Paracentral acute middle maculopathy in Susac syndrome after dual exposure to SARS-CoV-2 antigen

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SUMMARY

We report a case of Susac syndrome after SARS-CoV-2 infection and subsequent vaccination that presented with meningitis and retinal microembolisation in the form of paracentral acute middle maculopathy (PAMM). After presenting with headache, fever and myalgia followed by scotomata, a woman in her 50s was hospitalised for meningitis; she had had mild COVID-19 infection 2 months prior to admission, having received the first vaccine dose 1 month prior to the neurological manifestation. Eye fundus examination and optical coherence tomography were suggestive of PAMM. D-dimer levels and erythrocyte sedimentation rate were elevated. Before infectious investigation results were available, she was started on empirical antibiotic and antiviral treatment. Having ruled out infectious causes, she was started on high-dose prednisolone. After 1 month, there was partial resolution of retinal lesions. This case highlights that exposure to SARS-CoV-2 antigen may be related to this rare syndrome; treatment with steroids may improve central and retinal impairment.

BACKGROUND

Retinal findings following SARS-CoV-2 infection have been reported and are mostly related to the hypercoagulable state and consequent thrombotic microangiopathy.[1] Paracentral acute middle maculopathy (PAMM) is considered a tomographic finding of the acute phase of retinal intermediate and deep capillary plexuses ischaemia and has been previously associated with SARS-CoV-2 infection.[2] PAMM has also been described as a complication in association with Susac syndrome, a rare autoimmune microangiopathy of the brain, retina and inner ear that typically occurs in young women.[3] We herein report a case of Susac syndrome that presented with the atypical PAMM manifestation of retinal compromise, leptomeningitis and inner ear impairment, following dual exposure to SARS-CoV-2 antigen, the first being acute infection, with subsequent vaccination with an inactivated coronavirus vaccine. The highlight of this case is the presentation of this rare autoimmune complication related to a hypercoagulable state after exposure to the SARS-CoV-2 antigen.

CASE PRESENTATION

A woman in her 50s, a physician specialising in pathology, presented to the emergency department with fever, myalgia, headache and scotoma in the left eye (LE). Two months prior to admission, she had a mild case of SARS-CoV-2 infection which did not require hospitalisation. After a 1-month interval, following the Brazilian National Board of Health recommendation, she received the first dose of an inactivated virus COVID-19 vaccine (Sinovac Biotech, China) 1 month prior to admission. On emergency department admission, she underwent clinical, laboratorial and imaging investigation. Of note, she had a raised D-dimer level (1877 μg/mL, normal values <500), erythrocyte sedimentation rate (ESR) of 51 mm, raised factor VIII activity (169%, normal value <150%) and lymphocytopenia (600 cells).

Admission's orbit MRI showed a discrete gadolinium (Gd) enhancement of the perineural region in the orbitary segment of both optic nerves that was relatively symmetric, suggestive of perineuritis. Additionally, the brain MRI demonstrated a tenuous increase in signal intensity of posterior supratentorial cortical sulcus in the post-Gd fluid-attenuated inversion recovery (FLAIR) sequence and Gd enhancement of the internal acoustic canal, compatible with leptomeningitis. A subsequent MR angiography of intracranial vessels was unremarkable, except for the identification of increased signal intensity of the left cochlea in post-Gd FLAIR acquisition (figure 1).

INVESTIGATIONS

Laboratory investigation included serological tests and a nasal swab to rule out infections; the extensive infectious work-up was negative, including a negative test for SARS-CoV-2. Extensive rheumatological investigation was also negative.

Cerebrospinal fluid (CSF) analysis revealed a lymphocytic meningitis (70 cells/mm^3, 80% lymphocytes) with a high protein level (116 mg/dL) and normal glucose concentration. A molecular panel for meningitis/encephalitis (FilmArray) was carried out and resulted negative for bacteria, viruses, fungi, *Mycobacterium tuberculosis* and toxoplasma. Cultures for bacteria, mycobacteria and fungi were negative as well; SARS-CoV-2 was not detected in the CSF.

