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Published in:
World neurosurgery

DOI:
10.1016/j.wneu.2020.06.184

Publication date:
2020

Primary Cauda Equina T-Cell Lymphoblastic Lymphoma

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Key words
- Cauda equina
- Intradural
- Non-Hodgkin lymphoma
- T-cell lymphoblastic lymphoma

Abbreviations and Acronyms
CD: Cluster of differentiation
CNS: Central nervous system
CSF: Cerebrospinal fluid
EBV: Epstein-Barr virus
FDG-PET: Fluorodeoxyglucose-positron emission tomography
MRI: Magnetic resonance imaging
PCNSL: Primary central nervous system lymphoma
T-LBL: T-cell lymphoblastic lymphoma

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Citation: World Neurosurg. (2020) 142:227-232. https://doi.org/10.1016/j.wneu.2020.06.184

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

BACKGROUND: **T-cell lymphoblastic lymphoma (T-LBL) is a rare and aggressive form of non-Hodgkin lymphoma. This report describes, to our knowledge, the first adult case of a primary cauda equina T-LBL. Treatment consists of multiagent chemotherapy, and surgical removal of T-LBL does not improve outcome. We discuss the workup of patients with an intradural spinal mass, together with a review of the literature on primary spinal lymphoma of the cauda equina.**

CASE DESCRIPTION: **A 54-year-old woman with Crohn's disease, for which she was taking immunosuppressive medication, presented with progressive back pain radiating to both legs and deteriorating neurologic deficits caused by an intradural, contrast-enhancing lesion in the L1-5 region. During acute surgery, the tumor was partially resected. Immunohistochemical phenotyping revealed a T-LBL. No other lymphoma localizations were found after subsequent staging. Despite extensive treatment, the patient died of disseminated disease throughout the central nervous system, 6 weeks after the diagnosis.**

CONCLUSIONS: **Pain and progressive neurologic complaints can be symptoms of a (malignant) intradural spinal tumor. Intradural lymphoma must be considered as a differential diagnosis by clinicians because it can mimic neoplasms that often require urgent surgery. The histopathologic diagnosis should preferably be obtained by way of cerebrospinal fluid analysis or tumor biopsy because tumor resection has no beneficial effect on the oncologic outcome.**

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a relatively rare and aggressive hematologic malignancy and accounts for approximately 2% of all central nervous system (CNS) tumors. It can appear throughout the CNS, and primary indicates it has no systemic involvement at the time of diagnosis.[1] The median age at diagnosis is 66 years. The incidence has increased over the last decades, especially in older patients and immunocompromised patients.[2] On magnetic resonance imaging (MRI) with gadolinium, PCNSL generally presents as a nodular mass with homogenous contrast enhancement and well-defined borders.[3] The vast majority of PCNSLs are diffuse large B-cell lymphomas (±90%). Other forms are Burkitt, low-grade, or T-cell lymphomas. T-cell lymphomas make up for around 2% of all PCNCLs and can be T-cell, natural killer/T-cell, or lymphoblastic. Most PCNSLs in immunoincompetent patients are Epstein-Barr virus (EBV)—driven, whereas EBV-related PCNSL is uncommon in immunocompetent individuals.[4] The diagnosis of PCNSL is mostly established through cerebrospinal fluid (CSF) analysis or biopsy. Clinical evaluation should be completed with fluorodeoxyglucose-positron emission tomography (FDG-PET) scan, bone marrow biopsy, vitreous biopsy if applicable, and testicular ultrasound in men.[5]

Of all anatomic sites, the spinal and cauda equina localizations of PCNSL are the most seldomly encountered.[6] Clinical presentations vary widely because symptomatology depends on tumor localization. Symptoms can include nonspecific pain along the spinal axis and subsequent development of neurologic deficits such as limb weakness with gait abnormalities, sensory problems, sexual dysfunction, and bowel and bladder dysfunction.[7] The differential diagnosis of spinal intradural lesions with solid enhancement includes primary CNS tumors such as meningioma, nerve sheath tumors (schwannoma, neurofibroma), malignant peripheral nerve sheath tumor, infection, metastasis, inflammation (sarcoidosis), leukemia, and lymphoma.[4]

