• Letter to the Editor •

Persistent macular oedema following Best vitelliform macular dystrophy undergoing anti-VEGF treatment

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Dear Editor,

I am Dr. Tie-zhu Lin, from He Eye Specialist Hospital, Shenyang, China. I write to present the case of persistent macular oedema following Best vitelliform macular dystrophy (BVMD) undergoing anti-vascular endothelial growth factor (VEGF) treatment.

BVMD also called Best's disease, is a hereditary disease due to mutation in the *BEST1* gene located on chromosome 11[1-2] and has vastly variable phenotypic expression. During BVMD, a rare but severe complication known as choroidal neovascularization (CNV) can occur, which can rapidly decrease visual acuity[3]. Some studies reported that treatments such as intravitreal anti-VEGF agents and photodynamic therapy (PDT) have been effective on CNV associated with BVMD[4-11]. We report a case of a patient affected by CNV due to BVMD in the right eye (OD). We obtained the written informed consent from the patient, and this case study is in accordance with the tenets of the Declaration of Helsinki.

A 13-year-old Chinese girl presented with severe painless visual acuity reduction in her OD. During the first examination of the anterior segment and intraocular pressure (IOP) were within normal limits, best-corrected visual acuity (BCVA) was 20/200 OD and 20/32 in the left eye (OS). Fundus examination of the OD revealed a fibrous scarring in the macula (Figure 1A), a subretinal yellowish-grey lesion in the inferior part of the macula and subretinal flecks at the posterior pole was present on OS as showed in Figure 1B. Fundus autofluorescence (FAF) revealed hypofluorescence in the centre or macula with hyperfluorescent margin in the OD (Figure 1C) and punctuate hyperfluorescence in the fovea with hyperfluorescence in the inferior part of the macula in the OS (Figure 1D). Fluorescein angiography (FA) showed early hyperfluorescence with intense late leakage at the centre of the macula of the OD, indicating the presence of a subretinal neovascular membrane (Figure 1E). OS showed an area of mottled hyperfluorescence without leakage in the macula, indicating staining of vitelliform material around the foveal centre (Figure 1F). Indocyanine green angiography (ICGA) showed mild hyperfluorescence in the macula with hypofluorescence margin in the OD (Figure 1G), multiple punctuate hyperfluorescence in the macula of OS due to the staining of subretinal overlying vitelliform material (Figure 1H). Optical coherence tomography (OCT) revealed a sub-foveal protruding highly reflective lesion with subretinal fluid and intraretinal cystic oedema in the OD (Figure 1I), sub-foveal optically empty space with sub-retinal highly reflective nodular lesion in the OS (Figure 1J). The Arden ratio in electrooculogram (EOG) was found to be abnormal in the OS (OD: 1.93, OS: 1.31). Genetic test confirmed heterozygous mutations [c.913T>C(p.Phe305Leu)] in *BEST1* gene.

The patient was given intravitreal ranibizumab (0.05 mg/0.05 mL) in the OD following detailed informed consent was obtained from the family (Figure 2A). Post-injection period was uneventful and at 1mo follow-up, BCVA in the OD was maintained at 20/200. OCT revealed subretinal/intraretinal fluid was absorbed completely (Figure 2B). The retina of the OD kept dry at 2mo follow-up (Figure 2C). The patients didn't come back at 3mo follow-up due to COVID-19 prevalence. CNV of the OD was reactive at 4mo follow-up, but BCVA didn't change (Figure 2D). Though three more monthly intravitreal ranibizumab (0.05 mg/0.05 mL) were administered, CNV was still active, BCVA was always kept at 20/200 (Figure 2E-2G). Then ranibizumab was switched to aflibercept due to poor response. The patient got monthly intravitreal aflibercept (2 mg/0.05 mL)

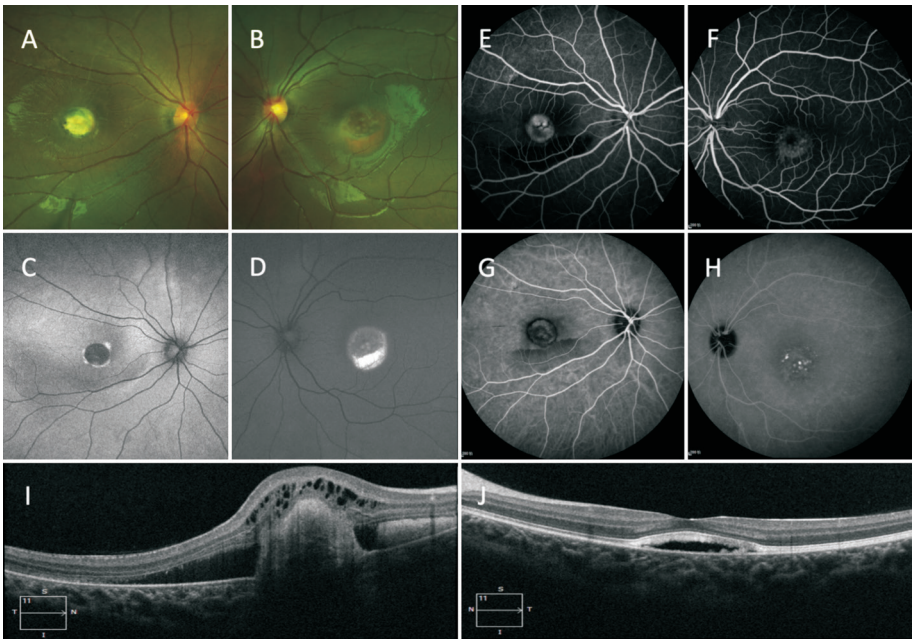

Figure 1 Ancillary exams at presentation.

