



The Retina Society

Diagnosis, treatment, and outcomes in patients with vitreous metastasis from cutaneous melanoma

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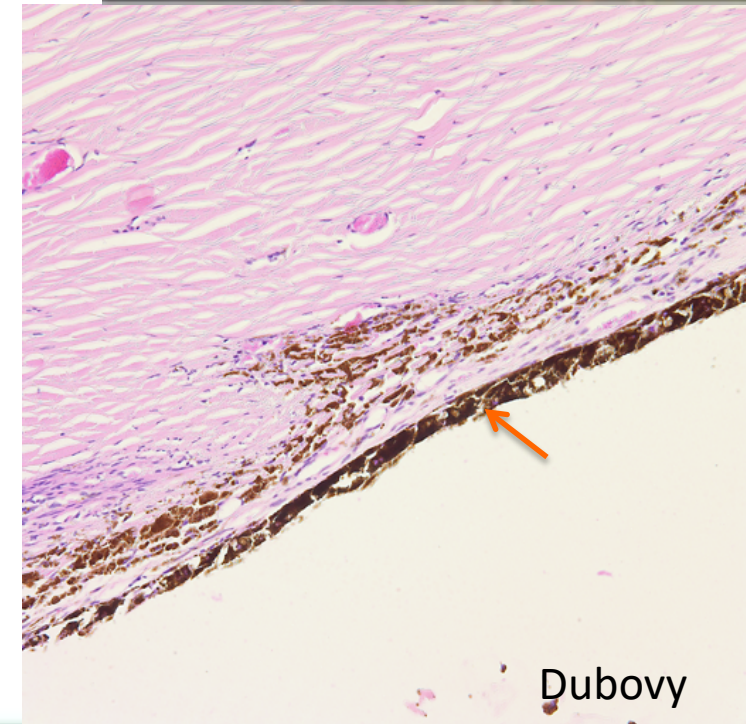
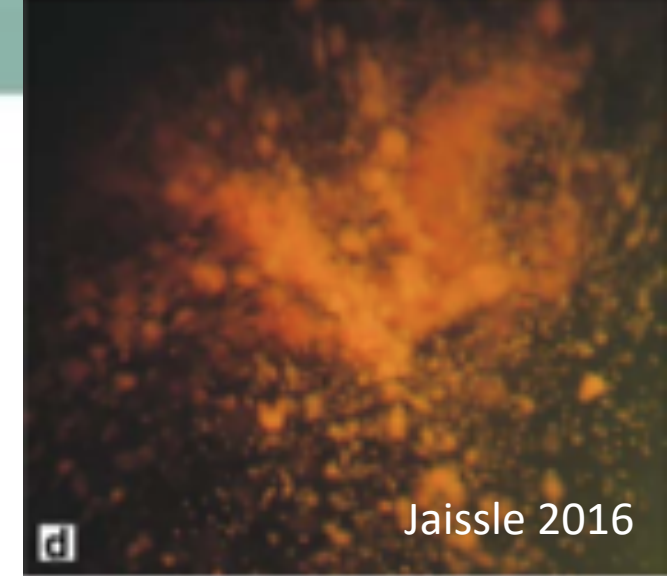
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Summary

- We report the clinical findings, treatment modalities, and outcomes in a series of 5 patients with biopsy-confirmed vitreous metastasis from cutaneous melanoma (1997-2019) at a single institution
- **Vitreous metastasis from cutaneous melanoma may occur despite good systemic response** to checkpoint inhibitor immunotherapy
- **We recommend:**
 - 1. PPV for diagnosis and debulking of tumor cells
 - 2. Followed by periodic intravitreal injections of melphalan
- **The optimal frequency and endpoint of injections are not known**
 - We recommend monthly injections to inhibit further pigment proliferation
 - Pigment infiltration is unlikely to disappear completely
 - Acellular, within melanophages, or growth-arrested melanoma cells

Intraocular metastasis of cutaneous melanoma is rare but well-described

- 0.5-1% of intraocular metastases
- 1/3 of metastatic melanoma patients have asymptomatic intraocular metastases at autopsy
- Chief complaint = decreased vision + floaters
- Presentation = discrete mass or vitreous cells (golden brown spherules in 60%, remainder amelanotic)
 - May masquerade as uveitis and glaucoma
 - Glaucoma in >50%
 - Due to tumor/pigment burden or NVG
- **Sites of ocular metastasis:** vitreous, retina, choroid, iris, ciliary body, optic nerve, anterior chamber, TM, orbit
- **Historically poor prognosis:** enucleation, 5% distant spread



2011: FDA-Approved Checkpoint Immunotherapy

Agent	Mechanism of Action
Ipilimumab (Yervoy, Bristol-Myers Squibb)	mAb targeting CTLA-4
CTLA-4 (cytotoxic T-lymphocyte-associated protein 4)	
Pembrolizumab (Keytruda, Merck)	mAb targeting PD-1
PD-1 (programmed death 1)	
Nivolumab (Opdivo, Bristol-Myers Squibb)	mAb targeting PD-1

5-year survival (ipi-nivo):

22% → 52%

→ Leads to immune activation

Effective in metastasis:

- >40% cutaneous
- <18% uveal

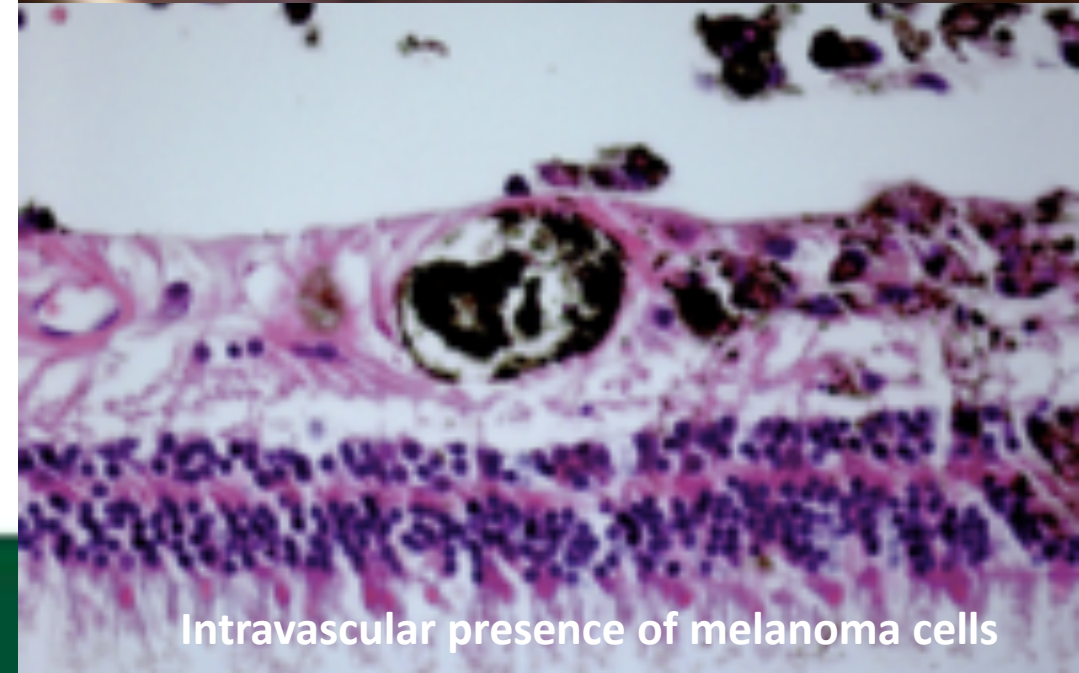
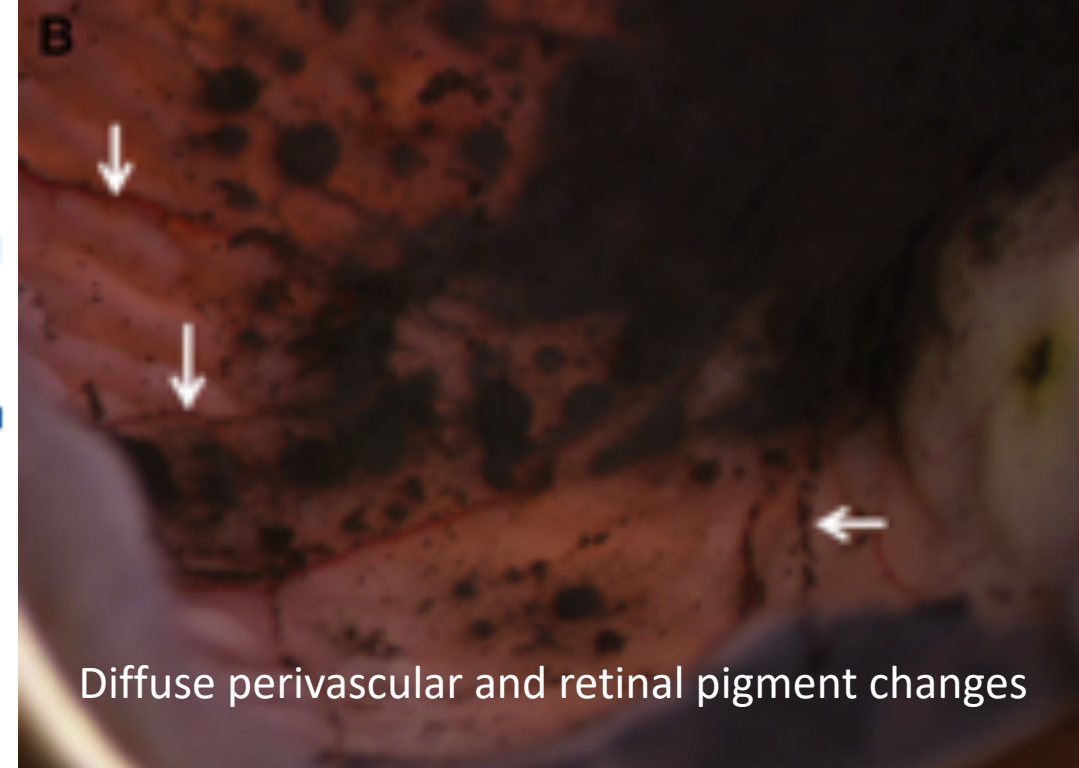
Intravitreal Cutaneous Metastatic Melanoma in the Era of Checkpoint Inhibition

Unmasking and Masquerading

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The largest multicenter, retrospective cohort study of 14 eyes in 11 patients

- 8 patients completed or are on CPIs
 - 5 eyes with elevated IOP (4 NVG)
 - VA range 20/20 to NLP
 - VA <20/200 in 8 patients
- Intravitreal melphalan introduced



Purpose

- To report the clinical findings, treatment modalities, and outcomes in a series of patients with vitreous metastasis from cutaneous melanoma.

Methods

- This was a single-center, retrospective case series of biopsy-confirmed vitreous metastasis from cutaneous melanoma managed at our institution from 1997 to 2019
- Charts were reviewed for demographics, ophthalmic findings, diagnosis, treatment, clinical course, and medical history

Results

- **Identified 5 eyes of 5 patients with metastatic cutaneous melanoma to vitreous**
 - Median age at presentation: 84 (range 37-88) years
 - Median follow up after ophthalmic diagnosis: 7 (range 4-8) months
 - Median time from primary diagnosis to vitreous metastasis: 2 (range 2-15) years
 - 1 patient had active systemic disease at the time of vitreous metastasis
- **Checkpoint inhibitor (CPI) immunotherapy in 3 cases** (all with partial/complete response)
- **Baseline pigment infiltration of:**
 - Vitreous 5/5 cases
 - Anterior segment 4/5 cases
 - Retina 3/5 cases

	Case 1	Case 2	Case 3	Case 4	Case 5
Prior Systemic Comorbidities	Healthy	Healthy	Healthy	Myelodysplastic Syndrome	Healthy
Time of Skin Melanoma	2 years prior	<2 years prior	2 years prior	15 years prior	3 years prior
Year of Ocular Diagnosis	2007	2017	2019	2019	2019
Site of Skin Melanoma	Right shoulder	Right cheek	Right thigh Head and neck	Left arm	Unknown
Metastasis	Lymph nodes Axilla Chest wall	Lymph nodes Parotid gland	CNS (brain, spine)	Unknown (Patient refused imaging)	Unknown (Not available)
Prior Systemic Treatment	Surgical resection Systemic interferon (subcutaneous, intravenous) External beam radiation (3600 Gy)	Mohs surgery, right cheek Nivolumab *	Chemotherapy Gamma knife External beam radiation Pembrolizumab *	Surgical resection only No systemic therapy	Nivolumab *
Systemic Treatment (Current)	Interferon	None (Last dose 3 weeks prior)	Pembrolizumab	No	None
Systemic Disease Status (by whole body imaging)	Active at time of eye DX	Remission	Inactive/Controlled	Unknown (Patient refused imaging, denies non-ocular symptoms)	Remission
Vital Status	Unknown (Unavailable)	Unknown (Lost to follow up)	Alive	Alive	Alive

Key: DX: diagnosis, CNS: central nervous system

Results

- **Ophthalmic treatments**

- Pars plana vitrectomy 5/5 cases
- Intravitreal melphalan (20 mg/0.05 mL) 3/5 cases
- Intravitreal methotrexate (500 mg/0.1 mL) 1/5 cases (*could not receive melphalan*)

- **Outcomes**

- **Visual Acuity, median LogMAR (range)**
 - Initial 0.7 (0.20-3.0)
 - Final 1.3 (0.3-1.7); 1 enucleated, 1 unavailable
- **Secondary glaucoma** 4/5 cases
- **Enucleation** 1/5 cases
 - *This patient underwent a trial of 2 monthly melphalan injections for progressive tumor burden before enucleation*

