Clinical Reports

Cryptococcal choroidoretinitis and immunodeficiency

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Summary: A 30 year old man with Hodgkin's disease, clinically in remission, presented with blurred vision in one eye due to a choroiditis. He developed headaches 10 days after commencing oral steroids and was subsequently found to have cryptococcal meningitis. The meningitis and choroiditis resolved on antifungal medication. This is the first case of cryptococcal choroiditis recorded in the United Kingdom.

Introduction

Cryptococcal infection, although uncommon, is now being diagnosed more frequently in the United Kingdom, where it mainly occurs in immunocompromised patients. We describe a patient with immune depression following treated Hodgkin's disease who developed cryptococcal choroiditis and meningitis.

Case report

In October 1973 an 18 year old Caucasian male presented with lower limb weakness, cervical and axillary lymphadenopathy and cord compression caused by an extradural mass. Subsequent histology showed this to be nodular sclerosing Hodgkin's disease and he received local radiotherapy and several courses of chemotherapy. He remained well and in remission from March 1977 until July 1985, when he complained of occasional night sweats at a routine clinic visit. A plain radiograph of the chest revealed a sub-pleural opacity in the left lung. In August 1985 he was referred to an ophthalmologist with a 4-day history of painless blurring of vision and floaters in the left eye, first noticed when driving his car.

Examination revealed a visual acuity of 6/6 in the right eye but vision reduced to finger counting only in the left. There were a few inflammatory cells in the anterior chamber and vitreous, a raised white lesion at the macula, and retinal folds between the lesion and the optic disc in the left eye (Figure 1). There was a similar but smaller lesion in the peripheral retina, the right eye being normal in all respects.

A provisional diagnosis of toxoplasma choro-

retinitis was made and he was treated with prednisolone 30 mg/day. Serological tests for toxoplasma and syphilis were subsequently found to be negative. Four weeks later he was admitted to hospital with headache, vomiting and photophobia, and was found to be pyrexial with signs of meningism.

Investigations showed haemoglobin 10.5 g/dl, white cell count $5.9 \times 10^9/l$ with a relative lymphopenia, erythrocyte sedimentation rate 15 mm/h. Serum urea and electrolytes and liver function tests were normal. A computerized tomography (CT) scan of the head was normal but cervical puncture yielded turbid cerebrospinal fluid (CSF) under increased pressure.

Figure 1 Left fundus photograph showing a raised macular lesion and retinal folds between the lesion and optic disc.

The CSF sugar concentration was low (1.1 mmol/l), the protein being normal (0.32 g/l) and the fluid contained 0.6×10^9 white cells/l, the majority being neutrophils. A Gram stain showed the presence of cryptococci (Figure 2) and cryptococcal antigen was detected at a titre of 1:200 in blood and CSF. No cryptococcal antibody was present. Treatment was commenced with intravenous amphotericin (50 mg/day) and oral flucytosine (2 g/6 hourly).

He rapidly improved but flucytosine had to be discontinued because of bone marrow depression. Two months after presentation the vision in his left eye had improved to 6/24 with clearing of the floaters and after a further 4 months the retinal lesions had healed and appeared as flat, pigmented scars. During his convalescence several other investigations were performed. A bronchoscopy was normal and several transbronchial biopsies in the region of the peripheral lung lesion showed no abnormality. A CT scan of the abdomen revealed enlargement of the para-aortic nodes consistent with recurrent Hodgkin's disease and chemotherapy was restarted. Tests of his immune function showed a severe T lymphocyte deficiency with a total lymphocyte count of 0.4×10^9 /l, a reduction of all T cell subsets, particularly T4 and severely depressed lymphocyte proliferative response to mitogen. Serum immunoglobulin G concentration was low at 4.2 g/l (normal range 6–16) and serological tests for human immunodeficiency virus infection were negative. After 6 months of treatment his cryptococcal antigen titre was negative. The amphotericin was discontinued after he had received a total dose of 4.2 g and he remains in good health.

Discussion

Cryptococcosis is an infection caused by the yeast *Cryptococcus neoformans*. The organism has been isolated from soil and pigeon droppings in many countries. The lung is the portal of entry but a meningitis is the most frequently recognized form of cryptococcal infection. Cryptococcosis is being diagnosed more frequently¹ and 15 to 18 cases are referred annually in the United Kingdom to the Mycological Reference Laboratory. It is more commonly reported from the USA, Australia, the Far East and Africa. Cryptococcal meningitis still has a 60% mortality in the United Kingdom, where 85% of cases have a serious underlying disease.² Predisposing conditions are lymphoma, sarcoidosis, collagen disease, carcinoma and systemic corticosteroid therapy, while more recently the acquired immunodeficiency syndrome has become an important underlying disease.¹³

Visual symptoms are common in cryptococcal meningitis, occurring in 40% of a series from the USA.⁴ Blurring, photophobia, and diplopia are

Figure 2 Gram stain of cerebrospinal fluid showing cryptococcal organisms and inflammatory cells.

thought to be the result of optic nerve, cranial nerve, or brain stem involvement in central nervous system disease, which takes the form of a meningitis, a meningoencephalitis or a space occupying lesion (cryptococcoma). Ocular cryptococcosis is uncommon, and if present usually occurs in association with meningitis, only 17 cases having been described in the world literature.⁵ The organism reaches the eye from the meninges, via the optic nerve, or blood stream, although one case was due to infected corneal graft material.⁶ Reported ocular findings include choroiditis,^{7,8,9} retinitis,^{10,11} endophthalmitis,¹² and exudative retinal detachment.¹³ Vitreous aspiration and culture have been used to confirm the diagnosis of ocular cryptococcosis¹⁴ while diagnostic enucleation of a blind eye has also demonstrated the presence of cryptococci.¹⁵ The relative lack of an inflammatory response to cryptococcal choroiditis and retinitis^{7,10,12} means that patients are likely to be asymptomatic unless there is macular involvement.

The usual treatment of cryptococcal meningitis is a combination of intravenous amphotericin B and oral flucytosine, which has been found to be more effective

than amphotericin used alone.¹⁶ Monitoring of total leucocytes, platelets, renal function and serum levels of flucytosine during therapy has been suggested,¹⁷ since toxic blood levels of flucytosine may occur as a result of impaired renal function due to the amphotericin. Bone marrow suppression due to flucytosine is dose related and it is possible to reintroduce flucytosine therapy at a lower dose when bone marrow function has improved. Intraocular injections of amphotericin, in combination with systemic therapy, have also been used in the treatment of ocular cryptococcosis¹⁴ while administration of systemic steroids has previously been known to cause exacerbation of cryptococcal meningitis,^{9,14} indeed, steroids given prior to lumbar puncture have been used as a provocative test in suspected cryptococcal meningitis. In our patient the symptoms of cryptococcal meningitis began 10 days after commencing prednisolone 30 mg/day. Although

cryptococcal choroiditis has not been confirmed histologically in our patient, the appearance of the lesions, the relative lack of inflammation in the eye, the negative tests for toxoplasmosis, histoplasmosis, tuberculosis, cytomegalovirus infection and syphilis, the CSF findings, and the response to antifungal therapy are highly suggestive of a cryptococcal aetiology. Tests for cryptococcal antigen and antibody on blood and cerebrospinal fluid are suggested in patients with an undiagnosed choroidoretinitis, particularly in association with lymphoma or immune deficiency.

Acknowledgements

We thank Dr J.B. Foster and Mr D. Cottrell for their permission to report this case. We also acknowledge Dr R.J. Hay and Dr H. Ingham for their advice.

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