

Letter to the Editor

Response to Ajay Kumar Mishra, et al. Lacunar strokes in *Cryptococcal meningitis*.

To the editor

We thank Dr. Ajay Kumar Mishra et al. for their post-publication commentaries highlighting the pathology of cryptococcal meningitis vasculopathy. The lack of neuro-imaging in some of our patients reflects unavailable information on retrospectively collected data rather than an informed clinical decision. Some of our patients had inaccessible imaging due to referrals from other institutions or old archived records. We agreed with the need for brain imaging in most cases, especially in the presence of altered mental status, seizures, signs or symptoms of increased intracranial pressure; or with focal neurologic deficits. We concur that MRI is more effective than CT to detect cryptococcomas or strokes.¹ However, in low resource settings, imaging is often not available and diagnostic or therapeutic lumbar punctures must not be delayed in the absence of contraindications.² Numerous differences in patient populations, including a higher rate of HIV infection (86% versus 56%), imaging timing, and the absence of solid organ transplant recipients in Mishra et al. cohort³ compared with our cohort⁴ could account for the clinical and radiographic differences in meningeal enhancement rates, mortality, and complications. We hypothesize against an inflammatory component of *Cryptococcus* mediated vasculopathy. We did not observe any significant differences in CSF WBC among patients with strokes. The CSF analysis of patients with advanced Cryptococcal meningitis uniformly shows a paucity of inflammatory cells. Postmortem specimens have shown extensive fungal burden in the brain parenchyma of patients succumbing to the infection.⁵ Finally, *Cryptococcus* secreted factors, and immunothrombosis might be partially responsible for vessel invasion and thrombosis.^{6,7} We agreed that it is crucial to rule out coinfections with other CNS opportunistic pathogens in patients diagnosed with cryptococcal meningitis. We, however, didn't observe patients with CNS coinfections in our cohort. Besides *Cryptococcus*; other fungi and *Mycobacterium tuberculosis* meningitis are the most commonly associated with basilar lacunar strokes. We indeed observed a high rate of disabling sequela in our cohort as discussed in the article: cognitive deficits (37.5%), hearing

impairment (18.8%), incoherent speech (11%), and muscle weakness (44%). All patients in our cohort received standard treatment regimens per Infectious Diseases Society of America (IDSA) guidelines.⁸ Although we anticipate different treatment regimens may affect outcomes including the rate of lacunar strokes, we postulate that delayed diagnosis plays a more significant role.

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References

1. Charlier C, Dromer F, Leveque C, et al. Cryptococcal neuroradiological lesions correlate with severity during cryptococcal meningoencephalitis in HIV-positive patients in the HAART era. *PLoS One* 2008;3:e1950.
2. Sloan DJ, Parris V. Cryptococcal meningitis: epidemiology and therapeutic options. *Clin Epidemiol* 2014;6:169-182.
3. Mishra AK, Arvind VH, Muliylil D, et al. Cerebrovascular injury in cryptococcal meningitis. *Int J Stroke* 2018;13:57-65.
4. Vela-Duarte D, Nyberg E, Sillau S, et al. Lacunar stroke in cryptococcal meningitis: clinical and radiographic features. *J Stroke Cerebrovasc Dis* 2019.
5. Benesova P, Buchta V, Cerman J, et al. Cryptococcosis—a review of 13 autopsy cases from a 54-year period in a large hospital. *APMIS* 2007;115:177-183.
6. Campbell LT, Simonin AR, Chen C, et al. *Cryptococcus* strains with different pathogenic potentials have

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- diverse protein secretomes. *Eukaryot Cell* 2015;14:554-563.
7. Gaertner F, Massberg S. Blood coagulation in immunothrombosis—at the frontline of intravascular immunity. *Semin Immunol* 2016;28:561-569.
 8. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of America. *Clin Infect Dis* 2010;50:291-322.