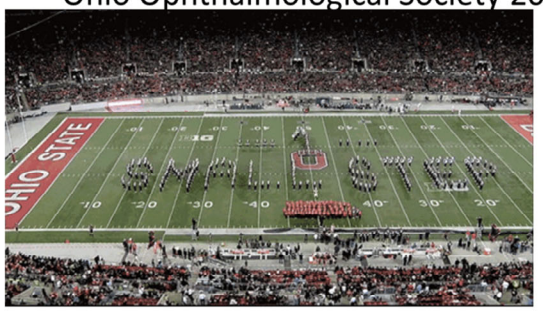
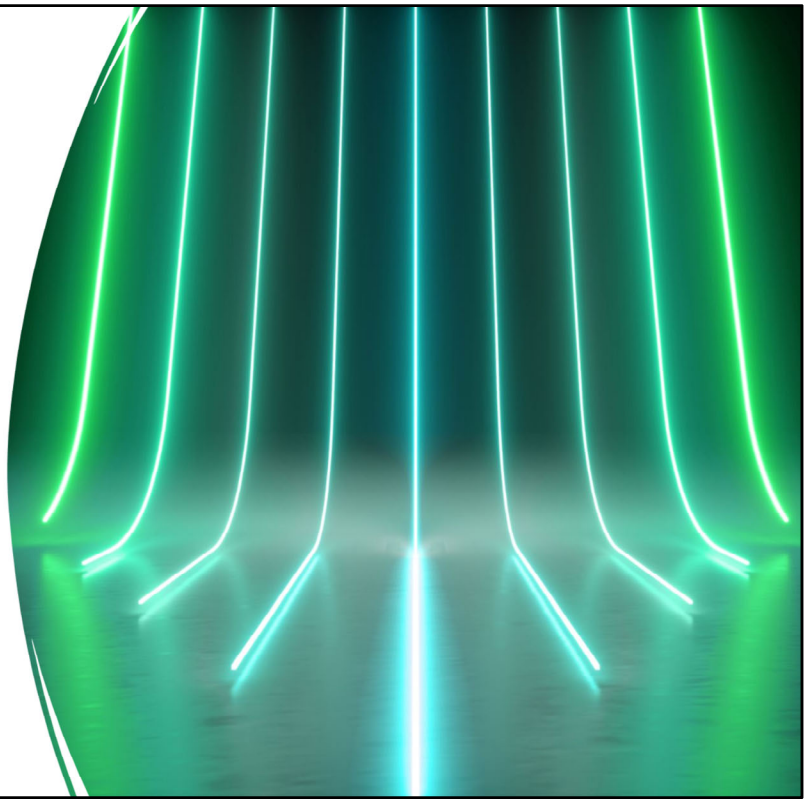
What not to miss!
Pearls in ocular oncology

Colleen M. Cebulla, MD, PhD
The Ohio State University

Ohio Ophthalmological Society 2025



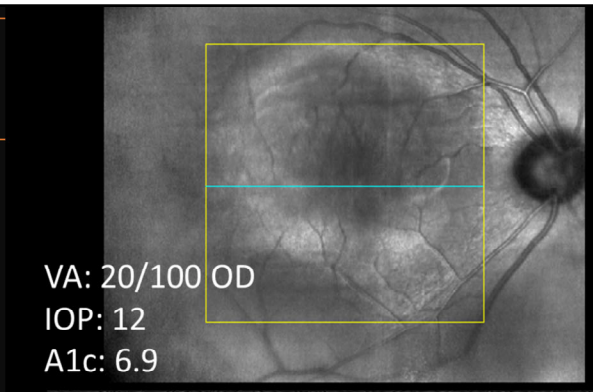


Disclosures

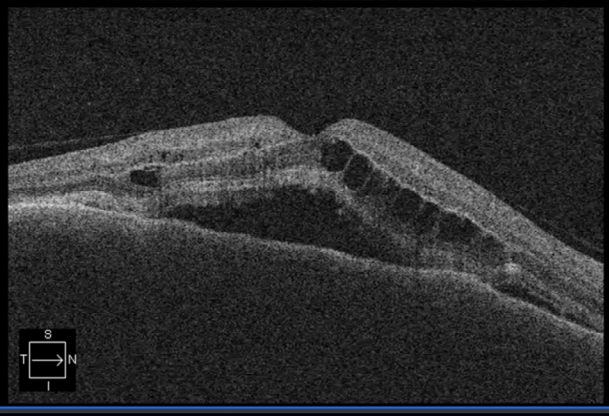
- No financial disclosures
- Off Label Use Discussed

Diabetes?

- 71yo WM Veteran, T2D
- “Dot in vision OD started President’s day”

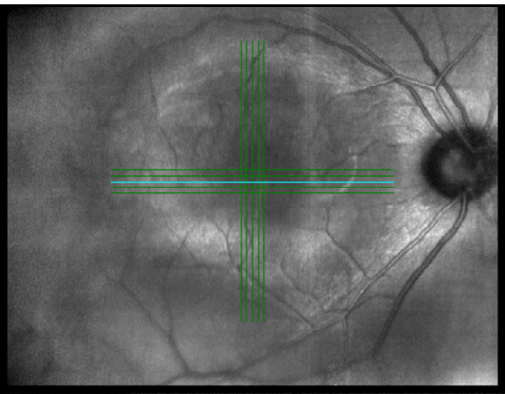


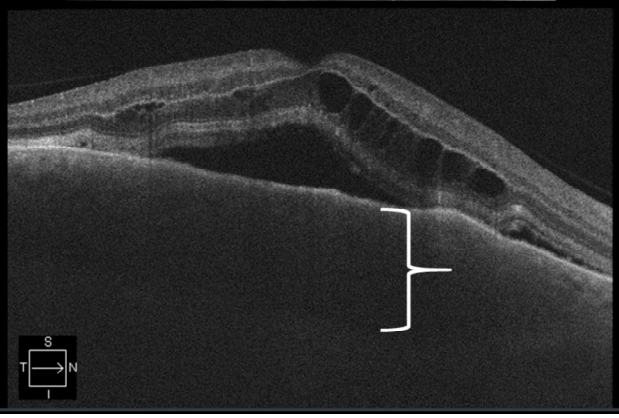
VA: 20/100 OD
IOP: 12
A1c: 6.9



Look a little deeper

- Lumpy choroidal mass
- Serous RD
- Loss of choriocapillaris



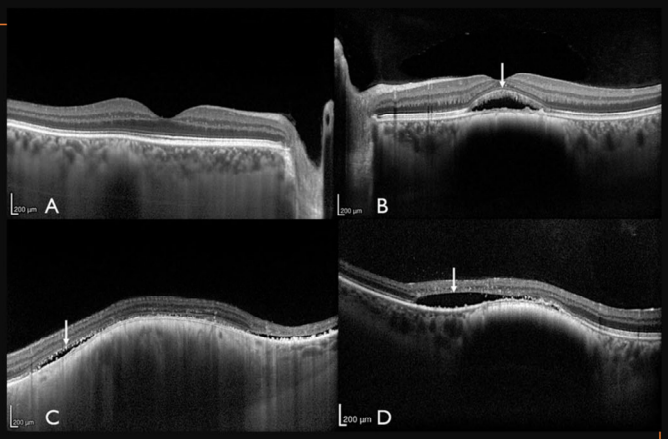


Double check before diagnosing CSR

- Frequent misdiagnosis
- Check the choroid to rule-out a lesion
  - Visualize choroid-sclera junction and RPE band
  - Look for loss of choriocapillaris and hyporeflectivity
  - Compare to fellow eye
  - Enhanced depth imaging (EDI) OCT to better image choroid
- Check the periphery – Indirect ophthalmoscopy
- Use multimodal imaging– Autofluorescence, FA+ICG, ultrasound

Choroidal nevus with “CSR”?

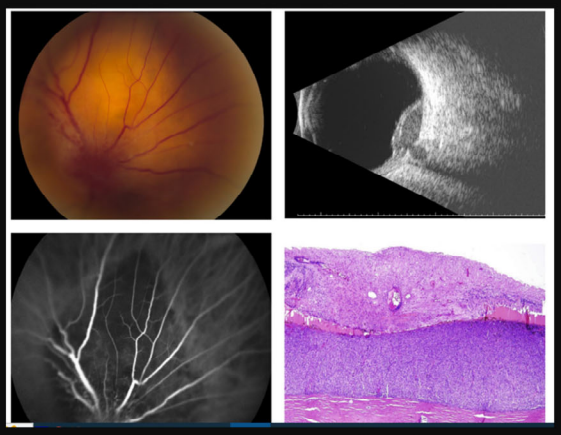
- Subretinal fluid with a choroidal nevus is a “high risk characteristic” for melanoma
- Consider Ocular Onc referral of these lesions



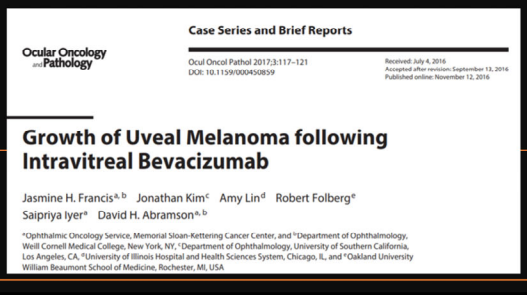
Yaghy et al. Photoreceptor morphology and correlation with subretinal fluid chronicity associated with choroidal nevus. BJO. 2019. https://doi.org/10.1136/bjophthalmol-2019-314755

Caution with anti-VEGF in untreated melanoma / choroidal nevi with subretinal fluid

- Caution to inject anti-VEGF in choroidal nevi with SRF.
- If undetected melanoma, tumor can progress and more difficult to diagnose
- Reports of growth of UNTREATED melanoma with bevacizumab
- Collaborate with Ocular Oncology



Lima et al. The Impact of Intravitreal Bevacizumab Therapy on Choroidal Melanoma. AJO. 2011;151:323-328.



