Ocular Tumors

H. V. Nema
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Editors

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Foreword

It is my privilege to write the foreword for *Ocular Tumors.*

Professor Nema has more than 50 years of experience in education and is well recognized as a prolific author and editor of ophthalmic textbooks. *Ocular Tumors* represents a contribution of leading experts in the field of ocular oncology from the major centers in India.

The book provides a broad spectrum introduction to not only intraocular tumors in adults and children but also tumors of the eyelid, conjunctiva, and the orbit. With high-quality illustrations, *Ocular Tumors* is certain to attract wide readership from India and abroad.

I congratulate all the authors for working collectively to represent their knowledge and experience in this masterfully edited book.

Arun D. Singh
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Preface

Literature on ocular tumors in the past six decades has undergone a sea change. Recent developments in the diagnosis and management of ocular tumors have greatly changed the prognosis and visual outcome.

Ocular tumors are seen in both pediatric and elderly age groups. Retinoblastoma is a common tumor of childhood. Delayed diagnosis of retinoblastoma can cause morbidity and mortality. In the past, the gold standard of treatment for retinoblastoma was enucleation to save the life of the child. Recent diagnostic techniques and treatment strategies such as brachytherapy and intra-arterial, intravitreal, and intracameral chemotherapy have dramatically improved the survival rate. Considering the importance of retinoblastoma in this region, three chapters have been devoted to this topic.

Malignant melanoma of choroid is the most common primary intraocular malignancy of adults. A number of risk factors for the development of choroidal melanoma and its metastasis are known. Genetic alteration in uveal melanoma slows the risk of metastasis and helps in determining its prognosis. Many benign lesions of choroid may cause a diagnostic dilemma as they clinical resemble choroidal malignant melanoma. Pitfalls in the diagnosis of choroidal malignant melanoma are critically discussed by Shanmugam and Sagar.

To adequately cover the subject, chapters on Intraocular Lymphoma, Vasoproliferative Retinal Tumor, Orbital Tumors, Leukemia and Eye, Choroidal Metastasis, and Phacomatoses have been included in this book. Chapters on Tumors of Conjunctiva and Eyelid Tumors are liberally illustrated for the benefit of readers.

The contributing authors of the book were selected on the basis of their expertise in the area covered. Some of the authors have been trained at Wills Eye Hospital, Philadelphia, Pennsylvania, USA, while almost all primary contributors head the Department of Ocular Oncology in their respective institutes.

We hope this book will help practicing ophthalmologists, fellows, and residents in ophthalmology and radiology in early diagnosis and effective management of ocular tumors in order to provide appropriate care and better quality of life to the patients.

Indore, Madhya Pradesh, India — H. V. Nema
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We are indebted to all the authors for their timely and valuable scientific contributions and to Prof AD Singh for writing the Foreword of the book.

Contents

About the Editors and Contributors

About the Editors

H. V. Nema has postgraduated from GR Medical College, Gwalior, India. He did his fellowship at the University of Manchester, England. He is a former professor and head, Department of Ophthalmology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India. He had been teaching ophthalmology to the undergraduate and postgraduate students at the Aligarh Muslim University, Aligarh and Banaras Hindu University, Varanasi for more than 30 years. Dr Nema has a distinguished academic career and is known for teaching, research, and publications. He had served as a consultant editor and advisory editor to the *Indian Journal of Ophthalmology*, *Afro-Asian Journal of Ophthalmology*, and *Indian Journal of Optometry*. He has many publications in national and international journals and authored and edited 24 books. Dr Nema has delivered guest lectures in many universities. He has served as an honorary general secretary and president of UP State Ophthalmological Society and was conferred Life Time Achievement Award by the society.

Nitin Nema is a professor of ophthalmology at Sri Aurobindo Medical College and PG Institute, Indore, India. He is an experienced vitreoretinal surgeon. After his postgraduation from the Department of Ophthalmology, Institute of Medical Sciences, Banaras Hindu University, India, he did his fellowship at Aravind Eye Hospital and PG Institute, Madurai, India. Additionally, he gained clinical and research experience from the University of Illinois at Chicago and the University of Wisconsin, Madison. He was awarded a fellowship by the All India Ophthalmological Society to work on a research project on uveitis at Sankara Nethralaya, Chennai, India. He was also awarded Dr Mohanlal Gold Medal for the best paper by the UP State Ophthalmological Society. He has published and presented many research papers, co-authored the *Textbook of Ophthalmology*, *Anatomy of the Eye and Adnexa*, and *Manual of Ophthalmology*, and co-edited 19 books.

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Abbreviations

A

ACC	Adenoid cystic carcinoma
AIDS	Acquired immuno deficiency syndrome
AJCC	American Joint Commission on Cancer
ALL	Acute lymphoid leukemia
AMD	Age-related macular degeneration
AML	Acute myeloid leukemia
AOX	Adult-onset xanthogranuloma
A-scan	Amplitude scan
ASCR	Autologous stem cell rescue
ASOCT	Anterior segment optical coherence tomography
AVM	Arterio-venous malformation

B

BAP1	BRCA1-associated protein 1
BCC	Basal cell carcinoma
BDUMP	Bilateral diffuse uveal melanocytic proliferation

C

CAM	Complexion-associated melanosis
CD	Cluster differentiation
CDK4	Cyclin-dependent kinase 4
CECT	Contrast-enhanced computed tomography
CIN	Conjunctival intraepithelial neoplasia
CLL	Chronic lymphoid leukemia
CML	Chronic myeloid leukemia
CO_2	Carbon dioxide
COMS	Collaborative Ocular Melanoma Study

COST Conjunctival stromal tumors
CSF Cerebrospinal fluid

D

DNA Deoxyribonucleic acid
DNS Dysplastic nevus syndrome
DLBCL Diffuse large B-cell lymphoma

E

EBRT External beam radiotherapy
EDI-OCT Enhanced depth imaging optical coherence tomography
EGFR Epidermal growth factor receptor
EIF1AX Eukaryotic translation initiation factor 1A, X linked
EMPSGC Endocrine mucin-producing sweat gland carcinoma
ERM Epiretinal membrane

F

FA Fluorescein angiography
FDA Food and Drug Administration
FISH Fluorescence in situ hybridization
FNA Fine needle aspiration biopsy
5-FU 5-Fluorouracil

G

GE Guanine nucleotide exchange factor
GEP Gene expression profiling
GFAP Glial fibrillary acid protein
GIST Gastrointestinal stromal tumor
GNA11 Guanine nucleotide-binding protein subunit alpha-11
GNAQ Guanine nucleotide-binding protein subunit alpha-Q
Gy Gray

H

HBID Hereditary benign intraepithelial dyskeratosis
HDM2 Human double minute 2
HIF Hypoxia-inducible factor

HIV Human immunodeficiency virus
HPV Human papilloma virus

I

IAC Intra-arterial chemotherapy
ICGA Indocyanine green angiography
ICRB International Classification of Retinoblastoma
IFN α2b Interferon alpha 2b
IGF1R Insulin-like growth factor 1 receptor
IgH/L Immunoglobulin heavy/light chain
IJCN Inflamed juvenile conjunctival nevus
IL Interleukin
IMRT Intensity-modulated radiotherapy
IOL Intraocular lymphoma
ISSVA International Society for the Study of Vascular Anomalies
IVitC Intravitreal chemotherapy

L

LAMB syndro Lentigines, atrial myxoma, mucocutaneous myxomas, and blue nevi syndrome
LOH Loss of heterozygosity
LUMPO Liverpool Uveal Melanoma Prognosticator Online

M

MALT Mucosa-associated lymphoid tissue
MAPK Miogen-activated protein kinase
MBAIT Melanocytic-BAP1-mutated atypical intradermal tumor
MITF Microphthalmia-associated transcription factor
MLPA Multiplex ligation-dependent probe amplification
MMC Mitomycin C
MRI Magnetic resonance imaging
MS Myeloid sarcoma
MSA Microsatellite analysis
MTS Muir–Torre syndrome

N

NCS Neurocutaneous syndrome
NGX Necrobiotic xanthogranuloma
NHL Non-Hodgkin's lymphoma

O

OCT	Optical coherence tomography
OCTA	Optical coherence tomography angiography
OSSN	Ocular surface squamous neoplasia

P

PAM	Primary acquired melanosis
PCNSL	Primary central nervous system lymphoma
PCR	Polymerase chain reaction
PCV	Polypoidal choroidal vasculopathy
PDT	Photodynamic therapy
PED	Pigment epithelial detachment
PEHCR	Peripheral exudative hemorrhagic chorioretinal degeneration
PET-CT	Positron emission tomography combined with computed tomography
PI3K	Phosphoinositide-3-kinase
PIOL	Primary intraocular lymphoma
PNET	Primitive neuro-ectodermal tumor
PPV	Pars plana vitrectomy
pRB Rb	Tumor suppressor protein
PRiMeU	Prediction of Risk of Metastasis in Uveal Melanoma
PUL	Primary uveal lymphoma
PVRL	Primary vitreoretinal lymphoma
PWS	Port-wine stain

R

RB	Retinoblastoma
RNA	Ribonucleic acid
RPE	Retinal pigment epithelium

S

SCC	Squamous cell carcinoma
SEER	Surveillance, Epidemiology, and End Results
SFRT	Stereotactic fractionated radiotherapy
SCC	Squamous cell carcinoma
SLET	Simple limbal epithelial transplant
SNP	Single-nucleotide polymorphism
SOAI	Selective ophthalmic artery infusion
SWS	Sturge–Weber syndrome

T

TCR	T-cell receptor
TNM	Tumor node metastasis
TRD	Tractional retinal detachment
TTT	Transpupillary thermotherapy

U

UL	Uveal lymphoma
USG	Ultrasonography
UV	Ultraviolet

V

VH	Vitreous hemorrhage
VHL	van Hippel–Lindau
VM	Venous malformation
VPRT	Vasoproliferative retinal tumor
VRL	Vitreoretinal lymphoma

W

WHO	World Health Organization

Overview of Ophthalmic Tumors

1

Lingam Gopal, Gangadhara Sundar, and Su Xinyi

1.1 What Constitutes Ophthalmic Oncology?

Ophthalmic oncology is one of the advanced and multidisciplinary ophthalmic subspecialties that involves the diagnosis and management of intraocular, ocular surface, and ocular adnexal (orbit, eyelid, and lacrimal system) tumors. Most tumors arise primarily from the site (one of the sites mentioned above) where they are found. Not infrequently, they can also metastasize from known or unknown primary malignancy elsewhere or spread by contiguity from adjacent sites such as paranasal sinuses, nasopharynx, or intracranial cavity. On occasions, the ophthalmologist may be the first to diagnose a systemic malignancy that has metastasized to the eye or orbit, causing ophthalmic symptoms before causing symptoms related to the primary malignancy.

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1.2 Who Are the Personnel Involved in the Management?

An ideal practice of Ophthalmic Oncology involves close collaboration between many specialists, both within ophthalmology and beyond. Apart from the ophthalmologist, other specialists involved include, the diagnostic and interventional radiologist, radiation oncologist along with radiation physicist, pediatric and adult oncologist, ocular pathologist, geneticist, ocular prosthetician and anaplastologist, etc. Each one serves a distinct and important role with the ophthalmologist playing the lead role. Depending on background training of the ophthalmic oncologist, additional help may be needed from other ophthalmic subspecialists such as corneal surgeon, vitreoretinal surgeon, oculoplastic and orbital surgeon, etc.

Considering the complexity of the issues and numerous advances in various fields like chemotherapy, targeted therapy, tele- and brachytherapy, etc., one often needs the help of super specialists within each of the above-mentioned specialties. For example: a pediatric rather than an adult oncologist would be appropriate to advise, administer, and monitor the chemotherapy for retinoblastoma. Likewise, a general pathologist may not be best equipped to interpret a vitreous biopsy done for suspected intra ocular lymphoma. One needs a pathologist with special interest in ophthalmic pathology—not just with histopathologic techniques but also immunohistochemical techniques and even molecular genetic studies to come to reliable conclusions. Similarly, one needs an interventional radiologist who has experience in children to be able to cannulate the ophthalmic artery in a small child.

Given the rapid expansion in knowledge and application of numerous techniques for organ/vision salvage, therefore, ideally, an ophthalmic oncologist should be fellowship trained—either a vitreoretinal surgeon (intraocular tumors) or an oculoplastic surgeon (ocular surface and ocular adnexal tumors), and not just a general ophthalmologist attempting to manage everything including tumors of the eye.

1.3 What Are the Commonest Tumors One Comes Across?

The incidence and prevalence of most ocular and adnexal tumors are generally constant in most ethnic groups worldwide and geographically as well. However, there are specific tumors that are more common in certain ethnic and geographical situations, which one should be aware of. While metastatic tumors in the choroid are said to be the commonest intra ocular tumors seen [1], retinoblastoma still remains the commonest intra ocular tumor that an ophthalmologist is called upon to manage—a tumor that threatens vision and life of a child. In the Asian population, choroidal melanoma is not as common as in the Caucasian population [2], but is still seen reasonably frequently—hence often misdiagnosed and mismanaged. On the contrary, both ocular surface neoplasms and sebaceous gland carcinomas of the eyelid are much more common in Asians compared to the Caucasian population [3]. Likewise, a combination of fair complexion and increased sun exposure has led to a

Table 1.1 Some common pediatric and adult ophthalmic neoplasms

	Pediatric	Adult
Intraocular		
Benign	Astrocytomas, choroidal osteoma	Choroidal nevus, choroidal hemangioma, retinal capillary hemangioma
Malignant	Retinoblastoma, medulloepithelioma	Metastasis, uveal melanoma, intraocular lymphoma
Ocular surface		
Benign	Conjunctival nevi	Nevi
Malignant		Ocular surface squamous neoplasia (OSSN), conjunctival melanoma
Ocular adnexal		
Benign	Eyelid: Xanthogranulomas, infantile hemangioma Orbit: Dermoid, neurofibroma	Eyelids: nevi, dermal adnexal tumors Orbit: solitary venous malformation (cavernous hemangioma), schwannoma, hemangiopericytoma, pleomorphic adenoma, osteoma, etc.
Malignant	Orbit: Rhabdomyosarcoma, neuroblastoma (metastatic), orbital retinoblastoma	Eyelid: basal cell carcinoma, squamous cell carcinoma, sebaceous gland carcinoma, melanoma Orbit: lymphoma, metastasis, adenoid cystic and adenocarcinoma of the lacrimal gland

significant increase in basal cell carcinoma and melanoma in the Australian population [4]. Patients with xeroderma pigmentosa, have been shown to have an increased risk of all cutaneous and ocular surface neoplasms [5]. An overview of common and less common intraocular and ocular adnexal tumors is shown in Table 1.1.

1.3.1 Presentation

Traditionally neglect and delay in presentation has been the norm in developing countries like India so much so that the commonest presentation of retinoblastoma in the 1970s was orbital presentation with proptosis [6]. Fortunately, the awareness levels have improved significantly and currently eye salvage is possible in a higher percentage of cases.

Ocular and adnexal tumors affect all ages. However, each type of tumor has usually a distinct age range of presentation. While retinoblastomas occur in children in the age group of 2–5 years [7], choroidal melanomas tend to occur in the adult age group. However, one must be cognizant of exceptions and be alert to avoid misdiagnosis. Retinoblastoma can occur in relatively older children and on occasion in adults [8], while choroidal melanoma has been reported in young children as well [9].

1.4 What Changes Were Seen in the Investigational Approach?

While most ocular and adnexal tumors can be reliably suspected and diagnosed based on history and clinical examination alone, imaging of the eye and orbit are frequently employed to narrow down and further refine preoperative diagnosis. Advances in technology have provided us with high resolution images of the eye and orbit. Ocular surface lesions may be imaged with (ASOCT) which may help in staging the disease and guide surgical treatment. For intra ocular tumors, ultrasonography still remains an important ophthalmologist performed investigation. It is an excellent cost-effective and reliable tool useful in diagnosis and follow up for some tumors. Additional information can be obtained from fluorescein and indocyanine green angiography. In case of tumors in ciliary body area, ultrasound biomicroscopy is valuable. Swept source optical coherence tomography has been a good addendum to imaging shallow tumors of the choroid [10, 11].

Contrast enhanced computed tomography (CECT) remains the imaging of choice for most orbital and ocular adnexal tumors, partly because of good bone and soft tissue differentiation, easy readability and also its cost-benefit ratio. However, in certain situations such as soft tissue tumors, apical orbital or optic nerve/sheath lesions and in young children who may require repeated imaging, magnetic resonance imaging (MRI) is the preferred modality of imaging, considering the possibility for greater soft tissue detail. In children with retinoblastoma, the radiation exposure of CT scan can increase the risk of second tumors and hence MRI is preferred—especially if the patient is less than 2 years old and with suspected germ line mutation [12].

When primary malignancy of the eye or adnexa or suspected, a positron emission tomography combined with computed tomography (PET-CT) is often employed to detect systemic spread and thus stage the disease prior to management.

Documentation has become easier with wide-angle imaging provided by Retcam and Optos fundus cameras. These not only provide crucial documentation but permit accurate comparison between visits to assess regression or otherwise of the tumor and appropriately change the approach to management [13]. They also help communicate with the patient/relatives better.

1.5 What Changes Have Taken Place in the Management Approaches?

In the management of retinoblastoma, several paradigm shifts have taken place. Historically most globes were enucleated. Currently with a combination of chemotherapy and local aggressive treatment, the threshold for enucleation is raised significantly, with attempts made to salvage most eyes even in unilateral cases. Chemotherapy has acquired the role of primary treatment. While systemic administration is still the most common route of administration, intra-arterial and intravitreal routes of administration of these agents have enabled salvage of many more

eyes than before. External beam radiation which was the treatment of choice in the past has now become the last therapeutic option. While plaque therapy is nothing new, the greater access to this facility has enabled its application to several posterior segment, anterior segment as well as surface tumors- both as primary treatment (choroidal melanoma) as well as salvage treatment after chemotherapy (retinoblastoma).

Direct high intensity thermal laser photocoagulation of retinoblastoma tumors has been replaced by slow heating using transpupillary thermotherapy. Photodynamic therapy has been found useful in eyes with choroidal hemangioma (with verteporfin) and some cases of retinoblastoma (with Indocyanine green dye) [14].

Ocular surface and adnexal tumors (sebaceous gland carcinoma of the eyelid, adenoid cystic carcinoma (ACC) of the lacrimal gland) which were managed with orbital exenteration are being managed by more conservative techniques of chemoreduction, topical immunotherapy (OSSN) [15], followed by local excision and a combination of postoperative adjuvant radiotherapy and chemotherapy(ACC) with better globe, vision and life preservation.

Targeted systemic therapy with Rituximab, BRAF inhibitors, etc. (based on histological type and molecular genetics) is playing increasing role in conditions such as orbital lymphoma and some metastatic melanomas [16–18].

1.6 Redefining the Role of Genetics and Molecular Markers

Genetics is no longer restricted to broad genetic counseling based on the known inheritance patterns of the tumors. Specific molecules can serve as biomarkers for the diagnosis and prognostication of intraocular malignancies. In addition, some distinctive molecules closely related to the growth profiles of different tumors can serve as valuable indicators of prognosis and for survival analysis.

In uveal melanoma, patients with monosomy of chromosome 3 have poorer prognosis (i.e., due to metastatic disease) [19] likely due to mutations identified in BAP1 (BRCA associated protein 1) [20]. Genetic testing of the trans vitreal retinochoroidal vitrector biopsy sample provided accurate stratification of patients with high, intermediate and low risk, based on copy number variations of chromosomes 3 and 8 [21].

Primary intraocular lymphomas (PIOL) are mostly monoclonal B-cell lymphomas that stain positively for B-cell markers, such as CD19, CD20, and CD22. They show restricted expression of either kappa or lambda chain, express germinal center markers such as BCL6 and CD10 and secrete high amounts of IL-10 (an immunosuppressive cytokine) [22]. MYD88 mutations detection by polymerase chain reaction significantly improves the diagnostic yield of vitrectomy specimens [23].

Retinoblastoma develops in the embryonic retina following biallelic loss of *RB1*. However, there are a wide range of genetic and epigenetic changes that can affect *RB1* resulting in different clinical outcomes. In addition, other transformations, such as MYCN amplification, have been known to generate particularly aggressive tumors [24, 25].

Further, genetic studies on specific molecules and pathways could reveal more detailed features of intraocular tumors and provide hints or identifying pivotal molecules that can be targeted therapeutically.

1.6.1 Region Specific Issues

Despite the progress in many fronts in the understanding of the disease, availability of newer chemotherapeutic drugs, etc. there are several challenges one faces in a country like India with diversity in cultures, beliefs, financial capabilities, and geographic locations. Cost of treatment remains the most important factor that controls the final outcome of treatment. Crucial to the success of treatment in a condition like retinoblastoma is the rigidity with which follow up schedules are maintained and interventional treatment is administered—a goal not always attained because of social issues. Reluctance to subject a child to enucleation based on religious beliefs is still an issue to reckon with.

1.6.2 Proactive Approaches

Traditionally medicine has been reactive—investigating and treating only when the patient comes with symptoms or signs. There are several situations in ocular oncology however, where being proactive is desired and probably mandated. Top in this list is the need to screen siblings of a child with retinoblastoma periodically till the risk of occurrence is estimated to be very low. This recommendation is applicable even to yet to be born siblings. Detecting the intra ocular tumor while the child is in utero has enabled early delivery of the child and prompt institution of treatment thus salvaging the eyes [26].

In cases of angiomatosis retinae, the routine evaluation with MRI brain, abdominal ultrasound, etc. for other known associated tumors in the body is a well-known practice.

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Retinoblastoma

2

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Retinoblastoma represents 3% of all childhood cancers, and is the most common intraocular malignancy of childhood. The management of retinoblastoma has gradually evolved over the past few decades, with an aim to not only preserve life and eye, but also optimize residual vision. The treatment of retinoblastoma is multimodal, with chemotherapy, focal treatment including transpupillary thermotherapy (TTT), cryotherapy and laser photocoagulation, radiation therapy, and surgery, all playing a vital role. Intravenous chemotherapy has been the mainstay of treatment for the past two decades, and still continues to be the most extensively used eye-saving treatment modality. Periocular and intravitreal chemotherapy have specific indications in the management of retinoblastoma. Intra-arterial chemotherapy has emerged as a promising alternative for advanced and refractory retinoblastoma, both as a primary and secondary therapy. Recent advances in genetics of retinoblastoma have also helped in improving the overall clinical management of this malignancy.

2.1 Epidemiology of Retinoblastoma

The incidence of retinoblastoma is 1 in every 15,000–18,000 live births [1]. There is no variation in the number among different races, although there is a diversity among different countries. There are an estimated 5000–8000 new cases worldwide annually, with India alone contributing to 1500–2000 cases. With increasing population in Asian and African countries, the number of retinoblastoma is also rising.

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Unfortunately, the mortality rates for retinoblastoma is also higher in these countries owing to delay in diagnosis, advanced disease at presentation, lack of access to advanced medical facilities, and absence of standard management protocols.

2.2 Clinical Features

Leukocoria (white pupil) is the most common sign of retinoblastoma, and strabismus is the second most important presenting sign. In majority of cases, the parents notice the white reflex first and seek the opinion of a pediatrician. This makes the pediatricians an important bridge between the retinoblastoma families and the treating ophthalmologist, making it extremely crucial that they have a basic knowledge of retinoblastoma (Table 2.1). Retinoblastoma is usually diagnosed at an average age of 18 months, with 95% of children diagnosed by 5 years of age. Germline retinoblastomas can present as early as first month and sporadic retinoblastomas are detected at an average age of 24 months [1]. Retinoblastoma can be unilateral or bilateral. All bilateral cases are positive for germline mutation, whereas only 10–15% patients with unilateral retinoblastoma carry a germline mutation.

A child with a suspicious retinoblastoma is best examined under anesthesia for a detailed fundus evaluation (Table 2.2). Retinoblastoma typically manifests as a unifocal or multifocal, well-circumscribed, dome-shaped retinal mass with dilated retinal vessels. Although initially transparent and difficult to visualize, it grows to become opaque and white. When small, the tumor is entirely intraretinal. As it enlarges, it grows in a three-dimensional plane, extending away from the vitreous cavity (exophytic) or toward it (endophytic) [1].

In the exophytic growth pattern, the tumor causes diffuse retinal detachment (Fig. 2.1a). It is most often associated with numerous small subretinal seeds. In contrast, an endophytic retinoblastoma progressively fills the vitreous cavity, and causes vitreous seeding (Fig. 2.1b). At times, the tumor maybe a combination of these two growth patterns. Diffuse infiltrating retinoblastoma is a rare pattern of presentation where there is no obvious mass, only a flat retinal infiltration, and is acalcific. It is generally seen in older children, and the incidence is less than 2%. Diffuse anterior retinoblastoma, a recent entity, is considered as an anterior variant of diffuse infiltrating retinoblastoma. It is thought to arise from the most peripheral parts of retina with anterior growth, and no retinal focus visible on examination [2].

Table 2.1 Presenting signs in retinoblastoma

Leukocoria
Strabismus
Poor vision
Red painful eye
Vitreous hemorrhage
Phthisis bulbi
Sterile orbital cellulitis
Proptosis

Table 2.2 Examination under anesthesia (EUA)

Visual acuity and slit lamp examination must be performed in the office for older children Age-appropriate visual assessment must be performed in the office for all children
Anesthesia care • Baseline investigations—Hb%, CBC, blood group • Pre-anesthesia examination by the anesthesiologist/pediatrician • Age-appropriate fasting • Sevoflurane or isoflurane-based EUA with a laryngeal mask by a pediatric anesthesiologist or an anesthesiologist with appropriate training in techniques of pediatric anesthesia • Monitoring is ideally performed during anesthesia and until recovery using multifunctional monitors • An intravenous access is mandatory • Complete recovery by an appropriately trained nurse under supervision of an anesthesiologist should be ensured before the child is handed over to the parents
Examination under anesthesia involves evaluation of both eyes in a detailed manner • Anterior segment evaluation • Corneal diameter • Intraocular pressure measurement by Perkins applanation tonometer • Total retinal evaluation up to ora serrata in both eyes5 • Retinal drawing—all tumors, subretinal fluid, subretinal seeds, and vitreous seeds are documented • Wide-angle fundus photography
Instrumentation • Hand-held slit lamp (optional) • Operating microscope • Indirect ophthalmoscope with +20 diopter lens • Eye speculum • Perkins applanation tonometer • Calipers • Cryotherapy machine with retinal cryotherapy probe • Large spot diode laser with indirect ophthalmoscope delivery • RetCam or similar wide field fundus photography • Facility for fluorescein angiography (optional) • Hand-held OCT (optional)

Patients with anterior extension of the tumor can present with white fluffy exudates in the anterior chamber resembling a hypopyon, called pseudohypopyon [1]. Neovascularization of iris and glaucoma are other clinical presentations seen in patients with advanced tumor (Fig. 2.1c). Orbital cellulitis-like picture occurs when a large tumor undergoes necrosis and induces inflammation in and around the eye (Fig. 2.1d). Retinoblastoma which has extended outside the confines of the eye is known as orbital retinoblastoma and this can occur when the tumor invades either the optic nerve, or full thickness of the sclera and beyond, and the patient generally presents with proptosis.

2.3 Differential Diagnosis

The most important differential diagnosis is Coats' disease [3]. There are several other lesions that can simulate retinoblastoma and are known as pseudoretinoblastomas. The important differential diagnoses are listed in Table 2.3.

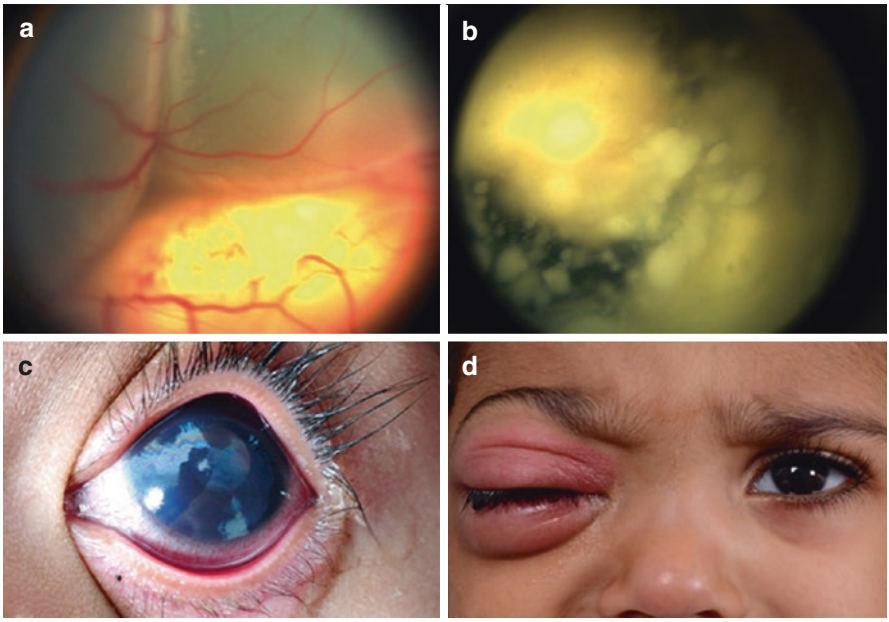

Fig. 2.1 Clinical presentation of retinoblastoma (**a**) Exophytic growth pattern with diffuse subretinal fluid (**b**) Endophytic growth pattern with diffuse vitreous seeds (**c**) Advanced retinoblastoma with neovascular glaucoma (**d**) Advanced retinoblastoma presenting as sterile orbital cellulitis

Table 2.3 Pseudoretinoblastoma

Coats' disease
Persistent fetal vasculature
Vitreous hemorrhage
Toxocariasis
Familial exudative vitreoretinopathy
Retinal detachment
Congenital cataract
Coloboma
Astrocytic hamartoma
Combined hamartoma
Endogenous endophthalmitis
Retinopathy of prematurity
Medulloepithelioma
X-linked retinoschisis
Incontinentia pigmenti
Juvenile xanthogranuloma
Norrie's disease

2.4 Imaging

While the diagnosis of retinoblastoma is mostly clinical, ancillary tests like ultrasonography, fluorescein angiography (FA), optical coherence tomography (OCT), computed tomography (CT), and magnetic resonance imaging (MRI) aid in the documentation of the disease and differentiation of pseudoretinoblastomas from retinoblastoma (Table 2.4) [4–6]. CT scan also helps diagnose extraocular

Table 2.4 Role of multimodal imaging in retinoblastoma

RetCam	• Wide-angle fundus camera that is used in documenting fundus findings at each visit and monitoring the treatment
Ultrasonography	• Detecting calcification • Establishing diagnosis in an opaque media • Measuring tumor thickness
Fluorescein angiography (FA)	• Visualizing tumor hyperfluorescence • Detecting capillary drop-outs, neovascularization, recurrences and occlusive vasculopathy in a child with a treatment history of IAC
Hand-held spectral domain OCT (SD-OCT)	• Documenting early intraretinal tumors • Differentiating from pseudoretinoblastomas like astrocytic hamartoma • Detecting small recurrences • Assessing fovea for visual potential
Computed tomography (CT)	Need • Detecting calcification • Identifying extraocular and optic nerve extension Caution • Avoid in known heritable retinoblastoma (family history, bilateral, unilateral, and multifocal) • Avoid "routine" CT scan in all children with retinoblastoma or for purely intraocular retinoblastoma Specifications • Spiral CT with rapid acquisition time • Non-contrast • Orbit • Axial and coronal • Sagittal reconstruction • 2 mm slice thickness Indications • To diagnose in the presence of opaque media precluding visualization of the tumor • To differentiate pseudoretinoblastoma or to rule out retinoblastoma in a simulating situation • Baseline scan to rule out extraocular extension in the presence of clinical risk factors—corneal diameter >11 mm, asymmetry of corneal diameter >1 mm, corneal edema, neovascularization of iris, IOP >20 mmHg, hypopyon, hyphema, vitreous exudates, vitreous hemorrhage, any media opacity precluding visualization, proptosis, phthisis bulbi • To monitor response in a child with extraocular retinoblastoma treated with neoadjuvant therapy after three cycles

(continued)

Table 2.4 (continued)

Magnetic resonance imaging (MRI)	Need • Delineating the intraocular tumor extent and detection of optic nerve or scleral extension • Disease staging • Ruling out pinealoblastoma in bilateral cases Caution • Needs monitored sedation or general anesthesia • Avoid "routine" MRI in all children with retinoblastoma or for purely intraocular retinoblastoma Specifications • Non-contrast for routine MRI; gadolinium enhancement for suspected intracranial extension • STIR T1 and T2, with and without fat suppression • Surface coil • Axial, coronal, sagittal • Orbit and brain Indications • Heritable retinoblastoma—baseline scan to screen for pinealoblastoma • Baseline scan to rule out extraocular extension and CNS involvement in the presence of clinical risk factors—corneal diameter >11 mm, asymmetry of corneal diameter >1 mm, corneal edema, neovascularization of iris, IOP >20 mmHg, hypopyon, hyphema, vitreous exudates, vitreous hemorrhage, any media opacity precluding visualization, proptosis, phthisis bulbi • To monitor response in a child with extraocular retinoblastoma treated with neoadjuvant therapy after three cycles
PET-CT scan	Need • To rule out systemic metastasis Caution • Needs monitored sedation or general anesthesia • Avoid "routine" PET in all children with retinoblastoma or for purely intraocular retinoblastoma Indications • Clinically suspected systemic metastasis at baseline or during/following treatment

extension, while MRI is most appropriate to detect optic nerve invasion and to screen for pinealoblastoma in heritable retinoblastoma.

2.5 Grouping and Staging

The grouping system is for retinoblastomas confined to the eye, where eye salvage is the end point, whereas the staging system is for predicting survival in patients with retinoblastoma. International Classification of Retinoblastoma (ICRB) was devised in 2003 and includes both grouping and staging [7]. The grouping is based on the tumor size, location, severity and presence of subretinal and vitreous seeds (Table 2.5).

Table 2.5 International classification of retinoblastoma

Grouping	
Group A: Small tumor	Retinoblastoma ≤3 mm in size
Group B: Larger tumor	Rb >3 mm Macular location (≤3 mm to foveola) Juxtapapillary location (≤1.5 mm to disc) Clear subretinal fluid ≤3 mm from margin
Group C: Focal seeds	Subretinal seeds ≤3 mm from retinal tumor Vitreous seeds ≤3 mm from retinal tumor Subretinal and vitreous seeds ≤3 mm from retinal tumor
Group D: Diffuse seeds	Subretinal seeds >3 mm from retinal tumor Vitreous seeds >3 mm from retinal tumor Subretinal and vitreous seeds >3 mm from retinal tumor
Group E: Extensive retinoblastoma	Rb occupying 50% globe Neovascular glaucoma Opaque media (from hemorrhage in anterior chamber, vitreous, or subretinal space) Invasion of postlaminar optic nerve, choroid (2 mm), sclera, orbit, anterior chamber
Staging	
Stage 0	Unilateral or bilateral retinoblastoma and no enucleation
Stage I	Enucleation with complete histological resection
Stage II	Enucleation with microscopic tumor residual (anterior chamber, choroid, optic nerve, sclera)
Stage III	Regional extension A. Overt orbital disease B. Preauricular or cervical lymph node extension
Stage IV	Metastatic disease A. Hematogenous metastasis 1. Single lesion 2. Multiple lesions B. CNS extension 1. Prechiasmatic lesion 2. CNS mass 3. Leptomeningeal disease

2.6 Management

Management of a child with retinoblastoma is aimed at achieving the three sequential goals of life salvage, eye salvage, and optimal vision. Management involves the identification of the tumor group and stage, decision-making regarding the appropriate therapeutic measure, and meticulous follow-up for monitoring the treatment progress and detection of any recurrence. While intravenous chemotherapy (IVC) remains the most extensively used modality of treatment, other tools available for the therapeutic intervention in retinoblastoma include chemotherapy using different delivery routes, focal treatment with cryotherapy, transpupillary thermotherapy (TTT), and laser photocoagulation, radiotherapy by teletherapy (external beam) or brachytherapy (plaque radiotherapy), and enucleation (Table 2.6).

Table 2.6 Decision-making in the management of retinoblastoma: treatment options

Primary tumor: options for treatment	
Unilateral advanced (D, E)	IAC, IVC, Enucleation
Unilateral less advanced (A, B, C)	IAC, IVC, focal therapy
Bilateral advanced (D, E)	IVC + POC
Bilateral less advanced (A, B, C)	IVC
Recurrent tumor: options for treatment	
Solid tumor	IVC, IAC, plaque radiation, enucleation
Subretinal seeds	IVC, IAC
Vitreous seeds	IVitC

2.6.1 Chemotherapy

In recent years, there has been a trend toward targeted therapy to manage retinoblastoma with minimal adverse effects on surrounding normal retina and general systemic health. The use of intra-arterial chemotherapy (IAC), periocular chemotherapy (POC), and intravitreal chemotherapy (IVitC) has enabled to focus direct drug delivery to the tumor. Unlike IVC which can be used in the primary management of all retinoblastomas, IAC, POC, and IVitC have specific indications.

2.6.1.1 Intravenous Chemotherapy

Currently, IVC is the most widely used treatment in India (Table 2.7). Used as a combination triple-drug therapy of vincristine, etoposide, and carboplatin, chemotherapy with focal consolidation achieves excellent success rates in the primary management of retinoblastoma. Chemotherapy alone can achieve an impressive tumor control in less advanced cases, with success rates of 100%, 93%, and 90% in ICRB groups A, B, and C, respectively (Fig. 2.2a–d) [8–10]. Rates of regression of retinoblastoma and eye salvage with standard triple-drug chemotherapy have been suboptimal for ICRB group D and E tumors. In group D eyes, approximately half of the eyes require either EBRT or enucleation for tumor control [11]. A combination of chemotherapy and radiation in eyes with vitreous seeds has yielded globe-salvage rates varying from 22 to 70% [12]. Periocular carboplatin and topotecan injection also resulted in higher intravitreal drug level (Table 2.8). Transscleral penetration of posterior sub-Tenon carboplatin leads to augmented vitreous concentration. High-dose chemotherapy with concurrent periocular carboplatin has been tried as a primary management strategy, specifically in eyes with diffuse vitreous seeds [11]. This has led to better tumor control in advanced cases, with 95% eye salvage rate in eyes with focal vitreous seeds and a 70% eye salvage rate in those with diffuse vitreous seeds (Fig. 2.3a–d) [12, 13].

2.6.1.2 Intra-arterial Chemotherapy

IAC for the treatment of intraocular retinoblastoma was first performed by Algernon Reese with direct internal carotid artery injection of the alkylating agent triethylene melamine in 1954. Suzuki and Kaneko described the technique of ‘selective

Table 2.7 Intravenous chemotherapy

Procedure IVC when given as a primary treatment for retinoblastoma causes reduction in tumor volume, and this is known as chemoreduction (CRD). Most commonly, a combination of three drugs of standard dose (SD) is used, although high dose (HD) may be necessary in advanced cases or tumors not responding to SD			
Drugs Triple-drug combination therapy of vincristine, etoposide, and carboplatin (VEC) is employed, generally given 4 weekly for six cycles Day 1: Vincristine + etoposide + carboplatin Day 2: Etoposide			
Drug	SD-VEC (≥3 years of age)	SD-VEC (< 3 years of age)	HD-VEC
Vincristine[a] Etoposide Carboplatin	1.5 mg/m^2 150 mg/m^2 560 mg/m^2	0.05 mg/kg 5 mg/kg 18.6 mg/kg	0.025 mg/kg 12 mg/kg 28 mg/kg
[a]Maximum dose <2 mg			
Indications (1) Primary tumor (2) recurrent tumor (3) recurrent subretinal seeds (4) as adjuvant therapy in post-enucleation patients with high-risk features (discussed elsewhere) (5) orbital retinoblastoma (6) as palliative therapy in metastatic retinoblastoma			
Advantages (1) Long-term tumor control (2) reduces incidence of pinealoblastoma (3) reduces incidence of second cancers (4) reduces incidence of systemic metastasis			
Disadvantages (1) Systemic side effects including thrombocytopenia, leucopenia, and anemia (2) allergic reactions to carboplatin and etoposide (3) long-term effects include hearing loss, renal toxicity, and secondary leukemia			

ophthalmic artery infusion' (SOAI) in 2004 by the balloon technique, where a micro-balloon catheter is positioned by a transfemoral artery approach at the cervical segment of the internal carotid artery just distal to the orifice for the ophthalmic artery [14]. At this point, the balloon catheter is inflated, and chemotherapy is injected with flow thereby directed into the ophthalmic artery. The authors noted there are several small, but nevertheless important, branches proximal to the origin of the ophthalmic artery (i.e., cavernous branches of the ICA) into which infused chemotherapy could flow, and concluded that this infusion method is not truly selective. In 2006, Abramson and Gobin pioneered direct intra-arterial (ophthalmic artery) infusion or superselective intra-arterial chemotherapy or "chemosurgery" [15].

