

# “Malignant Transformation”



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August 28, 2020

# Patient Presentation

## HPI

21 yo M who presents with complaints of slowly progressive blurry vision for the last 6 months. States he had some floaters before his vision started steadily decreasing. Denies flashes. Denies history of recent illness, weight loss, night sweats or body aches



# History

Past Ocular Hx – ocular melanocytosis OD

Past Medical Hx – GERD

Past Surgical Hx – none

Fam Hx – Leukemia (Father)

Meds – omeprazole

Allergies - NKDA

Social Hx – single, lives at home, nonsmoker, no drug use



# External Exam

	OD		OS
VA cc D	HM		20/20
Pupils	5 ->4mm, sluggish, 2+ RAPD		6→3mm
IOP	16mmHg		11mmHg
EOM	Full, no pain		Full, no pain
CVF	unable		full



# Anterior Segment Exam

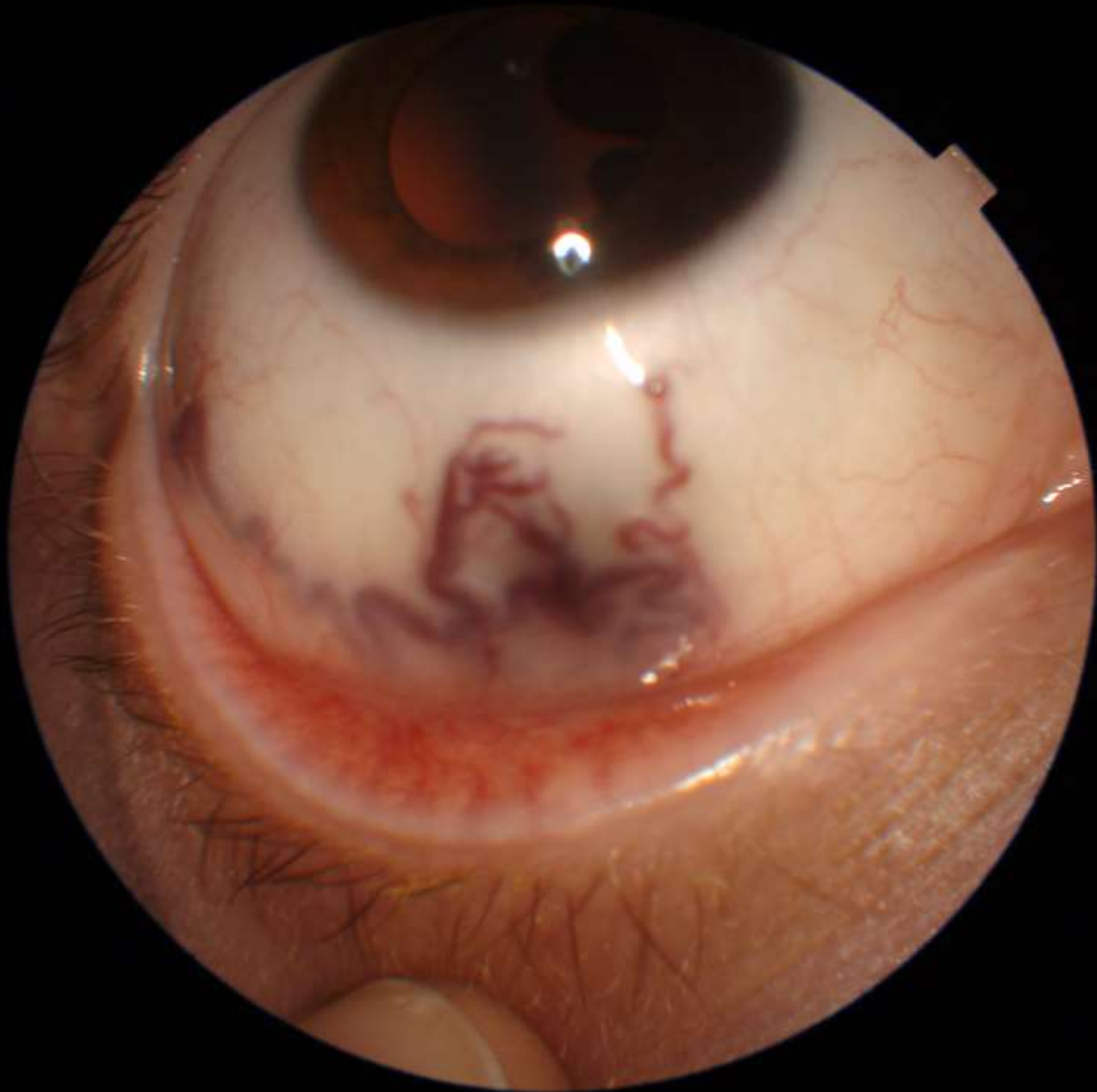
<b>SLE</b>	<b>OD</b>		<b>OS</b>
External/Lids	WNL		WNL
Conj/Sclera	Dilated sentinel vessels inferiorly		WNL
Cornea	Clear		Clear
Ant Chamber	Deep and Quiet		Deep and Quiet
Iris	Large area of iris hyperpigmentation and thickening from 2oc to 6oc with some lobulated cysts		Flat
Lens	Clear		Clear



