Things that go bump in the light. The differential diagnosis of posterior uveal melanomas

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Eye (2002) 16, 325–346. doi:10.1038/sj.eye.6700117

Introduction

The role of the ocular oncologist is two-fold: he must establish the correct diagnosis and then institute the appropriate therapy, if required. Prior to the establishment of ocular oncology as a speciality in its own right, the majority of patients with a uveal melanoma were treated by enucleation. It was recognised that inaccuracies in diagnosis occurred, but the frequency of these errors was not fully appreciated until 1964 when Ferry studied a series of 7877 enucleation specimens. He found that out of 529 eyes clinically diagnosed as containing a melanoma, 100 harboured a lesion other than a malignant melanoma.¹ Subsequent studies have shown a progressive improvement in the accuracy with which these tumours can be recognised. Shields and McDonald in 1974 found the misdiagnosis rate to have fallen to 1.9%.² More recent studies demonstrate a further improvement with the COMS study group in 1990 reporting an incidence of only 0.48%.³ These improvements in the accuracy of diagnosis can be attributed to an increased awareness of lesions that may simulate malignant melanomas, improved diagnostic techniques and increased referral to units specializing in the treatment of ocular tumours.

Many lesions that are mistaken for melanomas are non-malignant, nevertheless, they may pose a serious threat to vision and require prompt treatment in their own right. Others may be benign but have the potential to undergo malignant transformation and occasionally a benign lesion may be the harbinger of a neoplasm elsewhere.

The list of lesions that may simulate a malignant melanoma is extensive; Shields *et al*⁴ in a study of 400 patients referred to their service with a pseudomelanoma found these to encompass 40 different conditions at final diagnosis. Naturally, some lesions are mistaken for melanomas more frequently than others. In this study over one quarter of the patients referred with a diagnosis of a presumed melanoma were subsequently found to have a suspicious naevus. We have recently examined the records of patients referred to the ocular oncology service in Sheffield with the diagnosis of a malignant melanoma. Patients with iris lesions or where the diagnosis of a melanoma was not mentioned in the referral letter were excluded. During the period 1985–1999 1154 patients were referred with a presumed melanoma and of these the diagnosis was confirmed in 936 cases (81%). In 218 patients (19%) a different final diagnosis was made. Over half of the patients with pseudomelanomas (58%) were diagnosed as having an indeterminate melanocytic lesion (IML). This diagnosis will be discussed in detail later. Choroidal naevi (8.7%), haemangiomas (6.9%), and choroidal neovascularization (macula and eccentric disciforms) (5%) were the next most frequently misdiagnosed lesions. In all, 12 different conditions were found to have simulated choroidal melanoma (see Table 1) (manuscript in preparation).

Pseudomelanomas can be divided into pigmented and non-pigmented lesions. Pigmented lesions may be melanocytic in origin or derived from the iris, ciliary body or retinal pigment epithelium (Figure 1). Non-pigmented lesions are more diverse in nature, but can be divided into neoplastic, inflammatory or reactive, and vascular lesions (see Figure 2).

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Table 1 Diagnosis of pseudomelanomas 1985–1999.

Figure 1 Classification of pseudomelanomas of the choroid (pigmented lesions).

Pigmented lesions

Melanocytic origin

Naevi The commonest pigmented intraocular lesion is the naevus. Estimates of their frequency vary from 1 to 9% of the population. In 1998 Sumich⁵ *et al* examined a total of 3654 individuals aged 49–79 years using six standard field fundus photography and found that choroidal naevi were present in 6.5% of the study cohort. Correction of the data to account for possible naevi missed by the photography gave prevalence rates of 8.9% for women and 8.3% for men. These figures agree closely with post-mortem studies, which found that almost 9% of the eyes examined contained a nevus of either the ciliary body or choroid.⁶

Previous clinical studies have found a lower incidence. Ganley and Comstock⁷ found an incidence of 3.1% in a sample of individuals aged over 30 years. Earlier clinical studies have found an incidence of

Figure 2 Classification of pseudomelanomas of the choroid (non pigmented lesions).

approximately 1%.⁸ Whilst this variation may reflect sampling errors or improvements in clinical examination (for example the use of indirect ophthalmoscopy or fundus photography), it may also reflect the importance of age on the development of naevi. It is well recognised that choroidal naevi are uncommon in children and adolescents⁹ and are rarely observed in neonates. Naevi probably develop from nests of cells that are present at birth and then either proliferate or pigment at puberty. Tumour growth, although often taken as a sign of malignancy, may be observed in histologically proven benign naevi. MacIlwaine *et al*¹⁰ reported a case of a raised pigmented choroidal lesion that enlarged over a 6.5-year period and after enucleation was found to be a choroidal naevus.

Clinically, the typical choroidal naevus is a flat or minimally elevated pigmented lesion in the post equatorial choroid. The majority are brown to slate-grey in colour and range in size from 0.5–4.5 mm in diameter.⁵ The edges of the lesion may be distinct or blend slightly into the surrounding choroid. The surface is usually uniform in colour, although retinal pigment epithelial changes are common.¹¹ Drusen may be observed on the surface of naevi, particularly in the central portions of the larger lesions (Figure 3). Occasionally, large solitary drusen are present on the surface of the naevus.¹²

Whilst many naevi have a typical appearance, several clinical variants can be recognised; partial or even totally amelanotic naevi occur. One rather peculiar variant is the halo naevus where there is a yellowish ring surrounding the lesion. Interestingly, this latter variant has been observed in a patient with vitiligo.¹³ Abnormalities of visual function have in the past been taken as an indication that a pigmented fundal lesion is malignant and whilst visual symptoms undoubtedly

occur more frequently in malignant pigmented lesions, they may also be associated with benign naevi. Asymptomatic scotomas corresponding to the anatomical sites of the lesions can be demonstrated using careful perimetry.^{14–16} Reduced central visual acuity may be present if the naevus is subfoveal.¹⁷ Presumably these abnormalities of visual function are attributable to photoreceptor dysfunction either in the absence of or secondary to retinal pigment epithelial degeneration. Visual loss can also result from the development of either a serous retinal detachment or choroidal neovascularization.^{17–19} Serous retinal detachments can arise as a direct result of a retinal pigment epithelial disturbance, or secondary to choroidal neovascularization. Similarly, choroidal neovascularization can lead to visual loss as a result of subretinal haemorrhage and scarring or serous retinal detachment.

