Arun D. Singh
Bertil Damato
Editors

Clinical Ophthalmic Oncology

Retinal Tumors

Second Edition

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Preface

The management of patients with an ophthalmic tumor presents particular challenges. Ophthalmic tumors are rare and diverse so that their diagnosis can be quite complex. Treatment usually requires special expertise and equipment and in many instances is controversial. The field is advancing rapidly, because of accelerating progress in tumor biology, pharmacology, and instrumentation. Increasingly, the care of patients with an ocular or adnexal tumor is provided by a multidisciplinary team, consisting of ocular oncologists, general oncologists, radiotherapists, pathologists, psychologists, and other specialists. For all these reasons, we felt that there was a continued need for a textbook of ophthalmic oncology, which would amalgamate knowledge from several different disciplines, thereby helping the various specialists to understand each other better and to cooperate more efficiently, eventually moving ophthalmic oncology in the realm of evidence-based medicine.

As several important studies have been published in recent years, the purpose of *Clinical Ophthalmic Oncology* (2nd edition) is to provide up-to-date information on the whole spectrum of the eyelid, conjunctival, intraocular, and orbital tumors including basic principles of chemotherapy, radiation therapy, cancer epidemiology, angiogenesis, and cancer genetics. Several chapters authored by radiation oncologists, medical physicists, pediatric oncologists, hematologist-oncologists, and medical geneticists have been included to provide a broader perspective.

Although each section of *Clinical Ophthalmic Oncology* now represents a standalone volume, each chapter has a similar layout with boxes that highlight the key features, tables that provide comparison, and flow diagrams that outline therapeutic approaches. Each chapter has been edited (with author's approval) to present a balanced view of current clinical practice and special attention has been paid to make the text easily readable.

The authors followed a tight timeline to keep the contents of the book current. As we undertook this ambitious task of editing a multi-author, multivolume textbook, we were supported and guided by the staff at Springer: Sverre Klemp, Ulrike Huesken, Ellen Blasig, and M.V. Bharatwaj. Jennifer Brown kept the seemingly chaotic process under control.

It is our sincere hope that readers will find as much pleasure reading this volume as we had writing and editing it. If you find *Clinical Ophthalmic Oncology* informative, it is because (paraphrasing Isaac Newton), "we have seen further, by standing on the shoulders of the giants."

Cleveland, OH — Arun D. Singh, MD
San Francisco, CA — Bertil Damato, MD, PhD, FRCOphth

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To my parents who educated me beyond their means, my wife Annapurna, and my children, Nakul and Rahul, who make all my efforts worthwhile. (ADS)

To my family, Frankanne, Erika, and Stephen. (BED)

Contents

Classification of Retinal and Retinal Pigment Epithelium Tumors

1

Ehud Reich, Caroline Thaung, and Mandeep S. Sagoo

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1.1 Introduction

Tumor classification is important as it creates a common terminology that allows clinicians and researchers to accurately communicate, thus facilitating diagnosis by helping the clinician to include all conditions that are relevant in a differential diagnosis. Classification allows us to draw historical, international, or multicenter clinical and biological comparisons, thus improving our ability to understand the natural course of tumors and facilitate research into new treatments. In this chapter, the term "tumor" is used in its broadest sense as a mass without implication to its pathogenesis or its neoplastic or malignant properties.

Classification allows communication between surgeons, oncologists, and pathologists in treatment planning and assessment of treatment outcomes, as well as future treatment options and prognostication. Yet classification can be confusing due to multiple notions about the purposes and meaning of modern classifications, more recently due to the accumulation of emerging molecular and genetic results.

Tumors of the retina or retinal pigment epithelium can be classified in many ways. There is no "gold standard" classification, as new technology shifts the extent of knowledge and challenges previous classifications. Overall, classification is an organization of everything in a domain by hierarchical groups, according to features generalizable to the members of the groups [1].

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Table 1.1 Tumors of the retina and retinal pigment epithelium (RPE)

Retinal	Primary	Vascular	Prenatal[a]	Retinal cavernous hemangioma
				Arteriovenous malformations (retinal racemose hemangioma)
			Postnatal	Retinal capillary hemangioma
				Retinal vasoproliferative tumor
		"Primitive"	Retinoblastoma	
			Retinoma/retinocytoma	
		Neural/glial	Astrocytic hamartoma	
			Massive (pseudoneoplastic) retinal gliosis	
		Hematological	Primary intraocular (vitreoretinal) lymphoma	
	Metastases		Retinal metastases from systemic lymphoma	
			Retinal metastases from solid tumor (melanoma, lung adenocarcinoma, and others)	
RPE			Congenital hypertrophy of the RPE (CHRPE)	
			Simple hamartoma of the RPE	
			Adenoma of the RPE	
			Adenocarcinoma of the RPE	
Combined			Combined hamartoma of RPE and retina	

[a]Retinal vascular tumors of prenatal origin (retinal cavernous hemangioma and retinal arteriovenous communications) maintain retinal tight junctions and hence do not manifest retinal leakage (subretinal fluid or hard exudates). In contrast, vascular tumors of postnatal origin (retinal capillary hemangioma and retinal vasoproliferative tumor) are without retinal tight junctions and hence manifest retinal leakage (subretinal fluid or hard exudates)

Clinical classifications usually refer to the lists of primary tumors that are known to occur at a specific anatomical location. This proves a very useful tool for the clinician encountering a patient with a new lesion. However, this is not purely a taxonomic classification per definition because it includes tumors that are clinically, biologically, and histologically unrelated. It also creates repetition. Other classifications differentiate by various schema, such as cell type, genetics or metabolic variations, or indeed benign versus malignant elements within a tumor type.

The Tumor Node Metastasis (TNM) classification has recently been modified (seventh edition) and is another system that aids us in trying to unify our discussion but covers only malignant tumors, status, and spread. The data collected with the TNM system allows us better prognostication and to scrutinize our treatment modalities – past and future.

In this chapter, we classify the lesions a clinician encounters while examining a patient with a retinal or retinal pigment epithelium lesion. Therefore, this is an overview rather than an exhaustive list of the possible. Included are lesions that do not fit into a single neat box, such as combined hamartoma of the retina and the retinal pigment epithelium (RPE). There are some tumors that have only been described in a handful of case reports, and are not included in the general classification, as taxonomy cannot give weight to incidence of a disease. We also excluded lesions of the RPE and retina that do not resemble a tumor such as reactive pigmentation of the RPE.

Due to the complexity of classifying the specific lesions, we classified the tumors for the easiest reference, clinically by site, divided into retinal and RPE. The reader is invited to develop diagnostic algorithms based on our suggested framework (Table 1.1).

1.2 Tumors of the Retina

Retinal tumors can be benign or malignant and can occur across the age spectrum. The most frequently encountered intraocular tumor in children

is retinoblastoma. If treated inadequately, it is fatal. The cell of origin is controversial, but is thought to be a photoreceptor progenitor cell [2]. Its benign variant is retinoma or retinocytoma. Simulating lesions in children are Coats' disease, an idiopathic exudative retinopathy [3], persistent primary hyperplastic vitreous, and Toxocara retinitis. Vascular lesions include the capillary and cavernous hemangiomas of the retina and the racemose hemangioma, which is really an arteriovenous malformation [4]. A reactive tumor of adults, which can mimic the retinal capillary hemangioma, is the vasoproliferative tumor – a lesion that is benign and in the spectrum of Coats' disease [5]. Some retinal tumors are associated with systemic disease, such as the retinal capillary hemangioma (von Hippel-Lindau syndrome), the astrocytic hamartoma (tuberous sclerosis complex and neurofibromatosis), and the combined retinal and retinal pigment epithelial hamartoma (neurofibromatosis type 2). Massive retinal gliosis can mimic a retinal tumor [6]. Hematological malignancy can manifest in the eye as primary intraocular lymphoma, which is now described as vitreoretinal lymphoma as it infiltrates the subretinal space and the vitreous cavity, mimicking uveitis [7]. Secondary tumors to the retina are possible, though true retinal metastases are extremely rare.

1.3 Tumors of the Retinal Pigment Epithelium

Neoplasia of the retinal pigment epithelium are rare. Adenocarcinomas, and indeed their benign variants, adenomas, are reported [8]. Hamartomas of retinal pigment epithelium can be simple, involving only this cell type, or can be combined with retinal dysplasia [9]. Congenital hypertrophy (CHRPE) of the retinal pigment epithelium is very frequently encountered, but only rarely spawns an adenoma or adenocarcinoma. Atypical CHRPE lesions are associated with familial adenomatous polyposis.

Conclusion

When faced with a patient with an intraocular tumor, a process of deduction derived from pattern recognition leads to a differential diagnosis. Parameters such as age and ethnicity narrow possibilities and ancillary tests are used to confirm or refute the diagnosis made by careful clinical examination. Ultrasonographic examination, optical coherence tomography, and angiography all have a role to play in this process. Retina and retinal pigment epithelium can form several different tumor types. and a classification allows the ophthalmologist, pathologist, and oncologist to communicate with each other and colleagues. The TNM seventh edition now has an ocular oncology section to facilitate this in regard to malignant tumors. Over the next chapters, these tumor types are discussed in detail. As new knowledge becomes available in terms of genetics and molecular workup, classifications will evolve.

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Coats' Disease

2

Thomas M. Aaberg Jr. and Liliya Shevchenko

Contents

2.1 Introduction

In 1908, George Coats, curator of the Royal London Ophthalmic Hospital, described an ophthalmic disease which was typically unilateral, had a predilection for healthy males, and resulted in focal deposition of exudates within the fundus and "peculiar" retinal vascular findings [1]. Four years later, Coats classified his cases of "exudative retinitis" into three groups [2]. Group I manifested massive exudation but no discernable vascular abnormalities. Group II had marked vascular disease, intraretinal hemorrhage, and exudation. Group III presented with obvious arteriovenous malformations and exudation. Group III was later considered as a retinal hemangioma. During this same time, Theodor Leber described a nonexudative retinal vascular degeneration characterized by "multiple miliary aneurysms." [3] Leber's multiple miliary aneurysms are now believed to represent an early stage of Coats' disease [3]. In this chapter, we provide a comprehensive review of pathogenesis, clinical findings, treatment options, and prognosis of Coats' disease.

2.2 Etiology and Pathogenesis

Histologic preparations of eyes affected by Coats' disease reveal irregular dilation, thickening, and hyalinization of retinal vessels (capillaries, arteries, and veins), attenuation of endothelial cells, and disorganized and necrotic vessel walls [1, 4–7]. Large aneurysms (50–350 μm), seen

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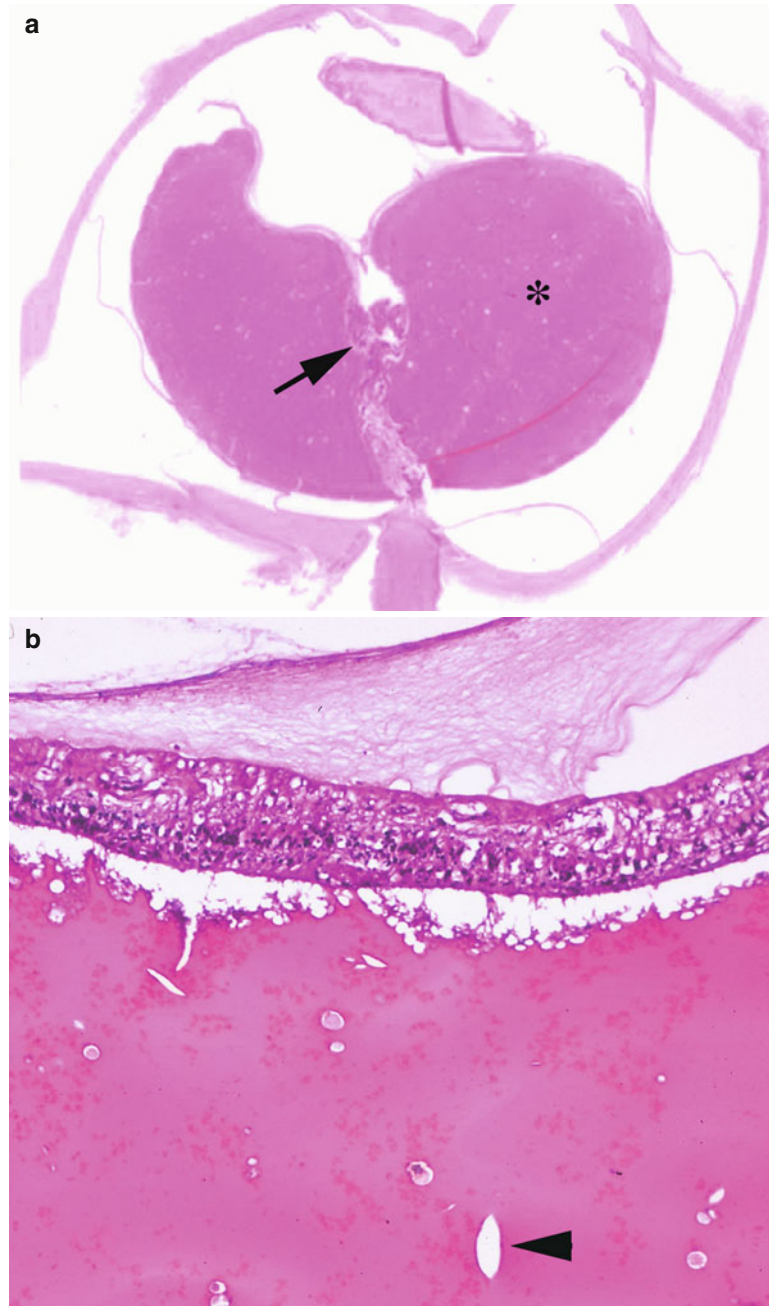


Fig. 2.1 Enucleated eye with Coats' disease. Note the total exudative retinal detachment (*arrow*) and the subretinal exudate (*asterisk*) (**a**, low-power hematoxylin and eosin). Cystic degeneration, disorganization, and deposition of PAS-positive material in the outer retina. Cholesterol clefts are seen in the subretinal exudate (*arrowhead*) (**b**, high-power hematoxylin and eosin)

after trypsin digestion, frequently formed large sausage-like or beaded outpouchings [6]. Other findings include PAS-positive deposits in vessel walls and the outer retinal layer, intraretinal and subretinal cysts, hemorrhage, cholesterol, and lymphocytic infiltrates (Fig. 2.1).

Unfortunately, the histologic findings have not led to the elucidation of the cause of Coats' disease. Polysaccharide deposition in the vessel lumen and retinal hypoxia have been suggested in the past as pathogenic mechanisms [8, 9]. More recently, attention has focused on the role of vascular endothelial growth factor (VEGF) as a potential player in pathogenesis of Coats' disease. Elevated levels of VEGF have been demonstrated in both aqueous and vitreous humor of affected

eyes [10, 11]. In addition, nitric oxide (NO)—mediator of vascular dilation and permeability—is elevated in the aqueous humor of the eyes affected by Coats' disease compared to controls [12].

Gene mutations found in conditions associated with Coats' disease are being researched as well. Mutation in *CTC1* gene, encoding conserved telomere protein, has been recently attributed to Coats' plus syndrome discussed later within this chapter [13]. Somatic mutation of the *NDP* gene encoding norrin, a protein with important role in retinal angiogenesis, and the *CRB1* (crumbs homolog1) gene have also been implicated in Coats' disease [14, 15]. Unfortunately, it is unclear if the Coats'-like changes are secondary events or due to an independent genetic mutation.

2.3 Clinical Features

The most common presenting signs in an affected child are strabismus and leukocoria. About 25 % of cases are detected by screening eye examination. There is a gender predilection for Coats' disease, affecting males eight times more than females. And while the majority of cases are unilateral, bilateral disease has been reported in up to 10 % of cases [16]. The majority of cases present before the second decade of life; however, there are reports of cases presenting within the first month of life and as late as the eighth decade of life [16–19].

Clinical findings vary in Coats' disease depending on the five different stages of the disease (Table 2.1) [20]. Early in the disease process, vascular telangiectasia occurs focally within the retina, most often near or anterior to the equator with predilection for temporal and inferior quadrants (Fig. 2.2) [16, 21]. Vitreoretinal traction is usually absent. The macula is involved in only 1 % of these early cases [16]. The entire retinal vasculature (arteries, veins, and capillaries) appears to be affected. The caliber of the involved vessels varies as aneurysmal dilation and progressive telangiectasia occur. The aneu-

Table 2.1 Classification of Coats' disease

Stage	Retinal findings
Stage 1	Retinal telangiectasia only
Stage 2	Telangiectasia and exudation
2A	Extrafoveal
2B	Foveal
Stage 3	Exudative retinal detachment
3A	Subtotal
1	Extrafoveal
2	Foveal
B	Total retinal detachment
Stage 4	Total retinal detachment and glaucoma
Stage 5	Advanced end-stage detachment

Modified from Shields et al. [20]

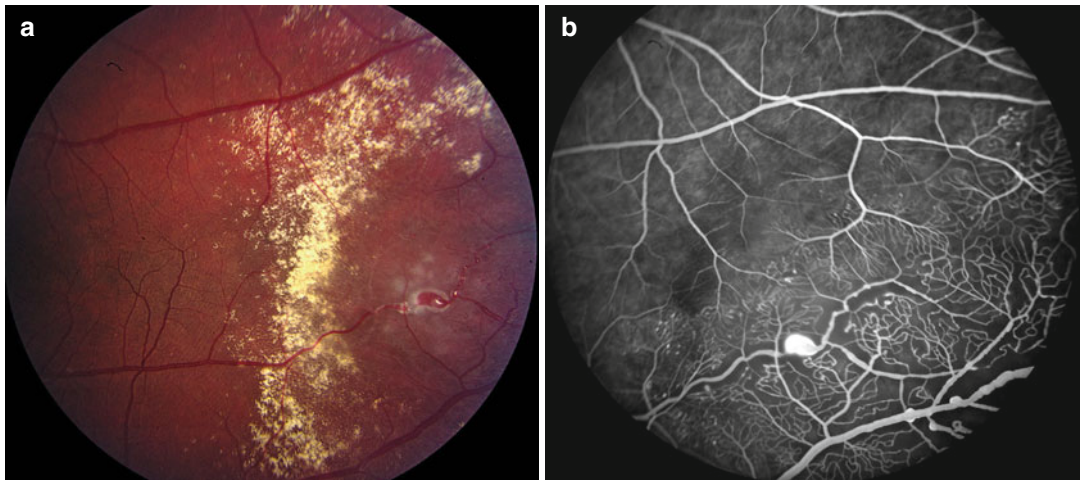


Fig. 2.2 Fundus photograph of the left demonstrates the circinate lipid exudation surrounding retinal telangiectasia (**a**). Fluorescein angiography demonstrates the area of bulbous aneurysms, vascular telangiectasia, and areas of capillary nonperfusion (**b**)

rysms may be saccular (sausage shaped) or bulbous (often described as having a "light-bulb" appearance). As the disease progresses, nearly all cases will develop intraretinal exudation and exudative retinal detachment. Intraretinal and subretinal exudates often migrate toward the macula. Macular fibrosis is reported to occur in 23 % and is hypothesized to be a result of intraretinal neovascularization [22]. Intraretinal macrocysts develop in 10 % of cases, most likely due to coalescence of microcystic spaces in chronically detached and edematous retina [16, 23]. Hemorrhagic macrocysts have been reported [24]. The anterior segment changes such as iris neovascularization, secondary glaucoma, corneal edema, suspension of lipid and protein in the aqueous humor, and cataract do not occur until late in the disease process [16, 21].

2.4 Diagnostic Evaluation

In most cases, Coats' disease can be diagnosed by clinical examination. However, fluorescein angiography is helpful both for diagnostic purposes and to assess the extent of the disease. Angiographic evaluation is particularly helpful in cases where the retinal telangiectasia is subtle or obscured by lipid exudation. Typical fluorescein angiographic findings include retinal telangiectasia, patchy areas of capillary dropout, and characteristic "light-bulb" vascular aneurysm (Fig. 2.2). Areas of capillary dropout are replaced with arteriovenous shunts. Fluorescein leaks from these incompetent vessels, resulting in cystoid macular changes or large areas of intra- and subretinal fluorescein collections.

In more advanced cases of Coats's disease, a total or near total exudative detachment exists. Clinical or angiographic examination of the retinal vasculature may be difficult if not impossible. In such cases, imaging with ocular ultrasonography, computerized tomography (CT), or magnetic resonance imaging (MRI) may be necessary. The characteristic ultrasonographic findings include a relatively immobile, thickened, detached retina with homogeneous subretinal fluid and medium reflective echogenic clefts (Fig. 2.3). Highly reflective foci representing calcium deposition, frequently

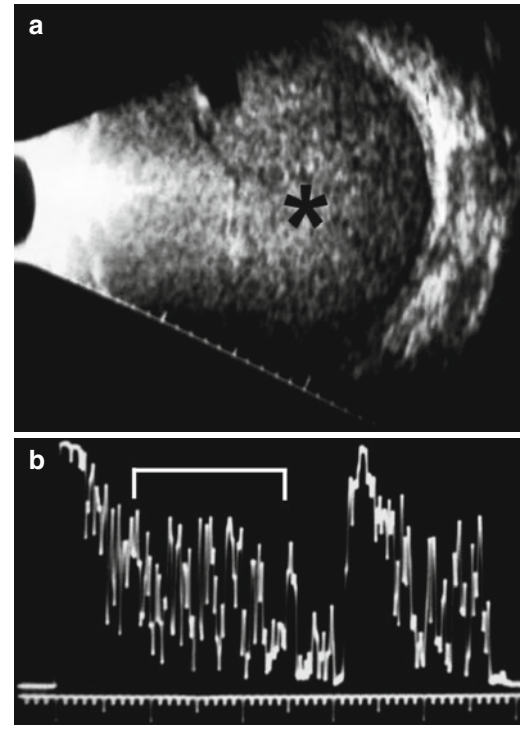


Fig. 2.3 Diagnostic ultrasonography of the eye in Fig. 2.1. Note the diffuse, homogeneous medium reflectivity of the posterior segment on B scan (*asterisk*). The numerous echogenic clefts represent cholesterol crystals within the subretinal exudates (**a**). These crystals account for the medium reflective spikes seen on the A scan (*bracket*, **b**)

associated with retinoblastoma, are rarely seen in Coats' disease. When present in Coats' disease, it usually represents osseous metaplasia of the retinal pigment epithelium in end-stage, phthisical eyes.

Computerized tomography can also detect calcium deposition, thereby facilitating differentiation of retinoblastoma from Coats' disease. CT has a sensitivity of 96 % in detecting calcification in retinoblastoma, while MRI sensitivity is 91.7 % [25]. Even though MRI cannot image bone or calcium, making this imaging mode somewhat suboptimal, recent concerns over cumulative biologic effects of radiation may sway physicians to elect MRI [26]. MRI does have superior soft tissue contrast resolution. On T1-weighted images, the subretinal space is hyperintense. T2-weighted images can be either hyper- or hypointense depending on the extent of the retinal detachment and composition of the exudate. While retina normally enhances following gadolinium contrast

infusion, there is no significant enhancement of the subretinal fluid associated with Coats' disease; this is in contrast to retinoblastoma, which shows post-gadolinium enhancement [26, 27].

Fine needle aspiration of the subretinal exudate demonstrates cholesterol crystals, lipid- and pigment-laden macrophages, and the absence of tumor cells [28]. Fine needle aspiration biopsy, while useful, should not be used routinely. Since retinoblastoma is a possible diagnosis, fine needle aspiration biopsy runs the risk of seeding the orbit with viable retinoblastoma cells. In non-seeing eyes with total retinal detachments and an uncertain diagnosis, enucleation should be preferred over the fine needle aspiration biopsy.

2.5 Associations

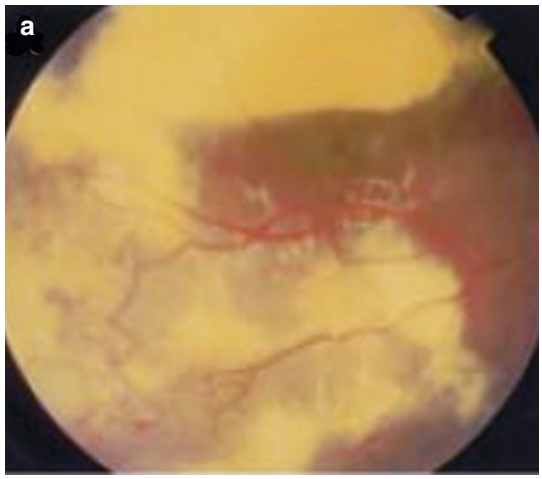
Ophthalmic and systemic associations have been reported with cases of Coats' disease and should be suspected particularly in cases diagnosed with bilateral involvement.

2.5.1 Ophthalmic

Bilateral retinal exudation, retinal telangiectasia, and even angioma can occur in patients with retinitis pigmentosa (Fig. 2.4) [29, 30].

2.5.2 Systemic

The most common association is with muscular dystrophy [31]. In a study of 64 patients affected with facioscapulohumeral muscular dystrophy, 48 (75 %) had angiographic findings of retinal telangiectasia (Fig. 2.5) [31, 32]. Concurrent CNS finding has also been reported, including central nervous system venous malformations [33] and cerebral calcifications [34, 35]. Beyond these cases, there exist only case reports of Coats' disease associated with a variety of syndromes such as dystonia with PANK2 mutation [36], Turner's syndrome [37], Cornelia de Lange syndrome [38], Hallermann-Streiff syndrome [39], Osler-Weber-Rendu disease [8], and Revesz syndrome [13, 40].



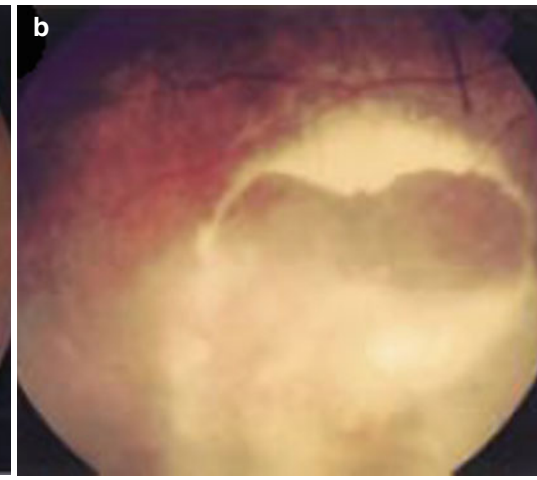


Fig. 2.4 Retinal telangiectasia, exudative retinopathy, and retinitis pigmentosa. A 12-year-old male presented with a 3-week history of blurred vision in both eyes. There was no significant medical or family history. Visual acuities were 20/400 in the right eye and 20/50 in the left eye. Anterior segment examination was normal. The posterior segment of both eyes showed extensive subretinal exudation, serous retinal detachment, and overlying retinal telangiectasia (**a**). There was cystoid macular edema with a lamellar macular hole in the left eye. The optic discs appeared normal. Additionally, mottled granularity of the retinal pigment epithelium (RPE) was noted in the mid-periphery of both retinas (**b**). Upon further questioning, he admitted to night blindness. A fluorescein angiogram confirmed retinal telangiectasia, serous retinal detachment, and macular edema (**c**). An electroretinogram (ERG) showed an isoelectric response under both scotopic and photopic conditions. Visual field testing revealed marked constriction in both eyes (Reproduced with permission from Singh et al. [30])

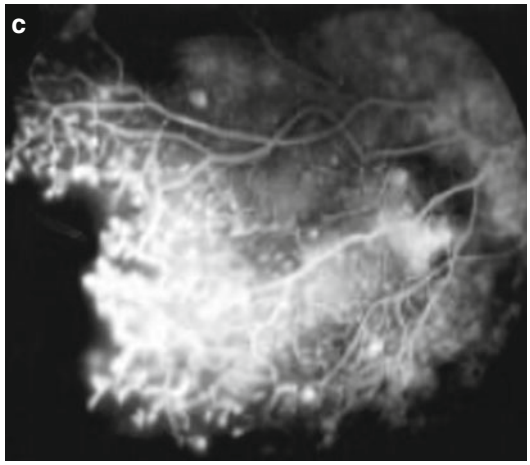


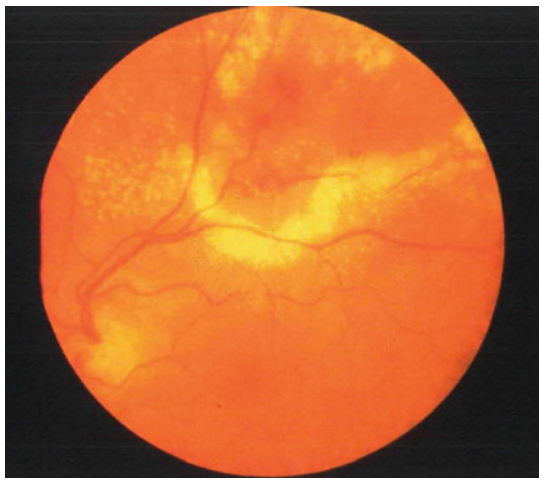
Fig. 2.4 (continued)

It is worth mentioning that Coats' disease is reported to be a part of Coats' plus syndrome, a pleiotropic telomeric shortening disorder characterized by bilateral retinal telangiectasias, exudative retinopathy, intracranial calcifications, bone marrow abnormalities, and gastrointestinal vascular ectasias. [13] It is caused by mutations in *CTC1* gene, which encodes a conserved telomere protein. Coats' plus is assumed to be due to an autosomal recessive trait [40].

2.6 Differential Diagnosis

The diagnosis of early stage Coats' disease is often straightforward. Foremost in the differential diagnosis of later stages is retinoblastoma, thereby making the stakes of an accurate diagnosis high (Table 2.2). Similar to Coats' disease, retinoblastoma most often presents with leukocoria and strabismus [41]. Exudative retinal detachments may be present in either condition. However, retinoblastoma typically presents at an earlier age and is more often bilateral (40 % of cases), and 10 % have a family history. Retinoblastoma tumors are white to flesh colored in contrast to the yellow coloration of lipid seen in Coats' disease. Retinoblastoma tumors have an intrinsic vascular supply and often have associated calcium deposits. Small and even medium size tumors do not typically have associated lipid exudation, though serous retinal detachments will occur in exophytic tumors.

Vitreoretinal traction rarely occurs in Coats' disease. In contrast, vitreoretinal traction frequently occurs in many childhood vitreoretinopathies which are associated with retinal telangiectasia, such as familial exudative vitreoretinopathy (FEVR), retinopathy of prematurity, persistent



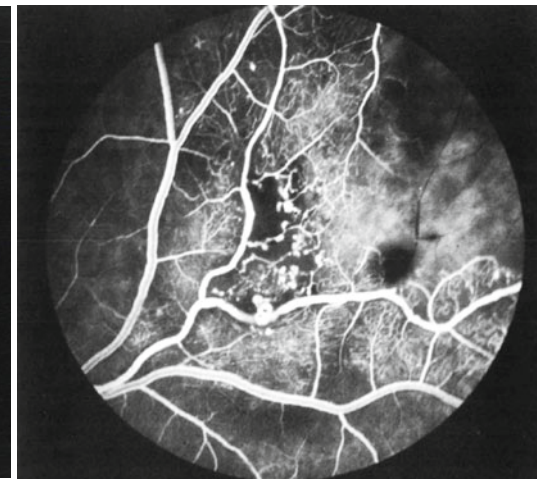


Fig. 2.5 Facioscapulohumeral muscular dystrophy masquerading as Coats' disease. Color photograph of left fundus demonstrating retinal oedema and exudate above macula, surrounding haemorrhage and tortuous telangiectatic vessels (**a**). Fluorescein angjogram demonstrating telangiectasis and capillary closure and leakage into the retina (**b**). Reproduced with permission from Fitzsimons et al. [32]

Table 2.2 Coats' disease and retinoblastoma

Feature			Coats' disease	Retinoblastoma
	Demographic	Mean age at diagnosis	5 years	1.5 years
		Male	76 %	50 %
		Family history	0 %	10 %
	Ophthalmic	Unilateral	95 %	60 %
		Retinal vessels	Irregular dilatation with telangiectasia	Regular dilatation and tortuosity
		Retinal mass	Absent	Present
		Retinal exudation	Present	Absent
		Vitreous seeds	Absent	Present
	Diagnostic	USG	Retinal detachment	Retinal detachment with calcification
		CT scan	Calcification absent	Calcification present
		MRI	Retinal detachment	Retinal detachment with enhancing mass

Modified from Shields and Shields [41]
USG ultrasonography, *CT* computerized tomography, *MRI* magnetic resonance imaging

hyperplastic primary vitreous, incontinentia pigmenti, Norrie's disease, and retinal capillary hemangioma (Table 2.3). For example, FEVR is a bilateral autosomal dominantly inherited vitreoretinal disease. These patients develop peripheral retinal telangiectasia and neovascularization, which may be associated with lipid exudation, shunt vessel formation, and aneurysmal dilations much like Coats' disease. However, another manifestation of FEVR is abnormal vitreoretinal adhesions resulting in retinal traction. When significant traction occurs, a falciform fold may develop from the disc to the involved peripheral retina, or the retinal may tractionally detach. Retinopathy of prematurity (ROP), another bilateral vitreoretinal disease, will have a history of premature birth and a demarcation separating vascularized and avascular retina. Persistent hyperplastic primary vitreous (PHPV) is a congenital, typically unilateral, malformation. The eyes are small, and the anterior chamber is often shallow. Echography can often elucidate a stalk emanating from the disc or another posterior pole location and extending to the lens capsule. Incontinentia pigmenti will have typical dermatologic and dental findings characteristic of the disease.

Retinal capillary hemangioma may most closely resemble Coats' disease. These cases have dilated tortuous arteries and veins, vascular shunts, and lipid exudation. Features, which differentiate these vascular tumors from Coats' disease, are the dilated tortuous feeding arterioles and draining veins, the focal nodularity of the tumor, and lack of telangiectasia.

2.7 Treatment

The natural history of Coats' disease is usually of a progressive disease. Though the rate of progression is variable, the majority of eyes will develop severe vision loss. Between 64 and 80 % of eyes will become phthisical and develop advanced glaucoma or retinal detachment [17]. Only rarely will the telangiectasia regress spontaneously [42].

2.7.1 Observation

Observation can be considered in some cases with early stage disease with little or no exudate or in advanced non-seeing but comfortable eyes.

2.7.2 Laser Photocoagulation

The treatment should be initiated once progression is documented. The first line of treatment is laser photocoagulation and/or cryotherapy. The goal is to ablate the nonperfused retina and areas

Table 2.3 Differential diagnosis of exudative retinopathy

	Demographics			Ophthalmoscopic findings				
Entity	Age	Sex (%)	Laterality	Exudation	Traction	Other	Inheritance	Systemic Features
Coats' disease	5 years	M (75)	Unilateral (95 %)	+	–	Telangiectasia	Sporadic	Absent
FEVR	0–3 months	M (50) F (50)	Bilateral	+	+	Peripheral retinal avascular zone	AD AR XR Sporadic	Absent
Retinopathy of prematurity	Premature neonate	M (50) F (50)	Bilateral	–	+	Neovascularization Vitreous hemorrhage	Sporadic	Complications of premature birth
PHPV	0–5 years	M (50) F (50)	Unilateral	–	+	Microphthalmia Cataract Shallow AC Vitreous stalk	Sporadic	Absent
Incontinentia pigmenti	0–16 years	F (100)	Bilateral	+	+	Optic atrophy Foveal hypoplasia	XD	Skin rash Hypodontia Dystrophic nails
Norrie's disease	At birth	M (50) F (50)	Bilateral	+	+	Retrolental mass	XR Sporadic	Cognitive Behavioral Hearing Loss
Retinal capillary hemangioma	25 years	M (50) F (50)	Unilateral or bilateral	+	–	Capillary hemangioma	AD Sporadic	VHL disease

M males, *F* females, *AC* anterior chamber, *FEVR* familial exudative vitreoretinopathy, *VHL* von Hippel-Lindau, *PHPV* persistent hyperplastic primary vitreous, *AD* autosomal dominant, *AR* autosomal recessive, *XR* X-linked recessive, *XD* X-linked dominant

of telangiectasia. The entire area of retinal telangiectasia needs to be treated. Even though laser photocoagulation works best when performed in cases of absent or minimal exudative retinal detachment, favorable structural response after green laser treatment has been observed in advanced Coats' disease (stage 3) when treatment was directed at vascular abnormalities [43].

2.7.3 Cryotherapy

Cases with a shallow exudative retinal detachment can be successfully treated with a double freeze-thaw cryotherapy (Fig. 2.6). Multiple treatment sessions every 3 months are usually necessary with either laser or cryotherapy.

2.7.4 Anti-vascular Endothelial Growth Factor (Anti-VEGF) Therapy

Successful use of anti-VEGF therapy in conjunction with ablative therapy (cryotherapy or panretinal laser photocoagulation) has been reported [44–46]. Both intravitreal triamcinolone and bevacizumab were used in the past to treat Coats' disease. In particular, it appears to be beneficial in advanced stages (stage 3 and above), when the laser cannot be applied. Some authors caution though that traction retinal detachment can develop [44, 46]. Prospective controlled trials are warranted to further elucidate the role of anti-VEGF therapy in Coats' disease.

2.7.5 Surgical Drainage

In advanced cases of Coats' disease where vision is still preserved but the retina is extensively detached, surgical drainage of the subretinal exudate can be considered. This is accomplished with a sclerotomy in the area of greatest exudation. Often, more than one sclerotomy is required. If a significant amount of exudate must be drained, balanced saline solution is infused via either an anterior chamber or a posterior chamber infusion cannula. A posterior chamber infusion cannula should only be placed if it can be safely passed through the pars plana without damaging the lens or retina and extends far enough that the tip does not end in the subretinal space. Once the subretinal exudate is drained, laser photocoagulation or cryotherapy is performed. Some surgeons elect to encircle the eye with a scleral buckle to minimize tractional forces generated at the vitreous base.

2.7.6 Vitreoretinal Techniques

The vitreoretinal techniques have also been used in cases with tractional detachment or epimacular membranes [47, 48].

2.7.7 Supportive Care

Protective eye wear must be stressed. These are often healthy active young boys potentially predisposed to incurring injuries. Every effort should be made to prevent injury to the unaffected eye, without deterring normal daily or sporting activities. For bilateral cases, visual rehabilitation with low vision aids and learning of Braille alphabet may have to be recommended.

2.7.8 Follow-Up

Disease recurrence in 7–10 % of eyes up to a decade from initial treatment has been reported [16, 20, 21]. Consequently, a lifetime of follow-up is necessary. Once stable, a patient should be seen every 6–12 months. Setting realistic expectations and providing a general timeline for follow-up care are essential.

2.8 Prognosis

Overall, it can be expected that roughly 75 % of patients will have an anatomic improvement or stabilization of the affected eye with treatment [20]. The remaining 25 % will worsen or require enucleation. As expected, patients with

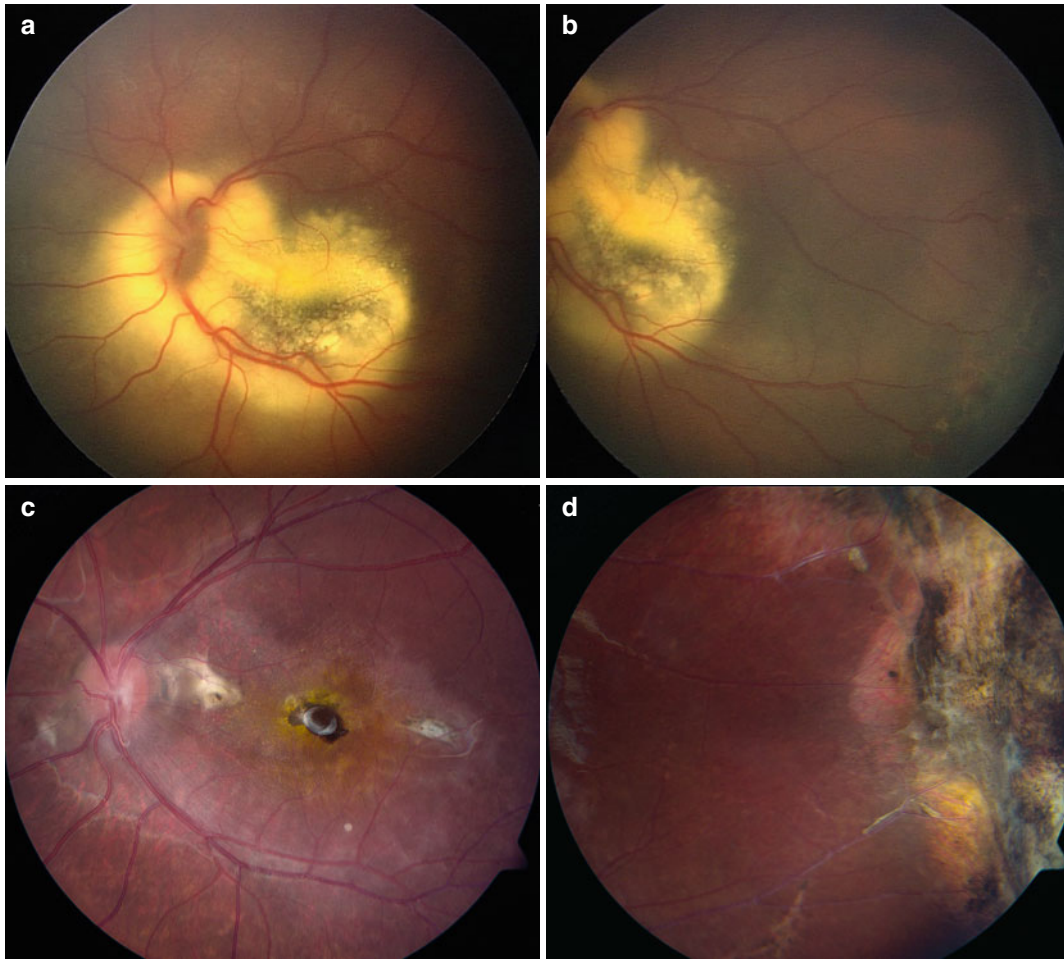


Fig. 2.6 A 20-month-old child with leukocoria OS. Note prominent exudation in the macular region (**a**) and retinal telangiectasia in the inferotemporal quadrant (**b**). He was treated with multiple sessions of laser photocoagulation and cryotherapy to the involved regions of the retina. One year later, there is marked reduction in the macular exudation accompanied by fibroglial and pigment proliferation at the foveola (**c**). Note chorioretinal atrophy with secondary pigment proliferation at the treatment site (**d**)

early stage disease fare far better than those with more advanced stages. In a series of 124 eyes (117 patients), 73 % of patients with telangiectasia with or without extrafoveal lipid exudate had better than 20/200 vision, whereas only 26 % of patients with partial or total exudative retinal detachments attained this level of vision [20]. The natural progression in advanced Coats' disease is toward the development of a blind, painful eye or to a phthisical state [49].

Conclusions

A definitive therapy for Coats' disease will largely depend on a better understanding of its pathogenesis. Without an adequate animal model or an implicated gene, future developments will be hindered. Associations with other disease entities such as muscular dystrophy will hopefully lead to the etiologic gene. In the mean time, our treatment of Coats' disease will need to concentrate on early detection and

modulation of the affected retina via retinal ablation (laser and cryotherapy) or pharmacologic stabilization of exuding vessels.

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Retinal Vascular Tumors

3

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Contents

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Retinal vascular tumors represent at least four distinct clinical entities which include retinal capillary hemangiomas, retinal cavernous hemangiomas, retinal arteriovenous communications (Wyburn-Mason syndrome), and retinal vasoproliferative tumor. Retinal vascular tumors can also be considered as congenital or prenatal in origin, maintaining retinal tight junctions and hence not manifesting retinal leakage, such as subretinal fluid or hard exudates (retinal cavernous hemangioma and retinal arteriovenous communications [Wyburn-Mason syndrome]), or acquired/postnatal in origin without retinal tight junctions and hence manifesting retinal leakage, such as subretinal fluid or hard exudates (retinal capillary hemangioma and retinal vasoproliferative tumor). Each of the subtypes has characteristic

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Table 3.1 Diagnostic features of various retinal vascular tumors

Type	Appearance	Location	Feeder vessels	Exudation	Systemic association
Capillary hemangioma	Round red mass	Juxtapapillary/ peripheral	Prominent	Present	VHL disease
Cavernous hemangioma	Grapelike clusters	Nonspecific	Absent	Absent	CNS hemangioma
Arteriovenous malformations	Dilated/tortuousretinal vessels	Near the disc	Absent	Absent	Wyburn-Mason syndrome
Vasoproliferative tumor	Globular pale mass	Periphery	Absent	Present	Absent

VHL von Hippel-Lindau disease

clinical features and an attempt should be made to differentiate them because of specific systemic associations, treatment, and prognosis associated with them. The clinical features and systemic associations of retinal vascular tumors are summarized in Table 3.1. Only a brief description of retinal capillary hemangioma and retinal arteriovenous communications (Wyburn-Mason syndrome) is included in this chapter as these topics are further discussed under neuro-oculocutaneous syndromes (phakomatoses) (Chap. 9).

3.1 Retinal Capillary Hemangioma

3.1.1 Introduction

Although these retinal vascular tumors have been characterized as hemangioblastomas, various authors have recommended that the term capillary hemangioma rather than hemangioblastoma or hemangioendothelioma be used to describe these vascular tumors [1]. Retinal capillary hemangiomas can be further classified on the basis of their location within the retina (peripheral and juxtapapillary), morphology (endophytic, exophytic, and sessile), effects on the retina (exudative form and tractional form), and their relationship to von Hippel-Lindau (VHL) disease (with or without VHL disease).

3.1.2 Clinical Features

Retinal capillary hemangiomas are multiple in about one-third of patients, and up to half of the cases have bilateral involvement. The mean age at diagnosis of retinal capillary hemangioma in VHL disease is approximately 25 years [2].

3.1.2.1 Symptoms

Patients typically notice progressive worsening of vision which may be associated with photopsia. Many patients are asymptomatic and are detected on a routine examination or on screening evaluation because of the family history of VHL disease [3].

3.1.2.2 Signs

Ophthalmoscopically, a retinal capillary hemangioma appears as a circumscribed, round retinal lesion with an orange-red color with prominent feeder vessels (Fig. 3.1). Intraretinal and subretinal exudates are often seen around the tumor or in the macula. The majority of retinal capillary hemangiomas are located in the superotemporal and inferotemporal peripheral retina [4]. Prominent retinal vessels emerging from the optic disc are highly suggestive of a peripherally located retinal capillary hemangioma. In contrast, juxtapapillary retinal capillary hemangiomas are not associated with visible prominent feeder vessels.

3.1.3 Diagnostic Evaluation

The fundus findings of retinal capillary hemangiomas are characteristic and the diagnosis can usually be made based solely on ophthalmoscopic examination. Fluorescein angiography is the most informative diagnostic tool because of the vascular nature of the tumor (Fig. 3.1) [5]. Fluorescein angiography also helps in differentiating the

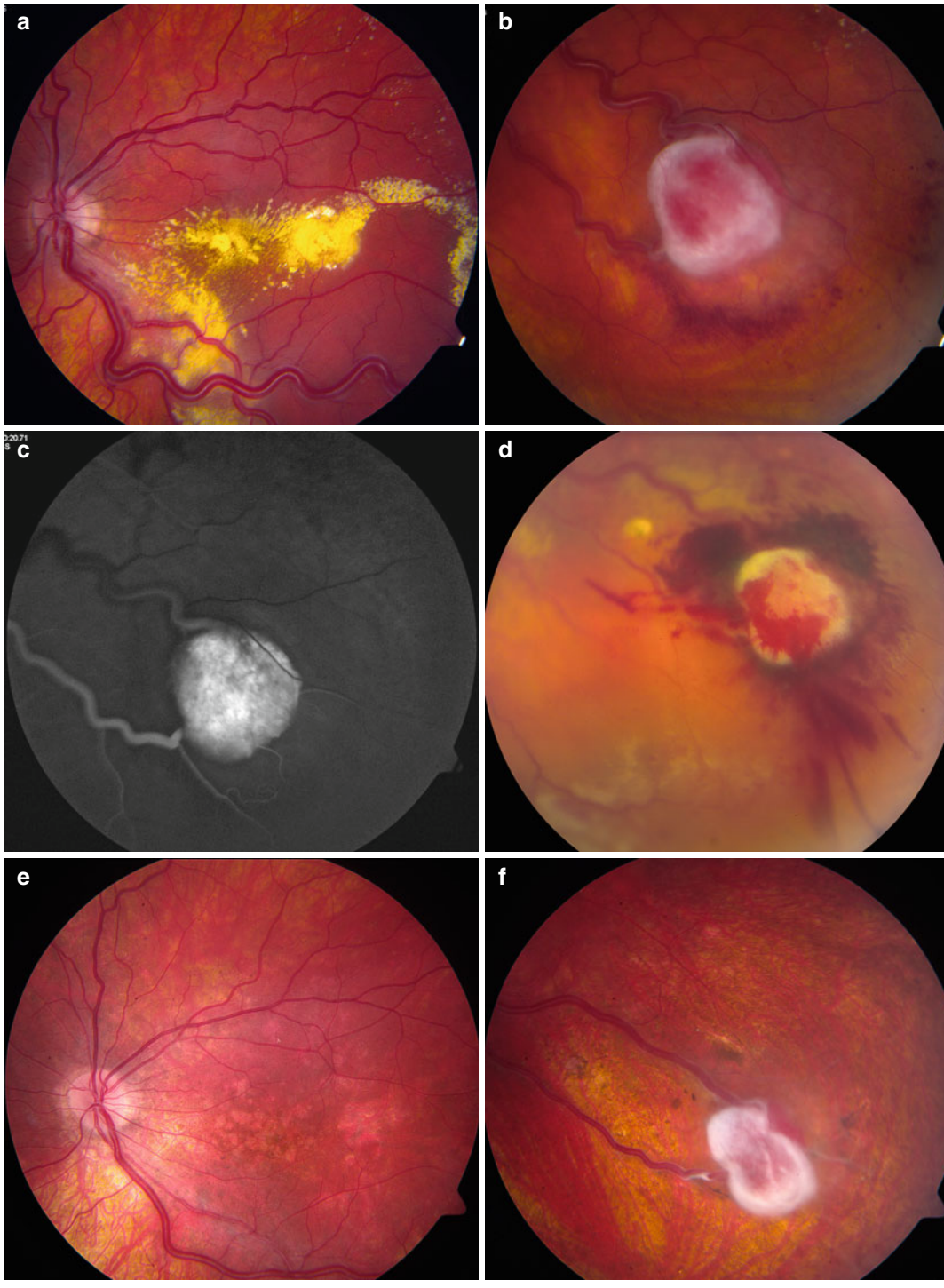

Fig. 3.1 Fundus photograph of a retinal capillary hemangioma. Note prominent feeder vessels and retinal exudation (**a**). The hemangioma has a rim of gliosis and surrounding and subretinal fluid and hemorrhage (**b**). Fluorescein angiography identifies the feeder artery (**c**). Marked hyperfluorescence and leakage are characteristic findings. One week after treatment with standard-fluence photodynamic therapy, increased gliosis hemorrhage (**d**). Six months after the treatment, there is complete resolution of macular exudates and reduction in size of the feeder vessels (**e**). The lesion has regressed with increased gliosis and total resolution of surrounding and subretinal fluid and hemorrhage

feeder arteriole from the draining vein and is therefore important for treatment planning.

3.1.4 Salient Diagnostic Findings (Box 3.1)

- Single or multiple, circumscribed, orange-red colored, round retinal lesion.
- Retinal exudation and or subretinal fluid surrounding the lesion which may extend into the macular region.
- Prominent feeder vessels extending from the optic disc (absent in juxtapapillary variant).
- Prominent and early filling on fluorescein angiography with late leakage.

3.1.5 Differential Diagnosis

Some of the conditions that should be considered in the differential diagnosis include Coats' disease, macroaneurysm, and other forms of retinal vascular tumor [6]. Coats' disease is an idiopathic unilateral retinal vascular disease of young males which is characterized by retinal telangiectasia and retinal exudation [7]. The younger age of onset, unilateral involvement, predilection for males, and lack of systemic features are helpful differentiating features. Moreover, Coats' disease has prominent areas of retinal telangiectasia rather than distinct retinal vascular tumors.

Retinal macroaneurysm has many features that differentiate it from retinal capillary hemangioma [8]. In general, macroaneurysm is seen as a single lesion in the posterior pole in older individuals and is more likely to present with subretinal, intraretinal, or vitreous hemorrhage rather than retinal exudation. Most importantly, the feeder vessels are absent and careful fundus examination reveals that the macroaneurysm is centered on the retinal arteriole.

Important findings that differentiate a retinal capillary hemangioma from a vasoproliferative tumor are the absence of prominent feeder vessels in a vasoproliferative tumor and its extreme peripheral location in the inferior retina [9]. Retinal capillary hemangioma is more commonly seen in the temporal quadrants of the mid-peripheral retina [6]. Unlike retinal capillary hemangioma, vasoproliferative tumors are nonfamilial and lack significant systemic association [9].

3.1.6 Treatment of Retinal Capillary Hemangioma

There are several methods of treating a retinal capillary hemangioma and the choice of treatment is determined by the size, location, and associated findings of subretinal fluid, retinal traction, and the visual potential of the eye [10]. The treatment can be challenging due to the presence of multiple tumors in both eyes and the potential for the onset of new tumors.

3.1.6.1 Observation

Careful observation in a reliable patient can be recommended if the retinal capillary hemangioma is very small (up to 500 μm), is not associated with exudation or subretinal fluid, and is not visually threatening [10]. Initial observation should always be considered in juxtapapillary retinal capillary hemangioma as they tend to remain stable [11].

