# Clinical Ophthalmic Oncology

## Retinal Tumors

Arun D. Singh
Bertil E. Damato
*Editors*

*Third Edition*

Springer

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*Editors*
Arun D. Singh
Cleveland Clinic Foundation
Cole Eye Institute
Cleveland Clinic Foundation
Cleveland, OH
USA

Bertil E. Damato
University of Oxford
Oxford, UK

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# Preface

Ophthalmic tumors are rare and diverse so 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 need for the new edition of the textbook providing a balanced view of current clinical practice. Although each section of *Clinical Ophthalmic Oncology*, *Third Edition*, 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.

The enormous task of editing a multi-author, multivolume textbook could not have been possible without the support and guidance by the staff at Springer: Caitlin Prim, Melanie Zerah, ArulRonika Pathinathan, and Karthik Rajasekar. Michael D. Sova kept the pressure on to meet the production deadlines.

It is our sincere hope that our efforts will meet the high expectation of the readers.

Cleveland, OH, USA — Arun D. Singh
Oxford, UK — Bertil E. Damato

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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 Arun D. Singh.

To my family, Frankanne, Erika, Stephen, and Anna Bertil E. Damato.

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# Editors and Contributors

## Editors

**Arun D. Singh, MD** Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA

**Bertil E. Damato, MD, PhD, FRCOphth** University of Oxford, Oxford, UK

## Contributors

**Thomas M. Aaberg Jr, MD** Department of Ophthalmology, Retina Specialists of Michigan, Michigan State University, Spectrum Health, Grand Rapids, MI, USA

**Manmeet S. Ahluwalia, MD** The Rose Ella Burkhardt Brain Tumor & Neuro-Oncology Center, Cleveland Clinic, Cleveland, OH, USA

**Mary E. Aronow, MD** Massachusetts Eye and Ear, Ocular Melanoma Center and Retina Service, Harvard Medical School, Boston, MA, USA

**Rafael I. Barraquer, MD, PhD** Centro de Oftalmología Barraquer, Barcelona, Spain

**Elaine Binkley, MD** Department of Ophthalmology, Cole Eye Institute (i32), Cleveland Clinic Foundation, Cleveland, OH, USA

**Maria de la Paz, MD, PhD** Centro de Oftalmología Barraquer, Barcelona, Spain

**Javier Elizalde, MD, PhD** Centro de Oftalmología Barraquer, Barcelona, Spain

**Christopher Seungkyu Lee, MD, PhD** Department of Ophthalmology, Severance Hospital, Yonsei University, College of Medicine, Seoul, South Korea

**Sungchul Lee, MD, PhD** Department of Ophthalmology, Severance Hospital, Yonsei University, College of Medicine, Seoul, South Korea

**Ilya Leskov, MD** Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic Foundation, Cleveland, OH, USA

**Prithvi Mruthyunjaya, MD, MHS** Department of Ophthalmology, Byers Eye Institute, Stanford University School of Medicine, Palo Alto, CA, USA

**David M. Peereboom, MD, FACP** The Rose Ella Burkhardt Brain Tumor & Neuro-Oncology Center, Cleveland Clinic, Cleveland, OH, USA

**Ehud Reich, MD** Department of Ophthalmology and Davidoff Center for Oncology, Rabin Medical Center/Sackler Medical School, Tel Aviv University, Petach Tikva, Israel

**Ian Rennie, FRCOphth** Sheffield Ocular Oncology Service, Royal Hallamshire Hospital, Sheffield, UK

**Paul A. Rundle, FRCOphth** Sheffield Ocular Oncology Service, Royal Hallamshire Hospital, Sheffield, UK

**Mandeep S. Sagoo, MB, PhD, FRCOphth, FRCS (Ed)** Department of Ocular Oncology, NIHR Biomedical Research Centre for Ophthalmology at Moorfields Eye Hospital and UCL Institute of Ophthalmology, London, UK

**Sachin M. Salvi, FRCOphth** Sheffield Ocular Oncology Service, Royal Hallamshire Hospital, Sheffield, UK

**Matteo Scaramuzzi, MD** Department of Pediatric Ophthalmology and Strabismus, Center for Genetic Eye Diseases, Cole Eye Institute, Cleveland Clinic Foundation, Cleveland, OH, USA

**Liliya Shevchenko, DO** Department of Ophthalmology/Vitreoretinal Disease, Retina Specialists of Michigan, Grand Rapids, MI, USA

**Peter H. Tang, MD, PhD** Department of Ophthalmology, Byers Eye Institute, Stanford University School of Medicine, Palo Alto, CA, USA

**Caroline Thaung, FRCOphth, FRCPath, DPhil** Department of Eye Pathology, UCL Institute of Ophthalmology, London, UK

**Elias I. Traboulsi, MD** Department of Pediatric Ophthalmology and Strabismus, Center for Genetic Eye Diseases, Cole Eye Institute (i-32), Cleveland Clinic Foundation, Cleveland, OH, USA

**Lejla Vajzovic, MD** Duke University Eye Center, Durham, NC, USA

# 1 Classification of Retinal and Retinal Pigment Epithelium Tumors

Ehud Reich, Caroline Thaung, and Mandeep S. Sagoo

## 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].

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. The drawback is that this schema 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, genetic or metabolic variations, or indeed benign versus malignant elements within a tumor type.

The tumor-node-metastasis (TNM) classification has recently been modified (eighth edition) and is another system that aids us in trying to unify our discussion but covers only malignant tumors, status, and spread [2]. The data collected with the TNM system allows us better

E. Reich
Department of Ophthalmology and Davidoff Center for Oncology, Rabin Medical Center/Sackler Medical School, Tel Aviv University, Petach Tikva, Israel

C. Thaung
Department of Eye Pathology, UCL Institute of Ophthalmology, London, UK

M. S. Sagoo (✉)
Department of Ocular Oncology, NIHR Biomedical Research Centre for Ophthalmology at Moorfields Eye Hospital and UCL Institute of Ophthalmology, London, UK
e-mail: Mandeep.sagoo@moorfields.nhs.uk


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

| Site | Primary/ secondary | Tissue type | Entities | |
|---|---|---|---|---|
| Retinal | Primary | Vascular | Prenatal[a] | Retinal cavernous hemangioma |
| | | | | Arteriovenous malformations (retinal racemose hemangioma) |
| | | | Postnatal | Retinal capillary hemangioma |
| | | | | Retinal vasoproliferative tumor[b] |
| | | "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 the 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)

[b]Recently published clinical histopathologic, immunohistochemical, and molecular findings indicate predominance of astrocytes rather than vascular components within these tumors. Hence, reactive retinal astrocytic tumor has been proposed as an alternate terminology to describe these retinal tumors rather than labeling them as a vasoproliferative tumor

prognostication and to scrutinize our treatment modalities – past and future. For the first time for any cancer, the TNM classification for retinoblastoma includes heredity (H) and hence has evolved to TNMH.

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 exclude 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 the retina and RPE. The reader is invited to develop diagnostic algorithms based on our suggested framework (Table 1.1).

## 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 [3]. Its benign variant is retinoma or retinocytoma. Simulating lesions in children include Coats' disease, an idiopathic exudative retinopathy [4], 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 [5]. A reactive tumor of adults, which can mimic the retinal capillary hemangi-

oma, is the vasoproliferative tumor – a lesion that is benign and in the spectrum of Coats' disease [6]. Recent histopathologic, immunohistochemical, and molecular findings indicate predominance of astrocytes rather than vascular components within these tumors and hence the notion that an alternative term for the vasoproliferative tumor is reactive retinal astrocytic tumor [7, 8].

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 [9]. 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 [10]. Secondary tumors to the retina are possible, though true retinal metastases are extremely rare.

## Tumors of the Retinal Pigment Epithelium

Neoplasia of the retinal pigment epithelium is rare. Adenocarcinomas, and indeed their benign variants, adenomas, are reported [11]. Hamartomas of the retinal pigment epithelium can be simple, involving only this cell type, or can be combined with retinal dysplasia [12]. 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. The 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 eighth edition 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 continue to evolve.

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# Coats' Disease

2

Thomas M. Aaberg Jr. and Liliya Shevchenko

## 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.

T. M. Aaberg Jr. (✉)
Department of Ophthalmology, Retina Specialists of Michigan, Michigan State University, Spectrum Health, Grand Rapids, MI, USA
e-mail: thomasaaberg@comcast.net

L. Shevchenko
Department of Ophthalmology/Vitreoretinal Disease, Retina Specialists of Michigan, Grand Rapids, MI, USA

## 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 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 their relatively large study, Zhao et al. demonstrated increasing VEGF concentration with progressively higher stages of Coats' disease by showing the correlation between the levels of intraocular VEGF and the extent of exudative retinal detachment [12]. However, it remains unclear whether the increased VEGF was the cause or the consequence of Coats' disease.


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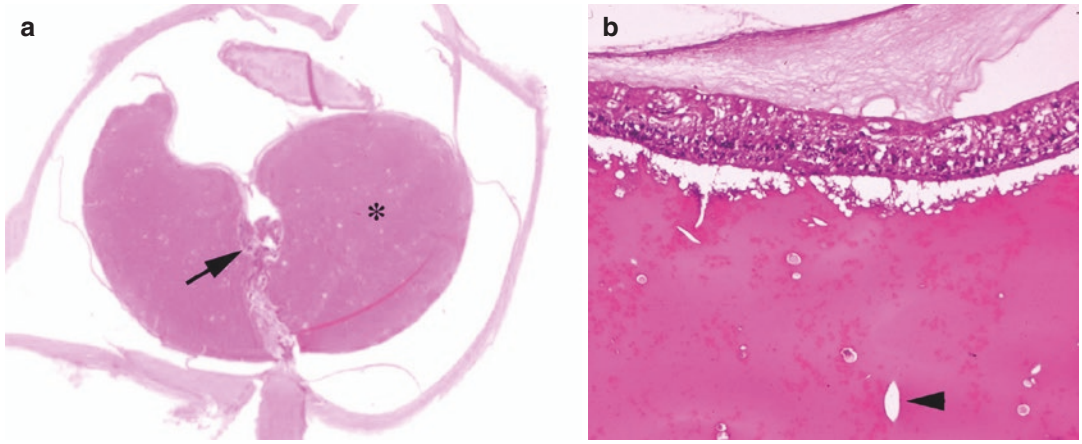


**Fig. 2.1** Enucleated eye with Coats' disease. Note the total exudative retinal detachment (arrow) and the subretinal exudate (asterisk) (**a**, low-power hematoxylin and eosin). Cystic degeneration, disorganization, and deposition of PAS-positive material in the outer retina. Cholesterol clefts are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

Nitric oxide (NO)—the mediator of vascular dilation and permeability—is also elevated in the aqueous humor of the eyes affected by Coats' disease compared to controls [13].

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 [14]. A somatic mutation of the *NDP* gene encoding norrin, a protein with important role in retinal angiogenesis, and the *CRB1* (crumbs homologue 1) gene has also been implicated in Coats' disease [15, 16]. Unfortunately, it is unclear if the Coats'-like changes are secondary events or due to an independent genetic mutation.

**Table 2.1** Classification of Coats' disease

| Stage | Retinal findings |
|---|---|
| Stage 1 | Retinal telangiectasia only |
| Stage 2 | Telangiectasia and exudation |
| 2A | Extrafoveal |
| 2B | Foveal |
| 2B1 | Without subfoveal nodule[a] |
| 2B2 | With subfoveal nodule[a] |
| Stage 3 | Exudative retinal detachment |
| 3A | Subtotal |
| 1 | Extrafoveal |
| 2 | Foveal |
| 3B | Total retinal detachment |
| Stage 4 | Total retinal detachment and glaucoma |
| Stage 5 | Advanced end-stage detachment |

Based on data from Ref. [17]
[a]Proposed new subcategories within stage 2B by Daruich et al. [26]

## 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 [17]. 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 [17–20].

Clinical findings vary in Coats' disease depending on the five different stages of the disease (Table 2.1) [21]. 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) [17, 22]. Vitreoretinal traction is usually absent. The macula is involved in only 1%

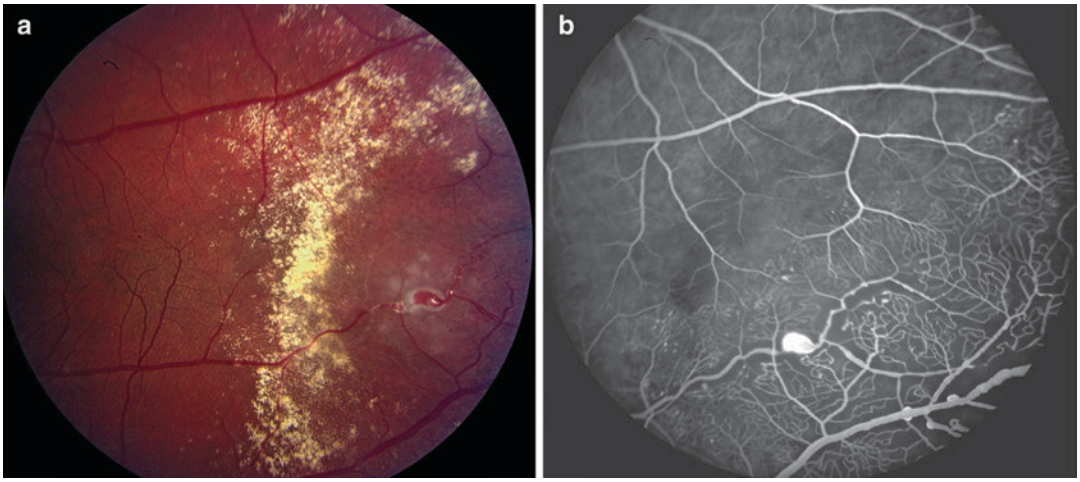


**Fig. 2.2** Fundus photograph of the left eye demonstrates the circinate lipid exudation surrounding retinal telangiectasia (**a**). Fluorescein angiography demonstrates the area of bulbous aneurysms, vascular telangiectasia, and areas of capillary nonperfusion (**b**)

of these early cases [17]. 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 aneurysms 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 [23]. Intraretinal macrocysts develop in 10% of cases, most likely due to coalescence of microcystic spaces in chronically detached and edematous retina [17, 24]. Hemorrhagic macrocysts have been reported [25]. 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 [21, 22].

## Diagnostic Evaluation

In most cases, Coats' disease can be diagnosed by clinical examination. However, various imaging modalities are implemented to confirm the diagnosis, monitor progression, and guide treatment of this condition.

Fluorescein angiography is helpful both for diagnostic purposes, to assess the extent of the disease and guide ablative therapy. 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.

Optical coherence tomography is helpful in assessing the extent and staging of central retinal involvement including the presence of sub- and intraretinal fluid and exudates, intraretinal edema, the size of lipid deposits, ellipsoid zone disruption, external limiting membrane disruption, subretinal fibrosis, and subfoveal nodule formation [27]. Gupta and colleagues report that microstructural abnormalities on OCT are predictive of baseline visual acuity and visual prognosis [28].

In recent years, new imaging modalities have become valuable in the evaluation and management of Coats' disease. Ultra-widefield (UWF) images are arguably able to identify more retinal

pathology than standard fundus photography, even in clinically unaffected fellow eyes. In one study, UWF angiography detected pathology in seven out of nine (78%) of clinically unaffected eyes [29]. Optical coherence tomography angiography (OCT-A) has shown limited usefulness. OCT-A is accurate in identifying type 3 neovascularization in Coats' disease by showing coarse vessels in foveal avascular zone (FAZ) suggesting vascularized fibrosis [29]. This is a useful test since indocyanine green (ICG) angiography is not routinely used in imaging Coats' disease. Abnormal FAZ structure with inner retinal vessels traversing the avascular zone in the superficial capillary plexus in both clinically affected and unaffected eyes has also been observed [30]. Stanga et al. noted a significant increase in the foveal vessel density of the superficial capillary plexus on OCT-A in unaffected fellow eyes [31]. Therefore, due to newer imaging modalities, what was always believed to be mostly unilateral disease is now being viewed as a highly asymmetric bilateral condition (Fig. 2.3).

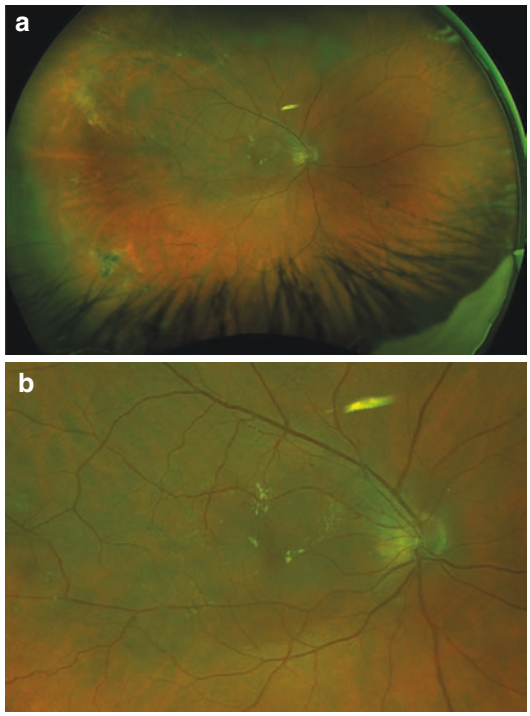


**Fig. 2.3** UFW photograph of the right eye in a 66-year-old male with Coats' disease showing multiple saccular aneurysms, retinal telangiectasia, vascular sheathing, and lipid exudation in the periphery (**a**) and macula (**b**)

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. 2.4). Highly reflective foci representing calcium deposition, frequently 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 differen-

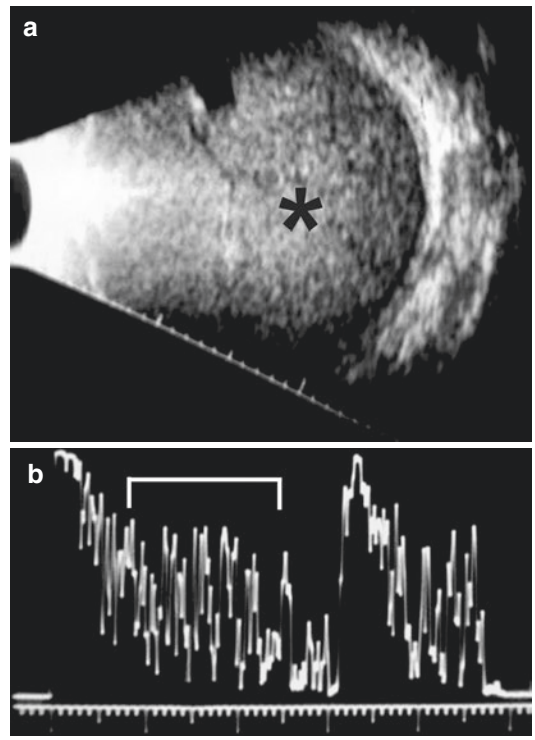


**Fig. 2.4** Diagnostic ultrasonography of the eye in Fig. 2.1. Note the diffuse, homogeneous medium reflectivity of the posterior segment on B scan (asterisk). The numerous echogenic clefts represent cholesterol crystals within the subretinal exudates (**a**). These crystals account for the medium reflective spikes seen on the A scan (bracket, **b**)

tiation of retinoblastoma from Coats' disease. CT has a sensitivity of 96% in detecting calcification in retinoblastoma, while MRI sensitivity is 91.7% [32]. 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 [33]. 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 the 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 [33, 34].

Fine needle aspiration of the subretinal exudate demonstrates cholesterol crystals, lipid- and pigment-laden macrophages, and the absence of tumor cells [35]. 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.

## Associations

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

## Ophthalmic

Bilateral retinal exudation, retinal telangiectasia, and even angioma can occur in patients with Coats'-like retinitis pigmentosa (Fig. 2.5) [36, 37]. Coats'-like retinitis pigmentosa is an atypical form of RP. Coats'-like changes occur in as many as 1.2–3.6% of patients with retinitis pigmentosa [36]. It can be differentiated from classic Coats' disease by older age of onset, no sex predilection, bilateral involvement, more severe progression, inferior and temporal retinal involvement, and diffuse pigment alteration in both eyes. Development of Coats'-like retinitis pigmentosa is strongly associated with mutations in crumbs homologue 1 gene (CRB1) [38].

Cataract formation, a common and a relatively benign condition in adults, is a frequent feature in pediatric population with Coats' disease and can aggravate visual prognosis. Total white cataracts and posterior subcapsular cataracts were found to be the most prevalent type in Coats' disease [39].

## Systemic

The most common association is with muscular dystrophy [40]. In a study of 64 patients affected with facioscapulohumeral muscular dystrophy, 48 (75%) had angiographic findings of retinal telangiectasia [40, 41]. Concurrent CNS finding has also been reported, including central nervous system venous malformations [42] and cerebral calcifications [43]. Beyond these cases, there exist only case reports of Coats' disease associated with a variety of syndromes such as dystonia with PANK2 mutation [44], Turner's syndrome [45], Cornelia de Lange syndrome [46], Hallermann-Streiff syndrome [47], Osler-Weber-Rendu disease [9], and Revesz syndrome [14, 48].

Coats' plus disease, also known as cerebroretinal microangiopathy with calcifications and cysts (CRMCC), is a pleiotropic telomeric shortening disorder characterized by bilateral retinal telangiectasias, exudative retinopathy, intracranial calcifications, bone marrow abnormalities, and gastrointestinal vascular ectasias [14]. It is an autosomal recessive disorder caused by homozygous or compound heterozygous mutations in the *CTC1* gene on chromosome 17p13.1, which is responsible for telomere replication. *CTC1* gene is expressed in endothelial cells, and disease features are thought to result from small vessel vasculopathy with retinal features similar to Coats' disease [49]. Retinal vascular abnormalities are often the presenting feature; therefore, an examiner has to be aware of this condition in order to coordinate prompt systemic management and genetic counseling.

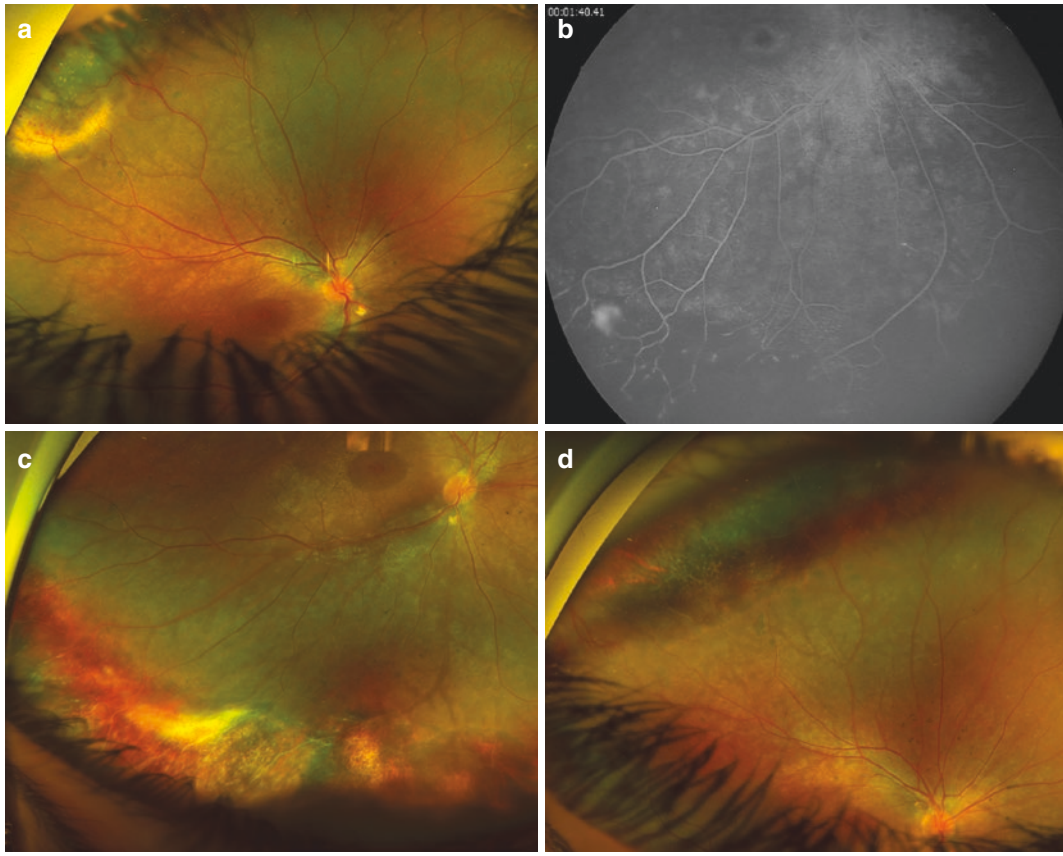


**Fig. 2.5** Retinal telangiectasia, exudative retinal detachment, and retinitis pigmentosa. A 12-year-old male presented with night blindness and constricted visual fields in both eyes. Family history includes an older sister with retinitis pigmentosa. Visual acuities were 20/40 in both eyes. Anterior segment examination was normal. The posterior segment of the right eye showed subretinal exudation in the superotemporal and inferotemporal quadrants, with associated serous retinal detachment, and overlying retinal telangiectasia (**a**, **b**). There was cystoid macular edema in both eyes. The optic discs had overlying gliotic tufts. Additionally, mottled granularity of the retinal pigment epithelium (RPE) was noted in the mid-periphery of both retinas (**a**, **b**). A fluorescein angiogram confirmed retinal telangiectasia and macular edema (**c**). He underwent successful treatment with cryotherapy (**c**) and laser photocoagulation (**d**). Genetic testing revealed heterozygous mutation in CRB1 gene

## 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 [50]. 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-sized tumors do not typically have associated lipid exudation, though serous retinal detachments will occur in exophytic tumors.

**Table 2.2** Coats' disease and retinoblastoma

| | | Coats' disease | Retinoblastoma |
|---|---|---|---|
| Demographics | Mean age at diagnosis | 5 years | 1.5 years |
| | Male | 76% | 50% |
| | Family history | 0% | 10% |
| Ophthalmic findings | 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 imaging | USG | Retinal detachment | Retinal detachment with calcification |
| | CT scan | Calcification absent | Calcification present |
| | MRI | Retinal detachment | Retinal detachment with enhancing mass |

*Abbreviations: USG* ultrasonography, *CT* computerized tomography, *MRI* magnetic resonance imaging
Based on data from Ref. [50]

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 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 retina 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.

Retinal arterial macroaneurysms can occur in patients with uveitis due to sarcoidosis in up to 17% of cases. Some authors have even suggested for patients with macroaneurysms and choroiditis to be evaluated for sarcoidosis [51].

## Treatment

The natural history of Coats' disease is usually of a progressive disease. Though the rate of progression is variable, the majority of affected eyes will develop severe vision loss. Between 64 and 80% of eyes will become phthisical and develop advanced glaucoma or retinal detachment [20]. Management of Coats' disease varies according to the stage of disease. Only rarely will the telangiectasia regress spontaneously [52].

**Table 2.3** Differential diagnosis of exudative retinopathy

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

*Abbreviations: 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, + present, – absent

## Observation

Observation can be considered in some cases with early telangiectasia (stage 1) or telangiectasias with exudation (stage 2) that is not vision threatening. Advanced non-seeing but comfortable eyes can be monitored as well.

## Laser Photocoagulation

The treatment should be initiated once progression is documented and exudation becomes significant. The first line of treatment is laser photocoagulation and/or cryotherapy (Fig. 2.5c, d). The goal is to ablate the nonperfused retina and areas 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 [53].

## Cryotherapy

Cases with a shallow exudative retinal detachment can be successfully treated with a double freeze-thaw cryotherapy (Figs. 2.5d and 2.6). Multiple treatment sessions every 3 months are usually necessary with either laser or cryotherapy.

## Intravitreal Therapy

Successful use of anti-VEGF therapy in conjunction with ablative therapy (cryotherapy

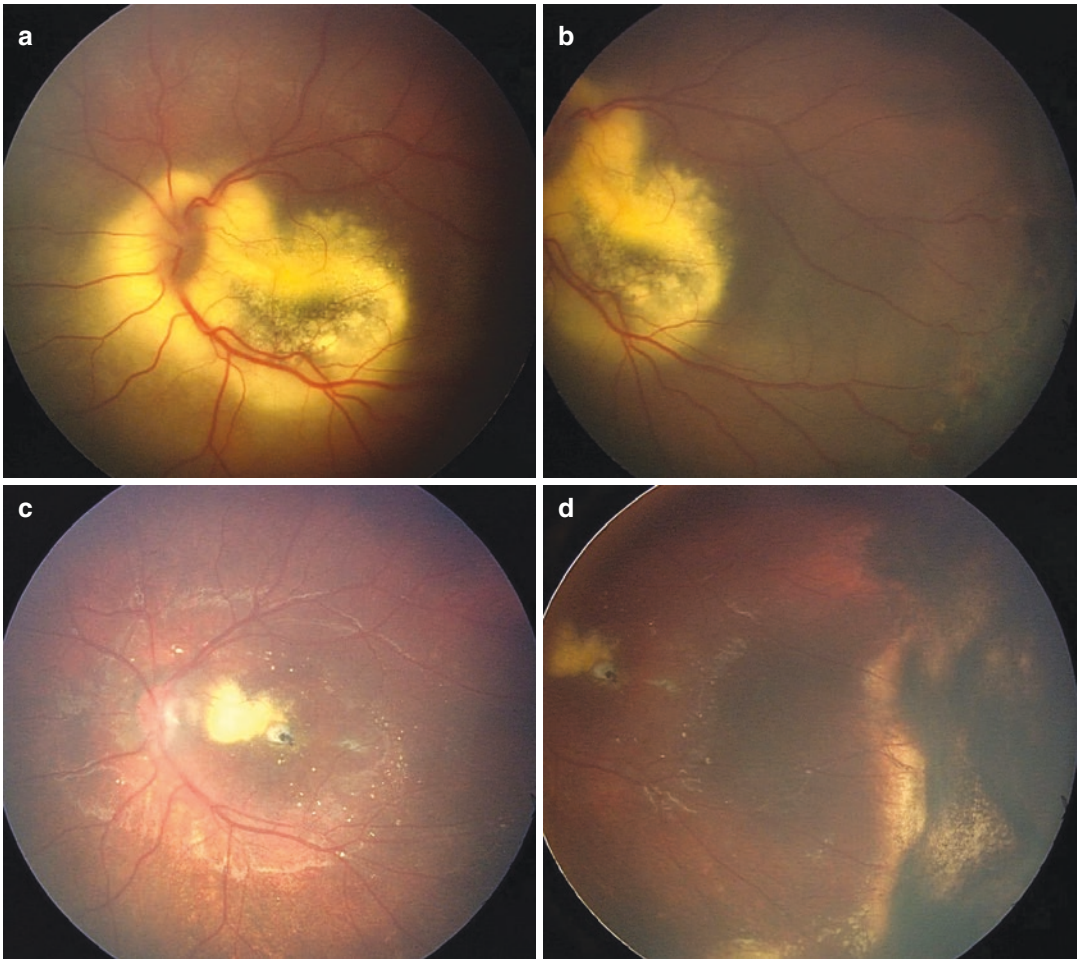


**Fig. 2.6** A 20-month-old child with leukocoria OS. Note prominent exudation in the macular region (**a**) and retinal telangiectasia in the inferotemporal quadrant (**b**). He was treated with multiple sessions of laser photocoagulation and cryotherapy to the involved regions of the retina. One year 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**)

or panretinal laser photocoagulation) has been reported [54–56]. Anti-VEGF therapy has been shown to decrease macular edema and exudates and even reverse tractional retinal detachment (TRD). However, Li and colleagues summarized multiple reports of patients with late- and early-stage Coats' disease in whom the use of intravitreal bevacizumab or ranibizumab was associated with development of vitreoretinal fibrosis and TRD [57]. Additional research is warranted to further elucidate the role of anti-VEGF therapy in Coats' disease.

Intravitreal corticosteroid injection may play a role in treatment of Coats' disease by suppressing inflammation, attenuating leukostasis, and decreasing vascular permeability. Intravitreal triamcinolone injection followed by ablative therapy has been successful in treatment of exudative retinal detachment [58]. This adjunct to ablative therapy has to be weighted against adverse effects of corticosteroids such as cataract formation and steroid response glaucoma. Dexamethasone implant, with its safer profile, can serve as a good alternative to intravitreal triamcinolone. There are several reports on successful use of dexamethasone implants for treatment

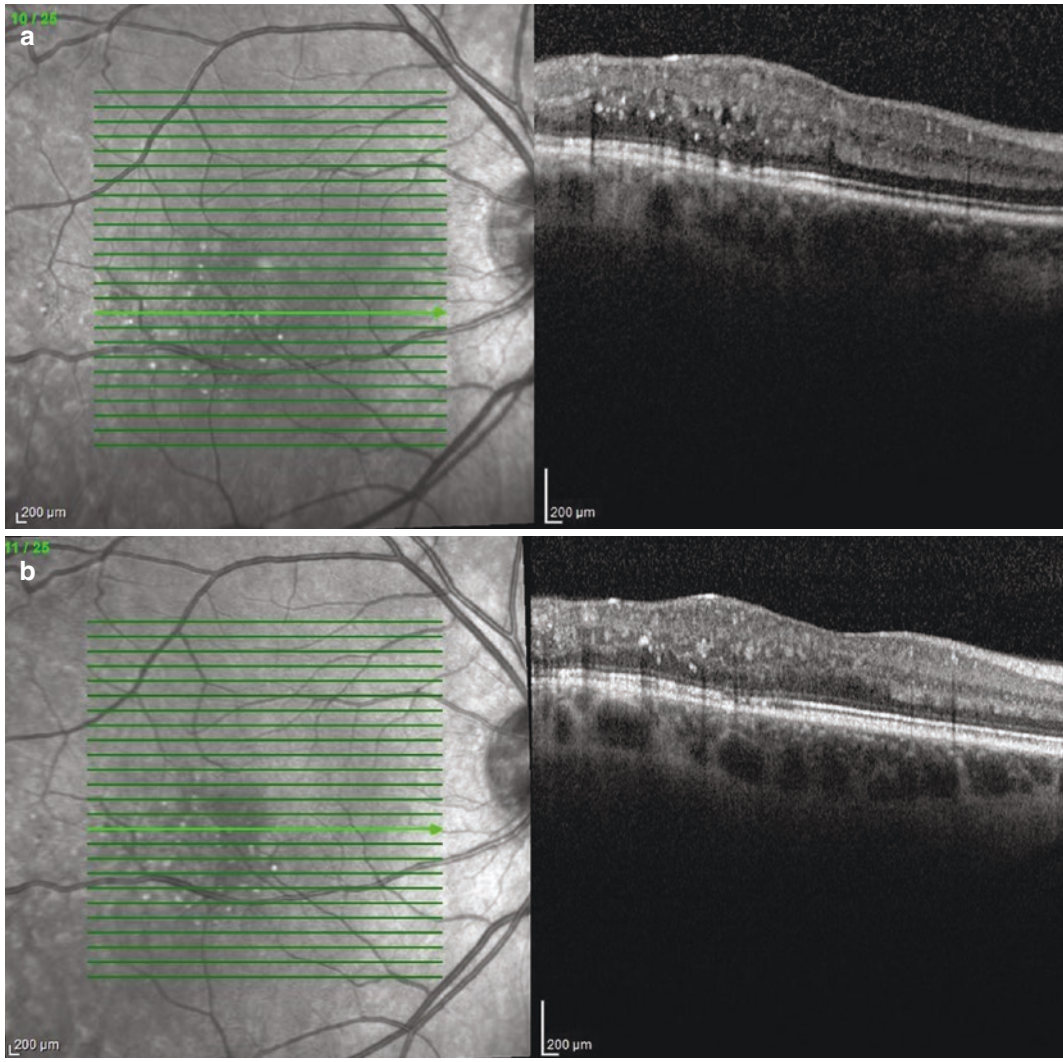


**Fig. 2.7** OCT of the right macula in a 25-year-old male depicting macular edema due to Coats' disease. Edema was not amenable to focal laser treatment due to central location (**a**). Patient underwent intravitreal dexamethasone injection and showed resolution of macular edema at 6-week follow-up (**b**)

of vasoproliferative tumors associated with Coats' disease [59]. The authors of this chapter have had good success treating Coats'-associated macular edema with an intravitreal dexamethasone implant (Fig 2.7a, b)

## 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. Transscleral drainage accompanied by intravitreal injection of anti-VEGF and laser photocoagulation has shown great success in management of advanced Coats' disease (stage 3) with exudative retinal detachment [60]. Li and his colleagues hypothesize that the success and benefit of external drainage come from clearing the toxic milieu in which the photoreceptors are bathed and eliminating proinflammatory cytokines and profibrotic signals, such as VEGF [57]. Some surgeons elect to encircle the eye with a scleral buckle to minimize tractional forces generated at the vitreous base.

## Vitreoretinal Techniques

Although ablative therapy is the mainstay for initial treatment for Coats' disease regardless of the stage, there are instances when a drainage procedure with or without vitrectomy is warranted, particularly in instances of severe exudative retinal detachment or tractional detachment due to retinal surface membrane proliferation [61, 62]. The argument for early vitrectomy comes from the theory that it may prevent TRD by clearing profibrotic signals from the vitreous cavity as well as removing vitreous collagen which serves as a scaffold for TRD's formation [57]. Despite those benefits, vitrectomy is still not advised as a first-line therapy for stage 3B disease.

## Supportive Care

Protective eyewear 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.

## Follow-Up

Disease recurrence in 7–10% of eyes up to a decade from initial treatment has been reported [17, 21, 22]. 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.

## Prognosis

Overall, it can be expected that roughly 75% of patients will have an anatomic improvement or stabilization of the affected eye with treatment [21]. The remaining 25% will worsen or require enucleation. As expected, patients with 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 [21]. The natural progression in advanced Coats' disease is toward the development of a blind, painful eye or to a phthisical state [63].

## Conclusion

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 meantime, 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

Sachin M. Salvi, Paul A. Rundle, Ian Rennie, and Arun D. Singh

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/reactive retinal astrocytic tumor). Each of the subtypes has characteristic 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 and further discussed under neuro-oculo-cutaneous syndromes (phakomatoses) (Chap. 9).

## Retinal Capillary Hemangioma

### 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).

### Clinical Features

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

S. M. Salvi (✉) · P. A. Rundle · I. Rennie
Sheffield Ocular Oncology Service, Royal Hallamshire Hospital, Sheffield, UK
e-mail: sachin.salvi@nhs.net

A. D. Singh
Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA


A. D. Singh, B. E. Damato (eds.), *Clinical Ophthalmic Oncology*,
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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 | Grape-like clusters | Nonspecific | Absent | Absent | CNS hemangioma |
| Arteriovenous malformations | Dilated/tortuous retinal vessels | Near the disc | Absent | Absent | Wyburn-Mason syndrome |
| Vasoproliferative tumor | Globular pale mass | Periphery | Absent | Present | Absent |

*VHL* von Hippel-Lindau disease

## Symptoms

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

## 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 exudation is 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.

## 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 feeder arteriole from the draining vein and is therefore important for treatment planning. OCT evaluation of these lesions shows a hyper-reflective lesion with little inner tumor detail, but macular evaluation by OCT is useful for detecting associated macular edema, epiretinal membranes, and subretinal fluid (Fig. 3.2). OCT-A appears to be promising non-invasive imaging tool in the diagnosis and monitoring of posterior non-leaking retinal capillary hemangiomas [6]. Compared to fluorescein angiography, OCT-A is able to identify tiny tumors, but only those closer to the posterior pole. Both FA and OCT-A could identify the intrinsic vasculature and feeder vessel in juxtapapillary tumors and small tumors not identified on ophthalmoscopic examination. However, the tumors and their feeding and draining vessel were better defined by OCT-A than by FA. OCT-A failed to image the peripheral tumors [6].

### Box 3.1 Salient Diagnostic Findings

- 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

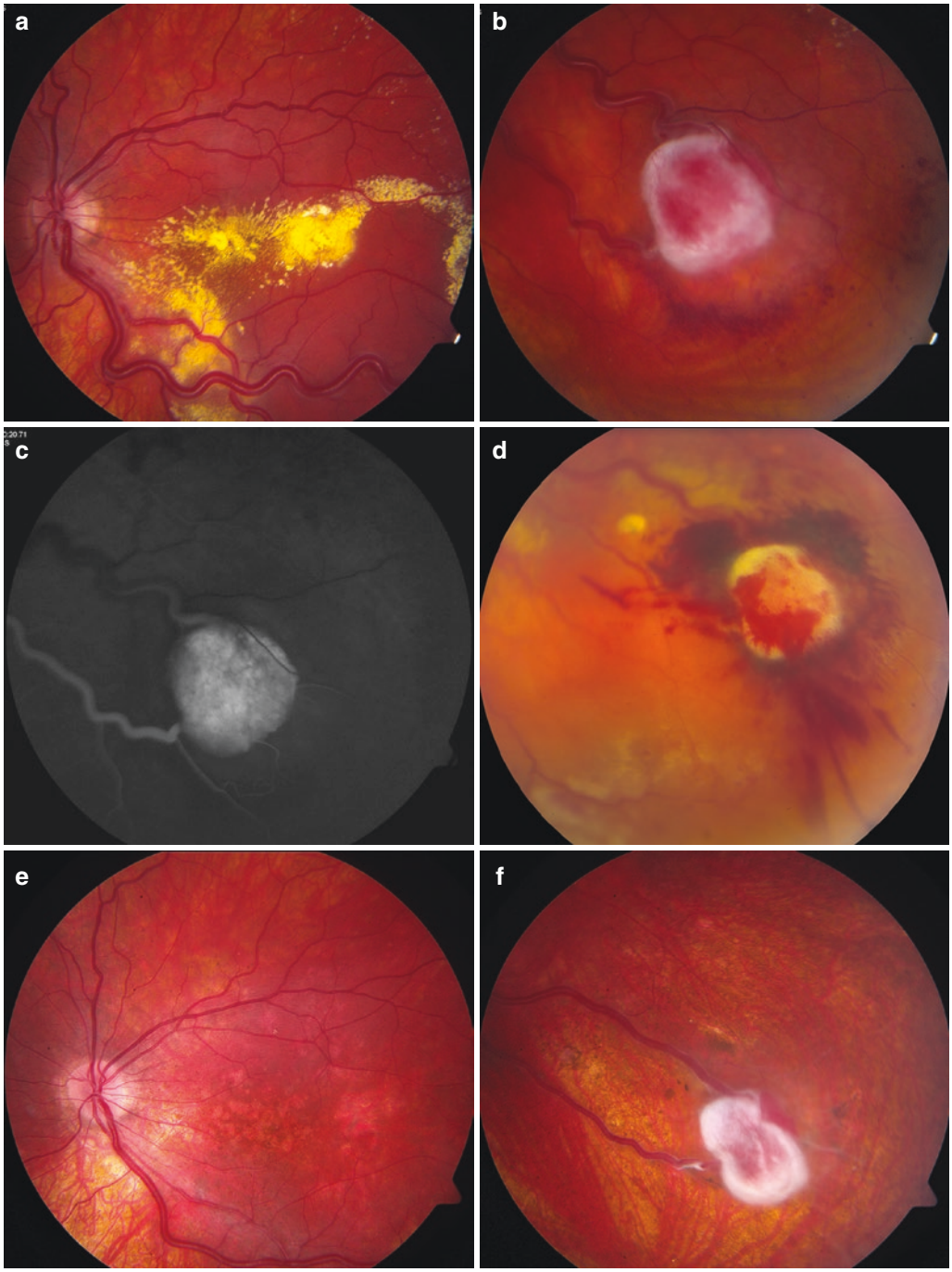



**Fig. 3.1** Fundus photograph of a retinal capillary hemangioma. Note prominent feeder vessels and retinal exudation (**a**). The hemangioma has a rim of gliosis and surrounding and subretinal fluid and hemorrhage (**b**). Fluorescein angiography identifies the feeder artery (**c**). Marked hyperfluorescence 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 ofmacular 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 (**f**)

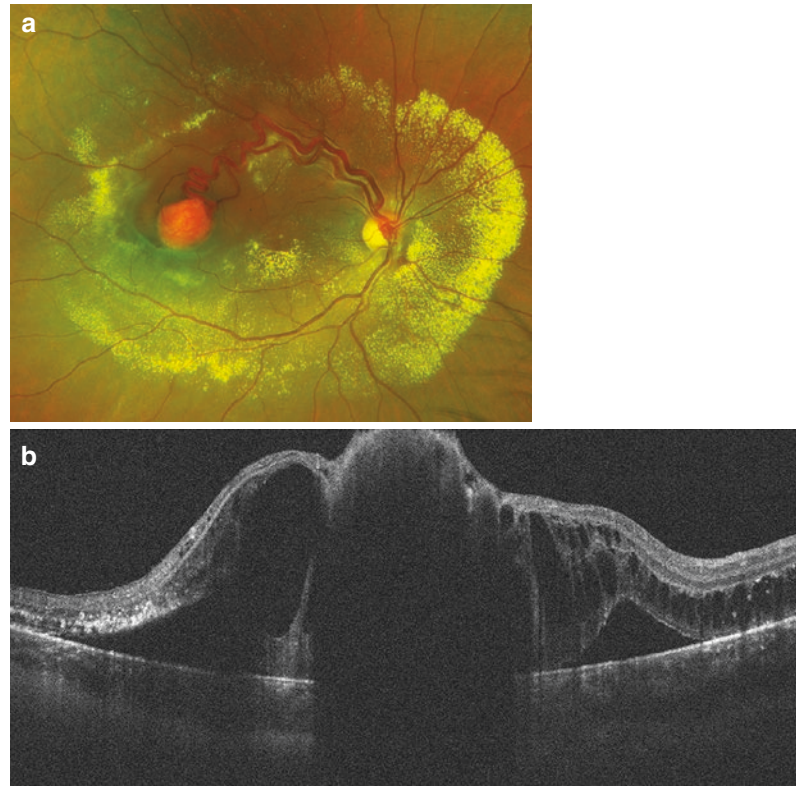



**Fig. 3.2** Retinal capillary hemangioma. Clinical appearance (**a**). OCT evaluation shows a round hyper-reflective lesion with little inner tumor details (**b**)

## Differential Diagnosis

Some of the conditions that should be considered in the differential diagnosis include Coats' disease, macroaneurysm, and other forms of retinal vascular tumors [7]. Coats' disease is an idiopathic unilateral retinal vascular disease of young males which is characterized by retinal telangiectasia and retinal exudation [8]. 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 [9]. 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 [10]. Retinal capillary hemangioma is more commonly seen in the temporal quadrants of the midperipheral retina [7]. Unlike retinal capillary hemangioma, vasoproliferative tumors are non-familial and lack significant systemic association [10].

