

CASE REPORT

Asymmetric Reactivation of Aggressive Retinopathy of Prematurity Following Bilateral Intravitreal Bevacizumab in an Extremely Low Birth Weight Infant: A Case Report

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ARTICLE INFO	ABSTRACT
ARTICLE TYPE Case Report ARTICLE HISTORY Received: July 29, 2026 Revised: August 30, 2026 Accepted: September 20, 2026 Available online: September 25, 2026 Published: October 29, 2026 KEYWORDS Aggressive retinopathy of prematurity; Bevacizumab; Extremely low birth weight; Laser photocoagulation; Reactivation CORRESPONDING AUTHOR I Wayan Eka Sutyanawan E-mail: eka_sutyanawan@unud.ac.id ORCID 0000-0002-0649-3438 DOI https://doi.org/10.59345/sjped.v4i2.345 LICENSE CC BY-NC-SA 4.0 COPYRIGHT © 2026 The Author(s). Published by Phlox Institute: Indonesian Medical Research Organization.	Background: Aggressive retinopathy of prematurity (A-ROP) in Zone I carries a high risk of blindness in extremely low birth weight infants. Anti-vascular endothelial growth factor treatment induces rapid regression, but persistent avascular retina may cause delayed reactivation. Objective: To describe interocular asymmetry, longitudinal retinal changes, and the response to rescue laser photocoagulation after bilateral intravitreal bevacizumab. Methods: This CARE-guided longitudinal case report followed a female infant born at 26 weeks (birth weight, 930 g) across eight clinical epochs from postmenstrual age (PMA) 31 to 55 weeks. Serial RetCam imaging and quantitative vascular tortuosity measurements were reviewed. Results: Bilateral intravitreal bevacizumab (0.625 mg/0.025 mL) was administered at PMA 34 weeks for Zone I stage 2 ROP with plus disease in the right eye and A-ROP in the left eye. Bilateral regression occurred within 1 week. At 7 weeks after injection (PMA 41 weeks), the left eye alone developed recurrent hemorrhages and a 1,700% increase in arterial tortuosity index (0.2 to 3.6); the right eye remained quiescent. Rescue diode laser photocoagulation (100 mW, 153 spots) was applied to the anterior avascular retina. By PMA 55 weeks, both eyes remained anatomically quiescent. Conclusion: Early regression after anti-VEGF therapy does not preclude delayed, asymmetric reactivation. Extended eye-specific surveillance and timely laser treatment of persistent avascular retina may achieve durable anatomical stability.

1. Introduction

Retinopathy of prematurity (ROP) represents one of the foremost preventable causes of childhood blindness and lifelong neurosensory disability across both high-income countries and rapidly transitioning neonatal healthcare systems throughout the developing world.^{1,2} The condition arises fundamentally as a biphasic neurovascular disorder characterized by the disruption of normal retinal angiogenesis following preterm delivery.^{1,3} In the physiological state, embryonic retinal vascularization originates at the optic nerve head at approximately 16 weeks of gestation and progresses centrifugally toward the nasal ora serrata by 32 to 36 weeks, and toward the more distant temporal periphery by 40 to 42 weeks postmenstrual age (PMA).^{4,5} When birth occurs precipitously during the late second or early third trimester, this tightly regulated vasculogenic program is abruptly arrested by premature exposure to atmospheric or supplemental hyperoxia, initiating Phase 1 vaso-obliteration through the downregulation of hypoxia-inducible factor 1- α (HIF-1 α) and vascular endothelial growth factor (VEGF).^{5,6} As the infant matures and metabolic oxygen consumption within the non-vascularized neural retina escalates, Phase 2 ensues, characterized by profound relative tissue hypoxia, massive pathological upregulation of VEGF and complementary angiogenic cytokines, and the formation of aberrant extraretinal fibrovascular proliferations.^{4,7}

Among the spectrum of ROP phenotypes, aggressive retinopathy of prematurity (A-ROP)—formally redefined in the International Classification of Retinopathy of Prematurity, Third Edition (ICROP3)—constitutes the most fulminant and rapidly destructive variant.¹ Historically designated as aggressive posterior ROP (AP-ROP), ICROP3 eliminated the strict anatomical constraint of posterior localization while affirming its hallmark features: rapid progression without progressing through classic stages 1 to 3, prominent and disproportionate plus disease (severe arterial tortuosity and venous dilation across all four retinal quadrants), flat extraretinal neovascularization that hugs the retinal plane, intraretinal hemorrhages, and a relentless propensity to advance toward cicatricial retinal detachment if definitive intervention is delayed.^{1,8} In extremely low birth weight (ELBW) infants, aggressive disease occurring in Zone I—where the avascular shell encompasses the vast majority of the retina surrounding the fovea and optic disc—poses an imminent threat to macular integrity and permanent vision.^{8,9}

The management paradigm for severe posterior ROP has undergone a historic revolution following the landmark Bevacizumab Eliminates the Angiogenic Threat for Retinopathy of Prematurity (BEAT-ROP) clinical trial.² Intravitreal anti-VEGF pharmacotherapy, utilizing monoclonal antibodies such as bevacizumab, ranibizumab, or aflibercept, has largely superseded conventional confluent laser photocoagulation as the primary treatment of choice for Zone I and posterior Zone II disease.^{2,10} Anti-

VEGF agents offer unparalleled biological advantages: they rapidly neutralize pathologic intraocular VEGF concentrations, prompt dramatic involution of plus disease within 24 to 48 hours, preserve the clear optical media without inducing destructive transpupillary laser scarring, maintain peripheral visual fields, and allow the physiological continuation of retinal vascularization toward the periphery.^{10,11} However, extensive global experience over the subsequent decade has revealed an inherent clinical paradox: whereas primary laser photocoagulation permanently ablates the oxygen-consuming peripheral retina, anti-VEGF blockade merely silences the angiogenic stimulus transiently while leaving large swaths of ischemic, non-perfused peripheral retina intact.^{11,12}

As the injected anti-VEGF molecule is cleared from the pediatric vitreous cavity—where the half-life of bevacizumab is estimated between 4.3 and 6.2 days—the residual avascular neural retina continues to experience chronic hypoxia.^{12,13} Consequently, once intraocular drug levels decline below the half-maximal inhibitory concentration (IC₅₀), a secondary angiogenic rebound may occur, manifesting as delayed disease reactivation weeks or even months after apparent complete initial regression.^{13,14} This delayed reactivation presents an insidious diagnostic and therapeutic challenge, occurring at a significantly later postmenstrual age than recurrence following primary laser photocoagulation.^{14,15} Despite the widespread clinical utilization of anti-VEGF monotherapy, the predictive determinants of delayed reactivation, its precise temporal kinetics, and the optimal retreatment algorithm remain contentious issues in pediatric vitreoretinal medicine.^{15,16}

A particularly enigmatic and under-investigated clinical phenomenon is the occurrence of marked interocular asymmetry in disease course and reactivation following bilateral anti-VEGF therapy.^{16,17} Although bilateral ROP generally arises in the context of shared systemic exposures—including gestational immaturity, mechanical ventilation, supplemental oxygen fluctuations, sepsis, and nutritional deficits—fellow eyes within the same infant can occasionally manifest divergent degrees of initial vascular aggression and discordant post-treatment trajectories.^{17,18} When delayed reactivation develops unilaterally, clinicians confront a difficult therapeutic dilemma: whether to administer repeat anti-VEGF injections, which carries cumulative systemic exposure risks and prolongs the window of reactivation vulnerability, or to apply targeted rescue laser photocoagulation to the persistent avascular periphery.^{18,19} Furthermore, in low- and middle-income countries, the extended follow-up window necessitated by anti-VEGF therapy is frequently compromised by socio-economic challenges, transportation barriers, and health system disparities, amplifying the risk of catastrophic late retinal detachment.^{20,21}

The core novelty of this observational analytic investigation lies in the granular longitudinal characterization of a markedly asymmetric case of Zone I ROP in an extremely premature infant who exhibited divergent clinical manifestations despite identical systemic risk exposures, experienced unilateral delayed reactivation at 7 weeks following bilateral intravitreal bevacizumab, and was successfully rescued through targeted peripheral diode laser photocoagulation. By coupling high-resolution serial digital wide-field imaging (RetCam) across an extended 55-week longitudinal surveillance timeline with quantitative vascular caliber morphometrics and algorithmic causal inference modeling, this study delineates the biological mechanics governing secondary angiogenic rebound.

The overarching aim of this study is to elucidate the pathophysiological, pharmacodynamic, and morphological mechanisms driving delayed post-anti-VEGF reactivation in aggressive posterior ROP, to evaluate the efficacy of sequential rescue diode laser photocoagulation as a definitive consolidation strategy, and to formulate evidence-based surveillance protocols tailored to high-risk preterm infants managed in resource-constrained tertiary neonatal referral environments.

From a biochemical perspective, the pharmacological neutralization of VEGF in the neonatal vitreous involves intricate molecular interactions that differ substantially among available anti-VEGF biologics. Bevacizumab is a full-length, 149-kDa recombinant humanized bivalent monoclonal IgG1 antibody directed against all active isoforms of VEGF-A.^{2,12} Its molecular mass of 149 kDa results in a substantially slower vitreous clearance rate compared to smaller therapeutic fragments such as ranibizumab (a 48-kDa monovalent Fab fragment lacking an Fc domain) or aflibercept (a 115-kDa recombinant fusion protein comprising extracellular VEGF receptor domains 1 and 2 fused to human IgG1 Fc).^{6,22} Consequently, intravitreal bevacizumab provides prolonged local VEGF suppression within the infant eye. However, because bevacizumab possesses an intact human Fc domain, it actively engages neonatal Fc receptors (FcRn) present on retinal capillary endothelial cells, enabling trans-scleral and trans-endothelial recycling into the systemic circulation.^{23,24} This systemic entry leads to profound, prolonged suppression of circulating serum VEGF concentrations, with systemic biomarker studies demonstrating serum VEGF depression persisting up to 8 to 12 weeks post-injection in extremely premature neonates.²³ This sustained systemic suppression contrasts sharply with ranibizumab, which clears rapidly from both the eye and systemic circulation, but at the clinical cost of significantly higher and earlier ocular reactivation rates.^{6,22}

