



Pure Sensory Stroke, Thrombotic Microangiopathy Post AstraZeneca/Covishield Vaccine for COVID-19: A Case Report

Sushil K. Mehandru¹

Supreet Kaur¹

Rizwana Khan¹

Aisha Masud¹

Eric Costanzo¹

Arif Asif¹

Tushar J. Vachharajani²

¹Department of Medicine, Hackensack Meridian School of Medicine, Jersey Shore University Medical Center, Neptune, New Jersey; USA.

²Department of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio; USA

Abstract

AstraZeneca/Covishield, COVID-19 vaccine AZ 1222/AZD 1222 (ChAdOx1-S[recombinant]), has been associated with cases of thrombotic and thromboembolic events. This unique case report is of Pure Sensory Stroke with left-sided facial, left upper and lower limb numbness, dysesthesias, paresthesias, and pain, with no weakness reported at any time. MRI of the brain was negative. Serum D-dimer and fibrinogen levels were elevated with normal platelet count and absence of disseminated intravascular coagulation. These neurological changes were most likely vaccine-induced through several different mechanisms. Possible thrombotic microangiopathy likely resulted from transient, partial thrombosis of right-sided thalamoperforate arteries. Thrombotic ischemia of both trigeminal and lemniscus in the dorsal paramedian pontine region is less likely because the trunk was spared. The patient was functional during this episode that started two weeks after administration of the vaccine and recovered within two weeks after the onset of this neurological occurrence. The patient tested negative for COVID-19 infection. Hypercoagulable state was most likely due to local cytokine storm with inflammation and partial thrombosis of the arteries, in response to the vaccine. Possibility of Pure Sensory Stroke without a motor deficit in patients post administration of adenovirus-based COVID-19 vaccine should be considered among differential diagnoses.

Running Title

COVID-19 Vaccine, Pure Sensory Stroke, Thrombotic Microangiopathy, Transient

Keywords

SARS-CoV-2, Covishield (ChAdOx1-S[recombinant]), thalamoperforating arteries, transient ischemia, thrombotic event, Pure Sensory Stroke

Conflict of Interest

None of the authors declare conflict of interest.

Introduction

COVID-19 vaccine by AstraZeneca is an adenovirus vector vaccine which received conditional marketing authorization in the European Union (EU) on January 29th, 2021, for active immunization against COVID-19 in individuals 18 years of age and older. A similar vaccine, Oxford-AstraZeneca Covishield, manufactured by the Serum Institute of India was approved for administration in India. Cases of thromboembolic events have been reported following the administration of the COVID-19 vaccine AstraZeneca in several European Economic Area (EEA) countries. Natural infection with SARS-CoV-2 has been associated with hypercoagulability, thrombotic microangiopathy (TMA), and venous or arterial thromboembolic events. One of the mechanisms hypothesized for hypercoagulable state seen in patients with severe COVID-19 is related to the high-grade systemic inflammatory response. The onset of venous or arterial thrombosis particularly at unusual sites such as in the brain or abdomen and thrombocytopenia beginning approximately 5 to 20 days after

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*Corresponding author:

Sushil K. Mehandru, MD

Professor of Medicine
Hackensack Meridian School of Medicine
Director, Mehandru Center for Innovation in Nephrology

Jersey Shore University Medical Center
1945 NJ-33 Neptune, NJ 07753

Tel: 732-974-0100

Email: doc1732@aol.com

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vaccination can represent a rare adverse effect of preceding COVID-19 vaccination [1]. Thrombotic events were reported in several cases e.g., deep vein thrombosis, hepatic vein thrombosis, mesenteric vein thrombosis, portal vein thrombosis, carotid artery thrombosis, peripheral artery thrombosis, and cerebral venous sinus thrombosis. Other reported events included pulmonary embolism, thrombocytopenia, and disseminated intravascular coagulation (DIC). No cases of pure sensory stroke following administration of adenovirus based COVID-19 vaccine have been reported to the best of our knowledge.

Although the main function of thrombin is to promote clot formation by activating platelets and by converting fibrinogen to fibrin, thrombin also exerts multiple cellular effects and can further augment inflammation via proteinase-activated receptors (PARs), principally PAR₁ [2]. Thrombin generation is tightly controlled by negative feedback loops and physiological anticoagulants, such as antithrombin III, tissue factor pathway inhibitor, and the protein C system. During inflammation, all three of these control mechanisms can be impaired with reduced anticoagulant concentrations due to reduced production and an increased consumption. This defective pro-coagulant-anticoagulant balance causes a predisposition to the development of micro-thrombosis, disseminated intravascular coagulation, and multi-organ failure. Raised D-dimer concentrations are a poor prognostic factor and DIC has been seen as a common occurrence in non-survivors [2].

