Correspondence

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A very rare cause of leukoencephalopathy: Lymphomatosis cerebri

Maurizio Giorelli[1,*], Sergio Altomare[1], Maria Stella Aniello[1], Maria Carmela Bruno[2], Ruggiero Leone[1], Daniele Liuzzi[1], Giuseppe Ingravallo[3], Pasquale Di Fazio[4], Tommaso Scarabino[5], Giuseppe Tarantini[6]

[1] Operative Unit of Neurology, "Dimiccoli" General Hospital, Barletta, ASL BT, Italy;
[2] Operative Unit of Neurosurgery, "Bonomo" General Hospital, Andria, ASL BT, Italy;
[3] Institute of Pathologic Anatomy, Faculty of Medicine, University of Bari, Italy;
[4] Operative Unit of Radiology, "Bonomo" General Hospital, Andria, ASL BT, Italy;
[5] Operative Unit of Nuclear Medicine, "Dimiccoli" General Hospital, Barletta, ASL BT, Italy;
[6] Operative Unit of Ematology, "Dimiccoli" General Hospital, Barletta, ASL BT, Italy.

SUMMARY Leukoencephalopathy is a common finding on Magnetic Resonance Imaging (MRI), particularly in the elderly. A differential diagnosis may represent a very bet for clinicians when clear elements for diagnosis are lacking. Diffuse infiltrative "non mass like" leukoencephalopathy on MRI may represent the presentation of a very rare aggressive condition known as lymphomatosis cerebri (LC). The lack of orienting data, such as contrast enhancement on MRI or specific findings on examination of Cerebrospinal Fluid (CSF) or blood tests, may even far more complicate such a difficult diagnosis and orientate toward a less aggressive but time-losing mimic. A 69-old man initially presented to the Emergency Department (ED) complaining the recent appearance of unsteady walking, limitation of down and upgaze palsy, and hypophonia. Brain MRI revealed the presence of multiple, confluent hyperintense lesions on T2/Flair Attenuated Imaging Recovery (FLAIR) sequences involving either the withe matter of the semi-oval centres, juxtacortical structures, basal ganglia, or bilateral dentate nuclei. DWI sequences showed a wide restriction signal in the same brain regions but without any sign of contrast enhancement. Initial 18F-labeled fluoro-2-deoxyglucose positron emission tomography (FDG PET) and CSF studies were not relevant. Brain MRI revealed a high choline-signal, abnormal Choline/N-Acetyl-Aspartate (NAA), and Choline/Creatine (Cr) ratios, as well as reduced NAA levels. Finally, a brain biopsy revealed the presence of diffuse large B-cell lymphomatosis cerebri. The diagnosis of lymphomatosis cerebri remains elusive. The valorisation of brain imaging may induce clinicians to suspect such a difficult diagnosis and go through the diagnostic algorithm.

Keywords lymphomatosis cerebri, MRI, Primary Central Nervous System lymphoma (PNCSL), leukoencephalopathy, ^{1}H-MRS

Leukoencephalopathy may present a diagnostic challenge, even in the elderly. A long list of different diseases such as vascular diseases, immune-mediated disorders, infections, neurodegenerative, dysmetabolic patterns, and myelin-dystrophic diseases may underlie such a condition. Although rare, lymphomatosis cerebri (LC) may be indistinguishable from other less aggressive and more frequent conditions responsible for diffuse leukoencephalopathy at an initial brain MRI assessment (*1*). Clinical presentation might not help in the orientation of the diagnostic work-up, as initial symptoms may include subacute cognitive impairment, focal motor deficits, movement disorders, and incoordination. The MRI features of LC are described as diffuse, infiltrative T2W, or FLAIR hyperintense lesions, but they lack contrast enhancement on T1 sequences (*2,3*). Lesions may involve any structure belonging to either the white or grey matter of the Central Nervous System, including the eye. These findings are very different from those of Primary Nervous System Lymphoma (PNCSL) (*4*), which is typically characterized by nodular lesions emerging either on T2W imaging or enriched by contrast enhancement on T1W sequences, especially of brain structures lying on the median line.

