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Unilateral recurrent central serous chorioretinopathy (CSCR) following COVID-19 vaccination- A multimodal imaging study☆

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ABSTRACT

Corona virus disease-19 (COVID-19) vaccines have been approved for emergency use. Ocular adverse effects following the vaccines have been reported.

Purpose: To report an unique case of recurrent central serous chorioretinopathy following both doses of COVID-19 vaccine.

Observations: A 40-year-old male presented with blurring of vision in the left eye during 2 days following COVISHIELD™ (Serum Institute of India). He had a previous history of central serous chorioretinopathy in the right eye 2 years back and was treated with micropulse laser. Ocular examination showed a best corrected visual acuity of 20/20 right eye and 20/60 left eye. Fundus evaluation of left eye showed central serous chorioretinopathy. Spectral domain optical coherence tomography of the left eye revealed neurosensory detachment. Fundus fluorescein angiography of the left eye showed multiple window defects and ink-blot appearance in the macula. Oral eplerenone 50mg once a day for a month showed significant reduction in the subretinal fluid. Patient developed central serous chorioretinopathy in the left eye 3 days after 2nd dose of COVISHIELD™.

Conclusion and Importance: CSCR following vaccination may be a temporal event. In our patient it occurred following the vaccination. This is the first case of a recurrent CSCR after either dose of COVID-19 vaccination. Ocular symptoms after vaccination warrant a thorough eye evaluation.

1. Background

Corona virus disease −19 (COVID-19) pandemic has taken a toll on the global health and finances with deaths exceeding over 3.3 million worldwide.[1] To combat the pandemic, vaccines have been developed to tackle this global health emergency. The COVID-19 vaccines have been approved for emergency use in various countries.

Ocular adverse effects observed following administration of COVID-19 vaccines include episcleritis, scleritis, anterior uveitis, acute macular neuroretinopathy, paracentral acute middle maculopathy, central serous chorioretinopathy (CSCR), ophthalmic vein thrombosis, Vogt-Koyanagi-Harada disease (VKH), acute zonal occult outer retinopathy (AZOOR), multifocal choroiditis, arteritic anterior ischemic optic neuropathy (AAION), non- arteritic anterior ischemic optic neuropathy (NA-AION), Graves disease, cranial nerve palsies like facial or abducens nerve palsies, acute zoster ophthalmicus (HZO), acute retinal necrosis and multiple evanescent white dot syndrome(MEWDS).[2–13]

CSCR has been reported following Pfizer-BioNTech™ mRNA COVID-19 vaccine (BNT162b2), Sinopharm™ inactivated COVID-19 vaccine and Astra Zeneca™ COVID-19 vaccine.[2–5]

We report the first case of recurrent unilateral acute CSCR following administration of COVISHIELD™ vaccine, a ChAdOx1 nCoV- 19 Corona Virus Recombinant Vaccine.[14]

2. Case report

A 40-year-old Asian Indian male presented to us with painless, acute onset of blurring of vision with distortion in his left eye (OS) during 2

☆ The study was approved by the ethics committee of our tertiary hospital where the study was done vide Ethics Committee approval number: C/2020/09/09. Patient's written informed consent for participation and publication of the study data was obtained.

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days. He had the first dose of COVISHIELD™ 2 days prior to onset of ocular symptoms and had no other systemic issues. Two years earlier, he had CSCR in the right eye (OD) and was treated with micropulse laser elsewhere and symptoms had resolved 20 days later. At this presentation, he was not on any systemic medications including steroids or had a recent stressful incident. He was an Arabic language scholar involved in teaching. Systemic evaluation was within normal limits. Psychiatrist assessment was done using an online interactive resource available at https://openpsychometrics.org/tests/AB.php did not reveal "type A personality" features. Ocular examination revealed best corrected visual acuity (BCVA) of 20/20 in OD and 20/60 in OS. Anterior segment evaluation of both eyes (OU) was within normal limits. Posterior segment examination of OS showed few pigmented cells in the anterior vitreous and a well demarcated round elevated area at the macula with loss of foveolar reflex suggestive of CSCR with retinal pigment epithelial (RPE) alterations (Fig. 1A). OD showed few RPE alterations in the macula.

