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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Clinical challenges

Shot in the dark

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(In keeping with the format of a clinical pathologic conference, the abstract and key words appear at the end of the article.)

1. Case report

A 43-year-old woman with a history of medically-controlled type 2 diabetes mellitus, arterial hypertension, secondary hypothyroidism following radioactive iodine treatment for Graves disease, and migraine headaches experienced flashing lights in the right eye associated with a frontal headache that was phenotypically distinct from her usual migraines. Four days later she awoke with blurred vision in the right eye associated with painful eye movement. The next day she was examined by a general ophthalmologist who noted a visual acuity of 20/40 in the right eye and 20/20 in the left eye, with a right relative afferent pupillary defect (RAPD). The remainder of the examination, including the fundus, was normal (Fig. 1A). Macular optical coherence tomography (OCT) was normal. The peripapillary retinal nerve fiber layer (pRNFL) thickness was 132 µm in the right eye and 123 µm in the left eye (Fig. 1B).

What do you think of the OCT pRNFL thickness?

What is your differential diagnosis of the visual loss?
What work-up would you recommend?

2. Comments by Dr. Spencer

There is conspicuously bilateral optic nerve edema per OCT, with the symptomatic eye (OD) mildly more edematous than OS. This suggests a bilateral and possibly systemic condition. The vision loss, symptomatology, examination, and RAPD strongly suggest some form of optic nerve disease, most likely optic neuritis. The apparent bilaterality (albeit asymmetric and asymptomatic OS) along with the headache strongly warrant brain and orbital imaging to assess for a mass lesion. I would also strongly consider a lumbar puncture (LP) for these reasons, after appropriate imaging. My differential includes a demyelinating disease or other causes of optic nerve inflammation (e.g., infectious, infiltrative, systemic

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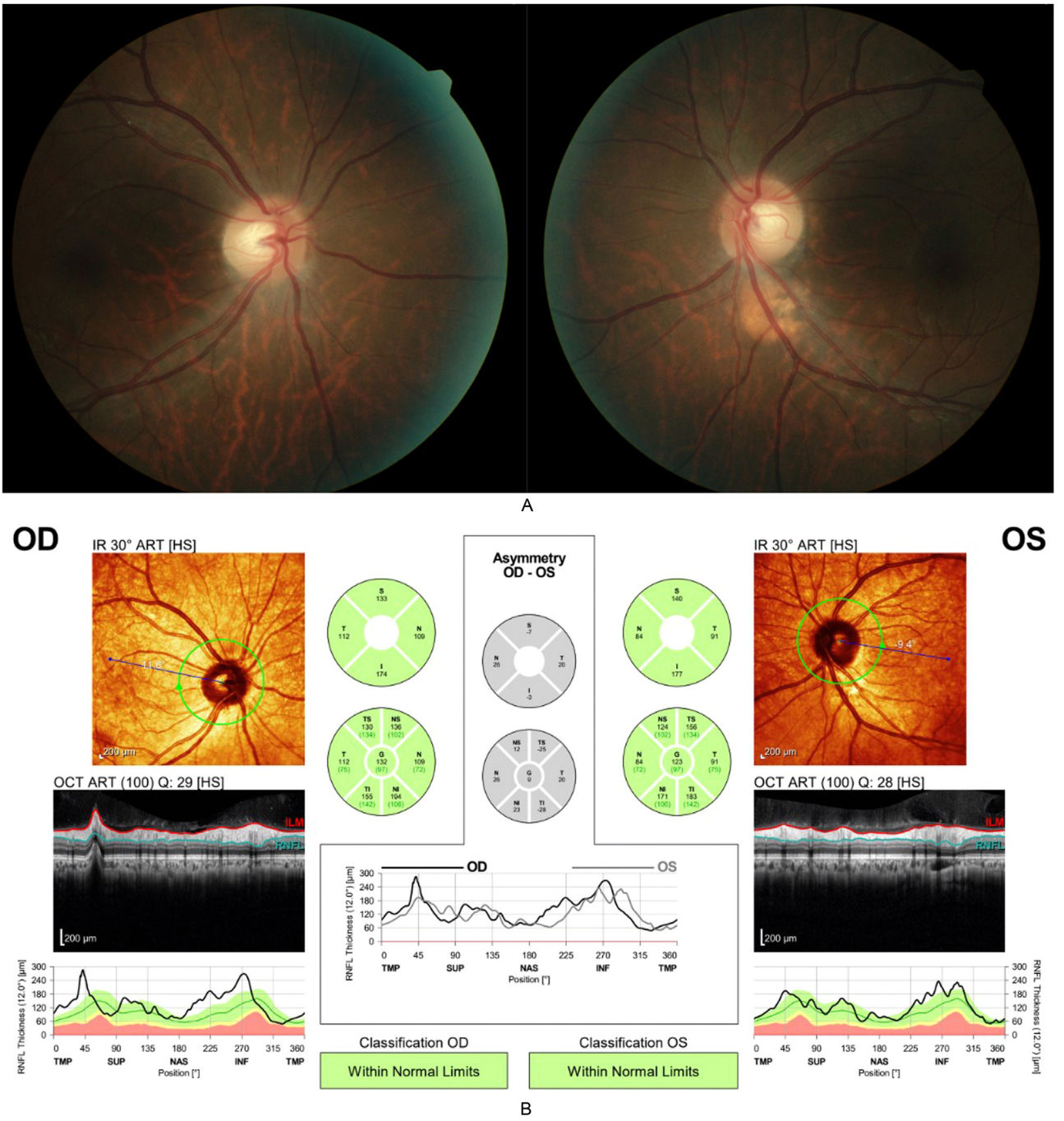

