DIFFERENTIAL DIAGNOSIS OF NON-PIGMENTED INTRAOCULAR TUMOURS

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In this chapter the non-pigmented tumours of iris and ciliary body and the retinoblastomas will be mentioned only briefly as they are discussed in detail elsewhere in this volume. We will discuss the clinical appearance, differential diagnosis, natural course, therapy, and histology of the non-pigmented tumours of the anterior and the posterior segment of the eye.

Cornea and anterior chamber

To our knowledge intraocular tumours originating in the cornea have never been reported. Cysts in the anterior chamber adherent to the cornea generally are of epithelial origin. A cystic diktyoma in the anterior chamber has been reported (Gifford, 1966).

Iris

Non-pigmented tumours in the anterior chamber arising from the iris or the chamber angle have been described as leiomyoma, neurofibroma (Lisch nodules), naevo-xantho-endothelioma or juvenile xanthogranuloma, choristoma (ectopic lacrimal gland tissue) (Gass, 1974), rhabdomyosarcoma, diktyoma, angioma (Gass, 1974), amelanotic iris naevus, metastatic tumour, retinoblastoma, leukaemic infiltrate, and benign lymphoid hyperplasia.

Granulomatous inflammations such as sarcoid, syphilis, tuberculosis, lepra, due to foreign bodies, abscesses, and primary cysts have to be considered in the differential diagnosis.

Fig. 1 Pseudophakia lipomatosa. Massive replacement of lens by adipose tissue, covered by wrinkled lens capsule within connective tissue. Thirteen year old boy. Haematoxylin and eosin; 15x. (Courtesy Prof. Manschot).

Fig. 2 Astrocytic hamartoma with mulberry appearance in a patient with tuberous sclerosis (fig. 3).

The iris tumours are described in detail by Foulds elsewhere in this volume.

Lens

Primary tumours of the lens are not known.

Ciliary body

Tumours of the non-pigmented epithelium of the ciliary body are usually classified as congenital and acquired tumours (Shields, 1983).

The congenital tumours are glioneuroma, non-teratoid medullo-epithelioma or diktyoma, and teratoid medullo-epithelioma or teratoneuroma; the diktyomas and teratoneuromas may be benign or malignant.

The acquired tumours are the pseudo-adenomatous hyperplasia with reactive hyperplasia or senile hyperplasia (Fuchs' adenoma), the adenoma that may be solid, papillary, or pleomorphic, and the adenocarcinoma or malignant epithelioma that has the same subdivision.

The tumours of the ciliary body are described in detail by Foulds elsewhere in this volume.

Vitreous body

Duke-Elder (1969) states that there are no primary tumours in the vitreous. One wonders, however, whether in some cases of persistent hyperplastic primary vitreous (PHPV) one is not justified to talk of primary vitreous tumours when mesenchymal tissue is found that has differentiated into fat tissue, rhabdomyoblasts, cartilage, or brain tissue (fig. 1). It is possible that these tissues are derived from a medullo-epithelioma, which normally grows in the iris or ciliary body at the average age of five years but may also start in the optic disc or retina (Broughton and Zimmerman, 1978). In any case one should keep in mind that PHPV may be concomitant with a medullo-

epithelioma that is either benign or malignant. The combination of PHPV with a retinoblastoma has been described in one patient (Morgan and McLean, 1981).

Retina

The non-pigmented retinal tumours are divided into tumours of the neuroretina, those of vascular origin, and pigment-epithelial neoplasms.

Neuroretinal tumours are retinoblastomas, astrocytomas or benign hamartomas, massive gliosis, glioneuromas, and mixed glial tumours. Retinoblastomas and astrocytomas are the most common ones, while the spontaneously involuted or arrested so called retinomas or retinocytomas will be seen less frequently.

In the differential diagnosis of retinoblastoma one should consider metastasis, medullo-epithelioma, pigment-epithelial hamartoma, incontinentia pigmenti; furthermore, Coats' disease, congenital cataract, toxocara, toxoplasmosis, coloboma of the choroid, optic disc dysplasia, PHPV, retinopathy of prematurity, dominant exudative vitreo-retinopathy, X-linked congenital retinoschisis with or without vitreous haemorrhage, Norrie's disease, myelinated nerve fibres, metastatic endophthalmitis, herpes or cytomegalovirus retinitis, bleached vitreous haemorrhage, old perforation, and uveitis must be considered. For a more elaborate discussion on retinoblastoma see the chapter by Tan and Schipper elsewhere in this volume.

