

# Intravitreally injected ranibizumab versus photodynamic therapy for CNV secondary to choroidal osteoma: a 7-year follow-up case report

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**Dear Editor,**

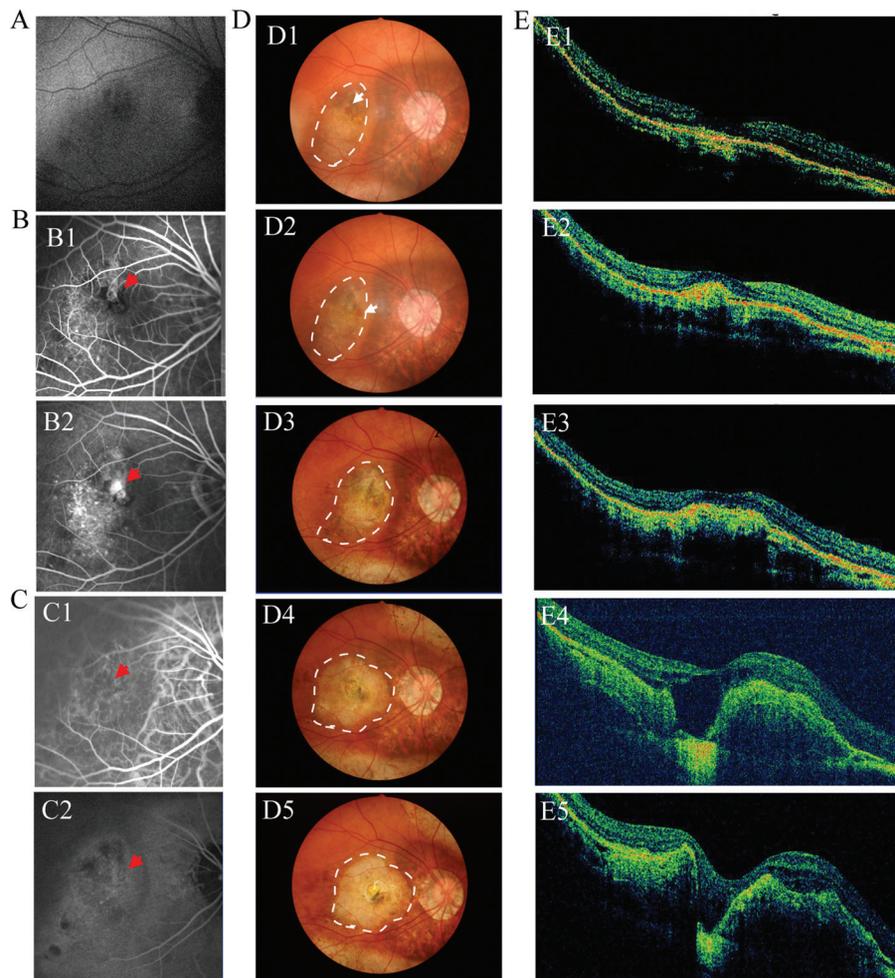
We present a case of bilateral choroidal neovascularization (CNV) secondary to choroidal osteoma involving the macula and investigate the effect of intravitreal injection of ranibizumab and photodynamic therapy (PDT) in a seven-year follow-up. Informed consent for patient information and images to be published was obtained from the patient included in the study based on the Declaration of Helsinki, which was approved by the Ethics Committee of Southwest Hospital. Choroidal osteoma is a rare, benign, ossifying intraocular tumor of the choroid that was first reported in 1978<sup>[1]</sup>. Recently, it has been reported to affect not only women

in their 20s or 30s but also men and children<sup>[2-4]</sup>. This benign tumor is classically detected as a yellow-white or orange plaque located in the juxtapapillary or macular region within the choroid<sup>[3-5]</sup>. Despite the benign nature of the tumor, visual loss of three lines or more (45% of patients) and of 20/200 or worse (56%) occurs after 10y<sup>[2,6]</sup>. Mounting evidence has demonstrated that vision is mainly compromised by tumor growth, decalcification, and CNV<sup>[2-3,7]</sup>.