## 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 [11]. The treatment can be challenging due to the

presence of multiple tumors in both eyes and the potential for the onset of new tumors.

### Observation

Careful observation in a reliable patient can be recommended if the retinal capillary hemangioma is very small (up to 500 microns), is not associated with exudation or subretinal fluid, and is not visually threatening [11]. Initial observation should always be considered in juxtapapillary retinal capillary hemangioma as they tend to remain stable [12].

### 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. 3.3) [13]. Photocoagulation can be applied directly to the

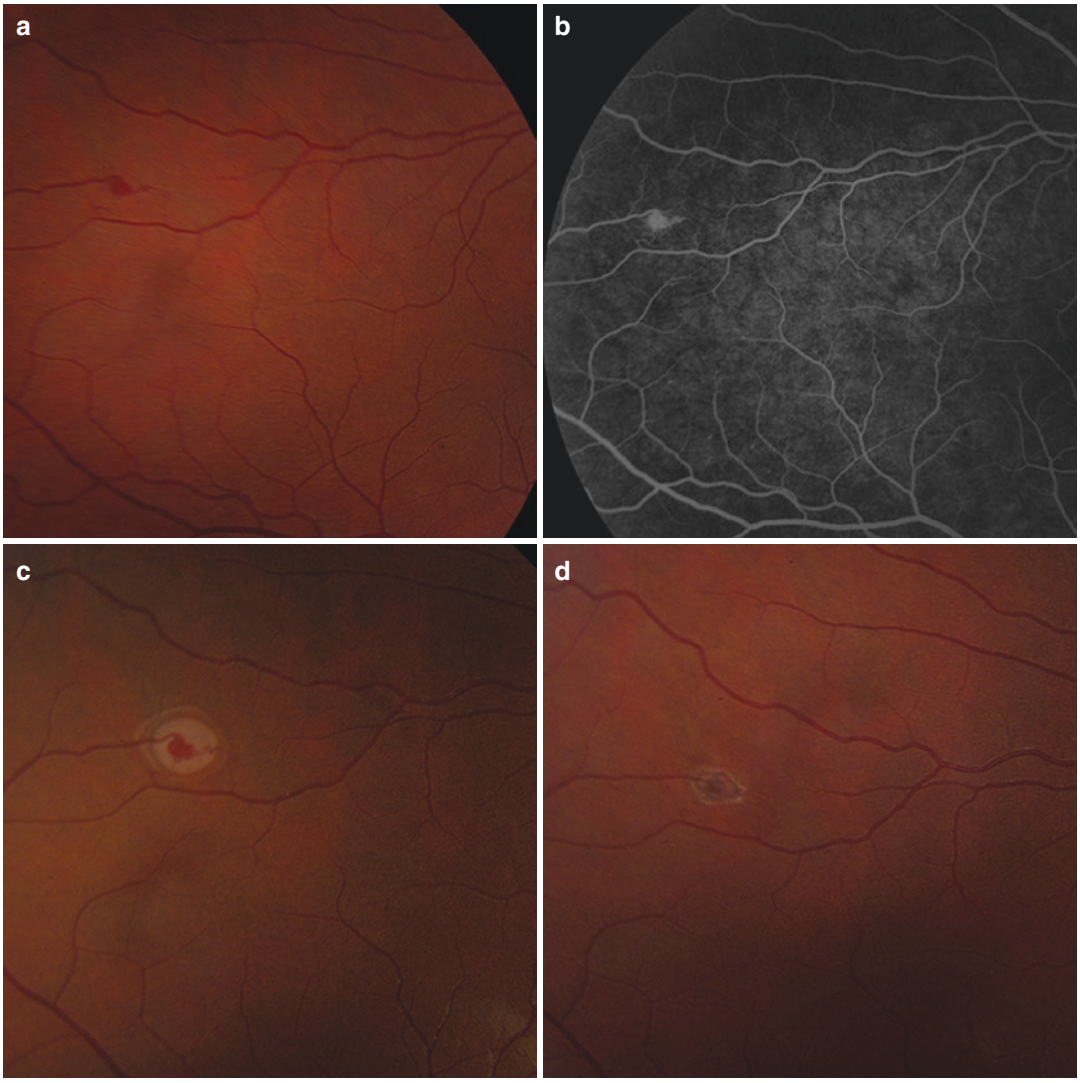



**Fig. 3.3** Small retinal capillary hemangioma observed on surveillance examination in a patient with VHL disease (**a**). The hemangioma could be visualized with fluorescein angiography (**b**). Appearance immediately after laser photocoagulation (**c**). Four weeks later, the hemangioma is partially regressed and surrounded by a chorioretinal scar (**d**). (Reprinted from Singh and Schachat [65]. With permission from Elsevier)

tumor or to the feeder artery, or a combination of both techniques can be used [14].

## 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. 3.4) [15]. Cryotherapy may also be preferred when there is moderate amount of subretinal fluid. The efficacy of cryotherapy is greater with smaller tumors (less than 1.5 mm) [11].

## Photodynamic Therapy

More recently, photodynamic therapy has been reported to induce occlusion of peripheral (Fig. 3.1) and juxtapapillary retinal capillary hemangioma (Fig. 3.5) [12, 16, 17, 18].

## 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 [19]. Low-dose external beam radiotherapy is also

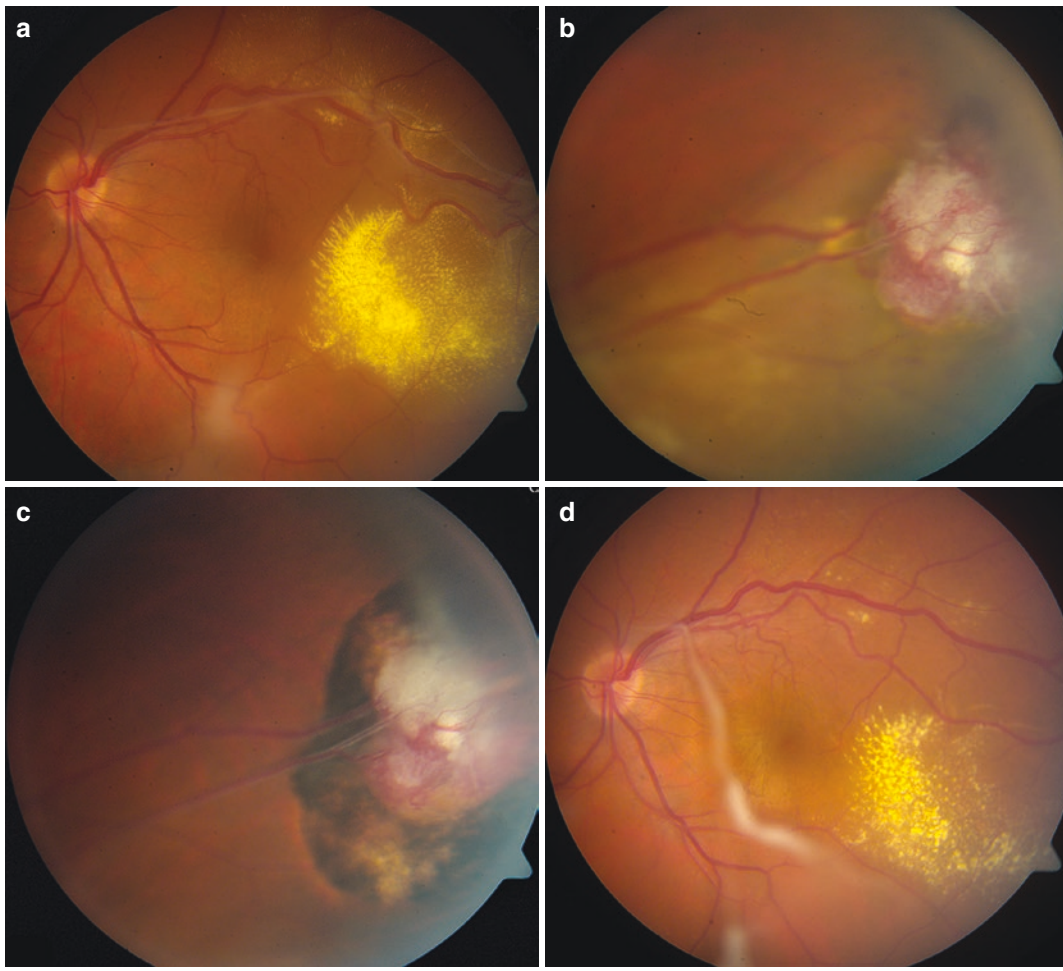



**Fig. 3.4** Cryotherapy for retinal capillary hemangioma. Macular exudation (**a**) and peripheral solitary retinal capillary hemangioma (**b**). Note reduction in tumor vascularity and surrounding reactive pigment proliferation 3 months after double freeze-thaw cryotherapy (**c**) and reduction in 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)

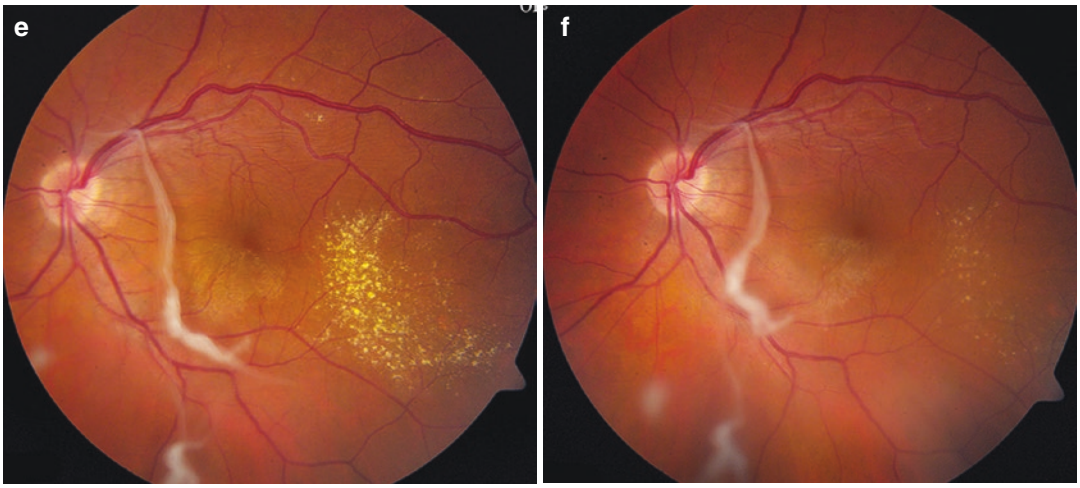



**Fig. 3.4** (continued)

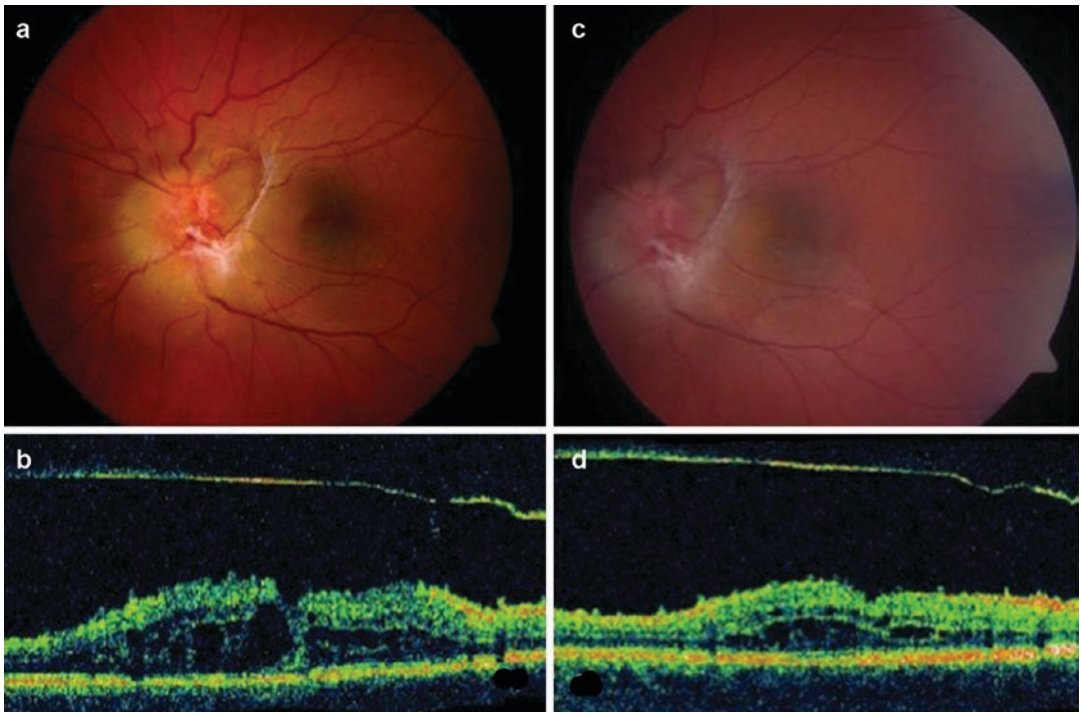



**Fig. 3.5** Initial fundoscopic photograph (**a**) and OCT (**b**, fovea) of the left eye of 27-year-old female (patient 1) with juxtapapillary retinal capillary hemangioma and associated cystoid macular edema. Fundoscopic photograph (**c**) and OCT (**d**) approximately 2 years following photodynamic therapy in same patient, which reveals stabilization of tumor with decreased edema. (Reprinted from Sachdeva et al. [16]. With permission from John Wiley & Sons)

an option in cases that do not respond to the usual methods of treatment listed above [20]. Low-dose proton beam therapy (22 Gy) can provide satisfactory anatomical outcome in severely advanced juxtapapillary capillary hemangiomas [21].

### 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 [22, 23].

### 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.

## Association with Von Hippel-Lindau Disease

Retinal capillary hemangiomas can occur sporadically or in association with VHL disease [7, 24]. The association of retinal capillary hemangioma with VHL disease is discussed in detail under neuro-oculo-cutaneous syndromes (phakomatoses) (Chap. 9).

## Prognosis

The visual prognosis, even in adequately treated cases, is guarded [7]. 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].

# Cavernous Hemangioma of the Retina

## Introduction

Cavernous hemangiomas of the retina are composed of multiple, thin-walled dilated vascular channels with surface gliosis [25]. The walls are lined by non-fenestrated endothelium, explaining the lack of exudation [26]. Two forms of cavernous hemangioma of the retina are recognized: sporadic and syndromic [25]. 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 [25].

## Clinical Features

Cavernous hemangiomas of the retina are believed to be a rare form of congenital hamartoma with a recent literature review identifying only 96 cases [27]. The age of presentation in a series of nine patients ranged from 1 to 55 years [28].

### 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. 3.6) [29].

### Signs

Retinal lesions appear as grape-like clusters of blood-filled saccular spaces in the inner layers of the retina or on the surface of the optic disc (Fig. 3.6) [25]. The size and location of the hemangioma are variable but most are solitary small (1–2 disc diameters) lesions involving the midperipheral or peripheral retina [24]. Epiretinal membranes are

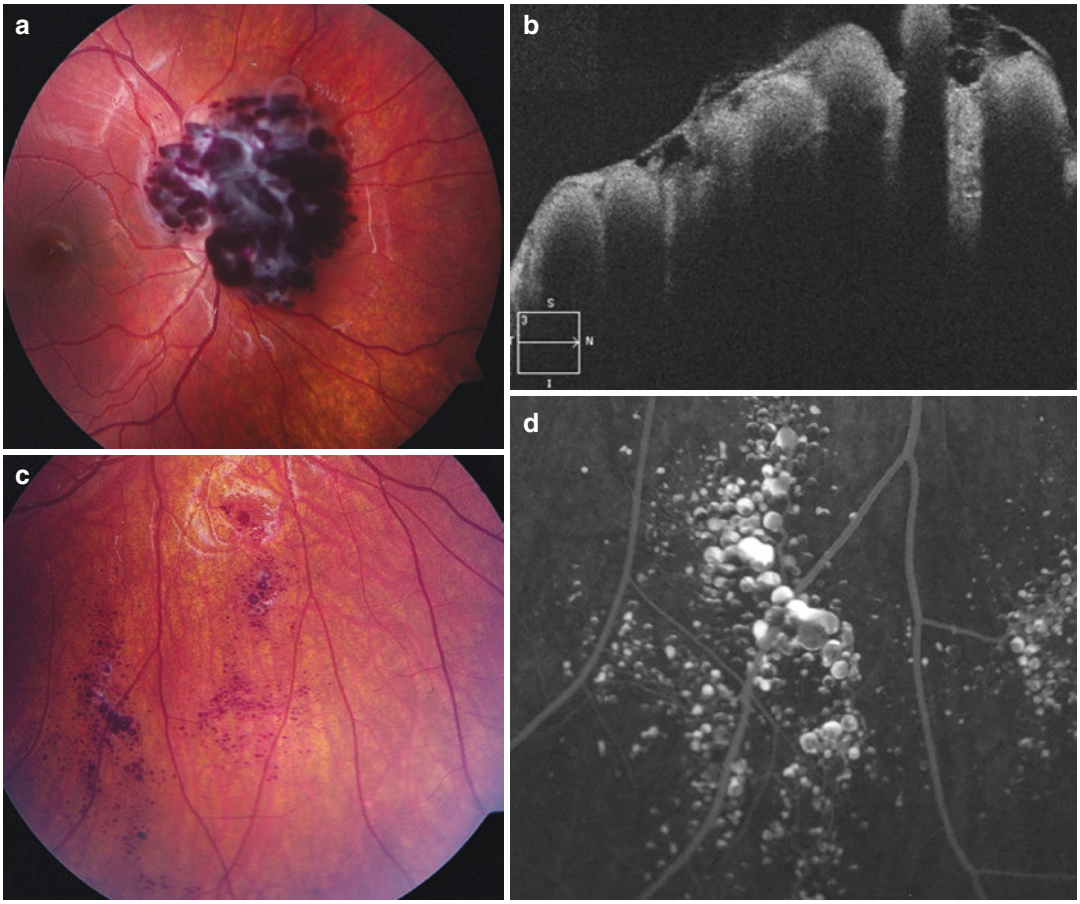



**Fig. 3.6** Fundus photograph of a papillary cavernous hemangioma of the retina (**a**). Note the absence of retinal exudation. Optical coherence tomography of the retinal cavernous hemangioma. An overlying epiretinal membrane is imaged as a continuous hyper-reflective signal attached to the saccules and forming bridges between them (**b**). Peripheral variant may not be prominent (**c**). On fluorescein angiogram characteristic hyperfluorescent saccular dilatations are evident (**d**)

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 midperipheral retina [30].

## 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 retinal origin of the hemangioma with a low-flow system and hence delayed filling in the venous phase (Fig. 3.6). 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.

OCT reveals a disorganized epiretinal membrane with cystic spaces within inner and outer retinal layers, these spaces representing the saccular aneurysms [31]. OCT-A reveals rarefaction of retinal vessels overlying the tumor and the absence of a flow signal at the superficial and deep plexi [32].

### Box 3.2 Salient Diagnostic Findings

- Retinal lesions appear as grape-like 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.

## 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. The presence of dilated feeder vessels and retinal exudation does not support the diagnosis of retinal cavernous hemangioma.

## Treatment of Retinal Cavernous Hemangioma

In general, cavernous hemangiomas of the retina are nonprogressive, may undergo spontaneous thrombosis, and rarely cause vitreous hemorrhage. No treatment is necessary in asymptomatic cases. Argon laser photocoagulation or cryotherapy can be attempted but does not eliminate the likelihood of relapse [25]. Proton beam therapy may be useful in symptomatic peripheral retinal cavernous hemangiomas [33].

## 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 [34–36]. The association between retinal and CNS hemangiomas is discussed in detail under neuro-oculo-cutaneous syndromes (phakomatoses) (Chap. 9).

## 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 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 [34].

# Wyburn-Mason Syndrome

## 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 [37, 38].

## Clinical Features

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

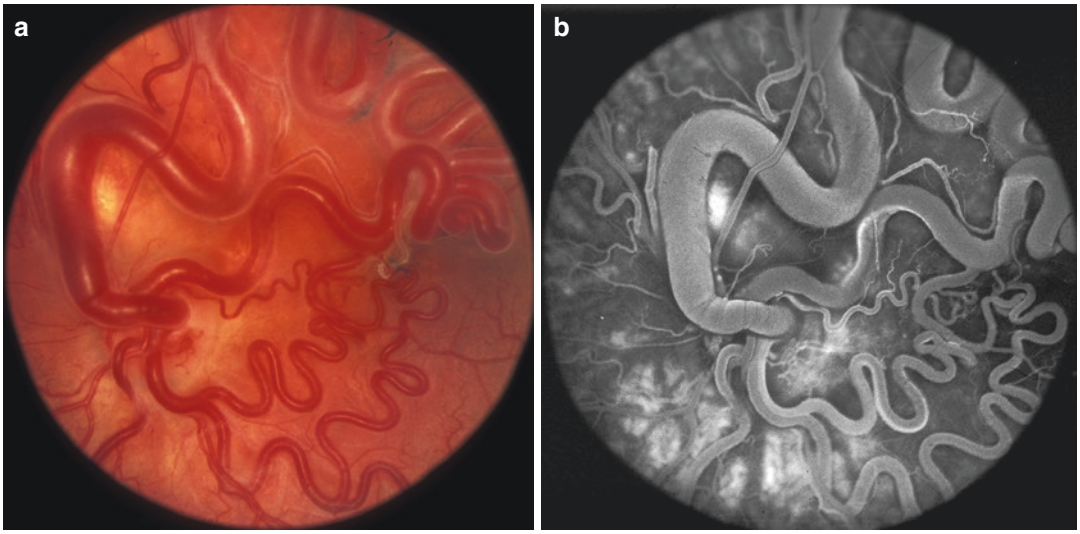



**Fig. 3.7** Fundus appearance of a typical retinal arteriovenous malformation (**a**). On fluorescein angiography arteries and veins appear undistinguishable (**b**)

## 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.

## Signs

Arteriovenous malformations are seen readily on ophthalmoscopic evaluation. These malformations have been classified into three groups depending upon the severity of vascular malformation [39]. 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. 3.7).

## 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. 3.7). Abnormal retinal vasculature characteristically demonstrates absence of leakage. On OCT, dilated intraretinal vascular channels are observed (Fig. 3.8).

### Box 3.3 Salient Diagnostic Findings

- 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.

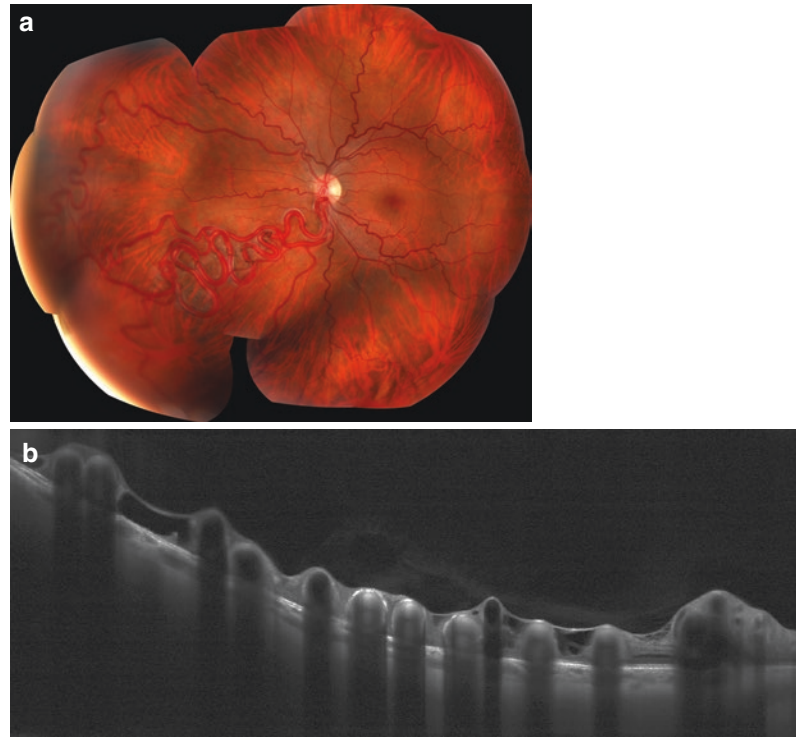



**Fig. 3.8** Wyburn-Mason syndrome. Clinical appearance of a typical lesion consisting of markedly dilated and tortuous vessels (**a**). On OCT, dilated intraretinal vascular channels are observed (**b**)

## Differential Diagnosis

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

## Treatment of Retinal Arteriovenous Communications

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

## 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.

## Prognosis

The retinal vascular anomalies may alter in configuration over many years exhibiting increasing tortuosity [40] and sometimes leading to vascular occlusions [41] and retinal ischemia with 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 [42, 43].

# Retinal Vasoproliferative Tumor

## 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 fibro-cellular membranes in five patients [44]. These lesions were

initially termed as "presumed acquired retinal hemangiomas" to differentiate them from capillary hemangiomas [45]. The nomenclature has varied in the literature, but at present vasoproliferative retinal tumors are the widely accepted terminology [10]. 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 [46, 47]. The clinical and histopathologic features of vasoproliferative tumor seem to overlap with recently described reactive retinal astrocytic tumor that can be observed in response to a degenerative, inflammatory, or ischemic retinal insult [48–50].

## Clinical Features

Vasoproliferative retinal tumor usually presents in the third or fourth decade, and both sexes are equally affected [10]. 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.

### Symptoms

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

### Signs

Vasoproliferative tumor appears as a globular yellowish-pink vascular mass in the peripheral retina (Fig. 3.9). 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 [51]. Vasoproliferative retinal tumors have a predilection for the inferotemporal retina. Subretinal exudation, which may be extensive, is common occurring in over 80% of cases [10]. Exudative retinal detachment, retinal and vitreous hemorrhage, and vitreous, epiretinal membrane cells are frequent associated findings (Fig. 3.10). Retinal pigment epithelial hyperplasia adjacent to the vasoproliferative retinal tumors may be evident especially in secondary tumors [10]. Macular fibrosis (31%) and edema (18%) may lead to visual loss.

## 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. 3.9). 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 [52]. The peripheral tumor location makes it difficult to image with OCT. Vision loss is usually due to epiretinal membrane or exudative macular detachment, and OCT is useful to identify these changes.

### Box 3.4 Salient Diagnostic Findings

- 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.
- Pre-existing ocular disease such as intermediate uveitis, other inflammation, or retinitis pigmentosa.

## Differential Diagnosis

Atypical lesions may be confused with adult Coats' disease, retinal capillary hemangioma, eccentric

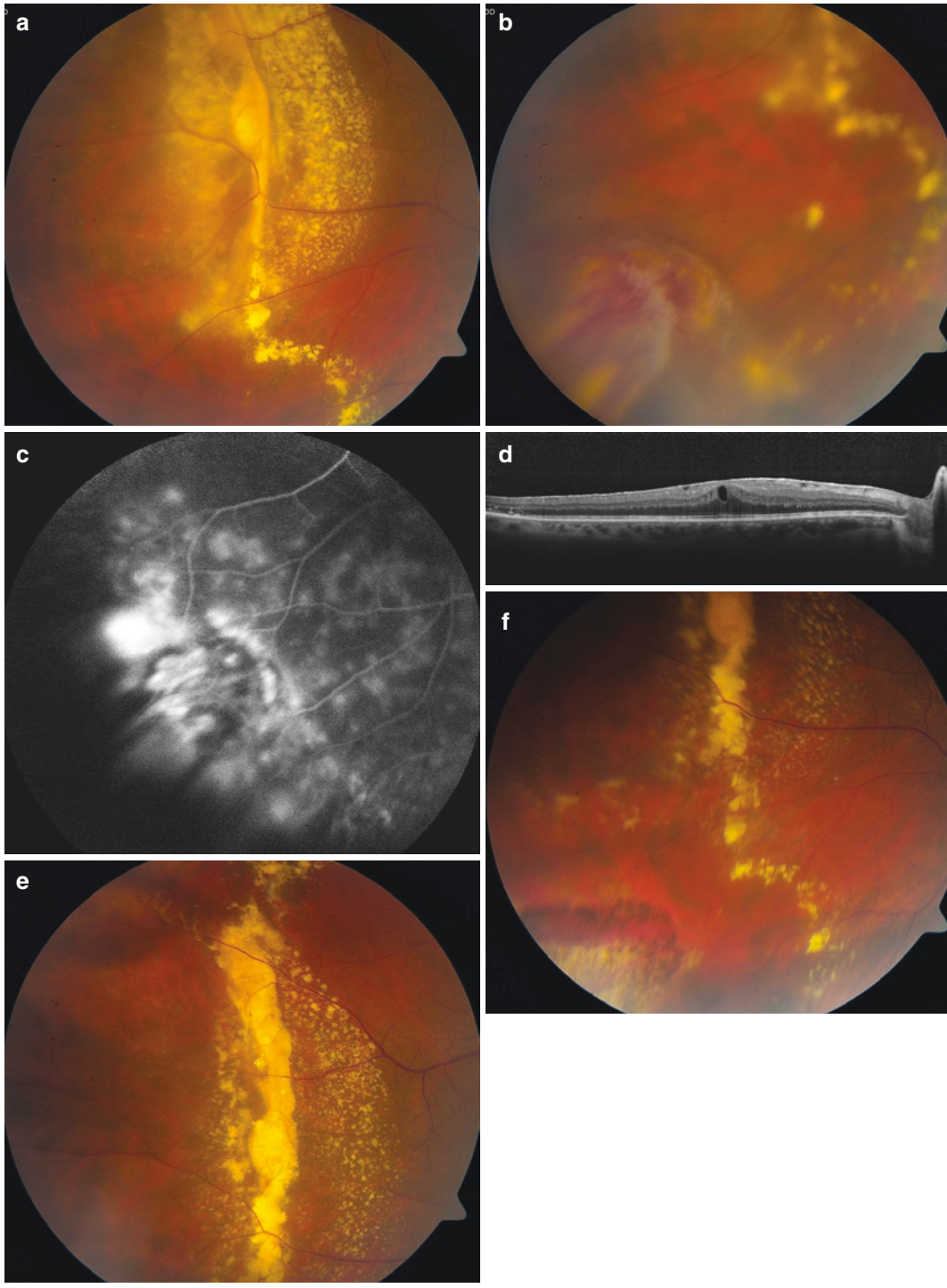



**Fig. 3.9** Fundus appearance of a retinal vasoproliferative tumor. Note prominent retinal lipid exudation and bullous exudative retinal detachment (**a**). The vasoproliferative tumor appears as a globular yellowish-pink vascular mass in the peripheral retina (**b**). Diffuse hyperfluorescence in the 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**)

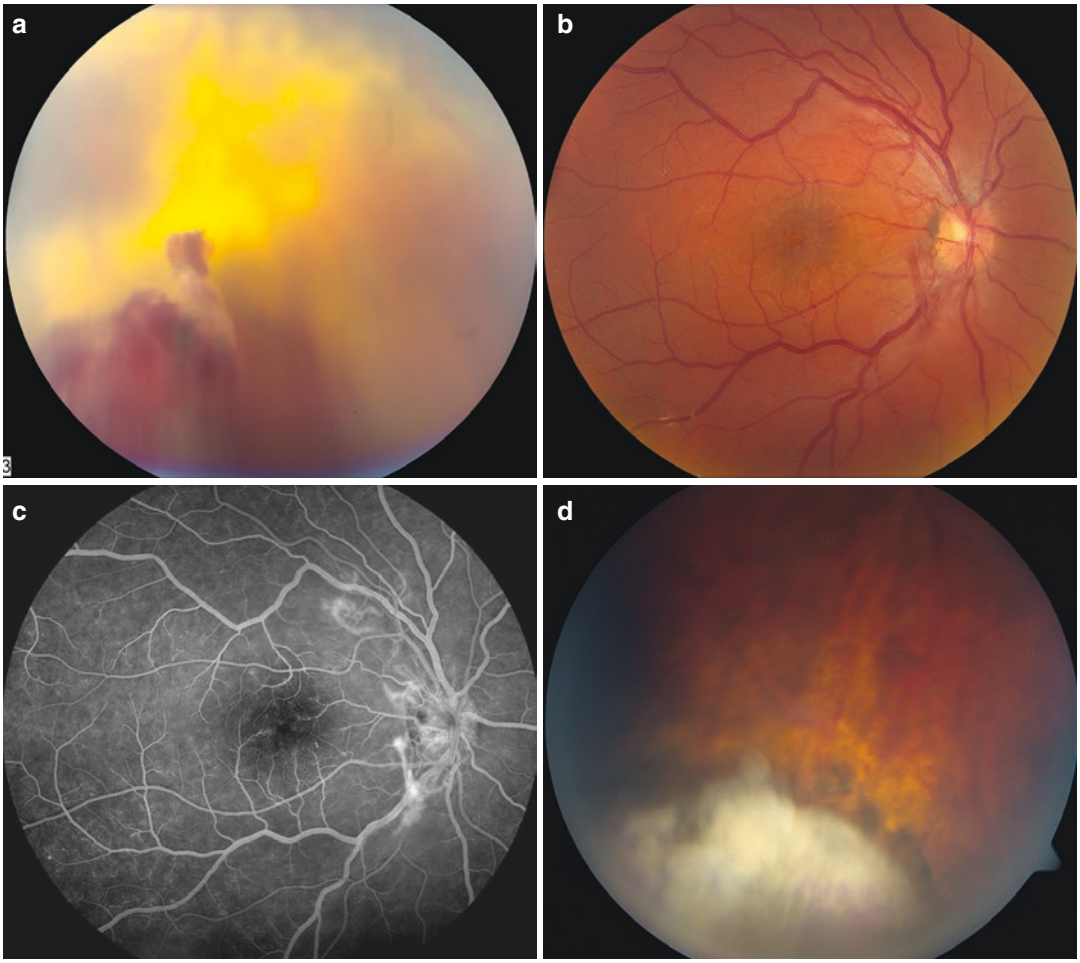



**Fig. 3.10** Fundus appearance of a retinal vasoproliferative tumor. Note prominent retinal lipid exudation and peripheral hemorrhagic tumor (**a**). Following treatment with plaque radiation therapy (35 Gy), there was increase in secondary epiretinal membrane (**b**) with onset retinal neovascularization (**c**) necessitating intravitreal injection of bevacizumab (1.25 mg. 0.05 ml). Four weeks later, the tumor appeared totally avascular and gliotic (**d**)

choroidal neovascularization (disciform), or even amelanotic melanoma. Adult Coats' disease is unilateral and usually in males. There is extensive lipid exudation and macular edema. The presence of retinal telangiectasia and areas of capillary nonperfusion with adjacent webs of filigree-like capillaries helps differentiate adult Coats' from a VPT [53].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. B-scan ultrasonography can help differentiate from amelanotic melanoma as VPT are solid lesions and without choroidal excavation.

## Treatment of Vasoproliferative Tumors

### 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.

### Cryotherapy

Vasoproliferative retinal tumors can be treated successfully with triple freeze-thaw transconjunctival cryotherapy, although repeat treatments may be required (Fig. 3.9) [10]. 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.

### Plaque Brachytherapy

Large lesions can be managed effectively using either ruthenium or iodine plaque brachytherapy (Fig. 3.10) [10, 54–56].

### Photothrombotic and Photodynamic Therapy

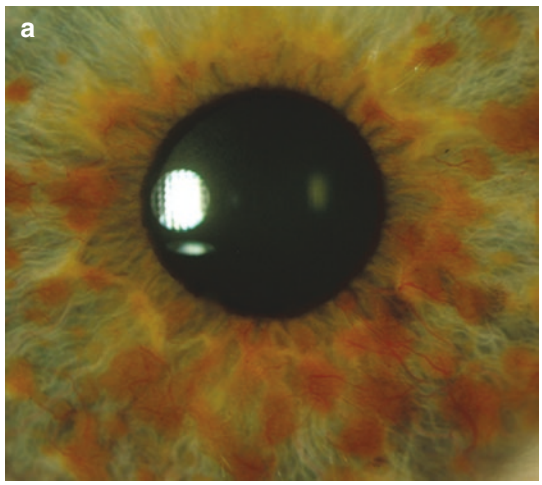
Indocyanine green-mediated photothrombotic therapy [57] and photodynamic therapy have been shown to be effective in the treatment of vasoproliferative tumors [58, 59].

### Intravitreal Anti-VEGF Therapy and Dexamethasone Implants

Intravitreal injections with anti-VEGF agents or dexamethasone implants are showing promising results though it is unclear if the results will be maintained in the long term. These agents may be used in isolation or as an adjunct to cryotherapy (Figs. 3.10 and 3.11) [60, 61] or PDT to prevent macular edema and diminish tumor vascular leakage [62].

## Association with Vasoproliferative Tumors

About 25% of all vasoproliferative tumors are secondary to a pre-existing congenital, inflammatory, vascular, traumatic, dystrophic, and degenerative ocular disease such as intermediate uveitis, retinitis pigmentosa, and ocular toxoplasmosis [10]. Rare occurrence in monozygotic twins [63], Waardenburg syndrome [64], neurofibromatosis 1 [61], and possible association with systemic hypertension and hyperlipidemia has been reported (Fig. 3.11) [10].



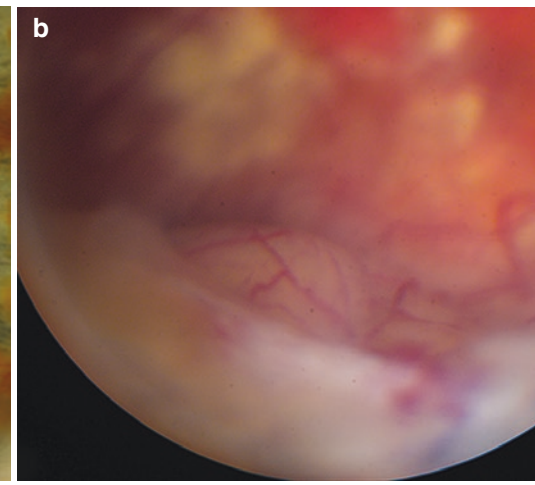




**Fig. 3.11** Slit lamp photograph of the right eye at presentation demonstrating multiple Lisch nodules and florid neovascularization of the iris (**a**). On gonioscopic examination there was 360° neovascularization of the angle. In the inferior fundus, there was a pink, elevated vascular mass with 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. (Reprinted from Hood et al. [61]. With permission from Slack Incorporated)

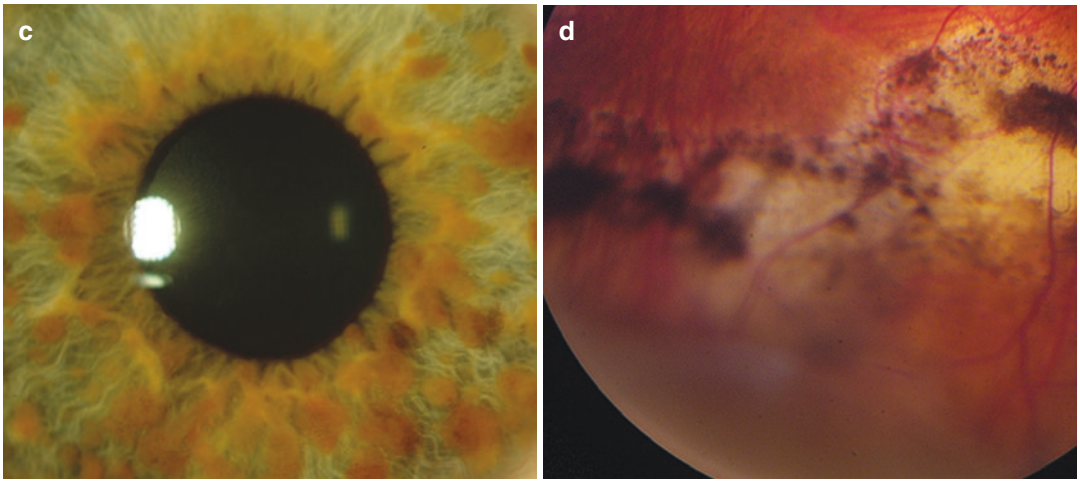



**Fig. 3.11** (continued)

## Prognosis

In a large series of 103 patients, up to one-third of cases were initially managed by observation [10]. 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.

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# Retinal Astrocytic Tumors

4

Christopher Seungkyu Lee, Sungchul Lee, and Arun D. Singh

## Introduction

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

## Retinal Astrocytic Hamartoma

Astrocytic hamartoma of the retina and optic nerve head typically occurs in patients with TSC (Bourneville's disease), but it may also rarely be found in patients with neurofibromatosis (von Recklinghausen's disease), retinitis pigmentosa, or as an isolated finding [1, 2]. In younger individuals, the semitranslucent tumors may arise where no lesion was earlier present (Fig. 4.1). Later in life, they may assume a more densely white color and develop multinodular mulberry-looking calcification.

## Pathogenesis and Pathology

It is postulated that astrocytic hamartomas in TSC arise from undifferentiated glioneurocytes during the embryonal development of the retina [3]. Genetic analysis has identified two distinct variants of TSC, which result from mutations in *TSC1* gene on chromosome 9q34 and the *TSC2* gene on chromosome 16p13 [4, 5]. *TSC1* and *TSC2* are tumor-suppressor genes, and their gene products, hamartin and tuberin, respectively, form a protein complex and act together to inhibit mammalian target of rapamycin (mTOR)-mediated signaling [6]. Clinical manifestations of TSC are more frequent and severe in patients with *TSC2* mutations than *TSC1* mutations [7–9]. As such, *TSC*2 mutations are more frequent in patients with retinal astrocytic hamartoma than in those without tumor [10].

Histopathologically, astrocytic hamartomas are typically 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

C. S. Lee · S. Lee (✉)
Department of Ophthalmology, Severance Hospital, Yonsei University, College of Medicine, Seoul, South Korea
e-mail: sunglee@yuhs.ac

A. D. Singh
Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA


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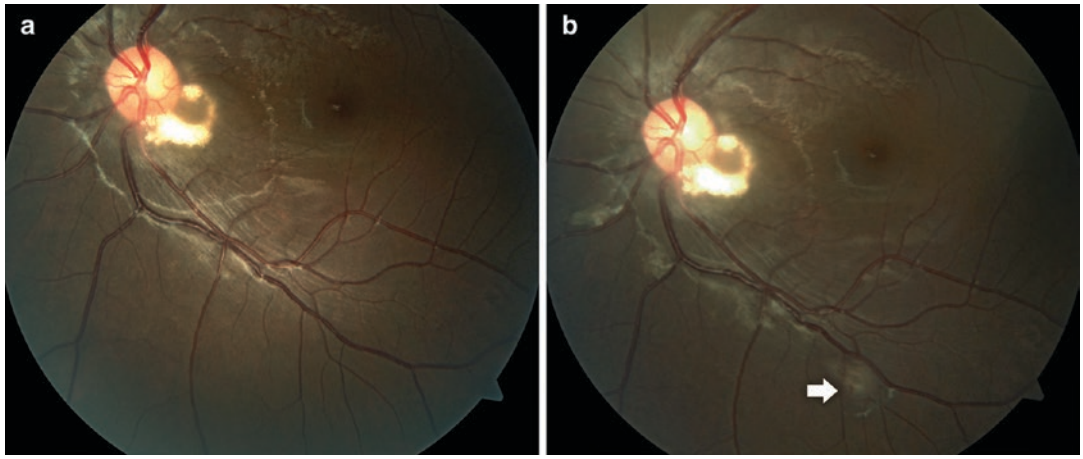


**Fig. 4.1** Fundus appearance of a 10-year-old Asian girl with tuberous sclerosis complex. Note retinal astrocytic hamartoma adjacent to optic nerve head with central calcification resembling mulberries (**a**). After 6 months, a new flat, smooth, semitranslucent lesion (*white arrow*), which was not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

possible Mülller cell origin [11]. Blood vessels and areas of calcification, often in the form of calcospherites, can be present. Mitotic figures are extremely rare.

## Clinical Features

### Symptoms

Patients are often visually asymptomatic and tumors are detected as part of screening for TSC. Visual symptoms could be caused by macular involvement, tumor growth, vitreous hemorrhage, vitreous seeding and vitritis, or intraretinal and subretinal exudation [12–15].

