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SEROUS MACULAR DETACHMENT ASSOCIATED WITH WALDENSTROM MACROGLOBULINEMIA MANAGED WITH IBRUTINIB: A CASE REPORT AND NEW INSIGHTS INTO PATHOGENESIS

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Purpose: To report a case of serous macular detachment in a patient with Waldenstrom macroglobulinemia treated with ibrutinib.

Methods: The patient underwent a complete ophthalmic examination and imaging at presentation and at follow-up visits up to 13 months.

Results: At presentation, there were serous macular detachments bilaterally with no dye leakage on fluorescein angiography or vasculature abnormalities on optical coherence tomography angiography. After treatment with ibrutinib, there was near resolution of the patient's retinopathy with an improvement in vision at 13 months' follow-up.

Conclusion: Serous macular detachments in Waldenstrom macroglobulinemia–associated retinopathy may be due to the disruption of the retinal pigment epithelium pump mechanism by hyperglobulinemia. The favorable course of this patient, treated with the novel tyrosine kinase inhibitor ibrutinib, suggests this may be the preferred treatment for Waldenstrom macroglobulinemia patients with associated retinopathy.

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Waldenstrom macroglobulinemia (WM) is an indolent lymphoproliferative disorder characterized by immunoglobulin M (IgM) overproduction and consequent serum hyperviscosity.[1] In up to 30% of patients, hyperviscosity leads to a syndrome that includes spontaneous hemorrhages, neurological symptoms such as headaches and seizures, and cardiorespiratory distress.[2] Retinal findings of hyperviscosity syndrome include microaneurysms and intraretinal hemorrhages, vascular dilation and tortuosity, and optic disk edema. More rarely, patients develop serous retinal detachments, which are characterized by a lack of dye leakage on fluorescein angiography. The source of subretinal fluid in these patients is unclear. We report the first use of optical coherence tomography (OCT) angiography to characterize this retinopathy in a patient who was treated with ibrutinib, a novel treatment for WM, and propose a theory regarding subretinal fluid accumulation in WM-associated retinopathy.

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Case Report

A 58-year-old woman presented with a 3-month history of decreased central vision in both eyes. Best-corrected visual acuity was 20/30 in the right eye and 20/40 in the left eye. The intraocular

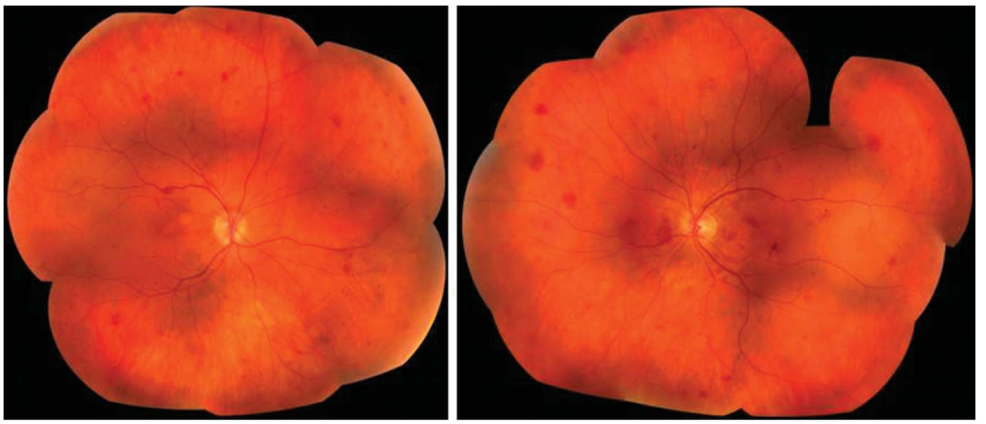

Fig. 1. Fundus photographs of the right and left eyes showed scattered intraretinal hemorrhages and somewhat dilated retinal vessels.

pressures and anterior segment examination were normal. Posterior segment examination revealed clear vitreous, normal-appearing nerves, somewhat dilated retinal vessels, and scattered intraretinal hemorrhages, more prominent in the left eye (Figure 1). Spectral domain OCT showed intraretinal fluid and pockets of subretinal fluid beneath the fovea and in the juxtapapillary regions of both eyes (Figure 2). Fluorescein angiography showed numerous microaneurysms in both eyes with no significant leakage except for one area in the right macula (Figure 3). Optical coherence tomography angiography did not reveal any abnormalities of the retinal or choroidal vasculature (Figure 4).

