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CASE REPORT

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# Blame it on the pump

**Kirk John Levins**[1] | **Mohamed Khan**[2] | **Thomas Drago**[3] | **Elena Roman**[4] | **Cillian Suiter**[1] | **Anurag Nasa**[3] | **Darren William Roddy**[3] | **Paul Murphy**[1]

[1]Department of Anaesthesia, Intensive Care and Pain Medicine, St. Vincent's University Hospital, Dublin 4, Ireland

[2]Department of Haematology, University Hospital Limerick, Dooradoyle, Ireland

[3]Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin 2, Ireland

[4]Royal College of Surgeons, Dublin 2, Ireland

**Correspondence**
Kirk John Levins, Department of Anaesthesia, Intensive Care and Pain Medicine, St. Vincent's University Hospital, Dublin 4, Ireland.
Email: kirklevins@aim.com

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**Abstract**

Although intrathecal pumps may lead to spinal symptoms that are likely related to the pump itself, the case presented herein underscores the importance of casting a broad differential diagnosis at the time of initial presentation.

**KEYWORDS**

granuloma, hematology, intrathecal pump, lymphoma, transverse myelitis

## 1 | INTRODUCTION

A patient presented with cauda equina signs following an intrathecal pump implantation for pain. Initial investigations suggested a granuloma with nonspecific CSF abnormalities. The patient represented later with neck signs and a B-cell lymphoma. This case highlights the importance of a wide differential diagnosis when reviewing patients with an intrathecal pump.

Intrathecal drug delivery is a method of directly administering opioid and spasmolytic medications to the site of action, the spinal cord.[1] Efficacy and safety of this delivery system are well documented in spasticity, and malignant/non-malignant pain.[2] There are, however, a number of recognized potential complications with this therapy. One of the most serious of which is the formation of a granuloma occurring at the intrathecal catheter tip, which appears to be related to the concentration and drug type being delivered.[1] Evidence has indicated that delivery of high concentration morphine can lead to the formation of these granulomas.[3,4] Occurring in less that 3% of all patients with an intrathecal catheter, granulomas can present as an inflammatory mass on spinal imaging with some resulting in compression of the spinal cord.[5] Patients may present with a host of neurological symptoms dependent on the location of cord compression caused by the granuloma, including neurological deficits, myelopathy, and radiculopathy.

An important differential to consider in patients with intrathecal catheters presenting with neurological deficits is transverse myelitis (TM). TM is a neuroinflammatory condition affecting the spinal cord. It can present as a loss of corticospinal, autonomic, and spinothalamic functional loss

Levins and Khan contributed equally to this study.

below the level of the lesion.[6] TM has been reported to result from intrathecal device-related infections, but may also be a consequence of demyelinating disorders, such as multiple sclerosis and neuromyelitis optica, vascular causes, and malignancies, such as lymphoma. Therefore, early recognition of the cause of TM is paramount in preventing irreversible paralysis and further neurological deficits.[7]

Here, we report a case of transverse myelitis, caused by a B-cell lymphoma, in a patient with an intrathecal catheter.

## 2 | CASE REPORT

A 56-year-old male patient presented with a 14-day history of bladder dysfunction and deteriorating mobility on a background of an intrathecal pump (SynchroMed™ II: Medtronic; Minneapolis, USA) insertion two months prior for pain related to stimulation-resistant failed back surgery syndrome. He had no other significant medical conditions. Neurological examination revealed a sensory deficit to T6. Urodynamics showed an atonic bladder that required catheterization. Biochemical and hematological blood results were unremarkable, and the patient's human immunodeficiency virus (HIV) test was negative.

Spinal magnetic resonance imaging (MRI) revealed a high T6-T8 cord signal surrounding a left T7 intradural lesion (mildly hyperintense with postcontrast enhancement on T1-imaging; centrally hyperintense with a peripherally hypointense rim on T2-imaging) (Figure 1). The adjacent cord showed significant edema. A catheter-associated granuloma was considered likely. A cerebrospinal fluid (CSF) sample was taken at this time. The sample consisted of 2 red blood cells per $mm^3$. Lymphocytosis and large- to medium-sized lymphoid cells were found following cytospin morphology and no evidence of pathogens. A high protein level was noted (three times higher than normal). Further flow cytometry analysis did not demonstrate a kappa/lambda restriction or evidence of a B-cell clone with only 13% B-lymphocytes and kappa/lambda ratio of 1.39.

After refilling the pump with saline, the patient was commenced on a methylprednisolone infusion (5.4 mg/kg/h) to reduce cord edema. The neurosurgical team were consulted for removal of the apparent granuloma. Over the following two days, the patient's condition improved somewhat prompting a further MRI scan. This scan revealed considerable edema resolution, and the T7 lesion was now felt to be a flow defect rather than a granuloma. Upon review, surgery was no longer indicated. Transverse myelitis was now considered the likely diagnosis, and investigation into its cause was commenced. Computerized tomography of the thorax, abdomen, and pelvis (CT-TAP) was performed with no malignancy detected. A repeat CSF sample demonstrated lymphocytosis (833/$cm^3$) with 74% CD4 T-lymphocytes. CSF IgG was elevated (174 mg/L) with no oligoclonal banding found in serum. Biochemical and hematological bloods remained unremarkable. Of note flow cytometry was not sent on this sample.

