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A Rare Case of Coronavirus Disease 2019 Vaccine-Associated Cerebral Venous Sinus Thrombosis Treated with Mechanical Thrombectomy

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 56-year-old
Final Diagnosis: Cerebral venous sinus thrombosis (CVST)
Symptoms: Altered mental status • left sided weakness
Medication: —
Clinical Procedure: Mechanical thrombectomy
Specialty: Critical Care Medicine • Neurology

Objective: Rare disease

Background: Vaccine-related thrombosis and thrombocytopenia syndrome (TTS) is a rare life-threatening syndrome reported after vaccination against COVID-19.

Case Report: We describe a case of 56-year-old postmenopausal, obese woman with hypothyroidism and hyperlipidemia, who presented to the Emergency Department (ED) with fluctuating mental status and left-side weakness for 5 days. She received her first and second dose of mRNA-1273 vaccine (Moderna) at 12 and 8 weeks, respectively, prior to presentation. She was found to have multiple hemorrhages and infarcts on a computed tomography (CT) scan of the head. She was intubated in the ED for airway protection and mechanically ventilated. Magnetic resonance angiogram and venogram showed multiple infarcts in right frontal, parietal, and left parietal lobes, along with occlusion of left-side transverse sinus, sagittal sinuses, and left internal jugular vein, suggesting cerebral venous sinus thrombosis (CVST). Despite anticoagulation, her clinical condition continued to worsen, and she was referred for emergent endovascular thrombectomy. Her clinical condition improved after thrombectomy, and she was discharged on warfarin. At 4-month follow-up, she was able to walk with an assistive device and able to carry out activities of daily living with assistance. She is planned for further work-up for hypercoagulable state at follow-up.

Conclusions: This case highlights the occurrence of vaccine-related thrombosis 3 months after vaccine administration. Only 2 cases of TTS have been reported so far after mRNA-1273 vaccination (Moderna). To the best of our knowledge, this is the first reported case of CVST presenting 3 months after the first dose of COVID-19 mRNA-1273 vaccine (Moderna).

Keywords: COVID-19 Vaccines • Intracranial Thrombosis • mRNA-1273 Vaccine • Sinus Thrombosis, Intracranial • Stroke • Thrombectomy

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Background

Coronavirus disease 2019 is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and has been the cause of a pandemic, which has affected people worldwide. Vaccines have been one of the most important tools to fight this infection. COVID-19 vaccine-related adverse effects have been very rare and should not deter people from receiving the vaccine, as the risk-benefit ratio hugely supports vaccination. However, it is important to be cognizant of life-threatening yet potentially treatable adverse effects of the vaccines. Vaccine-related thrombosis and thrombocytopenia syndrome (TTS) is one of such rare life-threatening syndromes reported after vaccination against COVID-19. Various case definitions have been used for TTS by different organizations. According to the Interim Brighton Collaboration case definition, TTS diagnosis requires presence of thrombocytopenia with platelet count <150 000 per microliter, no known recent exposure to heparin, and imaging, clinical, surgical, or pathological evidence of venous or arterial thrombosis. Based on the algorithm, cases can be divided into definite, probable, and possible [1]. The Centers for Disease control and Prevention (CDC) case definition of TTS divides cases into Tier 1 TTS cases or Tier 2 TTS cases. Tier 1 TTS cases include thrombosis in an unusual location, platelet count <150 000 per microliter, and positive heparin platelet factor 4 enzyme-linked immunosorbent assay heparin-induced thrombocytopenia antibody test (heparin PF4 ELISA HIT antibody). This antibody positivity supports a diagnosis but is not an absolute requirement. It first requires 2 criteria to be present, but does not require the presence of heparin-PF4 antibody. The Tier 2 TTS case definition includes thrombosis in a common location, low platelets as above, and a positive heparin-PF4 ELISA HIT antibody result [2]. To qualify as Tier 2 TTS, all 3 conditions have to be present (importantly, this requires thrombosis in common locations). In summary, to diagnose TTS, new-onset thrombocytopenia has to be accompanied by thrombosis; and if thrombosis is in common locations as such as pulmonary embolism, deep vein thrombosis, or axillary vein thrombosis, it has to be substantiated with presence of heparin-PF4 antibody. However, if thrombosis occurs in unusual locations such as cerebral veins or portal or splenic veins, it does not require demonstration of positive heparin-PF4 antibody.

