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# A case of anti-VEGF therapy application in Takayasu arteries with retinopathy

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ABSTRACT

*Purpose:* Takayasu arteritis (TA) is a systemic granulomatous large vessel vasculitis that involves mainly the aorta and its primary branches, and occurs most commonly in young females. Ocular manifestations of TA include small vessels dilation, microaneurysm, arteriovenous anastomosis, retinal ischemia and retinopathy. However, no specific and effective treatments for Takayasu retinopathy is applied. This case aimed to demonstrate the role of anti-VEGF (vascular endothelial growth factor) therapy in treating Takayasu retinopathy.

*Observations:* We herein reported an 18-year-old Asian woman who presented with typical wreath-like arteriovenous anastomosis around the disc in the right eye and vitreous hemorrhage in the left eye. The stenosis and occlusion of bilateral subclavian arteries, carotid arteries and other proximal arteries on angiography confirmed the diagnosis of TA. Meanwhile, elevated ESR and CRP revealed that TA was in the active stage. We applied anti-VEGF therapy in treating Takayasu retinopathy specially to inhibit neovascularization. Additionally, vitreous extraction was conducted in the left eye after the treatment of anti-VEGF therapy.

*Conclusions and importance:* This is the first report of effective application of anti-VEGF therapy in inhibiting wreath-like arteriovenous anastomosis and improving vitrectomy in TA.

## 1. Introduction

Takayasu arteritis (TA) is a chronic inflammatory disease of unknown etiology that affects large and medium caliber arteries, including the aorta and its main branches or large arteries in the proximal upper or lower extremities.[1,2] Epidemiologically, TA is seen more commonly in individuals of Asian females, aged from 10 to 30 years (80–90%).[3] TA is diagnosed based on the criteria set out by the American College of Rheumatology[1] and updated by Seeliger B and et al.,[2] which include the following: i) age ≤40 at the onset of symptoms; ii) claudication of an extremity; iii) decreased brachial artery pulse; iv) > 10 mmHg difference in systolic blood pressure between arms; v) a bruit over the subclavian arteries or the aorta; vi) and arteriographic evidence of narrowing of occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper of lower extremities. The presence of three or more of these criteria confirm the diagnosis of TA with specificity and sensitivity above 90%.

Ocular involvement in TA is common and even occurs as the primary manifestation in almost half of the patients.[4] The commonly recognized manifestations of TA are ocular ischemic syndrome and retinopathy due to chronic ocular hypoperfusion. On the basis of ocular findings, Takayasu retinopathy (TR) was classified into four stages, including dilatation of small vessels (I), capillary microaneurysm formation (II), arteriovenous anastomosis (III), and ocular complications (IV) such as vitreous hemorrhage, retinal detachment and optic atrophy.[4,5] Treatment strategies for TA include medical therapy with glucocorticoids, corticosteroids or immunosuppressive agents and revascularization procedures. Revascularization procedures commonly involve bypass surgery and percutaneous endovascular procedures.[6] However, no specific treatments for Takayasu retinopathy is applied.

We herein report a case of an 18-year-old Asian woman without a prior medical history of TA, who presented with visual acuity decline OD and sudden loss of vision OS. After the clinical diagnosis of TA, the woman received treatment with glucocorticoids. Additionally, it is the

*Abbreviations:* TA, Takayasu arteritis; TR, Takayasu retinopathy; VEGF, Vascular endothelial growth factor; OCT-A, Optical coherence tomography angiography; FFA, Fundus fluorescein angiography; CRP, C-reactive protein concentration; ESR, erythrocyte sedimentation rate; CMV, cytomegalovirus; HSV 1, herpes simplex virus 1; AMD, age-related macular degeneration; CRVO, central retinal vein occlusion; DME, diabetic macular edema