Patient is examined under anesthesia by the treating ocular oncologist. Documentation of each affected eye is performed by wide-angle fundus photography, FFA and B-scan ultrasonography. The decision to treat with IAC is undertaken in consultation with an ocular oncology team, an endovascular neurosurgeon, and a pediatric oncologist. The procedure is performed under general anesthesia using a sterile technique (Figs. 2.4a–d). Nasal decongestion is achieved by topical decongestant drops or spray. Anticoagulation with intravenous infusion of heparin is

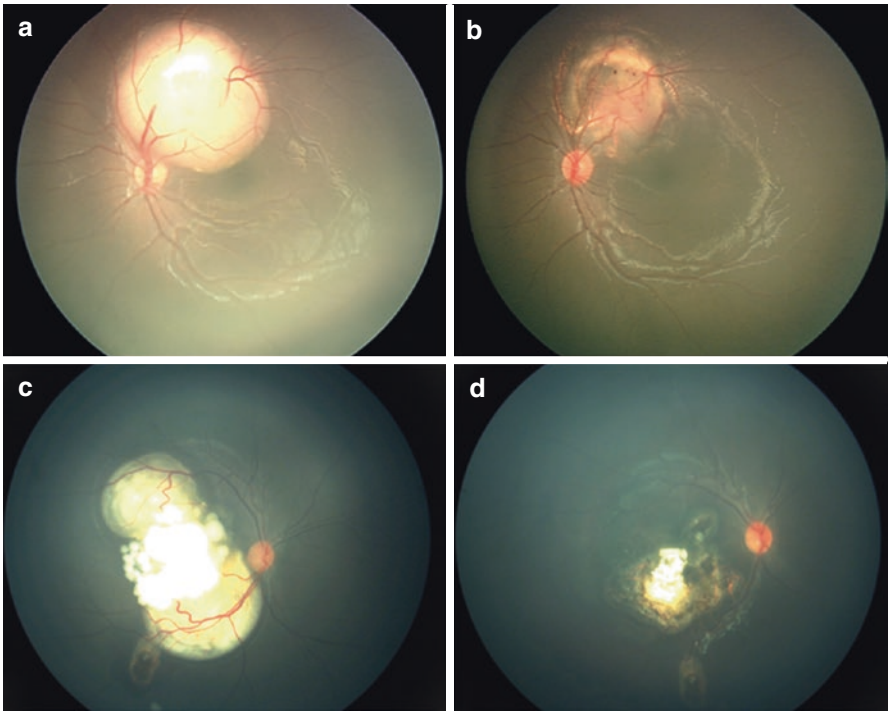

Fig. 2.2 Standard-dose chemotherapy in retinoblastoma (**a**) A group B eye (**b**) After six cycles of standard-dose chemotherapy (**c**) A group C eye with focal vitreous seeds (**d**) After six cycles of standard-dose chemotherapy

Table 2.8 Periocular chemotherapy

Procedure POC is administered by posterior sub-Tenon injection of the chemotherapeutic drug in the quadrant closest to the location of the vitreous seeds. Innovative delivery systems for POC include the use of episcleral implants, fibrin sealants, and nanoparticles of the drug
Drugs Carboplatin (1.5–2.0 mg) Topotecan (1–2 mg)
Indication Advanced groups D or E with diffuse vitreous seeds in which a higher local dose of chemotherapy is desired
Advantages (1) Achieves rapid levels within the vitreous in 30 min and can last for hours (2) achieves doses that are six to ten times higher than that achieved by IVC
Disadvantages (1) Orbital and eyelid edema and ecchymosis (2) orbital fat atrophy (3) muscle fibrosis leading to strabismus

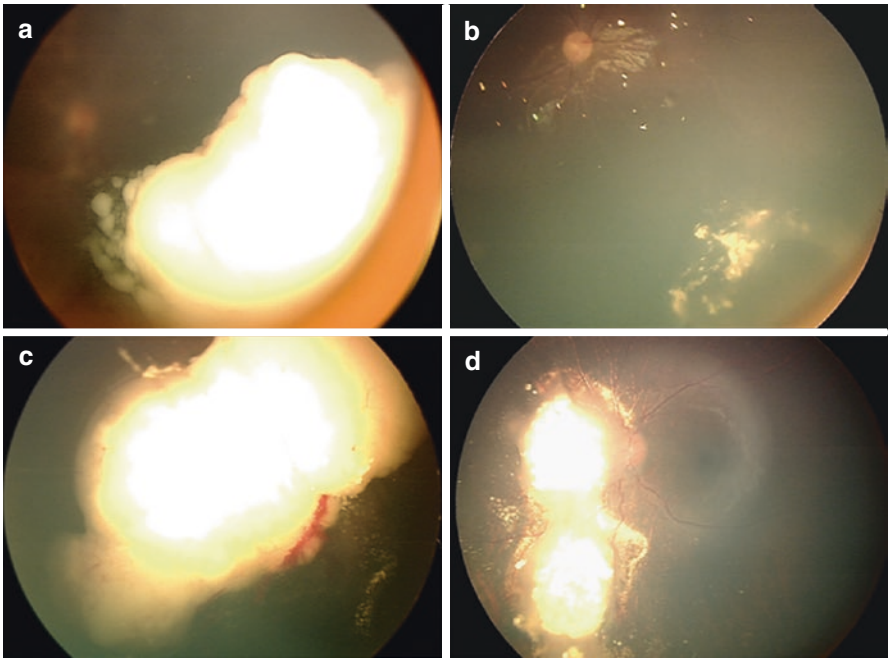

Fig. 2.3 High-dose chemotherapy in retinoblastoma with periocular chemotherapy (**a**) A group D eye with diffuse vitreous seeds (**b**) Clinical regression after six cycles of high-dose chemotherapy with three doses of concurrent periocular carboplatin (**c**) A group D eye with fine diffuse vitreous seeds (**d**) Complete regression after six cycles of high-dose chemotherapy with two doses of concurrent periocular carboplatin

delivered to a target activated clotting time of two to three times baseline. Through a transfemoral approach, the ipsilateral internal carotid artery is catheterized with a 4F pediatric guide catheter. The arterial anatomy is visualized with serial angiography runs, and the ostium of the ophthalmic artery is superselectively catheterized with a Prowler 10 microcatheter by the peep-in technique. A superselective injection through the microcatheter is performed to check adequate positioning and assessing the amount of reflux, if any, into the internal carotid artery before chemotherapy is injected. Each chemotherapy dose is diluted in 30 mL of saline and administered in a pulsatile fashion over 30 min to prevent lamination of medication and loss of dose to peripheral tributaries. Repeat angiography is performed immediately after the procedure to ensure patency of the vessels, and the catheter removed. At the end of the procedure, the heparin is reversed with intravenous protamine and hemostasis achieved with manual compression of the femoral artery upon removal of the catheter [15]. The child is monitored for 6 h before discharge.

IAC has emerged as an effective treatment for advanced retinoblastoma (Fig. 2.5a–d). It is increasingly being used in tumors as a primary treatment, especially in unilateral retinoblastoma. It can be used as a secondary therapy for those cases which have recurred or have not responded adequately to IVC (Table 2.9).

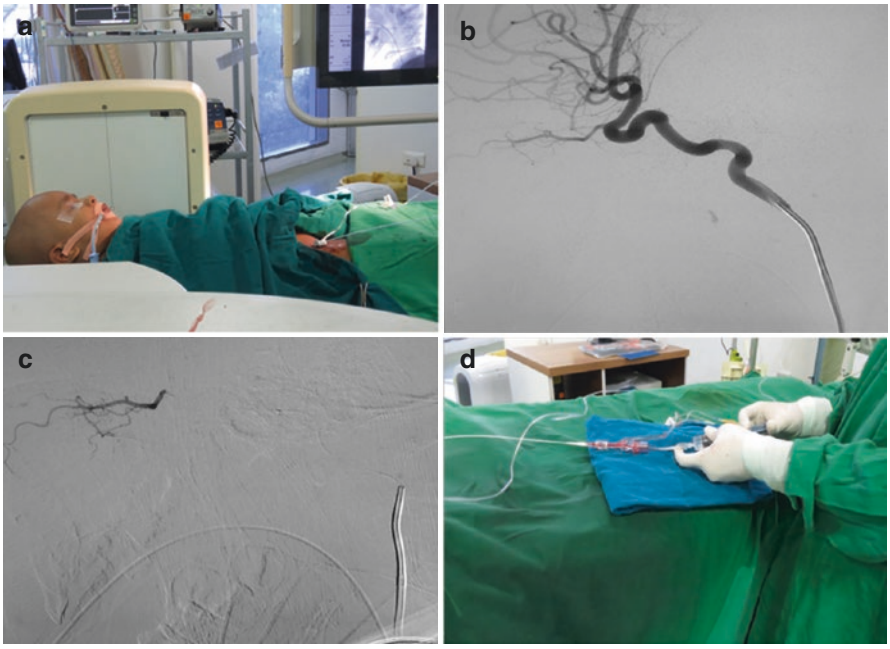

Fig. 2.4 Intra-arterial chemotherapy: Procedure in the cath lab (**a**) Patient under general anesthesia with a transfemoral cathether (**b**) An angiography performed at the beginning of the procedure, showing a patent internal carotid artery (**c**) An angiography performed with the microcatheter at the ostium of the ophthalmic artery, showing a patent ophthalmic artery (**d**) Infusion of the chemotherapeutic drug through the transfemoral cathether

Shields et al. observed 94% globe salvage in group D eyes, and 91% vitreous seed regression, when IAC was used as a primary therapy [16–18]. In a study comparing 2-year ocular survival rate between naïve eyes with vitreous seeds (IAC as a primary therapy) and previously treated eyes with vitreous seeds (IAC as a secondary therapy), Abramson et al. observed that IAC seemed to be more effective in eyes that have failed to respond to previous therapies. In an overall study on IAC in retinoblastoma, Abramson et al. observed that eyes with vitreous seeds tend to require higher treatment sessions and doses, and multiple agents, as compared to eyes without vitreous seeds [15].

2.6.1.3 Intravitreal Chemotherapy

Vitreous seeds are aggregates of tumor cells found in the avascular vitreous, which are relatively resistant to the effect of intravenous chemotherapy due to lack of blood supply (Table 2.10). These appear due to the disruption of the apical tumor either spontaneously (primary) or treatment-induced necrosis (secondary). Suboptimal concentration of chemotherapeutic agents in the vitreous results in persistence of vitreous seeds [19]. Refractory vitreous seeds are the persistent or recurrent vitreous seeds which do not respond to the standard treatment modalities.

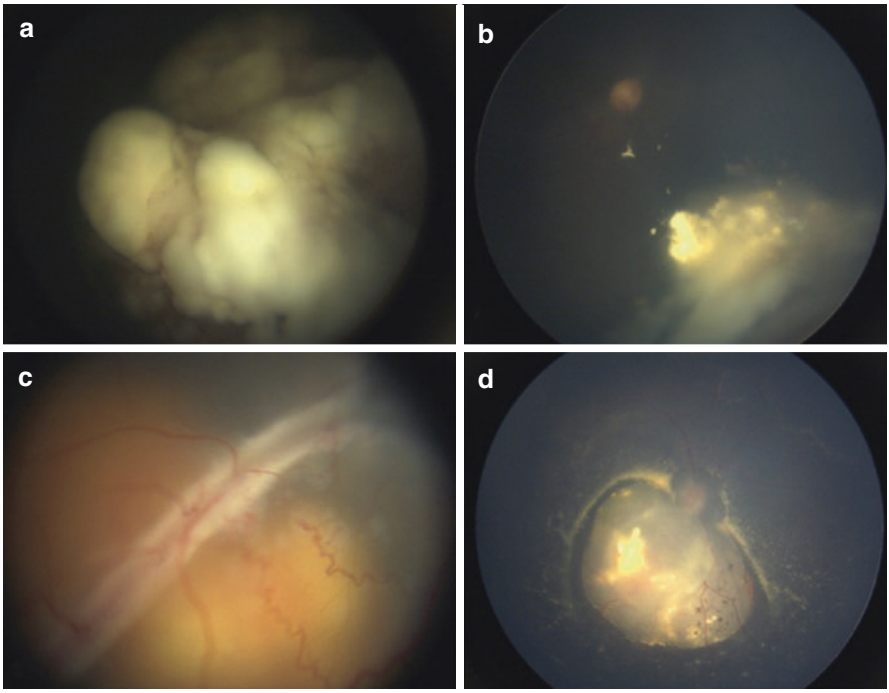

Fig. 2.5 Intra-arterial chemotherapy in advanced retinoblastoma (**a**) A group D eye with diffuse vitreous seeds (**b**) After three cycles of intra-arterial chemotherapy (**c**) A group E eye with a very large tumor and diffuse subretinal fluid (**d**) After three cycles of intra-arterial chemotherapy

Persistent seeds are those which are present during chemoreduction, and continue to persist after the completion of chemoreduction [19–21]. Recurrent seeds are those which appear after the completion of chemoreduction. IVitC achieves higher drug concentration within the vitreous and effectively causes regression of vitreous seeds, without associated systemic side effects.

IVitC in retinoblastoma was first introduced by Ericson and Rosengren using thiotepa in 1960. Methotrexate has also been tried as an intravitreal drug for retinoblastoma. In 1987, Inomata and Kaneko investigated the sensitivity of retinoblastoma to 12 anticancer drugs and found that the retinoblastoma cells were most sensitive to melphalan in vitro. Melphalan is now the most extensively used drug to control the vitreous disease in retinoblastoma (Table 2.11). Munier et al. discussed a potentially safe technique to perform intravitreal injections to prevent extraocular extension of the tumor [21]. They advocated the application of triple freeze-thaw cryotherapy at the injection site to prevent egress of the tumor cells in the needle track (Fig. 2.6a–d).

With melphalan, vitreous seed regression ranging from 85 to 100% of eyes and globe salvage in 80–100% of eyes have been reported [22–24]. Intravitreal melphalan is given as a weekly injection until regression. The disadvantage of melphalan is that it is not stable in solutions, and has to be used within an hour of reconstitution

Table 2.9 Intra-arterial chemotherapy

Procedure IAC involves the delivery of chemotherapeutic drugs directly in the eye through a fluoroscopy-guided microcatheter into the ostium of the ophthalmic artery, and is done in a cath lab by an interventional neuroradiologist. IAC can be a one-, two- or three-drug regimen, and each drug is delivered slowly over 30 min in a pulsatile fashion. It is repeated every 4 weeks, and most of the patients require three sessions to achieve complete tumor regression
Drugs Melphalan is the most extensively used drug in IAC, and topotecan is added if there is extensive vitreous seeding. In advanced cases, three drugs including carboplatin are employed to ensure complete tumor control One-drug regimen: Melphalan (3–7.5 mg) Two-drugs regimen: Melphalan (3–7.5 mg) + Topotecan (1–2 mg) Three-drugs regimen: Melphalan (3–7.5 mg) + Topotecan (1–2 mg) + carboplatin (15–50 mg)
Indications IAC can be used as a primary therapy or secondary therapy in eyes which have not achieved tumor control after intravenous chemotherapy. In general, it is preferred in children older than 4 months of age without a germline mutation. (1) Unilateral non-germline retinoblastoma (2) recurrent retinoblastoma following previous IVC or plaque radiotherapy (3) recurrent extensive subretinal seeds not controlled by IVC
Advantages (1) High intraocular concentration of the drug without associated systemic adverse effects of the drugs (2) shorter time for tumor control
Disadvantages (1) Expensive (2) Difficulty with catheterizations (3) Vitreous hemorrhage (4) Branch retinal artery obstruction (5) Ophthalmic artery spasm with reperfusion (6) Ophthalmic artery obstruction (7) Partial choroidal ischemia (8) Optic neuropathy (9) Complications associated with the technique including a risk for brain vascular events, hypoxia, hypotension, and bradycardia

Table 2.10 Vitreous seeds: classification

Primary VS Secondary VS	Present at the initial diagnosis Those which appear during the course of treatment due to necrotic disruption of the tumor
Persistent VS Recurrent VS	Primary VS which persist beyond chemoreduction VS which appear after the completion of chemoreduction
Focal VS Diffuse VS	Seeds located ≤3 mm from the main tumor Seeds located >3 mm from the tumor
Free-floating VS Pre-hyaloid VS Retro-hyaloid VS	Seeds dispersed in the vitreous Seeds present just anterior to the hyaloid membrane Seeds present just anterior to the internal limiting membrane of the retina
Dust formation Sphere formation Cloud formation	Minute VS formed following the apical disruption of the tumor Balls of VS resulting from clonal expansion of dust Massive VS resulting from the disruption of the tumor

Table 2.11 Intravitreal chemotherapy

Procedure Any intraocular procedure in retinoblastoma is generally avoided for fear of extraocular extension of the tumor. However, intravitreal injections by safety-enhanced technique have proven to prevent this risk. The injection site is carefully chosen after a thorough clinical examination to rule out the presence of tumor, vitreous seeds or subretinal fluid at the injection site. The injection is given using a 30 gauge needle by the transconjunctival pars plana route. After injecting the drug, the needle is withdrawn in the first ice ball formation of the chemotherapy followed by injection site triple freeze-thaw cryotherapy. This technique reduces the extraocular escape of any tumor cell through the needle track
Drugs Melphalan is the most widely used drug in IVitC, and topotecan is generally added if there is extensive vitreous seeding. Topotecan may also be used as a single drug Melphalan (20–30 μg) Topotecan (20–30 μg) Combination: Melphalan (20–30 μg) + Topotecan (20–30 μg)
Indications (1) Recurrent diffuse or focal vitreous seeds (2) persistent diffuse or focal vitreous seeds
Advantages (1) High intraocular concentration of the drug without associated systemic adverse effects of the drugs (2) complications associated with POC avoided
Disadvantages (1) Extraocular extension of the tumor associated with an improper technique

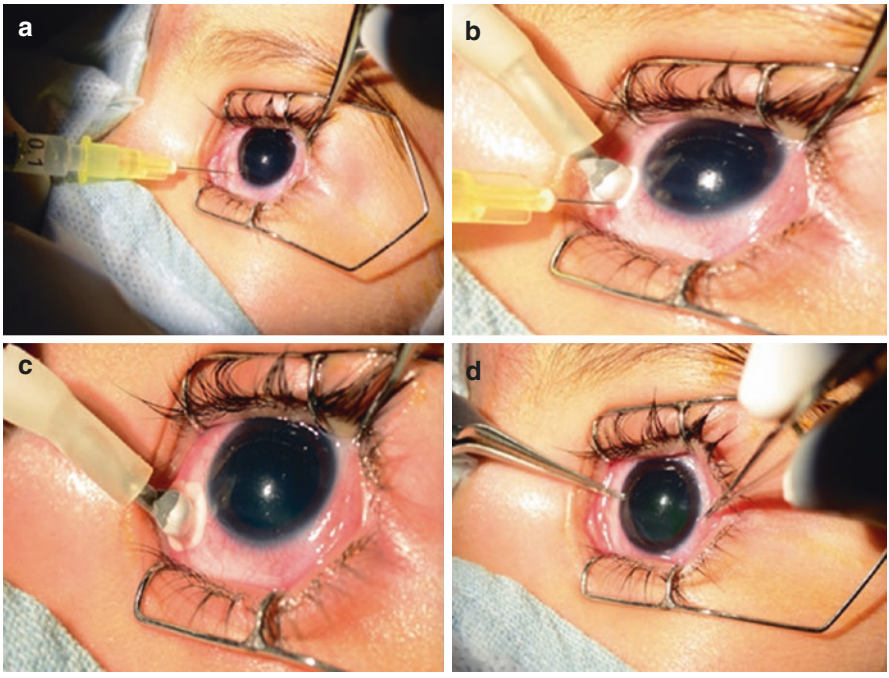

Fig. 2.6 Intravitreal chemotherapy: Safety-enhanced technique (**a**) Pars plana intravitreal injection of topotecan at a dose of 30 μg in 0.15 mL with a 30-gauge needle (**b**) Needle is withdrawn through the first ice ball of the cryotherapy (**c**) Triple freeze-thaw cryotherapy at the injection site (**d**) Forceps-assisted jiggling of the eyeball following the injection for an even dispersion of the chemotherapeutic drug

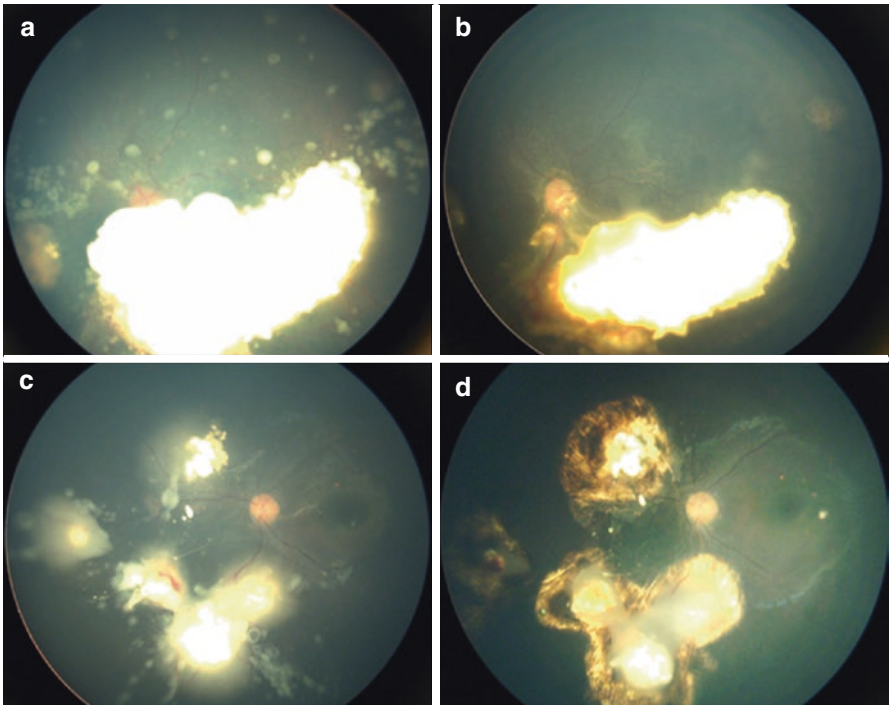

Fig. 2.7 Intravitreal chemotherapy with topotecan (**a**) Before and (**b**) after two doses of intravitreal topotecan injections in an eye with recurrent diffuse vitreous seeds after nine cycles of chemotherapy (**c**) Before and (**d**) after two doses of intravitreal topotecan injections for a massive recurrence of diffuse vitreous seeds in a one-eyed patient

of the drug. A combination of intravitreal melphalan and topotecan has also been used to achieve excellent regression in refractory vitreous seeds. Apart from melphalan, topotecan is also emerging as a potent intravitreal therapy with a safe toxicity profile (Fig. 2.7a–d). Topotecan is a very safe drug for intraocular use, is stable in solution and can be given as a 3-weekly injection [2, 13, 25, 26].

2.6.2 Radiation Therapy

Retinoblastoma is a highly radiosensitive tumor, and radiation therapy can be curative. Radiation in the form of EBRT was the most popular globe-salvage therapy in retinoblastoma before the introduction of chemotherapy in 1990s. Although it is no longer the primary modality of treatment for retinoblastoma due to the associated complications, it has its own therapeutic indications (Table 2.12). Episcleral plaque radiotherapy is a form of brachytherapy wherein the source of radiation is placed on the episclera adjacent to the tumor, and the tumor absorbs radiation, sparing other healthy ocular tissues from the ill-effects of radiation (Table 2.13) [27].

Table 2.12 External beam radiation therapy

Procedure Numerous methods and protocols to treat retinoblastoma with EBRT have been described. Lens-sparing technique with electron beam and photon beam using a linear accelerator has been traditionally employed. Newer techniques using stereotactic radiation therapy (SRT), intensity modulated radiation therapy (IMRT) and proton therapy have been described. The standard dose is 40–45 Gy, generally given in fractionated doses over 3–4 weeks
Indications (1) HRF on pathology after enucleation (described elsewhere) (2) as a part of multimodal management in orbital retinoblastoma (described elsewhere) (3) tumor and/or vitreous seeds refractory to other treatments
Advantages (1) Prevents orbital recurrence when given as an adjuvant therapy for indications 1 and 2 (2) excellent long-term tumor control when used for refractory tumor/vitreous seeds
Disadvantages (1) Orbital hypoplasia (2) Secondary cancers in the field of radiation (3) Cataract (4) Dry eye syndrome

Table 2.13 Episcleral plaque brachytherapy

Procedure Radioisotopes like Iodine-125 and Ruthenium-106 that emit radiation are used for the treatment of various ocular tumors including retinoblastoma. I-125 emits gamma radiation, and Ru-106 beta radiation, which can penetrate the tumor. For this, the radioisotopes are loaded on an applicator (gold or silver), and the plaque sutured onto the episclera. The duration of the treatment is calculated by a radiation physicist, and the plaque is removed at the end of the treatment duration
Indications (1) Recurrent tumor that is >3 mm in thickness which is not suitable for treatment by other forms of focal therapy (TTT, cryotherapy or laser photocoagulation)
Advantages (1) Direct treatment of the tumor with minimal scarring (2) deeper penetration as compared with other forms of focal treatment (3) single treatment session (4) surrounding healthy tissue is not effected (5) overlying focal vitreous seeds are also treated simultaneously
Disadvantages (1) Not effective in large recurrent tumors (2) not ideal in multifocal recurrences (3) delayed radiation-related complications like radiation retinopathy

2.6.3 Focal Therapy

Although episcleral plaque therapy may also be considered as a form of focal therapy, the term generally refers to the use of cryotherapy, TTT, and laser therapy in the treatment of retinoblastoma. These are generally used for consolidation once the tumor has attained a considerably lower volume with chemoreduction, usually after two or three cycles, or for the treatment or small recurrent tumors of subretinal seeds [28–30]. However, they can also be used as the sole therapy for small retinoblastomas (Tables 2.14, 2.15, and 2.16).

Table 2.14 Cryotherapy

Procedure Transscleral cryotherapy involves freezing the tumor under visualization using indirect ophthalmoscopy. The cryoprobe tip is centered directly under the tumor and the ice ball formed on freezing should adequately cover the tumor and any focal vitreous seeds. Triple freeze-thaw cycles of cryotherapy are generally applied. Cryotherapy destroys the tumor cells mechanically by disruption of the cell membranes during thawing of the intracellular ice crystals. Typically the treatment is repeated every 3–4 weeks
Indications (1) Peripheral tumors <4 mm in diameter and <3 mm in thickness (2) subretinal seeds
Advantages (1) Treatment of focal vitreous seeds overlying the tumor
Disadvantages (1) Large area of retinal scarring (2) retinal breaks

Table 2.15 Transpupillary thermotherapy

Procedure In thermotherapy, hyperthermia generated by infrared radiation at subphotocoagulation levels destroys the tumor. A slow and sustained temperature range of 40–60 °C within the tumor is generated using a semiconductor diode laser (810 nm) delivered as a 1300-μm large spot and long burn duration (1 min) with indirect ophthalmoscope delivery system. The tumor is heated until it turns a subtle gray. Complete tumor regression can be achieved in over 85% of tumors using three to four sessions of thermotherapy. Using indocyanine green dye to sensitize the tumor for TTT (ICG-enhanced TTT) is an effective alternative for tumor control, particularly for small tumors that show suboptimal response to standard TTT
Indications (1) Small tumors which are 4 mm in diameter and 2 mm in thickness (2) subretinal seeds
Advantages (1) Synergistic combination of thermotherapy with chemoreduction protocol (chemothermotherapy), with heat application amplifying the cytotoxic effect of platinum analogues
Disadvantages (1) Focal iris atrophy (2) focal paraxial lens opacity (3) large area of retinal scarring (4) retinal traction and serous retinal detachment

Table 2.16 Laser photocoagulation

Procedure Photocoagulation using argon green laser (532 nm) delivered with an indirect laser delivery system causes tumor apoptosis. Overlapping spots on the tumor edge are placed at a power setting of 250–350 mw for 0.3–0.5 s. The treatment destroys the tumor by restricting the blood supply to the tumor and also by hyperthermia. Typically, the treatment is repeated every 3–4 weeks
Indications (1) Small posterior tumors which are 4 mm in diameter and 2 mm in thickness
Advantages (1) Can be used when TTT is not available
Disadvantages (1) Retinal traction and serous retinal detachment (2) retinal vascular occlusion (3) retinal hole (4) large area of retinal scarring (5) not ideal while the patient is on active chemoreduction as it restricts the blood supply to the tumor thus reducing the intra-tumor concentration of the chemotherapeutic agent

2.6.4 Enucleation

Enucleation is the oldest form of treatment for retinoblastoma, and is still indicated in advanced cases [10]. Unilateral disease with no salvageable vision is best treated by enucleation and the patient can be rid of the disease for life. Enucleation is a simple procedure, although special precautions need to be taken when handling an eye with retinoblastoma (Table 2.17). These are necessary to avoid accidental perforation that can potentially cause orbital seeding of the tumor. Use of a primary silicone or polymethylmethacrylate implant by the myoconjunctival technique

Table 2.17 Enucleation

Enucleation is the removal of the eyeball, and is usually followed by replacement of the orbital volume using one of the several types of implants available including acrylic, silicone and hydroxyapatite implants, each with their own advantages and limitations
Enucleation by the myoconjunctival technique with a silicone orbital implant is a safe and cost-effective procedure with prosthesis motility comparable to biointegratable implants while minimizing the complications. This technique may also be used in those requiring periorbital radiotherapy following surgery • The surgery is usually performed under general anesthesia • A lateral canthotomy is performed • A 360° peritomy is done using a blunt tipped Westcott scissors, cutting as close to the limbus as possible • The underlying posterior Tenon's layer is undermined in all four quadrants in a spreading action using a blunt-tipped tenotomy scissors • Each of the rectus muscles is identified, hooked and double-tagged, first with 6-0 silk suture and then with 6-0 vicryl suture. 6-0 silk sutures serve as traction sutures while 6-0 vicryl sutures would later be used to suture the muscles through the conjunctiva • Each of the rectus muscles is then transected at a point between the two sutures using a radiofrequency probe • Superior oblique and inferior oblique muscles are transected and allowed to retract posteriorly • A conjunctival relaxing incision is made for easy manipulation • The eyeball is then prolapsed between the blades of the speculum • With a forward traction on the eyeball using the four silk sutures, a gently curved blunt tipped tenotomy scissors is passed along the lateral wall and the optic nerve is strummed along its length • With one bold cut, the optic nerve is transected just a little anterior to the superior orbital fissure, to gain a good optic nerve length and at the same time to avoid injuring the superior orbital fissure contents • After achieving adequate hemostasis, an appropriate-sized silicone orbital implant is placed posterior to posterior Tenon's • Posterior Tenon's is closed with interrupted 6-0 vicryl sutures • Each of the Recti muscles is sutured through the conjunctiva in its respective fornix, and these sutures are called the myoconjunctival sutures • Anterior Tenon's is closed with interrupted 6-0 vicryl sutures • Conjunctival closure is done in a continuous key-suturing pattern with 6-0 vicryl suture • An appropriate-sized conformer is placed and a median tarsorrhaphy done with 6-0 vicryl suture. • The suture tarsorrhaphy is removed after 1 week and a prosthesis can then be placed in the socket after 6 weeks

Table 2.18 High-risk features in retinoblastoma

High-risk features on pathology where adjuvant chemotherapy is indicated • Anterior segment invasion • Ciliary body infiltration • Massive choroidal invasion (invasion ≥3 mm in basal diameter or thickness) • Full thickness scleral extension • Extrascleral extension • Retrolaminar optic nerve invasion • Optic nerve invasion at line of transection • Combination of optic nerve infiltration till any level (pre-laminar/laminar/retrolaminar) and choroidal infiltration (any thickness)
High-risk features on pathology where adjuvant radiotherapy is indicated (in addition to chemotherapy) • Full thickness scleral extension • Extrascleral extension • Optic nerve invasion at line of transection

provides adequate static and dynamic cosmesis. Porous polyethylene or hydroxyapatite implants don't offer additional advantage unless pegged, and these are best avoided if a child is likely to need adjuvant chemotherapy or EBRT following enucleation since fibrovascular integration of these implants would be impeded.

An enucleated eyeball is always submitted for pathology to assess for high-risk factors (HRF). In a landmark paper by Honavar et al., the need for adjuvant chemotherapy has been emphasized to reduce the risk of secondary orbital recurrence and systemic metastasis [31]. The incidence of metastasis was 4% in those who received adjuvant therapy, compared with 24% in those who did not. Hence when HRF is positive, adjuvant treatment with chemotherapy and/ or EBRT is indicated (Table 2.18). Adjuvant chemotherapy consists of a combination of vincristine, etoposide, and carboplatin given 4-weekly for six cycles [31].

2.7 Orbital Retinoblastoma

Orbital retinoblastoma is an advanced form of retinoblastoma seen mostly in developing countries of Asia and Africa. The incidence varies among different countries, and is in the range of 18–40% [32]. Orbital disease can be classified as listed in Table 2.19. Primary orbital retinoblastoma is the orbital extension of the disease which is evident at presentation either clinically or radiologically. Most of the patients present with proptosis, or a large fungating mass which bleeds on touch. Tumor necrosis causes inflammation of the surrounding tissues and the patient may present with sterile orbital cellulitis. Secondary orbital retinoblastoma occurs in an enucleated socket after an uncomplicated surgery. It may present as an orbital mass with an unexplained displacement of the implant, or a palpable orbital mass. Accidental retinoblastoma occurs in the event of an inadvertent perforation of the eye harboring retinoblastoma. This can occur due to improper enucleation technique, or various intraocular surgeries in an eye with unsuspected intraocular

Table 2.19 Orbital retinoblastoma: classification

1. Primary orbital retinoblastoma Clinical or radiologically detected orbital extension of an intraocular retinoblastoma at the initial clinical presentation, with either optic nerve involvement or scleral extension of the tumor
2. Secondary orbital retinoblastoma Orbital recurrence following uncomplicated enucleation for intraocular retinoblastoma, presenting as unexplained displacement, bulge or extrusion of a previously well-fitting conformer or a prosthesis
3. Accidental orbital retinoblastoma Inadvertent perforation, fine-needle aspiration biopsy or intraocular surgery in an eye with unsuspected intraocular retinoblastoma are considered as accidental orbital retinoblastoma
4. Overt orbital retinoblastoma Previously unrecognized extrascleral or optic nerve extension discovered during enucleation as an episcleral nodule, or an enlarged and inelastic optic nerve with or without nodular optic nerve sheath
5. Microscopic orbital retinoblastoma Full thickness scleral infiltration, extrascleral extension or invasion of the optic nerve on histopathologic evaluation of an eye enucleated for intraocular retinoblastoma

retinoblastoma. Overt orbital retinoblastoma refers to previously unrecognized extrascleral or optic nerve extension discovered during enucleation as an episcleral nodule, or an enlarged and inelastic optic nerve with or without nodular optic nerve sheath. Microscopic orbital retinoblastoma is identified on histopathological examination of the enucleated eyeball as full thickness scleral infiltration, extrascleral extension or invasion of the optic nerve.

The presence of orbital disease is generally known to carry a poor prognosis. Orbital disease increases the risk of systemic metastasis by 10–27 times and the mortality rates range from 25 to 100% [32]. However, with an intensive multimodal management and careful monitoring, patients with orbital disease are known to do well (Table 2.20) (Fig. 2.8a–d).

2.8 Metastatic Retinoblastoma

With an incidence of less than 5% of all retinoblastoma cases, metastatic retinoblastoma is most often seen in developing countries. It usually occurs as a relapse following enucleation for intraocular retinoblastoma, especially in those who had high-risk pathologic features [33]. Most commonly, metastasis occurs to the central nervous system (CNS), bone, and bone marrow. The metastasis occurs in one of the three ways- by direct dissemination into the CNS via the optic nerve, choroidal invasion and hematogenous spread, or orbital extension with lymph node involvement and hematogenous spread. Bony metastasis, usually involving the long bones or the craniofacial bones, causes non-tender palpable mass.

Cerebrospinal fluid cytology, bone marrow evaluation and whole-body imaging are done in all cases of metastatic retinoblastoma for staging the disease. Use of high-dose chemotherapy with autologous stem cell rescue (ASCR) has offered

Table 2.20 Orbital retinoblastoma: treatment

Baseline investigations • CT or MRI to assess the tumor extent • Bone marrow biopsy • Cerebrospinal fluid cytology
Treatment Multimodal management involving chemotherapy, surgery, and radiation therapy is employed. Chemotherapy is essential for chemoreduction and to prevent systemic metastasis, surgery to reduce the tumor load and clear the orbit of most of the tumor, and radiation to take care of the residual disease and prevent orbital recurrence
Primary orbital retinoblastoma • Neoadjuvant high-dose chemotherapy is given for three cycles • Residual disease is assessed by CT or MRI • If orbital retinoblastoma has resolved, enucleation is performed. If orbital retinoblastoma has not resolved, no surgery is done at this stage and three more cycles of high-dose chemotherapy are given • Residual disease is again assessed by CT or MRI • If orbital retinoblastoma has resolved, enucleation is performed at this stage. In case there is residual orbital disease even after six cycles, exenteration is performed • EBRT given to the orbit (45–50 Gy) • Adjuvant high-dose chemotherapy are given for six or nine cycles, to complete a total of 12 cycles
Secondary orbital retinoblastoma • Neoadjuvant high-dose chemotherapy is given for three cycles • Residual disease is assessed by CT or MRI • If orbital retinoblastoma has regressed significantly, excision of the residual mass is performed. If orbital retinoblastoma has not resolved, no surgery is done at this stage and three more cycles of high-dose chemotherapy are given • Residual disease is again assessed by CT or MRI • If orbital retinoblastoma has resolved, excision of the orbital mass is performed at this stage. In case there is significant orbital disease even after six cycles, exenteration is performed • EBRT given to the orbit (45–50 Gy) • Adjuvant high-dose chemotherapy are given for six or nine cycles, to complete a total of 12 cycles
Accidental orbital retinoblastoma • If the intervention is limited such as a needle biopsy and the tumor is not advanced, high-dose chemotherapy is given for six cycles and the patient carefully monitored at frequent intervals • If the intervention is limited such as a needle biopsy and the tumor is advanced, enucleation with an en bloc excision of the conjunctiva at the needle site is performed and adjuvant high-dose chemotherapy is given for six cycles and the patient carefully monitored at frequent intervals • If the intervention is extensive such as pars plana vitrectomy, enucleation with an en bloc excision of the conjunctiva overlying the ports is performed and adjuvant high-dose chemotherapy is given for six cycles and the patient carefully monitored at frequent intervals • EBRT may be given in each case depending on the nature of the disease, type, and extent of the intervention and the findings at subsequent follow-ups, a decision best left on the treating doctor's expertise

Table 2.20 (continued)

Overt orbital retinoblastoma • If an extrascleral extension is macroscopically visualized during enucleation, special precaution is taken to excise the nodule completely along with the eyeball, also with the overlying Tenon's capsule in the involved area • If optic nerve extension is suspected during enucleation and the nerve stump obtained is short, extra efforts to excise an additional length is made • In both cases, EBRT is given followed by 12 cycles of adjuvant high-dose chemotherapy
Microscopic orbital retinoblastoma • If microscopic full thickness scleral involvement and/ or extrascleral extension and/ or optic nerve involvement up to the level of transection is detected, EBRT is given followed by 12 cycles of adjuvant high-dose chemotherapy
Follow-up • CT or MRI 6-monthly to look for tumor recurrence • Bone marrow biopsy 6-monthly • Cerebrospinal fluid cytology 6-monthly

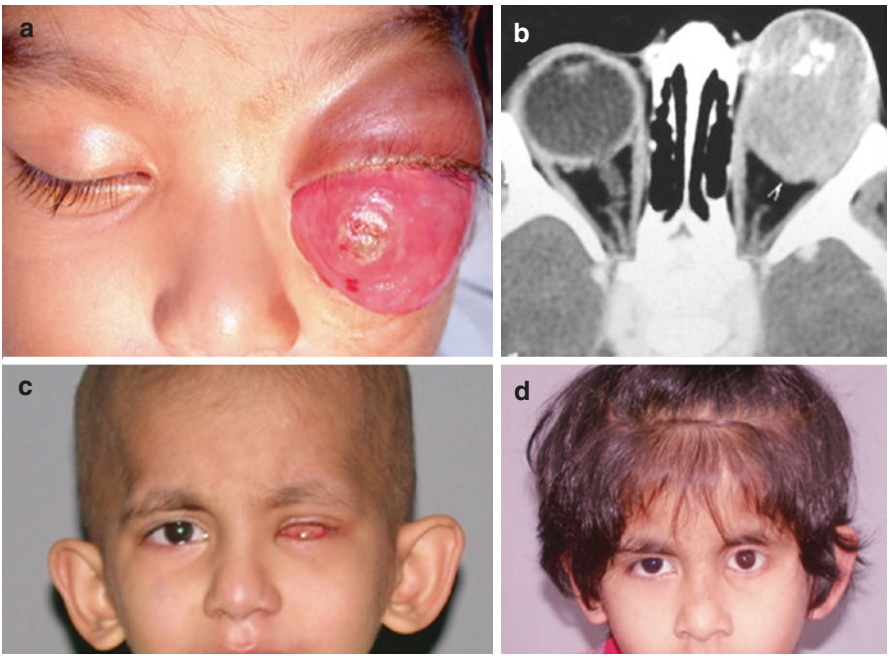

Fig. 2.8 Multimodal management in orbital retinoblastoma (**a**) External photograph of primary orbital retinoblastoma taken during examination under anesthesia (**b**) Axial computed tomography image displaying extraocular extension of the intraocular tumor (**c**) After 12 cycles of doses of high-dose chemotherapy, external beam radiotherapy and enucleation (**d**) Healthy child cured of orbital retinoblastoma, with a well-fitting prosthesis

some encouraging results. However, most of the experience is in stage 4a disease that does not involve the CNS. The use of radiotherapy and intrathecal chemotherapy for CNS lesions have been recommended, although the prognosis for such advanced metastatic retinoblastoma continues to remain grim [33].

2.9 Prenatal Genetics

Retinoblastoma is a malignancy associated with somatic mutation or germline mutation [1, 34]. Knudson proposed the two-hit hypothesis where he described the occurrence of two consecutive mutations for the conversion of a normal retinal cell into a malignant cell. In heritable retinoblastoma, the first mutation is in the germ cell, and this "first hit" is carried in every cell in the body, making them prone not only for retinoblastoma, but also for other second cancers (most commonly pinealoblastoma, osteosarcoma and soft tissue sarcomas) [34]. The "second hit" occurring in the retinal cells during retinal development causes retinoblastoma. In non-heritable retinoblastoma, both hits occur in the retinal cell, and thus the mutation is confined to one single cell in the retina. Heritable retinoblastoma constitutes 30–40% of all retinoblastomas, while the rest 60–70% are non-heritable. One-fourths of the germline mutations are familial with autosomal dominant inheritance pattern, and the others are de-novo non-familial germline mutations [34].

RB1 is a tumor suppressor gene that was identified in association with retinoblastoma and it validated the two-hit hypothesis. RB1 gene is located in the long arm of chromosome 13 (13q), and most of the mutations are nonsense codons or frame shifts. Sometimes retinoblastomas are caused by genomic deletion of chromosome 13q, a syndrome known as RB1 gene deletion syndrome, where the affected individual has varying degrees of dysmorphic features and neurodevelopmental delays [2].

To prevent transmission of the disease from parents to offspring, genetic testing for germline mutations can be done at specialized laboratories. RB1 is the only gene that is implicated in retinoblastoma. However, there are different types of mutations affecting this gene. Direct DNA sequencing detects 75% of the mutations, and PCR amplification detects yet another 20% of the mutations. Peripheral blood lymphocytes or tumor tissue, when available, are sampled for the detection of the mutation.

In heritable retinoblastoma, once the mutation is identified in the lymphocytes, the presence of the same mutation is tested in the fetus (sibling or offspring) by chorionic villus biopsy or amniocentesis. If the mutation is found, a decision to terminate the pregnancy can be made.

