

A prominent lactate peak as a potential key magnetic resonance spectroscopy (MRS) feature of progressive multifocal leukoencephalopathy (PML): Spectrum pattern observed in three patients

Duško Kozić^{1,2}, Mladen Bjelan^{1,2*}, Jasmina Boban^{1,2}, Jelena Ostojić¹, Vesna Turkulov^{1,3}, Aleksandar Todorović^{1,2}, Slobodanka Lemajić-Komazec^{1,4}, Snežana Brkić^{1,3}

¹Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia, ²Diagnostic Imaging Center, Oncology Institute of Vojvodina, Sremska Kamenica, Novi Sad, Serbia, ³Clinic of Infectious Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia, ⁴Clinic of Otorhinolaryngology, Clinical Center of Vojvodina, Novi Sad, Serbia

ABSTRACT

Progressive multifocal leukoencephalopathy (PML) is a rare, often fatal, opportunistic infection, associated with demyelinating process. PML is caused by John Cunningham (JC) polyomavirus, and predominantly affects patients with human immunodeficiency virus (HIV) infection or other immunocompromised patients. The purpose of this study was to determine the role of magnetic resonance spectroscopy (MRS) in establishing the diagnosis of PML. MRS with long and short echo time was performed in two patients with PML associated with HIV infection and in one PML patient associated with chronic lymphocytic leukemia. The most prominent peak on the obtained spectra was for lactate; it showed 2-3 times higher concentration of lactate compared to choline, almost 4-6 times higher lactate concentration compared to creatine, and 4-11 times higher lactate in comparison to N-acetylaspartate concentration. Similar spectrum pattern was observed in all patients. To the best of our knowledge, this is a new finding that might be useful in early diagnosis of PML. Nevertheless, further confirmation of our results is needed, since we analyzed the spectrum pattern only in three patients. Overall, our results could help in early detection of PML, especially in non-HIV patients, and thus prevent the fatal outcome of the disease. MRS could also be useful in detecting "tumefactive" demyelinating lesions in PML patients, associated with immune reconstitution inflammatory syndrome, to avoid misdiagnosis of neoplasm.

KEY WORDS: Progressive multifocal leukoencephalopathy; PML; magnetic resonance spectroscopy; MRS; lactic acid; JC virus; HIV

DOI: <http://dx.doi.org/10.17305/bjbms.2017.2092>

Bosn J Basic Med Sci. 2017;17(4):349-354. © 2017 ABMSFBIH

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a rare, often fatal, opportunistic infection, associated with demyelinating process. PML is caused by John Cunningham (JC) polyomavirus, and predominantly affects patients with human immunodeficiency virus (HIV) infection or immunocompromised patients with impaired cell-mediated immunity, such as transplant recipients, patients on monoclonal antibody therapy, or patients with various oncologic and hematologic disorders. These patients usually present with advanced immunosuppression at the time of diagnostic evaluation,

and are commonly late for the treatment to be effective [1]. PML is associated with high morbidity and mortality. The classical neuroimaging pattern shows the presence of diffuse, often multifocal white matter lesion, involving subcortical U-fibers, typically without associated contrast enhancement, mass effect, and vasogenic edema [2,3]. The histopathological examination reveals the presence of demyelination, macrophage infiltration, bizarre astrocytes, and enlarged oligodendrocyte nuclei [4,5]. Although the definite diagnosis of this disease is obtained by brain biopsy, non-invasive biomarkers of PML are helpful to eliminate the need for the aforementioned invasive procedure, especially considering the fact that brain biopsy is non-diagnostic in 4-36% of patients with HIV infection [6,7]. The Neuroinfectious Disease Section of the American Association of Neurology, has recently established the criteria for the diagnosis of PML. According to these criteria, the definitive diagnosis of PML requires the presence of

*Corresponding author: Mladen Bjelan, Diagnostic Imaging Center, Oncology Institute of Vojvodina, Put Dr. Goldmana 4, 21204 Sremska Kamenica, Novi Sad, Serbia. Phone: +381 21 4805604; Fax: +381 21 4805602. E-mail: mladen.bjelan@gmail.com

Submitted: 05 April 2017/Accepted: 10 May 2017

demyelination confirmed by histology, bizarre astrocytes, and enlarged oligodendrocyte nuclei, coupled with the techniques for JC virus detection. However, the evidence of clinical and imaging manifestations consistent with the diagnosis, combined with the presence of JC virus confirmed by polymerase chain reaction (PCR) of cerebrospinal fluid (CSF), and not explained by other disorders, is also considered diagnostic according to these new criteria [8]. The purpose of our study was to determine the role of magnetic resonance spectroscopy (MRS) in establishing the diagnosis of PML, since the early diagnosis could be crucial in preventing the fatal outcome. For instance, Pavlovic *et al.* [9] reported the regression of PML in a patient with lupus after early diagnosis and prompt discontinuation of immunosuppressive medications [9].

