Massive subhyaloid haemorrhage as a presenting feature of Cryptococcal meningitis (CM) in Acquired Immuno Deficiency Syndrome (AIDS)

SHEETAL A SAVUR, UMA D KULKARNI

ABSTRACT

Cryptococcal meningitis is a life and vision threatening complication in patients with AIDS. Ocular morbidity usually occurs secondarily to intracranial involvement and may manifest as papillo-oedema, optic neuritis and optic atrophy. Our patient however, had an unusual presentation of unilateral subhyaloid haemorrhage, which has not been reported earlier. The visual loss in cases of CM is usually due to secondary optic atrophy or optic neuritis. Cases of AIDS, presenting with subhyaloid haemorrhage, should be investigated for CM. An early recognition and prompt management can prevent vision loss.

Key Words : Opportunistic infections, AIDS, diagnosis, visual loss, cerebrospinal fluid, subhyaloid haemorrhage, Cryptococcus Neoformans, papillo-oedema.

KEY MESSAGES: Cases of AIDS presenting with subhyaloid haemorrhage should be investigated for cryptococcal meningitis.

INTRODUCTION

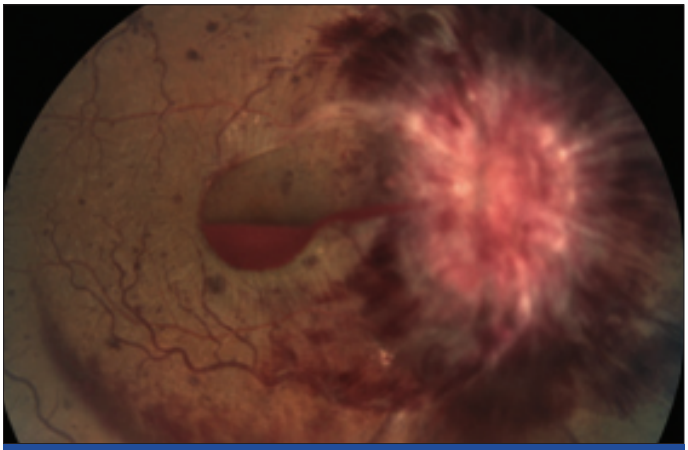
The incidence of CM is increasing with the rising numbers of AIDS patients. The clinical presentation and the course of CM may vary, relating in part to the underlying medical conditions and the immune status of the host. Ocular involvement is usually secondary to intracranial involvement and commonly manifests as papillo-oedema. Subhyaloid haemorrhage is generally seen in anaemia, thrombocytopaenia and proliferative diabetic retinopathy. Unilateral visual loss due to subhyaloid haemorrhage, as a presenting feature of CM, is rare. It is important to rule out CM in any patient with AIDS, presenting with loss of vision due to subhyaloid haemorrhage. Ethics: Written informed consent was obtained from the patient for using his clinical data and the photo-documentation for scientific publication.

CASE REPORT

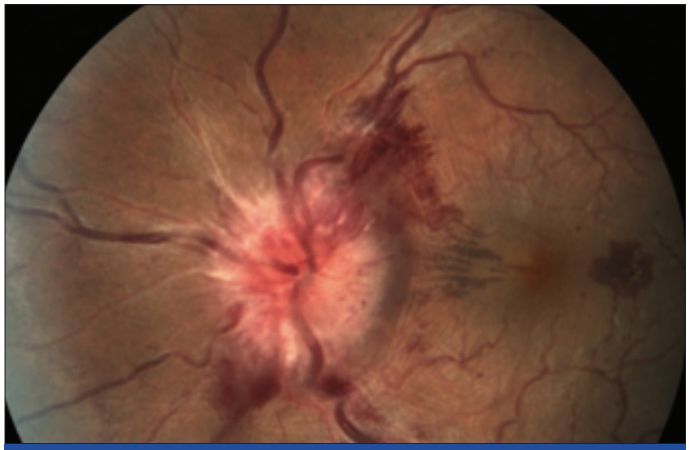
I am discussing here, the case of a 35 year old, sexually promiscuous, unmarried male who was diagnosed to have retroviral disease and who was receiving Anti Retroviral Treatment (ART) for 2 months. He complained of a throbbing headache which was associated with loss of appetite and disturbed sleep. The symptoms began one and a half months back and worsened in 15 days. He noticed the blurring of vision in the right eye, one week before presenting to us. He was otherwise apparently healthy, with his systemic examination including his central nervous system, being within normal limits.

