CASE REPORT

Primary intraocular central nervous system lymphoma masquerading as diffuse retinal vasculitis

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SUMMARY

A 49-year-old woman had blurred vision and floaters of 4 days duration in the right eye. Ocular examination revealed granulomatous panuveitis, vitritis and diffuse retinal vasculitis. Following a strongly positive tuberculin skin test, she received antitubercular therapy with oral steroids and immunosuppressants. A year later, despite therapy, vitritis and vasculitis persisted. Additionally, yellowish white lesions appeared beneath the retinal pigment epithelium. Fluorescein angiography revealed a leopard skin appearance. Following a negative vitreous biopsy, she was subjected to a chorioretinal biopsy which revealed non-Hodgkin's lymphoma. MRI was normal. The ocular lesions resolved following intravitreal methotrexate injections. MRI of the brain was repeated every 3 months to rule out central nervous system (CNS) involvement. About 2.5 years after initial presentation, she complained of ataxia, hypersomnia and speech difficulty. MRI of the brain now showed lesions in the thalamocapsular region and the corpus callosum splenium suggestive of CNS lymphoma. She underwent a whole brain radiation with symptomatic improvement followed by chemotherapy.

BACKGROUND

Primary intraocular lymphoma (PIOL) has a non-specific presentation including retinal vasculitis, vitritis, retinochoroiditis, subretinal pigment epithelial (subRPE) deposits, infiltrative optic neuropathy, multiple evanescent white dot syndrome like appearances, iritis, scleritis and multifocal choroiditis with panuveitis.^{1–3} Although retinal vasculitis as the initial masquerading sign of PIOL is well known, it may pose a diagnostic challenge. Progression to central nervous system (CNS) involvement is common and proves fatal. Failure to respond to therapy and a negative vitreous biopsy should prompt the ophthalmologist for a more vigorous diagnostic intervention in the form of chorioretinal biopsy to establish a definitive diagnosis and avoid treatment delay.

CASE PRESENTATION

A 49-year-old woman presented in July 2009 with diminished vision and floaters of 4 days duration in the right eye. The best-corrected visual acuity (BCVA) was 6/9 and intraocular pressure was 14 mm Hg. The slit-lamp examination revealed granulomatous keratic precipitates, and 1+ cells and flare in the anterior chamber. The fundus examination showed a dense vitritis (3+) that precluded retinal details (figure 1A). The left eye was normal.

INVESTIGATIONS

Fundus fluorescein angiography (FA) in the right eye showed diffuse vascular leakage suggestive of retinal vasculitis (figure 1B). A laboratory workup revealed a positive tuberculin skin test and a healed nodular lesion in the right lower lobe on the chest x-ray. Despite a 1-year therapy with four drugs—antitubercular therapy, oral prednisolone (1 mg/kg/day), topical steroids and cycloplegics followed by an immunosuppressive agent (azathioprine 2 mg/kg/day), the BCVA in the right eye dropped to 6/60, with a persistence of significant vitritis. The fundus now revealed subRPE deposits, yellowish white granular lesions temporally (figure 2A) that progressed rapidly with the appearance of new lesions nasally (figure 2B) within 1 month. These lesions showed a leopard skin appearance on FA (figure 2C). A diagnostic pars plana vitrectomy (PPV) was performed which was inconclusive. The patient underwent a repeat PPV to obtain a retinal and chorioretinal biopsy. Histopathology of the retinal tissue was normal. However, subretinal fluid aspirate on cytological examination showed lymphocytes with irregular cleaved nuclei, prominent nucleoli, opened up chromatin and frequent mitosis suggestive of non-Hodgkin's lymphoma (figure 2D). MRI of the brain and bone marrow biopsy were normal.

TREATMENT

The patient received intravitreal methotrexate (400 µg/0.1 ml) injections in the right eye twice weekly. She was closely monitored for progression or development of any new lesions. MRI of the brain was repeated once in 3 months. After 11 injections, corneal epitheliopathy developed which was managed by lubricants, and intravitreal injections were withheld after the 12th dose. At 2 years follow-up, she underwent phacoemulsification with intraocular lens implantation in the right eye and BCVA improved to 6/9. At 2 months following this, a small subRPE lesion was noticed in the right eye temporally which was observed closely for progression. At 7 months after cataract surgery, the left eye developed fresh lesions (figure 2E) and the right eye showed progression of the previous lesions. Intravitreal methotrexate was repeated in both the eyes till the lesions had resolved. The left eye also developed corneal epitheliopathy which was managed as in the right eye. She received a total of 18 injections in each eye.

OUTCOME AND FOLLOW-UP

MRI of the brain remained normal for two and a half years. At 35 months after initial presentation,

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Figure 1 Colour fundus photographs of the right eye in 2009 at an initial presentation showing vitritis in the right eye (A) and fundus fluorescein angiography of the right eye showing the diffuse vascular leak suggestive of retinal vasculitis (B).

she was hospitalised for excessive drowsiness, difficulty in speech and gait instability. A neurological examination revealed generalised reduction in the motor power. MRI of the brain now showed ill-defined T2/ fluid-attenuated inversion (FLAIR) hyperintense enhancing lesions in the bilateral thalamocapsular region and in the corpus callosum splenium showing moderate hyperperfusion on dynamic susceptibility contrast imaging (figure 3A,B). A whole-body positron emission tomography showed these lesions to be moderately 18F-fluorodeoxyglucose (FDG) avid with standardised uptake value (SUV) of 10.3 (figure 3C). No similar lesions were noted elsewhere in the body. The cerebrospinal fluid did not show any abnormal lymphocytes. Bone marrow biopsy was normal. As the lesions were deep seated, stereotactic biopsy was refused by the

neurosurgeons. A diagnosis of the CNS lymphoma was made. She received a whole brain radiation. Chemotherapy was subsequently planned. Ocular examination did not reveal any new lesions at 39 months of follow-up (figure 3D,E).