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years) at Presentation	37	87	88	88	82
Gender	Male	Male	Female	Female	Female
Duration of Symptom(s)	2 days	3 months (1 month worsening)	3 months	6 months	1 month
Laterality of Disease	Right	Left	Right	Right	Right
Presenting Symptom(s)	Vision loss Eye pain	Vision loss Floaters	Vision loss floaters flashes	Vision loss Floaters	Vision loss Floaters Referral (s/p PPV 3 months prior)
Presenting Sign(s)	Neovascular glaucoma Hyphema	Vitreous hemorrhage	Anterior uveitis Intermediate uveitis	Pigment on IOL capsule	Vitreous hemorrhage (Recurrent, with pigment)
Initial Exam Findings	Posterior synechiae Corneal edema No view of fundus	Cataract Pigment on capsule No view of fundus	Large pigmented KP 3+ AC cell Koepe nodules Pigment on capsule No view of fundus	Opacification of IOL No view of fundus	Cataract Pigment on capsule Hazy view of fundus Retina flat, pigment changes
B-scan ultrasound (Presentation)	Vitreous opacities Membrane No masses	Vitreous opacities Vascularized dome-shaped mass 9:30 (7.5r x 7.5c x 1.3 mm)	Vitreous opacities No masses	Focal hyperechoic source (attached to vitreous skirt) No marked vitreous cells	Vitreous opacities Opacity on vitreous skirt No masses
Intraoperative Findings (Additional)	CRVO (Diffuse DBH and CWS)	Retinal tear Pigmented ERM Choroidal mass (nasal)	N/A	N/A	N/A
Melanin Status	Melanotic	Melanotic	Melanotic	Amelanotic	Melanotic
VA (Initial)	20/100 (uncorrected)	Hand motions	0/300 (BCVA)	20/30+2 (BCVA)	20/100 (BCVA)
VA (Final)	Not available	Enucleated	0/40 (BCVA)	20/1000 (uncorrected)	20/400 (uncorrected)
Intraocular Pressure (Initial)	22	13	4	14	31
Intraocular Pressure (Final)	Not available	35	0	18	22
Ocular Treatments	1. Intravitreal bevacizumab 2. Glaucoma medications 3. Phaco/IOL/PPV/Vit biopsy/IV triamcinolone 4. Unavailable thereafter	1. PPV/Vit biopsy 2. PPV/MPV/EL/AFx 3. Melphalan x 2 (rescue) 4. Enucleation	1. Subtenon triamcinolone 2. PPV/Vit biopsy 3. Melphalan x 6 (monthly)	1. PPV/Vit biopsy (outside) 2. Nd:YAG capsulotomy 3. Glaucoma medications 4. PPV/Vit biopsy 5. Methotrexate x3 (w/k 1, 2, 6) (for amelanotic globules/haze)	1. PPV/Vit biopsy (outside) 2. Phaco/IOL/PPV/Vit biopsy/Melphalan 3. Melphalan x 3 (monthly)
Response to Ocular Treatments	Not available.	Poor (iris bombe, episcleral pigment 6 weeks after 1 st melphalan)	Good	Adequate	Good
Follow-up (Months) from DX	Not available.	8	5	7	4
Final Ocular Disease Status	Not available.	Enucleated	No melanoma cells Pigment on lens surface	Amelanotic globules/haze (lens capsule and retinal surface)	Inactive pigmented cells (vitreous and retinal surface)

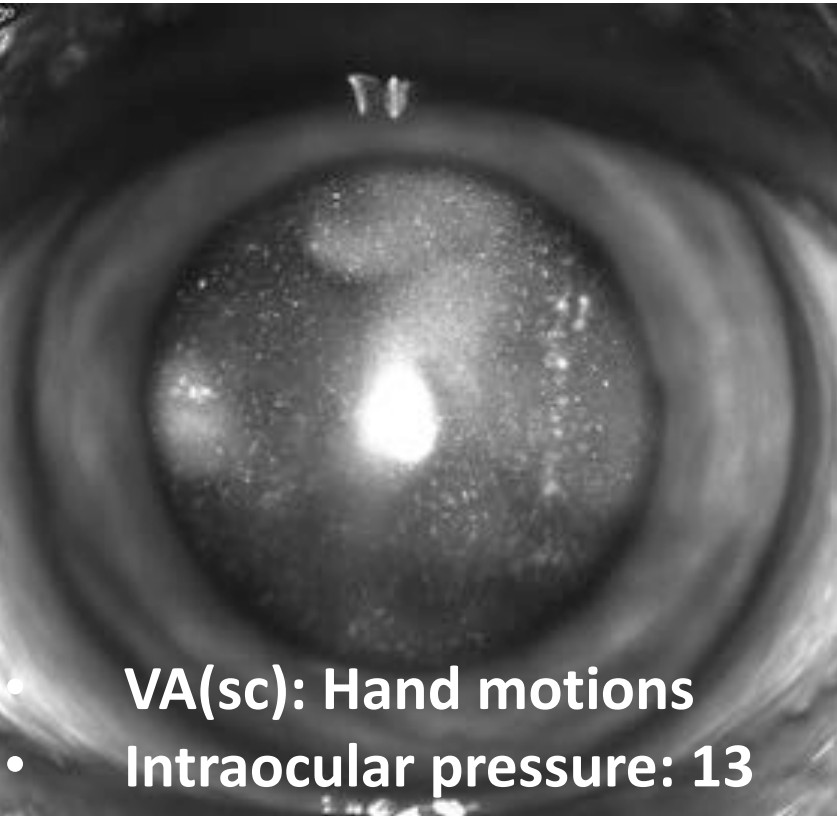
Key: DX: diagnosis, Vit: vitreous, AC: anterior chamber, CRVO: central retinal vein occlusion, DBH: dot blot hemorrhages, CWS: cotton wool spots, Nd:YAG: neodymium-doped yttrium aluminium garnet, Phaco: phacoemulsification, IOL: intraocular lens, PPV: pars plana vitrectomy

Case 2

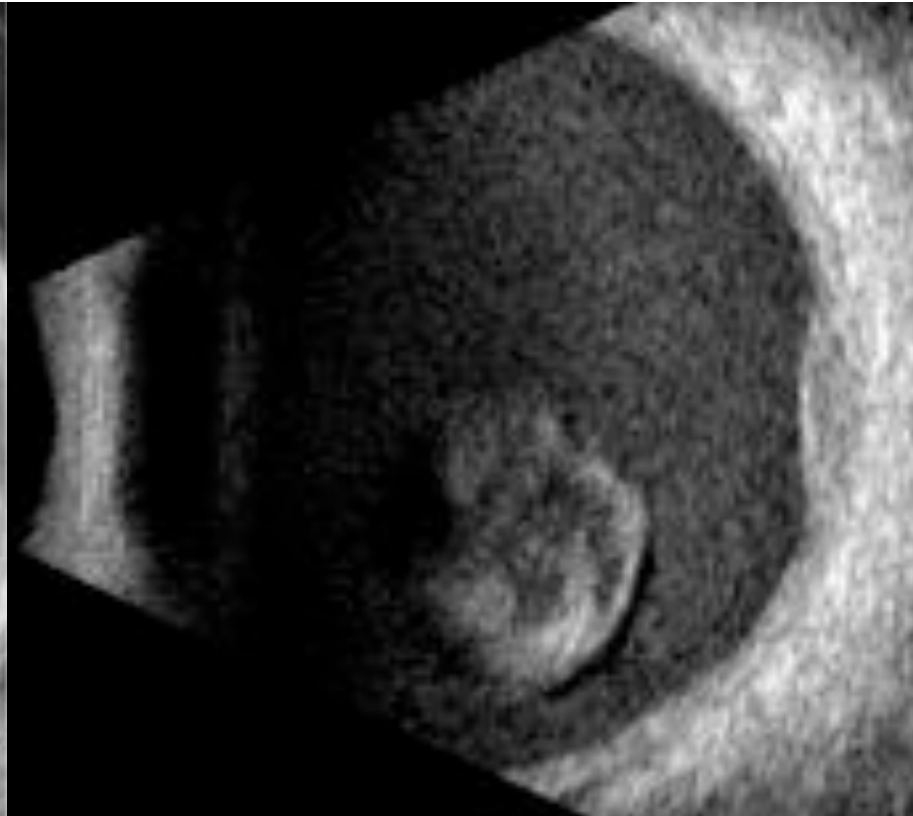
- 87 year-old M with decreased vision and floaters for 3 months in the left eye, worsening for 1 month
- History of stage 4 head and neck melanoma secondary to a cheek lesion
- s/p Mohs resection and received nivolumab with complete response (last dose 3 weeks prior)

