

Primary CNS Lymphoma with Intravitreal Metastasis – using vitreous cavity samples to monitor response to therapy

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Abstract

A fifty-eight year old male patient presented to the ophthalmic department with a 3 day history of reduced visual acuity, blurred vision and floaters, associated with recent lethargy, headaches and behavioural changes. Fundal examination revealed a bilateral vitritis. Steroid therapy was started. MRI of the brain revealed multiple hypodense and hyperdense lesions. Vitrectomy was performed in view of the poor response to steroids. A biopsy showed non-hodgkin B-Cell lymphoma. The patient was started on intravenous Methotrexate and Cytarabine. Repeat vitreous cavity biopsies were performed in order to assess response to therapy. All biopsies to date have revealed evidence of on-going lymphoma.

Key words

Lymphoma, Vitreal Metastasis, Cytarabine, Methotrexate, Vitrectomy

Background

Primary CNS Lymphoma is a high-grade extra nodal non-Hodgkin B-cell neoplasm that commonly masquerades as benign conditions that mimic an uveitis-like picture. It is to our knowledge that this is the first reported case on the Maltese Islands in which vitreal metastases have occurred. Due to the location of the lesions, stereotactic brain biopsies were not possible to perform in order to make a diagnosis. Vitrectomy served as both a diagnostic and therapeutic tool, where repeat vitreous cavity biopsies have also been used as a means of assessing response to therapy. Fortunately, all samples so far have confirmed the presence of lymphoma, making vitrectomy the only accurate and feasible means of assessing prognosis and response to therapy despite the well-documented poor positive predictive value of such techniques due to the fragility of the lymphoma cells in question.

Case presentation

A 58 year old male patient presented to the accident and emergency department with a three day history of left sided tunnel vision, distortion, blurring and floaters. There was no ocular pain or tenderness. Visual acuity on examination was 6/9 bilaterally. Pupils were reactive with no relative afferent pupillary defect seen. Fundoscopy revealed mild vitritis on the right and severe vitritis on the left. Intra-ocular pressures were 18mmHg bilaterally. The patient was started on topical steroids.

Review 6 weeks later revealed no change in the degree of vitritis. There was a quiet anterior segment and no evidence of retinitis or choroiditis. Visual acuity remained unchanged. B scan of the retina was unremarkable except for a very hazy vitreous. Subtenon Triamcinolone (Kenalog), with a view for follow up was given. An MR Brain was done.

Two weeks later, the patient was advised to return to the emergency department in view of his MR Brain findings. A thorough history revealed the patient had a

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two week history of worsening confusion associated with weakness, lethargy, headaches and night sweats. Relatives noted a gradual change in behaviour. Neurological examination was grossly normal. Repeat MR Brain on admission to A&E revealed no changes from the previous MR Brain. Lumbar punctures were insignificant.

A working diagnosis of lymphoma was made. Multiple sclerosis was also being considered. A concrete diagnosis was not possible without histological samples.

The diagnosis was clinched when a left vitreous body biopsy after a pars plana vitrectomy revealed B-lymphocystoid lymphocytes within the vitreous, in keeping with a high grade diffuse Non-hodgkin B-Cell lymphoma.

A central line was inserted and the patient was started on high-dose intravenous methotrexate and Cytarabine according to the Ferreri Protocol. Repeat vitreous cavity samples were taken in order to assess the response to therapy. Unfortunately due to the aggressive nature of the lymphoma, repeat vitreous biopsies continued to show evidence of ongoing lymphoma.

Investigations

Slit lamp examination usually reveals vitreous cells forming clumps or sheets in the posterior segment. Fundus examination commonly reveals large, multifocal, bilateral, well-demarcated, yellow-coloured subretinal infiltrates.¹ Unfortunately no such lesions were seen in this case (Fig 1).

