Int Ophthalmol (2019) 39:477–484
https://doi.org/10.1007/s10792-018-0830-5

CASE REPORT

Intravitreal aflibercept for the treatment of choroidal neovascularization associated with rubella retinopathy

Hasan Kiziltoprak · Esat Yetkin · Kemal Tekin · Mustafa Koc · İrfan Akalin · Mehmet Yasin Teke

Received: 22 July 2017 / Accepted: 20 January 2018 / Published online: 6 February 2018

Abstract
Purpose To report a case of choroidal neovascularization (CNV) associated with rubella retinopathy (RR) treated with intravitreal aflibercept.
Case presentation A 15-year-old girl presented a complaint of visual decrease in her left eye. She had a history of hearing decrease since she was 1 year old in addition to patent ductus arteriosus. On ocular examination, the best corrected visual acuity (BCVA) was 20/20 in the right eye and 20/400 in the left eye. Dilated fundus examinations revealed a classic salt-and-pepper appearance in both eyes and a whitish subretinal lesion with retinal hemorrhages in the left macula. Fundus fluorescein angiography (FFA) of the left eye illustrated a pattern of diffuse spotty fluorescence with an active subfoveal CNV lesion, that hyperfluoresces in the early phases of the FFA, maintains well-demarcated borders, and leaks. Spectral domain optical coherence tomography (SD-OCT) revealed thickened and elevated retinal layers at the macula due to the subretinal and intraretinal fluid with foveal and extrafoveal protruding hyper-reflective lesion in the left eye. Single dose of intravitreal aflibercept was performed to the left eye and at the first month after the injection, the BCVA improved to 20/100 and the OCT revealed scar formation. At the follow-up visits, the macula was similar to those at the first month post-injection, and the BCVA was preserved. No additional injections were needed.
Conclusion Intravitreal aflibercept may be a treatment alternative, which provides satisfactory anatomical and functional results and leads to a better visual acuity in cases with RR complicated by CNV.

Keywords Choroidal neovascularization · Intravitreal aflibercept · Rubella retinopathy

H. Kiziltoprak (✉) · E. Yetkin · M. Koc
Ulucanlar Eye Training and Research Hospital, 06240 Ankara, Turkey
e-mail: hsnkzltprk21@gmail.com

K. Tekin
Kars State Hospital, Kars, Turkey

İ. Akalin
Artvin State Hospital, Artvin, Turkey

M. Y. Teke
Department of Retinal Diseases, Ulucanlar Eye Training and Research Hospital, Ankara, Turkey

Introduction

Congenital rubella syndrome (CRS) is a major global cause of preventable hearing impairment, blindness, and intellectual impairment [1]. Rubella retinopathy (RR) is a common manifestation of CRS, a triad of congenital heart disease, sensorineural deafness, and ocular abnormalities including cataract, microphthalmia, and glaucoma that results from fetal exposure to maternal rubella in the first trimester of the

pregnancy [2]. Although the patients with RR have retinal pigment epithelium (RPE) alterations in fundoscopy, their visual acuities are usually not affected. However, severe vision loss may occur secondary to choroidal neovascularization (CNV) in RR [3].

Herein, we describe the case of a child with RR complicated by CNV who has treated with intravitreal aflibercept (Eylea®, Regeneron Pharmaceuticals Inc, Bayer) and report the anatomic and functional results during sixth-month follow-up period. To our knowledge, this is the first reported case of RR-associated CNV treated with intravitreal administration of aflibercept.