MATERIALS AND METHODS

MRS was performed in two HIV-positive patients and one patient with chronic lymphocytic leukemia, who had extensive brain lesions, involving the white matter on conventional magnetic resonance imaging (MRI) examination. Clinical course and PCR of CSF were consistent with the diagnosis of PML. MR spectra were recorded on a 3T MRI scanner (Siemens Magnetom Trio, Erlangen, Germany), using single voxel MR spectroscopy with long and short echo time (TE), with ¹H point resolved spectroscopy [PRESS] (*svs_se_135*): Repetition time (TR) 2000 ms, TE 135 ms, voxel size 20×20×20 mm, 128 averages, flip angle (FA) 90°, and acquisition time 4:24 minutes, and STimulated Echo Acquisition Mode (STEAM)-20 (*svs_se_20*): TR: 2000 ms, TE: 20 ms, voxel size 20×20×20 mm, 176 averages, FA 90° and acquisition time 6:00 minutes. A voxel was placed inside the lesion. The peaks of N-acetylaspartate (NAA), choline (Cho), creatine (Cr), lactate (Lac), and lipids (Lip) were documented, and the ratios were expressed using creatine as reference.

RESULTS

Patient 1

A 36-year-old HIV+ male presented with fever, headache, and gradual left hemiparesis. Computed tomography (CT) of the thorax revealed the presence of pneumonia.

MRI revealed a large zone of low signal intensity on T1-weighted (T1W) images and high signal intensity on the T2W and fluid-attenuated inversion recovery (FLAIR) images, which included right parietal and frontal white matter, extending from the subcortical region to the right lateral ventricle, with involvement of the splenium of corpus callosum (Figure 1A-C). The lesion measured 6×5 cm in the axial plane. There was no contrast enhancement, gray matter involvement, or significant mass effect. MRS documented an increased Cho/Cr ratio

(1.77), decreased NAA (NAA/Cr was 0.51), and extremely high Lac (Lac/Cr was 3.69) and Lip peaks (Lip/Cr was 3.15), which dominated in the obtained spectra both on the sequence with long (Figure 1D) and short TE (Figure 1E). Highly active antiretroviral therapy was administered but shortly after halted due to side effects, which were consistent with immune reconstitution inflammatory syndrome [IRIS] (Figure 2A and B). The death occurred 3 months after the hospitalization.

Patient 2

A 40-year-old HIV+ male presented with 3-week-long fever, rash, vertigo, and right hemiplegia. MRI showed a large, low-signal-intensity lesion on the T1W image, predominantly located in the subcortical area, and a high-signal-intensity lesion on the T2W and FLAIR images, predominantly located in the subcortical areas of the left parietal and frontal lobes, with sharp demarcation toward gray matter (Figure 3A-C). The axial dimensions of the lesion were approximately 6×4.5 cm. MRS documented an increased Cho/Cr ratio (2.29), decreased NAA (NAA/Cr was 0.82), and a high Lac peak (Lac/Cr was 2.30), which dominated in the obtained spectra both on the sequence with long (Figure 3D) and short TE (Figure 3E). The death occurred 43 days after hospitalization.

Patient 3

A 77-year-old male with chronic lymphocytic leukemia, treated with chemotherapy and immunosuppressive medications (chlorambucil and pronison), presented with left hemiparesis, horizontal nystagmus, and left-sided tongue deviation. MRI revealed the presence of a large, subcortical lesion located in the right frontal and parietal lobes, T1W hypointense, T2W and FLAIR hyperintense, with a sharp border toward gray matter, measuring 10×3.5 cm in the axial plane (Figure 4A and B). MRS revealed an increased Cho/Cr ratio (1.84), decreased NAA (NAA/Cr ratio was 0.88), and an extremely high Lac peak (Lac/Cr ratio was up to 2.03), which dominated in the obtained spectra both on the sequence with long (Figure 4C) and short TE (Figure 4D). The death occurred 19 days after hospitalization.

