Vaccine Induced Thrombotic Thrombocytopenia (VITT): First report from India and utility of risk score for diagnosis in resource limited settings.

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Research Article

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Abstract

Vaccine induced thrombotic thrombocytopenia (VITT) is a rare but devastating adverse event following adenoviral vector based vaccinations for COVID-19. Guidance statements and available reports lack clarity on the choice of imaging modalities and emphasize on the need for specialized tests as a requisite criterion. Such tests have practical limitations of availability likely to restrict the treatment and reporting of such catastrophic events and need reconsideration. We describe two young men with VITT who had no other contributory cause besides a recent ChAdOx1 nCoV-19 vaccination. They were treated with IVIG and full dose anticoagulation. In both our cases the primary neuroimaging was normal and the recommended PF-4 testing was not reported due to technical limitations. Diagnosis was based on a 4T inspired score. Clinicians should report and though counter intuitive; not delay the institution of full dose anticoagulation, IVIG and limit platelet transfusion in the appropriate setting.

Background

Vaccine induced thrombotic thrombocytopenia (VITT) is a rare but devastating adverse event that can be potentially fatal and associated with disabling morbidity (1). Here we report VITT for the first time from India in two previously healthy young men who presented with thrombocytopenia, intracerebral bleed and cerebral venous thrombosis. In both our cases the defining PF-4 report based on guidance from the west was not available due to technical limitations but delaying the diagnosis and instituting appropriate treatment could have been fatal. One completely recovered and the other subsequently required and is undergoing treatment.

Case 1

A previously healthy 25-year-old male presented to the Emergency Room with a history of subacute onset, progressive headache evolving over the last six days. He had recently received his first dose of the ChAdOx1 nCoV-19 (AstraZeneca) vaccine 15 days prior to presentation. One day prior he had been evaluated elsewhere with a CT brain which was normal and a hemogram which reported a platelet count of 60000/mm ^{3} . On the day of presentation, he had new onset weakness progressive over few hours of the left half of his body, evidenced by an inability to sit up from bed without support, and difficulty in gripping objects. Neurological examination confirmed hemiparesis with a hemi-sensory loss and dysmetria localized to the left with nystagmus (fast beating component to the left) on horizontal gaze to the left.

Diagnosis

Magnetic resonance (MR) imaging (Fig 1) of the brain showed a right high parietal hematoma measuring 4.7x2.3 cm with oedema, and signs of micro hemorrhage in the left parietal lobe and cerebellar hemisphere. CT angiography of the brain revealed thrombosis of the superior sagittal and right transverse sinus. Hemogram showed thrombocytopenia of 53000 /mm ^{3} [150,000 - 400,000]. D-Dimer was 6060.67 ng/mL (0.00 - 500.00). Routine coagulation tests and Bone marrow aspiration and biopsy was normal. The screening test for antibodies against platelet factor 4 (PF4)–heparin by chemiluminescenceimmunoassay (CLIA), was negative . Due to poor sensitivity for PF-4 antibodies by CLIA(2), blood samples were sent for PF-4 antibody by Enzyme Linked Immunosorbent Assay (ELISA, tests couriered offsite with a turnaround time of 4 weeks)(3). The sample degenerated in transit and was not reported. 6T (Table1) score -5/6.

Management

Due to the obvious bleed with thrombocytopenia, he received platelet transfusions on arrival. The unusual site of thrombosis coupled with a platelet count not usually associated with spontaneous intra cerebral bleeds strongly favored VITT. He was initiated on measures to reduce intracerebral edema and was admitted in the ICU. He was started on IV Dexamethasone and Intravenous Immunoglobulin (IVIG) at a dose of 1g/kg body weight on day 1 followed by a repeat dose on day 2 . In view of the bleed and thrombocytopenia initial anticoagulation was initiated with Apixaban at 2.5mg once daily. The patient deteriorated over the initial 24 hours with motor aphasia, and left facial palsy. Supported by a marginal increase in platelet levels, Apixaban was administered at 5mg twice daily thereafter from day 2. He remained on IV Dexamethasone and anticoagulation.