The intrathecal albumin index was 28.21 (normal value below 9.0); immunoglobulin G level was normal and the Felgenhauer and Reiber diagram suggested compromised blood–brain barrier without IgG production in the central nervous system. The CSF IgG level was high (9.60 mg/dL, normal values 0.30–3.40).

After 3 days of hospital admission, she complained of scotoma also in the right eye (RE), and visual acuity testing revealed 20/25 in RE and 20/100 in the LE. Anterior segment examination was

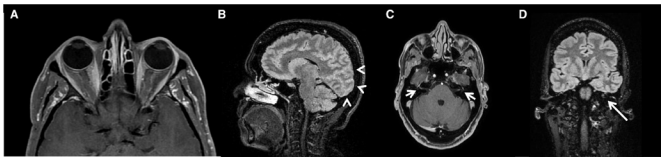

Figure 1 Neuroimaging. Brain and orbit MRI at the patient's admission showing discrete bilateral contrast enhancement of the perineural tissue surrounding the orbitary segment of the optic nerve (A); hypertense FLAIR post-Gd signal of posterior supratentorial cortical sulcus (B, arrowheads); bilateral hyperintensity of the internal acoustic canal in the FLAIR post-Gd acquisition (C, short arrows). Subsequent brain MRI with increased signal intensity of the left cochlea on a FLAIR post-Gd sequence (D, arrow). FLAIR, fluid-attenuated inversion recovery; Gd, gadolinium.

unremarkable. Dilated fundus evaluation showed subtle white lesions at the macula in RE and marked lesions in LE. Optical coherence tomography (OCT) showed focal hyper-reflective change in the inner nuclear layer and inner plexiform layers consistent with PAMM. Fluorescein angiography and OCT angiography showed enlargement of the foveal avascular zone (FAZ) bilaterally (figure 2).

Full-field eletroretinogram (ERG) showed a mild reduction of the ganglion cell function with normal photoreceptor responses

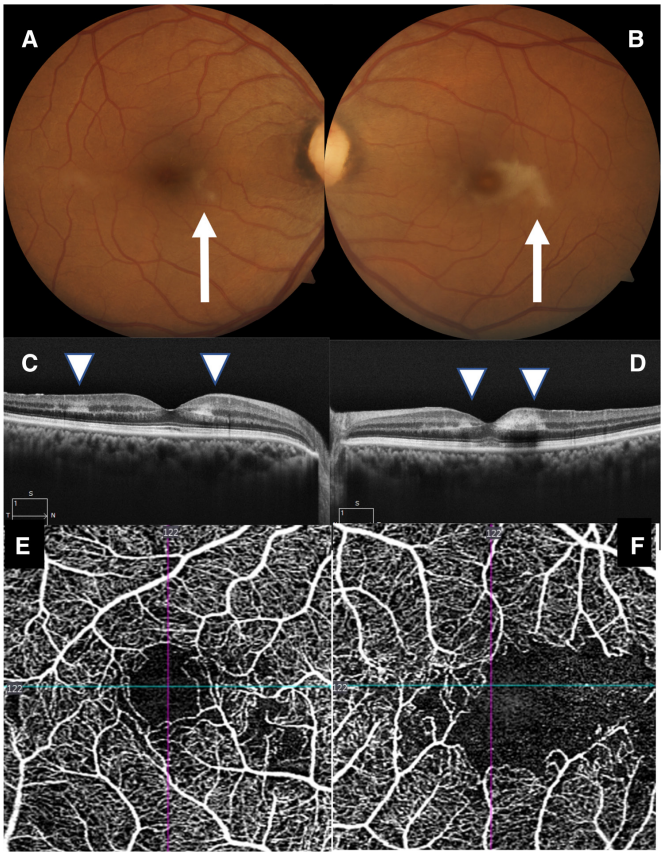

Figure 2 Baseline colour fundus photographs, OCT, OCT angiography. Colour fundus photographs depicting white lesions in the fovea of (A) the RE and (B) the LE (arrows); OCT showing intraretinal hyper-reflective band-like lesions affecting the middle layers of the retina (arrowheads) of (C) the RE and (D) the LE; OCT angiography depicting enlargement of foveal avascular zone of (E) the RE and (F) the LE. LE, left eye; OCT, optical coherence tomography; RE, right eye.

