# ASSOCIATION OF TEMPORAL LOBE INFLAMMATORY LEUKOENCEPHALOPATHY WITH TWO B CELL MALIGNANCIES

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Identification of etiological connections among virtually distinct diseases in a patient may be sometimes challenging. We report a unique case with two B cell malignancies and an inflammatory leukoencephalopathy. Three days prior to admission, the elderly male patient developed fatigue, headaches, recurrent vomiting, memory disturbances, depression and somnolence. Clinical, laboratory and imaging evaluations as well as post mortem histological studies were performed. Simultaneous presence of primary central nervous system B cell lymphoma, temporal lobe inflammatory leukoencephalopathy and multiple (smoldering) myeloma, was revealed by the detailed work up in the treatment-naïve patient. Based on recent data from genomic studies, we propose that a sequential evolution of molecular pathology lead to the co-occurrence of multiple myeloma and primary central nervous system B cell lymphoma in this patient, and interpret the development of the temporal lobe leukoencephalopathy as a likely paraneoplastic complication of smoldering myeloma.

***Keywords:*** *multiple myeloma, primary CNS lymphoma, B cell malignancy, paraneoplastic inflammatory leukoencephalopathy, somatic mutations*

**GYULLADÁSOS TEMPORALIS LEUKOENCEPHALOPATHIA EGYÜTTES MEGJELENÉSE KÉT B-SEJTES MALIGNOMÁVAL**

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A klinikus időnként olyan beteggel is találkozik, akinek egyszerre többféle, látszólag egymástól független betegsége van. Ilyenkor az esetleges kapcsolat felderítése komoly kihívást jelenthet számára. Ilyen bonyolult esetet mutatunk be, amelyben két malignus B-sejtes betegség és gyulladásos leukoencephalopathia fordult elő együtt. Az idős férfi a felvételt megelőzően három nappal gyengeségre kezdett panaszkodni, fejét fájdította, ismételten hányt, feledékeny lett, étvágytalanná, deprimálttá, majd aluszékonnyá vált. Klinikai, laboratóriumi, képalkotó és hisztológiai vizsgálatok történtek, melyek során primer központi idegrendszeri lymphoma, a temporalis lebeny gyulladásos leukoencephalopathiája és lappangó myeloma multiplex derült ki. A beteg korábban kemoterápiában nem részesült. Korábbi genomikai tanulmányok eredményei alapján feltételezhető, hogy a molekuláris abnormalitások B-sejtekben történő szekvenciális akkumulációja vezetett először a myeloma multiplex, majd a primer központi idegrendszeri lymphoma kialakulásához, míg a temporalis lebeny leukoencephalopathiája a lappangó myeloma multiplex paraneoplasiás következményeként értelmezhető.

***Kulcsszavak:*** *myeloma multiplex, primer központi idegrendszeri lymphoma, B-sejtes malignoma, paraneoplasticus gyulladásos leukoencephalopthia, szomatikus mutációk*

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The co-occurrence of common diseases is frequently seen in clinical practice and causes no diagnostic or therapeutic difficulties. In contrast, the co-occurrence of rare and apparently independent conditions may pose major challenges in clinical practice. It is particularly difficult to proceed with the therapeutic intervention without knowing whether or not there is a causal link among the associated conditions. Here we report such a complex case of a patient who presented with subacute memory loss, personality and behavioral changes and somnolence in our neurology department.

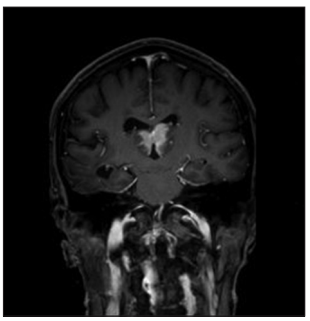

**Figure 1A** *Postgadolinium T1 weighted coronal image of the thalamic lesion. The image shows bilateral enhancing lesions representing the PCNSL*

## Case report

A 73 year old man was previously treated for hypertension and atrial fibrillation. His new complaints began three days prior to admission to the neurology department, and included fatigue, headaches, vomiting, memory problems, depression and personality changes. Neurological exam revealed no focal findings, but lack of facial expressions, psychomotor slowing, partial disorientation in time, memory difficulties with encoding of new information and somnolence when left alone.

