Clinical Ophthalmic Oncology

Retinal Tumors

Arun D. Singh
Bertil E. Damato
Editors

Third Edition

Springer

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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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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

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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.

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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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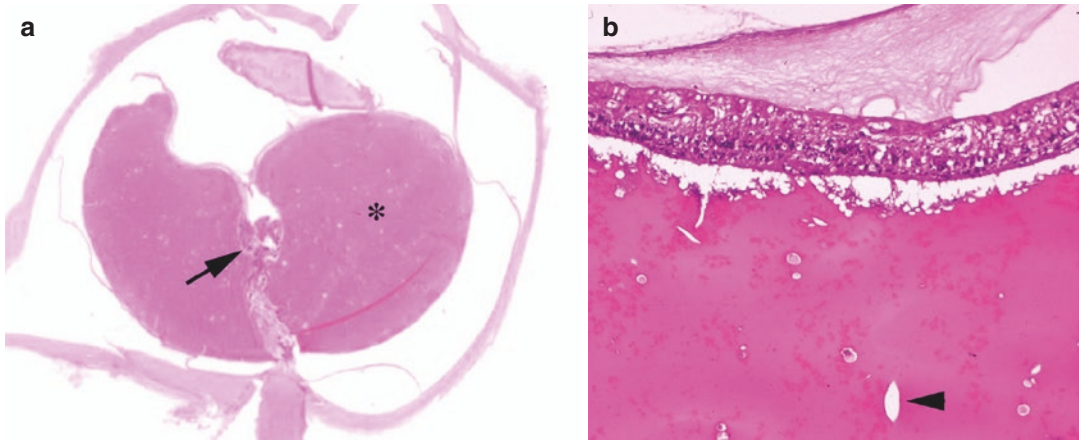

Fig. 2.1 Enucleated eye with Coats' disease. Note the total exudative retinal detachment (arrow) and the subretinal exudate (asterisk) (**a**, low-power hematoxylin and eosin). Cystic degeneration, disorganization, and deposition of PAS-positive material in the outer retina. Cholesterol clefts are seen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

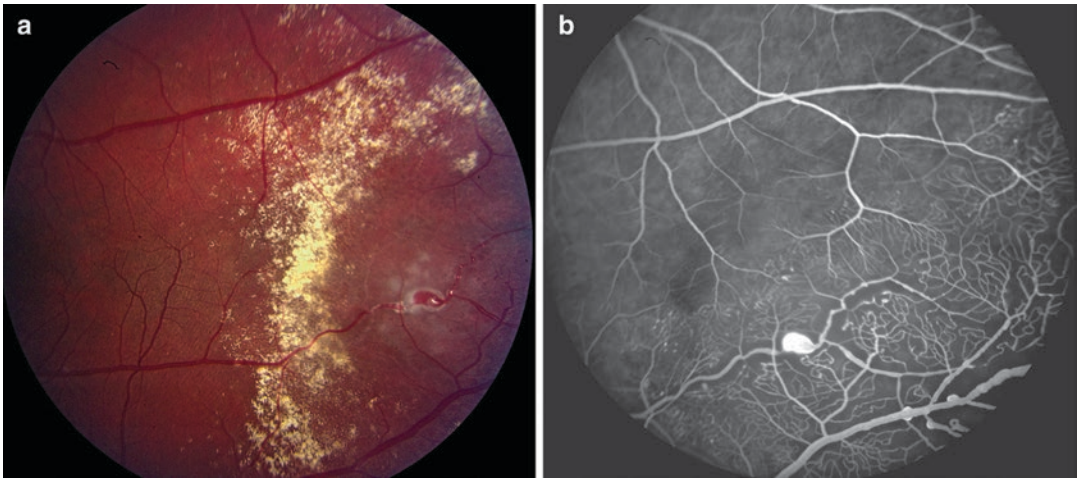

Fig. 2.2 Fundus photograph of the left eye demonstrates the circinate lipid exudation surrounding retinal telangiectasia (**a**). Fluorescein angiography demonstrates the area of bulbous aneurysms, vascular telangiectasia, and areas of capillary nonperfusion (**b**)

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).

