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CASE REPORT

Isolated Unilateral Infiltrative Cryptococcal Optic Neuropathy in an Immunocompetent Individual

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ABSTRACT

A 46-year-old male developed painful decrease in vision in the left eye which progressed to only perception of light over a period of 2 days. A fundus examination revealed optic disc oedema and multiple white-centred haemorrhages in the left eye. The patient had no fever nor any abnormal neurological signs. Magnetic resonance imaging showed thickening of the left intraorbital and intracanalicular optic nerve with extensive perioptic enhancement. Microscopic examination of cerebrospinal fluid showed the presence of *Cryptococcus neoformans*. An enzyme-linked immunosorbent assay for human immunodeficiency virus was negative and the patient had no history of immunosuppression. A course of amphotericin B and fluconazole resolved the lesion, which was noted after imaging on subsequent visits. The authors report a hitherto undocumented entity of isolated infiltrative cryptococcal optic neuropathy in an immunocompetent individual. A fungal aetiology may be the cause of drastic loss of vision due to infiltrative optic neuropathy even in immunocompetent patients.

KEYWORDS: Cryptococcus; infiltrative optic neuropathy; optic neuropathy

INTRODUCTION

Cryptococcus neoformans is a ubiquitous environmental saphrophyte found in soil contaminated with pigeon droppings. Exposure may be through inhalation of small, thinly encapsulated yeasts, or basidiospores. This may lead to an initial pulmonary infection, which, depending on host immune response, may be cleared, or contained within granulomata as a latent infection, or disseminated. The various sites for disseminated cryptococcal infection include the cerebrospinal fluid, bones, joints, kidneys, spleen, prostate, pancreas, adrenals, ovaries, lymph nodes, skeletal muscle, liver, gastrointestinal tract, and skin.[1–3] The minority of patients in whom the disease disseminates typically have defects in T-cell function, through malignancy, immunosuppressive medication, autoimmune disease, collagen vascular diseases, organ transplantation or sarcoidosis, or human immunodeficiency virus (HIV) infection.[4,5]

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CASE REPORT

We report a case of a 46-year-old male patient who presented with sudden painful decrease in vision in the left eye. On consultation with a local ophthalmologist, his vision was recorded to be 6/6 in the right eye and 6/9 in the left eye. On presentation at our institute 2 days later, his best-corrected visual acuity in the right eye was 6/6, N6, and perception of light with inaccurate projection of rays in the left eye. Pupillary examination revealed a gross afferent pupillary defect

in the left eye. Intraocular pressures in both eyes were within normal limits. Ptosis and restricted ocular motility in all directions of gaze were noted in the left eye. Anterior segment evaluation was unremarkable except for grade I nuclear sclerosis in both eyes. Whereas the fundus in the right eye was normal, a hyperaemic disc with massive disc oedema, multiple white-centred haemorrhages, and grossly thickened peripapillary nerve fibres were seen in the left eye (Figure 1). The patient's corneal sensation was intact and equal in both eyes. A systemic examination showed neither neurological deficits nor systemic signs. The patient was found to be neither hypertensive nor a diabetic and there was no history of immunosuppression. Based on a clinical suspicion of optic neuritis, the patient received 1 g intravenous methylprednisolone on day 1.

Magnetic resonance imaging (MRI) of the brain showed thickening of the left intraorbital and intracanalicular optic nerve with extensive perioptic enhancement (Figures 2, 3). With a possibility of infiltrative optic neuropathy in mind, a lumbar puncture was performed and a Gram-stained smear of the cerebrospinal fluid (CSF) revealed gram-positive round to oval budding cells measuring 3–5 microns in diameter morphologically resembling *Cryptococcus* species. Ziehl-Neelsen staining did not reveal any organisms; bacterial and fungal cultures of the CSF revealed no growth. Meanwhile, serological analysis for sarcoidosis was negative; as was the CSF polymerase chain reaction (PCR) test for *Mycobacterium tuberculosis*. Serology for antinuclear antibodies (ANAs) and anti-neutrophil cytoplasmic antibody (ANCA) were also negative. The testing for cryptococcal antigen was requested for this patient; however, given the rare entity that is cryptococcosis, our ophthalmic institute's laboratory did not have the necessary kits to conduct the tests. All blood parameters were normal except for an elevated erythrocyte sedimentation rate of 33 mm at the end of 1 hour. A chest X-ray showed clear fields with no evidence of pulmonary disease. An HIV enzyme-linked immunosorbent assay (ELISA) test was negative and the CD4/CD8 T-lymphocyte ratio was within normal limits. A banker by profession, our patient had no history of close contact with birds. A diagnosis of presumed cryptococcal optic neuritis was established and the patient was treated with eight doses of intravenous amphotericin B (0.7 mg/kg/day). The treatment was changed to oral fluconazole 400 mg PO for 10 weeks after acute renal failure necessitated the early change.

