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Deep vein thrombosis and acute hepatitis after ChAdOx1 nCov-19 vaccination in a Charcot-Marie-Tooth patient: a case report

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Monitoring of side effects after coronavirus disease 2019 (COVID-19) vaccination has become an important issue for health systems worldwide to ensure its safety. Recently cases of deep vein thrombosis (DVT), vaccine-induced immune thrombotic thrombocytopenia, and autoimmune hepatitis have been described: the underlying pathophysiological mechanisms are still debated. We report on a patient who presented with DVT and acute hepatitis 8 days after receiving the first dose of the ChAdOx1 nCoV-19 adenoviral vector vaccine against COVID-19. The patient is a 56-year-old male who was already affected by a rare form of axonal Charcot-Marie-Tooth disease linked to MME (membrane metalloendopeptidase) gene variation and associated with mild symptoms. His blood exams did not have any evidence of thrombocytopenia but D-dimer, troponin T, alanine transaminase, and aspartate aminotransferase were abnormal, suggesting the presence of a blood clot and acute hepatitis. The patient was treated with subcutaneous enoxaparin for 15 days and with rivaroxaban for the following 8 months: his symptoms improved and his exams showed recanalization of the veins and a healed liver. The pathogenesis of thrombosis and hepatitis after vaccination is still unclear, especially in subjects affected by rare comorbidities and this may affect the safety of vaccination in this type of population. We highlight the importance of careful monitoring of side effects after vaccination: clinical suspicion must rise when patients complain of symptoms that differ from their usual presentation.

Keywords: Adverse effects, COVID-19 vaccination, Charcot-Marie-Tooth disease, Case report

Introduction

The coronavirus disease 2019 (COVID-19) is an ongoing pandemic with a devastating impact on global public health, social life, and economy [1]. The development of vaccines has been shown to be an effective tool in fighting against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2].

Data on long-term studies, interaction with other vaccines, use in pregnancy/breastfeeding, use in immunocompromised subjects, and in subjects with comorbidities, autoimmune or inflammatory disorders are limited for vaccines against SARS Cov-2 [3].

Recently, vaccination with ChAdOx1 nCov-19 has been associated with the rare development of vaccine-induced immune thrombotic thrombocytopenia (VITT) mediated by platelet-activating antibodies against platelet factor 4 (PF4), which clinically mimics autoimmune heparin-induced thrombocytopenia: most patients developed

cerebral venous sinus thrombosis (CVST) but also splanchnic vein thrombosis, pulmonary embolism, deep veins, internal jugular vein, and portal vein thrombosis have been reported [4]. However, the underlying pathophysiology of these thromboembolic events after vaccination is not univocal because cases of thrombosis without thrombocytopenia have been described [5-7].

Another side effect that has been recently described is autoimmune hepatitis (AIH): vaccines can rarely trigger an immune-mediated reaction against hepatocytes, especially in predisposed individuals. Cases of hepatitis have been reported after Covishield [8], Moderna-COVID-19 [9,10], and Pfizer-BioNTech COVID-19 [11,12] vaccination. In this context, it is plausible to expect that there is currently no information about the interaction between COVID-19 vaccines and Charcot-Marie-Tooth (CMT) disease, which is a heterogeneous group of genetic disorders presenting with the phenotype of chronic progressive neuropathy affecting both the motor and sensory nerves [13]. Although CMT is a frequent hereditary cause of neurological disability, some forms such as the late-onset CMT2 are still largely genetically undetermined [14].

The following is a report of deep vein thrombosis (DVT)-leg and acute hepatitis after vaccination with ChAdOx1 nCov-19 in a 56-year-old man already affected by a rare type of CMT axonal motor and sensory neuropathy with late-onset.

Case Report

A 56-year-old man started feeling unwell and complained of abnormal swelling in the calf and in the right ankle, reporting an uncomfortable congested feeling and a general malaise with a fever lasting for a week. His anamnesis reported an initial injection of ChAdOx1 nCov-19 (AstraZeneca, Cambridge, UK) vaccine 8 days previously: on physical examination, his leg showed slight redness and was warm to the touch (Fig. 1). The patient's remote medical history was known to the visiting clinicians: he was affected by a rare type of axonal CMT and slight B12 hypovitaminosis. However, his neurological symptoms were mild: he was physically fit and regularly played football, swam, and exercised in the gym. Apart from B12 hypovitaminosis, his previous blood tests were unremarkable and no signs of autoimmune diseases or familiarity with DVT were detected.

