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Autopsy Case of Meningoencephalomyelitis Associated With Glial Fibrillary Acidic Protein Antibody

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Abstract

Background and Objectives

To describe the autopsy findings and neuropathologic evaluation of autoimmune meningoencephalomyelitis associated with glial fibrillary acidic protein (GFAP) antibody.

Methods

We reviewed the clinical course, imaging, laboratory, and autopsy findings of a patient with autoimmune meningoencephalomyelitis associated with GFAP antibody who had a refractory course to multiple immunosuppressive therapies.

Results

The patient was a 70-year-old man who was diagnosed as GFAP antibody-associated autoimmune meningoencephalomyelitis. MRI of the head showed linear perivascular enhancement in the midbrain and the basal ganglia. Despite treatment with high-dose corticosteroids, plasma exchange, IV immunoglobulins, and cyclophosphamide, he died with devastating neurologic complications. Autopsy revealed a coexistent neuroendocrine tumor in the small intestine and diffuse inflammation in the brain parenchyma, perivascular spaces, and leptomeninges, with predominant T-cells, macrophages, and activated microglia. B-cells and plasma cells were absent. There was no astrocyte involvement with change in GFAP immunostaining.

Discussion

This case illustrates autoimmune meningoencephalomyelitis associated with GFAP antibody in the CSF and coexistent neuroendocrine tumor. The autopsy findings were nonspecific and did not demonstrate astrocyte involvement. Further accumulation of cases is warranted to delineate the utility and pathogenic significance of the GFAP autoantibody.

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Glossary

AQP-4 = aquaporin 4; **CLIPPERS** = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; **GFAP** = glial fibrillary acidic protein; **WDNET** = well-differentiated neuroendocrine tumor.

Case

A 70-year-old Caucasian man with dyslipidemia and depression presented to the emergency department with hand tremors for several months, progressive imbalance and falls, confusion, and insomnia for 2 weeks. He was alert and oriented with psychomotor slowing, with a temperature of 37.5°C, tachycardia of 109 beats per minute, and restlessness. Neurologic examination revealed increased tone in the neck and the left leg, diffuse myoclonic jerks, bilateral endpoint tremor, and symmetric hyperreflexia. Admission laboratory test results were significant for mild leukocytosis of 12.1 × 10^3/mL and hyponatremia of 126 mEq/L; thyroid stimulating hormone, glucose, urinalysis, and creatine kinase were normal. CT head was unremarkable.

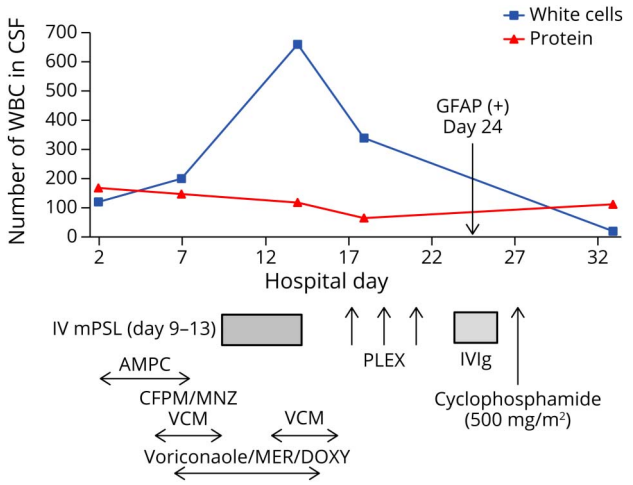
Initially, serotonin syndrome from concurrent bupropion and citalopram use was suspected, and cyproheptadine was started. However, he became lethargic and febrile (39.1°C) on day 2 of admission, requiring endotracheal intubation. CSF analysis on day 2 showed lymphocytic leukocytosis (nucleated cells 120/mm^3) and elevated protein (167 mg/dL). Abbreviated hospital course is shown in Figure 1. Hyponatremia was corrected with fluid resuscitation and cessation of citalopram not requiring prolonged fluid restriction. MRI of the head showed linear symmetric perivascular enhancement in bilateral crus cerebri and basal ganglia that were not present 10 days before admission (Figure 2, A–C), as well as thin subdural fluid collections in the posterior convexity concerning for subdural empyema and meningitis (Figure 2D). Magnetic resonance angiogram of the head was normal. MRI of the thoracic spine on day 6 showed long segment thoracic cord signal abnormalities with a possible enhancement (Figure 2F). Extensive infectious and rheumatological assessments were negative. SARS-CoV-2 polymerase chain reaction was not performed because this presentation occurred before the pandemic.