Case presentation

A 15-year-old girl was referred to our retina clinic with a complaint of visual decrease and central scotoma in her left eye for 4 weeks. There was no family history of eye disorders, and she was not the product of a consanguineous marriage. However, we have learned that her mother contracted rubella during her pregnancy. Blood tests had run and serum studies showed IgM and IgG antibodies that were positive for rubella. Moreover, the maternal immunity status was not known. However, neither ocular nor systemic abnormalities were detected at birth. The patient's physical examination revealed patent ductus arteriosus in the

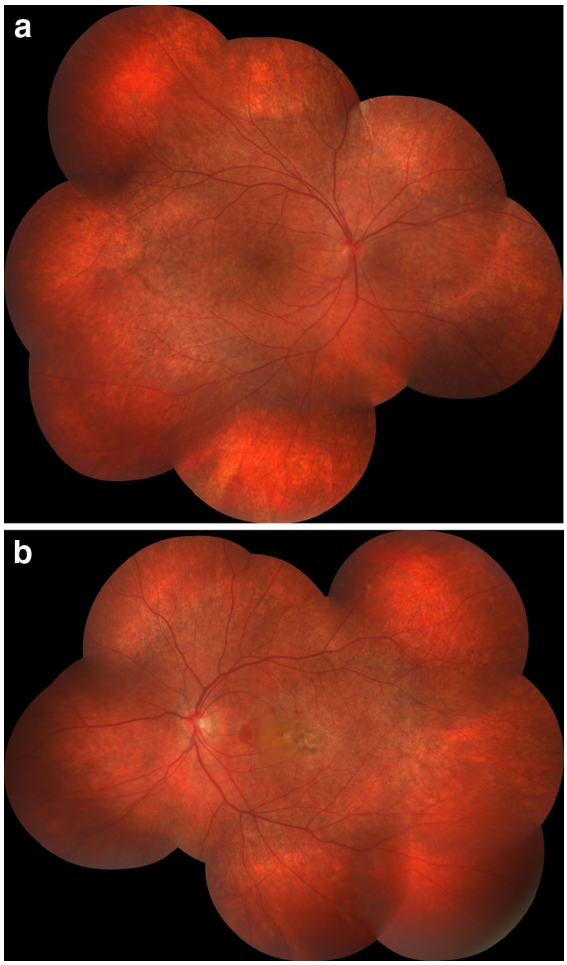


Fig. 1 **a** Composite colored fundus image of the right eye reveals a classical salt-and-pepper appearance of the retina with mottling of the RPE. **b** Composite colored fundus image of the left eye reveals a whitish subretinal lesion with retinal hemorrhages in the macula in addition to a classical salt-and-pepper appearance

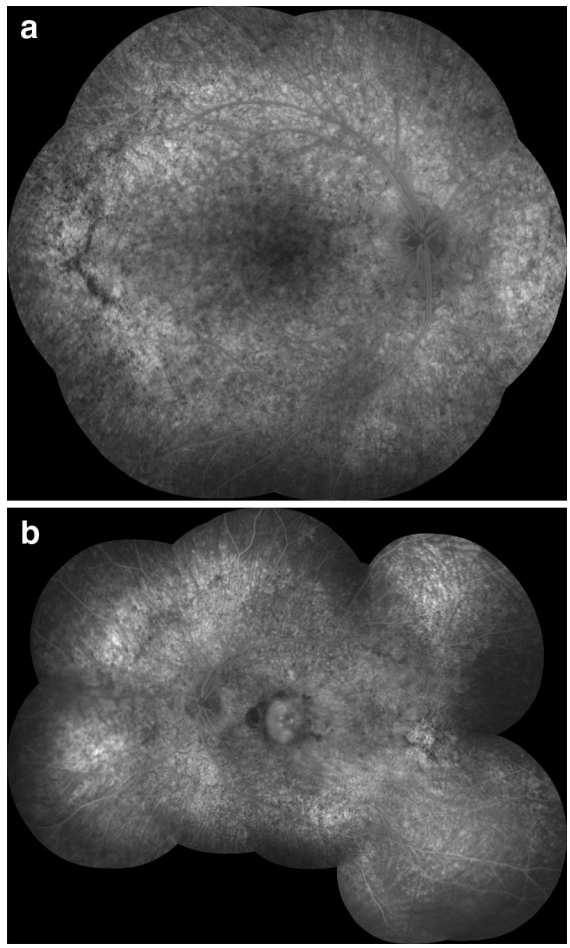


Fig. 2 **a** Fundus fluorescein angiography imaging of the right eye demonstrates a pattern of diffuse spotty fluorescence without any leakage or staining. **b** Composite fundus fluorescein angiography imaging of the left eye demonstrates an active subfoveal CNV lesion, that hyperfluoresces in the early phases of the FFA, maintains well-demarcated borders, and leaks

