A Simplified Approach to NK Diagnosis and Management

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Disclosures

- Serve on the speaker's bureau, advisory board, as a consultant to, and/or principal investigator for:
  - Bausch & Lomb Pharmaceuticals
  - Claris Biotherapeutics, Inc.
  - Dompe Pharmaceuticals
  - Kala Pharmaceuticals Inc.
  - Mallinckrodt Pharmaceuticals
  - ReGenTree LLC
  - Sun Pharmaceuticals

All relevant financial relationships have been mitigated. The content of this COPE-accredited CE activity was planned and prepared independently by John C. Affeldt, M.D. without imput from members of an ineligible company.

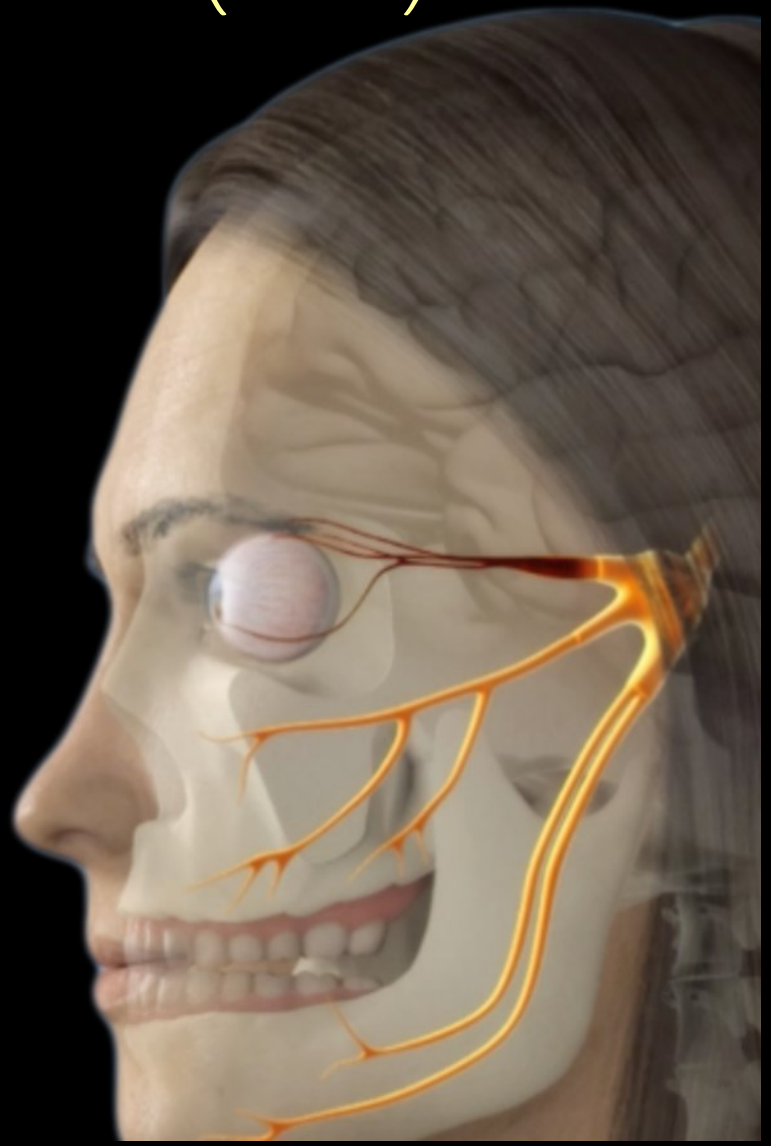
Introduction

Neurotrophic Keratitis

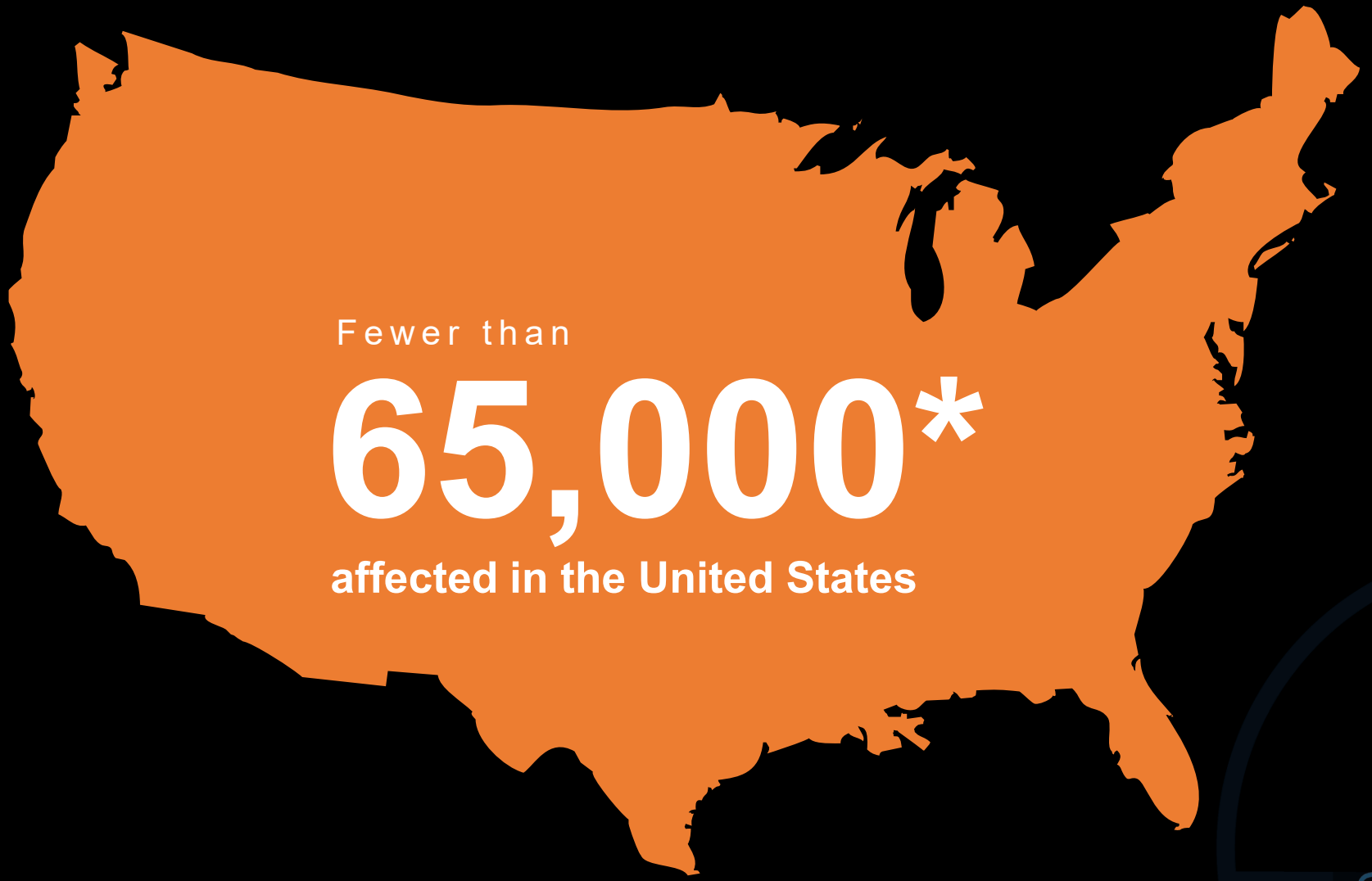
The New Queen of the Ocular Surface Realm

Neurotrophic Keratitis (NK)

- A *degenerative* ocular surface disease
- Secondary to damage related sensory loss of the ophthalmic division of the 5th or trigeminal cranial nerve (CN V1)

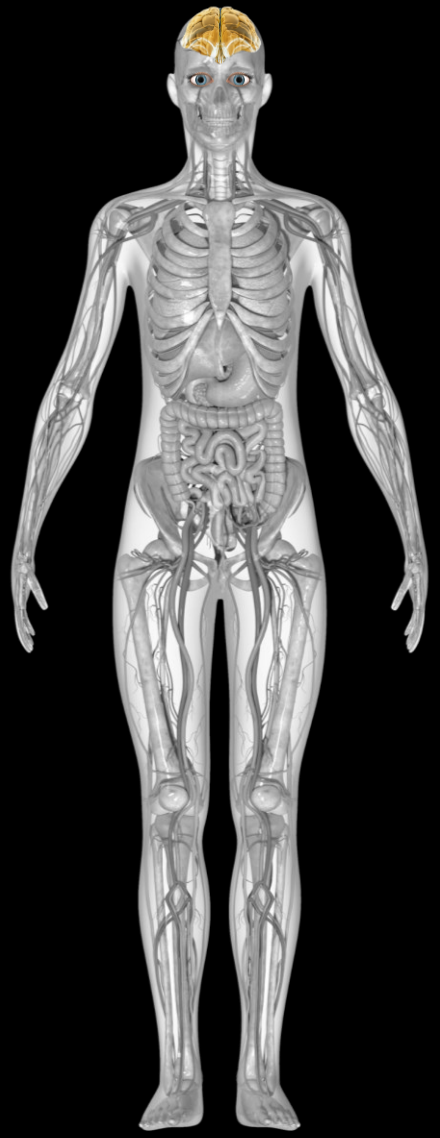


NK Is Classified as a Rare Disease



*Adapted number based on the United States population.

Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579.



Etiologies of NK

OCULAR

SYSTEMIC

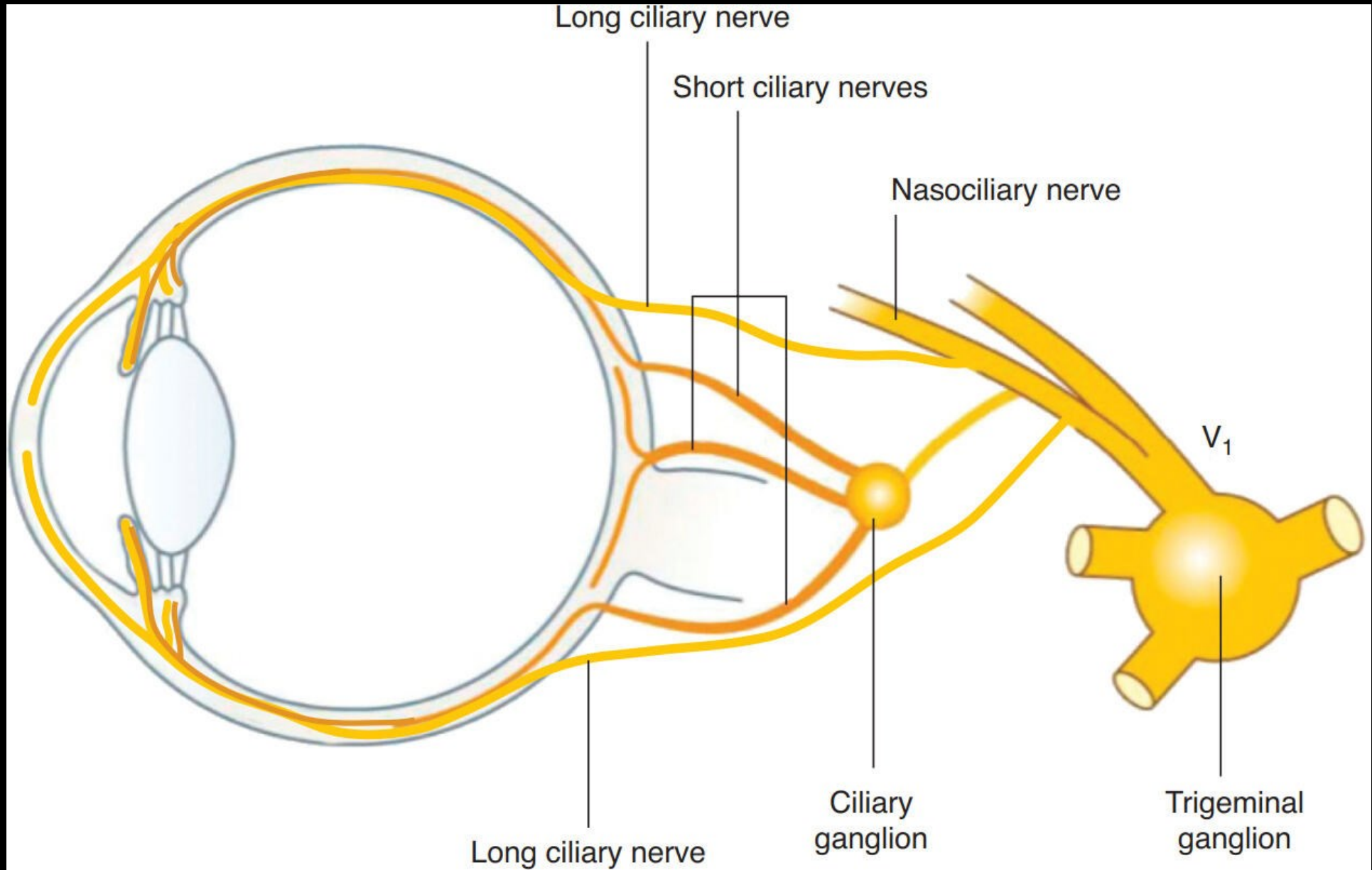
CENTRAL NERVOUS SYSTEM

GENETIC

- **Infectious** (eg, post-herpes
- **Ocular surgery** (eg, post-laser vision correction)
- Chemical and thermal burns
- Abuse of topical anesthetics
- Drug toxicity
- Chronic ocular surface injury

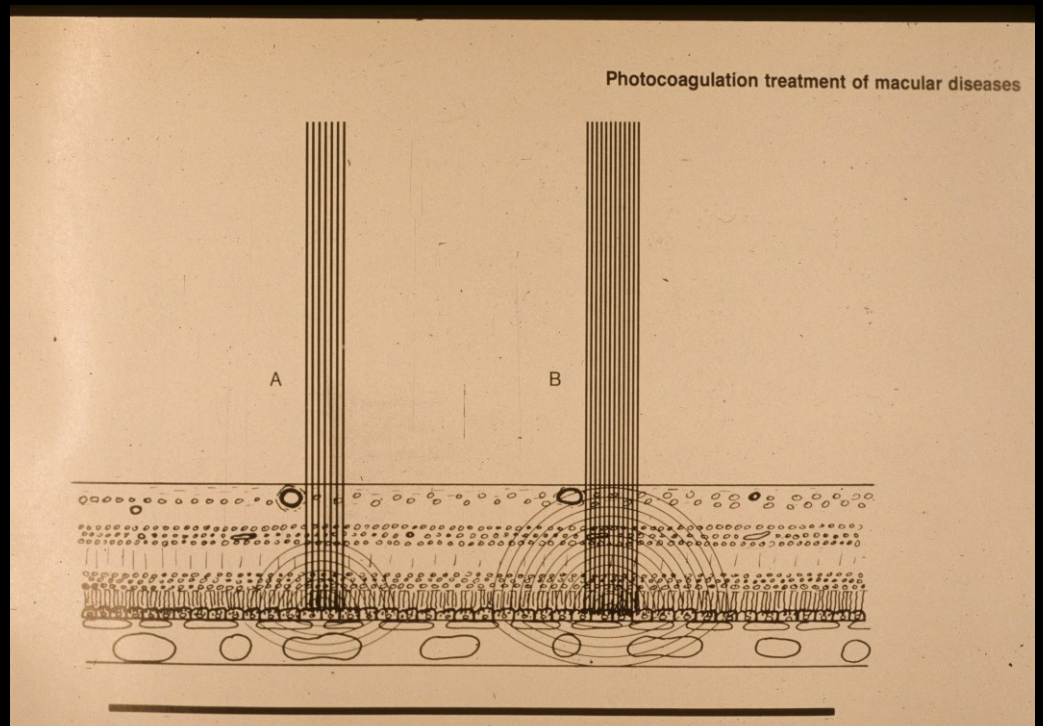
Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018;66:107-131.

Retinal Surgery Related NK

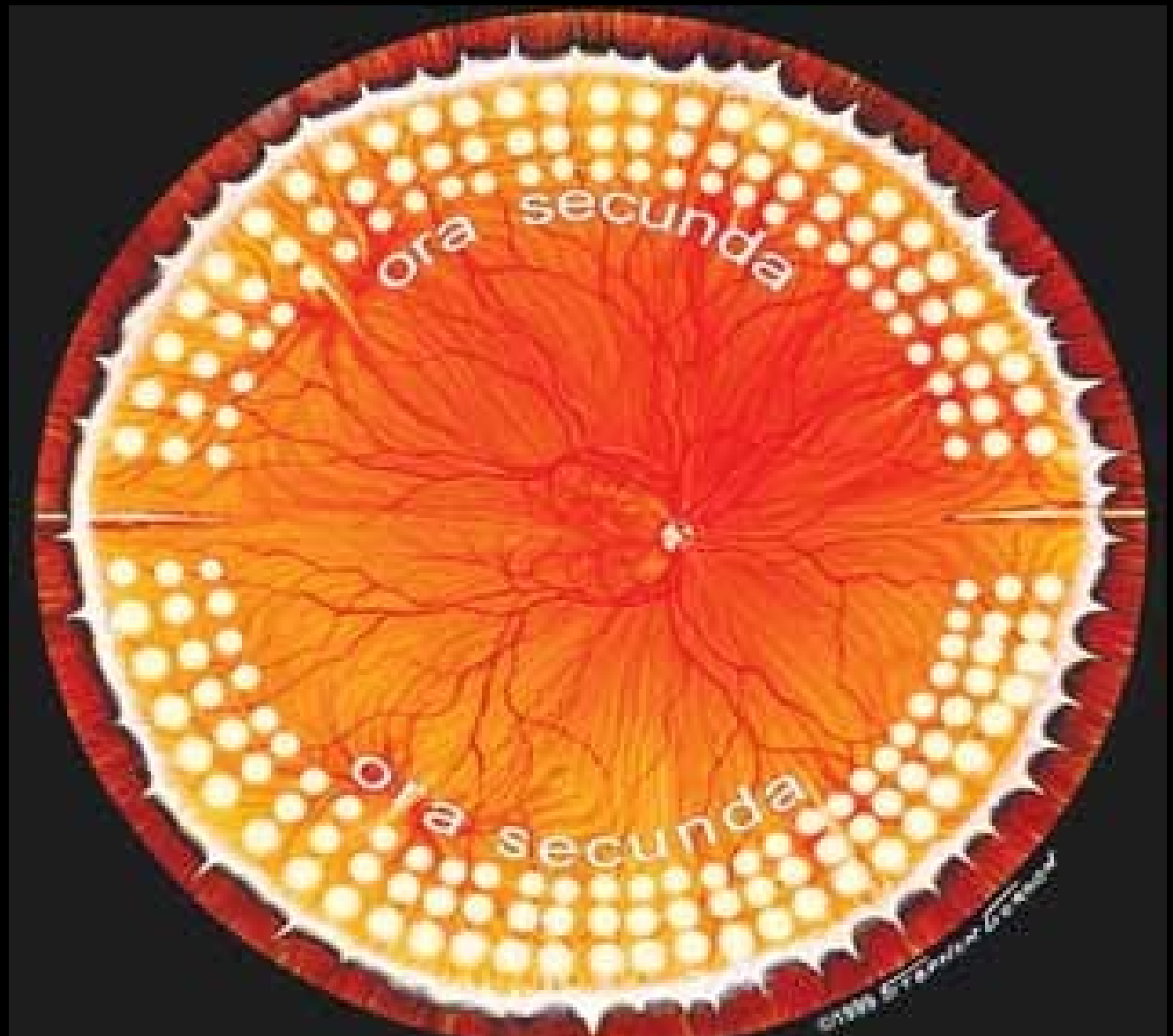


Retinal Surgery Related NK

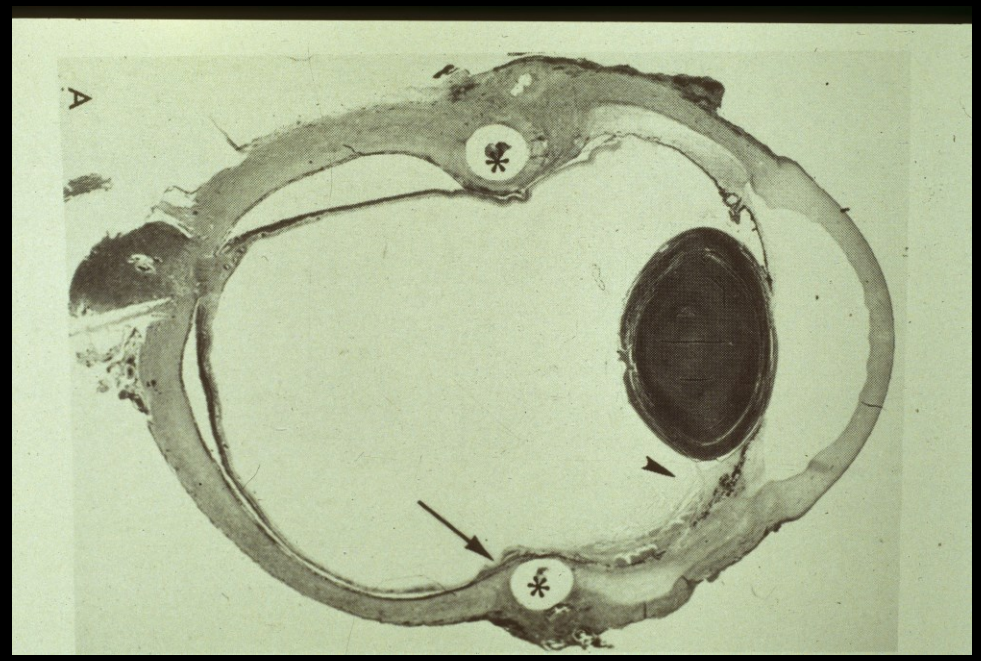
Jacobson E, Affeldt J, Agarwal M, Carlson J, Pesevento R, Flaxel C. Retinal Surgery Related NTK. ARVO 2002



PRP avoiding long posterior ciliary nerves at 3:00 + 9:00

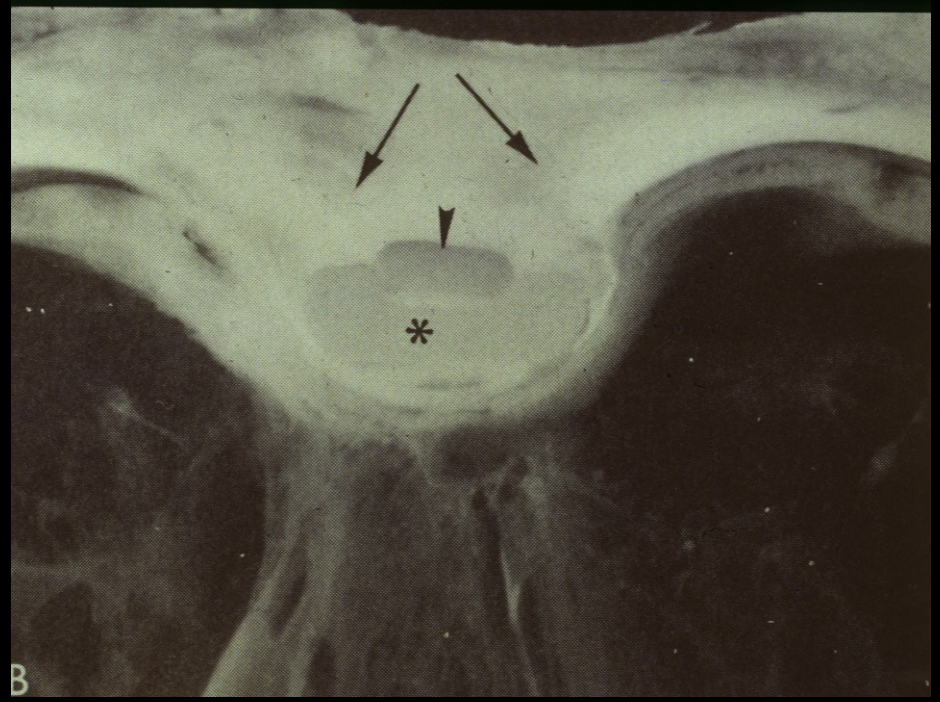


Retinal Surgery Related NK



SB “bending” mechanical nerve injury

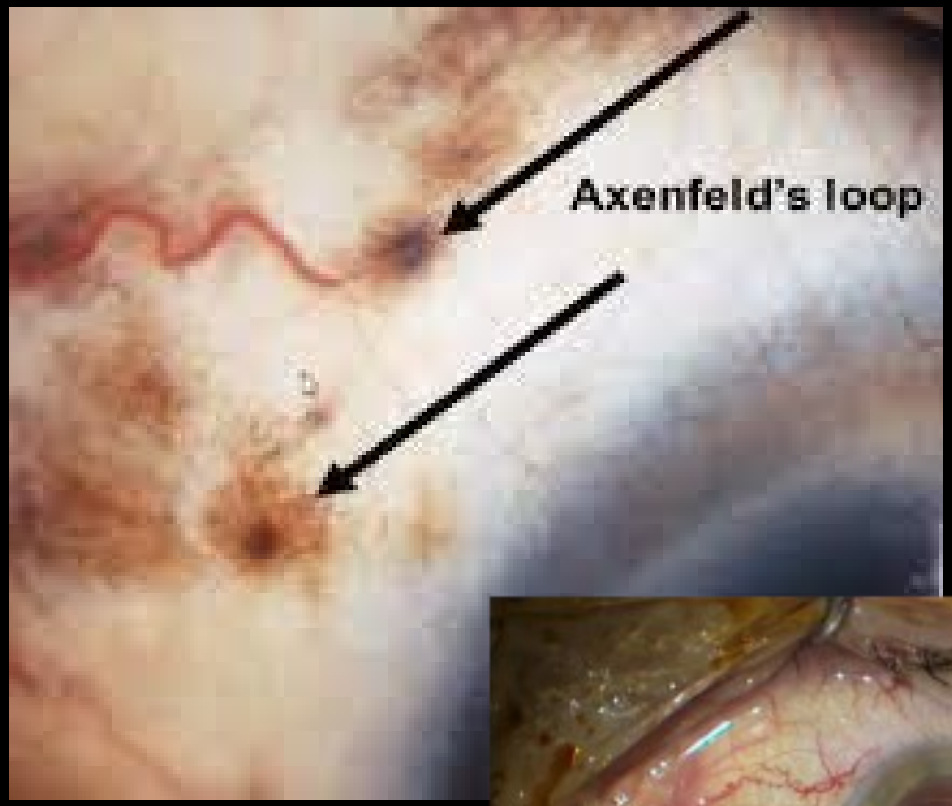
SB erosion through sclera

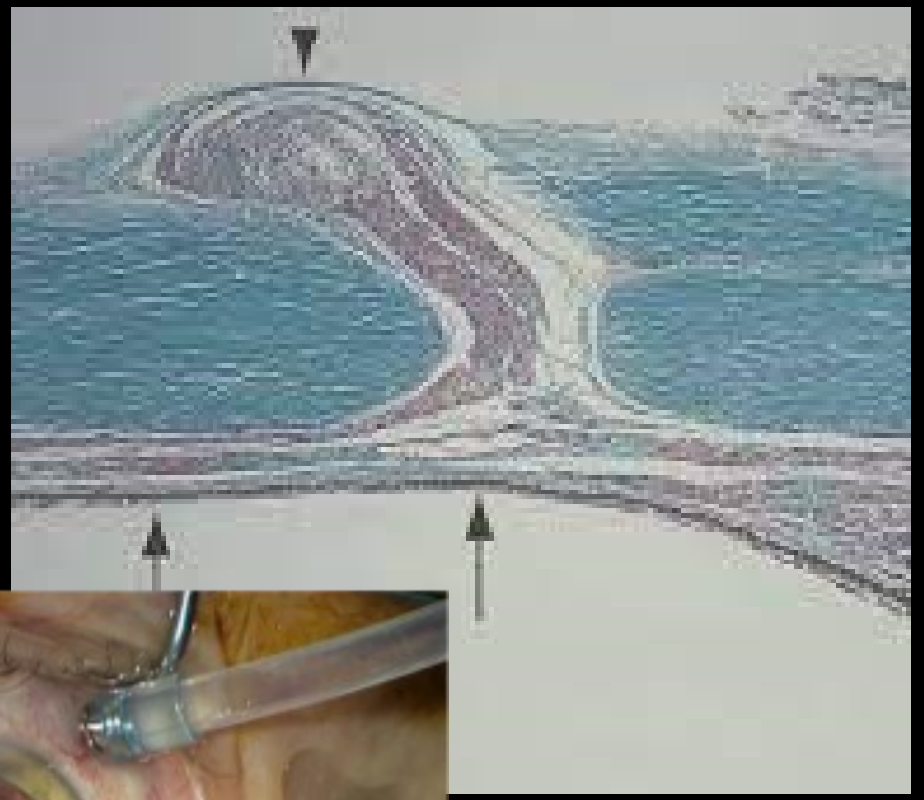


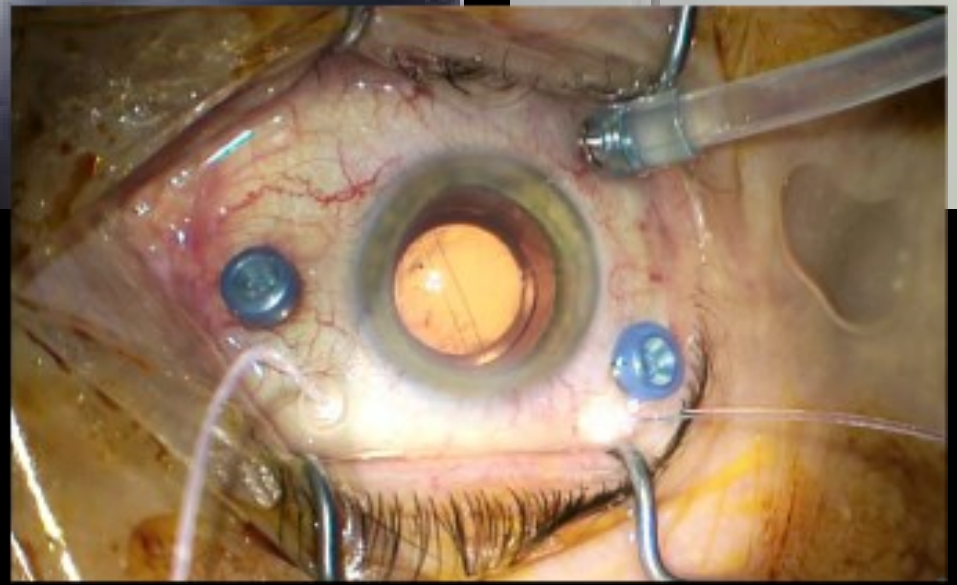
Jacobson E, Affeldt J, Agarwal M, Carlson J, Pesevento R, Flaxel C, Retinal Surgery Related NTK. ARVO 2002

Axenfeld's Nerve Loop

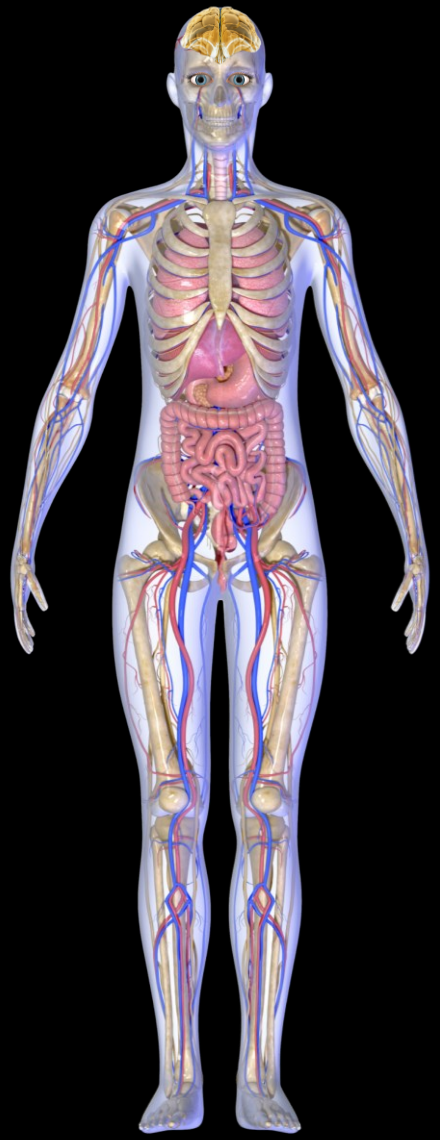
Anterior extension long posterior ciliary nerve
Overlies pars plana vitrectomy port incision site







Etiologies of NK



OCULAR

SYSTEMIC

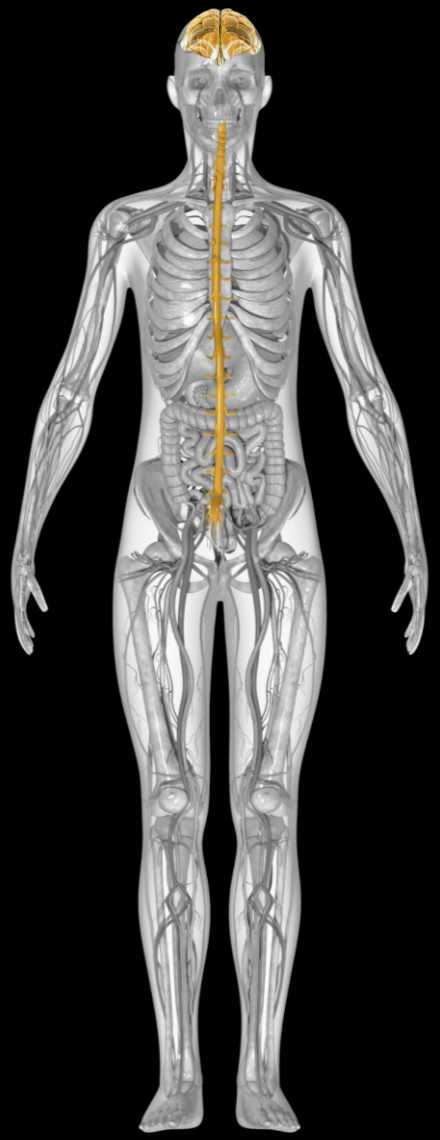
- **Diabetes**
- Multiple sclerosis
- Vitamin A deficiency
- Leprosy
- Amyloidosis

CENTRAL NERVOUS SYSTEM

GENETIC

Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018;66:107-131.