TTS was first reported in Europe with ChAdOx1-S/nCov-19 (recombinant) vaccine (AZD1222) (University of Oxford, AstraZeneca) [3]. As of July 26, 2021, 39 cases of TTS have been confirmed by the CDC and U.S. Food and Drug Administration (FDA) out of more than 13 million doses of Ad26.COV2.S (Johnson & Johnson) (COVID-19 vaccine, viral vector-Janssen) vaccine administration in the United States. After mRNA-1273 vaccine (Moderna) administration, 2 cases of TTS have been confirmed out of more than 328 million doses administered in the United States [4,5].

Case Report

We present a 56-year-old, obese, postmenopausal woman who presented with fluctuating sensorium for 5 days and left-side weakness of 1-day duration. She was otherwise well until her daughter noticed a sudden onset of confusion, when she was found to be mumbling incomprehensibly. Her daughter reported the symptoms to be fluctuating. On the day of presentation, she was noted to have sensory symptoms with a 'funny' feeling in her left arm when she tried to open the door with her left hand. She had a past medical history of hypothyroidism and hyperlipidemia. She denied smoking and any history of recreational drug use. She received 2 doses of mRNA-1273 vaccine, with the first dose around 12 weeks before presentation and the second dose 8 weeks before presentation. Her home medications included levothyroxine and atorvastatin.

In the ED, she was found to be restless, non-communicative, and confused, with left upper- and lower-extremity weakness. She was afebrile, with temperature of 37°C, blood pressure 126/67 mmHg, heart rate 67 beats per minute, respiratory rate of 17 per minute, and oxygen saturation 98% on breathing ambient air. Results of a physical examination were notable for confusion and restlessness, with the patient being non-communicative, and with predominant left-side weakness. She was intubated in the ED for airway protection. She underwent a CT scan of the head, which showed scattered hemorrhages and infarcts in both right and left cerebral hemispheres, as shown in **Figure 1A and 1B**. She was monitored in the Intensive Care Unit (ICU). Her laboratory findings were significant for hemoglobin of 12.8 g/dL (reference range, 12.0 to 16.0), white blood cell count of 10 100 per cubic millimeter (reference range, 4800 to 10 800), and platelet count of 139 000 per mL (reference range, 150 000 to 400 000). Her serum creatinine was 0.6 mg/dL (reference range, 0.5 to 1.5), potassium level was 2.7 meq per liter (reference range, 3.5 to 5), and her sodium level of 136 milliequivalent per liter (reference range, 135 to 145). Her lipid panel and liver function tests were within normal limits. Her thyroid-stimulating hormone level was 4.05 mIU/L (reference range, 0.4 to 4.5), and the hemoglobin A1C value was 5.5% (reference range, 4.7 to 6.4%). Her D-dimer levels were high at 16 666 nanograms per milliliter (reference range, 0 to 230), and partial thromboplastin time (aPTT) was 30.8 s (reference range, 27.2 to 39.6 s), prothrombin time (PT) was 12.0 s (reference range, 9.9 to 13.3 s), and her international normalized ration (INR) was 1.04 (reference range, 0.85 to 1.14). Her C-reactive protein was also high at 56.48 mg/L (reference range, <5). Urinalysis did not show any signs of infection, and a urine drug screen was negative. The initial chest X-ray did not show any infiltrates. She tested negative for COVID-19 based on reverse transcription polymerase chain reaction (RT-PCR) of a nasopharyngeal swab. Her antibodies against Spike protein for severe acute respiratory

