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Intravitreal Anti-Vascular Endothelial Growth Factor Treatment for Choroidal Neovascularization in Choroidal Osteoma: A Pilot Study

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Purpose: To determine the long-term visual and anatomical outcomes, recurrence risk, and prognostic factors after intravitreal anti-vascular endothelial growth factor (VEGF) treatment for choroidal neovascularization (CNV) in eyes with choroidal osteoma.

Methods: A retrospective review included patients diagnosed with choroidal osteoma and secondary CNV who received at least one intravitreal anti-VEGF injection at a single tertiary center between 2005 and 2023. Variables collected included demographics, baseline and final visual acuity, CNV location and type, imaging results, recurrence events, and adjunctive therapies. The main outcomes were change in visual acuity, proportion of eyes with final vision ≤20/200, and recurrence rate. Multivariable Firth-penalized logistic regression identified factors associated with poor prognosis.

Results: Of 17 eyes (mean age 32.0 years, 58.8% female), 15 (88.2%) achieved anatomical control, but only four (23.5%) achieved visual acuity improvement of two or more lines. Recurrences were observed in 12 eyes (70.6%), with most occurring within the first year after treatment. Lower initial visual acuity was associated with a worse prognosis (aOR 4.49, 95% CI 0.99–596.72), and non-subfoveal CNV location (aOR 0.27, 95% CI 0.02–2.29) and type 2 CNV (aOR 0.23, 95% CI 0.01–2.20) tended to be associated with a better visual outcome.

Conclusions: Anti-VEGF treatment was effective in achieving anatomical stabilization in CNV associated with choroidal osteoma, but visual recovery was limited. Given the high risk of recurrence, particularly within the first year after treatment, individualized strategies and early and long-term follow-up are essential.

Keywords: Bevacizumab; Choroidal neovascularization; Choroid, osteoma

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Introduction

Choroidal osteoma is an osseous tumor that develops in the choroid. Although benign, it can severely impair vision, resulting in a visual acuity of 20/200 or less, especially when accompanied by choroidal neovascularization (CNV) [1]. CNV development is common in choroidal osteoma, occurring in approximately 31%–47% of cases, and is an important factor affecting visual prognosis [1-3]. Choroidal osteoma is characterized by a progressive natural course involving tumor growth, spontaneous decalcification, and development of CNV. Decalcification leads to overlying retinal pigment epithelium atrophy, choriocapillaris compromise, and subsequent photoreceptor degeneration, often resulting in progressive visual decline independent of CNV activity [2,4,5].

Treatment of choroidal osteoma-associated CNV with intravitreal anti-vascular endothelial growth factor (VEGF) injection typically achieves better anatomical than functional outcomes [6-8]. Small case series have shown anatomical improvement in most patients but only modest visual benefits, reflecting a structure-function dissociation inherent to this condition [6,7]. However, owing to the extreme rarity of this tumor, most reports have described only small case series. Despite the clinical significance of CNV in choroidal osteoma, the long-term outcomes and prognostic factors following anti-VEGF treatment remain poorly characterized. Given the young age of affected patients and the potential for bilateral involvement, understanding the therapeutic efficacy and limitations of anti-VEGF injection is crucial for optimal patient management and counseling [1,3,9].

The aim of this study was to verify the therapeutic effect of intravitreal anti-VEGF as a primary treatment for CNV secondary to choroidal osteoma. To this end, we performed a review of the medical data of patients who received intravitreal anti-VEGF injection for CNV associated with choroidal osteoma at a single institute.

Materials and Methods

This retrospective study was approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine (IRB No. 4-2021-0855), with a waiver of informed consent, and was conducted in adherence to the Declaration of Helsinki. We reviewed the electronic medical records of patients diagnosed with choroidal osteoma between November 1, 2005, and April 20, 2023. Inclusion criteria were (1) diagnosis of choroidal osteoma and (2) receipt of at least one intravitreal anti-VEGF injection for secondary CNV between November 1, 2005 and March 20, 2023. Exclusion criteria were (1) patients with CNV who did not receive any intravitreal anti-VEGF injections; (2) patients without CNV who received intravitreal anti-VEGF injections for subretinal fluid (SRF) or hemorrhage alone; and (3) those with incomplete imaging or follow-up data.

