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An unusually fulminant case of encephalomyelitis in an 80 year old

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ABSTRACT

Background: There have been reports of demyelinating syndromes in association with COVID-19 and to a much lesser extent COVID 19 vaccines. The association between demyelination and vaccines, in general, remains controversial. We review a presentation of fulminant demyelination, and discuss antecedent COVID-19 vaccination, the formulation of a broader differential diagnosis and ultimately the pathologic diagnosis.

Case presentation: An 80-year-old woman presented with seizure, encephalopathy, quadriparesis and ultimately expired. She received a SARS-CoV-2 vaccine one day prior. Imaging revealed contrast enhancing cerebral lesions, longitudinally extensive transverse myelitis. CSF was markedly inflammatory. Pathologic examination of the CNS lesions revealed demyelination and inflammation beyond white matter, not restricted to a perivenular distribution.

Conclusion: This case depicts a seemingly fulminant course of a diffuse demyelinating syndrome characterized clinicopathologically as Marburg's variant of multiple sclerosis. There are several unique aspects of this case including the extremely rapid course, the unusual evolution of CSF abnormalities, with hypoglycorrhachia and markedly elevated protein. The proximity to vaccination is a pertinent association to document, though we cannot unequivocally prove causation.

Introduction

We discuss an atypical case of fulminant demyelination in an 80-year-old woman which was ultimately fatal. We report this case to outline a uniquely fulminant course, with rapidly evolving cerebrospinal fluid [CSF] findings including profound hypoglycorrhachia. We discuss the formulation of a broad differential diagnosis, including the temporal proximity to the COVID-19 vaccination and ultimately review the pathologic diagnosis.

Case presentation

An 80-year-old woman with a history of chronic obstructive pulmonary disease, hypertension, hyperlipemia and anemia presented with persistent encephalopathy and left hemiparesis after a generalized seizure.

At baseline she was fully independent and cognitively intact. She had been experiencing a constellation of symptoms for several months prior to this presentation, including migratory pains, depression, malaise, weight loss, night sweats and worsening of chronic anemia. Investigations for these symptoms included broad blood tests, bone marrow biopsy and gastrointestinal endoscopies, and were all unrevealing. Lung nodules were identified on chest imaging and led to a bronchoscopy which was also normal.

One day prior to presentation, she received the first dose of the COVID–19 vaccine [Pfizer-BioNTech]. Several hours later she developed headache and lower limb heaviness. The next morning, she experienced a generalized tonic clonic seizure lasting one minute followed by a postictal state. She was brought to a local hospital. On examination she exhibited decreased responsiveness and left hemiparesis. She was started on Levetiracetam. CT head showed no abnormalities. Lumbar puncture demonstrated CSF pleocytosis of 220 [76% lymphocytes], protein of 145 mg/dL, and glucose of 59 mg/dL. She was started on empiric treatment with ceftriaxone, vancomycin and acyclovir. MRI brain with diffusion weighted imaging [DWI], revealed foci of signal hyperintensity in the right periatrial white matter, left temporooccipital periventricular white matter and left mesial temporal lobe. [See Fig. 1A and B].

She was transferred to our facility and on day 1 suffered a cardiac arrest. She was resuscitated after 3 min and was transferred to the neurological intensive care unit. On examination she was afebrile throughout, she exhibited occasional eye opening to voice and did not follow commands. Pupillary and corneal reflexes were present. All limbs were flaccid and plegic. Blood serum infectious work was negative for galactomannan, beta-D-glucan, QuantiFERON and HIV. Serum NMO and