3.1.6.2 Laser Photocoagulation

Laser photocoagulation, applied over many sessions, is effective (91–100 %) in treating retinal capillary hemangiomas that are up to 4.5 mm in size, but is most effective in tumors that are 1.5 mm or smaller in size (Fig. 3.2) [12]. Photocoagulation can be applied directly to the tumor, to the feeder artery, or a combination of both techniques can be used [13].

3.1.6.3 Cryotherapy

Cryotherapy is preferable to photocoagulation when the retinal capillary hemangioma is located anteriorly and the retinal capillary hemangioma is more than 3.0 mm in diameter (Fig. 3.3) [14]. Cryotherapy may also be preferred when there is

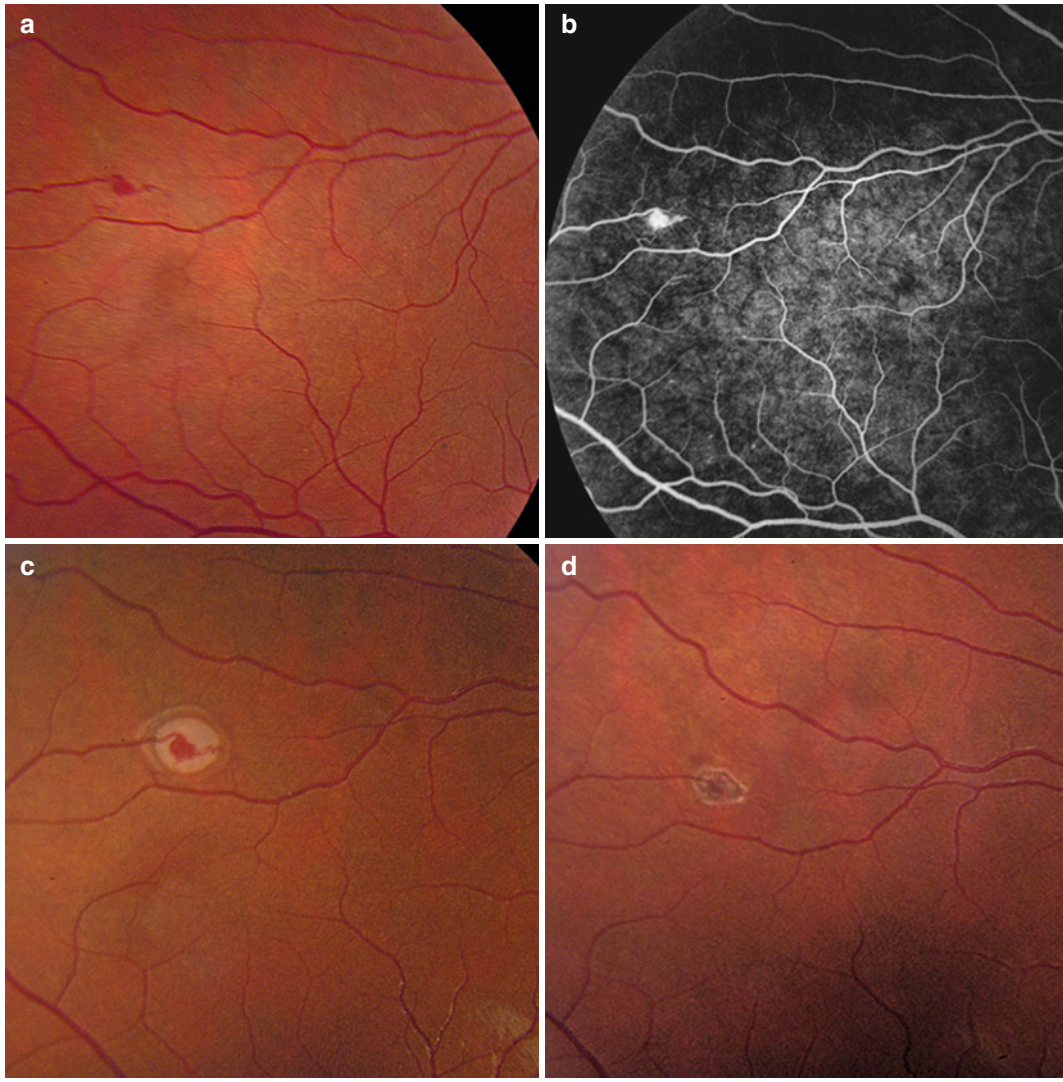

Fig. 3.2 Small retinal capillary hemangioma observed on surveillance examination in a patient with VHL disease (**a**). The hemangioma could be visualized with fluorescein angiography (**b**). Appearance immediately after laser photocoagulation (**c**). Four weeks later, the hemangioma is partially regressed and surrounded by a chorioretinal scar (**d**) (Reproduced with permission from Singh and Schachat [53])

moderate amount of subretinal fluid. The efficacy of cryotherapy is greater with smaller tumors (less than 1.5 mm) [10].

3.1.6.4 Photodynamic Therapy

More recently, photodynamic therapy has been reported to induce occlusion of peripheral (Fig. 3.1) and juxtapapillary retinal capillary hemangioma (Fig. 3.4) [11, 15–17].

3.1.6.5 Radiotherapy

Retinal capillary hemangiomas that are greater than 4 mm show a poor response to cryotherapy and laser photocoagulation and such tumors can be treated successfully with plaque radiotherapy [18]. Low-dose external beam radiotherapy is also an option in cases that do not respond to the usual methods of treatment listed above [19].

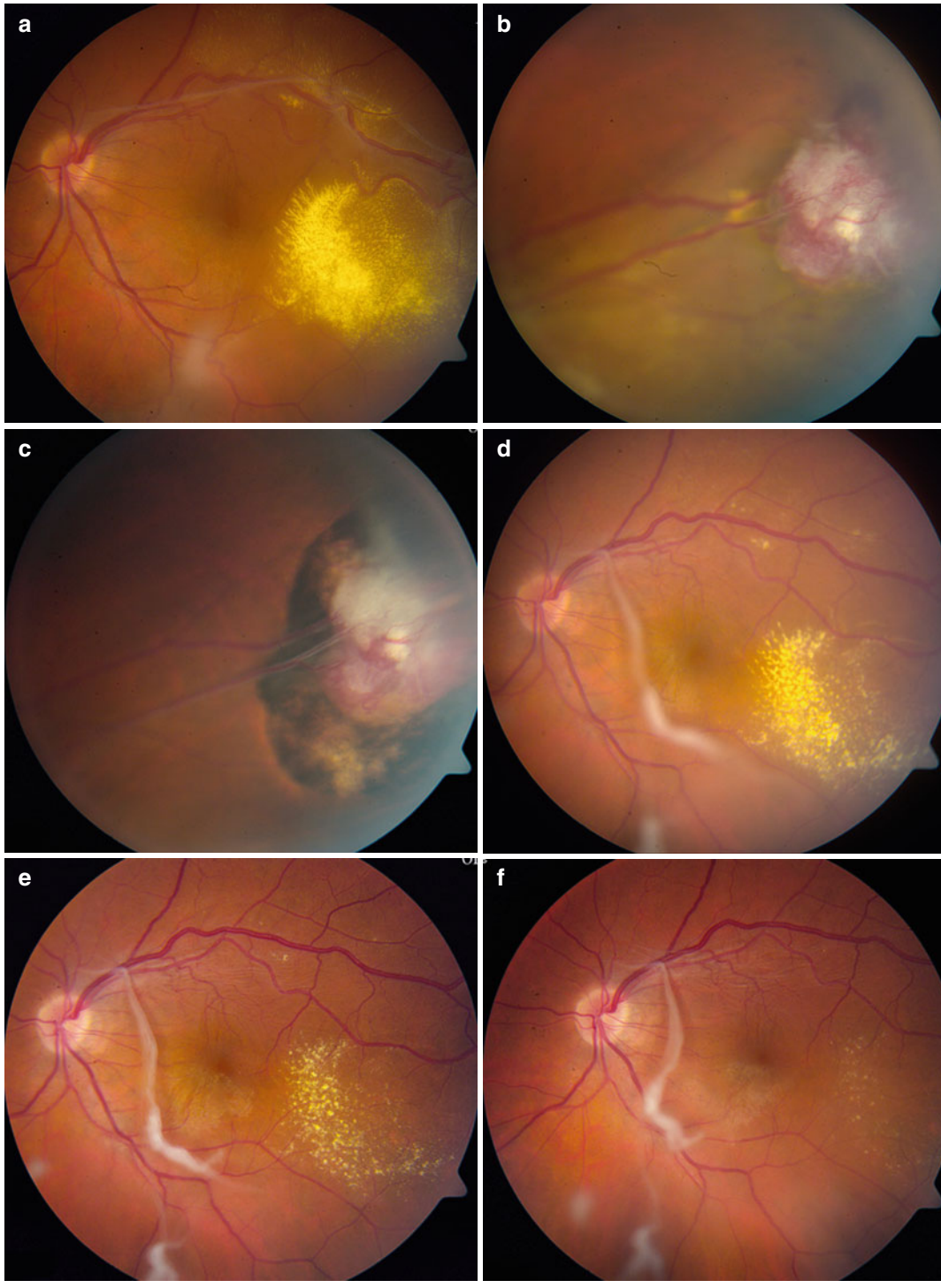

Fig. 3.3 Cryotherapy for retinal capillary hemangioma. Macular exudation (**a**) and peripheral solitary retinal capillary hemangioma (**b**). Note reduction in tumor vascularity and surrounding reactive pigment proliferation 3 months after double freeze-thaw cryotherapy (**c**) and reduction in macular exudation (**d**). The macular appearance continues to improve with slow resolution of exudation (**e**, 6 months) without additional intervention (**f**, 12 months). Cryotherapy also led to partial peeling of the epiretinal membrane (final visual acuity 20/20)

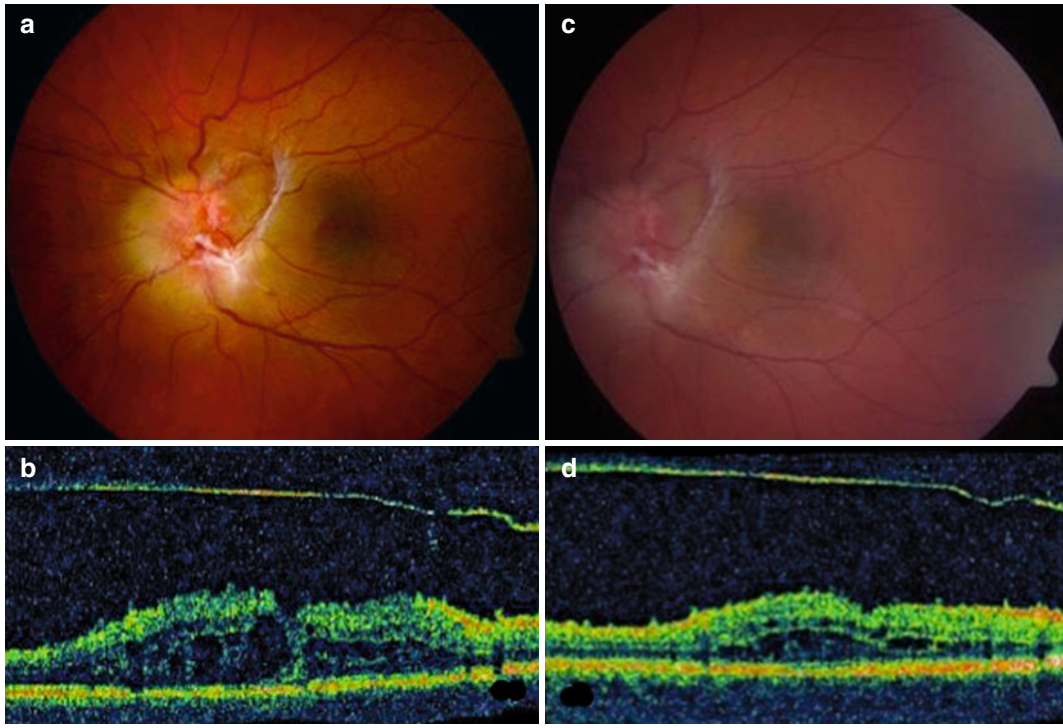

Fig. 3.4 Initial fundoscopic photograph (**a**) and OCT (**b**, fovea) of left eye of 27-year-old female (patient 1) with juxtapapillary retinal capillary hemangioma and associated cystoid macular edema. Fundoscopic photograph (**c**) and OCT (**d**) approximately 2 years following photodynamic therapy in same patient, which reveals stabilization of tumor with decreased edema (Reproduced with permission from Sachdeva et al. [15])

3.1.6.6 Anti-VEGF Therapy

Although anti-VEGF therapy is extensively used in a variety of retinal vascular conditions, its use in the treatment of retinal capillary hemangioma remains unproven with variable response in lesion size and exudation [20, 21].

3.1.6.7 Vitreoretinal Procedures

Pars plana vitrectomy, retinal detachment repair, and other related procedures are usually required for larger retinal capillary hemangiomas that are complicated by rhegmatogenous or tractional retinal detachments.

3.1.7 Association with Von Hippel-Lindau Disease

Retinal capillary hemangiomas can occur sporadically or in association with VHL disease [6, 22]. The association of retinal capillary hemangioma with VHL disease is discussed in detail under neuro-oculo-cutaneous syndromes (phakomatoses) (Chap. 9).

3.1.8 Prognosis

The visual prognosis, even in adequately treated cases, is guarded [6]. Overall, more than 25 % of affected patients show permanent visual loss, and about 20 % have vision of less than 20/100 in at least one eye [4]. However, the visual outcome is greatly dependent on the size, location, and number of retinal capillary hemangiomas and the presence of exudative or tractional retinal detachment. As retinal capillary hemangiomas progressively enlarge, the visual outcome is much better in cases that are diagnosed and treated before the onset of symptoms [4].

3.2 Cavernous Hemangioma of the Retina

3.2.1 Introduction

Cavernous hemangiomas of the retina are composed of multiple, thin-walled dilated vascular channels with surface gliosis [23]. The walls are lined by non-fenestrated endothelium, explaining the lack of exudation [24]. Two forms of cavernous hemangioma of the retina are recognized: sporadic and syndromic [23]. It has been suggested that the cerebral cavernous malformation syndromes should be included with the neuro-oculo-cutaneous (phakomatoses) syndromes, but the association of cerebral and cutaneous hemangiomas is inconsistent [23].

3.2.2 Clinical Features

Cavernous hemangiomas of the retina are believed to be a rare form of congenital hamartoma. The age of presentation in a series of nine patients ranged from 1 to 55 years [25].

3.2.2.1 Symptoms

Patients with cavernous hemangioma of the retina may be asymptomatic or may present with reduced vision from a macular location of the hemangioma, macular fibrosis, or vitreous hemorrhage. Recent OCT studies have revealed OCT an overlying epiretinal membrane forming bridges between the saccules, contraction of which could exert traction and cause vitreous hemorrhage (Fig. 3.5) [26].

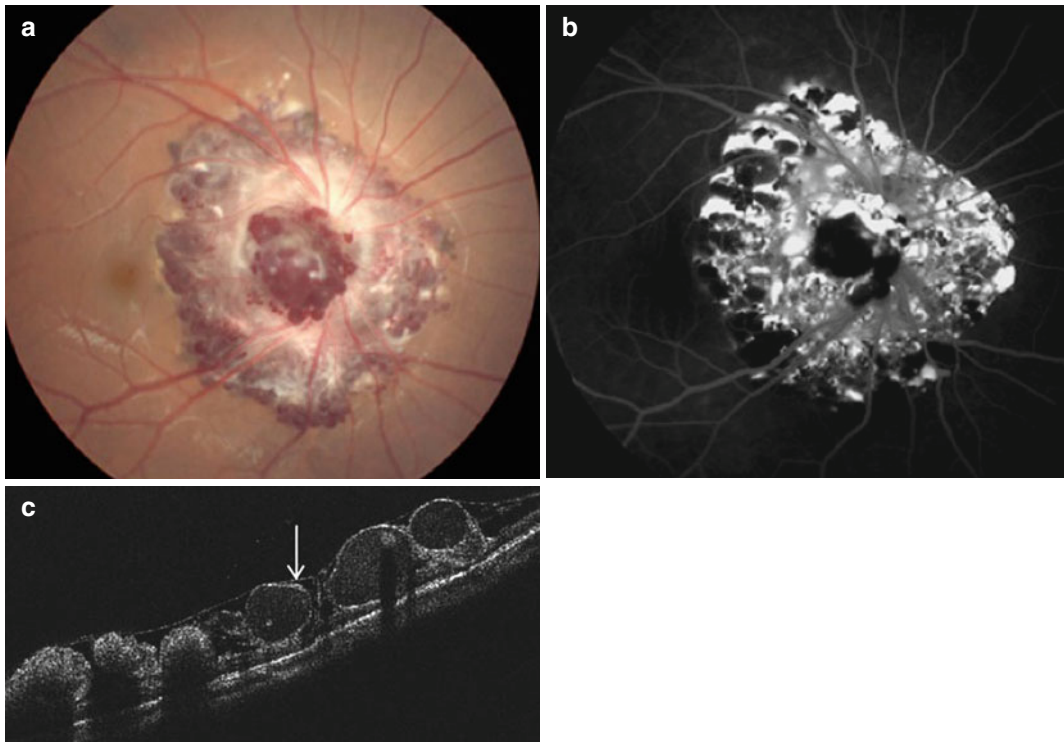

Fig. 3.5 Fundus photograph of a papillary cavernous hemangioma of the retina (**a**). Note the absence of retinal exudation. On fluorescein angiogram, characteristic hyperfluorescent saccular dilatations are evident (**b**) (Reproduced with permission from Patikulsila et al. [54]). Optical coherence tomography of the retinal cavernous hemangioma. An overlying epiretinal membrane is imaged as a continuous hyper-reflective signal attached to the saccules and forming bridges between them (**c**, *arrow*) (Reproduced with permission from Pringle et al. [26])

3.2.2.2 Signs

Retinal lesions appear as grapelike clusters of blood-filled saccular spaces in the inner layers of the retina or on the surface of the optic disc (Fig. 3.5) [23]. The size and location of the hemangioma are variable but most are solitary small (1–2 disc diameters) lesions involving the mid-peripheral or peripheral retina [22]. Epiretinal membranes are usually present. There are no prominent feeder vessels, and there is a lack of subretinal or intraretinal exudation. Rarely, cavernous hemangiomas may be multiple and extensive involving 360° of the mid-peripheral retina [27].

3.2.3 Diagnostic Evaluation

The ophthalmoscopic findings of cavernous hemangiomas of the retina are characteristic. Fluorescein angiography is the most helpful diagnostic test in establishing the correct diagnosis. It demonstrates the retinal origin of the hemangioma with a low flow system and hence delayed filling in the venous phase (Fig. 3.5). The saccular dilatations in the hemangioma appear as fluorescent caps due to staining of supernatant plasma overlying collections of sedimented erythrocytes. Although cavernous hemangiomas are distributed randomly in the fundus, they tend to follow the course of a major vein; however, feeder vessels are not prominent. There is characteristic absence of leakage.

3.2.4 Salient Diagnostic Findings (Box 3.2)

- Retinal lesions appear as grapelike clusters of blood-filled saccular spaces in the inner layers of the retina or on the surface of the optic disc.
- Overlying epiretinal membranes are usually present.
- Absence of prominent feeder vessels.
- Lack of subretinal fluid and intraretinal exudation.
- May be associated with CNS hemangioma.

3.2.5 Differential Diagnosis

Cavernous hemangiomas of the retina should be differentiated from other vascular disorders such as Coats' disease, retinal capillary hemangiomas, retinal arteriovenous communications, and retinal vasoproliferative tumors. Presence of dilated feeder vessels and retinal exudation do not support the diagnosis of retinal cavernous hemangioma.

3.2.6 Treatment of Retinal Cavernous Hemangioma

In general, cavernous hemangiomas of the retina are nonprogressive, may undergo spontaneous thrombosis, and rarely cause vitreous hemorrhage. No effective treatment is known or indeed required, although laser photocoagulation has been attempted in a few cases [23].

3.2.7 Association with CNS Hemangioma

Cavernous hemangiomas of the retina may be associated with cerebral cavernous malformations in the context of an autosomal dominant syndrome with high penetrance and variable expressivity [28–30]. The association between retinal and CNS hemangiomas is discussed in detail under neuro-oculo-cutaneous syndromes (phakomatoses) (Chap. 9).

3.2.8 Prognosis

The vast majority of cases of cavernous hemangioma of the retina remain asymptomatic, do not progress, and require no treatment. A small number of cases of may have an associated self-limiting vitreous hemorrhage. With time, cavernous hemangiomas of the retina undergo progressive thrombosis and often demonstrate an increase in surface gliosis. In contrast, cerebral cavernous hemangiomas may have serious consequences such as seizures, intracranial hemorrhages, and even death [28].

3.3 Wyburn-Mason Syndrome

3.3.1 Introduction

Wyburn-Mason syndrome is a rare sporadic disorder characterized by congenital arteriovenous malformations principally of the retina and brain. Other involved tissues may include the skin, bones, kidneys, muscles, and gastrointestinal tract [31, 32].

3.3.2 Clinical Features

Although usually congenital in origin, the diagnosis of retinal arteriovenous malformations is most commonly made later in childhood.

3.3.2.1 Symptoms

Patients with retinal arteriovenous malformations may be asymptomatic. These lesions are often detected as an incidental finding in an asymptomatic patient or as a cause of visual impairment in an "amblyopic" eye.

3.3.2.2 Signs

Arteriovenous malformations are seen readily on ophthalmoscopic evaluation. These malformations have been classified into three groups depending upon the severity of vascular malformation [33]. Those in group I have an abnormal capillary plexus between the major vessels of the arteriovenous malformations. Group II arteriovenous malformations lack any intervening capillary between the artery and vein. Group III arteriovenous malformations are the most extensive with dilated and tortuous vessels and no apparent distinction between the artery and vein (Fig. 3.6).

3.3.3 Diagnostic Evaluation

The ophthalmoscopic findings of arteriovenous malformations of the retina are characteristic. Fluorescein angiography is the most helpful diagnostic test in establishing the correct diagnosis. It demonstrates abnormal arteriovenous connections and presence or absence of intervening capillaries. In the most severe cases (grade III), arteries and veins cannot be differentiated even on angiography (Fig. 3.6). Abnormal retinal vasculature characteristically demonstrates absence of leakage.

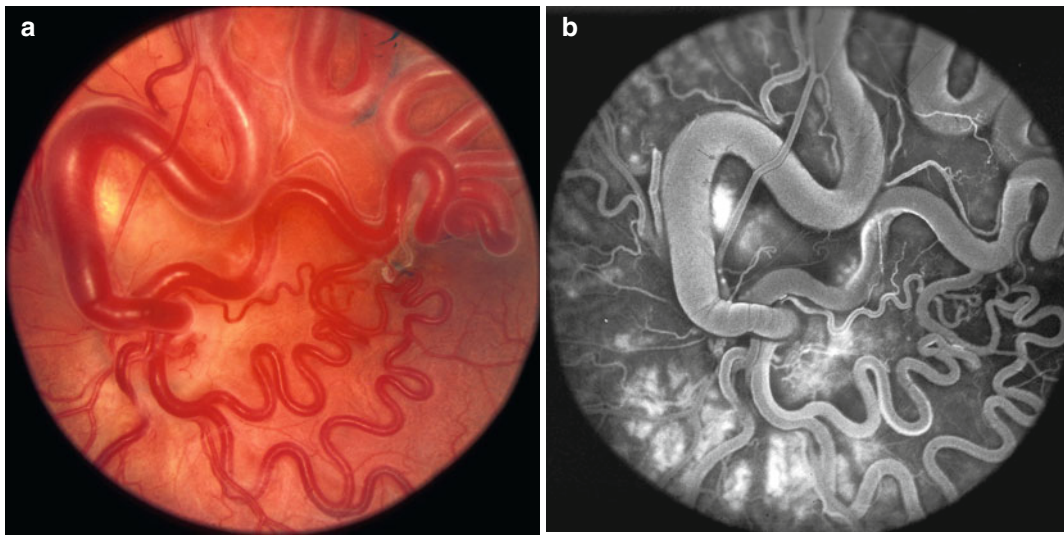

Fig. 3.6 Fundus appearance of a typical retinal arteriovenous malformation (**a**). On fluorescein angiography, arteries and veins appear undistinguishable (**b**)

3.3.4 Salient Diagnostic Findings (Box 3.3)

- Retinal arteriovenous malformations appear as abnormally dilated and tortuous retinal vessels.
- Absence of prominent feeder vessels.
- Lack of subretinal fluid and intraretinal exudation.
- May be associated with intracranial arteriovenous malformations.

3.3.5 Differential Diagnosis

Retinal arteriovenous communications should be differentiated from other vascular disorders listed above. Presence of dilated feeder vessels and retinal exudation goes against the diagnosis of retinal arteriovenous communications.

3.3.6 Treatment of Retinal Arteriovenous Communications

The retinal vascular malformations are usually not amenable to any therapy.

3.3.7 Association with Intracranial Arteriovenous Malformations

The exact incidence of intracranial arteriovenous malformations in patients with retinal arteriovenous malformations is not known. This topic is discussed in detail elsewhere.

3.3.8 Prognosis

The retinal vascular anomalies may alter in configuration over many years exhibiting increasing tortuosity [34] and sometimes leading to vascular occlusions [35] and retinal ischemia with the development of neovascular glaucoma. Patients with group III retinal arteriovenous malformations have a high risk of visual loss either as a result of retinal decompensation or via direct compression of retinal nerve fibers or optic nerve [36, 37].

3.4 Retinal Vasoproliferative Tumor

3.4.1 Introduction

Retinal vasoproliferative tumors are uncommon retinal lesions which have only been recognized as a distinct clinical entity since 1982 when Baines reported the combination of a peripheral telangiectatic nodules and posterior fibrocellular membranes in five patients [38]. These lesions were initially termed as "presumed acquired retinal hemangiomas" to differentiate them from capillary hemangiomas [39]. The nomenclature has varied in the literature, but at present, vasoproliferative retinal tumors are the widely accepted terminology [9]. Histologically, these lesions are composed of a mixture of glial cells, retinal pigment epithelial cells, and a network of fine capillaries with some larger dilated blood vessels [40, 41]. The histological appearances of vasoproliferative tumors have led to the speculation that these lesions are not true tumors but rather reactive proliferations [38]. Vasoproliferative retinal tumors may be primary (74 %) or secondary to a preexisting ocular disease (26 %) [9].

3.4.2 Clinical Features

Vasoproliferative retinal tumor usually presents in the third or fourth decade and both sexes are equally affected [9]. The majority of patients with primary tumors are solitary (87 %) in contrast to those with secondary tumors where multiple lesions were found in 42 % of cases.

3.4.2.1 Symptoms

Reduced vision, photopsia, and metamorphopsia are common presenting symptoms. Some asymptomatic cases are diagnosed incidentally on an ophthalmoscopic evaluation.

3.4.2.2 Signs

Vasoproliferative tumor appears as a globular yellowish-pink vascular mass in the peripheral retina (Fig. 3.7). These lesions lack the dilated, tortuous, feeder vessels typically seen in retinal capillary hemangioma, but retinal vessels of normal or near-normal caliber may be seen entering the lesion posteriorly. Vasoproliferative retinal tumors have a predilection for the inferior retina. Subretinal exudation, which may be extensive, is common occurring in over 80 % of cases [9]. Exudative retinal detachment, retinal and vitreous hemorrhage, vitreous, and epiretinal membrane cells are frequent associated findings (Fig. 3.8). Retinal pigment epithelial hyperplasia adjacent to the vasoproliferative retinal tumors may be evident especially in secondary tumors [9]. Macular fibrosis (31 %) and edema (18 %) may lead to visual loss (Fig. 3.7).

3.4.3 Diagnostic Evaluation

Ancillary investigations such as fluorescein angiography are of limited value because of the peripheral nature of most lesions. In cases where angiography is possible, the lesions typically fill rapidly in the early phase with increasingly hyperfluorescence and diffuse leakage in the late phases (Fig. 3.7). Telangiectatic and dilated vessels are frequently observed within the tumor mass. Ultrasonography confirms a raised solid lesion with high internal reflectivity on both A and B scans. Intraocular biopsy may be necessary to establish a diagnosis in difficult cases [42].

3.4.4 Salient Diagnostic Findings (Box 3.4)

- Vasoproliferative tumor appears as a globular yellowish-pink vascular mass.
- Inferior peripheral retinal location.
- Absence of dilated, tortuous, feeder vessels.
- Associated retinal exudation, subretinal fluid, and macular fibrosis.
- Preexisting ocular disease such as intermediate uveitis, other inflammation, or retinitis pigmentosa.

3.4.5 Differential Diagnosis

Atypical lesions may be confused with retinal capillary hemangioma, eccentric choroidal neovascularization (disciform), or even amelanotic melanoma. The absence of distinct feeder vessels or family history is of value in differentiating a vasoproliferative retinal tumor from a retinal capillary hemangioma. Careful examination of the tumor's vascular supply should confirm their retinal origin in contrast to an eccentric disciform which arises beneath the sensory retina. Similarly, choroidal hemangiomas are subretinal and are rarely surrounded by any significant degree of exudates.

3.4.6 Treatment of Vasoproliferative Tumors

3.4.6.1 Observation

Small peripheral vasoproliferative retinal tumors, lacking significant exudate or maculopathy, can be managed by periodic observation. If the lesion is symptomatic or associated with a significant amount of exudate or detachment, then treatment is warranted.

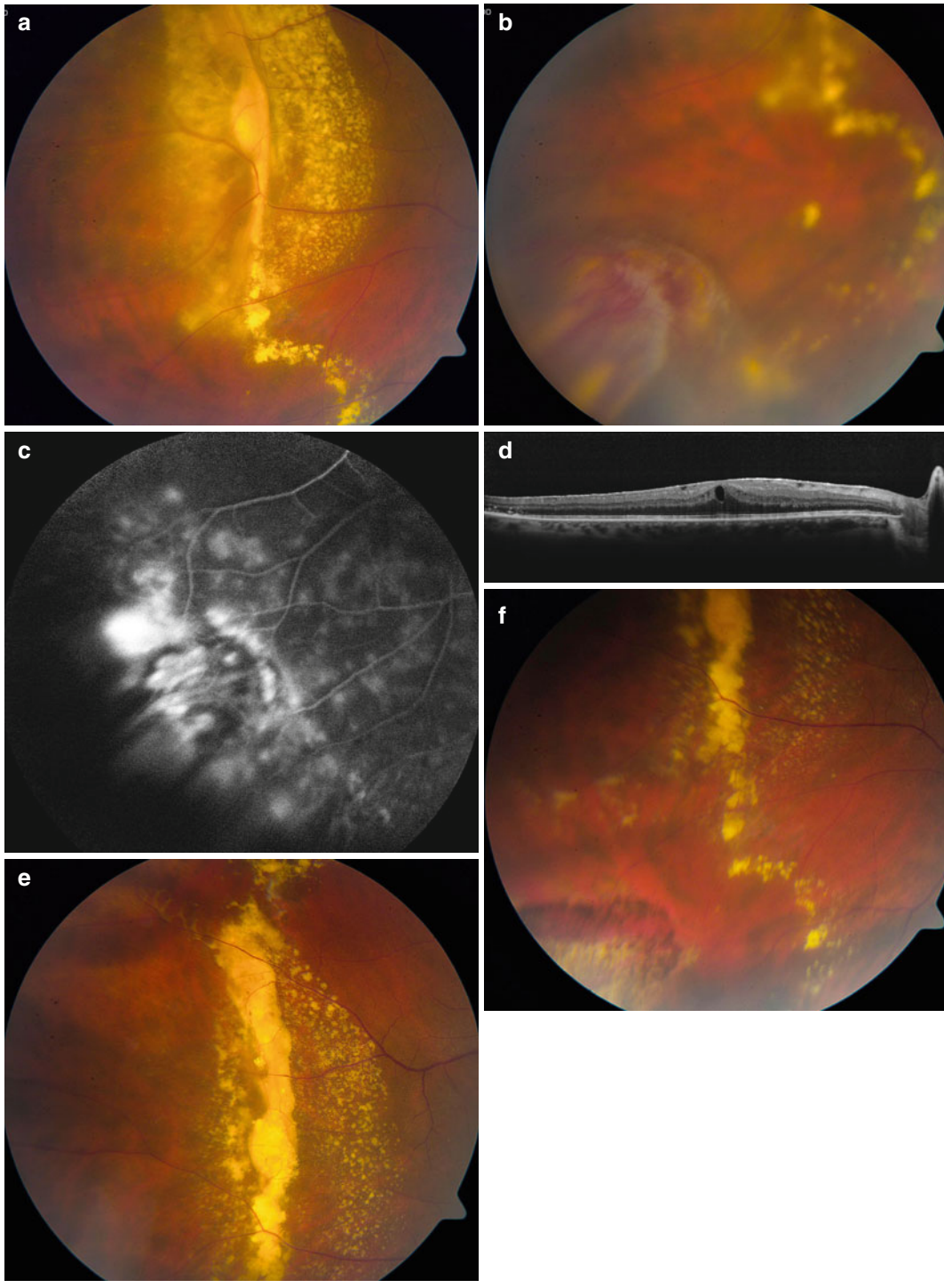

Fig. 3.7 Fundus appearance of a retinal vasoproliferative tumor. Note prominent retinal lipid exudation and bullous exudative retinal detachment (**a**). The vasoproliferative tumor appears as a globular yellowish-pink vascular mass in the peripheral retina (**b**). Diffuse hyperfluorescence in the late phase of the fluorescein angiogram (**c**) and secondary epiretinal membrane (**d**). Six weeks after cryotherapy, there is resolution of lipid exudation, bullous exudative retinal detachment, (**e**) and resolution of the peripheral tumor (**f**)

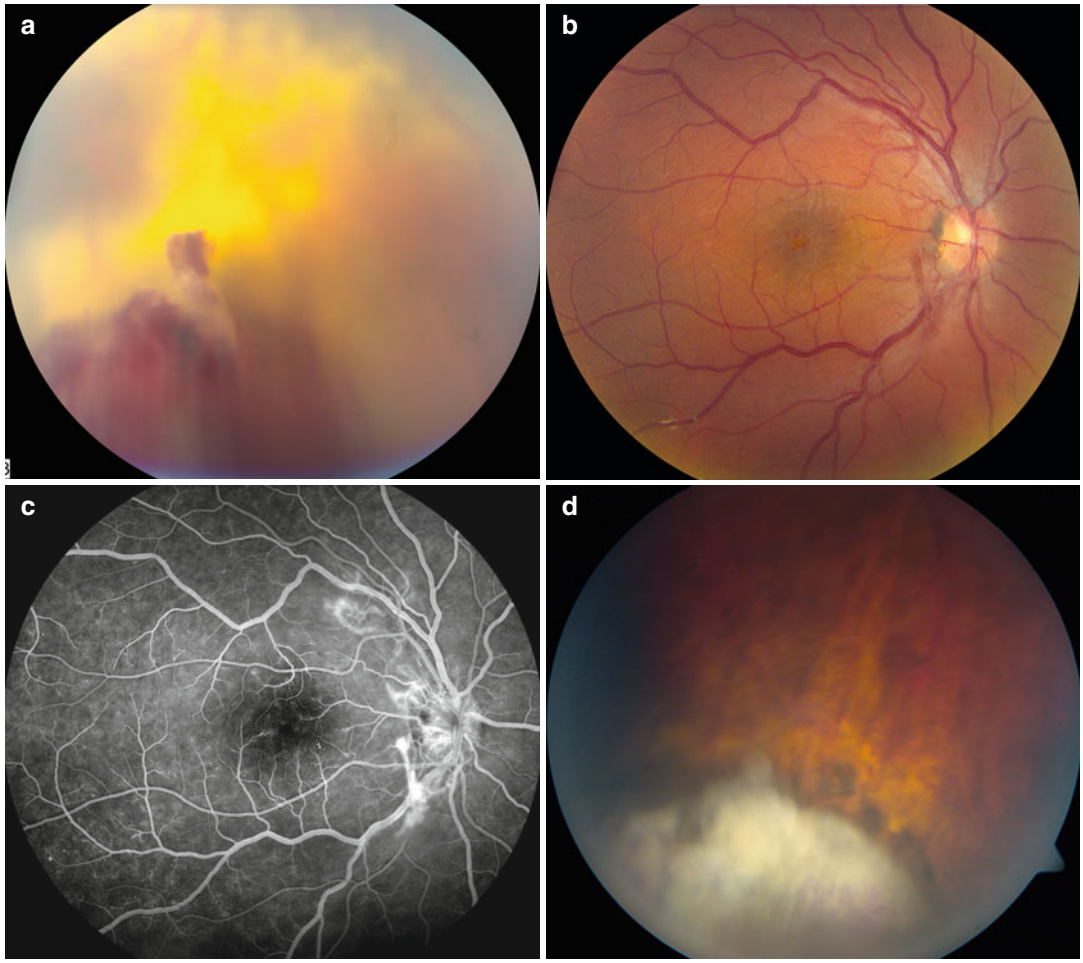

Fig. 3.8 Fundus appearance of a retinal vasoproliferative tumor. Note prominent retinal lipid exudation and peripheral hemorrhagic tumor (**a**). Following treatment with plaque radiation therapy (35 Gy), there was increase in secondary epiretinal membrane (**b**) with onset of retinal neovascularization (**c**) necessitating intravitreal injection of bevacizumab (1.25 mg. 0.05 ml). Four weeks later, the tumor appeared totally avascular and gliotic (**d**)

3.4.6.2 Cryotherapy

Vasoproliferative retinal tumors can be treated successfully with triple freeze-thaw transconjunctival cryotherapy, although repeat treatments may be required (Fig. 3.7) [9]. However, a large tumor may require heavy cryotherapy which in turn can result in significant complications and such tumors are probably best managed by other treatment modalities.

3.4.6.3 Plaque Brachytherapy

Large lesions can be managed effectively using either ruthenium or iodine plaque brachytherapy (Fig. 3.8) [9, 43–45].

3.4.6.4 Photothrombotic and Photodynamic Therapy

Indocyanine green-mediated photothrombotic therapy [46] and photodynamic therapy have

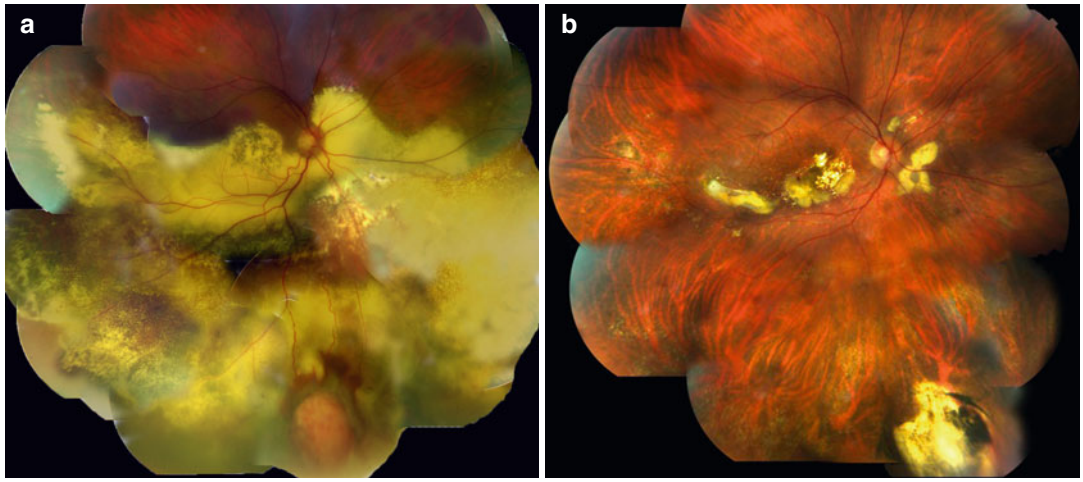

Fig. 3.9 31-year-old female patient presented with history of decreased vision (20/200) in her right eye. Fundus examination revealed a vasoproliferative tumor in the inferior nasal periphery, causing massive subretinal exudation extending to the macula (**a**). Ten months after treatment with indocyanine green-mediated photothrombosis (**b**). Note almost complete absorption of the exudates, RPE and choroidal atrophy, as well as RPE hyperplasia in the site of the lesion (Reproduced with permission from Bertelli and Pernter [46])

been shown to be effective in the treatment of vasoproliferative tumors (Fig. 3.9) [47, 48].

3.4.6.5 Anti-VEGF Agents

May be used as an adjunct to cryotherapy (Figs. 3.8 and 3.10) [49, 50].

3.4.7 Association with Vasoproliferative Tumors

About 25 % of all vasoproliferative tumors are secondary to a preexisting congenital, inflammatory, vascular, traumatic, dystrophic, and degenerative ocular disease such as intermediate uveitis, retinitis pigmentosa, and ocular toxoplasmosis [9]. Rare occurrence in monozygotic twins [51], Waardenburg syndrome [52], and neurofibromatosis 1 [50] and possible association with systemic hypertension and hyperlipidemia have been reported (Fig. 3.8) [9].

3.4.8 Prognosis

In a large series of 103 patients, up to one-third of cases were initially managed by observation [9]. However, even small peripherally located vasoproliferative tumors may be associated with a significant loss of vision. Advanced cases can progress to neovascular glaucoma requiring enucleation.

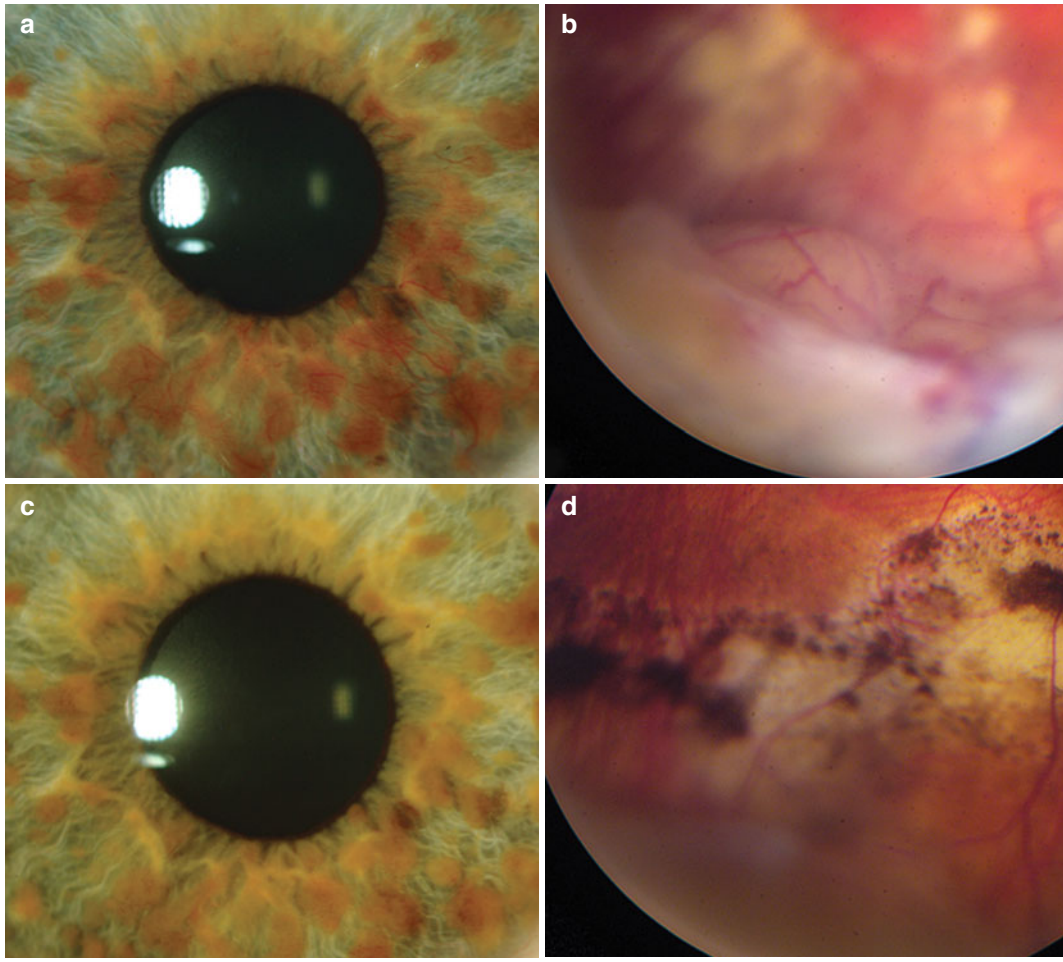

Fig. 3.10 Slit lamp photograph of the right eye at presentation demonstrating multiple Lisch nodules and florid neovascularization of the iris (**a**). On gonioscopic examination, there was 360° neovascularization of the angle. In the inferior fundus, there was a pink, elevated vascular mass with surrounding lipid exudate, consistent with vasoproliferative tumor (**b**). After treatment with cryotherapy and two intravitreal injections of bevacizumab, the neovascularization of the iris resolved almost completely (**c**). The vasoproliferative tumor appeared less vascular with chorioretinal atrophy and hyperpigmentation of the posterior margin (**d**). Note resolution of lipid exudates (Reproduced with permission from Hood et al. [50])

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Retinal Astrocytic Tumors

4

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4.1 Introduction

Retinal astrocytic tumors are benign tumors representing two clinical types: astrocytic hamartoma and "acquired" retinal astrocytoma. Retinal astrocytic hamartomas are frequently associated with tuberous sclerosis complex (TSC). "Acquired" retinal astrocytomas are rare astrocytic tumors that develop in somewhat older individuals who have no clinical manifestations of TSC or other systemic syndromes.

4.2 Retinal Astrocytic Hamartoma

Astrocytic hamartomas of the retina and optic nerve typically occur in patients with TSC (Bourneville's disease) and may also rarely be found in patients with neurofibromatosis (von Recklinghausen's disease) or retinitis pigmentosa [1, 2]. Retinal astrocytic hamartoma is generally believed to be congenital in most cases, but may occasionally arise de novo (Fig. 4.1).

4.2.1 Pathogenesis and Pathology

Recent genetic analysis has identified two distinct variants of TSC, which result from mutations in the *TSC1* gene on chromosome 9q34 and the *TSC2* gene on chromosome 16p13 [3, 4]. *TSC1* and *TSC2* encode hamartin and tuberin, respectively, both of which are expressed in a

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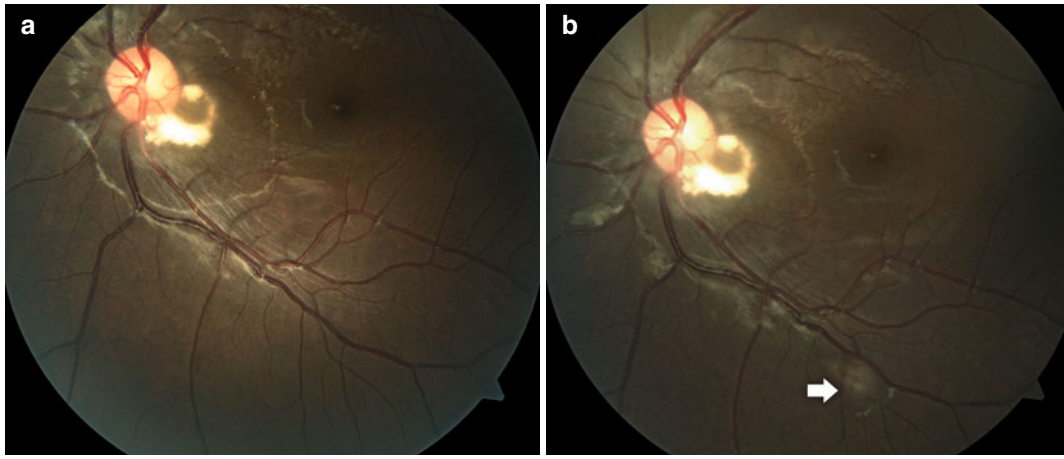


Fig. 4.1 Fundus appearance of a 10-year-old girl with tuberous sclerosis complex. Note retinal astrocytic hamartoma adjacent to optic nerve head with central calcification resembling mulberries (**a**). After 6 months, a new flat, smooth, semitranslucent lesion (*white arrow*), which was not evident previously became noticeable (**b**)

wide variety of normal human tissues including astrocytes and are involved in regulation of cellular growth [5, 6]. Due to mutations in these genes, undifferentiated glioneurocytes within the developing retina may give rise to retinal astrocytic hamartoma. The mutation of the *TSC*2 gene is more frequently associated with astrocytic hamartoma than *TSC*1 gene mutations [7].

Histopathologically, these tumors are usually composed of elongated fibrous astrocytes that have small oval nuclei and interlacing cytoplasmic processes. Others may be composed of large pleomorphic astrocytic cells. Some tumors may exhibit histopathological similarities to Müller cells, suggesting a possible Müller cell origin [8]. Blood vessels and areas of calcification, often in the form of calcospherites, can be present. Mitotic figures are extremely rare.

4.2.2 Clinical Features

4.2.2.1 Symptoms

Patients are often asymptomatic and tumors are detected as part of screening for TSC. Visual symptoms can be caused by macular involvement, tumor growth, vitreous hemorrhage, vitreous seeding and vitritis, or intraretinal and subretinal exudation [9–12].

4.2.2.2 Signs

Ophthalmoscopically, the tumor can exhibit considerable variation in appearance. In general, three basic morphological types have been recognized: (1) relatively flat, smooth, noncalcified, and semitranslucent lesions; (2) large, elevated, nodular, calcified lesions resembling mulberries; and (3) a mixed type of lesion possessing features of the previous two types, being calcified in the central portion and semitranslucent in the periphery (Fig. 4.2a) [13–16]. The first type is the most common, followed by the second and third. All three morphological types may be seen in the same patient.

4.2.3 Diagnostic Evaluation

In the majority of cases, diagnosis of retinal astrocytic hamartoma can be made with indirect ophthalmoscopy and a search for various manifestations of TSC, including the classic triad of seizures, mental deficiency, and sebaceous adenoma (fibroangiomas) (Chap. 9). However, fluorescein angiography, fundus autofluorescence, ultrasonography, and optical coherence tomography (OCT) can be useful ancillary studies, especially in subtle type 1 lesions (Box 4.1).

4.2.4 Salient Diagnostic Findings (Box 4.1)

- Single or multiple, circumscribed, semitranslucent round retinal lesion
- Single or multiple, large, elevated, nodular, and calcified mulberry lesion
- Absent or minimal retinal exudation or subretinal fluid surrounding the lesion
- Absence of prominent feeder vessels extending from the optic disc
- Prominent network of fine retinal vessels on fluorescein angiography
- Lack of growth over short periods of observation (weeks to months)

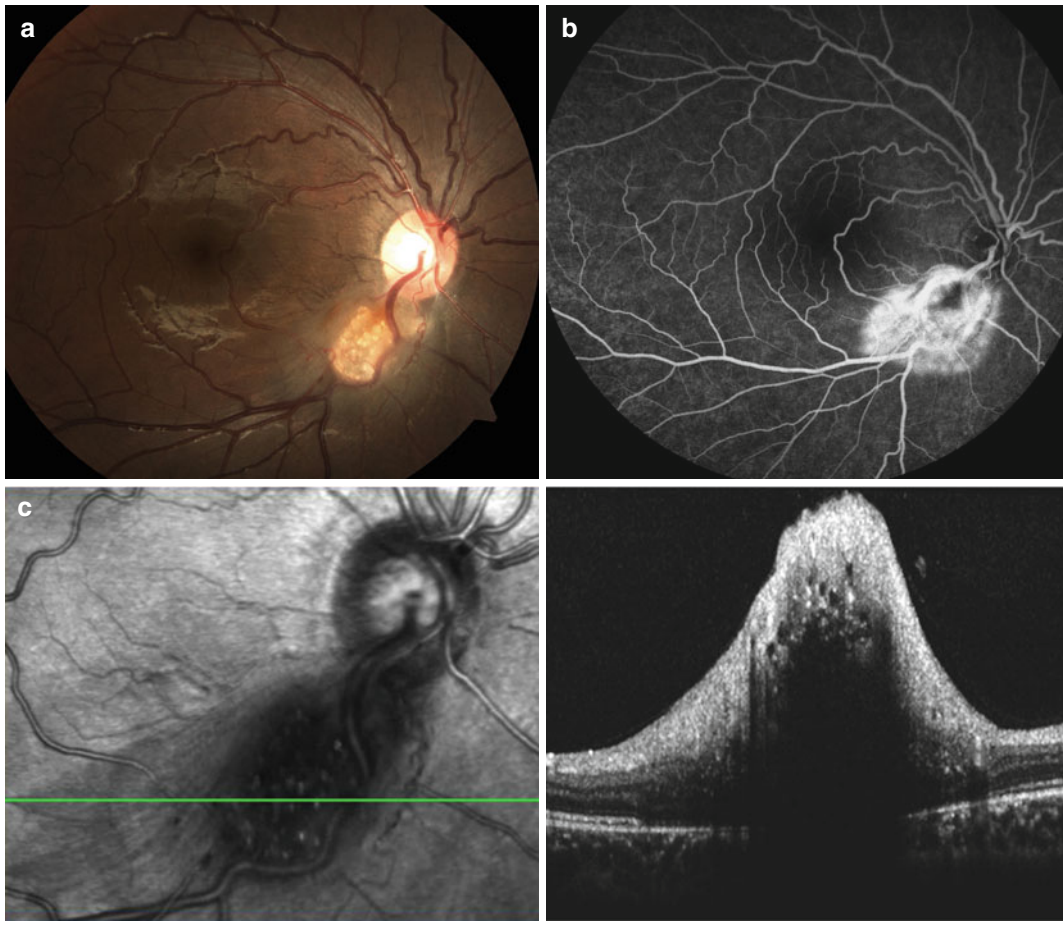


Fig. 4.2 Fundus appearance of a typical retinal astrocytic hamartoma. Note central area of calcification and peripheral semitranslucent noncalcified region (**a**). Late-phase fluorescein angiogram, showing relatively intense hyperfluorescence of the lesion due to leakage of dye from the tumor vessels (**b**). Spectral-domain optical coherence tomography imaging of the retinal astrocytic hamartoma showing thickening of retinal nerve fiber layer with posterior shadowing. Note the "moth-eaten" empty spaces that may represent intralesional calcification (**c**). Fundus autofluorescence imaging (confocal scanning laser ophthalmoscope, Heidelberg Retina Angiograph, Heidelberg Engineering, Heidelberg, Germany) showing strong autofluorescence of the central calcified multinodular part of the tumor with reduced autofluorescence of the peripheral semitranslucent rim (**d**)

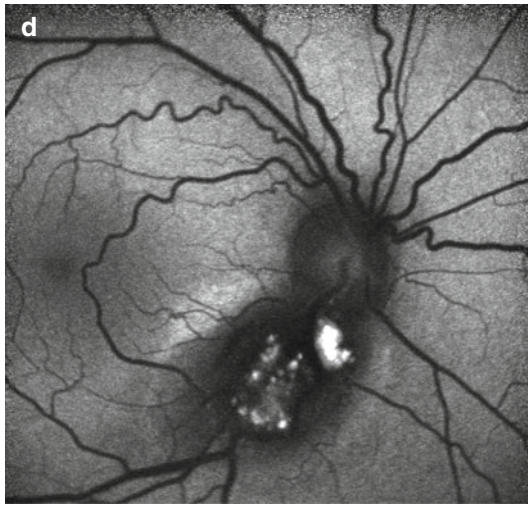


Fig. 4.2 (continued)

Fluorescein angiography of retinal astrocytic hamartoma shows a prominent superficial network of fine vessels in the arterial phase with leakage in the venous phase (Fig. 4.2b). Late angiograms show intense diffuse homogenous staining of the mass.