Etiologies of NK



OCULAR

SYSTEMIC

CENTRAL NERVOUS SYSTEM

- **Post-neurosurgical procedures**
- **Stroke**
- Neoplasm
- Aneurysms
- Degenerative disorders of the CNS

GENETIC

Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018;66:107-131.

Etiologies of NK

OCULAR

SYSTEMIC

CENTRAL NERVOUS SYSTEM

GENETIC

- **Riley-Day syndrome**
- Goldenhar-Gorlin syndrome
- Mobius syndrome
- Familial corneal hypoesthesia

Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018;66:107-131.

Diagnostic Considerations

- **HISTORY**
- **CORNEAL SENSITIVITY TESTING**
- **SIGNS AND SYMPTOMS** (may not correlate: stain without pain)

1. Versura P, Giannaccare G, Pellegrini M, et al. Neurotrophic keratitis: current challenges and future prospects. *Eye Brain*. 2018 Jun 28;10:37-45.
2. Milner M, Beckman K, Luchs J. Dysfunctional Tear Syndrome: Dry Eye Disease and Associated Tear Film Disorders - New Strategies for Diagnosis and Treatment. *Current Opinion in Ophthal*. Volume 28, Supplement 1. January 2017.
3. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018 Sep;66:107-131.
4. Semararo F, et al. Neurotrophic Keratitis. *Ophthalmologica*. 2014;231:191-197.

Corneal Sensation Testing: A Required Step in Diagnosing NK[1,2]

QUALITATIVE

- **Examples:** cotton swab, cotton wisp, dental floss, tip of a tissue
- Descriptive scales: normal, hypoesthesia, anesthesia

QUANTITATIVE

- **Example:** Cochet-Bonnet esthesiometer
- Often used in basic research and clinical trial settings
- May be limited in general clinical practice

2. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018 Sep;66:107-131

Cochet-Bonnet Esthesiometry

Normal = 45+mm

Rapid Diagnosis of Neurotrophic Keratitis

Pattern Recognition

Mackie Classification System

- Stage I: Punctate keratitis (~90% of cases)
- Stage II: Persistent epithelial defect (PED)
- Stage III: Stromal melt/ulceration

Mackie Classification System

- Stage I: Punctate keratitis (5 distinctive variants)
  - Galle spot
  - Central band
  - Blizzard/milky way
  - Hurricane/vortex
  - Dendriform
- Stage II: Persistent epithelial defect (PED)
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Mackie Classification System

- Stage I: Punctate keratitis (5 distinctive variants)
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All variants originate from the same pathophysiologic process

Ocular Surface Pathophysiology

- Two structural components:
  - Corneal epithelium:
  - Sub-basal nerve plexus:

They are physically and tropically interdependent

Ocular Surface Pathophysiology

- Two structural components:
  - Corneal epithelium: produces neuropeptides + NGF
  - Sub-basal nerve plexus:

They are physically and tropically interdependent

Ocular Surface Pathophysiology

- Two structural components:
  - Corneal epithelium: produces neuropeptides + NGF
  - Sub-basal nerve plexus: produces neuromediators

They are physically and tropically interdependent

Corneal Epithelium

- Epithelial surface very dynamic

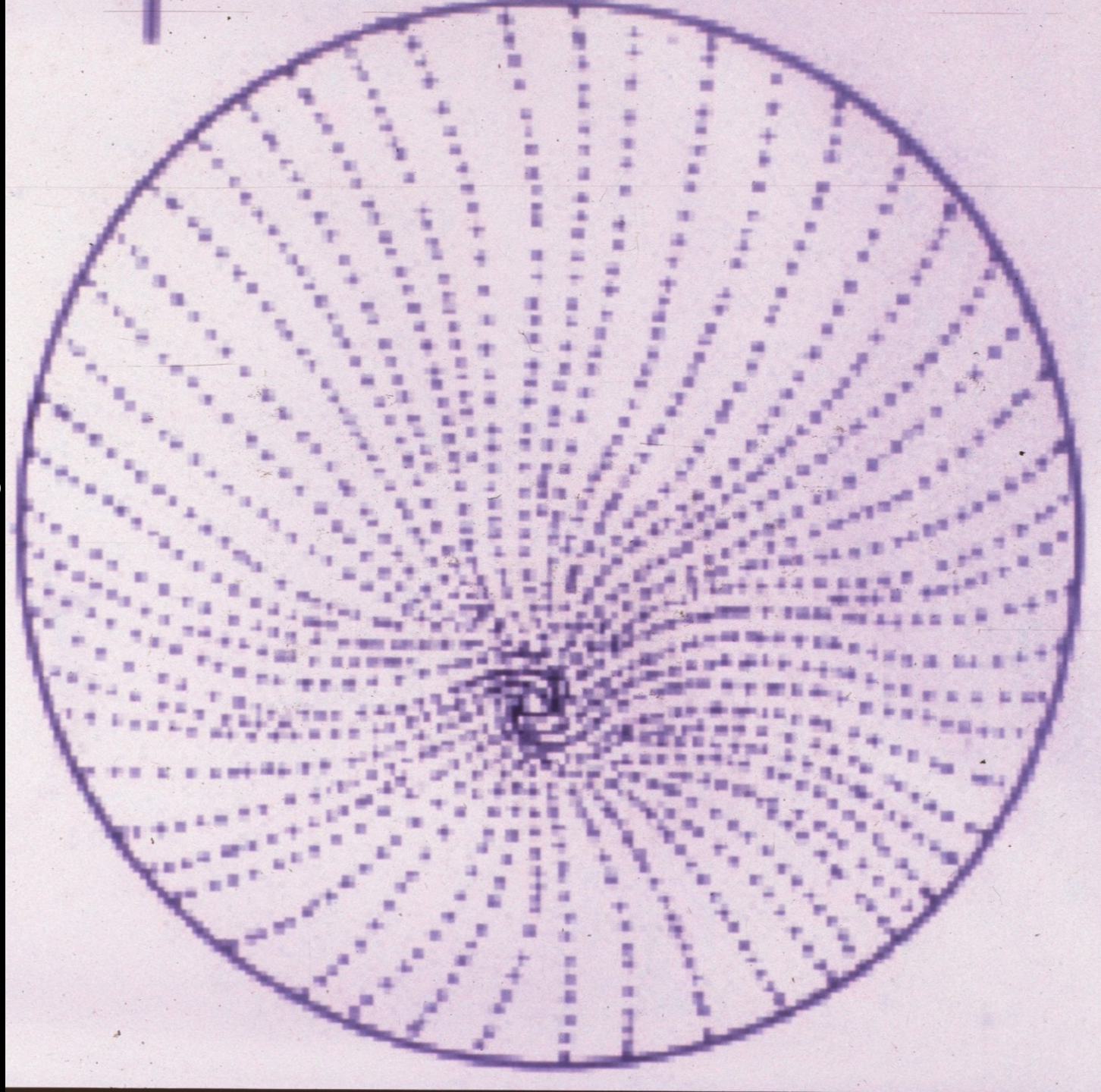
- Complete exfoliative turnover Q-6 days

- Replacement derived from limbal stem cells 360°

- Stream radially and centripetally

- On approach to corneal vertex, begin rotating
(clockwise ~90%)

- Rotation secondary to electromagnetic forces acting on ferromagnetic cellular deposits



Sub-basal Nerve Plexus

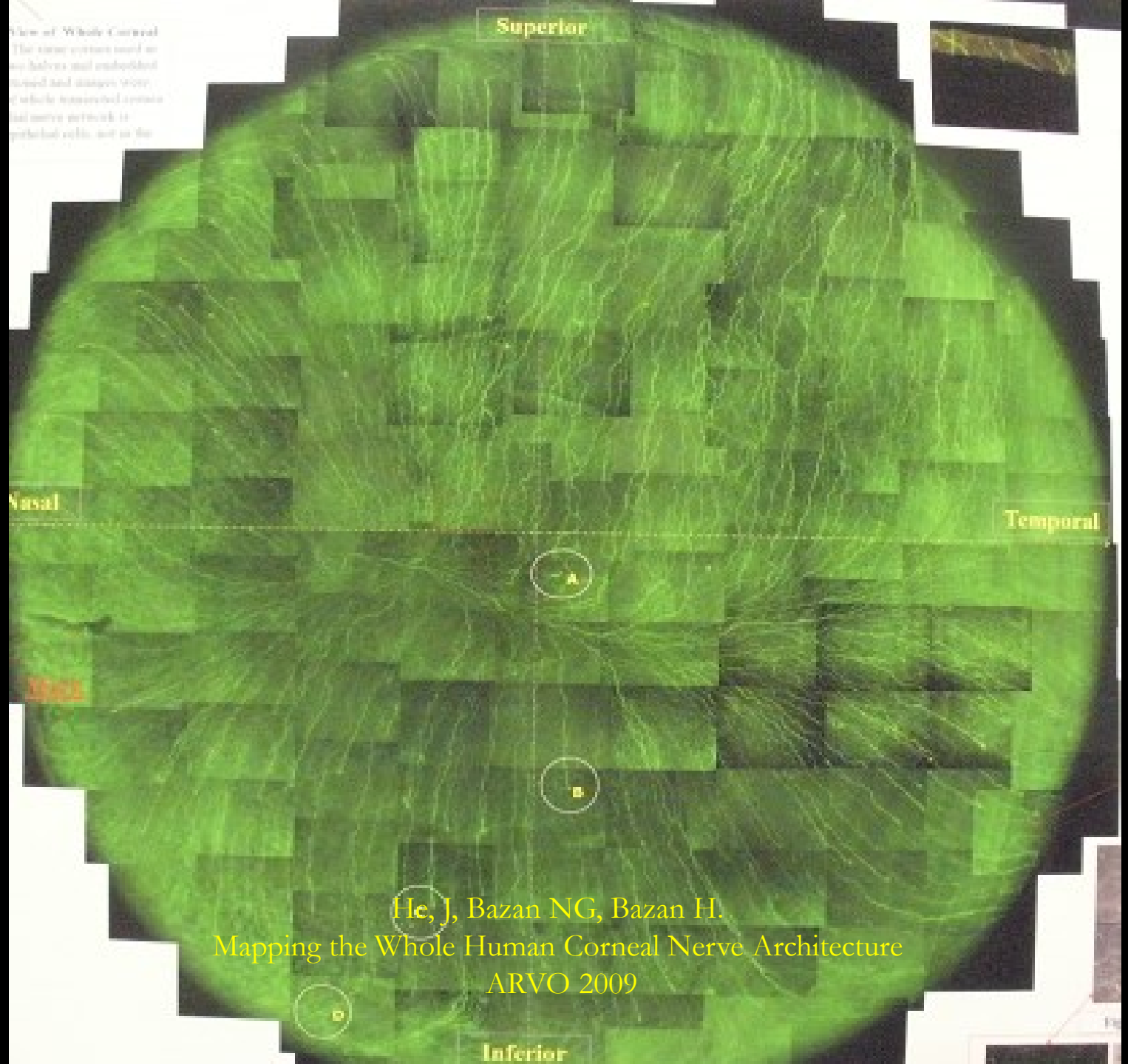
- Nerves emanate from limbus 360^0

- Located and anastomose extensively between Bowman's membrane and basal epithelium

- Innervate corneal epithelium

- *In tandem* with corneal epithelium;
  - Move radially and centripetally
  - Rotate on approach to corneal vertex
  - Forms a vertex seam or whorl

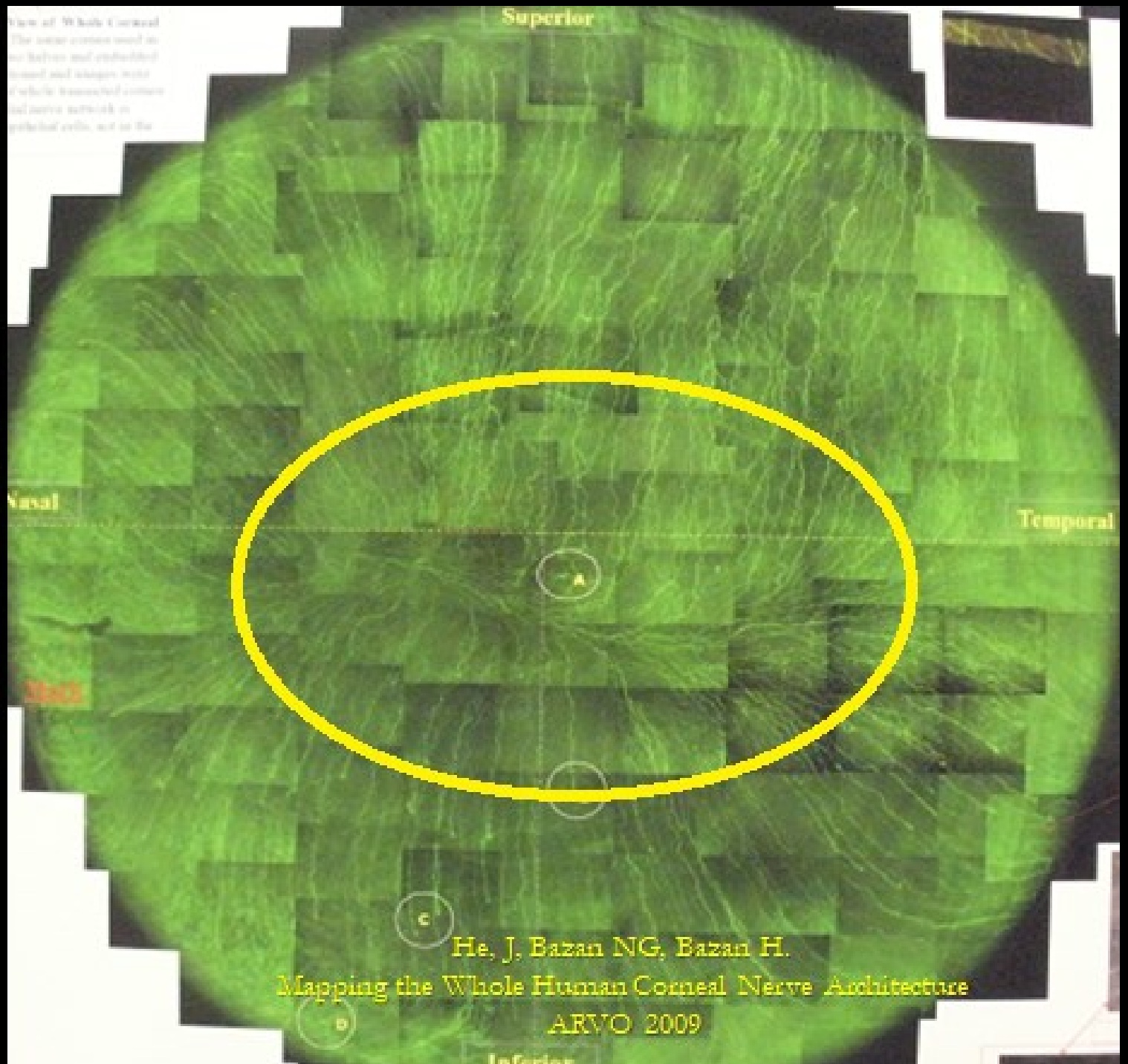
- Epithelium/SBNC complex establishes the *corneal vertex zone*



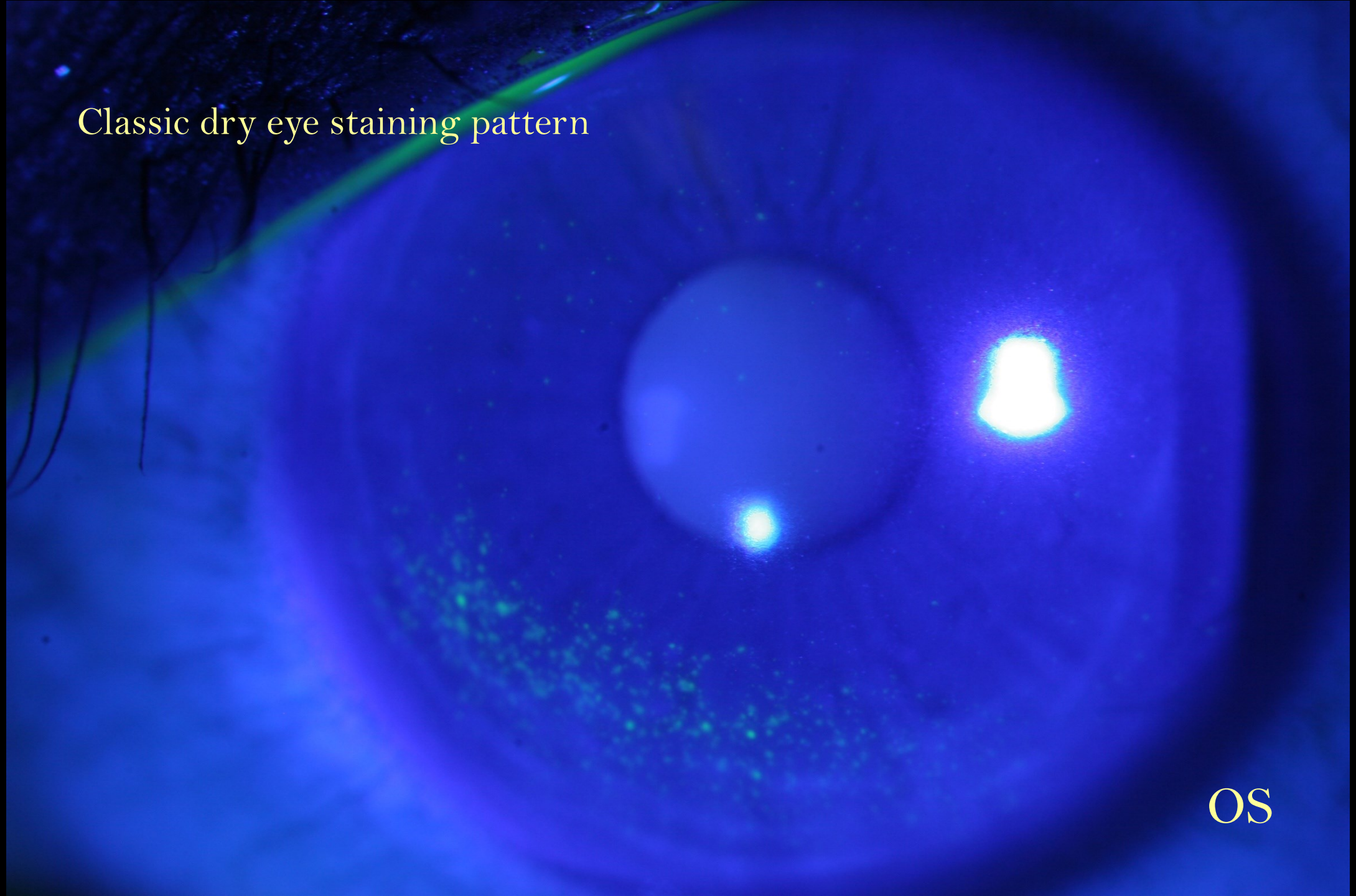
He, J, Bazan NG, Bazan H.
Mapping the Whole Human Corneal Nerve Architecture
ARVO 2009

Corneal vertex zone
is the

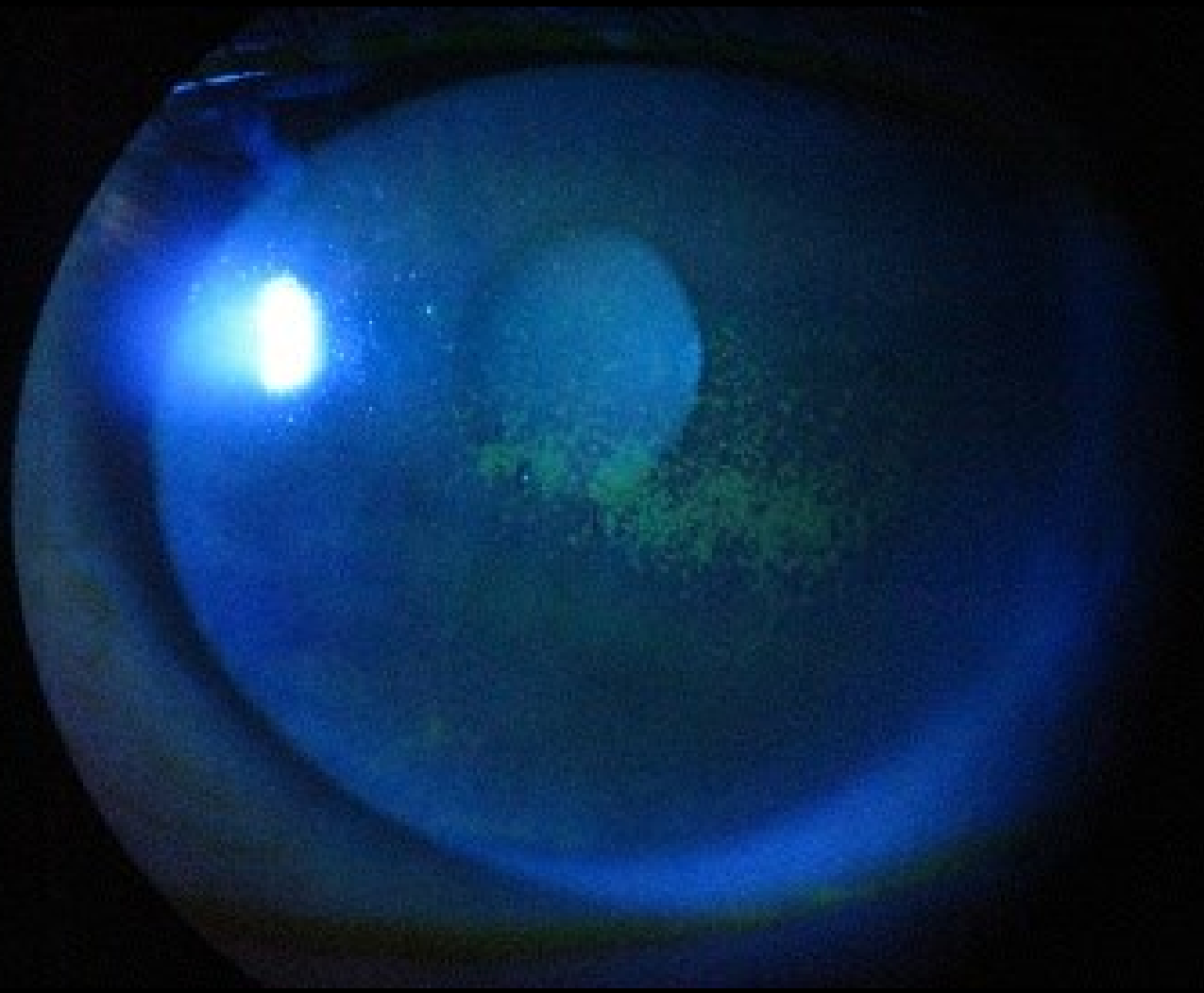
NK Hot Zone



NK Pattern Recognition


Classic dry eye staining pattern
OS

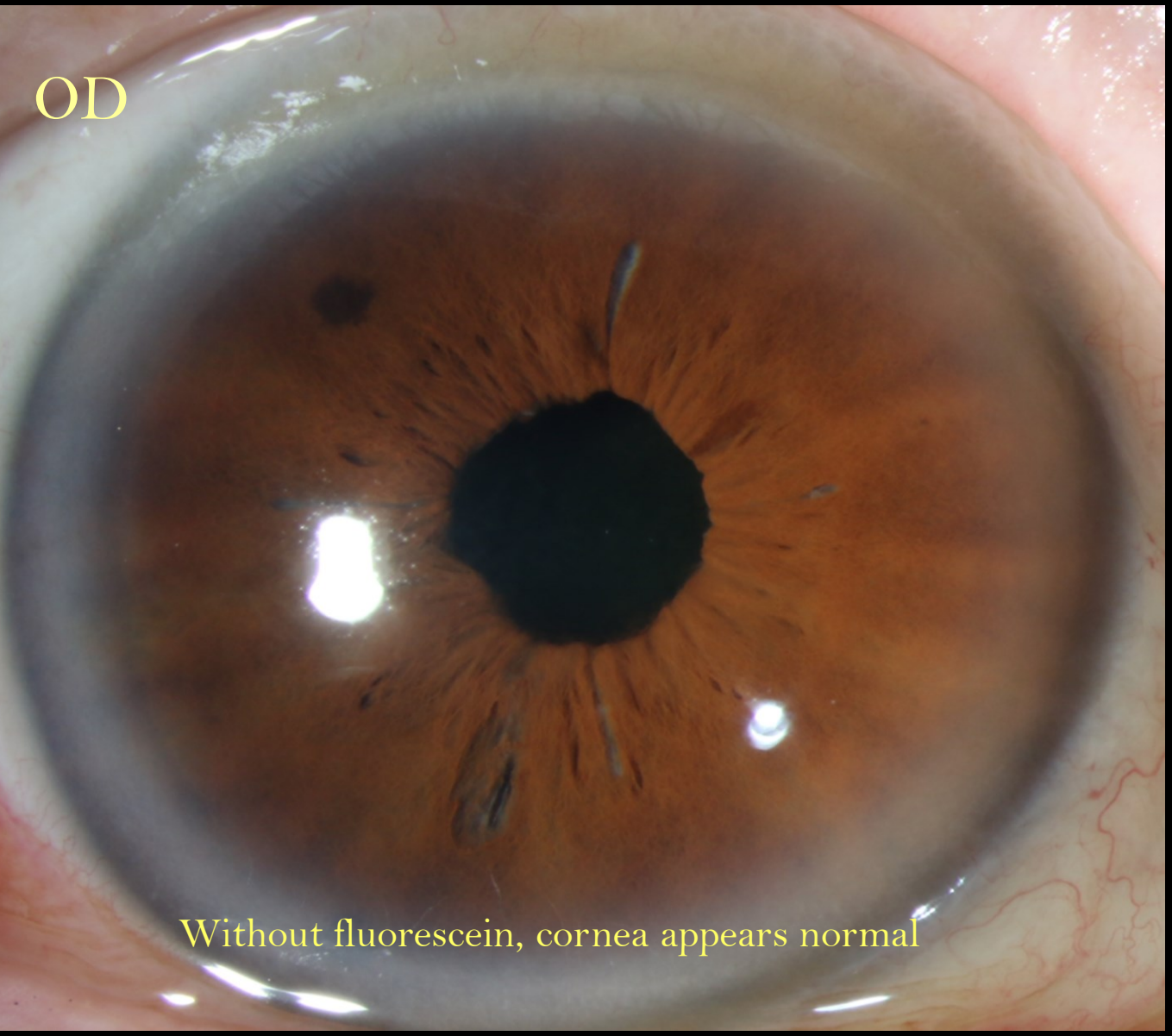
Stage I NK
Punctate Keratitis



Stage I NK
Punctate Keratitis

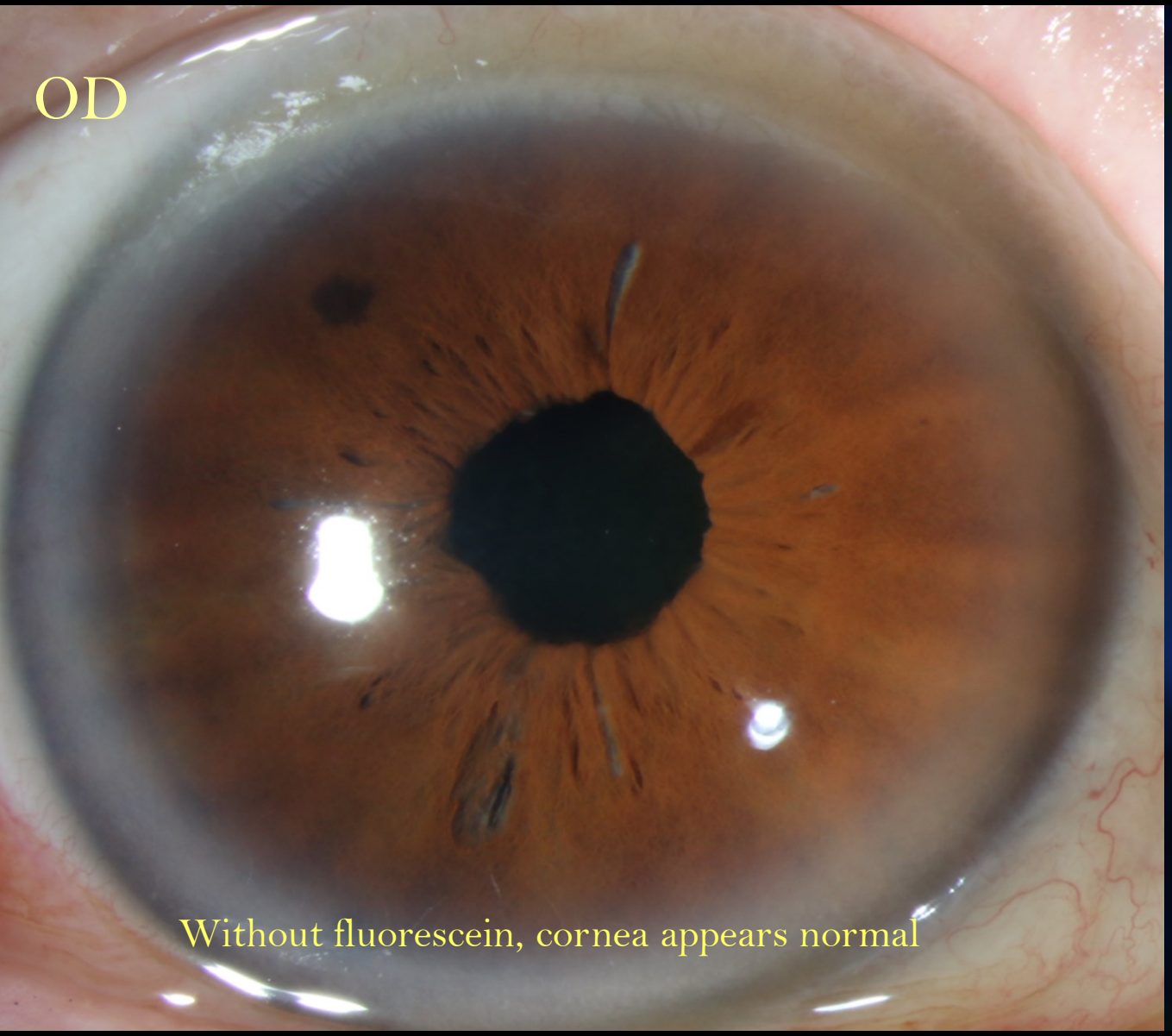
Must use fluorescein!