Spectral domain optical coherence tomography (SD-OCT) of OS revealed neurosensory detachment (NSD) with subretinal fluid (SRF) and few pigment epithelial detachments (PEDs) at the macula (Fig. 1B). Central macular thickness was 752μm. SD-OCT of OD showed multiple PEDs without any evidence of SRF. Enhanced depth imaging with SD-OCT showed a pachychoroid with dilated vessels in the Haller layer in OU. Fundus fluorescein angiography (FFA) of OS (Fig. 1C) showed an arm to retina time of 24 seconds, multiple RPE window defects at supero-temporal quadrant in the macula, multiple ink-blot appearances in the macula and pooling in a single ink blot with increasing hyper-fluorescence in the late phases. Similarly, OD FFA also revealed RPE window defects at superior and inferior quadrants of the macula. OCT Angiography (OCTA) of OS showed shadow effect on deep capillary plexus, outer retina, choriocapillary (CC) slabs. Multiple bright spots were more evident in choriocapillary layer (Fig. 1D).

Multicolor imaging (Fig. 1E) showed few bright refractile dendritic-like pattern at the posterior pole on pseudo-color image. A well-defined round greenish area was observed around fovea measuring around 3-disc diameters at its maximum dimension. Greyish halo around the fovea was noted in blue and green reflectance image with the presence of bright refractile dendritic pattern. The margin of this halo was better defined in infrared reflectance image suggesting a deeper pathology.

Blood investigations (normal values in brackets) included total serum bilirubin (mg/dL)1.1 (0–1.0), Serum glutamic oxaloacetic transaminase (SGOT) (units/L) 31 (8–45), Serum glutamic pyruvic transaminase (SGPT) (units/L) 40(5–40), Serum cortisol (μg/dL) 12.98 (5–25), Serum albumin (gm/dl) 4.2 (3.5–5.3), Serum globulin (gm/dl) 2.4 (2.3–3.5), Blood urea (mg/dL) 21 (14.0–40.0) Serum creatinine (mg/dL) 1.2 (0.6–1.4).

The patient was started on oral eplerenone 50 mg once daily as the patient wanted to resume his mentoring activities.

Patient was not keen on focal laser and also the fact that he had multifocal leaks it was not considered as an option.

At 1 month follow up, the color fundus photograph showed resolved elevation of the macula (Fig. 2A), with BCVA improving to 20/20 with eplerenone treatment and there was significant reduction in the SRF on SD-OCT (Fig. 2B). Central macular thickness had reduced to 296 μm. OCTA (Fig. 2C (1–4) showed reduction of the shadowing effect with projection of choriocapillaris (CC) on the outer retina due to reduction of fluid (Fig. 2C4). There were however few projection artefacts seen as well. Choroidal neovascular membrane was not seen.

