NHS
National Institute for
Health Research

TURKISH CONGRESS 2013
UVEITIS COURSE

Primary Ocular and CNS Lymphoma

Carlos Pavesio MD FRCOphth
Moorfields Eye Hospital
London

Primary Ocular and CNS Lymphoma

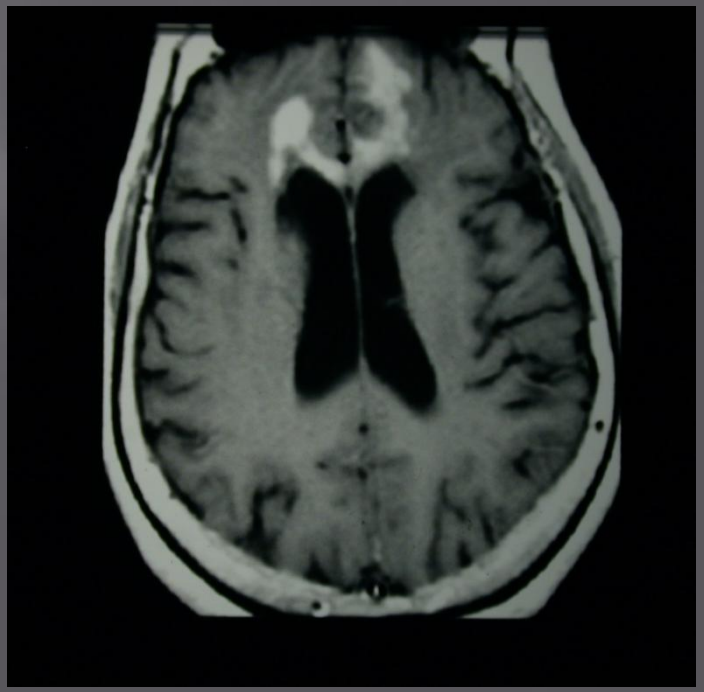
- Large B-cell lymphoma, a sub-group of high-grade non-Hodgkin lymphoma
- Primary CNS – 0.5-1% primary brain tumours
- Dramatic recent increase
- 20% CNS cases will have ocular involvement

Primary Ocular and CNS Lymphoma

- masquerade as chronic bilateral uveitis
- partially responsive to syst. steroids or steroid resist.
- posterior uveitis (vitritis) > anterior uveitis

- elderly patients

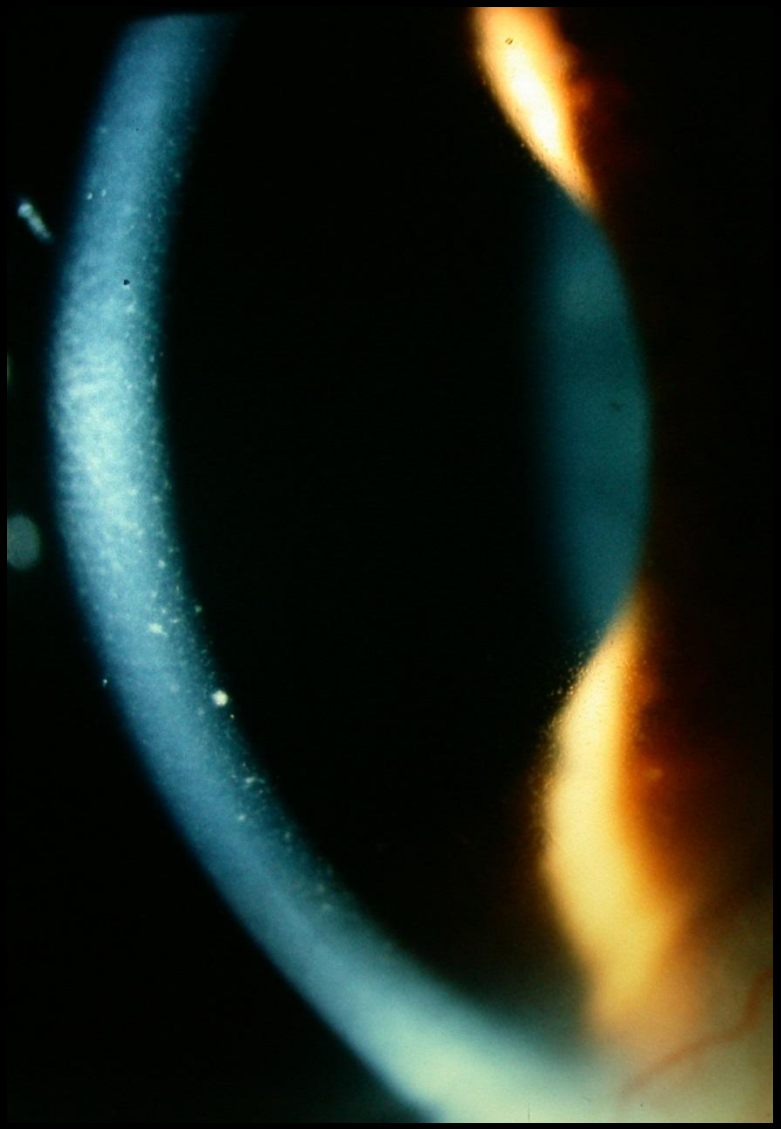
- 50% of ocular involvement
  are associated with
  CNS lesions at time of diag.

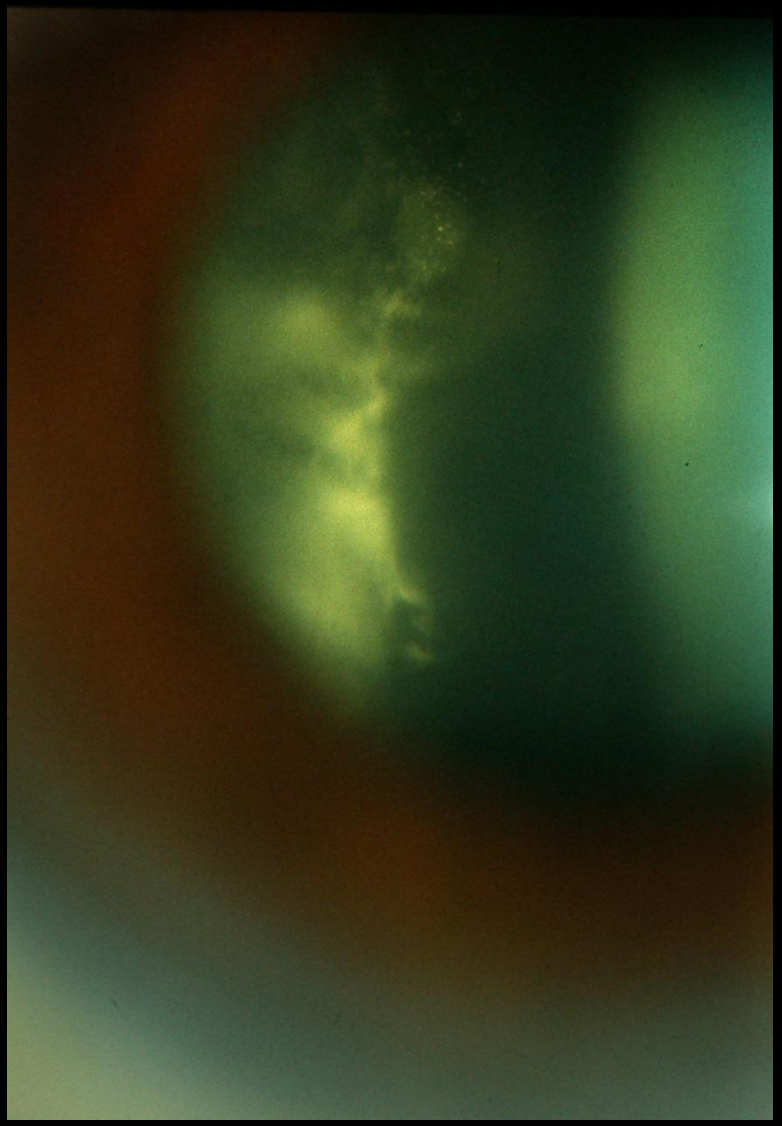


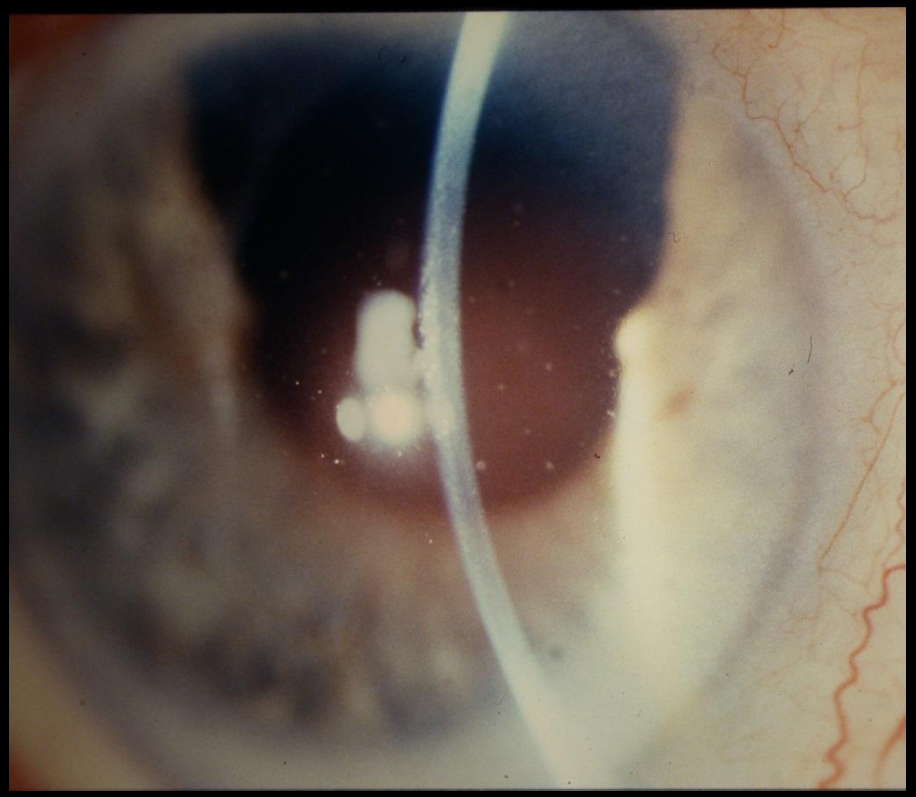
Primary Ocular and CNS Lymphoma

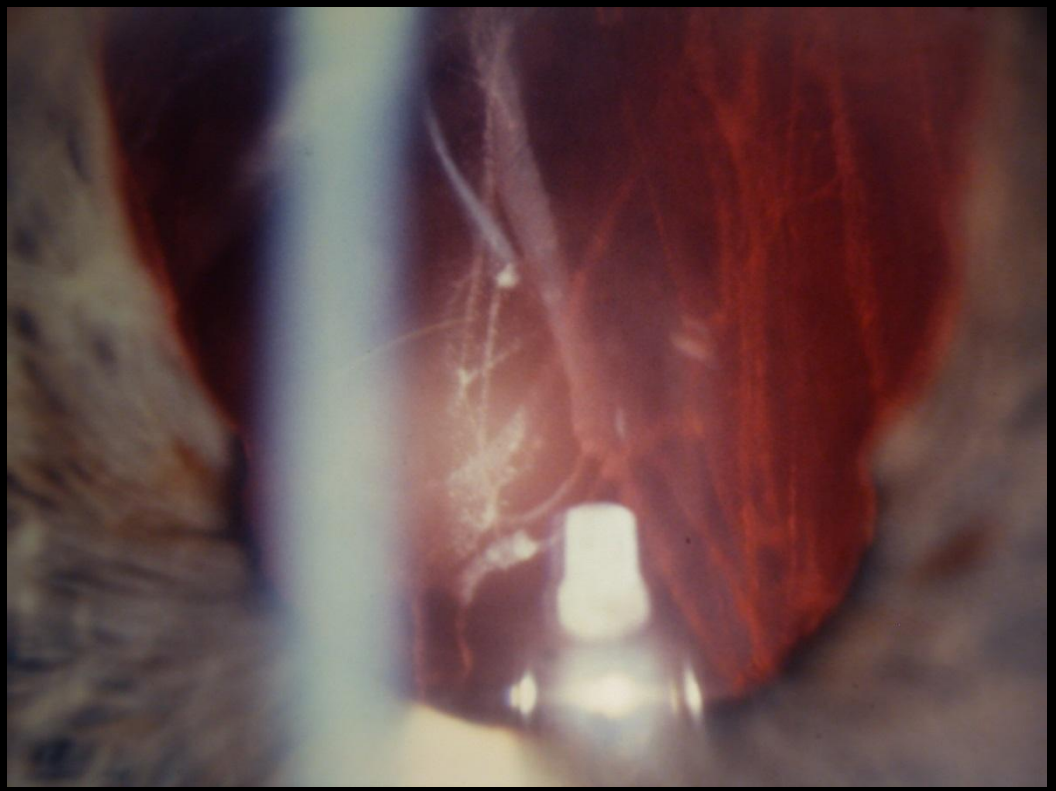
- Blurred vision, floaters
- Non painful and white eyes
- Minimal or no anterior segt. Inflammation

