INTRAOCULAR TUMOURS

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CHAPTER CONTENTS

AIMS

This unit aims to outline the diagnosis and management of intraocular tumours by developing:

- A protocol for assessing the signs of intraocular tumours
- A framework for making a differential diagnosis of the intraocular tumours
- Management guidelines for the intraocular tumours

LEARNING OBJECTIVES

At the end of these lectures and readings, the student will be able to:
1. Understand the diversity of presentations of intraocular tumours
2. Appreciate the complex nature of the aetiology of intraocular tumours
3. Develop a plan for clinical investigation of these conditions
4. Understand that the treatment options are complex

BACKGROUND

Intraocular tumours include the following:

- Uveal tumours (benign and malignant)
- Melanoma
- Retinoblastoma
- Primary and secondary intraocular lymphoma
- Secondary metastases to the eye
- Paraneoplastic syndromes

Treatment of an intraocular tumour is often very difficult.

UVEAL TUMOURS

Uveal tumours include:

- Iris naevus
- Iris melanoma
- Ciliary body melanoma
- Choroidal melanoma
- Choroidal naevus
- Choroidal haemangioma (circumscribed or diffuse)
- Choroidal metastatic carcinoma
- Choroidal osseous choristoma
- Melanocytoma (magnocellular naevus)

IRIS NAEVUS

The features of a naevus on the iris include:

- Flat pigmented lesion
- Usually static
- Less than 3 mm in diameter
- Less than 0.5 mm in thickness

IRIS MELANOMA

A melanoma of the iris is very rare, accounting for about 3% of all uveal melanomas.

Presenting characteristics include:

- Average age on presentation is about 40 years
- Often asymptomatic
- Diffuse or nodular forms
- Ring melanoma

- Very slow growth
- Low malignancy (spindle cell)
    - Spindle cell morphology, usually grows slowly
- Secondary glaucoma related to growth in the anterior chamber angle
- Excellent prognosis

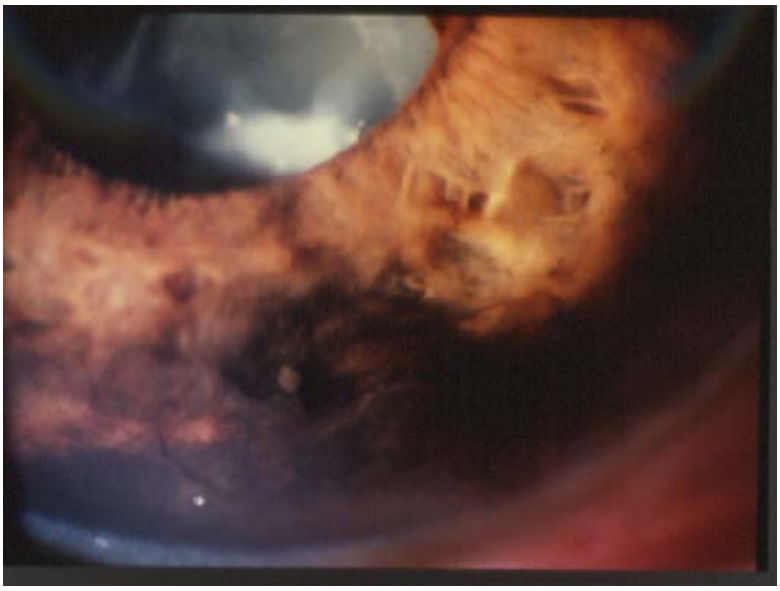

Figure 1: *Iris melanoma*

Treatment options include:

- Observation
- Excision
- Plaque
- Last resort is enucleation of the eye

CILIARY BODY/CHOROIDAL NAEVUS

Choroidal naevi, especially small ones, are common. Their prevalence can be from 5% to 10%of the general population.

Choroidal melanomas are rare, with an estimated incidence of approximately six per million. Nevertheless, choroidal melanoma is the most common primary intraocular malignancy in adults, and prompt and accurate diagnosis is very important.

A choroidal naevus is typically less than 5 mm in size and less than 1 mm thick.

Typical choroidal naevi features:

- Common (2% of population)
- Round slate-grey with indistinct margins
- Can be amelanotic (no melanin)
- Flat or slightly elevated (<1 mm)
- Diameter < 5 mm
- Surface drusen
- Located anywhere
- Asymptomatic
- Monitor very carefully

Suspicious choroidal naevus features:

- Diameter greater than 5 mm
- Elevation is 2 mm or more

- Surface lipofuscin is present (orange pigment)
- Posterior margin within 3 mm of optic disc
- May have symptoms due to serous fluid exudate

CILIARY BODY/CHOROID MELANOMA

Melanoma of the ciliary body is found in about 8-10% of cases. It presents in the choroid in about 85% of cases. The conditions are typically found in older patients.