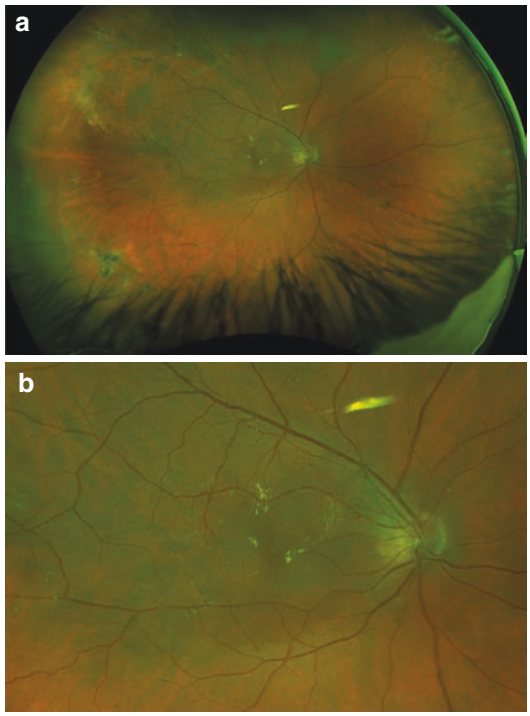

Fig. 2.3 UFW photograph of the right eye in a 66-year-old male with Coats' disease showing multiple saccular aneurysms, retinal telangiectasia, vascular sheathing, and lipid exudation in the periphery (**a**) and macula (**b**)

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-

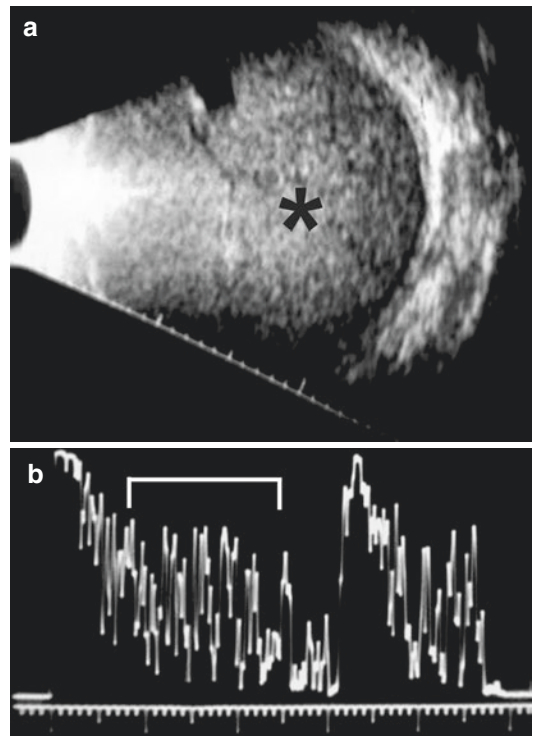

Fig. 2.4 Diagnostic ultrasonography of the eye in Fig. 2.1. Note the diffuse, homogeneous medium reflectivity of the posterior segment on B scan (asterisk). The numerous echogenic clefts represent cholesterol crystals within the subretinal exudates (**a**). These crystals account for the medium reflective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

