Radiology Case Reports 17 (2022) 1601–1604

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/radcr

Case Report

Stem cell induced inflammatory hypertrophy of the cauda equina ☆,☆☆

Aaron D. Brumbaugh, MD[a], *Alan Podolsky, MD*[a], *Matthew H. Kulzer, MD*[a], *Michael P. Spearman, MD*[a], *Michael F. Goldberg, MD, MPH*[a], *Warren M. Chang, MD, MBA*[a], *Nazia Khatoon, MD*[b], *Kossivi Dantey, MD*[b], *Charles Q. Li, MD*[a,*]

[a] *Imaging Institute, Allegheny Health Network, Pittsburgh, PA, USA*
[b] *Pathology Institute, Allegheny Health Network, Pittsburgh, PA, USA*

ARTICLE INFO

Article history:
Received 26 January 2022
Accepted 4 February 2022

Keywords:
Stem cell tourism
Inflammatory nerve root hypertrophy
Intrathecal stem cell
Adverse effects

ABSTRACT

Stem cell therapy can present clinicians with challenging clinical scenarios, as access to such treatments outpaces the research into their efficacy and safety due to the burgeoning trend of international travel to acquire stem cell therapy, or "stem cell tourism." Treatment of neurologic conditions remains an enticing potential application of stem cell therapy, often administered intrathecally. In response to such therapy, multiple adverse events have been described in the literature, including neoplasms, demyelinating disease, and seizures, among others. We present a case of symptomatic inflammatory cauda equina nerve root hypertrophy due to intrathecal stem cell infusion, representing a rare but significant complication.

Introduction

Stem cell therapy has long captivated the scientific, medical, and lay communities with the potential for a new era of regenerative medicine. Many unique, intrinsic properties of stem cells, including a high proliferative potential, capacity for self-renewal, and ability for differentiation into multiple cell types, are the basis for a wide range of putative clinical applications, including treatment of neurodegenerative diseases [1,2]. However, despite a near permanent place in the cultural and medical zeitgeist, only a narrow range of applications have demonstrated clinical benefit and safety, with the primary role of stem cell therapy being in bone marrow transplantation for the treatment of hematologic malignancies [2,3].

As of December, 2021, over 150 National Institutes of Health-affiliated clinical trials are ongoing to further elucidate the role of stem cells in the treatment of various neurologic conditions [4]. While this illustrates the typical pathway of determining safety and efficacy of potential therapies through randomized controlled trials, the potential to treat many debilitating conditions such as Parkinson disease, amyotrophic

☆ Acknowledgments: This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
☆☆ Competing Interests: The authors have declared that no competing interests exist.
* Corresponding author.
E-mail address: charles.li@ahn.org (C.Q. Li).
https://doi.org/10.1016/j.radcr.2022.02.021

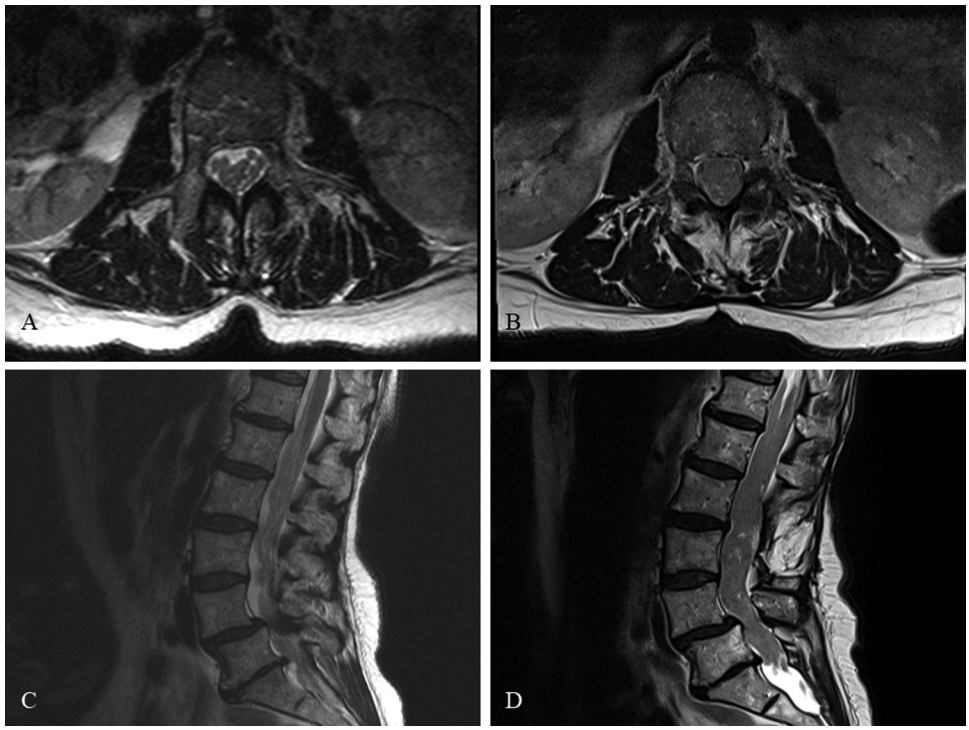

Fig. 1 – T2-weighted MRI sequences from June 2017 (A, C) and November 2020 (B, D). Progressive diffuse thickening of the cauda equina nerve roots with near complete effacement of the CSF from L1-L5 over a 3 year period despite posterior decompression.

