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.

Blood Cells, Molecules and Diseases 92 (2021) 102615

Contents lists available at ScienceDirect

Blood Cells, Molecules and Diseases

journal homepage: www.elsevier.com/locate/bcmd

Letter to the Editor

Severe immune thrombocytopenia after COVID-19 vaccination: Report of four cases and review of the literature

To the editor,

From December 2020, four COVID-19 vaccines have been worldwide administered under emergency use; in last months' cases of vaccine-related ITP have been reported [1–6] raising concern about this possible complication and the management of patients with preexisting autoimmune cytopenias.

Herein we report four cases of ITP following COVID-19 vaccination (Table 1) and a brief literature review.

#1: A 27-year-old man presented with hematomas and epistaxis, 10 days after receiving the first dose of BNT162b2 mRNA vaccine (Comirnaty). Blood tests showed a low platelet count (1×10^9/L), with normal WBC e Hb. Peripheral blood film did not show platelet clumping, schistocytes or blasts; no significant findings were observed in biochemical and coagulation tests. He was diagnosed with ITP and therapy with prednisone 1 mg/kg/d was started. Because of no response after 48 h and persistent hemorrhagic diathesis the patient received IVIG 1 g/kg/day for 2 consecutive days with rapid response. However, when we started steroid tapering, platelets soon decreased; therefore, we shifted to dexamethasone 40 mg/d for 4 days every 2 weeks: he underwent 3 cycles obtaining complete response.

#2: A 63-year-old man was admitted to hospital because of epistaxis and hematomas developed 14 days after receiving the first dose of ChAdOx1-S (Vaxzevria) vaccination. Medical history was positive for diabetes mellitus and arterial hypertension. Blood tests revealed severe thrombocytopenia (2×10^9/L) with only mild leukocytosis and a normal Hb. Coagulation times, kidney and liver function tests were normal. Autoimmune diseases, viral infections or heamatologic malignancies were excluded. In the hypothesis of ITP, steroid therapy with methilprednisolone 1 mg/kg/d was started with an immediate improvement of platelet count. After 3 weeks, steroid tapering was started and continued maintaining complete response. The second dose of vaccination mRNA-1273 Moderna vaccine (Spikewax) was performed after 9 weeks from the first one without any worsening of the platelet count.

#3: A 39-year-old woman with a history of ITP completely resolved with dexamethasone and IVIG in 2012 and 2019, six days after receiving the second dose of BNT162b2 mRNA vaccine (Comirnaty), presented to emergency room with ecchymosis; her platelet count was 1×10^9/L: she received methylprednisolone 1 mg/kg/d and IVIG 0,4 g/kg/d for 5 consecutive days obtaining a partial response (platelets 41×10^9/L). One week later she developed petechiae on her right arm and platelets were 3×10^9/L; IVIG 1 g/kg/d were again given for 2 consecutive days and TPO-mimetic eltrombopag 50 mg/d started with initial response; dosage needed to be increased to 75 mg/d the following week because of a new drop of platelets. Afterwards platelets collapsed again to 5×10^9/L: she therefore started romiplostim obtaining partial response. She is ongoing evaluation for splenectomy.

#4: A 24-year-old male with a history ITP successfully treated with IVIG, in 2018 was diagnosed with wAHA: a bone marrow and a lymph node biopsy excluded a lymphoproliferative syndrome. High doses steroids, IVIG and rituximab led to full recovery. In 2021, 21 days after the first dose of Modena mRNA vaccine he presented with a platelet count of 2×10^9/L. The rest of the blood count and LDH were normal. He had petechiae in the oropharynx and bilateral upper extremities. A tb CT was negative for lymphoproliferative disorders. The patient received IVIG 0,4 g/kg/day for 5 days and methilprednisolone 1 mg/kg/day. Despite an initial response, 17 days after he presented with bruises and a platelet count of 5×10^9/L. He received platelet transfusion and IVIG 1 g/kg/day for 2 days. He continued steroid therapy with a fast improvement in platelet count. A bone marrow biopsy yielded no evidence of lymphoproliferative disorder. Five weeks platelet count is normal and the steroid tapering is still ongoing.

Paulsen et al. reported 4 patients with severe ITP after having received of ChAdOx1 nCoV-19 adenoviral vector vaccine: three of four patients had a past medical history of autoimmune disorders or preexisting mild thrombocytopenia but a stable platelet count; time from vaccination was 2–11 days and all patients obtained complete response to treatment [1]. Also Pfizer-Biontech mRNA vaccine have been related to ITP: a platelet drop was described 3–18 days after administration of first or second dose and generally successfully treated with steroids with or without IVIG. Some had a previous diagnosis of ITP with stable platelet count at the moment of vaccine administration [2–4]. Moderna vaccine-related ITP cases have been described, in a case severe and refractory prompting therapy with dexamethasone, IVIG, platelet transfusions, rituximab and eltrombopag [4,5]. Reports of ITP following Johnson and Johnson COVID-19 vaccine are present in literature too [6]. An overall incidence of thrombocytopenia, including ITP, after vaccination with Pfizer-BioNTech COVID-19 Vaccine or Moderna COVID-19 Vaccine is described in the case-series reported to the Vaccine Adverse Event Reporting System published on June 2021. The reporting rate of thrombocytopenia was 0.80 per million doses for both vaccines, less than the annual incidence rate of 3.3 ITP cases per 100,000 adults [7].