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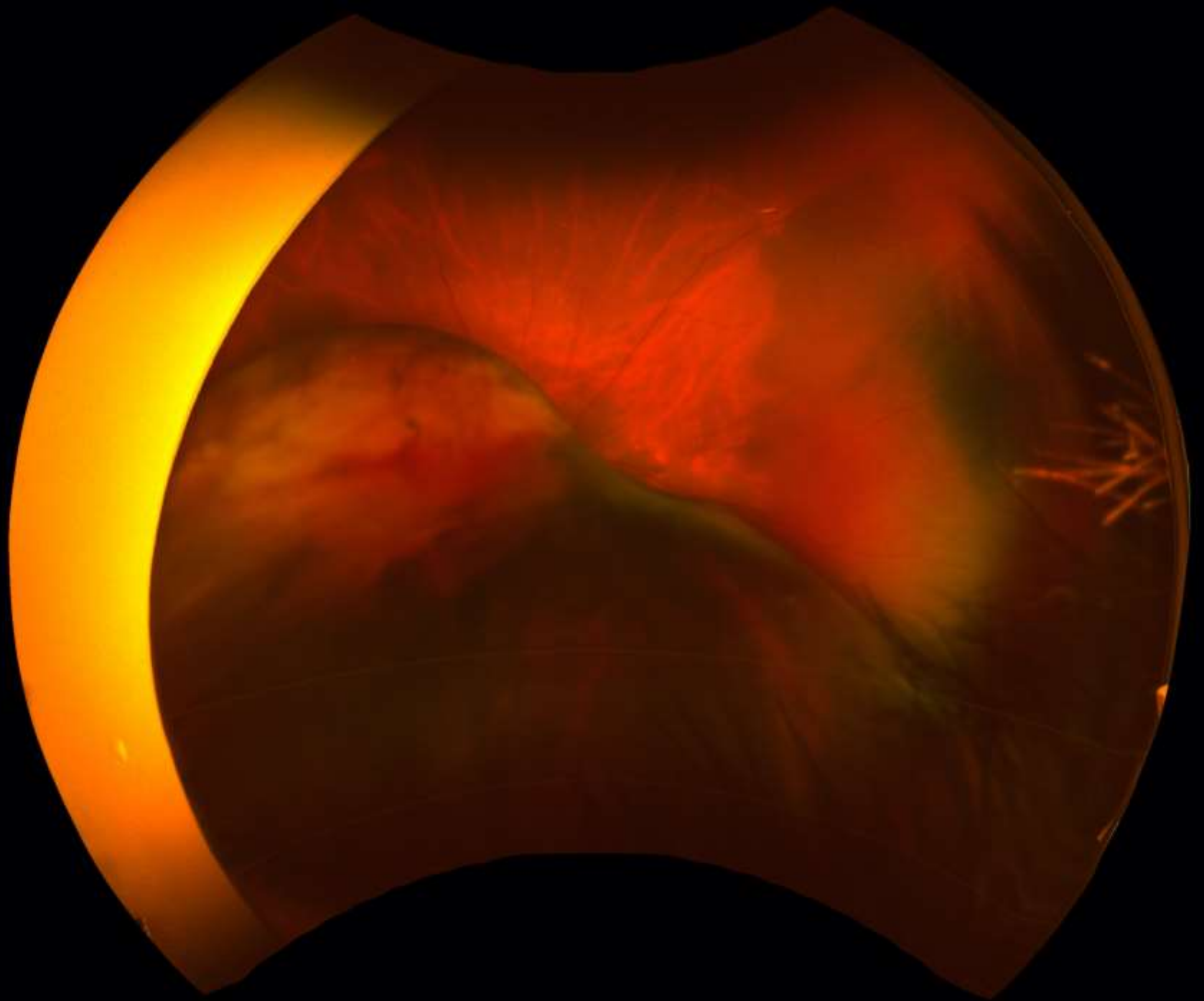




# Posterior Segment Exam

<b>Fundus</b>	<b>OD</b>		<b>OS</b>
Optic Nerve	No view		c/d ratio 0.3, no pallor or edema
Vitreous	3+ vit haze and pigmented cells		clear
Macula	No view		WNL
Vessels	WNL		WNL
Periphery	Large inferior choroidal mass with anterior and temporal extension, confluent with area of choroidal melanocytosis with thickening from 1-4oc		WNL

