Posterior Uveal (Ciliary Body and Choroidal) Melanoma

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July 27, 2010

Chief Complaint: 31-year-old man with "floaters and blurry vision" in the right eye (OD).

History of Present Illness: In August 2007, a healthy 31-year-old truck driver from Nebraska started noticing floaters in his right eye. The floaters gradually worsened and clouded his central vision. His family doctor tried changing his blood pressure medications, but this did not help. He later saw an ophthalmologist in his home state who told him there was a "mass" in his right eye. He was referred to the University of Iowa Department of Ophthalmology and Visual Sciences.

Past Ocular History: The patient has had no prior eye surgery or trauma.

Past Medical History: The patient reports prior excision of a benign skin nevus. He also has hypertension.

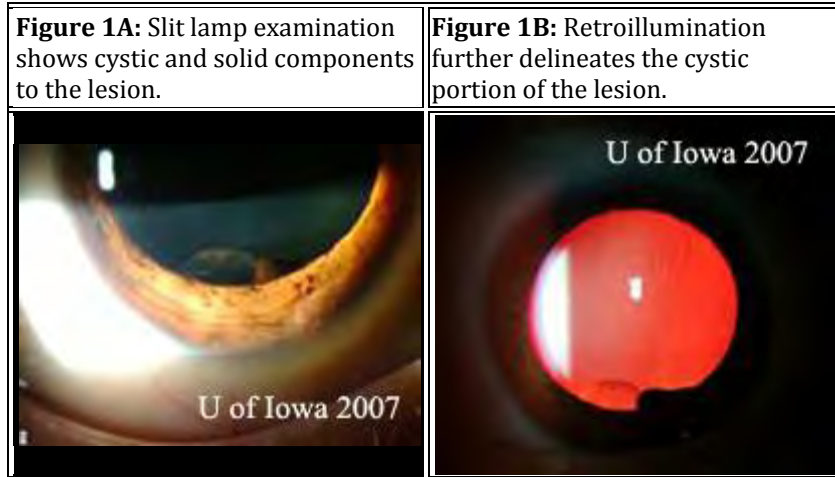**Medications:** Metoprolol and triamterene/hydrochlorothiazide

Family History: The patient's mother has a history of neurofibromatosis. His father had an enucleation for an "eye cancer" and subsequently died due to metastatic spread of the cancer. His grandmother had skin melanoma.

Social History: The patient lives in Nebraska with his wife and child. He has never smoked and only drinks on "special occasions".
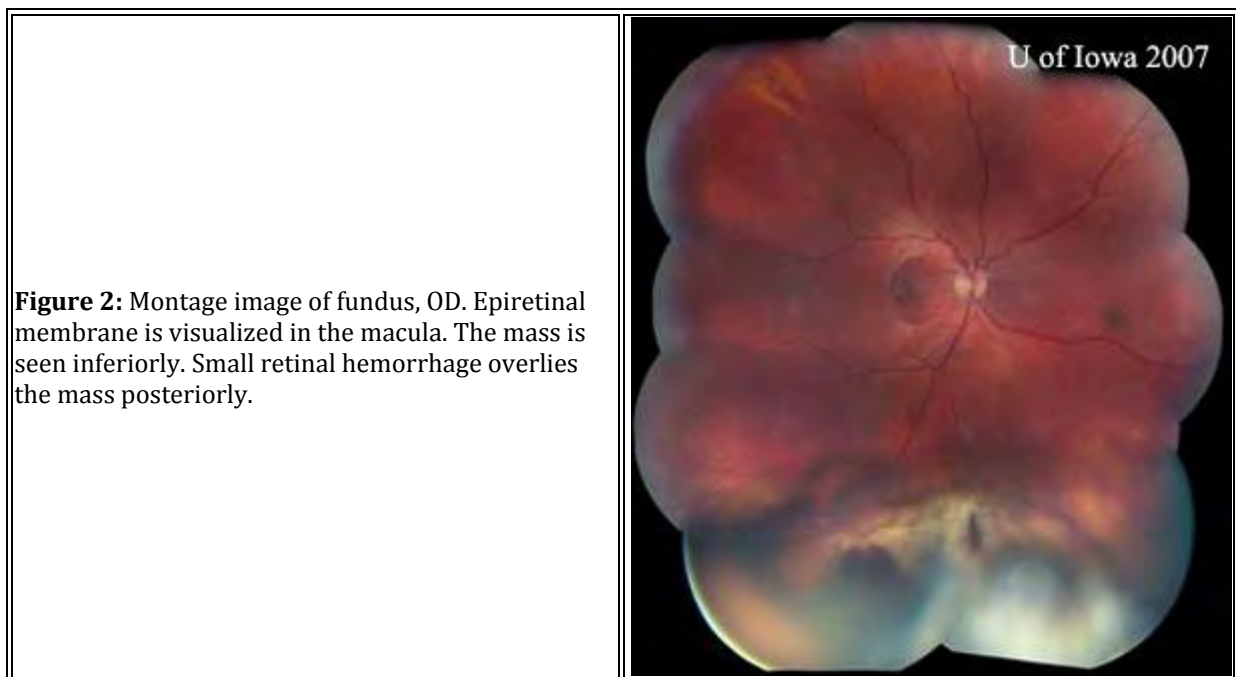
Review of Systems: Negative, except as noted above.