The patient underwent venous ultrasound scanning, which found thrombosis of the femoral, popliteal, posterior tibial, and gemellar vein. Initial blood tests were abnormal, showing a D-dimer >1,900 ng/mL, troponin T >20 ng/L, alanine transaminase (ALT) 300 U/L, and aspartate aminotransferase (AST) 486 U/L.

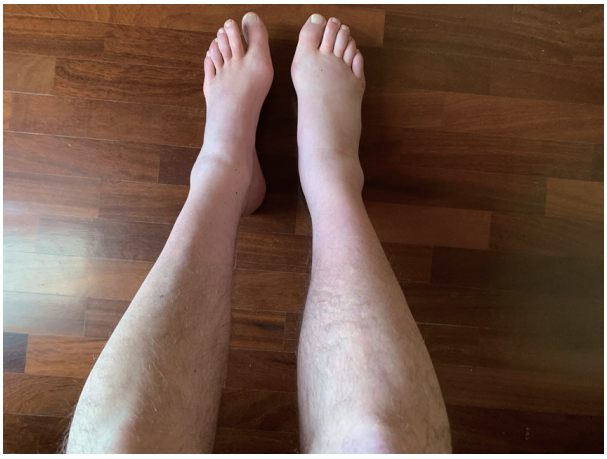

Fig. 1. Right leg showing deep vein thrombosis signs. Informed consent for the publication of this image was obtained from the patient.

The patient immediately received subcutaneous enoxaparin (8,000 UI AXa/0.8 mL) twice a day for 15 days, flavonoids 500 mg twice a day for 10 days and was advised to use compression stockings.

Eleven days after the first visit, the femoral vein showed partial recanalization on ultrasound scanning and the patient started taking rivaroxaban 20 mg twice a day and stopped subcutaneous enoxaparin. One month later, recanalization was good and blood tests were normal: ultrasound scanning found no damage for hepatitis and enzyme-linked immunosorbent assay (ELISA) screen was negative for antibodies for hepatitis B, hepatitis C, Epstein-Barr, human immunodeficiency virus (HIV)-1, and HIV-2 viruses.

The patient continued rivaroxaban 20 mg therapy for 8 months and had a second dose with Pfizer BNT162b2 vaccine (Pfizer, New York, NY, USA) 3 months after the blood clot episode and a third dose of mRNA-1273 from Moderna (Cambridge, MA, USA) at 9 months, with no adverse effects.

Informed consent to publish data anonymously was obtained from the patient: this study followed the tenants of the Declaration of Helsinki.

Discussion

To our knowledge, this is the first reported case of DVT and acute hepatitis after ChAdOx1 nCov-19 (AstraZeneca) vaccine in a patient with a rare comorbidity such as CMT axonal neuropathy related to MME (membrane metalloendopepti-

dase) gene mutation [14]. Although no research for anti-PF4 antibodies by ELISA method was performed, it is reasonable to exclude the occurrence of a COVID-19 VITT because the platelets count was not abnormal (320 10^3/μL), which is a key criterion for diagnosis of VITT [15]. Moreover, the patient's medical history suggested no signs of thrombocytopenia in blood tests performed before the DVT event.

Cases of thrombosis without thrombocytopenia have been reported in a 66-year-old woman who developed DVT after her second dose of mRNA COVID-19 vaccine (BNT162b2, Comirnaty, Pfizer/BioN-Tech) [5], in a 45-year-old woman who developed CVST with a single dose of viral vector Johnson & Johnson's Janssen COVID-19 (Ad26.COV2.S; Johnson & Johnson, New Brunswick, NJ, USA) [6], and in a 27-year-old female who developed acute thrombosis involving the right subclavian and axillary veins after her second dose of Moderna COVID-19 vaccine (mRNA1273 SARS-CoV-2) [7].

Interestingly, the increase in ALT and AST, which rapidly normalized, suggest short-term hepatitis, with no tissue damage. No autoantibodies screening was performed in our case, however several case reports have recently highlighted AIH few weeks after a COVID-19 vaccination [8-12].

