Vaccine-Induced Thrombotic Thrombocytopenia Due to Coronavirus Disease 2019 Vaccine From a Deceased Donor: A Case Report

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ABSTRACT

With the rapid and massive vaccination campaign against coronavirus disease 2019 (COVID-19) taking place across the globe, there are increasing reports of thrombotic complications with various COVID-19 vaccines such as the Pfizer−BioNTech mRNA, Moderna mRNA, AstraZeneca Oxford (serum institute), and Johnson & Johnson/Janssen vaccines. We report a case of successful organ donation from an 18-year-old woman who presented with cerebral venous thrombosis caused by vaccine-induced thrombotic thrombocytopenia following the first dose of the COVID-19 vaccine (AstraZeneca, University of Oxford, and Serum Institute of India), which caused brain death. Four recipients received 5 organs, kidneys (2), liver (1), and combined heart and lung (1). All 4 recipients had normal graft function without any thrombotic complications after 16 weeks of transplantation. This is first such case being reported from Asian countries.

WITH rapid and massive vaccination campaign against coronavirus disease 2019 (COVID-19) taking place across the globe, there are increasing reports of thrombotic complications with various COVID-19 vaccines such as the Pfizer−BioNTech mRNA, Moderna mRNA, AstraZeneca Oxford (serum institute), and Johnson & Johnson/Janssen vaccines. We report a case of successful organ donation from an 18-year-old woman who presented with cerebral venous thrombosis because of vaccine-induced thrombotic thrombocytopenia (VITT) following the first dose of the COVID-19 vaccine (AstraZeneca, University of Oxford, and Serum Institute of India), which caused brain death.

CASE DETAILS

An 18-year-old woman presented to the hospital on June 9, 2021, with symptoms of headache and fever of 3 days duration, vomiting and swaying while walking of 1 day duration, and 1 episode of a seizure on the day of presentation. She had received the first dose of COVID-19 vaccine (AstraZeneca, University of Oxford, and Serum Institute of India) on May 30, 2021. She had no previous comorbidities (eg, hypertension, diabetes, coagulation abnormality, and features suggestive of connective tissue disorder). She was not on any medication, and never used heparin. On examination at presentation, her vitals were stable, but her Glasgow Coma Scale (GSC) score was 3. She was immediately intubated and connected to a mechanical ventilator in view of poor GCS. Neuroimaging studies showed extensive cerebral venous thrombosis with right frontal hemorrhage and surrounding perilesional edema and mass effect with midline shift and intraventricular extension of hemorrhage. Neurosurgery consultation was completed, and right frontotemporal decompressive craniotomy was completed on the same day of admission. Further investigation revealed anemia with hemoglobin of 8.6 g/dL (12-15 g/dL), leukocytosis with total leukocyte count of 17,940/mm^3(4300-10,800/mm^3), thrombocytopenia platelet count of 50,000/mm^3 (150,000-450,000/mm^3), and folate of 3.5 nmol/L (6.12-38.52 nmol/L), and vitamin B_{12} deficiency of 37 pmol/L (118-701 pmol/L). Coagulation profile; prothombin time 15 second, international normalised ratio 1.5, plasma fibrinogen 250 mg/dL, the liver function tests; bilirubin 0.8mg/dL, aspertate aminotransferase 45U/L, alanine aminotransferase 35 U/L alkaline phosphatase 170U/L and the renal function tests; urea 45 mg/dL, creatinine1.2 mg/dL were within normal limits. D-dimer

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Table 1. Deceased donors with VITT

	Greenhall et al[8]	Centonze et al[10]	Loupy et al[9]	NHS Blood and Transplantation INF1569/3.1[7]	Present Case
No of donors consented	13	1	5	18	1
Median age in years	34	32	66	NA	18
Actual donations from deceased donors (n)	10	1	3	NA	1
Female n(%)	11 (85%)	1 (100%		NA	1 (100%)
DBD	13 (100%)	1 (100%)	3 (60%)	NA	1 (100%)
Time of vaccination to presentation to (days)	10	11	13	NA	9
Vaccine administered	ChAdOx1 nCoV -19 1st dose	ChAdOx1 nCov-19	ChAdOx1 n-CoV-19	NA	ChAdOx1 n-CoV-19 1st dose
CVST n(%)	13 (100%)	1 (100%)	4 (80%)	NA	1 (100%)
Intracranial hemorrhage n(%)	7 (54%)	Nil	5 (100%)	NA	1 (100%)
Extracranial thrombosis n(%)	6 (46%)	Nil	5 (100%)	NA	Nil
Splanchnic n(%)	3 (23%) 1: portal; 1: splenic; 1: mesenteric vein	1 (100%) hepatic vein thrombosis	4 (80%)	NA	Nil
Pulmonary n(%)	2 (15%)	Nil	2 (40%)	NA	Nil
Other	1 (7%) Aorta	Nil	1 (20%) adrenal vein thrombosis	NA	Nil
D- dimer ng/ml	41,000	12,080	>20,000	NA	14,360
Platelet count mm^3	26,000	35,000	25,000	NA	50,000
Anti-PF4 antibodies n(%)	13 (100%)	Nil	4 (80%)	NA	Nil

DBD, donation after brain death; CVST, cerebral venous sinus thrombosis; NA, not available; VITT, vaccine-induced thrombotic thrombocytopenia.

