Reversible Blindness in Cryptococcal Meningitis With Normal Intracranial Pressure: Case Report and Review of the Literature

Pooja A. Ghatalia,1 Amanda Vick,1 Surjith Vattoth,2 Glenn H. Roberson,2 and Peter G. Pappas3

1Tinsley Harrison Internal Medicine Residency Program, 2Division of Radiology, and 3Division of Infectious Diseases, University of Alabama at Birmingham

Ocular complications in cryptococcal meningitis (CM) are commonly attributed to elevated intracranial pressure (ICP). We report a case of reversible vision loss complicating AIDS-related CM with a normal ICP. We review other cases of blindness in CM with normal ICP and the potential role of corticosteroids as treatment.

Keywords. cryptococcosis; meningitis; intracranial pressure; blindness.

Cryptococcus neoformans is an encapsulated basidiomycetic yeast that is commonly found in pigeon excreta and decaying organic material. In the presence of immunodeficiency, C. neoformans disseminates widely, especially to the central nervous system (CNS), and is the most frequent CNS infection seen in patients with AIDS in sub-Saharan Africa [1]. While neurocryptococcosis commonly presents as diffuse meningoencephalitis, ocular involvement is usually a secondary phenomenon, occurring in up to 30% of patients with cryptococcal meningitis (CM) [2].

The mechanism of visual complications associated with CM remains unclear. Elevated cerebrospinal fluid (CSF) pressure is the major risk factor associated with blindness, and it is recommended that intracranial pressure (ICP) be decreased in order to prevent and reverse this. However, several case reports cast doubt on the hypothesis that elevated ICP alone causes vision loss.

CASE REPORT

Clinical Findings

Sixteen days prior to presentation at our institution, a 34-year-old heterosexual Hispanic male presented to another hospital with a 1-week history of fever and headache. He was diagnosed with human immunodeficiency virus (HIV) and CM. Lumbar puncture revealed normal intracranial pressure (80 mm H2O). Fourteen days before presentation he was treated with fluconazole, 5-flucytosine, ceftriaxone, and ampicillin/subactam and antiretroviral therapy (ART) with abacavir/lamivudine/raltegravir was initiated. Cultures of CSF at the outside hospital were positive for C. neoformans. Seven days before presentation at our institution, he developed sudden painless vision loss in both eyes, worse on the right than left.

Upon arrival to our hospital, he reported no headache, nausea, vomiting, or diplopia. He was afebrile, awake, and alert with no evidence of confusion or meningismus. He had decreased vision, right worse than left, without peripheral sparing. There was no light perception in the right eye and visual acuity was limited to counting fingers in the left eye. His right pupil was unresponsive to direct light, but consensual reflex was intact. His left pupil was responsive to light and consensual reflex. Rapid afferent papillary defect was also noted in the right eye. Fundoscopic examination showed no papilledema, vitritis, or chorioretinal lesions. There was no evidence of retinal artery occlusion. Extraocular motion was intact bilaterally. There was no other neurologic abnormality. The remaining physical exam was unremarkable.

Laboratory data revealed anemia with hematocrit 34%, leukocytes 3410/µL, and platelet count 163 400/µL. Blood and urine cultures for bacteria, mycobacteria, and fungi were negative. Cytomegalovirus antigen testing of peripheral blood was negative. Serum toxoplasma immunoglobulin G and rapid plasma reagin were negative. Absolute CD4 count was 6 cells/µL, with plasma HIV viral load of 619 copies/mL.

CSF examination showed clear fluid with opening pressure 40 mm H2O, protein 218 mg/dL, and white blood cell count 29/mm³ with 100% lymphocytes and 12/mm³ red blood cell count. Direct microscopic examination of CSF with India ink showed yeasts compatible with C. neoformans and CSF cryptococcal antigen was positive (1:512). Culture of CSF was negative at that time. Magnetic resonance imaging findings revealed leptomeningeal enhancement and dilated perivascular Virchow-Robin spaces with gelatinous pseudocysts, all classic findings in neurocryptococcosis (Figure 1).
Clinical Course

On presentation to our institution, the patient received tenofovir/emtricitabine/efavirenz, liposomal amphotericin-B (5 mg/kg/day), and 5-flucytosine (100 mg/kg/day). Multiple lumbar punctures throughout his hospitalization revealed normal ICP. On hospital day 2, intravenous methylprednisolone 1 g/day was begun and continued for 5 days followed by oral taper of prednisone over 15 days from 40 mg daily to 5 mg daily, then discontinued. After receiving the first dose of steroids, the patient’s vision dramatically improved. On day 4 of glucocorticoid therapy, vision testing revealed 20/40 OD (right eye) and 20/25 OS (left eye) with good pupillary response bilaterally. Amphotericin B and 5-flucytosine were continued for 2 weeks and transitioned to fluconazole. At 13 months following initial presentation, the patient continues to do well clinically and has preserved vision.