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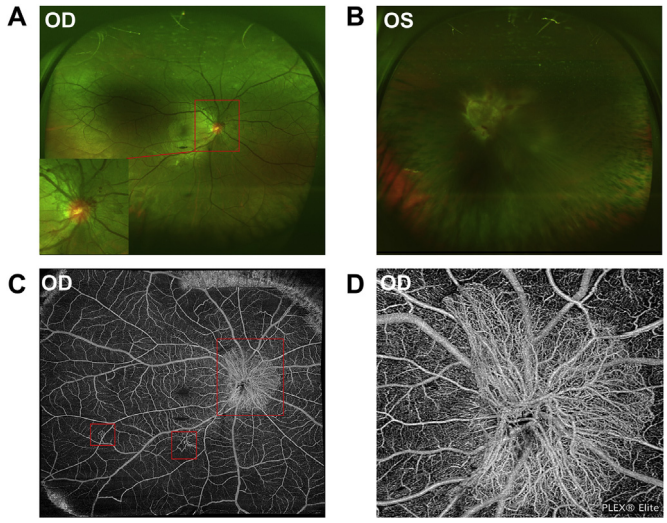


**Fig. 1.** Wide-angle fundus photography and Angio OCT of the fundus. Wide-angle fundus photography revealed the neovascularization around disc and microaneurysm formation in the peripheral retina in the right eye (A), vitreous hemorrhage and retinal detachment in the left eye (B). Angio OCT showed the whole retina with neovascularization, and wreath-like arteriovenous anastomosis around optic disc OD (C and D). The red frame showed the arteriovenous anastomosis. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

first time to apply anti-VEGF (vascular endothelial growth factor) therapy in inhibiting neovascularization and arteriovenous anastomosis in TA.

### 1.1. Case report

An 18-year-old Chinese female presented with acute and painless vision decrease in the left eye 3 months prior to examination in our ophthalmic clinic. She was found with vitreous hemorrhage, retinal detachment OS and optic arteriovenous anastomosis OD. The patient was alert and oriented. The best-corrected visual acuity was 20/25 OD and HM/10cm OS. Her pupils were sluggish to light OU and dilated. Slit lamp examination revealed normal anterior segment. The IOP measured was 9.5 mmHg OD and 10.8 mmHg OS. Wide-angle fundus photography exhibited the neovascularization around disc and microaneurysm formation in the peripheral retina OD, vitreous hemorrhage and retinal detachment OS (Fig. 1A and B). Optical coherence tomography angiography (OCT-A) showed the neovascularization around the retina, and typical wreath-like arteriovenous anastomosis around optic disc OD clearly (Fig. 1C and D). The Humphrey visual field test revealed slight contraction OD and global depression OS (Fig. 2A and B). The ocular B-scan ultrasound revealed vitreo-retinal adhesions temporally OD and sub-total retinal detachment OS (Fig. 2C–F). Fundus fluorescein angiography (FFA) conducted at another hospital showed hypoperfusion of arterioles and venules, and with hyperfluorescence of the optic disc OD, with hyperfluorescent leakage OS (not shown).

Laboratory tests revealed decreased hemoglobin (107.00 g/L), increased blood platelet ($348*10^9$/L), accelerated erythrocyte sedimentation rate (ESR, 70.00 mm/h), enhanced C-reactive protein concentration (CRP, 17.0 mg/L). The rheumatoid factor concentration was normal, and the antistreptolysin O, antinuclear antibody, extractable nuclear antigens, and antineutrophil cytoplasmic antibody titers were negative. Additionally, an infectious panel including hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis E virus, *Treponema pallidum* particle assay, and human immunodeficiency virus showed negative. Tuberculosis infection was also confirmed negative by T-SPOT test and tuberculosis infected T cells with A or B antigen quantification. However, the level of cytomegalovirus (CMV) IgG was 420.1 U/ml, and herpes simplex virus 1 (HSV 1) IgG was 33.12 COI (+). Further virus detections in aqueous humor also demonstrated the positive expression of CMV IgG and HSV 1 IgG that confirmed the infectious history.