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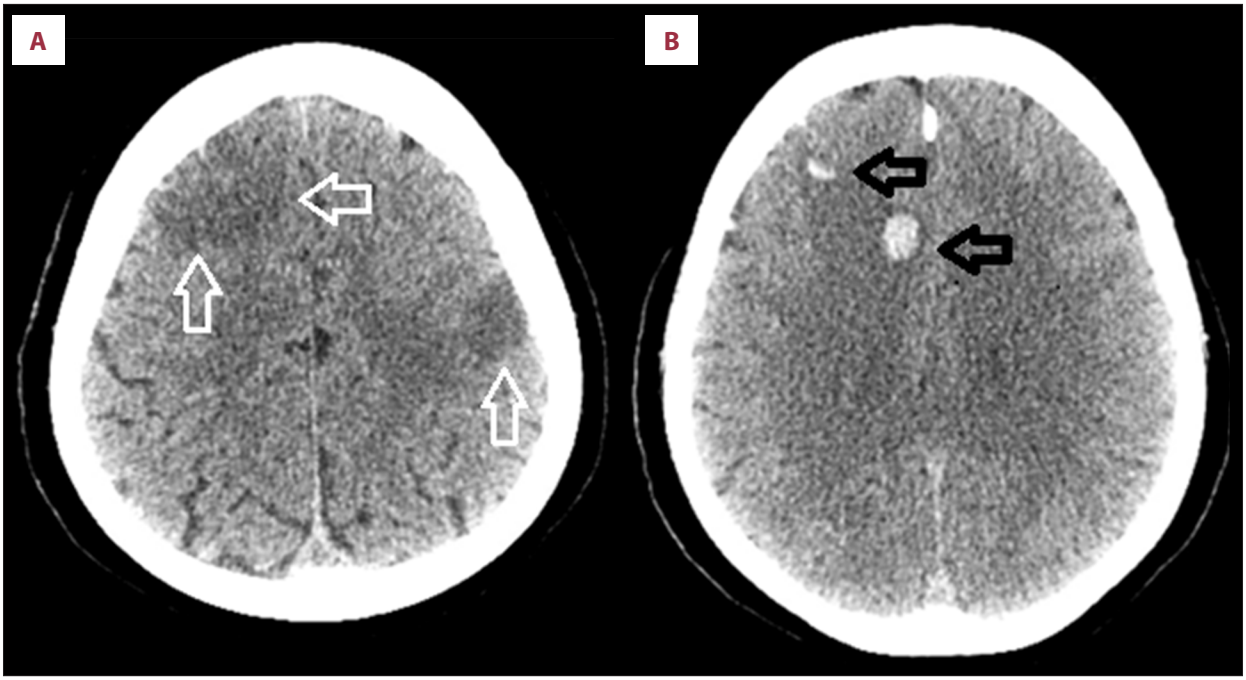

Figure 1. (**A**) Axial section of CT scan of the head shows hypodensities (white arrows) in right frontal, parietal, and left parietal regions, (**B**) multiple hemorrhagic foci noted (black arrows) in right frontal region.

