CME MONOGRAPH

DIAGNOSIS
TREATMENT
CURRENT OPINIONS
MODERN APPROACHES

CHALLENGING EYE CARE

FACULTY

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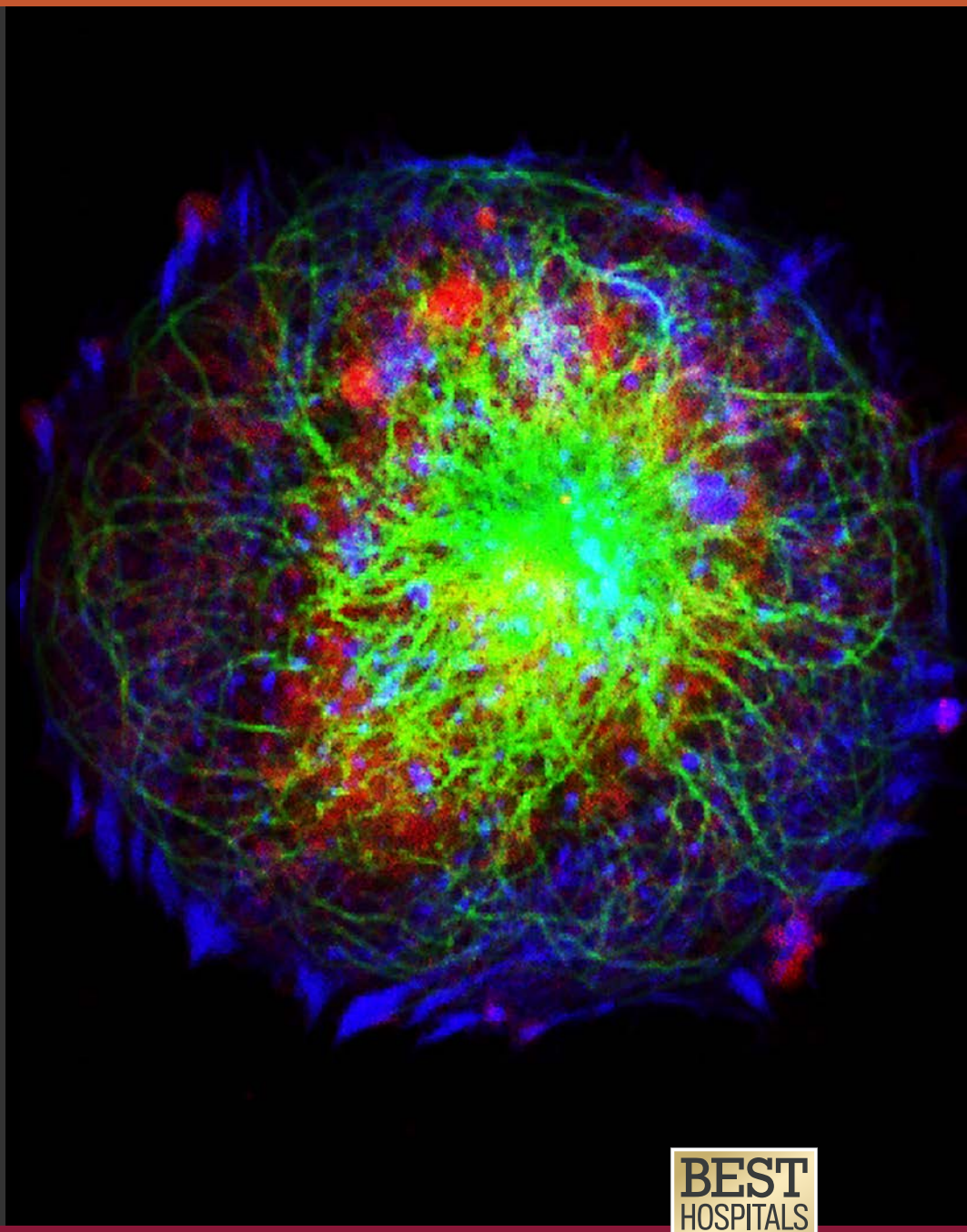

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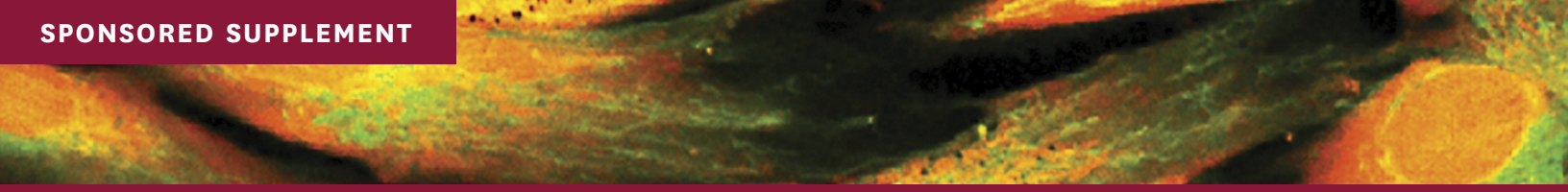

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This education activity consists of a supplement and nine (9) study questions. The participant should, in order, read the learning objectives contained in this supplement, read the supplement, answer all questions in the post test, and complete the Activity Evaluation/Credit Request form. To receive credit for this activity, please follow the instructions provided on the post test and Activity Evaluation/Credit Request form. This educational activity should take a maximum of 1.5 hours to complete.

CONTENT SOURCE

This continuing medical education (CME) activity collects some of our residents' most challenging and complicated grand rounds cases from LAC+USC Medical Center (LAC+USC).

ACTIVITY DESCRIPTION

LAC+USC is recognized as one of the largest public teaching hospitals in the U.S. and the largest single health care provider in Los Angeles County. LAC+USC treats more than 1 million ambulatory patients each year and is known as one of the busiest Level 1 trauma centers in the country.

TARGET AUDIENCE

This educational activity is intended for comprehensive community ophthalmologists.