Case 2

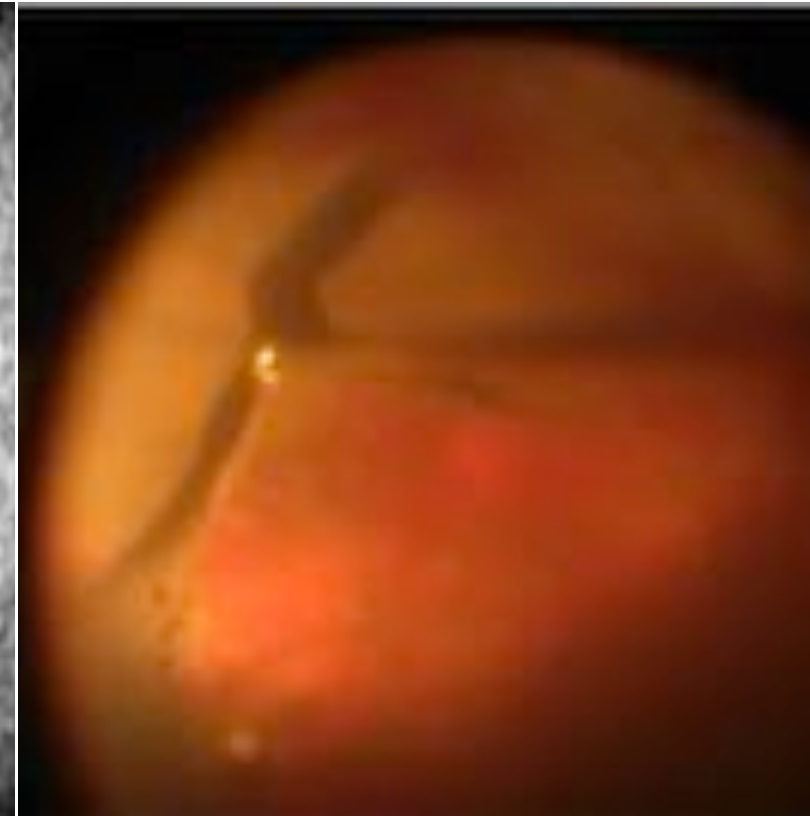
(a) Posterior lenticular opacities



(b) B-scan with a dome shaped, hyperechoic lesion of minimal vascularity measuring 7.2 x 7.2 x 1.3 cm

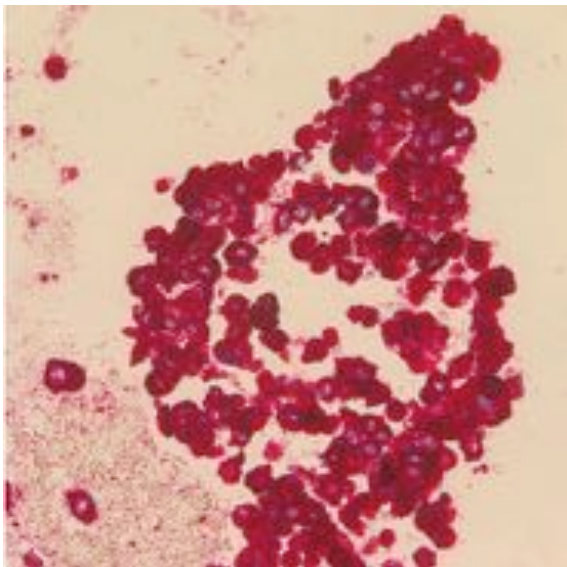


(c) intraoperative membrane peeling during diagnostic PPV

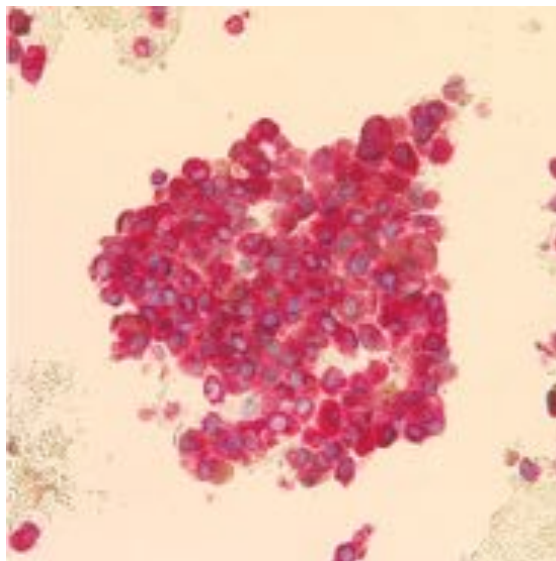


Vitreous

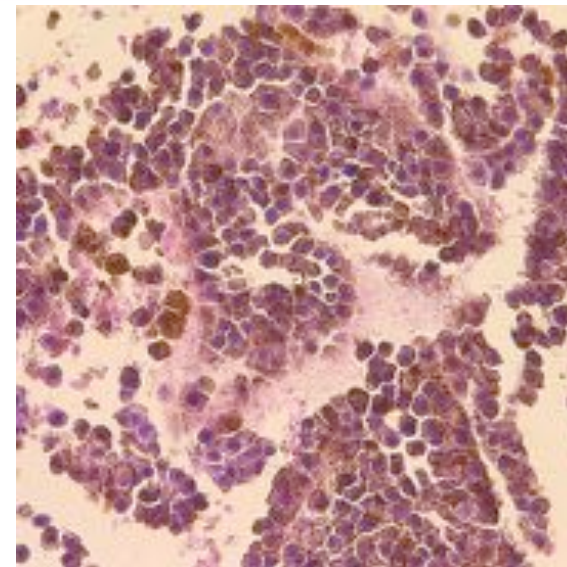
HMB45



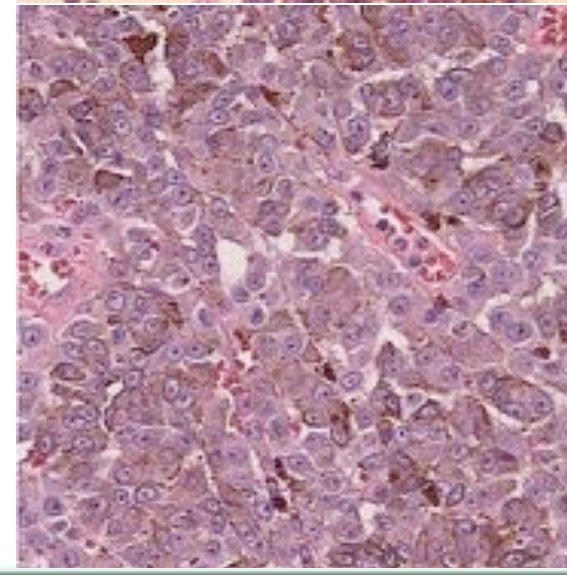
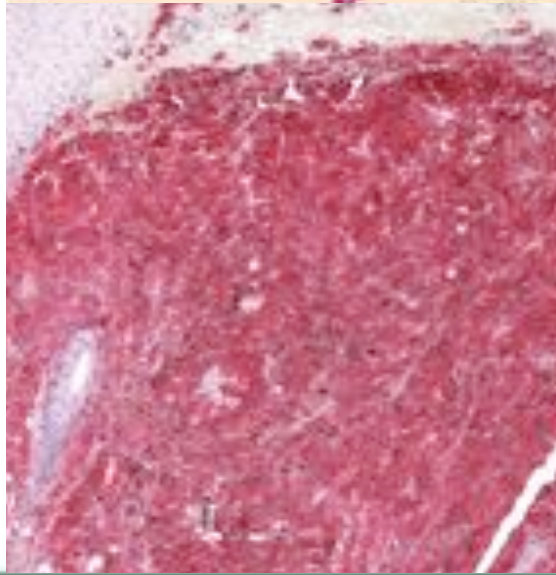
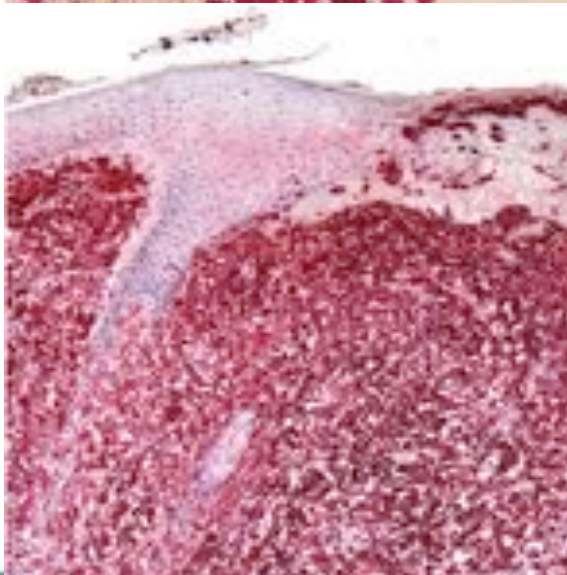
Melan-A



