Case Conference

27 February 2009

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HPI

- 13 year old girl with "bruise" on her left eye x4 weeks
- Gradually changed colors.
- Light senstivity, then recurrent redness
- Left eye became swollen.
- Treated for episcleritis with Tobradex which helped her redness but did not improve the swelling.

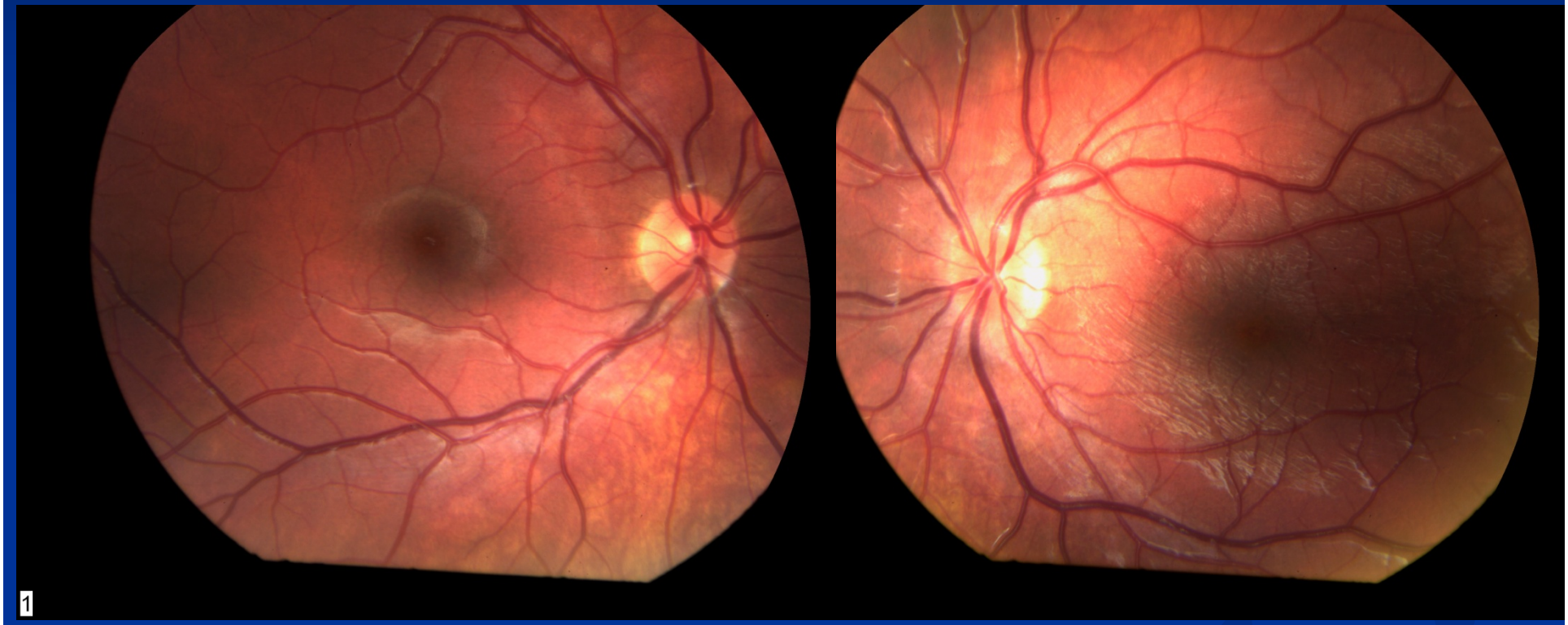
PMH

- Infantile diarrhea-Required synthetic formula
- Recurrent abdominal pain despite Lactaid milk.
- PSH: gastroenterologist at UMass performed an upper and lower endoscopy which was normal.
- ALL: gluten hypersenitivity. Eliminating carbonated beverages improved her symptoms
- ROS: URI prior to onset

Exam

- VA_{sc} 20/20 OU
- T_{pneum} 21/25
- PERRLA
- CVF full, OU
- OS: resistance to retropulsion, 2mm proptosis
- No orbital bruit

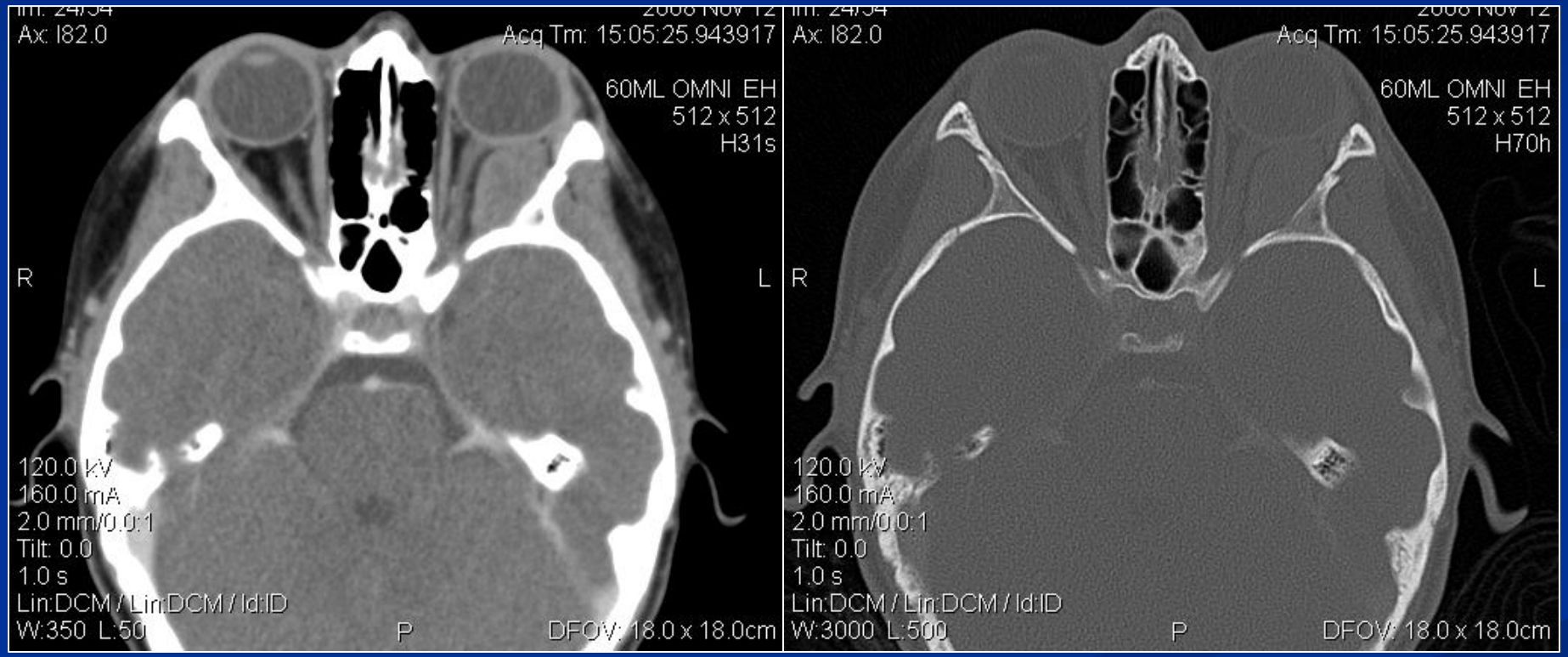
Fundus Photos



What is the next step in the work-up?

B scan

Axial CT orbits



Differential Diagnosis ?

Proptosis in Childhood

Malignant neoplastic

Benign proliferative

Infectious/inflammatory

Traumatic

Endocrine/metabolic

Developmental

Malignant neoplastic

- Rhabdomyosarcoma/other primary sarcoma
- Metastatic neuroblastoma/other secondary tumor
- Extraocular retinoblastoma
- Leukemic infiltration
- Burkitt lymphoma
- Malignant histiocytosis

Benign proliferative

- Capillary hemangioma
- Lymphangioma
- Optic glioma
- Meningioma
- Fibrous dysplasia
- Ossifying fibroma
- Juvenile fibromatosis
- Eosinophilic granuloma

Infectious/inflammatory

- Cellulitis
- Sinus mucocele
- Echinococcal cyst
- Idiopathic pseudotumor

Traumatic

- Hematoma
- Foreign body
- Carotid cavernous fistula
- Encephalocele

Endocrine/metabolic

- Graves disease
- Osteopetrosis
- Infantile cortical hyperostosis

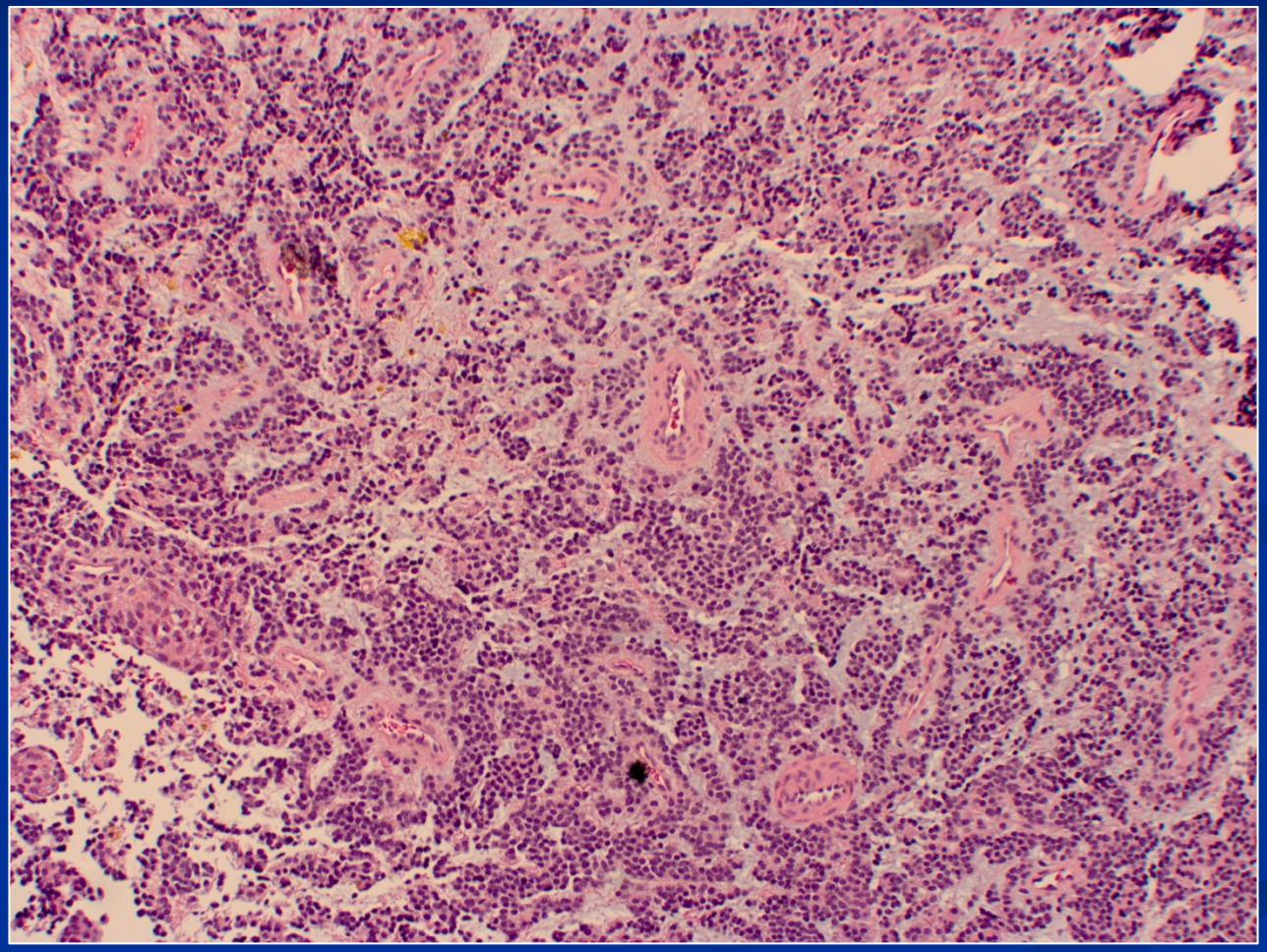
Developmental

- Infantile gluacoma
- Axial high myopia
- Craniofacial dysostosis
- Encephalocele
- Colobomatous cyst
- Dermoid cyst
- Teratoma

