Editorial

Vaccine-induced thrombotic thrombocytopenic purpura

The arrival of vaccination was a huge step in the prevention of COVID-19, and significantly decreased mortality and morbidity. However, with the large number of vaccine doses administered, a rare but distinct side effect emerged; vaccination was followed by thrombosis in unusual sites, leading to the description of a syndrome of vaccine-induced thrombotic thrombocytopenic purpura (VITT).

VITT was first reported in a non-reviewed preprint,[1] in February 2021, by a German group of researchers led by Andreas Greinacher, and by April, more than 100 cases were documented. The syndrome consisted of a triad of thrombosis in unusual sites, thrombocytopenia and high D-dimer. The death of healthcare workers who took the vaccine due to VITT created a stir and several European countries even banned the vector-based vaccines.[2] This was subsequently reversed following more data collated by August 2021, which showed this to be a very rare side effect. Hence, from the public health point of view, vaccination was encouraged to prevent COVID morbidity and mortality.

The mechanism of VITT is still unclear. With the discovery of PF4 antibodies, in several patients, the mechanism is said to be similar to that of heparin-induced thrombocytopenia (HIT). These antibodies promote cross-linking of FcγRIIa receptors on platelet surface, which is then followed by platelet activation and aggregation. However, the site of binding of the antibodies is different from that of heparin.[3]

Serotonin-release assays are used to identify heparin-associated platelet activation and aggregation in HIT. However, these assays show that VITT antibodies prevent rather than promote platelet aggregation in these assays. This, therefore, offers a potential method for differentiation of HIT versus VITT. The gold standard for identification of VITT in a clinical context is the presence of PF4 antibodies by ELISA technique.

VITT occurred typically 7–10 days after vaccination with the AstraZeneca vaccine, which is vector based and was also reported with Johnson & Johnson's vaccine.[4] Surprisingly, the mRNA-based Moderna and Pfizer vaccines did not seem to cause this, suggesting that the vector-based ones may have a specific mechanism which triggered it. However, the reason behind this distinction is unknown.

The clinical picture is characteristic, with young women being most affected. VITT followed vaccination by 7–42 days, though the first 2 weeks was probably the most common. Unusual sites of thrombosis, especially cerebral venous thrombosis and splanchnic and portal venous thrombosis, are common. The predilection for the cerebral venous involvement is unexplained.[5] This is in contrast to the thrombosis in COVID-19, which is usually confined to deep veins of limbs and pulmonary thrombosis.[6] Arterial thrombosis causing strokes and myocardial infarction can also occur in VITT. The thrombocytopenia can range from very low levels of <10,000 cells to near-normal values. The clinical presentation is accordingly varied, with only purpura and bruises, or severe bleeding, especially intracranial, which can contribute to significant mortality.

The laboratory abnormalities include: reduced platelet count (<150,000/mm^3) increased D-dimer (>10 mg/L) and positive PF4 antibodies. The diagnosis rests on one or more of these abnormalities being present in the right context of post-vaccination state.[7] However, not all abnormalities need to be present for diagnosis. The platelets can be normal initially, and then fall subsequently, and hence, the lowest platelet count may appear later during the illness. The D-dimer is not high in about 10% of patients. PF4 antibodies are again absent in a small proportion of patients. Further, they may be positive even in the normal population in about 3%–5% of patients. Hence, there are fallacies in all these criteria.

Therefore, the diagnosis has been classified as definite, probable and possible, based on various cut-offs of these clinical and laboratory criteria. The differential diagnosis includes other causes of this combination of thrombosis and thrombocytopenia such as HIT, thrombotic thrombocytopenic purpura, APLA syndromes

and sepsis. These can be ruled out by their context, other clinical features and appropriate tests.

Perhaps, the most important differential diagnosis is COVID-19 with thrombosis. It is easily distinguished by the positive COVID test, more traditional sites of thrombosis and very high D-dimer compared to VITT. The treatment of VITT rests on some basic principles. Anticoagulation is used for thrombosis, even in cases of cerebral thrombosis. The fear of haemorrhage in the cortical veins should not prevent using anticoagulation, as the treatment of venous thrombosis will decrease the backpressure and hence decrease cerebral oedema.[8]

The anticoagulant of choice would be non-heparin based, such as fondaparinux. However, studies have not shown any major adverse events even in those given heparin inadvertently, before the diagnosis of VITT was made. Thrombocytopenia, if severe, will need platelet transfusion. Here again, whether platelet transfusions will trigger more thrombosis is a moot question, as they are avoided in HIT. However, in VITT, especially if the patient needs surgery, many surgeons prefer to give platelet transfusions to keep the count above 30,000 cells/cmm. Again, no adverse events have been observed with platelet transfusions.

The early and timely use of intravenous immunoglobulin (IVIg) has changed the prognosis of VITT. It definitely brings down mortality and morbidity. It blocks the activation of platelets by PF4 antibodies by competitive blockade, and platelet counts increase in 3–5 days. Plasma exchange has also been tried with some success with decrease in mortality, especially in very sick patients.[9]

There is a controversial role for steroids. Some small studies have reported better results when steroids are combined with IVIg.[10] Monoclonal antibodies such as rituximab and eculizumab have also been tried with some success. Surgical intervention may be needed for intracranial thrombosis in patients with poor sensorium. However, there is risk of morbidity during surgery, as this is done in very sick patients whose prognosis is anyway poor. Patients with VITT can complete their second dose of vaccination with a Pfizer or Moderna vaccine, as per current recommendations.[11]

Prognosis is poor in patients with low platelet count, multiple sites of thrombosis or intracranial thrombosis. Recognition and early intervention with definitive treatment does make way for better survival. Anticoagulation has to be continued for a minimum period of 3 months. It is better to use non-Vitamin K-based oral anticoagulants, such as apixaban or dabigatran.

It is important to identify and document VITT, so that patients at risk for this condition are identified. Further, there are major differences in the treatment of VITT compared to other causes of thrombosis, and these make a difference to the ultimate prognosis and can save lives.

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