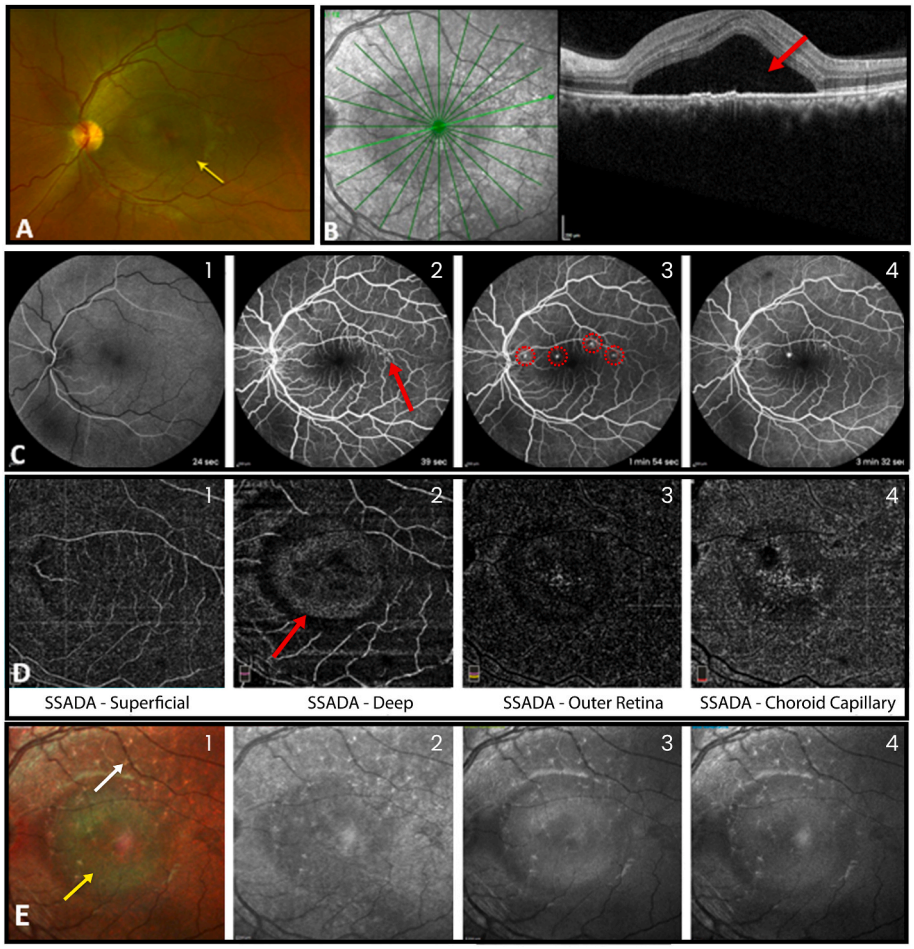

Fig. 1. Imaging findings of left eye on first presentation (A) Colored fundus photograph showing well demarcated round elevated area (yellow arrow) at macula with loss of foveolar reflex, (B) SD-OCT showing; (a) Neurosensory detachment (NSD) with subretinal fluid and few pigment epithelial detachments (PEDs) at macula (red arrow), (C) Fundus fluorescein angiography (FFA) showing; (1) delayed arm to retina time of 24 sec, (2) multiple RPE window defects (red arrow) at supero-temporal quadrant in macula, (3) multiple ink-blot appearances in the macula (red dotted circles), and (4) pooling in a single ink blot with increasing hyper-fluorescence in the late phases (D) OCTA(1–4) showing dark halo indicating a shadow effect on deep capillary plexus, outer retina, choriocapillary slabs with multiple bright spots in choriocapillary layer (E) Multicolor imaging (1) Pseudo-color imaging showing well defined round greenish area around fovea with few bright refractile dendritic-like pattern at the posterior pole, (2) Infrared reflectance showing dark well-defined halo around fovea, (3) & (4) Blue and Green reflectance image showing greyish halo around the fovea. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

