Diagnostic challenge in a patient with primary bilateral Dumbbell-shaped lumbar non-Hodgkin's lymphoma

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Abstract: *Objective*: Primary bilateral dumbbell-shaped lumbar non-Hodgkin lymphomas with epidural and extraspinal involvement, are rare occurrences. Patients presenting at advanced stages and rapid evolution towards neurological impairment lead to diagnostic dilemmas for which only immunohistochemistry can provide a correct, although delayed solution. *Case report*: We report the first case of a bilateral, dumbbell-shaped, lumbar lymphoma in a 65-year-old man with a medical history of chronic viral hepatitis type B and D under interferon treatment. The patient presented with back pain radiating down the right leg, with rapid progression to paraplegia and sphincter dysfunction. CT and MRI revealed a large dumbbell mass (approx. 5/5/10 cm) in the right paraspinal musculature, at the L4-L5 level, with intraspinal epidural extension. A similar mass of smaller size was described on the left side, almost mirroring the first lesion, the imagistic aspect suggesting a neural sheath tumor. Intraoperatively, in the right lumbar paraspinal musculature, a soft, yellowish region was discovered, the macroscopic appearance being rather suggestive for a diffuse infection. Clinical, imagistic and surgical findings were not conclusive, nor was the histological examination in light microscopy of the surgical specimen or of the bone marrow biopsy. Immunohistochemistry identified the presence of large B cells, leading to the diagnosis of B cell lymphoma. Although the patient was treated with systemic chemotherapy, his condition rapidly deteriorated and he died within 3 months. *Conclusions*: In the case of a lumbosacral, dumbbell shaped mass, developed both epidural and extraspinal, the differential diagnosis must include lymphoma. The histological examination, especially immunohistochemistry provided the final diagnosis. Delays in establishing a diagnosis, associated with a malignant evolution of lymphoma, diminish the chances of determining and applying a treatment strategy that could prolong survival.

Key words: dumbbell shaped tumor, non-Hodgkin lymphoma, lumbar spine, sciatica, paraspinal musculature

Case report

A 65-year-old patient was referred to our department for low back pain radiating to the posterior aspect of right thigh down to the heel associated with numbness and tingling on the plantar aspect of the right foot. Symptoms were resistant to NSAID treatment and were more pronounced during the night. His gait was difficult due to pain.

Significant medical history included chronic viral hepatitis type B and D treated with interferon up until 3 months prior to admission and diabetes mellitus type II.

Physical examination was normal, except for a firm region located superficially on the right paravertebral lumbar spine. He presented no fever, nor lymphadenopathy or weight loss.

Neurologic examination was normal at presentation with negative sciatic nerve stretch test.

Notable laboratory results included an ESR of 42 mm/h, total white cell count of 8720/μL, neutrophils 5940/μL (68.20%), lymphocytes 2030/μL (23.30%), eosinophils 100/μL (1.12%), basophils 20/μL (0.20%). No atypical lymphocytes were encountered.

Lumbar computer tomography revealed swelling of the iliopsoas muscle and the right paraspinal muscles adjacent to L4 and L5 vertebras, with post-contrast enhancement and enlargement of the corresponding neural foramina (Figure 1).

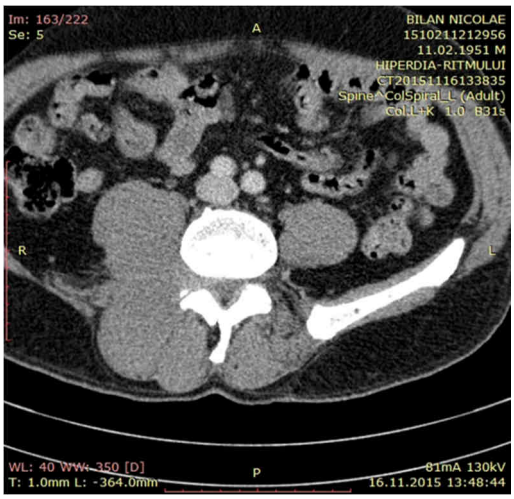


Figure 1 - Axial CT image at the level of the L4 vertebra that shows swelling of the iliopsoas muscle and the right paraspinal muscles with post-contrast enhancement