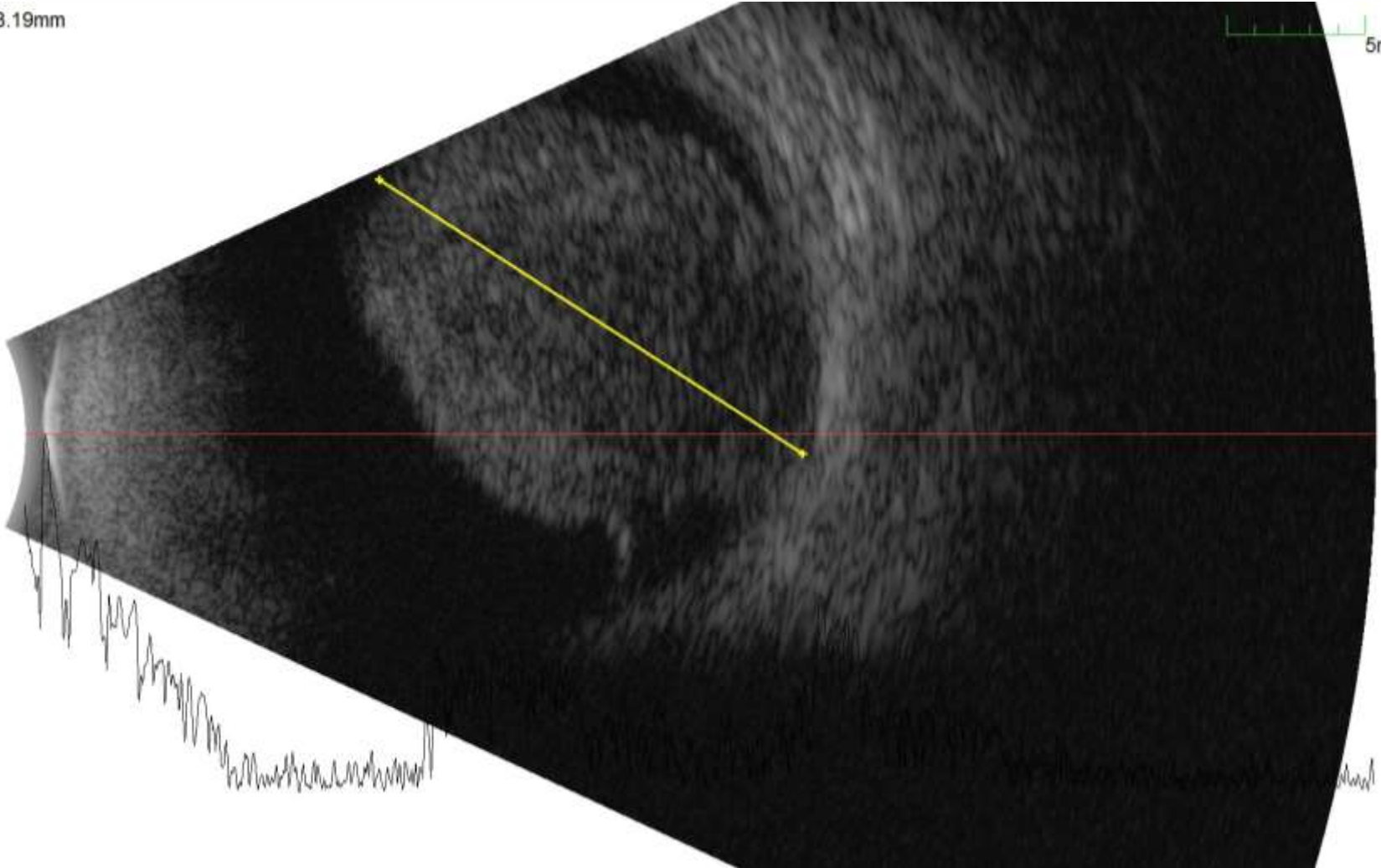




# B-scan

+ 18.19mm

5mm



# Assessment

- 21 yo M with history of iris hyperpigmentation, ocular melanocytosis found to have a large choroidal mass lesion
- Differential Diagnosis
  - Uveal melanoma
  - Other lesions:
    - Benign nevus
    - Metastatic tumor
    - Combined Hamartoma of retina and RPE
    - CHRPE
    - Hemangioma



# Plan

- Primary Enucleation in OR given the size of tumor
- Entire globe sent to pathology for grading, immunohistochemical staining and cytology
- Genetic testing ordered
- Imaging testing including CT chest/abdomen/pelvis, MRI brain