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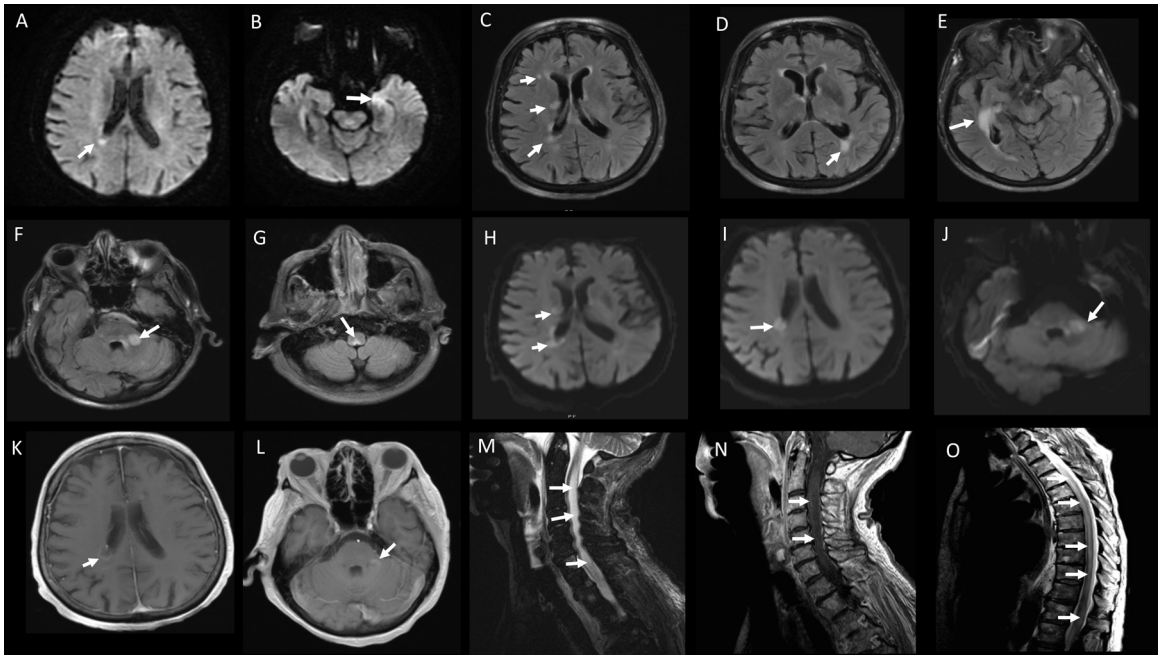

Fig. 1. MRI Brain Sequences; A & B: DWI; [A] Right periventricular restricted diffusion and [B]Left mesial temporal lobe restricted diffusion. C-G: T2 Flair; [C], multiple foci of high signal right periventricular, [D] high signal left temporal horn periventricularly, and [E] high signal right temporal horn perimetrically, [F] high signal left middle cerebellar peduncle, [G] high signal around the 4th ventricle. H, I & J: DWI; [H]and [I]; Restricted diffusion periventricularly and [J] restricted diffusion left MCP. K & L: T1– Post contrast, [K] Incomplete ring of enhancement right periventricular and left MCP [L]. M: MRI Cervical Cord T2: Increased signal throughout cervical spinal cord, N: MRI Cervical cord T1-Post contrast: Faint contrast enhancement in the ventral cervical cord, O: MRI Thoracic Spine T2: High signal throughout the thoracic cord.

MOG antibody were negative. Repeat MRI revealed FLAIR sequence hyperintense lesions periventricularly [Fig. 1C-E], in the left middle cerebellar peduncle [MCP] [Fig. 1F] and medulla [Fig. 1G]. The extent of restricted diffusion had increased in the periventricular regions [Fig. 1H and I] and a new area of restricted diffusion was apparent in the left MCP [Fig. 1J]. There was an incomplete ring of contrast enhancement in the periventricular and left MCP regions [Fig. 1K and L respectively]. MRI spine revealed high T2 signal with expansile appearances throughout the spinal cord [Fig. 1M, O], with associated contrast-enhancement, particularly in the ventral cervical cord [Fig. 1N]. Repeat CSF examination revealed pleocytosis of 28 [72% lymphocytes], protein of 610 mg/dL, and glucose of 28 mg/dL. She was treated with 5 days of IV methylprednisolone and empiric rifampicin, isoniazid, pyrazinamide and ethambutol to cover the possibility of tuberculosis.