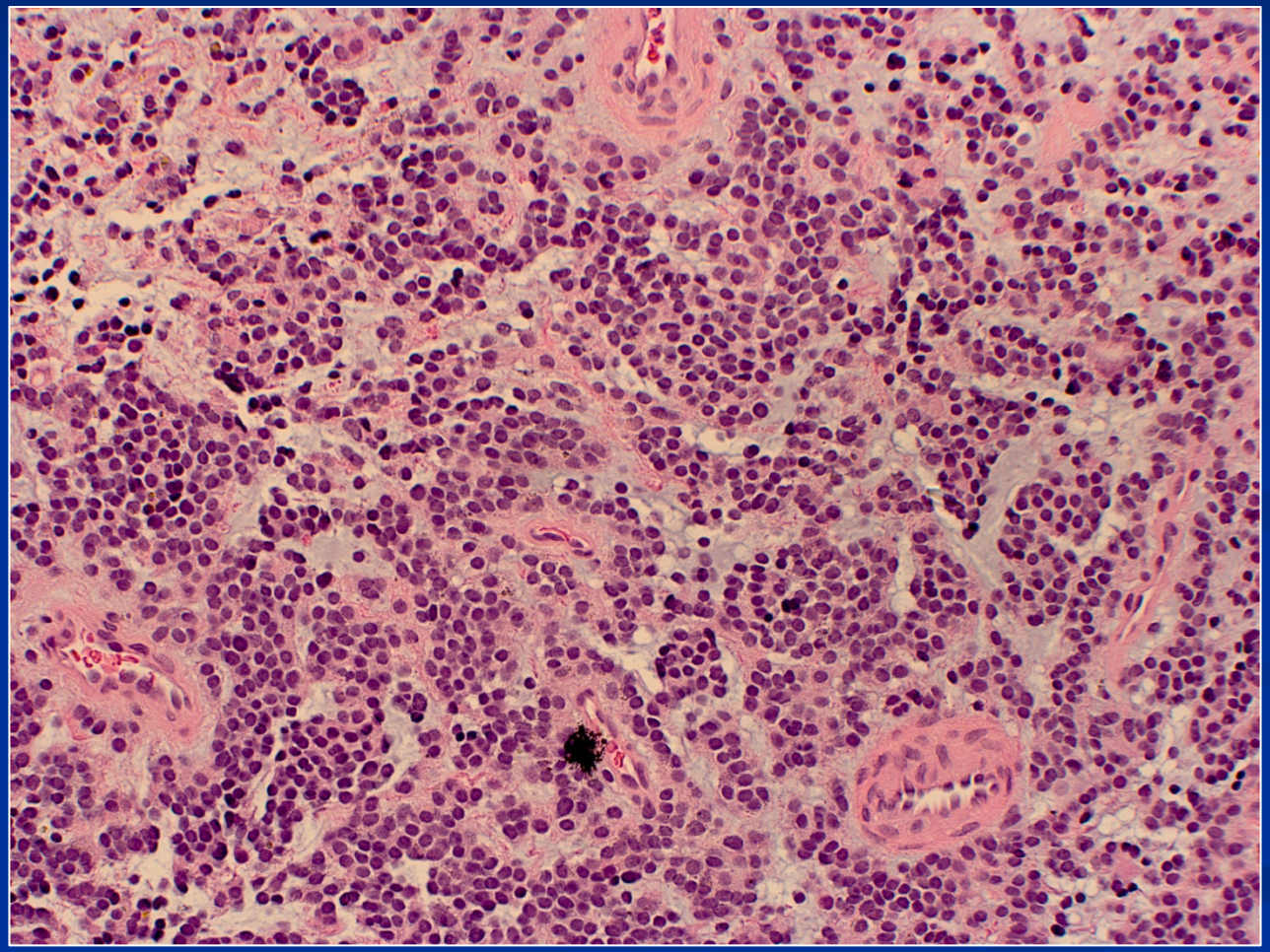
The 7am wake-up call

- Presented to BCH on advice of pediatrician due to increasing pain and swelling
- MR orbits concerning for rhabdomyosarcoma

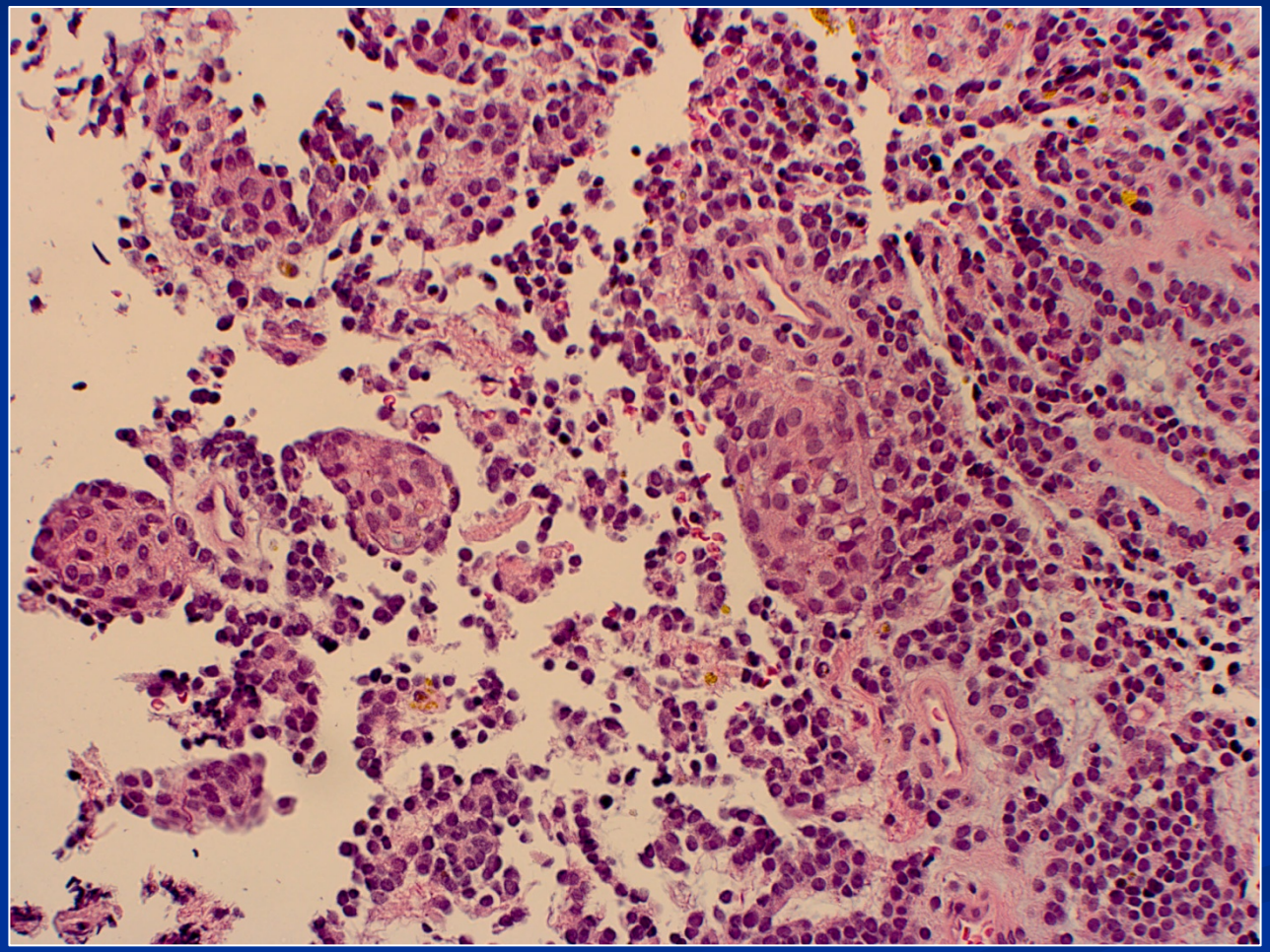
H&E: orbital biopsy



H&E: higher magnification



H&E high mag



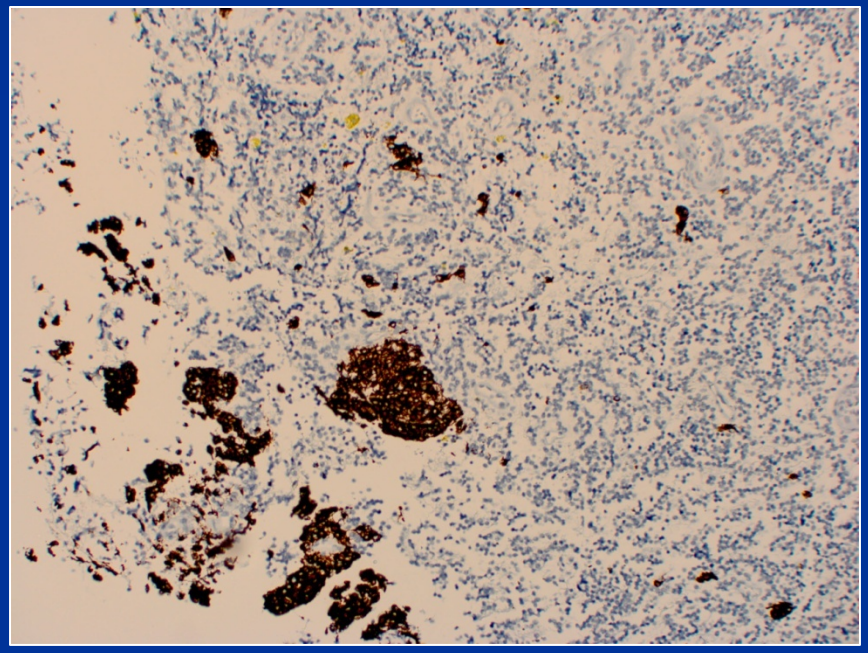
Differential for smalll blue round cell tumors of childhood

