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Implications for clinical practice in Vaccine-induced immune thrombotic thrombocytopenia associated with atypical vein thrombosis.

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All authors:

1. Made a substantial contribution to the concept or design of the work; or acquisition, analysis or interpretation of data,
2. Drafted the article or revised it critically for important intellectual content,
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PZ and PM researched literature and conceived the study. FS was involved in protocol development and data analysis. AS, PZ and CP wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

ABSTRACT

Objectives: Vaccine-induced immune thrombotic thrombocytopenia(VITT) is a new uncommon syndrome resulting from the largest vaccination campaign against SARS-CoV-2 in the history of mankind.Aim of this review is to clarify the disease mechanisms, pathology, diagnosis and therapy of VITT,with consequent clinical implications.

Methods: we performed a comprehensive literature review in order to collect all the clinical and treatment data about patients suffering from VITT.

Results: pathophysiology, clinical manifestations, diagnosis and medical or, rarely, surgical treatments are described.

Conclusions:VITT is often fatal due to cerebral hemorrhages.We observed several cases for judicial reasons always involving the vascular specialists.However, his/her advice has been hampered by the still partial knowledge on this recently observed syndrome. Indeed, after medical therapy have reached the goal of recovering a safe platelet count and halting thrombus progression, endovascular techniques may be able to provide further benefits, showing the advantage of not affecting hemostasis nor increasing the risk of bleeding.

INTRODUCTION

Since December 9th, 2020 and mainly in the first few months of 2021, the occurrence of thrombi at unusual and non-valvular venous sites (cerebral sinus and abdominal veins such as the portal, mesenteric and splenic) has been reported in patients recently vaccinated with the anti-SARS-CoV-2 vaccines Vaxzevria ChAdOx1nCov-19 (manufactured by University of Oxford/AstraZeneca) and Ad.26. COV2.S (manufactured by Janssen/Johnson & Johnson) (1-6). A feature common to both vaccines is that they use adenovirus vectors of the DNA sequences encoding the SARS-CoV-2 spike glycoprotein, even though Astra-Zeneca uses a replication-incompetent adenovirus from chimpanzee, the Janssen a replication-incompetent human adenovirus. In contrast, no similar case has been recorded until now among more than 500 million people vaccinated worldwide with the mRNA vaccines manufactured by Pfizer and Moderna that use no viral vector. Beside their unusual location a striking feature is that the thrombotic manifestations are accompanied by bleeding, because thrombosis is often associated with a marked decrease of platelet count and laboratory signs of consumption coagulopathy with low plasma fibrinogen and hugely increased D-dimer, a marker of intravascular fibrin formation with secondary hyperfibrinolysis (2-4).

Other peculiar features of the new syndrome, called vaccine-induced immune thrombotic thrombocytopenia (VITT), is that the thrombohemorrhagic manifestations occur within one to three weeks after the first vaccine injection, more often in people younger than 60 years and in women (2-4). These clinical manifestations are very rare, albeit more common than expected in the general population outside the context of anti-COVID-19 vaccination. According to the EudraVigilance system of pharmacovigilance at the censoring date of April 4th 2021 there have been 169 cases of cerebral vein sinus thrombosis (CVST) and 53 cases of splanchnic vein thrombosis (SVT) often associated with thrombocytopenia in the frame of 34 million

administered doses of the Vaxzevria vaccine, equivalent to 6.5 cases of VITT per million people who received the first dose. In the United Kingdom the most recent update by the MHRA (May 26, 2021) records a number of 348 VITT cases (all post Vaxzevria) in the context of 37.7 million doses. With a 19.5% mortality, 330 cases occurred after 24.3 million first vaccine doses and 18 after 13.4 million second dose, age being within the range of 18-59 years in 179 cases. With this background, a few European countries chose to use Vaxzevria only or preferably in older people. Pertaining to the frequency of events observed after the administration of the Janssen/Johnson & Johnson vaccine, the USA-based pharmacovigilance system reported until April 30 2021 17 cases of VITT after 7.98 million doses administered in North America, where the Janssen vaccine is currently being used with no age limitation (5,6).