Fundus autofluorescence imaging can aid visualization of tumors. Type 1 tumors show reduced autofluorescence, resulting from absence of autofluorescence from the tumor and its blockade of background physiologic autofluorescence. Smaller lesions may not show hypoautofluorescence and elude detection, possibly due to insufficient mass effect to block the background autofluorescence. Calcified type 2 tumors are highly autofluorescent. Type 3 tumors show increased autofluorescence of the central calcified portion of the tumor and reduced autofluorescence of the peripheral semitranslucent rim, resulting in a contrast between the two tumor compartments (Fig. 4.2c) [17].

Ultrasonography is not generally useful for small, noncalcified type 1 tumors. However, due to calcification within the mass, larger calcified lesions can show characteristic features, including acoustic shadowing, on B-scan ultrasonography (Fig. 4.3). A-scan ultrasonography shows a sharp anterior border, high internal reflectivity, and attenuation of orbital echoes posterior to the tumor.

Spectral-domain OCT offers superior resolution and enhanced tissue penetration in visualizing theretinal location of the tumor and ascertain the reason for visual loss. The retinal astrocytic hamartoma shows thickening of the retinal nerve fiber layer using OCT, which can compress the inner retinal layer. Large calcified tumors often show multifocal, round, confluent "moth-eaten" empty spaces with posterior shadowing, which may represent calcification foci or intratumoral cavities (Fig. 4.2d) [18, 19].

4.2.5 Differential Diagnosis

Despite the characteristic ophthalmoscopic features listed above, certain entities can closely resemble astrocytic hamartoma. Retinoblastoma, retinocytoma, myelinated nerve fibers, massive gliosis of the retina, retinal capillary hemangioma, and optic disc drusen can be difficult to differentiate ophthalmoscopically from astrocytic hamartoma (Table 4.1).

Small retinoblastomas can have a similar translucent appearance as astrocytic hamartomas, and both lack calcification when small. When calcification is present, it can demonstrate subtle differences, as it tends to be dull and chalky white in a retinoblastoma. The calcification in an astrocytic hamartoma is more of a glistening yellow, resembling fish eggs. In addition, dilated, tortuous retinal feeder vessels are more common in retinoblastomas. A larger retinoblastoma often produces vitreous or subretinal seeding and exudative retinal detachment, which rarely occurs in astrocytic hamartoma. However, the presence of a hard exudates supports the diagnosis of astrocytic hamartoma rather than retinoblastoma. Fluorescein angiography may be helpful in correct diagnosis because the blood vessels are of normal caliber in astrocytic hamartoma, which is in contrast to retinoblastoma. In doubtful cases, close follow-up over several weeks will demonstrate stability

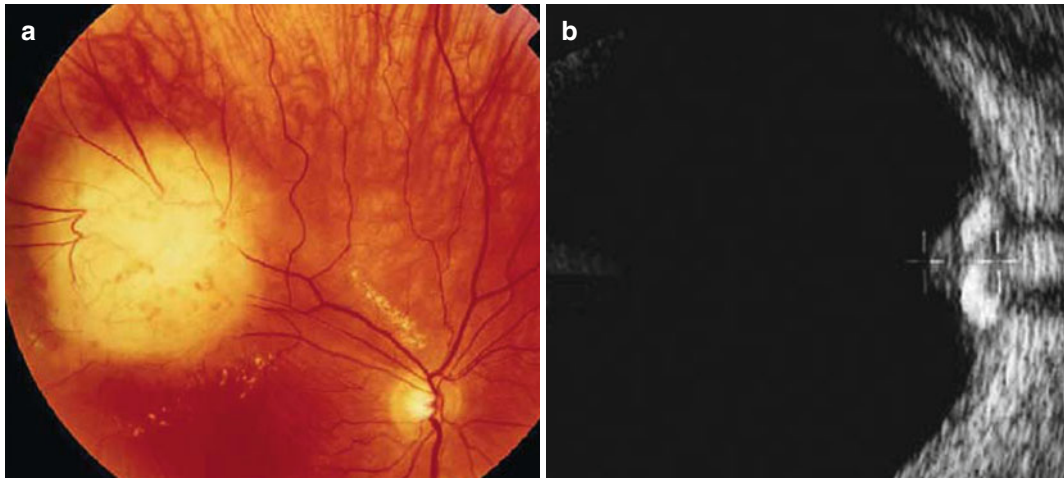


Fig. 4.3 Fundus appearance of calcified large astrocytic hamartoma. Note surrounding retinal exudation (**a**). B-scan ultrasonography indicative of intrinsic calcification (**b**) (Reproduced with permission from Giles et al. [9])

Table 4.1 Differential diagnosis of astrocytic hamartoma

Diagnosis	Appearance	Calcification	Feeder vessels	Exudation	RPE	Growth[a]	Association
Astrocytic hamartoma	Translucent or white mass	Present; yellow, spherical	Absent	Usually absent	Normal	Absent	Tuberous Sclerosis
Retinoblastoma Retinocytoma	White mass	Present; white, chunky	Present Absent	Absent Absent	Normal Proliferation	Present Absent	13 q deletion syndrome
Myelinated nerve fibers	White patch, no mass	Absent	Vessels obscured	Absent	Normal	Absent	None
Massive gliosis of retina	White mass	May be present	Absent	May be present	Atrophy and proliferation	Absent	None
Retinal capillary hemangioma	Round red mass	Absent	Prominent	Present	Normal	May be present	VHL disease
Optic disc drusen	White nodular mass	Present	Absent	Absent	Normal	Absent	Retinitis pigmentosa

RPE retinal pigment epithelium, *VHL* von Hippel-Lindau disease
[a]Short-term growth observed over weeks to months

in astrocytic hamartoma and growth in retinoblastoma [15, 20].

Retinocytoma, a benign counterpart of retinoblastoma can also closely resemble astrocytic hamartoma because both lesions may be calcified. Surrounding retinal pigment epithelial alterations are a common finding in retinocytoma, which are typically absent in astrocytic hamartoma because it is situated superficially in the retina.

Myelinated nerve fibers sometimes can mimic a small astrocytic hamartoma. However, myelinated nerve fibers are usually located at or adjacent to the optic disc margin, show a more

fibrillated margin, are flat without any elevation, and are not calcified.

Massive gliosis of the retina can be difficult to differentiate clinically from an astrocytic hamartoma, but prior history of ocular inflammation or trauma and a more degenerated eye are important clues.

Some astrocytic hamartomas have prominent vascularity, which makes the differentiation from retinal capillary hemangioma difficult. However, a capillary hemangioma is usually red or pink (rather than white), has dilated tortuous retinal feeder vessels, is more likely to produce retinal exudation, and is noncalcified.

The similarity between optic disc drusen and optic disc astrocytic hamartoma can be so great that the term "giant drusen" has been used to describe the calcified astrocytic hamartoma seen with tuberous sclerosis [21]. Although drusen of the optic disc show distinct calcification, they are usually bilateral and lie within the disc, whereas the calcified astrocytic hamartoma is characteristically unilateral, protrudes above the optic disc, and obscures the disc and retinal blood vessels.

4.2.6 Treatment of Astrocytic Hamartoma

The majority of retinal astrocytic hamartomas are small, extrafoveal, and stationary, so treatment is usually unnecessary. However, periodic ocular examination is warranted, as some tumors may demonstrate progressive enlargement, calcification, and vision-threatening complications, including vitreous hemorrhage, vitritis and vitreous seeding, or intraretinal and subretinal exudation.

The exudative complications can be self-limited within a few weeks [22]. However, photocoagulation, photodynamic therapy (using verteporfin), transpupillary thermotherapy, brachytherapy, intravitreal bevacizumab, vitrectomy, or endoresection could be considered in cases with persistent, progressive, and fovea-involving exudation (Fig. 4.4) [23–31].

Vitreous hemorrhage may spontaneously resolve, but persistent or recurrent hemorrhage can be managed with vitrectomy [12, 32, 33]. More aggressive cases showing progressive growth, tumor seeding, and neovascular glaucoma have been managed by enucleation [34, 35].

4.2.7 Association with Tuberous Sclerosis

Retinal astrocytic hamartomas are seen in approximately half of patients with TSC, but variability in frequency exists with studies reporting ranges from 34 to 87 % (Chap. 9) [7, 13, 14, 16, 36, 37]. When present, retinal astrocytic hamartomas are bilateral in about half and multiple in about one-third to half of patients [7, 13, 16, 36]. Some patients show only a retinal tumor without additional findings of TSC. It can be the first clinical manifestation of TSC or may represent a forme fruste of TSC.

In some patients with TSC, retinal achromic patches have also been observed, with frequencies ranging from 8 to 39 % [16, 38, 39]. They can look diffusely hypopigmented or they can be surrounded by some degree of pigment proliferation.

4.2.8 Prognosis

Most astrocytic hamartomas remain stable and do not cause complications. Occasionally, however, gradual enlargement and calcification of these tumors may be seen, particularly in younger patients [13]. In rare instances, they can show progressive growth with degenerative necrosis, leading to vitreous seeding, vitreous or subretinal hemorrhage, subretinal exudation or detachment, and neovascular glaucoma [11, 27, 31, 34, 40, 41]. New lesions may

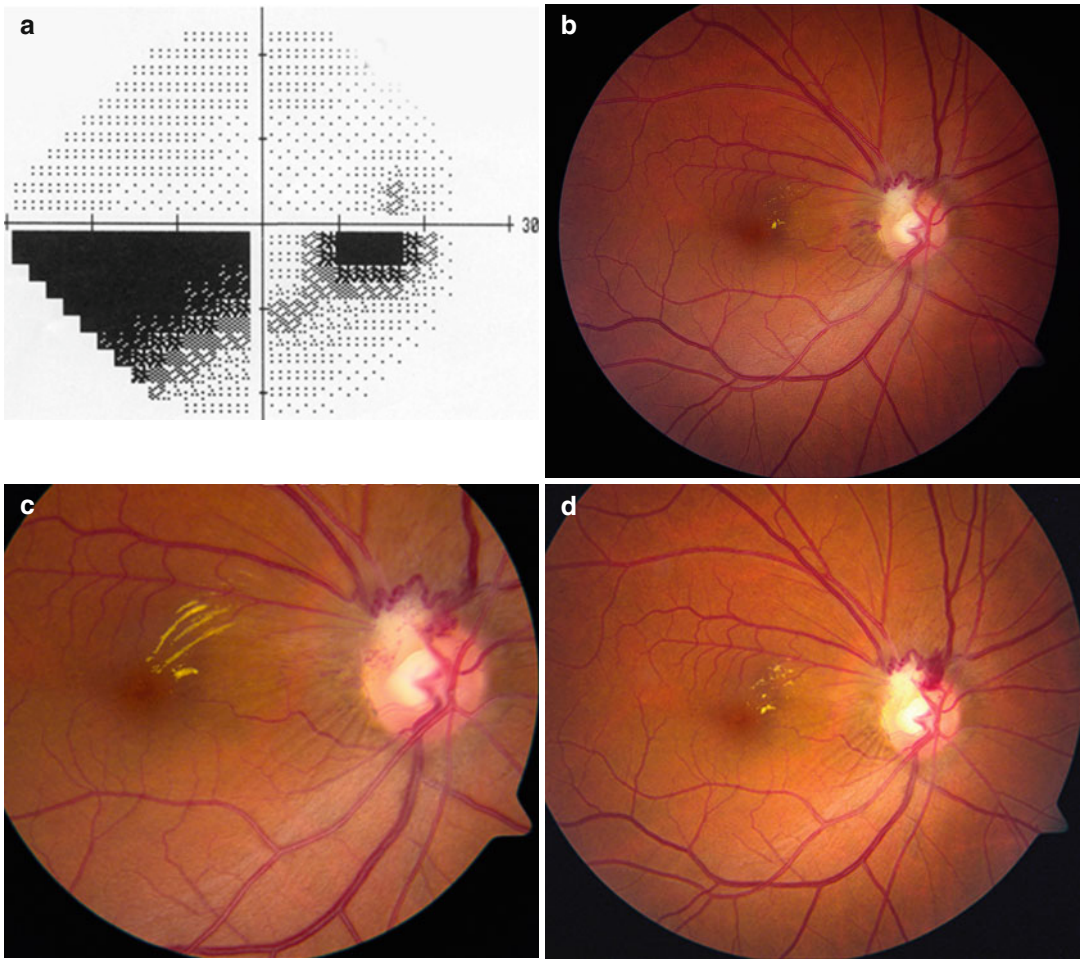


Fig. 4.4 A 45-year-old Caucasian female with an unremarkable past medical history was referred for evaluation of a peripapillary tumor associated with a scotoma in the right eye (**a**). On initial evaluation, visual acuities (VA) were 20/20 in both eyes. An ill-defined, translucent, yellow-white superficial mass along the superotemporal margin of the optic disc and extending into the retina was observed (**b**). Prominent intrinsic vessels as well as dilated collateral vessels were present. The macula was flat; however, lipid exudates were present superonasal to the fovea, and a few retinal striae were noted in the papillomacular area. Based on morphological characteristics, the diagnosis of retinal astrocytoma was made with a decision to observe for progression. At a 6-month visit, VA remained 20/20; however, the lipid exudates were noted to be approaching the foveola (**c**). Four months after two sessions of standard-fluence photodynamic therapy (TAP, 1.5-mm spot covering the entire tumor up to the superotemporal edge of the optic disc), VA remained 20/15, the lipid exudates were diminished, and some gliosis of the tumor could be appreciated (**d**) (Reproduced with permission from Singh [47])

develop from previously normal-appearing retina [15]. Spontaneous regression of retinal astrocytic hamartoma has been reported [42, 43]. In general, astrocytic hamartomas are silent with an excellent visual prognosis. They are not known to undergo malignant transformation and have no tendency to metastasize (Box 4.2).

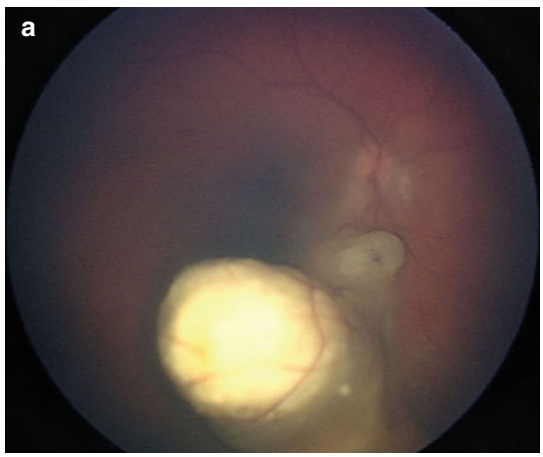
4.2.9 Clinical Features of Retinal Astrocytic Tumors (Box 4.2)

- Retinal astrocytic tumors are benign tumors representing two clinical types: (1) astrocytic hamartoma that is frequently associated with tuberous sclerosis complex, (2) acquired retinal astrocytoma.
- Three basic morphological types have been recognized for astrocytic hamartoma: (1) relative flat, semitranslucent, noncalcified lesion; (2) nodular, elevated, calcified lesion; and (3) a mixed type of (1) and (2).
- Tumor occurrence, growth, and calcification can be seen during follow-up.
- Malignant transformation or metastasis is not known.
- In general, visual prognosis is excellent and treatment is unnecessary, unless complicated by vitreous hemorrhage, exudation, or relentless tumor growth.

4.3 Acquired Astrocytoma

Retinal astrocytic hamartoma associated with TSC accounts for the majority of retinal astrocytic tumors. Occasionally, however, an "acquired" astrocytoma can develop at any age, without family history or association with TSC or other systemic syndromes (Fig. 4.5). The exact incidence of this rare tumor is not known, and it has been described in only a few reports [35, 41, 44–46].

An acquired astrocytoma typically begins as a solitary white to fleshy-pink intraretinal mass, usually in the posterior pole near the optic disc. Acquired retinal astrocytoma seems to have a propensity for progressive and relentless tumor enlargement, causing local complications. The true pathogenesis of acquired retinal astrocytoma is not known. It apparently arises from either typical retinal astrocytes or Müller cells. In most reported cases, the affected eye has been enucleated because of growth, secondary glaucoma, and/or suspicion that the tumor may be a uveal melanoma or retinoblastoma. The best management strategies have not been well established. Radiotherapy may prove useful in rare cases where diagnosis is established by a needle biopsy.



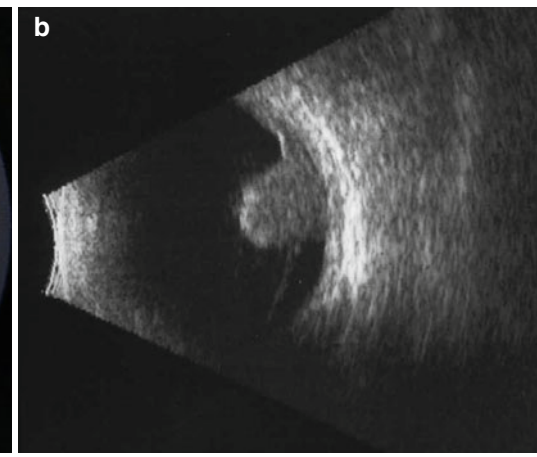
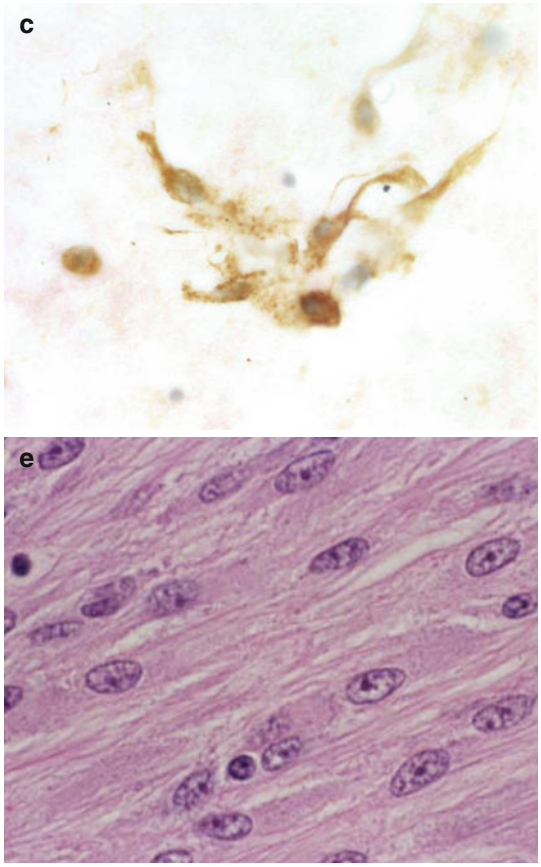


Fig. 4.5 A 5-year-old boy with a multilobulated white-gray retinal mass with overlying vitreous seeding (**a**). Ocular ultrasound examination showed a mushroom-shaped lesion measuring 9.0 mm in thickness (**b**). Note absence of tumor calcification. Cytopathologic analysis after fine-needle aspiration biopsy revealed slender cells with benign features that stained positively for vimentin and glial fibrillary acidic protein, consistent with retinal astrocytoma (**c**). Progressive tumor growth prompted enucleation. The gross specimen contained a homogeneous multilobulated retinal mass without optic nerve invasion (**d**). Histopathologic analysis revealed large glial cells with fibrillar cytoplasm and absence of mitotic figures (**e**) (Reproduced with permission from Cohen et al. [40])



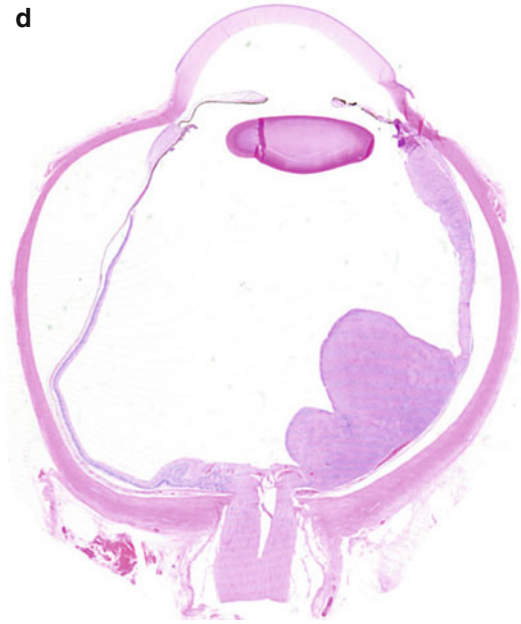


Fig. 4.5 (continued)

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Retinal Pigment Epithelial Tumors

5

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Tumors of the retinal pigment epithelium (RPE) can be congenital or acquired. They may also be classified as reactive, hypertrophic, hamartomatous, and neoplastic (Table 5.1) [1]. Those present at birth can be associated with systemic conditions such as familial adenomatous polyposis (FAP) or neurofibromatosis 2 (NF2). Acquired RPE tumors include benign and malignant lesions that are sometimes difficult to differentiate from choroidal neoplasms without ancillary tests such as ultrasonography, optical coherence tomography, and fluorescein angiography. In this chapter

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Table 5.1 Classification of RPE lesions

Type	Subtype	Variants	Other terminology	Association
Reactive	Hyperplasia Metaplasia			Trauma Inflammation Toxicity
Hypertrophic	Solitary	Pigmented Nonpigmented	Retinal nevus Benign melanoma of RPE	None
	Grouped	Pigmented Nonpigmented	Bear tracks Polar bear tracks	None
	POFLs		Atypical CHRPE	Gardner syndrome Turcot syndrome
Hamartoma	RPE	Superficial Full thickness With intrinsic vascularization	Congenital hamartoma	None
	RPE and retina		Combined hamartoma	Neurofibromatosis type 2
Neoplastic	Adenoma Adenocarcinoma			CHRPE (rare)

RPE Retinal pigment epithelium, *CHRPE* Congenital hypertrophy of retinal pigment epithelium, *POFLs* Pigmented ocular fundus lesions

we review the clinical features of congenital and acquired tumors of the RPE and their systemic associations.

5.1 Congenital Hypertrophy of the RPE (CHRPE)

5.1.1 Introduction

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is a round, darkly pigmented, flat lesion of the ocular fundus located at the level of the retinal pigment epithelium (Fig. 5.1). In the older literature, CHRPE was classified as a benign melanoma of the retinal pigment epithelium [2].

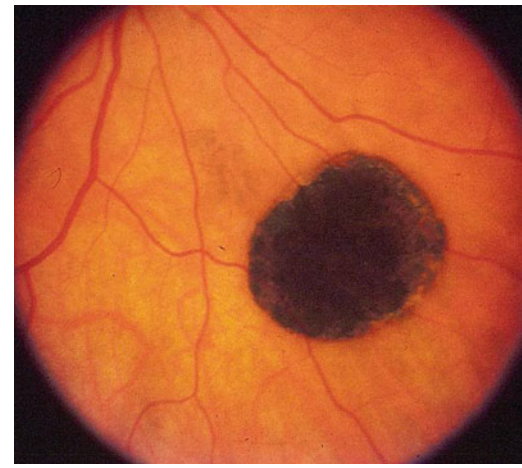


Fig. 5.1 Solitary CHRPE. A sharply demarcated pigmented flat retinal lesion representing solitary CHRPE. The lighter area represents lacunae which may enlarge slowly over many years

5.1.2 Etiology and Pathogenesis

Isolated, CHRPE lesions are sporadic and congenital, with no known underlying genetic basis.

5.1.3 Pathology

Histopathologically, isolated CHRPE lesions consist of a layer of hypertrophied RPE cells containing excessive pigment granules (Fig. 5.2) [3]. The underlying choriocapillaris and choroid are normal. The photoreceptor layer overlying the abnormal RPE may be normal or may be atrophic, causing a scotoma. The RPE cells contain granules of pigment that resemble melanin in the absence of lipofuscin, suggesting the inability of these RPE cells to perform their normal phagocytic function, leading perhaps to the associated photoreceptor degeneration [4]. In the areas of

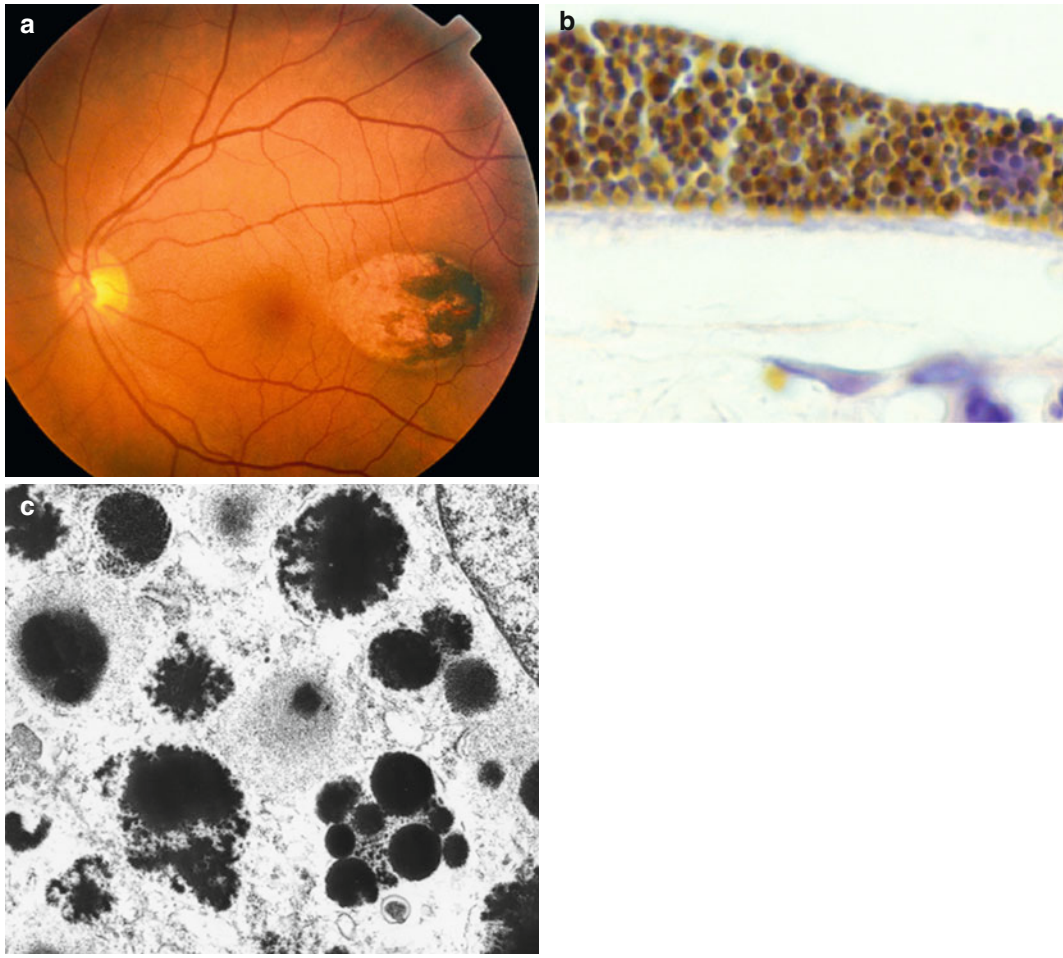


Fig. 5.2 A 62-year-old woman with a large ciliochoroidal melanoma (enucleated) and an elliptical retinal pigment epithelial lesion about 1 mm temporal to the foveola, in the horizontal meridian (**a**). The pathology of the "CHRPE" lesion varied across the lesion, correlating with the level of pigmentation. Highly pigmented temporal areas showed RPE hypertrophy. Thickened RPE cells showed some loss of nuclear basal polarity and were packed with variable numbers melanosomes in both apical and basal areas. (**b**, H&E × 500). Electron microscopy showing large, but fragmenting melanosomes (**c**, EM × 32000) (Reproduced with permission from Parsons et al. [3])

lacunae, RPE cells have reduced pigmentation or there may be drop out of RPE cells [3]. In these areas glial cells are present between Bruch's membrane and the RPE. The histopathology of CHRPE lesions has been studied in newborns, documenting the congenital nature of these lesions and their pigmentation pattern [5].

5.1.4 Clinical Features

5.1.4.1 Symptoms

Patients with CHRPE are generally asymptomatic unless the macula is involved.

5.1.4.2 Signs

Ophthalmoscopically, CHRPE patches have round and sometimes scalloped edges and are generally located in the fundus periphery. A peripapillary location is less common. The lesion is frequently surrounded by a hypopigmented halo and occasionally by a hyperpigmented ring [4]. Punched-out hypopigmented or depigmented lacunae may be present, and occasionally the whole CHRPE patch is depigmented and is referred to as an albinotic patch of the peripheral fundus (Fig. 5.3) [6]. The retina and retinal vessels overlying the CHRPE appear normal except for occasional areas of focal intraretinal pigmentation. Atrophy

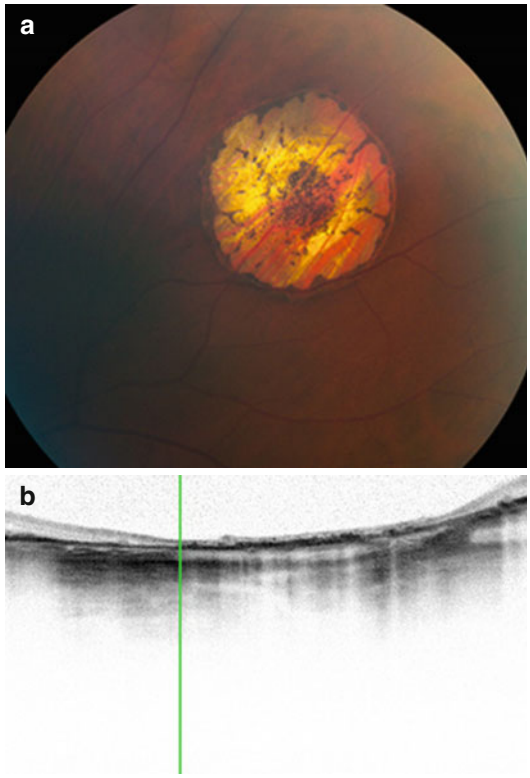


Fig. 5.3 Depigmented CHRPE. Fundus appearance (**a**). OCT reveals thickened retinal pigment epithelial layer and atrophy of the overlying retinal layers (**b**)

of the outer and, sometimes, inner retinal layers may be present, especially over larger lesions [4, 7]. Rarely, neovascularization has been noted in association with capillary and large vessel obliteration [8].

5.1.5 Diagnostic Evaluation

Visual field testing can map the scotoma associated with some CHRPE lesions. The scotoma is relative initially but may become absolute if photoreceptor atrophy occurs. ERG and EOG studies are normal in patients with CHRPE and in patients with familial adenomatous polyposis and multiple pigmented ocular fundus lesions (POFLs) [9]. OCT shows thickened RPE layer with atrophy of the overlying retina (Fig. 5.3). Hypertrophied RPE cells block choroidal fluorescence on angiography and no leakage of dye is observed (Fig. 5.4). The remainder of the normal appearing fundus has a normal fluorescein angiographic pattern.

5.1.6 Treatment

No treatment is necessary except for the very rare instance in which neovascularization develops at the edge of the CHRPE lesion [10].

5.1.7 Prognosis

CHRPE is a benign lesion that does not enlarge significantly except in very rare instances [11]. The significance and pathogenesis of minimal growth, observed in almost 50 % of the cases, are unclear [12]. The development of nodules at the edge of CHRPE lesions, suggestive of RPE adenoma, has also been observed [10, 13–15].

5.2 Congenital Grouped Pigmentation of the RPE

Multiple areas of circumscribed and flat retinal pigmentation that are arranged in clusters is described as congenital grouped pigmentation of the RPE [16]. The smaller lesions are located near the apex of the cluster closer to the posterior pole [16, 17]. Such an appearance is suggestive of animal footprints, so called bear tracks or animal tracks (Fig. 5.4) [16, 18]. Meyer et al. have suggested that the growth pattern of grouped CHRPE is similar to cutaneous sectorial pigmentations. They speculated that the sectorial distribution may reflect the migration of RPE cells during embryogenesis [19]. In the majority of cases, involvement is unilateral (84 %) and is limited

to one sector [17]. In contrast to isolated patches of CHRPE, there are no depigmented lacunae or overlying photoreceptor abnormalities in grouped pigmentation of the retina [18]. However, in rare instances, the lesions can lack pigmentation and appear albinotic (polar bear tracks) [1]. Although congenital grouped pigmentation of the RPE is not associated with FAP [16, 20], rare association with microcephaly has been reported [21].

5.3 Pigmented Ocular Fundus Lesions

5.3.1 Introduction

Pigmented ocular fundus lesions (POFLs) is a descriptive term that we have used to refer to fundus lesions observed in patients with FAP. It is preferred to use the term POFLs rather than CHRPE in FAP because, garden variety CHRPE

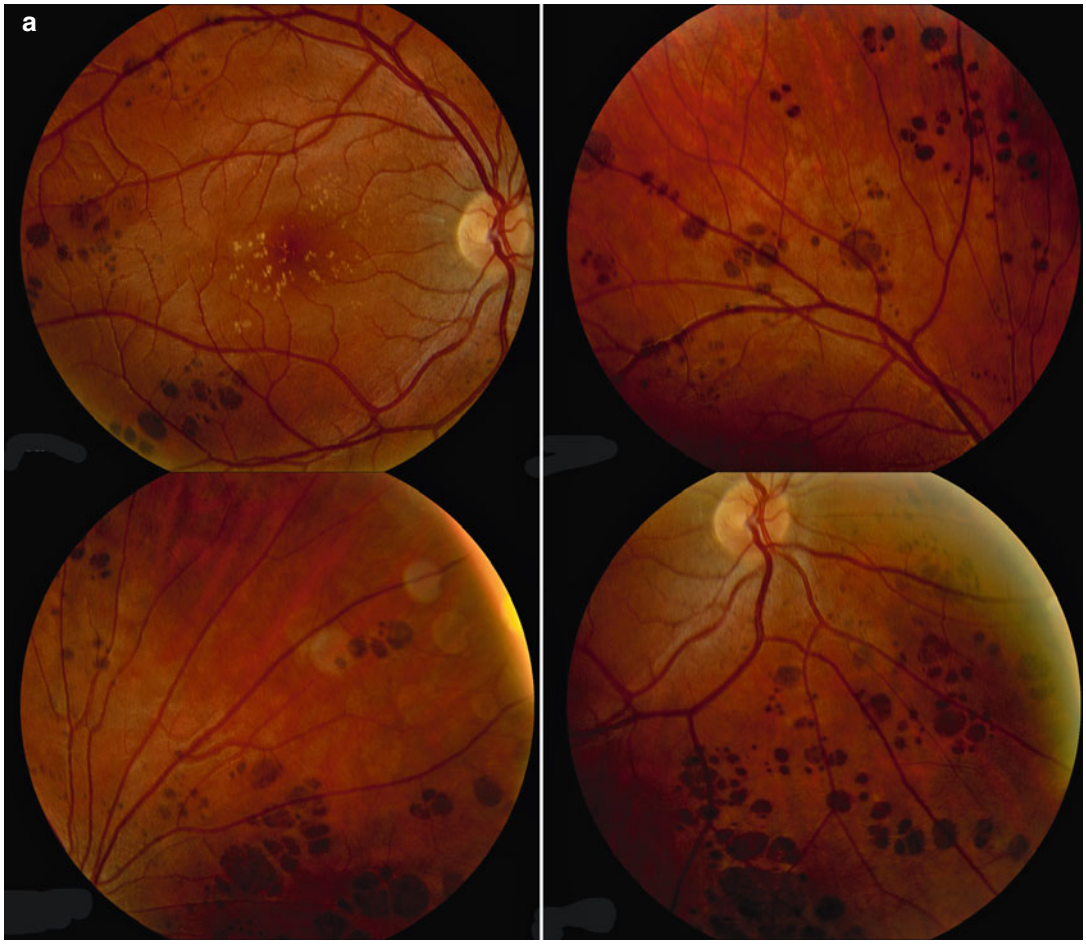


Fig. 5.4 A 28-year-old asymptomatic, Caucasian female demonstrated multiple small, flat, dark brown to black clusters of retinal pigment epithelium (RPE) hypertrophy on dilated fundus examination of the both eyes. These plaque-like lesions were circumferential along the peripheral fundus and were associated with smaller foci of pigmentation oriented towards to the posterior pole (**a**). The appearance was consistent with grouped pigmented CHRPE. A unique, coexisting feature was the presence of nonpigmented, punctate lesions located within the maculae suggestive of grouped nonpigmented CHRPE. Fluorescein angiography demonstrated persistent hypofluorescence correlating with the clinically observed areas of hyperpigmentation and hypopigmentation (**b**). Turell et al. [54]

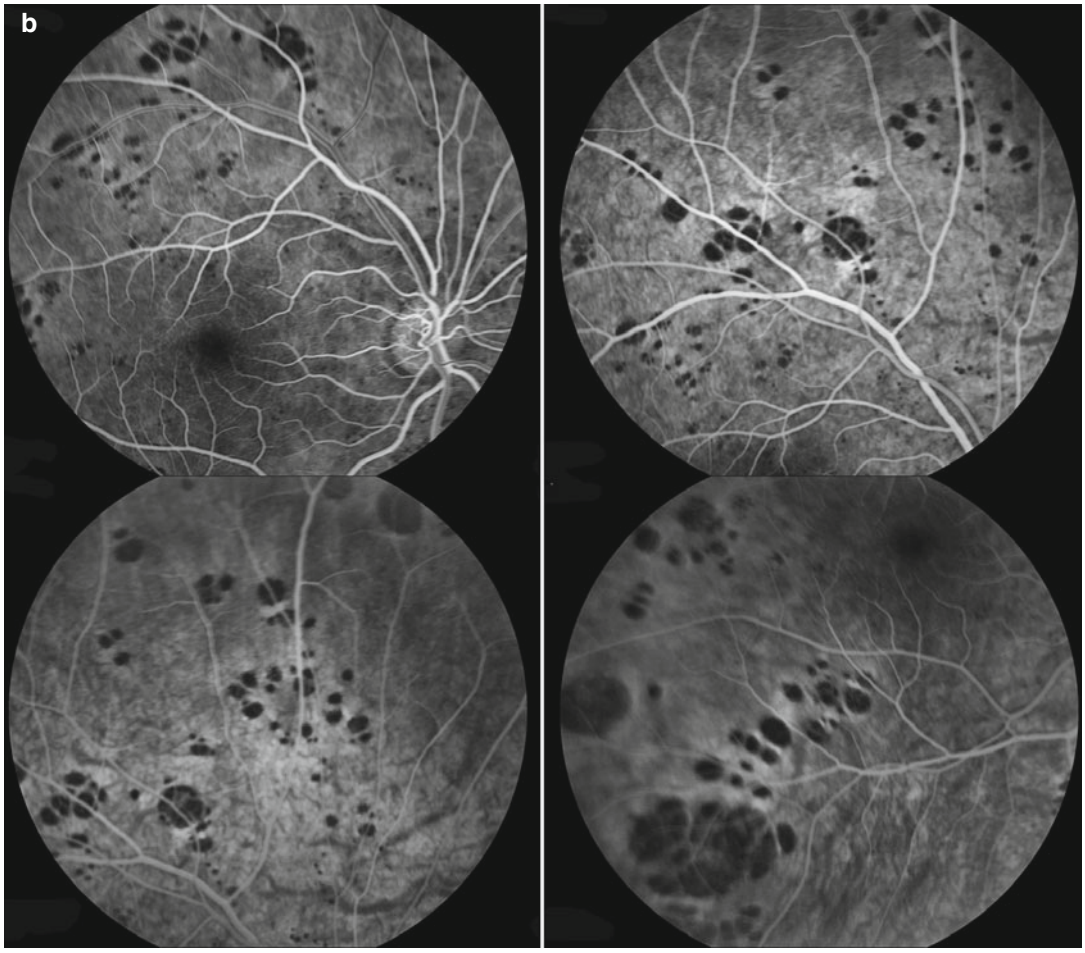


Fig. 5.4 (continued)

described above is generally not associated with FAP [20], there are distinct ophthalmoscopic features that distinguish CHRPE from lesions in FAP, and only some of the lesions have histopathologic characteristics compatible with CHRPE (Tables 5.2 and 5.3.) [22].

5.3.2 Etiology and Pathogenesis

The presence of multiple POFLs is highly specific (>90 %) and sensitive (70–80 %) marker for FAP [23]. Several hundred mutations have been described in the gene for FAP, designated as APC (adenomatous polyposis coli), which maps to chromosome 5q21-q22 [24]. Genotype-phenotype correlation has revealed that CHRPE and desmoid tumors are associated with FAP mutations between codons 311 and 1444 and after codon 1444, respectively [25].

5.3.3 Pathology

Histopathologic studies reveal diffuse RPE abnormalities in FAP, in addition to focal hyperpigmented lesions. RPE cells are hypertrophic and contain lipofuscin granules, multi-membranous inclusions, and macromelanosomes [22]. POFLs may be divided histopathologically into four types: (1) lesions consisting of a monolayer of hypertrophic RPE cells; (2) lesions composed of a small mound of two to three cell layers of RPE; (3) thick lesions, seven to eight cell layers high composed

Table 5.2 Histopathologic findings in variants of CHRPE

Type	RPE cells	Pigment granules			Other findings
		Size	Density	Shape	
Solitary	Hypertrophy Hyperplasia	Large Macromelanosomes	Increased	Spherical	Thickened Bruch's membrane Atrophic RPE (lacunae) Atrophic photoreceptors Absence of lipofuscin
Grouped	Normal	Large	Increased	Ellipsoid	Absent RPE hypertrophy Absent RPE hyperplasia Normal photoreceptors
Atypical	Hypertrophy Hyperplasia	Large	Increased	Spherical	RPE hamartoma Abnormal melanogenesis

RPE Retinal pigment epithelium, *CHRPE* Congenital hypertrophy of retinal pigment epithelium

Table 5.3 Relative differentiating features of CHRPE and POFLs

Feature	CHRPE	Grouped pigmentation	POFLs
Shape	Round	Variable	Oval
Depigmentation	Lacunae	Absent	Tail/lacunae
Size (basal diameter)	0.2–13 mm	Variable	0.15–4.5 mm
Laterality	Unilateral	Unilateral/bilateral	Bilateral
Number	Solitary or Grouped	Numerous	Four or more
Growth	Frequent but minimal	Unknown	Unknown
Malignant transformation	Rare	Never	Never
Histopathology (RPE changes)	Hypertrophy Hyperplasia	Hypertrophy	Hypertrophy Hyperplasia Hamartoma
Systemic association	None	Rare (microcephaly and other anomalies)	Gardner syndrome, Turcot syndrome

RPE Retinal pigment epithelium, *CHRPE* Congenital hypertrophy of retinal pigment epithelium, *POFLs* Pigmented ocular fundus lesions

of hyperplastic RPE cells; and (4) darkly pigmented lesions that occupy the full thickness of the retina and resemble RPE adenoma (Fig. 5.5). Hence, POFLs in FAP are probably better thought of as adenomas or hamartomas of the RPE.

5.3.4 Clinical Features

5.3.4.1 Symptoms

Patients with POFL are usually asymptomatic unless the macula is involved.

5.3.4.2 Signs

POFLs are present at birth in about three-quarters of patients. POFLs has been observed even in a preterm infant who was examined in the neonatal intensive care unit for retinopathy of prematurity [26]. They do not seem to increase in size or number with age, but no such data has been published.

Ophthalmoscopy underestimates the number of lesions because clinicopathologic correlation has revealed that almost three times more lesions were present histopathologically than were counted premortem (Fig. 5.5) [22]. We recommend a three-mirror contact lens exam to document all lesions. POFLs can take one of a number of several configurations. Very small (<0.1 disc diameter) round dark lesions are usually located in the peripheral fundus in the vicinity of vortex veins, while larger, more characteristic ovoid, tear-shaped or coffee bean-shaped lesions are located closer to the posterior pole (Fig. 5.5). Macular lesions have also been observed. Some POFLs have a hypopigmented halo and/or

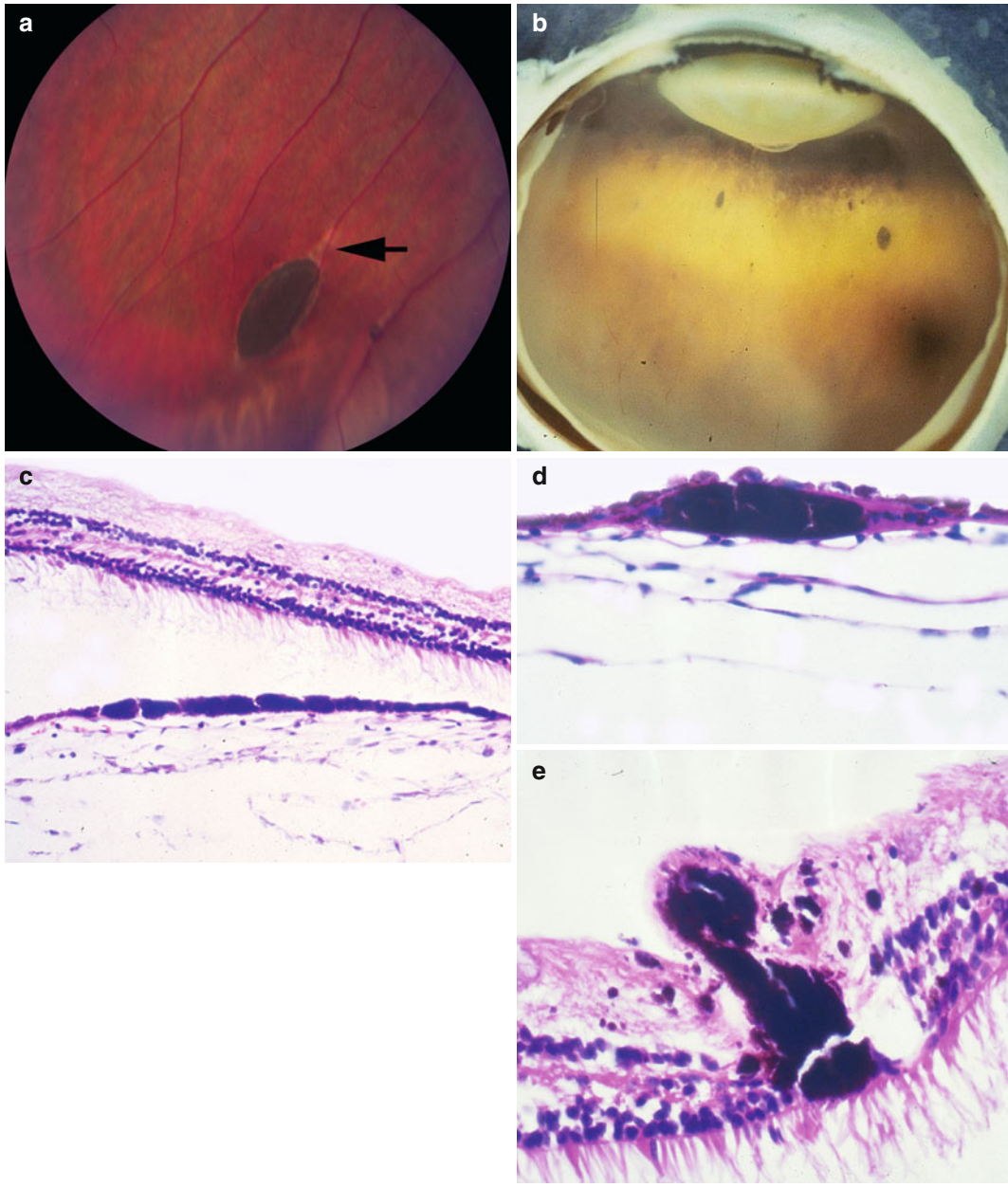


Fig. 5.5 POFLs in the right eye of a patient with Gardner syndrome (**a**). Two oval-shaped pigmented retinal lesions are evident. Note depigmentation along the posterior margin (*arrow*). Numerous peripheral small lesions are easily overlooked unless fundus examination is performed with a 3-mirror contact lens (**b**). On histopathology, POFL may appear as hyperpigmented and hypertrophic RPE (**c**), several layered thick RPE hamartoma (**d**), and even as nodular RPE adenoma (**e**). (Reproduced with permission from Traboulsi et al. [22])

posterior depigmented trail. It is often possible to note a diffuse fine stippling of RPE pigmentation in the peripheral fundus. There is a fair degree of intrafamilial consistency in the number of POFLs.

5.3.4.3 Associations

Familial Adenomatous Polyposis (Gardner Syndrome)

Familial adenomatous polyposis or Gardner syndrome is a rare autosomal dominant condition

characterized by the development of hundreds of adenomatous colonic polyps [27]. Adenocarcinoma of the colon inevitably develops unless prophylactic colectomy is performed. Many patients develop extracolonic benign lesions such as sebaceous cysts, lipomas, fibromas, and osteomas. Osteomas are most commonly present in the skull and have also been reported in the orbit [28]. POFLs [23] and opaque jaw lesions [29] are the most common and most characteristic extracolonic manifestations of the disease. Extracolonic cancers can occur in the thyroid, adrenal glands, and in the liver [30].

The presence of four or more POFLs is a highly sensitive (70–80 %) and specific (>90 %) clinical marker for the FAP [23]. Sensitivity and specificity are increased slightly if opaque jaw lesions are present at the same time [29]. The presence of POFLs is especially helpful in families where multiple affected individuals have numerous POFLs because of the intrafamilial consistency of expression of the ocular trait. Patients at risk for the disease who have the ocular lesions develop colonic polyps [31]. The absence of POFLs, however, does not rule out the disease. More recent studies have reported that patients with a mutation APC 1249-1549 develop polyposis at an early age and have a worse survival than patients with a mutation APC 0-178 or 312-412 [32].

Turcot Syndrome

Turcot syndrome is a variant of FAP in which patients develop brain tumors. Patients with Turcot syndrome may also have multiple POFLs [33].

Microcephaly

CHRPE-like lesions have been described in three siblings (two boys and one girl) with autosomal recessive microcephaly and without associated systemic features of Gardner syndrome and in one boy with microcephaly and a chromosomal abnormality [21, 34].

5.3.5 Diagnostic Evaluation

Patients suspected of having FAP need detailed ocular examination to determine if they show the ocular phenotype of the disease. If only one or two lesions are detected on ophthalmoscopy, three-mirror fundus examination may be necessary to find additional small lesions. ERG and EOG examinations are not necessary since they are normal. Patients suspected of having FAP should be evaluated by gastroenterologists, and the appropriate medical and surgical interventions should be instituted according to current protocols. Prophylactic colectomy is frequently performed in teenagers with this disease. Mutation analysis of the gene and protein truncation assays are available commercially.

5.3.6 Treatment

No treatment is necessary for the POFLs. If orbital osteoma causes significant ocular problems, it may need surgical excision.

5.3.7 Prognosis

The prognosis for vision is excellent. Early diagnosis of FAP results in good prognosis for life if appropriate therapeutic measures are instituted.

5.4 Simple Hamartoma of the RPE

5.4.1 Introduction

Simple hamartomas of the RPE are very rare congenital lesions that were first described by Laqua in 1981 [35]. The term RPE hamartoma was suggested by Gass [1] who reported three architectural patterns: (1) superficial retinal involvement, (2) full-thickness retinal involvement and preretinal extension, and (3) with intrinsic vascularization. Others have used the term congenital hamartoma of the RPE to describe these tumors [36].

5.4.2 Etiology and Pathogenesis

These tumors are congenital but no specific genetic etiology has been postulated or identified in any of the reported cases.

5.4.3 Pathology

Clinicopathologic correlation of simple hamartoma of the RPE has not been published.

