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Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Choroidal Neovascularization Due to Sorsby Macular Dystrophy

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Abstract

Purpose: To report the first case of intravitreal bevacizumab and ranibizumab to treat choroidal neovascularization secondary to Sorsby macular dystrophy.
Case: A 57-year-old male with metamorphopsia, color vision deficits, and ocular family history of Sorsby macular dystrophy was found to have a choroidal neovascular membrane (CNVM) in his left eye. He was initially treated with intravitreal bevacizumab and had visual acuity improvement and resolution of the subretinal fluid on OCT. After 8 injections, he developed presumed mild inflammation secondary to intravitreal bevacizumab and was switched to combination intravitreal bevacizumab/dexamethasone in his left eye, which consistently demonstrated efficacy in stabilizing his vision and the CNVM without producing intraocular inflammation. The right eye later developed the CNVM and he was started on intravitreal bevacizumab in this eye as well. After 8 injections in the right eye, he experienced a similar inflammatory reaction following intravitreal bevacizumab injections and was switched to combination intravitreal bevacizumab/dexamethasone in the right eye as well. Subsequently, he was switched to intravitreal ranibizumab in the left eye alone, which continued to stabilize his vision and OCT and did not cause an inflammatory reaction as he previously experienced with bevacizumab. After 5 ranibizumab injections, he experienced no inflammatory response that he appeared to have with bevacizumab, but chose to switch back to combination intravitreal bevacizumab and dexamethasone due to financial reasons. Initially, in his clinical course, he experienced consistent visual acuity improvements with intravitreal antivascular endothelial growth factor therapy and continues to enjoy functional vision nearly 7 years after his initial symptoms.
Conclusions: Intravitreal bevacizumab and ranibizumab demonstrated efficacy in this case in the treatment of CNVM associated with Sorsby macular dystrophy.

Introduction

Bevacizumab (Avastin), Genentech, South San Francisco, California, is a humanized monoclonal antibody that inhibits the vascular endothelial growth factor (VEGF) that is used off-label as an intravitreal injection for a variety of neovascular ocular diseases. Ranibizumab (Lucentis), Genentech, South San Francisco, California, is a smaller monoclonal antibody fragment that also inhibits VEGF and is FDA approved for the treatment of neovascular age-related macular degeneration (AMD). Both have come into increasing use as intravitreal agents in the treatment of choroidal neovascular membranes (CNVM) secondary to numerous etiologies, including exudative AMD, myopia, punctate inner choroidopathy, Best's vitelliform dystrophy, angioid streaks, and idiopathic CNVM, among others.[1–5] Sorsby macular dystrophy is characterized by bilateral CNVM typically associated with midperipheral drusen and presenting in the fourth to fifth decade of life, and associated with mutations in the tissue inhibitor of the metalloproteinase-3 (TIMP 3) gene.[6,7] Argon laser has proven ineffective for the juxtafoveal or extrafoveal CNVM.[8] One case has reported success with photodynamic therapy (PDT) with verteporforin in treating CNVM associated with Sorsby dystrophy.[9] Although intravenous bevacizumab has been used to treat CNVM secondary to Sorsby macular dystrophy, we report the first case of Sorsby macular dystrophy treated with intravitreal bevacizumab and ranibizumab.

Case Report

A 57-year-old male of Norwegian/French/English ancestry presented to the retina clinic noticing temporal metamorphopsia in the left eye. He had a family history of a

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niece with Sorsby's macular dystrophy. His deceased father was known to have a long history of night blindness and his deceased sister was believed to have AMD. His 3 sons, aged between 10 to 30 years old, had no ocular history. His past medical history was unremarkable except for hyperlipidemia.

On examination, the visual acuity was 20/15 in the right eye and $20/20^{+1}$ in the left eye. He had a mild myopia (spherical equivalent −1.00) in both eyes, and intraocular pressures were 13 mmHg OD and 15 mmHg OS. An anterior segment examination was unremarkable. On posterior segment examination, optic nerves were pink and sharp with a cup-to-disc ratio of 0.4 OU. The macula revealed scattered hard drusen, pigment clumping, and RPE atrophy. Mid-peripheral drusen and reticular degeneration were present with peripheral RPE atrophy and yellow RPE deposits.

