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CLINICAL STUDY

Intravitreal bevacizumab monotherapy for choroidal neovascularisation secondary to choroidal osteoma

VP Papastefanou[1,2], M Pefkianaki[2], L Al Harby[1], AK Arora[1], VML Cohen[1], RM Andrews[2] and MS Sagoo[1,2,3]

Abstract

Purpose **The purpose of this study is to present the outcomes of a series of patients with choroidal neovascular membrane (choroidal neovascularisation (CNV)) secondary to a choroidal osteoma undergoing anti-VEGF monotherapy.**

Patients and methods **Retrospective series of patients with choroidal neovascularization secondary to choroidal osteoma. All patients underwent clinical and imaging assessment (fundus photo, B-scan ultrasonography, fluorescein angiography, and optical coherence tomography—where available), and were managed with intravitreal anti-VEGF injections (Bevacizumab). Visual acuity and central retinal thickness were recorded pre treatment and at the end of the follow-up period.**

Results **Eight patients were included in this study. Of this, 6/8 had predominantly classic or classic and 2/8 patients had minimally classic or occult CNV. Each patient received 3–10 injections of bevacizumab. Median follow-up was 9 months (3–15 months). Visual acuity improved in 5 patients, by 2–6 Snellen lines. CNV completely regressed in 5 cases and partially regressed in 3 cases. Mean CRT reduction was 122 μm (6 to −230 μm).**

Conclusion **Intravitreal bevacizumab can be an effective treatment modality in the management of vision threatening CNV secondary to choroidal osteoma.**

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Introduction

Choroidal osteoma is a rare, benign, osseous choristoma presenting as a yellowish-orange, well-defined fundus mass. It is commonly encountered in young adults, mostly females, though it has been reported in children as well. Though benign in nature, choroidal osteomas usually grow very slowly over months to years, though sometimes growth can be quite extensive.[1] Almost 60% of eyes with osteoma may suffer significant visual loss.[2,3] One of the principal causes, in up to 30% of cases, is the development of choroidal neovascularisation (CNV).[1] CNV commonly develops subretinal haemorrhage and eventual disciform scarring. Various treatment modalities have been used in the past to destroy the CNV by argon laser photocoagulation,[4,5] photodynamic therapy (PDT),[6,7] transpupillary thermotherapy (TTT),[8,9] or even surgical removal of the CNV.[10]

More recently, anti-VEGF agents have been used not only in retinal diseases, such as age-related macular degeneration or high myopia, where CNV is frequent, but also where choroidal tumours, such as naevi form CNV.[11] In this report, we present the management and outcomes of a series of eyes with CNV secondary to choroidal osteoma with bevacizumab intravitreal injections monotherapy in a single centre.

Patients and methods

This is a retrospective case note review of eyes with choroidal neovascularization secondary to choroidal osteoma managed in the Medical Retina and Ocular Oncology Services of Moorfields Eye Hospital and St Bartholomew`s Hospital for the period of 2010 to 2014. The study complied with the Declaration of Helsinki and the ethics committee at Moorfields Eye Hospital approved the research protocol

[1]Ocular Oncology Service, St Bartholomew`s and Moorfields Eye Hospitals, London, UK

[2]Medical Retina Service, Moorfields Eye Hospital, London, UK

[3]UCL Institute of Ophthalmology, London, UK

Correspondence: MS Sagoo, Ocular Oncology Service, Moorfields Eye Hospital, 162 City Road, London EC1V 2PD, UK
Tel: +44 (0)20 7566 2255; Fax: +44 (0)20 7566 2019.
E-mail: Mandeep.Sagoo@moorfields.nhs.uk

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(number *PEFM1010s*). All patients underwent a full clinical and imaging assessment, including Snellen best-corrected visual acuity, slit-lamp fundus ophthalmoscopy, optical coherence tomography (OCT), baseline B-scan ultrasonography, and fluorescein angiography.