### Signs

Although tumors exhibit considerable variation from case to case, three basic types have been recognized based on ophthalmoscopic appearance: (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 (1) and (2), being calcified in the central portion and semitranslucent in the periphery [16–19] (Fig. 4.2a). The first type is the most common, followed by the second and third. All three morphological types may be seen in a given patient.

## 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 adenoma sebaceum (facial angiofibroma) (Chap. 9). However, fluorescein angiography, fundus autofluorescence, ultrasonography, and optical coherence tomography (OCT) can be useful ancillary studies, especially in subtle lesions (Box 4.1).

### Box 4.1 Salient Diagnostic Findings

- 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)

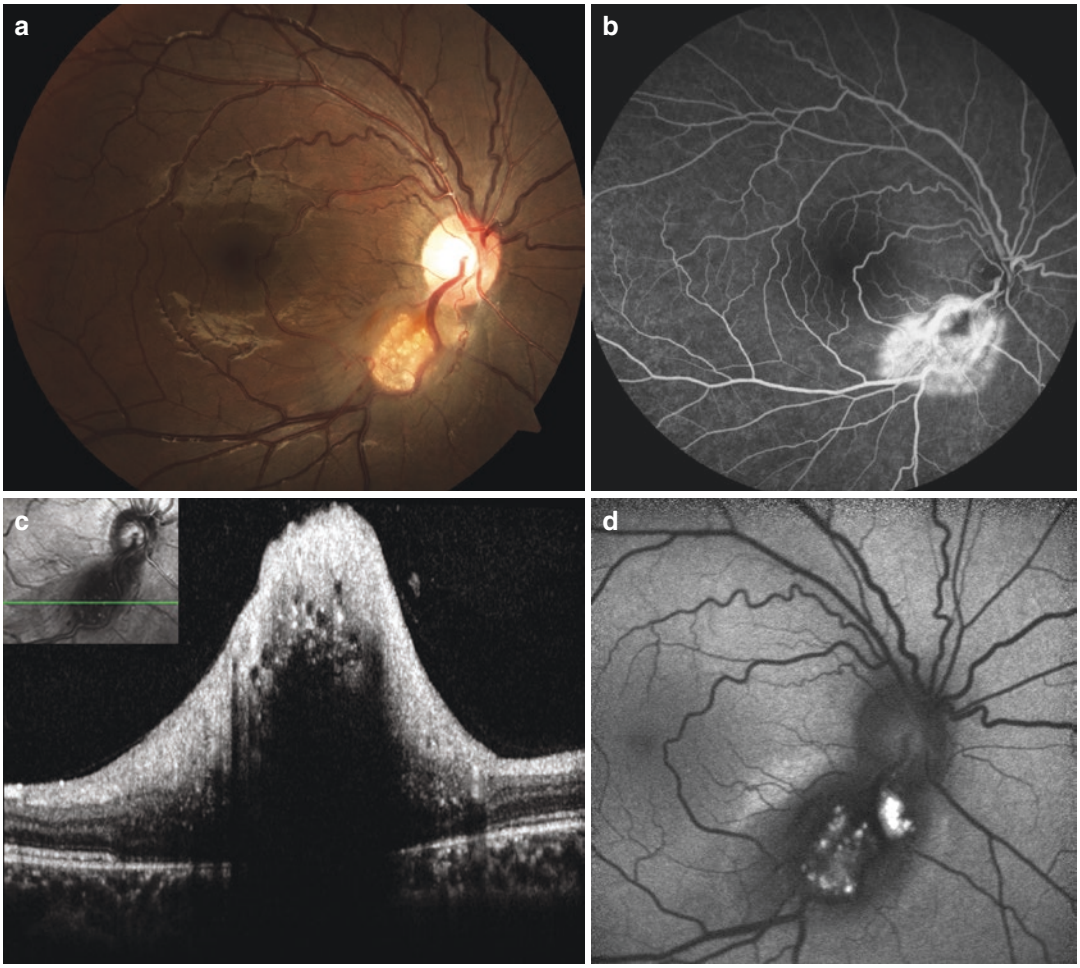


**Fig. 4.2** Fundus appearance of a typical retinal astrocytic hamartoma. Note central area of calcification and peripheral semitranslucent noncalcified region (**a**). Late-phase fluorescein angiogram, showing relatively intense hyperfluorescence of the lesion due to leakage of dye from the tumor vessels (**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**)

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) [20].

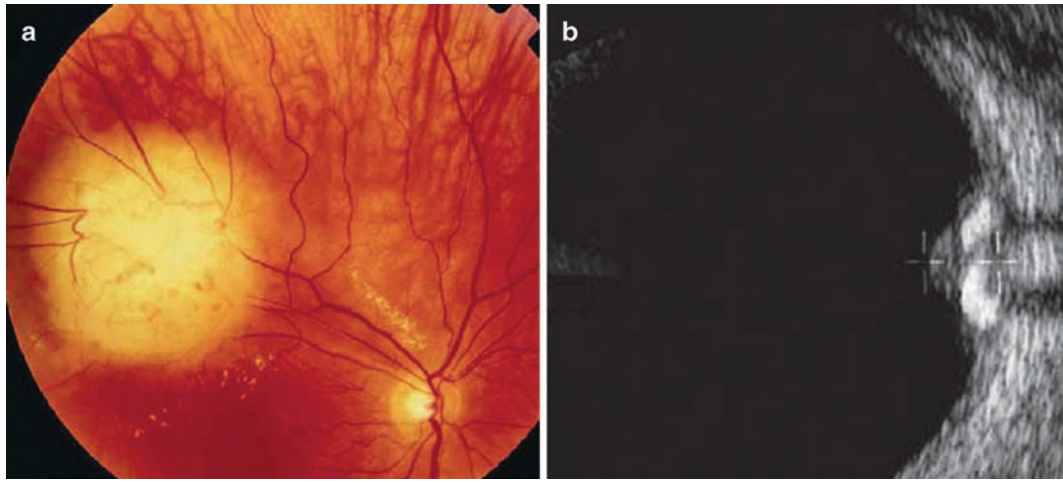


**Fig. 4.3** Fundus appearance of calcified large astrocytic hamartoma. Note surrounding retinal exudation (**a**). B-scan ultrasonography indicative of intrinsic calcification (**b**). (Reprinted from Giles et al. [12]. With permission from Springer Nature)

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 (SD) OCT offers superior resolution and enhanced tissue penetration in visualizing the retinal location of the tumor and ascertain the reason for visual loss. Tumors appear to be localized within retinal nerve fiber layer on SD-OCT, often compressing the underlying inner retinal layer [21]. 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) [21–24]. As SD-OCT can show more detail on intrinsic tumor features, an OCT classification has been proposed to further categorized tumors into four types [22] (1) a circular or oval-shaped nonpigmented flat mass within retinal nerve fiber layer with the intact underlying the retina, (2) slightly elevated mass above the nerve fiber layer with mild inner retinal disorganization and subtle vitreoretinal adhesion/traction, (3) a calcified mushroom-shaped mass with internal "moth-eaten" optically empty spaces representing intratumoral calcification, and (4) elevated dome-shaped mass with optically empty intratumoral cavity.

## Differential Diagnosis

Despite the characteristic 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

**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 | White mass | Present; white, chunky | Present | Absent | Normal | Present | 13 q deletion syndrome |
| Retinocytoma | | | Absent | Absent | Proliferation | Absent | |
| 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

a hard exudation 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 in astrocytic hamartoma and growth in retinoblastoma [18, 25].

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 TSC [26]. Although optic disc drusen 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.

## 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 (Fig. 4.4).

The exudative complications can be self-limited within a few weeks [27]. However, photocoagulation, photodynamic therapy using verteporfin, transpupillary thermotherapy, brachy-

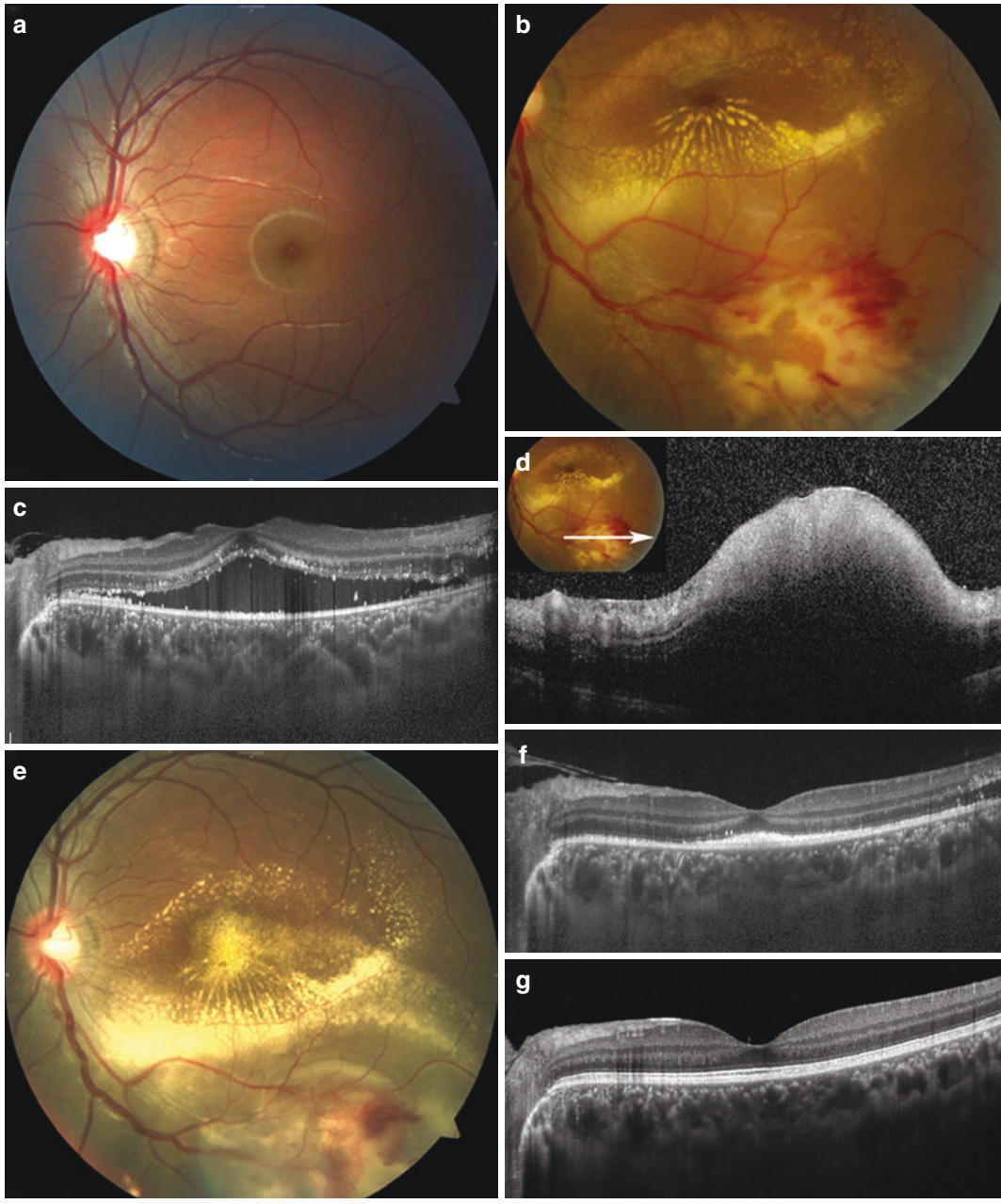


**Fig. 4.4** A 14-year-old Asian boy with tuberous sclerosis (*TSC1* mutation, exon3–7 deletion) was referred for routine ophthalmologic screening, and no retinal tumor was found (**a**). Just 4 months later, the patient presented with decreased visual acuity (VA) of 20/400. An ill-defined, semitranslucent yellow-white retinal mass with neovascularization and heavy lipid exudates at macula were observed (**b**). Spectral-domain optical coherence tomography (SD-OCT) scanned through macular center showed detachment of neurosensory retina with subretinal fluid (**c**). SD-OCT image across the tumor showed thickening of retinal nerve fiber layer with posterior shadowing (**d**). Two weeks after transpupillary thermotherapy on the tumor, lipid exudates increased (**e**), but subretinal fluid resolved (**f**). After multiple sessions of intravitreal bevacizumab due to vitreous hemorrhage from neovascularization on the tumor, macular lipid exudates regressed and VA increased to 20/30 with restoration of outer retinal structure on SD-OCT, taken 18 months from the first presentation (**g**)

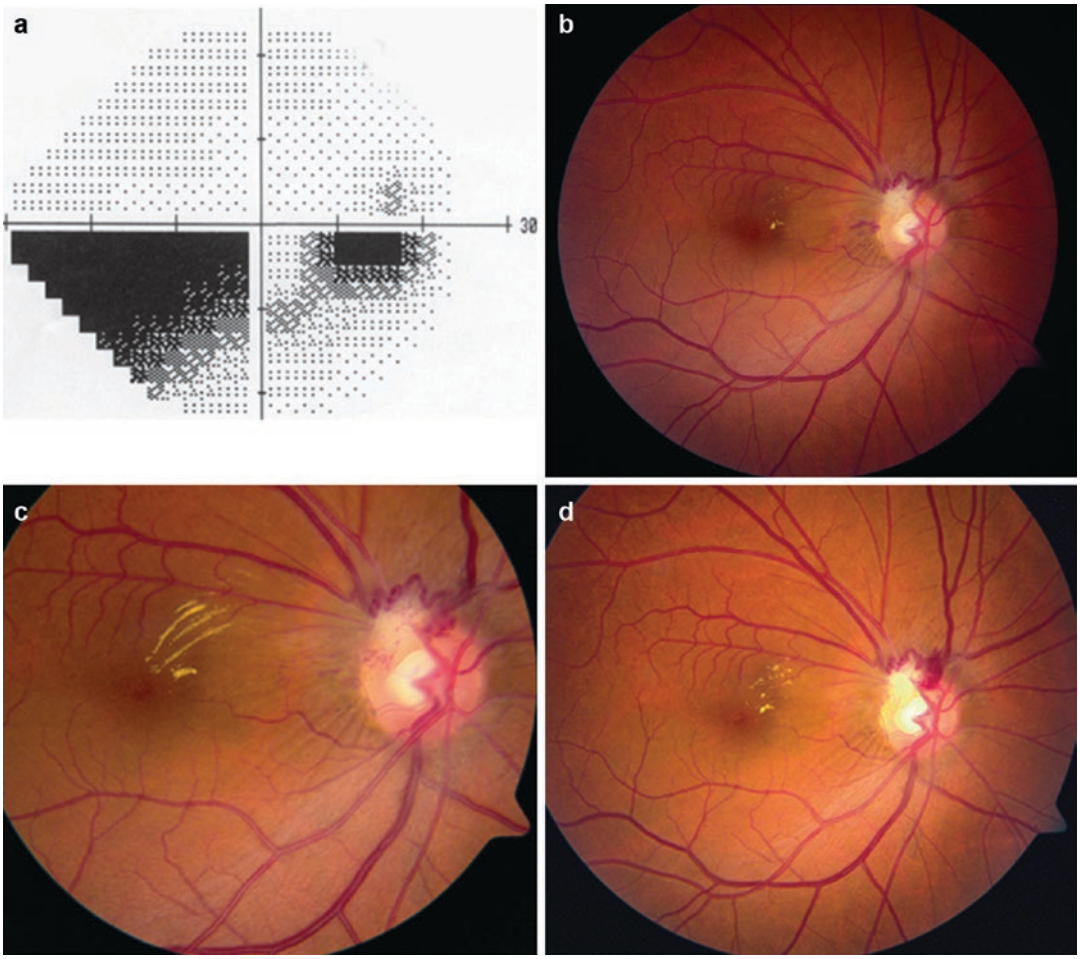


**Fig. 4.5** A 45-year-old Caucasian female with an unremarkable past medical history was referred for evaluation of a peripapillary tumor associated with a scotoma in the right eye (**a**). On initial evaluation, visual acuities (VA) were 20/20 in both eyes. An ill-defined, translucent, yellow-white 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**). (Reprinted from Singh [37]. With permission from Elsevier)

therapy, intravitreal bevacizumab, vitrectomy, or endoresection could be considered in cases with persistent, progressive, and fovea-involving exudation (Fig. 4.5) [28–36].

Vitreous hemorrhage may spontaneously resolve, but persistent or recurrent hemorrhage can be managed with vitrectomy [15, 38, 39]. The systemic mTOR inhibitors including sirolimus and everolimus have been employed to treat aggressive tumors with some success [40, 41]. More aggressive cases showing progressive growth, tumor seeding, and neovascular glaucoma have been managed by enucleation [42, 43].

### 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) [10, 16, 17, 19, 44, 45]. When present, retinal astrocytic hamartomas are bilateral in about half and multiple in about one-third to half of patients [10, 16, 19, 44]. Some patients show only a retinal tumor without additional findings of TSC. In such cases, which have been reported as high as 81% of retinal astrocytic hamartoma [21], the tumor is usually found as a solitary retinal mass. It is undetermined whether it represents a separate entity independent of TSC, the first clinical manifestation of TSC, or a forme fruste of TSC.

In some patients with TSC, retinal achromic patches have also been observed, with frequencies ranging from 8% to 39% [19, 46, 47]. They can look diffusely hypopigmented or be surrounded by some degree of pigment proliferation.

## 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 [16]. 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 [14, 32, 36, 42, 48, 49]. New lesions may develop from previously normal-appearing retina [18]. Spontaneous regression of retinal astrocytic hamartoma has been reported [50, 51]. In general, astrocytic hamartomas are silent with excellent visual prognosis. They are not known to undergo malignant transformation and have no tendency to metastasize (Box 4.2).

### Box 4.2 Clinical Features of Retinal Astrocytic Tumors

- Retinal astrocytic tumors are benign tumors representing two clinical types: (1) astrocytic hamartoma that is frequently associated with tuberous sclerosis complex and (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.

## 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, with no family history or association with TSC or other systemic syndromes (Fig. 4.6). The exact incidence of this rare tumor is not known, and it has been described in only a few reports [43, 49, 52–54].

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, caus-

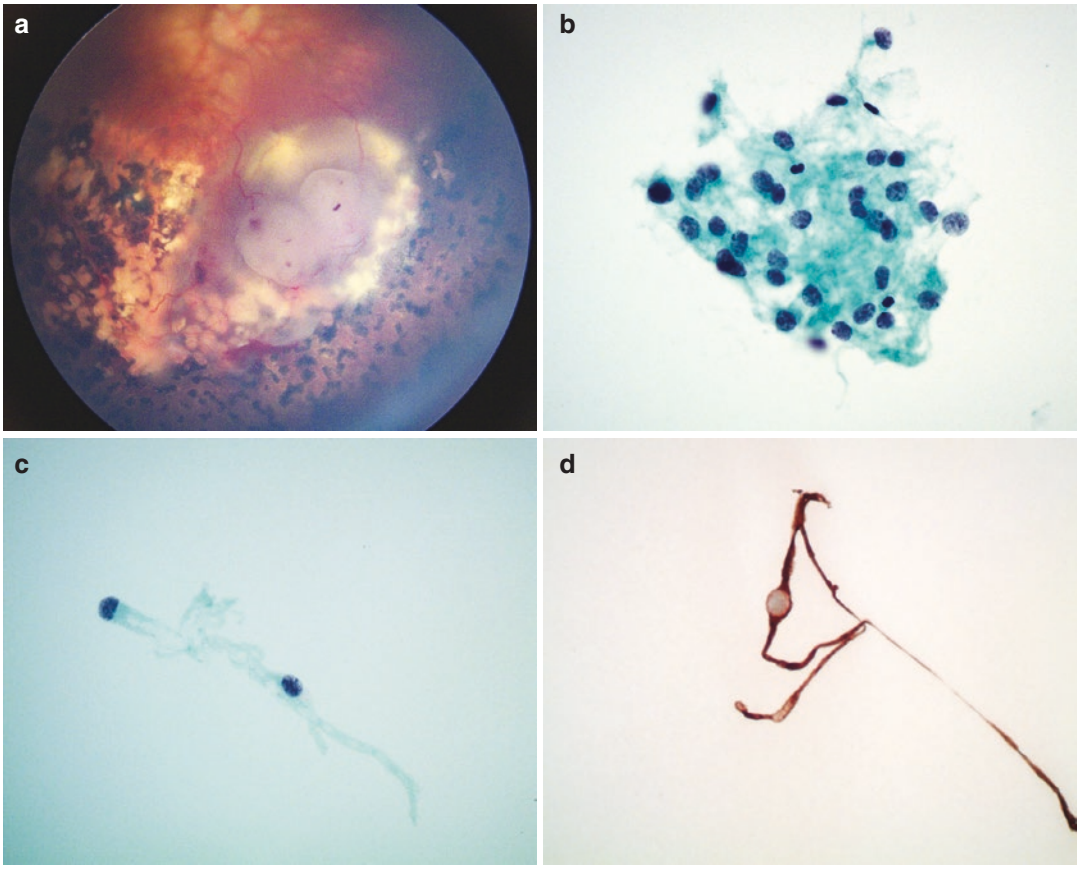


**Fig. 4.6** A solitary multi-lobulated, yellow-white, circumscribed retinal tumor with fine intrinsic vessels located just outside the inferior arcades centered over the band retinal photocoagulation scars. The tumor was 11 × 7.5 in basal dimensions with height of 2.8 mm. Note surrounding rim of lipid exudation (**a**). Abundant fibrillary cytoplasm surrounds relatively uniform nuclei characteristic of reactive astrocytic glial cells ((**b**), Papanicolaou stain 40x). The astrocytic cells have elongated cytoplasmic processes ((**c**), Papanicolaou stain 40x). The cytoplasmic processes stain strongly positive with the GFAP immunostain (**d**). (Reprinted from Singh et al, [55]. With permission from Karger Publishers © 2017 S. Karger AG, Basel)

ing local complications. The true pathogenesis of acquired retinal astrocytoma is not known. It apparently arises from either typical retinal astrocytes or Müller cells. The clinical features and pathogenesis of acquired astrocytoma seem to overlap with recently described reactive retinal astrocytic tumor that can be observed in response to a degenerative, inflammatory, or ischemic retinal insult [55–57].

The best management strategies have not been well established. Radiotherapy may prove useful in rare cases where diagnosis is established by a needle biopsy. 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.

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# Retinal Pigment Epithelial Tumors

5

Elias I. Traboulsi, Matteo Scaramuzzi, and Arun D. Singh

Tumors of the retinal pigment epithelium (RPE) can be congenital or acquired. They may also be classified as reactive, hypertrophic, hamartomatous, or 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 were it not for ancillary tests such as ultrasonography, optical coherence tomography, and fluorescein angiography. In this chapter we review the clinical features of congenital and acquired tumors of the RPE and their systemic associations.

E. I. Traboulsi (✉)
Department of Pediatric Ophthalmology and Strabismus, Center for Genetic Eye Diseases, Cole Eye Institute (i-32), Cleveland Clinic Foundation, Cleveland, OH, USA
e-mail: traboue@ccf.org

M. Scaramuzzi
Department of Pediatric Ophthalmology and Strabismus, Center for Genetic Eye Diseases, Cole Eye Institute, Cleveland Clinic Foundation, Cleveland, OH, USA

A. D. Singh
Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA

## Congenital Hypertrophy of the RPE (CHRPE)

### 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].

### Etiology and Pathogenesis

CHRPE lesions are isolated and sporadic with no known underlying genetic basis.

### Pathology

Histopathologically, isolated CHRPE lesions consist of a layer of hypertrophied RPE cells containing an excessive number of 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


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**Table 5.1** Classification of RPE lesions

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

*Abbreviations: RPE* Retinal pigment epithelium, *CHRPE* Congenital hypertrophy of retinal pigment epithelium, *POFLs* Pigmented ocular fundus lesions
*POFLs can include adenomas of RPE

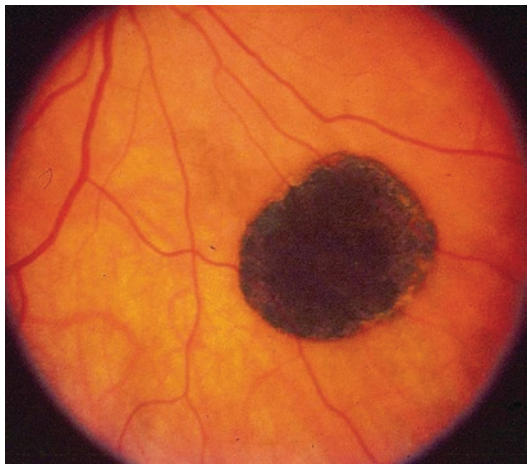

**Fig. 5.1** Solitary CHRPE. A sharply demarcated pigmented flat retinal lesion representing solitary CHRPE. The lighter area represents lacunae which may enlarge slowly over many years

cells to perform their normal phagocytic function, leading perhaps to the associated photoreceptor degeneration [4]. In the areas that have been termed lacunae, RPE cells have reduced pigmentation or may have dropped out completely [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].

## Clinical Features

### Symptoms

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

### 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 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 of the outer and, sometimes, inner retinal layers may be present, especially over larger lesions [4, 7]. Rarely, neovascularization has

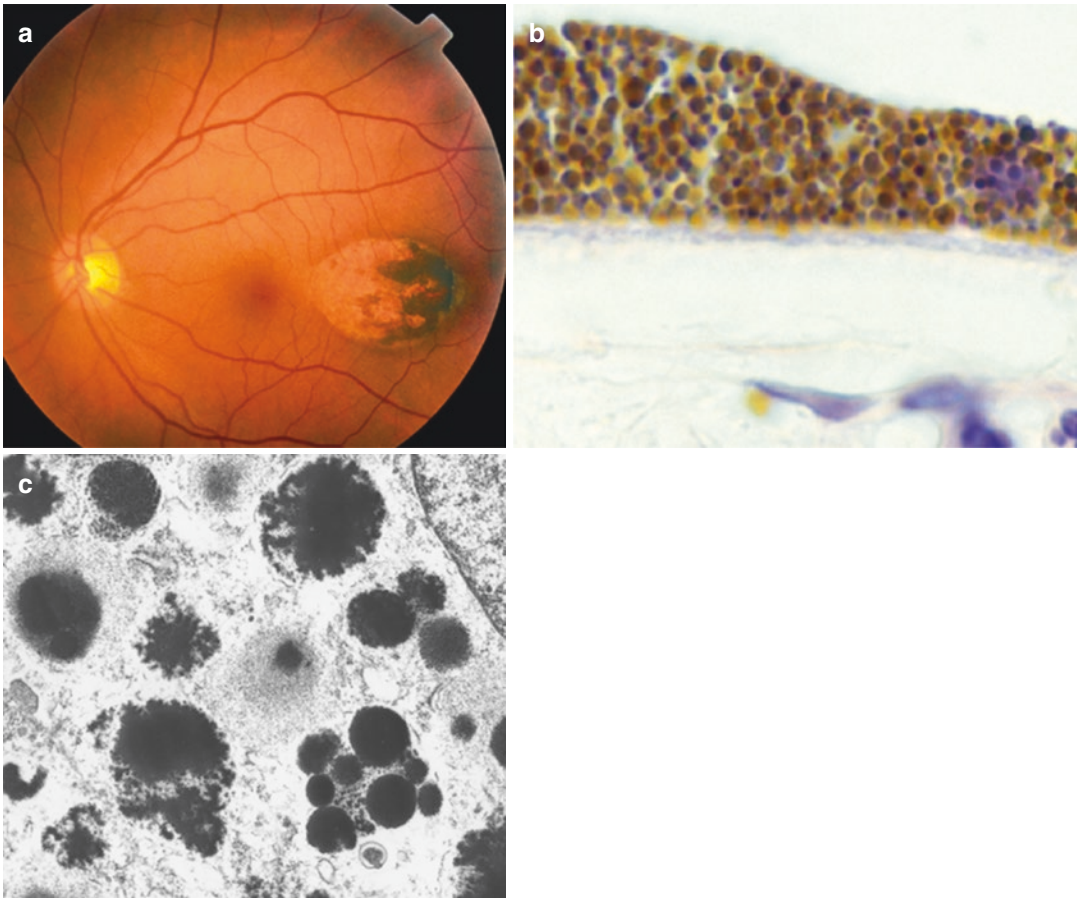


**Fig. 5.2** A 62-year-old woman with a large ciliochoroidal melanoma (enucleated) and an elliptical retinal pigment epithelial lesion about 1 mm temporal to the foveola, in the horizontal meridian (**a**). The pathology of the "CHRPE" lesion varied across the lesion, correlating with the level of pigmentation. 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 × 32,000). (Reprinted from Parsons et al. [3]. With permission from BMJ Publishing Group Ltd)

been noted in association with capillary and large vessel obliteration [8].

## 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 a 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.

To the unexperienced observer, CHRPE can simulate a choroidal melanoma, because peripheral lesions could appear elevated. In a review over 330 cases, a correct diagnosis of CHRPE was made in only 9% of patients, with referring diagnoses of choroidal nevus in 26%,

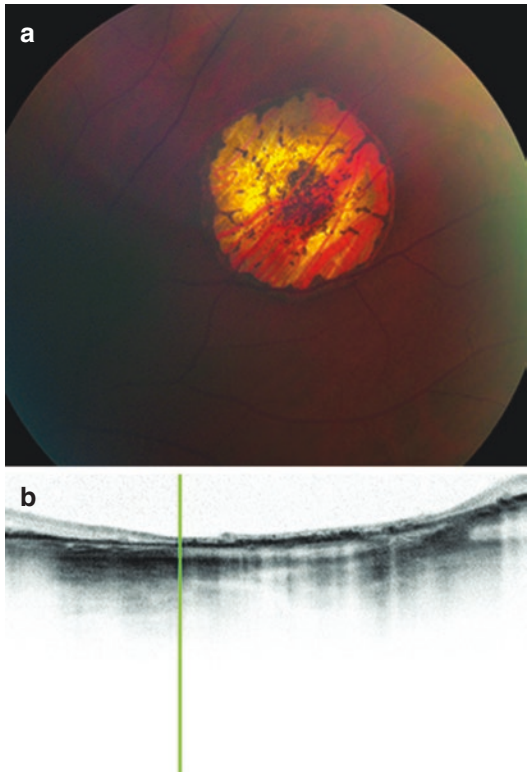


**Fig. 5.3** Depigmented CHRPE. Fundus appearance (**a**). OCT reveals thickened retinal pigment epithelial layer and atrophy of the overlying retinal layers (**b**)

choroidal melanoma in 15%, and unspecified fundus lesions in 48% [10].

## Treatment

The best management is periodic observation. No treatment is necessary except for the very rare instance in which neovascularization develops at the edge of the CHRPE lesion [11].

## Prognosis

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

# Congenital Grouped Pigmentation of the RPE

## Introduction

Multiple areas of circumscribed and flat retinal pigmentation that are arranged in clusters are 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]. Because of the similarity of the pattern to animal foot prints, they have been referred to as bear tracks (Fig. 5.4) [16, 18].

## Etiology and Pathogenesis

Meyer et al. have suggested that the growth pattern of grouped CHRPE is similar to cutaneous sectoral pigmentation and speculated that pigmentary mosaicisms may be the manifestation

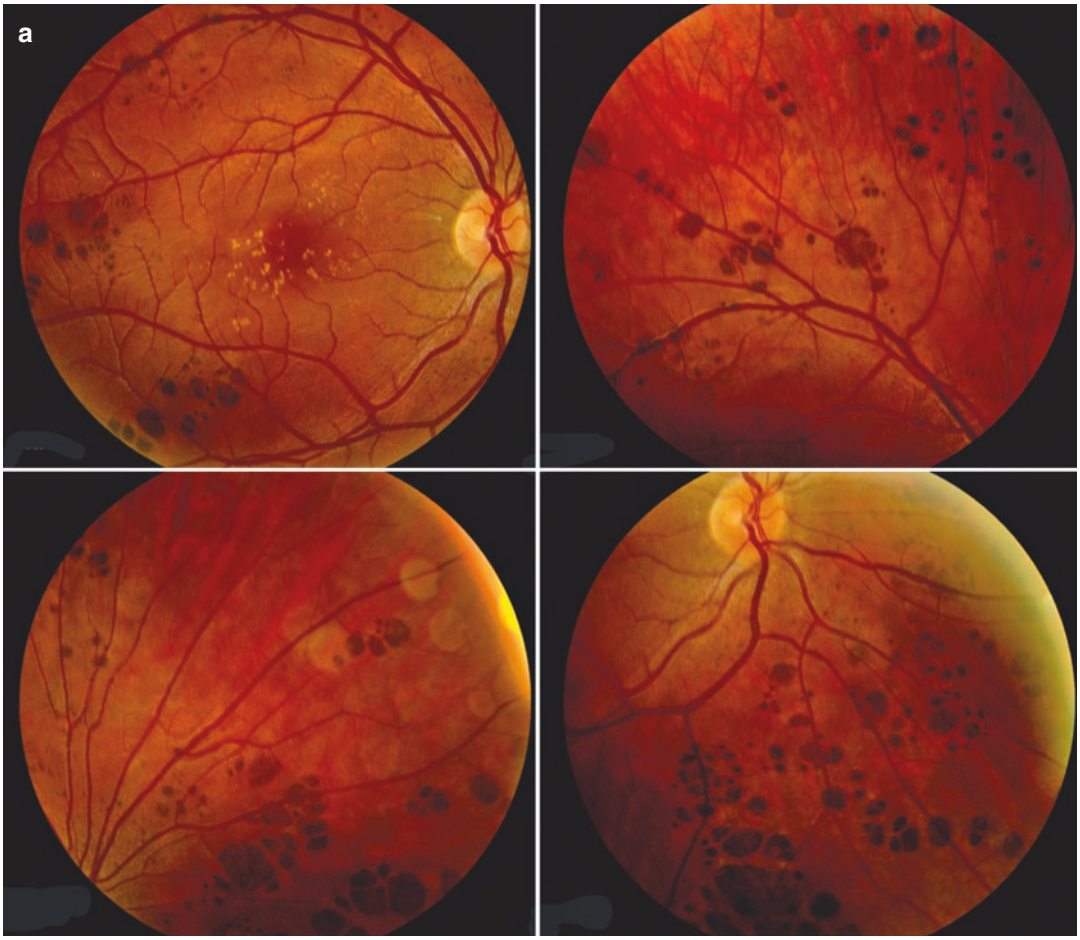


**Fig. 5.4** A 28-year-old asymptomatic Caucasian female demonstrated multiple small, flat, dark brown to black clusters of retinal pigment epithelium (RPE) hypertrophy on dilated fundus examination of the both eyes. These plaque-like lesions were circumferential along the peripheral fundus and were associated with smaller foci of pigmentation oriented toward 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**). (Reprinted from Turell et al. [65]. With permission from Taylor & Francis)

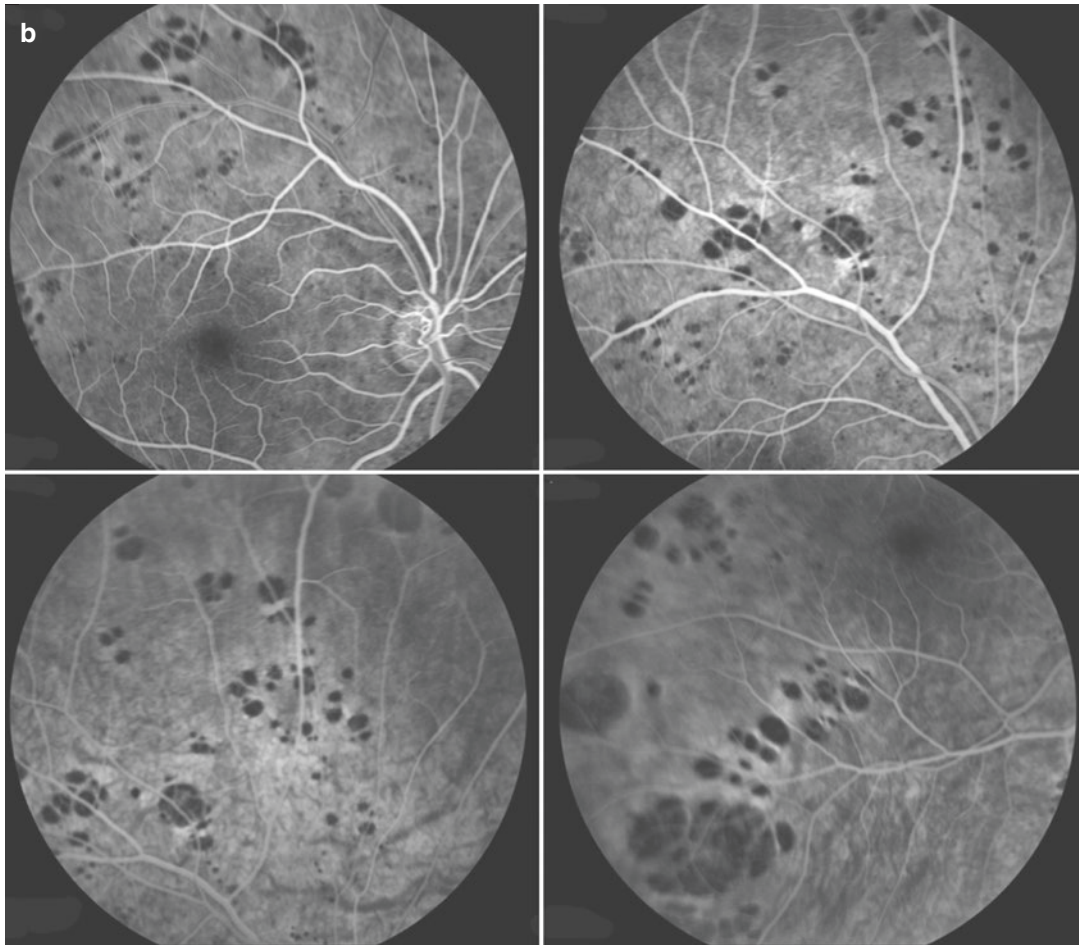


**Fig. 5.4** (continued)

of a modified wild-type allele in a somatic cell clone during early embryogenesis following developmental lines analogous to the cutaneous lines of Blaschko and that the sectoral distribution of grouped pigmentation of RPE may reflect the stream, outgrowth, and migration of retinal pigment epithelium cells during embryogenesis [19].

## Pathology

The histopathology of grouped pigmentation of the retina is very similar to that of solitary CHRPE; however, light and electron microscopy have suggested that the pigment granules retain their normal ellipsoid configuration and hypertrophy and hyperplasia are not significant features [20]. Histopathologic findings in variants of CHRPE are summarized in Table 5.2.

## Clinical Features

In the majority of cases, grouped pigmentation is unilateral (84%) and is limited to one sector of the fundus [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].

**Table 5.2** Histopathologic findings in variants of CHRPE

| | | Pigment granules | | | Other findings |
|---|---|---|---|---|---|
| Type | RPE cells | 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 |

*Abbreviation: RPE* retinal pigment epithelium

## Diagnostic Evaluation

The lesions are hypofluorescent on fluorescein angiography and hypoautofluorescent on fundus autofluorescence and demonstrate focal outer retinal atrophy overlying a flat lesion on OCT (Fig. 5.5) [21].

## Treatment

Grouped pigmentation can be just observed as part of routine ocular examination, no treatment is needed.

## Prognosis

Prognosis is excellent. Although congenital grouped pigmentation of the RPE is not associated with FAP [16, 22], rare association with microcephaly has been reported [23].

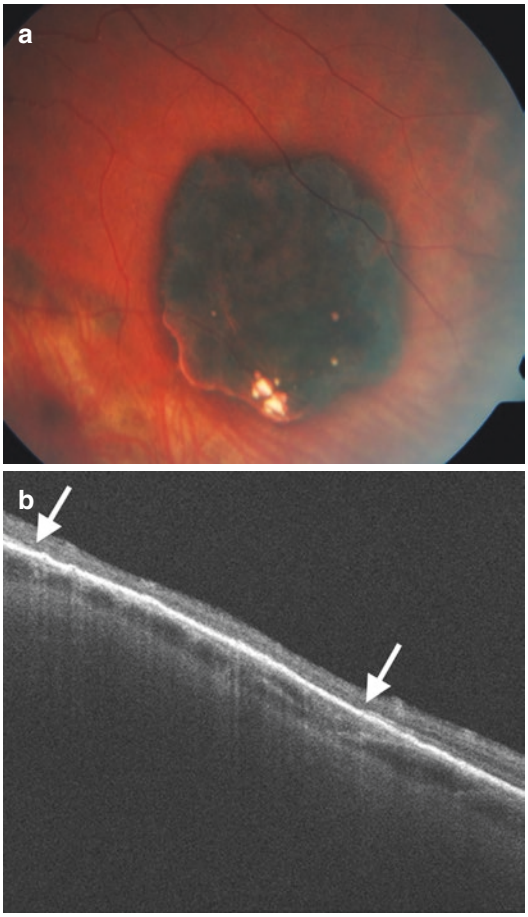


**Fig. 5.5** Pigmented CHRPE. Fundus appearance (**a**). OCT reveals atrophy of the overlying retinal layers (**b**, between arrows)

# Pigmented Ocular Fundus Lesions of Gardner Syndrome

## 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 the garden variety CHRPE lesions and grouped pigmentation of the retina and RPE as described above in this chapter are not associated with FAP [22]. There are distinct ophthalmoscopic features that distinguish CHRPE from lesions in FAP, and only some of the lesions have histopathologic characteristics compatible with CHRPE (Table 5.3) [24]. POFLs

**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 |

*Abbreviation: RPE* retinal pigment epithelium, *CHRPE* congenital hypertrophy of retinal pigment epithelium, *POFLs* pigmented ocular fundus lesions

have also been referred to as "RPE hamartomas associated with familial adenomatous polyposis" (RPEH-FAP) [25].

## Etiology and Pathogenesis

The presence of multiple POFLs is a highly specific (>90%) and sensitive (70–80%) marker for FAP [26]. Several hundred mutations have been described in the gene for FAP, designated as *APC* (adenomatous polyposis coli), which maps to chromosome 5q21-q22 [27]. Genotype-phenotype correlation has revealed that POFL and desmoid tumors are associated with FAP mutations between codons 311 and 1444 and after codon 1444, respectively [28–30].

## Pathology

In addition to the focal hyperpigmented lesions, histopathologic studies have revealed diffuse RPE abnormalities in FAP with hypertrophic RPE cells that contain lipofuscin granules, multimembranous inclusions, and macromelanosomes [31]. 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 of hyperplastic RPE cells; and (4) darkly pigmented lesions that occupy the full thickness of the retina and resemble RPE adenoma (Fig. 5.6). Hence, POFLs in FAP are probably better considered adenomas or hamartomas of the RPE.

## Clinical Features

### Symptoms

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

### Signs

POFLs are present at birth in about three-quarters of patients with FAP. We have observed them in a preterm infant who was examined in the neonatal intensive care unit for retinopathy of prematurity [32]. 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. 5.6) [31]. We recommend a three-mirror contact lens exam or pan-retinal photography 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

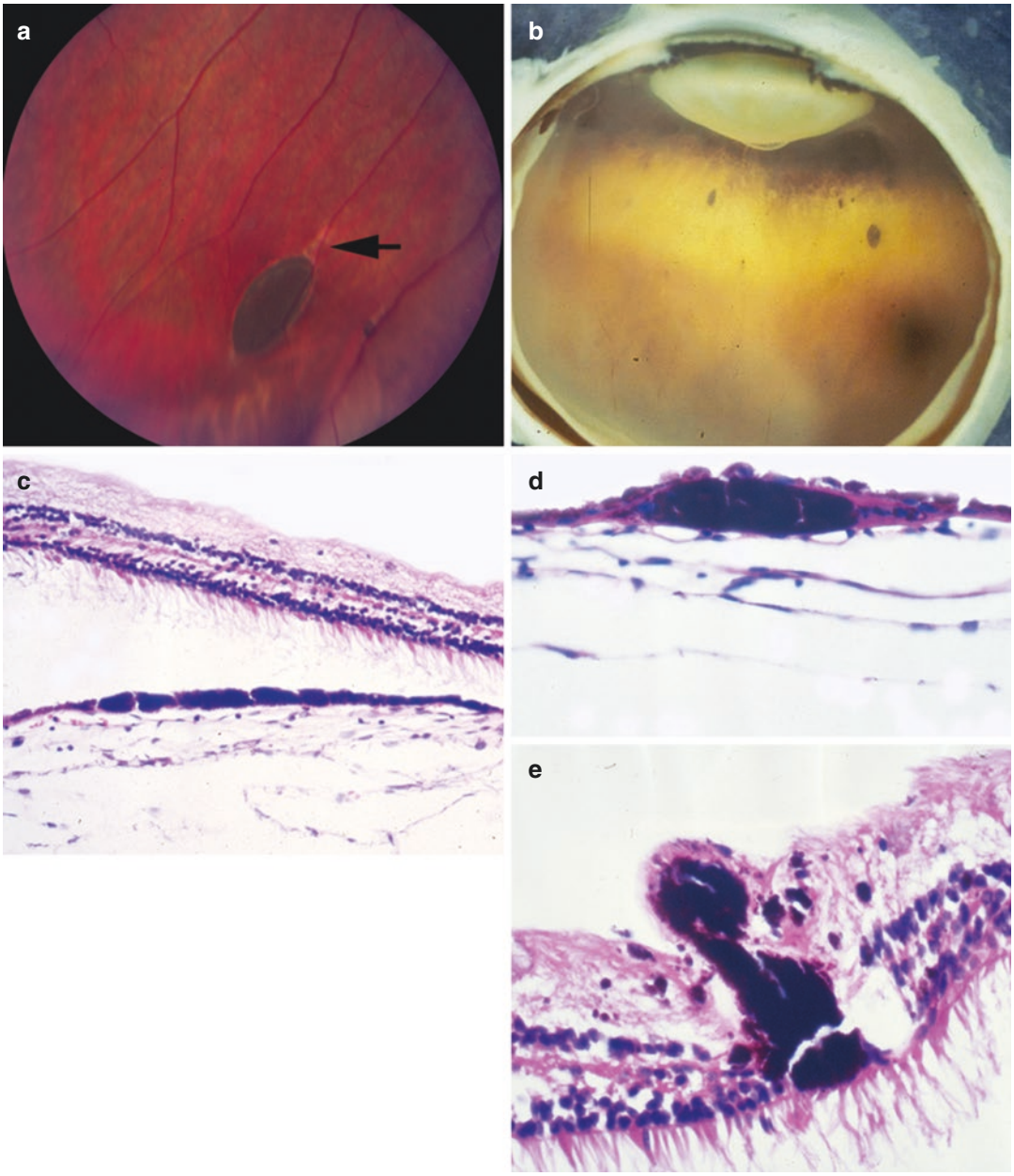


**Fig. 5.6** POFLs in the right eye of a patient with Gardner syndrome (**a**). Two oval-shaped pigmented retinal lesions are evident. Note depigmentation along the posterior margin (arrow). Numerous peripheral small lesions are easily overlooked unless fundus examination is performed with a three-mirror 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**). (Reprinted from Traboulsi et al. [31]. With permission from Elsevier)

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. 5.6). Macular lesions have also been observed. Some POFLs have a hypopigmented halo and/or 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.