5.4.4 Clinical Features

5.4.4.1 Symptoms

Patients with simple hamartoma of the RPE are generally asymptomatic unless the macula is involved when they can have variable loss of vision.

5.4.4.2 Signs

Simple hamartoma of the RPE appears as a discrete small (0.5–1.0 mm) black nodule and has a predilection for the macular area. They can be discovered in children or later in life if vision is not affected. A feeding arteriole and draining venule may be apparent ophthalmoscopically or observed on fluorescein angiography in all cases. A surrounding halo or associated retinal traction is present in the majority of patients.

5.4.5 Diagnostic Evaluation

The clinical features are characteristic. Ultrasonography shows a nodular echo-dense mass with high internal reflectivity. There is early nonfluorescence on early phases of the fluorescein angiogram, with some cases showing a central plaque of fluorescence and other only a ring of fluorescence at the edge of the lesions on late frames.

5.4.6 Treatment

No specific therapy is indicated and none has been tried or deemed necessary as vision is usually well preserved.

5.4.7 Prognosis

There has not been documentation of growth in any of the reported cases, some of which have been observed for up to 15 years.

5.5 Adenoma and Adenocarcinoma of the RPE

5.5.1 Introduction

These are rare acquired tumors of the RPE. The differentiation between adenoma and adenocarcinoma can only be made on the basis of histopathologic findings because of similar clinical findings in both types of tumor.

5.5.2 Etiology and Pathogenesis

The etiology of RPE adenomas and adenocarcinomas remains elusive, and no genetic factors have been identified to date.

5.5.3 Pathology

Histopathologically, the RPE adenoma is composed of proliferation of RPE cells. Tumors arising from the anterior portion of the RPE have vacuolated polygonal cells in glandular or tubular configuration with a vascularized connective tissue septa (Fig. 5.6). A prominent basement membrane is evident. Tumors demonstrating nuclear atypia and local invasiveness are classified as adenocarcinoma. However, RPE tumors including adenocarcinoma are not known to metastasize.

5.5.4 Clinical Features

5.5.4.1 Symptoms

Patients with adenoma may have varying visual symptoms including vision loss because of the macular involvement.

5.5.4.2 Signs

Most RPE adenomas are located in the peripheral fundus, although rare juxtapapillary tumors have been reported [37]. In a series of 13 adult patients (age range 28–79 years); ten were women and three were men; ten were white and three were African American [38]. All tumors were solitary, unilateral, and ranged from small

(2×2×1 mm) to large size (17×17×17 mm). The tumors were usually dark brown to black in color (Fig. 5.6). Prominent retinal feeder vessels were visualized in eight patients, five of whom had an exudative retinal detachment. Two patients had recurrent vitreous hemorrhage [37]. The presence of surrounding retinal hard exudates is an important diagnostic feature, as it is almost never associated with untreated choroidal melanoma.

5.5.5 Diagnostic Evaluation

Fluorescein angiography shows early hypofluorescence and late minimal hyperfluorescence of the tumor, without visibility of choroidal vessels. Ultrasonography typically demonstrates abrupt elevation of the tumor, and medium to high internal reflectivity and acoustic solidity. Despite clinical and diagnostic evaluation, it is not always possible to differentiate RPE adenoma

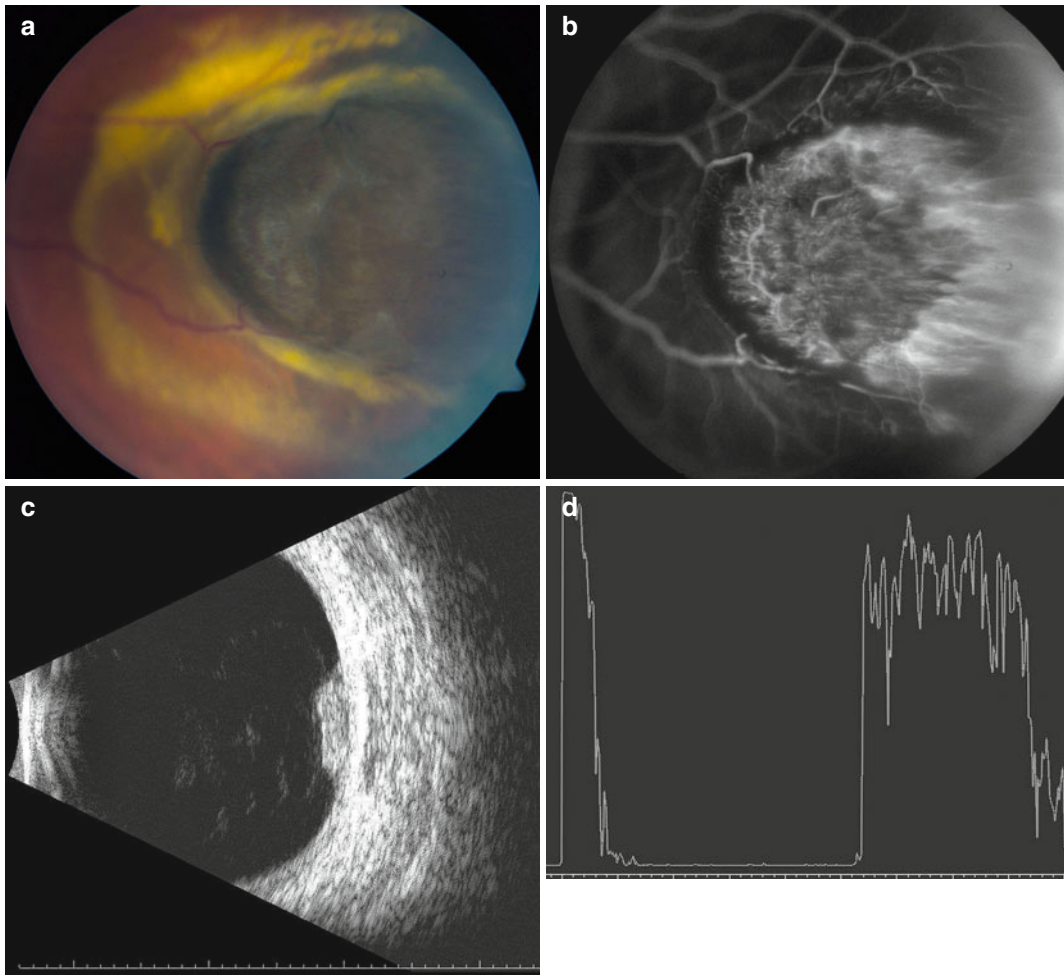
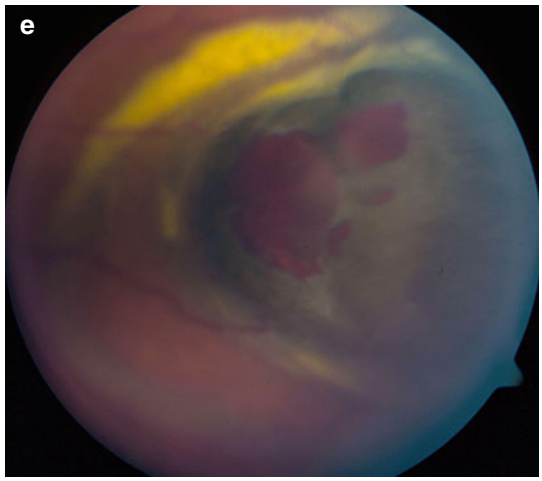


Fig. 5.6 A 40-year-old woman noted to pigmented fundus mass on a routine examination (**a**). Note dark uniform color with absence of drusen, orange pigmentation, or details of overlying retina. Prominent lipid exudation along the base of the tumor was also observed. The retinal vessels seem to lead into the tumor but the vessels were not dilated. Fluorescein angiography confirmed that intrinsic vasculature of the tumor was derived from of retinal vasculature (**b**). B-scan ultrasonography revealed a dome-shaped lesion that was located anterior to the choroid (**c**). The tumor had high internal reflectivity on A-scan (**d**). A clinical diagnosis of RPE adenoma was made and patient observed every 3 months. At 6-month visit, the tumor was noted to have enlarged. Transvitreal FNAB was performed without significant complications. One week postoperative appearance showing mild retinal hemorrhage at the biopsy site (**e**). Cytology specimen revealed bland cuboidal cells with granules of pigment suggestive of RPE cells rather than choroidal melanoma (**f**, courtesy of Dr. Biscotti)



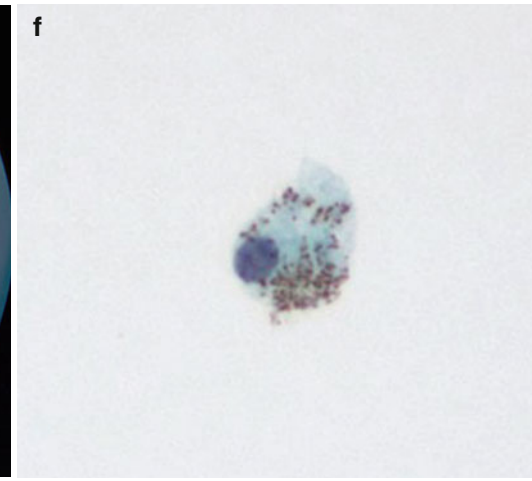


Fig. 5.6 (continued)

Table 5.4 Relative differentiating features of retinal pigment epithelial adenoma and choroidal melanoma

Feature		RPE Adenoma/adenocarcinoma	Choroidal melanoma
Shape		Dome	Dome or mushroom
Color		Black	Brown
Margins		Sharply demarcated	Undemarcated
Retinal feeder vessels		Present	Absent
Retinal exudation	Serous	Frequent	Frequent
	Lipid	Frequent	Almost never
Ancillary Studies	Fluorescein angiography	Communication with retinal circulation	Intrinsic abnormal choroidal vasculature
	Ultrasonography	Medium to high reflectivity	Low to medium reflectivity
Behavior	Growth	Slow	Rapid
	Metastasis	Never	Frequent
Histopathology	Cells	Polygonal cells	Spindle or epithelioid cells
	Arrangement	Glandular arrangement	Fascicular or absent
	Basement membrane	Prominent	Absent
	Immunohistochemistry	Epithelial antigens	Melan-A
			HMB-45

and adenocarcinoma from choroidal melanoma (Table 5.4). In such cases, fine needle aspiration biopsy that discloses cells of pigment epithelial origin can be diagnostic (Fig. 5.6). In rare instances, reactive proliferation of RPE can attain tumorous proportions simulating RPE adenoma and choroidal melanoma (Fig. 5.7) [39, 40].

5.5.6 Treatment

A variety of treatment modalities have been used depending on individual case characteristics, including observation, enucleation, local tumor resection, irradiation, and laser therapy [38, 41].

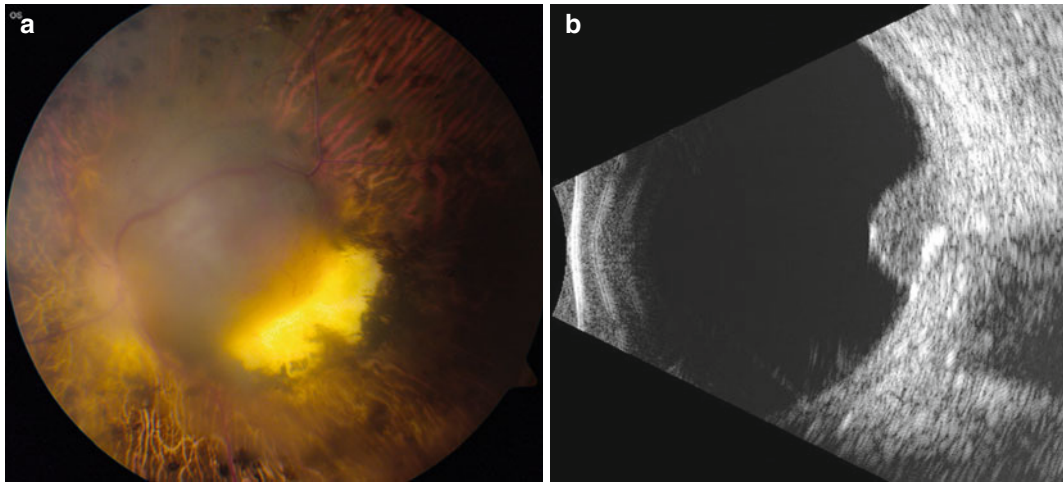


Fig. 5.7 Long-standing blind eye due to healed toxoplasma retinochoroiditis. Note nodular almost-translucent subretinal elevation adjacent to a healed chorioretinal scar (**a**). Suggestion of osseous metaplasia at the level of the RPE (**b**)

5.5.7 Prognosis

The visual prognosis is variable. RPE adenoma may remain stable or enlarged simulating a melanoma [37]. They may not respond even to brachytherapy necessitating enucleation [37, 41].

5.6 Combined Hamartoma of the Retina and RPE

5.6.1 Introduction

Combined hamartoma of the retina and retinal pigment epithelium (CHR), a term first coined by Gass, is a rare developmental disorder involving the retina and the retinal pigment epithelium [42].

5.6.2 Etiology and Pathogenesis

Hamartomas are benign proliferation of tissues that are normally present in the affected area. Although there is an association between CHR and NF2 [43], the mechanistic relationship between a disease with predilection for tumor of nerve sheath and tissues that do not contain myelinated axons remains to be elucidated. Diagnosis of CHR in infants supports the hypothesis that CHR is a congenital lesion, but there have also been reports of acquired cases of CHR. Ticho et al. have reported the development of CHR in a 3-year-old patient following parainfectious meningoencephalitis with optic neuritis [44].

5.6.3 Pathology

CHR is usually composed of varying amounts of vascular, glial, and pigment epithelial components.

5.6.4 Clinical Features

5.6.4.1 Symptoms

The most common presenting symptom of CHR is painless decrease in vision usually due to direct involvement of the optic disc, papillomacular bundle, or the fovea [45]. Secondary causes of decreased vision include tractional distortion of the macula and epiretinal membrane formation [45]. Other presenting symptoms include strabismus, floaters, and leukocoria [45].

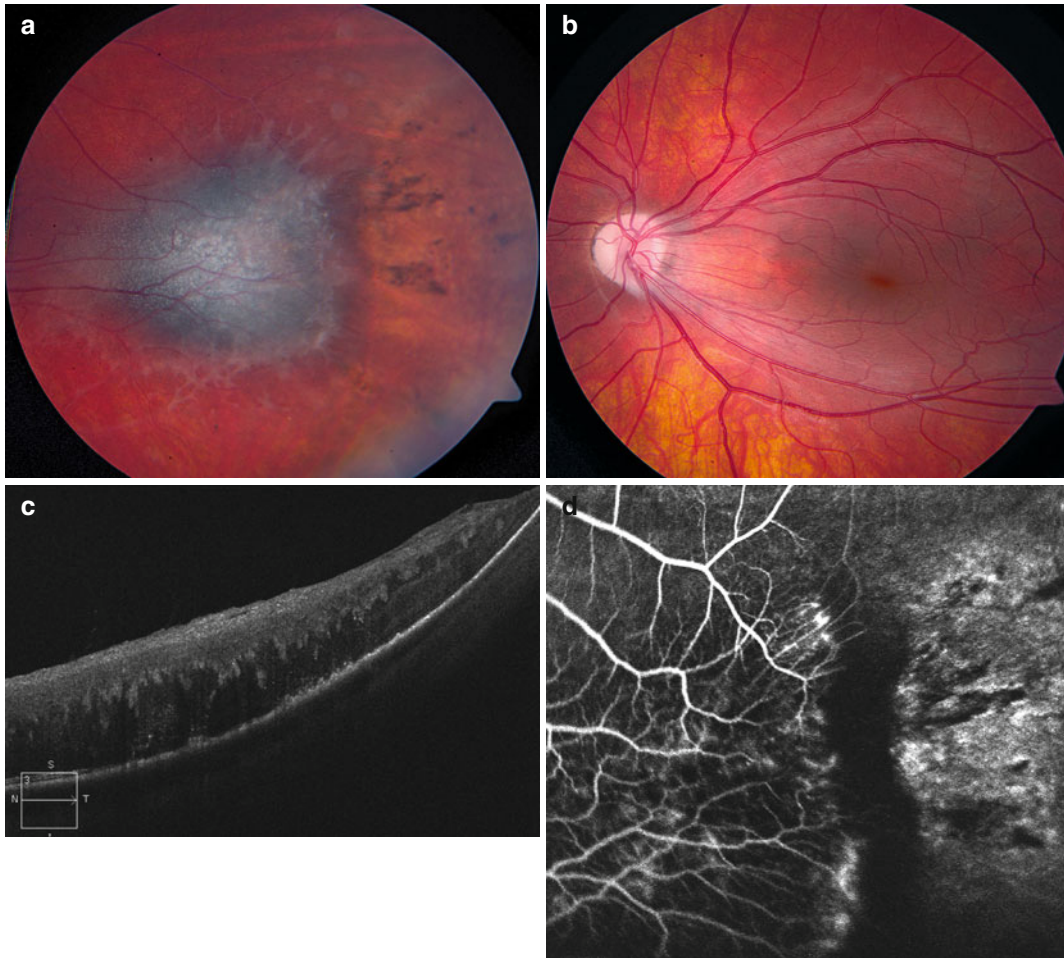


Fig. 5.8 Combined hamartoma of the retina and RPE usually appears as a unilateral grey-black colored lesion (**a**). Temporal dragging the vessels is evident on the examination of the posterior pole (**b**). OCT showing normal RPE layer, disorganization of retinal layers, and prominent epiretinal membrane (**c**). Fluorescein angiography demonstrated leakage within fine retinal vessels and hypofluorescence corresponding to the pigment proliferation at the margin (**d**)

5.6.4.2 Signs

CHR is usually unilateral and can occur at the optic disc or elsewhere in the fundus (Fig. 5.8). The tumor is grey-black in color, and the lesion typically has an epiretinal membrane that may cause retinal traction. The traction may be progressive, leading to a decline in vision. CHR does not undergo malignant transformation. Uncommon secondary effects include choroidal neovascularization, vitreous hemorrhage, retinoschisis, and formation of a macular hole [46].

5.6.4.3 Association

Although most cases of CHR are isolated, there have been reports of associated systemic disorders. In his original report, Gass noted that one of his patients had multiple café-au-lait spots [42], and there is another reported occurrence of CHR in NF1 [47]. However, the most frequent association of CHR is with NF2 [43, 48]. Sporadic observations of CHR in several syndromes such as branchio-oculo-facial syndrome [49], Gorlin syndrome [50], and ipsilateral Poland anomaly have also been reported [51].

5.6.5 Diagnostic Evaluation

CHR is important because it is often mistaken for malignancies such as retinoblastoma or choroidal melanoma, and there have been patients who were enucleated because of the suspicion of a malignant lesion. CHR can often be reliably diagnosed on indirect ophthalmoscopy. Ancillary studies such as fluorescein angiography are helpful in establishing the diagnosis. Angiographically, the lesion shows blockage of the choroidal fluorescence due to increased pigmentation of the retinal pigment epithelium. Vascular tortuosity is prominent in the arterial phase, and progressive hyperfluorescence is evident in the late phase due to leakage from the abnormal vessels [45]. Optical coherence tomography of CHR demonstrates a highly reflective lesion of the inner retina obscuring of the underlying retinal architecture that is useful in differentiating from a minimally elevated choroidal melanoma, which shows normal retinal architecture [52]. Although often isolated, patients diagnosed with CHR should undergo evaluation to exclude any systemic association, especially NF2.

5.6.6 Treatment

Most CHR cause decreased vision because they involve the macula and peripapillary region and lead to retinal traction and distortion. CNV can be treated with laser or submacular surgery. Vitrectomy and membrane peeling have been used in selected cases with modest visual improvement [53]. Peeling of the epiretinal membrane may not be possible in cases where the membrane is tightly adherent to the retina, and the role of vitrectomy and membrane peel remains controversial in management of vision loss in CHR.

5.6.7 Prognosis

In a survey of the 60 cases examined by members of The Macula Society, 41 patients had adequate follow-up information [45]. Ten patients (24 %) lost at least two lines of visual acuity, and four (10 %) had improved visual acuity following either amblyopia therapy or vitreous surgery for macular traction [45].

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Tumors of the Ciliary Epithelium

6

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6.1 Introduction

Tumors arising from the ciliary epithelium are quite uncommon. The extremely low prevalence of these tumors often causes them to be mistaken for other more common iridociliary tumors such as melanoma or uveal metastases. The location of these rare lesions growing behind the iris, the difficulty in differentiating between benign and malignant tumors, their histologically remarkable cellular polymorphism, and the possibility of dealing with either a congenital or acquired tumor make their diagnosis difficult [1].

6.2 Anatomy

Histologically, the pars plana and the pars plicata of the ciliary body have two layers of overlying epithelial cells. The outer layer of epithelial cells is the pigmented epithelium, and it is continuous anteriorly with the sphincter and dilator muscles of the iris and posteriorly with the retinal pigment epithelium. The inner layer, adjacent to the vitreous cavity, is the nonpigmented epithelium. It is a cuboidal or low columnar layer that lines the surface of the ciliary crests and extends posteriorly becoming continuous with the sensory retina. The nonpigmented epithelium is responsible for the production of aqueous humor and possibly of hyaluronic acid found within the vitreous gel.

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Table 6.1 Histological classification of ciliary epithelium tumors

Congenital	Glioneuroma		
	Medulloepithelioma	Teratoid	Benign
			Malignant
		Nonteratoid	Benign
			Malignant
Acquired	Pseudoadenomatous hyperplasia	Reactive	
		Age-related (Fuchs' or coronal adenoma)	
	Adenoma		
	Adenocarcinoma		

6.3 Classification

According to Zimmerman's histological classification, ciliary epithelium tumors may be grouped as congenital and acquired (Table 6.1) [1].

6.4 Congenital Tumors of Ciliary Epithelium

The congenital tumors of the ciliary epithelium arise from the primitive medullary epithelium, before its differentiation into its various adult derivatives. Thus, they tend to become clinically apparent in young children and have an embryonic appearance histologically.

6.4.1 Glioneuroma

Glioneuroma is perhaps the rarest tumor in the group, with only a few cases reported in the literature [2–5]. It is considered as a choristomatous malformation developed from the anterior margin of the primitive optic cup and without an evident neoplastic potential.

6.4.1.1 Clinical Features

Glioneuroma appears as a slowly enlarging white or fleshy unilateral mass in the inferior aspect of the anterior chamber angle, often with involvement of the corneoscleral limbus. The tumor may be adherent to the corneal endothelium, displace the pupil, the lens, or induce a cataract [2, 4, 5]. Sometimes an associated ciliary body colobomatous defect may be present. The intraocular pressure may also be elevated [2, 5]. Glioneuroma is usually recognized at birth or shortly thereafter, although it has been diagnosed in a 21-year-old woman [2].

6.4.1.2 Pathology

Glioneuroma infiltrates the stroma of the iris and ciliary body, may invade the choroid and the peripheral retina, and may even extend into the extrascleral space [2, 4, 5]. Light microscopy reveals a well-differentiated neural tissue similar to the brain, with eosinophilic fibrillary material, axonal processes, and glial cells within the matrix of the tumor [4].

6.4.1.3 Management

Because intraocular glioneuromas are rare, there is no clearly established treatment. Most recorded cases have been managed by enucleation of the involved eye. Occasionally glioneuromas have been removed by iridocyclectomy [2]. It also seems reasonable that the diagnosis could be established by a biopsy in selected cases.

6.4.2 Medulloepithelioma

Intraocular medulloepithelioma is a nonhereditary embryonal neoplasm that most often occurs in the ciliary body. Accordingly, it contains pure neuroepithelial structures (nonteratoid medulloepithelioma or diktyoma) or, more commonly, derivatives of the medullary epithelium, particularly cartilage, skeletal muscle, and brain tissue (teratoid medulloepithelioma or teratoneuroma) [6, 7].

6.4.2.1 Clinical Features

Medulloepithelioma is typically a disease of childhood that becomes clinically apparent during the first decade of life, although some

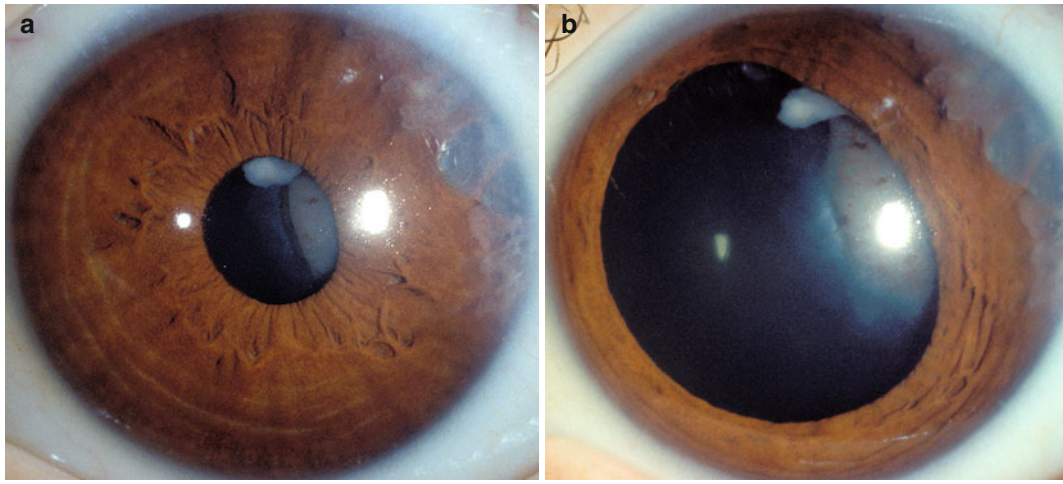

Fig. 6.1 Medulloepithelioma of the ciliary body. Translucent mass behind the iris and invading the anterior chamber through the iris root. Note a dense anterior polar cataract (**a**). Same eye with the dilated pupil (**b**)

cases are asymptomatic for quite some time and later on manifest during adulthood [8, 9]. The most relevant clinical signs and symptoms of medulloepithelioma are poor vision, pain, leukocoria, and the presence of an intraocular mass appearing behind the pupillary area (Box 6.1). The tumor is an irregular, variably-sized white or gray translucent mass arising from the ciliary region (Figs. 6.1 and 6.2). It is frequently vascularized and comes in contact with the iris and very seldomly appears pigmented. One well-known clinical feature that suggests the diagnosis of medulloepithelioma is the presence of cysts within the tumor (Fig. 6.3) [6, 7, 10]. Large cysts may break off from the tumor and float freely in the anterior chamber or into the vitreous cavity (Fig. 6.4). Iris neovascularization is a common and early finding in eyes with medulloepithelioma [7]. Children with neovascularization of iris of unknown cause should be evaluated to exclude underlying medulloepithelioma (Fig. 6.5) [11].

The presence of a sectorial or total cataract with or without subluxation is quite common. One of the earliest clinical manifestations may be a peculiar notch in the lens, producing a "lens coloboma" in the quadrant of the tumor [6–8, 10–12]. Other findings include a cyclitic neoplastic membrane, uveitis, hyphema, retinal detachment, vitreous hemorrhage, invasion of the optic nerve, and extraocular extension of the tumor [7].

6.4.2.2 Diagnostic features of Medulloepithelioma (Box 6.1)

- Manifests during the first decade of life
- Should be considered in the differential diagnosis of leukocoria
- White or gray translucent mass arising from the ciliary body
- Presence of cysts within the tumor, anterior chamber, or vitreous cavity
- Iris neovascularization, lens coloboma, sectoral or total cataract
- Other findings include a cyclitic neoplastic membrane, uveitis, hyphema, retinal detachment, and vitreous hemorrhage

6.4.2.3 Pathology

According to Zimmerman's classification, medulloepithelioma may be divided into nonteratoid and teratoid types, and either type may have benign or malignant cytologic features [1, 6, 13]. The nonteratoid medulloepithelioma contains multilayered sheets of cords of poorly differentiated neuroepithelial cells that are histologically similar to the embryonic retina and ciliary epithelium. In contrast to the nonteratoid medulloepithelioma, the teratoid type demonstrates variable degrees of heteroplasia (hyalin cartilage, rhabdomyoblasts, undifferentiated mesenchymal cells

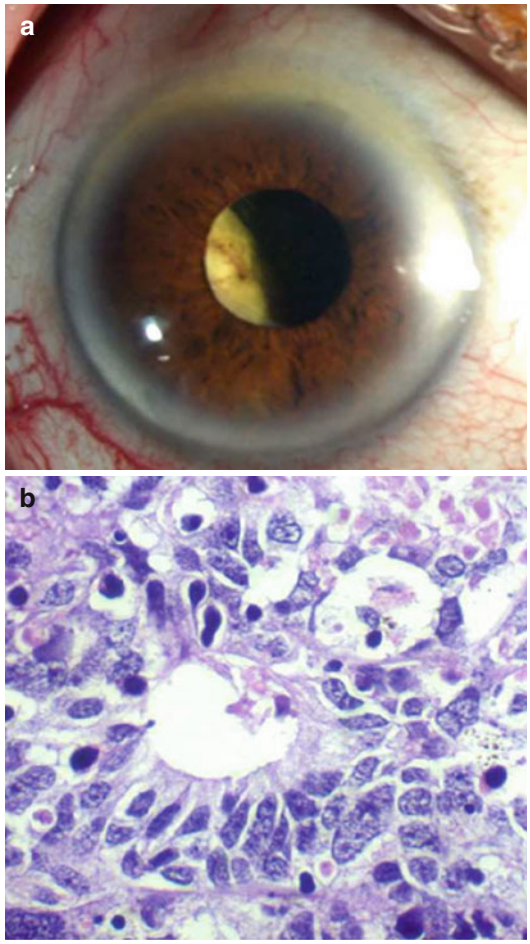

Fig. 6.2 Slit lamp photograph of a 67-year-old woman presenting with a large yellowish white, fluffy, ciliary body mass extended from 5 to 11 o'clock position (**a**). There were dilated episcleral vessels in the temporal quadrant. Powdery white material can be seen dispersed over the corneal endothelium and in the anterior chamber. Microscopic examination of the paraffin embedded sections showed a tumor composed of large irregular pleomorphic cells in the ciliary body and the base of iris. Heteroplastic elements such as skeletal muscle or cartilage were absent. The tumor cells were seen arranged in tubules and rosettes with central lumen resembling neural tube formation (**b**, H&E ×400) (Reproduced with permission from Ali et al. [9])

resembling embryonal sarcoma, neuroglial tissue resembling brain, and ependymal structures) [6–8, 10].

As most intraocular medulloepitheliomas do not demonstrate distant metastasis but do show variable degrees of local invasiveness, it may be difficult to classify them as benign or malignant. The histopathologic criteria of malignancy as defined by Broughton and Zimmerman are areas composed of poorly differentiated neuroblastic cells, greater pleomorphic or mitotic activity, sarcomatous areas resembling a chondrosarcoma, rhabdomyosarcoma, or embryonal sarcoma, and invasion of the uvea, cornea, or sclera with or without extraocular invasion [6].

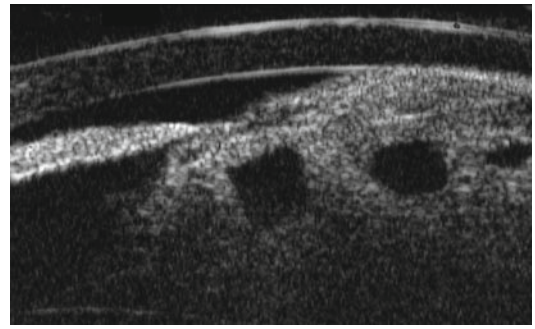

Fig. 6.3 Intra-tumoral cysts of medulloepithelioma detected by ultrasound biomicroscopy (Reproduced with permission from: Turell et al. [33]

6.4.2.4 Management

Because most of these tumors are cytologically malignant, infiltrate the adjacent vitreous, and proliferate in delicate sheets that may not be evident intraoperatively, enucleation of the affected eye is usually advisable. In carefully selected small tumors (<3 clock hours), local removal by iridocyclectomy may be considered as an initial management option, although local recurrence is usual. Brachytherapy might be a good option in circumscribed tumors, with the stipulation of a possible re-treatment in case of tumor recurrence [14, 15].

6.4.2.5 Pleuropulmonary Blastoma

An association with pleuropulmonary blastoma (PPB) has been recently reported by the International Pleuropulmonary Blastoma Registry (Fig. 6.6) [16]. PPB is a rare embryonic tumor (analog of retinoblastoma, neuroblastoma, Wilms' tumor) arising from primitive pleuropulmonary tissue and presenting as a lung and pleural tumor in early childhood. PPB may

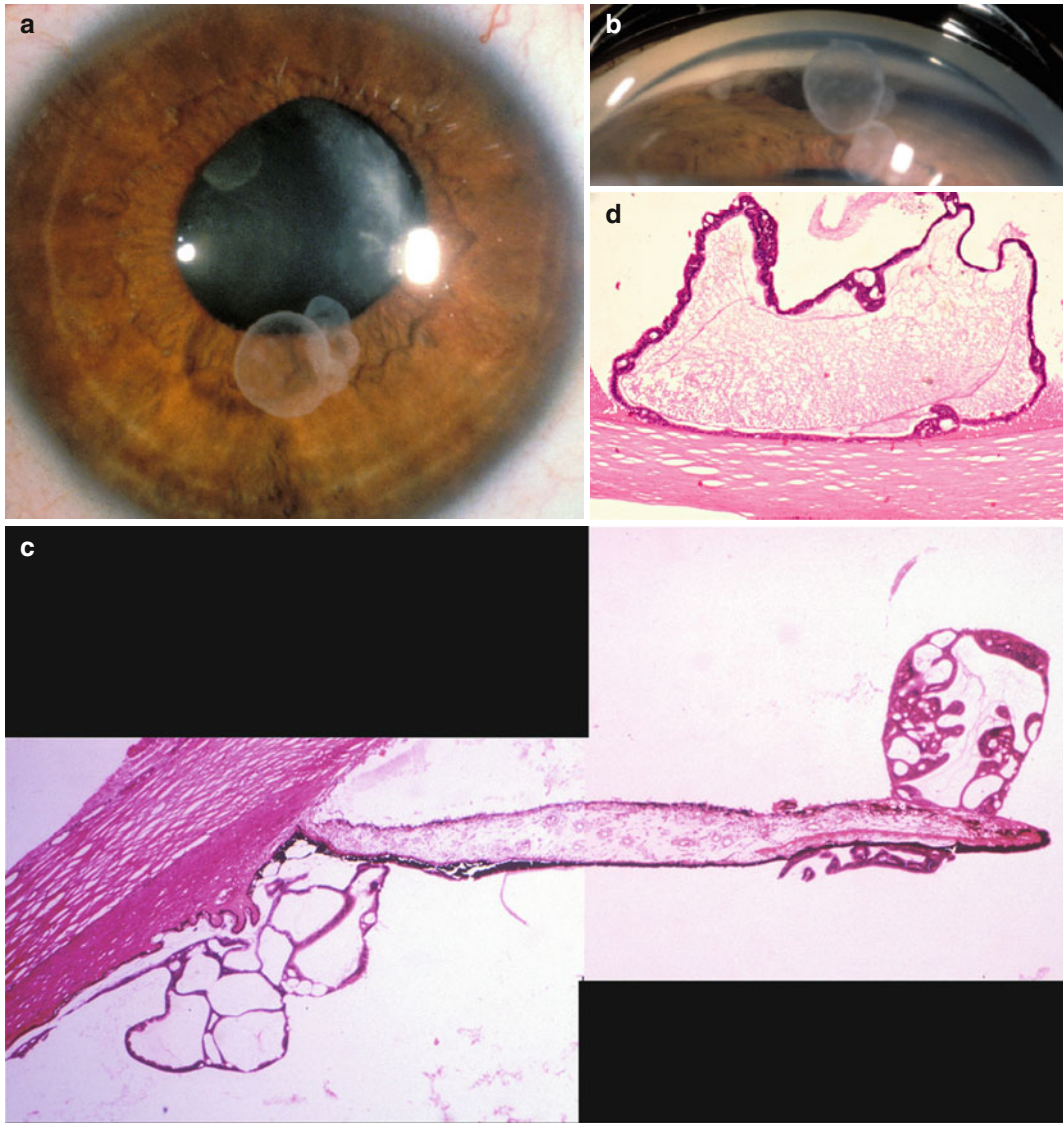

Fig. 6.4 Anterior chamber cysts secondary to medulloepithelioma of the ciliary body (**a**). Multiple cysts within the anterior chamber and emerging through the pupil (**b**, gonioscopic photographs). Histopathologic composite photograph showing a cyst adherent to the anterior border layer of the iris, another one behind the iris, and some cysts near the ciliary body. (**c**, hematoxylin-eosin ×75) Photomicrograph showing an irregular cyst on posterior surface of the corneal endothelium (**d**, hematoxylin-eosin ×35)

be part of a familial cancer syndrome due to DICER 1 mutation on chromosome 14q31 [16]. Additional features of the familial syndrome include lung cysts, neuroblastoma, cystic nephroma, Wilms' tumor, and rhabdomyosarcoma. The presence of medulloepithelioma should be considered in a child with a history of PPB and vice versa [16, 17].

6.5 Acquired Tumors of the Ciliary Epithelium

In contrast to the congenital tumors that arise from undifferentiated medullary epithelium, acquired tumors arise from fully differentiated ciliary epithelium and usually occur in older patients. They may take the form of reactive

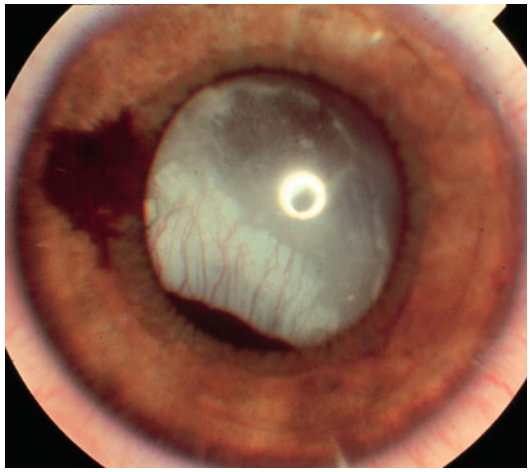

Fig. 6.5 A 38-month-old girl presented with leukocoria of 2 months duration. On examination, lens coloboma and a vascularized retrolental sheet (cyclitic membrane) were noted. A pigmented mass was seen in the ciliary body region from 6 to 8 o'clock position. Tumor recurred after PLSU necessitating enucleation. Histopathologically, the lesion was confirmed to be malignant teratoid medulloepithelioma (Reproduced with permission from Singh et al. [11])

proliferations (pseudoadenomatous hyperplasia) or neoplastic proliferations (adenoma or adenocarcinoma).

6.5.1 Pseudoadenomatous Hyperplasia (Reactive Proliferation)

6.5.1.1 Age-Related Hyperplasia (Fuchs' or Coronal Adenoma)

Fuchs' adenoma represents an acquired lesion that seems to be age related, with increasing frequency in older patients and with little clinical significance [18]. It is commonly observed as an opaque white mass usually confined to a ciliary process in eyes removed surgically or postmortem. Histologically, it is composed of irregular cords of cells of the nonpigmented ciliary epithelium. In rare instances, the tumor can erode into the anterior chamber, simulating an iris tumor [18, 19].

6.5.1.2 Reactive Hyperplasia

The nonpigmented ciliary epithelium contributes to the development of a cyclitic membrane, composed of a proliferation of benign cells from the nonpigmented ciliary epithelium, connective tissue, and blood vessels. Clinically it is characterized by a dense retrolental fibrovascular tissue that usually extends from the pars plicata on one side to the pars plicata on the other side. It usually does not take the form of a distinct tumor but rather occurs as a thickened sheet or membrane [20]. Reactive hyperplasia of the ciliary epithelium is usually seen in histopathologic specimens of traumatized or disorganized eyes and may adopt a pseudotumor appearance [20].

6.5.2 Adenoma and Adenocarcinoma of the Ciliary Epithelium

True acquired neoplasms of the pigment or nonpigmented ciliary epithelium are relatively rare. They may be benign (adenoma) or malignant (adenocarcinoma) and the clinical differentiation between the two may often be impossible. Similar tumors arise from the pigment epithelium in the region of the iris [21] and from the retinal pigment epithelium [22].

6.5.2.1 Clinical Features

Both adenoma and adenocarcinoma appear as a solid ciliary body mass presenting variable characteristics and simulating ciliary body melanoma. Tumors arising from the pigment ciliary epithelium are usually deeply pigmented [23, 24], and tumors arising from the nonpigmented ciliary epithelium are amelanotic [25]. The clinical course is either asymptomatic or involves a painless visual loss. Adenoma and adenocarcinoma of the ciliary body have an irregular and sometimes multilobulated surface [23–25]. Uveal melanoma tends to be more pigmented, with a smooth surface presenting as a mushroom-like growth pattern. Some cases may present with cellularity in the anterior chamber and with sentinel vessel

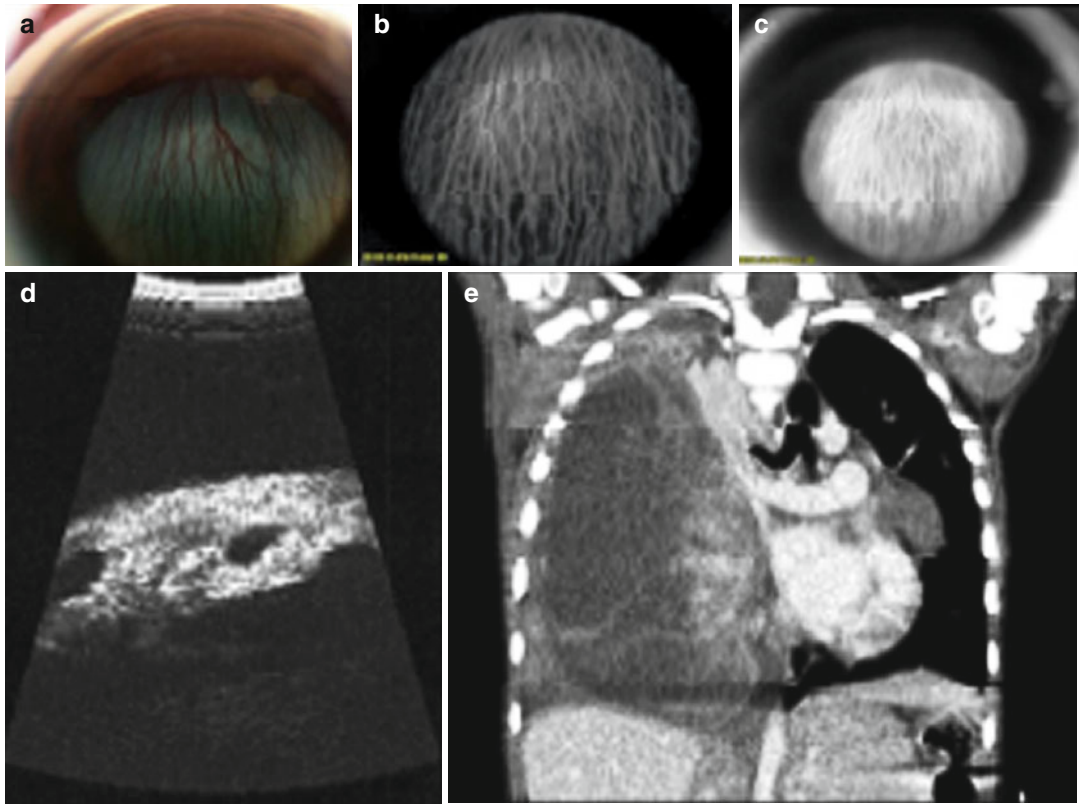

Fig. 6.6 Ciliary body medulloepithelioma associated with pleuropulmonary blastoma. A 7-year-old African American girl was found to have reduced vision in the right eye on routine screening. Visual acuity was hand motions in the right eye and 20/20 in the left eye. Intraocular pressure was 17 in each eye. Slit lamp exam of the right eye showed a normal anterior segment but immediately posterior to the lens an opaque vascularized cyclitic membrane that blocked visualization of the vitreous and retina (**a**). The blood vessels appeared to originate superiorly. Fluorescein angiography was performed which showed brisk circulation and late staining of the cyclitic membrane (**b**, **c**). B scan ultrasonography showed an elevated ciliary body lesion at 12:30 with irregular internal reflectivity and a height of 2.4 mm and basal diameters of 8.4 and 6.6 mm (**d**). Four years prior to visual symptoms, the patient was diagnosed with pleuropulmonary blastoma (**e**). She underwent surgical resection of the lung mass, radiation, and chemotherapy and was in remission (Reproduced with permission from Laird et al. [17])

in the overlying episclera – though this finding is more characteristic and evident in the case of uveal melanoma. Pigment dispersion in the vitreous is also seen more often with adenoma than with melanoma [26]. Adenoma of the nonpigmented ciliary epithelium may be associated with iris or disc neovascularization due to excessive production of vascular endothelial factor [27]. It is not uncommon to observe dyscoria and secondary cataract formation induced by tumor compression, and even secondary lens subluxation may occur. Although there are no large series on record, most acquired tumors arising from the ciliary epithelium appear to have a relatively benign course. The tumors may grow slowly and destroy the ocular structures, but they almost never metastasize or cause death. Relative differentiating features of adenoma and melanoma of the ciliary body are summarized in Table 6.2.

Table 6.2 Relative differentiating features of adenoma (adenocarcinoma) and melanoma of the ciliary body

Feature		Adenoma	Melanoma
Clinical	Shape	Irregular, multilobulated	Smooth dome, mushroom
	Color	Melanotic or amelanotic	Melanotic or amelanotic
	Sentinel vessels	Frequent	Infrequent
	Anterior chamber inflammation	Frequent	Infrequent
	Pigment dispersion in vitreous	Frequent	Infrequent
	Cyst/cavities	Frequent	Infrequent
	Growth	Slow	Rapid
Histopathological	Origin	Epithelial	Stromal
	Composition	Cuboidal or columnar cells	Spindle or epithelioid cells
	Pattern	Arranged in cords or tubules	No specific pattern
	Vimentin	Positive	Negative
	HMB-45	Negative	Positive
Behavior	Neoplasia	Usually benign, may be malignant	Always malignant
	Metastasis	Never	Frequent

6.5.2.2 Pathology

These tumors are composed of pigmented or nonpigmented cuboidal or columnar cells usually arranged in cords or tubules (Fig. 6.7). The adenocarcinomas may be more invasive and show more malignant features with cellular proliferations and loss of alveolar characteristics [28–30]. Positivity of the tumor cells to vimentin confirms the nonpigmented ciliary epithelial origin [31, 32]. In some cases immunopositivity with antibodies targeted to different cytokeratins may be also observed – though this pattern tends to be highly variable. Immunoreactivity to HMB-45, which is typical of melanoma, proves negative in these cases [31].

6.5.2.3 Management

If the lesion is small, asymptomatic and nonenlarging, simple periodic observation is the treatment of choice. Since adenoma of the nonpigmented ciliary epithelium is a slow-growing tumor with benign cytological characteristics and usually presents with good vision, management with local resection via iridocyclectomy may be advised. This procedure also serves to confirm histologic diagnosis. In the event of lens opacification, this procedure may be combined with small-incision cataract surgery. If tumor shows evidence of growth, or if a biopsy specimen indicates malignancy, local excision or enucleation should be considered [28, 29].

6.6 Summary

Tumors arising from the ciliary epithelium are quite uncommon. Medulloepithelioma is typically a disease of childhood that becomes clinically apparent during the first decade of life. Medulloepithelioma should be considered in the differential diagnosis of leukocoria, especially if there is a gray translucent mass arising from the ciliary region with cysts, iris neovascularization, lens coloboma, or cataract. Medulloepithelioma should be considered in a child with a history of PPB and vice versa.

Acquired neoplasms of the pigment or nonpigmented ciliary epithelium may be benign

(adenoma) or malignant (adenocarcinoma), and the clinical differentiation between the two may be impossible. Both adenoma and adenocarcinoma appear as a solid ciliary body mass simulating a ciliary body melanoma. These tumors may grow slowly and destroy the ocular structures, but they almost never metastasize or cause death. If clinically suspected, these tumors are best managed by local resection via iridocyclectomy.

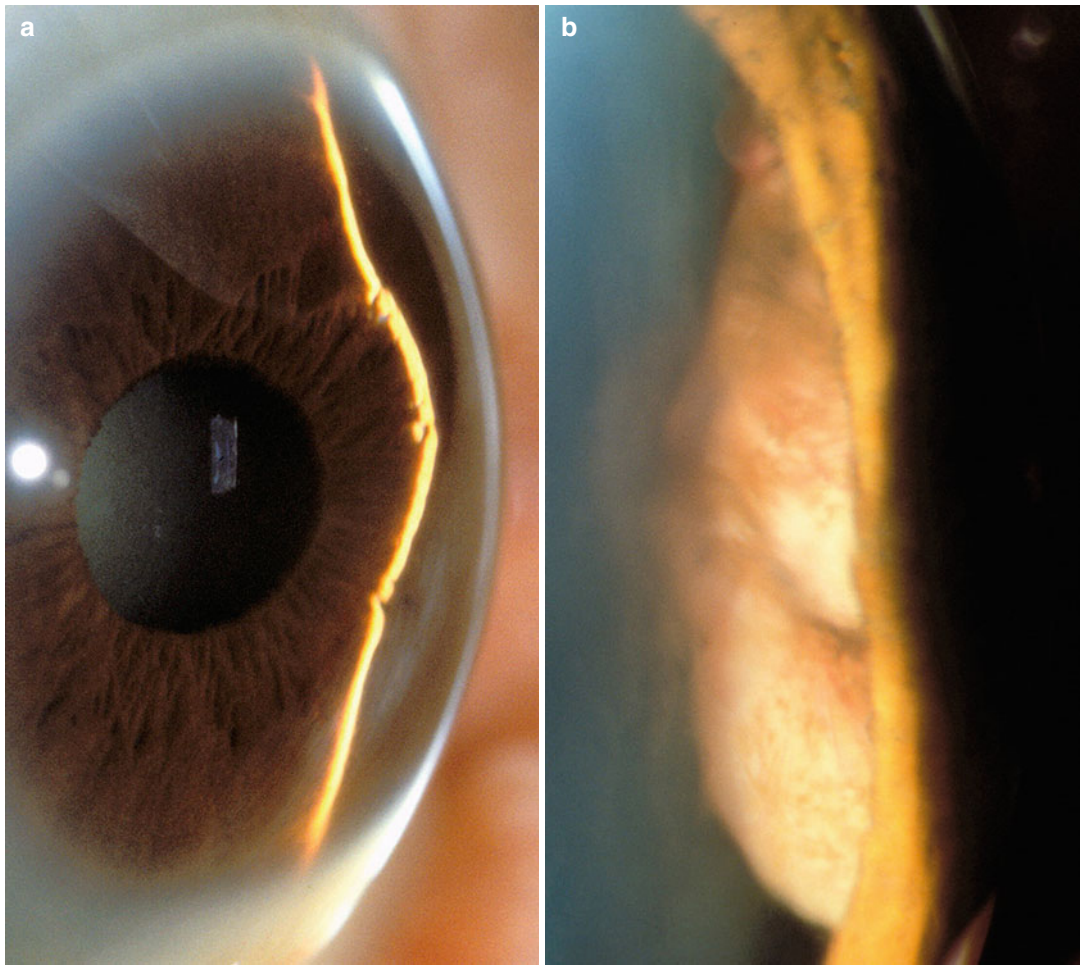

Fig. 6.7 Adenoma of the nonpigmented ciliary epithelium. Slit lamp photograph demonstrating an anterior displacement of the iris (**a**). A predominantly amelanotic nodular mass is located behind the iris (**b**). Histopathologic macroscopic photograph discloses a tumor of the nonpigmented epithelium extending from the anterior aspect of the ciliary processes and to the posterior surface of the iris and also a tumor located in the ciliary body and the root of the iris. (**c**, hematoxylin-eosin ×35) Microscopic structure of the tumor composed of cuboidal and columnar cells with abundant eosinophilic cytoplasm and hyperchromatic nuclei. The tumor cells are arranged in tubular, papillary, and solid pattern. (**d**, hematoxylin-eosin ×75) The tumor cells, which are arranged in a tubular or glandular pattern, are surrounded by thick basement membrane material (**e**, stain, periodic acid-Schiff; magnification, ×300). The neoplastic cells show positive reactivity to CAM 5.2. Immunoperoxidase staining (**f**, stain, avidin–biotin complex technique; magnification, ×300) (**e**, **f** Reproduced with permission from Laver et al. [32])

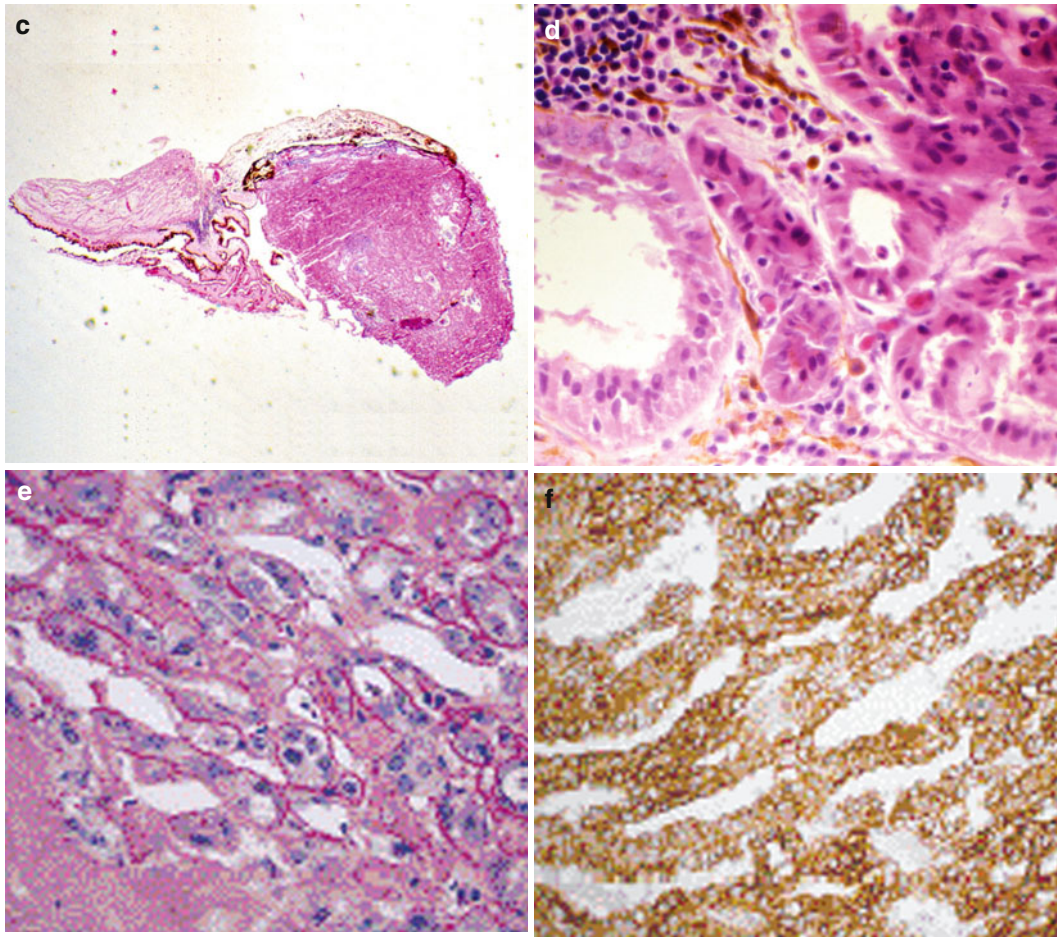

Fig. 6.7 (continued)

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Primary Central Nervous System and Retinal Lymphoma

7

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7.1 Introduction

Primary lymphoma of the central nervous system (CNS) is considered a variant of extra-nodal non-Hodgkin's lymphoma (NHL), a high-grade B-cell malignancy associated with a median survival ranging from one to 8 years depending on factors such as age and Karnofsky performance status [1]. Primary CNS lymphoma (PCNSL) originates in the brain parenchyma, spinal cord, leptomeninges, and eyes [2]. Formerly used descriptors such as "reticulum cell sarcoma" and "microgliomatosis" are no longer preferred as both misleadingly imply that the lymphoma arises from transformed reticulum or microglial cells. Primary intraocular lymphoma (PCNSL-O) is a variant of PCNSL with predominantly ophthalmic involvement. As vitreoretinal manifestations are the dominant feature, the term primary vitreoretinal lymphoma (PVRL) is commonly used. In contrast, other forms of ocular lymphoma typically affect the adnexal structures or uveal tract. The distinction is important as uveal and ocular adnexal lymphoma are usually low-grade, indolent, B-cell lymphomas that behave similarly to extra-nodal marginal zone lymphoma (EMZL) found elsewhere in the body [3].