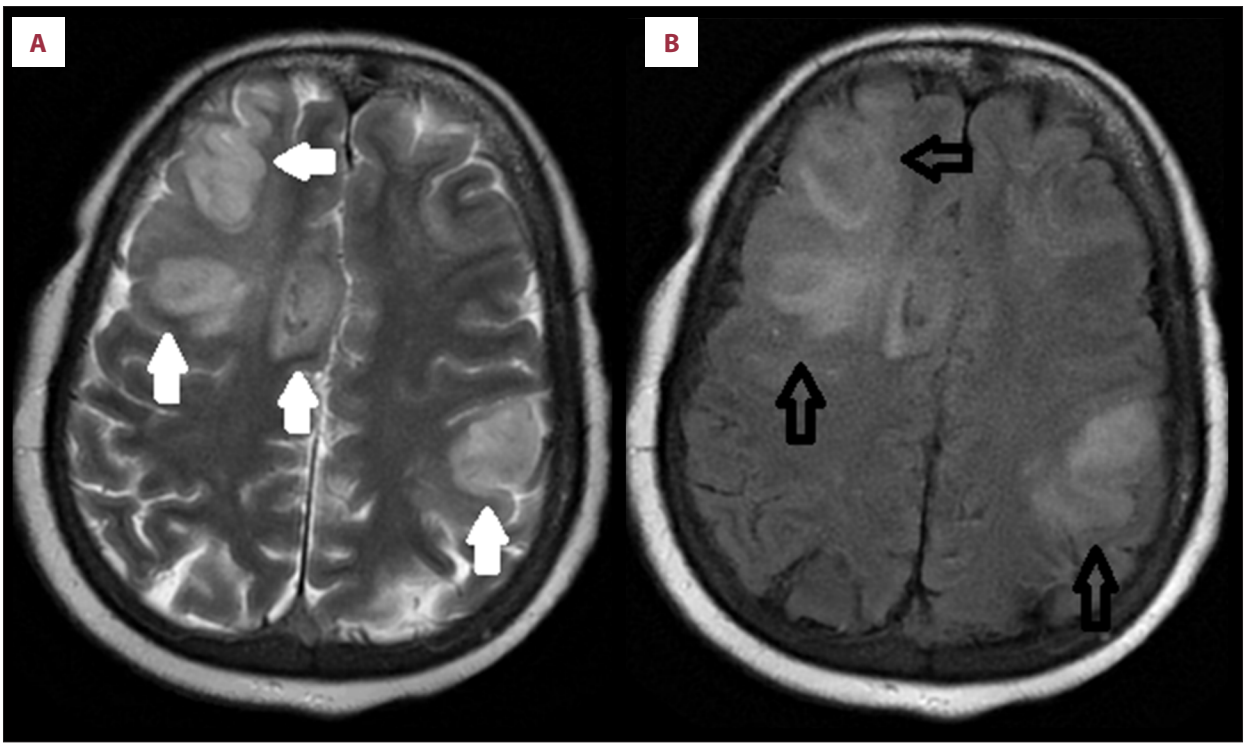

Figure 2. (**A**) T2-weighted image in axial section showing infarcts (solid white arrows) in right frontal and left parietal region, (**B**) T2-weighted FLAIR sequence showing infarcts (black arrows) in the above regions along with hemorrhage in the right frontal region near the midline.

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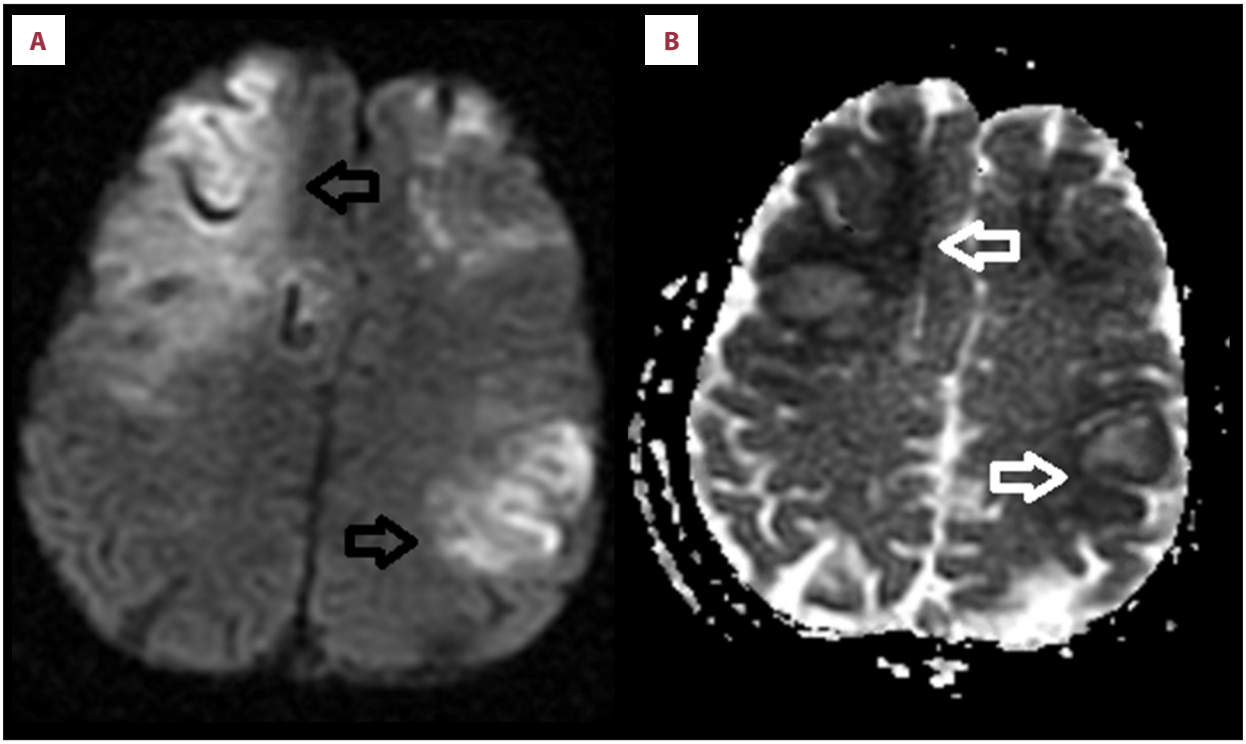