POFLs can be differentiated from solitary CHRPE, because they are multiple, bilateral, and usually less defined margins. Unlike congenital grouped pigmentation of the RPE, they are randomly distributed, without a sector preference.

## 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 [33]. 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 [34]. POFLs [26] and opaque jaw lesions [35] 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 [36].

The presence of four or more POFLs is a highly sensitive (70–80%) and specific (>90%) clinical marker for the FAP [26]. Sensitivity and specificity is increased slightly if opaque jaw lesions are present at the same time [35]. 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 [24]. 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 [37].

### Turcot Syndrome

Turcot syndrome is a variant of FAP in which patients develop brain tumors. Patients with Turcot syndrome may also have multiple POFLs [38].

### 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 [23, 39].

## 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 or pan-retinal photography may be necessary to find additional small lesions. ERG and EOG examinations are not needed 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 third decade of life [29]. Mutation analysis of the gene and protein truncation assays are available commercially [30].

## Treatment

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

## Prognosis

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

# Simple Hamartoma of the RPE

## Introduction

Simple hamartomas of the RPE are very rare congenital lesions that were first described by Laqua

in 1981 [20]. 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) retinal involvement with intrinsic vascularization. Others have used the term congenital hamartoma of the RPE to describe these tumors [40].

## Etiology and Pathogenesis

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

## Pathology

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

## Clinical Features

### Symptoms

Patients with simple hamartoma of the RPE are generally asymptomatic unless the macula is involved, in which case there may be loss of vision.

### 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. Tumors 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. Surrounding halo or associated retinal traction is present in the majority of patients.

## Diagnostic Evaluation

The clinical features are characteristic. Ultrasonography shows a nodular echodense mass with high internal reflectivity. There is early non-fluorescence on early phases of the fluorescein angiogram, with some cases showing a central plaque of fluorescence and others only a ring of fluorescence at the edge of the lesions on late frames. OCT shows abrupt elevation from the inner retina with posterior shadowing [41].

## Treatment

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

## 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.

# Adenoma and Adenocarcinoma of the RPE

## 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 tumors.

## Etiology and Pathogenesis

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

## Pathology

Histopathologically, the RPE adenoma is composed of proliferating RPE cells. Tumors arising from the anterior portion of the RPE have vacuolated polygonal cells in a glandular or tubular

configuration with a vascularized connective tissue septae (Fig. 5.7). Prominent basement membrane is evident. Tumors demonstrating nuclear atypia and local invasiveness are classified as adenocarcinoma. RPE tumors including adenocarcinoma are not known to metastasize. Interestingly, immunohistochemical studies reveal that tumor cells may co-express melanocytic and epithelial markers [42].

## Clinical Features

### Symptoms

Patients with adenomas in the macular area may exhibit visual symptoms including vision loss.

### Signs

Most RPE adenomas are located in the peripheral fundus, although rare juxtapapillary tumors have

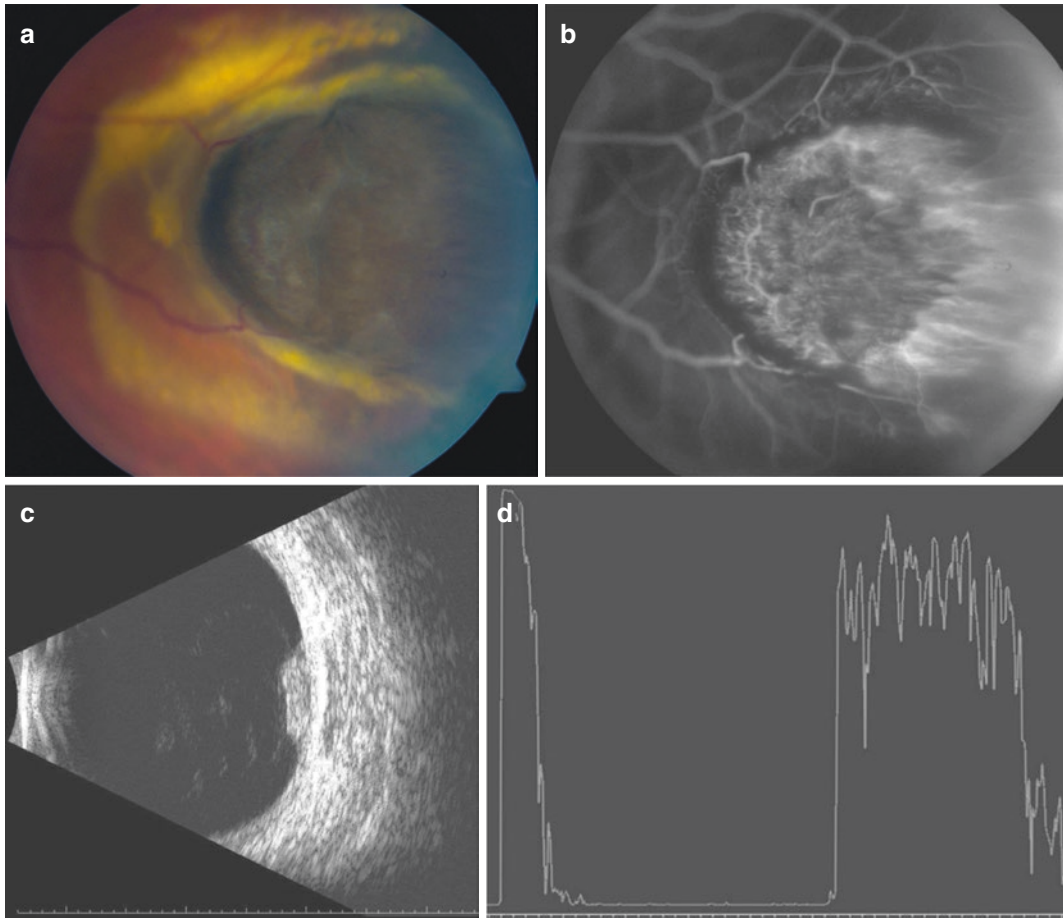


**Fig. 5.7** A 40-year-old woman noted to pigmented fundus mass on a routine examination (**a**). Note dark uniform color with absence of drusen, orange pigmentation, or details of overlying retina. Prominent lipid exudation along the base of the tumor was also observed. The retinal vessels seem to lead 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**). Three years after episcleral brachytherapy (Iodine-125; 85 Gy apical dose), the tumor regressed with surrounding chorioretinal atrophy (**g**). (**f**: Courtesy of Charles Biscotti, MD)

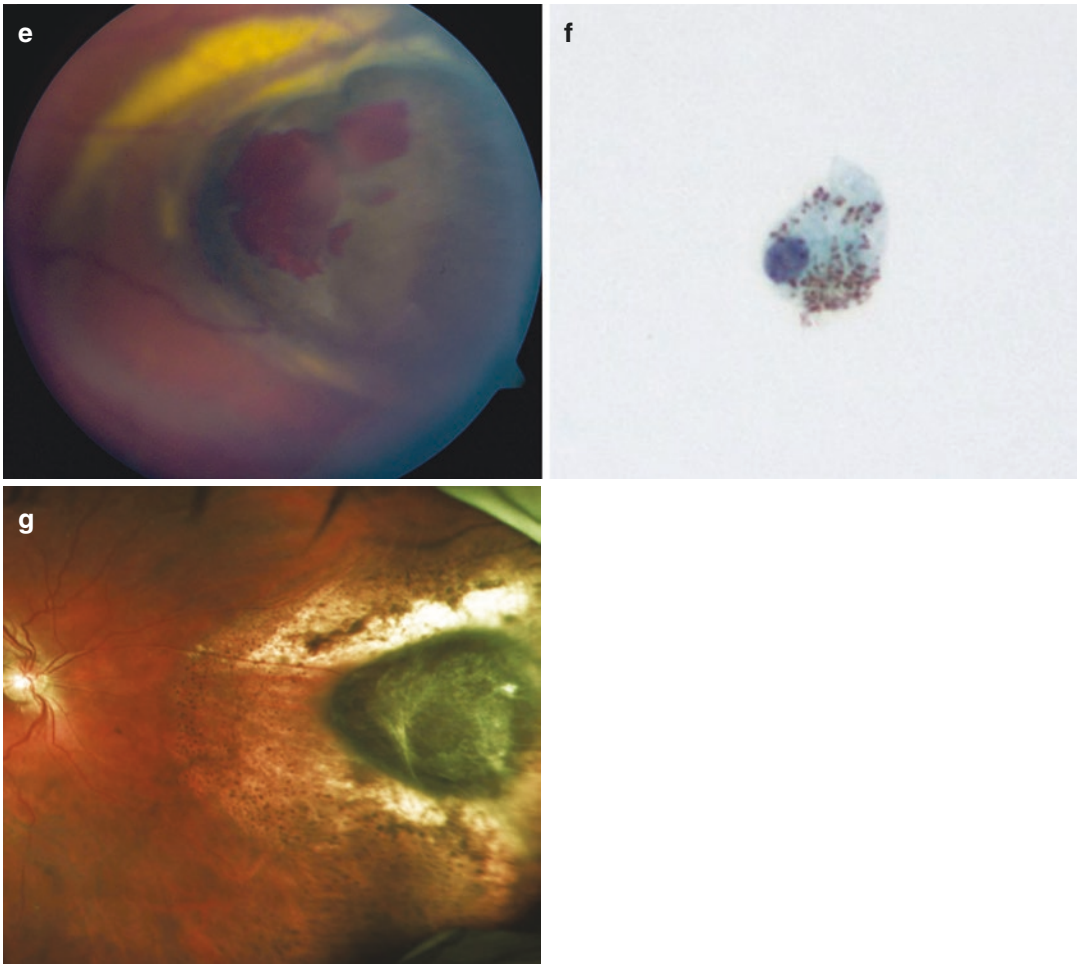


**Fig. 5.7** (continued)

been reported [14]. In a series of 13 adults patients with a mean age of 53 years (age range 28–79 years), 10 were women and 3 were men; 10 were white and 3 were African American [43]. All tumors were solitary and unilateral and ranged from small (2 × 2 × 1 mm) to large in size (17 × 17 × 17 mm). The tumors are usually solitary and unilateral and start as a small, deep retinal tumor that is dark brown to black in color (Fig. 5.7). The tumor usually grows very slowly, invading the overlying sensory retina, at which time it often is associated with a prominent retinal feeder artery and draining vein that were visualized in 8 of the 13 patients, 5 of whom had an exudative retinal detachment. Two patients had recurrent vitreous hemorrhage [44]. The presence of surrounding retinal hard exudates is an important diagnostic feature, as it is almost never associated with untreated choroidal melanoma.

## 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. Enhanced depth imaging OCT (EDI-OCT) shows irregular tumor surface with full-thickness retinal involvement and dense posterior optical shadowing [45], unlike choroidal melanoma which is located in the uveal layer [46]. Nevertheless, the majority of the patients are

**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<br>HMB-45 |

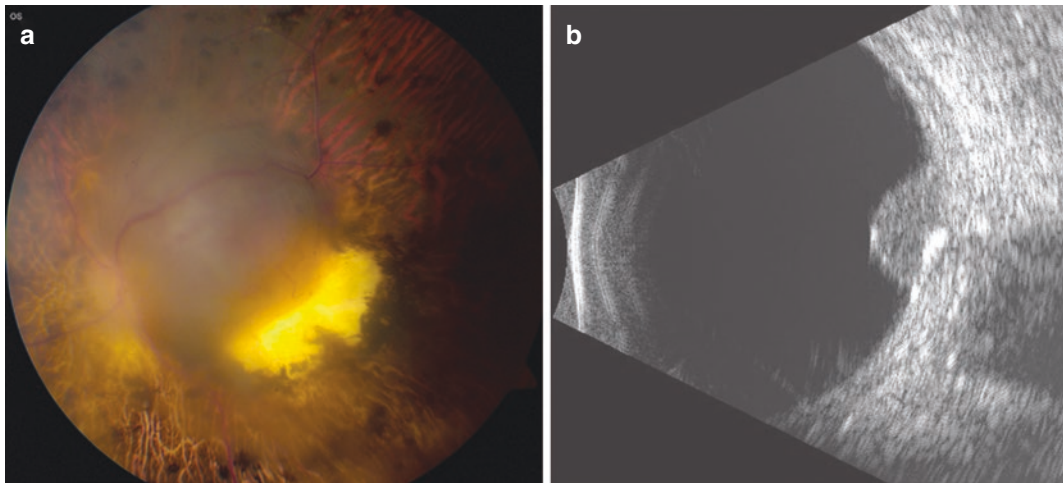


**Fig. 5.8** Longstanding blind eye due to healed toxoplasma retinochoroiditis. Note nodular almost translucent subretinal elevation adjacent to a healed chorioretinal scar (**a**). Suggestion of osseous metaplasia at the level of the RPE (**b**)

referred with a suspected diagnosis of choroidal melanoma. It is not always possible to differentiate RPE adenoma and adenocarcinoma from choroidal melanoma despite clinical and diagnostic evaluation (Table 5.4). In such cases, fine-needle aspiration biopsy that discloses cells of pigment epithelial origin can be diagnostic (Fig. 5.7). In rare instances, reactive proliferation of RPE can attain tumorous proportions simulating RPE adenoma and choroidal melanoma (Fig. 5.8) [47, 48].

## Treatment

A variety of treatment modalities have been used depending on individual case characteristics, including observation, enucleation, local tumor resection, irradiation, and laser therapy [43, 49]. Observation can be safe in small and asymptomatic lesions, whereas in medium/large tumors, plaque radiotherapy could be considered. Laser treatment, thermotherapy, or cryotherapy could be good options in the presence of exudation.

Moreover vitrectomy could be added in case of vision loss due to vitreoretinal traction.

### Prognosis

The visual prognosis is variable. RPE adenoma may remain stable or enlarge simulating a melanoma [44]. They may not respond even to brachytherapy necessitating enucleation [44, 49].

## Combined Hamartoma of the Retina and RPE

### 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 [50].

### 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 [51], the mechanistic relationship remains to be elucidated. Diagnosis of CHR in infants supports the congenital nature of the lesions, but there have also been reports of acquired cases of CHR; Ticho et al. reported the development of CHR in a 3-year-old patient following parainfectious meningoencephalitis with optic neuritis [52].

### Pathology

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

### Clinical Features

#### Symptoms

The most common presenting symptom of CHR is painless decrease in vision usually due to direct involvement of the optic disc, the papillomacular bundle, or the fovea [53]. Secondary causes of decreased vision include tractional distortion of the macula and epiretinal membrane formation [53]. Other presenting symptoms include strabismus, floaters, and leukocoria [53].

#### Signs

CHR is usually unilateral and can occur at the optic disc or elsewhere in the fundus (Fig. 5.9). If hamartomas are present in both eyes, an underlying systemic syndrome, such as neurofibromatosis type 2, has to be suspected [54]. The tumor is gray-black in color, and the lesion typically has an epiretinal membrane that may cause retinal traction, and there may be associated tortuous or straightened retinal blood vessels, probably due to secondary excessive glial tissue on the surface of the lesion [55]. The traction may be progressive, leading to a decline in vision.

Hamartomas are generally stable, but excessive glial proliferation can lead to retinal traction and visual loss [55]. CHRs do not undergo malignant transformation. Uncommon secondary effects include choroidal neovascularization, vitreous hemorrhage, retinoschisis, and formation of a macular hole [56].

#### 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 [50], and there is another reported occurrence of CHR in NF1 [57]. However, the most frequent association of CHR is with NF2 [51, 58]. Sporadic observations of CHR in several syndromes such as branchio-oculo-facial syndrome [59], Gorlin syndrome [60], and ipsilateral Poland anomaly have also been reported [61].

### Diagnostic Evaluation

CHR can be 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

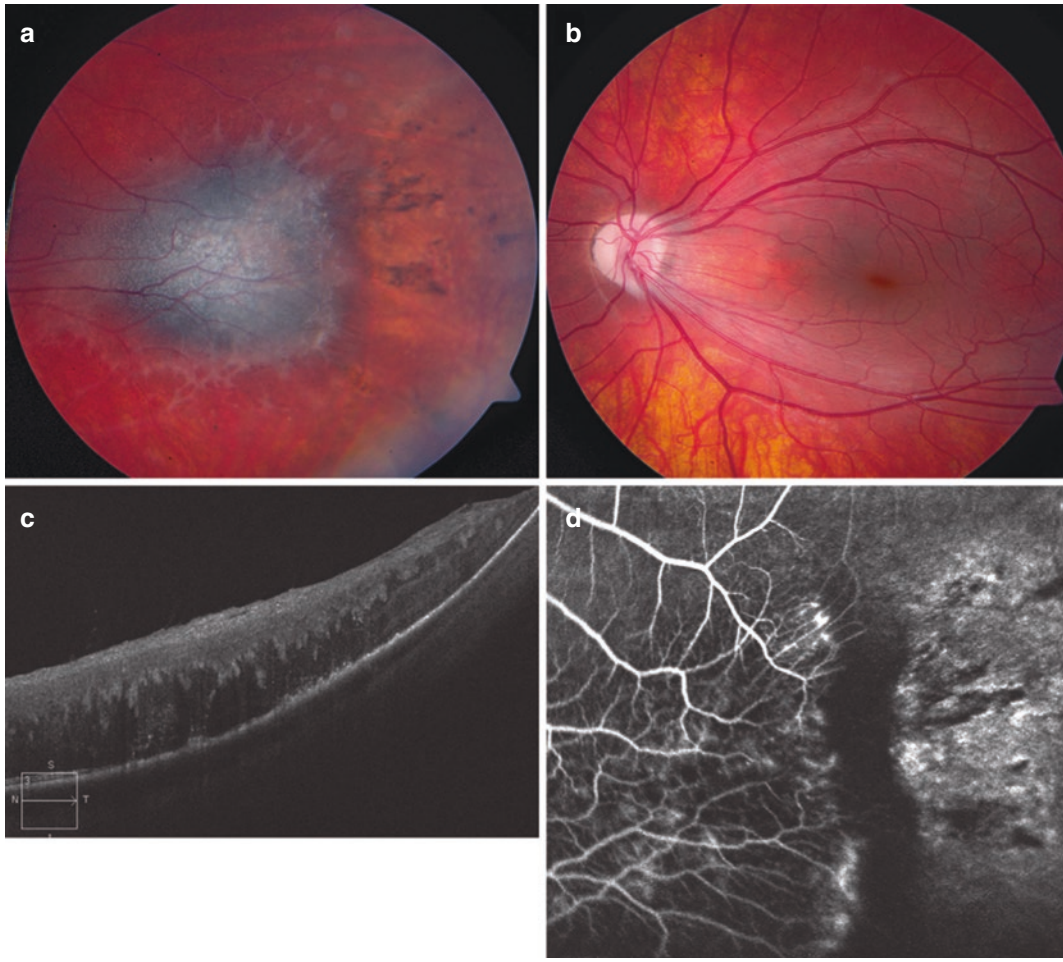


**Fig. 5.9** Combined hamartoma of the retina and RPE usually appears as a unilateral gray-black-colored lesion (**a**). Temporal dragging the vessels is evident on the examination of the posterior pole (**b**). OCT showing normal RPE layer, disorganization of retinal layers, and prominent epiretinal membrane (**c**). Fluorescein angiography demonstrated leakage within fine retinal vessels and hypofluorescence corresponding to the pigment proliferation at the margin (**d**)

often be reliably diagnosed on indirect ophthalmoscopy. Ancillary studies such as fluorescein angiography and OCT are helpful in establishing the diagnosis. Angiographically, the lesion shows blockage of the choroidal fluorescence due to increased pigmentation of the retina 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 [53]. Optical coherence tomography of CHR demonstrates full-thickness irregular highly reflective lesion of the inner retina with obscuring of the underlying retinal architecture which is useful in differentiating from a minimally elevated choroidal melanoma, which shows normal retinal architecture [62]. Although often isolated, patients diagnosed with CHR should undergo evaluation to exclude systemic association, especially NF2.

## 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. Peeling of the epiretinal membrane may not possible in cases where the membrane is tightly adherent or even part and parcel of the retina, and the role of vitrectomy and membrane peel remains controversial in management of vision loss in CHR. However, vitrectomy and membrane peeling have been used in selected cases with modest visual improvement, especially in those in which the hamartoma has not involved the full thickness of the retina in patients with vitreous hemorrhage and preretinal gliosis [63]. Hence OCT can be very useful in determining the extent and details of the lesion [55]. In fact, a classification system that incorporates OCT findings in addition to the fundus features (location and zone) has been proposed to guide management [64].

## Prognosis

In a survey of the 60 cases examined by members of the Macula Society, 41 patients had adequate follow-up information [53]. 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 [53].

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# Tumors of the Ciliary Epithelium

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Javier Elizalde, María de la Paz, Rafael I. Barraquer, and Arun D. Singh

## Introduction

Tumors arising from the ciliary epithelium are rare. 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 complexity in differentiating between benign and malignant tumors, their remarkable cellular polymorphism, and the possibility of dealing with either a congenital or acquired tumor make their diagnosis difficult [1–3].

## Anatomy

The epithelium of the pars plana and the pars plicata has two layers. The outer layer is the pigmented epithelium, which 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, which is cuboidal or low columnar and which lines the surface of the ciliary crests, extending posteriorly to be continuous with the sensory retina. The nonpigmented epithelium produces aqueous humor and possibly the hyaluronic acid found within the vitreous gel.

## Classification

Based on Zimmerman's histological classification, ciliary epithelial tumors may be grouped as congenital and acquired (Table 6.1) [1].

## 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 to have an embryonic appearance histologically.

## Glioneuroma

Glioneuroma is perhaps the rarest tumor in the group, with only a few cases reported in the literature [4–7]. It is considered to be a choristoma

J. Elizalde (✉) · M. de la Paz · R. I. Barraquer
Centro de Oftalmología Barraquer, Barcelona, Spain

A. D. Singh
Department of Ophthalmic Oncology,
Cole Eye Institute, Cleveland Clinic,
Cleveland, OH, USA


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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 | | |

arising from the anterior margin of the primitive optic cup, without any neoplastic potential.

### Clinical Features

Glioneuroma appears as a slowly enlarging white or fleshy unilateral mass in the inferior angle of the anterior chamber, often with involvement of the corneoscleral limbus. The tumor can be adherent to the corneal endothelium and can displace the pupil and the lens or induce a cataract [4, 6, 7]. An associated ciliary body colobomatous defect may be present. The intraocular pressure may be elevated [4, 7]. Glioneuroma is usually recognized at birth or shortly after, although it has been diagnosed in a 21-year-old woman [4].

### Pathology

Glioneuroma infiltrates the stroma of the iris and ciliary body and may invade the choroid, the peripheral retina, and also extrasclerally [4, 6, 7]. Light microscopy reveals a well-differentiated neural tissue similar to the brain, with eosinophilic fibrillary material, axonal processes, and glial cells within the tumor matrix [6].

### Management

Because intraocular glioneuroma is rare, there is no clearly established treatment. Most recorded cases have been managed by enucleation of the involved eye. Glioneuroma has been removed by iridocyclectomy [4]. Safety and efficacy of diagnostic biopsy in such cases has not been established.

## Medulloepithelioma

First described by Verhoeff as a teratoneuroma [8] and later by Fuchs as a diktyoma [8], this tumor came to be known as medulloepithelioma, as proposed by Grinker in 1931 [9]. Intraocular medulloepithelioma is a nonhereditary, embryonal neoplasm that usually occurs in the ciliary body. Accordingly, it contains pure neuroepithelial structures (nonteratoid medulloepithelioma or diktioma) or, more commonly, derivatives of the medullary epithelium, particularly cartilage, skeletal muscle, and brain tissue [2, 10].

### Clinical Features

Medulloepithelioma is typically a disease of childhood that is usually diagnosed during the first decade of life, although some cases are asymptomatic until adulthood [11–13]. The most relevant clinical signs and symptoms of medulloepithelioma are poor vision, pain, leukocoria, and the presence of an intraocular mass appearing behind the pupil (Box 6.1). The tumor is an irregular, variable-sized, white or gray, translucent mass arising from the ciliary region in contact with the iris (Fig. 6.1). It is frequently vascularized and rarely pigmented. One well-known clinical feature of medulloepithelioma is the presence of cysts within the tumor [2, 10, 14]. Large cysts may break off from the tumor and float freely in the anterior chamber or into the vitreous cavity (Fig. 6.2). Iris neovascularization is a common and early finding in eyes with medulloepithelioma [10]. Children with neovascularization of iris of unknown cause should be evaluated to exclude underlying medulloepithelioma [15].

The presence of a sectorial or total cataract, with or without subluxation, is 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 [2, 10, 11,

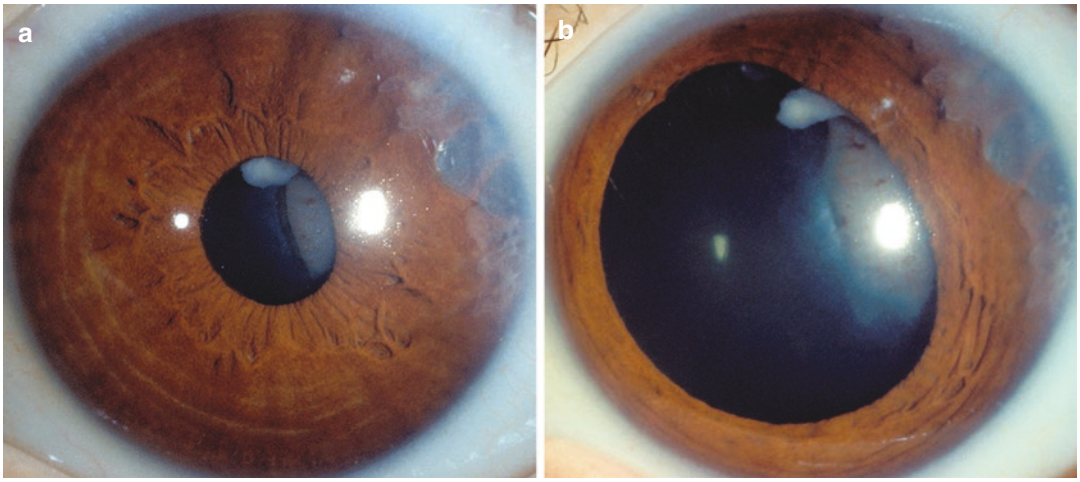


**Fig. 6.1** Medulloepithelioma of the ciliary body. Translucent mass behind the iris and invading the anterior chamber through the iris root. Note a dense anterior polar cataract (**a**, arrow). Same eye with the dilated pupil (**b**)

14–16]. Other findings include a cyclitic neoplastic membrane, uveitis, hyphema, retinal detachment, vitreous hemorrhage, optic nerve invasion, and extraocular extension of the tumor (Fig. 6.3) [10]. In adults, medulloepithelioma can resemble a uveal melanoma [12].

Local invasion and extraocular extension occur frequently, but metastasis is uncommon and does not occur in absence of extraocular extension [2, 17, 18].

### Box 6.1 Diagnostic Features of Medulloepithelioma

- 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

## Pathology

According to Zimmerman's classification, medulloepithelioma may be divided into nonteratoid and teratoid types, and either type can have benign or malignant cytologic features [1, 2, 19]. 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 (hyaline cartilage, rhabdomyoblasts, undifferentiated mesenchymal cells resembling embryonal sarcoma, neuroglial tissue resembling the brain, and ependymal structures) [2, 10, 11, 14, 20]. The rhabdomyoblastic component may completely replace the neuroepithelium, to the extent of resembling primary intraocular rhabdomyosarcoma [18].

It can be difficult to classify medulloepithelioma 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

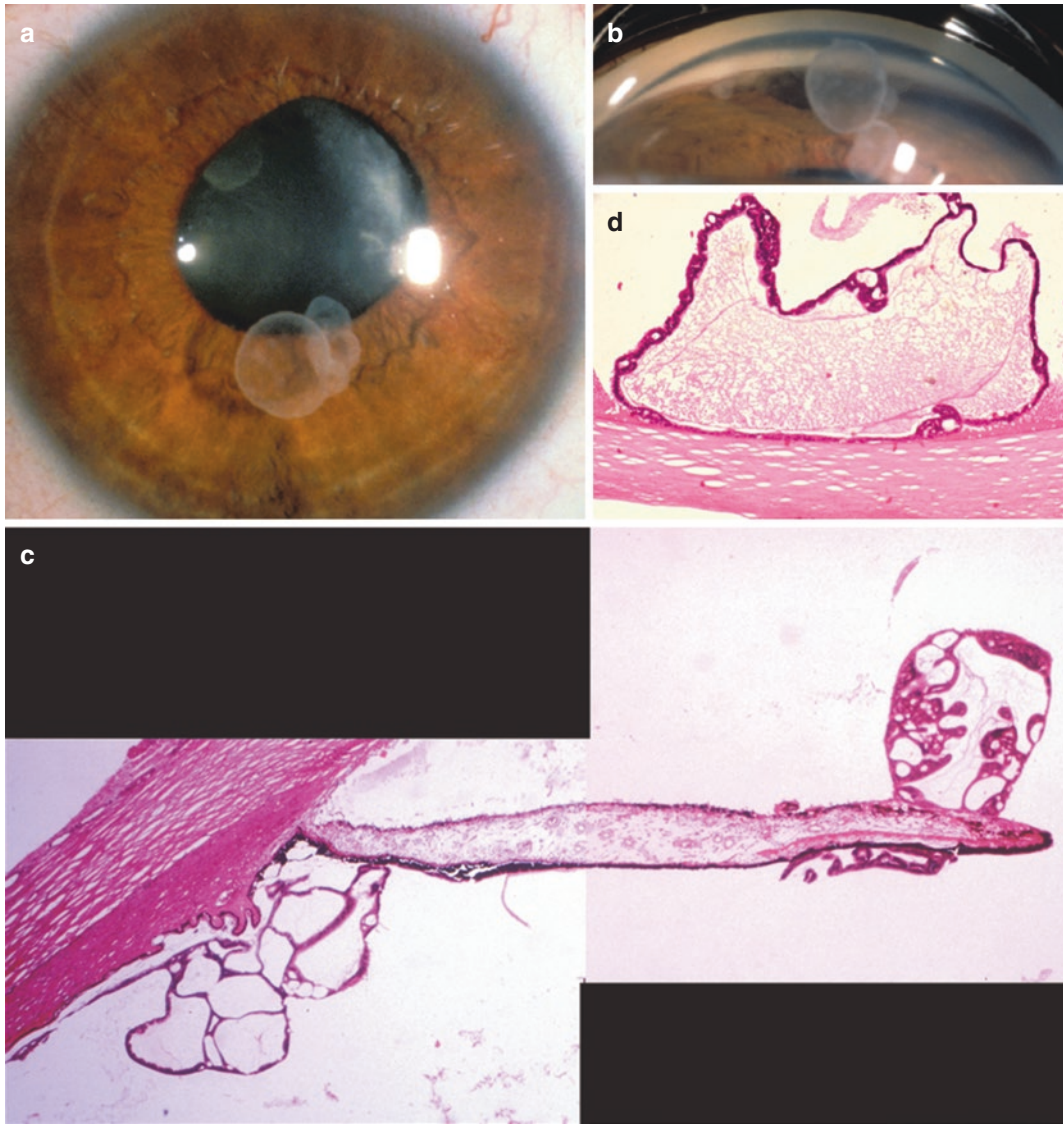


**Fig. 6.2** Anterior chamber cysts secondary to medulloepithelioma of the ciliary body (**a**). Multiple cysts within the anterior chamber and emerging through the pupil (**b**, gonioscopic photographs). Histopathologic composite photograph showing a cyst adherent to the anterior border layer of the 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)

[2]. More recently, Verdijk has proposed grading medulloepithelioma as grade 1 (benign), grade II (tumor progression as evidenced with pleomorphism, increased mitotic activity, and local invasion), and grade III (tumors with metastatic potential – presence of extrascleral extension or metastasis) [21].

## Management

In most cases, the diagnosis is suspected clinically and confirmed by enucleation [17]. Rare cases in adults may be diagnosed with fine needle aspiration biopsy [22]. Because most of these tumors are cytologically malignant, infiltrating the adjacent

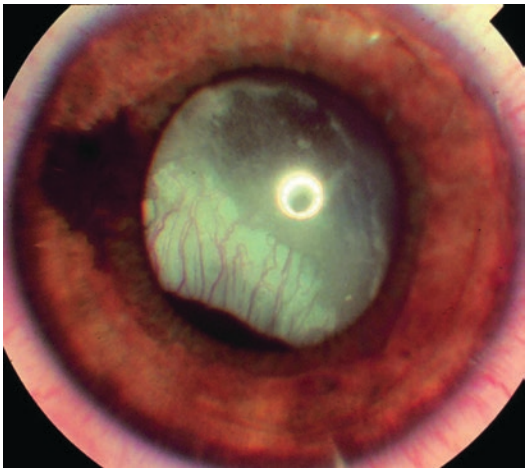

**Fig. 6.3** A 38-month-old girl presented with leukocoria of 2-month duration. On examination, lens coloboma and a vascularized retrolental sheet (cyclitic membrane) were noted. A pigmented mass was seen in the ciliary body region from 6 to 8 o'clock position. Tumor recurred after excision necessitating enucleation. Histopathologically, the lesion was confirmed to be malignant teratoid medulloepithelioma. (Reprinted from Singh et al. [15]. With permission from Slack Incorporated)

vitreous, and proliferating in delicate sheets, which may not be evident intraoperatively, enucleation of the affected eye is usually advisable [17]. 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 [17]. Brachytherapy might be a good option in circumscribed tumors, with the stipulation of a possible retreatment in case of tumor recurrence [23–25]. Distant metastasis does not respond to radiation therapy or chemotherapy [3].

### Pleuropulmonary Blastoma

An association with pleuropulmonary blastoma (PPB) has been recently reported by the International Pleuropulmonary Blastoma Registry [26]. 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 [27]. PPB may be part of a familial cancer syndrome caused by *DICER 1* mutation on chromosome 14q31 [26–28]. Additional features of the familial syndrome include lung cysts, neuroblastoma, cystic nephroma, Wilms tumor, and rhabdomyosarcoma [28]. Somatic mutations of *DICER1* and *KMT2D* are frequent in intraocular medulloepithelioma [29]. The presence of medulloepithelioma should be considered in a child with a history of PPB and vice versa [26, 30].

## 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. These tumors can take the form of reactive proliferations (pseudoadenomatous hyperplasia) or neoplastic proliferations (adenoma or adenocarcinoma).

## Pseudoadenomatous Hyperplasia (Reactive Proliferation)

### 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 [31]. It is commonly observed as an opaque white mass usually confined to a ciliary process and tends to be noted incidentally, in eyes removed surgically, or postmortem (Fig. 6.4) [32]. Histologically, it is composed of irregular cords of cells of the nonpigmented ciliary epithelium with abundant acellular eosinophilic basement membrane (Fig. 6.5) [33]. In rare instances, the tumor can erode into the anterior chamber, simulating an iridociliary tumor such as melanoma [31, 33, 34].

### 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

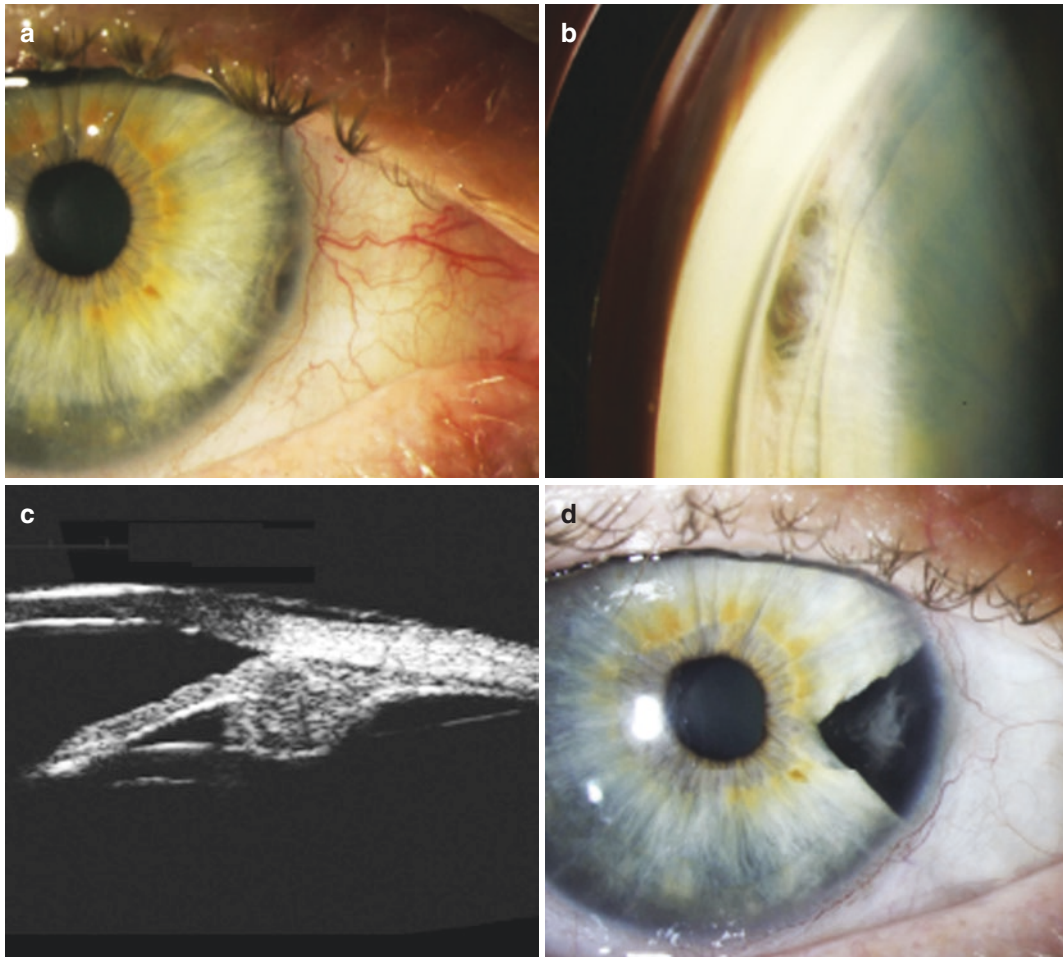


**Fig. 6.4** Fuchs' adenoma (clinical). Slit lamp colored picture with pigmented tumor present at ~3:30 eroding through the iris root (**a**). Gonioscopy demonstrating two foci of pigmented tumor extending through ciliary body band and iris root (**b**). Ultrasound biomicroscopy (longitudinal scan at 3 o'clock, 40 MegaHertz) showing ciliary body tumor with scale from 0 to 5 mm (**c**). Appearance of the eye 2 years postoperatively (**d**). (Reprinted from Nagarkatti-Gude et al. [33]. With permission from Elsevier)

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 [35]. Reactive hyperplasia of the ciliary epithelium is usually seen in histopathologic specimens of traumatized or disorganized eyes and may adopt a pseudotumor appearance [35, 36].

## Adenoma and Adenocarcinoma of the Ciliary Epithelium

True acquired neoplasms of the pigment or nonpigmented ciliary epithelium are rare. They may be benign (adenoma) or malignant (adenocarcinoma), and the clinical differentiation between the two may be impossible. Similar tumors arise from the pigment epithelium in the iris [37] and the retinal pigment epithelium [38].

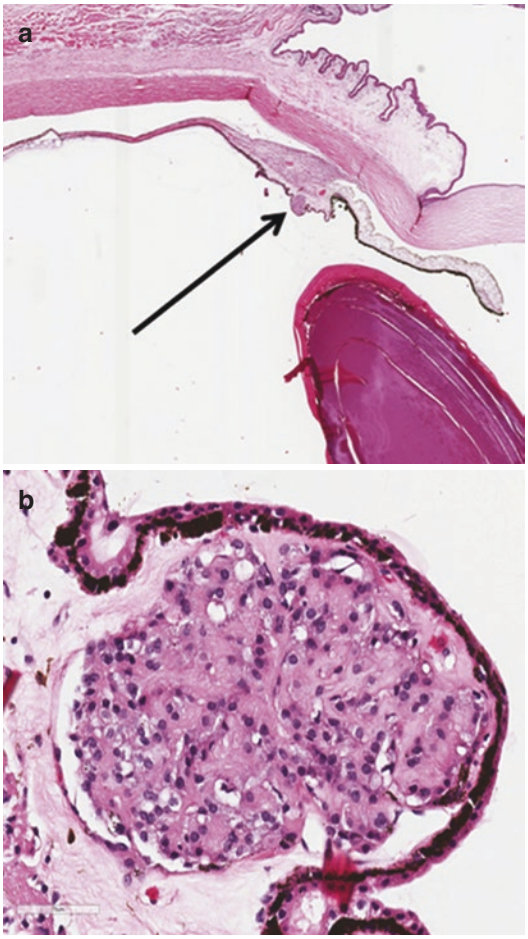


**Fig. 6.5** Fuchs' adenoma (histopathology). A 60-year-old man who underwent subtotal orbital exenteration for intraorbital spread of basal cell carcinoma. An incidental adenomatous proliferation can be seen on the nonpigmented ciliary epithelium with hematoxylin and eosin staining (**a**, arrow). The lesion consists of amorphous eosinophilic material and mucopolysaccharides (**b**). (Reprinted from: Surapaneni et al. [32]. With permission Elsevier)

## Clinical Features

Both adenoma and adenocarcinoma appear as a solid ciliary body mass, associated with secondary cysts [39] that present with variable characteristics and simulate ciliary body melanoma. Tumors arising from the pigment ciliary epithelium are usually deeply pigmented (Fig. 6.6) [40–42], and tumors arising from the nonpigmented ciliary epithelium are gray-white (i.e., amelanotic) (Fig. 6.7) [39, 43]. These tumors can be asymptomatic or can cause painless visual loss. Adenoma and adenocarcinoma of the ciliary body have an irregular and sometimes multilobulated surface [39–41, 43]. Uveal melanoma tends to present with a mushroom-like growth pattern. Some tumors may present with cells in the anterior chamber and with sentinel vessel in the overlying episclera – though this finding is more characteristic of uveal melanoma. Pigment dispersion over the iris surface and into the vitreous is also seen more often with adenoma of the ciliary pigment epithelium than with melanoma [42, 44]. Adenoma of the nonpigmented ciliary epithelium may be associated with iris or disc neovascularization due to excessive production of vascular endothelial factor [45]. It is not uncommon to observe dyscoria and secondary cataract formation induced by tumor compression, which can also cause lens subluxation. 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 unless there has been extraocular extension [36]. Examination of phthisical eyes can unexpectedly reveal adenocarcinoma of the pigmented [46] or nonpigmented ciliary epithelium [36, 47, 48]. However, the causal relationship between presence of the tumor and phthisis is not well understood. It is possible that factors that lead to phthisis such as chronic inflammation induce tumor formation rather than presence of tumor leading to phthisis [46]. All phthisical eyes that undergo evisceration or enucleation should be subjected to histopathologic examination [47]. Features differentiating adenoma from melanoma of the ciliary body are summarized (Table 6.2).

