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# Extra-CNS Target for Assessment and Treatment in Refractory Anti-NMDAR Encephalitis

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## Abstract

Anti-N-methyl-D-aspartate-type glutamate receptor autoimmune encephalitis can arise in the setting of ovarian teratoma and often responds to resection. When arising in the absence of tumor failure to respond to treatment may be more likely, and affected patients often require intensive care. To further understanding of mechanisms and potential management we present findings from an autopsy conducted on a young woman who died from refractory autoimmune encephalitis of this type. Rituximab was administered 70 days before death, and both 37 and 14 days before death CD19+ lymphocytes were only 0.1% of blood cells. 10 sessions of plasmapheresis were performed following rituximab treatment. Nonetheless, the auto-antibodies were present in serum 4 days before death, demonstrating ongoing antibody production. The hippocampus and medial temporal lobe demonstrated inflammation with T-cell and prominent microglial involvement, but no plasma cells or plasmablasts were found there, or anywhere in the brain, despite an extensive search. Examination of lymph node tissue identified many plasma cells along sinusoids. These findings demonstrate that the antibody-producing cells are long-lived and likely reside in lymphoid tissue. Awareness of continuing antibody production, the extra-CNS site, the indication for cytotoxic therapy, and the potential for biopsy assessment may lead to more effective treatment.

### Keywords

neuro-intensive care; anti-NMDAR encephalitis; refractory encephalitis; biopsy; autopsy

## Introduction

Production of self-reactive antibodies in the presence of tumor was first described three decades ago, and since the initial report, several dozen paraneoplastic auto-antibodies have been identified [1]. Encephalitis due to production of auto-antibodies in the presence of ovarian teratoma was reported in 1999 [2] and subsequently determined to be due to antibodies against the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor [3]. A



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This analysis of patient history and autopsy tissue has been approved by the Institutional Review Board of Johns Hopkins University.

later report documented the condition in patients free of teratoma, and found that such patients may fare worse [4]. The anti-CD20 antibody rituximab has been used to successfully treat this condition [5], and has become the standard of care in refractory cases [6]. To our knowledge autopsy findings from a patient who fails to respond to rituximab therapy have not previously been reported. In the present case these findings demonstrate both ongoing auto-antibody production and abundant plasma cells in lymphoid tissue, indicating both the need for aggressive therapy [7] and the potential utility of diagnostic biopsy.

## Results

A young adult with a family history of lupus and a personal history of herpes simplex infection diagnosed 1 year earlier during the birth of a child developed tongue swelling, mouth sores, and headache. Approximately three months later she would expire from the condition. Her initial symptoms progressed to confusion, word-finding difficulties and hallucinations, then she suffered a seizure. She visited and was released from an outside hospital emergency department two times. Five days after symptoms began she was admitted to an outside hospital with fluctuating mental status. One day after admission CSF, which showed 0 RBC/μL, 39 WBC/μL with 95% lymphs, protein of 24 mg/dL and glucose of 70 mg/dL, was positive for anti-NMDA receptor auto-antibodies. She continued to have seizure-like activity despite treatment with multiple anti-epileptic drugs. Cranial imaging studies were unremarkable.

MRI of the pelvis was significant only for a small Gartner cyst. Rheumatologic work-up revealed positive anti-nuclear antibody in titer of 1:640, anti-cardiolipin IgG of 1:58 (high positive), and anti-phospholipid antibodies. The following antibodies tested negative: anti-Jo, anti-dsDNA, anti-SM, anti-neuronal nuclear Ab Types 1-3, anti-glial nuclear Ab, Purkinje cell cytoplasmic Ab types 1,2 and Tr, anti-amphiphysin, anti-CRMP-5-IgG, Striational Ab, P/Q-type calcium channel, N-type calcium channel, ACh receptor (muscle), AchR ganglionic neuronal Ab, and neuronal (V-G) K+ channel Ab. HSV testing of CSF by PCR and ELISA was negative as were numerous other assays for infection. She received treatment with high-dose methylprednisolone, intravenous immunoglobulin, acyclovir, and rituximab, but did not improve.