Must use fluorescein!

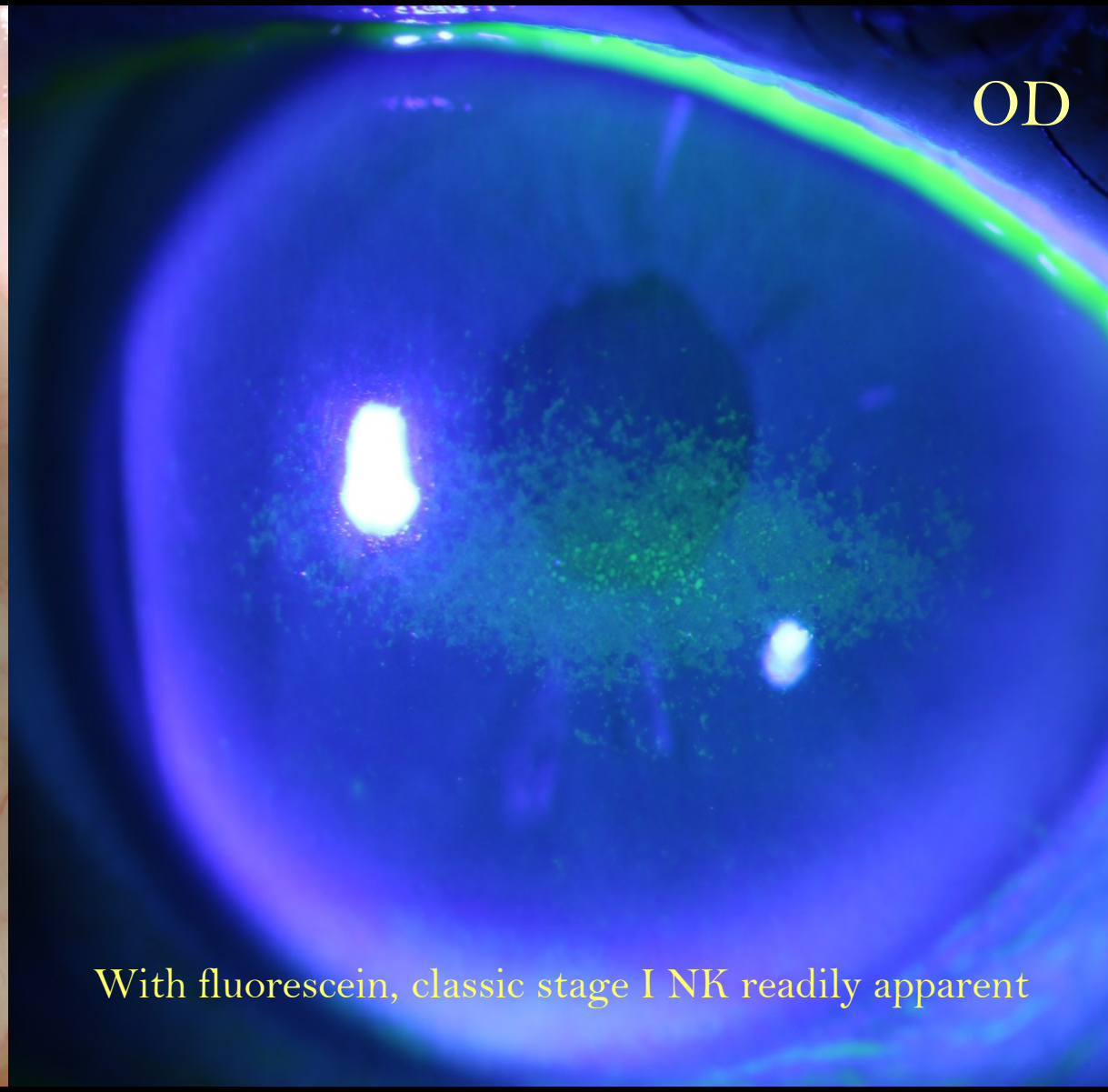


78 yo M Hx DM, CE/PC IOL, PDR, PRP. VA=20/40

Must use fluorescein!



Without fluorescein, cornea appears normal



With fluorescein, classic stage I NK readily apparent

78 yo M Hx DM, PDR, PRP, CE/PC IOL. VA=20/40

Stage I NK

(Five variants)

- Galle spot
- Central Band
- Blizzard/Milky Way
- Hurricane/Vortex
- Dendriform

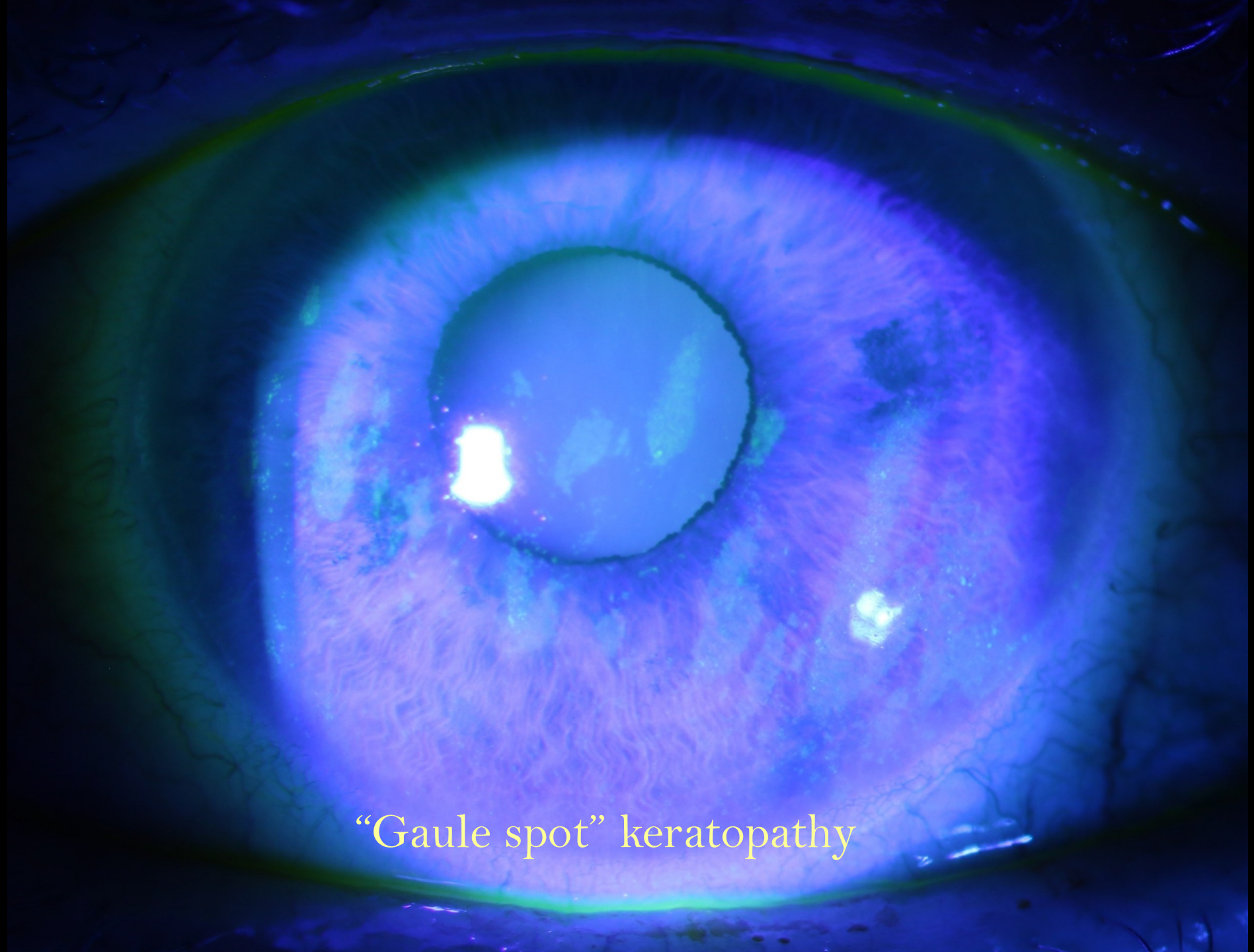
Galle Spot NK

Stage I Gaule Spot NK

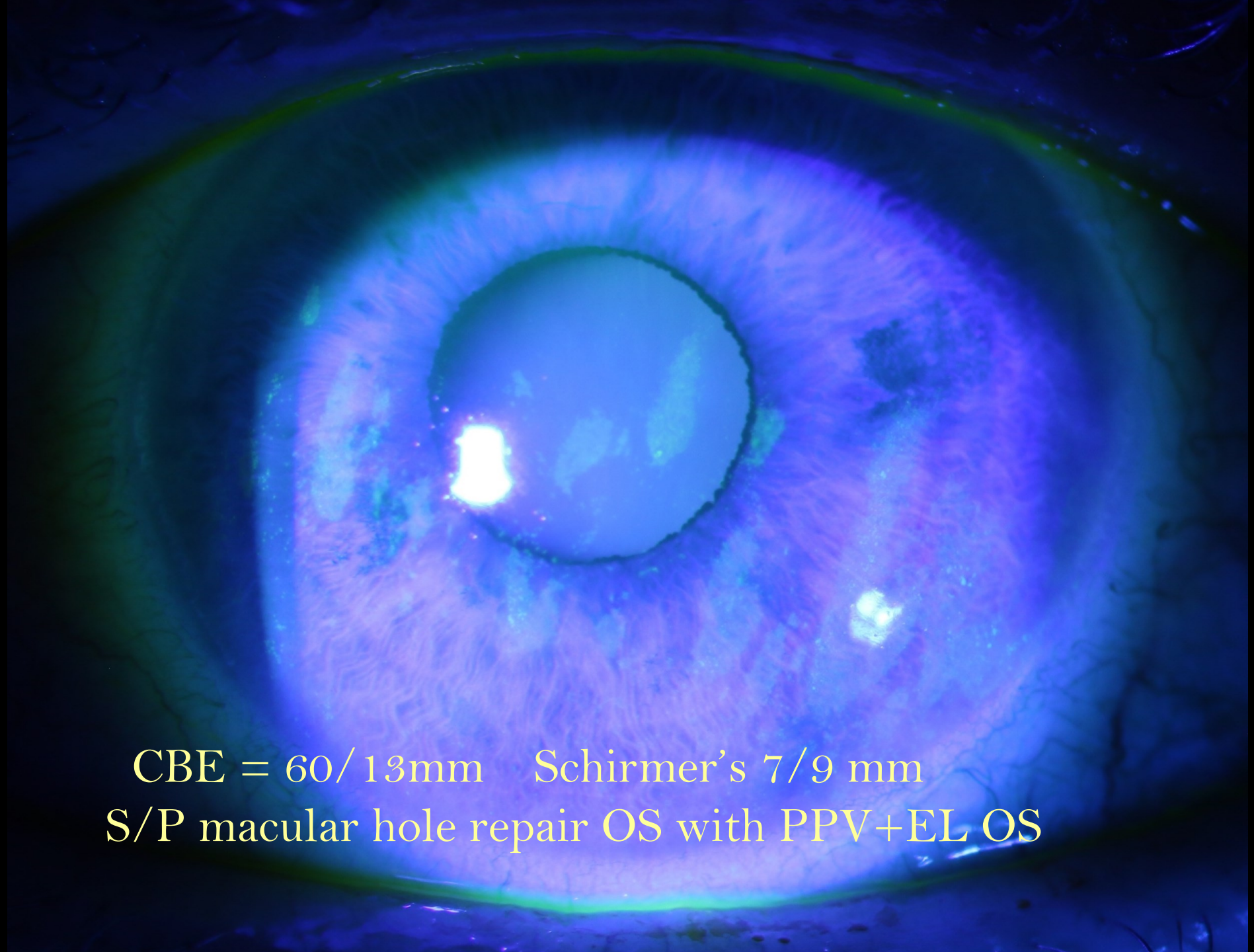
- Term originally coined by J. Gaule in 1891 to describe dellen-like lx's in rabbits
- In 1973, Ian Mackie connected the term to NK
- Considered the earliest sign of NK
- Demonstrates least amount of sensory loss
- Is most treatment responsive of all NK variants

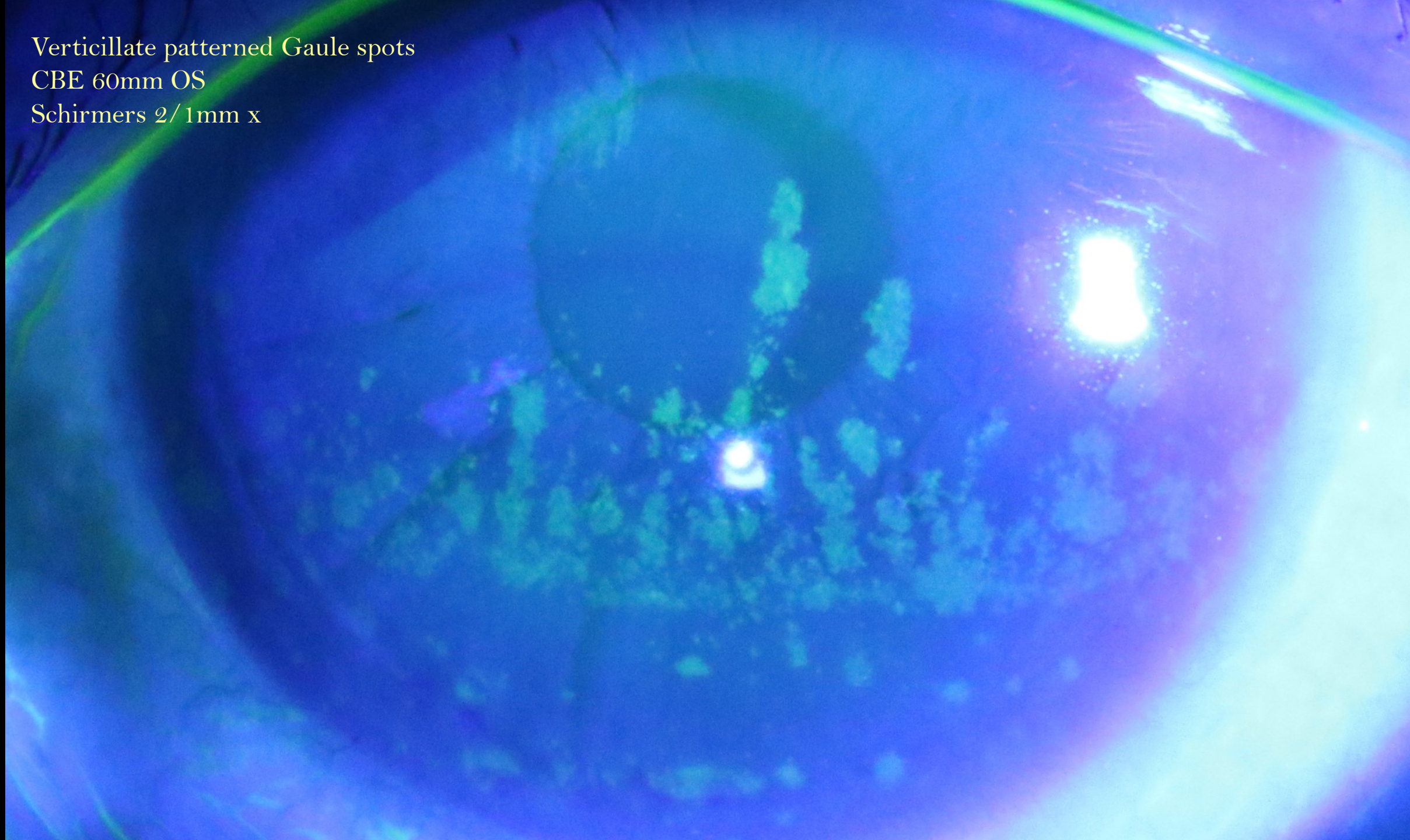
Stage I Gaule Spot NK

- Relatively rare, lesions morphologically unique and of an evanescent nature
- Presents as discrete, vertically elongated (columnar) facets of PEE's
- Located within/above the corneal vertex zone
- Can assume vortex/verticillate configurations



"Gaule spot" keratopathy


OS
CBE = 60/13mm Schirmer's 7/9 mm
S/P macular hole repair OS with PPV+EL OS

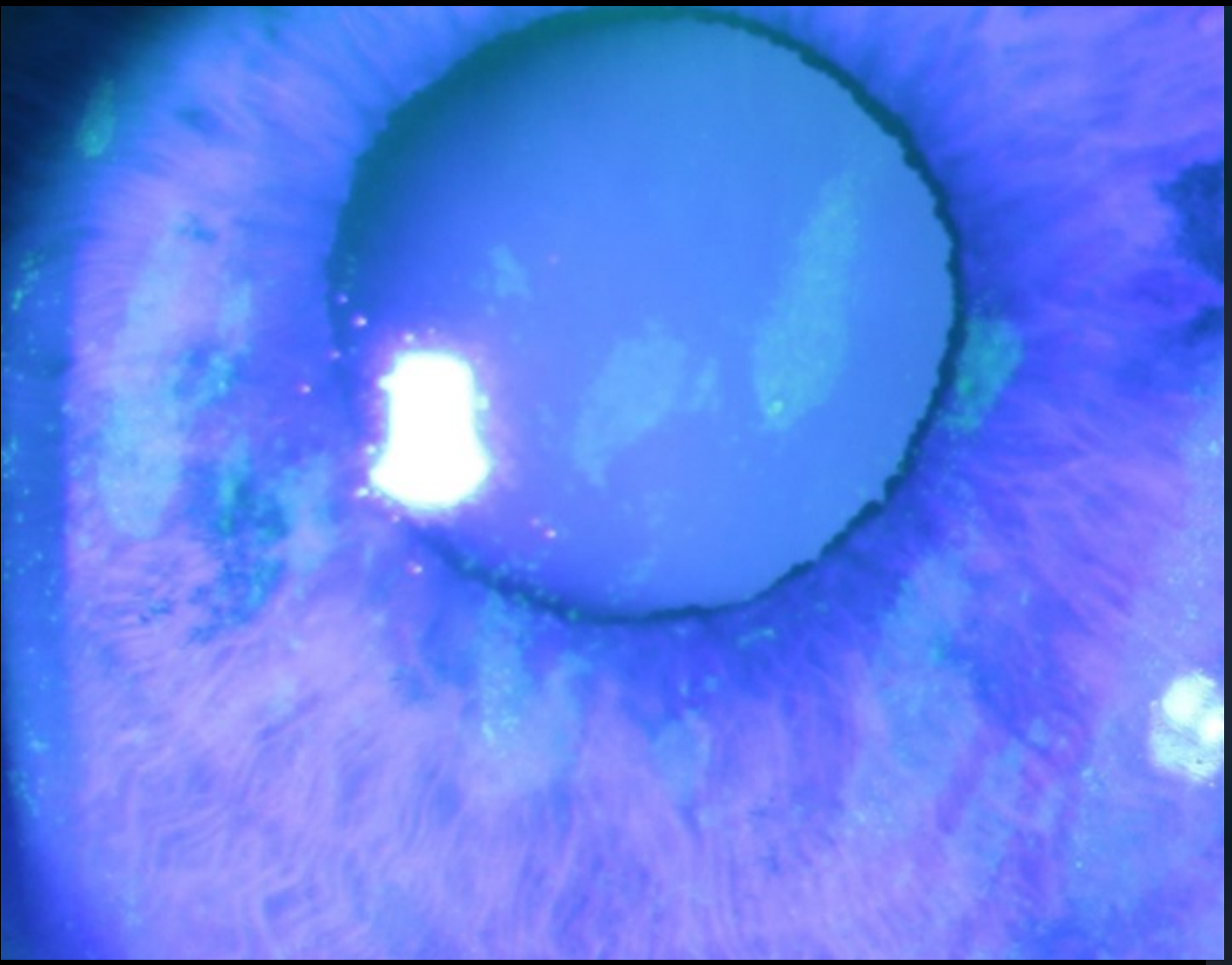

Verticillate patterned Gaule spots
CBE 60mm OS
Schirmers 2/1mm x

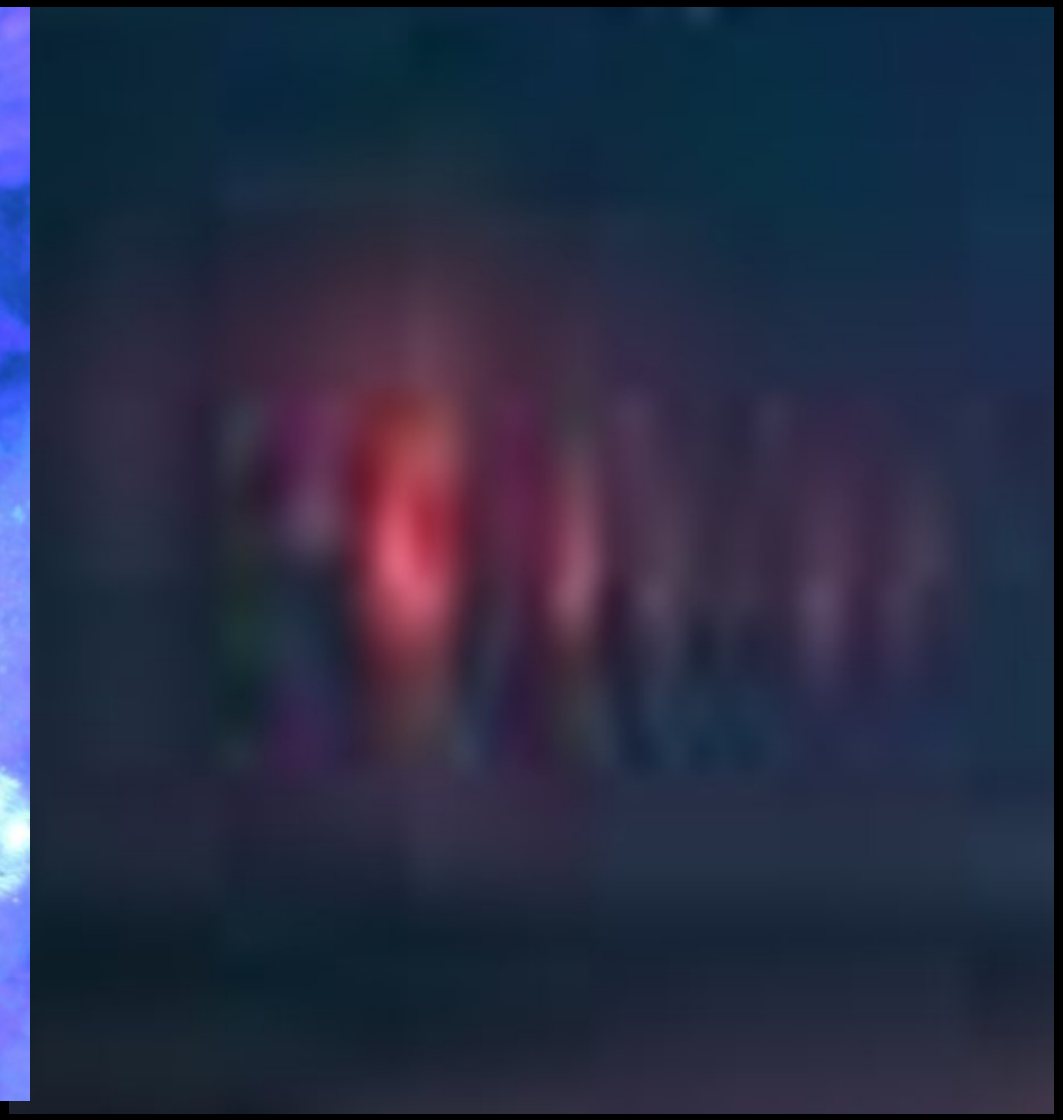
Stage I Gaule Spot NK

- With the exception of color, their columnar shape, evanescent nature and (theoretic) electromagnetically driven distribution,
- Lesions are intriguingly reminiscent of *red columnar sprites*

Gaule spots

Red columnar sprites

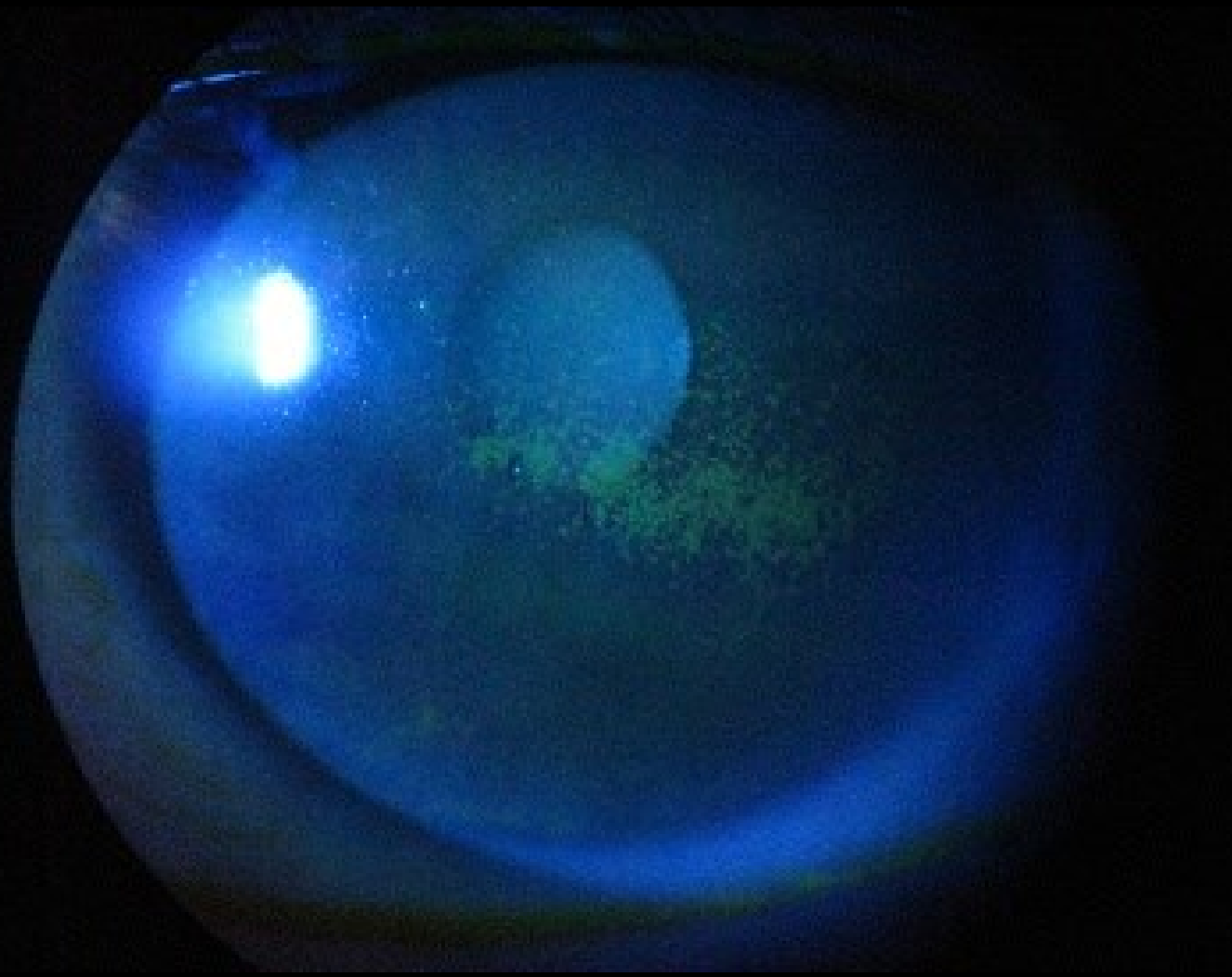




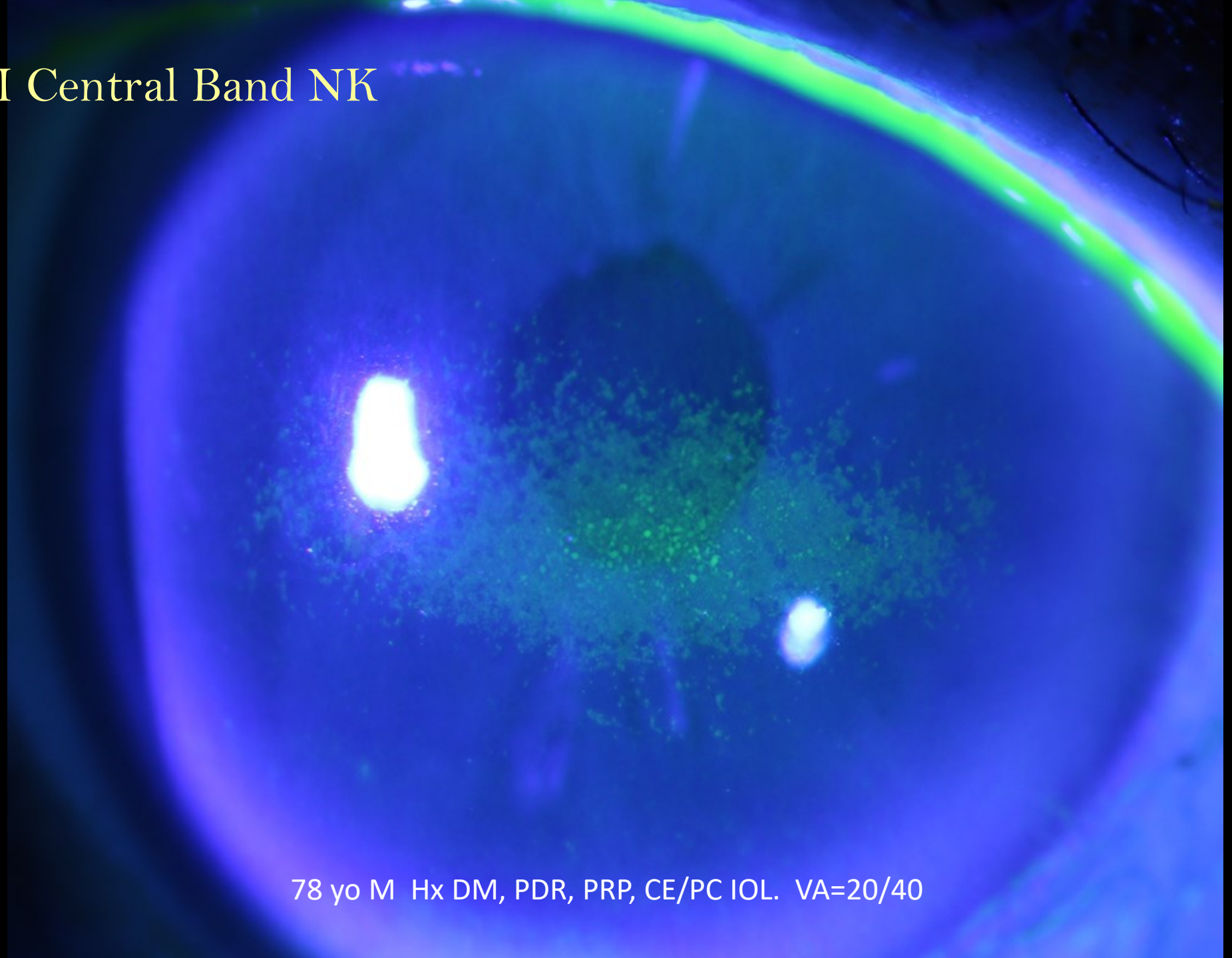
Consider renaming condition Sprite Keratopathy?