In non-heritable retinoblastoma, if the tumor tissue is available from an affected individual, it can be sampled to detect the type of mutation. If the same mutation is also found in the blood of the patient, the individual is positive for germline mutation and an offspring can be tested for the same mutation. However, if no mutation is found in the blood, the tumor is non-germline (sporadic), without any risk of transmission of the disease to the offspring. In case no tumor tissue is available, lymphocytes are sampled for the type of RB1 mutation, but the interpretation of a

negative result in these cases is difficult. Either the patient has a sporadic retinoblastoma, or a germline mutation that escaped detection by the currently available techniques.

Preimplantation genetic testing for carriers of mutation involves the identification of RB1 mutation in a blastomere (8-cell embryo) which is obtained by in vitro fertilization (IVF) technique. The small material is amplified by polymerase chain reaction (PCR) and the blastomere without the RB1 mutation maybe implanted for a successful pregnancy [34].

2.10 Screening for Retinoblastoma

Vision screening in newborn babies and children at appropriate ages and intervals can help identify tumors at early stages, when more effective treatment modalities can be applied, increasing the chances of cure. A thorough history is obtained from the parent (Table 2.21). Vision screening is simple and effective when appropriately performed (Table 2.22). The red reflex is a popular method to confirm leukocoria among the pediatricians. The tumors are generally located in the macular region in the newborn, and are much easier to detect. In older children, the tumors tend to be more peripheral. For this reason, the test is performed in all gazes.

2.11 Sibling Survey

Once retinoblastoma is diagnosed in a child, it is important that the treating doctor charts out a family tree, and lists every sibling of the affected child, with age and details of any prior eye exam. This is crucial in familial retinoblastoma and for

Table 2.21 History-taking

Presenting history
• Presenting symptom—leukocoria, strabismus, reduced vision, red painful eye, protruding eye
• Duration of symptoms
Perinatal history
• Weight and gestational age at birth of the child
• Need for oxygen administration (rule out possibility of ROP)
Family history
• History of intraocular tumor in any of the family members
• History of blindness in the family—at birth or in childhood
• History of any other cancers in the family
• Family tree should be charted for three generations indicating the ages of all the siblings
Treatment history
• Age at first diagnosis
• Complete details of previous treatment received, with the dates of examination and type of treatment received, including the names and dosage of drugs
• Details of the treating doctor, including the name and address

Table 2.22 Vision screening

Complete examination of the ocular adnexa, conjunctiva, cornea, iris, and pupils
Red reflex test • In a darkened room (to maximize pupillary dilation), a direct ophthalmoscope is focused on each pupil individually, 50 cm away from the eye. The red reflex obtained from each pupil is observed. It is useful to set the ophthalmoscope on +4 diopter setting for a focused image of the red reflex • After each eye has been assessed separately, the eyes are viewed together with the child focusing on the ophthalmoscope light (Bruckner test) at a distance of 1 m. Any asymmetry in pupil color, brightness, or size warrants a referral. A white reflex is an ominous sign that warrants an urgent referral to an ophthalmologist to rule out retinoblastoma. (It should be noted that if the child is looking 15° nasal to the path of the viewer, the optic nerve head can cause leukocoria, resulting in a false-positive red reflex test.) • Dilated direct ophthalmoscopic examination may improve the ability to detect early retinoblastoma. One drop of 0.5% cyclopentolate and one drop of 2.5% phenylephrine placed in both eyes 20–40 min before the red reflex test should provide an adequate pupillary dilation in those children with smaller resting pupil diameters
Urgent referral to an ophthalmologist is indicated when a white pupillary reflex is detected

Table 2.23 Sibling Survey in Retinoblastoma

Age of the child	Frequency of examination
Birth	First exam within 2 weeks of birth
Birth–3 months	Every 1 month
3 months–1 year	Every 2 months
1–2 years	Every 3 months
2–3 years	Every 4 months
3–5 years	Every 6 months

children in the family aged less than 5 years of age. With careful clinical screening alone, 50% cases can be diagnosed by 2 months of age, 85% by 6 months, and nearly 100% by 12 months. The frequency of screening depends on the age of the sibling (Table 2.23). These are empiric guidelines for sibling survey. Use of genetics-guided sibling survey would be ideal.

2.12 Conclusion

The management of retinoblastoma revolves around having a sound knowledge of the disease, choosing the best treatment for the patient among the various available options and careful monitoring for recurrences. Enucleation should be performed when deemed necessary in advanced retinoblastoma with no visual prognosis, without needless overenthusiasm for globe salvage in advanced tumors. Specific precautions during the surgery, use of a primary implant for cosmesis, and post-enucleation evaluation of histopathologic HRFs and adjuvant therapy, as appropriate, achieve optimal life salvage. Primary focal therapy with laser, TTT or cryotherapy for peripheral tumors can be used for ICRB group A tumors in visually noncritical

locations. IVC continues to be the standard treatment for ICRB groups B to D, and for bilateral retinoblastoma. Appropriate use of high-dose protocol and concurrent POC can help salvage group D and E eyes with diffuse vitreous seeds. IAC is a very promising treatment with high success for advanced retinoblastoma, but the cost factor must also be taken into consideration. IVitC should be performed with safety-enhanced technique. Radiation therapy should be employed only when indicated. Retinoblastoma has a very high cure rate, and is best managed in an integrated retinoblastoma clinic under the watchful monitoring of an expert ocular oncologist. The recent advances in management of retinoblastoma and a holistic approach have rendered it eminently curable—prognosis for life salvage is now around 98%, with 90% eye salvage, and 80% vision salvage.

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Genetics of Retinoblastoma

3

Smriti Jain and Vikas Khetan

3.1 Introduction

Retinoblastoma is the most common intraocular malignancy in children with an incidence of approximately 1 in 15,000–20,000 live births corresponding to almost 9000 new cases every year worldwide [1, 2]. India itself harbours around 20% of the retinoblastoma cases with around 1500 cases annually [3]. It is caused by mutations in the RB1 gene and has a very distinct pattern of inheritance and is also a prototype for understanding the genetic basis of other tumours as well. In fact, RB1 was the first tumour suppressor gene to be defined at molecular level [4]. Identification of heritable and somatic variants helps us in prognosticating the disease better and allows for proper counselling of the patient's family. Recently, the identification of patients with no detectable RB1 mutations has brought a paradigm shift to the current understanding of the genetic basis of retinoblastoma [5].

3.2 Heritable Versus Nonheritable Retinoblastoma

Approximately 60% of the patients have a unilateral involvement which may be multifocal and most of these patients have a sporadic disease i.e. there is no other affected member in the family. While approximately 40% of the patients present with bilateral involvement and amongst these only 10% patients have a positive

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family history and rest 30% have a new germline mutation [6]. The patients with bilateral or familial retinoblastoma have a predisposition to develop other secondary neoplasms elsewhere in the body including osteosarcoma, soft tissue sarcoma and malignant melanoma. The exposure to external beam irradiation increases the risk of developing these second tumours [7]. The age at diagnosis in patients with heritable disease is usually less than 1 year whereas the sporadic cases present later at around 2 years of age [6]. Patients with hereditary disease are also at increased risk of developing pineal gland involvement in the form of pinealoblastoma or primitive neuro-ectodermal tumour (PNET) also referred to as trilateral RB [8, 9].

3.3 Molecular Genetics

Initially all cases of RB were assumed to be hereditary but later it was identified that significant number of patients were sporadic. Before getting into the genetic aspects it is important to understand the basics about germline and somatic mutations. Germline mutations are those which affect the germ cells and are transmitted in all the cells of the body and can be transferred to the offspring while somatic mutations occur in cells other than germ cells and therefore cannot be transferred to the offspring. In case of retinoblastoma, any patient who has an RB1 mutation in cells outside the eye is germline or heritable whereas if the mutation is restricted only to the retinal precursor cells it is considered as somatic or non-heritable [10]. Alfred Knudson in 1971 in his landmark paper proposed a model to explain the genetic mechanism of RB. According to his hypothesis, two mutations occur in both the hereditary and nonhereditary retinoblastoma (better known as the second hit hypothesis) [11].

1. In heritable retinoblastoma, the first mutation is inherited via germ cells or is a new germ line mutation (first hit/M1) and tumour is initiated by a second mutation in the somatic retinal cells (second hit/M2). These can be either bilateral or unilateral with multifocal involvement.
2. In nonhereditary retinoblastoma, the two mutations occur in the somatic retinal cells (M1 and M2) and only one eye is affected.

The presence of further mutations (M3 to Mn) is responsible for tumour progression rather than initiation [12, 13].

Although RB follows an autosomal dominant pattern of inheritance with 50% risk of transmission to the progeny, the disease itself is autosomal recessive since it requires the inactivation of both alleles of RB1 gene.

After Knudson's hypothesis, further experiments recognised the target gene locus at chromosome 13q14 [14]. The RB1 gene is located here and spans 183,000 bases. It consists of 27 exons that encode the pRB protein (a 928 amino acid protein) which plays a major role in regulating the cell cycle progression [4, 15]. The second mutation is often due to loss of normal allele or the loss of heterozygosity

(LOH) wherein the RB1 gene is reduced to a homozygous state. This loss can be in the form of chromosomal nondisjunction, mitotic recombination, uniparental disomy or gene conversion or there could be promoter hypermethylation [14, 16].

3.4 Role of pRB Protein

pRB is a chromatin associated protein that plays a major role in the regulation of cell cycle transition from G1 to S phase [4]. This occurs primarily via its ability to bind with the E2F and DP families of transcription factors which are responsible for cell division. pRB is phosporylated by the cyclin dependent kinases (CDK). This causes release of the E2F/DP complexes and promotes the genes required for cell division. On the other hand, a hypophosphorylated pRB causes suppression of this E2F mediated transcription. Inactivation of pRB by mutations leads to dysregulation of the cell cycle control causing uncontrolled cellular proliferation [6, 17].

3.5 Genetic Variations

3.5.1 Low Penetrance RB-

In maximum retinoblastoma cases there is an autosomal dominant pattern of inheritance with propensity for complete penetrance and high expressivity. This is seen in almost 80–90% of the cases. However, in few families this expressivity and penetrance is reduced which is termed as low penetrance RB. Either the carrier may be unaffected (reduced penetrance) or have a unilateral RB or benign retinocytomas (reduced expressivity) [18]. A diseased eye ratio was formulated to assess this pattern in families with RB. It is the ratio of number of eyes with tumour to the number of mutation carriers in family. For a low penetrance family, the ratio would be less than 1.5 whereas with complete penetrance the ratio would be 1.5 or greater [17]. The mutations responsible for this presentation are typically missense mutations that produce low amount of Rb protein [19].

3.5.2 13 q Deletion Syndrome

It is a phenotypic variant characterised by the partial deletion of long arm of chromosome 13. It can have a wide array of presentations including dysmorphic features like microcephaly, broad nasal bridge, hypertelorism, micro-ophthalmos, cataract, epicanthus, ptosis, micrognathia, protruding teeth, short neck with lateral folds, thickened anteverted low set ears, facial asymmetry, urinary and genital malformations, limb defects, heart defects and psychomotor and mental retardation. Mid-face characteristically has prominent eye-brows, broad forehead and thick everted lower lip [12, 20, 21].

3.5.3 Mutations Other than RB1

Conventionally, for a retinoblastoma to form, the patient requires mutation in both the alleles of RB1 ($RB^{-/-}$). However, it has been reported that some unilateral sporadic cases may not have these RB1 mutations. Recently the role of MYCN gene amplification has been suggested as a unique mutation in such cases ($RB^{+/+}MYCN^{A}$) [5]. These unilateral retinoblastomas are characterised by distinct histopathological features and a very early age at diagnosis. On histopathology these were noted to have undifferentiated cells with large, prominent, multiple nucleoli, necrosis, apoptosis and little calcification. Prototype features of Flexner–Wintersteiner rosettes and nuclear moulding were absent. Clinically, the tumours were large and invasive with a median age of diagnosis of 4.5 months. In cases where the RB1 gene mutation cannot be established, looking for MYCN gene amplification may provide a new insight.

3.5.4 Mosaicism

Less frequently, during embryogenesis, the RB1 mutation can occur in one cell of a multicell embryo causing mosaicism in the proband [1]. Somatic mosaicism can occur in germ cells as well depending on whether the mutation occurred before or after differentiation of gonadal cells [22]. Rushow et al. reported that mosaicism is rare in unaffected parents of the affected child but found a 4.5% rate of somatic mosaicism in retinoblastoma patients [23]. Therefore, it makes it essential to screen for mosaicism and intronic mutations as a part of genetic screening.

3.6 Genetic Testing

Any patient with retinoblastoma is a candidate for genetic testing. Although the patients with hereditary RB can be clinically distinguished, still there are 5–15% of patients who have a unilateral disease with no family history. The identification of RB1 mutation may not change our clinical management but will be essential to counsel the parents, to assess the risk in siblings and off springs, risk of second tumours or trilateral RB and may also reduce the number of repeated ophthalmologic examinations under anaesthesia and also decrease the overall health expense.

Genetic counselling is a fundamental aspect of the standard care in coordination with a geneticist. If a parent has bilateral RB, there is 45% risk of transmitting it to another offspring. The risk of recurrence is summarised in the following Table 3.1 [22].

Once the germline mutation is identified, all the siblings and offsprings should be tested to determine the need for surveillance. If a similar mutation is identified, frequent evaluations are necessary to detect the development of RB at any early

Table 3.1 Empirical recurrence risks in families with retinoblastoma [22]

Clinical scenario	Recurrence risk (%)
Offspring of bilateral cases	45
Offspring of unilateral cases	7.5
Sibling of bilateral cases (parents unaffected)	6
Siblings of unilateral cases (parents unaffected)	1
Sibling of bilateral or unilateral cases (if either parent is affected)	45

stage. The frequency may be every month for first year of life, then every 2 months in the second year and every 3 months thereafter till the age of 4 years [22].

For testing the mutations, a high-quality DNA is required in the form of peripheral blood sample or saliva collected with specialised kits. Tumour tissue can also be obtained from an enucleated eye before formalin fixation. The processing should be done with utmost care. Ideally, two RB mutations should be identified in the tumour DNA. If it is also seen in peripheral leukocytes or saliva sample, the child has heritable form of disease. If neither mutation is identified, still the risk of low-level mosaicism or involvement of MYCN amplification should be borne in mind. Mosaicism can be detected with other sensitive methods like allele specific polymerase chain reaction [12, 24].

3.7 Preimplantation and Prenatal Diagnosis

Once the RB1 mutation is established, families can be given the option of prenatal and preimplantation diagnosis so that they can take an informed decision regarding the continuation of the pregnancy. A timely diagnosis will ensure prompt treatment and improve the overall prognosis [25].

Through preimplantation genetic diagnosis, embryos preferably blastomeres are tested for these mutations after in-vitro fertilisation and the ones that do not inherit these mutations are selected for implantation [26]. But parents should be informed that there is always a risk of misdiagnosis or de novo mutations occurring later in life.

Post-implantation, parents have the option of chorionic villus sampling or amniocentesis to detect whether the foetus is affected. Chorionic villus sampling can be done at 10–12 weeks of gestation and the pregnancy can be terminated if desired. Amniocentesis can be performed after 15 weeks of gestation to identify the mutation [12]. If affected, preterm delivery may be considered when deemed safe and treatment initiated as early as possible [27]. An early term delivery has higher chances of infants having a better outcome. These procedures are associated with minimal risk of miscarriage of around 0.5–1% [28]. Prenatal ultrasound can also be used to identify some large intraocular tumours. Any high-risk babies should be immediately screened after birth and examined regularly thereafter.

3.8 Conclusion

The increasing understanding of various genetic mechanisms associated with retinoblastoma will help in evolving our current clinical practice. It will pave the way for newer targeted therapies and innovative treatment strategies to prolong the survival of these children. Early detection through preimplantation techniques and proper counselling can reduce the psychosocial and economic burden on families providing a better quality of life.

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Pathology of Retinoblastoma: An Update

4

Dipankar Das, Panna Deka, Jyotirmay Biswas, and Harsha Bhattacharjee

4.1 Introduction

Retinoblastoma is the most common intraocular tumor in children [1–8]. It is a neoplasm of the retina which is the extension of the brain [5, 7, 9]. When retinoblastoma is confined to the eye, the survival prognosis is the best [1–5]. About 5000–6000 new cases of retinoblastoma are diagnosed every year in the world, whereas in India, the number lies between 1500 and 2000 [1, 3–6, 8]. Retinoblastoma constitutes 3% of all pediatric cancer [1–4]. The scenario of retinoblastoma survival has changed drastically over the last 50 years and has evolved from 95% mortality to 95% survival of retinoblastoma patients [1–4, 6, 7]. Presently, the mortality of retinoblastoma in developed country is approximately 3% and in developing country is 60% [1–3, 6–8]. Pathology of retinoblastoma is very important and primary focus of this chapter is recent development in gross and microscopic pathology with insight into the molecular pathologic studies [5, 7–9].

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4.2 Genetics

About 1 out of 3 cases of retinoblastoma are caused by RB1 gene-germline mutation [1, 9–12]. MYCN gene seen in younger age group and in the large tumor of retinoblastoma was seen apart from RB1 mutation [7, 9, 13]. 11 bp deletion exon 14 was detected recently, where a prenatal diagnosis of retinoblastoma was made and the baby was treated with laser cryotherapy [13, 14]. Knudson made a tremendous contribution to retinoblastoma research by studying the genetic loci and chromosomal aberrations in familial tree with history of retinoblastoma [7, 9, 12, 13]. Retinoblastoma gene is the first tumor suppressor gene which was cloned as RB1 [5, 7, 9, 12, 13]. Knudson proposed a "two-hit" hypothesis in 1971 [12–14]. The first is in the germline and second hit in the somatic cells, that is, in the retinal cells. Hereditary cases are associated with the development of non-ocular tumors such as various second malignancies including sarcomas like osteosarcoma of the long bones [12–14]. They are usually seen in bilateral retinoblastoma cases who are subjected to radiation therapy. In unilateral sporadic retinoblastoma, both the hits occur during the development of retinal layers by somatic mutation [12–14]. Examinations of sibling and parents should be done at the earliest and also blood samples should be taken for DNA studies to see mutations at 13q14 band and adjoining sites [5, 7–15]. Important points to be noted in genetics are that if the tumor is bilateral, germline mutation is 98%. The children of hereditary form of retinoblastoma survivor have 45% chance of developing retinoblastoma (50% of inheriting, 90% penetrance) [9–16]. Sporadic cases are 95% of which 60% have unilateral retinoblastoma with no germline mutation and remaining can have new germline mutation. In unilateral retinoblastoma, with germline mutation, there is a risk of early presentation. Five percent of all retinoblastoma cases are hereditary [5, 7–16]. Tests required for genetic analysis include karyotyping, gene sequencing by quantitative polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH), multiplex ligation-dependent probe amplification assay, RNA analysis, deletions screening, copy number gene analysis, and methylation assays give mutational location of RB1 gene mutation in retinoblastoma child [5, 7, 9–15]. Tumor samples studies in formalin-fixed tissues can also be done for these point mutations but this process is tedious [5, 7].

4.3 Gross Pathology

Fresh specimen can be trephined from the enucleated eyeball for genetic study and it should be done before the specimen is put in the formalin. After the eye is enucleated (Group D & E) by the surgeon, the specimen is sent to the ocular pathology laboratory in 10% neutral buffer formalin [5, 7, 9]. After 48-h fixation, the enucleated eyeball is grossly examined for any tumor dissemination from the external coat of the eyeball [5, 7, 9]. Thickening of optic nerve is also noted. The eyeball is measured from anterior to posterior, horizontally and vertically with measurement of cornea, pupil, optic nerve-length, and thickness [5, 7, 9]. The eyeball is subjected to

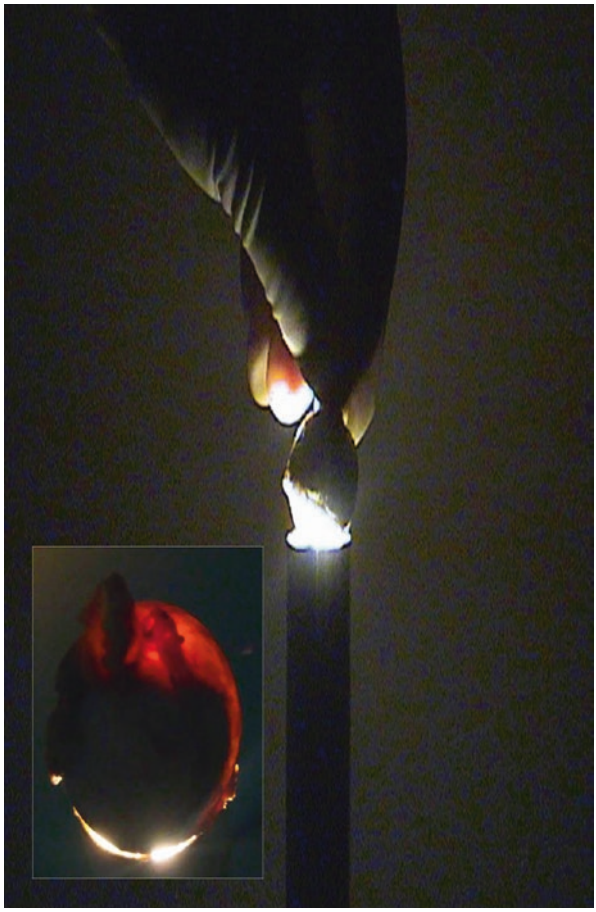

Fig. 4.1 Transillumination test (In darkroom) for retinoblastoma enucleated eyeball before sectioning

transillumination test in a dark room to know externally the position of intraocular tumor so as to have the correct sectioning of the eyeball (Fig. 4.1) [5, 7, 9]. Cut end of the optic nerve is submitted and then sectioning of eyeball is made [5, 7, 9]. According to the recent guidelines, central calotte and three lateral calottes are made in bread loaf technique (Fig. 4.2) [19]. Tumor is described as white mass with flecks of calcifications; seedlings in the vitreous, necrotic area which may be blood-filled or grayish in color. Cornea, anterior chamber, iris, ciliary body, lens, vitreous, gross tumor, any retinal detachment, gross choroidal thickening, scleral involvement are documented [5, 7–9]. Gross photographs are taken under the grossing microscope.

Retinoblastoma can be endophytic, exophytic or mixed [5, 7–9]. Sometimes diffuse infiltrating growth pattern is noted which can have an anterior segment extension [5, 7–9]. Diffuse infiltrating retinoblastoma can be seen in older children mimicking inflammation and present with pseudohypopyon [5, 7–9]. Endophytic tumors extend from inner layer of retina and there is no retinal detachment seen [5,

Fig. 4.2 Gross specimen of retinoblastoma eyeball (by bread loaf technique) with lateral calottes and cut end of optic nerve section

7, 9]. The tumors extend anteriorly into the vitreous cavity and retinoblastoma seeds can be seen in the anterior segment of the eye [5, 7–9]. Exophytic retinoblastoma originate from outer layer of the retina and move outward to the choroid-scleral complex and causes exudative retinal detachment and the retinal blood vessels can be traced over the retina in such situations similar to those seen in the Coat's disease [5, 7–9].

After grossing, eyeball specimen is put in a plastic cassette and then processed in different graded alcohol, xylene, and wax either in automated tissue processor or by manual processing method. The timing for processing is variable in manual and automated machine. After that, L-blocks are used for wax embedding. With a gap of few hours, blocks with specimen sectioning are done in an automated microtome. Tissues are stretched in coated slides in water bath at 58° centigrade. Slides are put in an incubator at 60° centigrade for 1 h. Slides are deparaffinized and stained with hematoxylin and eosin. At least five slides have to be studied by pathologist for the final reporting. Five slides include one central calotte, three lateral calottes (for choroidal involvements) and cut end of the optic nerve section. Histopathology findings are documented in different objective of compound microscope [5, 7, 9]. If immunohistochemistry is required, it is done for various markers on the basis of different laboratory standards [5, 7, 9, 18, 19].

4.4 Microscopy

Retinoblastoma tumors consist of small hyperchromatic cells with altered nuclear-cytoplasmic ratio and are slightly larger than lymphocytes [5, 7–9, 19]. In low power objective of microscope, three zones of involvement are usually visualized. First, basophilic zone (blue) consists of basophilic retinoblastoma cells. The second zone may show eosinophilic area (pink) which is necrotic with cellular debris. The third zone demarcates more basophilic area in an eosinophilic background showing intra-tumoral calcifications (Fig. 4.3) [5, 7, 9, 18–23]. Retinoblastoma tumor can be

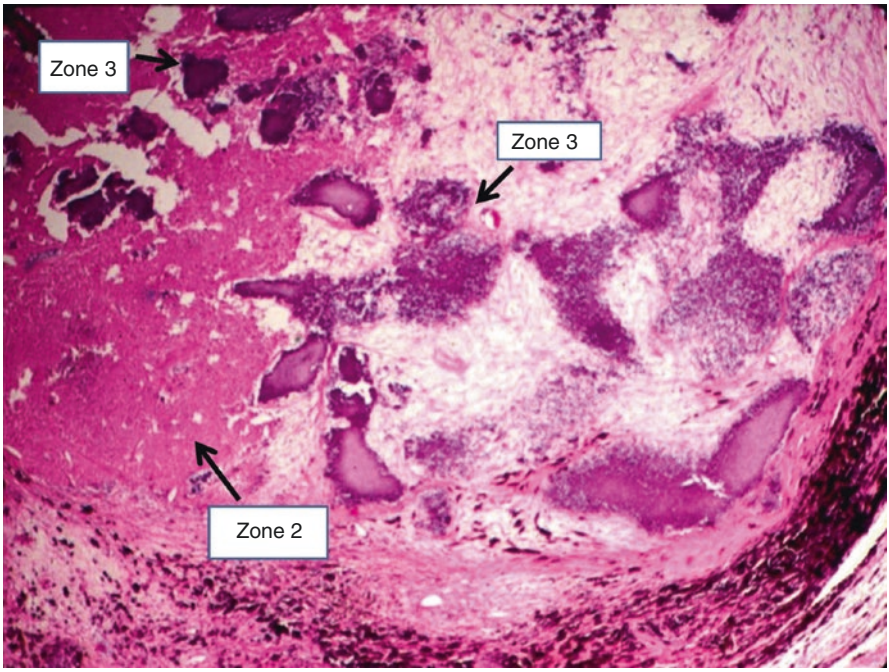

Fig. 4.3 Low-power objective (10×, H&E) showing three zones of involvement in retinoblastoma. First—basophilic zone with tumor cells involvement, second zone—an eosinophilic area of tumor necrosis, and third zone—tumor calcification within necrotic area

differentiated as well as undifferentiated [5, 7–9, 18–23]. A retinoblastoma tumor is considered to be well differentiated when more than 50% of tumor consisted of Homer-Wright rosettes and prominent fleurettes [5, 7–9]. Sometimes poorly differentiated retinoblastoma can be classified when less than 50% of the tumor consist of Flexner–Wintersteiner rosettes. Classical Flexner–Wintersteiner rosettes consisted of ring of cuboidal retinoblastoma cells surround a clear lumen (Fig. 4.4) [5, 7–9]. Clear lumen of Flexner–Wintersteiner rosettes can be stained with Alcian blue as it contains hyaluronidase-resistant mucopolysaccharides [5, 7–9, 18–25]. Homer-Wright rosettes lack clear lumen and the lumen is filled with central neural fibrillar component [5, 7, 9, 13]. Homer-Wright rosettes indicate neuroblastic differentiation and sometimes maybe non-specific (Fig. 4.4) [5, 7, 9, 13]. Homer-Wright rosettes can also occur in neuroblastoma, medulloblastoma, or medulloepithelioma but they seem to be relatively larger in size in these tumors as compared to retinoblastoma [5, 7, 9, 22, 23]. Fleurettes are made up of eosinophilic processes of cones of the retina in a bouquet-like arrangement [5, 7–9, 22, 23]. Retinal tumor composed entirely of fleurettes is thought to be benign variant of retinoblastoma called retinocytoma (Fig. 4.5) [5, 7–9, 22, 23]. Retinocytoma was initially thought to be spontaneously regressed retinoblastoma which has different form of calcifications [5, 7–9, 22, 23]. Das et al. found a third true rosette in retinoblastoma which consists of retinoblast cells within the clear lumen and the cells in the hollowed central space varied in numbers (Fig. 4.4) [20–22]. These rosettes were seen in retinoblastoma

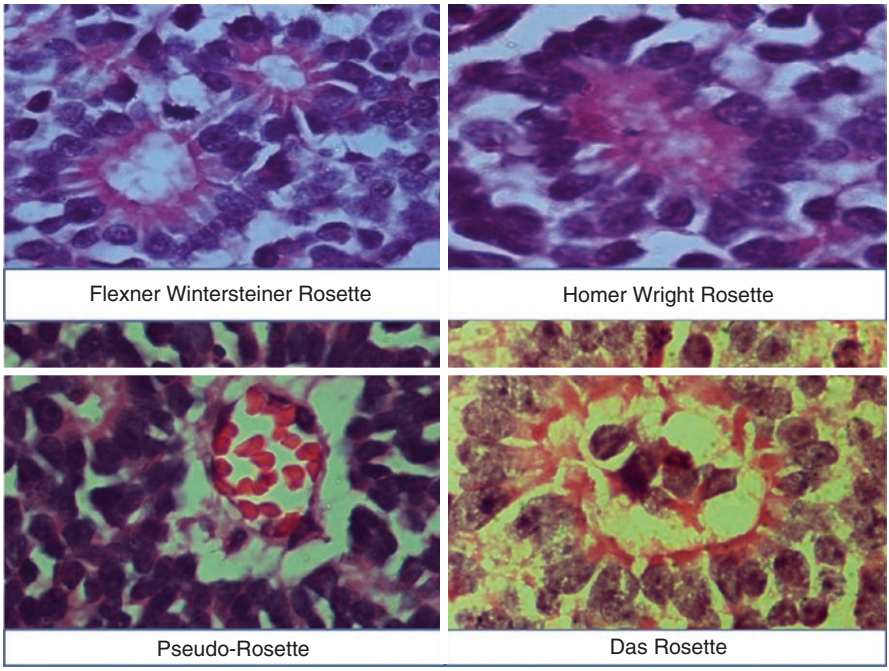

Fig. 4.4 Showing retinoblastoma true and pseudo-rosette. Note: Flexner–Wintersteiner rosette has a clear lumen. Homer-Wright had neurofibrillar component in the lumen and Das rosette has neuroblastic cells within the lumen. Pseudo-rosette has central blood vessel

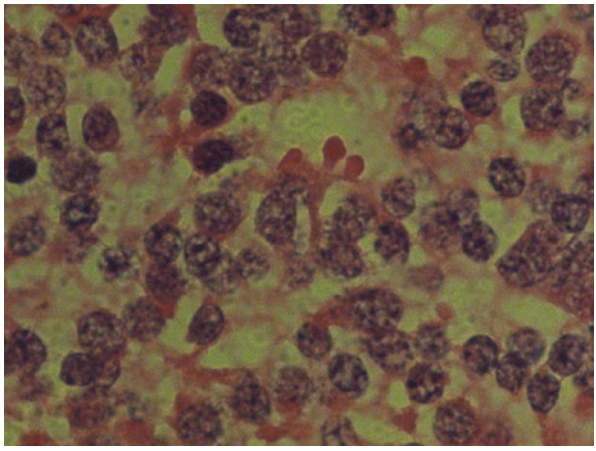

Fig. 4.5 Showing fleurettes in retinoblastoma (H&E, 40×)

with different histopathological high-risk factors [20–22]. Das rosettes were 3–4 times larger than the conventional Flexner–Wintersteiner and Homer-Wright rosettes (Figs. 4.4 and 4.6) [20–22]. Molecular pathologic studies on these rosettes were found to be associated with poor prognosis of retinoblastoma [20, 21]. Neuron-specific enolase, p53, BCL2, Bax, and p16 expressed in retinoblastoma with new

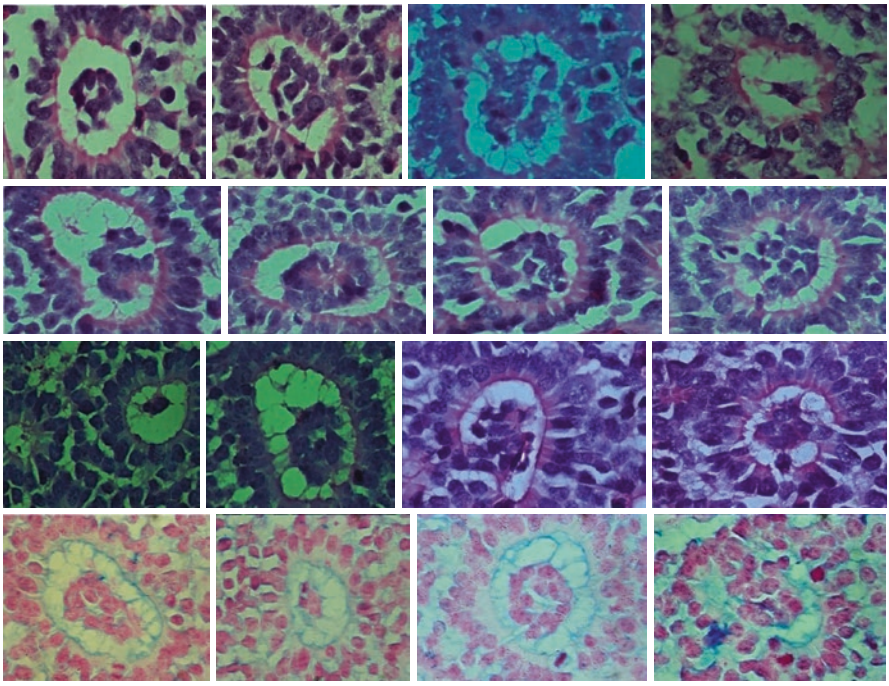

Fig. 4.6 Das rosette with variable cells in the center of rosette-lumen (H&E, 40×). Lower row showing Alcian blue stained Das Rosettes

rosettes [20–22]. P53 showed strong correlation with Das rosettes when compared with control specimens [20–22]. Sometimes pseudo-rosette can be seen in retinoblastoma which differs from true rosettes [5, 7, 9, 22]. Pseudo-rosettes have central blood vessels surrounded by concentric retinoblastoma cells (Fig. 4.4) [5, 7, 9, 22].

Anaplasia, necrosis of the tumor can be graded but not intra-tumoral calcifications [5, 7, 9, 18, 24, 26]. Necrotic retinoblastoma can present as an inflammatory process and can simulate orbital cellulitis in late stages [5, 7–9]. Extensive intratumoral necrosis can lead to poor prognosis for metastasis [5, 7–9, 18, 24, 26]. Calcification, on the other hand, can be seen as a purple deposition in hematoxylin and eosin-stained slide and presence of calcium can be established by Alizarin Red or Von Kosa stains [5, 7–9, 22]. Calcified portion stains red with Alizarin Red and black with Von Kosa stain respectively [5, 7–9, 22]. Scanning electron microscopy has shown these intra-tumoral calcifications probably occur within the mitochondria of necrotic cells [5, 7–9, 22]. Calcification of phthisical eye and that of retinoblastoma differs as retinoblastoma calcifications are within the tumor and bone formation in the phthisical eye is in the periphery, inside the coat of the eyeball [5, 7–9]. Sometimes DNA depositions are seen as basophilic materials surrounding the vessels, which are released by necrotic cells [5, 7, 9].

Histopathological high-risk factors consist of the cornea, anterior chamber, iris, ciliary body, Schlemm's canal, choroid, optic nerve and scleral, and extra-scleral involvement [19–37]. Optic nerve invasion can be further classified as pre-laminar,

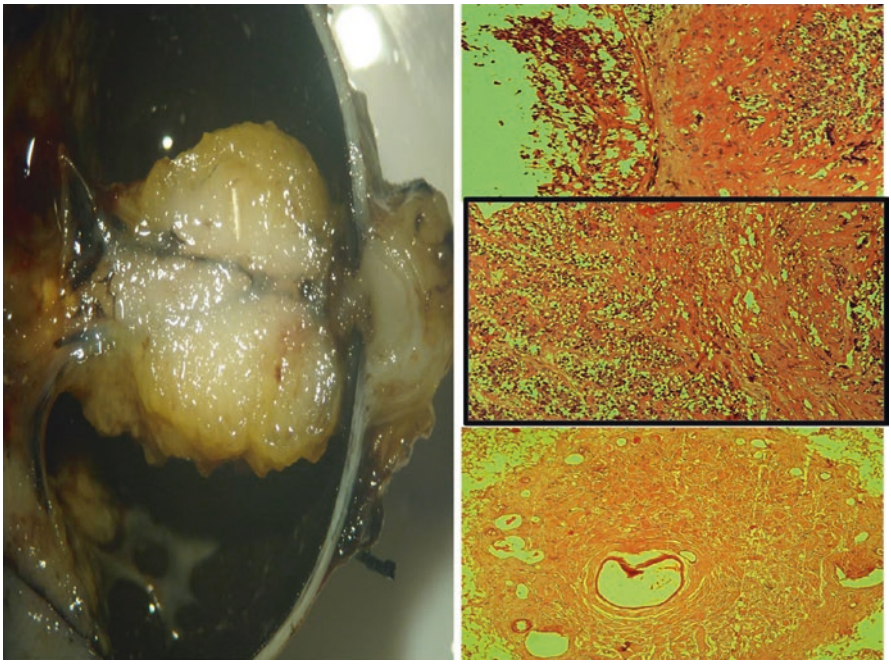

Fig. 4.7 Showing optic nerve involvement in gross and in histopathology (H&E, 20×)

laminar, post laminar, and involvement of cut end of the optic nerve (Fig. 4.7) [5, 7, 9, 20–23, 27–31]. In respect to optic nerve in pupil-optic nerve central section, when tumor crosses the laminar cribrosa, it becomes extraocular [5, 7–9]. Choroidal invasion can be focal when tumor involved less than 3 mm in any diameter both in width and thickness [5, 7, 9, 20, 22, 23, 27–31]. Massive choroidal invasion is described as invasion 3 mm or more in any diameter (Fig. 4.8) [5, 7, 9, 20, 22, 23, 27–31]. Biswas et al. had graded RPE- choroidal invasions in Indian RB patients on the basis of Schilling classification [23]. Choroidal invasions can sometimes be confused with extramedullary hematopoiesis [5]. Large tumor sizes with vitreous seeds, intra-tumoral angiogenesis, neovascularization of iris, secondary glaucoma, and orbital spread of retinoblastoma are also high-risk factors [5, 7–9]. Pathologist is required to differentiate artificial seeding of tumor cells in these demarcated zones [5, 7–9]. In a nutshell, retinoblastoma tends to spread to brain through optic nerve and meninges. Through choroid it spreads to the liver and the lungs (vascular spread). Lymphatic spread occurs if extraocular structures like conjunctiva and eyelid are involved [5, 7–9]. Kashyap et al. described various clinical features in retinoblastoma like older age at presentation; presence of hyphema, pseudohypopyon, orbital cellulitis, staphyloma and longer lag period, in their study [26]. These updated clinical prognostic factors can be correlated with histopathological high-risk factors for better management of retinoblastoma [1–38].

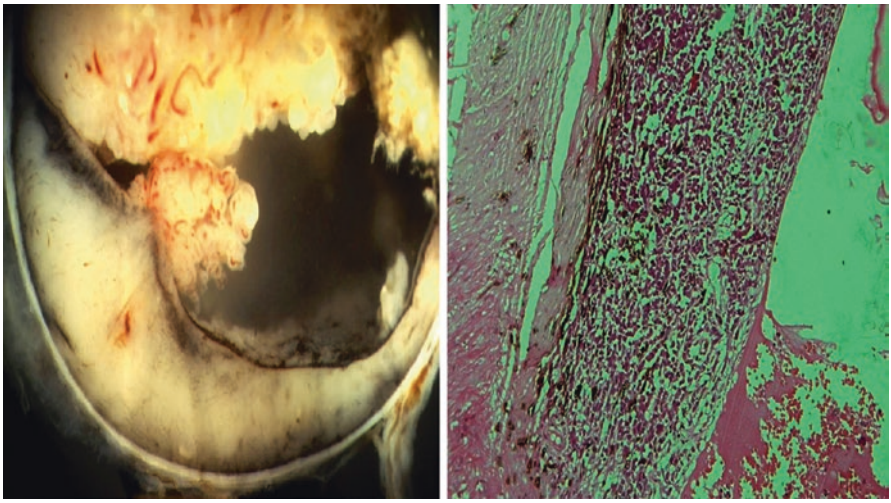

Fig. 4.8 Showing extensive choroidal involvement in gross and histopathology (H&E, 20×)

Additionally, there may be chemotherapeutic changes in retinoblastoma pathology following a local, systemic and intra-arterial chemotherapy (IAC) [5, 7, 9, 27–31]. Authors have observed post-chemotherapy retinal pigment epithelial (RPE) changes where central part of retinal pigment epithelium showed atrophic changes in the gross and histopathological examination of different segment of RPEs in an enucleated retinoblastoma eye (Unpublished observations). Intra-tumoral occluded blood vessels with tumor shrinkage were observed in local chemotherapy and IAC-treated eyes [5, 7, 9, 30]. Choroidal layers show markedly atrophic change following IAC [9, 30]. Calcified thrombi may sometime fill the vascular lumen and birefringent foreign bodies can be visualized near the occluded vessels under polarizer of the compound microscope (Fig. 4.9) [9, 30]. Tumor regression signs in histopathology after local or systemic chemotherapy can have regression scar where calcification and gliotic change may be evident [5, 7, 9, 30, 31].

