COVID-19-vaccines/immune-globulin/methylprednisolone

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Immune associated CNS-disorders, inflammatory disorders and no therapeutic response: 5 case reports

In a case-series within a single 23-hospital health system, five patients including three women and two men (aged 27-81 years) were described, who developed acute disseminated encephalomyelitis (ADEM), neuromyelitis optica spectrum disorder (NMOSD), multiple sclerosis (MS)-like syndrome or meningoencephalitis following administration of tozinameran or elasomeran for COVID-19 vaccination. One patient additionally exhibited no therapeutic response during treatment with methylprednisolone and immune-globulin for ADEM [*not all routes stated; dosages not stated*].

The 81-year-old man (case 1 of the article) presented to the emergency department with rapid-onset acute change in mental status with severe encephalopathy, which started 13 days following administration of the first dose of the elasomeran [manufactured by Moderna] for COVID-19 vaccination. He initially experienced prodromal symptoms of viral-like illness marked by several days of fatigue, low-grade fever and myalgia. He had a fever of 102°F. Neurological examination showed minimal horizontal eye movements upon oculocephalic testing, absent pupillary response to light, absent right corneal reflex, minimal response to noxious stimuli, right gaze preference, extensor plantar responses bilaterally and diffuse hypertonicity. Serologies revealed mild leukocytosis with WBC at 12,5000/µL, elevated ESR at 86 mm/hr and CRP at 10.8 mg/L. CSF analysis revealed opening pressure at 26 cmH2O. His neurological condition worsened rapidly to a comatose state within the subsequent 24 hours and required emergent intubation. He continued to have spike fevers despite receiving unspecified broad-spectrum antibiotics. On hospital day 5, brain MRI with gadolinium demonstrated a diffusion restricting lesion involving the right dorsal medulla with corresponding T2 FlAIR hyperintensity, very faint midbrain, left pontine and thalamic T2 FlAIR hyperintensity, and minimal T2 sulcal hyperintensity, which was suggestive of a CNS inflammatory disorder. On hospital day 9, repeat CSF analysis showed a mild lymphocytic pleocytosis with a WBC count of 11 cells/µL and protein of 52 mg/dL. For presumed CNS inflammatory disorder, he received a 5-day trial of IV immune-globulin [immunoglobulin] without clinical improvement. On day 10, he was found to have *Clostridium difficile* infection [*aetiology not stated*], for which he was treated with vancomycin. On hospital day 16, a right frontal lobe biopsy was performed including leptomeninges and cortex, which showed an acute inflammatory demyelinating process. On hospital day 17, repeated brain MRI with gadolinium revealed multiple, non-enhancing, T2 hyperintense lesions involving cerebral peduncles, bilateral frontoparietal lobes, thalami, lentiform nuclei, pons and right posterior medulla. His clinical and neuroradiological findings were consistent with ADEM. The occurrence of ADEM was associated with his recent COVID-19 vaccination. He received IV methylprednisolone, IV immune-globulin, later plasmapheresis for ADEM, without a clinical response. On hospital day 26, he eventually died due to ADEM and haemorrhagic shock of probable gastrointestinal origin.

The 63-year-old woman (case 2 of the article), who had hypothyroidism and hyperlipidaemia presented with a 2-week history of severe back pain, rapidly progressive paraparesis and urinary retention. Her neurological symptoms started at 1 week following first dose of tozinameran [manufactured by Pfizer-BioNTech] for COVID-19 vaccination. She was found to have leukopenia with WBC 2550/L. Neurological examination showed mild weakness of the right arm, moderate paraparesis of the lower extremities and reduced right facial sensation. The brain, cervical and thoracic cord MRI with gadolinium demonstrated a contrast-enhancing left thalamic lesion and a non-enhancing, longitudinally extensive T2 hyperintensity extending from T6 to T12 levels, consistent with longitudinally extensive transverse myelitis (LETM). CSF analysis showed a pleocytosis of 33 cells/µL with 91% lymphocytic predominance and an elevated protein of 57 mg/dL. Biopsy of the left thalamic lesion revealed a histiocytic inflammatory process, focal perivascular lymphocytosis and reduced astroglial density at the center of the lesion. Based on the subsequent detection of CSF anti-AQP4 antibody, and reduced astroglial staining reflective of astroglial injury known to be associated with anti-AQP4 antibody, a diagnosis of NMOSD was made. The occurrence of NMSOD was associated with her recent COVID-19 vaccination. She showed a notable clinical response to an extended course of methylprednisolone, followed by its tapering and plasmapheresis. Follow-up MRI of the brain and spinal cord at 6-months, showed persistent T2 hyperintense lesions in the left thalamus and thoracic cord. At 10-months follow-up, serum anti-AQP4 antibody utilising a CBA was found to be positive, solidifying the diagnosis of NMOSD.