Indeterminate melanocytic lesions The majority of melanocytic lesions of the choroid are either benign naevi or malignant melanomas; they are a group of lesions that clearly do not fit comfortably in either category. Such lesions are larger than normal naevi and often significantly elevated, and yet if merely observed, remain indolent for many years. I use the term indeterminate melanocytic lesions (IMLs) to describe such lesions. As such they probably correspond to lesions described as low-grade melanomas or suspicious naevi. Typically, IMLs appear as pigmented, elevated lesions in the mid-peripheral choroid. They vary considerably in size with the largest attaining 3–4 mm in thickness. The surface of the lesion may at least in part be covered by whitish tissue giving the lesion a sclerotic appearance. Drusen frequently cover the lesion; but orange pigment is invariably absent. Alteration of the overlying retinal pigment epithelium is often present and usually appears as a pigmentary clumping resembling the bone spicule appearances seen in retinitis pigmentosa. Whilst these pigmentary changes may cover the entire surface of the lesion, more often, they are located towards the anterior portion of the lesion (Figure 4). It is possible that these pigment epithelial changes have arisen as a result of a prior accumulation of subretinal fluid, which has subsequently reabsorbed. In the course of my practice, I have observed a number of such lesions; the majority of which have shown no discernible growth over a number of years. Whilst it appears that these lesions are melanocytic in lineage, in the absence of any histological examination, one can only speculate as to their precise nature. Clearly, their size and appearance suggest they have arisen by virtue of some neoplastic process; but the fact that their

growth appears to dramatically slow down or stop mitigates against them having the unrestrained growth of a malignant lesion. It is now recognized that malignant neoplasms arise by virtue of genetic mutations in the cell that in turn leads to a loss of regulation in cell cycling, leading to unrestrained growth. Furthermore, it is apparent from studies of other malignancies that tumours do not develop because of a single genetic mutation; but rather as a result of a series of, often sequential, changes which ultimately result in a lesion with unrestrained growth, invasiveness and metastatic capability. Indeed, studies in our own laboratory and those of others have identified specific chromosome alterations in uveal melanomas.^{20–23} Moreover, it would appear that some of these changes (notably alterations of 3 and 8) correlate strongly with prognosis,^{24–26} suggesting that these particular changes are relatively late changes in the progression to a metastatic phenotype. Thus if one accepts that uveal melanomas arise as a result of a sequence of several genetic mutations, then it is possible to speculate that some early genetic mutations may have occurred in IMLs; but that the process has arrested before a complete malignant phenotype has developed. Whilst this possible hypothesis remains unproven, it is at least in part supported by clinical observation; for although the majority of such lesions are indolent, I have observed growth in at least two tumours (in each instance manifest by a small herniation through Bruch's membrane) after many years of apparent dormancy (Figure 5): suggesting the eventual acquisition of further mutations which in turn, have led to the development of an invasive phenotype. In view of the fact that most lesions remain unchanged over many years I advocate that such lesions merely be observed.

Melanocytomas The term melanocytoma was first used by Zimmerman and Garron²⁷ to describe a deeply pigmented benign tumour arising from the optic disc. Prior to this, such lesions were thought to be peripapillary melanomas invading the optic nerve head. Melanocytomas are in fact merely a form of naevus which are characterised clinically by their dark brown or black colouration and histologically by the presence of rather plump, round to oval deeply pigmented cells with small round nuclei which lack significant pleomorphism. Since their original description, similar tumours have been described in all parts of the uveal tract. Melanocytomas occur more frequently in non-white races^{27,28} and may be slightly more common in females.

Melanocytomas of the optic disc typically appear as an elevated dark brown or black lesion, which

occupies part or occasionally the entire optic disc. Melanocytomas usually extend over the edge of the optic disc and in about half the cases appear to have an associated contiguous choroidal naevus,²⁸ which is merely an extension of the melanocytoma beneath the juxtapapillary retinal pigment epithelium. Whilst most melanocytomas of the optic disc are asymptomatic, disturbances of visual function have been reported; the commonest being a defect in the visual field which can be either an enlarged blind spot or a scotoma corresponding to a retinal nerve fibre bundle defect.^{29–31} Sporadic cases of sudden, profound loss of vision due to retinal vascular occlusion,^{32,33} ischaemic optic neuropathy³⁰ or neuroretinitis³⁴ have been reported. Spontaneous necrosis of optic disc melanocytomas^{32,35} can occur and this may be complicated by secondary (neovascular) glaucoma.³⁶ Rarely, seeding of the vitreous with pigment particles has been described; in one case this was associated with migration of the particles into the anterior segment.^{37–39} Although benign, optic disc melanocytomas may enlarge in size. Joffe *et al*²⁸ evaluated 27 cases of optic disc melanocytoma and an increase in size in four (15%) cases.

Melanocytomas of the uveal tract are very uncommon. The ciliary body is probably the most common non-peripapillary location.⁴⁰ These lesions are densely pigmented and may simulate a ciliary body melanoma. Extra-ocular extension of these tumours can be observed producing a deeply pigmented episcleral mass⁴¹ (Figure 6). I have observed three such cases and in each instance the accompanying ciliary body tumour was small in size. In general, ciliary body melanomas only develop extrascleral extension when they have attained a large size. Thus, the diagnosis of a ciliary body melanocytoma should be considered in the presence of a small, pigmented ciliary body tumour with apparent extrascleral extension. Pigment dispersion and secondary glaucoma can develop in association with ciliary body melanocytomas.^{42,43}

Once the basic pathology of melanocytomas was established, they were considered to have no malignant potential. Subsequent reports have shown that these tumours can, in rare instances, undergo malignant

transformation^{44–50} and for this reason periodic observation of such lesions is mandatory.

Bilateral diffuse uveal melanocytic proliferation (BDUMP) Bilateral diffuse uveal melanocytic proliferation (BDUMP) is a curious paraneoplastic syndrome occurring usually in patients with a systemic, often occult, carcinoma.⁵¹ The first reported case was probably described by Machemer⁵² in 1966 who reported the development of bilateral diffuse malignant melanomas of the whole uvea in a patient with an abdominal tumour that was believed to be a primary pancreatic carcinoma. In 1980 Ryll *et al*⁵³ reported a case of a 64-yr-old male who presented with bilateral visual loss associated with multiple darkly pigmented lesions scattered throughout the choroid of both eyes and was subsequently found to have a primary bronchial carcinoma. Progressive enlargement of the lesions occurred until his death 15 months later. Histological examination of the eyes showed multiple discrete benign melanocytomas within a naevus involving the entire uveal tract. Barr and Zimmerman in 1982⁵⁴ reported four cases of bilateral diffuse melanocytic tumours associated with a systemic neoplasm and suggested this constellation of findings represented a new syndrome. Since then, sporadic reports have appeared in the literature confirming this phenomena as a rare, but definite clinical entity.^{51,55–67}

Gass⁵¹ considered the syndrome clinically to have five cardinal features that accompanied the visual loss. These are: multiple round or oval, subtle red patches at the level of the retinal pigment epithelium in the posterior fundus; a striking pattern of multifocal areas of hyperfluorescence corresponding to these patches on angiography; the development of multiple slightly elevated, pigmented and non-pigmented melanocytic tumours (Figure 7) together with diffuse thickening of the entire uveal tract; exudative retinal detachment; and rapidly progressive cataracts. The retinal pigment epithelial changes are usually the first to appear and usually remain visible after the other retinal signs have appeared. Other features include conjunctival hyperaemia and/or dilated episcleral vessels,^{51,54,55,62,65,67} shallowing of the anterior chamber⁵⁷ and ciliary body cysts,⁵⁵ iridodonesis,⁵⁶ uveitis⁵¹ and raised intraocular pressure.^{51,54,57,60,62,67} Extrascleral extension of the melanocytic lesion through the emissary channels into the subconjunctival space has also been observed.^{54,66} Electroretinographic studies have demonstrated a variety of abnormalities including unrecordable electroretinograms or a marked reduction in both cone and rod function.^{56,58,60,62} Two further patients were found to have normal or slightly reduced