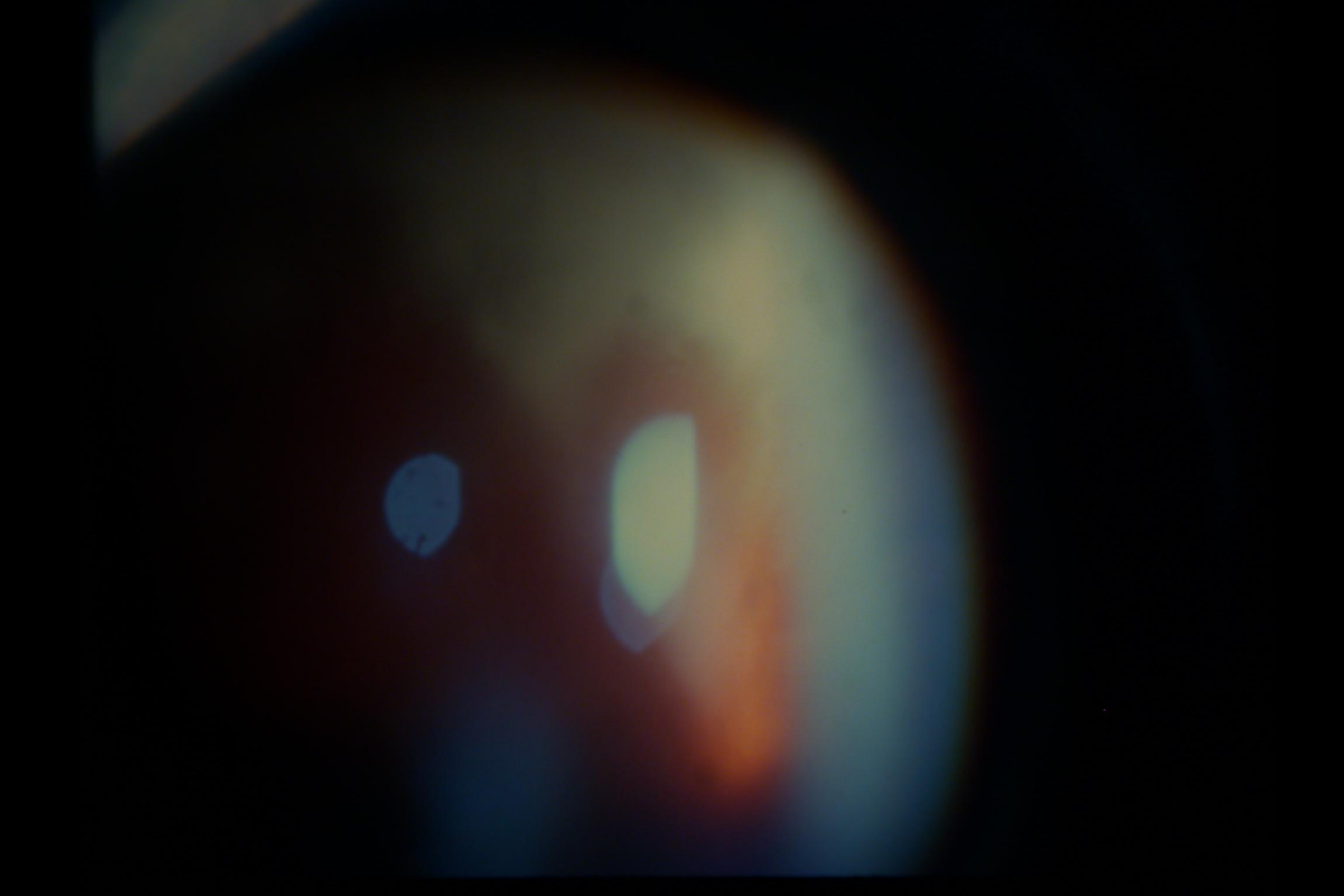
  (No posterior synechia, normal LCFM)
- Sheets of vitreous cells
- Subretinal infiltrates, vasculitis, CMO
- Poorly responsive to corticosteroid Rx

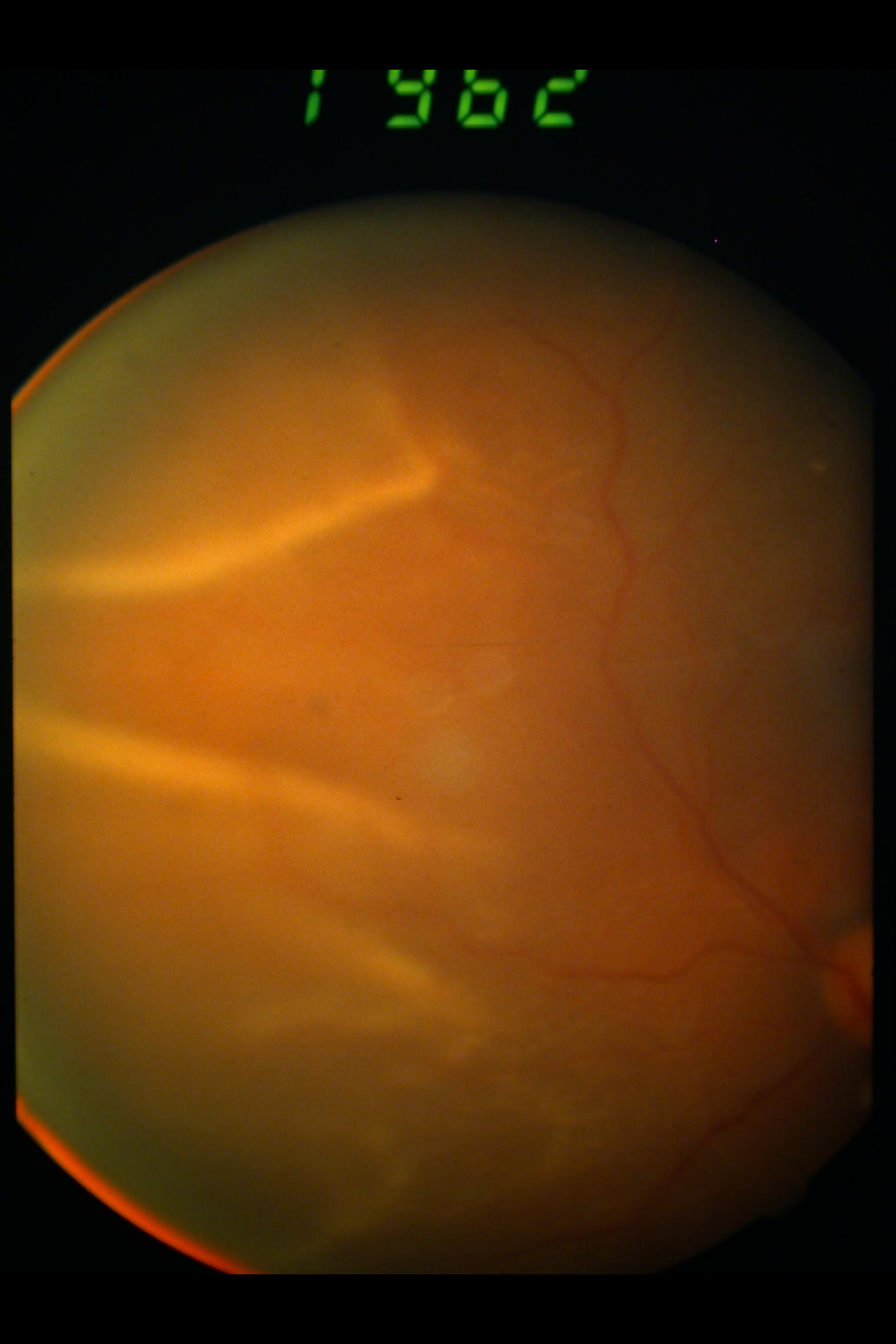








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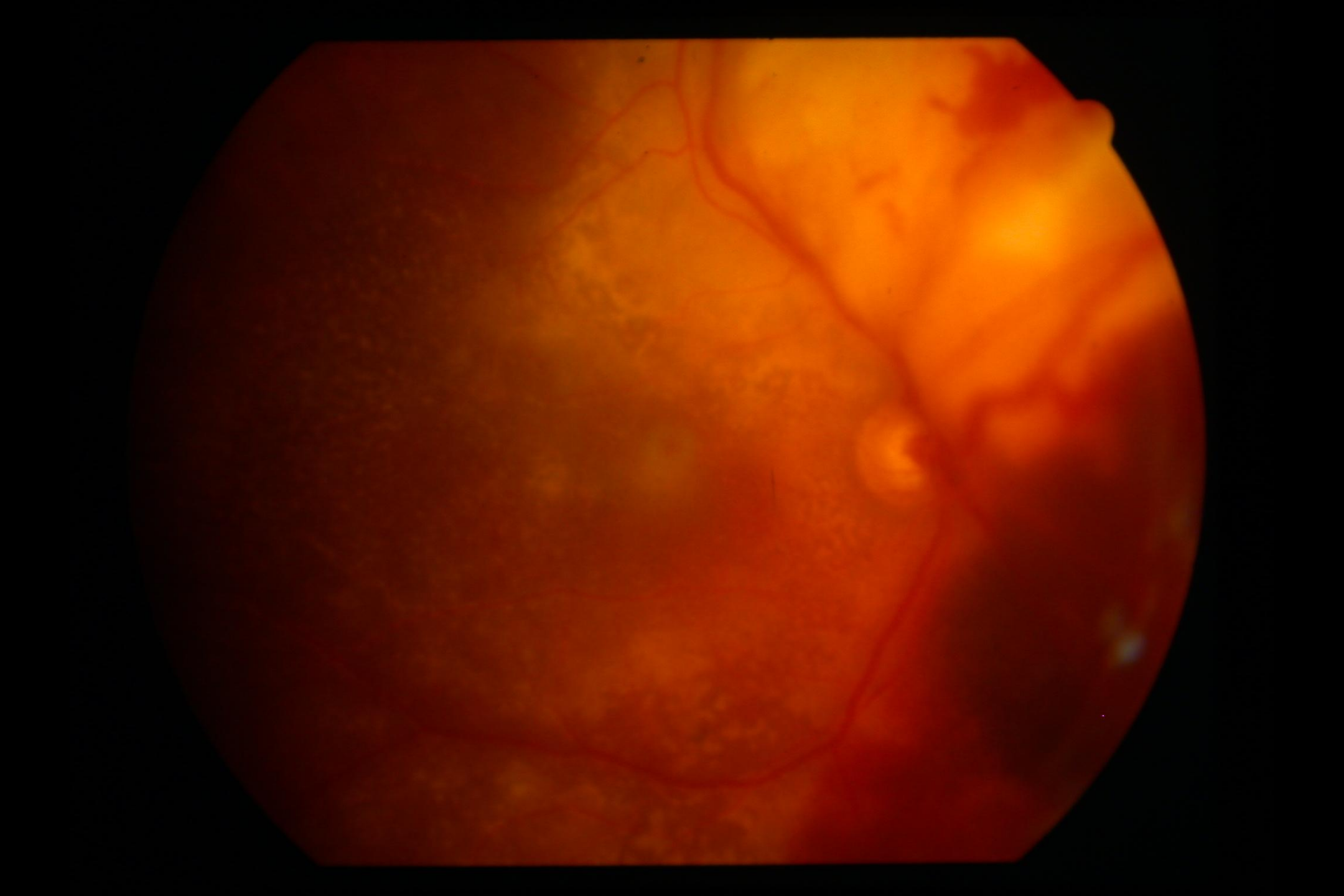