Further evaluation revealed a defect along the tritan axis on Farnsworth-Munsell color vision testing. The Humphrey visual field (24-2) and ERG were within normal limits, and fluorescein angiography showed no evidence of CNVM OU. Genetic testing was sent out to Stone Laboratories (Iowa City, IA) and revealed a normal coding sequence (codons 124-188 of the mature protein) of the TIMP 3 gene; however, since only 22% of Sorsby patients had variations in this coding sequence of the TIMP 3 gene, and 78% of patients tested normal, a high clinical suspicion was maintained and the patient was offered a 1-year follow-up appointment to monitor for CNVM.[10]

Seven months later, he presented with worsening vision in the left eye characterized as an enlarging blind spot. Vision was 20/20 OD and $20/30^{-2}$ OS, and the macula was remarkable for new shallow subretinal fluid (Fig. 1). The OCT showed an irregular subfoveal pigment epithelial detachment (PED) with subretinal fluid in the left eye, suggesting CNVM (Fig. 1). The patient was offered treatment with off-label intravitreal bevacizumab (1.25 mg in 0.05cc) to the left eye. One month later, his vision improved to $20/30^{+1}$ OS, and OCT showed a resolution of subretinal fluid with stable PED, and he was observed without treatment. He did need 4 repeat intravitreal bevacizumab injections over the next several months for reaccumulation of subretinal fluid associated with visual decline in intervals of 12 weeks, 10 weeks, 6 weeks, and 8 weeks later. After this point, he was switched to monthly follow-ups, and required intravitreal bevacizumab for each of his next 3 appointments for trace subretinal and intraretinal fluid recurrence with stable PED.

After the eighth bevacizumab injection, the patient presented for follow-up with visual decline to $20/100^{-1}$ in the left eye and stated that he was having prolonged recovery times with persistent eye pain after his last couple of injections that lasted for 1–2 weeks. A slit-lamp examination revealed posterior synechiae with trace vitreous cells. His history and examination suggested possible low-grade inflammation after bevacizumab injections. Fluorescein angiography of the left eye still revealed an occult CNV and OCT showed a PED with overlying intraretinal fluid. Combination therapy was offered with PDT, intravitreal dexamethasone (200 micrograms in 0.05cc), and intravitreal bevacizumab in the left eye. One month following this treatment, his vision had improved to $20/30^{+1}$ with a resolution of subretinal and intraretinal fluid and flattening of the PED. He also reported decreased injection recovery time and pain, further suggesting he may have been experiencing inflammation associated with intravitreal bevacizumab alone.

For the next 3 months, the patient had minimal intraretinal fluid with recurrence of a shallow PED in the left eye and was treated with intravitreal bevacizumab and dexamethasone at each monthly visit. One month following this series of combination treatment, his vision was $20/30^{+2}$ in the left eye with a stable PED and minimal overlying intraretinal fluid, and he elected observation, citing exhaustion from monthly injections. After 2 more months of observation, he