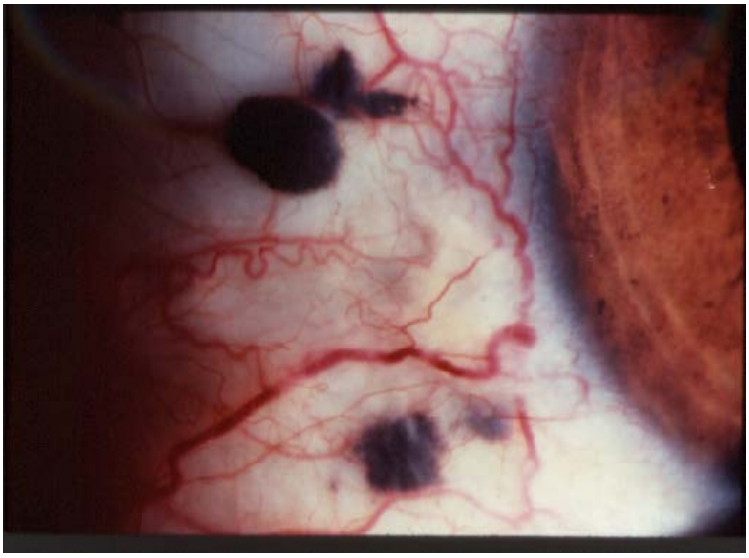

Figure 2: *Ciliary body melanoma*

Symptoms

Visual disturbance

- Flashes
- Floaters
- Visual field (VF) disturbance
- Secondary glaucoma (often goes undetected until advanced)

Treatments

Early detection and referral is vital.

- Monitor, resect, plaque therapy, proton beam, cryotherapy, chemotherapy (poor outcome), enucleation

Signs of ciliary body melanoma

- Scleral sentinel vessels
- Extraocular extension
- Erosion through iris root
- Lens subluxation or cataract
- Retinal detachment

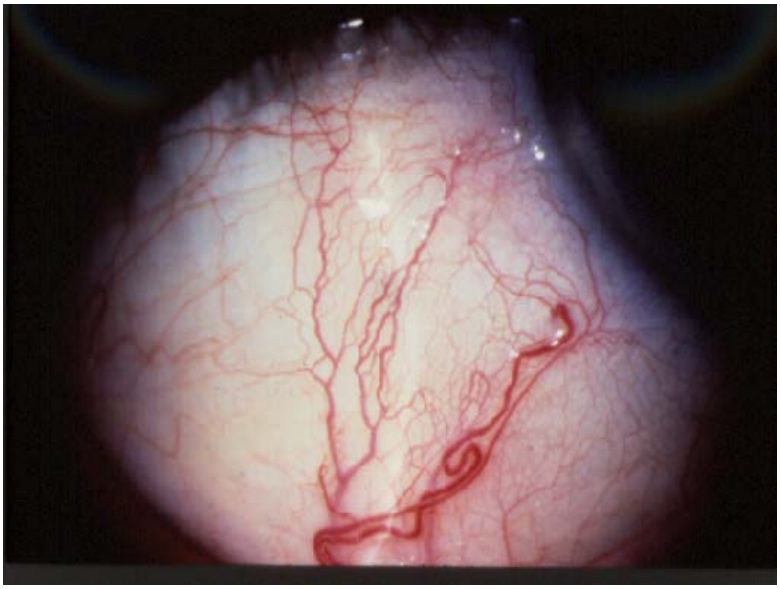

Figure 3: *Sentinel vessels*

Features

- Brown, elevated, subretinal mass
- Occasionally amelanotic
- Secondary retinal detachment
- Choroidal folds

CHOROIDAL MELANOMA

RECENT DEVELOPMENTS

Some of the recent developments in choroidal melanoma research include:

- Main clinical and histopathological features associated with metastatic death
  - Larger tumour size
  - Increased patient age
  - Epithelioid cytology and extracellular matrix patterns
- Genetic features associated with metastasis
  - Monosomy 3
  - Amplification of chromosome 8 (8Q)
  - Class 2 gene expression signature/gene expression profile
- Approximately 50% of uveal melanomas have GNAQ mutations
  - Encodes a G-protein-coupled receptor in RAF/MEK/ERK pathway
  - Also found in benign precursor lesions, such as congenital ocular melanocytosis
  - GNAQ mutations are an early or initiating event in pathogenesis of uveal melanoma (and other tumours)
- Over 80% of uveal melanomas have BAP1 mutation
  - Tumour suppressor, loss of melanocytic identity?
- Gain of chromosome 6p occurs mainly in non-metastasizing tumours
- Loss of chromosome 3 (monosomy) occurs mostly in metastasizing tumours
- Monosomy 3
  - Further genomic instability
  - Accumulation of aneuploidy
  - Loss of differentiation competence and a gain of metastatic competence
- Silencing of metastasis modifier locus on chromosome 8p is associated with shorter metastasis-free survival
- Class 1: similar to differentiated uveal melanocytes
  - Low metastatic risk <5%

- Class 2: similar to neural and ectodermal progenitor cells
    - Does this reflect a defect in differentiation leading to underlying tumour formation
    - High metastatic risk >90%

CHOROIDAL MELANOMA METASTASIS

- Means of dissemination: Haematogenous
- Most common site for metastasis: Liver, lung, then bone, skin, CNS (or multiple sites)
- Approximately 50% of cases get metastases within 15 years of treating primary uveal melanoma
- Median survival after diagnosis of liver metastases is 2-7months
    - Very bad prognosis

DIFFERENTIAL DIAGNOSIS OF CHOROIDAL AND CILIARY BODY MELANOMAS

Conditions that need to be considered in the differential diagnosis of choroidal and ciliary body melanomas includes the following:

- Choroidal naevus (including melanocytoma of optic disc)
- Metastatic carcinoma to choroid or ciliary body
- Disciform lesion (central or peripheral)
- Subretinal or subpigment epithelial hematoma
- Localized suprachoroidal haematoma
- Circumscribed choroidal haemangioma
- Nodular posterior scleritis
- Choroidal osteoma (bone-derived tumour)
- Congenital hypertrophy of retinal pigment epithelium (CHRPE)
- Reactive hyperplasia of retinal pigment epithelium
- Syndrome of bilateral diffuse uveal melanocytic proliferation associated with systemic carcinoma
- Massive gliosis of retina
- Ocular melanocytosis
- Choroidal detachment
- Choroidal granuloma

CHOROIDAL MELANOMA GUIDELINES

Risk factors for small tumour progression include the following:

- Size (> 1 mm thickness and > 5 mm diameter)
- Documented growth
- Orange pigment (lipofuscin) which displays autofluorescence
- Subretinal fluid (over the lesion or inferiorly)
- Absence of drusen
- Margin of the lesion at or near the optic disc
- Closer than 3 mm to the foveola
- Genetic predisposition

COMS classification of tumour by size

Size height (mm)	Basal diameter (mm)	Apical
Small	5.0 – 16.0	1.0 – 3.0
Medium	≤ 16.0	2.5 – 10.0
Large	> 16.0	> 10.0

(CfEH Newsletter; from COMS)

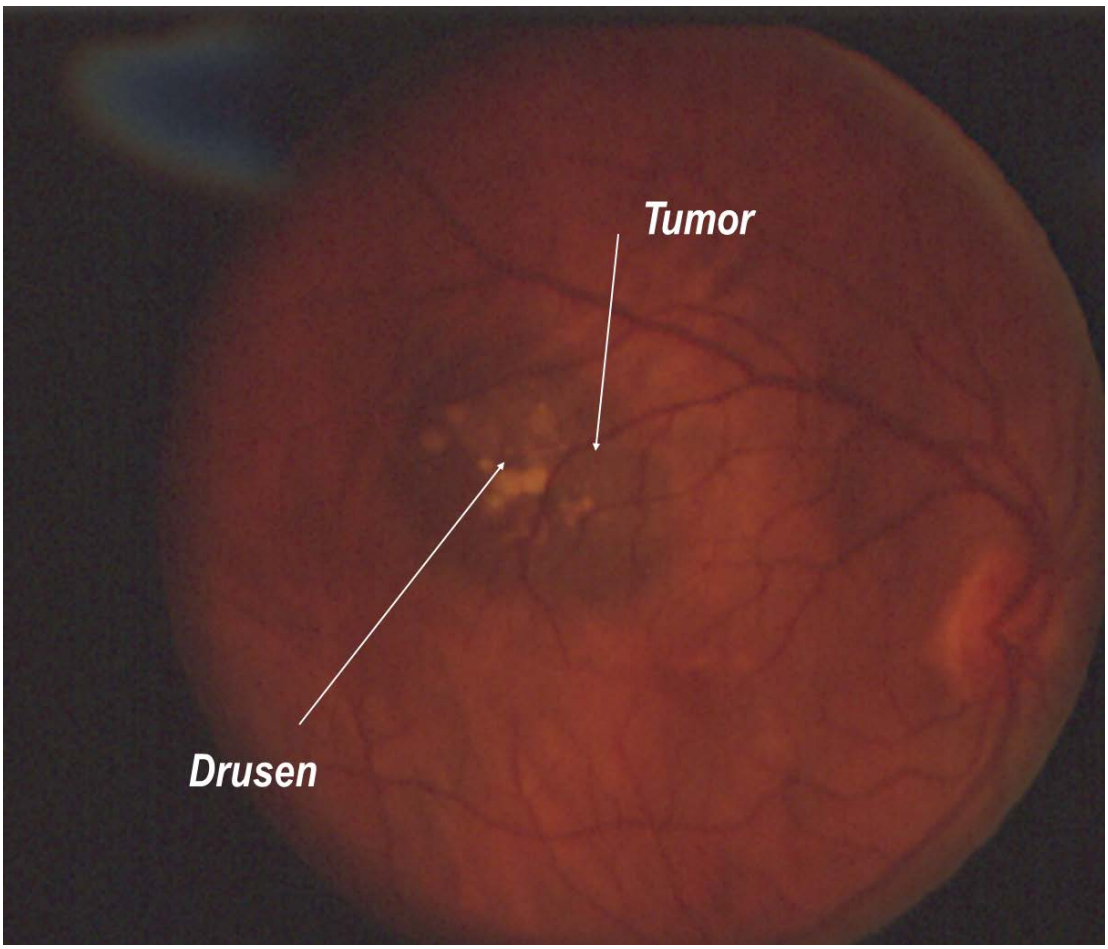

Figure 4: *Choroidal melanoma*

CLINICAL RISK FACTORS FOR GROWTH OF SMALL CHOROIDAL MELANOMA

To find a small ocular melanoma consider the following:

- Thickness > 2 mm
- Subretinal fluid is present
- Symptoms are present e.g.
    - Blurred vision from subfoveal fluid
    - Metamorphopsia
- Overlying orange pigment
- Margin of lesion is at the optic disc
- Irregular margins