Ocular Examination:
- General: Well-developed, well-nourished Caucasian man in a pleasant mood
- Skin: Several scattered macules and papules on the trunk and all four extremities
- Distance visual acuity (without correction):
  o 20/60-2 OD
  o 20/20 OS
- Near acuity (without correction)
  o 20/30 OD
  o 20/20 OS
- Ocular motility: Full OU. No nystagmus.
- Intraocular pressure (IOP): 18 mmHg OD, 21 mmHg OS
- Pupils: Equally reactive to light in each eye. No relative afferent pupillary defect (RAPD)
- Confrontation visual fields: Full OD and OS
- Amsler grid testing: Central area of metamorphopsia OD, normal OS
- Slit lamp examination:
  o OD:
    ▪ Large, dilated inferior episcleral vessel
    ▪ No abnormal conjunctival or scleral pigmentation
    ▪ Cornea clear and anterior chamber deep and quiet
    ▪ Brown, 2mm diameter nonpigmented cyst involving the posterior iris at 6 o'clock. Nasal to this, a 2mm diameter nonpigmented iris cyst arises from the posterior surface of the iris (Figure 1A). The cyst transilluminates with retroillumination (Figure 1B). There is no rubeosis.
  o OS: Normal

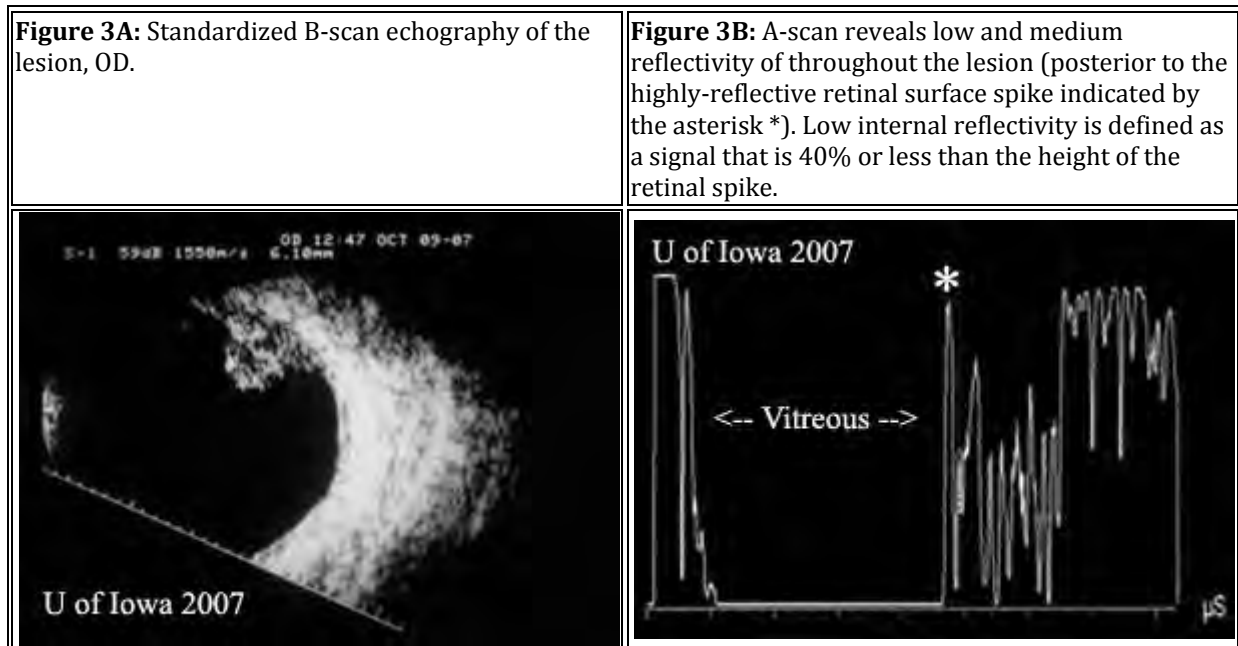| **Figure 1A:** Slit lamp examination shows cystic and solid components to the lesion.	**Figure 1B:** Retroillumination further delineates the cystic portion of the lesion.