Four weeks after symptom onset the patient was transferred to the ICU at our institution, where EEG showed the 'extreme delta brush' pattern characteristic of this entity. She received valacyclovir, prednisone and 10 sessions of plasmapheresis without response. She suffered mandibular fracture due to facial dyskinesia as a result of ongoing seizures. Propofol was necessary for seizure control. Bilateral salpingo-oophorectomy was performed but no evidence of teratoma was found and symptoms were unchanged. Repeated brain MRIs showed no definitive abnormality. Throughout her hospital course, she suffered marked fluctuations in heart rate, respiratory rate, and blood pressure. 93 days after the patient's first symptoms she was found unresponsive, and despite resuscitative efforts she expired, with autonomic instability the presumptive proximate cause. A serum sample from 4 days prior to death was positive for antibody to NMDAR NR1 subunit.

At autopsy the brain was grossly unremarkable. Microscopically, the hippocampus and adjacent medial temporal lobe demonstrated prominent elongated microglial nuclei apposed to intact pyramidal cells (figure, A). Immunohistochemical staining for Iba-1 confirmed the microglial identity of these cells and highlighted their processes encircling neuronal somata (figure, B). Immunohistochemical stain for CD3 demonstrated T-cells scattered throughout the parenchyma (figure, C). High power examination showed small numbers of T-cells in proximity to pyramidal neurons and microglia (figure, D). However, neither in these inflamed areas, nor elsewhere in the parenchyma, meninges, vessels, or Virchow-Robin or perivascular spaces of the cortex, basal ganglia, midbrain, cerebellum, brainstem, spinal cord, or eyes were plasma cells or lymphoid aggregates detected. The hippocampus and medial temporal lobes were sampled at three antero-posterior levels from both the right and left sides, and the thalamus, basal ganglia, and temporal lobe deep white matter were also sampled bilaterally. Immunohistochemical stains of selected brain areas for B-cell and plasmablast/plasma cell markers CD20, CD19, and CD138 disclosed no cells (not shown).

Examination of a somatic lymph node demonstrated many cells with plasma cell morphology distributed along sinusoids, often in clusters (figure, E). Immunohistochemical stain for CD138 confirmed plasma cell identity (Figure, F). Scattered cells with membranous staining for CD138 were also seen in bone marrow (not shown), though these were less readily identified morphologically, perhaps reflecting decalcification. Such cells were not found in spleen.

## Discussion

The development following HSV encephalitis of syndromes characterized by anti-NMDAR auto-antibodies [8] is important to consider in this patient with a history of mucocutaneous herpes simplex infection and no evidence of ovarian teratoma on microscopic examination, but the negative PCR and ELISA studies for HSV suggest that it did not contribute. Given her positive anti-nuclear and anti-cardiolipin antibodies, family history of lupus, and initial presentation with mouth sores, the patient's encephalitis may have arisen in association with an underlying undiagnosed autoimmune disease. Alternatively, prior exposure to fetal tissue could have led to the development of anti-NMDAR auto-antibodies.

Microglial activation and T-cells encircling neurons are reported in 'classic' paraneoplastic antibody-mediated encephalitides [9]. In patients with anti-NMDAR antibody encephalitis not treated with rituximab, perivascular lymphocyte aggregates can be pronounced, and these aggregates have been shown to harbor plasma cells [10;11]. In the present case no B-cells, plasmablasts or plasma cells were identified in any brain region. The absence of B-cells reflects the use of rituximab, which can lower their numbers for up to 12 months [12], whereas plasma cells are resistant to rituximab [13].