On June 1, 2022, a patient in the 60s presented to the ED complaining of unsteady walking, frequent falls, downgaze, and up gaze palsy, and hypophonia. Symptoms had started and slowly progressed in the previous two months. The patient was referred to

the neurological ward. Extensive blood examination included routine and rheumatologic tests, neoplastic markers, and an autoimmune panel. All results were un-relevant. Computed tomography (CT) scans of the chest and abdomen were obtained, and pathological findings were disclosed. Brain MRI showed diffuse infiltrative encephalopathy involving either the cerebral deep and juxtacortical white matter, basal ganglia, dentate nuclei, or cerebellar medulla (Figure 1, a-c). Notably, DWI and ADC sequences demonstrated wide restriction signals in the same areas (Figure 1, d and e). CSF studies demonstrated only a slight increase in protein concentration (2 cells/μL), normal glucose, lactate, and absent bilirubin. HIV, VDRL, and TPHA tests were negative. IgM and IgG titers in Borrelia Burgdoferi were normal. Polymerase Chain Reactions failed to detect the presence of DNA from all herpes viruses, coxachies, enterovirus, and JC virus. Antibodies to both surface and intracellular neuronal antigens were detected in the patient's serum and CSF and were found to be undetectable. Tests included anti-Hu, anti-Ri, anti-Yo, anti-CV2/CRMP5, anti-MA2, anti-amphiphysin, anti-GAD 65, anti-MA 1, anti-SOX 1, anti-TR (Dner), anti-Zic4, anti-LGI1, anti-CASPR2, anti-AMPA1, anti-AMPA2, anti-NMDA, anti-DPPX, and anti-IgLON5. Initial FGD-PET was not relevant for pathologic accumulation of radiotracer within the brain (data not shown). ^{1}H-MRS revealed increased Cho/Naa and Cho/cr ratios with reduced NAA absolute peak levels (Figure 1, f). We suspected a brain tumor and performed a brain biopsy. Meanwhile, awaiting results from microscopic studies on brain tissue, distressed by diagnostic uncertainty, we offered a trial of steroids at a therapeutic dosage to the patient in order to fight against his rapid clinical deterioration. Despite initial clinical improvement, the patient's condition worsened after a few days, prompting us to stop the steroid course definitively. Immunohistochemical analysis of the brain specimens demonstrated diffuse infiltration of lymphocytes, which were positively marked for CD3, CD20, and KI67 (Figure 2, a-e). A new brain MRI performed 30 days after the former imaging showed a T1

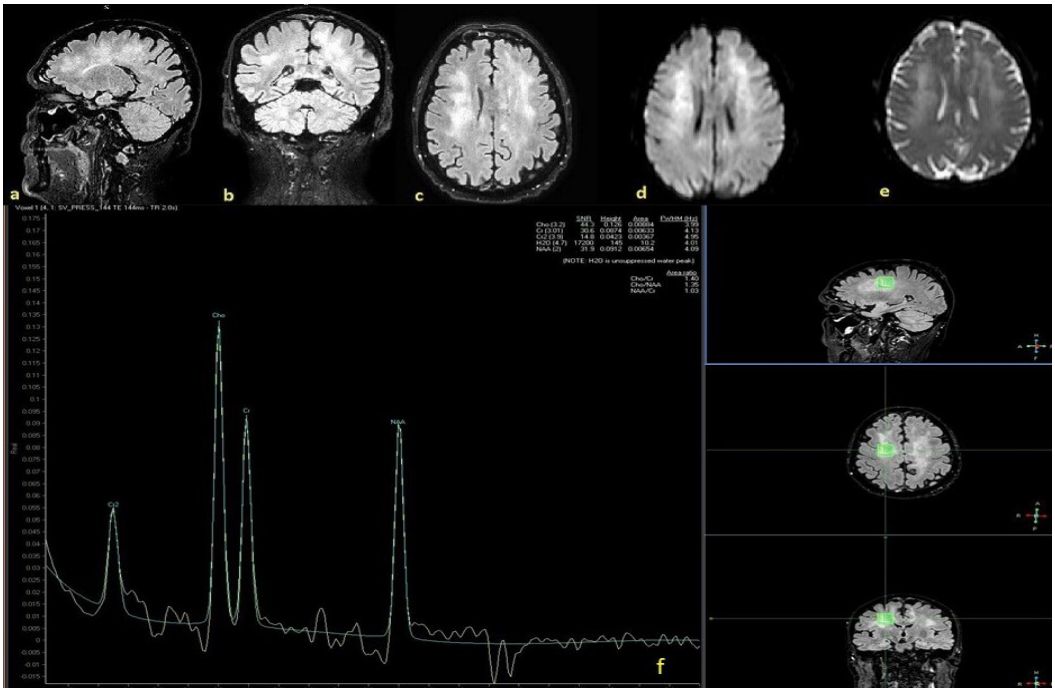

Figure 1. Imaging of Lymphomatosis cerebri. Sagittal **(a)**, coronal **(b)**, and axial **(c)** FLAIR images of the brain showing diffuse high signal intensity involving deep and juxtacortical white matter, basal ganglia, dentate nuclei and cerebellar medulla. DWI **(d)** and ADC **(e)** images showing reduced water diffusivity in the same affected regions, thus suggesting high cellularity. ^{1}H-MRS disclosing high Cho/NAA and Cho/Cr ratio indicating enhanced cell membrane turnover and reduced neuronal viability **(f)**.