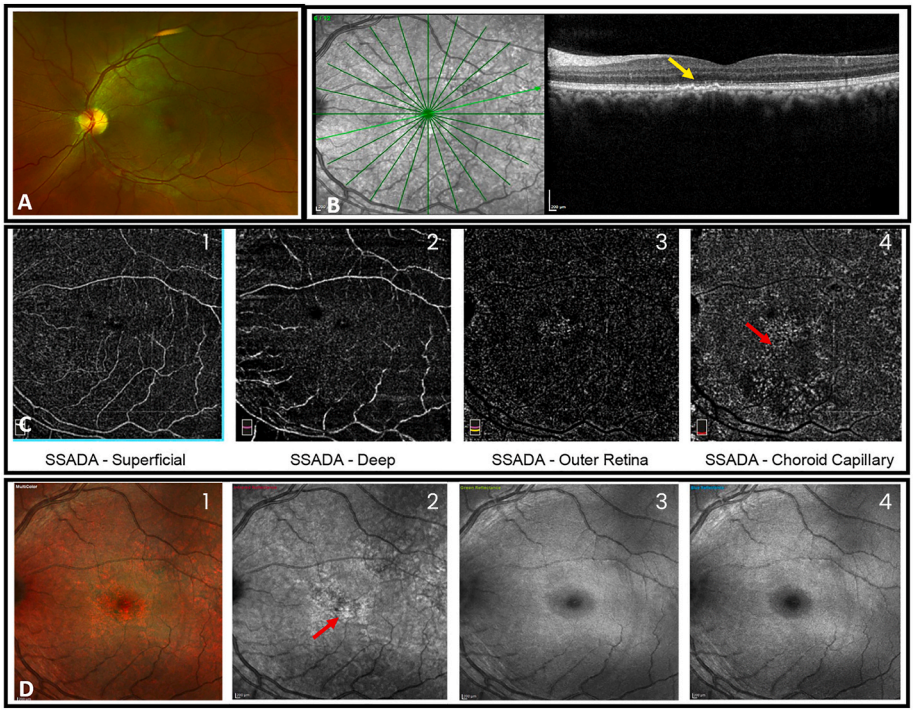

Fig. 2. Imaging findings of left eye at 2 months follow up (A) Colored fundus photograph showing reduction of round elevated area at the macula (B) SD-OCT showing resolution of CSCR with RPE irregularities (C) OCTA showing reduction of the shadowing effect with projection of choroidal vessels on the outer retina due to reduction of fluid in the last follow up, (D) Multicolor imaging (1) Pseudo-color imaging showing reduction in greenish halo around foveola with disappearance of refractile dendritic pattern, (2) Infrared reflectance image showing whitish granular appearance around fovea suggestive of some RPE abnormality, (3)&(4) Blue and Green reflectance image showing reduction in greyish halo around the fovea. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

The greenish halo around the fovea became less evident with disappearance of refractile dendritic pattern on pseudo-color imaging. Likewise, the greyish halo seen in the blue and green reflectance multicolor imaging had also reduced. However, a striking feature was noted in the infrared reflectance image which showed whitish granular appearance around fovea suggestive of RPE abnormalities (Fig. 2D).

Oral eplerenone was continued for another 1 month. At 2 months follow up, there was complete resolution of the detachment. Pigment epithelial detachments were still present.

Six weeks later, he took the second dose of COVISHIELD™ and developed severe body ache on the same day and blurring of vision 3 days later.

Ocular evaluation revealed best corrected visual acuity (BCVA) of 20/20 OD and 20/30 in OS. Anterior segment evaluations of OU were within normal limits. Posterior segment examination of OS showed CSCR (Fig. 3A).

After the second dose of the vaccination, SD- OCT of OS showed a smaller NSD (Fig. 3B) and few pigment epithelial detachments (PEDs) at