Clinical details at presentation included age, gender, ophthalmic, and medical history. Osteoma characteristics recorded were location (quadrant or foveal area, position in relation to foveola, and optic disc), dimensions (measured clinically and on ultrasound B-scan), and degree and distribution of decalcification. CNV was assessed clinically and with fluorescein angiography (predominantly classic or classic *vs* minimally classic or occult) and location on the osteoma was recorded. The presence of intraretinal or subretinal fluid was recorded for every visit either clinically or with OCT scans and central retinal thickness measurements were obtained with the use of automated software.

All patients underwent treatment with intravitreal anti-VEGF injections on a treat and observe basis. Bevacizumab (1.25 mg; Avastin; Genentech, South San Francisco, CA, USA) was used as an 'off-label' treatment for CNV secondary to choroidal osteoma, with informed consent from the patients. All procedures were performed using standard aseptic technique. The eye was topically anaesthetised and prepared using povidone-iodine (5%). Bevacizumab was injected via a 30-gauge needle through the pars plana 3.5 and 4.0 mm from the limbus for pseudophakic and phakic eyes, respectively. The number of injections was recorded. Retreatment was determined by persistence or recurrence of intraretinal or subretinal fluid. At the end of follow-up, complete regression of CNV was defined as no subretinal fluid overlying the osteoma and partial regression of CNV was defined as the presence of residual trace fluid overlying the osteoma.

Results

During the study period, there were eight eyes with a CNV over a choroidal osteoma. The mean age was 41 years (median 34, range 17–72 years). Clinical and demographic features are presented in Table 1.

Clinical features of osteomas

The location of the osteoma (Table 1) was subfoveal or juxtafoveal in 2/8 eyes, extrafoveal in 2/8 eyes, and juxtapapillary in 3/8 eyes. One osteoma spanned the juxtapapillary and macular area. All lesions had areas of decalcification. In 6/8 eyes of osteomas decalcification was located at the tumour epicentre and extending peripherally. At presentation, OCT scans were available for all patients. There were six eyes with subretinal fluid

Table 1 Patients with choroidal neovascular membrane (CNV) secondary to choroidal osteoma: dimensions, location, and features of osteomas and secondary CNV

Patient	*Age/ gender*	*Dimensions (mm)*	*Thickness (mm)*	*Distance to disc (mm)*	*Location of osteoma*	*Location of CNV*	*Type of CNV*	*Decalcification present*	*Location of decalcification*
1	36/F	5.1×4.1	1.3	0	Juxtapapillary	At tumour epicentre	Min Classic	Yes	Diffuse at tumour epicentre—extending peripherally
2	27/F	6×6	1.2	0.3	Juxtapapillary	Periphery towards the fovea	Classic	Yes	Diffuse at tumour epicentre—extending peripherally
3	32/F	9×7.2	1.4	0.2	Juxtapapillary	At decalcification site at fovea	Classic	Yes	At epicentre—extending peripherally
4	66/M	4.1×3.5	1.5	1	Subfoveal	Periphery not towards fovea	Classic	Yes	Diffuse
5	17/F	4.5×6	1.5	1.5	Extrafoveal	At tumour epicentre	Classic	Yes	At epicentre—extending peripherally
6	21/F	13×12	1.6	0	Juxtapapillary	Epicentre at fovea	Classic	Yes	Diffuse at tumour epicentre—extending peripherally
7	58/M	9.1×8.1	2.8	5	Juxtafoveal	Periphery towards the fovea	Classic	Yes	Diffuse at tumour epicentre—extending peripherally
8	72/M	15.3×13.8	2.2	3	Extrafoveal	RPE change location at fovea	Occult	Yes	At superotemporal periphery and towards the fovea

Abbreviation: RPE, retinal pigment epithelium.

and two eyes with intraretinal fluid. One case had a retinal pigment epithelial (RPE) detachment on OCT (PED). On B-scan, the mean thickness of osteomas was 1.7 mm (median 1.5 mm, range 1.2–2.8 mm) with a mean maximal diameter of 8.45 mm (median 7.5 mm, range 4.1–15.3 mm), and a mean minimal diameter of 7.45 mm (median 6.6 mm, range 3.5–13.8 mm).