Figure 3. (**A**) Diffusion-weighted image showing areas of infarcts (black arrows) in right frontal and left parietal regions. (**B**) Corresponding ADC images showing regions of hemorrhages (white arrows).

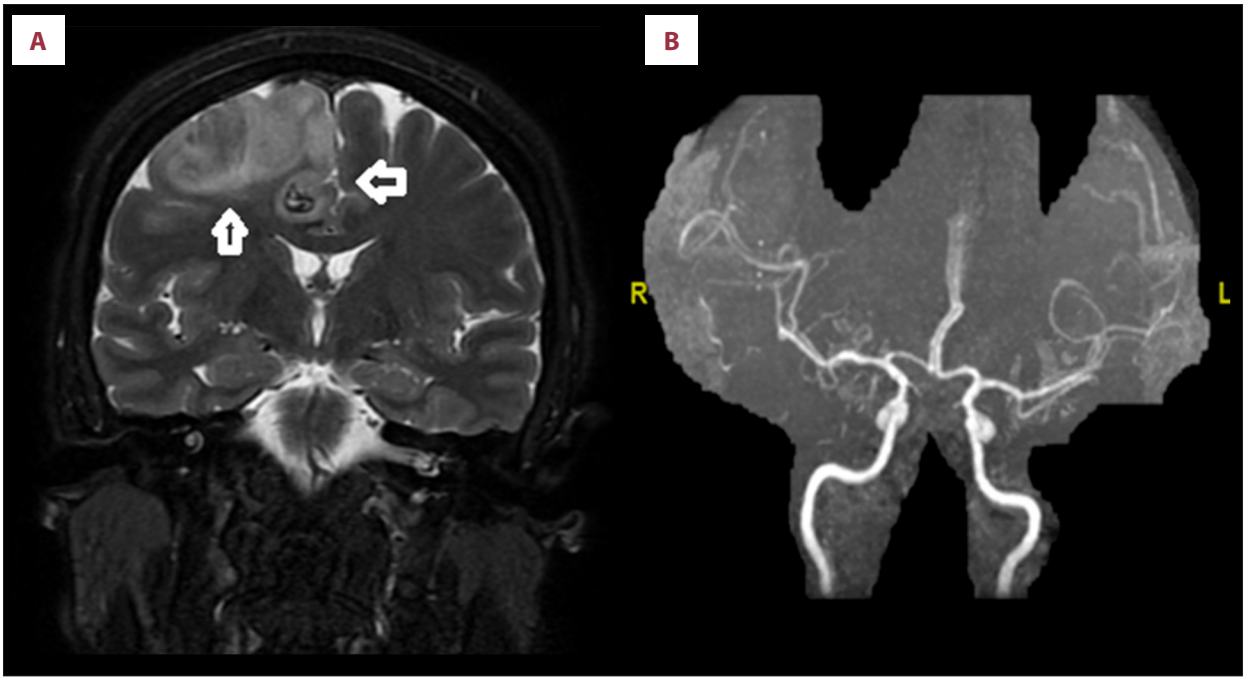

Figure 4. (**A**) Coronal section of T2-weighted MRI image shows infarct (white arrows) with areas of mosaic hemorrhage in right parietal region, (**B**) MR angiogram showing a patent arterial system.