At 1 week, the patient was symptomatically better; ocular motility being free, full and painless. The ptosis and disc oedema in the left eye had resolved with relatively less thickening of the peripapillary retinal nerve fibre layer (Figure 4). However, the vision had dropped to no perception of light in the left eye. MRI after 4 weeks showed partial resolution of the optic nerve thickening and perioptic enhancement (Figure 2).

On further follow-up after 6 months, examination of the left eye showed disc pallor (Figure 5) with gross

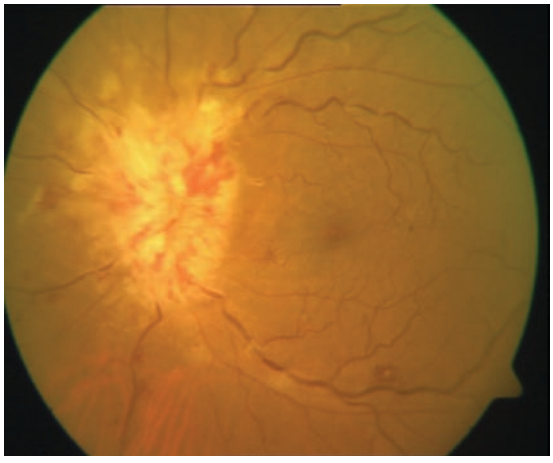

FIGURE 1 Fundus photograph of the left eye on presentation showing the massive disc oedema and a white-centred haemorrhage.

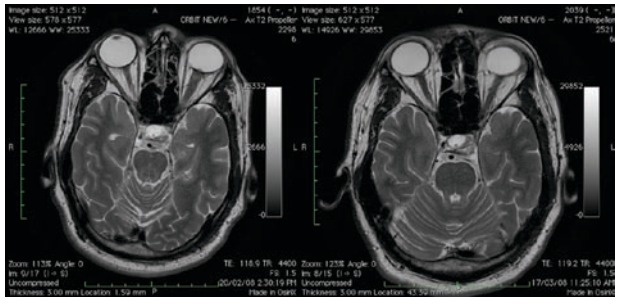

FIGURE 2 MRI of the brain and orbit: Axial T2-weighted images comparing the hypointense optic nerve thickening at presentation (left) and partial resolution at 4 weeks from presentation (right).

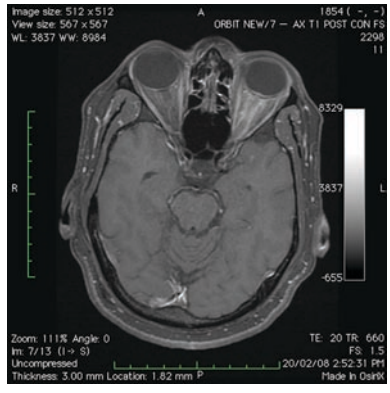

FIGURE 3 Axial T1 images after intravenous contrast showing intracanalicular and intraorbital optic nerve thickening and perioptic enhancement.

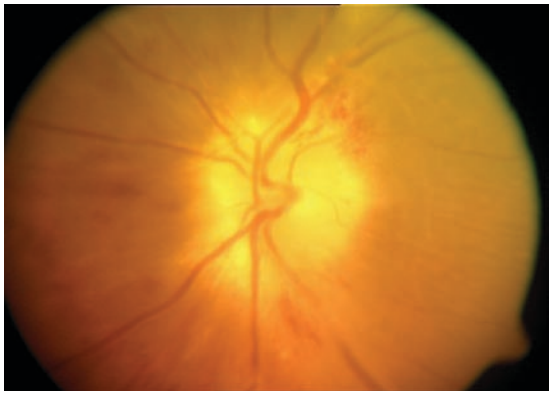

FIGURE 4 Resolving optic disc oedema after 1 week of treatment.