Role of Cytokine Storm

The overproduction of early response proinflammatory cytokines (Tumor necrosis factor [TNF], IL-6, and IL-1B) result in what has been described as a cytokine storm, leading to vascular hyperpermeability, multi-organ failure, and eventually death when cytokine concentrations are unabated over time [3]. Therefore, therapeutic strategies under investigation are targeting the overactive cytokine storm with anti-cytokine therapies or immune modulators, but this must be balanced while maintaining an adequate response to pathogen clearance. Local excessive release of cytokines is the decisive factor that induces pathological change and clinical manifestation [4]. Activation of coagulation pathways during an immune response to infection results in the overproduction of proinflammatory cytokines leading to multiorgan injury. Due to impairment of control mechanism the inflammatory balance is disturbed. Targeting thrombin, coagulation factor Xa or PAR₁ might therefore be an attractive approach to reduce SARS-CoV-2 induced micro thrombosis.

Role of D-Dimer

A positive D-dimer result may be indicative of the presence of an abnormally high level of a fibrin degradation product. It indicates that there may be significant thrombus formation and breakdown in the body, but it does not specify the location or the cause. The absence of D-dimer means that a blood clot is highly unlikely. D-dimer is crosslinked by (factor XIII) fibrin. It reflects the ongoing activation of the hemostatic system. Many previous studies have shown that the D-dimer test is highly sensitive (>95%) in acute deep venous thrombosis or pulmonary embolism, usually with a cut-off value of 500 µg FEU/l, which reasonably rules out acute venous thromboembolism, particularly in patients with low clinical probability (LCP) or intermediate clinical probability [5].

False positive readings of D-dimer can be due to various reasons such as liver disease, high rheumatoid factor, inflammation, malignancy, trauma, pregnancy, or recent surgery. False-negative readings can also occur if the sample is taken

either too early after thrombus formation or if testing is delayed for several days.

Infection due to viral, bacterial, or fungal pathogens initiates complex systemic inflammatory responses as a part of innate immunity. Activation of host defense systems results in subsequent activation of coagulation and thrombin generation as communication components among humoral and cellular amplification pathways, a term called immune thrombosis. There is a strong immune response that most likely comes after the vaccine. This may lead to DIC and microthrombus. Leukocytes themselves can enhance coagulation by expressing transmembrane protein tissue factor (TF) and by releasing TF & MV (Membrane Derived Microvesicles) [6]. More importantly, neutrophils release neutrophil extracellular trap (NETs) after activation [7, 8].

Due to elevated D-dimer and fibrinogen levels in this patient, the above mechanisms may have played a role in possible TMA occurrence in this case.

Case Report

The 72-year-old female started complaining of left facial, left upper and lower extremity tingling and pain, needlelike pricking, and numbness. She received the first dose of Covid-19 vaccine, Covishield two weeks prior to this event. She reported no initial reaction to the vaccine for the first two weeks. There were no reports of muscle weakness. Patient has a history of essential hypertension, well controlled with medication. MRI of the brain was negative. Laboratory reports showed a normal platelet count. D-dimer was elevated, 1020.8 µg FEU/l (normal: <500 µg FEU/l). Lab reports of fibrinogen levels also showed elevation, 391 mg/dL (normal: 180-350 mg/dL). Neurological examination revealed scattered sensory loss over the left side of the face as well as left upper and lower extremities. The trunk was spared of all neurological symptoms. Repeat test two weeks later showed improvement of D-dimer to 759 µg FEU/l and fibrinogen levels declined to 365 mg/dL. The patient had been taking Aspirin 81 mg daily that was increased to 325 mg daily. All neurological symptoms were abated within two-week period.