MRI showed a polylobed dumbbell-shaped mass, posterior to the insertion of the right psoas, extended in the right paraspinal muscles in close contact with the L4 and L5 posterior arches, entering the spinal canal through the L4-L5 and L5-S1 foramina, compressing and left-displacing the dural sack. Within the spinal canal, the tumor presented epidural extension over the entire length of the sacral canal. The mass, measuring 5/5/10 cm, appeared homogenous, with T1, T2 and STIR hyperintensity and homogenous enhancement. On the left side, an identical mass of smaller size was identified, located lateral to the L4-L5 intervertebral foramen, extending in the paraspinal musculature (Figure 2).

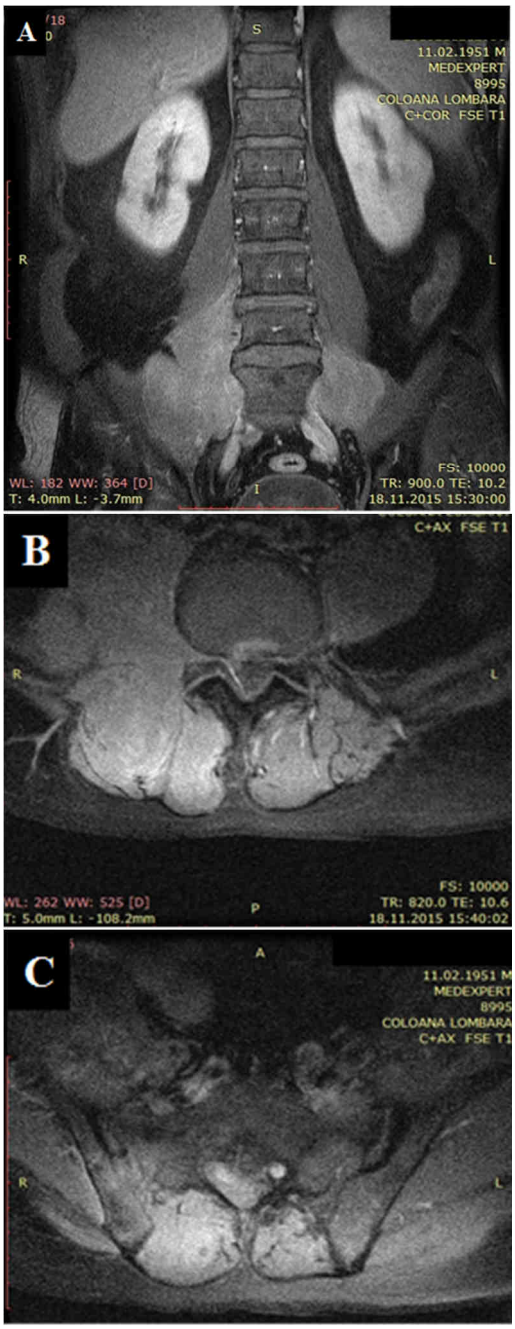


Figure 2 - Lumbar spine MRI, T1 weighted images after contrast administration in coronal plane that show a bilateral dumbbell shaped hyper intense mass that extends in the paravertebral muscles (A); the tumor enters the spinal canal at the L4-L5 level, with left displacement of the dural sack (B); axial image at S1 level reveals the epidural extension in the sacral canal (C)

Chest, abdomen and pelvic contrast CT scans as well as abdominal ultrasound were negative for enlarged lymph nodes or additional masses.

The patient underwent decompression of the L5 and S1 right spinal roots performed via L4 and L5 right hemilaminectomy. At this level the epidural tissue mass was debrided and its extension in the paraspinal musculature was partially resected. Intraoperatively, in the central area of the paraspinal tumor, a mass of yellowish color and soft consistency was found, the macroscopic aspect being rather that of a diffuse infection in a very infiltrative mass.

Immediately following the surgical decompression, the patient's pain was alleviated. He was able to walk with the aid of a cane.

