

## **The Eyes Have It: Looking Carefully at the Orbits and SARS-COV-2**

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See also the article by Lecler et al.

Just over one year ago, on December 28, 2019, ophthalmologist Dr. Li Wenliang, of Wuhan Central Hospital, warned medical colleagues via WeChat of 7 patients with eye findings and SARS-like pneumonia. Despite the risk of punishment by government authorities, Dr. Li further advised them to wear protection. Days later, police summoned him to the Public Security Bureau, accusing him of “making false comments...that severely disturbed the social order.” They added, “We solemnly warn you: If you keep being stubborn, with such impertinence, and continue this illegal activity, you will be brought to justice, is that understood?” He was forced to write “Yes, I do” and that he was “spreading rumors”(1). Just days later on New Year’s Eve, the World Health Organization (WHO) China Country office reported a patient cluster that had difficulty breathing and that the outbreak was likely from a Wuhan seafood market in Hubei Province. Twelve days later, after treating a glaucoma patient with coronavirus, Dr. Li developed a fever, cough, shortness of breath, and was hospitalized on January 20. He shared the letter he was forced to sign via Weibo, a microblogging website. The authorities later apologized (1). Two days later, the WHO termed the 2019 novel coronavirus (2019-nCoV). On January 20, 2020, the government of China declared the virus an emergency (2). Ten days later, Dr. Li was confirmed PCR positive for the virus. Tragically, Dr. Li, the ophthalmologist who had the vision to try to protect others from the virus, died from SARs-CoV-2 on February 7, 2020 (3). Five days later, the disease was renamed novel coronavirus COVID-19 (2,3). As of this writing, COVID-19 has caused 87.9 million cases worldwide with 1.9 million reported deaths (4).

Like all ophthalmologists, Dr. Li knew eyes are portals of infection. They allow the disease to spread to others via tears or into the nasal cavity via the nasolacrimal duct. Philosophers call eyes a “window to the soul.” Researchers refer to orbits as “a window to the brain.” This is

because orbital pathology can indicate central nervous system pathology (4). Orbital involvement from COVID-19 was reported in a case series from China, in up to 31.6% of patients. The ocular manifestations of COVID-19 included conjunctivitis, conjunctival hyperemia, chemosis, epiphora, and increased secretions (5). A systematic analysis of subsequent publications highlighted the orbital implications of coronavirus involvement and transmission during the global COVID-19 pandemic (6). In fact, in some patients, orbital conjunctivitis may be an early and only presenting finding of COVID-19 (7). As radiologists, we are acutely aware of how vital imaging is for identifying disease manifestation. But there is a paucity of articles in the imaging literature describing the orbital radiographic manifestations of COVID-19. Only a limited number of articles and case reports present radiographic features describing orbital cellulitis chemosis, retinopathy, and optic neuritis in patients with COVID-19 (8,9).

Johann Wolfgang Goethe once remarked, “We only see what we know.” As radiologists, we rely on our eyes to make critical findings. But disease manifestation can be “overlooked” (pardon the pun) if one is unaware of it, even in critically ill patients. Although it is well published that orbits are affected in up to a third of patients with COVID-19, very few articles highlight crucial orbital imaging manifestations. This makes the article by Lecler et al, “Ocular MRI Findings in Patients with Severe COVID-19: A Retrospective Multicenter Observational Study,” published in this issue of *Radiology* of vital importance (10). It is the first article to report on radiographic MRI ocular findings in a case series of 9 patients critically ill with COVID admitted to intensive care. Using 1.5 T and 3.0 Tesla MRI, the authors retrospectively report on finding isointense T1, hyperintense FLAIR nodules on either 1.5 or 3 Tesla MRI along the posterior globe macular region in 9 patients with COVID-19 in the intensive care unit. The ocular nodular findings occurred bilaterally in 8 of 9 patients (89%) and outside of the macular

region in 2 patients. The nodules were most prominent and preferentially located in the papillomacular bundles of globes (10). In this subset, 3 of 9 patients (33%) with the positive nodular lesions on MRI had a normal funduscopy of the posterior globe, and 1 of the 9 patients also had a normal optical coherence tomography (OCT). Although the etiology of these nodular ocular findings is unknown, the authors present well-documented evidence of how viruses cause microangiopathic damage by inflaming the retina, choroid, and optic nerve. As the authors note, SARS-CoV-2 targets angiotensin-converting enzyme related carboxypeptidase (ACE2) receptors, and these receptors are highly expressed in the retina and choroid of the orbit (10). Because ACE2 is vasoprotective to the retina via the renin-angiotensin system, if ACE2 becomes downregulated because of SARS-CoV-2, then a retinal ischemic event may occur. As discussed by the authors, additional studies using OCT also demonstrated hyper-reflective lesions along the ganglion cell level in inner plexiform layers with cotton wool exudates, most pronounced at the papillomacular bundles in both orbits (10). It is important to remember that these imaging studies are being done on critically ill patients. Additional potential etiologies also presented by the authors include how critically ill ICU intubated patients may be placed in Valsalva, which can create increased venous pressure and result in inadequate orbital venous drainage (10).

The authors recognize the limitations of their retrospective study. They realistically note that it was not always possible to obtain high resolution spatial dedicated ocular MRI sequences in critically ill ICU patients or obtain precise ocular conjunctival sampling for SARS-CoV-2. Nonetheless, it is critical to remember that eye problems can go unrecognized in the ICU, and clinicians need to be vigilant in first identifying if there is an orbital problem to protect the patient's vision. As the authors suggest, severe eye problems may go unnoticed when clinicians focus on life-threatening aspects of the COVID-19 disease. Ocular pathology, that may

otherwise go unnoticed, may be identified and appreciated by using high resolution spatial 3D T2-weighted and post-contrast fat-suppressed T1-weighted MRI, fundoscopy, and optical coherence tomography. This essential article is one of the first to report these ocular radiographic findings. Like all good articles, when first seen and now reported, others will start to “see” this finding and start reporting on it as well. To help and benefit patients, early recognition and awareness of a disease manifestation with accurate dissemination is critical, as when Dr. Li tried to warn others of the newly developing pneumonia that he saw early on as an ophthalmologist in patients with eye findings. Awareness of a new finding, the dissemination of this information, and sharing with colleagues leads to others recognizing the problem, education, research, understanding, and improved outcomes.

This important *Radiology* article is the first to present the MRI ocular imaging disease manifestations of COVID-19. Ocular pathology from the SARS-CoV-2 virus often signifies a more severe disease process and may be occurring with greater prevalence than currently reported and visually underappreciated on current MRI. By publishing this article, the authors will help others appreciate and recognize this critical ocular MRI finding. A true hallmark of a “landmark” article is one that recognizes and reports on a critical finding not yet reported, elucidates the findings so that others can see and find it, and helps improve outcomes for patients. This article reminds all radiologists to pay attention to the orbits on MRI, especially in patients critically ill with COVID-19 admitted to intensive care. The paper identifies where the orbital nodular macular pathology occurs and how best to appreciate it while highlighting potential disease mechanisms, enhancing our understanding of the COVID-19 disease process, and hopefully leading to improved outcomes for all affected in this pandemic.



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