Rapid Reversal of Complete Binocular Blindness With High-Dose Corticosteroids and Lumbar Drain in a Solid Organ Transplant Recipient With Cryptococcal Meningitis and Immune Reconstitution Syndrome: First Case Study and Literature Review

Zoe Weiss,1 Nihaal Mehta,2 Su Nandar Aung,3 Michael Migliori,4 and Dimitrios Farmakiotis5

1Department of Internal Medicine, Warren Alpert Medical School of Brown University, Providence, Rhode Island; 2Warren Alpert Medical School of Brown University, Providence, Rhode Island; 3Division of Infectious Disease, Warren Alpert Medical School of Brown University, Providence, Rhode Island; 4Division of Ophthalmology, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, Rhode Island; 5Division of Infectious Disease, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, Rhode Island

Blindness is a rare, devastating, usually permanent complication of cryptococcal meningitis (CM). We present the first case of complete vision loss in a solid organ transplant recipient with CM treated with placement of a lumbar drain who had a dramatic visual recovery that started after 3 doses of high-dose steroids.

Keywords. cryptococcal meningitis; immune reconstitution inflammatory syndrome; CM-IRIS; vision loss.

CASE PRESENTATION

A 62-year-old woman with history of renal transplantation 18 years earlier presented with headache, photophobia, and right facial droop. Her immunosuppressive regimen included mycophenolate, tacrolimus, and prednisone in the setting of chronic rejection. Brain MRI, MRA, and MRV were negative for stroke. Laboratory results on admission are summarized in Table 1. She underwent a lumbar puncture (LP) on day 3 with opening pressure (OP) of 28 cm H2O; her cerebrospinal fluid (CSF) had 208 nucleated cells (88% lymphocytes), glucose 51 mg/dL, and protein 222 mg/dL; Gram stain revealed yeast forms, and culture was positive for Cryptococcus neoformans. She was started on liposomal amphotericin-B and renally adjusted flucytosine; mycophenolate was discontinued, and tacrolimus dose decreased, aiming at a trough level of 4 ng/mL. Both blood and CSF cultures were negative by day 6 (day 3 of antifungal treatment).

She continued to have elevated OP, receiving sequential LP (Figure 1). All post-LP OP were <20 cm H2O. Funduscopic examination did not show papilledema. On hospital day 12 (day 9 of treatment), she developed right-sided vision loss with no light perception, right afferent pupillary defect (APD), decreased left-sided visual acuity with diminished color perception, and bilateral conjunctival chemosis. Computed tomography angiography of the brain and contrast magnetic resonance imaging of the orbits were unremarkable. On day 15, despite repeated LP, she had bilateral complete loss of vision with no light perception and grade I papilledema. An epidural drain was placed to allow for continuous CSF drainage without improvement. Prednisone 80 mg twice daily was started on day 16 for presumed early immune reconstitution inflammatory syndrome (IRIS). She recovered light perception after the first 3 doses. The lumbar drain was removed the following day. Her vision returned to baseline in both eyes by day 25 (Figure 1). Prednisone was tapered to 10 mg over 4 weeks. She had no further eye complaints. She completed 4 weeks of induction for cryptococcal meningitis, followed by 6 weeks of eradication treatment, and now receives renally adjusted maintenance fluconazole.

METHODS

We performed a literature search in the National Center for Biotechnology Information’s PubMed database using the term “cryptococcal meningitis;” in conjunction with “immune reconstitution syndrome,” “immune reconstitution inflammatory syndrome,” “IRIS,” “CM-IRS,” “CM-IRIS,” “ocular,” “optic,” “ophthalmic,” “ophthalmologic,” “blindness,” “visual loss,” and “visual.” After publications were identified, their references were reviewed. For the purposes of this analysis, we included cases of visual impairment independent of suspected etiology (eg, increased intracranial pressure, inflammatory optic neuropathy, direct infection of the optic nerve).

RESULTS AND DISCUSSION

CM is a highly morbid opportunistic fungal infection resulting in elevated intracranial pressure (ICP) and neurologic symptoms. Though classically described in the setting of HIV infection, CM is nowadays recognized at least as frequently in patients with other forms of immunosuppression, including...
solid organ transplant (SOT) and occasionally in immunocompetent hosts [1, 2]. Visual symptoms occur in approximately 35% [3], and, in some regions, 10% will suffer irreversible blindness [4]. Treatment involves antifungal therapy and control of ICP [1, 5].

Multiple pathophysiologic mechanisms of visual loss in CM have been described. The predominant mechanism is optic nerve damage due to elevated ICP, as a result of obstruction of CSF outflow by cryptococcal polysaccharide capsules or fungal organisms [3, 6]. Vision impairment secondary to elevated ICP progresses over weeks and may be accompanied by persistent, significant papilledema [7], which our patient did not have. In some cases, early and aggressive control of increased ICP—such as through serial lumbar punctures, optic nerve sheath fenestration, or CSF shunting—allowed for reversal of vision loss.

