BOOK CHAPTER

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Clinical Case of the Occurrence of Stroke Followed by Death After Vaccine Against SARS-CoV-2

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Abstract: **Introduction:** The current COVID-19 pandemic has involved developing vaccines to control the virulence of SARS-CoV-2. More than 4.1 million people have died from COVID-19.1 In response to this public health emergency, several vaccines against COVID-19 have been developed, with more than 3.7 billion doses administered worldwide. After the introduction of the adenovirus vector vaccine ChAdOx1, several cases of severe venous thrombosis with thrombocytopenia were reported worldwide. **Objective:** It was to present a case report of a 25-year-old female patient who presented extensive left intraparenchymal hematoma and rapid progression to brain death followed by death. **Case report:** A 25-year-old woman, CSS, was vaccinated against COVID-19 with the adenovirus ChAdOx1, 14 days after admission, evolved with a fever that started about 13 days ago, associated with holocranial, tight, moderate-intensity headache. On the day of admission, she was found by the torporous, unresponsive, and vomiting family, referred to the hospital emergency room. The patient was admitted to Glasgow 4 with evidence of anisocoria, with the left pupils larger than the right, rapidly progressing to mydriasis. Cranial computed tomography (CT) showed extensive left intraparenchymal hematoma, performing urgent decompressive craniectomy and placement of an intracranial pressure monitoring catheter. The cerebrospinal fluid exam did not show bacteria or fungi. CT angiography showed extensive thrombosis of the anterior portions of the superior sagittal sinus and probable thrombosis of the superficial drainage veins of the frontal regions. Skull CT revealed diffuse and bilateral ischemia. Laboratory tests showed mild thrombocytopenia and no change in the coagulogram. After one day, the patient evolved with worsening neurological status. Sedation was

turned off to start the brain death protocol, which was confirmed twice. Finally, an electroencephalogram was performed with evidence of a straight-line tracing, without evidence of electrical brain activity. **Final considerations:** Several studies have been published regarding cerebral thrombosis, stroke, and thrombotic thrombocytopenic events. Thus, safe and effective vaccines against COVID-19 are an urgent need, as they can leave pathophysiological responses of hypercoagulability and thrombo inflammation associated with acute infection.

Keywords: COVID-19, SARS-VoV-2, Thrombosis, Thrombotic thrombocytopenia, Stroke.

Introduction

The current COVID-19 pandemic has involved developing vaccines to control the virulence of SARS-CoV-2 [1]. Published investigations have taught lessons about vaccination strategies for this new coronavirus. This is attributed to the fact that SARS-CoV-2 uses human angiotensin-converting enzyme 2 (hACE2). Although efforts on COVID-19 vaccines started very early, initially in China as soon as the outbreak of a new coronavirus broke out and then worldwide when the disease was declared a pandemic by the WHO [2].

More than 4.1 million people have died from COVID-19 [1]. In response to this public health emergency, several COVID-19 vaccines have been developed, with more than 3.7 billion doses administered worldwide [2]. After the introduction of the adenovirus vector vaccine ChAdOx1, five cases of severe venous thrombosis with thrombocytopenia were reported in Norway, each starting 7–10 days after administration of the first vaccine dose. Four of these cases had cerebral venous sinus thrombosis [3]. This syndrome has since been termed vaccine-induced thrombotic thrombocytopenia (VITT) [3–5].

In this regard, a successful vaccine will require scientific evidence-based validation of its safety and efficacy, particularly in the high-risk population, particularly those with chronic comorbid conditions and front-line health professionals. In this regard, there are several types of vaccines under development such as virus vector vaccines, protein subunit vaccines, genetic vaccines, and monoclonal antibodies for passive immunization [6].

In this scenario, reports of venous thrombosis to coronavirus vaccines based on adenovirus ChAdOx1 and Ad26.COV2. S led to the suspension of use in several countries, such as Germany, France, Italy, and Portugal. Thus, thrombosis in cerebral and splanchnic veins among patients vaccinated in the previous 4 weeks was described in 17 patients out of 7.98 million recipients of the Ad26.COV2. S vaccine (with 3 fatalities) and 169 cases of cerebral vein thrombosis among 35 million ChAdOx1 recipients. The events were associated with thrombocytopenia and anti-PF4 (antibodies directed against platelet factor 4), leading to the designation of vaccine-induced immune thrombotic thrombocytopenia [7].

In this scenario, the present study presented a case report of a 25-year-old female patient who presented extensive left intraparenchymal hematoma and rapid progression to brain death followed by death.

