Chapter 11
Ocular Tumours

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There are many different ocular tumours, all with a wide variety of manifestations. Only a few are mentioned in this chapter.

Diagnosis of intraocular tumours is based on ophthalmoscopy, autofluorescence imaging, optical coherence imaging, ultrasonography, fluorescein angiography, indocyanine angiography and/or biopsy. Conjunctival tumours are diagnosed by slit-lamp examination and, if necessary, biopsy. The first priority of treatment is to save life, if possible conserving a comfortable eye with useful vision. Therapeutic modalities include various forms of surgical excision, radiotherapy, laser therapy, cryotherapy, chemotherapy, and immunotherapy, which are usually administered in various combination to ensure local tumour control while avoiding collateral damage to healthy tissues. Treatment of the primary tumour is followed by long-term surveillance to detect and treat any local recurrence and metastasis as well as any side effects and complications. Essential aspects of care include counselling, informed consent, prognostication, and psychological support addressing the needs both of the patient and close relatives.

Patients with an ocular tumour have increasingly been managed by ocular oncologists, working as part of a multidisciplinary team comprising specialist nurses, medical oncologists, radiotherapists, pathologists, geneticists, psychologists and others, usually at a supra-regional centre. Because of COVID-19, some aspects of care (e.g., diagnosis and monitoring) may shift from ocular oncology centres to local hospitals, and from hospital clinics to community optometrists, with expert advice from virtual specialist clinics. This trend will be facilitated by improved imaging, secure electronic communications, artificial intelligence, and video-conferencing.

Whenever possible, patients are enrolled in clinical trials, which usually involve multicentre collaboration under the auspices of organisations such as the European Ophthalmic Oncology Group and the International Society of Ocular Oncology.
as well as patient advocacy groups such as the Melanoma Research Foundation, CureOM, and A Cure in Sight. This collaboration requires standardised methods of examination, treatment, and disease definition using the TNM (Tumor, Node, Metastasis) staging system of the American Joint Committee on Cancer (AJCC), International Retinoblastoma Classification, and others.

11.1 Uveal Tumours

11.1.1 Naevus

Choroidal naevus (Fig. 11.1) is a benign tumour composed of uveal melanocytes. It occurs in up to 10% of the Caucasian population. It is usually asymptomatic and found on routine eye examination. Clinical features include:

- Flat tumour, with some showing slight thickening.
- Featureless surface, with some lesions showing drusen, especially if dome shaped.
- Grey appearance, although a few are amelanotic (i.e., yellow or white).
- Small size, usually less than three disc diameters (DD) (i.e., 4.5 mm) in diameter.
- Surround of normal choroid, but with an amelanotic halo in a few cases.

Iris naevus (Fig. 11.2) is rare. Clinical features include:

- Flat tumour, with some showing slight thickening.
- Diameter usually less than 3 mm.

Fig. 11.1 Typical choroidal naevus of the right eye
11.1.1  Management

Patients should be informed of any naevi that are discovered so that they will know that these are not new when these are noted at any subsequent examinations.

All lesions should be documented by photography if possible, to make it easier to detect any growth at a later date.

The risk of malignancy is extremely low with naevi that do not show any features of melanoma (listed in next section).

11.1.2  Melanoma

Choroidal melanomas (Fig. 11.3) are the most common primary ocular malignancy in adults. Presentation peaks around the age of 60 years and is rare before adulthood. In about 30% of patients, the tumour is detected on routine fundus examination before symptoms develop; otherwise, symptoms include blurred vision, metamorphopsia, photopsia, visual field loss or visible tumour in the iris or subconjunctivally.
Early treatment of choroidal melanoma improves any opportunities for conserving vision and may prevent metastasis in some patients; however, differentiating small choroidal melanomas from naevi can be difficult.