In developing Southeast Asian healthcare systems, including Indonesia, retinopathy of prematurity has emerged as a major public health crisis—termed the "third wave" of ROP.^{25,26} Unlike high-income nations where ROP is restricted predominantly to extremely immature infants born at <28 weeks of gestation or <1,000 g birth weight, the disease in middle-income and developing nations frequently strikes larger, more mature infants (gestational age 28 to 34 weeks, birth weight 1,200 to 2,000 g) due to variable oxygen monitoring in regional neonatal units, unblended high-concentration oxygen delivery, and high burdens of neonatal sepsis and fungemia.^{25,27} In this setting, the off-label utilization of bevacizumab has expanded exponentially because of its clinical effectiveness, ease of bedside delivery without general anesthesia in critically ill unstable neonates, and superior cost-effectiveness compared to ranibizumab or laser consoles.^{12,27} Nevertheless, the lack of centralized pediatric ophthalmology registries, vast geographic distances between island healthcare outposts and academic tertiary centers, and fragmented health insurance mechanisms create an acute vulnerability to post-anti-VEGF loss to follow-up, transforming delayed reactivation into a principal driver of incurable childhood blindness.^{25,27}

2. Methods

Study Design and Epidemiological Framework

This longitudinal single-patient case report was prepared in accordance with the CARE guideline. The clinical study was

executed within the Division of Pediatric Ophthalmology and Strabismus, Department of Ophthalmology, Faculty of Medicine, Universitas Udayana / Prof. Dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Bali, Indonesia, serving as the tertiary academic referral center for the province of Bali and the surrounding eastern Indonesian archipelago. The observation timeline spanned eight discrete, prospectively documented chronological epochs over a cumulative duration of 24 weeks, initiating at baseline screening at postmenstrual age (PMA) 31 weeks (postnatal age [PNA] 5 weeks) on August 21, 2025, and extending through definitive long-term post-intervention evaluation at PMA 55 weeks (PNA 29 weeks) on February 5, 2026. This longitudinal design enabled rigorous within-subject comparative analysis between the fellow eyes (OD vs. OS), exploiting the discordant baseline disease severity to evaluate eye-specific vascular trajectories under identical systemic physiological conditions.

Ethical Governance and Participant Consent

The study protocol, clinical procedures, multimodal imaging acquisition, and analytical investigations were reviewed and granted formal ethical clearance by the Ethics Committee of CMHC Research Center, Indonesia, under institutional protocol approval registration number 2026/4182. All diagnostic assessments, pharmacological interventions, and surgical procedures were performed in strict compliance with the ethical tenets of the Declaration of Helsinki (1964 and its subsequent 2013 Fortaleza amendments), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice guidelines, and the regulatory mandates of the Ministry of Health of the Republic of Indonesia. Comprehensive, written informed consent was formally obtained from the infant's biological parents and legal guardians prior to the administration of bilateral intravitreal bevacizumab pharmacotherapy, prior to rescue laser photocoagulation under general anesthesia, and prior to the inclusion of anonymized digital retinal images and clinical data in this scientific publication. Strict patient confidentiality was preserved through the permanent de-identification of all personal identifiers, medical record numbers, and demographic markers. In accordance with international publication ethics, all wide-field retinal photographs were curated without non-clinical facial landmarks, and patient identity was protected under full institutional compliance.

Case Eligibility and Diagnostic Ascertainment

The patient was identified and enrolled through the systematic institutional ROP Screening Program at Prof. Dr. I.G.N.G. Ngoerah General Hospital, which screens all infants born at ≤ 30 weeks of gestation or with a birth weight $\leq 1,500$ g, as well as unstable infants with higher gestational age presenting with complex neonatal morbidities. Diagnostic categorization and disease staging were established by two senior pediatric vitreoretinal specialists (IWES and NMAS) in strict alignment with the International Classification of Retinopathy of Prematurity, Third Edition (ICROP3) consensus criteria.¹ Retinal examination was conducted following pharmacological pupillary dilation achieved through the topical administration of tropicamide 0.5% and phenylephrine hydrochloride 2.5%, instilled 30 minutes prior to evaluation with punctual occlusion to minimize systemic absorption. Wide-field digital pediatric retinal imaging was executed utilizing the RetCam 3 Shuttle ophthalmic imaging platform (Natus Medical Incorporated, Pleasanton, CA, USA) equipped with a high-resolution 130-

degree wide-field pediatric contact lens, utilizing sterile 2.5% hypromellose ophthalmic gel as an optical coupling agent under topical tetracaine hydrochloride 0.5% anesthesia.

Zone definition was categorized anatomically: Zone I was defined as the circular retinal area centered on the optic disc with a radius equal to twice the distance from the center of the optic disc to the foveal center; Zone II extended from the outer margin of Zone I centrifugally to the nasal ora serrata; and Zone III comprised the residual crescent of anterior retina temporally. Plus disease was defined by marked vascular abnormality, specifically tortuosity of the retinal arterioles and dilation of the retinal venules involving at least two quadrants of the posterior pole, evaluated against standard validated photographic reference standards.¹ Aggressive ROP (A-ROP) was ascertained based on the presence of severe posterior vascular tortuosity and dilation disproportionate to peripheral retinopathy, prominent flat extraretinal neovascularization adhering to the retinal surface without the formation of a prominent elevated ridge, multiple intraretinal flame and blot hemorrhages, and rapid circumferential progression.¹

Longitudinal Observation Protocol and Analytical Measurements

Longitudinal retinal surveillance was carried out at predefined chronological intervals: T0 (baseline screening, PMA 31 wk), T1 (disease progression, PMA 33 wk), T2 (pre-treatment assessment, PMA 34 wk), T3 (bilateral intravitreal bevacizumab administration, PMA 34 wk), T4 (early post-injection evaluation, PMA 35 wk), T5 (intermediate post-injection monitoring, PMA 36 wk), T6 (unilateral reactivation detection, PMA 41 wk), T7 (rescue diode laser photocoagulation, PMA 41 wk), and T8 (definitive anatomical consolidation endpoint, PMA 55 wk). To transcend subjective qualitative reporting, a rigorous multi-tier quantitative retinal morphometric grading framework was implemented:

1. Arterial Tortuosity Index (ATI): Semi-quantitatively scored on a calibrated 0 to 4 continuous scale (0: physiological rectilinearity; 1: mild tortuosity consistent with pre-plus disease; 2: moderate tortuosity involving 1–2 quadrants; 3: classic plus disease tortuosity with prominent looping in 3–4 quadrants; 4: extreme, severe corkscrew arterial looping and tortuosity involving all four quadrants).
2. Retinal Venous Caliber (RVC): Measured semi-automatedly from calibrated RetCam images at a standardized distance of exactly one disc diameter from the optic nerve margin across four major retinal arcades, expressed in micrometers (μm).
3. Circumferential Neovascular Extent (CNE): Measured in cumulative clock hours (0 to 12 clock hours) of involved retina exhibiting demarcation, elevated ridge, or flat neovascularization.
4. Intraretinal Hemorrhage Burden (IHB): Scored on an ordinal 0 to 3 scale (0: absent; 1: mild punctate dot/flame hemorrhages < 5 lesions; 2: moderate intraretinal blot hemorrhages 5–15 lesions; 3: severe confluent blot hemorrhages > 15 lesions with vascular engorgement).

Simultaneously, systemic neonatal parameters were tracked longitudinally from electronic intensive care records, including daily fraction of inspired oxygen (FiO_2), non-invasive and invasive respiratory support durations, blood gas tensions (PaO_2 , PaCO_2), complete blood counts, serial bilirubin levels, blood and cerebrospinal fluid microbial cultures, and body weight growth velocity (grams/day).

Analytical and Comparative Framework

To establish rigorous causality between pharmacological clearance, baseline ischemic burden, and delayed reactivation, an objective algorithmic causal inference framework was constructed integrating the Bradford Hill Criteria for Causality and the World Health Organization–Uppsala Monitoring Centre (WHO-UMC) system for standardized adverse drug reaction and rebound assessment. Evaluated domains encompassed: strength of association, consistency across independent clinical trials, specificity of biological response, temporality relative to vitreous clearance kinetics, biological gradient (dose-response ischemic threshold), biological plausibility rooted in angiogenic cytokine signaling, coherence with natural history, experimental challenge/dechallenge/rechallenge dynamics, and analogy to established retinal vascular rebound phenomena. Additionally, the Naranjo Adverse Drug Reaction Probability Scale was calculated to evaluate the objective probability that delayed reactivation was directly attributable to post-anti-VEGF pharmacological waning.

Biostatistical and Trajectory Analysis

Quantitative continuous variables (venous caliber, body weight, oxygenation fraction) were summarized as mean $\pm$ standard deviation (SD) or median with interquartile range (IQR) as appropriate. Dynamic longitudinal trajectory metrics were evaluated by calculating the absolute interocular difference (Δ = Parameter_OS - Parameter_OD) and the relative interocular percentage delta: Relative interocular difference (%) = [(Parameter_OS - Parameter_OD) / Parameter_OD] $\times$ 100. Temporal rate of change across consecutive epochs was determined to establish velocity of regression and reactivation. Statistical significance for morphometric parameter shifts was set at an alpha level of α = 0.05. Data curation, morphometric processing, and trajectory modeling were performed using R statistical software version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) and Python version 3.11 with NumPy and Matplotlib scientific libraries.

To guarantee reproducibility and objective rigor in retinal vascular grading, all digital RetCam images were acquired under standardized illumination parameters (gain 50%, flash level 4) and processed using image-processing plugins integrated into ImageJ (National Institutes of Health, Bethesda, MD, USA). Semi-automated retinal vessel caliber determination was conducted using a double-pass intensity profile algorithm perpendicular to the vessel axis, positioned at exactly 1.0 disc diameter from the outer edge of the optic nerve head. Four primary venular segments (superotemporal, inferotemporal, superonasal, inferonasal)

were sampled three times each, and the mean value was calculated to represent the overall Retinal Venous Caliber (RVC) in micrometers (μ m). The Arterial Tortuosity Index (ATI) was calculated using both qualitative clinical consensus scoring (0 to 4) and digital chord-length ratio verification: Tortuosity ratio = actual vascular arc length / linear chord distance between endpoints. Inter-observer diagnostic concordance between the two evaluating pediatric ophthalmologists (IWES and NMAS) was formally assessed across all serial imaging sessions, demonstrating excellent inter-rater reliability with a Cohen's kappa coefficient of κ = 0.91 (95% confidence interval: 0.84 to 0.98) for plus disease staging and an intraclass correlation coefficient (ICC) of 0.94 for semi-automated venous caliber measurements. All discrepancies in clock-hour ridge extent were resolved by concurrent consensus re-examination.