H&E

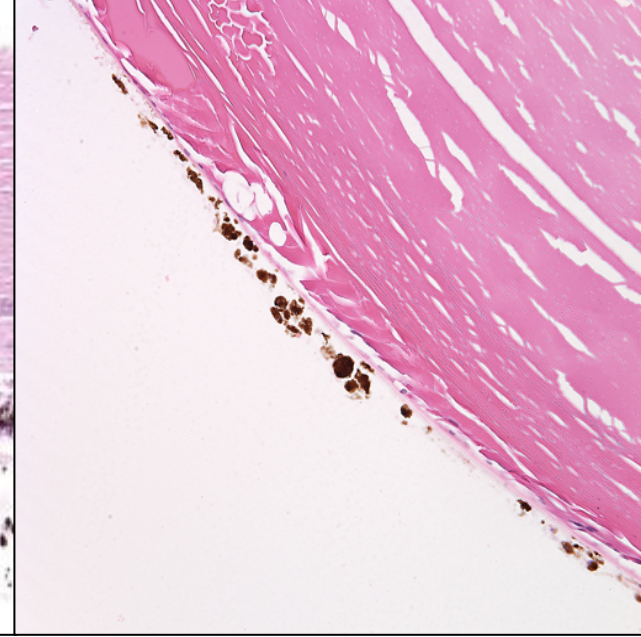
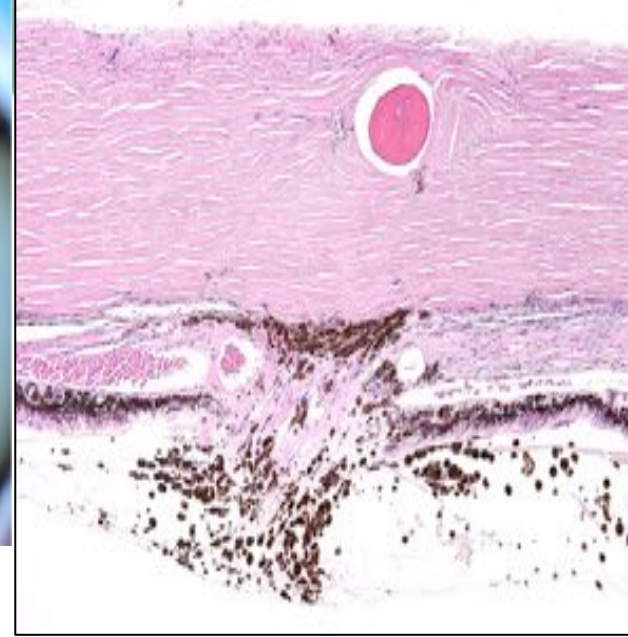
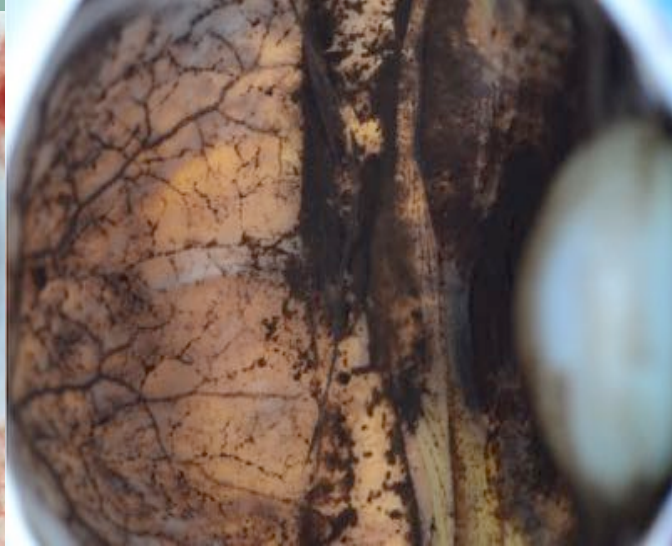
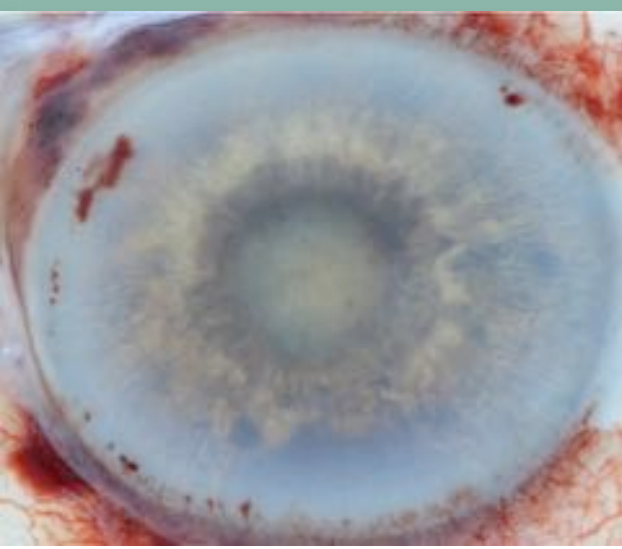