PATHOPHYSIOLOGY AND MECHANISM

Outside of the vaccination context, venous thromboembolism occurs seldom in the forementioned visceral veins, with a general incidence of cerebral venous sinus thrombosis (CVST) that varies between 0.2 and 1.5 cases per 100.000 people/year and a higher frequency in females (7,8). The most frequent risk factors are head infections and acquired conditions associated with hypercoagulability, such as the use of estrogen-progestogen contraceptives, pregnancy and puerperium. Congenital and acquired thrombophilia are additional risk factors, such as the gain-of-function polymorphisms of coagulation factor V (the so-called factor V Leiden) and prothrombin 20210A (7). Splanchnic vein thrombosis (SVT) is slightly more frequent than CVST, with an annual incidence of approximately 5-7 cases per 100.000 people (9). The main risk factors for SVT are abdominal cancers, liver cirrhosis, myeloproliferative neoplasms and carriership of gain-of-function gene polymorphisms (8,9). With this background, the mechanisms of VITT are completely different from those underlying CVST and SVT outside

the vaccination campaign in the general population. The type and time of syndrome presentation, i.e., in the time space of 5 to 20 days after vaccination and more frequently in young women, resembles such hemostasis disturbances characterized by autoimmune mechanisms as acquired thrombotic thrombocytopenic purpura (TTP), antiphospholipid antibody syndrome (APS) and particularly heparin-induced thrombocytopenia (HIT) (10,11). In the first few months of 2021 a series of reports from Germany, Austria, Norway and the United Kingdom (2-4) demonstrated that most VITT patients, albeit not recently exposed to therapeutic heparin, are characterized by enzyme immunoassay (ELISA) positivity for autoantibodies against a complex between the platelet protein factor 4 (PF4) and a still ill-defined polyanion endowed with the properties to form complexes with a cation such as PF4 (2-6) (Figure 1). It is also still ill-defined which component of the viral vector of both vaccines triggers the catastrophic autoimmune response that leads to the Fc□-receptor mediated activation of platelets, followed by the activation of the coagulation system. It is unlikely that the mechanism of VITT is mediated by vaccine-induced antibodies directed against the SARS-CoV-2 spike antigen, the so-called antibody-mediated enhancement, as supported by the evidence that the mRNA-based vaccines produced by Pfizer and Moderna are not associated with VITT. The most recently proposed mechanisms, yet not supported at this time by a peer review publication, suggest an antigenic effect exerted by changes in the spike protein of the SARS-2-CoV virus encoded by the adenovirus vectors of both vaccines. The occurrence of abnormal DNA splicing would produce protein neoantigens with an abnormal conformation that in turn produce anti-PF4 antibodies (Figure 1a). The vaccine induced consumption coagulopathy leads to the final cerebral hemorrhages (Figure 1b). The cerebral vasculature is the elective location of the fatal bleeding because the intracranial vessels are not affected by the atmospheric pressure. Thus, lack of the main external pressure component on the vascular wall on one side and the

increased internal venular pressure due to venous sinus thrombosis on the other strongly increase the transmural pressure leading to intracranial bleeding.

SYMPTOMS AND DIAGNOSIS

In the time interval of 5 to 20 days after administration of one of the products based upon adenovirus vectors vaccinated persons should consult a primary care physician if they develop such unusual symptoms as persistent, diffuse and severe headache refractory to analgesics, focal neurological symptoms such as blurred vision, speech and motion difficulties or strong abdominal pain often accompanied by nausea, vomiting and fever (2-6). Persons with these symptoms and signs should seek care at the emergency room of the nearest hospital in order to obtain a blood sample for a complete blood cell count. VITT is suspected if the platelet count is lower than 100.000/mm^3 and D-dimer is higher than the age-adjusted range (usually more than 1000 ng/L). These findings should lead to perform diagnostic imaging in order to rule out CVST and SVT. The vaccine-induced, immunomediated activation of the coagulation system has also been reported to cause arterial thrombosis including ischemic stroke, even though venous thromboembolism especially CVST appears by far the most frequent thrombotic manifestation.