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7.2 Pathogenesis

PCNSL is believed to originate from late-germinal center or post-germinal center lymphoid cells; however the neurotropic mechanism by which these cells localize to the CNS remains uncertain [4]. As the CNS and eyes lack lymphatics and lymph nodes, it has been hypothesized that the trafficking of lymphoma cells from the brain to the eye and vice versa involves either invasion of the optic nerve, seeding through shared venous drainage of the brain and eye, or common integrin expression of both organs [2, 4].

There are no known risk factors in immunocompetent individuals; however congenital immunodeficiency and iatrogenic or acquired immunosuppression (AIDS) are risk factors for PCNSL [5, 6]. PCNSL develops in as many as 6 % of patients with AIDS [7, 8]. Epstein-Barr virus infection of B lymphocytes in the absence of T suppressor function (due to immunosuppression) leads to an uncontrolled lymphocytic proliferation. Rare cases of PCNSL may be secondary to human T-cell lymphotropic virus type 1 (HTLV-1) infection [9]. The vast majority of PCNSL are diffuse large B-cell immunoblastic lymphoma [10, 11]. In contrast, PCNSL arising in T cells are composed of small-sized lymphocytes [12].

7.3 Clinical Features

Overall, PCNSL represents about 1–2 % of all cases of lymphoma and 3–5 % of all primary CNS tumors [13–15]. The age-adjusted incidence of PCNSL is approximately 4.8 per million population in the United States [13]. Until a few decades ago, this tumor was best known among patients with AIDS as a manifestation of late-stage disease. With the advent of highly active antiretroviral therapy, the incidence has decreased significantly in this population [16]. However, the incidence among immunocompetent patients has been rising for unclear reasons, although it still remains a rare disease [13]. While PVRL is frequently seen in the setting of PCNSL, the exact incidence is unknown due to the paucity of cases. Between 1999 and 2002, approximately 100 new cases of PVRL were reported in the United States [17].

Among immunocompetent individuals, the peak incidence of PCNSL occurs between the fifth and seventh decades, with a mean age of 60 years at diagnosis [18, 19]. In the immunocompromised population, PVRL occurs in younger individuals [20–22]. Intraocular involvement may precede, occur simultaneously, or follow the CNS disease. In general, intraocular involvement is the presenting feature in PVRL, and subsequent CNS involvement develops in 56–85 % of patients over a period of many months to several years [18, 23, 24]. Conversely, about 25 % of patients with PCNSL have concurrent intraocular involvement [10].

7.3.1 Symptoms

7.3.1.1 Ophthalmic

Patients may be asymptomatic, but up to 50 % present with painless blurred vision, floaters, or both [19, 25]. Bilateral involvement occurs in up to 80 % of cases and is typically asymmetric [24]. Asymptomatic individuals may be diagnosed at the time of ophthalmic screening in the setting of known PCNSL [24]. Owing to the nonspecific nature of the ophthalmic manifestations, a diagnosis of PVRL is difficult to make on clinical grounds alone, and a delay in diagnosis is common. A delay of up to 2 years between the initial presentation and histopathologic confirmation of the PVRL has been reported [23, 25].

7.3.1.2 Central Nervous System

Brain, spinal cord, and meninges either separately or in various combinations can be involved. Solitary involvement of the spinal cord is rarely seen. Personality changes are a common presenting feature because the frontal lobe is the most frequently involved region of the brain. Seizures are an uncommon feature.

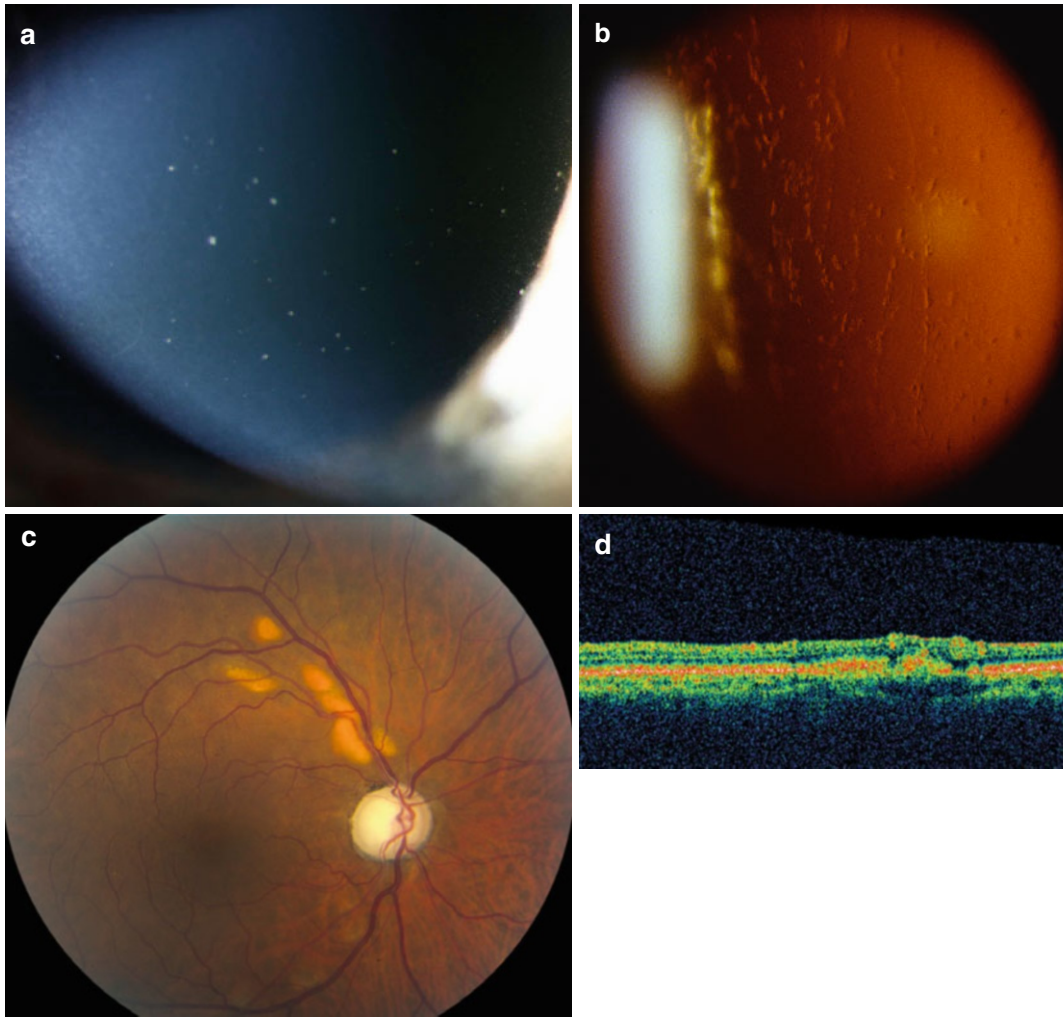

Fig. 7.1 Slit-lamp photograph showing keratic precipitates (**a**), vitreous cells (**b**, retroillumination), and creamy subretinal pigment epithelial infiltrates (**c**, fundus appearance and **d**, optical coherence tomography)

7.3.2 Signs

7.3.2.1 Ophthalmic

The anterior segment findings of PVRL are nonspecific and include keratic precipitates, aqueous cells, and aqueous flare suggestive of inflammation (Fig. 7.1) [25]. The hallmark feature is vitreous cells (50 %), combined anterior and vitreous cells (22 %), and chorioretinitis or subretinal pigment epithelial infiltrates (18 %) [23]. The presence of clumps of cells in the vitreous is a common finding. Multifocal or diffuse chorioretinal infiltrates may be seen with or without vitreous cells. Multifocal subretinal pigment epithelial infiltrates are considered to be pathognomonic (Box 7.1) [26]. Rare findings include perivasculitis, retinal artery occlusion, optic atrophy, and exudative retinal detachment [18, 27–30].

7.3.2.2 Diagnostic Findings of PCNSL-O (Box 7.1)

- Clumps of cells in the vitreous.
- Multifocal or diffuse chorioretinal infiltrates with or without vitreous cells.

- Multifocal subretinal pigment epithelial infiltrates are considered to be pathognomonic.
- Rare findings include choroidal mass, perivasculitis, retinal artery occlusion, and exudative retinal detachment.
- Keratic precipitates, aqueous cells, aqueous flare, and cystoid macular edema are suggestive of inflammation.

7.3.2.3 Central Nervous System

Unlike PVRL, PCNSL is a rapidly growing tumor; the diagnosis is frequently made within a few months of the onset of symptoms. The lesions in the CNS tend to be periventricular in location, thus allowing access to cerebrospinal fluid (CSF) and meninges. An associated meningeal involvement is present in approximately 40 % of cases. Brain lesions can be multifocal, particularly in immunosuppressed individuals.

7.4 Diagnostic Evaluation

Diagnostic evaluation should begin with a thorough history focused on ocular symptoms, changes in cognitive functioning, neurological deficits, and risk factors for immunosuppression. A complete ophthalmic examination of both the anterior and posterior segment is required to assess disease extent and laterality. In the setting of existing PCNSL, the diagnosis of PVRL is straightforward and biopsy of an ophthalmic site is unnecessary if the clinical findings are typical.

The relationship between PVRL and PCNSL is variable with intraocular involvement preceding, occurring simultaneously, or following CNS manifestations. It is therefore imperative that all cases of PVRL should be thoroughly evaluated by a medical oncologist to exclude CNS involvement at the initial diagnosis and periodically thereafter (Fig. 7.2). Conversely, periodic ophthalmic examinations should be part of the diagnostic evaluation and subsequent management of individuals diagnosed with PCNSL.

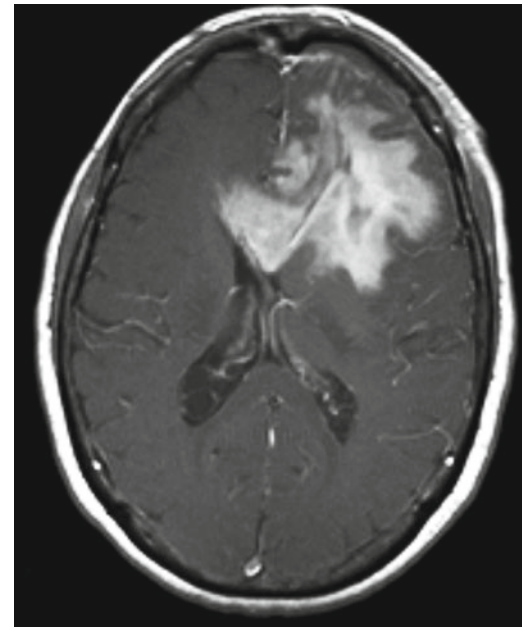

Fig. 7.2 T1-weighted MRI scan of the brain with gadolinium, showing a diffusely enhancing area in the left frontal lobe (Reproduced with permission from Singh et al. [5])

7.4.1 Ophthalmic

In the absence of known PCNSL, the diagnosis of PVRL is based upon clinical, histopathological, and cytological features. Biopsy should be considered in middle-aged or elderly patients with "idiopathic" unilateral or bilateral recurrent uveitis, particularly cases that are unresponsive to steroids. Several diagnostic techniques exist including vitreous, retinal, and subretinal biopsy. Neoplastic cells can be identified by an experienced cytologist, using an array of techniques such as liquid-based cytology, cytospin, and cell block preparations stained with modified Papanicolaou, Giemsa, or standard hematoxylin and eosin stains (Fig. 7.3). Proper and rapid handling of vitreous samples is a must, as aspirates are generally of low cellularity and neoplastic cells undergo rapid lysis.

Most commonly, diagnostic 23-gauge pars plana vitrectomy is performed. It is recommended that an undiluted vitreous sample of about 1–2 ml be collected prior to starting the infusion during vitrectomy [5]. Following

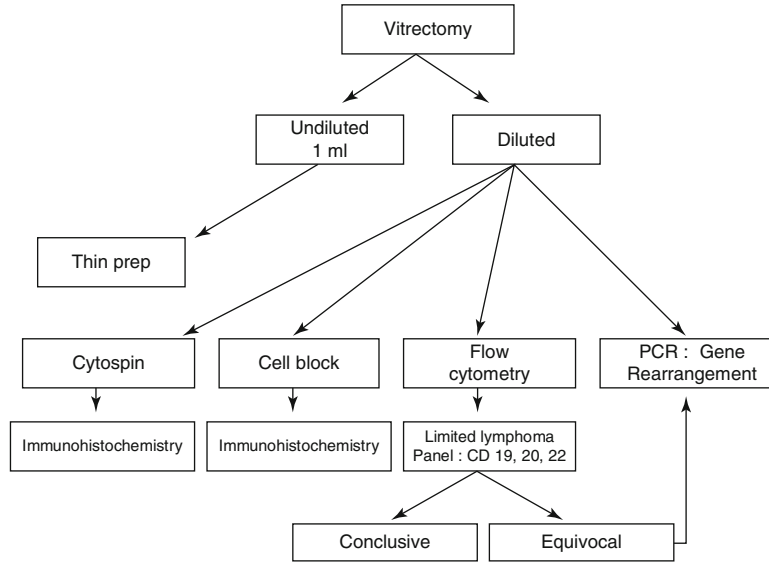

Fig. 7.3 Schema for analysis of vitreous samples for suspected lymphoma. Initial undiluted vitreous specimen (about 1 ml) is processed by ThinPrep for liquid-based cytology because it preserves the cellular details. The diluted vitreous sample is divided into four portions for cytospin, cellblock, and flow cytometry. Gene rearrangement studies are performed if the flow cytometry results are equivocal (Derived from Rishi et al. [33])

collection of the first sample, the infusion fluid is started, and a second diluted specimen is obtained using gentle vitreous cutting [31]. Some centers submit the vitreous cassette to pathology as a third sample [32]. Biopsy specimens should be delivered to the laboratory, without fixative, within 1 h of surgery [33, 34]. It is not uncommon for multiple vitreous biopsies to be performed before a definitive diagnosis is established. There is recent interest in using 25-gauge sutureless vitrectomy for diagnostic purposes, and these techniques may improve patient comfort and decrease operative times. This technique has been used with success in some centers [32].

In the presence of chorioretinal lesions, a chorioretinal or retinal biopsy may be required [11]. Using a standard three-port pars plana vitrectomy, an initial core vitrectomy is performed allowing access to the subretinal infiltrate. Vitreous separation is induced and thorough vitrectomy is performed overlying the biopsy site. A retinectomy large enough to allow entrance of the vitreous cutter and suction tubing is created. With gentle cutting, several samples are obtained [35]. Subretinal aspirates should be placed in a mild cytofixative, such as herpes-glutamic acid buffer-mediated organic solvent protection effect (H.O.P.E.) fixative or Cytolyt (Cytyc) [34].

Approximately 73 % of PVRL cases are diffuse large B-cell lymphomas with characteristic histologic and cytologic features [36]. Tumor cells are two to four times larger than normal lymphocytes, pleomorphic, and have scant cytoplasm [37]. The nuclei may be round, oval, or indented, with conspicuous nuclear membranes, occasional fingerlike protrusions, and multiple, prominent, eccentrically located nucleoli (Fig. 7.4). Mitoses are frequently observed [19]. With the use of electron microscopy, intranuclear inclusions, cytoplasmic crystalloids, and pseudopodal extensions of the cytoplasm, cytosomes, and autophagic vacuoles can be identified [38].

Due to the limited number of cells available for evaluation, it is often difficult to reach a conclusive diagnosis based solely on cytopathological findings. Ancillary histopathologic techniques include immunohistochemistry and flow cytometry to determine immunophenotypes of lymphocytes, gene rearrangement studies using polymerase chain reaction (PCR), and determination of interleukin levels. Greater than 1.0 ratio of interleukin-10 and interleukin-6 has been considered as an indicator of PVRL [39, 40]. However, the clinical utility of determining the interleukin ratio is not clearly established, as cases with PVRL with low interleukin ratios have also been reported [41]. PCR-based tests are used to detect

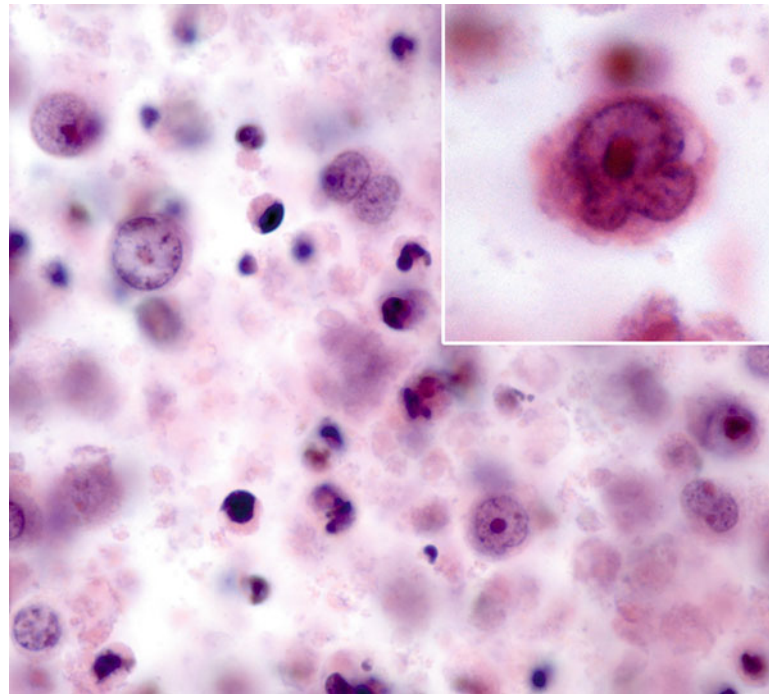

Fig. 7.4 Vitrectomy sample containing large atypical lymphocytes, necrotic lymphoid cells, and nuclear debris. Inset shows characteristic nuclear membrane protrusions and a prominent nucleolus (main figure, Millipore filter, hematoxylin and eosin, original magnification Å ~ 250) (Courtesy of RC Eagle Jr, MD) (Reproduced with permission from Singh et al. [5])

monoclonal proliferation of B lymphocytes, clonal heavy chain immunoglobulin gene rearrangement, bcl-2 gene translocation, and T-cell gene rearrangements [11, 42, 43].

7.4.2 Central Nervous System

Cranio-spinal magnetic resonance imaging (MRI) with gadolinium is the diagnostic procedure of choice. Cranial lesions appear as multiple isointense nodules on T1-MRI and demonstrate characteristic dense and diffuse contrast enhancement (Fig. 7.2). Meningeal enhancement with gadolinium is indicative of meningeal involvement. Many centers also perform CT scans of the chest, abdomen, and pelvis to exclude systemic involvement or systemic origin of the CNS involvement. Cerebrospinal fluid sampling should be performed in every patient with suspected or confirmed PCNSL. Testicular ultrasound examination is recommended in elderly patients because of frequent CNS involvement in testicular lymphomas.

Demonstration of malignant lymphocytes in the CSF is confirmatory for the diagnosis of PCNSL. The CSF shows lymphocytic pleocytosis, raised protein concentration, and normal or low glucose concentration. Visceral involvement is rare at the initial diagnosis but is not uncommon in the terminal stages.

7.5 Differential Diagnosis

In general, all causes of chronic posterior uveitis such as syphilis, sarcoidosis, tuberculosis, and Whipple's disease should be considered in the differential diagnosis. Syphilitic uveitis is a late disease manifestation and may be preceded by dermatologic signs (chancre or rash) and constitutional flu-like symptoms. Ocular syphilis is highly suggestive of CNS involvement and requires systemic therapy. Whipple's disease is a rare, multiorgan infection caused by the bacterium *Tropheryma whipplei.* Middle-aged Caucasian men in the United States and continental Europe are most frequently affected [44, 45]. While common symptoms include weight loss, diarrhea, polyarthralgia, and abdominal pain, extraintestinal manifestations including chronic uveitis can occur. Definitive diagnosis is based upon PCR of vitreous samples.

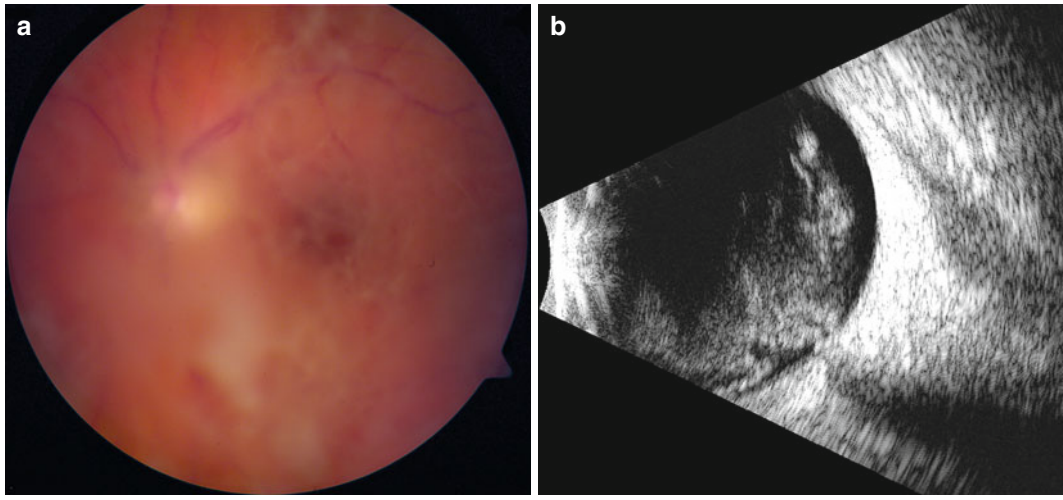

Fig. 7.5 Vitreous amyloidosis can mimic the clinical appearance of vitreoretinal lymphoma (**a**). The vitreous deposits are amorphous, predominantly in the posterior vitreous and overlying the posterior pole (**b**)

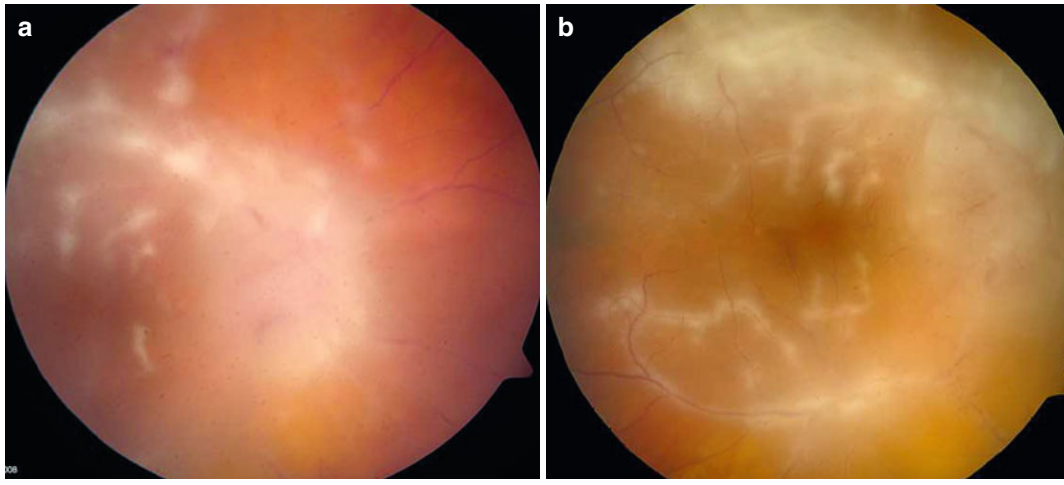

Fig. 7.6 The right optic disc, surrounding retina, and perivascular areas show inflammatory infiltrates in a patient with HTLV-1 retinitis (**a**). Following vitrectomy 6 weeks from initial photographs, the perivascular infiltrates are seen more distinctly (**b**). (Reproduced with permission from Agarwal et al. [50])

Vitreous amyloidosis can also mimic the clinical appearance of PVRL (Fig. 7.5). This rare entity is usually observed in the setting of systemic amyloidosis, although localized ocular involvement is known to occur [46]. Vitreous involvement appears to be linked to the hereditary neuropathies associated with mutation of amyloid protein transthyretin (TTR) [47–49]. Definitive diagnosis is made by vitreous biopsy. The specimen reveals an acellular mix of fibrillar aggregates and focal rosettes. The sample displays metachromatic properties under polarized light when stained with Congo red and toluidine blue, consistent with amyloidosis [46]. Treatment in symptomatic patients consists of total vitrectomy in combination with phacoemulsification and intraocular lens implantation.

Retinal lymphoma in the setting of adult T-cell leukemia/lymphoma (ATL) secondary to HTLV-1 infection may present with retinal vasculitis, retinal infiltration, and disc edema (Fig. 7.6) [50].

Retinal biopsy with subsequent light microscopy evaluation, immunophenotypic studies, and PCR to detect clonal T-cell receptor gene rearrangement may be required for definitive diagnosis [51, 52].

Infiltrative choroidal lesions such as metastatic tumors and amelanotic melanomas can also mimic PVRL. HIV infection predisposes to both opportunistic infections and PVRL; therefore, in an immunosuppressed patient, disseminated choroiditis due to *Nocardia* chorioretinitis and *Pneumocystis* choroiditis should be excluded. When the retina and the vitreous are involved, consideration must be given to entities such as viral or fungal retinitis, acute retinal necrosis syndrome, and toxoplasmosis. Multifocal subepithelial lesions of PVRL should be differentiated from diffuse unilateral subacute neuroretinitis, birdshot retinochoroidopathy, multifocal choroiditis, multiple evanescent white-dot syndrome, and punctate inner choroidopathy. When perivascular infiltrates are present, ocular sarcoidosis and retinal vasculitides must be considered. Patients with systemic lymphomas not arising in the CNS, who develop retinal infiltrates, are more likely to have a superimposed viral or fungal retinitis rather than an intraocular lymphoma [53].

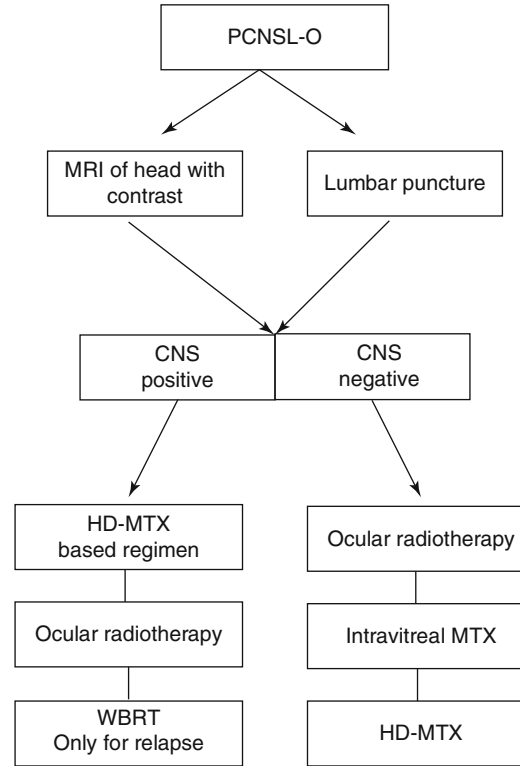

Fig. 7.7 Schema outlining our current approach of management of patients with PCNSL-O. HD-MTX, high-dose methotrexate; WBRT, whole-brain radiation therapy

7.6 Treatment

As PCNSL is very sensitive to corticosteroids, treatment with corticosteroids should be withheld in suspected cases until tissue diagnosis is obtained. The treatment of PCNSL has evolved in the last two decades, and there is a general consensus that regimens containing high-dose methotrexate, with or without whole-brain radiation therapy (WBRT), yield better response rates and outcomes than regimens that do not contain high-dose methotrexate. A schema outlining our current approach of management is shown (Fig. 7.7).

7.6.1 Ophthalmic Treatment

Management of PVRL should be undertaken in partnership with an oncologist who has an expertise in lymphoma. As a high percentage of patients with PVRL eventually develop CNS involvement, some experts recommend that the treatment goal for PVRL must be to eradicate the ocular disease and prevent subsequent CNS involvement. Others favor local therapy for disease confined to the eye with close follow-up and systemic therapy if evidence of CNS disease develops.

7.6.1.1 Local Therapy for PVRL

Local therapies for PVRL include ocular radiation and intravitreal chemotherapy. There has been no trial that has compared these therapies head to head. At the present time, some experts prefer intravitreal chemotherapy while others recommend ocular radiation as first-line therapy. Traditional therapy with ocular radiation (35–40 Gy in ~ 15 divided fractions) controls ocular involvement in the majority of cases [54], but most progress to develop CNS disease (Fig. 7.8) [24]. Irradiation of both eyes (because

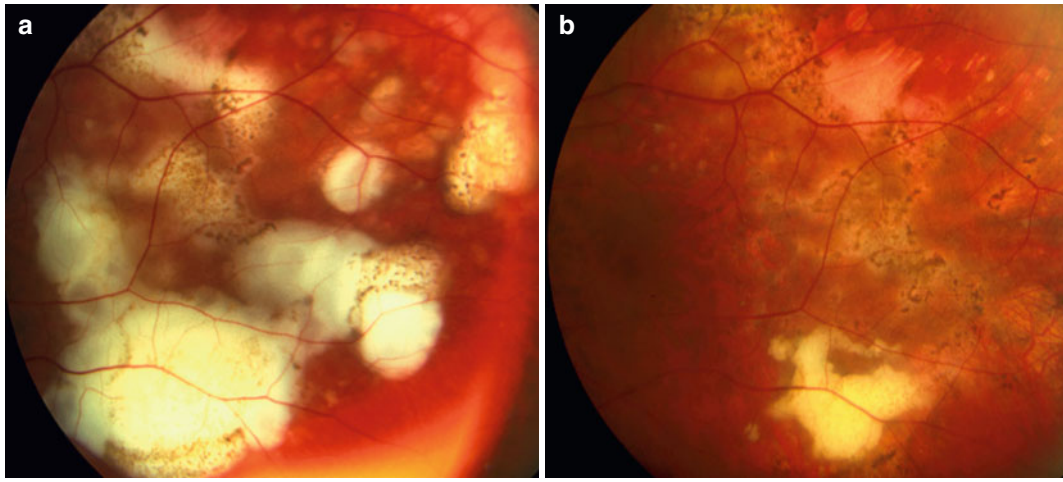

Fig. 7.8 Fundus photograph of the left eye demonstrating multiple creamy subretinal pigment epithelial deposits (**a**). Regression of the subretinal tumors following external beam radiotherapy (**b**, 45 Gy) (Courtesy of S. Seregard, MD.) (Reproduced with permission from Singh et al. [50])

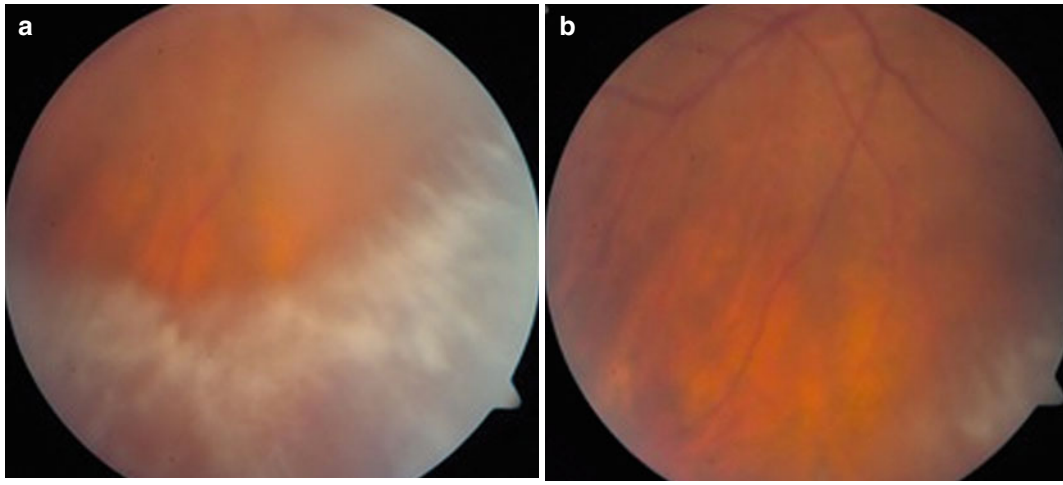

Fig. 7.9 Fundus appearance before (**a**) and after 3 months (induction and consolidation) of treatment with intravitreal methotrexate (**b**). Note dramatic clearance of vitreous cells

of the high incidence of bilaterality) should be strongly considered for patients with proven PVRL. Since radiation therapy to the brain may have significant side effects, its use for prophylaxis in patients without proven CNS involvement is not advisable.

Intravitreal methotrexate as an initial treatment, or for those with recurrence following ocular radiation therapy, has been investigated in a small number of patients with encouraging results (Fig. 7.9; Table 7.1) [5]. In a study involving 16 patients, intravitreal methotrexate (400 μg/0.1 ml) according to a standard induction–consolidation–maintenance regimen was given over a period of 1 year [55]. All patients showed initial tumor control after a maximum of 12 methotrexate injections, but three patients relapsed. The median follow-up was 18.5 months (range 6–35 months). Complications included cataract (73 %), corneal epitheliopathy (58 %), maculopathy (42 %), and vitreous hemorrhage (8 %). No patient had irreversible loss of vision.

Table 7.1 Chemotherapy for treatment of intraocular lymphoma (PCNSL-O)

Author	Year	Cases/eye	Treatment method			Response (%)	Side effects (%)
			Indication	Route	Agent		
Fishburne	1997	47 eyes	Recurrent	Intravitreal with BBB	MTX 400 µg	100	Visual loss 15
Sandor	1998	14		Intravenous and intrathecal	MTX, thiotepa, vincristine, cytarabine	79	Recurrence 71 Neurotoxicity 14
Soussain	2001	22	Refractory/recurrent	Intravenous	Multiagent chemotherapy with stem-cell rescue	75	Recurrence 10 Neurotoxicity 35
Smith	2002	16/26 eyes	Initial	Intravitreal	MTX 400 µg	100	Recurrence 12 Cataract 73 Epitheliopathy 58 Maculopathy 42 Vitreous hem 8 Optic atrophy 4 Endophthalmitis 4
Batchelor	2003	9	Initial	Intravenous	MTX High dose	78	Recurrence 40
Frenkel	2008	26/44 eyes	Initial/recurrent	Intravitreal	MTX 400 µg	91	Conjunctival hyperemia and some form of keratopathy 100
Soussain	2008	43	Refractory/recurrent	Intravenous	Multiagent chemotherapy with stem-cell rescue	61	Treatment-related mortality ~10
Jahnke	2009	10	Initial/recurrent	Intravenous/oral	Ifosfamide or trofosfamide	90	Thrombocytopenia or leucopenia 40

BBB blood–brain barrier disruption with mannitol, *MTX* methotrexate
Excluding single-case reports

Recently, Frenkel and colleagues reported their experience with intravitreal methotrexate in the largest series to date. They demonstrated clinical remission after a mean of 6.4 ± 3.4 (range, 2–16) injections of methotrexate, in 44 eyes of 26 patients with PVRL [56]. Intravitreal rituximab has been shown to penetrate the entire retina, and in recent times there has been interest in exploring its role in PVRL. Small studies have demonstrated the activity of intravitreal rituximab monotherapy for PVRL. There have been early reports of efficacy of combination of intravitreal methotrexate and rituximab, and this combination remains investigational [57]. This combination approach is attractive as it may decrease the need for multiple methotrexate injections and may help in reducing toxicity.

7.6.1.2 Systemic Therapy for PVRL

Disease relapse in the CNS is a major issue, particularly after local treatment with ocular radiotherapy or intravitreal chemotherapy. Systemic chemotherapy offers the advantage of simultaneous treatment of both ocular and microscopic intracranial disease (Table 7.1). High-dose methotrexate forms the backbone of treatment in PCNSL patients. Batchelor and colleagues reported their experience in nine patients with intraocular involvement of lymphoma treated with methotrexate at 8 g/m^2 [58]. Potentially cytotoxic, micromolar levels of methotrexate were detectable in the aqueous and vitreous humor in most patients. An intraocular response was reported in seven patients, with complete response (CR) in six and a partial response (PR) in one. Efficacy of ifosfamide or trofosfamide was assessed in a recent, prospective, single-center study of ten patients with PVRL that were treated with these therapies. There was a 100 % response rate (nine CRs, one PR) observed that resulted in a median overall survival (OS) of 32 months. Of the seven relapses seen in the study, five were ocular and two occurred in the CNS.

Unlike PCNSL, experience with combination chemotherapy in PVRL is extremely limited. Sandor and colleagues reported 100 % response rate (11 CRs, three PRs), in 14 patients (five with intraocular involvement) in patients treated with a complex treatment regimen consisting of intravenous methotrexate, vincristine, and thiotepa as well as intrathecal methotrexate and cytarabine. Although a high initial response was seen, the duration was limited and additional therapy was required at relapse.

High-dose chemotherapy followed by stem-cell transplantation has been studied in a limited number of trials that have included small numbers of patients with ocular disease. These studies have included both newly diagnosed patients and patients with refractory or recurrent disease [59–61]. Although ocular response has been reported with this aggressive approach, high relapse rates along with observed toxicities associated with stem-cell transplantation make this approach investigational at the current time.

In a report of 221 immunocompetent patients with PCNSL and/or PVRL, Grimm and colleagues reported no difference in disease progression rates or OS in patients treated with local therapy versus those who received systemic therapies. The report, although the largest series reported, was an uncontrolled, multicenter, and retrospective study that utilized different treatments depending on the preference of the treating physician [62]. Thus, as noted above, there is no consensus on treatment of PVRL. An individualized patient-specific approach should be taken (Box 7.2).

7.6.1.3 Treatment options for PCNSL (Box 7.2)

- External beam radiotherapy alone or combined with systemic chemotherapy has been used in treatment of PVRL. Side effects include radiation retinopathy and radiation maculopathy, and there is risk of recurrence of PVRL and PCNSL.
- Treatment options that include intravitreal chemotherapy using methotrexate and/or rituximab are increasingly been employed

in controlling the PVRL and avoid the side effects of EBRT. Major vision-threatening side effects have not been reported with intravitreal chemotherapy.

- Methotrexate-containing multiagent chemotherapy regimens are the preferred therapy for treatment of central nervous system disease. The timing and dose of whole-brain radiotherapy is unclear, given the significant risks of late neurotoxic effects.

7.6.2 Central Nervous System

Until recently, whole-brain radiotherapy was the mainstay of treatment, which improved the median survival to about 12–18 months from 4 months in untreated patients [63]. In 1992, trials using a combination of methotrexate-based chemotherapy and radiotherapy first reported an improved median survival of about 40 months [63]. However, the combination of whole-brain radiotherapy and chemotherapy is associated with a significant risk of neurotoxicity in older individuals [64]. Therefore, chemotherapy alone

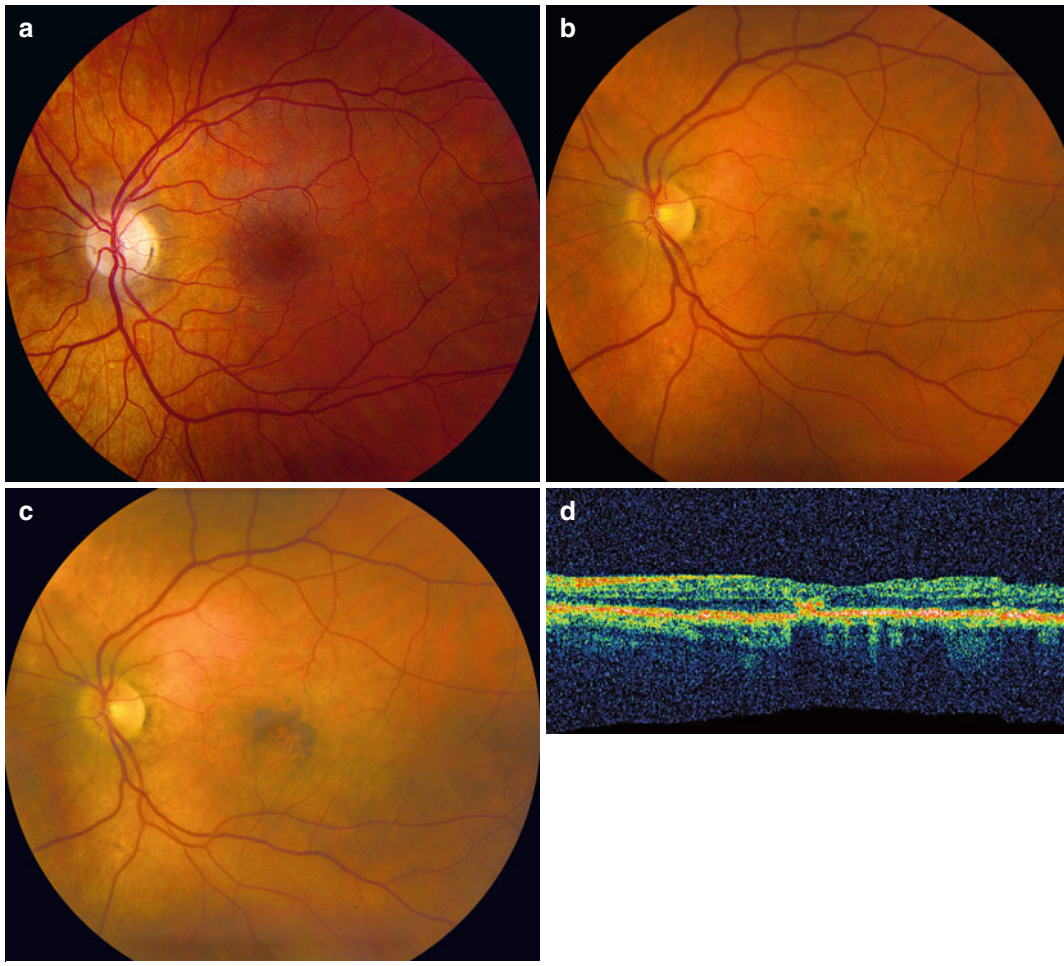

Fig. 7.10 Color photographs of left fundus from two patients with primary central nervous system lymphoma treated with blood–brain barrier disruption therapy demonstrating the spectrum of hyperpigmentation and retinal pigment epithelium (RPE) loss within the macula. (**a**) Mild and moderate severity (**b**). Four months after completion of treatment (patient **b**), note progression of retinal pigment epithelium changes(**c**). Optical coherence tomography showing irregular thickening of the retinal pigment epithelium (Reproduced with permission from Galor et al. [66])

is the initial treatment of choice in older individuals (60 years) [63]. As the blood–brain barrier is a limiting factor, which restricts drug entry into the CNS, various strategies to circumvent the blood–brain barrier have been evaluated. These include the use of high doses of chemotherapy, intrathecal drug delivery, intraventricular drug delivery by a reservoir, and temporary disruption of the blood–brain barrier (BBBD) with mannitol infusion [63]. In a large multi-institutional experience of 149 newly diagnosed PCNSL patients (with no prior WBRT) that were treated with osmotic BBBD and intra-arterial (IA) methotrexate, an overall response rate of 82 % (58 % CR; 24 % PR) was reported with a median PFS and OS of 1.8 and 3.1 years respectively [65]. Maculopathy is an ocular complication associated with BBBD with mannitol (Fig. 7.10) [66]. The characteristic findings include RPE clumping in the macula and hyperpigmentation in the foveal region associated with variable RPE atrophy. Mannitol maculopathy is typically bilateral but often asymmetric. Unlike age-related wet macular degeneration, there is absence of subretinal fluid or macular edema. The maculopathy may progress, even after completion of treatment.

In recent years high-dose methotrexate-containing multiagent regimens have been commonly adopted as the preferred treatment option for this disease entity. The timing and dose of whole-brain radiotherapy is still unclear, given the significant risks of late neurotoxic effects, and there is a large ongoing cooperative group study to evaluate the role of radiation in upfront treatment of PCNSL [67].

7.7 Prognosis

Survival after whole-brain radiation therapy ranges from 12 to 18 months. The survival increases to an average of 36–48 months following high-dose methotrexate-based chemotherapy regimen alone or chemotherapy followed by radiation [18, 23, 54]. Age less than 60 years at diagnosis and high initial performance status are well recognized favorable prognostic factors in PCNSL [1, 68].The International Extranodal Lymphoma Study Group also devised a prognostic scoring system comprising of 5 variables associated with poor prognosis that include age greater than 60 years, Eastern Cooperative Oncology Group performance status greater than 1, increased CSF protein level, increased serum lactate dehydrogenase level, and tumor involvement of the deep regions within the brain (basal ganglia, periventricular regions, brain stem, or cerebellum) [69]. Involvement of brain stem and meninges implies an unfavorable prognosis [68]. Expression of p53, c-Myc, or Bcl-6 also suggests a poor prognosis [70]. The presence or absence of retinal involvement in the setting of existing CNS disease is not a prognostic factor that influences survival [68].

7.8 Summary

Primary lymphoma of the central nervous system (CNS) is considered a variant of extra-nodal non-Hodgkin's lymphoma (NHL), a high-grade B-cell malignancy. There are no known risk factors in immunocompetent individuals; however congenital immunodeficiency and iatrogenic or acquired immunosuppression (AIDS) are risk factors for PCNSL. Brain, spinal cord, and meninges either separately or in various combinations can be involved. Patients may be asymptomatic, but up to 50 % present with painless blurred vision, floaters, or both. The hallmark diagnostic feature is vitreous cells (50 %), combined anterior and vitreous cells (22 %), and chorioretinitis, or subretinal pigment epithelial infiltrates (18 %). Several diagnostic techniques exist including vitreous, retinal, and subretinal biopsy. There is a general consensus that regimens containing high-dose methotrexate, with or without whole-brain radiation therapy (WBRT), yield better response rates and outcomes than regimens that do not contain high-dose methotrexate. Disease relapse in the CNS is a major issue, particularly after local treatment with ocular radiotherapy or intravitreal chemotherapy. Management should be undertaken in partnership with an oncologist who has an expertise in lymphoma.

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Retinal Metastatic Tumors

8

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8.1 Introduction

Intraocular metastasis is the most common intraocular malignancy. The most common primary tumor site is the lung in men and breast in women [1]. In the majority of cases, intraocular metastasis is limited to choroid. Other ocular structures, like the vitreous, optic nerve, and iris, may also be involved and rarely, a tumor may metastasize to the retina.

Metastatic disease to the retina was first described in 1879 by Schiess-Gemuseus and Roth in a patient with primary cutaneous melanoma [2]. In 2012, Srivastava and Bergstrom reviewed 37 reported cases of retinal metastasis and noted that the most common primary tumors were cutaneous melanoma, pulmonary carcinoma, and gastrointestinal adenocarcinomas [3].

We identified 42 reported cases of retinal metastasis, either isolated to retina or also involving the vitreous, published in the English literature from 1935 to 2012 (Table 8.1). There were 50 eyes of 42 patients with 25 (60 %) males and 17 (40 %) females with average age of 52 years (range 15–81 years).

