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

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Case Report

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EDITORIAL NOTE:

This study summarizes the clinical and laboratory features of one patient who exhibited cerebral venous blood clotting and anti-PF4 antibodies following vaccination with AstraZeneca's COVID-19 vaccine (AZD1222). The researchers suggest that this rare event has an immune-mediated pathogenesis that resembles a known disorder – heparin-induced thrombocytopenia (HIT) – and is treatable with intravenous immunoglobulin if identified promptly. At the time of this posting, the World Health Organization has stated that "a causal relationship between the vaccine and the occurrence of blood clots with low platelets is considered plausible but is not confirmed." The authors disclose conflicts of interest, including personal fees from pharmaceutical companies.

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 (48x10 9 /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 45x10 9 /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 27x10 9 /L to 318x10 9 /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 (48x10^9/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 43x10^9/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 score[3] (4Ts; 0-3 low risk, 4-5 intermediate risk, 6-8 high risk) for heparin-induced thrombocytopenia[4] 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 27x10^9/L to 381x10^9/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 Fc γ RIIa 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

1 Clinical course, laboratory findings and treatments. CT = computed tomography; MRI = magnetic resonance imaging; CVT = cerebral venous thrombosis; Ab = antibodies; PTT = thromboplastin time; IVIG = intravenous immunoglobulin; NIHSS = NIH Stroke Scale/Score (very severe >25; severe 15–24; mild to moderately severe 5–14; mild 1–5)[6]

14th March 2021 1st dose AZD1222 vaccine	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, aphasia, hemiparesis (NIHSS 14)	Stupor, aphasia, hemiplegia (NIHSS 22)	Stupor, aphasia, hemiplegia (NIHSS 22)	Drowsiness, aphasia, 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
PTT (seconds)	-	24.9	20.4	19.6	20.9	-	26.3	-	-	25.4
D-dimer (ng/ml)	-	27546	11341	8766	18272	17374	14876	9864	-	5666
Treatments	Paracetamol 1 g daily	Enoxaparin 8.000 UI x 2	Fundaparinox 7.5 mg	Fundaparinox 7.5 mg	Fundaparinox 5 mg IVIG 0.4 g/Kg/die	Fundaparinox 5 mg IVIG 0.4 g/Kg/die	Fundaparinox 7.5 mg IVIG 0.4 g/Kg/die	Fundaparinox 7.5 mg IVIG 0.4 g/Kg/die	Fundaparinox 7.5 mg IVIG 0.4 g/Kg/die	Fundaparinox 7.5 mg