To diagnose CVST the tests of choice are a cerebral computed tomography with angiography or magnetic resonance imaging. The neuroradiologist needs to be prompted on a clinical suspicion of CVST in order to pursue an accurate inspection of the cerebral veins by means of a contrast medium (9). When abdominal vein thrombosis is suspected an echo-Doppler should be used to diagnose portal and splenic vein thrombosis, but this test has poor diagnostic accuracy for mesenteric vein thrombosis (9). Thus, when this imaging approach is not

conclusive and diagnosis remains uncertain, a computed tomography scan with angiography of the abdomen should be chosen to evaluate more accurately whether thrombi are present, their localization and degree of extension.

The laboratory tests employed to detect the serum positivity for the PF4-polyanion complex are the Lifecodes PF4 IgG enzyme immunoassay (Immunocor) or the Asserochrom HPI IgG tRA EIA (Stago), whereas the chemiluminescence Hemosil Acustar HIT IgG assay (Werfen) is negative in most cases with VITT (11,12). While one of these tests is essential to first diagnose VITT, second-step functional assays for platelet activating antibodies in serum samples are warranted to confirm positive ELISA results or overrule negative results (11,12). Even though a large number of hospitals have set up ELISAs for anti-PF4s polyanion, only few of them do one of the more complex and cumbersome platelet activation assays (the heparin induced platelet activation HIPA test, P selectin platelet expression, serotonin release assays).

A frequently asked question by vaccination candidates is whether or not previous clinical events or laboratory tests help to predict the likelihood to develop this complication. At the moment and in the frame of our still limited mechanistic knowledge, there is no way to predict VITT, nor it is possible or advisable before vaccination to carry out any laboratory test or prescribe antithrombotic prophylaxis with anticoagulant or antiplatelet agents. By the same token, carriers of thrombophilia risk factors (such as the gain-function polymorphisms, and the intake of oral contraceptives) should not skip vaccination, because these are not risk factors for the onset of VITT-associated thromboembolism.

MEDICAL AND SURGICAL MANAGEMENT

Patients should be preferably admitted to large hospitals endowed with facilities for laboratory diagnosis, imaging and intensive care and should be attended by a multidisciplinary team including hematologists, neurologists, internists and vascular- and neurosurgeons because, even though acute treatment is mainly based on medicines, decompressive craniectomy and endovascular therapy may be indicated only in carefully selected patients (see below).

Medical treatment

Pertaining to the medical treatment of VITT, the recent identification and description of this new syndrome makes still impossible to provide evidence-based guidelines, even though a few learned societies offered early recommendations in order to treat these rare but clinically demanding cases (13,14). The snag is that any therapeutic strategy must tackle of the same time two competing manifestations such thrombosis and bleeding due to thrombocytopenia and consumption coagulopathy. Thus, the clinician must evaluate which clinical aspects of these two disease mechanisms prevail in each case and cause this life-endangering syndrome.

Platelet therapies

Increasing to a safe level a low platelet count is the first goal, because handling thrombosis by means of medicines or invasive therapies is impossible unless platelets are raised to at least a level of 50.000/mm^3. The most suggested medical approach is similar to that employed and recommended for heparin-induced thrombocytopenia, to which VITT resembles for the main laboratory findings (consumptive thrombocytopenia) and thrombosis in large vessels (mainly venous, but also arterial) (10). With the goal to tackle the autoimmune mechanism underlying thrombocytopenia, intravenous immunoglobins can be administered at a dosage 1 g/kg/day for two days (Figure 2). Moreover, this underlying immune mechanism as well the high likelihood of some degree of cerebral edema in CVST support the additional use of high-dose

