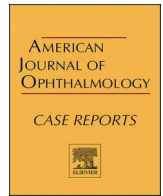




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Brolucizumab-related retinal vasculitis with exacerbation following ranibizumab retreatment: A clinicopathologic case study

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ABSTRACT

Purpose: To describe the clinical and pathologic characteristics of a case of retinal vasculitis and vitritis following brolucizumab administration and subsequent ranibizumab treatment.

Observations: A 76-year old Caucasian woman experienced pain, decreased vision and floaters one week after receiving her third monthly intravitreal brolucizumab injection in the right eye for exudative age-related macular degeneration. Examination was significant for 0.5+ anterior chamber cells, vitritis, mild peripheral vascular sheathing, and decreased vision from 20/70 to 20/200. She was started on topical 1% prednisolone acetate with improvement in her examination. She was switched to ranibizumab one month after her last brolucizumab injection of the right eye. Three weeks after her ranibizumab injection, she noticed photophobia, pain and decreased vision. Examination revealed worsening uveitis, vitritis, vascular sheathing, and decreased vision to count fingers. Despite starting on 0.05% difluprednate drops every 2 hours and oral high-dose methylprednisolone, the patient did not have any significant improvement in her symptoms or examination. She underwent pars plana vitrectomy and vitreous biopsy with intravitreal triamcinolone injection to the right eye. Vitreous biopsy and culture ruled out infectious endophthalmitis, and further cytopathologic analysis revealed chronic inflammatory infiltrate.

Conclusion and importance: Treatment with brolucizumab can result in intraocular inflammation and retinal vasculitis likely due to a delayed hypersensitivity reaction to the drug, supported by cytopathologic analysis of a vitreous sample. We demonstrate a case where retreatment with an alternative anti-VEGF agent resulted in worsening vision and vasculitis.

1. Introduction

Brolucizumab intravitreal anti-vascular endothelial growth factor (VEGF) therapy is the latest agent in the treatment of exudative age-related macular degeneration available since October 2019. It is a humanized, single-chain antibody fragment that inhibits VEGF-A, with a molecular mass of 26 kDa as opposed to 114 kDa for aflibercept and 48 kDa for ranibizumab.¹⁻⁴ The molar equivalent of 6.0 mg of brolucizumab is 12 times that of 2.0 mg of aflibercept, and 22 times that of 0.5mg of ranibizumab.¹⁻⁵ The HAWK and HARRIER phase 3 clinical trials comparing brolucizumab with aflibercept found brolucizumab to be non-inferior to aflibercept in terms of best corrected visual acuity at week 48 of the trial.⁶ In addition, a promising feature of brolucizumab

was that half of the study patients sustained 12-week injection intervals as opposed to 8-week intervals with aflibercept.⁶

However, an extended 96-week safety outcomes report from HAWK and HARRIER revealed a 4.4% rate of intraocular inflammation associated with brolucizumab, with 6 patients developing an occlusive retinal vasculitis.⁷ Post-marketing reports estimated the incidence of retinal occlusive vasculitis to be around 1–3 in 10,000 vials.^{7,8} Recently, two case reports and one case series published a variety of presentations for brolucizumab-related intraocular inflammation and occlusive vasculitis, including arterial sheathing, retinal whitening, plaque deposition, venous phlebitis, perivascular hemorrhages, optic disc swelling, and others.⁹⁻¹¹ The American Society of Retinal Specialists (ASRS) also released their Research and Safety in Therapeutics (ReST)

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committee report on 26 eyes with retinal vasculitis after treatment with brolocizumab.¹² To date, although multiple hypotheses have been made, the mechanism of action for intraocular inflammation and vasculitis due to brolocizumab has not been elucidated.

The current guidelines by ASRS recommend treating intraocular inflammation with aggressive steroids, and to avoid treating with anti-VEGF until inflammation has resolved.¹² We present a case of an elderly female patient with complications post-brolocizumab injections, retreated with ranibizumab.