Fig 1 – Optic disc photographs and optical coherence tomography at presentation. (A) Fundus photographs showing normal appearing optic discs in both eyes. (B) Peripapillary retinal nerve fiber layer thickness printout (132 µ right eye and 123 µ left eye).

inflammatory disease). It is unlikely to be caused by her well-controlled diabetes mellitus, hypertension and unlikely to be nonarteritic anterior ischemic optic neuropathy or idiopathic intracranial hypertension, although the latter will be assessed by the LP and opening pressure. The apparent absence of other systemic complaints and otherwise normal fundus examination argue against sarcoidosis, tuberculosis, and syphilis, although these should be assessed serologically. Additional history excluding environmental exposures is desirable, along with a systemic evaluation including complete blood count (CBC) and comprehensive metabolic panel (CMP).

3. Case report continued

That evening after visiting with the ophthalmologist, magnetic resonance imaging (MRI) of the brain and orbits with contrast demonstrated enhancement of both optic nerve

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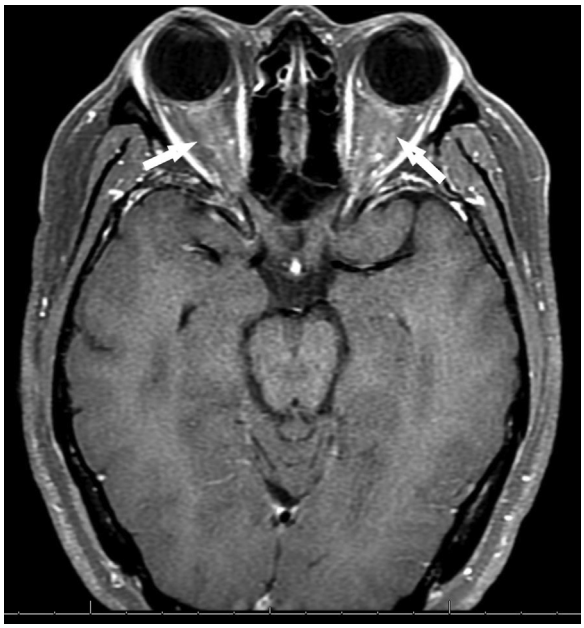

Fig 2 – Axial, T1 weighted, post contrast, fat suppressed magnetic resonance image demonstrating bilateral optic nerve sheath enhancement (arrows).

sheaths (Fig. 2), with the remainder of the brain appearing normal.