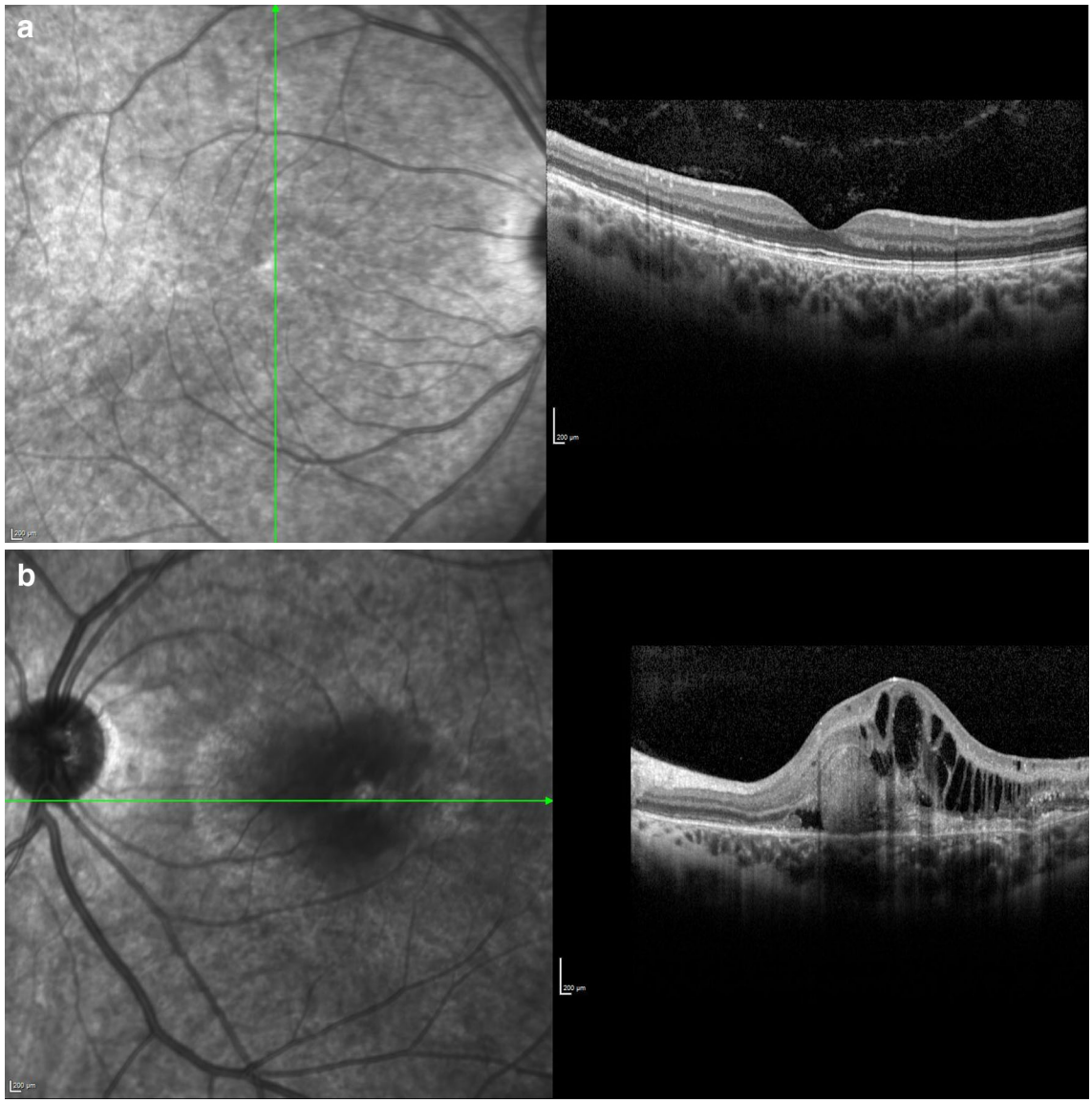


Fig. 3 Spectral domain optical coherence tomography (SD-OCT) reveals attenuated inner segment–outer segment junction, absent upward displacement of subfoveal ellipsoid zone band, and mottled retinal pigment epithelium for the right eye (**a**), while it shows thickened and elevated retinal layers at the macula due to the subretinal and intraretinal fluid with foveal and extrafoveal protruding hyper-reflective lesion in the left eye (**b**)

later years of her childhood. Moreover, she had a history of hearing decrease since she was 1 year old. Her hearing problem progressively developed and a cochlear implant procedure was performed at the age of 5. On ocular examination, the best corrected visual acuity (BCVA) was 20/20 in the right eye and 20/400 in the left eye. Intraocular pressure was within normal limits in both eyes. Axial length measured by A-mode ultrasonography was 21.05 mm in OD and 21.37 mm in OS. Anterior segment examinations were normal bilaterally with clear corneas, quiet anterior chambers, and clear lenses. Dilated fundus examination of the right eye revealed a normal optic disk with a classical RR findings—a classic salt-and-pepper appearance of the retina that is due to the distribution of areas of increased and decreased pigmentation (Fig. 1a). In the left eye, in addition to classical RR appearance, a whitish subretinal lesion with retinal hemorrhages in