Choroidal neovascular membrane

Three eyes had subretinal haemorrhage. On fluorescein angiogram 6/8 of eyes had the features of classic (Figure 1) and 2/8 had occult or minimally classic CNV (Figure 2). In three eyes CNV was located at the tumour epicentre, in three eyes in the periphery of the lesion, and in two eyes at the fovea in association with RPE changes.

Anti-VEGF treatment

The results of anti-VEGF treatment are summarised in Table 2. All cases received bevacizumab monotherapy of 1.25 mg/0.05 ml. The mean follow-up time was 9.5 months (median 9 months, range 3–15 months). Eyes received a mean of 5 injections (median 5, range 3–10). No ocular or systemic adverse effects occurred during treatment.

Visual acuity and OCT findings

Snellen visual acuity before treatment was in the range 6/12 to counting fingers. There were 2 eyes that had best-corrected visual acuity equal to 6/12 and 6 eyes with 6/18 to counting fingers. Visual acuity improved at the end of the follow-up period in five eyes by 2–6 Snellen lines, remained the same in one eye and worsened in two eyes by 1 and 5 Snellen lines, respectively. Following treatment with bevacizumab, five cases demonstrated complete regression and three cases partial regression of the CNV (Figures 1 and 2).

At the end of the follow-up period, OCT scan was not available in one patient. Six out of eight eyes demonstrated a reduction in central retinal thickness. In one eye there was no change. The mean reduction in central retinal thickness was 122 μm (range 6–230 μm). In four eyes retinal thickness reduction was associated with visual acuity improvement, in one eye visual acuity remained stable, and in two eyes visual acuity was worse.