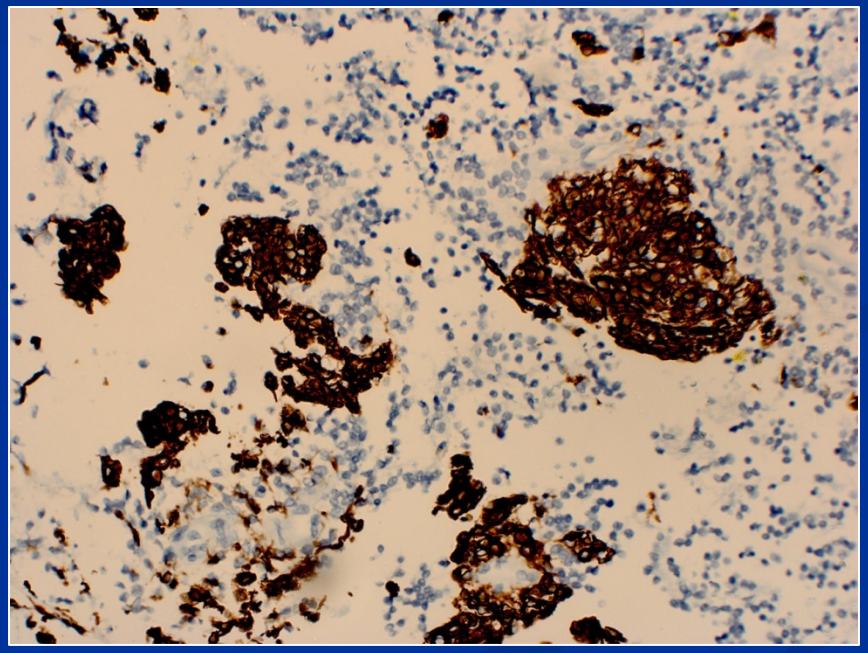
- Lymphoma
- Primary neuroendocrine tumor (PNET)
- Neuroendocrine
- Rhabdomyosarcoma
- Wilms
- Amelanotic melanoma

Morphology

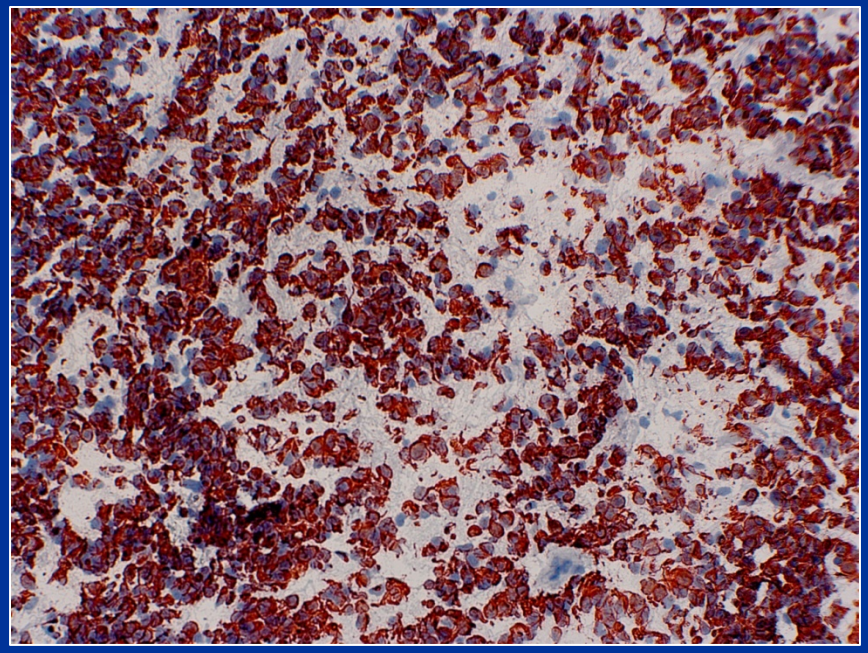
- Cells appear very bland (no pleomorphism, no high NC ratios, no dispolarity within the epithelial cells, no mitoses)
- Hence do not look malignant.
- Need immunohistochemistry