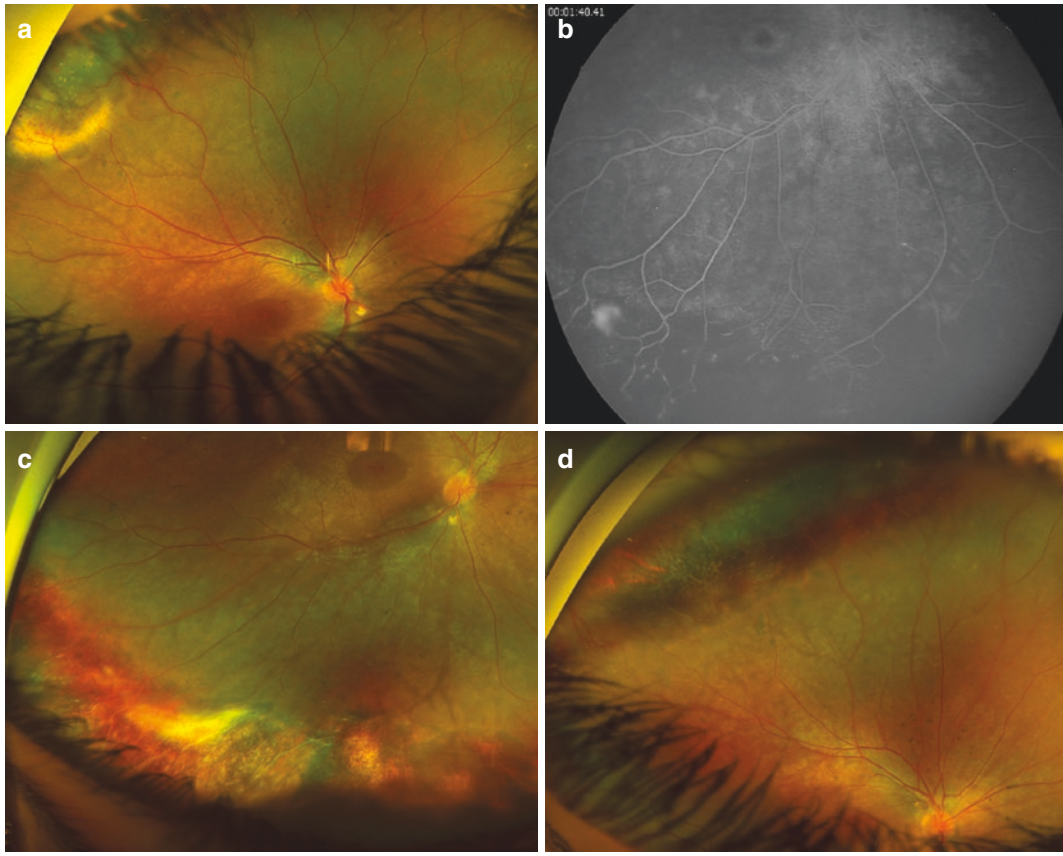

Fig. 2.5 Retinal telangiectasia, exudative retinal detachment, and retinitis pigmentosa. A 12-year-old male presented with night blindness and constricted visual fields in both eyes. Family history includes an older sister with retinitis pigmentosa. Visual acuities were 20/40 in both eyes. Anterior segment 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 AR XR Sporadic	Absent
Retinopathy of prematurity	Premature neonate	M (50) F (50)	Bilateral	–	+	Neovascularization Vitreous hemorrhage	Sporadic	Complications of premature birth
PHPV	0–5 years	M (50) F (50)	Unilateral	–	+	Microphthalmia Cataract Shallow AC Vitreous stalk	Sporadic	Absent
Incontinentia pigmenti	0–16 years	F (100)	Bilateral	+	+	Optic atrophy Foveal hypoplasia	XD	Skin rash Hypodontia Dystrophic nails
Norrie's disease	At birth	M (50) F (50)	Bilateral	+	+	Retrolental mass	XR Sporadic	Cognitive Behavioral Hearing loss
Retinal capillary hemangioma	25 years	M (50) F (50)	Unilateral or bilateral	+	–	Capillary hemangioma	AD Sporadic	VHL disease