Bacteriological examination of the debrided muscular tissue isolated Staphylococcus aureus, sensitive to Gentamicin, Linezolid and Trimethoprim/sulfamethoxazole.

Two weeks later the patient presented a difficult gait due to foot drop on the right side. He also showed sensory impairment of the L5 and S1 radicular territories. No sphincter disturbances were encountered.

The general physical examination revealed a painless, 1 cm diameter inguinal adenopathy of firm consistency, adherent to the adjacent planes. Organomegaly was absent.

Histological examination of the specimen with light microscopy was inconclusive, indicating an undifferentiated tumor, with medium/large cells, proliferating in a discohesive manner (Figure 3). Bone marrow obtained through biopsy showed at histopathological examination hematogenous marrow with age appropriate cellularity with the presence of all cellular series, light megakaryocytic reactive hyperplasia and extremely rare, small cell, mature lymphoid interstitial infiltrate (reactive aspect).

Immunostaining was used in order to establish the diagnosis. The microscopic characteristics made necessary an investigation of cell type as Vimentin and cytokeratin MNF116 were the first applied markers. The cytokeratin MNF116 was negativ and Vimentin was positive in a fashion suggesting a lymphoid proliferation. The common leukocyte antigen CLA (CD45) and CD20 were diffusely positive while CD3 showed only rare positive cells. For typing the Lymphoid B cell proliferation CD10 (for germinal center subtype) and MUM1 (for activated B cell type) were applied. MUM1 was diffusely positive, indicating the activated B cell and that the final diagnosis was diffuse large B cell non-Hodgkin's lymphoma activated subtype, infiltrating skeletal muscle. A high proliferative cell index reveals the aggresive nature of the tumor. (Figure 4). The origin of the lymphoid proliferation is more difficult to establish; it may be in a lymph node near the muscle, near the bone or even in the bone marrow of the vertebra.

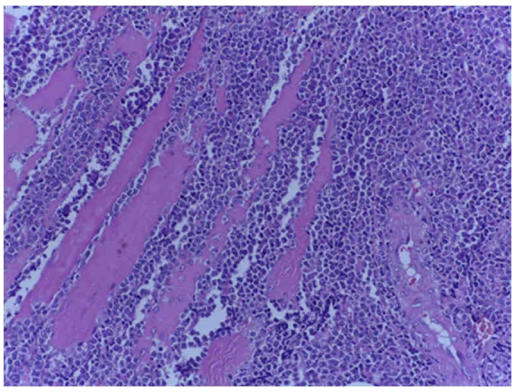
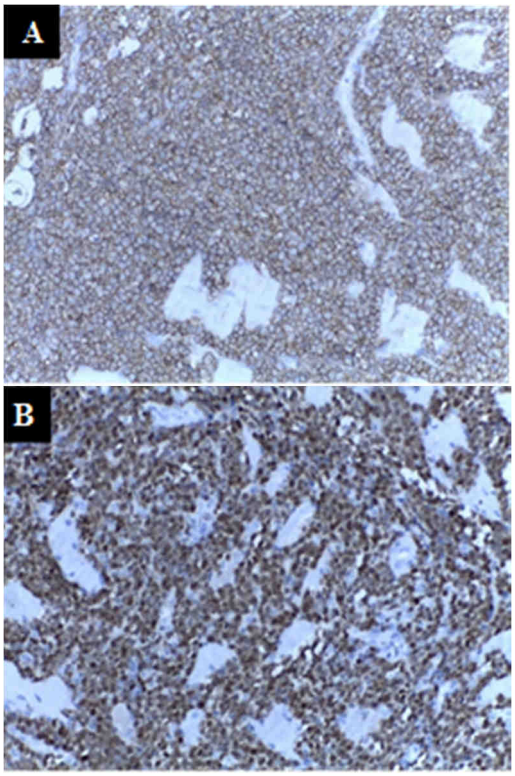


Figure 3 - Light microscopy examination of the tumor specimen revealing skeletal muscle with diffuse tumor invasion. Tumor cells are large, with scant cytoplasm and rounded nuclei with dispersed chromatin and with a discohesive feature (HE staining, 20x magnification)