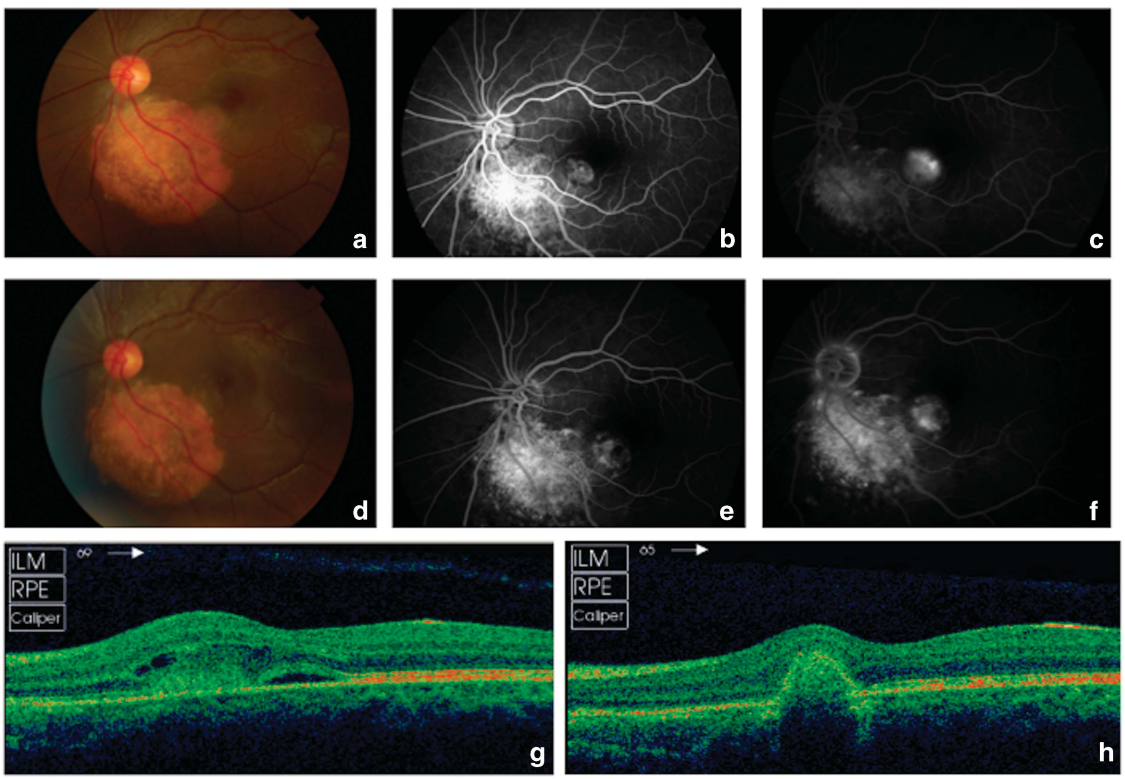

Figure 1 A 27-year old patient with CNV secondary to a choroidal osteoma (patient 6). (a–c) Classic CNV at the superotemporal aspect of the osteoma involving the fovea with intraretinal fluid and a PED (g). (d–f) 10 months following three bevacizumab injections leakage is reduced on fluorescein angiogram and residual fibrosis is noted on PED. There was no evidence of fluid (h). Visual acuity improved from 6/12 to 6/9 post treatment.

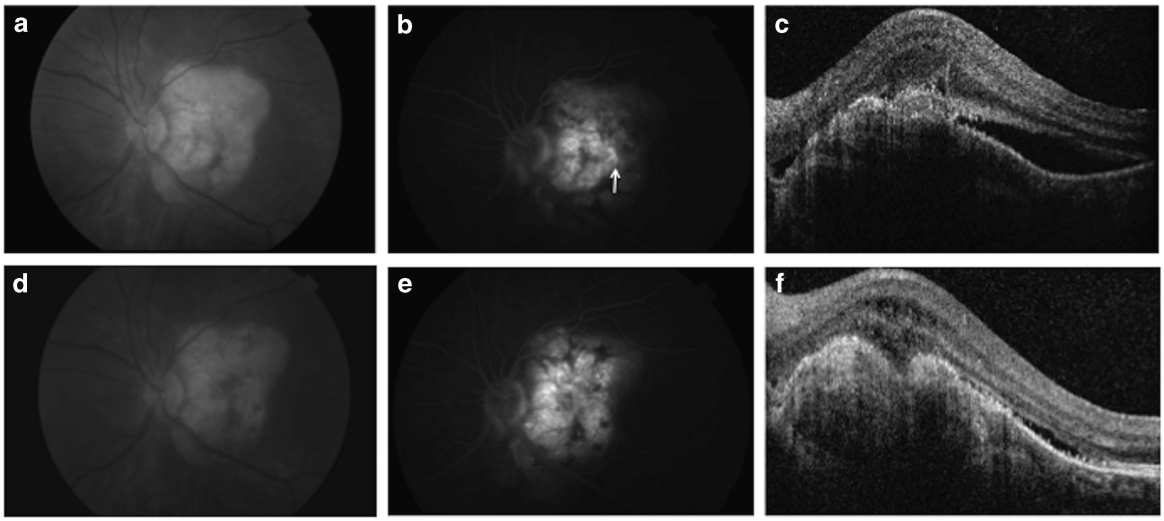

Figure 2 A 36-year old patient with choroidal neovascularization secondary to choroidal osteoma (patient 1). (a–c) A minimally classic CNV developed in the juxtapapillary area with considerable PED and subretinal fluid. (d–f) Staining because of fibrosis and reduction of subretinal fluid. Vision improved from count fingers to 6/24.