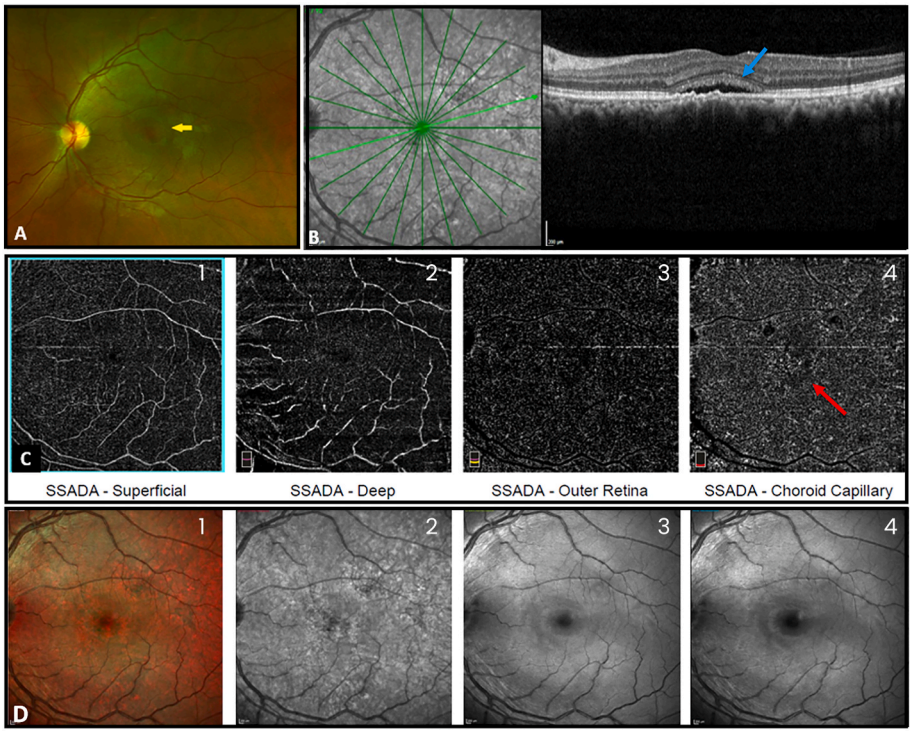

Fig. 3. Imaging findings of left eye on the final visit on day 3 after 2nd dose of COVID-19 vaccination (A) Color fundus photograph well demarcated round elevated area (yellow arrow) at macula with loss of foveolar reflex (B) Spectral domain optical coherence tomography (SD-OCT) showing smaller NSD compared to the first presentation
(C) OCTA showing normal superficial (1) and deep capillary plexus (2),with no evidence of choroidal neovascular membrane in the outer retina (3) or choriocapillaries (4). There are areas of dark spots in the choriocapillaries indicating shadow effect due to presence of sub retinal fluid. (D) Multicolor imaging (1) Pseudo-color imaging showing absence of greenish halo around foveola, (b) Infrared reflectance image showing whitish hyper-reflective dots around fovea and in the posterior pole indicative of RPE atrophy interspersed with dark spots, 3 & (4) Blue and Green reflectance image showing absence of greyish halo around the fovea seen at first presentation. . (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

the macula. Central macular thickness was 345 μm. Multicolor Imaging (Fig. 3C). At this presentation, the patient was not keen on FFA/intervention and wanted to observe as his symptoms were not as severe as the first presentation. The patient was subsequently lost for follow up.

3. Discussion

To the best of our knowledge, we report the first case of recurrent unilateral acute CSCR following second dose of COVISHIELD™ vaccination in an Asian Indian male. Acute onset CSCR have been recently reported following the first dose of COVID-19 vaccination, 2 cases following Pfizer-BioNTech™ messenger ribonucleic acid (mRNA) COVID-19 vaccine[2,5] and the other following Sinopharm™ inactivated COVID-19 vaccine.[3] A 41-year-old Asian female developed serous detachment in one eye and disc oedema in the other eye following Astra Zeneca™ COVID-19 vaccine.[4]

These case reports did not observe multifocality in CSCR unlike in our patient. Fowler et al. managed their patient with 50mg spironolactone and reported complete resolution of SRF at 3 months follow up.[2]

Activation of mineralocorticoid receptors in choroidal endothelial cells due to exogenous mineralocorticoids have been implicated in CSCR[15,16] which leads to choroidal vasodilation and fluid accumulation within the retina. Spironolactone and eplerenone are mineralocorticoid antagonists and may have a role in the treatment of CSCR.