# Gross Specimen



cm

1

2

3

4

5

6

SPECIMEN \_\_\_\_\_

DATE \_\_\_\_\_



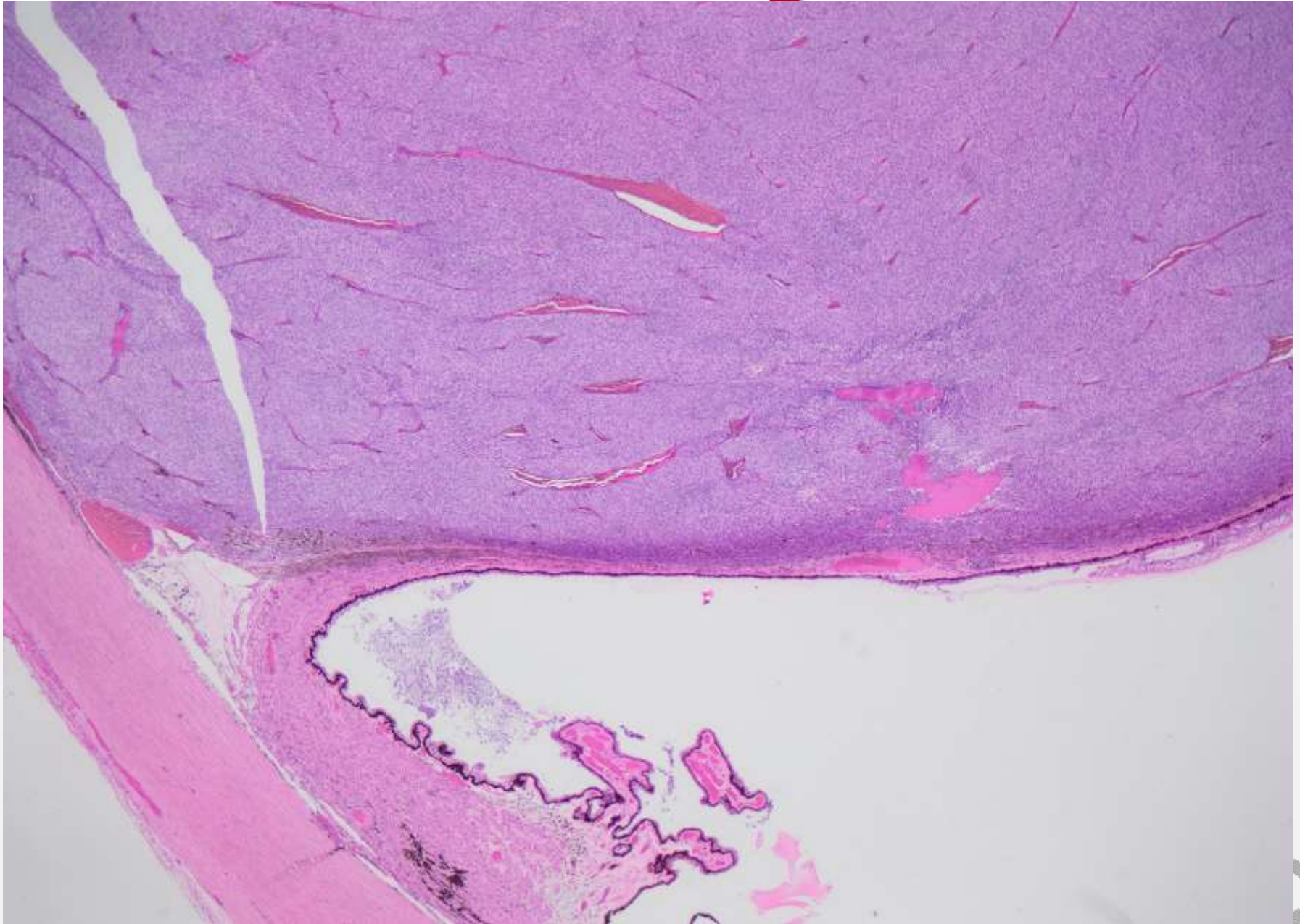
# Description

- 1.7 x 1.5 x 1.5 cm tan mass that grossly appears confined to the eye. The lesion grossly does not appear to invade the optic nerve or other surrounding structures.
- Anterior margin between ciliary body and iris
- Posterior margin between disc and equator



