Grand Rounds

November 20, 2014

SUNY Downstate Medical Center

Department of Ophthalmology

~Boleslav Kotlyar, MD~

Subjective

- HPI: 28 yo Hispanic F presents for initial eval, c/o gradually worsening vision and trouble reading. Never worn glasses. Denied photophobia
- PMH/meds: none
- PSH: none
- FH: denies blindness
- SH: No smoking/EtOH/drugs. Full diet. Stay-at-home mom

Objective

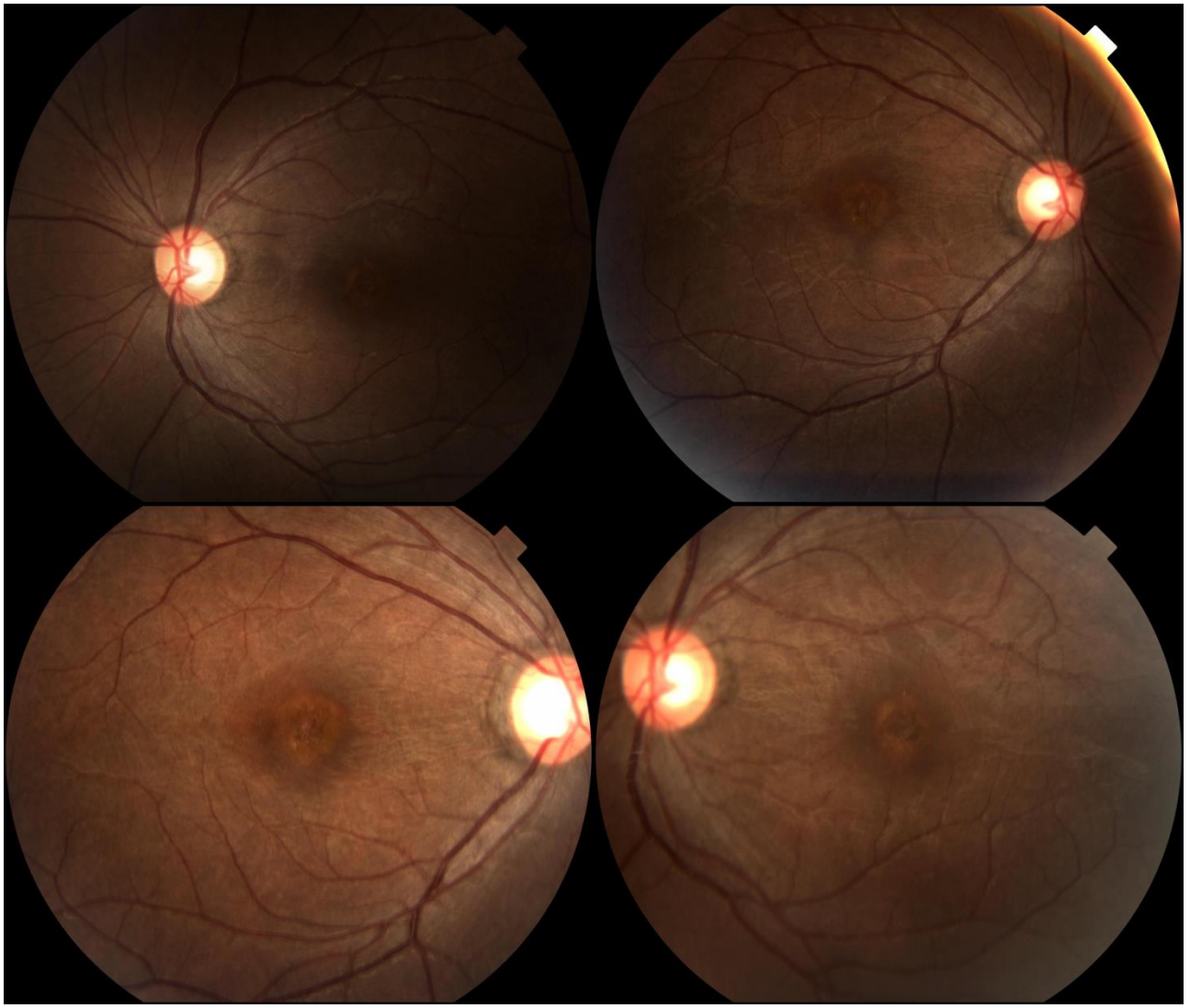
- dVAsc: 20/400 ou
- MRx:-1.00 -0.50x180→20/100 ; 20/80

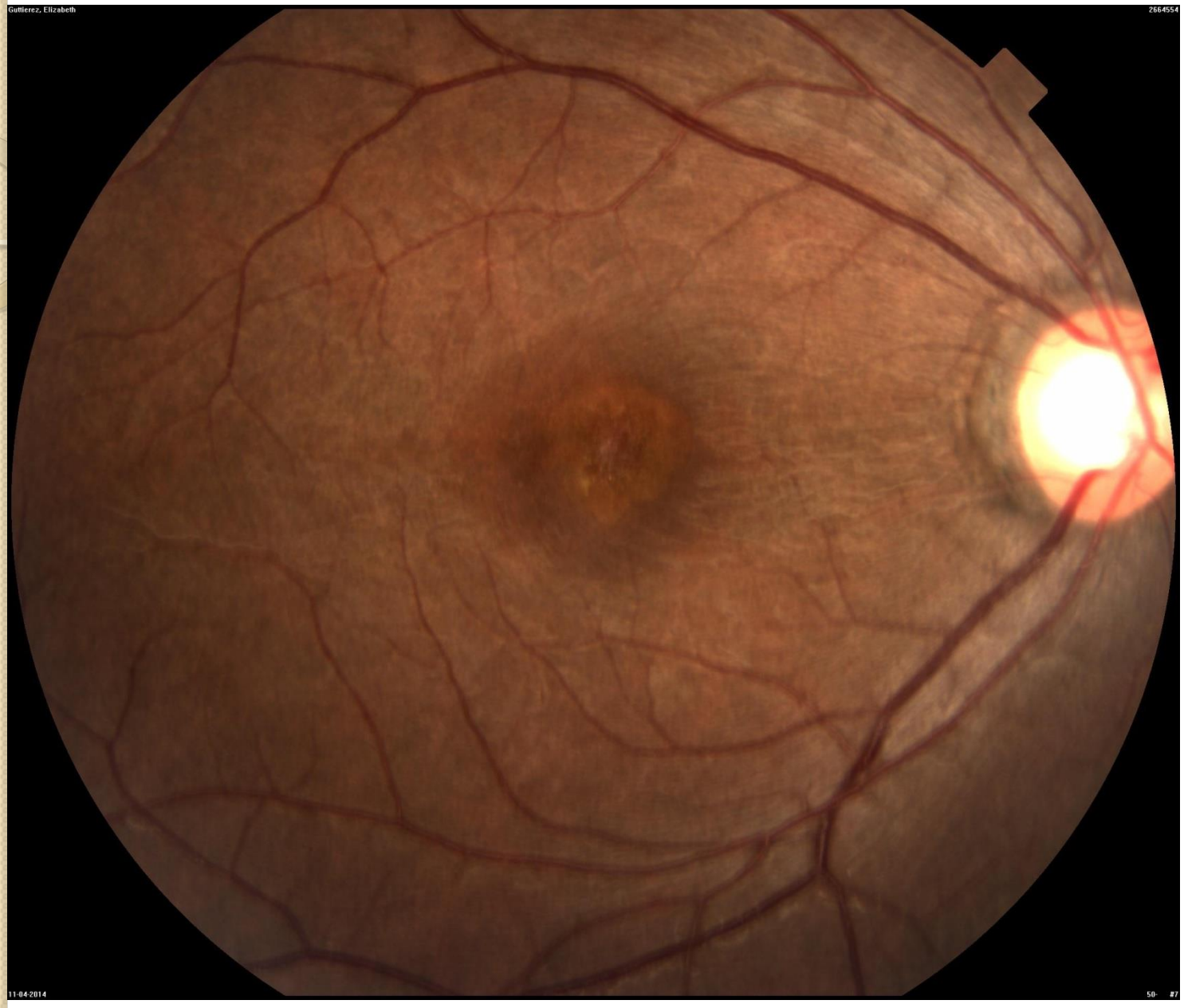
- EOM: full, no pain/diplopia. No nystagmus
- Pupils 4→2 ou, no APD
- CVF: full to count fingers ou
- Ishihara Plates: 1/10 ou
- Additional history: denied nyctalopia

