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Glioblastoma as an autoimmune limbic encephalitis mimic: A case and review of the literature

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Abstract

A 43-year-old woman presented with cognitive decline, focal seizures, brain MRI showing non-enhancing, bilateral hippocampal lesions, but normal cerebrospinal fluid findings, which fulfilled the Graus et al 2016 criteria for autoimmune limbic encephalitis (ALE). Subjective improvements were observed after immunotherapy. A repeat brain MRI showed new contrast enhancement and positron emission tomography revealed left hippocampal uptake. Biopsy of the right parahippocampus yielded high-grade glioma. Five similar cases, among the 14 with unilateral hippocampal lesions on MRI, were identified in the literature whereby suspected ALE preceded the high-grade glioma diagnosis. Gliomas confined to hippocampi can have clinical features overlapping with ALE

Key Words: Glioma; Limbic encephalitis; Glioblastoma; Autoimmune encephalitis

1. Introduction

Autoimmune limbic encephalitis (ALE) is an increasingly recognized manifestation of autoimmune neurologic illness, characterized by rapidly progressive cognitive impairment mediated by non-infectious inflammation (Graus et al., 2016, Tobin and Pittock, 2017). The diagnosis can be difficult to make and several mimics exist (Budhram et al., 2017, da Rocha et al., 2015, Blondin et al., 2011). We present an atypical case of high-grade, isocitrate dehydrogenase (IDH) wildtype glioma with bilateral limbic system infiltration, mimicking the clinical and radiographic features of ALE. We reviewed the literature for similar cases of high-grade glioma with bilateral hippocampal/limbic system involvement to emphasize this unusual and confusing clinical presentation.

2. Case Report

A 43-year-old previously healthy woman with no prior history of neurologic or psychiatric illness, presented to an epilepsy clinic within an academic medical center with three months of cognitive decline, including anterograde and retrograde amnesia, and a recent hospitalization for rapid memory loss, fever, and new-onset focal seizures with no clear diagnosis at that time. Seizures were characterized by acute onset loss of awareness and oral and hand automatisms. Despite antiepileptic therapy, cognitive decline persisted resulting in rehospitalization. Her exam at that time was notable for disorientation, perseverative speech, anxiety, and severe memory impairment. Cognitive testing revealed a Montreal Cognitive Assessment (MOCA) score of 21 out of a total of 30 points, with predominant deductions for memory impairment, including immediate and delayed recall not elicited with cues. Initial work-up was unrevealing, including blood counts, comprehensive metabolic panel, thyroid stimulating hormone (TSH), and anti-thyroperoxidase (TPO) antibodies. Cerebrospinal fluid (CSF) revealed a normal cell count, protein (36mg/dL), and glucose (77mg/dL), negative oligoclonal bands (OCB), negative herpes simplex virus 1 & 2 and varicella zoster virus polymerase chain reactions (PCR), and undetectable West Nile virus serum antibodies with negative reverse transcription-PCR. An initial contrasted magnetic resonance imaging (MRI) brain showed bilateral mesial temporal lobe non-enhancing, T2-fluid attenuated inversion recovery (FLAIR) hyperintensities (Figure 1A).

Autoantibody evaluations on serum and CSF performed at the Mayo Clinic Laboratories were negative, including antibodies against the N-methyl-D-aspartate receptor (anti-NMDA-R), voltage gated potassium channel (VGKC) complex, Glutamate decarboxylase-65 (GAD65), gamma-aminobutyric acid-B (GABA-B) receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, anti-Hu, and collapsin response-mediator protein-5 (CRMP-5). She was treated for probable ALE in the absence of an autoantibody with intravenous methylprednisolone over five days. Extended electroencephalogram monitoring showed interictal left temporal focal slowing and she was continued on antiepileptics. Subjective improvements in neuropsychiatric disturbances were noted in the days following treatment, although with no return to her cognitive baseline or objective improvement in cognition, and she was subsequently discharged home.

