Excellent response to high-dose intravenous immunoglobulin in anti-PF4 positive cerebral thrombosis following Oxford-AstraZeneca AZD1222 vaccine

Carla Zanferrari (carla.zanferrari@asst-melegnano-martesana.it)
Melegnano Hospital https://orcid.org/0000-0002-6001-1698

Simona Fanucchi
Melegnano Hospital

Nicola L. Liberato
Melegnano Hospital

Giuseppe Lauria
IRCCS Carlo Besta https://orcid.org/0000-0001-9773-020X

Alessandra Persico
IRCCS Mondino

Anna Cavallini
IRCCS Mondino

Case Report

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Abstract

One week after Oxford-AstraZeneca COVID-19 vaccine (AZD1222), a 40-year-old woman who did not report previous SARS-Cov2 infection developed headache resistant to analgesics, then nausea and vomiting. On admission, the neurological examination was negative and haematological exams showed thrombocytopenia (48x10⁹ /L; range 130-400), increased d-dimer (27,546 ng/ml; normal value <500), and normal partial thromboplastin time (PTT; 24.9; range 24-38). Brain computed tomography (CT) and magnetic resonance imaging (MRI) identified an extended thrombosis involving left sigmoidal and transversal sinuses, rectus and inferior longitudinal sinuses without parenchymal damages. Serum anti-platelet factor 4 (PF4) IgG antibodies tested strongly positive (2.59 optical density; normal <0.4) confirming the hypothesis of a mechanisms mimicking heparin-induced thrombocytopenia. Enoxaparin 8,000 units were administered twice in 24 hours, then changed with fondaparinux. Four days later the clinical picture worsened with drowsiness, aphasia and right-side hemiparesis. Brain CT and MRI disclosed left-side temporal-occipital hypodensity with haemorrhagic infarctions. Platelet count remained low (range 37 to 45x10⁹ /L) while PTT decreased below the lower normal value. Intravenous immunoglobulin (2 g/kg) was started. Over the following 5 days, the platelet count rapidly increased from 27x10⁹ /L to 318x10⁹ /L, while PTT normalized. The clinical picture significantly improved.

Anti-PF4 antibody assay and high-dose IVIG therapy should be immediately considered in patients with vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) and thrombosis to avoid life-threatening complications.

Case Report

A previously healthy 40-year-old woman received the first dose of Oxford-AstraZeneca AZD1222 vaccine on March 14th and shortly complained of fever, headache, and diffuse joint pain that recovered in two days. She had not SARS-Cov2 infection.

Headache reappeared on March 21st with increasing intensity, and it was resistant to analgesics. On March 24th she was admitted due to worsening of headache, nausea and vomiting. Her familiar and personal medical history were negative. She had regular delivery two years before and reported spontaneous abortions in the first quarter 5 years before and on the first week of March 2021. Nasopharyngeal SARS-Cov2 RT-PCR swab was negative.

The neurological examination was normal. Haematological exams showed thrombocytopenia (48x10⁹/L; normal 130-400) and increased d-dimer (27,546 ng/ml; normal <500), and normal partial thromboplastin time (PTT, 24.9”; normal 24-38). Brain CT showed hyperdensity of the left transversal sinus without parenchymal lesions. Fluid attenuated inversion recovery and diffusion-weighted magnetic resonance imaging with gadolinium disclosed an extended thrombosis involving left-side sigmoidal and transversal sinuses, and rectus and inferior longitudinal sinuses without parenchymal damages. Chest X-ray, thoracic CT, electrocardiogram, echocardiogram, and cardiological evaluation were negative. Enoxaparin 8,000 was given twice in the following 24 hours.

On March 25th, platelet count was 43x10⁹/L and PTT 20.4*. Anti-cardiolipin (IgM-IgG) and anti-nuclear antibodies, extractable nuclear antigen, fibrinogen, protein S and C, anti-thrombin III, vitamin B12, folate, homocysteine, procalcitonin were negative. We hypothesized a vaccine-induced prothrombotic immune thrombocytopenia (VIPIT).1,2 The patient scored 8 in a modified 4T score3 (4Ts; 0-3 low risk, 4-5 intermediate risk, 6-8 high risk) for heparin-induced thrombocytopenia4 in which vaccine substitutes heparin. Enoxaparin was changed with fondaparinux. Serum anti-platelet factor 4 (PF4)-heparin IgG antibodies tested positive (2.59 optical density; normal <0.4).

On March 28th, the clinical picture worsened with drowsiness, aphasia and right-side hemiparesis. Brain CT disclosed left-side temporal-occipital hypodensity with haemorrhagic infarctions at 24-hour follow-up. Haematological exams showed persistent low platelet count and PTT.

On March 30th, treatment with intravenous immunoglobulin (IVIG; 2 g/kg) was started. Over the following 5 days, platelet count rapidly increased from 27x10⁹/L to 381x10⁹/L and PTT normalised. The clinical picture improved with fully recovery of alertness and significant amelioration of aphasia and hemiparesis (table 1).

The immunomodulatory effect of IVIG depends upon the interaction between the Fc domain with the Fcγ receptors on the surface of target cells. VIPIT likely shares HIT pathogenesis in which, after PF4 binding and generation of anti–PF4 IgG, the FC domain binding to platelet FcγRIIa receptors induces Fcγ receptor clustering and intravascular platelet activation, aggregation, and consumption, thus leading to venous thrombosis.4 In vitro studies suggested that IVIG can inhibit this mechanism.2

When VIPIT is suspected, we emphasize that 4Ts can be used to score patient's risk, anti-PF4 antibody should be searched, non-heparin anticoagulant and high-dose IVIG immediately started to avoid life-threatening complications.5

Declarations
This is a clinical report and all the diagnostic and therapeutic procedures were clinical practice. Therefore, there was no need of ethical committee approval. We received the approval for publication from the IRB of the Melegnano Hospital where the patient has been admitted. The patient has given her consent to the publication.

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Table

| 14th March 2021 | 21st March | 24th March | 25th March | 28th March | 30th March | 31st March | 1st April | 2nd April | 3rd April | 6th April |
|-----------------|------------|------------|------------|------------|------------|------------|-----------|------------|------------|-----------|
| Clinical picture | Headache onset | Severe headache (NIHSS 0) | Severe headache (NIHSS 0) | Drowsiness, apasia, hemiparesis (NIHSS 14) | Stupor, apasia, hemiplegia (NIHSS 22) | Stupor, apasia, hemiplegia (NIHSS 22) | Drowsiness, apasia, hemiparesis (NIHSS 18) | Alert (NIHSS 18) | Alert (NIHSS 14) | Alert (NIHSS 11) |
| Diagnostic exams | Brain CT and MRI CVT; no lesions | Anti-PF4 IgG Ab | Brain CT and MRI CVT; Ischemic and haemorrhagic lesions | Anti-PF4 IgG Ab confirmed positive |
| Platelet count (x10^9/L) | 48 | 42 | 37 | 27 | 29 | 59 | 106 | 150 | 381 |
| D-dimer (ng/ml) | 24.9 | 20.4 | 19.6 | 20.9 | - | 26.3 | - | - | 25.4 |
| Treatments | Paracetamol 1 g daily | Enoxaparin 8,000 UI x 2 | Fundaparinux 7.5 mg | Fundaparinux 7.5 mg | Fundaparinux 5 mg | Fundaparinux 5 mg | Fundaparinux 7.5 mg | Fundaparinux 7.5 mg | Fundaparinux 7.5 mg | Fundaparinux 7.5 mg |