Two days later she noted dark vision in the left eye associated with painful eye movements and continued visual decline in the right eye. Visual acuity measured as\ counting fingers in each eye. She was admitted to the hospital. CBC, CMP, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies, antineutrophil cytoplasmic antibodies, angiotensin-converting enzyme, human immunodeficiency virus antigen, and antibodies to *Treponema pallidum, Borrelia burgdorferi,* and *Bartonella henselae* antibodies were all negative or normal. Live cell-based assay for myelin oligodendrocyte glycoprotein (MOG) immunoglobulin G (IgG) and aquaporin-4 (AQP-4) IgG were eventually reported to be negative (the results were not immediately available). Cerebrospinal fluid (CSF) analysis revealed 6/uL white blood cells (96% lymphocytes), 0/uL red blood cells, 113 mg/dL glucose, 23 mg/dL protein, non-reactive VDRL, negative cytology and absent oligoclonal bands. Whole body fluorodeoxyglucose (FDG) positron emission tomography (PET)-computed tomography (CT) was normal.

What do you think of the MRI findings?

What treatment would you recommend?

4. Comments by Dr. Spencer continued

The MRI findings are reassuring insofar as they do not reveal focal brain lesions (including demyelinating), and they suggest that the process is limited to the optic nerves, although the CSF reveals a lymphocytic pleocytosis with normal glucose that strongly points to an inflammatory or nonbacterial infectious process. The apparent non-toxic presentation with no mention of fever, arthralgia, myalgia or altered mental status argues against aseptic encephalitis and meningitis, along with the absence of known exposure history. Given the presumed noninfectious inflammatory process, I would recommend treatment with systemic steroids in an inpatient setting with close neurologic monitoring. I would consider sending the CSF for testing for infectious encephalitis agents.

5. Case report continued

Prior to obtaining the AQP-4 IgG results, she was given a presumptive diagnosis of neuromyelitis optic spectrum disorder (NMOSD)-optic neuritis and treated as such with 3 consecutive days of intravenous (IV) methylprednisolone (1 gram/day) and 7 treatments of plasma exchange (PLEX). Subjectively she started noticing improvement in vision after the last PLEX treatment.

During hospitalization, she informed the medical team that 6 days prior to the onset of her initial symptoms (10 days prior to the visual loss right eye) she had received the first dose of the Pfizer-BioNTech coronavirus disease 2019 (COVID-19) vaccine (Pfizer Inc, New York, NY)

What are your thoughts on the COVID-19 vaccination having been given prior to symptom onset?

6. Comments by Dr. Spencer concluded

The short interval between the COVID-19 vaccination and the onset of symptoms may suggest a causal association, although the timeframe is just about the minimum that I would find biologically plausible for an adaptive immune response. Given the heightened awareness about COVID-19 and vaccination for COVID-19, patients and clinicians are highly susceptible to a "recall bias" in associating one of these two with a physical ailment that may ensue within a short time frame thereafter. I frequently tell my patients that "over 100 million people in the US have been vaccinated with COVID-19 and/or been infected with COVID-19, so whatever was going to happen to 100 million people will occur and they happen to have been recently infected or vaccinated too." Nonetheless, vaccine-associated inflammatory conditions do (rarely) occur (typically at a much, much lower frequency than following the infection they're designed to protect against), I've seen them a few times myself (although much less frequently than COVID-19 related sequelae), and it's important for the medical community to be cognizant of this reality.

7. Case report concluded

Four weeks later, vision had subjectively improved slightly in both eyes, but 8 weeks later visual acuity returned to 20/20 in each eye, with optic disc pallor, inferior visual field defects, and pRNFL thinning (Fig. 3). Approximately 16 months later, vision was stable at 20/20 in each eye, with minor inferior visual field defects, more obvious optic disc pallor, and further pRNFL thinning (Fig. 4).

She declined any further COVID-19 vaccination injections.

