Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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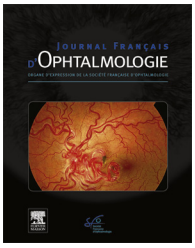

LETTER TO THE EDITOR

Frosted branch angiitis after booster vaccination with BNT162b2

L'angéite givrée après booster vaccination avec BNT162b2

Case report

The current and on-going coronavirus disease 2019 (COVID-19) pandemic has challenged the medical community and raised countless questions on how to end the exponential spread since its beginning in 2020. Silver linings were seen with the development of an effective vaccination against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at the end of 2020. Currently, 6 vaccines from different pharmaceutical companies were granted the emergency use authorization from the World Health Organization [1].

Worldwide, more than 12 billion doses of COVID-19 vaccinations have been administered, thereby probably saving millions of lives. So far, some case reports of retinal severe adverse events (SAE) after the first or second dose of mRNA vaccinations against COVID-19 have either been published or presented at conferences. These include branch retinal arterial occlusion, combined arterial and venous occlusion, venous stasis retinopathy, central serous chorioretinopathy and acute macular neuroretinopathy [2].

A 40-year-old Caucasian man was referred to the tertiary medical retina unit at Clinic Landstraße (Vienna Healthcare Group) due to acute vision loss to hand movement and vitreous hemorrhage in his right eye. The patient reported that he received the booster vaccination with BNT162b2 against SARS-CoV-2 three weeks earlier. His medical history comprised a recurrent uveitis intermedia (HLA B-51, B-5) with re-activation of vitreous and anterior segment inflammation in the same eye shortly after the first BNT162b2 vaccination this year. His previous medical and physical history were unremarkable for any B-51 specific symptoms or systemic conditions including Behçet's disease. The first episode subsided under topical and systemic corticosteroids, while the second vaccination was administered 3 weeks later and passed uneventfully under therapy. Urgent vitrectomy was performed on the day of admission and scattered intraretinal hemorrhages, vascular sheathing and abruptly terminating arterial and venous vessels consistent with a frosted branch angiitis were seen intraoperatively. Consequently, prophylactic laser treatment for retinal ischemia and silicon oil tamponade to avoid secondary retinal detachment were performed (Fig. 1A). Postoperatively, the wide-field fluorescein angiography showed extensive arteriovenous leakage of the remaining vascular trunks as well as retinal non-perfusion areas also pictured as broad inner retinal ischaemia and cystoid macular edema in optical coherence tomography (Fig. 1B—D). Vitreous and blood samples were negative for any causative infectious disease including Human Immunodeficiency Virus, Herpes Virus polymerase chain reaction, Toxoplasmosis, Tuberculosis, Treponema pallidum or any autoimmune disorder such as hemopathies, systemic lupus erythematodes or chronic inflammatory bowel syndromes. A reaction to the booster dose is suspected to be the origin of this retinal SAE. His vision improved minimally to counting fingers, while fundus examination showed persistent intraretinal hemorrhages along the inferior retinal arcade 4 weeks later.

To our best knowledge, this is the first case of a frosted branch angiitis after the booster vaccination with BNT162b2. The number of reported retinal SAE in the literature after the first or second dose of any COVID-19 vaccination is rising with increasing numbers of fully vaccinated people (Table 1) [2].

The exact underlying mechanism of vaccine-induced autoimmune activations is still in the dark; however, two theories have been postulated: an infection by the still active, but weakened virus strain is deemed possible regarding live attenuated vaccines such as measles-mumps-rubella immunization. The second mechanism might be caused by adjuvants, for example aluminium salts, which are used in inactivated or subunit or conjugate vaccines. These autoinflammatory and autoimmune conditions induced by adjuvants are better known as the Shoenfeld syndrome [3]. The BNT162b2 vaccine uses lipid nanoparticle encapsulated mRNA, encoding for a full-length spike protein of SARS-CoV-2. After injection, high levels of antigen-specific antibodies are being produced and a T helper 1 cell response is induced. Similarities between human proteins and the SARS-COV-2 glycoprotein are being postulated and might be responsible for a cross-reactivity, triggering or exacerbating autoimmune conditions [4]. Since the presented case had a history of uveitis intermedia, a severe reaction of the disease due to the booster vaccination with BNT162b2 might be causative, especially since the disease onset was within 3 weeks after the third injection and uveitis activation subsequent to a COVID-19 vaccination has been described before.

