ATYPICAL PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA OR CRYPTOGENIC LEUKOENCEPHALOPATHY. CASE REPORT

CĂTĂLIN COSMIN MUTU[1], VLAD-IOAN SUCIU[2]

[1]"Lucian Blaga" University of Sibiu, [1] [2]Clinical County Emergency Hospital Sibiu

Keywords: *central nervous system lymphoma, leukoencephalopathy*

Abstract: *We present a 67-year-old male patient with gait difficulties, disinhibited behaviour and bipyramidal syndrome with left hemiataxia. In 2012, cerebral metastases were suspected and whole brain radiation therapy was made with favourable evolution. No primary tumour or paraneoplastic/autoimmune encephalitis pathology could be demonstrated in spite of extensive tests (Magnetic Resonance Imaging - MRI studies, whole body Positron emission tomography/Computed tomography - PET/CT, serum and cerebrospinal fluid (CSF) biochemical and immunological tests including brain biopsy) during 3 years' time. In 2015, the patient status aggravated, presenting severe tetraparesis, left medullary syndrome and persistent altered consciousness. The patient received methotrexate (MTX) therapy but the outcome was unfavourable 3 months later. Conclusions: The cause of the Leukoencephalopathy remained uncertain although many tests were done. An atypical primary central nervous system lymphoma (PCNSL) or an autoimmune encephalitis could be taken into account.*

INTRODUCTION

The leukoencephalopathies are a group of diseases of great diversity which have as a common trait, lesions of the white cerebral matter. The causes may be inflammatory, vascular, toxic, hypertensive, metabolic, traumatic, hereditary or cryptogenic. When the etiology is not a common cause, extensive and repeated tests should be done. Primary central nervous system lymphoma and paraneoplastic or autoimmune encephalitis are the most difficult diseases to diagnose.(1,2)

CASE REPORT

We will present the case of a 67-year old male patient, non-smoker, known with type II diabetes mellitus and diabetic polyneuropathy, who, in 2012, presented with gait difficulties, disinhibited behaviour and bipyramidal syndrome with left hemiataxia. Then, the brain MRI showed supratentorial and pontine lesions suggestive for metastases (figure no. 1 and 2). Afterwards, he was treated with steroids and standard whole brain radiation therapy.

Figure no. 1. Native Cerebral MRI scan showing the supposed metastases (sagittal plane)

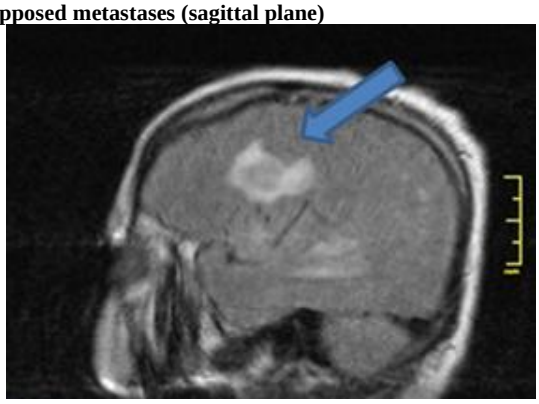
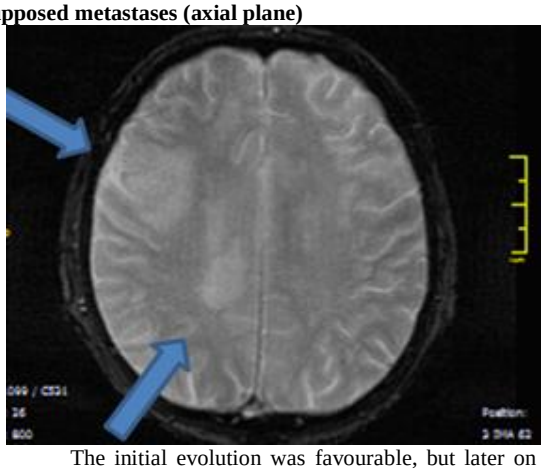


Figure no. 2. Native Cerebral MRI scan showing the supposed metastases (axial plane)



The initial evolution was favourable, but later on he had a progressive mental status decline and suggestive signs for post-irradiation cerebral lesions. Then, the patient was tested extensively in different European medical institutions for tumour or immune pathology.

