



Successful treatment of idiopathic retinal vasculitis with rituximab in two patients

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ABSTRACT

Purpose: To describe results of treatment of idiopathic retinal vasculitis with intravenous rituximab.

Observations: We present two patients with idiopathic retinal vasculitis who required steroid-sparing therapy and achieved steroid-free remission with intravenous rituximab. Rituximab was used as a first-line steroid-sparing agent after steroids in one patient and as a second-line steroid-sparing agent in the other patient. Both patients achieved steroid-free remission of disease with follow up of at least one year after rituximab initiation.

Conclusions and importance: Rituximab achieved steroid-free remission in two patients with idiopathic retinal vasculitis. It should be considered as a treatment option in these patients.

1. Introduction

Retinal vasculitis is an inflammation of retinal arterioles, venules and/or capillaries and can be associated with several systemic and ocular diseases. The non-infectious systemic diseases most commonly associated with primary retinal vasculitis are Behcet's disease, collagen vascular disease, and sarcoidosis.¹ Ophthalmic conditions associated with secondary retinal vasculitis include forms of posterior uveitis, such as birdshot chorioretinopathy, and intermediate uveitis.² Infectious posterior uveitis can also manifest with retinal vasculitis. Rarely, it may be a primary, idiopathic condition without uveitis or any extraocular manifestations which is termed idiopathic retinal vasculitis. Idiopathic retinal vasculitis accounts for approximately 8.7% of all cases of retinal vasculitis.³

Many agents have been used to achieve steroid-free remission for idiopathic retinal vasculitis. There have been publications showing the efficacy of anti-metabolites,⁴ anti-tumor necrosis factor (TNF)-alpha inhibitors,⁵ and alkylating agents.⁶ Rituximab is an anti-CD20 antibody biologic. Its treatment effect onset typically takes 6–16 weeks^{7,8} and lasts 6–9 months.^{9,10} Rituximab is currently approved for the treatment of several systemic immune-mediated diseases including rheumatoid arthritis and granulomatosis with polyangiitis (GPA).¹¹ Several studies have also shown promising therapeutic benefit of rituximab in patients with retinal vasculitis secondary to a variety of ocular and systemic conditions including GPA, systemic lupus erythematosus (SLE), and

intermediate uveitis.¹² To the best of our knowledge, treatment of idiopathic retinal vasculitis with anti-CD20 therapy has not been reported. Herein we present successful treatment of idiopathic retinal vasculitis with rituximab in two patients.

2. Case reports

2.1. Case 1

A 28-year-old woman was referred with the complaint of floaters, flashes of light, and blurred vision in the right eye for two weeks. Best-corrected visual acuities (BCVA) at presentation were 20/30 and 20/20 for the right and left eyes, respectively. There was no anterior chamber or vitreous cell. Fundus examination showed optic disc hyperemia, mildly engorged and tortuous retinal veins, nasal perivascular exudates and temporal retinal hemorrhages in the right eye (Fig. 1A). The left eye was normal. Fluorescein angiography (FA) showed retinal vascular leakage along the temporal and nasal retinal vessels and areas of non-perfusion nasally (Fig. 1B). She was diagnosed with occlusive retinal vasculitis in the right eye. Laboratory studies were negative for infectious and systemic etiologies including toxoplasmosis, syphilis, tuberculosis, Lyme disease, SLE, and GPA. MRI of the brain and orbit showed no evidence for multiple sclerosis. Position emission tomography – computerized tomography (PET-CT) scan of the chest and abdomen showed no lymphadenopathy, Magnetic resonance angiography (MRA)

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of the neck, cardiac echography and carotid ultrasound were also normal. She had consultations with pulmonology, rheumatology and dermatology and no extraocular disease was identified. She was treated with intravenous methylprednisolone 1000 mg daily for 3 days followed by an oral prednisolone taper. She had worsening of disease with prednisone tapering despite also being on subcutaneous adalimumab 40 mg every two weeks for several months. Fig. 1C and D show this worsening with a new peripapillary cotton wool spot, new hemorrhages temporally and persistent retinal vascular leakage. She was then treated with two loading intravenous rituximab 1000 mg infusions, two weeks apart. This was followed by two single 1000 mg maintenance infusions at 5-month intervals. Each rituximab infusion involved pre-treatment with methylprednisolone 100 mg intravenously to prevent infusion reactions. She completed her oral prednisone taper 5 months after rituximab initiation, at the time of her first rituximab maintenance infusion. She also received scatter laser to areas of nonperfusion. Thirteen months after rituximab initiation and three months after her second rituximab maintenance infusion, remission of the retinal vasculitis was achieved with resolution of retinal vasculitis on examination and imaging (Fig. 1E and F).