14360 ng/mL (100-250 ng/mL) was elevated. Vasculitis and connective tissue disorder work-up which included testing for anti nuclear antibodies, anti double standed DNA, C-anti nutrophilic cytoplasmic antibodies, P-anti nutrophilic cytoplasmic antibodies, anti phospholipid antibodies, were all negative. Infection workup was also negative, which included malaria, dengue viral markers, scrub typhus, Leptospira, chikungunya, and COVID-19 reverse transcription polymerase chain reaction. Heparin induces thrombocytopenia test was also negative.

Her sensorium worsened, and she gradually developed hypotension. She was treated with vasopressors, noradrenaline and dopamine infusions at 5 mL/hour, single-donor platelet transfusions, packed red blood cells transfusions, heparin 5000 unit every 8 hours, injection levetiracetam 500 mg infusion twice daily, injection piperacillin tazobactam 500 mg 3 times daily, injection mannitol 100 mg infusion every 24 hours, folvite 10 mg tablet daily, injection vitamin B_{12} once daily, and supportive care. Tracheostomy was done after a week, and she was continued on mechanical ventilation. VITT was considered because of the patient's thrombocytopenia, increased D-dimer, and thrombotic complications with a history of the COVID-19 vaccine a week before presentation and because no other cause explained her condition. However, an antibody against PF4 was negative. On June 19, 2021, the patient's condition worsened; her pupils were bilaterally dilated at 6 mm and fixed, and brain stem reflexes were absent. Electroencephalography showed isoelectric activity consistent with electrocerebral silence, without any discernible activity while recording at a sensitivity of 2uV. An apnea test was performed to confirm the diagnosis of brain death; both the apnea tests done 6 hours apart were positive, confirming the diagnosis of brain death. Brainstem death declaration was done on June 19, 2021. The patient's parents were counseled regarding the organ donation, to which they readily agreed. The challenges for the deceased donor transplantation organization were whether to accept this VITT case as an organ donor, to identify which formalities were to be reported to the state and central authorities as adverse events following immunization (AEFI) before the donation process, and to identify if the recipients would have a chance of recurrence of thrombotic thrombocytopenia after transplantation.

After thorough consultation with the state and central vaccination authorities, appropriate documentation was done with respect to AEFI; after completing the legal formalities, the heart, lungs, liver, and 2 kidneys were retrieved. The postmortem examination was also performed by the forensic department from the government general hospital. The organs were allocated as per the regional allocation policy. Postmortem examination showed extensive thrombosis and hemorrhage in the brain but no evidence of disseminated intravascular coagulation in any of the visceral organs.

The heart and lung recipient was a 26-year-old woman who had been waiting on the list since June 2018 for heart and lung failure secondary to ventricular septal defect. She had a long waiting period owing to nonavailability of size-matched donor. Combined heart and lung transplant was done with informed consent. She had a smooth postoperative course and was extubated within 24 hours. She had a stable platelet count and did not face any untoward hematologic consequences.

The liver recipient was a 64-year-old woman with decompensate liver disease with no history of portal vein thrombosis

Table 2. Recipients from deceased donor with VITT

	Organ transplanted	Number of Recipients	Median Age in Years (Range)	Female n(%)	Hemorrhage (n)	Thrombosis (n)	DGF/ Early Graft Dysfunction (n)	Graft Loss With Explants (n)	Graft Loss (n)	Patient Loss(n)	PF4 Antibodies (n)	Platelet Count 10^9/L	Follow-up Mean (Range) days
Greenhall et al [8]	Kidney	15	40 (2-63)	12(46%)	3	1	4	1	2	1	3	124 (32 – 267)	19(21-27)
	SPK	1				0		0	0				
	Islet cell transplant	1				0		0	0				
	liver	7			0	3		2	0				
	Heart	1			0	0		0	0				
	Lung	1			0	0		0	0				
Centonze et al [10]	Liver	1	62	1(100%)	0	1 (Hepatic vein from donor)	0	0	0	0	0	2 15 000/mm3	60
Loupy et al [9]	Kidney	6	60(42-70)	2 (33.3%)	1(peri graft)	2 (glomerular)	2(recovered)	0	0	0	0(1 NA)	152 (87-207	52 (16-77)
	Heart and liver	1	64	0	0	0	0				0	120	
	Heart	1	54	0	0	Pulmonary thromboembolism	0				0	130	
	Lung	1	58	1(100%)	0		0				0	465	
Present study	Kidney	2	22, 31	1(50%)	0	0	0	0	0	0	Not tested	150000	120
	Liver	1	64	1(100%)								60,000	
	Heart and lung	1	26	1(100%)								125000	
NHS Blood and transplantation INF1569/3.1[7]	Kidney	30	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Liver	9											
	Heart	3											
	Lung	1											
	Islet cell	1											
	SPK	1											

