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Title: Long-term Choroidal Vascular Changes after Iodine Brachytherapy versus Transpupillary Thermotherapy for Choroidal Melanoma

Short Title: Choroidal Vascular Changes after I-125 Brachytherapy versus TTT

Article Type: Original Article

Keywords: Choroidal Melanoma, Choroidal Vascular Changes, Iodine Brachytherapy, Long-term, Transpupillary Thermotherapy,

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Abstract: Purpose: To compare long-term choroidal vascular changes after iodine-125 brachytherapy (IBT) versus transpupillary thermotherapy (TTT) used as primary treatment of small choroidal melanoma.
Methods: Ninety-five small choroidal melanomas were randomized: 49 eyes with TTT and 46 eyes with IBT alone. Fluorescein and indocyanine green angiography (ICGA) were performed at 3-month intervals during the first year, and every 6 months thereafter.
Results: Mean follow-up was 56.2 months (range: 24-118 months, SD: 22.6). Tumor regressed in 45 (92%) TTT vs 45 (98%) IBT treated eyes (p=0.397). Four TTT and one IBT treated tumor

recurred. Occlusion of choriocapillaris was present in all TTT and IBT cases. Closure of medium and large choroidal vessels was observed in 17 (35%) TTT vs 44 (96%) IBT treated eyes ($p<0.001$). Choroidal vascular remodeling was detected in 20 (41%) TTT and 16 (35%) IBT treated eyes ($p=0.693$). Retinochoroidal anastomosis was present in 4 of the 37 (11%) TTT treated eyes with patency of medium and large choroidal vessels, but never observed in the IBT treated eyes, and was associated with tumor recurrence. Among IBT treated eyes segments of choroidal vascular wall ICG staining and choroidal aneurysmal changes were detected in 30 (65%) and 7 (15%) respectively. These changes were never detected in TTT treated cases ($p<0.0001$ and $p=0.015$ respectively).
Conclusions: The pattern of tumor choroidal vascular changes following IBT and TTT differs. TTT is less effective in closing all tumor vasculature. The role of long-term choroidal vascular remodeling observed after these two treatments needs longer follow-up. "

Response to Reviewers: Reviewer #1:

1. “The authors selected to treat "melanomas" from 3 mm diameter and 1 mm thickness. Are these lesions real melanomas? I would guess that many ocular oncologists would not treatment such small lesions at all, as most will probably not increase in size. Since there is a debate about the treatment of small choroidal lesions and since the focus of this study is vascular changes, the authors should at least explain the rationale for treating such small lesions”

Authors’ reply: We treated all small choroidal melanoma that showed ophthalmoscopic or ultrasonography evidence of growth, in thickness and in or on largest basal diameter

In the text at page 3 “Patients and Methods” we have specified :

“All tumors had ophthalmoscopic or ultrasonography evidence of growth”

2. “The authors treated (small) choroidal melanomas that recurred after brachytherapy by enucleation. Since the primary dose to the tumor base was probably low (because of the small thickness of the tumor), why did the authors choose to enucleate and not try to irradiate again the tumor? “

Authors' reply: when choroidal melanoma recurred after IBT (1 case) an extrascleral extension was documented by ultrasonography. Therefore, enucleation was chosen as more radical but probably safer procedure.

In the text at page 5 " Results" we have specified :

"Recurrences after TTT underwent IBT, while recurrence after IBT underwent eye enucleation for extrascleral extention."

Reviewer #2:

"I only take objection with the last sentence in the conclusion that "Tumor recurrences after TTT seem related to persistent choroidal vessels..." In presence of several alternative explanations for lack of effectiveness of TTT and with the limited number of cases showing recurrences overall, the authors can not reach such a conclusion."

Authors' reply: we have considered the reviewer's objection and the conclusions of the abstract have been modified in this way:

"Conclusions: The pattern of tumor choroidal vascular changes following IBT and TTT differs. TTT is less effective in closing all tumor vasculature. The role of long-term choroidal vascular remodeling observed after these two treatments needs longer follow-up. "

Long-term Choroidal Vascular Changes after Iodine Brachytherapy versus Transpupillary Thermotherapy for Choroidal Melanoma

Short title: Choroidal Vascular Changes after I-125 Brachytherapy versus TTT

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Purpose: To compare long-term choroidal vascular changes after iodine-125 brachytherapy (IBT) versus transpupillary thermotherapy (TTT) used as primary treatment of small choroidal melanoma.

Methods: Ninety-five small choroidal melanomas were randomized: 49 eyes with TTT and 46 eyes with IBT alone. Fluorescein and indocyanine green angiography (ICGA) were performed at 3-month intervals during the first year, and every 6 months thereafter.

Results: Mean follow-up was 56.2 months (range: 24-118 months, SD: 22.6). Tumor regressed in 45 (92%) TTT vs 45 (98%) IBT treated eyes (p=0.397). Four TTT and one IBT treated tumor recurred. Occlusion of choriocapillaris was present in all TTT and IBT cases. Closure of medium and large choroidal vessels was observed in 17 (35%) TTT vs 44 (96%) IBT treated eyes (p<0.001). Choroidal vascular remodeling was detected in 20 (41%) TTT and 16 (35%) IBT treated eyes (p=0.693). Retinochoroidal anastomosis was present in 4 of the 37 (11%) TTT treated eyes with patency of medium and large choroidal vessels, but never observed in the IBT treated eyes, and was associated with tumor recurrence. Among IBT treated eyes segments of choroidal vascular wall ICG staining and choroidal aneurysmal changes were detected in 30 (65%) and 7 (15%) respectively. These changes were never detected in TTT treated cases (p<0.0001 and p=0.015 respectively).

Conclusions: The pattern of tumor choroidal vascular changes following IBT and TTT differs. TTT is less effective in closing all tumor vasculature. The role of long-term choroidal vascular remodeling observed after these two treatments needs longer follow-up.

Keywords: Choroidal Melanoma, Choroidal Vascular Changes, Iodine Brachytherapy, Long-term, Transpupillary Thermotherapy,

Introduction

The ideal treatment of small choroidal melanoma is still under investigation (1). Although brachytherapy has an excellent tumor control rate, long-term radiation complications may significantly compromise final visual acuity, especially for tumors located near the macula or optic disc (2). Radiation retinopathy following both brachytherapy for choroidal melanoma and teletherapy (external beam irradiation) for malignant tumors near the eye is a well-known retinal microvascular disease (3-6). The introduction of indocyanine green angiography (ICGA) in clinical practice has documented that the damage due to teletherapy involves both retinal and choroidal circulation (7), but little is known about the choroidal effect of conservative treatment of choroidal melanoma.

In an attempt to reduce visual loss due to radiotherapy, transpupillary thermotherapy (TTT) has been proposed as sole treatment of selected choroidal melanoma (8-12). With TTT tumor necrosis up to a depth of 3.9 mm is achieved in human choroidal melanoma as demonstrated by histopathologic investigation (13-15). The sight-threatening TTT side effects are mainly related to the retinal vascular occlusion in the treated area (11, 16-17), but vascular changes due to TTT also involve choroidal vasculature at the treatment site (18).

In this study we compared, using dynamic and static ICGA, long-term choroidal vascular alterations observed in small choroidal melanoma after iodine- 125 brachytherapy (IBT) versus TTT, used as sole treatment modality.

Patients and Methods

This study complied with the tenets of the declaration of Helsinki and was approved by the IRB of Padova University Hospital. Each patient gave their informed consent prior to their inclusion in the study. Ninety-five eyes of 95 patients affected by small malignant choroidal melanoma and treated with TTT or IBT as sole treatment were prospectively followed. Inclusion criteria were: baseline largest basal tumor diameter smaller than 10 mm, tumor thickness smaller than

3.5 mm. All tumors had ophthalmoscopic or ultrasonography evidence of growth. After detailed information of the aim of the study, patients were randomly assigned to TTT or IBT. Exclusion criteria were: tumor located in the macular region or in the peripapillary area, tumor invasion of the retina, optic disc, vitreous or sclera; media opacity precluding clear view of the fundus; subretinal fluid overlying the tumor elevated more than 1.5 mm. Before treatment, the characteristics of the tumor were documented with color fundus photography, fluorescein and ICGA. A and B-ultrasonography were also performed.