- Dilated fundus examination (DFE), OD:
  - Normal optic nerve (Cup-disc ratio 0.20)
  - Epiretinal membrane encircling the fovea with a small extension to the foveal center
  - 1+ pigmented vitreous cell
  - Inferiorly, an approximately 17 x 15 x 5.2 mm amelanotic, lobulated choroidal mass extending circumferentially from 4:45 clockwise to 7:30 o'clock. Mass extends from the iris root to approximately 8mm from the disc and fovea (see Figure 2)
  - At the anterior portion of the ciliary body at 5:30, there is a 2.5 x 2.5 x 2.5 mm, elevated, dark brown, solid, ciliary body mass with a small amount of retinal hemorrhage overlying the posterior portion of this mass and a small preretinal hemorrhage over the temporal portion of the mass
  - Small amount of subretinal fluid is associated with the lesion, especially anteriorly
  - No orange pigmentation, no drusen

Figure 2: Montage image of fundus, OD. Epiretinal membrane is visualized in the macula. The mass is seen inferiorly. Small retinal hemorrhage overlies the mass posteriorly.

Standardized echography: Echography revealed a dome-shaped lesion at 5:30 measuring 6.2mm in height. There was a spherical-shaped extension over this lesion, consistent with the above-noted pigmented mass.

The lesion was irregular with low reflectivity and 2+ vascularity. There was no evidence of extraocular extension. There was a long, low reflective tail extending posteriorly into the choroid from 5:30 o'clock.

Figure 3A: Standardized B-scan echography of the lesion, OD.	**Figure 3B:** A-scan reveals low and medium reflectivity of throughout the lesion (posterior to the highly-reflective retinal surface spike indicated by the asterisk *). Low internal reflectivity is defined as a signal that is 40% or less than the height of the retinal spike.

Course: In summary, the patient's findings included an amelanotic, low reflective, ciliochoroidal mass with associated retinal hemorrhages in his right eye. There was mild vitreous cell and an epiretinal membrane. The lesion also had a pigmented, partially cystic component extending into the ciliary body and a sentinel vessel anteriorly on the ocular surface. The ocular findings were discussed extensively with the patient and his family; they were told that the mass might represent a primary uveal melanoma. Other possible explanations included metastatic disease to the eye or an atypical inflammatory lesion.

