

## CLINICAL VIGNETTE

# *Cryptococcus neoformans* Meningitis in a Patient with Systemic Lupus Erythematosus

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### Case Presentation

A 52-year-old female with complicated Systemic Lupus Erythematosus (SLE) presented to the emergency department from rheumatology clinic for two weeks of altered mental status. Her SLE was complicated by lupus nephritis, Anti-phospholipid Syndrome (APS), Evan's Syndrome treated with radiation therapy and splenectomy, and Myelodysplastic Syndrome (MDS). At home, the patient was occasionally disoriented to place and would fail to recognize her family members. At times, her speech was difficult to understand due to mumbling. The family reported associated hearing loss, blurry vision with photophobia, and emesis. She had no fever or chills, or recent travel. Medications include prednisone, hydroxychloroquine, and mycophenolate mofetil. Review of systems was notable for a six-month history of headache and dizziness.

The patient was afebrile with mildly elevated systolic blood pressure of 167. On neurological exam, she was drowsy but arousable. She was oriented to person and place, but would not state the year despite being asked multiple times. Speech was fluent but at times nonsensical and tangential. The patient would intermittently laugh inappropriately and had difficulty identifying family members by name. The eye exam was notable for left eye ptosis, which the family stated was new. Finally, she had bilateral impaired hearing to finger rub test. The rest of the patient's exam was unremarkable.

Laboratory testing showed mild leukopenia with a WBC count of 4.2, anemia with a Hgb level of 10.3, and a Cr level of 1.27, all of which were within the patient's baseline range. Her INR was supratherapeutic at 4.29 in the setting of warfarin therapy. Infectious laboratory studies were notable for a positive *Cryptococcus* serum antigen with a titer of 1:1280. Serum Coccidioidomycosis serologies, HIV screen, RPR, and TPPA were all negative. MRI of the brain showed mild leptomeningitis of the basilar cisterns and nonspecific FLAIR hyperintensity in both hemispheres. Initially, the elevated INR precluded bedside lumbar puncture. Given the high suspicion for cryptococcal meningitis, the patient was started on IV liposomal amphotericin B 5 mg/kg daily and oral flucytosine 100 mg/kg daily.

After the INR normalized, a lumbar puncture (LP) was performed. Opening pressure was normal at 17 cm H<sub>2</sub>O. CSF studies were notable for glucose <10 mg/dL, protein >620

mg/dL, pleocytosis (WBC 54, with 71% segmented neutrophils and 17% lymphocytes) and a positive *Cryptococcus* antigen with a titer >1:2560. The CSF West Nile IgG was positive, which in the setting of negative serum serologies suggested likely past infection. Fungal CSF culture eventually grew 1+ *Cryptococcus neoformans* and urine culture grew 2+ *Cryptococcus neoformans*. A non-contrast CT scan of the chest and orbits was done to evaluate disseminated cryptococcosis was negative. She also underwent inpatient ophthalmology evaluation without evidence of cryptococcal involvement of the optic nerves.

The hospital course was complicated by waxing and waning altered mental status prompting a repeat MRI of the brain which showed worsening leptomeningeal enhancements, new sub-acute infarcts in the left pons and cerebellar peduncle, and evolution of FLAIR hyperintensities in both hemispheres. The infarcts were thought to be secondary to vasculitis from SLE based on subsequent CTA. She was started on IV methylprednisolone with significant improvement in her mental status, then transitioned to oral prednisone with trimethoprim-sulfamethoxazole for pneumocystis prophylaxis.

Repeat lumbar punctures during her hospitalization approximately 2 weeks and 4 weeks after the first LP showed persistently high *Cryptococcus* titers (>1:2560) and proteinorrachia. However, opening pressures normalized and repeat CSF cultures remained negative, suggesting sterilization of the CSF.

The patient completed induction therapy with IV liposomal amphotericin B and flucytosine for 1 month, with resolution of her altered mental status and improvement in her other neurologic symptoms. She was discharged on fluconazole 400 mg daily. Three weeks after discharge, she was stable on her current regimen. She planned to continue a minimum of one year of therapy with an azole, with the final treatment duration to be determined by her clinical course.