lateral sclerosis, and multiple sclerosis has led to the development of commercial stem cell clinics with limited regulatory oversight [1,5-7]. Specifically, a trend of "stem cell tourism" has become increasingly popular, involving international travel for the explicit purpose of acquiring therapy at a stem cell clinic operating outside of the auspices of the Food and Drug Administration [5,7].

The rise in stem cell tourism presents clinicians with the potential for encountering new or poorly studied adverse events. We present 1 such example in a patient who received intrathecal stem cell infusions in Russia, leading to a symptomatic inflammatory hypertrophy of the cauda equina nerve roots.

Case Description

A 69-year-old female with a past medical history of Parkinson disease and lumbar stenosis was evaluated by her neurologist due to a subacute worsening of bilateral lower extremity weakness, urinary incontinence, and low back pain. Physical exam demonstrated symmetrically decreased lower extremity strength and bilateral patellar and Achilles hyporeflexia. She underwent an MRI of the lumbar spine with contrast, which was significant for diffuse, extensive thickening of the cauda equina nerve roots and abnormal enhancement spanning the conus medullaris to the sacral canal (Fig. 1, 2); this was new compared to an MRI from 2 months earlier. Based on the imaging findings, primary differential considerations included lymphoma, leptomeningeal metastatic disease, and acute or chronic inflammatory demyelinating polyneuropathy. The patient was admitted to the hospital for evaluation.

Further discussion with the patient uncovered a history of intrathecal stem cell infusions over a 3 year period in Moscow, Russia, in an effort to treat her Parkinson disease. Through correspondence with the provider arranging her stem cell treatments, it was determined that fetal progenitor non-embryonic stem cells arrested at 12 weeks gestation were administered annually into the thecal sac at L3-L4, with the most recent dose 2-3 months before symptom onset. No adverse events were reported during or immediately after her infusions, and the patient described initially feeling "better."

A CT of the chest, abdomen, and pelvis was performed and unrevealing for a primary tumor or other significant abnormalities. In addition, an MRI of the brain, cervical spine, and thoracic spine was obtained, which noted minimal thoracic syringohydromyelia without other abnormalities. Serologic tests including flow cytometry were unrevealing. A lumbar puncture was performed which demonstrated lymphopleocytosis, hypoglycorrhachia, and elevated protein. While hospitalized, her clinical exam remained stable, and the abnormality of her cauda equina nerve roots was suspected to be secondary to inflammatory hypertrophy due to intrathecal stem cell administration.

On follow-up exam 2 weeks after discharge, she reported a recent fall with worsening lower extremity weakness and was admitted to the hospital for a decompressive laminectomy and nerve root biopsy. Immunohistochemical staining revealed mature glioneuronal tissue with evidence of focal

