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CASE REPORT

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Serious events following COVID-19 vaccination with ChAdOx1 nCoV-19 vaccine (Vaxzevria): A short case series from Iran

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Abstract

In 2020, the SARS-COV-2 disease (COVID-19) imposed huge challenges on the health, economic, and political systems, and by the end of the year, hope had been born with the release of COVID-19 vaccines aimed at bringing the pandemic to an end. However, the COVID-19 vaccination programs have sparked several concerns and ongoing debates over safety issues. Here, we presented three cases of patients with serious adverse events, encephalopathy, vaccine-induced thrombotic thrombocytopenia, and leukocytoclastic vasculitis, after receiving the ChAdOx1 nCoV-19 vaccine. Therefore, it is critical to investigate and report the occurrence of adverse reactions following vaccination, particularly serious ones, as it contributes to the growing body of research and assists clinicians in better diagnosing and managing them.

KEYWORDS

adverse effects, ChAdOx1 nCoV-19 vaccine, COVID-19 vaccination, Leukocytoclastic Vasculitis due to vaccination, postvaccination encephalopathy, vaccine-induced thrombotic thrombocytopenia

1 | INTRODUCTION

The coronavirus disease (COVID-19) contributed to a worldwide crisis causing major morbidity and mortality as well as devastating economic and social consequences. As for previous infectious diseases, vaccination is considered vital to control the COVID-19 pandemic. With unprecedented speed, several vaccines were developed and licensed internationally. In addition, the European Medicines Agency (EMA) approved the recombinant

chimpanzee adenoviral vector vaccine ChAdOx1 nCoV-19 (Vaxzevria /previously COVID-19 vaccine AstraZeneca) for vaccination against COVID-19.

Among several side effects of vaccines, concerns about unusual thrombotic events following COVID-19 vaccination with AstraZeneca started to grow early in March 2021. Several researchers from Norway,[1] Germany,[2] and United Kingdom[3] reported a group of patients who had been admitted within three weeks of AstraZeneca vaccine inoculation with thrombocytopenia and cerebral venous sinus thrombosis (CVST). In terms of neurological adverse effects, headache, decrease in mental attention, paralysis or weakness of extremities, dizziness, paraesthesia, and numbness were the most prevalent ones. [4,5,6]Complaints such as loss of consciousness, seizures, and facial weakness were rare, though.[4] Skin manifestation of COVID-19 vaccination ranged wide spectrum including chilblain-like, urticarial, vesicular, maculopapular, livedoid, and vasculitic lesions.[7,8]Thus, it seems that COVID-19 vaccines have a wide spectrum of adverse effects and further investigations are needed to help clinicians for better diagnosis and management.

The current paper aims to report three post-AstraZeneca COVID-19 vaccination events causing hospitalization, including encephalopathy, CVST, and leukocytoclastic vasculitis (LCV).

2 | CASES

2.1 | Case 1. Postvaccination encephalopathy

The patient was a 56-year-old female laboratory technician with no remarkable medical history and drug consumption. She was admitted to the hospital with complaints of confusion, decreased level of consciousness, and some degree of disorientation. She had received the first shot of the AstraZeneca COVID-19 vaccine one week before the admission. Two days after vaccination, her symptoms initiated with general weakness, myalgia, headache, and low-grade fever that gradually worsened. The symptoms continued with decrease in consciousness, disorientation, bizarre behaviors, and agitation during 72 h that eventually led to hospital admission. At the time of hospital admission, the patient was confused, and her neurological examination demonstrated disorientation to time, place, and person. She also had impairment in gait and the finger-to-nose test. Glasgow coma scale revealed E3M5V3 (an eye,[3] verbal,[3] and motor[5] response). Other neurological examinations (i.e., sensory, cranial nerves, and speech) were normal. Her vital signs were stable except for fever (38.6°C).

With clinical suspicious of viral encephalitis, lumbar puncture was done and intravenous acyclovir, 10 mg/kg every 8 h, was started. The patient's orientation and consciousness improved within less than two days. Cerebral spinal fluid (CSF) was clear and colorless with a total WBC count of <5 cells/mm^3, a normal glucose level, and significantly raised protein concentration of 119mg/dl. However, CSF viral panels (HSV1, HSV2, CMV, EBV, VZV, HHV6, HHV7, and HHV8) polymerase chain reaction (PCR) were negative. Acyclovir was discontinued. Further laboratory studies including complete blood count (CBC), blood electrolytes (Na, K, P, Ca, and Mg), liver enzymes tests, urine analysis and culture, blood culture, blood and urine toxicology, blood gases test, coagulation tests, and SARS-COV-2 PCR were all unremarkable. She also underwent brain MRI that was normal. Rapidly, the patient's general condition was ameliorated, and she was discharged two days later and referred to the outpatient clinic for a follow-up visit. Clinical and neurological conditions were normal at the follow-up visit one month later.