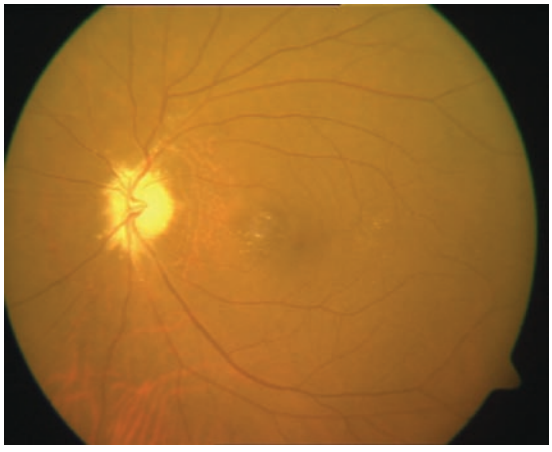

FIGURE 5 Fundus photo at 6 months showing disc pallor.

peripapillary nerve fibre layer thinning on optical coherence tomography (OCT). The left eye showed no improvement in vision. MRI showed further resolution of the optic nerve thickening when compared to the earlier studies.

Such a case of infiltrative cryptococcal optic neuritis in an immunocompetent individual, to the best of our knowledge, has not been previously reported.

DISCUSSION

Opportunitistic infections like cryptococcal meningitis have been reported in patients who are HIV negative, without other known causes of immunodeficiency, on more than one occasion.[5,6] Immunocompetent individuals with central nervous system (CNS) cryptococcal infection may not present with classical symptoms such as headache, meningeal signs, but rather with altered mental status, seizures, and strokes in multiple vascular territories.[6] In our case, a drastic painful decrease in vision was the only presenting symptom.

More specifically, cryptococcal optic neuropathy has been well documented in patients with acquired immunodeficiency syndrome[4,7] and also in immunocompetent patients secondary to established cryptococcal meningitis.[8] However, this case is the first reported case of isolated cryptococcal infiltrative optic neuropathy in an immunocompetent individual. It has been hypothesized that visual loss in immunocompetent patients with *C. neoformans* infection may reflect immune-mediated optic nerve dysfunction caused by either compression due to arachnoid adhesions or oedema and inflammatory cell-mediated damage.[2] The two postulated modes of damage to the optic nerve include: firstly, the cellular response in the meninges surrounding the optic nerve may result in adhesions, causing slow strangulation of the nerve and compromise its vascular supply[7,9]; and secondly, direct invasion of neural tissue by cryptococci, which may be compounded by the host response of inflammatory cell infiltration and oedema in the optic nerve.[9] The rapid vision loss and poor visual recovery noted in our patient could be explained by direct invasion of cranial nerves by the fungus,[10] thus suggesting an infiltrative mycotic focus of infection, although histopathological evidence was not available.

Microscopic examination of the various specimens such as sputum, bronchoalveolar aspirate, or CSF can be useful in identifying the organism. Calcofluor white—a fluorescent fungal stain—is the most sensitive.[11] Gram stain may also detect *Cryptococcus* species and India ink stain can, though with limited sensitivity and specificity, demonstrate negatively stained capsules in CSF specimens. *Cryptococcus* species can also be identified using a mucicarmine stain, in fixed tissue specimen.[12]

As in other bacterial infections, *Cryptococcus* also causes fungaemia before crossing the blood-brain barrier to cause meningitis.[13] *Cryptococcus* can be recovered on blood agar plates used routinely for bacterial culture; selective and enriched media may improve recovery of these yeasts, especially in the early stages of infection. For CSF, the sediment should be inoculated onto Sabouraud 4% dextrose agar plates and sheep blood agar plates, incubated at 30°C, and examined weekly for 4 weeks. Potato dextrose agar, birdseed agar, and canavanine-glycine-bromothymol agar are used for species differentiation.[12]