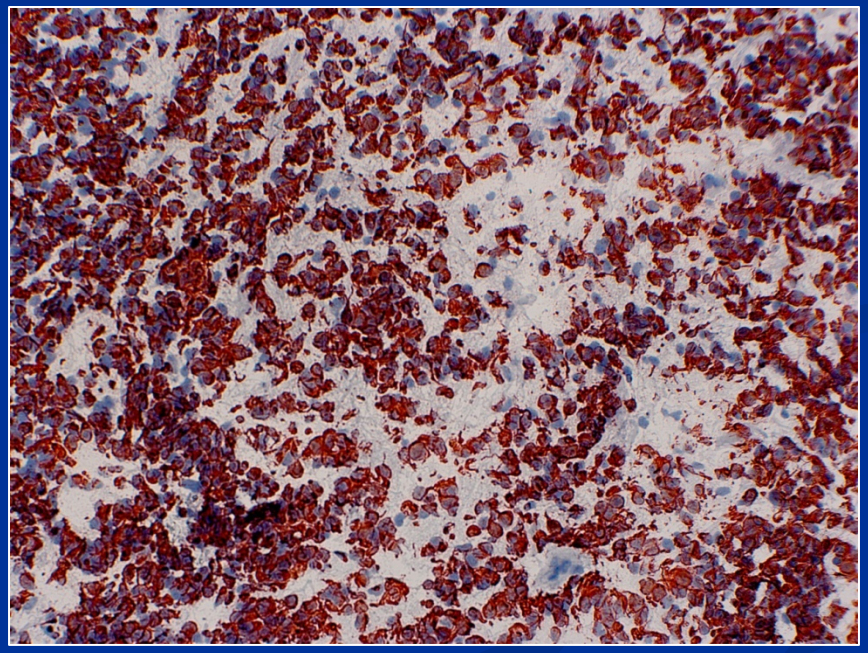
Keratin



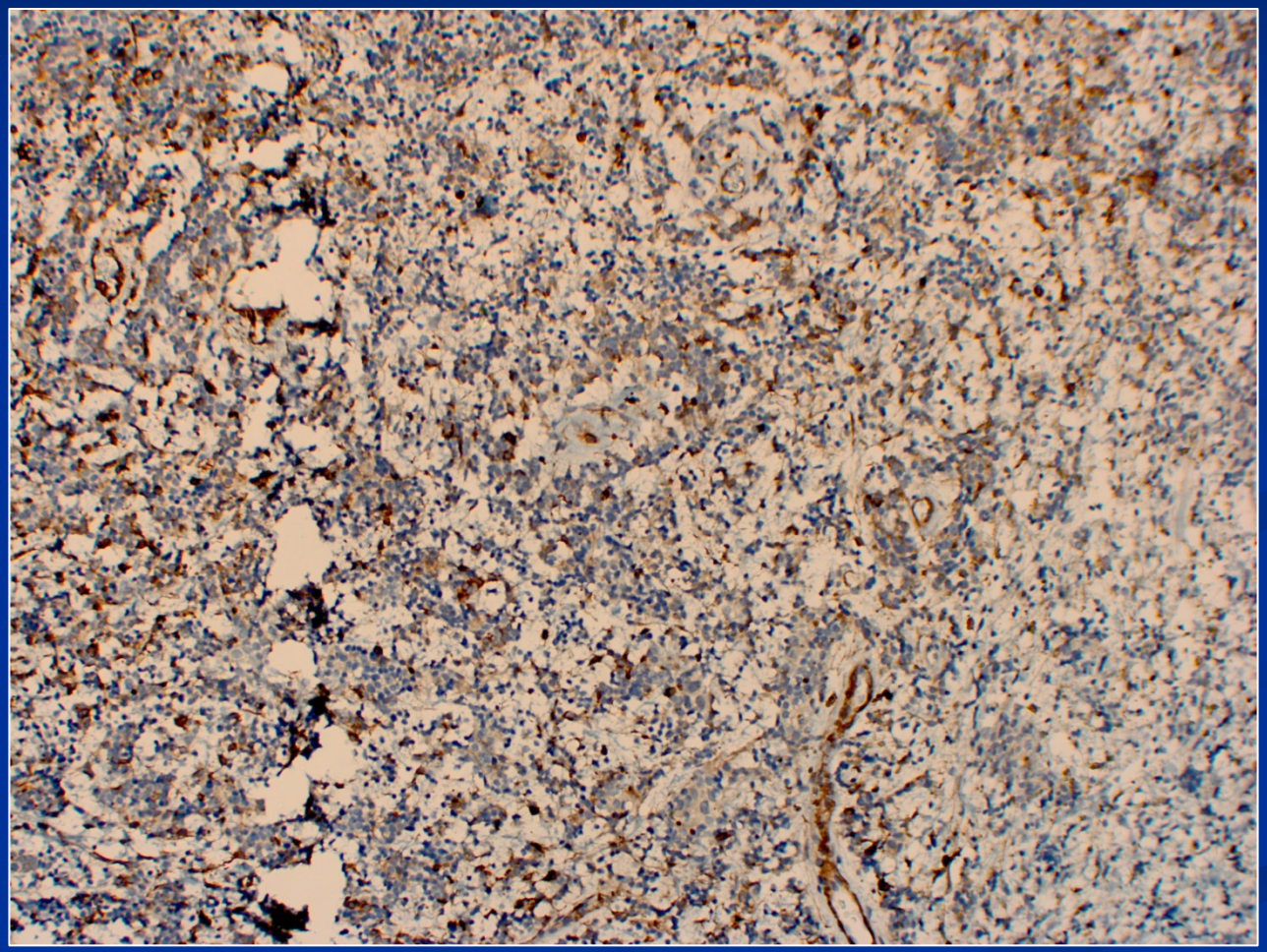


Desmin: muscle

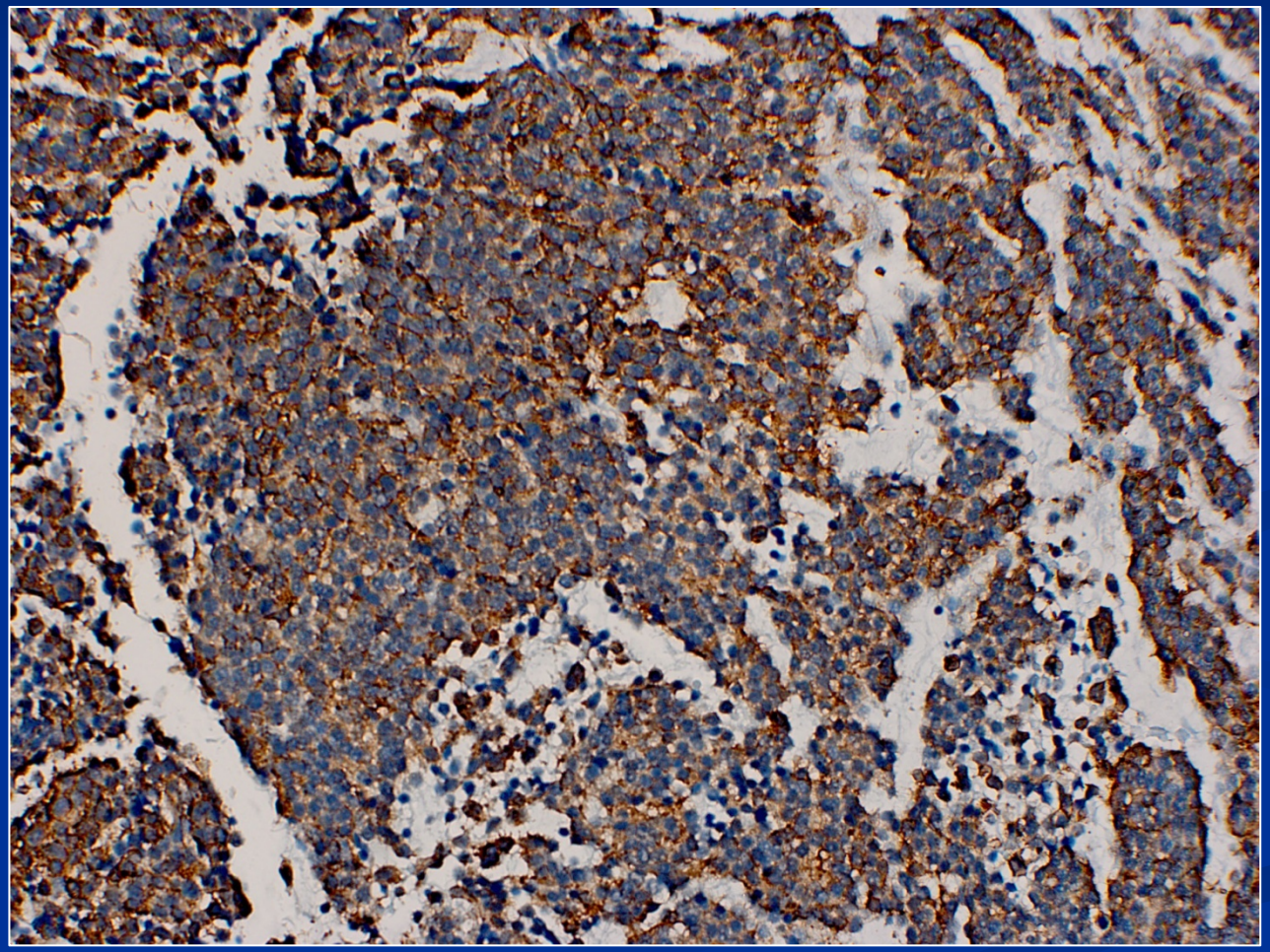




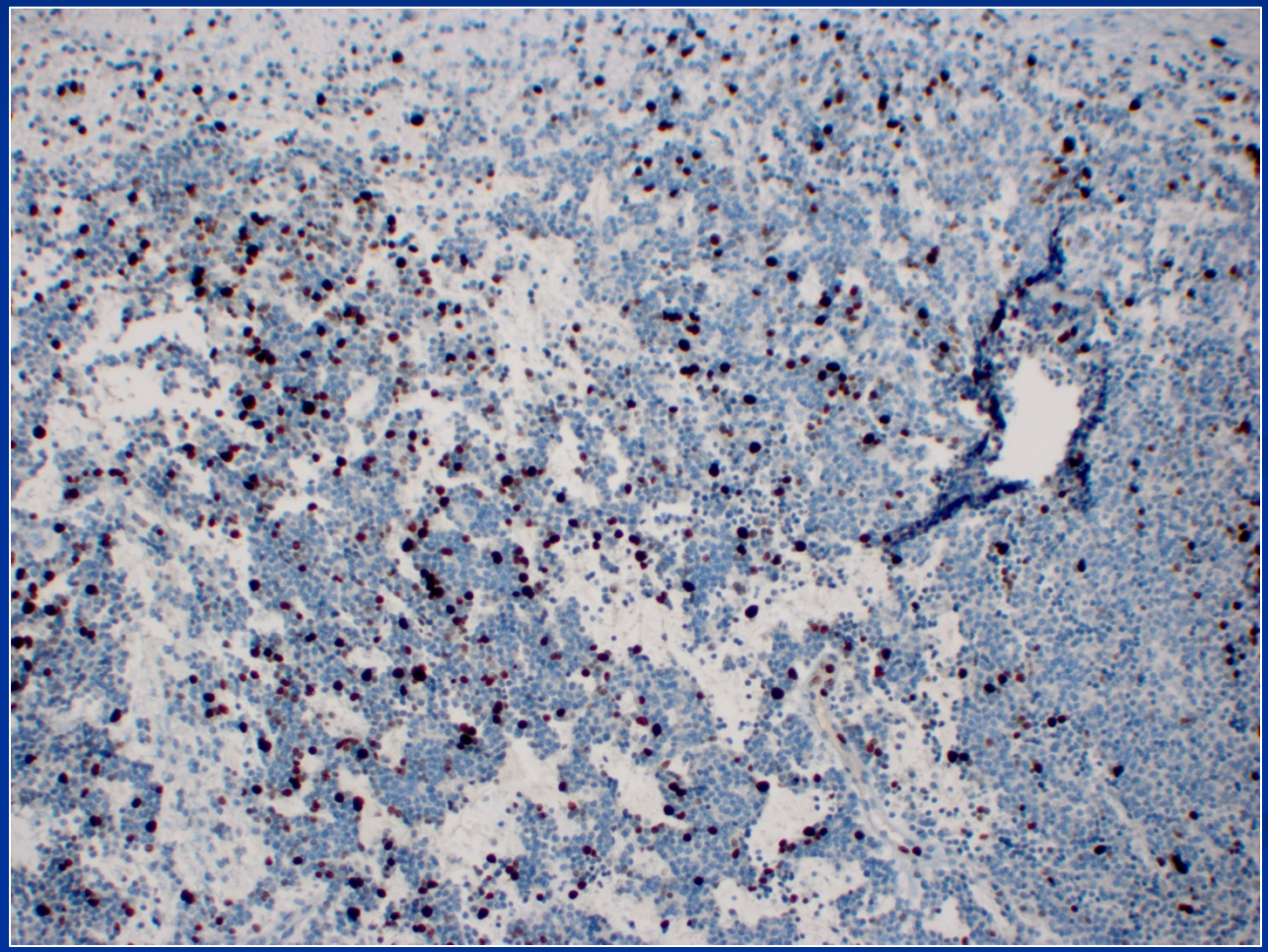
Calponin: myoepithelial cells



Muscle specific actin



Ki-67- proliferation marker detecting cells in the S-phase. Estimated rate 10% favors of a benign neoplasm



Pathologic diagnosis

- Benign myoepithelial tumor

Case II

- 38 yo G1P0 with “preeclampsia”
- C-section at 25.5 weeks due to pulmonary edema and BP 175/105.
- Postpartum systolic BP 140-150.
- One day post partum her vision became blurry.
- Left sided and occipital headaches the next day which awaken her from sleep
- Discharged with a rising creatinine

PMH

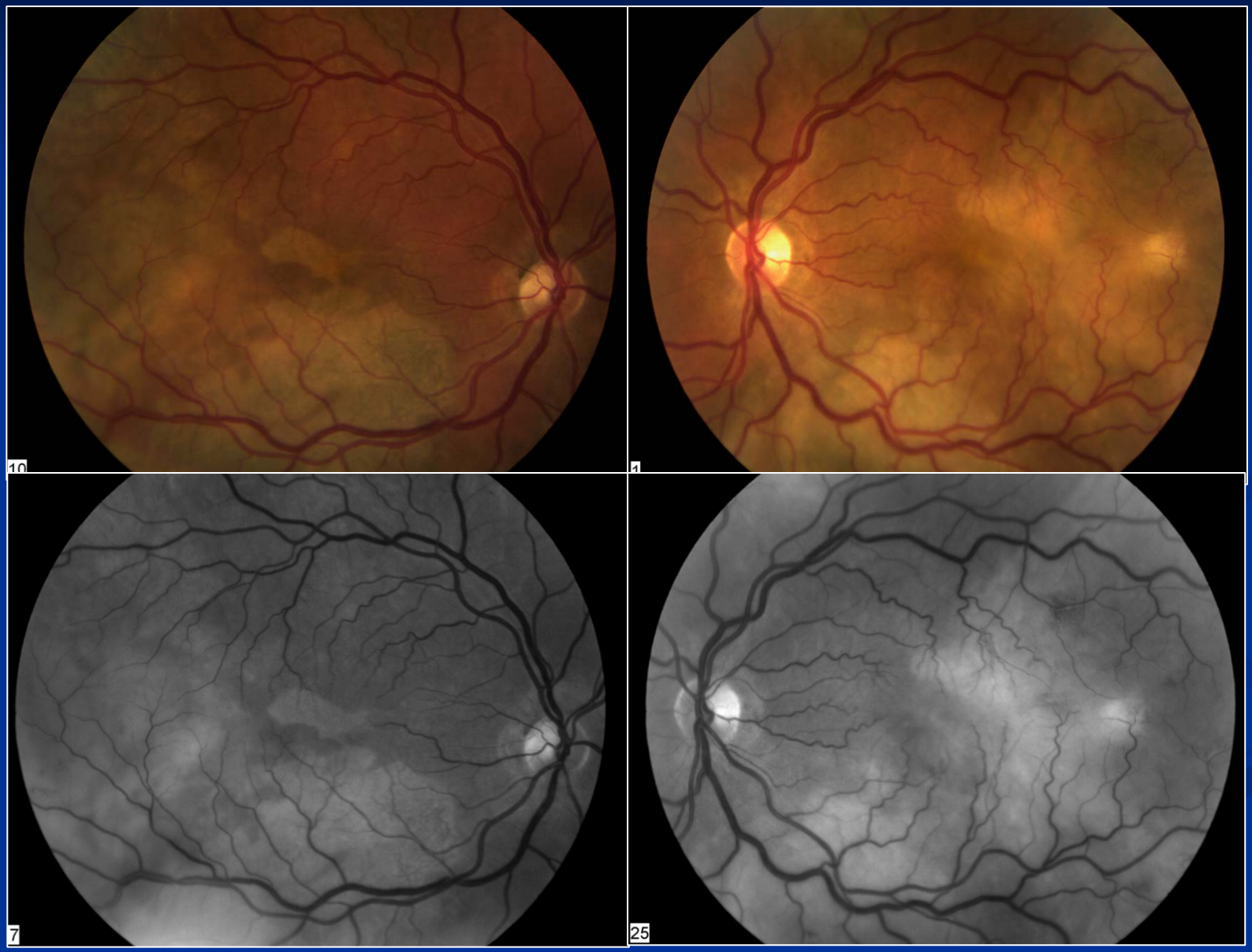
- DVT age 34
- POH: Remote history of uveitis attibuted to SLE (in remission since age 17).
- PSH: rhinoplasty
- ROS: recurrent herpes labialis reactivated this AM
- FH: mother-glaucoma, father deceased-lung CA
- MEDS: Atenolol, Maxitrol
- All: NKDA