Current treatments primarily target CNV; these include argon laser photocoagulation, PDT, transpupillary thermotherapy, surgical excision, and anti-vascular endothelial growth factor (VEGF) agents<sup>[2,5,7-8]</sup>. Unfortunately, the outcomes seem to be controversial. It also remains unclear how to stabilize the tumor.

A 25-year-old man who complained of gradual visual loss in the right eye (RE) was referred to our eye hospital (Southwest Eye Hospital, Southwest Hospital, Army Medical University, Chongqing, China) in 2008. On his first examination, the best-corrected visual acuity (BCVA) of the RE and left eye (LE) were 20/60 and 20/20, respectively. A fundus examination demonstrated a bilateral crescent-like yellow-orange elevated juxtapapillary choroidal mass with distinct borders at the posterior pole involving the macula area. A diagnosis of bilateral choroidal osteoma with CNV was established based on examinations.

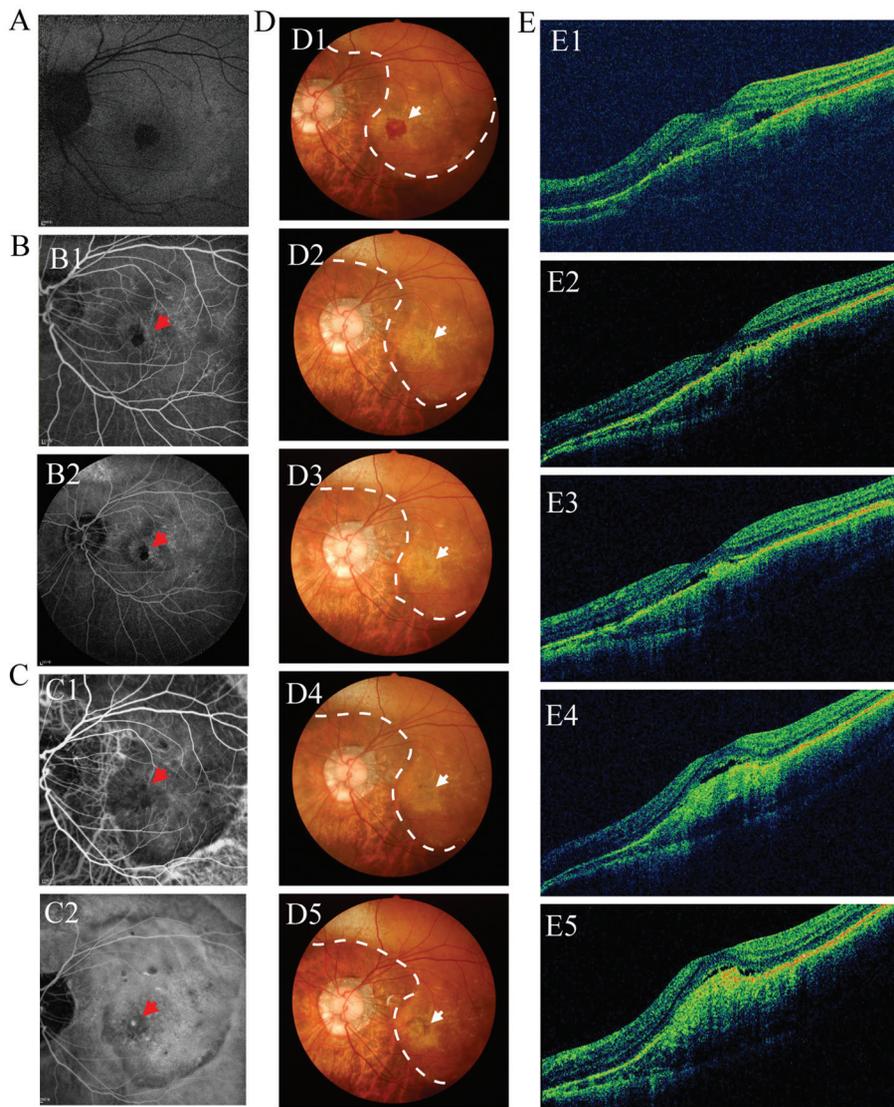
Further examinations were conducted on the RE. Fundus autofluorescence (FAF) images (Figure 1A) disclosed that the tumor displayed hyper- and hypoautofluorescence. Fundus fluorescein angiography (FFA; Figure 1B) demonstrated variable hyperfluorescence of the tumor from the early phase, representing CNV. Indocyanine green angiography (ICGA; Figure 1C) in the early (Figure 1C1) to late phases (Figure 1C2) showed a well-defined hypofluorescent tumor with CNV. The macular area of the RE also displayed petechial hemorrhage with some yellow-whitish portions (Figure 1D1). Optical coherence tomography (OCT) displayed a sponge-like choroidal lesion beneath the outer retina with horizontal hyperreflective lines inside the tumor (Figure 1E1). Subretinal fluid (SRF) was formed in the CNV overlaying the tumor (Figure 1E1).