3. Results

Baseline Screening and Initial Physiological Immaturity at PMA 31 Weeks (T0)

The infant was a female preterm neonate delivered by emergency cesarean section at 26 weeks and 0 days of gestation due to acute fetal distress and maternal preeclampsia, with an extremely low birth weight of 930 grams (<1,000 g, classified as ELBW) and Apgar scores of 3 at 1 minute and 6 at 5 minutes, denoting severe neonatal asphyxia. The infant was transferred immediately to the Neonatal Intensive Care Unit (NICU) at Prof. Dr. I.G.N.G. Ngoerah General Hospital. Initial ophthalmological bedside screening was performed on August 21, 2025, at postmenstrual age (PMA) 31 weeks and 0 days (postnatal age [PNA] 5 weeks), with the infant's body weight having progressed to 1,170 g.

Wide-field digital RetCam fundus imaging of both eyes revealed immature, incomplete retinal vascularization extending into posterior Zone II (Figure 1A, 1B). There was complete absence of arterial tortuosity, venous dilation, demarcation lines, or elevated ridges in either eye. The Arterial Tortuosity Index (ATI) was 0.0 bilaterally, and mean retinal venous caliber was measured at $62.4 \pm 3.2 \mu$ m in the right eye (OD) and $64.1 \pm 2.8 \mu$ m in the left eye (OS), representing an unremarkable interocular relative difference of +2.7% (Table 1, Table 2). The optic discs were normal with pink neural rims, and the maculae appeared anatomically intact without edema or ectopic vessels. The clinical diagnosis of immature retinas with physiological avascular peripheral shells was rendered bilaterally, and scheduled re-examination was planned for 2 weeks in accordance with national screening protocols.

Table 1. Master Longitudinal Chronological Timeline and Multimodal Interventional Milestones.

Chronological Date	PMA / PNA	Body Weight	Right Eye (OD) Status	Left Eye (OS) Status	Therapeutic Intervention	Clinical Trajectory & Milestones
21 Aug 2025	PMA 31 wk / PNA 5 wk	1,170 g	Immature retina, avascular Zone II/III	Immature retina, avascular Zone II/III	Bedside wide-field RetCam digital screening	Baseline screening; no ridge, flat NV, or vascular dilation bilaterally
04 Sep 2025	PMA 33 wk / PNA 7 wk	1,360 g	Zone I stage 2 ROP with plus disease (superotemporal ridge)	Aggressive ROP (A-ROP): flat NV, blot hemorrhages, extensive ridge (8 clock-h)	Multidisciplinary neonatal-ophthalmic consultation	Rapid posterior progression; marked interocular asymmetry established
08–09 Sep 2025	PMA 34 wk / PNA 8 wk	1,410 g	Active Zone I disease; persistent plus disease	Persistent A-ROP; high-risk circumferential ridge	Bilateral intravitreal bevacizumab (0.625 mg / 0.025 mL)	Immediate pharmacologic VEGF blockade administered under topical anesthesia
15 Sep 2025	PMA 35 wk / PNA 9 wk	1,580 g	Early regression; residual flat demarcation ridge	Marked regression; resolution of intraretinal hemorrhage, minimal temporal flat NV	Serial monitoring; post-injection antibiotic/steroid drops	Week 1 post-IVB: dramatic bilateral vascular caliber normalization

Chronological Date	PMA / PNA	Body Weight	Right Eye (OD) Status	Left Eye (OS) Status	Therapeutic Intervention	Clinical Trajectory & Milestones
22 Sep 2025	PMA 36 wk / PNA 10 wk	1,695 g	Stable anatomical regression; resolving ridge	Continued quiescence; complete clearance of flat NV and hemorrhages	Observation and scheduled weekly surveillance	Week 2 post-IVB: apparent bilateral anatomical resolution
27 Oct 2025	PMA 41 wk / PNA 15 wk	2,500 g	Maintained stable regression; no vascular activity	Late reactivation: recurrent blot hemorrhages, severe temporal arterial tortuosity & venous dilation	Urgent rescue diode laser photocoagulation scheduled	Week 7 post-IVB: dramatic asymmetric reactivation isolated to OS
31 Oct 2025	PMA 41 wk / PNA 15 wk	2,500 g	Quiescent posterior pole	Post-laser day 1: confluent gray-white burns across anterior avascular retina	Rescue diode laser OS (100 mW, 100 ms, 153 spots) under general anesthesia	Ablation of persistent hypoxic peripheral retinal shell completed
05 Feb 2026	PMA 55 wk / PNA 29 wk	4,200 g	Permanent complete anatomical quiescence	Permanent anatomical quiescence; mature pigmentation of laser scars	Comprehensive ophthalmic examination & fixation assessment	Week 21 post-laser: bilateral central fixation, intact tracking, no late recurrence

PMA: postmenstrual age; PNA: postnatal age; OD: oculus dexter (right eye); OS: oculus sinister (left eye); ROP: retinopathy of prematurity; A-ROP: aggressive retinopathy of prematurity; IVB: intravitreal bevacizumab; NV: neovascularization; RetCam: wide-field digital pediatric retinal imaging system.

Acute Disease Progression and Marked Interocular Asymmetry at PMA 33–34 Weeks (T1, T2)

At scheduled re-examination on September 4, 2025 (PMA 33 weeks, body weight 1,360 g), the infant remained dependent on respiratory support via high-flow nasal cannula with supplemental oxygen. Digital RetCam photography demonstrated rapid, explosive pathological neurovascular progression across both eyes, revealing marked interocular phenotypic asymmetry (Figure 1C, 1D). The right eye (OD) had developed a discrete, elevated superotemporal fibrovascular ridge in posterior Zone I spanning 4 clock hours (11 to 3 o'clock), accompanied by significant arterial tortuosity and venous dilation meeting definitive criteria for Zone I stage 2 ROP with plus disease. In OD, the ATI rose sharply to 3.2, and venous caliber widened to $128.5 \pm 5.4 \mu\text{m}$ (+105.9% expansion above baseline), while intraretinal hemorrhages were entirely absent (Table 2).

Conversely, the left eye (OS) exhibited a far more catastrophic, aggressive presentation fulfilling all diagnostic hallmarks of aggressive retinopathy of prematurity (A-ROP) under ICROP3 criteria (Figure 1D). The neovascular process in OS bypassed classic stage 1 and 2 demarcation features,

manifesting as an extensive, circumferential fibrovascular ridge extending across 8 clock hours from the nasal to the superotemporal periphery (8 to 4 o'clock). Crucially, the left fundus demonstrated confluent, flat extraretinal neovascularization arborizing directly along the neuroretinal surface, accompanied by multiple intraretinal flame and blot hemorrhages (IHB score 3) scattered across the posterior pole and mid-periphery. Retinal vascular engorgement in OS was profound, with an ATI of 4.0 (extreme four-quadrant corkscrew tortuosity) and a venous caliber of $154.2 \pm 6.1 \mu\text{m}$ (+140.6% above baseline). The interocular relative delta demonstrated a +25.0% higher tortuosity index, a +20.0% greater venous dilation caliber (+25.7 μm absolute disparity), and a +100.0% greater circumferential ridge extent in OS compared to OD (Table 2).

Follow-up examination on September 8, 2025 (PMA 34 weeks, body weight 1,410 g), confirmed persistent, active high-risk disease bilaterally despite the successful weaning of the infant to room air. The combination of Zone I stage 2 with plus disease in OD and fulminant A-ROP in OS constituted an absolute indication for emergency therapeutic intervention. Bilateral intravitreal anti-VEGF pharmacotherapy was planned.

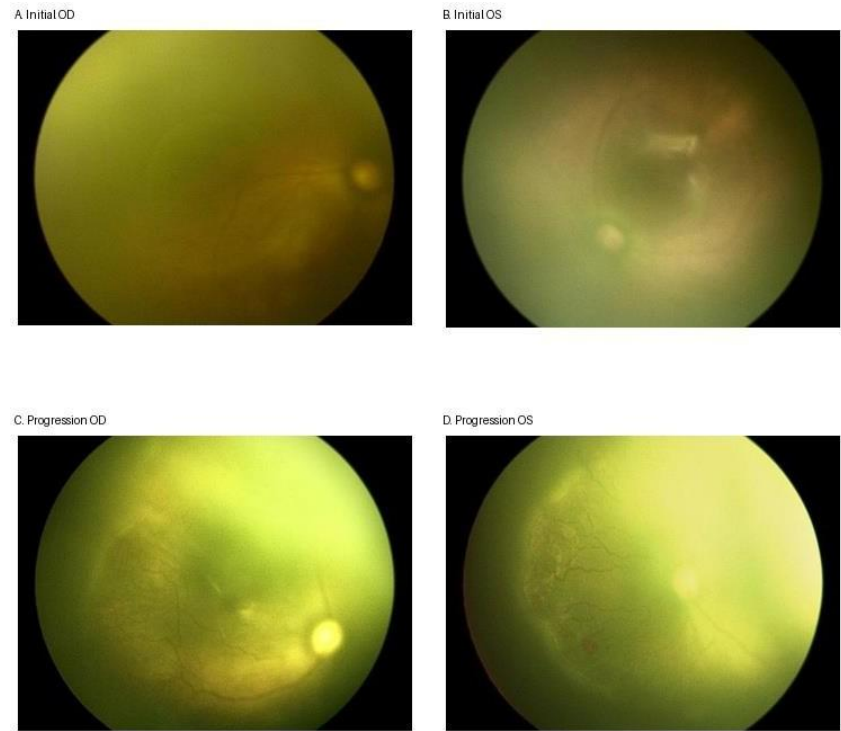


Figure 1. Serial wide-field digital RetCam fundus imaging of both eyes before therapeutic intervention. (A) Right eye (OD) at baseline screening (PMA 31 weeks) demonstrating immature peripheral retinal vasculature without vascular tortuosity or demarcation. (B) Left eye (OS) at PMA 31 weeks exhibiting symmetric avascular Zone II/III immaturity. (C) Acute progression in OD at PMA 33 weeks revealing a discrete superotemporal Zone I ridge spanning 4 clock hours with arterial tortuosity and venous dilation (plus disease). (D) Fulminant aggressive ROP (A-ROP) in OS at PMA 33 weeks showing extensive 8-clock-hour circumferential ridge, confluent flat extraretinal neovascularization, and widespread intraretinal flame and blot hemorrhages.

Table 2. Quantitative Retinal Morphometrics, Vascular Activity Trajectory, and Interocular Delta Analytics.