2.2 | Case 2. Vaccine-induced thrombotic thrombocytopenia

A 70-year-old female patient with a past medical history of diabetes mellitus type 2, hypertension, and coronary artery disease (had undergone percutaneous coronary intervention 10 years ago) received her first shot of COVID-19 AstraZeneca vaccine in late May 2021(Day 0). The following day she developed a generalized persistent headache that, despite consumption of acetaminophen, did not improve. The next day she experienced a single episode of generalized tonic-clonic seizure that led to refer to the local hospital. During the hospital stay, laboratory findings revealed a mild leukocytosis (WBC: 12,000/μl), mildly elevated aspartate aminotransferase test (AST: 60 U/L), an increased lactic acid dehydrogenase (LDH: 630 U/L), and a high creatine phosphokinase level (CPK: 450 mcg/L); however, the rest (BUN, Creatinine, ESR, CRP, and urine analysis) were normal. The neuroimaging findings including brain computed tomography (CT), magnetic resonance imaging (MRI) imaging, and magnetic resonance venography (MRV) were unremarkable, according to the radiologist report from that center. The patient was discharged 5 days later due to normal workups, no new seizure, and amelioration of her headache.

After a few days, headache and convulsions commenced again, and their severity and frequency worsened gradually that finally led to hospitalization at our center after approximately 2 weeks (Day 21). At the admission, the patient was lethargic and was experiencing seizure episodes 2–3 times per day, each one lasting 2–3 min. Clinical

and neurologic examinations showed no remarkable findings, and all her vital signs were within a normal range (BP: 120/80, T: 36.8°C, HR: 75, RR: 14, and O2sat:96%). The primary ECG showed no pathologic findings. At this time, moderate thrombocytopenia [78 × 103 /ml; normal reference range (NRR) 150–450 × 103 /ml] with normal peripheral blood smear morphology, markedly elevated D-dimer (11 μg/ml (<0.5)), a fibrinogen level at the lower limit of the normal range, anemia (Hgb: 9.4 g/dl), and elevated inflammatory markers (ESR: 45 mm/1h, CRP: 25 mg/L) were detected. Other blood tests were normal. Thus, Vaccine-induced thrombotic thrombocytopenia (VITT) was suggested,[9] and further investigations were requested.

The anti-PF4 IgG antibody ELISA tests were positive (380 ng/ml (42.1–313.40)). Brain CT venography findings were in favor of cerebral venous sinus (sagittal sinus) thrombosis (CVST), so the patient underwent brain MRI. In brain MRI, periventricular abnormal signals without diffusion restriction were seen in favor of small vessel, ischemic changes (FAZEKAS III) and T2 and diffusion-weighted signal changes representative of acute infarction were also visible in left occipital lobe. In brain, MRV filling defect in favor of left transverse sinus thrombosis was seen (Figure 1). Finally, brain and cervical MRA were also unremarkable, and no pathologic finding was observed.

During hospital stay, intravenous immunoglobulin (IVIG) (1 gr/kg/day for 2 days), corticosteroids (0.5 mg/kg prednisolone), rivaroxaban (15 mg/BID), sodium valproate, and levetiracetam were started. Convulsions ceased within two days, and platelet began going up on the 3rd day. The patient's general condition gradually improved, seizures were controlled, the patient's D-dimer decreased, and platelets and hemoglobin returned to normal, and after 10 days, the patient was discharged from the hospital with continued anticoagulants and anticonvulsants drugs.