The patient was started on IV methylprednisolone 1 g/day for 5 days with a protracted taper. Findings on the MRI of the head and T-spine continued to improve (Figure 2, D and E). Inflammation in CSF peaked on day 14 with 660/mm^3 lymphocytes, with 5 oligoclonal bands, and IgG synthesis rate of 21.22. The patient underwent 3 sessions of plasma exchange. On day 24, the autoimmune encephalitis CSF panel came back positive for glial fibrillary acidic protein (GFAP) antibody, and a diagnosis of GFAP antibody-associated meningoencephalomyelitis was made. Anti-NMDA receptor antibody was negative. IV immunoglobulins were given, followed by cyclophosphamide 500 mg/m^2. Whole-body CT, PET-CT, and scrotal ultrasound were negative for malignancy. Despite the improvement in CSF and MRI findings, the patient continued to have severe myoclonus, requiring continuous sedation and 3 antiseizure drugs; EEG developed bifrontal epileptic discharges while on these medications. The patient was palliatively extubated and died on day 47. His family agreed to proceed with an autopsy.

Autopsy Findings

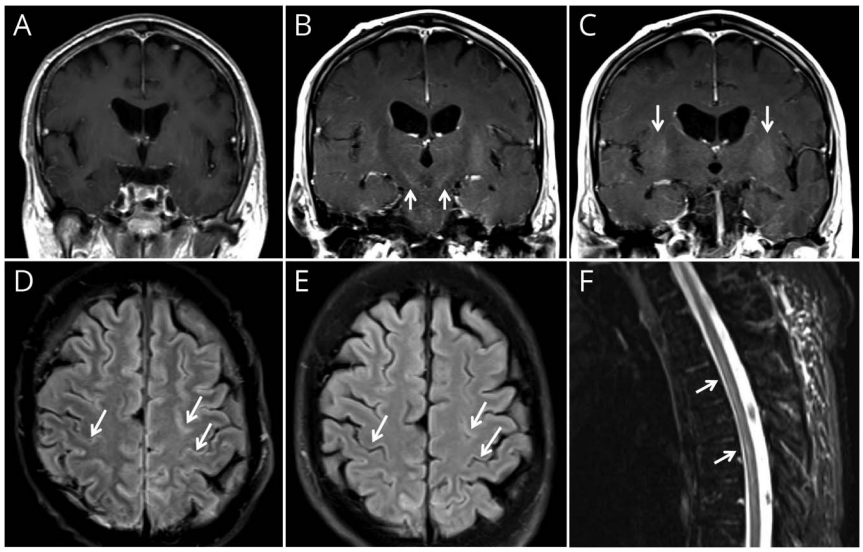
The autopsy revealed acute pneumonia and undiagnosed well-differentiated neuroendocrine tumor (WDNET) in the small intestine; this was negative for GFAP immunohistochemistry. Gross examination of the brain demonstrated diffuse mild leptomeningeal fibrosis over the convexities with scattered arachnoid granulations. Sectioning revealed severe edema of the cerebral hemispheres with enlarged gyri, narrow sulci, and central herniation affecting the midbrain. A thorough microscopic examination revealed variable degrees of inflammation involving the entire brain except for the cerebellum. The inflammatory infiltrates were perivascular with extension into the parenchyma (Figure 3A). There was no evidence of demyelination or loss of GFAP stain, nor