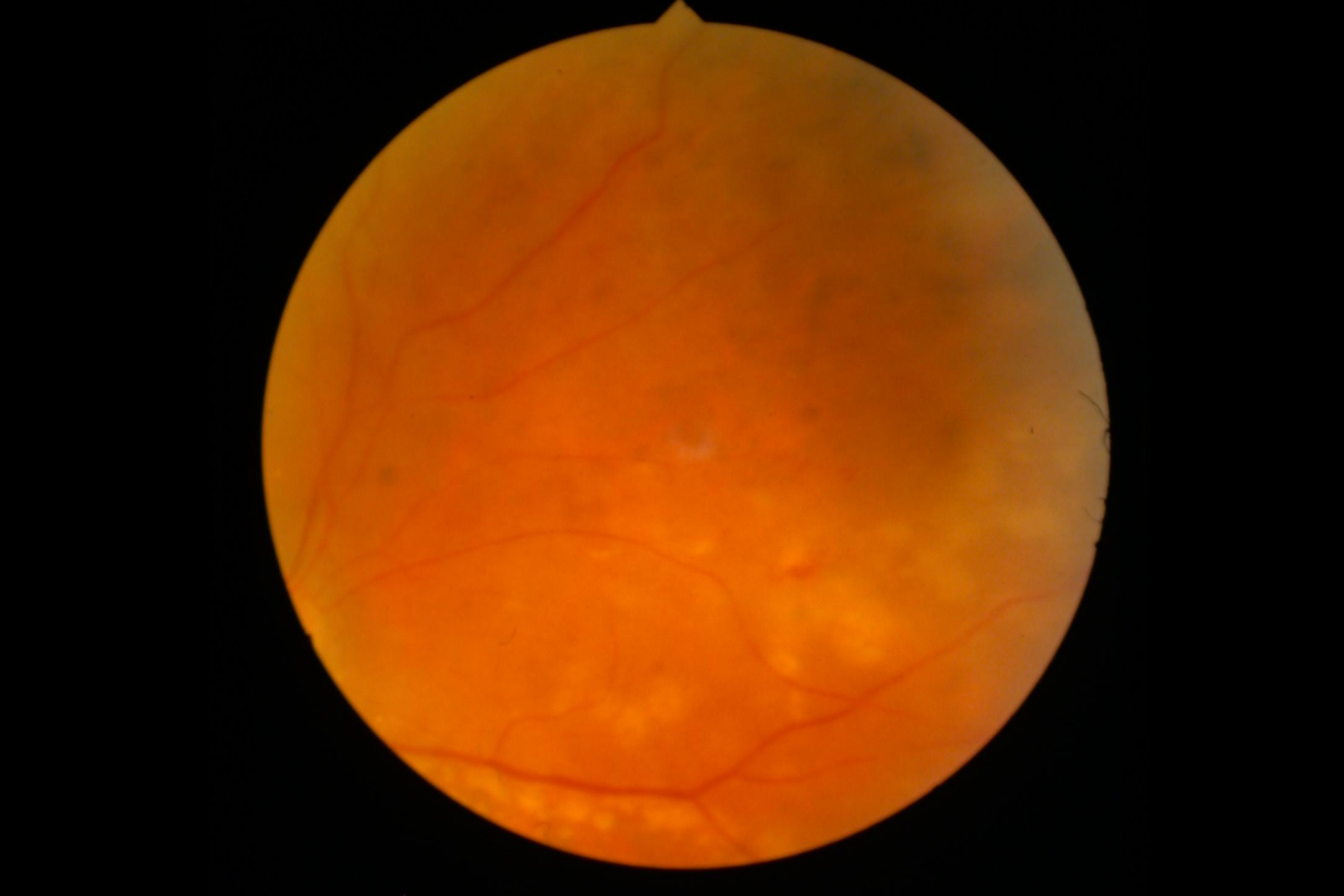

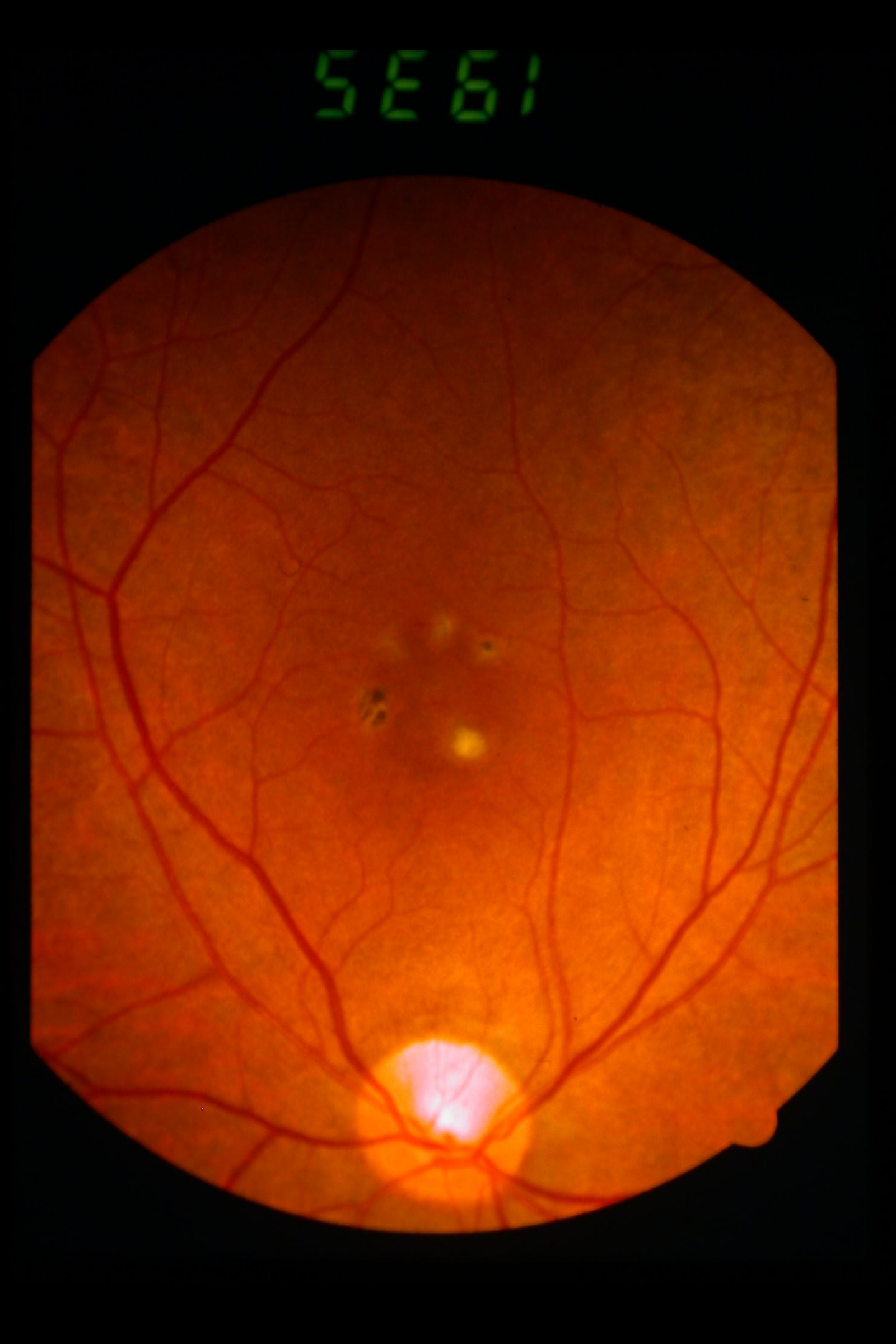
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