Table 2 Overview of results of patients with an osteoma-associated choroidal neovascular membrane (CNV) that were subjected to anti-VEGF treatment

Patient	*F/U (months)*	*VA initial*	*VA final*	*No of injections*	*CNV type*	*OCT CRT initial*	*OCT CRT final*	*CNV status*
1	15	CF	6/24	10	Min Classic	297	291	Partial regression
2	12	CF	6/12	4	Classic	269	238	Complete regression
3	12	6/24	6/12	5	Classic	500	270	Complete regression
4	4	6/60	6/60	3	Classic	NA	NA	Partial regression
5	7	6/12	6/7.5	5	Classic	376	266	Complete regression
6	10	6/12	6/9	5	Classic	204	203	Partial regression
7	3	6/18	6/60	3	Classic	577	355	Complete regression
8	9	6/60	CF	7	Occult	342	206	Complete regression

Abbreviation: CRT, central retinal thickness.

Discussion

Visual loss in eyes with choroidal osteoma can be the result of tumour growth, tumour decalcification, and choroidal neovascularization.[1] The development of CNV is not uncommon and has been reported to occur in 30% of patients in a series of 74 eyes.[1] The published case series and individual case reports of eyes with CNV secondary to choroidal osteoma amount to a total of 85 cases in the literature.[4,12–36]

Osteoma size has not been associated with the development of CNV. Growth of choroidal osteoma is slow over years with an average estimate of 0.37 mm/year.[1] Osteoma location in the majority of published cases is juxtapapillary with temporal extension toward the papillomacular bundle and involving the foveal area.[4,12–36] In our series, osteomas were similarly juxtapapillary in half of the cases with the remainder in the macular area.

Almost all the eyes in this study harboured a classic CNV with one case presenting with occult and one with minimally classic CNV. This agrees with previous reports.[4,12–36] Location of CNV was found to be mostly subfoveal or juxtafoveal in our series. Similarly, in 22/85 reported cases location was subfoveal, 18/85 was juxtafoveal and 21/85 cases were extrafoveal.[4,12–36] In the remainder of cases location was not described in relation to the fovea.[4,12–36] However, the fovea was still indirectly affected by associated haemorrhage or encroaching subretinal fluid.

Associated findings in relation to CNV are the presence of decalcification and RPE changes. It is interesting that growth appears halted at areas of decalcification and the lack of RPE changes is predictive of osteoma growth. A recent spectral domain OCT study demonstrated the gradual excavation of osteomas as a result of bone remodelling is association with the development of RPE changes over a period of 5 years.[37]

Previously reported cases have associated the development of CNV with areas of decalcification.[2] Decalcification is considered the cause for subsequent

RPE/choriocapillaris disturbance and irritation of the retinal tissue with possible effect on VEGF production.[13] In our series all osteomas had areas of decalcification with RPE changes. CNV developed at or at close proximity to these areas in the majority of cases. These findings suggest that choroidal neovascularization over a choroidal osteoma is a late-onset complication in the course of the lesion.

In this case series, there was evidence of subretinal fluid on OCT in all patients. The presence of subretinal fluid has been found to be predictive of CNV.[1] However, subretinal fluid and serous macular detachment can develop over a choroidal osteoma as a result of the RPE disturbance without evidence of a CNV.[27] Subretinal haemorrhage was present in three cases in this study. Subretinal haemorrhage has been considered a stronger predictive factor for CNV.[1] However, spontaneous haemorrhages can occur over an osteoma from Valsalva manoeuvres,[38] polypoidal choroidal vasculopathy,[39] or can even be idiopathic,[40] rather than from CNV. Use of anti-VEGF injections in these situations may not be efficacious. Assessment by fluorescein angiography is therefore an important part of the workup.

There is currently no standard treatment for a CNV arising from a choroidal osteoma. Various modalities have been used in the past including argon green laser, krypton red laser alone or in combination for extrafoveal CNVs, PDT with standard settings or as half-fluence alone or in combination with anti-VEGF agents, TTT alone in one case report[9] or in combination with anti-VEGF agents,[27] and anti-VEGF agents alone or in combination.

