

Cerebrospinal fluid Th1/Tc1 polarization in a patient with first-line immunotherapy-resistant GFAP astrocytopathy: a case report

Tie-jun Yang

The First Clinical Medical College of Ningxia Medical University

Long-nan Wang

General Hospital of Ningxia Medical University

Pan-kui Li

General Hospital of Ningxia Medical University

Chun-bo Ji

General Hospital of Ningxia Medical University

Si-qing Ma

General Hospital of Ningxia Medical University

Xiu-ying He

General Hospital of Ningxia Medical University

Ping Yang

yangping1999.good@163.com

General Hospital of Ningxia Medical University

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Abstract

Background

Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy generally responds well to corticosteroid therapy, but an extremely small subset of patients is refractory to first-line immunotherapy with high-dose corticosteroids combined with intravenous immunoglobulin (IVIG); the underlying mechanisms remain unclear. We report an EBV-DNA-negative patient with first-line immunotherapy-resistant GFAP astrocytopathy and analyze the pretreatment cerebrospinal fluid (CSF) cytokine profile to explore its possible association with treatment resistance.

Case presentation:

A 55-year-old male presented with fever, headache, meningeal signs, urinary retention, and long-segment spinal cord lesions. CSF GFAP-IgG was positive (1:32) and CSF EBV-DNA was negative. He received intravenous methylprednisolone 500 mg/d (days 3–5), 250 mg/d (days 6–8), and 125 mg/d (days 9–11) combined with IVIG 0.4 g/kg/d for 5 days as first-line immunotherapy, but showed no meaningful clinical improvement. Pretreatment CSF cytokine analysis revealed markedly elevated IFN- γ (160.73 pg/mL), MIG (68,534.15 pg/mL), IP-10 (54,682.19 pg/mL), IL-6 (319.53 pg/mL), IL-8 (626.08 pg/mL), and IL-10 (18.20 pg/mL), with MIG exceeding IP-10 and IFN- γ markedly higher than IFN- α . At discharge, he required tracheostomy with mechanical ventilation and showed no motor response to painful stimulation.

Conclusions

The pretreatment CSF Th1/Tc1-polarized profile in this case suggests CD8⁺ cytotoxic T cell-mediated CNS injury that may be relatively resistant to first-line corticosteroids and IVIG. For refractory GFAP astrocytopathy, early escalation to second-line immunotherapy may be considered; this hypothesis requires validation in prospective cohorts.

Background

Autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy, first reported by Fang et al. in 2016¹, is an autoimmune central nervous system disorder characterized by GFAP-immunoglobulin G (IgG) antibodies in serum and/or cerebrospinal fluid (CSF), with clinical manifestations including meningitis, encephalitis, and myelitis. The disease typically shows a favorable response to corticosteroid therapy². For severe or suboptimal responders, intravenous immunoglobulin (IVIG) is often added as first-line immunotherapy, with most patients achieving significant improvement. However, an extremely small subset exhibits refractoriness to high-dose corticosteroids combined with IVIG, and the underlying immunopathological mechanisms remain unclear.

Recent cohort studies have described elevated CSF cytokines in GFAP astrocytopathy^{3–5}, yet the association between specific cytokine ratios, immune polarization directions, and individual treatment responses remains unexplored. Here we report an EBV-DNA-negative GFAP astrocytopathy patient who showed no meaningful improvement despite first-line immunotherapy, and whose pretreatment CSF cytokine profile revealed a distinct Th1/Tc1-polarized signature (MIG exceeding IP-10, and IFN- γ markedly higher than IFN- α). We discuss the possible association between this immune polarization and resistance to first-line immunotherapy, and review the relevant literature.

Case presentation

A 55-year-old male was admitted on November 28, 2025, with intermittent fever and headache for 7 days, worsening with dysuria for 1 day. He developed fever with a maximum temperature of 40°C, accompanied by generalized myalgia, dizziness, and headache. One day before admission, he developed acute urinary retention with lower abdominal distension. On admission, neurological examination revealed clear consciousness but impaired memory, calculation, and orientation. Muscle strength was grade 5 in the upper limbs and grade 4 in the lower limbs. Meningeal signs were positive, with neck stiffness and a chin-to-chest distance of four fingerbreadths.

