Fatal Post COVID mRNA-Vaccine Associated Cerebral Ischemia

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Abstract

Background: Venous thromboses have been linked to several COVID-19 vaccines, but there is limited information on the Moderna vaccine's effect on the risk of arterial thrombosis. Here we describe a case of post-Moderna COVID-19 vaccination arterial infarct with vaccine-associated diffuse cortical edema that was complicated by refractory intracranial hypertension. **Case Summary:** 24 hrs after receiving her first dose of the Moderna COVID-19 vaccine, a 30-year-old female developed severe headache. Three weeks later she was admitted with subacute headache and confusion. Imaging initially showed scattered cortical thrombosis with an elevated opening pressure on lumbar puncture. An external ventricular drain was placed, but she continued to have elevated intracranial pressure. Ultimately, she required a hemicraniectomy, but intractable cerebral edema resulted in her death. Pathology was consistent with thrombosis and associated inflammatory response. **Conclusion:** Though correlational, her medical team surmised that the mRNA vaccine may have contributed to this presentation. The side effects of COVID-19 infection and vaccination are still incompletely understood. Though complications are rare, clinicians should be aware of presentations like this one.

Keywords

COVID-19, Moderna vaccine, cerebral edema, neurology, stroke

Consent

Family consent to publish this case was obtained both verbally and written. The conversation was documented in our institutions electronic medical record.

Case Presentation

A 30-year-old woman with prior asymptomatic COVID-19 infection three months earlier developed severe, throbbing bifrontal headache 24-hours after first dose of the mRNA COVID-19 vaccine (Moderna). The headaches were atypical, prompting evaluation by her primary care provider and three emergency department visits where vital signs and neurologic examinations were normal. She had a history of class I obesity, but no prior headaches. Symptomatic management for presumed migraine did not alleviate the headaches. Three weeks after vaccination, she developed blurred vision and confusion, prompting further emergency evaluation. At this time, imaging of her head was first obtained. Computed tomography (CT) of her head was normal, and lumbar puncture revealed an opening pressure of 27cmH20 with lymphocytosis (Table 1). A brain MRI with contrast showed multiple punctate areas of diffusion restriction in occipital regions but no evidence of large arterial or venous occlusion. There was no evidence of abnormal enhancement (Figure 1A). Upon transfer to this hospital, the patient endorsed a bifrontal headache with photophobia. Complete blood count was without leukocytosis, extended chemistry panel, and toxicology screening were normal. Repeat lumbar puncture revealed an opening pressure of 50mmH20 and rising lymphocytic pleocytosis (Table 1). Broad spectrum antimicrobial coverage was started. Her mental status acutely worsened later that evening, and she was noted to have a new left hemiparesis. Vitals were notable for fever and tachycardia. CT/CT angiography with perfusion were without major

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Table 1. Lab Test Analysis.

Cerebrospinal Fluid (CSF) Profiles:	TNC (cells/μl)	RBC (cells/μl)	Lymphocytes(%)	Protein (md/dl)	Glucose (mg/dl)	OP (mmH20)
CSF exam #1 via LP	143	243	96	67	57	27
CSF exam #2 via LP (24-hrs later)	238	5	96	110	57	52
CSF exam #1 via EVD (24-hrs later)	69	1900	94	35	113	

CSF Studies:	**Results**	**Serum Studies:**	**Results:**	
Arbovirus Ab IgM and IgG	Negative	HBsAg	Neg	
EBV Virus DNA, PCR	Negative	HBsAb	Pos	
Enterovirus RNA, Qualitative RT-PCR	Negative	HBcAb	Neg	
Meningitis/Encephalitis Panel	Negative	HCV Ab	Neg	
HIV-1 RNA, PCR	Negative	Lyme Ab	Neg	
HSV 1&2 Quantitative PCR	Negative	EBV PCR	Neg	
CMV DNA, Qualitative PCR	Negative	HIV	Neg	
MOG Ab	Negative	VZV	Neg	
		ANA	Neg	
		ANCA	Neg	
		CRP	5	
		C3	123	
		C4	29	\
		Cryoglobulin	Neg	
		anti-dsDNA Ab	Neg	
		anti-Smith Ab	Neg	
		anti-RNP	Neg	
		MOG Ab	Neg	

CSF Analysis: TNC indicates Total Nucleated Cells; RBC, Red Blood Cells; LP lumbar puncture; EVD External Ventricular Drain; OP opening pressure; Ab antibody; Ig immune globulin; Arborvirus panel includes: IgG and IgM for Calif Virus (LaCrosse), East Equine Encephalitis (EEE), St. Louis Encephalitis, West Equine Encephalitis; EBV Epstein Barr virus; PCR polymerase chain reaction; Meningitis Encephalitis Panel includes: Escherichia Coli, Haemophilus Influenzae, Listeria monocytogenes, Neisseria Meningitides, Streptococcus Agalactiae, Streptococcus Pneumoniae, Cytomegalovirus, Enterovirus, Herpes Simplex Virus 1, Herpes Simplex Virus 2, Human Herpesvirus 6, Human Parechovirus, Varicella Zoster Virus, Cryptococcus neoformans and gattii. HSV herpes simplex virus; CMV cytomegalovirus; MOG Myelin Oligodendrocyte Glycoprotein antibodies are associated with acute disseminated encephalomyelitis (ADEM). Serum Analysis: ANA antinuclear antibody, ANCA antineutrophil cytoplasmic antibod, C3 complement component 3, C4 complement component 4, CRP c-reactive protein, HBsAg hepatitis B surface antigen, HbsAb antibody to hepatitis b surface antigen, HbcAb hepatitis b core antibody, HCV Ab hepatitis c virus antibody, EBV epstein barr virus, HIV human immunodeficiency virus, VZV varicella zoster virus, dsDNA anti double stranded DNA antibody, anti-RNP anti-ribonucleoprotein antibody.