## Pathology

These tumors are composed of pigmented or nonpigmented cuboidal or columnar cells

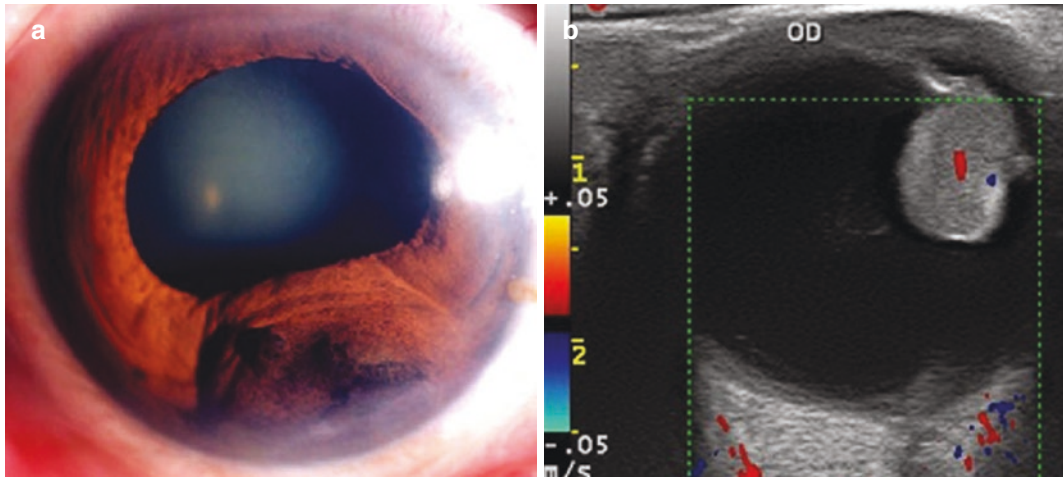


**Fig. 6.6** Adenoma of the pigmented ciliary epithelium. Clinical features. Slit lamp photograph (**a**). Clinical images. Ultrasonographic biomicroscopy showing a solid circumscribed mass (**b**). (Reprinted from Chang et al. [42]. With permission from John Wiley & Sons)

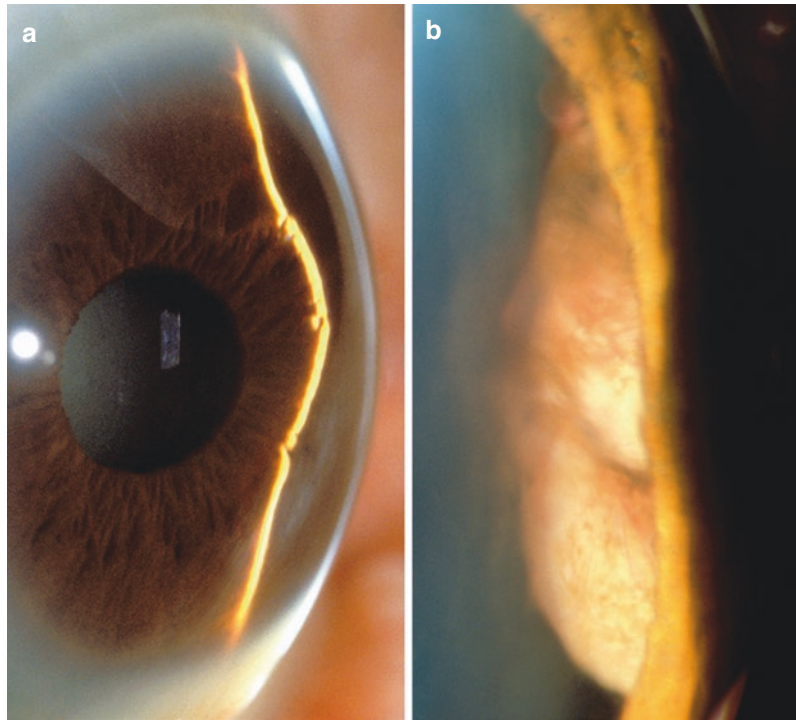


**Fig. 6.7** Adenoma of the nonpigmented ciliary epithelium. Slit lamp photograph demonstrating an anterior displacement of the iris (**a**). A predominantly amelanotic nodular mass is located behind the iris (**b**). Histopathologic macroscopic photograph discloses a tumor of the nonpigmented epithelium 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**: Reprinted from: Laver et al. [36]. With permission from Elsevier)

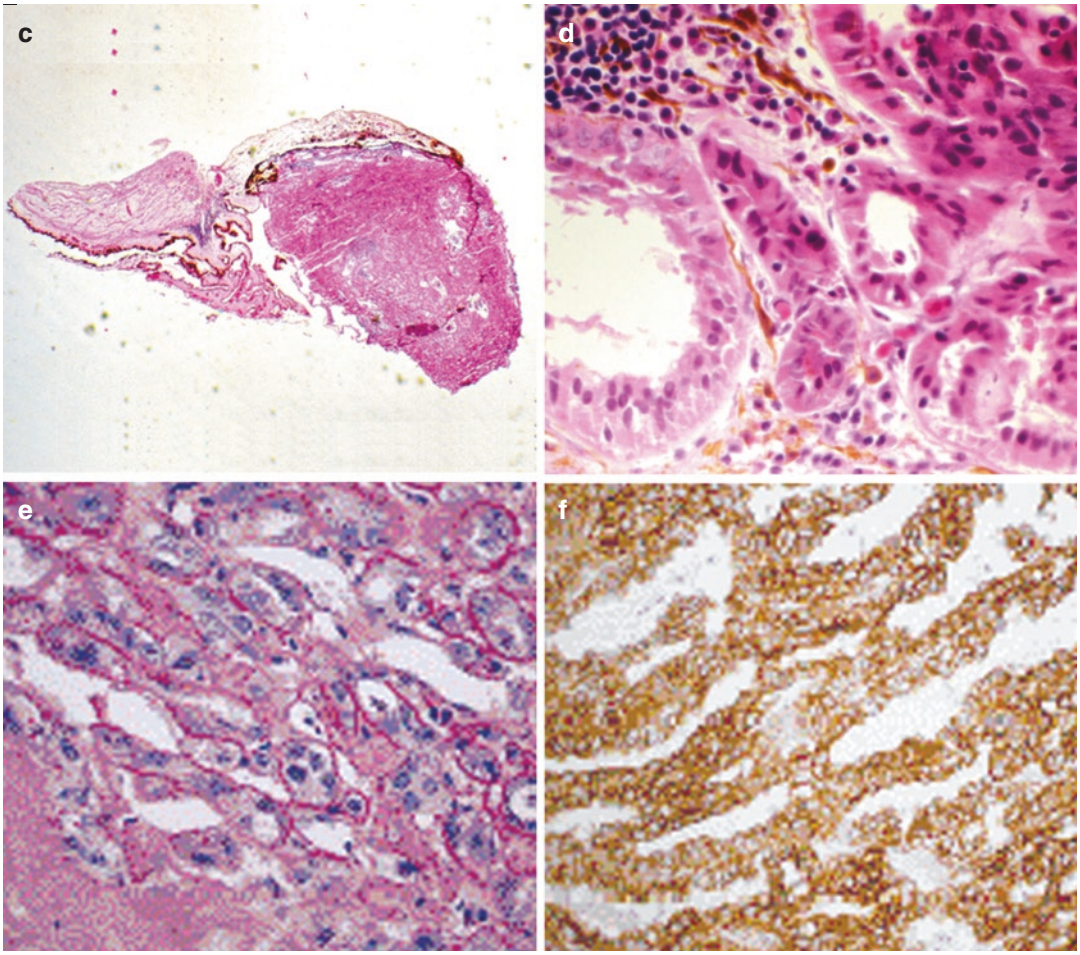


**Fig. 6.7** (continued)

**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 |

usually arranged in cords or tubules with a thick basement membrane [36, 42, 46, 49]. Adenocarcinomas exhibit more malignant features, such as cellular proliferations and loss of alveolar characteristics [50–52]. In addition, evidence of choroidal invasion and extraocular extension suggest adenocarcinoma rather than adenoma [46]. Positivity of the tumor cells to vimentin confirms the nonpigmented ciliary epithelial origin [36, 53]. In some cases, immunopositivity with antibodies targeted to different cytokeratins may be also observed, although this pattern tends to be highly variable. Immunoreactivity to HMB-45, which is typical of melanoma, proves negative in these cases [36, 48, 49, 53].

### 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 presenting with good vision, management with local resection via iridocyclectomy may be advised as recurrence is not expected after resection [39]. 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 there is evidence of growth or if a biopsy indicates malignancy, local excision or enucleation should be considered [50, 51]. Radiation therapy does not seem to be effective [36]. Proton beam radiotherapy of such a tumor was followed by neovascular glaucoma, which resolved only after the "toxic tumor" was excised [54].

## Summary

Tumors arising from the ciliary epithelium are rare. 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. The presence of medulloepithelioma should be considered in a child with a history of PPB and vice versa. Acquired neoplasms of the pigmented or nonpigmented ciliary epithelium may be benign (adenoma) or malignant (adenocarcinoma), and the clinical differentiation between the two may often 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. If clinically suspected, these tumors are often managed by local resection (iridocyclectomy), episcleral brachytherapy, or enucleation.

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# 7 Primary Central Nervous System and Retinal Lymphoma

Mary E. Aronow, Manmeet S. Ahluwalia, David M. Peereboom, and Arun D. Singh

## Introduction

Primary central nervous system lymphoma (PCNSL) is an aggressive, extra-nodal non-Hodgkin's lymphoma (NHL). This predominantly B-cell malignancy is associated with a median survival ranging from 1 to 8 years depending on factors such as age and Karnofsky performance status [1]. PCNSL originates in the brain parenchyma, spinal cord, leptomeninges, and eyes. Formerly used descriptors such as "reticulum cell sarcoma" and "microgliomatosis" are no longer used as both misleadingly imply that the malignancy arises from transformed reticulum or microglial cells. Vitreoretinal lymphoma (VRL) is a variant of PCNSL characterized by ophthalmic involvement. The distinction between VRL and other forms of ocular lymphoma that affect the adnexal structures and/or uveal tract is important, as the latter are most commonly indolent, B-cell lymphomas that behave similarly to their systemic counterparts [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 central nervous system (CNS) remains uncertain. As the CNS and eyes lack lymphatic networks, 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 or seeding through a shared vascular supply [3].

Animal models have the potential to improve our current understanding of lymphoma pathogenesis in humans. Early work in this area focused on murine models created by intraperitoneal or intravitreal injection of T-cell lymphoma, while more recent murine models have used human B-cell lymphoma cell lines in order to more closely mimic the human disease state [4]. Intravitreal injection of human B-cell lymphoma (cell line CA46) into severe combined immunodeficient (SCID) mice sacrificed at sequential time points revealed tumor infiltration first at the retinal surface, followed by migration through

M. E. Aronow (✉)
Massachusetts Eye and Ear, Ocular Melanoma Center and Retina Service, Harvard Medical School, Boston, MA, USA
e-mail: mary_aronow@meei.harvard.edu

M. S. Ahluwalia · D. M. Peereboom
The Rose Ella Burkhardt Brain Tumor & Neuro-Oncology Center, Cleveland Clinic, Cleveland, OH, USA

A. D. Singh
Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA


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the retina and progression through the subretinal space, and eventually spread to the choroid and the CNS [5]. While choroidal involvement is seen in animals, lymphoma cells typically do not cross Bruch's membrane in humans.

There are no known risk factors in immunocompetent individuals; however, congenital immunodeficiency and iatrogenic or acquired immunosuppression such as human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) are risk factors. PCNSL develops in as many as 6% of patients with AIDS [6]. Epstein-Barr virus infection of B lymphocytes in the absence of T-cell suppressor function (due to immunosuppression) leads to an uncontrolled lymphocytic proliferation [7]. While the vast majority of PCNSL are of the diffuse large B-cell lymphoma subtype, rare cases can be secondary to human T-cell lymphotropic virus type 1 (HTLV-1) infection [8].

## Clinical Features

### Epidemiology

PCNSL represents about 1–2% of extra-nodal lymphomas and 4–6% of primary brain tumors. The age-adjusted annual incidence of PCNSL is approximately 4.8 per million population in the United States. 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 (HAART), the incidence has decreased significantly in this population. However, the incidence among immunocompetent patients has been rising, for unclear reasons [9]. While VRL is frequently seen in the setting of PCNSL, the incidence is unknown due to the paucity of cases. Between 1999 and 2002, approximately 100 new cases of VRL were reported in the United States [10].

Among immunocompetent individuals, the peak incidence of PCNSL occurs between the fifth and seventh decades, with a mean age of 60 years at diagnosis [11]. In the immunocompromised population, the disease occurs in younger individuals. Intraocular involvement may precede, occur simultaneously, or follow the CNS disease. Intraocular involvement is the presenting feature in VRL, and subsequent CNS involvement develops in 56–85% of patients over a period of 8–29 months [12]. Conversely, nearly 25% of patients with PCNSL will have concomitant vitreoretinal lymphoma at the time of CNS diagnosis [13].

### Symptoms

#### Ophthalmic

Patients may be asymptomatic, but up to 50% present with painless blurred vision, floaters, or both. Bilateral involvement occurs in up to 80% of cases and is typically asymmetric [12]. Asymptomatic individuals may be diagnosed at the time of ophthalmic screening in the setting of known PCNSL. Owing to the nonspecific nature of the ophthalmic manifestations, a diagnosis of VRL is difficult to make on clinical grounds alone, and delay in diagnosis is common. An average time of 2 years from onset of symptoms to histopathologic confirmation of diagnosis of 2 years has been reported [14].

#### Central Nervous System

The brain, spinal cord, and leptomeninges either separately or in various combinations can be involved. Solitary involvement of the spinal cord is rare. 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.

### Clinical Features

#### Ophthalmic

Anterior segment findings in VRL are rare and are also nonspecific but include keratic precipitates, aqueous cells, and aqueous flare. The hallmark feature is vitreous cells (present in up to 50% of cases), combined anterior and vitreous cells (22% of cases), and subretinal pigment epi-

thelial (RPE) infiltrates (18% of cases) [15]. Clumps of cells in the vitreous with an "aurora borealis" appearance are a common finding. Multifocal subretinal pigment epithelial infiltrates are considered to be pathognomonic (Fig. 7.1). Rarer findings include perivasculitis, retinal artery occlusion, optic atrophy, and exudative retinal detachment (Table 7.1).

### Central Nervous System

PCNSL is a rapidly growing tumor, and diagnosis is often established 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 leptomeninges. Leptomeningeal disease is present in up to 40% of cases [16]. Brain lesions can be multifocal, particularly in immunosuppressed individuals.

## 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 segments is required to assess disease extent and laterality. Fundus auto-

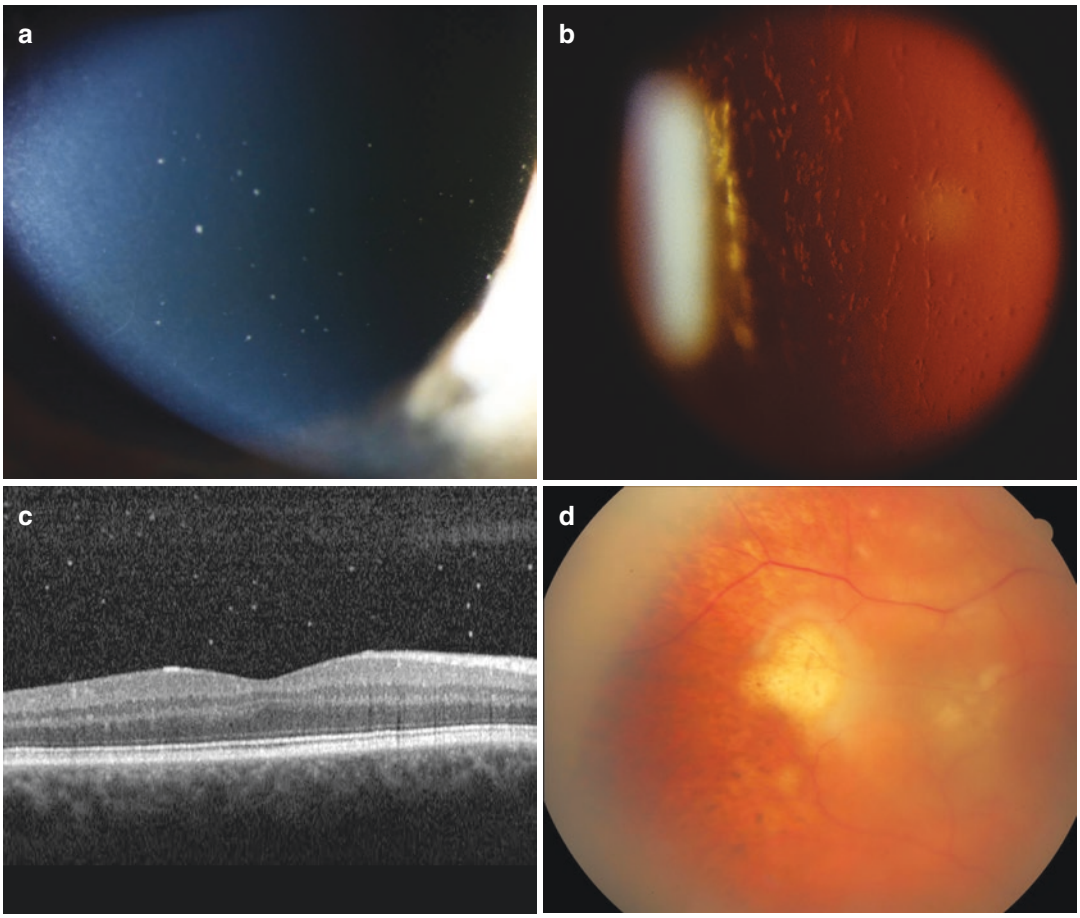


**Fig. 7.1** Slit-lamp photograph showing keratic precipitates (**a**), vitreous cells on transillumination (**b**), large clumped vitreous cells on optical coherence tomography (**c**), creamy subretinal pigment epithelium infiltrates on ophthalmoscopy (**d**), and subretinal pigment epithelium infiltration by optical coherence tomography (**e**). Fluorescein angiography reveals multiple hyperfluorescent pinpoint foci scattered throughout the fundus (**f**)

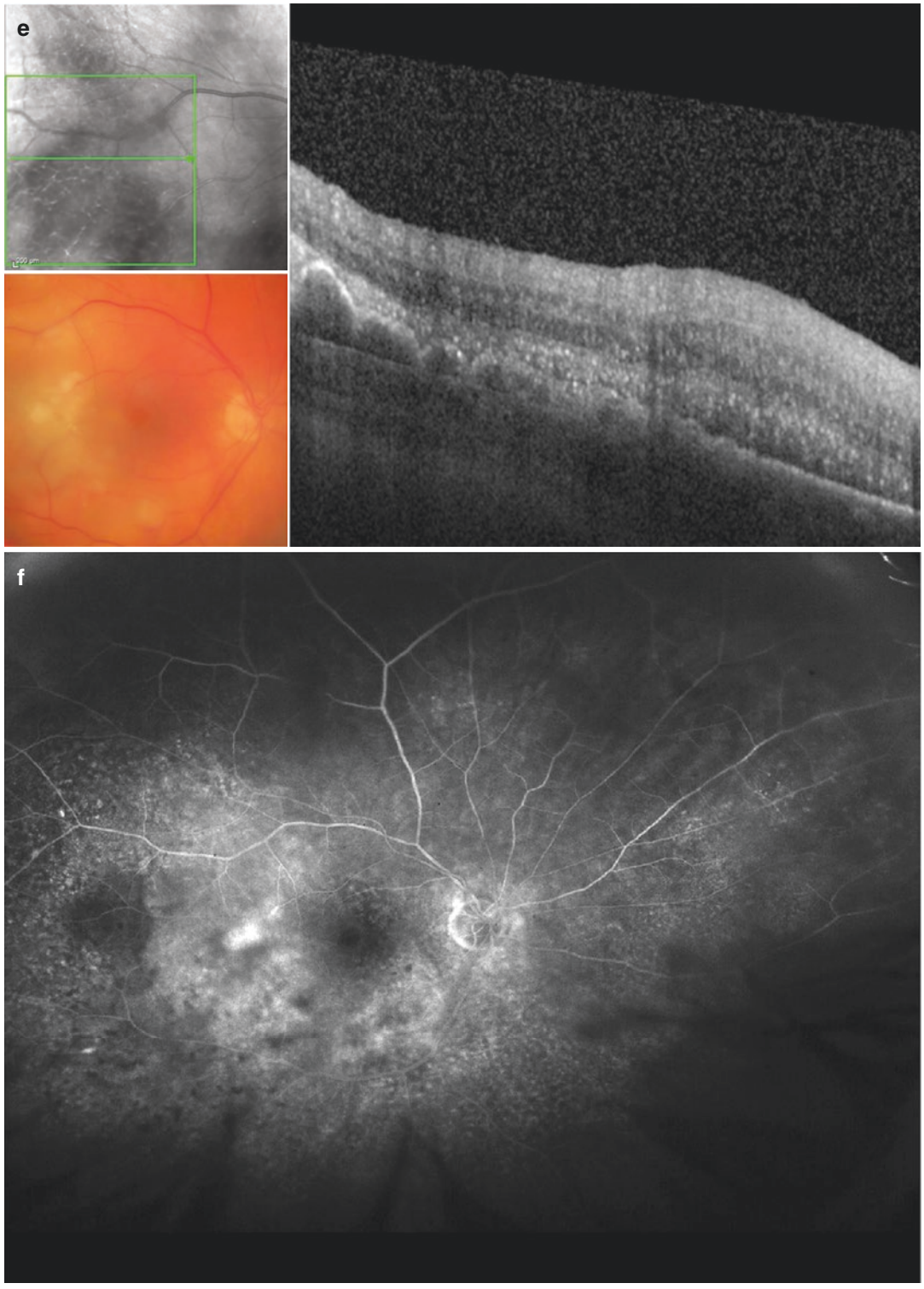


**Fig. 7.1** (continued)

**Table 7.1** Chemotherapy for treatment of primary vitreoretinal lymphoma (VRL)[a]

| Author | Year | Cases/ eyes | 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 + intrathecal | MTX, thiotepa, vincristine, cytarabine | 79 | Recurrence (71)<br>Neurotoxicity (14) |
| Soussain | 2001 | 22 | Refractory/ recurrent | Intravenous | Multiagent chemotherapy with stem-cell rescue | 75 | Recurrence (10)<br>Neurotoxicity (35) |
| Smith | 2002 | 16/26 eyes | Initial | Intravitreal | MTX 400 μg | 100 | Recurrence (12)<br>Cataract (73)<br>Epitheliopathy (58)<br>Maculopathy (42)<br>Vitreous hem (8)<br>Optic atrophy (4)<br>Endophthalmitis (4) |
| Batchelor | 2003 | 9 | Initial | Intravenous | MTX High dose | 78 | Recurrence (40) |
| Kitzmann | 2007 | 5 | Initial | Intravitreal + intravenous | Rituximab + MTX | 100 | None |
| 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 leukopenia (40) |
| Hashida | 2012 | 20 eyes | MTX intolerance | Intravitreal | Rituximab | 100 | IOP increase (60)<br>Iridocyclitis (35) |
| Larkin | 2014 | 48 eyes | Initial/ refractory | Intravitreal | Rituximab and/or MTX | 65 | Recurrence (23) |
| Riemens | 2015 | 21 | Initial | Intravitreal + intravenous | Multiagent chemotherapy | — | Recurrence (36)<br>Renal failure (10) |
| Akiyama | 2016 | 10 | Initial | Intravitreal + intravenous | MTX | 100 | Recurrence (40) |
| Shields | 2017 | 3 eyes | Initial | Intravitreal | Melphalan | 100 | None |
| Abu Samra | 2018 | 51 eyes | Initial | Intravitreal + intravenous | MTX and/or rituximab | 100 | — |

*Abbreviations: BBB* blood-brain barrier disruption with mannitol, *MTX* methotrexate
[a]Excludes single-case reports

fluorescence (AF) is helpful in diagnosis and in monitoring progression of vitreoretinal lymphoma [17]. Active lesions appear as hyper-AF lesions as compared with inactive (atrophic) lesions that appear as hypo-AF. In general, hyper-AF lesions correspond with hypofluorescent appearance on the fluorescein angiography [18]. The hyper-AF is explained on the basis of RPE and photoreceptor disruption by the sub-RPE lymphoma infiltrates, which can be appreciated on optical coherence tomography (OCT) [19]. After treatment, as active lesions become inactive (atrophic), the AF pattern correspondingly changes from that of hyper-AF to hypo-AF (Fig. 7.2) [20].

The relationship between VRL and PCNSL is variable with intraocular involvement preceding, occurring simultaneously, or following CNS manifestations. It is therefore recommended that

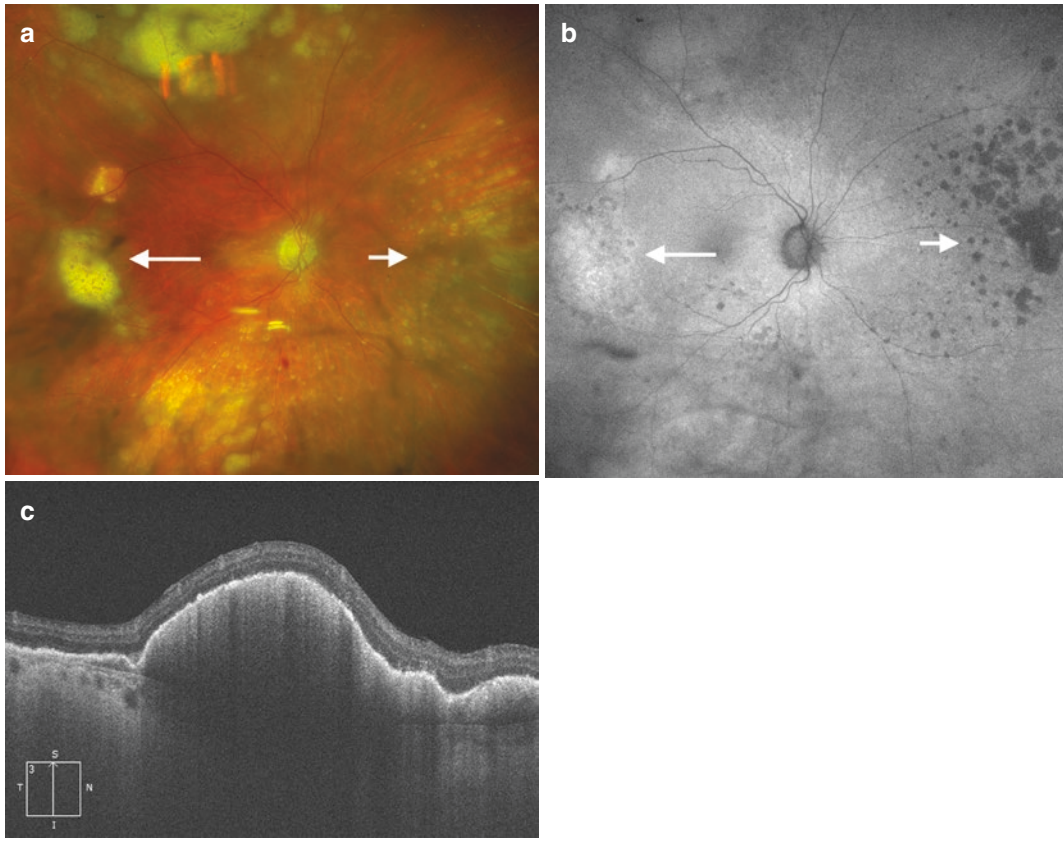


**Fig. 7.2** Fundus photograph of vitreoretinal lymphoma (**a**). Note active lesion (large arrow) and inactive atrophic lesions (small arrow). With AF using green laser source (532 nm, Optos system), the active lesion appears hyper-AF (large arrow) as compared with inactive (atrophic) lesions that appear hypo-AF (**b**, small arrow). The hyper-AF is explained on the basis of RPE and photoreceptor disruption by the sub-RPE lymphoma infiltrates (**c**)

individuals with VRL undergo a thorough evaluation by a medical oncologist to exclude CNS involvement at the time of initial diagnosis and periodically thereafter (Fig. 7.3). Similarly, periodic ophthalmic examinations should be part of the diagnostic evaluation and subsequent management of individuals diagnosed with PCNSL.

## Ophthalmic

In the absence of known PCNSL, the diagnosis of VRL may be suspected based upon clinical features, but diagnosis relies on confirmatory histopathology. Biopsy should be considered in middle-aged or elderly patients with "idiopathic" uveitis, particularly in cases that are initially responsive to steroids but are recurrent. 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. 7.4). When analyzing fresh samples, proper and rapid handling of vitreous samples is critical, as aspirates are generally of low cellularity and neoplastic cells undergo rapid lysis. The laboratory should therefore be informed of the impending arrival of the specimen even before the biopsy is performed. If a delay of more than 1 h is anticipated, then a mild fixative, such as CytoLyt, should be used.

Diagnostic pars plana vitrectomy is frequently performed for diagnostic confirmation. A com-

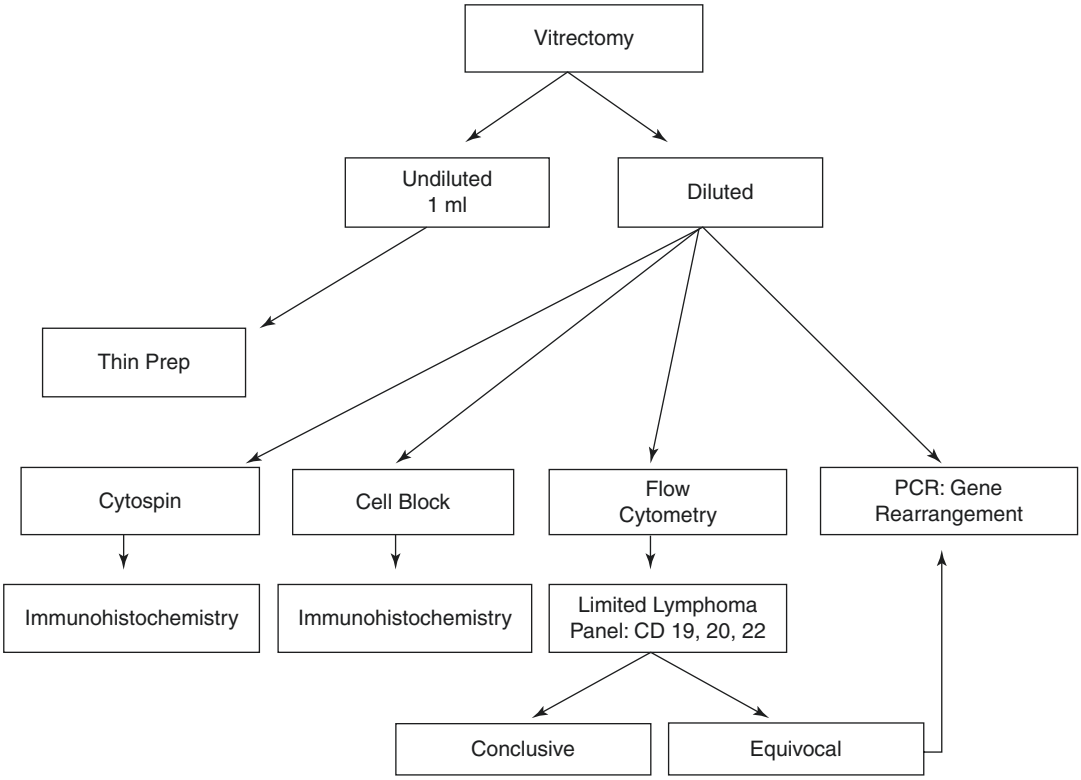


**Fig. 7.3** Schema for analysis of vitreous samples for suspected lymphoma. Initial undiluted vitreous specimen (about 1 ml) is processed by ThinPrep for liquid-based cytology because it preserves the cellular details. The diluted vitreous sample is divided into four portions for cytospin, cellblock, and flow cytometry. Gene rearrangement studies are performed if the flow cytometry results are equivocal. (Based on data from Rishi et al. [21])

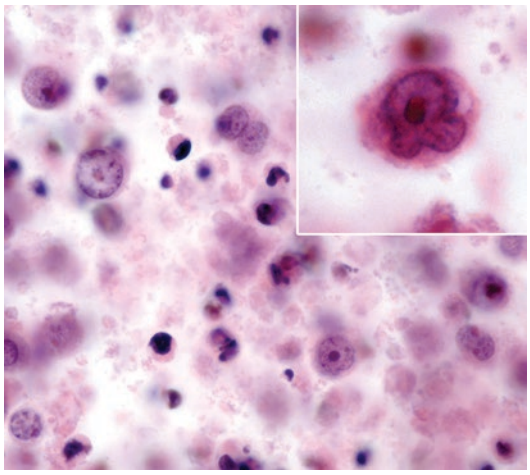

**Fig. 7.4** Vitrectomy sample containing large atypical lymphocytes, necrotic lymphoid cells, and nuclear debris. Inset shows characteristic nuclear membrane protrusions and a prominent nucleolus (main figure, Millipore filter, hematoxylin, and eosin; original magnification Å ~ 250). (Courtesy of Ralph C. Eagle Jr., MD)

mon technique is to obtain an undiluted vitreous sample of about 1–2 ml prior to the start of the infusion during vitrectomy. Some surgeons indent the globe to do this and others inject air. Following collection of the first sample, the infusion fluid is started, and a second diluted specimen is obtained using gentle vitreous cutting. Some centers submit the vitreous cassette as a third sample. If being processed fresh, specimens should be delivered to the laboratory within 1 h of surgery. Failure is not uncommon. Multiple vitreous biopsies may need 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 [22].

When vitreous cells are minimal or absent and subretinal pigment epithelial infiltrates are the pre-

dominant feature, a chorioretinal biopsy may be preferable. A technique has been described, where 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 is created that is large enough to allow the entrance of the vitreous cutter and suction tubing. With gentle cutting, several samples are obtained. Subretinal aspirates should be placed in a mild cytofixative, such as herpes-glutamic acid buffer-mediated organic solvent protection effect (HOPE) fixative or CytoLyt (Cytyc) [23].

Approximately 97% of VRL cases are diffuse large B-cell lymphoma (the remaining 3% are T-cell and other rarer forms) with characteristic histologic and cytologic features [24]. Cells are two to four times larger than normal lymphocytes and pleomorphic and have scant cytoplasm. The nuclei may be round, oval, or indented, with conspicuous nuclear membranes, occasional finger-like protrusions, and multiple, prominent, eccentrically located nucleoli (Fig. 7.4). Mitoses are frequently observed. With the use of electron microscopy, intranuclear inclusions, cytoplasmic crystalloids, and pseudopodal extensions of the cytoplasm, cytosomes, and autophagic vacuoles can be identified [25].

Due to limited cellularity, it can be difficult to reach a conclusive diagnosis based solely on cytopathologic findings. Ancillary techniques include immunohistochemistry, flow cytometry, gene rearrangement studies using the polymerase chain reaction (PCR), and determination of interleukin levels. Immunohistochemistry can be used to identify markers for leukocytes (CD45), B cells (CD20, CD79a, PAX-5), T cells (CD45RO), and macrophages (CD68) [26]. VRL frequently expresses MUM1/IRF4, BCL6, and BCL2 and typically lacks CD10 and plasma cell markers (such as Vs38c and CD138) [27]. The use of antibodies directed against $\kappa$ and $\lambda$ light chains can be used to establish clonality [28]. PCR-based tests are used to detect monoclonal proliferation of B lymphocytes, clonal heavy chain immunoglobulin gene rearrangement, bcl-2 gene translocation, and T-cell gene rearrangements. Flow cytometry provides a means to quantitatively assess the proportion of cells in a given sample that demonstrate these markers. An elevated ratio of interleukin-10 (IL-10) to interleukin-6 (IL-6) has been shown to be suggestive of VRL [29]. While helpful as supportive evidence for diagnosis, the interleukin ratio alone as a diagnostic tool is not clearly established, and cases with VRL with low interleukin ratios have also been reported [30]. Recently, MYD88 mutations have been shown to occur frequently in VRL, and their detection may improve the diagnostic yield of vitrectomy specimens [31].

## Central Nervous System

Cranial 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. 7.5). Meningeal enhancement with gadolinium is indicative of meningeal involvement. CT scans of the chest, abdomen, and pelvis are performed 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 males over age 60 years because of frequent CNS involvement in testicular lymphoma.

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. Systemic nodal and/or visceral involvement is rare at the initial diagnosis but is not uncommon in the terminal stages.

## 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 considered a CNS disease and requires systemic

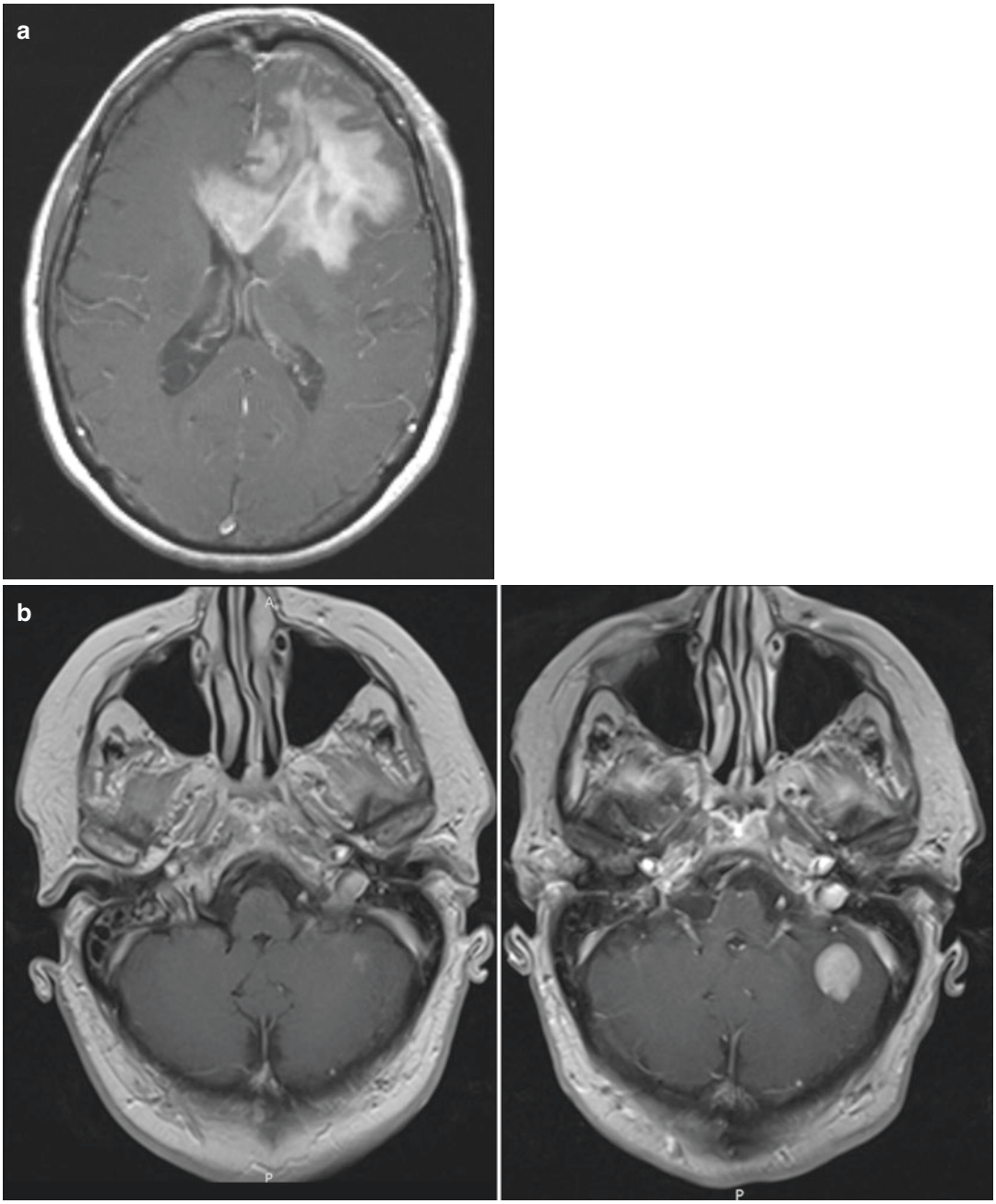


**Fig. 7.5** T1-weighted MRI of the brain with gadolinium contrast, showing a diffusely enhancing area in the left frontal lobe (**a**) T1-weighted MRI at the time of diagnosis of VRL (left) and 4 weeks following session of oral steroids (right). There is obvious CNS involvement in the cerebellum which underscores the importance of steroid avoidance at the time of initial staging (**b**). (**a**: Reprinted from Singh et al. [32]. With permission from Elsevier)

therapy. Whipple's disease is a rare, multi-organ infection caused by the bacterium *Tropheryma whipplei*. Middle-aged Caucasian men in the United States and continental Europe are most frequently affected [33]. 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.

Vitreous amyloidosis can also mimic the clinical appearance of VRL (Fig. 7.6). This rare entity is usually observed in the setting of systemic amyloidosis, although localized ocular involvement can occur. Vitreous involvement appears to be linked to the hereditary neuropathies associated with mutation of amyloid protein transthyretin (TTR) [34]. 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. 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. 7.7). Retinal

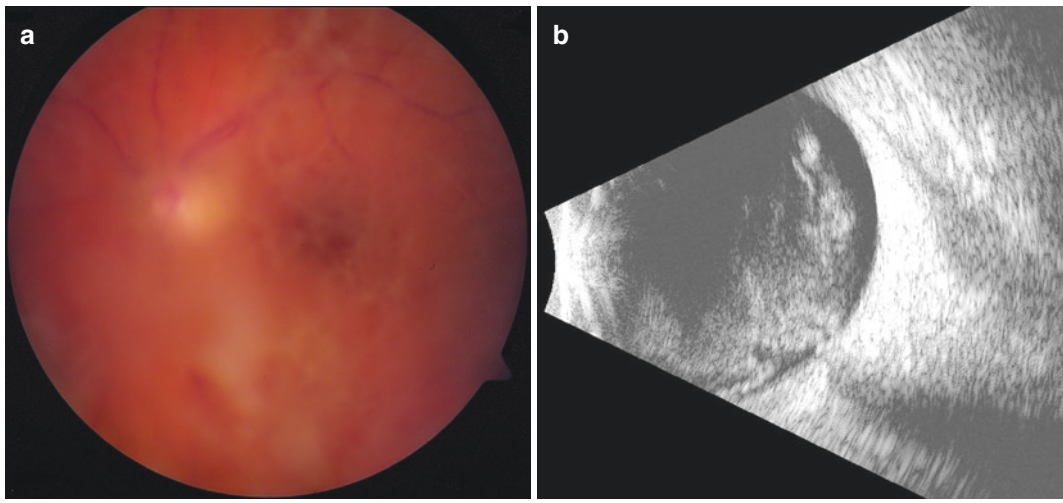


**Fig. 7.6** Vitreous amyloidosis can mimic the clinical appearance of vitreoretinal lymphoma. The vitreous deposits are amorphous, predominantly in the posterior vitreous and overlying the posterior pole (**a**) and be observed as dense vitreous opacities on ultrasonography (**b**)

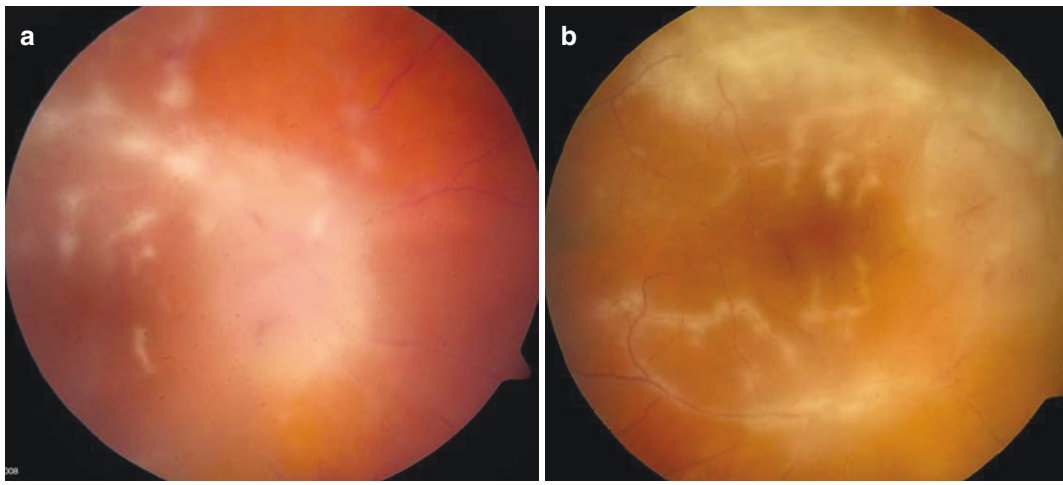


**Fig. 7.7** The right optic disc, surrounding retina, and perivascular areas show inflammatory infiltrates in a patient with HTLV-1 retinitis (**a**). Following vitrectomy 6 weeks from initial photographs, the perivascular infiltrates are seen more distinctly (**b**). (Reprinted from Agarwal et al. [35]. With permission from Wolters Kluwer Health, Inc.)

biopsy with subsequent light microscopy evaluation, immunophenotypic studies, and PCR to detect clonal T-cell receptor gene rearrangement may be required for definitive diagnosis [36].

Choroidal tumors including metastasis and amelanotic melanoma can also mimic VRL. HIV infection predisposes to both opportunistic infections and VRL; 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 VRL should be differentiated from diffuse unilateral subacute neuroretinitis, birdshot retinochoroidopathy, multifocal choroiditis, multiple evanescent white-dot syndrome, and punctate inner choroidopathy. While intravascular lymphoma can occur, when perivascular infiltrates are present, conditions such as ocular sarcoidosis and retinal vascular disorders should be considered. Patients with systemic lymphoma, not arising in the CNS, develop choroidal rather than retinal infiltrates and are more likely to have a superimposed viral or fungal retinitis rather than an intraocular lymphoma.