2.2. Case 2

A 57-year-old woman presented with blurry vision in the left eye for two months. Her BCVA at presentation was 20/20 in both eyes, but visual field testing showed an inferior hemianopia in the left eye. Anterior segment examination was normal and there was no anterior chamber or vitreous cell. Fundus examination revealed perivascular exudates of superior retinal vessels superiorly and temporally (Fig. 2A). FA showed

lack of perfusion of superior retina with distal areas of late leakage (Fig. 2B and C). The right eye was normal. Serologic testing was negative for infectious and non-infectious causes of retinal vasculitis, with the exception of an anti-nuclear antibody (ANA) that was positive at 1:320 with a dense fine speckled pattern. However, the patient had no systemic manifestations of SLE or other immune-mediated disease, anti-double stranded DNA was negative, and evaluation by rheumatology deemed this ANA to be non-clinically significant. She also had a normal CT-angiogram of the head and neck, brain MRI and cardiac echography. She was treated with intravenous pulse methylprednisolone 1000 mg daily for 3 doses followed by a prednisone taper. Her retinal vasculitis recurred with tapering of prednisone (Fig. 2D and E). Options for steroid-sparing therapy were discussed with the patient and she opted for rituximab as she was familiar with this medication because it has been used to treat her son's Henoch Schonlein Purpura successfully. She was treated with two initial intravenous rituximab 1000 mg infusions, two weeks apart. This was followed by two single 1000 mg maintenance rituximab maintenance infusions at 4 and 5-month intervals, respectively, over the subsequent year. Each rituximab infusion involved pre-treatment with methylprednisolone 100 mg intravenously to prevent infusion reactions. The patient was tapered off prednisone 3 months after rituximab initiation. Fifteen months after rituximab initiation and six months after her second rituximab maintenance infusion, remission of the retinal vasculitis was achieved with resolution of retinal vasculitis on examination and imaging (Fig. 2F and G). No further rituximab is planned unless there are signs of worsening.