Slit Lamp Exam

- LLA: wnl ou
- C/S: W+Q ou
- K: clear ou
- AC: D+Q ou
- I/P: round, reactive 4->2 ou, no APD
- Lens: clear ou

Dilated Fundus Exam

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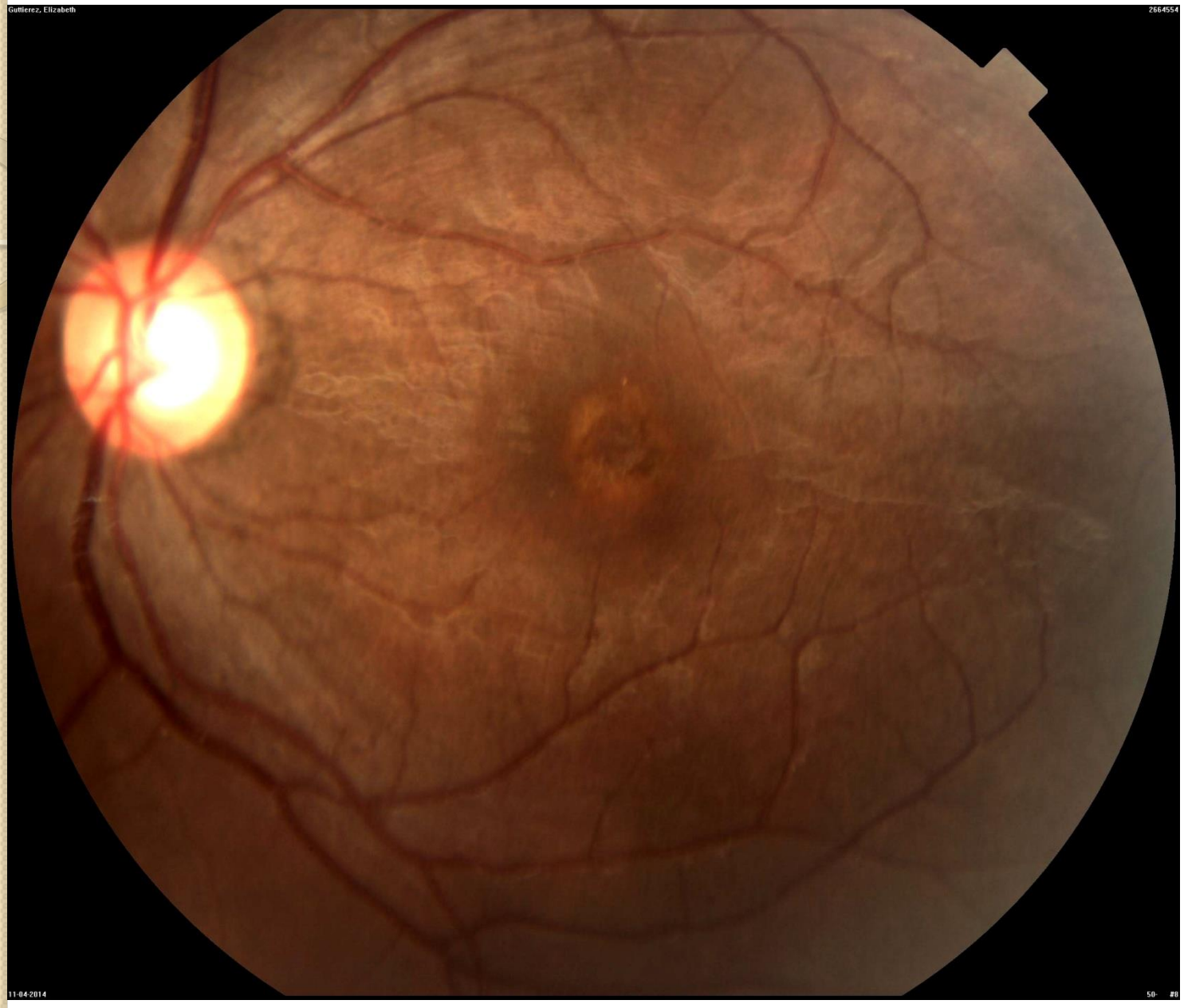