2.3 | Case 3. LCV

A 77-year-old female patient with hypertension (HTN) presented to our emergency room with complaint of a five-day extensive rash and edema, which was commenced two days after receiving her first shot of COVID-19 AstraZeneca vaccine. At the admission, she had extensive palpable purpura and non-pitting edema on both lower extremities, below the knees (Figure 2). Rests of her examinations were unremarkable, and the vital signs were within the normal range. Thus, she hospitalized and underwent further investigations. Initial laboratory tests revealed a pancytopenia (WBC: 1,300/ml (neutrophil: 60%, lymphocyte: 37%), Hgb: 7.7 gr/dl, and platelet: 75,000/ml), elevated erythrocyte sedimentation rate (71 mm/h; normal reference range (NRR) 0-30 mm/h), high lactic acid dehydrogenase(LDH) (584 U/L; normal reference range (NRR) 140–280 U/L), an elevated NT-PRO-BNP level (3780 pg/ml), and a significantly elevated D-dimer (2.5 μg/ml; normal reference range (NRR) <0.5 μg/ml); however, the rest (CRP, FBS, LFT, BUN, Cr, urine analysis, albumin, fibrinogen, and coagulation tests) were normal. The examination of peripheral blood smear (PBS) revealed Rouleaux formation and platelet aggregation (Figure 2). Polymerase chain reaction (PCR) test for COVID-19 was negative. Patients' characteristics are summarized in Table 1.

Due to patients' clinical manifestations and laboratory findings, a possibility of vasculitis was suggested. Prednisolone (0.5 mg/kg/day) prescribed and skin biopsy and further tests were ordered. HIV Ag/Ab and viral hepatitis panels were negative. Immunological screening including C3, C4, CH50, ANA, Antids DNA, ANCA-C, and ANCA-P were normal. Microscopic examination of skin specimen revealed vasculopathic changes characterized by perivascular lymphocytic infiltrate with few nuclear

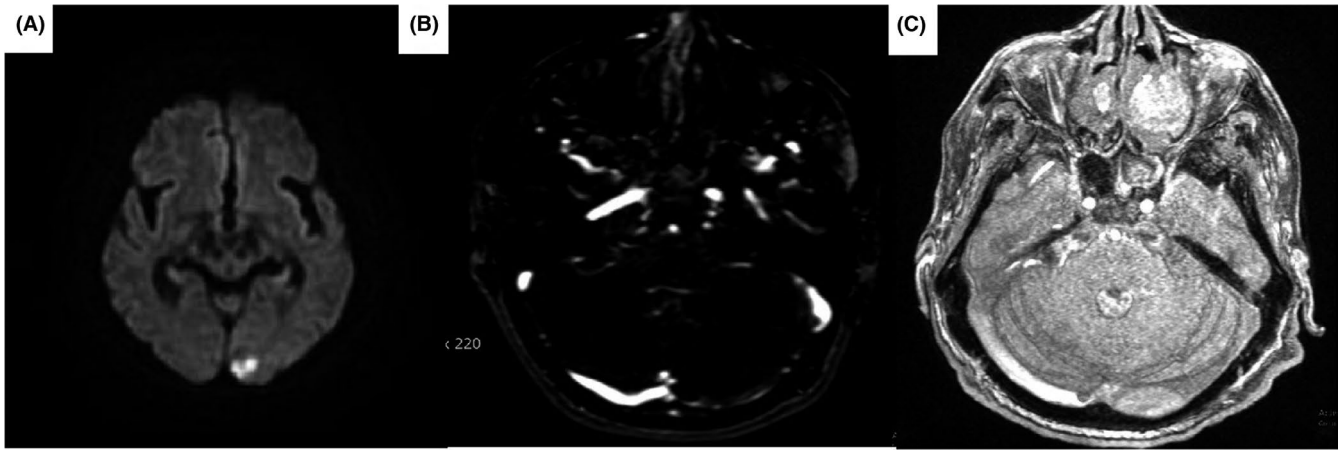

FIGURE 1 Patient 2 brain MRI, (A) acute infarction in left occipital lobe, (B and C) filling defect in left transverse sinus representative of thrombosis is visible