Abnormal laboratory results: cerebrospinal fluid: protein 0.83 g/l (normal 0.12-0.6), WBC 10/µl (normal 0-10) with 90% lymphocytes, 10% monocytes and no lymphoblasts; glucose 2.65 mmol/L (normal 2.20-3.90).

3 Tesla MRI: A symmetric space occupying lesion with edema, contrast enhancement and decreased average diffusivity is visualized in the medial thalami and inter-thalamic regions. The right temporal lobe appears with narrowed gyri and enlarged horn of the lateral ventricle. T1-weighted images show a hypointense, and T2-weighted images show a hyperintense lesion in this area extending to the insular region, but excluding the posterior part of the temporal lobe. In addition, increased diffusion is noted on the DWI images in the white matter, while equivocal diffusion alterations are seen in the amygdale and hippocampus of the right temporal lobe. T1-weighted images display no pathological changes in the hippocampal and parahippocampal cortices **(Figure 1A, B).**

These findings raised the suspicion of viral (Herpes simplex virus - HSV) encephalitis or tumor. Acyclovir, dexamethasone and enoxaparine were initiated. However, subsequent tests were negative for HSV, tick borne encephalitis and West-Nile viruses.

MRI-guided stereotactic biopsy of the right thalamus was performed at the Institute of

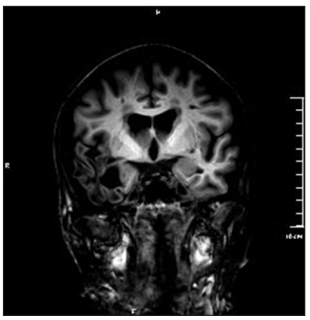

**Figure 1B.** *T1 weighted native coronal image of right temporal lobe. Thinning of the cortex, hypointensity within the atrophied white matter and the enlargement of the temporal horn are depicted*

Neurosurgery, University of Pécs (UP), Dr. F. Vető. Histology: Primary large B cell lymphoma of the brain with CD20+, Mum-1+, CD3-, and CD10- immunophenotype.

For further management the patient was transferred to the Hematology Department of our hospital.

Abdominal, mediastinal and pelvic computer tomography revealed moderate hepatomegaly without splenomegaly or mediastinal and abdominal lymphadenomegaly. The cranium, vertebrae and pelvis were free of osteolytic lesions.

Laboratory findings: Serum immune-electrophoresis: IgG 21.10 g/l (normal 8.0-17.0), IgA 0.29 g/l (normal 1.00-4.9), IgM 0.31 g/l (normal 0.50-3.2), Kappa-K chain 5.67 g/l (normal 2.00-4.40), lambda-k chain 0.24 g/l (normal 1.1-2.4). Interpretation: (1) 22.2% paraprotein in the gamma region, (2) IgG Kappa monoclonal gammopathy.

Bone marrow aspirate: > 20% clonally expanded plasma cells; IgG kappa monoclonal gammopathy and 22.2 g% M-protein. Interpretation: Multiple myeloma.