LEARNING OBJECTIVES

Upon completion of this activity, participants will be better able to:

- Recognize and diagnose debilitating eye conditions sooner
- Identify the most appropriate treatments available
- Distinguish which techniques and procedures can be applied into practice

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CASE STUDY:
YOU'VE GOT A LOT OF NERVE

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HISTORY

- 29-year-old male who presented with 2 weeks of gradual "darkening" of vision simultaneously in both eyes
- PMH of HIV/AIDS (CD4 94, recently restarted HAART 3 months ago), recurrent cryptococcal meningitis s/p VP shunt, diffuse large B cell lymphoma s/p chemotherapy, and testicular cancer s/p orchiectomy
- Reports lethargy, but denies nuchal rigidity, photophobia or headache

EXAM FINDINGS

- VA: 20/400, 20/150
- IOP: 9, 10
- Pupils: RR OU, + RAPD OD
- Brightness sense: wnl
- Red saturation: 50% decreased on OD
- Color plates: 1/9 OU
- EOM: full OU
- SLE: unremarkable

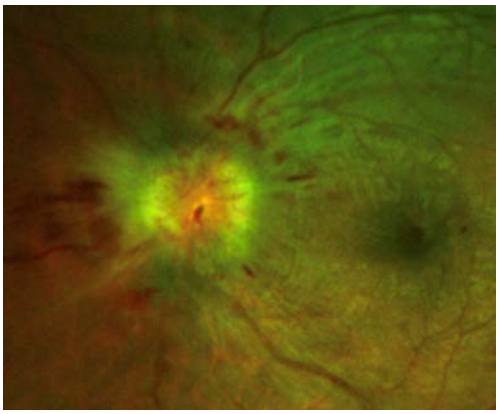


Figure 1: Left eye fundus photo at current presentation shows disc edema, retinal (Paton's) folds, and peripapillary hemorrhages.

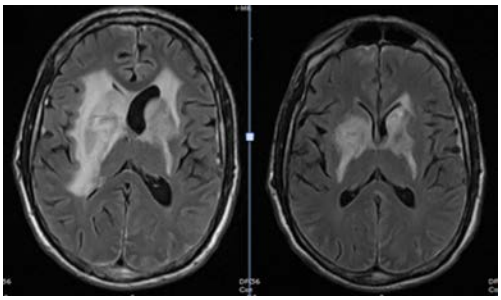


Figure 2: T2-FLAIR axial view MRI on left shows marked progression of signal abnormalities in deep parenchyma, compared with more subtle changes noted 3 months prior, pictured on right.

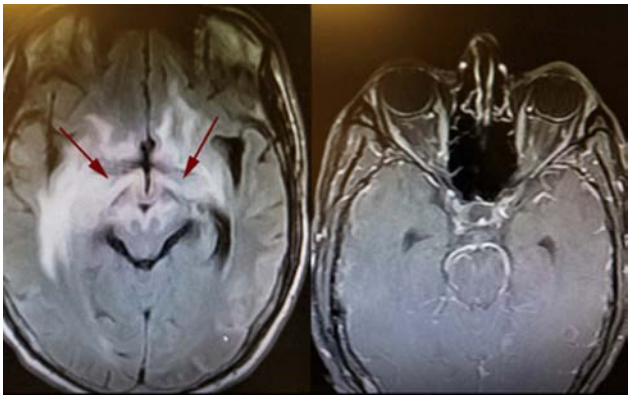


Figure 3: T2-FLAIR axial view MRI demonstrates new involvement of the optic tracts (arrows) and surrounding tissues (left image). The right image is T1-post-contrast orbital MRI, axial view showing subtle enhancement of the left > right optic nerve/sheath complex suggesting some degree of inflammation/infection/infiltration.

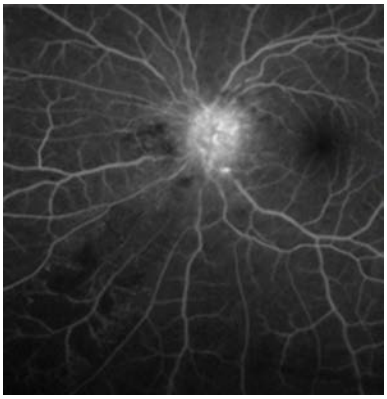
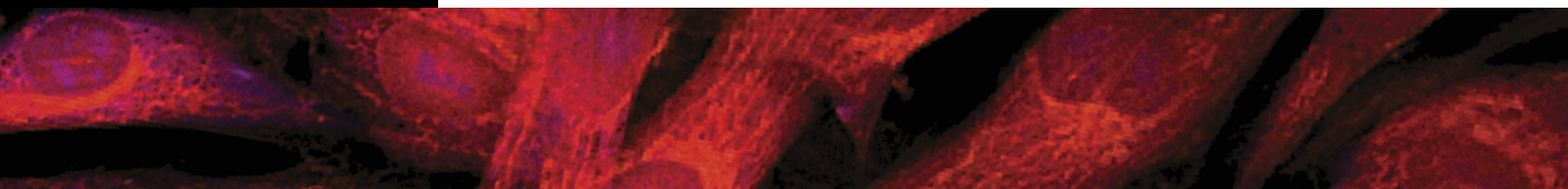


Figure 4: IVFA left eye shows disc leakage and inferonasal vascular non-perfusion consistent with a focal BRVO.