Three months later, a second, repeat lumbar puncture showed no evidence of inflammation with a normal CSF cell count, protein, glucose, immunoglobulin G (IgG) index, and no OCB detected. Given the concern for ALE recurrence, returning mood disturbances now accompanied by akathisia, and objective decline in cognition with a repeat MOCA scored at 18 out of 30, she underwent an additional five cycles of plasma exchange (PLEX) and intravenous steroids. A second MRI brain revealed new enhancement of the right parahippocampal gyrus (Figure 1B), and she was treated with PLEX and steroids for presumed recurrence. Whole-body fluorodeoxyglucose positron emission tomography (FDG-PET) revealed uptake in the left hippocampus (Figure 1C). With new contrast enhancement and worsening decline, biopsy of the right parahippocampal lesion was performed revealing diffuse astrocytic glioma with molecular features of glioblastoma, isocitrate dehydrogenase 1 (IDH1) wildtype, trisomy for chromosome 7P/7CEN sequences and positive for loss of phosphatase and tensin homolog (PTEN), consistent with whole chromosome 10 loss (Figure 1D). Histologically the tumor by World Health Organization (WHO) 2016 criteria yielded anaplastic astrocytoma, IDH-wildtype, WHO grade III, but by Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) criteria the presence of gain of whole chromosome 7 and loss of whole chromosome 10 (+7/-10) conceded "diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV" (Brat et al., 2018).

Cognitive decline progressed despite treatment with temozolomide and radiation and she ultimately transitioned to hospice care and succumbed nine months later, paralleling the expected course of glioblastoma, WHO grade IV. Figure 2 summarizes the disease course.

3. Literature Review

Studies were selected from PubMed and Ovid databases using the keywords "Glioblastoma", "Astrocytoma", "Limbic encephalitis," and "Encephalitis" and included if they reviewed observational data related to each case. Cases were excluded if: 1) pathology-confirmed diagnosis of glioma was not made; 2) final diagnosis was not glioma; 3) suspicion for ALE did not precede the final diagnosis.

We identified 14 cases of high-grade glioma with a presentation mimicking ALE in the literature (Athauda et al., 2014, Deramecourt et al., 2009, Fujii et al., 2013, Liu et al., 2017, Nagata et al., 2010, Nunes et al., 2012, Rokutanda et al., 2008, Schulz et al., 2009, Vogrig et al., 2018). Patients were disproportionately male (n=10, 71.4%) with ages ranging between 42-86 years. Several features overlapped in these cases including symptomology (seizures, 78.6%; cognitive decline 64.2%; amnestic symptoms, 35.7%), initial MRI findings with lesions of the mesial temporal lobes (100% of cases), and diagnostic delay to final glioma diagnosis (ranging from 1.5–24 months). Of these, five cases had bilateral involvement with clinical features summarized in Table 1. Autoantibodies were detected in four cases (anti-NMDA-R antibodies, n=2; anti-aquaporin-4 immunoglobulin G and anti-myelin oligodendrocyte glycoprotein, n=1; anti-VGKC antibodies, n=1). Biopsy was utilized in 13 cases (glioblastoma, 85.7%; anaplastic astrocytoma, 14.3%) and autopsy in one. When treatments directed at suspected ALE were described (n=6), improvements were noted in 66.7% of cases although no objective measures for response to therapy were mentioned.

4. Discussion

Autoimmune disease is becoming increasingly recognized as a cause of encephalitis, leading to greater clinician vigilance and advances in testing for neuronal autoantibodies. Our case of diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV, mimicked ALE in its presentation and diagnostic work-up. Disease mimicry in our case and 14 similar cases from

the literature led to misdiagnosis and diagnostic delay.

While the detection of autoantibodies can establish a diagnosis of ALE, it is not needed in the current diagnostic criteria (Graus et al., 2016). Rather, in the proposed criteria from Graus et al. patients can satisfy the definition of definite ALE when all four of the following have been met: 1) subacute onset of working memory deficits, seizures, or psychiatric symptoms, 2) bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes, 3) CSF pleocytosis and/or EEG with epileptic or slow-wave activity involving the temporal lobes and 4) reasonable exclusion of alternative causes. Testing for autoantibodies remains clinically important to help clarify the possibility of a paraneoplastic process and prognosis. Furthermore, the detection of a relevant autoantibody in those patients that do not fully meet the formal diagnostic criteria can help establish a diagnosis. The sensitivity and specificity of antibody testing is dependent on the method and compartment tested (e.g. CSF verse serum). Additionally, low titers of non-specific autoantibodies (e.g. GAD65, VGKC, voltage-gated calcium channel antibodies) do not always provide an accurate diagnosis and should be interpreted within the clinical context (McKeon and Tracy, 2017, Jammoul et al., 2016).