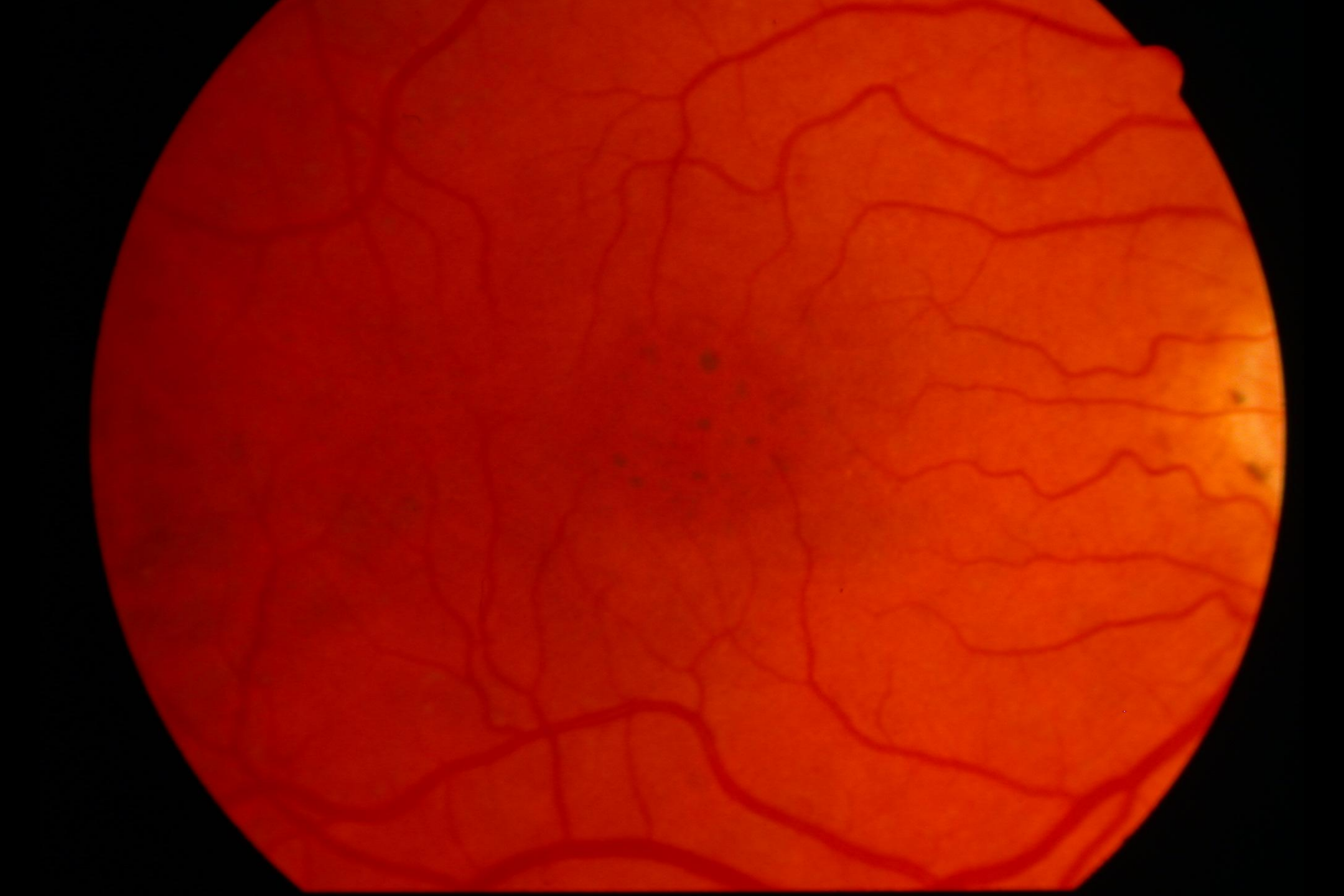
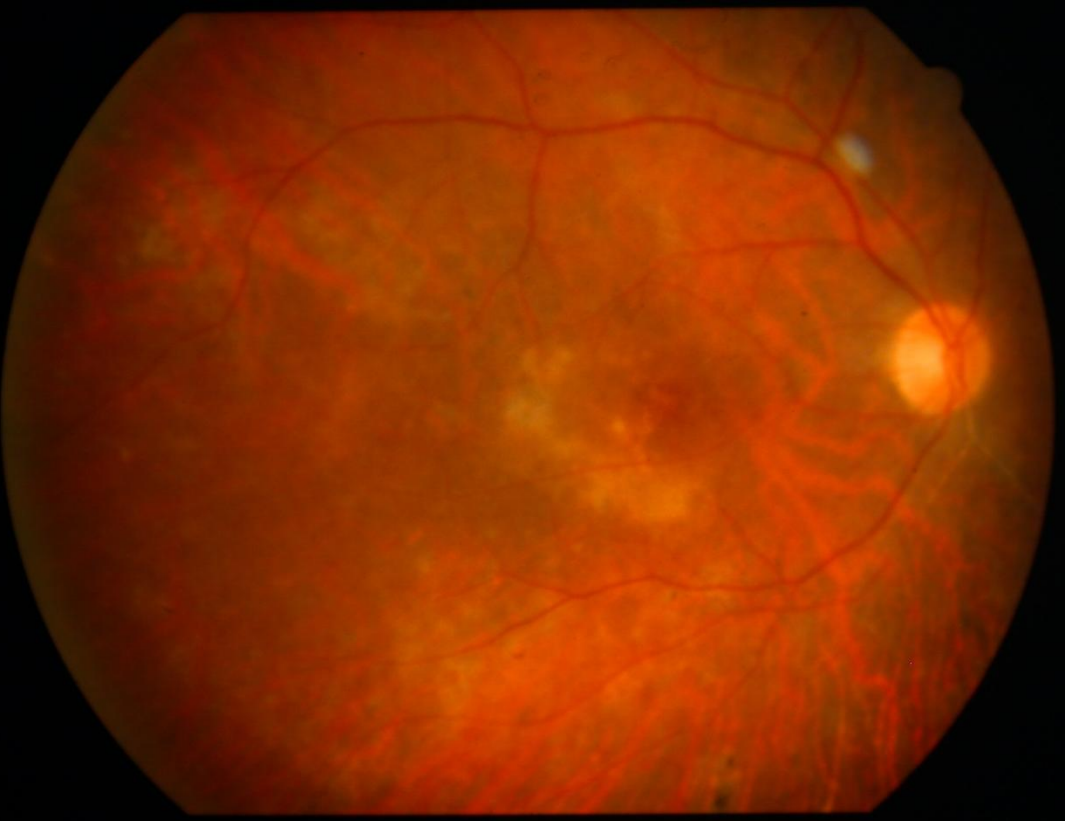
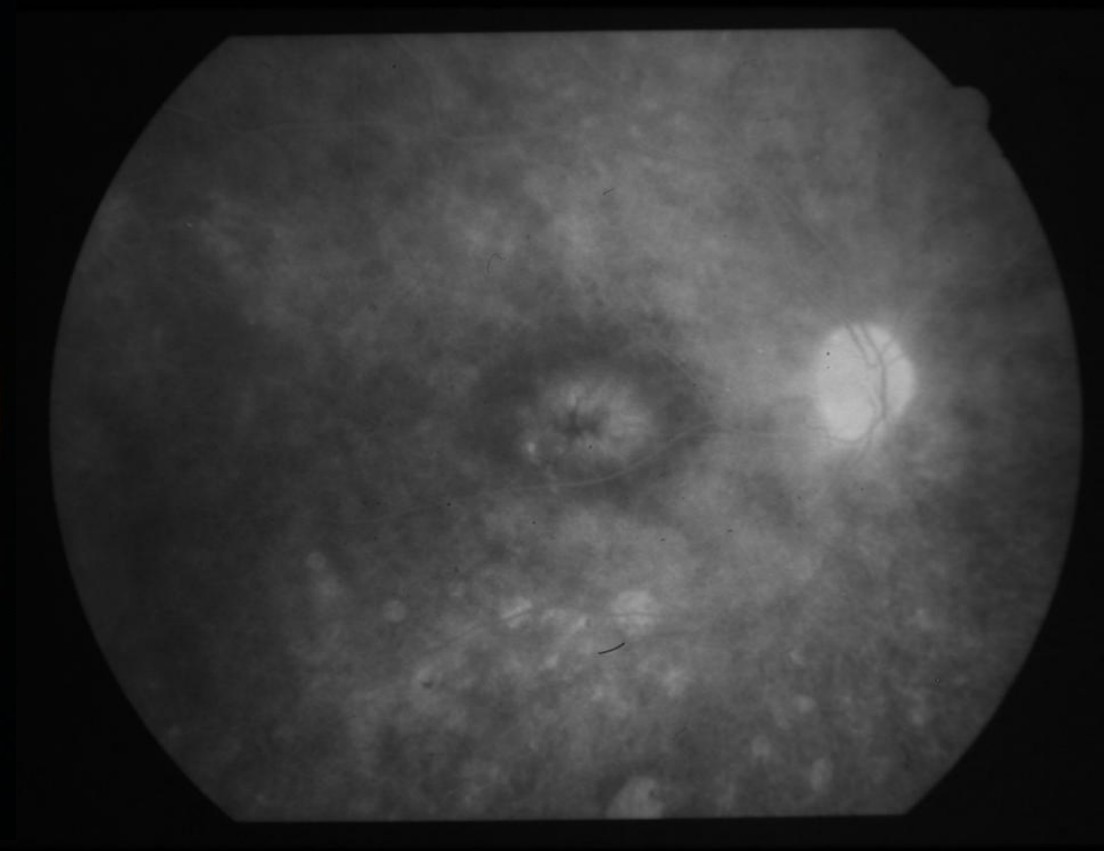
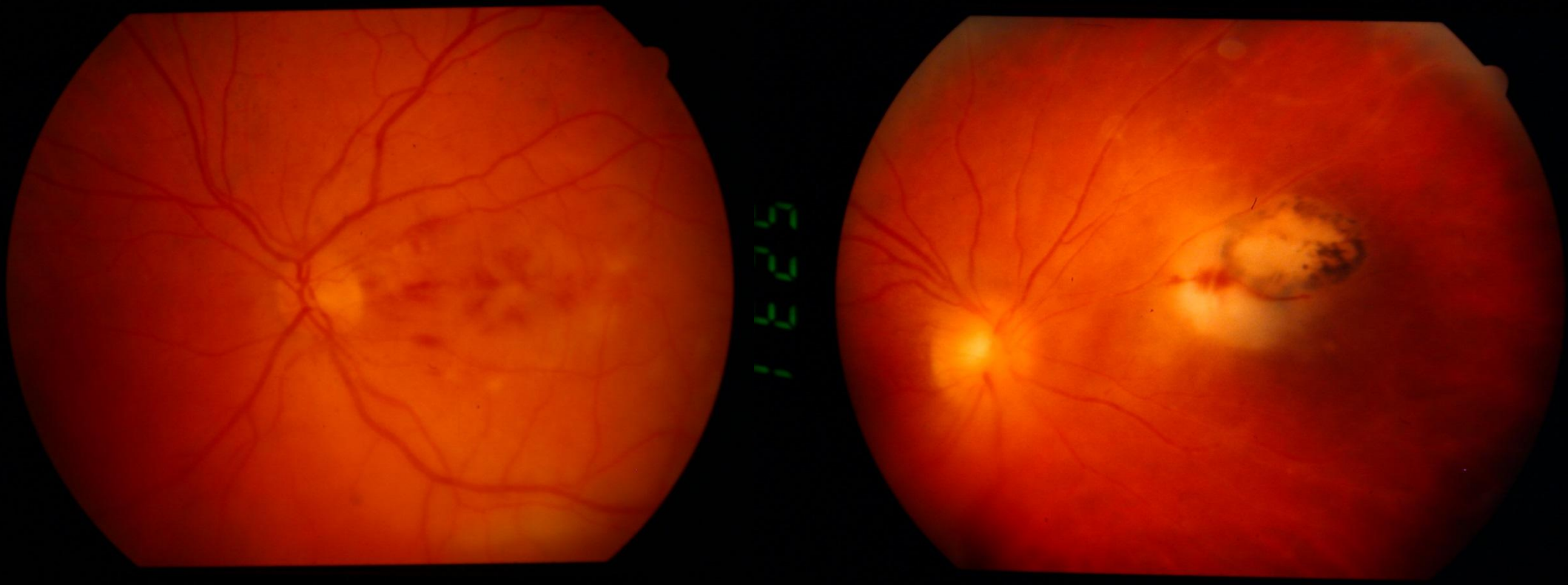