## Treatment

PCNSL is sensitive to corticosteroids; therefore, exposure to corticosteroids should be avoided in suspected cases until tissue diagnosis is confirmed. The treatment of PCNSL has evolved in recent years, and there is a general consensus that regimens containing high-dose methotrexate yield better response rates and outcomes than regimens that do not contain high-dose methotrexate. A schema outlining an approach of management is shown (Fig. 7.8).

## Ophthalmic Treatment

Management of VRL should ideally be undertaken in partnership with an oncologist with expertise in lymphoma. As a high percentage of patients with VRL eventually develop CNS disease, some experts recommend that the treatment goal for VRL should be to eradicate 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. At present there is a lack of compelling evidence to suggest that ocular treatment prevents subsequent development of CNS disease.

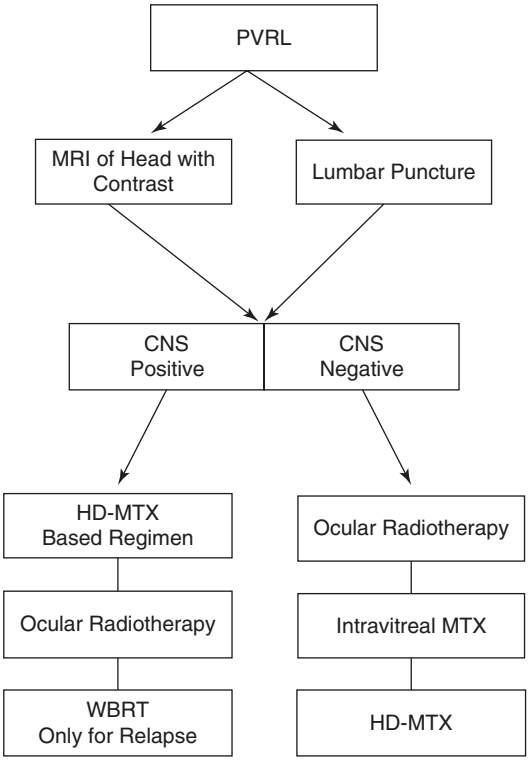


**Fig. 7.8** Schema outlining our current approach of management of patients with VRL. HD-MTX, high-dose methotrexate; WBRT, whole-brain radiation therapy

### Local Therapy for VRL

Options for local treatment for VRL include intravitreal delivery of therapy and ocular radiation. There has been no prospective, randomized clinical trial that has compared these two therapies directly. At present, most experts prefer intravitreal chemotherapy over ocular radiation as first-line therapy. Intravitreal methotrexate as primary therapy has been investigated with

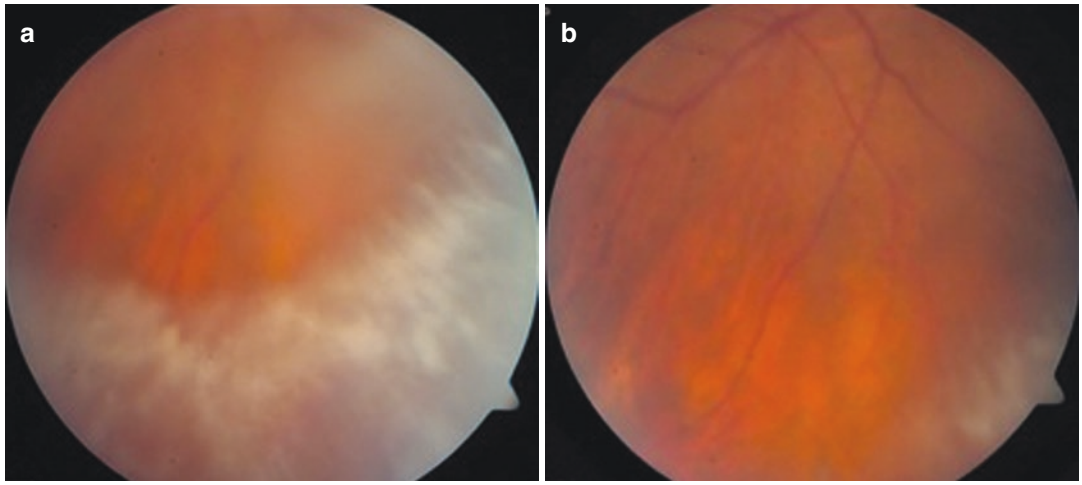


**Fig. 7.9** Fundus appearance before (**a**) and after 3 months (induction and consolidation) of treatment with intravitreal methotrexate (**b**). Note dramatic clearance of vitreous cells

encouraging results (Fig. 7.9; Table 7.1). In one study, 44 eyes (26 patients) were treated with intravitreal methotrexate (400 μg/0.1 ml saline) administered according to an induction-consolidation-maintenance regimen given over the course of 1 year [37]. Clinical remission was achieved after a mean of 6.4 ± 3.4 (range, 2–16) injections of methotrexate, and 95% of eyes required less than 13 injections to reach a complete response [37]. While intravitreal methotrexate is fairly well tolerated, complications of therapy include corneal epitheliopathy, conjunctival hyperemia, increased intraocular pressure, cataract, maculopathy, and rarely vitreous hemorrhage [37]. Rare instances of hypotony have been observed. Intravitreal rituximab alone or used in combination with methotrexate has also shown encouraging results in smaller series. In one study, 48 eyes (34 patients) were treated with a median of 3.5 intravitreal injections of rituximab (1 mg/0.1 ml saline) for new diagnosis of VRL (68.8%), progressive disease (29.9%), and maintenance therapy (2.1%) [38]. Intravitreal rituximab ± methotrexate was the sole treatment in 19 (39.6%) of these eyes. A total of 31 eyes (64.6%) achieved a complete response (CR), following a median of 3 injections. Another 11 eyes (22.9%) achieved partial response (PR). Recurrent disease developed in 7 eyes [38]. Using a combination approach with intravitreal methotrexate and rituximab is attractive, as it may decrease the number of methotrexate injections and overall treatment-related side effects. More recently, there has been early evidence that low-dose intravitreal melphalan (10 μg /0.1 ml saline) may be suitable as first-line local therapy. In a small series of three eyes with cytologically confirmed VRL, a single intravitreal injection of melphalan achieved rapid tumor clearance from the vitreous in two eyes, and tumor control was achieved after six bimonthly injections in the third eye [39]. While further investigation is needed, intravitreal melphalan may be a reasonable treatment option and has the potential advantage of requiring fewer injections.

Prior to the use of intravitreal therapy, external beam radiotherapy (EBRT) was widely used as first-line treatment. Radiation remains an important option, particularly for patients with advanced bilateral involvement, for those who may not tolerate intravitreal chemotherapy, or for individuals who cannot return for multiple repeated injections. EBRT, or more recently intensity-modulated radiation therapy (IMRT), is delivered with a dose range of 30–50 Gy, divided into small (1.5–2.0 Gy) fractions [40]. While radiotherapy can achieve ocular control in the majority of cases, there is no evidence to suggest that its use prevents the development of CNS disease (Fig. 7.10). Due to the high incidence of bilateral disease, irradiation to both eyes should be considered for patients with biopsy-confirmed

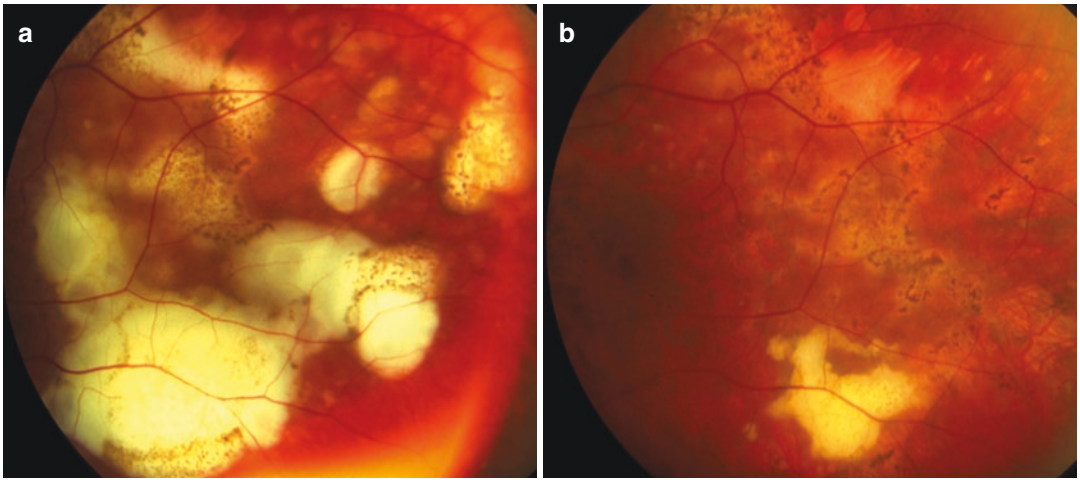


**Fig. 7.10** Fundus photograph of the left eye demonstrating multiple creamy subretinal pigment epithelial deposits (**a**). Regression of the subretinal tumors following external beam radiotherapy at a total dose of 45 Gy (**b**). (Reprinted from Agarwal et al. [35]. With permission from Wolters Kluwer Health, Inc.)

VRL. As whole-brain radiotherapy (WBRT) may have significant side effects, its use for prophylaxis in patients without proven CNS involvement is not advisable. Lenalidomide may be a reasonable alternative to radiation for relapsed or refractory cases [41, 42].

## Systemic Therapy for VRL and Risk of Subsequent CNS Disease

Disease relapse in the CNS is a major issue, particularly after local treatment with ocular radiotherapy or intravitreal chemotherapy. Systemic chemotherapy offers the potential advantage of simultaneous treatment of both ocular and microscopic intracranial diseases (Table 7.1). High-dose methotrexate is most commonly used in the treatment in PCNSL. Batchelor and colleagues reported their experience in nine patients with intraocular lymphoma treated with intravenous high-dose methotrexate at a concentration of 8 g/m$^2$ [43]. 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 CR in six and PR in one. Unlike PCNSL, experience with combination chemotherapy in VRL is extremely limited. Sandor and colleagues reported 100% response rate (11 CRs, 3 PRs) in 14 patients (5 with intraocular involvement) 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 observed, the duration was limited, and additional therapy was required due to relapse [44].

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. 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 [45].

In a report of 221 immunocompetent patients with PCNSL and/or VRL, Grimm and colleagues reported no difference in disease progression rates or overall survival in patients treated with local therapy versus those who received systemic therapies. This series, although the largest to date, was an uncontrolled, multicenter, and retrospective study that utilized different treatments depending on the preference of the treating physician [46]. It is possible that a combination of intravitreal and systemic chemotherapy may prolong the time to relapse [47].

A recent multicenter European study reported on outcomes of 78 patients treated at

17 centers based upon physician preference. Patients received ocular radiotherapy and/or ocular chemotherapy (31 patients), extensive systemic treatment (21 patients), and a combination of ocular and extensive systemic treatment (23 patients); 3 patients did not receive treatment. Extensive therapy included various combinations of systemic and intrathecal chemotherapy, whole-brain radiotherapy, and peripheral blood stem-cell transplantation. Overall, there was no difference at the rates of development of CNS disease (absent initially) between treatment groups (36% at a median follow-up of 49 months).

At the present time, there is a lack of compelling evidence that systemic chemotherapy will prevent the development of CNS disease. Moreover, its use has been associated with more severe adverse effects compared with local treatment [48]. An individualized patient-specific approach is generally recommended (Box 7.1).

### Box 7.1 Salient features of Primary Central Nervous System Lymphoma

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

## Central Nervous System

In the past, WBRT was the mainstay of treatment for PCNSL. This resulted in improvement in median survival to 12–18 months, compared to 4 months for untreated individuals [49]. In the 1990s, clinical trials using a combination of methotrexate-based chemotherapy and radiotherapy reported a further improved median survival of 40 months [49]. The combination of WBRT and chemotherapy is associated with a significant risk of neurotoxicity in older individuals (dementia); therefore chemotherapy alone is frequently selected over WBRT for individuals over age 60 years. More recently, reduced dose WBRT (23.4 Gy) has been combined with chemotherapy resulting in minimal neurotoxicity [50].

Gamma Knife radiosurgery (GKRS) has been studied in a prospective, observational cohort of 128 patients with histologically confirmed PCNSL. Patients were treated with either methotrexate (dose of 8 g/m$^2$) alone (control, 73 patients), or they received methotrexate plus GKRS (dose of 11–16 Gy, median 11 Gy) (55 patients). After a follow-up period of 24–49 months (mean, 36.9 months), the median survival rate from initial diagnosis was 26.8 months in the chemotherapy group and 47.6 in the chemotherapy, plus GKRS, group ($p$-value, 0.0034). All lesions treated with GKRS demonstrated a complete response based on MRI 3–8 weeks (mean range, 6.3 weeks) following therapy [51].

As the blood-brain barrier restricts drug entry into the CNS, various strategies to overcome this have been evaluated. These include the use of high-dose chemotherapy, intrathecal drug delivery, intraventricular drug delivery by a reservoir, and temporary disruption of the blood-brain barrier (BBBD) with mannitol infusion [49]. In a large multi-institutional experience of 149 newly diagnosed PCNSL patients (with no prior WBRT) who 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 progression-free survival and overall survival of 1.8 and 3.1 years, respectively [52]. Maculopathy is an

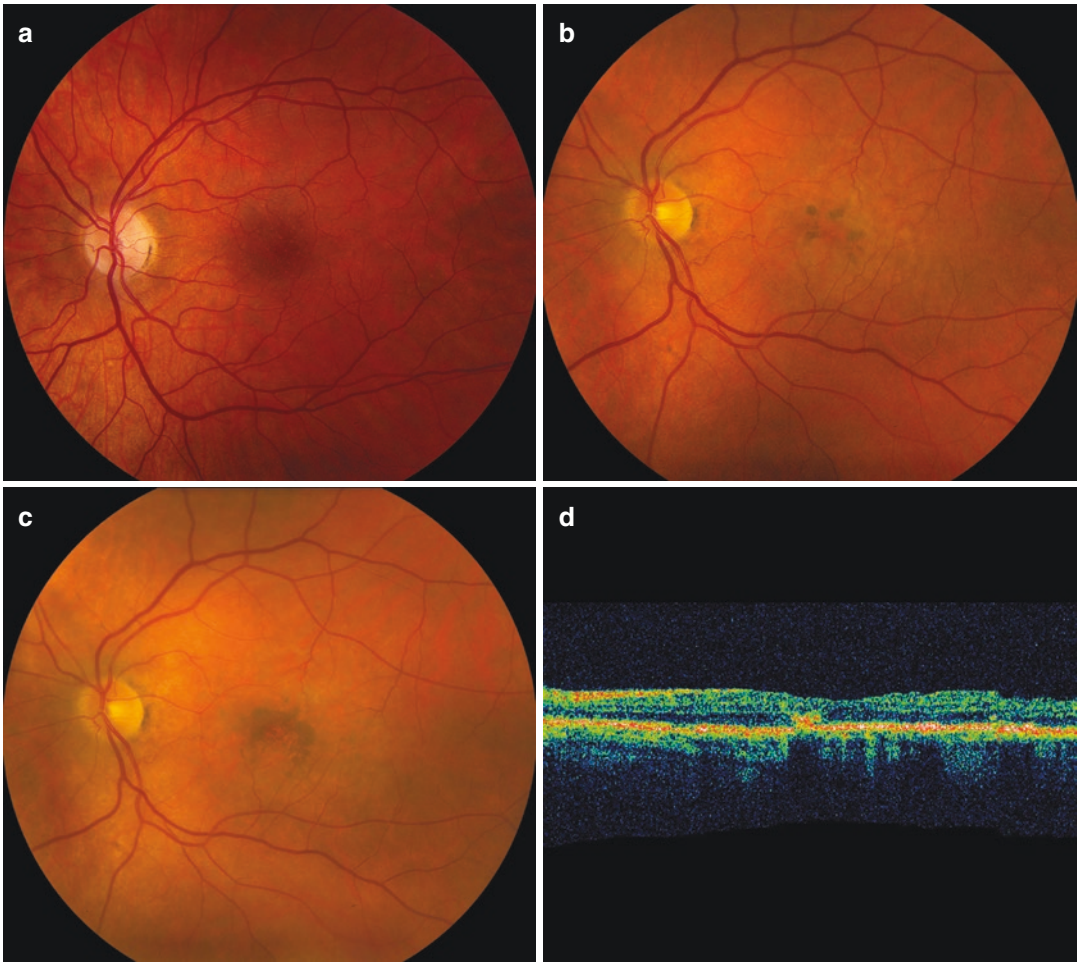


**Fig. 7.11** Color photographs of left fundus from two patients with primary central nervous system lymphoma treated with blood-brain barrier disruption therapy demonstrating the spectrum of hyperpigmentation and retinal pigment epithelium (RPE) loss within the macula. Mild and moderate severity (**a**). Second patient 4 months after completion of treatment (**b**). Note progression of retinal pigment epithelium changes (**c**). Optical coherence tomography showing irregular thickening of the retinal pigment epithelium (**d**). (Reprinted from Galor et al. [53]. With permission from Elsevier)

ocular complication associated with BBBD with mannitol (Fig. 7.11). 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 an 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 decision to use WBRT and its timing and dose are still unclear, given the significant risks of late neurotoxic effects. Further evaluation is needed to investigate the role of radiation in upfront treatment of PCNSL.

For recurrent or refractory PCNSL, small molecules have recently been investigated. Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, has been studied at doses of 560 mg and 840 mg daily. In the 560 mg trial, 52 patients with recurrent PCNSL or ocular lymphoma were enrolled

in a French study, and the overall response rate (ORR) was 50% after two cycles of ibrutinib [54]. In the 840 mg trial, 20 patients with recurrent PCNSL and secondary CNS lymphoma achieved an ORR of 75% [55]. Immune checkpoint inhibitors have also recently been investigated. In a recent series of five patients (four with relapsed/refractory PCNSL and one with CNS relapse of primary testicular lymphoma), the anti-PD1 antibody nivolumab resulted in a 100% clinical and radiographic response. Of these, three patients had progression-free survival at 13–17 months which suggested that nivolumab may be useful in the treatment of relapsed/refractory PCNSL [56]. This initial small study resulted in a subsequent multicenter trial to investigate single-agent nivolumab in PCNSL and testicular lymphoma (NCT02857426). In addition, a single-institution trial with pembrolizumab (NCT02779101) is ongoing to investigate the role of PD-1 blockade in PCNSL.

## Prognosis

Survival of patients with PCNSL following WBRT is poor, ranging from 12 to 18 months, but may increase following high-dose methotrexate-based chemotherapy alone or when used in combination with radiation [57]. Age less than 60 years at diagnosis and high initial performance status are well-recognized favorable prognostic factors in PCNSL. The International Extranodal Lymphoma Study Group has devised a prognostic scoring system utilizing five variables associated with poor prognosis: 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) [58]. Involvement of the brain stem and leptomeninges also portend an unfavorable prognosis. The presence or absence of vitreoretinal involvement in the setting of existing CNS disease does not appear to be a prognostic factor that influences overall survival.

## Summary

Primary central nervous system lymphoma (PCNSL) is a variant of extra-nodal non-Hodgkin's lymphoma (NHL), a high-grade malignancy predominantly of B-cell origin. There are no known risk factors in immunocompetent individuals; however, congenital immunodeficiency and iatrogenic and acquired immunosuppression (HIV/AIDS) are risk factors for PCNSL. The brain, spinal cord, leptomeninges, and eyes, either separately or in combination, can be involved. Patients may be asymptomatic, but up to 50% present with painless blurred vision, floaters, or both. The hallmark diagnostic features are vitreous cells and subretinal pigment epithelial infiltrates. Diagnostic techniques including vitreous, retinal, and subretinal biopsy are needed to establish diagnosis in most cases. There is a general consensus that regimens containing high-dose methotrexate (at least 3.5 G/m$^2$), with or without WBRT, yield better response rates than regimens that do not contain high-dose methotrexate. Disease relapse in the CNS is a major issue, particularly after local treatment with intravitreal therapy and/or radiation. Management should ideally be undertaken in partnership with an oncologist with expertise in lymphoma.

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# Retinal Metastatic Tumors

8

Peter H. Tang, Lejla Vajzovic, and Prithvi Mruthyunjaya

## Introduction

Metastatic tumors to the eye are the most common intraocular malignancy. The usual primary sites are lungs in men and breasts in women [1]. In most cases, intraocular metastasis is limited to the choroid; however, other ocular structures such as the vitreous, optic nerve, iris, and, rarely, the retina may be involved.

Retinal metastasis 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 (RM) and noted that the most common primary sites were cutaneous melanoma, pulmonary carcinoma, and gastrointestinal adenocarcinoma [3].

We identified 42 reported cases of RM, either confined to the retina or also involving the vitreous, published in the English literature from 1935 to 2017 (Table 8.1). Most cases present unilaterally. The right (OD) and left (OS) eyes are involved equally. In most cases, there is a known history of primary non-ocular malignancy at the time of RM diagnosis. The most common primary malignancies which develop RM are cutaneous melanoma, pulmonary carcinoma, breast adenocarcinoma, gastrointestinal carcinoma, and uterine adenocarcinoma.

## Pathophysiology

For tumors to metastasize to other regions of the body, such as the eye, they must dissociate from the primary tumor, transgress the basement membrane, and intravasate into the systemic hematologic and lymphatic circulation [47–50]. These processes are initiated by a complex series of cellular changes called epithelial-to-mesenchymal transition (EMT) [51, 52]. EMT allows cancer cells to gain migratory capabilities through changes in the expression of binding proteins such as cadherins and integrins as well as through production of proteolytic enzymes that degrade the extracellular matrix to facilitate invasion through surrounding connective tissue [47, 48, 50, 52–54]. EMT has also been shown to activate the TGFβ pathway to transform cancer cells to a stem cell-like state, which endows them with the capacity to self-renew and differentiate, contributing to metastasis [55–57].

Metastatic cells gain access to the eye hematogenously. The intraocular location of metastases depends on several factors, such as vascular circulation patterns and molecular factors that promote growth within specific tissue

P. H. Tang · P. Mruthyunjaya (✉)
Department of Ophthalmology, Byers Eye Institute, Stanford University School of Medicine, Palo Alto, CA, USA
e-mail: prithvi9@stanford.edu

L. Vajzovic
Duke University Eye Center, Durham, NC, USA


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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 | Gastroesophageal 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 veillike 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 | |

**Table 8.1** (continued)

| Author(s) | Age | Sex | Primary tumor (if known at time of eye symptoms) | Signs | Specimen for histopathology | Histopathology | Survival (months) |
|---|---|---|---|---|---|---|---|
| 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 | Transscleral 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 cytologic 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 |

**Table 8.1** (continued)

| Author(s) | Age | Sex | Primary tumor (if known at time of eye symptoms) | Signs | Specimen for histopathology | Histopathology | Survival (months) |
|---|---|---|---|---|---|---|---|
| | 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 ora serrata | | | |
| Spadea et al. (1998) [24] | 40 | F | Cutaneous melanoma (yes) | Vitreous pigment; yellow-white vascularized lesion in the superior peripheral retina | Transscleral resection | Epithelioid pigmented 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 nonpigmented cells; pigmented mass in superotemporal retina in OD | PPV in OD | Pigmented pleomorphic melanoma cells in OD | 12 |
| | | | | Dense vitreous hemorrhage mixed with large nonpigmented 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 | Suspected 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 |

(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) |
|---|---|---|---|---|---|---|---|
| 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 | | |
| 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 adenomatous 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 | | | |

**Table 8.1** (continued)

| Author(s) | Age | Sex | Primary tumor (if known at time of eye symptoms) | Signs | Specimen for histopathology | Histopathology | Survival (months) |
|---|---|---|---|---|---|---|---|
| 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) |
| Shields et al. (2014) [40] | 64 | F | Lung carcinoma (yes) | White retinal mass with intrinsic vascularity and vitreous hemorrhage | FNAB | Malignant cells | NS (alive 4 months later) |
| | 45 | M | Malignant melanoma (yes) | Vitreous seeds, retinal whitening | Enucleation | | NS (alive 17 months later) |
| | 59 | M | Malignant melanoma (yes) | Subretinal fluid, retinal whitening | Enucleation | | 1 month |
| | 85 | F | Malignant melanoma (yes) | Vitreous seeds, vitreous hemorrhage, retinal whitening | Enucleation | | 1 month |
| | 56 | F | Esophageal carcinoma (yes) | Retinal whitening, subretinal fluid | None | | 1 month |
| | 58 | F | Breast carcinoma (yes) | Retinal whitening, subretinal fluid | None | | 1 month |
| | 55 | F | Malignant melanoma (yes) | Retinal whitening | None | | 1 month |
| | 75 | F | Breast carcinoma (yes) | Yellow retinal mass with intrinsic hemorrhage and surrounding exudation | None | | NS |
| Taubenslag et al. (2015) [41] | 75 | M | Unknown (no) | Yellow-white retinal lesion with scattered hemorrhages, vitreous cell | PPV | Malignant cells | NS (alive 18 months later) |
| Ishida et al. (2017) [42] | 68 | F | Breast adenocarcinoma (yes) | Retinal whitening, peripapillary brown pigmentation, serous retinal detachment | None | | Unknown |
| | 65 | F | Lung adenocarcinoma (yes) | High dome-shaped subretinal lesion, retinal hemorrhages, subretinal fluid, vitreous hemorrhage | None | | NS (alive 3 years later) |
| Essadi I et al. (2017) [43] | 62 | M | Clear cell renal carcinoma (yes) | Retinal whitening with hemorrhage | None | | NS (alive 4 months later) |

(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) |
|---|---|---|---|---|---|---|---|
| Correa de Mello et al. (2017) [44] | 61 | F | Breast adenocarcinoma (yes) | Retinal whitening with intrinsic vessels | PPV | Neoplastic cells | NS |
| Gokmen et al. (2017) [45] | 11 | F | Anaplastic astrocytoma (yes) | Yellow retinal lesions along optic disc | None | | 12 |
| Praidou et al. (2017) [46] | 70 | M | Hepatocholangio-carcinoma (yes) | Single whitish elevated retinal lesion along inferior-temporal arcade, vitreous infiltration, subretinal fluid | PPV | Neoplastic cells | 12 |

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

types [47, 48, 58]. Metastases occur in the choroid commonly than in the retina because the posterior uvea is more vascular [59, 60]. The size of tumor emboli may also play a role [61]. On reaching the secondary site within the eye, tumor cells undergo a reversal process termed mesenchymal-to-epithelial transition so that they regain phenotypic and genotypic properties of the primary tissue [62–64].

## Clinical Features

Presenting symptoms typically include decreased vision (ranging from 20/20 to light perception), floaters, and eye pain. In general, clinical symptoms reflect the size and location of the metastases as well as vitreous involvement and retinal detachment (RD).

Retinal metastases most commonly present as focal yellow-white, intraretinal patches. They are almost always unilateral and solitary; however, bilateral and multifocal presentation has been reported (Fig. 8.1). The ophthalmoscopic appearance of RM may resemble a retinal infarct, since perivascular tumor infiltration can cause retinal opacification along with associated intraretinal hemorrhages and subretinal exudates. As the tumor grows, intraretinal opacification becomes more extensive. Coalescing patches of retinal whitening associated with retinal vascular changes may suggest an infectious necrotizing retinitis caused by cytomegalovirus, herpetic viruses, toxoplasmosis, or other etiologies [39].

In contrast to choroidal metastasis, RM often presents with overlying cellular vitreous infiltration and may masquerade as an intermediate uveitis [26]. Metastasis from cutaneous melanoma can present as large, golden-brown spherules in the vitreous [13, 65, 66]. These differ from other forms of metastatic carcinoma that usually present as nonpigmented vitreous opacities [14]. Irrespective of pigmentation, cellular aggregates within the vitreous in the form of spherules should alert the clinician to the possibility of a neoplastic rather than inflammatory etiology. Glaucoma secondary to the obstruction of aqueous outflow by the accumulation of tumor cells in the trabecular meshwork has been described as an additional feature of RM. RD is an uncommon presenting sign of retinal metastases.

## Diagnostic Evaluation

Clinical examination along with fundus photography and fluorescein angiography may enable differentiation of RM from retinal vasculitis or other vascular occlusive diseases. Optical coherence tomography (OCT) has been used to characterize intraocular tumors, but its precise role in diagnosing RM has yet be established [67].

Confirmatory diagnosis of a RM by biopsy may be beneficial to the patient in several ways. First, it assists in differentiating metastasis from inflammatory conditions having similar clinical features. Second, the cell type identified in the biopsy specimen may indicate the type of cancer and the likely site of origin. Third, biopsy may help guide therapy, for both the primary tumor and the ocular metastasis. Before 1979, most cases of RM were diagnosed at autopsy or after enucleation [3].

Biopsy is being performed more widely to enhance diagnosis. Vitreous infiltrates are sampled by pars plana vitrectomy (PPV), whereas chorioretinal biopsy is performed when there is no vitreous infiltration. In 1988, Eagle reported a case of carcinomatous retinitis which had been diagnosed by vitreous aspirate and eye wall biopsy [68]. In 1995, Balestrazzi et al. described local resection of a retinal metastasis from primary cutaneous melanoma [20], and Spadea et al. later described the technique for chorioretinal biopsy using a transscleral approach [24]. More recently, Payne et al. described an endoresection technique for retinal biopsy of metastases from small-cell lung cancer using PPV, subretinal fluid injection, diathermy, bimanual retinectomy, air fluid exchange, laser, and long-acting gas tamponade. The biopsy site for this procedure was chosen peripherally and at the junction of normal and abnormal retina to minimize visual sequelae and to improve histopathologic evaluation of active disease at the tumor margin [39].

PPV is currently the preferred technique for obtaining vitreous cells for cytologic evaluation. It is crucial to have an experienced cytopathologist interpret the minute quantity of tissue that is obtained. Immunohistochemical stains aid interpretation of the cytology specimen [22, 69]. A negative result does not necessarily rule out metastasis, especially when only the retina is involved [14]. If clinical suspicion is high, even in light of a negative diagnostic PPV, a chorioretinal biopsy may be needed to establish a diagnosis (Fig. 8.1) [38, 39]. We do not routinely recommend fine needle aspiration when there is no mass lesion.

In conjunction with an oncologist, systemic work-up for a primary tumor is recommended in all patients presenting with ocular features suggestive of a RM.

## Differential Diagnosis

Conditions most likely to mimic RM 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, and retinal lymphoma.

## Treatment (Surgical, Chemotherapy, and Radiotherapy)

Treatment of RM is ideally administered by a multidisciplinary team involving ophthalmology, hematology/oncology, radiation oncology, and the patient's primary care physician. It is influenced by several factors including the nature of the primary tumor, extent of systemic metastases, prior therapy, and the overall functional status of the patient.

Over the past 25 years, patients with RM have most often been treated with palliative, hyperfractionated external beam radiotherapy (EBRT). Stereotactic radiosurgery, also known as gamma knife radiosurgery (GKR), has also been shown to be effective in treating ocular malignancies [70–72]. Enucleation is reserved for those with intractable pain. Small groups of patients are treated with systemic chemotherapy alone or in combination with EBRT or local subconjunctival chemotherapy (Table 8.1). Resection of the RM lesion is reserved for patients with solitary, peripheral lesions and may be combined with systemic chemotherapy and EBRT [20, 24, 32]. There is a single report of successful verteporfin photodynamic therapy (PDT) of a well-circumscribed, vascularized tumor in the macula thought to be a RM from breast adenocarcinoma [34]. However, in a recently reported case of vitreous metastasis from melanoma, the metastasis was not effectively treated by systemic immune mod-

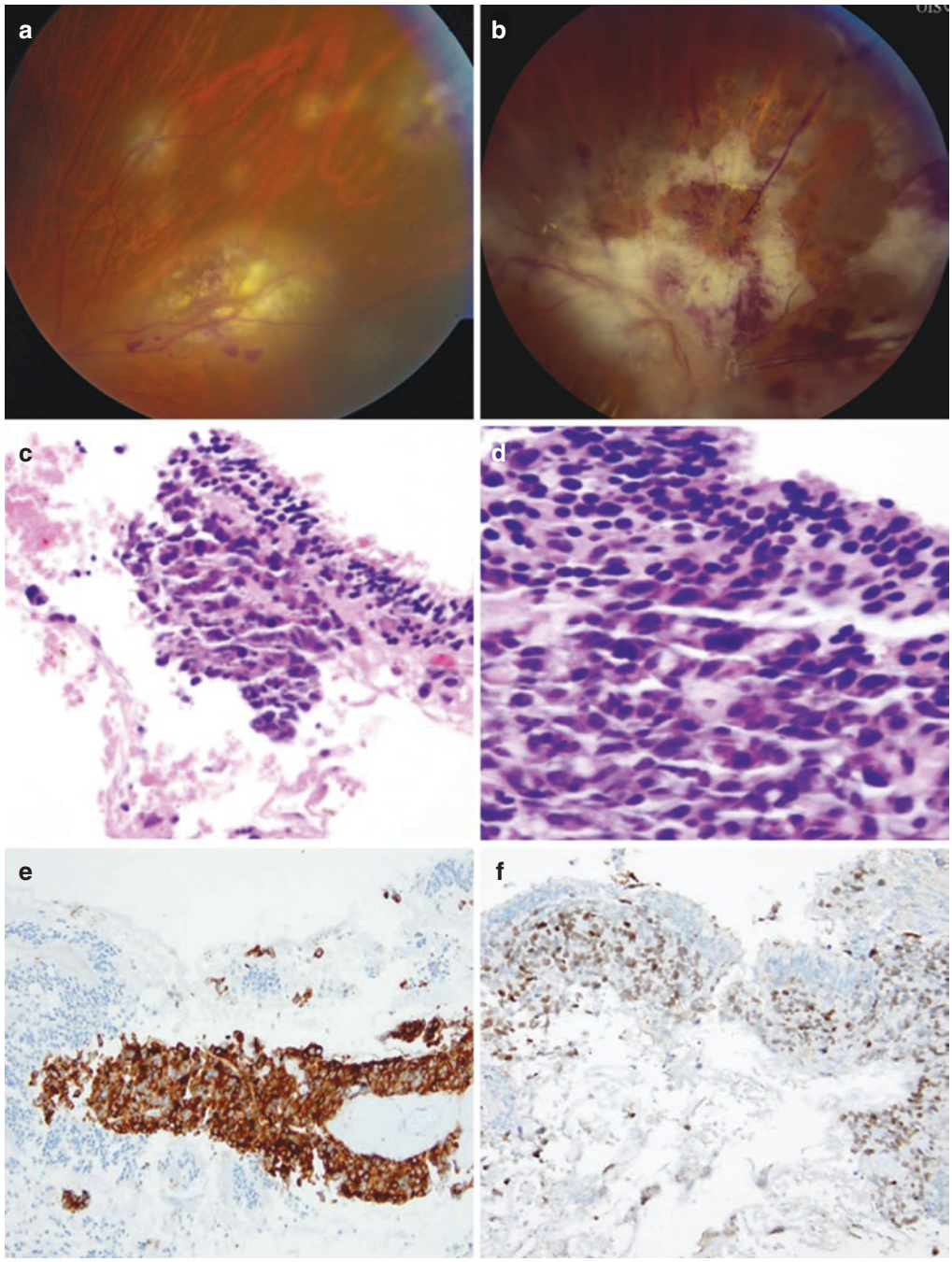


**Fig. 8.1** A 78-year-old Caucasian male with a past medical history of recurrent, small-cell lung cancer (SCLC) presented for evaluation for new-onset floaters and blurred vision in the right eye 10 days after the second cycle of chemotherapy. Anterior segment examination of both eyes and fundus examination of the left eye were unremarkable. The right eye showed a mild cellular vitreous infiltrate and numerous, patchy, white, retinal infiltrates with associated retinal hemorrhages (**a**). In this immunocompromised patient, the presentation was concerning for viral retinitis. The patient was given intravitreal foscarnet in October 2009 (1200 mcg/0.05 mL) and started on IV acyclovir. Intravitreal CMV, HSV, and VZV PCR assays were negative. Serum assays for HSV and CMV were also negative. The serum VZV IgG was positive (consistent with immunity to VZV). Despite antiviral therapy, the retinitis progressed (**b**). Retinal biopsy subsequently revealed small-cell carcinoma involving the retina (**c**)**.** The tumor 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)

ulator such as pembrolizumab [73]. Palliative vitrectomy may be effective [74].

## 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 RM.

## Conclusions

Retinal metastases are rare. The differential diagnosis includes retinal vasculitis and vascular occlusion. Biopsy is useful in confirming the diagnosis and may indicate the site of the primary tumor when this is not known. Treatment usually involves some form of radiotherapy. The management of the patient is best undertaken by a multidisciplinary team. The life expectancy of these patients is poor.

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# 9 Neuro-oculocutaneous Syndromes (Phakomatoses)

Elaine Binkley, Elias I. Traboulsi, and Arun D. Singh

The term phakomatosis is derived from the Greek word phakoma, which means "birth mark." In 1923, van der Hoeve grouped together von Hippel-Lindau disease, tuberous sclerosis, and neurofibromatosis because of their manifestations at birth, autosomal-dominant inheritance, and 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.

E. Binkley
Department of Ophthalmology, Cole Eye Institute (i32), Cleveland Clinic Foundation, Cleveland, OH, USA

E. I. Traboulsi
Department of Pediatric Ophthalmology and Strabismus, Center for Genetic Eye Diseases, Cole Eye Institute (i-32), Cleveland Clinic Foundation, Cleveland, OH, USA

A. D. Singh (✉)
Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: singha@ccf.org

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

### Box 9.1 Characteristic Features of the Phakomatoses

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

## Neurofibromatosis Type 1 (NF1)

### Introduction

Several distinct forms of neurofibromatosis have now been recognized [2]. The most common is


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**Table 9.1** Summary of organ system involvement in various phakomatoses

| Disorder | Clinical features | | | |
|---|---|---|---|---|
| | Neurological | Ocular | Cutaneous | Visceral |
| Neurofibromatosis 1 | Present | Present | Present | Absent |
| Neurofibromatosis 2 | Present | Present | 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 | 9q21 | GNAQ (somatic) | $G\alpha_q$ | Mediates signals between G-protein- coupled receptors and downstream proteins |
| Wyburn-Mason syndrome | Sporadic | – | – | – | – |
| Retinal cavernous hemangioma | Autosomal dominant | 7q21.2, 7p13, 3q26.1 | CCM1, CCM2, CCM3 | KRIT1, malcavernin, PDCD10 | Believed to be involved in endothelial cell function |
| Sebaceous nevus syndrome | Sporadic | – | – | – | – |
| Ataxia telangiectasia | Autosomal recessive | 11q22 | ATM | ATM protein | Protein kinase |
| Neurocutaneous melanosis | Sporadic | – | – | – | – |
| Phakomatosis pigmentovascularis | Sporadic | 19p13.3, 9q21 | GNA11, GNAQ (somatic) | $G\alpha_{11}$, $G\alpha_q$ | Mediates signals between G-protein- coupled receptors and downstream proteins |

neurofibromatosis type 1 (von Recklinghausen disease), followed by neurofibromatosis type 2 (also called central neurofibromatosis) [3]. Other less common types include multiple meningiomatosis, spinal schwannomatosis, and segmental neurofibromatosis [2, 4].

## Genetic Aspects

NF1 is an autosomal-dominant disorder caused by mutations of the *NF1* gene on chromosome 17q11.2 [4]. The penetrance of NF1 mutations is usually complete (100%) [5]. About 50% of all

index cases are due to new mutations, and the large majority (90%) of new mutations are paternal in origin [6]. A wide variety of *NF1* mutations have been described without any genotype-phenotype correlation [7]. The large size of the gene makes screening 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%) [8].

## Pathogenesis

The *NF1* gene codes for neurofibromin [4], a cytoplasmic GTPase-activating protein that negatively regulates oncoprotein *ras* [9]. Loss of *NF1* function in neurofibromas is limited to Schwann cells, indicating that the Schwann cell is the cell of origin of neurofibromas in NF1 [10, 11].

## 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 1/3000 with equal distribution in a variety of 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].

**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 (six or more) | >5 mm in diameter in prepubertal individuals |
| | >15 mm diameter in postpubertal individuals |
| Neurofibroma | Any type: two or more |
| | Plexiform: one or more |
| Axillary and inguinal freckles | |
| Optic nerve glioma | One or more |
| Lisch nodules | One or more |
| A distinctive osseous lesion | Sphenoid wing dysplasia |
| | Congenital bowing or thinning of the long bone cortex, with or without pseudoarthrosis |
| First-degree relative with NF1 | |

Based on data from Ref. [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]. With permission from Elsevier

### Café-au-Lait Macules

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). These spots are present at birth and increase in number and size during childhood. Other forms of hyperpigmentation occur, such as axillary and intertriginous freckling.

### Neurofibroma

Neurofibroma is the hallmark tumor and clinical finding of NF1. Neurofibromas tend to be multiple and develop toward 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.

### Lisch Nodules

The presence of melanocytic hamartomas of the iris, known eponymously as Lisch nodules, is

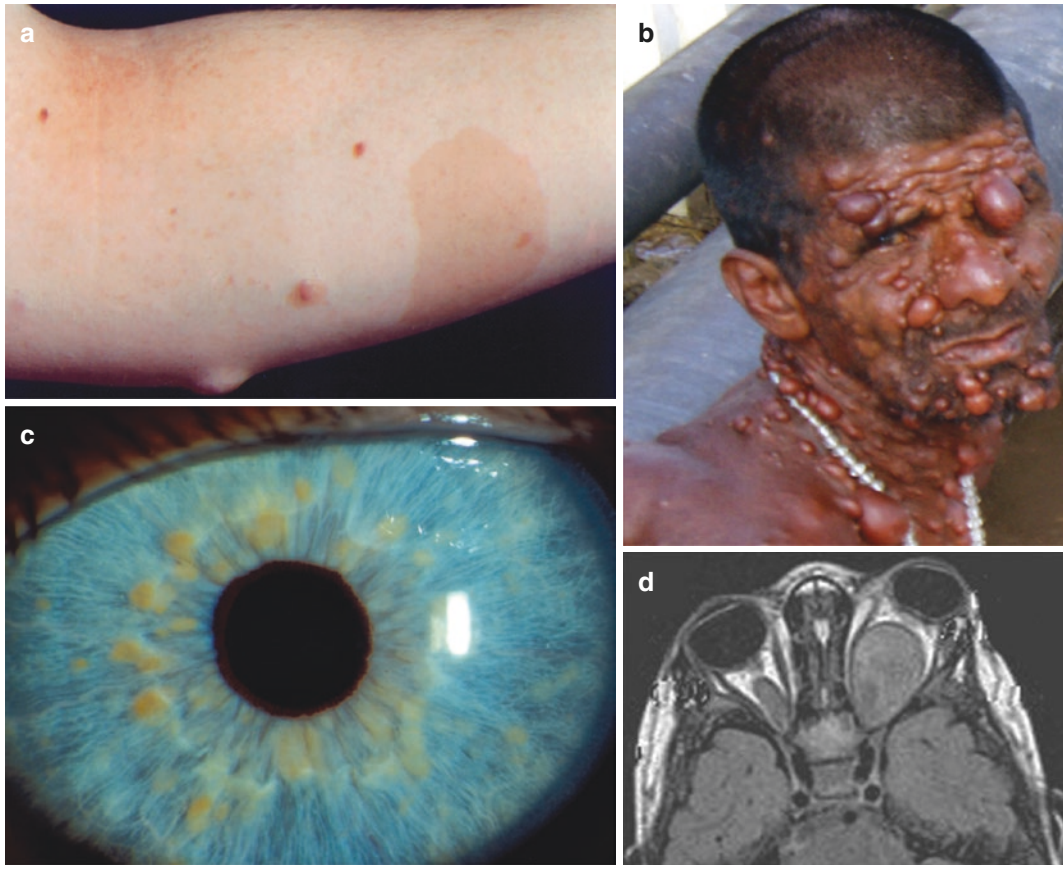


**Fig. 9.1** Common manifestations of NF1. Café-au-lait macules (**a**), multiple neurofibromas of the face (**b**), multiple Lisch nodules (**c**), optic nerve glioma (**d**), and contrast-enhanced magnetic resonance image

highly characteristic of NF1 [16, 17]. Lisch nodules are typically multiple, are tan-colored, and are best detected with the slit lamp on the anterior iris surface, mostly inferiorly (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% in adulthood [14, 18].

## 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 with NF1 (Fig. 9.1d) [20]. Bilateral optic nerve involvement is believed to be pathognomonic of NF1, whereas unilateral tumors tend to be unrelated to this syndrome [21].

## Glaucoma

Glaucoma is common in patients with NF1. There is an association between glaucoma and plexiform neurofibroma of the upper eyelid. Another feature that can be noted is the presence of ectropion uvea (at the pupil margin). This is present in NF1 and may be secondary to endothelialization of the anterior chamber angle. It 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 may be present on the lid, brow, or face of an infant or child, a circumstance commonly referred to as "orbitofacial neurofibromatosis" (OFNF).

