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CORRESPONDENCE

Neuroglial stem cell-derived inflammatory pseudotumor (n-SCIPT): clinicopathologic characterization of a novel lesion of the lumbosacral spinal cord and nerve roots following intrathecal allogeneic stem cell intervention

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Unproven commercial stem cell therapies are increasingly available to patients in the United States and internationally, where stem cell clinics offer treatments for an expanding list of neurologic, autoimmune, and degenerative conditions, often with limited regulatory oversight [7]. As a result, many patients who participate in "stem cell tourism" receive untested interventions that potentially oversell the benefits without adequately representing the risks. The majority of commercial stem cell clinics use autologous cells derived from adipose tissue or bone marrow sources, and while the administration of unproven therapies raises significant ethical and regulatory issues, the autologous cells appear to be relatively safe. However, a recent study of stem cell clinics in the United States found that approximately 20% use allogeneic stem cells, mostly derived from amniotic or placental sources [15]. These cells are more problematic, as they raise issues of immune rejection as well as increased risk of contamination due, in part, to increased handling, storage, and processing. The route of administration also contributes to risk. Stem cells delivered intravenously are usually filtered by the lungs and liver and are cleared within 24–72 h [5]. When stem cells are administered directly into tissues such as the kidney, eye, or cerebrospinal fluid (CSF), the consequences of infection, tumor formation, or inflammatory response are generally more serious [9, 14].

Following intrathecal injection of allogeneic stem cells, reported neurologic complications have ranged from mild to severe and include demyelinating encephalomyelitis, hemorrhagic retinopathy, meningitis, intracerebral hemorrhage, and death [1, 3, 12]. A more recently described complication is the development of glial or glioneuronal mass lesions at or near the site of intrathecal stem cell delivery, with molecular characterization showing derivation from the exogenous stem cells [2, 4, 10, 11, 13]. To date, however, the hallmark clinicopathologic features of this unique complication have not been summarized and a unifying diagnostic nomenclature has not been offered. Here, we contribute a new informative case to this early body of literature, review additional reported cases, and propose unifying diagnostic criteria based on the observed common features.

Our case is a 62-year-old man with a history of hypertension and bilateral ischemic optic neuropathy resulting in legal blindness, who presented with slowly progressive low back pain, bilateral radicular leg pain, and worsening gait.

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His symptoms began approximately 6 months after receiving multiple intrathecal and intravenous stem cell infusions within an 8-month period (in Beijing, China and Moscow, Russia), with the objective of restoring his vision. The neurologic examination revealed a distal and bilateral pattern of moderate leg weakness, producing a right worse than left steppage gait with ambulation. Nerve conduction studies demonstrated a pattern of abnormal findings that was consistent with bilateral L5 and S1 radiculopathies. Serial MR imaging studies of the lumbar spine revealed progressive thickening of the cauda equina with effacement of the CSF space, while PET-CT showed diffuse hypermetabolic activity of the lower spinal cord extending through the conus and lumbosacral nerve roots (Fig. 1a, b and Supplementary Fig. S1). Multiple lumbar punctures showed tawny CSF with persistent laboratory abnormalities including leukocytosis and elevated protein (Supplementary Table S1). Based on the clinical progression of his symptoms, concerning imaging findings, and inflammatory CSF profile, he underwent biopsy of the S1 sensory nerve root.

Intraoperatively, the nerve root was markedly thickened (Fig. 1c). Hematoxylin and eosin-stained sections of the biopsied tissue showed a fragment of spinal nerve root surrounded by moderately hypercellular, disorganized glioneuronal tissue composed of mildly atypical glial cells and scattered large, dysmorphic ganglion cells embedded in a fibrillar matrix (Fig. 1d–g). Mitoses were not identified, and there was no necrosis or microvascular proliferation. The glial component was immunopositive for GFAP, ATRX, and OLIG2, while dysmorphic ganglion cells showed weak to absent NeuN expression (Supplementary Fig. S2). Rare nuclei showed weak p53 positivity, and there was no expression of IDH1 R132H or BRAF V600E mutant proteins (not shown). Deeper levels revealed a robust inflammatory infiltrate composed of small T lymphocytes, scattered macrophages, and microglia (Supplementary Fig. S3). The nerve root itself demonstrated mild to moderate acute demyelination (not shown).