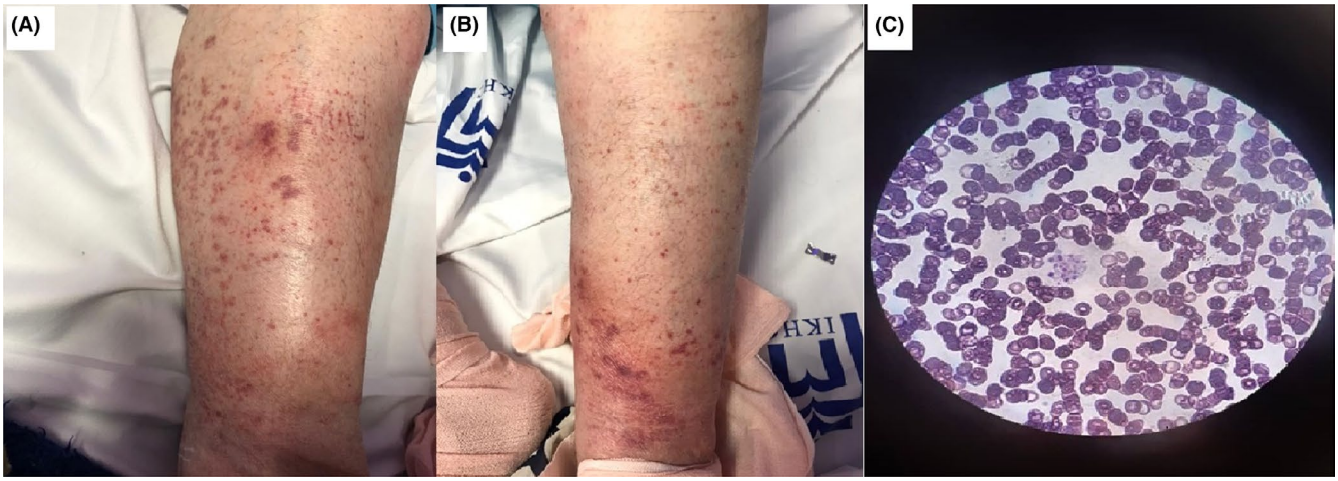

FIGURE 2 Patient 3, (A and B) Palpable purpura and non-pitting edema on lower extremities, (C) platelet aggregation and Rouleaux formation in PBS

debris, permeating into vessel wall with endothelia thickening and extravasated RBC. Foci of microhemorrhage in superficial dermis also identified. Purpuric vasculopathic reaction pattern of lymphocytic type in histopathology was compatible with purpric lymphocytic vasculitis diagnosis. Finally, one week after treatment rash and symptoms resolved, blood cell count improved (WBC: 4150, HB: 10.2, and PLT: 110,000) and the patient was discharged.

3 | DISCUSSION

Herein, we reported three cases of serious events of post-COVID-19 AstraZeneca vaccination that hospitalized and managed successfully, including encephalopathy, CVST, and LCV. However, all discussed cases were categorized as probable but not definite cases caused by COVID-19 vaccination according to causality assessment of adverse drug reaction (ADR) with COVID-19 vaccination based on ADR scales including Naranjo Probability Scale[10] and WHO-UMC causality system.[11] Severity of ADR by COVID-19 vaccination for presented cases was evaluated by J Seigel and PJ Schneider study[12] and also Karch and Lasanga study,[13] postvaccination encephalitis and VITT were classified as severe cases requiring intensive medical care which are life-threatening reactions, while LCV categorized with moderate severity requiring special treatment with an increase in hospitalization by at least one day.

There have been several side effects after injection of AstraZeneca vaccine including pain and tenderness at the injection site, fatigue, headache, malaise, chills, arthralgia, fever.[14] However, severe side effects of AZ raised the concerns on continuing vaccination with AZ vaccine in European countries with unusual thrombotic events,[12]or encephalopathy,[15] pericarditis, myocarditis, anaphylaxis, and Guillain–Barré syndrome.[16]

Encephalitis/encephalopathy is defined as inflammation of brain tissue provoked by an infection or an autoimmune response.[17] The occurrence of encephalitis, according to several publicly existing databases (Welcome to GOV.UK (www.gov.uk), European Medicines Agency | (europa.eu), Paul-Ehrlich-Institut - Startseite (pei.de)), estimated to be 8 per 10 million injected shots following AstraZeneca vaccination.[18] Possible or confirmed diagnosis of encephalitis is determined by combination of clinical manifestations, laboratory tests, neuroimaging, and electroencephalographic studies.[19] Our first case had the major criteria of encephalitis according to Venkatesan et al.[19] presenting to medical attention with altered mental status lasting ≥24 h with no alternative cause stated, and one minor criteria of documented fever within the 72 h prior or after presentation. The patient neuroimaging and CSF analysis were not compatible with encephalitis and EEG was not performed for her, so the complete criteria for encephalitis cannot be fulfilled and encephalopathy after vaccination may be more likely. However, it does not seem to be a just fever-related delirium due to patient's age, past medical history, and her clinical picture, and a CNS-related dysfunction is highly probable.