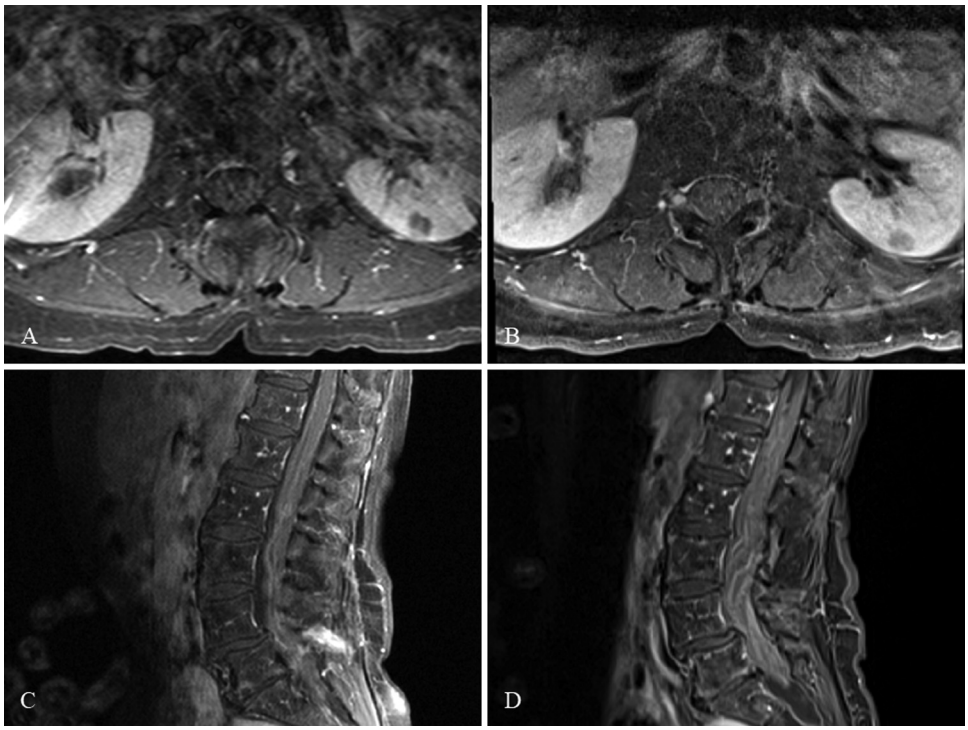

Fig. 2 – Fat saturated T1-weighted contrast-enhanced MR images from June 2017 (A, C) and November 2020 (B, D). Mild but diffusely abnormal enhancement of the cauda equina nerve roots spanning the conus medullaris through the sacral canal.

mild chronic inflammatory changes, consistent with inflammatory hypertrophy of the cauda equina nerve roots (Fig. 3). She was discharged to inpatient rehabilitation.

In the over 4 year period since her initial diagnosis, the patient's symptoms and imaging findings progressed, with now complete effacement of the CSF space due to nerve root hypertrophy from L1-L5 (Fig. 1, 2). During this time period, she has continued physical therapy, and reported symptomatic improvement following a course of methylprednisolone.

Discussion

Stem cell therapy remains an exciting frontier of medicine, with clinical applications being carefully elucidated through multiple ongoing randomized controlled trials [4]. While the potential of such treatments is exciting, clinical trial data and case reports from patients treated in commercial stem cell clinics illustrate the various potential adverse events associated with stem cell infusions, including seizures, infection, donor-derived brain tumors, and demyelinating encephalomyelitis [1,8].

In the presented case, the diffuse thickening of the cauda equina nerve roots has a limited differential including acute or chronic inflammatory demyelinating neuropathy, hereditary neuropathies including Charcot-Marie-Tooth disease type I and neurofibromatosis, lymphoproliferative disorders, leptomeningeal infection and inflammation, and leptomeningeal metastases [1]. In addition, several recent case reports have described similar findings following suspected or known intrathecal stem cell administration [1,2,5,8,9]. Given the acquired nature of this condition, composition of mature glioneuronal and lymphocytic tissue, and the close temporal relationship with stem cell therapy, an inflammatory etiology secondary to stem cell administration is favored.

While the exact mechanism for stem cell-induced cauda equina hypertrophy is unclear, reports of biopsy tissue containing DNA fingerprinting distinct from the host suggests engrafted donor stem cell proliferation as a possible contributing factor [1]. Such cases demonstrate some of the hurdles facing implementation of stem cell therapy, including unclear mechanisms of engraftment and the potential for migration or inadvertent implantation [1,5,8,9]. In contrast, the presence of inflammatory cells in the presented case, as well as others within the literature, suggests a component of host response to stem cells underlying the nerve root hypertrophy [2,9].

Currently, the basis of treatment involves surgical decompression, with a possible role for radiation and immunosuppression with methotrexate, intravenous immunoglobulin, or steroids [5,8,9]. In the presented case, a course of steroids provided reported symptomatic improvement, but did not alter progression of imaging findings. Furthermore, a similar case was reported to be refractory to not only medical but also radiation therapy, potentially related to stem cell dedifferentiation [9]. Due to the paucity of cases and spectrum of potential mechanisms underlying stem cell-mediated nerve root enlargement, the precise role of radiation and medical therapy remains unclear.

Given the excitement surrounding stem cell therapies and the severity of many conditions targeted by treatment, the trend of stem cell tourism is unlikely to abate. As such, it is

