Received: 15 November 2023 | Revised: 16 January 2024 | Accepted: 18 January 2024

DOI: 10.1002/ccr3.8508

CASE REPORT

Clinical Case Reports Open Access WILEY

Fulminant multiple sclerosis versus autoimmune encephalitis: A case report

Parastesh Rezvanian[1] | **Yalda Shams**[2] | **Farinaz Tabibian**[1] | **Vahid Shaygannejad**[1,2]

[1]Neurosciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

[2]Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran

Correspondence
Vahid Shaygannejad, Department of Neurology, Isfahan University of Medical Sciences, Isfahan, Iran.
Email: v.shaygannejad@gmail.com

Key Clinical Message

This case highlights the importance of early diagnosis and treatment in prognosis of fulminant multiple sclerosis, and its similar management with autoimmune encephalitis in some clinical settings, in which these diseases are indistinguishable. This case also supports the use of rituximab in these patients with an adequate response to plasmapheresis.

Abstract

Early diagnosis and treatment of fulminant multiple sclerosis (MS), also known as Marburg' or malignant variant of MS (MVMS), is of great value in reducing morbidity and mortality. Seronegative autoimmune encephalitis (AIE) is very similar to, and sometimes indistinguishable from, fulminant MS. However, the acute and long-term management of the two diseases is often the same. This article describes the clinical course of a patient suspected of having MVMS or AIE and the challenges of their differential diagnosis and management.

KEYWORDS

autoimmune diseases of the nervous system, case report, encephalitis, multiple sclerosis

1 | INTRODUCTION

Multiple sclerosis (MS) is the most common non-traumatic cause of disability in young adults.[1] Fulminant MS, also known as the malignant variant or Marburg's variant of MS (MVMS), was first described in 1906 and accounts for about 4% of MS cases.[2] The disease is best recognized by its aggressive course, radiologic, and pathologic findings; it presents as a single plaque or multiple lesions, with considerable mass effect and cerebral edema on magnetic resonance imaging (MRI) and severe axonal loss and necrosis as pathologic findings.[3] MVMS causes significant disability or even death if not diagnosed and treated promptly.[4] However, its diagnosis is still a challenge, particularly in terms of differentiation from another autoimmune disease of the brain, autoimmune encephalitis (AIE).[5,6] Here, we present the clinical course of a middle-aged woman suspected of presenting with MVMS or AIE, and discuss the challenges of differential diagnosis and management strategies.

2 | CASE

A 42-year-old female patient with no remarkable past medical, drug, health, and family history presented with sudden behavioral changes, mutism, dysarthria, dysphagia, and limb paresis. Her symptoms had begun 5 days prior to the admission following an emotional stress, starting

with bradykinesia, motor stereotypies, ataxia, bruxism, mutism, dysphagia and urinary incontinence. She was hospitalized due to a possible diagnosis of conversion disorder and treated accordingly with benzodiazepines and promethazine. However, her symptoms continued to deteriorate in addition to experience of two episodes of seizure. Upon admission, she was hemodynamically stable with normal breathing, though disoriented and unable to obey commands with a Glasgow Coma Scale (GSC) score of 10 (eye response to pain, localize to pain as motor response, inappropriate words as verbal response). Pupils were mid-sized, isocoric, and reactive to light. Physical examination revealed bilateral positive Babinski's sign and spastic limbs. Deep tendon reflexes of upper and lower extremities were graded 4+ and 3+, respectively. Due to the patient's lack of cooperation, further cerebellar and sensory function testing could not be performed.

Initial brain MRI (Figure 1) showed multiple confluent bilateral white matter high-signal lesions in frontoparietal lobes and corpus callosum, with peripheral edema and restriction on diffusion-weighted imaging. Nodular and partial ring-enhanced lesions were noted after contrast administration, with distinct oval shapes and perpendicular orientation to the lateral ventricle. Cervical MRI, chest, abdominal, and pelvic computed tomography scans were normal. Toxicology screening was negative except for benzodiazepines, which was prescribed for conversion disorder as the primary diagnosis. Blood chemistry results were within normal range except for magnesium level of 1.5 (normal range: 1.9–2.5) and C-reactive protein level of 11 (normal range: 0–6). Screening of human immunodeficiency virus, hepatitis B, and C was also negative.