Treatment failure in retinoblastoma can be attributed to various causes like vitreous and subretinal seeds, intraretinal tumors, and tumor resistance (Fig. 4.10) [5, 7, 9, 30, 31]. Seeds and intraretinal tumors are less prone to treatment due to the inability of anticancer drugs to reach the exact tumor by the mechanism of diffusion [5, 7, 9, 30, 31]. Tumor resistances can be due to well differentiation of the tumor and non-cyclin tumor cells that is resistance to tumor modalities depending on cell division. [5, 7, 9, 30, 31] Vitreous seeds can be classified as dust, cloud, sphere, or mixed type (Fig. 4.11) [5, 7, 9, 30, 31]. Seeds of retinoblastoma can be pre-hyaloid, sub-hyaloid, epiretinal, intraretinal, and subretinal. Intra-cameral seeds can be like deposits or infiltrated (Figs. 4.12 and 4.13) [5, 7, 9, 30, 31]. Vitreous seeds spread from the tumor are by breaching of internal limiting membrane. [5, 7, 9, 30, 31] Vitreous seeds usually have two forms [31]. First, being adherent independent

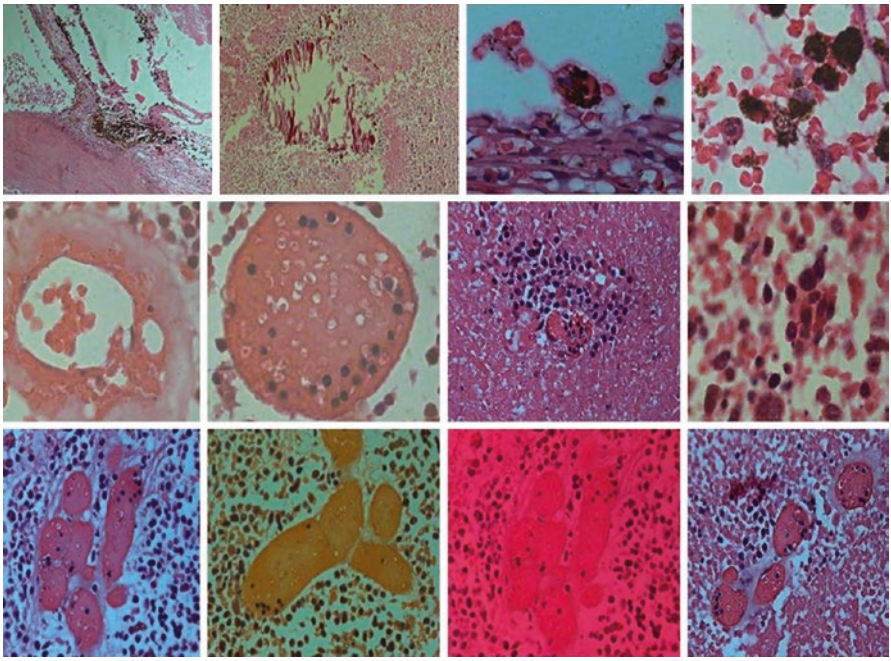

Fig. 4.9 Showing intra-tumoral vascular change following IAC

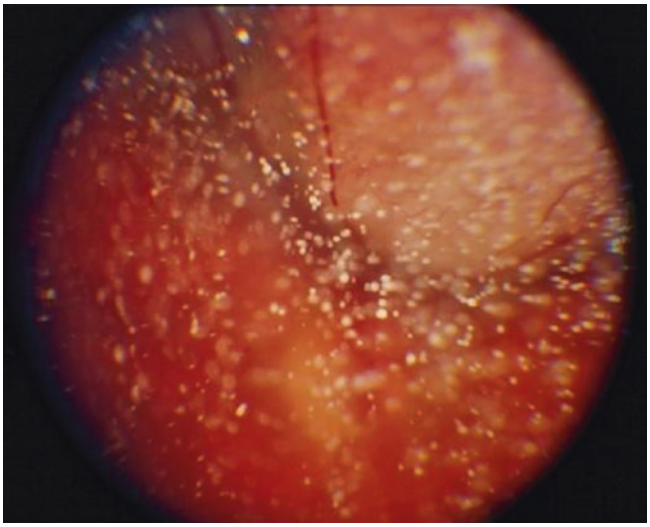

Fig. 4.10 Fundus photograph showing extensive vitreous seeding in Group D retinoblastoma

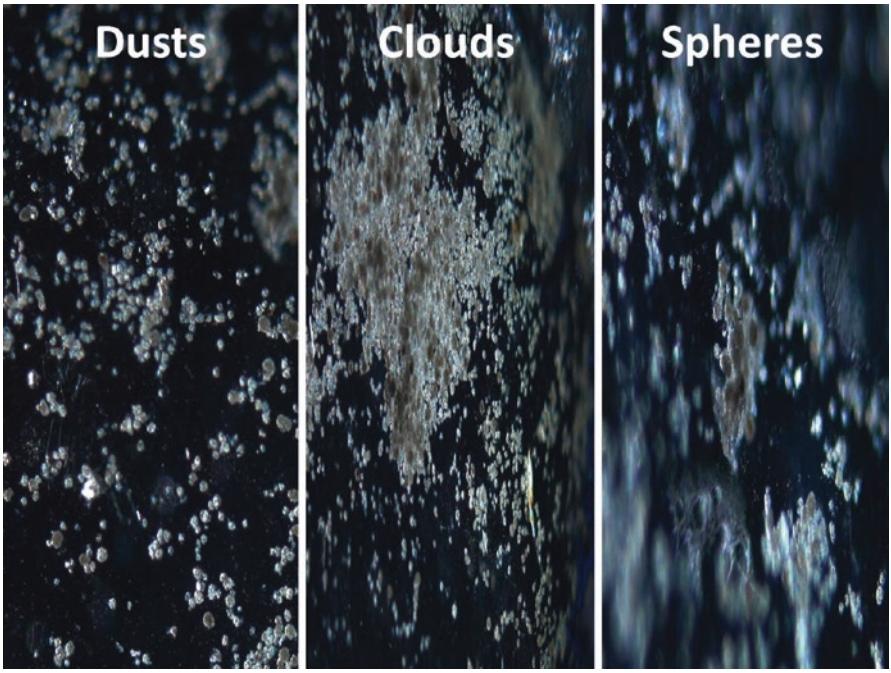

Fig. 4.11 Diffractive photographs under the compound microscope showing different vitreous seeds in an enucleated eyeball without staining (20×)

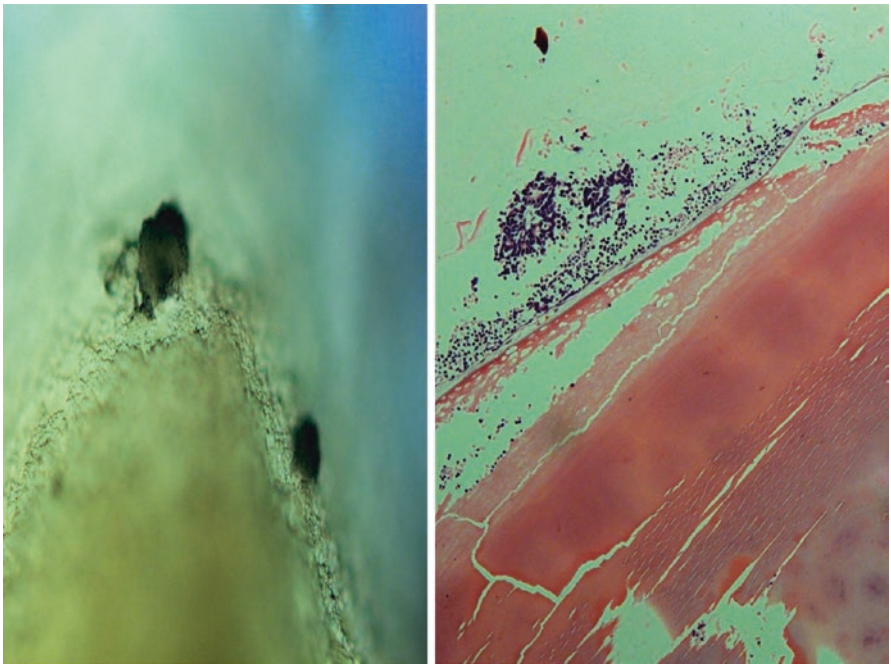

Fig. 4.12 Showing vitreous seeds in the anterior segment in gross and histopathology (H&E, 20×)

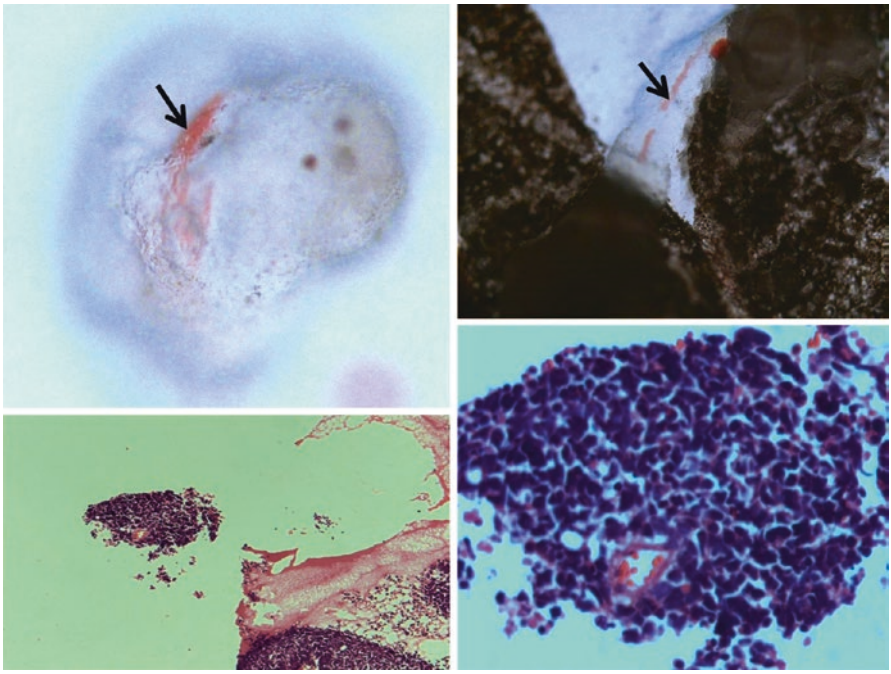

Fig. 4.13 Subretinal seeds with blood vessels in gross and histopathology (H&E, 40×)

growth form free-floating seeds and second, adherent dependent growth form epiretinal seeds (Fig. 4.14) [31].

Retinoblastoma classification guided by the American Joint Commission on Cancer (AJCC) and the Union International Control Cancer has classified the tumor, node, metastasis recognizing by incorporating in stage category "H-heritable" into the AJCC classification, 2017-8th edition [8]. The "H" is the only one distinguishable additional factor in retinoblastoma from other AJCC classifications meant for ocular cancers [8].

4.5 Molecular Pathology

Recent molecular pathologic studies in retinoblastoma open our mind in dealing with the basic questions in the pathology of retinoblastoma [8–38]. The discovery of oncogenes and proto-oncogenes modified our approach in the pathogenesis of this childhood eye cancer [8, 16–21, 34–38]. Various molecular markers such as CDC25 phosphatases (CDC25B) can be used as a potential marker for prognosis of retinoblastoma [8, 32]. PLK1 and PLK3 can also be used as a bad prognosis marker in retinoblastoma [6, 8, 17, 19–21, 34–38]. BCL2, p53, Bax has shown higher expression and they regulate the apoptosis in retinoblastoma [6, 8, 17, 19–21, 34–38]. New gene sequencing in RB1 can be used as a diagnostic procedure in

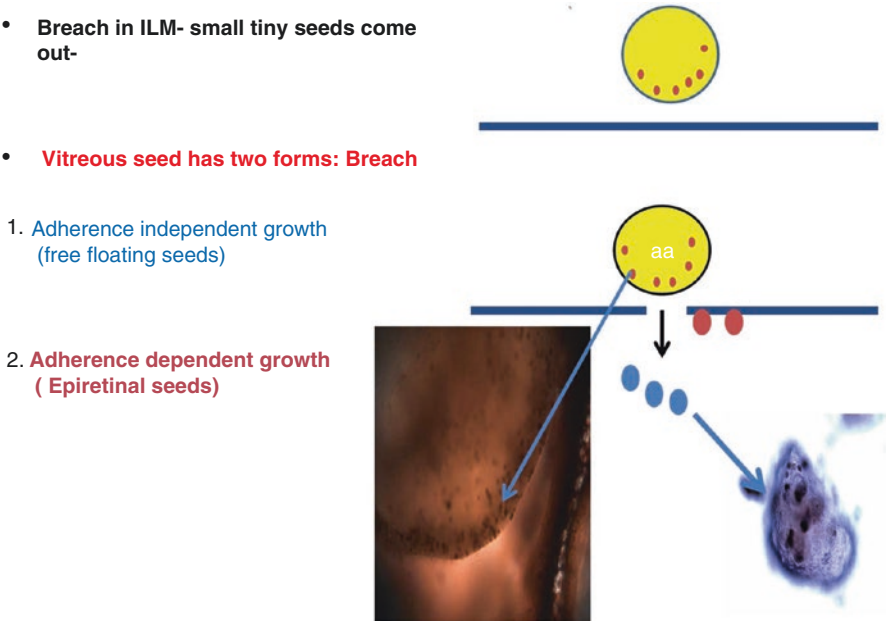

Fig. 4.14 Schematic diagram showing the formation of vitreous seeds by rupturing of internal limiting membrane

retinoblastoma [6, 8, 17, 19–21, 34–38]. Small insertion, deletion, copy number variation, and point mutation can be detected in retinoblastoma children [6, 8, 17, 19–21, 34–38]. Genomics application and analysis in paraffin fixed tissue block can discover various novel biomarkers for early detection of retinoblastoma [6, 8, 17, 19–21, 34–38]. Role of mitochondria in the cytoplasm of retinoblastoma cells can give a clue in tumor progression, apoptosis, and cellular differentiation [6, 8, 17, 19–21, 34–38]. Das et al. have published the apoptotic change particularly efferocytosis in retinoblastoma from where new pharmacodynamics application can be thought in future for anticancer drugs [33]. Fatty acid synthase, cytoplasmic expression for transcription factor (FOXO3a) can have translational role for newer chemotherapeutic agent in retinoblastoma [8, 34, 35]. Various reactive-oxygen byproduct expressions in tumor cells like NOX4 protein can indicate good prognosis for retinoblastoma [5, 8, 9, 11]. Similarly Sirt1 (Sirtuin1) has been found significance in retinoblastoma. PDK1 protein and gene expression have recently been found to be associated retinoblastoma vitreous seeds in a hypoxic area within the tumor [5, 8, 9, 11].

In conclusion, future trends in advanced pathology of retinoblastoma would be liquid biopsy and detection of pRB protein and other biomarkers that were expressed in the retinoblastoma tissue and serum and now possibly be detected in tears samples as a noninvasive diagnostic tool. Noninvasive diagnosis of retinoblastoma using cell-free DNA is already established in aqueous samples [37]. Finally,

retinoblastoma metastasis will always be a challenge for basic scientists, ocular oncologists, and pathologists [5, 7–9, 11, 27–37].

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Malignant Melanoma of Choroid

5

Yamini Attiku and Vikas Khetan

5.1 Introduction

Uveal melanoma is the most common intraocular malignancy in adults [1]. Among the uveal melanomas, 4% arise from the iris, 6% from ciliary body, and 90% from the choroid [2]. According to the Surveillance, Epidemiology, and End Results (SEER) registry database 4999 cases of primary uveal melanoma have been identified from 1973 to 2013. The mean age adjusted incidence was 5.2 cases per million in these four decades [3]. The median age of diagnosis of uveal melanoma is 59–62 years in Caucasian population, whereas it is a decade or two earlier in the Asian population [4].

Risk factors that have been identified for ocular melanoma include light eye color, iris or choroidal nevus, fair skin color, inability to tan, ocular or oculo-dermal melanocytosis, atypical cutaneous nevi, common cutaneous nevi, cutaneous freckles, welding and occupational cooking [5, 6].

5.2 Genetics

Loss of chromosome 3, 1p, 6q, 8p, or 9p and gain of 1q, 6p, or 8q are associated with choroidal melanoma. Loss of chromosome 3 and 1p, 8p, 6q loss and gain of chromosome 8q have been shown to reduce survival. Chromosome 6 with its gain

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has shown a better prognosis. BAP1 (BRCA1-associated protein 1) located on chromosome 3 has been associated with an increased malignant potential [7].

5.3 Symptoms

The symptoms of ciliary body and choroidal melanoma include blurred vision (38%), photopsia (9%), floaters (7%), visual field loss (6%), visible tumor (3%), pain (2%), metamorphopsia (2%), and 30% of patients are asymptomatic [8]. There is a delay in diagnosis of choroidal melanoma as the patient remains asymptomatic for long.

5.4 Clinical Signs

Posterior uveal melanomas present clinically as dome- or mushroom-shaped mass after breaking the Bruch's membrane or can be lobulated. Rarely, it can present as a diffuse variant. They can be pigmented, have mixed pigmentation or be amelanotic [2]. The melanoma may be associated with retinal detachment (71%), intraocular hemorrhage (10%), or extraocular extension (3%) [2].

Approximately, 50% of the patients with uveal melanoma develop secondaries due to micro-metastasis within 10 years of diagnosis [1]. The common sites of metastasis include liver (89%), lung (29%), and bone [9]. Clinical risk factors for metastasis are increasing age, ciliary body involvement, increasing tumor diameter, and thickness, brown tumor, presence of subretinal fluid, intraocular hemorrhage, and extraocular extension [2]. None of the available treatment options reduce the rate of metastasis.

5.5 Classification

The modified Callender histological classification of melanoma includes spindle cell, epithelioid cell, and mixed cell types [10]. Epithelioid cell type carries a poor prognosis. The Collaborative Ocular Melanoma Study (COMS) classified choroidal melanomas to small, medium, and large based on tumor dimensions [11].

5.5.1 Collaborative Ocular Melanoma Study (COMS)

In the 1980s the management of choroidal melanoma for differing tumor size was not well described, and hence the need for it was felt. In 1985 and 1986, the Collaborative Ocular Melanoma Study (COMS) was designed to answer these questions. COMS classified the tumors into small, medium, and large (Fig. 5.1, Table 5.1).

In 1990 the classification was revised (Table 5.2).

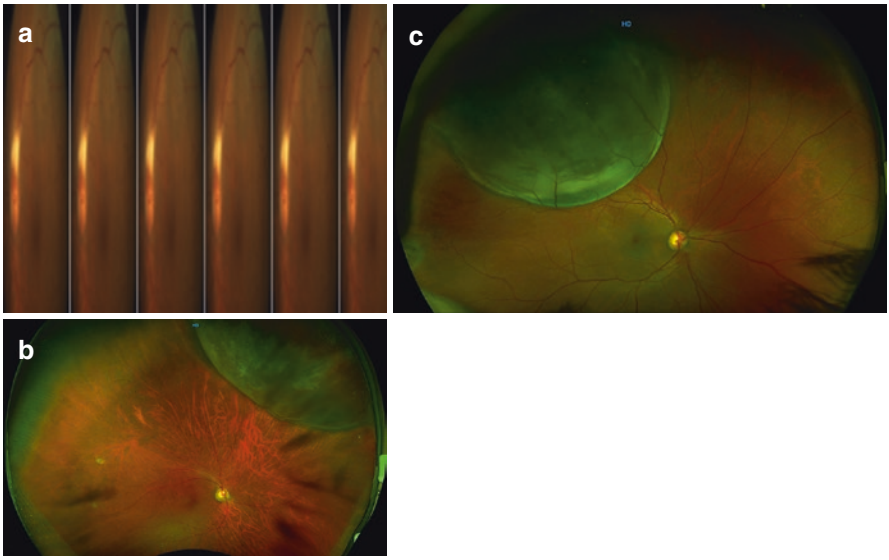


Fig. 5.1 (**a**) Small choroidal melanoma. (**b**) Medium choroidal melanoma. (**c**) Large choroidal melanoma

Table 5.1 COMS original classification of choroidal melanomas

Category	Largest basal diameter	Height
Small	5–16 mm and	1.0–3.0 mm
Medium	<16 mm and	3.1–8.0 mm
Large	>16 mm and	>2 mm– >8 mm??

Table 5.2 COMS revised classification of choroidal melanomas (Fig. 5.1)

Category	Largest basal diameter	Height
Small	5–16 mm	<2.5 mm
Medium[a]	<16 mm	2.5–10 mm
Large[a]	>16 mm	>2 mm– >10 mm

[a]Unless the tumor was located within 2.0 mm of the optic disk

The American Joint Commission on Cancer (AJCC) gave the eight edition of choroidal melanoma classification, the Tumor, Node, Metastasis (TNM) staging in 2017 [12]. The 7th edition of AJCC was modified based on clinical evidence from the COMS study. The T category classification was based on tumor thickness and basal diameter and subclassified based on presence of ciliary body involvement and extent of extraocular extension. The N category classification was based on presence or absence of spread to the regional lymph nodes and the M category classification was based on the presence or absence distant metastasis and the largest basal diameter of the metastasis. This classification system further categorizes each specific combination of the individual T, N, and M into prognostic stages, with the increasing stage indicating higher risk of metastasis.

5.6 Investigations

The diagnosis of choroidal melanoma is mainly clinical. Hence detailed fundus examination is of utmost importance. Serial fundus photographs help in monitoring the progression of the lesion. It also helps in evaluating the response to treatment.

Ultrasonography (USG) is an important investigation for measuring the dimensions of the tumor. The choroidal mass exhibits solid consistency having low-to-medium internal reflectivity and a regular internal structure. Important clinical findings on USG include acoustic hollowness, sound attenuation, kappa sign, and collar-stud appearance (Fig. 5.2) [13].

Ultrasound biomicroscopy is done to assess anteriorly located tumors.

Fundus fluorescein angiography (FFA) and indocyanine green (ICG) angiography are adjunctive diagnostic procedures which may show the characteristic double circulation. It represents the superimposition of the intravascular fluorescence of the intact retinal vasculature over the fluorescence of large caliber vessels within choroidal tumor (Fig. 5.3) [14].

On Magnetic Resonance Imaging (MRI), the uveal melanoma is hyperintense on T1 and hypointense on T2 weighted images and shows contrast enhancement (Fig. 5.4). MRI is superior to USG in diagnosing extrascleral extension [15].

Optical coherence tomography can help in distinguishing between small choroidal melanomas and nevus based on choroidal thickness. Presence of subretinal deposit, subretinal fluid, intraretinal edema, and photoreceptor damage is indicative of choroidal melanoma (Fig. 5.5) [16].

Fine needle aspiration biopsy (FNAB) helps may confirm the diagnosis in uncertain cases and also helps in molecular diagnosis. The biopsy can be taken via transcorneal, transscleral, or transvitreal approach (Fig. 5.6) [17].

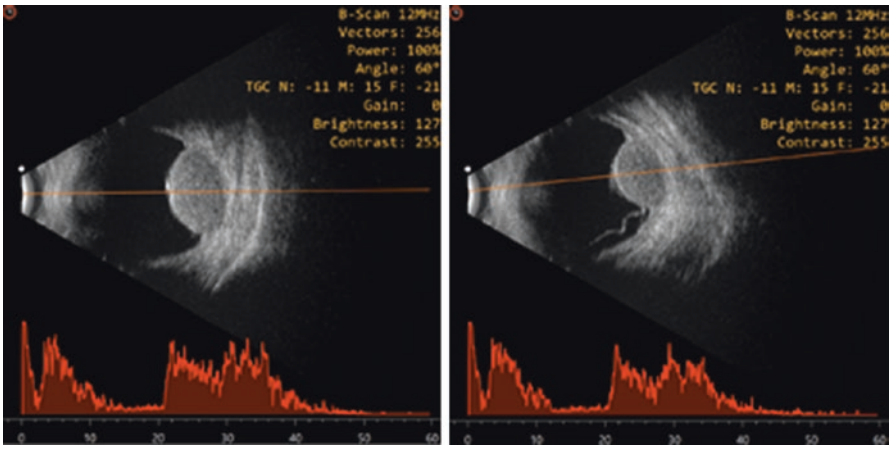


Fig. 5.2 Ultrasound image of a patient with choroidal melanoma showing a dome shaped lesion on B-scan, kappa sign on A-scan, and associated retinal detachment

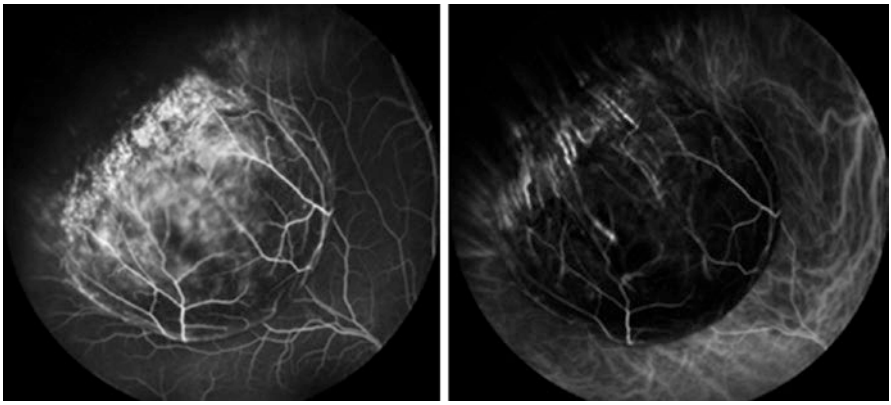


Fig. 5.3 Fluorescein angiography and Indocyanine green angiography showing double circulation

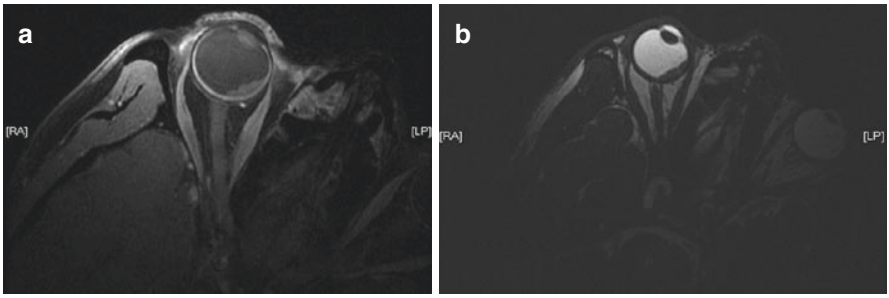
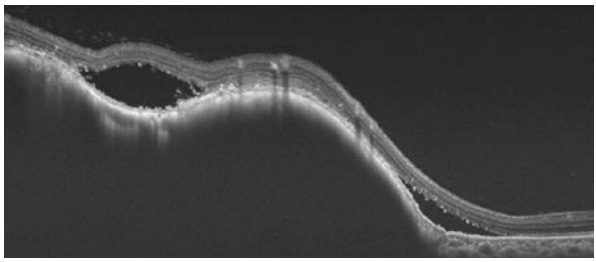


Fig. 5.4 (**a** and **b**) Magnetic resonance imaging of choroidal melanoma having hyperintensity on T1W images hypointensity on T2W images

Fig. 5.5 Small choroidal melanoma on OCT



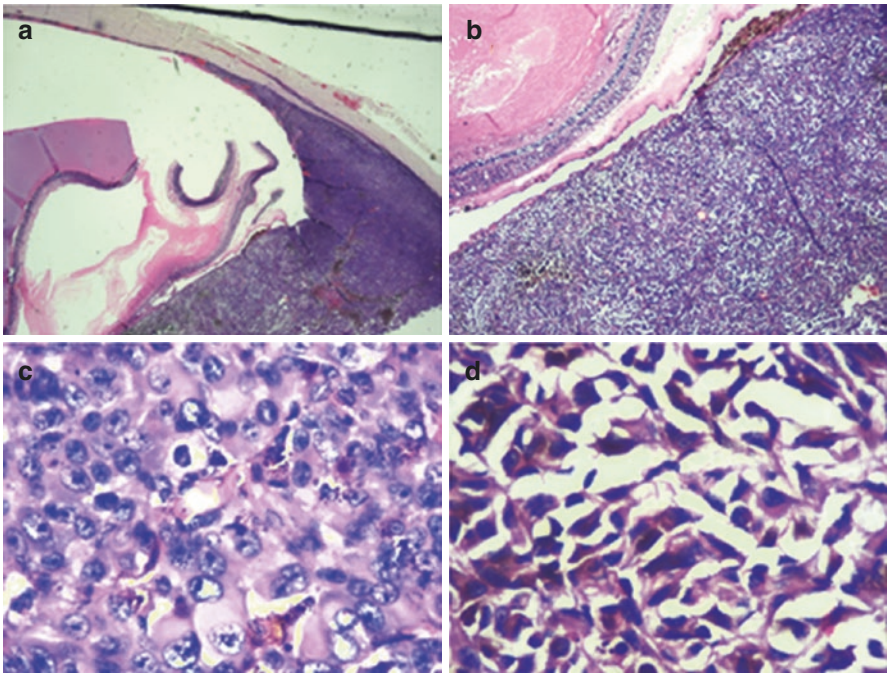


Fig. 5.6 Biopsy specimen of uveal melanoma showing (**a**) pigmented dome shaped tumor arising from the choroid with overlying retinal detachment. (Magnification 1×, Hemotoxylin and Eosin stain), (**b**) Tumor shows minimal pigmentation. (**c**) Higher magnification image showing the epithelioid cells (Magnification 40×), (**d**) Spindle B cells on high magnification (Magnification 40×)

5.7 Differential Diagnosis

Choroidal nevus is the most frequent pseudomelanoma [18]. It is more possible for a melanocytic lesion to be a nevus if it were less than 6 mm in diameter and less than 2.5 mm in thickness. But in case a lesion with the above dimensions had surface orange pigment, subretinal fluid, and documented growth, it is more likely a melanoma [19].

Risk factors predictive of transformation of choroidal nevus into melanoma include: tumor thickness >2 mm with symptoms, presence of subretinal fluid, orange pigment, margin within 3 mm of the disc, ultrasonographic hollowness, and absence of halos or drusen. Shields et al. gave a mnemonic to help remember the ocular melanoma risk factors [20]. TFSOM UHHD stands for 'To Find Small Ocular Melanoma Using Helpful Hints Daily', representing thickness, fluid, symptoms, orange pigment, margin, ultrasonographic hollowness, halo absence, and drusen absence. Presence of three or more of these features is suggestive of a melanoma.

Congenital hypertrophy of retinal pigment epithelium (CHRPE) is a dark brown or black flat lesion with well demarcated margins, pigmented or depigmented halo and depigmented lacunae.

Table 5.3 Differentials diagnosis of posterior uveal melanoma [18]

Diseases
Choroidal nevus
Choroidal tuberculoma
Diktyoma
Peripheral exudative hemorrhagic chorioretinal degeneration
Circumscribed choroidal hemangioma
Optic disc melanocytoma
Hemorrhagic choroidal detachment
Hemorrhagic detachment of the retina and RPE
Age-related macular degeneration
RPE hyperplasia
Choroidal metastasis

Peripheral exudative hemorrhagic chorioretinal degeneration (PEHCR) and age-related macular degeneration can be differentiated clinically by the presence of subretinal blood in various stages of resolution and subretinal exudates. It can be confirmed on FFA. The less common differentials for choroidal melanoma include circumscribed choroidal hemangioma, optic disc melanocytoma, hemorrhagic choroidal detachment and choroidal metastasis (Table 5.3).

5.8 Treatment

Treatment of malignant melanoma largely depends on the size, extent, location of the tumor, potential for vision salvage and systemic status. In the earlier years, enucleation was the treatment of choice.

1. **Observation and serial monitoring** can be done in indeterminate melanoma like lesions and in elderly and medically unstable patients [21]. In indeterminate lesions, biopsy will help in arriving at a conclusive diagnosis, though it can be associated with complications. Several factors need to be taken into consideration before arriving at a decision on whether to treat or observe.
2. **Photodynamic therapy** (PDT) is a noninvasive and an out-patient procedure for the treatment of small posterior uveal melanomas, especially the amelanotic ones [22]. It causes reactive oxygen species induced tissue damage. Variable results have been obtained till date with the use of PDT in clinical settings and the clinical experience is limited.
3. **Transpupillary thermotherapy** (TTT) can be used as an alternative or as an adjuvant to radiotherapy in small choroidal melanomas, especially the ones in the peripapillary and paramacular areas. It causes tumor necrosis by direct cell destruction. Recurrence rates up to 24% have been reported with TTT and hence is not preferred as a primary treatment modality [23].

4. **Radiation therapy** is considered for medium-sized melanomas [24]. It can also be done in small-sized melanomas with documented growth and in selected cases of large melanomas.
   (a) **Plaque brachytherapy** involves suturing the radioactive plaque episclerally adjacent to the area of interest. The plaque is removed in a second procedure after the prescribed dose is delivered. Radioactive isotopes most commonly used for the treatment of choroidal melanoma are Iodine-125 and Ruthenium-106. I-125 has greater penetration and can be used to treat tumors which are up to 10 mm thick. Following the results of COMS, it is the most common globe-salvaging technique for treatment of medium-sized melanomas.
   (b) **Charged particle therapy** delivered with protons, helium ions, or carbon ions has also been used to treat uveal melanoma. This is preferred in peripapillary tumors where a plaque cannot be inserted. A high dose of radiation is delivered to a small volume of tissue resulting in lesser rates of local recurrence, radiation retinopathy and cataract [25].
   (c) **Stereotactic radiosurgery** and **proton beam therapy** are other effective options to deliver radiation, with good tumor control and globe salvage rates. These require specific equipment and expertise for planning and execution of treatment [26].

   No significant difference has been reported between external beam radiotherapy or brachytherapy in terms of ocular survival. Complications related to radiotherapy included cataract, neuropathy, radiation retinopathy and secondary glaucoma and hence patient need to be on frequent follow up to monitor for complications following radiotherapy.
5. **Surgical Resection**
   (a) **Local resection** of the tumor is done at few centers over the world and is a challenging procedure. The approach may be transcleral (exoresection), suitable for anterior tumors or transretinal (endoresection) which is suitable for posterior tumors. This helps in preserving the globe and vision and provides tissue for histopathological and cytogenetic studies [24]. It is fraught with complications including retinal detachment, vitreous hemorrhage, cataract, and raised intraocular pressure [27].
   (b) **Enucleation** is done in large melanomas and in those with poor visual potential. In the 1960s, it was the only treatment option available for suspected posterior uveal melanomas. In the 1970s, Zimmerman and McLeod et al. hypothesized an increase in metastasis rates due to manipulation during surgery [28]. But this was later dismissed when it was understood that microscopic metastasis occurred even prior to diagnosis of melanoma or enucleation, and it was the nature of the disease.
   (c) **Exenteration.**

   In rare scenarios with orbital extension of the uveal melanoma exenteration is required.
6. The treatment of metastatic disease is mostly palliative.

5.9 Prognosis

Small uveal melanoma observational study: This study was done to identify the risk factors for tumor growth. COMS observational study reported that small melanomas with prominent orange pigment, without drusen and adjacent retinal pigment epithelial changes and those that were at least 2 mm thick and 12 mm by LBD were more likely to grow than small melanomas that lacked these features. Most tumors diagnosed as small-sized uveal melanomas that were enrolled within 1 year of initial diagnosis did not grow in 5 years [29].

Medium-sized uveal melanoma randomized trial: Enucleation versus iodine brachytherapy reports that both modes of the treatment are equally safe for the management of medium-sized melanoma as regards life prognosis [30].

Large choroidal melanoma randomized trial: Enucleation alone versus pre-enucleation irradiation reported that pre-enucleation irradiation does not statistically improve the 5-year survival of patients with a large uveal melanoma [31].

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Genetics of Uveal Melanoma

6

Pradeep Sagar and P. Mahesh Shanmugam

Uveal melanoma is the most common malignant primary intraocular tumor in the adult population. It is more commonly seen in Caucasians than Asian and African population. In spite of advances in the management of uveal melanoma and good control of local disease, about half of the patients develop metastases [1]. The genetic alterations in uveal melanoma are important factors in the development of metastatic melanoma. In the last few decades, the data on the genetic alterations in uveal melanoma is growing. Understanding the genetic alterations is clinically relevant in the following contexts.

1. Role in progression of choroidal melanoma
2. Role in hereditary or familial choroidal melanoma
3. Prognostication
4. Role in treatment
5. Development of novel therapeutic modalities

A large number of genetic mutations and chromosomal anomalies are described. In this chapter, we will discuss the anomalies which are clinically relevant.

6.1 Genetic Alterations and Progression of Melanoma

Genesis and progression of a tumor involves multiple steps. This includes cell cycle dysregulation, cell survival, and acquisition of malignant potential.

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6.1.1 Cell Cycle Dysregulation

Cell cycle in eukaryotes includes four phases: Gap 1 (G1) phase, synthesis (S) phase, gap 2 (G2) phase, and mitoses (M) phase. Cell increases in size and prepares for synthesis of deoxyribonucleic acid (DNA) in G1 phase. Replication of DNA occurs in S phase. Cell further increases in size and prepares for cell division in G2 phase. Cell divides into 2 daughter cells in M phase. The nondividing cells in eukaryotes enter the quiescent phase G0 [2]. Proper check mechanisms and controlled cell cycle is essential. Dysregulation of cell cycle is the first step in tumorigenesis. Dysregulation in cell cycle in uveal melanoma is secondary to mutations involving GNAQ [3], GNA11 [4], and INK4A [5].

6.1.1.1 Guanine Nucleotide-Binding Protein Subunit Alpha-Q and Guanine Nucleotide-Binding Protein Subunit Alpha-11 (GNAQ and GNA11)

GNAQ encodes G_q alpha subunit and GNA11 encodes G_{11} alpha subunit. G_q α, G_{11} α, G_{14} α, G_{15} α are distinct proteins in the G alpha subunit family. The function of G alpha is to activate intracellular signaling pathways in response to stimulation of G protein coupled receptors (GPCR). The intracellular transducer in GPCR is G protein. G protein is a trimer composed of Gα bound to complex of Gβ and Gγ. In inactive state, Gα is bound to guanosine diphosphate (GDP) and Gβγ. When ligand binds to GPCR, the GPCR promotes the dissociation of GDP from Gα and GTP binds to Gα. The GTP bound Gα dissociates from Gβγ and both activate the respective downstream signaling pathways. The downstream pathways are summarized in Fig. 6.1. Ultimately Gα mediates its activity by stimulation of protein kinase C [6, 7].

Mutations in GNAQ are reported in about 50% of cases of uveal melanoma. In 50% of cases without GNAQ mutation, GNA11 mutations are reported [6, 7]. The constitutional activation of G alpha unit leads to activation of protein kinase C and leads to overexpression of cyclin D [8]. Cyclin D/cyclin-dependent kinase 4 (CDK4) leads to inactivation of retinoblastoma (Rb) protein by hyperphosphorylation [9–12] (Fig. 6.2).

Retinoblastoma protein is a tumor suppressor gene and inhibits the progression of cell cycles at G1-S transition. Inactivation of Rb protein leads to uncontrolled cell cycle and cell proliferation [13]. Disruption of retinoblastoma tumor suppressor pathway is common in uveal melanoma. In about two-third of cases of uveal melanoma, this is due to the mutation in GNAQ and GNA11 by the above explained mechanism.

6.1.1.2 INK4A-ARF

INK4A-ARF locus encodes two proteins, $P16^{INK4A}$ and $P14^{ARF}$. Both the proteins are inhibitors of cell cycle [14]. P16 activates Rb protein by inhibition of cyclin D induced hyperphosphorylation (Fig. 6.2).

In about one-third of cases of uveal melanoma, expression of P16 is reduced due to inactivation of INK4A gene by hypermethylation [15]. So Rb protein is

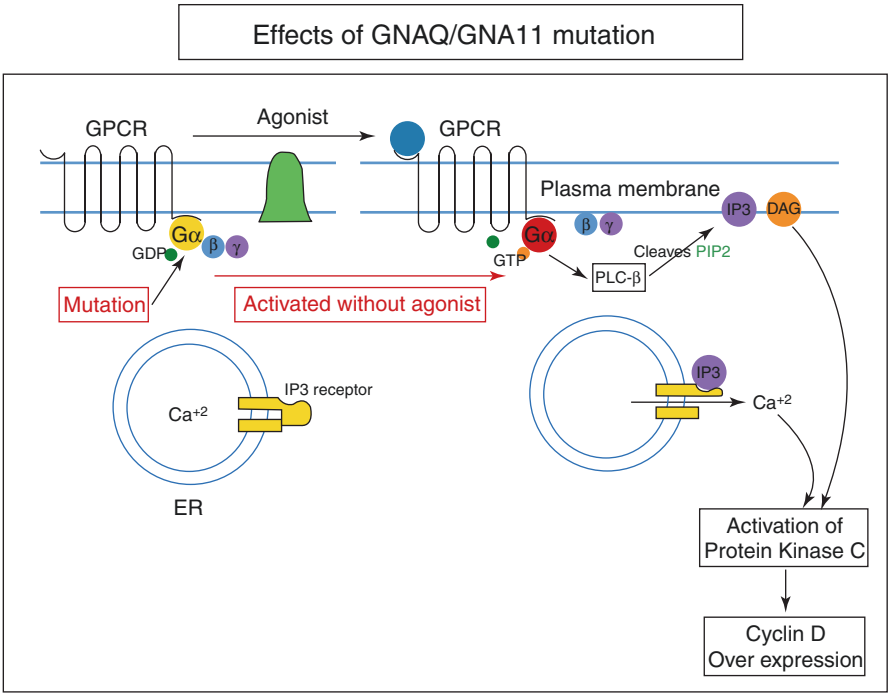

Fig. 6.1 Effects of GNAQ/GNA11 mutation. GNAQ/GNA11 mutation leads to constitutional activation of Gα subunit. Activated Gα-GTP activates phospolipase C-β (PKC-β). PKC-β cleaves phosphatidyl inositol 4,5-biphosphate (PIP2) into inositol-1,4,5-triphosphate (IP3) and diacylglycerol (DAG). IP3 bounds to IP3 receptor on endoplasmic reticulum (ER) and leads to release of calcium ions (Ca^{+2}) into cytoplasm. Calcium ions and DAG leads to activation of protein kinase C which causes cyclin D over expression

inactivated by hyperphosphorylation. This leads to uncontrolled cell cycle by the mechanism described above.

INK4A is a direct target of microphthalmia associated transcription factor (MITF). MITF is a master regulator of melanocyte development. MITF regulates development and proliferation of melanocytes through INK4A. Due to inactivation of INK4A, melanocytes escape MITF-related growth inhibition and enters cell cycle [5].

6.1.2 Inhibition of Apoptosis and Cell Survival

Cells with oncogenic mutations are usually eliminated by the tumor inhibitory mechanism through apoptosis. So neoplasms can progress only if the tumor suppressor mechanisms are inhibited in the neoplastic cells.