Follow up

Headaches resolved during the following days. An interval CT brain, done two days later, revealed no signs of hematoma expansion. He demonstrated near complete resolution of neurological deficits and was self-ambulatory at the time of discharge with repeat CT brain showing complete resolution of the thrombus. During his follow-up visit, all lab values were within normal ranges and his condition was normal.

Table 1: **6T** score sheet for VITT

Category	
Thrombocytopenia	>50% fall or nadir < 75000/mm^3
Test for PF4 antibody	Positive by ELISA
Timing	Within 30 days of the first dose of vaccination
Time/Age	Less than 30 years
Thrombosis	Documented thrombus (if suspecting CVT a venogram is needed)
Trephine/Other causes for **T**hrombocytopenia	Normal/ No alternate likley etiology
Treatment/high likelihood of VITT	Alteast 5 out of the 6 Ts

Case 2

19-year-old previously healthy male was brought to the emergency department in an unconscious state requiring prophylactic endotracheal intubation. He had received the first dose of ChAd-nCov-1 (AstraZeneca) 12 days prior to presentation. He subsequently developed a headache 8 days later for which he underwent evaluation in a hospital elsewhere including a computed tomographic (CT) imaging of the brain which revealed no abnormalities and was managed symptomatically.

Diagnosis

He underwent an emergent repeat CT imaging of the brain which revealed gross hematoma in the bifrontal region, suggestive of venous infarcts. MR Venogram (Fig 2) confirmed a superior sagittal sinus thrombosis. Laboratory investigations revealed thrombocytopenia of 42,000/mm ^{3} . D-Dimer was 7759.89 ng/mL. Routine coagulation tests and bone marrow aspiration & biopsy were normal. 6T score 5/6.The heparin-Induced platelet antibody was subsequently reported positive (Patient O.D 1.482).

Management

He underwent an emergency decompressive craniotomy under the cover of platelet transfusion. A detailed evaluation including Bone Marrow studies revealed no causes for thrombocytopenia. Due to strong suspicion of VITT, he underwent a magnetic resonance (MR) imaging of the brain with a venogram which revealed thrombosis of the superior sagittal sinus. He received Intravenous Immunoglobulin at a dose 1g/kg body weight at days 2 and 3, with IV steroids and full dose oral anticoagulation (Apixaban). He demonstrated a remarkable recovery from thrombocytopenia with platelets rising to within normal limits over 3 days. There was no further progression of neurological deficit.

Follow up

His hospitalization was complicated by a ventilator associated pneumonia which was treated to clinical resolution and bilateral pneumothorax for which he underwent bilateral intercostal tube drainage. He was managed conservatively without any further surgical intervention and weaned off mechanical ventilation after tracheostomy. He is in coma vigil and his neurological outcome remains guarded at the time of reporting.

Discussion

The estimated risk of vaccine induced thrombosis with thrombocytopenia (VITT) is at least 1:100,000 among patients 50 years of age or older and at least 1:50,000 among patients in the younger group(4). This risk is amplified in younger individuals and recipients of the first dose. The most commonly reported symptoms include persisting headache, of sudden onset, which may be associated with bleeding manifestations which may progress to gross neurological deficits, and an altered mental state(1, 5, 6). Though multiple accounts of thrombosis with thrombocytopenia have been reported following vaccination with the adenoviral vector based vaccines; the exact pathobiology and why this immunogenic thrombosis preferentially manifests in cerebral vessels is yet unclear (5, 7, 8). The most accepted pathogenic models implicate autoantibodies to platelet factor-4 (PF4), indicating a loss of immune tolerance as part of an inflammatory and immune stimulation. Such antibodies subsequently cause massive platelet activation via the Fc receptor in analogy to heparin-induced thrombocytopenia (HIT) (9, 10).