A metastatic evaluation was performed on the same day of presentation. Physical exam, laboratory evaluation, PET scan and CT scan were negative for metastatic disease. When the metastatic workup failed to reveal a primary tumor, a primary uveal melanoma seemed much more likely. At that point, we determined with the patient to definitively rule out an inflammatory lesion. After 10 days of oral prednisone, the lesion remained unchanged, which suggested primary melanoma as the diagnosis. At this point, a biopsy was recommended. The patient refused biopsy because he did not like the possibility of having two procedures. The patient was given the options of radiation, observation or enucleation. Radioactive plaque implantation (brachytherapy) was explained to the patient as an option for saving the eye, although he was told that he would likely lose most or all his vision over the ensuing few years and that he would need to return at least twice a year for follow-up. After a lengthy discussion, the patient preferred to have a single procedure and be "finished with the issue" rather than have to make further trips from Nebraska to Iowa for follow-up.
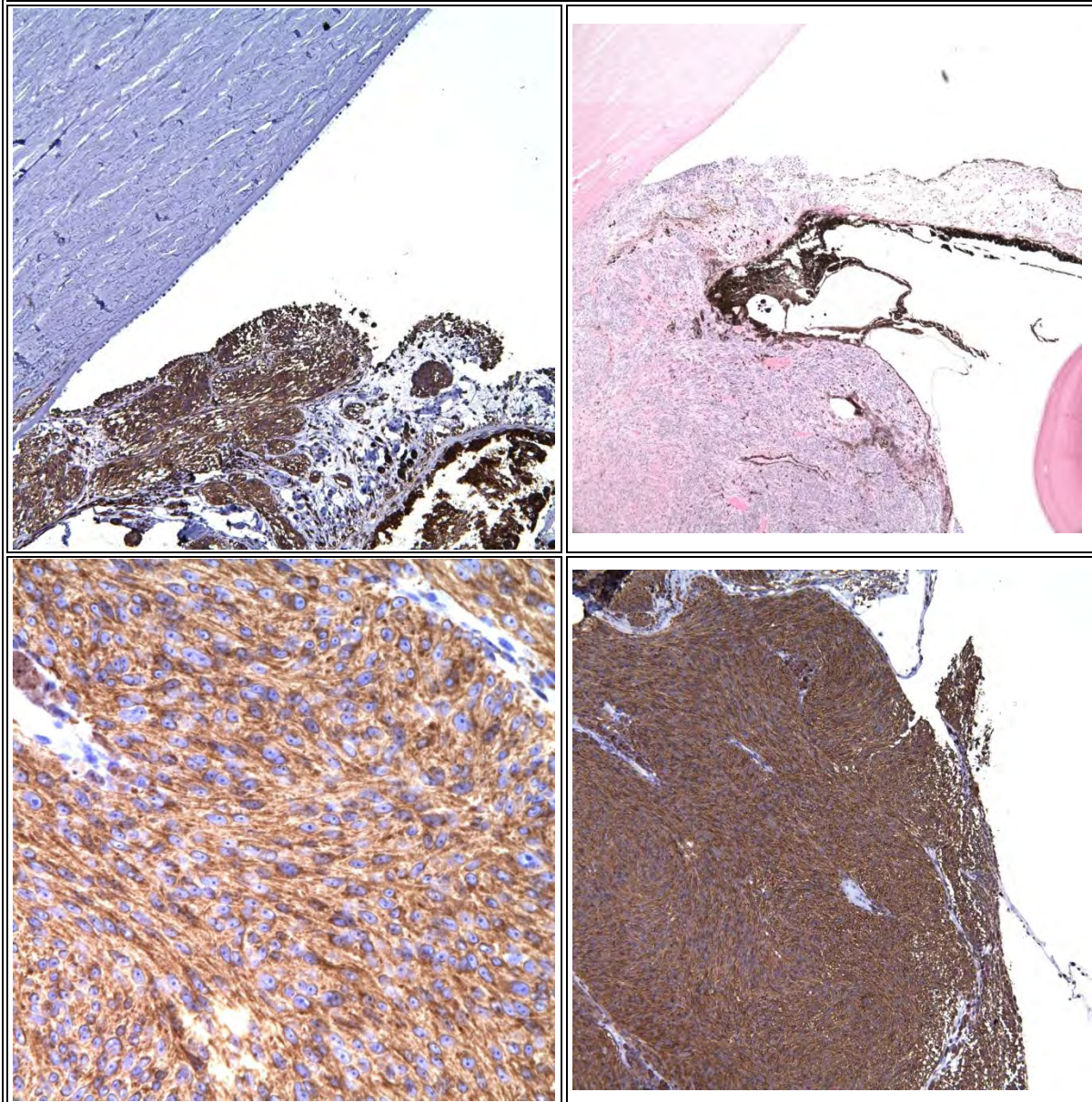
In November 2007, the patient returned to Iowa for enucleation of his right eye. He tolerated the procedure well and the globe was assessed by the F.C. Blodi Ocular Pathology Laboratory.

