INTERNAL MEDICINE JOURNAL

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doi:10.1111/imj.15783

CLINICAL PERSPECTIVES

Understanding vaccine-induced thrombotic thrombocytopenia (VITT)

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Key words
COVID-19 vaccination, thrombosis, thrombocytopenia.

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Received 21 December 2021; accepted 9 March 2022.

Abstract

Vaccine-induced thrombotic thrombocytopenia (VITT) is a rare, but serious, syndrome characterised by thrombocytopenia, thrombosis, a markedly raised D-dimer and the presence of anti-platelet factor-4 (PF4) antibodies following COVID-19 adenovirus vector vaccination. VITT occurs at a rate of approximately 2 per 100 000 first-dose vaccinations and appears exceedingly rare following second doses. Our current understanding of VITT pathogenesis is based on the observations that patients with VITT have antibodies that bind to PF4 and have the ability to form immune complexes that induce potent platelet activation. However, the precise mechanisms that lead to pathogenic VITT antibody development remain a source of active investigation. Thrombosis in VITT can manifest in any vascular bed and affect multiple sites simultaneously. While there is a predilection for splanchnic and cerebral venous sinus thrombosis, VITT also commonly presents with deep vein thrombosis and pulmonary embolism. Pillars of management include anticoagulation with a non-heparin anticoagulant, intravenous immunoglobulin and 'rescue' therapies, such as plasma exchange for severe cases. VITT can be associated with a high mortality rate and significant morbidity, but awareness and optimal therapy have significantly improved outcomes in Australia. A number of questions remain unanswered, including why VITT is so rare, reasons for the predilection for thrombosis in unusual sites, how long pathological antibodies persist, and the optimal duration of anticoagulation. This review will provide an overview of the presentation, diagnostic workup and management strategies for patients with VITT.

Introduction

The coronavirus disease-19 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has to date infected over 250 million individuals worldwide with almost 5 million deaths[1] and resulted in significant disruptions to healthcare and social systems globally. Vaccinations utilising various constructs were developed with unprecedented speed and demonstrated high degrees of efficacy against severe disease, hospitalisation and death with few safety issues in Phase III clinical trials.[2,3] The rapid implementation of vaccination programmes has meant that, to date, over 7 billion doses of COVID-19 have been delivered globally.[1] However, perhaps not surprisingly, in the face of such an enormous global vaccine programme, a number of rare, but serious, safety issues has emerged. Vaccine-induced thrombotic thrombocytopenia (VITT), also referred to as thrombotic thrombocytopenia syndrome (TTS), is one such rare adverse effect of the adenovirus vector COVID-19 vaccinations – ChAdOx1 nCoV-19 (AstraZeneca, Sydney, NSW, Australia) and Ad26.COV2.S (Janssen/Johnson & Johnson, Sydney, NSW, Australia). While the two terms (TTS and VITT) are used interchangeably, we favour VITT as there

Funding: J. McFadyen is supported by a National Health and Medical Research Council (NHMRC) Early Career Fellowship (APP1161499). H. Tran is supported by NHMRC – Medical Research Future Fund (MRFF) (APP2015305).
Conflict of interest: None.

are other syndromes characterised by thrombosis and thrombocytopenia with alternative aetiologies in which different treatment strategies are required. VITT was first reported by European investigators in March and April 2021,[4,5] with the first Australian case reported soon after.[6]

Epidemiology and clinical presentation

VITT is a rare disorder, with an incidence ranging from 1 in 26 000 in Norway[5] to 2.1 per 100 000 in Australia[7] after dose one of ChAdOx1 vaccination and 1 in over 500 000 in the USA with the Ad26.COV2.S vaccination.[8] VITT is extremely rare following second doses, with 0.3 cases reported per 100 000 s doses given in Australia and the United Kingdom.[7,9] Although there has been a small number of case reports of VITT occurring after mRNA vaccination, there remains debate as to whether these have a true causal association.[10]

