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Letter to the Editor

Lymphomatosis cerebri and anti-NMDAR antibodies: A unique constellation

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Dear Editor,

Anti-N-Methyl-D-aspartate receptor (NMDAR) encephalitis, an antibody-mediated disorder, commonly occurs in association with ovarian teratomas, but other tumors have been recognized [1–3]. Only few brain biopsy/postmortem studies have been performed in patients with anti-NMDAR antibodies [4]. We present a clinicopathologic report of a patient with lymphomatosis cerebri (LC) associated with anti-NMDAR antibodies and we discuss possible pathogenic mechanisms underlying this novel and intriguing association.

1. Case report

A 54-year-old man manifested depression and emotional lability, followed, 3 months later, by left hand intention tremor. Over the ensuing 6 months, bilateral Holmes' tremor and left hand dystonia were observed. Brain magnetic resonance imaging (MRI) and dopamine transporter imaging with single photon emission computed tomography (DAT-SPECT) were unremarkable. One year after onset, a whole-body positron emission tomography (PET) imaging disclosed only a reduced uptake of 18-F-fluorodeoxyglucose in bilateral frontotemporal regions. Five months later, disequilibrium, gait instability and dysarthria were observed. Brain MRI showed diffuse periventricular white matter changes (Fig. 1A). Thereafter, a stepwise neurological deterioration manifested, culminating, 20 months after onset, in dysexecutive syndrome, attention deficit, anosognosia, visuospatial impairment, and constructional apraxia. Repeated extensive electrophysiological, imaging, and laboratory investigations showed non-specific EEG changes, negative whole-body PET-CT imaging, and marked extension of brain MRI lesions (Fig. 1B–D). Cerebrospinal fluid (CSF) analysis with a tissue-based assay (indirect immunohistochemistry on rat brain; avidin-biotin-peroxidase technique) and cell-based assays (fixed HEK293T cells transfected with the GluN1 and GluN2B subunits; commercial kit, Euroimmun, Lübeck) revealed the presence of anti-NMDAR antibodies (strong positivity at titer 1:1, positive up to the final titration of 1:8 on immunofluorescence), while protein content and cell count were within normal limits, and oligoclonal bands were absent. Anti-NMDAR antibodies were not detectable in serum. Unfortunately, previous samples were not available for antibody testing. Despite sequential plasmapheresis and cyclophosphamide treatment, progressive alterations in mental status, opsoclonus and opisthotonus were noticed. Death occurred 24 months after onset. On autopsy only brain was studied. Gross examination showed bilateral areas of greyish discoloration of caudate nucleus, putamen, thalamus, midbrain and deep white matter. Histological examination was performed in multiple formalin-fixed and paraffin-embedded areas including frontal, temporal, parietal and occipital cortices, hippocampus, basal ganglia, thalamus, amygdala, brainstem, and cerebellum. Sections were stained with hematoxylin and eosin and analysed with immunohistochemistry (Supplementary Table 1, supplemental file). Perivascular and parenchymal infiltrates of highly atypical lymphoid cells with numerous mitotic figures (Fig. 1E) were observed diffusely in the cerebral white matter, thalamus, and basal ganglia. These cells strongly expressed the pan-B-cell marker CD20 (Fig. 1F) and kappa chains. No staining was noted by *in situ* hybridization for Epstein-Barr virus latency-associated RNA (EBER). Neoplastic cells, intermingled with sparse CD3-positive T-cell infiltrates (Fig. 1G), showed a high Ki-67 labelling index (Fig. 1H), and were positive for IgG (Fig. 1I). These findings were consistent with LC, a rare diffusely infiltrating subtype of primary central nervous system (CNS) lymphoma. In addiction, perivascular CD79a-positive mature plasma cells were noted in tumor-free frontal region and hippocampus (Fig. 1L). These areas did not show neuronal loss or other structural changes at light microscopy.

2. Discussion

Neuropathologic signatures of anti-NMDAR encephalitis include meningeal and perivascular B-cell/plasma cell infiltrates, sparse T-cell

Abbreviations: NMDAR, N-Methyl-D-aspartate receptor; LC, Lymphomatosis cerebri; MRI, magnetic resonance imaging; DAT-SPECT, dopamine transporter imaging with single photon emission computed tomography; PET, positron emission tomography; CSF, Cerebrospinal fluid; CNS, Central Nervous System; EBER, Epstein-Barr virus latency-associated RNA; LGI1, leucine-rich glioma-inactivated 1