Laboratory investigations revealed hypersensitive C-reactive protein 18.79 mg/L. EBV serology showed VCA-IgG 39.2 U/mL and EBNA-IgG 327 U/mL, indicating past infection. Complete blood count, renal function, electrolytes, liver function, cryptococcal capsular antigen, TORCH panel, Brucella agglutination test, CMV PCR, respiratory pathogen panel, SARS-CoV-2 testing, and blood cultures were all negative. Tumor markers and rheumatology-related tests, including immunofixation electrophoresis, rheumatoid factor, anti-streptolysin O, light chain panel, anti-cardiolipin antibody, anti-keratin antibody, anti-CCP antibody, ANCA panel, ESR, and thyroid function, were unremarkable.

On day 1 after admission, lumbar puncture revealed an opening pressure of 300 mmH₂O. CSF bacterial culture was negative. CSF analysis demonstrated strongly positive Pandy reaction (+++), protein 2.72 g/L (reference: 0.12–0.6 g/L), glucose 2.1 mmol/L (2.2–3.9 mmol/L), and chloride 109 mmol/L (120–130 mmol/L). CSF cytology showed leukocyte count 140 cells/mm³ with lymphocytes 79%, monocytes 9%, neutrophils 6%, eosinophils 4%, and basophils 2%. CSF IgG was 222 mg/L (reference: 0–34 mg/L).

Contrast-enhanced brain MRI demonstrated marked meningeal enhancement over bilateral cerebral hemispheres (Fig. 1). Based on these findings, a preliminary diagnosis of viral encephalitis was considered, and the patient was treated with ganciclovir and ceftriaxone. On day 2, he developed spontaneous dyspnea with decreased oxygenation and was transferred to the neurological intensive care unit, where he was intubated and mechanically ventilated.

On day 3, repeat lumbar puncture showed opening pressure 130 mmH₂O. CSF biochemistry: protein 1.39 g/L, with normal glucose and chloride. CSF cytology: leukocyte count 89 cells/mm³, with lymphocytes 90%, monocytes 8%, and eosinophils 2%. CSF IgG 88.70 mg/L. Autoimmune encephalitis antibodies in

CSF were negative. CSF GFAP-IgG antibody was positive (1:32), while serum GFAP-IgG was negative. CSF cytokine quantification was performed using cytometric bead array (CBA) technology on a BD FACSCanto II flow cytometer for eight cytokines: IL-1 β , IL-6, IL-8, IL-10, IFN- α , IFN- γ , IP-10, and MIG. CSF EBV-DNA was quantified by polymerase chain reaction and was negative. CSF cytokine profiling revealed: IL-1 β 8.99 pg/mL, IL-6 319.53 pg/mL, IL-8 626.08 pg/mL, IL-10 18.20 pg/mL, IFN- α 7.42 pg/mL, IFN- γ 160.73 pg/mL, IP-10 54,682.19 pg/mL, and MIG 68,534.15 pg/mL.

Contrast-enhanced cervical and thoracic spinal cord MRI demonstrated thickening of the medulla oblongata and spinal cord from C2 to T12 levels, with elongated abnormal signal intensities and mild enhancement, suggestive of an inflammatory process (Fig. 2).

A diagnosis of GFAP astrocytopathy was established. The patient received intravenous methylprednisolone 500 mg/d for days 3–5, then 250 mg/d for days 6–8, then 125 mg/d for days 9–11, followed by continued stepwise reduction, with mannitol and aescine for spinal cord edema, and IVIG 0.4 g/kg/day. Despite 9 days of corticosteroids and 5 days of IVIG, no meaningful clinical improvement was observed. At discharge, the patient remained conscious but required tracheostomy with mechanical ventilation, nasogastric tube, and urinary catheter. No motor response was elicited upon painful stimulation, and meningeal signs remained positive. Given the diagnosis of steroid-insensitive GFAP astrocytopathy without evidence of underlying neoplasm, the family was counseled regarding poor prognosis and subsequently requested transfer to another hospital. The overall clinical course and treatments are summarized in Fig. 3.

CSF cytokine profiling. Pretreatment CSF cytokine analysis revealed marked elevation of six cytokines relative to their respective reference ranges: IFN- γ (160.73 pg/mL), MIG (68,534.15 pg/mL), IP-10 (54,682.19 pg/mL), IL-6 (319.53 pg/mL), IL-8 (626.08 pg/mL), and IL-10 (18.20 pg/mL). IL-1 β (8.99 pg/mL) and IFN- α (7.42 pg/mL) were within the reference ranges (Table 1).