### 11.1.2.1 Diagnosis

Damato has devised the acronym, MOLES, to help diagnose and manage patients with choroidal melanocytic tumours of unknown malignancy:

|                          | 0 if absent; 1 if uncertain; 2 if definite. |
|--------------------------|--------------------------------------------|
| **Mushroom shape**       |                                            |
| **Orange pigment**       |                                            |
| **Large size**           | 0 if diameter < 3 DD and thickness < 1 mm. |
|                          | 1 if diameter = 3–4 DD and/or thickness = 1–2 mm. |
|                          | 2 if diameter > 4 DD and/or thickness > 2 mm. |
| (Ignore thickness if this cannot be assessed) | |
| **Enlargement over time**| 0 if absent or unknown; 1 if uncertain; 2 if definite. |
| **Subretinal fluid (SRF)**| 0 if absent; 1 if trace or uncertain; 2 if definite. |
|                          | (Assume SRF if unexplained blurred or distorted vision) |

A protocol is currently under evaluation for categorizing tumours and managing patients according to the total score:

- If score is 0, ‘common naevus’—optometry review at every routine checkup.
- If score is 1, ‘low-risk naevus’—monitoring with photos, OCT and autofluorescence imaging.
- If score is 2, ‘high-risk naevus’—refer non-urgently to local ophthalmologist.
- If score is >2, ‘probable melanoma’—refer urgently to ophthalmologist.

Features raising suspicion of the presence of a choroidal melanoma include:

- **Metamorphopsia** (i.e., distorted vision), caused by foveal disturbance by SRF or tumour
- **Eccentric visual phenomena**, such as photopsia (flashing lights) or visual field loss
- **Lens abnormalities**, such as cataract or astigmatism, caused by tumour pressing on the lens
- **Afferent pupillary defect**, caused by retinal damage from detachment or tumour
- **No improvement in visual acuity with optical correction**
- **Ocular hypertension**, if new vessels in the iris, tumour cells or macrophages blocking aqueous outflow
- **Melanoma visible externally** (i.e., extraocular or anterior chamber tumour spread)
- **Asymmetric episcleral ‘sentinel’ vessels**, if the tumour involves ciliary body

Iris melanomas are less common than other uveal melanomas (Fig. 11.4). They can be pigmented or amelanotic and nodular or diffuse.
11.1.2.2 Management

Ocular treatment is aimed at conserving a comfortable and seeing eye, possibly preventing metastasis in some patients. The most widely used modalities are:

1. Brachytherapy, administered by a saucer-shaped radioactive applicator, which is sutured to the globe adjacent to the tumour and removed a few days later, once the prescribed dose of radiation has been administered.

2. Proton beam radiotherapy, administered with a cyclotron, which precisely delivers a fine beam of protons, which can be collimated to match the shape of the tumour. The beam is targeted at the tumour using radio-opaque markers that are sutured to the sclera at known distances from the tumour before the radiotherapy.

3. Stereotactic radiotherapy, with multiple fine beams of radiation focused on the tumour from different directions, either simultaneously or sequentially.

4. Infra-red laser therapy that either heats the tumour (transpupillary thermotherapy) or activates a photosensitizer, such as verteporfin (photodynamic therapy).

5. Local tumour resection, either en-bloc through a scleral trapdoor (exoresection) or by nibbling and aspirating the tumour with a vitrector passed through a hole in the retina.

6. Ocular amputation (enucleation) or, if there is extensive extraocular spread, exenteration of the entire orbital contents.

Treatment is selected according to the tumour size, location and extent and often combines different modalities (e.g., brachytherapy with adjunctive laser therapy, exoresection followed by adjunctive brachytherapy, or endoresection preceded by neoadjuvant proton beam radiotherapy). After radiotherapy, some choroidal melanomas leak fluid into the macula and subretinally or cause iris neovascularization and painful glaucoma; such ‘toxic tumour syndrome’ can be treated with intra-vitreal injections of anti-angiogenic agents or by lasering or resecting the toxic tumour.
11.1.2.3 Prognosis

Despite successful excision or ablation of the choroidal melanoma, almost 50% of patients develop metastatic disease, which usually becomes apparent months or years after apparent good health. Metastases develop almost exclusively in patients whose tumour shows chromosome 3 deletion, a class 2 gene expression profile, and/or BAP1 gene inactivation, all of which are more prevalent in large tumours. Prognostic tumour biopsy is therefore being performed routinely in a growing number of centres. An online prognostic tool is available at www.LUMPO.net.

Metastatic disease almost always involves the liver, which is examined by ultrasonography or magnetic resonance imaging before ocular treatment and then every 6–12 months, indefinitely. Metastatic disease from uveal melanoma carries a poor prognosis, unless amenable to a partial hepatectomy, although encouraging results have recently been achieved with IMCgp100 (Tebentafusp), which binds cytotoxic T cells to melanoma cells, and with isolated liver perfusion with melphalan.