Lin et al. reviewed the latest literature on ophthalmic AE summarizing events after COVID-19 vaccinations [1]. They found several cases of COVID-19 vaccine-related uveitis, as well as other autoimmune conditions, such as Vogt-Koyanagi-Harada disease, bilateral acute zonal occult outer retinopathy and arteritic anterior ischemic optic neuropathy. However, the number of unreported cases of newly

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Table 1 Number of published cases of retinal severe adverse events following COVID-19 vaccination.

No.	Authors Journal	Year	Type	Eye	Sex	Age[a]	Vaccine	Dose	Interval[b]	Symptoms	Diagnosis
1	Mambretti et al. *Ocular Immunology and Inflammation*	2021	Case report		F	22	ChAdOx1	NA	2	Paracentral scotoma	AMN
2					F	28	ChAdOx1	NA	2	Paracentral scotoma	AMN
3	Bøhler et al. *Eye*	2021	Letter to editor	L	F	27	ChAdOx1	1st	2	Paracentral scotoma	AMN
4	Gabka et al. *Ophthalmologe*	2021	Case report	B	F	20	ChAdOx1	NA	1	Flickering Scotoma	AMN
5	Book et al. *JAMA Ophthalmology*	2021	Images	B	F	21	ChAdOx1	1st	3	Bilateral paracentral scotomas	AMN
6	Michel et al. *Journal of Ophthalmic Inflammation and Infection*	2021	Case report	L	F	21	ChAdOx1	1st	2	Central scotoma	AMN
7	Chen et al.	2021	Letter to editor	L	F	21	BNT162b2	1st	3	Paracentral scotoma	AMN
8	Fowler et al. *American Journal of Ophthalmology*	2021	Case report	R	M	33	BNT162b2	NA	3	Blurred vision, metamorphopsia	CSCR
9	Mudie et al. *Ocular Immunology and Inflammation*	2021	Case report		F	43	BNT162b2	2nd	3	Decreased VA	Panuveitis
10	Goyal et al. *Ocular Immunology and Inflammation*	2021	Case report	B	M	34	ChAdOx1	2nd	7	Visual loss	MFC
11	Maleki et al. *Journal of Ophthalmic and Vision Research*	2021	Case report	L	F	33	mRNA-1273	2nd	10	Nasal field defect, flashes in both eyes	AZOOR

Table 1 (*Continued*)

No.	Authors Journal	Year	Type	Eye	Sex	Age[a]	Vaccine	Dose	Interval[b]	Symptoms	Diagnosis
12	Papasavvas et al. *Journal of Ophthalmic Inflammation and Infection*	2021	Case report	B	F	43	BNT162b2	2nd	42	Decreased VA, photophobia, eye tenderness	VKH
13	Rabinovitch et al. *Retina*	2021	Article	L	M	39	BNT162b2	2nd	5	Blurred vision, visual field defect, photopsia	MEWDS
14				L	F	28	BNT162b2	2nd	30	Blurred vision, visual field defect, photopsia	MEWDS
15	Bolletta et al. *Journal of Clinical Medicine*	2021	Article	L	M	53	BNT162b2	1st	8	Blurred vision	Toxoplasma retinochoroiditis
16				L	F	58	BNT162b2	2nd	7	Blurred vision	Toxoplasma retinochoroiditis
17				R	F	52	Ad26.COV2	1st	7	Blurred vision	Toxoplasma
18				B	F	44	BNT162b2	2nd	12	Blurred vision	VKH
19				B	F	58	BNT162b2	2nd	5	Blurred vision	VKH
20				B	F	49	ChAdOx1	1st	7	Blurred vision	Pars planitis
21				B	F	18	BNT162b2	2nd	14	Blurred vision	Pars planitis
22				B	M	41	mRNA-1273	2nd	5	Blurred vision	Retinal vasculitis
23				R	F	59	BNT162b2	1st	10	Blurred vision	Retinal vasculitis
24				B	M	42	BNT162b2	2nd	30	Redness, blurred vision	Panuveitis
25				L	M	53	BNT162b2	2nd	28	Decreased VA, visual field defect	MEWDS
26				R	F	18	BNT162b2	1st	4	Blurred vision, visual field defect	MEWDS

(*Continued*)