Stage I Central Band NK

Stage I Central Band NK

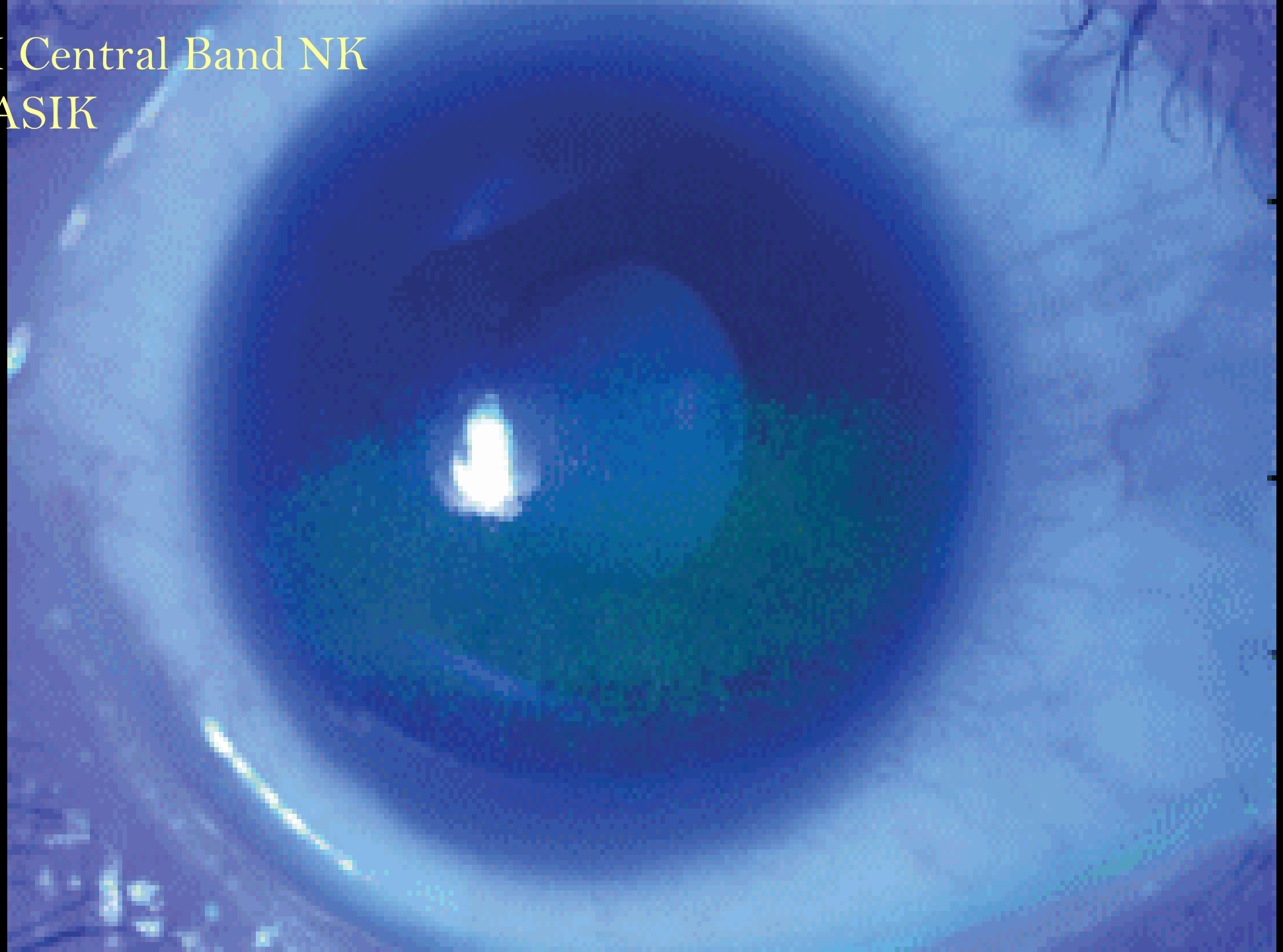


Stage I Central Band NK

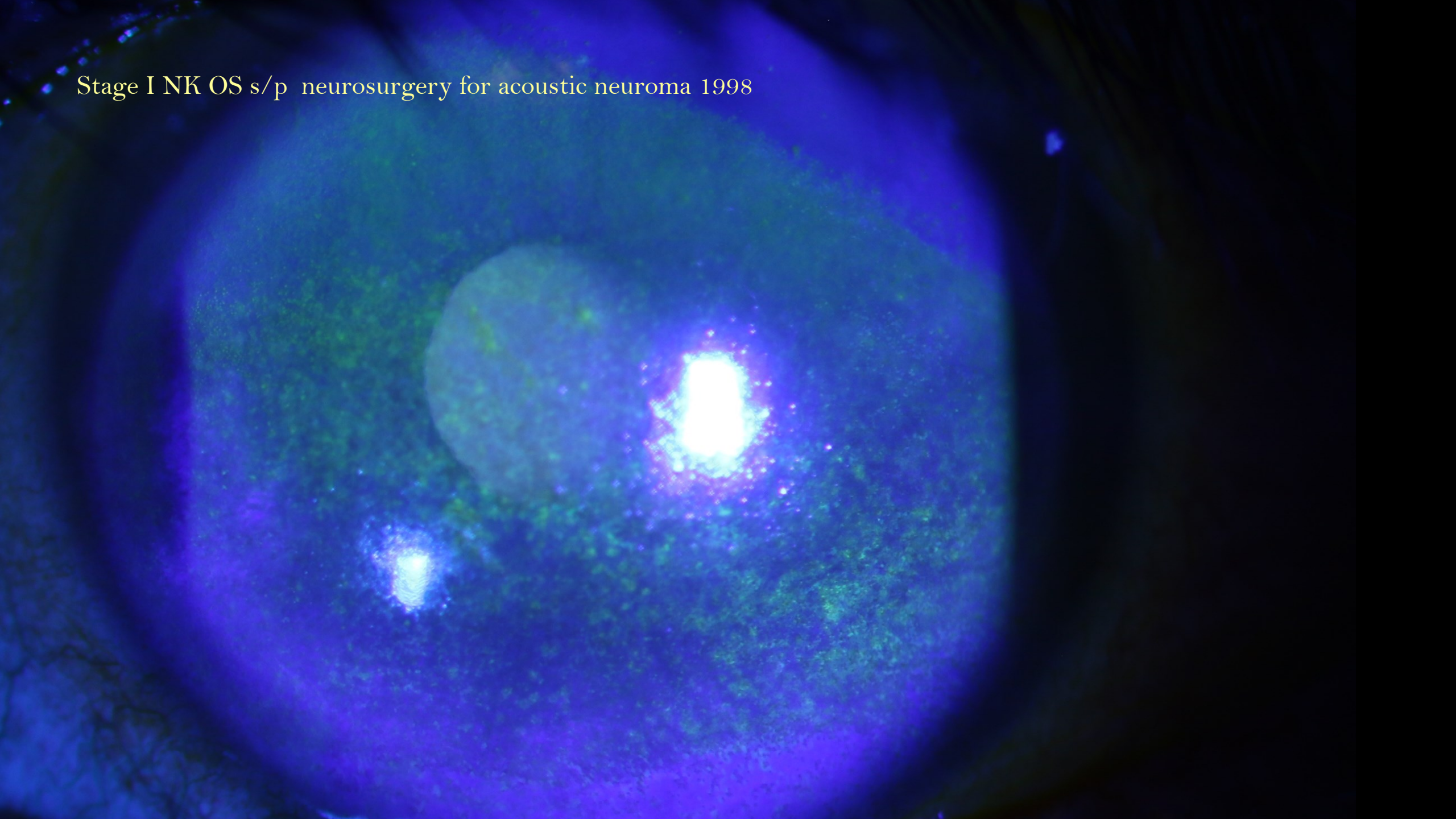


78 yo M Hx DM, PDR, PRP, CE/PC IOL. VA=20/40

Stage I Central Band NK
S/P LASIK



Blizzard/Milky Way


Stage I NK OS s/p neurosurgery for acoustic neuroma 1998

Hurricane/Vortex

Corneal Epithelium

Ocular surface very dynamic

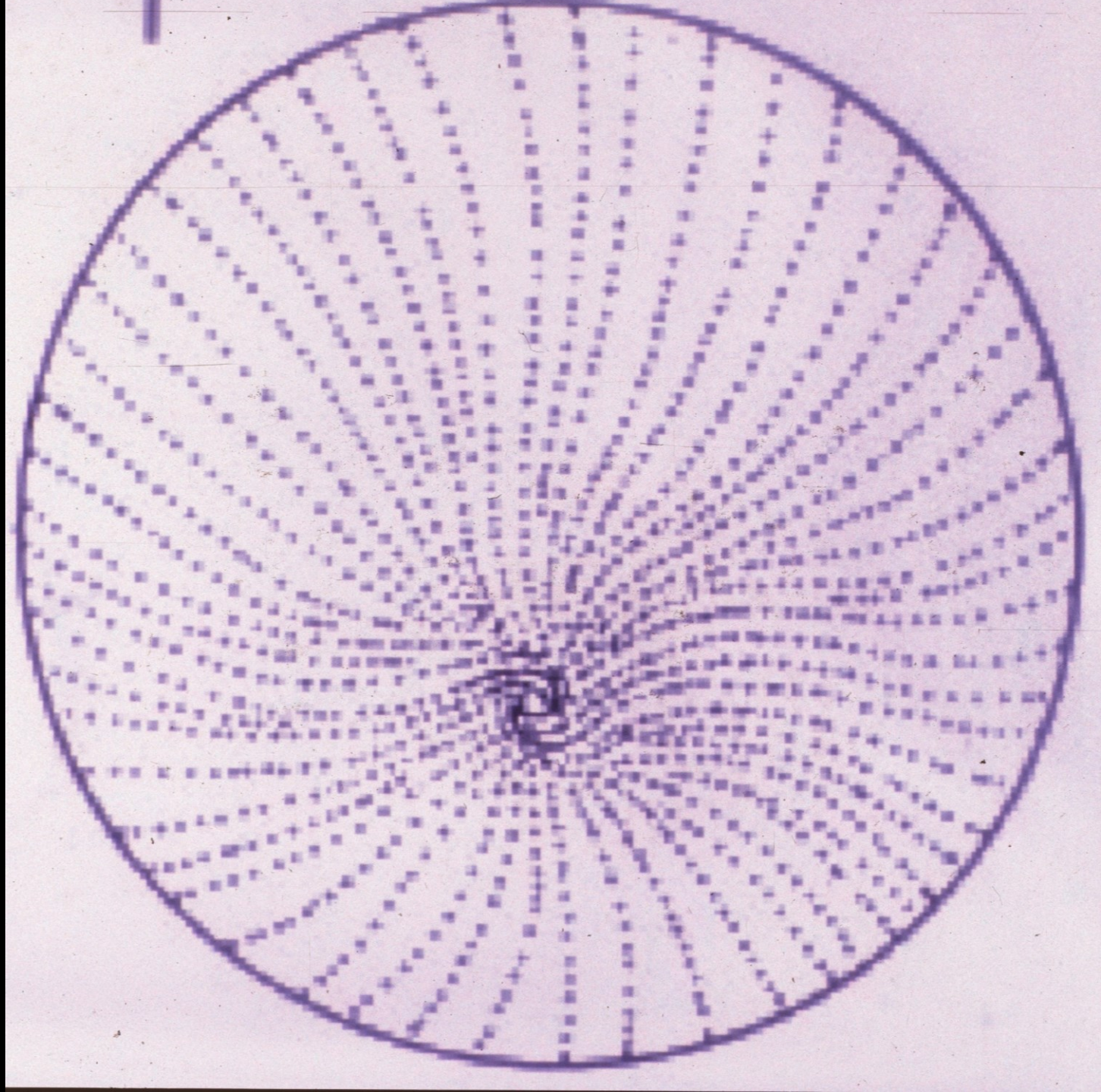
Complete exfoliative cellular turnover Q-6 days

New surface cells derived from limbal stem cells

New cells move centrally and centripetally

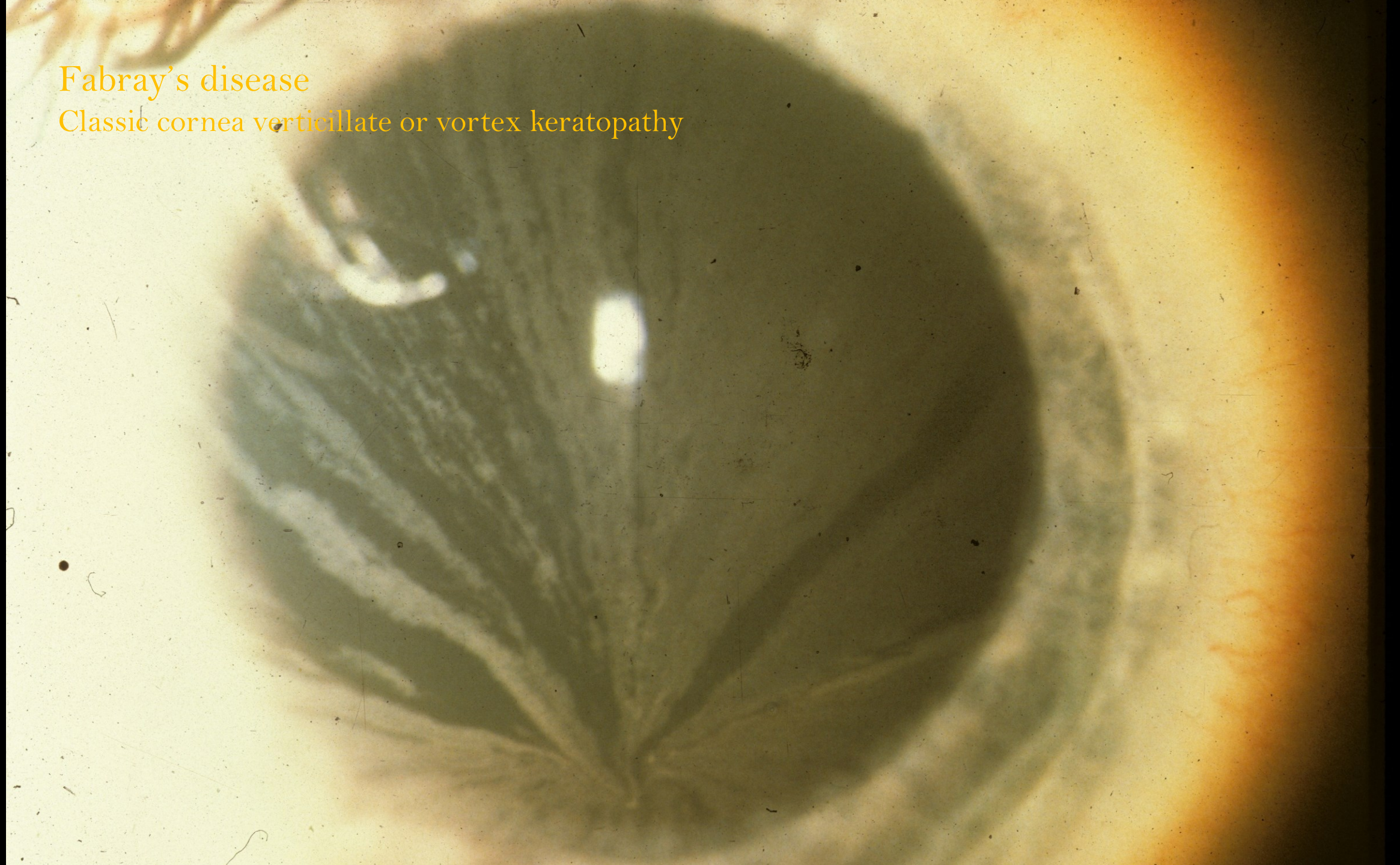
Apex of vertex/hot zone rotates clockwise (90%)

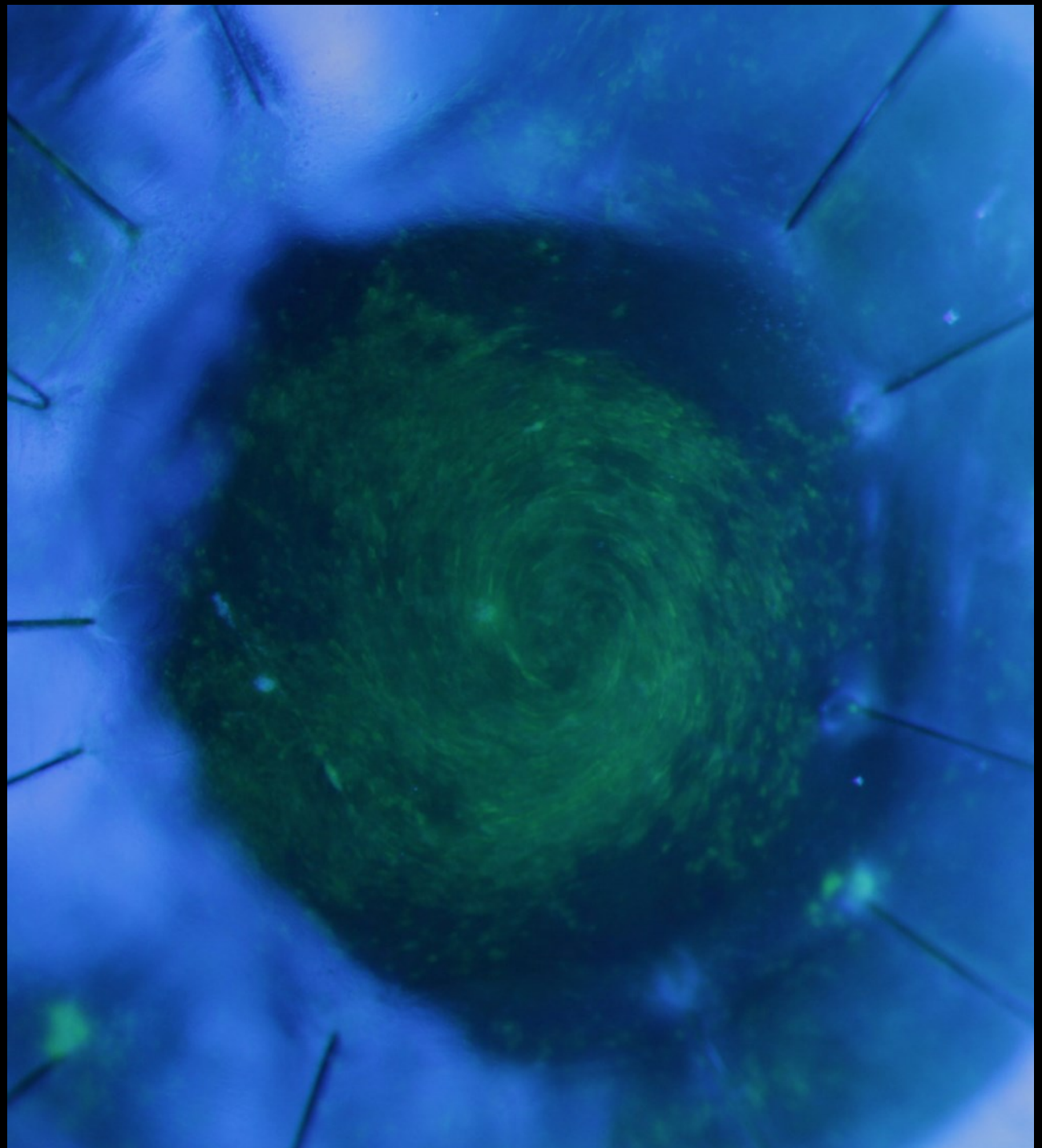
SBNP and epithelium move/exfoliate in tandem



Fabray's disease

Classic cornea verticillate or vortex keratopathy



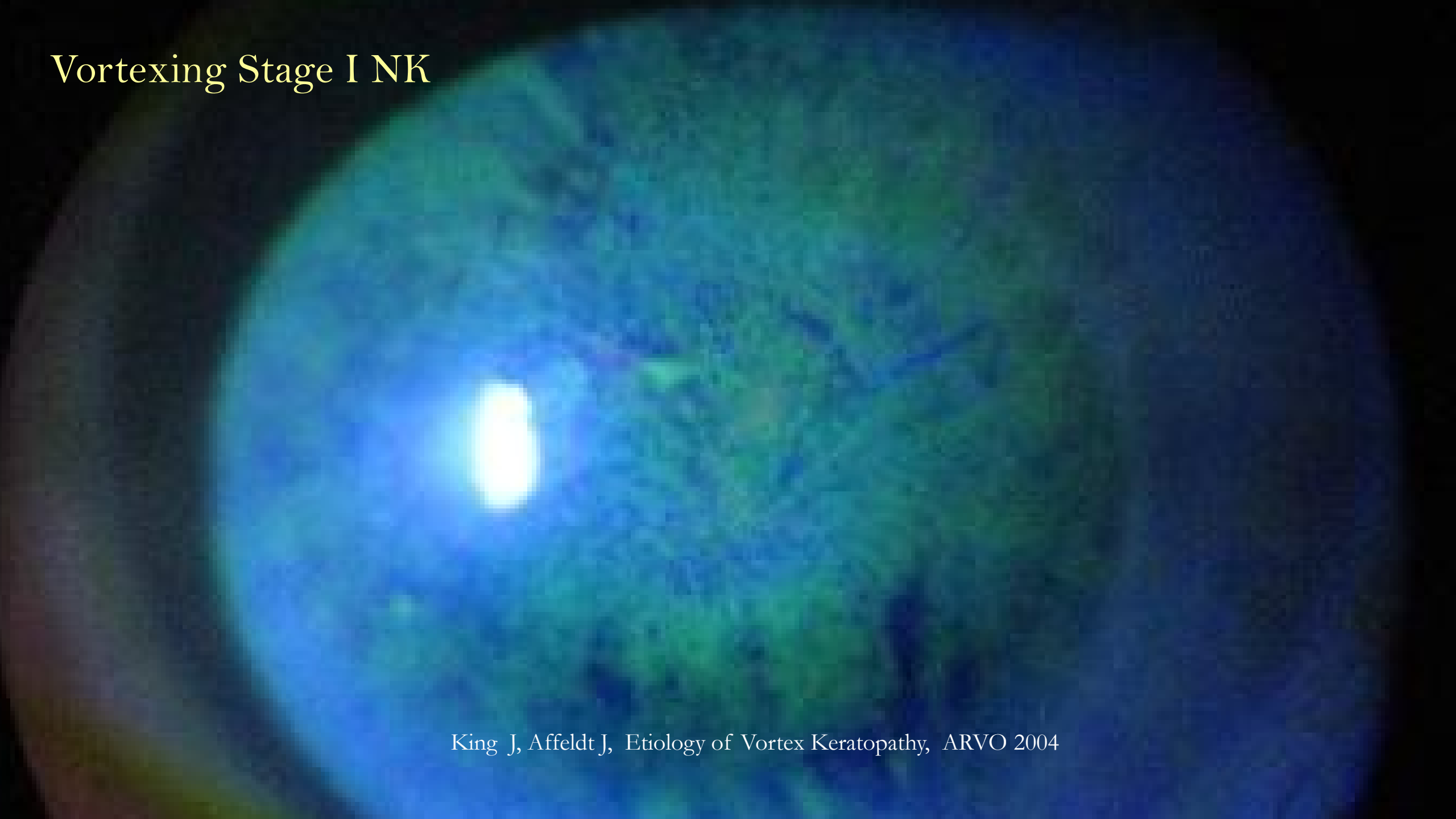


Vortexing Stage I NK

- Severe form of Stage I NTK
- Common (~ 50% of cases)
- Virtually pathognomonic of NTK [1]

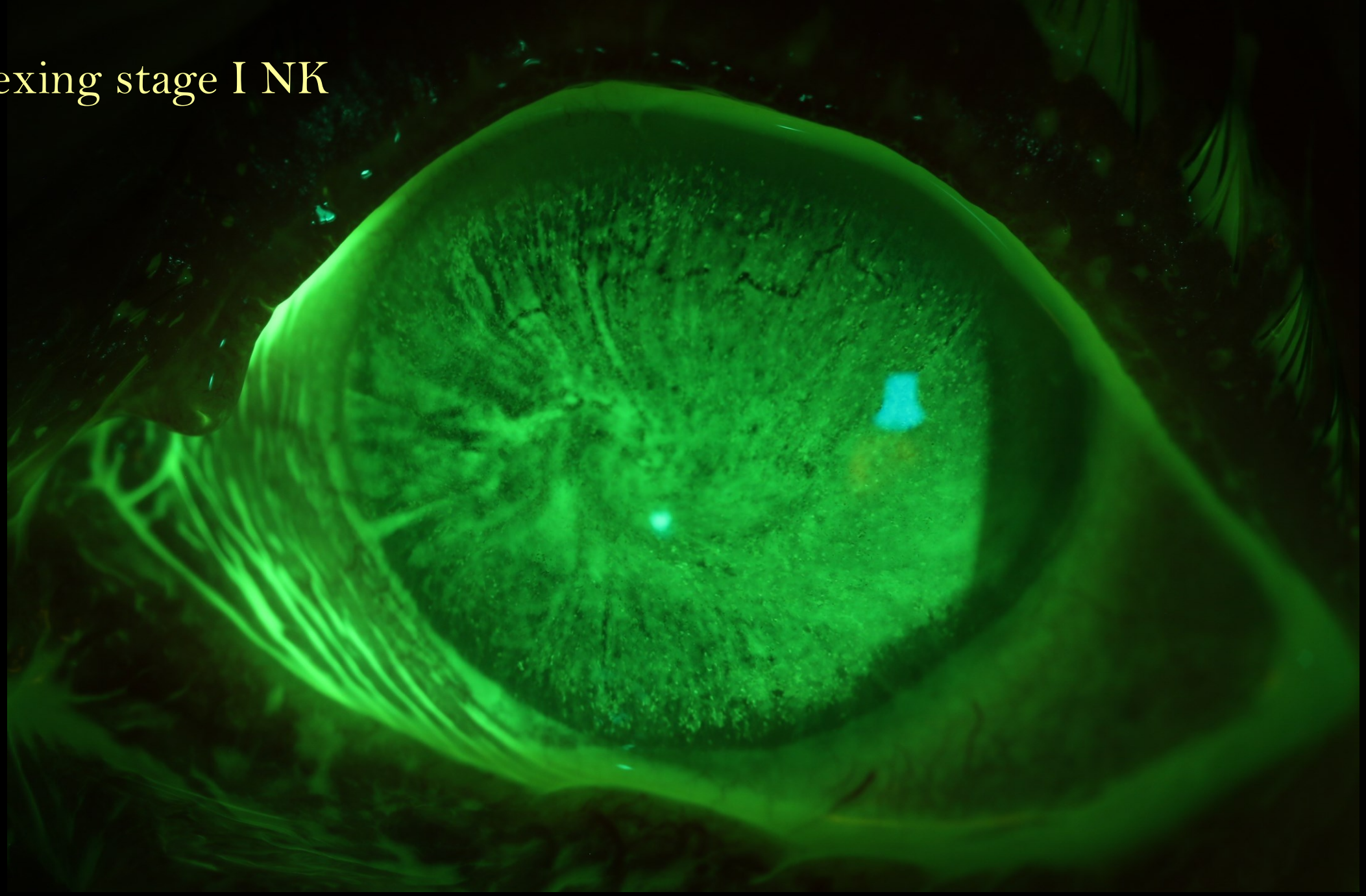
1. King J, Affeldt J, Etiology of Vortex Keratopathy, ARVO 2004