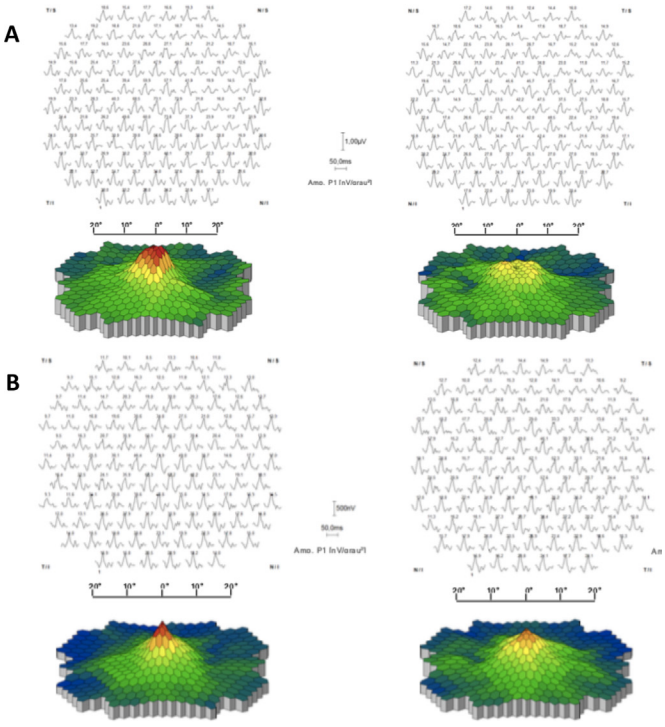

Figure 3 Multifocal ERG. (A) Multifocal ERG performed during the acute phase showing decreased amplitudes in both eyes, more accentuated in the left eye. (B) Multifocal ERG performed 6 moths after the initial presentation, showing diffuse worsening of responses in both eyes, compatible with presumed autoimmune retinopathy. ERG, eletroretinogram.

in both eyes; multifocal ERG showed reduced foveal and parafoveal responses in both eyes, the LE being more affected (figure 3).

The patient also complained of hearing impairment, and audiometry showed bilateral neurosensory loss in frequencies between 3000 and 8000 Hz (right ear) and 2000 and 8000 Hz (left ear). Speech recognition threshold was obtained at 20 dB, bilaterally. Speech recognition percentage index was 88% at 50 dB (right) and 84% at 50 dB (left) for monosyllables and 96% at 5 dB (right and left) for disyllables. Auditory brainstem response was normal.

DIFFERENTIAL DIAGNOSIS

Laboratory investigation for etiologic agents ruled out SARS-CoV-2 and other respiratory pathogens (enterovirus, rhinovirus, influenza, metapneumovirus, respiratory syncytial virus, *Bordetella pertussis*, *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*), dengue, HIV, syphilis, hepatitis C, Epstein-Barr virus, CMV, *Bartonella*, toxoplasma, tuberculosis (interferon-gamma release assay) and coxsackievirus. Rheumatological investigation resulted in the following negative results: antinuclear antibodies (ANA), rheumatoid factor, antineutrophil cytoplasmic antibodies (ANCA), anti-Ro, anti-La, anticardiolipin, anti-beta2 glycoprotein and serum anti- myelin oligodendrocyte glycoprotein (MOG).

Besides having ruled out infectious causes for meningitis/encephalitis with the molecular panel, metagenomic CSF analysis did not detect RNA associated with pathogenic microorganisms either.

