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CLINICAL CHALLENGE

Covid19 vaccination-associated portal vein thrombosis—An interdisciplinary clinical challenge

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Abstract Despite one of the largest vaccination campaigns in human history, the COVID-19 pandemic has not been yet defeated. More than 10 billion doses of COVID-19 vaccine have been administered worldwide. AstraZeneca’s Vaxzevria (ChAdOx1 nCoV-19 / AZD1222) was approved as the first viral vector-based vaccine in the EU on 29 January 2021. Thromboembolic events are a rare complication of vaccination with ChAdOx1 nCoV-19 in the context of, now known as vaccine-induced immune thrombotic thrombocytopenia (VITT), with an incidence of 1.5–3 in 100,000 vaccinations. VITT is clinically as well as pathophysiologically comparable to heparin-induced thrombocytopenia. Illustrated by a fulminant patient case, a multidisciplinary step-by-step guideline was developed for the recognition, diagnosis, and management of patients with severe acute portosplanchic venous thrombosis with mesenteric ischemia due to vaccine-induced immunogenic thrombotic thrombocytopenia.

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Background

The development and clinical evaluation of vaccines against SARS-CoV19 is an outstanding medical achievement. Despite one of the largest vaccination campaigns in human history, the COVID-19 pandemic has not yet been defeated. Since the omicron variant of coronavirus has become dominant, there have been unprecedented high incidences worldwide [1]. By mid-February 2022, more than 10 billion doses of COVID-19 vaccines had been administered worldwide, according to WHO data. Although various manufacturers have worked on the production of vaccine, only five vaccines have received emergency approval by the EMA and/or FDA [2].
AstraZeneca’s Vaxzevria (ChAdOx1 nCoV-19 / AZD1222) was licensed as the first viral vector-based vaccine in the EU on 29 January 2021. Unfortunately, vaccination with ChAdOx1 nCoV-19 has shown complications in the context of thromboembolic events, now known as vaccine-induced immune thrombocytopenia (VITT), with an incidence of 1.5–3 in 100,000 vaccinations [3,4]. The pathophysiology of VITT is not conclusively understood. VITT is caused by antibodies that recognize platelet factor 4 (PF4) bound to platelets. These antibodies of immunoglobulin G (IgG) type that activate platelets resulting in distinct stimulation of the coagulation system and clinically significant thromboembolic complications. Elevated PF4 levels in the plasma of patients with VITT and heparin-induced thrombocytopenia (HIT) as well as the platelet-activating activities via the Fc receptor of both antibodies highlight the close similarity between these immune-mediated coagulopathies (HIT mimicry).

Clinically, VITT manifests itself in rather unusual locations, such as cerebral venous sinus thrombosis (CVST), in the arterial bloodstream, e.g. as pulmonary artery embolism, or in the abdominal splanchnic veins [5]. The latter is a life-threatening disease, especially in its maximum form as complete portal vein thrombosis with simultaneous occlusion of the superior mesenteric vein (VMS) and splenic vein.

Here we would like to present a step-by-step process of clinical decision making (cf. Fig. 5) for this interdisciplinary clinical challenge for visceral surgeons, interventional radiologists, and intensive care physicians on the example of a patient case treated in our clinic.

**Step 1: Clinical symptoms and diagnosis of VITT-associated acute splanchnic vein thrombosis**

**Patients Course**

A 40-year-old patient without any comorbidities presented 10 days after vaccination with ChAdOx1 nCoV-19 to the emergency department of a primary care hospital with acute abdominal pain, nausea, and vomiting. A CT scan performed for further diagnosis showed a complete portal vein thrombosis with simultaneous occlusion of the splanchnic veins (Fig. 1a). The progressive clinical aggravation could be stabilised by initiating intensive volume therapy.

Due to severe abnormalities in the coagulation parameters (platelet count 32 /nl [163-337], D-dimer >34.4 mg/l [<0.5]), fibrinogen 99.8 mg/dl [210–400] and further progression of clinical symptoms, the patient was transferred to our maximum care clinical centre. A stabilization of the patient could only be achieved after intensive care treatment including intubation, ventilation and the start of catecholamine therapy in the emergency room. Laboratory tests and a CT scan were repeated immediately (Fig. 1b). Here, a clear deterioration with further progression of the thrombosis, as well as massive swelling of the small intestine was detected. Further laboratory diagnostic was performed. PF4 HIT chemiluminescence-based immunoassay (CLIA) was negative, but modified Heparin-induced platelet activation test (PIPA) showed strong platelet activation, confirming the diagnosis of VITT.