The patient was discharged with no symptoms following two weeks of steroids. He represented five weeks later with weight loss, odynophagia, and night sweats. MRI of the neck revealed a metabolically active large volume tumor mass arising in right tonsil (Figure 2). This mass was associated with active right and left cervical nodes. A second CT-TAP revealed multiple small subcentimeter active foci in liver that were suspicious for further malignant disease. No other active nodal or extranodal malignant disease was found. Proton emission tomography-computerized tomography (PET-CT) confirmed no spread, and bone marrow biopsy was unremarkable. Of note, these radiological findings were not present on the original MRI or CT scans. Core biopsy demonstrated a high-grade diffuse large B-cell lymphoma (DLBCL) showing a Ki67 proliferation index of over 50% with expression of CD20, PAX5, BCL2, BCL6, and MUM1 with focal c-myc. The patient is currently receiving R-CHOP (Rituxan—cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy.

## 3 | DISCUSSION

Neurological symptoms in patients with intrathecal pumps are often, and reasonably, attributed to complications related to the pump; however, this case report demonstrates that a broader differential diagnosis should also be considered early to prevent permanent consequences.

Central nervous system lymphomas (CNSLs) are a rare form of extranodal non-Hodgkin lymphomas found in the

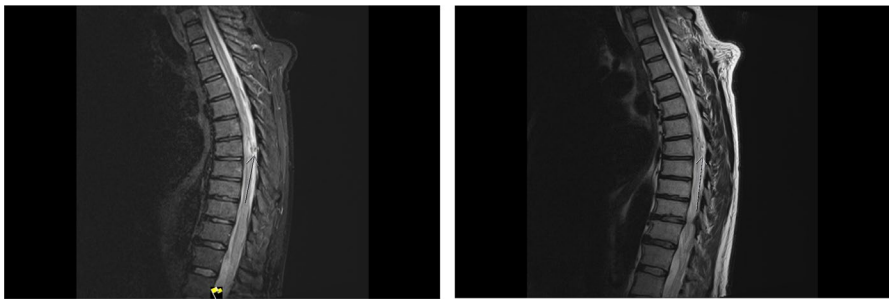

**FIGURE 1** T1 and T2 MRI of the spine demonstrating an enhancing intradural extramedullary lesion at the T7 level of the adjacent cord edema

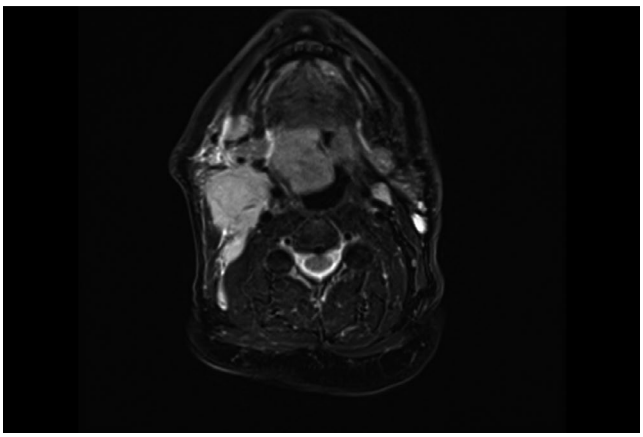

**FIGURE 2** MRI of 5.3 cm right tonsillar malignancy centered on the right palatine tonsil. This extends inferiorly to abut and displaces the epiglottis with effacement of the right vallecula. There is lateral involvement of the constrictor muscles and extension across the midline

central nervous system (CNS), including the brain/cord parenchyma, CSF, and ocular structures. They account for 4%-6% of all non-Hodgkin lymphomas and are associated with a poor prognosis.[8] CNSLs can be either primary (PCNSL), where the disease is isolated to the CNS, or secondary (SCNSL), where the CNS lymphoma in the presence of systemic lymphoma.