The majority of cases had unilateral presentation (81 %) and rarely (19 %) presented with bilateral retinal metastases. The right and left eyes were involved in 22 and 27 eyes, respectively. In 38 (90 %) cases at the time of retinal metastasis diagnosis, there was a known history of primary non-ocular malignancy. The most common primary malignancies were cutaneous melanoma (40 %), lung carcinoma (19 %), breast

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Table 8.1 Review of clinical findings in patients with retinal metastasis

Author(s)	Age	Sex	Primary tumor (if known at time of eye symptoms)	Signs	Specimen for histopathology	Histopathology	Survival (months)
Smoleroff and Agatston (1934) [4]	55	M	Gastroesophagel adenocarcinoma (yes)	White, elevated, irregular mass in inferotemporal retina with dilated, tortuous veins and a few scattered hemorrhages	Autopsy	Tumor cell invading primarily retina and subretinal space	1
Uhler (1940) [2]	26	M	Cutaneous melanoma (yes)	Infiltration of temporal retina	Autopsy	Spindle shaped malignant cells	NS
Kennedy et al. (1958) [5]	51	M	Rectosigmoid adenocarcinoma (no)	Sharply circumscribed grayish-white lesion in macula	Enucleation	Atypical pseudostratified columnar cells	9
Duke and Walsh (1959) [6]	60	F	Uterine adenocarcinoma (yes)	White elevated mass in macula with overlying vitreous opacities	Enucleation	Cuboidal/columnar pleomorphic cell sheets covering angle, iris, vitreous, retinal and optic nerve surface	6
Liddicoat et al. (1959) [7]	43	M	Cutaneous melanoma (yes)	Small retinal hemorrhage and perivascular white sheathing in temporal retinal midperiphery	Autopsy	Epithelioid tumor cells invading inner retinal layers only	2 weeks
Riffenburgh (1961) [8]	45	M	Cutaneous melanoma (yes)	Vitreous cells, irregular vascularized gray mass with sharp borders and overlying hemorrhage in nasal retina	Enucleation	Metastatic malignant melanoma in the retina only	NS (alive 5 years later)
Koenig et al. (1963) [9]	56	M	Undifferentiated bronchogenic pulmonary carcinoma (no)	Vitreous floaters; white lesion with soft exudative edges and neovascularization in temporal retina; considerable exudation and subretinal fluid was present	Enucleation	Undifferentiated carcinoma cells involving retina with focal invasion into choroid	13
Flindall and Fleming (1967) [10]	68	M	Unknown (no)	Dense vitreous exudate overlying the disk and veil-like exudate inferiorly	Enucleation	Anaplastic tumor cells of epithelial origin invading mainly inner retina, but also vitreous and optic nerve head	NS (alive 2 years later)
Klein et al. (1977) [11]	52	M	Squamous cell pulmonary carcinoma (yes)	Yellow-white infiltrate temporal to macula in OD	Autopsy	Carcinoma cells similar to primary tumor invading retina only in OD	3
				Yellow-white infiltrate superior and inferotemporal to the disk; inferior exudative retinal detachment in OS		Carcinoma cells invading retina, optic nerve and choroid in OS	

Young et al. (1979) [12]	63	M	Pulmonary carcinoma (yes)	Vitreous cells; white retinal macular mass with surface hemorrhages; perivascular white infiltrates	Vitreous biopsy, then autopsy	Adenocarcinoma cells; morphological changes related to EBRT, but few vitreous tumor cells seen	7
Robertson et al. (1981) [13]	43	F	Cutaneous melanoma (yes)	Brown plaque over and involving superior retina in OD			4
				Golden-brown vitreous spherules; brown plaque over and involving superior retina in OS	Vitreous biopsy in OS	Malignant pigmented, pleomorphic melanoma cells in OS	
	37	F	Cutaneous melanoma (yes)	Golden-brown vitreous spherules subsequently infiltrating anterior chamber with increased IOP in OD	Aqueous biopsy, then enucleation	Heavily pigmented, highly malignant epithelioid cells disseminated throughout anterior chamber, vitreous and surface retina	NS (alive 11 months later)
Piro et al. (1982) [14]	56	F	Breast infiltrative ductal carcinoma (yes); cerebral malignant astrocytoma (yes)	Vitreous opacities in OD	Postmortem enucleation in OD	Breast carcinoma cells in the vitreous and retina in OD	5
				White vitreous opacities in OS	PPV, then postmortem enucleation in OS	Breast carcinoma; tumor cells infiltrating vitreous, retina and inner surface of ciliary body in OS	
Letson and Davidorf (1982) [15]	44	M	Cutaneous melanoma (yes)	Superficial gray-brown retinal and perivascular infiltrates with feathery edges in OD	None		3
				Superficial gray-brown retinal and perivascular infiltrates with feathery edges in OS; brown choroidal lesion inferior to disk	None		
de Bustros et al. (1985) [16]	33	M	Cutaneous melanoma (yes)	Tan retinal mass	NS		5.5
Takagi et al. (1989) [17]	45	M	Pulmonary adenocarcinoma (yes)	Whitish vitreous opacities; white masses involving disk and inferotemporal retina; white exudate-like lesions with hemorrhages along retinal vessels	Enucleation (prevention of CNS spread)	Adenocarcinoma cell nests found in inner retina, optic nerve head and vitreous; tumor emboli within central retinal vein	3

(continued)

Table 8.1 (continued)

Author(s)	Age	Sex	Primary tumor (if known at time of eye symptoms)	Signs	Specimen for histopathology	Histopathology	Survival (months)
Best et al. (1990) [18]	71	F	Cutaneous melanoma (yes)	Thick yellow-white globular vitreous opacities	PPV, then enucleation	Large pigmented pleomorphic melanoma cells; melanoma cells infiltrating retina, optic nerve head, vitreous (also orbital tissue adjacent to PPV wound)	NS
Leys et al. (1990) [19]	49	M	Oat cell pulmonary carcinoma (yes)	White retinal plaque temporal to macula	Autopsy	Retinal tumor cells corresponding to the original oat cell carcinoma	1
	42	F	Breast adenocarcinoma (yes)	Vitreous opacities over the macula	PPV	Epithelioid malignant cells	18
Balestrazzi et al. (1995) [20]	40	F	Cutaneous melanoma (yes)	Vitreous hemorrhage; yellow-white vascularized mass in superonasal retina with vitreous condensation and pigment dusting	Transcleral resection	Retinal pigmented melanoma cells	17 (suicide)
Spraul et al. (1995) [21]	74	F	Adenocarcinoma of the breast or colon (yes)	Yellow-white, solid retinal tumor in the superotemporal quadrant associated with shallow serous retinal detachment	Enucleation	Adenocarcinoma tumor cells involving retina	NS (alive 10 months later)
Spraul et al. (1996) [22]	55	M	Cutaneous melanoma (yes)	Vitreous hemorrhage, pigmented mass in temporal retina	PPV, then enucleation	Pleomorphic pigmented cells; melanoma cells invading retina and vitreous	NS (several months)
	67	F	Cutaneous melanoma (yes)	Vitreous cells, yellowish subretinal infiltrates	PPV with subretinal aspirate	Pleomorphic pigmented cells with cyologic features identical to cutaneous melanoma cells	NS (alive 24 months later)
Gunduz et al. (1998) [23]	81	M	Cutaneous melanoma (yes)	Total hyphema, no posterior view	PPV, then enucleation	Nonpigmented pleomorphic melanoma cells; amelanotic melanoma infiltrating retina and vitreous; extrascleral seeding through the filtering implant	26
	58	M	Cutaneous melanoma (yes)	Clumps and sheets of pigmented vitreous cells	Vitreous biopsy (FNAB)	Pigmented pleomorphic melanoma cells	12
	36	M	Cutaneous melanoma (yes)	Clumps and sheets of nonpigmented vitreous cells, no view of fundus	PPV	Nonpigmented pleomorphic melanoma cells	3

				Clumps and sheets of nonpigmented vitreous cells, ill-defined retinal whitening at oraserata			
Spadea et al. (1998) [24]	40	F	Cutaneous melanoma (yes)	Vitreous pigment; yellow-white vascularized lesion in the superior peripheral retina	Transcleral resection	Epithelioid apigmented melanoma cells	12 (suicide)
Hutchison et al. (2001) [25]	63	F	Large bowel adenocarcinoma (yes)	Pale, elevated, vascular lesion superotemporal to the macula with associated serous retinal detachment involving the macula	None		NS (alive 3 months later)
Soheilian et al. (2002) [26]	49	M	Cutaneous melanoma (yes)	Mild vitreous hemorrhage mixed with large non-pigmented cells; pigmented mass in superotemporal retina in OD	PPV in OD	Pigmented pleomorphic melanoma cells in OD	12
				Dense vitreous hemorrhage mixed with large non-pigmented cells in OS	PPV × 2 in OS	Initial negative then pigmented pleomorphic melanoma cells in OS	
Truong et al. (2002) [27]	59	F	Breast adenocarcinoma (yes)	Milky, white intraretinal and subretinal fungating mass involving the temporal juxtafoveal macula associated with a shallow serous retinal detachment	None		Unknown
Zografos et al. (2003) [28]	48	M	Cutaneous melanoma (yes)	Beige-colored vitreous cell aggregates	PPV	NS	NS (alive 3 months later)
Zografos et al. (2004) [29]	57	F	? Primary pulmonary melanoma (yes)	Pale beige spherical vitreous mass over grayish-beige retinal mass; preretinal hemorrhage	None		NS (alive 11 months later)
Saornil et al. (2004) [30]	70	M	Gastric adenocarcinoma (yes)	Yellow-white solid retinal juxtapapillary mass	Enucleation	Pleomorphic signet ring cells	23
Rossi et al. (2005) [31]	41	M	Non-small cell lung cancer (yes)	White-elevated mass lesions with serous retinal detachment in superonasal and temporal macula in OD	None		3
				White-elevated mass lesion with serous retinal detachment in superotemporal macula in OS	None		

(continued)

Table 8.1 (continued)

Author(s)	Age	Sex	Primary tumor (if known at time of eye symptoms)	Signs	Specimen for histopathology	Histopathology	Survival (months)
Apte et al. (2005) [32]	39	M	Adenocarcinoma of the cecum (yes)	Intraretinal and subretinal hemorrhage along inferotemporal arcade	PPV, endoresection	Tall, hyperchromatic, pleomorphic, mucin-containing cells arranged in an adenomaotus papillary pattern and invading retina only	NS (alive 3 months later)
Sirimaharaj et al. (2006) [33]	60	F	Breast adenocarcinoma (yes)	Vitreous cells; white precipitates and hemorrhagic spots of nasal midperipheral retina and sheathing along the nasal retinal vessels	PPV	Malignant cells consistent with adenocarcinoma	8
Rundle and Rennie (2006) [34]	55	F	Breast adenocarcinoma (yes)	Well-circumscribed, solitary, vascular, white retinal lesion temporal to the fovea with subretinal fluid	None		NS (alive 2 months later)
Khurana et al. (2007) [35]	76	M	Cutaneous melanoma (no)	Anterior chamber and vitreous pigmented cells; preretinal pigmentation along vascular arcades in the posterior pole and periphery	PPV	Pigmented epithelioid and spindle melanoma cells	6
Alegret et al. (2009) [36]	15	M	Nasopharyngeal carcinoma (yes)	Amelanotic infiltration in the retina along inferotemporal arcade	None		NS
Kim et al. (2010) [37]	64	F	Gastric adenocarcinoma (yes)	Flat, whitish macular infiltrations with white to yellow vitreous seeds in OD	Vitreous biopsy in OD	Spherical clusters of tumor cells with formation of a gland-like empty plural spaces in OD	NS (alive 1 month later)
				Flat, whitish macular infiltrations with white to yellow vitreous seeds in OS			
Coassin et al. (2011) [38]	54	F	Small cell lung cancer (yes)	Vitreous cell, whitish retinal infiltrated with irregular margins, intraretinal hemorrhages, telangiectatic blood vessels and hard exudates in temporal macula	PPV, retinal biopsy	Small round neoplastic cells see on vitreous cytology (retinal biopsy tissue lost)	NS (alive 7 months later)
Payne et al. (2012) [39]	62	M	Small cell lung cancer (yes)	Vitreous haze, retinal whitening in the temporal macula and midperiphery associated with preretinal hemorrhages	Vitreous biopsy, then PPV, retinal biopsy	No neoplastic cells; sheets of adenocarcinoma cells	NS (alive 10 months later)

FNAB fine needle aspiration biopsy, *PPV* pars plana vitrectomy, *NS* not stated, *OD* ocular dexter, *OS* ocular sinister, *IOP* intraocular pressure

adenocarcinoma (14 %), gastrointestinal carcinoma (14 %), and uterine adenocarcinoma (2 %). In the remaining four cases, there was no prior knowledge of systemic malignancy. Subsequent evaluation led to identification of rectosigmoid adenocarcinoma, undifferentiated bronchogenic carcinoma, and cutaneous melanoma as the primary tumor. In one case primary site remained unknown. At the time of presentation, concurrent brain metastases were noted in 4 (10 %) cases.

8.2 Clinical Features

Presenting symptoms typically included decreased vision, ranging from 20/20 to light perception, floaters, and eye pain. In general, clinical symptoms vary based on the size, location, and association with vitreous involvement or concurrent retinal detachment.

Retinal metastasis most commonly presents as yellow-white, intraretinal patches that are unifocal, but bilateral and multifocal presentation is not uncommon (Fig. 8.1). There may be perivascular tumor infiltration leading to retinal opacification but may also have associated intraretinal hemorrhages and subretinal exudates, mimicking an ischemic retinal vascular event. As the tumor enlarges, intraretinal opacification continues and retinal transparency is lost. Coalescing patches of retinal whitening associated with retinal vascular changes may suggest an infectious necrotizing retinitis caused by cytomegalovirus, toxoplasmosis, or other infections [39].

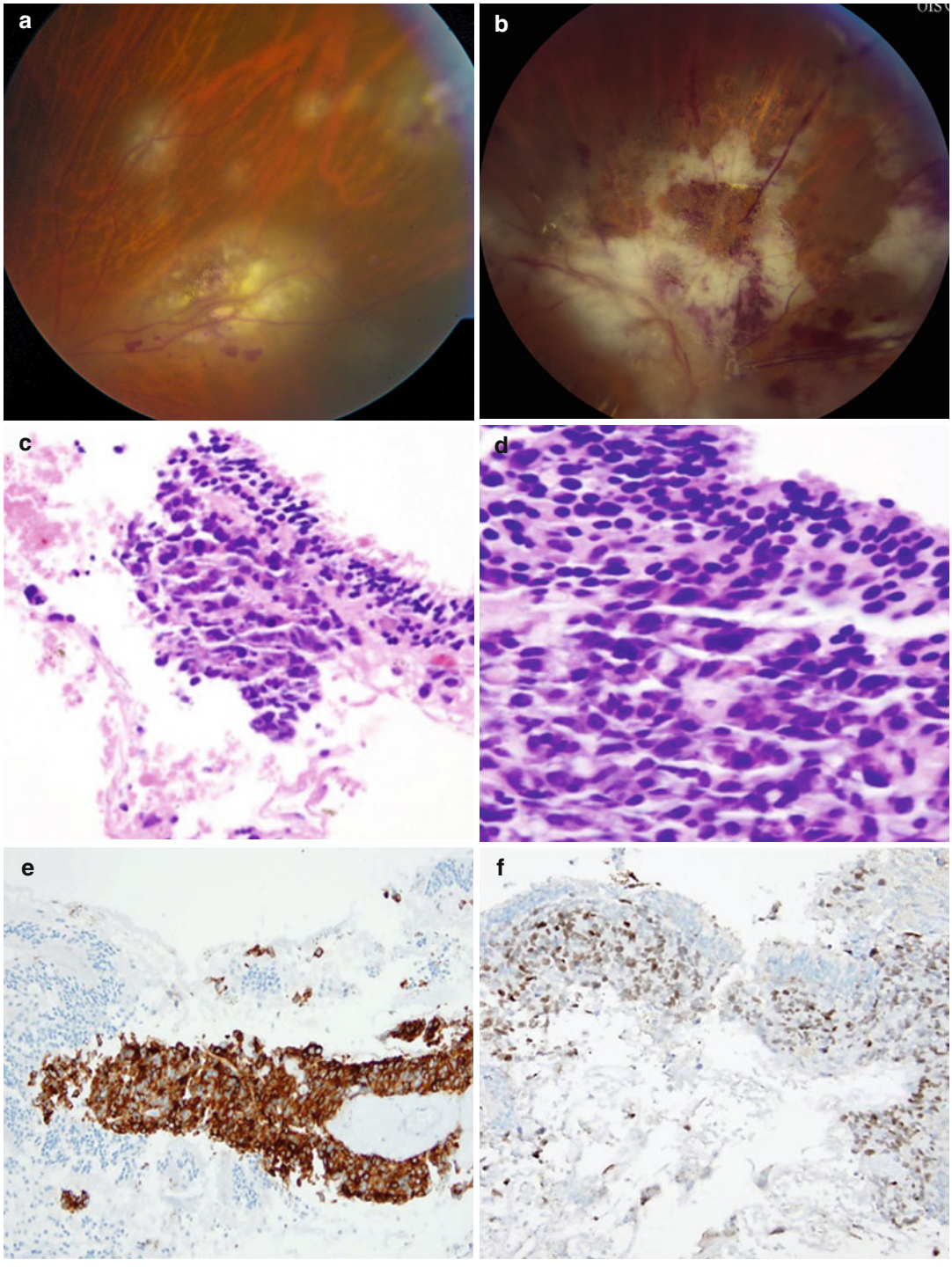
In contrast to choroidal metastasis, retinal metastasis often presents with overlying vitreous cellular infiltration and may masquerade as intermediate uveitis [26]. In cases of metastasis from cutaneous melanoma, vitreous infiltrates present as large, golden-brown spherules [13, 40, 41] In contrast, metastatic carcinoma may present with nonpigmented vitreous opacities [14]. Regardless, the clinical appearance of cellular aggregates in the form of regular spherules should alert the clinician to the possibility of a neoplastic rather than inflammatory cellular infiltration. Secondary glaucoma caused by obstruction of the anterior chamber angle by clusters of tumor cells has been described as an additional complication of retinal metastasis (Fig. 8.2) and was reported in 15 (36 %) eyes (Table 8.1). Retinal detachment is an uncommon presenting sign of retinal metastases.

8.3 Diagnostic Evaluation

Clinical examination combined with fundus photography and fluorescein angiography may be helpful in differentiating retinal metastasis from a retinal vasculitis or other retinal vascular occlusive condition. Optical coherence tomography (OCT) has been used to characterize intraocular and choroidal tumors [42], but its precise role in diagnosing retinal metastases has yet be ascertained.

Tissue diagnosis of a retinal metastasis may benefit the patient in several ways. First, it assists in differentiating a metastatic tumor with malignant cells from other causes of inflammatory retinitis that mimic the clinical appearance. Second, the cell type identified in the biopsy specimen points to the nature of the primary tumor and likely site of origin. Third, it may help guide the future treatment of the patient with systemic chemotherapy or radiation therapy to both the primary and ocular tumors. Prior to 1979, most cases of retinal metastasis were diagnosed at the time of autopsy or enucleation [3].

More recently, globe sparing biopsy approaches have been employed. Eyes with vitreous cellular infiltration may be approached by diagnostic vitrectomy for sample collection or retinal or retinochoroidal biopsy for eyes with no vitreous infiltrations. In 1988, Eagle reported a case of carcinomatous retinitis which had been diagnosed by vitreous aspirate and eye wall biopsy [43]. In 1995, Balestrazzi et al. described local resection of a retinal metastatic lesion secondary to primary cutaneous melanoma [20], and later Spadea et al. described the technique for a chorioretinal biopsy using a transscleral approach [24]. Recently, Payne at al. described endoresection technique for retinal biopsy of a metastases from small cell lung cancer using pars plana vitrectomy, subretinal fluid injection, diathermy, bimanual retinectomy,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air fluid exchange, laser, and long-acting gas tamponade. The biopsy site for this procedure was chosen peripherally and at the edge of normal and abnormal retina to minimize visual sequelae and to improve histopathologic evaluation of active disease at the margin [39].

Currently, pars plana vitrectomy is a preferred method of obtaining cells for cytologic evaluation. It is most important to have an experienced cytopathologist interpret the scanty number of cells. Immunohistochemical stains aid interpretation of the cytology specimen [22, 44]. A negative result does not necessarily rule out metastasis, especially in cases where the retina alone is involved [14]. If clinical suspicion is high, even in light of a negative diagnostic vitrectomy, a chorioretinal biopsy may be required for establishing the diagnosis [38, 39] (Fig. 8.1). We do not routinely recommend fine needle aspiration in cases where there is no associated mass lesion.

In conjunction with an oncologist, systemic work-up for primary tumor is recommended in all patients presenting with ocular symptoms and signs suggestive of a retinal metastases.

8.4 Differential Diagnosis

Conditions most likely to stimulate retinal metastasis include retinal infections and inflammatory retinitis, vaso-occlusive retinal disorders, choroidal metastasis with secondary retinal infiltration, and disorders with vitreous opacities such as intermediate uveitis, amyloidosis, or intraocular lymphoma.

8.5 Treatment (Surgical, Chemotherapy, and Radiotherapy)

The treatment of retinal metastases is ideally carried out in consultation with a multidisciplinary team involving hematologist oncologist, radiation oncologist, and the primary care physician. The treatment is influenced by several factors including the nature of the primary tumor, extent of systemic metastases, prior therapy, and overall functional status of the patient.

Over the past 25 years, patients with retinal metastasis have most often been treated with palliative, hyperfractionated external beam radiotherapy (EBRT). Enucleation has been reserved for those with intractable pain. Small groups of patients were treated with systemic chemotherapy alone or in combination with EBRT or local subconjunctival chemotherapy (Table 8.1). Tumor resection of the retinal metastatic lesion is reserved for patients with solitary, peripheral retinal lesions and may be combined with systemic chemotherapy and EBRT [20, 24, 32]. There is a single report of verteporfin photodynamic therapy (PDT) of a well-circumscribed, vascularized tumor in the macula thought to be a retinal metastasis from breast adenocarcinoma, that regressed after the treatment [34].

Overall regression of the retinal metastatic disease was reported in 9 (21 %) cases; all but one patient was treated with EBRT (one case treated with PDT) [22, 23, 25, 28, 29, 33, 34, 37, 39].

Fig. 8.1 A 78-year-old Caucasian male with past medical history of recurrent small cell lung cancer (SCLC) presented for evaluation for new-onset floaters and blurry vision in the right eye 10 days after second cycle of chemotherapy. Anterior segment examination of both eyes and fundus examination of the left eye were unremarkable. In the right eye, in addition to mild vitreous cell in the right eye, there were numerous, isolated, patchy, white retinal infiltrates (associated retinal hemorrhages) (**a**). In this immunocompromised patient, the presentation was concerning for viral retinitis. The patient was given intravitreal foscarnet on 10/28/09 and 10/29/09 (1,200 mcg/0.05 mL) and started on IV acyclovir. Intravitreal CMV, HSV, and VZV PCR assays were obtained and returned negative. Serum assays for HSV and CMV returned negative. The serum VZV IgG was positive (consistent with immunity to VZV). Despite antiviral therapy, the retinitis continued to progress (**b**). A retinal biopsy was subsequently obtained that revealed small cell carcinoma involving the retina (**c**). The tumoral cells showed the typical nuclear molding of small cell carcinoma (**d**). Immunoperoxidase stains were confirmatory with positive staining for EMA (**e**) and TTF-1 (**f**) (Courtesy of Rishi Singh MD, Peter Kaiser MD, and Nathan Steinle MD, Cleveland, Ohio)

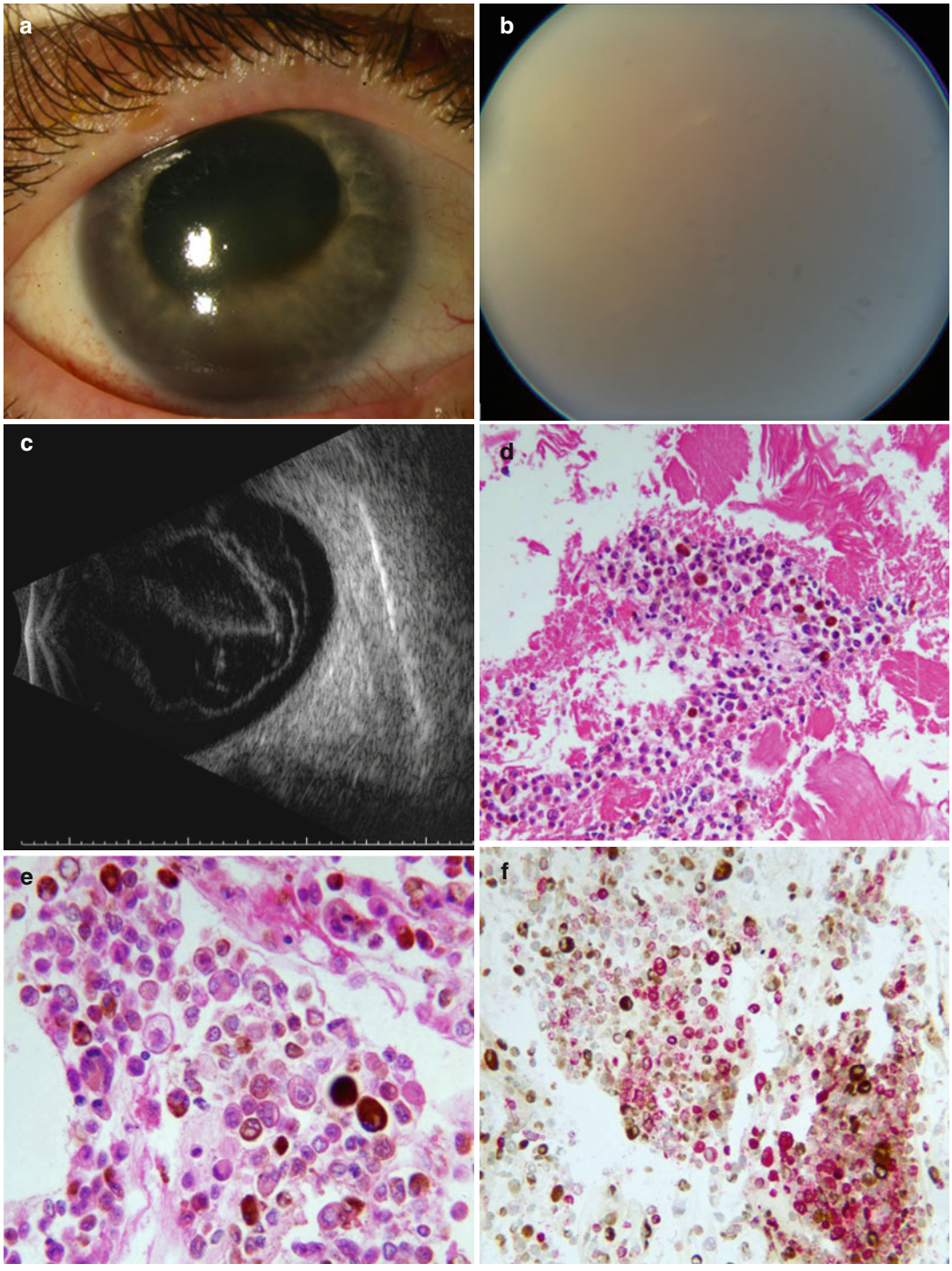
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Fig. 8.2 A 37-year-old male with history of cutaneous malignant melanoma status post-systemic chemotherapy presented with painful eye and decreased vision. He was found to have neovascular glaucoma (**a**) and diffuse vitreous opacities that precluded view of the fundus (**b**). B-scan ultrasonography demonstrated opacities mainly in the posterior vitreous and no formed mass in the choroid (**c**). Diagnostic vitrectomy was performed and golden-brown spherules were noted filling vitreous cavity. Vascular tortuosity, whitish retinal opacities, and diffuse intraretinal hemorrhages were noted resembling retinal metastasis and vaso-occlusive event. On histopathology, collections of epithelioid melanoma cells with occasional melanin-laden macrophages were identified in the vitreous sample (**d**, **e**, hematoxylin and eosin, 20× and 40× magnification respectively). The tumor cells were positive for the melanoma markers HMB-45 (**f**, 20× magnification), S-100 protein, and Melan A (Courtesy of Timothy G. Murray, MD and Sander R. Dubovy, MD, Miami, Florida)

8.6 Prognosis

The posttreatment visual acuity ranges from 20/20 to no light perception (Table 8.1). Systemic prognosis is guarded with an average survival of 10 months (range 2 weeks to 5 years) following diagnosis of the retinal metastasis.

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Neuro-oculocutaneous Syndromes (Phakomatoses)

9

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The term phakomatosis is derived from a Greek word phakomata which means "birth mark." In 1923, Van der Hoeve grouped together von Hippel-Lindau disease, tuberous sclerosis, and neurofibromatosis and called them phakomatoses because of their presence at birth, autosomal dominant inheritance, and the involvement of multiple systems [1]. Subsequently encephalofacial angiomatosis (Sturge-Weber syndrome) was added, although there have been no instances of clear-cut inheritance of this condition. Other common features of the phakomatoses include a predominance of neural and ocular involvement with variable cutaneous and visceral manifestations (Table 9.1). Wyburn-Mason syndrome, retinal cavernous hemangioma, and ataxia telangiectasia have also been grouped with the phakomatoses and have been included in this chapter. Phakomatosis pigmentovascularis and neurocutaneous melanosis are briefly described.

The characteristic systemic manifestations of the phakomatoses are due to the development of hamartomas, which are benign tumors arising from tissues normally present in a specific organ (Box 9.1). Patients with phakomatoses are also predisposed to cancer and have a decreased life span. Advances in molecular genetics have led to identification of genes responsible for von Hippel-Lindau disease, tuberous sclerosis, and neurofibromatosis and have allowed molecular genetic diagnosis (Table 9.2).

Table 9.1 Summary of organ system involvement in various phakomatoses

	Clinical features			
Disorder	Neurological	Ocular	Cutaneous	Visceral
Neurofibromatosis-1	Present	Present	Present	Absent
Neurofibromatosis-2	Present	Absent	Absent	Absent
von Hippel-Lindau disease	Present	Present	Absent	Present
Tuberous sclerosis complex (I)	Present	Present	Present	Present
Tuberous sclerosis complex (II)	Present	Present	Present	Present
Sturge-Weber syndrome	Present	Present	Present	Absent
Wyburn-Mason syndrome	Present	Present	Absent	Absent
Retinal cavernous hemangioma	Present	Present	Absent	Absent
Sebaceous nevus syndrome	Present	Present	Present	Absent
Ataxia telangiectasia	Present	Present	Present	Present
Neurocutaneous melanosis	Present	Variable	Present	Absent
Phakomatosis pigmentovascularis	Variable	Variable	Present	Absent

Table 9.2 Summary of inheritance pattern of various phakomatoses

Disorder	Inheritance	Genetic locus	Gene	Protein	Function
Neurofibromatosis-1	Autosomal dominant	17q11	NF1	Neurofibromin	Inhibits *ras* activity
Neurofibromatosis-2	Autosomal dominant	22q12	NF2	Merlin/schwannomin	Links cytoskeletal proteins and cell membrane
von Hippel-Lindau disease	Autosomal dominant	3p25	VHL	pVHL	Inhibits mRNA elongation
Tuberous sclerosis complex (I)	Autosomal dominant	9q34	TSC1	Hamartin	Regulates vesicular movement
Tuberous sclerosis complex (II)	Autosomal dominant	16p13	TSC2	Tuberin	Inhibits GTP binding proteins
Sturge-Weber syndrome	Sporadic	–	–	–	–
Wyburn-Mason syndrome	Sporadic	–	–	–	–
Retinal cavernous hemangioma	Autosomal dominant	3q, 7p, 7q	–	–	–
Sebaceous nevus syndrome	Sporadic	–	–	–	–
Ataxia telangiectasia	Autosomal recessive	11q22	ATM	ATM protein	Protein kinase
Neurocutaneous melanosis	Sporadic	–	–	–	–
Phakomatosis pigmentovascularis	Sporadic	–	–	–	–

9.1 The Characteristic Features of Phakomatoses (Box 9.1)

- Neuro-oculocutaneous syndrome
- Systemic hamartomatoses
- Familial predisposition to cancer
- Autosomal dominant inheritance (exceptions)

9.2 Neurofibromatosis Type 1 (NF1)

9.2.1 Introduction

Several distinct forms of neurofibromatosis have now been recognized [2]. The most frequent type is neurofibromatosis type 1 (von Recklinghausen disease) [3], followed by neurofibromatosis type 2 (also called central neurofibromatosis). Other rare types include multiple meningiomatosis, spinal schwannomatosis, and segmental neurofibromatosis [2, 4].

9.2.2 Genetic Aspects

NF1 is an autosomal dominant disorder caused by mutations of the *NF1* gene on chromosome 17q11.2 [5]. The penetrance of NF1 mutations is usually complete (100 %) [6]. About 50 % of all index cases are due to new mutations, and the majority (90 %) of new mutations are paternal in origin [7]. A wide variety of *NF1* mutations have been described without any genotype-phenotype correlation [8]. The large size of the gene makes screening the whole gene for mutations difficult. A combination of techniques such as heteroduplex analysis, fluorescent in situ hybridization (FISH), and protein truncation assays results in a high mutation detection rate (95 %) [9].

9.2.3 Pathogenesis

The *NF1* gene codes for neurofibromin [5], a cytoplasmic GTPase-activating protein that negatively regulates oncoprotein *ras* [10]. Recent studies have demonstrated that loss of *NF1* function in neurofibromas is limited to Schwann cells,

Table 9.3 Criteria for the clinical diagnosis of neurofibromatosis type 1 formulated by the National Institute of Health Consensus Development Conference

Presence of any two or more of the following is diagnostic	
Café au lait spots (6 or more)	>5 mm in diameter in prepubertal individuals >15 mm diameter in postpubertal individuals
Neurofibroma	Any type: 2 or more or Plexiform: 1 or more
Axillary and inguinal freckles	
Optic nerve glioma	1 or more
Lisch nodules	2 or more
A distinctive osseous lesion	Sphenoid wing dysplasia or Congenital bowing or thinning of long bone cortex, with or without pseudoarthrosis
First-degree relative with NF1	

Conference NIoHCD [13]

Table 9.4 Ophthalmic manifestations of neurofibromatosis type 1

Location	Lesion	Frequency (%)
Eyelid	Nodular neurofibroma	18
	Plexiform neurofibroma	5
	Café au lait spots	3
Conjunctiva	Neurofibroma	5
Cornea	Prominent corneal nerves	6–22
	Posterior embryotoxon	3–5
Angle	Congenital glaucoma	50
Uvea	Lisch nodules	70–92
	Choroidal hamartoma	51
	Choroidal nevus	3–5
Optic nerve	Pilocytic astrocytoma	2–12
	Optic disc drusen	1

Modified from Lewis and Riccardi [14]

indicating that the Schwann cell is the cell of origin of neurofibromas in NF1 [11].

9.2.4 Clinical Features

NF1 is one of the most common genetic disorders with protean manifestations involving neural tissues [2]. The disease has a prevalence of about 1/3,000 with equal distribution in various ethnic groups [12]. The National Institutes of Health Consensus Development Conference has suggested clinical criteria diagnostic for NF1 (Table 9.3) [13]. Significant ocular findings in NF1 are summarized in Table 9.4 [14, 15].

9.2.4.1 Café au Lait Spots

Large areas of flat cutaneous hyperpigmentation are the most frequent and earliest findings and occur in more than 99 % of individuals with NF1 (Fig. 9.1a). They are present at birth and increase in number and size during childhood. Other forms of hyperpigmentation occur such as axillary and intertriginous freckling.

9.2.4.2 Neurofibroma

Neurofibroma is the hallmark tumor and clinical finding of NF1. Neurofibromas tend to be multiple and develop towards the end of the first decade of life. They appear as discrete soft tumors on the face, hands, and trunk (Fig. 9.1b). Based on their appearance and extent of tissue involvement, neurofibromas can be classified as cutaneous, subcutaneous, nodular plexiform, and diffuse plexiform.

9.2.4.3 Lisch Nodules

The presence of melanocytic hamartomas on the iris, known eponymously as Lisch nodules, is highly characteristic of NF1 [16, 17]. Lisch nodules are typically multiple, tan-colored nodules and are best detected with the slit lamp on the anterior and more so on the inferior surface of the iris (Fig. 9.1c). The prevalence of Lisch nodules gradually increases from birth to about 50 % at 5 years, 75 % at 15 years, and more than 90 % of adults [14, 18].

9.2.4.4 Optic Nerve Glioma

Optic nerve gliomas are pilocytic hamartomas of the anterior visual pathways. Other more posterior gliomas represent more aggressive variants [19]. Gliomas occur in about 15 % of patients

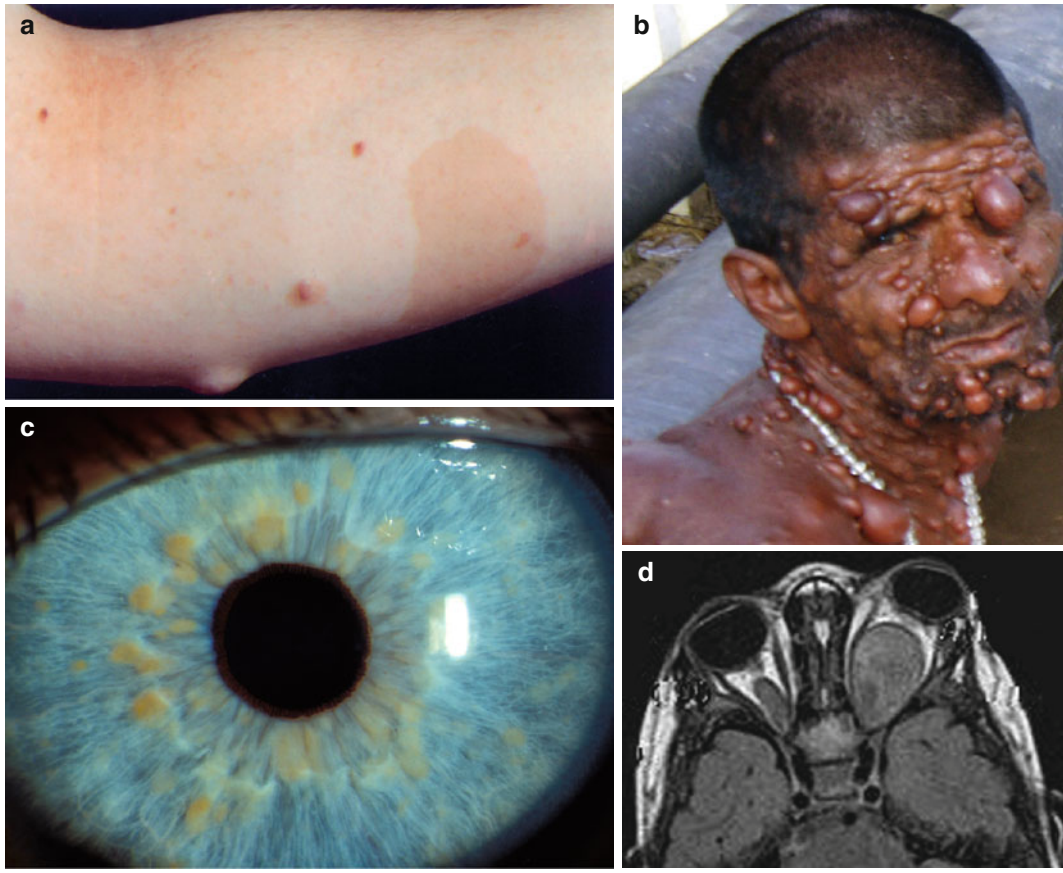

Fig. 9.1 Common manifestations of NF1. Café au lait spots (**a**), multiple neurofibromas of the face (**b**), multiple Lisch nodules (**c**), and optic nerve glioma (**d**), contrast-enhanced magnetic resonance image

with NF1 (Fig. 9.1d) [20]. Isolated optic nerve gliomas are usually unilateral, while bilateral involvement is believed to be pathognomonic of NF1 [21].

9.2.4.5 Glaucoma

Glaucoma is common in patients with NF1. There is an association between glaucoma and plexiform neurofibroma of the upper eyelid in these patients. Another feature that can be noted is the presence of ectropion uvea. This occurs in NF1 and may be secondary to endothelialization of the anterior chamber angle and is associated commonly with severe pediatric glaucoma in these patients. The endothelial cell proliferation may be related to overexpression of the Ras (Rat sarcoma)-MAPK genes in these eyes [22].

On occasion, neurofibromas in neurofibromatosis type 1 may be present on the lid, brow, or face of an infant or child, a circumstance commonly referred to as "orbitofacial neurofibromatosis" (OFNF). Visual loss in patients with orbitofacial neurofibromatosis (OFNF) is common, typically profound, and usually multifactorial. Some causes of visual loss (including congenital glaucoma with buphthalmos and retinal detachment, disconjugate gaze due in part to distorted skull development causing strabismic amblyopia, and optic nerve glioma) are difficult to treat adequately and tend to cause progressive, profound visual loss. Therefore, careful observation should be made during the period of visual immaturity for possible causes of amblyopia that might be treatable, such as refractive

changes, occlusion of the visual axis, or congenital glaucoma. As affected individuals get older, physicians must be vigilant for the progression of optic nerve disease due to glaucoma or optic nerve glioma and to the possibility that vision might be improved by refraction [23].

9.2.5 Diagnostic Evaluation

The NIH consensus criteria are useful in establishing the diagnosis of NF1 in adults as well as in young children. MRI is particularly helpful in establishing the diagnosis of optic nerve glioma. Characteristic "bright lesions" on MRI studies are present in about 15 % of patients with NF1 (Fig. 9.1e). The high-signal T2 lesions are present in the cerebral hemispheres, brainstem, and cerebellum [24].

9.2.6 Treatment

Once the diagnosis of NF1 is made, patients need detailed counseling regarding the prognosis, genetics, and psychological aspects of the disease. First-degree relatives should also be evaluated. Resectable neural tumors should be treated as in the general population. For malignant tumors, excision, chemotherapy, and/or radiotherapy may be indicated. The management of optic nerve glioma remains controversial. Therapeutic indication and outcomes with various forms of treatment including observation, chemotherapy, excision, and radiotherapy are discussed in detail under optic nerve tumors.

9.2.7 Prognosis

Some patients with NF1 have mental retardation, learning difficulties, and other behavioral problems [25]. Moreover, the likelihood of additional system manifestations of NF1 increases with age. Although the majority of tumors in NF1 are benign, their location in the CNS can lead to significant morbidity. The risk of developing malignant tumors particularly of the peripheral nerve sheath is about 5 %, and there is also an increased risk of early death [26].

Table 9.5 Criteria for the diagnosis of neurofibromatosis type 2

Presence of any one of the following		Features
Bilateral vestibular schwannoma		
First-degree relative with NF2	Plus	Unilateral vestibular schwannoma <30 year
First-degree relative with NF2	Plus	Any 2 of the following: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities/ juvenile cortical cataract

The criteria were formulated by the National Institute of Health Consensus Development Conference (Neurofibromatosis: Conference Statement [13])

9.3 Neurofibromatosis Type 2 (NF2)

9.3.1 Introduction

NF2 is also called "central NF" because the majority of its manifestations are related to central nervous system involvement. Unlike NF1, cutaneous findings are not a predominant feature of NF2. In contrast to neurofibromas that are hallmarks of NF1, schwannomas are the characteristic tumors of NF2 (Table 9.5).

9.3.2 Genetic Aspects

The inheritance pattern is autosomal dominant with complete penetrance. There is some evidence to suggest that maternally inherited cases have an earlier onset than paternally inherited cases (18 years vs. 25 years) [27]. About 50 % of the cases represent new mutations [27]. There is some evidence for genotype-phenotype correlation because patients with truncating *NF2* mutations are usually associated with severe phenotypes, while those with single codon alterations have mild NF2 [28, 29]. The *NF2* gene was mapped to chromosome 22q12 [30].

It encodes a 587 amino acid protein known as merlin or schwannomin.

9.3.3 Pathogenesis

Disruption of merlin-dependent links of membrane proteins to the cytoskeleton leads to tumor formation [31].

9.3.4 Clinical Features

The prevalence of NF2 is 1 in 33,000 to 40,000 [27]. One percent of patients with meningioma and 3 % of patients with schwannoma have NF2 [32]. Bilateral vestibular schwannomas (VS) are diagnostic of NF2 (Fig. 9.2a). Ocular abnormalities are present in more than two-thirds of NF2 cases and include cataracts, retinal hamartomas, and ocular motility disorders [33] The ocular features manifest in childhood and adolescence and are therefore extremely useful in early diagnosis of NF2 [34].

9.3.4.1 Vestibular Schwannoma

The mean age at onset is less than 25 years and clinical presentation beyond the age of 55 years is unusual. Symptoms are most commonly due to VS rather than to ocular involvement. Deafness with or without tinnitus is most common. Seizures, vertigo, and numbness are less common. Blindness occurs as a presenting symptom in only 1 % of cases [35].

9.3.4.2 Ophthalmic Findings

The ocular manifestations of NF2 include posterior subcapsular cataracts, combined hamartoma of the retinal and RPE, and epiretinal membranes (Box 9.2) [36–38]. Combined hamartoma of the sensory retina and retinal pigment epithelium is described as thickened retina with infoldings of the outer layers, gliosis, and associated disorganized proliferation of blood vessels and retinal pigment epithelium [39]. Children with VS are usually asymptomatic and ocular findings are therefore of diagnostic significance. In a clinical study of 49 patients with NF2 and their offspring,

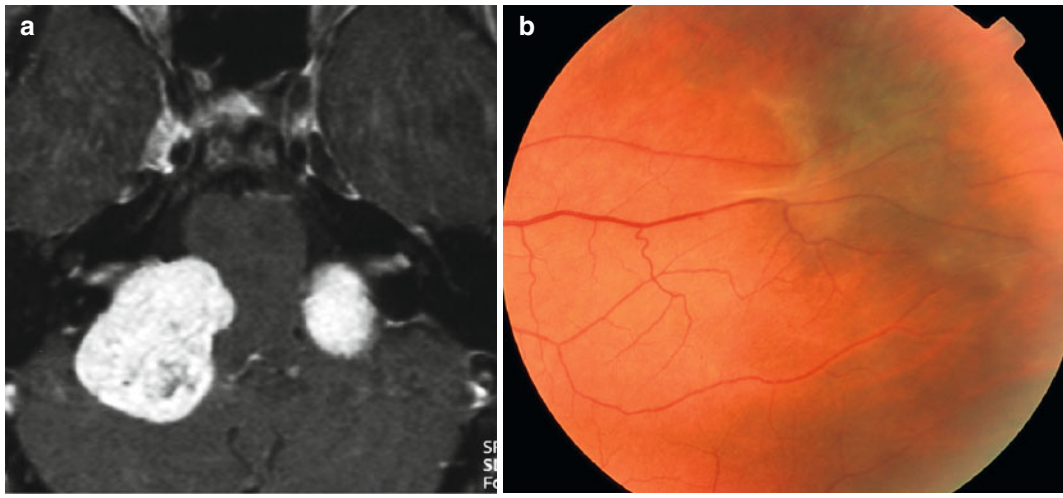

Fig. 9.2 Bilateral vestibular schwannoma on gadolinium-enhanced magnetic resonance imaging is diagnostic of NF2 (**a**). Fundus photograph of a combined hamartoma of retina and the retinal pigment epithelium (**b**). (**c**) [1–3], Spectralis (Heidelberg Engineering, Heidelberg, Germany) infrared reference images produced by scanning laser ophthalmoscope of the right macula of case 2 (1) and the right (2) and left (3) maculae of case 4 [4–6]. High-resolution raster OCT images corresponding to reference lines through the foveae of 1–3, respectively. Each raster line represents 30 averaged scanned images. Common features include epiretinal tissue that projects anteriorly into the cortical vitreous in the absence of a posterior vitreous detachment, loss of the foveal depression with inner retinal elements overlying the fovea, increased retinal thickness with preservation of retinal lamination and absence of cystoid spaces, and preservation of the inner segment/outer segment junction and retinal pigment epithelium continuity (Reproduced with permission from Sisk et al. [40])

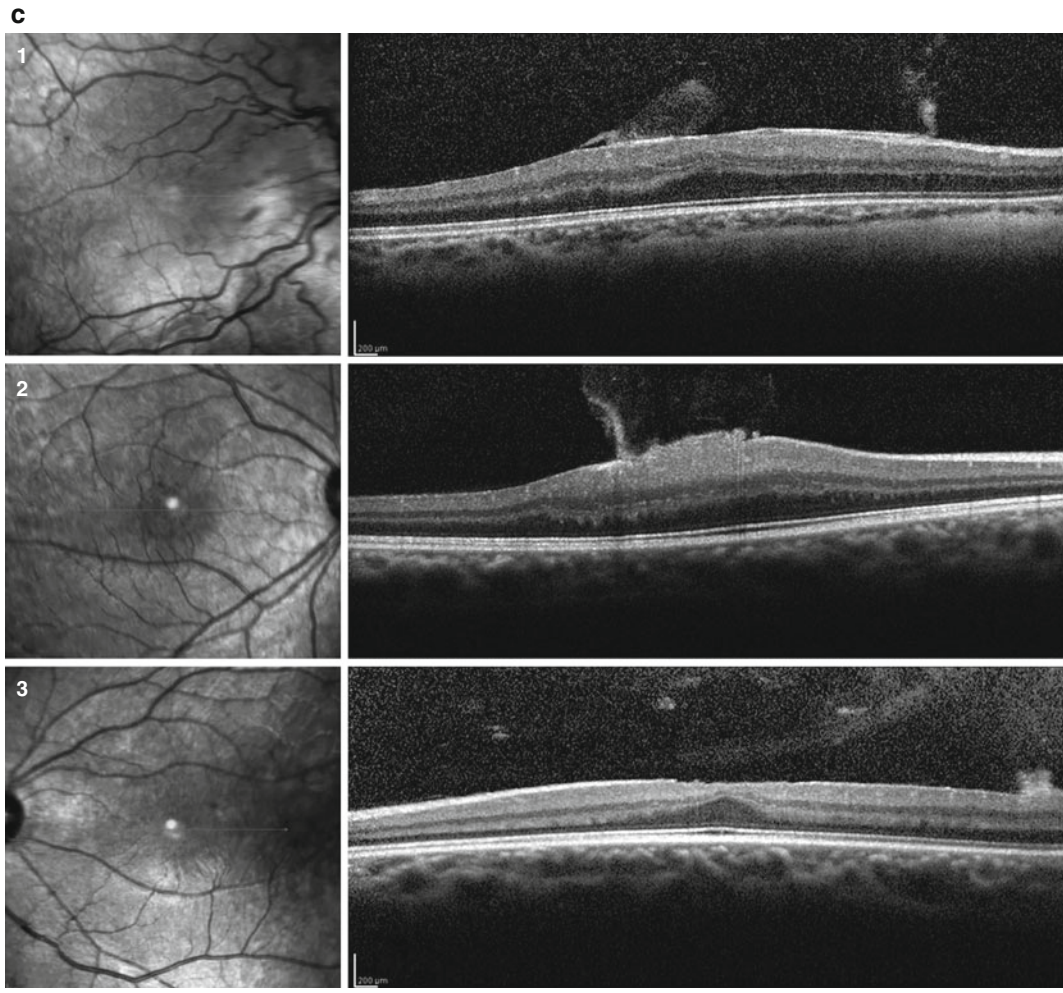

Fig. 9.2 (continued)

posterior subcapsular/capsular, cortical, or mixed lens opacities were the most common ocular abnormalities and were present in 67 % of patients [34].

Retinal hamartomas are less common than lens opacities and occur in about 20 % of cases [33]. Bilateral combined hamartomas of the retina and retinal pigment epithelium (RPE) in a young child should alert the clinician to the possibility of neurofibromatosis type 2 (Fig. 9.2b).

The specific biomicroscopic and optical coherence tomography (OCT) features of the epiretinal membranes (ERM) associated with NF2 include edges that project anteriorly into the vitreous despite an incomplete posterior vitreous detachment, lack of cystoid macular edema, mild undulation of retinal laminae, and an irregular and partially absent internal limiting membrane (Fig. 9.2c). In ERMs that covered the foveal center, the inner retinal layers usually are not displaced centrifugally from the umbo [40]. Recognition of ERM with a characteristic OCT appearance may permit early diagnosis in neurologically asymptomatic children with a severe phenotype of NF2. Unlike idiopathic or secondary ERMs that commonly result from other ocular conditions such as posterior vitreous separation, proliferative vitreoretinopathy, inflammation, vascular disorders, or trauma, NF2-specific ERMs are congenital lesions that may enlarge over time [40].

9.3.5 The Ocular Abnormalities in Neurofibromatosis 2 (Box 9.2)

- Cataracts: posterior subcapsular, capsular, cortical, and mixed
- Retinal hamartoma
- Epiretinal membrane
- Ocular motility disorders

9.3.6 Diagnostic Evaluation

Patients suspected to have NF2 are usually screened by neurological, ophthalmic, and neuro-otologic testing. Magnetic resonance imaging (contrast-enhanced, multi-planar T1-weighted sequences) is a cost-effective first-line investigation in the detection of VS [41].

9.3.7 Treatment

The management of vestibular schwannomas involves complex decision making and choosing among various options that include observation, stereotactic radiotherapy, and surgical resection [42].

9.3.8 Prognosis

The majority (90 %) of patients with NF2 present with bilateral vestibular schwannomas. The risk of developing a contralateral tumor in the absence of family history or other features of NF2 in patients with sporadic unilateral VS is low [43].

9.4 Von Hippel-Lindau Disease

9.4.1 Introduction

Eugen von Hippel, a German ophthalmologist, coined the term angiomatosis retinae in 1904 [44]. Arvid Lindau, a Swedish pathologist, established a relationship between cerebellar and retinal hemangioblastomas [45]. It was not until 1964, when Melmon and Rosen established the clinical spectrum of "von Hippel-Lindau" disease (VHL) when they reported cases of "von Hippel's disease" and "Lindau's disease" with overlapping manifestations [46]. Since then several investigators have studied the natural history of the disease and developed screening protocols [47–49].

9.4.2 Genetic Aspects

VHL disease follows an autosomal-dominant mode of inheritance with age-dependent penetrance [47]. Following the identification of the *VHL* gene on chromosome 3p25-26 in 1993, genetic testing with very high detection rates (99 %) has become commercially available [50, 51]. Because of significant social and ethical issues associated with genetic testing, patients considering the genetic testing for the VHL disease should undergo detailed genetic counseling [52].

9.4.3 Pathogenesis

The *VHL* gene encodes a 213 amino acid protein that binds with other proteins called elongin B, elongin C, and Cul 2 and forms a complex which targets hypoxia-inducible factors for degradation [53]. In the absence of pVHL, there is excessive production of vascular endothelial growth factor. Using tissue microdissection technique and PCR, it is now believed that the true neoplastic component (i.e., the cells with allelic deletion at the VHL gene locus) is the foamy stromal cells within the capillary hemangioma [54].

9.4.4 Clinical Features

The incidence of VHL disease is 1 in 40,000 to 1 in 54,000 live births. It is estimated that there are approximately 7,000 patients with VHL disease in the United States [55]. VHL disease is a multisystem disorder with the predilection for retina and the central nervous system (CNS). Significant clinical manifestations of VHL disease are included in the diagnostic criteria (Table 9.6). Retinal capillary hemangiomas (RCH) occur in less than 75 % of

Table 9.6 Diagnostic criteria for von Hippel-Lindau disease

Family history[a]	Required feature
	Any one of the following
Positive	One or more retinal capillary hemangioma
	One or more CNS hemangioma
	One or more visceral lesion[b]
Negative	Two or more retinal capillary hemangioma
	Two or more CNS hemangioma
	One retinal hemangioma with a visceral lesion
	One CNS hemangioma with a visceral lesion

[a]Family history of the following: retinal hemangioma, CNS hemangioma, or visceral lesion
[b]Visceral lesions include the following: renal cysts, renal carcinoma, pheochromocytoma, pancreatic cysts, islet cell tumors, epididymal cystadenoma, endolymphatic sac tumor, adnexal papillary cystadenoma of probable mesonephric origin

cases, CNS hemangiomas in more than 50 % of cases, renal carcinomas in less than 50 % of cases, and pheochromocytomas in less than 25 % of cases [47]. The cumulative probability of manifesting RCH, CNS hemangioma, and renal cell carcinoma increases with age (Fig. 9.3a) [47].

There seems to be a correlation between the clinical features and the type of *VHL* gene mutation (genotype-phenotype correlation), which has led to a new classification of VHL disease (Table 9.7) [56, 57]. There does not appear to be a specific type of germline mutation that correlates with presence of RCH [58].

9.4.4.1 Retinal Capillary Hemangioma

Retinal capillary hemangioma (RCH) is one of the most common manifestations of VHL disease [59]. Therefore, an ophthalmologist is frequently involved in the care of patients with VHL disease. The clinical features of VHL disease are discussed elsewhere (Chap. 3). The prevalence of underlying VHL disease in patients with solitary or multiple RCH is reported to be 20–58 % [60]. The presence of multiple RCH (two or more), other manifestations of VHL disease, or a positive family history indicates the presence of underlying VHL disease.