Fluorescein angiography and ICGA phases were documented with a Rodenstock scanning laser ophthalmoscope (Rodenstock, Munich, Germany). Late phase static images were also taken with a Topcon TRC50IA (Tokyo, Japan) digital equipped fundus camera. Both fluorescein angiography and ICGA were examined by two independent observers, who were masked about treatment.

Transpupillary thermotherapy was performed using an infrared diode laser at 810 nm with an adjustable beam width (1.2, 2.0 and 3.0 mm) (Iris, Mountain View, CA) attached to a slit lamp and delivered through a Quadraspheric fundus lens (Volk, Mentor, OH). The treatment was performed through a dilated pupil after retrobulbar anesthesia, according to the standard protocol previously described (11, 19). The aim was to achieve an end point of a light-gray appearance of the tumor at the completion of each treatment spot. Confluent spots were delivered in overlapping fields, including 0.5 mm of clinically normal tissue around the margin of the tumor.

Iodine-125 brachytherapy was administered using custom-made, steel non-rimmed plaques. The tumor margins were identified under general anesthesia using transcleral illumination and indirect ophthalmoscopy. A minimum safety margin of at least 0.5 mm was required. The prescription dose was usually 100 Gy to the tumor apex.

Follow-up examinations were performed at 3-month intervals during the first year, and every 6 months thereafter. Clinical examination, fundus photography, ocular ultrasonography, fluorescein angiography and ICGA were performed at each follow-up visit. Serum liver function

enzymes and liver ultrasonography were performed at 6-month intervals to check for liver metastasis.

Two-tailed Student's *t* test was used to analyze distribution of continuous quantitative variables. Qui-square test and Fisher exact test were used to analyze the association between qualitative variables. The threshold of significance was set at $p<0.05$. SAS statistical package was used for all analyses.

Results

Ninety-five eyes of 95 patients treated for small choroidal melanoma were evaluated for choroidal circulation changes after treatment. Mean age of patients at treatment was 65 years (range, 35-94 years; SD 13). Fifty-four were women and 41 were men. Mean largest tumor diameter was 6.4 mm (range, 3-10; SD, 1.8) and mean tumor thickness was 2.2 mm (range, 1-3.5; SD, 0.7). Visual acuity ranged from 1.3 to 0.0 LogMAR. Forty-nine eyes were treated with TTT as sole treatment, while 46 eyes were treated with IBT. Baseline characteristics of the treated patients are summarized in table 1.

Mean follow-up was 56.2 months (range: 24-118 months, SD: 22.6). Among patients treated with TTT 16 eyes required one treatment session (32.7%), 32 eyes (65.3%) required two and one eye (2%) required three treatment sessions.

Tumor regression was obtained in 45 (92%) TTT vs 45 (98%) IBT treated eyes. This difference was not statistically significant ($p=0.397$). Tumor recurrences occurred in four TTT (8%) and in one (2%) IBT treated eye. Recurrences after TTT underwent IBT, while recurrence after IBT underwent eye enucleation for extrascleral extension.

Among TTT treated eyes branch retinal vein occlusion on the tumor occurred in 9 eyes (18%) and retinal neovascularization in one eye (2%). Among IBT treated eyes radiation retinopathy occurred in 10 cases (22%) and macular edema occurred in 9 (17%), Radiation retinopathy was characterized by the presence of teleangectasia, microaneurysms, hard exudates and confluent areas of retinal ischemia (table 2).

Choroidal vascular changes after TTT and IBT are summarized in Table 3. ICGA revealed that changes of choroidal circulation were limited to the treated area after TTT, while they involved larger areas of the choroid beyond treatment margins after IBT. Early and permanent occlusion of choriocapillaris was observed in all eyes of both groups. Closure of medium and large choroidal vessels progressively occurred in 96% of IBT versus 35% of TTT treated eyes ($p < 0.05$) (*Fig 1, 2).* The patency of medium and/or large choroidal vessels, detectable in 37 (75%) TTT treated eyes, was associated with retinochoroidal anastomosis in four cases treated with TTT (11%), but never detected in the two IBT treated eyes with patency of medium and/or large choroidal vessels. Segments of choroidal vascular wall staining with ICG (30 eyes, 65%) and aneurismal changes (7 eyes, 15%) were observed among IBT treated eyes but never after TTT. In both the TTT and the IBT groups long-term choroidal vascular remodeling (41% and 35% respectively, $p= 0.693$) was observed (*Fig 3*). Among IBT treated eyes long-term choroidal vascular remodeling occurred in areas characterized by ICG leakage associated with segments of choroidal vascular wall staining (*Fig 4*) and choroidal aneurismal changes (*Fig 5*). In TTT treated eyes, choroidal remodeling was never characterized by intrachoroidal ICG leakage. Retinochoroidal anastomosis was observed in all cases of TTT failure (four cases of recurrent tumor). Among IBT treated eyes, tumor recurrence was detected in one case: neither choroidal aneurismal changes nor choroidal vascular leakage were documented.

Discussion

Radiotherapy is the gold standard in the treatment of choroidal melanoma (1-2). Unfortunately side effects are relevant, and new less invasive therapies should be implemented, particularly for small tumors (4-7).

TTT was considered superior to brachytherapy in the treatment of small choroidal melanoma due to similar regression rate, but more limited side effects (16). Now, after initial enthusiasm, TTT is still considered a useful procedure in the treatment of selected cases of small choroidal melanoma (11-12). Tumor vasculature is a key target of tumor treatment, because regression

depends on closure of tumor vessels. Moreover, closure of tumor choroidal vessels may prevent surviving malignant cells to escape the tumor area to initiate metastatic cascade.
A comparison about the effects of TTT vs IBT in choroidal circulation has never been previously reported. The introduction of ICGA in clinical practice has documented that the effects of TTT are not limited to the retinal circulation, but involve choroidal circulation too (18). Moreover, some studies have documented that the histological changes of local radiotherapy of choroidal melanoma include sclerosis of choroidal vessels, atrophy of choroidal layers and Bruch's membrane (20-21). Using ICGA, we have demonstrated that occlusion of choriocapillaris is constant in all IBT and TTT treated eyes. Whereas, patent medium and/or large choroidal vessels may be detected in TTT treated eyes. In TTT treated eyes, recurrent melanomas were characterized by patency of medium and large choroidal vessels and retinochoroidal anastomosis, never observed in IBT treated eyes. Therefore, patency of medium/large choroidal vessels after TTT should be strictly monitored for the risk of tumor recurrence. On the contrary, IBT induces slow, progressive and complete occlusion of medium and/or large choroidal vessels. Extensive choroidal ischemia is therefore a characteristic of radiation induced vascular changes.

In TTT and IBT treated eyes, choroidal vasculature progressively modifies with different network changes. In TTT treated eyes, choroidal remodeling is limited to the patent choroidal vessels in the treated area, while after IBT choroidal remodeling involves widespread areas beyond the borders of treated choroidal tumor. Remodeling of the choroidal vasculature, affecting small caliber choroidal vessels, may mimic choroidal neovascularization. Currie et al reported choroidal neovascularization in 14% of cases treated with TTT for choroidal melanoma (22). Focal choroidal neovascularization developing after brachytherapy has been also anecdotically described. Choroidal neovascularization is usually associated with serous detachment, bleeding and/or exudation. The choroidal neovascular net observed after IBT and TTT was never associated with serous detachment, exudation or bleeding at baseline or during follow-up. For these reasons, the term of choroidal remodeling, we previously suggested, better

reflects the angiographic and clinical aspects of the changes of choroidal circulation due to thermotherapy or radiotherapy (18, 23).