Case Series and Brief Reports

Ocular Oncology and Pathology

Ocul Oncol Pathol 2017;3:117–121
DOI: 10.1159/000450859

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Published online: November 12, 2016

Growth of Uveal Melanoma following Intravitreal Bevacizumab

Jasmine H. Francis[a, b] Jonathan Kim[c] Amy Lin[d] Robert Folberg[e]
Saipriya Iyer[a] David H. Abramson[a, b]

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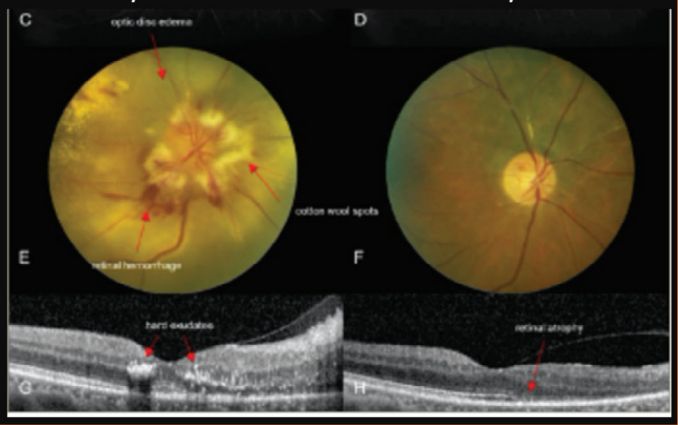
Good to us anti-VEGF in treated melanoma

Radiation Retinopathy & Optic Neuropathy

- Prophylactic treatment q4months x 2 years had significantly LESS:
  - CME
  - Clinically significant maculopathy
  - Moderate vision loss
  - Severe vision loss

Shah et al. Ophthalmology 2014;121:269-275

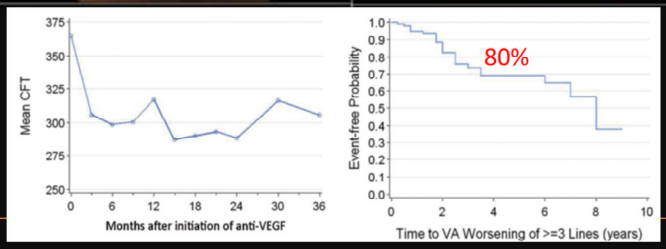
Baseline 20/60 | Ranibizumab 1 year 20/32



Taken from: Yu and Schefler. US Ophthalmic Review. 2020;13(1):34–9

Good to us anti-VEGF in treated melanoma

- Long-term suppression of Radiation Maculopathy - preservation of vision serial q4-12wk intravitreal anti-VEGF therapy
- 80% vision preserved at 3yr VS COMS 45% worse than 20/200
- Typically involved dose escalation (decreased time intervals and increased dose)
- Low rate of enucleation



Finger et al. Intravitreal anti-VEGF therapy for macular radiation retinopathy: a 10-year study. Eur J Ophthalmol 2016; 26 (1): 60-66

Stopping anti-VEGF

- "Anti-VEGF therapy suppresses and thus prolongs the evolution of radiation maculopathy.
- I have found that almost all patients who significantly delay or stop anti- VEGF treatment develop "off-treatment" recurrent macular edema.
- Although these cases respond (a second time) after restarting anti-VEGF therapy, measurable damage has typically occurred in the interim.
- These cases have cemented my conviction that anti- VEGF treatment works, but it merely suppresses radiation vasculopathy. The more consistent we are with treatment, the more likely it is that vision will be preserved. The bottom line is that we do not stop therapy until there is no useful vision."

Paul Finger, MD

https://eyecancer.com/eye-cancer/treatments/intravitreal-anti-vegf-therapy-for-radiation-retinopathy/

How should we treat radiation retinopathy?

DRCR Retina Network

Protocol AL

Faricimab or Fluocinolone Acetonide Implants vs Observation for Prevention of VA Loss due to Radiation Retinopathy

Protocol Chair, Arun Singh, MD

NIH National Eye Institute

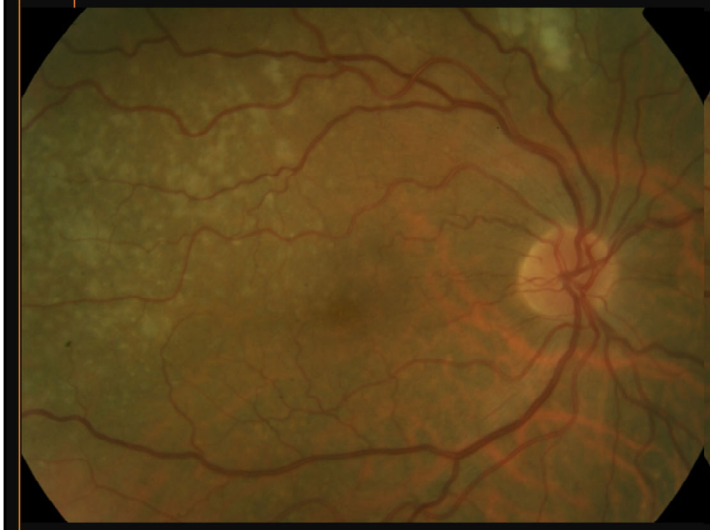
NIH National Institute of Diabetes and Digestive and Kidney Diseases

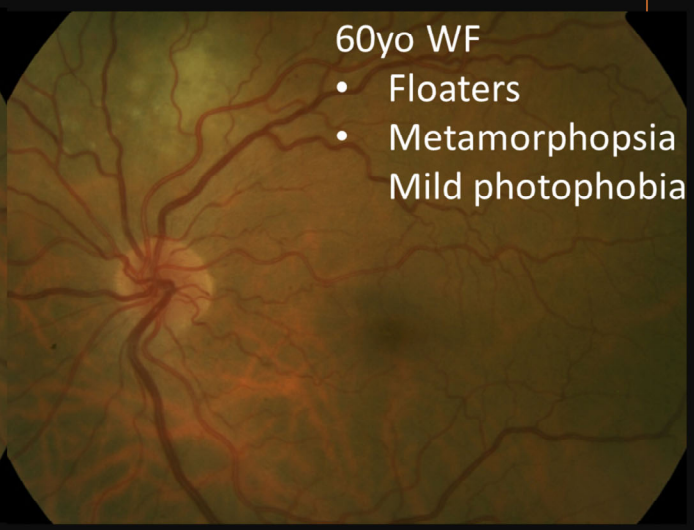
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Eye Institute

Don’t cut in eyes with tumors: How to avoid trouble?

- Excise conjunctival lesions with 4mm margin and no touch technique (AVOID incisional biopsy)
- Obtain B-scan in mature cataract / sectoral cataract eyes
- Gonio for pigmented lesions/ immersion ultrasound in recalcitrant glaucoma
- Vitrectomy: double freeze-thaw cryo ports and suture (NO biopsy if risk of retinoblastoma)
- Blind painful eyes have a tumor in 10%
  - DFE and carful ultrasound prior to any evisceration (even a ruptured globe can have an occult tumor)
  - Consider enucleation

Vitreitis: is it uveitis?