Age, performance scale, serum lactate dehydrogenase level, CSF protein concentration, and involvement of deep structures of the brain are independent prognostic factors of survival.[8] Median overall survival is 8—9 years in patients younger than 50 years of age, but substantially lower in older patients with lower performance scales.[9] Surgical

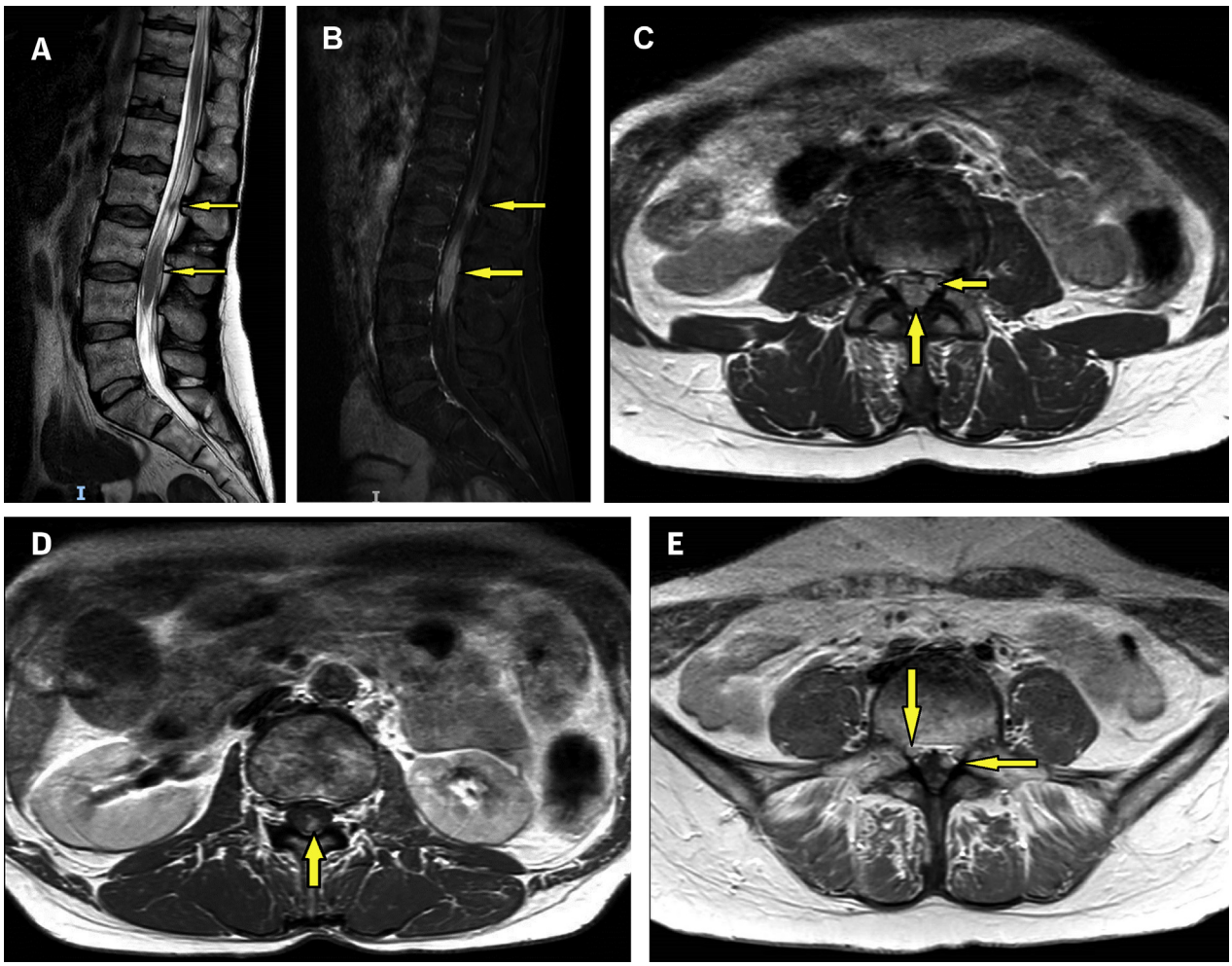

Figure 1. Sagittal T2 (**A**) and T1 magnetic resonance imaging with gadolinium of the lumbar region. A contrast-enhancing lesion at the L3-4 level is visible with a smaller satellite lesion cranially at the L2 level (**B**). Transversal imaging shows obliteration of the spinal canal because of tumor localization and enlarged nerves at the level of L4 (**C**), L2 (**D**) and L5 (**E**). *Yellow arrows* indicate the lesions.