Systemic arterial angiography MRI showed that multiple branches of aortic arch involved. Proximal extremities of bilateral subclavian arteries, bilateral carotid arteries and left vertebral artery were obstructed. Lower lumen of abdominal aorta was with severe stenosis. The initial extremities of bilateral arteries were slightly straight. Additionally, carotid ultrasound revealed that vascular wall of bilateral carotid arteries was thickened broadly, accompanying by the narrowed and even occlusive lumen.

The patient was diagnosed with Takayasu disease, and stage III TR of right eye, stage IV TR of left eye. Medical therapy for system included prednisone acetate 60 mg/d for three months, then decreasing 5 mg every week for another two months, and sustaining at 20 mg/d until last visit, leflunomide 20 mg/d, beraprost 60 μg/d and aspirin 100 mg/d. Considering that the patient was confirmed with optic arteriovenous anastomosis OD and vitreous hemorrhage, retinal detachment OS, immediate vitrectomy would not help improve her visual acuity OS. Based on the application of anti-VEGF therapy in inhibiting neovascularization in fundus diseases like age-related macular degeneration (AMD),[7] central retinal vein occlusion (CRVO),[8] diabetic macular edema (DME)[9] and et al., the patient and her family agreed to try the intraocular injection with ranibizumab (Lucentis, 0.5 mg) in both eyes.

One day postoperatively, the best-corrected visual acuity was 25/25 OD and HM/10cm OS. OCT-A demonstrated that the disc neovascularization regressed OD and this was sustained two weeks postoperatively (Fig. 3). By the follow-up (one month, three months and six months), no distinct neovascularization was observed via OCT-A and wide-angle fundus photography (Fig. 3A and B). This revealed that anti-VEGF therapy was effective in the early stage of TR in inhibiting neovascularization, and prevented rapid progression of TR in conjunction with systemic treatments.

Considering the left eye, although the visual acuity OS was not improved, the patient felt a bit brighter after injecting VEGF for one day. Slit lamp examination found alleviative vitreous hemorrhage OS. Two months later, vitrectomy and silicone oil filling were conducted in the left eye without fresh hemorrhage. After the operation, the aberrant angiogenic system of the left retina was firstly observed via wide-angle fundus photography (Fig. 4A). However, vascular morphology still could not be detected by OCT-A. No significant change was occurred during the follow-up after vitrectomy for one month and three months (Fig. 4A). Three months after vitrectomy, silicone oil was extracted. Two weeks later, the retina OS could be evaluated by both wide-angle fundus photography and OCT-A (Fig. 4B). Although the peripheral retinal vessels were obstructed, the central retinal vessels and the branches were recanalised. The best-corrected visual acuity was 25/25 OD and 1/20 OS. Therefore, the application of anti-VEGF treatment before vitrectomy for stage IV TR was promising for partly restoring visual function.

## 2. Discussion

In 1908, “A case of peculiar changes in the central retinal vessels” was reported by Mikito Takayasu, thus first defining Takayasu disease. The ocular symptoms of Takayasu disease are commonly considered to be due to vascular ischemia in the retina and choroid. The typical wreath-like arteriovenous anastomosis around the optic disc reported by Takayasu is found at a relatively late stage of this disease. The characteristic fundus manifestations of Takayasu arteries involve tortuosity and dilatation of the central retinal artery and vein, occlusion of retinal arterioles, microaneurysms in the capillaries, soft or hard exudate, retinal arteriovenous anastomosis, choked disc, and optic atrophy.[4,10] Especially, at the early stage, arteriovenous anastomosis initially appears in the periphery, and in the arteriovenous crossing at the advanced stage.