Figures 3–7 Figure 3 A choroidal naevus. Note the large drusen on the surface of the lesion. Figure 4 An indeterminate melanocytic lesion. There are characteristic retinal pigmentary changes at the periphery of the lesion. Figure 5 (a) An indeterminate melanocytic lesion. (b) The same lesion approximately 12 years later. The lesion has now started to grow and a small nodule of tumour tissue has herniated through Bruch's membrane. Figure 6 A melanocytoma of the ciliary body with extra-scleral extension. Figure 7 Bilateral diffuse uveal melanocytic proliferation.

cone function with a severe reduction in rod function.^{51,65}

In the majority of reported cases there has been an associated systemic malignancy which may have been diagnosed prior to the eye condition or which is found at the time of diagnosis as a result of a systemic examination. Occasionally, BDUMP may precede the diagnosis or occur in the absence of a systemic malignancy.^{51,62} BDUMP may arise in association with a variety of malignancies, however, gynaecological neoplasms including: ovary (in particular),^{51,56,61,63,68} cervix⁵¹ and uterus^{60,67} predominate. Other primary sites include: pancreas,^{51,52,54} lung,^{53,54,57,66} gall-bladder⁵⁸ and bowel.^{54,64} Recently, two cases of extraocular pigmentation associated with BDUMP have been reported. Gass and Glatzer⁶⁴ documented a case of a 74-year-old male with BDUMP related to an occult carcinoma of the colon who developed pigmentation of the mouth and penis reminiscent of the Peutz-Jeghers syndrome. More recently, Mooy *et al*⁶⁶ have described a similar case where multiple pigmented lesions developed on the penis, oral mucosa and skin of an 82-year-old man with BDUMP secondary to a bronchial carcinoma.

Despite the relative rarity of this condition, there have been a number of histological studies of the affected ocular tissues.^{51–54,56–62,65,66,69} The most consistent reported features are a diffuse thickening of the choroid with benign appearing naevus or spindle cells,⁵⁴ associated with discrete elevated lesions that may resemble melanocytomas.⁵³ Focal necrosis and infiltration of scleral channels are frequently observed. Although mitotic figures are uncommon, foci of epithelioid cells may be present. In such instances, the appearance may be indistinguishable from a diffuse melanoma of the uvea. Opinion is divided as to the true pathological nature of this condition; some consider it to be a benign hyperplasia of uveal melanocytes, whilst others point to the presence of epithelioid cells and scleral 'invasion' as indicative of a true malignant neoplasm. To date, there have been no reported cases of metastases from the ocular lesions in a case of BDUMP, however, as many individuals rapidly succumb to their systemic malignancy, this does not negate the possibility that malignant transformation has occurred. In a recent immuno-histochemical study, p53 protein expression was investigated in eight eyes from four cases of BDUMP.⁶⁹ The p53 protein is a phosphoprotein that occurs normally in cells and in its natural form it has a regulatory effect on cell proliferation. Under normal circumstances p53 is produced in quantities that are too small to be detected by immuno-histochemistry. Mutations of p53 occur which result in the production

of a defective protein that has little or no regulatory function. This protein may accumulate in the cell and be detectable by immuno-histochemistry. Over-expression of mutant p53 protein has been described in many malignancies. Its role in uveal melanoma is unclear. Some studies have found a constant over-expression of^{70,71} p53 whilst others have failed to do so.⁷² This study failed to detect p53 protein in any of the eight eyes with BDUMP suggesting that the proliferation of uveal melanocytes in BDUMP is not dependent on p53 over-expression.

The pathogenesis of BDUMP remains unclear. The frequent association of a systemic malignancy suggests that it is a paraneoplastic syndrome where uveal melanocytic cells proliferate in response to some as yet undefined cellular growth factor produced by the systemic tumour.^{51,65} The inability of the normal uveal melanocyte to proliferate has led some authors to suggest that eyes that develop BDUMP have congenital bilateral diffuse hypopigmented uveal melanocytic naevi, which proliferate when stimulated by the putative exogenous tumour related growth factor.^{51,53,65}

Metastatic cutaneous melanomas When considering intraocular melanocytic tumours, one naturally thinks of the uveal melanocyte as the progenitor cell; however cutaneous malignant melanomas may metastasise to the eye. Recently, Shields *et al*⁷³ reviewed 420 consecutive patients with uveal metastases; they found nine cases (2%) of cutaneous melanoma metastatic to the eye. Gunduz *et al*⁷⁴ in an extensive review of the literature found prior reports of 67 patients (82 eyes) of cutaneous melanoma metastatic to the eye. The choroid (46%) was the most frequently involved tissue followed by the retina (27%), iris (23%), ciliary body (22%), vitreous (18%), optic disc (12%) and anterior chamber (11%). Multiple metastases involving more than one anatomical location were common. Despite the relative paucity of reported cases of clinically detectable intraocular metastatic cutaneous melanoma, occult metastases may be relatively common in cases of widespread generalised metastatic disease. In a series of 15 autopsy cases of patients with disseminated cutaneous melanoma, Fishman *et al*⁷⁵ found evidence of microscopic deposits in five patients. The clinical appearances of intraocular metastases from cutaneous melanoma are very variable, and to a large extent, depend upon the precise location of the deposit. Solitary choroidal lesions may resemble primary uveal melanomas and may pose a diagnostic problem, particularly if they represent the first manifestation of disseminated disease.⁷⁶ Intraocular metastatic cutaneous melanoma is somewhat unusual in that it frequently involves the ciliary body,⁷⁷ retina^{78,79} and

vitreous;^{74,79} the latter often in the absence of other tissue involvement. Recently, I have observed a case of bilateral vitreous deposits in the absence of any apparent retinal or uveal involvement (Figure 8).

The prognosis for patients who develop intraocular metastases from cutaneous melanoma is extremely poor with a reported median survival time of only 5 months.⁸⁰

Tumours and related lesions of the retinal pigment epithelium

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) Congenital hypertrophy of the retinal pigment epithelium (CHRPE) was first described in 1956 by Reese and Jones⁸¹ who called them benign melanomas of the RPE. Fortunately, Buettner replaced this confusing and contradictory term with congenital hypertrophy of the retinal pigment epithelium in 1974.⁸² CHRPE may occur in a solitary or multifocal forms and a specific variant is associated with Gardner's syndrome.

