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Bevacizumab Therapy and Multimodal Ultra-widefield Imaging in Immunogammopathy Maculopathy Secondary to Waldenstrom's Macroglobulinemia

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Abstract

Waldenstrom's macroglobulinemia (WM) is associated with retinal findings of hyperviscosity such as venous dilation, and findings of immunogammopathy maculopathy such as serous macular detachment. The report describes a case of bilateral serous macular detachment with intraretinal schisis-like fluid in a patient with WM. Enhanced depth imaging OCT revealed a thickened choroid with hyper-reflective accumulations in the RPE layer. The ultra-widefield fundus autofluorescence demonstrated a central area of hyperautofluorescence corresponding to the area of serous macular detachment. Ultra-widefield fluorescein angiography was characteristically silent. Intravitreal bevacizumab therapy resulted in significant reduction in intraretinal fluid, but minimal change in subretinal fluid. Long-term follow-up demonstrated alterations in retinal architecture and improved serous detachments.

Introduction

Waldenstrom's macroglobulinemia (WM) is a lymphoplasmacytic lymphoma characterized by an overproduction of monoclonal IgM.¹ Increased serum viscosity from the accumulation of pentamers of IgM molecules can lead to classic retinal manifestations of hyperviscosity syndrome, such as diffuse intraretinal hemorrhages, venous dilation and optic disc edema.² More recently, reports have described an unusual maculopathy in patients with WM.^{3–6} In this report, we characterize the multi-modal imaging features, including enhanced depth imaging spectral domain optical coherence tomography (OCT), ultra-widefield fluorescein angiography (UWFA) and fundus autofluorescence (FAF) features. Additionally, we describe the effect of intravitreal bevacizumab treatment on the anatomic features of the condition.

Case Report

A 62 year old man with WM presented with visual acuity of 20/50 right eye and 20/100 left eye. His IgM level was 4920 mg/dl prior to beginning systemic rituximab therapy. Dilated

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exam showed diffuse intraretinal hemorrhages, severe macular edema in the right eye and serous macular detachment in the left eye. OCT demonstrated severe schisis-like intraretinal fluid with minimal subfoveal fluid in the right eye. OCT in the left eye demonstrated less severe intraretinal fluid in the left eye, but prominent serous macular detachment macula. The choroid appeared thickened bilaterally (Figures 1A-B). UWFA demonstrated diffuse peripheral microaneurysms, mild peripheral venous leakage, minimal peripheral non-perfusion, and no macular leakage (Figures 1C-D). Given the significant intraretinal fluid, treatment was initiated with bilateral intravitreal bevacizumab. Four weeks following therapy, OCT demonstrated significant improvement in the intraretinal fluid but with increased subretinal fluid in both eyes (Figure 2A-B). Treatment was continued with bevacizumab for 3 months and systemic plasmapheresis and bendamustine was initiated.

At 6 months from initial presentation his IgM reached a nadir at 902 mg/dl and his visual acuity was 20/60 in both eyes. At this time plasmapheresis was stopped. OCT demonstrated persistent serous detachment with hyperreflective material adherent to the subretinal surface and increasing granular hyperreflectance on the surface of the RPE. FAF demonstrated a central area of hyperautofluorescence corresponding to the chronic serous macular detachments (Figure 3). Fifteen months after presentation, his visual acuity was 20/150 right eye and 20/80 left eye. OCT demonstrated resolving serous macular detachments with increasing accumulation of irregular, nodular hyper-reflective material on the RPE and loss of the ellipsoid zone and outer retinal architecture (Figure 4).

Discussion

Waldenstrom's macroglobulinemia is a malignant plasma cell dyscrasia which may induce retinal changes through serum hyperviscosity as well as an immunogammopathy maculopathy. Hyperviscosity from accumulation of IgM pentamers leads to venous stasis that manifests in the retina as hemorrhages, venous dilation and tortuosity. Although there was no significant venous dilation or tortuosity, there was mild peripheral venous leakage as well as diffuse intraretinal hemorrhages. UWFA demonstrated little to no significant peripheral non-perfusion, which may be useful in distinguishing the condition from diabetic retinopathy and retinal vein occlusion.

As an immunogammopathy, WM can also produce a serous macular detachment that is characteristically silent on angiography.⁵⁻⁸ The pathogenesis of the maculopathy however remains speculative. It has been shown that other immunogammopathies such as multiple myeloma (which usually has normal serum viscosity) can also produce serous macular detachments.⁸ Post-mortem immunofluorescent labeling in a patient with WM has detected IgM within the cystoid spaces of the outer plexiform layer, in the superficial retina and around photoreceptors.⁹ IgM has also been detected by immunoelectrophoresis in the subretinal fluid of a patient with Waldenstrom's.¹⁰ The prevailing hypothesis is that focal outer retinal defects provide a tract for intraretinal IgM to enter the subretinal space.³ The accumulation of the large IgM molecules provides an osmotic force that draws fluid into the subretinal space, creating the neurosensory retinal detachment.