Vortexing Stage I NK



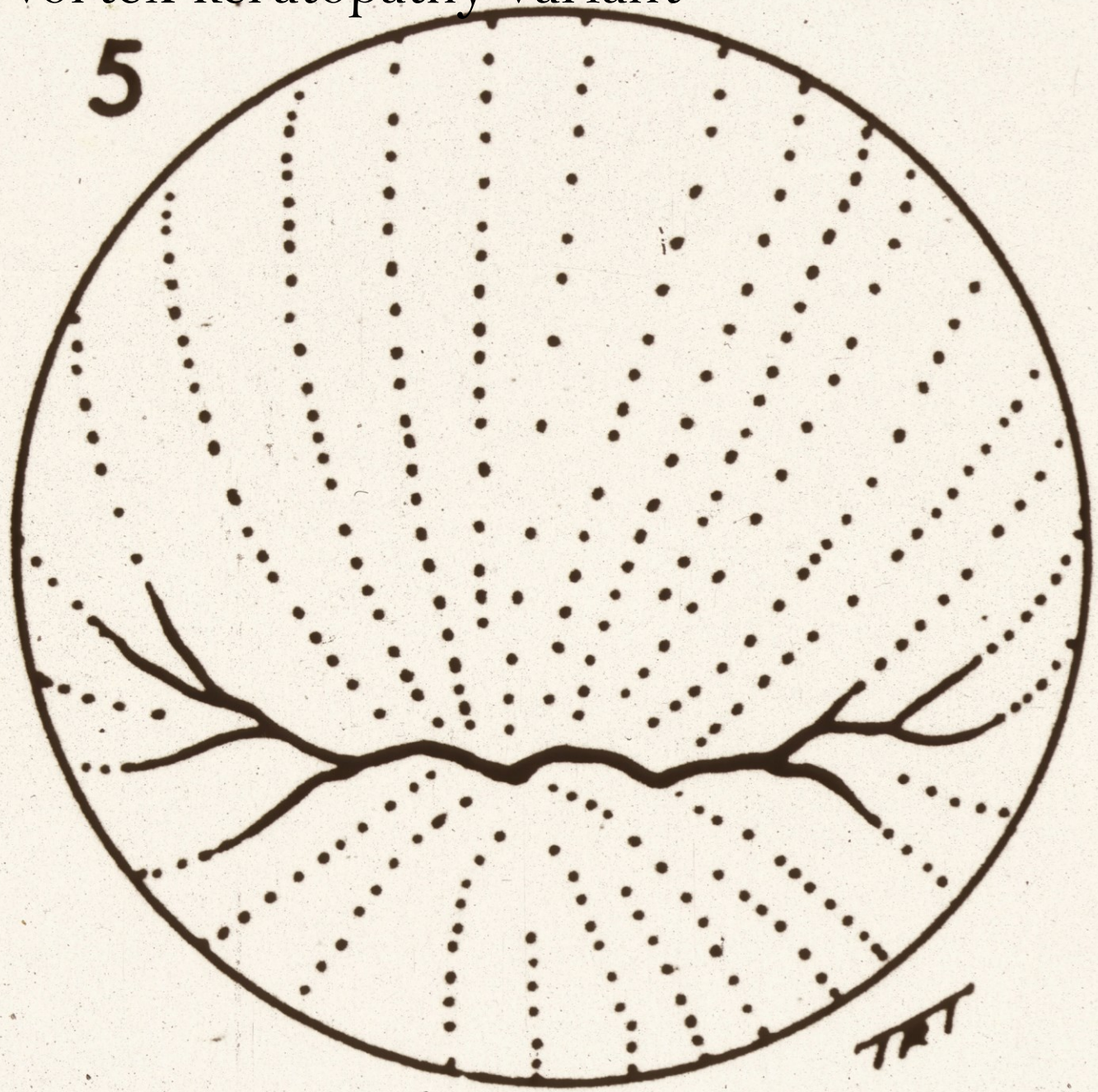
King J, Affeldt J, Etiology of Vortex Keratopathy, ARVO 2004

Vortexing stage I NK

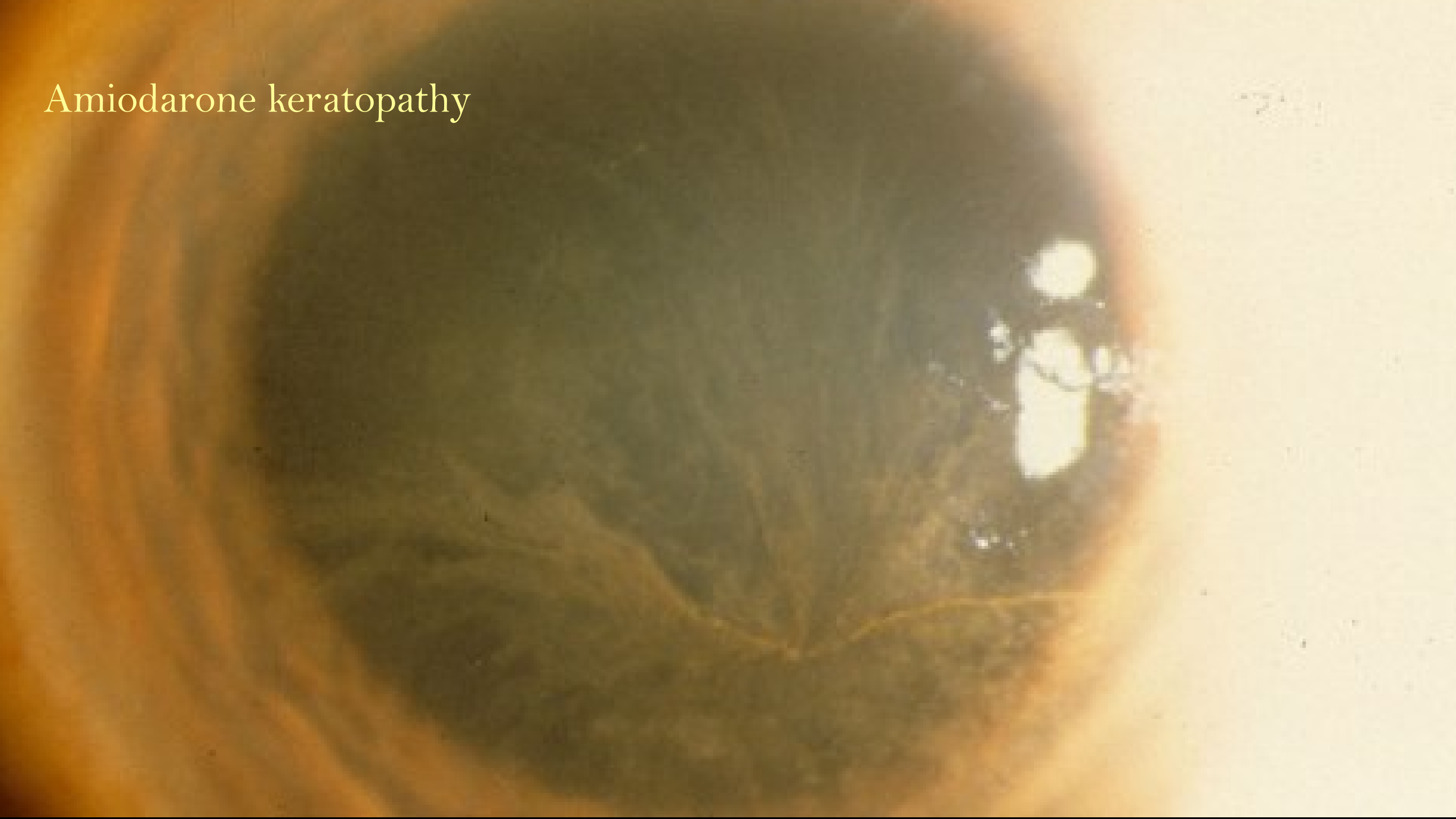


Dendriform

Dendritiform vortex keratopathy variant

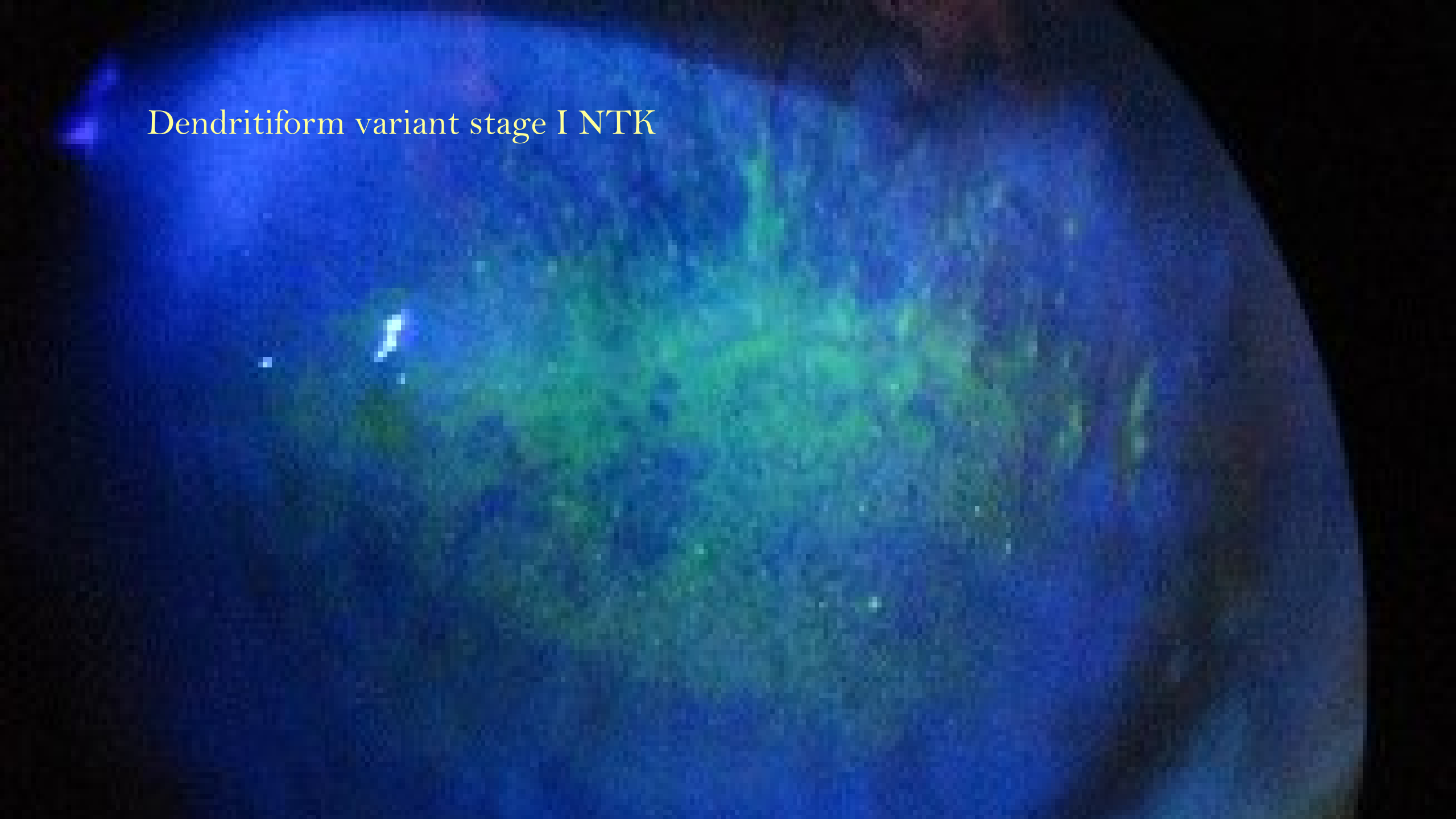


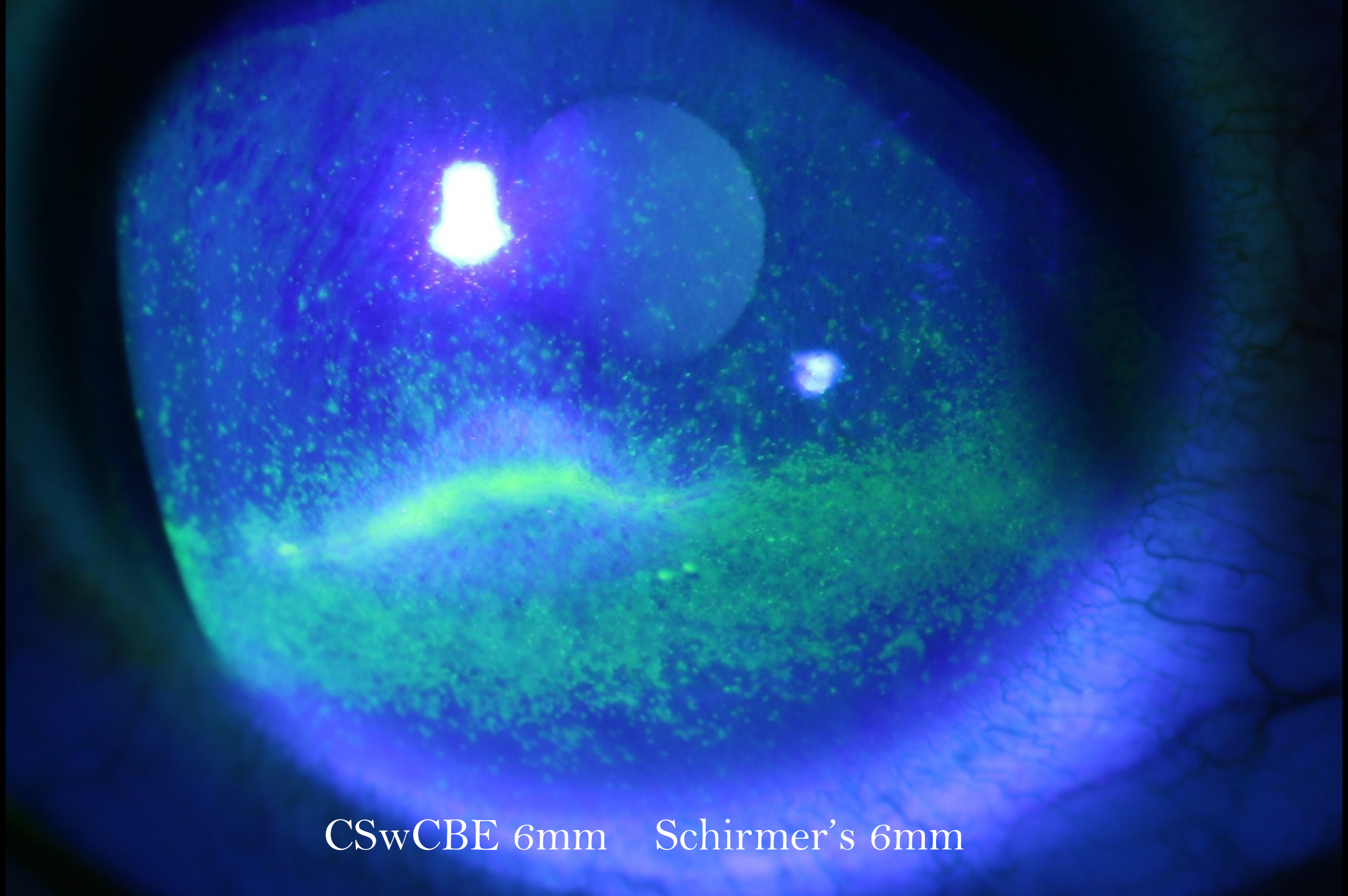
Amiodarone keratopathy

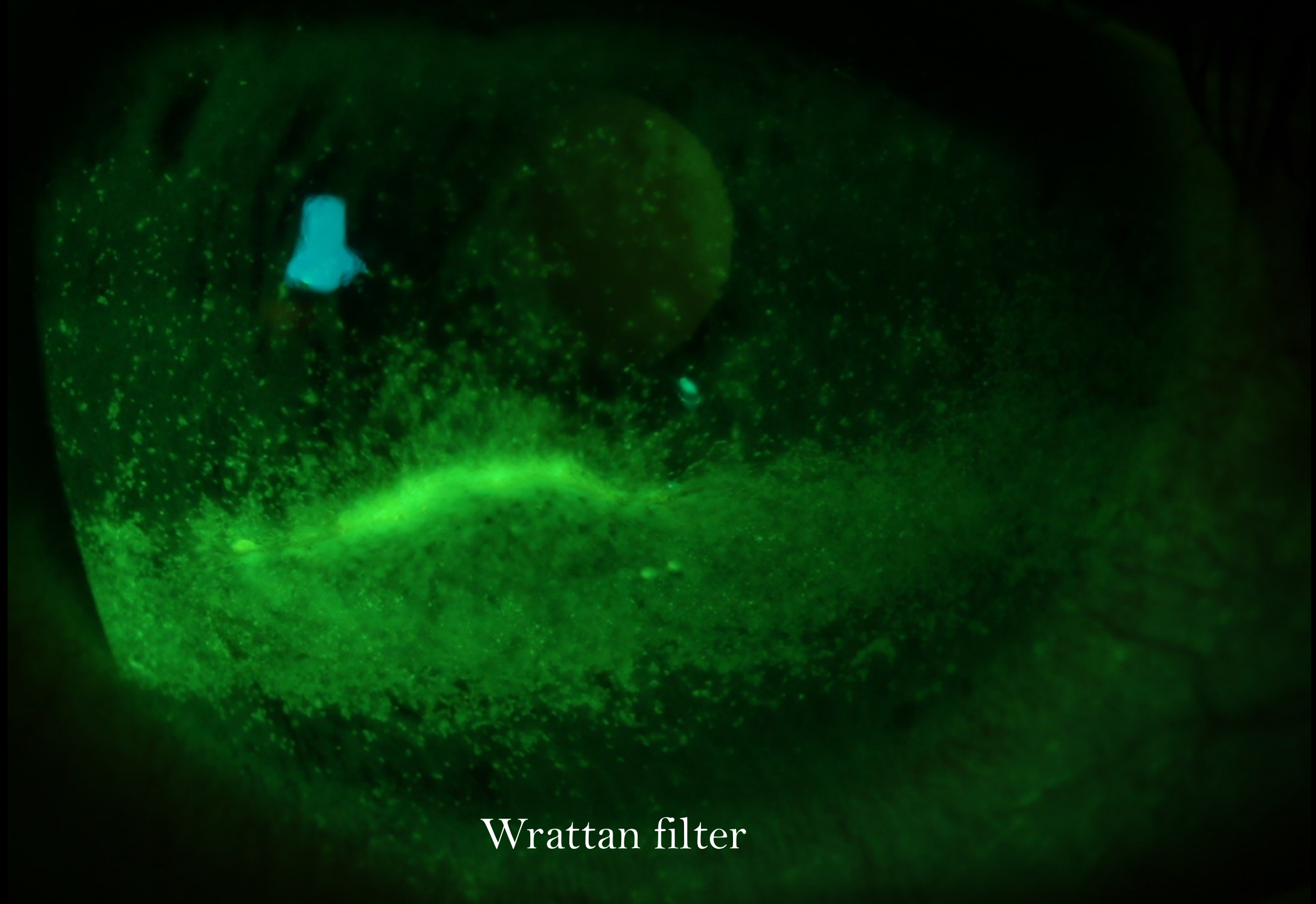


Herpes Simplex Keratitis

- Discrete randomly located lesions
- Dichotomous branching
- End bulbs
- No surrounding field of PEK