Solitary lesions are not uncommon and are still frequently mistaken for choroidal melanomas. They are flat or minimally elevated, well circumscribed, deeply pigmented lesions which may vary in size from less than 1 mm to occupy up to one quarter of the fundus.^{83–85} Typically, they are dark grey or black in colour and contain foci of depigmentation known as lacunae, which frequently enlarge with time^{84,85} (Figure 9). A circumferential depigmented ring (marginal halo) has been observed in over 75% of cases.⁸⁵ Fluorescein angiography shows a blocking of the normal choroidal fluorescence corresponding to the pigmented areas with hyperfluorescence corresponding to the lacunae and halo regions.⁸⁴ Retinal vascular abnormalities overlying the lesion are common and include capillary loss, microaneurysmal capillary ectasias and rarely, retino-choroidal anastomoses.^{86,87} Traditionally, CHPREs were believed to be indolent lesions and that growth only occurred in exceptional cases.^{88,89} However, in a recent study of 35 patients with solitary CHRPEs, enlargement although often subtle, was observed in 74% of cases.⁸⁵ To date, there have been no recorded cases of malignant transformation, Shields *et al*⁹⁰ recently reported five cases of a nodular tumour arising from a pre-existing CHRPE lesion. The lesions ranged in colour from light brown to black and had minimally dilated, non-tortuous feeder and drainage blood vessels supplying the tumour. Three cases were complicated by cystoid macular oedema and two had surface wrinkling of the retina. The authors speculate that these lesions

probably represent examples of acquired adenomas arising from solitary CHRPEs.

A multifocal form of CHRPE may occur which is also known as 'bear track' retinopathy or congenital grouped pigmentation of the retina. Usually, there are numerous groups of slate-grey or black lesions of varying size that often appear to radiate away from the optic disc. These lesions are asymptomatic and are found during routine fundal examination.

Familial adenomatous polyposis is an autosomal dominant condition characterized by the development in childhood or adolescence of hundreds or thousands of colonic polyps.⁹¹ The condition has a prevalence of approximately 1:5000 in the general population.⁹² When the condition is associated with a variety of extra-colonic manifestations including osteomas, epidermal cysts, desmoid tumours and extracolonic cancers, the condition is termed Gardner's syndrome.⁹¹

In 1980 Blair and Trempe⁹³ reported multiple foci of hypertrophy of the RPE in four members of a family with Gardner's syndrome. Since then, this ocular finding has been confirmed in a large number of affected families.⁹⁴ Clinically, the fundal appearances are of bilateral, multiple, discrete pigmented lesions which are often oval in shape with a peculiar fishtail-shaped hypopigmented change at one or both ends (Figure 10).⁸⁴ These differ clinically from the solitary or bear track lesions, which are not associated with Gardner's syndrome.⁹⁵

The gene responsible for familial polyposis coli is now known and has been mapped to chromosome 5q21–22.⁹² It has been called the adenomatous polyposis (APC) gene and consists of 15 exons and 14 introns spanning more than 100 kilobases. Over 700 mutations of the APC gene have been reported in FAP patients.⁹⁶ There is a strong correlation between site of the mutation and clinical phenotype: patients with profuse adenomatous polyps (more than 5000) have APC mutations predominantly located between codons 1255 and 1467 in exon 15.⁹⁷ Similarly, it has been found that patients with CHRPE occur almost exclusively with APC mutations between codons 312–1444.^{96–100} When mutations in the APC gene are located between codons 441–1444, the reported incidence of FAP patients with CHRPE lesions is over 95%, whilst mutations between codons 312–428 result in a variable occurrence of CHRPE lesions.¹⁰⁰ To date, the reason for the restriction of CHRPE-positive patients to a specific sub group of APC mutations remains unknown.

Tumours of the retinal pigment epithelium True tumours of the retinal pigment epithelium are extremely rare. Both adenomas and adenocarcinomas have been described; the distinction being based on the

histological degree of nuclear pleomorphism and local invasiveness.^{101–103} The distinction may be academic for although cases of metastatic adenocarcinoma of the RPE have been reported in the literature prior to 1935,^{104–107} none have been reported since. Conceivably, this could be due to a misinterpretation of the histological findings by the early authors and indeed Tso *et al* in a review of pathological conditions of the RPE cast doubt on the validity of the original diagnosis in these cases.¹⁰⁸ Even if the original diagnosis is accepted, as all of these four cases had extrascleral extension, the development of metastases may only occur in advanced cases when the sclera has been breached. Extrascleral extension has been reported only once in association with a posterior staphyloma¹⁰⁹ in the more recently reported cases.^{101,102,110–114} Although the number of cases studied is relatively few, adenomas and adenocarcinomas appear to occur mainly in women.¹⁰⁹

Clinically, adenomas and adenocarcinomas are indistinguishable and have frequently been mistaken for malignant melanomas. Ophthalmoscopically, neoplasms of the RPE are usually solitary, elevated dark brown or black lesions that appear to arise abruptly from the surrounding tissues.¹⁰⁹ Invasion of the retina occurs frequently and may be associated with the presence of a prominent retinal artery and vein supplying and draining the tumour.¹⁰⁹ Both intra and sub-retinal exudation can also occur leading to the development of an exudative retinal detachment.¹⁰⁹ Rarely, these lesions may arise adjacent to or on the optic disc and simulate either a juxtapapillary melanoma or melanocytoma.^{115–117}

Reactive hyperplasia of the retinal pigment epithelium The retinal pigment epithelium has a capacity to proliferate in response to certain stimuli. Hyperplasia or metaplasia may occur in response to trauma or inflammation producing a nodular mass.¹⁰⁸ Such proliferations may be present in eyes with opaque media and be detected on ultrasonography or when the eye is removed because of pain or phthisis. Rarely, post-traumatic RPE hyperplasia can be seen in eyes with clear media. I have previously reported two cases of post-traumatic RPE hyperplasia that occurred in

response to a retained metallic intraocular foreign body.¹¹⁸ One patient was referred with a raised pigmented mass close to the optic disc, which was thought to be a possible choroidal melanoma (Figure 11). The patient gave a history of a metallic foreign body entering his eye some years earlier and subsequent ultrasonography and plain radiology confirmed the presence of retained foreign body. Occasionally, reactive hyperplasia of the RPE may occur in the absence of any precipitating stimulus.^{119–121}

Combined hamartoma of the retina and retinal pigment epithelium

In 1973 Gass introduced the term: combined hamartoma of the retina and retinal pigment epithelium (CHR-RPE) to describe a series of patients with focal tumour-like lesions of the neuro-retina and RPE.¹²² Previous reports had described similar lesions as hyperplasia of the retinal pigment epithelium¹²³ or hamartomas of the retina.¹²⁴ Combined hamartomas of the retina and retinal pigment epithelium are rare with only about 100 cases reported in the literature.^{125,126} The clinical appearances of these lesions are quite diverse and differ depending on the location of the lesion within the fundus.¹²⁷ McLean¹²⁷ characterized them into either juxtapapillary or peripheral lesions noting that the location appeared to influence their appearance and presentation. He noted that juxtapapillary lesions appear to occur more frequently in males who presented with visual loss between 20 to 45 years of age. In contrast, peripheral lesions tended to occur at an earlier age and showed no sex predilection. Subsequent reports have not confirmed these relationships.¹²⁵

Nevertheless, the ophthalmoscopic appearances of lesions occurring in these two locations do appear to differ. Juxtapapillary lesions present as a solitary raised mass adjacent to or overlying the optic disc which is variably pigmented and contains varying degrees of abnormal blood vessels and white or gray fibro-glial material. Peripheral lesions appear as an elevated vascular ridge concentric to the optic disc, which is associated with dragging or distortion of the proximal retinal vessels (Figure 12). Vitreous haemorrhage, retinal exudation and occasionally retinal detachment may occur in association with CHR-RPE.^{125,128} Although some patients with CHR-RPE may have normal vision or minimally reduced vision, others may suffer a dramatic loss of vision, which usually occurs as a result of the direct involvement of the optic disc, papillo-macular bundle or fovea. Occasionally, visual loss may occur as a result of vitreous or retinal