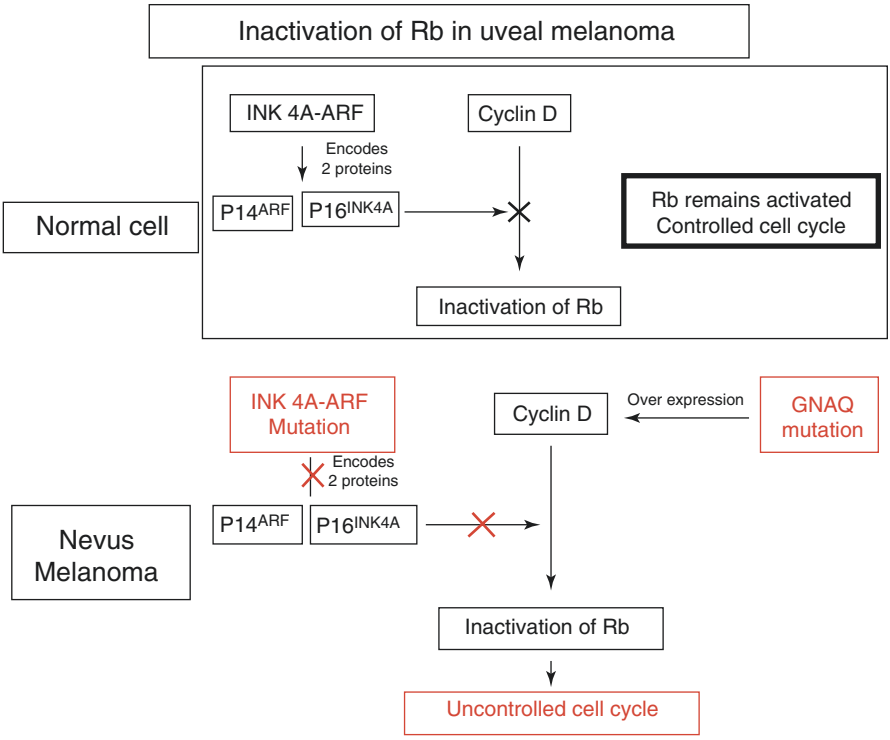

Fig. 6.2 Inactivation of Rb in uveal melanoma. Normal cell: INK4A-ARF encodes P16 and P14. P16 inhibits cyclin D induced inactivation of Rb. Nevus and melanoma cells: Cyclin D over expression due to GNAQ mutation leads to inactivation of Rb. Lack of P16 due to INK4A-ARF mutation, leads to unopposed inactivation of Rb by cyclin D

6.1.2.1 Human Double Minute 2 (HDM2)

HDM2 over expression is seen in uveal melanoma. HDM2 is an inhibitor of P53. P53 identifies oncogenic mutations and arrests cell cycle. P53 prevents survival of cells with oncogenic mutations and arrests progression of tumor. Inhibition of P53 by HDM2 in uveal melanoma leads to survival of cells with oncogenic mutations [11, 16, 17].

6.1.2.2 Phosphoinositide-3-Kinase (PI3K)/AKT

The PI3K/AKT is an intracellular pathway involved in regulation of cell cycle. It is involved in cellular proliferation and quiescence. Activation of PI3K phosphorylates AKT and activates it. Activated AKT affects transcription of factors involved in cell survival by downstream pathways.

This pathway is activated in many cases of uveal melanoma [18, 19].

The PI3K/AKT pathway is inhibited by phosphatase and tensin homolog (PTEN). PTEN is inactivated or down regulated in many cases of uveal melanoma [20, 21].

6.1.2.3 Insulin-Like Growth Factor 1 Receptor (IGF1R)

Insulin-like growth factor 1 receptor is expressed strongly in cases of uveal melanoma. Insulin-like growth factors regulate cell proliferation and differentiation through IGF1R. Over expression of IGF1R can lead to uncontrolled cellular proliferation [22–24].

6.1.3 Acquisition of Malignant Potential

The acquisition of malignant potential occurs due to development of aneuploidy. Presence of abnormal number of chromosomes in a cell instead of the usual 46 is known as aneuploidy. These abnormalities occur relatively late in the evolution of tumor.

6.1.3.1 Monosomy 3

Monosomy 3 (loss of one copy of chromosome 3) is commonly seen in metastatic uveal melanoma [20, 21]. In one study of 105 tumors, monosomy 3 was seen in 51% of cases. Monosomy 3 was associated with ciliary body involvement, larger basal diameter, and epithelioid cell type which are associated with higher risk of metastases (Table 6.1) [25].

In 5–10% of cases, isodisomy 3 is seen. In isodisomy 3, one copy of chromosome 3 is lost and the other copy is duplicated. Presence of isodisomy has similar prognostic implication as monosomy 3 [26].

Monosomy 3 is associated with presence of more chromosomal abnormalities such as gain of 8q, loss of chromosome 8p. Gain of 8q is common in monosomy 3, but does not have independent prognostic significance. Monosomy 3 would lead to genomic instability and accumulation of aneuploidy [27–29].

6.1.3.2 Loss of 8p

Loss of 8p is seen commonly in setting of monosomy 3. Loss of 8p has independent prognostic significance. It is associated with earlier metastases and poor survival [30].

6.1.3.3 Gain of 6p

Gain of 6p is commonly seen in nonmetastatic uveal melanoma and its presence indicates better prognosis.

These changes occur relatively late in the course of disease. The tumors undergo genetic bifurcation at this stage. Tumors that acquire monosomy 3 develop metastatic potential. Tumors that acquire gain of 6p are more stable [29].

Table 6.1 Genetic alterations and risk of metastases

High risk	Low risk
Monosomy 3	Gain of 6p
Isodisomy 3	EIF1AX mutation
Loss of 8p	
Loss of 1p	
BAP1 mutation	
EIF1AX mutation	

6.1.3.4 BRCA1 Associated Protein-1 (BAP1)

Breast cancer type 1 susceptibility protein is encoded by BRCA1. BRCA1 is a tumor suppressor gene involved in DNA repair [31]. BRCA1 associated protein-1 (BAP1) is a deubiquitinating enzyme involved in removal of ubiquitin chain from various proteins. BAP1 is located at 3p21.1 [32]. Loss of one copy of chromosome 3 and mutation in the other allele, leads to loss of tumor suppressor activity of BRCA1. So BAP1 mutation is seen mostly in class 2 tumors which is associated with monosomy 3 [33].

6.1.3.5 Eukaryotic Translation Initiation Factor 1A, X Linked (EIF1AX)

EIF1AX encodes eukaryotic translation initiation factor 1A which is required for initiation of translation by transfer of methionyl initiator tRNA to the 40s ribosomal subunit.

The mutation in EIF1AX is seen in 14–20% of cases with uveal melanoma [34, 35]. This mutation is usually seen in class 1 tumor and is associated with less risk of metastases [36].

6.2 Harvesting the Sample

The sample for genetic analysis can be obtained from the enucleated samples. But in cases treated with eye salvage modalities, tumor sample can be obtained by trans-vitreal or trans-scleral fine needle aspiration biopsy (FNAB).

Trans-scleral FNAB can be employed for anterior tumors. But posterior tumors need pars plana- trans-vitreal FNAB under visualization with indirect ophthalmoscope. The potential complications of the procedure include retinal breaks, vitreous hemorrhage, retinal detachment, and sub-macular hemorrhage [37–41].

Vitrectomy with 27G system and harvesting the sample with vitreous cutter was found to yield sufficient sample for GEP in small melanoma ≤2 mm in a series by Nagiel A et al. In this series, of 17 cases, 13 cases had focal vitreous hemorrhage, and 1 case had diffuse vitreous hemorrhage. None of the cases developed non resolving vitreous hemorrhage or retinal detachment [42].

Vitrectomy with 25G system and needle aspiration of tumor cells by 25G needle connected to a 10 mL syringe from two different points prior to brachytherapy in a series by Reddy DM et al. yielded adequate sample for GEP in 100% of cases. In this series of 57 eyes, only 1 case developed transient vitreous hemorrhage [43].

6.3 Test Employed

6.3.1 Karyotyping

Karyotyping involves isolation, staining, and visual examination of chromosomes to identify chromosomal abnormalities. Karyotyping can identify aneuploidy such as monosomy 3, gain of 6p and loss of 8p. Karyotyping is easy to perform and is less expensive. But individual genetic mutations cannot be identified by karyotyping.

6.3.2 Fluorescent In Situ hybridization (FISH)

Fluorescent in situ hybridization is a type of cytogenetic test in which fluorescent probes with complementary sequence to the chromosome are used to identify the respective chromosomes. It can identify chromosomal rearrangements and commonly deleted regions.

6.3.3 Whole Genome Single Nucleotide Polymorphism (SNP)

Whole genome SNP assess all the regions of all the chromosomes. It provides information across the entire genome with less chance of missing any information. But it is expensive.

6.3.4 Multiplex Ligation Dependent Probe Amplification (MLPA) and Microsatellite Analysis (MSA)

Both MLPA and MSA examines a limited number of foci of interest on the chromosome. It is less expensive than whole genome SNP.

6.3.5 Gene Expression Profiling

Gene expression profiling differentiates class 1 and class 2 tumors. GEP will be discussed in subsequent section.

6.4 Familial Choroidal Melanoma

A minority of cases of choroidal melanoma are familial. Certain germline mutations are associated with predisposition to multiple neoplasms. Syndromes known to be associated with familial choroidal melanoma are BAP1 tumor predisposition syndrome and dysplastic nevus syndrome.

6.4.1 BAP1 Tumor Predisposition Syndrome

BAP1 tumor predisposition syndrome is a cancer syndrome initially described in 2011 [33, 44, 45]. This syndrome is familial and is inherited in autosomal dominant manner. This syndrome is due to germline mutation in BAP1 gene located at 3p21.1. BAP1 is a tumor suppressor gene and the syndrome is associated with development of multiple neoplasms which includes, mesothelioma, uveal melanoma, cutaneous melanoma, renal cell carcinoma, breast cancer, atypical Spitz tumor, basal cell carcinoma, and other organ tumors [46].

6.4.2 Dysplastic Nevus Syndrome (DNS) or Atypical Mole Syndrome

Dysplastic nevus syndrome is characterized by the presence of multiple (50–100) cutaneous nevi. It is inherited in an autosomal dominant manner and is due to mutation in CDKN2A located on 9p21.3 [47]. Dysplastic nevus syndrome is associated with increased risk of cutaneous melanoma and pancreatic cancer.

It is also associated with presence of multiple pigmented lesions of the eye such as conjunctival nevi, iris nevi, iris freckle and choroidal nevi. The prevalence of choroidal nevi in DNS is reported to range from 5.2 to 18.48% [48]. Few families with DNS and choroidal melanoma in one of the family members are reported in literature [49].

6.5 Genetic Alterations and Prognostication

Gene expression profiling (GEP) of fresh tumor samples of uveal melanoma identified 2 distinct classes; class 1 and 2 [50]. Class 1 is subclassified as 1A and 1B. Class 2 is subclassified as 2A and 2B. The risk of metastases is least in class 1A and highest in 2B [51, 52]. Class 1 tumors resemble normal melanocytes and expresses melanocyte lineage genes. But in class 2 tumors, the melanocyte lineage genes are down regulated and genes from ectodermal and neural stem cells are expressed [53, 54] (Fig. 6.3).

Gene expression profiling is a technique in which the expression of thousands of gene is measured at once. This technique gives an idea about cellular functions such as active cell division or response to a particular treatment. At a given point of time, only a fraction of the genes is 'on'. GEP measures the mRNA levels and identifies the set of genes that are 'on' in a cell [55].

By GEP, four clusters of gene expression are identified. The gene expression in class 1 closely corresponds to gain of 6p (the genes in 6p are expressed in this cluster). Class 2A closely corresponds to monosomy 3 and 2B corresponds to loss of 8p [52]. Class 1B shows increased expression of RAB31/CDH1 compared to class 1A. Patients with class 1A were noted to be older than patients with 1B (Table 6.2).

Identification of chromosomal abnormalities and class of uveal melanoma by gene expression sequencing can help in prognostication.

Monosomy 3, loss of 8p, BAP1 mutation are predictors of high risk of metastases and poor survival. Gain of 6p, EIF1AX mutation are predictors of low risk of metastases.

Using GEP, the 5-year metastasis-free survival estimate for class 1 tumors is 97% for tumors with basal diameter of less than 12 mm and 90%, in tumors with basal diameter of more than 12 mm. In class 2 tumors, the survival estimate was 90% for tumors with a basal diameter less than 12 mm and 30% for those greater than 12 mm [56].

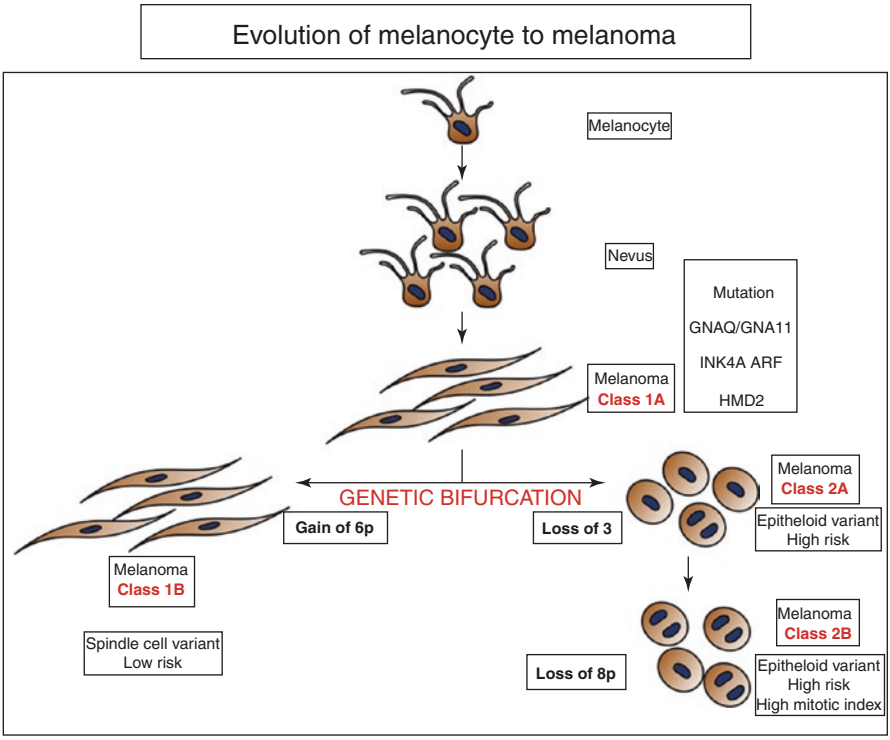

Fig. 6.3 Transformation of melanocyte into melanoma and acquisition of malignant potential

Table 6.2 GEP class and significance

GEP class	Corresponding genetic abnormalities[a]	Risk of metastases Field and Harbour [60]
1A		2% (at 5 years)
1B	RAB31/CDH1 over expression Gain of 6p	21% (at 5 years)
2A	Monosomy 3	72% (at 5 years)
2B	Monosomy 3 Gain of 8p	

[a]GEP classes are based on clustering of gene expression. It is not synonymous with specific aneuploidy. E.g.,: Majority of cases with class 2A would have monosomy 3, but it is not true that all cases will have monosomy 3

6.5.1 Correlation Between Genetic Alterations and Clinical and Histological Features

Monosomy 3 is more frequent in tumors with larger basal diameter, greater thickness, and advanced TNM stage and presence of epithelioid cells.

Liverpool Uveal Melanoma Prognosticator Online (LUMPO) is a model which utilizes a set of clinical, histological and chromosomal features to estimate relative overall survival in individuals with UM relative to an age and sex matched British population and adjusted for risk from death due to all other causes. This model is validated in an independent cohort of 390 UM individuals from University of California-San Francisco [57, 58].

Prediction of Risk of Metastasis in Uveal Melanoma (PRiMeUM) is an interactive web-based tool that can provide a personalized risk estimate of developing metastases. The accuracy of the risk prediction ranged between 80% using only chromosomal features were considered, 83% using clinical features only, and 85% using both clinical and chromosomal information [59].

6.6 Role in Treatment

6.6.1 Screening for Metastases

Prognostic testing is helpful in classifying the patients with uveal melanoma in to cases with low risk and high risk for metastasis. Guidelines from the Bascom Palmer Ocular Oncology Service are:

Low-risk class 1A patients: Annual imaging of the liver.

Intermediate-risk class 1B patients: Annual imaging of the liver. Blood liver enzymes level every 6 months.

High-risk class 2 patients: Liver imaging twice a year. Blood liver enzymes every 3 months.

This strategy targets intensive surveillance to the subset of patients who may benefit and spares the others [60].

6.6.2 Treatment of Small Choroidal Melanoma

The diagnosis of small melanoma is challenging due to its clinical overlap with choroidal nevi. Brachytherapy has significant visual morbidity secondary to radiation retinopathy and optic neuropathy. So most of the oncologists observe small lesions and document growth before deciding on a definitive treatment plan.

Studies comparing immediate and delayed treatment of medium size melanomas showed increased mortality in patients with delayed therapy [61, 62]. So observation of atypical nevi and small uveal melanomas may be associated with some risk of metastasis.

Vitrectomy with trans-vitreal biopsy and GEP allows prognostication for small uveal melanomas with lesser surgical complications. Vitrectomy, biopsy, and laser ablation of the tumor allows tumor ablation and helps in stratifying risk.

Small tumors identified as class 2 can be subjected to brachytherapy and those identified as class 1 can be observed closely. This protocol allows early treatment of high-risk tumors and may reduce the risk of distant metastases. It also prevents radiation related visual morbidity in low-risk tumors.

6.7 Development of Novel Therapeutic Modalities

6.7.1 Drugs Targeting Downstream Molecules of GNAQ/GNA11

GNAQ/GNA11 is seen in approximately three-fourth of cases of uveal melanoma. Though it is difficult to target the G protein coupled receptors, the molecules involved in the intracellular downstream pathway can be targeted. Mitogen activated protein kinase/extracellular signal regulated kinase pathway is upregulated in GNAQ/GNA11 mutated tumors [63]. This pathway involves activation of RAS by guanine nucleotide exchange factor (GEF). RAS activates BRAF, BRAF activates MEK, and MEK activates ERK.

Inhibition of MEK, decreases the proliferation of uveal melanoma cells in vitro and in vivo [64, 65]. Selumetinib is a MEK1/2 inhibitor. In a phase 2 trial, selumetinib was shown to increase the progression free survival compared to chemotherapy [66]. But in a phase 3 randomized controlled trial in metastatic uveal melanoma (SUMIT), the combination of selumetinib and dacarbazine, did not improve the progression free survival compared to dacarbazine [67].

Inhibition of ERK in uveal melanoma cell lines was shown to arrest cell cycle at G1. This in vitro study supports the evaluation of ERK inhibitors in treatment of uveal melanoma [68].

Combination of selumetinib, with inhibitors of ERK and mTOR was shown to be effective in uveal melanoma cell lines and patient-derived xenograft compared to selumetinib and dacarbazine [69].

6.7.2 Drugs Targeting BAP1 Function

BAP1 is a deubiquitinating enzyme involved in removal of ubiquitin chain from various proteins. Absence of functional BAP1 leads to hyper ubiquitination of H2A in the cells. H2A is a subunit of histone, around which the double stranded DNA is wrapped.

Histone deacetylase inhibitors causes shift from aggressive class 2 melanoma cells to less aggressive cells in cells with BAP1 mutation [70].

6.8 Summary

Knowledge of the genetic alterations in uveal melanoma is helpful in understanding the tumorigenesis and malignant potential. It helps in prognostication of uveal melanoma, screening for distant metastases, early treatment of high-risk small melanoma, and development of novel therapeutic modalities.

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Pitfalls in Diagnosis of Choroidal Malignant Melanoma

7

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Choroidal melanoma is the most common primary malignant intraocular tumor in adults [1, 2]. The diagnosis of choroidal melanoma is mainly based on clinical examination [3]. On fundus evaluation, choroidal melanoma is seen as a solitary dome shaped or dumb-bell shaped mass arising from the choroid. The color of the tumor varies from gray to brown. Overlying retinal vessels can be seen. Orange pigment is seen on the surface of the tumor secondary to deposition of lipofuscin in the retinal pigment epithelium (RPE) overlying the tumor. It can be associated with exudative retinal detachment. Rarely it can break through the retina into the vitreous and present with vitreous seeding.

Choroidal melanoma is classified as small, medium, and large based on height and basal diameter. Small melanoma has better survival rate compared to large melanoma [4]. Small tumors located away from the macula would remain asymptomatic and the diagnosis of choroidal melanoma would be delayed. So identification of people at risk of development of melanoma would help in diagnosis of choroidal melanoma in early stage. Other intraocular tumors and nonneoplastic lesions can mimic choroidal melanoma and can pose diagnostic challenge. In presence of media opacity, the tumor would not be seen and the diagnosis is mainly based on the imaging characteristics. In this chapter, we will discuss these topics under the following sections:

1. Identification of people at risk of choroidal melanoma
2. Differentiation of choroidal melanoma from other intraocular tumors
3. Differentiation of choroidal melanoma from nonneoplastic lesions
4. Diagnosis in cases with media opacity

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7.1 Identification of People at Risk

7.1.1 Choroidal Nevus

Choroidal nevus is a benign tumor composed of nevus cells. Nevus cells are atypical modified melanocytes [5]. There is no uniform definition for choroidal nevus [6]. Collaborative ocular melanoma study defined choroidal pigmented lesions ≤5 mm in largest basal diameter and ≤1 mm in height as choroidal nevus [7, 8].

The prevalence of choroidal nevus is reported to range from 0.34 to 7.9% in white population (includes studies with more than 1000 samples) [9]. The prevalence in Indian population is reported to be 0.15% which is significantly lesser than the Caucasian population [10]. The risk of malignant transformation of choroidal nevus is reported to range from <1 to 13%. In a hospital-based review of medical records of 2514 cases with choroidal nevus by Shields et al., the transformation was noted in 2%, 9%, and 13% of eyes over 1, 5, and 10 years, respectively [11]. In a systemic review of prevalence of choroidal nevus and choroidal melanoma in age matched white population by Singh et al., the rate of transformation was noted to be 1 in 8845 cases, assuming that all the cases of melanoma arise from preexisting nevus [9].

Giant choroidal nevus (defined as >10 mm in largest basal diameter by Chien JL et al) is associated with higher risk of malignant transformation and was reported to be 18% in over 10 years [5].

The features associated with high risk of transformation are

1. Thickness more than 2 mm
2. Presence of subretinal fluid
3. Symptoms of flashes or blurred vision
4. Presence of orange lipofuscin pigment on the surface of tumor
5. Nevus close to the optic disc (margin <3 mm from disc)
6. Presence of acoustic hollowness on ultrasonography
7. Absence of halo
8. Absence of drusen on the surface of tumor

Shields et al. described a mnemonic 'To Find Small Ocular Melanoma Using Helpful Hints Daily' to recall the risk factors which represent thickness, fluid (subretinal fluid), symptoms, orange pigment, margins, ultrasonographic hollowness, halo absence, and drusen absence.

Presence of three or more of the above mentioned features is associated with more than 50% risk of malignant transformation within 5 years [11].

Nevus with changes in overlying RPE such as presence of drusen, pigment epithelial atrophy, hyperplasia, fibrous metaplasia, is associated with lesser risk of malignant transformation. Overlying RPE changes are suggestive of chronicity and stable course [12, 13] (Fig. 7.1).

Halo nevus is characterized by the presence of hypo or depigmented halo around the central pigmented portion. Halo is composed of polygonal large cells with foamy cytoplasm. The halo is thought to be due to immune response. Halo nevus is associated with lesser risk of malignant transformation [14].

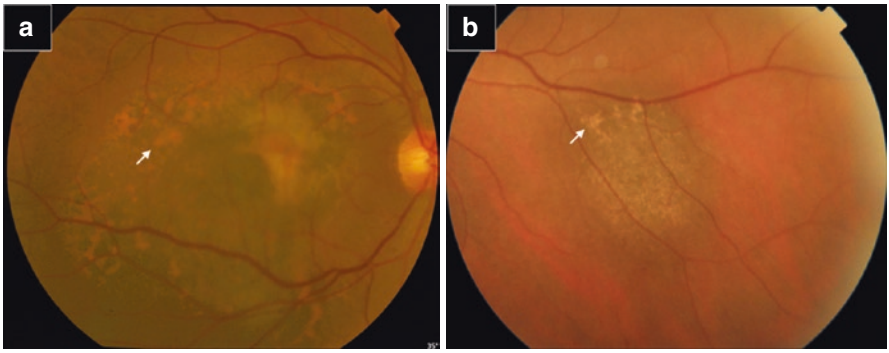

Fig. 7.1 Comparison of melanoma and nevus. (**a**) Color photograph of a case of choroidal melanoma. The tumor is brown in color. Overlying orange pigment (arrow) is in favor of melanoma. (**b**) Color photograph of a case of choroidal nevus. The lesion is relatively flat and is light brown in color. Multiple confluent drusen (arrow) is in favor of nevus

A definitive diagnosis of choroidal nevus or small choroidal melanoma cannot be made at one visit. Transformation into melanoma is defined as increase in basal dimension or thickness of at least 0.5 mm by Shields et al. [11] Hence eyes with choroidal nevus need regular follow up with dilated fundus evaluation, color photograph, ultrasonography, and optical coherence tomography.

Nevus with high risk features needs closer observation.

7.1.2 Oculocutaneous Melanosis

Oculocutaneous melanosis or nevus of Ota is characterized by the presence of grayish hyperpigmentation in the ophthalmic and maxillary division of trigeminal nerve. It is usually unilateral and involves conjunctiva, sclera, periocular, and facial skin [15, 16]. It is probably due to entrapment of melanocytes in the dermis and basal layer of epidermis [17]. The prevalence of oculocutaneous melanosis is estimated to be 0.038% in whites and 0.014% in blacks [18, 19].

Fundus examination may reveal asymmetric pigmentation. The affected eye shows hyper pigmented choroid compared to the fellow eye. The choroid would be thicker than the fellow eye and can be detected on ultrasonography and optical coherence tomography (OCT). The trabecular meshwork is hyperpigmented and the affected eyes are at higher risk of glaucoma [20].

Patients with oculocutaneous melanosis are at higher risk of development of uveal melanoma. Caucasians with oculocutaneous melanosis have higher of developing uveal melanoma compared to other races. Choroidal melanoma is known to occur in up to 4% of patients with oculocutaneous melanosis [20]. Mutations in GNAQ, which are commonly seen in the early stages of uveal melanoma are documented in oculocutaneous melanosis which would explain higher risk of uveal melanoma [21].

Patients with oculocutaneous melanosis should be screened for choroidal melanoma regularly by dilated fundus evaluation.

7.1.3 Dysplastic Nevus Syndrome

Dysplastic nevus syndrome (DNS) or atypical mole syndrome is characterized by the presence of multiple (50–100) cutaneous nevi. It is inherited in an autosomal dominant manner and is due to mutation in CDKN2A located on 9p21.3 [22].

Dysplastic nevus syndrome is associated with increased risk of cutaneous melanoma and pancreatic cancer.

It is also associated with presence of multiple pigmented lesions of the eye such as conjunctival nevi, iris nevi, iris freckle, and choroidal nevi. The prevalence of choroidal nevi in DNS is reported to range from 5.2 to 18.48% [23]. Few families with DNS and choroidal melanoma in one of the family members are reported in literature [24].

Though there is no data on the prevalence of uveal melanoma in cases with DNS, considering the higher prevalence of choroidal nevi, it would be better to screen the patients with DNS for choroidal melanoma by regular dilated fundus evaluation.

7.1.4 BAP1 Tumor Predisposition Syndrome

BAP1 tumor predisposition syndrome is a cancer syndrome initially described in 2011 [25–27]. This syndrome is due to germline mutation in BAP1 gene located at 3p21.1. BAP1 is a tumor suppressor gene and the syndrome is associated with development of multiple neoplasms which includes, mesothelioma, uveal melanoma, cutaneous melanoma, renal cell carcinoma, breast cancer, atypical Spitz tumor, basal cell carcinoma, and other organ tumors [28].

The patients with this syndrome develop a benign atypical melanocytic skin tumor named atypical Spitz tumor or melanocytic BAP1 mutated atypical intradermal tumor (MBAIT) or BAPoma. These tumors appear as skin toned dome shaped nodules [29].

This syndrome is familial and is inherited in autosomal dominant manner. So patients with BAPoma and their family members should be screened periodically for uveal melanoma and other tumors known to be associated with this syndrome.

7.2 Differentiation of Choroidal Melanoma and Other Intraocular Tumors

7.2.1 Choroidal Hemangioma

Choroidal hemangioma is clinically seen as round or oval orange red mass typically located in the post equatorial region. It can be associated with the presence of subretinal fluid or intraretinal fluid overlying the tumor [30].

Color of the tumor is an important clue to the accurate diagnosis of intraocular tumors. Choroidal melanoma is gray to brown in color and can be usually distinguished from hemangioma (Fig. 7.2). But amelanotic melanoma is yellow to orange

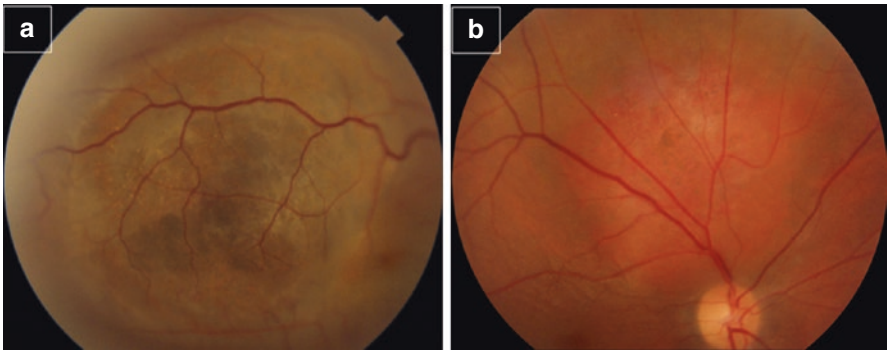

Fig. 7.2 Comparison of melanoma and hemangioma. (**a**) Color photograph of a case of choroidal melanoma. The tumor is brown in color with patchy hyperpigmentation. (**b**) Color photograph of a case of choroidal hemangioma. The tumor is orange red in color in contrast to brown color of melanoma

in color and can mimic hemangioma and pose diagnostic challenge [31]. Similarly, a solitary choroidal hemangioma may show surface fibrous metaplasia associated with pigment proliferation, which would mimic a melanoma. The pigment proliferation is patchy, black and is associated with fibrous metaplasia, offering clues to a diagnosis of hemangioma rather than a melanoma. Imaging cues can be helpful in differentiating amelanotic choroidal melanoma from hemangioma.

On ultrasonography, melanoma is homogenous with low internal reflectivity and hemangioma is heterogenous with high internal reflectivity. But the internal reflectivity can be medium in both the tumors [32, 33]. Choroidal melanoma exhibits choroidal excavation and acoustic hollowness. Choroidal melanoma with breakthrough Bruch's membrane is mushroom-shaped and exhibits angle kappa on ultrasonography, while a solitary choroidal hemangioma remains dome shaped (Fig. 7.3).

On OCT, both melanoma and hemangioma are seen as dome shaped elevation of RPE-Bruch's complex. Choriocapillaries are lost or compressed in choroidal melanoma, whereas it is usually preserved in hemangioma (Fig. 7.4) [34, 35].

On fundus fluorescein angiography (FFA), melanoma shows intrinsic vasculature and late leak though it is not pathognomonic of melanoma. In contrast, a choroidal hemangioma fills early and leaks profusely (Fig. 7.5) [30, 31].

Indocyanine green angiography (ICGA) is better than FFA in visualization of intrinsic vasculature of choroidal tumors. In choroidal melanoma, ICGA shows early phase hypofluorescence and visualization of intrinsic vascular network in mid phase. Whereas in choroidal hemangioma, ICGA shows early phase diffuse hyperfluorescence with washout in late phase [30, 31].

On magnetic resonance imaging (MRI), melanoma appears hyperintense on T1 weighted images and very hypointense on T2 weighted images. Choroidal hemangioma is hyperintense on T1, but isointense on T2 weighted images. Both the tumors do not differ on plain T1 images. But on gadolinium bolus injection, the increase in

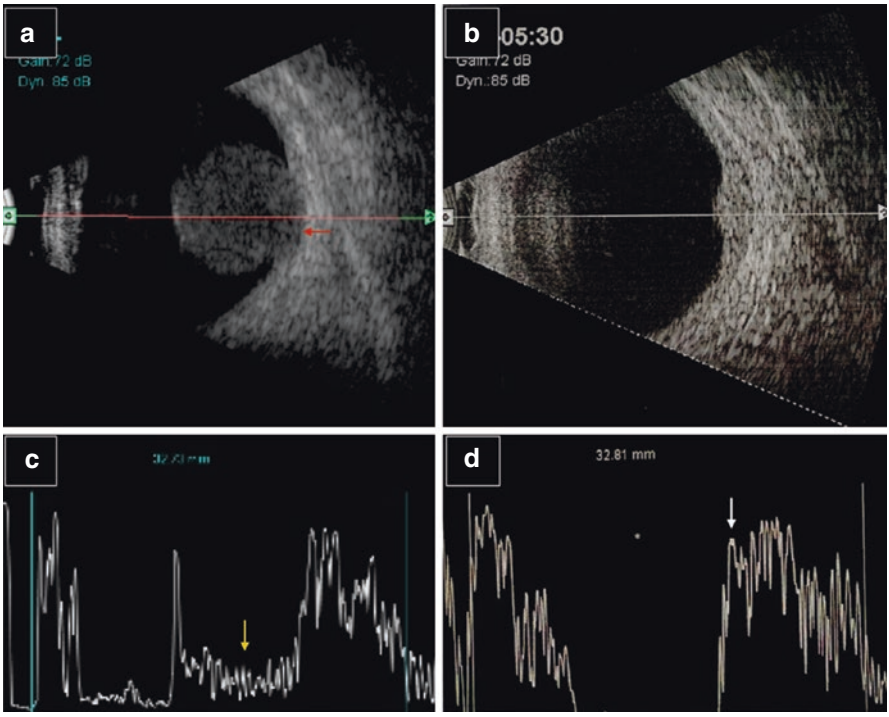

Fig. 7.3 Ultrasonography of melanoma and hemangioma. (**a**) B scan of a case of choroidal melanoma. The tumor is mushroom-shaped. Choroidal excavation is evident as an area of loss of choroid at the base of tumor (red arrow). Height to base ratio is higher. (**b**) B scan of a case of choroidal hemangioma. The tumor is dome shaped. It is seen as an area of focal choroidal thickening in contrast to excavation in melanoma (**c**) A scan of choroidal melanoma showing high surface reflectivity and low internal reflectivity (yellow arrow). (**d**) A scan of choroidal hemangioma showing high internal reflectivity (white arrow)

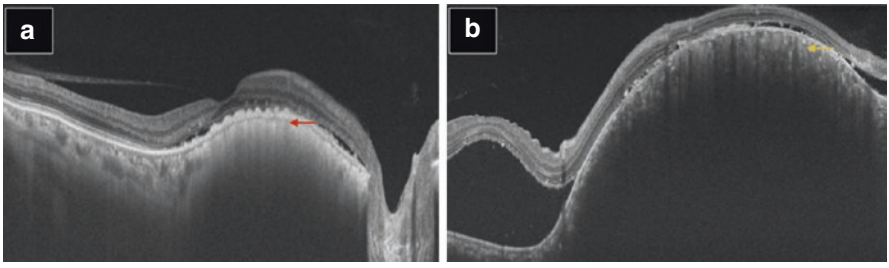

Fig. 7.4 OCT of melanoma and hemangioma. (**a**) Swept source OCT of choroidal melanoma showing loss of choriocapillaries (red arrow). (**b**) Choriocapillaries are preserved in choroidal hemangioma (yellow arrow)

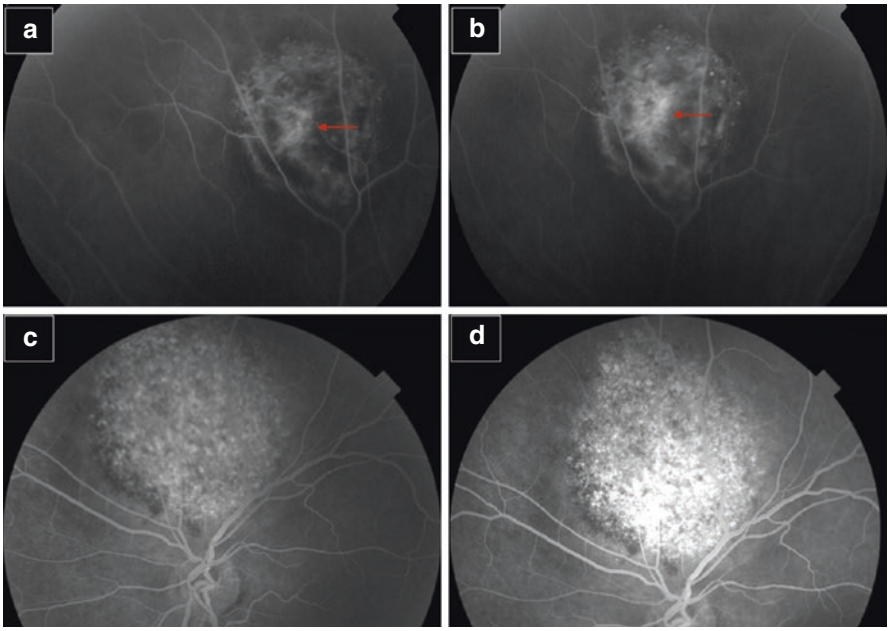

Fig. 7.5 FFA of melanoma and hemangioma. (**a** and **b**) Melanoma. Early phase (**a**) showing intrinsic circulation within the tumor (arrow) with leak in late phase (**b**). (**c** and **d**) Choroidal hemangioma. Early phase (**c**) hyperfluorescence with late leak (**d**)

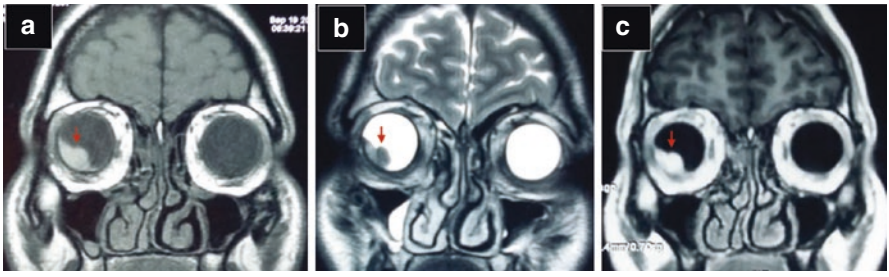

Fig. 7.6 MRI of choroidal melanoma. Mushroom-shaped tumor (arrow) is seen within the vitreous cavity. It is hyperintense in T1 weighted image (**a**), hypointense in T2 (**b**) and shows intense contrast enhancement (**c**)

signal intensity is higher in choroidal hemangioma than in choroidal melanoma (Fig. 7.6) [36].

Sometimes it would be difficult to differentiate amelanotic melanoma and hemangioma precisely and the diagnosis would depend on response to treatment. Choroidal hemangioma responds well to photodynamic therapy (PDT) with a response rate as high as 90%. Poor response to PDT, should alert the treating ophthalmologist to consider alternative diagnosis such as melanoma [31].

7.2.2 Melanocytoma

Melanocytoma is reported to occur in any part of the uveal tract, but is commonly seen in the optic disc. Optic disc melanocytoma can mimic juxta papillary choroidal melanoma and pose diagnostic challenge. Choroidal melanocytoma is rarely reported and can mimic choroidal melanoma.

The diagnosis of optic disc melanocytoma is relatively easy. Optic disc melanocytoma arises from the pigmented cells of optic disc and can secondarily involve the retina and choroid. It is heavily pigmented and is jet black in color and has feathery margins. Juxta papillary choroidal melanoma arises from the choroid and grows superficially around the posterior termination of Bruch membrane and secondarily involves optic disc. Juxta papillary melanoma is usually gray to brown in color (Fig. 7.7) [37].

Color is an important clue to the diagnosis. Melanocytoma is jet black and melanoma is gray to brown. Presence of subretinal fluid and orange pigment points toward melanoma. Melanocytoma is relatively stable and 10–15% of cases grow very slowly, whereas melanoma exhibits rapid growth [38]. A rare patient with melanocytoma of the optic disc can present with decreased vision due to optic neuritis / neuroretinitis due to necrosis of the tumor. Treatment with systemic steroids may result in regression of the optic disc edema and improvement in vision. But in some cases visual loss can be permanent [39].

Optical coherence tomography can identify predominantly choroidal component in juxtapapillary melanoma. In cases with clinical suspicion, trans-vitreal fine needle aspiration biopsy (FNAB) or an incisional biopsy of the tumor along with vitrectomy can help confirm the diagnosis.

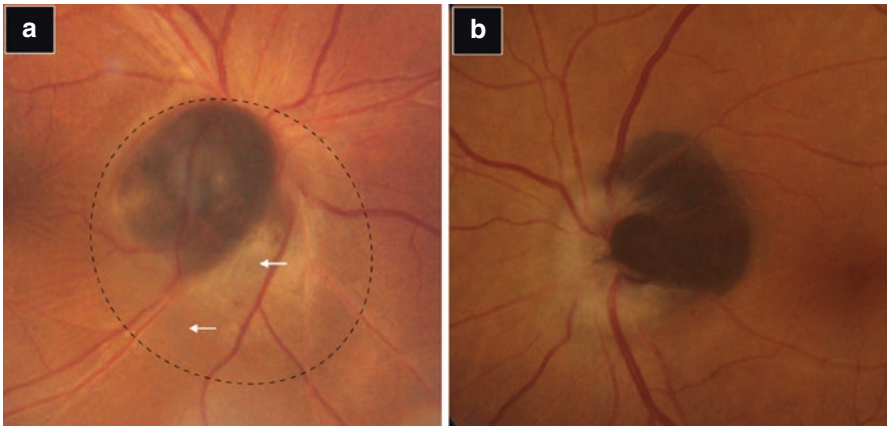

Fig. 7.7 (**a**) Color photograph of juxtapapillary melanoma. The extent of the tumor is indicated by dotted line. The part of tumor projecting anteriorly around the termination of Bruch's membrane is dark brown in color. The choroidal component is indistinct. Subtle light brown discoloration is indicated by white arrow. (**b**) Color photograph of optic disc melanocytoma. The tumor is black in color and is involving the adjacent retina

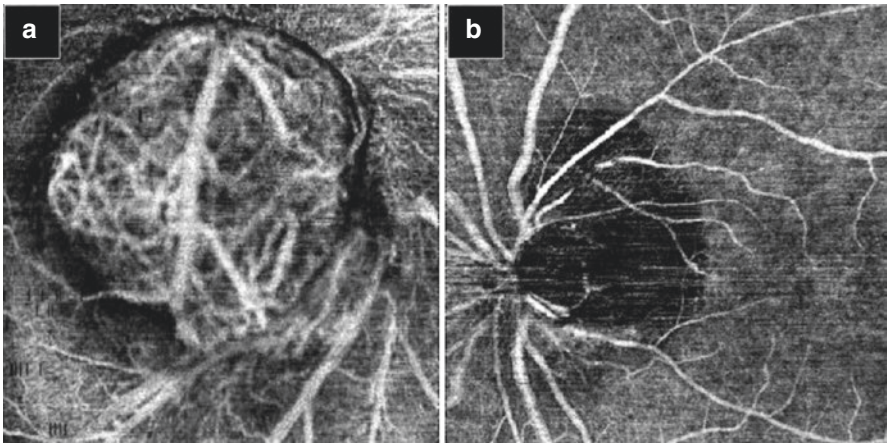

Fig. 7.8 (**a**) OCTA of tumor in Fig. 7.7a demonstrating intrinsic vascularity of tumor suggestive of melanoma. (**b**) OCTA of tumor in Fig. 7.7b demonstrating absence of vascular signals suggestive of melanocytoma

On OCT angiography (OCTA), intrinsic vascularity is seen clearly in juxtapapillary melanoma whereas melanocytoma is seen as signal void area (Fig. 7.8).