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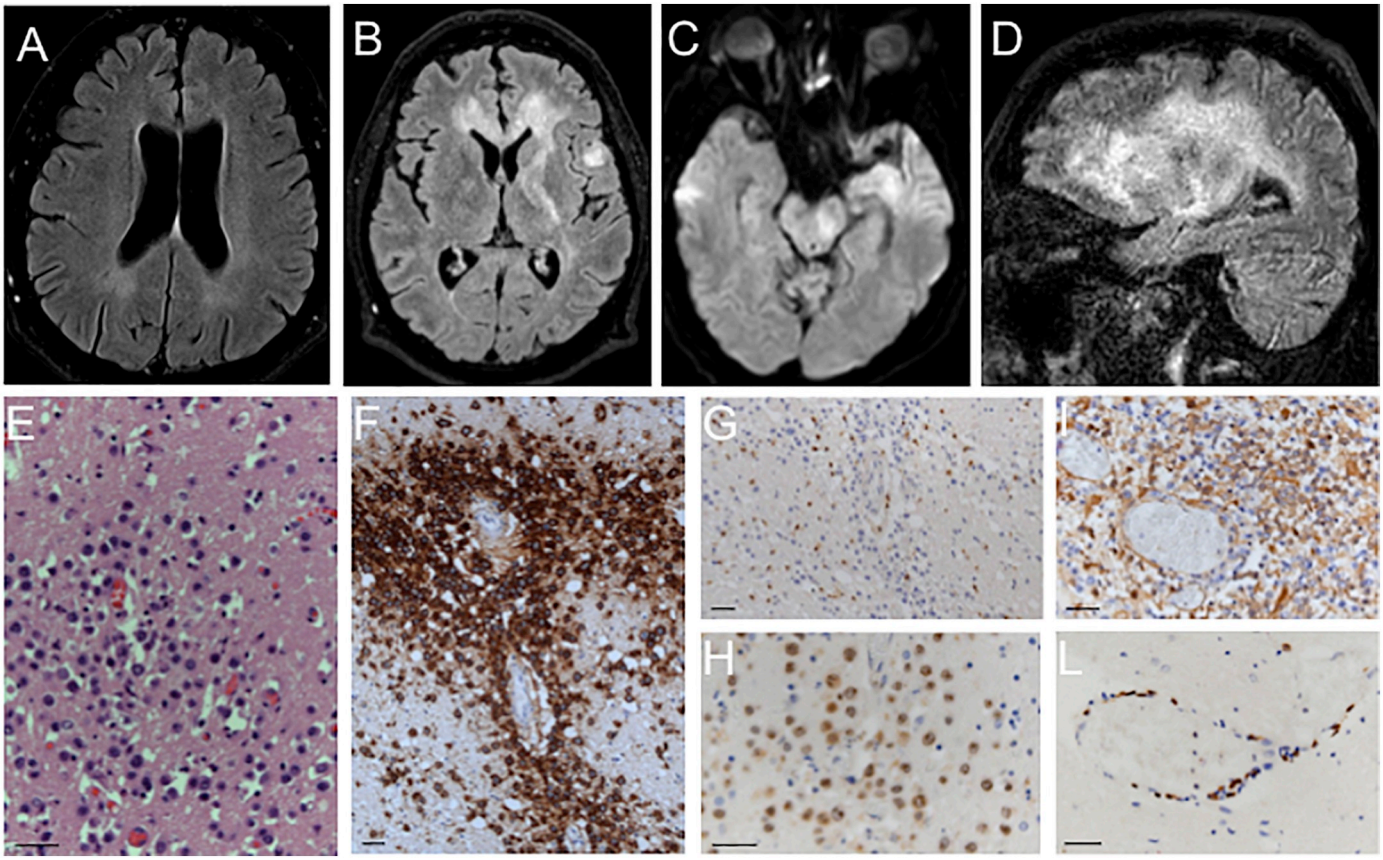

Fig. 1. Radiological findings and neuropathological observations.
(A) Slight confluent periventricular and subcortical T2/FLAIR hyperintensities were noted 17 months after onset. (B–D) Three months later, periventricular alterations, associated with subcortical temporal T2/FLAIR hyperintensity, brainstem and bilateral mesial temporal lobes involvement not enhanced after gadolinium were observed. (E) Infiltrates of atypical lymphoid cells and numerous mitotic figures were detected on hematoxylin and eosin (X100, original magnification) in the basal ganglia. (F) Large cell infiltrates were noted with CD20 immunostaining within the brain parenchyma, suggestive for B-cell lymphoma (X50, original magnification). (G) In the same region CD3 immunostaining revealed moderate perivascular infiltration of mature T lymphocytes compatible with accompanying inflammation (X50, original magnification). (H) Ki67 immunostaining reveals a high rate of cell proliferation (X100, original magnification). (I) Lymphomatous cells showing mitotic figures were also positive for IgG (thalamus, X40, original magnification). (L) Perivascular inflammatory infiltrates of CD79a positive plasma cells were noted in the hippocampus (X40, original magnification) Scale bar: 50 μm.