Testing of serum for anti-NMDAR Ab is less sensitive than CSF, but highly specific, with no false positives reported in 100 cases [14], so the serum test shortly before death confirms the presence of antibodies. Rituximab treatment was effective, as demonstrated by the two very low measurements of circulating CD19+ cells. The half-life of IgG, the most long-lived antibody, is approximately 20 days [15]. Thus 70 days after rituximab, only 8.8% of the

antibody would be expected to remain. As an alternative estimate, an older study found that at least 5% of IgG is turned over daily [16], which would result in 2.8% of the original antibody molecules being present 70 days after rituximab treatment. In addition, the patient underwent 10 cycles of pheresis. Hence the antibody molecules present in serum must have been produced after rituximab. Plasma cells are not sensitive to rituximab, so the presence of anti-NR1 auto-antibody in serum following rituximab and pheresis is most readily explained as continued antibody production by plasma cells that existed prior to the treatment.

Refractory anti-NMDAR encephalitis can cause prolonged status epilepticus, which has a mortality rate of approximately 65% [17]. Autopsy indicates that, despite the neurotropism of the anti-NMDAR auto-antibody, the immunoprivileged CNS is not the site of production. Clusters of plasma cells are found adjacent to lymph node sinusoids and are the likely producers of these antibodies, making them the therapeutic target. Localization of plasma cells to lymph nodes by biopsy could facilitate elimination by cytotoxic therapy, and be used to monitor response to such treatment or to targeted therapy such as IL-6 antagonism [18]. Better characterization of individual cases through biopsy assessment could improve outcome in refractory cases as likely to be encountered in the critical care setting.

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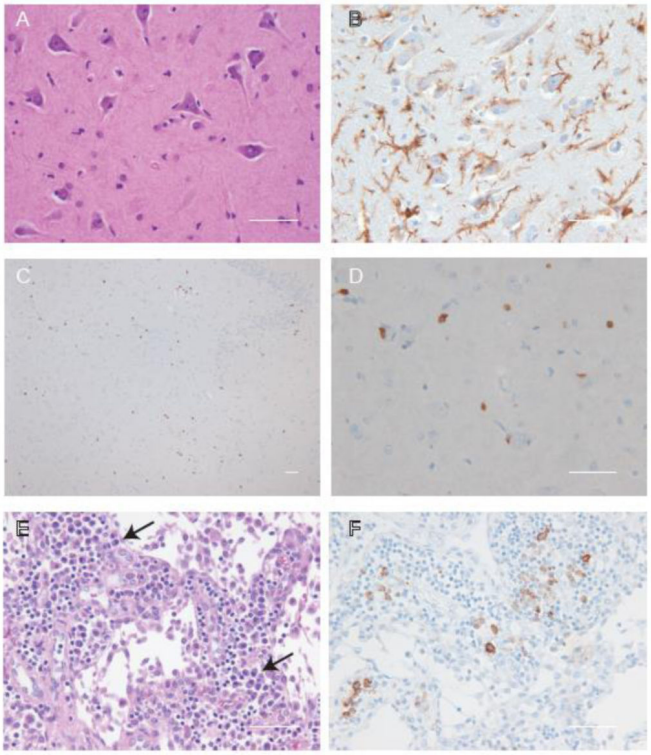


**Figure.**

T-cells and abundant microglia adjacent to neurons, with numerous plasma cells adjacent to lymph node sinusoids, in refractory autoimmune anti-NMDA receptor encephalitis. A) Hilar pyramidal neurons and numerous microglia with elongated nuclei in proximity to the morphologically normal neuronal cell bodies and processes. Hematoxylin and eosin, original magnification 400x. B) Immunohistochemical stain for Iba-1 (Wako Chemical USA) highlights microglial ramifications closely apposed to many pyramidal cell somata. Original magnification 400x. C) Immunohistochemical stain for CD3 (Leica Biosystems) demonstrates scattered T-cells in the hippocampal parenchyma. Note granule cell layer, upper right. Original magnification 100x. D) High-power examination emphasizes the proximity of the T-cells to pyramidal cell somata and microglial cells. Original magnification 400x. E) Examination of a lymph node demonstrates clusters of plasma cells (arrows), with distinctive chromatin, eccentric nuclear location, and perinuclear hof. Hematoxylin and eosin, original magnification 400x. F) Immunohistochemical stain for CD138 (Ventana) highlights plasma cells adjacent to lymph node channels. Original magnification 400x. All scale bars 50 microns.