At each visit, visual acuity was measured using the Snellen chart. Patients underwent several multimodal imaging tests, including fundus photography (Visucam pro NM/200/224; Carl Zeiss Meditec), panoramic ophthalmoscopy (Daytona P200T; Optos), standard fluorescein angiography/indocyanine green angiography (FA/ICG; Spectralis HRA+OCT; Heidelberg Engineering), ultra-widefield FA/ICG (Daytona P200T; Optos), spectralis OCT and OCT angiography (Spectralis; Heidelberg Engineering), time-domain OCT (Stratus OCT; Carl Zeiss Meditec), and B-scan ultrasonography (Eye Cubed; Ellex Inc.). Earlier cases were imaged using time-domain OCT with five discrete B-scan cuts, whereas later cases used spectral-domain OCT with continuous, higher-resolution scans. Computed tomography and magnetic resonance imaging were also performed when clinically indicated. For CNV treatment, patients received intravitreal injection of aflibercept (Eylea; Regeneron), ranibizumab (Lucentis; Genentech/Roche), or non-FDA-approved bevacizumab (Avastin; Genentech/Roche).

Demographic and clinical data, including visual acuity, follow-up duration, type and number of anti-VEGF injections, additional treatments, CNV location and type, presence of SRF or hemorrhage, and recurrence were extracted by two independent reviewers (H.J.S and C.S.L). CNV types were classified by multimodal imaging as type 1 (sub-retinal pigment epithelium, sub-RPE), type 2 (subretinal), or type 3 (intraretinal). The location of CNV was defined relative to the foveal avascular zone as subfoveal, juxtafoveal, or extrafoveal. Visual acuity was converted to logarithm of the minimum angle of resolution (logMAR) units.

The primary outcome was visual function, assessed as change in visual acuity (ΔlogMAR = final - baseline) and proportion of eyes with final visual acuity ≤20/200 (logMAR ≥1.0). We also assessed anatomical control on OCT, defined as a decrease in SRF or intraretinal fluid (IRF) after an-

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ti-VEGF injection. Active CNV was defined by the presence of SRF or IRF on OCT, while stable CNV was defined by absence of fluid. Retreatment was indicated upon recurrence of fluid with or without accompanying decline in visual acuity. Anti-VEGF responders were defined as ΔlogMAR ≤-0.2, worseners as ΔlogMAR ≥+0.2, and stable eyes (minimal changers) as -0.2 < ΔlogMAR < +0.2. Continuous outcomes were analyzed with the Wilcoxon signed-rank test and nonparametric bootstrap for confidence intervals (CIs). Visual outcomes between CNV subtypes (type 1 vs. type 2) were compared using the Wilcoxon rank-sum test. For the binary endpoint (final vision ≤20/200), we fitted a multivariable Firth-penalized logistic regression, reporting adjusted odds ratio (aOR) with profile penalized-likelihood 95% CI. Prespecified covariates were baseline logMAR, follow-up duration, CNV location, and CNV type. Time-to-recurrence was assessed using Kaplan–Meier survival analysis. All analyses were performed in R (version 4.2.2) using complete-case analysis (no imputation).

Results

Patient characteristics

This retrospective case series included 17 eyes of 17 patients with choroidal osteoma-associated CNV. The cohort consisted predominantly of females (10/17, 58.8%) with a mean age of 32.0 ± 16.8 years. Baseline visual acuity was poor, averaging 0.77 ± 0.72 logMAR, with a median of 0.398 (interquartile range [IQR] 0.398–0.823). Patients were followed for a median of 79 months (IQR 38–112). All eyes underwent intravitreal anti-VEGF treatment, with bevacizumab being the most frequently administered agent. Several patients required agent switching during treatment, and four eyes (23.5%) received adjunctive photodynamic therapy (Table 1).