Figure 4 (Pathologist's Comments)
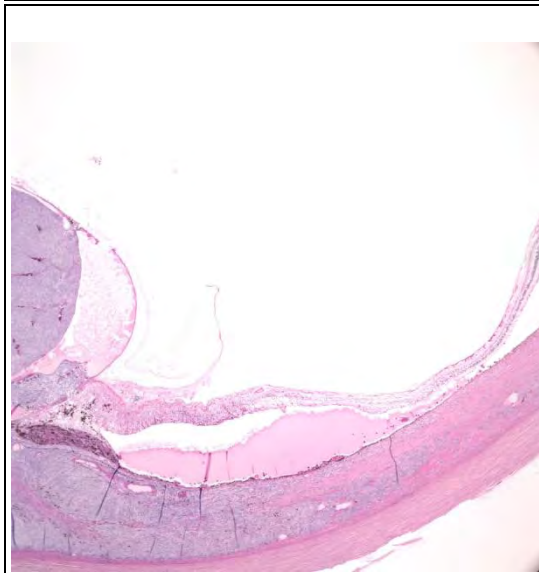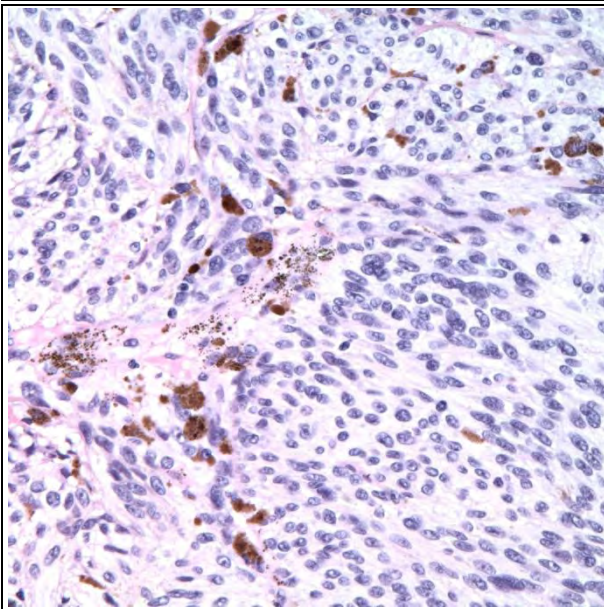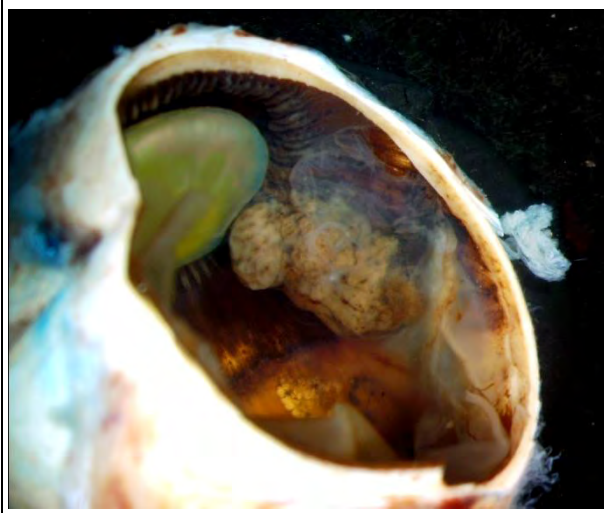
Figure 4. Continued

Histopathology: Microscopically, the inferior angle and iris structures are infiltrated by tumor cells. Tumor cells extend into the root of the iris and consist of nests of spindle A and B melanoma cells with little to no pigment. Tumor cells demonstrate a fascicular and nesting pattern in the iris and ciliary body. The majority of the mass is located in the region of the ciliary body and replaces ciliary muscle and epithelium. The mass breaks through the ciliary epithelial basement membrane and grows inward toward the vitreous. A few areas of erosion of the basement membrane are present at the apex of the tumor with spillage of a few tumor cells into the overlying vitreous. The lesion extends posteriorly into the choroid where there is marked sclerosis associated with tumor cells. The tumor extends just beyond the equator of the globe. The basal dimension of the tumor is approximately 16 mm and the apical height is 6 mm. Focal areas of retinal pigment epithelial hyperplasia and metaplasia are present overlying the tumor and a small serous detachment of the retina is present over the posterior portion of the tumor. Occasional drusen are seen along Bruch's membrane overlying the tumor (suggestive that some component of the lesion has been chronic). PAS without

hematoxylin demonstrates the presence of linear and arc-like intrinsic microvascular patterns. There are two mitoses in 40 high-power fields. Scattered melanin-containing macrophages are present throughout the tumor, particularly surrounding blood vessels. Ciliary epithelium can be seen engulfed within the tumor in many regions. The tumor does demonstrate focal areas of scleral invasion that reach approximately 50% in depth. MART-1 is positive in tumor cells when compared with appropriate positive and negative controls.

The histopathologic diagnosis was:

1. Ciliochoroidal malignant melanoma with the following features:

- Predominantly spindle cell type
- Medium tumor size
- Invasion of the trabecular meshwork and iris root
- Linear and arc intrinsic microvascular patterns
- Invasion of the ciliary epithelial basement membrane with seeding of tumor into the vitreous overlying the apex of lesion
- Focal areas of intrascleral extension extending to approximately 50% depth

2. Peripheral exudative retinal detachment overlying tumor.

Discussion

In our patient, the clinical differential diagnosis included amelanotic choroidal melanoma, choroidal metastasis, and an inflammatory lesion (such as granulomatous disease). Even though the ultrasound was suggestive of melanoma, other clinical features made the diagnosis more complicated. First, the lesion was amelanotic ophthalmoscopically. Most choroidal melanomas have some pigmentation. Second, the patient was only 31, which is younger than average for this disease. Shields lists an extensive differential to be considered for an amelanotic choroidal mass (see below).

Posterior uveal malignant melanoma (that arises in the choroid and ciliary body) is the most common primary intraocular malignancy in adults (Albert and Jakobeic 1994). Most uveal melanomas occur in the choroid (85%) and some occur in the ciliary body (10%) and iris (5%). Overall, posterior uveal melanoma is a highly aggressive neoplasm, and about half of patients die of disseminated tumor within 10 to 15 years of diagnosis.

