New Insights in Uveitis and Ocular Inflammatory Disease

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I do not have any financial interests or relationships to disclose.

Financial Disclosure

Learning Objectives

Upon completion of this course the participants should be able to

Explain the methods for identifying cases of drug induced ocular adverse effects

Describe the diagnosis and treatment of new and emerging forms of infectious and non-infectious ocular inflammatory disease.

Suspected Adverse Drug Reactions WHO Causality Assessment : Certain

A clinical event, including laboratory test abnormality

Occurring in a plausible time relationship to drug administration that cannot be explained by concurrent disease or other drugs or chemicals.

Response to withdrawal of the drug (dechallenge) should be clinically plausible.

Event must be definitive pharmacologically or phenomenologically, using satisfactory rechallenge procedure if necessary.

Suspected Adverse Drug Reactions WHO Causality Assessment: Possible

Clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug

Could also be explained by concurrent disease, or other drugs or chemicals, or underlying disease provide plausible explanations.

Suspected Adverse Drug Reactions WHO Causality Assessment: Unlikely

Clinical event, including laboratory test abnormality, with a temporal relationship to drug administration that makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide plausible explanations.

Known uveitis provacateurs

Systemic Drugs

Protease inhibitors

Bisphosphonates

Chlorpromazine

Cidofovir

Oral contraceptives

Diethlycarbamazine

Hydralazine

Ibuprofen

Interleukin 2, 3 and 6

Nitrogen mustard

Procainamide

Qunidine

Rifabutin

Streptokinase

Sulfonamides

Trimethoprim

Topical Ophthalmics

Amphotericin B

Anesthetics

Beta blockers (metipranolol and others)

Brimonidine

Cholinesterase inhibitors

Corticosteroids

Prostaglandin analogues

Mitomycin C

Thiotepa

Adapted from Foster CS, Vitale AT. Diagnosis and Treatment of Uveitis 2002

Known uveitis provacateurs

Intraocular preparations

Anesthetics

Antibiotics

Cidofovir

Urokinase

Air

Perfluorocarbons

Silicone oil

Alpha-chymotrypsin

Vaccines/other

BCG

Influenza

Hepatitis B

PPD

Petty surge sap

Skin tatoos

Adapted from Foster CS, Vitale AT. Diagnosis and Treatment of Uveitis 2002

Case report

A 54 year old woman with chronic sinusitis was treated for an acute exacerbation

amoxicillin clavulonic acid (Augmentin , GlaxoSmithKline, Research Triangle Park NC) 875/125mg bid for 15 days

azithromycin (Zithromax , Pfizer, New York NY) 250mg qd for 5 days.

moxifloxacin 400mg daily for 14 days.

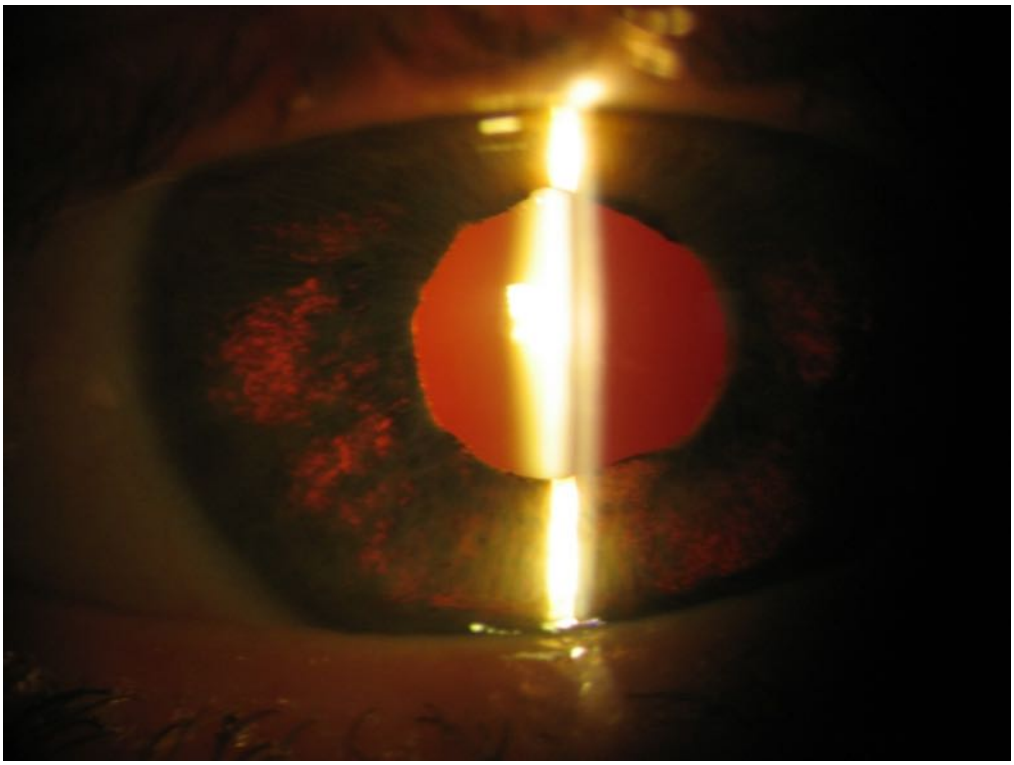
Case report

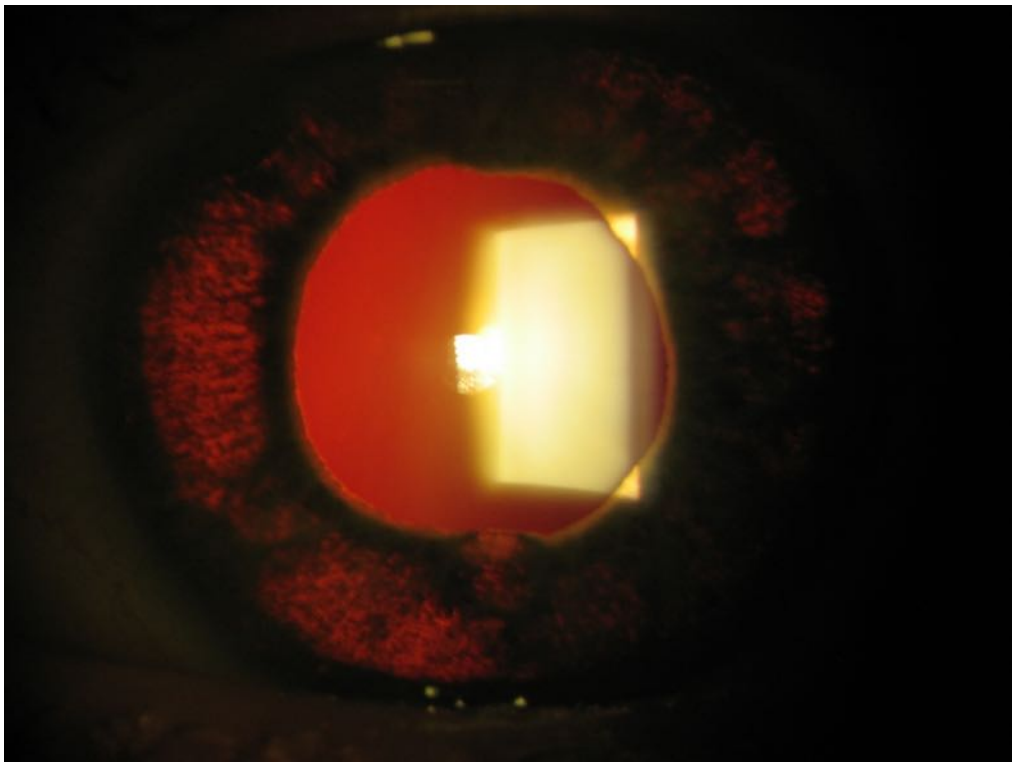
On the thirteenth day of treatment with moxifloxacin she developed bilateral eye pain and redness.

Three days later an ophthalmologist diagnosed bilateral, simultaneous anterior uveitis .

Treatment with topical prednisolone acetate 1% (Falcon, Fort Worth, TX) led to prompt resolution of intraocular inflammation.

Both pupils became poorly responsive to light and accommodation and developed diffuse iris transillumination





Evaluation

An extensive serologic work-up initiated by a uveitis specialist did not reveal a diagnosis .

PCR of aqueous humor from the right eye was negative for HSV, VZV, CMV and EBV.

Clinical Course

Treatment with oral acyclovir (Zovirax, GlaxoSmithKline, Research Triangle Park NC) was initiated for presumptive herpetic uveitis

Photophobia and visual blur persisted despite the use topical pilocarpine (Falcon, Fort Worth, TX).

Outcome

Topical dapiprazole (US Compounding, Conway AR) and dilute pilocarpine obtained from a compounding pharmacy provided symptomatic relief but caused intolerable headaches.

Bilateral cataract surgery was performed for symptomatic posterior subcapsular opacities.

A uveitis flare developed in the right eye despite peri -operative oral prednisone.

2004: Single case report: anterior uveitis and pigment dispersion

2009: Five additional cases

Eye (2009) 23, 2260–2262

www.nature.com/eye

CASE SERIES

Uveitis-like syndrome and iris transillumination after the use of oral moxifloxacin

M Wefers Bettink-Remeijer[1,4], K Brouwers[2,4], L van Langenhove[2], PWT De Waard[1], TO Missotten[1], JP Martinez Ciriano[1] and E Van Aken[3]

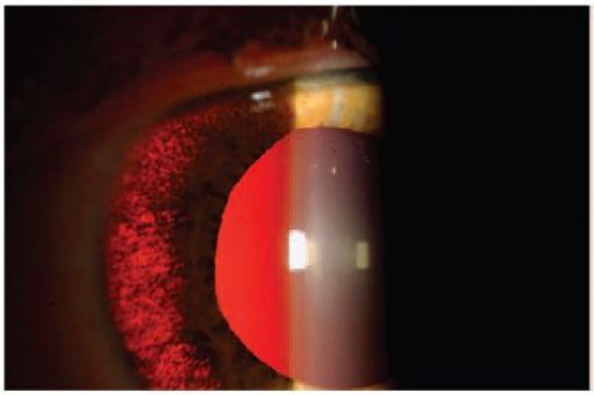


Figure 1 Patient 1.

Gonioscopy showed normal findings with mild pigmentation of the trabecular meshwork. Aqueous taps were performed, and were positive for herpes simplex genome only in the patient who had a former history of uveitis.

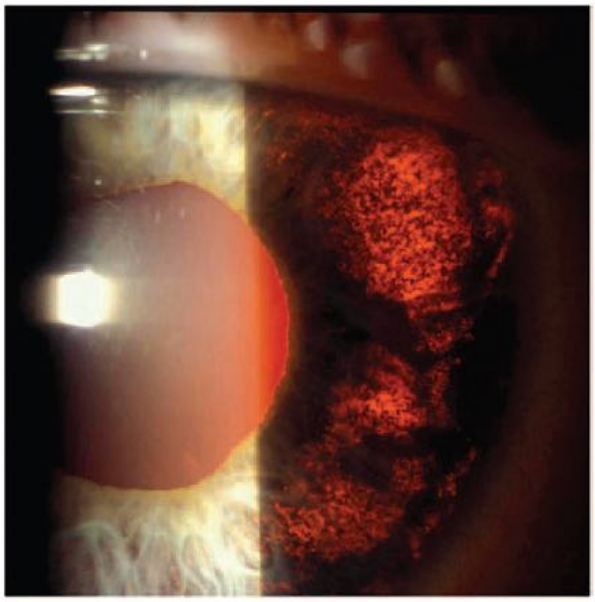


Figure 2 Patient 4.

Table 1 Signs and symptoms

Patient	*1*	*2*	*3*	*4*	*5*
Age and gender	56-year-old male	32-year-old female	59-year-old female	42-year-old female	74-year-old
Start of symptoms after use oral moxifloxacin (days)	8–11	10	14	10	12
Presenting symptoms	Accommodation problems, photophobia, pain	Photophobia, pain	Photophobia, pain	Photophobia, pain	Hyperemia pain
Pupil slitlamp examination	Mydriasis	Mydriasis	Mydriasis	Mydriasis	Miosis →n
Inflammatory signs	None[a]	None[a]	None[a]	Bilateral tyndall +, pigmentary cells, endothelial dusting	Bilateral ty posterior s endothelial
Iris transillumination	Severe	Severe	Severe	Severe	Moderate
Pigmentation at gonioscopy	Normal	Normal	Normal	Normal	Normal
Fundoscopy	Normal	Normal	Normal	Normal	Normal
Previous episode of uveitis	No	Yes	No	No	No
HSV aqueous humour	−	+	−	−	Not perfor

[a]In patients 1–3, interval between the start of symptoms and examination in our clinic was >4 weeks.

Eye 2009;23:2260-2262.

Patient	Gender	Age at onset	HLA-B haplotypes	Days between exposure and uveitis onset	Prior exposure to oral moxifloxacin	Aqueous PCR analysis	Prior history of uveitis
1	female	54	44/51	13	No	Negative	No
2	female	44	13/51	7-14	No	Negative	No
3	male	27	35/51	15	Yes	N/A	No
4	female	73	38/50	7-14	No	N/A	No
5	female	53	27 /unknown	7-14	No	N/A	No
6	female	42	unknown	uncertain	unknown	N/A	No
7	female	60	unknown	7	No	N/A	No
8	female	22	13/35	15	No	N/A	No
9	female	42	18/57	14	No	N/A	No
10	female	70	51/55	12	No	N/A	No

Moxifloxacin (Avelox , Bayer, Wayne NJ)

Fluoroquinolone antibiotic indicated for the treatment of

acute bacterial exacerbation of chronic bronchitis

complicated intra-abdominal abcess

community-acquired pneumonia

acute bacterial sinusitis

uncomplicated bacterial skin infections.

Orally administered moxifloxacin crosses the blood ocular barrier in non-inflamed eyes

Achieves plasma, aqueous and vitreous concentrations >MIC 90 within 4 hours.

Hariprasad SM, et al. Arch Ophthalmol 2006;124:178-82.

Phototoxicity , a class effect of fluoroquinolones, is uncommon with moxifloxacin

May be involved in the pathogenesis of iris atrophy, although absence of associated dermal toxicitiy in reported cases suggests another mechanism.

Iris changes have not been reported in intravitreal toxicity studies during the 14 days following injection of doses up to 320 micrograms.

Avdin E, et al. Retina 2006;26:187-90.

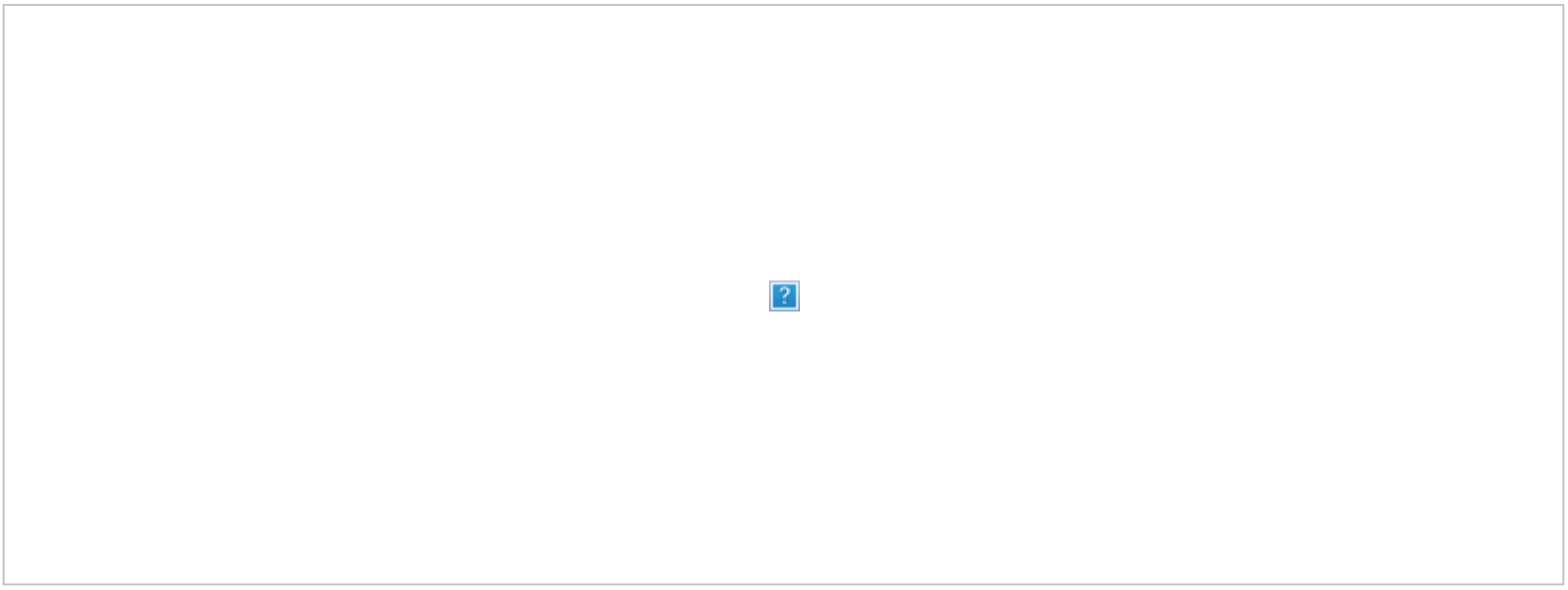
Is phototoxicity to blame?

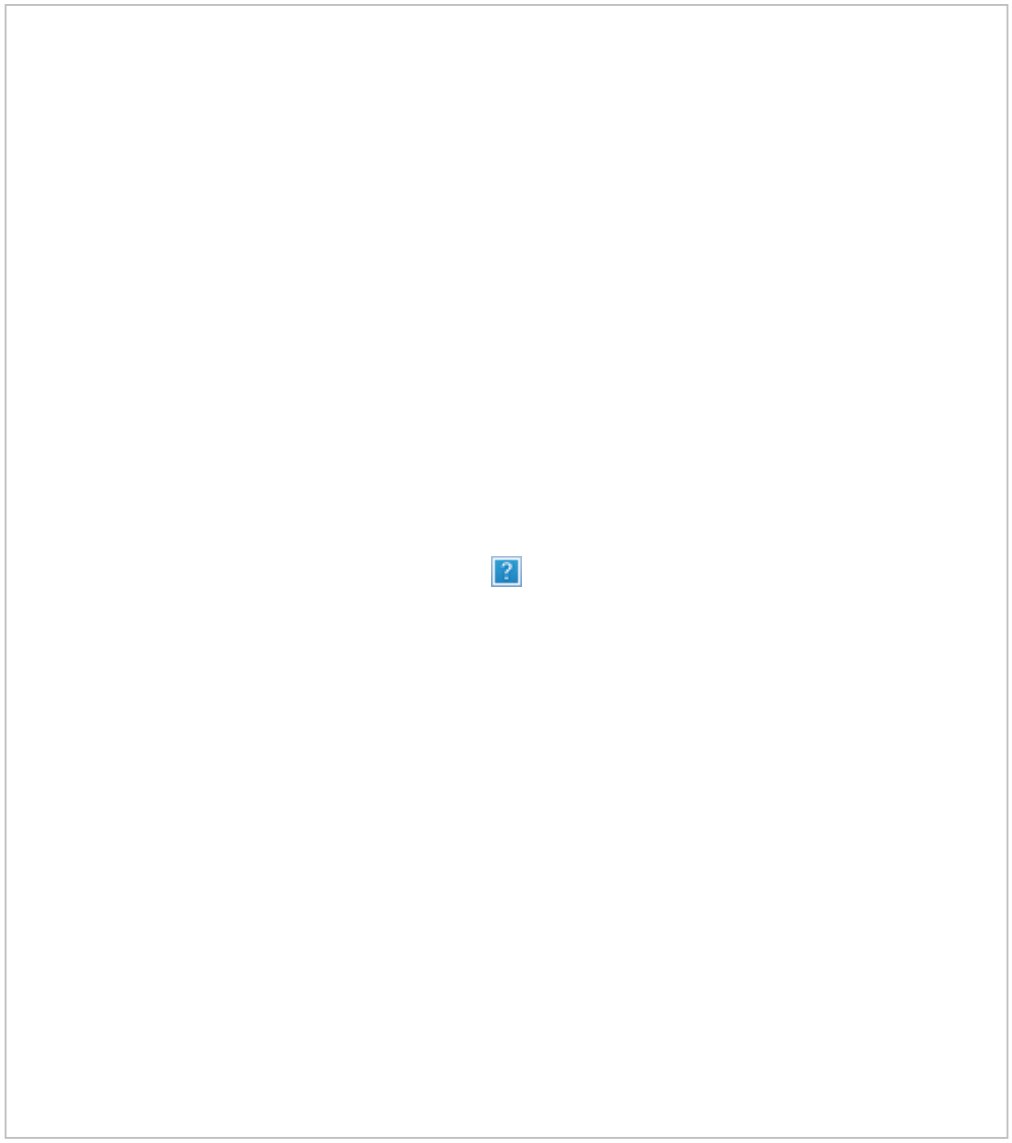
We observed

Preponderance of affected females (90%)

HLA-B51 haplotype in 44% of the individuals which were tested.

Suggest autoimmune predisposition.





7 patients (38%) did not receive antibiotics

Emerging respiratory virus proposed as causative agent

19/26 patients (62%) received antibiotics

35% moxifloxacin

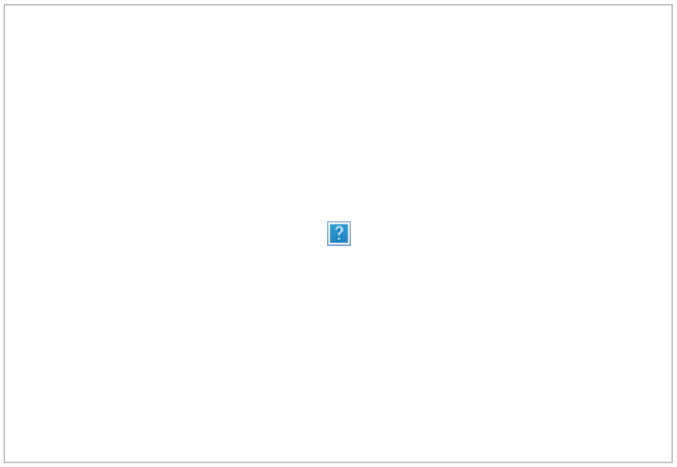
8% amoxicillin–clavulanate

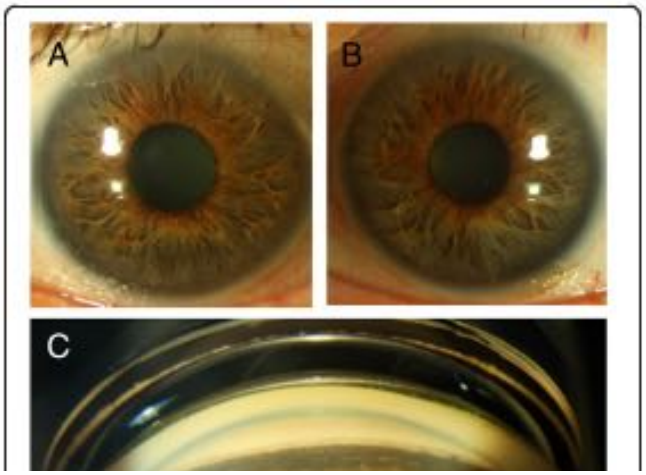
8% trimethoprim–sulfa

4% cefixime

4% penicillin V

3 patients could not recall antibiotic name




A
B
C

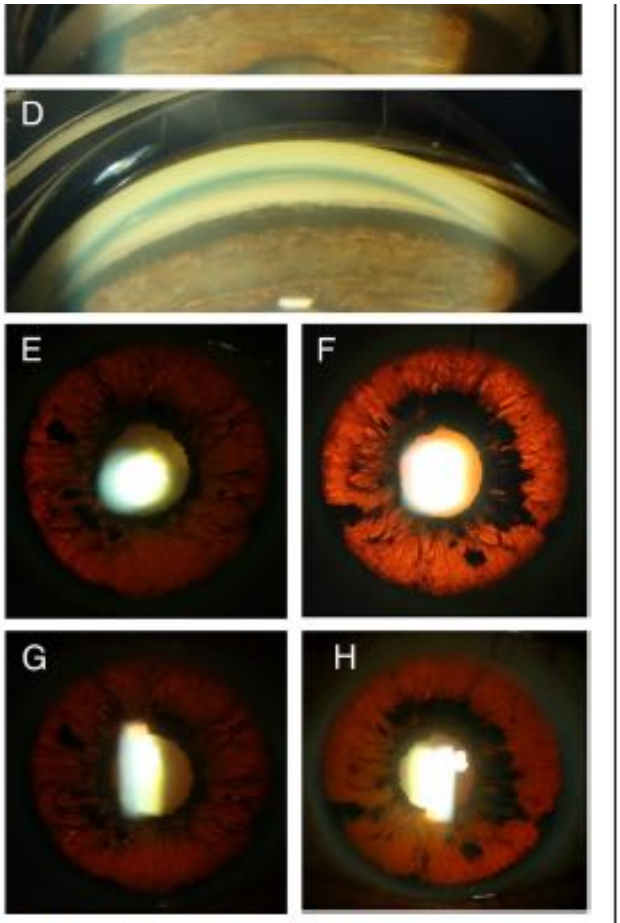


Figure 1 Clinical presentation of the anterior segment. Pigmented cells in the anterior chamber with deposition of a pigmented 'wreath' on the corneal endothelium adjacent to the limbus are seen in the right (**A**) and left (**B**) eyes. Gonioscopy shows pigment anterior to Schwalbe's line and extending on to the peripheral iris in the right (**C**) and left (**D**) eyes. Transillumination defects noted at presentation in the right (**E**) and left (**F**) eyes were stable 2 weeks later in the right (**G**) and left (**H**) eyes.

Methods

Mass spectrometry quantified the aqueous concentration of moxifloxacin in an affected individual.

Multiple reaction monitoring mass spectrometry yielded the peptide profile in the affected individual and unaffected control samples.

Universal Protein Resource (UniProt) human database was employed for peptide identification.

Calibration curve for both transition ions of moxifloxacin determined from response in matrix.