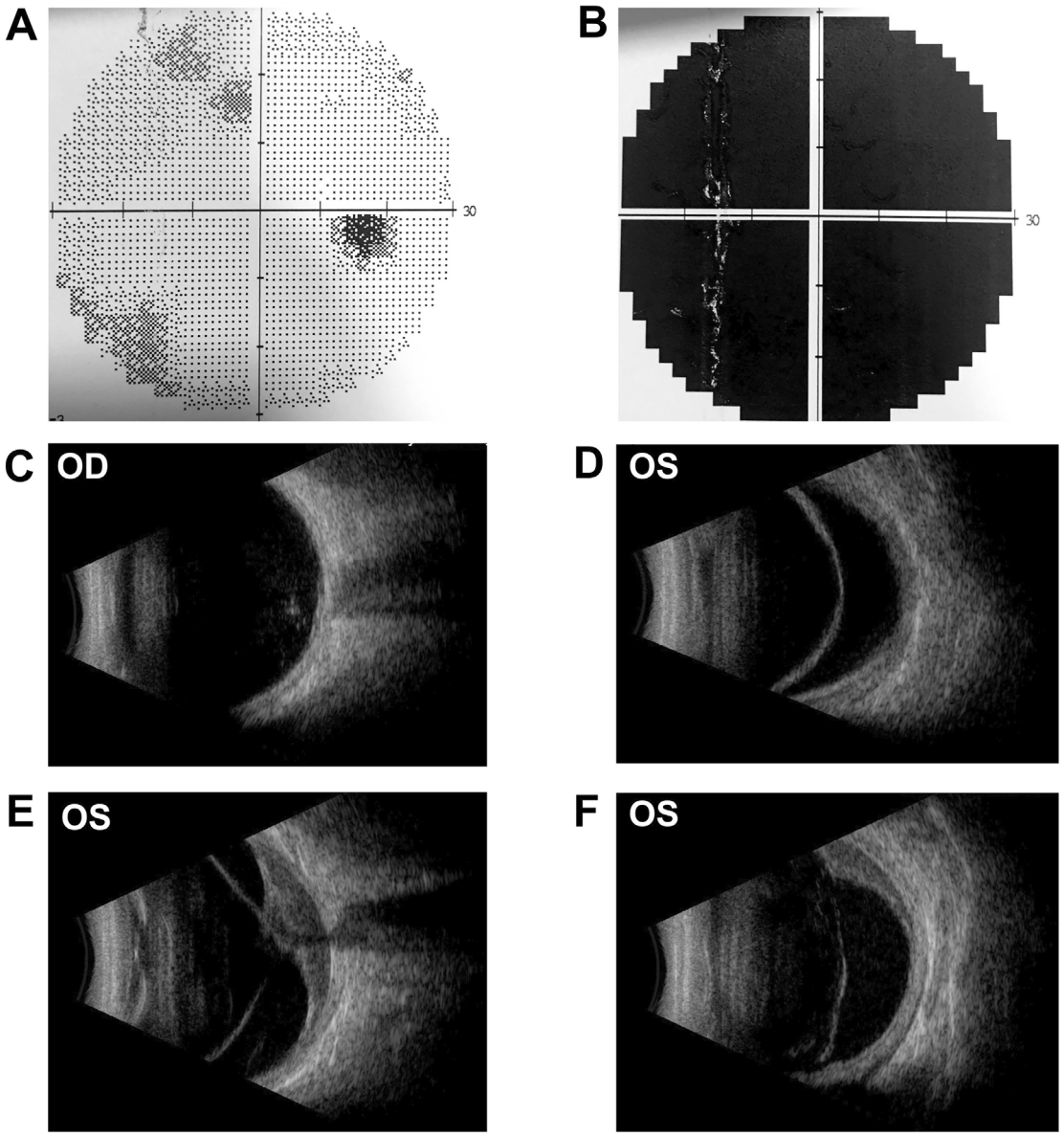


**Fig. 2.** Humphreyvisual field test exhibited slight contraction in the right eye (A) and a global depression in the left eye (B). Eye ultrasound revealed temporal side vitreo-retinal adhesions OD (C) and almost entire retinal detachment OS (D-F).