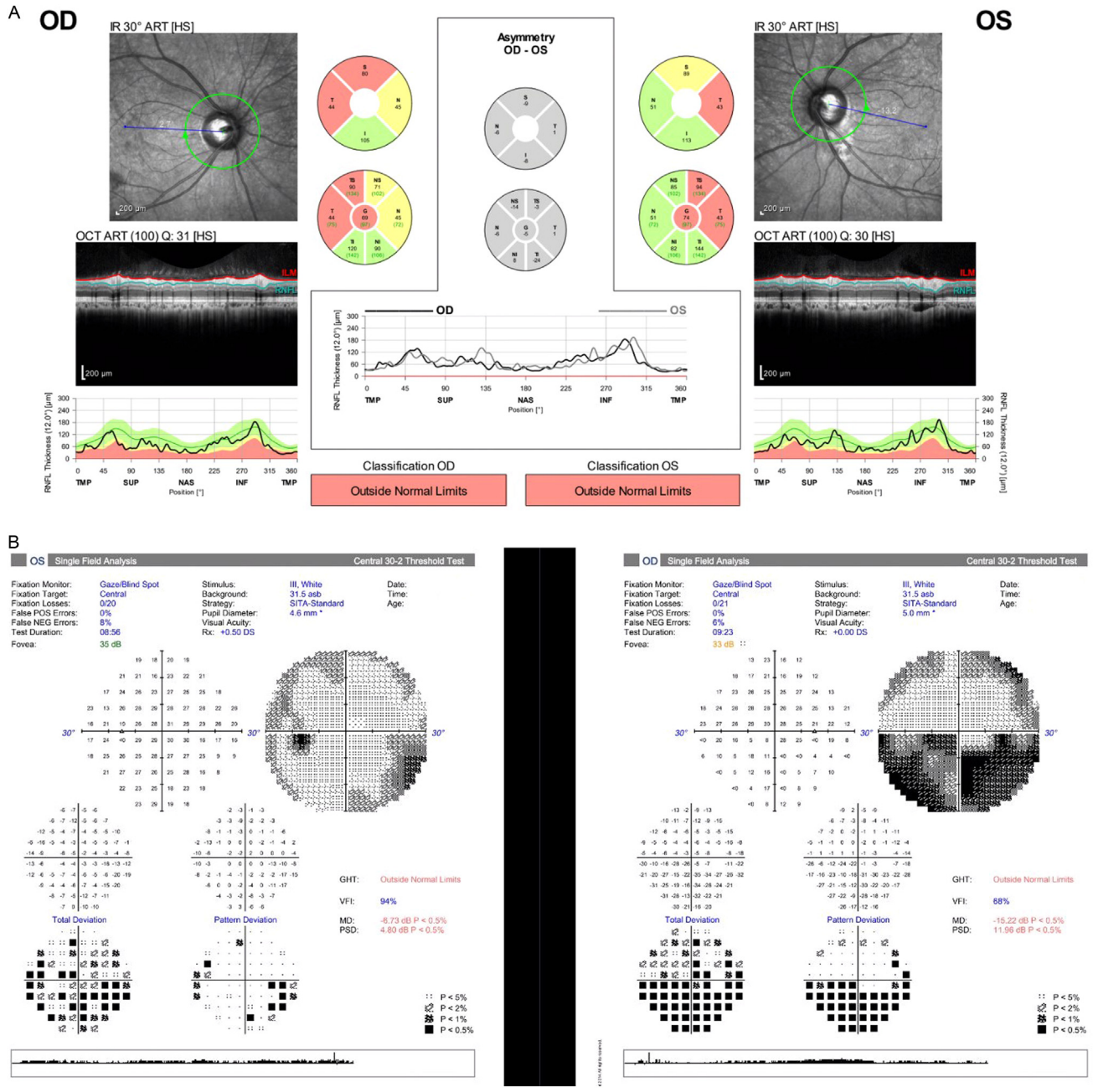

Fig 3 – Optical coherence tomography and automated visual field testing 2 months after presentation (A) Peripapillary retinal nerve fiber layer thickness printout (69 µ right eye and 74 µ left eye). (B) Bilateral inferior visual field defects more pronounced in the right eye.