Figures 8–13 *Figure 8* Cutaneous melanoma metastatic to the vitreous. *Figure 9* Congenital hypertrophy of the retinal pigment epithelium. *Figure 10* Congenital hypertrophy of the retinal pigment epithelium in association with Gardner's syndrome. *Figure 11* Reactive hyperplasia of retinal pigment epithelium secondary to a retained metallic intraocular foreign body. *Figure 12* Peripheral form of combined hamartoma of the retina and retinal pigment epithelium. *Figure 13* A choroidal haemangioma.

haemorrhage, or epiretinal membrane formation and macular hole.¹²⁹ In the majority of cases the lesion remains unchanged throughout life. In exceptional cases slow progressive enlargement may be observed.¹³⁰ The lesion is almost always unilateral; to date the author is only aware of seven reported cases of bilateral involvement.^{131–137}

Whilst most cases of CHR-RPE appear to be sporadic, there is increasing evidence that these hamartomas may be associated with both neurofibromatosis types 1 and 2 (NF-1, NF-2). Palmer *et al*¹³³ reported two children with multiple café-au-lait spots and CHR-RPEs and Destro *et al*¹³⁵ reported a case of a 25-year-old female with NF-1 who had a retinal mass, which was believed to be a CHR-RPE. They also reported a further case of a 3-year-old boy with presumed bilateral CHR-RPEs and multiple café-au-lait spots in whom the definite diagnosis of NF-1 or NF-2 was yet to be established. Tsai and O'Brien¹³⁸ recently reported a case of a 6-year-old child with unilateral visual loss, which was the presenting sign of her NF-1. Whilst the association between NF-1 and CHR-RPEs is limited to sporadic case reports, there is now good evidence to support the association between CHR-RPEs and NF-2. In 1977 Cotlier reported a case of 'café-au-lait spots' in the fundus of a patient with neurofibromatosis.¹³⁹ In retrospect this is probably the first documented case of CHR-RPE occurring in association with NF-2. Since then there have been a number of reports supporting this association.^{134,140–147} It is interesting to note that epiretinal membranes, retinal hamartomas and CHR-RPEs have all been reported in association with NF-2¹⁴³ and it is probable that they represent a spectrum of a continuous disease process.¹²⁵

Non-pigmented lesions

Primary choroidal tumours

Choroidal haemangioma Haemangiomas of the choroid may be either circumscribed or diffuse in nature. Diffuse haemangiomas occur almost exclusively in association with facial naevus flammeus or with some other manifestation of the Sturge–Weber syndrome¹⁴⁸ and as such they do not pose a diagnostic problem. Circumscribed choroidal haemangiomas, on the other hand, almost always occur as an isolated finding and are not associated with a cutaneous or systemic condition.¹⁴⁹ However, the author has recently seen three cases of an apparently circumscribed choroidal haemangioma in association with the Sturge–Weber syndrome. One of these cases has been reported in the

literature.¹⁵⁰ A further case has also been reported by Scott *et al*¹⁵¹ and given the relative infrequency of circumscribed choroidal haemangiomas and naevus flammeus it would suggest that occasionally these two conditions may be associated.

In contrast to diffuse lesions, circumscribed choroidal haemangiomas may be a cause of considerable diagnostic difficulty and are one of the lesions most commonly mistaken for a choroidal melanoma. Shields found in a series of 400 pseudomelanomas that 32 (8%) were choroidal haemangiomas.⁴ In a recent survey of the author's own practice, choroidal haemangiomas accounted for 6.7% of the pseudomelanomas (manuscript in preparation) and were indeed the most frequently misdiagnosed condition after naevi and IMLs. Circumscribed haemangiomas may present at any age, are most frequently diagnosed in the third and fourth decades; and affect both white and non-white individuals.¹⁴⁹ Choroidal haemangiomas were found to occur equally in males and females in one large series¹⁴⁸ whereas, males were found to be affected in over 70% of cases in another study of similar size.¹⁴⁹

Circumscribed choroidal haemangiomas have a curious predilection for the posterior choroid with over 85% occurring within 3 mm of the fovea.¹⁴⁹ Because of this they typically present with visual loss, induced hypermetropia or metamorphopsia. Extrafoveal lesions may be asymptomatic and be detected on routine ophthalmoscopic examination. On funduscopy they appear as a raised reddish-orange, dome-shaped mass, which may blend almost imperceptibly into the surrounding choroid (Figure 13). The overlying retinal pigment epithelium is almost always abnormal: often being replaced by foci of pale sclerotic tissue and/or small clumps of black granular pigment. Neuro-retinal abnormalities are also common and range from a subtle microcystic change to a large, shifting, secondary retinal detachment. Progressive enlargement of circumscribed choroidal haemangiomas is uncommon; Shields *et al* reported a case where a significant increase in size occurred over a 10-year period, the eye eventually being enucleated because an amelanotic melanoma could not be excluded.¹⁵² Histological examination suggested that the increase in size was due to vascular engorgement within the tumour rather than by cell multiplication.

Medlock *et al*¹⁵³ reported five cases of growth that occurred over a long time interval. Whilst these lesions do not appear to change greatly in size under normal circumstances, they may undergo significant changes during pregnancy. Pitta *et al*¹⁵⁴ reported a case of a 30-year-old female who presented with reduced vision when 5 months pregnant; a choroidal haemangioma

was found to be the cause of her visual loss. Following delivery the tumour and associated retinal detachment both regressed. The author has observed three similar cases where significant enlargement of a choroidal haemangioma and/or the associated retinal detachment accompanied an otherwise normal pregnancy (manuscript submitted for publication). In one case the accumulation of subretinal fluid was so extensive that the patient underwent an elective caesarian section at 37 weeks. There followed a dramatic resolution of the retinal detachment. It is probable that the altered haemodynamics experienced during pregnancy leads to engorgement of the tumour and an increased transudation of fluid.

In most instances the diagnosis of a circumscribed choroidal haemangioma is made on clinical grounds. Careful examination of the tumour with a 90-diopter lens is particularly valuable. Ancillary investigations are of some value in confirming the diagnosis. Some circumscribed choroidal haemangiomas have a characteristic appearance on fluorescein angiography: there is very early filling of the large vascular channels which gives a progressively hyperfluorescent irregular linear pattern. As the transit continues, these vascular channels leak dye into the tumour matrix to produce an intense diffuse fluorescence. The late angiograms often demonstrate intra-retinal fluorescence where the dye has leaked into the cystoid spaces within the retina.