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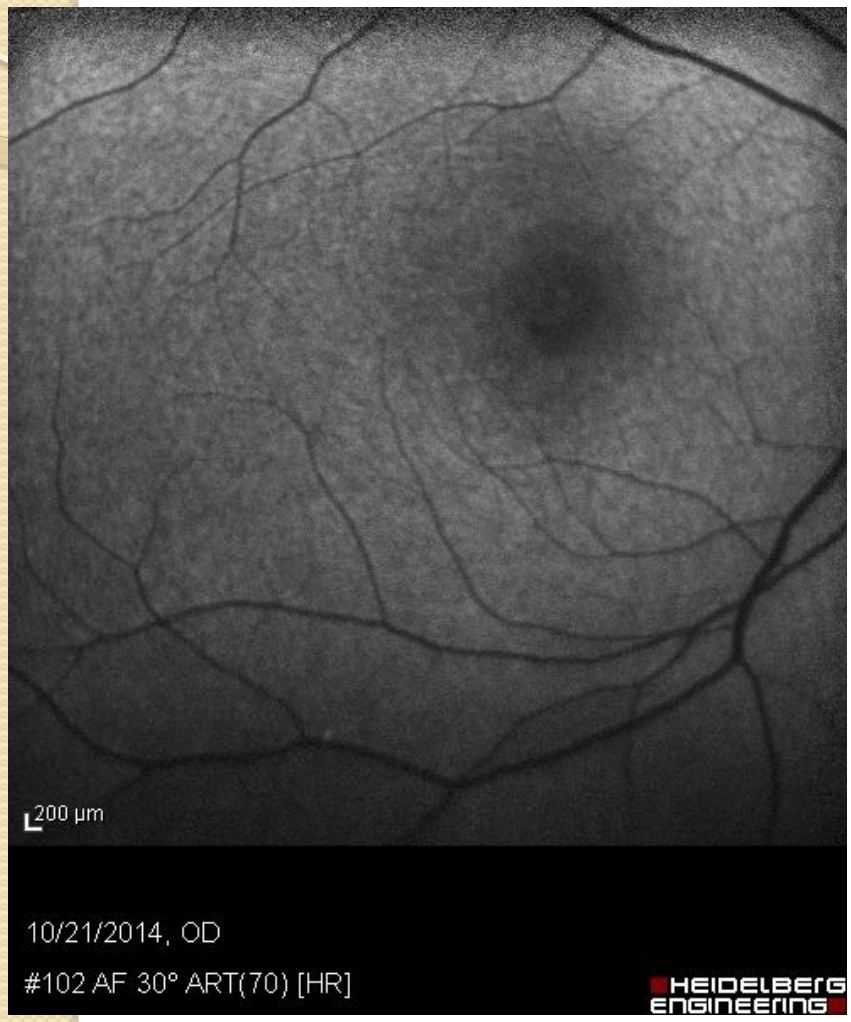
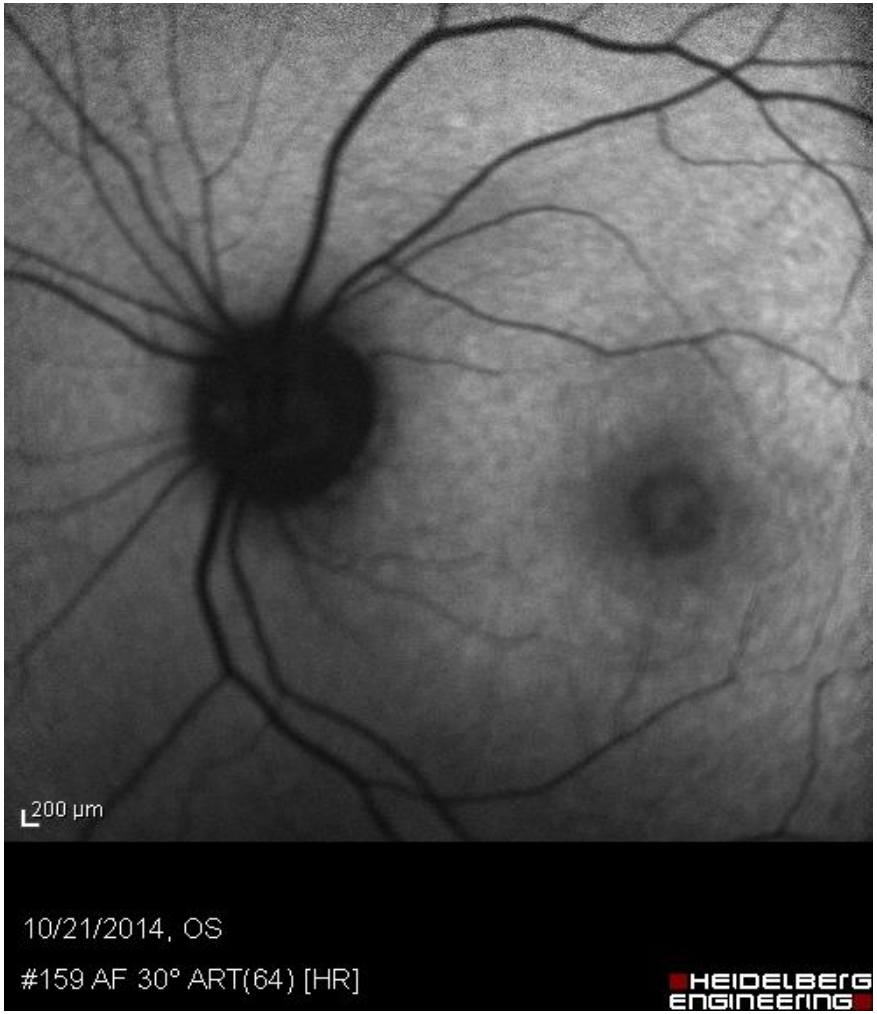
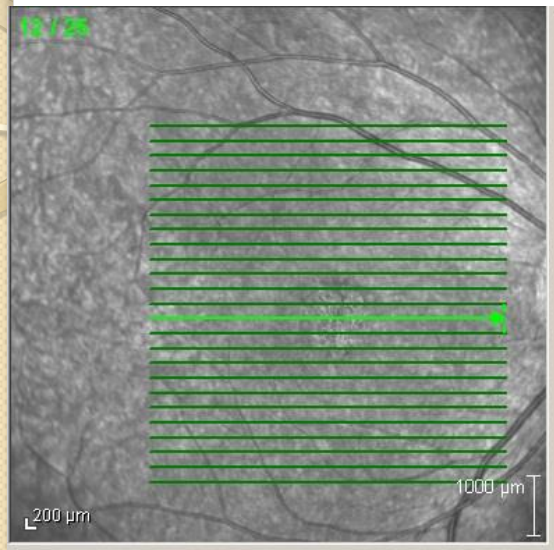
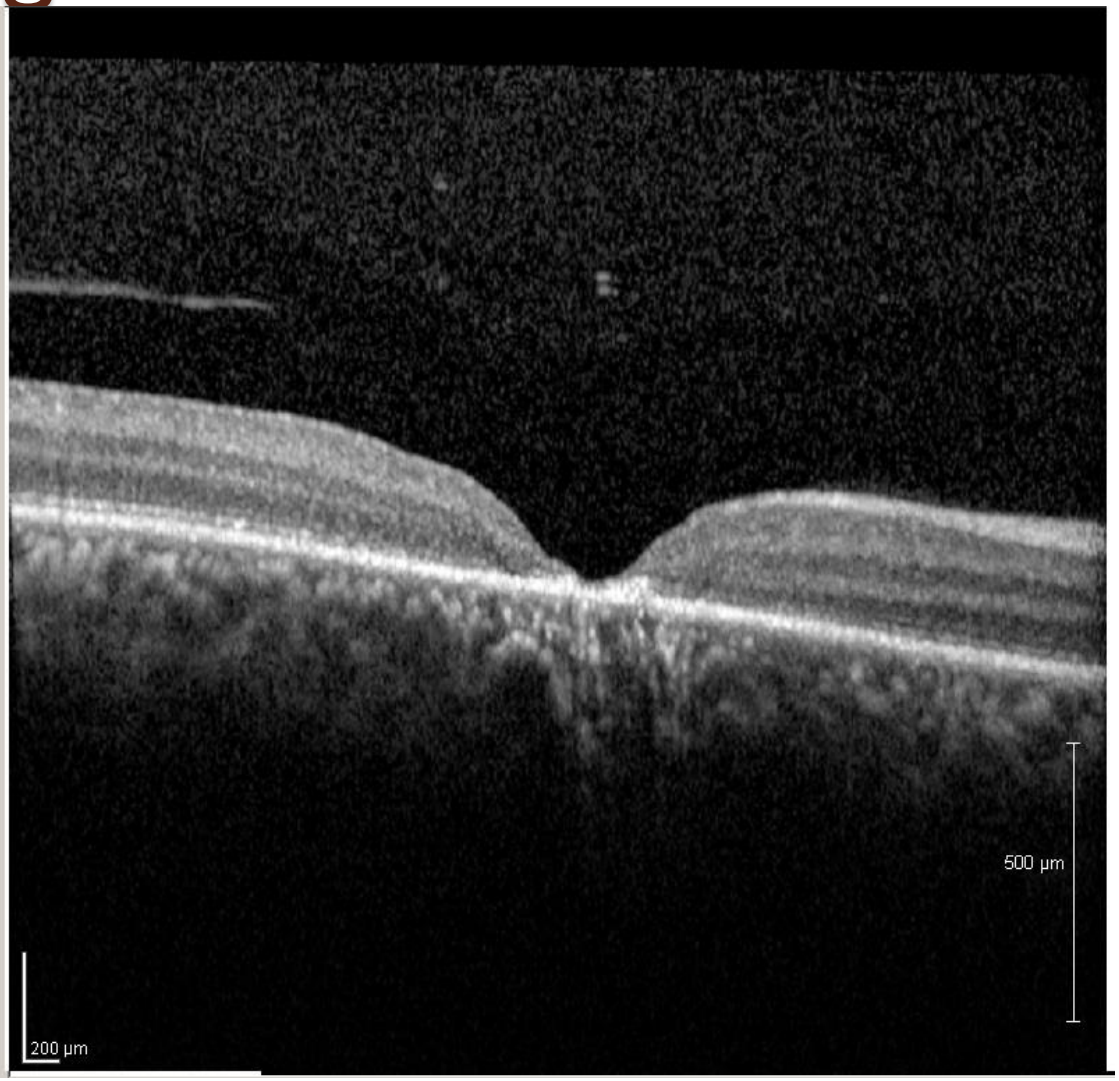
Autofluorescence