The hamartomas, astrocytomas or astrocytic hamartomas are solitary tumours or may appear in association with the autosomal dominantly inherited tuberous sclerosis (Bourneville-Pringle) (Fig. 2) or neurofibromatosis (Recklinghausen). One may see white-yellowish tumours in the retina or on the optic disc, sometimes with a mulberry or spawn appearance due to calcification.

The diagnosis can be difficult if the tumour looks like an amelanotic dome-shaped mass with dilated blood vessels on top of it or if it is small and looks like an ill-defined, transparent thickening of the nerve fibre layer. Astrocytomas mostly originate in the second to third decade. Diagnosis is usually made by ophthalmoscopy or by biomicroscopy. Especially for the small transparent tumours fluorescein angiography is useful, showing hypofluorescence in the arterial phase with a lacework of fine vessels in the venous phase and early leakage.

In the differential diagnosis in young patients retinoblastomas should be considered in the first place. The chalky bodies of retinoblastomas, however, are duller, those of astrocytomas more glistening. Retinoblastomas often have more prominent feeder vessels and show more seeding of tumour cells. The presence of general symptoms of tuberous sclerosis, especially sebaceous adenoma of the facial skin (fig. 3), or neurofibromatosis may help. In older patients one should consider drusen of the optic disc (both drusen and astrocytomas may be accompanied by haemorrhages), aspecific granulomas, myelinated nerve fibres, and amelanotic melanomas. Visual prognosis generally is good and treatment is not necessary except in very rare cases when the tumour shows rapid growth or when an exudative retinal detachment develops. In that case, therapy is the same as for capillary angiomas, which are discussed later.

Histologically one finds an eosinophylic mass in the neuroretina with well-defined fibrous astrocytes with oval or round nuclei and slight eosinophylic cytoplasm.

Massive gliosis is the final stage of many disorders resulting in glaucoma or atrophy of the eye. Clinically the diagnosis is seldom made. The disease is usually unilateral and the fundus often can not be examined, e.g. after trauma, inflammation, congenital anomaly, or secondary glaucoma. In those rare cases where the fundus could be visualised the diagnosis retinoblastoma or

Fig. 3 Adenoma sebaceum of the facial skin in tuberous sclerosis (Bourneville-Pringle).
(Courtesy Prof. Suurmond).

Fig. 4 Massive gliosis (low grade intraocular glioma).
Lens dislocated by benign mass of glial cells
which fills the eye. Twenty-six year old man;
birth weight 1.250 grams. Haematoxylin and eosin;
15x.
(Courtesy Prof. Manschot).

amelanotic melanoma was made. There are no specific diagnostic criteria. Ultrasound examination shows an aspecific intraocular mass with high reflectivity resembling these two tumours; CT scanning does not give additional information. There is no therapy available; pain or suspicion of another tumour may necessitate enucleation.

Histologically the retina is locally thickened and has partly or totally been substituted by glial tissue with abnormal blood vessels (fig. 4). The tumour is benign, non-invasive, and consists of well-differentiated glial cells.

Glioneuroma is a very rare choristomatous, benign tumour mostly discovered in the chamber angle shortly after birth. It arises from the medullary epithelium at the anterior border of the primitive optic cup. Sometimes it is present in the retina. Most eyes are enucleated on suspicion of a retinoblastoma.

Mixed glial tumours are tumours that are not really glial in origin but have a considerable glial component. An example is the capillary haemangioma, which will be discussed below.

Vascular tumours can be divided into two types, viz. the capillary haemangioma (von Hippel) and the cavernous haemangioma. The so-called racemose haemangioma such as the Wyburn-Mason syndrome is an arteriovenous malformation and not really a tumour.

Capillary (haem)angioma (fig. 5abc) starts as a very small, red tumour, hardly bigger than a microaneurysm (fig. 5a). When the tumour grows, arteriovenous fistulas are formed and gradually big, round, pink to red tumours appear with large vessels. If no treatment is applied, a serous retinal detachment develops and mostly at this stage the patient with a capillary angioma becomes aware that something is amiss. Capillary angiomas of the retina may grow from the inner retinal layers into the vitreous

Fig. 5 a. Fluorescein angiogram of smallest capillary haemangioma we have ever seen. On ophthalmoscopy it was hardly visible. Male patient aged 30 years.

b. Same patient. Slightly bigger haemangioma in the other eye.

c. Fullgrown capillary haemangioma at 6 o'clock position with secondary peripapillary exudation. Large exudate in the macular area. (Courtesy Dr Riaskoff).

cavity in an endophytical way or they may grow exophytically from the outer retinal layers into the choroid or the optic disc. Recently, a young patient with a bilateral exophytic parapapillary growth has been described (Yimoyines et al., 1982). The haemangioma may be located on and adjacent to the optic disc (fig. 6abcd). One of our patients had an optic atrophy due to an angioma in the intracranial part of the optic nerve. Capillary angioma is transmitted as an autosomal dominant trait. If cysts are present in the cerebellum, spinal cord, kidneys, pancreas, or other organs, it is called von Hippel-Lindau's disease.