Cerebrospinal fluid (CSF) analysis indicated 12 heterologous oligoclonal bands with no concurrent bands in the serum, positive for intrathecal immunoglobulin G (IgG) synthesis. CSF gram stain and culture, and polymerase chain reaction (PCR) for herpes simplex virus (HSV) types 1 and 2 resulted negative (Table 1). Paraneoplastic neurological profile and autoimmune encephalitis profile were indistinct both in CSF and serum samples. Serum IgG was within the normal range and autoantibodies were all negative (Table 1) except for cardiolipin IgM antibody (20 μg; positive: >18). The electroencephalogram (EEG) of the patient was notable for background slowing with no evidence of delta brush, compatible with an encephalopathic pattern.

Five days of intravenous 1 g methylprednisolone as well as plasmapheresis with albumin replacement were started with the impression of fulminant MS. During hospitalization, the patient experienced loss of consciousness and developed respiratory distress leading to intubation on Day 9 of admission. Continuing treatment with plasmapheresis improved the level of consciousness enabling the patient to open her eyes spontaneously, obey commands, maintain the gag reflex, and breath independently. After extubation, due to proper response to the plasmapheresis, rituximab (1 g in 500 mL of saline intravenously) was administered

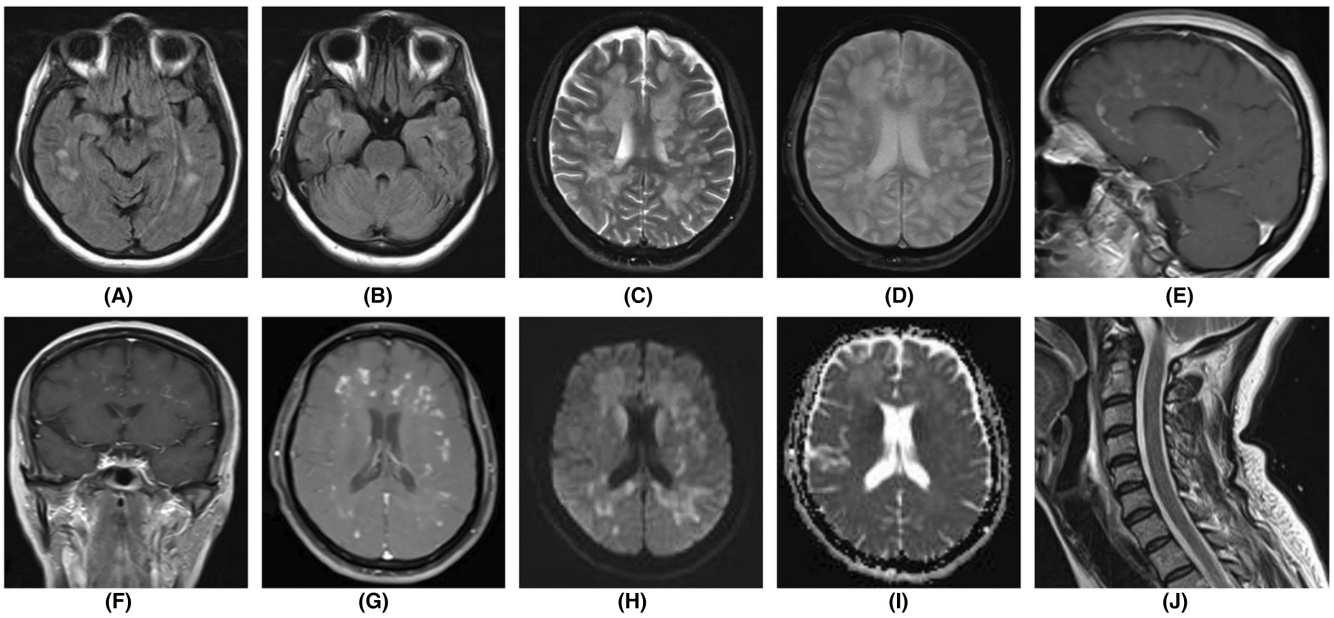

FIGURE 1 Brain and cervical magnetic resonance imaging of the case. Axial plane fluid-attenuated inversion recovery (FLAIR) (A, B); axial plane T2 (C); axial plane gradient-recalled-echo (GRE) (D); sagittal plane (E), coronal plane (F), and axial plane (G) T1 with contrast; diffusion-weighted imaging (DWI) (H) and apparent diffusion coefficient (ADC) (I) multiple confluent bilateral high-signal white matter lesions in frontoparietal lobes and corpus callosum with peripheral edema and restriction, in addition to nodular and partial ring-enhanced lesions after contrast administration with distinct oval shapes and perpendicular orientation to the lateral ventricle; sagittal plane T2 (J) normal cervical spine.

TABLE 1 Results of some laboratory tests of the case.