Unfortunately, many haemangiomas do not exhibit this characteristic pattern and may be confused with some choroidal melanomas. Recent studies suggest that indocyanine green videoangiography may be of greater value in differentiating choroidal haemangiomas from melanomas.^{155,156} Specific features on indocyanine green angiography include: early hyperfluorescence followed by late hypofluorescence and a hyperfluorescent rim.¹⁵⁶ A scan ultrasonography typically shows a high initial spike at the tumour surface followed by relatively high internal reflectivity within the tumour mass. On B scan ultrasonography the lesion usually appears as a dome-shaped mass with a relatively high internal signal, which lacks acoustic hollowness or choroidal excavation, which may be observed in similar sized melanomas. Once again, atypical lesions occur; Spraul *et al* recently reported a case of a choroidal haemangioma that was mushroom or collar stud-shaped and exhibited choroidal excavation.¹⁵⁷

Circumscribed choroidal haemangiomas, which are asymptomatic, may be managed simply by periodic observation. Symptomatic haemangiomas represent a serious therapeutic challenge. Traditionally argon laser photocoagulation over the tumour surface has been

used in an attempt to reduce the leakage and aid the re-absorption of subretinal fluid. Unfortunately repeated treatments are often required and even then the long-term visual prognosis is poor.^{149,158} Anand *et al*¹⁴⁹ found that although the visual acuity could be stabilized in 34 out of 64 patients (53%), the level of visual acuity at the most recent consultation was less than 6/15 in 72% of cases. Low dose external beam irradiation and plaque brachytherapy have also been used to treat these lesions. Schilling *et al*¹⁵⁹ recently reported the results of using low dose external beam irradiation in the treatment of choroidal haemangiomas; they found that of the 36 cases of circumscribed haemangioma, complete resolution of subretinal fluid was achieved in 23 patients (63.8%) and the vision was maintained or improved in 28 (77.8%) patients. Zografos *et al*¹⁶⁰ treated 54 patients with choroidal haemangiomas (48 circumscribed, 6 diffuse) using proton beam irradiation and found a resolution of the retinal detachment in all cases. The same group had previously reported the results of treatment of these lesions with Cobalt-60 brachytherapy¹⁶¹ and found that in all 41 cases there was reattachment of the retina and replacement of the tumour by a flat scar. Madreperla *et al*¹⁶² in a retrospective study of the treatment of circumscribed choroidal haemangiomas by photocoagulation, brachytherapy or external irradiation concluded that both forms of irradiation were an effective alternative to photocoagulation. We have recently reported the preliminary results of using indocyanine green enhanced transpupillary diode thermotherapy (TTT) in the treatment of circumscribed choroidal haemangiomas.¹⁶³ We treated six patients and found that all the tumours regressed following therapy and that the vision improved by two or more lines in four patients. Two published case reports have also documented similar encouraging results following the use of TTT.^{164,165}

Choroidal osteoma In 1978 Gass *et al*¹⁶⁶ reported five cases of an osseous tumour arising in the juxtapapillary choroids of otherwise normal eyes of four young healthy females. In one patient the eye had been removed because a radioactive phosphorous (32P) uptake test suggested the diagnosis of an atypical amelanotic melanoma. The histological appearances of the lesion reported by both Gass *et al*¹⁶⁶ and subsequently by Williams *et al*¹⁶⁷ demonstrated that it was composed of mature bone with numerous interconnecting marrow spaces filled with loose connective tissue and thin-walled, dilated blood vessels. Normal osteoblasts, osteocytes and osteoclasts were present in the bony matrix. Subsequent reports

have characterized the clinical features of this curious lesion.¹⁶⁸ Choroidal osteomas occur most frequently in young healthy females in either the second or third decades of life. A recent study of a large cohort of patients noted that 31 of 36 patients (89%) were female.¹⁶⁹ The lesion may be bilateral in a quarter to one third of cases. There appears to be no racial predilection and although in most instances their occurrence is sporadic, several cases of a familial development have been reported.^{170–172} Interestingly, all the familial cases reported to date have been bilateral in origin. Furthermore, three of the seven affected individuals were male; a much higher proportion than occurs in apparently sporadic cases.

Clinically, the affected patient may be asymptomatic at presentation or have metamorphopsia or variable visual loss depending on the location of the lesion.¹⁶⁸ Typically, the lesion appears as a round or ovoid, yellow or orange placoid subretinal juxta or peripapillary mass (Figure 14). Occasionally, the lesion involves the macular region and in these cases visual loss is usually significant. The surface of the lesion is frequently covered by multiple tufts of short vascular trunks that may stand out as linear silhouettes in the late phases of fluorescein angiography. In addition to these vessels, which represent the intrinsic vasculature of the osteoma, subretinal neovascular membranes occur and may lead to the development of subretinal fluid or haemorrhage. Aylward *et al* recently reported a long-term follow-up on a series of 36 patients with choroidal osteoma¹⁶⁹ and found that the probability of developing choroidal neovascularization was 47% by 10 years and 56% by 20 years. In these cases haemorrhage may lead to subretinal fibrosis and scarring and severe visual loss if it arises beneath the fovea.^{169,172,173} Aylward *et al* calculated the probability for loss of visual acuity to 6/60 or worse to be 58% by 10 years and 62% at 20 years.¹⁶⁹ Progressive enlargement^{169,174–178} or even the development of an osteoma^{172,175} in a previously unaffected eye has been reported. Growth may occur in over 40% of cases if followed for long enough.¹⁶⁹ Conversely, spontaneous decalcification^{179,180} or involution¹⁸¹ of a choroidal osteoma has also been observed.

In most cases, once the suspicion that a choroidal lesion may be an osteoma has been raised, the diagnosis can usually be established with the aid of one or two ancillary investigations. Ultrasonography is extremely useful; B scan ultrasonography demonstrates a minimally elevated, highly reflective choroidal mass with profound acoustic shadowing in the orbit. The reflectivity persists after attenuation of the sensitivity of the signal has rendered the other ocular tissues invisible. CT scans of the affected eye demonstrate a

high-density plaque in the affected choroid. Curiously, MRI imaging does not show the typical negative bone image; instead the lesion appears as a hyper-intense signal on T1-weighted images and as an area of relative low intensity on T2-weighted images. The tumour enhances with gadolinium on T1-weighted scans.¹⁸² Recently, the optical coherence tomographic patterns of choroidal osteomas have been investigated.¹⁸³ Two patterns were observed; multiple tracks of high reflectivity were noted posterior to the tumour and thick and irregular plate-like, high signal intensity areas were present in the choroid in the region of the tumour.