11.1.3 Haemangioma

Choroidal haemangiomas (Fig. 11.5) are rare, benign, vascular tumours, which can be circumscribed or diffuse. Diffuse choroidal haemangiomas are almost always associated with Sturge Weber Syndrome, whereas circumscribed choroidal haemangiomas (CCH) have no systemic associations. These tumours are characterised by:

- pink colour,
- posterior location,
- indistinct margins, and
- exudative retinal detachment, which can become total.

Fig. 11.5 Choroidal haemangioma inferior to the left optic disc. Note the pink colour
Treatment consists of photodynamic therapy or low-dose radiotherapy and is primarily aimed at conserving the eye and useful vision, although improvement in visual acuity occurs only in a few cases.

### 11.1.4 Metastases

Choroidal metastases (Fig. 11.6) are becoming more common as patients with cancer live longer. They mostly arise in breast or lung. Not unusually, the ocular metastasis is the presenting feature of lung cancer, unlike metastases from breast carcinoma, which arise in patients with a previous history of the disease. Many patients have metastases in other organs when they present with ocular disease. The clinical features of choroidal metastases are:

- location in posterior choroid in most cases
- yellow or white colour, except for metastases from skin melanoma
- placoid shape
- indistinct margins
- lack of visible tumour vessels (unlike amelanotic melanomas)
- serous retinal detachment
- multiple tumours affecting one or both eyes in some patients
- rapid tumour growth, which necessitates urgent referral and treatment

In patients with a solitary choroidal metastasis and no evidence of concurrent or previous extraocular malignancy, the clinical diagnosis may need to be established by intraocular tumour biopsy, which may also help to identify the site of the primary tumour. Choroidal metastases usually respond dramatically to radiotherapy, which can be administered in the first instance or if there is no tumour regression with systemic therapy.

Metastases to retina and vitreous are rare.

**Fig. 11.6** Multiple choroidal metastases from the lung in a middle-aged woman. The right eye showed similar appearances
11.2 Retinal Tumours

11.2.1 Vitreoretinal Lymphoma

Retinal lymphoma (Fig. 11.7) is rare but becoming more common. It is usually of the diffuse, large, B-cell type. In most patients, retinal lymphoma is associated with CNS involvement, which can present before or after the ocular disease. Most patients are elderly, except for those with immunodeficiency. The clinical features are:

- vitreous infiltrates, resembling uveitis unresponsive to steroids, and/or
- yellow or white subretinal infiltrates, accumulating under the retinal pigment epithelium
- size of subretinal infiltrates ranging from very small flecks or drusenoid deposits to large, irregular tumours
- multiple subretinal deposits in most cases, usually affecting both eyes
- other features, such as retinal vascular sheathing and occlusion, epiretinal membrane formation, macular oedema and optic disc swelling

Diagnosis is confirmed by vitreous or tumour biopsy. The lymphoma cells are fragile so that specimens must reach the laboratory within an hour unless special transport medium is used. Steroid therapy must be stopped as long as possible before biopsy as it can cause a false negative result.

Ocular treatment consists of low-dose radiotherapy or intravitreal injections of methotrexate or melphalan, but is often followed by fatal CNS lymphoma. In some centres, systemic therapy is therefore preferred, especially in view of encouraging survival data in studies combining chemotherapy with immunomodulatory agents.

Fig. 11.7 Subretinal infiltrates of lymphoma cells in a patient with CNS/retinal lymphoma. Vitreous infiltrates are not shown in this figure.
such as lenalidomide. The efficacy of such systemic therapy is enhanced by therapeu-
tic vitrectomy.

11.2.2 Retinal Capillary Angioma

Retinal capillary angioma (also known as haemangioblastoma) (Fig. 11.8) can be sporadic or hereditary, the latter arising as part of Von-Hippel Lindau dis-
ease. This syndrome is inherited in an autosomal dominant fashion and causes a wide variety of tumours, which include CNS haemangioblastoma, renal cell carcinoma, phaeochromocytoma, renal and pancreatic cysts, islet cell tumours, cystadenoma of the epididymis in men and the broad ligament of the uterus in women, and endolymphatic cell tumour. This syndrome should be suspected in patients with a positive family history, more than one retinal angioma or one retinal angioma and systemic evidence of this disease. The features of retinal capillary angioma are:

- Peripheral retinal location, especially temporally, in most cases.
- Tiny red spot (similar to microaneurysm) growing into an orange-red nodule with a prominent feeder vessel from the optic disc.
- Secondary effects—hard exudates, possibly forming a macular star; retinal haemorrhage, traction retinal detachment.
- Optic disc location in some cases.
- Spontaneous regression, with reduction in size of feeder vessel and resolution of exudation.
- Multiple lesions in one or both eyes if associated with VHL disease.
- Sessile or exophytic growth in some optic disc tumours.