DISCUSSION

The imaging characteristics of typical PML in patients who are HIV infected are well known [10]. An increasing number of patients on immunosuppressive therapy for autoimmune diseases are recognized in this context. Although the effective therapy has not been established yet, better management of patients may be achieved by withdrawal of immunosuppressive drugs and reconstitution of the immune system, with possible better long-term survival [11,12]. The early recognition is

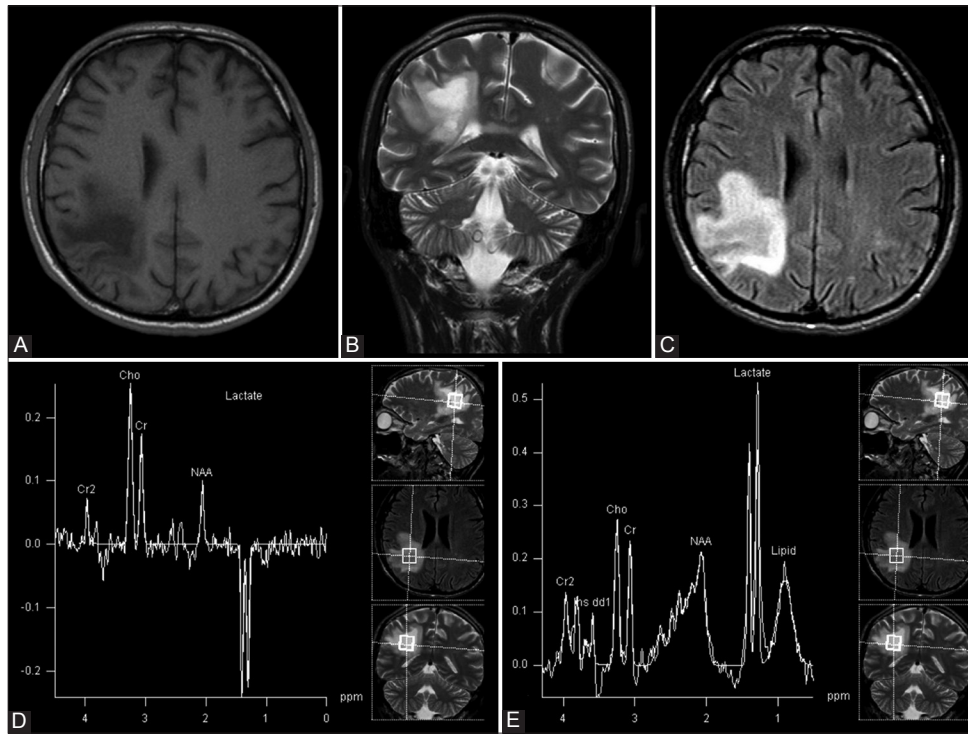


FIGURE 1. Magnetic resonance spectroscopy (MRS) signal characteristics of progressive multifocal leukoencephalopathy. (A) A large zone of low signal intensity on the axial T1-weighted (T1W) image and high signal intensity on (B) the coronal T2-weighted (T2W) and (C) axial fluid-attenuated inversion recovery images, in the right frontoparietal white matter. The involvement of the splenium of corpus callosum was also evident on the coronal T2W image. MRS with (D) long echo time [TE] and (E) short TE revealed increased choline, decreased N-acetylaspartate, and extremely high lactate and lipid peaks.