The clinical presentations of posterior uveal melanomas are determined by the location and size of the tumor (see "Symptoms" section below). In general, the farther away the tumor is from the optic nerve and fovea, the larger size it can reach before the patient notices a visual field defect. Ciliary body melanomas may be asymptomatic in the early stages as they remain hidden behind the iris. The typical choroidal melanoma is a pigmented, elevated, dome-shaped, sub-retinal mass (Shetlar 2007). The degree of pigmentation ranges from totally amelanotic to dark brown. Serous detachment of the retina is common.

Choroidal melanomas, when small, are confined to the uvea by Bruch's membrane and the tough collagenous sclera and are usually disc shaped. With enlargement of the tumor, the relatively weak Bruch's membrane eventually ruptures. This phenomenon allows the by now medium-sized tumor to expand into the subretinal space, first forming a "collar button" and then (with proportionally more subretinal than choroidal expansion) a "mushroom" appearance. Large, nodular tumors may eventually invade and destroy adjacent intraocular tissues, filling the posterior chamber. Subsequent enlargement may displace the iris and lens anteriorly, causing progressive narrowing of the anterior chamber angle and eventual obliteration of the anterior chamber.

Extraocular extension can be a consequence of tumor expansion. The sclera is a major barrier to expansion, so when tumors extend beyond the globe they usually do so at points where blood vessels (vortex veins, ciliary arteries, etc.) penetrate the sclera. Spreading tumor cells, however, will usually spread through the scleral channels around the vessels rather than within the vessels themselves; intravascular invasion is rarely seen in vortex veins. The relatively low frequency of observed intravascular tumor invasion of vortex veins probably indicates that invasion of small intratumoral blood vessels is the most important source of

hematogenous metastasis. Peripapillary choroidal malignant melanomas often invade the optic nerve head, but retrolaminar invasion of the optic nerve is rare, unlike the extension pattern of retinoblastoma.

The most important microscopic feature is the morphology of the tumor cells, and this remains one of the most reliable indicators of prognosis for individual tumors (Albert and Jakobeic 1994). In 1931, Callender described two main types of tumor cell type, spindle cells and epithelioid cells, and identified two subtypes of spindle cells on the basis of nuclear characteristics. The resulting three cell types are spindle A, spindle B, and epithelioid (see Figure 5).

The modified Callender classification contains A) spindle cell melanoma, B) epithelioid melanoma, and C) mixed-cell type (mixture of spindle and epithelioid cells). Occasionally, a melanoma undergoes extensive necrosis, which precludes proper classification. Spindle cell melanoma has the best prognosis and epithelioid melanoma the worst. Melanomas of the mixed cell type have an intermediate prognosis and totally necrotic melanomas assume the same prognosis as mixed cell melanomas (Shields 1992). More recently, intrinsic tumor microvascular patterns have been studied and shown to have prognostic significance. Tumors with more complex microvascular patterns such as networks of closed vascular loops, are associated with an increased incidence of subsequent metastasis (Folberg 1997).

Historically, enucleation has been the gold standard in the treatment of intraocular tumors. In 1882, Fuchs wrote that all intraocular melanomas were treated by enucleation and the only untreated cases were in the "older literature". Today, enucleation remains appropriate for many large choroidal melanomas particularly when useful vision is lost. The past hypothesis that surgical manipulation might lead to potential release of malignant cells into the bloodstream and orbital soft tissues during the procedure is no longer accepted today.

Some investigators have advocated preenucleation radiation of the eye as a way to improve survival. However, according to the Collaborative Ocular Melanoma Study (COMS), external beam radiation treatment (EBRT) did not positively or negatively affect the survival of patients with large choroidal melanomas (> 16.0 mm basal diameter or > 10.0 mm apical height) who were randomized to enucleation alone versus EBRT followed by enucleation This study established the appropriateness of primary enucleation alone in managing large choroidal melanomas that are not amenable to globe-conserving therapy (COMS 1998).

Today, the application of a radioactive plaque to the sclera overlying an intraocular tumor is probably the most common method of treating medium-sized uveal melanomas (6.0-16.0 mm basal diameter or 2.5-10.0 mm apical height). It allows the delivery of a high dose of radiation to the tumor and a relatively low dose to the surrounding structures. Radioactive plaques are sutured temporarily to the sclera underlying the melanoma and left in place for 3-7 days. Though many radioactive isotopes may be used, radioactive iodine (I-125) seeds are frequently the isotope of choice in plaques today. After brachytherapy the tumor gradually flattens over 2-3 years, usually leaving behind a residual pigmented mass surrounded by choroidal atrophy. Regrowth is diagnosed in only 4-5% of the treated tumors. As long as there is no tumor regrowth, further treatment is not needed. Late radiation-related complications (especially optic neuropathy and radiation retinopathy) are visually limiting in as many as 50% of patients.

