Amphotericin B induced ocular toxicity in cryptococcal meningitis

PHILIP K T LI AND KAR NENG LAI

From the Department of Medicine, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong

SUMMARY We report a case of acute visual loss after a test dose (1 mg) of intravenous amphotericin B administered to a patient with systemic lupus erythematosus and with cryptococcal meningitis. Her visual acuity was normal prior to the injection of amphotericin B. The meningitis subsequently responded to miconazole and flucytosine treatment. Our findings suggest that amphotericin B should be withheld in the treatment of cryptococcal meningitis if disease of the optic nerve is strongly suspected.

Amphotericin B has been used as a first-line treatment in cryptococcal meningitis.¹ We report a case of acute visual loss after a test dose (1 mg) of intravenous amphotericin B administered to a patient with systemic lupus erythematosus and cryptococcal meningitis. We believe that this is the first report of an intravenous test dose of amphotericin B leading to ocular toxicity in cryptococcal meningitis.

CASE REPORT

A 26-year-old Chinese woman was first diagnosed as suffering from systemic lupus erythematosus with diffuse proliferative glomerulonephritis in 1984. She was maintained on low-dose prednisolone (5 mg/day) and azathioprine (125 mg/day).

She presented to the medical clinic in September 1987 with a four-week history of low grade fever and headache. The clinical examination showed absence of neck rigidity with no localising sign. The appearances on funduscopy examination and visual acuity were normal. Her white cell count was $11 \times 10^9/l$ and the erythrocyte sedimentation rate was 94 mm in the first hour. Her renal and liver function tests and C3 and C4 levels were normal. Plasma C-reactive protein was 20 mg/l (normal range 0-9.9 mg/l), and the antinuclear antibodies titre was 1:80. Urine and blood cultures were negative. A computerised tomography of the brain did not show any lesion.

A lumbar puncture was subsequently performed because of persistent headache and fever. The cerebrospinal fluid was clear, with a pressure of 30 cm H₂O. Microscopic examination showed white cells ($30 \times 10^6/l$ with 100% polymorphs) and no red cell.

The protein and glucose concentrations in the cerebrospinal fluid were 0.4 g/l and 2.8 mmol/l respectively (simultaneous blood sugar 5.8 mmol/l). *Cryptococcus neoformans* was identified with Indian ink stain and later isolated on culture. Bacterial and viral cultures were negative in the cerebrospinal fluid.

The patient was prescribed amphotericin B and flucytosine. A test dose of 1 mg amphotericin B in 20 ml 5% dextrose solution was administered intravenously over 20 minutes. She developed fever, chills, and a rigor after receiving the test dose, so amphotericin B was withheld. Ten hours later the patient complained of bilateral visual impairment. Her visual acuity was reduced to light perception at 60 cm for the right eye and 30 cm for the left eye. Her fundi looked normal, with no papilloedema or optic atrophy. The intraocular pressure was normal. Her visual acuity deteriorated rapidly. The visual evoked potentials of both eyes were unrecordable three days later, and she was totally blind.

Four days later she developed ophthalmoplegia, with failure of abduction of both eyes and impaired upward and downward gaze of the left eye. A repeated computerised tomography of the brain 10 days later did not show any lesion. Intravenous miconazole 600 mg thrice daily and oral flucytosine 1.5 g four times daily were given for a total duration of 10 weeks. Repeated lumbar puncture performed after six and eight weeks' therapy showed no pleocytosis or cryptococcus, and the cultures were negative.

Her ophthalmoplegia subsided five weeks after treatment. The visual failure persisted, with no light perception and loss of light reflexes bilaterally. Bilateral optic atrophy developed 10 weeks after the administration of amphotericin B.

Correspondence to Dr K N Lai, Department of Medicine, Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, Hong Kong.

Discussion

Patients with systemic lupus erythematosus on immunosuppressive therapy are more susceptible than usual to cryptococcal infection. Cryptococcal meningitis may cause progressive visual disturbances such as decreased visual acuity, papilloedema, increased blind spot, optic atrophy, and extraocular muscle paresis.² Acute blindness with normal fundoscopic appearance has not previously been recognised in cryptococcal meningitis. Marked visual loss shortly after intrathecal injection of amphotericin B has been previously reported in two patients with cryptococcal meningitis.² Adhesive arachnoiditis or toxic neuritis has been suggested as a possible cause.² Our patient, whose vision was previously normal, received an intravenous test dose of amphotericin B and developed acute bilateral blindness within 24 hours. Blurring of vision is a well recognised but uncommon complication of intravenous amphotericin B, but acute blindness has never been reported.³ We cannot prove that the amphotericin B was the culprit, but a possible idiosyncratic reaction of optic nerves towards the drug is highly likely in view of the temporal relation between the acute onset of blindness and the administration of the test dose. *Cryptococcus neoformans* may rarely invade the optic nerve,^{2,4} and whether this would predispose the optic nerve to further injury by the amphotericin B remains speculative.

Amphotericin B has potential renal and neurological toxicity. Since such a low testing dose could

cause acute blindness in patients with cryptococcal meningitis, extreme caution should be exercised in administering it to these patients. We suggest that it should not be used as a first-line drug in patients with possible optic nerve involvement. Miconazole has been used successfully in treating cryptococcal meningitis.^{5,6} Our patient also showed a good clinical and laboratory response to the combination therapy of intravenous miconazole and oral flucytosine. Our findings suggest that miconazole and flucytosine should be considered as the initial treatment in cryptococcal meningitis in preference to amphotericin B if optic nerve pathology is strongly suspected.

References

- 1 Spickard A, Butler WT, Andriole V, Utz JP. The improved prognosis of cryptococcal meningitis with amphotericin B therapy. *Ann Intern Med* 1963; **58**: 66–83.
- 2 Okun E, Butler WT. Ophthalmologic complications of cryptococcal meningitis. *Arch Ophthalmol* 1964; **71**: 52–7.
- 3 Reynolds JEF, Prasad AB, eds. *Martindale: The extra pharmacopoeia*. 28th ed. London: Pharmaceutical Press, 1982: 716–9.
- 4 Duke-Elder S, Scott GI. Infections of the optic nerve: mycotic and parasitic infections. In: Duke-Elder S, ed. *System of ophthalmology*. (Neuro-ophthalmology) London: Kimpton, 1971; **12**: 191–4.
- 5 Deresinski SC, Lilly RB, Levine HB, Galgiani JN, Stevens DA. Treatment of fungal meningitis with miconazole. *Arch Intern Med* 1977; **137**: 1180–5.
- 6 Weinstein L, Jacoby I. Successful treatment of cerebral cryptococcoma and meningitis with miconazole. *Ann Intern Med* 1980; **93**: 569–71.

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