Review of: "Retinal Vasculitis Following COVID-19 Infection: A Systematic Review"

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Potential competing interests: No potential competing interests to declare.

Small English corrections in black

The article reads well and is well done

There are other works done and 3 reviews with the same orientation, so it adds few value

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COVID-19 due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has had significant systemic and ocular implications globally. COVID-19 infection has been associated with both a prothrombotic state and a hyperinflammatory state and the systemic implications include the vascular system of the eye. Numerous retinal and retinal vascular lesions have been reported including hemorrhages, cotton wool spots, arterial and venous occlusions, and vasculitis. We suggest that patients with vasculitis may constitute a distinct subset of patients as compared to patients with vascular occlusion, such **as** retinal arterial or venous occlusion. We conducted a systematic review of **the** literature to identify cases of vasculitis following COVID-19 infection and analyze their specific systemic and ocular features. Methods We conducted a systematic review to identify and analyze cases of retinal vasculitis following COVID-19 infection using the Pubmed database (www.pubmed.gov) for English language articles. This search was performed on 14/5/2023. We used the key-words “retina” AND “vasculitis” AND Vessels” AND COVID-19 to identify potential papers. We analyzed case series, and case reports but excluded reviews, editorials, and non-relevant papers. Demographic findings, systemic features, and ocular lesions detected were entered into a Microsoft Excel sheet. A total of 101 results were identified. Duplicates were excluded (n=1) as were papers that primarily dealt with OCT/OCTA findings (n=53), literature reviews (n=7), vasculitis following COVID-19 vaccination (n=6), vascular occlusions (n=9) or were unrelated (n=15). The PRISMA flowchart is shown in Figure 1

Results 10 papers that describing 12 patients contained enough data to permit analysis and these were included in the study [1][2][3][4][5][6][7][8][9][10] . There were seven female (58.3%) and five male patients (41.6%) with ages ranging from 11 to 66 (mean 42.6 years). Countries of origin included India (three patients, 25%); Turkey (two patients, 16.6%); Switzerland (three patients, 25%); Spain (one patient, 8.3%); Malaysia (one patient, 8.3%); USA (one patient, 8.3%) and France (one patient, 8.3%). Time from onset of the vasculitis following COVID-19 infection varied from three to 150 days (mean 41.0 days). Qeios, CC-BY 4.0 · Article, December 11, 2023 Qeios ID: TWA4JO · https://doi.org/10.32388/TWA4JO

3/8 Systemic investigations commonly included MRI of the brain; infectious disease panels to determine other potential causes of vasculitis (seven patients; all negative results) [1][3][4][5][6][7][9] ; autoimmune disease investigations (largely ANA/ANCA/Anti Ds DNA; seven patients; all negative results) [2][3][5][8][9][10] and chest imaging (x-ray or CT chest). Clinical findings were described in 15 of the 24 eyes of these 12 patients (62.5%) and included anterior uveitis (three eyes, 12.5%) [1][6] ; optic neuropathies (papillophlebitis/edema/optic neuritis: two eyes, 8.3%) [6.7]; retinal infiltrates (five eyes, 20.8%) [1][3][5] and clinical and in most cases, angiographic evidence of unilateral or bilateral retinal vasculitis (15 eyes (62.5%) [1][2][3][5][6][8][10] ; two described as frosted branch angiitis (8.3%)) [4][7] . Visual acuities ranged from 20/20 to CFCF. Virtually all patients (12 patients) underwent fundus photography, OCT and FFA which led to the primary diagnosis. Periocular or systemic steroids were the commonest treatment modality (six patients, 50%) [1][2][3][6][7][9] followed by antivirals (one patient, 8.3%) [4] and anticoagulants (one patient, 8.3%) [8] . No treatment protocols had been described for the remaining patients. seven patients (58.3%) had stable visual outcomes [4][6][7][8][10] whereas five (41.6%) had a full recovery [1][2][3][5][9] . The salient findings of these patients are summarized in Table 1.