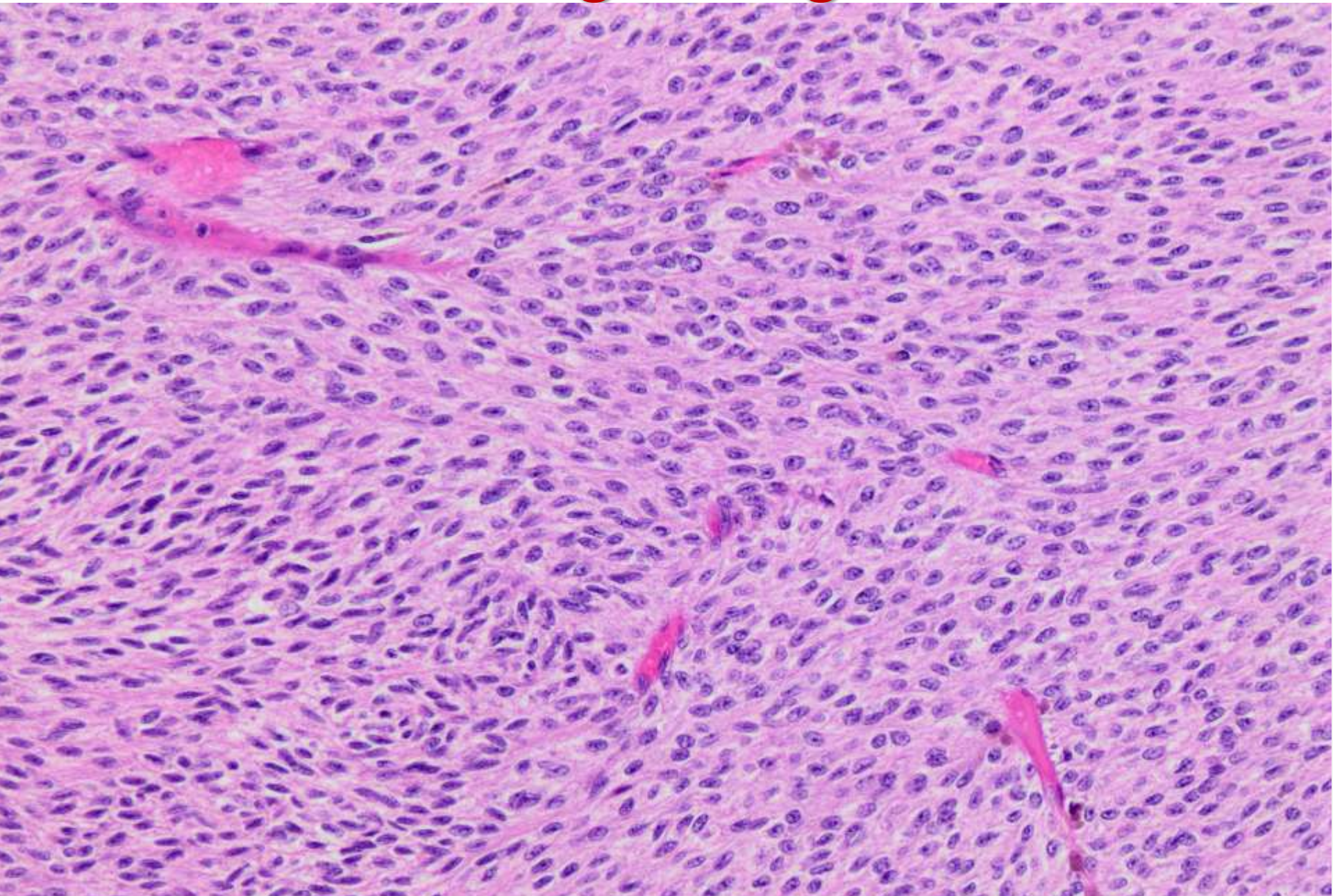


# Low Mag



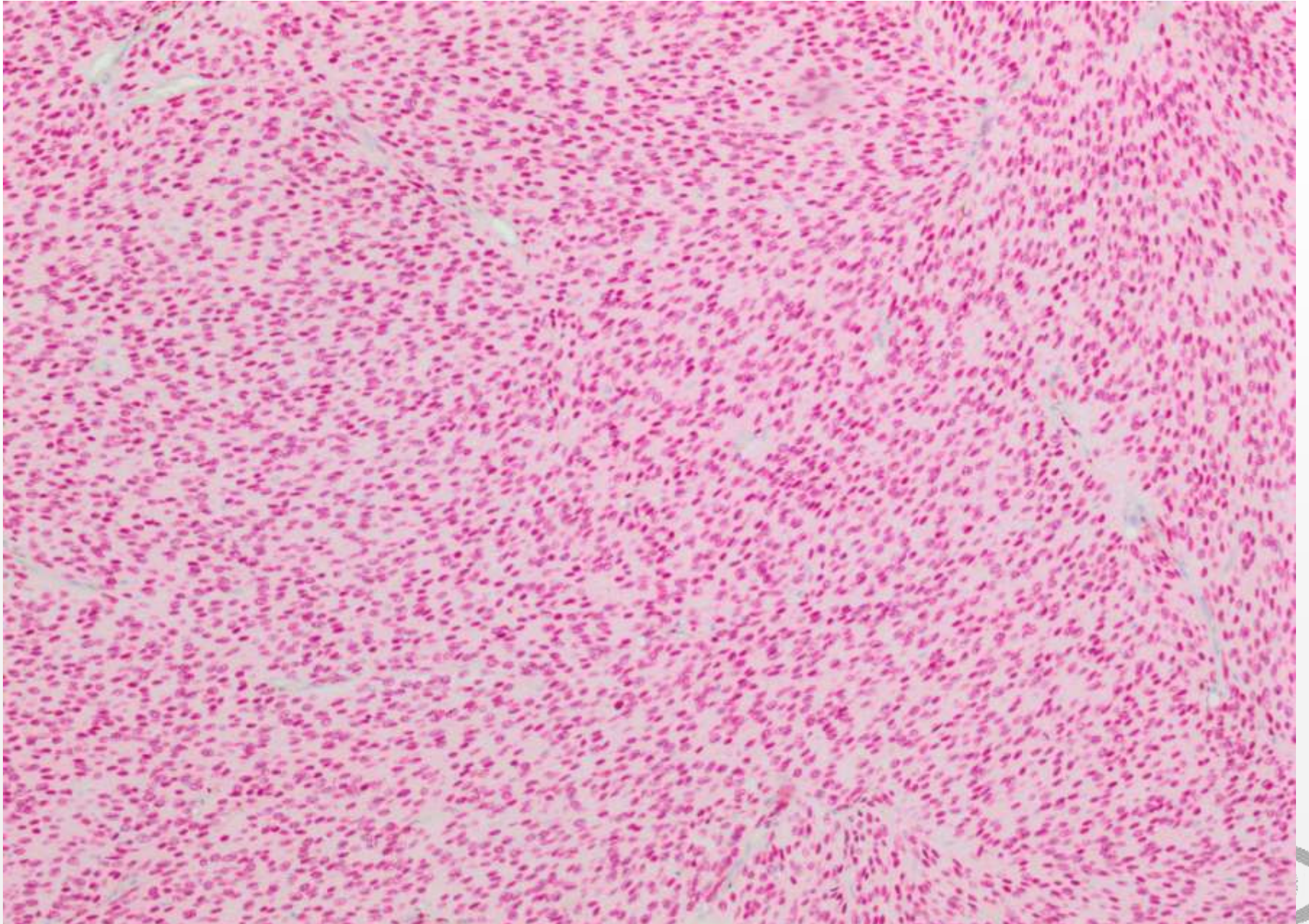


# High Mag





# SOX10



# Diagnosis

- Spindle cell melanoma
  - Often amelanotic
- SOX10 positive
  - Sensitive and specific marker for melanoma
  - Confirmed no extraocular extension
- PRAME negative
- Class 1A gene expression profile