The theoretical advantage of enucleation over globe-sparing treatments is a reduced risk of metastatic spread. However, the COMS group (where medium-sized tumors were treated with either I-125 brachytherapy or enucleation) found that the mortality rates following brachytherapy did not differ from the mortality rates following enucleation for up to 12 years after treatment (COMS 2001).

The choice of therapy depends on several factors. The most important are the size and location of the tumor, the patient's age, general health, occupation and motivation and the available skills and equipment. The results from the Collaborative Ocular Melanoma Study provide a framework for patient discussions.

In the future, it is expected that the treatment of primary uveal melanoma will be mainly directed toward eliminating subclinical metastasis (Shields 2008). Ideally, management would involve early detection of small uveal melanoma with prompt treatment combined with systemic therapy (Shields 2002). As effective systemic therapies, in the form of chemotherapy, immunotherapy, and/or gene therapies are identified, the management of uveal melanoma will be improved.

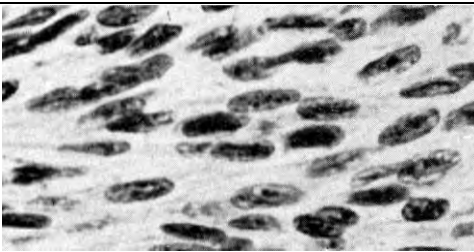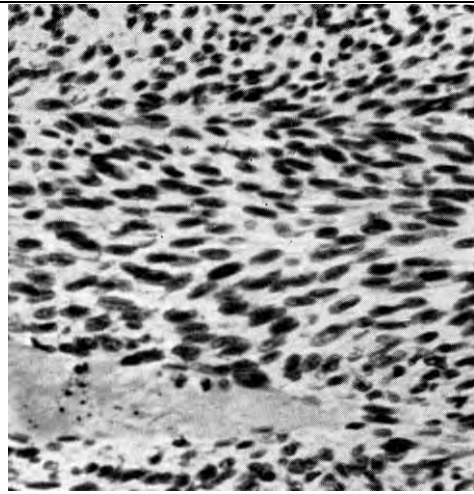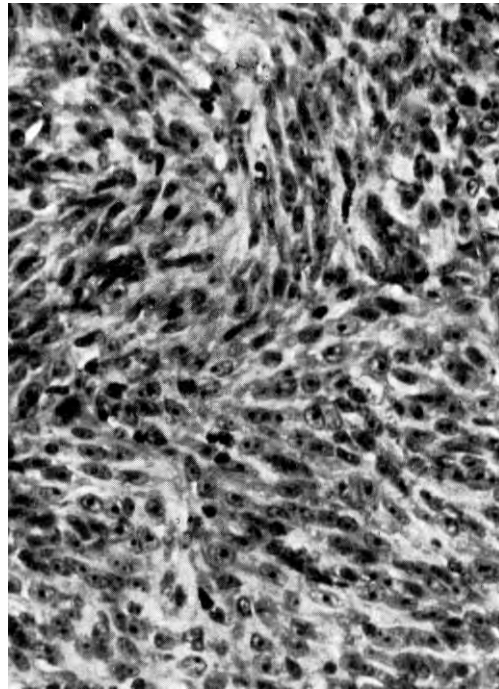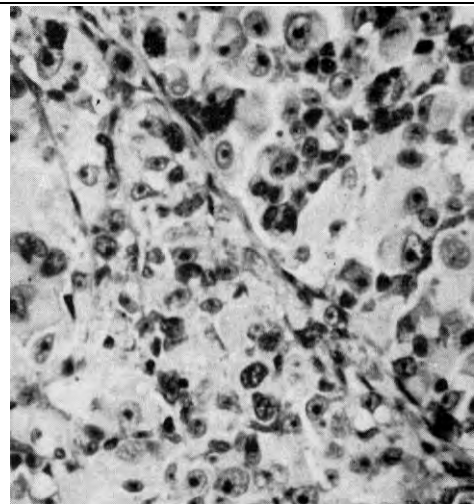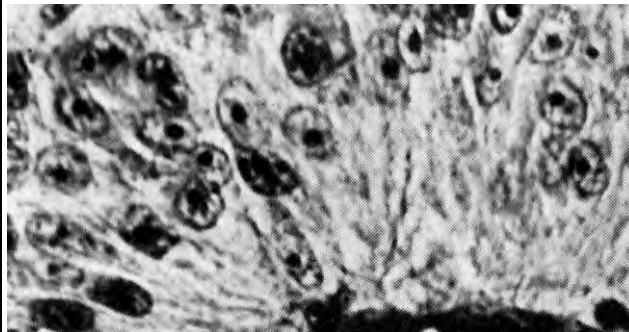|	
Figure 5A: Spindle A cells have a slender nucleus with a fold 	**Figure 5B:** Spindle B cells are more plump with prominent nucleoli
Figure 5C: Epithelioid cells have more cytoplasm and a rounded shape with large nuclei and prominent nucleoli 	**Figure 5D**: Fascicular cells showing a palisading pattern above vessel
	Images from Callender 1931