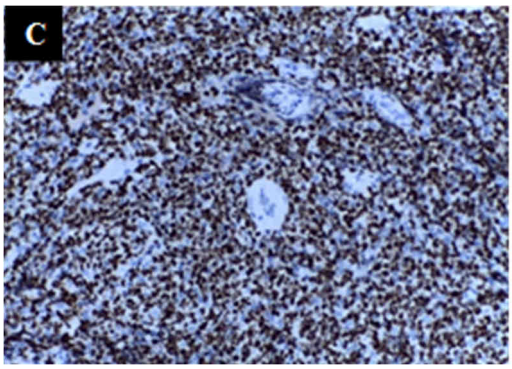


Figure 4 - Immunostaining of the tumor tissue. A: CD20 appears diffusely positive, revealing the lymphoid nature of the tumor proliferation. (CD20 staining, 20x magnification); B: MUM1 staining is positive for activated B cells (MUM1 staining, 20x magnification); C: The proliferative cell index is very high (~90%), illustrating the aggressive character of the tumor (Ki67 staining, 20x magnification)

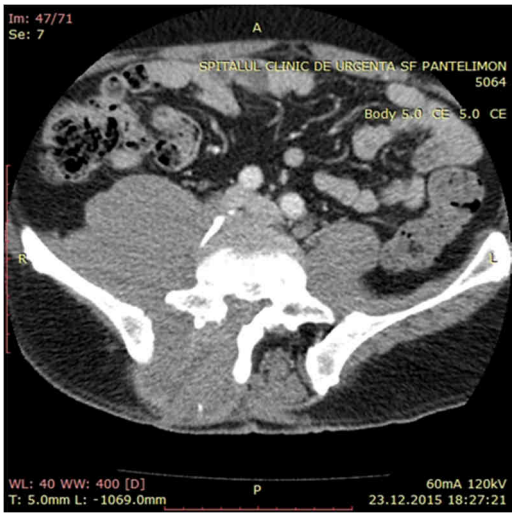


Figure 5 - Postoperative (1 month) contrast lumbar CT at the level of the L5 vertebra showing the increase in size of both paravertebral masses

Neurological deficits rapidly progressed to paraparesis and urinary retention.

A lumbar CT was repeated at 1 month after surgery that showed the increase in size of both paravertebral masses with central necrosis and also bony erosion of the right iliac bone and sacrum (Figure 5).

Repeated laboratory tests revealed an increased CRP of 47,2 mg/dl and LDH of 719 mmol/L.

The patients' postoperative course included pain relief medication, antibiotherapy, Dexamethasone, Zoledronic acid, Filgrastim and 3 cycles of chemotherapy with Cyclophosphamide and Doxorubicin.

The patient's general condition progressively worsened, in parallel with gradual neurological impairment, followed by death at 3 months postoperatively.

Discussion

Basic notions regarding the immune system and non-Hodgkin lymphomas

The human body has defensive immune mechanisms through which it triggers immune responses:

•The innate immune response consists of macrophages, monocytes, granulocytes and natural killer cells that detect pathogens and rapidly respond to the nonspecific signals that appear in case of infection and tissue damage

•The adaptive immune response is provided by lymphocytes. They are immunocompetent cells that present specificity and memory for foreign agents. Lymphocytes present specific receptors: B cell receptor or T cell receptor. The adaptive immunity can be humoral or cellular, depending on the receptor type expressed by lymphocytes. (1)

The humoral immune system consists primarily of B cells and plasma cells that

secrete antibodies. The B cell receptor is located at the surface of the cell and has specificity for antigens. Antibodies represent the weapons of the humoral immune system, secreted by B cells.

The cellular immune system is provided by T cells that can express CD4 or CD8 co-receptors. CD8+ T-cells are also called cytotoxic lymphocytes. CD4+ T-cells are known as T-helper cells that regulate the function of other immune cells via the cytokines that they secrete.