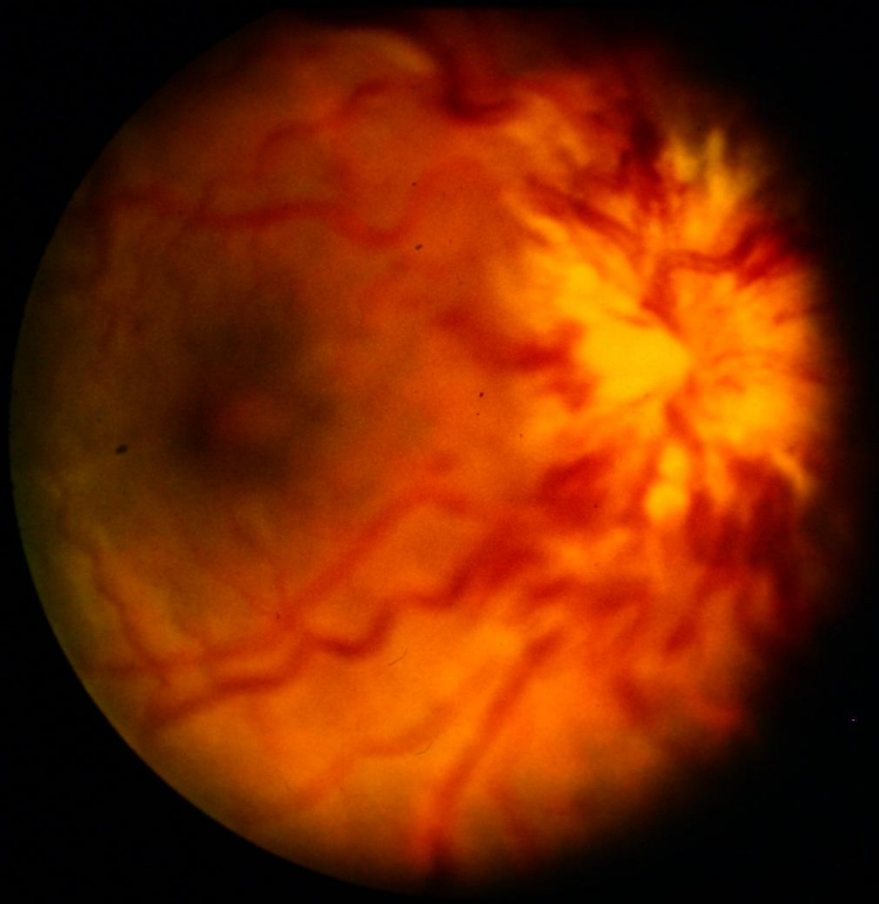


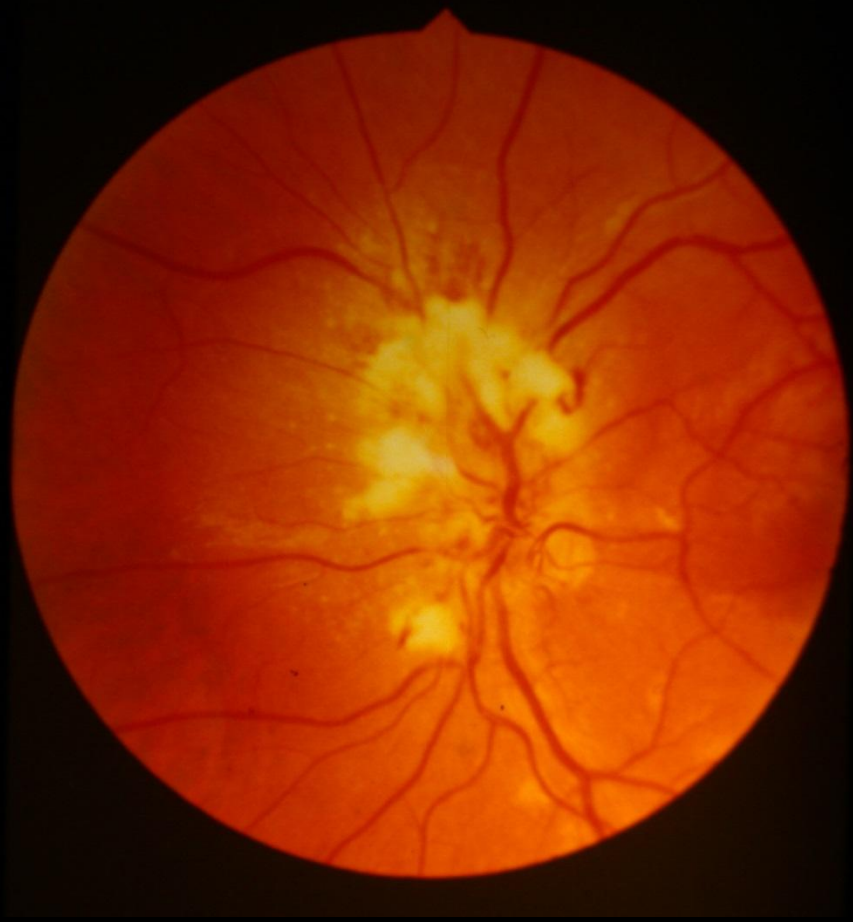




NHL

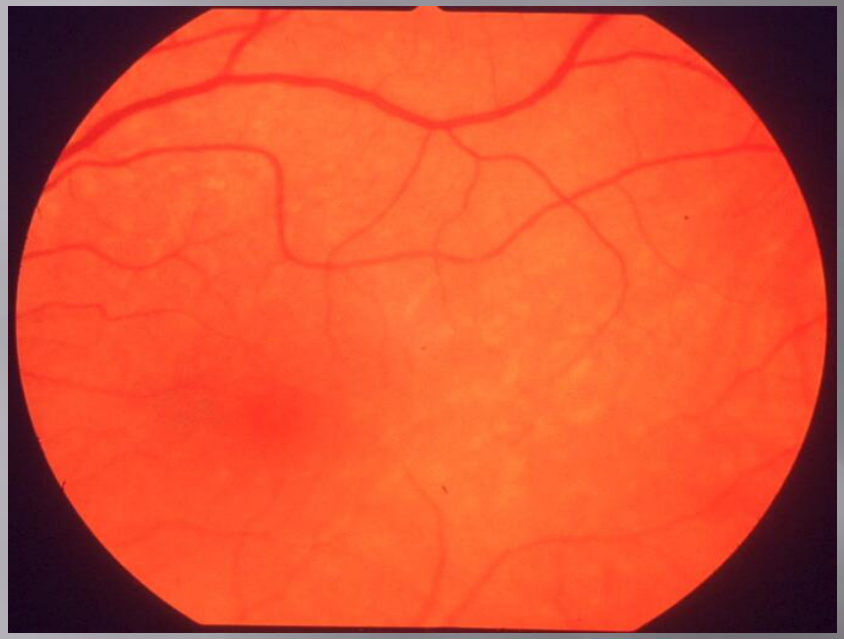
Toxoplasmosis

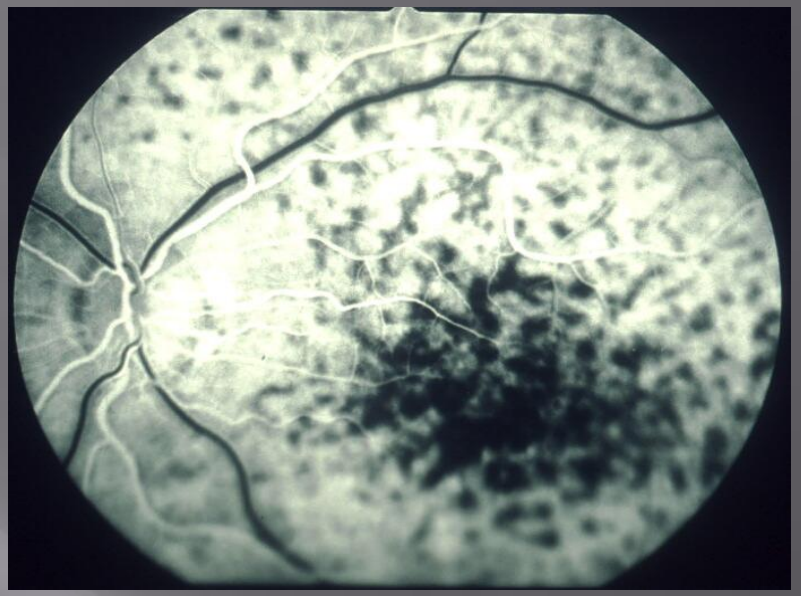


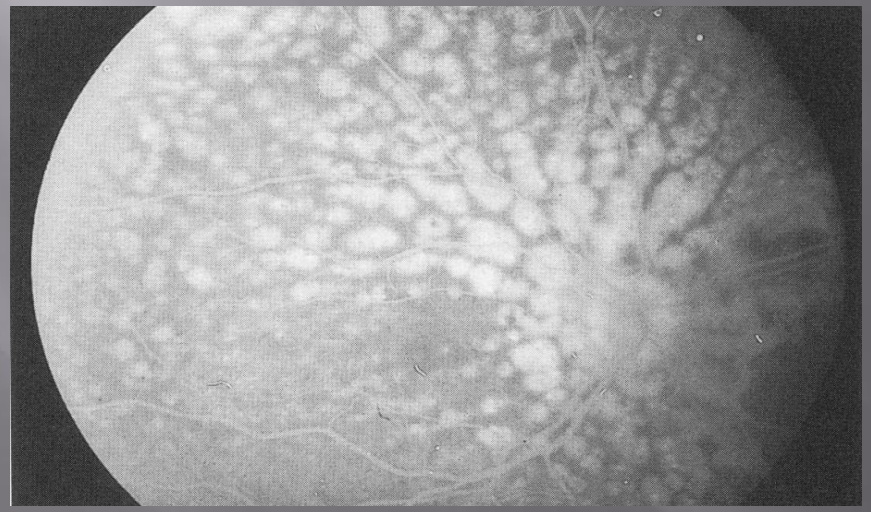


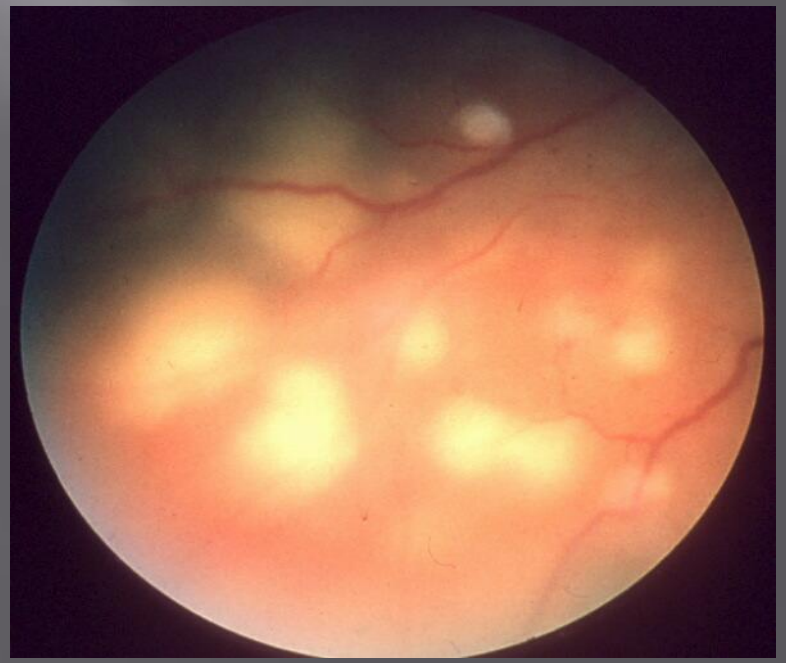
PIOL

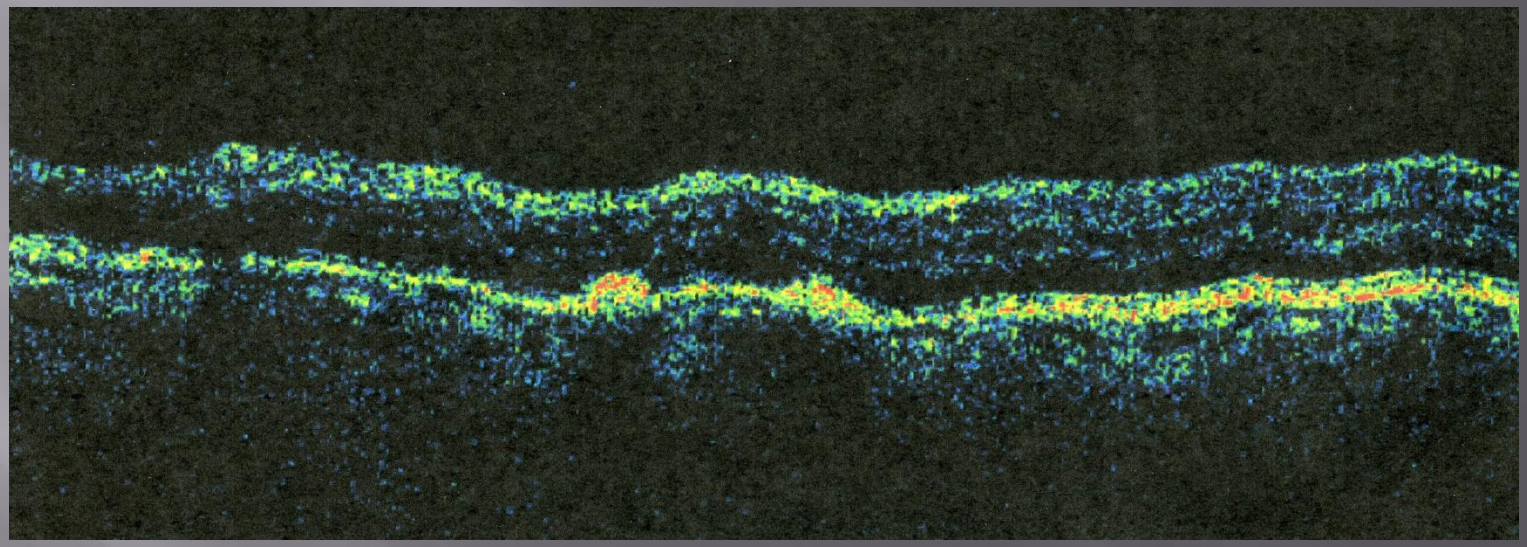
- Multifocal solid sub-RPE deposits
- Yellow speckles
- RPE disturbance
- FA shows blockage with a granular characteristic