We identified four ALE mimics, glioma cases with positive autoantibodies in the literature, one of which had bilateral medial temporal lobe involvement. These findings are confounded by clinical irrelevance or incorrect compartment detection. Where NMDA-receptor autoantibodies were found, only NMDA-receptor subtype 2 was described which is an epitope not associated with disease (Rokutanda et al., 2008). In another case, anti-aquaporin-4 immunoglobulin G (anti-AQP4) and anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibodies were detected in CSF (Liu et al., 2017). This case in particular has a number of weaknesses including no mention of the assays used – with improbable unit concentrations – and the finding of double antibody positivity – prior literature suggest there is no overlap between these two antibodies in an individual (Waters et al., 2015). Report of assays used for autoantibody detection is critical as enzyme-linked immunosorbent assay (ELISA) testing often results in false positive results, especially at low titers, compared with cell-based assay (CBA). Given the

complexity and ongoing discovery of novel neuronal autoantibodies, interpretation of antibody positivity may require specialist interpretation. Consultation with an autoimmune neurologist for interpretation of autoantibody results may avoid such diagnostic pitfalls.

Furthermore, the current criteria for ALE include "reasonable exclusion of alternative causes," including "neoplastic disorders," and recommends biopsy as the diagnostic test of choice for investigation. Although, as in our case, the criterion of *bilateral* brain abnormalities highly restricted to the medial temporal lobes is highly suggestive of an autoimmune etiology rather than glioma. The most commonly associated MRI changes in ALE include increased T2/FLAIR signal within the medial temporal lobes (Tobin and Pittock, 2017). Nevertheless, this pattern was seen in all cases of high-grade glioma ALE mimics in our review, emphasizing the practical limitation of this criterion. While the diagnosis of ALE has greater support when bilateral involvement is present, unilateral involvement can occur and should raise suspicion for an alternative diagnosis according to Graus et al. 2016 criteria. Bilateral distribution within the hippocampi in our case, parallels the fact that nearly 9% of high-grade gliomas can present initially with unilateral findings which become multifocal over time (Thomas et al., 2013). Tumor spread is hypothesized to occur via white matter pathways between lesions. An important clinical clue in our case was the presence of gadolinium enhancement on repeat imaging, which is common in glioma and prompted further work-up with biopsy. Interestingly, the contrast enhancement was not present until later in the clinical course. Without clear enhancing lesions and given the characteristics which strongly suggested ALE, biopsy would have been considered premature and an unnecessary risk at the time of her initial presentation. Thus, a trial of adequate immunotherapy was deemed the next best step.

As in our case, the response to immunotherapy can confound the clinical picture. Our patient had subjective improvements in neuropsychiatric symptoms following the first round, suggesting a treatment response and supporting the leading diagnosis of ALE. Therefore, repeat immunotherapy was pursued when she experienced recurrent psychiatric symptoms with persistent cognitive decline. None of the cases

in our literature review used objective measures for monitoring treatment response. Objective measures for monitoring treatment response, such as repeat imaging, serial neuropsychologic testing, and/or bedside cognitive testing (e.g. MOCA, mini-mental status exam [MMSE]) may aid in decision-making and minimize diagnostic error.

5. Conclusion

Autoimmune limbic encephalitis and high-grade gliomas that involve bilateral hippocampi and limbic system can result in similar clinical and neuroimaging features. We highlighted 14 similar cases of high-grade glioma. ALE is a well-established entity and hence negative serological workup does not exclude ALE. Conversely, the finding of positive autoantibodies does not exclude the presence of high-grade glioma and autoantibody type, subtype, and compartment sampling, should be considered when interpreting resultant titers. Biopsy may be necessary to distinguish ALE from alternative causes, especially in the setting of any atypical features or lack of objective improvement following immunotherapy.