Figure 1: Fundoscopy: Posterior segment photo showing hazy vitreous with poor fundal details

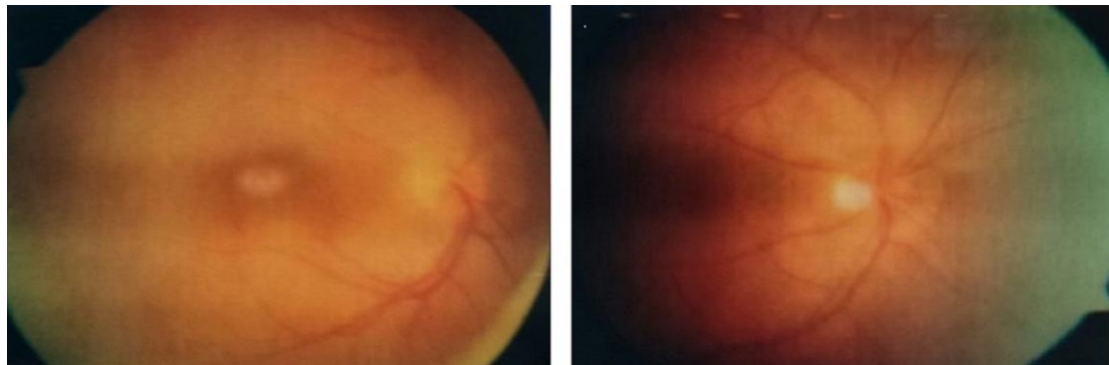


Figure 2: MR Brain: (A) Axial Diffusion Weighted Image (DWI) showing restricted diffusion predominantly in the frontal areas (B) Axial T2FLAIR showing white matter hyperintensities (C) Axial T1 with contrast showing enhancement of the left frontal lesions

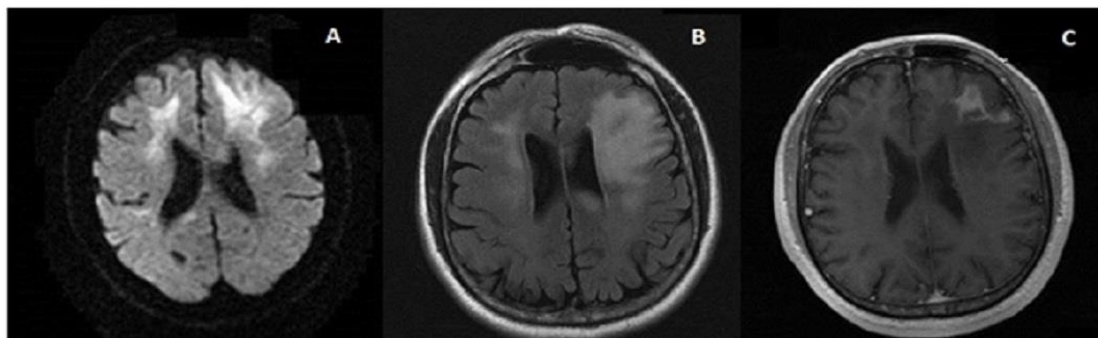
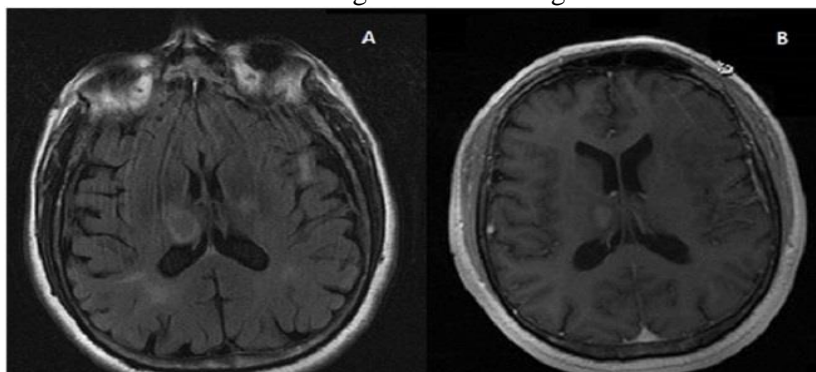


Figure 3 - MR Brain at the level of the thalami: (A) Axial T2 FLAIR (B) Axial T1 with contrast showing a 1.5cm enhancing lesion in the right



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Fluorescein angiography may show hypofluorescent or hyperfluorescent lesions.² No such lesions were seen in this case.

Ultrasound commonly reveals vitreous debris, choroidoscleral thickening or chorioretinal lesions.³ No lesions were found on US examination.

Baseline blood investigations such as CBC, CRP, ESR, routine blood biochemistries as well as a CXR were found to be within normal limits.