Among IBT treated eyes, choroidal vascular remodeling affects medium and large choroidal vessels with beading or irregular caliber variation, teleangiectatic-like dilatations and large choroidal aneurismal changes. These changes affect not only peri-lesion choroidal vasculature but also widespread areas, beyond treated site. These choroidal aneursysmal changes, mimicking smaller retinal microaneurysmatic lesions secondary to eye irradiation, recall the vascular blebs of choroidal neovascularization described after radiotherapy or external eye radiation (7, 24, 25).

Segments of choroidal vascular wall staining, detectable in the late phase of ICGA, may be detected before the appearance of choroidal remodeling. It is suggested that radiation induces endothelial cell loss and/or dysfunction, which can justify dye leakage (26). Segments of choroidal vessels with staining have also been described by Amoaku and associates (26) that retrospectively analyzed ICGA of patients treated with ruthenium-106 brachytherapy for choroidal melanoma. These authors reported that some wall ICG staining choroidal vessels eventually became non-perfused. Histopathological studies (20, 27) never reported signs of vasculitis within the irradiation field that could justify choroidal wall staining with ICG. But to the best of our knowledge, histopathologic analysis has never been performed in eyes treated with IBT and with documented segments of choroidal vascular wall staining detected by ICG. Moreover, choroidal vascular changes in IBT treated eyes were never associated with tumor recurrence. These lesions may be an early and immature form of choroidal vessels and confirm the plastic reaction of choroidal vascular system to radiation damage (21, 24, 28).

In conclusion, our data demonstrate a different pattern of choroidal vascular changes following TTT vs IBT. The higher rate of choroidal vascular closure after IBT compared with TTT may be the key factor to explain a better local tumor control by brachytherapy. The significant of long-term choroidal vascular remodeling observed after these two treatments is still under investigation and need longer follow-up.

Figure legends

Figure 1. Choroidal melanoma 12 months after Iodine-125 brachytherapy. Fluorescein (**a**) and indocyanine green angiography (**b**) show the atrophy of medium and large choroidal vessels.

Figure 2. Choroidal melanoma 12 months after transpupillary thermotherapy. Indocyanine green angiography shows the patency of medium and large choroidal vessels.

Figure 3. Choroidal vascular remodeling in the center of two cases of successfully treated choroidal melanoma. **a**,**b**, Choroidal vascular remodeling after transpupillary thermotherapy (a, 12 months; b, 36 months) and **c**,**d**, after Iodine-125 brachytherapy (c, 12 months; d, 36 months).

Figure 4. Choroidal melanoma treated with Iodine-125 brachytherapy. **a**, The intermediate phase of indocyanine green angiography (ICGA) shows segments of choroidal vascular wall staining in the whole treated area and in the surrounding choroid. **b**, The late phase of the ICGA detects diffuse areas of indocyanine green choroidal staining.

Figure 5. Iodine-125 brachytherapy successfully treated choroidal melanoma. **a**,**b**, Early phase indocyanine green angiography shows remodeling of choroidal vasculature with aneurysmal changes in the treated area 12 months (a) versus 48 months after treatment (b).

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Figure 1A

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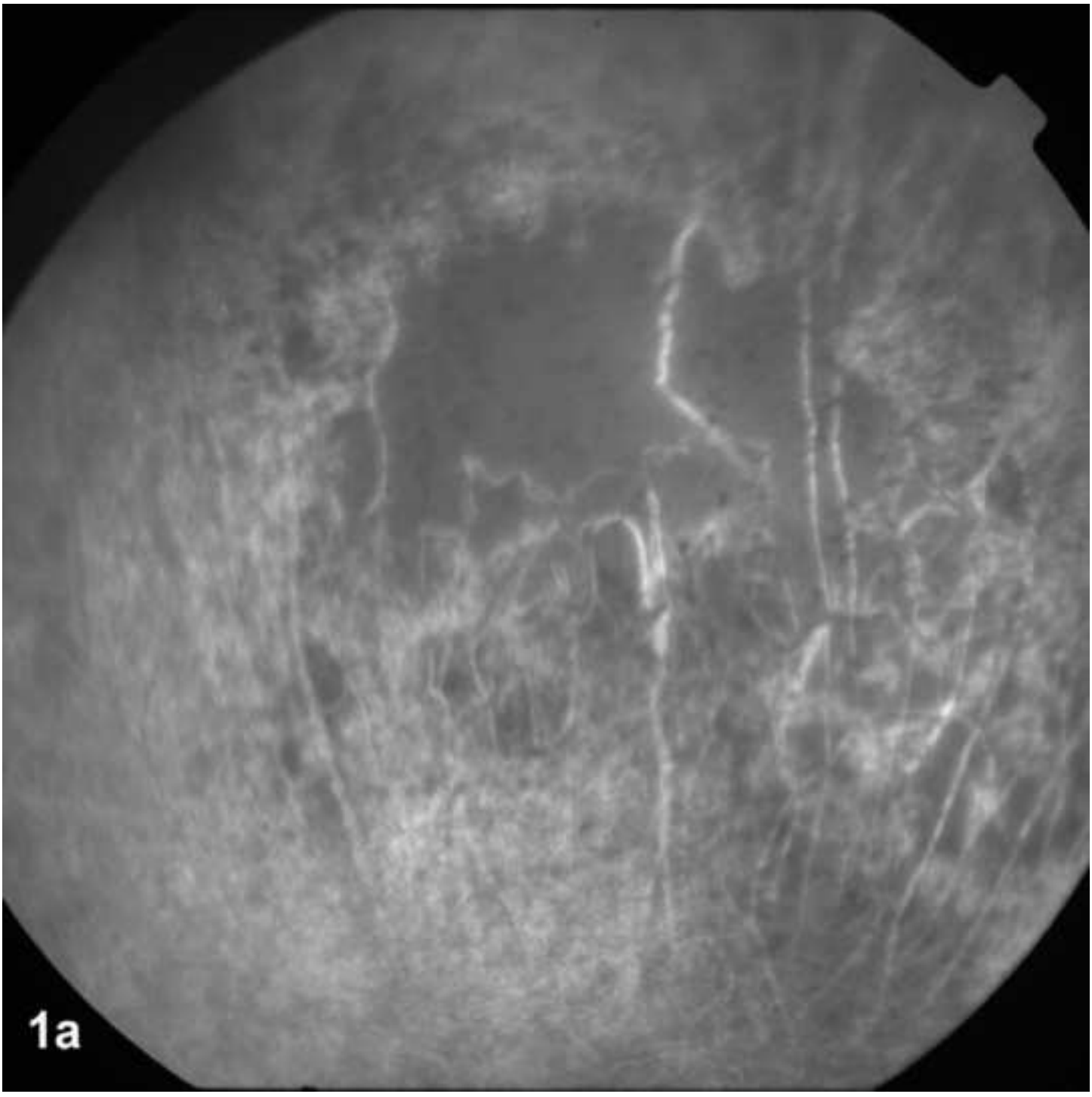