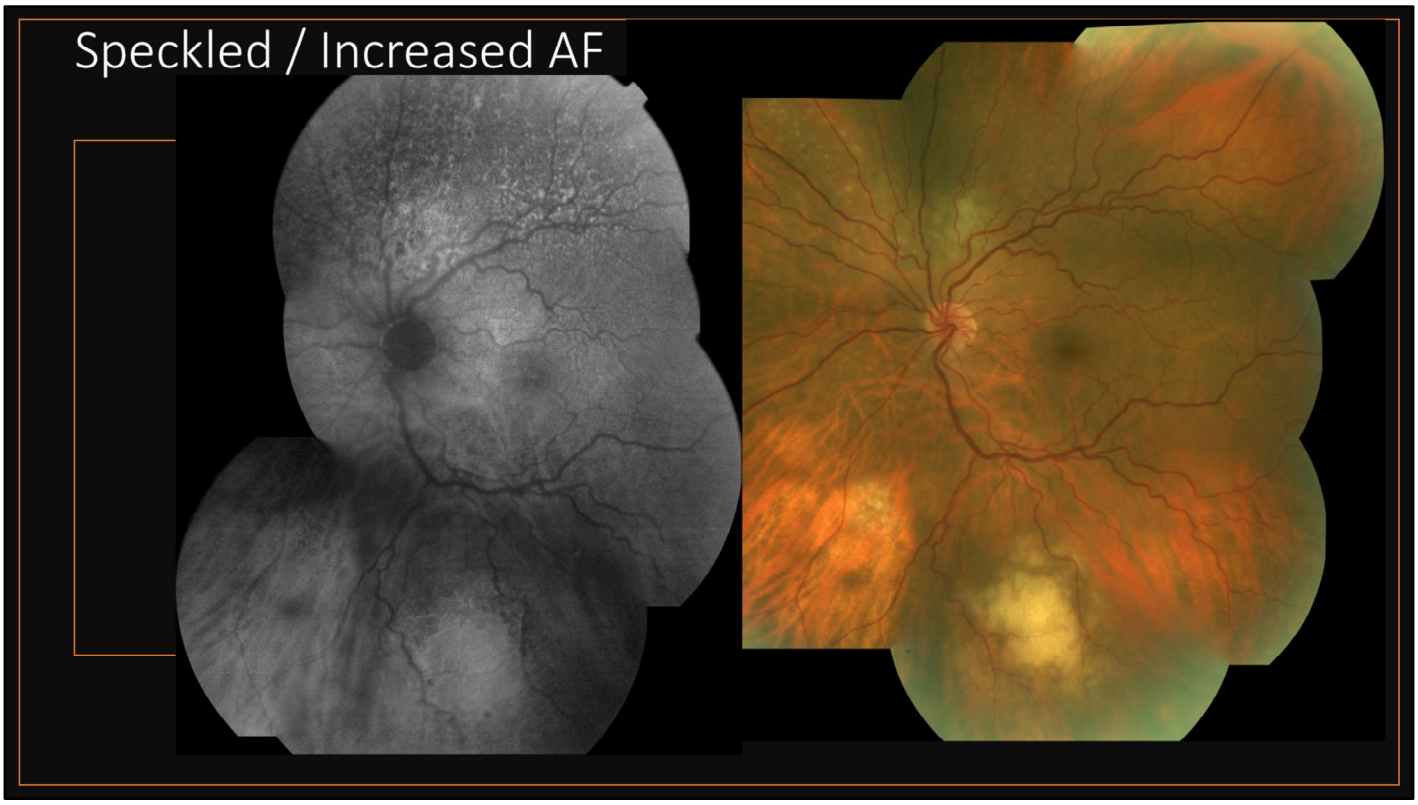




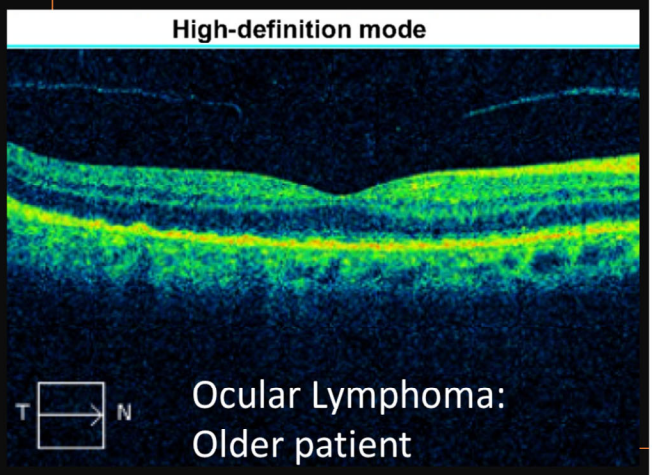
60yo WF

- Floaters
- Metamorphopsia

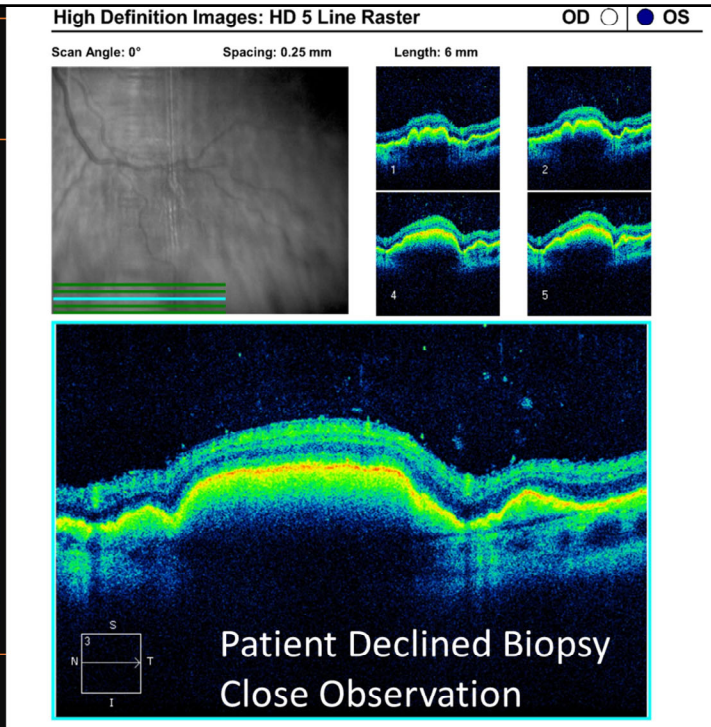
Mild photophobia


Speckled / Increased AF

OCT



Ocular Lymphoma:
Older patient
Vitreitis
LOVES RPE



Patient Declined Biopsy
Close Observation
Order MRI brain and orbit

Primary Vitreoretinal lymphoma / Primary CNS Lymphoma

- "Dominant population of highly atypical B-cells co-expressing CD19 and CD20 consistent with **B-cell lymphoproliferative disorder**"

