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Case Reports & Case Series

Endovascular mechanical thrombectomy for cerebral venous sinus thrombosis after mRNA-based SIRS-CoV-2 vaccination

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ABSTRACT

Background: As vaccinations against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continue worldwide, increased rates of venous thrombotic events, mainly as cerebral venous sinus thrombosis (CVST), have been reported following adenovirus vector-based SARS-CoV-2 vaccination. However, few reports have described the occurrence of venous thrombosis after messenger RNA (mRNA)-based vaccination. Here, we describe a case of CVST after a first dose of mRNA-based vaccination that was treated with emergent endovascular mechanical thrombectomy and systemic heparinization.

Case Description.

A 43-year-old, previously healthy man suffered severe headache and partial seizures affecting the left arm 4 days after receiving the first dose of an mRNA-based SARS-CoV-2 vaccination (FC3661; Pfizer/BioNTech). Computed tomography showed intraparenchymal hemorrhage. Seven days after vaccination, symptoms worsened and he was transferred to our tertiary hospital. Magnetic resonance venography revealed CVST with occlusion of the superior sagittal sinus (SSS) and right transverse sinus (TS). Since no findings suggested thrombosis with thrombocytopenia syndrome, the patient underwent systemic heparinization and emergent mechanical thrombectomy with balloon transluminal angioplasty, a stent retriever and an aspiration catheter. Complete SSS and right TS recanalization were achieved and the patient was discharged without neurological deficits.

Conclusion: Clinicians should be aware that apparently healthy individuals with no risk factors can develop CVST after receiving an mRNA-based vaccine and appropriate treatment including EMT need to be performed immediately.

(228 words)

1. Background

Cerebral venous sinus thrombosis (CVST) is a relatively uncommon cause of stroke, a potentially life-threatening cerebrovascular disease comprising around 0.5% of all strokes. [2,4] Over 80% of patients with CVST show at least one identifiable risk factor for thrombosis and half have multiple predisposing factors, including pregnancy, puerperium, use of oral contraceptives, central nervous system infection, or head trauma. [9,10,20] As vaccinations against the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continue worldwide, venous thrombosis has been suggested to pose a potential problem as an adverse reaction. Cases of thrombocytopenia have recently been reported to develop within 4–28 days of vaccination with the coronavirus disease 2019 (COVID-19) vaccines ChAdOx1nCov-19 (AstraZeneca/Oxford, Oxford, UK) and Ad26.COV2.S (Janssen/Johnson & Johnson, New Brunswick, NJ), and many of those reported patients displayed CVST, which can be fatal. [11,19] To account for the development of CVST with thrombocytopenia after ChAdOx1nCov-19 vaccination, a mechanism similar to autoimmune heparin-induced thrombocytopenia (HIT) has been proposed, in which platelet-activating antibodies occur in the absence of heparin exposure. [11,18] Several terms have been used to describe this phenomenon, including vaccine-induced immune thrombotic thrombocytopenia and thrombosis with thrombocytopenia syndrome (TTS). Importantly, it remains to be determined whether the possible mechanisms are relevant only to adenovirus vector-based COVID-19 vaccines or more broadly to all COVID-19 vaccines, including the messenger RNA (mRNA)-based vaccines COMIRNATY (Pfizer/BioNTech, Brooklyn, NY) and mRNA-1273 (Moderna,

