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.

Thrombosis Research 210 (2022) 91–93

Contents lists available at ScienceDirect

Thrombosis Research

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

Letter to the Editors-in-Chief

Immune Thrombotic Thrombocytopenic Purpura following Pfizer-BioNTech anti-COVID-19 vaccination in a patient healed from lymphoma after allogeneic hematopoietic stem cell transplantation

ARTICLE INFO

Keywords
Thrombotic Thrombocytopenic Purpura
Thrombotic microangiopathy
ADAMTS13
Covid-19
Vaccination

Dear Editor,

Over the last year, reports of adverse events from SARS-CoV2 vaccines are proliferated, so we want to help improve knowledge on this subject by describing a case of de novo immune Thrombotic Thrombocytopenic Purpura (TTP) after Pfizer anti-SARS-CoV2 vaccination in a patient who achieved a long full remission of gray zone lymphoma after allogeneic hematopoietic stem cell transplantation.

Several cases of TTP are generally idiopathic, but different inducing agents have been described, such as malignancies, viral or bacterial infections, pregnancy, autoimmune disorders and drugs. H1N1 influenza, pneumococcal or rabies vaccination has led to the development of several immune-mediated pathological conditions, and many cases of atypical thrombosis such as TTP [1–3]. AstraZeneca-Oxford COVID-19 vaccine has been correlated with vaccine-induced thrombotic events, such as atypical thrombosis, the new clinical picture known as vaccine-immune thrombotic thrombocytopenia (VITT) [4] and rare cases of immune TTP [5].

Anti-SARS-CoV2 m-RNA vaccines, such as Pfizer and Moderna, may also lead to immune mediated thrombocytopenia [6], but no increase of immune-mediate thrombosis following COVID-19 vaccination has been reported in literature [7].

Our case describes a 33-year-old white female who was admitted to Emergency Room of our hospital for marked asthenia, drowsiness, headache, nausea with abdominal pain, and lower extremity purpura, 9 days after I dose of Pfizer-BioNTech COVID19 vaccine. Physical examination revealed a Glasgow Coma Scale (GCS) score 4. Laboratory tests revealed severe anemia (hemoglobin 68 g/L) with reticulocytosis and critical thrombocytopenia (platelets 1210^9/L), elevated lactate dehydrogenase (1.280 U/L) and total bilirubin (2.3 mg/dL), and decreased haptoglobin level (<0.06 g/L), suggesting a hemolysis. Direct and indirect Coombs test was negative, standard coagulation tests were normal, creatinine was slightly altered (1.38 mg/dL), and negative was the search for antiphospholipid antibodies. Peripheral blood smear (PBS) test showed the presence of 3% schistocytes, which indicated iTTP diagnosis. Baseline analysis of enzymatic activity of ADAMTS13 with rapid test HemosIL AcuStar was performed, revealing reduced activity (8%), but the detection of antibodies against the metalloprotease was not valuable, due to defects in the sample. Brain Computed Tomography scan documented the presence of hyper-attenuating micro-lesions, while microbiological tests on blood and urine showed negative results. The patient's basal laboratory results are shown in Table 1.