Table 1. Baseline characteristics of the cases in the series

Variable	Value (n = 17)
Age (years)	32.0 ± 16.8
Female	10 (58.8)
Baseline logMAR	0.77 ± 0.72
Follow-up (months)	79 (38–112)
Laterality	
OD	8 (47.1)
OS	9 (52.9)
Concurrent SRF /SRH	16 (94.1)
CNV location	
Subfoveal	6 (35.3)
Juxtafoveal	4 (23.5)
Extrafoveal	6 (35.3)
Indeterminate	1 (5.9)
CNV type	
Type 1	9 (52.9)
Type 2	8 (47.1)
Number of Anti-VEGF injections	6.4 ± 4.5
Types of Anti-VEGF	
Bevacizumab	15 (88.2)
Dual	2 (11.8)
Other treatments	
PDT	4 (23.5)
TTT	1 (5.9)
IVTA	1 (5.9)
Recurrence	12 (70.6)
Anatomical control at final visit	15 (88.2)

Values are presented as mean ± standard deviation, number (%), or median (interquartile range).
LogMAR = logarithm of the minimum angle of resolution; OD = oculus dexter; OS = oculus sinister; SRF = subretinal fluid; SRH = subretinal hemorrhage; CNV = choroidal neovascularization; VEGF = vascular endothelial growth factor; Dual = bevacizumab + aflibercept or bevacizumab + ranibizumab; PDT = photodynamic therapy; TTT = transpupillary thermotherapy; IVTA = intravitreal triamcinolone acetonide.

Anatomical and functional outcomes

At the final visit, anatomical control was observed in 15/17 eyes (88.2%) (Table 1). However, mean best-corrected visual acuity (BCVA) tended to worsen (ΔlogMAR = +0.47, bootstrap 95% CI, 0.05–0.90), but this was not statistically significant (Wilcoxon test $p = 0.171$) (Fig. 1). Four eyes (23.5%) were anti-VEGF responders (≥2-line gain), eight eyes (47.1%) were worseners (≥2-line loss), and five eyes (29.4%) were minimal changers (±2 lines; Table 2).

Visual outcomes differed significantly between CNV subtypes. Type 1 lesions showed a greater decline in vision (median ΔlogMAR, 0.575), whereas type 2 lesions demonstrated a modest improvement (median ΔlogMAR, -0.153). This difference was statistically significant (Wilcoxon rank-sum test, $p = 0.027$).

Disease recurrence

Recurrence, defined as CNV reactivation (presence of fluid on OCT with or without visual decline) after cessation of intravitreal injections, occurred in 12 of 17 patients (70.6%). A

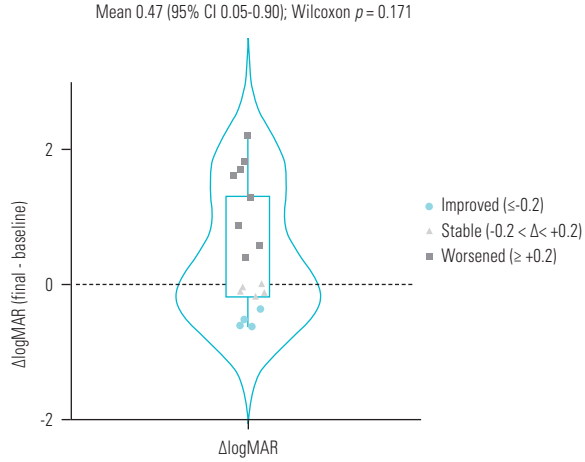

Figure 1. Distribution of change in BCVA (ΔlogMAR). Violin plot with overlaid boxplot and individual eyes (shapes denote ≥2-line improved/stable/worsened). The dashed line marks no change (Δ = 0). Mean ΔlogMAR with bootstrapped 95% CI and paired Wilcoxon *p* are shown in the subtitle. BCVA = best-corrected visual acuity; lovMAR = logarithm of the minimum angle of resolution; CI = confidence interval.

Table 2. Clinical response by change in logMAR (ΔlogMAR; ±0.2 Cutoff)

Variable	Value
Improve (≤-0.2)	4 (23.5)
Stable (-0.2 < Δ < 0.2)	5 (29.4)
Worsen (≥0.2)	8 (47.1)

Values are presented as number (%).
logMAR = logarithm of the minimum angle of resolution.