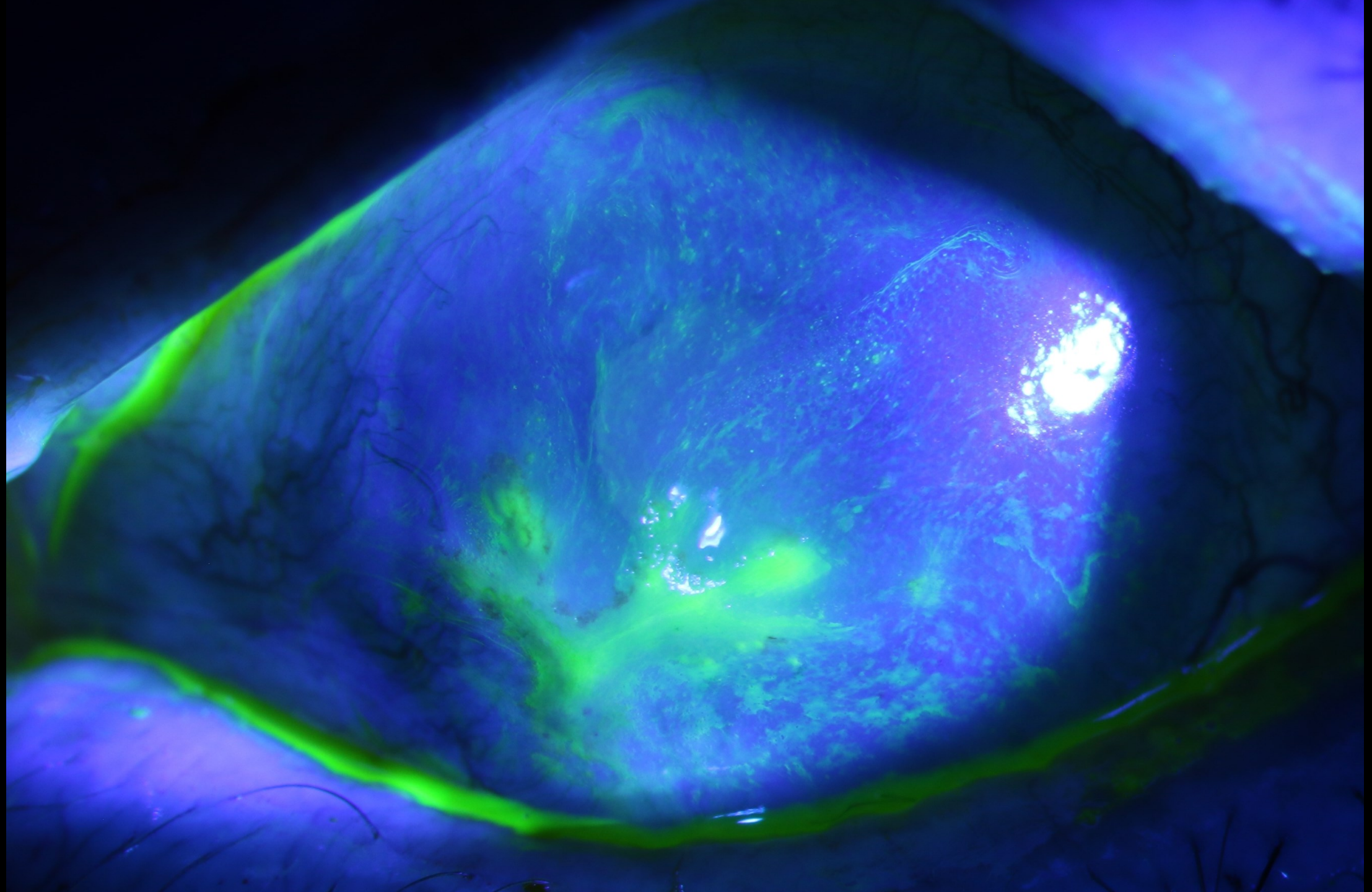

Dendritiform variant stage I NTK

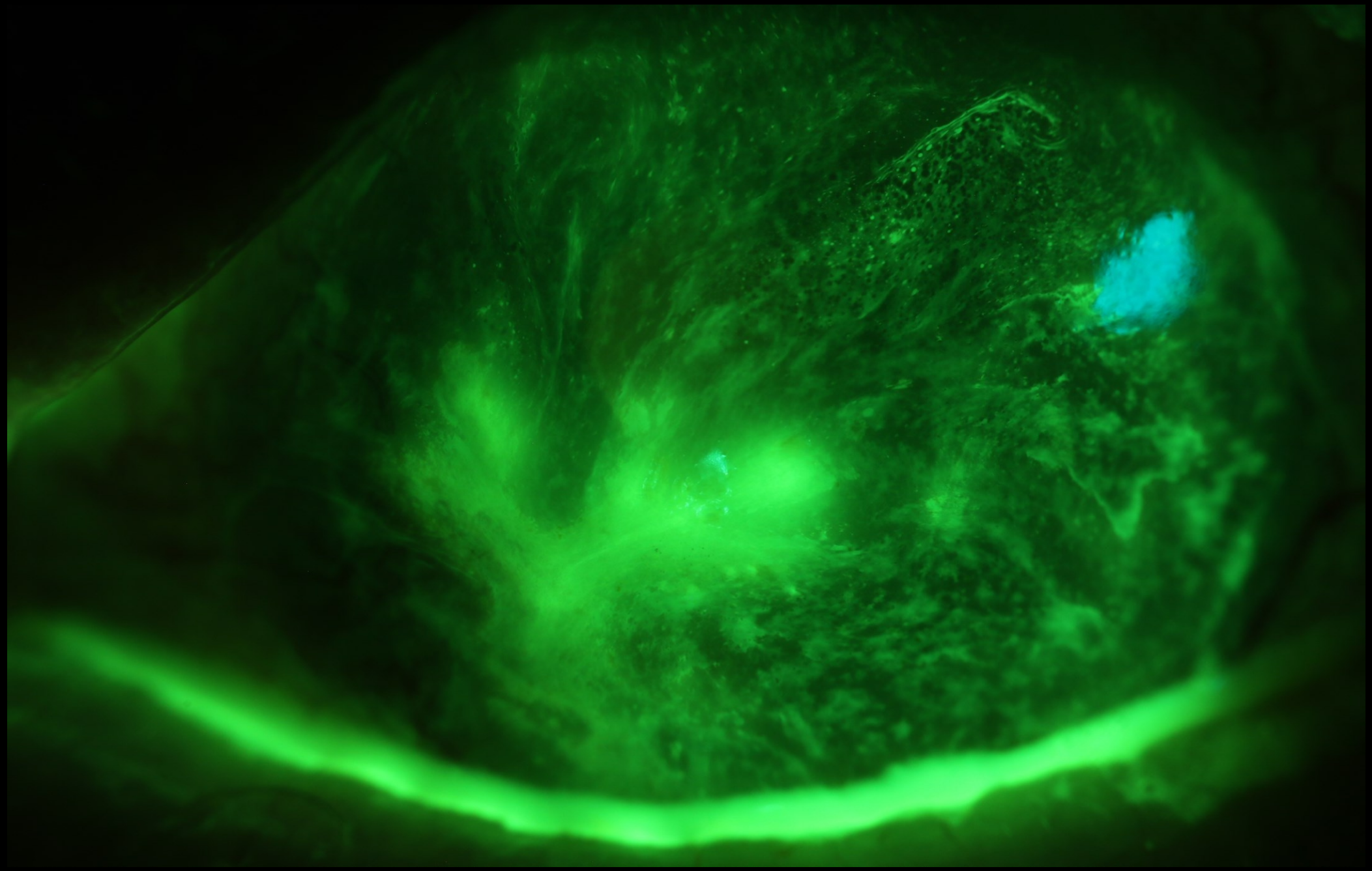

CSwCBE 6mm
Schirmer's 6mm
JB

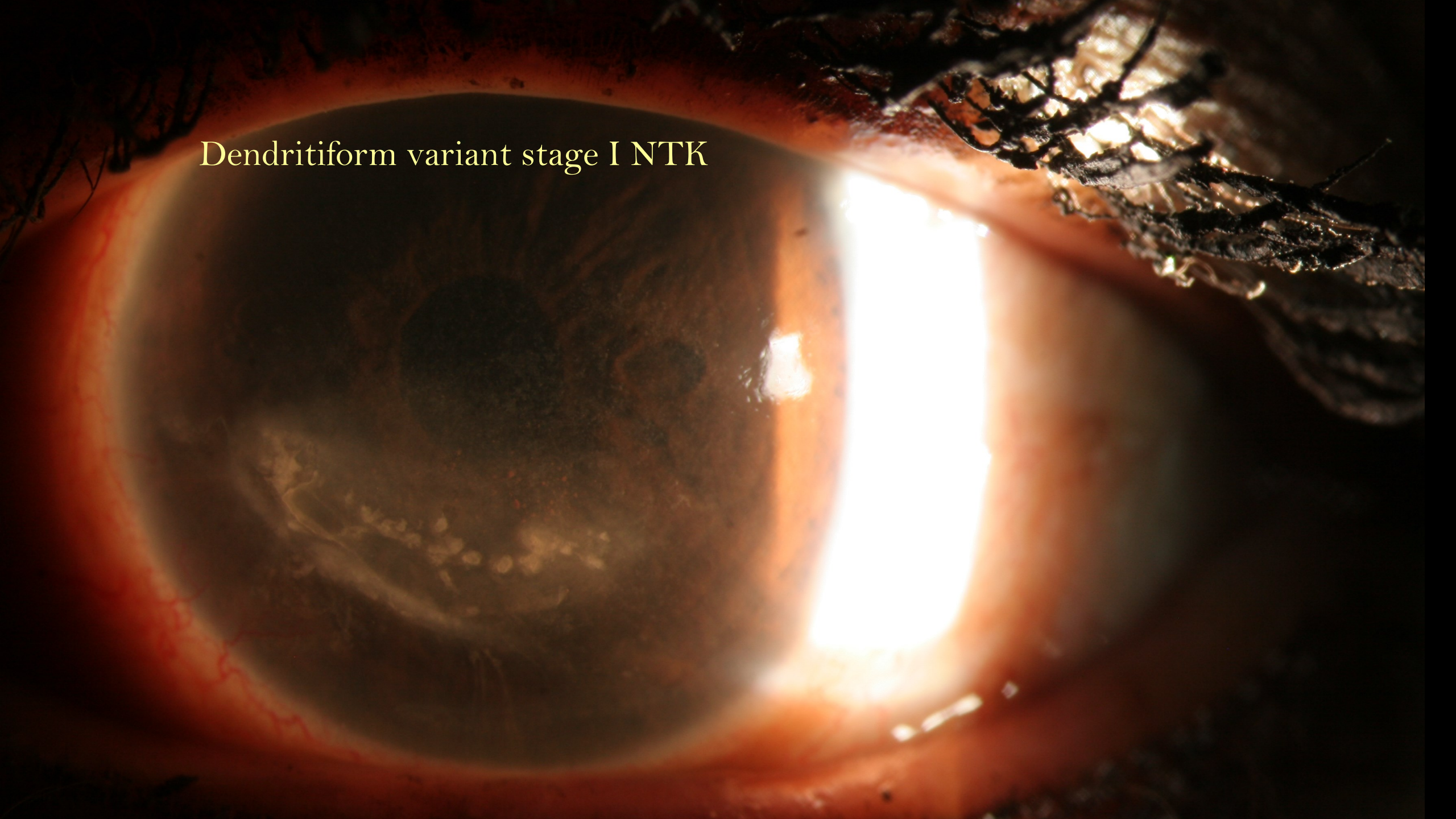


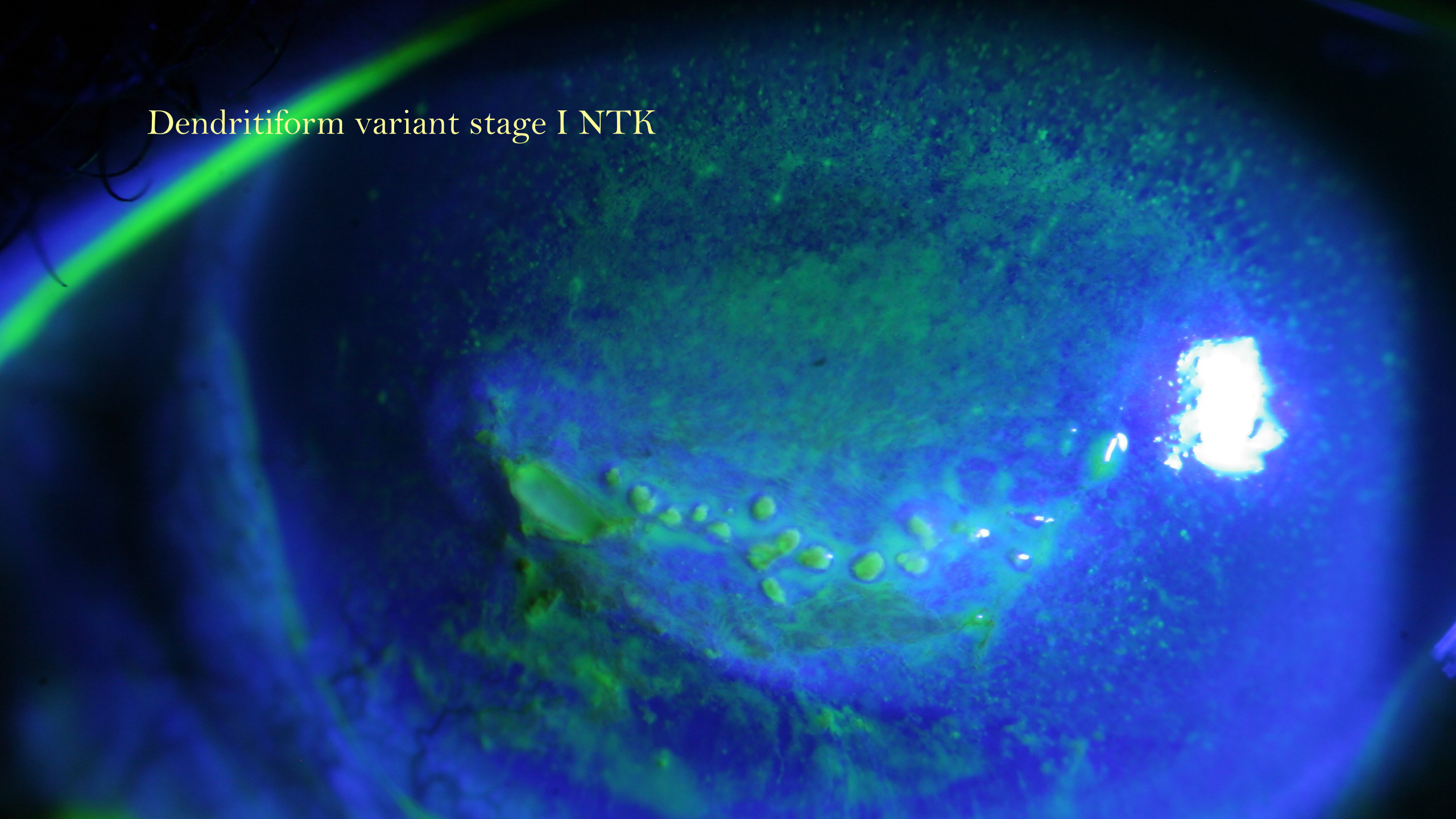
Wrattan filter

JB

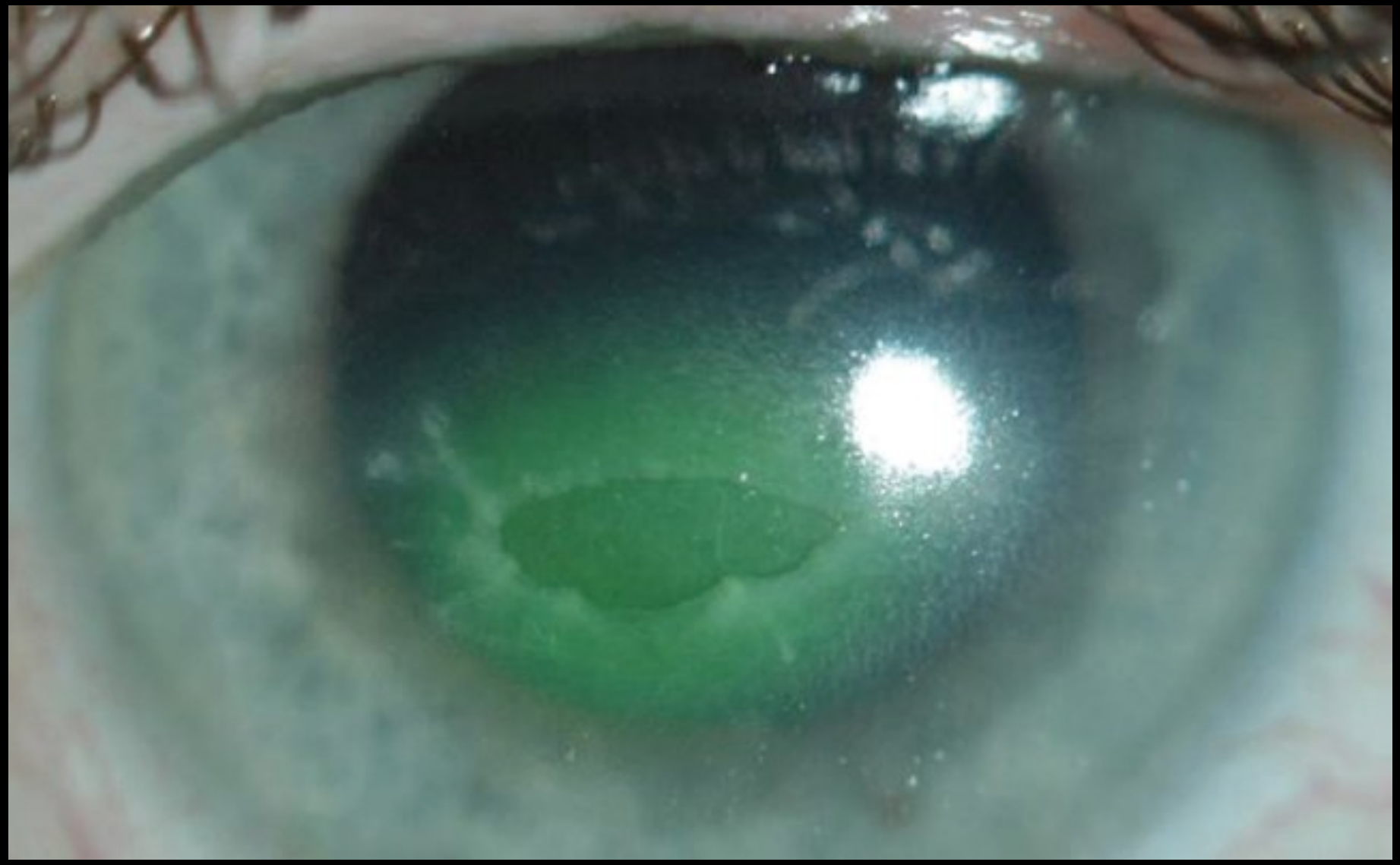




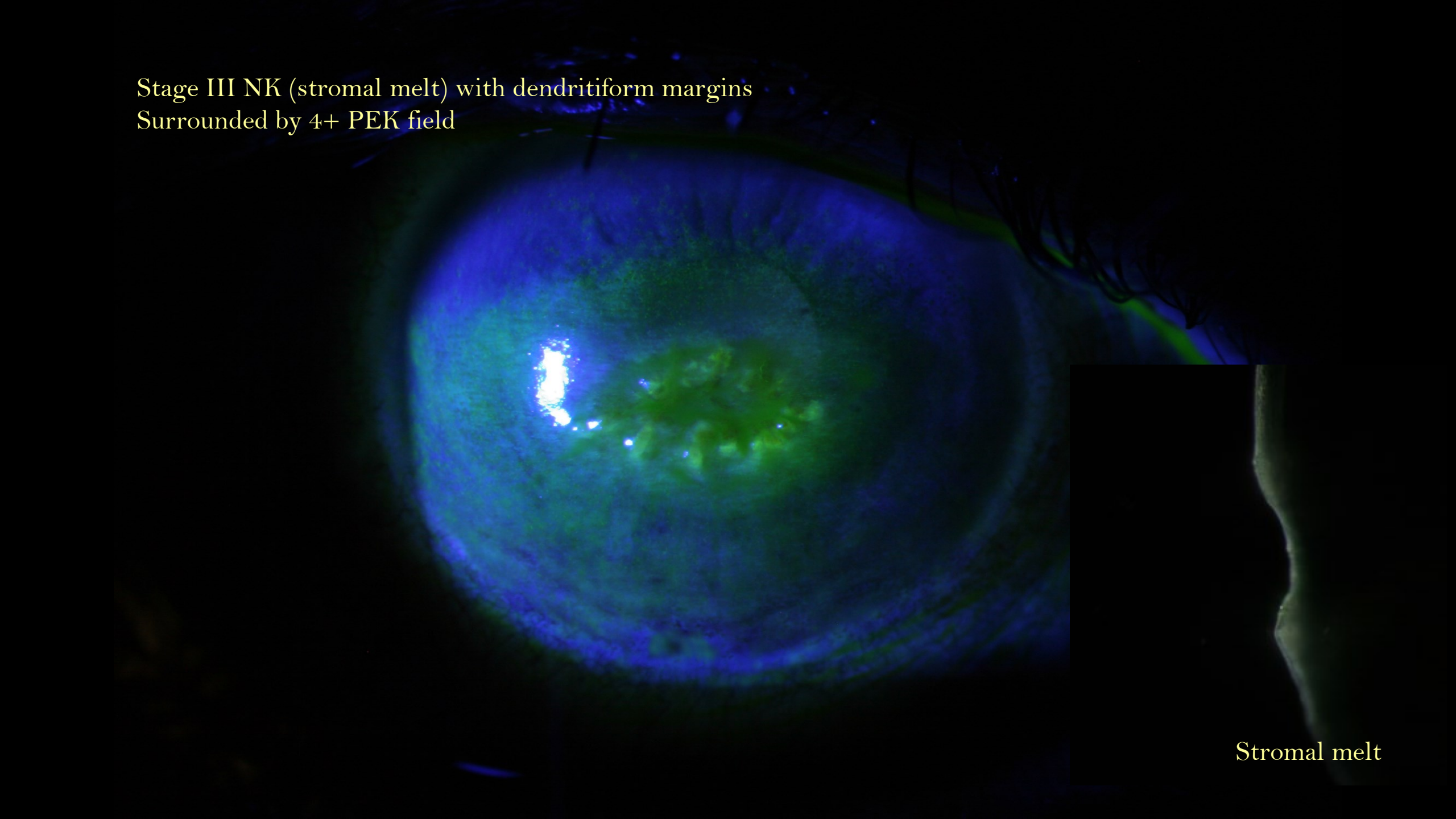

Dendritiform variant stage I NTK


Dendritiform variant stage I NTK

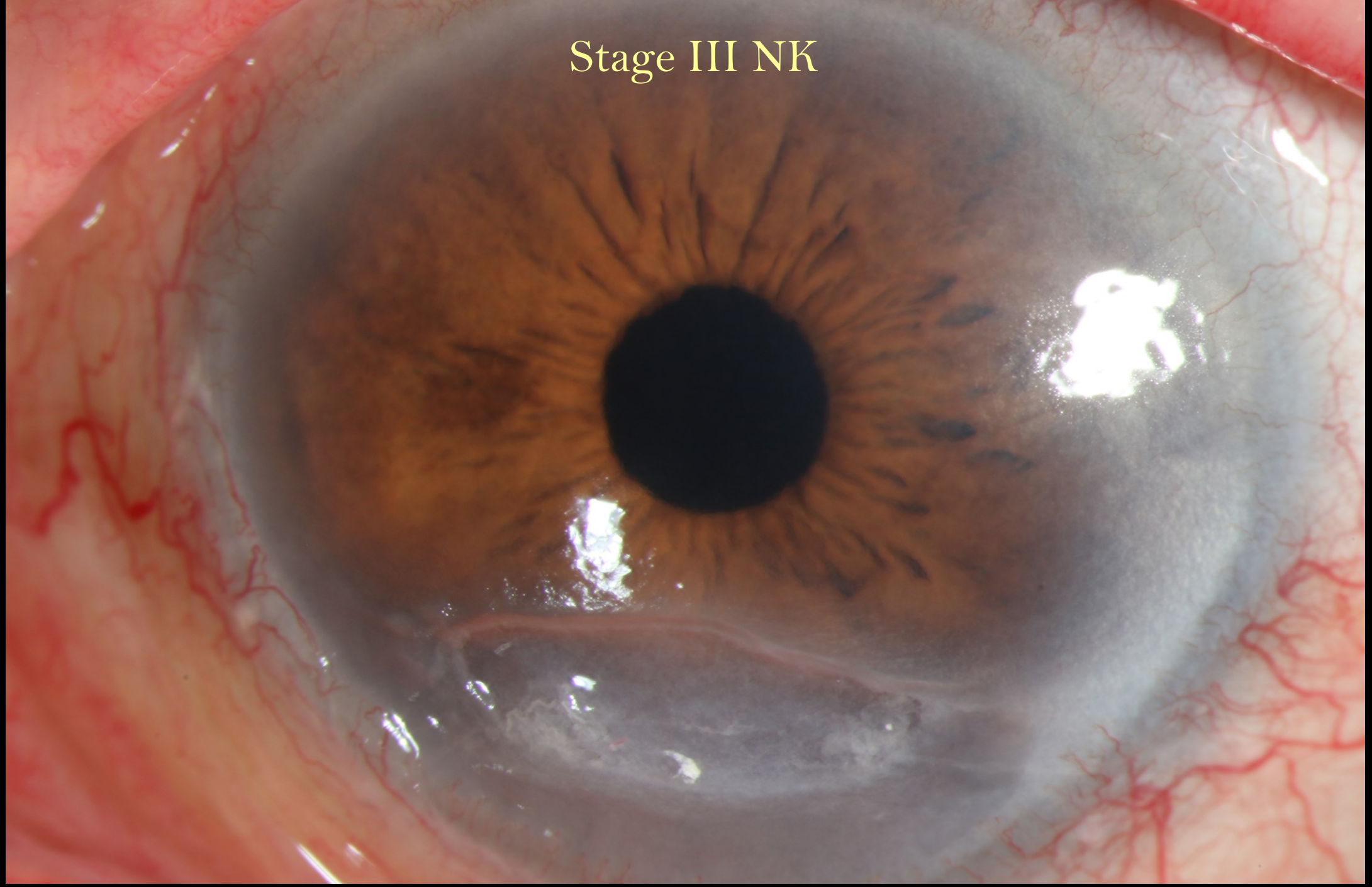
Stage II: Persistent epithelial defect (PED)



Stage III NK (stromal melt) with dendritiform margins
Surrounded by 4+ PEK field



Stromal melt

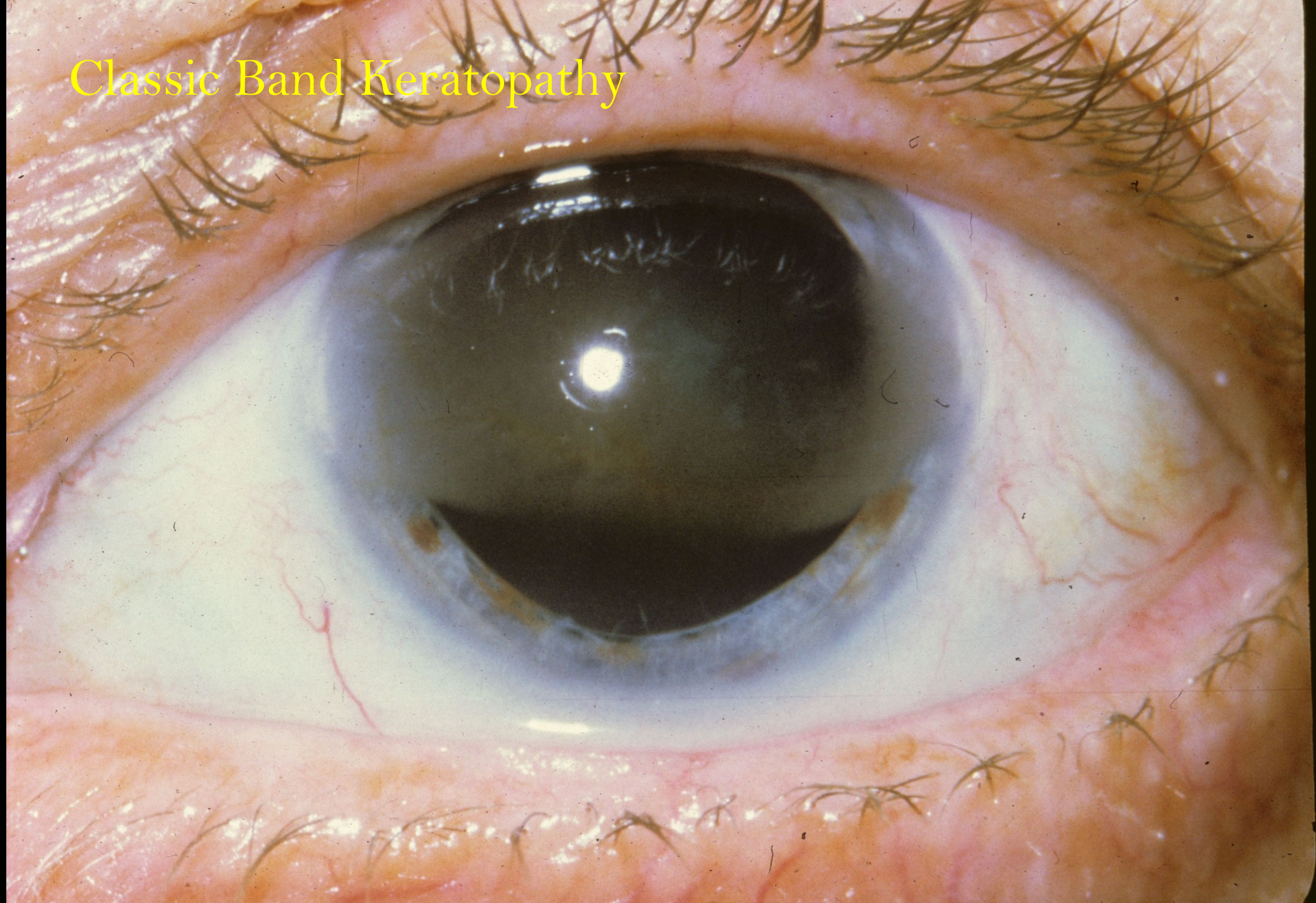

Stage III NK

Stage III NK

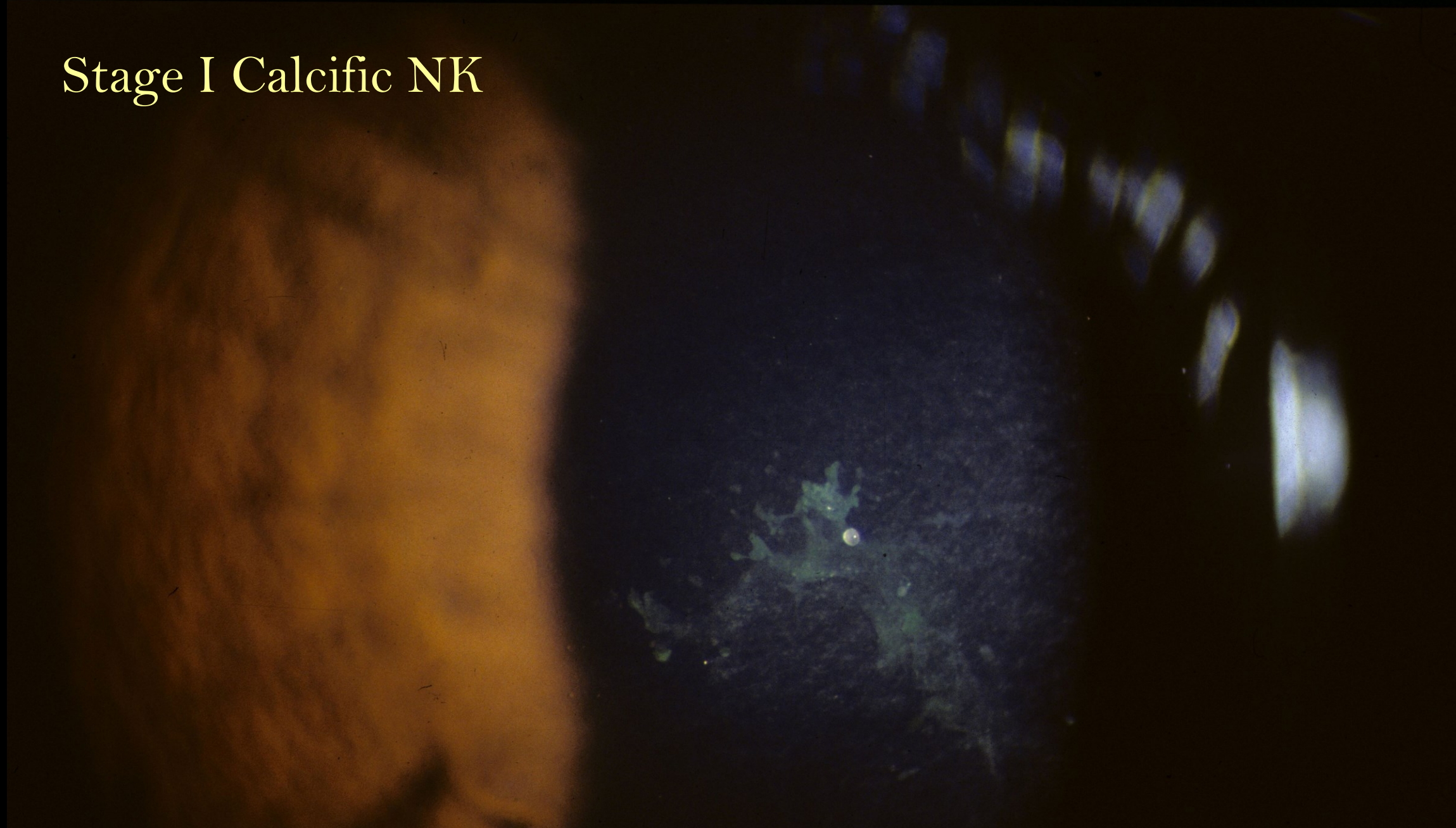
(**S**tromal melt with descemetocele)

Central Isolated Calcific NK

- Represents calcium deposition within the NK activity zone
- Secondary to chronic NK
- Can assume any of the NK variant patterns


Classic Band Keratopathy

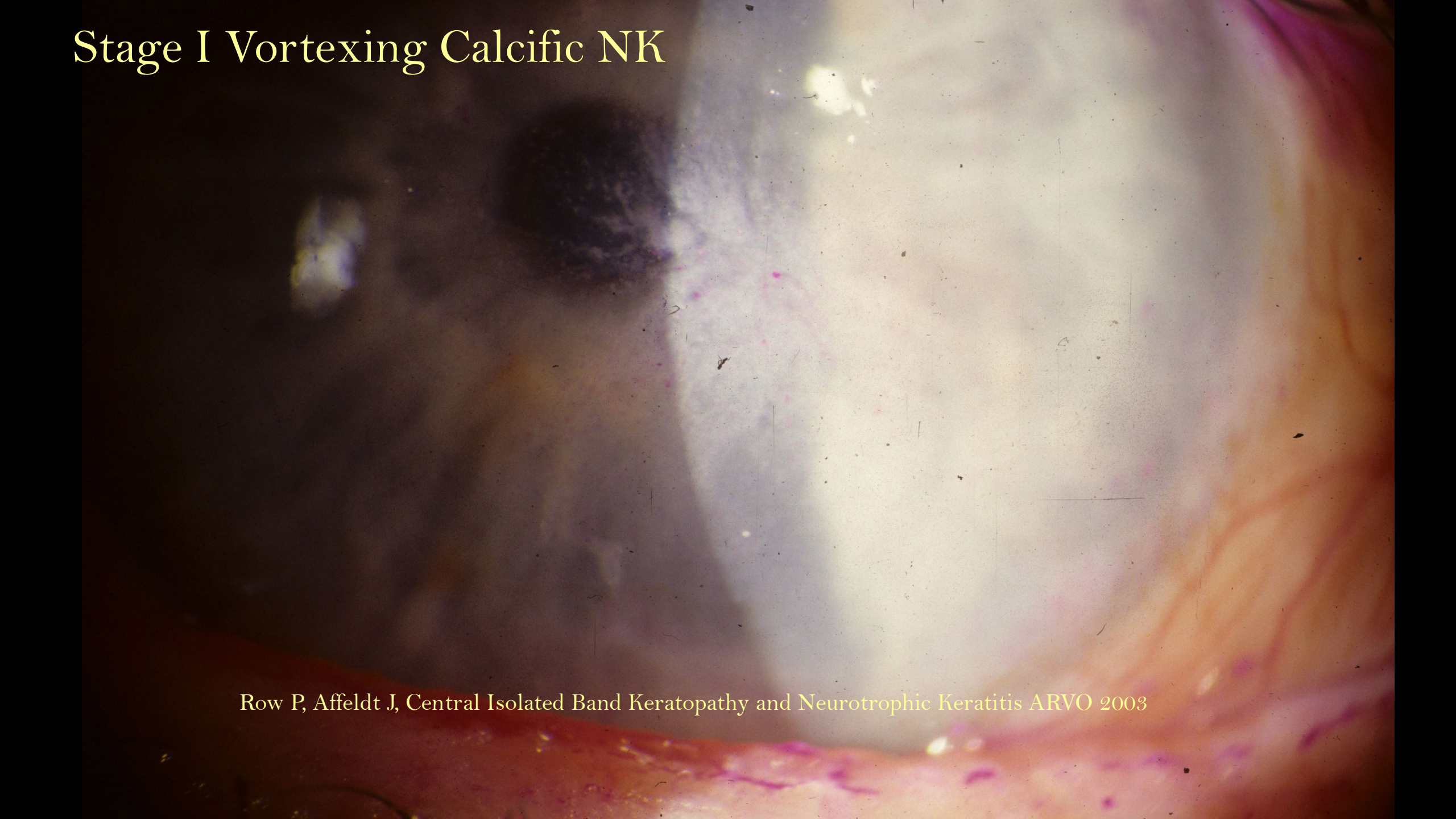
Stage I Calcific NK



Row P, Affeldt J, Central Isolated Band Keratopathy and Neurotrophic Keratitis ARVO 2003