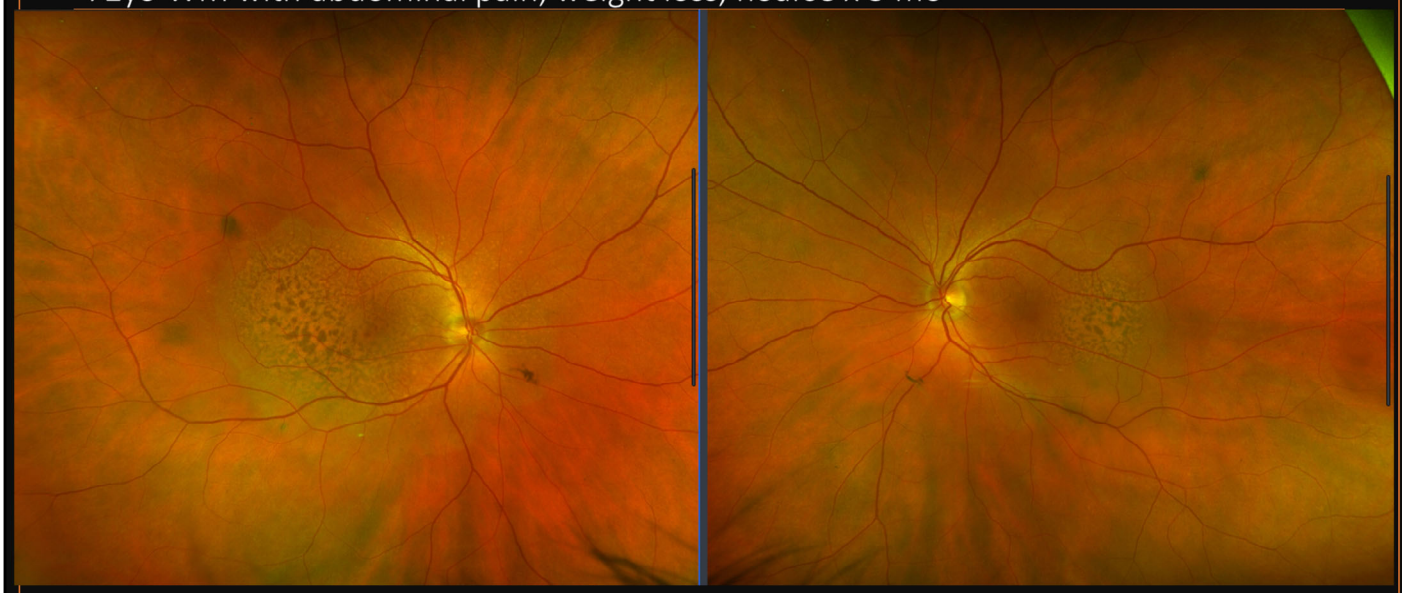
Advances in Ocular Lymphoma diagnosis

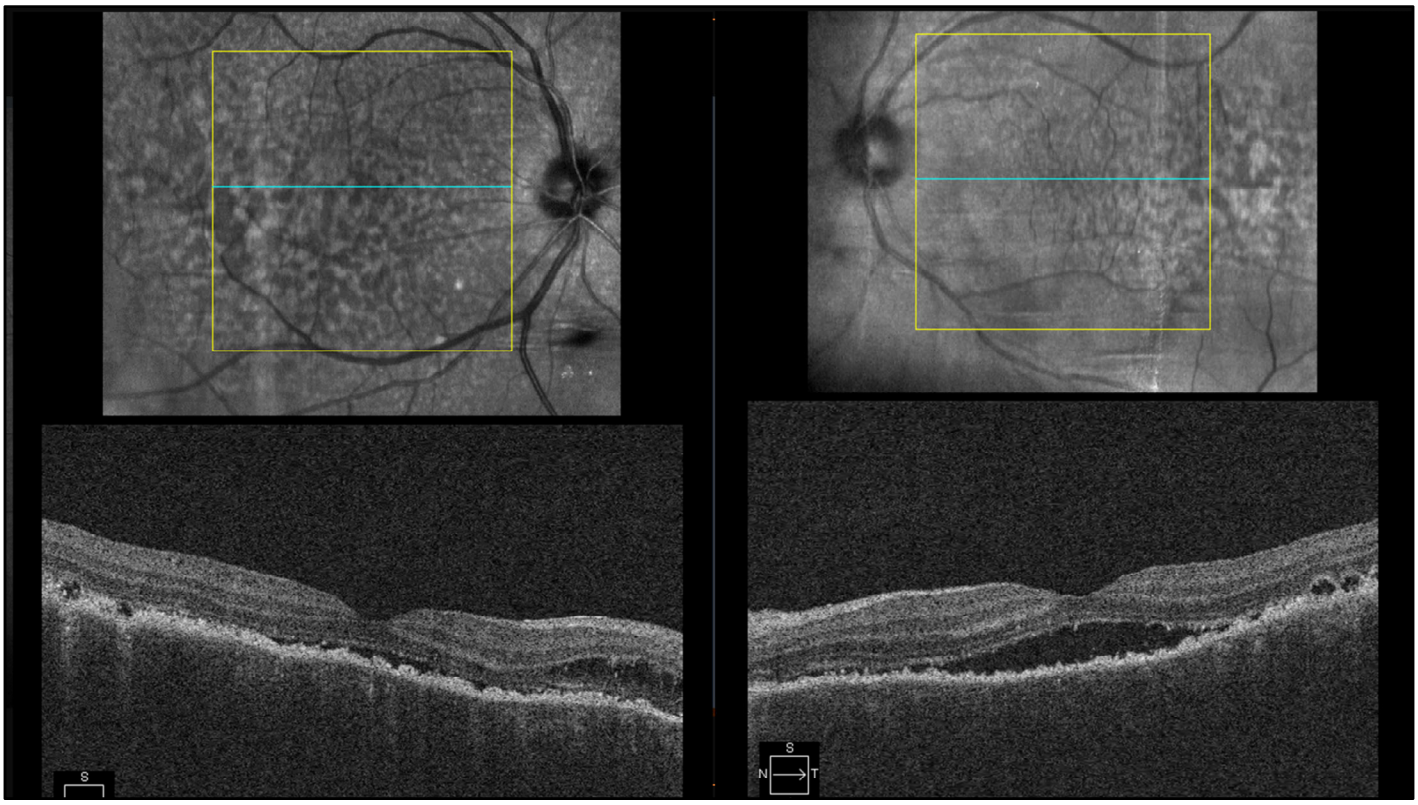
- MYD88 and IgH/IgK molecular testing
- Cytokine profiling: IL-10 / IL-6 ratio >1 supports lymphoma

What is this?

-72yo WM with abdominal pain, weight loss, hoarse x 3 mo

VA: 20/60;20/40
IOP: 18;14

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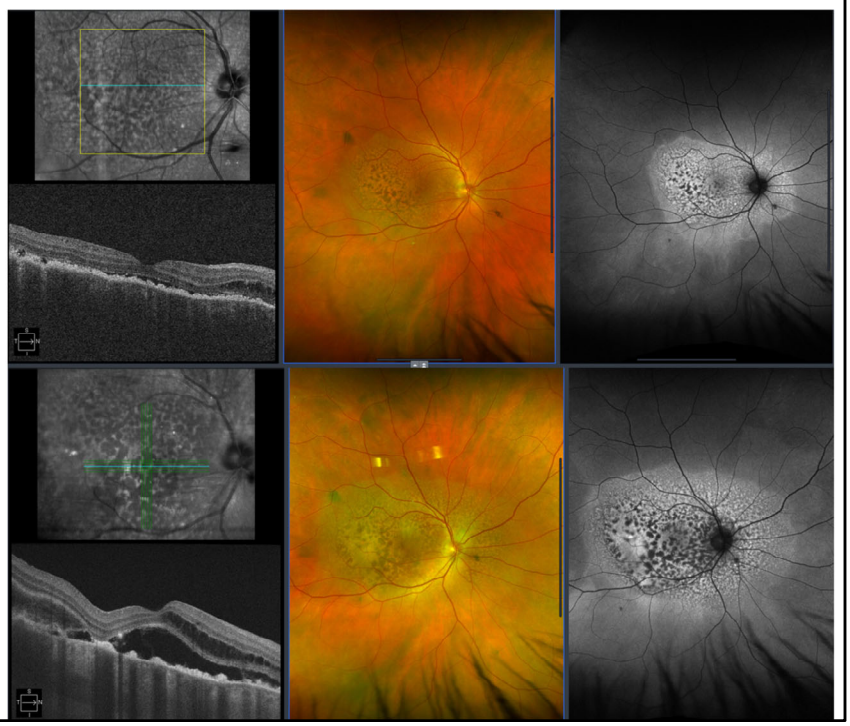
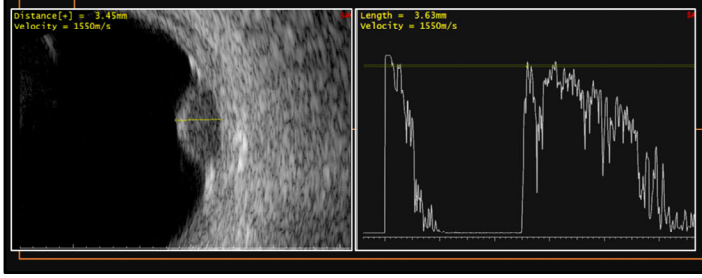
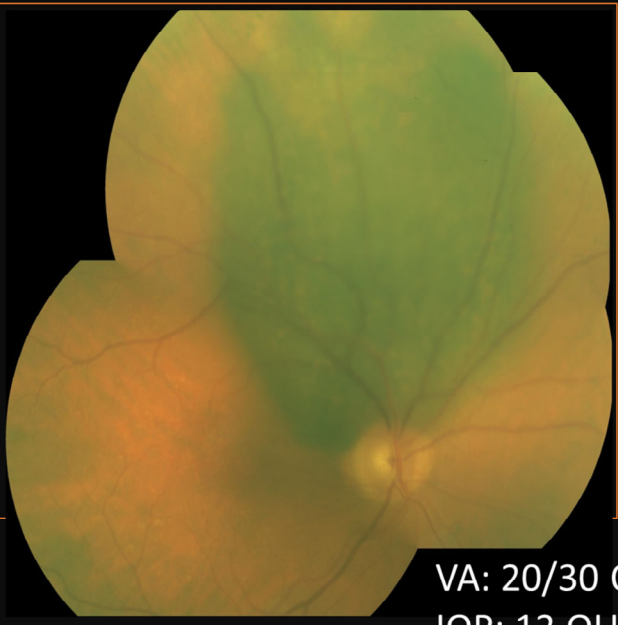
- BDUMP
  -Metastatic esophageal cancer
  - Numerous round or oval red spots->spicules
  - Choroidal thickening sparing choriocapillaris
  - Serous RD and rapid cataract formation
  - Pigmented uveal lesions



Small Choroidal Melanoma

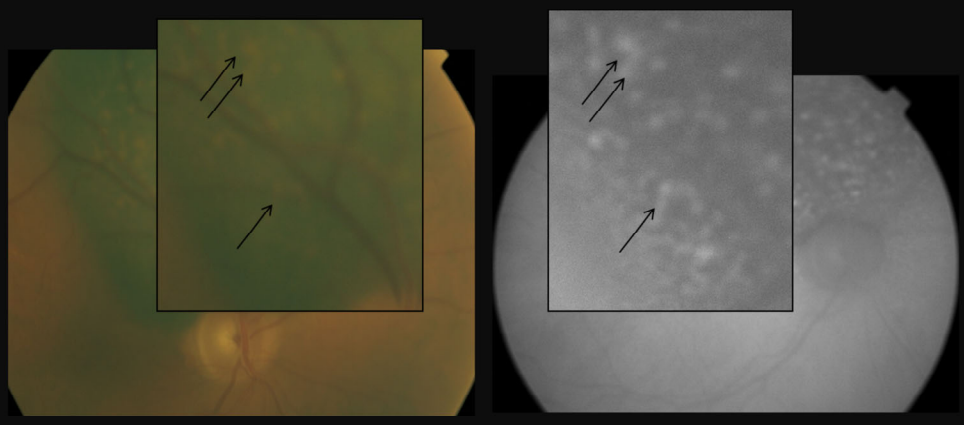
- 84yo WM
- Shadow in vision x 3 mo
- Refused brachytherapy