The positive diagnosis and the cause of lesions has remained unknown, in spite of the following procedures: repeated cerebral MRI studies, PET/CT (cerebral, thorax, abdomen), upper gastrointestinal (GI) tract endoscopy, abdominal echography, biochemical and immunological tests (both serum and CSF) searching for HIV, Syphilis, Toxoplasma, Borrelia infections, oligoclonal bands and antiphospholipid antibodies. The tests for amphiphysin, CV2, PNMA2, Ri, Yo, Hu, recoverin, SOX1, titin antibodies were negative. A brain biopsy (interpreted in 3 different centers) was made in 2015.

In 2013 a whole body PET-CT showed fluoro-deoxy-glucose (FDG) taken up intensely in the genu of the corpus callosum, basal nuclei and pulmonary hilum bilaterally.

[1]Corresponding author: Cătălin Cosmin Mutu, Str. Pompeiu Onofreiu, Nr. 2-4, Sibiu, România, E-mail: cosminmutu@yahoo.com, Phone: +40742 931011

Article received on 16.11.2016 and accepted for publication on 05.12.2016
ACTA MEDICA TRANSILVANICA December 2016;21(4):19-21

In July 2015, his symptoms aggravated rapidly and he had asymmetrical tetraparesis, more pronounced on the left side, altered consciousness, left medullary syndrome with difficulty in swallowing liquids and urinary incontinence. Cerebral imaging studies revealed diffuse periventricular lesions, relatively similar with earlier findings, consistent with delayed irradiation leukoencephalopathy (figure no 3) and a contrast enhancing lesion in the genu of the corpus callosum (figure no. 4) and a pontine focal cerebral lesion. MRI spectroscopy of the lesion in the corpus callosum was non-specific for tumour.

Figure no. 3. Cerebral CT scan showing diffuse fronto-parietal hypodensities

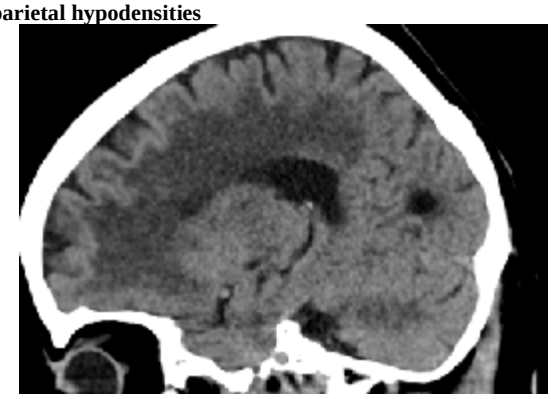
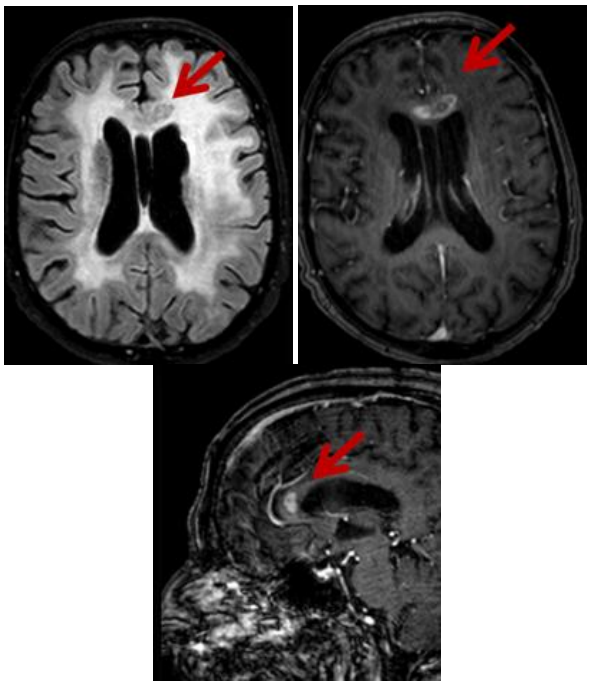