RCHs are unilateral in 42 % and bilateral in 58 % of patients. No correlation has been detected between the age, gender, and laterality of involvement. Of involved eyes, 86 % have tumors that can be individually visualized; of these, tumors are commonly found in the peripheral retina (85 %) only and less commonly in the juxtapapillary area (15 %). Severe visual impairment (visual acuity < or =20/160) in affected eyes is more likely to be associated with increasing age, the presence of juxtapapillary lesions, and an increasing number and extent of peripheral lesions [61].

9.4.4.2 Central Nervous System Hemangioma

Commonly involved sites include the cerebellum (75 %) and spinal cord (15 %) [47]. The CNS hemangiomas associated with VHL disease tend to be multiple and occur at a younger age as compared to sporadic cases. Headache is the most frequent initial symptom of cerebellar hemangiomas, and pain is the most common symptom of spinal cord hemangiomas (Fig. 9.3b) [62]. Pregnancy in patients with VHL disease can induce the progression of cerebellar hemangioblastoma and a high VHL disease-related pregnancy complication rate [63].

9.4.4.3 Renal Cell Carcinoma

Renal cell carcinoma is the leading cause of mortality in VHL disease [47]. Renal cell carcinomas in VHL disease are bilateral in 93 % of cases; they are multiple, are associated with renal cysts, and occur at a younger age (5 % by age 30 and greater than 40 % by age 60), compared to sporadic cases.

9.4.4.4 Pheochromocytoma

When pheochromocytomas, rare benign tumors of the adrenal medulla, are associated with VHL disease, they tend to be multiple and bilateral [64]. Absence (type I) or presence (type II) of pheochromocytoma forms the basis of National Cancer Institute classification of the VHL disease (Table 9.7). Pheochromocytoma produces elevated serum levels of catecholamines (norepinephrine and epinephrine) that lead to symptoms such as palpitations, headaches, and sweating, sometimes simulating anxiety attacks.

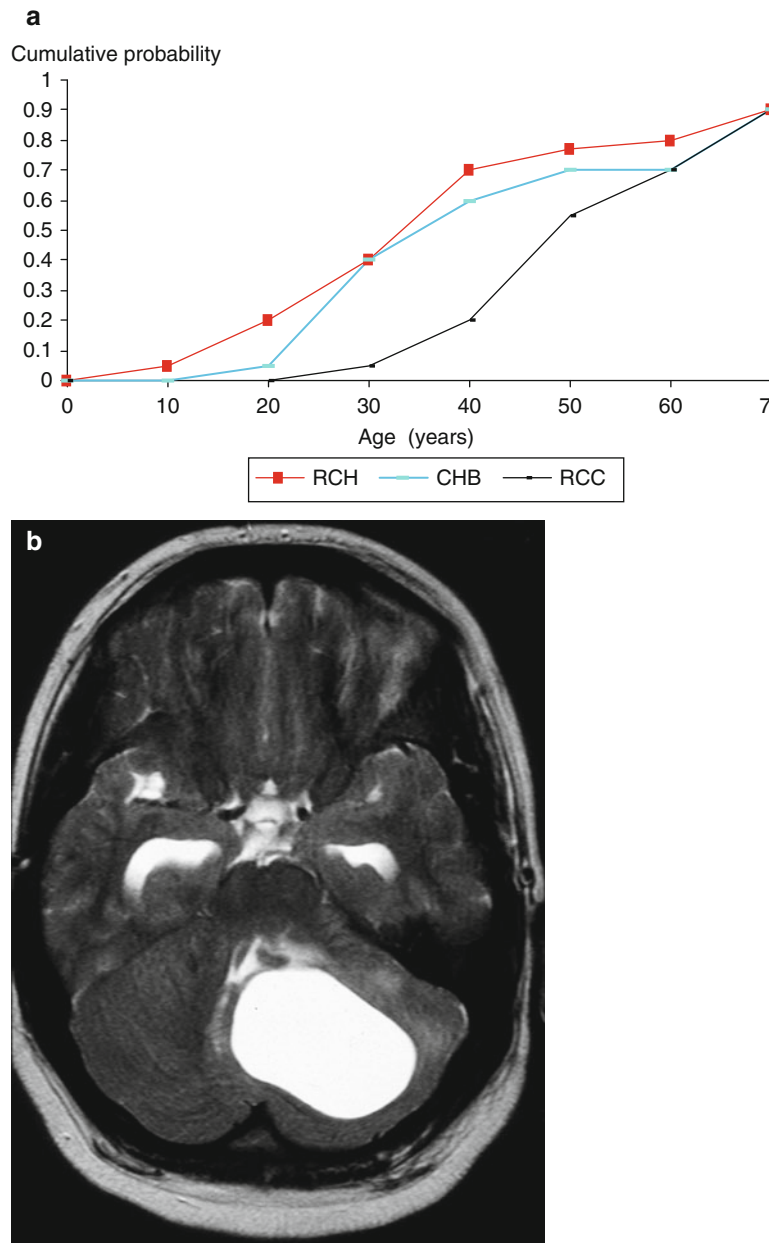

Fig. 9.3 Cumulative probability of developing retinal capillary hemangioma, cerebellar hemangioma, and renal cell carcinoma in von Hippel-Lindau disease (**a**) (Adapted from Maher et al. [47]). Magnetic resonance image (T-2 weighted) of a cerebellar hemangioma appearing as a cystic lesion (**b**)

Table 9.7 National Cancer Institute classification of von Hippel-Lindau disease

	Clinical features				
Type	CNS hemangioma	RCH	RCC	Pheochromocytoma	Mutation
I	Present	Present	Present	Absent	Deletions Insertion Nonsense
IIA	Present	Present	Absent	Present	Missense
IIB	Present	Present	Present	Present	
IIC	Absent	Absent	Absent	Present	

CNS central nervous system, *RCH* retinal capillary hemangioma, *RCC* renal cell carcinoma

Table 9.8 National Institutes of Health (USA) screening protocols for patients with or at risk for von Hippel-Lindau disease

Investigation	Age (years)	Frequency
Urinary catecholamine	From age 2	Every year
Ophthalmoscopy	From age 1	Every year
Enhanced MRI brain and spine	11–60 61 and above	Every 2 years Every 3–5 years
Abdominal USG	11–20	Every year
Abdominal CT	From age 21	Every 1–2 years

CT computed tomography, *MRI* magnetic resonance imaging, *USG* ultrasonography

9.4.4.5 Other Cancers

Pancreatic tumors and cystadenoma of the epididymis occur less commonly. Endolymphatic sac tumor, present in 11 % of patients, is a recently recognized feature of VHL disease [65].

9.4.5 Diagnostic Evaluation

The retinal findings of RCH are usually typical and the diagnosis can be usually made based on ophthalmoscopic examination and fluorescein angiography. Gadolinium-enhanced magnetic resonance imaging is the diagnostic method of choice for CNS hemangioma [62]. Asymptomatic renal, adrenal, and other organ involvement can be detected by enhanced computed tomography [49] and 24-h urinary biochemical excretion tests. Patients with or at risk for VHL disease should be screened as per National Institutes of Health screening protocol (Table 9.8).

Recently, quantitative studies have been developed that enable a full characterization of the impact of von Hippel-Lindau disease on eye health and visual function. Establishing correlations between the genotype of the von Hippel-Lindau mutation and the phenotype of eye disease may inform us as to how ocular von Hippel-Lindau disease arises and help guide molecular interventions in ocular von Hippel-Lindau disease [66].

9.4.6 Treatment

The decision to treat RCH and various methods of management are discussed elsewhere (Chap. 3). Details of treatment of other organ involvement are beyond the scope of this chapter. Intravitreal injections of anti-VEGF therapy have shown promising results in a small pilot study. They may be useful in decreasing retinal thickening and reduce retinal hard exudates in some patients with advanced retinal capillary hemangiomas but with minimal effects on size of the lesions [67].

9.4.7 Prognosis

The manifestations and complications of RCH even in adequately treated cases are visually significant. More than 25 % of patients with RCH show permanent visual loss (vision of <20/40 in one or both eyes) [58]. VHL disease is associated with significant morbidity from CNS hemangioma or renal cell carcinoma. In addition, there is significant mortality from renal cell carcinoma which is the leading cause of mortality in VHL disease [47]. The life expectancy of patients with VHL disease may be improved by early detection and treatment of the various tumors using surveillance protocols [49].

9.5 Tuberous Sclerosis Complex

9.5.1 Introduction

The name tuberous sclerosis was suggested by a French physician, Desire Magloire Bourneville (1840–1909), who dedicated his life to the study of mentally abnormal and epileptic children. In 1880 Bourneville described a patient with seizures, hemiplegia, mental subnormality, and renal tumors. He based the terminology tuberous sclerosis on the neuropathologic observations of multiple potato-like (tubers) lesions in the brain [68].

Table 9.9 Revised diagnostic criteria for tuberous sclerosis complex

Definite diagnosis	Two major features One major feature plus two minor features
Probable diagnosis	One major feature plus one minor feature
Possible diagnosis	One major feature Two minor features

Major features	Minor features
1. Facial angiofibroma or forehead plaque	1. Multiple dental enamel pits
2. Ungual/periungual fibroma	2. Hamartomatous rectal polyps
3. Hypomelanotic macules (3 or more)	3. Bone cysts
4. Shagreen patch	4. Cerebral white matter migration lines
5. Multiple retinal hamartomas	5. Gingival fibromas
6. Cortical tuber	6. Nonrenal hamartoma
7. Subependymal nodule	7. Retinal achromic patch
8. Subependymal giant cell astrocytoma	8. "Confetti" skin lesions
9. Cardiac rhabdomyoma (1 or more)	9. Multiple renal cysts
10. Lymphangiomyomatosis	
11. Renal angiomyolipoma	

The criteria formulated by the Tuberous Sclerosis Complex Consensus Conference 1998 (Roach et al. [85])

9.5.2 Genetic Aspects

Tuberous sclerosis complex (TSC) includes two genetic diseases (TSC1 and TSC2) with autosomal-dominant inheritance and high penetrance (95 %) [69]. Two-thirds of cases are sporadic and are thought to represent new mutations. The genes responsible for TSC, *TSC1* (chromosome 9q34) [70], and *TSC2* [71] have now been identified. The mutation detection rate is about 80 % using a combination of molecular genetic techniques [72].

9.5.3 Pathogenesis

Tuberous sclerosis is associated with mutations in the *TSC1* and *TSC2* genes, which encode hamartin and tuberin, respectively. Hamartin and tuberin interact with each other and influence a common cellular pathway [73]. These findings provide the basis for identical clinicopathologic manifestations of TSC1 and TSC2 that result when either of these proteins is inactivated.

9.5.4 Clinical Features

The incidence of TSC is 1 in 10,000 [69]. What may appear to be a higher incidence in recent years is due to diagnosis of patients with milder phenotypes with the advent of sophisticated imaging techniques [74]. Tuberous sclerosis is characterized by hamartomas in various organs. The hamartomas in the brain (astrocytoma and ependymoma) lead to childhood seizures and mental retardation. The skin manifestations (facial angiofibromas, subungual fibromas, hypomelanotic macules, and Shagreen patches) are mainly of diagnostic significance. The ocular involvement is limited to the retina. Visceral hamartomas most commonly involve the lungs, kidney, and heart [69]. The classic triad of epilepsy, mental retardation, and adenoma sebaceum is present in only one-third of cases Table 9.9 [75].

In general, the clinical manifestations of TSC1 and TSC2 are similar except that TSC1 represents a milder phenotype with a reduced risk of mental retardation as compared to TSC2 [76]. Other findings of TSC1 such as seizures, renal involvement, facial angiofibroma, and retinal

hamartomas are also less frequent or less severe compared to TSC2 [77].

9.5.4.1 Retinal Astrocytic Hamartoma

Approximately one-third to one-half of patients with TSC have retinal or optic nerve hamartomas, and the hamartomas occur bilaterally in half of these patients [78]. Clinical features of retinal astrocytic hamartoma are discussed in detail elsewhere (Chap. 4).

A population-based survey of patients with TS confirmed the presence of retinal hamartomas in 44 % cases (of which 70 % eyes had flat, translucent lesions; 55 % eyes had multinodular "mulberry" lesions and the transitional type lesion was seen in 9 % eyes). Punched out areas of retinal depigmentation were seen in 39 % eyes (Fig. 9.4a). Approximately 40 % patients have angiofibromas of the eyelids [79].

9.5.4.2 Brain and Neurological Manifestations

Epilepsy, mental retardation, and behavior problems are the most significant clinical manifestations that cause most of the morbidity associated with TSC. As evident from the revised diagnos-

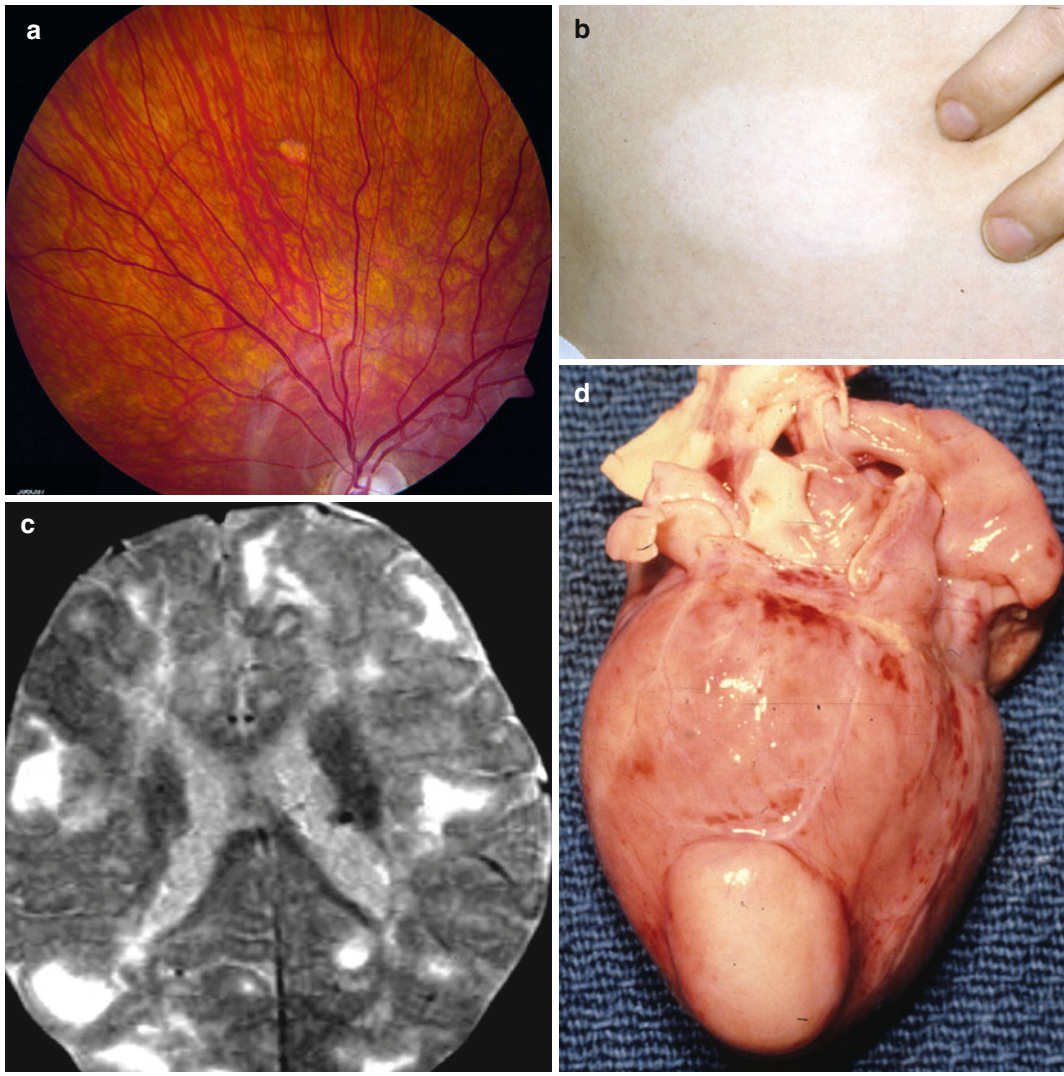

Fig. 9.4 Common manifestations of TSC. Retinal achromic patch (**a**). The hypomelanotic macules "ash-leaf" sign (**b**), multiple subcortical tubers (**c**), T2-weighted axial magnetic resonance image), and cardiac rhabdomyoma (**d**). (Reproduced with permission from Seki et al. [84])

tic criteria, neurological manifestations are not necessary for the diagnosis of TSC. Epilepsy may present as infantile spasms. About 50 % of TSC patients are mildly to profoundly mentally retarded. The severity of neurological disease directly correlates with the extent and number of cortical tubers detected on MRI scans (Fig. 9.4b) [80].

9.5.4.3 Skin Manifestations

Cutaneous manifestations of TSC are mainly of diagnostic significance (Fig. 9.6c). The hypomelanotic macules are the most frequent and the earliest finding of TSC and occur in up to 97 % of children (Fig. 9.4c) [81]. They are best visualized with Wood's lamp (UV light). Fibrous plaque appears as reddish-orange patches on the forehead. Facial angiofibromas are not present at birth and appear usually by age 5 years. Subungual fibromas appear later in life [82].

9.5.4.4 Visceral Manifestations

Visceral manifestations of TSC include pulmonary lymphangiomyomatosis [82], renal angiomyolipoma [83], and cardiac rhabdomyoma (Fig. 9.4d) [84].

9.5.5 Diagnostic Evaluation

The diagnosis of TSC is clinically based on diagnostic criteria [85]. Imaging studies such as magnetic resonance imaging of the brain and computerized tomography of the abdomen are important to detect CNS and visceral involvement [86]. Individuals with retinal findings are more likely to have concomitant subependymal giant cell astrocytomas, renal angiomyolipomas, cognitive impairment, and epilepsy. TSC2 mutations are more frequent in patients with retinal findings than in those without retinal findings [87].

9.5.6 Treatment

The treatment of TSC depends upon the location and the extent of organ involvement. Retinal astrocytic hamartomas usually need only periodic evaluation by ophthalmoscopy and fundus photography. Symptomatic changes are very rare in retinal hamartomas secondary to tuberous sclerosis. Spontaneous resolution of subretinal fluid may occur within 4 weeks. If macular edema with increasing lipoid exudates persists over a period of 6 weeks, treatment should be considered. Although some reports demonstrated possible visual stabilization after argon laser photocoagulation, vision-threatening complications can occur. Current treatment strategies may include PDT based on recent favorable anatomical and functional results [88].

9.5.7 Prognosis

Retinal astrocytic hamartomas are generally stable with slow growth over several years or new calcification in some cases [78]. TSC leads to significant morbidity mainly due to neurological and visceral involvement. The majority (85 %) of patients with TSC-related mental retardation require supervision for daily living. In general, patients with TSC have reduced survival as compared to the general population. The common causes of mortality are renal disease, brain tumors, and status epilepticus. Patients with TSC need lifelong follow-up for early detection of potentially life-threatening complications [86].

9.6 Sturge-Weber Syndrome

9.6.1 Introduction

In 1879, Sturge described a syndrome characterized by a facial hemangioma, ipsilateral buphthalmos, and contralateral seizures [89]. Weber in 1922 described radiological evidence of cortical calcification secondary to leptomeningeal hemangioma causing hemiplegia [90]. Since both descriptions applied to the same entity, the triad of leptomeningeal hemangioma, choroidal hemangioma, and cutaneous hemangioma has been called Sturge-Weber syndrome (SWS). In the absence of CNS involvement, patients should only be given a diagnosis of port-wine stain or facial angioma to avoid the stigmata associated with a diagnosis of Sturge-Weber syndrome.

Table 9.10 Clinical features of Sturge-Weber syndrome

Organ system	Clinical features
Central nervous system	Leptomeningeal angiomatosis[a]
	Cortical atrophy
	Seizures
	Developmental delay
	Behavioral problems
Eye and adnexa	Nevus flammeus
	Prominent episcleral vessels
	Glaucoma
	Diffuse choroidal hemangioma[a]
Cutaneous	Nevus flammeus[a]

[a]Any two of three features essential for diagnosis

9.6.2 Genetic Aspects

Unlike other phakomatoses, Sturge-Weber syndrome is not inherited.

9.6.3 Pathogenesis

The predominant manifestation is a diffuse hemangioma in the leptomeninges, choroid, and the facial skin. The other term for this disorder, encephalofacial hemangiomatosis, emphasizes only the non-ocular manifestations. The pathogenesis of SWS is believed to be failed regression of the primitive cephalic venous plexus during the ninth week of gestation. This error results in angiomatosis of the related tissues instead of maturation [91, 92].

9.6.4 Clinical Features

Infantile glaucoma and diffuse choroidal hemangioma may be associated with some visual loss. Sturge-Weber syndrome with its neural involvement leads to intractable seizures, developmental delay, and behavioral problems. The cutaneous manifestations of nevus flammeus, although most evident, are mainly of diagnostic significance (Table 9.10). Differential diagnoses for Sturge-Weber syndrome include Klippel-Trenaunay and Beckwith-Wiedemann syndrome.

9.6.4.1 Glaucoma

Glaucoma is the most frequent manifestation of SWS and occurs in about 70 % of all cases [93]. Various pathogenetic mechanisms such as angle maldevelopment or raised episcleral venous pressure can lead to glaucoma [94]. The glaucoma is usually diagnosed within the first 2 years of life. The incidence of glaucoma is higher if the eyelids are involved with nevus flammeus [95].

9.6.4.2 Diffuse Choroidal Hemangioma

About half the patients with SWS have a diffuse choroidal hemangioma [93]. The choroidal hemangioma is usually unilateral and ipsilateral to the nevus flammeus. The clinical features of choroidal hemangioma are discussed in detail under uveal vascular tumors.

9.6.4.3 Leptomeningeal Hemangiomatosis

The leptomeningeal hemangiomatosis is ipsilateral to the cutaneous involvement. This can lead to as a seizure disorder due to the effects on underlying cerebral cortex. Seizures are present in about 80 % of all patients with SWS with onset within the first year of life [96]. There is a correlation between early onset of seizures and the likelihood of developmental delay and behavior problems [97].

9.6.4.4 Nevus Flammeus

The cutaneous hemangioma is also called nevus flammeus or port-wine stain (Fig. 9.5a). In general, only about 10 % of all nevus flammeus cases are associated with SWS [98]. SWS only occurs in patients who have involvement in the region of V1 or V2 distribution of the trigeminal nerve [98]. Bilateral port-wine stains have a higher likelihood of being associated with SWS than unilateral lesions. Conversely, leptomeningeal and ocular involvement in SWS is always associated with port-wine stain involving the eyelids, the upper eyelid more often than the lower eyelid [98].

9.6.5 Diagnostic Evaluation

Contrast-enhanced MRI is most suited for detecting cerebral atrophy and leptomeningeal angiomatous malformations (Fig. 9.5b) [99]. If the

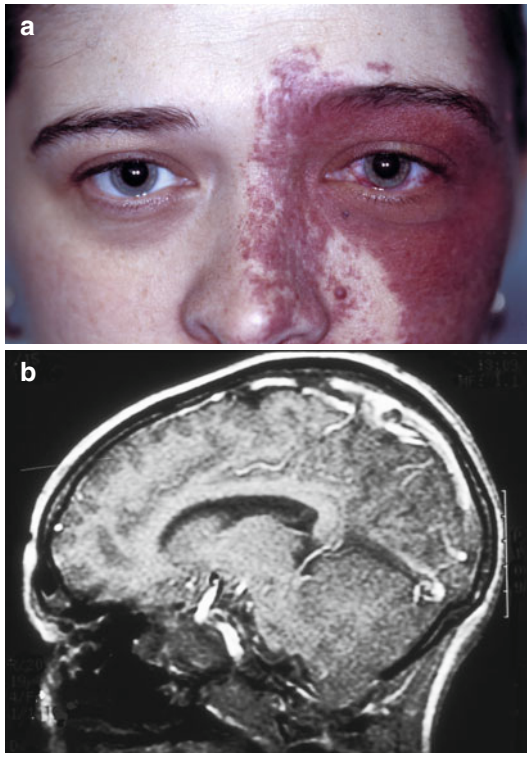

Fig. 9.5 Typical facial distribution of cutaneous hemangioma (**a**) and leptomeningeal hemangioma (**b**) in Sturge-Weber syndrome

MRI is normal, CT scan should be used to detect intracranial calcifications.

9.6.6 Treatment

Medical therapy of glaucoma is effective in some cases [95], but many patients eventually require multiple trabeculectomies, combined trabeculotomy with trabeculectomy [100], or even drainage implants [101]. The choroidal hemangioma can be treated with low-dose standard radiotherapy or with proton beam radiotherapy [102, 103]. The treatment of choroidal hemangioma is discussed under uveal vascular tumors. The seizures are generally controlled with medications, but intractable cases require surgical resection of the leptomeningeal angiomatosis with underlying cerebral cortex [104].

PDT is an effective treatment option for visual deterioration from exudative retinal detachment in patients with diffuse choroidal hemangiomas [105–107].

9.6.7 Prognosis

Only limited information is available about the long-term prognosis of patients with SWS. Mental retardation, behavioral, and social problems are more common in older children. Overall, about 40 % of patients with SWS are self-sufficient and about 50 % get married [96].

9.7 Wyburn-Mason Syndrome

9.7.1 Introduction

Wyburn-Mason in 1943 described several cases of racemose hemangiomatosis of the retina and brain and established an association between these malformations [108]. Some authors refer to this entity as Bonnet-Dechaume-Blanc syndrome [109]. Unlike other phakomatoses, there is no cutaneous involvement in Wyburn-Mason syndrome.

9.7.2 Genetic Aspects

Wyburn-Mason syndrome is a nonhereditary sporadic disorder.

9.7.3 Pathogenesis

The pathogenesis of the vascular abnormalities in Wyburn-Mason syndrome is not understood.

9.7.4 Clinical Features

The clinical findings are usually congenital in origin, but the diagnosis is usually made later in childhood as there are no prominent external features. A review of published cases indicates that the incidence of intracranial arteriovenous malformations in patients with retinal arteriovenous malformations is 30 % [110]. Conversely, only

about 8 % of cases with intracranial arteriovenous malformations have retinal arteriovenous malformations (Table 9.11) [110].

9.7.4.1 Retinal Arteriovenous Malformation

The ophthalmoscopic appearance of the retinal arteriovenous malformation is striking with dilated and tortuous retinal vessels extending from the optic disc to the retinal periphery. Similar arteriovenous malformations within the orbit, with or without retinal changes in the setting of WMS, have also been reported [111]. The clinical features of retinal arteriovenous malformations are described in details elsewhere (Chap. 3).

9.7.4.2 Intracranial Arteriovenous Malformation

The intracranial arteriovenous malformations in the chiasmal region can lead to neuro-ophthalmic presentations [112]. Patients present in their second or third decade with signs and symptoms of acute cerebral or subarachnoid hemorrhage such as severe headache, nuchal rigidity, and loss of consciousness.

There is a distinct difference between patients with congenital retinocephalofacial vascular malformation syndrome and those with isolated retinopathy without cerebral or facial malformations. Extensive retinal malformations of vessels of most parts of the fundus occur more often in patients with retinal and cerebral arteriovenous malformations. In contrast, local retinal arteriovenous malformations occur in all patients with isolated retinopathy without cerebral or facial malformations and rarely in patients with congenital retinocephalofacial vascular malformation syndrome. Hence, patients with arteriovenous communications of the retina should be examined early with brain and orbital neuroimaging to rule out cerebral arteriovenous malformations [113].

Table 9.11 Clinical features of Wyburn-Mason syndrome

Organ system	Clinical features
Central nervous system	Racemose hemangioma
Retina	Racemose hemangioma
Orbit	Racemose hemangioma

9.7.5 Diagnostic Evaluation

The diagnosis of retinal arteriovenous malformation is essentially clinical, but fluorescein angiographic studies can be utilized to document the vascular pattern. The intracranial arteriovenous malformation is best detected by magnetic resonance imaging or arteriography (Fig. 9.6).

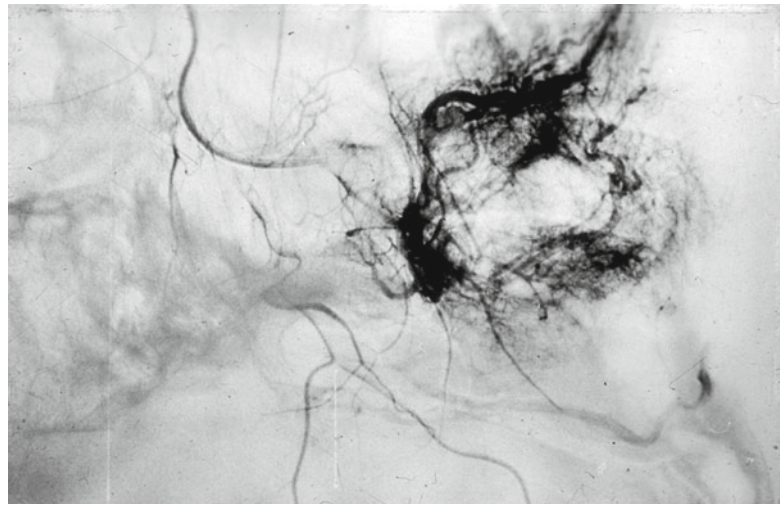

Fig. 9.6 The intracranial arteriovenous malformation seen on arteriography

9.7.6 Treatment

The retinal vascular malformations are usually not amenable to any therapy. Unlike the intracranial arteriovenous malformations that have a tendency to bleed, the retinal arteriovenous malformation does not bleed. If neovascular glaucoma occurs, symptomatic treatment can be offered. Because of their location in midbrain, intracranial arteriovenous malformations are usually inoperable. Embolization may be effective in some cases.

9.7.7 Prognosis

The retinal vascular anomalies may sometime lead to vascular occlusions [114] and retinal ischemia with development of neovascular glaucoma [115]. Hemorrhages from midbrain hemangiomas can be fatal.

9.8 Retinal Cavernous Hemangioma

9.8.1 Introduction

Retinal cavernous hemangioma is a rare benign vascular tumor. Clinically, two forms are recognized: sporadic and syndromic [116]. Retinal cavernous hemangiomas can be associated with cerebral cavernous malformations as an autosomal-dominant syndrome with high penetrance and variable expressivity [117, 118]. It has been suggested that the cerebral cavernous malformation syndromes should be included with the neuro-oculocutaneous (phakomatoses) syndromes, but the association of cerebral and cutaneous hemangioma is inconsistent [116].

9.8.2 Genetic Aspects

Cerebral cavernous malformations (CCM) are genetically heterogeneous. CCM1 is caused by mutation in the KRIT1 gene on chromosome 7q21-q22; CCM2 is caused by mutation in the malcavernin gene, and CCM3 is caused by mutation in the PDCD10 gene [119, 120].

9.8.3 Pathogenesis

Cavernous hemangiomas are considered to be congenital hamartomas that are composed of dilated multiple thin-walled dilated vascular channels and surface gliosis [116]. The walls are lined by normal appearing endothelium, explaining the lack of exudation [121].

9.8.4 Clinical Features

All patients diagnosed with a retinal cavernous hemangioma should undergo detailed neuroimaging studies even if they are asymptomatic because of their possible association with cerebral hemangiomas [122]. The diagnosis of familial cerebral cavernous malformations requires histopathologic or imaging documentation of cavernous hemangiomas in at least two family members.

9.8.4.1 Retinal Cavernous Hemangioma

Retinal lesions appear as grapelike clusters of blood-filled saccular spaces. The clinical features are described in detail elsewhere (Chap. 3).

9.8.4.2 Cerebral Cavernous Malformation

CCM may involve any part of the central nervous system, but supratentorial regions are more frequently involved than infratentorial ones [123]. The tumors can occasionally involve the spinal cord. Seizures, hemorrhages, or progressive focal neurological deficits are common manifestations.

9.8.5 Diagnostic Evaluation

The ophthalmoscopic features and fluorescein angiographic findings of retinal cavernous hemangiomas are characteristic (Chap. 3). Cavernous hemangiomas of the CNS are best visualized by MRI, which shows a central enhancing core and a dark ring from previous hemorrhages (Fig. 9.7). Because these lesions are venous in origin, they are not detected by angiography. Genetic testing is available for CCM1.

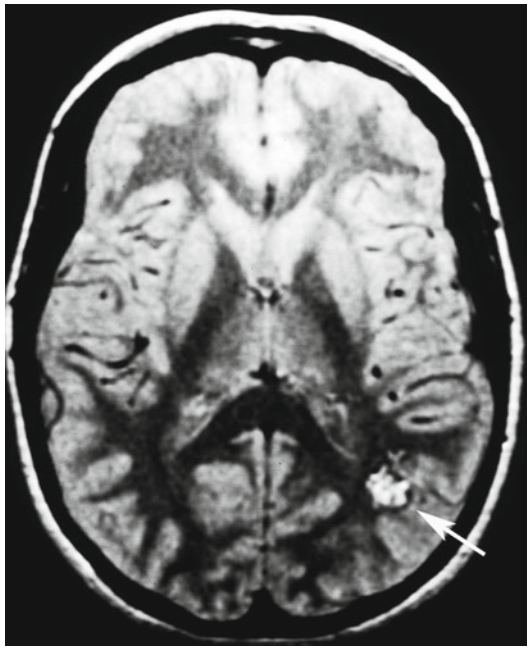

Fig. 9.7 Cortical cavernous hemangioma of the CNS appears in a MRI as a central enhancing core surrounded by a dark ring from previous hemorrhages (*arrow*)

9.8.6 Treatment

No effective treatment is known, although laser photocoagulation has been attempted in a few cases [116]. Intracranial cavernous hemangioma can be managed by observation, surgical excision, or gamma knife radiosurgery depending upon location and other considerations [124].

9.8.7 Prognosis

In general, retinal cavernous hemangiomas are nonprogressive. Spontaneous thrombosis and vitreous hemorrhage are rare complications [116]. Cavernous hemangiomas of the CNS carry an annual risk of 0.25–5 % for a clinically significant hemorrhage [124].

9.9 Sebaceous Nevus Syndrome

9.9.1 Introduction

Sebaceous nevus syndrome (of Jadassohn) [125], also known as Schimmelpenning-Feuerstein-Mims syndrome [126, 127], is a distinct clinical disorder within the spectrum of epidermal nevus syndrome (of Solomon) [128] characterized by cutaneous sebaceous nevus and extracutaneous manifestations [129].

Table 9.12 Clinical manifestations of the sebaceous nevus syndrome

Organ	Feature
Neural	Seizures, mental retardation, structural brain defects
Ocular	Conjunctiva/corneal/episclera choristoma
	Lid coloboma
	Chorioretinal coloboma
	Optic nerve coloboma, pit, hypoplasia
	Intrascleral cartilage/bone
Cutaneous	Midline linear nevus, alopecia, sebaceous lobules, basal/squamous cell carcinoma

9.9.2 Genetic Aspects

Sebaceous nevus syndrome is a sporadic disease.

9.9.3 Pathogenesis

The term sebaceous nevus is used to emphasize epidermal and adnexal composition (sebaceous glands, sweat glands, and hair follicles) of cutaneous hamartoma (organoid nevus) and to differentiate them from typical melanocytic nevi [130, 131].

9.9.4 Clinical Features

In addition to prominent cutaneous involvement, neural and ocular manifestations are common in sebaceous nevus syndrome (Table 9.12).

9.9.4.1 Cutaneous Features

Cutaneous lesions are most commonly found on the head and neck region and appear irregular linear lesions with alopecia (Fig. 9.8a). Three stages of age-dependent evolution of the organoid nevus have been described [132]. During infancy, the skin appears atrophic due to underdevelopment of

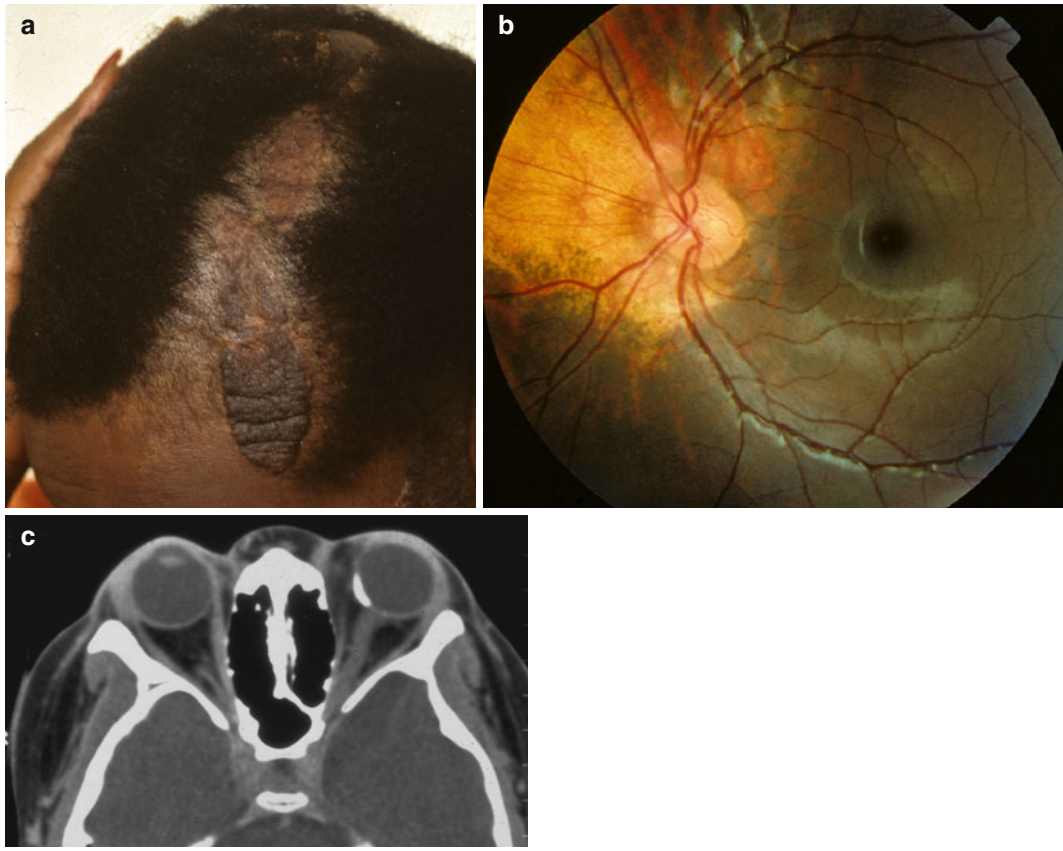

Fig. 9.8 Characteristic manifestations of sebaceous nevus syndrome. Facial and scalp involvement with sebaceous nevus (**a**), yellowish-orange scleral choristoma of the superonasal quadrant (**b**), and computed tomography at bone density shows nasal plaque-like lesion in the left globe (**c**). (Reproduced with permission from Traboulsi et al. [138])

sebaceous glands. During the second stage, observed during puberty, there is overdevelopment of sebaceous glands which clinically appears as hypertrophic and papillomatous. In adulthood, there is a tendency to form benign and malignant skin tumors such as sebaceous adenoma and basal cell carcinoma within the area of the organoid nevus [133].

9.9.4.2 Ophthalmic Features

Ocular involvement is observed in about 40 % of cases with epibulbar choristomas and coloboma being the most common [134]. The limbal choristomas can be simple or complex and usually are dermoid or lipodermoid in nature (Fig. 9.8b) [135, 136]. Ophthalmoscopic examination can reveal coloboma, disc anomalies, or features suggestive of intrascleral cartilage (Fig. 9.8c) [137]. Intrascleral calcification due to ossification of cartilage can also be observed [137, 138]. Several other less frequent ophthalmic anomalies observed as part of sebaceous nevus syndrome have also been reported [137, 138].

9.9.4.3 Neurological Features

Mental retardation and seizures are the most frequent neurological manifestations of sebaceous nevus syndrome.

9.9.4.4 Other Manifestations

Skeletal abnormalities, cardiovascular defects, and genitourinary defects are occasionally observed indicating multisystem nature of the sebaceous nevus syndrome [129].

9.9.5 Diagnostic Evaluation

The diagnosis of sebaceous nevus syndrome is essentially based on clinical findings supported

by appropriate imaging studies such as magnetic resonance imaging of the brain. Ophthalmic manifestations of intrascleral cartilage/ossification can be demonstrated by ultrasonography or computed tomography. Cutaneous biopsy may prove organoid nature of the nevus with presence of adnexal components. Other diagnostic studies should be ordered as based upon suspicion of specific organ involvement.

9.9.6 Treatment

Eyelid and episcleral choristomas can be excised, and attempts to maximize vision may include corneal grafting, refraction, and amblyopia management [139]. The organoid nevus should be removed for cosmetic correction and to prevent risk of malignant transformation observed in later stages of life [140].

9.9.7 Prognosis

The visual prognosis is usually guarded in presence of limbal choristoma, chorioretinal coloboma, and optic disc anomalies. Morbidity associated with sebaceous nevus syndrome is due to neurological manifestation of mental retardation and seizure. The risk of malignant transformation of the organoid nevus is about 20 % over long term [133].

9.10 Ataxia Telangiectasia

9.10.1 Introduction

Madame Louis-Bar in 1941 described a young boy with progressive cerebellar ataxia and oculocutaneous telangiectasia [141]. The term ataxia telangiectasia was proposed by Boder and Sedgwick in 1958 when they described seven cases of familial progressive cerebellar ataxia, with oculocutaneous telangiectasia and sinopulmonary infections [142]. Other features such as lymphoreticular malignancy and immune dysfunction were not reported until later [143].

9.10.2 Genetic Aspects

Ataxia telangiectasia (AT) follows an autosomal recessive pattern of inheritance. A gene that causes AT was identified on chromosome 11q22-23 [144]. Although at least five complementation groups have been defined, linkage studies have failed to show linkage heterogeneity. It is now believed that the complementation groups may represent different intragenic mutations or separate ataxia telangiectasia genes clustered within the 11q22.3 region [145].

9.10.3 Pathogenesis

A region of the *ATM* gene that is homologous to phopshoinositiol-3 kinases mediates cell growth signals. A second region homologous to *RAD3* and *MEC1* regulates cell cycle explaining diverse manifestations of AT [146].

9.10.4 Clinical Features

The incidence of AT is about 3 per million live births. The minimum frequency of AT gene mutations in the US white population is estimated to be 0.0017 [147]. Although AT is included by some within the phakomatoses, it has only limited similarity to other disorders in this group because it lacks dominant inheritance and a tendency for systemic hamartomatosis.

Ataxia telangiectasia is a childhood neurodegenerative disorder with neural, ocular, and cutaneous manifestations associated with immune dysfunction. In addition to some of the features outlined below, premature aging, chromosomal instability, and hypersensitivity to ionizing radiation are also important aspects of this disorder (Table 9.13) [148].

9.10.4.1 Cerebellar Ataxia

Progressive cerebellar ataxia in early childhood is the hallmark of AT and is present in all cases [149]. The majority of patients present with truncal ataxia by age 2 years and almost all develop this neurological sign before age 6 years. Other

Table 9.13 Common manifestations of ataxia telangiectasia

Clinical features	Laboratory features
Progressive cerebellar ataxia	Elevated serum alpha-fetoprotein after 2 years of age
Oculocutaneous telangiectasia	Elevated plasma carcinoembryonic antigen
Hypotonic facies	Low serum antibody levels (IgA, IgG2, IgE)
Oculomotor apraxia	Spontaneous chromosome breaks and rearrangements (in vitro studies)
Dysplasia of the thymus gland	Increased sensitivity to ionizing radiation
Recurrent pulmonary infections	
Susceptibility to neoplasia	
Endocrine abnormalities	
Progeric changes	

associated neurological findings include choreoathetosis, dysarthria, facial hypotonia, and ocular motility disorders. The combination of oculomotor apraxia with cerebellar ocular motor abnormalities is highly suggestive of AT [150].

9.10.4.2 Telangiectasia

The telangiectasias have a later onset than the ataxia and usually develop by age 6 years; they may be absent in some cases. The telangiectasia involves the bulbar conjunctiva and skin of the arms, neck, and shoulder regions.

9.10.4.3 Other Manifestations

Other significant manifestations of AT are dysplasia of the thymus gland, recurrent pulmonary infections, susceptibility to neoplasia, endocrine abnormalities, and progeric changes [151]. Lymphoma or leukemia develops in early adulthood in about 15 % of cases, representing a 1,000 times greater incidence than the general population [152].

9.10.5 Diagnostic Evaluation

The diagnosis of AT is essentially based on clinical findings. The laboratory markers include elevated serum alpha-fetoprotein after 2 years of age, elevated plasma carcinoembryonic antigen, and low serum antibody levels (IgA, IgG2, and IgE). In vitro studies on lymphocytes show spontaneous chromosome breaks and rearrangements; and cultured fibroblasts show increased sensitivity to ionizing radiation. It is now possible to identify disease causing mutations in more than 80 % of patients with AT including prenatal genotyping [145, 153].

9.10.6 Treatment

AT patients are likely recurrent sinopulmonary infections because of immune dysfunction for which they need appropriate long-term care. AT-associated malignancies such as lymphoma and leukemia require modified chemotherapy and radiotherapy dosages because of hypersensitivity to radiation and chemotherapy-induced DNA damage [151, 154].

9.10.7 Prognosis

AT is a progressive disease with poor prognosis [155]. About one-third of cases die by age 15 years, and survival beyond age of 30 years is very unusual [156].

Ataxia telangiectasia-like syndrome (ATLD) is a more recently recognized condition due to homozygous mutation in MRE11, a gene also involved in the cellular repair response to double-stranded DNA breaks; ophthalmic features of ATLD are not well described. Saccadic dysfunction without head thrusts and convergence abnormality are common in ATLD secondary to homozygous W210C MRE11 mutation. Older patients have nystagmus with abnormalities in smooth pursuit and vestibular ocular reflex. Eye movement control systems deteriorate with time. Ophthalmic features of AT that are not observed in ATLD patients include conjunctival telangiectasia, head thrusting, and manifest strabismus at distance [157].

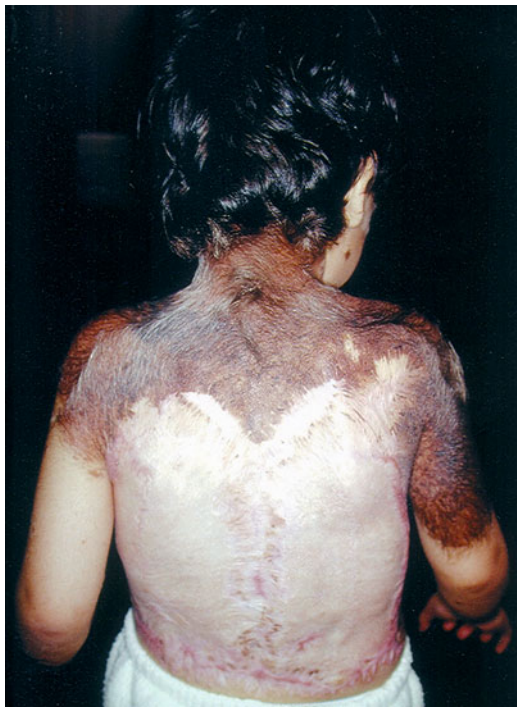

Fig. 9.9 Large cutaneous melanocytic nevi of the trunk in a patient with neurocutaneous melanosis. (Reproduced with permission from Kiratli and Sahin [159])

9.11 Neurocutaneous Melanosis

Neurocutaneous melanosis (NCM) is a nonfamilial phakomatosis, characterized by multiple and large congenital cutaneous nevi in association with meningeal melanosis or melanoma (Fig. 9.9) [158]. Rare cases with ocular abnormalities such as uveal coloboma-like lesions have been reported [159].

9.12 Phakomatosis Pigmentovascularis

Ota in 1947 described cases with combination of vascular and melanocytic nevi in Japanese population (phakomatosis pigmentovascularis [PPV]) [160]. Five types of PPV are known with recent attempt to reclassify them into only three subtypes [161]. Systemic associations with Sturge-Weber syndrome or Klippel-Trenaunay-Weber syndrome can occur. Ocular involvement can vary from congenital glaucoma, iris mammillations, oculodermal melanocytosis, and even choroidal melanoma (Fig. 9.10) [162].

9.13 Intracranial Cavernous Angiomas (Cavernomas)

Cavernomas are an uncommon lesion seen in neurosurgical practice that can occasionally rupture. Recent developments in neurosurgical technique and microbiology have brought greater insight into the treatment and molecular pathogenesis of cavernoma. There appear to be a number of controversies regarding management of this lesion. These include risk factors faced by the patient, controversy over the importance of resection, and modality through which the treatment should occur.

The most widely cited risk factor for clinically significant hemorrhage, apart from family history, is prior history of hemorrhage. Another important risk factor is found in young women wishing to become pregnant. The hormonal state of pregnant women is such that endothelial cell proliferation may increase the risk for hemorrhage substantially.

The clinical presentation of these lesions is highly variable, ranging from incidental finding at neuroimaging to discovery in autopsy after fatal hemorrhage. The most common symptom of cavernous malformation is seizure followed by focal neurological deficits, acute hemorrhage, and headache.

The well-circumscribed nature of these lesions, the low-flow arterial supply, and the free communication with venous drainage make resection of accessible cavernous angiomas relatively easy. In removing the cavernoma, the neurosurgeon must take care not to remove associated venous angioma, which provides anatomically disordered but physiologically essential drainage, because of the possibility of inducing venous infarction. Lesions located deep within the brain are difficult to remove and represent a special challenge to the practicing neurosurgeon. Excellent results have been achieved through stereotactically guided microsurgical excision of lesions [124].

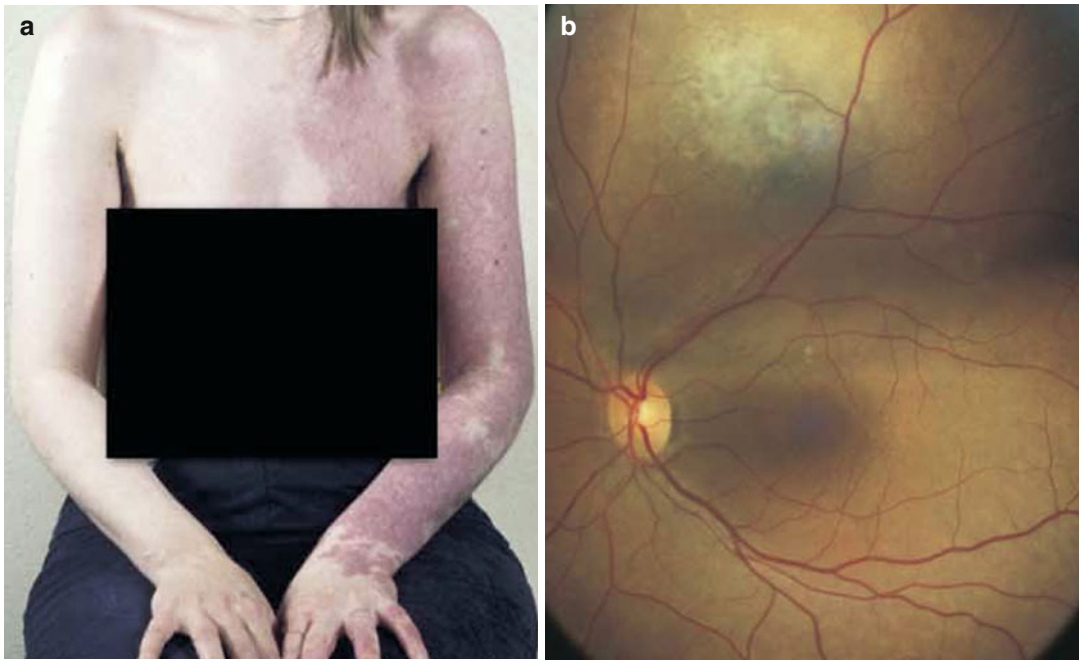

Fig. 9.10 Extensive nevus flammeus with a midline separation on the thorax and abdomen (**a**) and fundus photograph showing choroidal hyperpigmentation (ocular melanocytosis) and choroidal melanoma (**b**). (Reproduced with permission from Tran and Zografos [162])

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Ocular Paraneoplastic Diseases

10

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Contents

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10.1 Introduction

Paraneoplastic disorders are defined as syndromes in which the effects on the end organ are not a direct consequence of the mass or of distant metastasis. Instead, autoimmune responses to the primary tumor cause end organ disorder and dysfunction. Paraneoplastic illnesses can occur before, at the time of diagnosis, or after the identification of the primary malignancy, and in rare cases the primary malignancy may never be discovered.

Ocular paraneoplastic diseases include a wide range of clinical manifestations ranging from color deficiencies to complete blindness. Their diagnosis is complicated by the fact that cancer

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Table 10.1 Clinical features of paraneoplastic retinopathies

Feature	CAR	MAR	BDUMP
Symptoms	Bilateral visual loss Positive visual phenomenon Nyctalopia	Near normal acuities Normal color vision Normal central visual fields	Severe visual loss Cutaneous/mucosal focal melanocytic proliferation
Fundus exam	Vessel attenuation, chorioretinal atrophy, optic atrophy	Majority have normal appearance. Few have vascular attenuation, RPE changes, and vitreous cells	Multiple elevated uveal melanocytic tumors Exudative retinal detachment
Visual field	Central/paracentral scotoma	Paracentral scotoma	Central/paracentral scotomas
ERG findings	Depressed scotopic and photopic response	"Negative" ERG	Depressed scotopic and photopic response
Associated malignancy	Lung carcinoma (small cell) Gynecological carcinoma Breast carcinoma	Cutaneous melanoma	Small-cell carcinoma and others
Antibodies	Anti-recoverin, Anti-enolase Anti-65-kDA Heat shock cognate protein 70	Rod bipolar "on" cells	None
Prognosis	Progression to severe visual loss	Progression to severe visual loss	Progression to severe visual loss

CAR cancer-associated retinopathy, *MAR* melanoma-associated retinopathy, *BDUMP* bilateral diffuse uveal melanocytic proliferation

can also affect ocular structures remotely due to toxicity from antineoplastic agents, nutritional deficiencies, and opportunistic infections. Moreover, the characterization of ocular paraneoplastic disorders is made difficult by the rarity with which it occurs; there are insufficient epidemiologic data to estimate its incidence or prevalence. This chapter summarizes the salient features of most frequently encountered ocular paraneoplastic diseases such as cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR), paraneoplastic vitelliform retinopathy, bilateral diffuse uveal melanocytic proliferation (BDUMP), paraneoplastic optic neuropathy, and opsoclonus manifesting as paraneoplastic ocular disease (Table 10.1).