Our report describes four more cases of severe ITP following COVID-19 vaccination with both mRNA and adenoviral vector vaccine. Two patients had a new onset of severe ITP while two had a history of ITP but stable platelet values. Of note, while the first two were well managed

https://doi.org/10.1016/j.bcmd.2021.102615
Received 30 September 2021; Accepted 1 October 2021
Available online 7 October 2021

Table 1
Characteristics of the patients.

	#1	#2	#3	#4
Age (years)	27	63	39	24
Sex	M	M	F	M
Medical history	Silent	DM, hypertension, dyslipidemia	Hashimoto's thyroiditis	Silent
Previous autoimmune cytopenia	No	No	Chronic ITP	ITP, AIHA
Allergies	None	None	None	None
Vaccine received	BNT162b2 mRNA (Pfizer)	ChAdOx1-S (Vaxzevria)	BNT162b2 mRNA (Pfizer)	mRNA-1273 (Moderna)
Firs/second dose	First dose	First dose	Second dose	Second dose
Time from vaccination to ITP (days)	10	14	6	21
Symptoms	Hematomas, epistaxis	Hematomas, epistaxis	Petechiae, ecchymosis	Petechiae
PLT count nadir	1×10^9/L	2×10^9/L	1×10^9/L	2×10^9/L
Treatment	IVIG - Prednisone - dexamethasone	Prednisone	IVIG – prednisone- eltrombopag-romiplostim	IVIG – prednisone - IVIG
Response	CR	CR	PR	CR

with oral corticosteroids, in the latter two cases thrombocytopenia was more difficult to manage: they experienced relapses and one of them failed treatment with steroids, IVIG and eltrombopag, obtaining only partial remission with romiplostim. This, together with available literature data, underlies that hematologic monitoring in patients with ITP is advisable before and after vaccination [8]. To date, it is not defined which vaccine should be administered to patients who developed ITP after the first dose, as all of them (mRNA and adenoviral vector) have been linked to possible ITP: from our experience, it appears reasonable to complete vaccination carefully monitoring CBC in order to early recognize a platelet drop.

As vaccination against COVID-19 infection is still ongoing it is mandatory to collect more data and, waiting for more information and guidelines, it appears safer to pay attention to possible hemorrhagic events and carefully monitor patients with previous history of ITP as their management could be demanding and difficult as showed by our experience. Anyway, there are no doubts that, considering mortality and morbidity risk after COVID-19 infection, benefits of vaccination outweigh the risk to develop ITP as a vaccine-related adverse event.

References

[1] FO Paulsen C Schaefers F Langer et al Immune thrombocytopenic purpura after vaccination with COVID-19 vaccine (ChAdOx1 nCov-19) Blood 2021 Jul 23; blood.202101279010.1182/blood.2021012790 Online ahead of print.
[2] M Jawed A Khalid M Rubin et al Acute immune thrombocytopenia (ITP) following COVID-19 vaccination in a patient with previously stable ITP Open Forum Infect. Dis. 2021 Jun 2487ofab343 2021 Jul10.1093/ofid/ofab343 eCollection.
[3] E.R. King, E. Towner, A case of immune thrombocytopenia after BNT162b2 mRNA COVID-19 vaccination, Am. J. Case Rep. 21 (22) (2021), e931478, https://doi.org/10.12659/AJCR.931478. Jul.
[4] E.J. Lee, D.B. Cines, T. Gernsheimer, et al., Thrombocytopenia following Pfizer and moderna SARS-CoV-2 vaccination, Am. J. Hematol. 96 (5) (2021) 534–537.
[5] J.M. Helms, K.T. Ansteatt, J.C. Roberts, et al., Severe, refractory immune thrombocytopenia occurring after SARS-CoV-2 vaccine, J. Blood Med. 222 (12) (2021) 221–224.
[6] S.R.A. Shah, S. Dolkar, J. Mathew, P. Vishnu, COVID-19 vaccination associated severe immune thrombocytopenia, Exp. Hematol. Oncol. 10 (1) (2021) 42, https://doi.org/10.1186/s40164-021-00235-0. Jul 15.
[7] K.J. Welsh, J. Baumblatt, W. Chege, R. Goud, N. Nair, Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the vaccine adverse event reporting system (VAERS), Vaccine 39 (25) (2021 Jun 8) 3329–3332, https://doi.org/10.1016/j.vaccine.2021.04.054. Epub 2021 Apr 30. PMID: 34006408; PMCID: PMC8086806.
[8] B. Fattizzo, N. Cecchi, W. Barcellini, J.A. Giannotta, SARS-CoV-2 vaccination in patients with autoimmune cytopenias: the experience of a reference center, Sep 3, Am. J. Hematol. (2021), https://doi.org/10.1002/ajh.26345. Online ahead of print.

Angelo Gardellini, Francesca Guidotti*, Elena Maino, Sara Steffanoni, Michelle Zancanella, Mauro Turrini
Division of Hematology, Department of Medicine, Valduce Hospital, Como, Italy

* Corresponding author at: Via Dante Alighieri 11, 22100 Como, Italy.
E-mail address: fguidotti@valduce.it (F. Guidotti).
Editor: Mohandas Narla