Non-Hodgkin lymphomas (NHLs) are caused by lymphocytic proliferation in the lymph nodes, spleen or bone marrow. NHLs can develop in any site of the body where lymphatic tissue is present. (2, 3)

The non-Hodgkin lymphoma is a systemic condition that has the tendency to disseminate even at the level of the central nervous system, both intra and extracranial, spine (4), spinal epidural space, at the level of the nerve roots, nerve plexuses, even cranial or peripheral nerves (5–9) and can be primary or secondary lesions of the nervous system. Because it is capable of mimicking any other condition at affected sites, the diagnosis is sometimes delayed, and the outcome is grim, despite therapeutic advances in recent years.

NHLs are heterogeneous, blood cell tumors composed of B and T cells. There are several types of lymphoma that are classified by the WHO in:

- large, diffuse B-cell lymphomas
- T-cell lymphomas
- plasmablastic lymphomas
- natural killer T-cell lymphomas (NK/T-cell)

There are approximatively 30 subtypes of non-Hodgkin lymphomas, with variable severity, from mild to aggressive.

Non-Hodgkin lymphomas with spinal cord compression are often aggressive (10–13). NHL is the seventh most common cancer in the United States (14).

Monnard et al (15) have reported that 4% of spinal epidural lymphomas were developed at the lumbosacral level and 27% in the lumbar area. Spinal cord compression occurred in 0,1% to 3,3% of patients with non-Hodgkin lymphomas (15, 16) and up to 10,2% in aggressive forms (11, 12).

While their cause is unknown, several risk factors have been identified. Although NHLs can develop at any age, they most frequently occur in the seventh and eight decades. Men are more frequently affected than women. Various risk factors are mentioned in the literature: viral or baterial infections (Epstein-Barr virus, HIV), immune system defficiencies in immunosupressed patients, under immunosupresive theraphy, after organ transplant, autoimmune diseases and radiation exposure (8, 17, 18).

Immune system compromise in the presence of a risk factor predisposes patients to develop lymphomas.

Surgical intervention followed by chemotherapy and radioterapy, can improve neurological function and can prolong the patient's lifespan (19).

Differential Diagnosis

In the presented case, the patient was under interferon treatment for chronic viral hepatitis type B and D. The presence of this element in recent case history was not a sufficiently powerful aspect to guide towards the diagnosis

of lymphoma at the time of admission.

CT and MRI revealed a bilateral, dumbbell-shaped mass, at the level of the lumbar spine, extending in the paraspinal muscles and intrapinally that raised the suspicion of malignant nerve sheath tumor at the L4 and L5 level. According to Tsai (5), lymphomas can grow in patterns that are indistiguishable from nerve sheath tumors. The radiological characteristics of the lession are not fully consistent with the diagnosis of malignant nerve sheath tumor because it is highly unlikely for this tumor type to develop bilaterally, at two levels simultaneously and also extend epidurally along the entire length of the sacral canal, while also presenting an extraspinal globular shape and not stretched along the length of the sciatic nerve roots. Also, nerve sheath tumors appear iso or hypointense in T1 weighted images and hyperintense in T2 with heterogenous enhancement. In the presented case, the tumor showed hyperintensity in T1 and T2 sequences and homogenous enhancement.

Increased lab test values corellated with the inflamatory aspect of the central area of the lesions developed in the paraspinal muscles along with the bacteriological examination positive for Stafilococcus aureus suggest a defficiency of the patient's immune system. All these elements sustained the diagnosis of an infectious process and to begin treatment according to the germ's sensitivity, but at the same time further strengthened the diagnostic dilemma. Bobba et al (20) reported a Hodgkin lymphoma with a bilateral fluid collection in the epidural space and paraspinal region at the L4-L5 level which was initially treated with Vancomycin.

The diagnosis of NHL was not solved with the help of histopathological examination in light microscopy.

We include in the differential diagnosis soft tissue tumors like rhabdomyosarcoma or metastases but these were ruled out by histopathological examination in light microscopy.

The diagnosis of lymphoma could only be made with the help of immunohistochemistry. The tumor cells were positive for Vimentin that suggested a lymphoid proliferation, also diffusely positive for CLA and CD 20, while only rare CD3 positive cells were encountered. MUM1 was diffusely positive, establishing the final diagnosis of diffuse large B cell non-Hodgkin lymphoma, activating subtype, infiltrating skeletal muscle. Not even immunostaining could pinpoint the origin of the lymphoid proliferation.