In the case reported here, blood tests, liver inflammation and recanalization normalized quickly after initiation of treatment: anticoagulation was performed with heparin treatment because this was a nonheparin-dependent pathophysiological mechanism. In addition, the patient received the 3rd dose of mRNA-1273 from Moderna vaccine even after the completion of rivaroxaban therapy, suggesting susceptibility of the subject to the adenovirus vector mechanism of the AstraZeneca vaccine.

Our findings highlight the importance of clinical suspicion when patients complain of abnormal feelings even in the context of an ongoing disease: in this case, the signs of DVT (e.g., tingling, pain, reduced functioning) could easily be confused with common CMT symptoms.

In conclusion, the incidence of serious adverse events attributable to COVID-19 vaccination remains difficult to establish. Although the association between VITT syndrome and ChAdOx1 nCov-19 vaccines seems to become stronger, very little is known about the DVT and acute hepatitis risk after COVID-19 vaccination in people affected by rare neuropathies such as axonal CMT.

Careful monitoring in this population would appear essential, thereby enabling clinicians to identify adverse events early and implement rapid treatment.

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References

1. Mahase E. COVID-19: WHO declares pandemic because of "alarming levels" of spread, severity, and inaction. BMJ 2020;368:m1036.
2. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on COVID-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. BMJ 2021;373:n1088.
3. Hernandez AF, Calina D, Poulas K, Docea AO, Tsatsakis AM. Safety of COVID-19 vaccines administered in the EU: should we be concerned? Toxicol Rep 2021;8:871-9.
4. Waqar U, Ahmed S, Gardezi SM, et al. Thrombosis with thrombocytopenia syndrome after administration of AZD1222 or Ad26.COV2.S vaccine for COVID-19: a systematic review. Clin Appl Thromb Hemost 2021;27:10760296211068487.
5. Carli G, Nichele I, Ruggeri M, Barra S, Tosetto A. Deep vein thrombosis (DVT) occurring shortly after the second dose of mRNA SARS-CoV-2 vaccine. Intern Emerg Med 2021;16:803-4.
6. Di Pietro M, Dono F, Consoli S, et al. Cerebral venous thrombosis without thrombocytopenia after a single dose of COVID-19 (Ad26.COV2.S) vaccine injection: a case report. Neurol Sci 2022;43:2951-6.
7. Bhan C, Bheesham N, Shakuntulla F, Sharma M, Sun C, Weinstein M. An unusual presentation of acute deep vein thrombosis after the Moderna COVID-19 vaccine: a case report. Ann Transl Med 2021;9:1605.
8. Rela M, Jothimani D, Vij M, Rajakumar A, Rammohan A. Auto-immune hepatitis following COVID vaccination. J Autoimmun 2021;123:102688.
9. Vuille-Lessard E, Montani M, Bosch J, Semmo N. Autoimmune hepatitis triggered by SARS-CoV-2 vaccination. J Autoimmun 2021;123:102710.
10. Tan CK, Wong YJ, Wang LM, Ang TL, Kumar R. Autoimmune hepatitis following COVID-19 vaccination: true causality or mere association? J Hepatol 2021;75:1250-2.
11. Bril F, Al Diffalha S, Dean M, Fettig DM. Autoimmune hepatitis developing after coronavirus disease 2019 (CO-

VID-19) vaccine: causality or casualty? J Hepatol 2021; 75:222-4.
12. Rocco A, Sgamato C, Compare D, Nardone G. Autoimmune hepatitis following SARS-CoV-2 vaccine: may not be a casuality. J Hepatol 2021;75:728-9.
13. Szigeti K, Lupski JR. Charcot-Marie-Tooth disease. Eur J Hum Genet 2009;17:703-10.
14. Auer-Grumbach M, Toegel S, Schabhuttl M, et al. Rare variants in MME, encoding metalloprotease neprilysin, are linked to late-onset autosomal-dominant axonal polyneuropathies. Am J Hum Genet 2016;99:607-23.
15. Sharifian-Dorche M, Bahmanyar M, Sharifian-Dorche A, Mohammadi P, Nomovi M, Mowla A. Vaccine-induced immune thrombotic thrombocytopenia and cerebral venous sinus thrombosis post COVID-19 vaccination; a systematic review. J Neurol Sci 2021;428:117607.