10.2 Cancer-Associated Retinopathy

10.2.1 Introduction

The first published report of photoreceptor degeneration occurring as a result of a remote cancer was a series of three patients with small-cell lung cancer (SCLC) published by Sawyer et al. in 1976 [1]. While it remains most commonly associated with SCLC, CAR has also been associated with hematologic malignancies; gynecological and breast carcinoma, and less commonly, non-small cell carcinoma of the lung, cancers of the larynx, bladder, thyroid, prostate, colon and liver, thymoma, and Langerhans cell histiocytosis [2–7]. Despite improved recognition of the disorder and an expanding appreciation of its associations, there remains much to understand of the underlying pathogenesis and treatment of CAR.

10.2.2 Etiology and Pathogenesis

The paraneoplastic retinopathies are presently considered an autoimmune condition: expression of antigens within a developing tumor stimulates the immune system to cross-react with similar or identical antigens within the retina, resulting in retinal degeneration. Recoverin was the first identified antigen, as characterized by Thirkill and associates [8, 9]. Since its identification, nearly 20 different antigens have been proposed, though recoverin and α-enolase are the best studied [10, 11].

Aberrant expression of recoverin has been demonstrated in a number of cancer cell lines and is thought to play a role in cell proliferation [12]. Tumor-expressed recoverin is known to be antigenic and anti-recoverin antibodies are commonly identified in patients with various cancers [13, 14]. Systemic administration of recoverin in a rat model was found to result in immunization and subsequent retinal degeneration; [15] and intravitreal injection of anti-recoverin antibodies in rats has also been shown to cause retinal degeneration [16]. Interestingly, intravenous anti-recoverin antibodies given to mice were not able to cross the blood-retina barrier, and no retinal degeneration occurred [17]. Vascular endothelial growth factor has been investigated as a potential mediator of blood-retina barrier modification, though its role remains unclear [18]. It appears that the cellular immune system may provide the additional component necessary to induce antibody-related damage. Maeda and associates demonstrated that, in addition to immunization with recoverin, inhibition of the cytotoxic T lymphocyte antigen 4 pathway (thus blocking inhibition of T cell activation) is necessary to produce CAR-like retinal degeneration in a murine model [19].

In the photoreceptors, recoverin functions in light and dark adaptation by regulating rhodopsin phosphorylation and dephosphorylation in a calcium-dependent manner [20]. While the exact mechanism by which anti-recoverin antibodies reach the retina remains to be elucidated, it is believed that anti-recoverin antibodies mediate photoreceptor degeneration by apoptosis. Once internalized by the cells of the retina, anti-recoverin antibodies lead to an increase in intracellular calcium and activation of mitochondrial caspase 3 and caspase 9 driven apoptosis, ultimately resulting in retinal degeneration [21, 22]. Considering anti-recoverin mediated retinal degeneration as a model for paraneoplastic retinopathies, it appears that tumor expression of an antigen results in a cross-reacting autoantibody that, coupled with a related T cell response, ultimately elicits retinal degeneration by triggering apoptosis pathways.

10.2.3 Clinical Features

10.2.3.1 Symptoms

Cancer-associated retinopathy is generally characterized by painless progressive visual loss over weeks to months, often accompanied by early complaints of decreased near vision, and positive visual phenomena such as shimmering lights (Fig. 10.1). While there is much overlap, the underlying antigen may predict a distinctive profile of symptoms. Symptoms of anti-recoverin-related retinopathy reflect widespread retinal dysfunction, including nyctalopia, photopsia, and peripheral and pericentral scotoma, whereas anti-enolase retinopathy may more commonly cause hemeralopia, color disturbance, photopsia, and variable central field defects [23].

10.2.3.2 Signs

Early in the course, the eye may appear to be entirely normal. Anterior segment findings have rarely been reported in cases of CAR except for iritis. Posterior segment findings predominate and include narrowing of retinal vessels, chorioretinal atrophy, and optic nerve atrophy. Vitritis, periphlebitis, and arteriolar sheathing occur later in the disease course [24].

10.2.4 Diagnostic Evaluation

Assessment of retinal function using Goldmann or Humphrey visual fields, Farnsworth color assessments, and electroretinography (ERG) are important for establishing the diagnosis. Visual field testing can manifest variable defects such as central, paracentral, or arcuate/ring scotomas and generalized field depression. However, the most common finding is a constriction within the central 20° of the visual field [25]. Electroretinographic studies are helpful in confirming the diagnosis (Fig. 10.2). The classic picture seen with CAR includes suppression of the photopic and scotopic response [26], though the profile of loss may correspond to the underlying antibody—diffuse rod and cone loss in anti-recoverin retinopathy and more central cone loss in anti-enolase retinopathy [23].

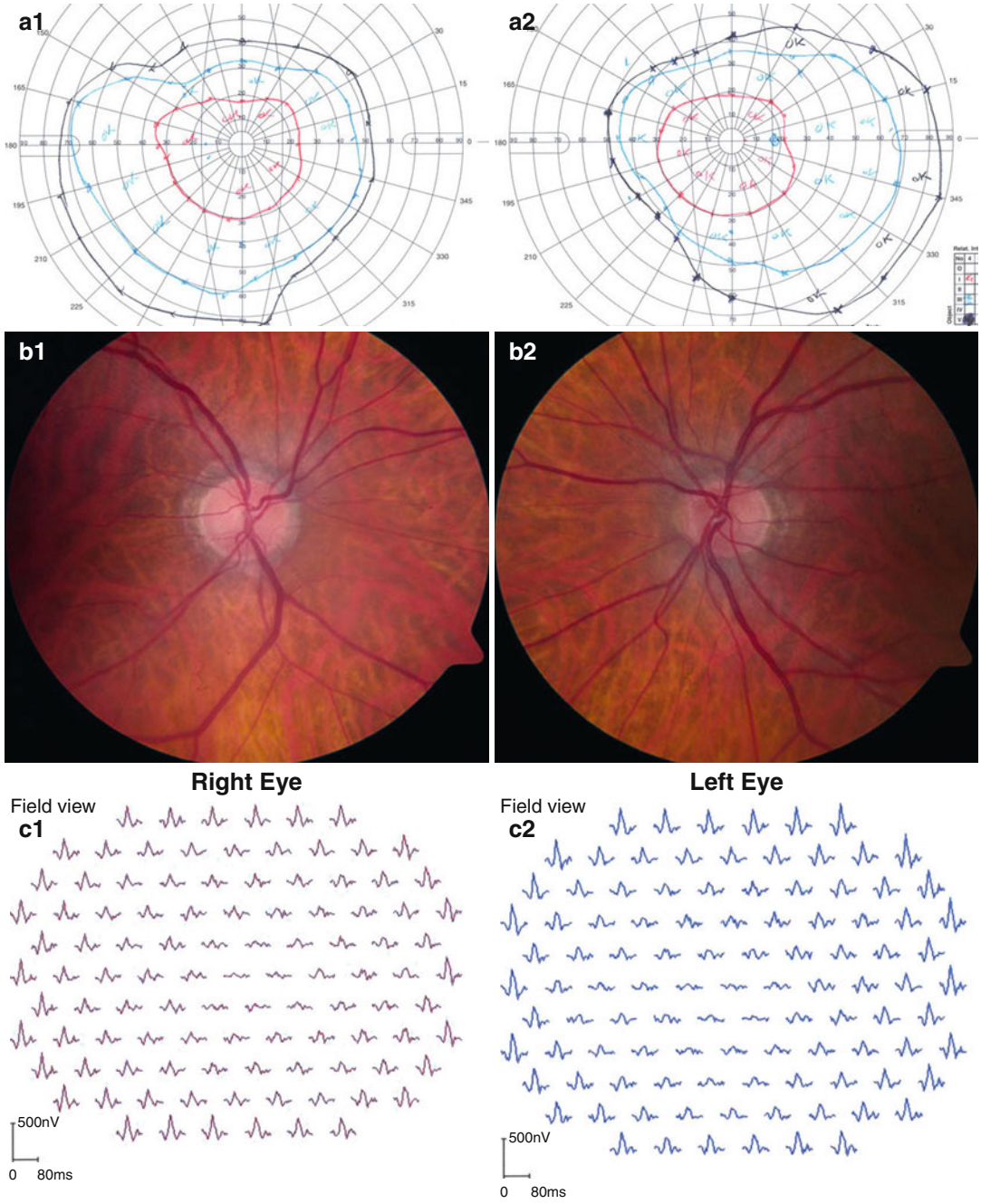


Fig. 10.1 A 61-year-old white male presented to the neuro-ophthalmology service in consultation for bilateral progressive decrease in vision that started approximately 1 year prior to presentation. He saw an ophthalmologist 1 month prior to his presentation who noted mild sheathing of his retinal vessels without anterior uveitis or vitritis. Past medical history was significant for asthma and the patient had previous hernia repair and sinus surgery. He denied diabetes, known malignancies, or autoimmune diseases. On ophthalmic examination, his best-corrected visual acuity was 20/80 OD and 20/40 OS. IOP was 19 OU and pupils were equal and reactive without an afferent pupillary defect. His extraocular movements were full OU, and a Goldmann visual field showed peripheral constriction with the I-4 targets OU (**a**). Dilated fundus exam showed mildly attenuated retinal arterioles but was otherwise unremarkable (**b**). There was no sheathing noted on fundus examination. Multifocal ERG revealed severe attenuation of a- and b-waves centrally OU (**c**). Serum anti-retinal antibody tests showed the presence of anti-**α** enolase antibodies with staining of the inner nuclear layer on immunohistochemistry. The patient was diagnosed with probable cancer-associated retinopathy. Further work-up revealed the presence of a peripheral lung nodule whose biopsy showed the presence of signet-ring cell carcinoma (Courtesy Martin Heur MD and Gregory S. Kosmorsky, MD)

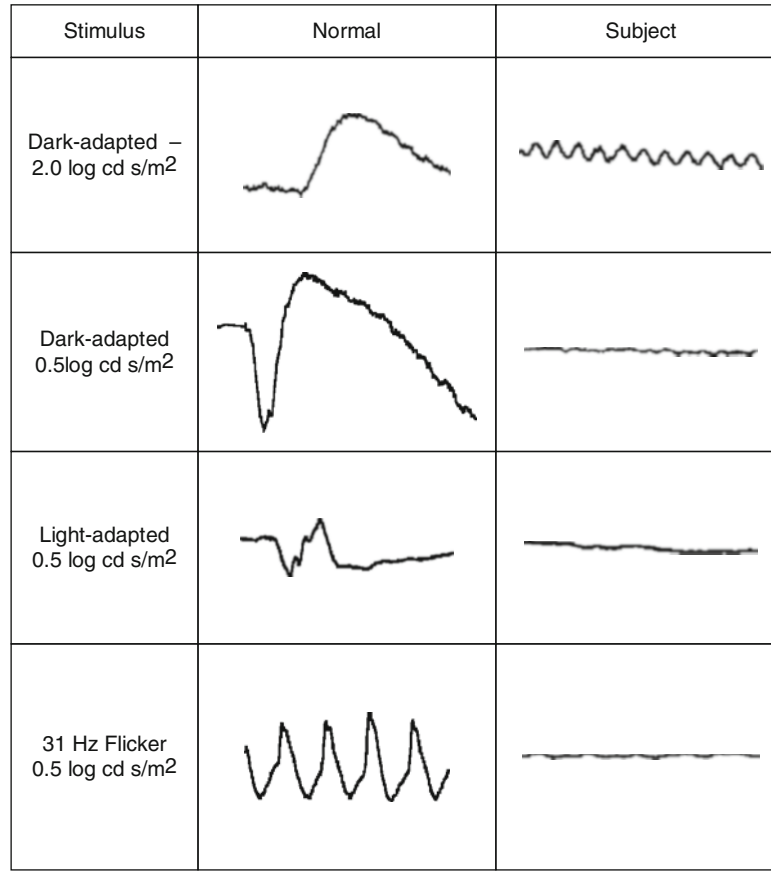


Fig. 10.2 A 67-year-old man with a known history of lung cancer presented with halos in both eyes. Electroretinograms recorded from a normal control subject and from the patient. Responses recorded from the two eyes of the patient were averaged together. Extinguished ERG responses in the patient were suggestive of cancer-associated retinopathy (Courtesy Neal Peachey, PhD, Cleveland, Ohio)

Another critical component of the evaluation of patients with suspected CAR is serum assay for anti-retinal antibodies which can be performed by commercial or academic laboratories. Unfortunately, serum antibody testing is fraught with not only a lack of standardization between laboratories but also the heterogeneity of autoantibodies found in patients. Not all patients with suspected CAR have identifiable anti-retinal antibodies, while a significant number of patients with nonneoplastic autoimmune retinopathy have anti-retinal antibodies [27]. Moreover, some patients may have multiple antibodies but the offending antibody is not always identifiable [27]. The discovery of anti-recoverin antibodies however should raise a high level of suspicion for malignancy as several studies have shown recoverin to be strongly associated with CAR [27] though the possible occurrence of anti-recoverin in certain forms of retinitis pigmentosa (RP) has been suggested [28]. Finally, anti-retinal antibodies may be demonstrated in the normal population [27].

Retinal imaging may be normal or nonspecific for CAR. Retinal vein leakage and perivascular window defects have been reported on fluorescein angiography [29]. In a patient with acute vision loss found to have CAR, time domain optical coherence tomography (OCT) demonstrated macular thinning primarily related to loss of the inner highly reflective layer; however, anti-retinal antibody studies were not reported [30]. In a series of patients with autoimmune retinopathy including CAR, OCT again demonstrated macular thinning but localized the findings primarily to outer retinal loss as well as inner segment/outer segment junction disruption but with only mild thinning of the nerve fiber layer in some patients [31].

10.2.5 Differential Diagnosis

Cancer-associated retinopathy must be distinguished from other paraneoplastic ocular disease including MAR and paraneoplastic optic neuropathy, as well as non-paraneoplastic autoimmune retinopathy, hereditary retinal disease, and other causes of retinal degeneration. Furthermore, infiltration by the primary carcinoma or anterior ischemic optic neuropathy must be ruled out. Anterior visual pathways may also be affected by chemotherapeutic agents such as vincristine, and in the absence of fundus findings, optic neuropathy may be erroneously suspected.

10.2.6 Treatment

Though numerous modalities have been investigated including steroids, immunomodulation, intravenous immunoglobulin (IVIG), plasmapheresis, and calcium channel blockers, the visual improvement after treatment for CAR—if any—is generally modest and often transient. Early diagnosis is critical, since once photoreceptor degeneration has begun, treatment may at best only stabilize vision. Anti-retinal antibody titers may be useful in guiding treatment as some authors have reported successful management using increased titers as an indication to resume therapy [27, 32]. Unfortunately, treatment of the primary tumor, including the use of chemotherapy, radiotherapy, and local excision of the primary tumor, has shown no effect on CAR [2].

Intravenous high-dose methylprednisolone and less commonly oral steroids are generally the first-line approach to management either alone or in combination with systemic immunomodulator therapy. Ferreyra and colleagues reported an improvement in visual acuity or expansion of visual fields in a series of CAR patients treated with combination therapy of prednisone, azathioprine, and cyclosporine [33]. Intravenous immunoglobulin was successful in improving visual acuity or visual fields in a small case series [34]. Single-case reports of successful preservation of vision with alemtuzumab and improvement of vision with rituximab have been reported [35, 36]. Likewise, a single patient with CAR has been successfully managed with plasmapheresis in combination with systemic steroids [37]. As increased intracellular calcium has been implicated in the pathogenesis of CAR, calcium channel blockade has shown benefit in experimental models though success in humans has yet to be reported [38]. While it is generally held that systemic management is required, local treatment with either intravitreal or sub-Tenon steroid injections may be beneficial in a subgroup of patients [33, 39].

10.2.7 Prognosis

The visual prognosis with CAR is generally very poor; without treatment vision may deteriorate to light perception or no light perception. In a retrospective review, severe deterioration in vision (less than 20/200) was found in 47 % of all patients [25].

10.3 Melanoma-Associated Retinopathy

10.3.1 Introduction

It was Gass who first presented a case of remote ocular disease occurring in the setting of metastatic cutaneous melanoma in 1984, in which he described a patient with acute vision loss, uveitis, and large areas of depigmentation of the choroid [40]. Melanoma-associated retinopathy was eventually coined as a distinct clinical entity when Berson showed in 1988 that this night blindness was a paraneoplastic phenomenon [41]. The syndrome became characterized by nyctalopia, shimmering photopsias, and an unremarkable or atrophic fundus exam in a patient with metastatic melanoma and characteristic ERG findings. Unlike CAR, which may be diagnosed before or after identification of the underlying malignancy, MAR is nearly always diagnosed when metastatic disease is already evident. In a review of the cases of MAR published in the literature, only two patients

presented prior to any diagnosis of melanoma and six before metastases were found [2].

10.3.2 Etiology and Pathogenesis

Similar to CAR, patients with MAR have antibodies to tumor antigens which cross-react with antigens on retinal cells, most commonly targeting the rod bipolar cell [42]. As with CAR, numerous antibodies have been identified, including S-arrestin, recoverin, α-enolase, aldolase A, aldolase C, and rhodopsin, among others [43, 44]. More recently, autoantibodies specific to the TRPM1 cation channel of ON bipolar cells have been described [45]. This selective damage of bipolar and Mueller cells produces a negative appearing scotopic response on electrophysiology termed the "negative ERG." [26] In paraneoplastic vitelliform maculopathy, antibodies against RPE have been implicated, while others have suggested, based on a single histopathologic report, that the findings may be related to subclinical choroidal metastasis [46, 47].

10.3.3 Clinical Features

The vast majority of patients with MAR are male, most often with the established diagnosis of cutaneous melanoma, though it may also occur with choroidal or ciliary body melanoma [44, 48]. In contrast, both genders are equally affected in paraneoplastic vitelliform retinopathy, and nearly a third may have uveal melanoma as the primary [49].

10.3.3.1 Symptoms

The clinical features of MAR are similar to that seen in other paraneoplastic retinopathies. Patients typically report shimmering, flickering photopsias, peripheral scotomas, acute onset night blindness, and slowly progressive visual loss [48, 50]. Patients with paraneoplastic vitelliform retinopathy present with similar symptoms [49]. Subclinical MAR as detected by electroretinography, perimetry, and nyctometry appears to be more common than previously suspected in patients with cutaneous melanoma [51].

10.3.3.2 Signs

Patients typically have near normal visual acuities, color vision, and central visual fields unlike CAR patients who manifest more severe deficits at presentation [50]. Few patients with MAR manifest fundus changes. In a series of 34 patients with proven MAR, 44 % of patients had normal findings at presentation, 30 % had vascular attenuation, and 28 % had RPE changes. Vitreous cells were present in 30 % patients, and 23 % had optic-disc pallor [50, 52]. The fundus appearance in paraneoplastic vitelliform retinopathy is characterized by multiple large, round, white to yellow subretinal deposits predominantly affecting the macula and may show areas of shallow serous retinal detachment [53].

10.3.4 Diagnostic Evaluation

As with other paraneoplastic retinopathies, initial diagnostic evaluation should consist of Goldmann or Humphrey visual fields, Farnsworth color assessments, and ERG. Visual field testing can reveal mid-peripheral defects or peripheral field depressions. Melanoma-associated retinopathy manifests typical ERG abnormalities including absent or reduced b-waves even after dark adaptation with preserved a-waves [48]. A positive history of cutaneous malignant melanoma and circulating antibodies directed toward human rod bipolar cells supports the diagnosis (Fig. 10.3).

10.3.5 Differential Diagnosis

Melanoma-associated retinopathy must be differentiated from similar clinical presentations with an electronegative ERG such as congenital stationary night blindness (CSNB), juvenile retinoschisis, and nonischemic central retinal vein occlusion [54]. Systemic treatment for melanoma with interferon may also cause a retinopathy, though this is easily distinguished by its features of intraretinal hemorrhage and

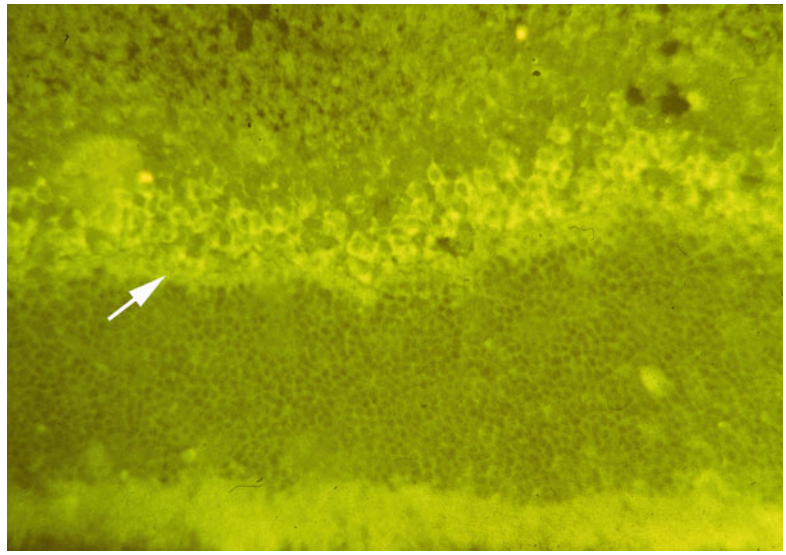


Fig. 10.3 A 64-year-old man presented with photopsia, difficulty with night vision, and reduced peripheral visual field in both eyes of 3 months duration. He had been recently diagnosed with malignant melanoma of the maxillary sinus. The corrected visual acuity was 20/20 in both eyes. Results of the anterior segment and fundus examination were normal in both eyes. An electroretinogram showed marked reduction in the b-wave amplitude under scotopic testing conditions to a bright flash. Indirect immunofluorescence was performed on cryosections of unfixed human retina using serum and IgG from the patient. Fluorescein isothiocyanate-labeled antihuman IgG and IgM were used as secondary antibodies. A weak but specific labeling of bipolar cells was observed (*arrow*). Patients visual status remained stable for the next 12 months when he died from metastatic disease (Reproduced with permission from Singh et al. [95])

cotton-wool spots [55]. While eye history and exam can help distinguish some of these entities, ancillary testing with ERG and serum antibody testing establish the diagnosis. Congenital stationary night blindness can be distinguished on ERG from MAR, since blue cones are typically spared in CSNB. Paraneoplastic vitelliform retinopathy may be mistaken for Best's disease, RDS/peripherin spectrum dystrophies, and Harada syndrome.

10.3.6 Treatment

The key to management is early detection since MAR causes irreversible destruction of bipolar and Mueller cells. As with CAR, there is no treatment paradigm; however, there is more deference given to cytoreduction, either by means of metastasectomy, or chemotherapy and radiation [56]. Intravenous immunoglobulin is also frequently employed, often in combination with cytoreduction of the primary tumor by radiation, plasmapheresis, and steroids [50, 57, 58]. There are few reports describing treatment for paraneoplastic vitelliform retinopathy though prednisone may reduce subretinal fluid accumulation with a corresponding improvement in visual acuity [46]. Unfortunately, the results of treatment are generally unimpressive; a meta-analysis of the literature found that only 4 % of patients with MAR had visual improvement or improvement in fundus appearance after treatment [2].

10.3.7 Prognosis

Visual loss in MAR is progressive due to the decline in retinal function seen late in the disease

course. In a review of 34 patients with MAR, there was a significant decline in acuities with only 10 patients retaining visual acuity better than 20/60 [50].

10.4 Paraneoplastic Vitelliform Retinopathy

10.4.1 Introduction

More recently, a MAR-like retinopathy with associated detachments of the RPE and neurosensory retina has been described, although this entity may actually have been alluded to by Gass [52, 59–64]. In 2001 Borkowski et al. described two cases of a MAR-like syndrome with unusual fundus features [52]. In the first case, there were oval, white lesions at the level of the RPE, and in a second, there were scattered, well-circumscribed, atrophic lesions in the posterior pole and mid-periphery [52]. Other groups have reported MAR-like presentations with multiple serous retinal and RPE detachments [59, 61, 64, 65]. In 2005 Sotodeh et al. reported two cases of a MAR-like retinopathy with serous macular detachments and a third case with small, yellow, curvilinear, vitelliform lesions [63]. This group was the first to use the term *paraneoplastic vitelliform retinopathy*. Since that time, others have also described similar cases of paraneoplastic vitelliform retinopathy with multiple serous retinal detachments [49, 60, 62].

10.4.2 Etiology and Pathogenesis

Anti-CAII autoantibodies have the capacity to induce cellular damage by impairing CAII cellular function through inhibition of the catalytic activity of CAII in a dose-dependent manner. This causes decreased intracellular pH and increased intracellular calcium, which results in decreased retinal cell viability [66]. Autoantibodies against the ON bipolar TRPM1 channels result in abnormal synaptic transmission, which appears to be the main mechanism for paraneoplastic vitelliform retinopathy [67].

10.4.3 Clinical Features

10.4.3.1 Symptoms

Males and females are equally affected. The majority have metastatic cutaneous melanoma, while less than a third have metastatic uveal melanoma. Most individuals reported some degree of visual loss, nyctalopia, and photopsia.

10.4.3.2 Signs

Characteristic multiple yellow to white lesions scattered throughout the posterior pole and mid-periphery of both eyes that are flat, well demarcated, and located within the deep retinal layers are observed (Fig. 10.4).

10.4.4 Diagnostic Evaluation

Visual field testing has yielded variable results from normal to cecocentral scotomas [60, 63]. Color vision testing may reveal errors along the tritan axis on Farnsworth D-15 testing [60]. Reduction in both the a-wave and b-wave amplitudes for both scotopic and photopic ERG testing is common. EOG may show a pathologically reduced Arden ratio or be normal [49, 60].

Either by Western blot or by immunohistochemistry, retinal autoantibodies most commonly directed against bipolar cells, carbonic anhydrase II, interphotoreceptor retinoid-binding protein (IRBP), bestrophin, α-enolase, myelin basic protein, and rod outer segment proteins and transient receptor potential M1 cation channels of retinal ON bipolar cells have been reported (Table 10.2) [67].

10.4.5 Treatment

There is no known effective treatment. The role of immunosuppression in treatment of such cases is not known [33].

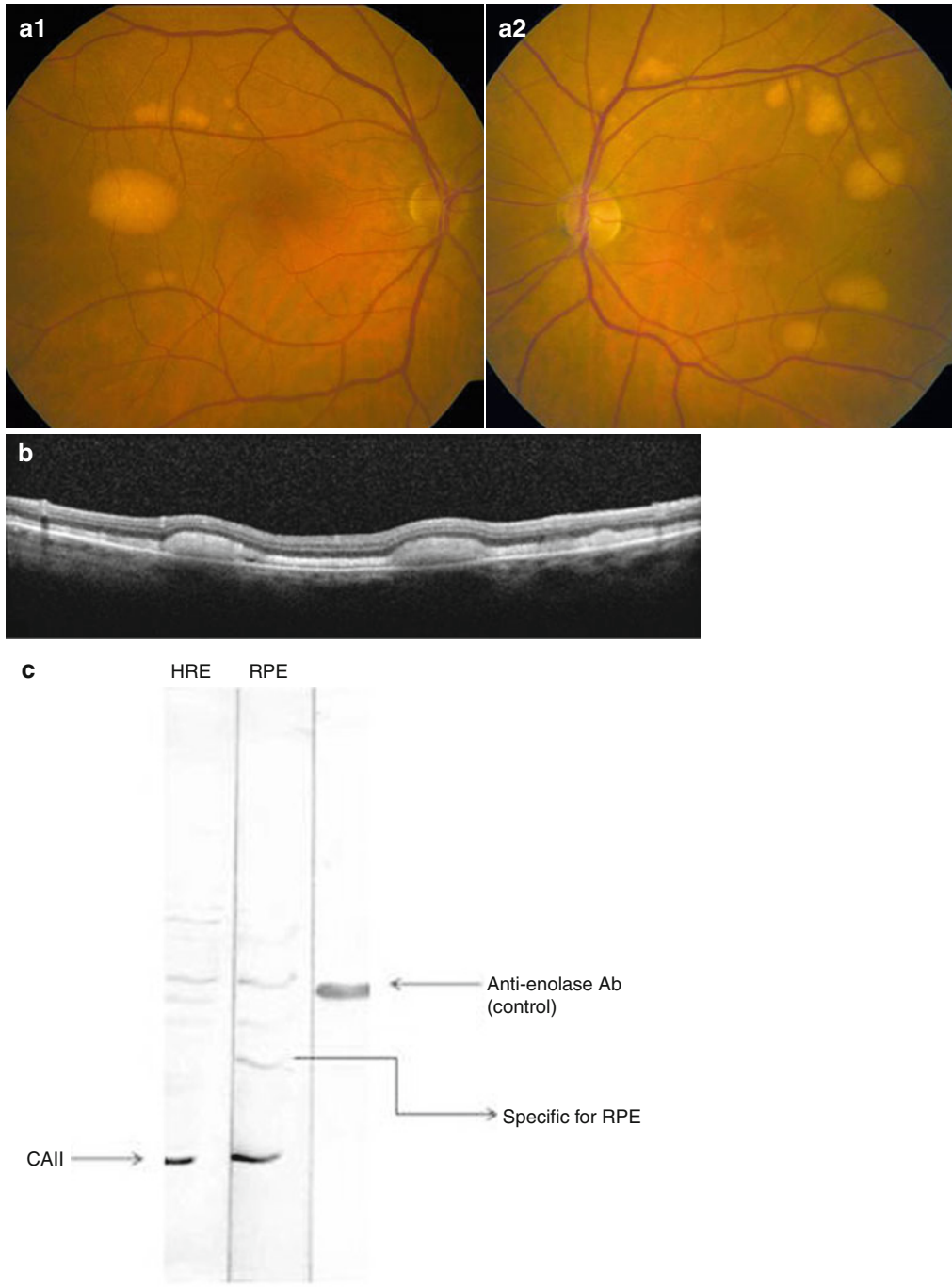


Fig. 10.4 Fundus appearance of paraneoplastic vitelliform retinopathy in an 80-year-old man with metastatic cutaneous melanoma (*A-1* right eye; *A-2* left eye). Spectral domain optical coherence tomography revealed high-resolution imaging of all retinal layers and confirmed the location of these lesions in the deep retina between the outer nuclear layer and the RPE (**b**). Western blot of the patient's serum tested against human retinal (*HRE*) proteins and human retinal pigment epithelium (*RPE*) proteins revealed that the serum had a high titer of retinal autoantibodies directed against carbonic anhydrase II (*CAII*) in retina and RPE (**c**). Postmortem microscopic examination showed focal retinal edema (*asterisks*) and loss of nuclei in the inner nuclear layer, likely without bipolar cell preservation. Hematoxylin and eosin (original magnification ×200) (**d**). Transmission electron micrograph showing cross-section of the inner nuclear layer illustrating the damage targeted by autoantibodies. Signs of deterioration include stacked filaments (*arrowheads*), vacuoles/phagosomes (*arrows*), and disintegrated mitochondria (*concave arrowhead*) (E) (Reproduced with permission from Aronow et al. [49])

Fig. 10.4 (continued)

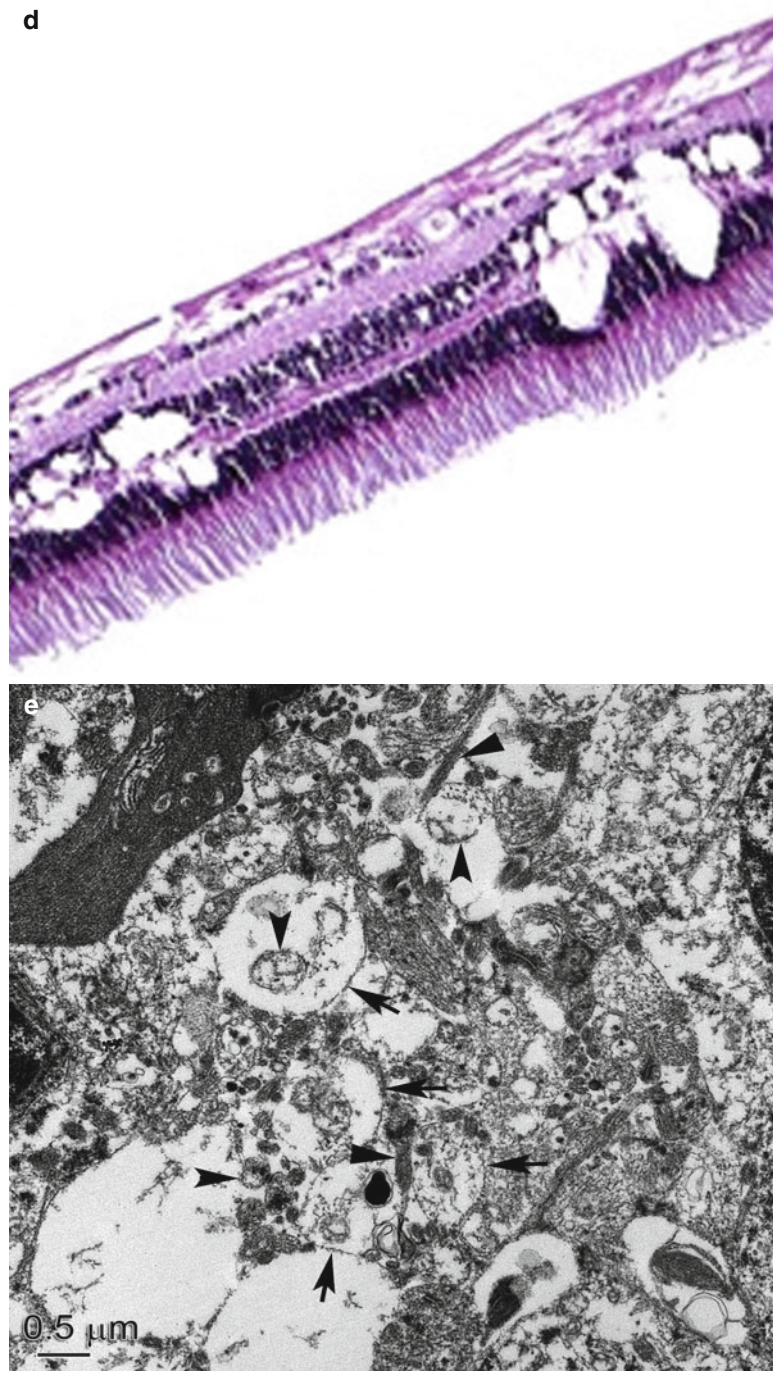


Table 10.2 Presence of symptoms, ophthalmic testing, and autoantibodies directed against retinal antigens in cases of paraneoplastic vitelliform retinopathy

Case	Dec Va	N/P	VF	Color	ERG	EOG	Autoantibodies
1	–	+	NP	NP	+	NP	Bipolar cells
2	+	+	NP	NP	NP	NP	Bipolar cells
3	+	+	NP	NP	+	NP	Bipolar cells
4	–	+	–	NP	+	–	Bipolar cells, MBP
5	–	+	NP	NP	NP	NP	NP
6	–	+	NP	NP	NP	NP	NP
7	+	–	NP	NP	NP	–	NP
8	+	+	NP	NP	NP	NP	NP
9	+	–	+	NP	+	NP	ROS protein
10	+	–	–	NP	–	–	None
11	+	+	+	+	–	+	Bestrophin, α-enolase
12	+	–	NP	NP	–	NP	IRBP
13	–	+	–	–	+	+	CAII (retina and RPE) TRPM1 cation channels of bipolar cells

Dec Va decreased visual acuity, *N/P* nyctalopia and/or photopsias, *ERG* electroretinography, *EOG* electrooculography, *VF* visual field testing, *Color* color vision testing, *MBP* myelin basic protein, *ROS* rod outer segment, *IRBP* interphotoreceptor retinoid-binding protein, *CAII* carbonic anhydrase II, *NP* testing not performed, *TRPM1* transient receptor potential M1

10.4.6 Prognosis

Most individuals succumb to metastatic disease within months of diagnosis [49].

10.5 Bilateral Diffuse Uveal Melanocytic Proliferation (Paraneoplastic Melanocytic Proliferation)

10.5.1 Introduction

Bilateral diffuse uveal melanocytic proliferation (BDUMP) is a rare paraneoplastic disorder which causes bilateral painless visual loss with diffuse uveal thickening and pigmentary changes of the fundus in patients with a systemic carcinoma. Since its original description by Machemer in 1966 [68] and subsequently Barr in 1982 [69], approximately 30 cases have been published [70, 71]. Often, the primary carcinoma is unknown at presentation, and recognition of the characteristic ocular findings prompts a systemic work-up. The primary tumor may arise from numerous sites; however, gynecological neoplasia as well as lung and pancreatic cancer predominates; [70] other sites including colon, gallbladder, breast, and esophagus have been reported [2].

10.5.2 Etiology and Pathogenesis

The exact pathogenesis of BDUMP remains unknown. It is believed that production of hormonal or other oncogenic stimulus by the primary carcinoma causes activation and proliferation of preexistent melanocytes within the uveal tract, mucosal membranes, and the skin. Histopathology shows melanocytic infiltration composed predominately of benign nevus cells with few mitotic figures in the uvea and the skin [72]. Since the proliferation of melanocytes is not limited to the uvea, paraneoplastic melanocytic proliferation may be a more descriptive terminology [72]. Interestingly, RPE atrophy is also a component that is poorly understood. Some have speculated that the increased metabolic demand of proliferating melanocytes leads to RPE hypoxia, while others have proposed that the RPE atrophy occurs as a separate paraneoplastic process [73, 74].

10.5.3 Clinical Features

The mean age at diagnosis of BDUMP syndrome is 64 years and occurs equally in both genders [70]. Ovarian cancer and lung or pancreatic cancer are the most common underlying malignancies in females and males, respectively [70].

10.5.3.1 Symptoms

In half of the reported cases, the ocular symptoms manifest before the diagnosis of an underlying malignancy. Patients typically present with unexplained, acute to subacute bilateral vision loss (Fig. 10.5).

10.5.3.2 Signs

Systemic examination may disclose focal cutaneous and mucosal melanocytic proliferation [72]. Mucosal involvement may even be widespread, with pigmentation of the oral mucosa and lips, penis, and rectum [72]. Similarly, the acquired cutaneous pigmentation appears to be site nonspecific with head, neck, shoulder, and vulval involvement [70]. Gass established the five cardinal ocular signs associated with the diagnosis of BDUMP: (1) the typical fundus pattern found in BDUMP consisting of multiple elevated red round patches at the level of the retinal pigment epithelium, (2) multifocal pattern of early hyperfluorescence corresponding to the patches, (3) pigmented and nonpigmented uveal melanocytic tumors and diffuse thickening of the uvea, (4) coexistent exudative retinal detachment, and (5) the rapid development of cataracts [75]. Other slit lamp findings may include anterior chamber cells, vitreous cells, pigmented iris patches, and signs of ciliary body enlargement such as dilated episcleral vessels, shallow anterior chamber, and iridodonesis.

10.5.4 Diagnostic Evaluation

As with other paraneoplastic ocular disorders, initial diagnostic evaluation should consist of Goldmann or Humphrey visual fields, ERG, and color assessments. Additionally, ultrasonography may be useful in demonstrating peripheral serous detachments and choroidal thickening though this is sometimes subclinical [70]. ERG studies show a nonspecific pattern of decreased cone and rod responses. Fundus autofluorescence of the reddish patches shows hypoautofluorescence; correspondingly, fluorescein angiography demonstrates early window defect hyperfluorescence due to focal destruction of the pigment epithelium with sparing of the choriocapillaris [76]. In late frames, there is marked choroidal hyperfluorescence with patches of hypofluorescence [75]. Spectral domain OCT findings of focal RPE loss with adjacent RPE thickening and overlying subretinal fluid in the macula were recently reported [76].

10.5.5 Differential Diagnosis

Bilateral diffuse uveal melanocytic proliferation should be distinguished from other inflammatory or neoplastic disorders which cause multifocal or diffuse cellular infiltration of the choroid. These can be separated into two categories based on the presence or absence of pigmented choroidal tumors. Idiopathic uveal effusion syndrome, large-cell lymphoma, metastatic carcinoma, leukemia, multifocal and diffuse choroiditis, posterior scleritis, and benign-reactive lymphocytic hyperplasia can mimic BDUMP prior to the presence of multifocal-pigmented choroidal tumors. Metastatic melanoma to the uvea and multiple choroidal nevi can resemble the multifocal-pigmented choroidal tumors observed in BDUMP syndrome.

10.5.6 Treatment

Previously, BDUMP was considered to be an untreatable condition. Early experience with corticosteroids and ocular external radiotherapy did not prevent the progression of the disease [77]. Similarly, vitrectomy, silicone oil injection, and panretinal photocoagulation all failed to prevent the retinal detachments seen in the late stages of BDUMP [75]. Intravitreal anti-vascular endothelial growth factor therapy has also been tried unsuccessfully to treat subretinal fluid involving

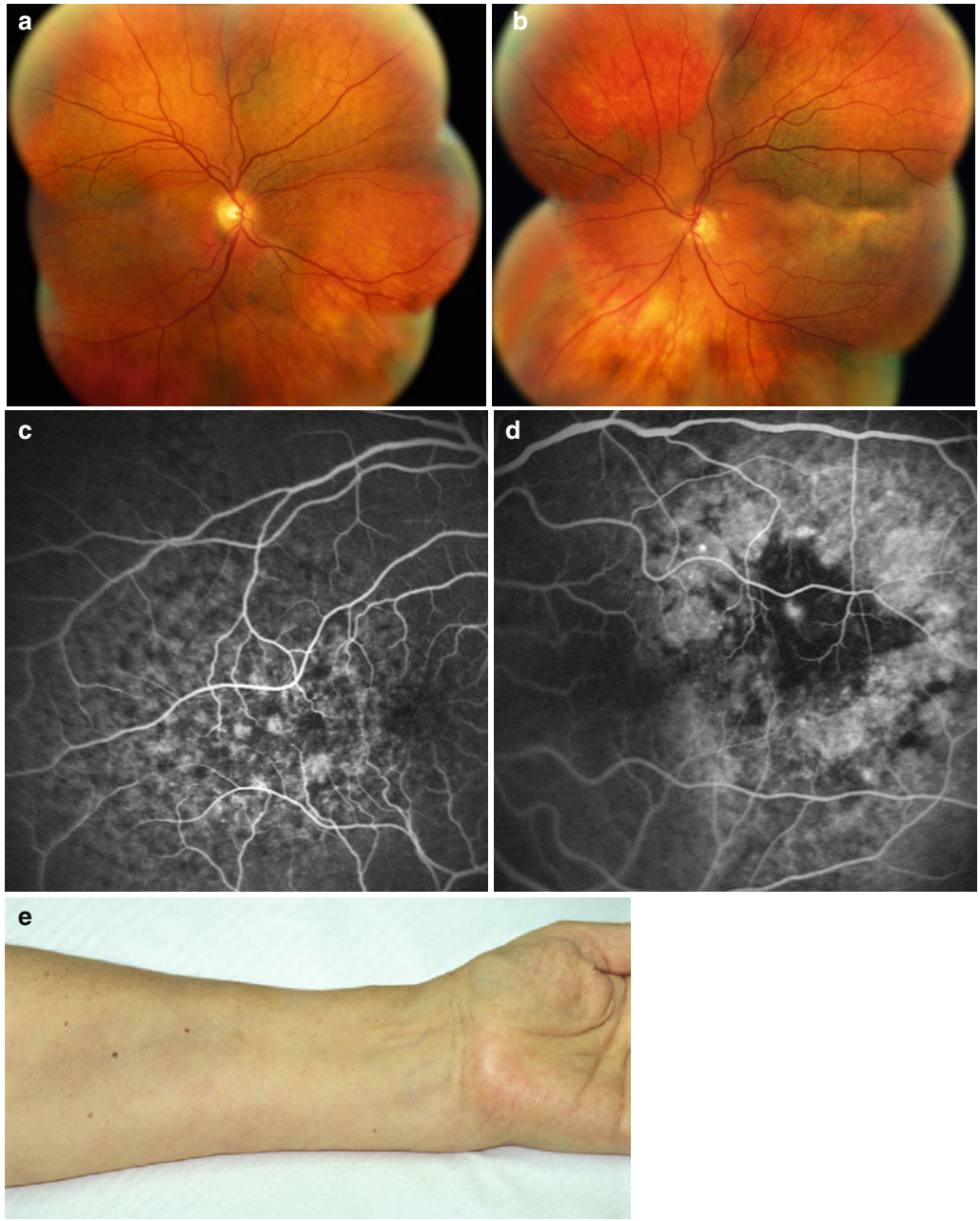
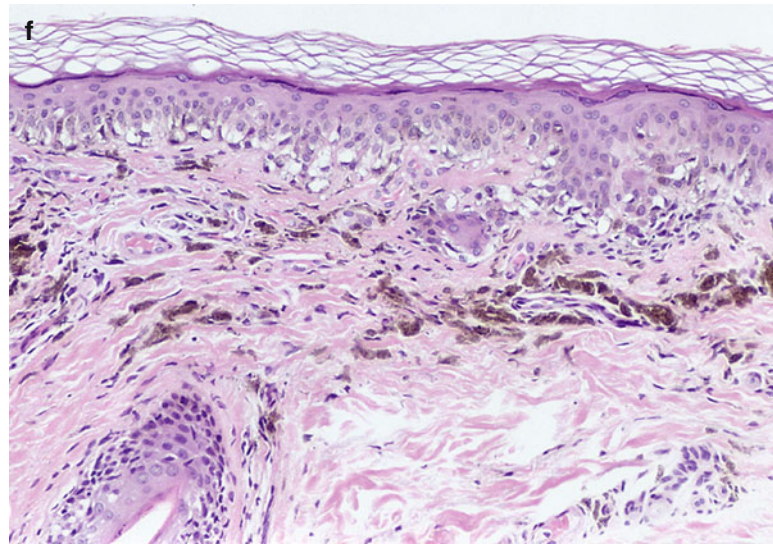


Fig. 10.5 A 56-year-old woman presented with progressive deteriorating vision in both eyes for the last 6 months. The onset of visual symptoms coincided with the diagnosis of large-cell carcinoma of the lung. She was not known to have metastasis and was receiving chemotherapy. The corrected visual acuity was 20/40 in the right eye and 20/60 in the left eye. Anterior segment examination was unremarkable. On ophthalmoscopic examination, the choroid was diffusely thickened in both eyes (*A*-right eye; *B*-left eye). The choroid was also markedly hypermelanotic with scattered areas of orange pigmentation. The choroidal thickening was confirmed by B-scan ultrasonography. Fluorescein angiographic studies showed hypofluorescence corresponding to the distribution of the orange pigment and multifocal patchy hyperfluorescence in the right eye (**c**). The angiographic findings were similar but were more pronounced in the left eye (**d**). The patient had recently noticed new onset-pigmented lesions on her forearms and thighs for the last few months (**e**). Histopathologic evaluation of one of the cutaneous lesions showed confluent proliferation of cytologically atypical melanocytes in the basal layers of the epidermis with focal extension into the mid-epidermis (**f**). Patients' visual status worsened for the next 6 months when she died from metastatic disease (Reproduced with permission from Singh et al. [72])

Fig. 10.5 (continued)



the macula [76]. Recently, there have been case reports of plasmapheresis or plasma exchange as a means of stabilizing or even improving the vision in three patients [71, 78].

10.5.7 Prognosis

Since BDUMP is often the first manifestation of an occult carcinoma, early diagnosis is important for initiating appropriate therapy and prolonging survival. Unfortunately, the identification of BDUMP typically heralds a poor prognosis with death typically occurring within 2 years. There have been no reported cases of metastasis from the choroidal lesions found in BDUMP, though this may reflect the relatively short survival of most patients [70]. Visual acuity loss is typically profound, with a majority of patients reaching hand motion or light perception [70].

10.6 Paraneoplastic Optic Neuropathies

10.6.1 Introduction

Paraneoplastic optic neuropathies (PON) tend to occur within the clinical spectrum of cerebellar and brainstem paraneoplastic disorders though on rare occasion may occur in isolation [79]. These optic neuropathies are most typically found in association with small cell lung cancer but have also been reported in non-small cell lung cancer, Hodgkin's and non-Hodgkin's lymphoma, neuroblastoma, bronchial carcinoma, nasopharyngeal carcinoma, thymoma, prostate cancer, papillary renal cell cancer, and various neuroendocrine tumors [2, 80–83].

10.6.2 Etiology and Pathogenesis

As with CAR and MAR, cross-reacting antitumoral and anti-neuronal antibodies have been identified. Antibodies to collapsing response-mediating protein-5 (CRMP-5) are the best characterized and most commonly identified, though there have been reports of other antibodies [83, 84]. Presumably reaction with the CRMP-5 antigen results in the pathologic findings of inflammatory cell infiltration, demyelination, or both [84].

10.6.3 Clinical Features

10.6.3.1 Symptoms

Neurological symptoms may precede or follow the ocular manifestations of the syndrome. Patients present with unilateral, subacute, painless vision loss that progresses over weeks to months,

often with loss developing in the fellow eye. Additional ophthalmic symptoms may include blurred vision, tunnel vision, and photopsias.

10.6.3.2 Signs

Decreased visual acuity on Snellen assessment is nearly universally present, and unless the optic nerve involvement is symmetric, the patient will have a relative afferent pupillary defect. Exam may disclose a normal fundus and optic nerve, disc pallor, or papilledema as well as vitritis and retinitis [2]. In addition, patients can present with neurological findings of encephalomyeloradiculopathy which can include mental status, cranial nerve, motor, autonomic, and movement disorders [84].

10.6.4 Diagnostic Evaluation

Color plates and visual field testing are useful complements to afferent pupillary defect testing in the clinic. Electrophysiology, unless a combined retinitis is present, is typically normal and useful in excluding CAR and MAR; [85] visual evoked response may be delayed [84]. Visual fields may show a range of defects but peripheral constriction and cecocentral scotomas are particularly common [84]. Cerebrospinal analysis often shows mild to moderate lymphocytosis and elevated protein levels but no evidence of malignant cells. While antibodies to CRMP-5 are a useful component of diagnostic testing and may be demonstrated in the serum or cerebral spinal fluid, they are not required for the diagnosis [83, 84].

10.6.5 Differential Diagnosis

Paraneoplastic optic neuropathy should be distinguished from paraneoplastic retinopathy, acute ischemic optic neuropathy, neoplastic, infectious or inflammatory infiltration of the optic nerve, and demyelinating disease such as neuromyelitis optica and multiple sclerosis. Additionally, discerning paraneoplastic optic neuropathy from an adverse effect of a chemotherapeutic agent may be a difficult diagnostic challenge.

10.6.6 Treatment

Treatment of the underlying malignancy with excision, radiation, and chemotherapy coupled with corticosteroids may improve visual acuity and visual field defects [2]. Sometimes the improvement is substantial, while in other cases the vision continues to decline despite all treatment efforts [86, 87].

10.6.7 Prognosis

The prognosis of paraneoplastic optic neuropathy is quite mutable—patients may have significant recovery of visual function or be left with significant visual loss. The fact that nearly complete visual recovery can follow successful treatment of the underlying cancer emphasizes the importance of early diagnosis [86, 88–90].

10.7 Opsoclonus and Paraneoplastic Eye Movement Disorders

Paraneoplastic eye movement disorders may arise from involvement of the cerebellum and brainstem or result from direct interaction with cellular receptors, such as in Lambert-Eaton syndrome. Opsoclonus is part of a larger group of ocular disorders caused by paraneoplastic cerebellar degeneration. Ocular findings often are abnormal, including horizontal or vertical nystagmus, dysconjugate gaze, ocular dysmetria, and opsoclonus. In opsoclonus the clinical picture is referred to as "dancing eyes" due to the rapid ocular movements [91]. Lung cancer and neuroblastoma are the most common malignancies reported with opsoclonus in adults and children, respectively [92], but it has also been described in tumors of the breast, ovary, and uterus [91]. In the case of cerebellar degeneration, unlike CAR and MAR, antibodies do not appear to cause the damage. Rather, "killer T cells," or cytotoxic CD8+ T lymphocytes, are the most likely mediator of neuronal injury [93]. Nevertheless, assays for antibodies such as anti-RI, anti-Yu, and anti-Ho are useful

when making the diagnosis of paraneoplastic opsoclonus [94]. Opsoclonus is sensitive to the treatment of the underlying malignancy, corticosteroids, and infusion of IVIG.

10.8 Summary

Paraneoplastic ocular disorders can present with a multitude of ocular symptoms with overlapping characteristics. Ancillary testing with ERG and commercially or academically available assays for suspected antibodies elicited by the primary tumor have proven to be quite useful. The correct and early identification of the occult malignancy through the ocular exam leads to earlier therapeutic interventions and a better prognosis for the patient. Future therapies will focus on the potential benefits of new immunomodulatory medications in treating the paraneoplastic condition and on tumor surveillance through serial antibody evaluations.

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