In one study, glaucoma was found to be more common in the ipsilateral side in the eyes with orbitofacial involvement and was associated with globe enlargement [23]. Visual loss in patients with orbitofacial neurofibromatosis (OFNF) is common, typically profound, and usually multifactorial. The causes of visual loss include congenital glaucoma with buphthalmos and retinal detachment, disconjugate gaze due in part to distorted skull development causing strabismic amblyopia, and optic nerve glioma. These 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 causes of amblyopia that might be treatable, such as refractive changes, occlusion of the visual axis, and congenital glaucoma. As affected individuals get older, physicians must be vigilant for progressive optic nerve damage caused by glaucoma or optic nerve glioma and must be alert to the possibility of improving vision by refraction [24].

### Other Malignancies

Patients with NF1 also have increased and lifelong risks of developing a variety of malignant tumors, which include breast cancer, duodenal carcinoid tumors, glioblastoma and other brain tumors, gastrointestinal stromal tumors, leukemia, malignant peripheral nerve sheath tumors, pheochromocytoma, and rhabdomyosarcoma [25]. Clinicians need to be aware of these associations so that patients can be appropriately monitored for symptoms associated with the development of these tumors [25–29].

## Diagnostic Evaluation

The NIH consensus criteria are useful for establishing the diagnosis of NF1 in adults as well as in young children. MRI is particularly helpful in detecting optic nerve gliomas. Characteristic "bright lesions" on MRI 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 [30].

## Treatment

Once the diagnosis of NF1 is made, patients need referral to a provider with expertise in managing NF1 for evaluation and counseling regarding the prognosis, genetics, and psychological aspects of the disease [31, 32]. First-degree relatives should also be assessed for signs and symptoms consistent with NF1 [31]. Care of patients with NF1 is complex and may require coordination with experts from multiple subspecialties including dermatology, genetics, neurology, neurosurgery, oncology, ophthalmology, orthopedics, radiology pediatrics, and plastic surgery [25, 31, 32]. Children with NF1 should be examined with an annual physical exam with special attention given to the neurologic exam, skin exam, and monitoring for the development of hypertension that could be due to renal artery stenosis or pheochromocytoma [27, 31]. They should additionally have an ophthalmic exam every 6–12 months from 0–8 years and every 1–2 years until they turn 18 [27, 33]. Exams should include an assessment of visual acuity, pupils, optic disc appearance, and ocular motility [27, 33]. Visual fields and color vision should be assessed once the patient is able to cooperate with these tests [27, 33]. If an optic glioma is diagnosed, MRI should be performed four times a year for 1 year with an increase in the imaging interval over the subsequent 2–3 years [25]. The management of optic nerve glioma remains controversial, and treatment is generally initiated when there is concern for a risk of permanent vision loss [33]. These lesions are often treated with chemotherapy; radiation is avoided because of the risk of inducing secondary malignancy [25]. Therapeutic indications and outcomes with various forms of management, which include observation, chemotherapy, excision, and radiotherapy, are discussed in detail under optic nerve tumors. Children diagnosed with orbital plexiform neurofibromas should also be assessed at least every 6 months prior to age 8 to monitor for amblyopia [34]. While the timing of surgical intervention is controversial, treatment is usually indicated in children under 10 years of age with concern for amblyopia [34].

### Prognosis

Some patients with NF1 have mental retardation, learning difficulties, and other behavioral problems [35]. It is important to note that some manifestations of NF1 tend to develop or increase over time and are not always present at initial diagnosis [36]. For example, Lisch nodules and cutaneous neurofibromas appear more commonly in teenage and young adult patients, while pheochromocytoma and paraspinal plexiform neuroma are more common in adults [36]. 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 from malignancy [37].

## Neurofibromatosis Type 2 (NF2)

### 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).

**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 years |
| First-degree relative with NF2 | Plus | Any two of the following: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract |

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

### 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) [38]. About 50% of the cases represent new mutations [39]. 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 [38, 40]. The *NF2* gene has been mapped to chromosome 22q12 [41]. It encodes a 587 amino acid protein known as merlin or schwannomin.

### Pathogenesis

Merlin acts as a tumor suppressor gene [42]. Disruption of merlin-dependent links of membrane proteins to the cytoskeleton leads to tumor formation [43].

### Clinical Features

The prevalence of NF2 is 1 in 33,000–40,000 [39]. One percent of patients with meningioma and 3% of patients with schwannomas have NF2 [43]. Bilateral vestibular schwannomas (VS) are diagnostic of NF2 (Fig. 9.2a). Ocular abnormalities are present in more than two-thirds of NF2 cases, and common findings include cataracts and retinal hamartomas [44]. The ocular features manifest themselves in childhood and adolescence and are therefore extremely useful in early diagnosis of NF2 [45].

#### Vestibular Schwannoma

Ninety-five percent of patients with NF2 have bilateral VS [46]. The mean age of symptom onset is around 25 years [47]. This is important for the ophthalmologist to note since ophthalmic findings may precede the development of symptoms from VS and identification of characteristic ophthalmic findings may help to lead

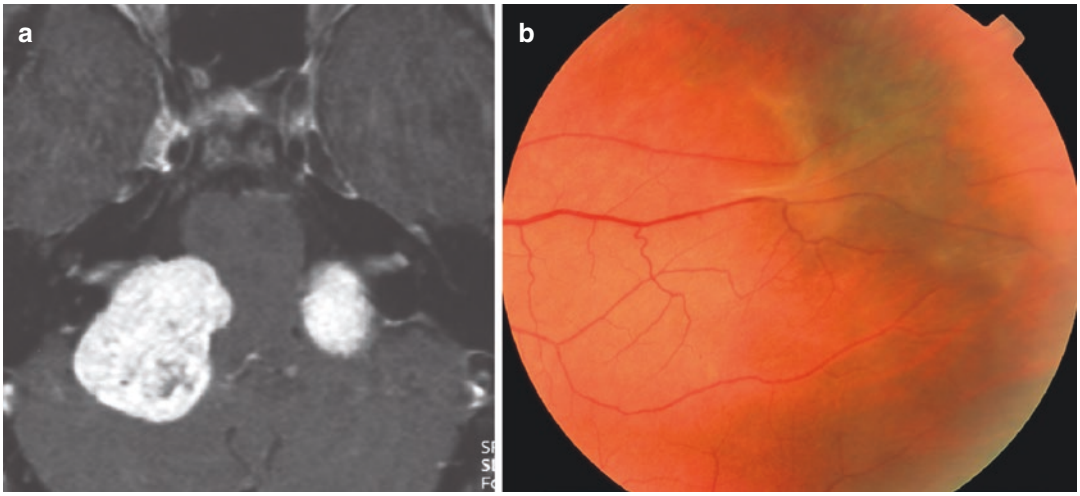


**Fig. 9.2** Bilateral vestibular schwannoma on gadolinium-enhanced magnetic resonance imaging is diagnostic of NF2 (**a**). Fundus photograph of a combined hamartoma of the retina and the retinal pigment epithelium (**b**)

to an earlier diagnosis of NF2 [47, 48]. Symptoms, though, are most commonly due to VS rather than ocular involvement. Deafness with or without tinnitus is most common. Seizures, vertigo, and numbness are less common [49]. There is increased morbidity in NF2 patients with VS due to an increased tumor growth rate [46].

## Ophthalmic Findings

Characteristic ocular manifestations of NF2 include posterior subcapsular cataracts, combined hamartoma of the retina and retinal pigment epithelium (RPE), and epiretinal membranes. Patients may also develop optic disc atrophy caused by optic nerve sheath or intracranial meningioma, and recent work has also suggested that strabismus is more common in patients with neurofibromatosis 2 (Box 9.2) [44, 50–53]. Children with vestibular schwannomas are usually asymptomatic, and ocular findings are therefore of diagnostic significance. In a clinical study of 49 patients with NF2 and their offspring, posterior subcapsular/capsular, cortical, or mixed lens opacities were the most common ocular abnormalities and were present in 67% of patients [45]. Combined hamartoma of the sensory retina and RPE is described as thickened retina with infoldings of the outer layers, gliosis, and associated disorganized proliferation of blood vessels and retinal pigment epithelium [54]. 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 [55] (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. With ERMs that cover the foveal center, the inner retinal layers usually are not displaced centrifugally from the umbo [48]. 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 [48].

### Box 9.2 Characteristic Ocular Abnormalities in Neurofibromatosis 2

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

## Diagnostic Evaluation

Genetic testing is recommended for children of individuals affected with NF2 given that the clinical features may not meet the criteria for diagnosis until later in life [46]. Patients suspected to have NF2 are usually screened by neurological, ophthalmic, and neuro-otologic testing. Magnetic resonance imaging (contrast-enhanced, multiplanar T1-weighted sequences) is a cost-effective first-line investigation in the detection of VS [56].

## Treatment

The management of vestibular schwannomas involves complex decision-making and choosing among various options that include observation, stereotactic radiotherapy, and surgical resection [57].

## Prognosis

Patients with NF2 have a reduced life expectancy. Early age of onset, presence of truncating mutations, and increased number of meningiomas are associated with a worse prognosis [38, 58].

# Von Hippel-Lindau Disease

## Introduction

Eugen von Hippel, a German ophthalmologist, coined the term angiomatosis retinae in 1904 [59]. Arvid Lindau, a Swedish pathologist, established a relationship between cerebellar and retinal hemangioblastomas [60]. It was not until 1964 that 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 [61]. Since then several investigators have studied the natural history of the disease and developed screening protocols [62–64].

## Genetic Aspects

VHL disease follows an autosomal-dominant mode of inheritance with a 90% penetrance by the age of 60 [62, 65]. 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 [66, 67]. Because of significant social and ethical issues associated with genetic testing, patients considering the genetic testing for the VHL disease should undergo expert genetic counseling [68].

## Pathogenesis

The *VHL* gene encodes a 213 amino acid protein that binds with elongin B, elongin C, and Cul 2 to form a complex that targets hypoxia-inducible factors (HIFs), which are the transcription factors that promote angiogenesis, for degradation by proteasomes [69–71]. In the absence of VHL protein (pVHL), there is excessive production of vascular endothelial growth factor [69, 70]. 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 cell within the capillary hemangioma [70].

## Clinical Features

The incidence of VHL disease is 1 in 40,000 to 1 in 54,000 live births. It is estimated that there

**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 lesions[b] |
| Negative | Two or more retinal capillary hemangiomas |
| | Two or more CNS hemangiomas |
| | 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

are approximately 7000 patients with VHL disease in the United States [72]. VHL disease is a multisystem disorder with the predilection for tumors of the 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 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 [62]. Polycythemia can be seen in up to 17% of patients [73]. The cumulative probability of manifesting RCH, CNS hemangioma, and renal cell carcinoma increases with age (Fig. 9.3a) [62].

There seems to be a correlation between the type of *VHL* gene mutation and the clinical features (genotype-phenotype correlation), which has led to a new classification of VHL disease (Table 9.7) [74, 75]. However, a variety of phenotypes can be caused by mutations in the same codon, suggesting that factors such as modifier genes, environmental factors, and the specific amino acid substituted may also play a role [76]. There does not appear to be a specific type of germline mutation that correlates with the presence of RCH [77].

## Retinal Capillary Hemangioma

Retinal capillary hemangiomas (RCH) are the most common tumor in VHL patients and often occur earlier than other tumors [62, 78]. Therefore, the 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% [79]. 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, sex, and laterality of involvement. Eighty-six percent of involved eyes have tumors that can be individually visualized. Tumors are commonly found in the peripheral retina (85%) only and less commonly in the juxtapapillary area (15%). Severe visual impairment (visual acuity = 20/160 or worse) in affected eyes is more likely to be associated with increasing age, the presence of juxtapapillary lesions, and a greater number and extent of peripheral lesions [80].

## Central Nervous System Hemangioma

Commonly involved sites include the cerebellum (75%) and spinal cord (15%) [62]. 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) [81]. Pregnancy in patients with VHL disease can induce the progression of cerebellar hemangioblastoma, and there is a high VHL disease-related pregnancy complication rate [82].

## Renal Cell Carcinoma

Renal cell carcinoma is one of the leading causes of mortality in VHL disease [62, 83, 84]. The risk of developing renal cancer in patients with VHL increases with age. Approximately 70% of patients will develop renal cell cancer if they live to the age

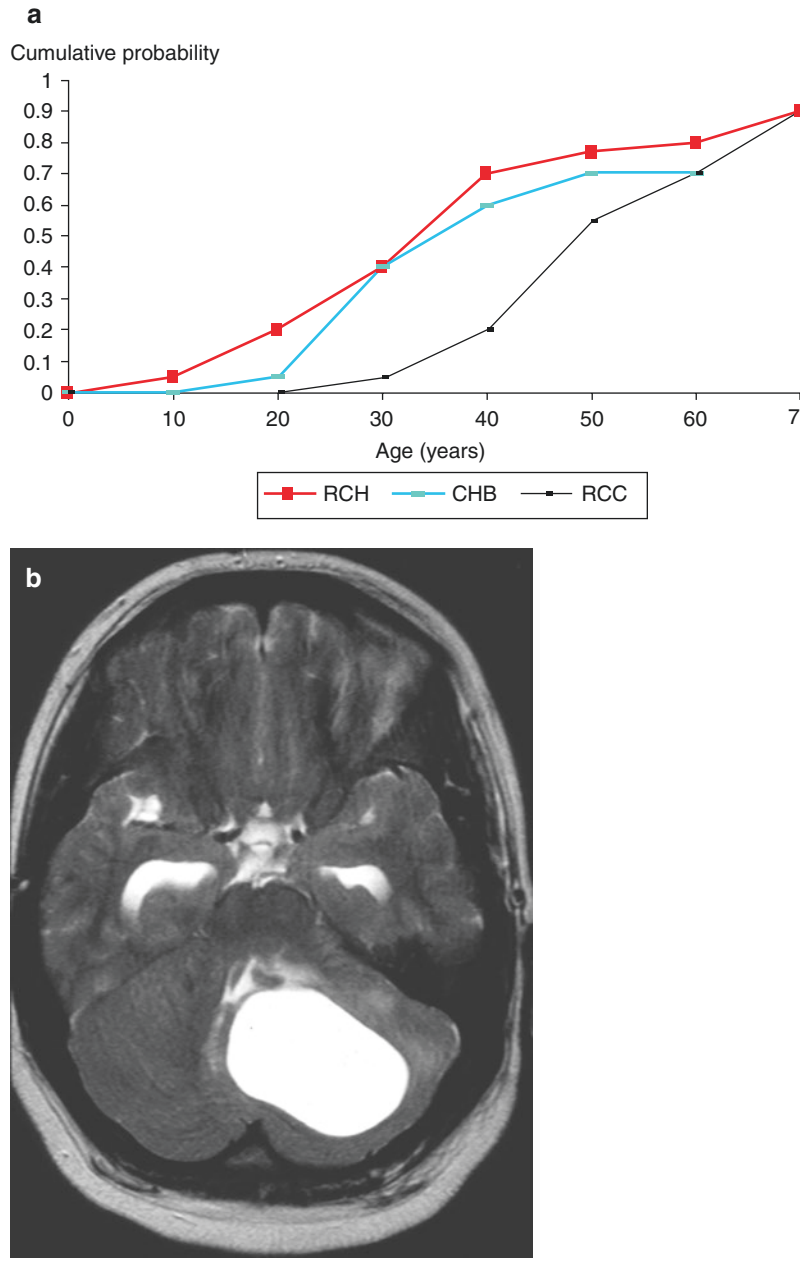


**Fig. 9.3** Cumulative probability of developing retinal capillary hemangioma, cerebellar hemangioma, and renal cell carcinoma in von Hippel-Lindau disease (**a**). Magnetic resonance image (T2 weighted) of a cerebellar hemangioma appearing as a cystic lesion (**b**). A, based on data from Ref. [62]

**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

of 60 years [84]. Compared to patients with sporadic tumors, patients with VHL are more likely to have bilateral and multifocal disease [84].

### Pheochromocytoma

Pheochromocytomas are rare benign tumors of the adrenal medulla. In patients with VHL disease, they tend to be multiple and bilateral [85]. 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), which cause symptoms such as palpitations, headaches, and sweating, sometimes simulating anxiety attacks.

### Other Cancers

Pancreatic tumors and cystadenoma of the epididymis occur less commonly than other tumors. Endolymphatic sac tumor, present in 11% of patients, is a recently recognized feature of VHL disease [86].

## 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 [81]. Asymptomatic renal, adrenal, and other organ involvement can be detected by enhanced computed tomography [64] 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 could help guide molecular interventions in ocular von Hippel-Lindau disease [87].

**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 | Every 2 years |
| | 61 and above | 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

## 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. Treatment options for RCH may include laser photocoagulation, photodynamic therapy (PDT), cryotherapy, and external beam radiation [78]. While there are no large-scale studies investigating the use of intravitreal anti-VEGF injections in treating RCH, several case reports and case series have suggested effectiveness either alone or in combination with PDT [88–90].

## Prognosis

The complications of RCH can be severe and visually significant even in adequately treated cases. More than 25% of patients with RCH show permanent visual loss (vision of <20/40 in one or both eyes) [77]. VHL disease is associated with significant morbidity from CNS hemangioma and renal cell carcinoma. In addition, there is significant mortality from renal cell carcinoma [62]. Recent work has shown that the life expectancy of people with VHL is improving, likely due to improved surveillance and treatment protocols [83].

## Tuberous Sclerosis Complex

### Introduction

The name tuberous sclerosis was suggested by the French physician Désiré-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 [91].

### Genetic Aspects

Tuberous sclerosis complex (TSC) includes two genetic diseases (TSC1 and TSC2), both with autosomal-dominant inheritance and high penetrance (95%) [92]. Two-thirds of cases are sporadic and result from fresh genetic mutations. The genes responsible for TSC, *TSC1* (chromosome 9q34) [93], and *TSC2* [94] have now been identified.

### 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 as well as over 50 other proteins and influence a common cellular pathway [95, 96]. These findings provide the basis for identical clinicopathologic manifestations of TSC1 and TSC2 that result when either of these proteins is inactivated or abnormal in structure.

### Clinical Features

Tuberous sclerosis is characterized by hamartomas of 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. Ocular findings can include astrocytic hamartomas involving the retina and optic disc, hypopigmented areas and hamartomas of the uveal tract, colobomas of the iris and choroid, and eyelid angiofibromas [97]. Visceral hamartomas most commonly involve the lungs, kidney, and heart [92]. 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 [99]. Other findings of TSC1, such as seizures, renal involvement, facial angiofibroma, and retinal

**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 (three 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 (one or more) | 9. Multiple renal cysts |
| 10. Lymphangiomyomatosis | |
| 11. Renal angiomyolipoma | |

The criteria were formulated based on data from the tuberous sclerosis complex consensus conference 1998 (Roach et al. [98])

hamartomas, are also less frequent or less severe compared to TSC2 [100].

### 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 [101]. 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 chorioretinal depigmentation were seen in 39% eyes (Fig. 9.4a). Approximately 40% of patients have angiofibromas of the eyelids [102].

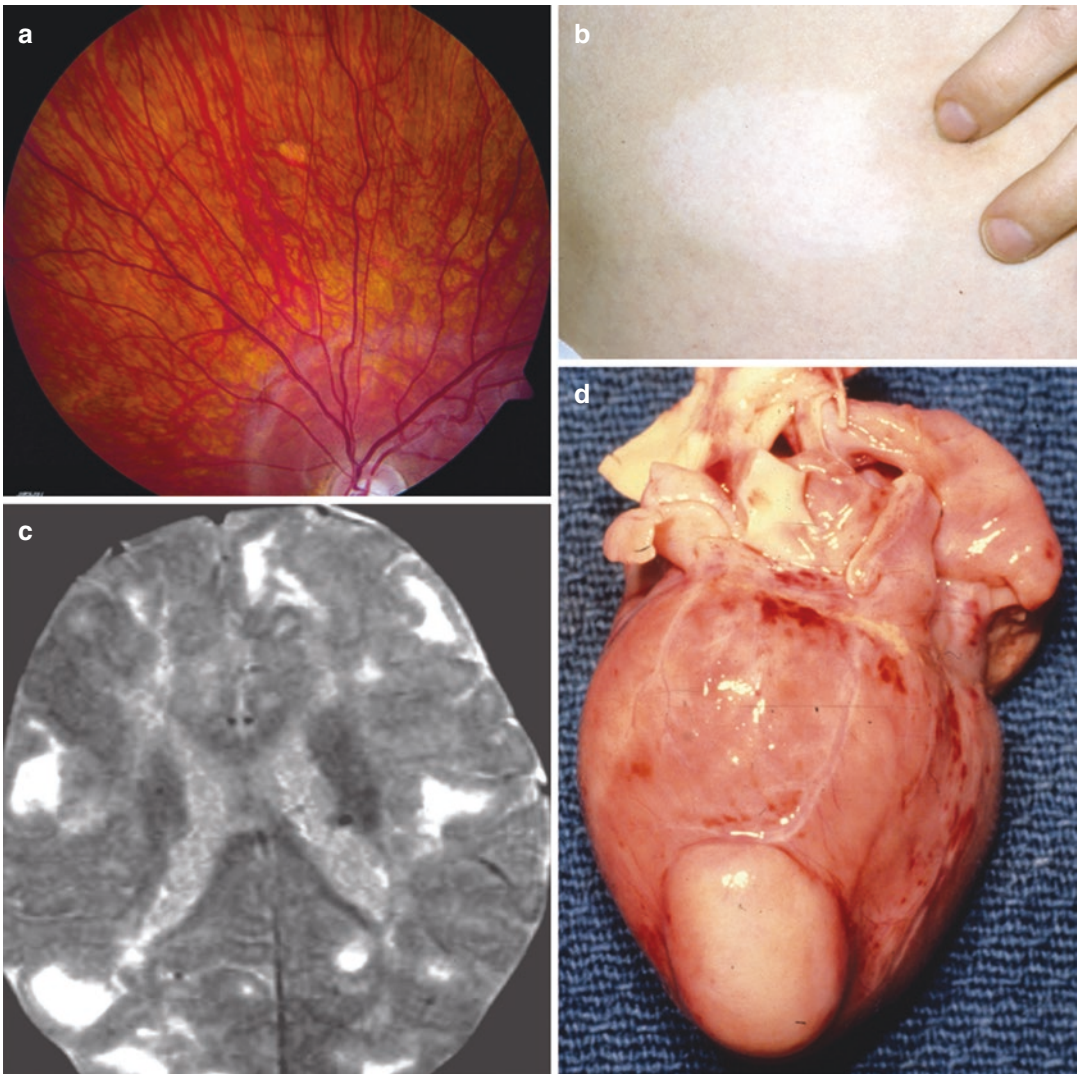


**Fig. 9.4** Common manifestations of TSC. Retinal achromic patch (**a**). The hypomelanotic macules "ash-leaf" sign (**b**), multiple subcortical tubers (**c**), T2-weighted axial magnetic resonance image and cardiac rhabdomyoma (**d**). (Reprinted from Seki et al. [107]. With permission from American Medical Association)

### 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 diagnostic 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. 9.4c) [103].

### Skin Manifestations

Cutaneous manifestations of TSC are mainly of diagnostic significance (Fig. 9.4b). The hypomelanotic macules are the most frequent and the earliest finding of TSC and occur in up to 97% of children (Fig. 9.4b) [104]. They are best visualized with Wood's lamp (UV light). Fibrous plaques appear as reddish orange patches on the forehead. Facial angiofibromas are not present at birth and usually appear by age 5 years. Subungual fibromas appear later in life [105].

### Visceral Manifestations

Visceral manifestations of TSC include pulmonary lymphangiomyomatosis [105], renal angiomyolipoma [106], and cardiac rhabdomyoma (Fig. 9.4d) [107].

## Diagnostic Evaluation

The diagnosis of TSC is clinically based on diagnostic criteria [98]. Imaging studies such as magnetic resonance imaging of the brain and computerized tomography of the abdomen are important to detect CNS and visceral involvement [108]. 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 [109].

## 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. They can cause vision loss through local retinal degeneration or the production of subretinal and intraretinal fluid [110]. Spontaneous resolution of subretinal fluid may occur within 4 weeks. If macular edema with increasing lipid exudates persists for longer than 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 [111]. Intravitreal bevacizumab and intravitreal steroids have also been used to manage symptomatic lesions [110].

Given that mutations in the TSC1 and TSC2 genes result in dysregulation of the mammalian target of rapamycin (mTOR) pathway, a number of recent studies have investigated the use of mTOR inhibitors such as everolimus and sirolimus for the treatment of tumors associated with tuberous sclerosis. This work has shown promise in using systemic everolimus to treat aggressive retinal astrocytic hamartoma, cardiac rhabdomyomas, and renal angiomyolipoma [112–118]. Topical sirolimus has been used to successfully treat cutaneous lesions in a small series of patients [117].

## Prognosis

Retinal astrocytic hamartomas are generally stable with slow growth over several years or new calcification in some cases [101]. 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 [108].

## Sturge-Weber Syndrome

### Introduction

In 1879, Sturge described a syndrome characterized by a facial hemangioma, ipsilateral buphthalmos, and contralateral seizures [119]. Weber in 1922 described radiological evidence of cortical calcification secondary to leptomeningeal hemangioma causing hemiplegia [120]. 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. The predominant manifestation is a diffuse hemangioma of the leptomeninges, the choroid, and the facial skin. The other term for this disorder, encephalofacial hemangiomatosis, emphasizes only the non-ocular manifestations.

### Genetic Aspects

Unlike other phakomatoses, Sturge-Weber syndrome is not inherited. Recent work has shown that Sturge-Weber syndrome is likely caused by somatic activating mutations in the gene *GNAQ* [121].

### Pathogenesis

Shirley et al. have identified somatic activating mutations in *GNAQ* as the likely etiology of Sturge-Weber syndrome [121]. They hypothesize that the *GNAQ* mutation in Sturge-Weber syndrome differs from the *GNAQ* mutations seen in uveal melanoma in that it results in moderate activation of the ERK pathway but has only a limited effect on the JNK pathway. The effects on these pathways may result in the findings seen in Sturge-Weber syndrome by increasing basal signaling downstream of $G\alpha_q$ or by dysregulating G-protein-coupled receptor signaling for proteins such as endothelin during development, which could result in the vascular abnormalities seen in Sturge-Weber syndrome [121]. The precise mechanism by which these mutation result in this syndrome remains under investigation [121].

### 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 syndromes.

#### Glaucoma

Glaucoma is the most frequent manifestation of SWS and occurs in about 70% of all cases [122]. Various pathogenetic mechanisms, such as angle maldevelopment or raised episcleral venous pressure, can lead to glaucoma [123]. The glaucoma is usually diagnosed in the first 2 years of life; however, there is a lifetime risk of developing

**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 the three features essential for diagnosis

glaucoma. The incidence of glaucoma is higher if the eyelids are involved with nevus flammeus [124].

### Diffuse Choroidal Hemangioma

About half of the patients with SWS have a diffuse choroidal hemangioma [122]. 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.

### Leptomeningeal Hemangiomatosis

The leptomeningeal hemangiomatosis is ipsilateral to the cutaneous involvement. This can lead to 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 [125]. There is a correlation between early onset of seizures and the likelihood of developmental delay and behavior problems [126].

### 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 [127]. SWS only occurs in patients who have involvement in the region of V1 or V2 distribution of the trigeminal nerve [127]. 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 [127].

## Diagnostic Evaluation

Contrast-enhanced MRI is most suited for detecting cerebral atrophy and leptomeningeal angiomatous malformations (Fig. 9.5b) [128]. If the MRI is normal, CT scan should be used to detect intracranial calcifications.

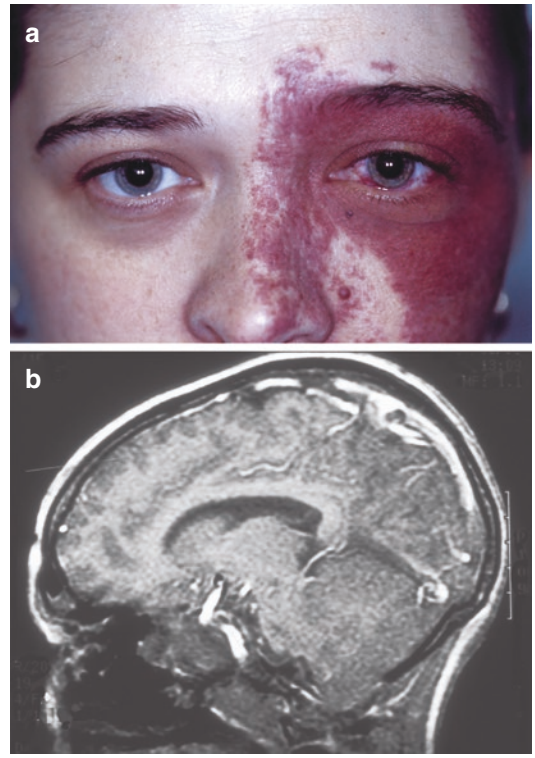


**Fig. 9.5** Typical facial distribution of cutaneous hemangioma (**a**) and leptomeningeal hemangioma (**b**) in Sturge-Weber syndrome

## Treatment

Medical therapy of glaucoma is effective in some cases [124], but many patients eventually require multiple trabeculectomies, combined trabeculotomy with trabeculectomy (Mandal [129]), or even drainage implants [130]. The choroidal hemangioma can be treated with low-dose standard radiotherapy or with proton beam radiotherapy [131, 132]. The treatment of choroidal hemangioma is discussed under uveal vascular tumors. Seizures are generally controlled with medications, but intractable cases require surgical resection of the leptomeningeal angiomatosis with underlying cerebral cortex [133].

PDT is an effective treatment option for visual deterioration from exudative retinal detachment in patients with diffuse choroidal hemangiomas [104–106, 134–136].

### Prognosis

Only limited information is available about the long-term prognosis of patients with SWS. Mental retardation and 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 [125].

## Wyburn-Mason Syndrome

### Introduction

In 1943, Wyburn-Mason described several cases of racemose hemangiomas of the retina and brain and established an association between these vascular malformations [137]. Some authors refer to this entity as Bonnet-Dechaume-Blanc syndrome [138]. Unlike other phakomatoses, there is no cutaneous involvement in Wyburn-Mason syndrome.

### Genetic Aspects

Wyburn-Mason syndrome is a nonhereditary sporadic disorder.

### Pathogenesis

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

### Clinical Features

The clinical findings are usually congenital in origin, but the diagnosis is generally not made until 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% [139]. Conversely, only about 8% of cases with intracranial arteriovenous malformations have retinal arteriovenous malformations (Table 9.11) [139].

**Table 9.11** Clinical features of Wyburn-Mason syndrome

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

#### 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 [140]. The clinical features of retinal arteriovenous malformations are described in detail elsewhere (Chap. 3).

#### Intracranial Arteriovenous Malformation

The intracranial arteriovenous malformations in the chiasmal region can lead to neuro-ophthalmic presentations [141]. Patients present in the second or third decades of life 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 [142].

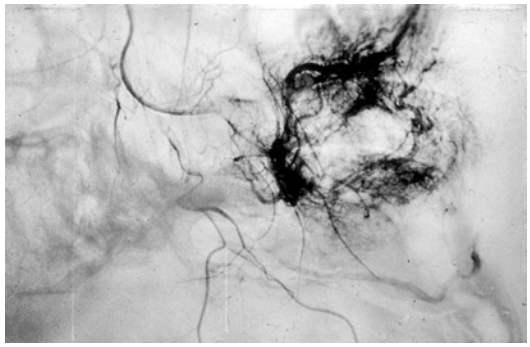

**Fig. 9.6** The intracranial arteriovenous malformation seen on arteriography

## 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).

## 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.

## Prognosis

The retinal vascular anomalies may sometime lead to vascular occlusions [143] and retinal ischemia with development of neovascular glaucoma [144]. Hemorrhages from midbrain hemangiomas can be fatal.

# Retinal Cavernous Hemangioma

## Introduction

Retinal cavernous hemangioma is a rare benign vascular tumor. Clinically, two forms are recognized: sporadic and syndromic [145]. Retinal cavernous hemangiomas can be associated with cerebral cavernous malformations as an autosomal-dominant syndrome with high penetrance and variable expressivity [146, 147]. 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 [145].

## 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 (*MGC4607*); and CCM3 is caused by mutation in the *PDCD10* gene [148, 149]. It is thought that the proteins encoded by these genes are involved in endothelial cell function [150]. Familial CCM has autosomal-dominant inheritance [151].

## Pathogenesis

Cavernous hemangiomas are considered to be congenital hamartomas that are composed of multiple, thin-walled, dilated, vascular channels and surface gliosis [145]. The walls are lined by normal-appearing endothelium, explaining the lack of exudation [152].

## Clinical Features

All patients diagnosed with a retinal cavernous hemangioma should undergo detailed neuroimaging studies even if they are asymp-

tomatic because of their possible association with cerebral hemangiomas [153]. The diagnosis of familial cerebral cavernous malformations requires histopathologic or imaging documentation of cavernous hemangiomas in at least two family members. Bilateral cases are strongly associated with a positive family history. Family members of patients with bilateral CCM should be screened [154].

### Retinal Cavernous Hemangioma

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

### Cerebral Cavernous Malformation

CCM may involve any part of the central nervous system, but supratentorial regions are more frequently involved than infratentorial ones [155]. The tumors can occasionally involve the spinal cord. Seizures, hemorrhages, or progressive focal neurological deficits are common manifestations.

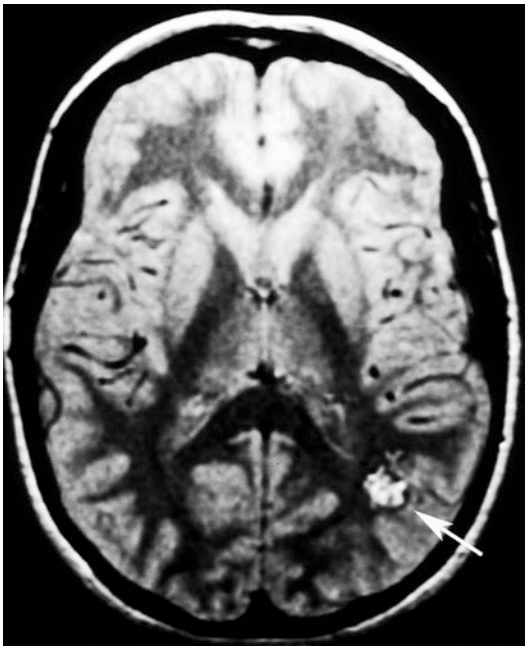

**Fig. 9.7** Cortical cavernous hemangioma of the CNS appears in a MRI as a central enhancing core surrounded by a dark ring from previous hemorrhages (arrow)

## 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 CCM1-3 [151].

## Treatment

No effective treatment is known, although laser photocoagulation has been attempted in a few cases [145]. Intracranial cavernous hemangioma can be managed by observation, surgical excision, or gamma knife radiosurgery depending upon location and other considerations [156]. Vitreous hemorrhage is usually mild and resorbs spontaneously without need for vitrectomy [154].

## Prognosis

In general, retinal cavernous hemangiomas are nonprogressive. Spontaneous thrombosis and vitreous hemorrhage are rare complications [145]. Cavernous hemangiomas of the CNS carry an annual risk of 0.25–5% for a clinically significant hemorrhage [156].

# Sebaceous Nevus Syndrome

## Introduction

Sebaceous nevus syndrome (of Jadassohn) [157], also known as Schimmelpenning-Feuerstein-Mims syndrome [158, 159], is a distinct clinical disorder within the spectrum of epidermal nevus

syndrome (of Solomon) [160] characterized by cutaneous sebaceous nevus and extracutaneous manifestations [161].

## Genetic Aspects

Sebaceous nevus syndrome is a sporadic disease.

## 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 [162, 163].

## Clinical Features

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

### Cutaneous Features

Cutaneous lesions are most commonly found on the head and neck region and appear as irregular, linear lesions with alopecia (Fig. 9.8a). Three stages of age-dependent evolution of the organoid nevus have been described [164]. During infancy, the skin appears atrophic due to underdevelopment of 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 [165].

**Table 9.12** Clinical manifestations of the sebaceous nevus syndrome

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

### Ophthalmic Features

Ocular involvement is observed in about 40% of cases, with epibulbar choristomas and coloboma being the most common [166]. The limbal choristomas can be simple or complex and usually are dermoid or lipodermoid in nature (Fig. 9.8b) [167, 168] Ophthalmoscopic examination can reveal coloboma, disc anomalies, or features suggestive of intrascleral cartilage (Fig. 9.8c) [169]. Intrascleral calcification due to ossification of cartilage can also be observed [169, 170].Though rare, circumscribed choroidal hemangioma has also been described in linear nevus sebaceous syndrome [171].

### Neurological Features

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

### Other Manifestations

Skeletal abnormalities, cardiovascular defects, and genitourinary defects are occasionally observed indicating the multisystem nature of the sebaceous nevus syndrome [161].

## 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 the presence of adnexal components. Other diagnostic studies should be ordered based upon suspicion of specific organ involvement.

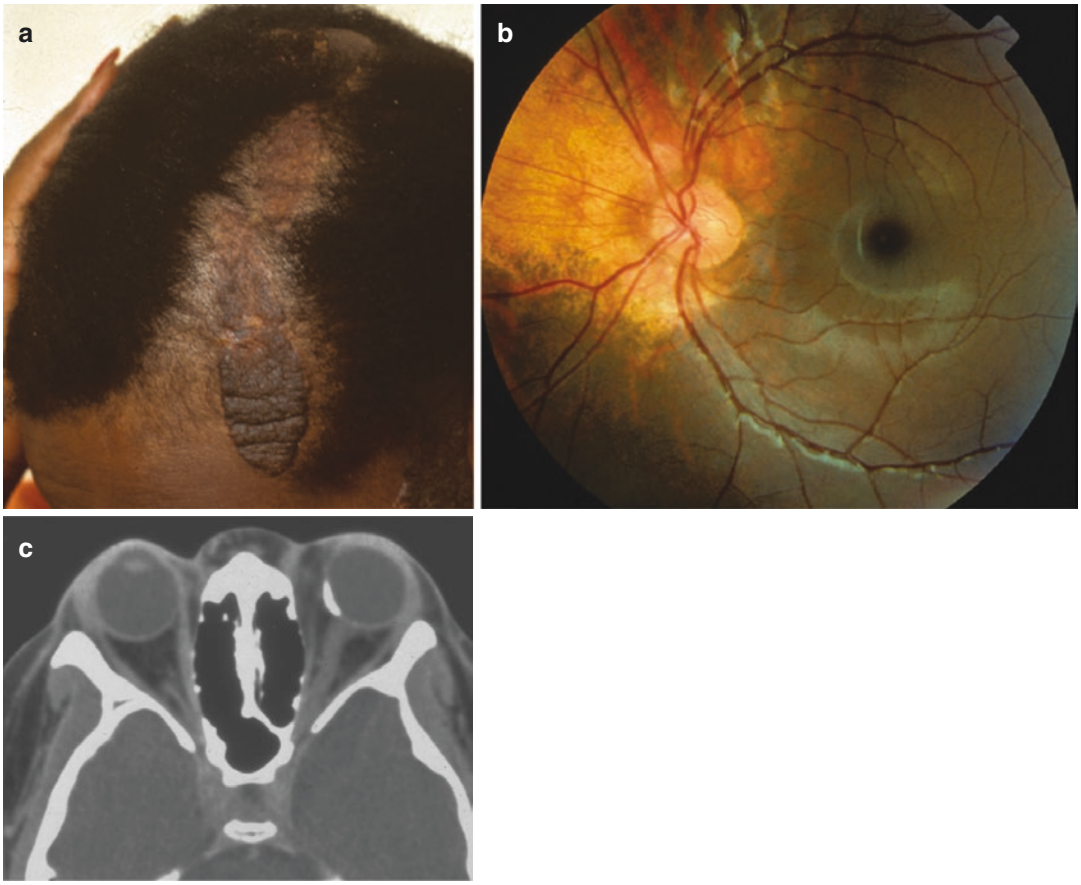


**Fig. 9.8** Characteristic manifestations of sebaceous nevus syndrome. Facial and scalp involvement with sebaceous nevus (**a**), yellowish orange scleral choristoma of the superonasal quadrant (**b**), and computed tomography at bone density shows nasal plaque-like lesion in the left globe (**c**). (Reprinted from Traboulsi et al. [170]. With permission from Elsevier)

## Treatment

Eyelid and episcleral choristomas can be excised, and attempts to maximize vision may include corneal grafting, refraction, and amblyopia management [172]. The organoid nevus should be removed for cosmetic correction and to prevent risk of malignant transformation observed in later stages of life [173].

## 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 manifestations of mental retardation and seizures. In a series of 707 cases of sebaceous nevi, malignant neoplasms developed in 2.5% of lesions. Most of these occurred in adults suggesting that surgical excision can be delayed [174].

# Ataxia Telangiectasia

## Introduction

In 1941, Madame Louis-Bar described a young boy with progressive cerebellar ataxia and oculocutaneous telangiectasia [175]. 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 [176]. Other features such as lymphoreticular malignancy and immune dysfunction were not reported until later [177].

## Genetic Aspects

Ataxia telangiectasia (AT) follows an autosomal recessive pattern of inheritance. A gene that causes AT was identified on chromosome 11q22-23 [178]. 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 [179].

## Pathogenesis

A region of the *ATM* gene that is homologous to phosphoinositide-3 kinases mediates cell growth signals. A second region homologous to *RAD3* and *MEC1* regulates cell cycle explaining diverse manifestations of AT [180].

## Clinical Features

The incidence of AT is about three per million live births. The minimum frequency of AT gene mutations in the US white population is estimated to be 0.0017 [181]. 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 has 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) [182].

**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 | |

### Cerebellar Ataxia

Progressive cerebellar ataxia in early childhood is the hallmark of AT and is present in all cases [183]. The majority of patients present with truncal ataxia by age 2 years, and almost all develop this neurological sign before age 6 years. Other 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 [184].

### 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.

### Other Manifestations

Other significant manifestations of AT are dysplasia of the thymus gland, recurrent pulmonary infections, susceptibility to neoplasia, endocrine

abnormalities, and progeric changes [185]. Lymphoma or leukemia develops in early adulthood in about 15% of cases, representing a 1000 times greater incidence than the general population [186].

## 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. 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 [179, 187].

## Treatment

AT patients are prone to 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 [185, 188].

## Prognosis

AT is a progressive disease with poor prognosis [189]. About one-third of patients die by age 15 years, and survival beyond age of 30 years is very unusual [190].

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 seen in ATLD patients include conjunctival telangiectasia, head thrusting, and manifest strabismus at distance [191].

## 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) [192]. Rare cases with ocular abnormalities such as uveal coloboma-like lesions have been reported [193].

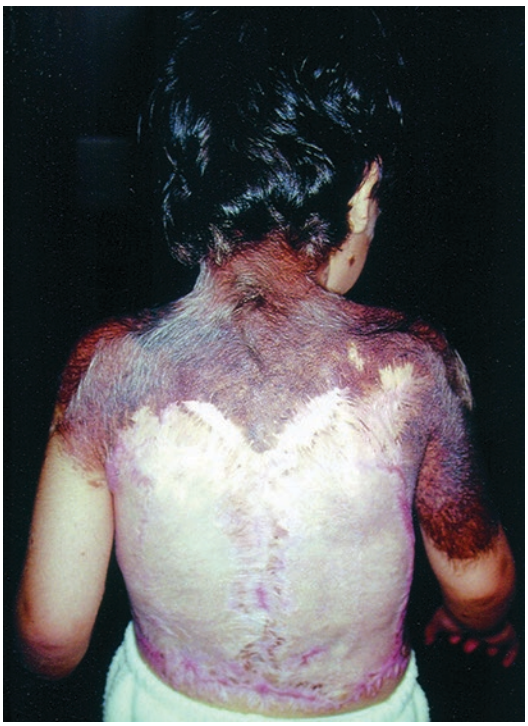

**Fig. 9.9** Large cutaneous melanocytic nevi of the trunk in a patient with neurocutaneous melanosis. (Reprinted from Kiratli and Sahin [193]. With permission from Taylor and Francis)

## Phakomatosis Pigmentovascularis

Ota, in 1947, described patients with a combination of vascular and melanocytic nevi in a Japanese population (phakomatosis pigmentovascularis [PPV]) [194]. Five types of PPV are known, but there has been an attempt in the dermatology literature to reclassify this order into three subtypes: (1) phacomatosis cesioflammea (one or more blue spots with one or more port-wine stains), (2) phacomatosis spilorosea (speckled lentiginous nevus of macular type with telangiectatic nevus), and (3) phacomatosis cesiomarmorata (blue spot with cutis marmorata telangiectatica congenital) [195]. Systemic associations with Sturge-Weber syndrome or Klippel-Trenaunay-Weber syndrome can occur. Recent work has shown that this is likely caused by activating mutations in *GNA11* and *GNAQ* [196]. Importantly, patients with this condition may also develop choroidal melanoma and should be monitored carefully for this [197]. Ocular involvement can also include congenital glaucoma, iris mammillations, and oculodermal melanocytosis (Fig. 9.10) [198].