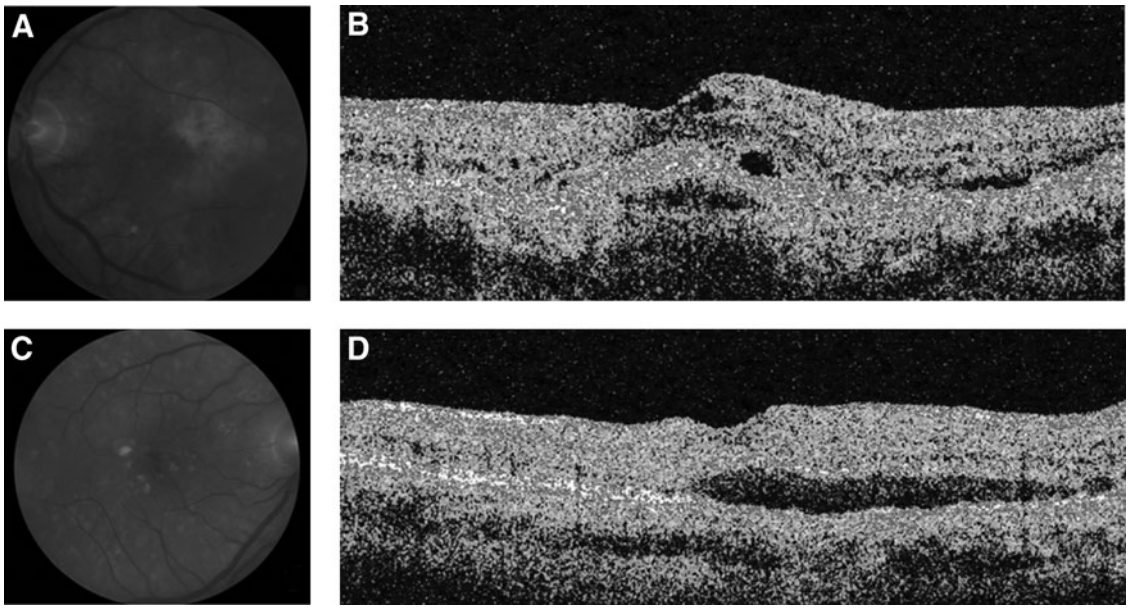

FIG. 1. **(A)** Fundus photo of the left eye shows choroidal neovascular membrane (CNVM) (*arrow*) with scattered drusen and RPE clumping. **(B)** Stratus OCT of the left eye shows subfoveal pigment epithelial detachment (PED) with overlying intraretinal fluid. **(C)** Fundus photo of the right eye shows shallow subretinal fluid tracking from extrafoveal CNVM (*arrow*). **(D)** Stratus OCT of the right eye shows subretinal and intraretinal fluid tracking from extrafoveal CNVM.

had recurrence of subretinal fluid and visual decline to 20/40^{-2} and elected resuming treatment with intravitreal bevacizumab and dexamethasone.

Our patient then continued monthly intravitreal bevacizumab and dexamethasone injections in the left eye every 4–6 weeks for 3 more months. He then presented to clinic with metamorphopsia in the contralateral (right) eye with visual decline to $20/40^{-2}$. An examination suggested extrafoveal CNVM, and OCT revealed subretinal and intraretinal fluid tracking into the fovea, suggesting CNVM formation in the right eye (Fig. 1). He was commenced on combined intravitreal bevacizumab and dexamethasone treatment in the right eye with follow-up every 4–6 weeks. He required additional combination bevacizumab and dexamethasone treatment in the right eye 3 months and 8 months later for recurrent intraretinal and subretinal fluid. Retreatment in either eye from this point with combination intravitreal bevacizumab and dexamethasone was administered whenever visual acuity decline was associated with subretinal or intraretinal fluid on OCT. After 8 bevacizumab injections and 18 bevacizumab/dexamethasone combination injections in the left eye, an attempt was made to switch the patient to ranibizumab only in the left eye. After 5 ranibizumab injections, he experienced no inflammatory response that he appeared to have with bevacizumab, but chose to switch back to combination intravitreal bevacizumab and dexamethasone due to financial reasons.

Nearly 7 years after his initial symptoms, his visual acuity in the initially affected left eye is $20/50^{+1}$, but he has had a more insidious course in the right eye with a current vision of $20/200^{-1}$. His IOP in both eyes has remained stable throughout his course. OCT testing reveals subfoveal scar formation with shallow PEDs and minimal intraretinal fluid in both eyes (Fig. 2). Early in our patient's course, he had consistent visual acuity improvements associated with improved subretinal/intraretinal fluid on OCT testing after intravitreal anti-VEGF treatment. He did subsequently experience gradual visual acuity decline due to scarring, atrophy, and cataract progression over the course of his 7 years of follow-up.