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Author Contributions

Name	Location	Role	Contribution
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Karen Orjuela, MD	University of Colorado School of Medicine, Aurora, CO	Author	Revision of the manuscript revision for intellectual content.
Daniel M. Pastula, MD, MHS	University of Colorado School of Medicine, Aurora, CO	Author	Drafting and revision of the manuscript revision for intellectual content.
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Table 1. Clinical, imaging and pathologic findings in 5 cases of high grade glioma with bilateral hemispheric involvement.

	Case #	Sex	Age (years)	Diagnostic Delay*	Symptomology & Clinical Findings	Seizures	Encephalitis Treatment (Response)	Initial MRI Features	CSF Profile & Autoantibody Testing	Diagnosis (Pathology)	Outcome
Nunes J et al. 2012	1	Male	58	2 months	Three weeks of progressive disorientation and memory disturbances.	Yes	NA	Bilateral mesial temporal lobe T2/FLAIR hyperintensities involving the hippocampus, amygdala, parahippocampus and fornix. + Gad contrast enhancement of the right mesial temporal lobe	NA	Glioblastoma (NA)	NA
Rokuntanda T et al. 2008	1	Male	53	3 months	Episodes of loss of consciousness, topographic agnosia, sensory loss of the right hand	Yes	NA	Bilateral T2/FLAIR hyperintensity within the mesial temporal lobes and splenium DWI hyperintensities + Gad enhancement of the periventricular white matter of the posterior horns of the lateral ventricles	CSF profile NA Positive NMDA-receptor subtype GluRε2	Glioblastoma (NA)	NA
Nagata R et al. 2010	1	Male	72	3 months	Headache, fever, and subacute disorientation two weeks. persistent short-term memory loss and relapsing disorientation and confusion.	No	IV dexamethasone (improvements in cognition noted)	Bilateral T2/FLAIR hyperintensity within the frontal, left parietal, left temporal lobe, and periventricular white matter of the bilateral ventricles. Weak enhancement of the left temporal lesion	Mild pleocytosis (11-20 cells/mm^3), elevated protein (74-84 mg/dL), cytology negative for malignant cells No autoantibody testing mentioned.	Glioblastoma (NA)	NA
Vogrig A et al. 2018	1	Female	63	1.5 months	New onset focal status epilepticus with language dysfunction and right upper extremity clonus, neuropsychologic testing with memory deficits and "frontal syndrome."	Yes	NA	Bilateral temporal lobe T2/FLAIR hyperintensity (left to a great extent than right) with no contrast enhancement.	Lymphocytic pleocytosis (10 cells/mm^3), elevated protein (50 mg/dL), positive OCBs). Negative autoantibody testing	Glioblastoma, IDH1 wild type (NA)	Continued progression with death occurring 17 months from initial presentation, cause of death determined to be related to increased intracranial pressure.
Deramecourt A et al. 2009	1	Male	42	8 months	Two months of anterograde amnesia disorientation emotional lability, irritability, Neuropsychologic testing with verbal and nonverbal episodic memory impairment and mild reductions in working memory, executive function and attention	[illegible]	NA	Bilateral mesial temporal lobe T2/FLAIR hyperintensities with predominance over the left pulvinar and bilateral posterior cinguli with no contrast enhancement	NA Negative autoantibodies in serum and CSF.	Focal high grade astrocytoma with gliomatosis cerebri; Oligodendroglioma, WHO Grade II; (NA)	Underwent left temporal lobectomy. Postoperative outcome not described.

* Diagnostic delay defined as the time between ALE diagnostic suspicion to high grade glioma diagnosis

ALE = autoimmune limbic encephalitis; CSF = cerebrospinal fluid; NA = not available; FLAIR = T2-fluid attenuated inversion recovery; Gad = Gadolinium; DWI = diffusion-weight imaging; NMDA = N-methyl-D-aspartate; GluRε2 = glutamate receptor epsilon-2 subunit; GluRδ2 = glutamate receptor delta-2 subunit; IV = intravenous; ALE = autoimmune limbic encephalitis; WHO = World Health Organization; VGKC = Voltage gated potassium channel; OCB = oligoclonal bands; IDH = isocitrate dehydrogenase; IVIG = intravenous immunoglobulin; anti-AQP4-IgG = anti-aquaporin-4 immunoglobulin G; GFAP = glial fibrillary acidic protein; ATRX = Alpha-Thalassemia/Mental Retardation;; EGFR = epidermal growth factor receptor.