Discussion COVID-19 is an infection caused by SARS–CoV 2 that can involve a wide range of organs, especially the vascular system. Endothelial cell inflammation is common and occurs in association with arterioles, veins and capillaries, thus leading to tissue hypoperfusion and consequent injury. COVID-19 infection may thus be associated with several different types of systemic vasculitis. Wong and co-authors, in a systematic review, were able to identify leucocytoclastic vasculitis (LCV), IgA vasculitis, and Kawasaki disease like vasculitis in patients with COVID-19 infection. They described the endothelial inflammation, apoptosis, and dysfunction that commonly **occur** as potential causative mechanisms. Kawasaki disease (KD), a medium vessel vasculitis, is an acute inflammation that largely affects the coronary arteries of children younger than 5 years of age. SARS-CoV-2 infection may potentially cause inflammation within the endothelium triggering the development of KD. IgA Vasculitis is a small-vessel vasculitis that is caused by immune-complexes deposits containing IgA and **is** thought to occur following an upper respiratory tract infection of SARS-CoV-2 and the subsequent upregulation of IL-6. The cytokine storm frequently associated with SARS-COV-2 infection may have a causative role as well. Leukocytoclastic vasculitis (LCV) is a small vessel vasculitis characterized by immune complex-mediated inflammation of skin capillaries usually linked to a rise in IL6 levels [11] . Increasingly many studies and case reports have described the retinal vascular lesions associated with COVID-19. D' Alessandro conducted a systematic review of vascular retinal manifestations and described the cumulative findings of 21 studies. The review described a range of findings that ranged from cotton wool spots **and** hemorrhages to retinal artery and vein occlusions [12] . With an emphasis on retinal vascular occlusions, Yeo and co-workers conducted a systematic review and analyzed the prevalence and clinical findings in such patients. They were able to identify 13 cases of retinal artery occlusion (RAO) and 14 cases of retinal vein occlusion (RVO) from COVID -19 recovered with 50% of both groups lacking any other potentially contributory systemic illness. The authors note that COVID-19 per se is associated with thrombosis possibly via endothelial injury and vessel wall inflammatory reactions. Additional factors include hypercoagulability and platelet activation. They noted that most cases of arterial occlusion present with abnormal coagulation markers likely due to the overwhelming systemic inflammation, whereas patients with retinal vascular occlusion may, in addition, also possess local pathogenic factors such **as** arteriovenous crossing pathology or localized vasospasm. The authors did not describe signs of intraocular inflammation in any of these patients [13] . Similar findings have also been reported following COVID-19 vaccination. Li et

al, in their case series, have described the occurrence of intraocular inflammation following vaccination. 1 case of frosted branch angiitis was observed in this series. They have postulated that molecular mimicry due to an antigenic similarity between vaccine derived proteins and uveal peptides may play a causative role [14] . Bolletta et al described the lesions of 34 patients and reported the presence of two cases of retinal vasculitis. They suggest that an increase in IFN-I secretion may potentially cause or exacerbate autoimmune **phenomena** [15] . We describe the findings of 12 patients with retinal vasculitis following COVID-19 infection. This group of patients appears Qeios, CC-BY 4.0 · Article, December 11, 2023 Qeios ID: TWA4JO · https://doi.org/10.32388/TWA4JO 6/8 to be distinct from the group that presents with retinal vascular occlusion such as RAO/RVO as suggested by the frequent association with other signs of intraocular inflammation such as anterior uveitis or vitritis and a good response to steroids with almost all patients maintaining vision or recovering vision. Potential causative mechanisms include the presence of a prothrombotic state due to endothelial injury or inflammation. The naturally occurring antithrombotic activity of the endothelium may be lost due to direct viral infection or the resultant inflammation [16] . Immune system dysregulation with a subsequent cytokine storm with the production of TNF-alpha and IL-6 may also contribute to **vessel** wall inflammation and thrombosis. We suggest that while multiple pathogenic mechanisms appear to cause retinal vascular pathology and may exist simultaneously, this may cause a clinical spectrum of disease. Patients with a predominantly inflammatory reaction may present with a vasculitic picture, whereas those with a predominantly prothrombotic reaction may present as a vascular occlusion with minimal signs of intraocular inflammation. This group of patients may benefit from primary steroid treatment as opposed to anticoagulant treatment as described for vascular occlusions.