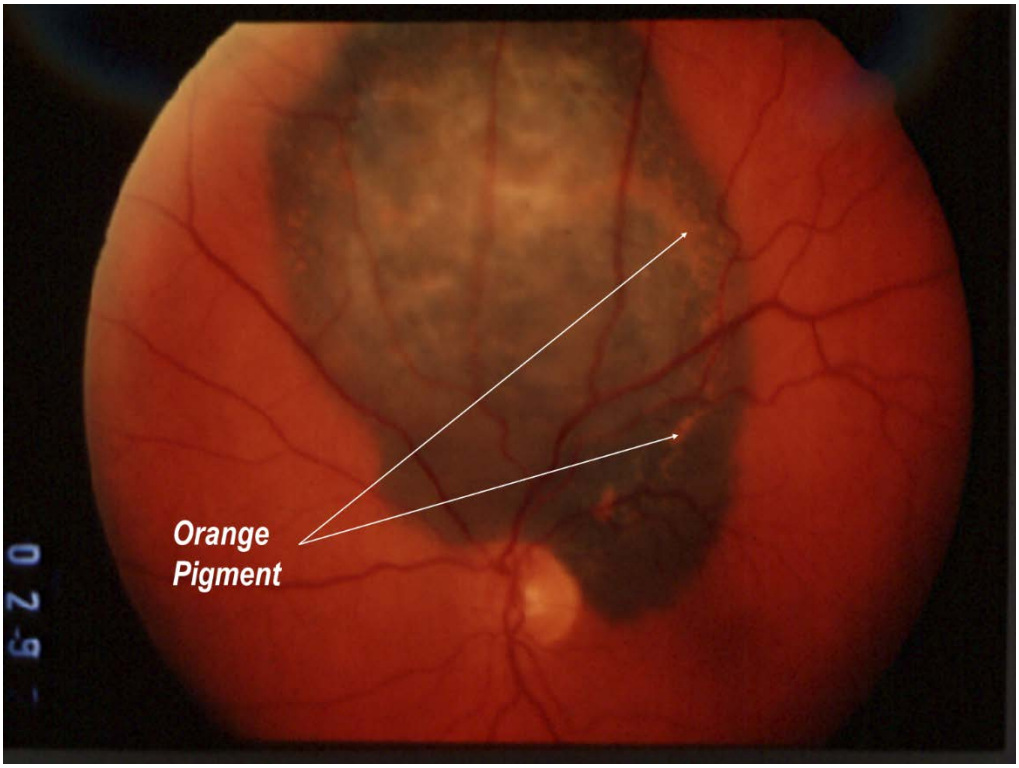

Figure 5: *Choroidal melanoma*

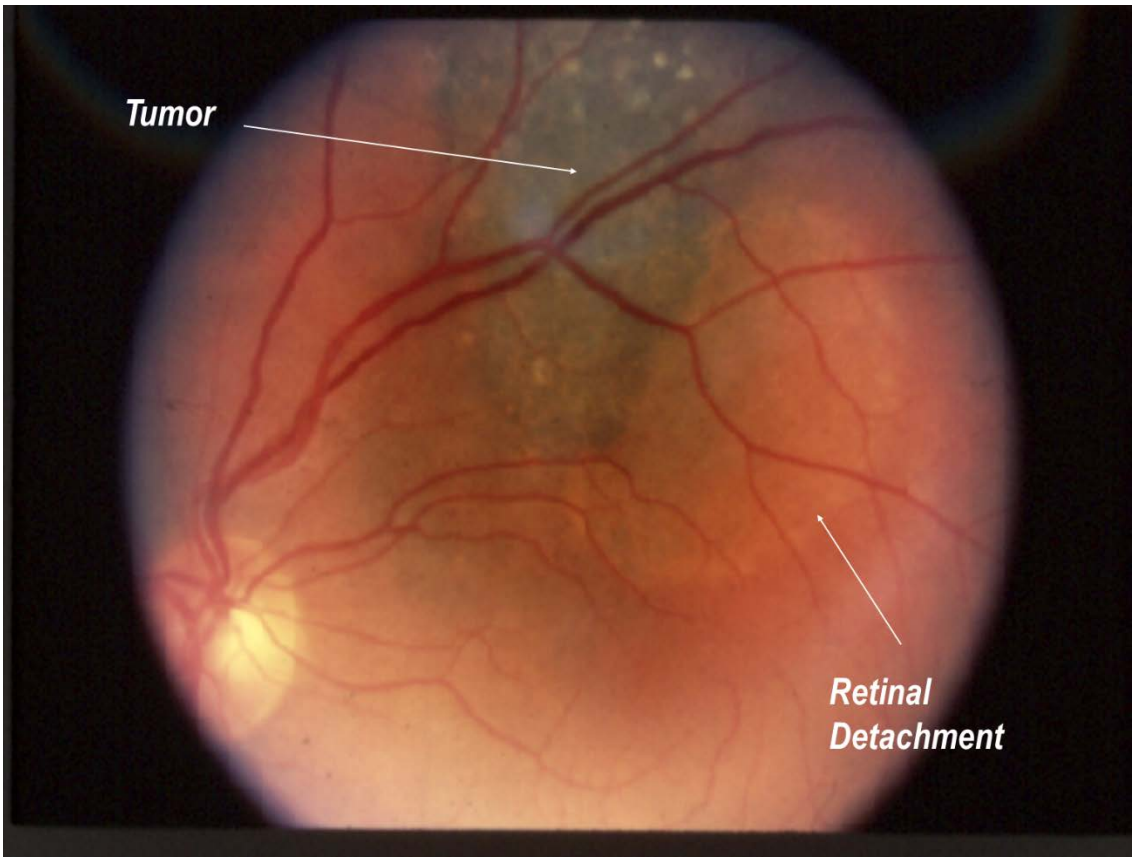

Figure 6: *Choroidal melanoma*

MELANOCYTOMA

Melanocytoma is a rare, normally benign lesion that can be localized in the optic nerve head, choroid, iris or ciliary body. It may be diffusely localized in the uvea or found on the conjunctiva and sclera.