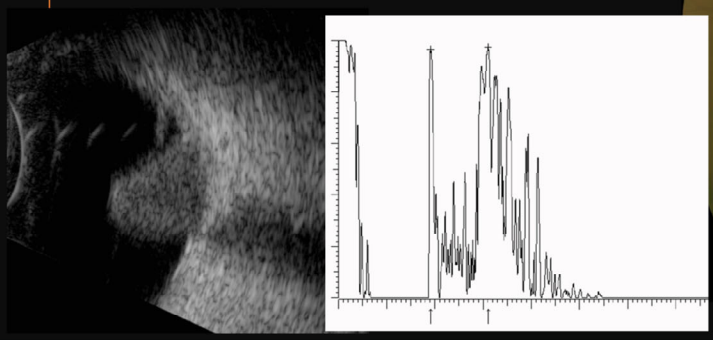
VA: 20/30 OU
IOP: 12 OU

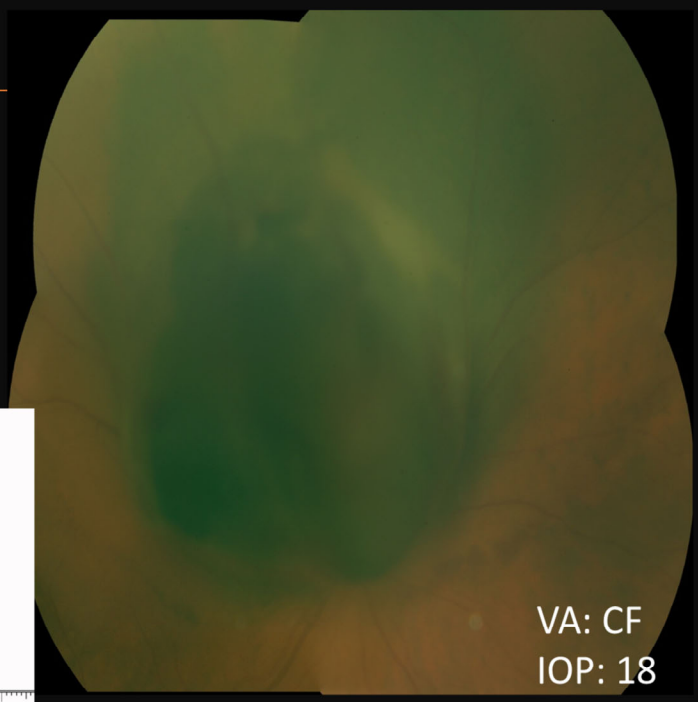
Autofluroescence highlights orange pigment



8 months later…

- Growth 3.6mm to 9.5mm height

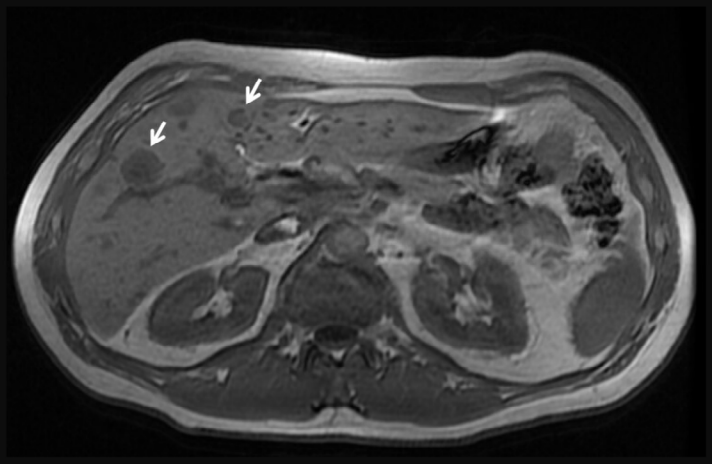




VA: CF
IOP: 18

Imaging

- Liver Metastasis 3 years later
- Any options?



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Three-Year Overall Survival with Tebentafusp in Metastatic Uveal Melanoma

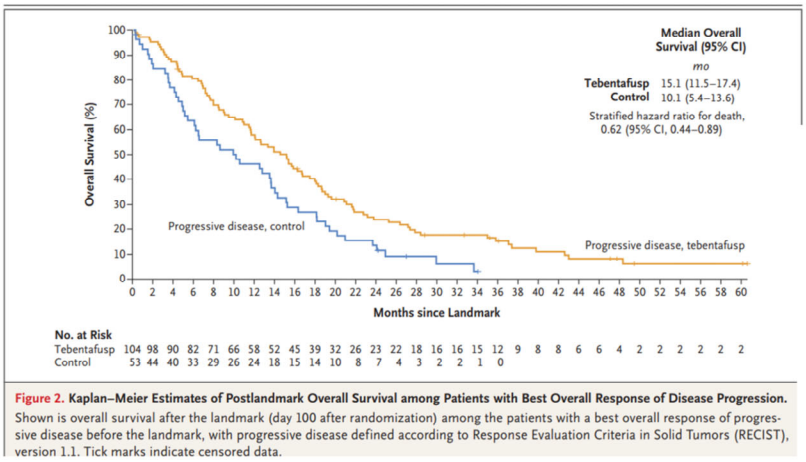
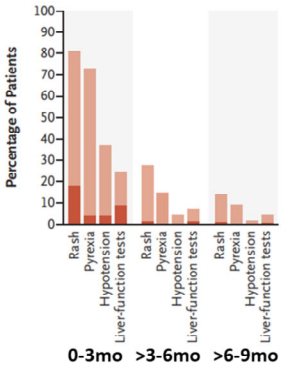


Figure 2. Kaplan–Meier Estimates of Postlandmark Overall Survival among Patients with Best Overall Response of Disease Progression. Shown is overall survival after the landmark (day 100 after randomization) among the patients with a best overall response of progressive disease before the landmark, with progressive disease defined according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Tick marks indicate censored data.

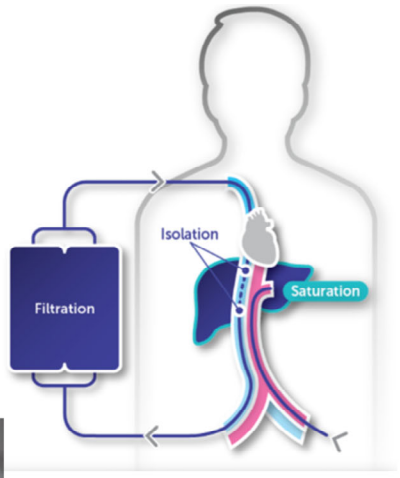
Hassel and Piperno-Neumann et al. NEJM 2023. DOI: 10.1056/NEJMoa2304753

- Median overall survival
  - **Tebe** 21.6 months
    (19.0 - 24.3 95% CI)
  - **Control** 16.9 months
    (12.9 - 19.5 95% CI)

Surviving	1 year	3 years
• **Tebe**	72%	27%
• **Control**	60%	18%



Percutaneous Hepatic Perfusion (Melphalan)