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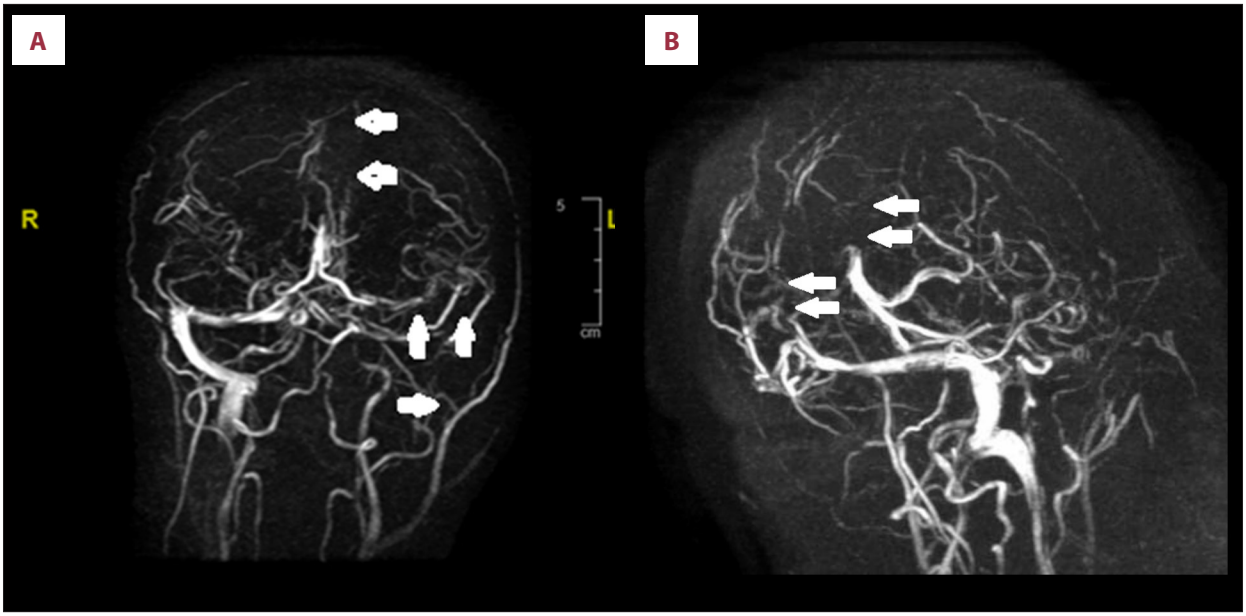

Figure 5. (**A**) MR venogram in coronal section shows absence of opacification (white arrows) of superior sagittal sinus, inferior sagittal sinus, transverse sinus, sigmoid sinus, straight sinus, and great cerebral vein. (**B**) MR venogram in sagittal section showing absence of opacification (white solid arrows) of the same sinuses.

syndrome coronavirus-2 (SARS-CoV-2) were 1726 units per milliliter (reference range, non-reactive), signifying an adequate immune response to the vaccine, and antibodies against nucleocapsid protein were negative, signifying absence of prior SARS-CoV-2 infection.

The preliminary differential diagnoses included cerebral metastasis, vasculitis, and CVST, based on her initial CT scan findings. She underwent MRI brain with angiogram (MRA) and venogram (MRV), which confirmed infarcts in watershed areas, along with foci of hemorrhages, and 'signal void' in superior sagittal and inferior sagittal sinuses, left transverse sinus, left sigmoid sinus, and left internal jugular, suggestive of CVST, as shown in **Figures 2-5**. After the MRV confirmed CVST, hypercoagulable state, malignant process, and TTS were considered to be the most probable causes, especially in the presence of thrombocytopenia. She was evaluated for hypercoagulable state, but her direct platelet IgG antibody, lupus anticoagulant, and anti-cardiolipin antibodies were negative. Her Platelet factor-4 (PF-4) antibody (ANA) was later reported as negative, and anti-nuclear antibodies (ANA) were reported as positive in a nucleolar pattern at low titers of 1: 80. Her antithrombin-III was reported as 105 (reference range, 80% to 135% normal). In view of her acute thrombosis, further work-up was planned at follow-up. She met the CDC criteria for Tier-1 case definition of TTS in view of low platelet count, history of COVID-19 vaccination, and thrombosis in the unusual locations of cerebral veins and dural sinuses. She had an episode of seizure, which was treated with levetiracetam. She was started on anticoagulation and received unfractionated heparin infusion according to weight-based nomograms, but in view of her rapid symptom progression, comatose state, and extensive CVST, she was referred for endovascular mechanical thrombectomy. Subsequently, she underwent thrombectomy, with successful restoration of venous blood flow, as shown in **Figure 6A and 6B**. She improved after the procedure and was extubated. Her mentation and left-sided weakness improved and she was moved from the ICU to the stroke unit. At 4-month follow-up, she showed remarkable recovery. She can now perform activities of daily living with moderate assistance and walks using a cane. She is receiving coumadin with monitoring of INR, and is planned for further work-up for hypercoagulable state at follow-up.