Ion	R 2	SD of y	LOD (ng)	LOQ (ng)
358.00	0.98	51.42	25.83	86.11
384.00	0.97	63.29	12.34	41.13

Results

Sample	Ion	Role	calculated concentration injected (ng/µL)	concentration of moxifloxacin in sample (ng/µL)
OD	358	Quantitation	268.32	44.72
OD	384	Confirmation	20.73	below LOQ
OS	358	Quantitation	101.33	93.82
OS	384	Confirmation	27.38	below LOQ

Aqueous Proteome

Albumin

Serotransferrin

Alpha-1-antitrypsin

Ig gamma-1 chain C region

Prostaglandin-H2 D-isomerase

Transthyretin

Ig kappa chain C region

Alpha-1-acid glycoprotein 1

Hemopexin

Ig lambda-2 chain C regions

Complement component C4B

Pigment epithelium-derived factor

Vitamin D-binding protein

Ceruloplasmin

Alpha-1B-glycoprotein

Isoform 2 of Clusterin

Apolipoprotein A-I

F-box/SPRY domain-containing protein 1

Zinc-alpha-2-glycoprotein

Hemoglobin subunit beta

Alpha-1-antichymotrypsin His-Pro-less

Retinol-binding protein 3

Complement C3

Ig gamma-2 chain C region

Ig gamma-4 chain C region

Apolipoprotein A-II

Haptoglobin

Alpha-2-HS-glycoprotein chain A

Antithrombin -III

Ig gamma-3 chain C region

Gelsolin

Protein shisa-7

Dickkopf -related protein 3

Aqueous proteins reduced significantly by ANOVA in the patient samples compared to the control

Identified Proteins	Accession Number	ANOVA Test (P-Value)
Ig gamma-1 chain C region	IGHG1_HUMAN	0.022
Retinol-binding protein 3	RET3_HUMAN	0.016
Serotransferrin	TRFE_HUMAN	0.011
Prostaglandin-H2 D-isomerase	PTGDS_HUMAN	0.0028
Ig gamma-3 chain C region	IGHG3_HUMAN	0.0027
Ceruloplasmin	CERU_HUMAN	0.0014
Pigment epithelium-derived factor	PEDF_HUMAN	0.00053
Hemoglobin subunit beta	HBB_HUMAN	0.000059
Ig gamma-4 chain C region	IGHG4_HUMAN	0.00004
Ig gamma-2 chain C region	IGHG2_HUMAN	0.0000056

Discussion

Intraocular moxifloxacin is advocated for prophylaxis and treatment of endophthalmitis

No reports of this complication associated with intravitreal use to date.

Unlikely given rapid clearance of intravitreal moxifloxacin with undetectable levels within 12 hours.

Iyer MN, et al. Trans Am Opthalmolol Soc 2005;103:76-81.

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Aqueous humor tyrosinase activity is indicative of iris melanocyte toxicity

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ABSTRACT

Antibiotics such as fluoroquinolones (FQLs) are commonly used to treat ocular infections but are also known to cause dermal melanocyte toxicity. The release of dispersed pigments from the iris into the aqueous humor has been considered a possible ocular side effect of the systemic administration of FQLs such as Moxifloxacin, and this condition is known as bilateral acute iris transillumination (BAIT). Bilateral acute depigmentation of iris (BADI) is a similar condition, with iris pigment released into the aqueous, but it has not been reported as a side effect of FQL. Iris pigments are synthesized by the melanogenic enzyme tyrosinase (TYR) and can be detected but not quantified by using slit-lamp biomicroscopy. The correlation between dispersed pigments in the aqueous and the extent of melanocyte toxicity due to topical antibiotics in vivo is not well studied. Here, we aimed to study the effect of topical FQLs on iris tissue, the pigment release in the aqueous humor and the development of clinically evident iris atrophic changes. We evaluated this process by measuring the activity of TYR in the aqueous humor of 82 healthy eyes undergoing cataract surgery following topical application of FQLs such as Moxifloxacin (27 eyes, preservative-free) or Ciprofloxacin (29 eyes, with preservative) or the application of non-FQL Tobramycin (26 eyes, with preservative) as a control. In addition, the patients were questioned and examined for ocular side effects in pre- and post-operative periods. Our data showed a significantly higher mean TYR activity in the aqueous humor of Ciprofloxacin-treated eyes compared to Moxifloxacin- (preservative free, $p < 0.0001$) or Tobramycin-treated eyes ($p < 0.0001$), which indicated that few quinolones under certain conditions are toxic to the iris melanocytes. However, the reduced TYR activity in the aqueous of Moxifloxacin-treated eyes was possibly due to the presence of a higher drug concentration, which inhibits TYR activity. Consistently, immunoblotting analysis of the aqueous humor from both Ciprofloxacin- and Moxifloxacin-treated eyes showed the presence of soluble TYR enzyme, thus reflecting its toxicity to iris melanocytes and corresponding to its activity in the aqueous humor. Intriguingly, none of these patients developed any clinically appreciable ocular side

	0.008	0.108	0.008
	0.008	0.093	0.008
	0.008	0.081	0.008
	0.008	0.067	0.008
	0.008	0.049	
		0.039	
		0.030	
0.021±0.0002 U	0.016±0.004 U	0.134±0.009 U	0.063±0.012 U

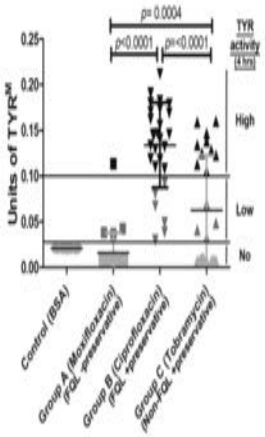


Fig. 2. Plot diagram showing the activity of TYR in aqueous humor samples. Aqueous TYR activity was measured at 4 h in all patients from Groups A, B and C along with the control BSA. Each data point represents the average activity of duplicate or triplicate samples. Aqueous TYR activity above the BSA level is indicative of the presence of TYR. Likewise, TYR activity below the BSA level represents either the absence of TYR enzyme or its lack of activity in the aqueous. Within the group, a few samples cluster together and show more than 0.1 U of TYR^M, which specifies the presence of high TYR enzyme in the aqueous, possibly corresponding to high iris melanocyte toxicity. Statistical value $p < 0.05$ = *; $p < 0.01$ = ** and $p < 0.001$ = ***.

samples. Detection of TYR protein in the aqueous samples by immunoblotting identified a unique band corresponding to a size above 50 kDa in samples from both Groups A and B (Fig. 4A). Consistently, the TCA precipitated aqueous lysates also showed similar results (Fig. 4A). In contrast, the mouse melanocyte lysate that was used as a positive control highlighted a TYR band of the expected size, above 75 kDa (Jani et al., 2015). However, the ~50 kDa band was completely absent in the negative controls, such as TYR^M and BSA (Fig. 4B), indicating that the observed band in the aqueous is specific to TYR. In line with these results, keratinocyte and HeLa cell lysates (human) showed non-specific bands (below or above ~ 50 kDa) with the anti-TYR antibody (Fig. 4B). These results clearly detected the presence of an altered isoform of TYR (size ~50 kDa) in the aqueous humor of fluoroquinolone-treated eyes. We predict that this TYR isoform corresponds to the soluble TYR identified in the cell extracts of bovine eyes (Wittbjer et al., 1990b). Nevertheless, the characterization of aqueous TYR requires future investigation using mass spectrometry.

4. Discussion

Dermal phototoxicity, cardiotoxicity, arthropathy and tendinitis are known adverse reactions to systemic FQL usage (De Sarro and De Sarro, 2001). Likewise, dispersed pigments, which are the characteristic feature of BAIT and BADI (Tugal-Tutkun et al., 2011), could be a possible phototoxic effect of FQLs on iris melanocytes or

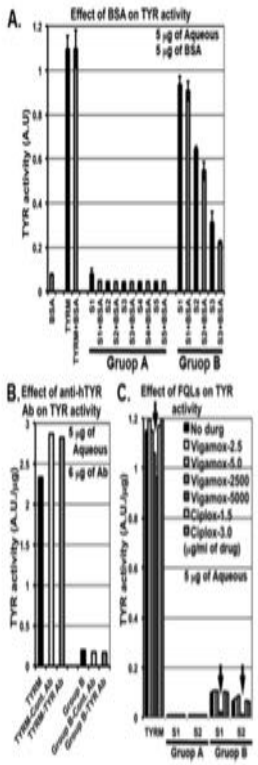


Fig. 3. Plot diagrams showing the effect of non-specific protein, anti-human TYR antibody or FQLs on TYR activity in aqueous humor samples. Aqueous TYR activity was measured at 4 h in a few samples (S) of Group A (S1 – S5) and Group B (S1 – S3) before and after the addition of 5 µg of BSA (A). TYR^M (TYRM) and BSA were used as controls. Note that TYR activity was not affected in Group A samples or TYR^M, but slightly declined in Group B samples after the addition of 5 µg of BSA, indicating either a sequestration of the aqueous TYR enzyme or a reduction of the conversion of L-DOPA into melanins by BSA. Similarly, TYR activity in Group B samples and TYR^M was measured before and after the addition of either control rabbit antibody (Ab) serum or anti-human TYR antibody serum (6 µg of serum) (B). Note that neither control serum nor anti-TYR Ab showed an effect on TYR activity. Likewise, TYR activity in Group A, B samples (S1, S2 each) and TYR^M was measured before and after addition of the indicated antibiotics at µg/ml concentration (C). Arrows indicate the reduced TYR activity observed in samples with 2500 or 5000 µg/ml of Vigamox (Moxifloxacin) added including TYR^M. In all graphs, TYR activity values are presented as arbitrary units (A.U.) or per µg of sample.

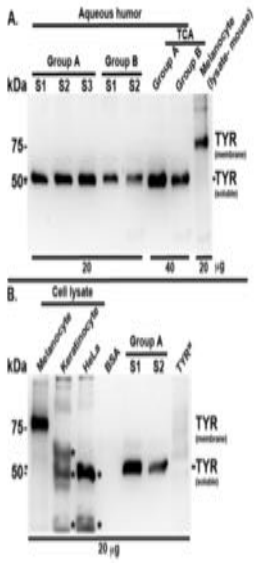
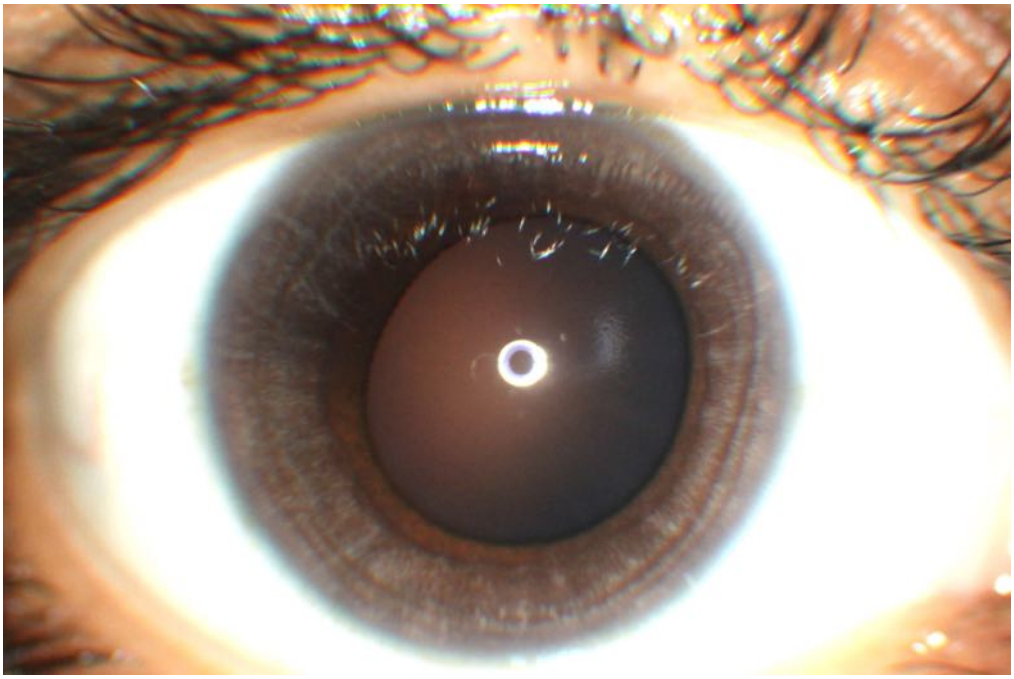


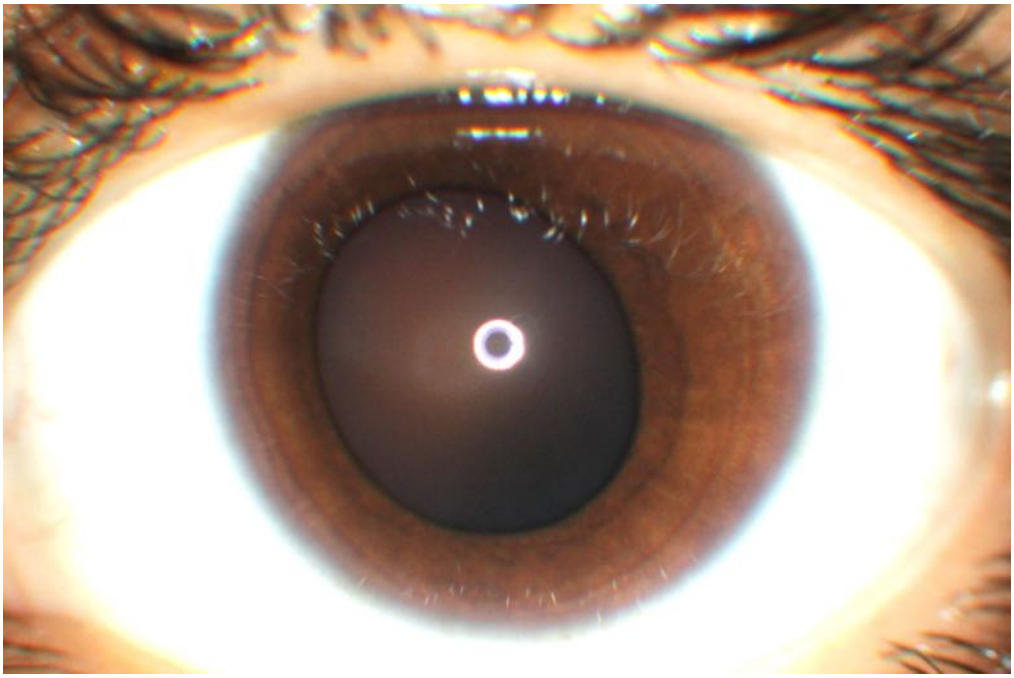
Fig. 4. Immunoblots representing the detection of soluble TYR in aqueous humor. Samples equivalent to 20 or 40 µg from Group A (S1 – S3), Group B (S1, S2) and TCA precipitated aqueous from Groups A and B were fractionated, immunoblotted and probed with anti-human TYR antibody. Mouse melanocyte lysate was used as a positive control. Note that the anti-TYR antibody detected ~75 kDa band in mouse melanocyte lysate that corresponds to the melanosome bound TYR and ~50 kDa band in all aqueous humor samples, possibly corresponding to soluble TYR, as observed in bovine eye extracts (Wittjes et al., 1980b). The specificity of the ~50 kDa band in the aqueous humor was tested by repeating the immunoblotting experiment using cell extracts from human primary keratinocytes and HeLa; BSA or TYR^M as negative controls; two samples from Group A and melanocyte lysate (mouse) as positive controls. * indicates the non-specific band detected with the antibody. Note that the anti-TYR antibody could not detect any bands in BSA or TYR^M, but identified a unique TYR band in the aqueous humor samples.

iris stroma (Ibringas Calvo and Iglesias Cortinas, 2004; Hinkle et al., 2012; Wefers Bettink-Remeijer et al., 2009; Willermain et al., 2010). However, BAIT but not BADI has been described as an ocular side effect of systemic FQLs (Hinkle et al., 2012). In addition, emerging viral etiology has been suspected for both BADI and BAIT (Tugal-Tutkun et al., 2009, 2011; Tugal-Tutkun and Urgancioglu, 2006). Nevertheless, the accumulation of dispersed pigments in the aqueous or the occurrence of BAIT or BADI upon the topical use of

2015b), Sparfloxacin (Beberok et al., 2015a) and Ciprofloxacin (Beberok et al., 2011) are known to affect both human skin melanocyte viability and TYR activity *in vitro*. Studies have also reported an increase in aqueous TYR activity in melanoblastoma (Xloucek and Matous, 1972). However, studies on the effect of FQL on iris depigmentation and melanocyte toxicity *in vivo* have not been reported. We hypothesize that FQL may cause iris melanocyte toxicity and result in the release of dispersed pigments into aqueous humor and that these products can be detected in slit-lamp biomicroscopy but not quantitatively. Melanins are synthesized by membrane bound melanogenic TYR enzyme within the melanosomes (Raposo and Marks, 2007; Sitaram and Marks, 2012). We predict that the dispersed pigments present in the aqueous are also enriched with TYR enzyme and that their activity can be measured using L-DOPA assay (Atul Jani et al., 2016). Thus, for the first time, we have standardized (Fig. 1) and quantified the TYR activity in the aqueous of 82 healthy eyes undergoing cataract surgery (Fig. 2 and Table 1). Our studies show that the topical medication of FQLs has different effects on aqueous TYR activity (Fig. 1). The increase in aqueous TYR activity (upon incubation with L-DOPA *in vitro*) possibly indicates

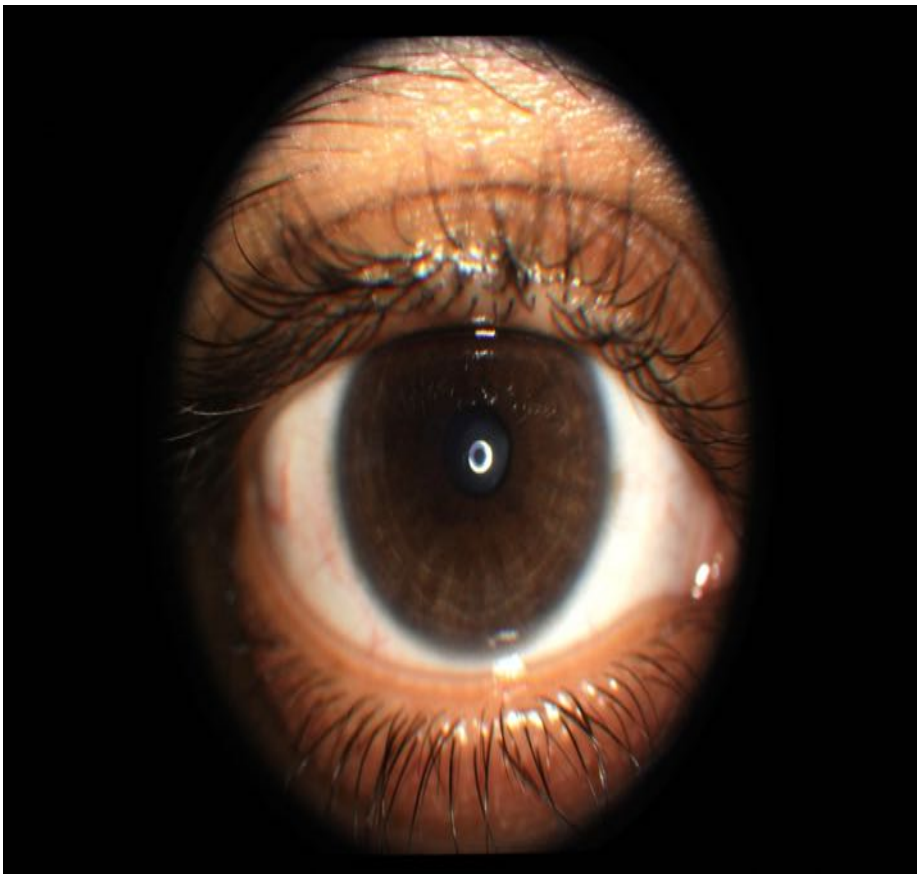
Hinkle DM, Kruh -Garcia NA, Kruh JN, Broccardo C, Doctor P, Foster CS. Moxifloxacin concentration and proteomic analysis of aqueous humor in human uveitis associated with oral moxifloxacin therapy. Open Ophthalmol J. 2017.

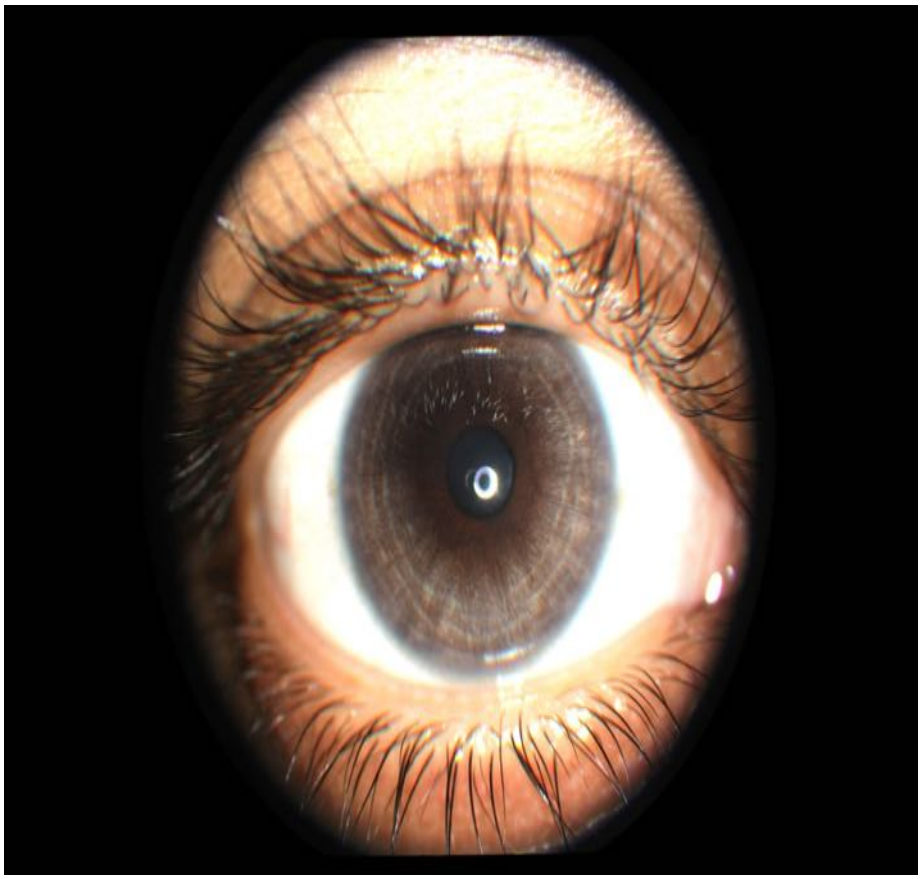




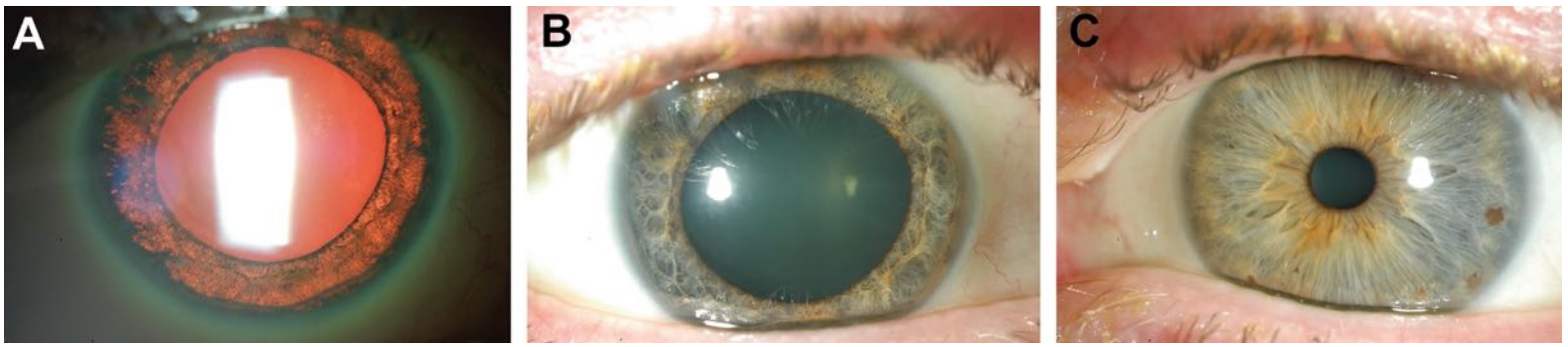
Iris depigmentation of right eye after treatment with moxifloxacin for presumed bacterial conjunctivitis

2012 2013





Open Ophthalmol J. 2017;11:107-116.



JCRS Online Case Reports 2019 7, 3-5DOI: (10.1016/j.jcro.2018.08.001)

Unilateral bilateral acute iris transillumination -like syndrome after intracameral moxifloxacin injection for intraoperative endophthalmitis prophylaxis

Jacob G. Light, MD, Suzanne M. Falkenberry , MD

JCRS Online Case Reports

Volume 7, Issue 1, Pages 3-5 (January 2019)

DOI: 10.1016/j.jcro.2018.08.001

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Re: Haripriya et al.: Endophthalmitis reduction with intracameral moxifloxacin prophylaxis: an analysis of 600 000 surgeries

(Ophthalmology. 2017;124:768-775)

TO THE EDITOR: Haripriya et al[1] reported the outcomes of 600 000 cataract surgeries. This study had no standardized protocol and included 10 different hospitals. Although the sample size is impressive, the study is necessarily limited by its retrospective design. Clearly, the highest level of evidence comes from prospective randomized clinical trials.[2]

The study by Haripriya et al[1] includes limited information about follow-up and visual acuity testing. Of note, that the final visual acuities provided in Table 6 (in the original article) are pinhole visual acuities, not Snellen visual acuities, which makes it difficult to compare these outcomes with randomized clinical trials that used standardized refraction protocols, such as the Endophthalmitis Vitrectomy Study. In addition, the microbial flora and practice patterns featured in this study may differ from those in other parts of the world, including the United States. Therefore, the results may not apply to other geographical locations.

The use of intracameral antibiotics during cataract surgery is controversial. Three antibiotics for intracameral use during cataract surgery have been primarily reported. These are vancomycin, cefuroxime, and moxifloxacin. All 3 antibiotics have limitations and risks that must be considered before their use in general. Vancomycin is associated with hemorrhagic occlusive retinal vasculitis, a poorly understood and potentially devastating complication.[3] Cefuroxime has been studied in a randomized controlled trial, but a prepackaged formulation indicated for intracameral use is unavailable in many nations, including the United States, India, and Japan. Perhaps owing to these concerns, intracameral moxifloxacin is used increasingly as the drug is readily available.

The investigators used moxifloxacin (Autrovox, Aurolab, Tamil Nadu, India) that was prepared by a pharmaceutical company affiliated with their hospital/clinic system, and the intracameral injection was reconstituted from a sterile vial. The risks of compounding errors, contamination, storage, and transport of the drug are important concerns. Cakir et al[4] reported a case series of Pseudomonas endophthalmitis in 8 patients in whom compounded intracameral cefuroxime was used. There is a potential risk for toxic anterior segment syndrome and corneal endothelial toxicity with all intracameral agents.

Aside from toxicity, there are concerns about fluoroquinolone antimicrobial efficacy. Coagulase-negative *Staphylococcus* is the most common cause of postcataract surgery endophthalmitis. In the United States, fluoroquinolone (including moxifloxacin) resistance rates among coagulase-negative *Staphylococcus* endophthalmitis isolates have been reported as high as 40% to 60%.[5]

All intracameral antibiotics are associated with increased costs (moxifloxacin costs average retail price ranges from $175 to $225 per vial in the United States), as well as increased risks of emergence of drug resistance. The risk of post cataract surgery endophthalmitis in the United States without the use of intracameral antibiotics is about 0.078% to 0.10%. Even using a 0.1% incidence rate for calculations, it would require intracameral injection in 999 cases to prevent one case of endophthalmitis. These 999 patients would be exposed to increased costs in addition to risks of dilution errors, toxic anterior segment syndrome, and corneal endothelial toxicity.