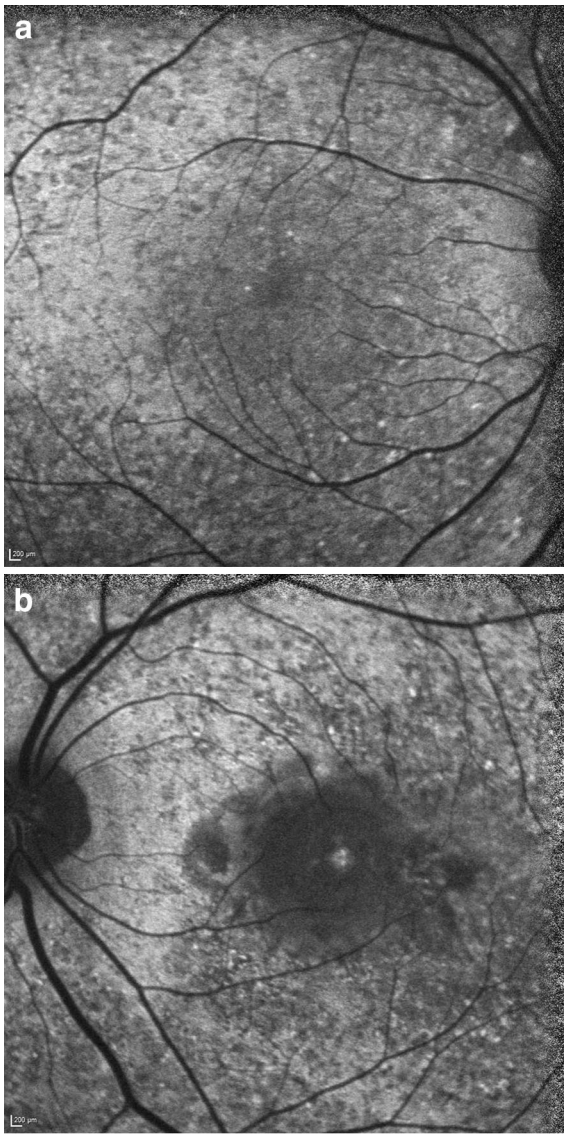


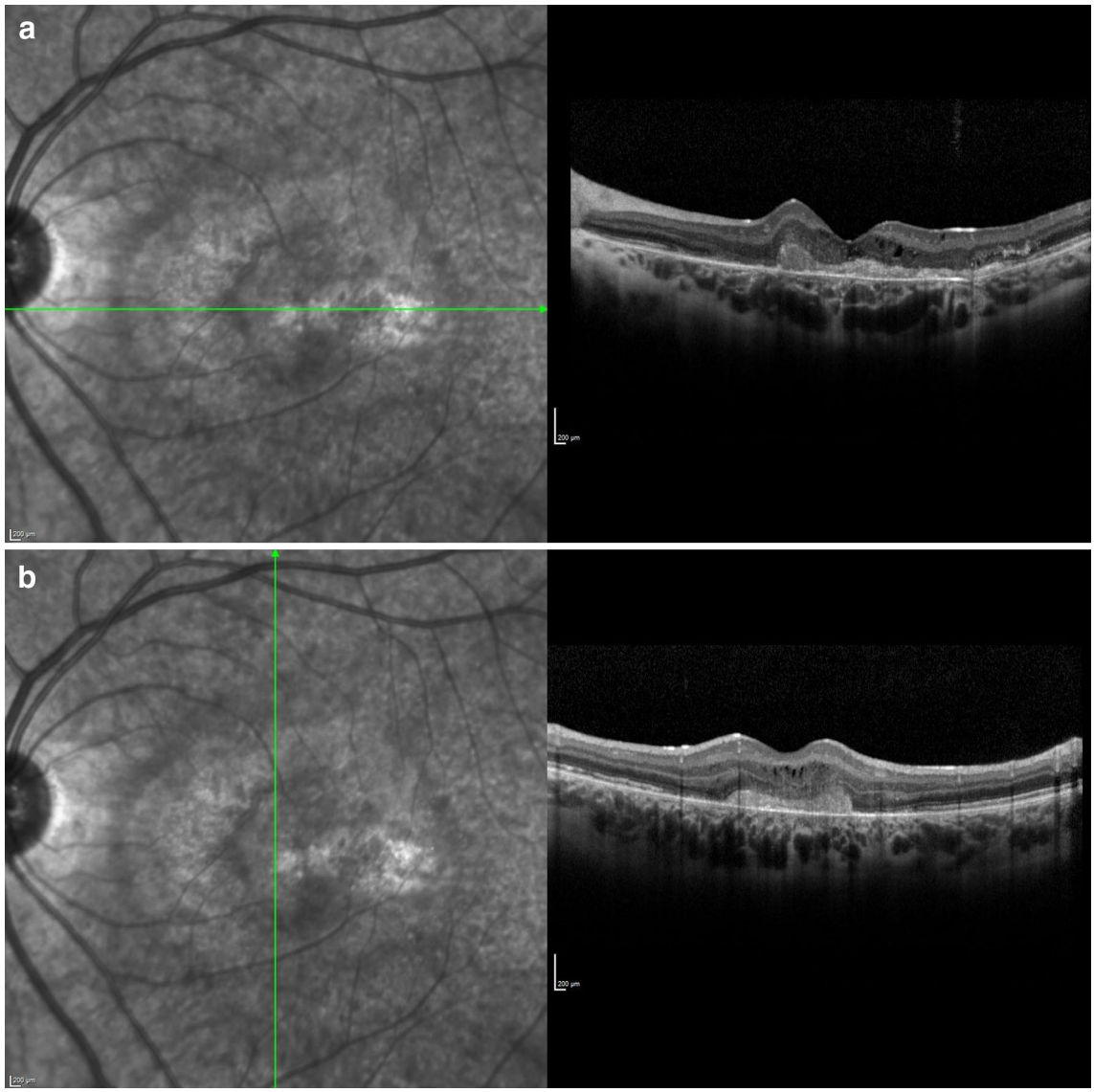
Fig. 4 Fundus autofluorescence imaging highlights the fundus abnormalities patchy autofluorescence with a stippled hypo-fluorescence in both eyes, and also a hypo-autofluorescence area corresponding to the area of CNV in the left eye