# Uveal Melanoma

- Most common primary intraocular tumor in adults
- Classified by location
  - Choroid (80-85%)
  - Ciliary Body (12-15%)
  - Iris (2-5%)



# Clinical Presentation

”To Find Small Ocular Melanomas Using Helpful Hints Daily”

- Thickness
- Fluid
- Symptoms
- Orange pigment
- Margin (to disc)
- Ultrasound hollowness
- Halo absence
- Drusen absence

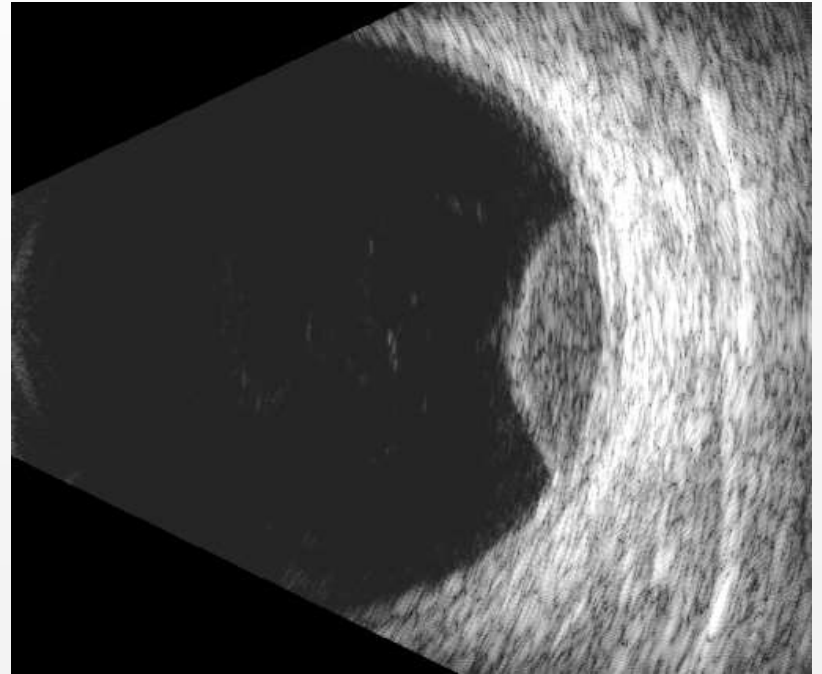




# Clinical Presentation

”To Find Small Ocular Melanomas Using Helpful Hints Daily”

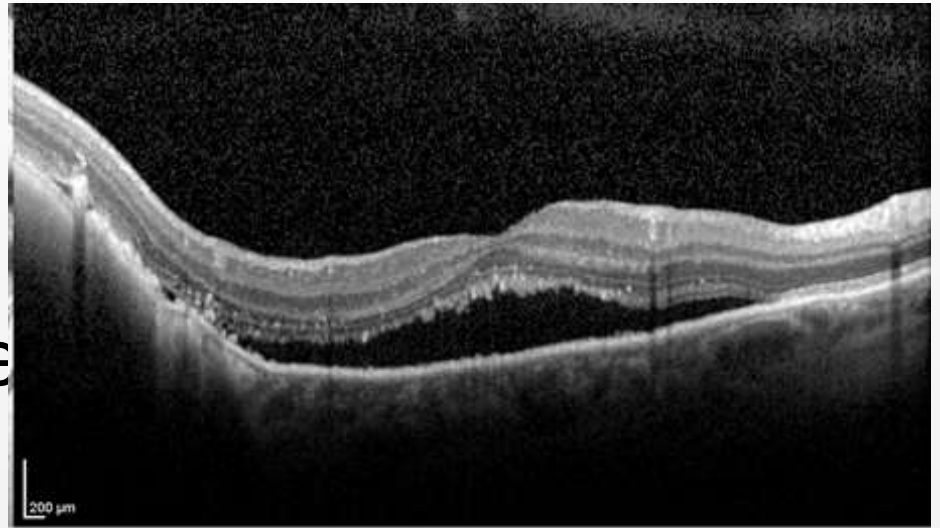
- **Thickness - >2mm thick**
- Fluid
- Symptoms
- Orange pigment
- Margin (to disc)
- Ultrasound hollowness
- Halo absence
- Drusen absence



# Clinical Presentation

”To Find Small Ocular Melanomas Using Helpful Hints Daily”

- Thickness
- **Fluid – presence of SRF**
- Symptoms
- Orange pigment
- Margin (to disc)
- Ultrasound hollowne
- Halo absence
- Drusen absence



# Clinical Presentation

”To Find Small Ocular Melanomas Using Helpful Hints Daily”

- Thickness
- Fluid
- **Symptoms – blurred vision, field loss, floaters, photopsias**
- Orange pigment
- Margin (to disc)
- Ultrasound hollowness
- Halo absence
- Drusen absence





# Clinical Presentation

”To Find Small Ocular Melanomas Using Helpful Hints Daily”

- Thickness
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- Symptoms
- **Orange pigment**
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# Clinical Presentation

”To Find Small Ocular Melanomas Using Helpful Hints Daily”