Test	Result	Reference range
CSF		
Color and appearance	Colorless, clear	Colorless, clear
RBC	0	0
WBC	0	0–5
Glucose	67 mg/dL	60%–70% of serum level (blood glucose: 104 mg/dL)
Protein	31 mg/dL	0–60
Albumin	30.75	10–30
IgG	8.07	1–4
CSF IgG index	0.7	Neg. <0.65 Borderline 0.65–0.8 Pos. 0.8
Antibodies		
Anti AQP4 IgG	Neg.	Neg.
Anti-MOG Ab	Neg.	Neg.
Lupus anticoagulant IgG	Neg.	Neg.
Anti-Sjögren's-syndrome-related antigen A IgG	Neg.	Neg.
Anti-Sjögren's-syndrome-related antigen B IgG	Neg.	Neg.
Anti-double-stranded deoxyribonucleic acid IgG	Neg.	Neg.
Anti-phospholipid IgM and IgG	Neg.	Neg.
Amphiphysin Ab, IgG	Neg.	Neg.
CRMP-5 (CV2 Ab), IgG	Neg.	Neg.
PNMA2 (Ma-2/Ta) Ab	Neg.	Neg.
Ri Ab, IgG	Neg.	Neg.
YO Ab, IgG	Neg.	Neg.
Hu Ab, IgG	Neg.	Neg.
Recoverin Ab, IgG	Neg.	Neg.
SOX1 Ab, IgG	Neg.	Neg.
Titin Ab, IgG	Neg.	Neg.
Zic4 Ab, IgG	Neg.	Neg.
GAD65 Ab, IgG	Neg.	Neg.
Tr (DNER) Ab, IgG	Neg.	Neg.
Anti-glutamate receptor (type NMDA) Ab	Neg.	Neg.
Anti-glutamate receptor (type AMPA) Ab	Neg.	Neg.
Anti-GABA-B receptor Ab	Neg.	Neg.
Anti-LGI1 Ab	Neg.	Neg.
Anti-CASPR2 Ab	Neg.	Neg.
Anti-DPPX Ab	Neg.	Neg.

Abbreviations: Ab, antibody; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; anti-MOG, anti-myelin oligodendrocyte glycoprotein; AQP4, anti-aquaporin 4; CASPR2, contactin-associated protein-like 2; CRMP-5, collapsin response mediator protein 5; CSF, cerebrospinal fluid; DNER, delta/notch-like epidermal growth factor-related receptor; DPPX, dipeptidyl-peptidase-like protein-6.GABA-B, gamma aminobutyric acid receptor-type B; GAD65, glutamic acid decarboxylase 65-kilodalton isoform; IgG, immunoglobulin G; LGI1, leucine-rich glioma-inactivated 1; mg/dl, milligram/deciliter; Neg., negative; NMDA, anti-*N*-methyl-d-aspartate; PNMA-2, paraneoplastic antigen Ma 2; Pos., positive; RBC, red blood cell; SOX1, anti-Sry-like high mobility group box 1; WBC, white blood cell.

to the patient. She was discharged with only mild paresis of the lower limbs. At the 1-year follow-up in December 2023, she had mild clumsiness of the upper limbs, bilateral positive Babinski's sign, and an expanded disability status scale (EDSS) score of 2 and was living a normal life.