His best corrected visual acuity right eye was 5/60, N12; left eye was 6/9, N8, with normal colour vision in each eye. The anterior segment examination of both the eyes was normal, with normally reacting pupils. Amsler grid testing in the right eye revealed metamorphopsia. The right fundus revealed fresh vitreous haemorrhage, established papillo-oedema, extensive peripapillary haemorrhage and a massive subhyaloid haemorrhage involving the fovea. [Table/Fig.1]

The left fundus revealed established papillo-oedema, peripapillary haemorrhages and dot haemorrhages in the macula and in the internal limiting membrane folds, with the absence of the foveal reflex. [Table/Fig.2]



[Table/Fig-1] : Ocular fundus- Right eye



[Table/Fig-2] : Ocular fundus- Left eye

Laboratory evaluation: Haemoglobin was 9.3gm%; otherwise, the complete haemogram was normal. The peripheral smears showed a microcytic hypochromic blood picture with leucopaenia. The liver and renal function tests were normal. The absolute CD4 count was 21.74 cells/mcl., the absolute CD8 count was 102 cells per mm3 and the CD4/CD8 ratio was 0.37 (normal range: 0.60 - 2.80).

Abdominal and pelvic ultrasound revealed mild splenomegaly. CT scan and MRI of the brain showed a normal picture.
A guarded lumbar puncture was done. The opening pressure was 25mmHg, with the patient lying down. The analysis of the CSF revealed sugar- 52mg/dl (normal range 50-80mg/dl) and protein-20mg/dl (normal range15-45mg/dl). The CSF for the India ink preparation was positive for Cryptococcus neoformans and the Z-N stain was negative for Acid Fast Bacilli. Gram staining did not show inflammatory cells or organisms. The cytological features of CSF suggested CM. The CSF culture was positive for Cryptococcus neoformans.

A clinical diagnosis of 'AIDS with cryptococcal meningitis, with bilateral papillo-oedema, with massive sub-hyaloid haemorrhage (Right eye)', was made.
The patient received intravenous Amphotericin B 25 mg in 5% dextrose OD for 2 weeks, along with oral Fluconazole 400 mg in divided doses for 8 weeks, followed by a maintenance dose of oral Fluconazole 200 mg/day.
After one month, an improvement was noticed with the resolution of the headache, improvement in the vision to 6/24 and partial resolution of the subhyaloid haemorrhage, the disc oedema and the peripapillary haemorrhage. Further follow-up was advised.

DISCUSSION

Cryptococcus neoformans is an encapsulated yeast and it reproduces by budding. Worldwide, the C neoformans serotype A causes the most cryptococcal infections in immunocompromised patients, including those in patients who are infected with HIV. Although C neoformans enters the body via the lungs, the CNS is the main site of clinically evident infection in both the immunocompetent and the immunocompromised hosts.

CM is common in immunocompromised patients including those with HIV infections. It is usually seen with a CD4+ cell count which is less than 75-125 cells per mm.[1]. The primary ocular manifestations include chorioretinitis, choroiditis,[2] retinovitreal abscess, neuroretinitis and endophthalmitis. The ocular involvement in CM is usually secondary to intracranial involvement and it may manifest as papillo-oedema, optic atrophy, and ophthalmoplegia.[3] Pseudotumour cerebri can occur in CM.[4] The mechanism is presumably defective CSF absorption at the level of the arachnoid villi, due to direct inflammation or in some cases, the raised CSF protein contributes to the failure of CSF absorption.[4]

The present case had bilateral papillo-oedema with peripapillary haemorrhages. This may be a direct result of cryptococcal meningitis [5].

A massive, sub-hyaloid haemorrhage is seen in severe anaemia and thrombocytopaenia,[6,7]. In this case, it occurred in the absence of these associations. One must therefore keep CM in mind as one of the rare causes of subhyaloid haemorrhage. Subhyaloid and vitreous haemorrhages generally result from the forward dissection of severe peripapillary haemorrhages, whereas the scattered posterior pole haemorrhages probably represent the central retinal vein compromise from the optic disc swelling . An increased intracranial pressure is accompanied by an elevated ophthalmic venous pressure[8].