DIFFERENTIAL DIAGNOSIS

- Consider papilledema vs. non-papilledematous disc edema
- If elevated ICP (indicating papilledema), consider infectious etiologies (recurrent cryptococcal meningitis and associated impairment of arachnoid granulations), malignancy (CNS lymphoma, metastasis) or mechanical etiology (VP shunt malfunction)
- If normal ICP, consider infiltrative optic neuropathy (cryptococcal infiltration, lymphomatous infiltration) or other opportunistic infection (CNS toxoplasmosis, brain abscess, etc.)
- Also need to keep immune reconstitution inflammatory syndrome (IRIS) and progressive multifocal leukoencephalopathy (PML) on differential

ADDITIONAL INVESTIGATIONS

- VP shunt evaluation: no elevation of ICP
- CSF studies: Cryptococcal antigen 1:160
- MR spectroscopy: more consistent with infectious rather than malignant etiology

DIAGNOSIS

- Cryptococcal optic neuropathy/neuritis
- IRIS producing worsening brain parenchymal involvement with involvement of optic tracts

PATHOPHYSIOLOGY

With the determination of normal ICP, it was concluded that the optic neuropathy was most likely related to infiltration and inflammation of the optic nerves secondary to worsening cryptococcal infection rather than the more commonly seen scenario of papilledema secondary to elevated ICP from cryptococcal meningitis. It is estimated that approximately 75% of patients with cryptococcal meningitis will develop elevation of ICP (often severe) thought to result from the depositing of proteins and inflammatory byproducts along the arachnoid granulations. This impairs absorption of CSF. In our case, the hypothesis of worsening cryptococcal infection was supported by the observed increase in enhancing cystic lesions on follow-up brain MRI. There is also likely a component of IRIS given the patient's history of cryptococcal infection and re-initiation of HAART 3 months prior. The worsening parenchymal edema on MRI is consistent with this heightened inflammatory response.

TREATMENT

- High dose oral prednisone
- Fluconazole
- Continued HAART

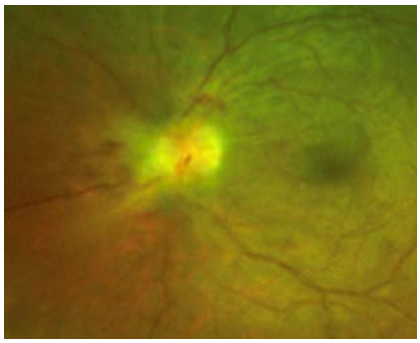


Figure 5: Left eye fundus photo 2 weeks after initial presentation shows improvement in disc edema and peripapillary hemorrhages while on anti-fungal treatment and prednisone.

PROGNOSIS AND FUTURE DIRECTIONS

- Mainstay of treatment is to continue to treat the presumed underlying infection while attempting to mitigate the immune reconstitution inflammatory response with steroids while continuing HAART.
- Our patient experienced improvement in vision bilaterally, reduction in disc edema and associated hemorrhages with the above treatment.
- Needs close follow-up for potential development of recurrent elevation of ICP.
- If worsening white matter involvement despite adequate anti-microbial control, then PML will need to move up on the differential, potentially requiring brain biopsy.

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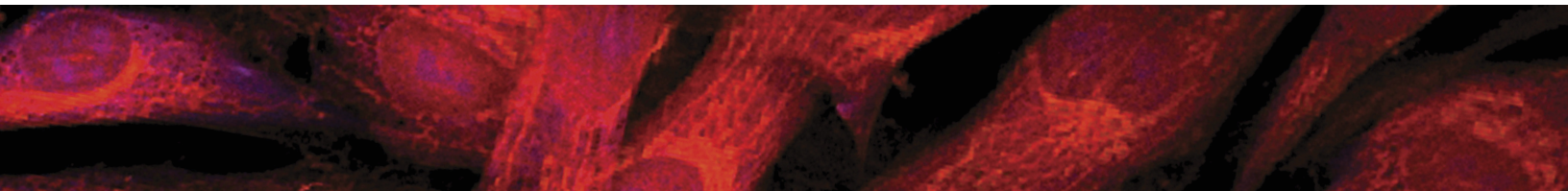

CASE STUDY:
IT SWELLS BUT ENDS WELL (THIS TIME)

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HISTORY

- 70-year-old woman with history of juvenile idiopathic arthritis (JIA), chronic smoldering uveitis controlled on Remicade (infliximab) infusions, topical prednisolone
- Advanced uveitic glaucoma OD
- History of cataract extraction OU at four years of age with aphakia, complicated by retained lens fragment OS
- OS lens fragment migration to visual axis with central macular edema
- Post-op week six status post (s/p) pars plana vitrectomy (PPV) OS with removal of lens fragment
- Persistent postoperative pressure spike OS on maximally tolerated topical anti-hypertensive drops, and oral methazolamide 25 mg TID
- s/p Ahmed Glaucoma Valve OS without complications
- POD1 exam unremarkable with patent tube
- POD2 patient with acute onset blurry vision OS, acute 10/10 eye pain presents to outside hospital emergency department
- Found to have OS intra-ocular pressure (IOP) of 50 decreased to 15 with topical regimen of Xalatan (latanoprost), CoSopt (timolol+dorzolamide), Alphagan (brimonidine) and oral Diamox (acetazolamide)

EXAM FINDINGS

- OS VA Light perception (preoperative 20/100)
- OS IOP 10 (max drops, Diamox)

Anterior Segment Exam OS

- Lids, lashes: Within Normal Limits (WNL)
- Conjunctiva/Sclera: supratemporal tube covered with subconjunctival hemorrhage
- Cornea: Decreased tear film; clear
- Iris: Superior surgical peripheral iridectomy; iris transillumination defects
- Anterior Chamber: 3 mm inferior hyphema with large central blood clot; tube in position, patent
- Lens: Aphakia

DIAGNOSIS

Suprachoroidal hemorrhage

DIFFERENTIAL DIAGNOSIS

- Suprachoroidal hemorrhage
- Choroidal effusions
- Endophthalmitis
- Retinal detachment

ADDITIONAL INVESTIGATION

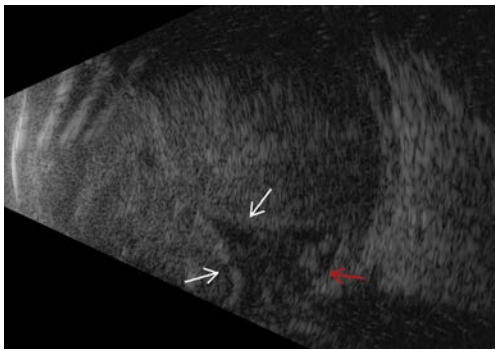

Figure 1: B-scan of the left eye L0300 showing appositional membranes (white arrows). Submembrane region is filled with hyperechoic matter (red arrow).