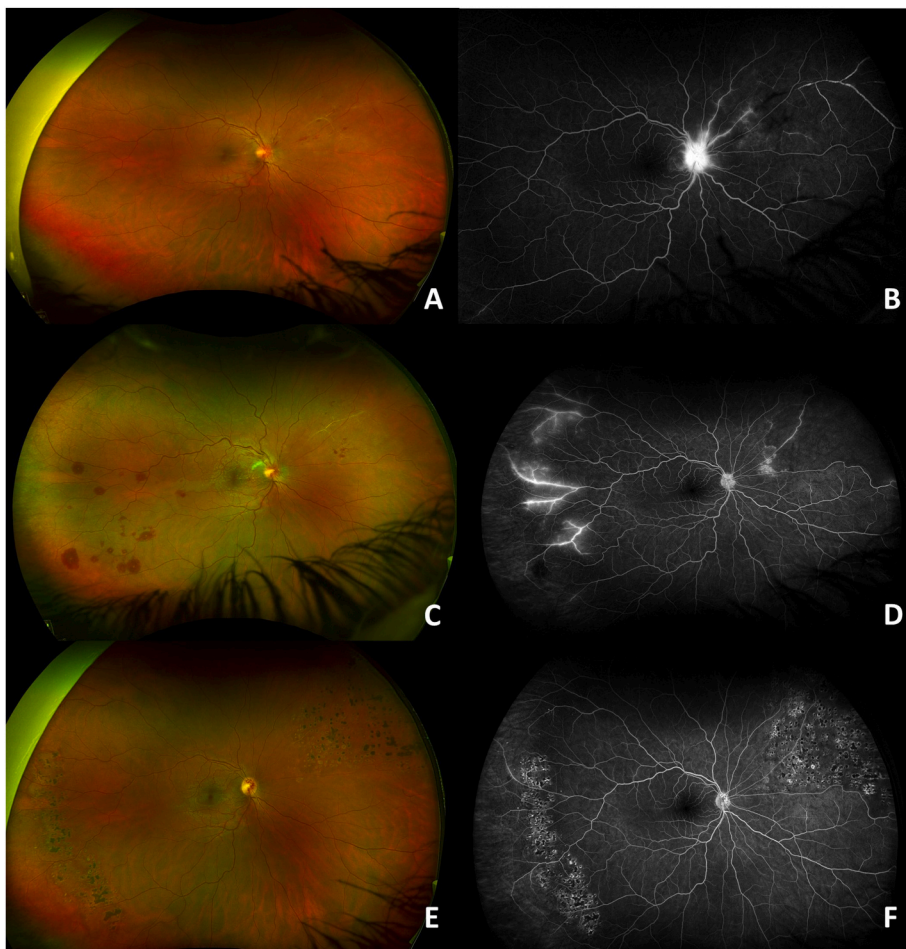


Fig. 1. Fundus photograph of the right eye of Patient 1 at initial presentation (A) showed optic nerve hyperemia, cotton wool spots superotemporal to optic disc, mild retinal vein dilatation, nasal perivascular exudates, and intraretinal hemorrhages. Fluorescein angiography (FA) showed leakage from the optic disc, vascular leakage nasally, and segmental retinal vascular nonperfusion nasally (B). While being treated with adalimumab and tapering prednisone, she had worsening with increased retinal hemorrhages temporally in the right eye (C). FA at that time (D) showed retinal vascular leakage temporally and nasally and retinal non-perfusion nasally. Fundus photograph 13 months after rituximab initiation (E) showed a sharp pink optic disc with opticociliary shunt vessels and scatter laser photocoagulation scars temporally and superonasally. FA showed staining of the laser scars and no vascular leakage of the right eye 13 months after rituximab initiation (F). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