**Figure 1 Progress of the RE before and after PDT treatments** A 25-year-old male patient with bilateral CNV secondary to choroidal osteoma. A: Representative images display the FAF; B: FFA; C: ICGA images at first visit. Early phase: B1, C1. Late phase: B2, C2. D, E: Representative images of fundus examinations (D) and horizontal OCT (E) before PDT treatments (D1, E1), 3mo post-PDT (D2, E2), 1y post-PDT (D3, E3), 5y post-PDT (D4, E4), and 7y post-PDT (D5, E5). Red arrows indicate the CNV foci. White arrows indicate the CNV hemorrhage foci. The white dashed line represents the area of the tumor in the macula.

The details suggested that CNV involving the macular area in the RE had led to visual loss at that time. Thus, according to the guidelines, the patient received PDT targeting CNV in the RE. Based on a previous protocol<sup>[9]</sup>, PDT was conducted with a laser spot at 689 nm (50 J/cm<sup>2</sup>) after an intravenous infusion of verteporfin (6 mg/m<sup>2</sup>). Unfortunately, it failed to improve the patient's visual acuity. A new macular CNV hemorrhage developed 3mo post-PDT (Figure 1D2 and 1E2), although the macular SRF was absorbed (Figure 1E2). In addition, the tumor of the RE gradually grew larger, with more yellow-whitish portions, choroidal atrophy, and depigmentation of the overlying retinal pigment epithelium (RPE), especially in the macular area (Figure 1D). OCT images disclosed that CNV quickly developed and drove the retina toward the vitreous body, forming a new traction and again resulting in SRF (Figure 1E). No management was performed at this time. The BCVA of the RE decreased to 20/400 in the fifth year post-PDT (Figure 1D4 and 1E4). After that, the tumor remained

stable until the 7-year follow-up (Figure 1D5 and 1E5). The patient complained of a quick visual loss in his LE in 2014, with the BCVA dropping from 20/20 to 20/400. The tumor was yellow-whitish in color, and a macular hemorrhage occurred (Figure 2D1). FAF, FFA, ICGA examination, and OCT images displayed CNV in the fovea (Figure 2A-2C, 2E1). Considering that no benefit had been observed after PDT treatment in the RE, ranibizumab was considered for the LE at that time. The patient received three consecutive monthly injections of ranibizumab (0.05 mL) in his LE. The BCVA improved and remained at 20/25 after the injections. No significant changes of the tumor were noted, including blood, enlargement, or coloration (Figure 2D1-2D3, 2E1-2E3). OCT demonstrated that the SRF was finally absorbed with an old CNV left 1mo after the third injection (Figure 2E3). Unfortunately, the SRF recurred again in the LE 6mo after the initial resolution (Figure 2D4 and 2E4), and the BCVA dropped to 20/40. Thus, a fourth injection of ranibizumab was given.