Conclusions

The diagnosis of Sorsby macular dystrophy in this case was supported by history, clinical examination, and testing. The patient's history included color vision deficits and night blindness, in addition to a family history of Sorsby dystrophy in his niece and night blindness in his father. His presenting age of symptoms is more consistent with Sorsby's (typical age 29–56, with numerous familial reports of CNV presenting in late 60's) rather than CNV associated with AMD (average age of 75).[11,12] Clinical examination revealed typical midperipheral drusen associated with CNVM, which is much more typical of Sorsby dystrophy than AMD. Testing in this patient before CNV formation confirmed color vision deficits along the tritan axis, which is also much more consistent with Sorsby dystrophy than AMD.[13]

Sorsby macular dystrophy has been associated with genetic defects in TIMP-3, which is believed to play an important role in inhibiting angiogenesis. Previous studies suggest that the pathophysiology of choroidal neovascularization in Sorsby macular dystrophy is related to defects in TIMP-3, which arrest its typical role in inhibiting VEGF-mediated angiogenesis.[14] The efficacy of bevacizumab and ranibizumab, potent VEGF-inhibitors, in inducing regression of active choroidal neovascularization further corroborates previous studies suggesting VEGF-mediated choroidal neovascularization in Sorsby dystrophy. Although a single previous report has documented the efficacy of intravenous bevacizumab, intravitreal delivery adds the important advantages of ease of delivery and an improved safety profile. Systemic bevacizumab has a myriad of risks, including increased risk of stroke, hypertension, and gastrointestinal hemorrhage.[15] Our patient appeared to experience inflammation related to his bevacizumab injections, which has been described previously and is likely unrelated to his

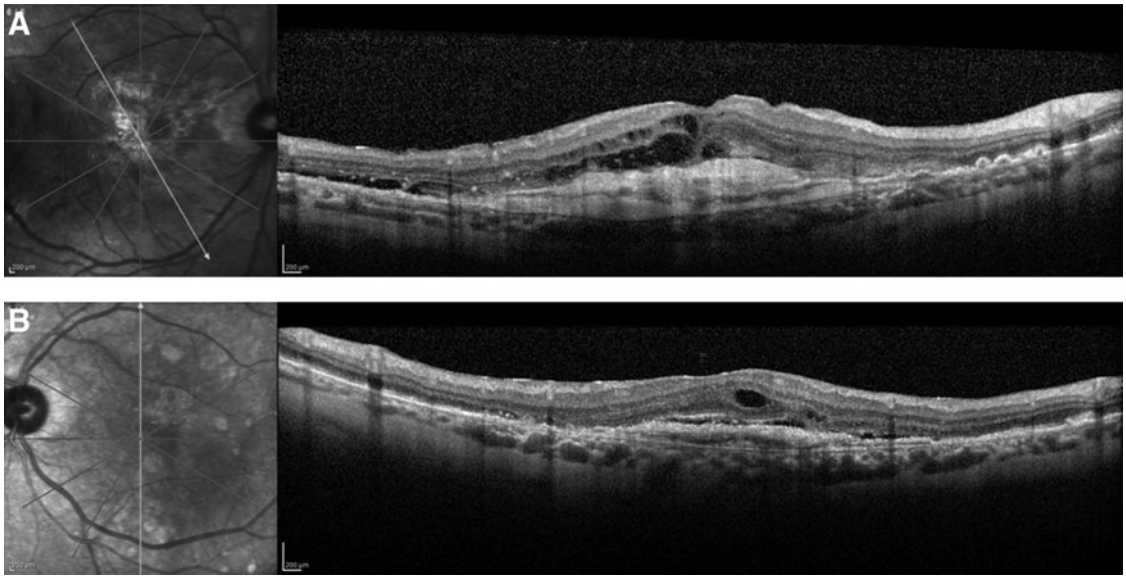

FIG. 2. **(A)** Spectralis OCT of the right eye shows the subfoveal scar with shallow PED and intraretinal fluid. **(B)** Spectralis OCT of the left eye shows the subfoveal scar with shallow PED and trace intraretinal fluid.

underlying diagnosis.[16] His clinical course was stable with the combination treatment of intravitreal bevacizumab and dexamethasone, and appears to remain stable so far on intravitreal ranibizumab alone. Early in his course, treatment with intravitreal bevacizumab repeatedly demonstrated efficacy in improving his vision and OCT findings, but he did subsequently experience a gradual decline in vision due to scarring, atrophy, and cataract progression. This initial case report demonstrates that intravitreal bevacizumab and ranibizumab are effective and safe treatment options for CNVM secondary to Sorsby macular dystrophy. Further studies and larger case series are needed to clarify the role of anti-VEGF therapy in managing CNVM secondary to Sorsby dystrophy.

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Author Disclosure Statement

The authors have no proprietary interests to disclose.

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