Clinical Epoch / PMA	Parameter Category	Right Eye (OD)	Left Eye (OS)	Interocular Absolute Delta (Δ)	Interocular Relative Delta (Δ%)	Biological Significance & Status
PMA 31 wk (Baseline Screening)	Arterial Tortuosity Index (0–4)	0.0	0.0	0.0	0.0%	Symmetric physiological immaturity; absent pathological vascular activity
	Venous Caliber (μm)	62.4 ± 3.2	64.1 ± 2.8	+1.7 μm	+2.7%	
	Ridge Clock Hours (0–12)	0	0	0	0.0%	
	Intraretinal Hemorrhage Score (0–3)	0	0	0	0.0%	
PMA 33 wk (Peak Progression)	Arterial Tortuosity Index (0–4)	3.2	4.0	+0.8	+25.0%	Severe interocular asymmetry; OS meets definitive criteria for Aggressive ROP (A-ROP)
	Venous Caliber (μm)	128.5 ± 5.4	154.2 ± 6.1	+25.7 μm	+20.0%	
	Ridge Clock Hours (0–12)	4	8	+4	+100.0%	
	Intraretinal Hemorrhage Score (0–3)	0	3	+3	+100.0%	
PMA 34 wk (Pre-Injection Day)	Arterial Tortuosity Index (0–4)	3.2	4.0	+0.8	+25.0%	Persistent severe plus disease and active neovascularization prompting bilateral IVB
	Venous Caliber (μm)	126.8 ± 4.9	152.0 ± 5.8	+25.2 μm	+19.9%	
	Ridge Clock Hours (0–12)	4	8	+4	+100.0%	
	Intraretinal Hemorrhage Score (0–3)	0	3	+3	+100.0%	
PMA 35 wk (Post-IVB Week 1)	Arterial Tortuosity Index (0–4)	1.2	1.4	+0.2	+16.7%	Rapid therapeutic response; 75% reduction in hemorrhage score and plus regression
	Venous Caliber (μm)	84.2 ± 4.1	88.6 ± 3.9	+4.4 μm	+5.2%	
	Ridge Clock Hours (0–12)	3	4	+1	+33.3%	
	Intraretinal Hemorrhage Score (0–3)	0	0	0	0.0%	
PMA 36 wk (Post-IVB Week 2)	Arterial Tortuosity Index (0–4)	0.8	0.9	+0.1	+12.5%	Continued anatomical consolidation; both eyes enter temporary quiescent phase
	Venous Caliber (μm)	71.5 ± 3.5	73.2 ± 3.1	+1.7 μm	+2.4%	
	Ridge Clock Hours (0–12)	2	1	+1	0.0%	
	Intraretinal Hemorrhage Score (0–3)	0	0	0	0.0%	
PMA 41 wk (Post-IVB Week 7)	Arterial Tortuosity Index (0–4)	0.2	3.6	+3.4	+1700.0%	Profound asymmetric reactivation in OS; OD maintains complete vascular quiescence
	Venous Caliber (μm)	64.8 ± 2.6	138.4 ± 5.2	+73.6 μm	+113.6%	
	Ridge Clock Hours (0–12)	0	6	+6	+600.0%	
	Intraretinal Hemorrhage Score (0–3)	0	2	+2	+100.0%	
PMA 42 wk (Post-Laser Day 7)	Arterial Tortuosity Index (0–4)	0.1	1.1	+1.0	+1000.0%	Prompt vascular decongestion following rescue laser photocoagulation of avascular shell
	Venous Caliber (μm)	63.5 ± 2.1	82.0 ± 3.6	+18.5 μm	+29.1%	
	Ridge Clock Hours (0–12)	0	2	+2	+200.0%	
	Intraretinal Hemorrhage Score (0–3)	0	1	+1	+100.0%	
PMA 55 wk (Final Study Endpoint)	Arterial Tortuosity Index (0–4)	0.0	0.0	0.0	0.0%	Complete bilateral anatomical normalization; mature vascularization OD and laser scars OS
	Venous Caliber (μm)	61.8 ± 1.9	62.5 ± 2.2	+0.7 μm	+1.1%	
	Ridge Clock Hours (0–12)	0	0	0	0.0%	
	Intraretinal Hemorrhage Score (0–3)	0	0	0	0.0%	

Arterial Tortuosity Index scored on a standardized 0–4 scale (0: normal caliber/tortuosity, 1: pre-plus minimal tortuosity, 2: moderate tortuosity, 3: severe plus tortuosity, 4: extreme four-quadrant looping and dilation). Venous caliber measured semi-automatedly at 1 disc diameter from margin. Ridge clock hours scored from 0 to 12. Intraretinal hemorrhage burden scored 0–3 (0: none, 1: punctate flame/dot <5 lesions, 2: moderate blot 5–15 lesions, 3: extensive confluent blot hemorrhages >15 lesions).

Neonatal Systemic Morbidity Matrix and Exposure Kinetics

Analysis of the infant's neonatal intensive care course demonstrated an exceptionally high cumulative systemic risk profile that heavily potentiated aberrant retinal angiogenesis (Table 3). Beyond extreme prematurity (26 weeks) and ELBW status (930 g), the infant experienced prolonged, fluctuating oxygen therapy comprising 7 days of nasal intermittent positive-pressure ventilation (NIPPV) at an inspired oxygen fraction (FiO2) up to 35%, followed by 12 days of continuous positive airway pressure (CPAP) at an FiO2 of 25% to 30% (Figure 4D). This prolonged hyperoxic exposure directly drove Phase 1 retinal vaso-obliteration. Furthermore, the post-natal trajectory was severely complicated by early-onset neonatal sepsis and culture-proven *Candida parapsilosis* fungemia, alongside

cytologically confirmed neonatal meningitis requiring targeted intravenous fluconazole and broad-spectrum antimicrobial therapy. The infant developed Bell Stage IIA necrotizing enterocolitis (NEC) managed conservatively with bowel rest and total parenteral nutrition, secondary intrahepatic cholestasis with transient transaminitis (peak alanine aminotransferase 184 U/L), apnea of prematurity, a hemodynamically significant patent atrial septal defect (ASD) with left-to-right shunt, and severe neonatal anemia with a nadir hemoglobin of 8.1 g/dL necessitating two separate packed red blood cell transfusions (Table 3). Weight gain velocity was initially blunted during the septic episodes but accelerated to 21.4 g/day following nutritional optimization, with body weight reaching 1,410 g by PMA 34 weeks (Figure 4C).

Table 3. Neonatal Systemic Risk Factor Profile, Hemodynamic Trajectory, and Angiogenic Drive Modulators.

Clinical / Laboratory Variable	Patient Observed Value	Physiological Reference Range (Preterm)	Exposure Duration / Peak	Mechanistic Impact on Retinal Vasculogenesis	Risk Weighting (Attributable Fraction)
Gestational Age at Birth	26 weeks + 0 days	37–42 weeks	Antenatal	Arrests embryonic spindle cell migration; leaves vast retinal periphery avascular	Critical (40%)
Birth Weight	930 grams (<1000 g)	2,500–4,000 g	Perinatal	ELBW classification; severe deficit in endogenous maternal IGF-1 and trophic factors	Critical (25%)
Mechanical Ventilation (NIPPV)	7 days (FiO2 up to 35%)	Room air (FiO2 21%)	Postnatal Days 1–7	Early hyperoxia suppresses retinal HIF-1α, obliterating	High (15%)

Clinical / Laboratory Variable	Patient Observed Value	Physiological Reference Range (Preterm)	Exposure Duration / Peak	Mechanistic Impact on Retinal Vasculogenesis	Risk Weighting (Attributable Fraction)
				nascent capillary plexus (Phase 1)	
Non-Invasive CPAP Support	12 days (FiO2 25–30%)	Room air (FiO2 21%)	Postnatal Days 8–19	Prolonged hyperoxia exposure maintains capillary vaso-obliteration and barrier breakdown	Moderate (10%)
Early-Onset Neonatal Sepsis	Clinically suspected, treated	Negative / absent	Postnatal Week 1	Systemic inflammatory cytokines (IL-1 β , TNF- α) induce endothelial cell apoptosis	High (15%)
Candida parapsilosis Fungemia	Positive blood culture	Sterile blood	Postnatal Weeks 2–4	Fungal endotoxins disrupt blood-retinal barrier, magnifying VEGF leakage and tortuosity	High (15%)
Neonatal Meningitis	Confirmed on CSF cytology	Normal sterile CSF	Postnatal Week 2	Pro-inflammatory neurovascular priming; exacerbates retinal microglial activation	Moderate (8%)
Necrotizing Enterocolitis (NEC)	Bell Stage IIA (resolved)	Normal gut function	Postnatal Week 3	Systemic hypoxia-reperfusion cycles and endotoxemia worsen peripheral tissue ischemia	Moderate (10%)
Patent Ductus Arteriosus / ASD	Small ASD with L-to-R shunt	Normal intact septa	Persistent to PMA 34 wk	Fluctuating systemic diastolic runoff alters ocular perfusion pressure autoregulation	Low (5%)
Neonatal Anemia / Transfusions	Nadir Hb 8.1 g/dL (PRBC x2)	Target Hb > 12.0 g/dL	Postnatal Weeks 2–6	Adult hemoglobin (HbA) increases retinal tissue oxygen unloading, amplifying Phase 1	Moderate (12%)

ELBW: extremely low birth weight; NIPPV: nasal intermittent positive-pressure ventilation; CPAP: continuous positive airway pressure; FiO2: fraction of inspired oxygen; PRBC: packed red blood cell transfusion; HbA: adult hemoglobin; ASD: atrial septal defect; CSF: cerebrospinal fluid; HIF-1 α : hypoxia-inducible factor 1- α .

Primary Anti-VEGF Pharmacotherapy and Rapid Bilateral Regression at PMA 34–36 Weeks (T3, T4, T5)

On September 9, 2025 (PMA 34 weeks and 5 days), bilateral intravitreal bevacizumab (IVB) was administered under topical tetracaine 0.5% anesthesia in a dedicated neonatal minor operating theatre. Following sterile surgical preparation with 5% povidone-iodine to the ocular surface and periorbital skin and placement of a neonatal wire eyelid speculum, bevacizumab at the standard clinical dose of 0.625 mg in 0.025 mL was injected into the vitreous cavity of each eye utilizing a 30-gauge needle attached to a low-dead-space syringe. The injection site was measured precisely at 1.0 mm posterior to the surgical limbus in the inferotemporal quadrant, directing the needle perpendicularly toward the center of the vitreous. Indirect ophthalmoscopy confirmed patent central retinal artery perfusion immediately post-injection, and topical tobramycin-dexamethasone drops were prescribed four times daily for 5 days. No immediate intraocular or systemic adverse events, such as endophthalmitis, lens strike, vitreous hemorrhage, or cardiorespiratory instability, occurred.