Past medical history showed that in 2008 the patient was diagnosed with Nodular Sclerosis classical Hodgkin Lymphoma (NScHL), in stage VI B disease, and treated upfront with ABVD (Adriamycin, Bleomycin, Vinblastine, and Dacarbazine) polychemotherapy regimen for six cycles, achieving a negative interim PET2 scan. However, during the sixth ABVD cycle, B symptoms were coming out again, with documented progression of disease. In May 2009 the patient started second-line treatment with four cycles of IGEV chemotherapy (Ifosfamide, Gemcitabine, and Vinorelbine), with contextual peripheral blood stem cell collection. In October 2009 high-dose melphalan (HDM, 200 mg/mq) conditioning regimen was performed, followed by autologous stem cell transplant (ASCT). The patient then had an early relapse, so she was carrying out a new lymph nodal biopsy, compatible with a diagnosis of Gray Zone Lymphoma. Therefore, in February 2010 she received four cycles of immunochemotherapy with Rituximab, Etoposide, Prednisone, Vincristine, Cyclophosphamide, and Doxorubicin (R-EPOCH), followed by 2 cycles with Bendamustine in May 2010. Due to skeletal isolated progression at third lumbar vertebrae, in June 2010, 12 radiotherapy sessions have been administrated (total 30 Gy), and in August 2010 patient undergone to allogeneic hematopoietic stem cell transplantation (HSCT) from matched unrelated donor (MUD), after Thiothepa/Fludarabine/Cyclophosphamide/ATG conditioning regimen. Cytomegalovirus reactivation was happening at 34th day post-transplant, so antiviral therapy was initiated with valganciclovir, followed by foscavir. After 40 days from HSCT full donor chimerism was observed. No other grade >3 toxicities were reported, seasonal flu-vaccinations without adverse reactions were normally performed later, and the patient had not experienced increased susceptibility to infections over the years. The pharmacological history has been silent over the past five years, except for estroprogestinic continuous therapy extended until the day of hospitalization and then rapidly stopped.

Having the patient the clinical criteria for TTP diagnosis, with high risk of ADAMTS13 deficiency according the PLASMIC scoring evaluation

https://doi.org/10.1016/j.thromres.2021.12.029
Received 6 October 2021; Received in revised form 17 December 2021; Accepted 28 December 2021
Available online 4 January 2022

Table 1
Patient's basal laboratory results.

Parameters	Patient's results	Normal ranges
Hemoglobin (g/dL)	68	13.6–17.2
Reticulocytes (10^9/L)	896	25–75
Schistocytes on PBS (%)	3	0
White Blood Cells (10^9/L)	10,98	4.30–10.30
Platelets (10^9/L)	12	156–373
Total Bilirubin (mg/dL)	2.3	0.2–1.2
Lactate dehydrogenase (U/L)	1.280	125–243
Haptoglobin (g/L)	< 0.06	0.32–2
C reactive protein (mg/dL)	11.6	0.01–0.50
Alanine aminotransferase (U/L)	38	7–55
Prothrombin time (INR)	1.04	0.9–1.3
Activated partial thromboplastin time (*sec*)	36.4	28–40
D-dimer (ng/mL)	> 10,000	< 500
Fibrinogen (mg/dL)	456	150–400
SARS-CoV2 PCR	Negative	Negative
Anti-SARS-CoV2 RBD-Spyke (U/mL)	0.9	Negative: < 0.8
Anti-PF4	Negative	Negative
ADAMTS13 activity	8%	20–100%
Anti-ADAMTS13 IgG antibodies[a] (U/mL)	5	n.v.: 12–15
Direct and Indirect Coombs tests	Negative	Negative
Blood and urine microbiological tests	Negative	Negative

Abbreviations: PBS: Peripheral blood smear; RBD: receptor binding domain; Ab-PF4: anti-platelet factor 4.

[a] Data acquired at the second determination, after 3 days of PEX + Caplacizumab treatment.