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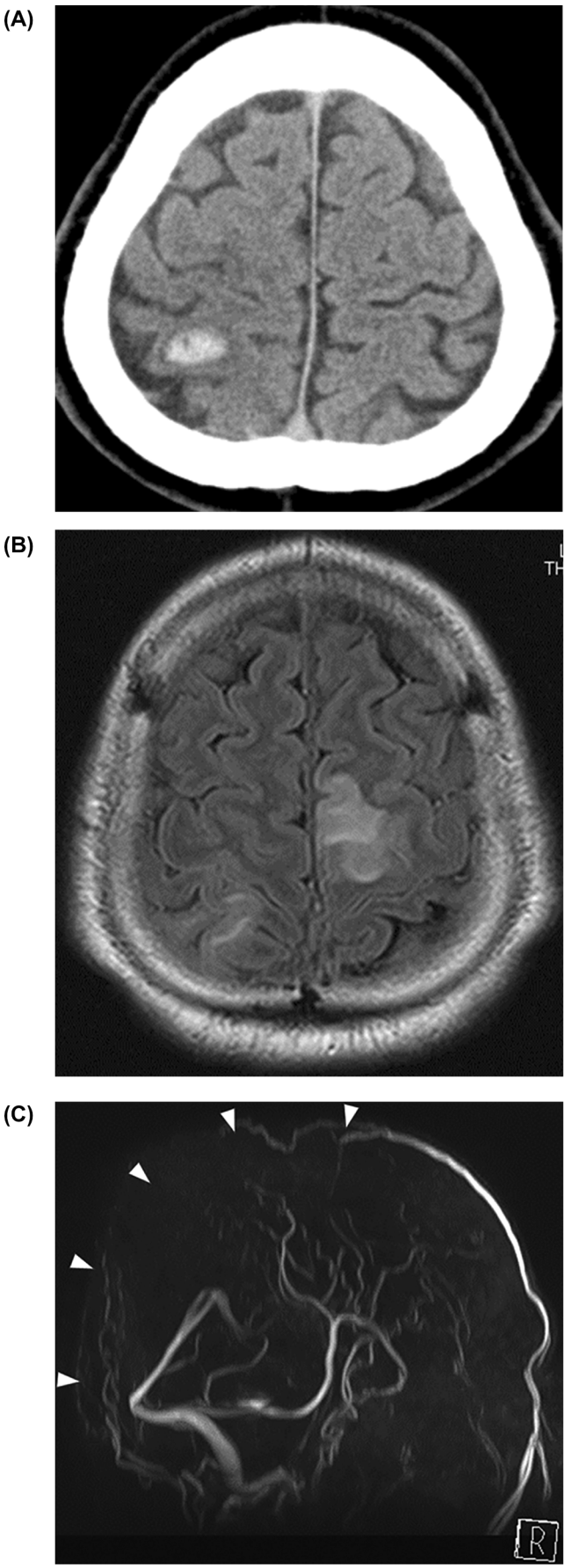

Fig. 1. A) Computed tomography shows a small intraparenchymal hemorrhage in the right postcentral gyrus. B) Fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging shows a high-intensity lesion in the left precentral gyrus. C) Lateral view of magnetic resonance venography (MRV) reveals occlusion of the superior sagittal sinus (SSS) and right transverse sinus (arrowheads).

(caption on next column)

Cambridge, MA). A recent study provided evidence of an excess rate of CVST among recipients of adenovirus vector-based COVID-19 vaccines, [11,16,18,19] but the risk of developing CVST after vaccination has yet to be determined, particularly in terms of mRNA COVID-19 vaccination. Here, we describe a case of CVST after the first dose of an mRNA vaccination that was successfully treated with emergent endovascular mechanical thrombectomy (EMT) and systemic heparinization.

2. Case report

The patient was a 43-year-old man with a history of diabetes mellitus who was receiving sitagliptin phosphate hydrate (MSD, Tokyo, Japan) at 50 mg/day and luseogliflozin hydrate (Taisyo, Tokyo, Japan) at 2.5 mg/day. He was a smoker (20/day) and body mass index was 28.3 kg/m^2. He had received his first dose of intramuscular mRNA COVID-19 vaccine (FC3661; Pfizer/BioNTech) on June 9, 2021 (day 0), and experienced no immediate adverse reactions. Four days later (June 13; day 4), he developed severe headaches and partial seizures affecting the left arm. He was transferred to an emergency hospital, where computed tomography (CT) of the head revealed a small intraparenchymal hemorrhage in the right post-central gyrus (Fig. 1A). Laboratory tests for full blood count, coagulation profile, and C-reactive protein were normal. He was admitted to a hospital and received conservative therapy with oral levetiracetam (UCB Pharma, Tokyo, Japan) at 1000 mg/day. Seven days after vaccination (June 16; day 7), he suddenly developed motor weakness of the right foot. Fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) showed a new high-intensity lesion in the left precentral gyrus with no hemorrhagic changes (Fig. 1B). Magnetic resonance venography (MRV) revealed occlusion of the superior sagittal sinus (SSS) and right transverse sinus (TS) (Fig. 1C). He was subsequently transferred to our tertiary hospital. Laboratory tests for full blood count, coagulation profile, and C-reactive protein remained normal. In particular, the platelet count was 26.4 $\times$ 10^4/μL, international normalized ratio was 0.91, activated partial thromboplastin time was $<$ 23.0 s, and D-dimer concentration was 1.6 μg/mL. SARS-CoV-2 reverse transcriptase-polymerase chain reaction assay of a nasopharyngeal swab yielded negative results (Table 1). No symptoms suggesting thrombosis of other organs were apparent. Since no findings suggested TTS, with neither thrombocytopenia nor markedly increased D-dimer, systemic heparinization was started and emergent EMT was

Table 1
Results of laboratory studies.