corticosteroids. For instance, intravenous dexamethasone 40 mg/day for at least 4 days or oral prednisone at a dosage of 1 mg/kg/day for no less than 7 days are warranted before considering an anticoagulant when an adequate increase of the platelet count has been achieved (Figure 2). When a patient is severely bleeding, for instance in the presence of intracranial bleeding, we should first attempt to increase the platelet count at a more rapid pace than that obtainable with immunoglobulins or corticosteroids. Even though after transfusion the platelet increase is usually not sustained owing to rapid cell removal from the circulation by autoantibodies, there are reports of the successful use of this transfusion, based approach in order to handle such a dramatic clinical condition such as intracerebral bleeding. Another approach that has been attempted in some cases with apparent success is therapeutic of plasma-exchange (PEX). This procedure has the double goal to remove the circulating autoantibodies and replace fibrinogen and other coagulation factors in cases presenting with consumption coagulopathy.

Anticoagulant therapies

As in HIT, unfractionated or low molecular weight heparins should not be used as an upfront anticoagulant to stop or slow the progress of thrombosis (10). No alternative anticoagulant nor antithrombotic drug should be considered in VITT if and when the platelet count is lower than 25.000/mm^3, because the ensuing hemorrhagic risk is unacceptably high and outweighs that of thrombosis progression (Figure 2). When at presentation or after therapy the platelet count is higher, i.e., between 25.000 and 50.000, an anticoagulant with a short plasma half-life such as argatroban should be first considered (Figure 2). However, this drug is not available nor widely used in most hospitals not specialized in the management of thrombosis. An alternative, non-heparin based anticoagulant medicine is fondaparinux, to be initially considered at doses approximately half those commonly used to treat venous thrombosis (Figure 2). When the platelet count is or becomes higher than 50.000/mm^3, anticoagulants other than heparin can

be used at standard therapeutic doses with an acceptable degree of safety. Also direct oral anticoagulants have been used, but experience is limited.

Surgical therapies

Once the platelet-associated primary hemostasis defect and thus the bleeding tendency are stabilized by medical therapy, an endovascular treatment (EVT) may be considered in the most extensive and severe forms of mesenteric or portal vein thrombosis. However, this approach should be confined to severe clinical courses and/or when thrombosis involves the superior mesenteric vein, because mortality rates up to 75% are reported (15). EVT has the goal to ameliorate intestine recanalization and drainage and reduce portal hypertension through the creation of a transjugular and/or transhepatic access and the reestablishment of blood drainage through the main portal trunk and selective local thrombolysis (16). The efficacy and safety of this approach is currently improved following the introduction of devices for mechanical thrombo-aspiration, which permit to use lower dosages of thrombolytic drugs (17,18).

Pertaining to the cerebral aspects of the VITT battle, no reports are at the moment available on the use of EVT in vaccine-induced CVST. EVT has the goal to achieve a rapid recanalization of the cerebral sinuses through the local application of a thrombolytic drug, mechanical thrombectomy or a combination of both (19). However, EVT for treating standard CVST is indicated only when patients deteriorate clinically despite anticoagulants (20), because a randomized clinical trial has shown that EVT does not improve functional outcomes if compared to standard medical treatment (21). All in all, in this difficult scenario of VITT-associated CVST characterized by a mortality much higher than that of standard CVST, the use of EVT should be considered as a last resort option. This also applies to the role of the neurosurgeon. When intracranial hypertension (due to space-occupying brain oedema, infarction, intracranial

hemorrhage) is prolonged and uncontrolled by median treatments, brain herniation with severe organ injury and death often occurs. Thus, decompressive craniectomy might be an option in order to favor collateral vein drainage by reducing intracranial pressure. Even though evidence is lacking and no RCTs are available, observational studies, case reports or case series suggest that decompressive craniectomy is a lifesaving procedure, with a favorable outcome in more than half the patients and a mortality of 15-18%. (22). Guidelines from the European Stroke Organization recommend decompressive craniectomy in patients with evidence of parenchymal lesions, midline shift of more than 5 mm, impending herniation or intracranial pressure higher than 20 cm H2O. (23) However, a discussion with the patient's family or caregiver must be done when proposing surgery because, notwithstanding a mortality reduction, there is a high likelihood of a poor functional outcome in survivors.