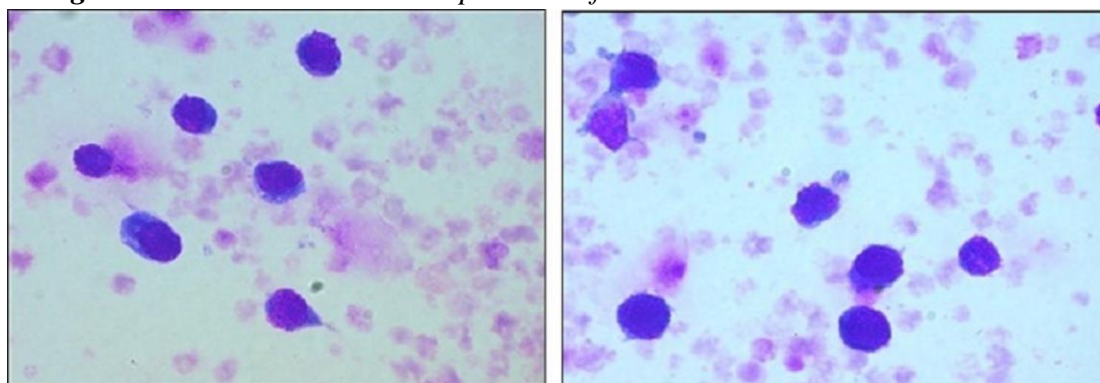
MRI revealed hyperdense lesions in T1-weighted images and hypodense lesions within deep structures of the brain when using T2-weighted sequencing (Fig 2-3).³

Lymphoma cells may also be identified in the cerebrospinal (CSF) fluid in 25 % of cases. Lymphoma cells are usually large and pleomorphic with a scanty basophilic cytoplasm.⁴ No cells were isolated when lumbar punctures were performed.

Cytometry with Cytospin preparation was carried out using Wescor Stainer, while the remaining sample

was used for Flow Cytometric (FC) analysis. The cells were stained with the following fluorochrome-labelled monoclonal antibodies: CD20FITC, CD19APC, CD10PE, CD22APC, CD79a, CD138, CD38, CD5FITC CD4PE, CD8FITC, CD3APC and CD45PerCP. Examination of the cytospin preparation showed the presence of a homogenous cell population composed of medium to large sized plasmacytoid cells with scanty and bluish cytoplasm. (Fig 4). FC evaluation showed a population of cells with moderate expression of CD45 and low Side Scatter. When gated on the cell population the cells showed weak positivity to B-cell markers CD19, CD20 and CD38, moderate positivity to CD22 and CD79a and light chain restriction with strong positivity to Lambda but no expression of Kappa light chain. CD10 was negative. All T-cell markers, CD5, CD3, CD4 and CD8 were negative thus ruling out T-cell phenotype and also CD138 showed lack of positivity excluding a plasmacytoid malignancy.

Figure 4: Cells show medium expression of CD45 and moderate Side Scatter



Treatment

The initial management on presentation included the use of high dose steroids. Unfortunately there was no response and no change in the degree of vitritis.

On confirmation of the diagnosis the patient was started on high-dose intravenous methotrexate and Cytarabine according to the Ferreri Protocol. Repeat vitreous cavity samples were taken in order to assess response to therapy. Unfortunately, owing to the aggressive nature of the lymphoma, biopsies showed evidence of on-going lymphoma.

Maintenance treatment was alerted from a monthly dose of methotrexate to a biweekly regimen. The combined use of MTX and radiation has been shown to decrease recurrence rates. However, it is associated with a 60% risk of developing dementia or leukoencephalopathy. Such therapy is currently being considered.

Outcome and follow up

Follow up is crucial, usually undertaken on a monthly basis with repeat MRI examination or CSF analysis from lumbar puncture. The following may

constitute a failure in treatment:

- Greater than 25% enlargement of previous areas of gadolinium-contrast enhancement
- Appearance of new contrast-enhancing lesions
- Appearance of malignant cells in the CSF or vitreous if not previously present

If treatment does in fact fail, there are several options that may be used. Initially, maintenance treatment may be altered from a monthly dose of methotrexate to a biweekly regimen. Radiation therapy may be implemented, often being the best second-line anti-PCNSL treatment. One may also attempt combination therapy. The combined use of MTX and radiation has been shown to decrease recurrence rates. Intravitreal methotrexate is also an option. This however is not being considered as of yet due to the uncertainty of any long term benefits keeping the aggressive and recurrent nature of the lymphoma in question.