Variable	Result (Reference value)
Polymerase chain reaction test for SARS-CoV-2 virus	Virus not detected
Platelet count (per mm^3)	264 000 (158 000–348 000)
Fibrinogen (mg/dL)	448 (200–400)
D-dimer peak (nmol/L)	1.6 (≤1.0)
Antithrombin III (%)	105 (80–130)
International normalized ratio	0.91 (<1.1)
Activated partial thromboplastin time (sec)	<23.0 (25–35)
Prothrombin time (sec)	14 (9.8–12.1)
Lupus anticoagulant	1.2 (≤1.2)
Anticardiolipin antibody level	≤ 8 (<10)
HIT antibody	<0.6 (<1.0)
Protein S activity	90 (67–164)
Protein C activity	147 (64–147)
Antinuclear antibody	<40 (<40)
Anti-ss-DNA IgG	<10 (0–25)
Anti-ds-DNA IgG	<10 (1–12)

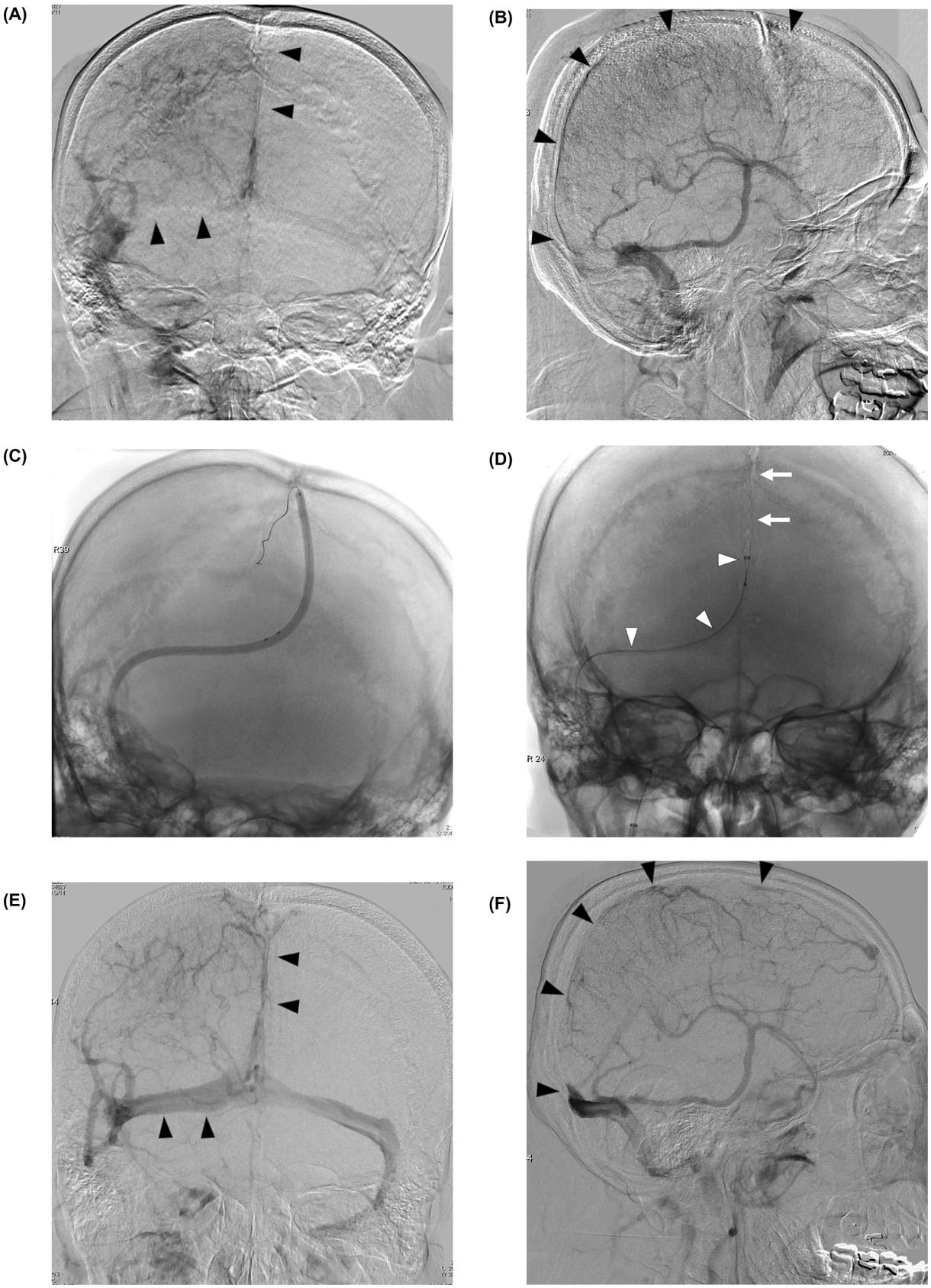

Fig. 2. A, B) Anteroposterior (AP) and lateral views in venous-phase digital subtraction angiography (DSA) give the same diagnosis as MRV and endovascular mechanical thrombectomy was performed (arrowheads). C) AP live view shows balloon percutaneous angioplasty from SSS to right sigmoid sinus. D) AP live view shows mechanical thrombectomy with stent retriever (arrows) and aspiration catheter (arrowheads). E, F) AP and lateral view in venous-phase DSA shows partial recanalization of the SSS and full recanalization of the right transverse sinus (arrowheads).

performed. Digital subtraction angiography (DSA) showed occlusion of the SSS and right TS (Fig. 2A, B). A microcatheter (Phenom 27; Medtronic, Minneapolis, MN) was navigated to the anterior part of the SSS with a 6-Fr guiding sheath (Destination; Terumo, Japan). At the beginning