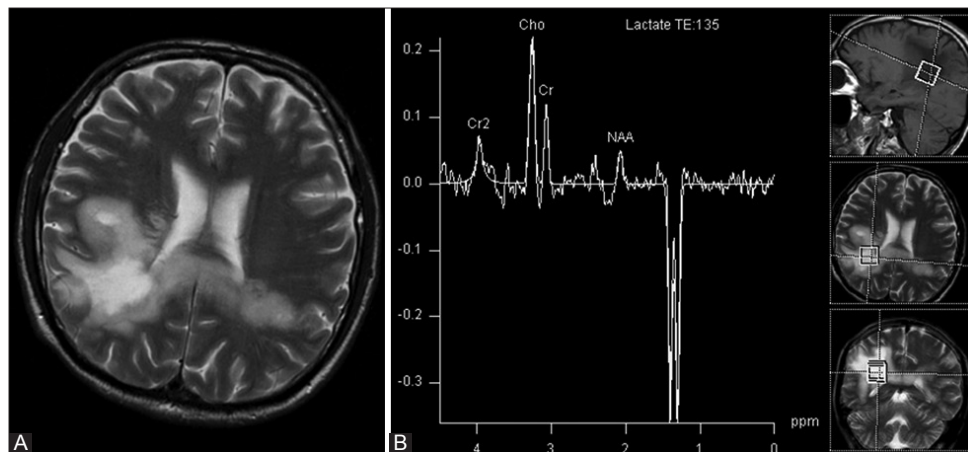


FIGURE 2. Rapid deterioration after treatment, associated with immune reconstitution inflammatory syndrome (IRIS), (A) mimicking the extension of high-grade glioma through the corpus callosum, on the axial T2-weighted (T2W) sequence. (B) An extremely high peak of lactate on magnetic resonance spectroscopy with long echo time (TE), that was more prominent compared to choline and N-acetylaspartate peaks, and consistent with non-neoplastic, tumefactive demyelinating lesions.

especially important in non-HIV patients where, combined with appropriate therapy, it could lead to better healing. A recent report showed that PML was the first manifestation in a patient with a clinically occult sarcoidosis [13]. PML has also been described in an immunocompetent patient, in whom the administration of serotonin receptor targeted therapy improved the outcome [14]. This emphasizes the need for prompt diagnosis and monitoring of the disease process. Patients with autoimmune disorders should be particularly monitored for the development of PML during immunosuppressive therapy.

Diffusion-weighted MRI (DW-MRI or DWI) can be used as an additional tool for monitoring the disease activity in patients with PML. Moreover, a report showed that DWI findings in PML patients are related to the disease stage [10]. Newer lesions and the advancing edges of large lesions showed normal-to-low apparent diffusion coefficient (ADC) values and a high signal on DWI, compared to older lesions and the centers of the large lesions that had increased ADCs and a low signal on DWI. These findings might also help to differentiate PML from mimicking diseases [10].