Figure 1. (A) Initial MRI brain with and without contrast, demonstrating non-enhancing, bilateral T2/FLAIR hyperintensities of the mesial temporal lobes. (B) Repeat MRI brain, post-contrast, obtained five months into the patient's disease course, revealing right parahippocampal contrast enhancement. (C) FDG-PET imaging of the brain showing left hippocampal uptake. (D) Hematoxylin and eosin staining of right hippocampus biopsy showing diffuse astrocytic glioma with molecular features of glioblastoma. Abbreviations: MRI = Magnetic resonance imaging; FLAIR = fluid attenuated inversion recovery; FDG-PET = fluorodeoxyglucose positron emission tomography.

Figure 2. Timeline of Clinical Course and Diagnostic Testing

Graphical abstract

Highlights

- Gliomas invading the limbic system can mimic autoimmune limbic encephalitis (ALE)
- Autoantibody testing is best interpreted in clinical context to avoid misdiagnosis
- Biopsy may be necessary for differentiating ALE from high-grade glioma

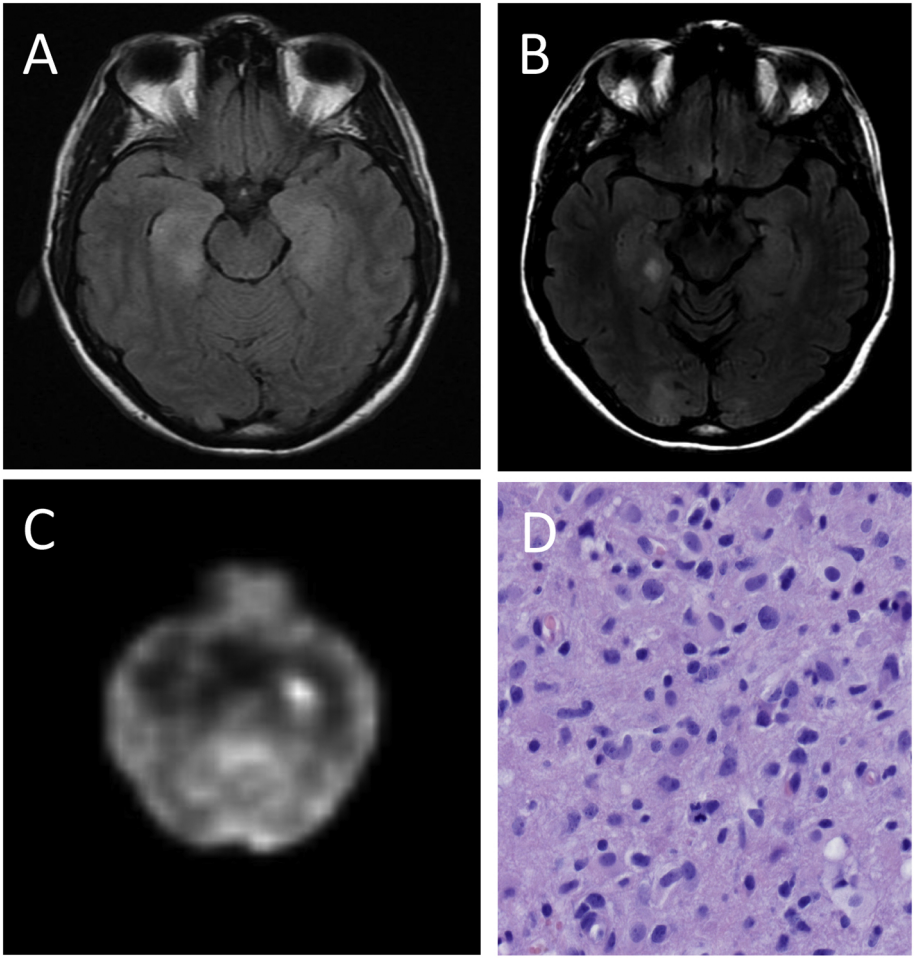

Figure 1