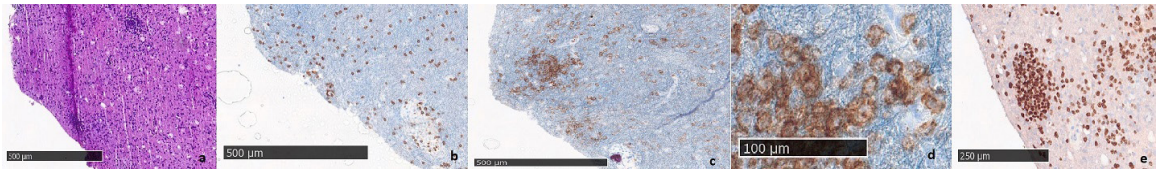

Figure 2. Microscopical Features of Lympomathosis cerebri. Hematoxylin-eosin staining of brain specimens showed diffuse infiltration of lymphocytes in the perivascular and in tissue brain **(a)**. Immunohistochemistry showed infiltration of CD3+ reactive lymphocytes **(b)**, CD20+ large lymphomatous cells **(c,d)**, all characterized by increased expression of KI67 receptor, a marker of cellular proliferation **(e)**.

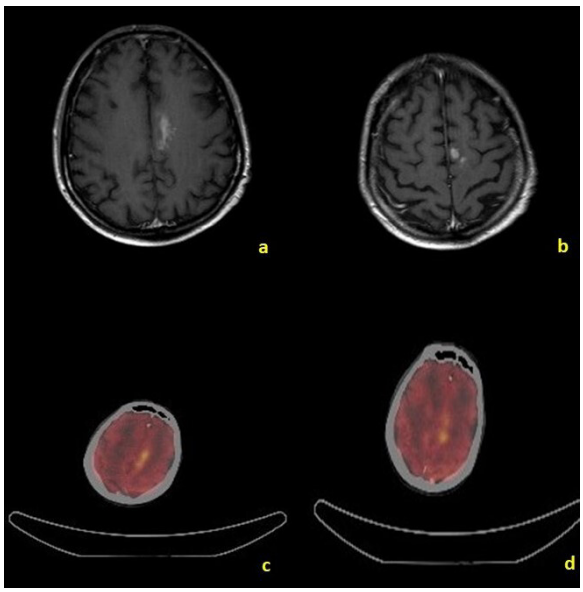

Figure 3. Imaging of Primary Central Nervous System Lymphoma as evolution of Lymphomatosis cerebri. T1-wheighed contrast enhanced sequences showed nodular lesions characterized by intense contrast enhancement in the cortex and subcortex of frontal left hemisphere **(a,b)**. FDG-PET showed focal glucose hypermetabolism of the frontal lesions **(c,d).**

contrast-enhanced subcortical nodular lesion within the left hemisphere (Figure 3, a and b), which also showed pathologic accumulation on brain FDG PET (Figure 3, c and d). Finally, a diagnosis of primary large B-cell brain lymphoma was made, and the patient underwent treatment according to international protocols including Metotrexate (MTX) and Cytosine Arabinoside (ARA-c). The patient died in March 2023, six months after having received diagnosis and having started specific therapeutics.

Lymphomatosis cerebri (LC) is a rare and aggressive variant of Primary Central Nervous System lymphoma (PNCSL) and may be undistinguishable from other less aggressive and more frequent conditions responsible for diffuse leukoencephalopathy at an initial brain MRI assessment (*1-3*). In contrast to the classic form of cerebral lymphoma, LC is characterized by diffuse infiltration of brain structures, predominantly of the withe matter, without forming a cohesive mass of malignant lymphoid cells (*1,2*). Sugie *et al*. (*4*) demonstrated that PNCSL may initially present as diffuse leukoencephalopathy without any T1W contrast-enhancing nodular lesions on brain MRI, thus resembling the imaging features of LC. As a result, the brain imaging of LC may give rise to dangerous misdiagnosis, as it is not specific of any disease (*1*).

Diagnosis in our patient was extremely challenging due to the lack of pathological findings, including normal initial brain FDG PET and CSF studies, the last showing only a mild increase in protein concentration with a slight increase in the albumin ratio.