**Figure 2 Progress of the LE before and after ranibizumab treatments with a 3-year follow-up** A: Representative images display the FAF; B: The FFA images; C: The ICGA images before treatment. Early phase: B1, C1. Late phase: B2, C2. D, E: Representative images of fundus examinations (D) and horizontal OCT (E) before ranibizumab treatments (D1, E1), 1mo after the second ranibizumab treatment (D2, E2), 1mo after the third ranibizumab treatment (D3, E3), 6mo after the third ranibizumab treatment (D4, E4), and 2y after the fourth ranibizumab treatment (D5, E5). Red arrows indicate the CNV foci. White arrows indicate the CNV hemorrhage foci. The white dashed line represents the area of the tumor in the macula.

The BCVA improved and stayed at 20/28 for another 6mo, but it eventually dropped again to 20/100. OCT disclosed that the CNV seemed to keep developing and pushing the retina into a more curved shape 2y post-injection (Figure 2E5). However, there was no obvious enlargement of the tumor on the fundus examination (Figure 2D5). No serious or minor adverse events have been reported in the patient to date.

Choroidal osteoma is a rare, benign tumor composed of mature bone that replaces the choroid<sup>[5,9]</sup>. Unlike other life-threatening intraocular tumors, such as retinoblastoma<sup>[10]</sup>, it only threatens vision, mainly by the tumor growth, decalcification of the tumor, CNV, and accompanying SRF<sup>[5]</sup>; it does not pose risks of metastasis, enucleation, or death in patients. However, the rational treatment for this benign but potentially vision-

threatening tumor has not been determined, especially for secondary CNV.

PDT was the first therapy introduced to treat choroidal osteoma accompanied by CNV, but its therapeutic effect remains controversial<sup>[8-9,11]</sup>. It was reported that PDT could reduce the CNV size and improve visual acuity in some cases of choroidal osteoma<sup>[9,12-13]</sup>. In our case, however, after PDT treatment in the RE according to the guidelines of that time, the BCVA failed to improve, with a new macular CNV hemorrhage developing after 3mo. This was similar to a case reported by Palamar *et al*<sup>[11]</sup> of an 8-year-old boy with choroidal osteoma; in this case, a subretinal hemorrhage over the lesion was detected the day after PDT. PDT is known to cause inflammation, ischemia, and increased VEGF in the retina, which may lead to hemorrhage

via angiogenesis and to increased vascular permeability, as reported in cases of age-related macular degeneration<sup>[14-15]</sup>. Intriguingly, PDT has recently been reported to induce focal tumor decalcification, minimize tumor growth, and improve regression of the extrafoveal choroidal osteoma<sup>[9,13]</sup>. Shields *et al*<sup>[6]</sup> found that tumor growth appeared to be random along the margins except for a decalcified margin. However, in our case, compared with the LE, the decalcification of the RE seemed to accelerate after PDT, together with the enlargement of tumor lesions and the occurrence of a new hemorrhage. Trimble *et al*<sup>[16]</sup> were the first to report a case in which a tumor grew over 5y and then began to decalcify, resulting in CNV in the sixth year. This suggested that PDT rather than anti-VEGF therapy could accelerate the decalcification activity of choroidal osteoma to minimize tumor growth; however, this included the risk of enlarging the tumor in the macular area, resulting in new CNV or hemorrhage that could lead to poor vision. Thus, PDT should be carefully considered when applied in CNV secondary to choroidal osteoma and should not be extrapolated to subfoveal osteomas.