The fact that at the time of admission no adenopathies were found at general physical examination, nor organomegaly and the thoracic, abdominal and pelvic CT scan did not reveal enlarged lymph nodes, demonstrates that this particular tumor is a primary lymphoma with an uncommon radiological appearance, presenting a lumbar, bilateral, dumbbell-shaped development. Swelling of the inguinal lymph node appeared as the condition progressed and so was not the origin of the lymphoma.

The purpose of the surgical procedure was to obtain a tissue sample for histopathologic examination ant to decompress the neural roots in accordance with recommendations of Hong et al (21).

Postoperative survival was short because, although primary lymphomas are sensitive to chemotherapy, only 3 cycles could be administered, without iradiation. Radiotherapy, some authors claim, is no longer justified (22, 23).

Conclusions

Primary non-Hodgkin lymphomas have to be taken into consideration in the differential diagnosis of patients presenting with low back pain and radiculopathy.

We report a very rare case of primary lumbosacral and paraspinal lymphoma with late discovery which was correctly diagnosed only after immunhistochemical examination.

Late presentation associated with an aggressive form of disease prevent an optimal and complete treatment protocol with a chance to prolong survival.

In the diagnosis and treatment of patients with primary non-Hodgkin lymphoma, a multidisciplinary team is necessary.

References

1. Prins RM, Liau LM. Immunology and immunotherapy in neurosurgical disease. Neurosurgery. 2003;53(1):144-152; discussion 152-153. http://www.ncbi.nlm.nih.gov/pubmed/12823883. Accessed May 4, 2016.

2. Eeles RA, O'Brien P, Horwich A, Brada M. Non-Hodgkin's lymphoma presenting with extradural spinal cord compression: functional outcome and survival. Br J Cancer. 1991;63(1):126-129. http://www.ncbi.nlm.nih.gov/pubmed/1989650. Accessed May 16, 2016.

3. Mora J, Wollner N. Primary epidural non-Hodgkin lymphoma: spinal cord compression syndrome as the initial form of presentation in childhood non-Hodgkin lymphoma. Med Pediatr Oncol. 1999;32(2):102-105. http://www.ncbi.nlm.nih.gov/pubmed/9950197. Accessed May 16, 2016.

4. Tahiri L, Benbouazza K, Amine B, Allali F, El Mesbahi O, Hajjaj-Hassouni N. Primary non-Hodgkin's lymphoma presenting as radicular syndrome: report of two cases. Rheumatol Int. 2009;30(1):113-117. doi:10.1007/s00296-009-0898-3.

5. Tsai M-C. Non-Hodgkin's B-cell lymphoma of a lumbar nerve root: a rare cause of lumbar radiculopathy. J Clin Neurosci. 2013;20(7):1029-1031. doi:10.1016/j.jocn.2012.06.017.

6. Cappellari M, Benedetti F, Fiaschi A, Benedetti MD. Multiple radiculopathy as the presenting manifestation of primary spinal leptomeningeal B cell lymphoma detected by flow cytometry of cerebrospinal fluid. Neurol Sci. 2011;32(6):1171-1174. doi:10.1007/s10072-011-0613-5.

7. Gonzalvo A, McKenzie C, Harris M, Biggs M. Primary non-Hodgkin's lymphoma of the radial nerve: case report. Neurosurgery. 2010;67(3):E872-E873; discussion E873. doi:10.1227/01.NEU.0000374852.65670.7D.

8. Abdel Aziz KM, van Loveren HR. Primary lymphoma of Meckel's cave mimicking trigeminal schwannoma: case report. Neurosurgery. 1999;44(4):859-862; discussion 862-863. http://www.ncbi.nlm.nih.gov/pubmed/10201312. Accessed May 16, 2016.

9. da Cunha-Bang SA, Crone C, Christensen T. Non-Hodgkin lymphoma presenting with foot drop. Clin Neurol Neurosurg. 2012;114(8):1201-1203. doi:10.1016/j.clineuro.2012.02.051.