In addition, the severe disc swelling may interfere with the central retinal venous flow, as well as with the local capillary perfusion,[9]. It seems that in our patient, it was likely that the retinal haemorrhages resulted from an unusually severe, central retinal venous pressure which was associated with the papillo-oedema.

Loss of vision in the present case was the result of a massive sub-hyaloid haemorrhage and vitreous haemorrhage. Cryptococcal meningitis in HIV patients per se can cause either rapid or slow visual loss. The rapid visual loss is usually due to optic neuritis, with the direct invasion of the optic nerve by Cryptococcus neoformans. Papillo-oedema and raised intracranial pressure may cause a slow progressive visual loss. Bilateral blindness has also been reported after starting antiretroviral therapy in a patient with CM. [10] Optic atrophy which was secondary to papillo-oedema and visual failure, was the most important cause of morbidity among the survivors. [5] In the present case, an early management may have prevented the occurrance of the optic atrophy which was secondary to the papillo-oedema.

The diagnosis of CM requires a high index of suspicion, especially where there is a dearth of standard medical laboratory facilities and expertise. The diagnosis also involves making the CSF smears, cryptococcal antigen (CRAG) detection in the CSF and/or serum, and the culturing of C.neoformans from the CSF.

The CRAG test is an extremely important diagnostic procedure. Cryptococcal polysachharides can be detected by the latex agglutination technique in the serum and the CSF of people with CM. CSF CRAG is locally produced in the subarachnoid space by the invading C. neoformans, but not by active or passive diffusion from the serum.[11] Positive CRAG in either the serum or the CSF, has more than 95% sensitivity and more than 95% specificity in the diagnosis of CM.[12] India ink staining is commonly used to identify C.neoformans on the direct examination of the CSF.[13] It is positive in more than 80% of the AIDS cases with CM. Imaging studies have little or no diagnostic significance in CM. Polymerase chain reaction (PCR): This test finds either the RNA of the HIV virus or the HIV DNA in white blood cells which are infected with the virus. PCR testing is not done as frequently as antibody testing, because it requires technical skill and is expensive. The PCR test is very useful to find a very recent infection and to determine whether an HIV infection is present when the antibody test results are uncertain.

Combined therapy with oral fluconazole and intravenous amphotericin B has been the recommended treatment of choice for patients with disseminated or meningeal cryptococcosis.[14] Fluconazole has been found to be beneficial in the resolution of the papillo-oedema which is caused by cryptococcal meningitis.
The recommended first-line treatment for people with AIDS and CM is based on the results of the Mycoses Study Group (MSG)/ AIDS Clinical Trials Group (ACTG).[15, 16, 17]ox It comprises the

administration of amphotericin B, 0.7 mg/kg/day, plus flucytocin, 100mg/kg/day (in four divided doses), for 2 weeks of initial treatment , followed by fluconazole, 400mg/day for 8 weeks of consolidation treatment and 200 mg/day for maintenance or secondary prophylaxis, as the relapse rate is more than 50% within the first year. Studies by the California Collaborative Treatment Group (CCTG) and the MSG/ACTG have firmly established that oral fluconazole, 200mg/day, is the drug of choice for maintenance treatment. [18, 19, 20]

CONCLUSION

Our report indicates that papillo-oedema with unilateral subhyaloid haemorrhage, with vitreous haemorrhage, can be the presenting feature in a patient of cryptococcal meningitis with AIDS.