Figure 1 Schema of Hospital Course With Cerebrospinal Fluid White Blood Cells and Protein, and Attempted Treatments



X-axis represents hospital day, and Y-axis represents WBC in cerebral spinal fluid (CSF). AMPC = amoxicillin; CFPM = cefepime; DOXY = doxycycline; Ig = immunoglobulin; MER = meropenem; MNZ = metronidazole; mPSL = methylprednisolone; PLEX = plasma exchange; VCM = vancomycin; WBC = white blood cell.

Figure 2 MRI of the Head and Thoracic Spine Findings



(A) MRI of the head, T1 postcontrast 10 days before the admission without perivascular enhancement; (B) MRI of the head T1 postcontrast on day 4 of admission with linear perivascular enhancement in crus cerebri, and (C) in basal ganglia, pointed with arrows; (D) MRI of the head FLAIR on day 4 of admission showing areas of abnormal sulcal FLAIR hyperintensity along the cerebral convexities with pointed arrows; (E) MRI of the head FLAIR on day 26 of admission with resolution of sulcal abnormality; (F) MRI thoracic spine T2 on day 6 of admission, T2, sagittal view showing longitudinal intrinsic thoracic cord hyperintensity. FLAIR = fluid-attenuated inversion recovery.

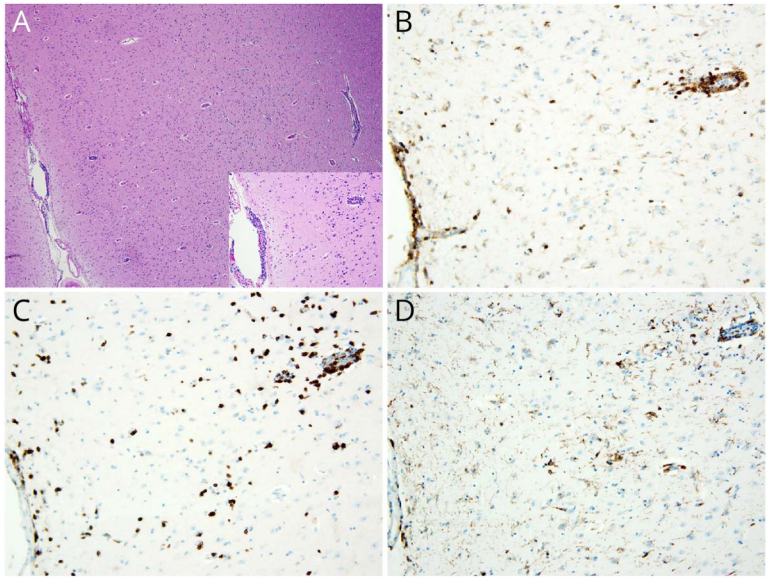
fragmented or macrophage-engulfed astrocytes; GFAP stain showed focal moderate cortical gliosis and some subpial gliosis. Aquaporin 4 (AQP-4) stain was not performed. There was no vasculitis or necrosis. The inflammatory cells were a mixture of $CD4^+$ and $CD8^+$ T lymphocytes and macrophages (Figure 3, B and C). No B lymphocytes or plasma cells were identified. CD68 immunostain showed prominent microglial activation and macrophages throughout the cortex and white matter, as well as highlighting perivascular and leptomeningeal infiltrates (Figure 3D). There were diffuse severe acute hypoxic-ischemic leukoencephalopathy and severe edema throughout the cortices. There were no Lewy bodies, inclusions, senile plaques, or neurofibrillary tangles as demonstrated by α-synuclein, β-amyloid, and Tau immunostains. The spinal cord was not examined.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This was a case report and no IRB approval was needed. The consent for autopsy was obtained from the patient's wife.