8. Discussion

The rapid and unprecedented development of vaccines against infection from the novel severe respiratory syndrome coronavirus 2 (SARS-CoV-2) has been a phenomenal feat of modern medicine.[A] It is beyond the scope of this discussion to review in detail the mechanism of action of each COVID-19 vaccine, but for the interested reader, there are many excellent review articles published on the subject.[21,35,36] In general, the COVID-19 vaccine development program can be divided into traditional and novel approaches. The traditional vaccine platform consists of live attenuated virus, inactivated virus, and protein. The novel vaccine platform is viral vector-based, mRNA, or DNA.[28] As of the time of writing this discussion, the World Health Organization (WHO) has recognized 11 COVID-19 vaccines for use around the world (Table 1).[B] In the United States, the Food and Drug administration (FDA) has approved 2 vaccines (Comirnaty or Pfizer-BioNTech COVID-19 [Pfizer Inc, New York, NY] and Spikevax or Moderna COVID-19, mRNA-1273 [Moderna US, Cambridge, MA]); and two other vaccines (Janssen COVID-19 vaccine [Janseen, Horsham, PA]

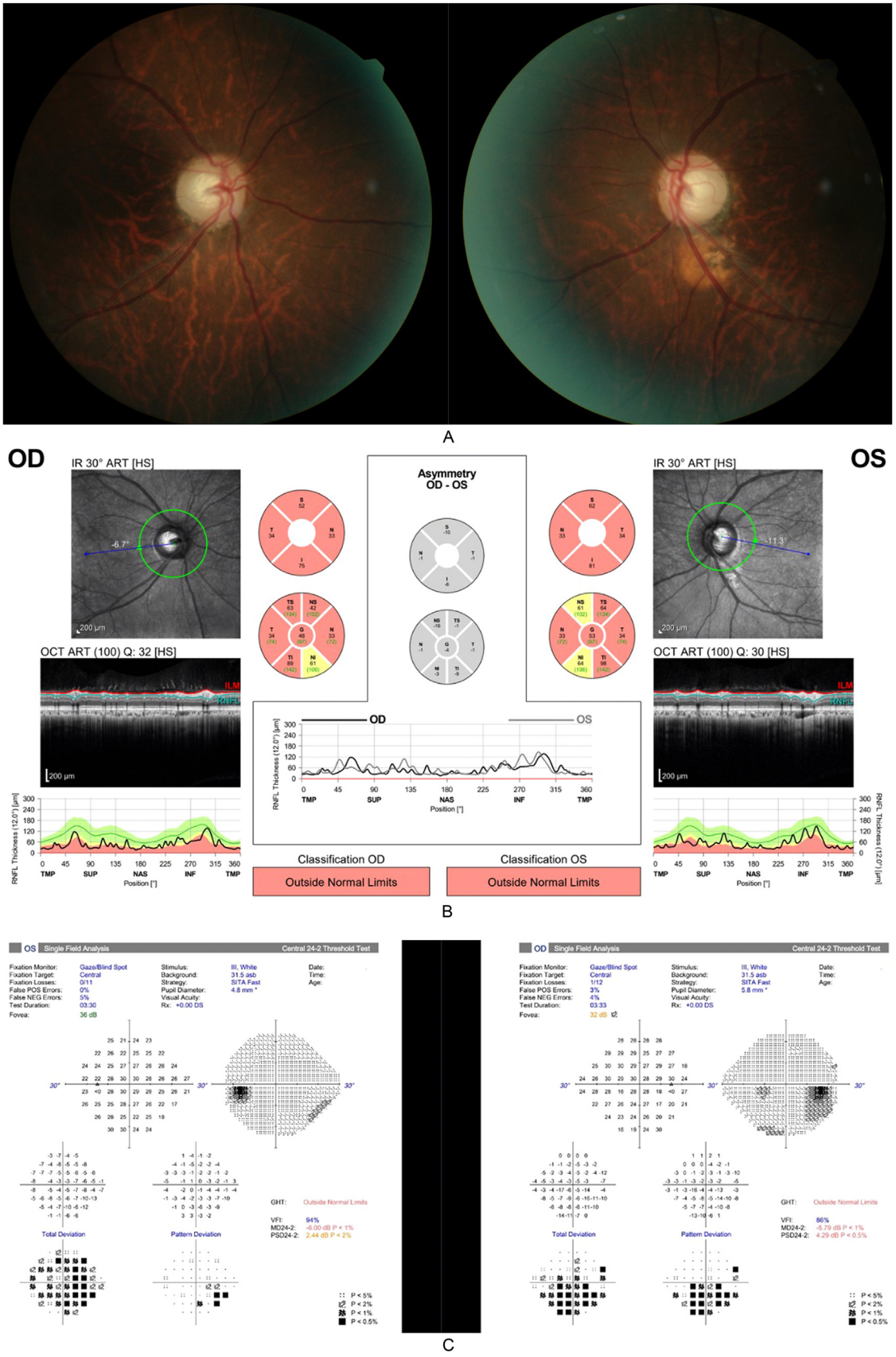

Fig 4 – Optic disc photographs, optical coherence tomography and formal perimetry approximately 16 months after presentation. (A) Fundus photographs showing diffuse bilateral optic disc pallor. (B) Peripapillary retinal nerve fiber layer thickness printout (48 µ right eye and 53 µ left eye). (C) Static perimetry showing bilateral inferior visual field defects, right eye slightly worse compared to left eye.