Referring retinologist

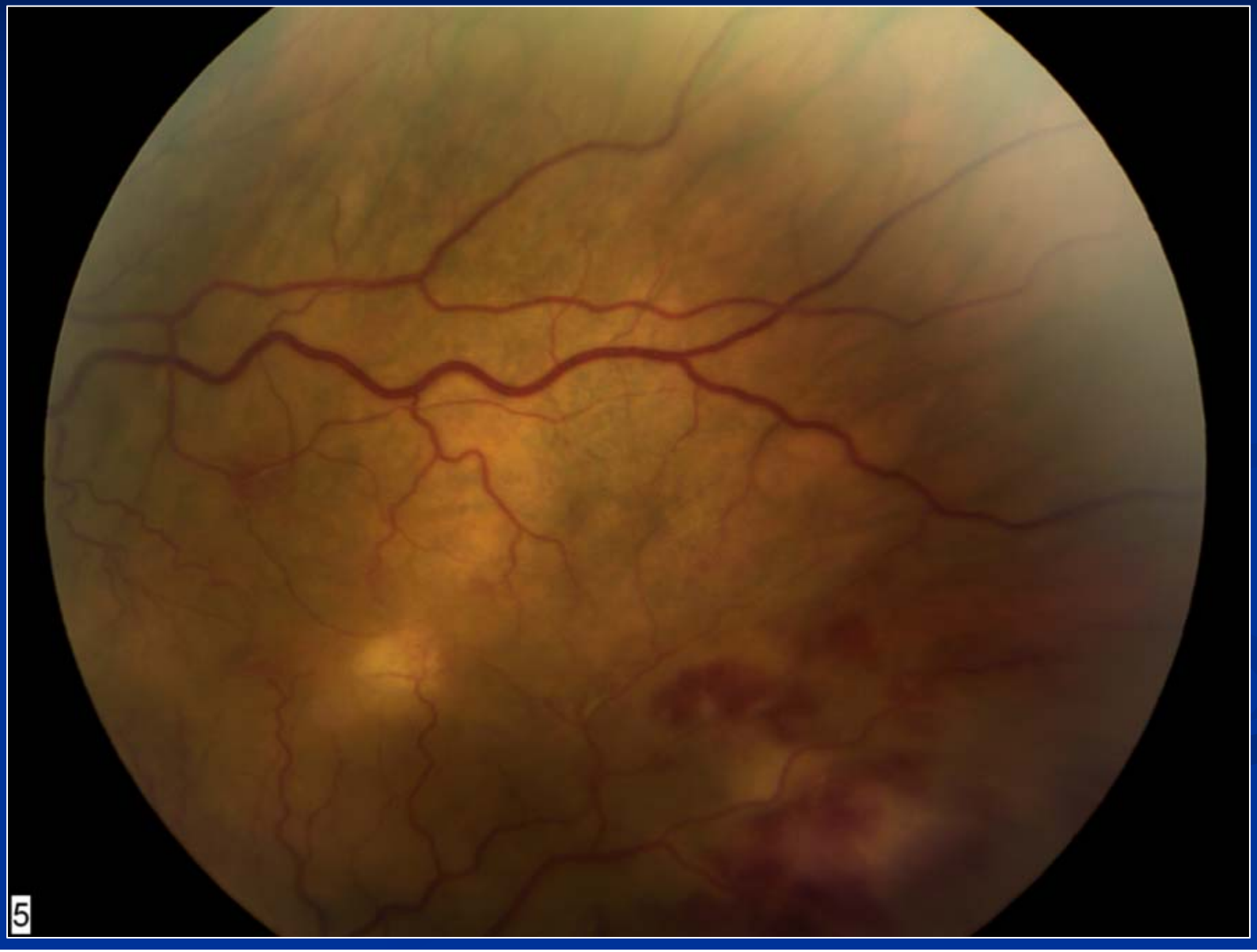
- Observed anterior uveitis and narrow angles
- Elected not to dilate pupils but made note of posterior pole findings despite extreme photophobia