Early diagnosis in patients from afflicted families is made primarily with fundoscopy and biomicroscopy for the very small tumours (fig. 5ab). In the differential diagnosis one should consider the arteriovenous malformation of the racemose angioma (fig. 7); this remains stationary and does not show round tumours, hard exudates, retinal detachments, nor does it show leakage on the late angiogram. At a later stage one should exclude Coats' disease (fig. 8), macroaneurysmata, cavernous haemangioma, proliferative retinopathy due to diabetes, hypertension or sickle cell anaemia, and peripheral disciform reactions. Most entities in the differential diagnosis of retinoblastoma are also included in the differential diagnosis of capillary angiomas and the other non-pigmented intraocular tumours. The end stages are massive gliosis, secondary glaucoma, and phthisis bulbi. We have seen two patients with a completely calcified sclera resulting in a stone hard atrophic eye.

Therapeutical results for tumours smaller than 2.5 disc diameters are equally favourable after photocoagulation, cryotherapy, or diathermy. For larger tumours repeated freeze-thaw cryotherapy is advocated, while partial thickness scleral diathermy with a buckling procedure is advised when secondary detachments have developed.

Fig. 6 a. Capillary haemangioma on and adjacent to the inferior half of the optic disc.

b. Fluorescein angiogram of same fundus, showing dense network of capillaries.

c. Histologic specimen of a juxtapapillary retinal angiomatosis in 76-year old man; haematoxylin and eosin; 60x.
(Courtesy Prof. Manschot).

d. Detail of fig. 6c, showing capillary and cavernous spaces; 380x.
(Courtesy Prof. Manschot).

Fig. 7 Fundus aspect of a retinal racemose angioma (Wyburn-Mason syndrome).

Fig. 8 Typical fluorescence pattern in Coats' disease, showing a coarse capillary pattern and irregular dilatation of the large vessels.

a

b

Fig. 9 a. Cavernous haemangioma of the retina with white glial tissue.
b. Late phase fluorescein angiogram of same fundus, showing the fluorescein-blood interfaces in the caverns.
(Courtesy Dr Bos).

a

b

Fig. 10 a. Leber's military retinal aneurysms.
 b. Fluorescence angiogram of same fundus,
 showing hyperfluorescent retinal capillaries
 and microaneurysms temporal to the central
 avascular zone.

Histology shows normal capillaries with proliferating endothelial cells and pericytes combined with many interstitial glial cells and big vacuoles.

The cavernous (haem)angioma of the retina is most often a coincidental finding in patients with cutaneous haemangiomas. Ophthalmoscopically it resembles clusters of microaneurysms, sometimes covered with glial tissue. It is a non-progressive tumour with an unknown heredity but sometimes familial occurrence. The fluorescein-blood interface in the aneurysms in the late phase fluorogram is the most typical diagnostic tool (fig. 9ab). Differential diagnosis covers Coats' disease (fig. 8), teleangiectasis or Leber's miliary aneurysms (fig. 10ab), macroaneurysms, and the more common retinal diseases with microaneurysms such as diabetes, hypertension, etc. Photocoagulation is hardly ever indicated unless vitreous haemorrhages have developed.

Pigment-epithelial hyperplasia may be jet black but may also be hypopigmented, sometimes with a white rim. It is a non-elevated lesion, often seen on routine ophthalmoscopy, probably congenital, and it does not require treatment.