Table 1 – World Health Organization (WHO) accepted COVID-19 vaccines.

Name (generic/brand)	Manufacturer	Platform
BNT162b2/Comirnaty	Pfizer-BioNTech	Nucleoside modified mRNA
COVID-19 vaccine AstraZeneca)/Vaxzevria	AstraZeneca	Recombinant adenovirus vector encoding Spike protein
ChAdOx1nCoV-19 (AZD1222)/Covishield	Serum Institute of India PVT LTD	Recombinant adenovirus vector encoding Spike protein
Ad26.COV2.S/Jcovden	Janssen pharmaceuticals companies of Johnson & Johnson	Recombinant, replication-incompetent adenovirus vector encoding Spike protein
mRNA-1273/Spikevax	Moderna Biotech	mRNA-based encapsulated in lipid nanoparticle
Sinopharm BIBP COVID-19 vaccine or BBIBP-CorV	China National Pharmaceutical Group Co., Ltd (Sinopharm) and Beijing Institute of Biological Products Co., Ltd.	Inactivated virus
Sinovac COVD-19 vaccine/CoronaVac	Sinovac Life Sciences Co., Ltd.	Inactivated virus
BBV152/ Covaxin	Bharat Biotech, India	Inactivated virus
NVX-CoV2373/Covovax	Serum Institute of India PVT LTD	Recombinant nanoparticle prefusion Spike protein formulated with matrix-M adjuvant
NVX-CoV2373/Nuvaxovid	Novavax	Recombinant nanoparticle prefusion Spike protein formulated with matrix-M adjuvant
Ad5-nCoV/ Convidecia	CanSinoBIO	Recombinant adenovirus vector encoding Spike protein

Source: https://extranet.who.int/pqweb/sites/default/files/documents/Status_COVID_VAX_07July2022.pdf Assessed August 1, 2022

and Novavax COVID-19 vaccine, adjuvanted [Novavax, Inc, Gathersburg, MA]) have been given emergency use authorization status to aid in the fight against the COVID-19 pandemic.[C]