10. Barnard M, Perez-Ordoñez B, Rowed DW, Ang LC. Primary spinal epidural mantle cell lymphoma: case report. Neurosurgery. 2000;47(5):1239-1241; discussion 1242. http://www.ncbi.nlm.nih.gov/pubmed/11063119. Accessed May 16, 2016.

11. Epelbaum R, Haim N, Ben-Shahar M, Ben-Arie Y, Feinsod M, Cohen Y. Non-Hodgkin's lymphoma presenting with spinal epidural involvement. Cancer. 1986;58(9):2120-2124. http://www.ncbi.nlm.nih.gov/pubmed/3756827. Accessed May 16, 2016.

12. Perry JR, Deodhare SS, Bilbao JM, Murray D, Muller P. The significance of spinal cord compression as the initial manifestation of lymphoma. Neurosurgery. 1993;32(2):157-162. http://www.ncbi.nlm.nih.gov/pubmed/8437651. Accessed May 16, 2016.

13. Cho H-J, Lee J-B, Hur JW, Jin S-W, Cho T-H, Park J-Y. A Rare Case of Malignant Lymphoma Occurred at Spinal Epidural Space: A Case Report. Korean J Spine. 2015;12(3):177-180. doi:10.14245/kjs.2015.12.3.177.
14. Alterkruse SF, Kasary C, Kraycho M, et al. SEER Cancer Statistics Review, 1975-2007.; 2010. http://seer.cancer.gov/csr/1975-2007/.
15. Monnard V, Sun A, Epelbaum R, et al. Primary spinal epidural lymphoma: patients' profile, outcome, and prognostic factors: a multicenter Rare Cancer Network study. Int J Radiat Oncol Biol Phys. 2006;65(3):817-823. doi:10.1016/j.ijrobp.2006.01.002.
16. Vanneuville B, Janssens A, Lemmerling M, de Vlam K, Mielants H, Veys EM. Non-Hodgkin's lymphoma presenting with spinal involvement. Ann Rheum Dis. 2000;59(1):12-14. http://www.ncbi.nlm.nih.gov/pubmed/10627420. Accessed May 16, 2016.
17. Boffetta P, de Vocht F. Occupation and the risk of non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev. 2007;16(3):369-372. doi:10.1158/1055-9965.EPI-06-1055.
18. Roug IK, McCartney LB. Metastatic non-Hodgkin lymphoma presenting as low back pain and radiculopathy: a case report. J Chiropr Med. 2012;11(3):202-206. doi:10.1016/j.jcm.2012.05.008.
19. Tang Y, Yang X, Xiao J, et al. Clinical outcomes of treatment for spinal cord compression due to primary non-Hodgkin lymphoma. Spine J. 2013;13(6):641-650. doi:10.1016/j.spinee.2012.11.054.
20. Bobba RK, Arsura EL, Sawh AK, Naseem M. Diagnostic challenge posed by the clinical presentation of foot drop in a patient with Hodgkin's lymphoma. Eur J Intern Med. 2006;17(8):572-574. doi:10.1016/j.ejim.2006.07.010.
21. Hong B, Hermann EJ, Reuter C, Brandis A, Krauss JK. Outcome of surgical decompression of spinal mass lesions in non-Hodgkin's lymphoma and plasmacytoma. Clin Neurol Neurosurg. 2013;115(12):2476-2481. doi:10.1016/j.clineuro.2013.09.037.
22. McAllister LD, Doolittle ND, Guastadisegni PE, et al. Cognitive outcomes and long-term follow-up results after enhanced chemotherapy delivery for primary central nervous system lymphoma. Neurosurgery. 2000;46(1):51-60; discussion 60-61. http://www.ncbi.nlm.nih.gov/pubmed/10626935. Accessed May 16, 2016.
23. Davis TA, Horning SJ. Advances in the management of Hodgkin's and non-Hodgkin's lymphoma. Curr Opin Hematol. 1998;5(4):259-263. http://www.ncbi.nlm.nih.gov/pubmed/9747632. Accessed May 16, 2016.