Cryptococcus antigen detection using latex-agglutination assays on CSF or serum specimens is useful in the initial diagnosis. The reported sensitivity for latex agglutination assays ranges from 54% to 100%, with higher sensitivity in patients with CNS infection or pneumonia.[12] Potential reasons for false-negative results include low titres, prozone phenomenon of high titres, blocking antibodies, early infection, poorly

encapsulated cryptococcal strains, and agglutination kits.[14]

Growth of the organism in cultures and demonstration of cryptococcal antigen are confirmatory of the presence of cryptococcus species. However, microscopic demonstration of the organism in CSF is known to have a high sensitivity.[15] Cryptococcosis can be effectively diagnosed on the basis of microscopic visualization in a Gram-stained smear.[16]

Although there is no specific guidelines regarding the treatment of cryptococcal optic neuropathy, the current regimen to treat cryptococcal meningitis is to administer amphotericin B (with or without 5-flucytosine) initially for the first 2 weeks, and then to administer fluconazole for at least 10 weeks, both to complete initial treatment and to prevent relapse. In patients with acquired immunodeficiency syndrome (AIDS), lifelong treatment with fluconazole is recommended. The recommended appropriate dose of amphotericin B is a minimum of 0.7 mg/kg/day.[17] Dammert et al. have stated that in AIDS patients, who were treated with intravenous amphotericin B 0.7 mg/kg/day for 2 or 3 weeks followed by oral fluconazole 400 mg/day for 7 or 8 weeks, long-term CSF sterilisation rates were successfully achieved.[18] Furthermore, use of flucytosine as initial therapy was associated with a lower risk of later relapse. If used, a dose of 37.5 mg/kg four times daily is recommended, with regular measurement of levels to minimize toxicity. Fluconazole can be used to treat (or complete a course of treatment in) patients who cannot tolerate amphotericin B.[17]

Amphotericin B deoxycholate (AmBD), however, is associated with a high rate of side effects, both infusion related as well as nephrotoxicity. The reported incidence of amphotericin B nephrotoxicity varies between 49% and 65%. Amphotericin B is associated with vasoconstriction causing ischaemic injury and direct interaction with epithelial cell membranes causing tubular dysfunction.[19] Three lipid formulations of amphotericin B were developed to bypass the nephrotoxic effect of the parent drug, AmBD: a liposomal preparation (liposomal amphotericin B), a lipid complex (amphotericin B lipid complex), and a colloidal dispersion (amphotericin B colloidal dispersion). These formulations differ in their lipid composition, shape, physicochemical properties, and pharmacokinetic parameters. Although the newer lipid formulations of amphotericin B have been shown to be equally effective and less toxic compared to AmBD, their prohibitive cost often limits the availability and use, especially in a developing country such as India.

Most treatment regimes involve amphotericin B, flucytosine, and fluconazole, but the addition of steroid therapy may help to improve the patient's course by the reduction of the intense inflammatory response during the early stages of the infection.[2] Corticosteroids may help in preventing visual deterioration because of their anti-inflammatory or immunomodulatory effects preventing the development of optic atrophy following optic disc swelling. Seaton et al. have compared patients received varying doses of corticosteroid along with amphotericin B andthose who received only anti-fungal therapy. They concluded that visual deterioration occurred less frequently in those treated with corticosteroids, blindness was less frequent, and in three patients vision improved. Corticosteroids may have a role in preventing or halting visual loss in *C. neoformans* var. *gattii* meningitis in immunocompetent patients.[20] Clinical trials in the future, focussing on the role of steroids, would help in studying this in detail.

Such a case of isolated infiltrative cryptococcal optic neuropathy in an immunocompetent individual has not been reported before. Although very rare, infiltrative optic neuropathy may be of fungal origin, even in an immunocompetent patient. With microscopic visualization of the organism and a high index of suspicion, a diagnosis of CNS cyptococcosis can be established especially in a low infrastructure setting; enabling the timely use of antifungals.[21]

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

***Note*:** Figures 1, 4 and 5 of this article are available in colour online at www.informahealthcare.com/oph

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