Table 1
Pretreatment cerebrospinal fluid cytokine levels and reference ranges.

Cytokine	Abbreviation	Patient value (pg/mL)	Reference range (pg/mL)
Interleukin-1 β	IL-1 β	8.99	0–12.40
Interleukin-6	IL-6	319.53	0–5.30
Interleukin-8	IL-8	626.08	0–20.60
Interleukin-10	IL-10	18.20	0–4.91
Interferon- α	IFN- α	7.42	0–8.50
Interferon- γ	IFN- γ	160.73	0–7.42
IFN- γ -inducible protein 10	IP-10/CXCL10	54,682.19	0–156.24
Monokine induced by IFN- γ	MIG/CXCL9	68,534.15	0–756.84
Values exceeding the reference range are shown in bold. Reference ranges were provided by the CBA kit manufacturer.			

Discussion and Conclusions

Recent studies have reported abnormal cytokine expression in the CSF of patients with autoimmune GFAP astrocytopathy. Luo et al. found significantly elevated NLRP3 inflammasome, IL-1 β , and IL-6 in patient CSF, correlating positively with clinical disability and GFAP antibody titers³. Kimura et al. detected elevated TNF- α , IL-27, IL-6, and CCL20 during the acute phase⁴. A recent large-sample retrospective study confirmed that multiple cytokines, including IFN- γ , MIG (CXCL9), IP-10 (CXCL10), IL-8, IL-10, GM-CSF, and TNF- α , were significantly elevated in patient CSF compared with controls⁵. These studies primarily described which factors are elevated at the cohort level and have not yet deeply explored the association between specific cytokine ratios and immune polarization directions, nor individualized the correlation between cytokine profiles and clinical treatment responses.

The clinical manifestations of the present patient (meningeal signs, spinal cord lesions, and urinary retention) were consistent with typical GFAP astrocytopathy phenotypes. However, pretreatment CSF cytokine analysis revealed a distinct immune polarization signature. The MIG (CXCL9) level (68,534.15 pg/mL) exceeded that of IP-10 (CXCL10, 54,682.19 pg/mL). Concurrently, IFN- γ (160.73 pg/mL) was markedly higher than IFN- α (7.42 pg/mL). This pattern carries immunological implications: IP-10 can be induced by both type I interferons (IFN- α/β) and type II interferon (IFN- γ), whereas MIG production is predominantly dependent on IFN- γ -mediated regulation via the myeloid transcription factor PU.1. Therefore, MIG predominance over IP-10 suggests that the chemotactic environment may be dominated by adaptive Th1/Tc1 immunity rather than innate antiviral responses^{6–8}. Similarly, the markedly elevated IFN- γ relative to IFN- α indicates that the CNS immune response may have shifted from an innate antiviral

pattern toward an adaptive cytotoxic pattern^{9,10}. Type I IFNs are produced early during infection and activate innate antiviral immunity, whereas IFN- γ is predominantly produced by CD4⁺ Th1 and CD8⁺ cytotoxic T lymphocytes during the adaptive immune response, acting as a critical link between innate and adaptive immunity¹¹. IFN- γ enhances antigen presentation through upregulation of MHC class I expression and promotes Th1 polarization, thereby facilitating CD8⁺ T cell-mediated cytotoxicity^{9,11,12}.

Notably, this patient showed no significant clinical improvement following first-line immunotherapy. Glucocorticoids primarily exert anti-inflammatory effects through inhibition of NF- κ B and AP-1 pathways, with significant suppressive effects on B cell activation, antibody production, and innate inflammation. IVIG modulates immunity through multiple mechanisms, including neutralization of autoantibodies, modulation of Fc receptor expression, and regulation of T cell function. However, the effector functions of differentiated CD8⁺ cytotoxic T lymphocytes (CTLs) are relatively insensitive to both corticosteroids and IVIG. CTL-mediated tissue damage primarily depends on perforin/granzyme release and the Fas-FasL pathway; these effector mechanisms are not entirely regulated by the NF- κ B pathway, and activated effector T cells exhibit resistance to the modulatory effects of IVIG¹³. Therefore, when CSF presents Th1/Tc1 polarization characterized by markedly elevated IFN- γ and MIG, it raises the hypothesis that tissue damage may be predominantly executed by activated CD8⁺ T cells, which cannot be effectively blocked by first-line immunotherapy alone. This hypothesis may help explain the poor treatment response observed in this patient, though it remains to be validated in larger cohorts^{14,15}.