The largest case series of VITT patients published by UK investigators found 85% of cases occur in individuals younger than 60 years of age, despite the predominance of ChAdOx1 vaccination in older adults.[11] There appears to be no preponderance of sex and no medical condition found at higher frequency in VITT cases, including prior thrombosis, presence of a thrombophilia, autoimmune disease or malignancy.[11,12] While most cases of VITT have been reported in the Caucasian population, it is not clear whether there is a true variation in incidence with ethnicity due to the relatively small case numbers and the potential challenges with diagnosing VITT in low- and middle-income countries. Indeed, there have been few case reports of VITT in South East Asia.[13]

A key clinical feature of VITT is the timeframe it occurs post-vaccination. Although constitutional symptoms are common in the first 24–48 h following vaccination, including myalgias, mild headache and/or fevers, VITT typically occurs between 4 and 30 days post-vaccination, with a median onset of 14 days;[11] however, some cases might present later, with cases reported up to 42 days post-vaccination.[11] Therefore, patients presenting with persistent or new symptoms for thrombosis within this timeframe following vaccination should be evaluated and consideration given to underlying VITT.

Thrombosis can occur at any site and can affect multiple vascular beds simultaneously, including both the venous and arterial systems, which is extremely unusual in other clinical scenarios.[11] Indeed, thrombotic complications including cerebral venous sinus (CVST), splanchnic vein thrombosis, deep vein thrombosis (DVT), pulmonary embolism (PE) and arterial thrombosis are all well reported.[12] Thromboses can evolve quickly and initial symptoms might be subtle (Table 1), such as a mild headache with CVST or anorexia with splanchnic circulation thromboses, therefore a high index of clinical suspicion needs to be maintained with a low threshold for further investigation. There have been reports of an associated 'flu-like' syndrome in association with VITT, with persisting fevers and fatigue.[4,14] Patients may present with thrombocytopenia alone, as an incidental finding or with bleeding symptoms or petechiae.

Table 1 Sites of thrombosis and possible associated symptoms

Thrombosis site	Symptom
CVST	Headache
	Visual change
	Seizures
	Focal neurological deficits
	Encephalopathy
Splanchnic circulation	Anorexia
	Abdominal pain
	Gastrointestinal bleeding
Deep vein	Calf or thigh pain
	Oedema
	Redness
Pulmonary	Pleuritic chest pain
	Shortness of breath
Arterial	Myocardial infarct: chest pain, shortness of breath
	Limb ischaemia: limb pain, sensory change, colour change
	Cerebrovascular: limb weakness or sensory change, speech disturbance, visual change, vertigo/unsteadiness

CVST, cerebral venous sinus.

Pathophysiology

It is currently thought that VITT occurs as a consequence of pathogenic IgG antibodies that can bind to platelet factor-4 (PF4).[4] These antibodies bind to the platelet FcγRIIa receptor and form immune complexes with PF4 that can cluster the FcγRIIa receptor resulting in widespread and marked platelet activation.[15,16] These highly activated platelets support thrombin generation and are cleared from the circulation, thus explaining why patients with VITT present with thrombosis and thrombocytopenia.[15] Although the precise mechanisms that lead to the generation of pathogenic VITT antibodies remain to be elucidated, it has been postulated that they are the result of an idiosyncratic immune response directed against PF4 in complex with a component of the

Table 2 Case definition criteria for VITT, UK expert haematology panel (EHP) and THANZ criteria

