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Case Report

Anti-PF4 antibody negative cerebral venous sinus thrombosis without thrombocytopenia following immunization with COVID-19 vaccine in an elderly non-comorbid Indian male, managed with conventional heparin-warfarin based anticoagulation

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Introduction

The most neoteric, mercendized disquietude has been promoted by sporadic cases of COVID-19 vaccine induced thromboses [1,2]. From perspective of neurologists, infrequent cases of post-vaccination cerebral venous sinus thrombosis (CVT) have been a matter of consternation [3] apart from sporadic reports of other (non-CVT) neurological manifestations [4]. Several cases of CVT following immunization with adenovirus-vector vaccines ChAdOx1 nCOV-19 (Oxford-AstraZeneca) and Ad26.COV2.S (Janssen/J&J) have been reported [5,6] which is promoting "vaccine hesitancy", endangering vaccine implementation, and summoning strict vaccine surveillance and monitoring [5,7]. These two vaccines, do not require ultra-cold chain maintenance for storage, are befitting for middle/low-income countries [8]. However, amidst two, only Oxford-AstraZeneca vaccine is available in India branded as COVISHIELD [8].

CVT is a well-recognized form of stroke, especially affecting young women, resulting from partial or complete occlusion of cerebral venous sinus system or the small-caliber draining veins further leading to physiologic venous backflow, venous hypertension and reduced cerebrospinal fluid (CSF) absorption [9]. These will consequently result in localized parenchymal edema, infarction and rarely hemorrhage and raised intracranial pressure (ICP). It has kindred well-studied genetic and non-genetic risk factors [9]. COVID-19 itself has thrombogenic potential, which is managed by therapeutic/prophylactic anticoagulation [10]. Recently, COVID-19 vaccines too have been alleged to have similar potential [1–3,5,6,11]. Several patho-mechanistic models have been proposed to explain such vaccine induced immune-thrombosis [12]. Salient most amongst them is breach of immune tolerance and production of autoantibodies to platelet factor-4 (PF4) and has been termed as vaccine-induced thrombotic thrombocytopenia (VITT), having extraordinary resemblance to the well-known entity heparin-induced thrombocytopenia (HIT) [12]. A cascade of micro-events following intramuscular COVISHIELD inoculation includes microvascular injury, microhemorhage and activation of platelets with release of PF4, adenovirus cargo-dispersement with DNA-PF4 engagement might breach immune tolerance resulting in anti-PF4 directed autoimmunity [12]. The alternative pathomechanisms deciphered have stressed upon molecular mimicry, contaminants in vaccine proteins, vector-viral proteins, buffers or immunity against SARS-CoV-2 spike proteins [12].

Herein, the authors, report a case of CVT following immunization with COVISHIELD vaccine in an elderly Indian male without any pre-existing comorbidities. This is arguably the first report of such kind from India, and case will add to the tally of cases of CVT following COVISHIELD vaccination; besides, the fact that this patient had neither anti-PF4 antibodies nor thrombocytopenia and responded remarkably with low-molecular weight heparin (LMWH) therapy, will provide insights regarding other elusive mechanisms of CVT following COVISHIELD vaccination; questions

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the much-hyped "causal link" between vaccine and CVT and reinforces the concept of vaccination benefits against COVID-19 always outweigh risks.