Figure 3 Neuropathologic Finding on Autopsy



Sections are from hippocampus. (A) H-E stain, 40×, representing inflammation in perivascular space, parenchyma, and leptomeningeal space; the inset represents H-E stain, 200×. (B) CD4 immunostain, 200×, representing helper T-cells; (C) CD8 immunostain, 200×, representing cytotoxic T-cells; (D) CD68 immunostain, 200×, representing microglial activation. H-E = hematoxylin-eosin.

Table 1 Pathologic Findings of GFAP Antibody Associated Autoimmune Encephalitis

Reference	N	GFAP antibody	Concurrent auto-antibodies	Response to immunosuppressive therapies	Type of specimen	Location of inflammation	Astrocyte involvement	Neuron loss	Demyelination	Types of inflammatory cells
Long et al.[3]	19	CSF, CBA	13 patients had serum antinuclear/endothelial cell/ cardiolipin/neutrophil cytoplasmic/double-stranded DNA/RA33/SS-A/Ro52 antibodies	18/19 patients were initially treated with corticosteroids, and 11 received IVIG; all discharged, 2 were lost to follow-up	Brain biopsy; 4	Perivascular space, brain parenchyma, Virchow-Robin spaces	Complete loss of AQP-4 and GFAP in a patient; local decreased GFAP and AQP-4 were found in the other 3 patients Reactive hypoplasia	Yes	Yes	Lymphocytes, monocytes, neutrophils, and activated microglias Prominent perivascular B cells ($CD20^+$) and T cells ($CD3^+$) distributed in the brain parenchyma Abundant antibody-secreting cells (CD138+) were noted in the Virchow–Robin spaces
Iorio et al.[5]	22	Serum and/or CSF, IFA, CBA	5 patients (GABAAR-IgG, 1; Yo-IgG, 1; IgG binding to unclassified antigens (UNCA), 3)	Response in 16 patients (84%)	Meningeal biopsy; 1	N/A	N/A	N/A	N/A	Necrotizing inflammatory process with $CD8^+$ lymphocytes, macrophages, and multinucleated giant cells
Shu et al.[4]	1	CSF, IFA and CBA	None	No improvement after corticosteroids and IVIG	Brain biopsy	Perivascular space, white and gray matter	None	None	None	Abundant $CD3^+$ and $CD4^+$ T lymphocytes; a few $CD8^+$ T cells and CD20 $^+$ B lymphocytes; scattered CD68 $^+$ macrophages and CD138 + plasma cells
Current case	1	CSF, IFA and CBA	None	No improvement after corticosteroids, IVIG, plasma exchange, and cyclophosphamide	Autopsy, whole brain	Perivascular space, brain parenchyma	None	Hypoxic-ischemic leukoencephalopathy	None	$CD4^+$ and $CD8^+$ T lymphocytes and macrophages; CD68 $^+$ activated microglias macrophages

Abbreviations: CBA = cell-based assay; GFAP = glial fibrillary acidic protein; IFA = immunofluorescent assay; IVIG = IV immunoglobulin.

Data Availability

All the data appear in the article.

Discussion

This article reports a case of autoimmune meningoencephalomyelitis with a positive GFAP antibody with an autopsy and complete neuropathologic evaluation of the whole brain. Autoimmune GFAP astrocytopathy defined by GFAP IgG positivity in the CSF is an emerging disease entity first described in 2016 as angiography-negative, corticosteroid-responsive subacute meningoencephalomyelitis with CSF lymphocytic pleocytosis.[1,2] Neuropathologic evaluation of the condition is limited to brain and meningeal biopsies of 5 patients to date, as summarized in Table 1.[3-5] One case series from China showed astrocytopathy with a loss or decrease of GFAP and AQP-4 stain with GFAP antibody in CSF, notably with concurrent autoantibodies such as p-ANCA, anti-endothelial cell, anti-MOG, antinuclear, anti-SSA, and anti-Ro-52 antibodies in 3 of 4 cases.[3] In our case, AQP-4 immunostaining or antemortem serum testing was not performed; however, there was no signs of astrocyte involvement with GFAP immunostaining, including loss or decrease of GFAP, fragmentation, or phagocytosis of the astrocytes. Our case goes against the causal pathogenicity to astrocyte decay of the GFAP antibody in CSF, in contrast to the well-documented pathogenicity of AQP-4 antibody in neuromyelitis optica spectrum disorders resulting in astrocytopathy.[6-9]