3 | DISCUSSION

The diagnosis and treatment of MVMS still pose a dilemma in medical practice. In our case, the acute onset, fulminant monophasic course, and rapid deterioration of disease were highly suggestive of MVMS.[7] Moreover, multiple T2 hyperintense lesions, their confluent structure, perpendicular orientation to the lateral ventricles, peripheral edema, and incomplete ring enhancement further indicated the diagnosis.[8] The CSF was also positive for oligoclonal bands, as seen in 40%–95% of patients with MS.[9] Nevertheless, other infectious, vascular, and fulminant demyelinating diseases were among the differential diagnoses.

The absence of massive edema, the improvement after treatment, and the absence of a source on abdominal and pelvic imaging argued against the diagnosis of brain metastasis.[10] The pattern of brain involvement and response to treatment also ruled out stroke.[11] Normal CSF cell count and biochemistry, negative gram stain, culture, and PCR for HSV, and negative toxicology result ruled out infectious and toxic agents as the etiology.[12] Given the monophasic course and rapid progression of disease, Balo's concentric sclerosis could also be suspected. However, the lack of imaging features known as *alternating layers of myelin preservation* made this unlikely.[4] Another fulminant demyelinating disease is neuromyelitis optica spectrum disorder (NMOSD), characterized by optic nerve and spinal canal involvement and positive serum anti-aquaporin-4 IgG (AQP4-IgG). The patient was negative for AQP4 IgG and did not meet the diagnostic criteria for *NMOSD without AQP4-IgG*.[13]

Due to the presence of psychological symptoms, motor abnormalities, and seizures, AIE could also be suspected.[14] In 2016, Graus et al.[6] developed a diagnostic approach for AIE that eliminates the need for antibody results at the onset of disease; the patient should at least meet three requirements: First, subacute (<3 months) short-term memory loss, psychiatric symptoms, or changes in mental status; second, new focal central nervous system abnormalities, inexplicable seizures, CSF pleocytosis, or MRI findings consistent with encephalitis; third, exclusion of other possible causes. After fulfilling three criteria, the first step is to rule out limbic encephalitis, which was unlikely in our case as the temporal lobes were spared on MRI and there was no pleocytosis. Moving forward in the algorithm, AQP4, NMADR and myelin oligodendrocyte glycoprotein (MOG) antibodies need to be assessed due to the presence of demyelination signs on MRI. Since the patient tested negative for the mentioned antibodies, the next clinical question is whether there will be an improvement on MRI, and the answer would help distinguish acute disseminated encephalomyelitis (ADEM) from other differential diagnoses, rather than AIE. This cannot be anticipated at the onset of disease, making ADEM a diagnostic challenge in our case. However, there were some points that favor MVMS over ADEM. Initially, the patient's medical history was vacant of an immunologic trigger such as vaccination or infection in the past few weeks. It may not be feasible to differentiate ADEM from the first attack of MS solely based on radiologic features. Still, the involvement of the corpus callosum and periventricular area and sparing of basal ganglia, thalamus, and deep gray matter are more frequently seen in MS.[5] Additionally, positive oligoclonal bands in the CSF, as seen in our patient, is quite uncommon in ADEM, presenting in less than 7% of the cases.[15] Although due to various similarities between seronegative AIE and MVMS they cannot be fully differentiated in many clinical settings, patients of both diseases benefit from same treatments.[5]

There are no established guidelines for treatment of MVMS; as with other fulminant demyelinating diseases, treatment is initiated with high-dose methylprednisolone, followed by intravenous immunoglobulin (IVIG), plasmapheresis, or both. Generally, methylprednisolone is administered 1 g daily for 3–5 days, but longer treatment with steroids has been reported to be beneficial.[16] Plasmapheresis or plasma exchange (PLEX) is considered to be advantageous in patients with fulminant demyelinating diseases.[17] There are reports regarding worsening the condition following PLEX,[18] while others report considerable resolution of symptoms.[19,20] A randomized clinical trial of 22 patients with fulminant demyelinating diseases showed improvement in 42% of patients treated with PLEX compared to 5.9% in sham-treated controls.[21] Our case manifested an adequate response to PLEX. To evaluate the effectiveness of IVIG, Visser et al. compared the EDSS score 4, 8, and 12 weeks after starting the treatment with intravenous methylprednisolone plus placebo or plus IVIG; two groups showed no significant difference in outcome or the number of future relapses.[22] Due to insufficient supporting data, we decided not to administer IVIG to the patient.