It is also referred to as ocular melanocytosis.

OPTIC NERVE MELANOCYTOMA

An optic nerve melanocytoma is composed of melanocytes and myelin. Uveal melanocytes in the optic nerve head (ONH) lamina cribrosa can extend into the retinal NFL. A deeply pigmented lesion is seen on, or is part of, the optic nerve head.

A melanocytoma typically has edges that are indistinct (appear feathery), and radiate from the optic nerve head in an arcuate fashion. The retinal vasculature appears undisturbed. Due to its hyper-reflective nature, internal characteristics are seen best using an OCT.

Differential diagnosis includes:

- Malignant melanoma
- Reactive retinal pigmented epithelium hyperplasia
- Retinal pigmented epithelium adenoma
- Choroiditis

A melanoma is more varied in presentation with patches of lighter pigmentation and they tend to distort blood vessels. In aggressive cases feeder vessels may be visible. There may be surface deposits and they can cause retinal or disc oedema, haemorrhages and retinal detachment as it increases in size. A circumpapillary melanoma can grow to cover and extend into the optic nerve.

Symptoms:

- Do not usually produce symptoms

Signs:

- Following the first observation a short follow-up time of 3-6 months is suggested
- Once stability of the lesion is established, photos once per year is recommended but any suspicion of malignancy requires referral to an ophthalmological oncologist
- If they grow slowly, optic nerve melanocytomas can produce relative afferent pupillary defects (30%), subretinal fluid (10%) and an enlarged blind spot (75%)
    - e.g. growth next to the optic nerve can compress the nerve and cause loss of vision (e.g. nerve fiber layer defects)
    - Growth can also cause compressive vascular problems such as central retinal vein occlusion

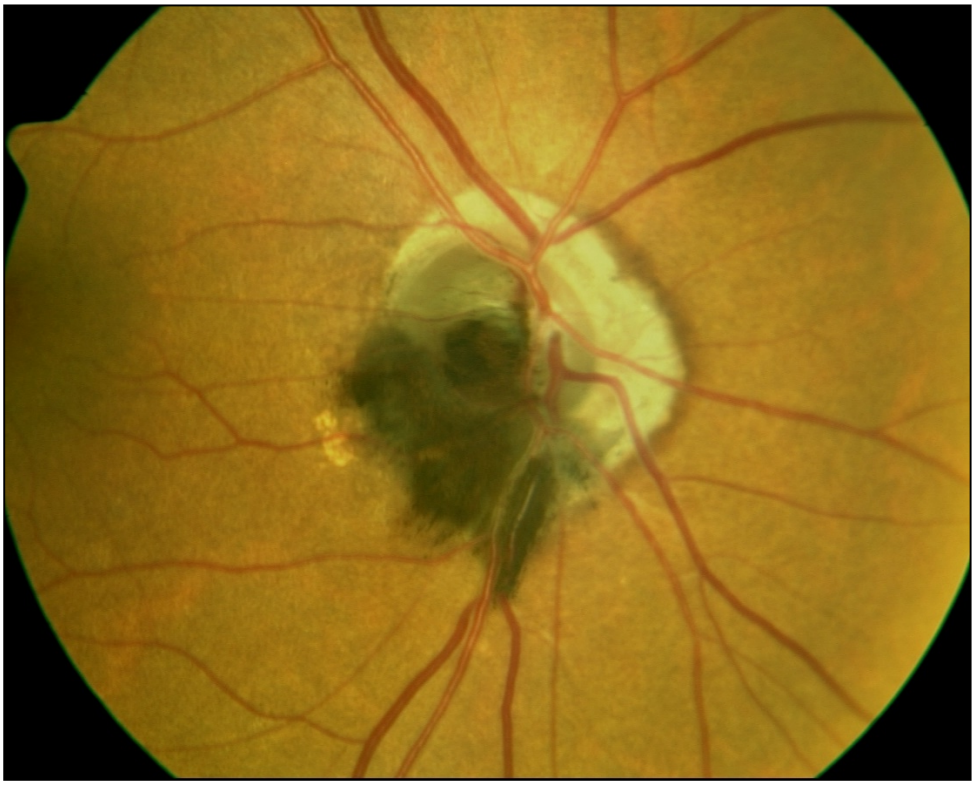

Figure 7: *Optic nerve melanocytoma*

CHOROIDAL HAEMANGIOMA

A choroidal haemangioma normally presents in adults as a dome-shaped or placoid, red-orange mass that is located commonly at the posterior pole.

The mass may blanch with external globe pressure.

Signs:

- Surface cystoid retinal degeneration
- Exudative retinal detachment

Referral is required and, if vision is threatened, commence radiotherapy treatment.

CHOROIDAL OSSEOUS CHORISTOMA

The condition is a very rare, benign, slow-growing ossifying ('bony') tumour. It is most commonly detected in females from the age of 20 to 30 years.