infiltration, minimal microglial activation, and IgG deposition predominantly in the hippocampus, basal forebrain and basal ganglia, with notably absent neuronal injury. These features suggest a complement-independent antibody-mediated process [4]. In the present case we observed the unique association of LC and anti-NMDAR antibodies, an intriguing pathogenic dilemma. In paraneoplastic neurological syndromes it has been hypothesized that the ectopic expression of onco-neuronal antigens may initiate an autoimmune process, with anti-neuronal antibodies being produced at regional lymph nodes, where memory B-cells are generated. After reaching the CNS, memory B-cells differentiate into antibody-producing plasma cells [5]. In our case we excluded *in vivo* the presence of extra-cerebral tumors, and it is unlikely that the lymphoma developed secondarily to immunosuppression, since *in situ* hybridisation for EBER resulted negative. Dysregulated lymphoma cells could be the main protagonists of the production of anti-NMDAR antibodies, directly or through cytokine-mediated signaling. This hypothesis is supported in our case by the expression of IgG in a population of tumor cells. On the other hand, the exposure of specific antigens after neuronal damage induced by neoplastic cells could lead to intrathecal antibody synthesis. Indeed, we observed tissue destruction in particular in the bilateral cerebral white matter, basal ganglia, and thalamus with massive lymphomatous infiltrates and neuronal loss. This scenario reminds the one observed in NMDAR encephalitis occurring post-*herpes simplex virus* encephalitis, where the release of antigens by viral-induced neuronal lysis might lead to the synthesis of anti-NMDAR antibodies [6]. In the case here reported, the primary pathogenic relevance of LC is supported by several elements including (1) the clinical picture and the very poor final outcome; (2) the radiological findings, showing extensive bilateral hemispheric damage in absence of contrast enhancement; (3) the diffuse infiltrates of highly atypical cells with numerous mitotic figures observed on neuropathological evaluation. However, the differential diagnosis between CNS lymphoma and an inflammatory disease is often challenging, as confirmed by a recently described case [7]. Thomas et al. reported a patient with incipient primary CNS lymphoma closely resembling limbic encephalitis. After the detection of low-titer serum anti-LGI1 antibodies, the subject was diagnosed and treated for anti-LGI1 encephalitis. However, histopathological examination of a stereotactic biopsy led to the final diagnosis of primary CNS lymphoma, also supported by radiological findings. In comparison and in support of the possible role of anti-NMDAR antibodies, we herein observed intrathecal high titer antibodies, associated with neuropathological findings of perivascular plasma cells infiltrates in tumor-free areas. The role of CSF clonally expanded plasma cells in producing anti-NMDAR antibodies has been recently reported using recombinant antibody technology [8] and has been confirmed by neuropathological findings of plasma cells/plasmablasts infiltrating the brain in cases with NMDAR encephalitis [4]. Although not a widely investigated subject, it is known that primary B cell lymphoma of the CNS display a biased usage of variable region genes and a high level of somatic hypermutation of immunoglobulin genes

[9]. This points to antigen-driven clonal selection and it is therefore tempting to speculate that neoplastic B-cells might be directly involved in the antibody-mediated CNS damage. Taken together, our findings suggest that also intracerebral tumors, and in particular LC, may be a trigger for the production of anti-NMDAR antibodies, either by neuronal antigen exposure or intracerebral foci of antibody-producing B-cells.

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Conflicts of interest statement

The authors declare no conflict of interest.

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Sara Mariotto[a,*], Alberto Zamó[b,c], Enrica Franchini[a], Bruno Bonetti[d], Alice Parisi[c], Romana Höftberger[e], Ellen Gelpi[e,f], Salvatore Monaco[a], Sergio Ferrari[a]

[a] *Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Italy*

[b] *Department of Oncology, University of Torino, Italy*

[c] *Department of Pathology & Diagnostics, University and Hospital Trust of Verona, Italy*

[d] *Neurology Unit, S. Maurizio Hospital, Bolzano, Italy*

[e] *Institute of Neurology, Medical University of Vienna, Austria*

[f] *Neurological Tissue Bank of the Biobanc-Hospital Clinic-IDIBAPS, Barcelona, Spain*

E-mail address: sara.mariotto@gmail.com (S. Mariotto).

[*] Corresponding author at: Department of Neuroscience, Biomedicine and Movement Sciences, University of Verona, Italy, Policlinico GB Rossi, P.le LA Scuro 10, 37134 Verona, Italy.