Discussion

Pure sensory stroke (PSS) is a well-defined clinical entity showing prominent hemisensory manifestations without other major neurologic signs [9]. Fisher attributed this syndrome to a lacunar infarct in the ventroposterior (VP) nucleus of the thalamus. Although thalamic stroke is the most frequent cause of PSS, nonthalamic strokes involving the brainstem, internal capsule, or cerebral cortex also have been reported to produce PSS [10, 11]. The common clinical manifestation of PSS is a sudden onset of persistent sensory deficits (decreased superficial and deep sensations) and numbness (dysesthesias and paresthesias) of the face, arm, leg, and trunk on one side in the absence of weakness, homonymous hemianopsia, aphasia, agnosia, and apraxia [12]. (Table)

mRNA-based vaccine by Pfizer and Moderna is characterized by lipid nanoparticles formulated nucleotide modified mRNA that encodes perfusion stabilized membrane-anchored SARS-CoV-2 full-length spike protein. This vaccine has been reported to cause local or systemic reaction, fatigue, headaches, fever, lymphadenopathy, and ventricular arrhythmias. No thrombotic event leading to cause pure sensory loss has been reported. Rare cases of paresthesias and facial tingling have been reported. A PSS manifesting with isolated paresthesias may be secondary not only to a thalamic lacunar stroke, but also a small ischemic region confined to both trigeminal and medial lemniscus in the dorsal

Condition	Thalamic Region	Pontine Region
Dysesthesias (Burning, wetness, itching, electric shock, pins & needles) (Painful)	Less severe	Severe
Paresthesias (Tingling, pricking, chilling, burning, numbness) (Painless)	Less severe	Severe
Vibration	Not present	Present
Position Sense	Not present	Present
Trunk PSS	Spared	Present

paramedian pontine region [13]. This was not evident in our case because the trunk was spared.

Adenovirus recombinant vector protein vaccine by AstraZeneca, Johnson and Johnson, Covishield, Covaxin, and several others have been reported to cause many cases of thrombosis, thromboembolic events, and DIC. The antigen binds to platelets and causes platelet preactivation. Many cases of venous and arterial thrombosis in unusual sites have been reported beginning 5 to 14 days after vaccination. Post-vaccination anti PF4 antibody-associated thrombocytopenia and thrombosis, especially as a strong positive immunoassay result obtained in a patient not exposed to heparin.

One hypothesis is that mRNA vaccine (Pfizer and Moderna) and those using adenovirus (AstraZeneca and Johnson & Johnson) could induce synthesis of the COVID spike protein within platelets, which may then trigger autoimmune reactions against platelets [14]. Greinacher et al., have speculated on a possible mechanism, an adenovirus engineered to infect cells and prompt them to produce the virus' spike protein [15]. Among 50 billion or so virus particles in each dose, some may break apart and release their DNA [15]. Like heparin, DNA is negatively charged, that helps to bind with PF4, which has a positive charge. The complex might then trigger the production of antibodies, especially when the immune system is already on high alert because of vaccine administration. Greinacher further notes that free DNA itself can signal the body to increase blood coagulation [1]. Alternatively, the antibodies may already be present in the patient and the vaccine may just boost them. Many healthy people harbor such antibodies against PF4, but they are kept in check by an immune mechanism called peripheral tolerance; these mechanisms may get disrupted post-vaccine administration.

During AstraZeneca's phase 3 trial in the United Kingdom, a small number of people accidentally received a lower dose and had fewer side effects in general, it may be likely that the lower dose did not trigger a strong inflammatory response that boosts PF4 antibodies. These individuals were slightly better protected because high levels of inflammation can block the formation of antibodies, leading to poor response to the vaccine.