the macula was detected (Fig. 1b). Mottling of the RPE was evident in both eyes (Fig. 1a, b). Fundus fluorescein angiography (FFA) illustrated a pattern of diffuse spotty fluorescence because of the defective RPE without any leakage or staining in the right eye (Fig. 2a). On the left eye, in addition to diffuse spotty fluorescence, an active subfoveal CNV lesion, that hyperfluoresces in the early phases of the FFA, maintains well-demarcated borders, and leaks, was detected (Fig. 2b). Spectral domain optical coherence tomography (SD-OCT) of the right eye showed attenuated inner segment–outer segment junction, absent upward displacement of subfoveal ellipsoid zone band, and mottled retinal pigment epithelium (Fig. 3a), while it revealed thickened and elevated retinal layers at the macula due to the subretinal and intraretinal fluid with foveal and extrafoveal protruding hyper-reflective lesion in the left eye (Fig. 3b). Fundus autofluorescence (FAF) highlighted the fundus abnormalities patchy autofluorescence with a stippled hypo-fluorescence in both eyes, and also a hypo-autofluorescence area corresponding to the area of CNV in the left eye (Fig. 4a, b). After discussions with the patient's parents about the possible risks and benefits of the available treatments for CNV, intravitreal aflibercept injection was recommended to the patient. Written informed consent was obtained from the parents for the off-label use, and a single dose of intravitreal aflibercept injection (2 mg/0.05 ml) was performed. One month later, the BCVA improved to 20/100 in the left eye, and the SD-OCT revealed contraction of the lesion with a scar formation and markedly reducing of the fluid (Figs. 5, 6). Additionally, FFA of the left eye showed staining of the scar with no leakage (Fig. 7). No other injections were performed. After 3 months, the BCVA was maintained, and the SD-OCT was similar to those at the first month post-injection (Figs. 8, 9). No recurrence was observed in the last examination at the sixth month, and the BCVA was preserved. Intraocular pressure was normal all over the follow-up.

Discussion

RR is the most frequent ocular complication in children whose mothers contracted rubella during pregnancy [4]. Maternal rubella infection in pregnancy may lead to a spectrum of fetal outcomes: an infant may be born normally, with congenital abnormalities, or spontaneously abort [5]. The constellation of clinical features of CRS consists of sensorineural hearing impairment, intellectual impairment, cardiac defects, and ocular findings. Deafness is the most common abnormality [5, 6].

There is a wide spectrum of ocular findings in CRS. A "salt and pepper" retinopathy is most commonly observed and seen in 40–60% of the cases but does not



Figs. 5, 6 One month after the injection of intravitreal aflibercept, spectral domain optical coherence tomography scans of the left eye illustrate contraction of the lesion with a scar formation and markedly reducing of the fluid

typically have visual consequences unless CNV develops [7]. Nuclear cataracts may occur in about one-third of all cases and bilateral in 50% [5, 6]. Microphthalmia, glaucoma and choroidal neovascularization are the other findings in CRS [2–5].

The differential diagnosis of both salt-and-pepper retinopathy and hearing loss includes congenital rubella, congenital syphilis, and Usher syndrome. Syphilis is excluded by serologic workup and physical findings which may include Hutchinson's triad of interstitial keratitis, peg-shaped incisors, and eighth cranial nerve deafness. Usher syndrome is distinguished by nyctalopia and markedly abnormal ERG, and FAF frequently shows a parafoveal ring of increased autofluorescence that constricts progressively over time [8]. In our patient with pathognomonic retinal findings, associated systemic findings, and a history of maternal exposure to rubella suggest the diagnosis of CRS.