resection of PCNSL has proven to be of no substantial benefit for survival and must therefore be avoided.[10] High-dose methotrexate-based multiagent chemotherapy is considered the standard first-line therapy for PCNSL, and autologous stem cell transplantation is an effective consolidative treatment.[11]

CASE PRESENTATION

A 54-year-old woman had nocturnal back pain for over 8 months. She was taking azathioprine for Crohn's disease. There was no history of fever, infections, or overseas travel. She had a normal appetite and bodyweight. She did not report signs of fatigue, night sweats, or dyspnea. Back pain was not worsened by change of stature. The pain radiating to her legs that developed over the previous 3 weeks had a radicular pattern involving the L4 and L5 dermatomes. Concomitant was the development of a dropping foot. Besides a less prominent urge for micturition, there was no symptomatology of a complete cauda equina syndrome. Because of rapid deterioration of neurologic symptoms over the last 24 hours, the patient was admitted to the hospital.

Neurologic Examination

On examination, her vital signs were within normal range. Neurologic examination showed a paresis of both lower limbs, most prominent of the right foot extensors. The worst Medical Research Council score was 2. Deep tendon reflexes were low on both sides. No loss of sensation was found. Gait instability was evident, and the patient could not walk without support.

Laboratory Findings

Laboratory results showed that she had a normal blood count and white blood cell differentiation, normal C-reactive protein and lactate dehydrogenase, and normal kidney and liver function tests.

Radiologic Findings

MRI of the lumbosacral spine displayed multifocal solid homogenous enhancing intradural lesions at the level of the cauda

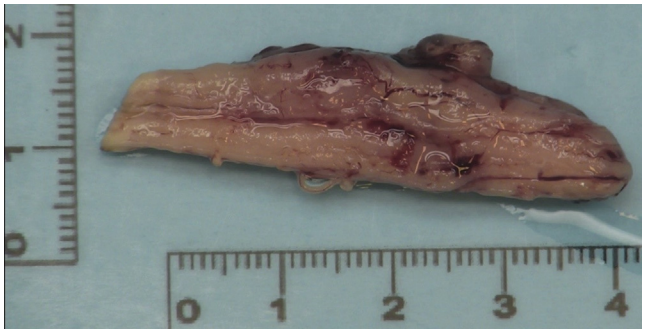

Figure 2. Macroscopic aspect of the tumor specimen after resection.

equina involving multiple roots at L1-4 and a central mass at L3-4. On T1 and T2 images, the lesions were isointense to the spinal cord with homogenous enhancement after contrast (Figure 1). There was no sign of hemorrhage (cap sign). There was no enhancement of the pial surface of the spinal cord. No abnormalities were found in the brain and in the cervical and thoracic spine. Diffusion-weighted imaging is not routinely performed for spinal lesions.

Surgical Findings

Because of the progressive symptomatology, it was decided to perform an emergency decompression of the cauda equina. A laminectomy of L3 and L4 was performed. There was no extradural abnormality, and the dura mater had a normal aspect. During intradural exploration, a partial mass reduction of the tumor was possible. Multiple nerve roots were enlarged because of tumor infiltration. There were signs of previous intradural hemorrhage at the tumor localization. The surgical goal was to decompress the surrounding neural structures and obtain tissue for histopathology (Figure 2). Because of the emergency setting, with an operation in the evening hours, intraoperative neuromonitoring was not available in our institution.

Pathologic Findings

Histopathologic review showed small blue round tumor cells in hematoxylin-eosin staining (Figure 3). Microscopic analysis showed a vague, nodular growth pattern. The tumor cells were polymorphic and had hyperchromatic nuclei and a nucleolus in some cells. There was hardly any cytoplasm. Multiple mitotic figures were spotted and small, thin-walled vessels. Focal points of necrosis were apparent. The lesion mainly consisted of cluster of differentiation (CD)−3 positive cells. Further analysis showed positive results for the following: terminal deoxynucleotidyl transferase and CD-1a, CD-99, CD-4, and CD-8. Weakly positive were T-cell markers CD-2, CD-5, and CD-7. Negative results came out for CD-34, CD-20, CD-30, anaplastic lymphoma kinase, CD-10, granzyme B, T-cell intracytoplasmic antigen, and synaptophysin. The lesion showed a Ki-67 proliferation fraction of 90%. EBV in situ hybridization came out negative. These findings are compatible with T-cell lymphoblastic lymphoma (T-LBL).