Laboratory evaluation demonstrated pancytopenia with a hemoglobin level of 9.0 g/dL, leukocyte count of 3.0, and platelet count of 22. Serum viscosity was elevated at 2.45 cP (normal range 1–1.87 cP). Serum protein electrophoresis showed an elevated total protein with IgM levels of 5,170 mg/dL (normal range: 40–230 mg/dL). Bone marrow biopsy confirmed a diagnosis of WM, with malignant B cells positive for the L265P mutation in the MYD88 gene.

The patient was treated with ibrutinib, a specific inhibitor of Bruton's tyrosine kinase that was recently approved by the FDA for treatment of WM. Over the course of the subsequent 13 months, the patient's pancytopenia resolved, serum IgM decreased to 1,640 mg/dL, and serum viscosity decreased to 1.26 cP (within normal range). Her vision improved to 20/25 in both eyes. At the 13-month follow-up visit, there was near resolution of her intraretinal hemorrhages (Figure 5) and subretinal fluid (Figure 6) in both eyes; however, a small amount of intraretinal fluid did persist in the left eye (Figure 6).

Discussion

Waldenstrom macroglobulinemia is an indolent lymphoproliferative disease characterized by immunoglobulin M (IgM) overproduction and consequent serum hyperviscosity.[2] At the time of diagnosis, over one-third of WM patients were found to have hyperviscosity-related retinopathy, characterized by microaneurysms, intraretinal hemorrhages, retinal vascular dilation and tortuosity and, more rarely, serous retinal detachments.[3] Unlike other conditions that result in serous retinal detachments (such as diabetic retinopathy, exudative age-related macular degeneration, retinal vein occlusions, and central serous retinopathy), patients with WM-associated retinopathy do not show dye leakage on either fluorescein or

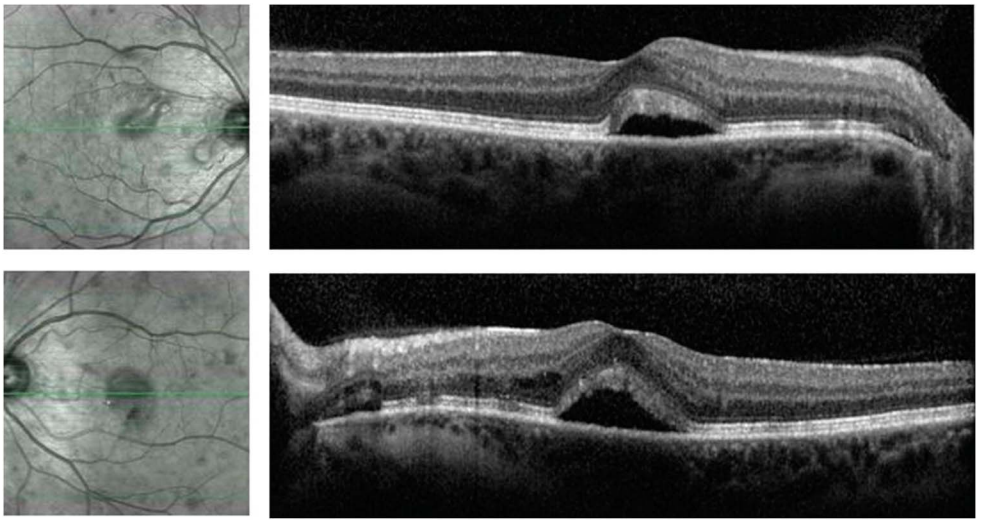

Fig. 2. Spectral domain OCT showed intraretinal fluid and pockets of subretinal fluid beneath the fovea and in the juxtapapillary regions of both the right (top) and left (bottom) eyes.