PATHOPHYSIOLOGY

Suprachoroidal space is a potential space external to choroid, deep to the sclera

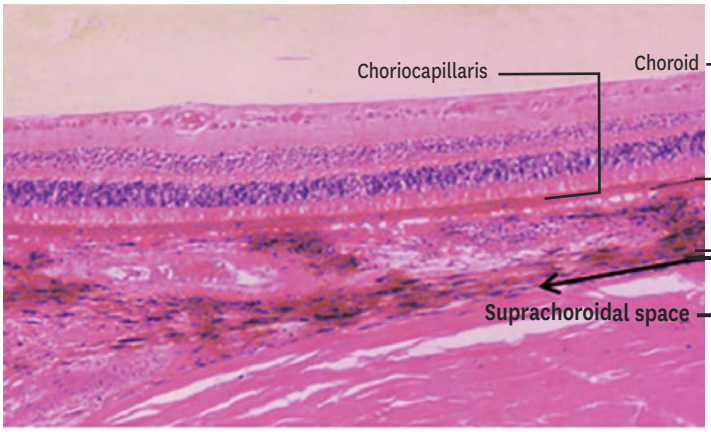

Figure 2: Significant pressure changes during intraocular surgery can cause shearing trauma to the highly vascularized choroid, resulting in hemorrhage of the posterior ciliary vasculature. (Image from BCSC Fundamentals)

TREATMENT

- If an intraoperative suprachoroidal hemorrhage is suspected, prompt closure of the surgical sites is recommended
- Increased IOP is managed with topical medications and oral carbonic anhydrase inhibitors
- Transscleral drainage is often performed to decompress the hemorrhage
- Primary data on timing of decompression is limited, but our department consensus suggests close monitoring for clot liquefaction on B-scan (seen as less echogenic than active clot) with drainage afterward
- Patient underwent successful transscleral drainage

PROGNOSIS AND FUTURE DIRECTIONS

- Classical risk factors of suprachoroidal hemorrhage include advanced age, glaucoma, myopia, aphakia, arteriosclerotic cardiovascular disease, hypertension, choroidal hemangiomas associated with Sturge-Weber syndrome, and intraoperative tachycardia.
- Delayed suprachoroidal hemorrhage occurs most often after glaucoma surgery, although it can occur after cataract extraction and posterior segment surgeries.
- Modern retrospective studies have determined risk factors for delayed suprachoroidal hemorrhages after glaucoma filtration procedures. Significant risk factors in these studies include anticoagulation, type of procedure (tube shunt higher risk than trabeculectomy), axial myopia and prior intraocular surgery.
- Prognosis is guarded. Glaucoma studies with delayed suprachoroidal hemorrhage show that patients had a preoperative mean VA logMAR of 0.8 (~20/125), with a post-event mean VA logMAR of 1.34 (Count Fingers to Light Perception range).

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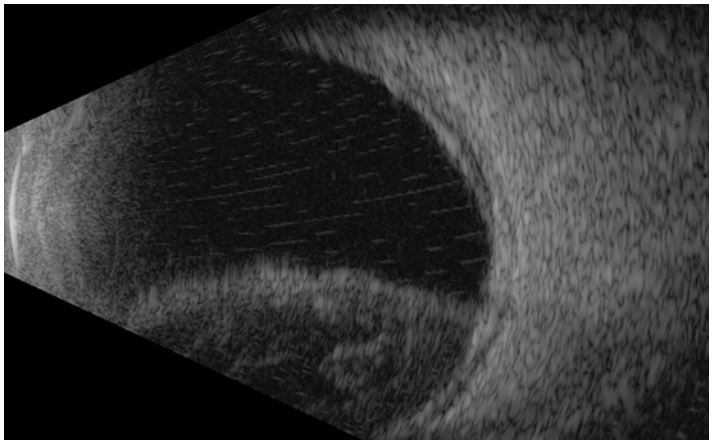

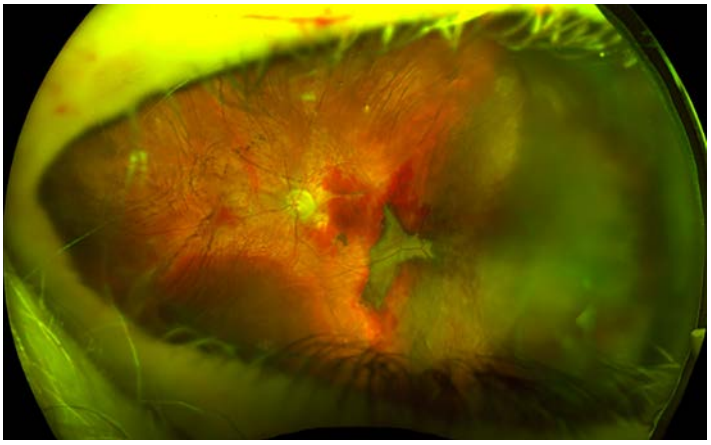

Figure 3: Left image is post-op week two B-scan (T600) showing temporal hemorrhage. Right image is color fundus at post-op month two showing residual temporal hemorrhage. Final best corrected visual acuity at post-op month four: 20/200.