In refractory cases with worsening clinical conditions or ongoing lesions on MRI, the successful use of immunosuppressive agents such as cyclophosphamide and mitoxantrone has been reported.[23–28] Alemtuzumab, a monoclonal antibody against CD52, was administered to a 51-year-old patient and significantly improved the clinical condition.[18] Kryshani et al. used natalizumab early in the disease to prevent further attacks.[20] Parfenov et al.[19] suggested that in patients with significant clinical response to plasmapheresis, rituximab should be considered due to the humoral component of disease. This was the rationale for the administration of rituximab in our patient.

Factors like male gender, young age, large lesions on imaging, and high cell count on CSF have been reported to show poor prognosis in MVMS.[20] In our case, none of the above factors were present, and with treatment initiated early at diagnosis, she was able to make a full recovery and return to work without disability.

4 | CONCLUSION

Early diagnosis and treatment play an important role in prolonging the survival of MVMS patients. MVMS and AIE may be clinically indistinguishable in some clinical settings, but their management is similar. This case provides further supportive data for the use of rituximab in patients with an adequate response to plasmapheresis.

AUTHOR CONTRIBUTIONS

Parastesh Rezvanian: Data curation; resources; writing – original draft. **Yalda Shams:** Data curation; resources; writing – original draft. **Farinaz Tabibian:** Methodology; supervision; writing – original draft; writing – review and editing. **Vahid Shaygannejad:** Conceptualization; supervision; writing – original draft; writing – review and editing.

FUNDING INFORMATION

This study had no funding.

CONFLICT OF INTEREST STATEMENT

We declare that all authors have read and approved the submission. The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data will be available via the email address of the corresponding author.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Farinaz Tabibian https://orcid.org/0000-0003-2245-6968
Vahid Shaygannejad https://orcid.org/0000-0002-6226-0161