Out of the available anti-VEGF agents, bevacizumab, has been most commonly used mostly as monotherapy or in combination with ranibizumab, PDT, or TTT. Ranibizumab has been used to a lesser degree in combination with PDT consolidation.[2] Aflibercept use has been reported in one case,[14] as third-line treatment following failure of bevacizumab and ranibizumab in a case with poor therapeutic response with positive results.

Our series has the advantage that all cases were treated with bevacizumab injections alone without adjuvant or combined treatment with another anti-VEGF agent or PDT in a single centre. An additional strength is that all patients were treatment naive. The number of injections per patient in our series ranged from three up to ten. Half the cases had complete regression of the subretinal fluid and clinical improvement. Visual acuity was improved by 2–4 lines in 4 eyes, was stable in 1, and was worse in 2 eyes. Mean central retinal thickness was improved by 122 microns. The two eyes that had a drop in visual acuity had signs of complete regression of CNV but structural retinal damage limited the visual outcome.

In the largest publication on CNV in osteomas, there were 26 eyes treated in 23 centres.[12] In that report, 17 eyes received bevacizumab and the remainder received ranibizumab, or combination of the two with 5 cases receiving PDT consolidation. Eliminating 2 eyes that had chronic CNV, there were 18 eyes treated with anti-VEGF injections alone, with a mean number of 4.5 injections, and with a 4.9 Snellen line improvement at 2 years. In another series[2] PDT consolidation was required in four out of eight cases treated with anti-VEGF injections. In those without additional PDT, the number of injections ranged from 3–40 with 3 out of 4 cases having satisfactory control of CNV. Though anatomical response was achieved, the visual gains were only modest. In the current study, visual acuity stabilised or improved in six out of eight eyes. Finally, there are collectively a further 15 cases in the literature that have received bevacizumab monotherapy, from a small case series[13] and individual case reports, and that report improvement in visual acuity in 11 eyes and worsening in 2 eyes. All worsening eyes had areas of decalcification at the fovea.

The most suitable therapeutic algorithm for subfoveal or juxtafoveal CNV secondary to osteoma is difficult to determine as reported regimens and therapeutic responses have been variable. On the basis of the current data, treat and observe has been the norm. Treat and extend is an alternative approach,[2] but as this is a rare tumour with the possibility of reactivation of CNV, RPE damage, and decalcification the course of treat and extend may be less predictable than for other disorders with CNV.

We recognise the weaknesses of our study include the small numbers even though it is a single institution, monotherapy report of a rare complication of a rare tumour. PDT consolidation was not tested in this study. Despite encouraging results, PDT has been associated with osteoma decalcification, further photoreceptor atrophy,[2] and worsening of choroidal perfusion.[13] Alteration of PDT parameters might be beneficial. So far there is one recorded case[23] of half-fluence PDT with positive results used concomitantly and not as consolidation treatment along with one injection of ranibizumab.

In summary, CNV secondary to choroidal osteoma is a late-onset complication developing following decalcification and RPE changes, is usually classic in angiographic type and has variable location on the tumour developing either on the epicentre or at the margins. Bevacizumab monotherapy as a treatment modality is a safe and relatively effective treatment with stabilised or improved visual acuity in 75%. Whilst randomised trials of a rare complication in a rare disease would be difficult to realise, these results indicate that anti-VEGF monotherapy currently has a role for first line treatment for osteomas with CNV in juxtafoveal or subfoveal location.

Summary

What was known before

- Choroidal osteoma is a rare, benign, osseous choristoma Almost 60% of eyes with osteoma may suffer significant visual loss with one of the principal causes being the development of choroidal neovascularisation (CNV).
- Various treatment modalities have been used including laser, PDT, TTT or combination treatment of anti-VEGF agents with PDT consolidation.

What this study adds

- Bevacizumab monotherapy for CNV secondary to choroidal osteoma is a safe and relatively effective treatment with favourable anatomic and functional outcomes.

Conflict of interest

The authors declare no conflict of interest.

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