Immune thrombocytopenic purpura after SARS-CoV-2 vaccine

In this paper, we describe the first case of immune thrombocytopenic purpura (ITP) after an adenovirus-based SARS-CoV-2 vaccine. Some cases of ITP have already been described after the administration of both commercially available mRNA SARS-CoV-2 vaccines.[1] A 28-years-old male presented to our Emergency Department (ED) on 8 March, 2021, because of oral bleeding and the appearance of petechiae over the trunk, arms, and legs for three days (Fig 1). He underwent a complete blood count showing 4×10^9/l platelets. Being a healthcare worker, he received the first dose of the AstraZeneca vaccine for Sars-CoV-2 on 14 February, 2021. Starting the next day, he experienced fatigue and headache for 10 days and fever for two days. His past medical history was completely negative, and his family history was negative for auto-immune and haematological diseases. The patient had undergone all the mandatory vaccinations without adverse effects. Physical examination showed purpura over the trunk, all four limbs, and bleeding lesions within the oral cavity. No hepatosplenomegaly and superficial lymphadenomegaly were observed.

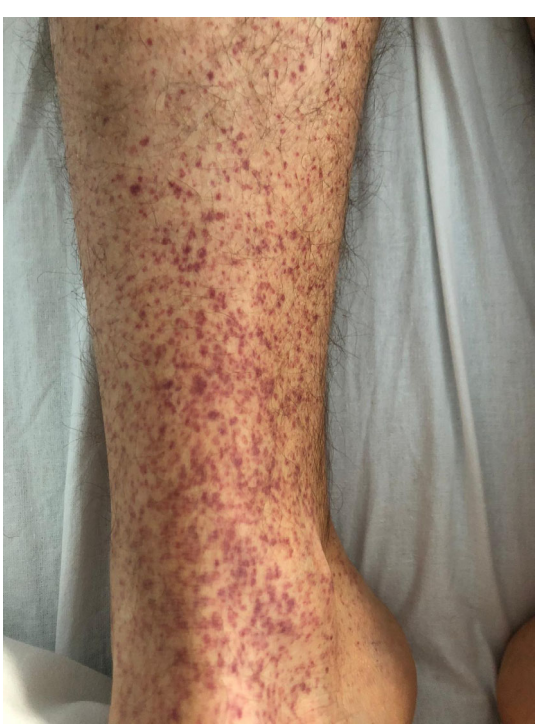

Fig 1. Petechiae on the patient's right leg in the Emergency Room. [Colour figure can be viewed at wileyonlinelibrary.com]

During the visit to the ED, a complete blood test showed 2×10^9/l platelets (confirmed on citrate blood tube), while white blood cells (WBCs), red blood cells (RBCs) and heamoglobin (Hb) levels were within normal limits, as well as the international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen, serum glucose, nitrogen urea, creatinine, sodium, potassium, calcium, total proteins, albumin, glutamate pyruvate transaminase (GPT), lactate dehydrogenase (LDH), total bilirubin, and amylase. A nasopharyngeal swab for SARS-CoV-2 resulted negative. The clinical and laboratory findings being compatible with ITP, treatment with dexamethasone (40 mg/day) was started and the patient was admitted to our Haematology ward. A second complete blood test showed 7×10^9/l platelets, lymphocyte typing tested resulted normal. Protein electrophoresis was negative for any qualitative alteration of gamma-globulins; anti-thrombin, anti-coagulant protein C, free protein S, normalized activated protein C sensitivity ratio, homocysteine, folic acid, vitamin B-12 and C-reactive protein were within the normal limits. High values of blood factor VIII activity (226·3%) and D-dimer (2270 iu/l) were found. Autoimmune screening tested positive for lupus anti-coagulant (LA) with a dilute Russell viper venom time ratio (DRVVTr) of 1·78, but negative for anti-cardiolipin antibodies, anti-β2-glycoprotein, anti-thyroglobulin, anti-thyroid peroxidase, anti-neutrophil cytoplasmic anti-bodies (ANCA), rheumatoid factor, and anti-nuclear anti-bodies. Serological tests for hepatitis B virus, hepatitis C virus, cytomegalovirus, Epstein–Barr virus and human immuniodeficiency virus RNA were negative. Urine chemical analysis found traces of RBCs and a chest X-ray resulted normal. Abdominal ultrasound showed normal spleen dimension and morphology, and no alterations to the kidney, urinary tract, biliary tract, liver, or pancreas. During his hospital stay, the patient maintained a good clinical condition, and cutaneous purpura progressively improved. The control blood test after four days of dexamethasone 40 mg/day showed 27×10^9/l platelets and the patient was discharged on 12 March, 2021, with instructions for a short-term outpatient follow-up. After 10 days of follow-up, platelet count was 31×10^9/l, and another cycle of four days of dexamethasone was planned (Fig 2).