POST-MORTEM INVESTIGATIONS AND PATHOLOGY

Post-mortem investigation is the gold standard to define the exact cause of death and related pathology findings after a fatal vaccination. However, in these early phases of the COVID-19 pandemic, only a small number of autopsies were performed worldwide, perhaps because a few countries discourage or even prohibit post-mortem investigations (24). Nevertheless, the causality relationship should be investigated in each case with a fatal outcome after COVID-19 vaccination, considering also that recent publications offered a specific causality algorithm according to the WHO eligibility diagnosis (25,26).

Only 6 post-mortem reports are currently published (Supplementary table 1). Out of a total of 10 VITT cases, 7 are related to ChAdOx1 nCoV-19 administration and 3 cases to the Pfizer vaccine BNT162b. In the latter, Edler et al. (27) excluded any causality relationship after having evaluated the role of comorbidities in two cases and positivity for COVID-19 infection in the

other case. In the remaining 10 fatal cases related to ChAdOx1 nCoV-19 vaccination the positive causality relationship was fully established only in our report that adopted the proposed WHO algorithm (25,26).

Althaus et al. (28), who analyzed two fatal cases after ChAdOx1 nCoV-19 administration, found massive cerebral hemorrhage, bilateral pulmonary thromboembolism and presence of microthrombi in glomeruli. Bjørnstad – Tuveng et al. (29) analyzed the case of a woman who died for intracranial hemorrhage and detected thrombi in the transverse sinus, frontal lobe and pulmonary artery. In the report by Scully et al. (2) post-mortem examination was performed in one case only, with evidence of thrombosis in the microcirculation of lungs and intestine, in addition to extensive intracerebral hemorrhage that was the main cause of death. In the frame of a medico legal investigation Pomara et al. (25,26) analyzed at autopsy two cases who died after vaccine administration owing to the presence of extensive cerebral hemorrhages in both. In one of them portal and mesenteric thrombosis with extension into the splenic vein were documented, while in the remaining case there was a massive thrombosis of the whole venous tree of left upper limb, extending from the hand to the axillary vein with symmetric lesions in the veins of the right hand and the right axillary vein, not previously shown by imaging during life. Greinacher et al. (3) reported post-mortem findings only in two cases who died for CVST. Microscopic findings showed widespread microvascular thrombosis in the lung and kidney and multiple organ thrombi. Overall, the main macroscopic pathology findings in persons who died after ChAdOx1 nCoV-19 administration were intracranial hemorrhages and the confirmation of the venous thrombosis locations identified by imaging during life.

Microscopic evaluation, fully reported in one study only (25,26), showed several vascular thrombi and hemorrhagic areas at the brain level. In addition, diffuse thrombi were observed in the small and medium-sized vessels, due to endothelial activation following an inflammatory

reaction, a procoagulant process and subsequent thrombotic reactions. The same group conducted immunohistochemical investigations (25,26) that revealed the expression of adhesion molecules and activated inflammatory cells in the vascular and perivascular tissues of such different organs as the heart, lung, liver, kidney, ileum and deep veins. The inflammatory cells were arranged in clusters with aggregated platelets at the endoluminal level, confirming a pro-thrombotic state.