Case Report

The present study was elaborated according to the rules of **CARE case report** (https://www.care-statement.org/) [8].

Patient Information and Clinical Findings

A woman, CSS, 25 years old, was vaccinated against covid-19 with the adenovirus ChAdOx1, 14 days after admission, evolved with a fever that started about 13 days ago, associated with holocranial headache, tight, of moderate intensity, with improvement partial 10 days ago. For 5 days, the patient had progressively worsened the condition, with intense daily headache, holocranial, and daily fever that was not measured. On the day of admission, she was found by the torporous, unresponsive, and vomiting family in a jet sent to the emergency room of the hospital for accidents and maternity Sao Lucas in Cacoal, Rondônia, Brazil. The patient was admitted to Glasgow 4 with evidence of anisocoria, with the left pupils larger than the right, rapidly progressing to mydriasis. The patient was evaluated by the neurosurgical team with evidence of fixed mydriasis, with the presence of the cough reflex, with decerebration, in Glasgow 2 (1 + 1 + 2 - 2).

Timeline

After 14 days of vaccination, the patient was admitted. After 17 days, the patient died after being diagnosed with brain death.

Diagnostic Assessment

A cranial computed tomography (CT) was ordered urgently, with evidence of extensive left intraparenchymal hematoma, with midline deviation and important effacement of the base cisterns (**Figures 1-3**).

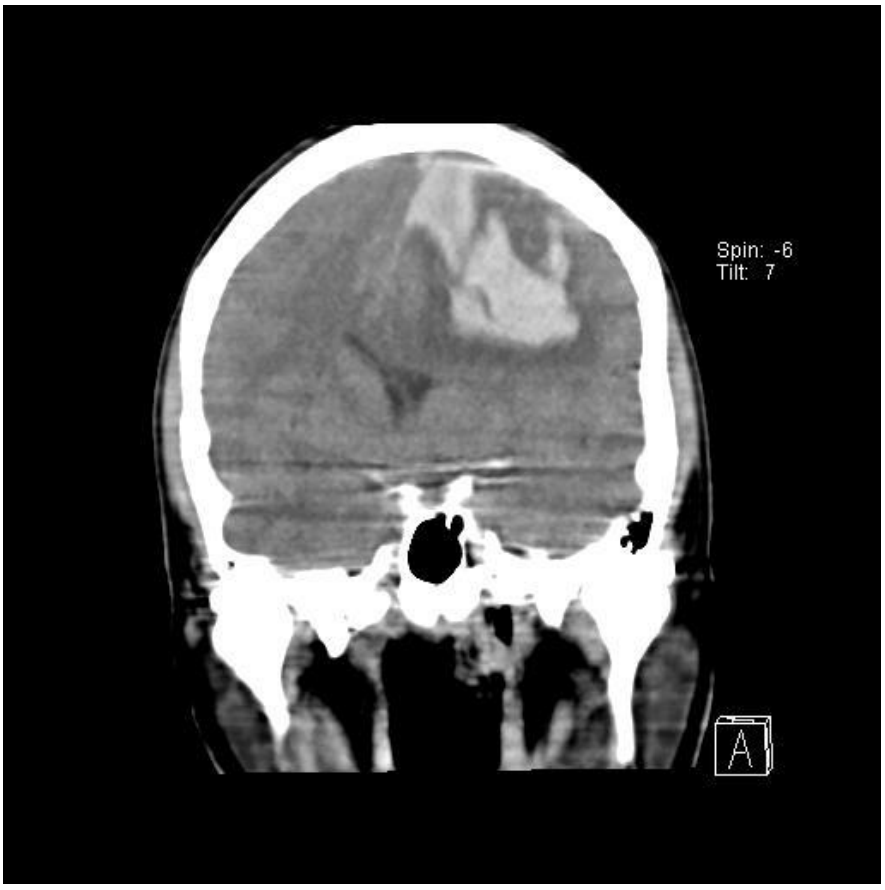

Figure 1 Evidence of extensive edema in the left hemisphere, with intraparenchymal hematoma, from the cortical region to close to the basal ganglia, with significant deviation from the midline.