20/300

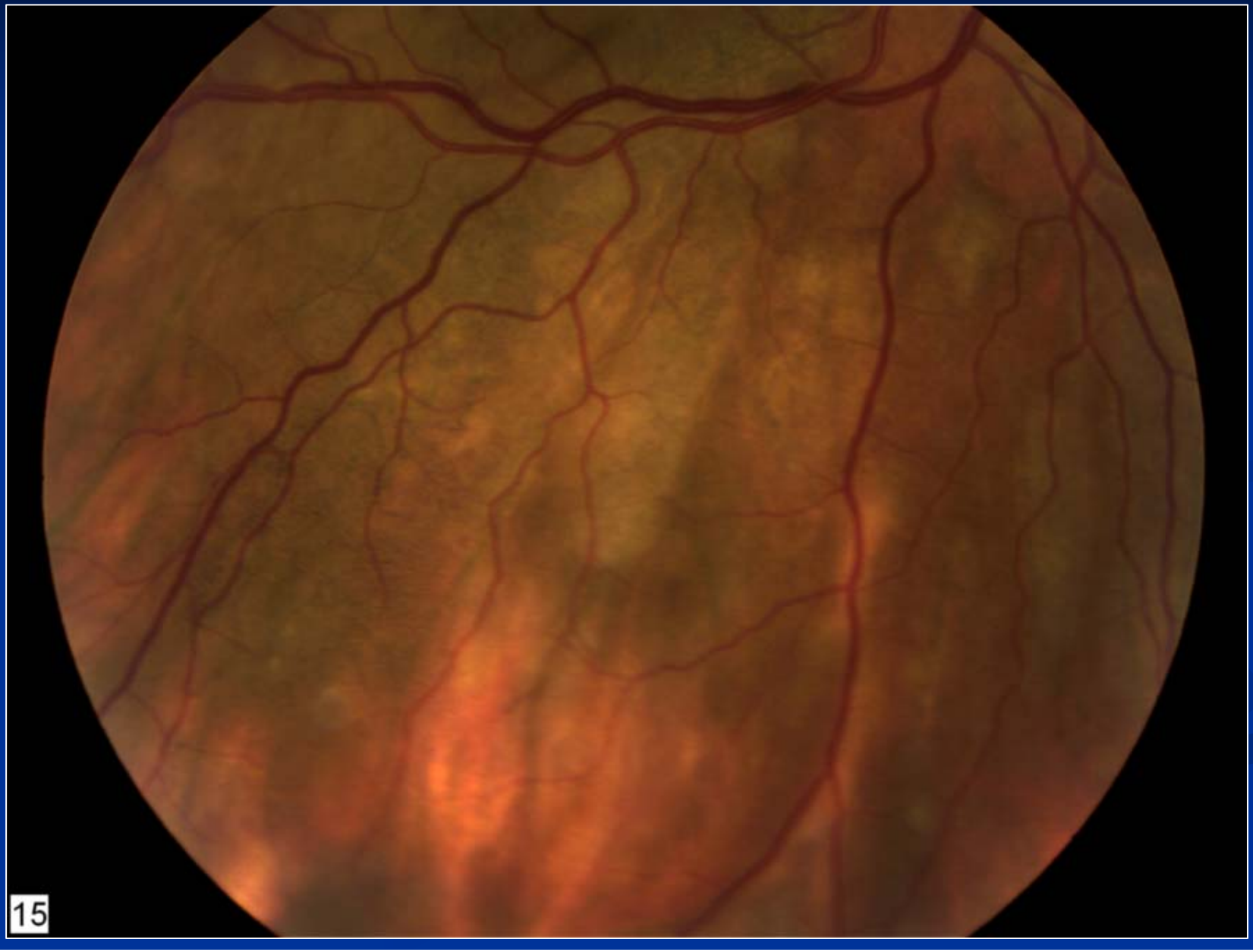
20/200

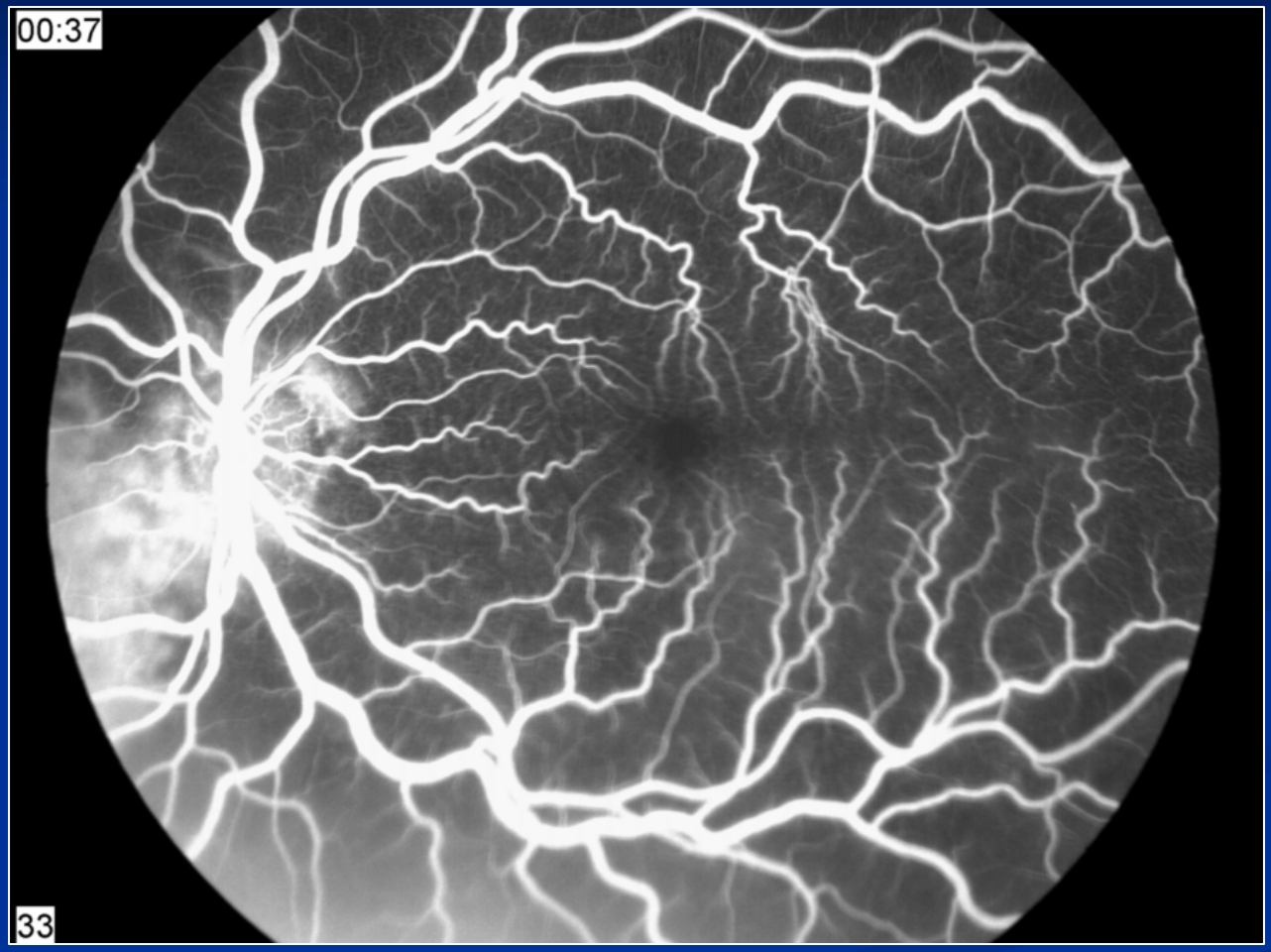


Temporal macula, OS



Mid periphery, OS

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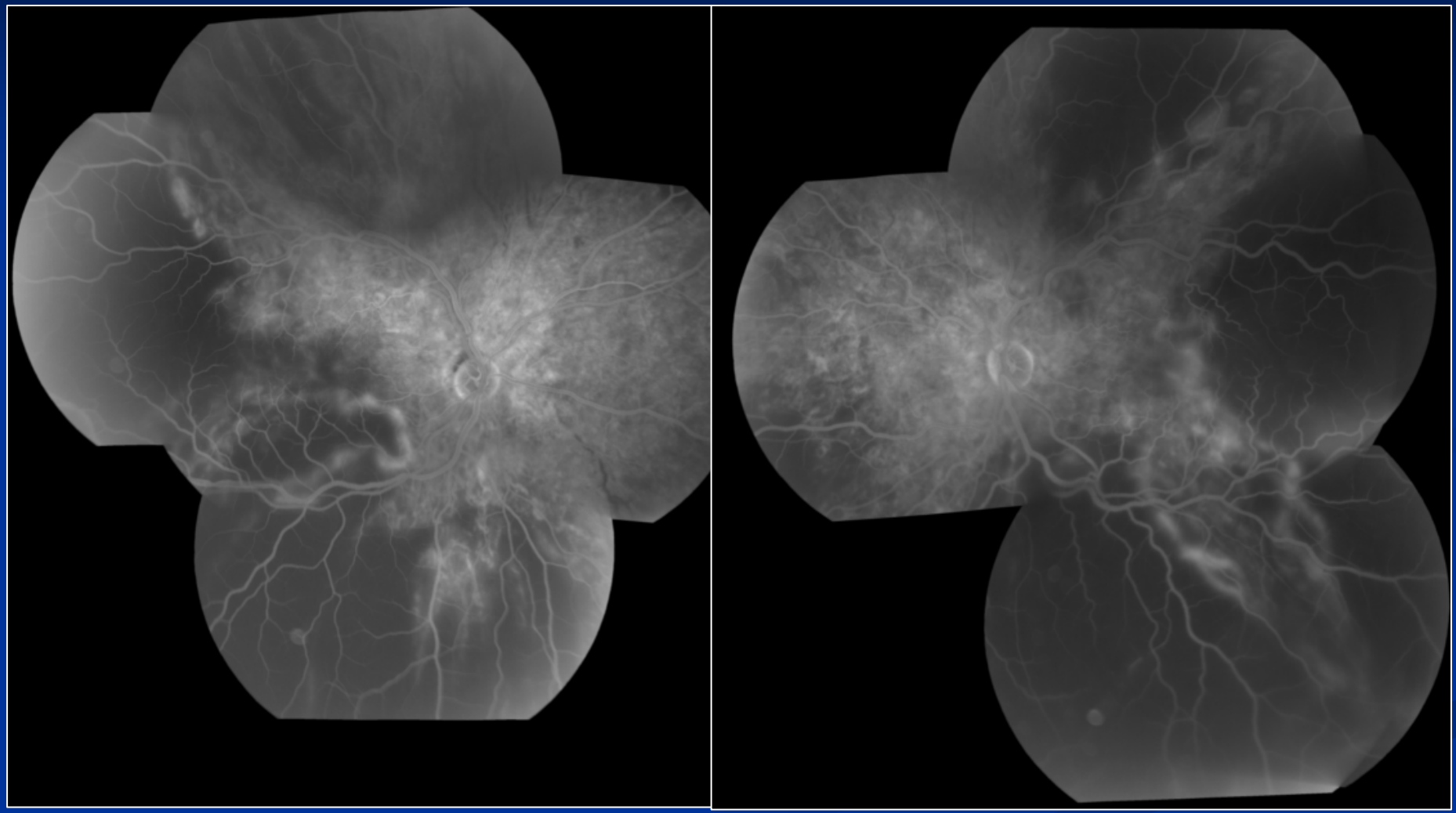


Clinical course

- Acute pulmonary edema during Cytoxan infusion
- Began consuming complement, forming immune complexes at MGH despite corticosteroid therapy
  - Acute renal failure
  - Pancytopenia
  - Dilated cardiomyopathy
  - Suspected cerebritis
- Rheumatology consultant felt uveitis was JIA
- ANA 1:160 homogeneous

Differential diagnosis?

Renal failure + choroidal infarction

- SLE
- Churg-Strauss syndrome
- Polyarteritis nodosa
- Microscopic polyangiitis
- ABD
- Wegener's granulomatosis
- Anti-phospholipid syndrome

Serologies

- CBC
  - WBC: 10.9 (high nl)
  - Hgb 11.6
  - Plt: 233 (nl)
- BUN 36
- Creatinine 2.3
- ESR 116
- CRP 30.9
- ssDNA IgG 416
- IL-2R 1771
- IL-6 8.48
- +HSV I IgG/IgM
- U/A
  - 3+ protein 3+
  - 20-40 RBC

- Normal or negative
  - ANA (2 substrates)
  - SM
  - SM/RNP
  - SSA
  - SSB
  - dsDNA
  - Cryoglobulins
  - C4
  - CH50
  - C3d
  - IL-12
  - TNF-alpha

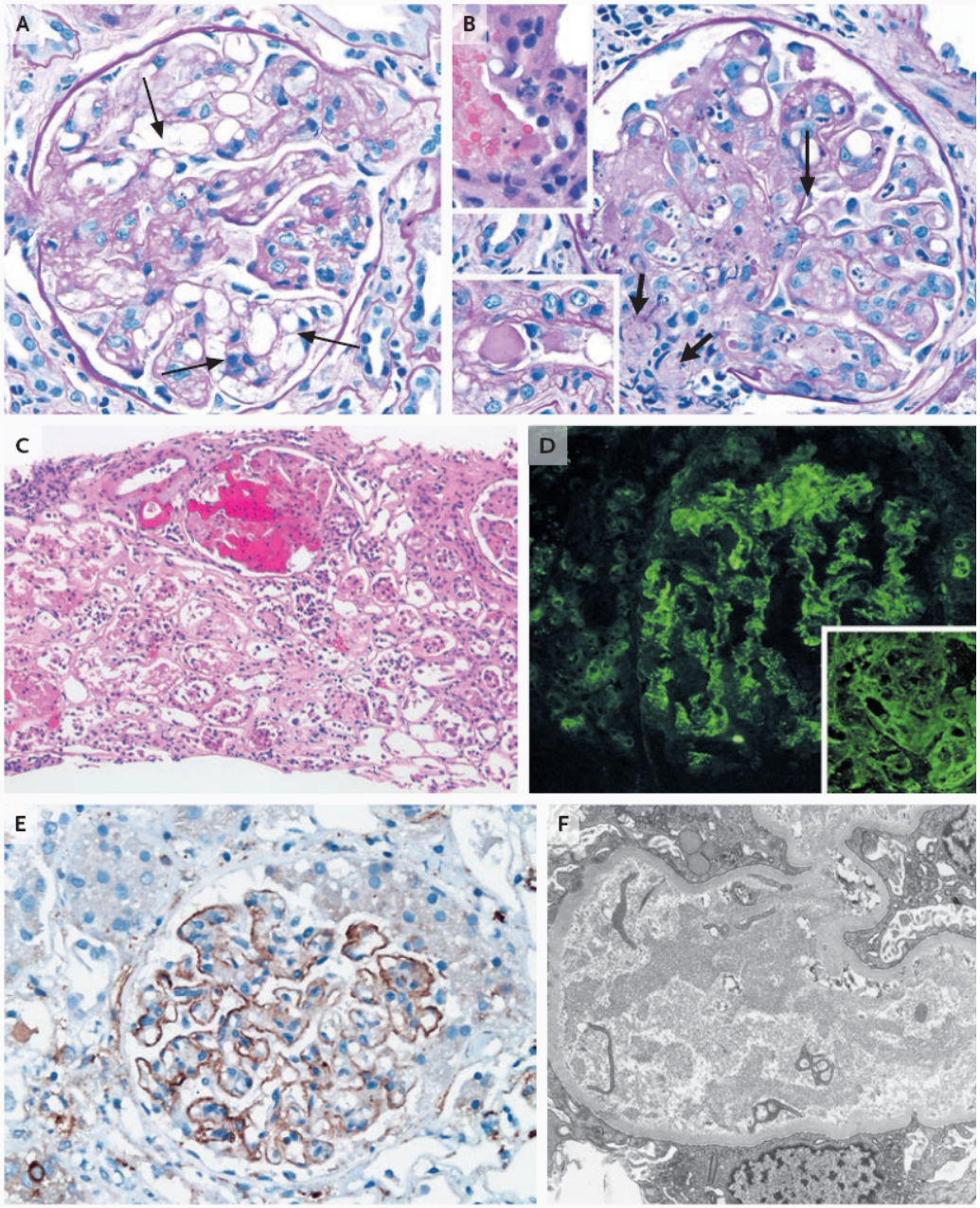


Figure 3 (facing page). Findings in the Renal-Biopsy Specimen.

Widespread endothelial swelling is present, with endothelial foam cells (Panel A, arrows; periodic acid–Schiff stain). Endothelial swelling has been described as the characteristic feature of preeclampsia ("endotheliosis"), but it is also found in cases of thrombotic microangiopathy. Segmental glomerular necrosis and congestion are prominent (Panel B, periodic acid–Schiff stain), with karyorrhexis and fibrin deposition. Red cells are seen in tubules (top inset). The afferent and efferent arterioles of this glomerulus are thrombosed (arrows), and the bottom inset shows another artery with thrombosis. The cortex shows patchy necrosis (Panel C, hematoxylin and eosin), with sloughing of the tubular epithelial cells. Immunofluorescence microscopy of glomeruli (Panel D) shows that IgM is prominent in the mesangium and along capillary loops. C3 was present in a distribution similar to that of IgM. The inset in Panel D shows fibrin in segments with necrosis and also in capillaries with less severe damage. Immunoperoxidase staining for the complement fragment C4d in formalin-fixed, paraffin-embedded tissue specimens (Panel E) shows prominent deposition of C4d along the glomerular, but not peritubular, capillaries, a feature that has been described in preeclampsia but not in thrombotic microangiopathy. Electron microscopy (Panel F) shows destruction and loss of the normal glomerular endothelial lining, with amorphous deposits and cell debris filling the lumen.

Pathologic diagnosis

- Renal biopsy revealed antiphospholipid antibodies
- Any hope for survival, visual improvement?

Antiphospholipid syndrome Sydney revision criterion

- Thrombosis
  - Arterial, venous, or vasculopathy
- Pregnancy morbidity
  - 3 or more first trimester losses
  - 1 or more late fetal losses
  - Severely preterm birth due to placental insufficiency
- Laboratory criteria
  - Lupus anticoagulant
  - Anticardiolipin IgG/IgM
  - Anti-beta 2 glycoprotein 1 IgG/IgM

Table 4. Classification of Catastrophic Antiphospholipid Antibody Syndrome.*

Preliminary criteria
Involvement of three or more organs or tissues
Development of manifestations simultaneously or in <1 wk
Histopathological evidence of small-vessel occlusion in at least one type of tissue
Presence of lupus anticoagulant, anticardiolipin antibodies, or both
Definite diagnosis
All four criteria met
Probable diagnosis
Involvement of two organs or tissues, and second, third, and fourth criteria met; or
All four criteria met, and a negative test for lupus anticoagulant or anticardiolipin antibody ≥6 wk after the first positive test or death within that period; or
First, second, and fourth criteria met; or
First, third, and fourth criteria met and development of a third manifestation in >1 wk but <1 mo despite anticoagulation

* Criteria are from Asherson et al.[4]

Catastrophic Antiphospholipid syndrome (CAPS)