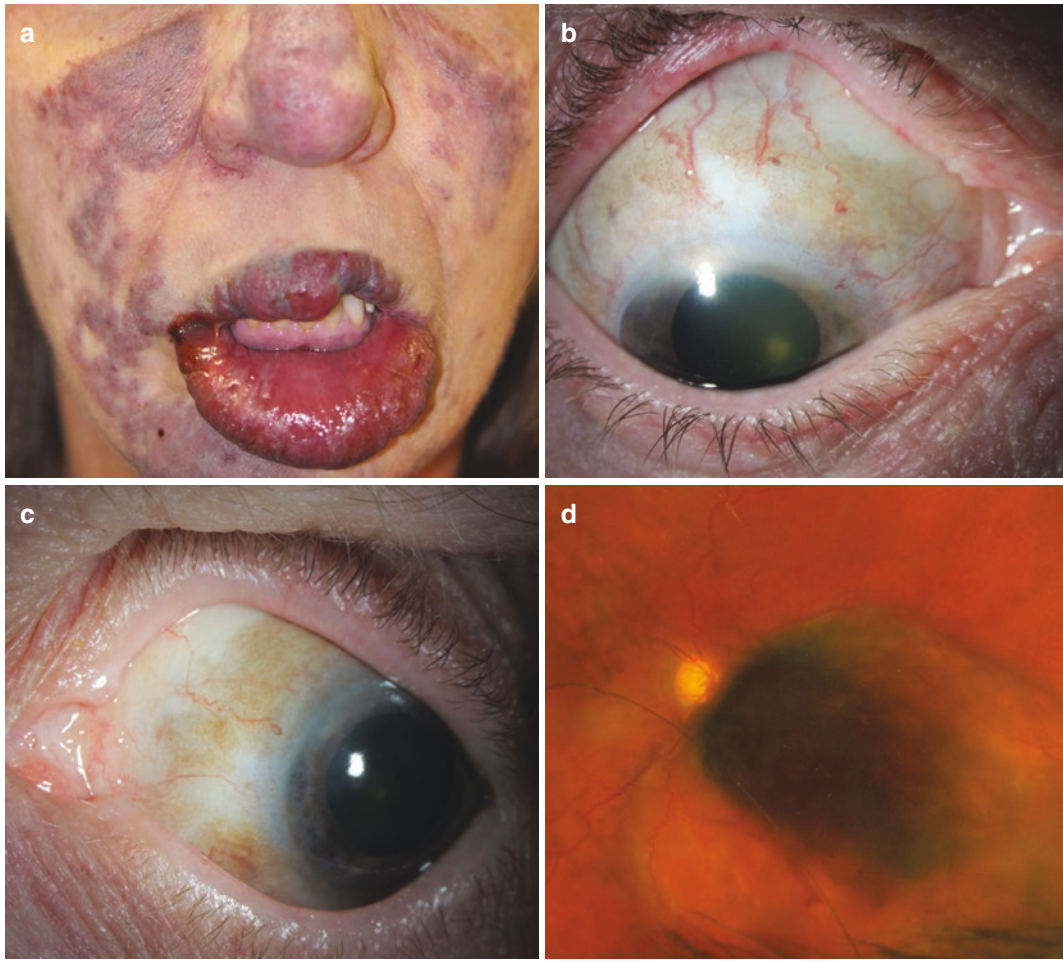


**Fig. 9.10** Phakomatosis pigmentovascularis. Bilateral cutaneous hemangioma of Klippel-Trenaunay-Weber syndrome (**a**) with bilateral scleral hyperpigmentation (**b**, **c**, ocular melanocytosis) and choroidal mass in the right eye causing exudative retinal detachment (**d**). Ultrasonography B-scan (**e**, dome-shaped mass) and A-scan (**f**, low internal reflectivity) and ICG (**g**, hypofluorescence with intrinsic vessels) were suggestive of choroidal melanoma rather than hemangioma. Uveal melanoma was confirmed upon enucleation

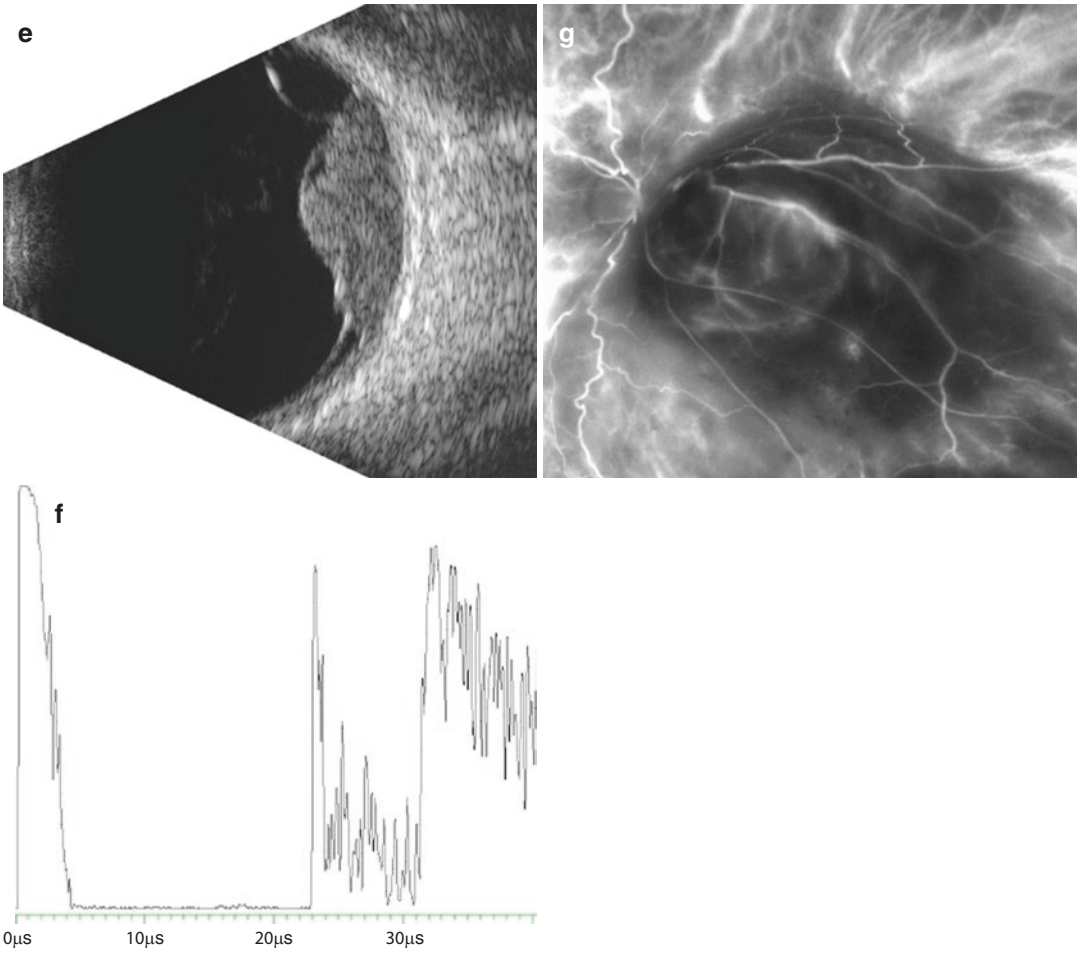


**Fig. 9.10** (continued)

## Intracranial Cavernous Angiomas (Cavernomas)

Cavernomas angiomas have an estimated prevalence of 0.16–0.5%. They are uncommonly seen in neurosurgical practice because they can occasionally rupture [151]. Recent developments in neurosurgical technique and microbiology have brought greater insight into the treatment and molecular pathogenesis of cavernoma. Familial cases can occur due to mutations in the genes *CCM1* (*KRIT1*), *CCM2* (*MGC4607*), and *CCM3* (*PDCD10*) [151]. There are a number of controversies regarding management of these lesions. These include risk factors faced by the patient, controversy over the importance of resection, and debate regarding the treatment modality of choice.

The two most important risk factors for hemorrhage are previous hemorrhage and brainstem location [151]. 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 an incidental finding on neuroimaging to discovery at autopsy after fatal hemorrhage. The most common symptom of cavernous malformation is seizure followed by focal neurological deficits, acute hemorrhage, and headache.

Asymptomatic lesions are generally observed without surgical excision [151]. In cases requiring surgical excision, the well-circumscribed nature of these lesions, 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 angiomas, which provide anatomically disordered but physiologically essential drainage. Removal of the venous angiomas can induce 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 [156].

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# Ocular Paraneoplastic Diseases

# 10

Ilya Leskov and Arun D. Singh

## Introduction

Paraneoplastic retinopathies are presently considered as autoimmune conditions (Table 10.1). Secreted tumor antigens are internalized by antigen-presenting cells that direct the antitumor humoral response, stimulating the production of antitumor antibodies. Some of these antibodies may cross-react with similar or identical antigens in the retina, resulting in retinal degeneration. Recoverin was the first such identified antigen, as characterized by Thirkill and associates [1, 2]. Since then, numerous other retinal antigens have been proposed, including proteins in photoreceptor cells that mediate phototransduction cascade (arrestin, guanylate cyclase-activating protein, transducin, rhodopsin), as well as proteins in retinal bipolar and ganglion cells involved in glycolysis (enolase, aldolase, glyceraldehyde-3-phosphate dehydrogenase) and stress and homeostatic responses (heat shock proteins, carbonic anhydrase) [3–5].

It is thought that an initial antitumor humoral response produces antibodies that react to a specific epitope on a given antigenic protein. With time, a process called "epitope spreading" occurs, wherein antibodies cross-react with a different epitope on the same protein [5]. These subsequently generated antibodies may be the ones that ultimately lead to retinal pathology. This explains why some individuals with antibodies against cancer-associated retinopathy targets, such as recoverin, enolase, and carbonic anhydrase II, do not develop retinopathy [5–7].

Pathogenic antibodies are able to penetrate retinal tissues and cross cell membranes to enter cells that express their targets [5]. Their effect depends on the function of their target. Recoverin, for example, functions in light and dark adaptation by regulating rhodopsin phosphorylation and dephosphorylation in a calcium-dependent manner [8]. Once internalized by photoreceptors, anti-recoverin antibodies lead to increase in intracellular calcium and activation of mitochondrial caspase 3 and caspase 9-driven apoptosis, ultimately resulting in retinal degeneration [9, 10]. Anti-enolase antibodies bind to Muller cells and ganglion cells, inactivating their target enzyme, inhibiting glycolysis, and inducing apoptosis [11]. Anti-carbonic anhydrase II antibodies impair their target enzyme as well, resulting in lower intracellular pH and increase in intracellular calcium, ultimately reducing cell viability [12]. Antibodies against transient receptor potential channel protein 1 (TRMP1) expressed

I. Leskov
Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic Foundation, Cleveland, OH, USA

A. D. Singh (✉)
Department of Ophthalmic Oncology, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: singha@ccf.org


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**Table 10.1** Clinical features of paraneoplastic retinopathies

| Feature | CAR | MAR | BDUMP |
|---|---|---|---|
| Symptoms | Bilateral visual loss<br>Positive visual phenomenon<br>Nyctalopia | Near normal acuities<br>Normal color vision<br>Normal central visual fields | Severe visual loss<br>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<br>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)<br>Gynecological carcinoma<br>Breast carcinoma | Cutaneous melanoma | Small cell carcinoma and others |
| Antibodies | Anti-recoverin,<br>Anti-enolase<br>Anti-65-kDA<br>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

on ON bipolar cells are associated with retinopathy in patients with cutaneous melanoma (MAR). These antibodies target an intracellular sequence of TRMP1; their intracellular uptake and accumulation result in bipolar cell dysfunction characteristic of MAR. [13, 14] It is likely that aberrant autoantibodies targeting other retinal antigens result in the apoptosis of cells expressing their targets in similar fashion.

## Cancer-Associated Retinopathy

### 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) by Sawyer et al. in 1976 [15]. While it remains most commonly associated with SCLC, CAR has also been associated with hematologic malignancies, gynecologic and breast carcinoma, and less commonly non-small cell carcinoma of the lung, laryngeal, bladder, thyroid, prostate, colon, and hepatocellular cancer, carcinoid tumor of the small bowel, seminoma, thymoma, and Langerhans cell histiocytosis [16–23]. Analysis of a series of 209 patients with CAR showed that disease onset generally occurs after age 45, with average age of 65; women were affected twice as frequently as men [21]. 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.

### Etiology and Pathogenesis

Antibodies found to be associated with CAR include ones directed against the phototransduction protein recoverin, the glycolytic enzymes enolase and glyceraldehyde 3-phosphate dehydrogenase, tubby-like protein 1 (TULP1) that participates in transport of phototransduction components, heat shock cognate protein 70, and carbonic anhydrase II, among others [24].

Aberrant expression of recoverin has been demonstrated in a number of cancer cell lines and is thought to play a role in cell proliferation

[25]. Tumor-expressed recoverin is known to be antigenic and anti-recoverin antibodies are commonly identified in patients with various cancers [26, 27]. Systemic administration of recoverin in a rat model was found to result in immunization and subsequent retinal degeneration [28]; and intravitreal injection of anti-recoverin antibodies in rats has also been shown to cause retinal degeneration [29]. Interestingly, intravenous anti-recoverin antibodies given to mice were not able to cross the blood-retina barrier, and no retinal degeneration occurred [30]. Vascular endothelial growth factor has been investigated as a potential mediator of blood-retina barrier modification, though its role remains unclear [31]. It appears that the cellular immune system may provide the additional component necessary to induce antibody-related damage. Maeda et al. 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 [32].

## Clinical Features

### Symptoms

Cancer-associated retinopathy is 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 [33].

### 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 [34].

## Diagnostic Evaluation

Assessment of retinal function using Goldmann or Humphrey visual fields, Farnsworth color assessments, and electroretinography (ERG) is 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 constriction of central 20 degrees of the visual field [35]. Electroretinographic studies are helpful both in the confirmation of the diagnosis, especially when the clinical findings are subtle (Fig. 10.2). The classic picture seen with CAR includes suppression of both the photopic and scotopic responses [36], 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 [33].

Another critical component of the evaluation of patients with suspected CAR is a 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 [24]. Not all patients with suspected CAR have identifiable anti-retinal antibodies, while a significant number of patients with non-neoplastic autoimmune retinopathy have anti-retinal antibodies [37]. Though, as noted above, these may bind to different epitopes of their target. Moreover, some patients may have multiple antibodies, but the offending antibody is not always identifiable [37]. The discovery of anti-recoverin antibodies, however, should raise a high level of suspicion for malignancy, as several studies have shown these to be strongly associated with CAR [37].

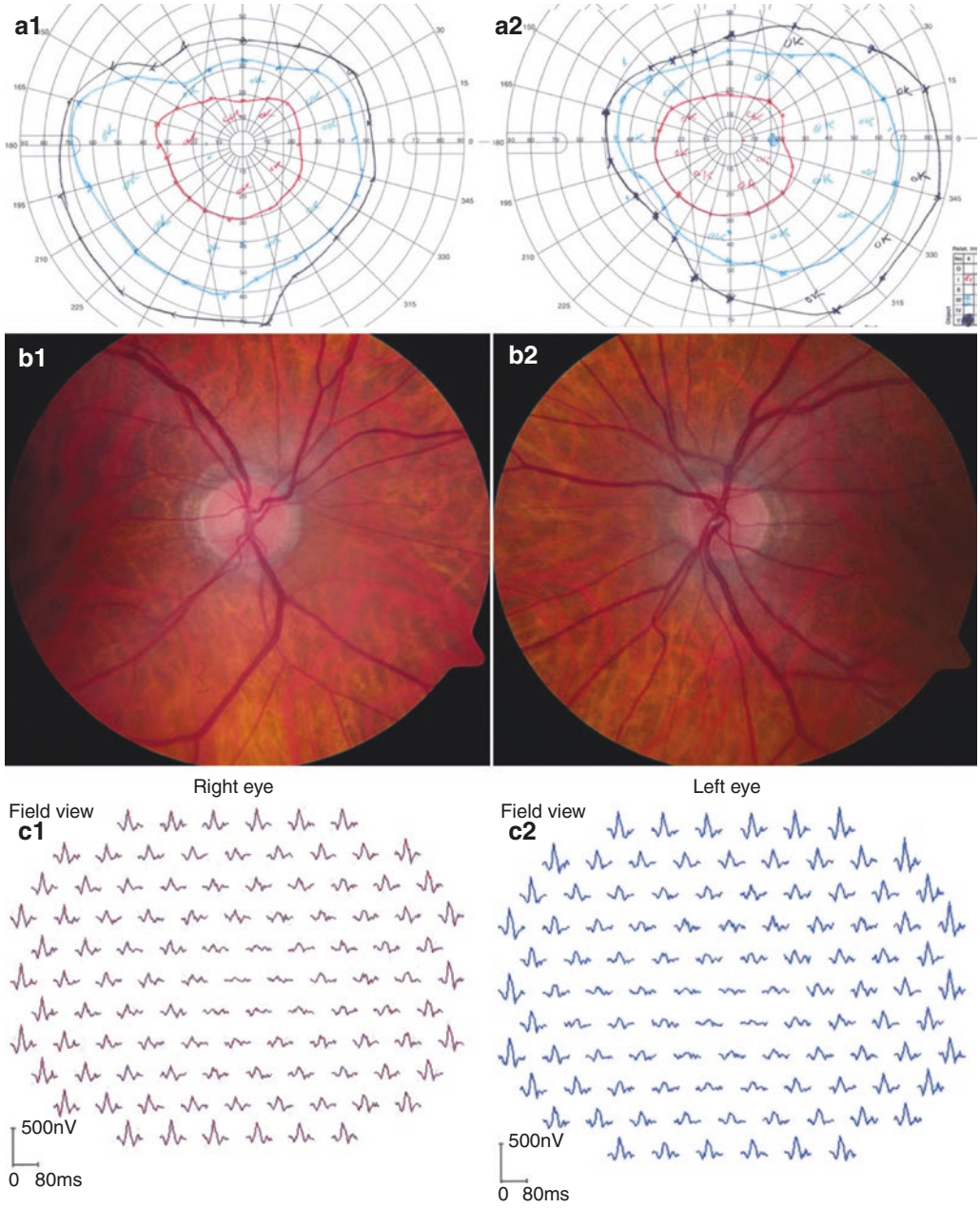


**Fig. 10.1** A 61-year-old white male presented to the neuro-ophthalmology service in consultation for bilateral progressive decrease in vision that started approximately 1 year prior to presentation. He saw an ophthalmologist 1 month prior to his presentation who noted mild sheathing of his retinal 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 workup revealed the presence of a peripheral lung nodule whose biopsy showed the presence of signet-ring cell carcinoma. (Courtesy of Gregory S. Kosmorsky, MD)

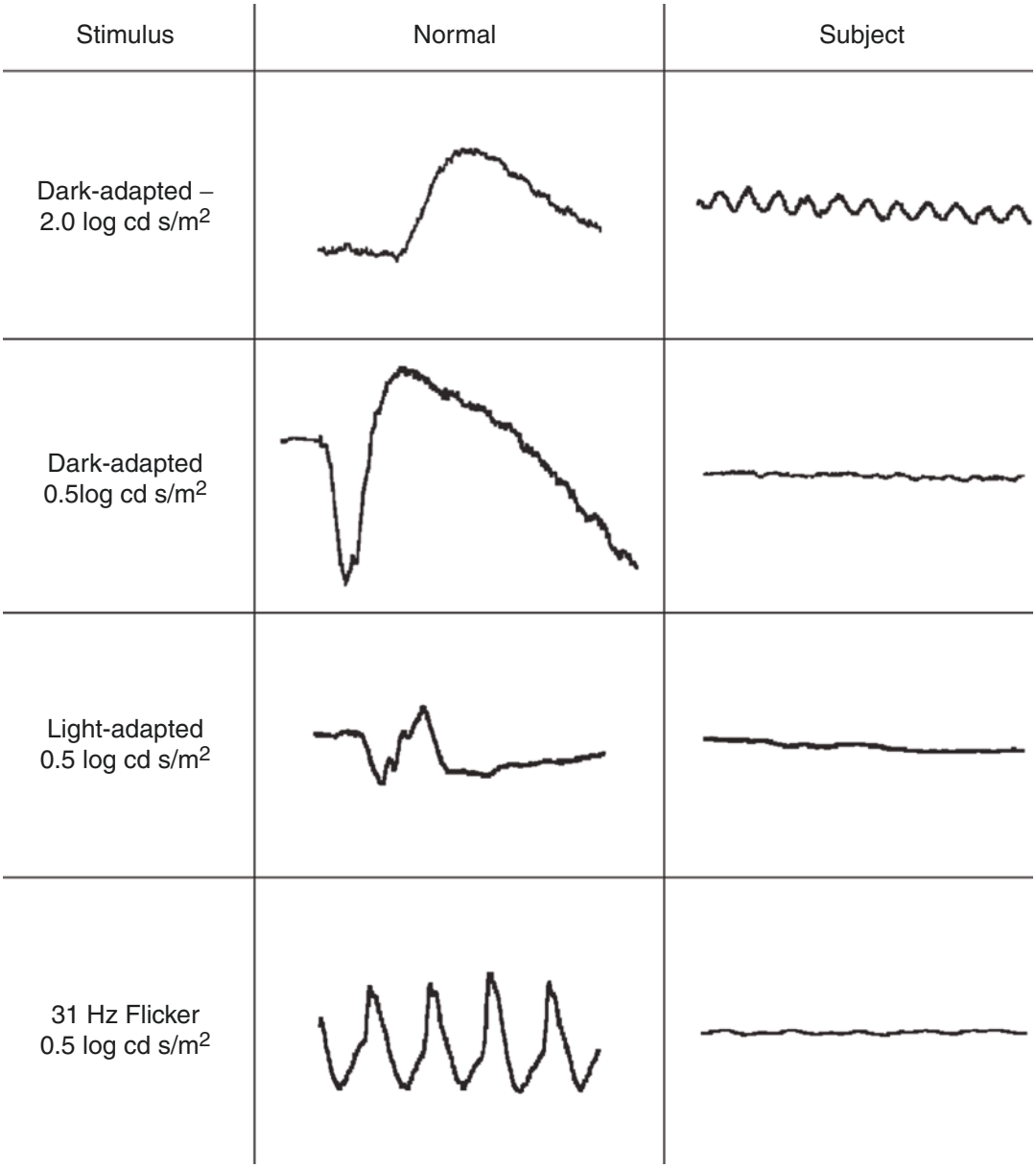


**Fig. 10.2** A 67-year-old man with a known history of lung cancer presented with halos in both eyes. Electroretinograms recorded from a normal control subject and from the patient. Responses recorded from the two eyes of the patient were averaged together. Extinguished ERG responses in the patient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

Retinal imaging may be normal or nonspecific to CAR. Retinal vein leakage and perivascular window defects have been reported on fluorescein angiography [38]. Spectral domain OCT usually shows loss of outer retinal structures, including the outer nuclear layer, the external limiting membrane, and the ellipsoid layer, as well as the appearance of cystoid and schisis-like changes [39–41].

## Differential Diagnosis

Cancer-associated retinopathy must be distinguished from other paraneoplastic ocular diseases, including retinopathy associated with melanoma (MAR) and paraneoplastic optic neuropathy, as well as non-paraneoplastic auto-

immune retinopathy, hereditary retinal disease, and other causes of retinal degeneration. Furthermore, optic neuropathies due to adverse effects of chemotherapeutic agents such as vincristine, optic nerve infiltration by a primary carcinoma, or anterior ischemic optic neuropathy must be ruled out.

## 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 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 [37, 42]. Unfortunately, treatment of the primary tumor, including the use of chemotherapy, radiotherapy, and local excision of the primary tumor, is rarely effective against CAR [16], with only rare reports describing improvement in retinal appearance on OCT and recovery of visual function following systemic chemotherapy for the patient's primary malignancy [43, 44].

Intravenous high-dose methylprednisolone and less commonly oral steroids are generally the first-line approach to management of CAR, 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 [45]. Intravenous immunoglobulin was successful in improving visual acuity or visual fields in a small case series [46]. Single-case reports of successful preservation of vision with alemtuzumab, improvement of vision with rituximab, and with plasmapheresis in combination with systemic steroids have been published [47–50]. 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 [51]. While it is generally held that systemic management is required, local treatment with either intravitreal or sub-Tenon steroid injections may be beneficial in some patients [45, 52].

## 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 [35].

# Melanoma-Associated Retinopathy

## Introduction

The first case of remote ocular disease occurring in the setting of metastatic cutaneous melanoma was presented by Gass in 1984, when he described a patient with acute vision loss, uveitis, and large areas of depigmentation of the choroid [53]. Melanoma-associated retinopathy was eventually coined as a distinct clinical entity when Berson showed in1988 that this night blindness was a paraneoplastic phenomenon [54]. The syndrome is characterized by nyctalopia, shimmering photopsias, and an unremarkable or atrophic fundus exam in a patient with metastatic cutaneous melanoma and characteristic ERG findings. Unlike CAR, which may be diagnosed before or after the 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 [16].

## Etiology and Pathogenesis

Similar to CAR, patients with MAR have antibodies toward tumor antigens which cross-react with antigens on retinal cells, most commonly targeting the rod bipolar cell [55]. As with CAR, numerous antibodies have been identified, including S-arrestin, recoverin, α-enolase, aldolase A, aldolase C, and rhodopsin, among others [56, 57]. More recently, autoantibodies specific to the TRPM1 cation channel of ON bipolar cells have been described [13]. This selective damage of bipolar and Mueller cells produces a negative-appearing scotopic ERG response, termed the "negative ERG" [36].

## 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 [57, 58].

### 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 [58, 59]. Subclinical MAR as detected by ERG, peripheral visual field evaluation, and nyctometry appears to be more common than previously suspected in patients with cutaneous melanoma [60].

### Signs

Patients typically have near normal visual acuities, color vision, and central visual fields unlike CAR patients who manifest more severe deficits at presentation [59]. 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 [59, 61].

## 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 [58]. A positive history of cutaneous malignant melanoma and circulating antibodies directed toward human bipolar cells support the diagnosis (Fig. 10.3).

## Differential Diagnosis

Melanoma-associated retinopathy must be differentiated from similar clinical presentations with an

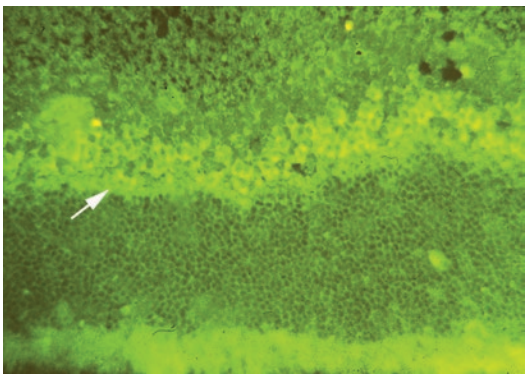

**Fig. 10.3** A 64-year-old man presented with photopsia, difficulty with night vision, and reduced peripheral visual field in both eyes of 3-month duration. He had been recently diagnosed with malignant melanoma of the maxillary sinus. The corrected visual acuity was 20/20 in both eyes. Results of the 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). Patient's visual status remained stable for the next 12 months when he died from metastatic disease. (Reprinted from Singh et al. [111]. With permission from Elsevier)

electronegative ERG, such as congenital stationary night blindness (CSNB) [62], juvenile retinoschisis [63], and non-ischemic central retinal vein occlusion [64]. Systemic treatment for melanoma with interferon may also cause a retinopathy, though this is easily distinguished by its features of intraretinal hemorrhage and cotton wool spots [65]. 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.

### Treatment

The key to management is early detection, since MAR causes irreversible destruction of bipolar and Mueller cells. The treatment is similar to CAR in that there is no established treatment paradigm; however there is more deference given to cytoreduction, either by means of metastasectomy, or chemotherapy and radiation [66]. Intravenous immunoglobulin is also frequently employed, often in combination with cytoreduction of the primary tumor by radiation, plasmapheresis, and steroids [59, 67, 68]. Unfortunately, the results of treatment are generally unimpressive; a meta-analysis of the literature found that only 4% in MAR had visual improvement or improvement in fundus appearance after treatment [16].

### 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 acuity with only ten patients retaining visual acuity better than 20/60 [59].

## Paraneoplastic Vitelliform Retinopathy

### 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 [61, 69–71]. In 2001 Borkowski et al. described two cases of a MAR-like syndrome with unusual fundus features [61]. 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 [61]. Other groups have reported MAR-like presentations with multiple serous retinal and RPE detachments [69, 71, 74, 75]. 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 [73]. This group was the first to use the term *paraneoplastic vitelliform retinopathy*. Since that time, others have also described similar appearing cases of paraneoplastic vitelliform retinopathy with multiple serous retinal detachments [70, 72, 76, 77].

### Etiology and Pathogenesis

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 [78].

### Clinical Features

#### Symptoms

Males and females are equally affected [76]. 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.

#### Signs

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 [79]. (Fig. 10.4).

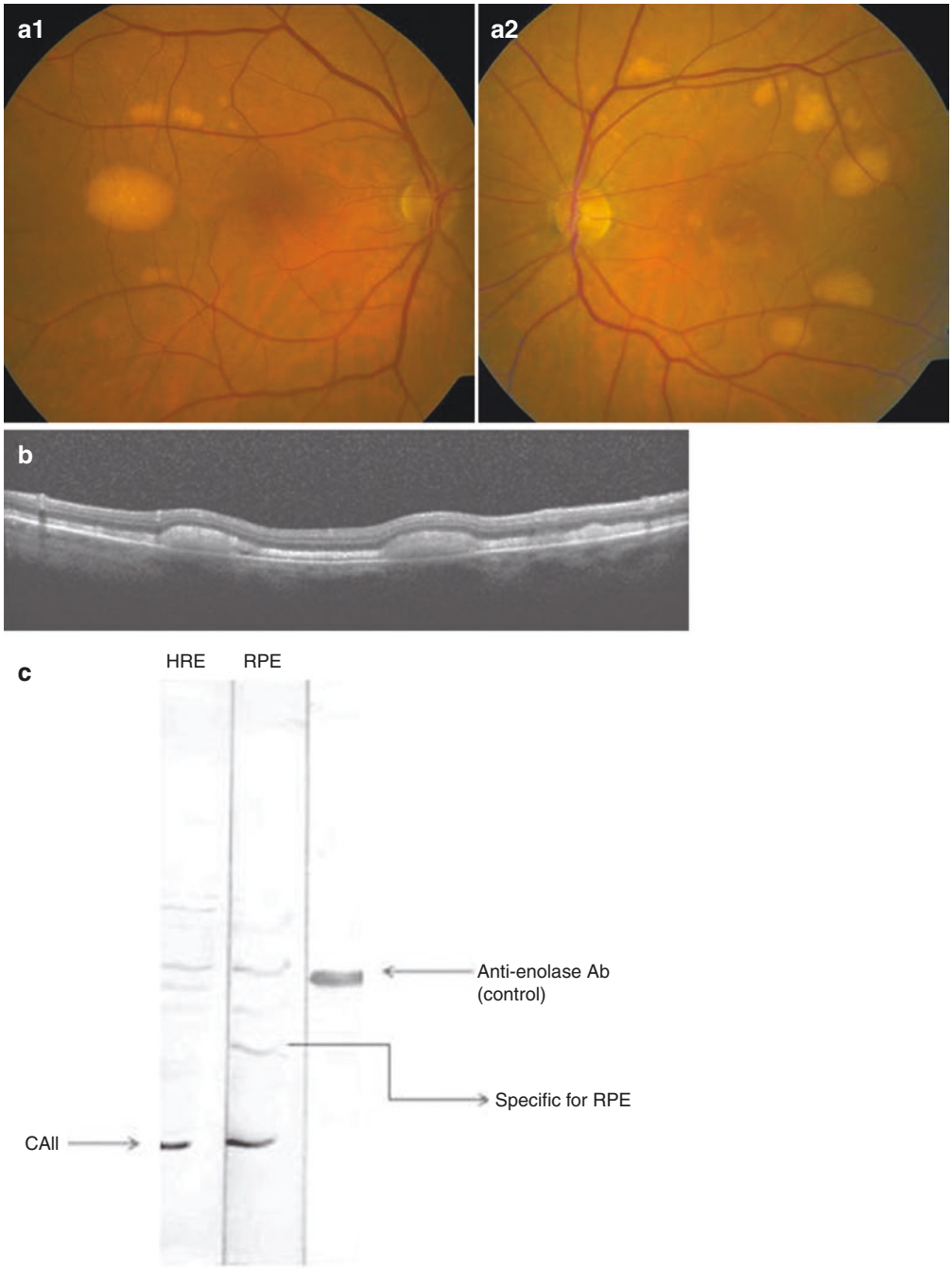


**Fig. 10.4** Fundus appearance of paraneoplastic vitelliform retinopathy in an 80-year-old man with metastatic cutaneous melanoma (**a**-1 right eye, **a**-2 left eye). Spectral domain optical coherence tomography revealed high-resolution imaging of all retinal layers and confirmed the location of these 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**). (Reprinted from: Aronow et al. [76]. With permission from Elsevier)

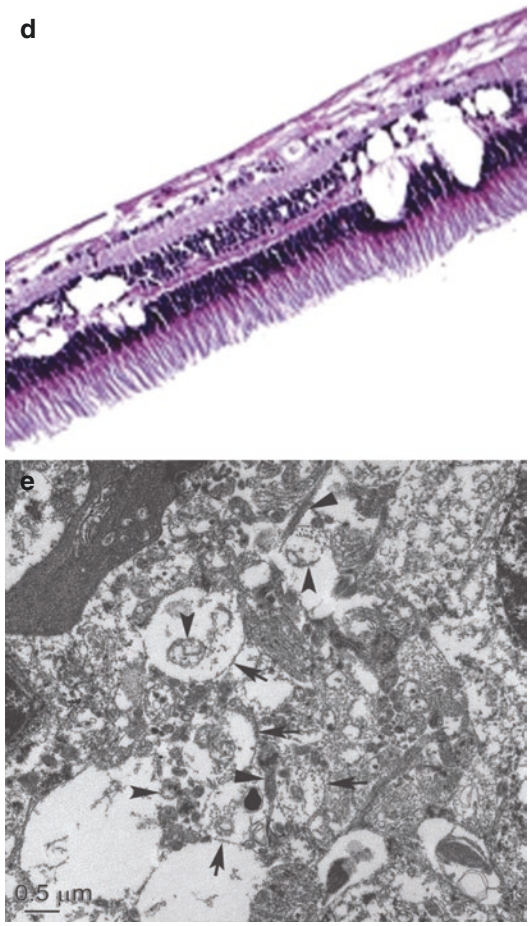


**Fig. 10.4** (continued)

## Diagnostic Evaluation

Visual field testing has yielded variable results from normal to cecocentral scotomas [70, 73]. Color vision testing may reveal errors along the tritan axis on Farnsworth D-15 testing [70]. Reduction in both the a-wave and b-wave amplitudes for both scotopic and photopic ERG testing is common. EOG may be normal or may show a pathologically reduced Arden ratio [70, 76]. Paraneoplastic vitelliform retinopathy may be mistaken for Best's disease, RDS/peripherin spectrum dystrophies, and Harada syndrome.

## Treatment

There is no known effective treatment. There are few reports describing treatment for paraneoplastic vitelliform retinopathy, though prednisone may reduce subretinal fluid accumulation with a corresponding improvement in visual acuity [80]. The role of more aggressive immunosuppression in treatment of such cases is not known [45].

## Prognosis

Most individuals succumb to metastatic disease within months of diagnosis [76].

# Bilateral Diffuse Uveal Melanocytic Proliferation (Paraneoplastic Melanocytic Proliferation)

## 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 systemic carcinomas. Since its original description by Machemer in 1966 [81] and subsequently Barr in 1982 [82], approximately 60 cases have been published [83–85]. Often, the primary carcinoma is unknown at presentation, and recognition of the characteristic ocular findings prompts a systemic workup. The primary tumor may arise from numerous sites; however, gynecological neoplasia and lung and pancreatic cancer predominate [83]; other sites including the colon, gallbladder, breast, and esophagus have been reported [16, 85].

## Etiology and Pathogenesis

The exact pathogenesis of BDUMP remains unknown. Histopathology shows melanocytic infiltration composed predominately of benign

nevus cells with few mitotic figures in the uvea and the skin [86]. Since the proliferation of melanocytes is not limited to the uvea, paraneoplastic melanocytic proliferation may be a more descriptive terminology [86]. It is believed that production of hormonal or other oncogenic stimulus by the primary carcinoma causes activation and proliferation of preexistent nevus cells within the uveal tract, mucosal membranes, and the skin. Miles et al. demonstrated that human melanocytes proliferate when exposed to sera or plasma of patients with BDUMP; this so-called "cultured melanocyte elongation and proliferation" (CMEP) factor was then localized in the IgG fraction of the sera [87]. In a follow-up study, sera from patients who had undergone plasmaphoresis failed to stimulate melanocyte proliferation, suggesting this as a promising treatment modality [88]. Indeed, there have been several reports of patients whose visual loss was stabilized and even reversed following this treatment [84, 88, 89]. RPE atrophy in BDUMP 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 [90, 91].

## Clinical Features

The mean age at diagnosis of BDUMP syndrome is 64 years and it has no sex predilection [83]. Ovarian cancer and lung or pancreatic cancer are the most common underlying malignancies in females and males, respectively [83].

### 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).

### Signs

Systemic examination may reveal focal cutaneous and mucosal melanocytic proliferation [86]. Mucosal involvement may even be widespread, with pigmentation of the oral mucosa and lips, penis, and rectum [86]. Similarly, the acquired cutaneous pigmentation appears to be site nonspecific with the head, neck, shoulder, and vulval involvement [83]. Gass established the five cardinal ocular signs associated with the diagnosis of BDUMP: (1) the typical fundus pattern found in BDUMP consists 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 [92]. Other slit lamp findings may include anterior chamber cell, vitreous cell, pigmented iris patches, and signs of ciliary body enlargement such as dilated episcleral vessels, shallow anterior chamber, and iridodonesis.

## 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 these are sometimes subclinical [83]. ERG studies show a nonspecific pattern of decreased cone and rod responses. Fundus autofluorescence of the reddish patches show patchy hypoautofluorescence; correspondingly, fluorescein angiography demonstrates early window defect hyperfluorescence due to focal destruction of the pigment epithelium with sparing of the choriocapillaris [93]. In late frames, there is marked choroidal hyperfluorescence with patches of hypofluorescence [92]. Spectral domain OCT confirms patchy RPE atrophy in areas of hypoautofluorescence, with adjacent RPE thickening, photoreceptor loss, and occasionally mild subretinal fluid [93].

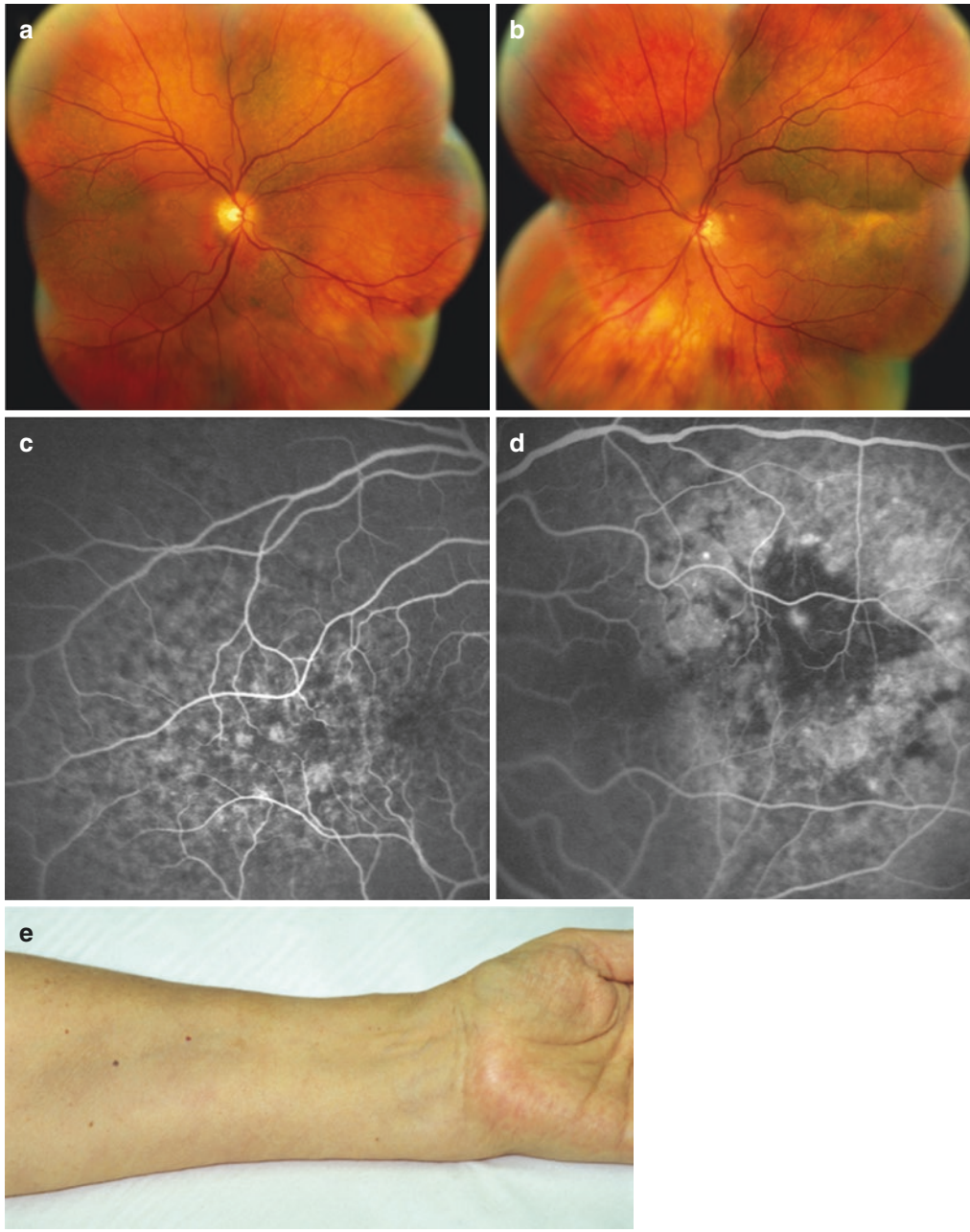


**Fig. 10.5** A 56-year-old woman presented with progressive deteriorating vision in both eyes for the last 6 months. The onset of visual symptoms coincided with the diagnosis of large cell carcinoma of lung. She was not known to have metastasis and was receiving chemotherapy. The corrected visual acuity 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**). Patient's visual status worsened for the next 6 months when she died from metastatic disease. (Reprinted from Singh et al. [86]. With permission from American Medical Association)

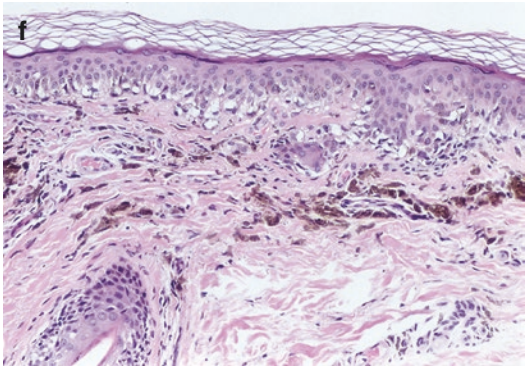


**Fig.10. 5** (continued)

## 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 emergence of multifocal pigmented choroidal tumors. Metastatic melanoma to the uvea and multiple choroidal nevi can also resemble the multifocal pigmented choroidal tumors observed in BDUMP syndrome.

## Treatment

As with other paraneoplastic retinopathies, BDUMP has no effective treatment. Early experience with corticosteroids and ocular external radiotherapy did not prevent the progression of the disease [94]. Similarly, vitrectomy, silicone oil injection, and panretinal photocoagulation all failed to prevent the retinal detachments seen in the late stages of BDUMP [92]. Intravitreal anti-vascular endothelial growth factor therapy has also been tried unsuccessfully to treat subretinal fluid involving the macula [93]. Recently, there have been case reports of plasmapheresis or plasma exchange as a means of stabilizing or even improving the vision in three patients [84, 88, 89].

## 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 [83]. Visual acuity loss is typically profound, with a majority of patients reaching hand motion or light perception [83].

# Paraneoplastic Optic Neuropathies

## 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 [95]. 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 [16, 96–99].

## Etiology and Pathogenesis

As with CAR and MAR, cross-reacting antitumoral and anti-neuronal antibodies have been identified. Antibodies to collapsin response-mediating protein-5 (CRMP-5) are the best characterized and most commonly identified, though there have been reports of other antibodies [99, 100]. Presumably reaction with the CRMP-5 antigen results in the pathologic find-

ings of inflammatory cell infiltration, demyelination, or both [100].

## Clinical Features

### Symptoms

Neurologic 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.

### 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 [16]. In addition, patients can present with neurological findings of encephalomyeloradiculopathy which can include mental status, cranial nerve, motor, autonomic, and movement disorders [100].

## 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 [101]; visual-evoked response may be delayed [100]. Visual fields may show a range of defects, but peripheral constriction and cecocentral scotomas are particularly common [100]. Cerebrospinal fluid 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 [99, 100].

## 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.

## Treatment

Treatment of the underlying malignancy with excision, radiation, and chemotherapy coupled with corticosteroids may improve visual acuity and visual field defects [16]. Sometimes the improvement is substantial, while in other cases the vision continues to decline despite all treatment efforts [102, 103].

## 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 [102, 104–106].

## 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 [107]. Lung cancer and neuroblastoma are the most common malignancies reported with opsoclonus in adults and children, respectively [108], but it has also been described in tumors of the breast, ovary, and uterus [107]. 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 [109]. Nevertheless, assays for antibodies such as anti-RI, anti-Yu, and anti-Ho are useful when making the diagnosis of paraneoplastic opsoclonus [110]. Opsoclonus is sensitive to the treatment of the underlying malignancy, corticosteroids, and infusion of IVIG.

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