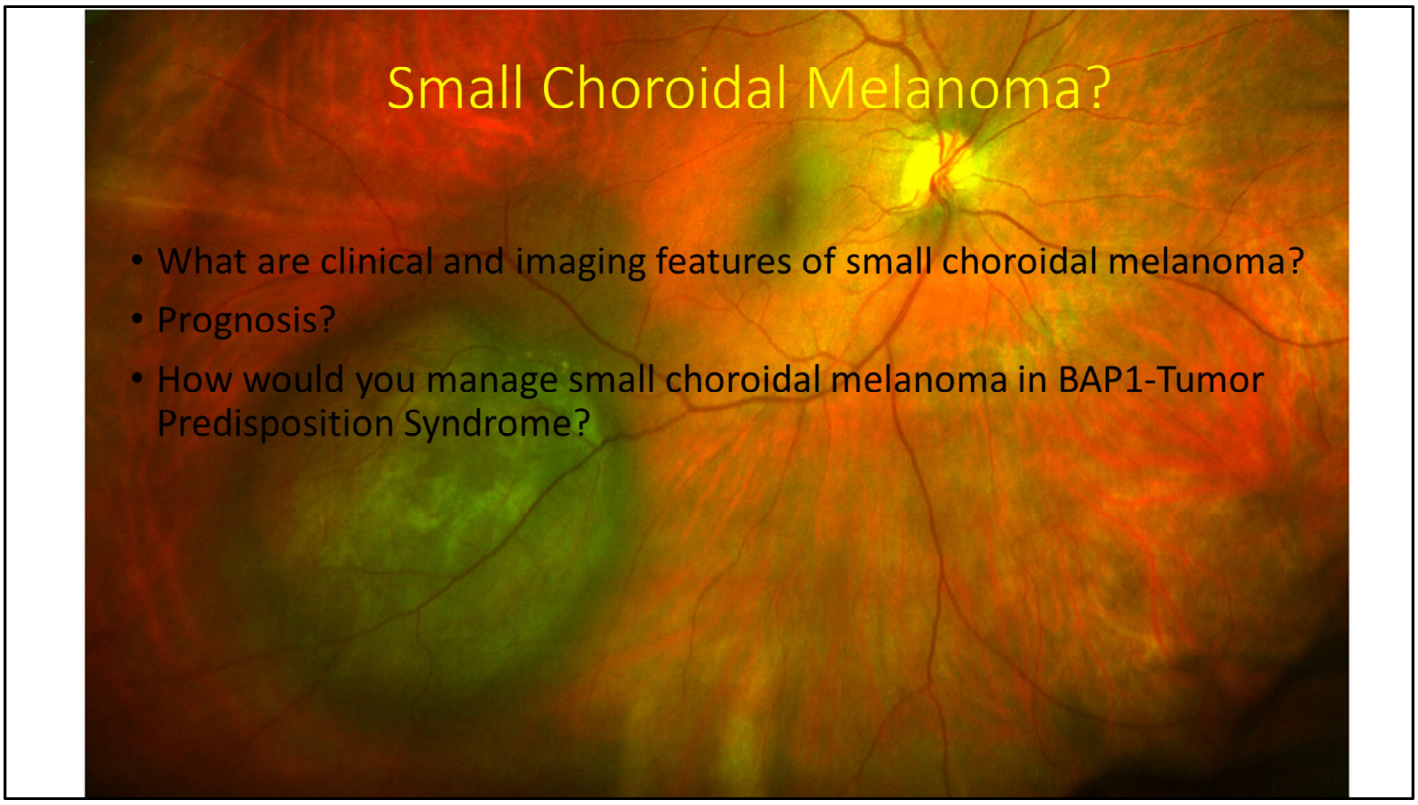
FDA Approved for UM <50% of liver

FOCUS 3 Trial:

- -Overall Response 35.2 % for PHP vs. 12.5 % controls (p = 0.015)
- -Disease control rate for PHP 73.6 % vs. 37.5 % (p = 0.0002)
- -Median Progression free survival for PHP 9mo vs. 3.1mo (p = 0.0007)
- -SAE: for PHP, 42.6 % , most were hematological and transient

Carlo Contreras MD

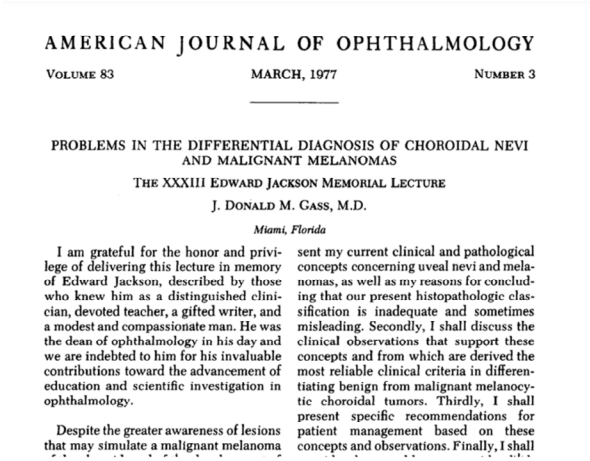
Balsay-Patel C et al. Advances in the management of regionally metastatic melanoma. Surgical Oncology, 2025.57:102143


Small Choroidal Melanoma?
• What are clinical and imaging features of small choroidal melanoma?
• Prognosis?
• How would you manage small choroidal melanoma in BAP1-Tumor Predisposition Syndrome?

Small Uveal Melanomas

- Practically impossible to distinguish from atypical nevi
  - High risk criteria
  - Growth rate
  - Cytology

High risk criteria (Gass): “Clinical features of prognostic significance”



AMERICAN JOURNAL OF OPHTHALMOLOGY

VOLUME 83 MARCH, 1977 NUMBER 3

PROBLEMS IN THE DIFFERENTIAL DIAGNOSIS OF CHOROIDAL NEVI AND MALIGNANT MELANOMAS

THE XXXIII EDWARD JACKSON MEMORIAL LECTURE

J. DONALD M. GASS, M.D.

Miami, Florida

I am grateful for the honor and privilege of delivering this lecture in memory of Edward Jackson, described by those who knew him as a distinguished clinician, devoted teacher, a gifted writer, and a modest and compassionate man. He was the dean of ophthalmology in his day and we are indebted to him for his invaluable contributions toward the advancement of education and scientific investigation in ophthalmology.

Despite the greater awareness of lesions that may simulate a malignant melanoma

sent my current clinical and pathological concepts concerning uveal nevi and melanomas, as well as my reasons for concluding that our present histopathologic classification is inadequate and sometimes misleading. Secondly, I shall discuss the clinical observations that support these concepts and from which are derived the most reliable clinical criteria in differentiating benign from malignant melanocytic choroidal tumors. Thirdly, I shall present specific recommendations for patient management based on these concepts and observations. Finally, I shall

- Visual symptoms: photopsia
- Degree of elevation (2mm or higher)
- Subretinal fluid and orange pigment - possible bioactivity
- FA: multiple pinpoint leaks, tumor vessels – high risk

- Drusen and CNV – chronic, unlikely to grow

Gass, JDM. Problems in the differential diagnosis of choroidal nevi and melanomas. The XXXIII Edward Jackson Memorial Lecture. AJO. 1977;83:299-323

High Risk Criteria (Shields): TFSOM Mnemonic

- To: Thickness (>2mm)
- Find: Subretinal Fluid
- Small: Symptoms
- Ocular: Orange Pigment
- Melanomas: Margin (within 3mm of optic
- Using Helpful: Ultrasound Hollowing
- Hints: Absence of Halo

Shields et al. Arch Ophthalmol. 2009 Aug;127(8):981-7.

TFSOM Mnemonic

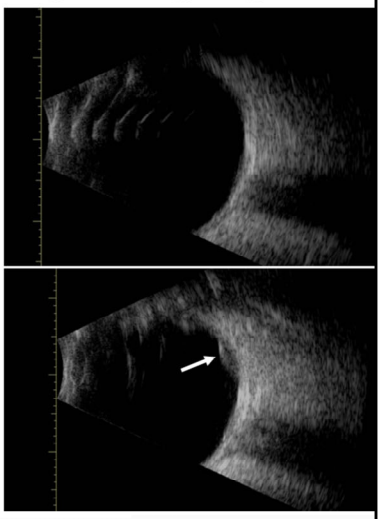
- Tumors without any factors: 3% grow
- Tumors with one factor: 38% grow
- Tumors with two factors: 50% grow

- Recommended consider treatment with 2 or more factors

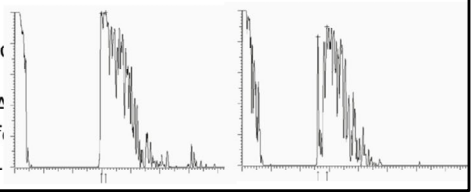
Shields et al. Can J Ophthalmol. 2004 Jun;39(4):351-7.

UPDATE: To find small ocular melanomas doing imaging: TFSOM-DIM Mnemonic

- To: Thickness (>2mm) - Ultrasound
- Find: Subretinal Fluid - OCT
- Small: Symptoms - Vision loss
- Ocular: Orange Pigment – Autofluorescence
- Melanoma Hollow: Ultrasound
- DIaMeter (5mm base photography)



- Dalvin LA, Shields CL, et al. Combination of multimodal imaging features predictive of melanoma. Br J Ophthalmol. 2019 Oct;103(10):1441-1447.
- Shields CL, Dalvin LA, Ancona-Lezama D, Yu MD, Di Nicola M, Williams BK Jr, Lucio-A Shields JA. Choroidal nevus imaging features in 3,806 cases and risk factors for transf 2020 Taylor R. Smith and Victor T. Curtin Lecture. Retina. 2019 Oct;39(10):1840-1851.



To find small ocular melanomas doing imaging: TFSOM-DIM Mnemonic

- The mean 5-year estimates of nevus growth into melanoma were
  - 1% (HR 0.8) for those with 0 risk factor
  - 11% (HR 3.09) with 1 factor
  - 22% (HR 10.6) with 2 factors
  - 34% (HR 15.1) with 3 factors
  - 51% (HR 15.2) with 4 factors
  - 55% (HR 26.4) with 5 risk factors

Consider treatment with 2 or more factors

- Dalvin LA, Shields CL, et al. Combination of multimodal imaging features predictive of choroidal nevus transformation into melanoma. Br J Ophthalmol. 2019 Oct;103(10):1441-1447.
- Shields CL, Dalvin LA, Ancona-Lezama D, Yu MD, Di Nicola M, Williams BK Jr, Lucio-Alvarez JA, Ang SM, Maloney S, Welch RJ, Shields JA. Choroidal nevus imaging features in 3,806 cases and risk factors for transformation into melanoma in 2,355 cases: The 2020 Taylor R. Smith and Victor T. Curtin Lecture. Retina. 2019 Oct;39(10):1840-1851.

Advantages for finding small melanomas

- Preferable treatment options
- Better prognosis
  - "…at 5 years, metastasis occurs in **16%** of patients with small choroidal melanomas (less than 4 mm thick), compared with **32%** of those with medium-sized (4-8 mm thick) choroidal melanomas and **53%** of those with large (more than 8 mm thick) choroidal melanomas"

Shields et al. Can J Ophthalmol. 2004 Jun;39(4):351-7.