Given that Apparent Diffusion Coefficient (ADC) maps are particularly low in cerebral lymphoma (*2*) and positively correlate with the expression KI 67 (*5*), we emphasized Diffusion Weighted Imaging (DWI) and ADC imaging from the initial brain MRI of our patient and, suspecting a brain tumour, decided him undergo MRI spectroscopy.

^{1}H-MRS was critical to our diagnostic workup due to the finding of abnormal Cho/NAA and Cho/Cr ratios as well as reduced NAA levels, strongly suggesting a proliferative disease involving the brain (*6*). These results prompted us to perform a diagnostic brain biopsy and immunohistochemical study. Initial results from brain specimens were interlocutory, and we administer high-dose steroids to stop the rapid worsening of the patient's clinical condition. Such behaviour, although frequent, should be avoided when suspecting a brain LC unless necessary as a lifesaving therapy. Steroids may delay diagnosis and selection of resistant clones (*1*). Accurate microscopic analysis of specimens and immunohistochemical studies later revealed the presence of LC and allowed the application of internationally accepted therapeutic protocols.

Notably, in contrast to the initial imaging, a brain MRI performed one month after hospital admission showed the appearance of a T1-contrast-enhanced nodular lesion, which was also characterized by increased glucose metabolism on brain FDG PET. Similar behaviour of LC has already been reported (*4*). It is tempting to suggest that LC might be an early step of CNS invasion by malignant lymphomatous cells, which later aggregate to form nodular lesions of classic PNCSL. This might depend on the differential and time-dependent expression of adhesion molecules such as CD31 (PECAM), whose expression was not detected by immunohistochemical study of brain biopsy in our patient. Similarly, the Lack of CD29 and CD54 adhesion molecules has been described in intravascular lymphomatosis (*7*).

The relevance of data from diffusion MRI and MR spectroscopy has already been suggested for diagnosing lymphomatosis cerebri, especially when basic MRI sequences are un-informative (*4,6*). Our case report adds significance to both imaging studies in the diagnostic workup of LC, before lymphomatous cells aggregate in the solid masses typical of PNCSL.

Suspecting lymphomatosis cerebri based on a picture of aspecific leukoencephalopathy is a challenge for clinicians. Increased Cho/cr and Cho/NAA ratios, reduced NAA peak as revealed by brain ^{1}H-MRS, and abnormal signals in ADC sequences from brain MRI should prompt clinicians to perform biopsy in undetermined leukoencephalopathy, even in the elderly.

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References

1. Patra A, Jasper A, Vanjare H, Chacko G, Susheel S, Sivadasan A, Hephzibah J, Mannam P. Diffuse Infiltrative Non-mass-like Brain Parenchymal Lesions on MRI: Differentiating Lymphomatosis Cerebri from its Mimics. J Clin Imaging Sci. 2021; 11:41.
2. Ruan Z, Chu L, Liu C, Hu Y, Huang J. Lymphomatosis cerebri: Multimodality imaging features and misdiagnosis analysis. Oncol Lett. 2021; 22:701.
3. Yu H, Gao B, Liu J, Yu YC, Shiroishi MS, Huang MM, Yang WX, Guan ZZ. Lymphomatosis cerebri: a rare variant of primary central nervous system lymphoma and MR imaging features. Cancer Imaging. 2017; 17:26.
4. Sugie M, Ishihara K, Kato H, Nakano I, Kawamura M. Primary central nervous system lymphoma initially mimicking lymphomatosis cerebri: An autopsy case report. Neuropathology. 2009; 29:704-707.
5. Surov A, Meyer HJ, Wienke A. Associations between apparent diffusion coefficient (ADC) and KI 67 in different tumors: a meta-analysis. Part 1: ADC_{mean}. Oncotarget. 2017; 8:75434-75444.
6. Hourani R, Brant LJ, Rizk T, Weingart JD, Barker PB, Horská A. Can proton MR spectroscopic and perfusion imaging differentiate between neoplastic and nonneoplastic brain lesions in adults? AJNR Am J Neuroradiol. 2008; 29:366-372.
7. Ponzoni M, Arrigoni G, Gould VE, Del Curto B, Maggioni M, Scapinello A, Paolino S, Cassisa A, Patriarca C. Lack of CD 29 (beta1 integrin) and CD 54 (ICAM-1) adhesion molecules in intravascular lymphomatosis. Hum Pathol. 2000; 31:220-226.

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**Address correspondence to:*
Maurizio Giorelli, Operative Unit of Neurology, "Dimiccoli" General Hospital, Viale Ippocrate 11, Barletta 76121, Italy.
E-mail: maurizio.giorelli@aslbat.it

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