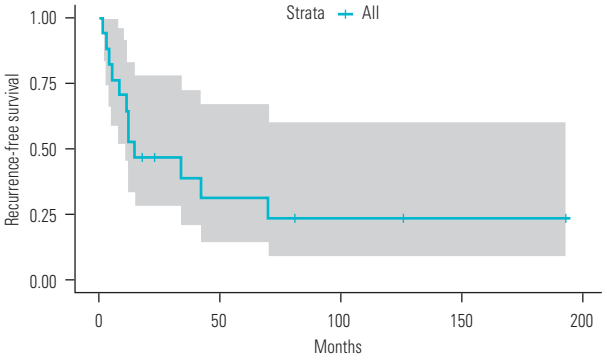

Figure 2. Recurrence-free survival after intravitreal anti-VEGF for osteoma-related choroidal neovascularization. Kaplan–Meier recurrence-free survival after anti-VEGF therapy. The curve drops steeply early (suggesting early recurrences) and then plateaus; shaded area indicates 95% confidence interval. VEGF = vascular endothelial growth factor.

Kaplan–Meier curve showed an early steep decline in recurrence-free survival within the first year, followed by a gradual plateau. The wide CIs reflect the small sample size and censoring (Fig. 2). Due to the limited number of events and variable follow-up periods, the median time to recurrence could not be determined.

Predictors of poor final vision

Multivariable Firth-penalized logistic regression was performed to identify factors associated with final vision ≤20/200, adjusting for baseline logMAR, follow-up duration, CNV location, and CNV type. In the primary model, location was coded as a binary variable (non-subfoveal vs. subfoveal). Worse baseline visual acuity showed a trend toward association with poor final vision (final BCVA ≤20/200) (aOR 4.49, 95% CI 0.99–596.72, $p = 0.05$). Non-subfoveal location was associated with better outcomes compared to subfoveal location (aOR 0.27, 95% CI 0.02–2.29, $p = 0.24$), while type 2 CNV showed a protective association relative to type 1 (aOR 0.23, 95% CI 0.01–2.20, $p = 0.20$); however, these associations did not reach statistical significance (Table 3).

In a prespecified exploratory model, location was analyzed as a three-level categorical variable (juxtafoveal, extrafoveal; reference: subfoveal). The extrafoveal location demonstrated a particularly strong protective association (aOR 0.07, 95% CI 0.00045–1.10, $p = 0.06$), while the beneficial effect of type 2 CNV remained consistent (aOR 0.08, 95% CI 0.00040–1.25, $p = 0.08$) (Supplementary Table 1). The wide CIs observed in both models reflect the small sample size inherent to this rare condition. Despite variations in point estimates between the binary and three-level specifications, a common phenomenon in penalized regression with sparse data, the direction of effects remained consistent across models.

Representative cases

Three illustrative eyes are shown in Fig. 3. Case 1 (Fig. 3A, B), an extramacular tumor with extrafoveal CNV, achieved SRF resolution and visual improvement (logMAR 0.40 to 0.22) despite an interim recurrence. Case 2 (Fig. 3C, D), a macular-involving tumor with subfoveal CNV, also achieved SRF resolution but experienced progressive visual deterioration (logMAR 0.40 to 1.70), likely due to tumor-related atrophic change. Case 3 (Fig. 3E, F), a juxtafoveal tumor with subfoveal CNV, had persistent SRF at the final visit and showed only modest visual gain (logMAR 0.30 to 0.18).

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Discussion

In this study, anatomic dryness was observed in most cases after intraocular injection, and severe visual loss was frequent. This discrepancy between anatomic improvement and functional outcome is thought to be due to the complex characteristics of choroidal osteoma including choroidal neovascular exudates, tumor-related degeneration, and irreversible macular damage [2,10].

Table 3. Primary multivariable firth-penalized logistic regression of predictors of final vision ≤20/200 with binary lesion location (non-subfoveal vs. subfoveal)

Variable	aOR (95% CI)	*p*-value
Baseline logMAR (per 1)	4.49 (0.99–596.72)	0.05
Follow-up (per month)	1.01 (0.98–1.04)	0.42
Non-subfoveal vs. Subfoveal	0.27 (0.02–2.29)	0.24
Type 2 vs. Type 1	0.23 (0.01–2.20)	0.20

aOR = adjusted odds ratio; CI = confidence interval; logMAR = logarithm of the minimum angle of resolution.
aORs with profile penalized-likelihood CIs are reported.
Baseline logMAR (per 1) denotes the OR per 1.0 logMAR increase.
Follow-up (per month) denotes the OR per one month increase.
Reference categories: subfoveal location and type 1 CNV.