**Recommendations**

Special attention should be given to all recently vaccinated (4–42 days) patients who present with one or more of the following symptoms: headaches, dizziness, visual changes, nausea, vomiting, abdominal, shortness of breath, acute pain in chest, abdomen, or extremities. In addition, if any type of venous or arterial thrombosis is seen on imaging performed in a symptom-oriented manner, immediate laboratory diagnostic testing should include a complete blood count (CBC) to rule out/detect thrombocytopenia, determination of fibrinogen and D-dimer levels, and further tests to rule out/detect VITT (PF4-chemiluminescence-based immunoassay CLIA, HIPA, PIPA) [6–8]. If VITT is highly suspected in a primary care clinic, the patient should be transferred as soon as possible to a clinic that provides 24-hour care by intensive care physicians, interventional radiologists, visceral surgeons and neurosurgeons.
Step 2: Pharmacological therapy of VITT-associated acute portal vein thrombosis

Patients Course

According to the recommendations presented below, the patient received 1 g/kg body weight intravenous immune globulin (IVIG) with a cotherapy of 40 mg dexamethasone. In addition, heparinization initiated by the primary care physicians was stopped and therapeutic anticoagulation with argatroban was started. Fig. 2 presents an overview of the patient’s clinical course over time.

Recommendations

After diagnosis, conservative therapy should be guided by the treatment of a severe HIT. This includes primarily intensive care stabilization of the patient, adequate anticoagulation with a non-heparin anticoagulant, administration of IVIG, and in case of refractory disease, plasma exchange.

Anticoagulation

One of the most important steps in the treatment of portal vein thrombosis caused by VITT is the adequate management of anticoagulation. The selection of the anticoagulant is based both on the patient’s clinic and on the possibility of having to stop the anticoagulation quickly in the course of time due to severe bleeding or the necessity of operations. Therefore, it is essential to evaluate the patient’s risk of bleeding and thrombosis.

Considering the pathomechanism, the anticoagulation has to be based on a non-heparin HIT compatible anticoagulant. In a critical ill patient, parenteral anticoagulation with danaparoid or the direct thrombin inhibitor argatroban is generally preferred. Argatroban is almost exclusively eliminated hepatically with a half-life period of approximately 45 min. Due to the short half-life (in contrast to danaparoid) we initiated anticoagulation with argatroban to achieve a target aPTT ratio of 1.5 to 3 times the initial baseline value. The pentasaccharide fondaparinux should not be used in the early phase of VITT and due to its long half-life of approximately 17 h and the lack of an antidot it is not suitable for patients in whom invasive procedures may be performed. Generally, the direct oral Xa inhibitors apixaban, edoxaban and rivaroxaban and the direct oral thrombin inhibitor dabigatran are an alternative option, although less studied. However, the administration of these anticoagulants is limited in critically ill patients due to their oral route of application and possible drug-drug interactions.

Nevertheless, it is crucial to avoid the use of any heparins at all times. Several publications have shown that anticoagulation with heparin - both unfractionated and low molecular
weight - can lead to a deterioration [9,10]. Especially "hidden" heparins such as in dialysis solutions, heparin-wetted surfaces of catheters or PPSB products pose a special challenge to the attending physicians. The recommendation of additional inhibition of platelet aggregation by aspirin or other inhibitors is controversially discussed due to the increased risk of bleeding.

IVIG
The second important component in the therapy of VITT is the urgent administration of IVIG. Pathophysiologically, the efficacy of IVIG is described by a competitive mechanism of displacement of platelet-activating PL-4 antibodies by these IgG antibodies [11]. Great attention must be paid to the timing of the start of therapy with IVIG.

On the one hand, according to the American and British Society for Haematology, the earliest possible administration of IVIG positively favours the progression of the disease [6,12]. On the other hand, it is not possible to diagnose VITT or even HIT after the start of IVIG therapy, as most laboratory tests will yield false negative results [13]. The recommended dosing regimen is 1 g/kg over the course of two days, using 'ideal body weight' as the basis for body weight [14,15]. Steroids should be given as a comedication to the immunoglobulins to reduce side effects as much as possible.

Stabilization of coagulation
Transfusion of platelets and replacement substitution of fibrinogen should be restricted to life-threatening complications or bleeding depending on the platelet count and fibrinogen level. In the case of very severe or therapy-resistant VITT, plasma exchange for the rapid removal of PL-4 antibodies represents an extended therapy option [16].