REFERENCES

[1] Rao NA. Acquired immunodeficiency syndrome and its ocular complications. Ind J Ophthalmol 1994;42:51-63.
[2] Biswas J, Gopal L, Sharma T, Parikh S, Madhavan HN, Badrinath SS. Recurrent cryptococcal choroiditis in a renal transplant patient. Retina 1998;18:273-76.
[3] Kestelyn P, Taelman H, Bogaerts J, Kagame A, Aziz MA, Batungwanayo J, et al. Ophthalmic manifestations of infections with Cryptococcus neoformans in patients with acquired immune deficiency syndrome. Am J Ophthalmol 1993;116:721-27.
[4] P D Cremer, I H Johnston, G M Halmagyi Pseudotumour cerebri syndrome due to cryptococcal meningitis J Neurol Neurosurg Psychiatry 1997 January ;62(1):96-98.
[5] Tan CT, Kuan BB, Cryptococcus meningitis, clinical-CT scan considerations. Neuroradiology 1987;29:43-46.
[6] Majji AB, Bhatia K, Mathai A. Spontaneous bilateral peripapillary, subhyaloid and vitreous hemorrhage with severe anemia secondary to idiopathic thrombocytopenic purpura. Indian J Ophthalmol 2010;58:234-6
[7] Rubenstein RA, Yanoff M, Albert DM. Thrombocytopenia, anemia, and retinal hemorrhage. Am J Ophthalmol 1968;65:435-9.
[8] Hayreh SS,Edwards J.Ophthalmic arterial and venous pressures:Effects of acute intracranial hypertension.Br J Ophthalmol 1971;55:649.
[9] Keane JR. Sudden blindness after ventriculography: Bilateral retinal vascular occlusion superimposed on papilloedema. Am J ophthalmol 1974;78:275-78.
[10] De Schacht C, Smets RM, Callens S, Colebunders R. Bilateral blindness after starting highly active antiretroviral treatment in a patient with HIV infection and cryptococcal meningitis. Acta Clin Belg 2005;60:10-2.
[11] Currie BP, Freundlich LF, Soto MA, Casadevall A. False negative cerebrospinal fluid cryptococcal latex agglutination testswith culture positive cryptococcal meningitis. J Clin Microbiol 1993; 31: 2519-22 (s)
[12] Tanner DC, Weinstein MP, Fedorciw B, Joho KL, Thorpe JJ, Reller L. Comparison of commercial kits for detection of cryptococcal antigen. J Clin Microbiol 1994;32:1680-84 (s)
[13] Grant AD, De Cock KM. ABC of AIDS: HIV infection and AIDS in the developing world. BMJ 2001;322:1475-78 (s)
[14] Battu RR, Biswas J, Jayakumar N, Madhavan HN, Kumarsamy N, Solomon S. Papilloedema with peripapillary retinal haemorrhages in an acquired immunodeficiency syndrome (AIDS) patient with cryptococcal meningitis. Indian J Ophthalmol 2000;48(1):47-9.
[15] van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with acquired immune deficiency syndrome. National Institute of Allergy and Infectious Disease Mycoses Study Group and AIDS Clinical Trials Group. N Engl J Med 1997; 337:15-21 (s)
[16] Graybill JR, Sobel M, Saag M, et al. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses Study Group and AIDS Cooperative Treatment Groups. Clin Infect Dis 2000; 30:47-54 (s)
[17] Jaruratanasirikul S. Amphotericin B with or without flucytosine followed by fluconazole as a primary therapy for cryptococcal meningitis in patients with AIDS. Southeast Asian J TropMed Public Health 1996; 27(4):719-723 (s)
[18] Bozzette SA, Larsen RA, Chin J, et al. A placebo-controlled trial of maintenance therapy with fluconazole after treatment of cryptococcal meningitis in the acquired immune deficiency syndrome. California Collaborative Treatment Group. N Engl J Med 1991; 324;580-84 (s)
[19] Saag MS, Cloud GA, Graybill JR, et al. A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. NIAID Mycoses Study Group. Clin Infect Dis 1999; 28:291-99 (s)
[20] Benson CA, Kaplan JE, Masur H, Paci A, Holmes KK. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health and the Infectious Disease Society of America. MMWR RecommRep 2004; 53:1-112 (s)

AUTHOR:
1. DR SHEETAL A SAVUR
2. DR UMA D KULKARNI

NAME OF DEPARTMENT(S)/INSTITUTION(S) TO WHICH THE WORK IS ATTRIBUTED:
Ophthalomogy, Yenepoya Medical College, Mangalore

NAME, ADDRESS, TELEPHONE, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sheetal A Savur
Assistant Professor, Department of ophthalmology, Yenepoya Medical College, Deralakatte , Mangalore 575003
Phone: 0824-2204672, Mobile : 09632352678
Email:sheetalsavur@gmail.com

DECLARATION ON COMPETING INTERESTS: No competing Interests.

Date of Submission: **Nov 09, 2010**
Date of Peer Review: **Dec 29, 2010**
Date of acceptance: **Jan 18, 2011**
Date of Publication: **Apr 11, 2011**