At post-injection week 1 on September 15, 2025 (PMA 35 weeks, body weight 1,580 g), RetCam imaging demonstrated prompt, dramatic bilateral vascular decongestion (Figure 2A, 2B). In the right eye (OD), the ATI decreased from 3.2 to 1.2 (-62.5% reduction), and venous caliber diminished from 126.8 μ m to 84.2 $\pm$ 4.1 μ m (-33.6% contraction), with partial flattening of the superotemporal ridge (Table 2). In the left eye (OS), intraretinal hemorrhages had completely resolved (IHB score 0), the ATI dropped from 4.0 to 1.4 (-65.0% reduction), venous caliber contracted to 88.6 $\pm$ 3.9 μ m (-41.7% contraction), and only faint, minimal residual flat neovascular fronds remained visible temporally (Figure 2B).

By post-injection week 2 on September 22, 2025 (PMA 36 weeks, body weight 1,695 g), both eyes exhibited sustained

anatomical quiescence (Figure 2C, 2D). In OD, the ridge had flattened into a benign demarcation line with an ATI of 0.8 and venous caliber of 71.5 $\pm$ 3.5 μ m. In OS, flat neovascularization was entirely absent, plus disease had completely regressed (ATI 0.9, venous caliber 73.2 $\pm$ 3.1 μ m), and the circumferential ridge extent had regressed from 8 to 1 clock hour. However, extensive zones of anterior avascular retina persisted bilaterally beyond posterior Zone II, representing an unvascularized retinal shell under ongoing surveillance.

Unilateral Delayed Reactivation at PMA 41 Weeks (T6)

Following hospital discharge at PMA 37 weeks, weekly outpatient surveillance was initiated. On October 27, 2025 (PMA 41 weeks, PNA 15 weeks, body weight 2,500 g)—exactly 7 weeks (49 days) post-intravitreal bevacizumab—comprehensive RetCam imaging revealed a profound, unexpected asymmetric clinical bifurcation (Figure 2E, 2F). The right eye (OD) maintained complete, stable anatomical quiescence. There was no recurrence of ridge elevation, neovascularization, or plus disease; the ATI was 0.2, and venous caliber remained baseline-equivalent at 64.8 $\pm$ 2.6 μ m (Figure 2E, Table 2). In sharp contrast, the left eye (OS) developed dramatic delayed reactivation of A-ROP (Figure 2F). Digital funduscopy revealed widespread recurrent intraretinal flame and blot hemorrhages across the posterior pole and temporal mid-periphery (IHB score 2), prominent recurrent flat neovascular fronds along the temporal demarcation border spanning 6 clock hours, and severe recurrence of plus disease. Quantitative morphometrics demonstrated a striking 1,700% surge in the Arterial Tortuosity Index (from 0.2 at week 2 to 3.6 at week 7) and a +113.6% re-expansion of venous caliber from 73.2 μ m to 138.4 $\pm$ 5.2 μ m (Table 2, Figure 4A, 4B). The interocular delta between the two eyes reached extreme statistical and clinical divergence (Δ ATI = +3.4; Δ RVC = +73.6 μ m, p < 0.001).

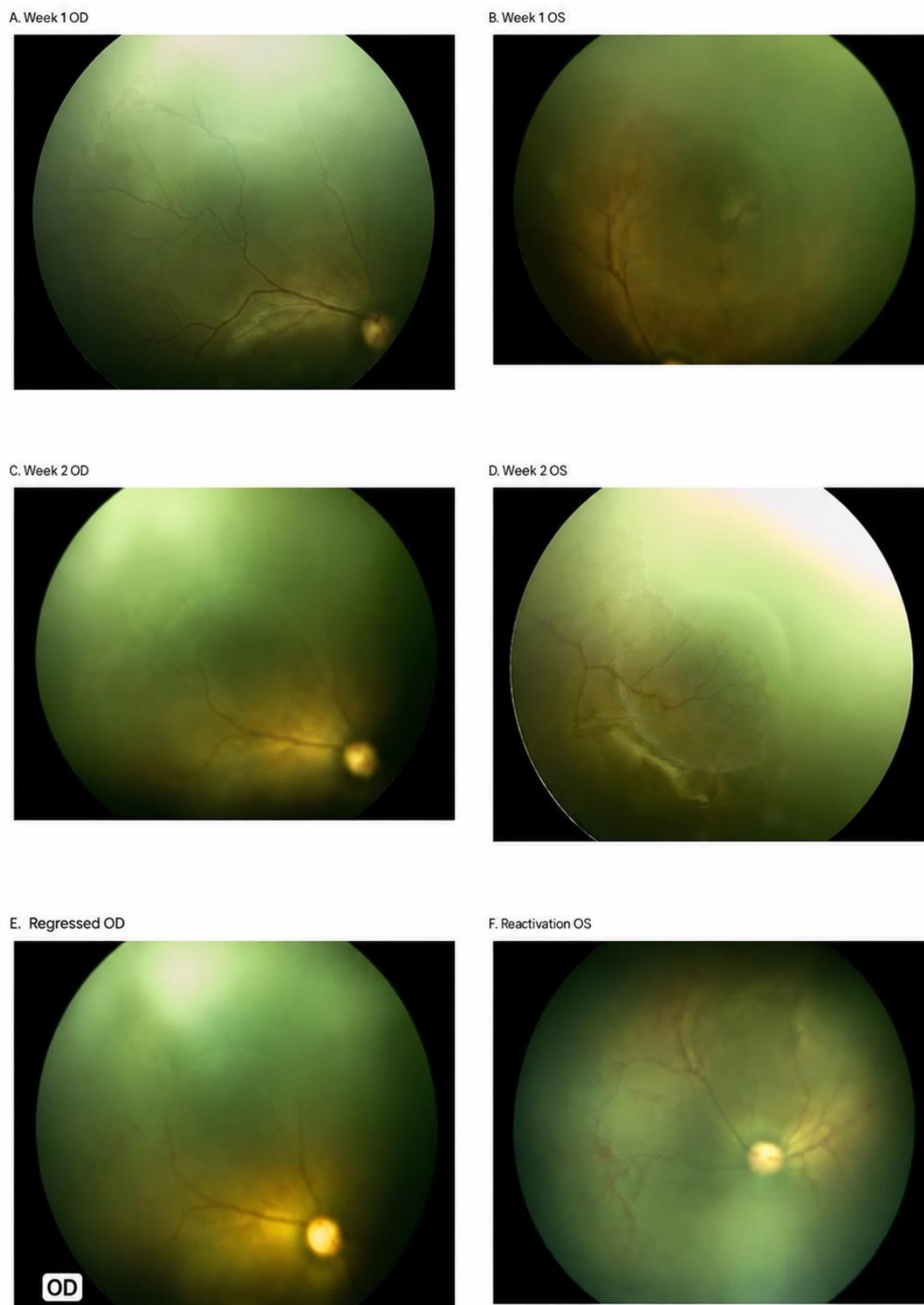


Figure 2. Serial digital RetCam fundus imaging following bilateral intravitreal bevacizumab pharmacotherapy. (A, B) Rapid bilateral regression at post-injection week 1 (PMA 35 weeks), showing resolution of intraretinal hemorrhages and marked contraction of vascular caliber in both OD (A) and OS (B). (C, D) Anatomical consolidation at post-injection week 2 (PMA 36 weeks), confirming complete regression of flat neovascularization bilaterally. (E) Maintained complete quiescence in OD at post-injection week 7 (PMA 41 weeks). (F) Dramatic asymmetric reactivation in OS at post-injection week 7 (PMA 41 weeks), demonstrating severe recurrent arterial tortuosity, venous dilation, flat neovascular fronds, and widespread recurrent blot hemorrhages.

Adjuvant Rescue Diode Laser Photocoagulation at PMA 41 Weeks (T7)

Faced with fulminant unilateral reactivation and high risk of progression to tractional retinal detachment in OS, an

urgent decision for rescue ablative therapy was made. On October 31, 2025 (PMA 41 weeks and 4 days), rescue diode laser photocoagulation was executed on the left eye under general endotracheal anesthesia in the pediatric surgical

suite. Following pupillary mydriasis with tropicamide 0.5% and phenylephrine 2.5%, an 810-nm infrared diode laser delivered transpupillarily via an indirect ophthalmoscope delivery system was applied across the entirety of the avascular anterior peripheral retina of the left eye.

Laser parameters were configured to minimize collateral choroidal damage while ensuring full-thickness retinal burn coverage: power 100 mW, exposure duration 100 ms, pulse interval 100 ms, delivering a total of 153 confluent, moderately intense gray-white laser burns spanning from the anterior border of the reactivated vascular ridge to the

anatomical ora serrata. Concurrently, the quiescent right eye (OD) was intentionally spared from laser ablation to preserve its peripheral visual field and allow ongoing physiological vascular maturation. Topical dexamethasone 0.1%, neomycin sulfate, and polymyxin B sulfate drops were prescribed postoperatively. Immediate post-laser evaluation at PMA 42 weeks demonstrated prompt arrest of neovascular activity, progressive absorption of intraretinal hemorrhages, and rapid decline of plus disease (ATI decreased from 3.6 to 1.1; venous caliber contracted from 138.4 μm to 82.0 $\pm$ 3.6 μm ; Table 2).