Fig. 11.8 Retinal capillary angioma, with dilated feeder vessel and hard exudates
Patients with VHL need screening for retinal angiomas and vice versa. The detection of retinal lesions can be aided by wide-angle fluorescein angiography. Systemic disease can be revealed by genetic testing, palpitations, headaches, deafness, hypertension, haematuria, urinary catecholamines, and tumours found on CNS and abdominal imaging.

Depending on their size and location, retinal angiomas are treated by photocoagulation, photodynamic therapy, cryotherapy or radiotherapy, and possibly intravitreal anti-angiogenic agents.

### 11.2.3 Retinoblastoma

Retinoblastoma (Fig. 11.9) is almost always caused by mutation of both the maternal and paternal copies of the RB1 gene (i.e., ‘two-hit hypothesis’). The RB1 gene is located on chromosome 13. The disease depends on when the mutation occurs:

- If the two RB1 mutations both occur in the same retinal cell, then a solitary, somatic, non-hereditary retinoblastoma develops.
- If one copy of the retinoblastoma gene is mutated during embryonic life, then every cell in part of the body carries the mutation (i.e., mosaicism).
- If a germline mutation from one parent is inherited, then it is present in all cells throughout the body of the patient. Malignancy develops whenever and wherever the homologous gene from the other parent mutates so that both copies of the gene become abnormal. Patients with such hereditary, germline retinoblastoma tend to develop multiple retinoblastomas in one or both eyes as well as pineoblastoma, osteosarcoma, melanoma and a wide variety of other cancers. The mutation is

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Fig. 11.9  Multiple retinoblastomas in the left eye of a baby with germline disease
autosomal dominant, so that it is inherited by 50% of the patient’s children, 90% of whom will develop retinoblastoma.

With regards to the clinical features of retinoblastoma:

- When very small, the tumour is translucent, pearly, flat or dome-shaped.
- When larger, the tumour is nodular or multinodular, yellow-white, with visible blood vessels.
- When tumour necrosis occurs, a craggy, white, irregular, calcified mass develops.
- Vitreous seeding has the appearance of white dust, pearls or clouds.
- Subretinal seeding appears as tiny, yellow or white tumours, which become confluent.
- Anterior chamber seeds form white tumours or a pseudohypopyon.
- Extra-ocular spread into the orbit causes proptosis if advanced.
- Secondary effects include retinal detachment, vitreous haemorrhage, glaucoma and panophthalmitis.
- Diffuse retinoblastomas infiltrate the retina without forming a discrete mass.

Patients usually present:

- at birth or in the first year of life if bilateral disease is present,
- in the second or third year of life if only one eye is affected, and
- in later childhood if there is diffuse retinoblastoma affecting only one eye.

Modes of presentation include leukocoria, strabismus, glaucoma, buphthalmos, orbital cellulitis and proptosis. Management involves:

- Induction of labour at 38 weeks if family history of retinoblastoma, to detect and treat any tumours as early as possible.
- Full ocular examination, commencing ocular treatment 1 or 2 days after birth.
- For small tumours (<3 mm), focal therapy, comprising laser if posterior or cryotherapy if anterior.
- For larger tumours, systemic or intra-arterial chemotherapy followed by focal therapy.
- For vitreous seeds, intra-vitreal injections of chemotherapy.
- For advanced tumours, enucleation, especially if unilateral disease.
- If invasion of orbit or significant extension to optic nerve or choroid, systemic adjuvant chemotherapy.
- Genetic studies to identify retinoblastoma mutation, if not known.
- Genetic studies to determine whether disease is familial, if not known.
- Screening for pineoblastoma, if hereditary retinoblastoma.
- Advice re avoidance of carcinogens (e.g., smoke, alcohol, sunburn, etc.).
- Survivorship clinic if hereditary retinoblastoma or systemic chemotherapy.
- Genetic counselling when childbearing age is reached.