Case report

51-year-old non-comorbid male, was admitted with subacute onset progressive persistent holocranial headache, for last 14 days, which was associated with vomiting on a couple of occasions without any definite aggravating or relieving factors. Headache had developed 6 days following immunization against COVID-19 with first-dose of COVISHIELD. Initially he took paracetamol (2g/day) as an over-the-counter remedy, which used to mitigate pain temporally to a certain extent and period. For last 2 days, alongside headache, he started complaining of double vision which appeared in horizontal gaze (double vision in right gaze was more than that of left gaze). His daughter also noticed loss of parallelism of her father's eyeballs in neutral position. There was no history of convulsion, diminution of vision or focal weakness. He never had been diagnosed with COVID-19 in past. He had no history of addiction and was not on any regular medication. There was no history of cranio-cervical trauma or infection in recent or remote past. Neurological examination was marked by presence of bilateral, asymmetric lateral rectus palsy (right more than left). Other systemic and neurologic examinations were noncontributory. Ophthalmoscopic examination revealed bilateral grade-2 papilloedema. Presence of holocranial headache, vomiting, bilateral lateral rectus palsy and papilloedema pointed towards raised ICP and possibility of CVT. Magnetic resonance imaging (MRI) of brain with contrast revealed no intraparenchymal lesion but MR venography revealed thrombosis in superior sagittal sinus and transverse sinus with presence of extensive venous collaterals (Fig. 1). Systemic risk factors for development of CVT i.e. myeloproliferative disorders, malignancies, neuroinflammatory pathologies (sarcoidosis, Behçet's disease, and systemic lupus erythematosus), antiphospholipid antibody syndrome, and thyroid disorders were excluded detailed relevant investigations. Complete hemogram, blood sugar, lipid profiles, liver and kidney function tests were normal. Tests for known genetic causes of thrombophilia had a negative result (protein C, protein S, anti-thrombin III, homocysteine levels were normal; factor V Leiden mutation was not detected). Serologies for HIV (1,2), hepatitis B and C were nonreactive. Electrocardiogram and echocardiography were normal too. Considering the temporal association and potential thrombotic potential of COVISHIELD vaccine, a probable diagnosis of vaccine induced CVT was made. However, in this case repeated tests for detection of thrombocytopenia and anti-PF4-antibodies were futile and thus a diagnosis of VITT could not be claimed. Other relevant investigations conclusively ruled out other systemic thromboses (i.e. pulmonary thromboembolism, splanchnic/abdominal thromboses, and thromboses involving the limbs). Patient was immediately put on subcutaneous LMWH (60mg twice/day for 14 days; considering normal platelet count and absence of anti-PF4 antibodies) with strict monitoring of activated partial thromboplastin time, prothrombin time international normalized ratio and D-dimer. It was followed by addition of warfarin (2mg/day from day 9 of LMWH therapy and subsequently 5mg/day after omission of LMWH) without any new complications. Patient was followed up for 3 weeks in our inpatient care with significant improvement in his clinical status. Headache and papilloedema had subsided completely in 1 week and 2 weeks, respectively, following anticoagulation therapy. Double vision and extraocular movements had improved remarkably after 3 weeks. This case was reported to the regional authorities concerned with adverse events following immunization (AEFI) and has been kept under close follow up. Expert opinion has been sought from the concerned national authorities for recommendation of the second-dose of the vaccine.

Discussion

New-onset uncharacteristic headache, a cardinal yet nonspecific symptom of CVT, is quite often present in vaccine recipients without CVT; thus creating diagnostic dilemma [9]. In case of CVT, there is no definite character of this new-onset headache but it is commonly associated with features of raised ICP, vomiting, papilloedema, unilateral or bilateral abducens nerve palsies [9], as in this case. Focal and global neurodeficits is common in CVT [9] but was absent in our case.

Following publication of several sporadic reports of post-immunization thrombosis following the Oxford-AstraZeneca vaccine, solicitude regarding safety has been the bailiwick of national/international healthcare administrations [1–3,5–7], even after unfailing evidences of excellent vaccine-efficacies in preventing severe disease and death from COVID-19, over several continents [13]. On instances, CVT following immunization with COVISHIELD vaccine have been found to have surprising resemblance with autoimmune HIT with anti-PF4 autoantibody positivity [14,15]. The antibody portion of PF4-HIT-IgG complexes bind Fc-Y receptors on platelets leading to crosslink formation and platelet activation further resulting in thrombin generation and thrombosis and thrombocytopenia [12,14,15]. The pathomechanism associated with anti-PF4 autoantibody production occur against non-enveloped double-stranded DNA vector vaccines (adenoviral vector vaccines) remains elusive. Again, Sputnik V which happens to be another recombinant adenovirus vaccine, against which no similar cases has been yet reported [16]. Some researchers have demonstrated that biodistribution of vaccines like COVISHIELD might be triggering spike-protein production in brain cells leading to consequent immune response culminating into thrombosis [17]. Apart from anti-PF4 autoantibodies and thrombocytopenia, raised D-dimer and disseminated intravascular coagulation (DIC)-like coagulopathy have been demonstrated in several other cases of CVT, unlike this patient [12,14,15,17].

Chance associations/clusters of rare events tend to occur commonly in analysis of large groups, and thus establishment of causal link is exquisitely difficult at times [18]. Gradual piling up of similar cases of cases in Europe and United States over short period of time [6,14,15], unusually remarkable presence of thrombocytopenia in many of the published data [6,14,15], dearth of similar cases in recipients with Moderna and Pfizer vaccines [6,14,15], high-levels of autoantibodies found against PF4-antigenic complexes (as seen in HIT) and occurrence of CVT and abdominal venous thromboses out of proportion to limb and pulmonary thromboses (most commonly involved in other forms of spontaneous venous thrombosis) [6,14,15] were robust cues that there might be something in addition to just a random association. Further studies termed this phenomenon as VITT [6,14,15].