Eplerenone is a selective mineralocorticoid antagonist with higher affinity and lesser side effects as compared to spironolactone.[17]

Eplerenone (50mg) was started in our patient at the time of the first consultation and we observed significant resolution of SRF within a month. Eplerenone has lower affinity for progesterone, androgen, and glucocorticoid receptors, thus associated with lesser sexual side effects unlike spironolactone.[17]

Our case comes in the category of **probable** adverse drug reaction (total score 5–8) according to Naranjo Algorithm - ADR Probability Scale.[18]

Vaccine-associated CSCR has also been reported in the past with the vaccines against smallpox, influenza, yellow fever and anthrax.[2,19,20]

CSCR associated with mRNA vaccines showed elevated serum cortisol levels. Raised serum cortisol level is a common association found with CSCR.[21] This association was encountered in a study on tetanus toxoid vaccination. They postulated that activation of hypothalamic-pituitary-adrenal (HPA) axis occurs following administration of the protein antigen tetanus toxoid resulting in increase in the plasma adrenocorticotrophic hormone (ACTH) and serum cortisol.[2] Cases of CSCR following COVID-19 vaccination did not have raised serum cortisol level which was also noted in our patient.[2,3]

Fischer et al. in their study found an increased permeability of brain microvascular endothelial cells. This was associated with extracellular RNA mediated through vascular endothelial growth factors (VEGFs).[22] Based on this concept, Fowler et al. hypothesised that free extracellular messenger ribonucleic acid (mRNA) could be responsible for the leaky choriocapillaris.[2] Additionally, mRNA may also enhance blood coagulation and thrombus formation.[23]

Inflammatory cytokines associated with vaccination have also been postulated to play a role as seen with influenza vaccine. Moreover, pain at injection site and raised body temperature were also associated with a pro-inflammatory cytokine release.[2]

COVID-19 vaccines have adjuvants like aluminium based salts, toll-like receptors agonists, emulsions or other novel molecules with distinct physicochemical properties which can regulate the strength, duration and type of immune response.[24]

There are three methods to make a vaccine. These include the whole virus, parts of the virus which elicit an immune response or the genetic material of the virus.[25]

The whole viral approach has 3 methods which include *inactivated vaccine* (where the virus has been neutralised by the chemicals Eg; Polio, flu vaccines), *live attenuated vaccine* (where the virus has been weakened or a similar virus is used Eg Measles, Mumps, Rubella),*viral vector vaccine* (uses a safe virus to deliver specific sub-parts – called proteins – of the germ of interest so that it can trigger an immune response without causing disease).[25] The Janssen/Johnson & Johnson COVID-19 vaccine/AstraZeneca (COVISHIELD™) and the University of Oxford are vector COVID-19 vaccines. Chimpanzee adenovirus vector displaying Spike protein(S protein) on its surface is used.[25]

A subunit vaccine is one that only uses the very specific parts (the subunits) of a virus or bacterium that the immune system needs to recognize. It doesn't contain the whole microbe or use a safe virus as a vector. The subunits may be proteins or sugars. Novovax™ is a recombinant, protein-based nanoparticles and their proprietary Matrix-M adjuvant.[25]

A nucleic acid vaccine delivers a specific set of instructions to our cells, either as DNA or mRNA, for them to make the specific protein that we want our immune system to recognize and respond to. Both the Pfizer-BioNTech™ and the Moderna™ COVID-19 vaccines use mRNA.[25]

Fowler et al. also hypothesised that presence of polyethlene glycol (PEG) in Pfizer-BioNTech COVID-19 vaccine could be responsible for the occurrence of acute CSCR.[2] In murine models subretinal PEG-8 may lead to choroidal neovascularization and choroidal vessel thickening by activating complement pathway.[2] Nonetheless, COVISHIELD™ vaccine does not contain PEG but polysorbate 80 and is useful for patients with PEG allergy. The excipients in COVISHIELD™ vaccine may regulate the immune response and also possible side effects.[14]

CSCR has also been reported in patients treated with steroids for COVID-19.[26,27] The mechanism however is different from those following vaccines. Steroids have a definite causal mechanism for CSCR, while COVID-19 per se has no role.

4. Conclusion

We would like to conclude by stating that COVISHIELD™ may not have a proven causal role in CSCR and may be only a temporal event. CSCR is usually a self-limiting condition, but may need treatment with oral eplerenone/focal laser if faster resolution is required as in our patient. Systemic work up and assessment of Type A personality may be needed in certain cases.

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Patient's consent

Written and informed consent obtained for publication.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

None.

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