2. Case report

76-year old Caucasian woman with a history of exudative age-related macular degeneration in both eyes presented with persistent subretinal fluid and a large pigment epithelial detachment in the right eye despite receiving regular intravitreal treatments with multiple anti-VEGF agents including bevacizumab, aflibercept, ranibizumab. She was switched to brolocizumab in the right eye and one month later had an improvement in her visual acuity from 20/100 to 20/80. She received two additional intravitreal injections of brolocizumab to the right eye four weeks apart. One week after her 3rd brolocizumab injection, she returned to the clinic complaining of pain, ocular aches, floaters and decreased vision. Visual acuity in the right eye had dropped from 20/70 at her last visit to 20/200. Examination revealed 0.5+ anterior chamber cells and significant vitreous debris. Fundus examination of the right eye had arterial plaques, mild vascular sheathing and boxcarring temporally (Fig. 1A). The patient was started on topical 1% prednisolone acetate with

improvement in pain, inflammation and vascular sheathing over the next week.

Given the inflammatory response following brolocizumab, the patient was switched to ranibizumab which was administered to the right eye four weeks following her previous brolocizumab injection. Three weeks later, the patient awoke with intense light sensitivity, pain, and decreased vision in the right eye. Examination revealed a drop in her vision to count fingers at 3 feet, fine keratic precipitates, and 2+ anterior chamber cells. Posterior examination demonstrated significant debris and haze with an occlusive vasculitis (Fig. 1B). The pigment epithelial detachment had collapsed and the subretinal fluid had resolved (Fig. 1B). She was started on 0.05% difluprednate drops every 2 hours while awake and oral high-dose methylprednisolone pulse therapy. Our patient returned 3 days later with only mild improvement in her symptoms and persistent vasculitis. She underwent pars plana vitrectomy to remove the inflammatory mediators the following day with vitreous biopsy and intravitreal triamcinolone injection (Fig. 2A and B).

Fluorescein angiography performed on post-operative day one revealed delayed vessel perfusion, boxcarring of the vessels, and late optic disc hyperfluorescence (Fig. 2C–E). Two weeks later, the vision was 20/400 with mild, persistent vascular changes (Fig. 2F). One month later, the retina remained stable with vision improving to 20/200; she was re-injected with ranibizumab without inflammation.

3. Histopathology

The specimen consisted of approximately 1.5 mL of clear fluid.