Pigment-epithelial hamartomas, congenital retinopigment-epithelial malformations or juxtapapillary hamartomas, are unpigmented or greenish blue or slate coloured, often parapapillary lesions with a non-pigmented apex on the vitreous side and a pigmented base (fig. 11abc). They all show tortuosity of the retinal vessels, sometimes not in accordance with the visible amount of glial membranes on their surface. Usually the lesion will be found unilaterally in healthy, hypermetropic children or teenagers; it is not hereditary, not progressive, and is considered to be a congenital anomaly of the pigment epithelium and the overlying neuroretina. Birth trauma, e.g. a subretinal haemorrhage with resulting periretinal

Fig. 11 a. Juxtapapillary pigment-epithelial hamartoma.
b. Typical early fluorescence pattern of same fundus.

c

c. Late phase fluorescence pattern of same fundus.

a

Fig. 12 a. Haemangioma of the choroid.

fibrosis and reactive pigment-epithelial hyperplasia may also be an explanation for this tumour. The differential diagnosis covers preretinal fibrosis with reactive pigment-epithelial hyperplasia, granulomatous tumours, disciform lesions, melanoma, and toxocariasis. The prognosis for the eye is favourable, for the visual acuity, however, it is poor. Treatment is not indicated. The fluorescein angiogram shows a typical picture.

Histologically the top of the lesion is made up by thickened and malformed retina with intraretinal gliosis; the base is formed by hyperpigmented and hypertrophic pigment epithelium. There is no unanimity regarding the histological subdivision of the lesions with respect to the presence or absence of pigment-epithelial cells and strands in the neuroretina (Laqua and Wessing, 1979).

Choroid

Non-pigmented choroidal tumours are the haemangiomas, amelanotic naevi and melanomas, metastases, choristomas, neurilemmomas or schwannomas, reticuloses, and lymphomas.

Choroidal haemangiomas are benign vascular hamartomas; hamartomas are local tumours formed by differentiated cells normally encountered in the same tissue (fig. 12abc). In the choroid there are localised and diffuse haemangiomas, the latter often concomitant with encephalofacial haemangiomas (Sturge-Weber). As a rule, the diffuse haemangiomas are discovered around the age of eight years, the localised ones in the fourth decade (Witschel and Font, 1976). An eye with a diffuse tumour has a much redder fundus reflex than the fellow eye and this makes diagnosis easy. Usually the tumours are discovered on routine control of children with a Sturge-Weber syndrome or by a drop of visual acuity due to a serous detachment or cystoid macular oedema. Localised tumours also present themselves with metamorphopsia or a serous detachment. In those cases differentiation from

b **c**

- b. Early phase fluorescence angiogram of same haemangioma, showing filling of its vascular structure.
- c. Late phase fluorescence angiogram of same haemangioma, showing diffuse intense staining of the tumour; note absence of pigmentation.

melanomas, metastases, choristomas, posterior scleritis, sympathetic uveitis, retinal detachment, Harada's disease, choroidal effusions, central serous chorioretinopathy, and pigment-epithelial detachment may be difficult. This also holds true for granulomatous inflammations, reticuloses, colobomata, and retinoschisis, and sometimes a posterior staphyloma may mimic a tumour on ophthalmoscopy. Haemangiomas are often solitary, pink, poorly demarcated, rather flat, and they may bleach on pressure on the eye (blanching phenomenon). Amelanotic melanomas and metastases, on the other hand, are more yellow, better demarcated, and more elevated. Choroidal metastases of distant tumours are often multifocal or bilateral. Central serous chorioretinopathy or pigment-epithelial detachments have a typical fluorescein angiographic pattern. Ultrasonography can help to differentiate between haemangioma (high reflectivity), melanoma (choroidal excavation), and choristoma (high reflectivity with shadowing), and P32 is useful to differentiate between the first and the second.

Treatment with photocoagulation is only indicated in case of an exudative detachment. The aim should be not to eradicate the tumour but to create a chorioretinal scar on the tumour large enough to keep the retina attached and to serve as a barrier against penetration of the subretinal fluid. At this moment argon laser treatment seems to be the best modality. In case of a big retinal detachment one should try to exchange the subretinal fluid with intravitreal Ringer's solution or air and to perform photo- or cyrocoagulation (Sanborn et al., 1982).

On histological examination the solitary haemangiomas are most often of the cavernous type, whereas the diffuse ones usually have a mixed cavernous-capillary appearance. Pure capillary choroidal haemangiomas are very rare.

For the diagnosis of unpigmented naevi and melanomas see the chapter on pigmented intraocular tumours in this volume.

Metastatic tumours of the choroid are usually not diagnosed until the patient has visual complaints. In 80% of the females breast carcinoma is the primary tumour; in the males lung carcinoma accounts for 30%, unknown tumours for 28% and skin carcinoma for 17%. The metastases are often multifocal and bilateral, and usually grow faster than haemangiomas or melanomas. The differential diagnosis has been discussed under the heading of choroidal haemangiomas. In 75% a serous detachment develops. When no primary tumour is known or found, one can perform external irradiation with 3000 Rad to assess the diagnosis *ex juvantibus* if the tumour regresses afterwards. P32 examination can only differentiate metastases from benign tumours, not from malignant ones. In very difficult cases one may consider needle biopsy.