Most cases of choroidal osteoma once the diagnosis has been established can be managed by periodic observation. In cases where symptomatic subretinal neovascularization occurs laser photocoagulation has been used with varying success.^{169,172,184–187} One study found that only 25% of patients with choroidal neovascularization were successfully treated with laser photocoagulation.¹⁶⁹ There is a solitary case report of laser photocoagulation for subretinal neovascularization apparently fortuitously leading to partial reabsorption of the osteoma.¹⁸⁸

Secondary choroidal neoplasms In 1984 Horner¹⁸⁹ documented the first case of an intraocular metastasis and although, for many years, this was considered a rare event, it is now recognized that metastases are the most common intraocular malignancy.^{190–192} The precise incidence of intraocular metastases is difficult to establish; estimates based upon clinical studies differ significantly from autopsy studies. Figures derived from the latter are understandably greater, for many patients with occult metastases will be asymptomatic and too ill to undergo routine ophthalmoscopic examination. Moreover, in many cases the metastatic deposits will be microscopic and too small to be detected clinically. An early clinical study undertaken by Godtfredson in 1944¹⁹³ found only six cases (0.07%) out of 8712 patients referred for radiotherapy for the treatment of a metastatic carcinoma. Albert *et al*¹⁹⁴ in 1967 found ophthalmoscopic evidence of intraocular metastases in five out of 213 (2.3%) patients with known metastatic carcinoma. This increasing frequency probably reflects a combination of increasing survival and the introduction of the indirect ophthalmoscope in routine fundal examination. Bloch and Gartner in 1971¹⁹⁰ reported the results of a large postmortem study of the eyes from patients dying from metastatic carcinoma. They found that out of 230 patients intraocular metastatic foci were found in 25 cases (10.9%). In a prospective histopathological study of 716 eyes of patients who had malignant disease at the time

of death, Nelson *et al*¹⁹⁵ found ocular metastases in 52 patients (7.3%). In a recent study Eliasssi-Rad *et al*¹⁹² compared the frequency of metastases found in eye bank specimens obtained between 1988 and 1993 with those obtained at autopsy between 1976 and 1980. They found that of the eyes from 302 patients, which had not been used for transplantation, and were subsequently submitted for pathological examination, three (1%) had a gross intra-ocular metastasis. In the autopsy group a total of 741 patients had died from a malignant disease and, of these, microscopic metastases were found in 93 cases (12.6%). Ocular involvement was observed in 40 out of 115 (34.8%) of patients dying from various forms of leukaemia, 14 out of 60 (23%) patients with lymphoma and 25 out of 510 (5.1%) patients dying from carcinoma. When comparing the eye with other target organs it would appear to be a relatively uncommon site for the development of metastases. In patients with disseminated disease, tissues such as the lung, brain, kidneys and bone are involved much more frequently. This might suggest that the eye is a relatively unfavorable site for metastases to develop. It is well recognized that the metastatic process is extremely complex and does not rely on the mere chance passage of tumour cells to target organs via the blood stream. There is a complex interaction between circulating tumour cells and the target tissue.¹⁹⁶ Weiss¹⁹⁷ calculated the metastatic efficiency index (MEI), which is an analytical method of comparing the propensities of different target sites for metastatic development, of intraocular tissues as targets for metastasis from primary cancers of the breast, lung and colo-rectum. He found that the calculated MEI values for the uvea, as a target site for metastases from these cancers was in fact the highest for any previously investigated cancer and target site. This suggests that the uvea is, in fact, an extremely favourable tissue to develop metastases.

Ferry and Font¹⁹¹ found that males and females were approximately equally affected by intraocular metastases; subsequent reports have indicated a definite female preponderance.^{73,198} Shields *et al*⁷³ in a study of 420 patients found that 283 (67%) were female. This bias can be attributed to the fact that breast carcinoma accounts for the majority of cases of intraocular metastases. Indeed, in this latter series the breast was the primary location in 47% of patients. Lung was the next most frequently involved site (21%) followed by gastrointestinal tract (4%), kidney (2%), skin (2%) and prostate (2%). Interestingly, the primary site remained unknown in 17% of cases.

The choroid is the most frequent site for intraocular metastases: Shields *et al*⁷³ found a total of 950 uveal

metastases in a total of 420 patients and, of these, 838 (88%) were located in the choroid. Ninety (9%) metastases were located in the iris and only 22 (2%) in the ciliary body. They found that the right and left eyes were equally affected and that bilateral involvement occurred in 23.8% of patients and of these bilateral cases 64% were metastatic breast carcinomas. Solitary metastases were found in 71% of cases, with 12% of the eyes containing two lesions and 17% containing three or more.

Choroidal metastatic breast carcinomas typically appear as minimally elevated, cream or pale yellow lesions, which tend to blend imperceptibly into the surrounding choroid. The surface of the tumour is frequently covered with brown or golden clumps of retinal pigment epithelium, which may coalesce to form a reticular pattern (Figure 15). Occasionally, breast metastases may present as a large elevated solitary mass, although in the author's experience this is less common. Retinal detachment is common, particularly in the case of larger lesions. As stated previously these lesions are often multifocal and bilateral. Although fluorescein angiography is, in general, of little value in establishing the diagnosis it may reveal a more extensive lesion than was thought on ophthalmoscopy, or demonstrate further lesions, which were not apparent clinically.

Metastases derived from other sites usually present, in my experience as a pale cream, elevated dome-shaped mass, which in many cases may resemble an amelanotic melanoma (Figure 16). Fine granularity of overlying RPE may be present on the tumour surface, but the pronounced reticular pattern seen on metastatic breast lesions is uncommon.

When confronted by a patient with typical multifocal and/or bilateral lesions and a prior history of neoplasia the diagnosis is straightforward. However, when presented with a patient who has a solitary amelanotic lesion and no prior history of malignancy, the diagnosis can be more challenging. Shields *et al*⁷³ noted that approximately one third of patients with a uveal metastasis have no history of a primary cancer at the time of ocular diagnosis. In such cases a careful search for an occult primary lesion prior to treatment is mandatory. Whilst non invasive techniques such as fluorescein angiography or ultrasonography may be of value in distinguishing choroidal metastases from certain other lesions, I have found them of little value in differentiating them from amelanotic melanomas. In such circumstances fine needle aspiration biopsy may be of considerable value in assisting with the diagnosis.

Vascular lesions

Vasoproliferative tumours of the retina (presumed acquired retinal haemangiomas)

In 1982 Baines *et al* reported the presence of peripheral telangiectatic nodules, associated with a proliferation of a posterior fibro-cellular membrane in seven eyes of five patients.¹⁹⁹ They noted that the nodules resembled angiomas but lacked the dilated feeder vessels seen in Von Hippel–Lindau disease. The following year Shields *et al* described 12 patients with non-familial unilateral solitary vascular lesions of the neuro-retina.²⁰⁰ Although these tumours again resembled the angiomas seen in Von Hippel–Lindau syndrome they differed in a number of respects: they presented at an older age (the mean age at diagnosis was 58 years), there was no family history or associated systemic problems, they were unilateral, solitary, and there was no macular exudation and in keeping with the previous report they also lacked tortuous feeder vessels supplying the lesion. In the absence of histological verification, the authors coined the term presumed acquired retinal haemangioma (PARH) to describe the lesion. Similar lesions have been reported in the literature both prior and subsequent to these reports using a variety of terms which, to some extent, delayed the recognition of this condition as a distinct disease entity. Such lesions have been termed: peripheral retinal angiomas,²⁰¹ angioma-like mass²⁰² or lesion^{203,204} retinal angiomatous mass,²⁰⁵ retinal angiomatosis in the elderly,²⁰⁶ haemangioma-like mass²⁰⁷ or lesion²⁰⁸ and peripheral retinal telangiectasia.²⁰⁹ Shields *et al* in 1995²¹⁰ reported a large series of 103 affected patients, and renamed the condition as a vasoproliferative retinal tumour. This term has now gained wide acceptance. In this latter study, the lesions were classified as idiopathic (74%) or secondary to a preexisting ocular disease (26%) and morphologically were found to be solitary (87%), multiple (6%) or diffuse (6%). Patients with idiopathic tumours had an average age of 40 at presentation (range 11–76 years). Males and females appeared equally affected and there appeared no predilection for either eye. Interestingly the lesion appears to have a curious affinity for the inferior retina and was found in the infero-temporal quadrant in almost half of the cases. Clinically, the lesion appears as a raised vascular lesion in the peripheral retina (Figure 17). Intra or

subretinal exudation is present in over 80% of cases. A secondary retinal detachment is present in approximately half of the cases and a vitreous haemorrhage is found in nearly one quarter of the patients. Macular changes are common and include preretinal fibrosis and oedema. The lesions are sometimes associated with a mildly dilated feeding arteriole and draining vein, these do not however have the dimensions of the vessels seen supplying von Hippel–Lindau angiomas.