DGF, delayed graft function; NA, not available; SPK, simultaneous pancreas and kidney transplant; VITT, vaccine-induced thrombotic thrombocytopenia.

or variceal bleed in the last 2 weeks and no history of vaccination in the last 4 weeks. Liver transplant was done after informed consent. She had an uneventful postoperative course except for mild elevation in D-dimer from 385 ng/dL (100-250 ng/mL) on day 1 of the postoperative period to a maximum of 3182 ng/dL (100-250 ng/mL) on day 8, and the nadir platelet count reported was 60,000/cumm (1,50,000-450,000/mm^3) on day 7 postopertative . She received injection fondaparinus (Arixtra) 2.5 mg for a week followed by antiplatelet asprin 75 mg a day along with triple immunosuppression of prednisolone, tacrolimus and mycophenolate mofetil. Her liver function test normalized by day 5 and was discharged after 2 weeks.

The recipient of the first kidney was a 31-year-old woman who had been on the waiting list for 3 years with a diagnosis of presumed chronic interstitial nephritis and end-stage renal disease; she had been on maintenance hemodialysis for the past 4 years. Kidney transplantation was done after informed consent. She was given anti thymocyte globulin 3 mg/kg as induction and triple immunosuppression (prednisolone, tacrolimus and mycophenolate mofetil as maintenance therapy). She had immediate graft function with brisk diuresis. Her platelet count, D-dimer, and coagulation profile were normal throughout the postoperative period, and no hematologic complications were observed.

The recipient of the second kidney was a 22-year-old man with presumed chronic intestinal nephritis who had been on dialysis for 4 years and was waiting on a deceased donor list for 3 years. Kidney transplantation was done with informed consent, anti thymocyte globulin induction 3mg/kg, and triple immunosuppression. The postoperative course was uneventful with normal graft function and no hematologic complications.

DISCUSSION

Ever since the first report of thrombotic thrombocytopenic complications following the COVID-19 vaccine, [1] there has been a spurt of thrombotic complications reported with Pfizer−BioNTech mRNA vaccine and the Moderna mRNA SARS-CoV-2 vaccination [2], the AstraZeneca Oxford (serum institute), and the Johnson & Johnson/Janssen Ad26.COV2.S adenoviral vector vaccines across the world [3−5].

European Medicines Agency included at least 169 possible cases of cerebral venous sinus thrombosis and 53 possible cases of splanchnic vein thrombosis among 34 million recipients of the ChAdOx1 nCoV-19 vaccine, 35 possible cases of central nervous system thrombosis among 54 million recipients of the Pfizer−BioNTech mRNA vaccine, and 5 possible cases of cerebral venous sinus thrombosis among 4 million recipients of the Moderna mRNA vaccine [6].

The incidence of VITT was estimated to be 1 case per 100,000 exposures [6].

The sites of thromboses in the majority of cases were cerebral venous sinus thrombosis, splanchnic thrombosis, and, rarely, pulmonary embolism. The risk factors identified were young age and female sex.

Approximately 40% of the patients died, and common causes of death were ischemic brain injury, superimposed hemorrhage,

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or both conditions, often after anticoagulation. Hence it is quite common to encounter brain death in patients with VITT, giving scope for organ donation.

While considering patients with VITT as a brain dead donor, there are several challenges that need to be addressed: (1) the legalities of documentation and reporting as an AEFI to the concerned national authorities, particularly during a mass immunization program as part of a global pandemic and the conduct of postmortem examination with preservation of specimens to ascertain the cause of death; (2) viability of the organs, as these organs could be damaged by hematologic complications and (3) despite organs being functional and structurally normal, the change of the recurrence of hematologic complications and graft thrombosis in the recipient after transplantation needs to be considered.