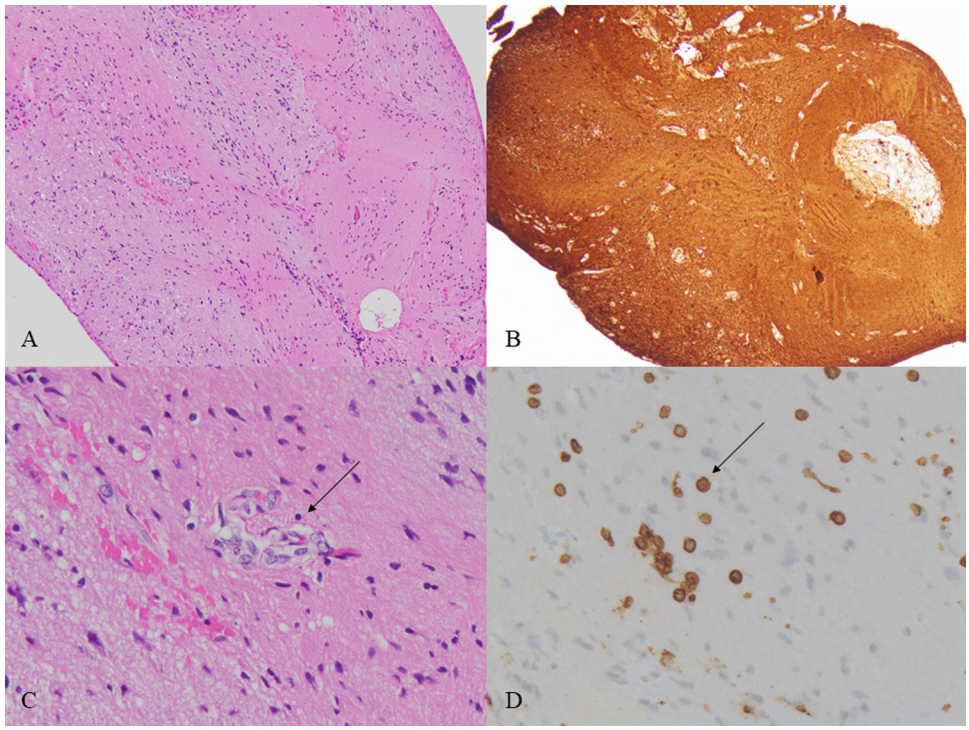

Fig. 3 – Histologic evaluation of nerve root biopsy. (A) Hematoxylin and eosin staining at x100 magnification; (B) Positive immunohistochemical staining for glial fibrillary acidic protein (GFAP), indicating the presence of mature glial cells; (C) Hematoxylin and eosin staining at x400 magnification demonstrating the presence of lymphocytes (black arrow); (D) CD3 immunohistochemical staining highlighting the presence of T-cell lymphocytes (black arrow) and ongoing chronic inflammation.

essential to raise awareness of new and poorly understood complications such as inflammatory hypertrophy of the cauda equina. In addition, stem cell-related pathologies should be considered in diagnostic workups, particularly when encountering unusual imaging findings in the appropriate patient population.

Informed Consent

Informed consent for patient information to be published in this article was obtained.

Authors' contributions

All authors made substantial contribution to manuscript design and intellectual content.

REFERENCES

[1] Hurst RW, Bosch EP, Morris JM, Dyck PJB, Reeves RK. Inflammatory hypertrophic cauda equina following intrathecal neural stem cell injection. Muscle Nerve 2013;48(5):831–5. doi:10.1002/mus.23920.

[2] Aoun SG, Reyes VP, El Ahmadieh TY, Davies M, Patel AR, Ban VS, et al. Stem cell injections for axial back pain: a systematic review of associated risks and complications with a case illustration of diffuse hyperplastic gliosis resulting in cauda equina syndrome. J Neurosurg Spine 2019;31:906–13. doi:10.3171/2019.6.SPINE19594.

[3] Kimbrel EA, Lanza R. Next-generation stem cells – ushering in a new era of cell-based therapies. Nat Rev Drug Discov 2020(7):463–79. doi:10.1038/s41573-020-0064-x.

[4] National Institutes of Health. ClinicalTrials.gov. Accessed 18 December 2021.

[5] Berkowitz AL, Miller MB, Mir SA, Cagney D, Chavakula V, Guleria I, et al. Glioproliferative lesion of the spinal cord as a complication of "stem cell tourism". N Engl J Med 2016;375:196–8. doi:10.1056/NEJMc1600188.

[6] Bauer G, Elsallab M, Abou-El-Enein M. Concise review: a comprehensive analysis of reported adverse events in patients receiving unproven stem cell-based interventions. Stem Cells Transl Med 2018;7(9):676–85. doi:10.1002/sctm.17-0282.

[7] Turner L, Knoepfler P. Selling stem cells in the USA: assessing the direct-to-consumer industry. Cell Stem Cell 2016;3(2):154–7 19doi:. doi:10.1016/j.stem.2016.06.007.

[8] Lee BS, Achey RL, Yeaney GA, Bosler DS, Zarmeneh A, Ontaneda D, et al. Stem cell-injection induced glioneuronal lesion of the cauda equina. Neurology 2018;90:1–3. doi:10.1212/WNL.0000000000005219.

[9] Madhavan AA, Summerfield D, Hunt CH, Kim DK, Krecke KN, Raghunathan A, et al. Polyclonal lymphocytic infiltrate with arachnoiditis resulting from intrathecal stem cell transplantation. Neuroradiol J 2020;33(2):174–8. doi:10.1177/1971400920902451.