Type of VITT	UK EHP[11]	THANZ[12]
Definite VITT	All five of the following: • Onset of symptoms 5–30 days after vaccination against SARS-CoV-2 (or up to 42 days in those with isolated DVT or PE) • Presence of thrombosis • Thrombocytopenia (<150 $\times 10^9$/L) • D-dimer >4000 FEU • Positive anti-PF4 antibodies on ELISA	• Exposure to ChAdOx1 nCov-19 (AstraZeneca) within 4–42 days of symptom onset • Thrombocytopenia (platelet count <150 $\times 10^9$/L) or falling platelet count, AND elevated D-dimer (>5 times the upper limit of normal) or reduced fibrinogen • Thrombosis: any DVT, PE or arterial thrombosis. Thrombosis in uncommon sites such as CVST and splanchnic vein thrombosis are strongly suggestive • Antibodies detected against PF4 and/or functional assay indicating patient derived plasma/serum induction of prothrombotic phenotype in healthy donor platelets
Probable VITT	D-dimer level u >4000 FEU but one criteria not met (timing, thrombosis, thrombocytopenia or anti-PF4 antibodies) OR D-dimer level unknown or 2000–4000 FEU and all other criteria met	Meets platelet count, D-dimer (and/or fibrinogen) criteria, with thrombosis but PF4 antibody negative
Possible VITT	D-dimer level unknown or 2000–4000 FEU with one other criterion not met, or two other criteria not met	Meets platelet count, D-dimer (and/or fibrinogen) criteria but no thrombosis found
Unlikely VITT	Platelet count <150 $\times 10^9$/L without thrombosis, with D-dimer <2000 FEU OR thrombosis with platelet count >150 $\times 10^9$/L and D-dimer <2000 FEU regardless of PF4 antibody result, and alternative diagnosis more likely	'Less likely' if platelet count >150 $\times 10^9$/L but D-dimer elevated or fibrinogen reduced with thrombosis 'Much less likely' if platelet count is stable and >150 $\times 10^9$/L, D-dimers are not elevated and fibrinogen is normal with thrombosis

Adapted from Pavord *et al*.[11] and Chen *et al*.[12]
CVST, cerebral venous sinus; DVT, deep vein thrombosis; ELISA, enzyme-linked immunosorbent assay; PE, pulmonary embolism; PF4, platelet factor-4; VITT, vaccine-induced thrombotic thrombocytopenia.

adenoviral vaccine.[17] Similarly, why VITT is so rare and why it appears to have a predilection to manifest in atypical sites such as the cerebral and splanchnic circulations remains unknown.

Insights regarding the nature of the VITT antibody have been afforded by elegant structural studies that have demonstrated key differences regarding VITT and heparin-induced thrombocytopenia (HIT) antibodies. In contrast to HIT antibodies that require heparin to induce immune complex formation and platelet activation, VITT antibodies demonstrate a stronger binding affinity to PF4 and therefore support the formation of immune complexes independent of heparin.[18] Indeed, VITT antibodies bind to a distinct epitope within the heparin-binding region of PF4, which can be inhibited with high doses of heparin, thus helping to explain how VITT antibodies can cause platelet activation in the absence of heparin or heparin exposure.[18] As such, VITT is thought to more closely resemble autoimmune HIT (aHIT) – spontaneous development of HIT – in which the generation of thrombotic thrombocytopenia is heparin independent.[18]

Diagnosis and differential diagnosis

Diagnosis of VITT relies on a combination of clinical, laboratory and radiological features. Laboratory features include thrombocytopenia (platelet count <150 $\times 10^9$/L) and high D-dimer (over five times the upper limit of normal); some patients also have a hypofibrinogenaemia.[12] In the largest case series, the median platelet count at presentation was 47 $\times 10^9$/L; however, it is noteworthy that patients may initially present with a normal platelet count.[11,12] In these cases, particularly if there is confirmed thrombosis within the correct time frame, this might represent an 'early' case and platelet counts may rapidly deteriorate. Therefore, repeated testing should be performed. Diagnostic criteria vary slightly between countries, the UK and Australian criteria are shown in Table 2.

Table 3 Differential diagnosis of VITT

Differential diagnosis	Difference to VITT
Vaccination-associated immune thrombocytopenic purpura (ITP)	Absence of thrombosis D-dimer normal Response to ITP therapy
Non-VITT thrombosis	Normal platelet count Moderate D-dimer rise Negative anti-PF4 ELISA
HIT	Recent heparin exposure in prior 3 months Positive non-ELISA HIT assay (in addition to positive ELISA)
DIC	Abnormal coagulation profile (prolonged PT and/or APTT) Red cell fragments on blood film smear Presence of a disorder associated with DIC (such as malignancy or infection)
Thrombotic thrombocytopenic purpura (TTP)	Usually has microvascular thrombosis Red cell fragments on blood film smear Presence of anaemia and positive haemolytic markers ADAMTS13 deficiency

ELISA, enzyme-linked immunosorbent assay; VITT, vaccine-induced thrombotic thrombocytopenia.