**Table 1. Pertinent Initial Laboratory Results and Reference Ranges**

| Laboratory Test       | Value      | Reference Range          |
|-----------------------|------------|--------------------------|
| WBC                   | 14.3 × 10^9/L | 3.5–11.0 × 10^9/L        |
| Creatinine            | 2.6 mg/dL (baseline) | 0.44–1.03 mg/dL         |
| CSF Nucleated cells   | 208        | 0–5 cells/µL             |
| Lymphocyte %          | 88%        | 63%–99%                  |
| Glucose               | 51 mg/dL   | 38–85 mg/dL              |
| Protein               | 222 mg/dL  | 15–45 mg/dL              |
| Bacterial and fungal culture | +Cryptococcus neoformans. |                  |
| Cryptococcal antigen titer | >1:256 |                       |
| Blood culture         | +Cryptococcus neoformans. |                  |
| HIV 1/2 antibody/antigen | Negative |                |

**Figure 1.** Timeline of opening pressure and CSF results, visual acuity, medical interventions, funduscopic exam, and eye images. Funduscopic exam on day 9 (A, B) demonstrates grade 1 papilledema with disc hyperemia, diminished cup size, marginal polar disc blurring and early nerve fiber bundle definitions (arrow A), and increased vessel tortuosity (arrow B). On day 20 (C, D), there is stable grade 1 papilledema, disc hyperemia, persistent polar disc blurring (arrow C), and vessel tortuosity (arrow D), no significant optic nerve ischemia, and improved nerve fiber bundle definition. Abbreviations: CSF, cerebrospinal fluid; WBC, white blood cell.
had significant conjunctival chemosis, often seen in ocular antifungal therapy, reduction of immunosuppression, and with CSF pleocytosis and elevated ICP after initiation of therapy and persistently negative cultures [11, 15]. Vision loss has graphic findings in the setting of appropriate antifungal therapy in HIV-infected patients. However, IRIS also occurs with immune recovery, initially described during treatment of an opportunistic infection and initiation of antiretroviral therapy in HIV-infected patients. However, IRIS also occurs with reduction of immunosuppressive therapy and host response to treatment of opportunistic infections in SOT recipients, and it is an underrecognized complication in the SOT patient population, most commonly associated with cryptococcosis [11]. Discontinuation of the calcineurin inhibitor (CNI), but not decrease in CNI dose or discontinuation of mycophenolate or azathioprine, has been identified as a risk factor for adverse clinical outcomes in SOT recipients with CM [11, 12]. This observation may be due to the antifungal activity of CNI [13, 14] although the development of IRIS may be a contributing factor [11]. In SOT recipients with CM, IRIS usually occurs at a median of 6 weeks after initiation of antifungal treatment, but onset as early as 2 weeks has been described [11], similar to our case.

Proposed diagnostic criteria for CM-IRIS are worsening clinical features, CSF pleocytosis and increased ICP, or radiographic findings in the setting of appropriate antifungal therapy and persistently negative cultures [11, 15]. Vision loss has not been previously described as a defining feature of IRIS. Our patient’s clinical decline manifested as blindness associated with CSF pleocytosis and elevated ICP after initiation of antifungal therapy, reduction of immunosuppression, and with fungal clearance in blood and CSF. Furthermore, our patient had significant conjunctival chemosis, often seen in ocular inflammatory conditions, which also resolved after high-dose steroids.

Our literature review identified 8 additional patients with CM, presumed IRIS, and vision loss, all of whom were HIV positive. Four patients had elevated ICP and prominent optic disc edema [16]. The remaining 4 were felt to have inflammatory optic neuropathy with either normal or mildly elevated ICP, and minimal papilledema. Three of these patients were treated with steroids and had rapid improvement within 1–5 days [8, 9, 17, 18]. To our knowledge, ours is the first reported case of steroid-responsive inflammatory optic neuropathy in an SOT recipient, presumably due to CM-IRIS.

Although steroids are indicated for the management of patients with intracranial hypertension and cerebral edema in pneumococcal and tuberculous meningitis, their role in CM has been controversial [19]. In HIV-infected patients, the process leading to blindness in CM is presumably one of pauci-immune inflammation [3, 20]. Thus, use of corticosteroids has been associated with higher morbidity and mortality [10, 20]. Beardsley et al. conducted a randomized controlled trial assessing the effect of adjunctive high-dose dexamethasone in 451 HIV-infected patients initiating therapy for CM. The study was stopped when preliminary results showed higher mortality and slower fungal clearance with corticosteroids, compared with patients receiving placebo [19]. However, these findings may not apply to patients treated with steroids after demonstrated fungal clearance or in those without HIV, that is, patients who can probably mount a strong immune host response.

Indeed, HIV-negative patients seem to have a more robust, and potentially steroid-responsive, inflammatory response to CM [21]. One study of 16 non-HIV immunocompetent patients showed a 10-fold reduction in blindness among patients with CM receiving low-dose steroids [22]. Current Infectious Diseases Society of America guidelines recommend steroid use only in patients with CM who develop either acute respiratory distress syndrome or IRIS [1]. These patients, like ours, should have documented negative CSF cultures [5, 19].

Our case study has limitations. We cannot exclude the possibility that our patient experienced visual recovery as a delayed response to placement of a lumbar drain. However, this is less likely given rapid onset and reversal of her symptoms with steroid administration and minimal papilledema. Other pathogen-induced mechanisms may have played a role, although funduscopic findings, negative cultures, and rapid response to corticosteroids make these less likely, as detailed above.

In conclusion, this is the fourth reported case of blindness in a patient with CM who rapidly improved with steroids, presumably due to CM-IRIS, and the first in an SOT recipient. Corticosteroids should not be part of the standard treatment for CM. However, clinicians should consider using high-dose steroids in patients with suspected CM-IRIS, including those...
with sudden visual loss late in the course of treatment, documented clearance of CSF cultures, and no clinical response to CSF drainage.

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