Intravitreal anti-VEGF therapy is well known to improve visual acuity in secondary CNV, for example, myopic CNV and idiopathic CNV<sup>[17]</sup>. Recently emerging case series studies have been conducted on choroidal osteoma with CNV or SRF; their results have shown that intravitreal injection of anti-VEGF antibodies resulted in both visual and anatomical improvements<sup>[3,8,18-19]</sup>. It was even reported to be superior to PDT and was suggested as the first-line therapy<sup>[19-20]</sup>. In our case, four injections of ranibizumab (0.05 mL) in the LE, with the first three injections at 1-month intervals, were administered. The BCVA was improved and SRF was resolved 1mo after the single injection, without obvious changes in tumor size. This was similar to previous studies that reported monthly injections of ranibizumab improving visual acuity and bringing about the resolution of SRF after 1mo<sup>[18-19]</sup>. However, Yoshikawa and Takahashi<sup>[2]</sup> reported on three patients in whom intravitreal injections of bevacizumab for subfoveal CNV associated with decalcified choroidal osteoma resulted in poor visual acuity, where the patients were monitored with a follow-up of 23-56mo. The different outcomes may relate to the different anti-VEGF medications. Shields *et al*'s<sup>[21]</sup> reported treatment of intravitreal bevacizumab followed by ranibizumab in a female patient showed that the ranibizumab treatment resolved persistent SRF, and visual acuity improved to 20/30 at the 6-month follow-up, which took longer than bevacizumab treatment. Further randomized clinical studies with large samples could be performed on different anti-VEGF therapies for CNV or SRF secondary to choroidal osteoma. It should be noted that our study, together with previous research<sup>[21-22]</sup>, demonstrated that the patient's vision

deteriorated 6 or 7mo after the last injection. This implied that the injection of ranibizumab was useful for a certain time without obvious tumor enlargement but that it should be applied serially or monthly until the tumor is controlled.

In conclusion, we presented long-term follow-up outcomes with different treatment methods on both eyes in a bilateral choroidal osteoma patient. The results demonstrated that intravitreal injection of ranibizumab alone may have a therapeutic effect on CNV secondary to choroidal osteoma for a certain time, especially in subfoveal tumors. Serial monthly injection of ranibizumab could consolidate the therapeutic effects until control is achieved. PDT should be avoided in subfoveal cases, but it may be useful for inducing decalcification in the margins of the tumor to slow or even stop tumor growth. Larger studies are needed to clarify the therapeutic effect of anti-VEGF therapy with or without PDT for CNV with respect to calcification and decalcification.

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#### REFERENCES

- 1 Gass JD, Guerry RK, Jack RL, Harris G. Choroidal osteoma. *Arch Ophthalmol* 1978;96(3):428-435.
- 2 Yoshikawa T, Takahashi K. Long-term outcomes of intravitreal injection of bevacizumab for choroidal neovascularization associated with choroidal osteoma. *Clin Ophthalmol* 2015;9:429-437.
- 3 Khan MA, DeCroos FC, Storey PP, Shields JA, Garg SJ, Shields CL. Outcomes of anti-vascular endothelial growth factor therapy in the management of choroidal neovascularization associated with choroidal osteoma. *Retina* 2014;34(9):1750-1756.
- 4 Papastefanou VP, Pefkianaki M, Al Harby L, Arora AK, Cohen VM, Andrews RM, Sagoo MS. Intravitreal bevacizumab monotherapy for choroidal neovascularisation secondary to choroidal osteoma. *Eye (Lond)* 2016;30(6):843-849.
- 5 Song JH, Bae JH, Rho MI, Lee SC. Intravitreal bevacizumab in the management of subretinal fluid associated with choroidal osteoma. *Retina* 2010;30(6):945-951.
- 6 Shields CL, Sun H, Demirci H, Shields JA. Factors predictive of tumor growth, tumor decalcification, choroidal neovascularization, and visual outcome in 74 eyes with choroidal osteoma. *Arch Ophthalmol* 2005;123(12):1658-1666.
- 7 Huang YM, Zhang L, Liang J, Yuan RD. Bilateral choroidal osteoma with unilateral polypoidal choroidal vasculopathy treated with conbercept. *Int J Ophthalmol* 2020;13(6):1009-1012.