Discussion

TTS is a rare but potentially serious adverse effect of COVID-19 vaccination. It has affected women less than 60 years of age, occurring after a median duration of 14 days after vaccination; however, cases have been reported up to 48 days after vaccination [6]. Predominant risk factors for thrombosis include systemic estrogen use, diabetes, obesity, current cigarette smoking, hypertension, malignancy, hypothyroidism, fertility treatment, and coagulation disorders [2]. Our patient had obesity and hypothyroidism as risk factors and received the mRNA-1273 vaccine (Moderna) 12 weeks before presentation. Interestingly, hypothyroidism was found in 3 out of 39 cases of TTS after administration of the Ad26.COV2.S (Johnson & Johnson) (COVID-19 vaccine, viral vector-Janssen) vaccine [2].

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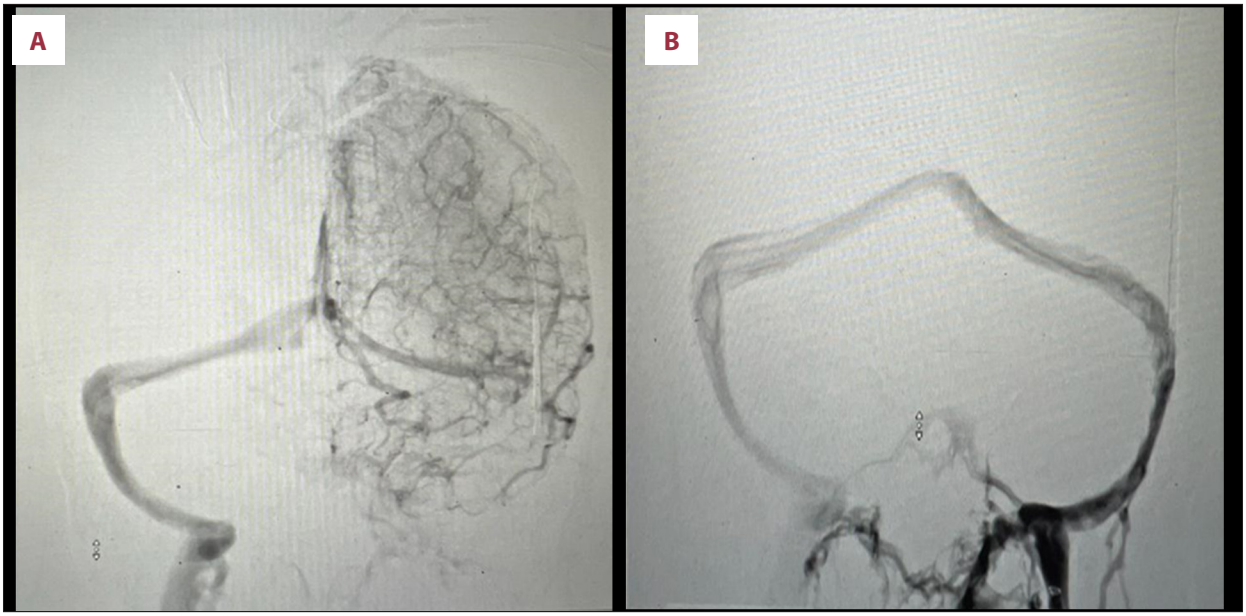

Figure 6. (**A**) Antero-posterior caudally (AP Caudal) tilted fluoroscopic view before endovascular thrombectomy shows contrast filling right internal jugular vein with no flow in the superior sagittal sinus, left sigmoid sinus, and left internal jugular vein (background cerebral blush suggesting increased venous pressure). (**B**) AP caudal fluoroscopic view after thrombectomy shows restored flow in the left transverse and left sigmoid sinuses, along with left internal jugular vein.