Despite the results from this large retrospective study, the role of off-label prophylactic intracameral moxifloxacin still has to be validated by a prospective randomized controlled trial. Haripriya et al[1] conclude, "This study does not constitute level I evidence, however, and there is no consensus that intracameral antibiotic prophylaxis should be the standard of care." We agree with this statement.

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A.G.: Grants, Personal fees, Nonfinancial support – Bayer, Grants, Nonfinancial support – Novartis, Alcon, Thea, Santen, Valeant, outside the submitted work.
H.W.F.: Supported in part by NEI Center Core grant P30EY014801 (Bethesda, Maryland), Research to Prevent Blindness Unrestricted grant (New York, NY), and the Department of Defense (DOD grant no. W81XWH-13-1-0048) (Washington, DC).

Available online: July 25, 2017.

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2. [illegible]

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A. [illegible]

Reply: We agree with Topcuk et al. that inter-rater reliability assessment would have been a valuable addition to our study. In our study, the rater (G.P.K.) did a single assessment of the AS-OCT images and was not blinded to the clinical information; however, the surgeon was blinded to the information.

We appreciate Topcuk et al.'s suggestion to use ImageJ software for further processing the AS-OCT image of the posterior capsule. Topcuk et al. traced the posterior capsule after image processing in 2 of 3 eyes that we classified as deficient. However, the risk for posterior capsule rupture in eyes with posterior polar cataract might also be attributed to extreme fragility of the posterior capsule because of its thinness.[2] This thin posterior capsule can be enhanced with image processing; however, it might give a false impression to the operating surgeon. The main objective of our study was to highlight which cases are at high risk for posterior capsule rupture. Hence, we strongly recommend that if plain AS-OCT imaging shows a doubtful posterior capsule status, it is better to be cautious and take necessary precautions to avoid further complications.—*Pavan Kumar Gurudatta, DO, DNB, Pratha Bhaskaran, MS, Rengaraj Venkatesh, DO, DNB*

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2. [illegible]

Endophthalmitis after intravitreal triamcinolone-moxifloxacin

Kibler et al.[1] recently published a report of 4 cases of acute postoperative endophthalmitis after cataract surgery using prophylaxis with intravitreal triamcinolone-moxifloxacin. This article highlights a very real problem with the intravitreal use of triamcinolone-moxifloxacin. Intravitreal moxifloxacin, in the concentration used in dropless cataract surgery, does not provide adequate prophylaxis against bacteria introduced into the eye during surgery.

Our laboratory recently published an experimental study with rabbits[2] showing that intravitreal triamcinolone-moxifloxacin does not provide adequate prophylaxis against an intravitreal *Staphylococcus aureus* challenge. We infected the vitreous in rabbit eyes with clinical endophthalmitis isolates of *S aureus* with different minimum inhibitory concentrations (MICs) to moxifloxacin (0.032 μg/mL, 2.0 μg/mL, and 16 μg/mL) and immediately treated the eyes with pars plana injections of triamcinolone-moxifloxacin and triamcinolone-moxifloxacin-vancomycin that were equivalent to the human intravitreal doses of the antibiotics. The next day, we examined the eyes for clinical signs of endophthalmitis and cultured the vitreous for viable *S aureus*.[2]

Our study indicated that triamcinolone-moxifloxacin intravitreal injection did not prevent endophthalmitis against bacteria with high MICs. After intravitreal triamcinolone-moxifloxacin treatment, all eyes infected with *S aureus* (MIC = 0.032 μg/mL to moxifloxacin) did not develop endophthalmitis whereas all eyes infected with the *S aureus* isolates (MIC ≥ 2.0 μg/mL to moxifloxacin) developed endophthalmitis. Many ophthalmologists favor moxifloxacin because of its penetration into the cornea and anterior chamber; however, many fail to realize its short half-life in the eye. The half-life of moxifloxacin in the vitreous is only 1.72 hours.[3,4] In contrast, the half-life of vancomycin is 25.1 hours.[5] The initial moxifloxacin concentration of 46.60 μg/mL decreases below 2.0 μg/mL in 8 hours.[3] In our laboratory, the MIC_{90} of *S aureus* and coagulase-negative *Staphylococcus* isolated from endophthalmitis ranged from 8 to 16 μg/mL, indicating that the current formulation of triamcinolone-moxifloxacin would be ineffective against the majority of human staphylococcal endophthalmitis isolates.[2]

In contrast to monotherapy with moxifloxacin, triamcinolone-moxifloxacin-vancomycin prevented endophthalmitis in all eyes infected with *S aureus* (MIC = 16 μg/mL to moxifloxacin). The vancomycin contained in the formulation was required for preventing endophthalmitis. All 3 *S aureus* isolates were susceptible to vancomycin (MIC = 2.0 μg/mL).[2]

A study was presented at the ASCRS meeting in 2014[6] describing a retrospective chart review of 2308 consecutive eyes that had cataract surgery with transzonular injection of triamcinolone-moxifloxacin.[6] There were no cases of postoperative endophthalmitis.[6] This study might have provided cataract surgeons with a false sense of security regarding the use of transzonular triamcinolone-moxifloxacin. It is not known whether the eyes of these patients were challenged with bacteria or whether the antibiotic prophylaxis was effective given the low frequency of postoperative endophthalmitis. This study just showed the safety of the formulation.

Based on the case reports and the results in our experimental study, the use of intravitreal triamcinolone-moxifloxacin in its current formulation for prophylaxis after cataract surgery might not be effective in preventing endophthalmitis.

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Regis P. Kowalski, MS, M(ASCP)
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REFERENCES
1. [illegible]

Second, the dose of intravitreal moxifloxacin in 0.2 mL of commercial triamcinolone-moxifloxacin formulation is only 200 μg, 40% of the usual 500 μg intravitreal dose used for bacterial endophthalmitis.[7] Third, moxifloxacin is actively pumped out from the vitreous cavity by monocarboxylate transporter-mediated uptake by the retinal pigment epithelium.[8] Therefore, unlike vancomycin, which exits the eye via the trabecular meshwork, moxifloxacin's direction of flow is posterior, away from the anterior chamber, which is the site of entry of bacteria into the eye during or after cataract surgery. Given its high lipid solubility, which allows it to

Conclusions

Anterior uveitis may follow fluoroquinolone therapy.

A thorough medical history and identification of pathognomonic signs of this rare, potential complication of fluoroquinolone therapy will avoid unnecessary diagnostic evaluations and therapies.

Conclusions

Moxifloxacin was detected in the aqueous humor 18 days following last oral dose

Moxifloxacin toxicity may be responsible for the clinical findings of uveitis -like syndrome with pigment dispersion associated with moxifloxacin therapy in our patient.

BAIT appears to be most common in middle aged, phakic women with light to moderate skin pigmentation

Fraunfelder and Fraunfelder

Clinical Ocular Toxicology

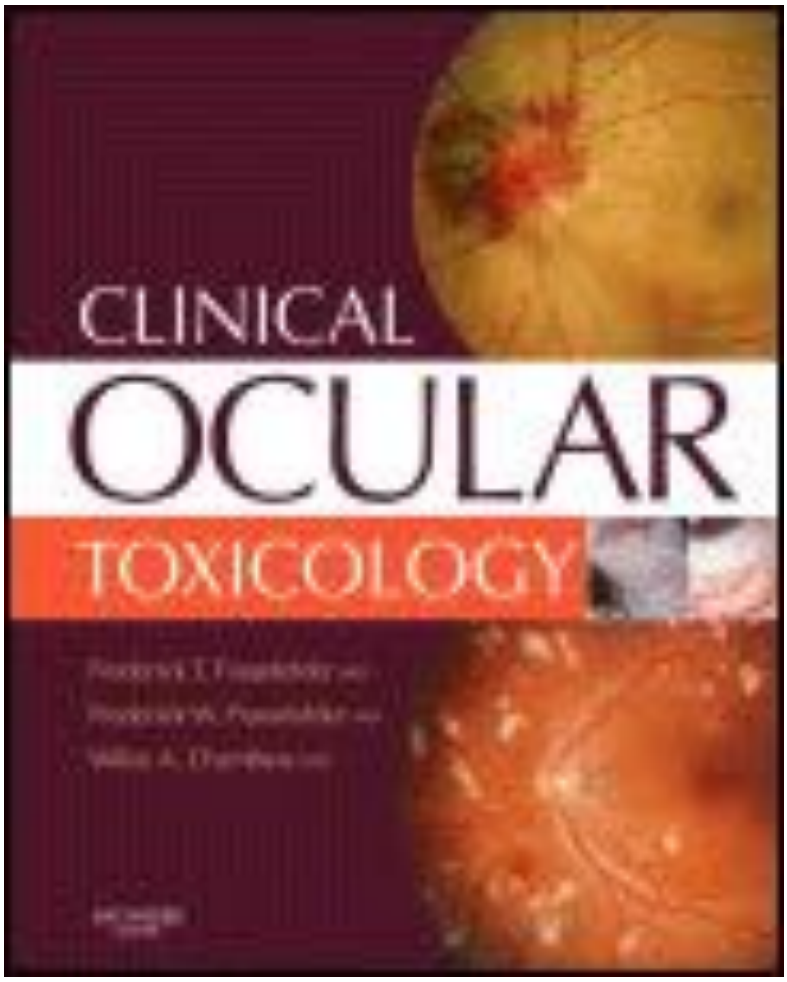
fomerly Drug Induced

Ocular Side Effects

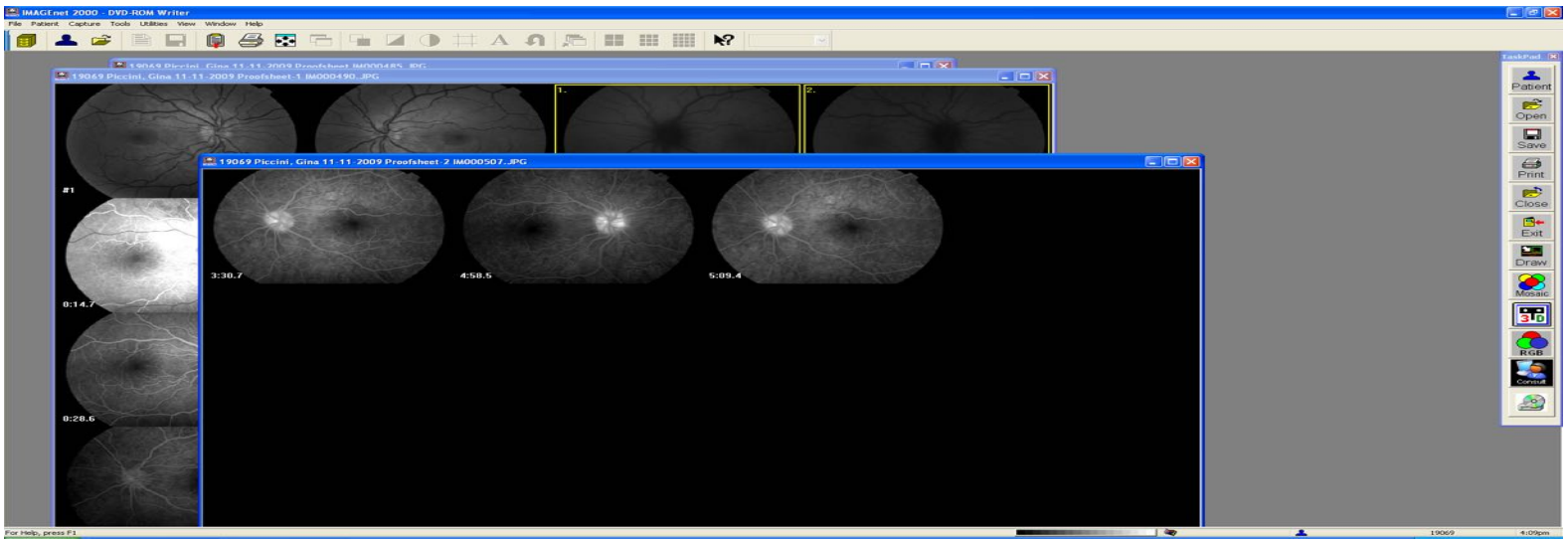
National Registry of

Drug Induced

Ocular Side Effects



Human Papilloma Virus Vaccine



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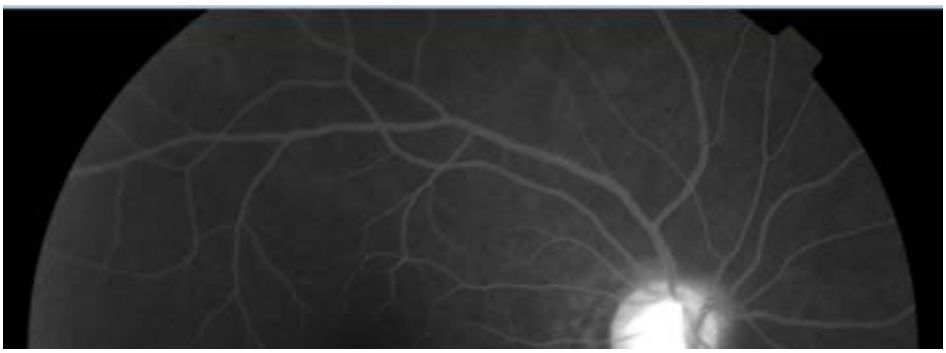
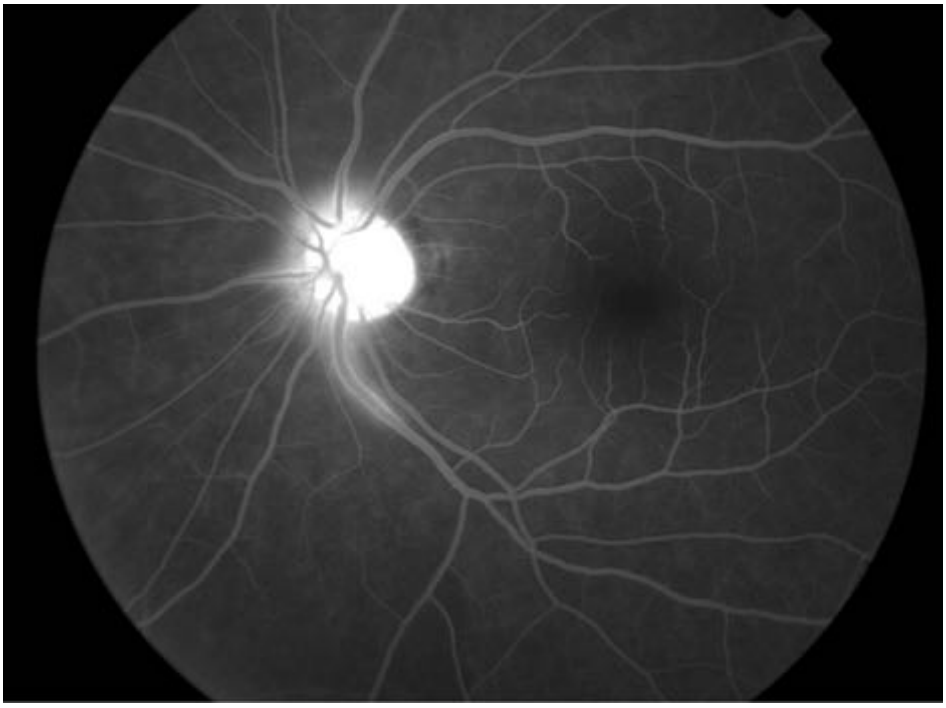
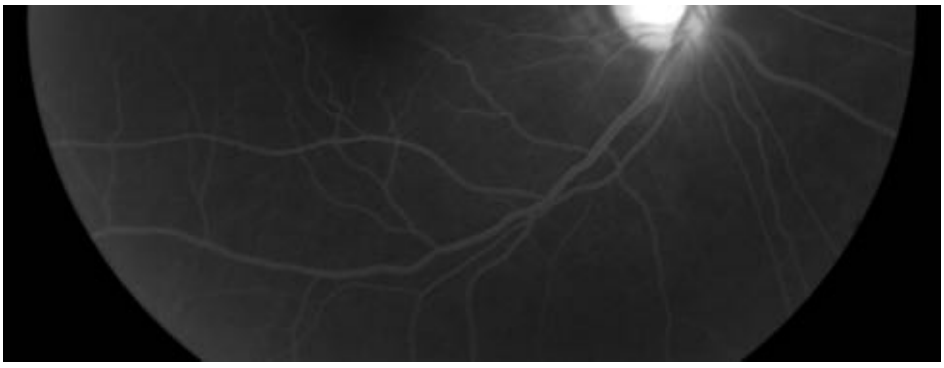
Diptheria Tetanus acellular Pertussis







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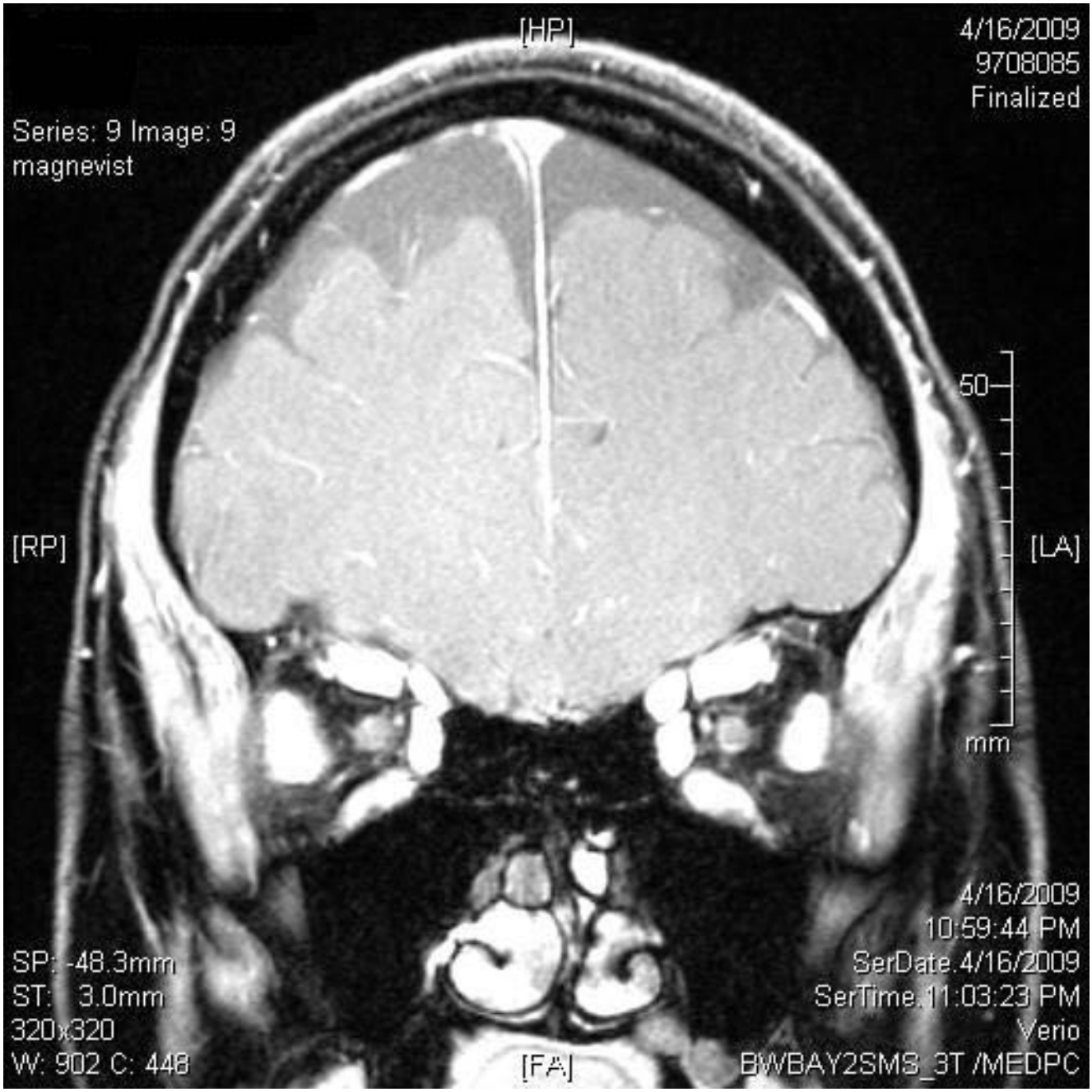
224 **Table 1.** Various tetanus, diphtheria, and pertussis vaccine formulations.
225

Vaccine	Trade Name	Abbreviation	Manufacturer	Type/Route	Approved	Comments
DTaP	Daptacel	DTaP	Sanofi	Inactivated Bacterial/IM	2002	Tetanus & diphtheria toxoids and acellular pertussis vaccine
DTaP	Infanrix	DTaP	GlaxoSmithKline	Inactivated Bacterial/IM	1997	Tetanus & diphtheria toxoids and acellular pertussis vaccine
DT	Generic	DT	Sanofi	Inactivated Bacterial/IM	1978	Pediatric formulation through age 6
DTaP, Polio	Kinrix	DTaP-IPV	GlaxoSmithKline	Inactivated Bacterial & Viral/IM	2008	Licensed for 5th (DTaP) and 4th (IPV) booster at 4-6 years
DTaP, hepatitis B, Polio	Pediatrix	DTaP-HepB-IPV	GlasoSmithKline	Inactivated Bacterial & Viral/IM	2002	Licensed for doses at 2, 4, & 6 months (through 6 years of age). Not licensed for boosters
DTaP, Polio, *Haemophilus influenza* type b	Pentacel	DTaP-IPV/Hib	Sanofi	Inactivated Bacterial & Viral/IM	2008	Licensed for 4 doses at 2, 4, 6, and 15-18 months
Tetanus, (reduced) Diphtheria	Decavac	Td	Sanofi	Inactivated Bacterial Toxoids/IM	1955	Adult formulation (age 7 and older)
Tetanus, (reduced) Diphtheria	Tenivac	Td	Sanofi	Inactivated Bacterial Toxoids/IM	2003	Adult formulation (age 7 and older)
Tetanus, (reduced) Diphtheria	Generic	Td	Massachusetts Biological Labs	Inactivated Bacterial Toxoids/IM	1967	Adult formulation (age 7 and older)
Tetanus, (reduced) Diphtheria, (reduced) Pertussis	Boostrix	Tdap	GlaxoSmithKline	Inactivated Bacterial/IM	2005	Tetanus, diphtheria toxoids & pertussis vaccine. Minimum age = 10 years
Tetanus, (reduced) Diphtheria, (reduced) Pertussis	Adacel	Tdap	Sanofi	Inactivated Bacertial/IM	2005	Tetanus, diphtheria toxoids & acellular pertussis vaccine. Age 10 through 64 years
Tetanus Toxoid	Generic	TT	Sanofi	Inactivated Bacterial Toxoids/IM	1970	Used for adults or children. Discontinued April 2013. Last doses

	expired January 2015.

226 **Table 2.** Spontaneous reports of eye inflammation and uveitis following vaccination with
227 various tetanus, diphtheria, and pertussis vaccine formulations between 1993 and 2016.