- 8 Zafar S, Burq MA, Ifhtikar M, Ali A. Intravitreal ranibizumab for treatment of choroidal neovascularization secondary to a bilateral choroidal osteoma. *Am J Ophthalmol Case Rep* 2016;4:7-10.
- 9 Shields CL, Materin MA, Mehta S, Foxman BT, Shields JA. Regression of extrafoveal choroidal osteoma following photodynamic therapy. *Arch Ophthalmol* 2008;126(1):135-137.
- 10 Gündüz AK, Mirzayev I, Temel E, Ünal E, Taçyıldız N, Dinçaslan H, Köse SK, Özalp Ateş FS, Işık MU. A 20-year audit of retinoblastoma treatment outcomes. *Eye (Lond)* 2020;34(10):1916-1924.
- 11 Palamar M, Uretmen O, Gunduz K: Transient subretinal hemorrhage after photodynamic therapy of subfoveal choroidal osteoma. *Retin Cases Brief Rep* 2012;6(2):166-168.
- 12 Blaise P, Duchateau E, Comhaire Y, Rakic JM. Improvement of visual acuity after photodynamic therapy for choroidal neovascularization in choroidal osteoma. *Acta Ophthalmol Scand* 2005;83(4):515-516.
- 13 Mazlouni M, Dalvin LA, Ancona-Lezama D, Mashayekhi A, Shields CL. Photodynamic therapy for extrafoveal choroidal osteoma. *Retina* 2020;40(5):966-971.
- 14 Oh IK, Huh K, Oh J. Risk factors for retinal hemorrhage after photodynamic therapy in age-related macular degeneration. *Ophthalmologica* 2009;223(2):78-84.
- 15 Matsushita S, Naito T, Takebayashi M, Sato H, Shiota H. The prognosis of cases with massive subretinal hemorrhage after photodynamic therapy. *J Med Invest* 2008;55(3-4):231-235.
- 16 Trimble SN, Schatz H, Schneider GB. Spontaneous decalcification of a choroidal osteoma. *Ophthalmology* 1988;95(5):631-634.
- 17 Ruiz-Moreno JM, Arias L, Montero JA, Carneiro A, Silva R. Intravitreal anti-VEGF therapy for choroidal neovascularisation secondary to pathological myopia: 4-year outcome. *Br J Ophthalmol* 2013;97(11):1447-1450.
- 18 Narang S, Sindhu M, Sheoran K, Kaur R. Choroidal osteoma: the varied response of subretinal fluid to anti-VEGF agents. *BMJ Case Rep* 2020;13(5):e234357.
- 19 Furino C, di Antonio L, Grassi MO, Rispoli M, Reibaldi M, Niro A, Alessio G. Choroidal neovascularization due to choroidal osteoma treated with anti-vascular endothelial growth factor therapy: an optical coherence tomography angiography study. *Eur J Ophthalmol* 2019;29(3):323-329.
- 20 Song WK, Koh HJ, Kwon OW, Byeon SH, Lee SC. Intravitreal bevacizumab for choroidal neovascularization secondary to choroidal osteoma. *Acta Ophthalmol* 2009;87(1):100-101.
- 21 Shields CL, Salazar PF, Demirci H, Benson WE, Shields JA. Intravitreal bevacizumab (avastin) and ranibizumab (lucentis) for choroidal neovascularization overlying choroidal osteoma. *Retin Cases Brief Rep* 2008;2(1):18-20.
- 22 Sarigül Sezenöz A, Akça Bayar S, Yılmaz G. Choroidal osteoma and secondary choroidal neovascularization treated with ranibizumab. *Turk J Ophthalmol* 2017;47(4):243-246.