Moderate hypothyroidism has been putatively associated with decreased fibrinolysis, while severe hypothyroidism has been linked with increased fibrinolytic activity [7]. There have been a few case reports linking hypothyroidism with CVST, but the association has not been studied systematically [8].

Based on a study of the ChAdOx1-S/nCov-19 (AstraZeneca) vaccine, vaccine-associated CVST (VA-CVST) is considered to be due to development of platelet-activating antibodies against platelet factor-4 (PF-4), which mimics heparin-induced thrombocytopenia [9]. These antibodies were negative in 2.7% of the cases [9]. The exact mechanism leading to VA-CVST remains to be elucidated. It is important to consider TTS, especially CVST, in the differential diagnosis of patients presenting with neurological complications after receiving COVID-19 vaccination. Although delayed presentation has not been reported in the literature, our case highlights that distinct possibility. The American Society of Hematology included vaccine administration within 42 days as one of the factors in defining TTS (also termed vaccine-induced thrombotic thrombocytopenia) [10].

VA-TTS (vaccine-associated TTS) can cause thrombosis in various vascular beds, including cerebral veins and dural sinus, pulmonary embolism, mesenteric artery, and vein thrombosis. However, cerebral veins and dural sinuses have been found to be the most common sites of involvement, for reasons not presently known [6]. Clinical features of CVST include headache, altered mental status, stroke-like presentation, seizures, coma, and death. Seizure is usually a rare association and does not require initiation of anti-epileptic therapy if it occurs within 2 weeks of symptom onset. However, patients with seizures and focal deficits usually require initiation of anti-epileptics [11]. Our patient had seizures in the setting of CVST and was treated with levetiracetam. Diagnosis relies on imaging with CT or MR angiogram with venogram [12,13]. Imaging can show infarcts in unusual locations along with hemorrhages, and “empty delta sign”, which signifies signal voiding in the sagittal sinus due to thrombus [14]. Anticoagulation is the cornerstone of therapy in CVST, with continuation of treatment up to at least 3-6 months. Once VA-CVST is suspected, it is important to avoid heparin and use of Argatroban, fondaparinux, and Apixaban, and Dabigatran is recommended instead [12]. However, since it is an evolving syndrome and the literature is lacking regarding management guidelines, many patients have also received heparin-based anticoagulation. In a study of VA-TTS after patients received ChAdOx1-S/nCov-19 (AstraZeneca), a statistically non-significant increase in mortality was found in patients receiving heparin [6].

Various treatment options have been used, including, anticoagulation, intravenous immunoglobulins, steroids, and plasma exchange [6]. If patients show signs of clinical deterioration on anticoagulation or develop new or worsening intracerebral hemorrhage and/or are comatose, it is important to consider endovascular interventions [15], including direct catheter thrombolysis, balloon-assisted thrombectomy, rheolytic catheter thrombectomy, and stent-retriever thrombectomy [16,17]. Mechanical thrombectomy has a good safety profile, and complete radiographic resolution is seen in up to 69% patients, while

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new or worsening intracranial hemorrhage occurs in 8-9% of patients [16]. Overall prognosis remains poor after VA-CVST, with a case-fatality rate of 22% reported after ChAdOx1-S/nCov-19 (AstraZeneca) vaccine administration [6]. However, timely recognition and intervention can be potentially lifesaving.

Conclusions

VA-CVST should be considered in patients presenting with mental status changes after COVID-19 vaccination. TTS is reported with Ad26.COV2.S (Johnson & Johnson) (COVID-19 vaccine, viral vector-Janssen) vaccine in the United States and ChAdOx1-S/nCov-19 (AstraZeneca)vaccine in Europe and other parts of the world, but it has also been reported after mRNA-1273 vaccine (Moderna) administration. Most cases occurred within 28 days after vaccination. However, our case illustrates that delayed presentation may occur, and timely diagnosis and treatment are essential to prevent mortality and morbidity from this life-threatening adverse event.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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