Age	Gender	Drug	Start Date	Onset Date	Time to Onset (days)	Dechallenge	Side Effect
50	FEMALE	TETANUS		12/23/93			UVEITIS
0.167	MALE	TETANUS/DIPHTHERIA/PERTUSSIS	12/18/97	12/18/97	0		EYE INFLAMED
15	MALE	TETANUS/DIPHTHERIA	11/19/98	11/20/98	1		EYE INFLAMED
45	FEMALE	TETANUS	8/28/00	9/2/00	4		EYE INFLAMED
0.167	MALE	TETANUS/DIPHTHERIA/PERTUSSIS	5/23/00	5/24/00	1		EYE INFLAMED
1	MALE	TETANUS/DIPHTHERIA/PERTUSSIS		7/22/98		POSITIVE	EYE INFLAMED
49	FEMALE	TETANUS/DIPHTHERIA	10/22/02	10/22/02	0		EYE INFLAMED
2	MALE	TETANUS/DIPHTHERIA/PERTUSSIS	6/21/02	6/21/02	0		EYE INFLAMED
16	FEMALE	TETANUS/DIPHTHERIA	10/20/02	10/20/03	0		EYE INFLAMED
17		TETANUS/DIPHTHERIA	10/20/03	10/20/03	0		EYE INFLAMED
5	FEMALE	TETANUS/DIPHTHERIA/PERTUSSIS	11/25/04	11/26/04	1		EYE INFLAMED
4	MALE	TETANUS/DIPHTHERIA/PERTUSSIS	10/3/05	10/3/05	0		EYE INFLAMED
0.333	FEMALE	TETANUS/DIPHTHERIA/PERTUSSIS	3/1/05	3/1/05	0		EYE INFLAMED
0.279	MALE	TETANUS/DIPHTHERIA/PERTUSSIS/ POLIO/HEP B	12/7/07		1		EYE INFLAMED
50	FEMALE	TETANUS/DIPHTHERIA	10/17/08				IRITIS
14.8	MALE	TETANUS/DIPHTHERIA	10/20/95	10/29/95	9		IRITIS
12	MALE	TETANUS/DIPHTHERIA/PERTUSSIS	7/11/12	7/12/00	1		IRIDOCYCLITIS
0.6	FEMALE	TETANUS/DIPHTHERIA/PERTUSSIS	12/12/00	12/31/00	19		EYE INFLAMED
0.5	FEMALE	TETANUS/DIPHTHERIA/PERTUSSIS	8/24/00	9/1/00	7		UVEITIS
46	FEMALE	TETANUS/DIPHTHERIA	2/25/00	2/27/00	2		CHROIDITIS
44	FEMALE	TETANUS/DIPHTHERIA	5/18/02	5/19/02	1		EYE INFLAMED
0.5	MALE	TETANUS/DIPHTHERIA/PERTUSSIS	11/22/02	11/22/02	0		EYE INFLAMED
0.5	FEMALE	TETANUS/DIPHTHERIA/HEP B/ PERTUSSIS/POLIO	1/7/04	1/15/04	8		EYE INFLAMED
1.3	FEMALE	TETANUS/DIPHTHERIA/PERTUSSIS	5/10/04	5/11/04	1		EYE INFLAMED
47	FEMALE	TETANUS/DIPHTHERIA	11/30/04	12/20/04	20		IRITIS
67	MALE	TETANUS/DIPHTHERIA	1/25/06	1/27/06	2		EYE INFLAMED
17	FEMALE	TETANUS/DIPHTHERIA	9/6/05	9/6/05	0		CHORIORETINITIS
0.5	MALE	TETANUS/DIPHTHERIA/HEP B/ PERTUSSIS/POLIO	9/13/06	9/14/06	1		EYE INFLAMED
12	MALE	TETANUS/DIPHTHERIA/PERTUSSIS	1/5/07	3/20/07	74		IRITIS & IRIDOCYCLITIS
	FEMALE	TETANUS/DIPHTHERIA/HEP B/ PERTUSSIS/POLIO	8/14/07	8/16/07	2		EYE INFLAMED
52	FEMALE	TETANUS/DIPHTHERIA/PERTUSSIS	2/19/07	3/5/07	14		IRITIS
4	FEMALE	TETANUS/DIPHTHERIA/PERTUSSIS	1/23/09	1/31/09	8		EYE INFLAMED
15	FEMALE	TETANUS/DIPHTHERIA/PERTUSSIS	12/28/09	12/29/09	1		UVEITIS
0.9	MALE	TETANUS/DIPHTHERIA/PERTUSSIS	1/13/10	1/13/10	0		EYE INFLAMED
14	FEMALE	TETANUS/DIPHTHERIA	5/1/02	5/1/02	0		EYE INFLAMED
4	FEMALE	TETANUS/DIPHTHERIA/PERTUSSIS	8/18/03	8/18/03	0		EYE INFLAMED
3	MALE	TETANUS/DIPHTHERIA/PERTUSSIS	10/10/03	10/10/03	0		EYE INFLAMED
0.75	FEMALE	TETANUS/DIPHTHERIA/PERTUSSIS		11/19/03			EYE INFLAMED
4	FEMALE	PERTUSSIS & TETANUS/DIPHTHERIA/ POLIO	1/9/03	1/19/03	10		UVEITIS
39	FEMALE	TETANUS	1/21/04	1/30/04	9		UVEITIS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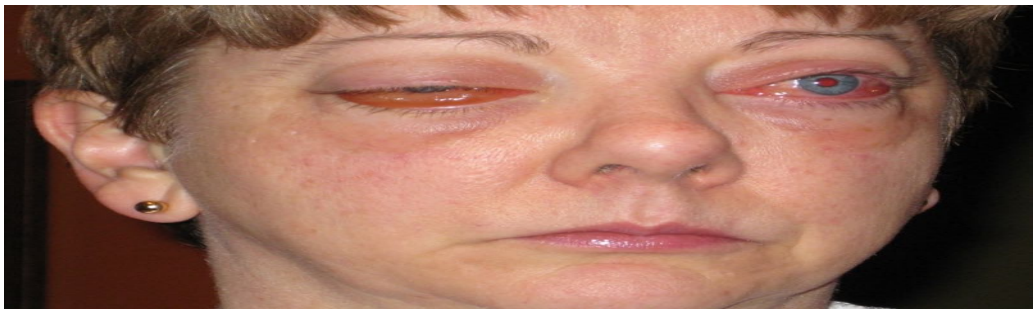
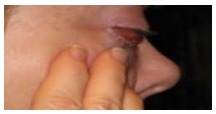
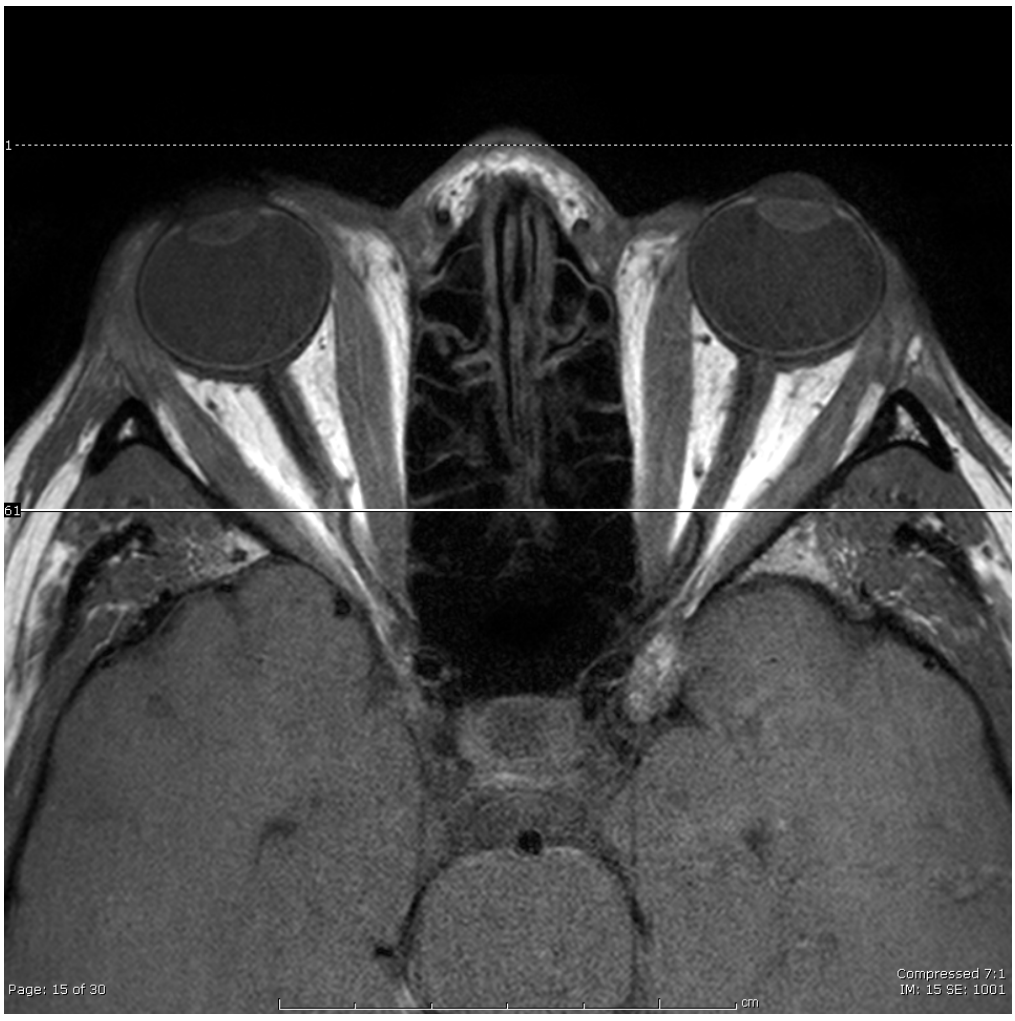




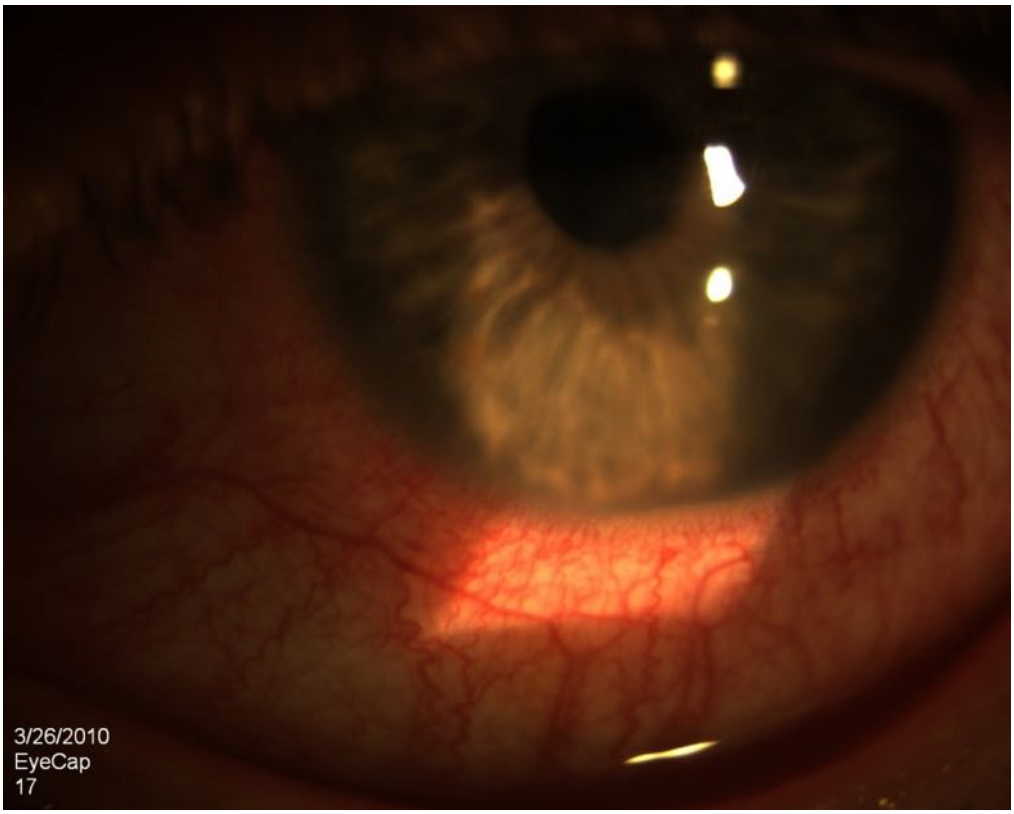


Ipilimumab (anti-CTLA4 antibody) can

induce autoimmune conditions

Borodic G, Hinkle DM, Cia Y. Drug Induced Graves Disease from CTLA-4 Receptor Suppression. OPRS 2011;27:e87-88.

Bilateral hypopyon in JIA on golimumab



Failed/intolerant to methotrexate, cyclosporine, infliximab, etanercept, adalimumab, rituximab

Conclusions

A large number of systemic medications can impact the eye from the ocular surface to the retina and optic nerve

A thorough past medical history is critical in order to identify potentially offending medications

What we have learned about Ebola virus from the eye

David M. Hinkle MD Associate Professor of Ophthalmology WVU Eye Institute

Objectives

Review the epidemiology and pathogenesis of Ebola virus disease

Provide an update on the ocular complications of Ebola and related filoviruses

Discuss the current state of Ebola virus prevention and treatment

Filoviridae – hemorrhagic fever

Marburg

Ebola

Bundibugyo

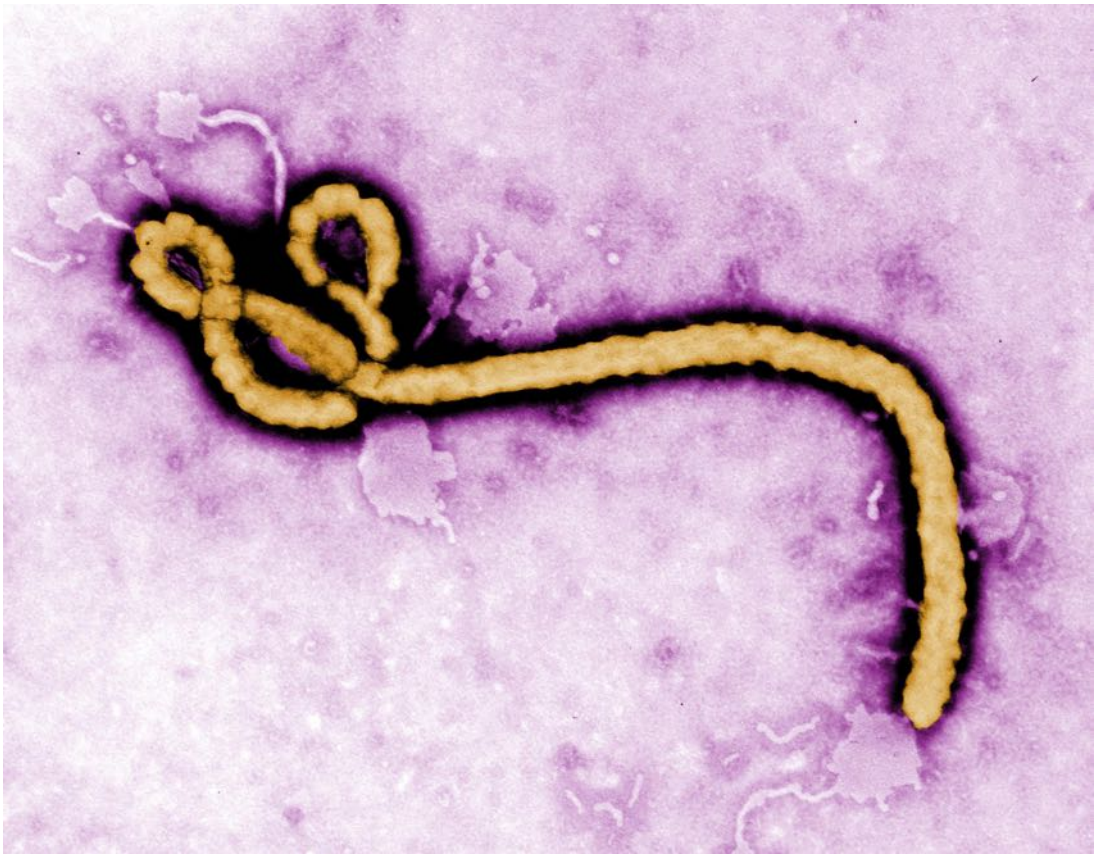
Reston

Sudan

Tai Forest

Zaire

Cuevavavirus



Marburg Virus

1967: Initial outbreak

1975: Second outbreak in Johannesburg

2/3 patients died, 2 months later, third patient developed pancreatitis, unilateral hypertensive uveitis

Virus cultured from anterior chamber

Stool, urine and throat cultures negative

Resolution after several weeks of topical steroid and atropine

Recurrence 2 and 10 months later resolved without sequelae

Br Med J 1975

Br Med J 1975

1995 Ebola Virus epidemic, Congo

315 cases, 250 deaths

4 cases of uveitis

All resolved with topical steroids and atropine

J Infect Dis 1999

Ebola Virus Disease (EVD)

Fever

Severe headache

Muscle/abdominal pain

Weakness/fatigue

Diarrhea

Emesis

Unexplained bleeding or bruising

Ebola Virus Diagnosis

Antigen capture ELISA

Polymerase chain reaction (PCR)

Viral culture

Antibodies or immunohistochemistry (late or post-mortem)

Ebola Virus Outbreak 2014-2015

Guinea, Liberia, Sierra Leone

28,616 cases; 11,310 deaths

Uveitis in 13.5-40%

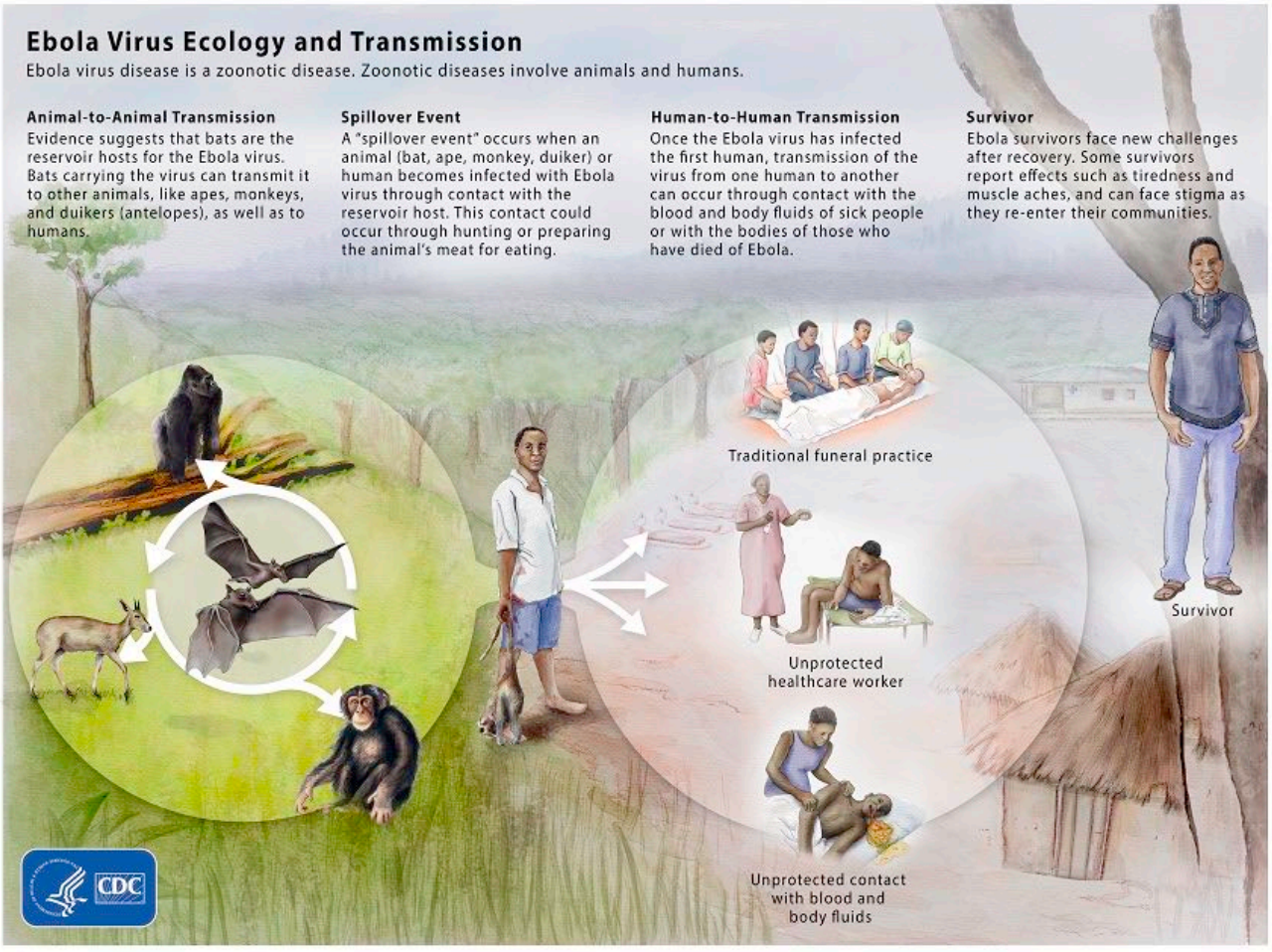
78% unilateral

48% anterior

Rare scleritis , stromal keratitis,

optic neuropathy

1 eye enucleated


Ebola Virus Ecology and Transmission
Ebola virus disease is a zoonotic disease. Zoonotic diseases involve animals and humans.
Animal-to-Animal Transmission
Evidence suggests that bats are the reservoir hosts for the Ebola virus. Bats carrying the virus can transmit it to other animals, like apes, monkeys, and duikers (antelopes), as well as to humans.
Spillover Event
A "spillover event" occurs when an animal (bat, ape, monkey, duiker) or human becomes infected with Ebola virus through contact with the reservoir host. This contact could occur through hunting or preparing the animal's meat for eating.
Human-to-Human Transmission
Once the Ebola virus has infected the first human, transmission of the virus from one human to another can occur through contact with the blood and body fluids of sick people or with the bodies of those who have died of Ebola.
Survivor
Ebola survivors face new challenges after recovery. Some survivors report effects such as tiredness and muscle aches, and can face stigma as they re-enter their communities.
Traditional funeral practice
Unprotected healthcare worker
Unprotected contact with blood and body fluids
Survivor
CDC

Initial Uveitis Case of 2014: Acute phase

52 yo male physician providing healthcare in Liberia developed fever

Plasma PCR positive for Ebola virus

Evacuated to Nebraska Medical Center biocontainment facility

Received investigational drug TKM-100-802 siRNA LP (Tekmira Pharmaceuticals, Burnaby, British Columbia, Canada)

Transfused convalescent-phase plasma from EVD survivor on day 9

Bilateral conjunctivitis spontaneously resolved, declined ophthalmic exam at time of hospital discharge

Initial 2014 Case: Convalescent phase

35 days after EVD onset developed fever, non-productive cough

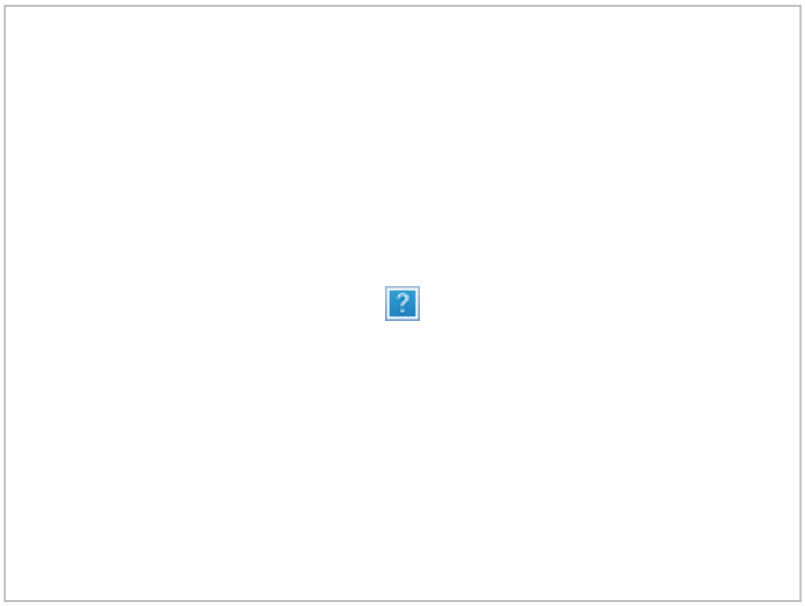
40 days after onset developed unilateral painful vision loss with ocular redness

Anterior uveitis with fibrin formation

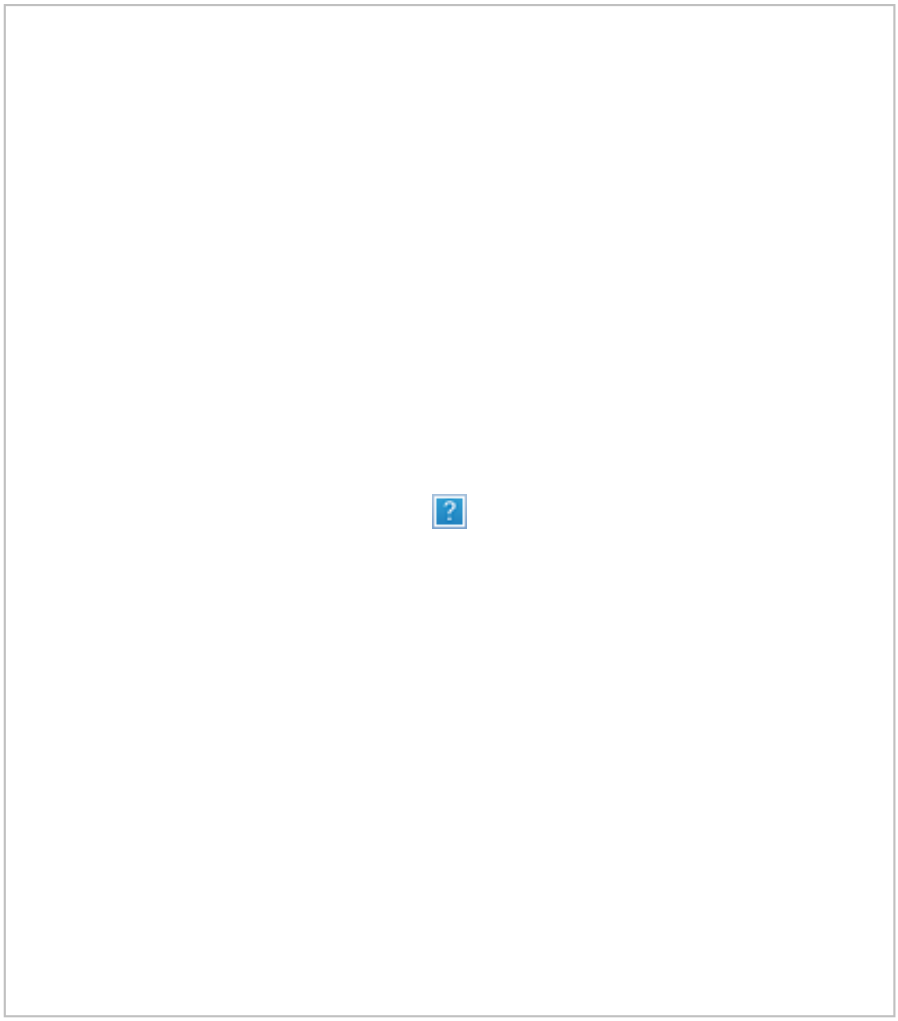
Initial treatment with homatropine,

and prednisolone acetate 1%

Emerg Infec Dis 2016;22:295-297.