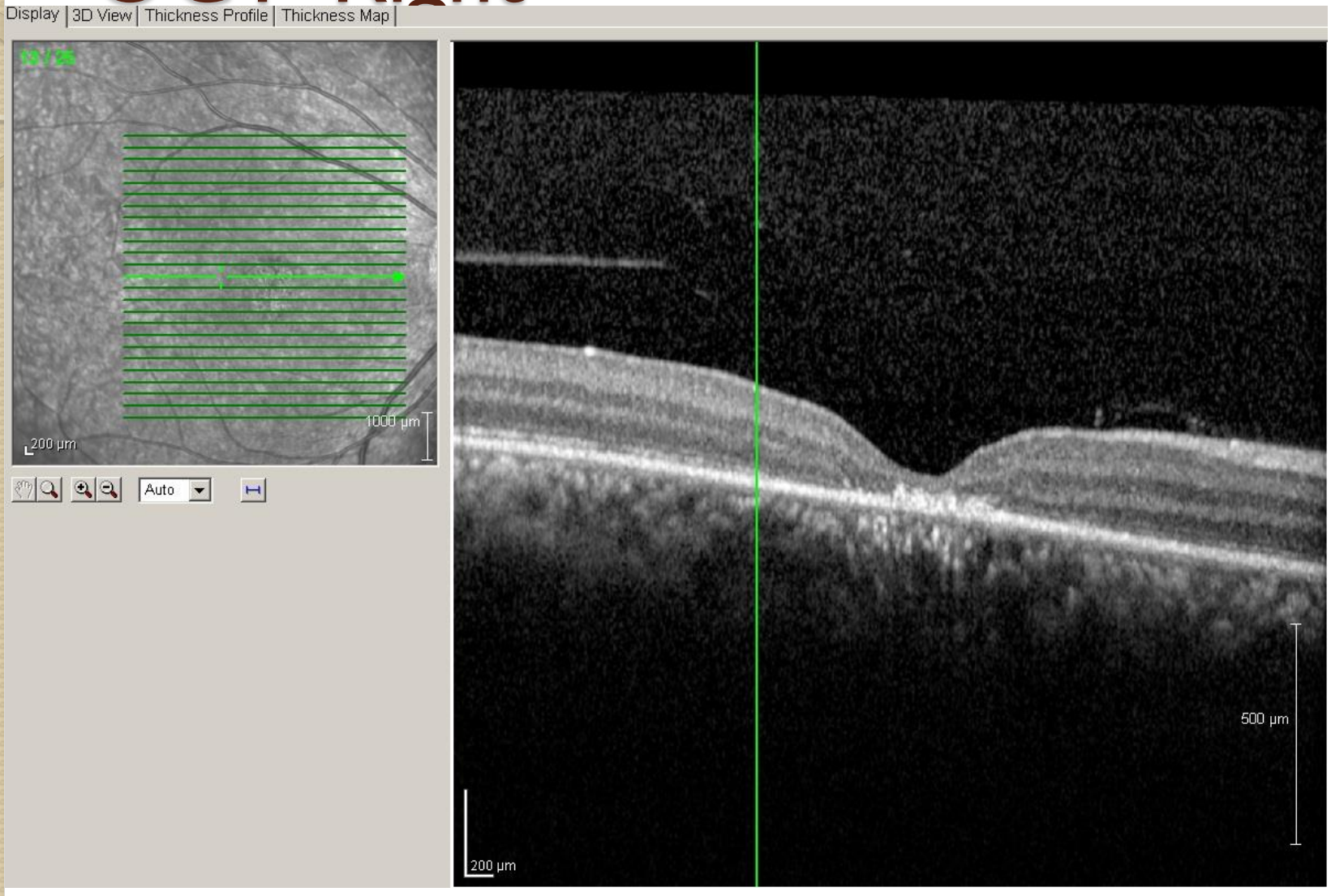


OCT - Right

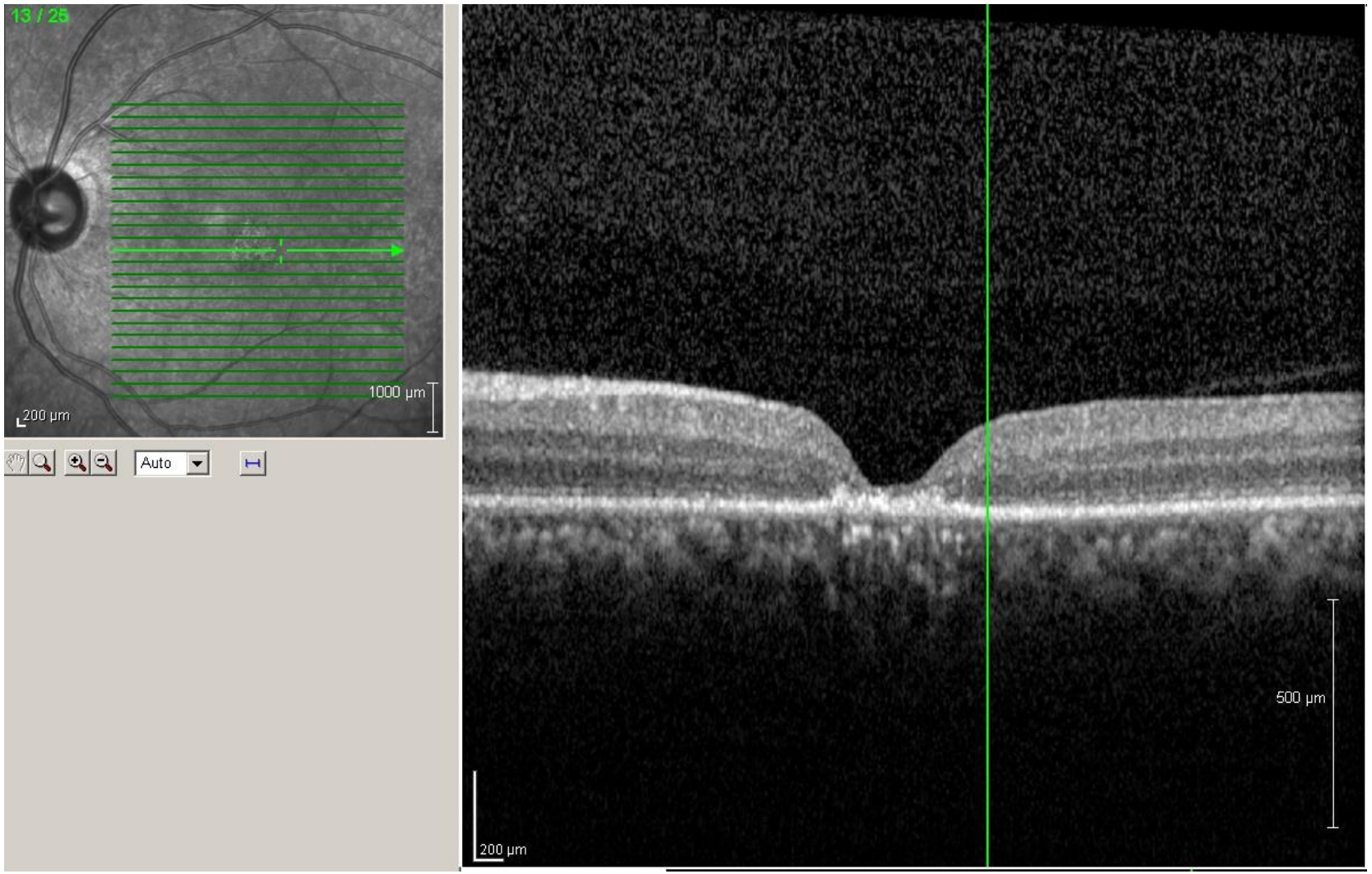




OCT- Right


Display
3D View
Thickness Profile
Thickness Map
1000 µm
200 µm
Auto
500 µm
200 µm