The case reported here is unique in several aspects. The development of CVT without previous evidences of natural SARS-CoV-2 infection and conventional risk factors, following the COVISHIELD vaccination might well establish a temporal relationship with immunization as found in previous literatures. However, normal platelets counts, negative anti-PF4 autoantibodies, and incredible therapeutic response to LMWH-warfarin therapy were the striking dissimilarities. However, umpteen number of doubts remains to be resolved regarding CVT following COVISHIELD vaccination either associated with VITT or not. Notably, even after the roll-out of Oxford-AstraZeneca vaccine, incidence rate of CVT has remained similar [19]. Conscientious research will be urgently needed to delineate etiopathogenesis, natural history, incidence, probable risk

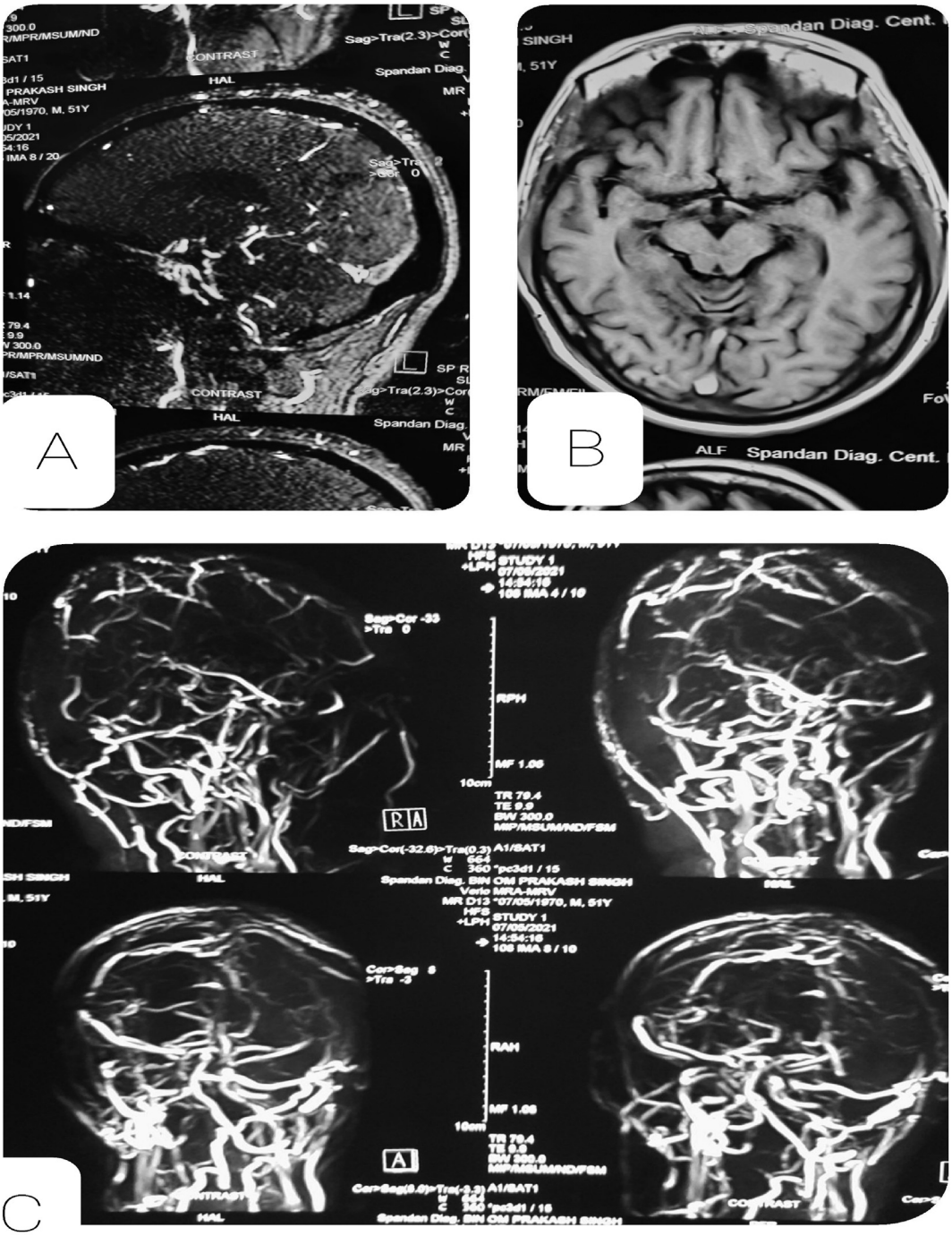

Fig. 1. A MR contrast venogram showing thrombus in confluence of sinuses. B- MR T1 weighted image showing thrombus in straight sinus, C- MR Venogram revealed non visualisation of superior sagittal sinus and extensive venous collaterals.

factors, earliest clinico-radiological diagnostic clues and specific management for this new entity of post-vaccination CVT with or without VITT.

In conclusion, the link between COVISHIELD vaccination and CVT has remained a field of rigorous research in good faith. The regulatory authorities should put forth the real data and analytics besides their conclusion on this topic swiftly to hasten roll-out of vaccines. First and foremost, keeping in mind that benefits of receiving any of the approved COVID-19 vaccines by far outweigh the potential risks, vaccination should be accepted at the earliest when offered. Secondly, of course, if any AEFI occurs, it should be promptly notified. Observing this duo will prevent death from both AEFI and COVID-19 itself.

Declaration of competing interest

Authors declare no conflict of interest.

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