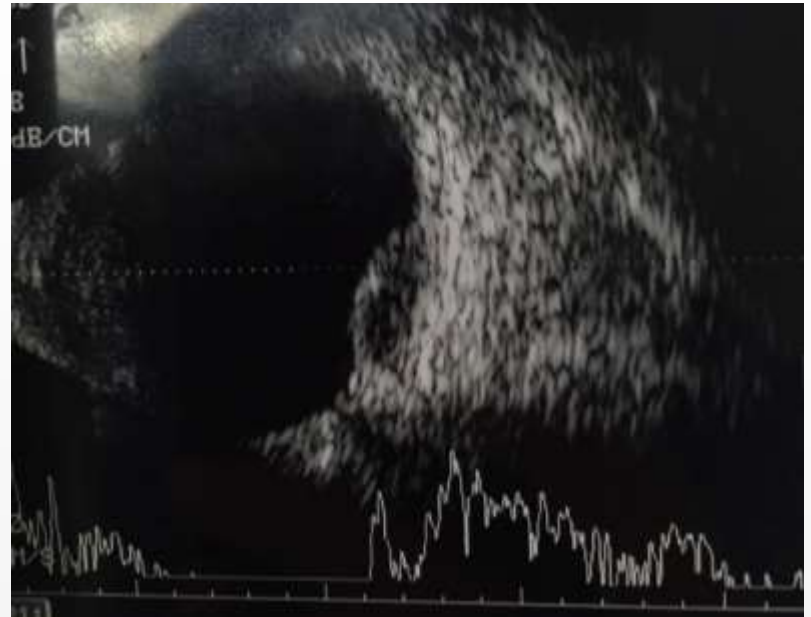
- Thickness
- Fluid
- Symptoms
- Orange pigment
- **Margin (to disc) - <3mm to optic disc**
- Ultrasound hollowness
- Halo absence
- Drusen absence



# Clinical Presentation

”To Find Small Ocular Melanomas Using Helpful Hints Daily”

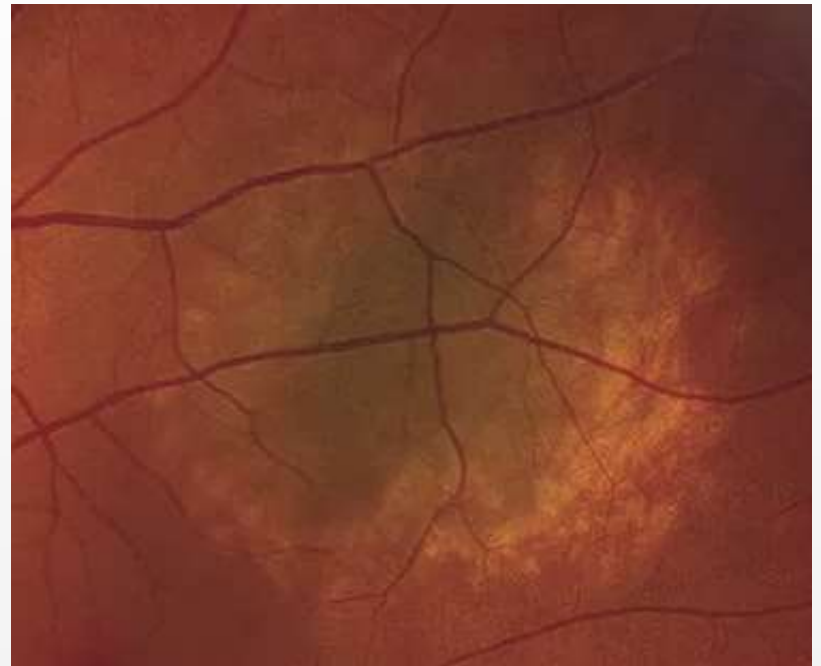
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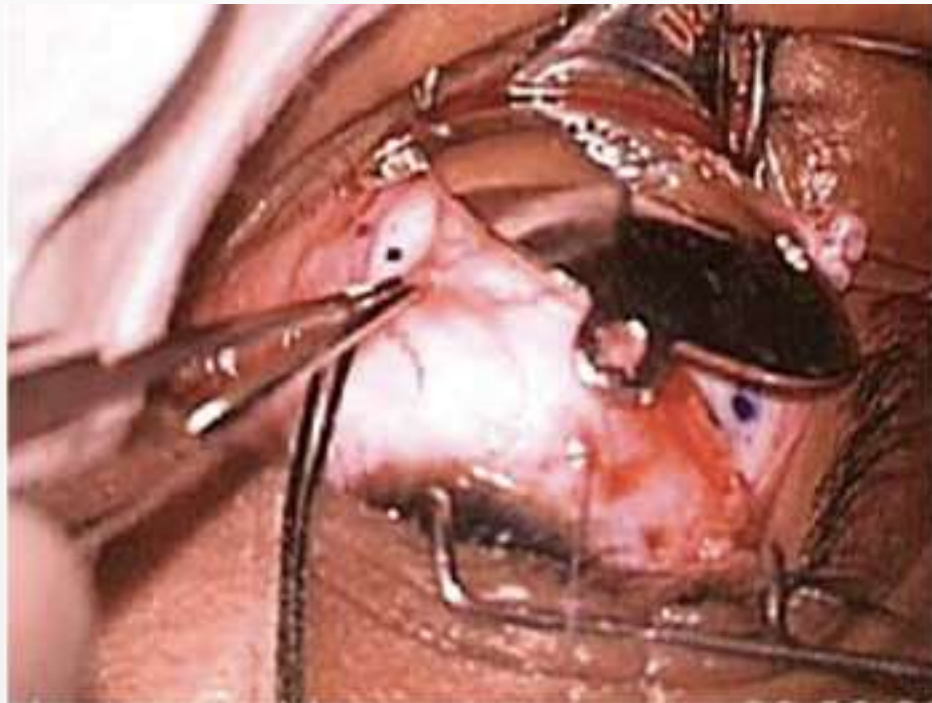
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- **Drusen absence**