We herein reported a young Asian woman without previous diagnosis of TA, but with initial features of ocular manifestation. By the systemic MRI and laboratory tests, this patient fulfilled more than three criteria described by the American College of Rheumatology[1]: onset at age 18, decreased brachial artery pulse, a bruit over the subclavian arteries or the aorta, and narrowing or occlusion of the aorta and its primary branches. The decreased hemoglobin, increased blood platelet, elevated ESR and CRP confirmed that TA was in the active stage. At the same time, her fundus findings in both eyes revealed the stage III TR in the right eye and stage IV TR in the left eye. Although the definite cause of TA is not clear, the infectious history of CMV and HSV 1 may be associated with arousing immune reactions and damaging arteries. In the treatment of this case, not only glucocorticoids, steroids and immunosuppressive agents were included for systemic treatment, but also specific ocular therapy was performed. To our knowledge this is the first report of using anti-VEGF therapy to inhibit stage III TR with wreath-like arteriovenous anastomosis or stage IV TR with vitreous hemorrhage prior to vitrectomy. The strategy was effective to prohibit arteriovenous anastomosis, neovascularization and alleviating vitreous hemorrhage. Patients who underwent anti-VEGF therapy with systemic treatment at Stage III or less of TR had excellent outcomes with complete regression of neovascularization and normalization of visual acuity. Moreover, anti-VEGF treatment applied in the eyes with neovascular complications (Stage IV) before vitrectomy surgery may effectively enhance outcomes.

Although this case is limited by the short-term of follow-up, it does highlight the effective inhibition of anti-VEGF therapy in TR at Stage III or less. Long-term follow-up and more studies on larger number of TA patients need to be undertaken to conclusively prove the superiority of anti-VEGF therapy in patients with TR to sustain the visual acuity and help the operation of vitrectomy.

## 3. Conclusions

This is the first report of effective application of anti-VEGF therapy in inhibiting neovascularization and delaying the development of TR. Treatment of anti-VEGF ocular injection before vitrectomy could increase the possibility of recovering visual function for stage IV TR.