In our review of the literature, bevacizumab therapy has not been described previously in this condition. The decrease in vascular permeability secondary to bevacizumab may explain the significant decrease in intraretinal fluid. In this case, it almost appeared that bevacizumab resulted in the movement of fluid from the intraretinal space to the subretinal space. IgM likely persists in the subretinal space and may contribute to the maintenance of the serous detachment, either through direct accumulation or osmotic effects. Systemic treatment to reduce IgM levels may represent a viable treatment for the maculopathy, however it is unknown how long IgM may persist in the subretinal space and to what degree continued RPE and or choriocapillaris dysfunction contribute to the pathogenesis.

The present case demonstrates a significant increase in choroidal thickness. Previous reports in other immunogammopathies, such as multiple myeloma, have also documented choroidal thickening.¹⁰ A post-mortem histopathologic study of the eyes of a patient with light chain deposition disease identified light chain deposition in the uvea and choroid.¹¹ In this case, increased IgM deposition in the choroid may contribute to choroidal thickening.

Serial OCT and FAF document the evolution of bilateral serous macular detachments. The FAF demonstrates hyperautofluorescence in the distribution of the serous detachments, similar to the findings in patients with multiple myeloma and light chain deposition disease.⁸ The etiology of the altered FAF is likely multifactorial: autofluorescence occurs due to fluorophores generally found at the level of the RPE with RPE lipofuscin the most studied signal. In serous retinal detachment, the physical separation of the RPE from the photoreceptors impairs phagocytosis of the outer segments, leading to an accumulation of fluorophores that appear hyperautofluorescent on fundus autofluorescence.^{8,12} The progression of the OCT supports the changes on FAF. Initially, there is a thick irregular border of hyperreflective material on the under surface of the detached retina likely representing degenerating photoreceptor outer segments. With time, this layer decreases on the outer retinal surface and a pre-RPE layer of granular hyperreflective material develops. This significant accumulation of material may represent degenerated outer segments, precipitation of immunoglobulin, or a combination of the two.

In summary, this reports demonstrates features of immunogammopathy maculopathy with the multi-modal imaging secondary to WM. Bevacizumab therapy results in dramatic reduction in intraretinal fluid without substantial change in vision and persistent subretinal fluid. Further research is needed to characterize the pathogenesis and treatment of immunogammopathy maculopathies.

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Figure 1. Immunogammopathy Maculopathy at Initial Presentation

(A) Optical coherence tomography (OCT) of the right eye with massive schisis-like intraretinal fluid (asterisk) with minimal subretinal fluid (white arrow). Choroidal thickening is present. (B) OCT of the left eye demonstrates less prominent schisis-like intraretinal fluid (asterisk) and significant serous macular detachment (white arrow). Choroidal thickening is present. (C-D) Ultra-widefield fluorescein angiography demonstrating diffuse microaneurysms, minimal peripheral non-perfusion, mild peripheral vascular leakage but no leakage in the macula.

Figure 2. Immunogammopathy Maculopathy Following Initial Bevacizumab Therapy
Optical coherence tomography 1-month following bevacizumab therapy demonstrates dramatic reduction in intraretinal fluid (asterisk) in both eyes (A,B) with concurrent significant increase in subretinal fluid (white arrow) in the right eye (A). Shaggy hyperreflective material is noted on the outer retinal surface and the inner retinal pigment epithelial surface (arrowheads) in both eyes (A, B).

Figure 3. Immunogammopathy Maculopathy 6-Months After Presentation Following Serial Intravitreal Bevacizumab Injections and Systemic Chemotherapy/Plasmapheresis

Optical coherence tomography demonstrates near-resolution of intraretinal fluid in the right eye (A) and complete resolution of intraretinal fluid in the left eye (B). Subretinal fluid persists in both eyes. Shaggy hyperreflective material (arrowheads) is now less prominent on the outer retinal surface and more prominent layered on the retinal pigment epithelial surface in both eyes (A, B). Ultra-widefield fundus autofluorescence reveals normal peripheral autofluorescence with significant increased hyperautofluorescence in the posterior pole corresponding to the chronic macular detachments (C, D).

Figure 4. Immunogammopathy Maculopathy 15-Months After Initial Presentation

Optical coherence tomography of both eyes (A, B) reveals significant reduction in serous macular detachment with outer retinal architecture loss, particularly related to the ellipsoid zone. Increased nodular accumulations of hyperreflective material are present either on the retinal pigment epithelial surface or within the retinal pigment epithelium. The choroid appears thickened and with focal areas of increased hyper-reflectance in the region of the choriocapillaris.

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