CASE STUDY:
THAT DON'T KILL ME

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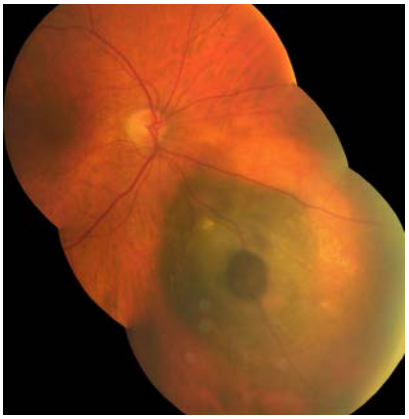
HISTORY

- 69-year-old Caucasian female presented for yearly dilated fundus exam for diabetic screening
- Patient had no visual complaints
- PMH: Well controlled T2DM, Lasik OU few years prior
- ROS negative

EXAM FINDINGS

- BCVA 20/20 OD, 20/25 OS, IOP WNL and EOMI OU with no APD
- Anterior segment exam on slit lamp only notable for 1+ NSC of the lens OU
- DFE revealed choroidal lesion nasal and inferior to optic nerve OD, WNL OS



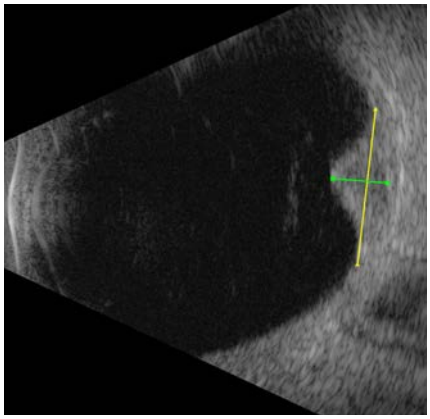


Figure 1: Dilated fundus exam on the left revealed a pigmented lesion located inferior and nasal to the optic nerve in the right eye with a central area of retinal invasion. Ultrasonography of the right eye illustrated a dome shaped choroidal lesion with measurements of 9.64 mm at the base, with thickness of 3.37 mm.

DIFFERENTIAL DIAGNOSIS

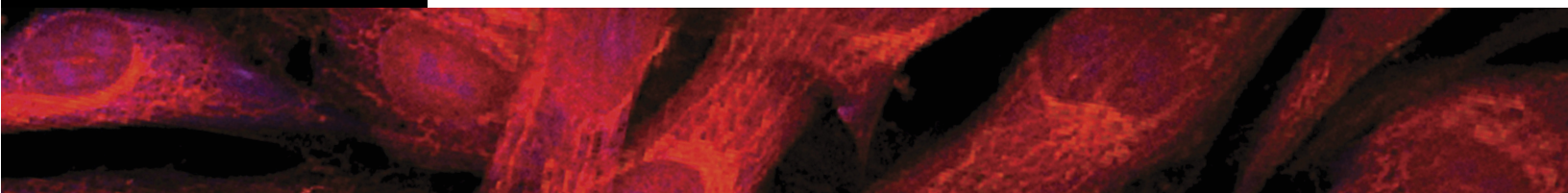
- Choroidal melanoma: most common primary intraocular tumor in adults

Risk factors include:

- Ages 50-70 years
- Caucasian
- Sun exposure especially in fair skinned individuals
- Visual symptoms are variable with 30% of patients asymptomatic at diagnosis
- Choroidal Nevus (present in ~5% of Caucasians, by strict size definitions —<1x5mm)

High risk features for growth of nevus include:

- Thickness greater than 2 mm
- Subretinal fluid
- Visual symptoms
- Orange pigment
- Margin near the optic disc
- Ultrasonographic hollowness
- Absence of halo or drusen
- Peripheral exudative hemorrhagic chorioretinopathy (however, no fluid, no drusen, no anticoagulation or other risk factors)
- Congenital hypertrophy of the RPE (however, would not be a new finding; color of lesion is atypical)
- Circumscribed choroidal hemangioma (however, this lesion is the wrong color)
- Choroidal metastasis (however, generally amelanotic unless from melanoma)



ADDITIONAL INVESTIGATIONS

CT chest, abdomen, pelvis done for evaluation of metastatic disease and staging was negative

DIAGNOSIS

Choroidal melanoma

PATHOPHYSIOLOGY

- Melanomas arise from the abnormal proliferation of melanocytes, which are melanin-producing cells derived embryologically from neural crest cells.
- It is the most common primary intraocular tumor, although accounting for only 5% of all cases of melanoma with an incidence of 5.1 per million per year in the United States.
- Genetic alterations such as monosomy of chromosome 3 or mutation/inactivation of BRCA associated protein 1 (BAP1) have been found to have a higher risk of metastasis.

TREATMENT

Depending on the tumor's size treatment options include:

- Plaque radiotherapy
- Proton beam therapy
- Stereotactic radio surgery
- Enucleation

- Given that the tumor dimensions were classified as medium-sized, iodine-125 radioactive episcleral plaque brachytherapy was pursued with the USC Eye Physics plaques, developed at USC. A CT orbits was done for 3D treatment planning.
- The plaque was placed in the right eye with an Rx of 85 Gy to the apex of the tumor and then removed one week later after the completion of brachytherapy.
- The USC Ocular Oncology Service has described a novel method for plaque placement using a toric marker.
- A surgical video of placement of the USC Eye Physics plaques can be found online here (link: http://www.eye-physics.com/PS/PS6/UserGuide/EyePlaqueMovie.html) or on the USC Ocular Oncology Facebook page (link: https://www.facebook.com/usceyeonc/).
- A fine needle aspiration biopsy for gene expression profiling was offered to the patient, which she declined.