Figure 1B

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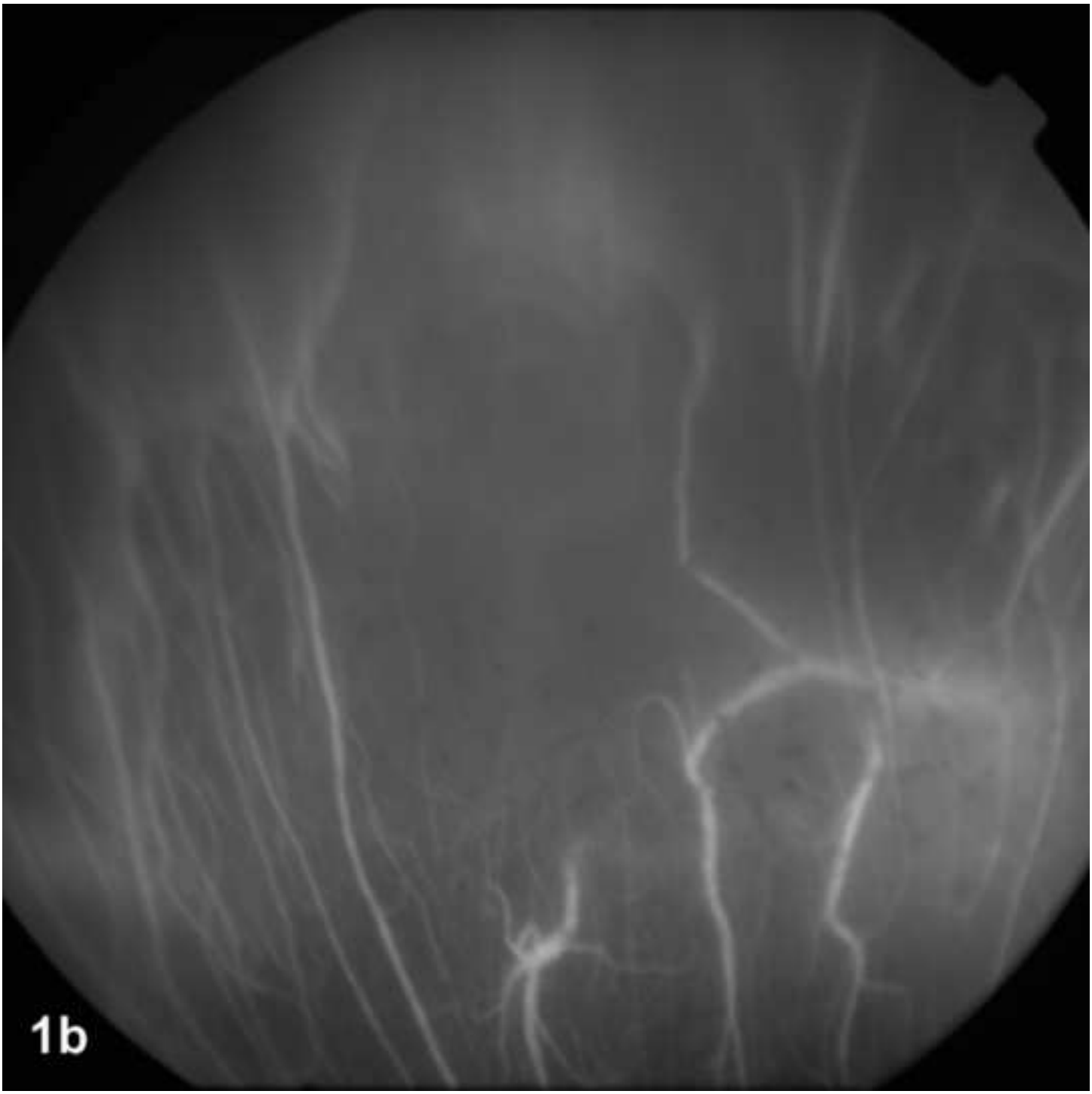

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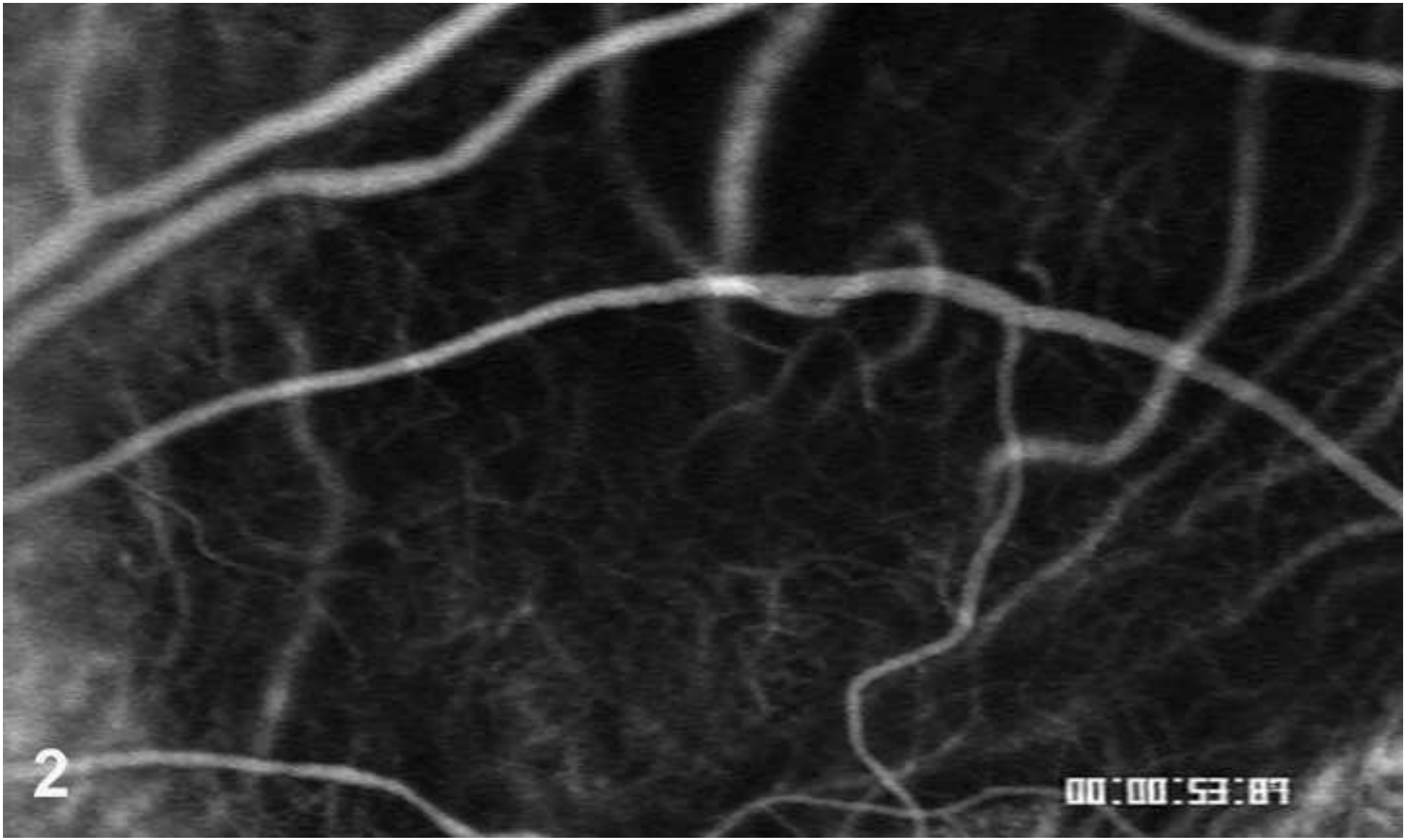