PCNSL is associated with a slight male predominance, it affects immunosuppressed patients such as those with HIV, and it is confined to the brain, cranial nerves, eyes, leptomeninges, and/or spinal cord.[9] PCNSL is usually classified as a high-grade DLBCL of nongerminal center cell origin with up to 16% having CARD11 mutations affecting the NFKB pathway.[10] Prognosis of PCNSL shows high remission rates despite treatment with corticosteroid/chemotherapy/radiation therapies in immunocompetent patients or methotrexate-based multiagent chemotherapy in immunocompromised patients.[11]

SCNSL occurs in up to 5% of high grade and <3% of indolent lymphoma patients. The risk of SCNSL is increased in lymphomas involving the paranasal sinuses, testes, marrow, or adrenals and can be assessed by the CNS lymphoma score (CNS-IPI).[12] Although advances in conventional treatment via stem cell transplantation, liposomal cytarabine, and intrathecal rituximab have been used for SCNSL management, CNS recurrence is common and is nearly always fatal.[13] Adverse prognostic features for CNSL include SCNSL, age >60 years, elevated lactate dehydrogenase (LDH), elevated CSF protein, and involvement of deep regions of the brain.[14]

This case report also highlights various dilemmas with difficulties in diagnosis when biopsy is not amenable. CSF immunophenotyping, MRI findings, and polymerase chain reaction (PCR) showing immunoglobulin heavy chain gene (IgHV) rearrangement [15] can sometimes be used to diagnose CNS lymphoma independent of biopsy. Our initial CSF showed a high protein level (three times higher than normal) and large- to medium-sized lymphoid cells with cytospin morphology.

Flow cytometry analysis did not demonstrate a kappa/lamda restriction (ratio 1.39) or evidence of a B-cell clone with only 13% B-lymphocytes. Due to the absence of adenopathy or intracerebral pathology, a paraneoplastic or lymphoma etiology was felt to be unlikely at this stage. However, it should be noted that although CSF flow cytometry is highly sensitive, it is also highly dependent on the cellularity and volume of the sample as well as the time between postsample procurement and analysis.[16] CSF flow cytometry is particularly dependent on contamination with RBCs.[16] The first CSF sample contained RBCs possibly due to contamination or leakage into the intrathecal space. Furthermore, only a small sample volume of 1 mL was sent for analysis. This may impact CSF flow cytometry interpretation. Unfortunately, flow cytometry was not performed on the second CSF sample due to the nonsignificant findings of the first CSF cytometry.

This case report also showcases the dilemma of steroid use without histology.[17] This patient responded remarkably well to high-dose steroids until the final presentation two months later. At this stage, following the tapering of steroids, the tonsillar masses became noticeable. As described, the histology of these masses had a Ki67 proliferation index of over 50% with expression of CD20, PAX5, BCL2, BCL6, and MUM1 with focal c-myc. This is consistent with a high-grade nongerminal center DLBCL. In general, investigation of a patient suspected of having paraneoplastic syndrome might fail to reveal the tumor until it becomes symptomatic, typically 3-13 months later.[18] The TM presentation in this case report may have been induced by direct tumor infiltration, intravascular infiltration, or an immunogenic paraneoplastic syndrome.[19] It is hard to establish whether the TM is correlated to the DLBCL or is a paraneoplastic SCNSL effect, but the latter is likely given the unique and rapid clinical course of events in this case.

DLBCL most commonly presents as enlarged lymph nodes with other disease-specific symptoms, such as fevers, fatigue, and weight loss[20]; however, the presentation can occasionally be less typical resulting in misdiagnosis. Documented unusual DLBCL presentations include progressive forearm swelling,[21] posterior mandibular swelling misdiagnosed as periapical periodontitis,[22] erythematous face lesions suggestive of erysipelas,[23] and paraplegia misdiagnosed as disk herniation.[24] This patient displayed myelopathy as presenting symptom of DLBCL, initially believed to be related to the intrathecal pump, and therefore was only diagnosed after 1 month of presenting to the clinic. The histology of nongerminal center B-cell subtype high-grade DLBCL determines a high-risk individual.[25] Treatment should involve CNS penetrating regimes or prophylactic intrathecal methotrexate

with potential consolidation with either autologous stem cell transplant (ASCT) dependant on risk assessment with a multidisciplinary team and fitness.[26]

## 4 | CONCLUSION

In summary, while it is a common occurrence that spinal symptoms in patients with intrathecal pumps are automatically attributed to pump complications, it is evident that a wider differential diagnosis should be considered in such patients. Additionally, this case demonstrates that lymphoma may present in a variety of unusual ways and may therefore delay diagnosis. Timely diagnosis may result in improvement of symptoms and prevent metastasis.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### AUTHOR CONTRIBUTION

Kirk John Levins: served as a pain clinician and was involved in writing, editing, and formatting manuscript. Mohamed Khan: served as a hematologist and was involved in writing, editing, and formatting manuscript. Thomas Drago, Elena Roman, Cillian Suiter, Darren William Roddy, and Anurag Nasa: involved in writing, editing, and formatting manuscript. Paul Murphy: served as a lead clinician and involved in writing, editing, and formatting manuscript.

### ETHICS

The patient has consented to publication the case, imaging and all data. The patient has also been offered the opportunity to read the manuscript prior to publication.

### DATA AVAILABILITY STATEMENT

All data have been retained.

### ORCID

*Kirk John Levins* https://orcid.org/0000-0001-5051-805X
*Thomas Drago* https://orcid.org/0000-0002-6380-3930
*Anurag Nasa* https://orcid.org/0000-0002-5498-9817

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