of the procedure, balloon transluminal angioplasty from the mid- to posterior SSS and right TS (Rapid cross 3 × 150 mm; Medtronic) was performed. Subsequently, thrombectomy with 4 passes of a combined stent retriever (Trevo XP 6 × 25 mm; Stryker, Fremont, CA) and catheter aspiration (ACE 68; Penumbra, Alameda, CA) was performed (Fig. 2C, D). The duration of procedure was 4 h and partial recanalization of the SSS and full recanalization of right TS were achieved by the end of the procedure (Fig. 2E, F). Motor weakness of the right foot was improved immediately after the procedure and the patient was maintained on anticoagulation. Follow-up laboratory examination showed no evidence of thrombocytopenia and extensive tests for thrombophilia markers (protein S/protein C activity, lupus inhibitors and HIT antibody) were all negative. However, 4 days after EMT (June 20; day 11), the patient experienced a sudden deterioration to a Glasgow Coma Scale score of 9 (E2V3M4), and FLAIR image depicted a new, high-intensity lesion in the right temporal lobe (Fig. 3A, B). Emergent DSA depicted occlusion of the right vein of Labbe, right TS and SSS. A second EMT was performed, using aspiration catheter, achieving partial recanalization of the vein of Labbe and full recanalization of the posterior SSS and right TS by the end of the procedure. The day after this second EMT procedure (day 12), the patient showed alert consciousness and improvement of gait disturbance. The patient was maintained on unfractionated heparin and