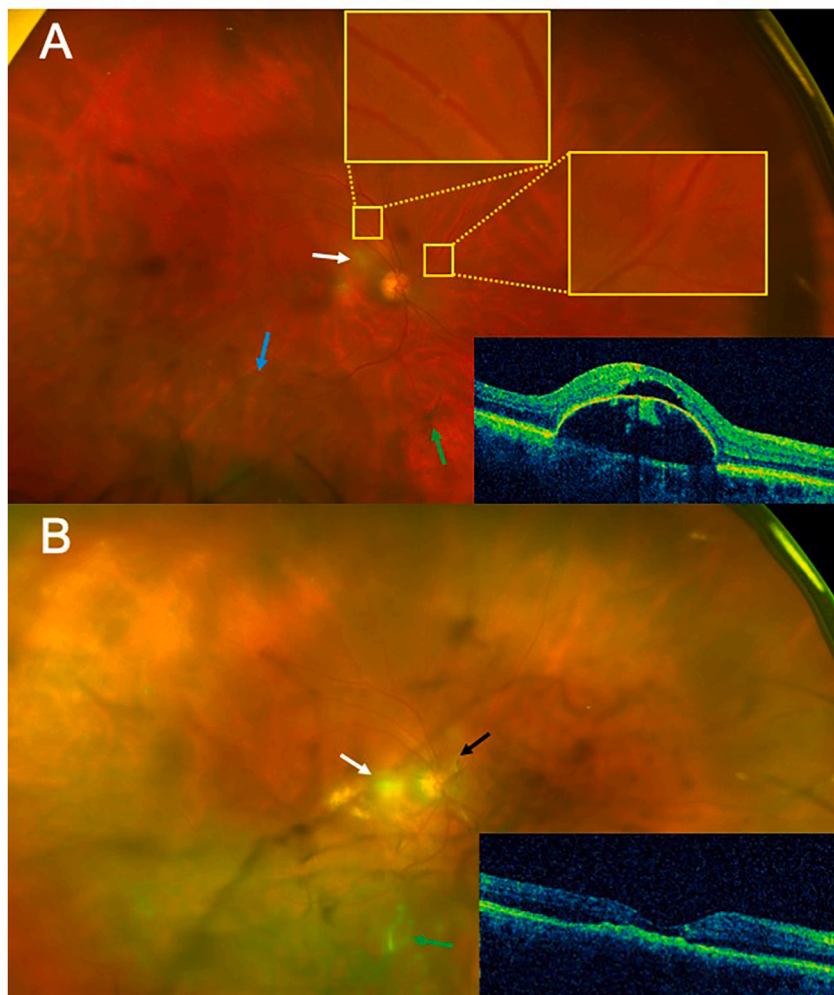


Fig. 1. (A) Fundus photograph of the right eye one week after the 3rd injection of brolocizumab. Near the disc there are areas of retinal whitening (white arrow). Plaques with associated sheathing are present in the superotemporal artery (yellow boxes). In addition, in the periphery there is boxcarring of the vessels (blue arrow). Multiple vitreous debris was also seen (green arrows). Optical coherence tomography insert demonstrates a large pigment epithelial detachment with subretinal fluid. (B) Fundus photograph of the right eye 21 days after treatment with ranibizumab. Fundus has significant debris and haze (green arrow), worsening retinal whitening (white arrow), vascular sheathing nasal to disc (black arrow), and persistent boxcarring of the vessels. Optical coherence tomography insert reveals a collapsed pigment epithelial detachment with retinal atrophy and resolution of the subretinal fluid. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