The main visual impairment of RR is due to CNV. The visual acuity is generally normal unless CNV and secondary subretinal fluid damage to the

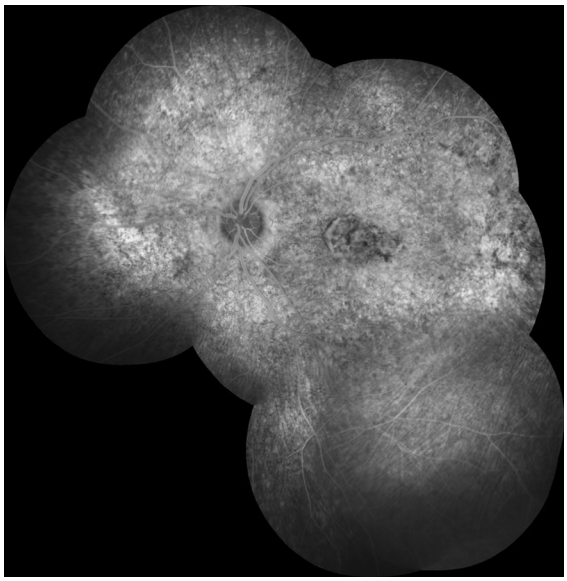
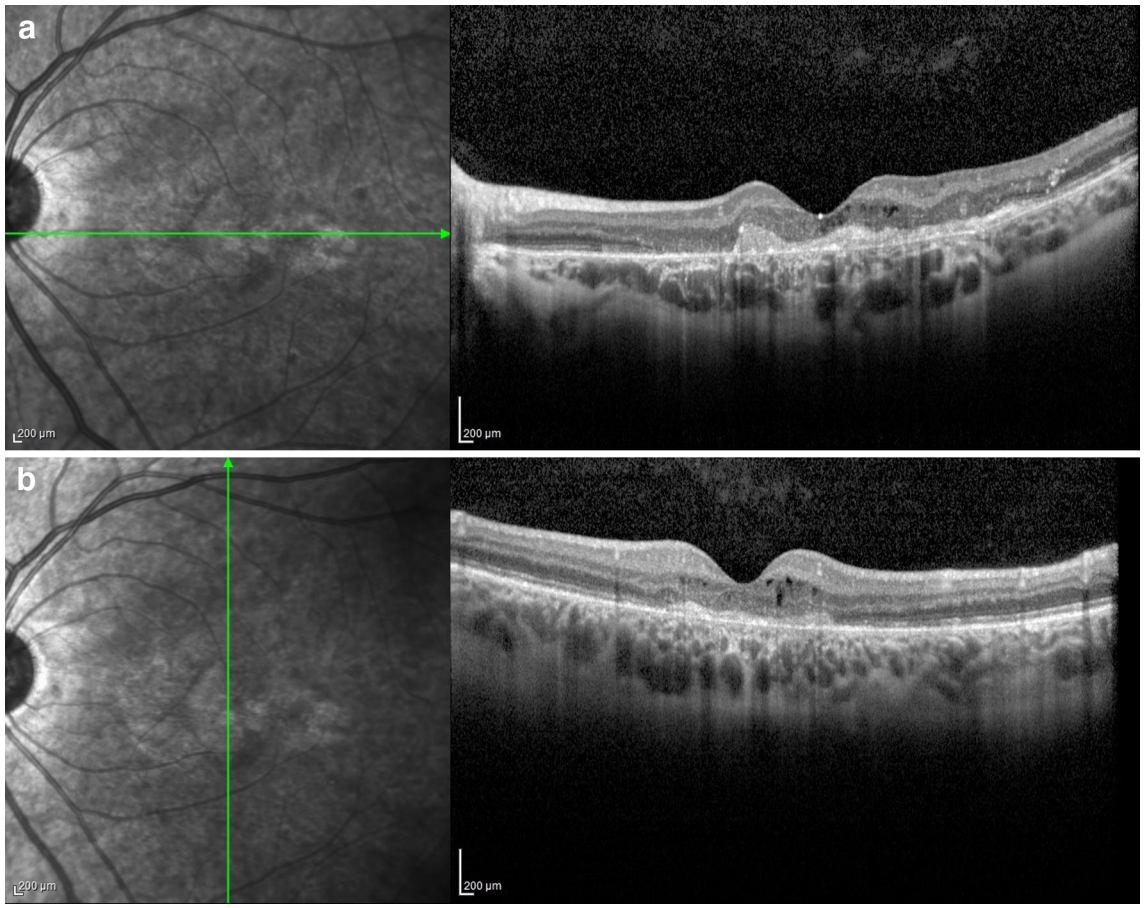