# Treatment

- Plaque Brachytherapy
- Charged particle radiotherapy (RT)
- Transpupillary thermotherapy (TTT)
- Enucleation



# Collaborative Ocular Melanoma Study (COMS)

Small (<2.5mm thickness, <12mm diameter)

or

Medium (2.5-10mm thickness, 12-16mm diameter)

- Plaque brachytherapy, charged particle RT, TTT

Large (>10mm thickness or >2mm thick and >16mm diameter)

- Enucleation



# Cytogenetics

- Tumor gene expression profiling (GEP) is becoming a major prognostic factor
- Tests 12-15 genes, classifies tumors as either Class 1A, 1B or Class 2
  - Class 1 (60%) – Low metastatic potential
    - 1.1% metastasized at 18 months
  - Class 2 (40%) – High metastatic potential
    - 25.9% metastasized at 18 months
  - GNAQ, GNA11, LZTS1 (8p22), DDEF1 (8q24.21), PTP4A3 (8q24.3), TCEB1 (8q21.11), BAP1, NOTCH and others
- Primary advantage of GEP assays is to stratify patients into risk groups for recurrence or metastasis
  - Closer follow-up for patients with Class 2 tumors
  - 8% vs 45% 5-year mortality rate from metastasis for Class 1 vs Class 2 tumors





# Cytogenetics

- PRAME gene expression is an independent biomarker
- A total of 389 consecutive patients were assigned to Class 1 or Class 2 using a prospectively validated 12-gene prognostic classifier
- The 5-year actuarial rate of metastasis was 0% for Class1(PRAME-), 38% for Class1(PRAME+), and 71% for Class 2 tumors.
- PRAME is an independent prognostic biomarker in UM, which identifies increased metastatic risk in patients with Class 1 tumors

Clin Cancer Res. 2016 Mar 1;22(5):1234-42. doi: 10.1158/1078-0432.CCR-15-2071.

**PRAME as an Independent Biomarker for Metastasis in Uveal Melanoma.**

Field MG<sup>1</sup>, Decatur CL<sup>1</sup>, Kurtenbach S<sup>1</sup>, Gezgin G<sup>2</sup>, van der Velden PA<sup>2</sup>, Jager MJ<sup>2</sup>, Kozak KN<sup>1</sup>, Harbour JW<sup>3</sup>.



# Prognosis

## Tumor size and class:

- The most significant prognostic factor was GEP classification
- The only other variable that provided independent prognostic information was size
- 339 patients
- 5-year metastasis-free survival were
  - 97% for class 1 with diameter of less than 12 mm
  - 90% for class 1 with diameter of at least 12 mm
  - 90% for class 2 with diameter of less than 12 mm
  - 30% for class 2 with diameter of at least 12 mm

[JAMA Ophthalmol.](#) 2016 Apr 28. doi: 10.1001/jamaophthalmol.2016.0913. [Epub ahead of print]

**Prognostic Implications of Tumor Diameter in Association With Gene Expression Profile for Uveal Melanoma.**

[Walter SD](#)<sup>1</sup>, [Chao DL](#)<sup>1</sup>, [Feuer W](#)<sup>1</sup>, [Schiffman J](#)<sup>1</sup>, [Char DH](#)<sup>2</sup>, [Harbour JW](#)<sup>3</sup>.



# Ocular Melanocytosis

- Characterized by slate-gray appearance of sclera, hyperpigmentation of iris or choroid
- In a study of 230 pts with ocular melanocytosis
  - Involved sclera (92%), iris (17%), choroid (12%)
- Affects 1 in 5000 people
- Approx double lifetime risk of uveal melanoma (1 in 400) compared to general population
- Also have an increased risk of glaucoma from pigment blocking TM outflow
- On a spectrum of disease including oculodermal melanocytosis (nevus of Ota)



# Followup

- Pt was healing well from the enucleation
- Receiving adjuvant pembrolizumab by oncology given size of tumor



# Take Away

- Uveal melanoma is the should be suspected in cases with clinical features as discussed with TFSOM-UHHD
- Small and medium size melanomas can be treated safely with globe-sparing techniques
- Gene expression testing is becoming a prominent prognostic factor



# References

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- Correa ZM, Augsburger JJ. Sufficiency of FNAB aspirates of posterior uveal melanoma for cytologic versus GEP classification in 159 patients, and relative prognostic significance of these classifications. *Graefes Arch Clin Exp Ophthalmol*. 2014; 252(1): 131–135.



# Thank You

- Dr. Adeniran
- Dr. Compton
- Dr. Mathew (ULH pathology)