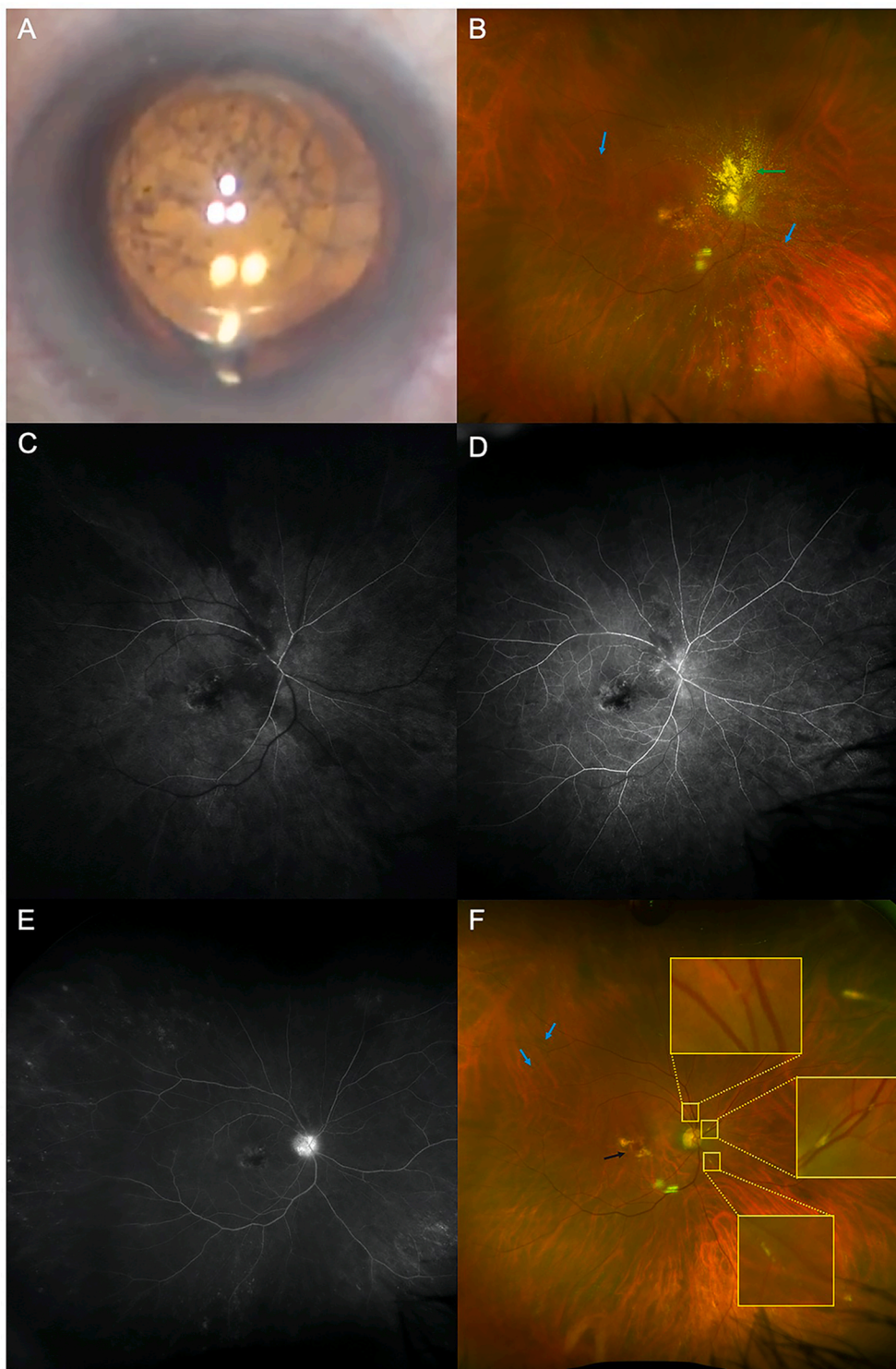


Fig. 2. (A) Pre-operative image reveals vitreous debris. (B) Post-operative image from day 1 status post pars plana vitrectomy, vitreous biopsy and intravitreal triamcinolone of the right eye (green arrow). Persistent sheathing, plaques and boxcarring of the vessels (blue arrows) is present (C) Early fluorescein angiography had delayed perfusion of both veins and arteries. Mid- and late-phase fluorescein angiography showed vessel boxcarring (D) and late disc leakage (E). (F) Fundus photograph two weeks status post pars plana vitrectomy demonstrates new plaques (yellow boxes), persistent boxcarring (blue arrows), macular hemorrhage (black arrow) and resolution of vitritis. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Examination of 12 cytospin prepared slides of the vitreous aspirate were reviewed. Examination disclosed a chronic inflammatory cell infiltrate composed of lymphocytes, histiocytes, and vitreous strands. Rare CD20 positive B cells were present (Fig. 3B), and the majority of the lymphocytes were CD3 positive T cells (Fig. 3C). Some CD4 and CD8 positive helper and cytotoxic T cells were present (Fig. 3D and E). A mild amount of CD68 positive histiocytes were present (Fig. 3F). No organisms were identified on gram, Grocott's methenamine silver (GMS), and acid-fast bacilli (AFB) staining.

4. Discussion

Retinal occlusive vasculitis with intraocular inflammation has been a devastating adverse event for brolicizumab, leading to blinding visual outcomes for many patients. Although intraocular inflammation has been seen with other anti-VEGF medications,¹³⁻¹⁵ severe vision loss due to retinal occlusive vasculitis has not been reported. This case report is a unique scenario where our patient was treated with three injections of brolicizumab, resulting in retinal vasculitis and intraocular inflammation one week after the third injection; after improvement with topical

