a representative axial CISS image at the level of vertebra L2 (left upper panel), a representative axial CISS image at the level of vertebra L3 (left lower panel), and a representative sagittal T2W image (right panel). (B) The motor and sensory function of the patient. (C) Urodynamic investigation of the patient after the 2nd cell infusion.

report. We are fully aware that studies with a larger number of patients need to be conducted to confirm these findings and to draw accurate conclusions. Although BMMNCs and AD-MSCs have been used separately in many clinical trials, we herein employed both autologous BMMNCs and AD-MSCs for this specific patient. The choice of a single cell source or combination of different cell sources in the future should also be further studied to accurately investigate the efficacy of the therapy. Cell therapy should not be recommended for patients with underlying health conditions that could potentially interfere with stem cell transplantation or pose risks to the patient during the procedure, such as those with acute infections, coagulopathy, heart failure, liver failure, kidney failure, respiratory failure, cancer, or severe exhaustion or those with virus infection, such as human immunodeficiency virus or hepatitis virus.

Our findings suggest that cell therapy may be applied for medullar compression due to vertebral trauma or bleeding from aneurisms. These findings may also have broader implications for other neurological conditions presenting with similar symptoms, thereby providing a potential avenue for future therapeutic interventions. However, importantly, different neurological conditions may present unique challenges and complexities that need to be considered when applying cell therapy. Factors such as the underlying cause of the neurological conditions and the location and extent of the damage can influence the potential efficacy and safety of the therapy. Thus, further research is needed to explore the applicability of cell therapy across different neurological conditions and to optimize the treatment strategies accordingly.

3. Conclusion

Our study demonstrated that infusion of BMMNCs and AD-MSCs may improve neurological sequelae occurring after prolonged spinal hematoma due to local anesthesia and suggested a new treatment direction and therapeutic option for cases of permanent nerve damage due to a spinal-canal hematoma related to regional anesthesia. We believe that this case will support the growing evidence for the efficacy of cell therapy for the treatment of neurologic sequelae.

Ethics approval and consent to participate

Ethics approval to report this case report was obtained from the Ethical Committee of Vinmec International Hospital (No. 101/2022/CN-HĐĐĐ VMEC). The study was explained in detail to the participant. Informed consent was obtained from the patient before cell therapy.

Consent for publication

Informed consent for publication was signed by the patient.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Data availability statement

All data generated or analyzed during this study are included in this published article.

CRediT authorship contribution statement

Liem Nguyen Thanh: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Huong Thu Le:** Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Quyen Thi Nguyen:** Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Doan Van Ngo:** Data curation, Formal analysis, Software, Visualization. **Du Gia Hoang:** Data curation, Formal analysis. **Phuong-Anh Thi Nguyen:** Data curation, Formal analysis. **Viet-Anh Bui:** Data curation, Formal analysis. **Phuong T.M. Dam:** Data curation, Formal analysis.

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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