Secondary lesions, were morphologically similar to the primary lesions, but were associated with a variety of ocular conditions including: intermediate uveitis, retinitis pigmentosa, toxoplasmosis and toxocariasis. Marked retinal pigment epithelial proliferation was found adjacent to the vasoproliferative lesion in over half of the cases and was present in all the cases that were associated with retinitis pigmentosa. A recent study has confirmed the finding of vasoproliferative retinal tumours associated with hypertrophic retinal scars secondary to presumed congenital toxoplasmosis.²¹¹

Ancillary investigations such as fluorescein angiography are often difficult due to the frequent peripheral nature of these lesions. When angiograms of sufficient quality are obtained they show a connection between the retinal feeder vessels and a rich capillary network within the tumour which are often telangiectatic.²¹² Several vasoproliferative retinal tumours have now been examined histologically and have shown that the lesions are composed of a mixture of slender spindle-shaped cells which stained positively for GFAP, suggesting a glial origin together with a vascular component which comprised a fine capillary network together with larger dilated blood vessels, characterized by marked hyalinization of their walls.^{212–214} Although the pathogenesis of vasoproliferative tumours remains unclear, it is probable that a variety of disease processes can initiate a proliferation of retinal glial cells and blood vessels to produce a discernible tumour mass.²¹² A variety of modalities have been used to treat vasoproliferative retinal tumours including: laser photocoagulation,²¹⁰ cryotherapy^{210–212} plaque brachytherapy,^{210,212} and vitrectomy.^{210,215}

Age related choroidal neovascularization

Age related disciform lesions either macular or peripheral may be mistaken for an amelanotic melanoma and accounted for 6.5% of pseudomelanomas referred to the author's unit. Whilst small macular lesions usually pose no diagnostic difficulty; large, elevated, peripheral lesions can be a

Figures 14–18 Figure 14 An osseous choristoma. Figure 15 A choroidal deposit of metastatic breast carcinoma. Figure 16 A peripapillary deposit of metastatic carcinoma of the bronchus. Figure 17 A vasoproliferative tumour of the retina. Figure 18 An eccentric disciform (peripheral) choroidal neovascularization.

considerable cause of confusion. In general, these lesions can be differentiated from amelanotic melanomas by the presence of extensive subretinal exudation (Figure 18). Although a small amount of exudation may occasionally be observed at the base of a melanoma, it rarely, if ever attains the same degree as seen surrounding a disciform lesion. Some amount of subretinal haemorrhage either fresh or denatured is almost invariably present overlying the surface of a disciform lesion. Vitreous haemorrhage may occur, which can in some cases, obscure fundal detail. Again, vitreous bleeding may develop in the presence of a choroidal melanoma; however, this frequently arises from tumours that have a small herniation of tissue through Bruch's membrane.²¹⁶ Careful ultrasonography may detect these small herniations facilitating the diagnosis. In contrast, disciform lesions do not typically produce such breaches in Bruch's membrane, but rather produce dome-shaped lesions with high internal reflectivity. In cases where ultrasonography is unhelpful, it is often prudent to merely observe the patient for a short period, in the expectation that the haemorrhage will clear allowing sufficient visualization of the lesion to establish the diagnosis. In cases where the haemorrhage persists, pars plana vitrectomy accompanied by trans-vitreous fine needle biopsy may be of considerable value in establishing the diagnosis.²¹⁷ In cases where the ocular media is clear, fluorescein angiography can be utilized to confirm the diagnosis. Disciform lesions demonstrate hyperfluorescence corresponding to the areas of active neovascularization and profound hypofluorescence in areas of subretinal haemorrhage. However, caution must be exercised in interpreting the angiography results, for occasionally disciform lesions may be observed on the surface of choroidal melanomas that may provide a diagnostic pitfall for the unwary.

Inflammatory lesions

Posterior scleritis

Patients with posterior scleritis can present with large elevated lesions, which may simulate an amelanotic choroidal melanoma.²¹⁸ In many instances, the presence of pain coupled with either a prior history of anterior scleritis or evidence of active anterior segment involvement would strongly point to the diagnosis of posterior scleritis. Occasionally, however, a patient presents with a painless posterior scleritis in the absence of any anterior segment involvement. Finger *et al* reported a case of a 66-year-old male who presented with a large painless intraocular mass in his right eye which was enucleated and found upon histological

examination to contain grossly thickened necrotic sclera.²¹⁹ Recently, Demirci *et al*²²⁰ reported a case of a 41-year-old asymptomatic woman with a 7.5 mm thick intraocular mass, which was initially thought to be a malignant melanoma. Subsequent evaluation, including scleral biopsy confirmed the lesion to be nodular posterior scleritis. Careful evaluation can usually differentiate these lesions from true neoplasms. Scleritic nodules are orange in colour and are frequently associated with choroidal folds, which radiate from the lesion. Ultrasonography, may confirm a thickening of the sclera and presence of oedema in the adjacent tenons capsule. Moreover, posterior scleritis will usually show a marked response to therapy with either systemic non-steroidal anti-inflammatory agents or systemic corticosteroids in contrast to uveal melanomas, which will usually fail to demonstrate any response to therapy.

In contrast, occasionally, patients with a choroidal melanoma may present with symptoms suggestive of posterior scleritis. Yap *et al*²²¹ reported three cases where the patients presented with clinical features of scleritis and where the ultimate diagnosis was that of a choroidal melanoma. Interestingly, in all three cases the lesion demonstrated at least a partial response to corticosteroid therapy. More recently, Bhagat *et al*²²² reported a case of acute scleritis and scleral necrosis associated with a choroidal melanoma.

Conclusions

There are many lesions that may be mistaken for a choroidal melanoma. It is vital that such lesions are correctly diagnosed in order that, not only inappropriate treatment be avoided, but also appropriate treatment not be withheld.

Acknowledgements

I am indebted to a number of individuals in preparing this lecture: Rhona Jacques, Lesley Hinchliffe, Michelle Evans and Paul Rundle, my colleagues in the ocular oncology service in Sheffield for their constant help and support. Chris Mody, Laura Ferguson and Michele Best for their skill in constantly photographing the impossible. Robin Farr for his considerable technical assistance. John Talbot, Michael Nelson and Andy Parsons for all their encouragement over the years. My fellow consultant colleagues, who over the years, have been kind enough to refer me these interesting patients. Finally, my wife Sharon, who has had to endure me during the long weeks preceding this lecture.

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