OCT - Left



Thickness Map Single Exam Report OU

SPECTRALIS® Tracking Laser Tomography

HEIDELBERG ENGINEERING

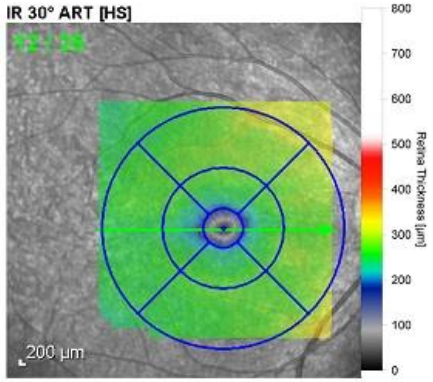
Patient: **DOB:** **Sex:**

Patient ID: **Exam.:**

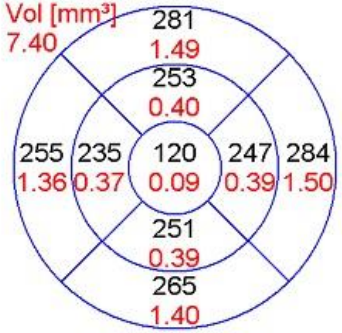
Diagnosis: --- **Comment:** ---

OD

IR 30° ART [HS]

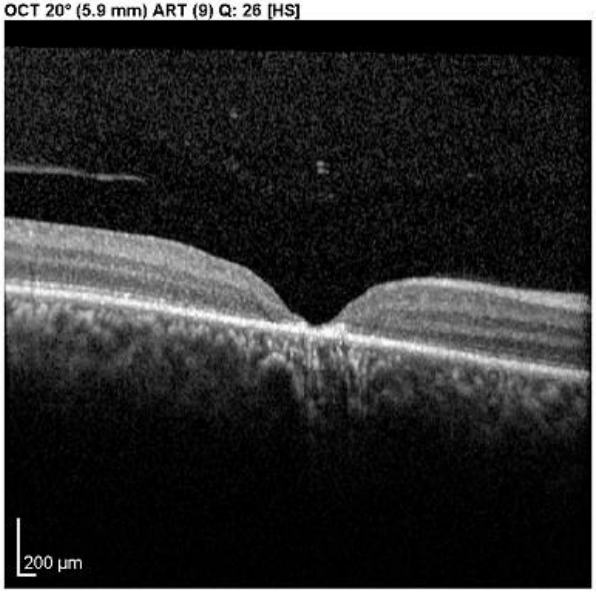


Average Thickness [µm]



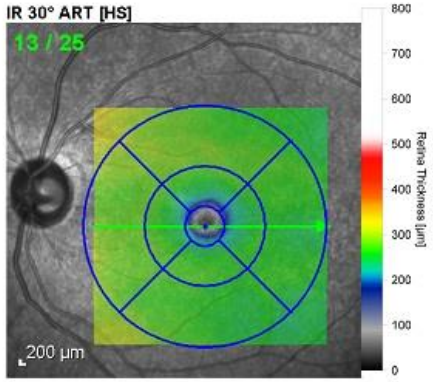
Center:	5 µm
Central Min:	4 µm
Central Max:	206 µm
Circle Diameters:	1, 3, 6 mm ETDRS

OCT 20° (5.9 mm) ART (9) Q: 26 [HS]

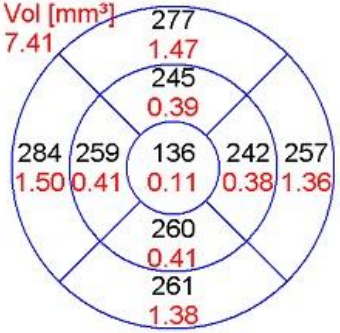


OS

IR 30° ART [HS]

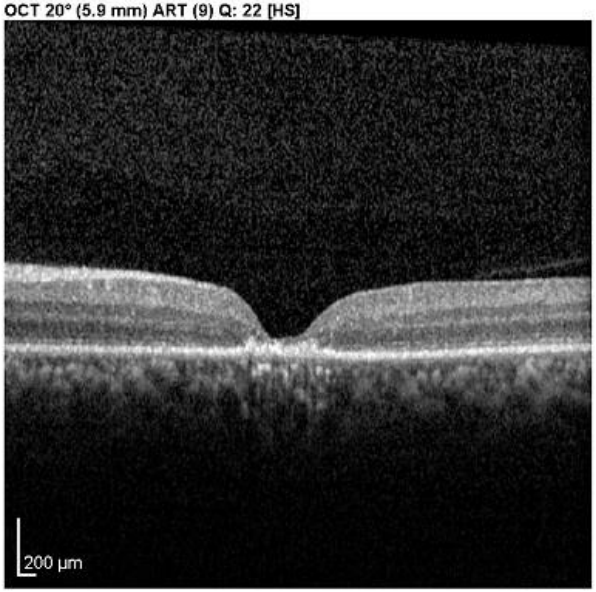


Average Thickness [µm]



Center:	49 µm
Central Min:	24 µm
Central Max:	233 µm
Circle Diameters:	1, 3, 6 mm ETDRS

OCT 20° (5.9 mm) ART (9) Q: 22 [HS]

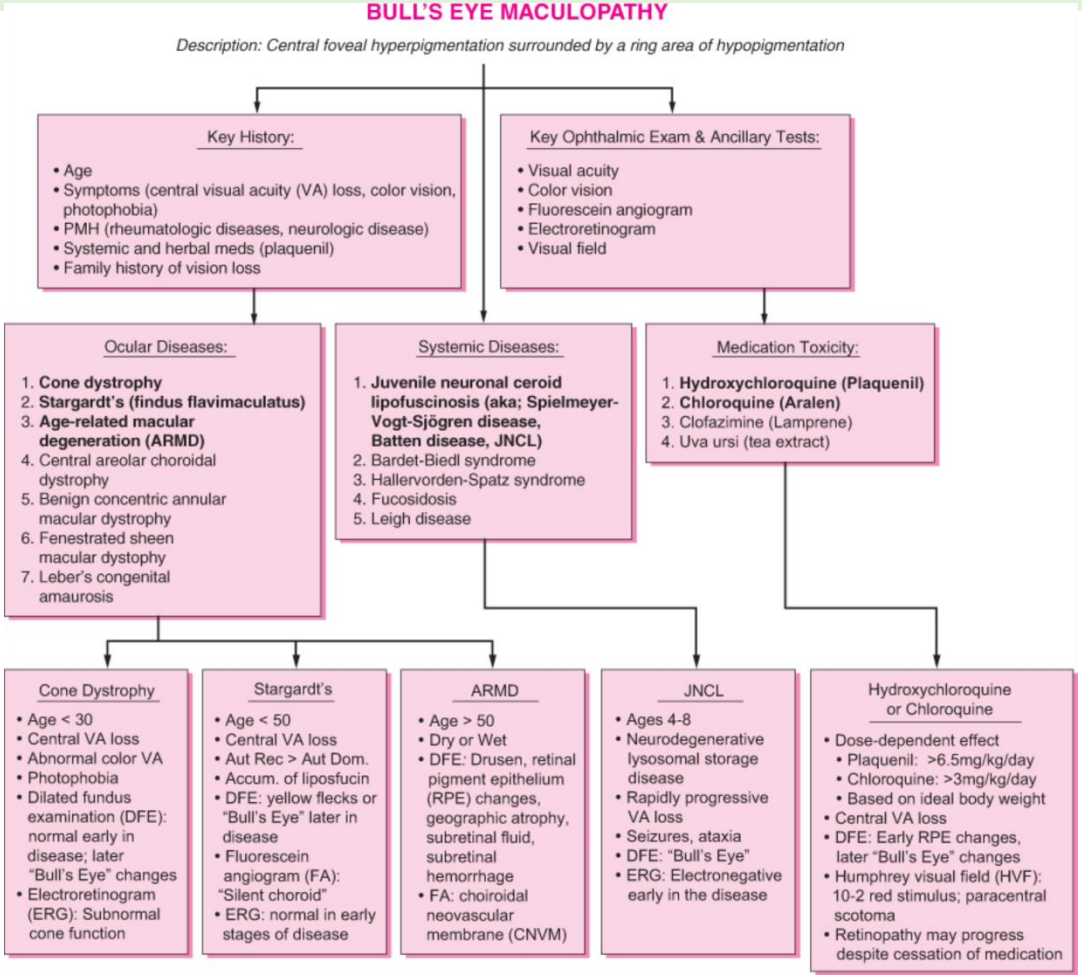


DDx

- Stargardt Disease
- Cone Dystrophies
- Medication
- Age-Related Macular Degeneration
- Idiopathic Chronic Macular Holes
- Benign Concentric Annular Dystrophy
- Central Areolar Choroidal Dystrophy
- Speilmeyer-Vogt-Batten-Mayou (Juvenile neuronal ceroid lipofucinosis)
- North Carolina Dystrophy