As demonstrated in a prior clinical study [11], subfoveal CNV is a key risk factor closely associated with final visual acuity decline. When CNV is located directly beneath the central macula, chronic exudation and subsequent atrophic changes can easily damage central photoreceptors, limiting visual recovery despite aggressive treatment. In contrast, lesions that do not directly invade the macula often do not impair vision. Therefore, accurately identifying the lesion of CNV is essential for prognosis, treatment planning, and patient counseling.

Visual outcomes differed significantly between CNV subtypes. Type 1 CNV demonstrated greater visual decline (median ΔlogMAR, 0.575), whereas type 2 CNV showed

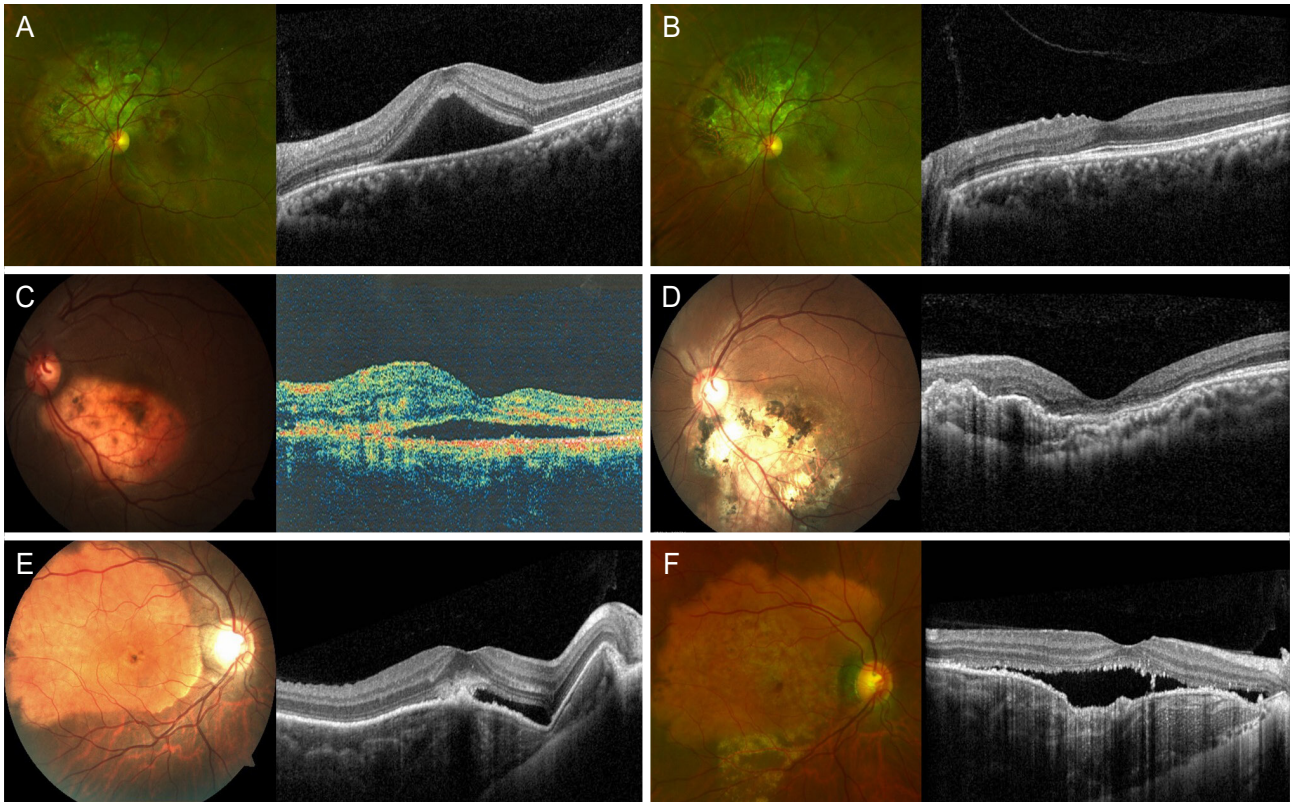

Figure 3. Three illustrative cases showing diverse anti–vascular endothelial growth factor treatment responses in choroidal osteoma-associated CNV. (A, B) Case 1: extramacular tumor with extrafoveal CNV. (C, D) Case 2: juxtafoveal tumor with subfoveal CNV. (E, F) Case 3: macular-involving tumor with subfoveal CNV. Images are fundus photography and optical coherence tomography at baseline and final visits. CNV = choroidal neovascularization.

modest improvement (median ΔlogMAR, -0.153), with a significant difference between the two groups (p = 0.027). This result aligns with prior reports suggesting that type 2 CNV can respond more favorably to anti-VEGF therapy, potentially due to its more superficial location and better drug accessibility [12,13].

Despite the high rate of initial anatomic drying, CNV recurrence was very common, particularly within the first year after discontinuation of anti-VEGF treatment. This trend suggests the need for early follow-up and patient education regarding the risk of recurrence, alongside long-term observation. Given the accompanying visual impairment, vigilant monitoring remains critical.

Regarding treatment strategies, decisions in this cohort were individualized based on patient clinical course rather than a standardized protocol. Bevacizumab was used as the initial anti-VEGF agent in most patients, with a switch to ranibizumab or aflibercept if SRF recurred or worsened. Adjuvant therapy was administered in select cases: four patients underwent photodynamic therapy due to progressive visual loss, tumor extension into the macular area, or recurrent SRF, and one patient underwent two transpupillary thermotherapy for persistent visual loss. Due to this heterogeneity in treatment response and regimens, direct comparisons between groups were limited. Recent guidelines suggest that adjuvant photodynamic therapy can be considered when primary anti-VEGF therapy is inadequate or recurrent, but a standardized protocol is not yet available [14,15]. A tailored approach, considering lesion location, anatomic features, and visual acuity, remains essential for optimal treatment.