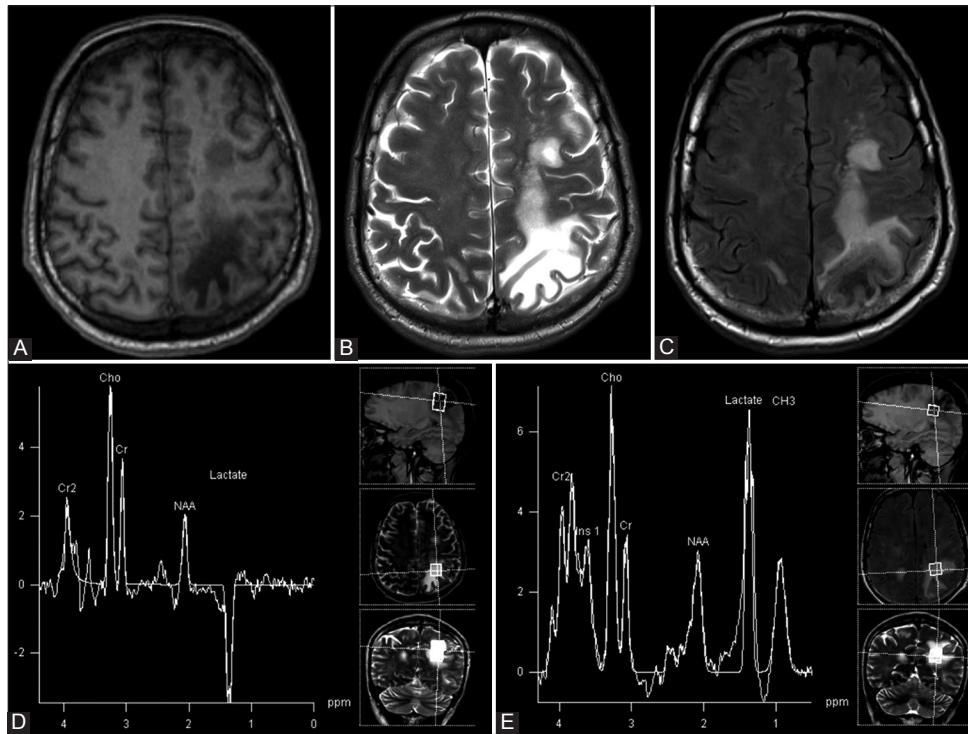


FIGURE 3. (A) Axial T1-weighted [T1W], (B) T2W, and (C) fluid-attenuated inversion recovery (FLAIR) images showed a large T1W hypointense lesion, and a T2W and FLAIR hyperintense lesion in the left parietal and frontal lobes, consistent with progressive multifocal leukoencephalopathy. Magnetic resonance spectroscopy (MRS) with (D) long echo time [TE] and (E) short TE, showed an increased choline, decreased N-acetylaspartate, and extremely high lactate peak.

MRS is a non-invasive technique that evaluates the metabolic profile of the brain, by measuring the levels of several neurochemicals. The important peak, seen at 2.06 ppm in the proton spectrum of a healthy person, is related to NAA, a marker of neuronal integrity and function. A typical ^1H -MRS study of PML lesions shows a decrease of this metabolite. The increased Cho concentration, seen in patients with PML, highlights the presence of demyelination and increased cell membrane turnover. The elevated Lac peak observed in this disorder indicates increased macrophage activation after cell membrane breakdown, with consequent neuronal mitochondrial dysfunction and activation of anaerobic glycolysis. Since the level of Cr does not significantly change in the disease state, it is used as an internal standard. The myo-inositol (mI), a marker of glial inflammation, increases early in PML, but a decrease is seen in the later stages [15,16]. Several authors explained the typical MRS pattern of PML, which is associated with the increased Cho/Cr ratio, reduced NAA/Cr ratio, as well as the presence of Lac, Lip and mI peaks [10,17]. It was found that the acute lesions of PML survivors had a markedly increased mI to Cr ratio, compared to the lesions in patients whose disease progressed, suggesting that the inflammation limits the disease progression [18].

However, a number of other brain diseases, neoplastic as well as inflammatory, are characterized by the same neurometabolic MRS pattern [17,19]. In addition, spectra with only Lac and/or Lip peaks have been evident in posttraumatic

or neoplastic cavities [4,19]. Gheuens et al. [17] detected major differences in the metabolic profile of the brain lesions of PML patients with IRIS compared with the patients without IRIS. However, in their study, the Lac peak was not separated from the Lip peak due to the overlapping of these metabolites in the sequence with short TE, used for evaluation [17]. IRIS is defined as paradoxical worsening of a patient's clinical condition associated with a recovery of the immune system after the initiation of combined antiretroviral therapy. The radiological finding may mimic high-grade glioma on conventional MRI, as shown in our patient (Figure 2A). However, MRS findings showing the presence of all metabolites, with Lac being the most prominent metabolite (Figure 2B), is not characteristic for glioblastoma or anaplastic astrocytoma. To the best of our knowledge, no other disorder has been documented in the literature, in which Lac is observed as the dominant metabolite (with higher concentration compared to Cho), in the spectra in which all metabolites are present. This finding was especially prominent in our study using 135 ms echo time in ^1H PRESS sequence, offering better signal-to-noise ratio and unequivocal assignment of the Lac peak, due to its characteristic phase modulation. The increased Lac peak in patients with PML appears to be associated with the infiltration of macrophages and not caused by cellular hypoxia, since the "recovery" of Lac peak was revealed in the report of Pavlovic et al. [9], after the discontinuation of immunosuppressive medications in a patient with PML [9]. Cuvinciuc et al. [20] reported serial