Skin

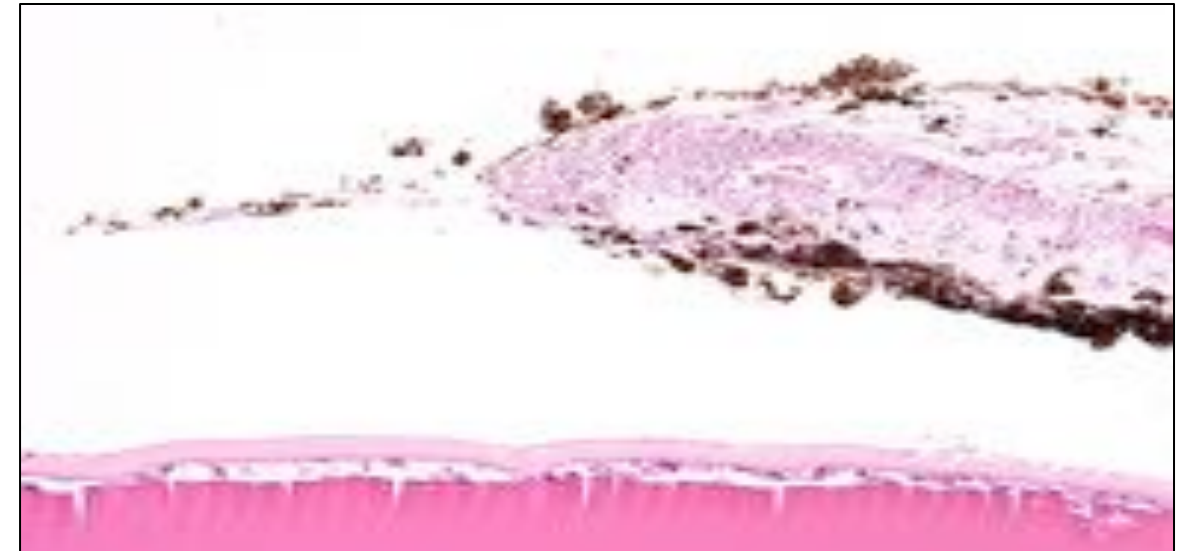


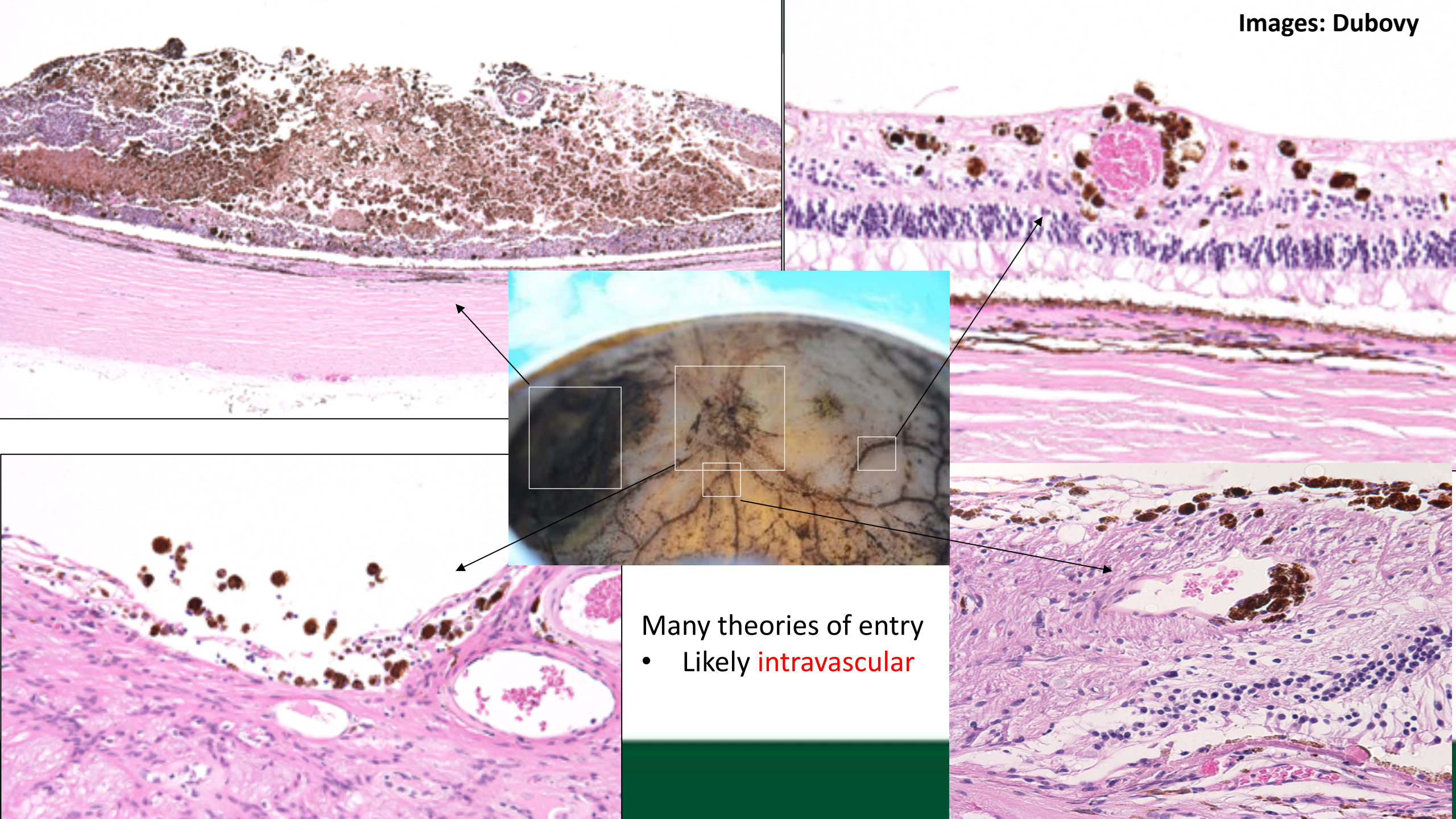
Complicated Clinical Course

- **Enucleation was indicated due to** new episcleral pigmentation on the bulbar surface, iris bombe at POM3
 - MRI brain and PET/CT were negative



- Histopathology of the enucleation specimen demonstrated melanoma cells invading the trabecular meshwork, angle, and retina, optic nerve, with perivascular spread
- No disease recurrence 6 weeks after enucleation
 - Then lost to follow up