Step 3: Interventional therapy of VITT-associated acute portal vein thrombosis

Patients Course
Due to the severity of the portal vein thrombosis with complete splanchnic occlusion, angiographic insertion of a TIPS as a transjugular approach to the portal vein was also immediately necessary (Fig. 3 b/c). A purely drug-based therapy did not appear likely to be successful. Recanalization of the portal vein flow could was successfully achieved using an aspiration thrombectomy device. Prophylactically to maintain portal vein flow, lysis catheters were placed both retrograde via the TIPS into the thrombosis and antegrade via a cobra catheter placed in the superior mesenteric artery via transfemoral artery access (Fig. 3d). For lysis therapy, rt-PA was used at a total dosage of 1.0 mg/h, applied through both catheters at a dosage of 0.5 mg/h.

Recommendations
Interventional methods are considered when systemic anticoagulation has not been effective or therapeutic systemic anticoagulation is not possible. The renewed Baveno VII Consensus [17] for Personalized Care of Patients with Portal Hypertension provides guidance for this interdisciplinary evaluation based on clinical parameters and early imaging.

Here, it is recommended to make the decision dependent on (I) persistent severe abdominal pain despite anticoagulation therapy, (II) bloody diarrhea, (III) lactic acidosis, (IV) bowel loop distention, or (V) occlusion of second-order radicles of the superior mesenteric vein.

Catheter-based treatment is an effective and safe method to treat portal vein thrombosis. The success of the intervention is based on recanalization, reestablishment of portal vein flow and local-high lysis concentration.

Interventional restoration of venous outflow via the portal vein
The portal veins can be accessed via a transjugular intrahepatic portosystemic (stent) shunt (TIPS), transhepatic or transsplenic approach and allows catheter-based intervention. If surgical exploration is performed, intraoperative access to the portal vein is also possible via the transluminal omental vein.

The jugular vein access in comparison to the percutaneous transhepatic and transsplenic approach has the advantage of a lower risk of bleeding and subcapsular haematoma in the presence of poor clotting [18,19]. Implantation of a TIPS improves portal venous outflow by acting as a bypass. Due to the improved outflow, the risk of rethrombosis is reduced.

The transjugular entry route to the portal vein also allows a local drug thrombolysis or thrombectomy, mechanically or by aspiration.

Thrombolytic intraluminal drug therapy or clot dissolution therapy (CDT)
Additionally to restoration of the portal venous flow, local drug thrombolysis with alteplase (rt-PA) or urokinase directly into the portal vein in the region of the clot itself or indirectly via the SMA is a therapeutic option as well. The success rate of pharmacological thrombolysis is almost identical for alteplase and urokinase. However, alteplase requires significantly lower doses than urokinase [20]. For direct intraluminal thrombolysis, a dose of 0.05 mg/kg/h up to a maximum of 4 mg/h is used [21], respectively doses for urokinase range from 200,000 to 600,000 IU/day [22].

Direct application of lysis to the thrombus via an endovascular catheter (4-5 French) in combination with a TIPS is superior to systemic thrombolysis in terms of efficiency, recurrence rates and therapy-associated risks [21]. Contraindications for this procedure are: Gastrointestinal bleeding, stroke, orthopaedic or craniospinal trauma, and an intracranial tumour.

Step 4: Surgical therapy of VITT-associated acute portal vein thrombosis

Patients Course
Despite interventional treatment and relief of venous pressure on the intestine, the patient developed an abdominal compartment syndrome. Due to this life-threatening aggravation with the risk of intestinal infarction, an emergency laparotomy was performed. Intraoperatively, the entire small intestine showed massive venous swelling, edema and lividity (Fig. 4a). Arterially, however, good pulses could still
be palpated in the mesentery. To further improve venous outflow, open surgical thrombectomy of the peripheral thromboses of the mesenteric and splenic veins would have been indicated at this point. However, as intraoperative duplex sonography showed reocclusion of the TIPS and portal vein, was not an option anymore. For compartment therapy, the abdominal fasciae were not closed postoperatively, but an open abdominal situation was established using a negative pressure dressing.

Reangiography with aspiration thrombectomy performed immediately postoperatively successfully achieved venous outflow via the TIPS again. Further intensive care stabilization as well as local and systemic lysis finally made it possible to perform extensive surgical thrombectomy from the confluence to the periphery of the VMS and splenic vein on the third day after diagnosis (Fig. 4b). The surgical re-explo- ration performed two days later confirmed a clearly recovered bowel, so that the abdomen could be closed again at the end of this operation (Fig. 4c). Lysis therapy was subsequently stopped. Therapeutic anticoagulation with argatro- ban was continued and supplemented with antiplatelet therapy with clopidogrel and ASA.

