

Central Retinal Vein Occlusion Following mRNA COVID-19 Vaccination

COVID-19 mRNA Aşısı Sonrası Gelişen Santral Retinal Ven Oklüzyonu

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ABSTRACT We report a case of visual loss after the Pfizer-BioNTech mRNA coronavirus disease-2019 (COVID-19) vaccine injection. Two days after COVID-19 vaccination, a 56-year old female experienced visual loss in her right eye and she admitted to the ophthalmology clinic. After detailed ophthalmologic examination and investigations, including optical coherence tomography and fundus fluorescein angiography, right non-ischemic central retinal vein occlusion was diagnosed. The temporal relationship of the disease and vaccination, and the well-known association of COVID-19 disease with coagulopathy raised concerns about vaccine coagulopathy-related etiology. This is the case presenting a possible relationship between central retinal vein occlusion and COVID-19 vaccination.

Keywords: COVID-19 disease; Pfizer-BioNTech vaccine; central retinal vein occlusion; coagulopathy

ÖZET Bu olgu sunumu ile Pfizer-BioNTech mRNA koronavirus hastalığı-2019 [coronavirus disease-2019 (COVID-19)] aşısı enjeksiyonu sonrası görme kaybı gelişen vakayı rapor ettik. mRNA COVID-19 aşılamaından 2 gün sonra, 56 yaşındaki kadın sağ gözde görme kaybı şikâyeti ile göz polikliniğine başvurdu. Oftalmolojik muayene ve optik koherens tomografi ve fundus florescein anjiyografisi içeren görüntüleme yöntemleri ile sağ gözde noniskemik santral retinal ven tıkanıklığı tanısı konuldu. Sağ santral retinal ven oklüzyonu ve mRNA COVID-19 aşılması arasındaki zamansal ilişki ve COVID-19 hastalığının koagülopatisi özelliği, bu vakada aşısı koagülopatisine bağlı etiyolojiyi düşündürmüştür. Bu vaka ile retinal ven oklüzyonu için muhtemel bir etiyopatenez olarak mRNA COVID-19 aşılması arasındaki ilişki irdelenecektir.

Anahtar Kelimeler: COVID-19 hastalığı; Pfizer-BioNTech aşısı; santral retinal ven tıkanıklığı; koagülopati

Since the onset of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic, millions of patients have died because of the infection itself or complications of the infection. Vaccines to control the disease were developed within a short time and millions of people have been vaccinated under emergency use licenses. Inactivated viral vaccine (Sinovac, Sinovac Biotech, China), virus-vector vaccines [AstraZeneca (BARDA, OWS, Cambridge, UK) and Johnson & Johnson (US)], and mRNA-based vaccines [Pfizer-BioNTech (Germany) and Moderna (US)] are among the

vaccines that the World Health Organization (WHO) have listed for emergency use.

While the vaccination programs continue to control the pandemic, postmarketing studies are also very important to improve our knowledge about the safety and efficacy of the vaccines and to identify the risk/benefit profile. For this reason, reporting adverse effects of vaccines is critically important.

There are reports about ocular arterial and venous thromboembolic events following coronavirus disease-2019 (COVID-19) infection.¹

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Peer review under responsibility of Türkiye Klinikleri Journal of Ophthalmology.

Received: 25 Feb 2022

Received in revised form: 13 Apr 2022

Accepted: 13 Apr 2022

Available online: 20 Apr 2022

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Likely, some recent reports show the ocular thromboembolic side effects of the COVID-19 vaccines.^{2,3} We report a case of central retinal vein occlusion (CRVO) occurring 2 days after the 2nd dose of Pfizer-BioNTech mRNA COVID-19 vaccination.

CASE REPORT

Both authors declare that informative consent was obtained from the patient to publish this case report and all the information and images belong to the case.

A 56-year-old female was admitted to the ophthalmology clinic complaining of decreased vision in her right eye 2 days after the 2nd dose of immunization with Pfizer-BioNTech mRNA COVID-19 vaccine, which persisted for 15 days. Her past ocular history was insignificant and her past medical history was significant with insulin resistance and well-controlled hypertension. On her ophthalmologic examination, the best-corrected visual acuity was 20/125 in her right eye and 20/20 in the left. Anterior segment

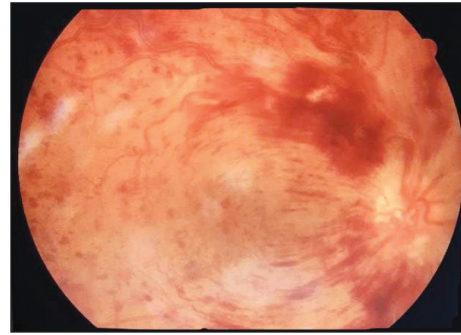


FIGURE 1: Right fundus colored photography, diffuse flame, and dot-blot hemorrhages, disc edema and hazy appearance due to vitreous hemorrhage are evident.

examination was not significant. Dilated fundoscopic examination was insignificant in the left eye except for mild hypertensive arterial changes, whereas for the right eye, the optic disc was swollen, with extensive flame and deep hemorrhages, and vascular tortuosity was consistent with right central retinal vein occlusion. Intraocular pressure was 15 mmHg in the right and 14 mmHg in the left eye.