The current SARS-CoV-2 pandemic is cornering the global healthcare system and all countries are committed to a rush to vaccinate most of the population in the shortest possible time. So far, in western countries, four vaccines against Sars-Cov-2 have been approved in Europe. Two of them,

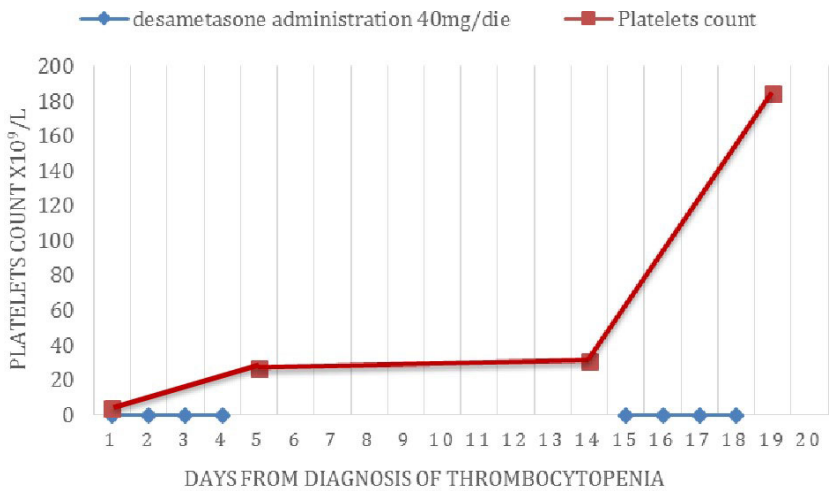

Fig 2. Platelets count and treatment over time. [Colour figure can be viewed at wileyonlinelibrary.com]

Pfizer-BioNTech and Moderna contain the mRNA from the virus that provides our cells instructions for making the SARS-CoV-2 spike proteins. The AstraZeneca and Johnson & Johnson vaccines are made up of a chimpanzee adenovirus that has been modified to contain the genetic information for producing the same SARS-CoV-2 spike proteins. Safety studies provided by each pharmaceutical company show how the incidence of severe adverse effects is low and similar between vaccines and placebo groups. Among these, there is no mention of ITP.[2-5] ITP is an immune-mediated disorder characterized by a low platelet blood count that causes mucocutaneous petechial brush, and — rarely — fatal gastrointestinal or cerebral bleedings. Several triggers can induce ITP. Among these, vaccines are thought to act by a viral molecular mimicry.[1] In particular, ITP has been associated with measles–mumps–rubella (MMR) and varicella/zoster vaccines.[1] However, a few cases of ITP following Pfizer-BioNTech and Moderna have been reported recently.[1] Moreover, it has been shown that human adenoviral vectors can induce thrombocytopenia in mice through complex mechanisms involving endothelium, platelets, and macrophages mediated by both Von Willebrand factor and P-selectin.[6] According to the current literature, this is the first case of ITP following the AZD1222 administration. The positivity to LA in our patients is not surprising since it is found in around 15–20% of patients with ITP. The presence of LA, however, may indicate a pre-existing auto-immune coagulation disorder revealed by the administration of the vaccine. The presence of LA, anyway, has to be confirmed after 12 weeks. Our patient presented with a clear condition of thrombocytopenic purpura. Because he had been recently vaccinated against SARS-CoV-2 with AZD1222 vaccine, and after having carefully excluded several alternative etiologies, the diagnosis of AZD1222-induced ITP was suspected. However, we cannot completely rule out the other described mechanisms or the possibility of a random temporal association between the onset of ITP and vaccination. The rarity of these events does not affect, in our opinion, the benefits provided globally by vaccination.