Initial 2014 Case Serologies



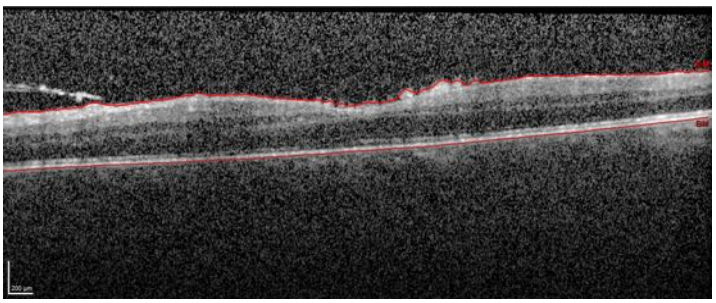
Initial Uveitis Case of 2014

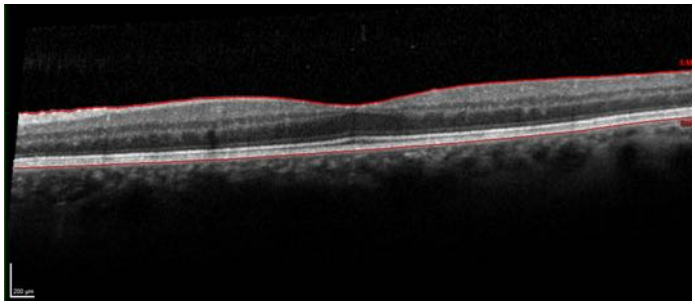
Bilateral conjunctival swab PCR negative for Ebola

Vitritis developed 2 weeks later

Given diagnostic uncertainty, vitrectomy advised; patient deferred

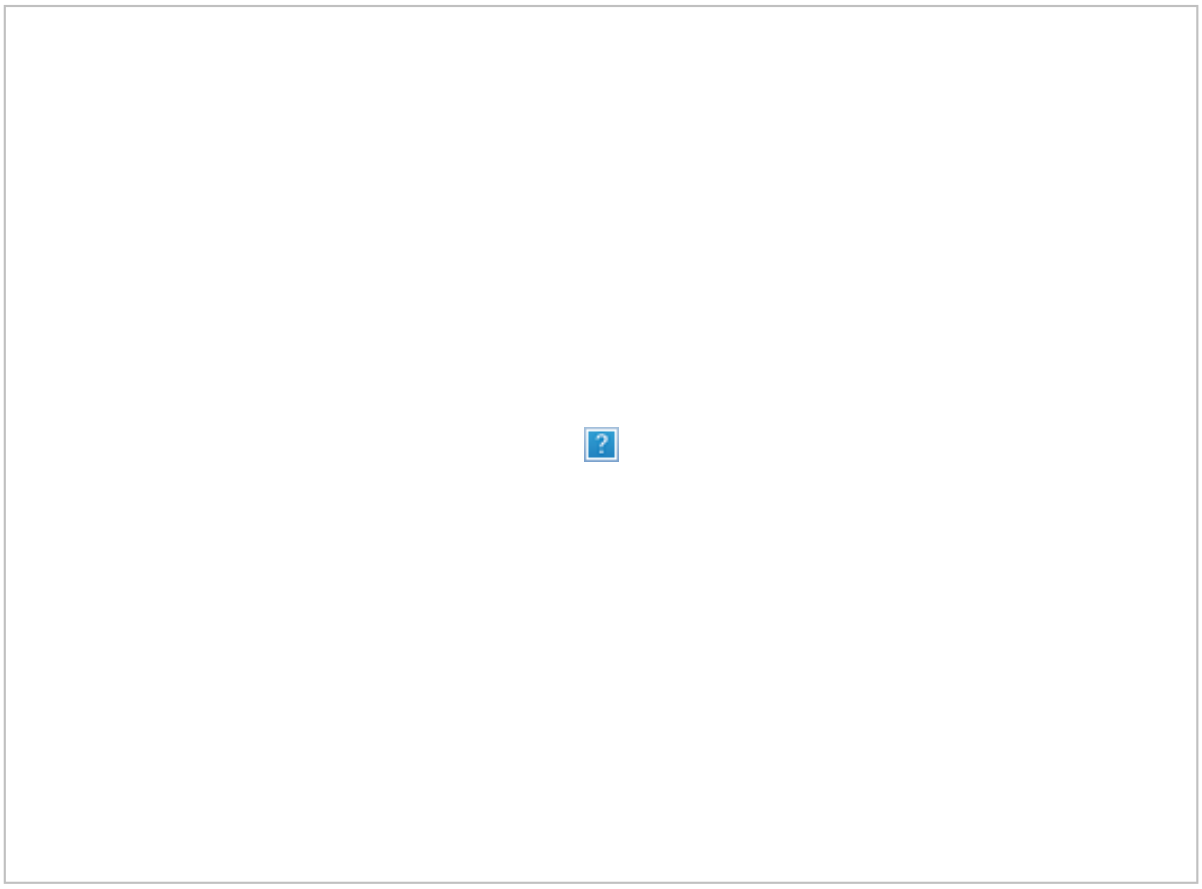
Oral prednisone 60mg QD commenced with significant improvement within 4 days



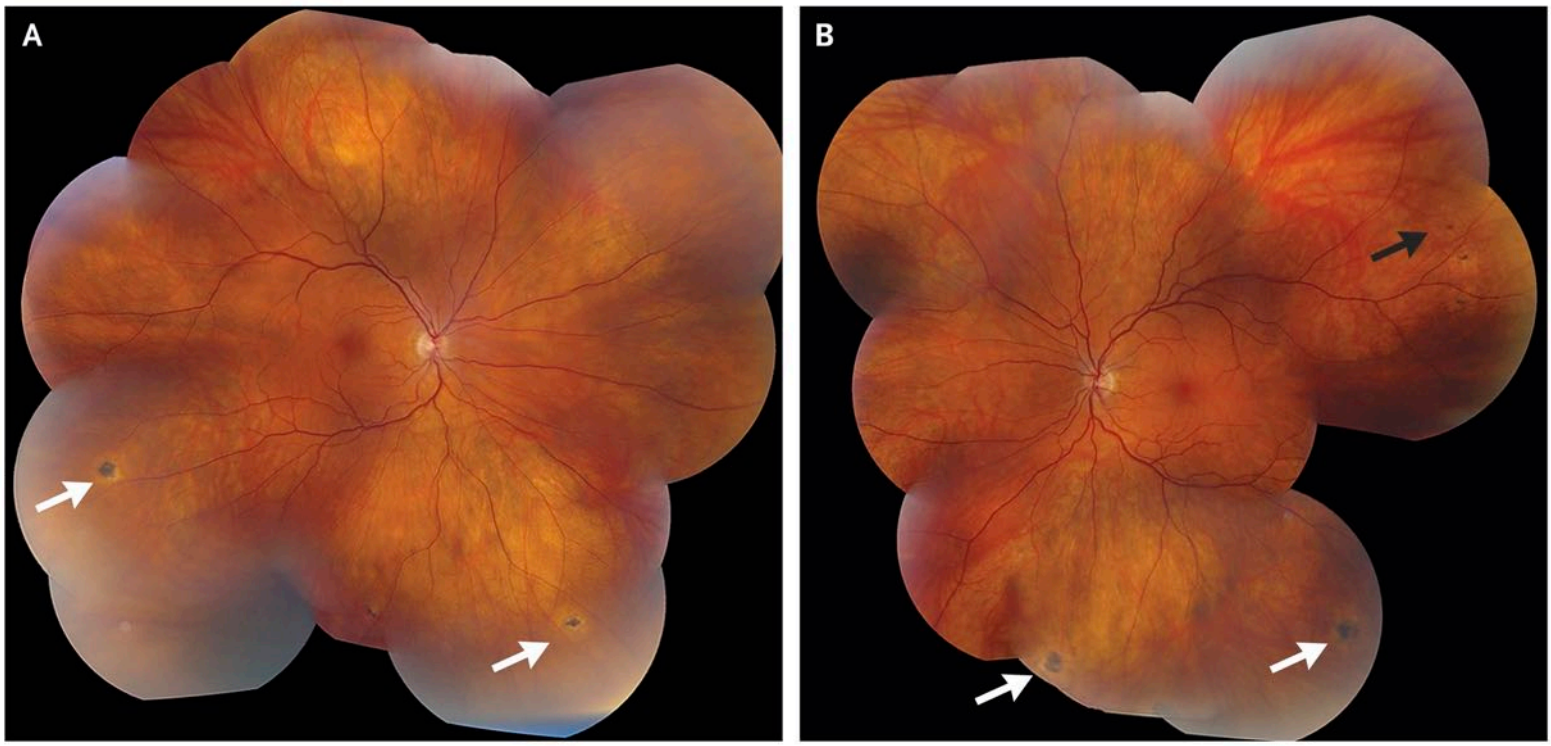


N Engl J Med 2015; Ophthalmology 2016

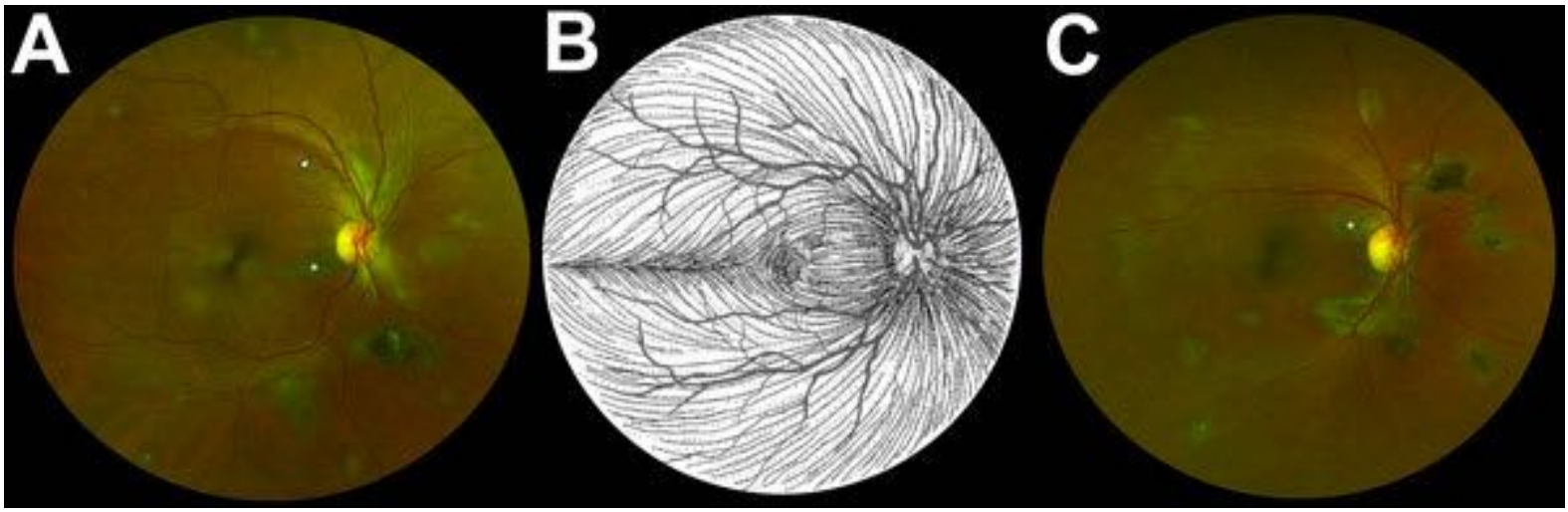
Persistence of Ebola Virus in Ocular Fluid during Convalescence



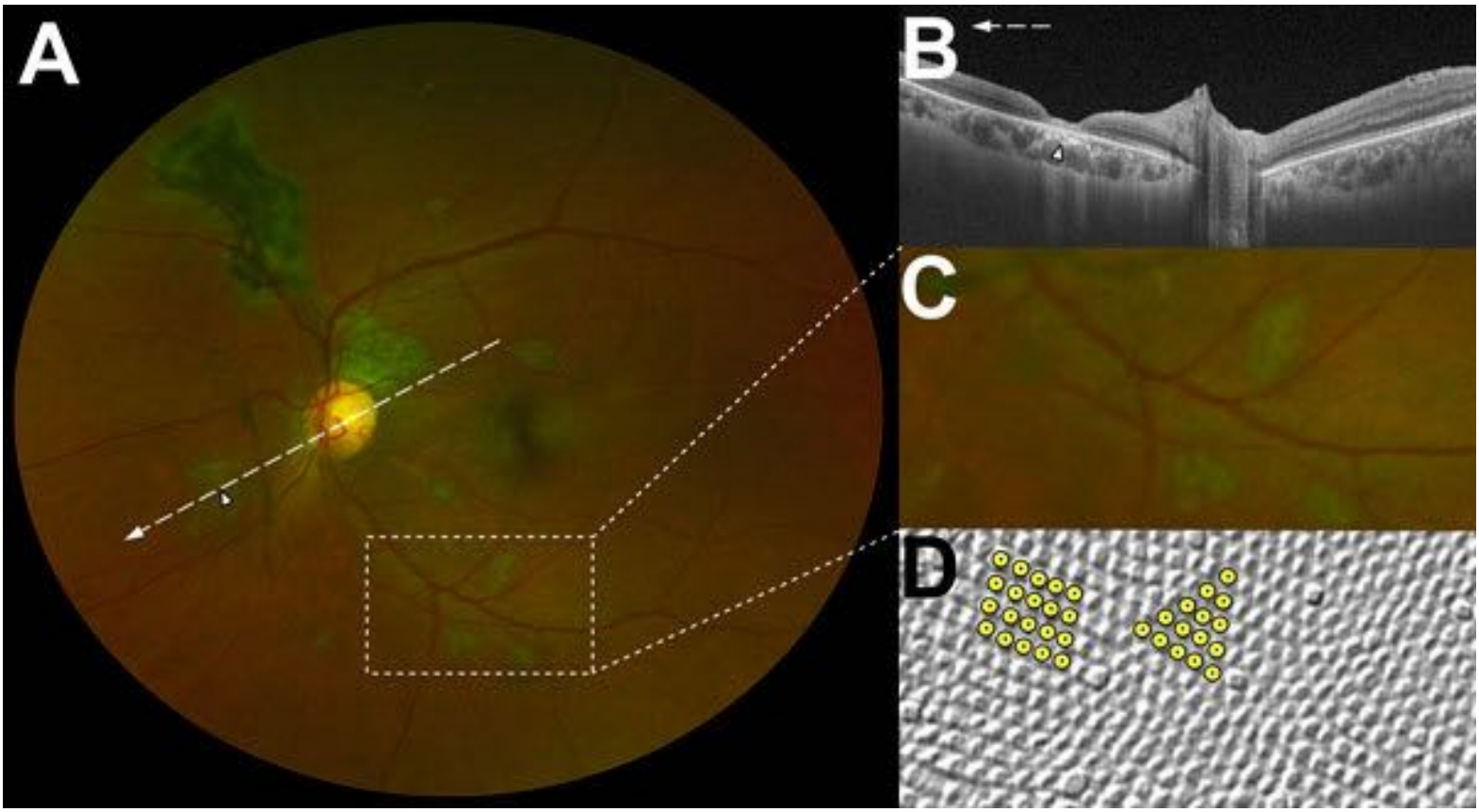
N Engl J Med 2015; 372:2423-2427



Emerg Infect Dis 2017;23:1102-1109



Emerg Infect Dis 2017;23:1102-1109



Cataracts in Ebola Survivors

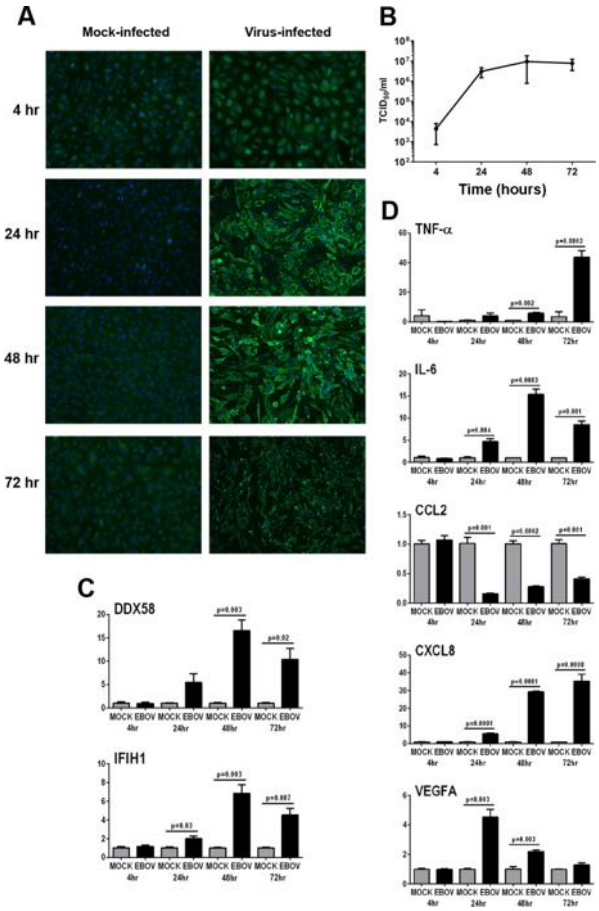
>50 cases

5-70 years of age

Frequently mature

Aqueous PCR negative in all cases this far

Retinal Pigment Epithelial Cells are a Reservoir for Ebola Virus in the Human Eye



ARPE-19 human cells

Inoculated with EBOV

Active viral replication

Infected cells expressed immunomodulatory molecules linked to ocular immune privilege

Transl Vis Sci Technol . 2017;6:12.

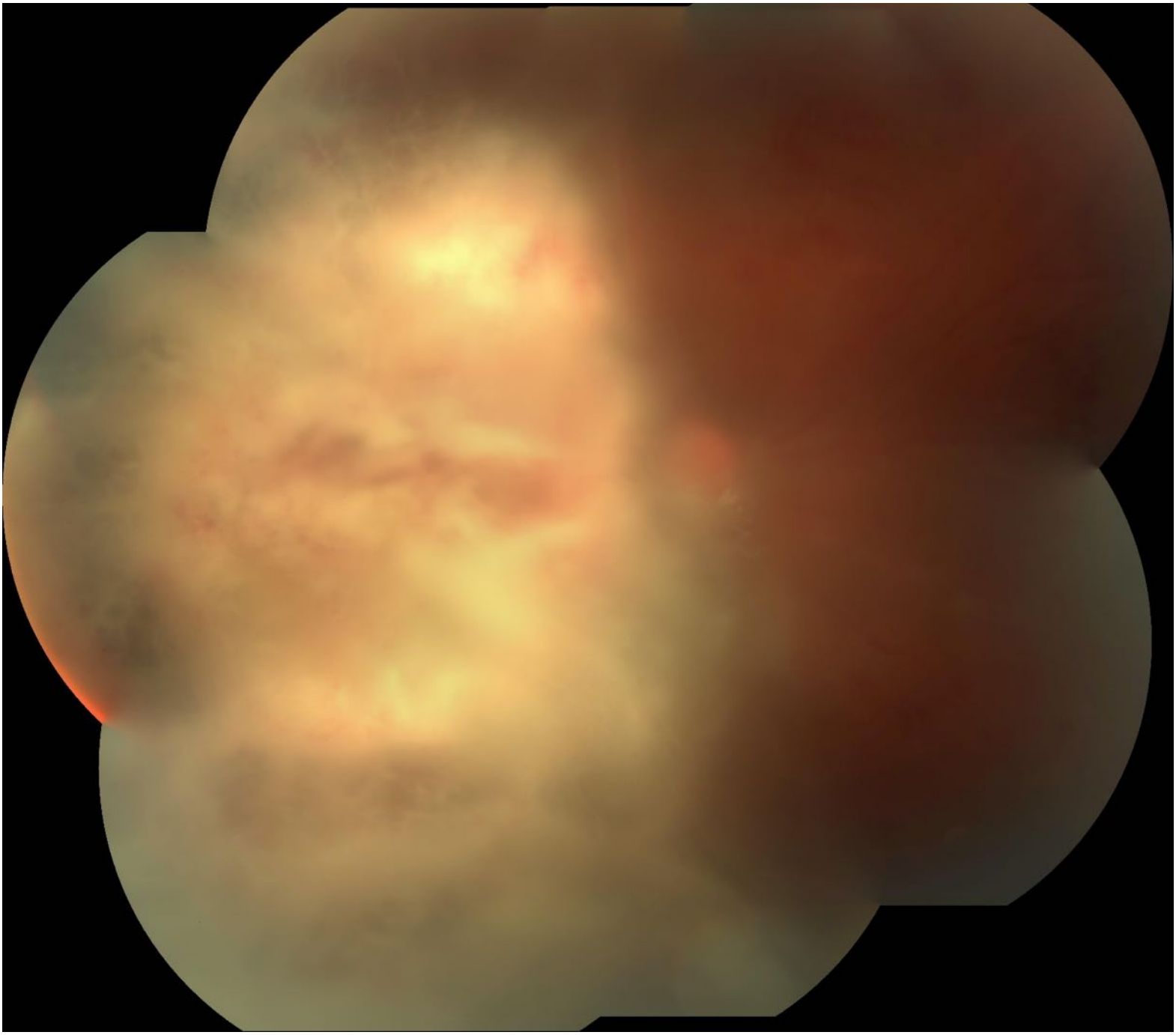
Conclusions

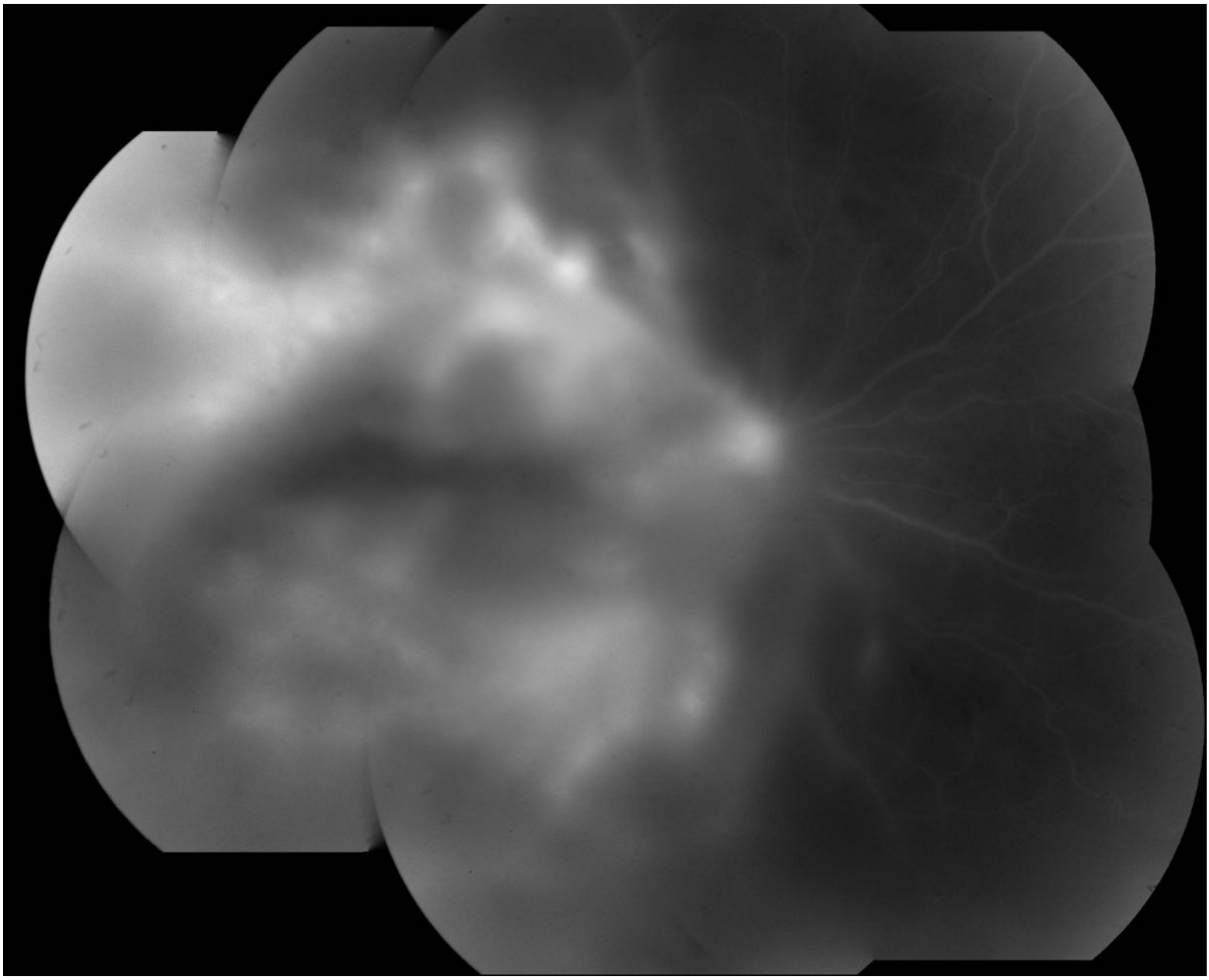
EVD is an emerging infectious cause of acute and recurrent anterior and panuveitis

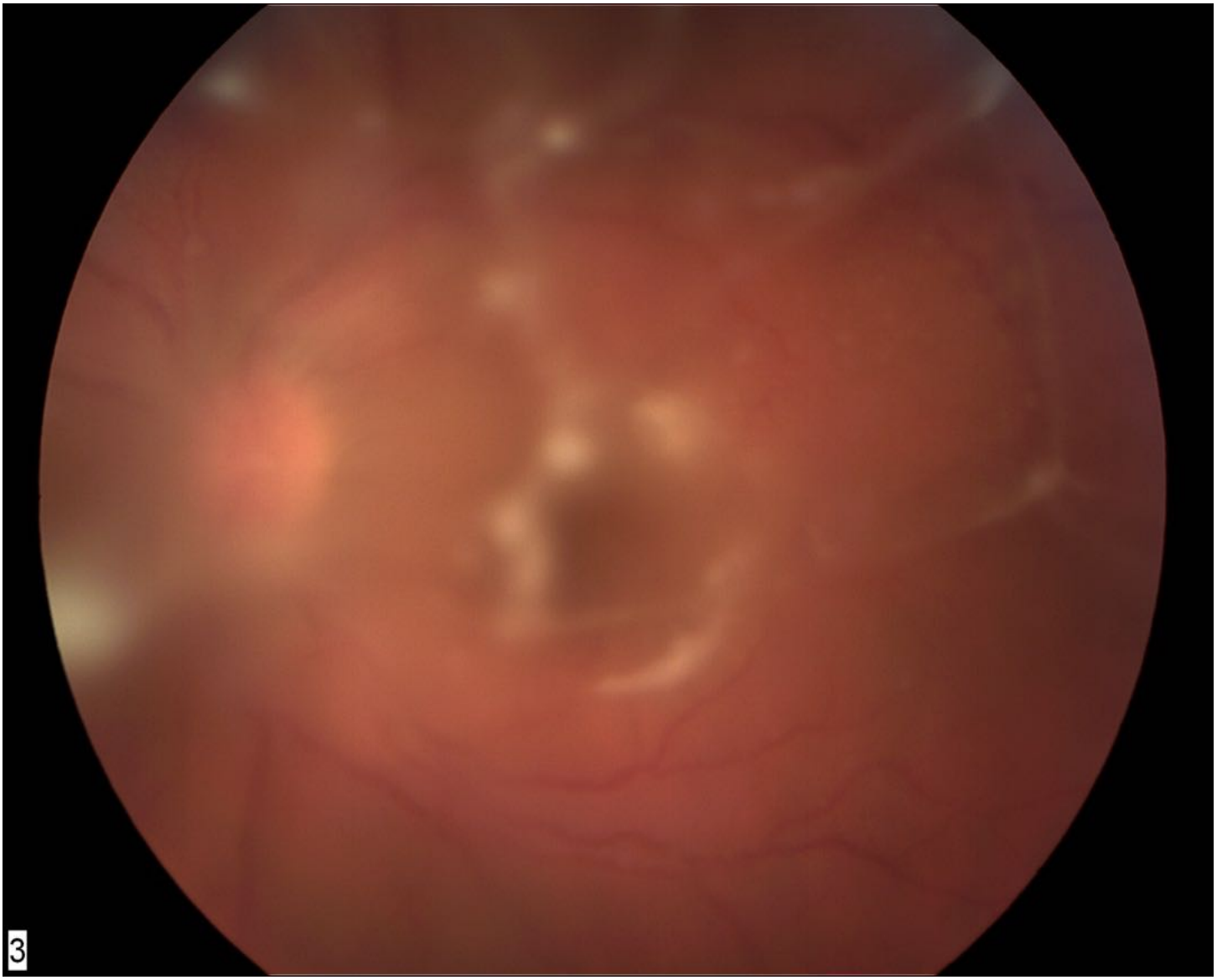
Some cases are severe and sight threatening

Co-morbid cataract is common

Cataract extraction with intraocular lens implantation yields favorable outcomes in most cases