### Discussion

Cryptococcal meningitis is an opportunistic infection caused by invasion of the CNS with the *Cryptococcus* species of encapsulated yeast, which is acquired by inhalation. *C. neoformans* and *C. gattii* are the two main pathogens in humans. Although

globally it is most commonly seen in individuals with HIV, in developed countries, many of the cases occur in immunosuppressed individuals without HIV, including transplant recipients, patients with SLE, malignancy, or cirrhosis.<sup>1</sup> Furthermore, the prognosis is worse for non-HIV patients, regardless of their immune status.<sup>2</sup> Studies report non-HIV, immunocompetent patients may be genetically predisposed to *Cryptococcus* infections due to multiple polymorphisms in mannose-binding lectin (MBL) and the Fc-gamma receptor 2B (FCGR2B), or may have anti-GM-CSF autoantibodies that impair host control of *Cryptococcus*.<sup>3,4</sup>

Cryptococcal meningitis is a common cause of CNS infections in patients with SLE and is associated with high mortality.<sup>5-7</sup> It can present with non-specific symptoms over several weeks, including headache, altered mentation, fever, emesis, and vision and hearing changes. The insidious onset can present a challenge to initial diagnosis in patients with SLE, but is important to guide clinical suspicion.<sup>8,9</sup>

The definitive diagnosis of cryptococcal meningitis is made by culture from the CSF. Evaluation includes performing a lumbar puncture with prior neuroimaging if there is concern for high intracranial pressure (ICP), obtaining opening pressure, cryptococcal antigen, fungal culture, and routine CSF studies.<sup>8</sup> Positive cryptococcal antigen in the CSF or serum strongly suggests infection before the cultures become positive. Sensitivity of antigen testing ranges from 93% to 100% with a 93% to 98% specificity.<sup>8,10</sup> Furthermore, as seen in this patient, higher antigen titer generally correlates with a higher burden of organisms.<sup>11</sup> CSF studies frequently show high opening pressure, low glucose levels and elevated protein levels with pleocytosis with lymphocytic predominance. However, some patients present with normal CSF glucose and protein.<sup>12</sup>

Once a diagnosis is made, treatment of cryptococcal meningitis involves a three-part regimen of induction, consolidation, and maintenance therapy. Guidelines for dosing and length of therapy depend on the patient population being treated. For non-HIV-infected and non-transplant individuals like this patient, treatment involves induction therapy with IV liposomal amphotericin B at 3–4 mg/kg/day plus oral 5-flucytosine at 100 mg/kg/day for at least 4 weeks, although induction therapy may be extended for a total of 6 weeks in patients with neurological complications.<sup>13</sup> Following induction therapy, consolidation therapy is given with fluconazole 400 mg daily for 8 weeks. Maintenance therapy is lower dose oral fluconazole 200 mg daily for 6-12 months.<sup>13</sup>

Clinical monitoring of patients with cryptococcal meningitis includes regular assessment for resolution of symptoms, signs of elevated ICP, as well as monitoring for toxicity associated with antifungal therapy. If the initial CSF pressure is  $\geq 25$  cm of H<sub>2</sub>O and there are symptoms of increased ICP, therapeutic lumbar punctures should be repeated to relieve the pressure by 50% to a goal of  $\leq 20$  cm H<sub>2</sub>O.<sup>13</sup> Regardless of the initial opening pressure, another LP should be repeated two weeks into induction therapy to ensure sterilization of the CSF.<sup>13</sup>

Serum cryptococcal antigen is not monitored due to its poor correlation with improvement in clinical status.<sup>14</sup> Close monitoring of the patient's clinical course is important overall to identify persisting or relapsing infection and addressing the cause.

### Conclusion

In developed countries, many cases of cryptococcal meningitis occur in immunosuppressed individuals without HIV, and meningitis due to *Cryptococcus* is a common cause of CNS infections in patients with SLE. Its insidious onset with non-specific symptoms can present a challenge to initial diagnosis. Evaluation involves performing a lumbar puncture. A definitive diagnosis is made by culture from the CSF, but a positive cryptococcal antigen in the CSF or serum strongly suggests the infection before the cultures become positive. After diagnosis, patients are treated with a three-part regimen consisting of induction, consolidation, and maintenance therapy. Another LP should be repeated two weeks after initiation of induction therapy to ensure sterilization of the CSF. Treatment lasts at least 9 months in non-HIV-infected and non-transplant hosts, and requires close monitoring for symptom resolution and therapy-associated toxicity.

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