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Conflict of interest

The authors report no conflicts of interest for the submitted manuscript.

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Patient consent statement

Written consent for publication and the use of personal data and pictures was obtained from the patient involved.

Marcello Candelli[1]
Elena Rossi[2]
Federico Valletta[1]
Valerio De Stefano[2]
Francesco Franceschi[1]
[1]Emergency Medicine Department, Fondazione Universitaria Policlinico A. Gemelli - IRCCS – Catholic University of Sacred Heart of Rome and [2]Diagnostic Imaging, Oncological Radiotherapy, and Hematology Department, Fondazione Universitaria Policlinico A. Gemelli - IRCCS

– *Catholic University of Sacred Heart of Rome, Rome, Italy.*
E-mail: marcello.candelli@policlinicogemelli.it

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Immune responses and therapeutic challenges in paediatric patients with new-onset acute myeloid leukaemia and concomitant COVID-19

Acute myeloid leukaemia (AML) is a medical emergency often presenting with hyperleucocytosis, coagulopathy and pulmonary infiltration necessitating emergent initiation of therapy. AML with concomitant severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection presents a unique challenge given the lack of evidence-based guidelines or historical experience. While cohort studies have shown early serological responses to SARS-CoV-2 in healthy adults,[1,2] little is known about the serological responses to infection in patients with AML and the impact of chemotherapy on this response. In the present study, we detail the clinical presentations, treatments, serological and virological responses, and outcomes of two adolescents who presented with AML and concurrent coronavirus disease 2019 (COVID-19).

Two adolescents presenting with AML and COVID-19 were enrolled on an Institutional Review Board-approved protocol to collect prospective/residual specimens used for SARS-CoV-2 serological and virological testing. Nasopharyngeal (NP) real-time reverse transcription polymerase chain reaction (RT-PCR), antibody testing by enzyme-linked immunosorbent assay (ELISA), live-virus focus reduction neutralisation assay-mNG, surface plasmon resonance (SPR) assay and viral genetic sequencing were performed (Data S1). Patient details, treatment and outcome data were abstracted from medical records.

Patient 1 was a 16-year-old Caucasian male with a history of classical Hodgkin lymphoma who presented with fever, cough and hyperleucocytosis [white blood count (WBC) 176×10^9/l]. His NP SARS-CoV-2 RT-PCR test was positive and peripheral blood flow cytometry (PBFC) confirmed a diagnosis of therapy-related AML. He received hydroxyurea, followed by cytarabine starting on hospital day (HD) 3. Treatment for COVID-19 included hydroxychloroquine, remdesivir and supplemental oxygen (Fig 1).

On HD4, the patient had detectable immunoglobulin (Ig) M and IgG antibodies to SARS-CoV-2 (Table I). The patient did not become lymphopenic throughout his COVID-19 course and maintained detectable binding and neutralising antibodies to SARS-CoV-2. SPR demonstrated that binding antibodies to the pre-fusion conformation of S, the receptor-binding domain (RBD) and S2 subunits all peaked by HD26. The patient had detectable IgM, IgA and IgG1 titres in the final sample on HD70 (Figure S1). He cleared the virus on HD16. Bone marrow (BM) on HD20 showed rare blasts on morphology in the setting of pancytopenia, with no disease detected by flow cytometry. He received additional chemotherapy with azacitidine and gemtuzumab starting on HD26. His treatment complications included bacteraemia and perirectal abscess with *Pseudomonas aeruginosa* and Epstein–Barr virus (EBV) viraemia resulting in multi-organ failure and death on HD74.