Figure no. 4. Cerebral contrast-enhanced MRI scan in different planes showing periventricular and callosal contrast enhancing lesions



In august 2015, the patient is admitted in our clinic with altered general status, hemodynamically unstable, blood pressure (BP) 90/50 mmHg, heart rate (HR) 60 bpm, with a neurological status similar to July 2015. Our team suspected then a primary CNS Lymphoma associated with post-irradiation Leukoencephalopathy. During this admission many tests were done in this order:

A brain biopsy was scheduled for histopathological examination. The fragments were analysed in 3 different institutions in Romania. As a common conclusion of the histopathological exam: focal reactive hyperplasia, minimal edema, microscopic hemorrhagic regions, the glial cells contain nuclei with minimal shape variations. No clear evidence of malignity.

An osteo-medullary biopsy was ordered and showed 40% cellularity, light megacariocitary hyperplasia.

The blood panel showed the following parameters modified: decreased albumin (3g/dL); decreased IgG 5.84 g/L; (normal CRP 0.8). Normal IgG index 1.48 (Normal value<3).

The first CSF exam showed: high glucose levels 79 mg/dl; modified immunological panel: IgA 2mg/dl ↗ ; IgG 8.37mg/L↗ ; IgM 0.26 ↗ ; increased lactic acid 23mg/dl; increased number of Lymphocytes 71%; normal Monocytes 29%; increased albumin 1.31 g/L; normal cellularity 7/mm3; no oligoclonal bands; macroscopically normal impression.

The second CSF exam showed: increased albumin 0.9 g/L; normal glucose levels 70 mg/dl; 5 cells/mm3 with small atypical Lymphocytes-like cells with increased nuclei/cytoplasm ratio, irregular chromatin, and negative for CD 45, CD 8, CD 4, CD 11, CD 3, CD 56.

The anti-neural antibodies test for Amphiphysin, CV2, PNMA2, Ri, Yo, Hu, Recoverin, SOX1, Titin were negative.

Following these tests, we concluded that the neurological diagnoses could be: delayed irradiation leukoencephalopathy, supratentorial contrast enhancing nonspecific lesion (probably primary CNS lymphoma), tetraparesis with left side predominant deficit, frontal lobe syndrome and left medullary syndrome. He received methotrexate therapy. The patient's evolution was not favourable.

DISCUSSIONS

Despite the fact that the patient has been extensively tested, the type of these lesions is still unknown. We do not exclude an atypical type of primary cerebral lymphoma.

For the differential diagnosis we can include the following: metastasis (no primary lesion found by the PET-CT scan); acute disseminated encephalomyelitis (no characteristic MRI findings, no infections prior to 2012); multiple sclerosis (absent oligoclonal bands, normal IgG ratio); cerebral toxoplasmosis (toxoplasmosis does not take up FDG in the PET-CT scan); glioma (central necrosis absent, MRI spectroscopy excluded this lesion); brain abscess (no characteristic MRI finding; no inflammatory response-creatine reactive protein CRP negative); HIV infection, Borrelia, Syphilis (no inflammatory response, specific markers being negative); Posterior reversible Leukoencephalopathy (no occipital lesions, no hypertension); Paraneoplastic lesions (excluded by negative anti-neural panel); autoimmune lesions (no inflammatory response, no specific clinical context).(1,3)

The primary CNS lymphoma (PCNSL) is a form of non-Hodgkin B Lymphocytes Lymphoma which represents 1 % of all intracranial malignant tumours. The origin of the lesion may be in the CNS, eye or spinal cord. The prototype patient is a 65-year-old man with secondary immunosuppression.(1,3)

Clinically, nonspecific focal neurological signs, ocular signs and intracranial hypertension syndrome (ICHy) may appear (43% neuropsychiatric signs, 33% ICHy, 14% convulsions, 4 % ocular signs).(1)

Histologically, PCNSL lesions could be located in the cortex, subcortical white matter or basal nuclei, but frequently these are located deep within the brain, and performing a cerebral biopsy is not always feasible.(4)