Furthermore, the marked elevation of IL-6 (319.53 pg/mL), together with detectable IL-1 β (8.99 pg/mL), suggests strong activation of the NLRP3 inflammasome. Glucocorticoids exhibit incomplete suppression of already assembled and activated inflammasomes, which may also contribute to the persistence of IL-1 β -driven inflammation despite high-dose corticosteroid administration.

The above cytokine profile forms an important in vivo-histological correlation with the pathological study by Guo et al.¹⁶, which demonstrated that parenchymal damage in GFAP astrocytopathy is primarily caused by direct attack of CD8⁺/perforin⁺/granzyme A/B⁺ cytotoxic T cells on astrocytes, accompanied by significant upregulation of MHC class I molecules and complement C4d deposition. GFAP antibodies themselves do not directly mediate cytotoxicity and serve merely as biomarkers of tissue damage. The extremely elevated IFN- γ and MIG in the pretreatment CSF of this patient may constitute the in vivo humoral counterparts of this pathological process: IFN- γ is the signature product of Th1 cells and cytotoxic T cells and can upregulate MHC class I molecule expression on astrocytic surfaces, rendering them recognizable targets for CD8⁺ T cells. MIG, as a specific ligand for CXCR3, can further recruit additional Th1/Tc1 cells into the CNS, potentially forming a self-amplifying cycle of T cell-mediated tissue damage⁶.

The negative CSF EBV-DNA in this patient excluded confounding by active Epstein-Barr virus intracranial infection, rendering the above Th1/Tc1-polarized inflammation more "pure"—it is not driven by persistent viral antigen stimulation but rather represents the immune microenvironment characteristic of the autoimmune self-sustaining phase. This finding suggests that, within the disease spectrum of GFAP

astrocytopathy, even after intracranial viral clearance, GFAP-specific T cell responses can persist and amplify independently, maintaining the inflammatory cascade through continuous recognition of the self-antigen (GFAP). This does not exclude a role for EBV in the disease-triggering phase: serological evidence of past EBV infection may still have broken initial self-tolerance through molecular mimicry or B cell polyclonal activation mechanisms^{17,18}. However, once GFAP-specific T cell clones are established, subsequent immune damage can autonomously proceed in the absence of persistent viral presence¹⁹.

The limitations of this study must be acknowledged. First, as a single observational study (n = 1), individual variation or confounding factors (such as age, sampling time, and disease stage) cannot be excluded, and the conclusions cannot be generalized to the entire patient population. The cytokine patterns observed here represent a proof-of-concept observation that requires validation in prospective cohorts. Second, this case lacked longitudinal post-treatment CSF cytokine monitoring. If cytokine levels could have been reassessed following methylprednisolone pulse therapy combined with IVIG, observing whether IFN- γ and MIG decreased would have more strongly informed the inhibitory effect of first-line immunotherapy on T cell-derived cytokines. Third, T cell receptor (TCR) sequencing or human leukocyte antigen (HLA) typing was not performed, precluding direct verification of the existence of GFAP-specific T cell clones. Future prospective cohort studies are needed, enrolling both first-line immunotherapy-sensitive and -resistant patients, with standardized pre- and post-treatment time windows for CSF collection, combined with T cell profiling and longitudinal cytokine monitoring, to test the hypothesis that Th1/Tc1 polarization is associated with resistance to first-line immunotherapy in GFAP astrocytopathy.

In conclusion, this EBV-DNA-negative GFAP astrocytopathy patient demonstrated pretreatment CSF Th1/Tc1 polarization (markedly elevated IFN- γ and MIG, with MIG exceeding IP-10, and high IFN- γ relative to IFN- α), suggesting CD8⁺ cytotoxic T cell-mediated CNS adaptive immune injury. The poor response to first-line corticosteroids plus IVIG likely reflects resistance of activated T cell effectors to these agents. This single case generates the hypothesis that pretreatment CSF Th1/Tc1 polarization might be associated with first-line immunotherapy resistance in GFAP astrocytopathy; however, this proof-of-concept observation requires validation in larger prospective cohorts before any clinical predictive value can be established. For similar cases with refractory disease, early escalation to second-line immunotherapy (e.g., plasma exchange, cyclophosphamide, or T cell-targeted therapies) may be considered.