Choroidal melanocytoma can develop as a paraneoplastic syndrome, bilateral diffuse uveal melanocytic proliferation (BDUMP) or as an isolated condition. In BDUMP, the lesions are multiple, bilateral, very dark and can grow rapidly [40–42]. Isolated choroidal melanocytoma rarely exceed more than 1 disk diameter in size and is stable and few cases can show mild growth [43, 44].

Fluorescein angiography shows intrinsic vascularity in choroidal melanoma and leak in late phase, whereas melanocytoma shows blocked choroidal fluorescence owing to its relative avascularity and dense pigmentation.

On ultrasonography, melanocytoma exhibits high internal reflectivity, though cases with low internal reflectivity are reported in literature [44].

7.2.3 Choroidal Nevus

The differences between choroidal melanoma and nevus are described in detail in the section of ‘identification of people at risk’. The imaging cues will be discussed in this section.

Optical coherence tomography is helpful in differentiating nevus from small melanoma. Melanoma is usually thicker than nevus and the deeper extent may not be seen on OCT. Presence of subretinal fluid and intraretinal fluid, shaggy photoreceptors points toward melanoma, though retinal schisis overlying the nevus can be seen rarely (Fig. 7.9) [34, 35].

On OCTA, choroidal vascularity is relatively unaffected in choroidal nevus, whereas vascular loops and network are seen in choroidal melanoma (Fig. 7.10) [45].

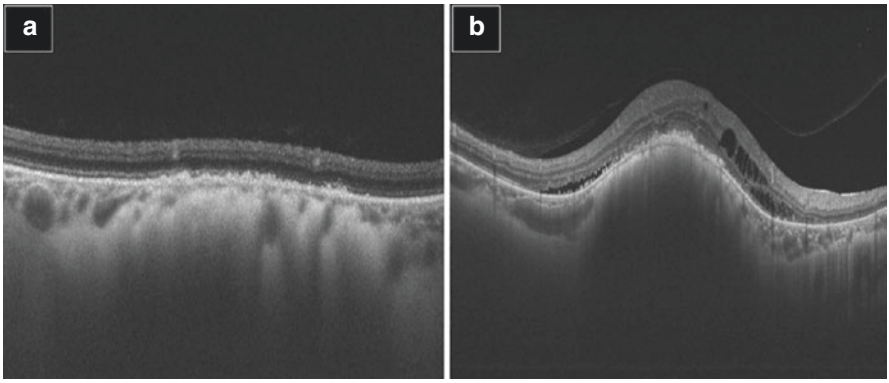

Fig. 7.9 (**a**) OCT of nevus showing irregularity of overlying RPE. No evidence of SRF or shaggy photoreceptors. (**b**) OCT of melanoma showing dome shaped elevation of Bruch's membrane. SRF and intraretinal fluid are evident. Shaggy photoreceptors are seen

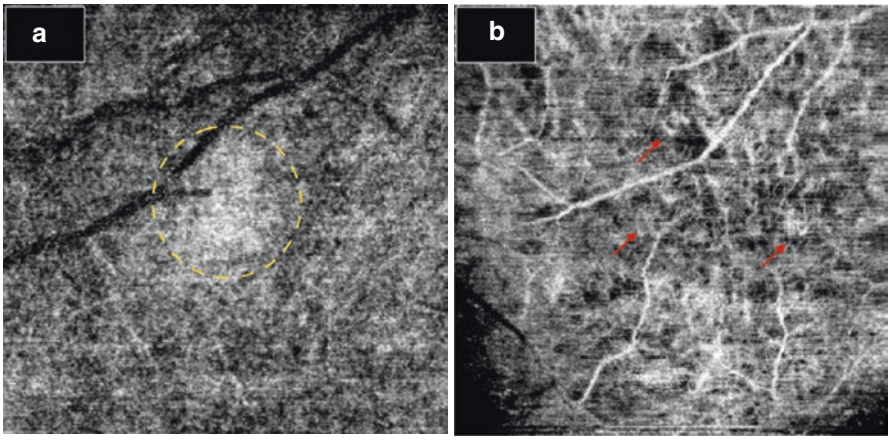

Fig. 7.10 (**a**) OCTA of nevus showing no alterations in the choroidal vascularity. (**b**) OCTA of melanoma showing vascular loops and network (arrow)

On ultrasonography, presence of acoustic hollowness suggests higher risk of malignant transformation of choroidal nevus [12].

7.2.4 Choroidal Metastases

Choroidal metastases is usually creamy white to yellow in color and may mimic an amelanotic melanoma. History of systemic malignancy and presence of multifocal, bilateral tumors confirm the diagnosis of choroidal metastases conclusively.

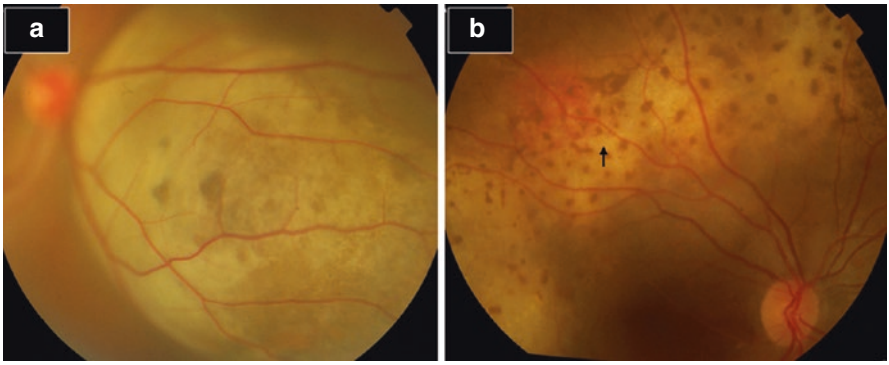

Fig. 7.11 Comparison of melanoma and metastases. (**a**) Color photograph of choroidal melanoma. The lesion is light brown in color. (**b**) Color photograph of choroidal metastases. The lesion is creamy yellow in color in contrast to brown color of melanoma

Melanomas are usually solitary and multifocal tumors are extremely rare. If choroidal metastases is the initial presentation of systemic malignancy and if the lesion is unifocal and elevated, the diagnosis may be difficult. Pigmented metastases arising from metastatic skin melanoma may be confused for a primary choroidal melanoma (history of skin melanoma being the key clue in differentiation). Similarly, an orange carcinoid metastasis may be mistaken for an amelanotic choroidal melanoma.

Melanoma is fairly circumscribed, whereas metastases can be irregular in shape (Fig. 7.11). Exudative retinal detachment is disproportionately more compared to the size of tumor in metastases.

On ultrasonography, the height to base ratio is significantly higher in melanoma compared to metastases as metastases tend to infiltrate and replace the normal choroid diffusely and remain relatively flat. On amplitude scan (A scan), the internal reflectivity is medium to high in metastases, compared to low reflectivity in choroidal melanoma (Fig. 7.12). Melanoma also exhibits mushroom shape and choroidal excavation, which is not seen in metastases [46].

On FFA, metastases exhibits hypofluorescence in early phase and staining of the lesion in late phase along with leakage of the dye in the subretinal space. In some cases, multiple hypofluorescent patches can be seen within the hyperfluorescent background. The border of the lesion shows retinal capillary dilatation and pin point leak throughout the angiogram. In a study comparing metastases and melanoma, pin point leaks were seen in 73.91% of cases with metastases and 6.13% of cases with melanoma [47].

On ICGA, metastases is hypofluorescent in early and mid-phase, whereas internal vascularity is seen in melanoma.

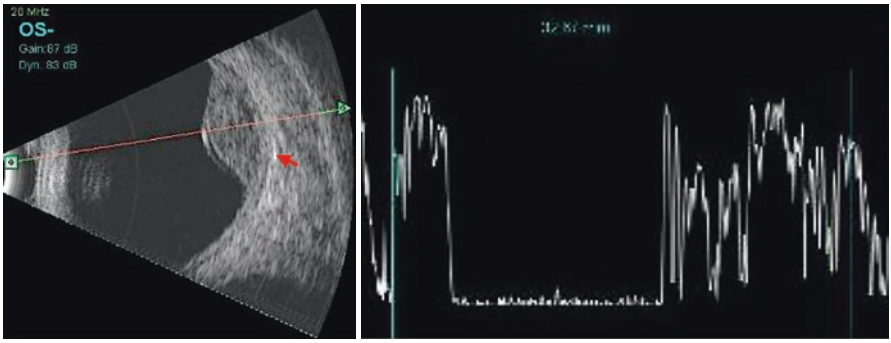

Fig. 7.12 Ultrasonography of choroidal metastases The lesion is dome shaped with a higher base to height ratio. The underlying choroid is intact without excavation (red arrow). A scan shows medium internal reflectivity. Overlying retinal detachment is evident.

7.2.5 Retinal Pigment Epithelial Adenoma/Adenocarcinoma

Neoplastic lesions of RPE are very rare intraocular tumors. RPE adenoma has stuck on appearance and can vary from yellow-pink to brown in color. On FFA and ICGA, tumor exhibits early phase hypofluorescence in early phase with hyperfluorescence and leak in late phase. On MRI, the tumor is hyperintense on T1 and hypointense on T2 images. It can mimic hemangioma or melanoma. It is very difficult to diagnose this tumor clinically and in many cases it would be diagnosed only after histopathological examination [48–50].

7.2.6 Leiomyoma of the Choroid

Leiomyoma of the choroid is a rare tumor and occurs in suprachoroidal space. It is usually non-pigmented and appears to elevate the overlying normal choroid considering its suprachoroidal location. It is brilliantly trans-illuminant and occurs in young in contrast to a melanoma that occurs in the elderly. It may be difficult to differentiate it from a melanoma as the imaging characteristics often mimic that of a melanoma. Quiet often the eye is enucleated for a suspected melanoma, and leiomyoma is diagnosed on histopathological examination. Younger age group, an amelanotic, trans-illuminant lesion that appears to be beneath the peripheral choroid are some of the clues to the diagnosis [51, 52].

7.3 Differentiation of Choroidal Melanoma from Nonneoplastic Lesions

7.3.1 Peripheral Exudative Hemorrhagic Chorioretinopathy (PEHCR)

Peripheral exudative hemorrhagic chorioretinopathy is a less common entity affecting older individuals and presents with peripheral mounds of subretinal or sub RPE hemorrhage (Fig. 7.13a).

Presence of bilateral, multiple mounds of subretinal or sub RPE hemorrhage usually points toward a diagnosis of PEHCR. But a solitary mound can mimic choroidal melanoma.

Choroidal melanoma is usually located posterior to the equator (80% of cases), whereas PEHCR is located anterior to equator [53]. PEHCR is dark in color and can be associated with presence of subretinal hard exudates. Examination of the other

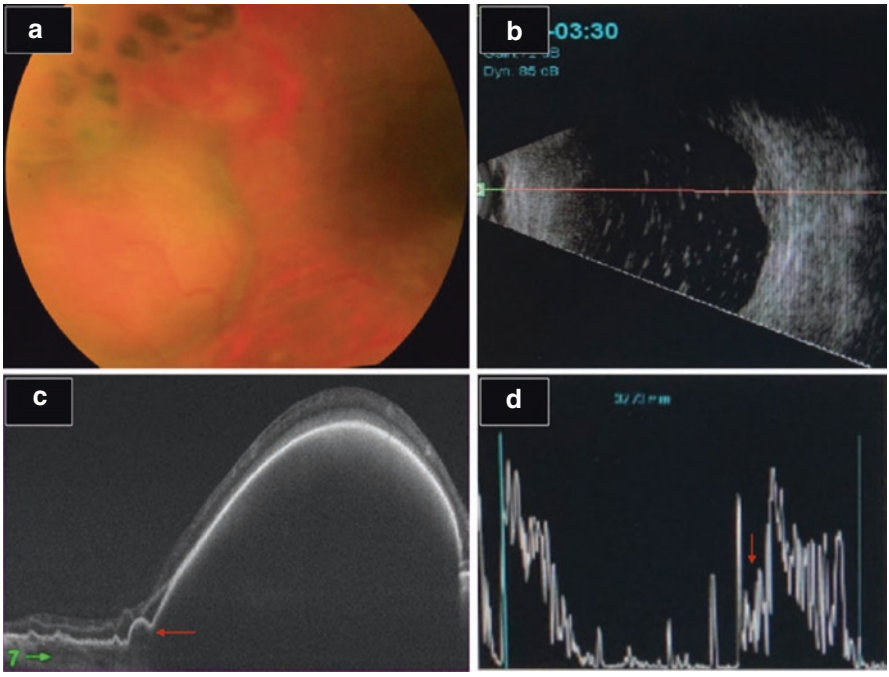

Fig. 7.13 Peripheral exudative hemorrhagic chorioretinopathy. (**a**) Color photograph showing a mound in inferotemporal quadrant which is light brown in color. (**b**) B scan through the lesion shows absence of choroidal excavation. (**c**) OCT showing presence of small PED at the edge of lesion (red arrow) pointing towards a diagnosis of PEHCR. (**d**) A scan showing low internal reflectivity

eye often gives a clue to the diagnosis, with the peripheral fundus showing drusen or signs of fibroglial scarring suggestive of spontaneously resolved hemorrhagic pigment epithelial detachments. Some eyes may also show posterior disease such as disciform macular scar or clinical evidence of polypoidal choroidal vasculopathy that may at times be associated with PEHCR.

Swept source OCT at the margin of PEHCR can detect pigment epithelial detachment (PED) with intact Bruch's membrane beneath the lesion, whereas the Bruch's membrane is elevated in cases with melanoma. In some cases, small PEDs can be seen closer to the margins of PEHCR lesion (Fig. 7.13b).

On ultrasonography, in about half of the cases, the PEHCR lesion is dome-shaped and in other half it is multi-lobular. Multi lobular appearance is in favor of PEHCR. PEHCR exhibits variable internal reflectivity ranging from low to high. In a study by Shields et al., 41% of cases had low, 36% had medium and 19% had high reflectivity [54]. While the presence of high reflectivity is in favor of PEHCR, low reflectivity can be seen in both the lesions. Choroidal excavation was not seen in any of the cases of PEHCR in two case series [54, 55]. Hence, presence of choroidal excavation points to a diagnosis of melanoma (Fig. 7.13c, d). PEHCR is characterized by the presence of clot retraction cleft. The retraction cleft is seen as hypoechoic cleft between the clot (mass) and the choroid [54]. It is never seen in choroidal melanoma.

On FFA, the PEHCR lesion is seen as an area of blocked fluorescence and may show late hyperfluorescence in few cases, whereas dual circulation is seen in choroidal melanoma.

Wide field ICGA can detect choroidal vascular network and polyp like lesions in cases with PEHCR [55]. It can also identify presence of vascular network in periphery of the fellow eye.

7.3.2 Subretinal Hemorrhage or Sub-RPE Hemorrhage Associated with Polypoidal Choroidal Vasculopathy (PCV) and Age-Related Macular Degeneration (AMD)

Subretinal or sub RPE hemorrhage secondary to PCV or AMD usually involves the posterior pole. Retinal pigment epithelial rip can present with massive subretinal hemorrhage. Presence of drusen or advanced AMD in the fellow eye can point toward a diagnosis of AMD-related hemorrhage. The imaging characteristics of hemorrhage are similar to the features described for PEHCR and can help in differentiating from melanoma (Figs. 7.14 and 7.15).

At times hemorrhagic lesions of the choroid may be difficult to differentiate from a choroidal melanoma due to the presence of an associated vitreous hemorrhage, the imaging also being non-confirmative. In such situations, it is prudent to review the patient 2–4 weeks later when one may find a hemorrhagic lesion to have decreased in size with absorption of the hemorrhage in contrast to a malignant lesion. A massive subretinal hemorrhage and vitreous hemorrhage most often point to a

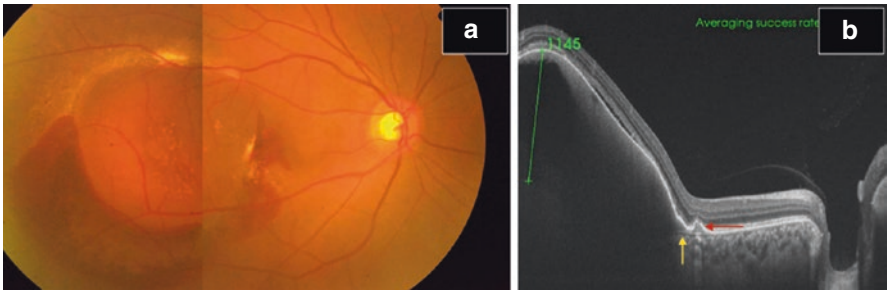

Fig. 7.14 (**a**) Color photograph of sub RPE hemorrhage secondary to PCV. Hard exudates are seen superior to the lesion and subretinal hemorrhage is seen inferior to lesion. (**b**) OCT shows the lesion to be a large pigment epithelial detachment and the Bruch's membrane is seen at the edge and is flat (yellow arrow). But in choroidal melanoma the RPE-Bruch's complex is pushed forward along with compression of choriocapillaries (Fig. 7.8b). A small PED adjacent to the lesion (red arrow) also points in favor of PCV

peripheral exudative choroidal pathology rather than a melanoma, the caveat being that a choroidal melanoma can rarely present with extensive intraocular hemorrhage.

7.3.3 Posterior Nodular Scleritis

Posterior nodular scleritis is an inflammatory condition characterized by the presence of pain, and nodular elevation of choroid on fundus evaluation. The nodular elevation seen on fundus evaluation can mimic choroidal melanoma (Fig. 7.16a) [56–58]. In a review of 4000 cases referred to ocular oncology service, nodular scleritis accounted for 1.5% of cases of pseudomelanoma [59].

Posterior nodular scleritis can manifest with wide array of clinical presentation. It can present acutely and in such cases it is associated with pain. Pain in reported in 64% of cases with posterior scleritis [60]. In some cases, the presentation can be subacute without any pain. But careful examination of the sclera may reveal conjunctival and episcleral congestion posteriorly (Fig. 7.16b). Associated signs of a melanoma such as orange pigment are not seen in nodular scleritis.

Ultrasonography reveals thickening of adjacent choroid and sclera (Fig. 7.16c, d). Choroidal excavation is typically not seen in scleritis. Nodular scleritis leaks fluorescein profusely and may be associated with disc staining indicative of the inflammatory pathology. A therapeutic challenge with systemic steroid can also aid in diagnosing a particularly difficult patient.

7.3.4 Posterior Scleral Cyst

Scleral cysts are congenital lesions typically located close to the limbus. We reported one case of post-equatorial scleral cyst referred to our ocular oncology service as

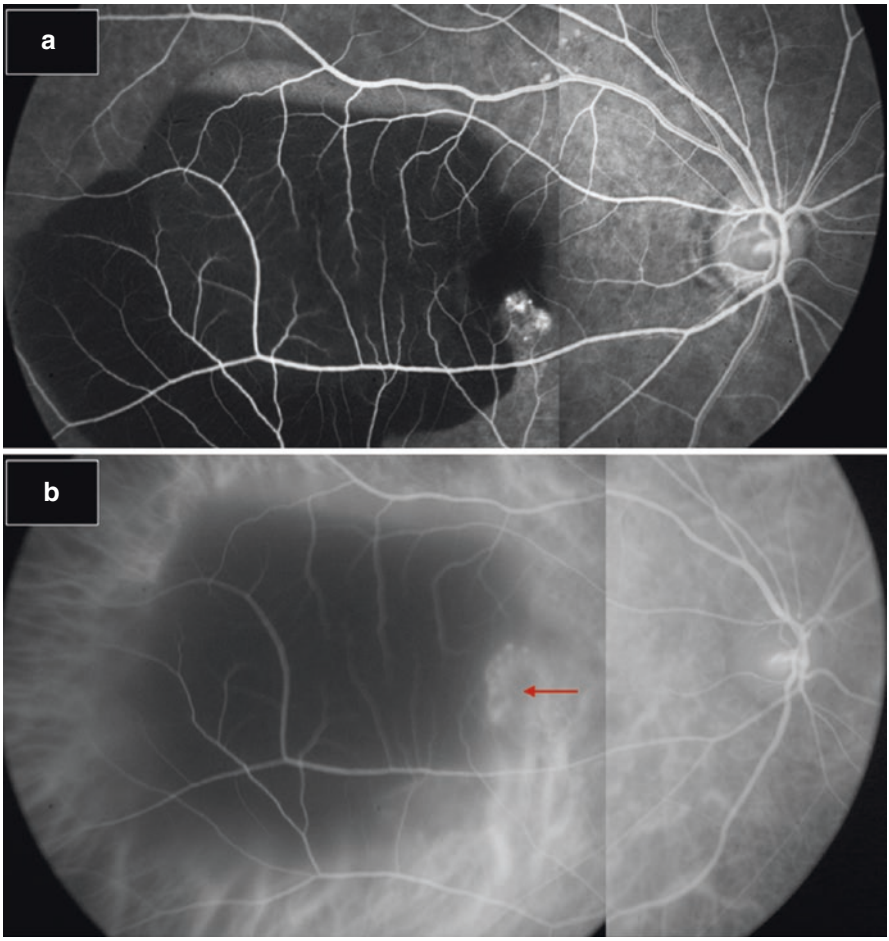

Fig. 7.15 (**a**) FFA of the lesion in Fig. 7.13 showing blocked fluorescence due to sub RPE hemorrhage. (**b**) ICGA of the lesion showing polyps at the edge of lesion suggestive of PCV

choroidal melanoma in a young boy. The lesion was seen as a well-defined nodular elevation of the choroid. Ultrasonography detected cystic nature of the lesion. On OCT, hyporeflective cavity was seen within the sclera (Fig. 7.17) [61].

7.4 Diagnosis in Cases with Media Opacity

7.4.1 Painful Blind Eye

Large choroidal melanoma can lead to development of complicated cataract and neovascular glaucoma and can present as painful blind eye. So any case of painful bind eye should be evaluated by ultrasonography to rule out the presence of

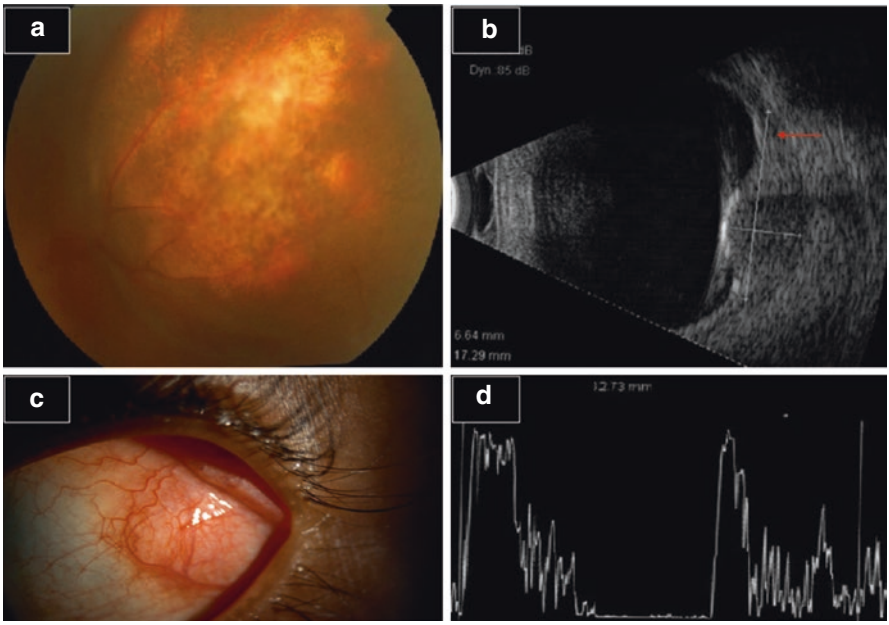

Fig. 7.16 Nodular scleritis. (**a**) Color photograph showing nodular mass which is light brown in color with areas of hypopigmentation. (**b**) B scan showing a dome shaped mass with evidence of thickening of retino-choroido-scleral complex in the adjacent area (arrow). No evidence of choroidal excavation. (**c**) Examination of temporal sclera by adducting the eye shows congestion. (**d**) A scan showing low internal reflectivity

intraocular mass. In presence of intraocular mass, if ultrasonographic features are inconclusive MRI would be essential. If the possibility of melanoma cannot be ruled out, enucleation with histopathological examination of the tumor has to be considered to confirm the diagnosis.

7.4.2 Vitreous Hemorrhage or Subretinal Hemorrhage

Choroidal melanoma can rarely present with subretinal hemorrhage. It can break through the retina and can lead to vitreous hemorrhage. Sometimes choroidal melanoma can break through the retina and can lead to vitreous seeding and vitreous hemorrhage. So any case of vitreous hemorrhage with media haze sufficient to obscure the visibility of retina should be evaluated with ultrasonography to rule out the presence of intraocular tumor.

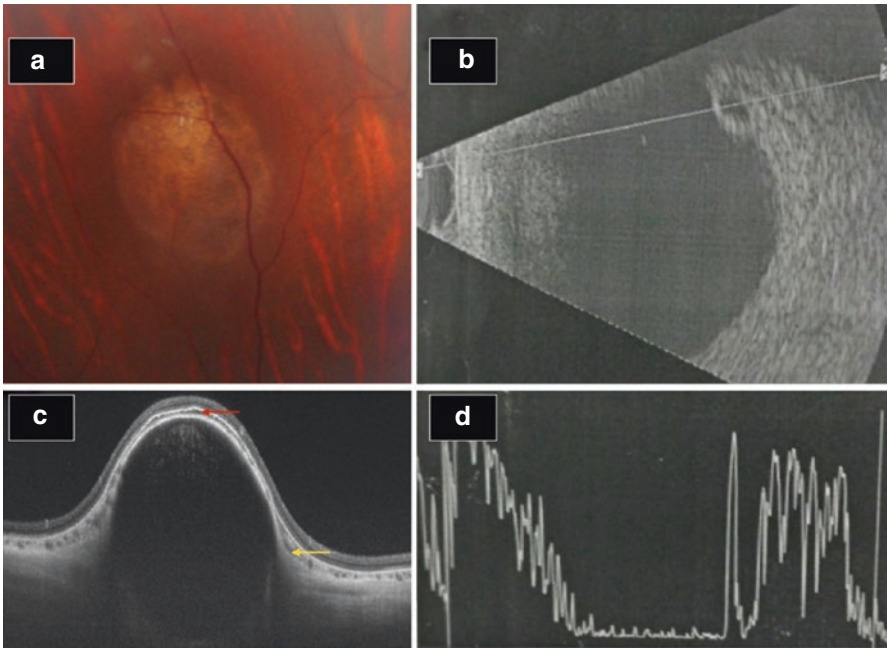

Fig. 7.17 Scleral cyst. (**a**) Color photograph showing an elevated mass which is light brown in color with areas of hypopigmentation. (**b**) B scan shows cystic nature of the lesion. (c) Swept source OCT of the lesion showing an elevated lesion with hyper reflective anterior surface compressing the choroid (red arrow). The hyper reflective anterior surface of the lesion is continuous with sclero-choroidal junction (yellow arrow) suggestive of scleral cyst. (**d**) A scan shows absence of internal reflectivity conforming the cystic nature

7.4.3 Mature Cataract

Mature cataract precludes examination of the posterior segment of eye. Though the prevalence of choroidal melanoma is very low, it would be advisable to consider evaluation of the posterior segment with ultrasonography to rule out the presence of intraocular tumor.

7.4.4 Exudative Retinal Detachment

Exudative retinal detachment can be seen secondary to choroidal inflammatory diseases, nanophthalmos and intraocular tumors. Choroidal hemangioma, melanoma, retinal capillary hemangioblastoma, vasoproliferative tumor of the retina can present with exudative retinal detachment. Ultrasonography should be considered in cases of exudative retinal detachment without obvious cause to rule out the presence of intraocular tumors.

7.5 Special Considerations

7.5.1 Diffuse Choroidal Melanoma

Diffuse choroidal melanoma is a rare form of melanoma accounting for around 3% of cases of choroidal melanoma. This form is relatively flat with large basal diameter with irregular shape. It usually presents with exudative retinal detachment. The diagnosis of diffuse form is difficult and may mimic metastases or inflammatory choroidal disease. High index of suspicion and FNAB would be required to diagnose diffuse melanoma [62, 63].

7.5.2 Previously Treated Tumors

Choroidal melanoma exhibits changes on the surface of tumor such as fibrous metaplasia if it is treated with PDT [31]. In such cases clinical diagnosis would be difficult and needs multimodal imaging cues to reach conclusive diagnosis.

7.6 Summary

Choroidal melanoma is the most common primary intraocular malignancy and about half the patient would develop systemic metastases. Hence early and accurate diagnosis of choroidal melanoma is of paramount importance. Patients with high risk of development of melanoma such as choroidal nevus, oculocutaneous melanosis, dysplastic nevus syndrome, BAP1 cancer predisposition syndrome should be screened periodically to diagnose choroidal melanoma in early stage. Many intraocular neoplastic and nonneoplastic lesions can mimic choroidal melanoma. In a series by Shields et al., 14% of cases referred to ocular oncology service with presumptive diagnosis of melanoma were found to have lesions that mimic choroidal melanoma [64]. In a series by Ghassemi et al., 37.6% cases were diagnosed to have lesions that mimic choroidal melanoma [65]. The most common lesion mimicking choroidal melanoma is choroidal nevus followed by PEHCR, choroidal metastases, melanocytoma, choroidal hemangioma, hemorrhagic PED, vasoproliferative tumor of retina. Good knowledge of clinical and imaging characteristics of these conditions and multimodal imaging would guide towards proper diagnosis. Special care should be taken while evaluating cases with media opacities and imaging should be considered to rule out the presence of choroidal melanoma.

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Intraocular Lymphoma

8

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8.1 Introduction

Intraocular lymphoma (IOL) is defined as a heterogenous group of rare lymphocytic malignancies involving different intraocular tissues, each of which have different morphological, immunophenotypical and genetic features, and completely different clinical courses [1]. In the past, IOL was known as reticulum cell sarcoma, a misnomer. It is derived from monoclonal proliferation of predominantly B-lymphocytes, uncommonly from T-lymphocytes and rarely, natural killer cells. The clinical course of intraocular lymphoma is relatively aggressive compared to orbital and adnexal lymphoma. The tumor provides a diagnostic and therapeutic challenge due to its rarity, nonspecific presentation and aggressive course.

8.2 Classification

Classification of intraocular lymphoma, like other lymphoid tumors, is complex. Various classification systems have been used over the years to classify lymphomas like the Rappaport Classification, the National Cancer Institute Working Formulation,

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and the Revised European-American Lymphoma (REAL) Classification. Currently used classification system, a modern and comprehensive, for lymphoma was proposed by World Health Organization (WHO) with a worldwide consensus [2]. In general, IOL is described primarily based on the source of origin, the ocular tissue involvement, and the proliferating lymphocytic type. Further classification and characterization of IOL is done based on WHO classification, which correlates clinical features with distinct morphologies, immunophenotypes and genetics [1].

Based on the origin, IOL could be primary or secondary. Primary intraocular lymphoma (PIOL) is considered as a subset of primary central nervous system lymphoma (PCNSL), in which lymphoma cells initially invade the ocular tissues with or without concomitant CNS involvement. The most common form of PIOL is primary vitreoretinal lymphoma (PVRL). Secondary intraocular (SIOL) develops from ocular metastasis originating from non-ocular non-CNS lymphoma. Majority of SIOL present as uveal lymphoma affecting iris, ciliary body, and choroid. The most common subtype is systemic diffuse large B-cell lymphoma (DLBCL) [1, 3, 4].

Based on the involvement of ocular tissue, IOL could be referred as vitreoretinal lymphoma (VRL) or uveal lymphoma (UL). Vitreoretinal lymphoma may involve the vitreous or retina or both, and rarely optic nerve. Though majority of VRL are PIOL, rarely it could be secondary lymphoma resulting from metastasis. Uveal lymphomas may involve choroid, ciliary body or iris. Uveal lymphoma may be considered primary if the uvea is the only or the initial site of involvement, which is extremely rare. Majority of uveal lymphomas are secondary arising from systemic non-Hodgkin lymphoma [1, 3, 5].

Based on the proliferating lymphocytic cell type, IOL could be B-cell or T-cell lymphoma. Majority of intraocular lymphomas, primary or secondary, are of B-cell origin. All PVRL are B-cell lymphomas most commonly associated with primary CNS non-Hodgkin's lymphoma, while majority of primary uveal lymphomas are low-grade B-cell lymphomas most commonly, extra-nodal marginal zonal B-cell lymphomas [5]. The most common cause of B-cell SIOL is systemic diffuse large B-cell lymphoma. IOLs of T-cell origin are uncommon, and are usually secondary lymphoma resulting from metastatic systemic T-cell lymphomas including primary cutaneous peripheral T-cell lymphoma, NK T-cell lymphoma, and rarely adult T-cell lymphoma/leukemia. These lymphomas are usually confined to the iris, ciliary body and peripheral choroid [3].

8.3 Epidemiology

Uveal melanoma and retinoblastoma form the majority of cases of primary intraocular malignancies. IOL is a rare malignancy whose exact incidence is not known. Considering lymphoma only, primary vitreoretinal lymphoma is relatively common, while primary uveal lymphoma (PUL) and SIOL are rare. No geographic or racial predilection has been described for PIOL [1, 3].

Primary vitreoretinal lymphoma accounts for less than 1% of all intraocular malignant tumors. IOLs represent 4–6% of primary intracranial tumors, and 1–2%

of all extra-nodal non-Hodgkin's lymphoma. Primary CNS lymphomas present ophthalmic manifestations in 15–25% cases while PIOL shows CNS involvement in 35–90% cases [1, 3, 6]. Bilateral involvement may occur in 80% cases, though initial presentation may be unilateral and asymmetric [6].

The incidence of PVRL, being a disease of adulthood, increases with age. The usual age of presentation is between fifth and sixth decades. However, rarely cases have been reported in young adults as well as in pediatric age group.

There is no clear gender predilection. It appears that incidence is more common in women compared to men, some studies have reported even greater incidence in men [1, 3, 6]. A clear male predominance, up to 70%, has been reported for uveal lymphoma [4, 5]. Choroidal lymphoma is usually unilateral [5].

Although the overall incidence of PIOL is still very low, the incidence has increased in the recent years, most likely due to concomitant rise in PCNSL [6]. The increased incidence of PCNSL can partly be accounted to the increasing number of patients with immunodeficiencies and immunosuppression, increased life expectancy, and aging population. Hence, immunodeficiency and immunosuppression are considered as risk factors for development of PIOL [1, 3]. Increased incidence has been reported even in immunocompetent patients. Improvements in understanding about the disease and the quality of diagnostic investigations are other factors contributing to recent increase in incidence.

8.4 Etiology

The exact etiopathogenesis of IOL is not known. Consequently, several mechanisms of lymphomagenesis have been hypothesized including the role of infectious agents, the chemokine hypothesis, selective homing of malignant lymphocytes to the eye, and clonal transformation of local polyclonal inflammatory cells. Therefore, PIOL can be considered as the result of interactions between genetic, immunologic, and microenvironmental factors.

Infectious agents with suspected role in PIOL development are Epstein-Barr virus, Human herpes virus-8, and *Toxoplasma gondii* with different mechanisms [1]. The preferential entry of malignant B cells to the retina with subsequent clonal proliferation is another suggested mechanism of PVRL development. The preferential entry is facilitated by presence of chemokines and chemokine receptors selective for B-lymphocytes in retinal pigment epithelium (RPE) and malignant B-cells respectively leading to selective attracting of the latter to RPE from the choroidal circulation [1]. Another hypothesis suggests that initially a polyclonal proliferation of inflammatory cells is triggered by infectious and non-infectious uveitis. Later, infectious antigens or endo-antigens cause mutagenesis of polyclonal inflammatory cells leading to a monoclonal proliferation resulting in PIOL [3].

Lymphomas are characterized by monoclonality resulting in expression of identical cellular surface markers and gene restriction observed in either immunoglobulin heavy/light chain (IgH/L) or T-cell receptor (TCR). Gene rearrangements are most commonly observed in the complementarity determining region 3 (CDR3)

region of IgH gene in B-cell lymphoma, and TCR-γ region of TCR gene in T-cell lymphoma. These genetic rearrangements are used as reliable markers for the diagnosis and classification of PVRL [7].

A translocation of BCL2 gene from its normal position at 18q21 to the IgH enhancer at 14q32, termed as BCL2 t(14:18), results in ectopic BCL2 expression. The BCL2 t(14:18) translocation positivity is reported in 55% of PVRL patients, and these patients present at significantly younger age compared to those who lack this translocation [8]. Mutations of BCL6 gene, a proto-oncogene, are frequently detected in DLBCL, with translocation of BCL6 at 3q27 being the most characteristic abnormality. In PVRL cases, a high expression of BCL6 transcript is detected [9]. Analysis of intraclonal heterogeneity of IgH variable region gene mutation helps to reveal the cell origin (germinal center B cell or activated B cell) and stage of tumor transformation [10].

8.5 Clinical Features

PIOL often presents as masquerade syndrome mimicking chronic posterior uveitis. Early transient response to steroids prescribed for suspected uveitis makes the diagnosis more challenging. The onset of all PIOL is typically insidious, however, the mode of presentations differs for PVRL and primary uveal lymphoma.

In PVRL, visual blurring with floaters is the most common initial symptom. This results from sheets or clumps of lymphoma cells causing significant vitreous haze. However, visual acuity is often better than would be expected based on ocular examination [6]. As CNS is involved in more than 50% cases at the time of presentation, behavioral changes, and alteration in cognitive function may be noticed [6]. Clinically, PVRL presents most commonly as vitirits, and less commonly with subretinal lesions or both. On ocular examination, anterior segment inflammation is usually absent. Keratic precipitates, anterior chamber cells, and pseudohypopyon may be seen rarely. Posterior segment examination shows mild to moderate vitreous haze with sheets or clumps of vitreous cells in cases with vitiritis. In cases with subretinal lesion, large multifocal yellow-white creamy subretinal infiltrates are seen resulting from proliferation of lymphoma cells along Bruch's membrane, under the RPE (Figs. 8.1 and 8.2). A characteristic "leopard-skin" or "speckled" pigmentation overlying the mass is often noted. Rare forms of presentation include optic disc swelling and vasculitis with retinal hemorrhage (Fig. 8.2). Vascular sheathing, either reactionary or due to lymphoma cellular infiltrates, could be noted [1, 3, 6]. Vitreoretinal lymphoma can also present with "pseudo-viral retinitis" picture that includes vitreous cells, and necrotizing retinitis [11].

Primary uveal lymphoma has a typical indolent nature with low-grade appearance**.** Recurrent, painless blurred vision and metamorphopsia are the most common presentation of choroidal lymphoma. Rarely, painful eye due to increased intraocular pressure could be the presenting symptom [4, 5]. Clinically, the most dominant

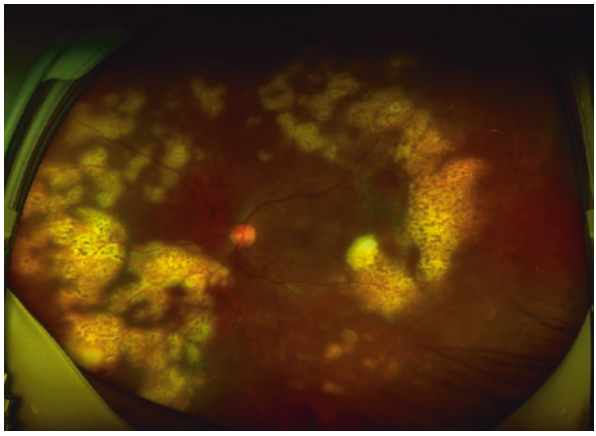

Fig. 8.1 Optos ultra-widefield fundus photograph of a typical case of PVRL showing multifocal creamy-yellow subretinal lesions with characteristic overlying "leopard-skin" or "speckled" pigmentation

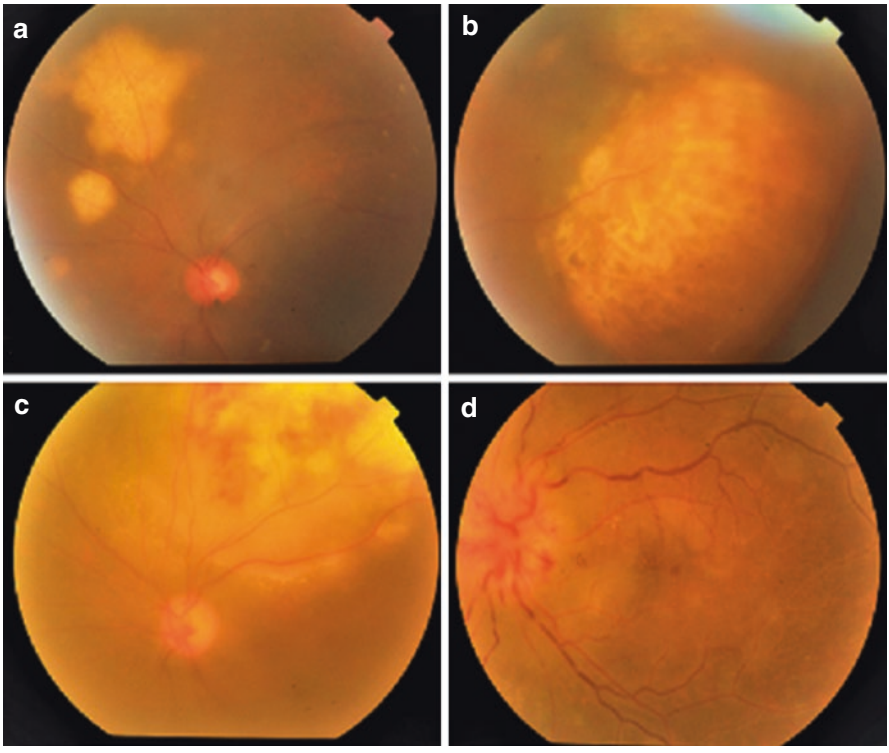

Fig. 8.2 Fundus pictures of various form of PVRL: Multifocal subretinal yellow-white creamy lesions (**a**); Large creamy-yellow subretinal lesion with "speckled" pigmentation (**b**); Large yellow subretinal mass with exudative retinal detachment and retinal hemorrhage (**c**); Rare form of PVRL presentation with optic disc swelling and vasculitis with retinal hemorrhage (**d**)

finding of early stage is multifocal yellow-white choroidal infiltrates seen in almost all cases. In late stage, coalescence of these infiltrates results in diffuse thickening of the uveal tract. Uveal lymphoma can extend into the extraocular space through scleral canals for emissary veins [12]. The vitreous remains usually clear [4, 5].