A notable strength of this study is that it provides long-term data on a condition with no standardized treatment approach and limited evidence on sustained anti-VEGF outcomes. This study provides comprehensive, real-world data characterizing the anatomic response, visual changes, recurrence patterns, differences in CNV subtypes, and prognosis according to lesion location during a median follow-up of 79 months for anti-VEGF treatment. These multidimensional, long-term observational findings provide clinically relevant insights that can support treatment planning and patient counseling in routine practice.

This study has several limitations that should be considered when interpreting its results. First, as a retrospective, single-center study with a small cohort, selection and information biases are possible, and there is the potential for confounding variables. Second, the lack of standardized management strategies, including anti-VEGF agent selection and injection intervals, results in need for caution in data interpretation. Third, imaging modalities varied over time; although the presence or absence of SRF or IRF could be reliably assessed across devices, inter-device variability might have affected more detailed quantitative assessments. Fourth, despite the relatively long follow-up period, inconsistencies in visit schedules resulted in some informational censoring and survival bias. Finally, as this patient cohort consisted mainly of East Asians referred to tertiary care centers, results might not fully reflect other clinical settings or patient populations. Despite these limitations, this study provides valuable long-term, real-world data on a rare disease and highlights the need for future multicenter, prospective studies to guide treatment and patient counseling.

Taken together, these observations underscore the importance of vigilant, personalized management initiated soon after CNV diagnosis, particularly because choroidal osteoma tends to occur in relatively young patients and CNV is prone to early recurrence with suboptimal visual outcomes. Future large-scale, collaborative prospective studies are necessary to refine prognostic models and therapeutic approaches for this challenging condition.

Conflicts of Interest

The authors declare no conflicts of interest relevant to this article.

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Author Contribution

Conception (All authors); Design (All authors); Data acquisition (H.J.S.); Analysis (All authors); Interpretation (All authors); Writing (H.J.S.); Review (C.S.L.); Final approval of the article (All authors)

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Availability of Data and Material

I had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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