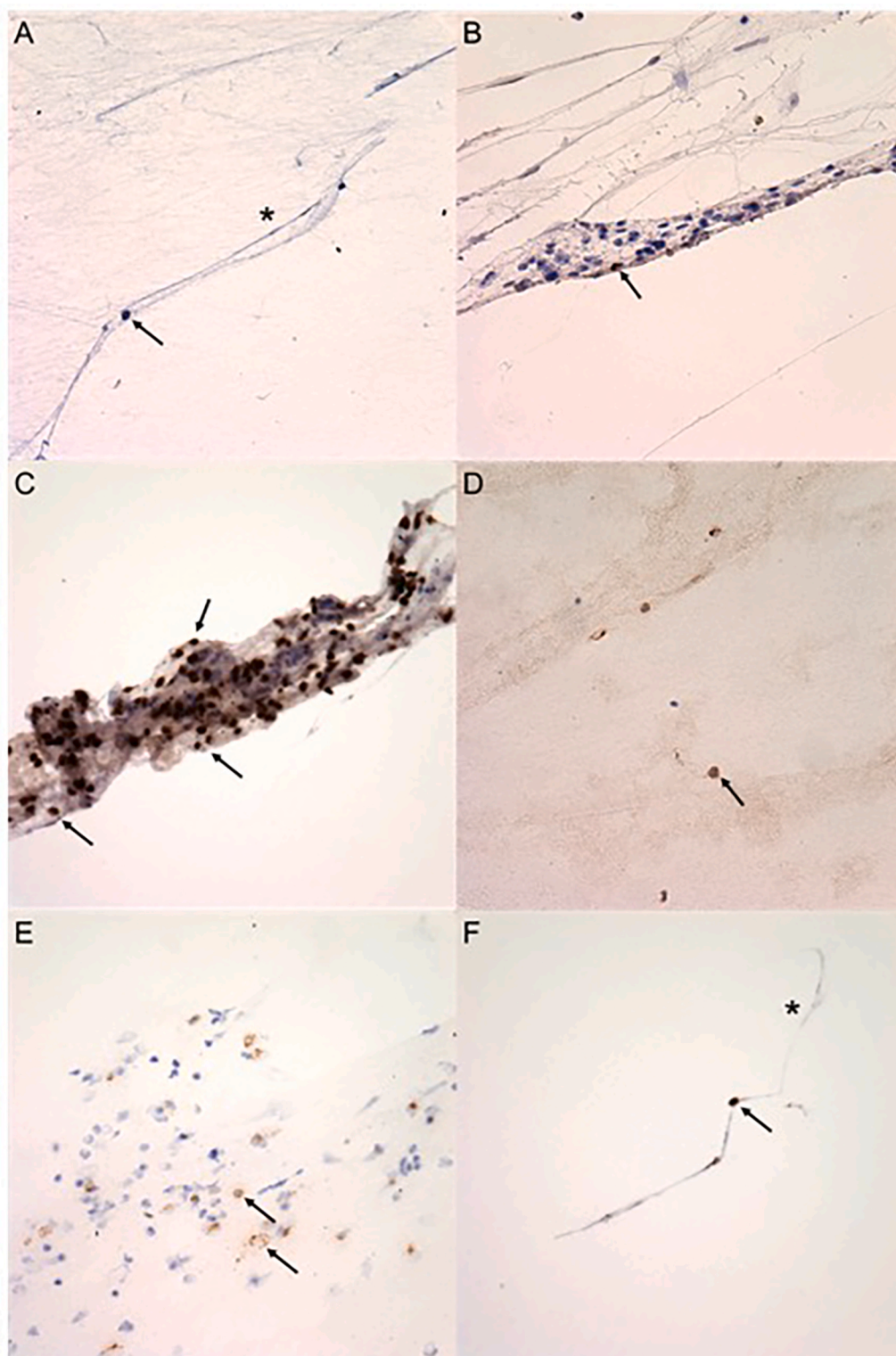


Fig. 3. Cytopathology of the vitreous biopsy: (A) Cytospin vitreous sample demonstrates lymphocytes (black arrow) and vitreous strands (asterisk) (PAP, original magnification $\times 400$). (B) Rare CD20 positive B-cells are present (black arrow) (CD20, original magnification $\times 400$). (C) Many CD3 positive T-cells are present (black arrows) (CD3, original magnification $\times 400$). (D) Few CD4 positive T-helper cells are present (black arrow) (CD4, original magnification $\times 400$). (E) A moderate number of CD8 positive T-cytotoxic cells are present (black arrows) (CD8, original magnification $\times 400$). (F) CD68 positive histiocytes (black arrow) are present with foci of vitreous strands (asterisk) (CD68, original magnification $\times 400$).

steroids, approximately one month later she was retreated with ranibizumab resulting in a delayed onset of vitritis, occlusive vasculitis, disc edema and worsening vision. We were able to analyze the vitreous as a surrogate for retinal vasculature in an attempt to better understand the pathophysiology of this inflammatory process.