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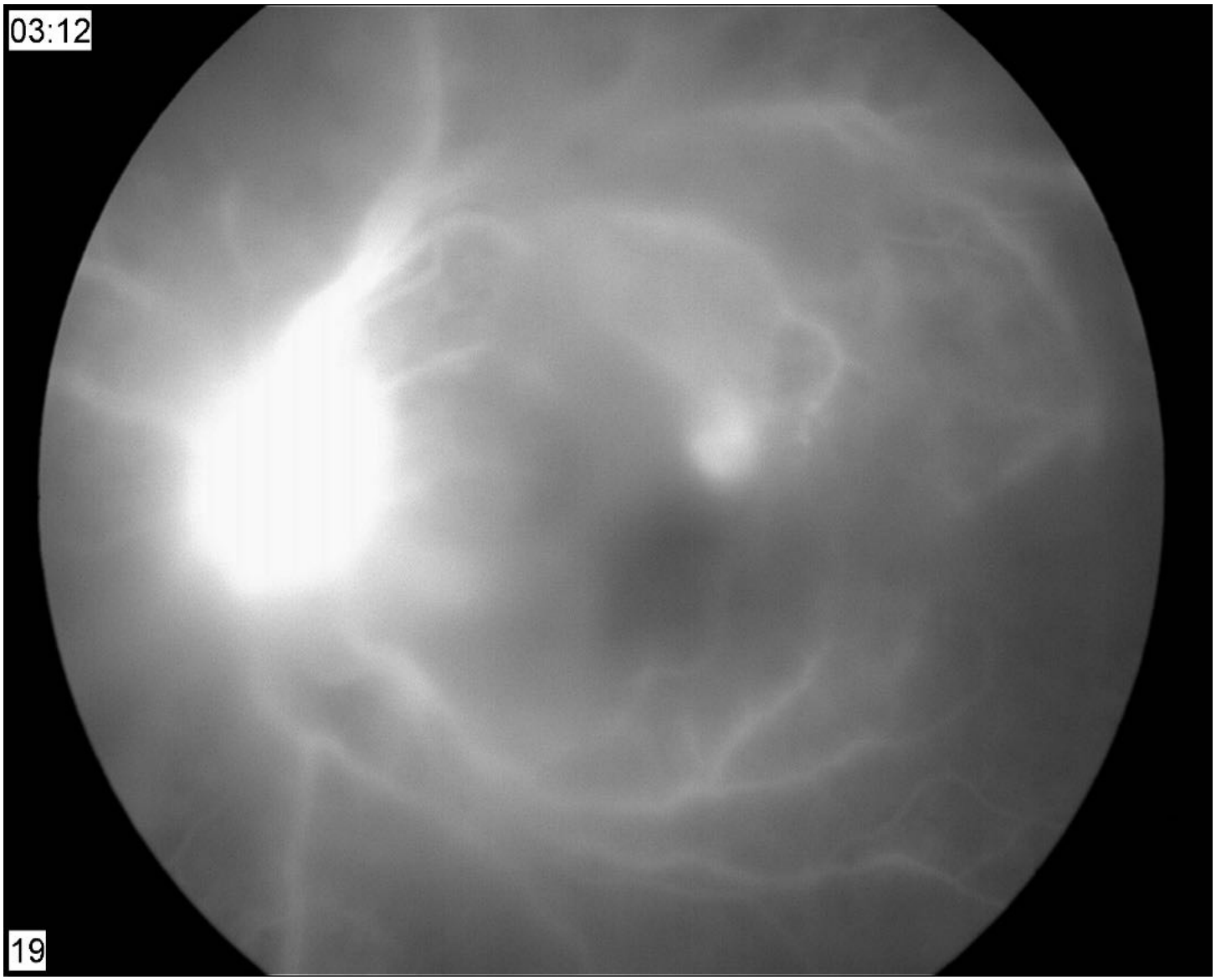
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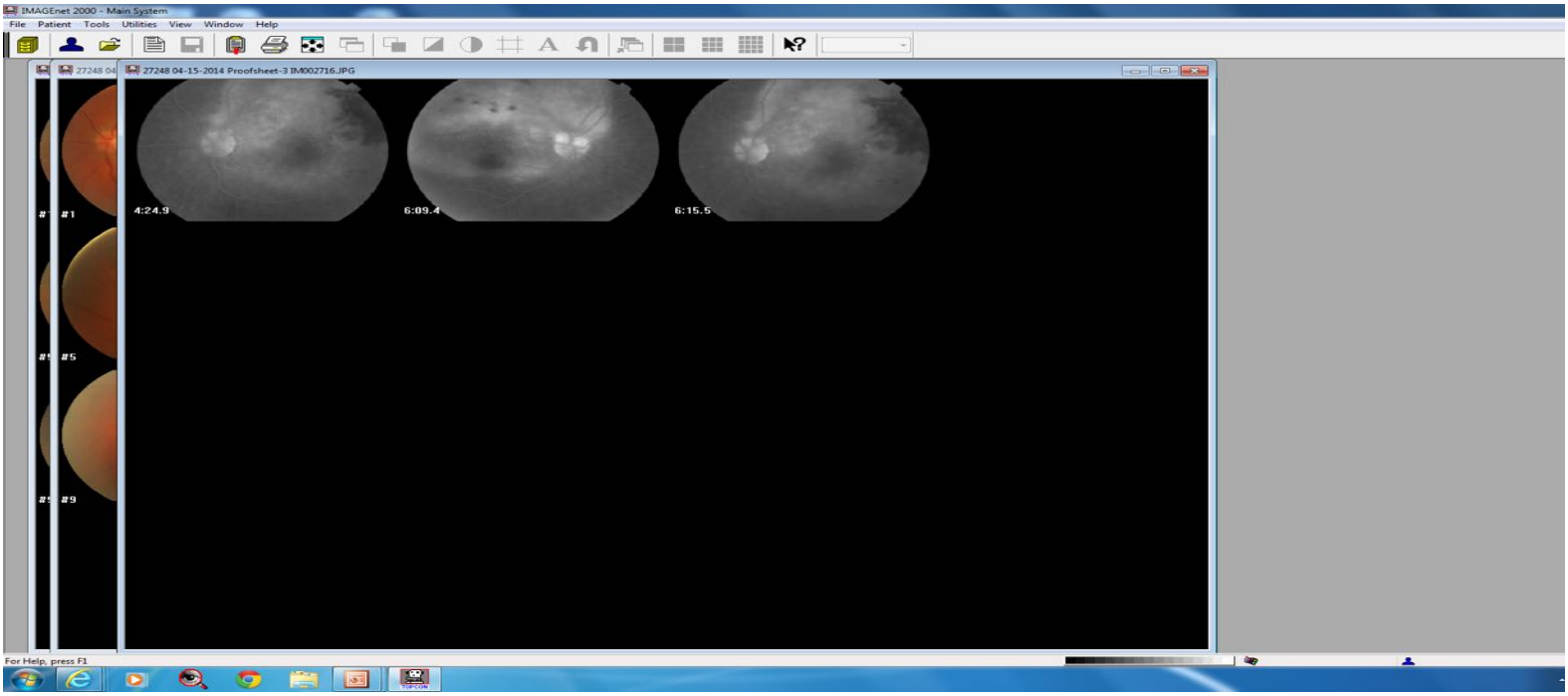
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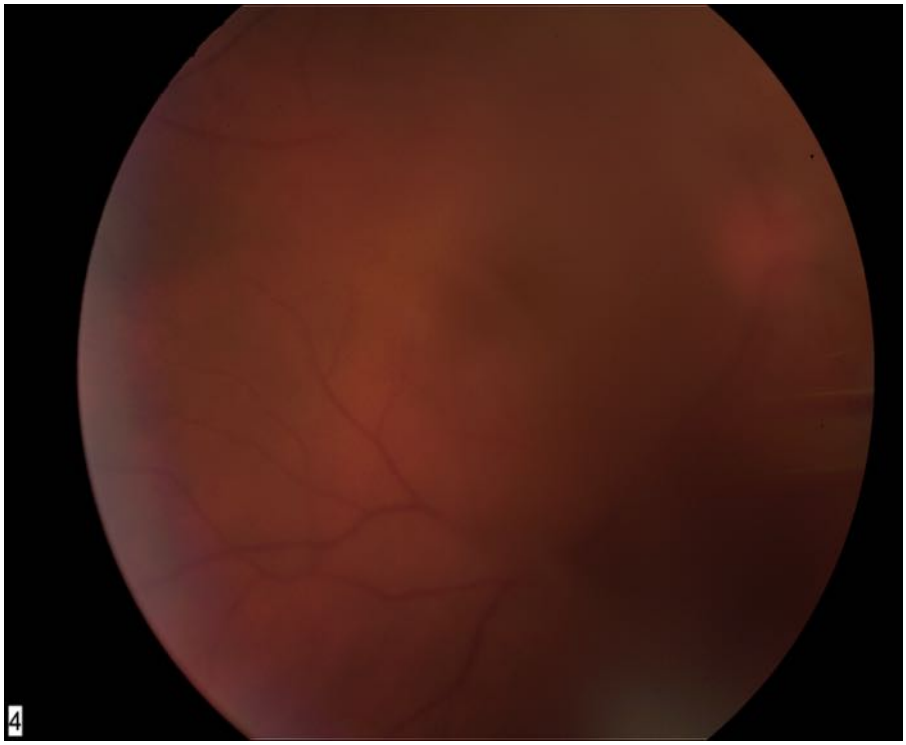
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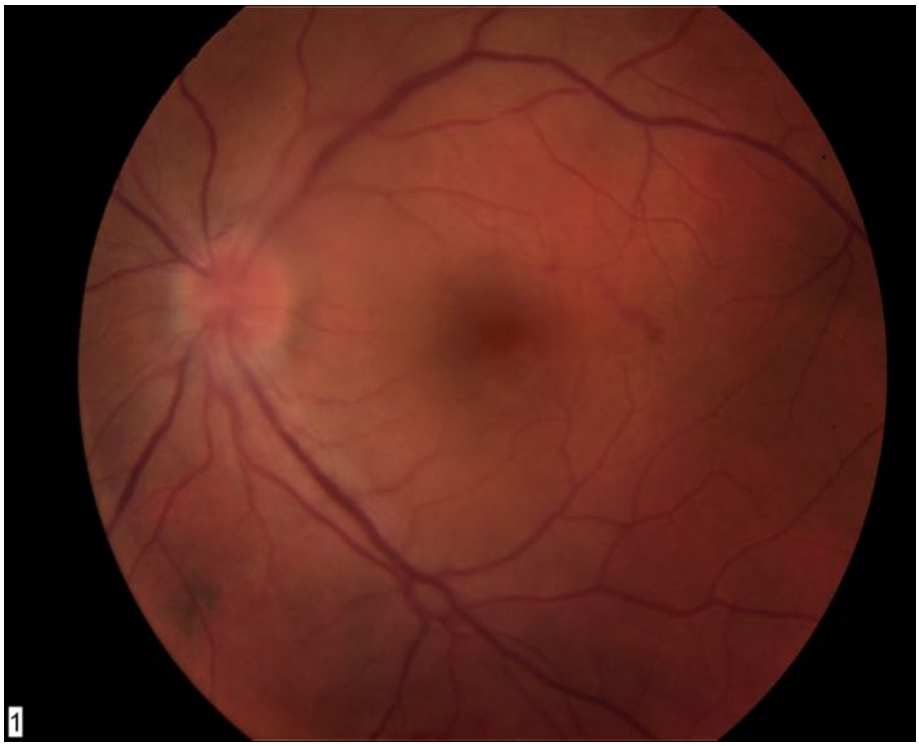
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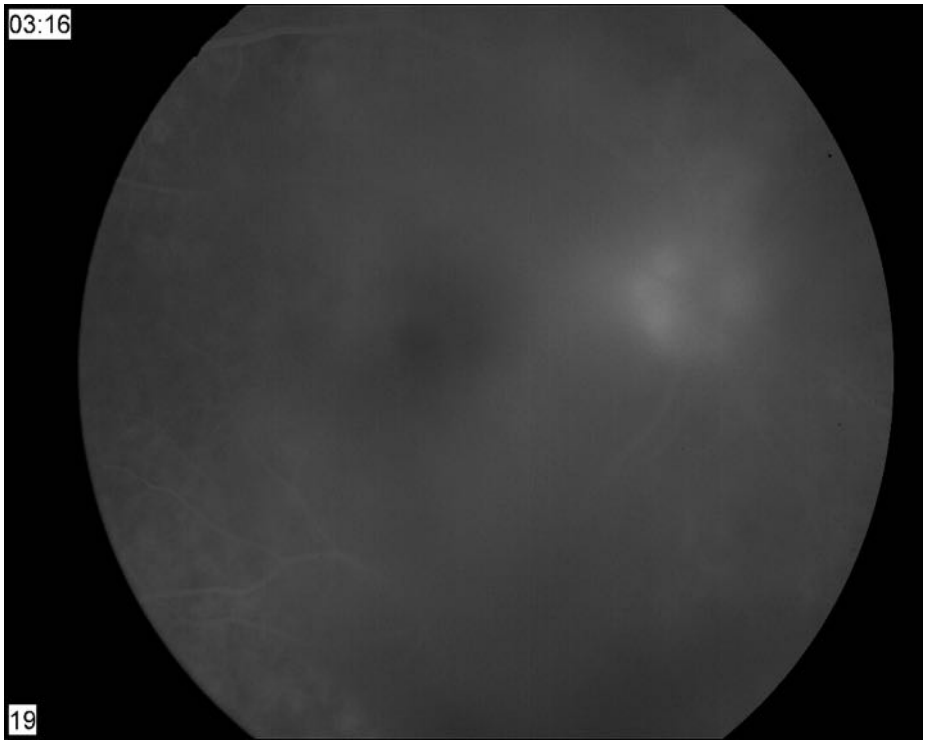
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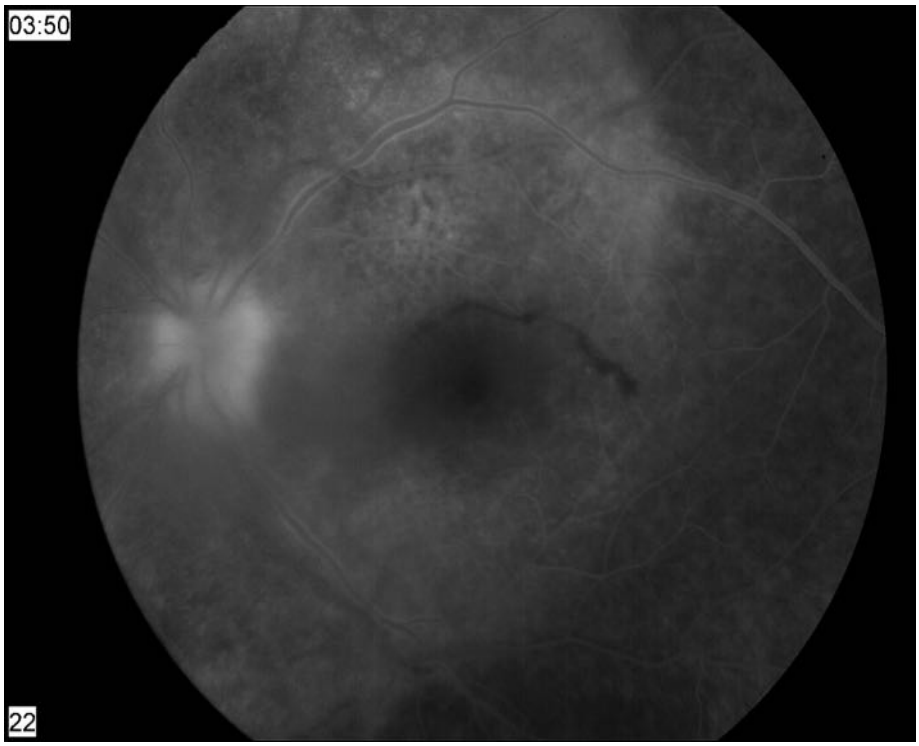
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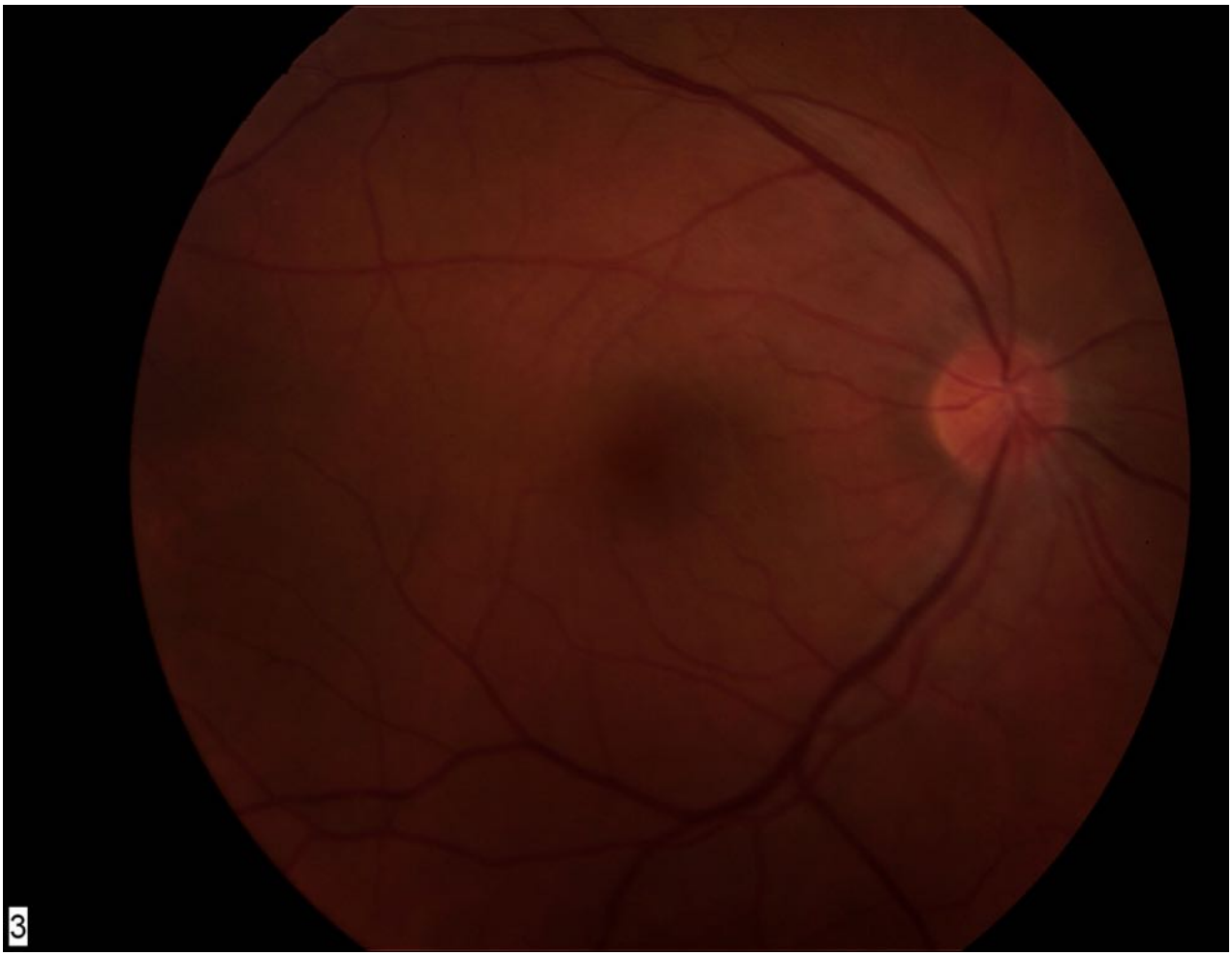
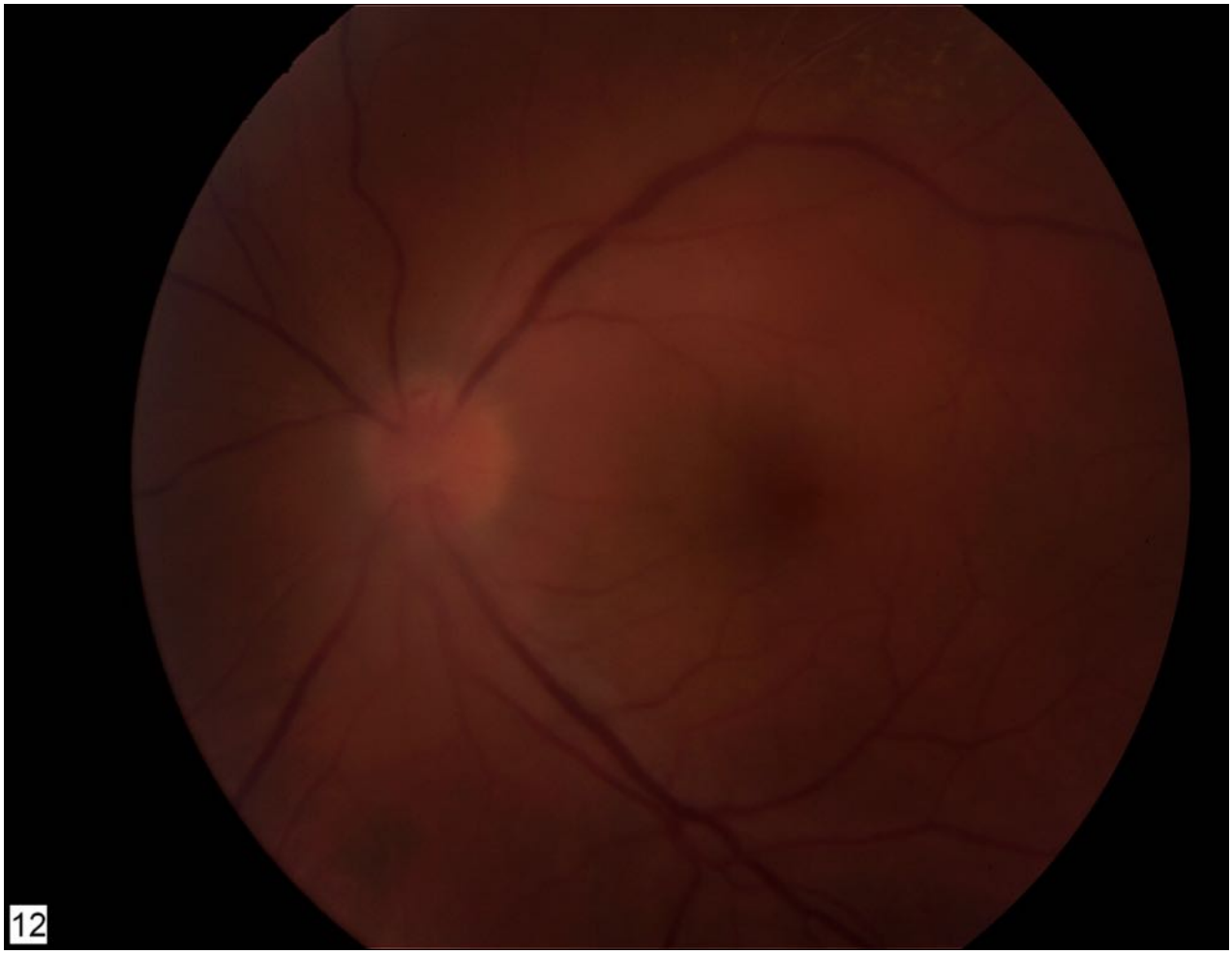
+HIV, RPR, FTA-ABS - appearance following IV PCN