Previously reported postvaccination encephalopathy cases were all older than 50 years of age except for one 21-year-old female patient and were more common following ChAdOx1 nCov-19 administration. [18,20,21]Fever and myalgia were commonly seen. Alike our patient, brain imaging was normal in all of these reports and no remarkable finding was seen.[18,20,21]Two cases had abnormal findings in EEG, a 77-year-old male showed moderate diffuse slowing and another 77-year-old male presented generalized slow background in the theta range.[20,21]In terms

TABLE 1 Clinical characteristics of cases

Variables	Case 1. EncephalitisEncephalitis	Case 2. VITT	Case 3. CV
Sex	Female	Female	Female
Age (years)	56 years	70 years	77 years
Past medical history	None	DM II, HTN, CAD	HTN
Vaccination to first symptoms (day)	2 days	1 days	2 days
Complaints	Decreased level of consciousness, disorientation, fever, headache, myalgia	Headache, seizure	Extensive rash, edema in lower extremities
Examination	Mild disorientation to time, place, and person/ impaired gait and the finger-to-nose test	None	Palpable purpura and non-pitting edema on both lower extremities
Laboratory tests	High CSF Protean Positive CSF culture: *Staphylococcus epidermidis* Increased BUN, Cr Hyponatremia	Thrombocytopenia, anemia, elevated D-dimer, ESR, CRP/ Positive anti-PF4 IgG	Pancytopenia, Elevated D-dimer, ESR, LDH, NT-PRO-BNP
Imaging	Brain MRI: NL	CT venography: CVST MRI: Ischemic changes (FAZEKAS III), acute left occipital infarction brain MRV: Transverse sinus thrombosis	NA
Treatment	Acyclovir	IVIG, corticosteroids, rivaroxaban, sodium valproate, levetiracetam	Prednisolone
Outcome	Discharged	Discharged	Discharged

Abbreviations: CAD, coronary artery disease; DM II, diabetes mellitus type II.

of CSF analysis, in contrast with our patient, pleocytosis was a common finding being seen in 4 out of 5 cases and only one patient had normal WBC count with an elevated protein level.[18,20,21]

Vaccine-induced thrombotic thrombocytopenia is well-established side effect of AZ, and many studies reported the post AZ vaccination VITT. A review by Franchini et al.[22] on previous VITT cases due to AZ vaccine showed thrombotic complications occurred 5–25 days after first dose of AZ vaccination and in majority of cases site of thrombosis was cerebral veins, while splenic vein thrombosis and pulmonary embolism were in second and third place. Our patient showed initial symptoms on first day after vaccination and admitted to hospital but discharged due to improvement of patient's conditions, but on second admission, few days after discharge, CVST was detected on imaging and laboratory data confirmed the VITT by positive HIPA, PIPA, and anti-PF4 IgG ELISA tests.

Although the exact mechanism by which adenovirus-vectored COVID-19 vaccines cause VITT is unknown, previous studies have shown that VITT patients have anti-PF4 antibodies that bind to a highly restricted site on PF4,[23] and VITT antibodies can mimic the effect of heparin by binding to a similar site on PF4, allowing PF4 tetramers to cluster and form immune complexes, causing thrombosis and thrombocytopenia.[24]

Leukocytoclastic vasculitis is a cutaneous small vessel vasculitis of dermal capillaries and venules and typically presents with a painful, burning rash predominantly in lower extremities. It is often idiopathic but can be associated with infections, neoplasms, or medications.[25] However, relation between vaccination or immunization with vasculitis is not well determined; vasculitis precipitation has been reported secondary multiple vaccines including influenza virus, hepatitis B virus (HBV), Basil Calmette-Guerin (BCG), and human papillomavirus (HPV).[26]

Skin vasculitis with cutaneous lesions have been reported during mild and fulminant COVID-19 disease.[7] On the contrary, vasculitis was also reported after COVID-19 vaccination. Several case reports were reported skin vasculitis following vector-based vaccines including AZ[27,28,29] and Johnson Johnson.[30]

4 | CONCLUSION

Due to different and diverse side effects of COVID-19 vaccine, it is important for healthcare providers and patients to be aware that COVID-19 vaccination could rarely precipitate serious side effects, which caused hospitalization and extensive treatment.

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CONFLICT OF INTEREST

The authors state no conflict of interest that could negatively affect the study.

AUTHOR CONTRIBUTIONS

AZD, MS, and NK designed the study. HK and SAD helped in planning and supervised the work. MAA help with reviewing and reporting images. AHG helped in data collection. All authors participated in drafting and reviewing the manuscript.

ETHICAL APPROVAL

The study was approved by ethical committee of Tehran University of medical sciences.

CONSENT

The patients have provided written informed consent for the publication of the paper.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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