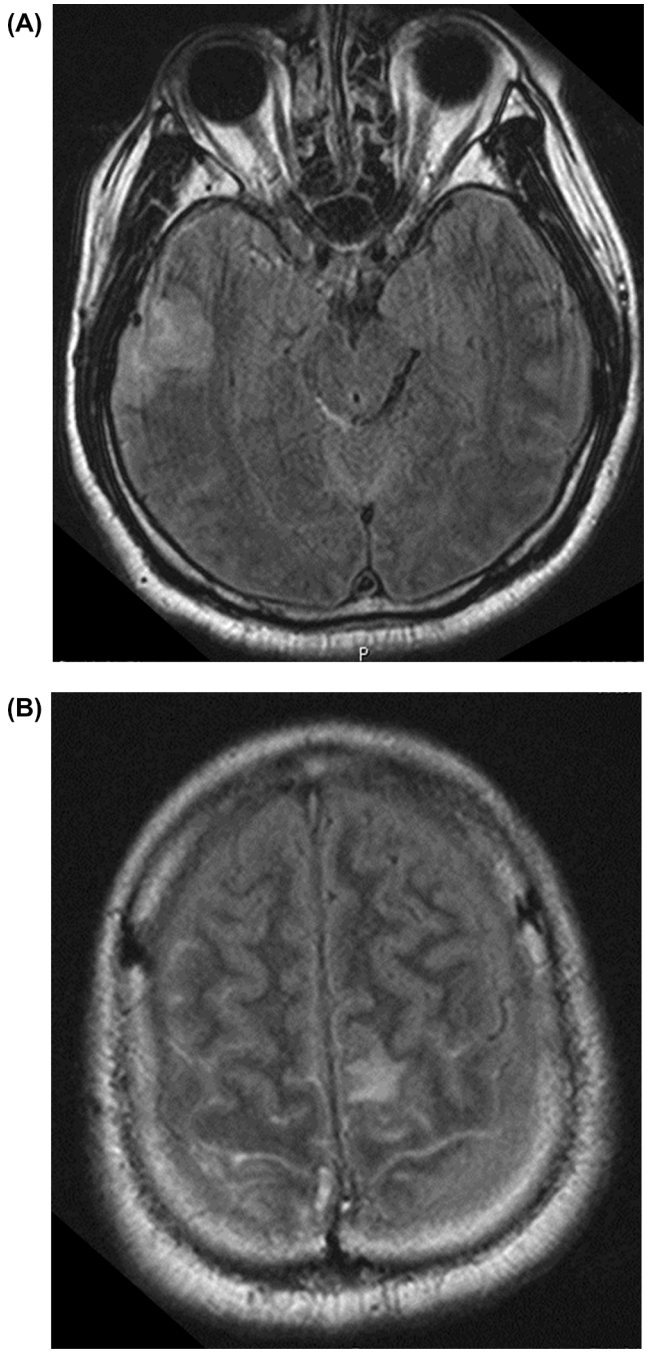

Fig. 3. A, B) FLAIR imaging on day 11 depicts a new high-intensity lesion in the right temporal lobe (A), but improvement in the left frontal high-intensity lesion (B).

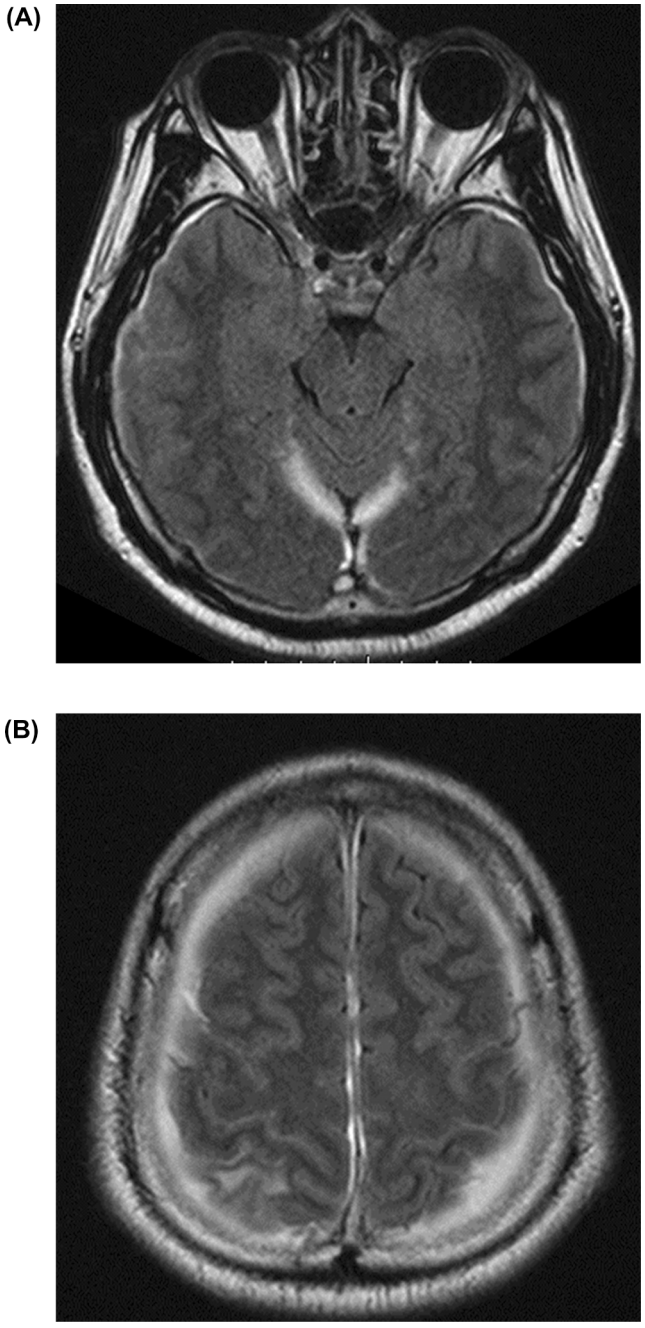

Fig. 4. A, B) FLAIR imaging on day 26 depicts improvement of edema in the right temporal lobe (A) and left frontal lobe (B).