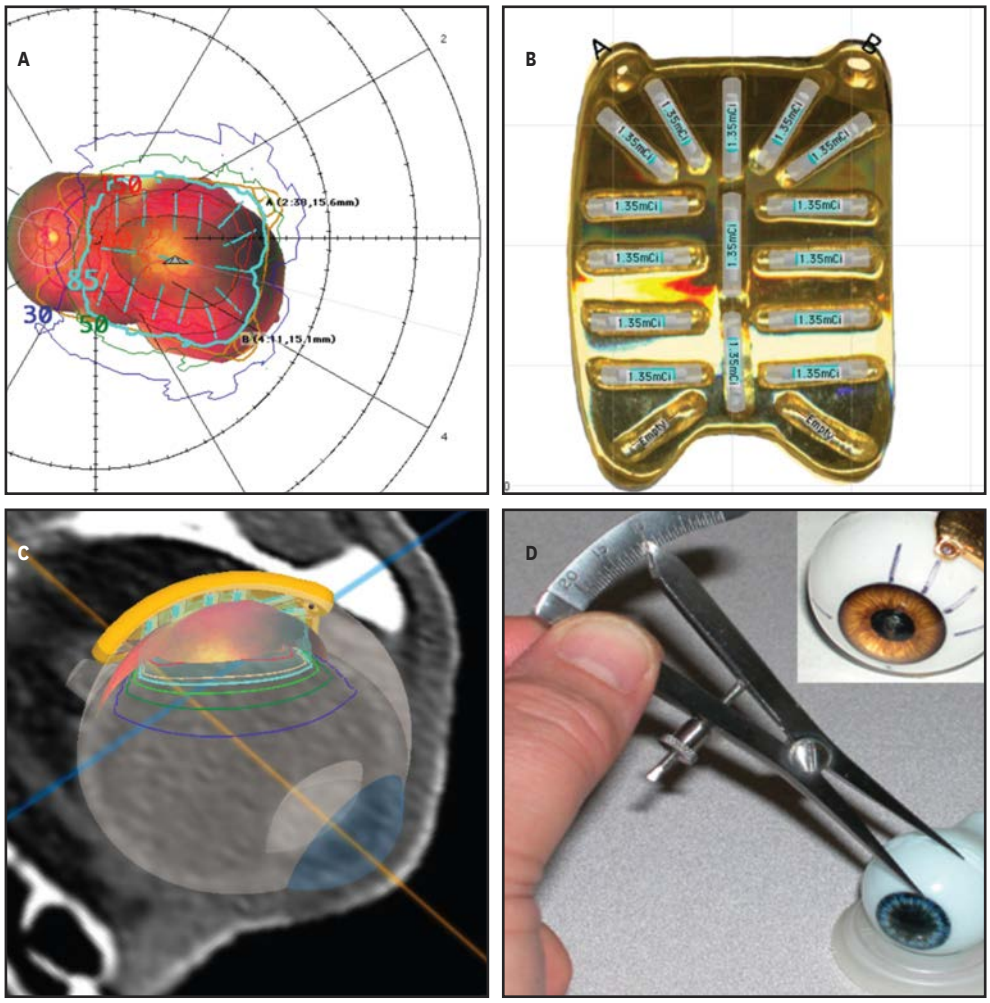
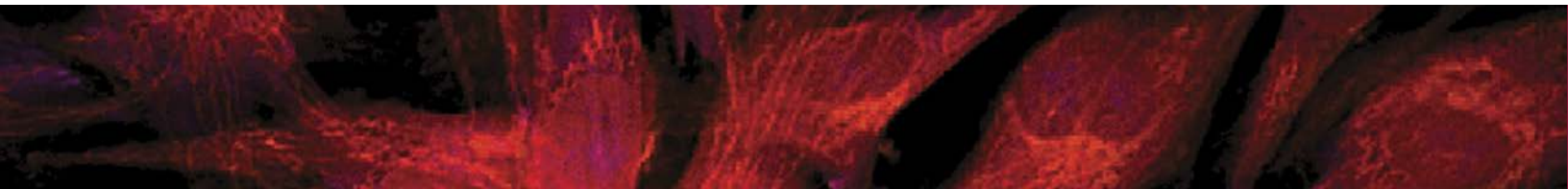
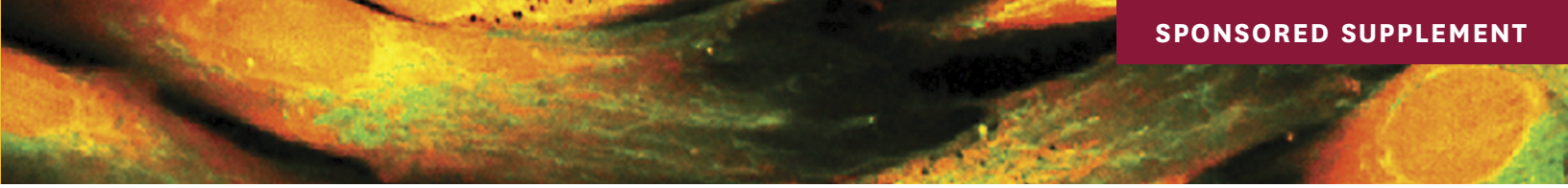


Figure 2: Panel A shows the digitized retina tumor margins. **Panel B** shows an iodine-125 plaque with collimating slots. **Panel C** shows the use of Plaque Simulator software as it integrates the fundus photography and ocular ultrasonography with CT images to create a three-dimensional model of the eye, tumor, plaque and seeds for planning purposes. **Panel D** shows an example of plaque placement measurement from the limbus along meridians (clock hours) on the eye (Taken from Berry JL et al. *JAMA Ophthalmol* 2013).





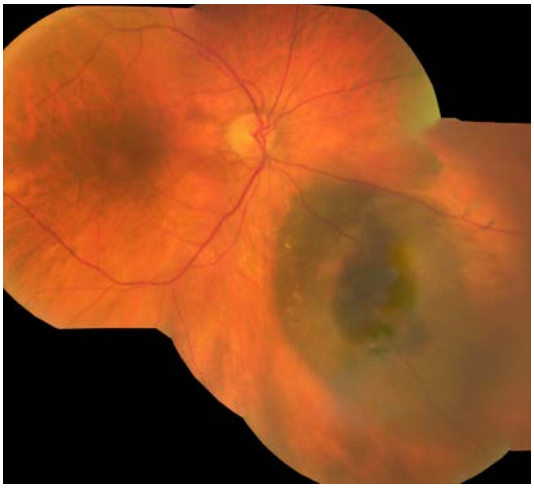
PROGNOSIS AND FUTURE DIRECTIONS

- As described in COMS report No. 28, the risk of metastatic disease is similar whether patients undergo enucleation or brachytherapy for medium-size melanoma. This risk is 17-21% at 12 years.
- The most common site of metastasis is to the liver.
- As reported by Berry JL et al. *JAMA Ophthalmol* 2013, the USC Eye Physics plaques have compared favorably to the COMS plaques given its customization to the patient's tumor characteristics.