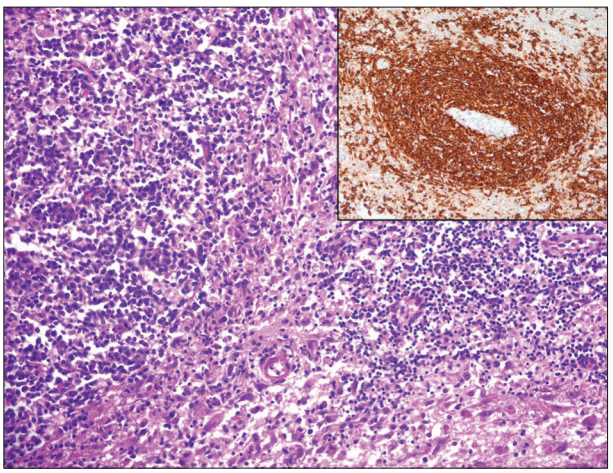

**Figure 2.** *H&E stained section and IHC of the PCNSL from the thalami. Small and medium size tumor cells with fine chromatin structure and round shaped, occasionally prominent nucleoli are demonstrated. The cytoplasm appears thin and slightly eosinophilic. Inset: IHC reveals strong CD20 positivity of the cells*

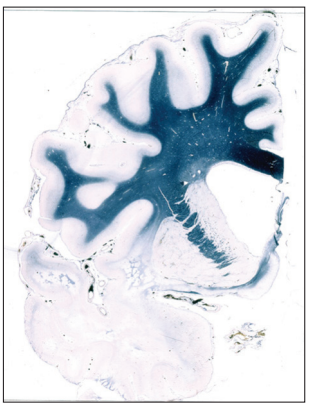

**Figure 3A.** *Woelcke stained section of the right hemisphere. Extensive loss of myelin is demonstrated in the temporal lobe*

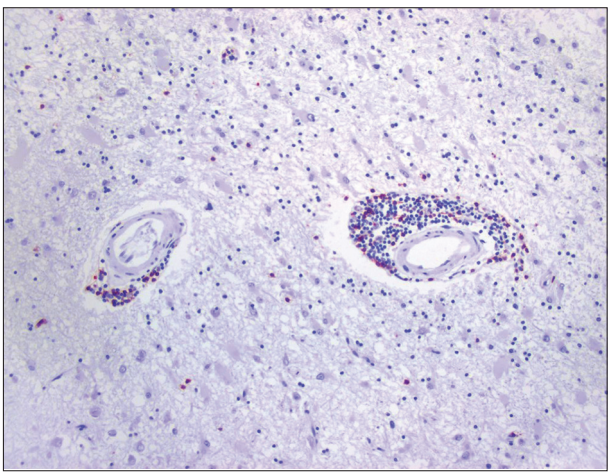

**Figure 3B**. *Anti-CD8 immunohistochemistry of the temporal lobe. Perivascular and parenchymal infiltration of CD8 lymphocytes is seen in the white matter of the right temporal lobe*

Bone marrow (iliac crest) biopsy (Institute of Pathology, PTE): The cellularity is below 20-30% in many areas. Moderate CD138+ plasma cell proliferation with mostly CD20+, CD56- co-staining is seen in an uneven diffuse and cluster-like distribution occasionally reaching 10-15%. IgG kappa chain positivity is abundant.

Comparison of the bone marrow and thalamus biopsies: The brain biopsy (PCNSL) contained cells of markedly more immature phenotype, predominantly immunoblastoid cells with central nucleolus, a few with plasmocytoid features, but repeatedly with CD138- and strongly CD20+ staining and with a proliferation rate of >70% that would be very unusual in MM. Analyses of IgG heavy chain gene rearrangements in the brain - and bone marrow - derived specimens revealed multiple, but distinct rearrangement patterns, supporting two clonally different processes (B cell PCNSL in the brain and plasma cell myeloma in the bone marrow).

The patient received 1x intravenous (3 g/m$^2$) and 3x intrathecal methotrexate treatment for the PCNSL. In a week, severe myelosuppression developed. The anemia was treated with RBC concentrate, while the neutropenia was managed with a granulocyte colony-stimulating factor preparation. For the treatment of MM, dexamethasone was administered. His neurological condition was unchanged, but he developed fever and died of sepsis.