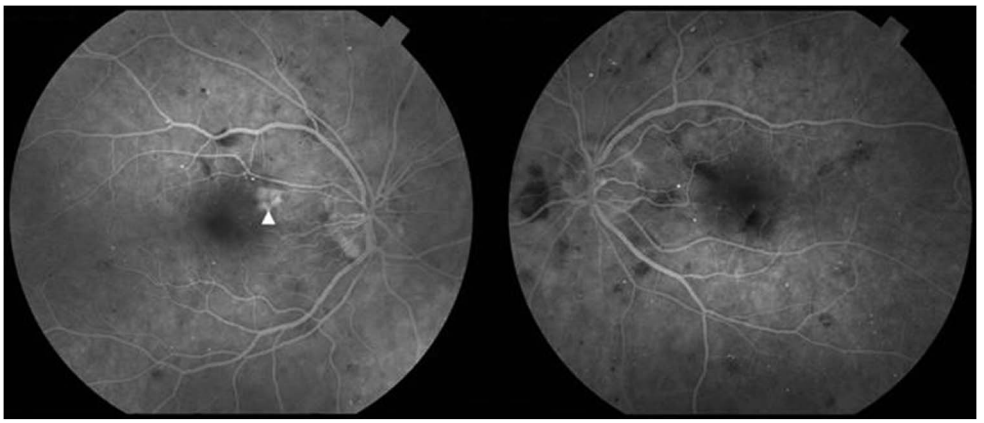

Fig. 3. Fluorescein angiogram showed numerous microaneurysms in both eyes, and no leakage except in one area in the right macula only (arrowhead).

indocyanine green angiography.[4] The source of intraretinal fluid and subretinal fluid in these patients remains unclear.

Two structures normally prevent fluid from entering the subretinal space: the inner barrier formed by the external limiting membrane and the outer barrier by the retinal pigment epithelium (RPE).[5] Intraretinal cystic spaces in WM patients were previously found to have elevated levels of IgM, suggesting that IgM extravasation leads to an increased osmotic gradient and subsequent edema.[6] Elevated levels of IgM were also found in subretinal fluid,[7] suggesting a similar osmotic gradient may be the cause of serous retinal detachments in these eyes. How IgM might penetrate the external limiting membrane to reach the subretinal space, however, was not elucidated. Examining four patients with WM-associated retinopathy with OCT, Baker et al[8] found large outer retinal disruptions overlying pockets of subretinal fluid in three of these patients. The authors proposed that these defects in the external limiting membrane allow IgM to track into the subretinal space, creating an osmotic gradient and resulting in subsequent serous retinal detachment. Notably, however, patient three in the Baker et al[8] series lacked such outer retinal defects overlying his serous detachment. Furthermore, it is unclear why breaks in the external limiting membrane would result in IgM preferentially tracking into the subretinal space and how an osmotic gradient would persist with such breaks providing unimpeded communication between intraretinal and subretinal spaces.

Similar to patient three in the Baker et al[8] series, our patient did not demonstrate outer retinal defects overlying any pockets of subretinal fluid except a small one in the nasal macula. Fluorescein angiography showed no leakage other than a minimal amount in the area of outer retinal disruption as noted above. Optical coherence tomography angiography reveals macular vasculature and architecture with a level of detail much greater than fluorescein angiography.[5] This is the first report of a patient with WM-associated retinopathy and serous retinal detachments examined