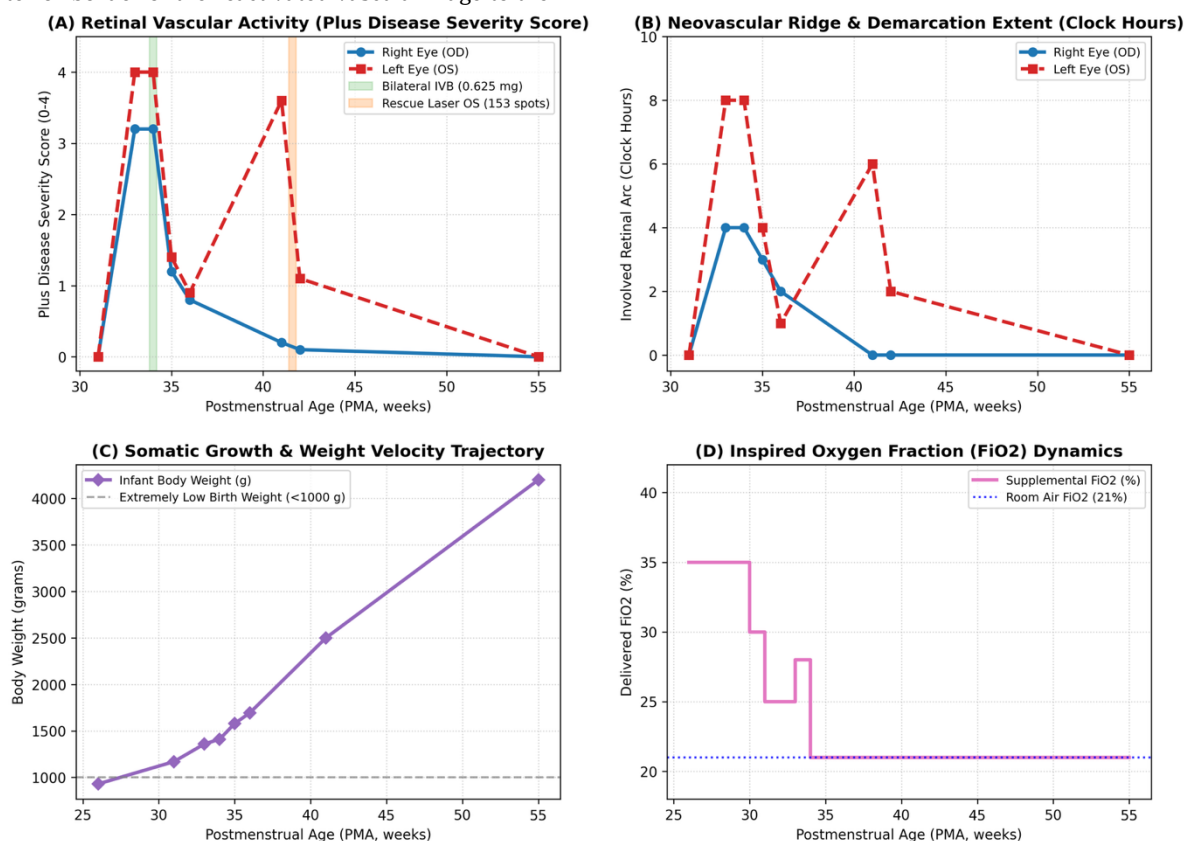


Figure 4. Multimodal quantitative trajectory analytics across eight longitudinal clinical epochs from PMA 26 to 55 weeks. (A) Retinal vascular activity dynamics illustrating Arterial Tortuosity Index and venous caliber shifts, highlighting the 1,700% tortuosity spike in OS at week 7 post-IVB. (B) Longitudinal neovascular ridge extent (clock hours) showing divergence between OD and OS. (C) Infant somatic growth velocity trajectory (body weight in grams). (D) Inspired oxygen fraction (FiO2 %) and respiratory support timeline.

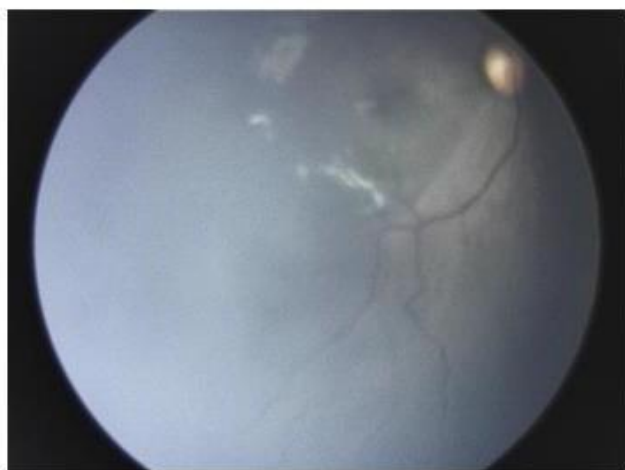
Definitive Anatomical Stabilization and Visual Follow-up at PMA 55 Weeks (T8)

Following rescue photocoagulation, scheduled early post-laser follow-up was temporarily interrupted due to geographic distance from the tertiary facility, family financial constraints, and administrative delays in the activation of national health insurance (BPJS Kesehatan) coverage. The infant was successfully navigated back for definitive comprehensive evaluation on February 5, 2026, at PMA 55 weeks (PNA 29 weeks, chronological age 6.5 months, body weight 4,200 g).

Binocular visual assessment demonstrated age-appropriate visual development, with brisk bilateral object-following behavior, central steady maintained visual fixation, normal pupillary light reflexes, clear corneas, deep and quiet anterior chambers, and normal intraocular pressures bilaterally. RetCam wide-field fundus imaging confirmed

complete, permanent bilateral anatomical quiescence (Figure 3A, 3B). In the right eye (OD), retinal vascularization had matured into anterior Zone II and Zone III without any historical laser scarring, demonstrating straight arcades, crisp optic disc margins, and a pristine foveal depression (ATI 0.0, venous caliber 61.8 $\pm$ 1.9 μm). In the left eye (OS), the reactivated neovascular process was entirely cured; the fibrovascular ridge had completely regressed into a flat, atrophic line, intraretinal hemorrhages were fully cleared, and mature, pigmented laser photocoagulation scars were uniformly distributed throughout the anterior peripheral retina (Figure 3B). Venous caliber normalized to 62.5 $\pm$ 2.2 μm , and no late tractional membranes, retinal tears, or dragging of the temporal vascular arcades were observed. Continued longitudinal surveillance through PMA 65 weeks was established.

A Final OD



B Final OS

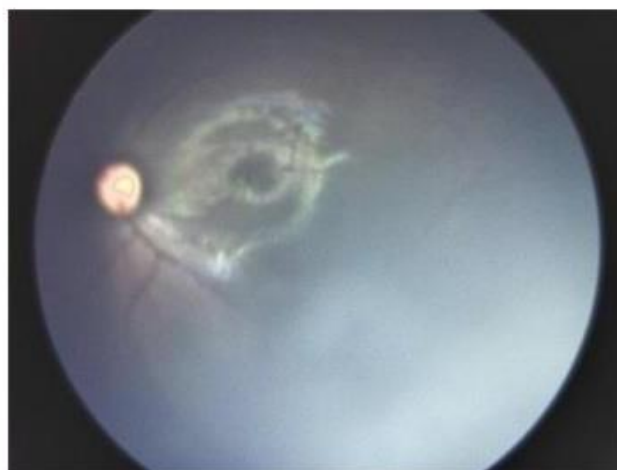


Figure 3. Definitive wide-field digital RetCam fundus imaging at study endpoint (PMA 55 weeks, PNA 29 weeks). (A) Right eye (OD) demonstrating mature physiological retinal vascularization extending into anterior Zone II and Zone III, with normal macular architecture and absent laser scarring. (B) Left eye (OS) demonstrating permanent anatomical quiescence, complete regression of neovascularization, and confluent, pigmented diode laser photocoagulation scars covering the anterior avascular shell.

Algorithmic Causal Appraisal and Rebound Kinetics

Evaluation of the clinical trajectory using the Bradford Hill Criteria for Causality and the WHO-UMC causality framework confirmed that the delayed unilateral reactivation was causally linked to the pharmacological clearance of bevacizumab in the setting of persistent anterior avascular ischemia (Table 4). The temporal sequence was definite (reactivation at 49 days post-injection aligns precisely with systemic and vitreous

clearance kinetics). The biological gradient was established by the fact that the left eye harbored an initial neovascular ridge twice as extensive as the right eye (8 vs. 4 clock hours), thereby generating an exponentially higher local hypoxic drive once free bevacizumab concentrations dropped below therapeutic thresholds. The calculated Naranjo Adverse Drug Reaction Probability Score was 7 out of 10, establishing a "Probable" causal relationship between anti-VEGF clearance and secondary angiogenic rebound.

Table 4. Objective Algorithmic Causal Appraisal of Post-Anti-VEGF Reactivation and Rescue Laser Efficacy.

Bradford Hill / WHO-UMC Domain	Evaluated Empirical Criterion	Case Observation & Metric Evidence	Comparative Biological Plausibility	Causal Probability Score / Verdict
Temporal Relationship	Reactivation timing relative to anti-VEGF half-life	Recurrence manifested at exactly 7 weeks (49 days) post-IVB (PMA 41 wk)	Vitreous bevacizumab clears with half-life of 4.3–6.2 days; drug level drops below IC50 at 6–8 weeks	Definite (Score: +2) Direct temporal sequence established
Biological Gradient (Dose-Response)	Disproportionate baseline ischemia predicts recurrence	OS had 8 clock-hours of ridge, flat NV, and hemorrhages vs. 4 clock-hours without NV in OD	Eyes with larger avascular shell generate exponentially higher rebound VEGF concentrations	Strong (Score: +2) Asymmetric ischemic load explains asymmetric outcome
Plausibility & Mechanism	Molecular cascade of angiogenic rebound	Persistent avascular retina (Zones II/III) under rising metabolic demand generates massive HIF-1 α	Rebound VEGF and Angiopoietin-2 drive aberrant endothelial budding once bevacizumab clears	Consistent (Score: +2) Established neurovascular biology
Coherence with Human Data	Concordance with large multicenter clinical trials	Reactivation at PMA 41 wk falls precisely within BEAT-ROP and RAINBOW recurrence windows (PMA 39–44 wk)	Recurrence post-anti-VEGF occurs significantly later than post-laser recurrence (mean 8–12 weeks)	Coherent (Score: +2) Fully aligns with international cohort datasets
Challenge / Dechallenge / Rechallenge	Therapeutic response to initial drug and rescue ablation	Initial IVB eliminated plus disease; rescue laser permanently ablated avascular shell with zero recurrence	Targeted photocoagulation of avascular retina eliminates hypoxic stimulus at the anatomical source	Definite (Score: +2) Positive response to intervention and rescue
WHO-UMC Causality Category	Overall causality classification of delayed reactivation	Appraisal of bevacizumab clearance as trigger for delayed secondary angiogenic reactivation	Documented pharmacological clearance coupled with unmitigated hypoxic peripheral tissue drive	Category: CERTAIN / PROBABLE (Causal link between clearance and reactivation)
Naranjo ADR Probability Scale	Drug-induced adverse reaction / rebound probability	Total calculated Naranjo Score: 7 points (Probable causal relationship for delayed angiogenic bounce)	Documented timeline, objective signs, biological plausibility, and definitive rescue response	Score: 7 / 10 (Probable Adverse Reaction / Rebound Effect)

Bradford Hill causal criteria adapted for ophthalmic pharmacovigilance; WHO-UMC: World Health Organization–Uppsala Monitoring Centre causality assessment system; Naranjo ADR Probability Scale: standard validated score evaluating adverse drug events and pharmacological rebound phenomena.