SIOL cases present with bilateral sudden drop in vision. Ocular examination shows severe anterior segment inflammation which is refractory to treatment. It can be recurrent. Conjunctival follicles are seen in the fornices. Anterior chamber reaction and keratic precipitates are more commonly seen in SIOL. The most common ocular manifestation of SIOL is non-granulomatous anterior uveitis and vitritis. The presentation is always in the setting of systemic lymphoma, especially cutaneous lymphoma [3]. Patients with uveal lymphoma must be screened for gastrointestinal lymphoma.

8.6 Differential Diagnosis

Intraocular lymphoma is one of the most challenging masquerade syndromes. The differential diagnoses include a long list of infectious and non-infectious pathologies. The infectious entities are viral retinitis (acute retinal necrosis, CMV retinitis), retinochoroidal toxoplasmosis, syphilitic retinitis, Whipple disease, and endophthalmitis. Non-infectious differential diagnoses include sarcoidosis, tuberculosis, posterior scleritis, birdshot chorioretinopathy, Behçet's disease, idiopathic uveitis, uveal metastasis, multiple evanescent white dot syndrome, and diffuse or amelanotic melanoma [1, 4, 5, 13, 14]. Consequently, IOL is often misdiagnosed as uveitis and treated with corticosteroids or, infrequently as viral retinitis and is treated with antiviral medications. Prompt diagnosis of PIOL is imperative because timely consultation with oncologist and the initiation of appropriate treatment can extend patient's life. The most important step toward the diagnosis is high clinical suspicion based on thorough ophthalmic examination, and the clinical setting depending on patient's immune status, age, and other risk factors [13]. IOL should be suspected in any elderly patient with nonresponsive, chronic uveitis [14].

8.7 Diagnostic Workup

The diagnosis of intraocular lymphoma requires a multidisciplinary approach. Although ocular imaging along with clinical examination helps in clinical diagnosis of IOL, the definitive diagnosis requires histopathologic evidence of malignant lymphoma cells in ocular specimens such as vitreous, aqueous, or chorioretinal biopsy. Complete blood count and a battery of serological tests are considered during early presentation to rule out other causes of uveitis. In addition to ancillary ocular imaging, neuroimaging using magnetic resonance imaging (MRI) and systemic evaluation using computed tomography (CT) or combined CT and positron emission tomography (PET) play an important role in the diagnosis and management of IOL patients.

8.7.1 Diagnostic Ocular Imaging

Optical Coherence Tomography (OCT): Enhanced depth imaging (EDI) with spectral-domain OCT (SD-OCT) and swept source OCT (SS-OCT) are reliable noninvasive imaging tools which help to evaluate choroid and outer as well as inner retina in cases of PVRL and choroidal lymphoma. Scans reveal hyperreflective dots, bands and nodules at the level of RPE or sub-RPE representing the lymphomatous infiltrations. In late stage, large confluent solid RPE detachments are seen with sub-RPE proliferation, while disruption of IS-OS junction, subretinal fluid and foveal thinning may be seen in cases with retinal infiltration (Fig. 8.3) [15–17]. Direct retinal infiltration by lymphoma cells with focal proliferation creates a semi-opaque interface appearing homogenous on OCT, therefore, it is always better to compare OCT images with the corresponding autofluorescence image to look for any RPE atrophic areas [1].

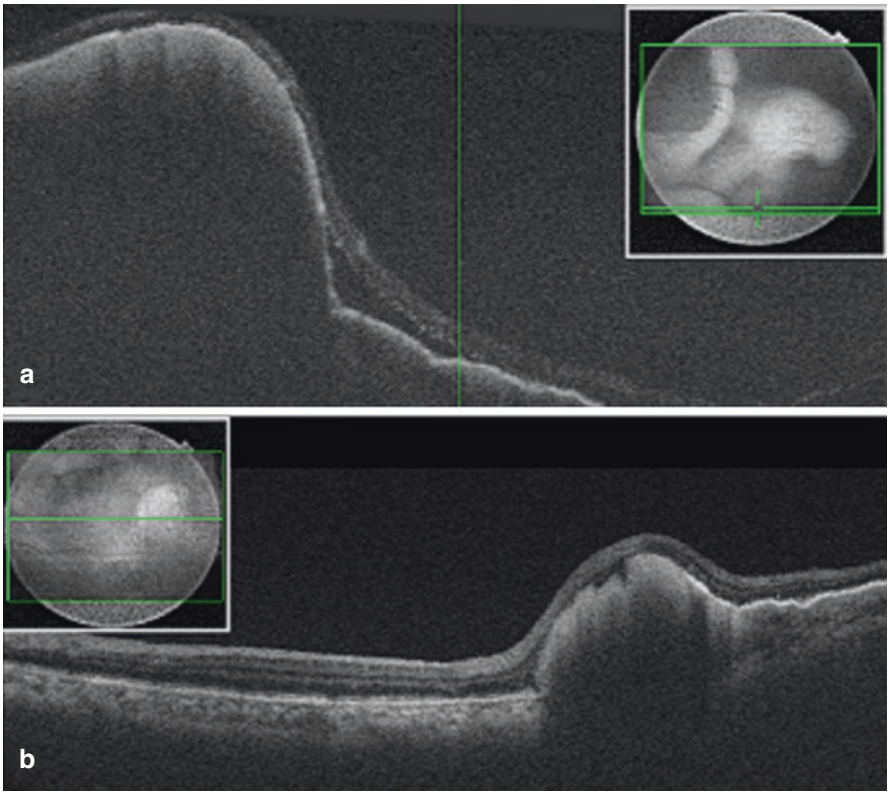

Fig. 8.3 OCT images showing solid retinal pigment epithelial (RPE) detachment with bands at the level of RPE representing the lymphomatous infiltrations with disruption of IS-OS junction and subretinal fluid (**a** and **b**)

Fundus Autofluorescence (FAF): Sub-RPE infiltrates show granular pattern with hypoautofluorescent spots surrounded by hyperautofluorescent ring, while pattern of autofluorescence reverses with infiltration above the RPE. Hyperautofluorescent spots on FAF correspond to hypofluorescent lesions seen on FFA [18, 19].

Fundus Angiography: Fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA) provide useful information with a high positive and negative predictive value when used together [15]. FFA shows punctate hyperfluorescent window defects corresponding to the areas of RPE atrophy in more than half cases with classic "leopard-skin" pigmentation being more prominently in early stage [20]. One-third cases show round hypofluorescent spots due to the subretinal deposits of lymphoma cells in one-third cases of PVRL, while areas of retinal infiltration appear as hyperfluorescent (Fig. 8.4) [15, 20]. Venous leakage and periarteriolar staining suggestive of vasculitis may be seen uncommonly [20]. ICGA shows small hypofluorescent lesions in the early phase, which become less apparent in the later phase [21].

Ultrasonography (USG): USG is indicated in cases where patients present with diffuse vitreous haze. Although the findings are not specific for PIOL, it shows abnormalities like vitreous debris, secondary retinal detachment, elevated chorioretinal lesions, and widening of the optic nerve (Fig. 8.5) [21]. Crescentic thickening and a discrete mass is noted in early cases of choroidal lymphoma, while diffuse sclerochoroidal thickening is seen in late stage. Subretinal fluid may be seen on USG. Absence of sub-Tenon fluid/"T" sign helps in ruling out posterior scleritis [4].

8.7.2 Neuroimaging

Since up to 90% of patients with PVRL develop CNS lymphoma, therefore in suspected cases, a contrast-enhanced cranial MRI is the best imaging modality for staging of CNS lymphoma. MRI shows unifocal or mutifocal, periventricular,

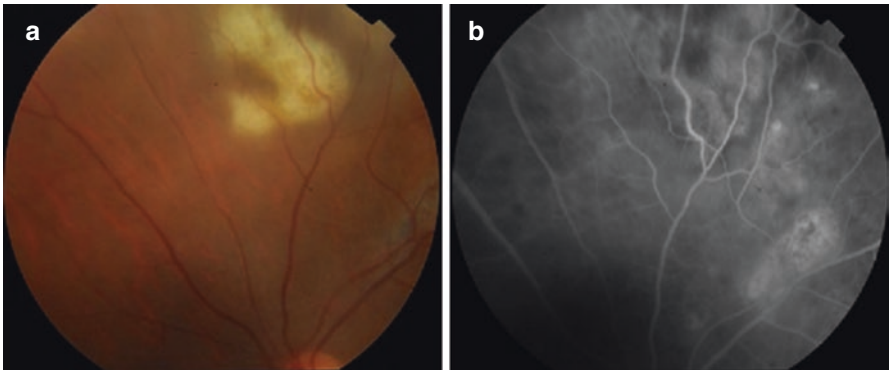

Fig. 8.4 Color fundus photo of a PVRL patient showing subretinal lymphoma lesion (**a**); Fluorescein angiography shows hypofluorescent and hyperfluorescent spots corresponding to the subretinal deposits of lymphoma cells and areas of retinal infiltration respectively (**b**)

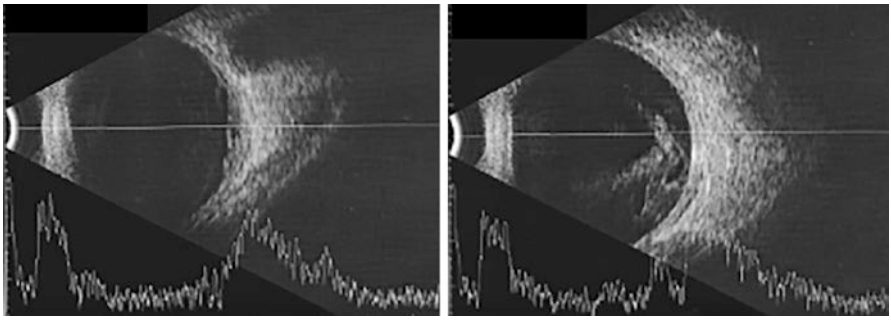

Fig. 8.5 Ultrasound B-scan images of a 44-year-old male patient, who presented with primary vitreal lymphoma following renal transplant, show moderately echogenic vitreous opacities with exudative retinal detachment

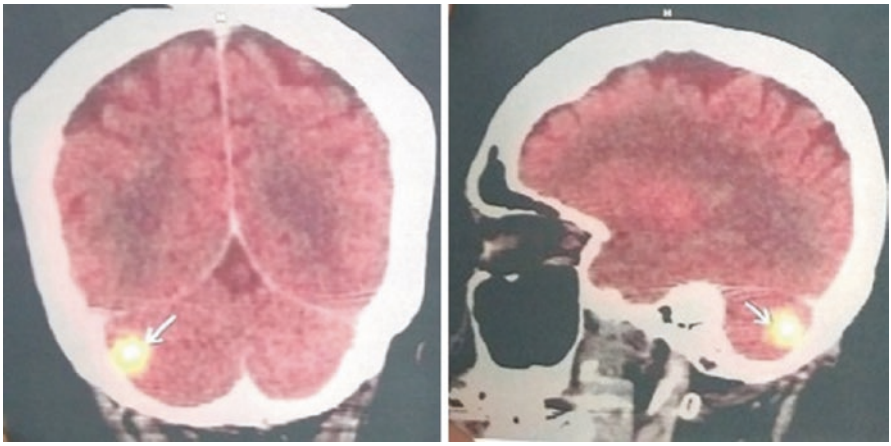

Fig. 8.6 PET scan of brain in a patient with PCNSL showing lymphoma lesion in left occipital lobe (white arrows)

homogenously and strongly enhancing lesions with variable surrounding edema. Lesions are often isointense to hypointense on T2-wieghted MRI [3].

8.7.3 Whole Body CT or PET-CT Imaging for Systemic Evaluation

Whole body CT or PET-CT imaging of the thorax, abdomen, and pelvis should be done to rule out systemic involvement in cases of IOL. Whole body PET scan can play an important role in PCNSL staging at diagnosis or in the follow-up as it can diagnose a systemic disease with higher sensitivity than conventional imaging such as CT scan (Fig. 8.6) [22].

8.7.4 Diagnostic Tissue Sampling and Analysis

Histopathological analysis of tissue sample to demonstrate the presence of malignant lymphoma cells remains the gold standard for diagnostic confirmation. Various tissue samples collected for this purpose include cerebrospinal fluid (CSF), aqueous, vitreous, retinal and chorioretinal biopsy, and brain biopsy depending upon the type and extent of suspected IOL.

CSF sampling: Cases of suspected PVRL, being a subset of PCNSL, should undergo lumbar puncture to collect CSF sample for microscopic identification of lymphoma cells. Identification of lymphoma cells in CSF in PVRL cases obviates the need for further diagnostic procedures of vitreous collection [1, 13]. However, the yield of lymphoma cells in CSF is low, resulting in positive CSF cytology in only 25% patients with CNS lesions [18]. When CSF analysis turns out negative, ocular tissue sampling is warranted to confirm diagnosis.

Aqueous humor tap: Aqueous is another ocular fluid used for histological and molecular analysis. Anterior chamber aspiration cytology enhanced by the cytospin technique may provide a less invasive alternative to diagnostic vitrectomy [23]. The handling and processing of CSF and aqueous sample is same as vitreous sample as described later.

Vitreous sampling: Vitreous sampling remains the mainstay for tissue analysis in PVRL, when the CSF analysis and neuroimaging are not consistent with CNS lymphoma. Vitreous samples can be collected through pars plana vitrectomy (PPV) providing 1–2 mL of undiluted specimen using low cut rate with infusion off. In order to make the procedure safer and avoid hypotony related lens or retina touch, air infusion can be turned on for volume compensation, while still being able to collect undiluted sample. A diluted specimen up to 100 mL can be collected from vitrectomy cassette, which can be utilized to perform additional tests. PPV can also help to clear the media by removing vitreous debris resulting in visual improvement. Tissue samples need to be transported to the laboratory without delay as lymphoma cells undergo morphological degradation within 60 min. In case of expected transportation delay, immediate fixing of sample is done using a fixative containing ethanol, methanol, and propranolol in 8:1:1 ratio but an appropriate preservative may be used to protect the lymphoma cells. Other preferred fixative agents are Shandon cytofix or HEPES-glutamic acid buffer mediated organic-protection effect (HOPE) solution, and RPMI 1640 medium. There may be false negative results in cases with purely sub-RPE infiltrates without any vitreous invasion. Tumor seeding through the sclerotomy port to the epibulbar space is a potential complication of vitreous biopsy [24–28].

Retinal and Chorioretinal biopsy: A negative vitreous sample is common mainly due to sparse number of lymphoma cells, and also due to presence of many reactive T-lymphocytes, necrotic cells, debris, and fibrin. Negative vitreous analysis is more common in cases of purely retinal lymphoma and choroidal lymphoma, where retinal or chorioretinal biopsies may be required for diagnostic confirmation. Chorioretinal biopsy can be obtained either by external or transvitreal approach [13, 29].

Brain biopsy: Image-guided stereotactic brain biopsy is considered in select cases with suspicious MRI lesions but a negative CSF cytology. However, a prior confirmation of ocular disease eliminates the need for brain biopsy [1, 13].

Microscopic cytology: Histologic identification is one of the essential procedures in diagnosing IOL. For better visualization of malignant cells, Giemsa or Diff-Quick stains are preferred for staining of pathological specimen since they outline the characteristics of lymphoma cells better. However, malignant cells can be seen with easily available stains such as Papaniclou or Hematoxylin-Eosin stains. Microscopically, B-cell lymphomas contain large, pleomorphic cells with an elevated nuclear/cytoplasm ratio, scanty basophilic cytoplasm, deeply stained large round, oval, bean-shaped or hyper-segmented nuclei, and prominent or multiple nucleoli (Fig. 8.7). T-cell lymphomas are difficult to diagnose based on these features. Necrosis and inflammatory cells may be seen in the background [6, 26–29].

Molecular analysis: Molecular analysis of vitreous sample help in demonstration of monoclonal lymphoid cells using kappa (κ) or lambda (λ) chain restriction. A κ:λ ratio of 3 is highly sensitive marker for IOL. Flow cytometry can be used for a greater number of cell surface markers and thus distinguishing T cell lymphoma from B-cell lymphoma and reactive lymphoid infiltrates. Most of B-cell IOLs express CD19, CD20, and CD 22. Diffuse large B-cell does not express CD10, which distinguishes them from extramarginal zone lymphomas (MALT lymphomas). Polymerase chain reaction (PCR) technique is used to amplify the immunoglobulin heavy chain DNA. Molecular analysis is to detect T-cell receptor gene rearrangement help in the diagnosis of T-cell lymphoma, while detection of IgH gene rearrangements or k light chain rearrangement is used to diagnose B-cell lymphoma. T-cell specific PCR is used when differentiation of T-cell lymphoma from reactive lymphocytic proliferation becomes difficult due to CD3 expression. The diagnostic efficiency of PCR has been shown up to 99.5%. Analysis of various cytokines especially Interleukins (IL) and its ratios aid in the diagnosis of IOL. It is now

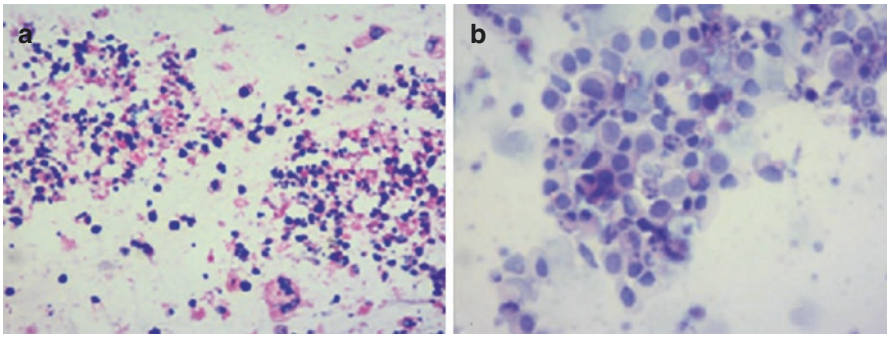

Fig. 8.7 Cytopathology of the vitreous specimen from a patient of PVRL. Examination of smears showing predominantly large lymphocytes mixed with small and intermediate-sized lymphocytes (Hematoxylin & Eosin stain, magnification ×100) (**a**). The large atypical lymphoid cells with scanty basophilic cytoplasm and large nuclei with fine chromatin and prominent nucleoli, with necrotic lymphoid cells and nuclear debris (Hematoxylin and Eosin stain, magnification ×400) (**b**)

well established that IL-10 levels are high in malignant B-cells and IL-6 levels in inflammatory states. Elevated IL-10 level and an IL-10:IL-6 ration >1 are helpful for the diagnosis, while inflammatory conditions typically show elevated IL-6 in vitreous sample. Another effective method to diagnose IOL is detection of the BCL-2 t (14;18) translocation, which is reported to be seen in 55% PIOL patients [6, 30–34]. Detection of MYD88 L265P in vitreous sample by highly sensitive droplet digital polymerase chain reaction (ddPCR) helps in confirmation of VRL diagnosis (sensitivity = 75%, positive predictive value = 100%) [35].

8.8 Treatment

There is lack of validated standard treatment protocol for management of intraocular lymphoma. Treatment modalities include intravitreal chemotherapy, systemic chemotherapy, and radiotherapy, used alone or in an appropriate combination. The international PCNSL collaborative group has recommended the use systemic chemotherapy in cases of IOL with CNS or systemic involvement, and local therapy for disease localized only to the eye [36].

1. ***External Beam radiotherapy (EBRT)***: PIOL and PCNSL are radiosensitive tumors. For PIOL without CNS involvement, ocular irradiation is done to control IOL and to prevent CNS involvement. For the treatment of PCNSL, a combination of EBRT and systemic chemotherapy is treatment of choice. EBRT is also used as the first line of treatment for localized uveal lymphoma. Low dose radiotherapy with average dose of 40Gy can be given in 15 fractions to both globes. Figure 8.8 shows the regressing PVRL following EBRT. Ocular side effects include radiation retinopathy, dry eye, vitreous hemorrhage, neovascular glaucoma, conjunctivitis, optic atrophy, and cataract. It can also cause neurological toxicity [3, 4, 37].
2. ***Systemic chemotherapy***: Intravenous methotrexate is the drug of choice for IOL with CNS or systemic involvement requiring systemic chemotherapy. It achieves good remission of the lesions. Even with high-dose methotrexate chemotherapy, relapse can be seen commonly. In such cases, intense chemotherapy with high-dose thiotepa, busulfan, and cyclophosphamide combined with autologous stem cell transplantation gives complete remission of the disease. Chemotherapy combined with radiation gives a better outcome than individual treatment options. However, ocular disease recurs in 50% of cases, which is treated with local intraocular chemotherapy. Relapsed or refractory PIOL with PCNSL has been treated with intrathecal methotrexate and cytarabine [1, 6, 38–40]. In another chemotherapy protocol, methotrexate is combined with temozolomide and rituximab (MT-R) [41].
3. **Intraocular chemotherapy**: Intravitreal chemotherapy is treatment of choice for unilateral or bilateral IOL without concurrent systemic evaluation. An intensive induction–consolidation–maintenance regimen of 25 injections of intravitreal methotrexate (0.4 mg in 0.1 mL) delivered over 1 year shows optimal

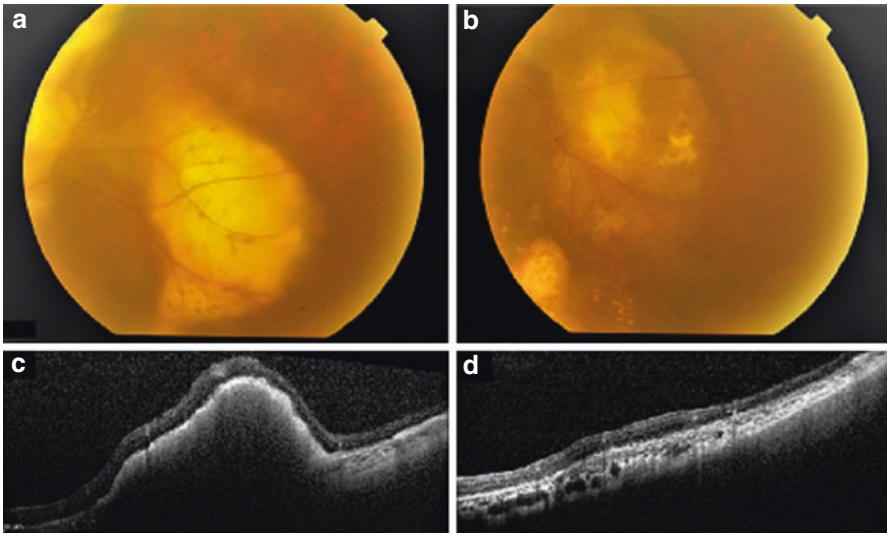

Fig. 8.8 Fundus pictures showing active subretinal lymphoma lesion (**a**); and regressed lesion following EBRT (**b**). OCT images of the same patients showing large confluent solid RPE detachment before treatment (**c**); and regressed subretinal lymphoma lesion following EBRT (**d**)

response. The injections are given twice weekly for 4 weeks, followed by weekly once for 8 weeks, and then finally monthly once for 9 months. Frequent methotrexate injections carry risk of keratopathy and maculopathy. Widely spaced intravitreal methotrexate in combination with therapy rituximab (1 mg in 0.1 mL) may achieve good outcomes in methotrexate-resistant IOL and also reduce methotrexate-induced toxicity. Rituximab monotherapy can also achieve good outcomes, but relapses are seen more commonly. Ocular relapses require combined intravitreal chemotherapy and ocular irradiation [1, 6, 42, 43].

8.9 Prognosis

The reported mortality rate of intraocular lymphoma is very inconsistent, ranging between 9 and 81%. The high mortality rate is due to rarity of the disease, the delayed diagnosis, variation in treatment modalities, CNS involvement, and T-cell lymphoma. Tumor recurrence is common [3].

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Vasoproliferative Retinal Tumor

9

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9.1 History

Vasoproliferative retinal tumor (VPRT) was first identified as a telangiectatic peripheral nodule with associated proliferation of fibrocellular epiretinal membranes by Baines and co-workers in 1982 [1]. In 1983, Shields et al. published their observation of 12 cases which they named as presumed acquired retinal hemangiomas based on their clinical, fluorescein angiography and sonography studies and differentiated this subset from von Hippel–Lindau's presentation [2]. Involvement of peripheral retina, presence of telangiectasia and exudation have misled the clinicians to describe this entity to be possible Coats or adult-onset Coats disease. In 1995 Shields et al. changed the name of the presumed acquired retinal hemangiomas to vasoproliferative retinal tumors. They called these lesions as VPRT because they were not true hemangiomas and they had varying histogenesis and histopathological features [3].

9.2 Pathology

VPRT is considered as a reactive proliferation of pigment epithelial and retinal vessels, and a gliosis in response to retinal inflammation, injury, or ischemia. It is possible that ocular neovascularization could assume a tumorous proportion [3]. The blood vessels proliferate in a loose glial matrix and form a vascular mass. Over time, the reactive gliosis exceeds the vascular component. Hence the pinkish yellow

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tumor turns into yellow white tumor in the late stage. On histopathology, glial cells interlaced with a fine capillary network are seen with dilated, hyalinized partially occluded blood vessels, exudates, macrophages, and foreign-body giant cells [4]. Heiman et al. studied the histopathology features of two tumor biopsy specimen and reported the presence of spindle-shaped cells which were strongly positive for glial fibrillary acid protein (GFAP). It confirmed the glial origin, and the presence of dilated blood vessels which had marked hyalinization of the vessel wall. There is absence of mitotic activity. MIB-1 determined growth fraction has also been found to be low in VPRT [5].

The retinal pigment epithelial (RPE) proliferation has been ascribed to a reactionary process by various authors however, Perry et al. hypothesized that subretinal fibrous and osseous metaplasia of the retinal pigment epithelium could be due to a reaction to irritative products of the tumor or substances derived from the leaking vasculatures [6].

9.3 Classification

Shields et al. classified VPRT into two categories [3]:

1. Primary or idiopathic.
2. Secondary.

9.3.1 Primary VPRT

Majority of primary VPRTs (Fig. 9.1) are unilateral and considered sporadic but bilateral presentation has been reported in monozygotic twins [7].

9.3.2 Secondary VPRT

Causes of secondary VPRT include retinitis pigmentosa (Fig. 9.1b), toxoplasmosis, intermediate uveitis, sickle cell disease, toxocariasis, Coats disease, retinopathy of prematurity, long-standing retinal detachments, pars planitis, repair of retinal detachment, idiopathic peripheral retinal vasculitis, familial exudative vitreoretinopathy, congenital hypertrophy of retinal pigment epithelium, idiopathic choroiditis, and histoplasmosis [8, 9].

VPRT may be associated with systemic hypertension, Waardenburg syndrome and neurofibromatosis Type 1 [10–12]. Age of presentation is usually third and fourth decades and there is no gender predilection, although few reports have mentioned female predilection after the fifth decade of life [13].

Published reports from India have shown preponderance of secondary VPRT. Honavar et al. found 60% of the cases were secondary in their studies [4], and Walinjkar et al. reported that 68% of their cases were secondary. However, a very high occurrence (80%) of primary VPRT is found in Western literature [14].

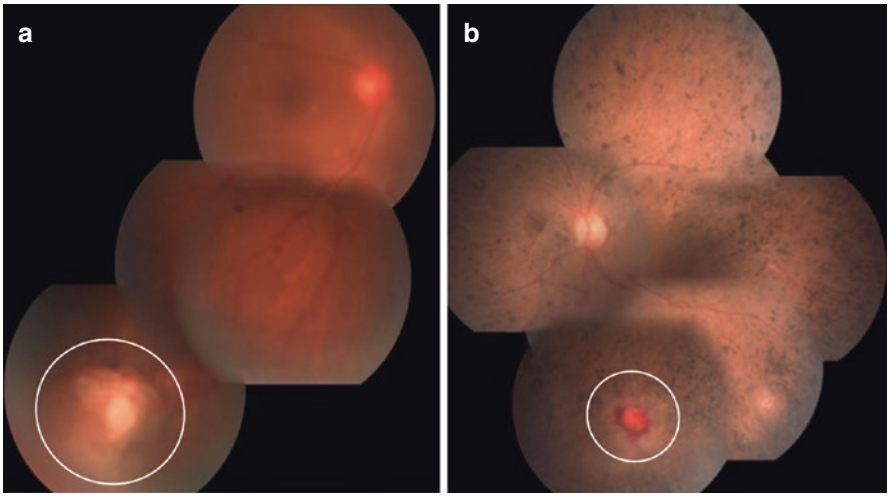

Fig. 9.1 (**a**) Primary VPRT. Fundus photograph showing yellowish white mass in the inferotemporal periphery. The rest of the fundus is essentially normal. (**b**) Secondary VPRT. Fundus photograph showing orange lesion with surrounding hemorrhage. Rest of the fundus shows bony spicule pigmentation and arterial attenuation suggestive of RP

Table 9.1 Showing staging of vasoproliferative retinal tumors

Stage 1
1a: VPRT with focal exudates less than 5 mm from the lesion
1b: VPRT with diffuse exudates more than 5 mm from the lesion
Stage 2
2a: VPRT with remote exudates not involving fovea
2b: VPRT with remote exudates involving fovea
Stage 3
3a: VPRT with epiretinal membrane not involving fovea
3b: VPRT with epiretinal membrane involving fovea
Stage 4
4a: VPRT with RD not involving fovea
4b: VPRT with RD involving fovea
Stage 5
5a: VPRT with complications with visual potential (vitreous hemorrhage, neovascularization of the iris, and secondary glaucoma)
5b: VPRT with complications with no visual potential or painful blind eye

Taking in to consideration the presence of exudates, epiretinal membrane, retinal detachment and foveal involvement, a staging system for VPRT is proposed (Table 9.1) [4].

9.4 Clinical Features

Blurred vision can occur due to macular edema and pre-macular fibrosis and visual loss due to sub retinal exudation, hemorrhage, tractional retinal detachment, and vitreous hemorrhage.

Lesions look yellowish to pinkish in color but at times could be white, gray, or reddish.

Morphologically, the most common form of presentation is a circumscribed mass, though diffuse form has also been described. The diffuse lesions have female predilection. They are bilateral at presentation and show multiple feeder vessels. They are usually seen at inferotemporal quadrant due to unknown reasons.

Characteristically, the tumor appears as sessile or dome-shaped but occasionally it is ill-defined or may appear as ill-defined fusiform retinal thickening. The mean tumor basal diameter is 6 mm (0.5–25 mm) and mean tumor thickness 2.9 mm (0–9.7 mm) [5]. The vessels are minimally dilated in contrast to markedly dilated feeding artery and draining vein seen in von Hippel–Lindau disease.

Associated vitreoretinal findings in primary VPRT include the presence of vitreous hemorrhage, subretinal or intraretinal hemorrhage, subretinal or intraretinal exudation, subretinal fluid, tractional retinal detachment, retinal neovascularization, exudative retinal detachment, and cystoid macular edema. Most common vitreoretinal findings in secondary VPRT are the presence of vitreous cells and RPE alteration which are noted adjacent to tumors [14].

Visualization of the tumor at times is hampered due to vitreous hemorrhage, subretinal or intraretinal retinal exudation [3]. The main causes of low visual acuity in patients with VPRT are an epiretinal membrane, cystoid macular edema, vitreous hemorrhage, and tractional retinal detachment.

9.5 Investigations

Investigations are not mandatory since primarily diagnosis of VPRT is clinical. However, ultrasound B scan, fundus fluorescein angiography (FFA) and optical coherence tomography (OCT) are often helpful in confirmation.

Ultrasonography shows tumor as a solid, solitary elevated mass with medium to high internal reflectivity in A-scan. Internal reflectivity can be low, medium, or high and there is no distinct pattern [15]. It could be differentiated from choroidal melanoma by the absence of choroidal excavation [16] (Fig. 9.2).

Fundus fluorescein angiography (FFA) is difficult procedure in VPRT because of the peripheral location of tumor. It shows early hyperfluorescence in arterial and diffuse leakage in late phases [16] (Fig. 9.3).

Wide field angiography is helpful in imaging the peripheral tumors [17].

Optical coherence tomography (OCT) is helpful in detection of macular edema and epiretinal membrane. Owing to the peripheral location, the lesions are less amenable to OCT imaging. In a study by Shields et al and Shields, the tumor was seen as ill-defined mass lesion and showed the presence of intralesional cystoid edema [16].

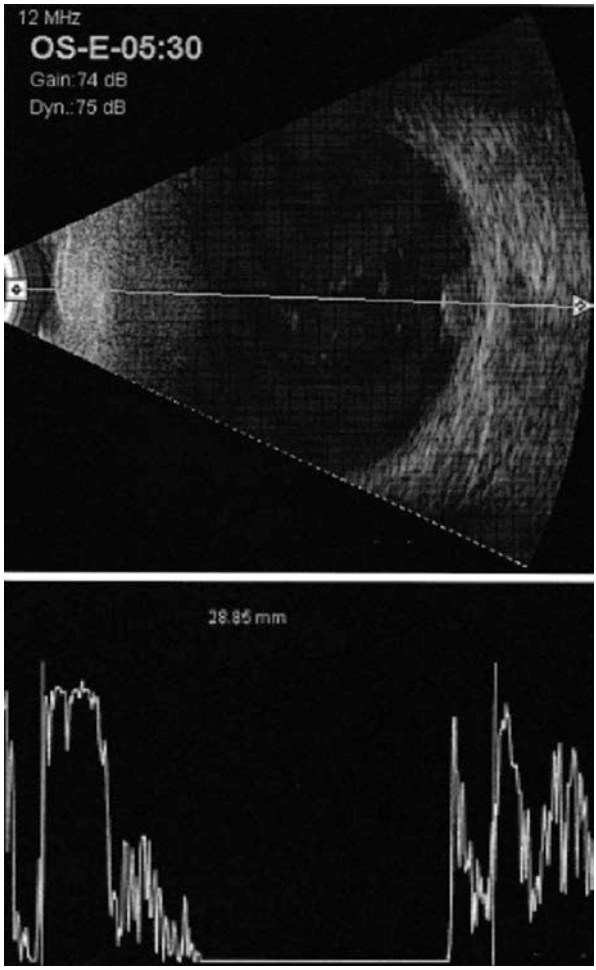

Fig. 9.2 Ultrasonography showing a dome-shaped mass. Choroidal excavation is not seen. A scan showing medium to low internal reflectivity (Internal reflectivity varies from low to high in cases of VPRT)

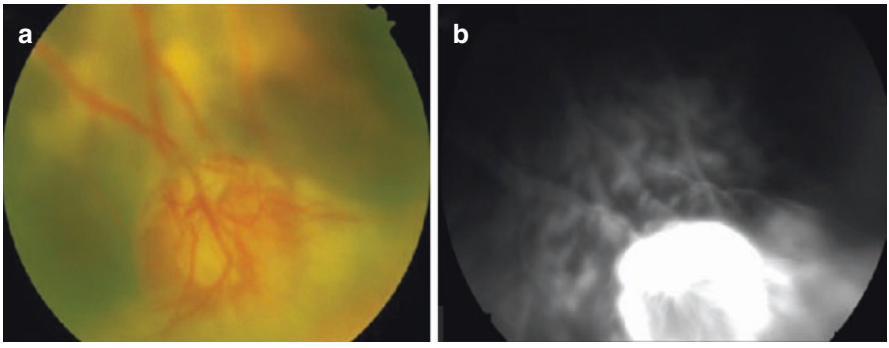

Fig. 9.3 (**a**) Color photograph showing yellowish white tumor with surface vascularity in the inferior quadrant. (**b**) Fundus fluorescein angiography showing extensive leak from the tumor

9.6 Treatment

Due to the rarity of this condition, there are no evidence-based treatment protocols. Various treatment options and indications are listed in Table 9.2. Considering its peripheral location, smaller tumors with limited exudation are kept under observation. Larger tumors and tumors associated with visual loss due to exudation, macular pucker, vitreous hemorrhage, retinal detachment needs treatment. The treatment options include:

1. Triple free thaw cryotherapy: Transconjunctival triple freeze thaw cryotherapy is the most commonly used modality to treat the peripheral tumors. It is found to be successful in a few case series [3] (Fig. 9.4).
2. Laser photocoagulation: Confluent laser spots are applied directly over the tumor surface. It is found to be successful in smaller tumors [3].
3. Transpupillary thermotherapy.

Table 9.2 Treatment modalities in management of VPRT

Mode of treatment	Indication
Observation	Peripheral tumor Less than 2 mm Non exuding
Cryotherapy Standard triple freeze thaw	Tumor with apical diameter < 2 mm
Plaque radiotherapy Ruthenium/iodine	Thickness > 2.5 mm Presence of exudation Recalcitrant to cryotherapy—large tumors with exudative retinal detachment
Intravitreal anti-VEGF/ Steroids	Adjuvant treatment for macular edema
Vitreoretinal surgery	ERM, Tractional RD, VH

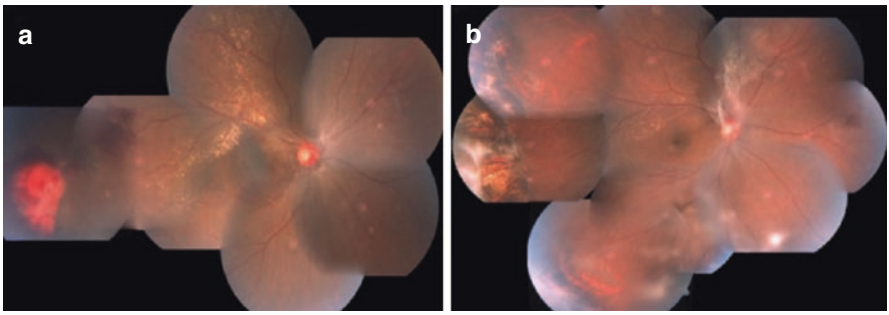

Fig. 9.4 (**a**) Orange red VPRT in the temporal periphery. (**b**) Whitish glial tissue replacing the tumor after two sessions of cryotherapy

4. Plaque brachytherapy: Iodine I^{125} and ruthenium-106 brachytherapy are reported to be effective in the treatment of VPTR [18–20]. In a series of 30 eyes with mean tumor thickness of 3.7 mm (range: 2.5–6.3 mm) treated with I^{125} plaque, tumor regression was seen in 97% of the eyes, complete resolution of retinal detachment in 65% of the eyes and visual acuity improved or stabilized in 77% of eyes [18]. In a series of 35 patients with mean tumor thickness of 2.8 mm treated with Ru-106 plaque, the tumor activity was controlled in 88.6% of cases. However, reduction in visual acuity was noted [19]. Epiretinal gliosis, transient vitreous hemorrhage, and cataract were seen.
5. Photodynamic therapy (PDT): In some studies, different protocols of PDT were used in the treatment of VPRT. Three eyes with VPRT were treated with intravenous injection of 6 mg/m^2 body surface area of verteporfin and a dose of 100 J/cm^2 at 689 nm delivered in 166 s. A significant reduction in the size of tumor and resolution of macular hard exudates was seen in all the cases [21]. In another study, cases of VPRT treated with a dose of 100 J/cm^2 delivered over 83 s, involution of tumor and improvement in visual acuity was seen [22].
6. Anti-VEGF agents: Immunohistochemistry of a resected VPRT showed a strong immunoreactivity to VEGF [23]. Hence bevacizumab was used as a treatment option in a few small case series. Nine eyes with VPRT treated with one injection of 1.25 mg bevacizumab, two small tumors regressed completely, but additional therapy was required for large tumors. Improvement in visual acuity and central retinal thickness were also noted [23]. In a series of six eyes treated with bevacizumab, temporary reduction in tumor thickness was seen in three eyes. But there was no statistically significant change in visual acuity or tumor thickness in long term [24]. Based on the available evidence, bevacizumab can be used as an adjunct to decrease macular edema and neovascularization in VPRT along with an additional treatment modality.
7. Intravitreal steroids: Intravitreal steroids can be used in the treatment of subretinal exudates. In a case of adult-onset Coats disease with VPRT, dexamethasone implant and laser photocoagulation resulted in resolution of hard exudates [25] (Fig. 9.5).
8. Indocyanine green (ICG) mediated photothrombosis: In this technique, 1 mg/kg of ICG is administered intravenously. Thirty minutes later, multiple, confluent, 810 nm diode laser spots are applied over the surface of tumor. ICG dye in the tumor vessels absorbs the laser energy and leads to thrombosis of tumor vessels. In one case report, VPRT was treated with two sessions of ICG-mediated photothrombosis, a complete resolution of tumor was noted [26].
9. Systemic infliximab: Infliximab is an antitumor necrosis factor monoclonal antibody. In a single case report, when infliximab was administered to treat a patient with collagen vascular disease, incidental regression of bilateral VPRT was seen. But there is no evidence to prove its efficacy in the disease [27].
10. Vitrectomy: Vitrectomy is indicated in cases with macular pucker, tractional retinal detachment, and vitreous hemorrhage. After vitrectomy tumor is treated with cryotherapy or laser photocoagulation.