From: **Bull's Eye Maculopathy (Algorithm)**

Wills Eye Institute 5-Minute Ophthalmology Consult, 2011

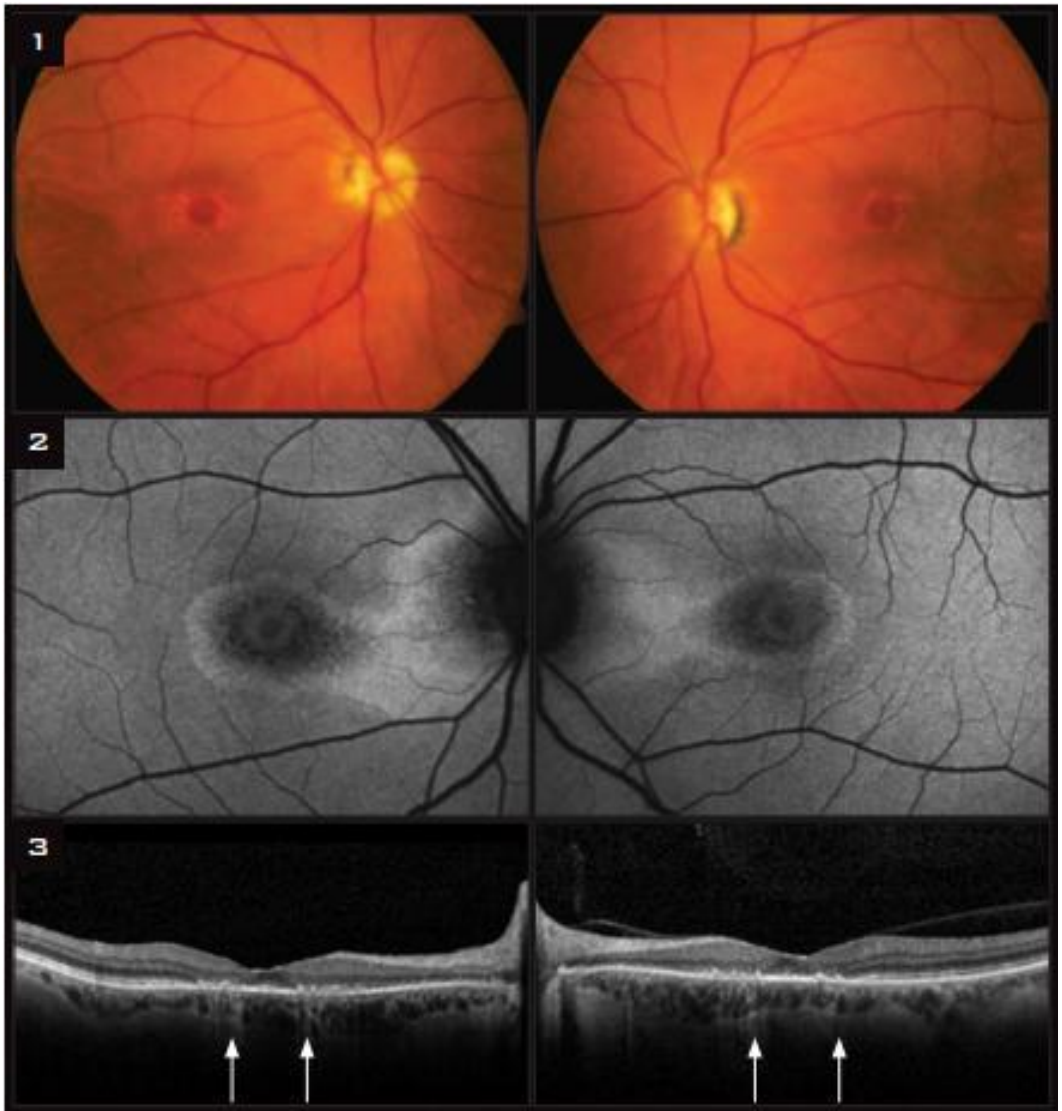


Medication

- "Bull's eye" to describe ring-like atrophy at posterior pole, introduced by Kearns and Hollenhorst (1966) for cases of toxic retinopathy due to synthetic antimalarial agents
- Hydroxychloroquine (Plaquenil)
  - Total Life Dose >1000g
  - Daily dosing - >6.5mg/kg/day (often used 200mg BID is too much for women <5'7", men <5'5")
  - Medication use >5 years
  - Concomitant Renal/Hepatic disease
  - Screening: Thorough exam+ 10-2 VF +, at least one of: SD-OCT, autofluorescence, Multi-focal ERG. Not Amsler grids. TD-OCT lack sensitivity.

Mechanism Plaquenil

- Not fully elucidated
- Studies show affect on metabolism of retinal cells and also binding to melanin in the RPE, which could explain the persistent toxicity after discontinuation of the medication. However, these findings do not explain the clinical pigmentary changes causing a bull's-eye maculopathy