(6 points), treatment with intravenous standard dose methylprednisolone (1 mg/kg), daily PEX (plasma exchange) with 40 ml/kg of fresh frozen plasma (FFP) and Caplacizumab 10 mg intravenous infusion within 6 h from the admission was started, followed by two units of packed red cell transfusions, achieving a progressive improvement of the clinical status and lab tests. ADAMTS13 enzymatic activity and detection of autoantibodies against the metalloprotease were repeated after 3 days of therapy with plasmapheresis and Caplacizumab, revealing low levels of ADAMTS13 enzymatic activity (< 10%), but anti-ADAMTS13 antibodies were even low (5 U/mL; n.v. 12–15 U/mL), according to enzyme-linked immunosorbent assay (ELISA), as shown in Table 1. After 7 sessions of plasmapheresis in combination with Caplacizumab subcutaneous injection, the patient achieved a complete remission of TTP, the CGS has normalized (score 15) at day two, and she was discharged from intensive care unit and transferred into the ordinary medical ward. At discharge Cell Blood Count (CBC) showed hemoglobin 103 g/L, reticulocytes into normal range, platelets 135 × 10^9/L, lactate dehydrogenase 248 U/L (normal range 135–225), total bilirubin 0.8 mg/dL, creatinine 0.76 mg/dL. No evidence of schistocytes at PBS. According to drug datasheet, the patient carried on subcutaneous daily administrations of Capacizumab 10 mg for 28 days total, continuing steroid tapering until suspension. ADAMTS13 activity was assessed again on days +15 and +30, revealing normal values (0.8 UI/mL and 1.2 UI/mL, respectively). At the last check, on day 42 from the immune TTP onset, the patient has normal CBC and chemical-clinical tests, no symptoms are reported, and the patient resumed estroprogestinic therapy after negative thrombophilia evaluation.

The correlation between immunological thrombotic microangiopathy of our patient and anti-SARS-CoV2 vaccination cannot be confirmed, but the absence of pre-existing symptoms and her recent clinical history has led us to assume a possible relationship. In this regard, the purpose of our report is to widen as much as possible the knowledge and the case-studies on probable adverse events that these new types of vaccines can determine, also trying to outline a likely risk profile of each patient. The vaccinations, in fact, might display autoimmune side effects and potentially even trigger a full-blown autoimmune disease. The event of VITT after viral vector vaccines, such as ChAdOx1-S nCoV-19 (AstraZeneca) or Johnson & Johnson Ad26.COV2.S, have been frequently described in literature and reported by the European Medicine Agency [7–9]. However extremely rare is the onset of an immune TTP [10].

The immunocompromised status of our patient, due to previous chemotherapy and autologous and allogeneic stem cell transplantations, could be assumed to be a contributing factor in triggering immune TTP. However, she has not shown more susceptibility to infections over the years, following allogeneic transplantation, and we have not sufficient data to claim that the dysregulation of her immune system may have encouraged the development of TTP.

With increasing anti Covid-19 vaccine distribution, it is essential for emergency clinicians to be aware of the evaluation and management of some life-threatening autoimmune condition, such as immune TTP or VITT, similar clinical conditions but with different pathogenesis, that deserve different ready-to-use therapeutic approaches.

CRediT authorship contribution statement

Conceptualization, V.I. and U.C.; validation, V.I. and U.C.; formal analysis, V.I., S.U. and U.C.; investigation, V.I., S.U., M.I. and A.B..; data curation, V.I., M.I. and A.B.; writing—original draft preparation, V.I. and M.I.; writing—review and editing, V.I. and U.C.; supervision, U.C. All authors have read and agreed to the published version of the manuscript. All authors contributed equally to research data for the article, to discussion of content, to writing, and to reviewing/editing the manuscript before submission.

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.