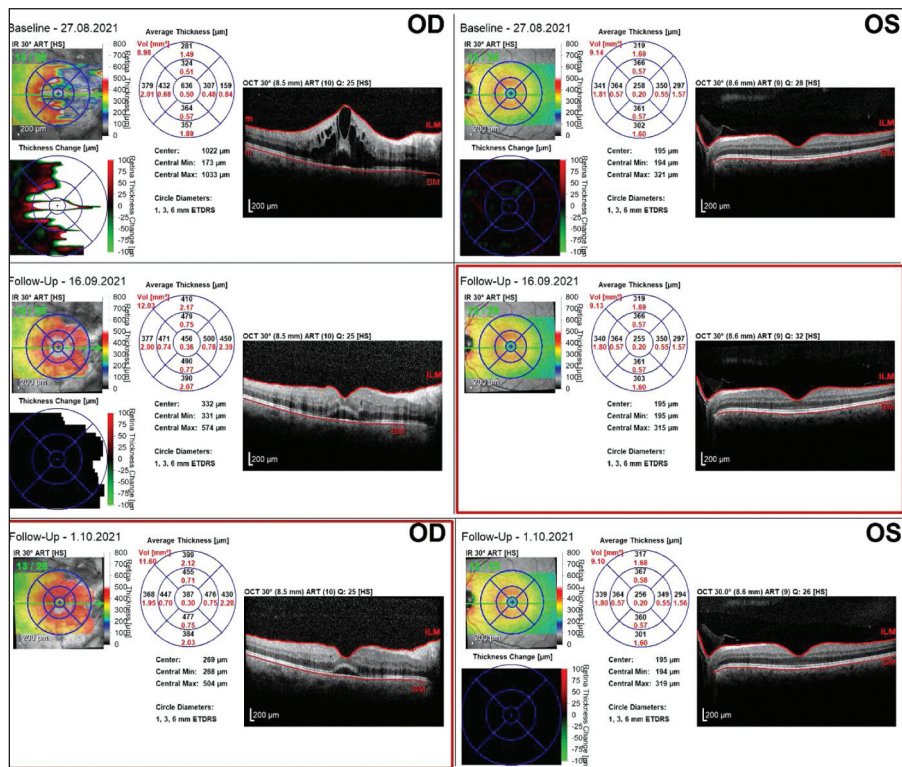


FIGURE 2: OCT; serous macular detachment and cystoid macular edema on the right, normal appearance on the left (top), and follow-up scans after right intravitreal aflibercept injection (middle and bottom); decrease in macular edema and regression of serous detachment, decrease in the thickness map. OCT: Optic coherence tomography.

Colored photography and optic coherence tomography (OCT) are seen in [Figure 1](#) and [Figure 2](#), respectively. OCT revealed right serous retinal detachment and cystoid macular edema. Subfoveal macular thickness was 613 μm in the right and 264 μm in the left eye. Fundus fluorescein angiography showed hypo-fluorescence due to hemorrhage, delayed arterial to venous passage time, increased venous tortuosity and fluorescein retention on the venous walls with relatively good retinal perfusion in the right eye ([Figure 3](#)). Peripapillary nerve fiber thickness was increased on the right.

Systemic workup including full blood count, C-reactive protein, protein C and S, antithrombin 3 activity, homocysteine level, anticardiolipin antibodies, antinuclear antibodies, von Willebrand factor antibody, ferritin, and fibrinogen were performed to reveal the traditional and non-traditional risk factors because of the relatively young age of the patient. Blood tests revealed a normal hemogram, minimally increased protein C activity (140%, n:70-130), increased antithrombin 3 activity (122%, n:80-120), and D-dimer (0.69 $\mu\text{g}/\text{mL}$, n:0-0.52).