Despite the evolving understanding of this adverse event; the potential mortality and morbidity has encouraged useful guidance and reports from societies(11–13). However more definition is needed. Though the need for imaging has been acknowledged, the best modality needs clarity. Both our patients had a normal CT scan just prior to their clinical deterioration and had an intracerebral bleed later when picked up by the CT scan. In keeping with the recommendations it is likely that; as in our case a follow up or primary venogram (CT or MRI) could likely identify a venous thrombosis and help institute earlier treatment(14). Besides, though testing for PF4 antibodies adds more evidence to establish the diagnosis and is being recommended it has a practical limitation in not being universally available or accessible. It is likely that the current pandemic and the national lockdowns might add to the challenges of outsourcing or couriering such tests. With a significantly younger population demographics in the developing world; possibly, the existence of such criterion might lead to under reporting of VITT despite such massive vaccination drives like in India(15).This is important to public health and resource allocation. In both our cases the defining PF-4 report was not avialable due to technical limitations but delaying the diagnosis and instituting appropriate treatment could have been fatal.

Though the unprecedented rapidity of vaccine production has been integral to the timely response to COVID − 19(7); it is important that surveillance shouldn't be limited by the lack of tests not universally available. With all recommendations on VITT based on extrapolation from HIT and non–heparin-dependent autoimmune thrombotic thrombocytopenia's, it will be helpful if a scoring system analogous to the 4T score could help make the diagnosis more easily reportable (Table 1). Such risk scores require validation and could be helpful in many resource constrained countries and help improve reporting which is reassuring and also critical against the backdrop of emergency use authorizations of vaccines.

Conclusion

India has delivered more than 300 million doses to those between 18–44 years of age. This is the first report to the best of our knowledge on Vaccine Induced Thrombotic Thrombocytopenia from India with the largest vaccination drive in the world.(16) In our initial and limited experience, VITT typically presents in younger male patients with no prior comorbidities making the severity of illness alarming in them. It is our opinion that in the appropriate setting such patients should undergo a preferential neuroimaging with a venogram (CT or MRI). While testing for PF4 antibodies adds more evidence to establish the diagnosis, clinicians though counter intuitive should not delay the institution of full dose anticoagulation, IVIG and limit platelet transfusion. Clinicians should readily evaluate, report and develop accessible risk scores to treat VITT in the appropriate setting.

Declarations

A statement on participant consent - The need for consent was waived by the approving ethics committee.

The approving ethics committee was our institutional ethics committee: Believers Church Medical College Hospital - Institutional Ethics Committee

Competing interests: The authors declare no competing interests.

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Figures

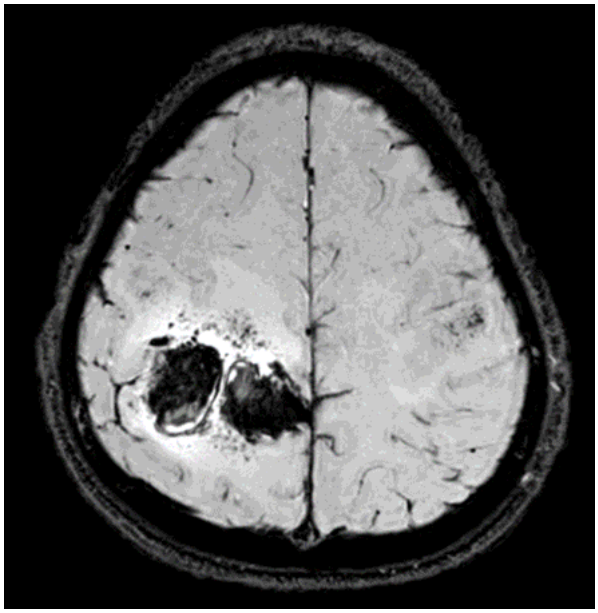

Figure 1

MRI brain: Right high fronto-paretial hematoma with perilesional edema.

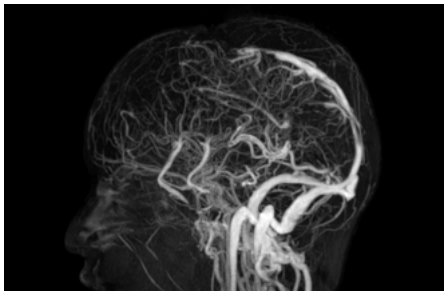

Figure 2

MR Venogram: Non-Visualized Anterior Superior Sagittal Sinus

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- Supplementaryfile.docx