Imaging should be performed directed at presenting symptoms, to assess for thrombosis, noting that initial symptoms might be very subtle and there should be a very low threshold for radiological assessment. In addition, in any patient with suspected VITT, further investigation should be performed to assess for anti-PF4 antibodies. PF4 antibody testing needs to be assessed using an enzyme-linked immunosorbent assay (ELISA) assay (Asserachrom (Diagnostica Stago) or Zymutest (Hyphen Biomed) kits in Australia), rather than rapid HIT assays that will produce false negative results due to differential antibody specificities between HIT and VITT antibodies.[19] The reason why rapid HIT assays are less likely to identify VITT antibodies than ELISA assays is incompletely understood, but might be related to their different epitopes or differences in composition and concentration of the anti-PF4 complexes. It is important to note that anti-PF4 antibodies are present in over 90% of cases of definite or probable VITT.[11] Therefore, a negative result does not completely exclude VITT and if clinical suspicion is high, patients should be treated for VITT regardless of the result.

Functional testing for platelet activation can be useful to confirm the diagnosis, particularly for cases who meet clinical and laboratory criteria but are anti-PF4 ELISA negative. A number of methodologies has been described, including the serotonin release assay, traditionally a confirmatory assay for HIT, which can be modified to identify platelet activation in VITT, flow cytometry-based procoagulant platelet assays,[20] modified heparin-induced platelet aggregation assay, and platelet function testing using multiplate.[19,21] It is important to obtain blood samples for functional testing prior to treatment with intravenous immunoglobulin (IVIg), as IVIg can inhibit functional assays. While there have been similarities drawn between HIT and VITT, these are distinct clinical syndromes, and importantly, as described above, in functional platelet assays, a key difference is that low-dose heparin with serum from VITT patients typically inhibits rather than activates platelets.[4]

It is important to note that VITT is not typically associated with any diagnostic features on the blood film, therefore if red cell fragments or spherocytes are present, an alternative diagnosis should be considered. Similarly, there are other syndromes consisting of thrombosis and thrombocytopenia that might occur coincidentally following vaccination and these should be considered. Differential diagnoses of VITT are outlined in Table 3.

Management

The mainstays of management of VITT are anticoagulation and IVIg, with additional strategies such as plasma exchange for severe or refractory cases. Treatment should not be delayed, as these patients have the potential to deteriorate rapidly.

Anticoagulation

Anticoagulation should be started in any patient with probable or definite VITT. Although there remains no definitive evidence that heparin lacks efficacy in VITT, given the presence of anti-PF4 antibodies and early case reports of worsening clinical status with heparin treatment, non-heparin anticoagulants are currently recommended despite *in vitro* evidence that heparin inhibits antibody binding to PF4.[4,16] Anticoagulant options include parenteral direct thrombin inhibitors (DTI; bivalirudin and argatroban), fondaparinux, and the direct oral anticoagulants (DOAC) apixaban and rivaroxaban. Where non-heparin anticoagulants are not available, heparin should be used, as delaying therapeutic anticoagulation in this setting is likely to pose significantly more risk than heparin administration.[22]

In situations of bleeding, severe thrombocytopenia, hepatic or renal impairment or the potential requirement for surgical intervention, titratable parenteral DTI are preferred. Although neither have a specific reversal agent, they have a very short half-life and therefore the anticoagulant effect wanes quickly after cessation.

Despite this benefit, monitoring the DTI can be difficult – they are both monitored using the activated partial thromboplastin time (APTT) and in these critically unwell patients whose factor VIII can be very high there can be significant difficulties in maintaining a therapeutic APTT. Specific monitoring approaches, such as using the dilute thrombin time, might be used, but these assays are not widely available. Therefore, as soon as there is clinical stabilisation accompanied by improving platelet counts, early transition to a DOAC should be considered given their predictable pharmacokinetic profile that obviates the need for monitoring.