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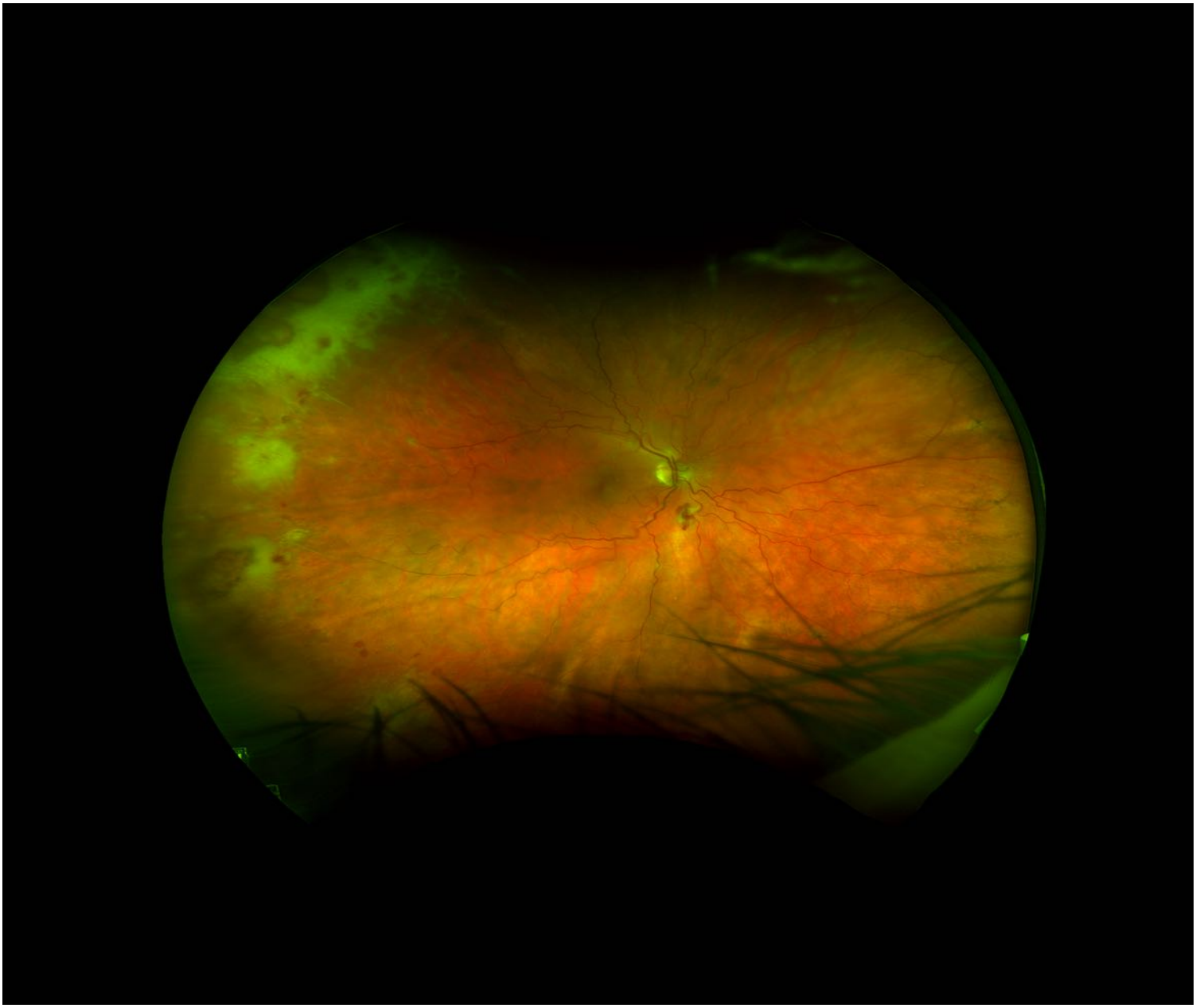
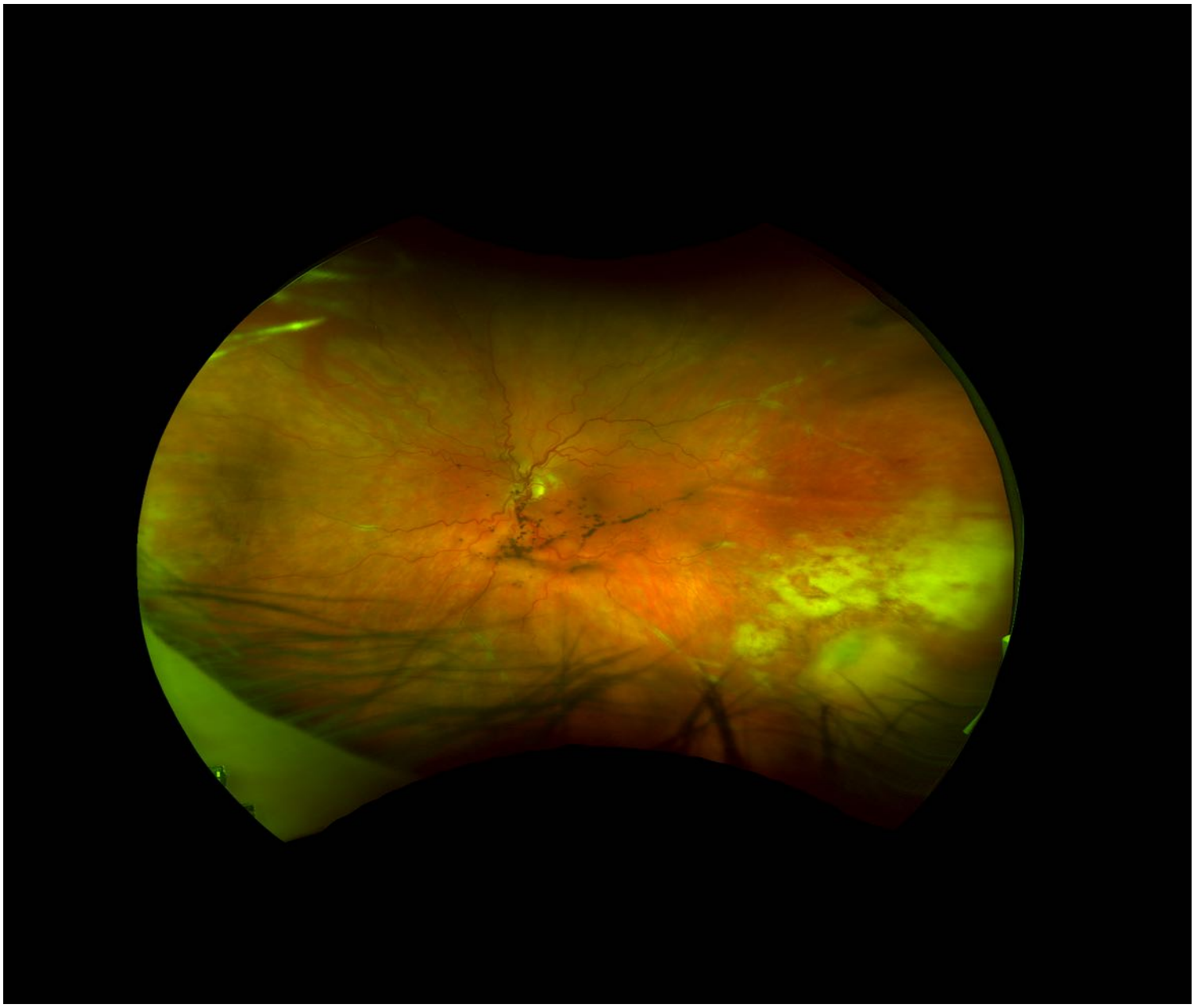
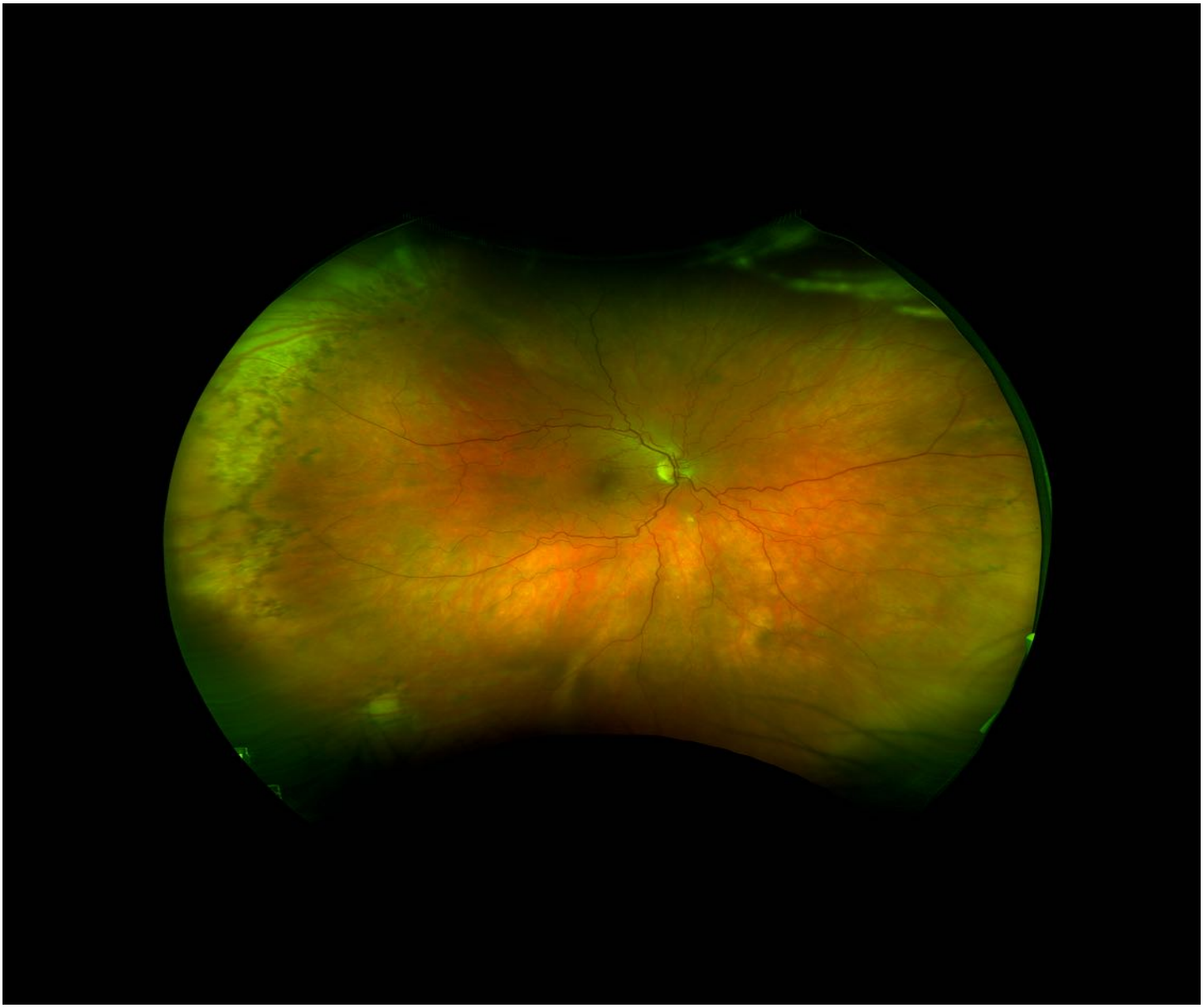
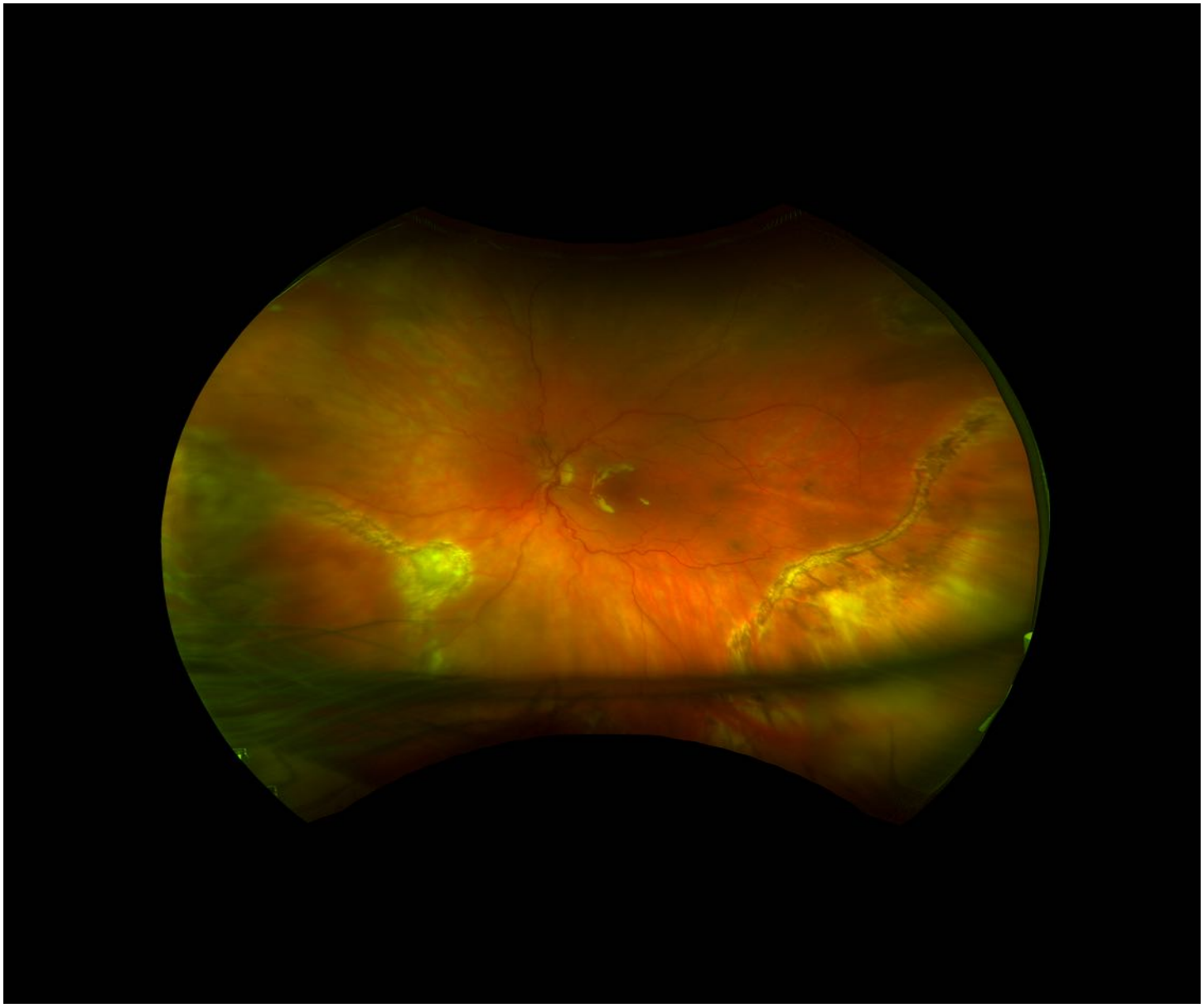
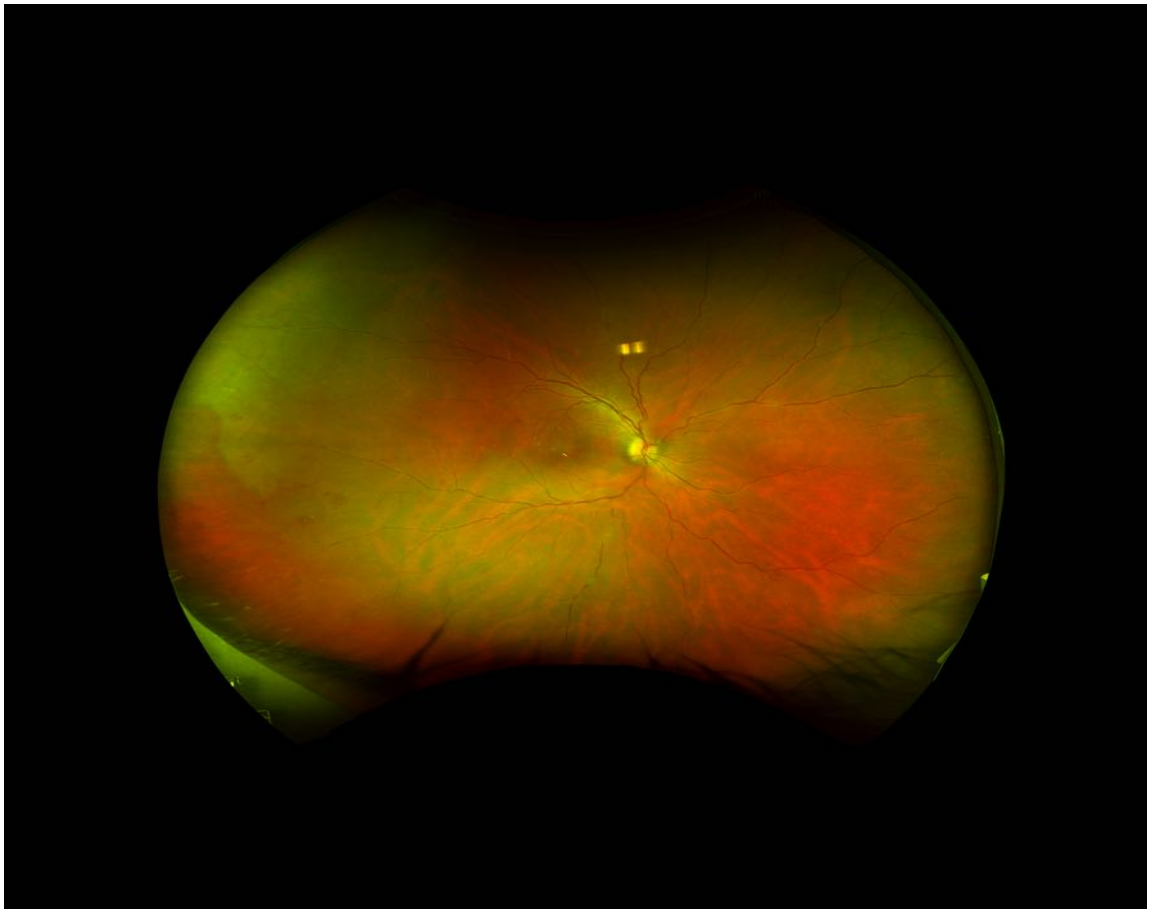
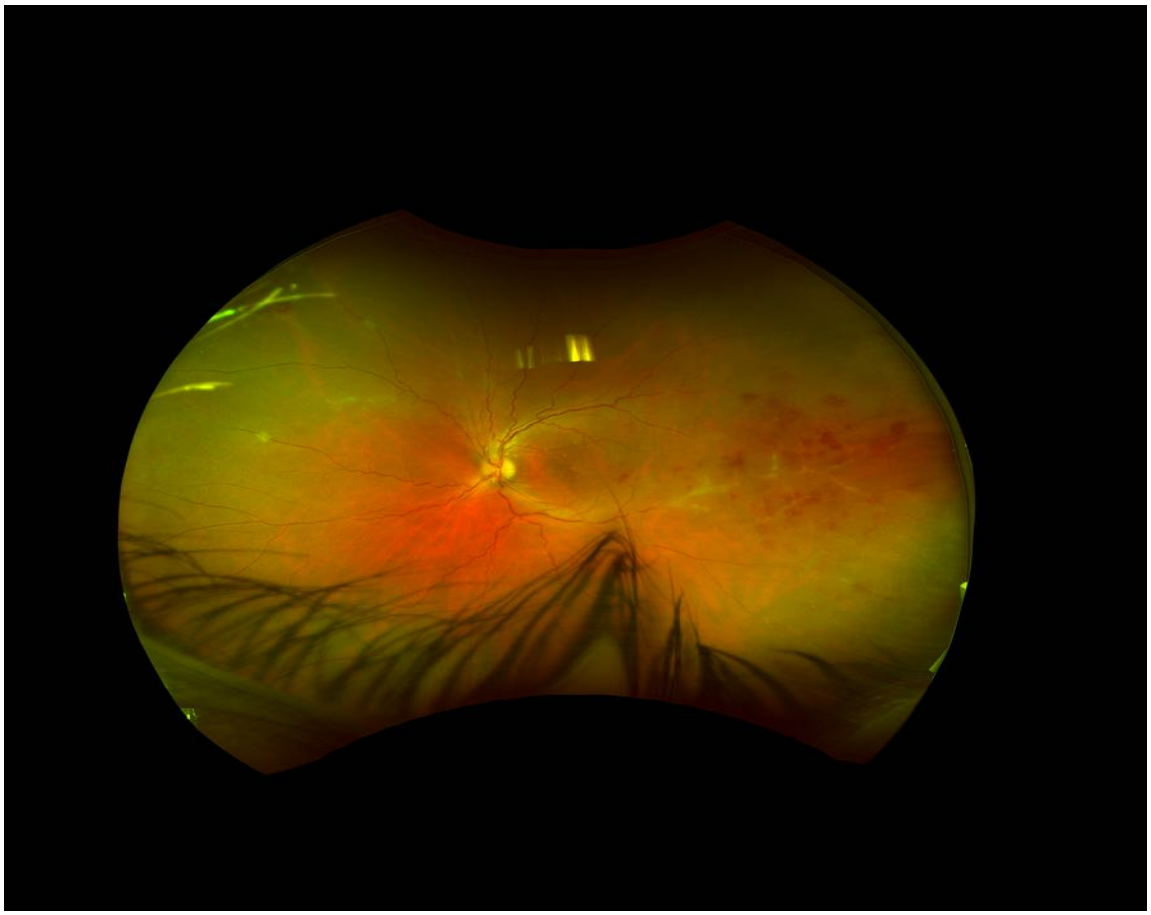