REVIEW OF LITERATURE

We performed a literature review of cases of vision loss associated with CM with normal ICP or normal fundoscopic exam since 1964 (Table 1). We reviewed postulated theories of vision loss other than elevated ICP. We also reviewed the literature supporting the role of adjuvant corticosteroids in the treatment of vision loss caused by cryptococcosis [3-11].

Several authors have argued that even in cases of elevated ICP, multiple mechanisms may be instrumental in vision loss. Golnik et al reported 3 such cases and Duggan et al reported another such case [12, 13]. They postulated optic neuropathy due to either cryptococcal infiltration of optic nerves or restrictive arachnoiditis, which limits vascular supply to the nerve, as likely causes of vision loss. There were no autopsy results to support their hypotheses. However, Corti et al and Ofner et al reported cases of sudden vision loss associated with CM with elevated ICP where autopsy revealed infiltration of optic nerves with C. neoformans [9, 10]. Interestingly, Kupfer et al reviewed 6 cases of CM with elevated ICP and observed that on autopsy, those patients with blindness had organisms invading the visual pathways and those patients with preservation of vision had no cryptococcal invasion in their optic nerves [14].

Of the 2 cases of vision loss with normal ICP that we reviewed, 1 reported improved vision with use of methylprednisolone (Table 1). Seaton et al performed a retrospective analysis of corticosteroid use and visual outcome in immunocompetent patients with CM [15]. All 26 patients received intravenous amphotericin-B and flucytosine as a standard treatment for 6 weeks; 16 patients received hydrocortisone daily. The observations suggested that adjuvant corticosteroids prevent vision loss in patients with at least some light perception at presentation.

DISCUSSION

There are 2 distinct forms of vision loss in CM: rapid loss associated with a clinical syndrome that is suggestive of optic neuritis and a slower, more progressive loss that may be due to the effects of increased intracranial pressure and/or intraocular pressure [6, 16]. Our patient had rapid vision loss with a normal opening CSF pressure and no papilledema or fundoscopic abnormalities on exam, suggesting optic neuritis, cerebral vasculitis, or arachnoiditis as possible mechanisms. Also, the presence of leptomeningeal enhancement with enhancing nerve sheaths on MRI suggests inflammation as a likely etiology of vision loss (Figure 1).