Importantly, neither the presence of intracranial haemorrhage (ICH) secondary to CVST, nor severe thrombocytopenia, are contraindications to anticoagulation. Haemorrhage in the context of CVST is due to venous outflow obstruction, therefore measures to treat the thrombotic occlusion should be initiated without undue delay. The safety of anticoagulation in CVST with concurrent ICH has previously been demonstrated.[11] In addition, those with severe thrombocytopenia are likely most at risk of thrombosis, in whom anticoagulation is critical to improve outcomes.

IVIg

IVIg is the only known treatment that modifies both hypercoagulability and thrombocytopenia, by preventing FcγRIIa-mediated platelet activation.[23,24] IVIg should be given at a dose of 1–2 g/kg a day for two consecutive days to all cases of VITT.[12] This is particularly important in patients with a high risk of deterioration, such as those with severe thrombocytopenia (platelet count $<30 \times 10^9$/L), severe thrombosis or presence of hypofibrinogenaemia (fibrinogen <1.5 g/L).[12] Markers of platelet activation have been shown to reduce to levels comparable with a healthy donor following IVIg administration.[23] In addition, IVIg is critical in patients with profound thrombocytopenia, as raising the platelet count along with anticoagulation should reduce bleeding risk.[22] Although IVIg administration has been associated with an increased incidence of thrombotic complications in other clinical contexts, the risk is thought to be negligible in the setting of VITT, particularly when given in conjunction with therapeutic anticoagulation.

'Pre-VITT'

There is a subset of patients with clinical and laboratory features of VITT but no thrombosis on initial imaging – an entity known as 'pre-VITT'.[25] These patients remain at very high risk of developing thrombosis and careful follow up and repeat imaging should be performed according to any change in clinical symptoms. Patients who present with 'pre-VITT' should also be anticoagulated in most circumstances.[25] A recent case series of 11 patients presenting with headache and laboratory features of VITT but no thrombosis on initial investigations found that those who were treated as if they had VITT (i.e. with anticoagulation and/or IVIg and/or corticosteroids) did not subsequently develop thrombosis, while those who were not anticoagulated, or had it stopped prematurely, all went on to develop overt thrombosis.[25] This suggests that headache might precede CVST by several days, potentially due to microvascular thrombosis involving the small cortical veins, and if laboratory features (thrombocytopenia, very high D-dimer and positive anti-PF4 ELISA) are present, early treatment with anticoagulation and/or IVIg might arrest the development of overt CVST.[25] These cases of 'pre-VITT' should also have close monitoring of full blood count, D-dimer and fibrinogen and a very low threshold for repeated imaging.[22]

Additional strategies for severe and/or refractory cases

Certain cases of CVST, particularly if associated with severe thrombocytopenia and/or ICH, should be considered for early plasma exchange upfront, which removes pathological antibodies, and has been shown to improve survival.[11] Furthermore, in these severe cases, early referral to neurosurgeons and interventional radiologists should be made for consideration of craniectomy, thrombectomy or catheter-directed thrombolysis. A recent small case series identified those with extensive clot burden, concomitant haemorrhage, rapid clinical progression or persistent rise in intracranial pressure as patients that should be considered for endovascular and/or surgical treatment.[26]