Therapy is indicated when visual symptoms arise, and will consist of external irradiation. Enucleation is only indicated in case of severe pain due to secondary glaucoma or if one can not differentiate between metastasis and a malignant primary tumour. Diagnostic enucleation to find the nature of the primary tumour is not advocated as the location of the primary tumour is rarely identified histologically.

Choristomas are tumours of ectopic tissues. In the eye there are five types of choristomas, viz. limbal dermoid, glioneuroma of the anterior chamber angle, iris choristoma with lacrimal gland tissue, PHPV with ectopic tissue, and choroidal choristoma with osseous tissue. The latter is a benign tumour, often encountered unilaterally in young women. Its colour is orange-yellow with brown pigment clumps due to pigment-epithelial proliferation; its borders are sharply demarcated and slow progression over the years has been documented. Differential diagnosis covers organised subretinal haemorrhages, amelanotic naevi or melanomas, metastases, and choroidal haemangiomas. Choroidal choristoma has been described after trauma, posterior scleritis (Trimble and Schatz, 1983) and an unknown fatal disease with eosinophilic granuloma (Kline et al., 1982). Diagnosis is easy

because of the reflectivity and density of the osseous tissue on ultrasonography and CT scan. Therapy is not advocated unless subretinal neovascular membranes or serous detachments make photocoagulation necessary. Histology shows well differentiated osseous tissue in the choroid.

Neurilemmomas or schwannomas are not easily differentiated from amelanotic melanomas or solitary dome-shaped astrocytomas on examination. The only way of differentiation would be a needle biopsy, which has its drawbacks (Shields et al., 1981).

Non-pigmented choroidal reticuloses may be benign or malignant. The benign reactive lymphoid hyperplasia is usually encountered unilaterally around the age of 55 due to complaints of visual loss. On ophthalmoscopy an amelanotic choroidal tumour with serous detachment is often found. From time to time a salmon-pink mass is found in the conjunctiva and the diagnosis can be made from a biopsy. Further signs are elevated intraocular pressure, retinal detachments, and iridocyclitis. For the differential diagnosis see choroidal haemangiomas. The visual prognosis is doubtful, the prognosis for life is good. Treatment consists of systemic or sub-tenonial corticosteroids and, if not successful, a low dose of external irradiation. On macroscopy a diffuse thickening of the choroid is found with some specific histological features (Ryan et al., 1972).

Among the malignant lymphomas are the reticulum cell sarcoma, Hodgkin's disease, Burkitt's lymphoma, and mycosis fungoides. Reticulum cell sarcomas often show keratitic precipitates, a varying amount of vitreous cells, or sub-retinal white tumours. Diagnosis is often made by a vitreous biopsy. The differential diagnosis covers panuveitis, disseminated choroiditis, leukaemia, amelanotic naevi or melanomas, haemangiomas, and benign lymphoid reactive hyperplasia. Treatment consists of external irradiation with 1500 to 3000 Rad. Leukaemias become manifest by vascular sheathing, nerve fibre infarcts, venous engorgement, haemorrhages, and Roth's spots. Also yellowish retinal or choroidal infiltrates may

be seen. Often the diagnosis is already known from systemic signs. In case of doubt the differentiation between mycotic endophthalmitis, viral retinitis, and leukaemia can be made by vitreous biopsy.

Optic disc

Most non-pigmented tumours have already been discussed. Capillary and cavernous haemangiomas of the optic disc show the same characteristics as the retinal ones. The arterio-venous malformations or racemose haemangiomas always extend from the disc; they have been mentioned with the retinal vascular tumours. The differential diagnosis with astrocytoma covers retinoblastoma and drusen of the optic disc. All three may reveal deep parapapillary haemorrhages. Myelinated nerve fibres may resemble beginning astrocytomas or retinoblastomas. The combined pigment-epithelial hamartoma has also been discussed. A juvenile xanthogranuloma of the optic disc, retina and choroid has been described (Wertz et al., 1982). Parapapillary amelanotic melanoma may resemble an optic disc tumour. Metastases, reticulum cell sarcoma, and leukaemias may arise in the optic disc. From the optic nerve astrocytomas and meningiomas may grow into the optic disc. The differential diagnosis in these cases consists of morning glory disc, coloboma, and granulomatous inflammation.

Sclera

No primary scleral tumours are known.

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