Body PET scan revealed abnormal radiotracer uptake involving the cervical spinal cord and to a lesser extent the thoracic spinal cord, in addition to the left cerebellar peduncle, and right mesial temporal lobe. Multifocal consolidative opacities in the lung were moderately FDG avid, which was felt to reflect an infectious or inflammatory process. She underwent bronchoscopy and fine needle aspirate revealed scant Aspergillus species, Stenotrophomonas maltophilia and no evidence of neoplasia. Bactrim was added for Stenotrophomonas coverage. A 3rd CSF examination revealed 33 nucleated cells, protein of 790 mg/dL and glucose of 15 mg/dL. CSF beta-d-glucan was positive and galactomannan was negative. All CSF bacterial, fungal and mycobacterial cultures were negative. Repeat MRI brain after 4 days of IV methylprednisolone demonstrated that the left middle cerebellar peduncle lesion was slightly increased in extent and conspicuity, with decreased enhancement. The majority of the other lesions also demonstrated an increase in extent and conspicuity of predominantly peripheral restricted diffusion and enhancement. EEG monitoring revealed focal epileptiform discharges over the left posterior quadrant and diffuse delta-theta slowing of the background.

Further consideration was given to plasmapheresis, intravenous immunoglobulin and empiric amphotericin however the patient died before this was done. Postmortem examination of the brain and spinal cord revealed widespread destructive sharply demarcated demyelinating lesions with sheets of macrophages, associated with focal leptomeningeal and perivascular chronic inflammation composed of numerous T-cells, scant B-cells, and scattered plasma cells. The demyelinating areas did not display a perivenular distribution. The inflammatory infiltrate extended beyond the white matter in some areas. No organisms or evidence of neoplasia was identified. [See Fig. 2A-F]

Discussion

In formulating the differential diagnosis, several factors were considered. The preceding malaise, weight loss, night sweats, and migratory pain, invoked the possibility of an inflammatory or infectious process. The CSF beta-d-glucan raised concern for fungal infection; this was undermined by the negative serum beta-d-glucan, galactomannan, and CSF galactomannan.

On the basis of the clinicoradiological syndrome of an encephalomyelitis after vaccination, a fulminant demyelinating syndrome, was a major consideration. A perplexing component was the profound hypoglycorrhachia, markedly proteinaceous and pleocytotic CSF, which is unusual in ADEM and again invoked consideration of infective etiologies. (Pohl et al., 2016a) In ADEM, CSF leukocytosis is typically $<50/mm^3$, and protein is less 100 mg/dL. Interestingly, a case report of post COVID-19 infection related ADEM did describe the development of hypoglycorrhachia. (Zoghi et al., 2020) Ultimately serial CSF examination and direct pathology did not demonstrate evidence of Central Nervous System [CNS] infection.

The relationship between vaccinations and demyelination remains controversial, due to rare occurrence of this phenomenon and the inherent difficulty in proving causality. Review of the literature strongly