Key findings illustrated in Table 1 are:

- Reduced tumor recurrence and enucleation rates at 5 years compared to the COMS plaques.
- Reduced adverse radiation effects including radiation optic neuropathy, retinopathy and cataracts from USC Eye Physics plaques, in a smaller cohort of patients.
- Patient BCVA 20/20 OU with no adverse symptoms of optic neuropathy, radiation retinopathy, or accelerated cataracts noted, however she will be followed closely for adverse effects.
- Patient undergoes liver ultrasound and liver function tests every six months, which have been negative to date.
- While declined by this patient, many patients choose to have a biopsy for a PCR-based gene expression profiling of 15 genes, which classifies tumors as Class 1A, 1B and 2. The risk of developing metastatic disease at five years, as reported by Castle Biosciences, is 2%, 21% and 72% respectively. Class 2 tumors have a much higher risk of metastatic disease and imaging surveillance can be appropriately targeted with this information.
- Patient follows up with the USC Ocular Oncology Service every three-to-four months to monitor for tumor regression, surveillance for recurrence, and adverse effects of radiation.

	Collaborative Ocular Melanoma Study	University of Southern California
Baseline Clinical Characteristics		
Patients, No.	638	82
Median follow up, mo	67	47
Patients, %		
White	98	94
Male	50	60
Mean tumor height, mm	4.2	4.6
Mean basal diameter, mm	11.5	10.7
Anterior border posterior to equator, %	55	57
Tumor Control		
Dose to tumor apex, Gy	85	85
Dose to optic nerve, Gy	52.1	46.6
Dose to macula/fovea, Gy	79	66.6
Dose to lens, Gy	15.6	15.2
Kaplan-Meier-estimated tumor recurrence at 5 y, %	10	3.0
Enucleation at 5 y, %	13	3.0
Metastatic disease at 5 y, %	10	11
Visual and Ocular Outcomes, %		
Preoperative visual acuity		
20/40 or better	70	63
20/200 or worse	10	18
Postoperative visual acuity		
20/40 or better	34	35
20/200 or worse	43	43
Optic neuropathy	27	15
Radiation retinopathy	49	38
Cataracts	83	32



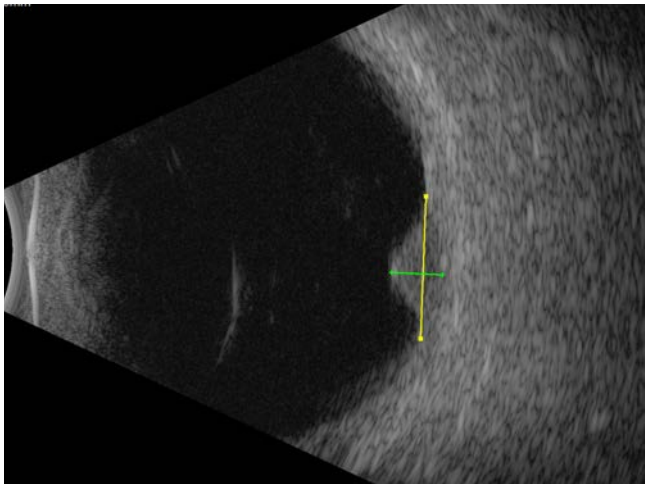
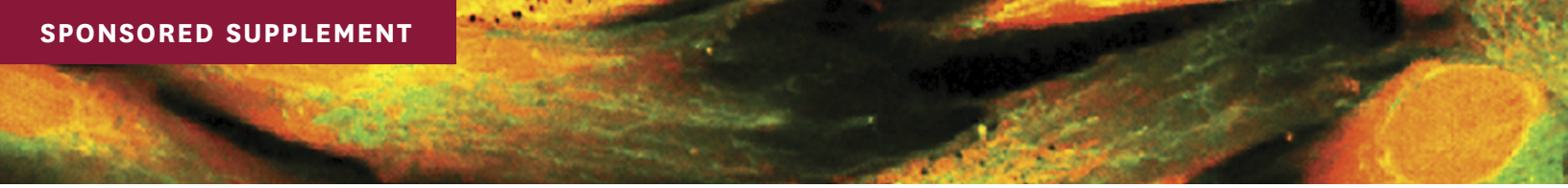


Figure 3: At six month post-operative follow-up, fundus imaging shows early choroidal atrophy and ultrasonography demonstrates regression of tumor parameters with measurements of 8.07 mm at the base, with thickness of 2.86 mm.



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CME Post Test Questions

See detailed instructions under the heading To Obtain *AMA PRA Category Credit* on the following page.

To obtain *AMA PRA Category 1 Credit* for this activity, complete the CME Post Test by writing the best answer to each question in the Answer Box located on the Activity Evaluation/ Credit Request form at the bottom of the following page. Alternatively, you can complete the CME Post Test online at https: usceye.org/challengingcases

1. Vision loss in the setting of cryptococcal meningitis can occur due to:

   a) Raised intracranial pressure
   b) Direct infection / infiltration of the optic nerves
   c) Involvement of central visual pathway
   d) All of the above

2. IRIS refers to:

   a) Infection of the pupillary dilator muscle
   b) Activation of the immune system following re-institution of HAART therapy
   c) Intracranial pressure syndrome
   d) HIV infection-related retinopathy

3. Progressive Multifocal Leukoencephalopathy (PML) most often occurs in the setting of:

   a) Multiple Sclerosis
   b) HIV-related immunosuppression
   c) Drug reaction
   d) CNS Herpes virus infection

4. What are the risks for suprachoroidal hemorrhage?
   a) Aphakia
   b) Glaucoma
   c) Advanced age
   d) All of the above