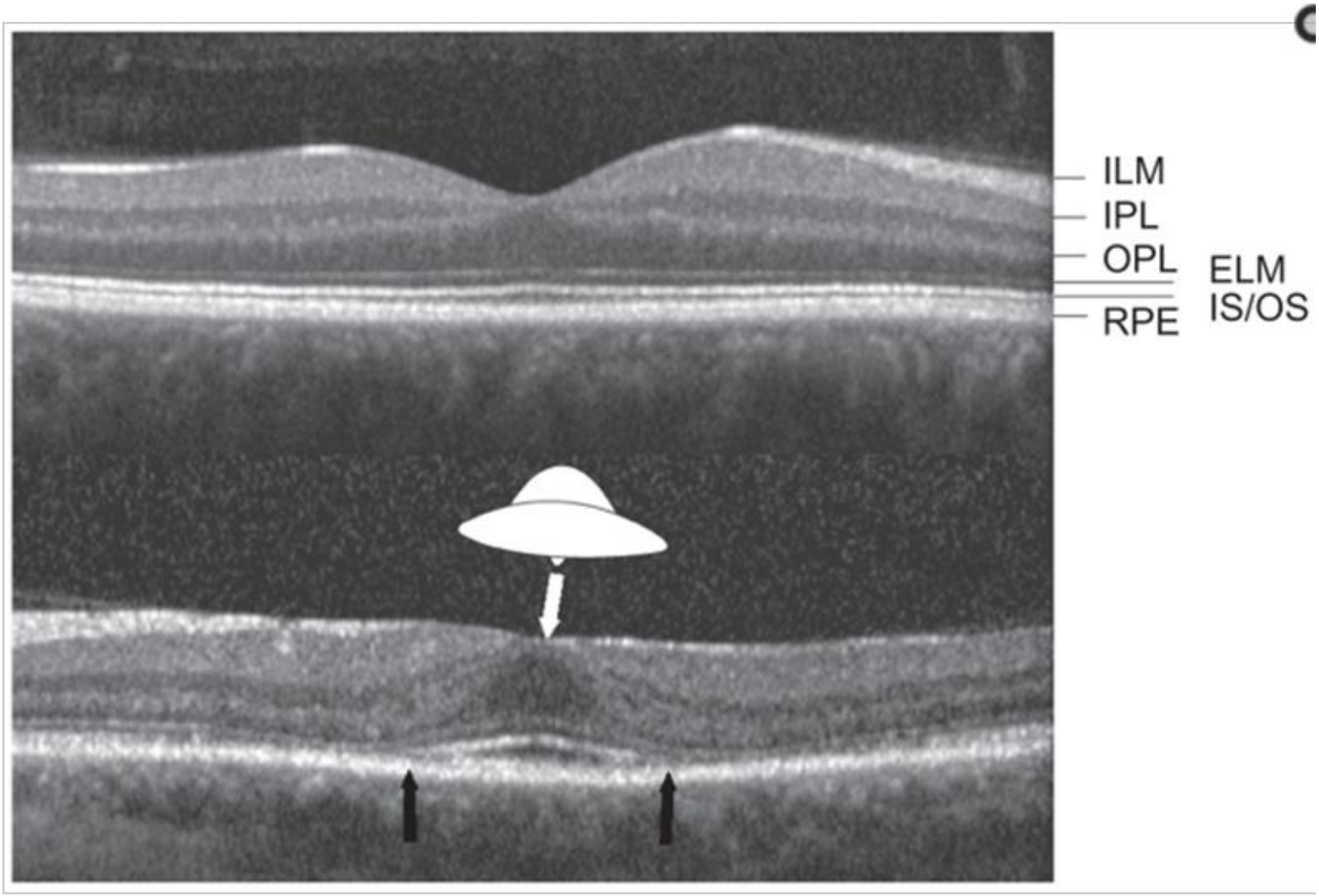


ADVANCED BULL'S-EYE RETINOPATHY. A 55-year-old female who had been taking hydroxychloroquine for 10 years before the onset of symptoms. Color fundus photos showing bull's-eye maculopathy (1). Fundus autofluorescence with central mottled hypoautofluorescence with surrounding rim of hyperautofluorescence (2). SD-OCT shows marked parafoveal thinning of the retina (arrows), especially of the outer photoreceptor layers (3).

Eye Net Magazine June 2011

PMC full text: Clin Ophthalmol. 2010; 4: 1151–1158.
Published online Oct 21, 2010. doi: 10.2147/OPTH.S14257

Figure 1



Stargardt Disease

- Fundus Flavimaculatus
- Most common form of juvenile macular degeneration
- Usu starts age 6-12, vision loss within 1st-2nd decade of life. Usu stabilizes 20/200
- Incidence 1/8-10,000
- Usually Autosomal Recessive

Stargardt Disease

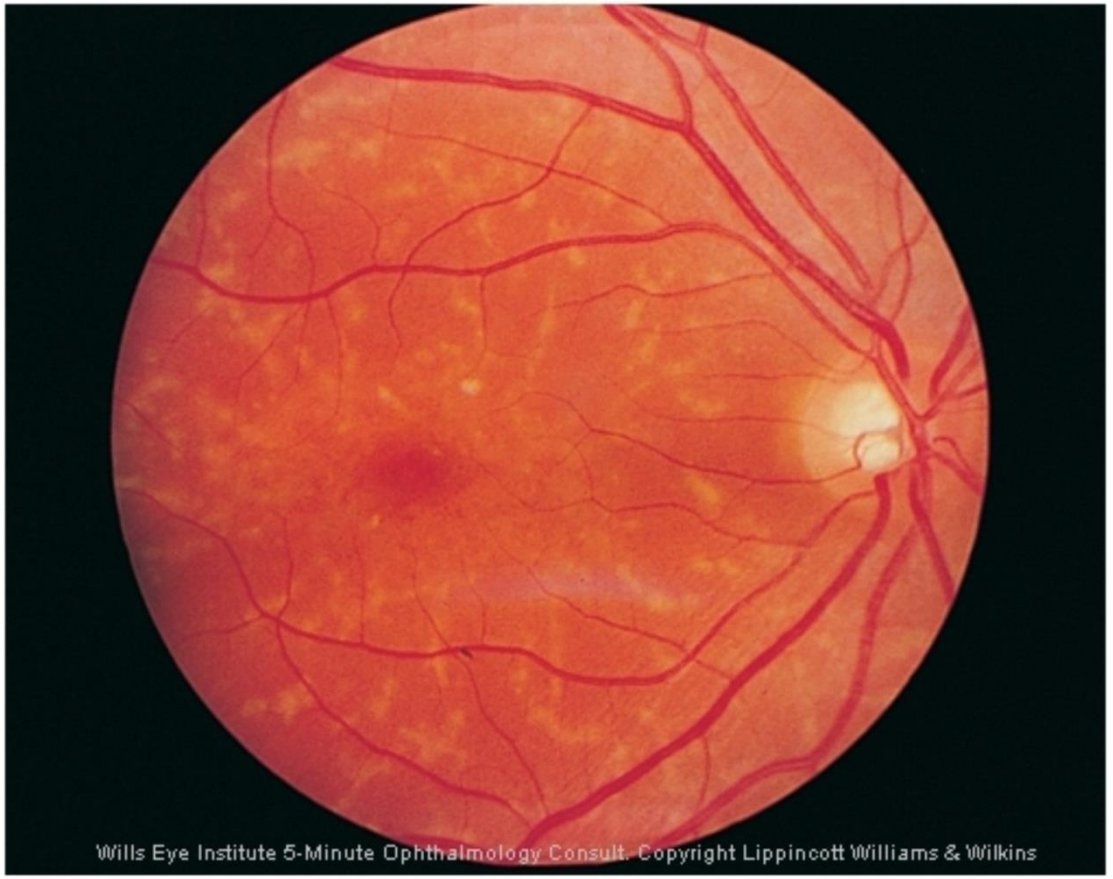
- Classic Disease = mutations in *ABCA4* on chromosome 1p13-p21. ATP-binding cassette transporter is defective, leading to build-up of toxic metabolite, lipofuscin, in RPE
- >400 sequence variations described
- Mutations in same gene linked to autosomal recessive cone-rod dystrophy and Retinitis Pigmentosa
- Interference with transport of Vitamin A between photoreceptors and underlying RPE
- High Concentration of photoreceptors at fovea leads preferential damage
- Butterfly pattern- mutation in gene coding for membrane bound protein involved in elongation of very long chain fatty acids (*ELOVL4*)

Physical Changes (Stargardt)

- Usually Bilateral
  - Nonspecific RPE mottling, may take on a "beaten-bronze" appearance
  - Ill-defined yellow-white deep retinal flecks at RPE level, described as fish-like, pisciform
  - More advanced disease with atrophic macula with Bull's Eye or geographic atrophy appearance

From: **Stargardt Disease**

Wills Eye Institute 5-Minute Ophthalmology Consult, 2011



Legend:

Pisciform lesions and macular bull's-eye atrophy in patient with Sargardt's disease.

Stargardt Research

- Advanced Cell Technology
- Retinal cells derived from Human embryonic stem cells (hESC)
- 9/2011 Phase I/II =safe
- 3/2013 treated 18 patients, given approval to test therapy on patients with 20/100 vision
- 11/2013=New drug to remove lipofuscin from RPE, soraprazan
  - Orphan Status for Stargardt disease by European Medicines Agency
  - Potassium Competitive Acid Blocker

Cone Dystrophy

- Progressive Degeneration resulting in triad of central vision loss, photophobia, color vision problems due to selective degeneration of cones
- Cone-Dysfunction syndromes
  - Shortly after birth or infancy, non-progressive, Achromatopsia in 1:30,000 and infants have photophobia, poor vision, pendular nystagmus
- Cone Dystrophies
  - Anytime during childhood or early adulthood and are progressive

- Cone-Rod Dystrophy
  - Involve cones and rods at early age resulting in central visual deficits and poor night vision
- Cone Dystrophy
  - Primarily Cones affected, but could also have some rod dysfunction
  - Incidence 1/40,000
  - Most cases sporadic, but all inheritance patterns reported. Autosomal Dominant is most commonly inherited form.