Signs:

- Diffuse, mottled appearance
- RPE degeneration over lesion with a yellowish appearance
- Scalloped margins
- Mostly located peripapillary or at the posterior pole
- Gradual vision loss if macula is involved
- Can get secondary choroidal new vessel

RETINOBLASTOMA (RB)

Retinoblastoma is a common primary intraocular tumour of childhood with an incidence of approximately 1 in 18,000 live births. It accounts for approximately 1% of childhood cancer deaths in the USA and about 5% of blindness in children.

It is typically bilateral in about 30% of cases. The average age at diagnosis is 18 months and with approximately 90% of patients diagnosed before the age of 3 years.

Less than 10% of cases have a positive family history with the other 90% of cases occurring sporadically. Of the sporadic cases, the responsible mutation is in a germ cell in 25% of cases and in a somatic cell in 75% of cases.

- Chromosome 13q14 mutation/mistranslation (sporadic vs. germ cell)

Mortality from retinoblastoma overall has decreased from 95% (Western countries) to 50% worldwide. Modern diagnostic and therapeutic advances have seen the mortality rate from metastatic or recurrent RB fall to as low as 5%.

Secondary cancers may occur later in life e.g. osteosarcoma (bone tumours).

If RB is suspected then an urgent referral is necessary as any delay may result in death.

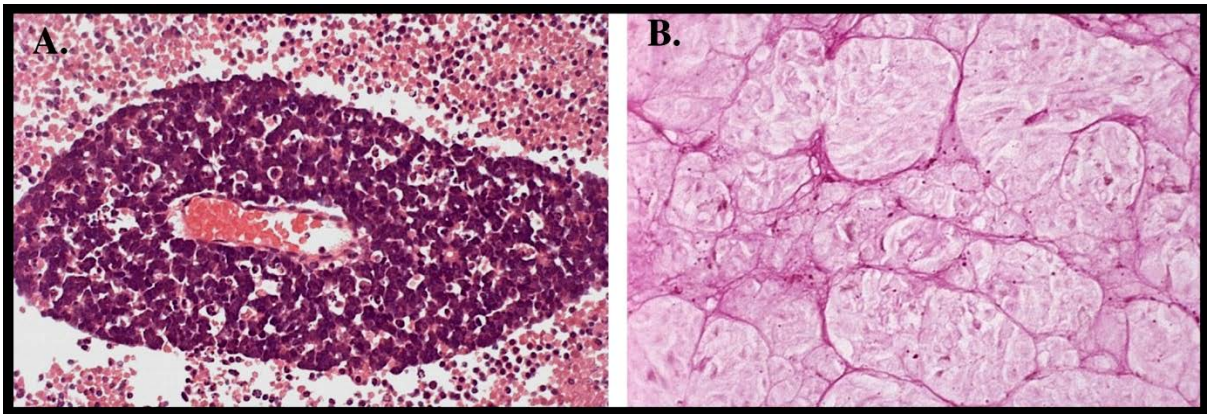

Figure 8a: *Retinoblastoma: 'cuffs' live tumour cells around a blood vessel, surrounded by cell death (limited by oxygen)*

Figure 8b: *Melanoma: little cell death despite tumour size, extravascular 'networks' plus blood vessels (increased tumour perfusion)*

POOR PROGNOSTIC FACTORS IN RB

Factors that suggest a poor prognosis in RB cases include for example:

- Optic nerve involvement
- Choroidal/orbital invasion
- Large tumour
- Anterior location
- Poor cellular differentiation (few rosettes)
- Cytogenetic factors

MAIN CLINICAL SIGNS IN RB

The main clinical signs in RB include:

- Leukocoria - 60%
- Strabismus - 20%
- Anterior segment invasion
- Secondary glaucoma

- Orbital inflammation and invasion

Other signs that are rarer include:

- Uveitis
- Orbital cellulitis
- Hyphaema
- Iris heterochromia
- Glaucoma
    - Buphthalmos

A CT scan in cases of RB can help to assess the following:

- Degree of calcification
- Any optic nerve involvement
- Orbital and CNS extension
- Pinealoblastoma (involving the pineal gland)