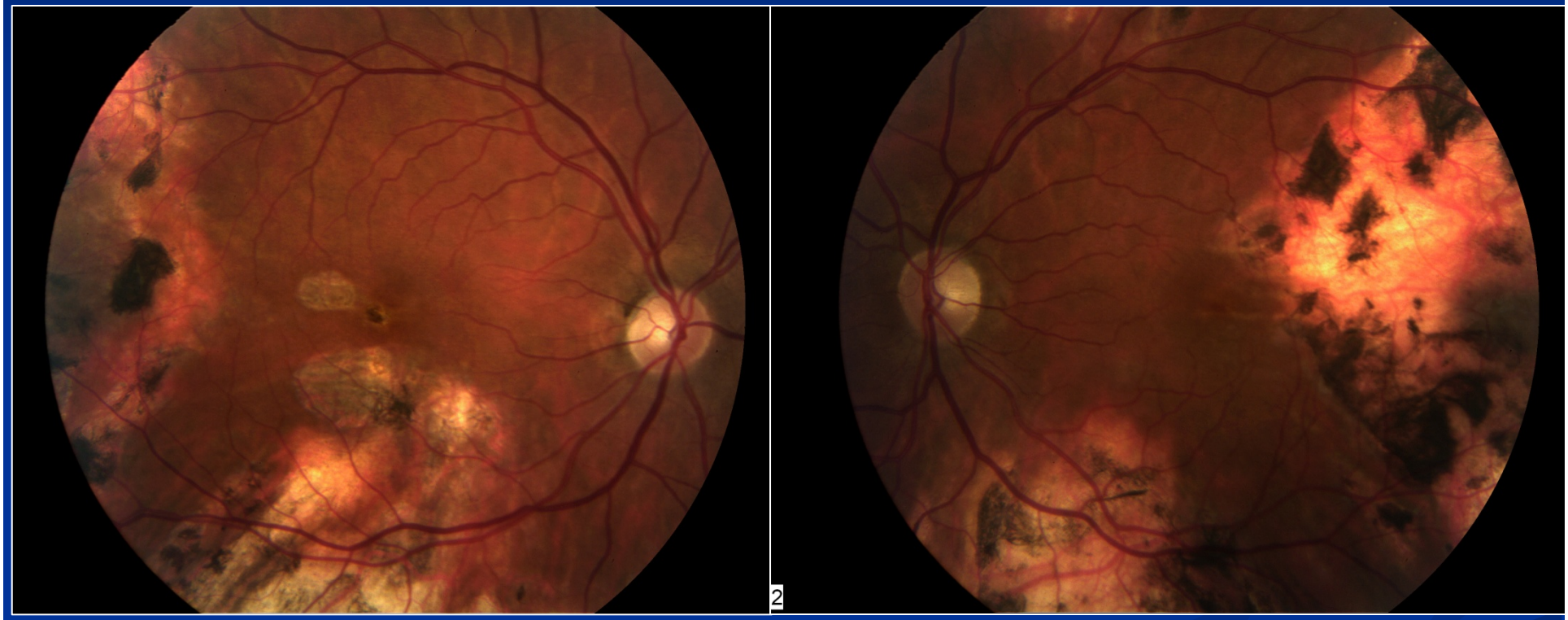
- Cytokine storm produced by intense endothelial dysfunction
- 50% mortality rate despite aggressive treatment at academic centers

Inpatient therapy

- IV methylprednisolone
- IV cyclophosphamide
- Plasmapheresis
- Rituxumab
- Heparin and warfarin

After 18 months: Off peritoneal dialysis

20/50 20/25



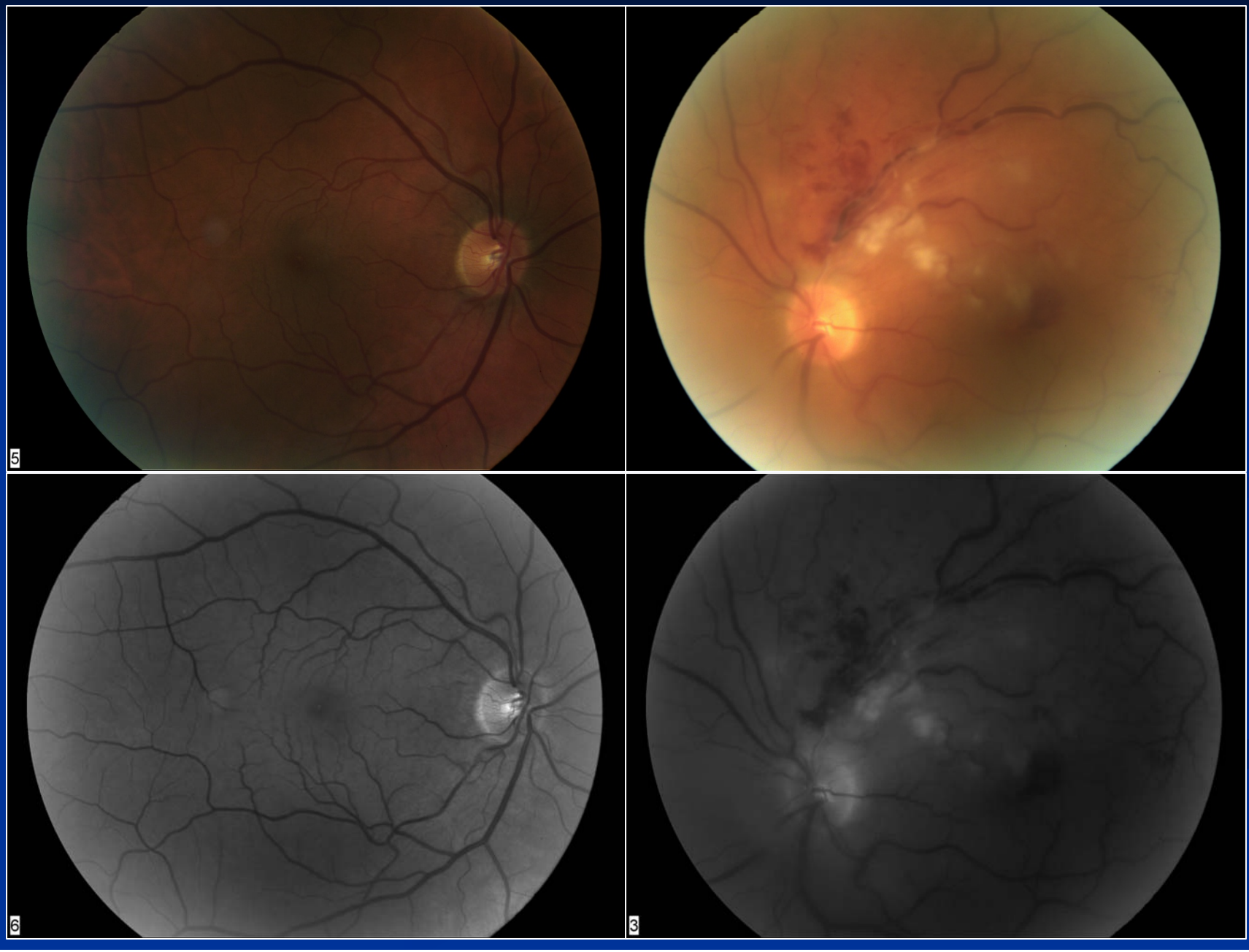
Magee CC, et al. NEJM 358:

Case III

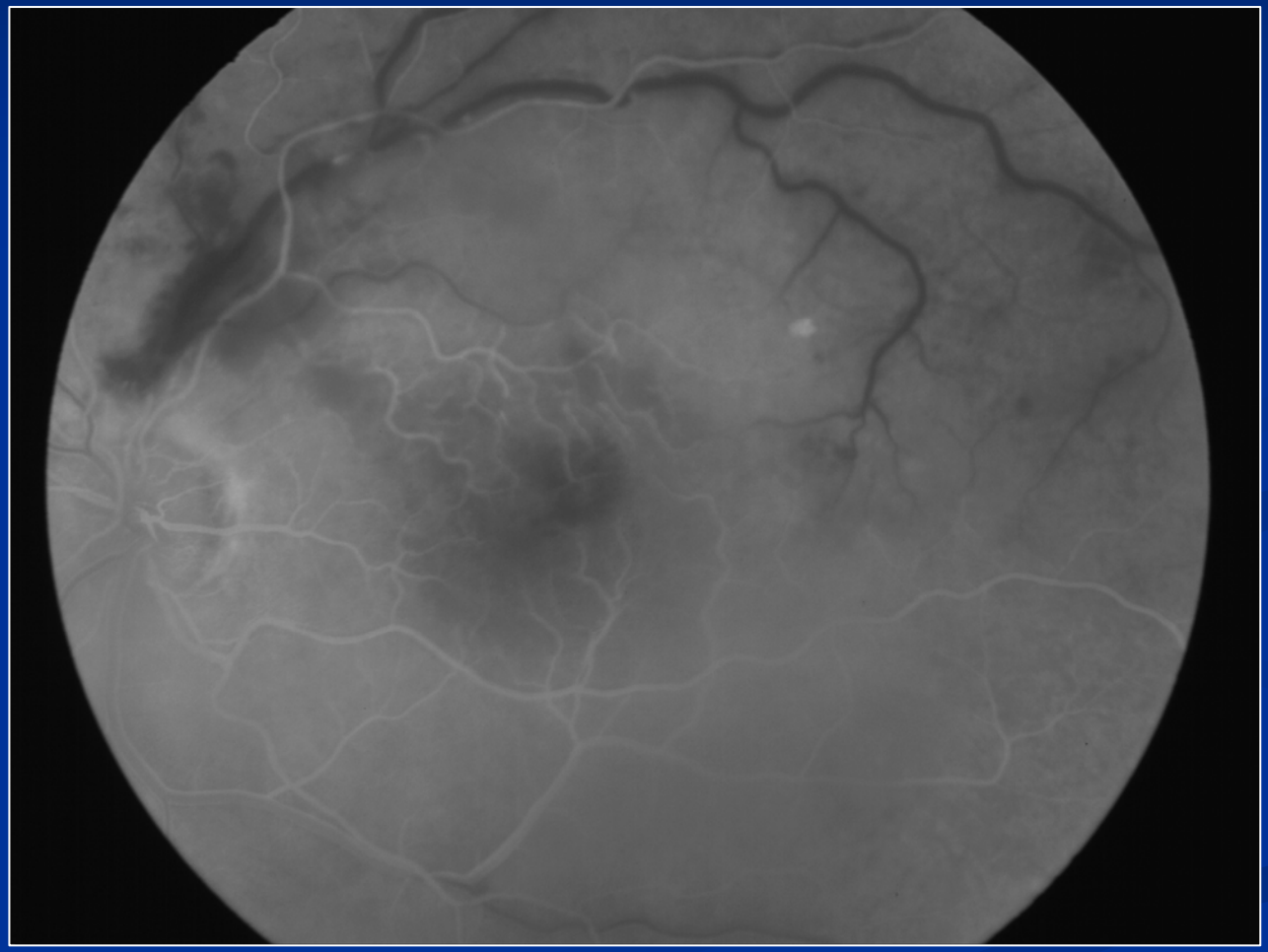
- 56 yo man referred for painless decreased vision OD of 2-3 months duration with inferior field loss
- PMH: TB, Lyme, Varicella, TIA age 28 after chiropractic manipulation
- MEDS: Valtrex (1 month), prior Acyclovir
- Allergies: NKDA
- ROS: night sweats
- SLE: traumatic iridectomy OD (sutured)