Postoperative Course

The radicular pain improved, but there was limited improvement of other neurologic symptoms after surgery. A postoperative MRI 3 days after surgery showed progression of the disease at the L1 and L2 level just below the conus (Figure 4). On day 4 after surgery, dexamethasone was initiated for recurrent radicular pain. At confirmation of the diagnosis T-LBL at day 7 after surgery, therapy was switched to a short course of high-dose prednisolone followed by a hyper-cyclophosphamide, vincristine, doxorubicin and dexamethasone (CVAD) B chemotherapy regimen (methotrexate, cytarabine, and leucovorin and sodium bicarbonate). Bone marrow aspirate and FDG-PET scan (Figure 5) on day 7 and 10 after surgery, respectively, did not show disease activity elsewhere. The disease progressed during

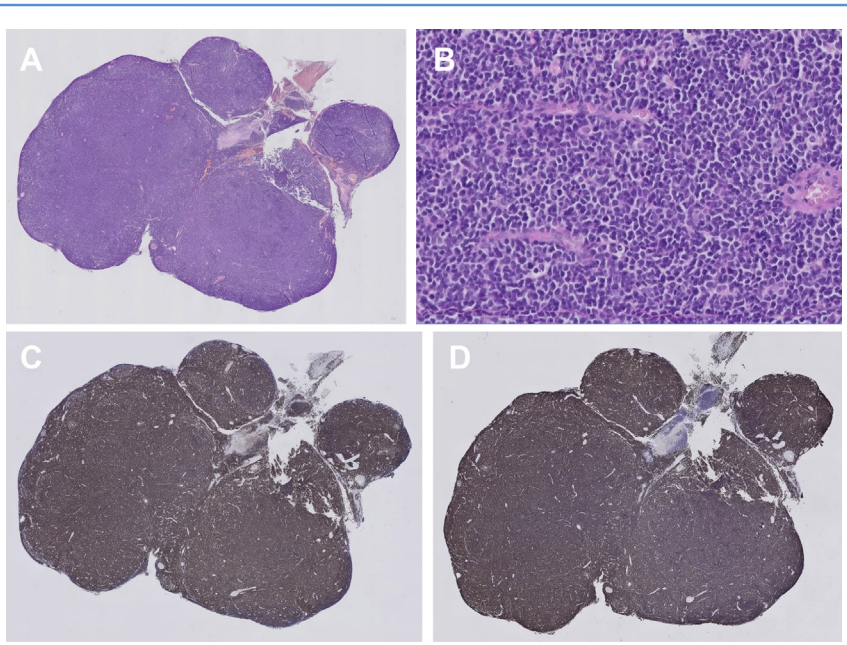

Figure 3. Histopathologic imaging of the resected specimens: (**A**) hematoxylin-eosin staining, magnification 1×; (**B**) hematoxylin-eosin staining, magnification 20×; (**C**) Ki-67 labeling shows proliferation index of 90%, magnification 1×; (**D**) cluster of differentiation 3 staining: T-lymphocytes, magnification 1×.

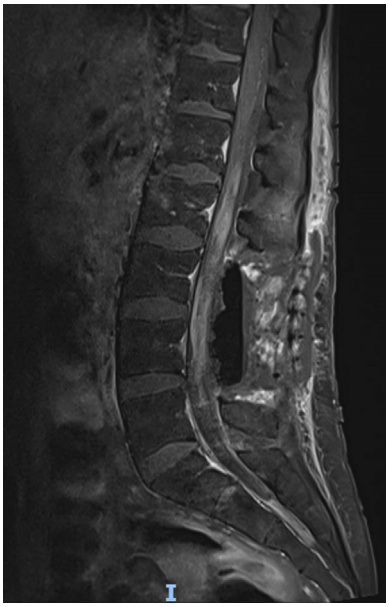

Figure 4. Sagittal T1 magnetic resonance imaging of the lumbar region with gadolinium 3 days after surgery shows marked progression of the intradural abnormality.

first-line therapy and 1-month rescue radiation therapy (5 × 4 Gy) was administered to treat lower back and radicular pain. The patient developed difficulty in swallowing and dysarthria 5 weeks after the initial surgery, which were suspicious for leptomeningeal spread of the lymphoma. An Ommaya reservoir was inserted to administer methotrexate intrathecally, and salvage therapy with nelarabine, etoposide, and cyclophosphamide was initiated. Nevertheless, the condition of the patient deteriorated and she succumbed to disease progression 6 weeks after the initial diagnosis.