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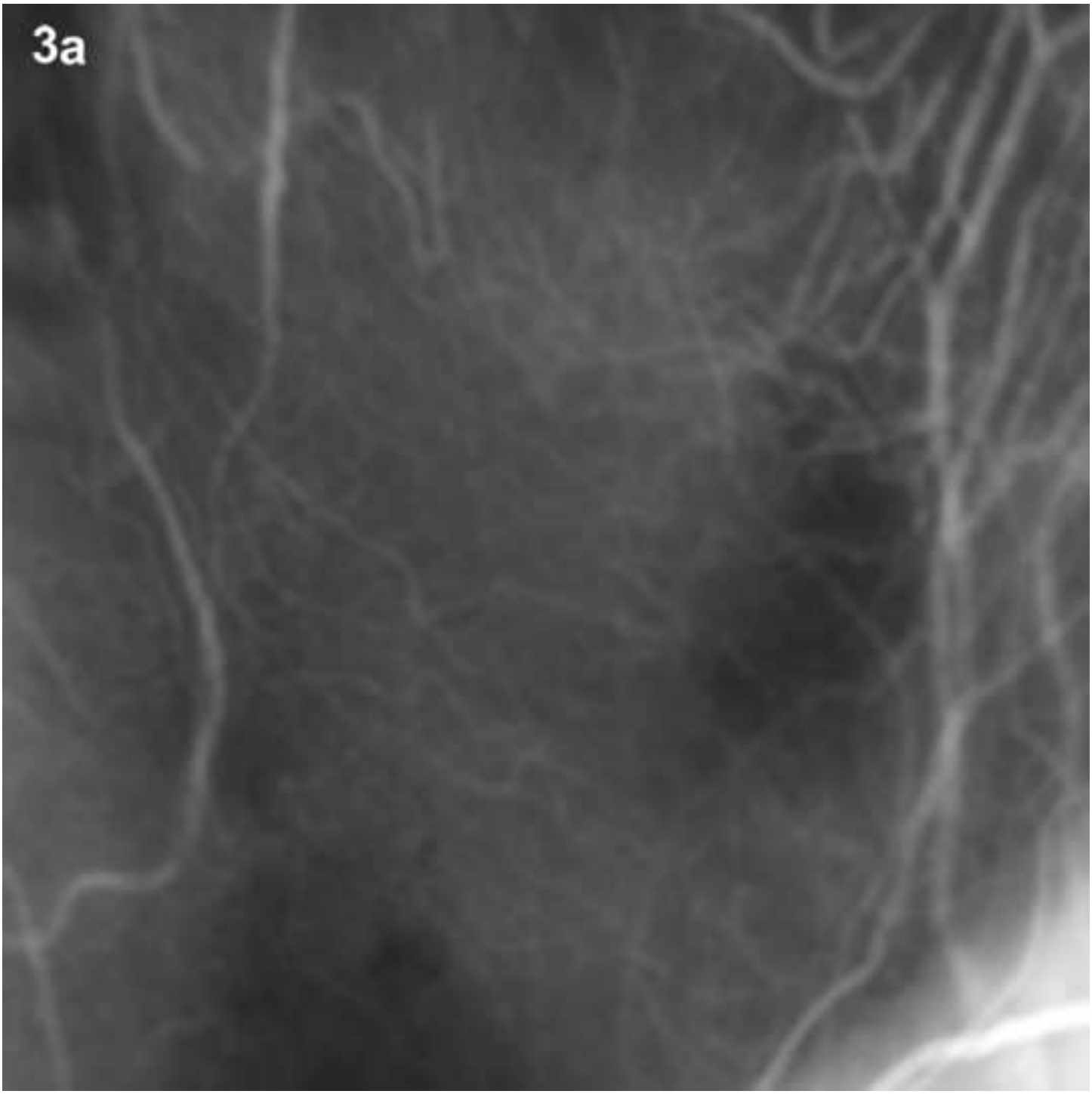

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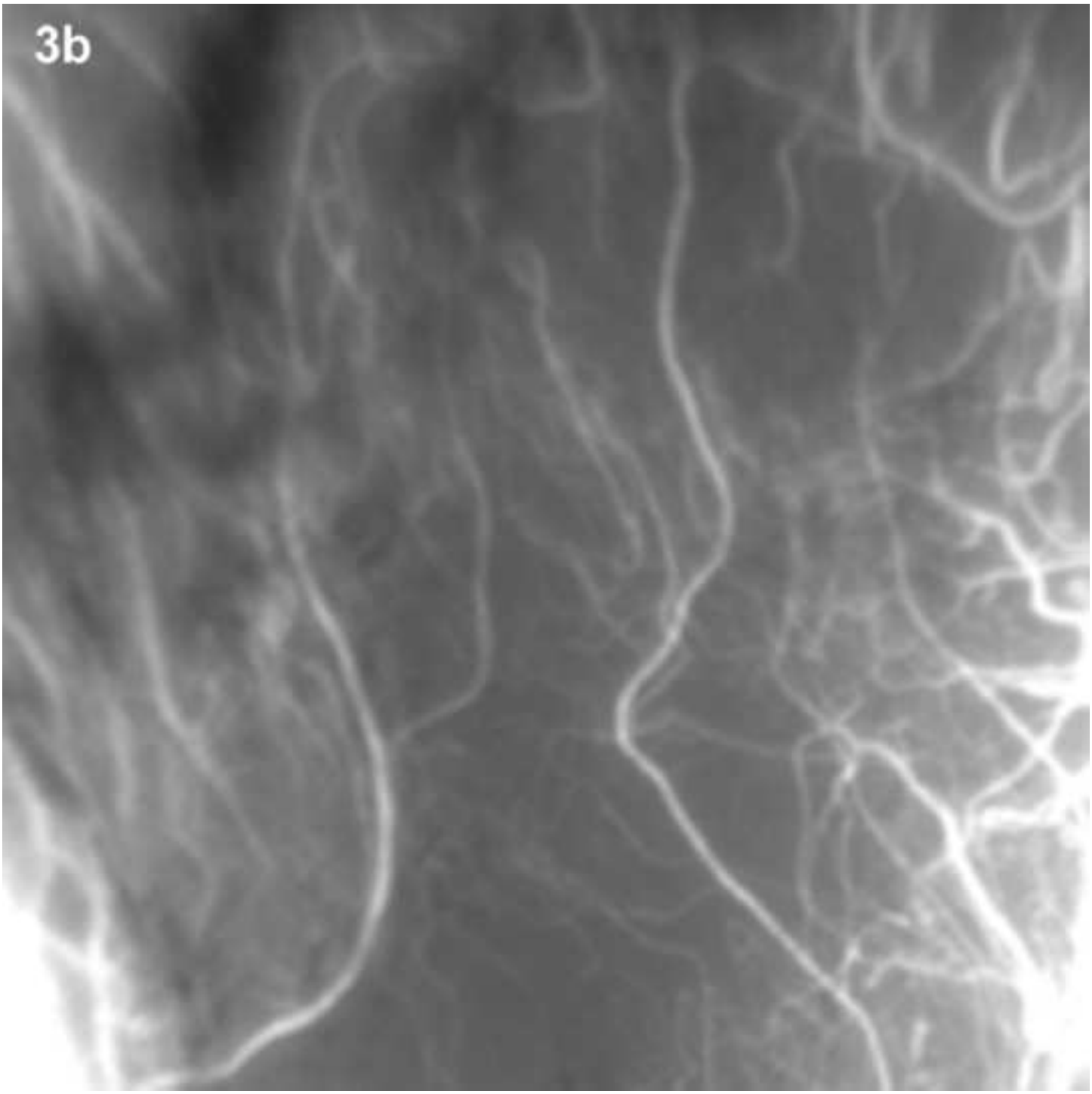