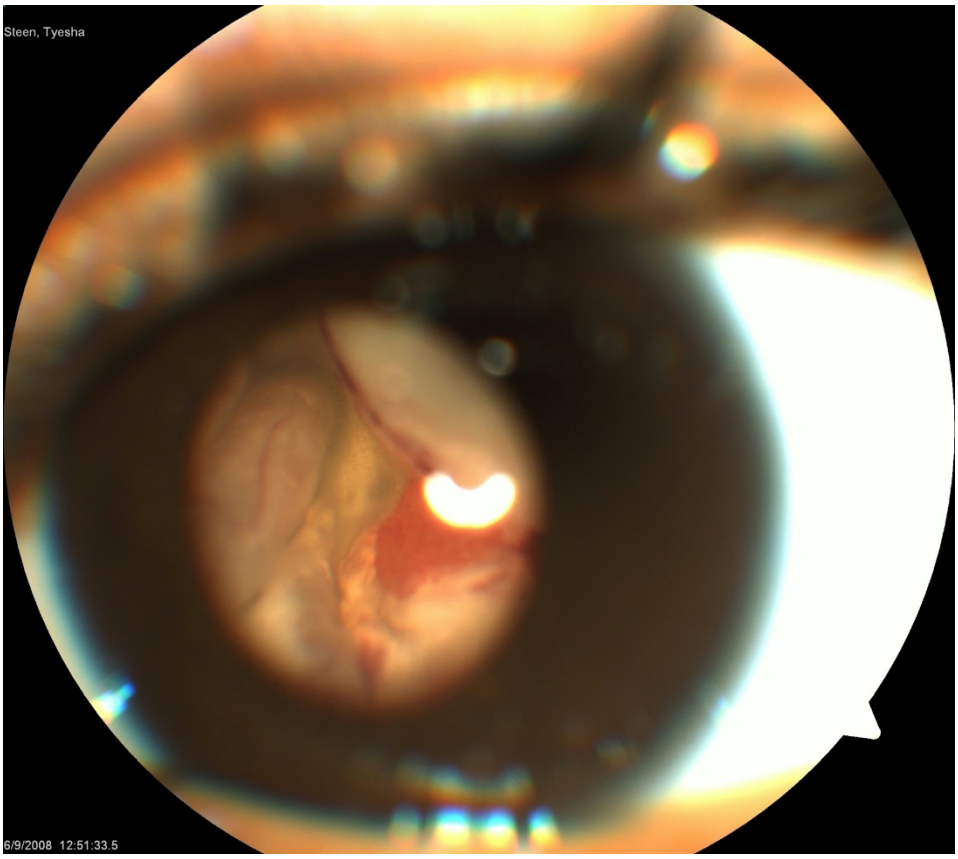

Figure 9: *Retinoblastoma*

DIFFERENTIAL DIAGNOSIS OF LEUKOCORIA

Leukocoria is a sign in many conditions including RB so it is of vital importance to make the correct differential diagnosis.

Other conditions with associated leukocoria include:

- Cataract
- Posterior pole toxocara granuloma
- Coat's disease (vascular leak/proliferation)
- Retinopathy of prematurity (ROP)
    - Always bilateral but may be asymmetrical
- Congenital cataract
    - Unilateral or bilateral

- Persistent hyperplastic primary vitreous (PHPV)
    - Unilateral
- Inflammatory uveitic membrane
    - Unilateral or bilateral
- Other conditions include:
    - Retinal detachment
    - Coloboma (chorioretinal)
    - Retinal dysplasia
    - Norrie's disease
    - Morning glory anomaly

MORE ADVANCED ENDOPHYTIC RETINOBLASTOMA

Endophytic tumours (those growing into the vitreous): grey-white and smooth surfaced. Vitreous seeding may be evident. Larger tumours exhibit darker grey areas of necrosis, brown foci of haemorrhage, and firm white granules or flecks of dystrophic calcification.

- Friable white mass
- Fine surface blood vessels
- "Cottage cheese" appearance
- Vitreous seedings

EXOPHYTIC RETINOBLASTOMA

Exophytic tumours are tumour proliferations in the subretinal space and secondary exudation contributes to retinal detachment.

Extraocular spread will only be seen in advanced untreated cases.

- Pinkish mass, with overlying retinal detachment
- May be difficult to visualize with detachment

SOME TREATMENT OPTIONS FOR RB

1. Small tumours
    - Laser photocoagulation
    - Transpupillary thermotherapy
    - Cryotherapy
2. Medium tumours
    - Brachytherapy
    - Chemotherapy
    - External beam radiotherapy
3. Large tumours
    - Chemotherapy plus local treatment
    - Enucleation
4. Extraocular extension
    - External beam radiotherapy
5. Metastatic disease
    - Chemotherapy

SECONDARY MALIGNANCIES IN RB

Children with RB gene mutation who survive primary intraocular cancer have an increased risk of death from one or more non-retinoblastoma malignancies over the course of their lifetimes e.g. osteosarcoma

- Up to 35% of children with bilateral RB and external beam radiation therapy will develop a second cancer by the age of 25

OCULAR LYMPHOMA

There are three major groupings used for classifying intraocular lymphoma:

A. High-grade malignant lymphomas
    a. Mostly B-cell, primary vitreoretinal lymphomas or primary intraocular lymphomas
B. Primary lymphomas arising mainly in the uveal tract (choroid)
    a. Most commonly low-grade malignant B-cell lymphomas (can also get T-cell lymphomas but these are very rare)
C. Intraocular involvement secondary to systemic lymphoma
    a. Mainly choroidal (disseminating disease)
    b. Primary CNS lymphoma

The iris is very rarely involved in primary and secondary manifestations of lymphoma.

This disease typically affects patients over 50 years of age. Approximately 15 to 20% of patients with primary CNS lymphoma go on to have ocular lymphoma.

56 to 90% of those with primary vitreoretinal lymphoma (PVRL) go on to primary CNS lymphoma, usually within 29 months.

METASTATIC CARCINOMAS OF THE EYE

Most metastases from primary tumours elsewhere in the body are to the choroid. It is a relatively common finding – approximately 20–25% of all deaths are attributable to cancer.

Microscopic metastatic intraocular lesions are found in at least one eye in 5–10% of these individuals (i.e. 1 to 2.5% of all people have metastatic carcinoma in at least one eye at the time of death).

The cumulative lifetime incidence of clinically detected metastatic intraocular tumours is approximately 0.1% (1 in 1000) to 0.25% (1 in 400).

Some tumours are not detected until shortly before death, when the patient is already in the terminal stage of cancer.