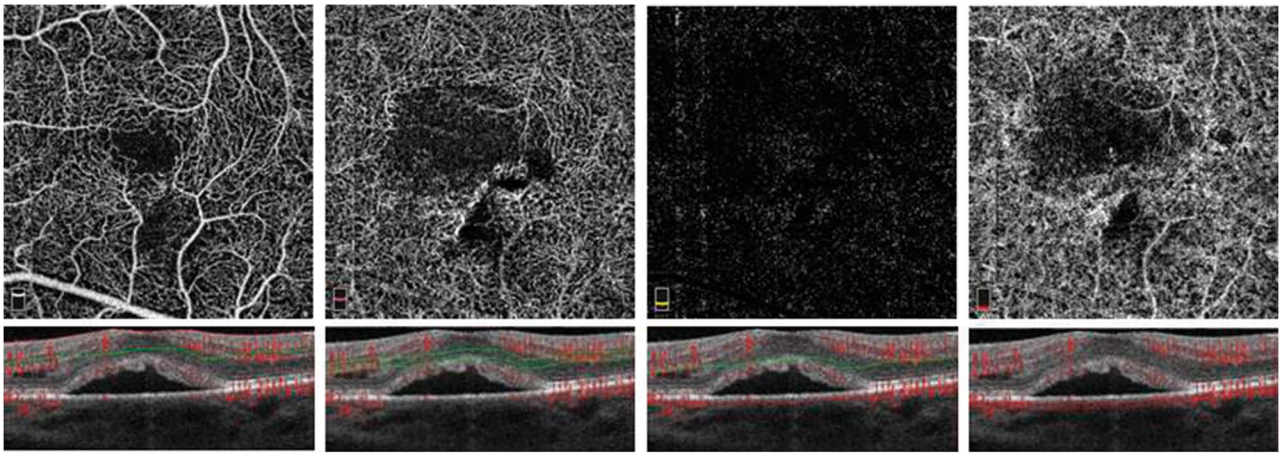

Fig. 4. Optical coherence tomography angiogram confirmed the presence of intraretinal fluid and subretinal fluid, but did not reveal any abnormalities in the retinal or choroidal vasculature in either eye (left eye shown). Top panels: en face angiograms of the (left to right) superficial capillary plexus, deep capillary plexus, outer retina, and choriocapillaris; bottom panels show the B-scan through the fovea with the corresponding segmentation.

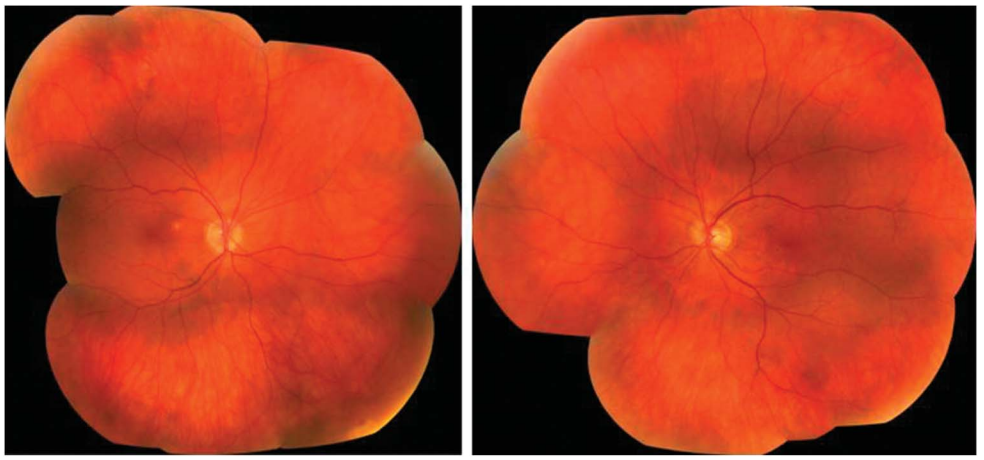

Fig. 5. At 13 months' follow-up, fundus photographs of the right and left eyes showed near resolution of intraretinal hemorrhages and normalization of retinal vascular appearance.

with OCT angiography. We found no retinal or choroidal vascular abnormalities on OCT angiography that could account for the accumulation of subretinal fluid. Finally, indocyanine green angiography in our case revealed no hyperpermeability, suggesting that the choroid is not the source of subretinal fluid.