COMS Small Melanoma Mortality

Clinical Trial > Arch Ophthalmol. 1997 Jul;115(7):886-93.

Mortality in patients with small choroidal melanoma. COMS report no. 4. The Collaborative Ocular Melanoma Study Group

No authors listed

- Kaplan-Meier melanoma-specific mortality
  - 5-year: 1.0% (95% CI, 0%-2.5%)
  - 8-year: 3.7% (95% CI, 0.7%-6.6%).

Ocular Oncology and Pathology

Research Article

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Small Choroidal Melanoma: Correlation of Growth Rate with Pathology

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[a]Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA; [b]Quantitative Health Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA

Keywords
Small choroidal melanoma · Growth rate · Histopathology · Diagnosis

Abstract

Purpose: The aim of the study was to evaluate equivalence of growth rate and pathologic confirmation in small choroidal melanoma (SCM). ***Design:*** This study is a case series. ***Subjects, Participants, and Controls:*** A total of 61 patients with a choroidal melanocytic tumor of size 5.0–16.0 mm in the largest basal diameter and 1.0–2.5 mm in thickness were classified into the pathology-confirmed group (n = 19), growth-confirmed group (n = 30), and with combined observations (n = 12). ***Methods:*** Distribution of clinical variables (age, gender, laterality, tumor dimensions, tumor location, and presence of orange pigment, subretinal fluid, drusen, and retinal pigment epithelial (RPE) atrophy) between the groups was analyzed. Patient and disease characteristics were summarized as the median and interquartile range for continuous variables and the frequency and percentage for categorical variables. Comparisons were made using the Wilcoxon rank sum test for continuous variables and either Fisher's exact test or the χ^2 test for categorical variables with a p value threshold of 0.05 for statistical significance. Growth rate (change in basal dimension/12 months) diagnostic of SCM was quantified. ***Main Outcome Measures:*** The primary aim of this study was to test the hypothesis that "growth" was diagnostic of SCM with the secondary aim of quantifying the malignant "growth rate" (growth rate of SCM). ***Results:*** The clinical characteristics among all 3 groups were similar except more patients with symptoms (68 vs. 20 vs. 42%, p = 0.004) and juxtapapillary location (p = 0.03) were in the pathology group than in the growth-confirmed group. Those in the combined and growth-confirmed groups had more patients with drusen (11 vs. 60 vs. 50%, p = 0.003) and RPE atrophy (11 vs. 23 vs. 67%, p = 0.003), respectively, than in the pathology group. The median time to detect growth was 9 months (range 3–26 months). The mean growth rate in basal dimension was 1.8 mm/12 months (range, 0.0–7.4 mm; [95% CI: 1.32–2.28]). ***Conclusions and Relevance:*** Choroidal melanocytic lesions exhibiting a defined growth rate can be clinically diagnosed as SCM without a need for biopsy.

Introduction

Pathologic confirmation is the gold standard for diagnosis of malignancy prior to definitive therapy by surgery, radiation, or chemotherapy. Ophthalmic oncology seems to be the only exception to this standard particularly when it relates to management of uveal melanoma [1]. Even though hesitation for performing biopsy seems to be partially overcome with increasing acceptance of prognostic biopsy, diagnostic biopsy is not routinely per-

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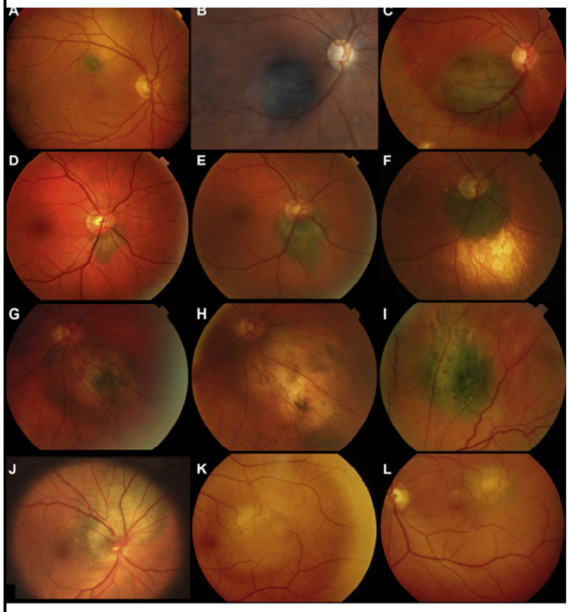
What is the smallest melanoma?

Small Fatal Choroidal Melanomas



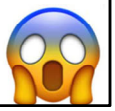
The Small Fatal Choroidal Melanoma Study. A Survey by the European Ophthalmic Oncology Group

SUSANNA JOUHI, MARTINE J. JAGER, STEFAN J.R. DE GEUS, LAURENCE DESJARDINS, NILS ANDREAS EIDE, JEAN-DANIEL GRANGE, JENS FOLKE KIILGAARD, STEFAN SEREGARD, EDOARDO MIDENA, RAFFAELE PARROZZANI, JEAN-PIERRE CAUJOLLE, IWONA ROSPOND-KUBIAK, AND TERO T. KIVELÄ

• PURPOSE: To determine the size at which choroidal melanomas can metastasize and to report the characteristics of small fatal choroidal melanomas (SFCM).
• DESIGN: Retrospective case series.
• METHODS: Ten ocular oncology services submitted 45 patients with a choroidal melanoma 3 mm or less in thickness and 9 mm or less in largest basal diameter (LBD), when treated, who developed metastases.
• RESULTS: Median tumor thickness was 2.4 mm (range, 1.0–3.0 mm) and LBD 7.3 mm (range, 3.0–9.0 mm). Of 14 (31%) tumors that were first observed, 12 grew a median of 0.5 mm (range, 0.1–1.2 mm) in thickness and 1.0 mm (range, 0–3.0 mm) in LBD within a median of 7 months; 3 were initially smaller than 3 mm in LBD. Number of risk factors for growth and metastasis was 0 for 4% of the tumors; 60% were over 2 mm in thickness, 63% had subretinal fluid, 84% caused symptoms, respectively. By the time of analysis, 37 patients had died of metastasis after a median of 7 months.
• CONCLUSIONS: Choroidal melanomas less than 3.0 mm in LBD are highly unlikely to metastasize. Risk factors of an SFCM are similar to those for all choroidal melanomas of similar size.

SMALL CHOROIDAL MELANOCYTIC TUMORS ARE treated if their appearance or growth suggests malignancy. Several studies have identified risk factors for growth[1–6] and metastasis[1–3] of suspicious small melanocytic choroidal lesions so as to aid in making treatment

45 tumors fatal tumors from 10 centers: 9mm LBD, 3mm ht



Tumors <3mm diameter unlikely to be fatal

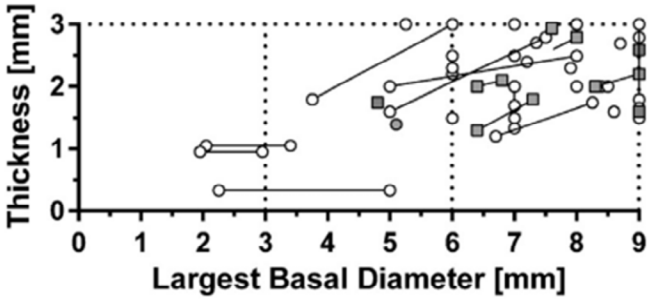


FIGURE 1. The size of 45 small fatal choroidal melanomas. Scatterplot of largest basal tumor diameter against tumor thickness. White circles indicate tumors without local recurrence and gray squares tumors that recurred; connected symbols indicate tumors that were observed to grow before diagnosis and treatment (measurements at initial visit and at last visit before treatment).

Smaller risk of metastasis with smaller size

The natural history of malignant melanoma of the choroid: small vs large tumors.

Davidorf FH , Lang JR

Transactions. Section on Ophthalmology. American Academy of Ophthalmology and Otolaryngology, 01 Mar 1975, 79(2):OP310-20

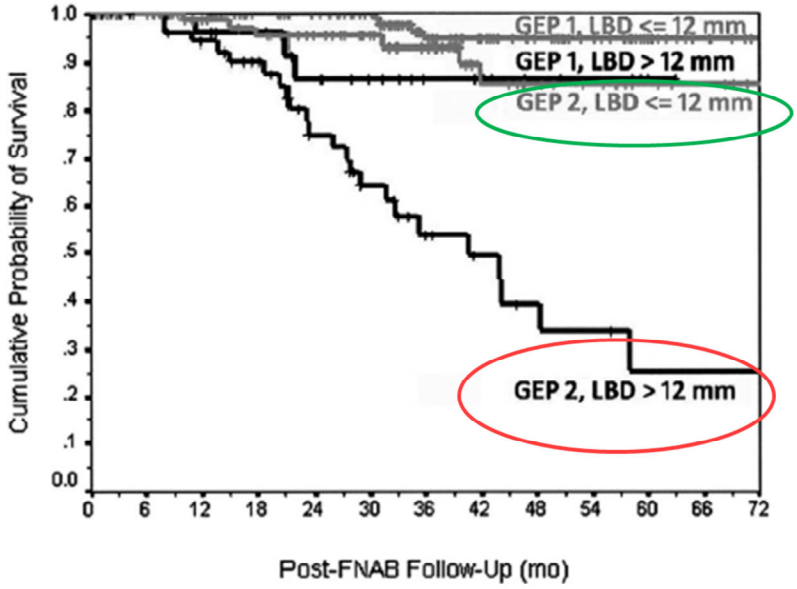
PMID: 1145955

- 50 small melanomas

(<10 mm LBD and <3 mm height)

  - 22.0% of higher risk path (mixed and epithelioid tumors)
  - 5 year: 2/33 patients (6.1%) died of metastases
  - 10 year: 5/22 possible ten-year follow-ups, (22.7%) died of metastatic melanoma
  - **No patient died with base <7mm x 2mm ht**

Size (plus genetics) does matter



Goal: to find and treat small ocular melanomas

Increased risk with GEP 2, LBD>12mm

Independent Prognostic Significance of Gene Expression Profile Class and Largest Basal Diameter of Posterior Uveal Melanomas

ZÉLIA M. CORRÊA AND JAMES J. AUGSBURGER

When should we be more aggressive?