The neuropathologic finding of our case was relatively nonspecific. Differential diagnoses of the neuropathologic findings include chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) and anti-NMDA encephalitis. In CLIPPERS, the mainstay of inflammatory cells is CD4 T-cells, indicating possible major histocompatibility complex class II-restricted antigen presentation or allergic reaction, along with microglia, histiocytes, and B cells. Vascular damage with necrosis, fibrin deposition astrocytic fragmentation, neuronophagia, and focal demyelination have been seen.[10] Our case with inflammation in gray and white matter of whole brain contradicts CLIPPERS, which has the predilection to the white matter of the hindbrain. As for NMDA encephalitis, the hallmark of pathology is perivascular B-cell cuffing and scattered T cells in the parenchyma, which were not seen in our autopsy. Our case possibly was paraneoplastic autoimmune encephalitis with the GFAP-negative WDNET; this could infer that the GFAP antibody in the CSF was a byproduct of the ongoing inflammation, and rather not a causative cross-reacting autoantibody induced by the concurrent neoplasm.

Periventricular perivascular enhancement is perceived as a classic finding of autoimmune astrocytopathy seen in half of cases; however, it is unknown if this directly indicates astrocyte involvement.[2,3,11] In our case, the perivascular enhancement in the midbrain and basal ganglia on MRI did not correlate with astrocyte involvement in the autopsy. Collectively, because positive GFAP antibody in CSF or periventricular perivascular enhancement on MRI does not confirm astrocytes involvement in the inflammation, the term "astrocytopathy" should be used carefully until the pathologic demonstration. Nevertheless, we believe that identifying associated autoantibodies would help to guide care of otherwise indistinguishable autoimmune encephalitides, possibly augmenting cancer screening in select cases. Further accumulation of cases is needed to better define this emerging disease entity.

We have important limitations in our report. First, this was a postmortem study after a prolonged disease course, and the cardiopulmonary compromise shortly before death likely affected the pathology with hypoxic-ischemic changes. The extensive immunotherapies also likely altered the pathology findings, evidenced by antemortem oligoclonal bands in the CSF without postmortem B and plasma cells. Finally, we did not assess the spinal cord or stain for AQP-4.

GFAP antibody is implicated in autoimmune meningoencephalitis; however, there is limited evidence that this is the causative antibody provoking downstream inflammation with astrocytes. Our case with CSF-positive GFAP antibody did not have astrocytic involvement in the autopsy, suggesting that GFAP antibody was a bystander autoantibody with the inflammation. The causality of GFAP antibody has to be investigated with more pathologic evaluations of similar cases.

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Appendix Authors

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Mai Yamakawa, MD	Department of Neurology, University of Kansas Medical Center	Drafting/revision of the manuscript for content, including medical writing for content
Keenan O. Hogan, MD	Department of Pathology and Laboratory Medicine, University of Kansas Medical Center	Major role in the acquisition of data and analysis or interpretation of data
John Leever, MD	Department of Neurology, University of Kansas Medical Center; Department of Radiology, University of Kansas Medical Center	Major role in the acquisition of data and analysis or interpretation of data
Yasir N. Jassam, MBChB, MRCP (UK)	Department of Neurology, University of Kansas Medical Center; Hoag Memorial Hospital Presbyterian, Pickup Family Neuroscience Institute, Newport Beach, CA; Dr. Jassam's affiliation has changed since the completion of this work.	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data

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