We propose that in patients with WM, hyperglobulinemia may lead to a disruption of the RPE pump mechanism, resulting in accumulation of subretinal fluid in patients with WM. Interference with RPE-mediated fluid regulation has been implicated in the formation of multifocal shallow serous retinal detachments in MEK inhibitor-associated retinopathy[9] as well as in acute exudative polymorphous vitelliform maculopathy (AEPPVM).[10] In acute exudative polymorphous vitelliform maculopathy, these detachments are often vitelliform- and lipofuscin-rich, suggesting that paraneoplastic autoantibodies associated with acute exudative polymorphous vitelliform maculopathy cause a disruption of RPE phagocytic function as well as its pump function.[10] Lack of such vitelliform lesions in WM-associated retinopathy suggests instead that hyperglobulinemia disrupts the RPE's pump function without affecting its phagocytic ability. Unlike tumors the result in AEPPVM, which are often rapidly fatal, WM is generally indolent and treatable. We postulate that with treatment, as IgM levels and hyperviscosity normalize, the RPE pump function recovers and subretinal fluid is eliminated. By contrast, intraretinal IgM that had extravasated from the retinal vasculature is likely more difficult to clear, explaining the long-term persistence of cystoid macular edema.

In over 90% of patients with WM, malignant cells possess the L265P mutation in the MYD88 receptor adaptor molecule, which then initiates a signaling cascade through Bruton's tyrosine kinase.[11] Ibrutinib is a specific inhibitor of Bruton's tyrosine kinase. In 2015, the US Food and Drug Administration approved its use in patients with WM after it was shown to be highly potent in patients who have the MYD88-L265P mutation.[12] Our case is the first

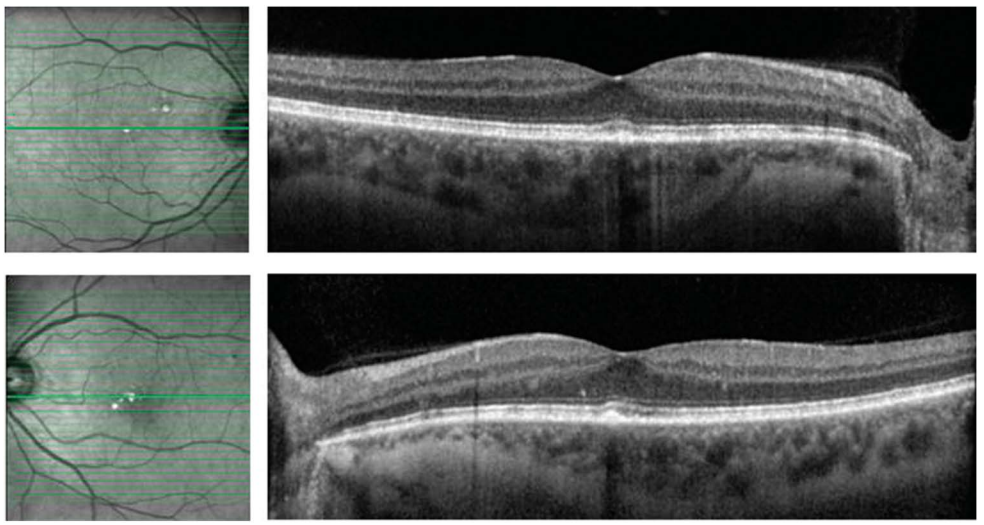

Fig. 6. At 13 months' follow-up, subretinal fluid resolved in both eyes; intraretinal fluid resolved in the right eye, but a small amount persisted in the left eye only.

description of WM-associated retinopathy treated with ibrutinib. Although in the majority of previously reported cases of WM-associated retinopathy subretinal and intraretinal fluid persisted, our case demonstrated resolution of subretinal fluid and near resolution of intraretinal fluid with improvement in visual acuity. This favorable course suggests that ibrutinib may be the preferred treatment for WM with associated retinopathy, although further studies are warranted.

Key words: Waldenstrom macroglobulinemia, retinopathy, serous macular detachment, optical coherence tomography angiography, ibrutinib.

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