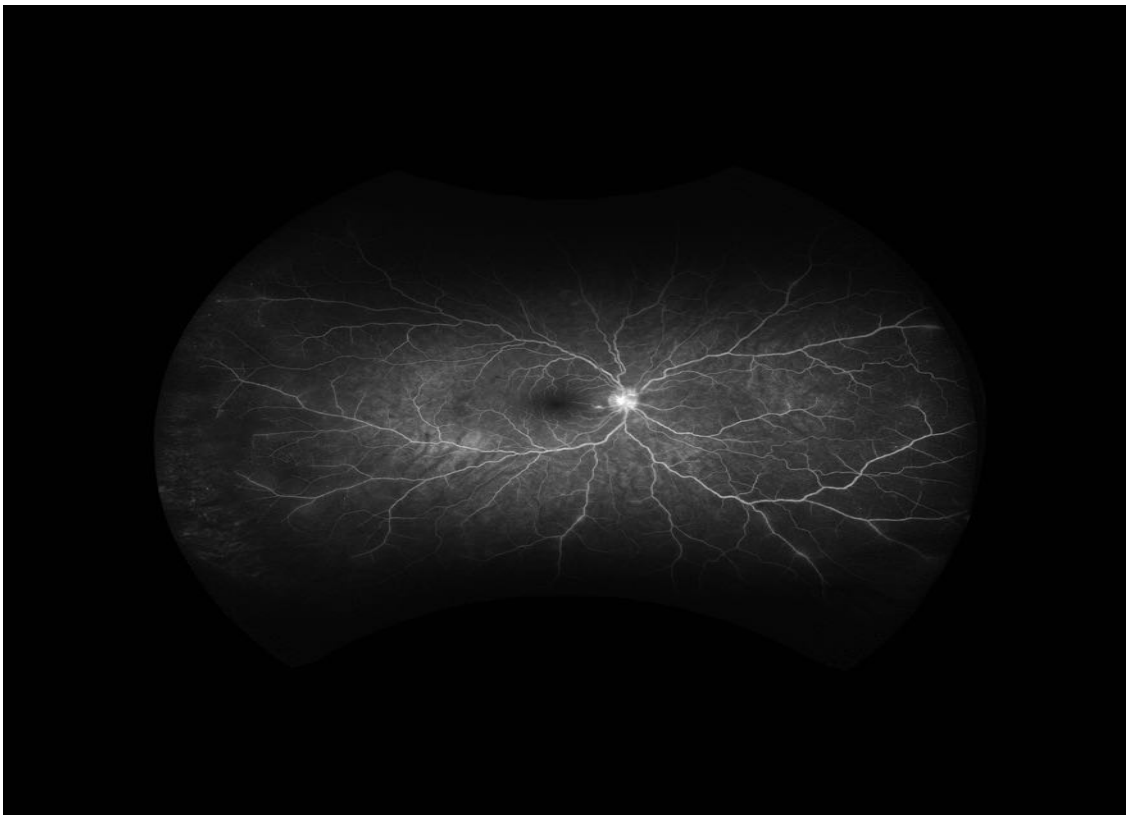


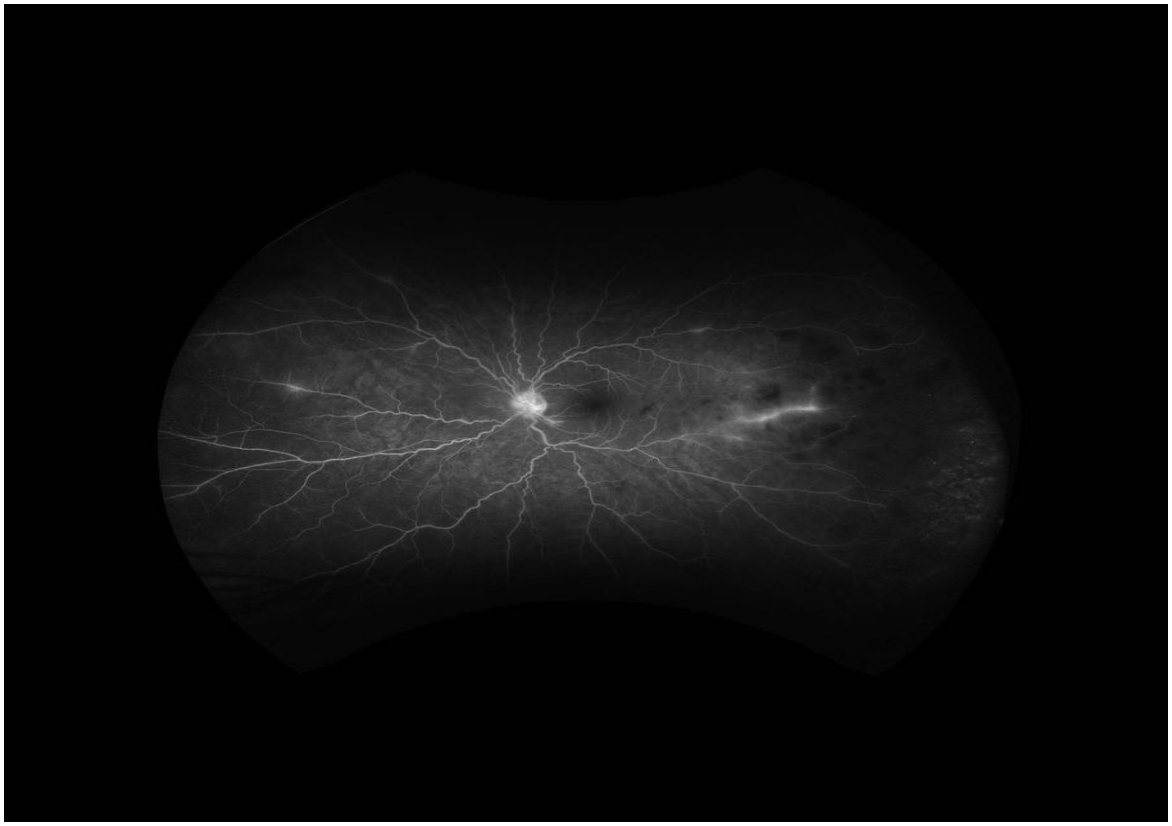


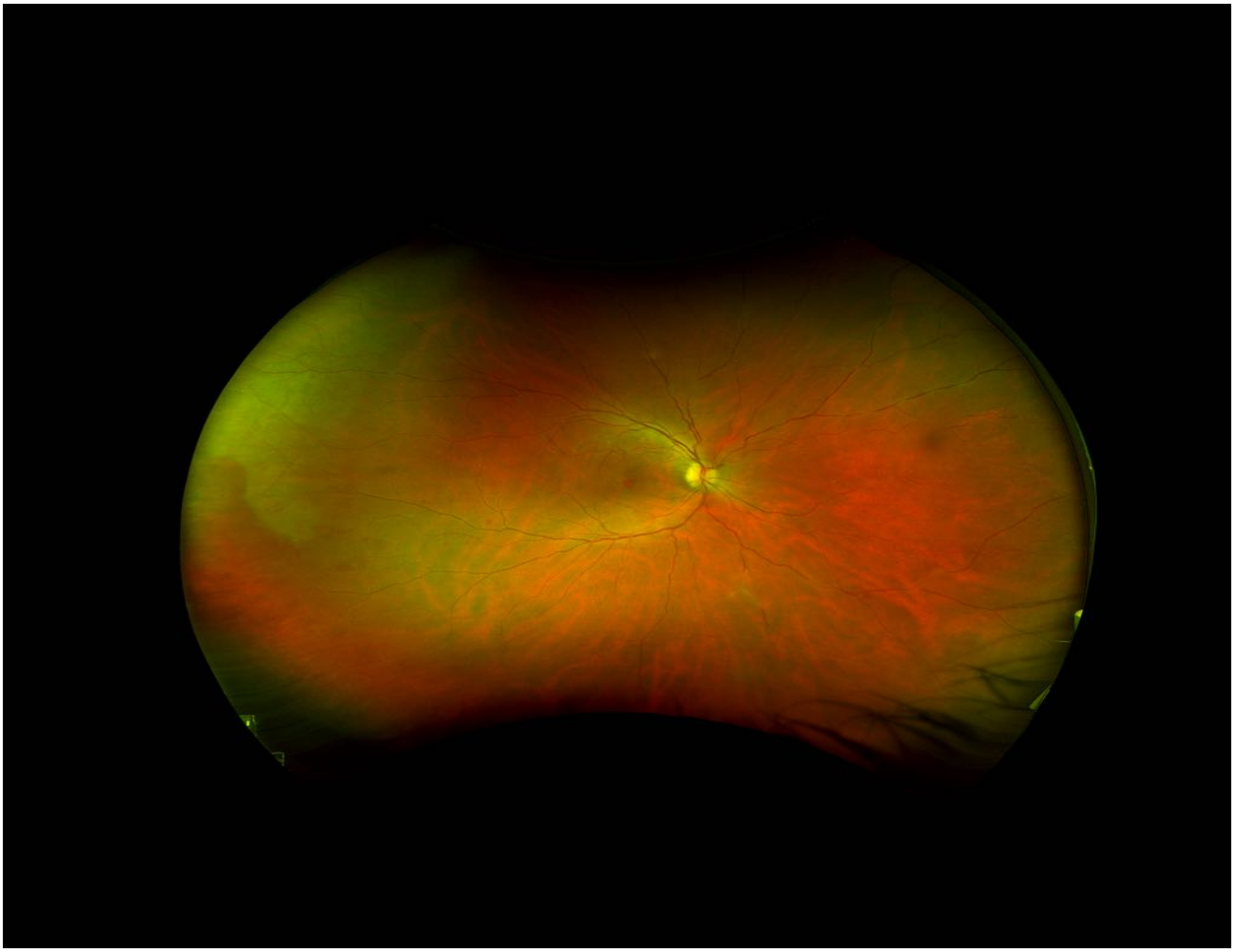


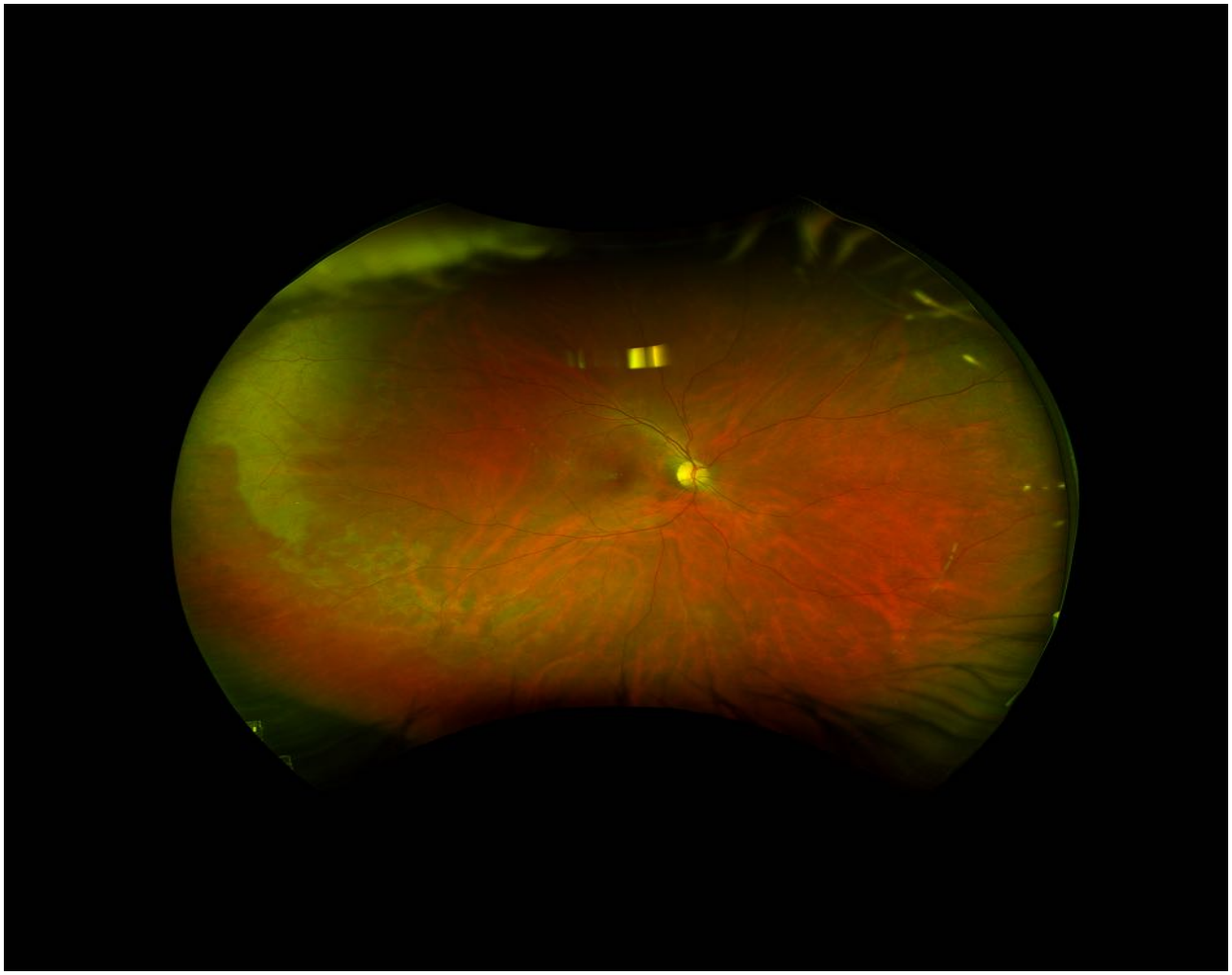


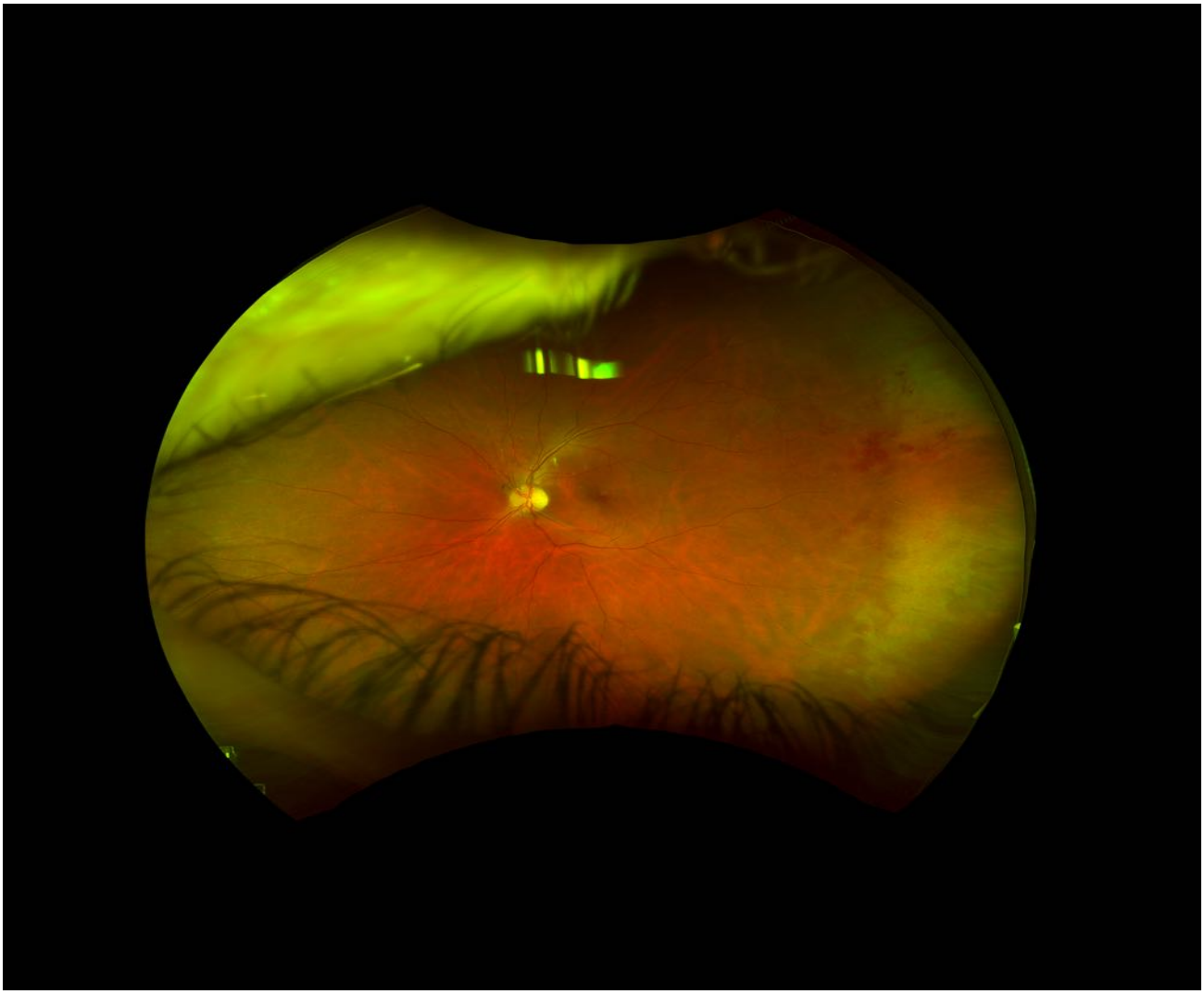


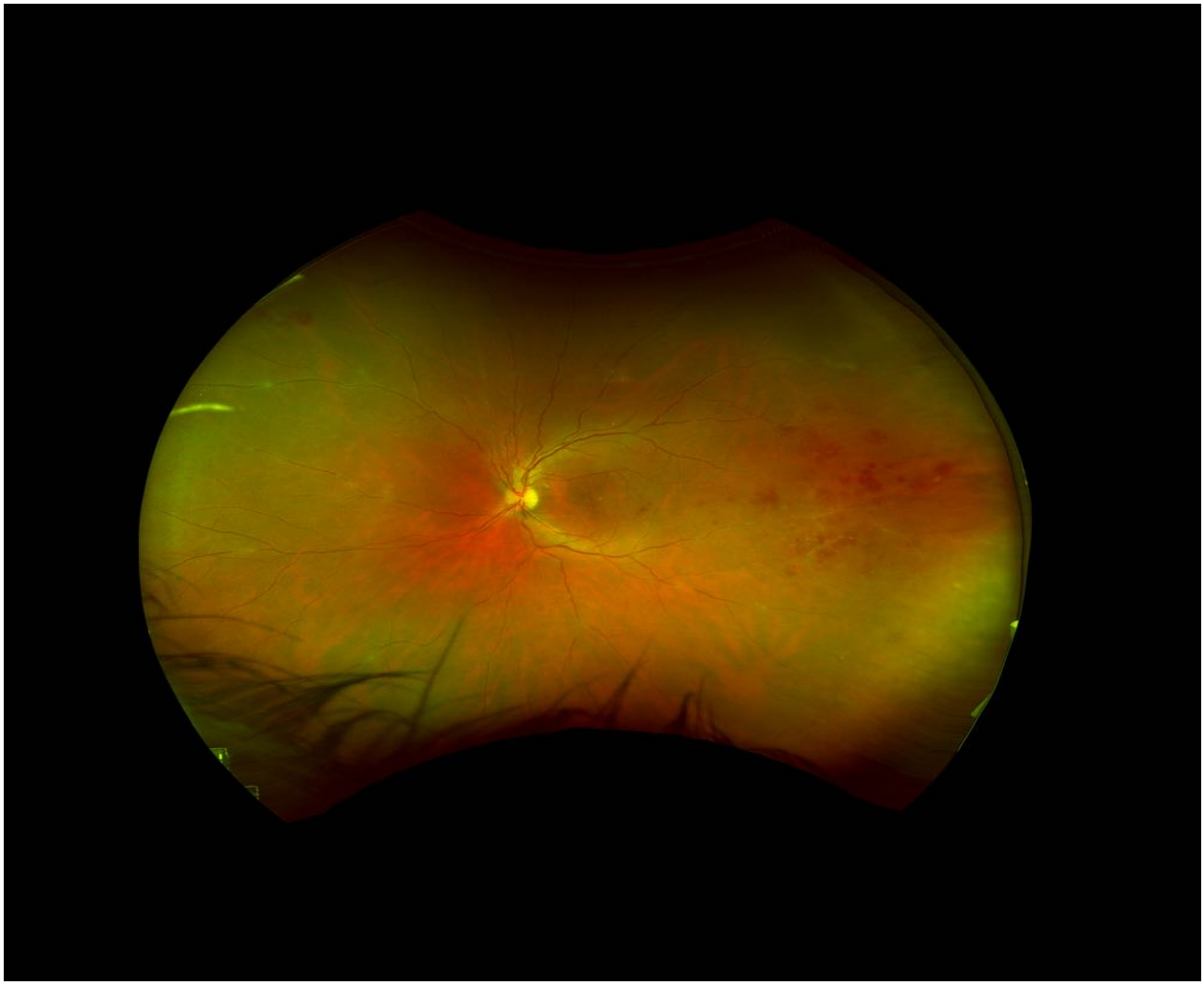


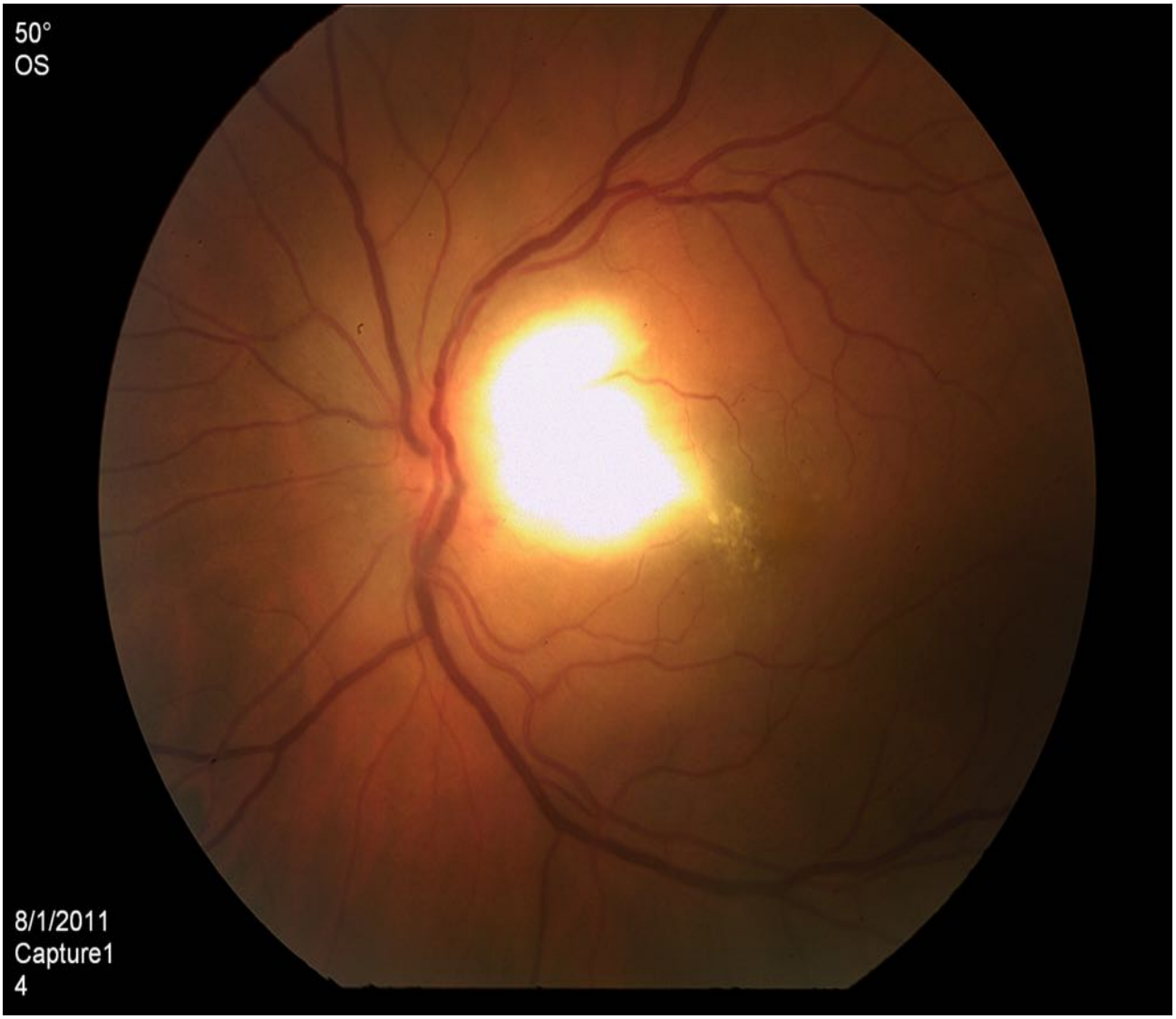








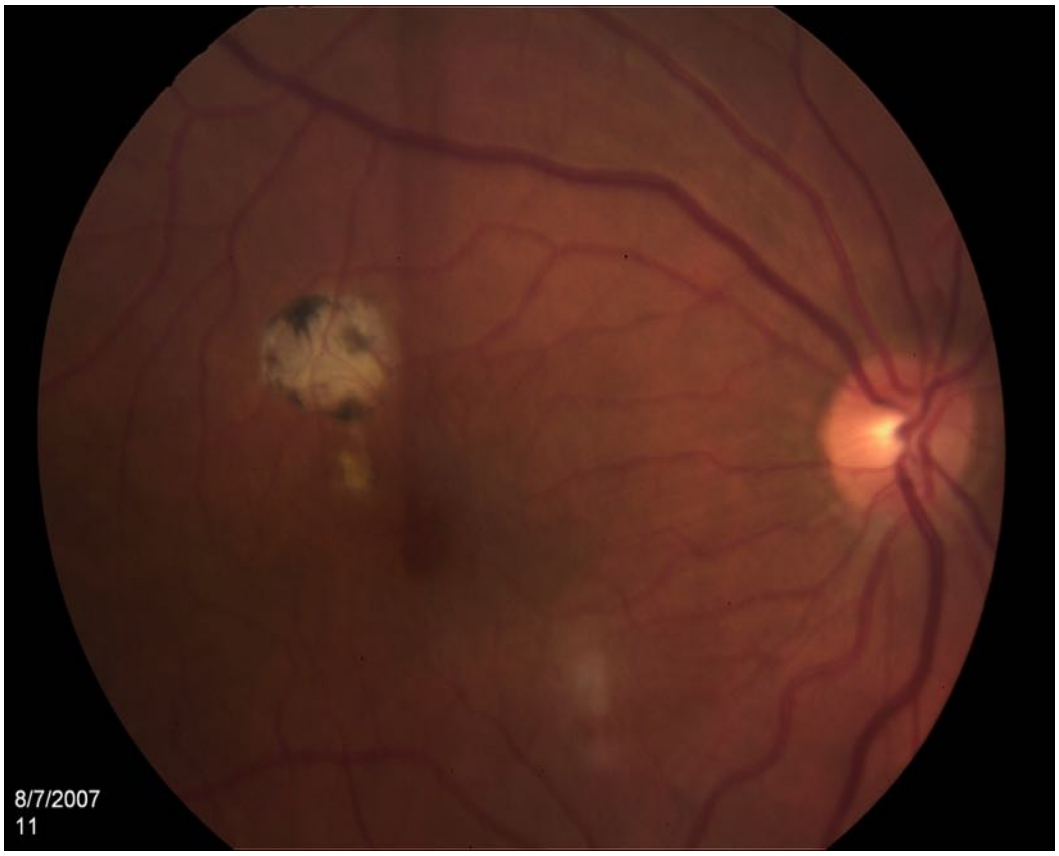


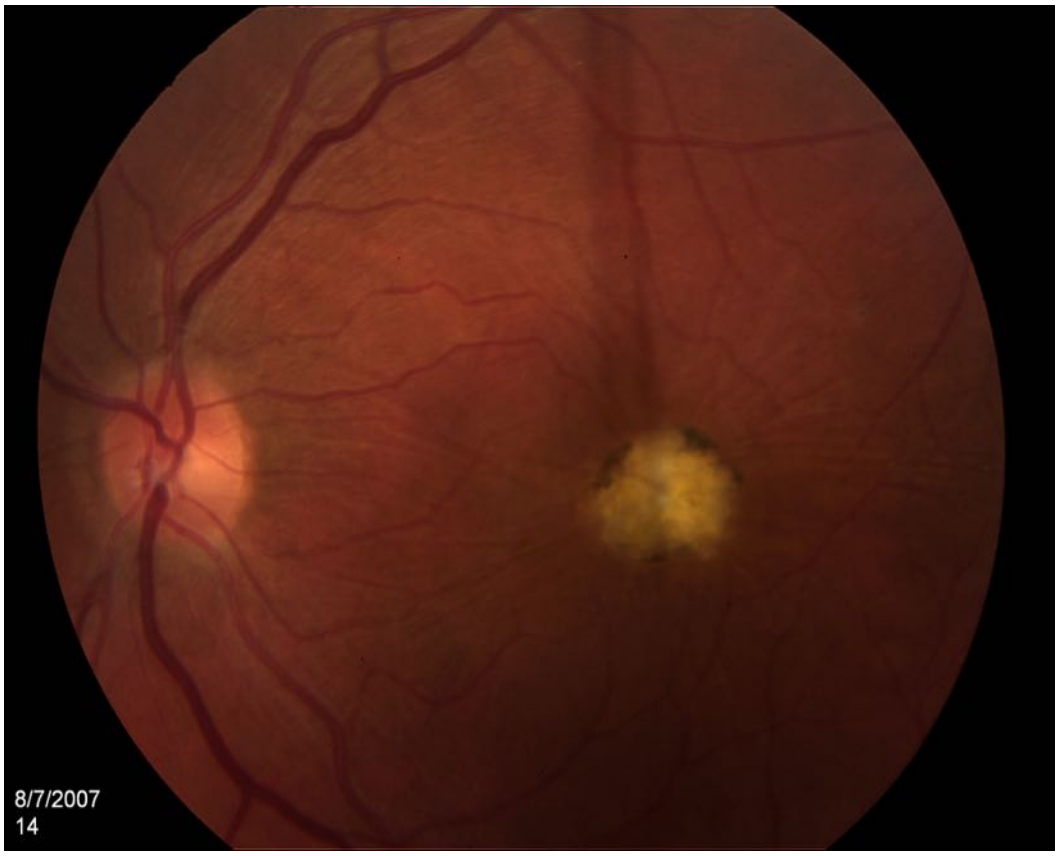


Toxoplasmosis retinochoroiditis in UC patient on Humira and prednisone

Radwan A, Arcinue C, Baheti U, Hinkle D. Retinal Cases Brief Reports 2013.

Bilateral endogenous Candida endophthalmitis in UC patient on infliximab and azathioprine

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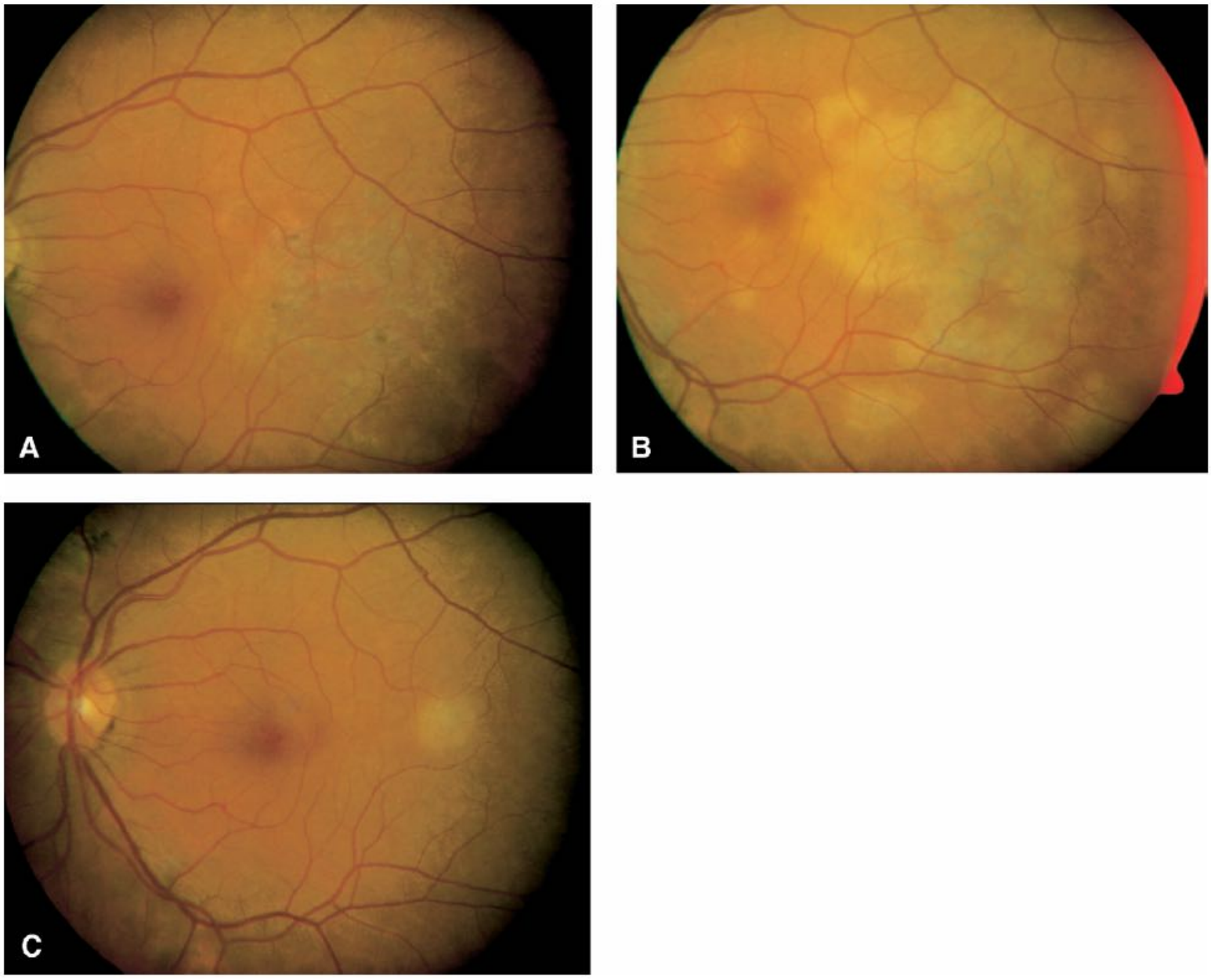
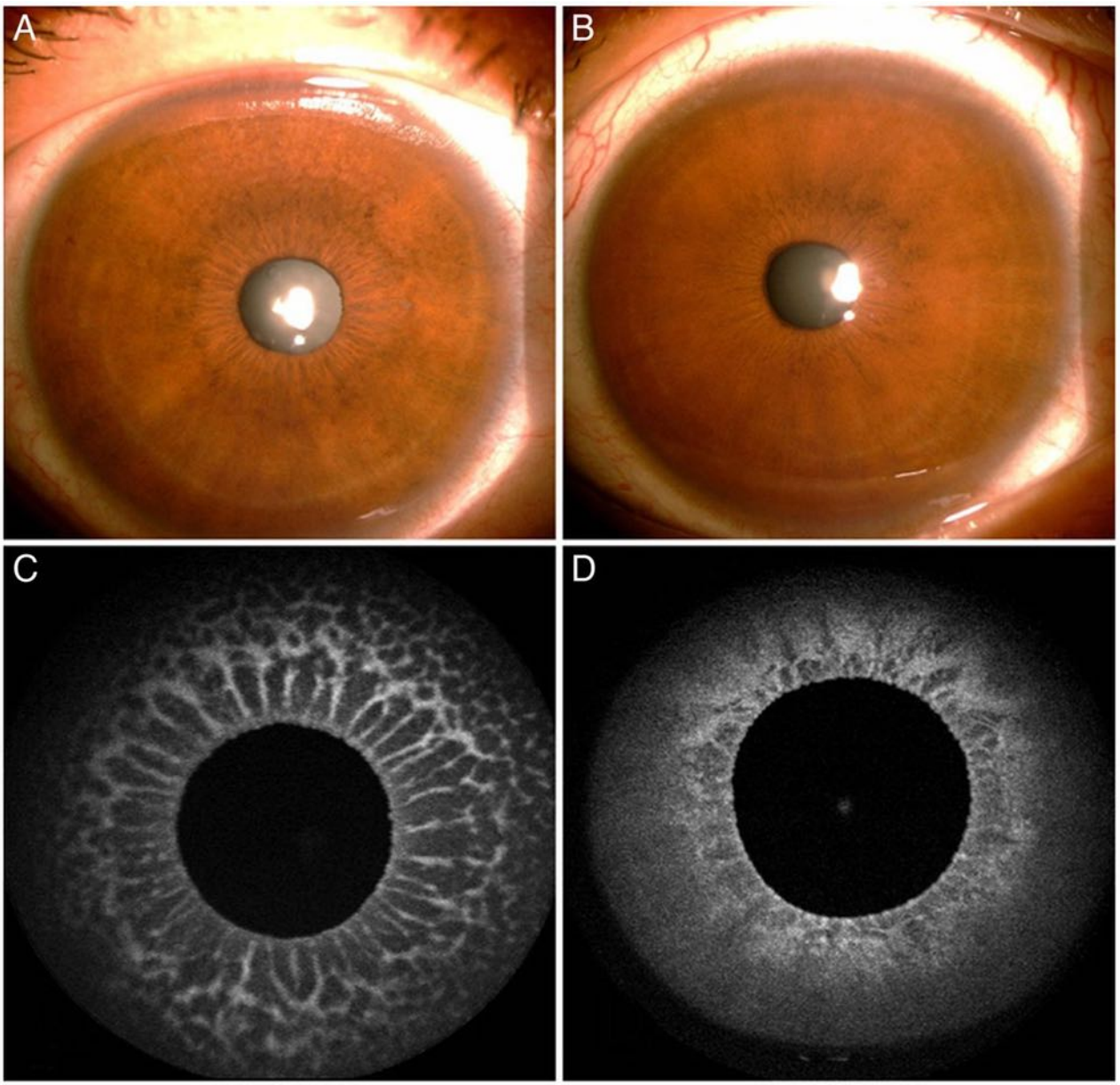
Unrecognized TB Serpiginouslike Choroiditis



Ophthalmology. 2008;1159:1633.

Colour images (A and B) and near-infrared autofluorescence (C and D) in both eyes of a patient (35 years old).



Qian Liu et al. Br J Ophthalmol 2016;100:1397-1402