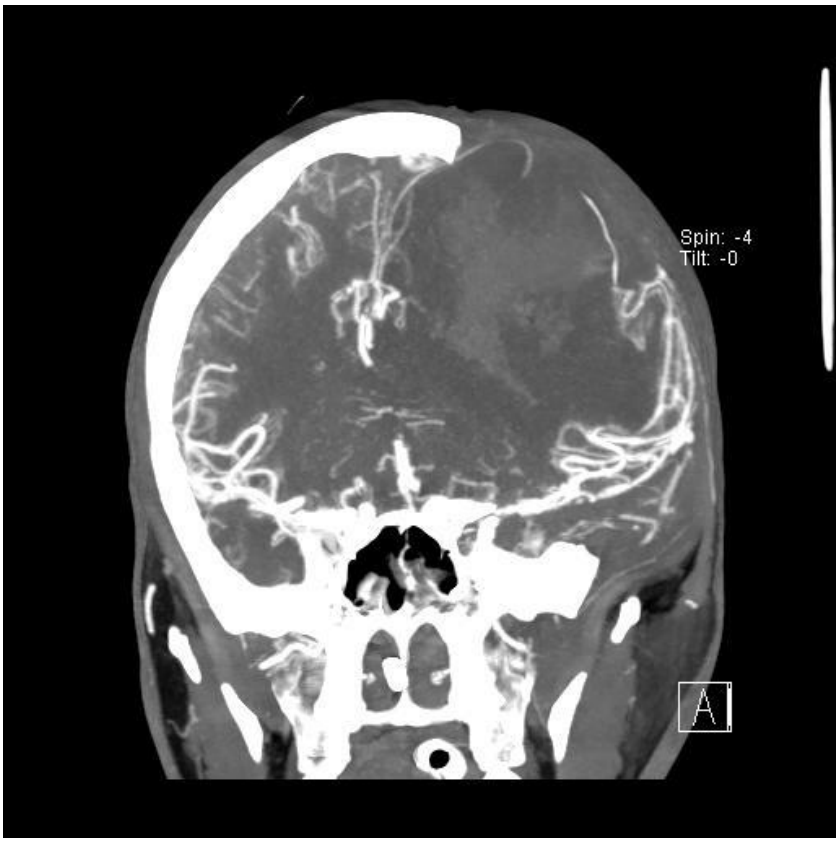

Figure 2 Evidence of partial contrast in the superior sagittal sinus with a significant reduction in the left convex drainage veins.

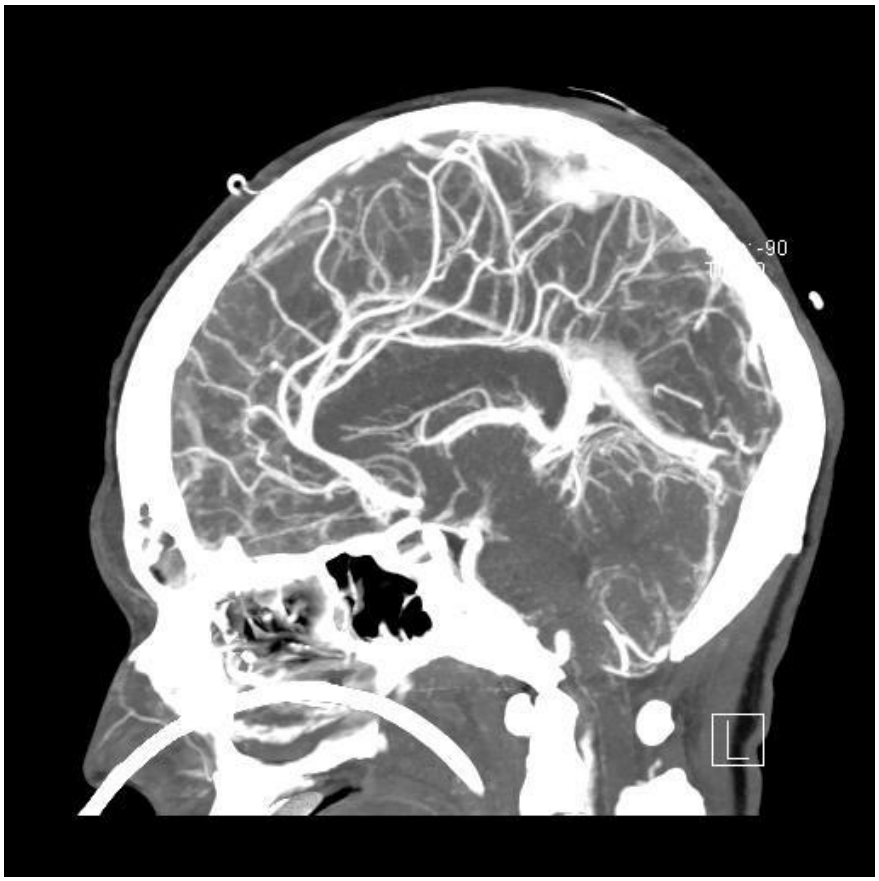

Figure 3 Failure of filling the superior sagittal sinus by iodinated contrast.