Autopsy: The immediate cause of death was pneumonia with abscesses accompanied by a hematological spread. Bone fragments showed decalcification and hypocellular marrow with significantly decreased erythro- and myelopoesis. Atypia was observed among megakariocytes. Plasma cell proliferation was seen with cytomorphological atypia and uneven distribution. Internal organs were free of MM ("smoldering myeloma").

Both thalami were moderately swollen. Lymphocytic parenchymal infiltration accompanied by astrogliosis, and perivascular infiltration at the lesion edges, were seen in the medial nuclei of both thalami **(Figure 2.)**. The tumor cells were small and medium sized with fine chromatin structure, round shape and occasionally prominent nucleoli. The cytoplasm appeared thin and slightly eosinophilic. Immunohistochemistry revealed almost 100% CD20+ and CD79a+ tumor cells. There were a few CD8+ T lymphocytes localized around blood vessels and in inflammatory infiltrates.

The right temporal lobe had thin gyri and grayish, softened WM. The WM was rarified and cystic **(Figure 3A)** with only a few remaining fragments of SMI31+ axonal and myelin fragments amidst prominent glial scarring involving gemistocytes, fibrillary astrocytes and scattered macrophages. Strong CD68+ staining was noted in lipid-laden macrophages. Predominantly CD8+ cytotoxic T and CD20+ B cell infiltration occurred in perivascular distribution, without signs of malignancy. CD8 cells diffusely infiltrated the parenchyma **(Figure 3B)**. The cortical gray matter was rarified and focally spongiform with some inflammatory activity extending from the WM, but without microglial nodules or gliosis. Immunohistochemistry was negative for HSV-1,-2, JC and SV40 viruses. These observations suggested an inflammatory leukoencephalopathy of non-viral origin. Epstein-Barr virus detection was equivocal due to poor RNA quality. Direct immunfluorescence revealed no IgG and complement C3 deposition in the temporal WM specimens.

## Discussion

The clinical work up established that the patient had two diseases of the CNS: 1. a primary B cell CNS lymphoma occupying both thalami and 2. a white matter disease affecting *almost* the entire right temporal lobe and causing atrophy. In addition to the CNS pathology, this case was further complicated by the clinical recognition of a smoldering multiple myeloma that only affected the bone marrow and caused no apparent complaints. Unfortunately, the patient died from sepsis after 1.5 months of immune suppressive therapy.

In our work up two major questions arose

1. Could the co-occurrence of two B cell malignancies (PCNSL and MM) be a co-incidence, or related to a common molecular cause in this patient who was treatment naive at the time of clinical recognition? Unless treatment of MM by chemotherapy induced immune suppression and a secondary cancer (e.g. PCNSL), the simultaneous detection of two B cell malignancies in a single patient is unusual *(1)*. Searching Pubmed, we found a single report describing a tri-lineage hematological disease with sideroblastic anemia, MM and B-cell non-Hodgkin's lymphoma *(2)*. The Multiple Myeloma Genomics Initiative using massively parallel sequencing of tumor genomes and the corresponding normal DNAs revealed that the number of somatic point mutations in the tumor is high (2.9 / million bases translating into 7,450 mutations in a tumor), and the mutations involve several functionally important genes that define a mechanistic framework of tumorgenesis *(3)*. Relevant to our case, mutations were detected in regions of known somatic hypermutations which comprise immunoglobulin-coding genes and a lymphoid oncogene, *BCL6*. Further, mutations were observed within non-coding regions of *BCL7A*, a putative tumor suppressor gene involved in the B-cell malignancy, Burkitt lymphoma. In the light of these findings we propose that the accumulation of somatic mutations in malignant cells of the bone marrow may result in some clonal diversity over time. Mutations affecting lymphoid oncogenes or tumor suppressor genes may occur in myeloma subclones and drive the genesis of a new, phenotypically different B cell malignancy. If these mutated daughter clones express appropriate adhesion molecules, they may migrate to the CNS and give rise to PCNSL. Therefore, the PCNSL in this patient could be explained as a result of the somatic molecular changes evolving in the bone marrow B cell lineages which primarily cause MM and subsequently also PCNSL.