Abbreviations

CARE
Case Report guidelines
CBA
cytometric bead array
CNS
central nervous system
CSF

cerebrospinal fluid
CTL
cytotoxic T lymphocyte
EBV
Epstein-Barr virus
GFAP
glial fibrillary acidic protein
HLA
human leukocyte antigen
IFN
interferon
IgG
immunoglobulin G
IL
interleukin
IP-10
IFN- γ -inducible protein 10 (CXCL10)
IVIG
intravenous immunoglobulin
MIG
monokine induced by IFN- γ (CXCL9)
MRI
magnetic resonance imaging
PCR
polymerase chain reaction
TCR
T cell receptor

Declarations

Ethics approval and consent to participate. This study was approved by the Ethics Committee of Ningxia Medical University (approval number: KYLL-2026-1243) and conducted in accordance with the Declaration of Helsinki. Written informed consent to participate was obtained from the patient's legal guardians.

Consent for publication. Written informed consent for publication of this case report and any accompanying images, including the magnetic resonance imaging scans of the brain and spinal cord (Fig. 1 and Fig. 2) and the clinical timeline (Fig. 3), was obtained from the patient's legal guardians. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Availability of data and materials. All data generated or analysed during this study are included in this published article.

Competing interests. The authors declare that they have no competing interests.

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Authors' contributions. YT collected the clinical and laboratory data, performed the cytokine data analysis, and was a major contributor to writing the manuscript. LW, CJ, SM, and HX contributed to patient management and data interpretation. PY conceived and supervised the study and revised the manuscript. All authors read and approved the final manuscript.

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Figures

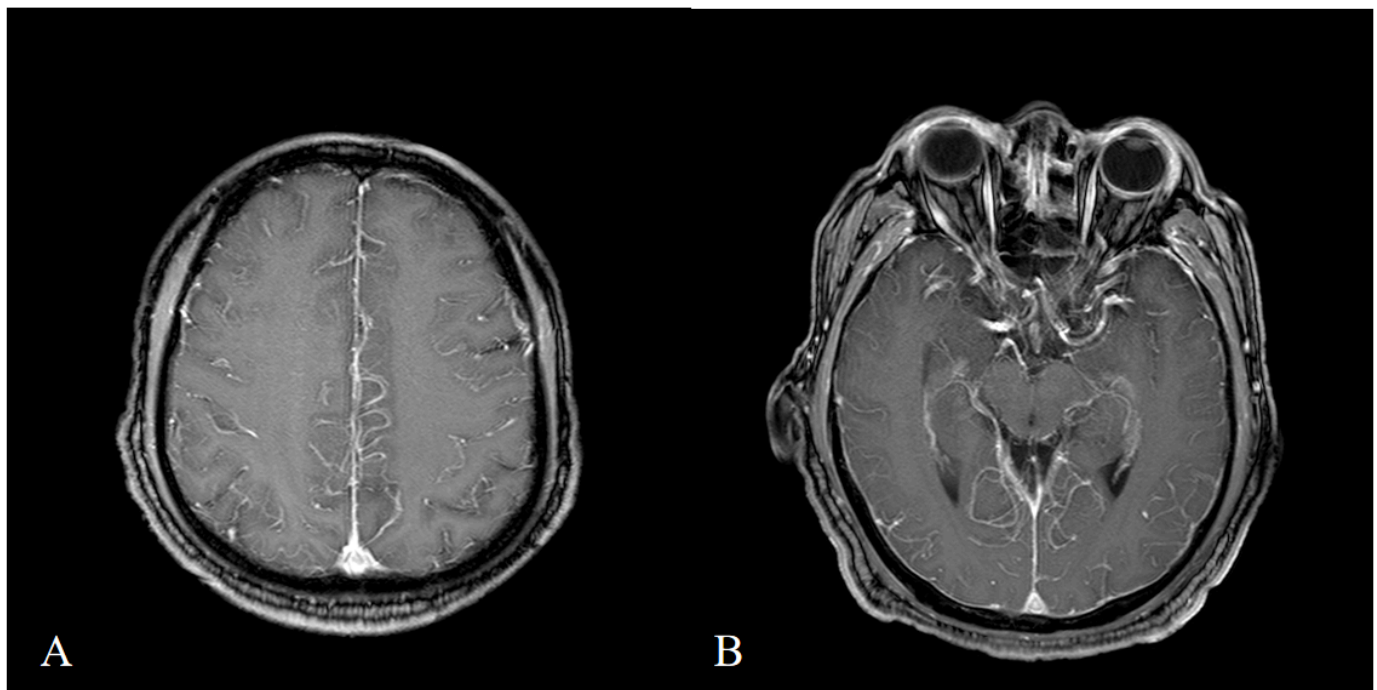


Figure 1

Contrast-enhanced brain magnetic resonance imaging (MRI) performed on Day 1 after admission demonstrated marked meningeal enhancement over bilateral cerebral hemispheres, suggestive of an infectious process (A, B).