Described therapies in the context of inadequate responses to IVIg and therapeutic anticoagulation, or clinical worsening following initial response. Include additional doses of IVIg, plasma exchange, corticosteroids, rituximab and eculizumab, although the evidence for their use is limited to case reports. These can be considered if there is an inadequate response or progression despite the use of IVIg and anticoagulation after 2–3 days,[27] or in those with initial poor prognostic signs. These include severe CVST, thrombosis at multiple sites, secondary bleeding or platelet count $<30 \times 10^9$/L.[27] National Institute for Health and Care Excellence (NICE) guidelines suggest plasma exchange using fresh frozen plasma (FFP);[27] albumin could be considered if there are delays in obtaining FFP, although it is possible this could worsen coagulopathy. Corticosteroids may be given as methylprednisolone 1 g for 3 days or dexamethasone 20–40 mg for 4 days, and rituximab at a dose of 375 mg/m^2 weekly for 4 weeks.[27] Complement inhibition with

eculizumab has also been reported in several patients with progressive deterioration despite IVIg and anticoagulation with evidence for clinical improvement.[28]

Therapies to avoid

While initial case series reported worsening clinical status of VITT patients following platelet transfusion, it remains unclear if platelet transfusions do actually worsen thrombosis in this context. Indeed, the patients given platelets were critically unwell and might have had poor outcomes regardless.[4] Patients with severe thrombocytopenia and/or bleeding might need a platelet transfusion, particularly those requiring invasive procedures. Vitamin K antagonists should be avoided in acute VITT, as they cause protein C deficiency that can increase the risk of microcirculatory thrombosis.[22]

Follow up

There have been reports of clinical worsening following discharge from hospital and patients require close clinical follow up. Therefore, it is recommended to measure D-dimer, fibrinogen and platelet count every 2–3 days for the first 2 weeks, weekly for 4 weeks, and then monthly for 6 months.[27] Repeat anti-PF4 antibody testing should be performed at 6 weeks, 3 months and 6 months, and prior to cessation of anticoagulation.[12] It is currently unknown if VITT patients can safely receive a second adenovirus vector vaccination and mRNA-based vaccines are currently preferred for subsequent doses. While we do not have long-term data, it is currently thought that a history of VITT is not a contraindication to future use of heparins, particularly once VITT antibodies are no longer detectable.

Unanswered questions

The optimal longer-term follow up of patients with VITT, particularly regarding the duration of anticoagulation and persistence of anti-PF4 antibodies, remains unclear. Recent data suggest that although VITT antibodies persist for more than 3 months in most patients, interestingly platelet functional tests normalise much earlier.[29] This raises the possibility that platelet functional testing might help guide the duration of anticoagulation. However, it is currently thought that anticoagulation for 3–6 months, similar to non-VITT-provoked VTE, is sufficient for the majority of cases. Given the first cases of VITT were described in March 2021, follow-up data are eagerly awaited and will no doubt provide important information regarding decision-making around duration of anticoagulation.

In addition, while most individuals have B cells that produce antibodies that bind to PF4/heparin complexes, what is not known in VITT is the 'co-factor' that binds to PF4 to induce immunogenic neoepitopes that triggers the generation of pathological antibodies.[16] Further research into this is required to understand fully the pathophysiology of VITT, and importantly potentially to guide the design of adenovirus vector vaccinations in the future.

Outcomes

VITT is associated with significant morbidity and mortality. Mortality in the largest published case series from the United Kingdom was 22%; however, in those with a platelet count $<30 \times 10^9$/L and the presence of ICH the mortality rate was 73%.[11] The odds of death are increased in those with CVST, with more severe thrombocytopenia, with higher D-dimer and with a lower fibrinogen level.[11] Awareness to encourage early presentation combined with a streamlined pathway for diagnosis and immediate treatment in Australia has reduced morbidity and mortality here to less than 5%.[7] VITT can have a significant psychological impact, and referral to psychological and other supports should be considered.

Conclusion

VITT is a rare, potentially life-threatening, condition characterised by thrombosis and thrombocytopenia mostly following the first dose of adenovirus vector vaccination. The underlying mechanism remains incompletely understood but involves anti-PF4 antibody-mediated massive platelet activation. Early presentation, prompt diagnosis and effective treatment with therapeutic anticoagulation and IVIg can reduce morbidity and mortality. Ongoing close follow up of VITT patients is important for improved long-term outcomes.

Acknowledgments

Open access publishing facilitated by Monash University, as part of the Wiley - Monash University agreement via the Council of Australian University Librarians.

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