Many theories of entry

- Likely **intravascular**

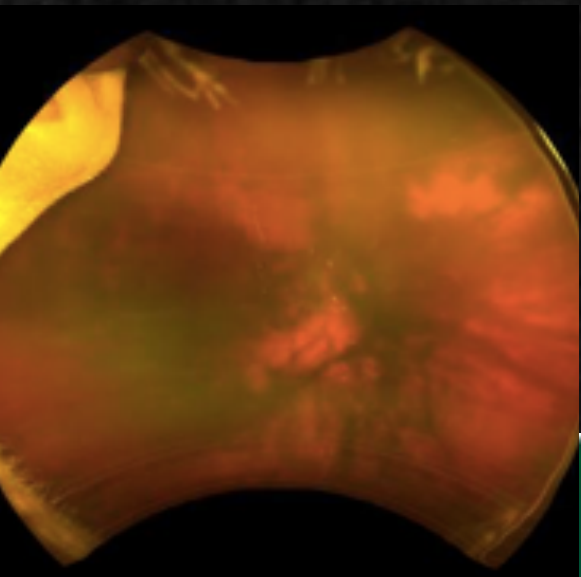
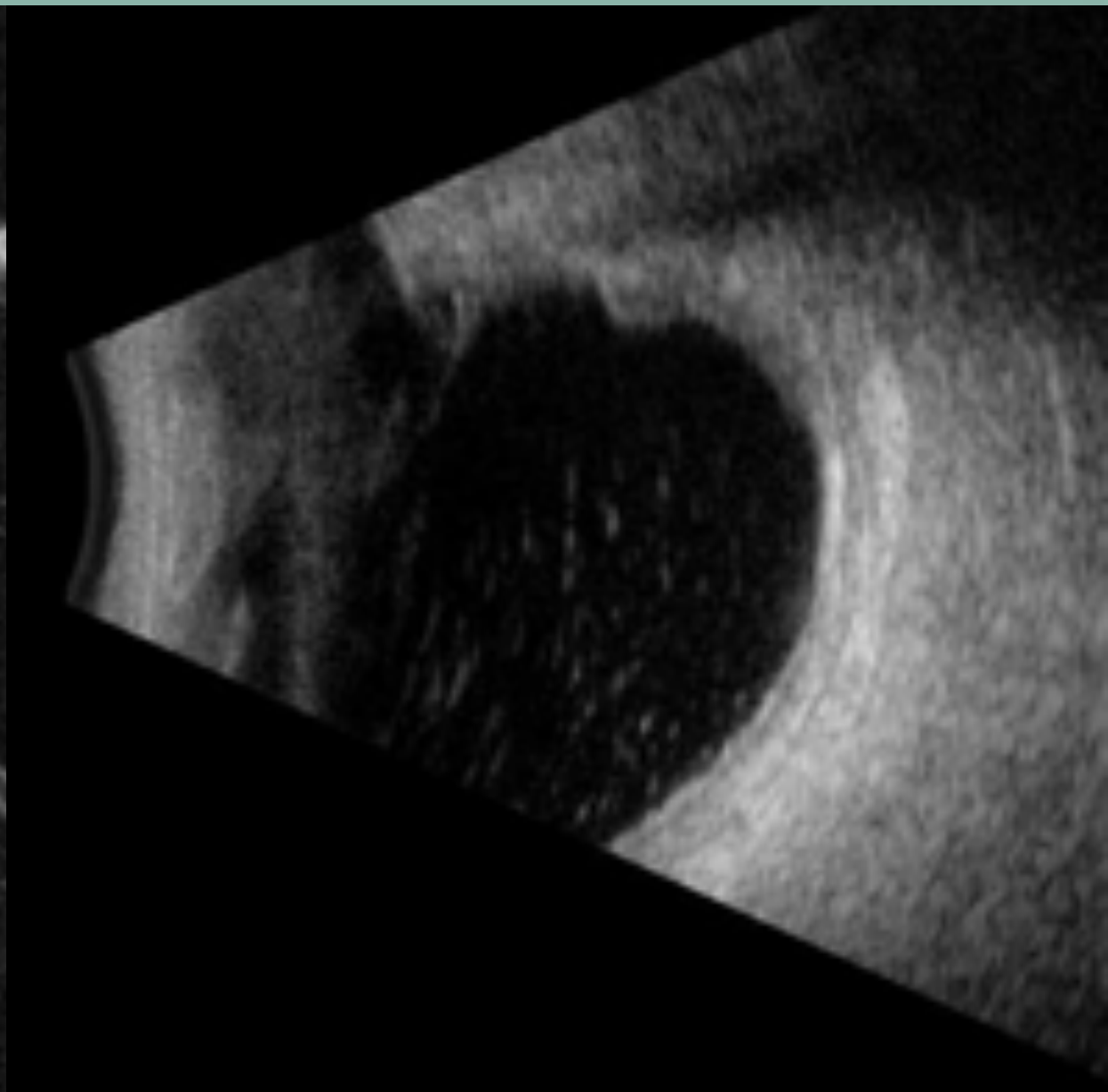
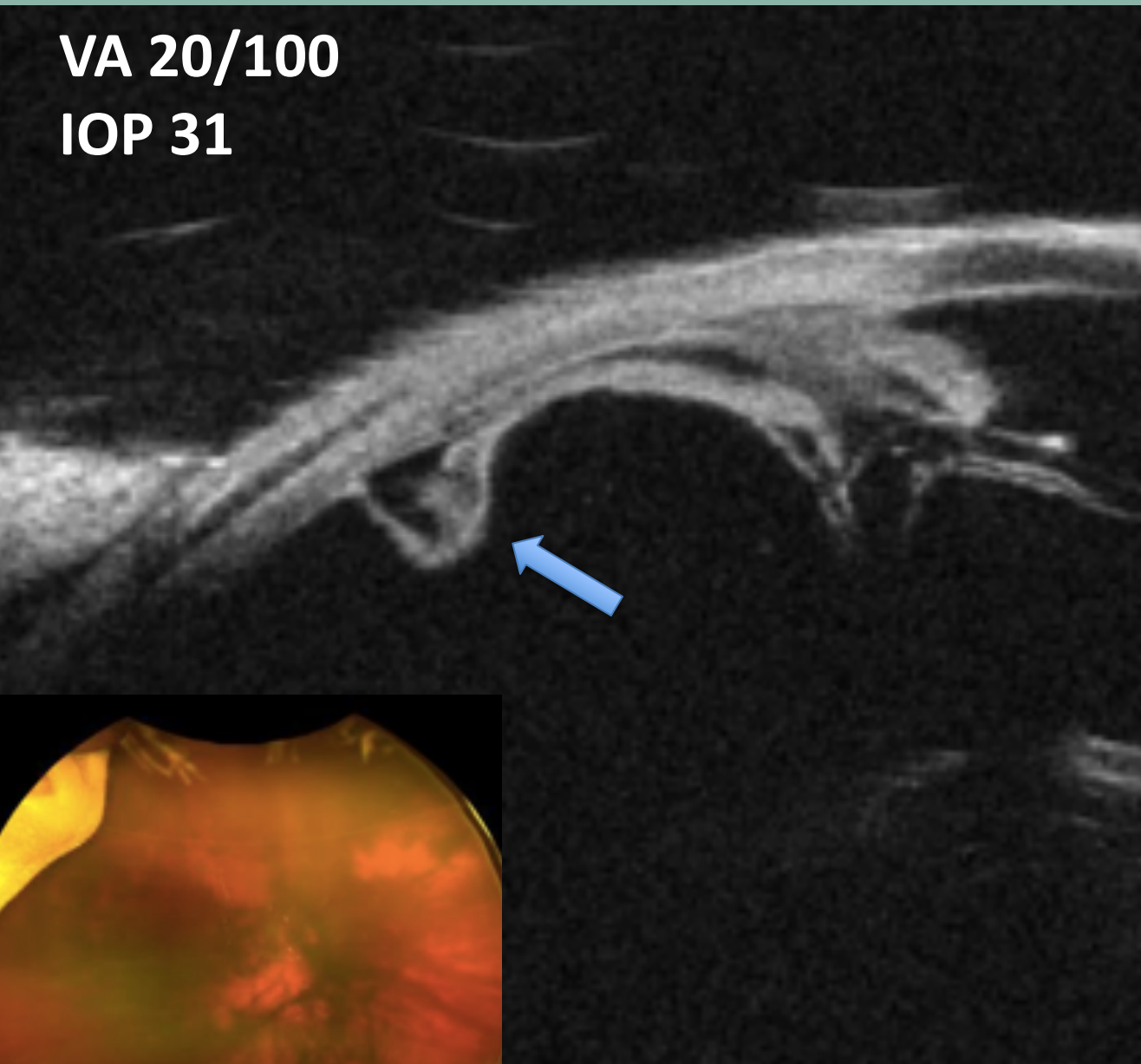
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Final Ocular Disease Status	Not available	Enucleated	No melanoma cells Pigment on lens surface	Amelanotic globules/haze (lens capsule and retinal surface)	Inactive pigmented cells (vitreous and retinal surface)

