Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editors-in-Chief

Cerebral venous thrombosis and thrombocytopenia post-COVID-19 vaccination

We report the case of a 50-year-old white man who had always been in good health. He was a voluntary periodic blood donor (his last whole blood donation was on December 1, 2020) and all laboratory checks performed before donations, including blood cell count, were always within the normal range. His personal and family history was negative for thrombotic or hemorrhagic disorders. He had never suffered from COVID-19 and all molecular screens for SARS-CoV-2 (performed routinely every month as he worked in the public administration) were always negative. On March 4, 2021, he received the first dose of the anti-COVID-19 vaccine produced by AstraZeneca without any immediate adverse reaction. Seven day later (11 March 2021) he suffered from a worsening headache but, despite this symptom, he continued to work under analgesic medications. On March 15, 2021 the patient was referred unconscious to the emergency room of the city hospital of Mantua (Italy). Computed tomography (CT) scans of the brain showed intra-parenchymal hemorrhage in the left cerebral hemisphere while CT angiography of intracranial circle vessels showed multiple small bleeding spots in the context of the left parenchymal hemorrhage and lack of opacification of the left transverse and sigmoid sinuses, compatible with cerebral venous sinus thrombosis (CVST). The patient was immediately transferred to the Intensive Care Unit and underwent urgent neurosurgery in a desperate attempt to stop and remove the intracerebral hemorrhage, but 18 h after the intervention he died. Overall, the patient was transfused with 9 red blood cell units and 4 platelet apheresis units. Thromboelastogram (TEG6S, Haemonetics) studies performed before and during the operation showed a prolonged reaction time, decreased platelet function and the absence of fibrinogen, measured with a functional fibrinogen assay, with a consequent markedly reduced maximum amplitude of the clot (8.4 mm, normal range 52–69 mm) only partially and temporarily restored by an infusion of fibrinogen concentrate (10 g total). The most relevant abnormal laboratory results (Table 1), performed on admission to hospital, were severe thrombocytopenia and hypofibrinogenemia associated with factor XIII deficiency. In addition, heterozygous *MTHFR* C677T together with increased levels of homocysteine, which have been associated with an increased CVST risk [1,2], and concomitant folate deficiency were observed. Notably, like previous observations by other investigators [3,4], anti-PF4 antibodies were detected. Further studies are needed to assess the pathogenesis of thrombocytopenia (i.e., immune-mediated or protein spike-mediated) [5] and its relationship with the development of CVST following anti-COVID vaccination.

CRediT authorship contribution statement

M.F.: study design and concept, writing a draft of the manuscript; S.T.: coagulation assays, writing a draft of the manuscript; M.P.: study design and concept, interpretation of the data; C.G.: coagulation assays; B.C.: coagulation assays; I.T.: coagulation assays; C.P.: interpretation of the data from clinical point of view; S.A.B.: revising the manuscript; G.C.: interpretation of the data from clinical point of view, revising the manuscript.

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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Table 1
The patient's basal laboratory profile (abnormal results are shown in bold).

Parameter	Patient's values	Normal values
Hemoglobin (g/dL)	14.6	13.5–17.5
RBC (10^{12}/L)	5.18	4.50–5.90
Schistocytes on peripheral blood smear (%)	<1	<1
White cells (10^9/L)	10.87	4.40–11.0
Platelets (10^9/L)	**15**	**150–400**
Prothrombin time (INR)	**1.19**	**0.88–1.12**
Activated partial thromboplastin time (ratio)	0.88	0.82–1.18
Thrombin time (seconds)	**23.5**	**16–20**
Fibrinogen (mg/dL)	**98**	**150–450**
D-dimer (ng/mL)	**>10,000**	**<500**
Antitrombin (%)	101	75–125
Protein C (%)	73	70–140
Protein S (%)	**60**	**72–123**
Alanine aminotransferase (IU/L)	16	5–45
Total bilirubin	0.57	0.20–1.00
C reactive protein (mg/L)	**17.6**	**<5**
SARS-CoV-2 screening		
PCR	Negative	Negative
Anti-SARS-CoV-2 Ab (ECLIA, Roche)	Negative	Negative
Anti-SARS-CoV-2 IgGAb (CLIA, Diasorin) (UA/mL)	6.4	<12
Lactate dehydrogenase (IU/L)	337	150–450
Coagulation factor II (%)	71	50–150
Coagulation factor IX (%)	>150	50–150
Coagulation factor V (%)	71	50–150
Coagulation factor VII (%)	68	50–150
Coagulation factor VIII (%)	114	50–150
Coagulation factor X (%)	69	50–150
Coagulation factor XI (%)	103	70–120
Coagulation factor XII (%)	99	70–120
Coagulation factor XIII (%)	**35**	**70–150**
VWF:Ag (%)	>120	50–120
VWF:RCo (%)	>150	50–150
VWF:CB (%)	>150	50–150
ADAMTS13 activity (FRET assay) (%)	48	45–138
Lupus anticoagulant	Negative	Negative
Anti-beta2 glycoprotein Ab		
IgG (U/mL)	<0.6	<7
IgM (U/mL)	<0.9	<7
Anti-cardiolipin Ab		
IgG (U/mL)	2.6	<10
IgM (U/mL)	0.8	<10
Thrombophilia mutations		
Factor V Leiden (G169A)	Absent	Absent
Prothrombin (G20210A)	Absent	Absent
MTHFR (C677T)	**Heterozygous**	Absent
JAK2	Absent	Absent
Homocysteine (μmol/L)	**16.7**	**<12**
Folic acid (ng/mL)	**0.9**	**3.9–26.8**
Vitamin B12 (pg/mL)	246	197–771
Complement (g/L)		
C3	**0.76**	**0.81–1.57**
C4	0.14	0.13–1.39
Anti-PF4 antibodies (nm) (PF4 Enhanced ELISA, Immucor)	**2.6**	**<0.4**
Anti-platelet antibodies[a]		
Autoantibodies (PakAuto ELISA, Immucor)	Absent	Absent
Alloantibodies (PakPlus ELISA, Immucor)	Absent	Absent

Legend: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction; Ab, antibodies; CLIA, chemiluminescence immunoassay; ECLIA, electrochemiluminescence assay; VWF, von Willebrand factor; Ag, antigen; RCo, ristocetin cofactor; CB, collagen binding; ADAMTS13, A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13; FRET, fluorescent resonance energy transfer; RBC, red blood cells; ELISA, enzyme-linked immunosorbent assay.

[a] PakAuto test detects specific autoantibodies against platelet glycoproteins IIb/IIIa and Ia/IIa present in plasma or serum or eluted from platelet surface. PakPlus test detects in serum anti-HLA class I antibodies and platelet-specific antibodies against glycoproteins IIb/IIIa, Ia/IIa, Ib/IX and IV.

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