DISCUSSION

Knowledge on spinal PCNSL is based on case reports. We searched the databases of PubMed and Web of Science on the topic of primary cauda equina lymphoma and reviewed all publications from 1990 to the present (Table 1). Fifteen cases of primary cauda equina lymphoma were previously reported, and most of these were diffuse large B-cell lymphomas.

Two case reports describe the T-cell subtype of cauda equina lymphoma. Morita et al.[16] mention the NK/T-cell subtype in an adult patient and Ooi et al.[14] present a 16-year-old boy with primary cauda equina T-LBL. Besides that, we found 1 case of proven primary T-LBL in the epidural space.[26] To our knowledge, we present the first case of an adult with primary cauda equina T-LBL.

T-LBL typically presents as an advanced, widely disseminated disease. The thymus is often involved as are the testes or ovaries. At presentation, CNS involvement is seen in 5%–10% of cases, as part of the systemic spread of the disease. Most lymphoblastic lymphomas are thought to be idiopathic.[27] Postsurgical assessment in the case described here showed no other disease localizations on the FDG-PET scan. A bone marrow biopsy did not show T-LBL activity. This is exceptional in the context of T-LBL.

Although rare, spinal lymphoma is likely to become more prevalent with a growing group of acquired immunodeficient patients. The present patient had a history of Crohn's disease. She was treated with the immunosuppressive agent azathioprine. This is a thiopurine that inhibits expansion and proliferation of

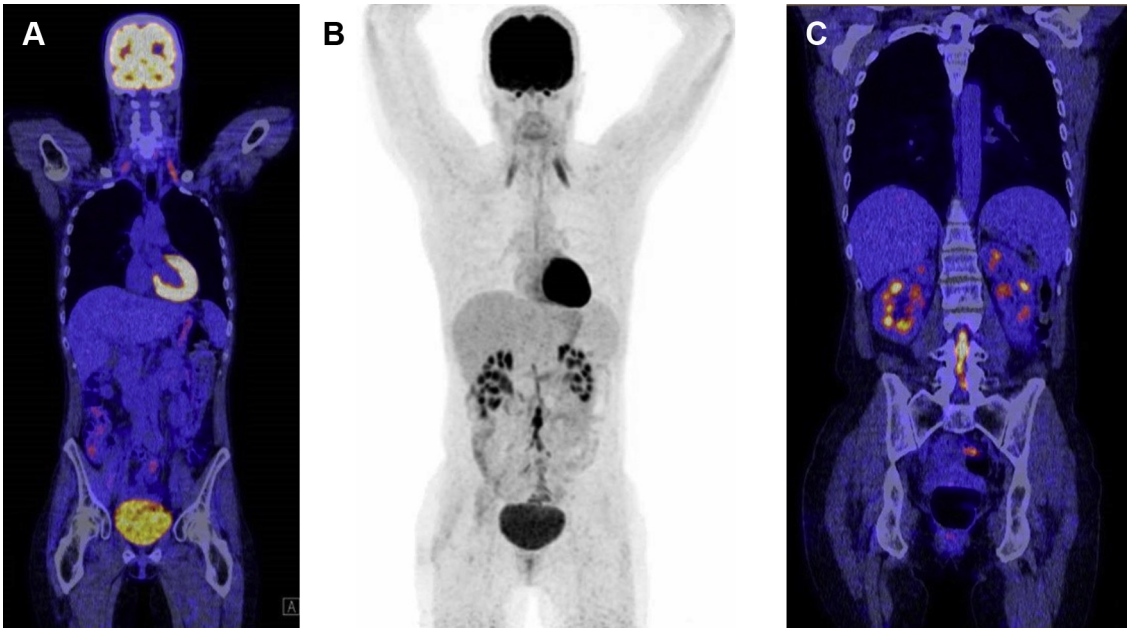

Figure 5. Fluorodeoxyglucose-positron emission tomography scan showed no signs of disease activity elsewhere in the body. (**A** and **B**) A clear positive activity signal is visible at the intraspinal L4-5 level. (**C**) Imaging was performed on day 10 after surgery.