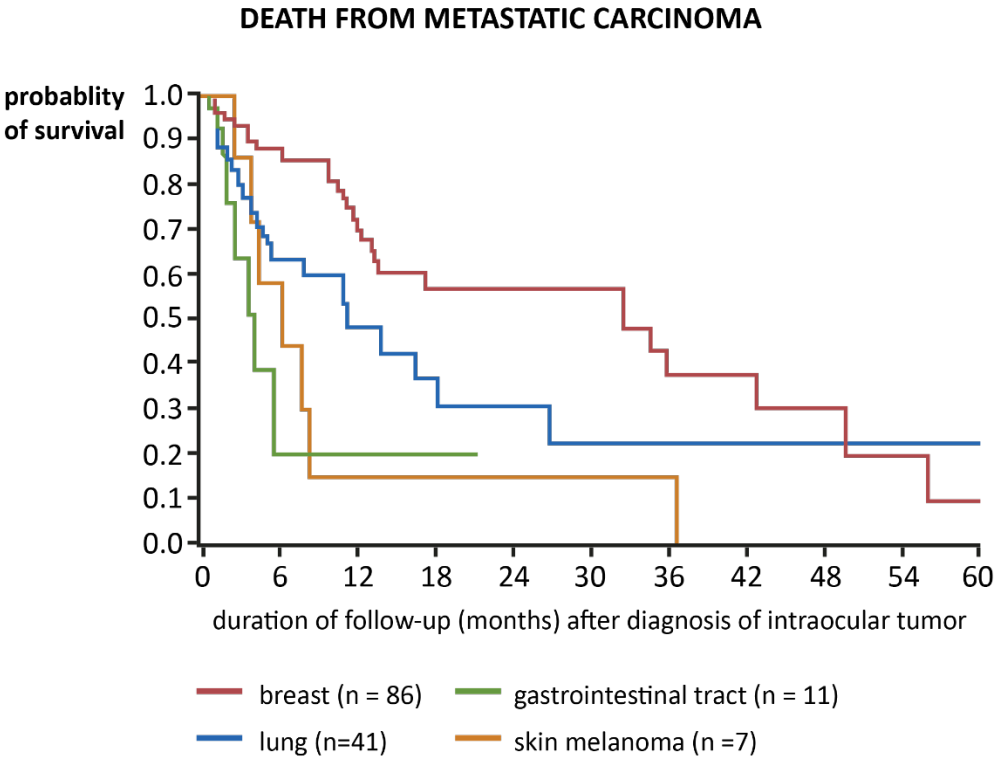

Figure 11: *Actuarial survival curves of patients with specified types of primary cancer metastatic to the eye. These curves are based on deaths from metastatic carcinoma only. (Yanoff & Duker, 2008)*

The most frequent primary tumour sites are the breast and the lung. Ocular signs associated with a metastatic tumour include:

- Fast-growing
- Creamy-white placoid lesion
- Deposits may be multiple
- Most frequently found at the posterior pole
- Overlying retinal detachment
- Bilateral in 10-30% of cases

PARANEOPLASTIC SYNDROMES

Tumour expression of proteins that normally are restricted to the nervous system triggers an immune response against the tumour which then also affects the nervous system. Examples of this are cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR).

In these rare syndromes CAR often precedes the diagnosis of cancer. Usually when paraneoplastic-related cancer is identified, it is small, non-metastatic and indolently growing.

The mechanism involved is proposed to be a cross-reactivity of antibodies to common antigen within the tumour and neural tissue (targets the retina).

Often, the associated condition is e.g. small-cell lung cancer, melanoma, ovarian, prostate cancer. The result is episodic visual obscurations, night blindness, light-induced glare, photosensitivity, impaired color vision progressing to painless vision loss.

Melanoma-associated retinopathy (MAR) differs from CAR in that the visual symptoms (e.g. shimmering lights, nyctalopia) occur after, rather than prior to, the diagnosis of cutaneous melanoma. The condition results in a gradual loss of central vision.

The specific antigen responsible has not been identified but autoantibodies from MAR react against ON-bipolar cells in human retina (e.g. TPRM1 antibodies). Clinical and electrophysiological data also implicate bipolar cells as the disease target abnormality in MAR.

In MAR, the ERG shows a marked decrease in the dark-adapted and light-adapted b-wave but there is preservation of the a-wave (indicating normal photoreceptor function). Both amplitude and implicit time of the b-wave are abnormal.

In these syndromes the treatment of the underlying tumour may be successful but the vision problems still persists.

APPROACHES TO TREATMENT

The key components of correctly treating intraocular tumours involves careful observation, accurate recording of the condition and appropriate referral as required.

The choroidal melanoma (COMS) study discusses treatment options such as the following:

- Excisional biopsy, fine-needle aspiration biopsy (FNBA)
- Topical therapies
    - Mitomycin C
    - 5-Fluoroacil
    - Interferon
- Physical therapies
    - Laser
    - Cryotherapy
    - Radiation (external beam, local plaque), proton beam
- Local versus general
    - Radioactive plaque
    - Chemotherapy (systemic vs. localised)
    - Targeted therapy antibodies (experimental procedures)
- Evisceration
    - Removal of the contents of the globe while leaving the sclera and extraocular muscles intact
- Enucleation
    - Removal of eye from orbit while preserving all other orbital structures
- Exenteration
    - Removal of eye, orbit contents (adnexa) and part of bony orbit