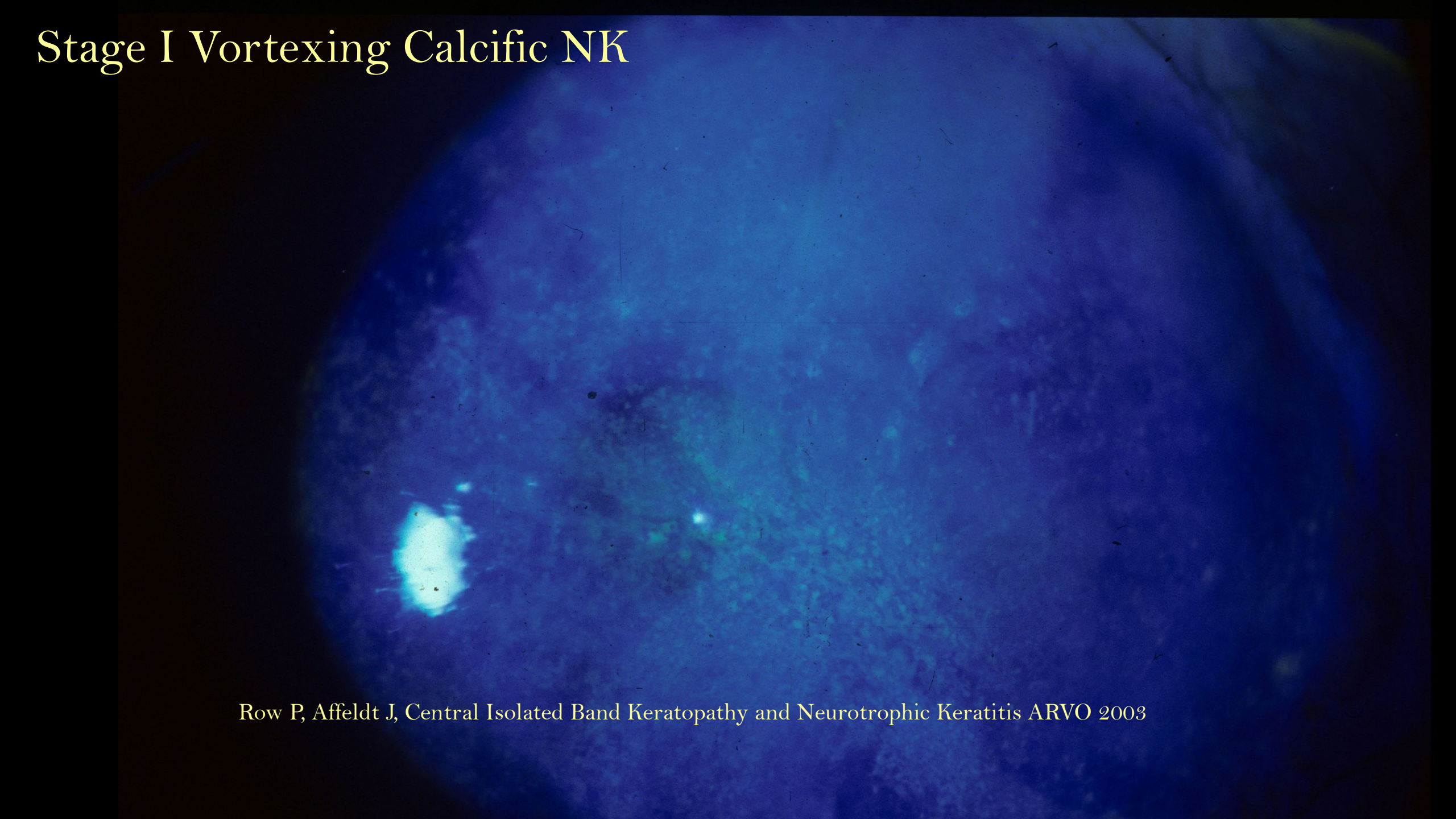

Stage I central isolated calcific NK
VA 20/50
CBE=60/16
Chronic idiopathic NK

Stage I Vortexing Calcific NK



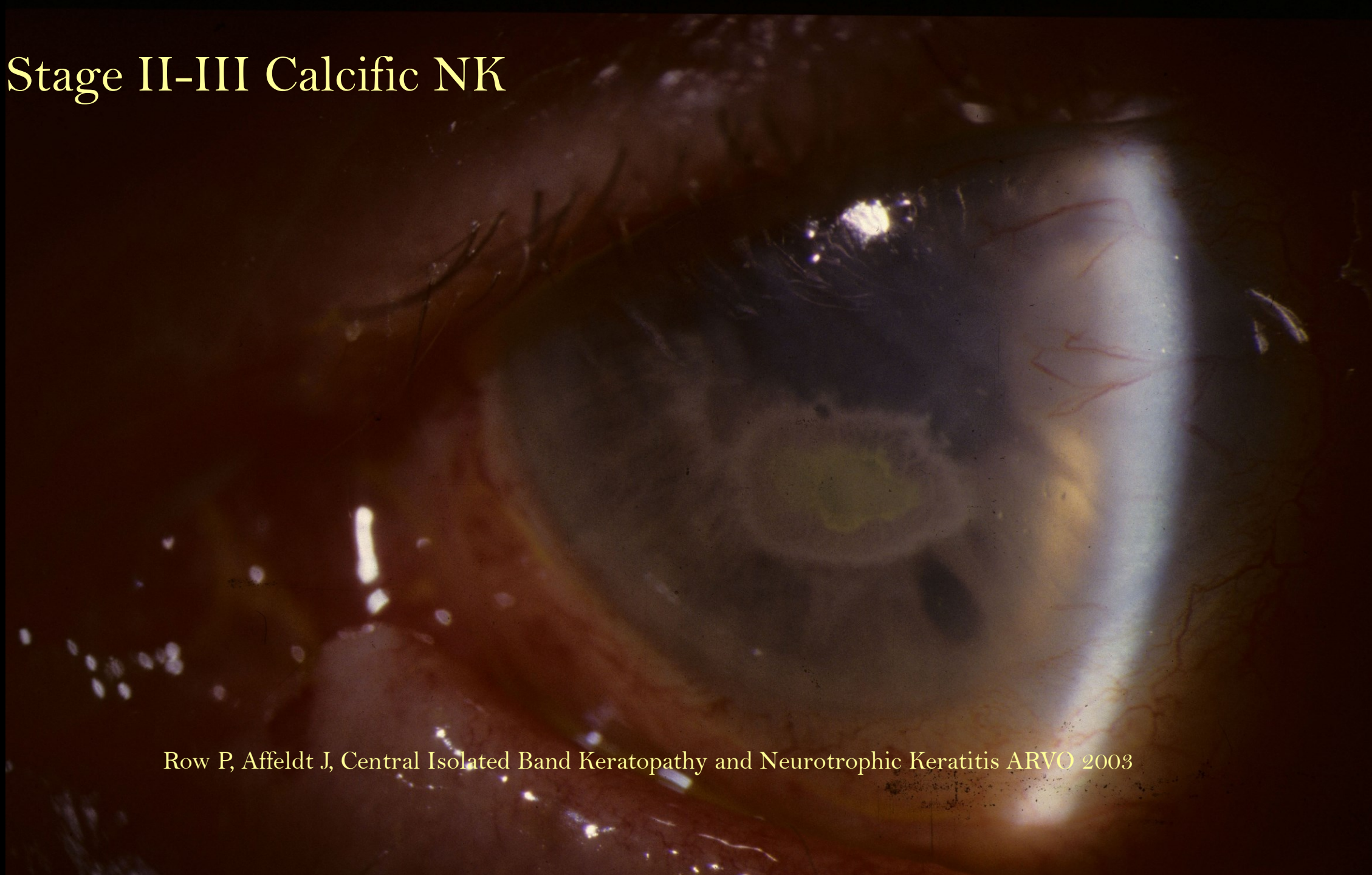
Row P, Affeldt J, Central Isolated Band Keratopathy and Neurotrophic Keratitis ARVO 2003

Stage I Vortexing Calcific NK



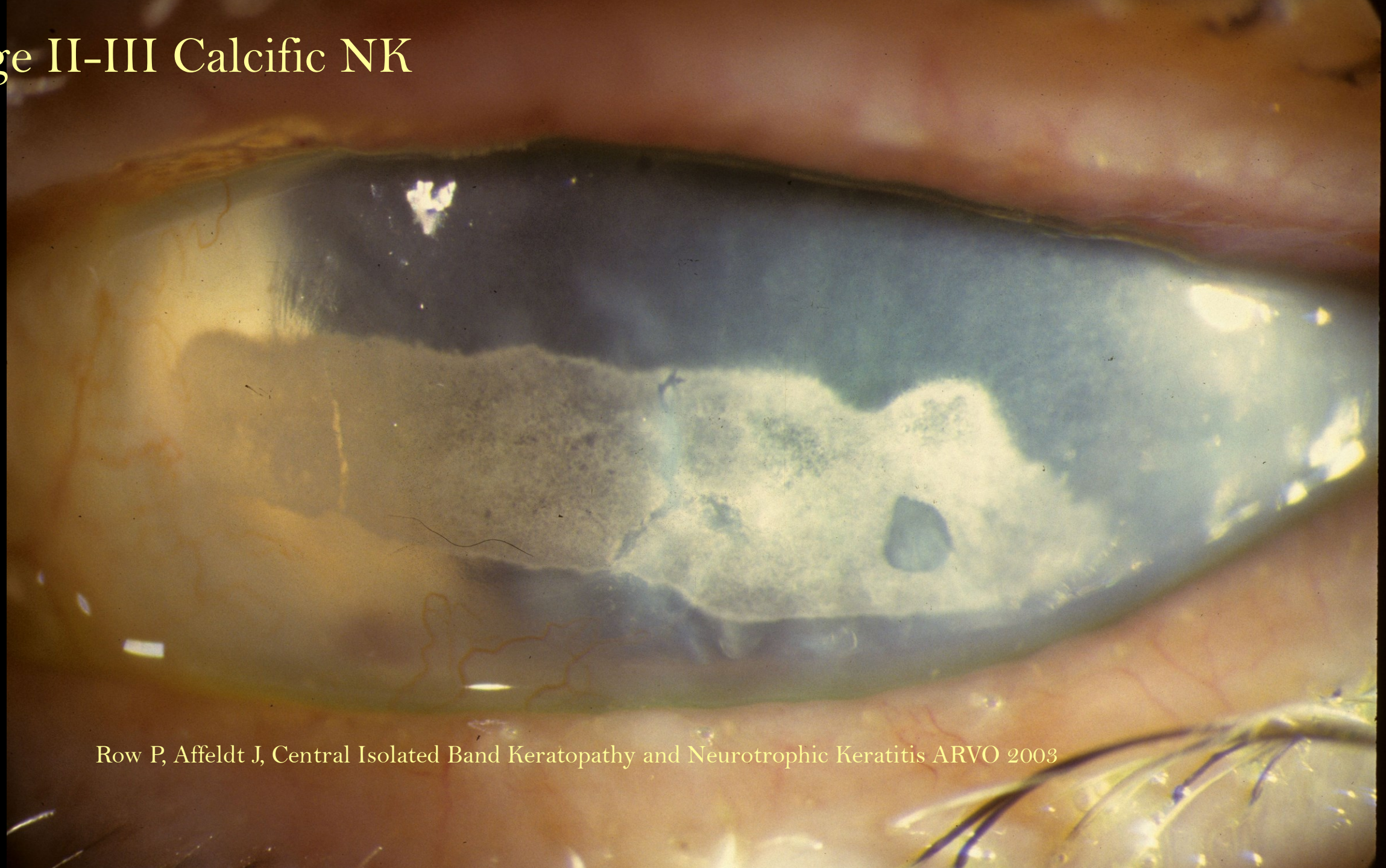
Row P, Affeldt J, Central Isolated Band Keratopathy and Neurotrophic Keratitis ARVO 2003

Stage II-III Calcific NK



Row P, Affeldt J, Central Isolated Band Keratopathy and Neurotrophic Keratitis ARVO 2003

Stage II-III Calcific NK



Row P, Affeldt J, Central Isolated Band Keratopathy and Neurotrophic Keratitis ARVO 2003

NK Treatment Options[1-3]

Treatments are typically used according to NK stage/severity but are not mutually exclusive of one another.

.

Topicals

- Artificial tears
- Corticosteroids
- Autologous serum eye drops
- Antibiotics

In-Office Procedures

- Therapeutic contact lenses
- Punctal occlusion
- Non-surgical eyelid closure
- Amniotic membranes
- Tissue adhesives

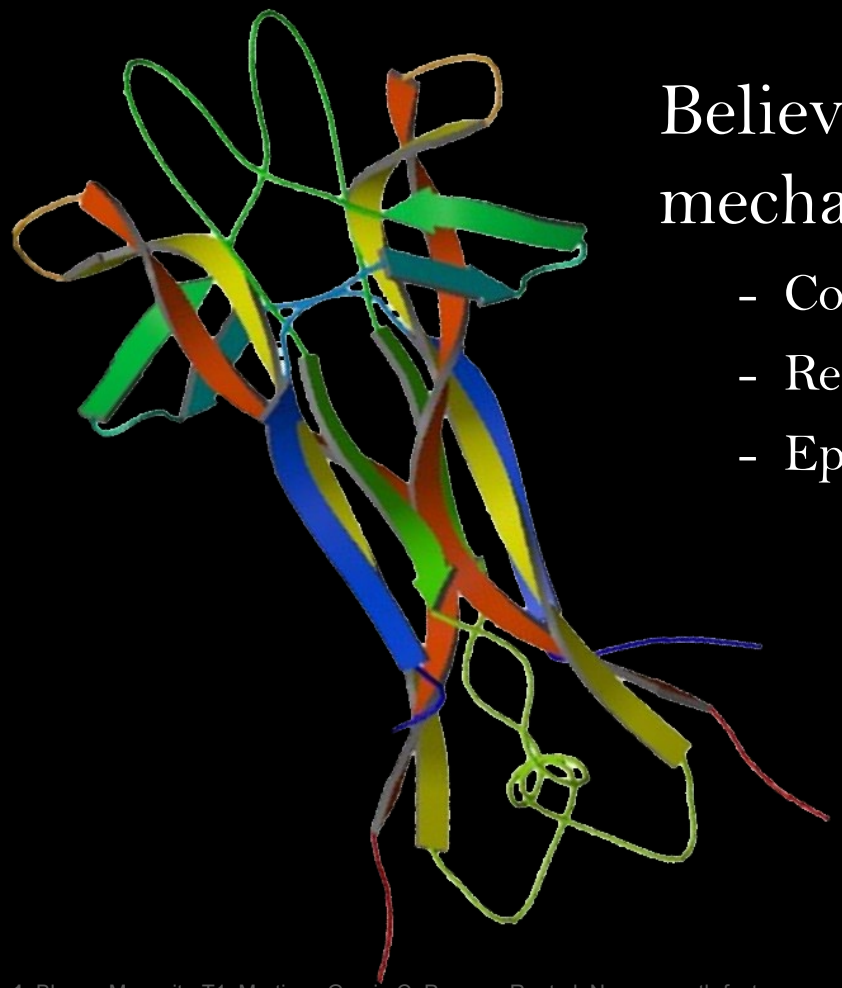
Surgical Intervention

- Tarsorrhaphy
- Conjunctival flap
- Corneal transplant
- Direct neurotization

1. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res.* 2018;66:107-131;
2. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol.* 2017;232:717-724.
3. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol.* 2014;8:571-579;

Molecular Pathophysiology of NK

Nerve Growth Factor



Believed to support corneal integrity through *3* mechanisms[2-6]

- Corneal innervation (neuron differentiation and maintenance)
- Reflex tear secretion
- Epithelial cell proliferation, differentiation and survival

1. Blanco-Mezquita T1, Martinez-Garcia C, Proença R, et al. Nerve growth factor promotes corneal epithelial migration by enhancing expression of matrix metalloprotease-9. *Invest Ophthalmol Vis Sci*. 2013;54(6):3880-3890. **2.** OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% (20 mcg/mL) [US package insert]. Boston, MA: Dompé U.S. Inc.; October 2019. 3. Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol*. 2017;232:717-724. 4. Müller LJ, Marfurt CF, Kruse F, Tervo TM. Corneal nerves: structure, contents and function. Exp Eye Res. 2003;76(5):521-542. 5. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2014;8:571-579. 6. Muzi S, Colafrancesco V, Sornelli F, et al. Nerve Growth Factor in the Developing and Adult Lacrimal Glands of Rat With and Without Inherited Retinitis Pigmentosa. *Cornea*. 2010;29:1163–1168.

oxervate® (cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

Oxervate

Recombinant human nerve growth factor (rhNGF)

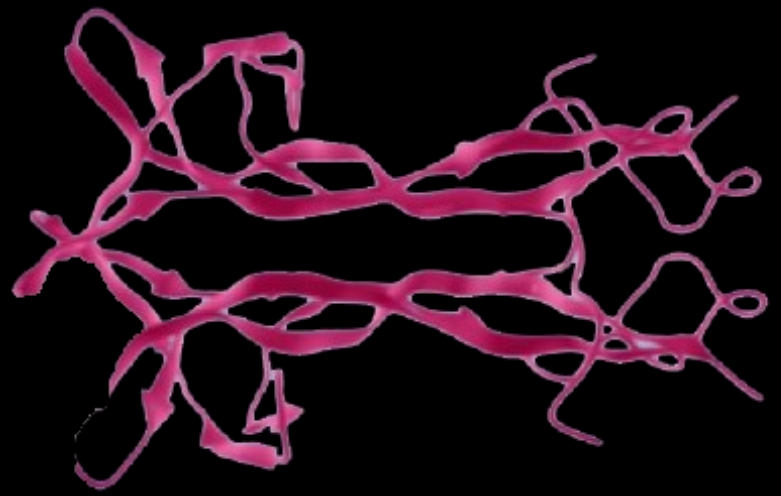
First topical *biologic* therapy in ophthalmic history

Approved by FDA in 2018 for treatment of all stages of NK

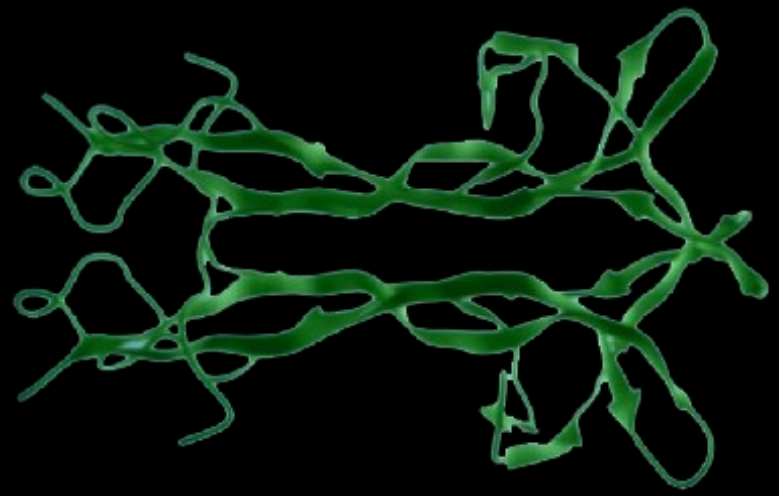
Accorded o*rphan drug* status and deemed a *"breakthrough"* therapy

Cenegermin (active ingredient in OXERVATE) is structurally identical to endogenous NGF found in ocular tissues

Cenegermin



Endogenous NGF



Voelker R. New Drug Treats Rare, Debilitating Neurotrophic Keratitis. *JAMA*. 2018;320(13):1309.

Oxervate Clinical Trials

Pivotal Studies Overview

	NGF0212/REPARO[1] (n=156)	NGF0214[2] (n=48)
Geography	Europe	USA
Design	3 treatment arms*: vehicle, cenegermin 10 mcg/mL, cenegermin 20 mcg/mL	2 treatment arms: vehicle, cenegermin 20 mcg/mL
Course of Therapy	8 weeks	8 weeks
Duration of follow-up	48 weeks	24 weeks
Uni/bilateral disease	Unilateral	Unilateral and bilateral
Endpoints	**Complete corneal healing**† at Week 8 (based on a post-hoc analysis‡) Primary analysis was <0.5 mm maximum diameter of fluorescein staining in the lesion area at Week 4	**Complete corneal healing**† at Week 8

*The formulation that was tested in study NGF0214 included the antioxidant methionine and is the final formulation that is marketed. More than one study was conducted with the final commercial formulation. No difference in safety was seen in any of the trials.

†Defined as 0.0 mm maximum diameter of fluorescein staining in the lesion area) and no persistent staining in the rest of the cornea.

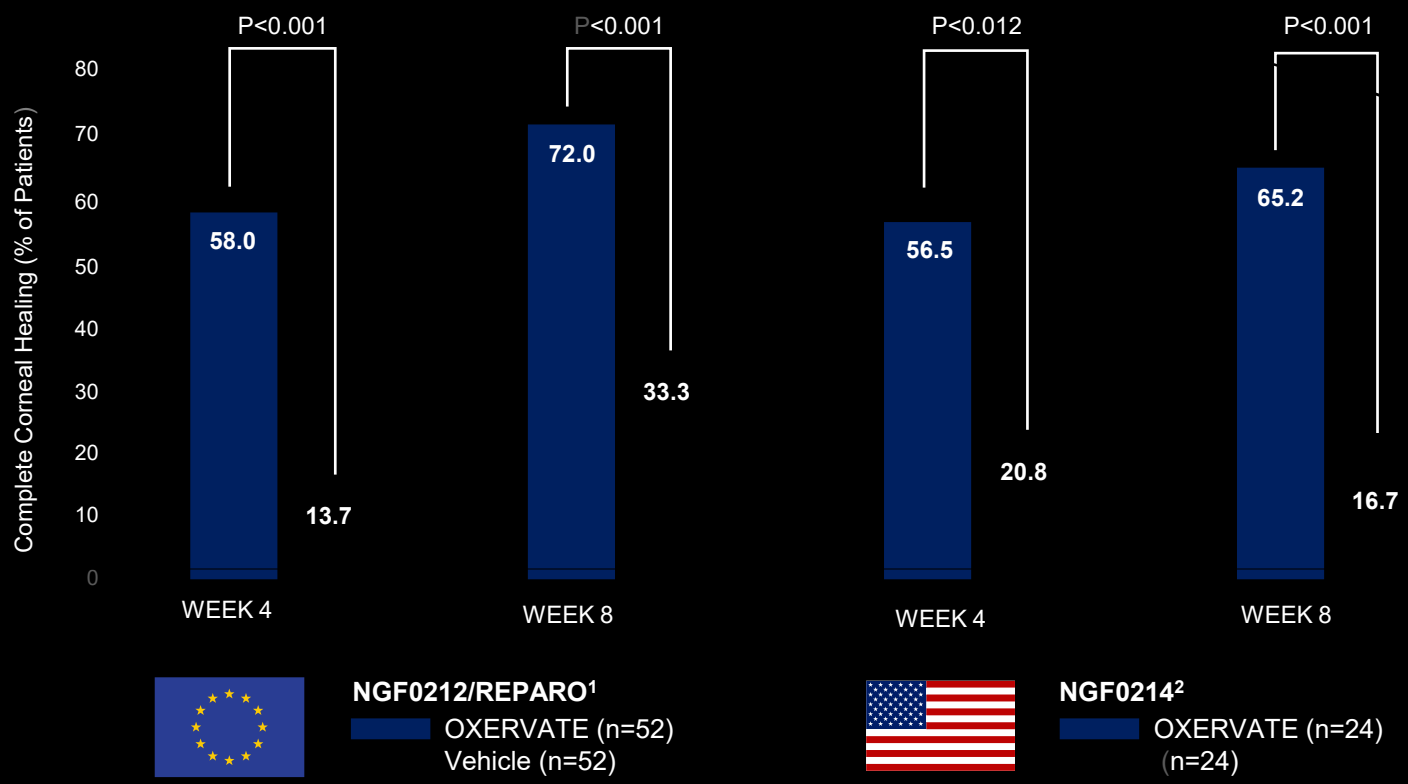
‡FDA approval was based on complete corneal healing defined as absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of treatment.

Please see Important Safety Information in this presentation and a Dompé representative for Full Prescribing Information

1. Bonini S, Lambiase A, Rama P et al. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology*. 2018;125:1332-1343. **2.** Pflugfelder SC, Massaro-Giordano M, Perez VL et al. Topical Recombinant Human Nerve Growth Factor (Cenegermin) for Neurotrophic Keratopathy: A Multicenter Randomized Vehicle-Controlled Pivotal Trial. *Ophthalmology*. 2020;127(1):14-26.

oxervate® (cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

Complete Corneal Healing at 8 Weeks



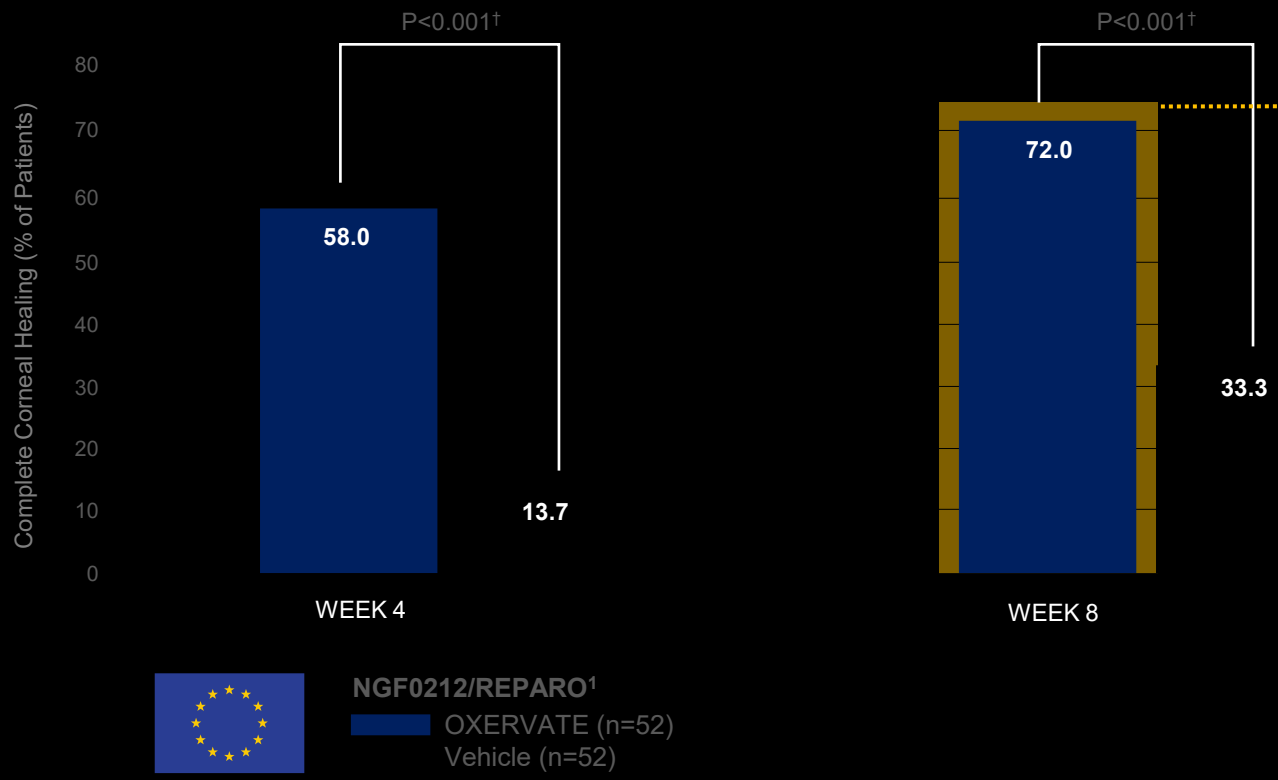
The formulation that was tested in REPARO (Study NGF0212) did not include the antioxidant methionine and is not the final formulation that is marketed as OXERVATE. Methionine is an excipient added to the commercial formulation to improve its stability. More than one study was conducted with the final commercial formulation. No difference in safety was seen in either of the trials.

†Last post-baseline observation carried forward; chi-squared test

1. Bonini S, Lambiase A, Rama P *et al*. Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology*. 2018;125:1332-1343. **2.** Pflugfelder SC, Massaro-Giordano M, Perez VL et al. Topical Recombinant Human Nerve Growth Factor (Cenegermin) for Neurotrophic Keratopathy: A Multicenter Randomized Vehicle-Controlled Pivotal Trial. *Ophthalmology*. 2020;127(1):14-26.

oxervate® (cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

Most Patients Remained Completely Healed 48 Weeks After One 8-week Treatment Cycle[1,2]



80%

of patients who achieved complete corneal healing* in Study NGF0212/REPARO were still healed 48 weeks after completing one 8-week OXERVATE treatment cycle

(*complete corneal healing defined as absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of treatment)

The formulation that was tested in REPARO (Study NGF0212) did not include the antioxidant methionine and is not the final formulation that is marketed as OXERVATE. Methionine is an excipient added to the commercial formulation to improve its stability. More than one study was conducted with the final commercial formulation. No difference in safety was seen in either of the trials.