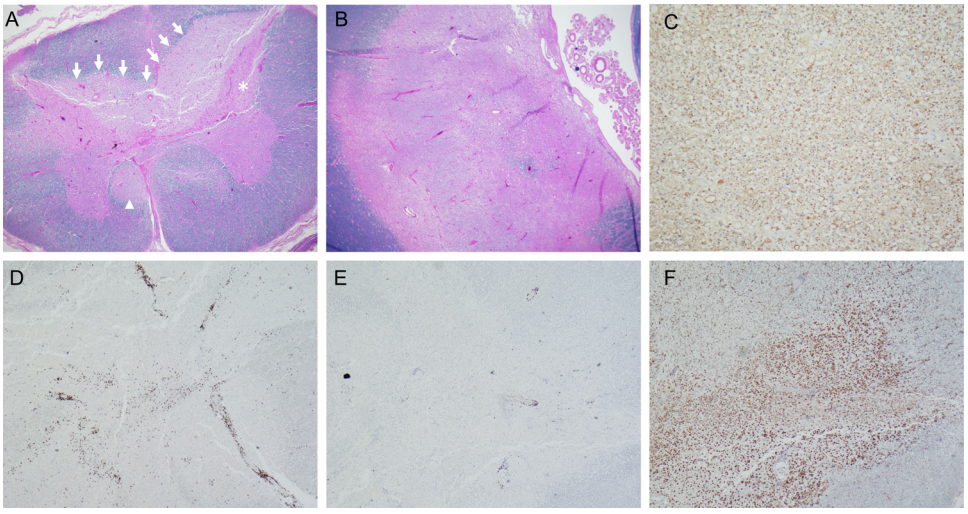

Fig. 2. Microscopic postmortem findings. Cross section of the cervical spinal cord stained with Luxol H&E (panel A) demonstrates a large area of demyelination with a sharp border (arrows), predominantly affecting the dorsal columns with focal extension into the gray matter (posterior horn, asterisk) and less prominent involvement of the anterior white matter tracts (arrowhead; original magnification 20x). Coronal section of the right periventricular lesion stained with Luxol H&E (panel B) displays a sharply demarcated area of demyelination characterized by pink appearance due to loss of myelin (original magnification 50x). Immunohistochemistry for neurofilament protein (panel C, original magnification 200x) highlights relative preservation of axons in an area of myelin loss in the cervical spinal cord, consistent with a demyelinating process. Immunohistochemistry for inflammatory markers in the cervical spinal cord shows a moderate perivascular and parenchymal T-cell infiltrate (CD3, panel D, original magnification 100x); with scant associated B-cells (CD20, panel E, original magnification 100x). Immunohistochemistry for CD68 (panel F, original magnification 200x) labels sheets of macrophages representing the main population of cells in all lesions.

suggest that infections convey a much greater risk of ADEM than vaccination. (Karussis and Petrou, 2014). One feature that is atypical for vaccine-related ADEM is the fulminant onset of demyelination within one day of vaccination. The onset of ADEM is typically 2 days to 4 weeks after antigenic trigger. Thus vaccination less than one day prior, would be an unusually accelerated immunogenic response were this to be the culprit antigen. (Tenembaum et al., 2007)(Pohl et al., 2016b)

There have been at least 13 reports of post COVID-19 infection related ADEM. (Maury et al., 2021) In contrast, to our knowledge, no cases of post mRNA vaccine related ADEM have been described. 2 cases of post COVID-19 vaccine ADEM have been reported in relation to inactivated vaccination [sinovac]. (Cao and Ren, 2021) (Ozgen Kenangil et al., 2021) One case described a 24 year old woman with onset of encephalopathy, followed by seizure, and typical MRI brain appearances, 2 weeks following vaccination. (Cao and Ren, 2021) The second case describes a 46 year old woman who presented, 4 weeks after vaccination, with seizure, and typical MRI findings though without encephalopathy. (Ozgen Kenangil et al., 2021)

ADEM is most often seen in children and young adults, though onset in adults is recognized. (Tenembaum et al., 2007) The sudden onset encephalopathy, seizure and imaging appearances of diffuse T2 FLAIR changes in brain and spinal cord, was felt consistent with ADEM. The incomplete ring of contrast-enhancement in the left MCP and periventricularly were typical in location and morphology for demyelination. (Tenembaum et al., 2007)(Pohl et al., 2016b)

Pathology examination demonstrated demarcated demyelination and inflammatory infiltrates beyond the perivenular distribution typically seen in ADEM. (Pohl et al., 2016a) (Popescu and Lucchinetti, 2012) The pathology was thus more consistent with multiple sclerosis. In the context of the rapid course and pathologic findings, this case is perhaps characterized clinicopathologically as a fulminant Marburg Variant with manifest encephalomyelitis. Some authors consider monophasic presentations of Marburg's to be a fulminant iteration of ADEM. (Rovira et al., 2016)

Conclusion

This case depicts a seemingly fulminant course of a diffuse demyelinating syndrome characterized clinicopathologically as Marburg's variant of multiple sclerosis. There are several unique aspects of this case including the extremely rapid course, the unusual evolution of CSF abnormalities, with hypoglycorrhachia and very elevated protein. The temporal proximity to vaccination is a pertinent association to document, though we of course are unable to unequivocally prove causation.

Author roles

The first draft of the manuscript was written by Kevin Kyle. All authors contributed to the manuscript conception and organization. All authors commented and revised previous versions of the manuscript. All authors read and approved the final manuscript.

Ethical compliance statement section

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Declaration of Competing Interest

The authors declare that there are no conflicts of interest relevant to this work

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