Capture-based next-generation sequencing (NGS) was performed on paired lesional and constitutional DNA samples as previously described [8], and showed approximately 90 nonsynonymous variants that were present in the aberrant glioneuronal tissue but not in the constitutional buccal swab sample; the vast majority of these variants were single nucleotide polymorphisms (SNPs) common in human populations (Supplementary Table S2). These findings indicate that the aberrant glioneuronal tissue was derived from foreign human donor(s), with the allele frequencies likely representing heterozygous (20%) and homozygous SNPs (40%) in the foreign donor(s). There were no known pathogenic variants, including hotspot mutations known to be important in the pathogenesis of gliomas. Additionally, research-based metagenomic NGS was performed on total RNA extracted from a CSF sample collected approximately 1 year after presentation, as previously described [16], and did not detect pathogenic organisms.

We next surveyed the existing literature for similar cases and compared their clinicopathologic features (Supplementary Table S3). Of the six identified cases (including ours), all patients pursued intrathecal injection of stem cells outside of the United States, often receiving cells of fetal and/or neural progenitor origin. Imaging revealed thickened, clumped cauda equina or lumbosacral nerve roots in five cases, with enhancement on post-contrast imaging (reported in five cases) and a lumbar mass in the remaining case, while available CSF profiles showed lymphocytic pleocytosis and increased protein (two of three cases). Histopathologic examination typically showed low-grade glial or neuroglial proliferations (five cases), but one high-grade glial proliferation with primitive morphology was also reported. T cell-predominant chronic inflammatory infiltrates were common (four cases). A variety of molecular techniques was used to confirm that these lesions were derived from exogeneous stem cells (reported for five cases).

Based on these findings, we propose the name "neuroglial stem cell-derived inflammatory pseudotumor" (n-SCIPT) to define this rare but increasingly reported entity; in doing so, we also anticipate the possibility that "SCIPT" lesions with other types of cellular differentiation may be described in the central nervous system or other organ systems where stem cell therapy is utilized, and can be named accordingly. The clinical, radiologic and pathologic criteria that can be used to make a n-SCIPT diagnosis are summarized in Table 1. Of note, these unifying features are seen in the present dataset, but further studies are necessary to determine whether a more parsimonious set of diagnostic criteria can be made.

Together, these features distinguish n-SCIPT lesions from several similarly presenting neurologic disorders (Supplementary Table S4), including another potential complication of experimental intrathecal stem cell infusions—the development of a host-versus-graft-like immune response to allogeneic stem cells [6]. Although both conditions suggest that allogeneic stem cells retain sufficient immunogenicity to provoke an inflammatory response, their treatment modalities may differ, as an intact immune system may be beneficial in restricting the growth of n-SCIPTs. With the global increase in stem cell interventions, cases such as these will likely become more common and require greater understanding.

In the recent past, patients with medical conditions not treatable by conventional medical therapy would often seek stem cell treatments outside of the United States, fueling a stem cell tourism industry in countries serving as havens for unregulated practitioners. However, lax regulatory compliance has recently led to a proliferation of stem cell clinics across the United States. This alarming trend suggests that