CONCLUSIONS

Cognizant that vaccines are one of the greatest medical and scientific achievements of the modern era, we are convinced that in the frame of the SARS-CoV-2 pandemic a medico legal perspective on vaccination is warranted to provide a critical viewpoint. The COVID-19 vaccine campaign involves different issues, such as the possibility of side effects that led to a diffuse suspicion and rejection, especially when a fatal case temporally related to vaccine administration did occur in a young healthy subject. In general, the use of vaccines also generates various ethical and legal problems, including the possibility of conflicts between individual and collective rights. All in all, the great challenge for the scientific community in the fight against COVID-19 is witnessed by the success of a global vaccination campaign. In this context, it is important to provide scientific evidence in order to dissolve the doubts of the public opinion. Finally, despite the rarity of VITT, in cases observed by us for forensic reasons, both the vascular specialist and the neurosurgeon have been always involved. However, their advice has been hampered by the still partial knowledge of this new and recently observed syndrome. The present review was designed to update those colleagues who, in the future, for the magnitude of the vaccination campaign, are expected to be increasingly consulted to confirm or exclude the occurrence of venous thrombosis in the frame of a VITT syndrome.

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Figure Legends

Figure 1a. The mechanism of VITT and the cascade of dramatic events leading to fatal cerebral hemorrhage. Once thrombosis and thrombocytopenia become both clinically evident there is time frame to promptly establish an effective therapy. Point 5= massive portal-mesenteric/cerebral venous sinuses thrombosis.

Figure 1b. The reason of the cerebral venules as locus minoris resistentiae. The combination of reduced external pressure for the lack of atmospheric pressure at the intracranial level, with increased internal pressure in the cerebral venules in consequence of venous sinus thrombosis dramatically increases the transmural pressure and facilitates intracranial hemorrhage. Legend: TMP=transmural pressure; IVP=internal venular pressure; EVP= external venular pressure.

Figure 2. Proposed medical management of vaccine-induced immune thrombotic thrombocytopenia (VITT) according to the platelet count. Legend: Dex: dexamethasone; Ig: intravenous immunoglobulin; Fond: fondaparinux; aPTT; activated partial thromboplastin times; d: days; PT: prothrombin time. Reproduced with permission from references 13 and 14.

Supplementary Table: papers reporting post mortem findings in fatal cases of VITT.

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All authors:

1. Made a substantial contribution to the concept or design of the work; or acquisition, analysis or interpretation of data,
2. Drafted the article or revised it critically for important intellectual content,
3. Approved the version to be published,
4. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

PZ and PM researched literature and conceived the study. FS was involved in protocol development and data analysis. AS, PZ and CP wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