VA 20/20

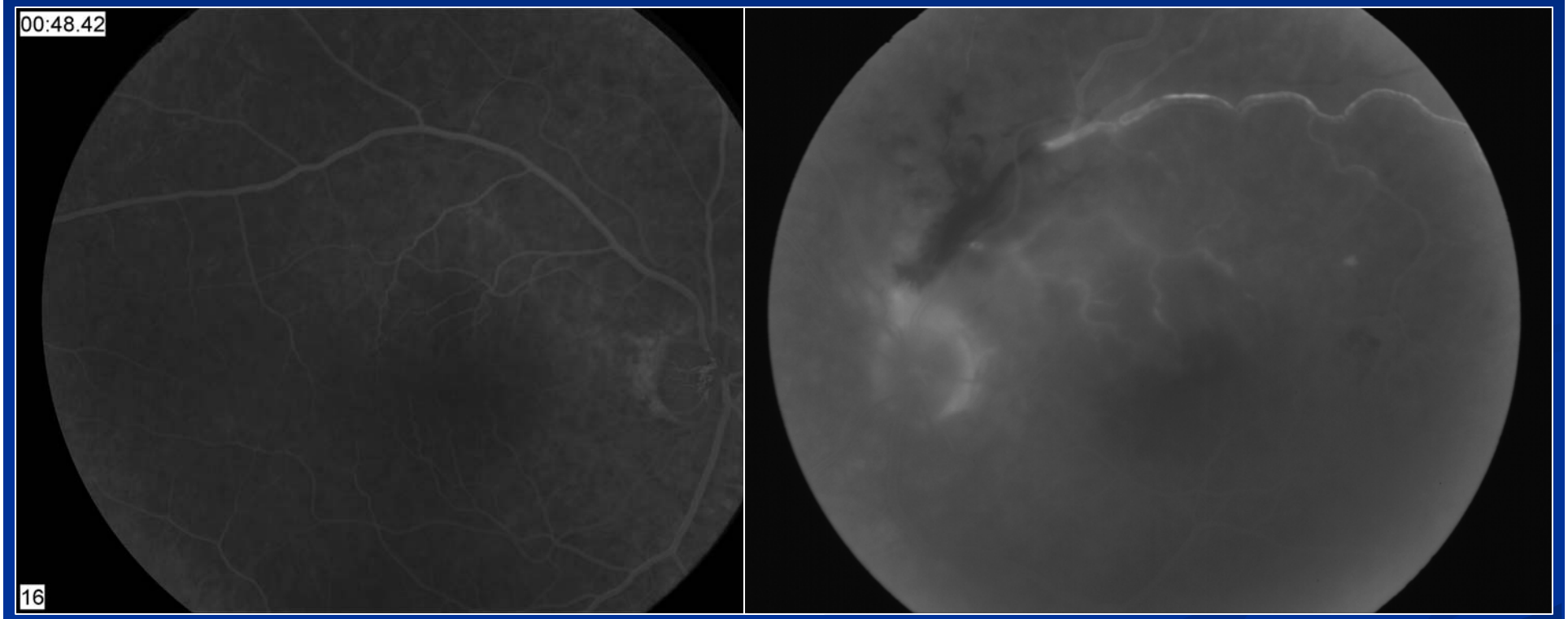
20/25 OS



AV Phase



Venous phase



Differential Diagnosis

- Atypical BRVO
- Atypical/resistant viral retinitis
- Lyme disease
- Retinal vasculitis (Eales)
- Masquerade syndrome

Serologic work-up

- Homocysteine elevated
- Factor V Leiden heterozygote
- Elevated Anti-thrombin III

- Normal or negative
  - ANA
  - c-ANCA
  - p-ANCA
  - HBV/HCV Ab titers
  - Complement levels
  - Immune complexes
  - IL-6 and TNF-alpha

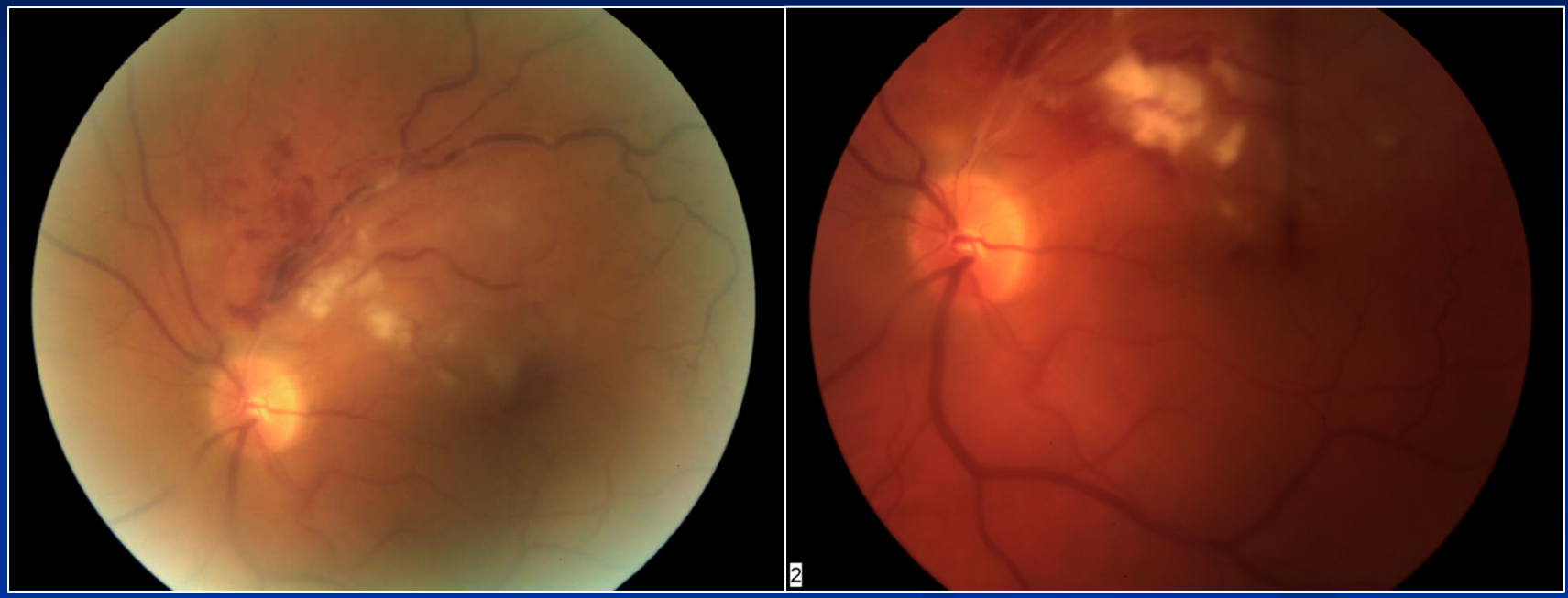
Treatment

- Acyclovir 1000mg IV
- Aspirin
- B complex vitamin and folic acid

Cardiology consultation

- Full anticoagulation not recommended
- Aspirin recommended
- Counseled on smoking cessation

Worsening clinical course



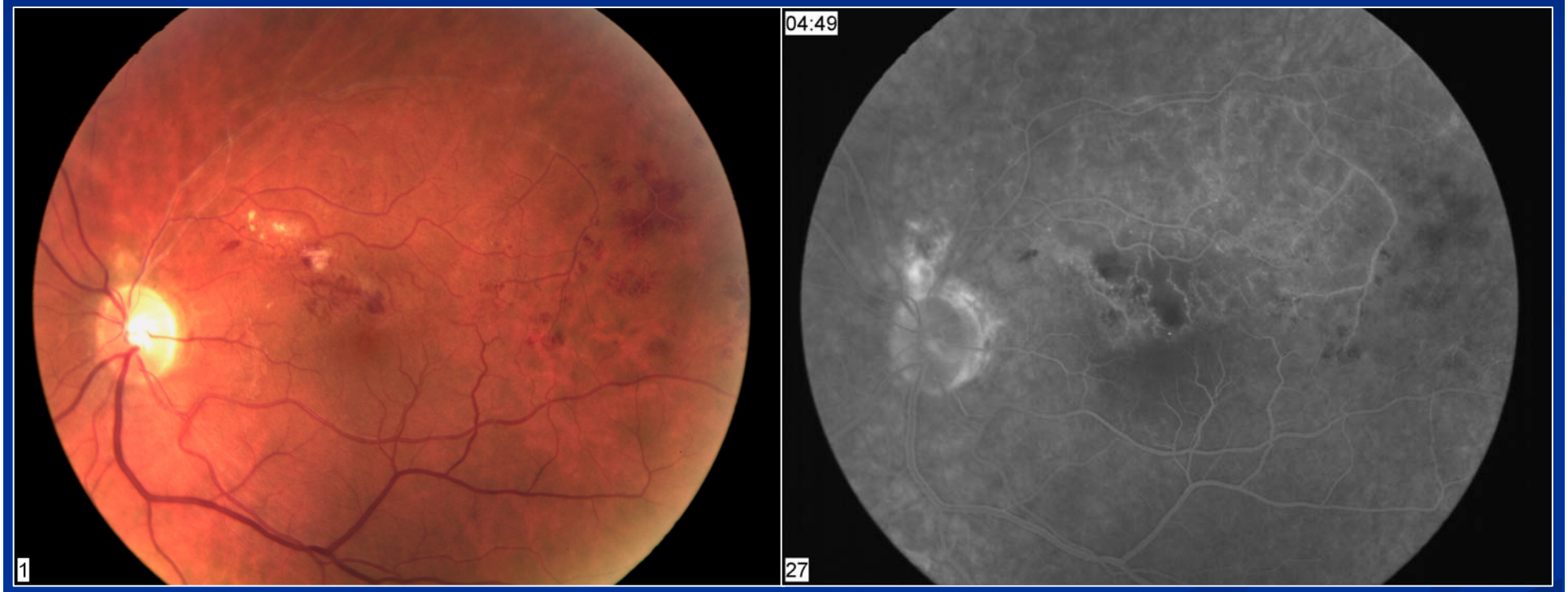
- Progression over 3 week period
- Diagnostic vitrectomy
  - Vitreous cytology: chronic inflammation
  - Vitreous HSV I/II, Toxo, and TB PCR negative

IgH gene rearrangement present

- Metastatic work-up
  - MR brain/orbits - normal
  - Lumbar puncture – normal
  - Bone marrow biopsy – normal
  - Whole body CT/PET - negative

Follow-up

- High dose IV methotrexate 10 week cycle



Large cell lymphoma masquerading as a viral retinitis.

- 37 year old woman with bilateral vitritis
- Initially developed necrotizing retinitis, OS compatible with acute retinal necrosis.
- Vitritis worsened over 2 months on acyclovir and systemic steroids.
- Diagnostic vitrectomy revealed large B-cell lymphoma with a predominance of lambda light chains.

de Smet MD, Nussenblatt RB, Davis JL, Palestine AG. Int Ophthalmol. 1990;14:413-7.

End of story?

- What is the risk of CNS involvement?
- What about the hematologic abnormalities?

Doctor, I have some questions…

Beware the engineer!

- What other types of tests might be done?
- What other cancers might develop?
- Do you recommend a special diet?
- When should I see you next?
- Should my eye be enucleated to reduce the risk of recurrence?
- What about colonoscopy?
- What about my upcoming dental procedure?
- Do I need a mental capacity test?
- What about more surgery?
- How will my Lyme disease affect all of this?
- How should I take care of my infusion port?

Recurrence risk?

- Dr. Hochberg stated 50%

The first shoe drops…

- 4 month follow-up MR brain reveals 1.2cm lesion adjacent to atrium of left lateral ventricle
- Good response to cycle of IV methotrexate; follow-up MR brain reveals size now 2mm

The second shoe drops…

- Developed pulmonary embolism after flight to New Mexico
- Rx: warfarin x6mo
- Dr. Hochberg recommends lifelong Rx if second event

Remain suspicious