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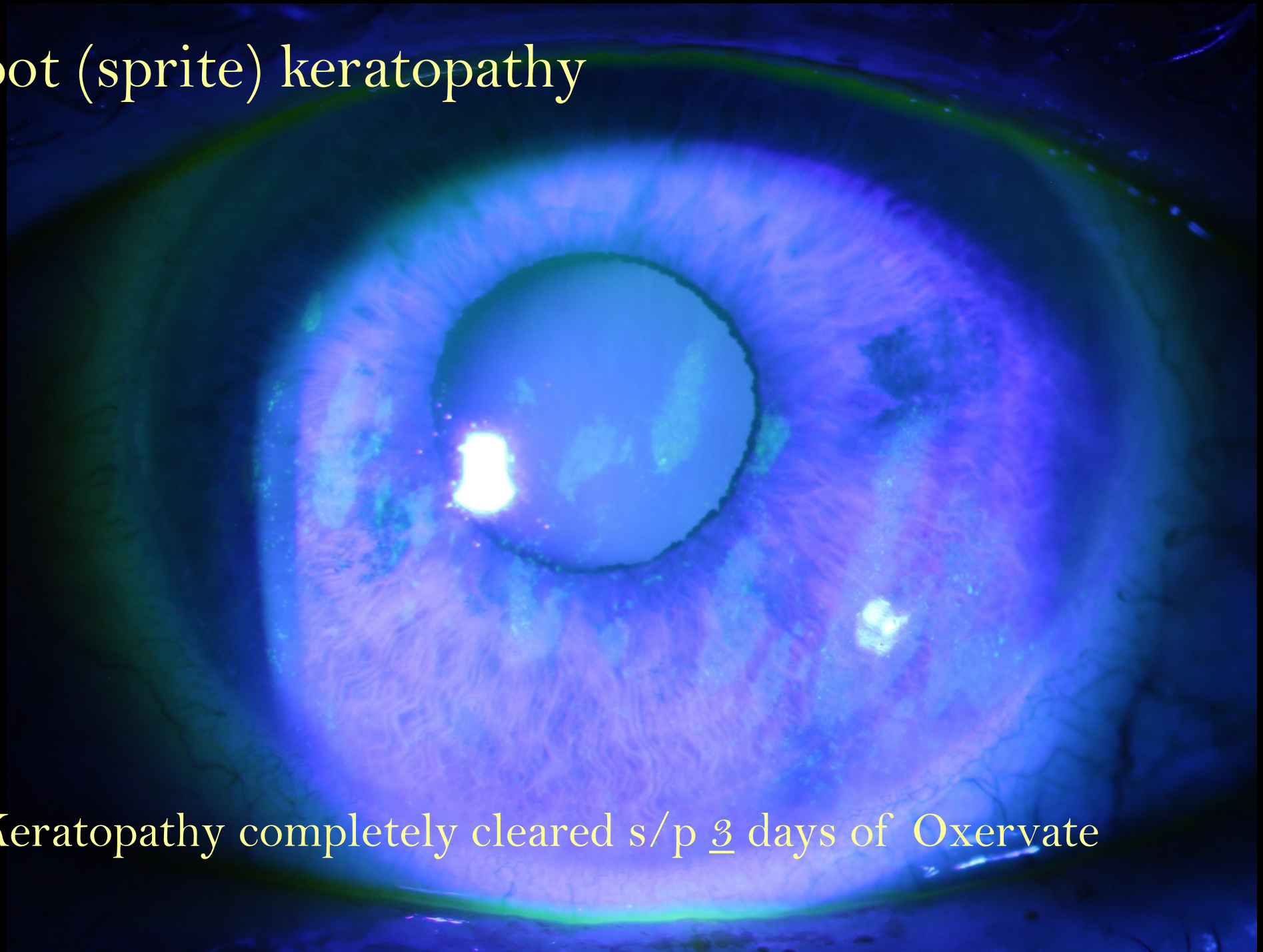
1. Bonini S, Lambiase A, Rama P *et al.* Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology* 2018;125:1332-1343. **2.** Data on file. NGF0212 (REPARO) CSR.

oxervate® (cenegermin-bkbj ophthalmic solution) 0.002% (20 mcg/mL)

Case Study #1

Gaule Spot (sprite) keratopathy

OS



Keratopathy completely cleared s/p 3 days of Oxervate

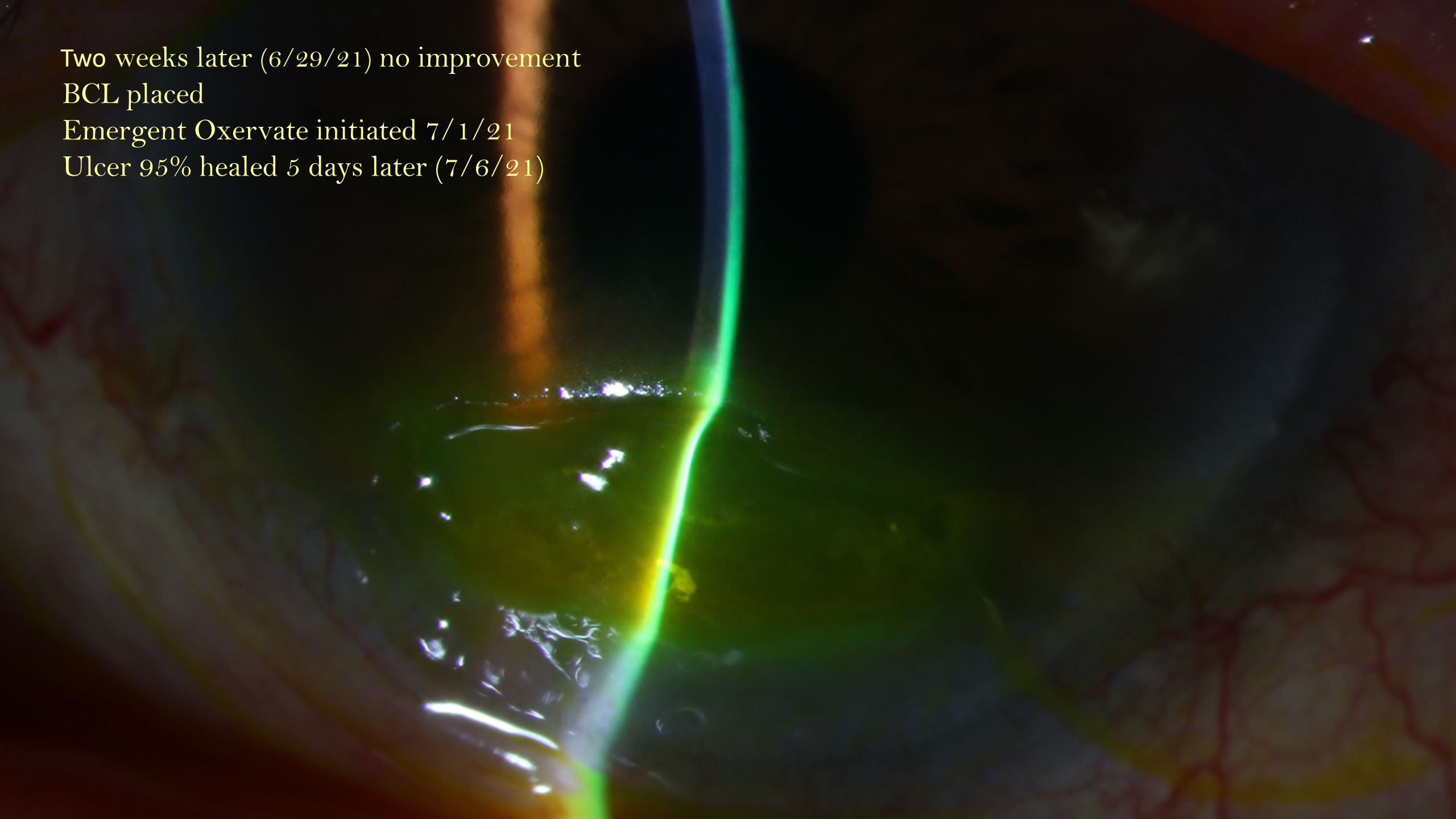
Case Study # 2

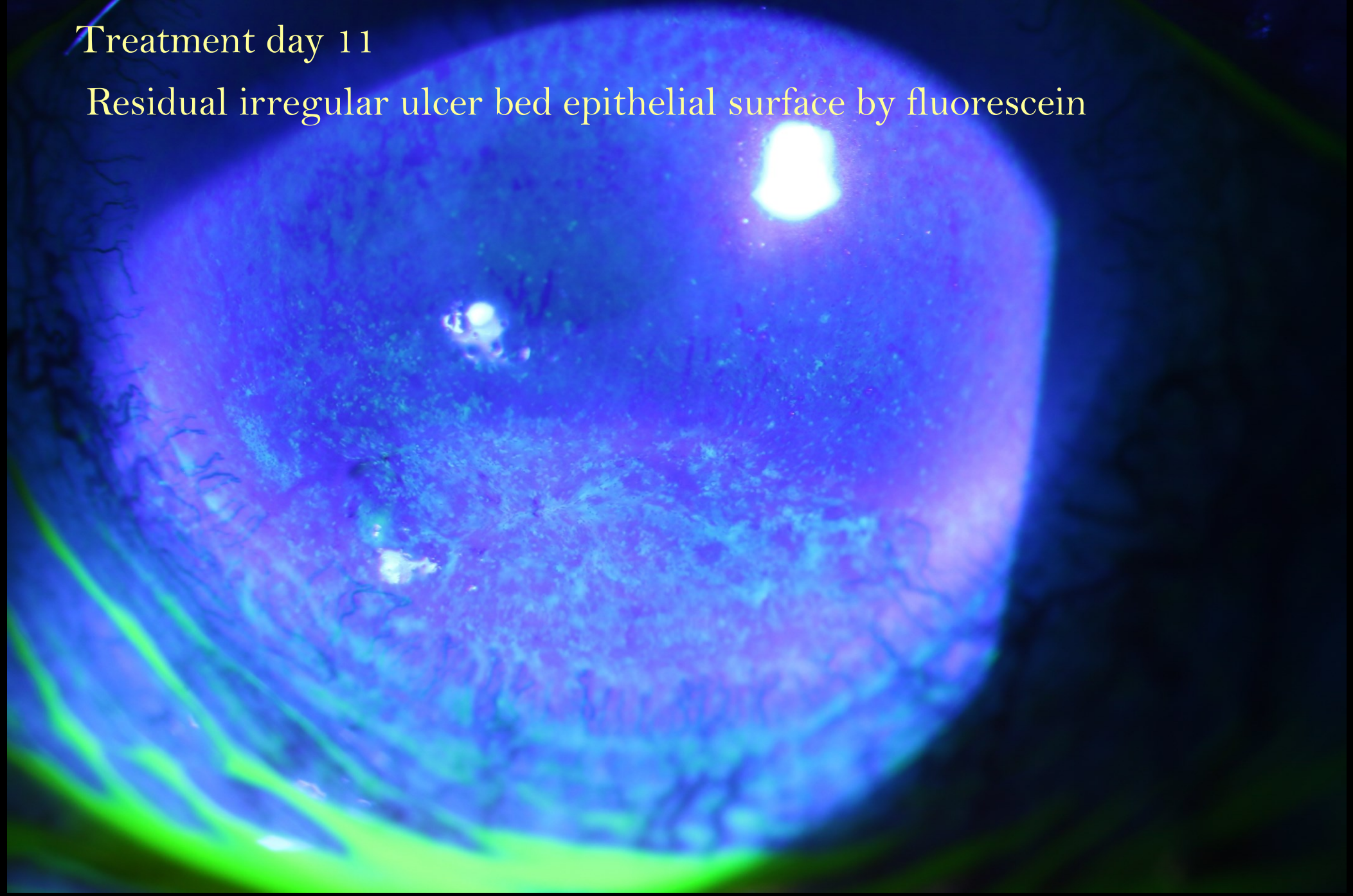
Stage III NK OS

CSwCBE = 7mm (45mm 4 mos prior)

Tx'ed with new replacement plug LLL, Moxi QID, E-mycin oint QID, Acyclovir 800mg 5x/day, DC PF

Ordered Oxervate

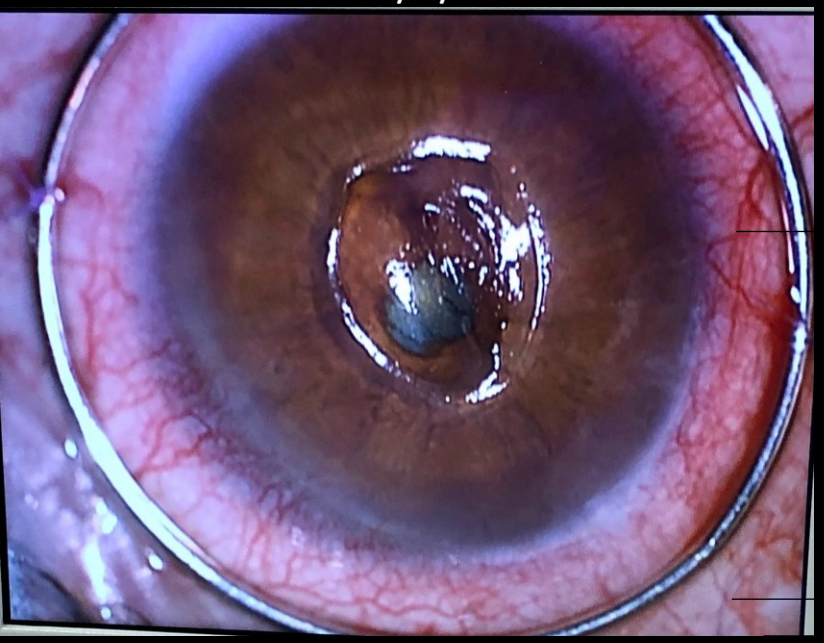

Two weeks later (6/29/21) no improvement
BCL placed
Emergent Oxervate initiated 7/1/21
Ulcer 95% healed 5 days later (7/6/21)


Treatment day 11
Residual irregular ulcer bed epithelial surface by fluorescein

Case Study # 3

59 Year-old Caucasian male

11/1/18



VA = CF @ 1 ft

MEDICAL HISTORY

- HZO OS 22 years prior

PREVIOUS TREATMENT

(2 cornea specialists; ~6 mos)

- Copious preservative free artificial tears
- Moxifloxacin QID
- Erythromycin ointment Q-2hrs
- Topical FML
- Timolol BID (for steroid related ocular hypertension)
- Acyclovir 800mg BID
- Multiple punctual plugs to both upper and lower lids
- Serial BSCL's
- Serial amniotic membranes (x3)

CORNEAL SENSATION

- Absent by Q-tip

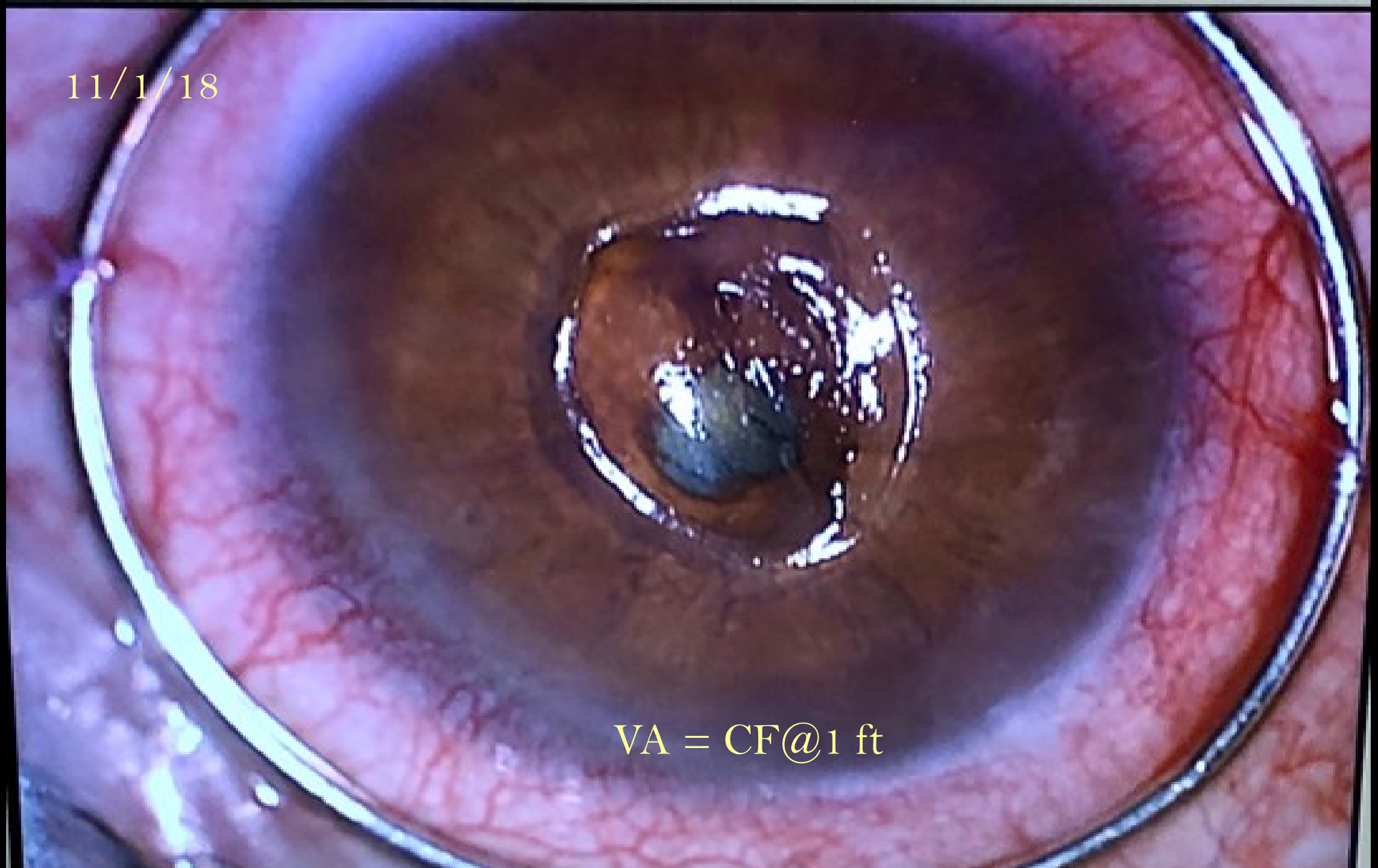
DIAGNOSIS

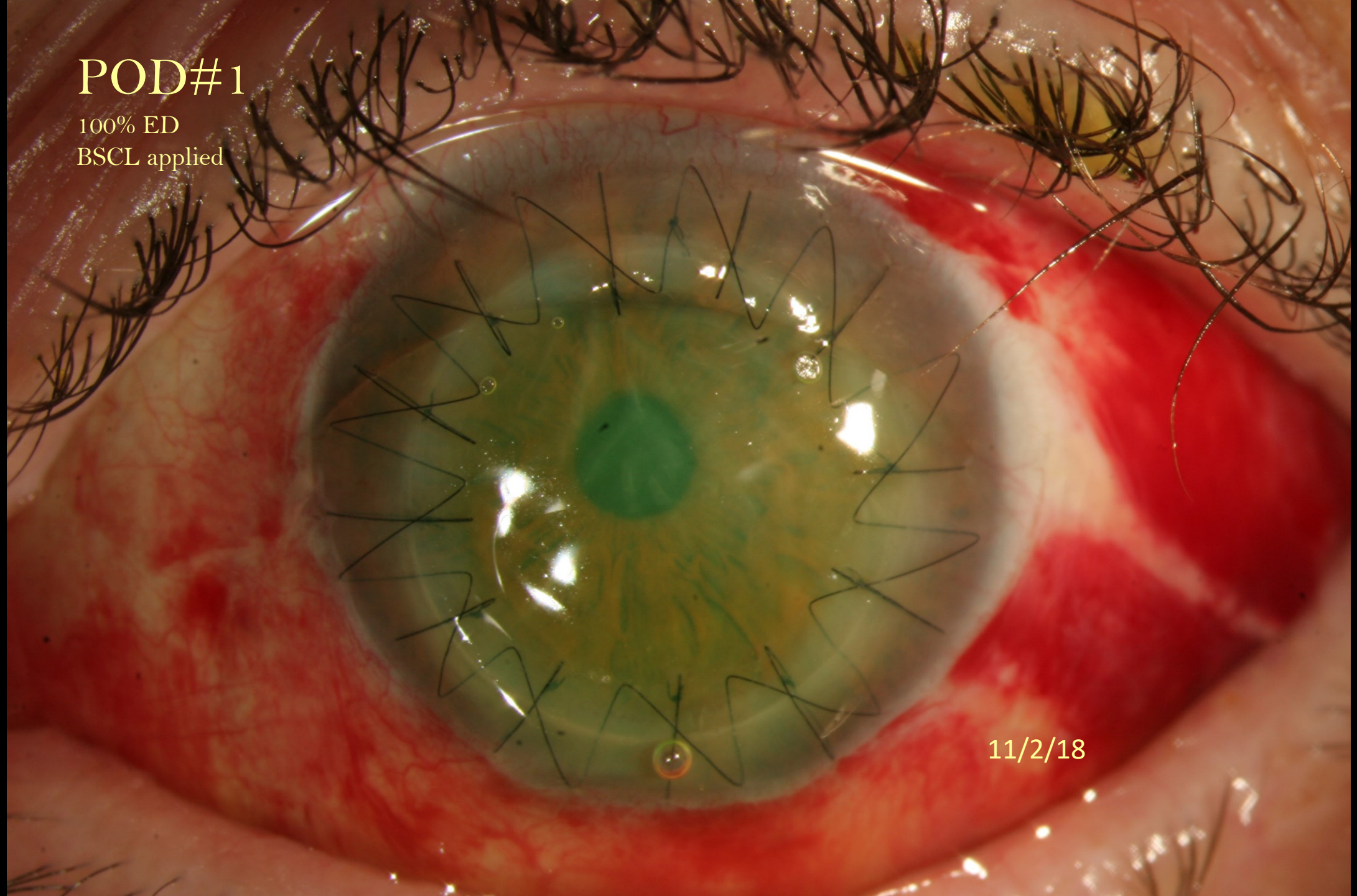
- Severe Stage III NTK with impending perforation

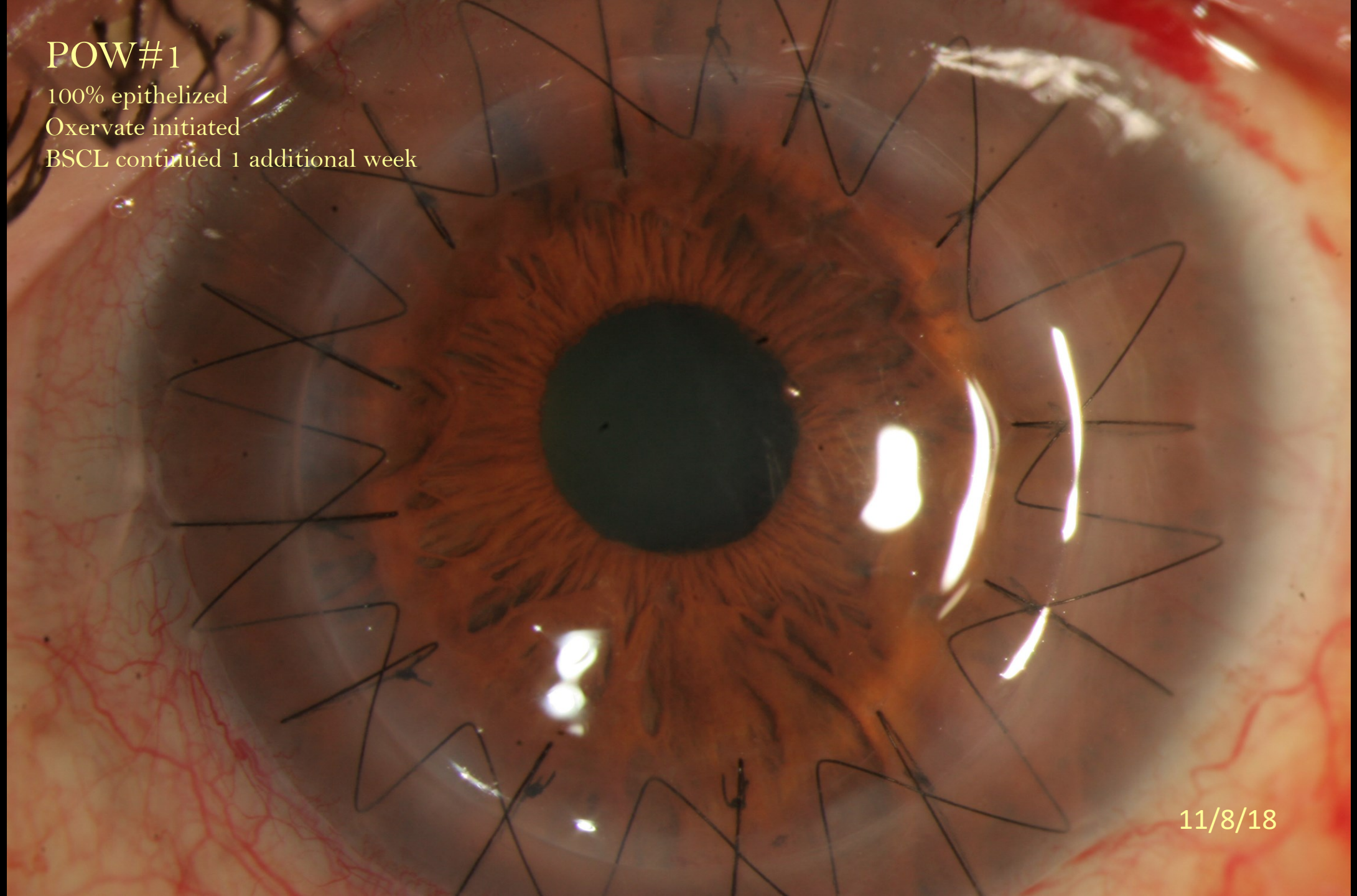
INTERVENTION

- Emergency PK 3 days post presentation

Case presentation is based on an actual patient, not from an OXERVATE clinical trial.

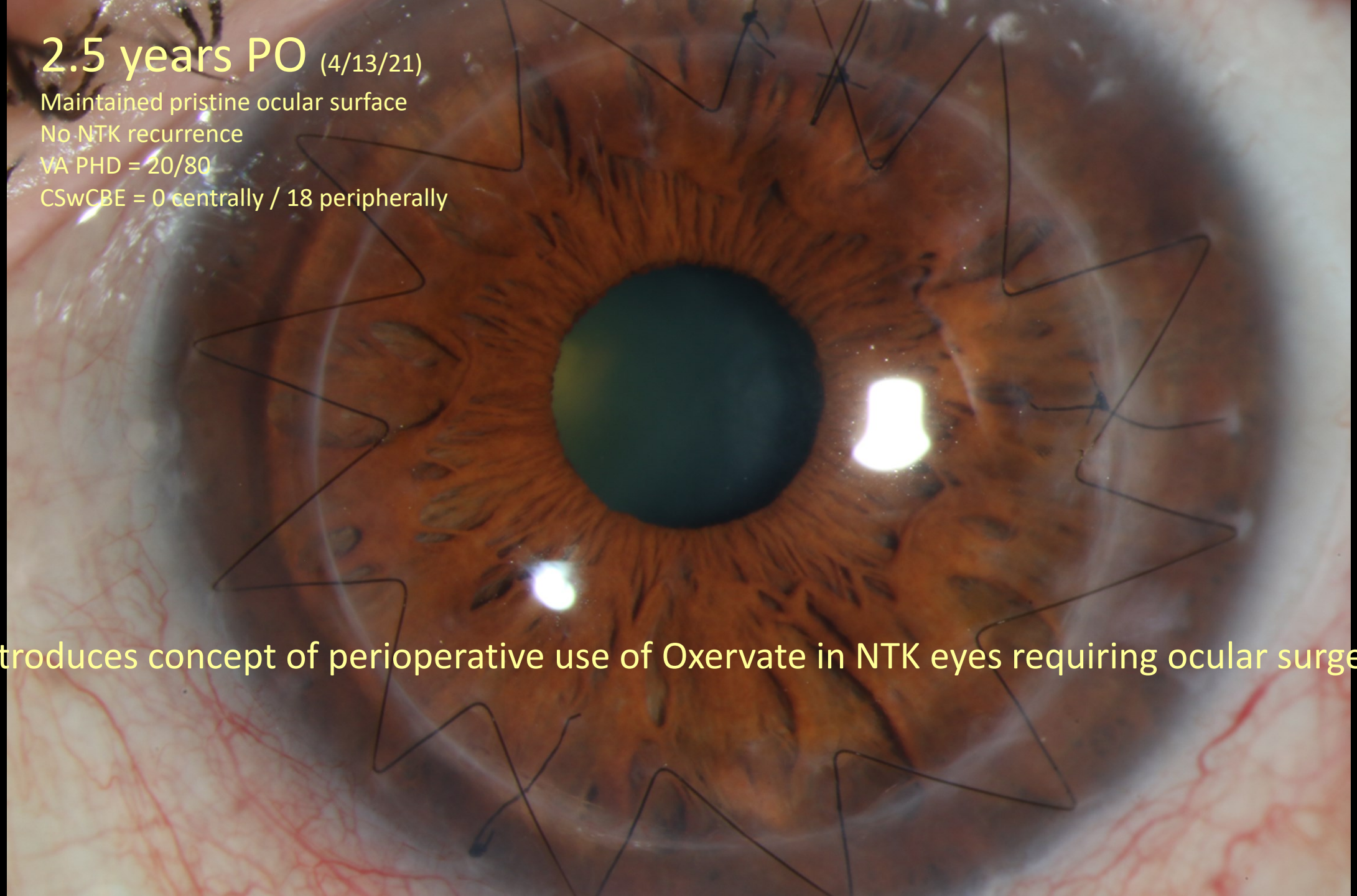

11/1/18
VA = CF@1 ft


POD#1
100% ED
BSCL applied
11/2/18


POW#1
100% epithelized
Oxervate initiated
BSCL continued 1 additional week
11/8/18

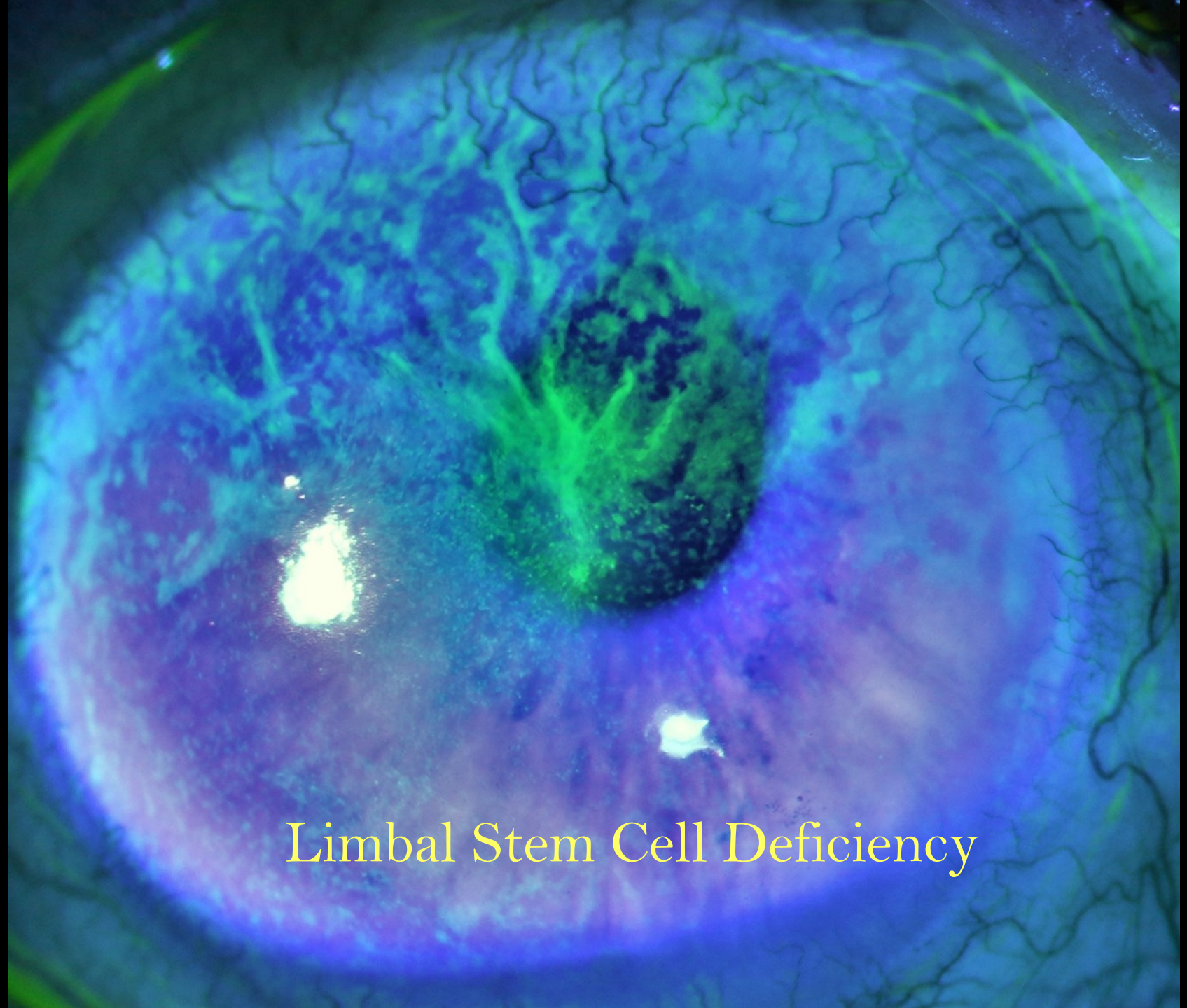

POM #2
Continuously maintained stable ocular surface
No NK recurrence
VAsc = 20/40


2.5 years PO (7/13/21)
Maintained pristine ocular surface
No NTK recurrence
VA PHD = 20/40
CSwCBE = 0 centrally / 18 peripherally


2.5 years PO (4/13/21)
Maintained pristine ocular surface
No NTK recurrence
VA PHD = 20/80
CSwCBE = 0 centrally / 18 peripherally
Introduces concept of perioperative use of Oxervate in NTK eyes requiring ocular surgery

Future Treatment Directions

- *Hepatocyte Growth Factor (NK + scar revision)* Claris Biotherapeutics Inc.
- *Mesenchymal Stem Cell Secretome (PED)* Kala Bio
- *RGN-259 (NK)* ReGen Tree
- *NEXAGON® (NK)* Amber Ophthalmics Inc.


Limbal Stem Cell Deficiency


Thank You