In the ophthalmologic workup, the patient had right CRVO with relatively good peripheral retinal perfusion and cystoid macular edema with central serous macular detachment. Because no other systemic thrombosis was found in the patient, we did not prescribe any drug for anticoagulation. Intrav-

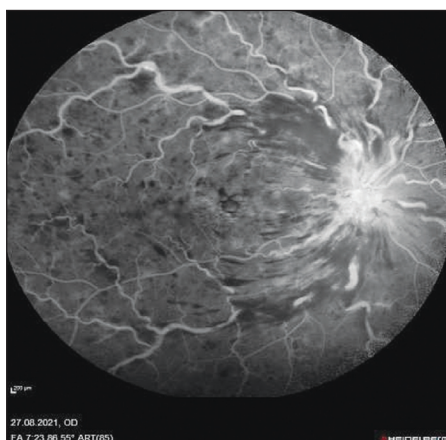


FIGURE 3: Fundus fluorescein angiography; right late phase; cystoid macular edema is seen because of macular dye pooling and disc hyperfluorescence due to leakage.

itreal aflibercept injections were planned for cystoid macular edema. In her first month of follow-up, macular edema was found to decrease with improvements in her visual acuity to 20/100 ([Figure 2](#)).

DISCUSSION

The most common COVID-19 symptoms are respiratory but gastrointestinal, neurological, and other atypical symptoms can also be seen.^{3,4} Recent studies showed several coagulation abnormalities in patients with COVID-19 and called this COVID-19-associated coagulopathy (CAC).⁴ The proposed pathophysiology seems to be related to endothelial injury, stasis, and hypercoagulable state due to abnormalities caused by elevated circulating prothrombotic factors.⁴⁻⁶ Some reports suggest that COVID-19 may predispose patients to arterial and venous thrombosis and venous thromboembolic diseases are common in patients with severe COVID-19. Coagulopathy seen in COVID-19 disease is also explained by Virchow's triad and some coagulation factors like elevated von Willebrand factor (vWF), Factor VIII, D-dimer, fibrinogen, protein C, antithrombin, neutrophil extracellular traps, and prothrombotic microparticles are proposed to be responsible for hypercoagulopathy.^{4,7} Recently, Cavalcanti et al. reported a series of three young patients, less than 41 years of age, with COVID-19 presenting with cerebral venous system thrombosis.⁸ As COVID-19 has a strong association with immunothrombosis, COVID-19 mRNA vaccination could recapitulate the thrombotic complications of COVID-19 disease. The WHO cautioned that "COVID-19 vaccination itself may be associated with an increased risk of developing COVID-19-like disease or its complications." Hence, several weeks after Pfizer-BioNTech mRNA COVID-19 vaccination, the spike protein, which carries higher thrombogenic potential as does the SARS-CoV-2 virus itself, is detected in the bloodstream.⁹

In our literature review, we found some recent reports about ocular thromboembolic complications of COVID-19 vaccines. Left CRVO immediately after the second dose of Pfizer-BioNTech mRNA COVID-19 vaccination in a 50-year-old healthy male was reported by Bialasiewicz et al. Goyal et

al. reported a 28-year-old healthy male with right superior hemi-retinal vein occlusion in his right eye 11 days after receiving the second dose of the Gam-COVID-Vac/Sputnik V (Gamaleya Institute, Russia).^{2,3}

In our case, the patient was a 56-year-old female, with relatively younger age as over 50% of CRVO cases occur in patients older than 65 years and with systemic history of well-controlled hypertension and insulin resistance as risk factors for CRVO.¹⁰ She was not a smoker, and not taking any drugs leading to hypercoagulation like oral contraceptive or hormone replacement therapy. She had no other intraocular risk factor for CRVO like glaucoma. The temporal relationship with Pfizer-BioNTech mRNA COVID-19 vaccination and the occurrence of right CRVO raised suspicion about the vaccine as a causative factor. In the systemic assessment of the patient, increased D-dimer levels, protein C and antithrombin III levels were remarkable. In literature research, CAC was found to be associated with increased levels of fibrinogen, D-dimer, vWf, Factor VIII activity, antithrombin, protein C, anticardiolipin antibody positivity, normal or increased PT, aPTT, and normal/increased or decreased levels of platelet counts.⁴ As with COVID-19 disease, COVID-19 immunization also increases the risk of coagulation-related problems in selected patients with certain underlying disorders that can be neither predicted nor anticipated. Cerebral venous thrombosis and immune-mediated

thrombotic, thrombocytopenic purpura may be seen like black swan effects and we evaluate this case in this category.^{9,11}

In conclusion, although it is rare, COVID-19 immunization may lead to ocular and systemic thromboembolic complications. It is well known that vaccination decreases mortalities from the COVID-19 disease and at the same time, awareness of the complications attributable to vaccines improves vaccine adherence and helps to early intervention.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Yasemin Un, Nur Demir; **Design:** Yasemin Un, Nur Demir; **Control/Supervision:** Yasemin Un; **Data Collection and/or Processing:** Nur Demir; **Analysis and/or Interpretation:** Yasemin Un; **Literature Review:** Yasemin Un, Nur Demir; **Writing the Article:** Yasemin Un; **Critical Review:** Yasemin Un, Nur Demir.

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