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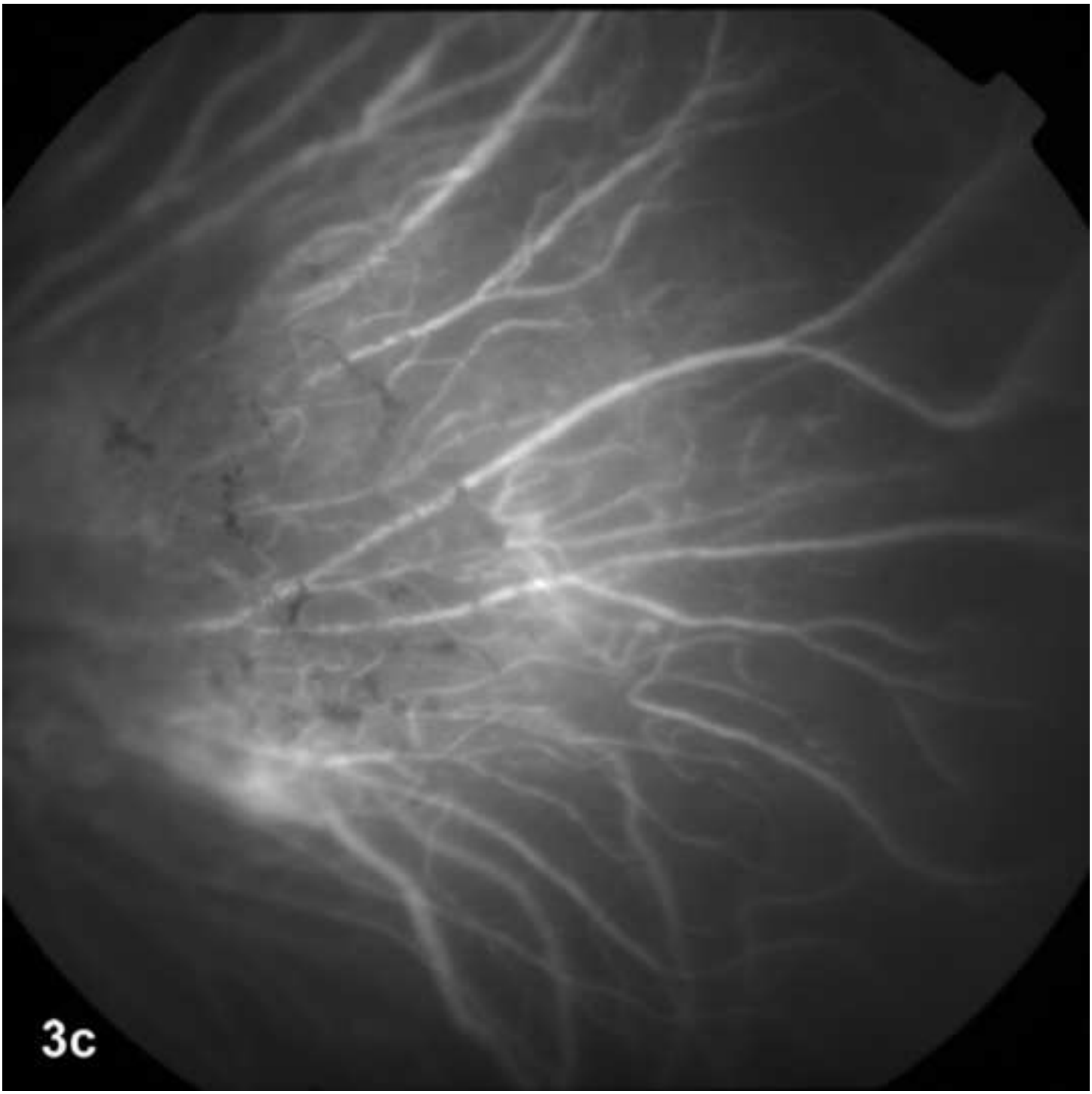

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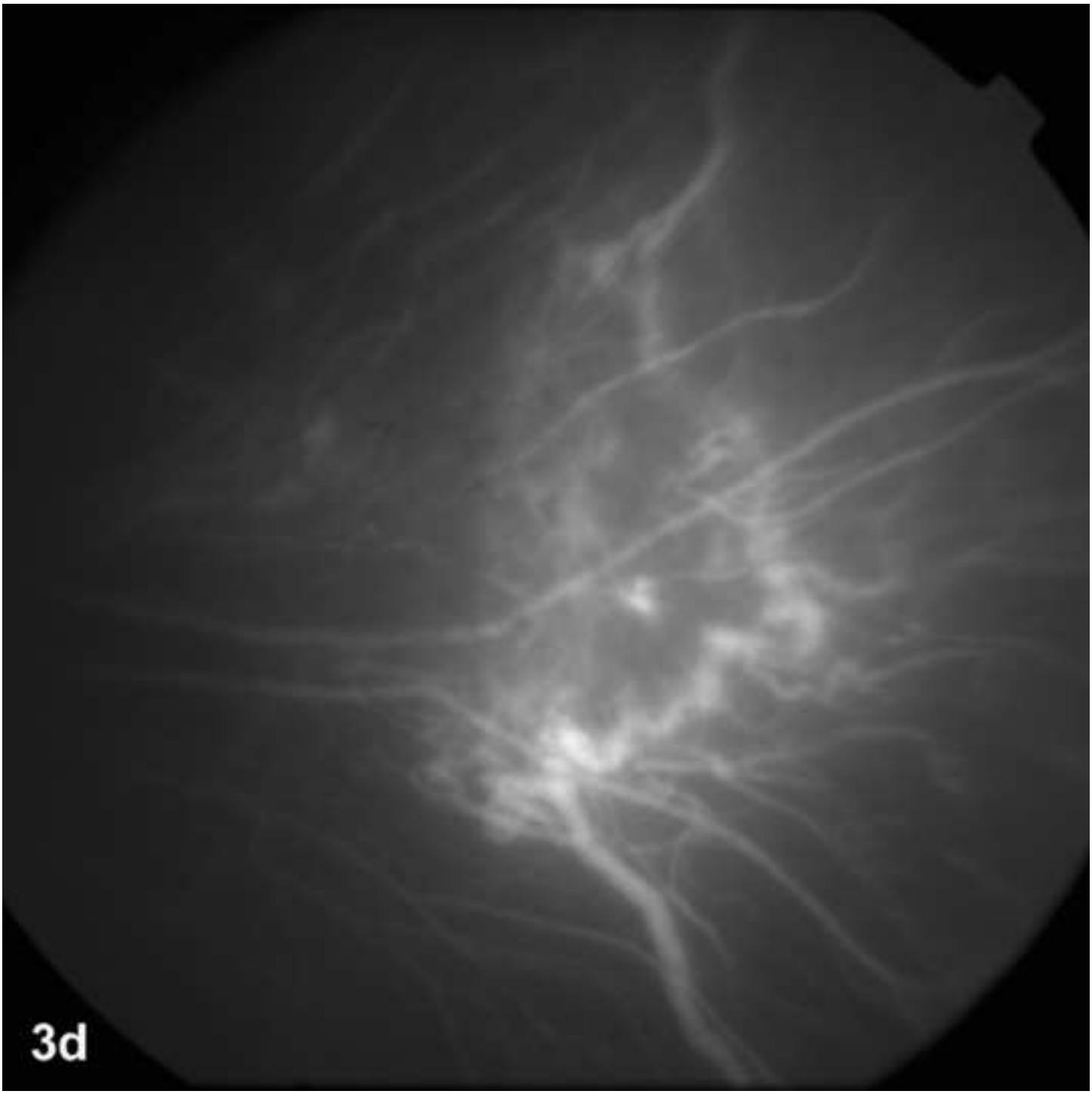