Brolucizumab may be more immunogenic than other anti-VEGF agents by virtue of its relative small size and consequent ability to unfold which exposes epitopes that may not be recognized by the immune

system.¹⁶ Alternatively during the post-translational modification process of protein fragments like brolucizumab, structural changes such as cleavage and cross-linking of the protein may result in the creation of new protein epitopes.¹⁷ These new protein structures could lead to formation of aggregates, which can significantly enhance immunogenicity.¹⁷

Possible mechanisms for brolucizumab-related intraocular inflammation are infection and direct cytotoxicity of the drug or vehicle to the

ocular tissues. There was no evidence of infection on gram stain, Grocott's methenamine silver (GMS) stain, and acid-fast bacilli (AFB) stain. Toxicity can often cause intraocular inflammation, as seen in conditions such as toxic anterior segment syndrome (TASS) or toxic posterior segment syndrome.¹⁸ TASS causes cellular and extracellular damage postulated to be from detergents, metallic compounds, sterilization techniques, bacterial endotoxins, ophthalmic viscosurgical devices, and irrigation solutions.^{19–21} TASS is associated with an increase in granulocytes, including a high neutrophil/lymphocyte ratio.^{19,22} In addition, toxicity from medications can also cause a sterile intraocular inflammation. An example is retinal toxicity due to intravitreal gentamicin seen in the primate model, with retinal infarction thought to be due to granulocytic plugging of the capillary bed.^{23,24} Typically, TASS and other toxic reactions occur within 12–48 hours from exposure, whereas in the present case there was a week between the last injection and clinical presentation. While the presence of granulocytes may indicate a toxic reaction, neutrophils, basophils and eosinophils were not seen in the vitreous sample from our patient making a toxic reaction less likely.

Inflammatory mechanisms with delayed onset include type III and IV hypersensitivities as defined by Gell and Coombs.²⁵ Type III hypersensitivity is often associated with systemic autoimmune conditions involving vasculitis, and this has been suspected as the mechanism for intraocular inflammation due to brolocizumab.^{26,27} Type III hypersensitivity reactions involve non-clearing complement that bind to excess antigen, leading to an immune complex formation and eventual inflammatory response.^{26,27} This type of immune mechanism is primary humoral i.e. antibody dependent. Immunohistochemical markers that might be expected in a type III hypersensitivity reaction include plasma cells, kappa chain, lambda chain and IgG, which were rarely present in the evaluated vitreous sample. Among findings favoring type III hypersensitivity are frequent demonstration of anti-drug antibodies in the Hawk and Harrier trials, delayed onset retinal vasculitis, and some clinical overlap with hemorrhagic occlusive retinal vasculitis which is also postulated to involve type III hypersensitivity.²⁸

Type IV hypersensitivity requires CD4⁺ T cells, which sense an initial exposure to an antigen (such as brolocizumab) through antigen presenting cells displaying the antigen peptide on MHC II molecules.^{26,29,30} This type of mechanism is termed cellular mechanism, because it is completely dependent on T lymphocytes. This process involves sensitization of the immune system in preparation for a second exposure. Upon re-exposure, the antigen peptide is displayed by antigen presenting cells once again. The antigen-specific T-cells generated during the initial exposure recognize the peptide on MHC II and release a variety of cytokines including interferon gamma that stimulates histiocytes and other cells to react to the antigen.^{26,29,30} The vitreous sample stained positively for CD3, CD4, and CD8 cells indicating the presence of T cells, (including helper and cytotoxic T cells) (Fig. 3C–E) as well as CD68, a marker of histiocytes (Fig. 3F). Although the vitreous sample was located adjacent to the presumed focus of the retinal inflammatory process, the cellular composition of the infiltrate favors a type IV hypersensitivity reaction. Of the recognized types of hypersensitivities, type IV is the most delayed in onset and requires repeat exposure to antigen. The ASRS ReST committee report stated that 56% of patients developed an occlusive retinal vasculitis after the 2nd or 3rd brolocizumab injection.¹² In eyes treated with brolocizumab, retinal vasculitis can be delayed as long as 8 weeks after an injection, with an average time of 25.5 days from the most recent brolocizumab injection.^{11,12} Without better pathologic data and/or an animal model it will be impossible to determine definitively whether type III, type IV hypersensitivity, or some combination of both mechanisms are implicated in brolocizumab induced retinal vasculitis. The current case demonstrates that both T cell and B cells were present, potentially implicating both humoral and cellular mechanisms.