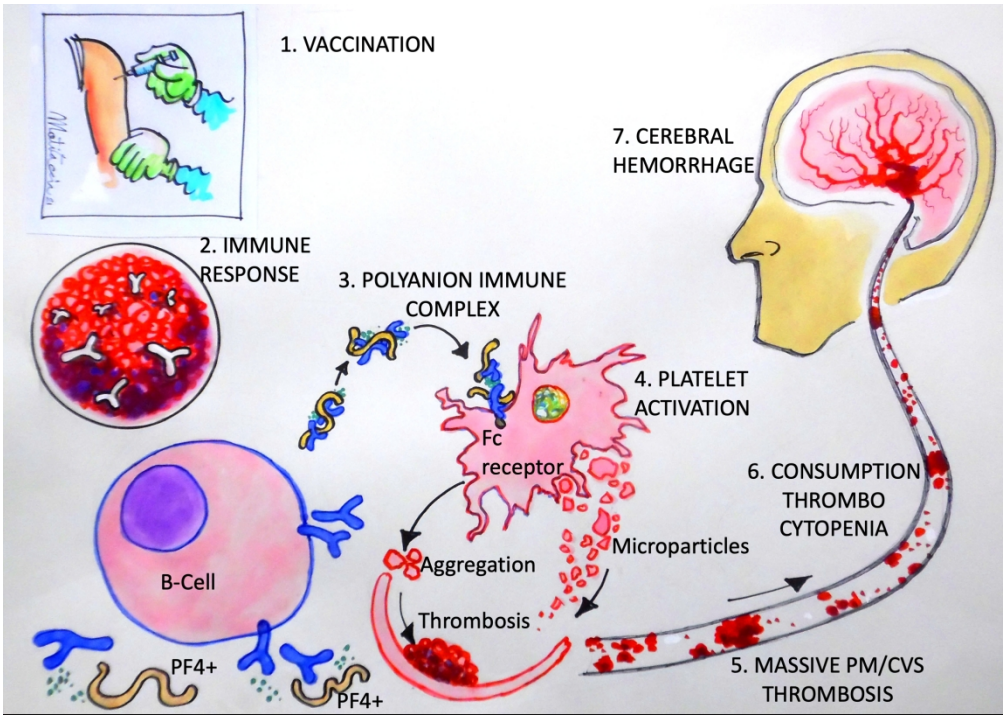

Figure 1a

1014x720mm (57 x 57 DPI)

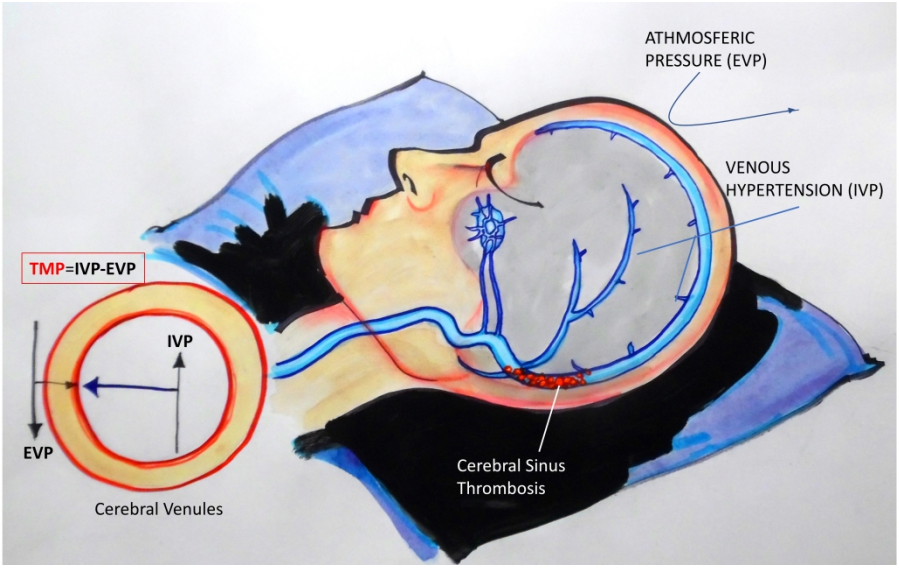

Figure 1b

2281x1283mm (57 x 57 DPI)

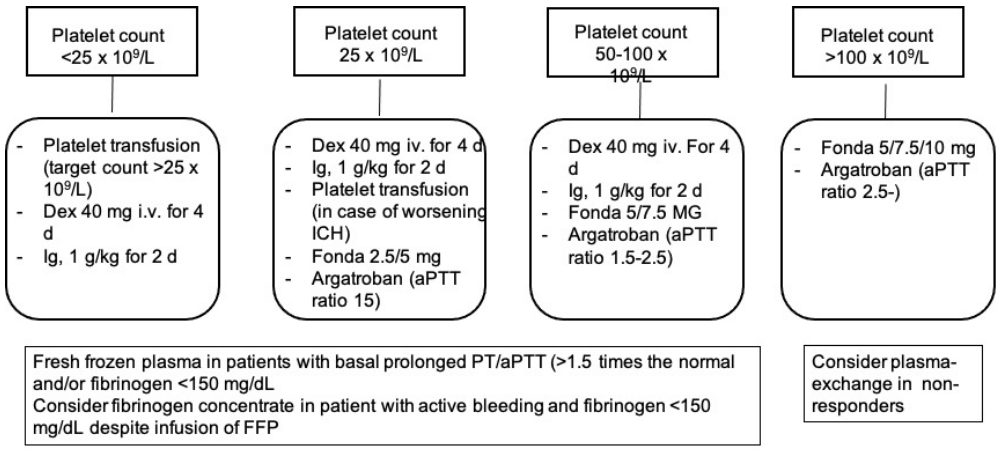

Figure 2

304x135mm (72 x 72 DPI)