Diagnosis: Ciliochoroidal malignant melanoma

EPIDEMIOLOGY	SIGNS
- Most common primary intraocular malignancy in adults **Incidence:** In US, 6-7 cases per million (Shields 1992) **Age:** rare in children, primarily affects patients in 50s and early 60s **Sex**: men (55%) slightly more frequently than women (45%) **Race**: Incidence in whites is 8.5 times greater than in blacks. **Among whites, blue-eyed blondes have the highest incidence.** Asians have an incidence intermediate between white and black persons. **"Geographic"** variations reflect racial groupings and do not correlate with sun exposure. **Predisposing Lesions:** include congenital ocular melanocytosis & uveal nevi **Familial and Genetic Factors:** reported to affect successive generations of a small number of families, however, no specific genetic defects have been found	- Choroidal melanoma - posterior signs - Pigmented, elevated, dome-shaped subretinal mass - If tumor erupts through Bruch's membrane - **mushroom or "collar-button"** - Clumps of **orange pigment** over surface of tumor at RPE level **Serous retinal detachment** - Choroidal melanoma - anterior signs **Neovascularization** of the iris - Dilated episcleral **sentinel vessels** - Erosion through iris root may be visible on gonioscopy - Extension through sclera may be seen as a dark epibulbar mass - If large enough, may cause subluxated lens, sectoral or diffuse cataract, and retinal detachment - Echography - A scan ultrasonography reveals **low to medium internal reflectivity**, often with significant vascularity of the mass
SYMPTOMS	TREATMENT
- Wide range of clinical presentation determined by the size of the tumor: - Stage 1. Asymptomatic, discovered incidentally on routine eye exam; small tumors confined to the uvea, with possible small scotoma associated with degeneration of overlying retina - Stage 2. Progressive blurring and loss of vision resulting from retinal degeneration and detachment - Stage 3. Ocular pain due to associated glaucoma (pupillary block, rubeosis, or angle invasion) or inflammation - Stage 4. Effects of extraocular extension, such as subconjunctival mass and proptosis	A complete review of the details of ocular melanoma therapy will not be attempted here. Some basic options and principles of therapy include: **Brachytherapy (radioactive plaque): for lesions** <10 mm elevation and < 20 mm diameter **Charged-particle radiation:** If unsuitable for brachytherapy **Enucleation:** Large tumors, particularly if useful vision lost **Alternative treatments:** **External-beam radiation** (usually as adjunct to enucleation) **Transpupillary thermotherapy** (small tumor) **Surgical excision** (small tumor) **Proton beam radiotherapy** **Chemotherapy or Immunotherapy** is indicated under the direction of the oncology service for metastatic disease **Exenteration:** Used in cases of extrascleral extension into the orbit Collaborative Ocular Melanoma Study (COMS) findings can be found at: www.jhu.edu/wctb/coms

Differential Diagnosis of Amelanotic Choroidal Mass:

- Amelanotic melanoma
- Choroidal metastasis
- Choroidal hemangioma
- Choroidal osteoma
- Age-related macular or extra-macular degeneration with eccentric disciform scar
- Choroidal detachment
- Uveal effusion syndrome
- Posterior scleritis
- Chorioretinal granuloma
- Toxoplasmic retinochoroiditis
- Rhegmatogenous retinal detachment
- Degenerative retinoschisis
- Presumed acquired retinal hemangioma
- Less common tumors (neurilemmoma, leiomyoma, or combined hamartoma of the retinal pigment epithelium)
- Retinal cavernous hemangioma

Acknowledgement:

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Suggested citation format:

Pham LTL, Graff JM, Boldt HC. Posterior Uveal (Ciliary Body and Choroidal) Melanoma. EyeRounds.org. July 27, 2010; Available from: http://www.EyeRounds.org/cases/117-Posterior-Uveal-Melanoma.htm.