In our patient, after the 3rd injection of brolocizumab there was a mild episode of inflammation and retinal sheathing; presumably, the initial exposure was from the previous brolocizumab injections. After

injecting ranibizumab, retinal occlusive vasculitis, worsening intraocular inflammation and severe vision loss occurred. The rationale for using ranibizumab was that previous reports from the ASRS ReST committee already documented cases after rechallenge with aflibercept without worsening inflammation, and recommended re-treatment with anti-VEGF agents after inflammation resolved.¹² In this patient, apparent vascular inflammation had subsided at the time of re-treatment and she had also previously responded more favorably to ranibizumab. One possibility is that during an inflammatory event when an immune response is directed to proteins such as brolocizumab, the body upregulates its immunogenicity to other similar proteins with decreased specificity. Since both brolocizumab and ranibizumab are humanized antibody sequences produced in *Escherichia coli*,^{2,3} ranibizumab may have some cross-reactivity and antigenic similarity to brolocizumab, thus becoming a target through an already primed immune system. Another possibility is that the adverse effects of the brolocizumab hypersensitivity was delayed and its full effects were only seen coincidentally after injecting ranibizumab.

Although majority of retinal occlusive vasculitis occurs after multiple injections of brolocizumab, 44% can develop occlusive retinal vasculitis an average of 26 days after the 1st injection according to the ASRS ReST committee report.¹² This may be due to the fact that the presence of pre-existing local serum antibodies to brolocizumab have been noted to be higher than other anti-VEGF agents. Specifically, 36–52% of treatment naïve patients were found to have anti-brolocizumab antibodies.³ Pre-treatment serum antibodies to brolocizumab have been shown to correlate with intraocular inflammation in clinical trials, and may also play a role in developing intraocular inflammation sooner especially for patients treated for the first-time.¹¹

The ASRS recommends not to inject brolocizumab or any other anti-VEGF agent until inflammation has resolved.¹² In our case, the intraocular inflammation after brolocizumab had improved with topical steroids, and retreatment with ranibizumab one month after brolocizumab still resulted in worsening inflammation with vision loss. While the ASRS recommends treatment of intraocular inflammation with aggressive steroids, intraocular inflammation and retinal occlusive vasculitis in our patient persisted without improvement despite topical and oral steroid treatments. A case by Haug et al. also demonstrated that even after treatment with intravitreal dexamethasone, retinal occlusive vasculitis progressed several weeks later.¹⁰ Prompt treatment with aggressive corticosteroid treatment may be helpful but should be continued for several weeks until there is significant clearance of the drug from the vitreous. Vitrectomy may expedite this clearance but may only be helpful early on, prior to evidence of vascular occlusion. Anti-VEGF retreatment should also be withheld until drug has been adequately cleared from the vitreous or at least until all inflammation has resolved.

5. Conclusion

We report a case of an elderly woman with exudative macular degeneration who had brolocizumab-related intraocular inflammation and mild retinal vasculitis to the right eye, which improved on topical prednisolone. When retreated with ranibizumab 28 days later, she developed severe vitritis with worsening occlusive retinal vasculitis. She failed topical difluprednate and oral steroids, and was taken for pars plana vitrectomy and vitreous biopsy. Cytopathology of the vitreous sample ruled out a toxic reaction and favored an immune response, specifically a delayed-type hypersensitivity reaction either a humoral or cellular immune process over a toxic or infectious cause. Identifying symptoms and signs of this immunogenic response early and prompt corticosteroid treatment is essential, as retinal arterial vascular occlusions can ensue with profound, irrecoverable vision loss.

Patient consent

Consent to publish this case report has been obtained from the patient.

Financial disclosure and conflicts of interest

Marc C Peden is an investigator for Allergan, Alkermes, Apellis, Genentech, Kodiak and Novartis. He is a consultant and speaker for Genentech.

Ivan J. Suñer is an investigator for Allergan, Alkermes, Apellis, Genentech, Kodiak, Novartis and Regeneron. He is a consultant for Allergan, Genentech, Novartis, and Regeneron. He is also a speaker for Novartis and Regeneron.

Thomas A. Albini is a consultant for Allegro Allergan, Genentech, Ophthalmics, Beaver Visitec, Clearside Biomedical Inc, Eyepoint Pharmaceuticals, Inc, Janssen Biotech Inc, Notal Vision, Novartis.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

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