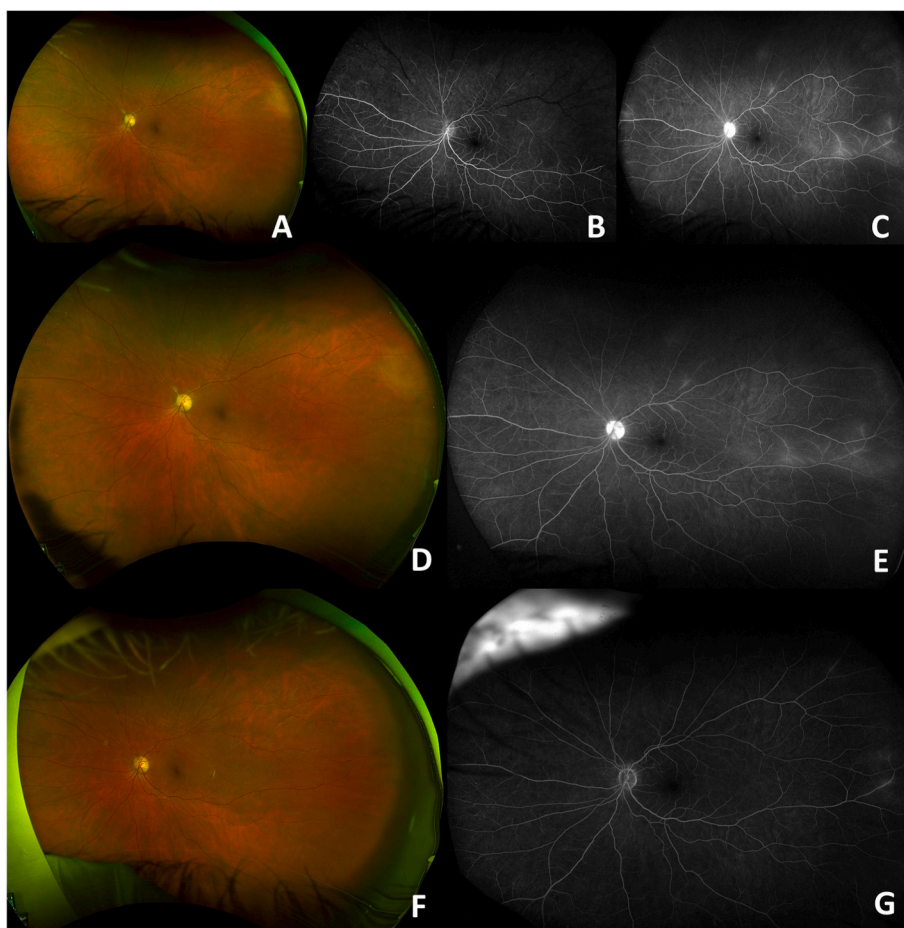


Fig. 2. Fundus photograph (A) of Patient 2 at initial presentation shows perivascular exudates superiorly in the left eye. FA showed significant delayed vascular filling superiorly (B) with late vascular leakage superiorly and temporally (C). Fundus photograph after treatment with 1000 mg pulse methylprednisolone and prednisone taper (D) shows perivascular fibrosis of two arterioles off disc superiorly. FA showed persistent late vascular leakage (E). Fundus photograph (F) 15 months after rituximab initiation showed no perivascular exudates, and FA (G) showed no vascular or optic disc leakage.

3. Discussion

This report documents the successful treatment of idiopathic retinal vasculitis with intravenous rituximab in two patients. In both patients, rituximab monotherapy allowed the patients to taper off corticosteroids completely. In Patient 1, rituximab was employed after the patient failed anti-TNF-alpha biologic therapy, and in Patient 2 it was used as the first line steroid-sparing agent. The fact that the retinal vasculitis was well controlled with rituximab alone argues that it was primarily responsible for inducing remission. They did receive intravenous methylprednisolone 100 mg with each rituximab infusion; given the low dose and episodic administration, it is less likely that the methylprednisolone, rather than the rituximab, was responsible for inducing remission. Both patients tolerated the medication well without any significant side effects with a mean follow up time of over one year after rituximab initiation.

Rituximab is an anti-CD20 monoclonal antibody that kills CD20⁺ B cells by inducing structural changes to the cell plasma membrane that lead to apoptosis.¹³ The mechanism of action also includes interfering with both complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity.¹³ The pathogenesis of retinal vasculitis involves B cell activation to a foreign antigen with subsequent antibody-antigen complex creation and deposition that leads to vascular endothelial dysfunction.² Given that rituximab causes B cell death and attenuates antibody-dependent cell-mediated cytotoxicity, there is a good rationale for its use in retinal vasculitis.

Rituximab has been reported to be efficacious for the treatment of retinal vasculitis in the setting of other underlying systemic diseases, particularly GPA and SLE.^{14,15} However, we are not aware of reports of its efficacy for retinal vasculitis in the absence of an underlying systemic

etiology. Patient 1 had an extensive work up including laboratory testing, MRI brain/orbit, PET-CT scan, and medical subspecialty consultations for an underlying etiology that were unrevealing. Twenty-two months after her initial presentation, she remains without any systemic manifestations and the unilaterality of her disease also argues against an underlying systemic etiology. Patient 2 also had unilateral disease and an extensive work up and rheumatologic consultation that failed to reveal a systemic disease, and she has not developed any systemic symptoms over 21 months of follow up from initial presentation. She did have a positive ANA but this finding is nonspecific and can be found in 27% of the normal population.¹⁶ Furthermore, in one study, an elevated ANA, defined as greater than two standard deviations above the mean, was present in 2.5% of normal subjects, including at titers as high as seen in this patient.¹⁶

In conclusion, we demonstrate the therapeutic efficacy of rituximab in the treatment of idiopathic retinal vasculitis. In these two patients, it was successful in achieving steroid-sparing remission after failure with anti-TNF-alpha therapy but also as a first line agent following corticosteroids. However, rituximab can have serious side effects including long term immunosuppression, thus it should be used with caution and further studies are needed to determine longer term treatment outcomes and optimal dosing and intervals.

Patient consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

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Authorship

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

Declaration of competing interest

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