BAP1 Uveal Melanomas

Frequent Mutation of *BAP1* in Metastasizing Uveal Melanomas

J. William Harbour,[1,3]* Michael D. Onken,[1] Elisha D. O. Roberson,[2] Shenghui Duan,[2] Li Cao,[2] Lori A. Worley,[1] M. Laurin Council,[2] Katie A. Matatall,[1] Cynthia Helms,[2] Anne M. Bowcock[2,3]*

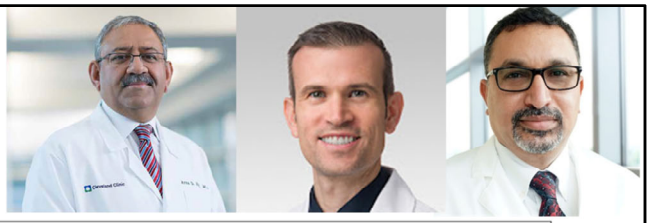
Metastasis is a defining feature of malignant tumors and is the most common cause of cancer-related death, yet the genetics of metastasis are poorly understood. We used exome capture coupled with massively parallel sequencing to search for metastasis-related mutations in highly metastatic uveal melanomas of the eye. Inactivating somatic mutations were identified in the gene encoding BRCA1-associated protein 1 (*BAP1*) on chromosome 3p21.1 in 26 of 31 (84%) metastasizing tumors, including 15 mutations causing premature protein termination and 5 affecting its ubiquitin carboxyl terminal hydrolase domain. One tumor harbored a frameshift mutation that was germline in origin, thus representing a susceptibility allele. These findings implicate loss of BAP1 in uveal melanoma metastasis and suggest that the BAP1 pathway may be a valuable therapeutic target.

Uveal melanoma (UM) is the most common primary cancer of the eye and has a strong propensity for fatal metastasis (*1*). UMs are divided into class 1 (low metastatic risk) and class 2 (high metastatic risk) based on a validated multi-gene clinical prognostic assay included in the TNM classification system (*2*, *3*). However, the genetic basis of metastasis remains unclear. Oncogenic mutations in the $G\alpha_q$ stimulatory subunit *GNAQ* are common in UM (*4*), but these mutations occur

ER 2010 VOL 330 **SCIENCE** www.sciencemag.org

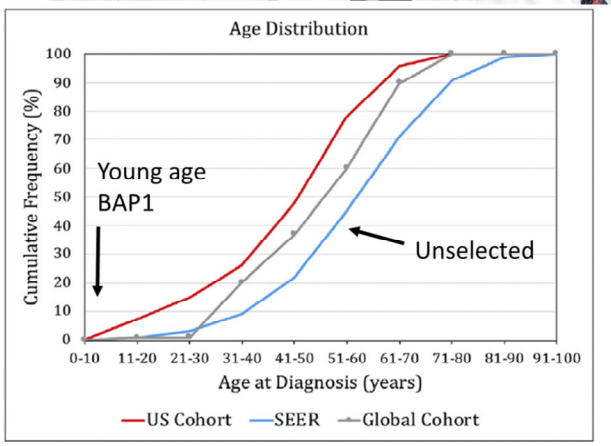
What about patients with BAP1 – Tumor Predisposition Syndrome?

Who is at risk for BAP1 – TPDS?



- Younger patients (age ≤40yo for uveal melanoma)
- Two or more confirmed *BAP1*-TPDS tumors*
  - Bilateral, multifocal, familial
- One *BAP1*-TPDS tumor and a first-or second-degree relative with a confirmed *BAP1*-TPDS tumor*

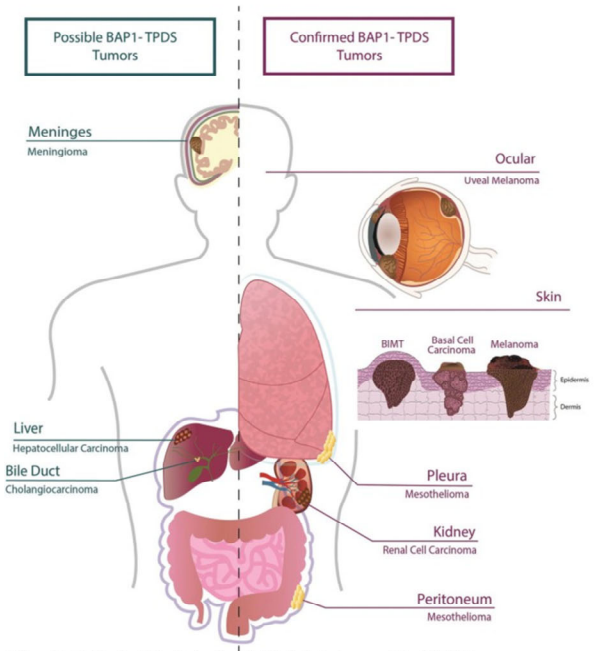
Gene Review Guidelines, 2020



Nakul Singh, Rahul Singh, Randy Chris Bowen, Mohamed H. Abdel-Rahman, Arun D. Singh. Uveal Melanoma in BAP1 Tumor Predisposition Syndrome: Estimation of Risk. Am J Ophthalmol 2021;224:172–177.

BAP1-TPDS MANIFESTATIONS

- Uveal melanoma
- Renal cell carcinoma
- Mesothelioma of pleura and peritoneum
- Cutaneous melanoma and BCC
- Association with:
  - Meningioma
  - Hepatocellular carcinoma
  - Cholangiocarcinoma
  - Sex-cord stromal tumors



Pilarski R, Carlo MI, Cebulla C, Abdel-Rahman M. *BAP1* Tumor Predisposition Syndrome. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. *GeneReviews®*. Seattle (WA): University of Washington, Seattle; October 13, 2016.

Now that you've been introduced to the cancers a/w BAP1 by Dr. Cebulla, you can see that many different organ systems are affected. Our specialty, of course, is ophthalmology, but we could not have our clinic without specialists in all of these other fields

Uveal melanoma diagnosis and treatment
BAP1 TPDS

- Higher risk of metastatic UM in germline BAP1

OPEN ACCESS Freely available online

PLoS one

Germline *BAP1* Inactivation Is Preferentially Associated with Metastatic Ocular Melanoma and Cutaneous-Ocular Melanoma Families

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Abstract

Background: *BAP1* has been shown to be a target of both somatic alteration in high-risk ocular melanomas (OM) and germline inactivation in a few individuals from cancer-prone families. These findings suggest that constitutional *BAP1* changes may predispose individuals to metastatic OM and that familial permeation of deleterious alleles could delineate a new cancer syndrome.

Design: To characterize *BAP1*'s contribution to melanoma risk, we sequenced *BAP1* in a set of 100 patients with OM, including 50 metastatic OM cases and 50 matched non-metastatic OM controls, and 200 individuals with cutaneous melanoma (CM) including 7 CM patients from CM-OM families and 193 CM patients from CM-non-OM kindreds.

Results: Germline *BAP1* mutations were detected in 4/50 patients with metastatic OM and 0/50 cases of non-metastatic OM (8% vs. 0%, p = 0.059). Since 2/4 of the *BAP1* carriers reported a family history of CM, we analyzed 200 additional hereditary CM patients and found mutations in 2/7 CM probands from CM-OM families and 1/193 probands from CM-non-OM kindreds (29% vs. 0.52%, p = .003). Germline mutations co-segregated with both CM and OM phenotypes and were associated with the presence of unique nevoid melanomas and highly atypical nevoid melanoma-like melanocytic proliferations (NEMMPs). Interestingly, 7/14 germline variants identified to date reside in C-terminus suggesting that the BRCA1 binding domain is important in cancer predisposition.

Uveal melanoma diagnosis and treatment in BAP1-TPDS

- Consider treatment with 2 or more HRC criteria
- Melanoma growth rate (0.5mm / 6mo)

In Summary

- Pearls to find the oncology mimics
- Pearls to avoid surgical issues
- Anti-VEGF with uveal melanoma
- Find Small Melanomas

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