Due to the severity of clinical presentation, empirical antibiotic and antiviral treatment was introduced before test results became available. The patient received empirical intravenous

antibiotic therapy with ceftriaxone (100 mg/kg/day) and ampicillin (200 mg/kg/day), sulfamethoxazole–trimethoprim (800–160 mg two times per day) and the antiviral acyclovir (10 mg/kg three times a day).

TREATMENT

Three days after empirical therapy was started, investigation came back negative for infectious causes; having ruled out infection, empirical therapy was stopped.

Due to the clinical presentation of central nervous system, retinal and cochlear involvement, the exclusion diagnosis of Susac syndrome was made, and the patient was started on intravenous pulse therapy, which consisted of methylprednisolone (1 g/day) for 5 days and prophylactic enoxaparin 40 mg/day. After 5 days of intravenous pulse therapy with methylprednisolone, she noted an improved vision: 20/20 RE and 20/30 LE; she also showed reduction in the ESR and normalisation of CSF parameters (3 cells/mm^3 and 22 mg/dL of protein). After completing intravenous steroid treatment, she received oral steroids, starting with 60 mg/day and gradual tapering down (10 mg/week).

OUTCOME AND FOLLOW-UP

The patient presented 1 month later with improvement of visual acuity (20/25 RE and 20/30 LE); the affected areas on the retina evolved with resolution of the white lesions and very subtle retinal thinning, which is consistent with the natural history of PAMM and better evidenced at the follow-up OCT scan. Due to the favourable clinical response to steroid therapy, it was considered there was no need to introduce further immunosuppressive therapy. OCT angiography showed persistence of FAZ enlargement (figure 4).

After 6 months of the initial complaints, there was improved visual acuity (20/15 OU); ERG showed diffusely decreased responses in both eyes compatible with sequelae of the original autoinflammatory insult (figure 3).[4 5] During steroid tapering, the patient presented with a headache, and 10 mg/day was found to be the cut-off dose. There were no other neurological symptoms or neuroimaging signs of disease activity. Despite not receiving chronic immunosuppressive therapies, the patient did not experience any relapses after 6 months of follow-up.

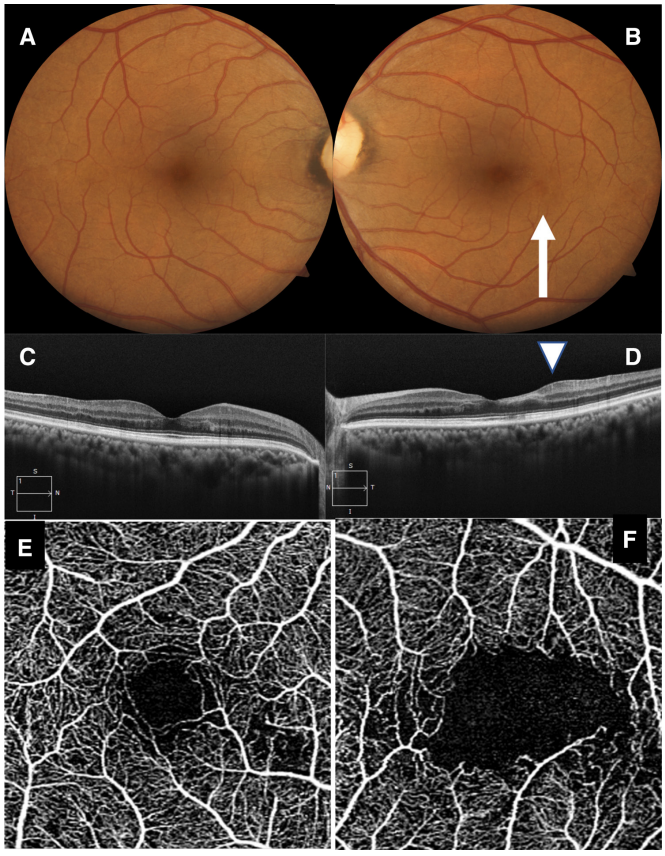

Figure 4 Follow-up colour fundus photographs, OCT, OCT angiography. Colour fundus photographs depicting (A) resolution of white lesions in the RE and (B) subtle thinning of the retina in the LE (arrow); OCT showing (C) resolution of intraretinal hyperreflective bands in the RE and (D) thinning of the middle layers of the retina (arrowhead) in the LE; OCT angiography showing sustained enlargement of the foveal avascular zone of (E) the RE and (F) the LE. LE, left eye; OCT, optical coherence tomography; RE, right eye.