Therapeutic Intervention and Follow-up

Urgent decompressive craniectomy with drainage of intraparenchymal hematoma and placement of an intracranial pressure monitoring catheter was indicated. The patient was referred to the intensive care unit in a very serious condition, with inaudible BP, severe hypotension and high titers of vasoactive drugs, transfusion of two packed red blood cells, and volume reexpansion, with progressive improvement in the hemodynamic condition. The patient was kept sedated, RAMSAY VI, RASS-5 for 2 days, maintaining mydriatic and non-photoreactive pupils, with the corneal-palpebral reflex present only in the right eye, significant edema in the left hemicrania, maintaining a febrile condition that was difficult to control, and intracranial pressure (ICP) of 8 cmH_2O.

An uneventful cerebrospinal fluid (CSF) collection was performed, with no evidence of bacteria or fungi. Also, cranial computed tomography angiography was performed with evidence of extensive thrombosis of the anterior portions of the superior sagittal sinus and probable thrombosis of the superficial drainage veins of the frontal regions. Cranial computed tomography revealed diffuse and bilateral ischemia, reduced intraparenchymal bleeding volume, and small contralateral frontal intraparenchymal bleeding. Also, an important hypodensity was observed in the region of the diencephalon and superior mesencephalon.

Follow-up was requested with hematology, which observed leukocytosis with a left shift and mild thrombocytopenia. Changes in transaminases were observed, secondary to the infectious process, with no change in the coagulogram, concluding that a hematologic cause is unlikely. The patient was evaluated by the infectology team, which started ceftriaxone empirically until the result of CSF culture. Serology was requested.

After one day, the patient evolved with worsening of the neurological condition, with bilateral fixed mydriasis, without corneal-palpebral reflex and bilateral oculocephalic reflex, without cough reflex. Sedation was turned off to start the brain death protocol.

After 24 hours without sedation, the first test for brain death was performed, but the patient presented instability, with desaturation during the apnea test. After 24 hours, repeated opening of the brain death protocol with all positive tests. Furthermore, it was repeated after 6 hours by another doctor, confirming the first test. Finally, an electroencephalogram was performed with evidence of a straight line tracing, without evidence of electrical brain activity.

Informed Consent

Those responsible for the patient signed the consent form.

Discussion

In the present case report, cerebral comorbidities (stroke) presented rapid evolution (17 days) after vaccination. There was no change in the coagulogram, concluding that it is unlikely that the stroke was due to hematological reasons. In one day, the patient evolved with worsening of the neurological condition, with bilateral fixed mydriasis, without corneal-palpebral reflex and bilateral oculocephalic reflex, without cough reflex. Sedation was turned off to start the brain death protocol. An electroencephalogram was performed with evidence of a straight line tracing, without evidence of electrical brain activity. In this sense, several studies have been published about these events, confirming the risk presented.

Therefore, based on the rapid evolution of comorbidities followed by death due to the vaccination of ChAdOx1 nCoV-19 in the patient in this study, it is assumed that the safety and efficacy of immunizing vaccines against

COVID-19 in the world are still not correctly known, despite the vaccines represent the most efficient means to control and stop the COVID-19 pandemic. Therefore, safe and effective vaccines against COVID-19 are an urgent need. Researchers around the world are developing 213 COVID-19 vaccine candidates, of which 44 are in human trials [9].

In this sense, vascular endothelial damage is a hallmark of acute infection, both at the microvascular and macrovascular levels. SARS-CoV-2 infection leaves pathophysiological responses of hypercoagulability and thrombo inflammation associated with acute infection. The acute lung injury that occurs initially in COVID-19 results from vascular and endothelial damage from viral injury [10].

In this context, cerebral venous thrombosis is the most common manifestation of this syndrome, but it has not yet been described in detail. Thus an important multicenter cohort study documented the worst characteristics of post-vaccination cerebral venous thrombosis with and without vaccine-induced immune thrombotic thrombocytopenia (VITT). Of the total of 95 patients, 70 had VITT, and 25 did not. The median age of the VITT group (47 years, 32-55) was lower than that of the non-VITT group (57 years; 41-62). Patients with cerebral venous thrombosis associated with VITT had more thrombosed intracranial veins than non-VITT patients and more often had extracranial thrombosis compared to non-VITT patients. The primary outcome of death or dependence occurred more frequently in patients with cerebral venous thrombosis associated with VITT (47%) compared to the non-VITT control group (16%) [11].