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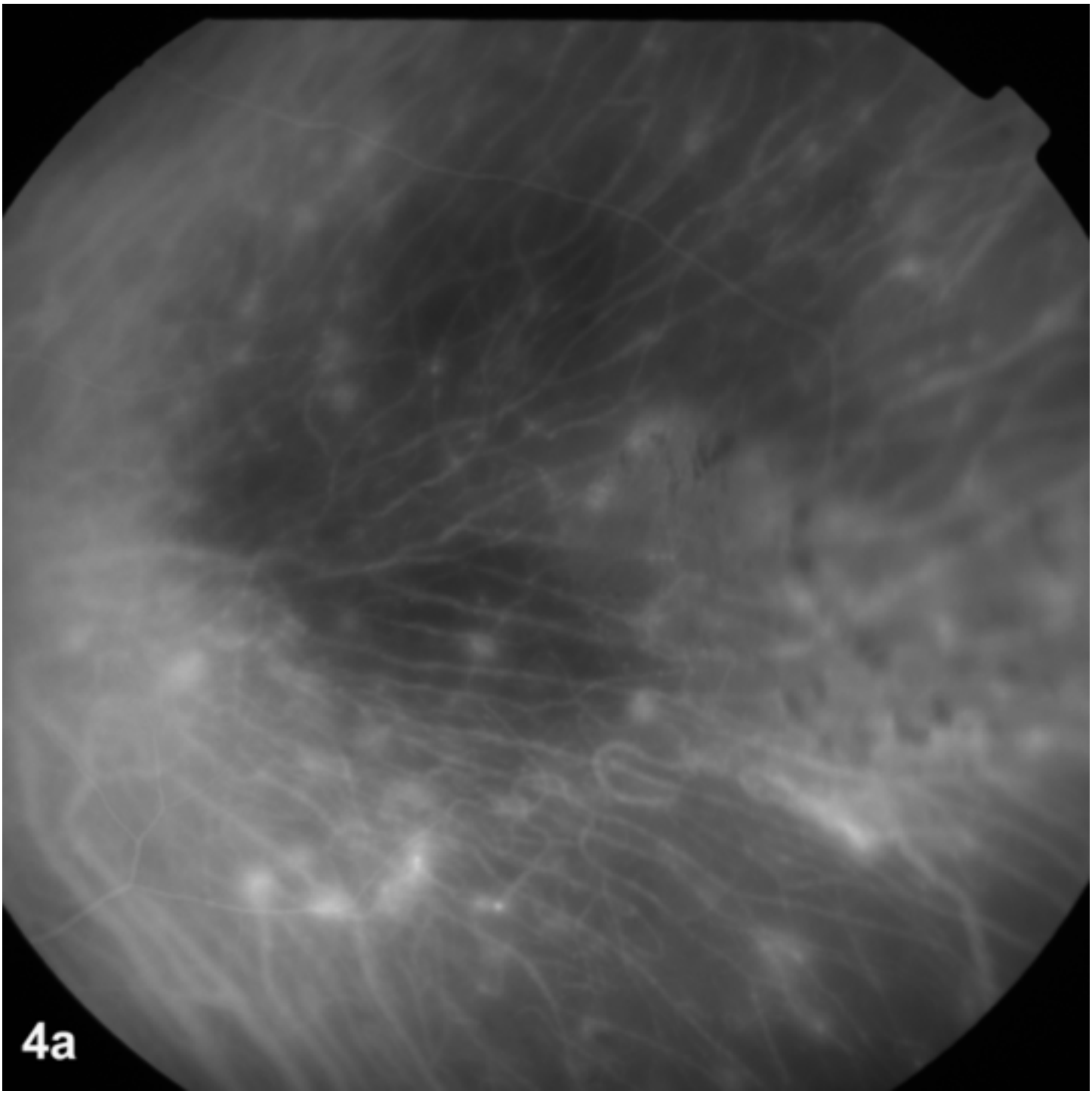

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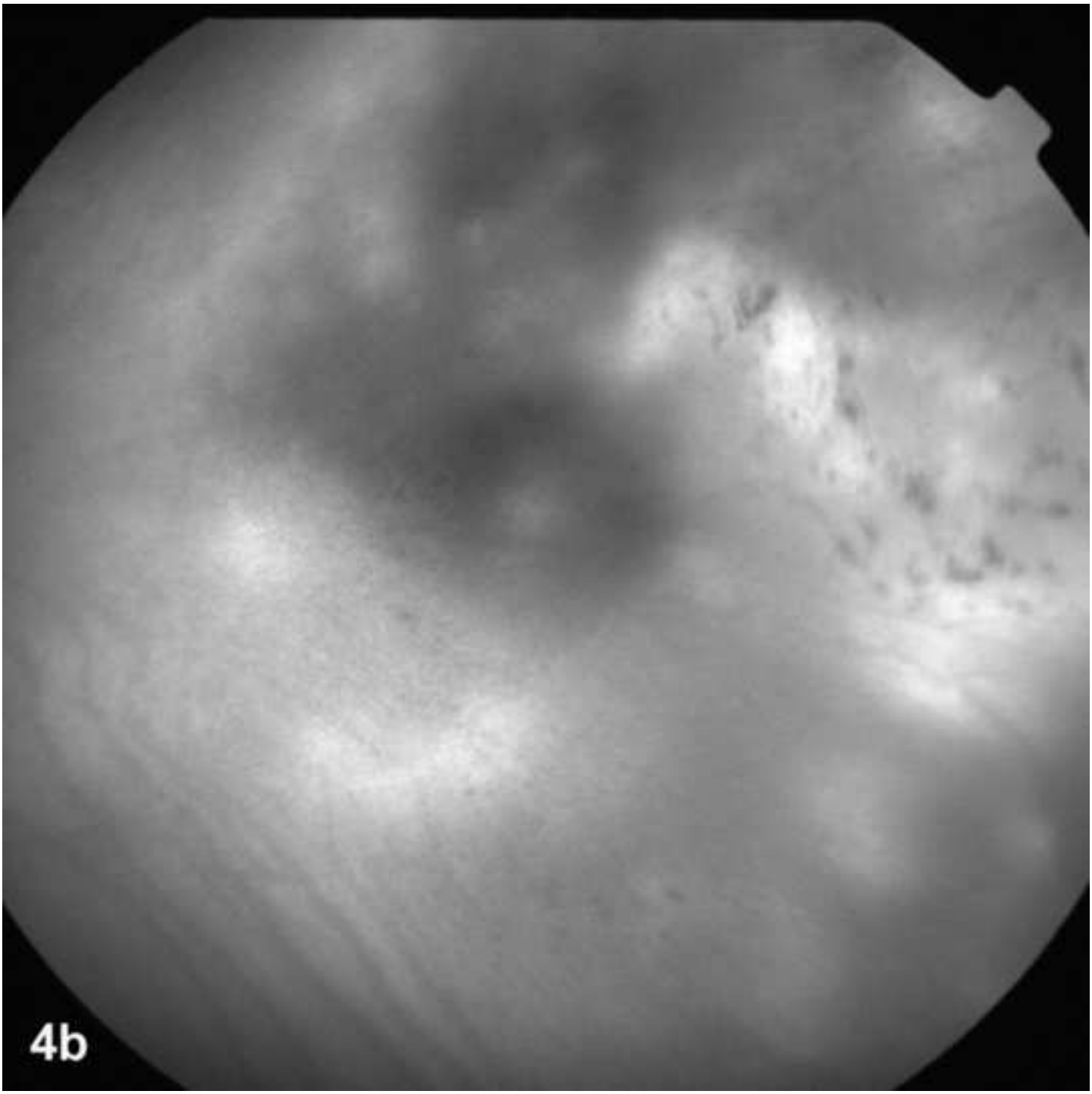

Figure 5A

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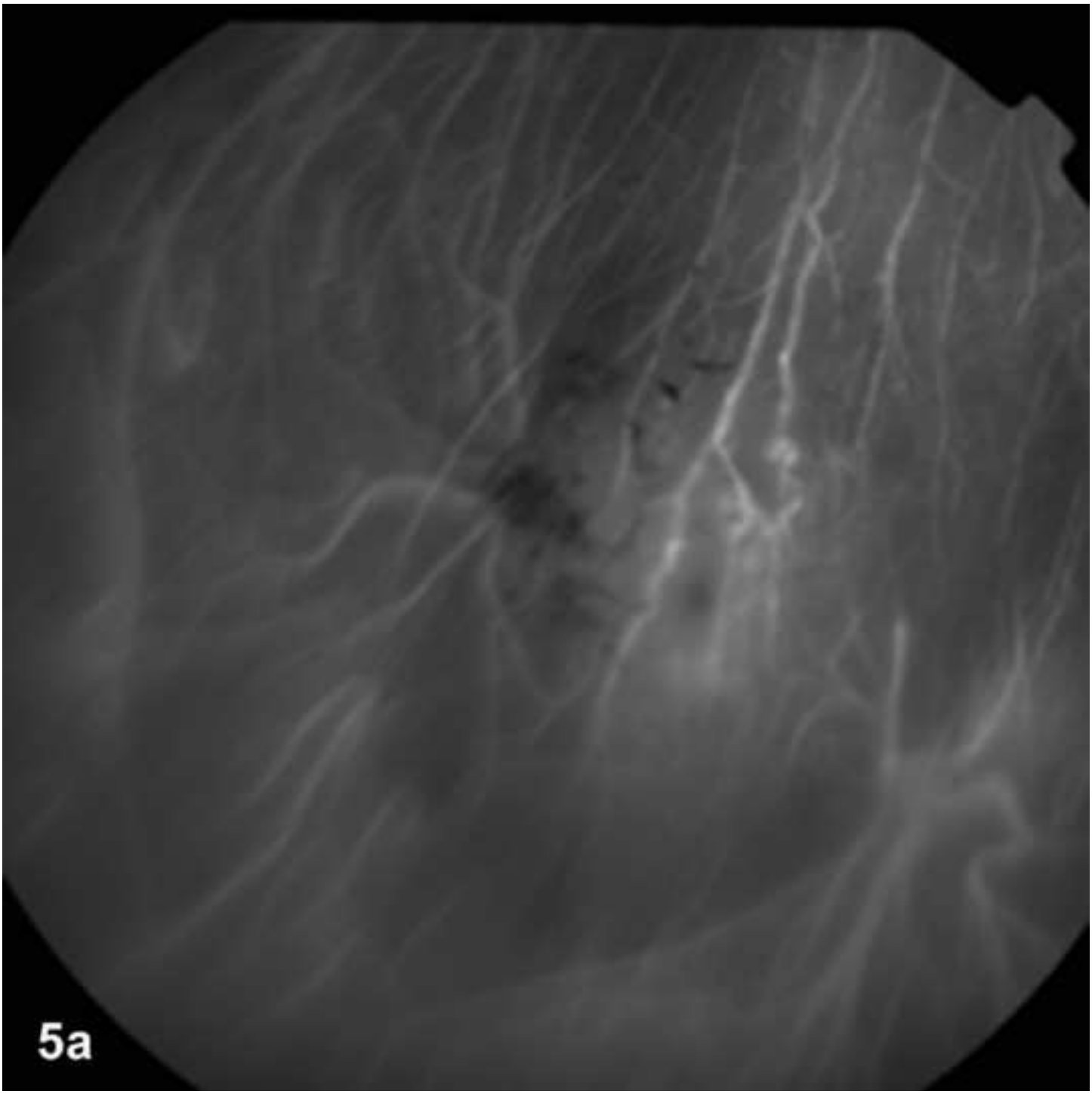