We report successful organ donation from a case of VITT following the COVID-19 vaccination with AstraZeneca Oxford (Serum Institute of India) in an 18-year-old woman who presented with cerebral venous thrombosis superimposed with right frontal hemorrhage evolving into brain death. All 4 recipients (1-combined heart and lung, 1-liverand 2-kidneys) had good graft function with no hematologic complication after 16 weeks of transplantation. Only the liver recipient developed transient thrombocytopenia and increased D-dimer in the first week but without any graft dysfunction, which was managed with short course of anticoagulants. To our knowledge, this is first case of deceased donation from a case of VITT caused by the COVID-19 vaccine being reported from Asian countries.

The United Kingdom reported 18 deceased donors with proven or probable VITT (Table 1), from which were donated 46 allografts to 45 recipients: kidney (30), simultaneous pancreas and kidney (1), liver (9), lung (1), islet (1), and heart (3) transplants [7] (Table 2).

US experience showed 13 consented deceased organ donors with VITT following the first dose of the ChAdOx1 nCoV-19 vaccine. Ten donors proceeded to donate 27 allografts to 26 recipients. After a median follow-up of 19 days, 21 of 27 (78%) allografts had satisfactory function, 5 experienced graft loss, and 1 death resulted. There were 7 major thrombotic or hemorrhagic complications (3 bleeds and 4 venous or arterial allograft thromboses) within 9 postoperative days in 6 recipients, resulting in the loss of 3 transplants [8].

Loupy et al [9] identified 5 potential deceased donors with VITT after ChAdOx1 n-CoV-19 adenoviral vector vaccine. Four patients presented with cerebral venous thrombosis, and all patients had intracranial hemorrhage an extracranial thrombosis. Three organ procurement procedures were achieved, and 2 were refused in view of family refusal and severe disseminated intravascular coagulation, respectively. Ten grafts (6 kidneys, 2 hearts, 1 lung, and 1 liver) were transplanted to 9 recipients. After a median follow-up of 52 days (range, 16−77 days), all recipients were alive with adequate functioning transplants. Patients experienced neither severe thrombotic nor hemorrhagic events. No recipient had detectable anti-PF4 antibodies.

Centonze et al [10] reported successful liver transplantation from a 32-year-old female brain dead donor with cerebral venous sinus thrombosis and hepatic veins thrombosis after ChAdOx1 nCov-19 vaccination to a 69-year-old female recipient with multifocal hepatocellular carcinoma and hepatitis C virus cirrhosis. There have been no reports of deceased donation from VITT following the COVID-19 vaccine from developing countries.

Despite sparse literature, VITT following the COVID-19 vaccine can still be accepted as a deceased donor, considering the following: (1) There has been a significant reduction in deceased donation and transplantation during the COVID-19 pandemic, increasing the organ shortage, particularly in developing countries where deceased donation is miniscule; (2) the mortality rate on the waiting list has increased; and (3) there has been increasing reports of VITT with the COVID-19 vaccine, the most common site being cerebral venous thrombosis, and with ongoing massive vaccination program across the world; it's possible that there might be more cases of deceased donor secondary to VITT in the future. However, necessary precautions should be taken before considering deceased patients with VITT as deceased donors. All the required documentation should be done with respect to AEFI in additional to legal documentation of brain death and informed consent. A thorough evaluation of the organ status should be done at the time of donor optimization and during the retrieval process. Heparin as an anticoagulant should be avoided during organ retrieval, as it can trigger antiplatelet factor 4 antibodies. Postmortem examination/autopsy should be conducted by the concerned authority at the time of organ retrieval at the donor hospital so as to not miss any of the findings that could interfere with the diagnosis of cause of death. Informed consent should be taken from the prospective recipients, mentioning that there could be a chance of recurrence of hematologic complications in the recipients causing graft thrombosis and graft loss. The activated B lymphocytes in the donor are passively transferred into the recipient's circulation through the donor organ and can produce antibodies and VITT in recipients, which is called passenger leukocyte syndrome. It is most often seen with liver, lung, small bowel, and pancreas transplantation. Transplantation should be avoided in patients who have received the vaccine against COVID-19 within 4 weeks prior to transplantation and in those with a prior risk of hemorrhagic or thrombotic complications. After transplantation, all the recipients should be closely monitored with platelets counts, D-dimer, coagulation profile, and anti-PF4 antibodies. Heparin can be safely used unless anti-PF4 antibodies are positive or VITT is suspected in the recipient. No change in the immunosuppression protocol is required.

CONCLUSIONS

Considering the organ shortage, suspected or proven VITT secondary to COVID-19 vaccination can be accepted as a deceased donor, gauging the risk and benefit to the recipient. The following precautions should be taken: thorough evaluation and optimization of the donor and meticulous recipient selection, informed consent before transplantation, and close postoperative monitoring of the recipient after transplantation.

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