REFERENCES

1. Filippi M, Bar-Or A, Piehl F, et al. Multiple sclerosis. *Nat Rev Dis Primers*. 2018;4:43. doi:10.1038/S41572-018-0041-4
2. Marburg O. Die sogenannte "akute multiple Sklerose". *J Psychiatr Neurol*. 1906;27:211-312.
3. Hu W, Lucchinetti CF. The pathological spectrum of CNS inflammatory demyelinating diseases. *Semin Immunopathol*. 2009;31:439-453. doi:10.1007/s00281-009-0178-z
4. Capello E, Mancardi GL. Marburg type and Balo's concentric sclerosis: rare and acute variants of multiple sclerosis. *Neurol Sci*. 2004;25:s361-s363. doi:10.1007/s10072-004-0341-1
5. Bevan C, Cree B. Fulminant demyelinating diseases of the central nervous system. *Semin Neurol*. 2015;35:656-666. doi:10.1055/s-0035-1564682
6. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol*. 2016;15:391-404. doi:10.1016/S1474-4422(15)00401-9
7. Karussis D. The diagnosis of multiple sclerosis and the various related demyelinating syndromes: a critical review. *J Autoimmun*. 2014;48–49:134-142. doi:10.1016/j.jaut.2014.01.022
8. Simon JH, Kleinschmidt-DeMasters BK. Variants of multiple sclerosis. *Neuroimaging Clin N Am*. 2008;18:703-716. doi:10.1016/j.nic.2008.06.003
9. Rohani M, Ghourchian S. Fulminant multiple sclerosis (MS). *Neurol Sci*. 2011;32:953-957. doi:10.1007/s10072-011-0723-0
10. Derks SHAE, van der Veldt AAM, Smits M. Brain metastases: the role of clinical imaging. *Br J Radiol*. 2022;95:20210944. doi:10.1259/BJR.20210944
11. Kamalian S, Lev MH. Stroke imaging. *Radiol Clin N Am*. 2019;57:717-732. doi:10.1016/J.RCL.2019.02.001
12. Dubey D, Pittock SJ, Kelly CR, et al. Autoimmune encephalitis epidemiology and a comparison to infectious encephalitis. *Ann Neurol*. 2018;83:166-177. doi:10.1002/ana.25131
13. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology*. 2015;85:177-189. doi:10.1212/WNL.0000000000001729
14. Lancaster E. The diagnosis and treatment of autoimmune encephalitis. *J Clin Neurol*. 2016;12:1-13. doi:10.3988/jcn.2016.12.1.1
15. Wingerchuk DM, Weinshenker BG. Acute disseminated encephalomyelitis, transverse myelitis, and neuromyelitis optica. *Continuum*. 2013;19:944-967. doi:10.1212/01.con.0000433289.38339.a2
16. Rahmlow MR, Kantarci O. Fulminant demyelinating diseases. *Neurohospitalist*. 2013;3:81-91. doi:10.1177/1941874412466873
17. Cortese I, Chaudhry V, So YT, Cantor F, Cornblath DR, Rae-Grant A. Evidence-based guideline update: plasmapheresis in neurologic disorders: report of the therapeutics and technology assessment subcommittee of the American academy of neurology. *Neurology*. 2011;76:294-300. doi:10.1212/WNL.0b013e318207b1f6
18. Gobbin F, Marangi A, Orlandi R, et al. A case of acute fulminant multiple sclerosis treated with alemtuzumab. *Mult Scler Relat Disord*. 2017;17:9-11. doi:10.1016/j.msard.2017.06.007
19. Parfenov V, Du Pasquier R, Schluep M. Management of fulminant multiple sclerosis with rituximab. *Neurologist*. 2015;19:155-157. doi:10.1097/nrl.0000000000000030
20. Fernando KTM, James M. Early predictors of rapidly evolving multiple sclerosis: a case report. *J Neuroimmunol*. 2017;307:42-46. doi:10.1016/j.jneuroim.2017.03.017
21. Weinshenker BG, O'Brien PC, Petterson TM, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. *Ann Neurol*. 1999;46:878-886. doi:10.1002/1531-8249(199912)46:6<878::aid-ana10>3.0.co;2-q
22. Visser LH, Beekman R, Tijssen CC, et al. A randomized, double-blind, placebo-controlled pilot study of IV immune globulins in combination with IV methylprednisolone in the treatment of relapses in patients with MS. *Mult Scler J*. 2004;10:89-91. doi:10.1191/1352458504ms978sr
23. Avila-Ornelas J, Labat E, Alfonso G, Serrano C, Fiorito F. An extremely aggressive case of Marburg's disease treated with high dose cyclophosphamide. A case report. *Mult Scler Relat Disord*. 2019;31:51-53. doi:10.1016/j.msard.2019.03.014
24. Nozaki K, Abou-Fayssal N. High dose cyclophosphamide treatment in Marburg variant multiple sclerosis. *J Neurol Sci*. 2010;296:121-123. doi:10.1016/j.jns.2010.05.022
25. Zaeem Z, Emery D, Blevins G. Fulminant multiple sclerosis in a 36-year-old man. *CMAJ*. 2022;194:E776. doi:10.1503/cmaj.211807
26. Jeffery DR, Lefkowitz DS, Crittenden JP. Treatment of Marburg variant multiple sclerosis with mitoxantrone. *J Neuroimaging*. 2004;14:58-62. doi:10.1111/j.1552-6569.2004.tb00217.x
27. Manuel A, Vasudevan MC. A case of Marburg's variant of multiple sclerosis successfully treated with IVIg and mitoxantrone. *Ann Indian Acad Neurol*. 2021;24:92-94. doi:10.4103/aian.AIAN_117_20
28. Capet N, Levraut M, Delourme A, et al. Marburg multiple sclerosis variant: complete remission with very early administration of mitoxantrone – a case report. *Neurol Ther*. 2022;11:507-513. doi:10.1007/s40120-021-00308-6

How to cite this article: Rezvanian P, Shams Y, Tabibian F, Shaygannejad V. Fulminant multiple sclerosis versus autoimmune encephalitis: A case report. *Clin Case Rep*. 2024;12:e8508. doi:10.1002/ccr3.8508