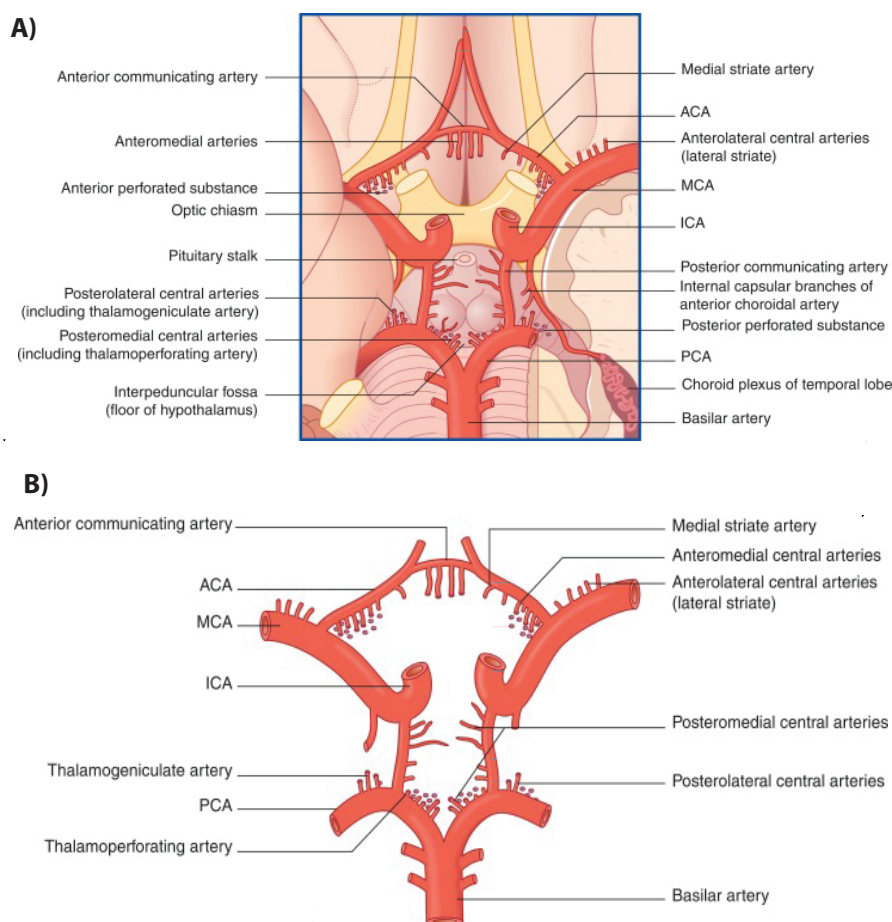
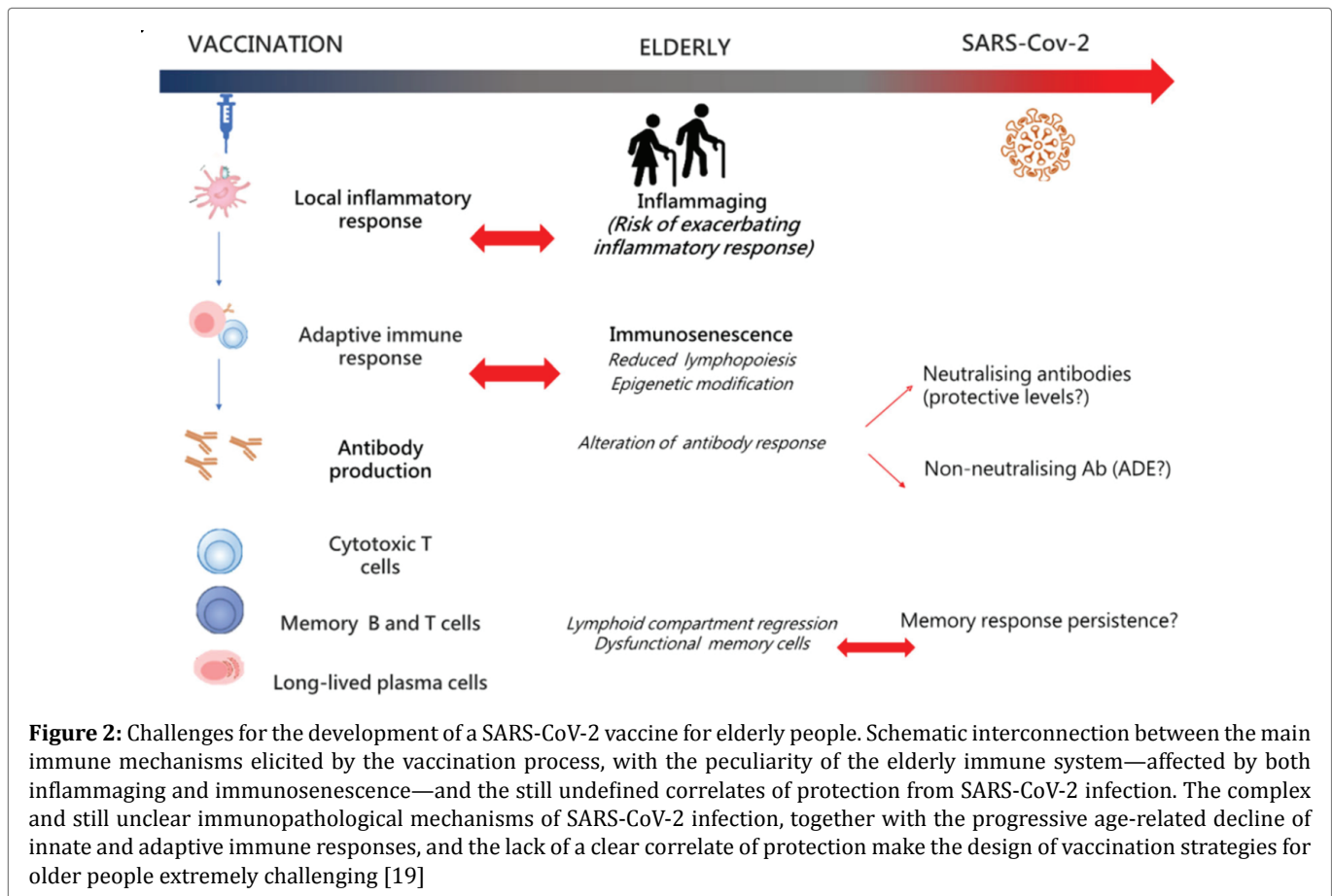