A vitrectomy was planned and performed on the accompanying eye. Vitreous biopsy also revealed evidence of lymphoma metastasis.

Repeated vitreous cavity samples are being taken in order to assess response to the Ferreri Protocol implemented. Unfortunately, due to the aggressive nature of the lymphoma, response has been poor. Repeated samples have shown evidence of ongoing disease.

Repeat MRIs did not show marked regression of the lesions. That being said, the patient is clinically stable and has not suffered any set backs. Regular neurological outpatients follow up showed no new focal or widespread neurological deficit.

Discussion

PCNSL accounts for about 4-6% of all primary brain neoplasms and 2% of all extranodal lymphomas.⁵ It occurs mostly in patients aged between 50-60 years. Ocular dissemination occurs in 15-25% of patients being bilateral in 80% of cases.⁶

The average duration of symptoms prior to diagnosis is usually 3 months. PCNSL with intra-ocular involvement commonly presents in older patients with a non-specific chronic uveitis like picture which is unresponsive to topical and systemic corticosteroid treatment.

Ocular symptoms tend to precede cerebral symptoms by months or years in many cases.⁷ Behavioural change is the most common neurological symptom at presentation, occurring in 25-75% of patients.⁸ Initial assessment of MR Brain favoured a demyelinating or inflammatory pathology. This was excluded after repeat MR Brains showed no significant interval change.

Adequate management and treatment of such patients is dependent on early, accurate and timely diagnosis. Corticosteroids must be avoided during the initial workup and management because their administration may have a direct antitumor effect. Similarly, corticosteroids should be avoided during chemotherapy as they stimulate repair of the blood-brain barrier, decreasing the delivery of methotrexate into the brain parenchyma.⁹

The mainstay of treatment is chemotherapy. However, the main difficulty with using chemotherapy is the blood-ocular barrier.¹⁰ Studies show that systemic high dose chemotherapy resulted in relatively low drug levels in the vitreous, implicating the importance to focal ocular treatment.¹¹ Studies also show that intrathecal MTX may also be beneficial when combined to systemic MTX treatment.¹²

It is crucial that ocular disease is seen to because if left untreated, it may act as a reservoir of persistent active disease.¹³ Intravitreal MTX is able to maintain cytotoxic levels in the vitreous for hours as opposed to systemic MTX, also resulting in less complications. Intravitreal MTX has not been initiated in the patient in question but is being discussed as the next possible

option in management.

While intravitreal MTX should be added to the standard systemic chemotherapy regimen, ocular treatment simply appears to improve local control, but has no proven long term survival benefit.¹⁴

Unfortunately, prognosis remains poor, commonly as a result of the high degree of recurrence and late diagnosis.¹⁵

Learning points/take home messages

1. CNS lymphoma with vitreal metastasis may easily masquerade as a benign uveitis.
2. Lymphoma should be one of the differential diagnosis in cases of uveitis resistant to steroid treatment.
3. A multidisciplinary approach to patient care and management is vital in the proper follow up and treatment of such cases. Adequate co-operation between the ophthalmic and neurological department was necessary.
4. Vitreous samples should be handled with care to protect fragile lymphoma cells. Unfortunately, 40% of vitrectomy specimens remain non-diagnostic after corticosteroid use as they are cytolytic to lymphoma cells.
5. A multidisciplinary team is essential. Neurological and ophthalmic follow up must be accompanied by adequate oncological input in order to keep up to date with the attest chemotherapeutic protocols and guidelines. Social services also play a role in making sure the patient is comfortable and is making use of all the services available.

Patient's perspective

"Things happened very fast. Treatment was started straight away but it was not the best treatment. More tests were needed to finalize the diagnosis. I was happy with the way I was treated and I thank everyone for taking care of me. I worry because I am always in and out of hospital and I can never get rid of this condition. I underwent a vitrectomy in my other eye in order to help with the hazy vision. To be honest, my vision was the most important issue and had it not been for that, I do not think we would have started to treat my cancer condition so early because I felt fine."

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