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

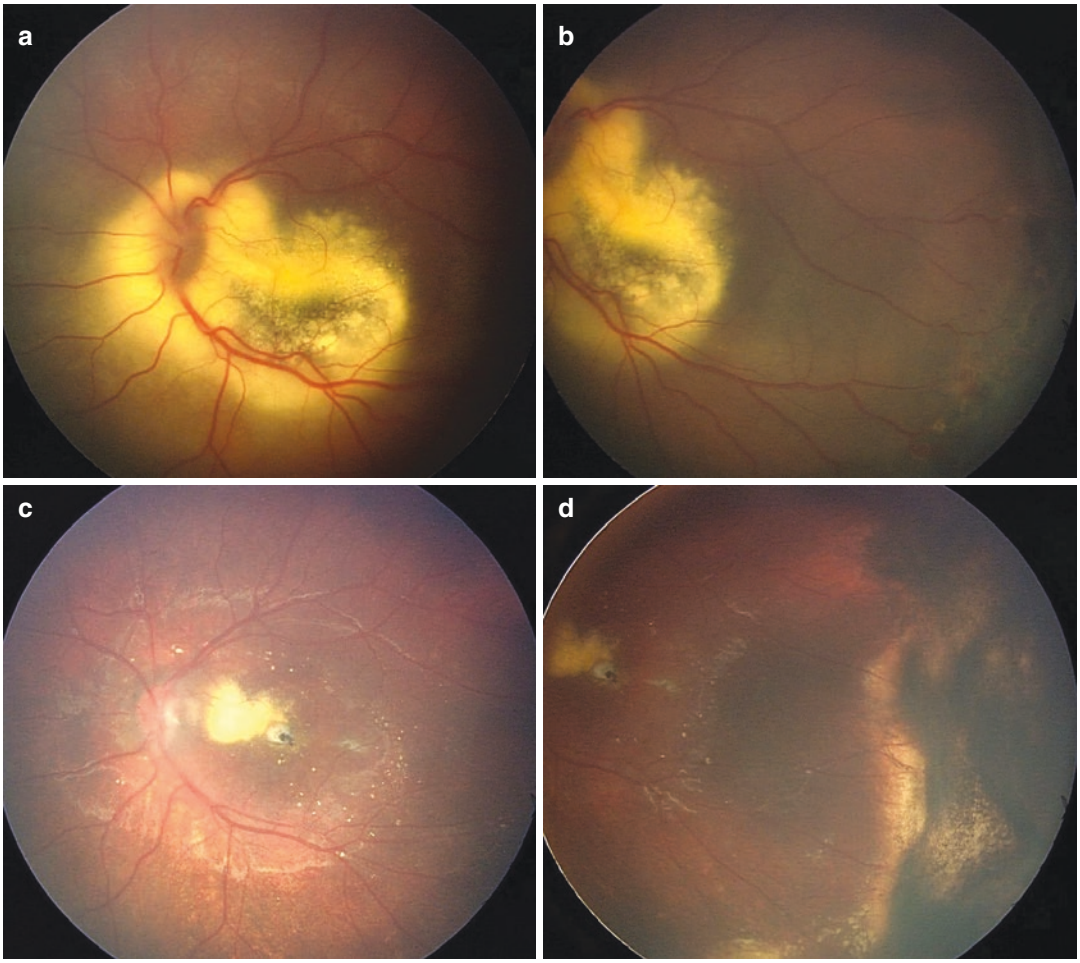

Fig. 2.6 A 20-month-old child with leukocoria OS. Note prominent exudation in the macular region (**a**) and retinal telangiectasia in the inferotemporal quadrant (**b**). He was treated with multiple sessions of laser photocoagulation and cryotherapy to the involved regions of the retina. One year later,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

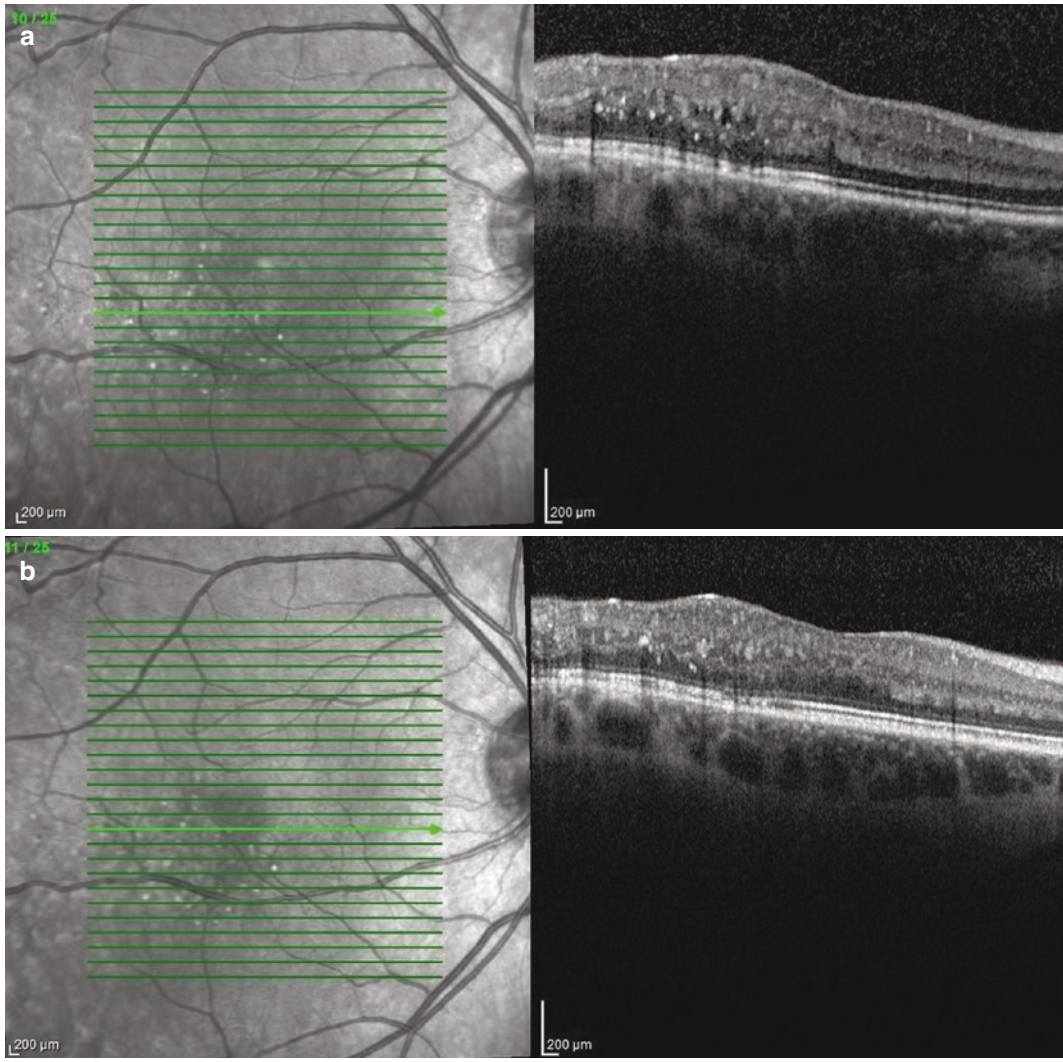

Fig. 2.7 OCT of the right macula in a 25-year-old male depicting macular edema due to Coats' disease. Edema was not amenable to focal laser treatment due to central location (**a**). Patient underwent intravitreal dexamethasone injection and showed resolution of macular edema at 6-week follow-up (**b**)

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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