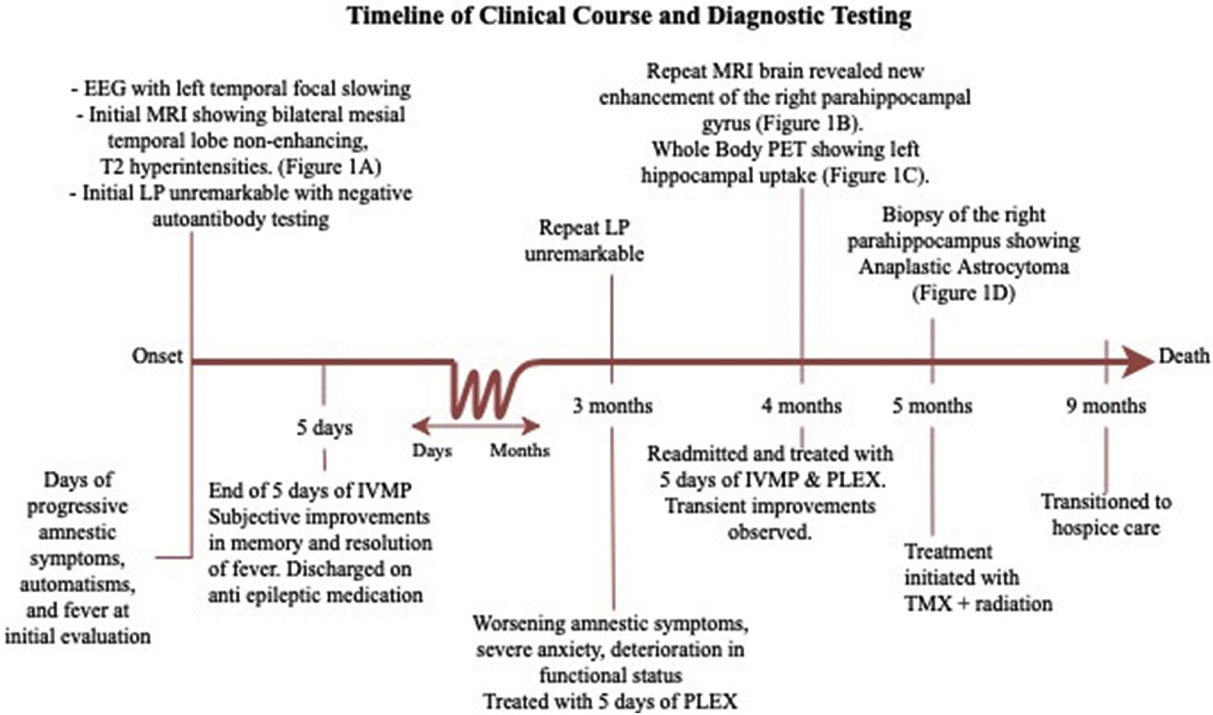
Timeline of Clinical Course and Diagnostic Testing
- EEG with left temporal focal slowing
- Initial MRI showing bilateral mesial temporal lobe non-enhancing, T2 hyperintensities. (Figure 1A)
- Initial LP unremarkable with negative autoantibody testing
Repeat MRI brain revealed new enhancement of the right parahippocampal gyrus (Figure 1B).
Whole Body PET showing left hippocampal uptake (Figure 1C).
Repeat LP unremarkable
Biopsy of the right parahippocampus showing Anaplastic Astrocytoma (Figure 1D)
Onset
Death
5 days
Days
Months
3 months
4 months
5 months
9 months
Days of progressive amnestic symptoms, automatisms, and fever at initial evaluation
End of 5 days of IVMP
Subjective improvements in memory and resolution of fever. Discharged on anti epileptic medication
Worsening amnestic symptoms, severe anxiety, deterioration in functional status
Treated with 5 days of PLEX
Readmitted and treated with 5 days of IVMP & PLEX.
Transient improvements observed.
Treatment initiated with TMX + radiation
Transitioned to hospice care

Figure 2