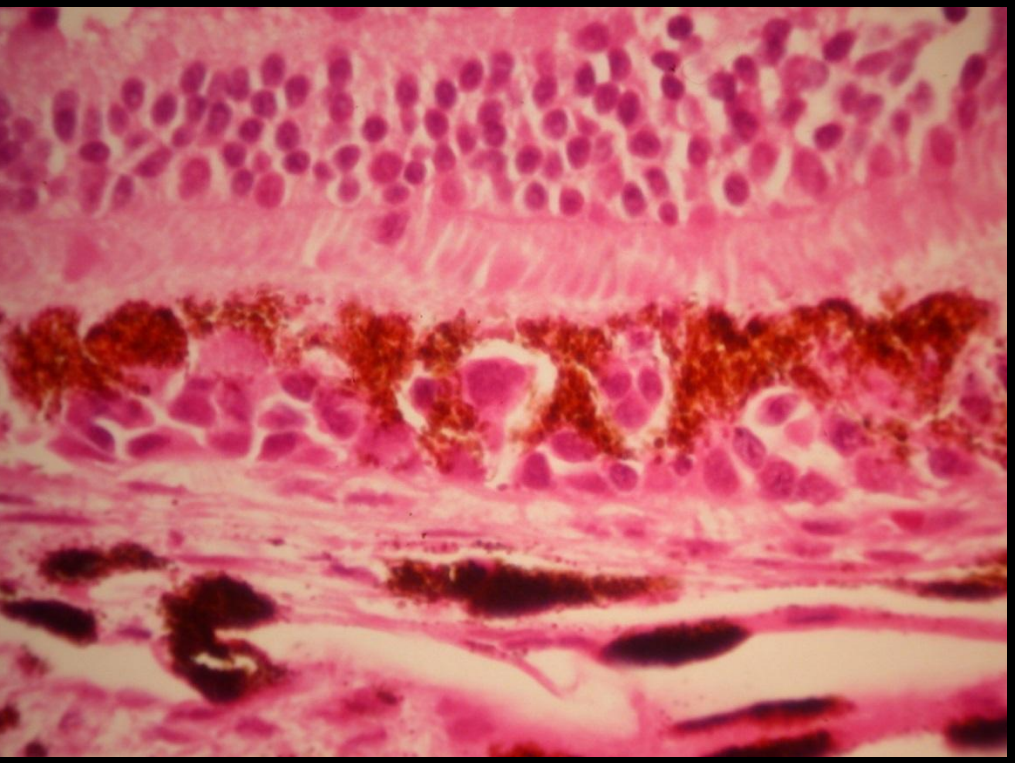


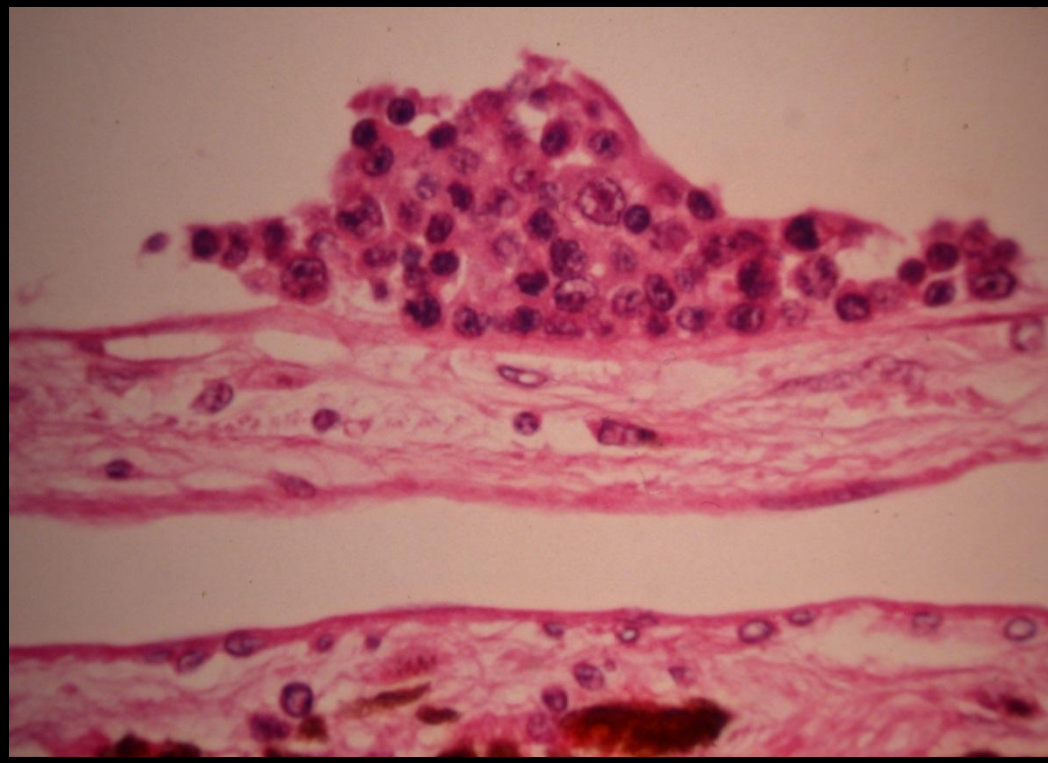






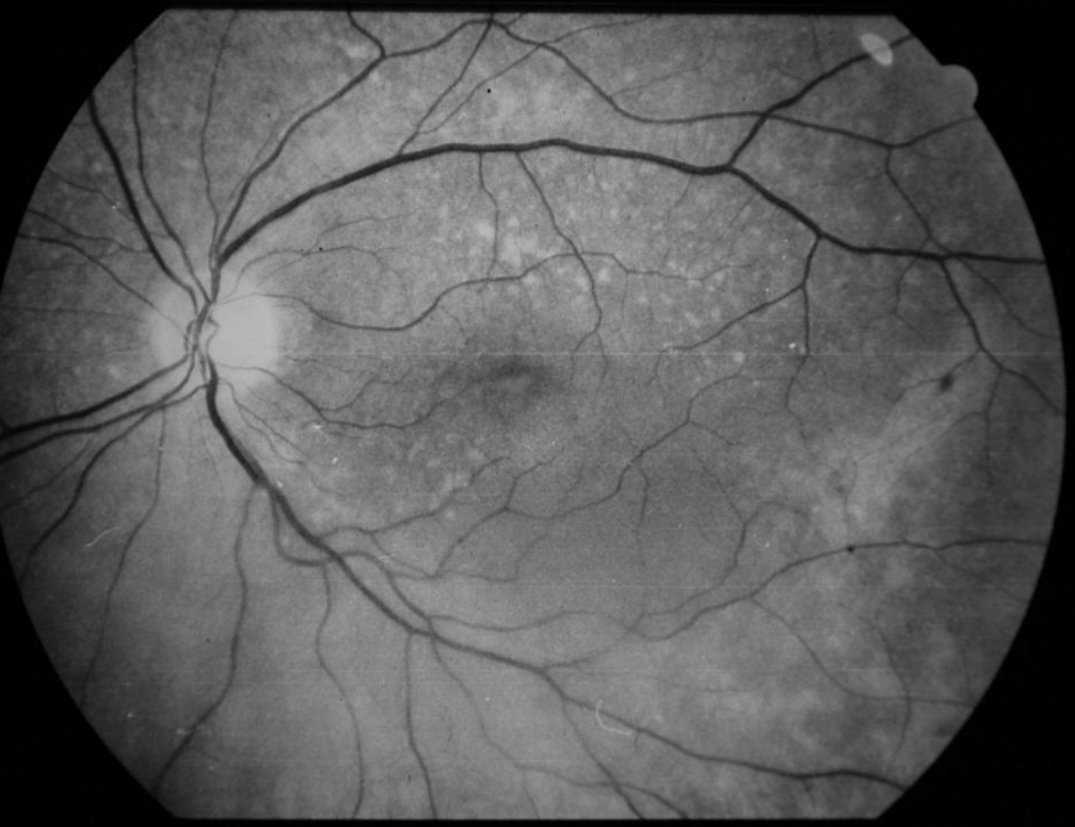


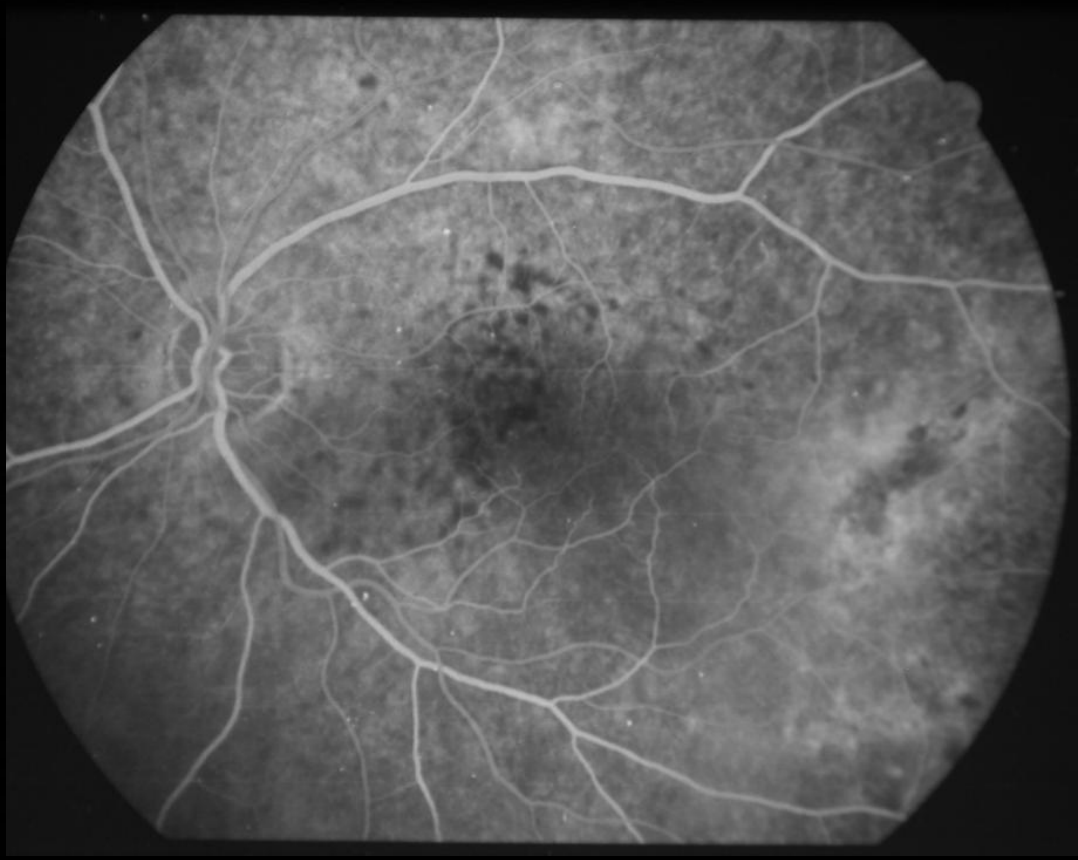


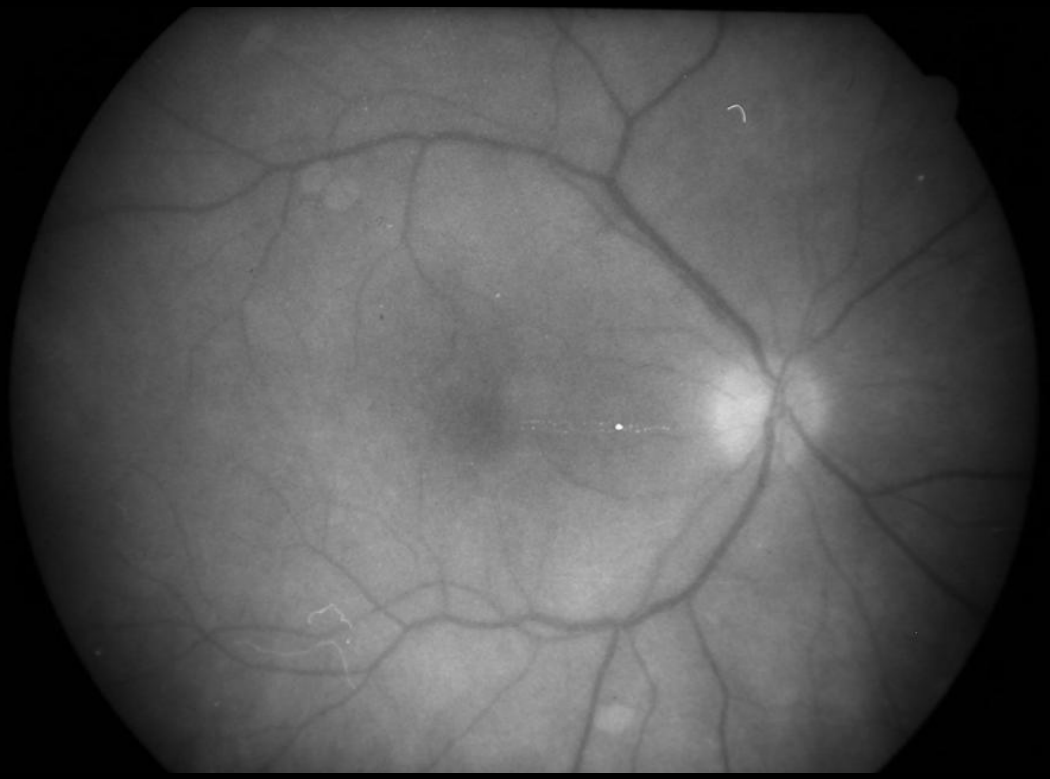


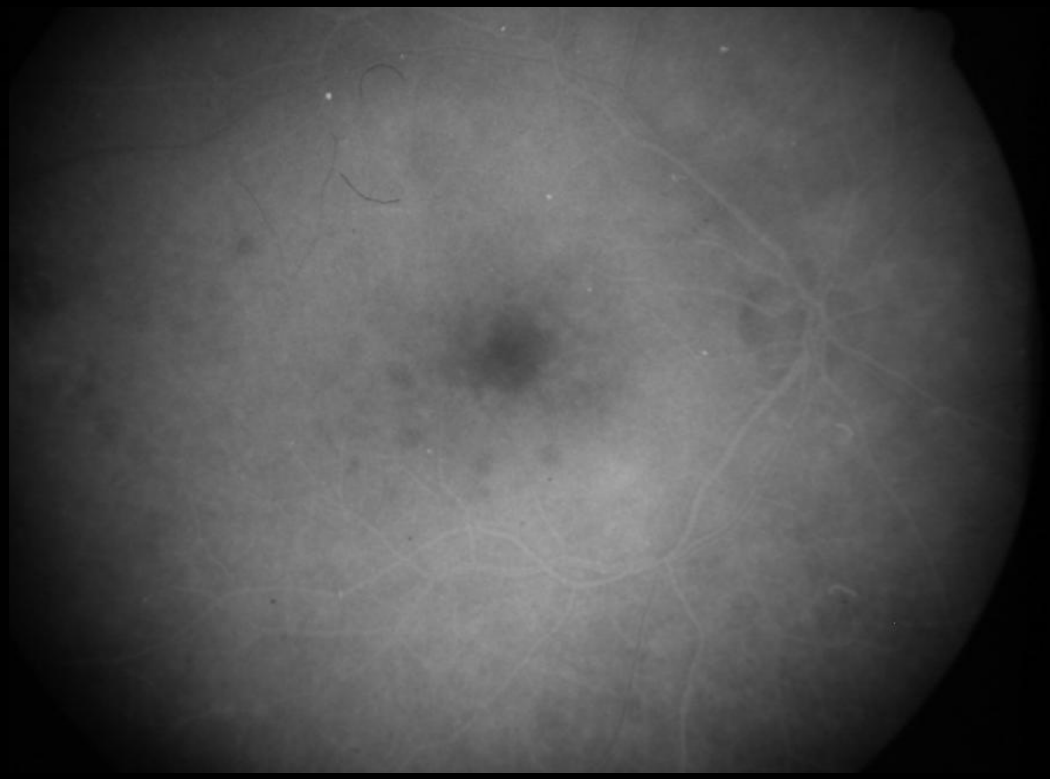
PIOL - Diagnosis

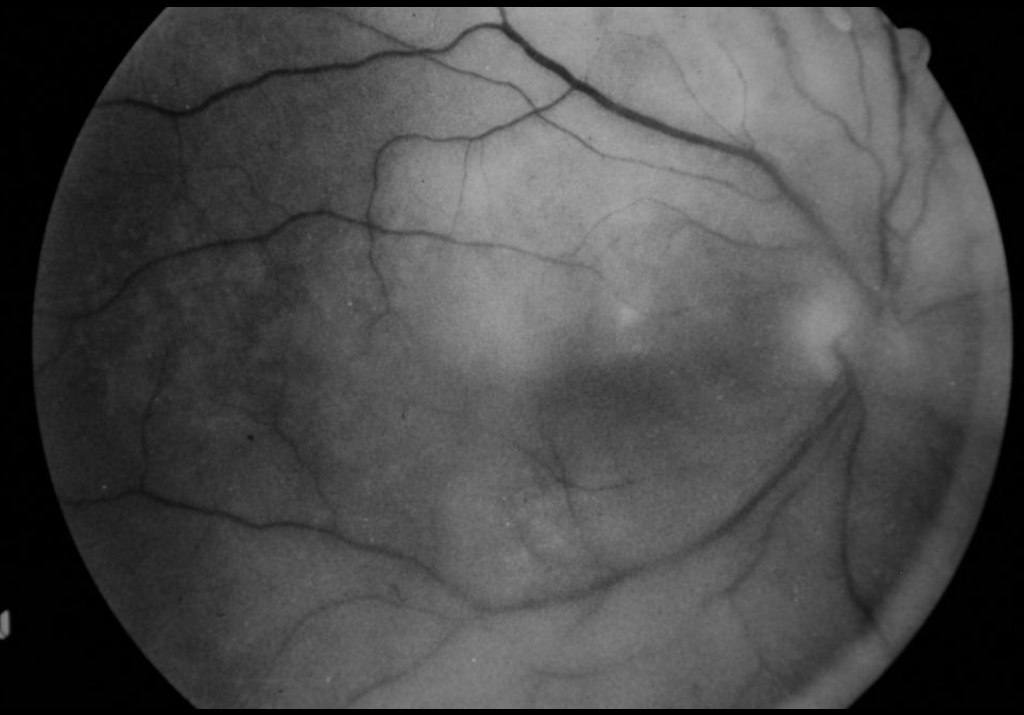
- Usually delayed – average of 21 months
- Clinical suspicion
- Fluorescein angiography
- Vitreous biopsy
  - Cytology
  - Immunohistochemistry
  - Cytokines
  - Molecular techniques
- Chorio-retinal biopsies

