Intravitreal bevacizumab: a viable treatment for bilateral central retinal vein occlusion with serous macular detachment secondary to Waldenström macroglobulinaemia

Waldenström macroglobulinaemia (WM), also known as Waldenström lymphoma, is one of the malignant monoclonal gammapathies. The World Health Organization defines WM as a lymphoplasmacytic lymphoma associated with a monoclonal immunoglobulin M (IgM) protein (Buske et al., 2013). It is characterized by the presence of high levels of IgM, elevated serum viscosity and the presence of lymphoplasmacytic infiltrate in the bone marrow. Due to the elevated serum viscosity, central retinal vein occlusion (CRVO) in the eye is a known, albeit rare, complication. Conventional treatment options for CRVO include treatment of the underlying predisposing factors, retinal photocoagulation, intravitreal steroids and, most recently, intravitreal anti-vascular endothelial growth factors (VEGF) and steroid implants. However, cases of CRVO in patients with WM are usually refractive to treatment (Caimi et al., 2013). We report a rare case of WM presenting as CRVO with serous macular detachment, which was responsive to intravitreal bevacizumab.

A 65-year-old gentleman presented to an ophthalmologist with right eye (OD) blurring of vision (1/60) and was diagnosed with CRVO with macular oedema. He had history of hypertension but this was under control. A week later his left eye (OS) became blurred with vision 6/60, which was also noted to be CRVO. Fundus examination showed extensive retinal haemorrhages and macular oedema bilaterally. Optical coherence tomography (OCT) was undertaken, which

![Optical Coherence Tomography showing retinal oedema with accumulation of subretinal fluid in the macular region of the left eye before initiation of systemic and ocular treatment.](image)

Fig 1. Optical Coherence Tomography showing retinal oedema with accumulation of subretinal fluid in the macular region of the left eye before initiation of systemic and ocular treatment.
showed extensive cystoid macular oedema with serous macular detachment bilaterally (Fig 1).

Blood investigations showed anaemia of 65.0 g/l and thrombocytopenia of 129 × 10^9/l. Other blood investigations were initially rejected due to high viscosity and because serum was not separable from whole blood. An urgent peripheral blood film was performed, which was suggestive of a lymphoid proliferative disorder with many abnormal lymphoid cells seen. A bone marrow trephine biopsy revealed that patient had WM.

Three cycles of therapeutic plasma exchanges were implemented monthly followed by systemic chemotherapy. Intravitreal bevacizumab was given concurrently with the therapeutic plasma exchange. After three monthly injections of bevacizumab his visual acuity improved to 6/18 OD and 6/24 OS, with reduction of central macular thickness and serous macular detachment (OS shown in Fig 2). However, complete anatomical resolution was not achieved despite treatment.

Central retinal vein occlusion as the presenting feature of WM is rare (Alexander et al., 2008) and is a consequence of hyperviscosity of the blood. WM is characterized by high levels of IgM. About 80% of the IgM is intravascular and this contributes greatly to the hyperviscosity of the serum in WM patients (Owen et al., 2003). CRVO caused by hyperviscosity in a variety of pathologies usually carries a poor visual prognosis. The reason for this is attributed to the onset of static hypoxia caused by the sluggish blood flow. The serous macular detachment on the other hand is postulated to be caused by IgM that accumulates in subretinal space through disruption of the outer retinal layers and generation of an osmotic fluid shift (Baker et al., 2013). A range of treatments have been described in managing this condition. However, previous reports state the poor response of treatment of serous macular detachments in CRVO in patients with WM. Among the modes of treatment used were plasma exchange, intravitreal triamcinolone, intravitreal anti-VEGF and recently- intravitreal injection of dexamethasone implant as reported by Fenicia et al (2013). The only case series, consisting of three patients with bilateral CRVO secondary to WM, was published by Alexander et al (2008). In that case series, CRVO was the presenting feature before a diagnosis of WM was made. The patients were treated early in the presentation with plasma exchange followed by systemic chemotherapy. No intravitreal injections were given. Two of the three patients had significant visual improvement following treatment (Alexander et al., 2008). Besirli and John- son (2013) reported a case of WM with bilateral CRVO that

**Fig 2.** Repeat Optical Coherence Tomography shows gross reduction in the retinal oedema and subretinal fluid accumulation in the macular region of the left eye following treatment.
was refractive to conventional treatment for macular oedema. The patient was treated with plasmapheresis followed by systemic chemotherapy. Only after no visual improvement was recorded following systemic treatment for WM was the patient started on intravitreal bevacizumab, with no additional benefit (Besirli & Johnson, 2013). On the other hand, Fenicia et al (2013) reported a case of bilateral CRVO who achieved partial anatomical resolution following intravitreal dexamethasone implant (Ozurdex) with no improvements in the final visual acuity. In that case however, no systemic therapy for WM was initiated. All these case reports and series differ from our case. In our case, concurrent treatment with plasmapheresis and repeated intravitreal bevacizumab started early due to the course of the disease had brought about partial anatomical resolution and significant improvements in visual acuity.

Treatment guidelines are lacking as this entity is rare and management methods are based on reviews of case reports and clinical judgements. In cases of CRVO in WM, serous macular detachment, macular oedema and secretion of VEGF may not be the only mechanism contributing to the drop in vision. Other factors, such as neurotrophic factors, which are released together with VEGF in retinal ischaemia may contribute to the pathology (Subrayan et al, 2013). Anti-VEGF aids in regulating these factors as well as reducing macular oedema. On the other hand, hyperviscosity causes static hypoxia, which leads to progressive retinal non-perfusion (Hyun et al, 2014). Early initiation of systemic therapy for WM will enable retinal circulation to be restored promptly and anti-VEGF therapy will buy precious time to protect the retina from the effects of retinal hypoxia due to retinal non-perfusion as well as improving macular oedema and regulating inflammatory factors.

In conclusion, CRVO as the presenting feature in WM is rare. Prompt and early treatment is required in such cases. We propose the use of a combination therapy of systemic plasmapheresis and intravitreal anti VEGF in cases of CRVO in WM.

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Author contributions

Dr Mohanarasan Ratanam: wrote the paper. Professor Dr Visvaraja Subrayan: wrote up the case and proof read the manuscript. You Siang Ngim: contributed information from literature search. Ass. Prof. Nurliza Khalidin: performed literature research and proof read the manuscript.

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References