Cone Dystrophy

- Symptoms typically before 20 yo
- Color vision problems occur early in disease, unlike many other macular dystrophies
- Earlier onset – more severe disease
- Nyctalopia makes rod disease more likely

Associated Systemic Conditions

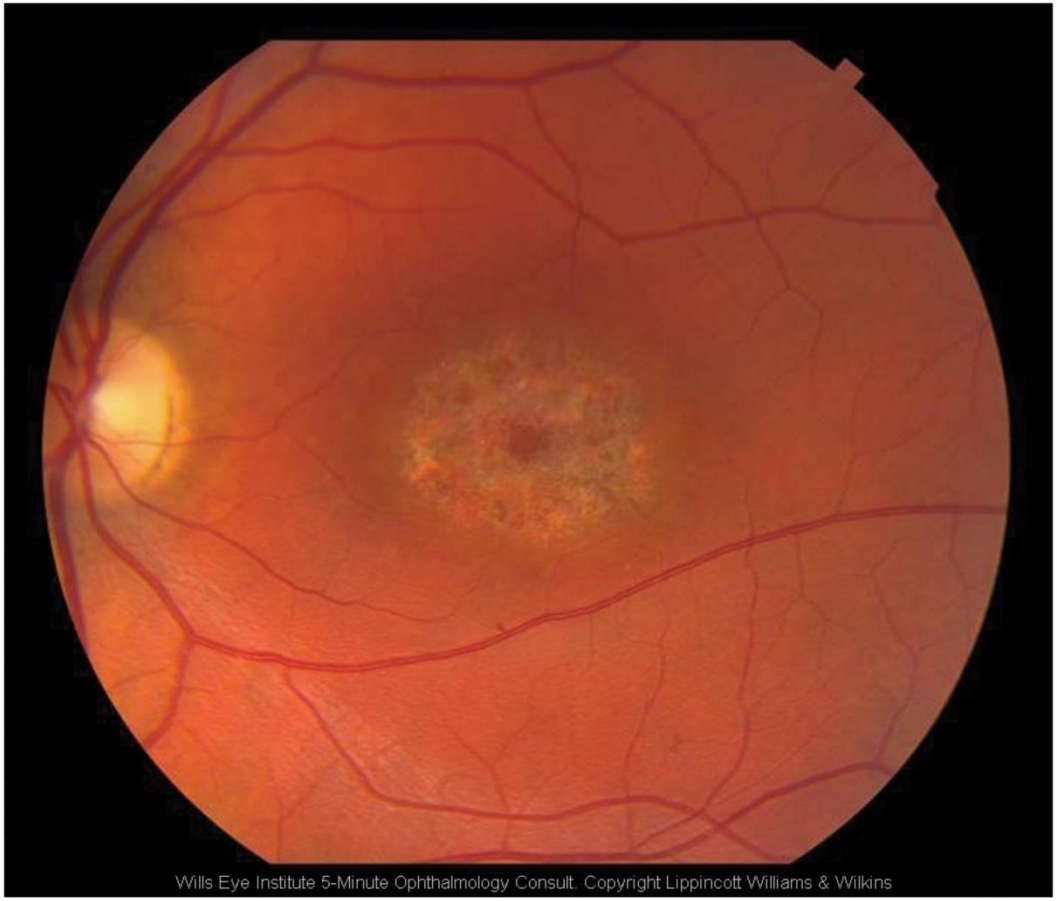
- Neurofibromatosis I
- Spinocerebellar Ataxia type 7
- Amelogenesis
- Pierre-Marie Ataxia
- Trichomegaly
- Bardet-Biedl Syndrome
- Alstrom Syndrome

Physical changes (Cone Dystrophy)

- Initially normal as dysfunction occurs before ophthalmologic changes
- Then, variable from macular granularity to well-demarcated, circular, depigmented area of macular atrophy
- Optic Discs may have temporal pallor
- VA from 20/20 to CF
- Color Plates often with varying degrees of abnormality

From: **Cone Dystrophy**

Wills Eye Institute 5-Minute Ophthalmology Consult, 2011



Legend:

There are pigmentary changes throughout the macula.The rest of the retina looks normal.

Diagnosis (Cone Dystrophy)

- ERG (full-field and multi-focal)
  - Characteristic markedly abnormal light response (photopic- cone), with normal to slightly abnormal dark response (scotopic-rod)
  - Selective decrease in photopic B-wave along with decreased amplitude on 30-Hz flicker may exist
- OCT
  - May show transverse photoreceptor loss with disruption/focal loss of IS/OS junction

More Testing (Cone Dystrophy)

- Fundus Autofluorescence
  - May show foveolar hyper-autofluorescence (nonspecific)
- Fluorescein Angiography
  - May show early hyperfluorescence
- Visual Fields
  - Often with full peripheral fields, but bilateral central scotomas
- No single test/finding sufficient for diagnosis

Therapy

AMERICAN JOURNAL OF OPHTHALMOLOGY

Volume 137, Issue 4, Pages 774–775, April 2004

Red contact lenses for alleviation of photophobia in patients with cone disorders

William L. Park, OD, FAAO, Janet S. Sunness, MD

- 23 pts with achromatopsia or acquired cone dystrophy with severe photophobia
- Mean age 17 [4-55]
- Vacc 20/200 [20/80-20/400]
- Mean improvement 20/125; all with rapid elimination oh photophobia
- 8 patients legally eligible to drive

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EMBRYONIC STEM CELLS/INDUCED PLURIPOTENT STEM CELLS

17 FEB 2010

Induced Pluripotent Stem Cells Generate Both Retinal Ganglion Cells and Photoreceptors: Therapeutic Implications in Degenerative Changes in Glaucoma and Age-Related Macular Degeneration

SOWMYA PARAMESWARAN,[a] SUDHA BALASUBRAMANIAN,[a] NORBERT BABAI,[a] FANG QIU,[b] JAMES D. EUDY,[c] WALLACE B. THORESON,[a] IQBAL AHMAD[a]

[a]Department of Ophthalmology and Visual Sciences; [b]Department of Biostatistics, College of Public Health; [c]Department of Genetics Cell Biology and Anatomy, University of Nebraska Medical Center, Omaha, Nebraska, USA

- Embryonic Stem cells are great, but supply and immune rejection are a problem
- Mouse fibroblast induced pluripotent stem cells (iPSC) are a renewable and robust source of retinal progenitors
- Retinal ganglion cells, cone, rod photoreceptors

Our Patient

- Patient is pending Fluorescein Angiography
- Referred to SUNY Optometry for ERG
- Referred to Light House
- Children were examined with our pediatric ophthalmology staff (so far they look great!)

Take Home Points

- Look for causes for vision being worse than you would expect
- If you see a bull's eye, obtain family history, age of onset, night-time symptoms, photophobia, color deficits, medication use
- Fundus photography, autofluorescence, OCT, VF, ERG may help

Reflective Practice

- This case represented application of careful history taking, ophthalmic examination and creation of a complete differential diagnosis to evaluate and treat complex retinal disorders

Core Competencies

- Patient Care: The case involved thorough patient care, ability to explain findings, and need for treatment to the patient. Once diagnosed, the patient is receiving proper management and care.
- Medical Knowledge This presentation allowed us to review the presentations, proper evaluation/work up, and differential of bull's eye maculopathies
- Practice-Based Learning and Improvement: This presentation included a current literature search of bull's eye maculopathies
- Interpersonal and Communication Skills: The patient was treated with respect and every effort was made to communicate with the patient and treat in accordance with her wishes.
- Professionalism: The patient was treated in the proper manner.
- Systems-Based Practice: The patient was discussed with colleagues and treated appropriately

Thank you!

- Our patient
- KCHC Eye Clinic Staff
- Dr Rony Gelman
- Dr Christopher Fecarotta

Works Cited

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