The lesions are characterized by perivascular B Lymphocytes infiltrations (90%). Usually, there is a solitary

supratentorial tumour (75-85%). The tumour expresses CD 19, CD 20, CD 22 and CD 79a.(5)

CSF analysis shows increase levels of protein, decrease level of glucose, and increased number of B Lymphocytes.(3,6) Finding very high levels of CSF neopterin in patients with a suspected PCNSL might be helpful for the positive and differential diagnosis with other type of tumours.(7) The extension is contralateral through the corpus callosum, without perilesional edema, without mass effect and with contrast uptake, hypointense on T1 images and iso-to-hyperintense on T2 images.(8,9)

The specific treatment is with high doses of Methotrexate (MTX) when the diagnosis of PCNSL is confirmed. High doses of MTX determines a good and sustained response for 12-48 months even for the patients with brain tumors without histological confirmation but suspected for PCNSL based on clinical, morphological and imagistic criteria.(10)

Steroids shrink the lesion leading to a good but inconsistent remission, rendering PCNSL difficult to diagnose.(1,3) This may be the case here, because the patient received steroid treatment before certifying the diagnosis. Steroid therapy associated with whole brain irradiation determined a good remission for 3 years.

Whole-brain irradiation is a rescue therapy for the patients who do not respond to MTX or steroids. Mean survival time is 30 months after diagnosis.(1,3,10)

CONCLUSIONS

The primary cause of the contrast enhancing lesion has remained uncertain despite numerous tests. We had arguments to believe that the initial lesion was a primary CNS lymphoma, which had probably a good remission due to steroid therapy associated with whole brain irradiation at the first admission in 2012. Other unusual causes of autoimmune encephalitis could be taken into account.

REFERENCES

1. Louis ED, Mayer SA, Rowland LP. Merritt's Neurology. Thirteenth Edition. Philadelphia: Wolters Kluwer; 2016.
2. Ayuso-Peralta L, Ortí-Pareja M, Zurdo-Hernández M, et al. Cerebral lymphoma presenting as a leukoencephalopathy. J Neurol Neurosurg Psychiatr. 2001;71(2):243-6.
3. Ropper AH, Samuels MA, Klein JP. Adams and Victor's Principles of Neurology. Tenth Edition. China: McGraw-Hill; 2014.
4. Miller DC, Hochberg FH, Harris NL, Gruber ML, Louis DN, Cohen H. Pathology with clinical correlations of primary central nervous system non-Hodgkin's lymphoma. The Massachusetts General Hospital experience 1958-1989. Cancer. 1994;74(4):1383-97.
5. Montesinos-Rongen M, Schmitz R, Courts C, et al. Absence of immunoglobulin class switch in primary lymphomas of the central nervous system. Am J Pathol. 2005;166(6):1773-9.
6. Fischer L, Martus P, Weller M, Klasen HA, Rohden B, Röth A, et al. Meningeal dissemination in primary CNS lymphoma: prospective evaluation of 282 patients. Neurology. 2008;71(14):1102-8.
7. Viaccoz A, Ducray F, Tholance Y et al. CSF neopterin level as a diagnostic marker in primary central nervous system lymphoma. Neuro Oncol. 2015;17(11):1497-503. doi: 10.1093/neuonc/nov092. Epub 2015 May 25.
8. Haldorsen IS, Kråkenes J, Krossnes BK et-al. CT and MR imaging features of primary central nervous system lymphoma in Norway, 1989-2003. AJNR Am J Neuroradiol. 2009;30(4):744-51. doi:10.3174/ajnr.A1447.
9. Johnson BA, Fram EK, Johnson PC, et al. The variable MR appearance of primary lymphoma of the central nervous system: comparison with histopathologic features. AJNR Am J Neuroradiol. 1997;18(3):563-72.
10. Kiewe P, Loddenkemper C, Anagnostopoulos I, et al. High-dose methotrexate is beneficial in parenchymal brain masses of uncertain origin suspicious for primary CNS lymphoma. Neuro-oncology. 2007;9(2):96-102.