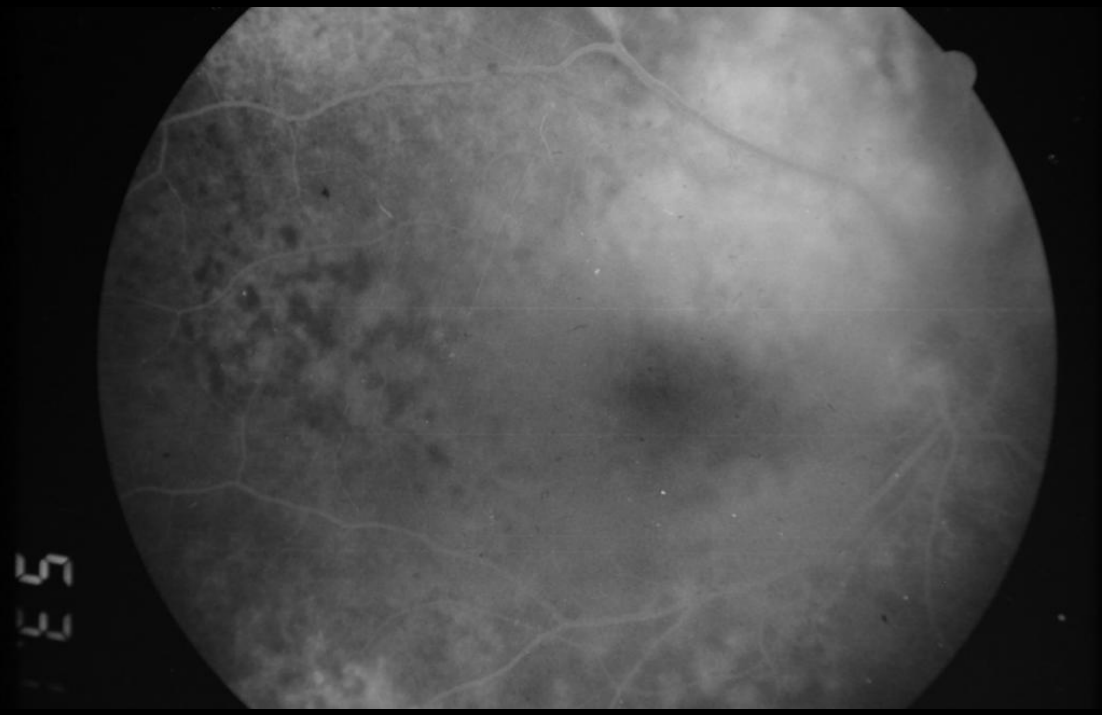


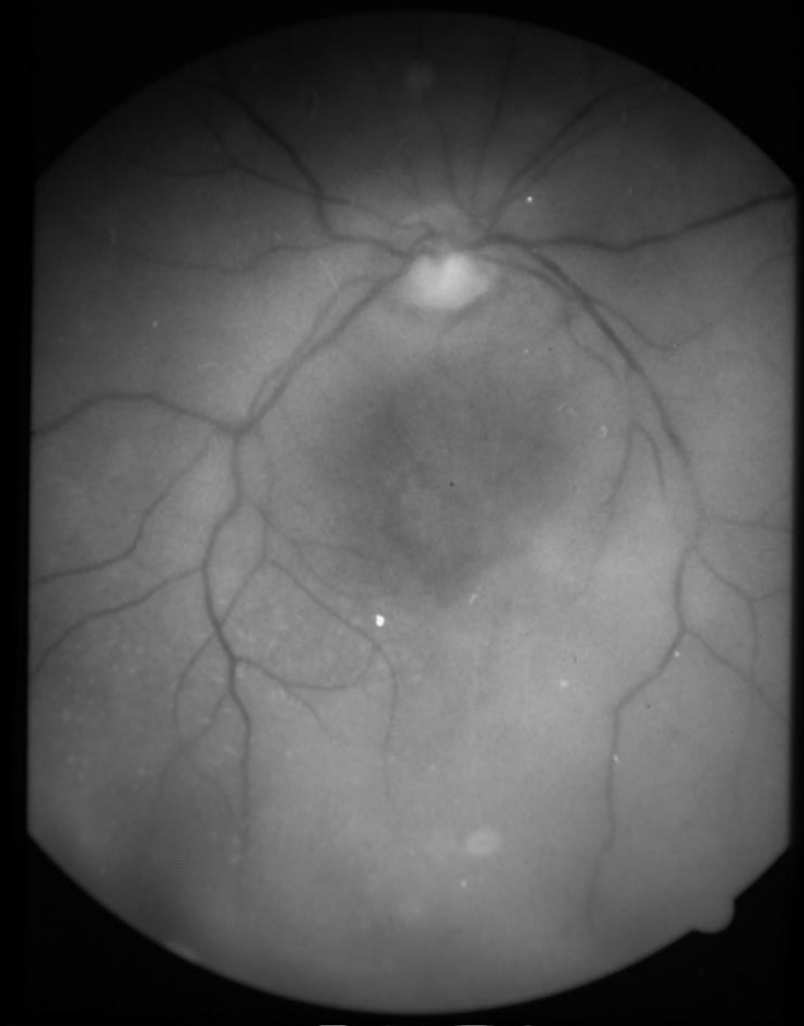


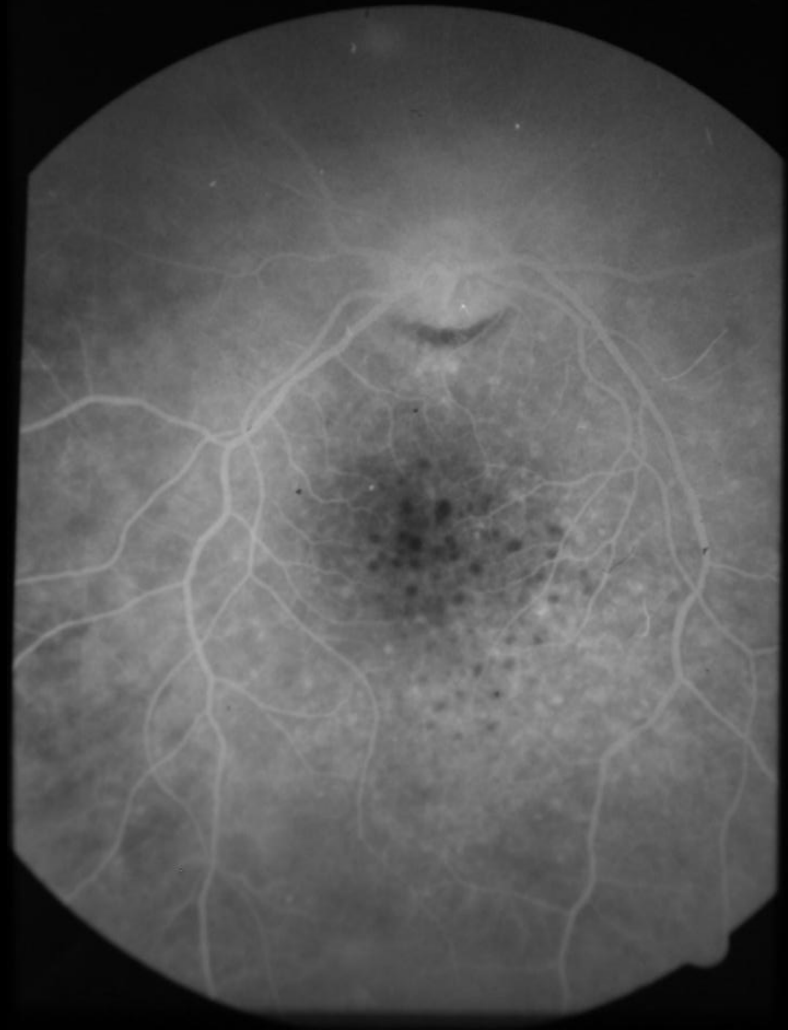






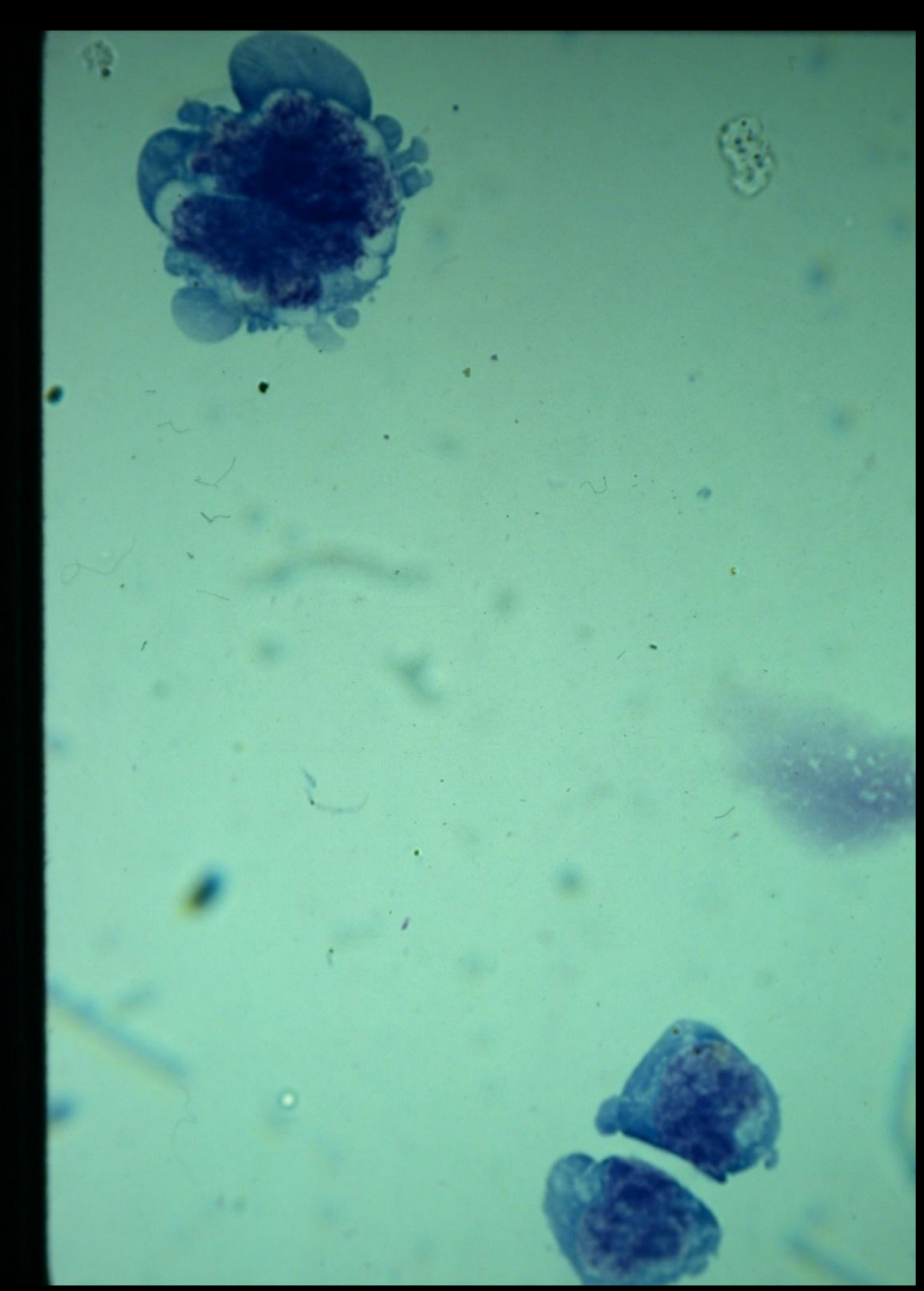


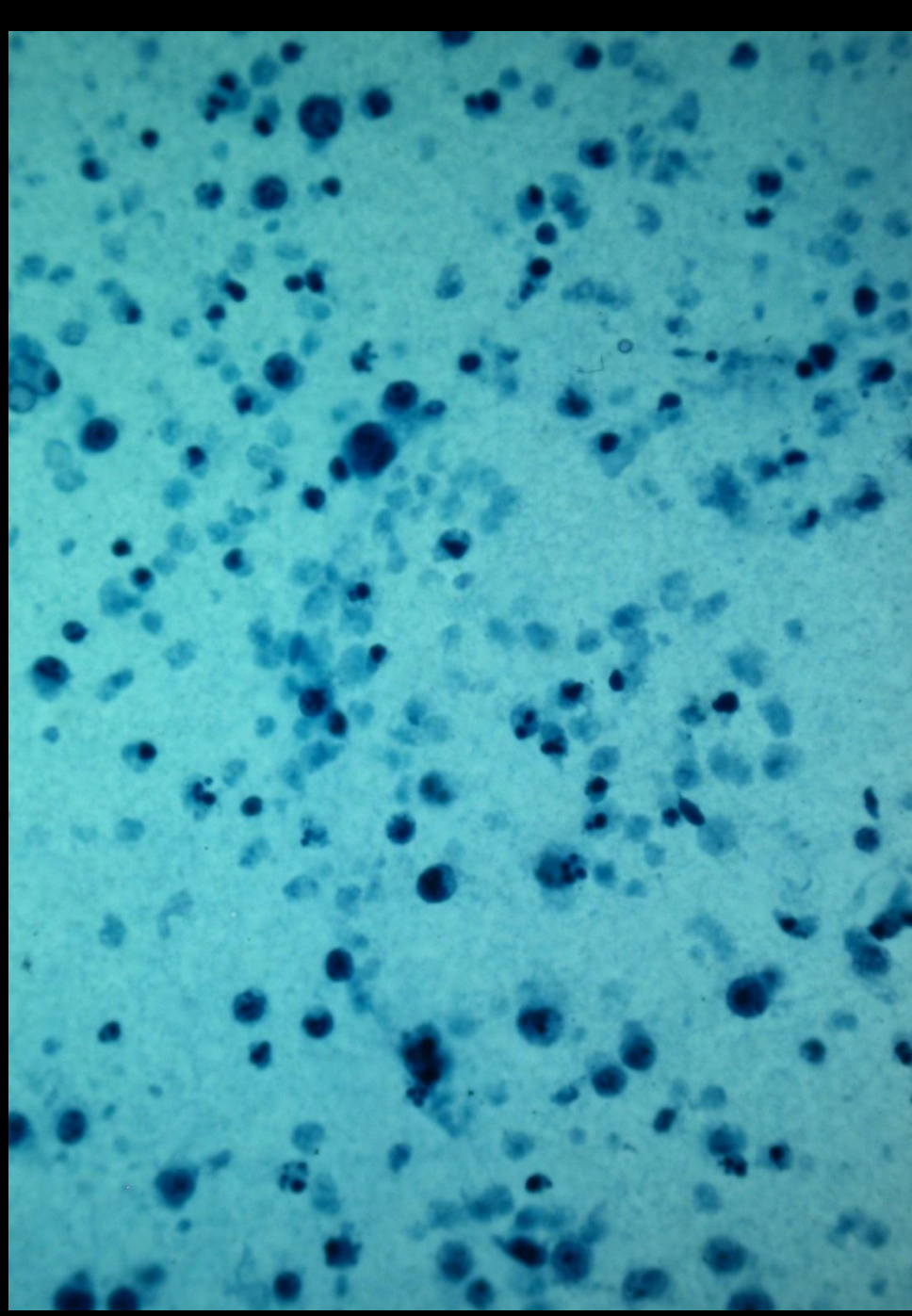




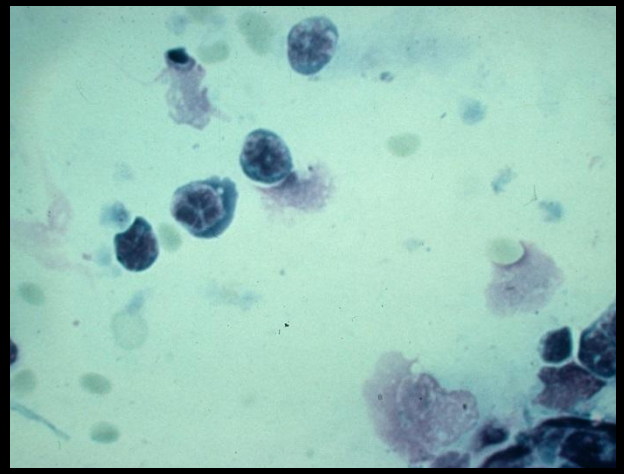
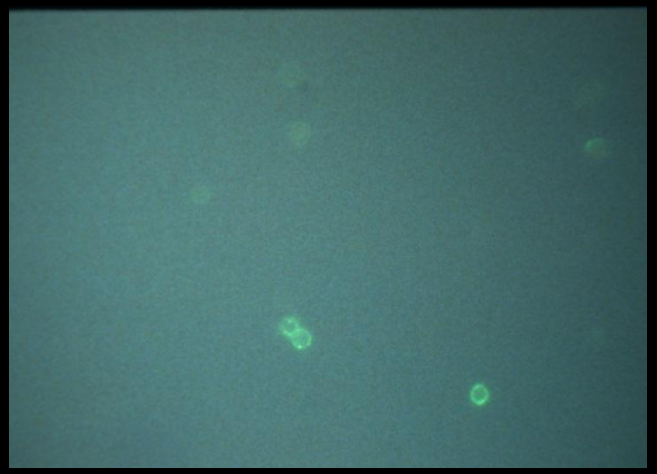
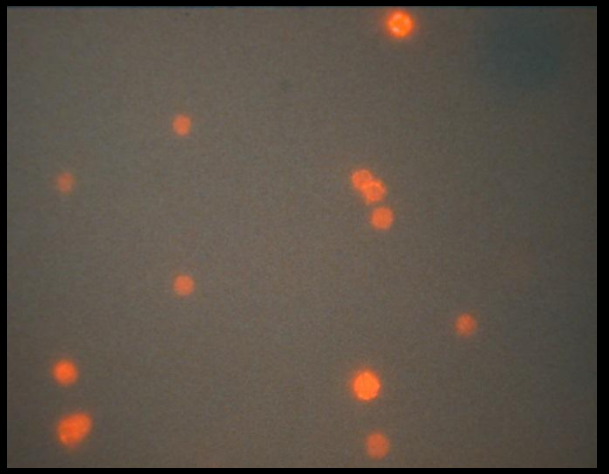
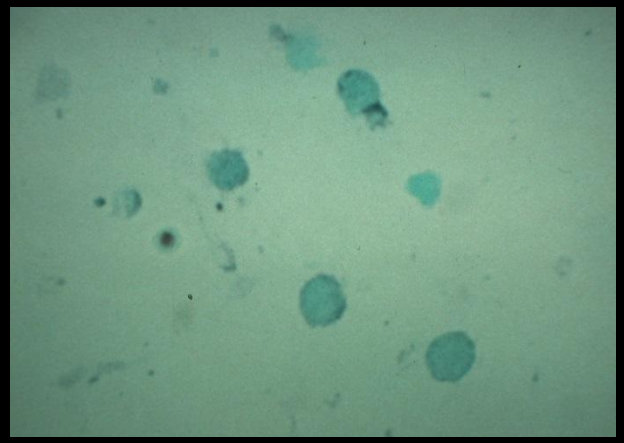
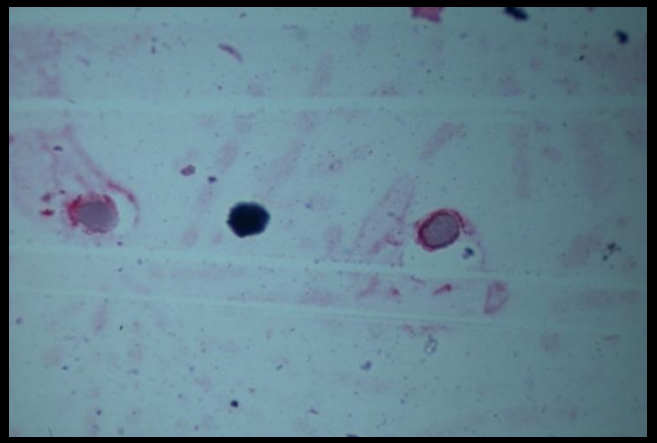
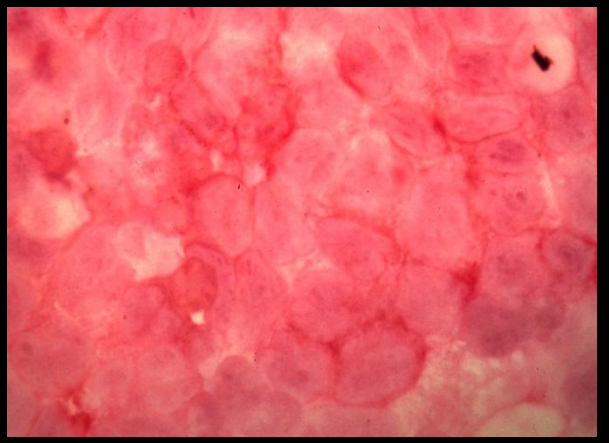
Cytology

- Immediate transportation
- Tissue culture medium
- Special staining techniques
- Experienced cytopathologist
- Influence of steroids





Primary IntraOcular Lymphoma

Immunohistochemistry

- Identification of cell surface markers
- Markers may remain even when morphology is poor
- Microscopic examination of stained cells – a separate slide is needed for each marker
- Panel – cell type, activation marker, cell-surfeca immunoglobulins
- Fluorescence activated cell sorter (FACS) – colour coding allows multiple test

Diagnosis of Intraocular Lymphoma
Davis JL. Ocular Infl & Immunol 2004; 12:7-16.

Marker	*Specificity*	*Interpretation*
T-cell markers		
CD2, CD3, CD5, CD7	Pan T cell	High expression in active uveitis or T-cell lymphomas. Aberrant expression of some of the 'pan' markers but not others increases suspicion of lymphoma
CD4	T helper	Increased relative to CD8 in active uveitis; mycosis fungoides
CD8	T suppressor	Increased relative to CD4 in inactive uveitis; mycosis fungoides with shift in immunophenotype
B-cell markers		
CD19, CD20	Pan B cell	High expression in B-cell lymphomas. Increased in inactive uveitis relative to active uveitis
CD22	Early B cell	Supportive of B-cell lymphoma, but can also be present on normal cells
Kappa; Lambda	Light-chain immunoglobulin	Heterogeneous populations of B cells have roughly equal proportions of kappa and lambda light-chain immunoglobulins. B-cell lymphomas usually have K:L or L:K ratio of >3. Lack of kappa or lambda expression in a predominantly B-cell population is suggestive of lymphoma
Activation markers		
HLA-DR	MHC Class II	Immunologically active cells consistent with inflammation
CD25	IL-2 receptor	Immunologically active cells consistent with inflammation. Expressed on activated T and B lymphocytes
Other cell lineages		
CD14	Monocyte/macrophage	May be increased in infections. Consistent with a heterogeneous inflammatory response
CD56	Natural killer cells	May be increased in infections. Consistent with a heterogeneous inflammatory response
CD33	Pan myeloid	Neutrophils, eosinophils, basophils. May be increased in infections. Consistent with a heterogeneous inflammatory response

PIOL - Cytokines

- IL-10 acts on B cells stimulating Ab production
- Preferentially expressed by B-cell malignancies
- IL-6 (IL-12) produced by inflammatory cells
- IL-10/IL-6 or IL-12 > 1
- Some results showed > 1 in uveitis (8 out of 14)
- Other found < 1 in 4 confirmed cases
- Use of undiluted vitreous – more reliable
- Useful adjunct in the diagnosis of PIOL, but not specific.

Ocular and CNS lymphoma: clinical features and diagnosis.
Cassoux N, et al