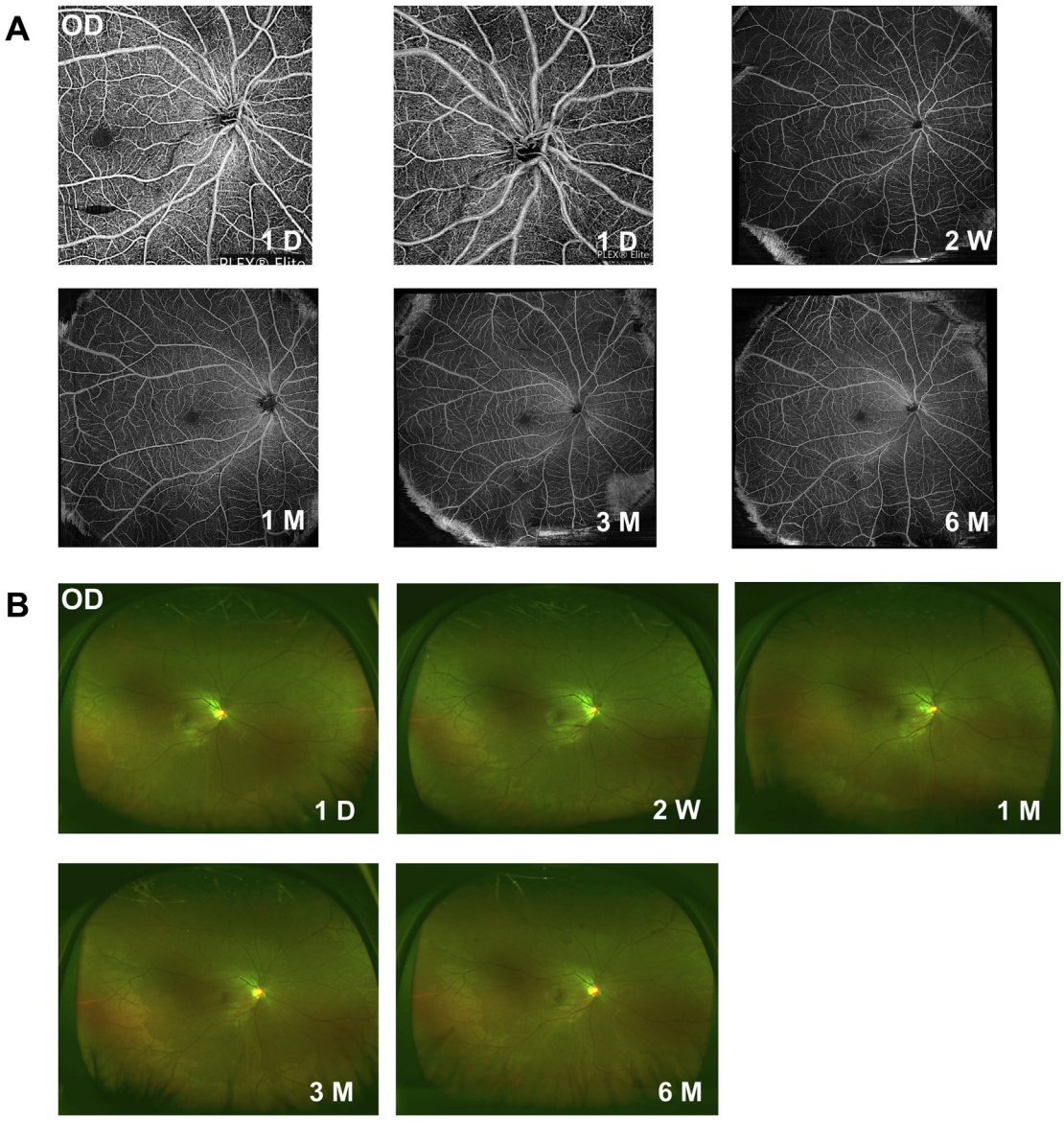


**Fig. 3.** Angio OCT (A) and wide-angle fundus photography (B) showed fading away of arteriovenous anastomosis around optic disc OD after anti-VEGF therapy one day, two weeks, one month, three months and six months.

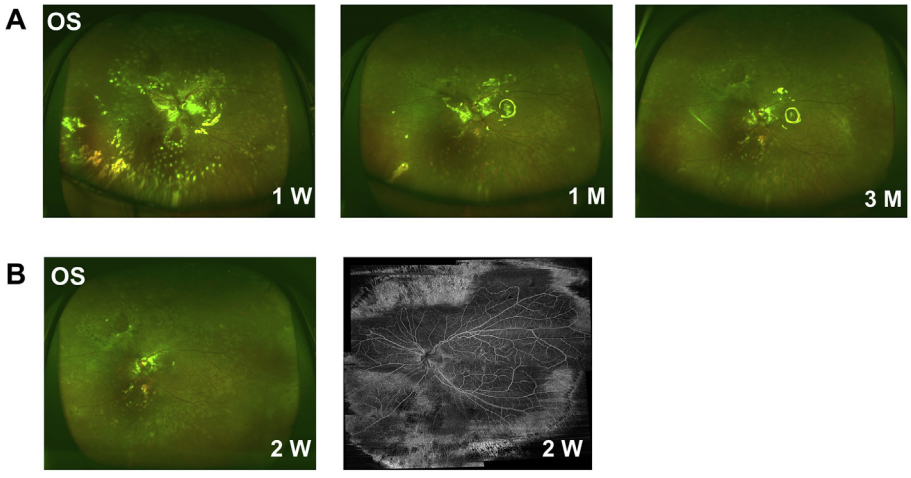


**Fig. 4.** The retinal recovery OS treated with vitrectomy after application of anti-VEGF therapy. (A) Wide-angle fundus photography showed the retina OS after the vitrectomy with silicone oil filling for one week, one month and three months. (B) Wide-angle fundus photography and angio OCT demonstrated the retinal morphology two weeks after the oil extraction operation.

## 4. Patient consent

The patient's legal guardian consented to publication of the case in orally. Informed consent was obtained from the patient we reported in this paper. The ethical standards are complied with Shanghai General Hospital.

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## Authorship

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

## Declaration of competing interest

The Authors declare that there is no conflict of interest.

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