Reference	Vaccine	Fatal cases				Post mortem findings
		Sex, Age	D	H	R	
Althaus et al.[9]	ChAdOx1 nCoV-19	F, 48	6	10	n.a.	Complete thrombotic obstruction of the straight, sagittal and transversal cerebral sinuses, subarachnoidal haemorrhage, cerebral edema and bilateral pulmonary embolism in midsized arteries and obstruction of glomerular arterioles and capillaries by hyaline microthrombi containing fibrin and platelets
		M, 24	10	7	Het. FVL	massive cerebral hemorrhage and cerebral edema, bilateral pulmonary thromboembolism and obstruction of glomeruli by hyaline microthrombi
Bjørnstad – Tuveng et al. [10]	ChAdOx1 nCoV-19	F, n.a.	7	n.a.	None	Intracranial haemorrhage. Moreover, small thrombi were found in the transverse sinus, frontal lobe and pulmonary artery.
Scully et al. [11]	ChAdOx1 nCoV-19	F, 55	6	n.a.	n.a.	Results of a postmortem evaluation showed evidence of thrombosis in many small vessels, especially vessels in the lungs and intestine, cerebral veins, and venous sinuses, as well as evidence of extensive intracerebral hemorrhage
Pomara et al. [2,4]	ChAdOx1 nCoV-19	M, 50	10	6	None	Autopsy findings confirmed portal and mesenteric thrombosis

						with extension into the splenic vein. Moreover, extensive cerebral haemorrhages was described.
		F, 37	13	10	None	Post-mortem findings showed beside cerebral sinus thrombosis a massive thrombosis of the whole venous tree of left upper limb extending from the hand to the axillary vein, with symmetric lesions in the veins of the right hand and the right axillary vein
Greinacher et al. [3]	ChAdOx1 nCoV-19	M, 49	10	1	n.a.	Autopsy revealed cerebral venous thrombosis, while CT imaging showed progression of portal-vein thrombosis to include the splenic and upper mesenteric veins; in addition, small thrombi were visualized in the infrarenal aorta and both iliac arteries.
Edler et al. [5]	BioNTech / Pfizer (Comirnaty®)	F, n.a. (elderly)	5 (she was found death)	0	coronary heart disease, cardiac insufficiency, arterial hypertension, dementia and hyperthyroidism	The cause of death was pulmonary artery embolism with infarction of the right lower lobe of the lung with deep leg vein thromboses on both sides.
		M, n.a. (elderly)	10	2	chronic renal failure, anemia, atrial fibrillation, pulmonary artery embolism, arterial hypertension, peripheral artery disease, right thalamic infarction with	Nasopharyngeal swab for SARS-CoV-2 RNA was positive. Autopsy revealed chronic and acute pancreatitis. Pneumonia was confirmed as the cause of death.

					left hemiparesis, recurrent tonic-clonic seizures, gait disorder with polyneuropathy, rheumatoid arthritis and prostate carcinoma with prostatectomy.	
		M, n.a.	2 (he was found death)	0	Apoplexy and myocardial infarction as well as arterial hypertension and type II diabetes mellitus.	The known pre-existing conditions were confirmed, and further organ pathologies typical of old age were found in the form of signs of chronic obstructive pulmonary disease (COPD) and chronic renal dysfunction. The cause of death was a recurrent myocardial infarction

Table 1. The main data of the post-mortem examination performed on cases temporally related to the COVID-19 vaccination: on a total of 10 cases, 7 patients were vaccinated with ChAdOx1 nCoV-19, while the other 3 cases with BioNTech / Pfizer (Comirnaty).

Legend: (D) first symptoms after vaccination (days);
(H) Hospitalization (days)
(R) thrombotic risk factors
(n.a.) not available/performed
(FVL) Factor V Leiden
(Het.) Heterozygous