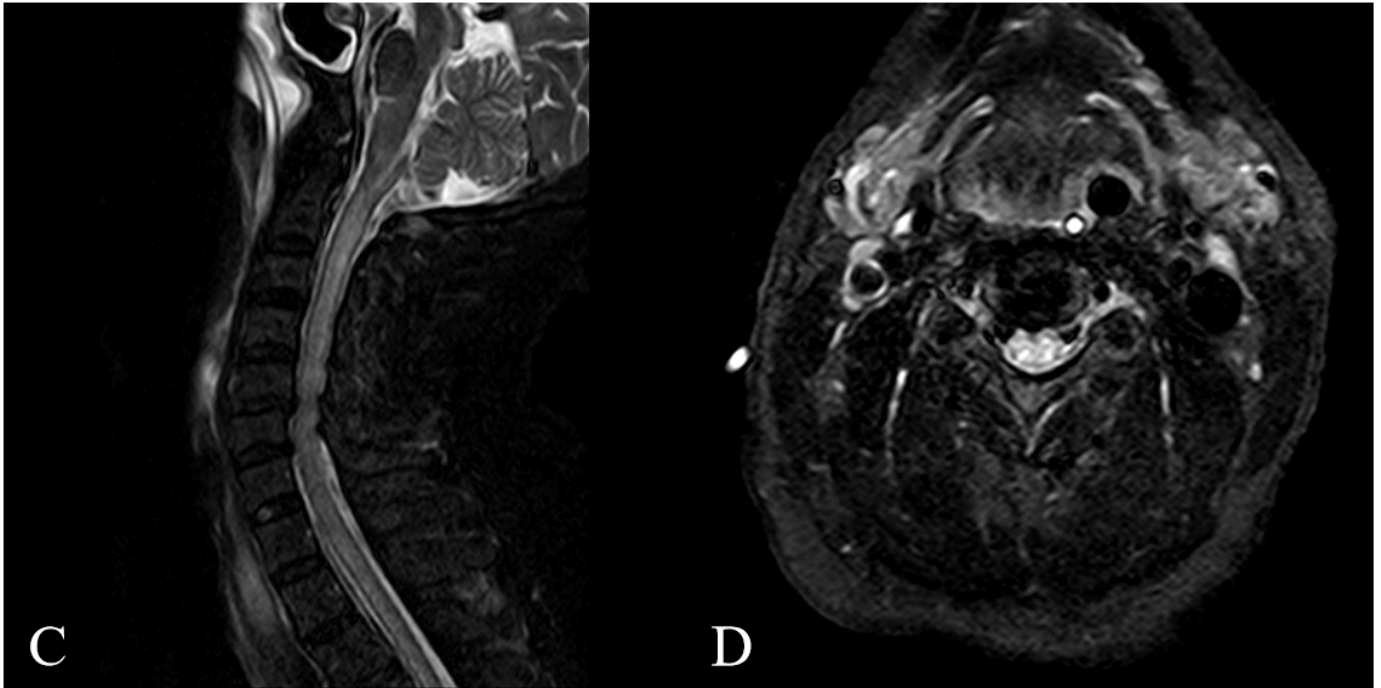


Figure 2

Contrast-enhanced cervical and thoracic spinal cord MRI demonstrating (C) sagittal thickening of the medulla oblongata and spinal cord from C2 to T12 levels with elongated abnormal signal intensities and mild enhancement, and (D) axial spinal cord thickening with central abnormal signal intensity and mild enhancement at the C5 level, suggestive of an inflammatory process.