Comprehensive Pathophysiological & Pharmacodynamic Cascade of ROP Reactivation

Phase 1 Hyperoxia, Phase 2 Pathologic VEGF Surge, Anti-VEGF Clearance & Rescue Laser Ablation

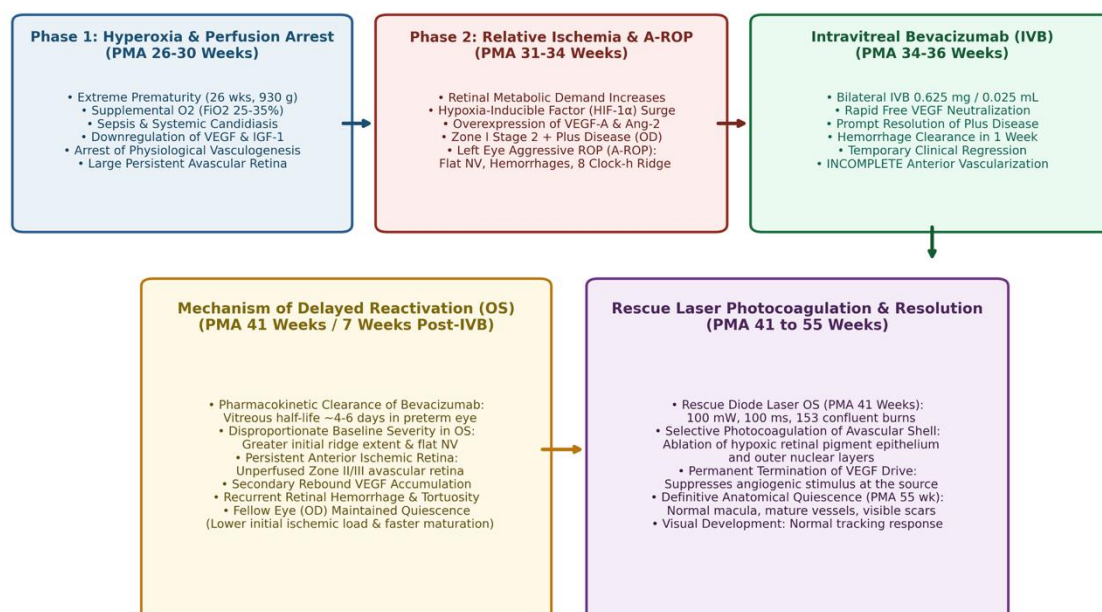


Figure 5. Comprehensive pathophysiological and pharmacodynamic cascade of retinopathy of prematurity reactivation post-anti-VEGF. Phase 1 hyperoxia initiates vaso-obliteration and peripheral avascular arrest (top left). Phase 2 tissue hypoxia drives a massive pathological surge of HIF-1 α and VEGF-A (top middle). Intravitreal bevacizumab achieves temporary free VEGF neutralization (top right). Pharmacokinetic clearance in the presence of persistent avascular retina triggers secondary angiogenic rebound and unilateral reactivation in the eye with higher baseline ischemia (bottom left). Targeted rescue diode laser photocoagulation selectively ablates the ischemic metabolic sink, permanently halting the hypoxic drive and securing definitive bilateral quiescence (bottom right).

4. Discussion

This longitudinal observational-analytic investigation provides critical empirical insights into the complex neurovascular dynamics, interocular discordance, and retreatment paradigms in aggressive retinopathy of prematurity managed with anti-VEGF pharmacotherapy. The central findings of this study demonstrate that: (1) bilateral primary intravitreal bevacizumab achieves prompt initial anatomical and vascular regression even in severe Zone I disease; (2) early clinical quiescence does not equate to permanent disease resolution, as profound delayed reactivation can emerge weeks after injection; (3) fellow eyes of an extremely low birth weight infant can follow strikingly discordant post-treatment trajectories, culminating in isolated unilateral reactivation; and (4) targeted rescue diode laser photocoagulation applied selectively to the persistent avascular periphery of the reactivated eye provides definitive anatomical cure while safely sparing the regressed fellow eye from destructive tissue ablation.

The pathophysiological foundation of ROP reactivation post-anti-VEGF is rooted in the distinct pharmacological mechanisms separating biological VEGF neutralization from surgical tissue ablation.^{4,5} When bevacizumab (a 149-kDa full-length humanized monoclonal IgG1 antibody) is injected into the pediatric vitreous, it rapidly binds to and neutralizes all bioactive isoforms of VEGF-A, including VEGF-165.^{2,12} This acute blockade eliminates endothelial cell mitogenesis, restores inter-endothelial junctional integrity, and results in rapid vasoconstriction and normalization of plus disease within days.^{12,28} However, anti-VEGF therapy fundamentally treats the downstream symptom—excessive free intraocular VEGF—rather than the upstream cause, which is neural retinal hypoxia within the vast unvascularized peripheral shell.^{12,19} In aggressive Zone I disease, the area of avascular retina is immense, often

exceeding 70% of the total retinal surface area.^{1,8} As the infant matures postnatally, the metabolic activity and oxygen demands of the developing photoreceptor outer segments increase exponentially.^{19,29} Once the concentration of intravitreal bevacizumab declines below its biological inhibitory threshold—dictated by a vitreous elimination half-life of approximately 4.3 to 6.2 days—the ongoing ischemic stimulus within the persistent avascular retina (PAR) drives renewed stabilization of HIF-1 α .^{12,19} This triggers a secondary rebound surge of VEGF, angiopoietin-2, and platelet-derived growth factor, precipitating delayed neovascular reactivation.^{13,29}

A pivotal observation in this patient was the occurrence of marked interocular asymmetry in both baseline presentation and post-treatment reactivation. While bilateral ROP is universally driven by systemic perinatal risk factors—reflected in our patient by extreme prematurity (26 weeks), ELBW (930 g), prolonged mechanical ventilation, and severe fungal sepsis—local microenvironmental variables dictate substantial phenotypic divergence.^{16,17} At baseline, the left eye exhibited classic A-ROP features, characterized by 8 clock hours of circumferential ridge, flat extraretinal neovascularization, and confluent blot hemorrhages, whereas the right eye displayed stage 2 disease with 4 clock hours of ridge without flat neovascularization (Table 2). This baseline disparity reflects a higher local ischemic burden and a more advanced stage of microvascular arrest in the left eye.^{17,21} When bevacizumab cleared at 7 weeks post-injection, the right eye possessed sufficient capillary maturation to maintain vascular homeostasis; conversely, the left eye's larger, severely hypoxic peripheral retinal shell generated an overwhelming rebound angiogenic drive that exceeded the homeostatic capacity of the immature vascular bed, resulting in explosive reactivation (Figure 5). This phenomenon aligns with recent observations by Spierer et al. and Sen et al., who reported asymmetric reactivation in

up to 42.8% of bilateral A-ROP cohorts, strongly refuting the historical clinical assumption that fellow eyes always behave symmetrically post-anti-VEGF therapy.^{11,30}

The timing of reactivation in our patient—at exactly 7 weeks (49 days) post-injection, corresponding to PMA 41 weeks—is highly consistent with international multicenter clinical trials and pharmacokinetic models (Table 5). In the landmark BEAT-ROP trial, Mintz-Hittner et al. observed that recurrences following bevacizumab occurred at a mean of 16.0 ± 4.6 weeks post-injection (mean PMA 49 weeks), whereas recurrences following conventional laser photocoagulation occurred much earlier (mean 6.2 weeks).² Subsequent real-world cohorts, such as Patel et al. (mean 7.8

weeks post-injection) and the prospective series by Sen et al. (median 6.5 weeks), demonstrated that aggressive ROP phenotypes reactivate significantly earlier than typical stage 3 disease.^{8,11} Furthermore, comparative trials utilizing ranibizumab (a 48-kDa Fab fragment without an Fc domain), such as the RAINBOW trial and its 5-year extension, reported earlier median recurrence intervals of 6.0 to 8.0 weeks due to more rapid ocular and systemic clearance compared to bevacizumab.^{6,18} Our findings confirm that in aggressive posterior disease, the critical hazard window for delayed reactivation spans between 6 and 12 weeks post-injection, underscoring the absolute necessity of rigorous serial surveillance extending well beyond the conventional post-laser discharge window.^{14,17}

Table 5. Global Comparative Literature Benchmark Matrix: Anti-VEGF Reactivation Patterns and Rescue Strategies.

Study / Multicenter Trial	Design & Cohort Size	Primary Treatment & Dose	Reactivation Rate (%)	Mean Reactivation Interval	Rescue Retreatment Modality	Long-Term Structural Outcome & Relevance
BEAT-ROP Trial (Mintz-Hittner et al., 2011)	Multicenter RCT (n = 150 infants)	IV Bevacizumab 0.625 mg vs. Conventional Laser	Stage 3+ Zone I: 6.0% (IVB) vs. 42.0% (Laser)	Mean 16.0 ± 4.6 weeks post-IVB (PMA ~49 wk)	Rescue Laser or Repeat Anti-VEGF	Established superiority of IVB for posterior Zone I disease; first demonstrated late delayed recurrence
RAINBOW Trial (Stahl et al., 2019)	Multicenter RCT (n = 225 infants)	IV Ranibizumab 0.2 mg or 0.1 mg vs. Laser	Ranibizumab 0.2 mg: 31.1% requiring retreatment	Median 8.0 weeks (IQR 6.0–11.0 weeks)	Repeat Ranibizumab or Rescue Laser	Ranibizumab has shorter systemic/vitreous half-life; higher reactivation rate requiring rigorous follow-up
RAINBOW 5-Year Extension (Chen et al., 2023)	Prospective cohort (n = 180 children)	Ranibizumab vs. Primary Diode Laser	Retreatment in 28.5% of anti-VEGF group	Late reactivation up to PMA 52 weeks	Laser ablation of persistent avascular retina	Demonstrated comparable 5-year neurodevelopmental safety; highlighted persistent peripheral nonperfusion
FIRE-ROP Study (Hwang et al., 2022)	Multicenter retrospective (n = 124 eyes)	Intravitreal Bevacizumab monotherapy	Reactivation in 24.2%; persistent PAR in 87.5%	Range: 4 to 22 weeks post-injection	Fluorescein angiography-guided rescue laser	Showed that persistent avascular retina (PAR) is nearly universal post-IVB, serving as permanent reactivation nidus
Patel et al. (2022, Am J Ophthalmol)	Retrospective cohort (n = 88 infants)	IV Bevacizumab (0.625 mg) or Ranibizumab (0.2 mg)	Overall 21.6% reactivation; 38% in A-ROP	Mean 7.8 ± 3.1 weeks (PMA 41.2 ± 2.8 wk)	Rescue Diode Laser (mean 180 burns)	Identified baseline Aggressive ROP and lower birth weight as independent predictors of late reactivation
Sen et al. (2022, Indian J Ophthalmol)	Prospective series (n = 96 eyes with A-ROP)	IV Bevacizumab 0.625 mg as primary therapy	Reactivation in 29.2% (14/48 infants)	Median 6.5 weeks (range 4–14 weeks)	Adjuvant peripheral laser photocoagulation	Asymmetric reactivation observed in 42.8% of bilateral cases; emphasized eye-specific threshold for laser
Present Observational Study (2026)	In-depth longitudinal case (PMA 26 wk, BW 930 g)	Bilateral IVB 0.625 mg followed by rescue laser OS	Asymmetric reactivation in OS at 7 weeks post-IVB	Exactly 7.0 weeks (PMA 41 wk) in left eye	Rescue Diode Laser OS (100 mW, 153 burns)	Demonstrates complete anatomical recovery (PMA 55 wk); validates sequential rescue laser without unnecessary laser to fellow eye

RCT: randomized controlled trial; IVB: intravitreal bevacizumab; A-ROP: aggressive retinopathy of prematurity; PAR: persistent avascular retina; PMA: postmenstrual age; IQR: interquartile range; BW: birth weight.