vessel occlusion and no evidence for low pressure/post-LP herniation. Labs were notable for mild thrombocytopenia (119 K/u) and elevated D-dimer (3457) with a negative platelet factor 4 antibody (PF4). Given elevated ICP, hyperosmolar therapy was given and an external ventricular drain (EVD) was placed. Studies to evaluate for infectious etiology, primary angiitis of the CNS, secondary CNS vasculitis, or one of its mimics were sent (Table 1). CSF cultures and PCR testing returned negative (Table 1), and she was started on high dose intravenous methylprednisolone followed by intravenous immune globulin. Intracranial pressure remained refractory to maximal medical management including deep sedation, paralysis and hypothermia, prompting a right decompressive hemicraniectomy. Subsequent brain MRI showed extensive bilateral subacute infarcts without evidence of infection or cerebral venous sinus thrombosis (CVST) (Figure 1B). Upper extremity and bilateral lower extremity ultrasounds to evaluate for systemic thromboses were negative for deep vein thrombosis. The patient expired from refractory cerebral edema. Brain autopsy showed leptomeningeal, perivascular and focal intraparenchymal infiltrates of CD8 and CD4-positive T-cells in association with intravascular thrombi (Figure 1C and D). There was no CVST or demyelination. Fungal and bacterial stains were negative.

Discussion

The diffuse endothelial damage and vessel wall inflammation seen on pathology suggested an underlying pro-thrombotic state and T cell inflammatory response. A number of case reports have demonstrated cerebral venous sinus thrombosis and systemic thromboses post-COVID-19 vaccination.[1-3] While this patient did not have CVST, CVST has been previously associated with COVID-19 vaccination[1-3] where thrombocytopenia is frequent and termed 'vaccine-induced prothrombotic immune thrombocytopenia' (VIPIT). VIPIT is similar to heparin-induced thrombocytopenia (HIT) with antibodies directed against platelet factor 4 (PF4).[1,4,5] Mild thrombocytopenia occurred in this case, but PF4 antibodies

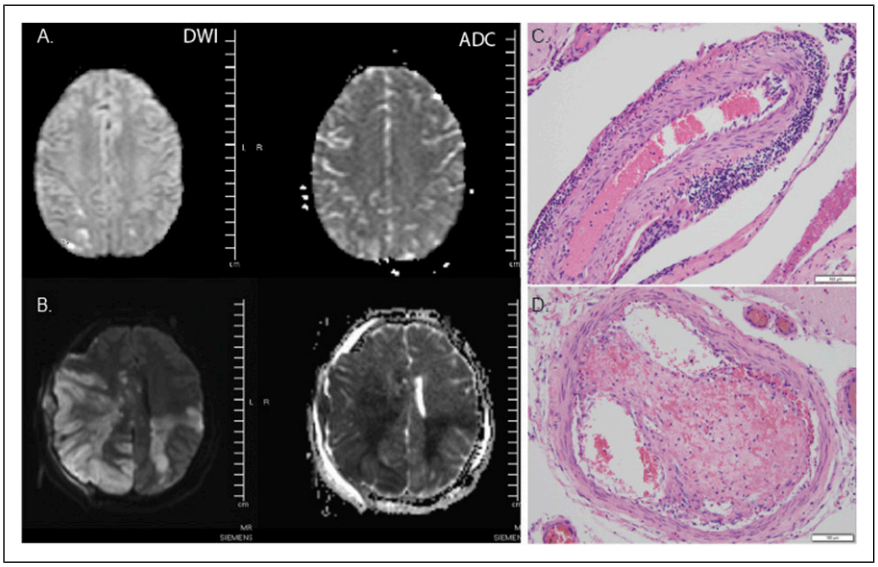

Figure 1. Imaging **A**: Representative axial MRI brain images on day of admission. **B**: Eight days after admission, left panels represent diffusion weighted (DWI) sequences and right apparent diffusion coefficient (ADC) images. **C.** Hematoxylin and eosin **(**H&E)-stained section of leptomeningeal vessel with lymphocytic cuff **D.** H&E-stained section of leptomeningeal blood vessel with intraluminal organizing thrombus. Scale bars =100um.

were negative. The arterial infarct in this case is likely related to a pro-thrombotic state but with a different underlying mechanism to that seen in venous thrombosis. Due to the large volume of infarction, the patient was not started on anticoagulation after extensive discussion of the risks vs potential benefit.

In summary, administration of COVID-19 vaccine was considered a possible cause of the extensive multifocal arterial thromboses with associated inflammatory response and elevated intracranial pressure given the temporal association. The mechanism for initial elevation in intracranial pressure is not known but may relate to cerebral autoregulatory changes in the setting of cortical microvascular thrombosis. Review of the medical literature and vaccine adverse event reporting system (VAERS) produced no similar cases, suggesting the condition is extremely rare, but a potentially fatal vaccine-associated event.

Declaration of Conflicting Interests

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