switched to oral edoxaban tosilate hydrate (Daiichi-Sankyo, Tokyo, Japan) at 60 mg/day on day 21. Follow-up MRI on day 26 revealed improvement of the high-intensity lesions seen on previous FLAIR (Fig. 4A, B). The patient was discharged without neurological deficits.

3. Discussion

Increased rates of venous thrombotic events, mainly as CVST, have been reported after adenovirus vector-based vaccination, but few reports have described the occurrence of venous thrombosis after mRNA-based vaccination. [5,7,8,21,22] TTS after adenovirus vector-based vaccination is mediated by platelet-activating antibodies against platelet factor 4 (PF4), which clinically mimics HIT, a well-known prothrombotic disorder caused by platelet-activating antibodies that recognize multimolecular complexes between PF4 and heparin. This is because TTS antibodies bind to a similar site to HIT antibodies on PF4, forming immune complexes that in turn cause platelet activation. [1,11,13] In contrast, mRNA-based vaccine contains mRNA particles that bind to antigen recognition receptors, initiating pro-inflammatory cascades and this immune response might contribute as a trigger for thromboembolic events. [5,8] This pathogenesis may thus differ from that of adenovirus vector-based vaccination.

Zakaria et al. reported a 49-year-old, previously healthy man in whom headache and giddiness worsened after the second dose of vaccine (EP2163; Pfizer/BioNTech). [22] As the laboratory data in that case showed a lack of suspected TTS, anticoagulation therapy with Clexane (1 mg/kg twice daily) was started and symptoms improved. In the present case, a 43-year-old, previously healthy man presented intraparenchymal hemorrhage 4 days after mRNA-based vaccination (EP3661; Pfizer/BioNTech), with subsequent worsening of symptoms and progression of CVST. Since laboratory data showed the absence of suspected TTS [15], systemic anticoagulation with unfractionated heparin and emergent EMT were performed. However, the patient deteriorated further on day 11 because of new occlusion of the right vein of Labbe, necessitating second EMT. The recurrence of CSVT due to thrombogenicity resistant to anticoagulation therapy, related to vaccination, would have caused the deterioration. Since the pathophysiology of thrombotic and hypercoagulable states after mRNA-based vaccination is not yet fully understood, strict follow-up will be necessary.

The standard treatment for acute CVST is currently systemic anticoagulation with low molecular weight heparin and unfractionated heparin, which can lead to recanalization and symptomatic improvement. [6,10] However, because of the formation of HIT antibodies in TTS, heparins may aggravate the pathophysiology. Attention must therefore be paid to avoid systemic heparinization of CVST after COVID-19 vaccination in patients with suspected TTS. The use of high-dose intravenous immunoglobulin (IVIg) plus anticoagulation including argatroban, fondaparinux, and direct-acting anticoagulants is recommended for the treatment of TTS, [12] and three cases have been documented in which serum-induced platelet activation was suppressed after treatment with IVIg. [1] Consequently, clinicians need to consider the possibility of CVST associated with TTS after any type of COVID-19 vaccines, because it remains to be determined whether the possible mechanism of TTS is relevant only to adenovirus vector-based vaccines or to all COVID-19 vaccines, including mRNA-based vaccines since a case of TTS after mRNA-based vaccination with Moderna has been reported. [17].

A systematic review of CVST described EMT as an effective salvage therapy with a ratio of favorable outcomes (modified Rankin Scale scores 0–2) of almost 80%, compared to 8.7% showing worsening or new intracerebral hemorrhage [14]. However, the recent TO-ACT randomized clinical trial showed that endovascular treatment with standard anticoagulation did not appear to improve functional outcomes for patients with CVST. [3] This case used balloon percutaneous transluminal angioplasty, a stent retriever, and catheter aspiration devices, but the technical details of how and when to perform mechanical thrombectomy remain contentious.

4. Conclusion

Clinicians should be aware that apparently healthy individuals with no risk factors can develop CVST after receiving an mRNA-based vaccine and appropriate treatment including EMT need to be performed immediately.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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