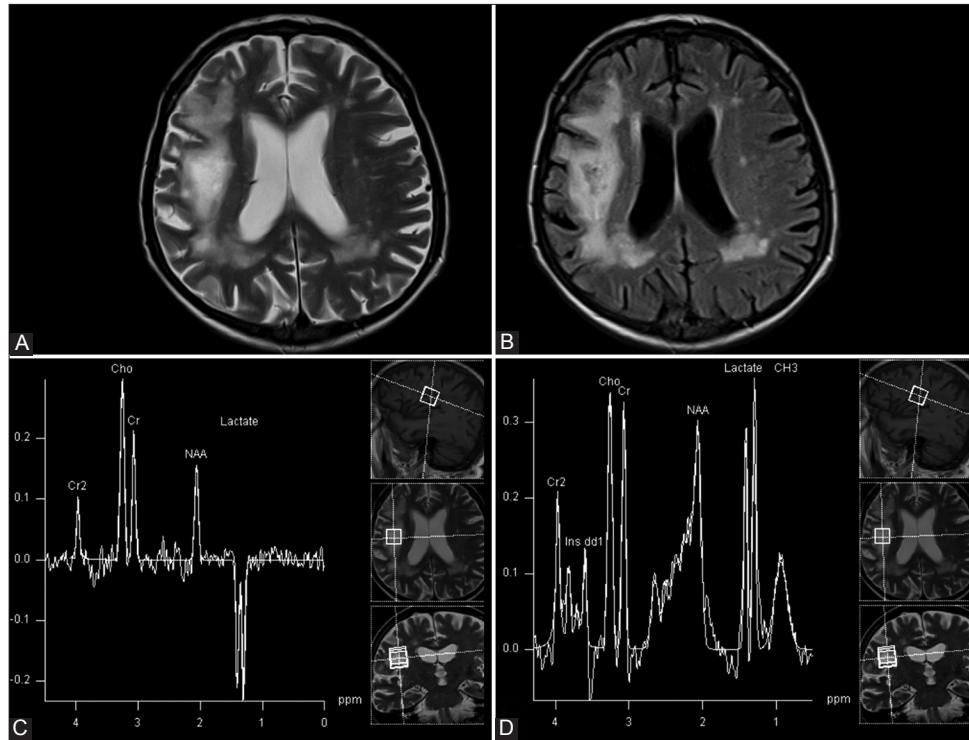


FIGURE 4. A subcortical lesion in the right frontal and parietal lobe, hypointense on T1-weighted (T1W) image (not shown), hyperintense on (A) T2W and (B) fluid-attenuated inversion recovery (FLAIR) images, with a sharp border toward gray matter, typical for progressive multifocal leukoencephalopathy. Magnetic resonance spectroscopy (MRS), with (C) long echo time [TE] and (D) short TE showed an increased choline, decreased N-acetylaspartate, and extremely high lactate peak.

short TE ¹H-MRS in a patient with PML-IRIS, where it was obvious that the Lac-Lip peak increased with time [20]. This may suggest that a Lac peak does not have to be increased at the onset of the disease. Future studies, with a larger cohort of PML patients, should confirm these observations and their diagnostic and prognostic value.

DECLARATION OF INTERESTS

The authors declare no conflict of interests.