No.	Authors Journal	Year	Type	Eye	Sex	Age[a]	Vaccine	Dose	Interval[b]	Symptoms	Diagnosis
27				R	M	48	BNT162b2	1st	7	Decreased VA	MEWDS
28				B	F	25	ChAdOx1	1st	2	Visual field defect	AMN
29				R	M	39	mRNA-1273	2nd	30	Decreased VA	CRVO
30				L	F	53	ChAdOx1	1st	2	Decreased VA	BRVO
31				L	F	61	ChAdOx1	2nd	2	Decreased VA	BRVO
32				L	M	50	BNT162b2	2nd	3	Decreased VA	BRVO
33				L	M	48	BNT162b2	2nd	23	Blurred vision	BRVO
34				R	F	47	BNT162b2	1st	8	Decreased VA	Uveitic CNV
35				R	F	68	BNT162b2	2nd	10	Decreased VA	Uveitic CNV
36				R	F	66	BNT162b2	2nd	1	Blurred vision	Myopic CNV
37				B	M	41	BNT162b2	2nd	13	Blurred vision	CSCR
38	Pichi et al. *JAMA Ophthalmology*	2021	Brief report	L			BBIBP-CorV	1st	5	Acute vision loss	AMN
39							BBIBP-CorV	1st	NA	Acute vision loss	AMN
40				L			BBIBP-CorV	1st	NA	Blurred vision & paracentral scotoma	PAMM
41							BBIBP-CorV	1st	NA		CSCR
42	Bayas et al. *Lancet*	2021	Case report	B	F	55	ChAdOx1	1st	10	Conjunctival congestion, retro-orbital pain, diplopia	Vein thrombosis
43	Panovska-Stavridis et al. *Mediterranean Journal of Hematology and Infectious Diseases*	2021	Case report	L	F	29	ChAdOx1	1st	10	Blurred vision	Vein thrombosis

(*Continued*)

No.	Authors Journal	Year	Type	Eye	Sex	Age[a]	Vaccine	Dose	Interval[b]	Symptoms	Diagnosis
44	Smith et al. *Ocular Immunology and Inflammation*	2022	Letter to editor	L	F	15	BNT162b2	2nd	14	Blurred vision and black floaters	MEWDS
45				R	F	21	BNT162b2	2nd	21	Blurred vision and headaches	MEWDS
46	Delbarre et al. *Journal français d'ophthalmologie*	2022	Letter to editor	L	M	38	BNT162b2	1st	7	Blurred Vision	CSCR
47	Mechleb et al. *Journal français d'ophthalmologie*	2022	Article	B	F	32	BNT162b2	1st	5	Painless loss of vision	CSCR
48	Janhart et al. *Journal français d'ophthalmologie*	2022	Article	R	M	35	BNT162b2	1st	2	Visual disturbances	CSCR
49				R	M	45	BNT162b2	1st		Blurred vision	CSCR
50				R	F	65	BNT162b2	1st	2	Visual disturbances	CSCR
51				R	M	44	BNT162b2	1st	10	Blurred vision	CSCR
52	Haas et al.	2022	Letter to editor	R	M	40	BNT162B2	3rd	21	Acute vision loss	Frosted branch angiitis

NA: not announced; F: female; AMN: acute macular neuroretinopathy; L: left eye; B: bilateral; R: right eye; M: male; VA: visual acuity; CSCR: central serous chorioretinopathy; MFC: multifocal choroiditis; AZOOR: acute zonal outer occult retinopathy; VKH: Vogt-Koyanagi-Harada disease; MEWDS: multiple evanescent white dot syndrome; CRVO: central retinal vein occlusion; BRVO: branch retinal vein occlusion; CNV: choroidal neovascularization; PAMM: paracentral acute middle maculopathy.

[a] In years.

[b] In days between vaccination and onset of symptoms.