Fig. 7 Composite fundus fluorescein angiography imaging of the left eye shows staining of the scar with no leakage on the third-month follow-up visit after the injection

photoreceptor cells. There are a few treatment options for CNV described in the literature such as photodynamic therapy (PDT) and anti-vascular endothelial growth factor (VEGF) agents. PDT has also been investigated for the treatment of age related macular degeneration (AMD) related subfoveal CNV and non-AMD causes of subfoveal CNV such as pathological myopia, angioid streaks, presumed ocular histoplasmosis syndrome, and idiopathic CNV [9]. However, the evidence base for PDT therapy in other causes of CNV has necessarily been developed from published case reports and small case series [10]. PDT found an effective treatment option for subfoveal CNV and resulted in involution of the neovascular membrane, resolution of subretinal hemorrhage, and improvement in visual acuity [11]. Additionally, it has been demonstrated that PDT may be associated with some potential complications such as RPE changes, choroidal hypo-perfusion, and CNV despite its beneficial effects [12]. Battaglia et al. [13] reported a case of bilateral CNV secondary to RR and late development of large choroidal excavation (LCE). They treated the case with PDT and after 6 years of annual follow-up examinations, SD-OCT scans of the patient uncovered the development of LCE. In light of these findings, they proposed that PDT may have induced or facilitated this formation [13]. Aflibercept is a recombinant fusion protein with some intrinsic differences from bevacizumab and ranibizumab that affect its in vivo activity. As distinct from both bevacizumab and ranibizumab, aflibercept additionally binds the VEGF-B which is critical for blood vessel survival under some pathological conditions [14]. Moreover, aflibercept additionally binds the placental growth factor and has a considerably higher binding affinity for VEGF [14]. On the other hand, Veloso et al. [15] reported a spontaneous involution of choroidal neovascularization secondary to rubella retinopathy. The underlying mechanisms related to the spontaneous involution of CNV occasionally observed in the younger population remain unclear [15]. The anti-VEGF treatment is another option for the treatment of CNV. In our patient, we successfully injected intravitreal aflibercept and first month of the injection, involution of the neovascular membrane and improvement in visual acuity from 20/200 to 20/60 was obtained. To the best of our knowledge, this is the first reported case of the use of intravitreal aflibercept in CNV secondary to RR in the literature.

In conclusion, RR is a common manifestation of CRS and can result ocular abnormalities including cataract, microphthalmia, glaucoma, and CNV. Severe vision loss generally occur secondary to CNV. Intravitreal aflibercept may be a treatment alternative, which provides satisfactory anatomical and functional results and leads to a better visual acuity in cases with RR complicated by CNV.



Figs. 8, 9 Three months after the injection of intravitreal aflibercept, spectral domain optical coherence tomography scans do not show any evident alterations when compared to those at the first month post-injection

Compliance with ethical standards

Conflicts of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this paper.

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