DISCUSSION

Even though rare, we considered Susac syndrome as the most likely diagnosis after the extensive work-up ruled out other causes for the central, retinal and auditory involvement. Autoimmune-mediated microvessel occlusion is considered the hallmark of Susac syndrome.[6] A prothrombotic state has been found during and after SARS-CoV-2 infections and vaccination as well, and is a significant cause of morbimortality related to COVID-19.[7] SARS-CoV-2 infection is also believed to be the trigger for autoimmune manifestations.[8] SARS-CoV-2 causes endothelial cell dysfunction by attaching to the ACE receptor on endothelial cells and triggering a cytokine cascade which leads to coagulopathy[6]; additionally, raised D-dimer values, commonly found in SARS-CoV-2 infection, lead to the activation of the coagulation cascade secondary to systemic inflammation and are related to the thrombotic milieu which ultimately may have caused retinal capillary plexus ischaemia leading to PAMM.[2] In our case, we believe Susac syndrome, which is considered an autoimmune disease, manifested in the spectrum of post-COVID-19 inflammatory vasculopathy.[9] This case has raised the question of whether further antigen exposure in the form of vaccination with inactive virus after a recent episode of SARS-CoV-2 infection has played a role in triggering the autoimmune endotheliopathy and the prothrombotic state.[10]

PAMM is associated with the acute phase of ischaemia of intermediate and deep capillary plexuses and has been reported as a manifestation of COVID-19 and raised blood D-dimer levels[2]; it has also been recently reported in a rare association with Susac syndrome,[3] itself a rare condition.

Even though ocular complications including PAMM have been reported shortly after vaccination with an inactivated COVID-19 vaccine, a causal relationship generally could not be established[11]; furthermore, so far, over 1.5 billion doses of COVID-19 vaccinations have been administered worldwide and likely will save hundreds of thousands of lives, hopefully putting an end to the pandemic. Many retinal abnormalities reported after vaccination are seen occasionally in unvaccinated patients, raising the question whether such findings are coincidental, the establishment of a causal relationship remaining a challenge.[12] On the one hand, central and retinal signs and symptoms should be thoroughly investigated in a patient with prior exposure to COVID-19 infection and/or vaccination; on the other hand, continuous surveillance for adverse events and further studies are needed to possibly confirm or help rule out such associations.

Patient's perspective

- After experiencing blurred vision and noticing a central dark spot, I decided to seek medical attention. I was shocked as the initial exams showed signs of thromboembolism.
- The investigations were intense; however, it was very difficult to accept that all the investigations were negative without a definitive aetiology after 2 weeks in hospital. At least, I have now the results of every single test for viruses (antibodies and genome) currently available in Brazil.
- Leaving the hospital, I was still overwhelmed by the headache and visual loss. The experience shared by some friends in adapting to their visual loss, due to different causes, was fundamental to give me strength to recover from gloomy and dark feelings.

Learning points

- Paracentral acute middle maculopathy may be a retinal sign of Susac syndrome, a rare autoimmune neurological disease that presents with microvessel thromboembolism.
- This case highlights Susac syndrome after COVID-19 infection and subsequent vaccination, with SARS-CoV-2 antigen possibly playing a role in triggering autoimmunity.
- Prompt recognition of a prothrombotic state is critical in patients with post-COVID-19.
- Causality of rare adverse events is still questionable after COVID-19 vaccination and should be interpreted with caution, pending further studies and surveillance.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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