DISCUSSION

PIOL is a subset of primary CNS lymphoma (PCNSL), which initially presents in the eye with or without simultaneous CNS involvement. PIOL/PCNSL is generally an extranodal non-Hodgkin, diffuse large B-cell lymphoma and rarely a T-cell tumour.⁴ The median age of onset is late 50s and 60s with a female preponderance.⁵ Approximately 25% of patients with PCNSL without an initial ocular involvement are known to subsequently develop ocular disease. Alternatively, 60–80% of PIOL without the CNS

Figure 2 Development of yellowish subretinal pigment epithelial (subRPE) deposits of the granular discrete lesions in the right eye 1 year after presentation (A), appearance of new lesions nasally 1 month later (B), lesions showing 'leopard skin appearance' on fluorescein angiography (C), subretinal fluid aspirate obtained from chorioretinal biopsy showed lymphoma cells (D) and development of new subRPE lesions in the left eye at 31 months follow-up (E).

Figure 3 Axial T2-weighted (A) and gadolinium-enhanced T1-weighted fat-saturated (B) MRI depicting T2-hyperintense, moderately enhancing bilateral thalamocapsular lesions which on FDG-positron emission tomography (C) demonstrate moderate FDG avidity suggestive of central nervous system lymphoma at 35 months follow-up. Fundus photographs showing the right (D) and the left (E) eyes at 39 months follow-up.

disease subsequently develop CNS lymphoma, usually within 29 months.^{1 6} The median survival after CNS involvement has been reported to be 12–18 months which makes the establishment of diagnosis critical for these patients. The diagnosis of PIOL requires definitive identification of malignant lymphoid cells in the eye. Surgical intervention in the form of vitreous, retinal or chorioretinal biopsy is prompted by a strong clinical suspicion.⁷ Prompt transportation of the specimen is required as PIOL cells are known to undergo rapid degeneration and necrosis. Cytology and histopathology of the specimen should be performed by an expert considering the small sample that can be recovered from the eye. Other adjuncts in the diagnosis include CD20 positivity, elevated interleukin 10 (IL-10) and/or IL-10/IL-6 in the intraocular fluid, and PCR detection of IgH gene arrangements. The local therapy for the ocular disease is with intravitreal methotrexate/external beam radiation and CNS lesions require high dose methotrexate-based chemotherapy with or without adjuncts.

Our patient developed corneal epitheliopathy which is a common but bearable side-effect of the intravitreal methotrexate injections.^{8 9} The other common injection-related adverse effects have been reported as conjunctival hyperaemia and diffuse punctate keratopathy.⁸ The less common side-effects include cataract development or acceleration, which was also seen in our patient. However, cataract development in our patient cannot be solely attributed to intravitreal injection as our patient received prolonged course of topical and oral corticosteroids. The rare adverse events include severe intraocular inflammatory reaction mimicking sterile endophthalmitis or a toxic anterior segment syndrome and a band-shaped keratopathy.⁸

PIOL is frequently known to masquerade as chronic posterior uveitis. It has a wide spectrum of differential diagnosis including infectious and non-infectious uveitic entities, leading to a series of laboratory tests, diagnostic procedures and various therapeutic regimens.¹⁰ Hence, the diagnosis of PIOL is often delayed. Retinal vasculitis is a known presenting feature of PIOL.^{11–15} The blood vessels of both the retina and the brain are known to be the preferential sites for malignant lymphoma

cells.¹¹ In our case, diffuse retinal vasculitis with a dense vitritis in an elderly woman, failure to respond to the targeted conventional therapy, progressive loss of vision, presence of yellow-white subRPE deposits or leopard skin appearance in the fundus were the alarming signs that led to a clinical suspicion of PIOL. Laboratory evidence of latent tuberculosis and an initial non-contributory vitreous biopsy results were misleading, and created a significant diagnostic delay. A high relapse rate and a subsequent CNS involvement worsen the prognosis, necessitating an early definitive diagnosis through a more vigorous diagnostic approach in the form of a retinal or chorioretinal biopsy.

Learning points

- ▶ Primary intraocular lymphoma (PIOL) masquerading as a dense vitritis and diffuse retinal vasculitis may pose a significant diagnostic challenge, and a therapeutic delay.
- ▶ A high index of suspicion is required for diagnosing PIOL.
- ▶ Subretinal pigment epithelial deposits provide a strong clue, particularly in a patient not responding to the conventional anti-inflammatory therapy.
- ▶ Repeated diagnostic intraocular biopsies may be attempted for an early definitive diagnosis of a disease that often proves fatal.

Competing interests None.

Patient consent Obtained.

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