Table 1. Review of the Literature on Cauda Equina Primary Central Nervous System Lymphoma

Study	Age (years)/ Sex	Location	Subtype	Immunocompetent	Follow-Up (months)	Outcome
Klein et al., 1990[12]	29/F	L1-2	B-cell	Yes	1—2	Death
Knopp et al., 1994[13]	69/F	L2-3	NS	No	NS	NS
Ooi et al., 1996[14]	16/M	L2-4	T-LBL	NS	8	Death
Giobbia et al., 1999[15]	30/F	L4-5	DLBCL	No	12	Alive
Morita et al., 2009[16]	67/M	L3-5	NK/T-cell	NS	14	Death
Beitzke et al., 2010[17]	69/M	L1-S1	DLBCL	Yes	NS	Death
Nishida et al., 2012[18]	47/M	L1-5	DLBCL	NS	18	Alive
Cugati et al., 2012[19]	11/M	L2-3	B-cell	NS	12	Alive
Iwasaki et al., 2012[20]	69/M	Th12-L1	DLBCL	NS	18	Death
Teo et al., 2012[21]	58/M	Th11-L4	DLBCL	NS	24	Alive
Nakashima et al., 2014[22]	59/M	Th12-S1	DLBCL	Yes	12	Alive
Broen et al., 2014[23]	75/F	L1-3	DLBCL	Yes	10	Death
Broen et al., 2014[23]	71/F	L1-5	DLBCL	Yes	>10	Alive
Geevarghese et al., 2017[24]	46/M	L4-S2	B-cell	Yes	30	Alive
Suzuki et al., 2018[25]	65/M	L1-S1	DLBCL	No	81	Alive
Present case	54/F	L1-4	T-LBL	Yes	1.5	Death

F, female; NS, not stated; M, male; T-LBL, T-cell lymphoblastic lymphoma; DLBCL, diffuse large B-cell lymphoma; NK/T-cell, natural killer/T-cell lymphoma.

B- and T-lymphocytes. Thiopurines are linked with a low risk of EBV-driven lymphomas. The risk increases with age and is higher in combined therapy with anti—tumor necrosis factor agents.[28]

In retrospect, the initial MRI had atypical aspects for the differential diagnosis of a nerve sheath tumor (schwannoma, neurofibroma) or (myxopapillary) ependymoma. Especially the multiple contrast-enhancing lesions and the T2 signal intensity (isointense to spinal cord) should have raised suspicion of a broader differential diagnosis in an immunocompromised patient. Lumbar puncture to obtain CSF was deemed impossible because of extensive tumor localization in the caudal sac. Progression of neurologic symptoms was the reason to opt for a mass reduction by way of a partial surgical resection. During surgery, it was obvious that complete resection was not possible. We decided to resect the largest tumor mass to decompress and spare as many cauda fibers as possible.

In case of a spinal lymphoma, swift diagnostics and immediate start of the oncologic treatment is pivotal. This is especially important in the case of compression of neural structures and deteriorating neurologic deficits.[29] The substantial increase in clinical trials, investigating small molecules and novel agents, renders more future treatment options for this patient population. This stresses the advice to obtain a swift diagnosis even further.[30]

The case presented here underscores that clinicians should be alert for primary spinal lymphoma; however, this is a very rare diagnosis. If the clinical presentation and the radiographic findings give reason to believe there is a broader differential than a typical spinal tumor, especially in an immunodeficient patient, PCSNL of the cauda equina should be considered. In certain cases, this may prevent unnecessary surgery with significant risks.

CONCLUSIONS

Here we describe, to our knowledge, the first adult case of a primary cauda equina T-LBL. In case of a spinal intradural tumor with atypical radiologic findings, especially in an immunocompromised patient, the diagnosis of PCNSL should be considered. Preferably, this diagnosis is established by way of CSF analysis or tumor biopsy. Early consultation of a hemato-oncologist and immediate installation of oncologic treatment after diagnosis is advised.

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Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 13 May 2020; accepted 22 June 2020

Citation: World Neurosurg. (2020) 142:227-232.
https://doi.org/10.1016/j.wneu.2020.06.184

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

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