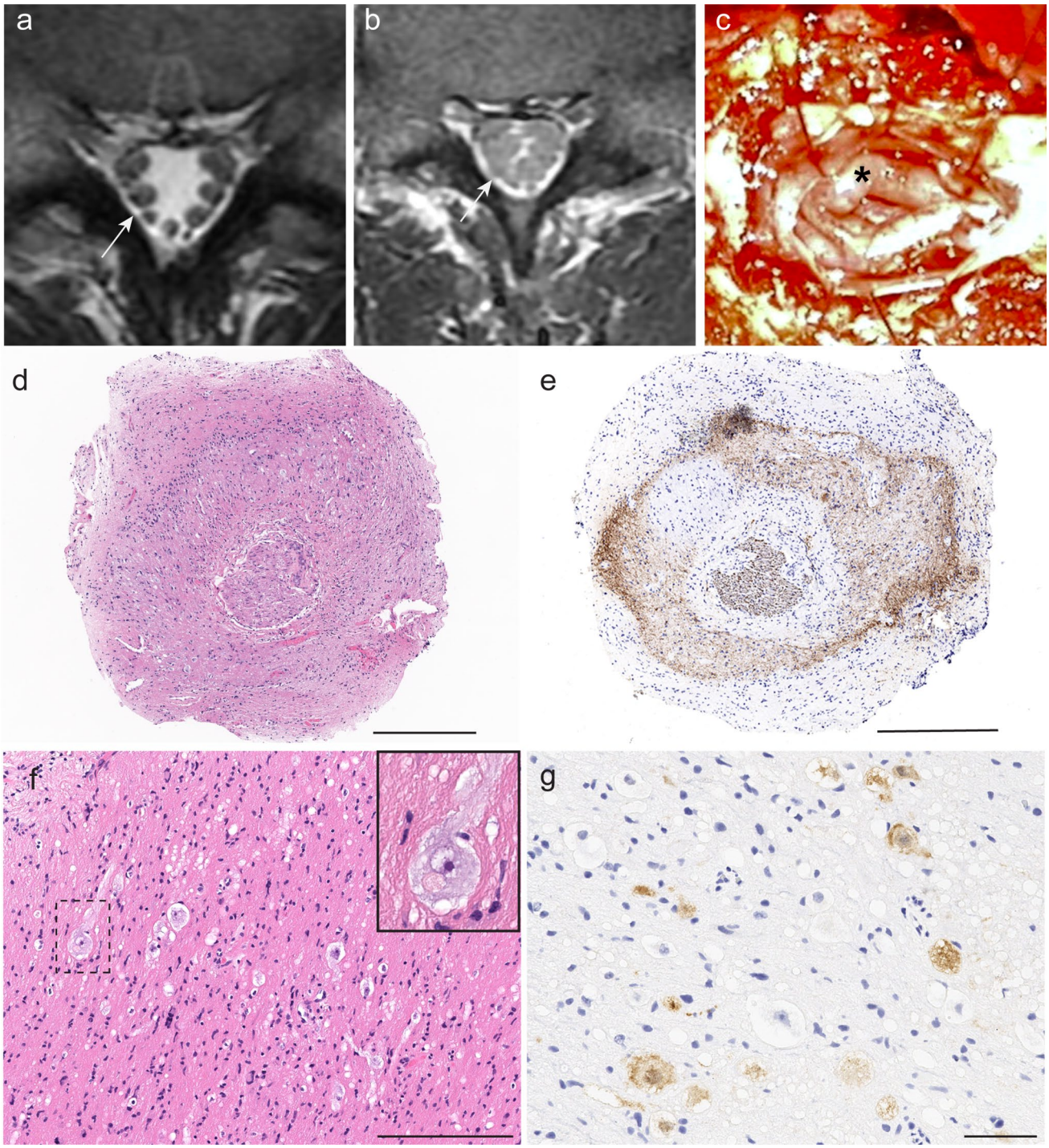

Fig. 1 Radiologic, intraoperative, and histopathologic findings. **a**, **b** Serial magnetic resonance (MR) images obtained approximately 16 months apart show progressive thickening of all of the nerve roots of the cauda equina with effacement of the CSF space (arrows). **c** Intraoperative photograph of enlarged spinal nerve root (*). **d** H&E-stained section showing S1 spinal nerve root (center) encased by aberrant neuroglial tissue (scale bar 400 µm). **e** Immunohistochemistry for neurofilament protein highlights bilayered appearance of aberrant neuroglial tissue including a dense fibrillar matrix (scale bar 400 µm). **f** The aberrant neuroglial tissue is composed of disorganized, mildly atypical glial cells and dysmorphic ganglion cells, one of which is shown at higher magnification in the inset (scale bar 200 µm). **g** Dysmorphic ganglion cells show weak to absent NeuN expression (scale bar = 100 µm)

Table 1 Clinical, radiologic, and pathologic diagnostic criteria of neuroglial stem cell-derived inflammatory pseudotumor (n-SCIPT)

Neuroglial stem cell-derived inflammatory pseudotumor (n-SCIPT): unifying features
1. History of stem cell injection into the CSF space
2. Subacute-to-chronic onset of focal neurologic symptoms
3. Presence of a mass lesion or progressive spinal cord/nerve root thickening at or near the site of injection, as visualized by CT or MR imaging
4. Evidence of inflammation, measured in the CSF or determined by the presence of abnormal enhancement on MRI
5. Tissue biopsy demonstrating glial or mixed neuroglial histology with or without associated chronic inflammation
6. Molecular studies demonstrating presence of non-patient tissue

more cases similar to ours will emerge; as such, it is important that the diagnostic possibility of n-SCIPT is recognized and addressed by pathologists, clinicians, and basic scientists alike.

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Compliance with ethical standards

Conflict of interest ARK is a co-founder and member of the board of Neurona Therapeutics. Other authors have no conflicts of interest relevant to this article.

Informed consent Informed consent was obtained from the individual participant described in the study.

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