In patients with germline retinoblastoma, computerized tomography, X-rays, and radiotherapy are avoided if possible as exposure of healthy tissues to any ionizing radiation increases the incidence of second malignant neoplasms.
11.3 Conjunctival Tumours

Conjunctival tumours are rare and are therefore described only briefly in this section. When assessing a patient with a conjunctival tumour, it is essential to examine the entire conjunctiva, including the upper and lower palpebral conjunctiva and the fornices, as well as palpating the regional lymph nodes for metastases.

11.3.1 Melanocytic Tumours

Conjunctival naevi (Fig. 11.10) can be pigmented or amelanotic and usually contain multiple cysts. They tend to grow during teenage years and in early adulthood. Transformation to melanoma is estimated to occur in about 1 in 400 cases.

Primary acquired melanosis (PAM) (Fig. 11.11) consists of a flat, brown area of pigmentation, which is not present at birth and not associated with any systemic conditions. It can be benign (PAM without atypia) or malignant (PAM with atypia), the latter having the potential to develop into in situ and invasive melanoma. Biopsy is required to differentiate between the two types of PAM, with atypia recognised by the presence of melanocytes that have large nuclei, prominent nucleoli and that have separated from the basement membrane to infiltrate the more superficial layers of the epithelium. Treatment for PAM with atypia is with topical mitomycin C chemotherapy drops.

Conjunctival melanoma (Fig. 11.12) is genetically distinct from uveal melanoma and similar to cutaneous melanoma. It comprises:

- In situ conjunctival melanoma, confined to the epithelium.
- Invasive melanoma, which has broken through the basement membrane to spread to the lamina propria, where tumour cells may invade lymph channels and veins to spread to regional lymph nodes and other parts of the body.

Conjunctival melanomas can be nodular or diffuse and pigmented or amelanotic. These tumours tend to seed easily to other parts of the conjunctiva and down the nasolacrimal duct so that incisional biopsy should be avoided.

Fig. 11.10 Large conjunctival naevus in the left eye of a child. Note the clear cysts in the lesion
Treatment is by surgical excision, taking care to use fresh instruments for wound closure. Adjunctive cryotherapy, radiotherapy and/or topical chemotherapy with mitomycin C are administered to prevent local tumour recurrence.

11.3.2 Squamous Tumours

Squamous papillomas are benign tumours associated with the human papilloma virus. They are irregular and pink, with visible blood vessels, and can be solitary or multiple, unilateral or bilateral, occurring anywhere in the conjunctiva but are usually inferiorly and medially (Fig. 11.13). Treatment is by excision and cryotherapy, taking care to avoid iatrogenic seeding, possibly with local administration of adjuvant interferon-α2b. Recurrence is common.
Conjunctival squamous cell carcinoma (Fig. 11.14) is caused by sunlight or human papilloma virus, and shows more aggressive growth in immunocompromised individuals. Conjunctival squamous intra-epithelial neoplasia (i.e., carcinoma in situ) is also termed ‘conjunctival and corneal intra-epithelial neoplasia (CCIN)’ and ‘ocular surface squamous neoplasia (OSSN)’.

The clinical appearances include:

- Location on bulbar conjunctiva, in the inter-palpebral fissure, especially at limbus, in most cases
- Translucent, gelatinous, white, pink, yellow or, in dark skinned individuals, a black or brown conjunctival tumour,
- Nodular, diffuse or papillary growth patterns,
- Areas of keratinization on the tumour surface, giving it a frosty appearance,
- Discrete, grey patches on the cornea,
- Dilated feeder vessels.
Biopsy confirms the diagnosis and differentiates between in situ and invasive disease.

Treatment is usually by excision with adjunctive cryotherapy, brachytherapy and/or interferon, administered in drop form or by intralesional injection, or 5-FU or mitomycin-C drops.

As with conjunctival melanomas, squamous cell carcinomas can metastasise to regional lymph nodes and systemically, albeit rarely.

### 11.3.3 Sebaceous Gland Carcinoma

Sebaceous gland carcinoma is highly aggressive. It tends to be mistaken for unilateral blepharo-conjunctivitis, resistant to topical antibiotics, or recurrent chalazion after curettage. Successful treatment has been reported with topical mitomycin C chemotherapy but many patients require exenteration.

### Further Reading

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