Figure 1: (A) Brain viewed from below, showing background structures related to the circle of Willis. Part of the left temporal lobe (to the right of the picture) has been removed to show the choroid plexus in the inferior horn of the lateral ventricle. **(B)** The arteries comprising the circle of Willis. The four groups of central branches are shown; the thalamoperforating artery belongs to the posteromedial group, and the thalamogeniculate artery belongs to the posterolateral group. ACA, MCA, PCA, anterior, middle, posterior cerebral arteries; ICA, internal carotid artery [17].



The presumed cause of “pure sensory stroke” was small artery disease, thrombosis, or ischemia. The inferolateral region (thalamogeniculate arteries) was involved in patients with pure sensory stroke [16]. Sensory symptoms and signs were the only clinical abnormality. Out of 22 patients studied with this condition, 6 complained of pain and/or dysesthesias, 5 of them had involvement of the nucleus ventrocaudalis, one patient had involvement of nucleus ventro-oralis intermedius. 18 out of 22 patients complained of paresthesias of the contralateral part of the body. 4 patients developed delayed pain and/or dysesthesias. Restricted sensory abnormalities correlate with very small lesions located in the critical area within these nuclei (Figure 1) [9].

The perforating arteries arising at the base of the brain from the posterior communicating arteries and the basilar bifurcation, which contribute part of the blood supply to the thalamus, are designated as thalamoperforating arteries (Figure 1) [18].

A common characteristic of the elderly population is the onset of sterile low-grade increase of the basal inflammatory state named “inflammaging”, which is considered a universal etiological agent of most age-related diseases [20]. It is likely that some specific components of inflammaging phenotype could both influence vaccine efficacy and then increases the risk of the early massive production of inflammatory cytokines, termed “cytokine storm syndrome” (Figure 2) [19]. For RNA viruses, such as Coronavirus, different pattern recognition receptors (PRR) are triggered on the innate cells during the early phase of infection [19].

Local Inflammatory Response to Vaccine

Cytokine storm is a general term applied to maladaptive cytokine release in response to infection and other stimulants such as a vaccine. The pathogenesis is complex but includes loss of regulatory control of pro-inflammatory cytokine production,

both at the local and systemic level [21]. Local cytokine storm can occur with lower cytokine levels. At high enough levels, cytokines can also have systemic activation [22].

Another possible mechanism behind the thrombosis is mentioned by Merrill et al. They state that disorder causing thrombosis in COVID-19 infection is not typical DIC, rather it might be more similar to complement mediated thrombotic microangiopathy (TMA) [23].

Conclusion:

Arterial and venous thrombosis has been widely reported after administration of the adenovirus-based SARS-CoV-2 vaccine. Pure sensory stroke with dysesthesias, paresthesias, and pain, to the best of our knowledge, has not been reported before. This vaccine may have resulted in a local cytokine storm, inflammation, and thrombosis of the thalamoperforating arteries. Thrombosis in this patient most likely resulted from partial obstruction of these tiny arteries supplying the thalamus whereas ischemia of both trigeminal and lemniscus in the dorsal paramedian pontine region is less likely because the trunk was not involved in the neurological event. The patient recovered completely within two weeks post-onset of the symptoms.

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