5. What is the time frame for drainage of suprachoroidal hemorrhage?
   a) Immediately
   b) Two months later
   c) Two weeks later
   d) No consensus

6. What is the priority of managing patients with suprachoroidal hemorrhage?

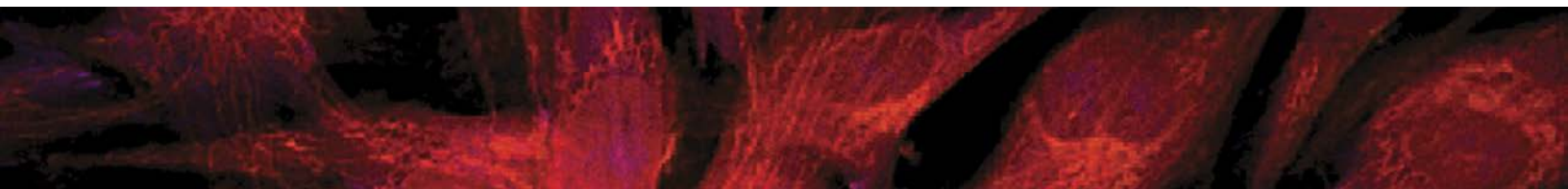
   a) Maintaining adequate IOP
   b) Improving vision
   c) Referring to retina physician immediately
   d) Drainage of hemorrhage

7. The best diagnostic imaging for choroidal melanoma is:

   a) Fluorescein angiography
   b) B-scan ultrasonography
   c) CT orbit
   d) Orbital MRI with gadolinium

8. True or False: BAP1 mutations carry a higher prognostic risk of metastatic disease.

9. True or False: A patient presents with a choroidal melanoma which is 9.8mm in height and 14mm at the base. The eye with the melanoma MUST be enucleated to decrease the risk of metastatic disease?



ACTIVITY EVALUATION/CREDIT REQUEST

Original Release: November 1, 2017
Last Review: September 28, 2017
Expiration: November 30, 2018

Challenging Eye Care: Diagnosis, Treatment, Current Opinions, Modern Approaches

To receive *AMA PRA Category 1 Credit*™, you must complete this **Evaluation** form and the **Post test**. Record your answers to the **Post test** in the **Answer Box** located below. Mail or fax this completed page to **Keck School of Medicine of USC** – **Office of Continuing Medical Education**, 1540 Alcazar Street, CHP 223, Los Angeles, CA 90033 (Fax: 323-442-3454). Your comments help us to determine the extent to which this educational activity has met its stated objectives, assess future educational needs, and create timely and pertinent future activities. Please provide all the requested information below. This ensures that your certificate is filled out correctly and is mailed to the proper address. It also enables us to contact you about future CME activities. Please print clearly or type. Illegible submissions cannot be processed.

PARTICIPANT INFORMATION (*Please Print*) ❑ Home ❑ Office

Last Name _____ First Name _____

Specialty _____ Degree ❑ MD ❑ DO ❑ OD ❑ PharmD ❑ RPh ❑ NP ❑ RN ❑ PA ❑ Other _____

Institution _____

Street Address _____

City _____ State _____ ZIP Code _____ Country _____

Email _____ Phone _____ Fax _____

Please note: We do not sell or share email addresses. *They are used strictly for conducting post-activity follow-up surveys to assess the impact of this educational activity on your practice.*

Learner Disclosure: To ensure compliance with the US Centers for Medicare and Medicaid Services regarding gifts to physicians, **Keck School of Medicine of USC- Office of Continuing Medical Education** requires that you disclose whether or not you have any financial, referral, and/or other relationship with our institution. **CME certificates cannot be awarded unless you answer this question.** For additional information, please call the KSOM CME Office at (323)442-2555.

❑ Yes ❑ No I and/or my family member have a financial relationship with USC Roski Eye Institute and/or refer Medicare/Medicaid patients to it.

❑ I certify that I have participated in the entire activity and claim 1.5 AMA PRA Category 1 Credits.

Signature Required _____ **Date Completed** _____

OUTCOMES MEASUREMENT

❑ Yes ❑ No **Did you perceive any commercial bias in any part of this activity? IMPORTANT! If you answer "Yes," we urge you to be specific about where the bias occurred so we can address the perceived bias with the contributor and/or in the subject matter in future activities.**

_____

Circle the number that best reflects your opinion on the degree to which the following learning objectives were met:
5 = Strongly Agree 4 = Agree 3 = Neutral 2 = Disagree 1 = Strongly Disagree

Upon completion of this activity, I am better able to:

• Demonstrate the ability to differentiate between papilledema vs. non-papilledematous disc edema	5	4	3	2	1
• Recognize the risks for suprachoroidal hemorrhage	5	4	3	2	1
• Identify the best diagnostic imaging for choroidal melanoma	5	4	3	2	1
• Distinguish which techniques and procedures can be applied into practice	5	4	3	2	1

1. Please list one or more things, if any, you learned from participating in this educational activity that you did not already know. _____

_____

2. As a result of the knowledge gained in this educational activity, how likely are you to implement changes in your practice?
4 = definitely will implement changes 3 = likely will implement changes 2 = likely will not implement any changes 1 = definitely will not make any changes

4 3 2 1

Please describe the change(s) you plan to make: _____

_____

3. Related to what you learned in this activity, what barriers to implementing these changes or achieving better patient outcomes do you face?

_____

_____

4. Please check the Core Competencies (as defined by the Accreditation Council for Graduate Medical Education) that were enhanced for you through participation in this activity.
❑ Patient Care ❑ Practice-Based Learning and Improvement ❑ Professionalism
❑ Medical Knowledge ❑ Interpersonal and Communication Skills ❑ Systems-Based Practice

5. What other topics would you like to see covered in future CME programs? _____

_____

ADDITIONAL COMMENTS _____

_____

_____

_____

POST TEST ANSWER BOX

1	2	3	4	5	6	7	8	9