Also, a retrospective study described the clinical manifestations and management of patients with cranial venous sinus thrombosis after the first exposure to the ChAdOx1 nCoV-19 vaccine. Three women were found with intracranial venous sinus thrombosis after their first vaccination with the adenovirus ChAdOx1 nCoV-19. Patient 1 was 22 years old and developed headaches four days after vaccination. On day 7, she had a generalized epileptic seizure. Patient 2 was 46 years old and had severe headaches, right hemianopia, and mild aphasia 13 days after vaccination. Magnetic resonance imaging showed left occipital intracerebral hemorrhage. Patient 3 was 36 years old and 17 days after vaccination had acute somnolence and right hemiparesis. All three patients were diagnosed with extensive sinus venous thrombosis. They were treated by heparinization and endovascular recanalization of their venous sinuses. All had elevated levels of D-dimers, factor 4 antiplatelet antibodies, corona peak protein antibodies, and thrombocytopenia [12].

Besides, a case report showed a major hemorrhagic stroke 5 days after vaccination with ChAdOx1 nCoV-19. A 57-year-old woman took the first dose of the ChAdOx1 nCoV-19 vaccine and shortly thereafter developed mild systemic symptoms and started taking aspirin. On day 5, she had a sudden onset of sweating and pallor, followed by left hemiparesis, vomiting, and drowsiness. Computed tomography showed a large parenchymal hematoma of the deep right frontal lobe with flooding of the entire ventricular system. Platelet count, fibrinogen, prothrombin time, and D-dimer were normal. Digital subtraction angiography showed no signs of thrombosis or aneurysms in the cerebral circulation [13].

Also, one study estimated the incidence of cerebral venous thrombosis (CVT) within 1 month of administration of the first dose and the frequency of vaccine-induced immunologic thrombotic thrombocytopenia (VITT) after vaccination with BNT162b2, ChAdOx1 and mRNA-1273, in Germany. A total of 45 cases of CVT have been reported. In addition, 9 primary ischemic strokes, 4 primary intracerebral hemorrhages, and 4 other neurological events were recorded. Of the patients with CVT, 35 (77.8%) were female

and 36 (80.0%) were under 60 years of age. Fifty-three events were observed after vaccination with ChAdOx1 (85.5%), 9 after vaccination with BNT162b2 (14.5%) and none after vaccination with mRNA-1273. In the general context, after 7,126,434 first doses of vaccine, the incidence rate of CVT within 1 month of administration of the first dose was 0.55 (100,000 person-months (corresponding to a risk of CVT). in the first 31 days) for all vaccines, and 1.52 for ChAdOx1 (after 2,320,535 first doses of ChAdOx1). The adjusted incidence rate ratio was 9.68 for ChAdOx1 compared to mRNA-based vaccines and 3 .14 for women [14]. In this regard, there are strategies for rapid assessment and treatment of CVT in the context of possible VITT, including measurements of inflammatory markers, PF4 assays, and heparin-free anticoagulation [15].

In this setting, a review study provided up-to-date information on the critical issue of thrombosis with thrombocytopenia syndrome (TTS) related to the COVID-19 vaccine. Most cases of TTS developed in women within 2 weeks of the first dose of ChAdOx1 nCoV-19 and Ad26.COV2.S vaccines. STT occurs mainly in patients under 55 years of age and is associated with high morbidity and mortality. Non-heparin anticoagulants such as fondaparinux, argatroban, or a direct oral anticoagulant (eg apixaban or rivaroxaban) and intravenous immunoglobulins are recommended for the treatment of TTS [16].

In this sense, thrombosis with associated thrombocytopenia may be related to interactions of the spike protein of SARS-CoV-2 with different C-type lectin receptors, heparan sulfate proteoglycans (HSPGs) and the CD147 receptor, or different splice variants soluble spike protein, adenovirus vector interactions with the CD46 receptor or platelet factor 4 antibodies. Furthermore, the immunological mechanisms triggered by viral vectors related to cell distribution may play a relevant role in individuals with a genetic background, and risk groups such as the elderly, chronic smokers, and individuals with pre-existing incidences of thrombocytopenia [17]. Despite these findings, the risk of serious adverse effects is low after vaccination of more than 400 million people worldwide [18].

Final Considerations

Several studies have been published regarding cerebral thrombosis, stroke, and thrombotic thrombocytopenic events. Thus, safe and effective vaccines against COVID-19 are an urgent need, as they can leave pathophysiological responses of hypercoagulability and thromboinflammation associated with acute infection.

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