**Recommendations**

The surgical approach to portal vein thrombosis is clearly inferior to catheter-based intervention due to the risk-benefit profile. Therefore, according to the current guidelines, surgical steps should be considered depending on the symptoms and the abdominal findings. The indication for
emergency laparotomy arises when there is evidence of acute mesenteric ischaemia, abdominal compartment syndrome or complications that cannot be managed by interventional means. If surgical intervention is necessary in very severe and complicated cases, open thrombectomy should be performed during the operation.

Surgical thrombectomy
After median laparatomy and assessment of the bowel, surgical thrombectomy via the superior mesenteric vein (SMV) is possible. The vessel can be exposed at the inferior border of the pancreas. The SMV is dissected from the surrounding tissue and controlled using two vessel loops. A transverse semicircular venotomy can be performed after two holding sutures are placed at both ends. Thrombotic material is removed mechanically using a Fogarty catheter or by suction thrombectomy [23]. Non-absorbable running sutures are recommended for vessel closure.

Even if the primary surgery was successful, assessment of the extent of bowel ischaemia is often inaccurate. Therefore, a second-look laparotomy is recommended after 24–48 h [24].

The disadvantages of a surgical thrombectomy are, on the one hand, that it is not possible to execute a complete peripheral thrombectomy and, on the other hand, that a protective portal venous/central venous shunt cannot be
created. As a result of the correspondingly low portal vein flow, the risk of renewed thrombosis is very high. Therefore, prior TIPS is recommended.

Abdominal compartment syndrome
Abdominal compartment syndrome (ACS) is characterized by intra-abdominal pressure exceeding 20 mmHg. This can be caused by various serious pathologies, such as arterial or venous circulatory disorders. Since the abnormal abdominal pressure itself impairs organ perfusion, it results in a vicious circle. This cycle can be broken by decompression by emergency laparotomy and open abdomen treatment [25].

This open abdomen situation can be managed either by inserting a fascial mesh or by using negative pressure wound therapy. It is recommended to re-explore the patient every 24–48 h or sooner if deterioration occurs.

**Step 5: Prevention and follow-up of VITT-associated acute splanchnic thrombosis**

**Patients Course**

Thirteen days after admission to the intensive care unit, the patient could be extubated. Because of a newly occurring
reduction of vigilance, a cMRI was performed. This revealed a jugular vein thrombosis that extended into the sigmoid sinus. The patient’s neurological condition continued to stabilize and he was discharged from the intensive care unit after a total of 26 days. Anticoagulation was switched to apixaban at therapeutic dosage (5 mg twice daily) and dual platelet inhibition was reduced to clopidogrel monotherapy. Duplex sonographic scans of the TIPS and the portal vein, which were subsequently carried out for control purposes, always showed sufficient blood flow (Fig. 4d). Transfer to a rehabilitation clinic for follow-up treatment was finally possible on day 35.

The current 6-month follow-up showed stable clinical findings. Both, sonography confirmed sufficient visceral blood flow and laboratory chemistry ruled out a recurrence of the thrombosis. After appropriate rehabilitation, the patient was able to resume most of his daily activities.

Anticoagulation is still being continued. A re-evaluation should take place in six months after the diagnosis of thrombosis at the earliest.

Recommendations

Despite rare thromboembolic side effects of AstraZeneca vaccination, prophylactic anticoagulation or antiplatelet therapy is not recommended by scientific communities. Prophylactically, patients, especially those at risk, should be instructed to practice general measures for thrombosis prophylaxis after vaccination, such as exercise, sufficient fluid intake and wearing compression stockings. The incidence of VITT following vaccination against covid-19 with mRNA-based vaccines is lower compared to vector-based vaccines, so their use should be preferred for the planned second or booster vaccination. Re-vaccination with a vector-based vaccine against covid-19 as well as combined vaccinations should be avoided after VITT.

After a VITT-associated acute portal vein thrombosis, close follow-ups of the patient with regular platelet counts, D-dimer measurements, and assessment of symptoms are essential. Anticoagulation should be continued, especially if elevated anti-PF4 antibody titres persist thus the associated risk of relapse. Discontinuation is justifiable once the platelet count, D-dimer and fibrinogen are normal and PF4 antibodies are negative.

Authorship

N.B. and F.B. conceived the study and collected the data and wrote the manuscript.

All authors were involved in the interdisciplinary clinical treatment of the patient. All agreed to submit the manuscript, read, improved and approved the final draft.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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