In general, most patients do very well after mRNA based COVID-19 vaccination; however, while typically minor and transient, post COVID-19 vaccination side effects such as fatigue, muscle pain, headache, and injection site reaction are quite common.[1] But serious systemic side effects such as thrombosis can also occur in some patients.[13] There have also been cases of specific immune-mediated diseases (e.g., myocarditis, pericarditis thrombocytopenia) presenting after COVID-19 vaccination.[5] The etiopathogenesis of such an autoimmune response is not entirely clear but it is thought to occur in a susceptible individual in reaction to either the vaccine product (i.e., protein) or the preparation adjuvant, as a result of molecular mimicry, activation of the innate and adaptive immune system or production of proinflammatory cytokines.[5,9,29,32]

Haseeb and coworkers conducted a systemic review of the literature and categorized the reported ocular complications following COVID-19 vaccination into eyelid, orbit, uveitis, retina, vascular, neuro-ophthalmic, ocular motility disorders, and others.[14] Specific ocular and neuro-ophthalmic adverse events include eyelid edema, blepharospasm, corneal graft rejection, uveitis, episcleritis, scleritis, choroiditis, acute macular neuroretinopathy, acute zonal occult outer retinopathy, multiple evanescent white dot syndrome, Vogt-Koyanagi-Harada disease, central serous retinopathy, retinal vein occlusion, anterior ischemic optic neuropathy (arteritic and nonarteritic), Leber hereditary optic neuropathy, neuroretinitis, tonic pupil, Tolosa-Hunt syndrome, ocular motor cranial neuropathies, facial nerve palsy, myasthenia gravis, ophthalmic vein thrombosis, and optic neuritis.[2,3,10,12,15-17,19,20,22-26,33]

In a single center retrospective study from South Korea, 17 eyes from 16 patients who developed ocular disease within 1 to 7 days of receiving the COVID-19 vaccine had the following diagnoses: retinal vein occlusion (n=9 eyes), retinal artery occlusion (n=1 eye), uveitis (n=3 eyes), and angle-closure glaucoma (n=4 eyes). Twelve patients received the Janssen COVID-19 vaccine and 4 patients the Pfizer-BioNTech COVID-19 vaccine. Ten of the 16 patients developed ocular side effects following administration of the initial vaccine dose.[7]

From a neurological perspective, a systemic review of the literature by Sriwastava et al found that the most common post-COVID-19 vaccination central nervous system complication was cerebral venous thrombosis, followed by demyelination, i.e., transverse myelitis, acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS), or NMOSD.[30] Based on an analysis from the vaccine adverse event reporting system (VAERS), there were only 0.03% of neurological adverse events reported from approximately 306 million doses administered, with most cases associated with the Janssen COVID-19 vaccine. The analysis also found that the risk of neurological events following SARS-CoV-2 infection was 617 times higher than after COVID-19 vaccination.[11]

Post-vaccination-associated optic neuritis has been reported following a number of antiviral vaccines: rabies, influenza, measle, human papilloma, *Herpes zoster*, measles/mumps/rubella, tetanus/diphtheria/pertussis, and hepatitis B.[6,31] Rosziewicz and Shoenfeld identified 48 cases reported in the literature of post-vaccination optic neuritis between 1949 and 2018, and 537 cases from the VAERS database.[27] Most of the cases were isolated optic neuritis but in some cases the optic neuritis preceded the development of MS, NMOSD, or ADEM. The mean interval time between vaccine injection and onset of optic neuritis in the VAERS

database was approximately 26 days. The authors were not able to state definitively whether there was a causal relationship between vaccination and the development of optic neuritis.

Lotan and associates identified 61 cases from the literature of post-COVID-19 vaccination-associated optic neuritis, which included optic perineuritis and MOG IgG positivity.[18] Martinez-Alvarez et al collected and analyzed data from 55 patients in 10 countries who received 3 COVID-19 vaccines (AstraZeneca, Pfizer-BioNTech and Sinovac) and then developed optic neuritis.[D] The AstraZeneca vaccine had the highest number of cases (n=38) followed by Pfizer-BioNTech (n=13) and then Sinovac (n=4). Forty-four patients were White, with a median age of 44 years. Ten patients had a history of autoimmune disease. The median time from vaccine injection to onset of optic neuritis was 18 days. Forty-one patients had unilateral optic neuritis, and 14 had bilateral optic neuritis. Sixteen of 20 patients demonstrated optic nerve enhancement, and 11 of 29 patients had optic nerve sheath enhancement on MRI. Pain was present in 4 patients, and 27 patients had optic disc edema. Fourteen patients were positive for MOG IgG (none for AQP-4 IgG). The mean visual acuity at presentation was 20/200 with a mean final visual outcome of 20/20 (5 patients had a final visual acuity of <20/200). Forty patients were treated with IV steroids, 8 with oral steroids, and 6 with PLEX. Visual outcome based on treatment type was not reported.