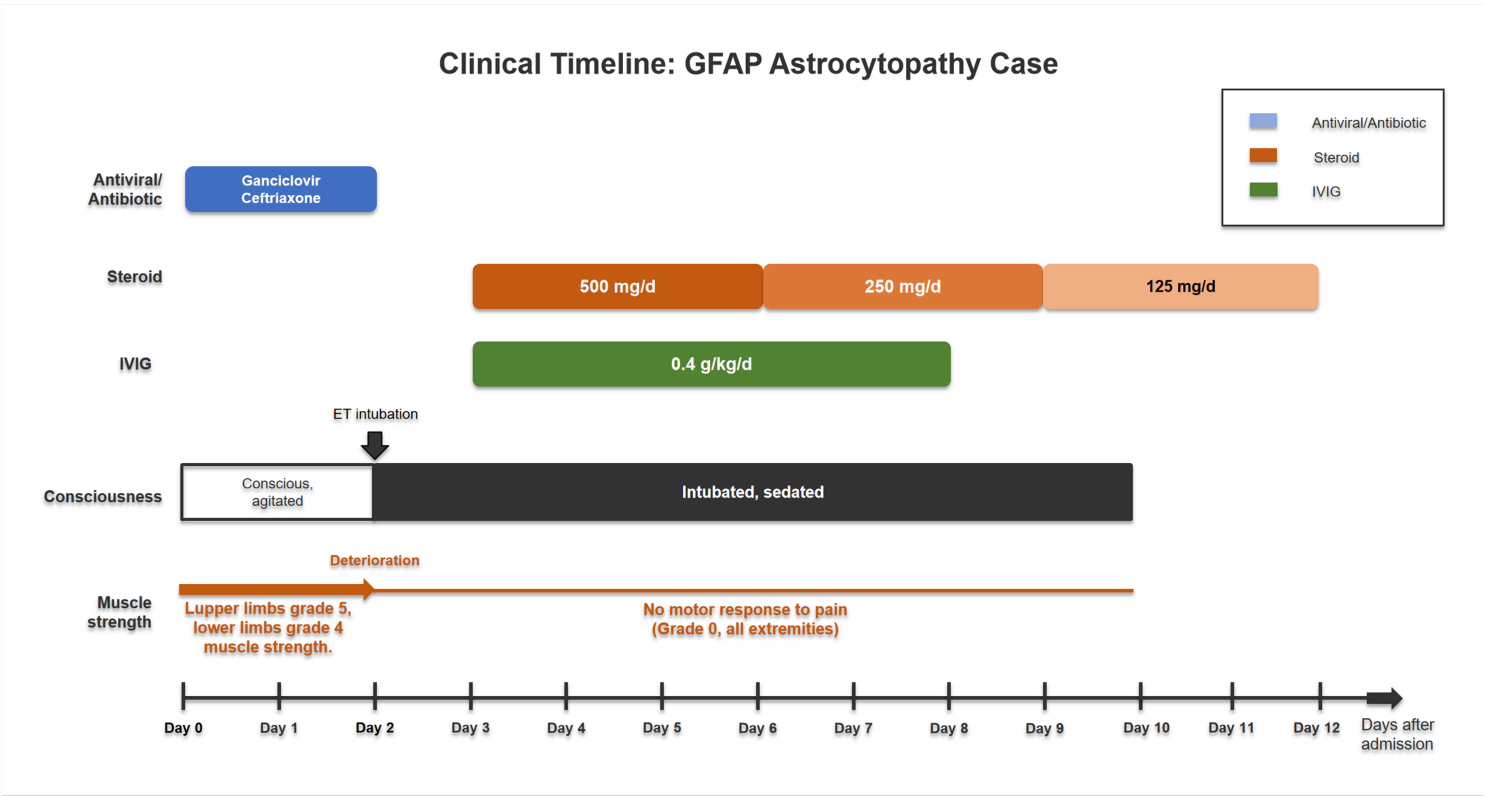


Figure 3

Clinical timeline of the patient from admission (Day 0) through Day 12 of hospitalization. Empirical ganciclovir and ceftriaxone were administered for suspected infection (Days 0–2); intravenous methylprednisolone (500 mg/d for days 3–5, 250 mg/d for days 6–8, and 125 mg/d for days 9–11) and IVIG 0.4 g/kg/d (5 days) were administered as first-line immunotherapy. Endotracheal intubation was required on Day 2 owing to respiratory failure, followed by sustained intubation and sedation. Motor function deteriorated progressively from grade 5 in the upper limbs and grade 4 in the lower limbs at baseline to absent motor response to pain (grade 0 in all extremities), despite ongoing immunotherapy.