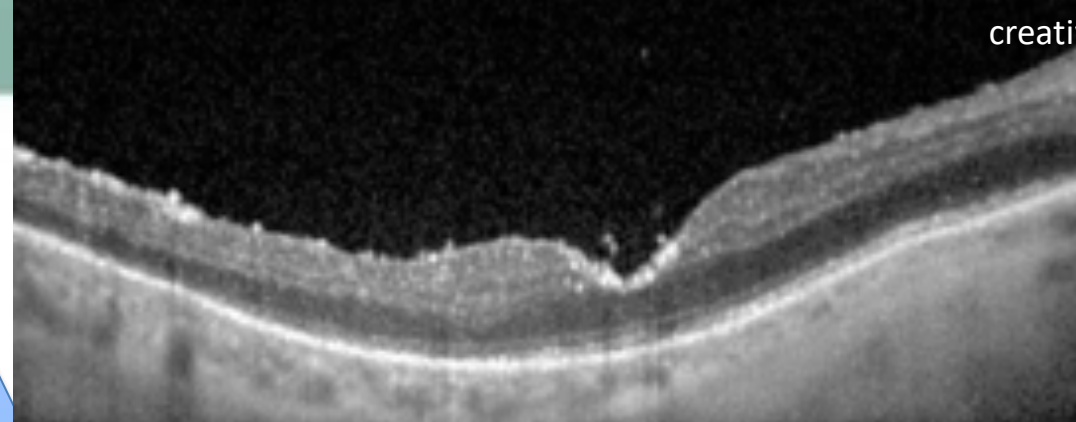
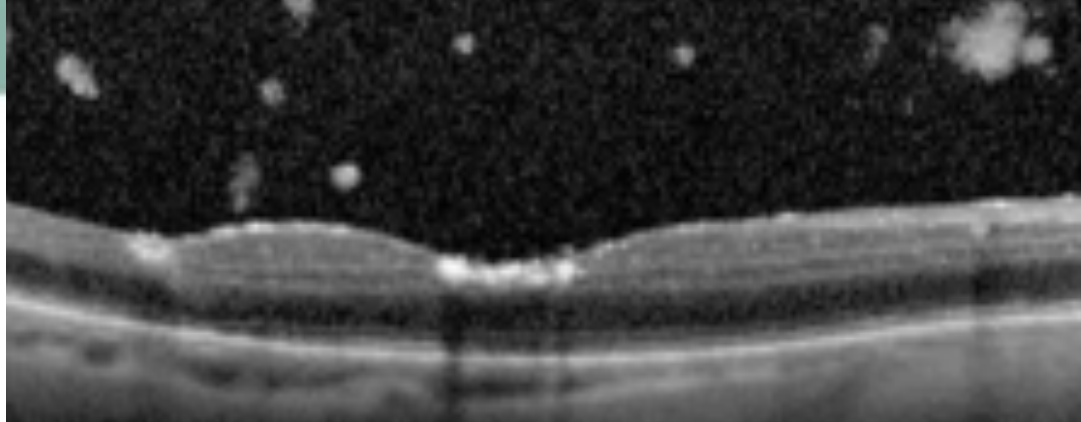
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Case 5

- 82 year old F with decreased vision in the right eye
- S/P PPV for a non-clearing vitreous hemorrhage
- Arrived for 2nd opinion for pigmentary deposits
- Has a history of metastatic cutaneous melanoma
 - s/p Nivolumab (last 2 years prior)
- PET/CT scan negative (1 month prior)

VA 20/100
IOP 31





Phaco/PPV
(12/10/19)



POM1
VA 20/200
IOP 22



POM2
VA 20/200
IOP 23

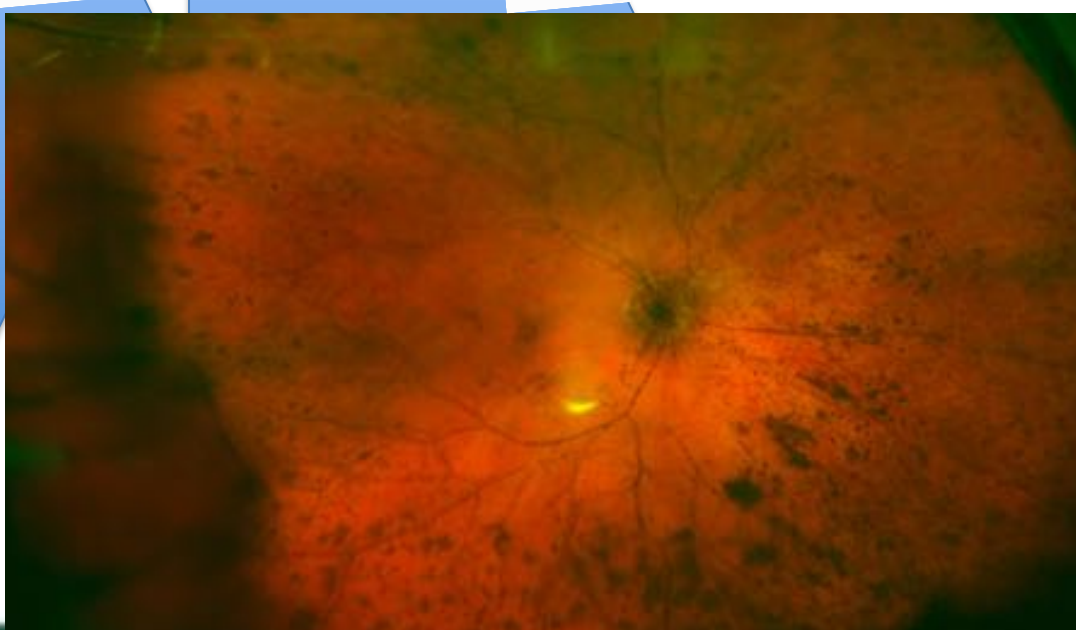
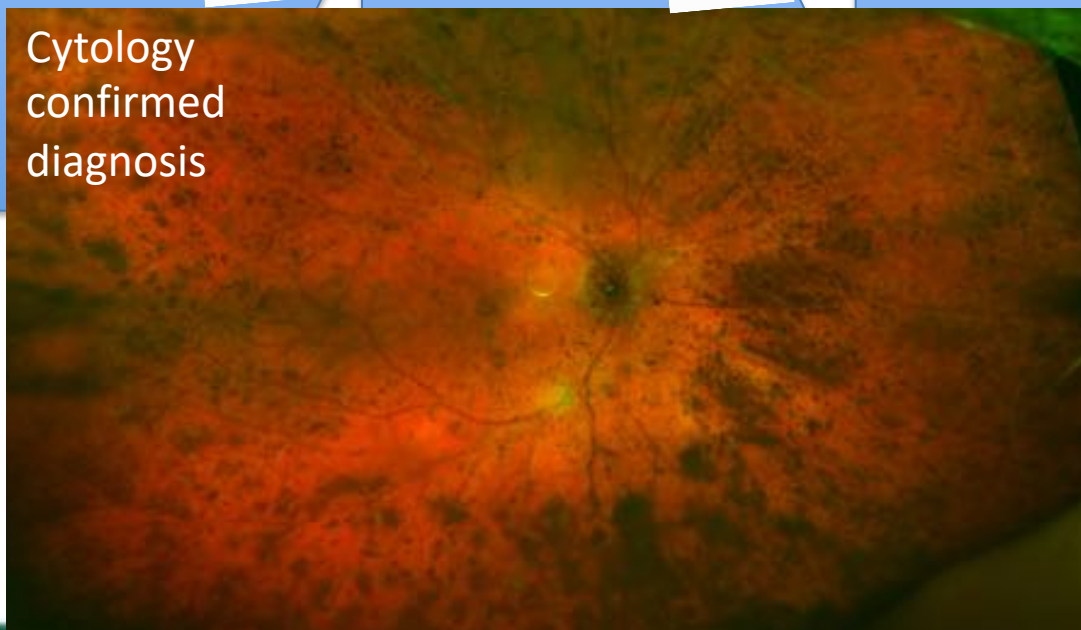


POM3
VA 20/400
IOP 22



*Melphalan holiday
commenced*

Cytology
confirmed
diagnosis



Summary

- **Vitreous metastasis from cutaneous melanoma may occur despite good systemic response to checkpoint inhibitor immunotherapy**
- **We recommend:**
 - 1. PPV for diagnosis and debulking of tumor cells
 - 2. Followed by periodic intravitreal injections of melphalan
- **The optimal frequency and endpoint of injections are not known**
 - We recommend monthly injections to inhibit further pigment proliferation
 - Pigment infiltration is unlikely to disappear completely
 - Acellular, within melanophages, or growth-arrested melanoma cells

References

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