Despite the many published case reports and case series, the incidence of ocular and neuro-ophthalmic complications following COVID-19 vaccination is low[34]; however, patients who have had a side effect after the first dose may be disinclined to have additional vaccination doses. Aside from research that supports a low risk of a repeat severe immediate allergic reaction from a second dose in patients who developed a severe immediate allergic reaction from the first dose, the risk of a repeat systemic inflammatory event from a second dose in patients who had a systemic inflammatory event from the first dose is unknown.[8] The American College of Rheumatology convened a task force to develop guidelines for COVID-19 vaccination in patients with rheumatological diseases, and based on a moderate level of consensus it was stated that, "a theoretical risk exists for autoimmune and inflammatory rheumatic disease flare or disease worsening following COVID-19 vaccination; however, the benefit of COVID-19 vaccination for rheumatic and musculoskeletal disease patients outweighs the potential risk for new onset autoimmunity".[E]

In summary, post-COVID-19 vaccine-associated optic neuritis is uncommon but should be in the differential diagnosis of any patient presenting with optic neuritis, and inquiry regarding recent vaccination should be sought. Our case supports the argument for a link between COVID 19 vaccination and the development of optic neuritis but in of itself does not establish causation; however, the literature on post-vaccination associated optic neuritis seems to support cause and effect in some patients. It appears that the visual outcome is very good for most patients with post-COVID-19 vaccine-associated optic neuritis. The initiation of treatment with IV steroids and possibly PLEX should be determined by the severity of visual loss and based on the guidelines for acute inflammatory demyelinating optic neuritis.[4] Patient counseling regarding additional future COVID-19 vaccination should be done on a case-by-case basis with a risk-benefit analysis requiring mutual decision making.

9. Method of Literature search

We performed a search of current and previous literature via PubMed (https://pubmed.ncbi.nlm.nih.gov/). The main search words were ["vaccine" or "COVID-19" or "SARS-CoV-2" or "side effects"] and ["optic neuritis" or "autoimmunity"]. Inclusion criteria included articles with English or translatable abstracts, involved the following subjects: optic neuritis, vaccination, COVID-19, SARS-CoV-2, adverse events, and autoimmunity, that were published within indexed scientific journals. Exclusion criteria included articles without possibility of English translation or inaccessible by our institution's subscription access and editorials or articles not published in scientific journals.

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Disclosure

None of the authors have a conflict of interest in the material contained in the manuscript.

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A B S T R A C T

A 43-year-old woman presented with decreased vision in the right eye associated with painful eye movements 10 days after receiving her first dose of Pfizer-BioNTech coronavirus disease 2019 (COVID-19) vaccine (Pfizer Inc, New York, NY). Two days later she developed painful loss of vision in the left eye. Clinical presentation and magnetic resonance imaging findings were consistent with bilateral optic perineuritis transitioning to optic neuritis. Extensive evaluation including aquaporin-4 immunoglobin G (IgG), myelin oligodendrocyte glycoprotein IgG, and lumbar puncture was unrevealing. Visual acuity at nadir was counting fingers in both eyes, but after receiving intravenous steroids and plasma exchange vision eventually improved to 20/20 in each eye, although she was left with inferior visual field defects and bilateral optic disc pallor. This case highlights the diagnostic challenge in the evaluation of atypical optic neuritis with a review of post-COVID-19 vaccination-associated optic neuritis.