2. What could be the cause of the observed temporal lobe leukoencephalopathy? Vascular, traumatic, metabolic or inherited disorders could be readily excluded based on clinical and histological features. Despite the absence of characteristic signs of Herpes Simplex (HS) encephalitis (the patient had no fevers, the MRI showed a chronic lesion predominantly in the white matter without the involvement of the cortex, and there was no hemorrhagic transformation in this lesion), this diagnosis was assumed as a potential, treatable cause of temporal lobe pathology and empirically treated until serological, virological and / or histopathological studies from the stereotactic brain biopsy unequivocally excluded the presence of this and several other viruses (HSV-1, -2, West Nile, JC, SB40)**.** When PCNSL in the thalami was recognized, the possibility of paraneoplastic origin of the temporal lobe pathology arose. The association between paraneoplastic limbic encephalitis and peripheral B cell lymphomas is well known (4). However, a paraneoplastic mechanism requires chronic exposure to and priming of the adaptive immune system by the lymphoma antigens in the peripheral immune system. Therefore, it is difficult to associate a paraneoplastic mechanism with a lymphoma restricted to the CNS, and the literature is also rather spares in this regard.

Could the temporal lobe pathology still be paraneoplastic in origin? The bone marrow malignancy caused no complaints, but the disease probably persisted for years as a smoldering myeloma, allowing the development of a long-standing, secondary

pathology in the CNS. However, both the MR images and the pathology work up showed that the limbic system was largely spared, while the white matter of the right temporal lobe was predominantly affected in this patient. The histological studies also suggested that it was the inflammatory and spongiosus white matter lesion that extended towards the gray matter of the right temporal lobe, not the other way around, and beside the extensive white matter involvement, the gray matter pathology was sparse. Such a temporal lobe leukoencephalopathy, would not be compatible with paraneoplastic limbic encephalitis that primarily affects the mesial temporal lobe region and gray matter structures *(5)*. In the absence of IgG kappa paraprotein, C3 complement, viruses and malignant B cells in the right temporal lobe, the inflammatory leukoencephalopathy with many infiltrating CD8 cells and myelin and axonal loss was likely a T cell driven paraneoplastic leukoencephalopathy and mostly resembled the histological characteristics of ADEM (acute demyelinating encephalomyelitis). The lesion's MRI characteristics were also compatible with this conclusion. ADEM-like paraneoplastic leukoencephalomyelitides in association with MM were described without the presence of common paraneoplastic antibodies or microorganisms *(6–8)*. However, in the light of the long standing nature of and lack of anti-myelin paraproteins in the CNS WM lesion, our observation, similar to the previously published cases, only provides circumstantial evidence for the existence of a paraneoplastic ADEM-like pathology and may be more appropriate to call it inflammatory leukoencephalopathy associated with MM.

As inflammatory CNS lesions can be caused by Epstein-Barr virus (EBV) infection in both pediatric *(9, 10)* and adult patients *(11, 12)*, the ethiological involvement of EBV in the temporal lobe pathology of this patient also had to be considered. However, PCNSLs are typically negative for EBV in immunocompetent patients, as was our patient too at the time of PCNSL diagnosis. Nevertheless, a recent report described EBV detection in a very low frequency of PCNS in immunocompetent individuals *(13)*. Unfortunately, testing for EBV in the PCNSL lesion failed to provide unequivocal result in our patient. Considering the typically EBV negative nature of PCNSL in an immunocompetent patient, the cause of the temporal lobe lesion in our case appears unlikely to be EBV-related and is mainly compatible with an inflammatory leukoencephalopathy, possibly of paraneoplastic origin, in association with MM.

## Conclusions

The current case exemplifies the complexity of MM pathology and suggests that clonal diversity and autoimmune processes may contribute to associated neurological complications.

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