Clinical Ophthalmic Oncology

Retinal Tumors

Arun D. Singh
Bertil E. Damato
Editors

Third Edition

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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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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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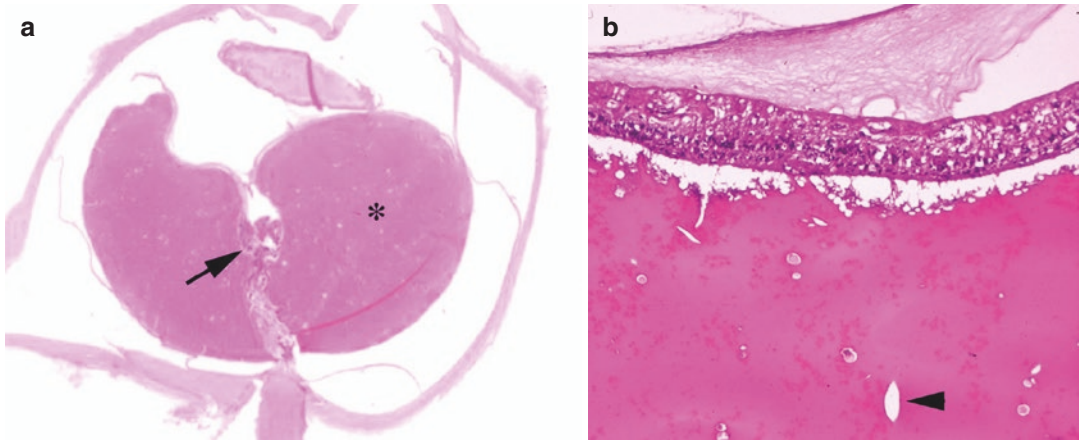

Fig. 2.1 Enucleated eye with Coats' disease. Note the total exudative retinal detachment (arrow) and the subretinal exudate (asterisk) (**a**, low-power hematoxylin and eosin). Cystic degeneration, disorganization, and deposition of PAS-positive material in the outer retina. Cholesterol clefts are seen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

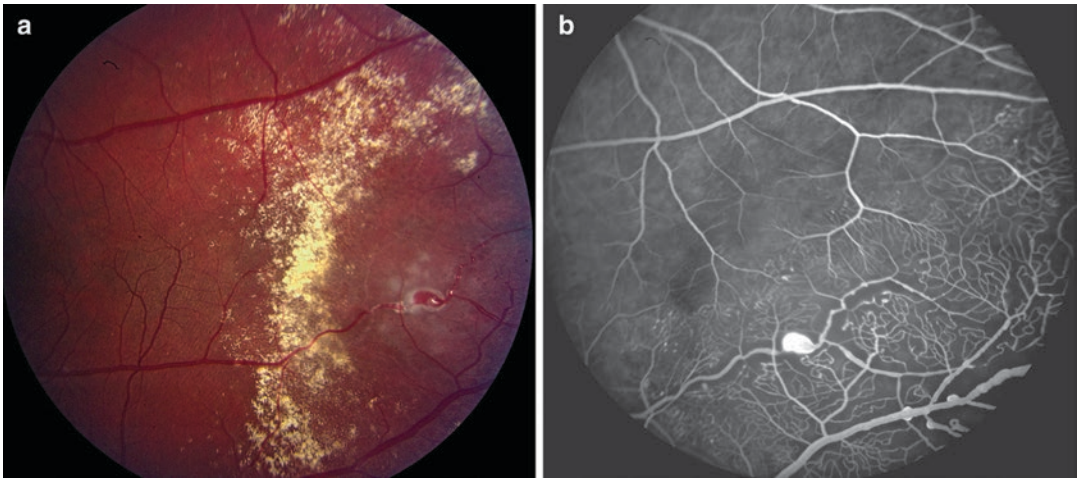

Fig. 2.2 Fundus photograph of the left eye demonstrates the circinate lipid exudation surrounding retinal telangiectasia (**a**). Fluorescein angiography demonstrates the area of bulbous aneurysms, vascular telangiectasia, and areas of capillary nonperfusion (**b**)

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