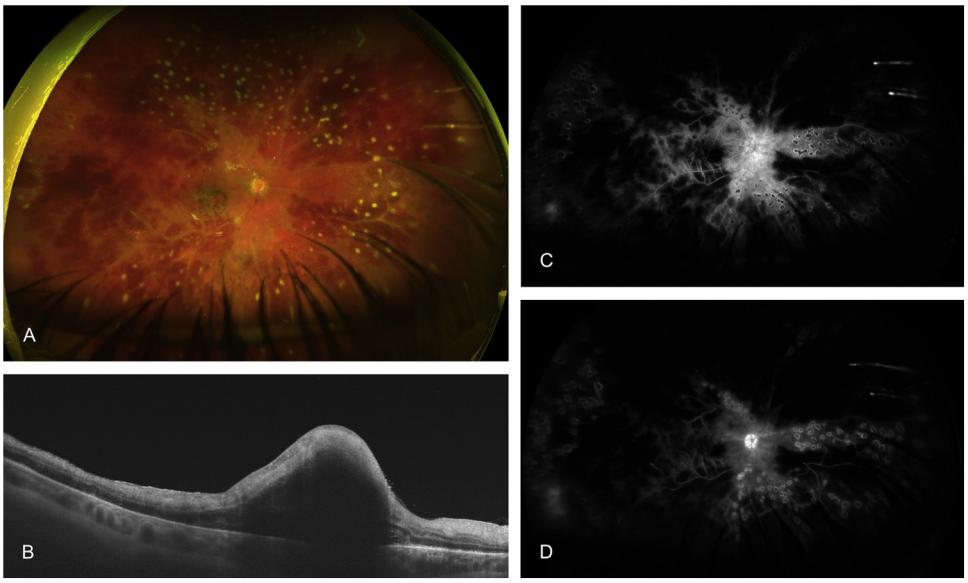

Figure 1. Composite of a frosted branch angiitis one day after surgery. A. Widefield digital fundus photography of the right eye showing confluent retinal hemorrhage, sheathed major vessels, abruptly terminating vascular endings and panretinal sectorial laser treatment. B. Swept source-optical coherence tomography b-scan of the central retina through the foveal umbo with broad inner retinal hyperreflectivity as an expression of intracellular edema as well as a prominent cystoid macular edema of the outer retina due to acute ischemia. C. Early widefield fluorescein angiography demonstrating the frosted branch appearance of the remaining central arteriovenous perfusion next to extensive blockage caused by retinal hemorrhage or ischemia of the inner retinal capillaries. D. Late fluorescent leakage of the optic disc and major vascular trunks with marked staining of peripheral laser spots.

diagnosed or re-activated ocular autoimmune diseases is still unknown and almost impossible to estimate. Most of these patients are seen in a private practice in case of an acute event, where a mild course of the disease can be perfectly managed, thereby remaining without further notice to scientific reports. We hereby added this case to the already published literature of retinal SAE after any COVID-19 vaccination (Table 1). Patients with a severe autoimmune disease are commonly treated with local or systemic immunosuppressive agents, such as corticosteroids or tumor necrosis factor-α-blocker. The aim of any vaccination, however, is the stimulation of the recipient's immune system, so that antibodies against certain antigens are being produced to protect against a disease. Hence, the question arises, whether patients with a known autoimmune disease should take corticosteroids as preventive measurements before receiving a COVID-19 vaccination. On the other hand, it is unclear if the vaccination has the intended effect on patients under immunosuppression [5]. Supervising clinicians should keep a possible re-activation of an autoimmune disease after vaccination in mind and balance advantages and disadvantages of a prophylactic immunosuppressive treatment individually.

In conclusion, the COVID-19 vaccination has brought about substantial benefits to the management of the current pandemic. Its safety profile is considered similar to that of other viral vaccines already being administered for decades. Clinicians should be aware that the booster COVID-19 vaccination can evoke a retinal SAE even in the absence of an earlier SAE. A meticulous uveitis screening for any signs of activity should be performed on patients with a known history of an autoimmune disease before immunization, especially with mRNA vaccines. Having said that, if the vaccination is causative or just coincidental remains a challenge for the scientific society at the moment.

Submission declaration and verification

The authors have not published or submitted any related papers from this study and the paper was not presented at a meeting before.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Lin TPH, Ko CN, Zheng K, Lai KHW, Wong RLM, Lee A, et al. COVID-19: update on its ocular involvements, and complications from its treatments and vaccinations. Asia Pac J Ophthalmol 2021;10:521—9, http://dx.doi.org/10.1097/APO. 0000000000000453.

[2] Nyankerh CNA, Boateng AK, Appah M. Ocular complications after COVID-19 vaccination, vaccine adverse event reporting system. Vaccines 2022;10:941, http://dx.doi.org/10.3390/vaccines10060941.

[3] Cunningham ET, Moorthy RS, Fraunfelder FW, Zierhut M. Vaccine-associated uveitis. Ocul Immunol Inflamm 2019;27:517—20, http://dx.doi.org/10.1080/09273948.2019.1626188.

[4] Maleki A, Look-Why S, Manhapra A, Foster CS. COVID-19 recombinant mRNA vaccines and serious ocular inflammatory side effects: real or coincidence? J Ophthalmic Vis Res 2021;16:490—501, http://dx.doi.org/10.18502/jovr.v16i3.9443.

[5] Chau CY, Chow LL, Siddharth Sridhar, Shih KC. Ophthalmological considerations for COVID-19 vaccination in patients with inflammatory eye diseases and autoimmune disorders.

Ophthalmol Ther 2021;10:201—9, http://dx.doi.org/10.1007/s40123-021-00338-1.

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