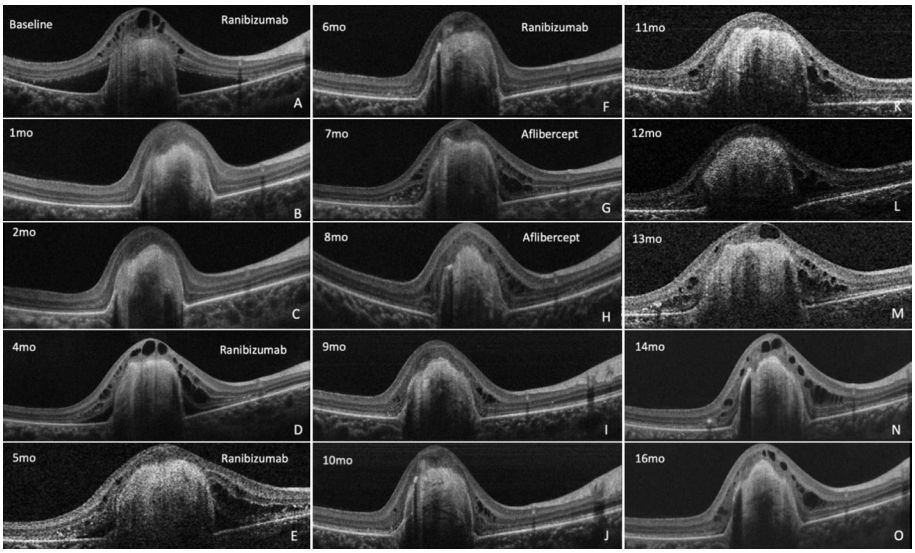

Figure 2 Timeline of macular OCT horizontal scanning.

for two injections, but mild leakage was continuous observed on OCT. OD BCVA was maintained at 20/200 (Figure 2H-2I). The observation was poor response to anti-VEGF treatment and stable vision acuity. OD BCVA remained at 20/200 during the next 7mo follow-up, and OCT showed persistent macular oedema (Figure 2J-2O). During 16mo follow-up, BCVA was maintained at 20/32 in the OS, and the morphology on OCT and fundus examination did not change much.

DISCUSSION

Best[12] first identified Vitelliform macular dystrophy in 1905 and the age of onset is usually from 3 to 15y. A typical yellow yolk-like macular lesion may be present, usually bilateral, but in some cases unilateral. Slow visual deterioration is the usual course. EOG is usually abnormal with a reduced Arden ratio <1.5, most often 1.0 and 1.3, but this value is not absolute, as the Arden ratio decreases with age. Splitting and elevation of outer retina and retinal pigment epithelial layer with dome-like hyporeflective or hyperreflective material and subretinal fluid, intraretinal cystoid could exist in CNV stage. Gene testing could confirm the mutations of genetic locus.

The standard treatment for individuals with sub-foveal CNV is anti-VEGF agents. Some studies have reported that intravitreal bevacizumab/ranibizumab injections for CNV secondary to BVMD had positive outcomes with visual recovery and regression of the CNV in most cases, the age of cases in these studies were between 5 to 17y, and the follow-up time between 7 to 24mo[4-7]. However, currently no reports on the use of aflibercept have been published and long-term follow-up of these patients are unspecified. Some studies also treated this type of CNV with PDT, most cases had stable visual acuity, and the longest follow-up time was 33mo[8-11]. In the current case, macular edema was persistent with multiple intravitreal

ranibizumab and aflibercept injections. Interestingly, the patient had steady BCVA, even during the 7mo observation time. The patient didn't feel any change with or without treatment. Though previous studies reported positive outcomes with intravitreal anti-VEGF injections or PDT, but the follow-up time was not long enough to support that, and BVMD patients are usually very young, the expectation of life are decades.

Intravitreal anti-VEGF agents are also widely used in other CNV diseases and macular edema (ME). Many studies reported poor response or resistance to some anti-VEGF agent in the real word and switched agents. In Protocol T, persistent DME was in 65.6% patients with bevacizumab, 31.6% patients with aflibercept, and 41.5% patients with ranibizumab through 24wk[13]. To the best of our known, this is the first case reporting CNV secondary BVMD resistant to intravitreal anti-VEGF treatment.

Intravitreal therapies targeting VEGF have revolutionised treatment of ocular neovascular diseases as VEGF is implicated in a wide variety of pathophysiologic processes and therefore the ocular and systemic safety of anti-VEGF agents is of importance. The primary ocular adverse event detected in clinical trials regarding anti-VEGF drugs was a low frequency of ocular inflammation and systemic adverse events such as slightly elevated risk of stroke. The sporadic adverse events included retinal detachments, retinal tears, elevated intraocular pressure, ischemia, transient global amnesia, sixth nerve palsy, *etc*. We do not know if long term anti-VEGF treatment could influence children physical development either. Currently, the long term use of anti-VEGF treatment lacks sufficient evidence[14].

Though PDT therapy could make CNV lesion stable, but previous studies didn't find any visual acuity improvement from that[15]. In the current case, BCVA is stable during follow-up, so we didn't choose this option.

In conclusion, our case shows persistent macular oedema secondary CNV to BVMD after anti-VEGF treatment. The patient kept stable BCVA during the 16mo follow-up. We suggest close observation for this kind of disease.

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