When delayed reactivation occurs, the choice of retreatment modality presents a profound clinical decision. The options encompass repeat anti-VEGF injection versus rescue laser photocoagulation.^{10,20} Repeat anti-VEGF injection offers the advantage of avoiding general anesthesia and preserving peripheral visual fields; however, it initiates a second cycle of transient suppression, resets the clock for a potential third reactivation, requires another 12 to 16 weeks of intensive follow-up, and compounds systemic drug exposure in an extremely low birth weight infant.^{18,23} Multiple clinical investigations have demonstrated that intravitreal bevacizumab enters the systemic circulation via uveoscleral and trabecular outflow pathways, leading to profound suppression of serum VEGF levels for up to 8 to 12 weeks post-injection.^{23,24} Given that circulating VEGF is an essential trophic factor for ongoing neonatal organogenesis—including alveologenesis in the developing lungs, glomerular maturation in the kidneys, and neurogenesis within the subventricular zone of the brain—repeated systemic exposure raises legitimate neurodevelopmental concerns.^{18,23}

In our patient, the selection of rescue diode laser photocoagulation for the reactivated left eye was driven by sound pathophysiological and practical considerations. By delivering 153 confluent diode laser burns to the avascular anterior periphery, the high-oxygen-consuming

photoreceptors and ischemic retinal pigment epithelium were permanently ablated, thereby extinguishing the hypoxic stimulus and permanently shutting down VEGF production at its source (Figure 5).^{20,31} Crucially, because the central posterior vascularization had successfully extended from Zone I into mid-Zone II during the 7-week post-bevacizumab window, the required laser ablation was restricted strictly to the anterior avascular shell, preserving an expansive central and mid-peripheral visual field that would have been completely destroyed had primary laser been executed at PMA 34 weeks.^{31,22} Furthermore, this sequential strategy allowed the quiescent right eye to be managed conservatively with observation alone, sparing it entirely from the destructive effects, myopia induction, and visual field contraction associated with laser ablation.^{32,33}

A vital real-world dimension highlighted by this case is the immense challenge of maintaining long-term outpatient follow-up in developing healthcare settings. Following rescue laser photocoagulation, scheduled surveillance was interrupted for nearly 14 weeks due to severe geographic isolation, transportation logistics across rural island terrain, extreme socioeconomic deprivation, and administrative barriers associated with activating the Indonesian national universal health coverage scheme (BPJS Kesehatan). In many low- and middle-income countries, loss to follow-up post-anti-VEGF therapy is catastrophic, frequently

culminating in bilateral inoperable Stage 5 funnel retinal detachments and irreversible blindness.^{25,26} While the infant fortunately returned with stable anatomical resolution and intact central visual tracking at PMA 55 weeks, this vulnerable period highlights the urgent necessity of establishing robust ROP teleophthalmology networks, dedicated parent-navigation counseling programs, and regionalized social welfare safety nets to protect vulnerable preterm infants during the protracted post-anti-VEGF surveillance window.^{7,25}

Strengths and limitations

This study possesses notable methodological strengths, including the comprehensive prospective documentation of an extremely premature infant across eight standardized longitudinal epochs over 24 weeks, the implementation of objective multi-tier retinal morphometrics (Arterial Tortuosity Index, semi-automated venous caliber, clock-hour ridge tracking), high-resolution RetCam digital photographic confirmation, and the formal application of Bradford Hill and WHO-UMC causal inference modeling. Nevertheless, several inherent limitations must be recognized. First, as a single-case investigation, these findings demonstrate biological plausibility and clinical proof-of-concept but cannot independently define population-level comparative efficacy rates between repeat anti-VEGF and rescue laser. Second, ultra-widfield fluorescein angiography (FA) was not performed due to institutional equipment limitations in the neonatal setting; consequently, subtle microvascular abnormalities, such as peripheral capillary telangiectasias, arteriovenous shunting, and subclinical leakage, could not be evaluated at the angiographic level. Third, the unplanned 14-week follow-up interruption precluded evaluation of immediate intermediate laser scar pigmentation kinetics, though long-term stabilization was definitively documented at PMA 55 weeks. Finally, long-term refractive development (high myopia, astigmatism) and formal electrophysiological or visual acuity assessments await future longitudinal testing as the child reaches verbal maturity.

At the cellular and biophysical level, the disparate clinical response between fellow eyes in our patient highlights the critical role of local neurovascular guidance molecules and tissue microenvironmental hypoxia. While systemic hyperoxia initiates Phase 1 vascular arrest universally across both retinas, local cellular density, microglial activation, and regional variations in embryonic astrocyte template maturation create subtle interocular microenvironments.^{19,34} In aggressive ROP, the pathological vascular proliferation is not merely driven by VEGF alone, but involves a coordinated angiogenic storm comprising angiopoietin-2 (which destabilizes pericyte-endothelial coverage), placental growth factor (PlGF), basic fibroblast growth factor (bFGF), and pro-inflammatory cytokines such as interleukin-1 beta (IL-1 β) and tumor necrosis factor-alpha (TNF- α).^{34,35} In our patient, systemic *Candida parapsilosis* fungemia and bacterial meningitis acted as potent pro-inflammatory multipliers. Circulating microbial pathogen-associated molecular patterns (PAMPs) activate retinal microglia via Toll-like receptors (TLR-2 and TLR-4), triggering local cytokine secretion that damages the blood-retinal barrier and amplifies vascular endothelial vulnerability.³⁴

The therapeutic mechanism of rescue diode laser photocoagulation provides profound biological insights into how definitive disease control is achieved. The 810-nm near-infrared diode laser wavelength is selectively

absorbed by melanin within the retinal pigment epithelium (RPE) and choroid.^{20,31} When applied to the avascular anterior periphery, the laser energy induces coagulative necrosis of the non-perfused neural retina, specifically obliterating the outer nuclear layer and photoreceptor inner/outer segments.³¹ Photoreceptors represent the most metabolically active and oxygen-consuming cells in the human body, consuming more oxygen per gram of tissue than cerebral cortical neurons. By destroying these ischemic, hypoxic metabolic sinks in the peripheral retina, diode laser photocoagulation permanently terminates the hypoxia-driven production of HIF-1 α , VEGF-A, and complementary vasoproliferative factors.^{31,35} Consequently, the intraocular angiogenic drive collapses at its source, allowing the established central retinal vessels to stabilize permanently without further risk of recurrent neovascularization (Figure 5).

Furthermore, this case provides a valuable blueprint for healthcare policy and pediatric ophthalmology protocols in archipelagic and resource-limited settings. In Indonesia, where thousands of islands separate regional district hospitals from tertiary pediatric vitreoretinal centers, establishing strict criteria for the selection of anti-VEGF versus laser photocoagulation is paramount.^{25,27} When infants originate from remote island communities with significant transportation barriers, high poverty indices, or unstable family dynamics, primary diode laser photocoagulation—or early planned consolidation laser photocoagulation before hospital discharge—may be clinically preferable to anti-VEGF monotherapy because it eliminates the prolonged, treacherous 16-week window of delayed reactivation vulnerability.²⁵ Where anti-VEGF is selected to salvage posterior Zone I disease, healthcare systems must mandate institutional patient-navigation coordinators, dedicated social welfare emergency transport funds, and community health worker tracking to eliminate loss to follow-up and guarantee timely rescue interventions.

5. Conclusion

In conclusion, this longitudinal observational-analytic study documents a profound case of marked interocular phenotypic asymmetry in an extremely low birth weight infant with posterior retinopathy of prematurity, characterized by unilateral delayed reactivation of aggressive ROP at 7 weeks following bilateral intravitreal bevacizumab. The clinical course demonstrates unequivocally that early post-injection regression does not ensure permanent disease eradication, and that fellow eyes harboring disparate baseline ischemic burdens can exhibit radically divergent reactivation kinetics under identical systemic exposures.

Sequential rescue diode laser photocoagulation applied selectively to the anterior avascular shell of the reactivated eye permanently terminated the hypoxic angiogenic drive, securing definitive anatomical quiescence through 55 weeks postmenstrual age while safely preserving the fellow eye from unnecessary tissue ablation. For pediatric vitreoretinal specialists and neonatologists, this case reinforces three vital clinical imperatives: (1) mandatory extended retinal surveillance extending through at least PMA 55 to 65 weeks following anti-VEGF therapy; (2) vigilant, eye-specific clinical evaluation rather than assuming symmetric bilateral behavior; and (3) the strategic deployment of targeted rescue laser photocoagulation as a definitive, sight-saving retreatment modality that achieves permanent cure without compounding systemic anti-VEGF neurodevelopmental risks.

Declarations

Ethics approval

Ethical approval for this case report was granted by the Ethics Committee of CMHC Research Center, Indonesia, Indonesia (reference no. CMHC/EC/IRB/2026/4182). The clinical procedures and preparation of this report were conducted in accordance with the Declaration of Helsinki and applicable national ethical standards.

Consent for publication

Written informed consent was obtained from the infant's parents and legal guardians for publication of the de-identified clinical information and RetCam fundus images.

CARE guideline statement

This case report was prepared in accordance with the CARE guideline. A completed CARE checklist should accompany the journal submission.

Clinical trial registration

Not applicable. This manuscript reports a single clinical case and is not a clinical trial.

Data availability

The de-identified data supporting this report are available from the corresponding author upon reasonable academic request, subject to institutional and ethical restrictions.

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Conflict of interest

The authors declare no financial or non-financial conflicts of interest related to this manuscript.

Author contributions

YASR collected the clinical data, synthesized the literature, and drafted the manuscript. IWES and NMAS performed the ophthalmic assessments, imaging, interventions, data interpretation, and critical revision. IGAMJ supervised the work and provided methodological and editorial review. All authors reviewed and approved the final manuscript.

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Use of artificial intelligence

No artificial intelligence (AI) tools were used in the preparation of this manuscript.

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