- Retrospective review of 44 immunocompetent patients with ICNSL
- Average age 54 years (36-90)
- Average time between symptoms and cytologic diagnosis was 40 months (1-144)
- 66% had CNS involvement
- CNS preceded eye disease in 24%
- Cytology established diagnosis in 86%
- PCR was helpful in 12 patients
- IL-10 showed no false-positives
- New techniques may improve time to diagnosis and prognosis

Ocular Immunol & Inflam. 2000;8:243-250

Molecular Techniques

- PCR detection of gene rearrangements
- Amplification of CDR3 of the immunoglobulin heavy chain (IgH)
- Translocation between cromossomes 14 and 18 results in gene rearrangement at the major breaking point of the bcl-2 (oncogene) protein
- Only useful for B-cell lymphomas
- Collection of suspicious cells by microdissection increases yield of positive results (probably best for tissue biopsy specimens)

Diagnosis of Intraocular Lymphoma
Davis JL. Ocular Infl & Immunol 2004; 12:7-16.

Test	*Result*	*Advantages*	*Disadvantages*
Cytology	Nuclear irregularity, multiple nucleoli, granular chromatin	Accepted gold standard	30% false-negative rate.[30] Often requires expert review
Immunohistochemistry	Predominance of B-cell surface markers with expression of either kappa or lambda light chain, but not both	Captures most cases of PIOL. Adjunct to cytologic interpretation	Limited number of markers can be reviewed. Not useful for T-cell lymphomas. Predominant T-cell an CD4 marker suggestiv of active uveitis
Flow cytometry (cytofluorography)	Same as immunohistochemistry. Additional information regarding cell lineage and activation status.	Same as immunohistochemistry. Cells can later be processed for molecular studies. More useful for T-cell lymphomas as more markers can be tested for aberrant expression	May require special techniques to permit passage of vitreous through the flow cytometer[16]
Cytokine analysis	Elevated IL-10 or elevated IL-10:IL-6 ratio	Requires small amounts of fluid. High biological plausibility	Useful only for B-cell lymphomas. No definit diagnostic standards. Unknown frequency of false-positives and -negatives
Gene rearrangement	Detection of a monoclonal cell population based on PCR amplification of an aberrant sequence of the IgH gene, bcl-2 gene, or T-cell receptor gamma gene	Appears highly sensitive. Adaptable to both B- and T-cell lymphomas	Little clinical experience as yet

Primary Intraocular Lymphoma

Clinical, cytologic, and flow cytometric analysis

Zaldivar RA, et al

- 10 patients who had PPV to rule out PIOL
- Mean age 62y (30-85)
- 3 had diagnosis of chronic uveitis
- 7 patients has diagnosis of PIOL
- 6 had bilateral involvement
- 4 had more than one vitrectomy
- Diagnosis reached in a mean time of 4 months
- Cytology remains the preferred technique
- Importance of subretinal aspirate
- FCI provides corroborative support for the diagnosis

Ophthalmology 2004; 111:1762-1767.

TREATMENT OF PIOL

- Chemotherapy >>> radiation therapy

(systemic and intrathecal)

- Intravitreal chemotherapy

(400 microg MTX inj. Twice weekly for three weeks, thiotepa 2 mg once a week for three weeks)