The 54-year-old woman (case 3 of the article) had a history of immune thrombocytopenia purpura and family history of myasthenia gravis. She presented to the emergency department of with a 2-week history of progressively ascending numbness, which started 3 days following the second dose of the elasomeran [manufactured by Moderna] for COVID-19 vaccination. Neurological findings were notable for a T3 sensory level, non-sustained ankle clonus, extensor plantar response bilaterally and diffuse hyperreflexia. Contrast-enhanced thoracic spine MRI showed a longitudinally extensive T2 hyperintense lesion extending from T2 to T9 level, with gadolinium enhancement between T5 and T7 levels, consistent with LETM. Serum and haematological assays showed leucopenia at 2240/µL, elevated ANA titers of 1:320, and elevated serum anti-AQP4 antibody titers at 1417.3 U/mL. CSF analysis revealed pleocytosis of 26 cells/µL with 86% lymphocytic predominance, elevated protein of 71 mg/dL and MBP of 27.0 ng/mL. Her clinical presentation was consistent with NMSOD, which was probably associated with her recent COVID-19 vaccination. For treatment, she received unspecified steroids for 5 days with notable improvement of her sensory symptoms.

The 49-year-old man (case 4 of the article) presented with a 3-week history of nightly numbness of both feet, diplopia, low-grade fever and unsteady gait. He started experiencing his neurological symptoms at 4 days following the administration of the second dose of elasomeran [manufactured by Moderna] for COVID-19 vaccination. His past medical history was significant for COVID-19 infection with a full recovery about 3 months before his current illness. His neurological findings were notable for gait ataxia, right leg appendicular ataxia and slightly diminished vibration sense of both lower extremities. Contrast-enhanced brain MRI demonstrated numerous supratentorial and infratentorial demyelinating lesions, the vast majority of them displayed enhancement, involving white matter, thalami and basal ganglia. His findings were indicative of fulminant-onset. There were a few old non-enhancing lesions, which was suggestive of prior clinically-silent demyelination. A cervical spine MRI with gadolinium showed two enhancing cervical cord lesions. CSF analysis demonstrated a pleocytosis of 41 cells/µL with 70% lymphocytic predominance and elevated protein of 125 mg/dL. Her findings were consistent with MS-like syndrome secondary to his recent COVID-19 vaccination. Additionally, preexisting clinically-silent demyelination disease also led to fulminant onset of MS-like syndrome. For treatment, he received a 5-day course of methylprednisolone, which resulted in substantial clinical improvement. At 10-month follow-up, he remained in clinical remission with brain MRI showing persistent T2-hyperintense lesions with complete resolution of gadolinium enhancement and lack of new demyelinating lesions.

The 27-year-old woman (case 5 of the article), presented to the emergency department with a 2-day history of acute-onset confusion and anxiety, which developed at 6 days following administration of tozinameran [manufactured by Pfizer-BioNTech] for COVID-19 vaccination, which resulted in transient fatigue and headache, he had a fever of 100.4◦ F. Neurological examination showed dysfluent speech with paraphasic errors, psychomotor agitation and difficulty with writing. Serological assays were notable for a mildly elevated ESR to 21 mm/hour. CSF analysis was relevant for pleocytosis of 19 WBCs with 84% lymphocytic predominance. The EEG revealed mild generalised slowing. Her findings were consistent with autoimmune meningoencephalitis,

which was potentially caused by her recent COVID-19 vaccination. For treatment, she started receiving methylprednisolone, which led to a significant clinical improvement. She was subsequently discharged on methylprednisolone taper with a steady improvement. She achieved a full recovery in about 1 month after discharge.

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