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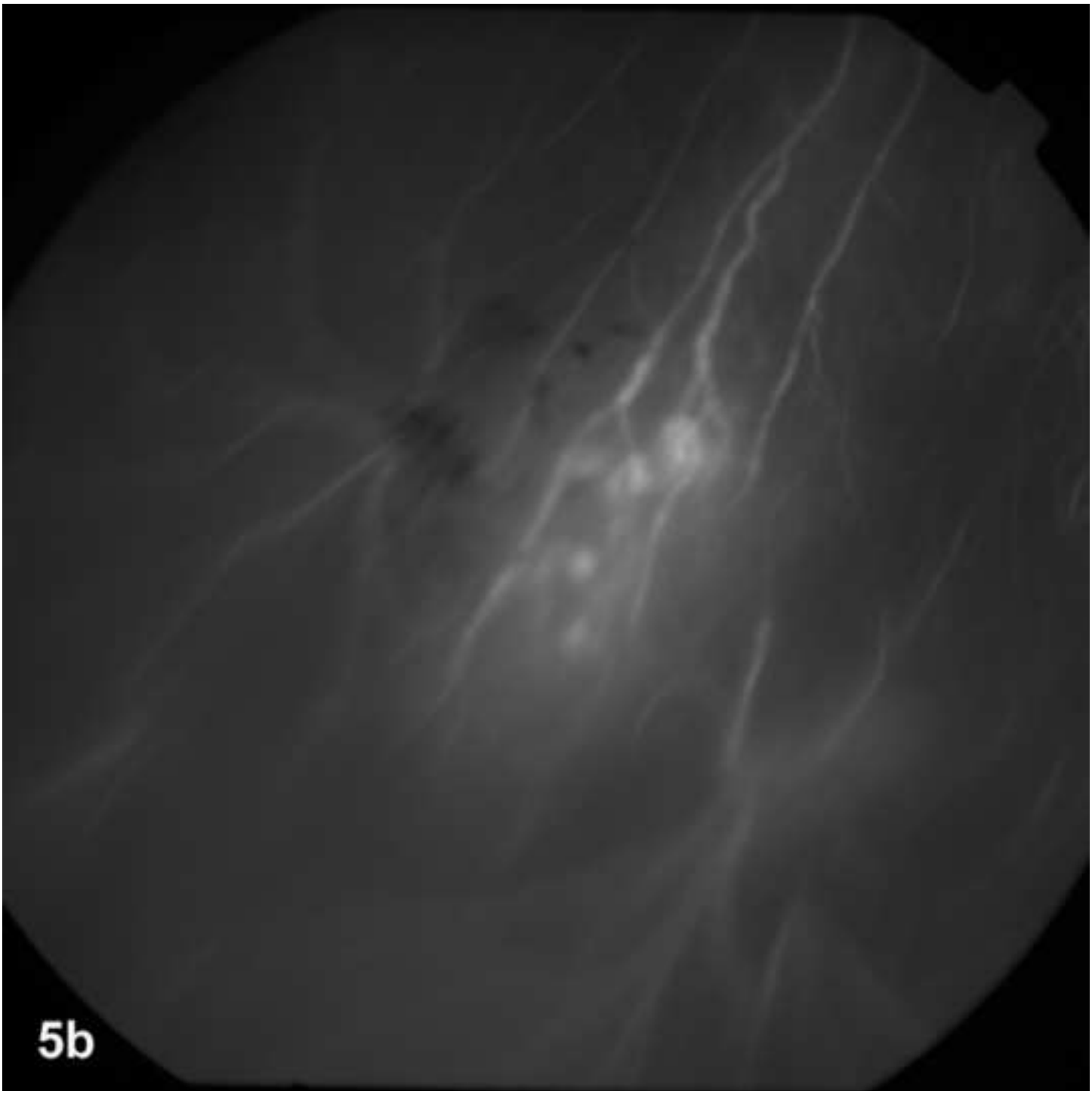

Table 1

Table 1. Comparison of baseline characteristics of 95 patients who were treated for a choroidal melanoma.

Characteristic	**Transpupillary Thermotherapy** (N = 49)	**Iodine-125 Brachytherapy** (N = 46)	**p**
Median Age (SD, range)	65 (13.1, 36-84)	66 (14.4, 35-94)	0.724
Male : Female	23:26	18:28	0.535
Mean tumor diameter (SD, range)	6,0 (2.1, 3-10)	6,7 (1.4, 3.5-10)	0.061
Mean tumor thickness (SD, range)	2.1 (0.7, 1-3.5)	2.3 (0.5, 1.2-3.5)	0.114
Visual Acuity (LogMAR)(SD, range)	0.3 (0.4, 1.3- 0.0)	0.3 (0.4, 1.3-0.0)	1.000
Mean Follow-up (SD, range)	53.5 (15.5, 25-81)	59 (28.1, 24-118)	0.237

Table 2. Retinal vascular changes after TTT and IBT for Choroidal Melanoma detected by Fluorescein Angiography.

Retinal vascular change	**Transpupillary Thermotherapy** (N = 49) **No. of eyes (%)**	**Iodine-125 Brachytherapy** (N = 46) **No. of eyes (%)**
Retinal vascular occlusion	9 (18)	-
Retinal neovascularization	1 (2)	-
Macular edema	9 (18)	9 (17)
Radiation retinopathy	-	10 (22)

Table 3

Table 3. Long-term choroidal vascular changes after TTT vs. IBT for Choroidal Melanoma detected by Indocyanine Green Angiography.

Long-term changes of choroidal circulation	**Transpupillary Thermotherapy** (N = 49) **No. of eyes (%)**	**Iodine-125 Brachytherapy** (N = 46) **No. of eyes (%)**	**p**
Occlusion of choriocapillaris	49 (100)	46 (100)	n.a.
Closure of medium and large choroidal vessels	17 (35)	44 (96)	p<0.0001*
Choroidal vascular remodeling	20 (41)	16 (35)	p=0.693
Retinochoroidal anastomosis	4 (8)	0 (0)	p=0.120
Choroidal vascular wall staining	0 (0)	30 (65)	p<0.0001*
Choroidal aneurismal changes	0 (0)	7 (15)	p=0.015*

*p< 0.05 significant