We hypothesize that our patient had dramatic improvement in visual acuity after receiving 2 doses of IV methylprednisolone because he was suffering from the effects of rapid immune reconstitution. Immune reconstitution inflammatory response (IRIS) is a paradoxical inflammatory response to previously or recently treated infections or the unmasking of subclinical infections when patients regain the ability to mount a suitable immune response. “Paradoxical” IRIS, presenting as worsening
<table>
<thead>
<tr>
<th>Reference</th>
<th>Age, Sex</th>
<th>Tempo of Vision Loss</th>
<th>Relationship of Onset of Vision Symptoms to Antifungal Therapy</th>
<th>Visual Acuity</th>
<th>Imaging/Autopsy</th>
<th>Cerebrospinal Fluid Opening Pressure (mm H2O)</th>
<th>Therapy</th>
<th>Final Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal intracranial pressure/normal fundoscopic exam</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hong [3]</td>
<td>58, M</td>
<td>5 d</td>
<td>Before therapy</td>
<td>LP OU</td>
<td>MRI: normal</td>
<td>160</td>
<td>IV amB</td>
<td>Improved visual acuity</td>
</tr>
<tr>
<td>De Socio [4]</td>
<td>35, M</td>
<td>Rapid</td>
<td>7 d after therapy</td>
<td>OS LP</td>
<td>MRI:OU ectasia of the optic nerve sheath with contrast enhancement around the OS optic nerve sheath intracranially, retrobulbar optic neuritis</td>
<td>60</td>
<td>Antiretroviral therapy, IV amB, IV methylprednisolone X3d, IV acyclovir</td>
<td>Vision improved on day 2 of steroids</td>
</tr>
<tr>
<td>This case</td>
<td>34, M</td>
<td>Rapid</td>
<td>7 d after therapy</td>
<td>CF OS, NLP OD</td>
<td>MRI: enhancement of optic nerve sheaths and internal auditory canals bilaterally</td>
<td>40</td>
<td>Fluconazole and 5-FC before vision loss; after vision loss, amB IV and 5-FC, later switched to fluconazole; methylprednisolone X5 d started 2 d after starting IV amB</td>
<td>Vision improved on day 2 of steroids</td>
</tr>
<tr>
<td>Winward [5] (case 4)</td>
<td>26, F</td>
<td>Overnight</td>
<td>9 d after therapy</td>
<td>CF OU</td>
<td>MRI: normal</td>
<td>NR</td>
<td>IV amB</td>
<td>Died</td>
</tr>
<tr>
<td>Rex [6]</td>
<td>18, M</td>
<td>2 wk</td>
<td>3 wk after therapy</td>
<td>LP OU</td>
<td>MRI: brain swelling, no hydrocephalus</td>
<td>NR</td>
<td>5-FC + IV amB and IT</td>
<td>20/200 OU</td>
</tr>
<tr>
<td>Rex [6]</td>
<td>30, M</td>
<td>2 mo</td>
<td>1 wk after therapy</td>
<td>NR</td>
<td>MRI: mild hydrocephalus</td>
<td>NR</td>
<td>IV and IT AmB + 5-FC, ventriculoperitoneal shunt</td>
<td>CF OU</td>
</tr>
<tr>
<td>Rex [6]</td>
<td>24, M</td>
<td>Rapid</td>
<td>Before therapy</td>
<td>NLP OU</td>
<td>MRI: diffuse cerebral atrophy, but normal optic nerves</td>
<td>NR</td>
<td>IV + IT amB</td>
<td>NR</td>
</tr>
<tr>
<td>Lipson [7] (case 2)</td>
<td>31, M</td>
<td>NR</td>
<td>Before therapy</td>
<td>20/50 OD, 20/30 OS</td>
<td>MRI: bilateral lower signal of optic nerves in one plane</td>
<td>NR</td>
<td>IV amB, dexamethasone, maintenance fluconazole</td>
<td>NLP OU</td>
</tr>
<tr>
<td>Torres [8]</td>
<td>28, F</td>
<td>6 d</td>
<td>9 d after therapy</td>
<td>CF OD, NLP OS, in a week NLP OU</td>
<td>MRI: infiltration of optic nerves with Cryptococcus neoformans</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autopsy with organisms in optic pathways</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corti [9]</td>
<td>34, M</td>
<td>Sudden</td>
<td>10 d after therapy</td>
<td>NLP OU</td>
<td>Elevated, NR</td>
<td>CT: enlarged optic nerve OU; biopsy of optic nerve: invasion of C. neoformans in nerve</td>
<td>IV amB</td>
<td>Died, NLP OU</td>
</tr>
<tr>
<td>Ofner [10]</td>
<td>43, M</td>
<td>Gradual over 6 mo</td>
<td>6 mo after therapy</td>
<td>OU NLP</td>
<td>CT: normal; autopsy: infiltration of intracranial optic nerves with C. neoformans</td>
<td>350</td>
<td>IV amB, optic nerve fenestration</td>
<td>NLP OU</td>
</tr>
<tr>
<td>Cohen [11]</td>
<td>38, M</td>
<td>2 d</td>
<td>Before therapy</td>
<td>20/200 OU</td>
<td>CT: normal; autopsy: infiltration of intracranial optic nerves with C. neoformans</td>
<td>&gt;600</td>
<td>IV amB, daily LP, dexamethasone on day 2</td>
<td>CF, died</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FC, 5-fluorocytosine; amB, amphotericin B; CF, count fingers visual acuity; CT, computerized tomography; IT, intrathecal; IV, intravenous; LP, light perception; MRI, magnetic resonance imaging; NLP, no light perception; NR, not reported; OD, right eye; OS, left eye; OU, both eyes.
or recurrence of treated cryptococcal disease after ART initiation, is a reasonable explanation of sudden blindness in our patient. Early ART initiation probably contributed to this.

Two recent randomized clinical trials in sub-Saharan Africa have shown excess mortality with early ART initiation [17, 18]. The latter trial was terminated early due to significant mortality in patients who started ART 1–2 weeks after diagnosis of CM when compared with ART deferred until 5–6 weeks. Despite the lack of objective data on IRIS-related mortality in these patients, in the context of early ART initiation, IRIS may be an important contributing factor. The immune-modulatory effects of steroids may have dampened the inflammation, which had led to blindness in our patient.

CONCLUSION

Here we report a case of vision loss in a patient with CM and normal ICP. Dramatic improvement of vision in our patient temporally associated with corticosteroids suggests that there was an inflammatory component to the vision loss associated with this condition, possibly due to IRIS caused by early intervention with ART.

Notes

Financial support. None.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

18. Boulware DR, Meya D, Muzoora C, et al. ART initiation within the first 2 weeks of cryptococcal meningitis is associated with higher mortality: A multisite randomized trial [abstract 144]. In: Conference on retroviruses and opportunistic infections (CROI), Atlanta, USA, 6 March 2013.