References

[1] R. Herman, A. Pfeil, M. Busch, C. Kettner, D. Kretzschmar, A. Hansch, P. La Rosée, G. Wolf, Very severe thrombotic thrombocytopenic purpura (TTP) after H1N1 vaccination, Med. Klin. (Munich) 105 (2010) 663–668, https://doi.org/10.1007/s00063-010-1107-6.
[2] Y. Kojima, H. Ohashi, T. Nakamura, H. Nakamura, H. Yamamoto, Y. Miyata, H. Iida, H. Nagai, Acute thrombotic thrombocytopenic purpura after pneumococcal vaccination, Blood Coagul. Fibrinolysis 25 (2014) 512–514, https://doi.org/10.1097/MBC.0000000000000058.
[3] G. Kadikoylu, I. Yavasoglu, Z. Bolaman, Rabies vaccine-associated thrombotic thrombocytopenic purpura, Transfus. Med. 24 (2014) 428–429, https://doi.org/10.1111/tme.12160.
[4] N.H. Schultz, I. ISørvoll, A. Michelsen, I. Munthe, F. Lund-Johansen, M. Ahlen, M. Wiedmann, A. Aamodt, T. Skattør, G. Tjønnfjord, P. Holme, Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination, N. Engl. J. Med. 384 (2021) 2124–2130, https://doi.org/10.1056/NEJMoa2104882.
[5] M. Al-Ahmad, M. Al-Rasheed, N.A.B. Shalaby, Acquired thrombotic thrombocytopenic purpura with possible association with AstraZeneca-Oxford COVID-19 vaccine, EJHaem (2021), https://doi.org/10.1002/jha2.219. May.
[6] E. Lee, D.S. Cinez, T. Gernsheimer, C. Kessler, M. Michel, M. Tarantino, J. Semple, D. Arnold, B. Godeau, M. Lambert, J. Bussel, Thrombocytopenia following Pfizer and moderna SARS-CoV-2 vaccination, Am. J. Hematol. 96 (2021) 534–537, https://doi.org/10.1002/ajh.26132.
[7] I. Elalamy, G. Gerotziafas, S. Alamowitch, J.P. Laroche, P. Van Dreden, W. Ageno, J. Beyer-Westendorf, A.T. Cohen, D. Jimenez, B. Brenner, S. Middeldorp, P. Cacoub, SARS-CoV-2 vaccine and thrombosis: an expert consensus of vaccine-induced immune thrombotic thrombocytopenia, Thromb. Haemost. 121 (2021) 982–991, https://doi.org/10.1055/a-1499-0119.
[8] K. Muir, A. Kallam, S. Koepsell, K. Gundabolu, Thrombotic thrombocytopenia after Ad26.COV2.S vaccination, N. Engl. J. Med. 384 (2021) 1964–1965, https://doi.org/10.1056/NEJMc2105869.
[9] A. Greinacher, K. Selleng, J. Wesche, S. Handtke, R. Palankar, K. Aurich, M. Lalk, K. Methling, U. Völker, C. Hentschker, S. Michalik, L. Steil, L. Schönborn, M. Beer, K. Franzke, C. Rangaswamy, R.K. Mailer, T. Thiele, S. Kochanek, L. Krutzke, F. Siergerist, N. Endlich, T.E. Warkentin, T. Renné, Insights in ChAdOx1 nCov-19 vaccine-induced immune thrombotic thrombocytopenia (VITT), Blood (2021), https://doi.org/10.1182/blood.2021013231. Sep.
[10] G. Giuffrida, A. Condorelli, M.A.Di Giorgio, U. Markovic, R. Sciortino, D. Nicolosi, F.Di Raimondo, Immune-mediated thrombotic thrombocitopenic purpura following Pfizer-BioNTech COVID-19 vaccine, Haematologica (2021), https://doi.org/10.3324/haematol.279535. Sep.

Vanessa Innao[a,*], Salvatore Urso[b], Monica Insalaco[b], Albino Borraccino[c], Ugo Consoli[a]

[a] *U.O.C di Ematologia, Azienda ospedaliera di rilievo nazionale e di alta specializzazione, ARNAS - Garibaldi di Catania, Catania, Italy*

[b] *U.O.C. di Nefrologia, Azienda ospedaliera di rilievo nazionale e di alta specializzazione, ARNAS - Garibaldi di Catania, Catania, Italy*

[c] *U.O.C. di Anestesia e Rianimazione, Azienda ospedaliera di rilievo nazionale e di alta specializzazione, ARNAS - Garibaldi di Catania, Catania, Italy*

[*] Corresponding author at: U.O.C di Ematologia, Azienda ospedaliera di rilievo nazionale e di alta specializzazione, ARNAS - Garibaldi di Catania, Via Palermo 636, Catania, Italy.

E-mail address: vanessainnao@gmail.com (V. Innao).