REFERENCES

- [1] Sharma SK, Soneja M, Ranjan S, Miglani S, Hari S, Sinha S, et al. Progressive multifocal leukoencephalopathy in HIV/AIDS: Observational study from a tertiary care centre in northern India. *Indian J Med Res* 2013;138(1):72-7.
- [2] Hurley RA, Ernst T, Khalili K, Del Valle L, Simone IL, Taber KH. Identification of HIV-associated progressive multifocal leukoencephalopathy: Magnetic resonance imaging and spectroscopy. *J Neuropsychiatry Clin Neurosci* 2003;15(1):1-6. <https://doi.org/10.1176/jnp.15.1.1>.
- [3] Kastrup O, Maschke M, Diener HC, Wanke I. Progressive multifocal leukoencephalopathy limited to the brain stem. *Neuroradiology* 2002;44(3):227-9. <https://doi.org/10.1007/s00234-001-0714-6>.
- [4] Kozic D, Ostojic J, Bjelan M, Koprivsek K. The role of MR spectroscopy in neurooncology. *Prilozi* 2012;33(1):425-33.
- [5] Sweet TM, Del Valle L, Khalili K. Molecular biology and immunoregulation of human neurotropic JC virus in CNS. *J Cell Physiol* 2002;191(3):249-56. <https://doi.org/10.1002/jcp.10096>.
- [6] Holloway RG, Mushlin AI. Intracranial mass lesions in acquired immunodeficiency syndrome: Using decision analysis to determine the effectiveness of stereotactic brain biopsy. *Neurology* 1996;46(4):1010-5. <https://doi.org/10.1212/WNL.46.4.1010>.
- [7] Iranzo A, Moreno A, Pujol J, Marti-Fabregas J, Domingo P, Molet J, et al. Proton magnetic resonance spectroscopy pattern of progressive multifocal leukoencephalopathy in AIDS. *J Neurol Neurosurg Psychiatry* 1999;66(4):520-3. <https://doi.org/10.1136/jnnp.66.4.520>.
- [8] Berger JR, Aksamit AJ, Clifford DB, Davis L, Koranik IJ, Sejvar JJ, et al. PML diagnostic criteria: Consensus statement from the AAN Neuroinfectious Disease Section. *Neurology* 2013;80(15):1430-8. <https://doi.org/10.1212/WNL.0b013e31828c2fa1>.
- [9] Pavlovic AM, Bonaci-Nikolic B, Kozic D, Ostojic J, Abinun M, Svabic-Medjedovic T, et al. Progressive multifocal leukoencephalopathy associated with mycophenolate mofetil treatment in a woman with lupus and CD4⁺ T-lymphocyte deficiency. *Lupus* 2012;21(1):100-2. <https://doi.org/10.1177/0961203311416693>.
- [10] Yoon JH, Bang OY, Kim HS. Progressive multifocal leukoencephalopathy in AIDS: Proton MR spectroscopy patterns of asynchronous lesions confirmed by serial diffusion-weighted imaging and apparent diffusion coefficient mapping. *J Clin Neurol* 2007;3(4):200-3. <https://doi.org/10.3988/jcn.2007.3.4.200>.
- [11] Aksamit AJ Jr. Progressive multifocal leukoencephalopathy. *Continuum (Minneapolis)* 2012;18(6 Infectious Disease):1374-91. <https://doi.org/10.1212/01.CON.0000423852.70641.de>.
- [12] Dahlhaus S, Hoepner R, Chan A, Kleiter I, Adams O, Lukas C, et al. Disease course and outcome of 15 monocentrically treated natalizumab-associated progressive multifocal leukoencephalopathy patients. *J Neurol Neurosurg Psychiatry* 2013;84(10):1068-74. <https://doi.org/10.1136/jnnp-2013-304897>.
- [13] Davis MJ, Khan A, Royal W 3rd. Progressive multifocal leukoencephalopathy as the first manifestation of occult sarcoidosis: Case report and review of the literature. *Neurologist* 2013;19(1):26-9.

- <https://doi.org/10.1097/NRL.0b013e31827c6c3d>.
- [14] Christakis PG, Okin D, Huttner AJ, Baehring JM. Progressive multifocal leukoencephalopathy in an immunocompetent patient. *J Neurol Sci* 2013;326(1-2):107-10. <https://doi.org/10.1016/j.jns.2013.01.010>.
- [15] Sahraian MA, Radue EW, Eshaghi A, Besliu S, Minagar A. Progressive multifocal leukoencephalopathy: A review of the neuroimaging features and differential diagnosis. *Eur J Neurol* 2012;19(8):1060-9. <https://doi.org/10.1111/j.1468-1331.2011.03597.x>.
- [16] Shah R, Bag AK, Chapman PR, Curé JK. Imaging manifestations of progressive multifocal leukoencephalopathy. *Clin Radiol* 2010;65(6):431-9. <https://doi.org/10.1016/j.crad.2010.03.001>.
- [17] Gheuens S, Ngo L, Wang X, Alsop DC, Lenkinski RE, Koralnik IJ. Metabolic profile of PML lesions in patients with and without IRIS: An observational study. *Neurology* 2012;79(10):1041-8. <https://doi.org/10.1212/WNL.0b013e318268465b>.
- [18] Katz-Brull R, Lenkinski RE, Du Pasquier RA, Koralnik IJ. Elevation of myoinositol is associated with disease containment in progressive multifocal leukoencephalopathy. *Neurology* 2004;63(5):897-900. <https://doi.org/10.1212/01.WNL.0000137420.58346.9F>.
- [19] Kozic D, Nagulic M, Samardzic M, Ostojic J, Rasulic L, Cvetkovic-Dozic D. Intrapontine malignant nerve sheath tumor: MRI and MRS features. *Acta Neurol Belg* 2008;108(2):67-71.
- [20] Cuvinciu V, Martin-Blondel G, Marchou B, Bonneville F. Proton MR spectroscopy of progressive multifocal leukoencephalopathy-immune reconstitution inflammatory syndrome. *AJNR Am J Neuroradiol* 2010;31(8):E69-70. <https://doi.org/10.3174/ajnr.A2160>.