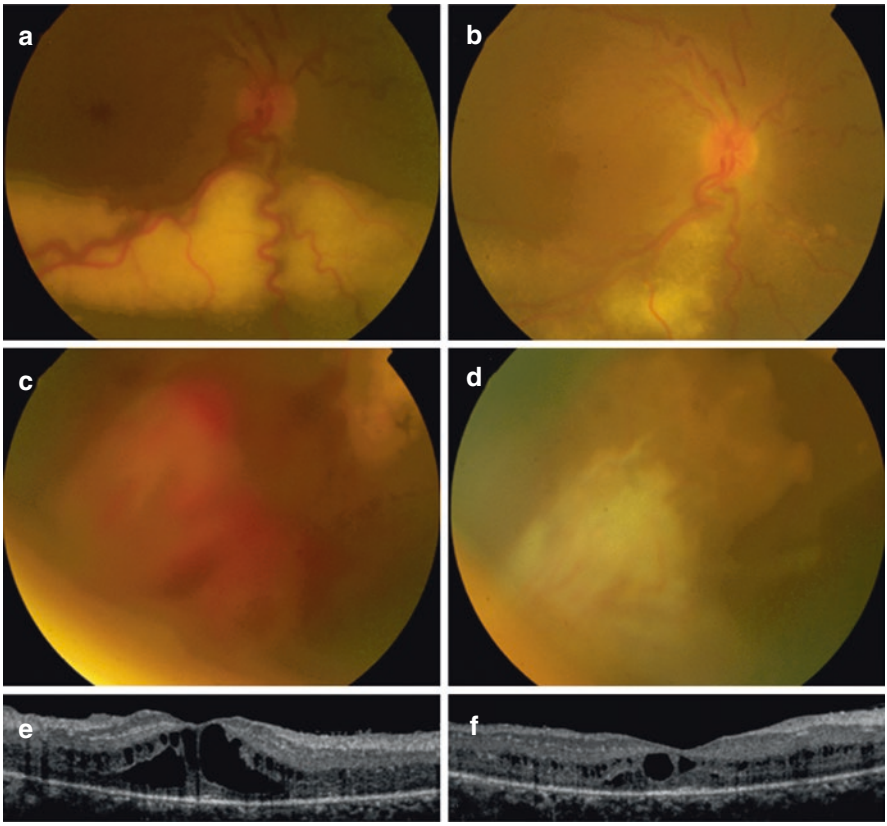

Fig. 9.5 (**a**) Orange red VPRT with surrounding hemorrhage (**a**) with subretinal exudates (**b**) and macular edema (**c**). The tumor was treated with triple freeze thaw cryotherapy and intravitreal dexamethasone implant. Decrease in subretinal exudates (**d**) and macular edema (**f**) is seen. Reduction in tumor vascularity is seen (**e**)

11. Tumor resection: Some surgeons consider resection of tumor [28, 29]. In a comparative study of 17 eyes, tumor was resected in 8 eyes and was conservatively treated in 9 eyes. In the group with conservative treatment, 33% of the cases had tumor activity. Visual acuity improvement was found to be better in the tumor resection group than the conservative group [30].
12. Enucleation: Enucleation may be required in cases with neovascular glaucoma.

Clinical Pearls

1. The main differentiating feature of VPRT from VHL is the sheer absence of dilated and tortuous artery and veins, lack of familial history other than being unilateral and solitary.
2. A young patient with unilateral spontaneous vitreous hemorrhage, rule out VPRT.
3. All cases of VPRT are not primary.

4. Cause of low visual acuity in VPRT are:
   (a) Vitreous hemorrhage.
   (b) Tractional retinal detachment.
   (c) Cystoid macular edema.
   (d) Epiretinal membrane.

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Choroidal Metastasis

10

Vijitha S. Vempuluru and Swathi Kaliki

10.1 Introduction

Uveal metastasis is the most frequent intraocular malignancy [1–5]. Choroidal metastasis accounts for 88% of the uveal metastasis, 7.8–9% occur in iris, and about 2% in the ciliary body [5]. The first report of choroidal metastasis dates back to 1872, described by Perl and since then they have been extensively studied [6]. Prevalence of choroidal metastasis has been estimated from postmortem examinations and ocular examinations in patients diagnosed with cancer. It ranges from 4 to10% in the former and 2–27% in the latter in various studies [7–10].

Recent reports show a decreased incidence owing to improved cancer therapeutics, however, they are still a common manifestation of metastatic cancer and can be the first presenting feature of metastatic disease [2, 3].

The most common primary tumor site is the breast (40–53%), followed by lungs (20–29%), and less frequently the gastrointestinal tract, prostate, kidney, and skin [1–5]. Other rare causes include primary tumor from the salivary glands, thyroid, testes, female genitourinary tract, urothelial tract, neuroendocrine tumors, and sarcomas [11–17]. Cutaneous and mucosal melanomas are also an important cause of choroidal metastasis [18]. In 8–30% of patients, choroidal metastasis precedes the diagnosis of systemic cancer, but more often history of systemic cancer is usually present [19].

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10.2 Pathogenesis

Despite the lack of a lymphatic system, uveal metastasis is quite frequent [1–5]. There are three major theories proposed to explain the same [20–22]:

1. Anatomical-mechanical mechanism: Vascular and lymphatic drainage from the primary site causes the tumor cells to be retained nonspecifically in the capillary bed of the first organ encountered. Abundant blood supply from posterior ciliary vessels accounts for choroid being a common site.
2. Seed and soil mechanism: This theory proposed by Paget suggests that tumor cells which reach systemic circulation (seed) localize and replicate when they reach a suitable microenvironment (soil).
3. Wound oncogene wound healing mechanism: Meng et al. [22] hypothesized that cell migration is not essential for the development of metastasis and cancer results from the body's response to heal to a "wound." As a result, "wound molecules" or the cytokines release can cause activation of oncogenes in distant tissues.

10.3 Clinical Features

10.3.1 Symptoms

Patients can be asymptomatic, or present with decreased vision, floaters, or field defects. Large untreated lesions may present with pain due to secondary glaucoma [1–5, 7, 8].

10.3.2 Signs

Choroidal metastases are often bilateral and multifocal [1–5]. About 40% of choroidal metastases commonly involve the macula and nearly 80% occur posterior to the equator [7, 8, 19]. On ophthalmoscopy, they appear as an ill-defined, dirty yellowish subretinal elevations. Presence of massive exudative retinal detachment is highly characteristic [1–5, 8, 19]. They are usually flat or mildly elevated, rarely mushroom shaped [19]. Overlying retinal pigment epithelium may have a leopard-spot like appearance and sometimes lipofuscin deposits may be seen [1–5]. On an average, the lesions measure 9 mm in largest basal diameter and 3 mm in thickness [7, 8]. Orange colored lesions are seen in metastases from carcinoids, renal cell carcinoma, or thyroid cancer [23–25]. Metastatic cutaneous melanomas manifest as brown colored choroidal lesions similar to primary choroidal melanomas, however they are usually multifocal and show rapid growth [18].

10.4 Differential Diagnosis

Choroidal metastasis being predominantly amelanotic, its differential diagnoses include other amelanotic choroidal lesions such as amelanotic melanoma, amelanotinevus, hemangioma, peripheral exudative hemorrhagic chorioretinopathy (PEHCR), sclerochoroidal calcification, osteoma, lymphoma, choroidal granuloma, and other rare differentials including choroidal schwannoma and leiomyoma [26–28].

10.5 Investigations

Definitive diagnosis of choroidal metastasis may be difficult in cases without a history of primary malignancy. One important clinical feature is that, metastatic lesions tend to be more often multifocal (mean, 1.4–1.6) and bilateral (15–50%) in contrast to primary tumors. Diffuse lesions can be seen with breast cancer [7, 8, 19]. Multimodal imaging aids in establishing the diagnosis of choroidal metastasis in equivocal cases (Figs. 10.1 and 10.2).

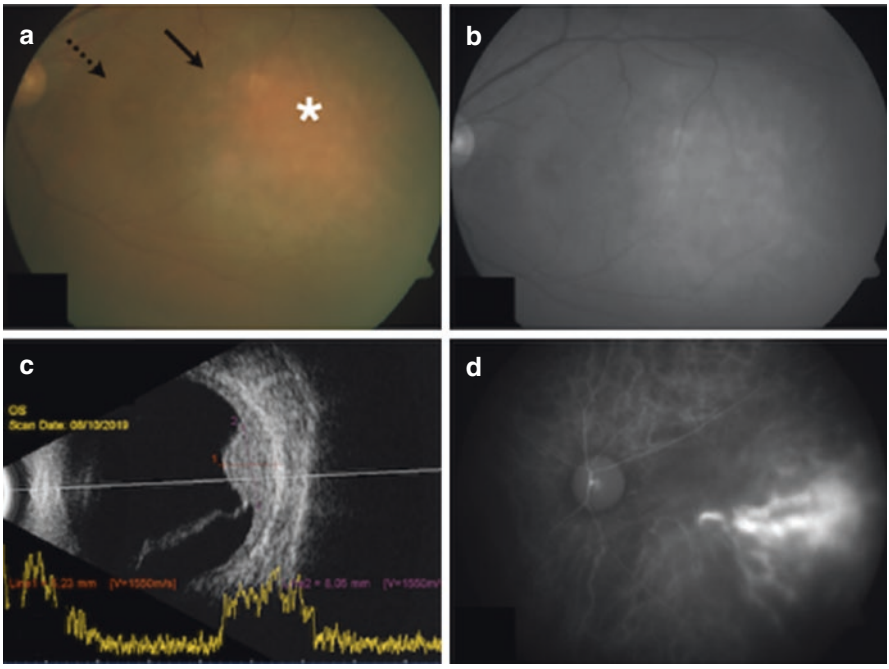

Fig. 10.1 (**a**) Color fundus photograph showing a 10 × 10 × 3 mm fairly well-defined dirty yellowish gray lesion (arrow) temporal to fovea with orange lipofuscin deposits (asterix). Subretinal fluid is seen to involve the fovea (dotted arrow); (**b**) hyperautofluorescence in seen in the area corresponding to the lipofuschin deposits; (**c**) ultrasonography of the choroidal metastatic lesion showing high surface echogenicity with heterogenous high internal echoes. Linear membranous echo corresponds to the exudative retinal detachment surrounding the lesion; (**d**) indocyanine green angiography shows absence of any vascular networks within the lesion and pooling of dye within the subretinal space

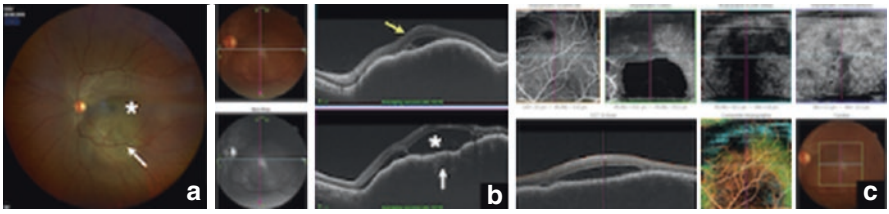

Fig. 10.2 (**a**) Color fundus photograph of 37-year-old lady on treatment for breast cancer, shows an yellowish subretinal lesion along the inferotemporal arcade (arrow) with subretinal fluid involving fovea (asterix); (**b**) OCT through the lesion shows a hyporeflective choroidal lesion with compression of overlying choriocapillaris and a "lumpy bumpy contour" of retinal pigment epithelium (arrow). There are multiple pockets of subretinal fluid (arrow). Inner retinal layers are intact; (**c**) OCT angiography through the lesion shows absence of normal choroidal vasculature or any abnormal vascular plexus

(a) ***Ultrasonography***

Evaluation of tumor surface and echogenicity, internal structure and vascularity by ultrasonography (USG) aids in distinguishing choroidal metastasis from other amelanotic lesions. In addition, the location and dimensions of the tumor can be assessed to monitor tumor progression or response to treatment [29]. On USG, choroidal metastasis appear as flat or slightly raised lesions with a hyperechoic tumor surface. They can also be multilobular and irregular [30, 31]. Subretinal fluid is usually evident and choroidal detachment is rarely seen [30–32]. Internally, the lesion is nonhomogenous with moderate to high echogenicity due to the heterogeneous tissue structure producing multiple interfaces of variable acoustic densities [30].

(b) ***Angiography***

Indocyanine green angiography (ICG) provides better assessment of choroidal tumors than fluorescein angiography (FA) in terms of delineation of the tumor margin, visibility of the choroidal and retinal vessels [29, 33, 34]. On fluorescein angiography, nearly all tumors appear hypofluorescent in early phase with heterogenous hyperfluorescence in late phase, with variable focal leakage [29]. In contrast, on ICG, choroidal metastasis appears hypocyanescent in early and late phases against an isocyanescent background. Dual circulation seen in choroidal melanomas is absent. As the lesion is better delineated on ICG, the extent of tumor may be larger than that evident on clinical examination [33, 34].

(c) ***Optical Coherence Tomography***

Enhanced depth imaging optical tomography (EDI-OCT) is a very useful tool for assessment of choroidal tumors and to distinguish various choroidal lesions. Most striking feature of choroidal metastasis is the irregular or "lumpy bumpy" anterior contour unlike choroidal melanoma, nevus or a hemangioma which have a dome-shaped smooth anterior surface. Subretinal fluid, compression of choriocapillaris overlying the lesion and posterior shadowing are other

features which are often present. Other changes include RPE abnormalities, alteration or loss of cone outer segment tips, ellipsoid zone of photoreceptors and external limiting membrane. Inner retina is usually normal. Intra retinal edema, loss of outer nuclear and plexiform layers, and subretinal lipofuscin deposits are much less commonly seen [35, 36].

OCT angiography (OCT-A) shows no flow within the lesion and absence of pathological blood flow in outer retinal layers unlike melanoma, hemangioma, and osteoma which show dense irregular vascularity within the lesion and increased flow in outer retinal layers as well [37].

(d) ***Autofluorescence***

Fundus autofluorescence detects lipofuscin and hence shows a heterogenous areas of hypo and hyper autofluorescence, which is not only present in choroidal metastasis but also seen with choroidal melanoma and hemangioma [38].

(e) ***Systemic evaluation***

In cases with no prior history of cancer, a detailed history followed by a complete physical examination helps in tailoring appropriate investigations to identify the site of primary tumor, such as mammogram, chest X ray, or whole-body positron emission tomography scan as indicated. When primary tumor is known, extent of metastatic disease should be assessed.

(f) ***Choroidal biopsy***

The only indication for biopsy from choroidal metastasis is when a thorough systemic evaluation fails to identify the primary tumor [19].

10.6 Treatment Modalities and Decision-Making

Various treatment modalities include systemic chemotherapy, radiotherapy in the form of external beam radiotherapy or plaque brachytherapy, focal therapy by transpupillary thermotherapy and photodynamic therapy and enucleation with latter reserved for unsalvageable eyes with intractable pain. Several factors which determine the treatment decision in a patient with choroidal metastasis include: number, size, location of choroidal metastatic foci, the nature, location and status of the primary tumor, presence of other metastatic foci in the body, age and life expectancy, feasibility for administering focal therapy or multimodality treatment, etc. Primary oncologist should always be involved in the decision-making process [4, 8, 19].

Small asymptomatic lesions may be observed without any treatment while continuing systemic treatment. Large symptomatic lesions can be treated with systemic therapeutics, external beam radiotherapy or plaque brachytherapy. Smaller lesions can be treated with photodynamic therapy and transpupillary thermotherapy [1, 2, 4].

In cases with long life expectancy, definitive treatment should be attempted and in those with short life expectancy palliative care aim toward maintaining the quality of life is the primary concern [8]. Treating the choroidal lesion to improve vision or retarding its deterioration has a role to play in both the aforementioned scenarios.

1. Systemic therapeutic agents

   This includes chemotherapy, hormonal therapy, and targeted molecular treatments. Choroidal metastases have shown partial to complete response with systemic treatment in lung and breast cancers and occasional cases of renal cell and prostate cancers [39–44].
2. Radiotherapy

   Radiotherapy can be delivered in the form of plaque brachytherapy, external beam radiotherapy, intensity modulated radiotherapy, stereotactic radiosurgery and proton beam radiotherapy. Complications are a concern and irradiation to macula and disc is avoided [8].
3. Focal therapy

   Photodynamic therapy (PDT) utilizes the property a photosensitizer dye verteporfin to produce free radical-mediated tumor destruction by a trifold mechanism of direct cell death, damage to tumor vasculature, and activation of immune mechanism against the tumor cells [45, 46]. PDT has shown to achieve tumor control and good visual acuity in eyes with choroidal metastatis [46]. Tumors close to optic disc, size greater than 4 mm in thickness and presence of bullous retinal detachments are not suitable for PDT [46]. Trans pupillary thermotherapy with diode laser also has been shown to be effective in treating choroidal metastasis [47].
4. Antivascular endothelial growth factor (VEGF) injections

   Harnessing the antiangiogenic property of anti-VEGFs have been used in choroidal metastasis from the breast, lung, and colon carcinomas with good response [2].

   Enucleation is reserved for eyes with untreatable disease to relieve intractable pain [1, 2].

10.7 Prognosis

Prognosis depends on the primary tumor, extent of metastasis, and treatment options available. Metastases from breast cancer have a favorable prognosis and metastases from lung and melanoma have the worst prognosis [1]. Metastasis from carcinoid tumor carries a good prognosis, and these tumors are known to remain dormant from months to years [1]. In general, however prognosis in patients with choroidal metastasis is quite poor with a median survival of 7 months. Utility of office-based procedures, anti-VEGF agents and radiotherapy lies in maintaining the visual acuity to improve quality of life [2].

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Leukemia and Eye

11

Arpita Maniar and Swathi Kaliki

11.1 Introduction

The term "leukemia" was coined by Virchow in 1845. The disease can involve practically every organ in the body, and the eye is no exception. Since the initial description of leukemic retinopathy by Liebreich in the 1860s, it has been shown that nearly all eye structures may be affected in leukemia patients [1]. Ophthalmic manifestations in acute leukemia range from 46 to 52% according to several studies [2–5]. In some patients with leukemia, ophthalmic signs can precede the systemic features and can help in early diagnosis of systemic leukemia. An ophthalmologist should be well-versed with ocular manifestations to ensure prompt referral and appropriate treatment.

11.2 Systemic Leukemia and Classification

Based on the rapidity of disease evolution, leukemias are classified into acute and chronic types. In acute leukemias, leukocyte precursors rapidly proliferate, producing severe anemia, hemorrhage and infection, and also infiltration of the liver, spleen, lymph nodes, and skin [6, 7]. Acute leukemias have low hemoglobin and platelet levels with higher white blood cell count. With chronic leukemia, the symptoms may not appear for years. Each type is further divided depending on the cell of origin into myeloid and lymphoid forms.

In acute myeloid leukemia (AML), malignant clones of immature myeloid cells proliferate and replace the normal bone marrow. When these immature blast cells are released in the blood circulation, they reach distant extramedullary sites

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including the eye and orbit [8]. Acute lymphocytic leukemia (ALL) is a malignant clonal disorder of the bone marrow lymphopoietic precursor cells. As they lack potential for differentiation and maturation, there is progressive accumulation of medullary and extramedullary lymphoblasts.

Chronic myelogenous leukemia or chronic myeloid leukemia (CML) is characterized by an uncontrolled proliferation of granulocyte cell line. It accounts for 20% of all leukemias affecting adults. The clinical manifestation changes as the disease passes through three stages: chronic, accelerated, and blast, with the blast stage being the most severe, mimicking acute leukemia (one-third behave as ALL; two-third behave as AML).

Chronic lymphocytic leukemia (chronic lymphoid leukemia, CLL) is the most common form of leukemia found in adults in Western countries [9]. CLL is a monoclonal disorder characterized by a progressive accumulation of dysfunctional lymphocytes. About 25–50% of patients are asymptomatic at the time of presentation.

11.3 Ocular Manifestations of Leukemia

Ocular involvement occurs in 9–90% of all leukemia patients and affects the retina most commonly [10, 11] (Table 11.1). This large difference in the prevalence of ocular involvement of leukemia is presumed to be due to difference in the age group of the study populations. Ocular manifestations can precede the systemic involvement or occur concurrently with diseased or relapsed state. The relationship between the prognosis of leukemia and ocular manifestations remains uncertain.

Leukemia can cause ocular manifestations. Ocular involvement in leukemia can be classified as specific—due to leukemic infiltration of ocular tissues), nonspecific (due to blood abnormalities like anemia, thrombocytopenia, and leukocytosis), or iatrogenic, complicated by chemotherapy [12].

In a study of orbital and ocular manifestations in patients with acute childhood leukemia, Russo et al. noted specific lesions in 66% of their 180 patients with AML, which were more severe in high-risk leukemia patients than in patients with standard risk leukemia. Higher frequency of leukemic relapses in the bone marrow and/or CNS was noted in patients with specific lesions (63%) compared to patients with nonspecific lesions (42%), and in patients without orbital or ocular lesions (29.2%). Overall, ocular manifestations are seen more commonly with AML than ALL (66.6% vs. 15.1%) [12].

Table 11.1 Ophthalmic manifestations of leukemia

Eyelids
Eyelid swelling/mass
Ptosis
Preseptal cellulitis
Conjunctiva
Atypical conjunctivitis
Conjunctival/caruncular mass
Peri-limbal infiltrates
Subconjunctival hemorrhage
Cornea and sclera
Corneal ulcer
Pannus
Scleritis
Anterior segment
Iridocyclitis
Pseudohypopyon
Iris neovascularization
Iris nodules
Retina
Dilated and tortuous veins
Hemorrhages (flame-shaped, dot-blot, intraretinal, subretinal, or subhyaloid)
Roth's spots
Cotton wool spots
Subretinal mass
Retinal detachment
Retinal pigment epithelial alterations
Optic disc and optic nerve
Papilledema
Optic nerve thickening
Choroid
Choroidal thickening or mass
Orbit
Proptosis
Dacryoadenitis
Dacryocystitis

11.4 Eyelid

Leukemic infiltration in eyelids can present as lid swelling, lid mass, ptosis or extremely rarely, a preseptal cellulitis [13–15]. Dermal infiltration of leukemic cells presenting as cellulitis is called Sweet's syndrome or acute febrile neutrophilic dermatosis. Sweet's syndrome is characterized by fever, neutrophilic leukocytosis, erythema, and tenderness of skin lesion responding well to corticosteroid therapy [16, 17]. Ptosis can be due to leukemic infiltration or secondary to CNS invasion or due to neurotoxic effects of chemotherapeutic agents [18].

11.5 Conjunctiva

Conjunctival involvement is seen in all types of leukemia [2, 19–22], more so with lymphocytic leukemia. Conjunctival involvement is usually in the form of subconjunctival hemorrhage. Direct infiltration of conjunctival tissue is rare [2, 19–21, 23–29]. It can present as conjunctival or caruncular mass or as peri-limbal infiltrates. Conjunctival involvement is usually considered as an early sign of relapse of previously treated disease.

11.6 Cornea and Sclera

Leukemic infiltrate can present extremely rarely as a corneal ulcer with iritis and pannus [30]. As cornea is an avascular structure, direct infiltration is rare. Scleral infiltration is generally perivascular in location, manifesting as scleritis.

11.7 Anterior Segment

Leukemic infiltration of the anterior segment of the eye is uncommon, found only in 0.5–2.5% cases of leukemic relapses [31]. When patients with a known history of leukemia present as "uveitis" or "atypical conjunctivitis," the possibility of anterior segment infiltration should be kept in mind. Slit lamp examination shows leukemic cells in the anterior chamber presenting as pseudohypopyon (Fig. 11.1) or uveitis. Neovascularization of the iris can be seen. The patient is usually put on steroids to contain inflammation and hence, the diagnosis is often delayed in the absence of known systemic disease. Cytopathological examination is required to confirm diagnosis [32].

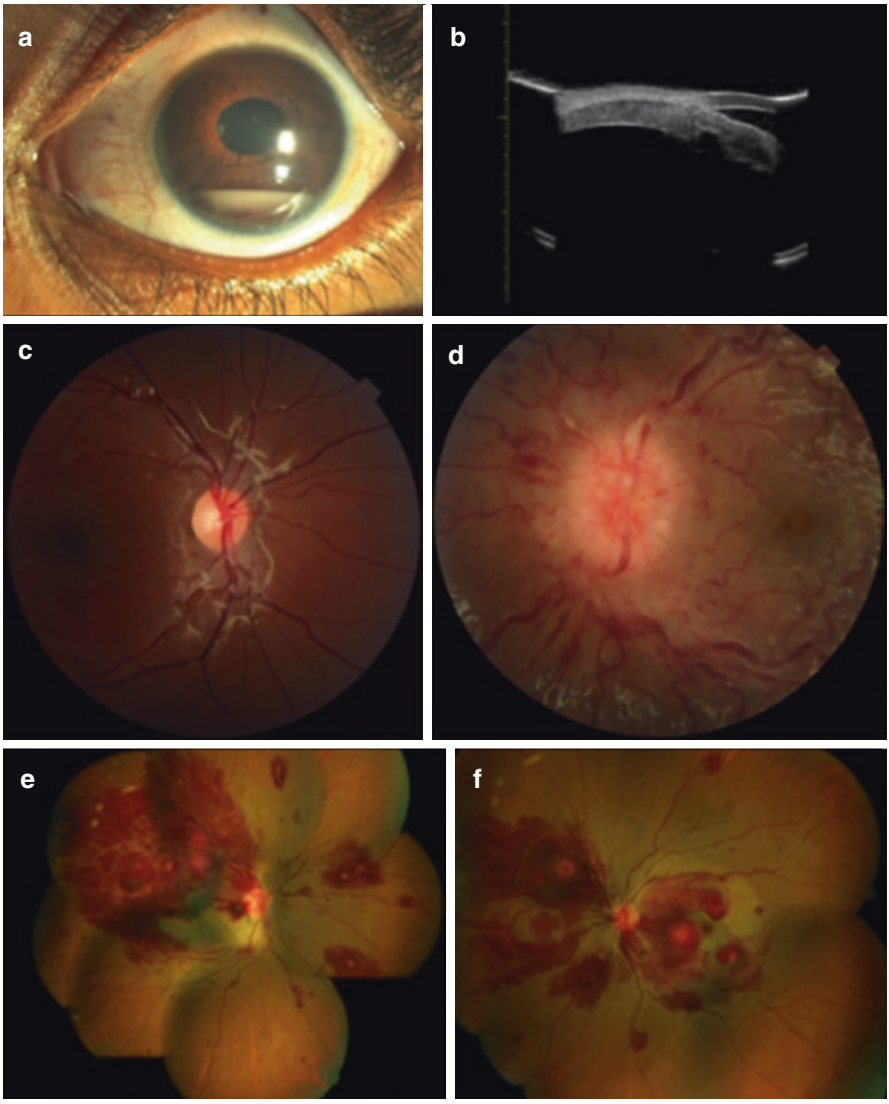

Fig. 11.1 Ocular manifestations of leukemia. An 8-year-old girl with a known history of acute lymphoblastic leukemia developed (**a**) pseudohypopyon in the left eye during the remission phase. The child had already completed the course of systemic chemotherapy 1 year back and had received external beam radiotherapy to the brain. (**b**) Ultrasound biomicroscopy also revealed thickened iris and ciliary body. An 8-year-old girl with a known history of acute lymphoblastic leukemia developed frontal headache, projectile vomiting, and outward deviation of left eye for 2 weeks. The child had already completed the course of systemic chemotherapy 2 years back. Fundus examination revealed (**c**) normal optic disc and retina in the right eye, and (**d**) infiltrative optic disc lesion in the left eye with increased tortuosity of retinal vessels and superficial flame-shaped retinal hemorrhages. A 22-year-old female presented with sudden decrease in vision in both eyes. On examination, the patient had (**e**, **f**) extensive intraretinal and subretinal hemorrhages in both eyes along with Roth spots. Peripheral blood smear revealed a diagnosis of acute myeloid leukemia

11.8 Retina

The posterior segment of the eye is more commonly involved than the anterior (89% versus 11%). Ocular involvement is more common due to the secondary changes (83%) compared to direct leukemic infiltration (17%) [3–5]. Duke-Elder [33] estimated that up to 90% of all persons with leukemia will show fundoscopic abnormalities at some point in the course of disease; one of the earliest changes is dilatation and tortuosity of veins, followed by hemorrhages at all levels of retina (Fig. 11.1) manifesting as flame-shaped, dot-blot, intraretinal, subretinal, or subhyaloid hemorrhage. These are secondary to anemia and thrombocytopenia, and in most instances, they are bilateral and symmetrical.

Occasionally, there are Roth's spots with central white area constituted by leukemic cells, platelet-fibrin aggregates or septic thrombi. Studies have shown that retinal manifestations are closely related to hemoglobin and platelet levels. Maintaining the hemoglobin level above 7 g/dL and platelet count above 50,000/mm^3 significantly reduces the risk of subhyaloid hemorrhage [4]. Cotton wool spots resulting from ischemia or leukemic infiltration are often seen. Leukemic infiltration can present as subretinal mass with associated retinal detachment. Serous retinal detachment is an uncommon presentation of new or relapsed leukemic disease. In most cases, the patient has known systemic disease. In cases with relapse, the time from remission to presentation with ocular symptoms can be as little as just a few weeks [6, 7, 34]. Retinal manifestations in general, are more common with AML than ALL.

11.9 Optic Disc and Optic Nerve

Optic disc infiltration is rarely seen in both acute and chronic leukemias. Studies have shown optic nerve involvement to be co-existent with central nervous system [CNS] leukemia and impart a poor prognosis. It can be an extension of CNS involvement causing direct infiltration of the optic nerve or it can affect the retrolaminar portion of the optic nerve resulting in passive nerve swelling causing papilledema [35]. Direct optic nerve infiltration is associated with typical perivascular infiltrate [36] which differentiates it from papilledema (Fig. 11.1). Symptoms of CNS leukemia are seizures, nausea, vomiting, lethargy [37]. Involvement of cranial nerves can cause blurred vision, strabismus, and diplopia. Vision is more likely compromised when there is retrolaminar optic nerve involvement [38].

11.10 Choroid

Choroidal infiltration as the initial manifestation is rare [39]. Leukemic infiltration of choroid can be seen as choroidal thickening and retinal pigmentary changes associated with serous retinal detachments due to decreased blood flow to the

choriocapillaries and resulting disruption of retinal pigment epithelium [40, 41]. Although retina is more commonly involved clinically, choroid shows consistent infiltration by leukemic cells on histopathological examination [29].

11.11 Orbit

Orbital involvement is seen in all types of leukemia, with AML being the commonest [42]. Infiltration of orbit and adnexa with immature cells of granulocytic series is known as granulocytic sarcoma or myeloid sarcoma of orbit (MS). Chromosomal abnormalities like t (8;21), inv (16) and 11q23 are the most frequent associations with MS. They comprise of MLL rearrangements seen most frequently in an infant with AML. Cytogenetically, core binding factor AML (which includes t (8; 21) and inv (16)) holds favorable prognosis but there are many conflicting reports [43]. It was previously termed as "chloroma" owing to its green color, attributed to the enzyme myeloperoxidase. The presenting signs and symptoms are due to mass effect or disruption of function of the infiltrated tissue. A rare variety of isolated, primary, or non-leukemic MS is known in which MS precedes AML, with bone marrow biopsy revealing no hematological disease; it is extremely rare with an incidence of 2/1,000,000 in adults [44]. Diagnosis is critical in these cases, where the systemic diagnosis is not established, and can often be delayed.

Orbital MS usually occurs in the first decade of life, average being 8.8 years. It mostly presents as an unilateral proptosis (Fig. 11.2), though rarely it can involve bilateral orbits [45–48]. This can be accompanied with eyelid edema, chemosis, and dystopia. Occasionally a firm rubbery mass can be palpated within the orbit or seen as a red-pink conjunctival mass. The patient may have associated pain and restricted ocular motility and diplopia. The initial picture can sometimes simulate an inflammatory process and an occasional history of trauma in children can be misleading. Other ominous diseases like rhabdomyosarcoma, lymphoma, and metastatic neuroblastoma can also present in a similar manner.

Diagnosis is established by orbital biopsy and bone marrow biopsy. Rarely leukemic cells can infiltrate the lacrimal gland presenting as lacrimal gland enlargement, mostly seen bilaterally [49, 50]. Once chemotherapy is initiated, the swelling subsides. Rarely leukemic infiltrate of the nasal and nasolacrimal duct mucosa can cause medial canthal mass and an acute dacryocystitis like picture. This is also known to resolve following initiation of chemotherapy.

The median survival of patients is 5 years (range, 0.1–24 years) after the diagnosis of orbital disease [51]. Primary cases of orbital MS in the pediatric population have better survival rates, ranging from 50% to 92%, depending on the stage of leukemia and treatment strategy.

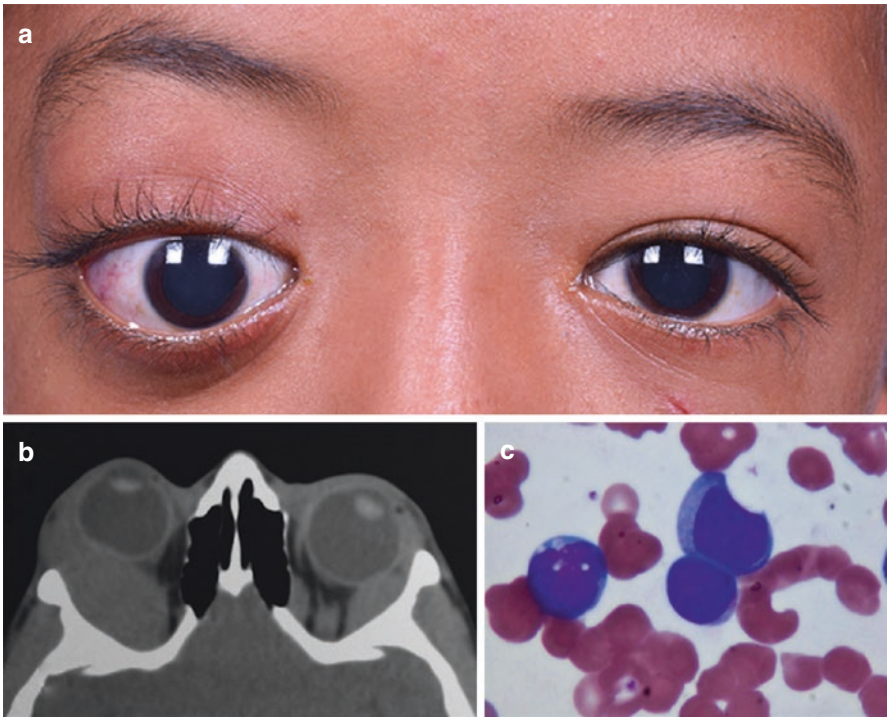

Fig. 11.2 Orbital manifestations of leukemia. A 7-year-old boy presented with painless progressive forward protrusion of the right eye since 25 days. He also had history of fever 10 days back, which subsided within 2 days with conservative treatment. There was no other significant systemic history. Examination of the child revealed (**a**) proptosis of the right eye with downward displacement of the globe. On palpation, a firm mass was noted in the superior orbit. There was also associated fullness of the left upper eyelid without any palpable mass. (**b**) Computed tomography of the orbit revealed well-defined homogenous mass in the superior and lateral aspects of both orbits. A clinical diagnosis of leukemia was made and peripheral blood smear was requested. (**c**) Peripheral blood smear was suggestive of acute leukemia showing leukocytosis with 72% circulating blasts and mild left shift. A final diagnosis of acute lymphocytic leukemia was made by flowcytometry

11.12 Opportunistic Infections

Patients with leukemia are immunosuppressed either due to diseased state, chemotherapy or due to bone marrow transplantation. As a result, they are susceptible to wide variety of bacterial, viral, fungal, and protozoan infections [10]. One of the most common viral agents in leukemic infection is cytomegalovirus. It invades the retina causing retinal necrosis, hemorrhage, vascular sheathing, and exudative retinal detachments. The fundus appearance can simulate leukemic infiltrates in these patients. In lesions involving the macula, severe visual loss can ensue.

11.13 Diagnosis and Imaging Findings

In an ophthalmology set-up, the diagnosis of leukemia is based on the clinical features, orbital imaging, peripheral blood smear, and bone marrow biopsy with immunohistochemistry and immunocytochemistry [52]. Orbital incisional biopsy may be required in cases that present with orbital mass and no history of systemic disease.

11.14 Computed Tomography (CT) Orbit

On CT scan of the orbit, the orbital leukemic mass presents as a well-defined homogenous contrast enhancing mass lesion which may be isodense to the surrounding muscles These lesions mold around the globe or around any orbital wall without causing any bony destruction [53]. The lesions are most often bilateral.

11.15 Magnetic Resonance Imaging (MRI) Orbit

On MRI orbit, the lesion may appear isointense on T1-weighted and hyperintense on T2-weighted images, and enhance intensely with contrast administration [53].

11.16 Peripheral Blood Smear

Peripheral blood smear shows high leucocyte count with immature blast cells and relative neutropenia.

11.17 Bone Marrow Biopsy

Acute leukemia is characterized by ≥20% marrow blasts (based on World Health Organization guidelines) or ≥ 30% marrow blasts (based on French-American-British Classification). Chronic leukemias are characterized by >70% marrow cellularity. In MS, marrow shows proliferation of blast cells positive for myeloperoxidase [54].

11.18 Orbital Incisional Biopsy

Histopathological examination shows numerous blast cells with high nuclear cytoplasmic ratio, round or oval nucleus with dispersed chromatin and less well-defined nucleoli. Cytoplasm is agranular with varying degree of basophilia. Immunohistochemistry shows reactivity with CD34, CD43, CD117, and lysozyme [54].

11.19 Treatment

After thorough systemic work-up of intraocular and orbital leukemia, systemic chemotherapy is the primary treatment. This is under the direction of medical oncologist and radiation oncologist. Ophthalmologist has limited role in recognizing the ocular and orbital manifestations and prompt referral.

The goal of treatment is to eliminate leukemic cells by using cytotoxic drugs. The basic strategy consists of three phases-remission induction phase, consolidation phase and maintenance therapy phase. Initial treatment of ALL uses combination of vincristine, doxorubicin, prednisone and L-asparagine until remission is obtained. Mercaptopurine is used as maintenance therapy for 2–3 years following remission. AML uses daunorubicin, cytarabine, and thioguanine to obtain induction and remission. If chemotherapy is not an option or if the ocular disease is not responsive, ocular radiation may be implemented. The dose of external beam radiotherapy is usually 20 Gy delivered at fractions of 1.5–2 Gy daily [10, 55].

If left untreated, leukemic ocular infiltrative disease may cause significant visual loss; however, it is usually very responsive to chemotherapy, local radiation treatment to the eye, or a combination of both.

Despite the advances in chemotherapeutic regimens, an allogenic bone marrow transplantation from a matched family donor still remains the best long-term option that may provide a remission-free survival for most patients [56].

11.20 Conclusion

In conclusion, an ophthalmologist must be aware of ocular and orbital manifestations of leukemia. Timely referral to an oncologist can be lifesaving in these cases.

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Orbital Tumors

12

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Tumors affecting the orbit include benign and malignant neoplasms arising from the various structures in the orbit including the blood vessels, nerves, bones, orbital fat, and other soft tissues. The first step in the management of orbital tumors is to differentiate the malignant tumors from the benign ones. A thorough clinical evaluation, aided by ancillary tests including imaging and biopsy, when necessary, can lead to an accurate diagnosis. Treatment of these tumors requires a basic knowledge of their biological behavior and their response to the currently available therapeutic modalities including surgery, chemotherapy, immunotherapy and radiotherapy. In the following chapter, some of the benign and malignant tumors of the orbit (Table 12.1) and their management are discussed.

12.1 Orbital Dermoid Cyst

Dermoid cyst is the most common orbital cystic tumor [1, 2]. They arise at the site of bony sutures secondary to the entrapment of the surface epithelium in the sutures during embryogenesis. The most frequent location is the superotemporal orbital rim (external angular dermoid), followed by the superonasal orbital rim (internal angular dermoid). In some instances, a dermoid cyst can have both extraorbital and intraorbital component connected through a defect in the bone, called as the dumbbell dermoid. Intraosseous dermoids can occur less frequently.

Anterior dermoids present as a well-circumscribed, firm, slow-growing subcutaneous mass (Fig. 12.1a–f). Dermoid cyst can also occur in the deeper orbital soft

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Table 12.1 Benign and malignant tumors of the orbit

Tumors of the orbit	Benign	Malignant
1. Cystic tumors	Orbital dermoid cyst Orbital teratomas Orbital mucocele	
2. Vascular tumors	Orbital capillary hemangioma Orbital cavernous hemangioma Orbital lymphangioma Orbital varix	Orbital hemangiopericytoma Orbital angiosarcoma Orbital glomus tumor
3. Peripheral nerve tumors	Orbital neurilemmoma Orbital neurofibroma Orbital paraganglioma	Orbital malignant peripheral nerve sheath tumor Orbital alveolar soft part sarcoma
4. Optic nerve and meningeal tumors	Optic nerve glioma Optic nerve sheath meningioma Orbital sphenoid wing meningioma	Optic nerve malignant astrocytoma Orbital neuroblastoma
5. Myogenic tumors	Orbital leiomyoma	Orbital malignant rhabdoid tumor Orbital rhabdomyosarcoma Orbital leiomysosarcoma
6. Fibrocytic tumors	Orbital fibroma Orbital solitary fibrous tumor Orbital myxofibroma	Orbital fibrosarcoma
7. Osseous and cartilaginous tumors	Orbital osteoma Orbital fibrous dysplasia Orbital ossifying fibroma Orbital giant cell reparative granuloma Orbital cartilaginous chondroma	Orbital osteosarcoma Orbital chondrosarcoma
8. Lipomatous tumors	Orbital dermolipoma Orbital lipoma	Orbital liposarcoma
9. Histiocytic tumors	Orbital juvenile xanthogranuloma Orbital Langerhans' cell histiocytosis Orbital Erdheim–Chester disease Orbital Rosai–Dorfman disease	
10. Lacrimal gland tumors	Lacrimal gland pleomorphic adenoma	Lacrimal gland pleomorphic adenocarcinoma Lacrimal gland adenoid cystic carcinoma
11. Lymphoid and leukemic tumors		Orbital non-Hodgkin's lymphoma Orbital plasmacytoma Orbital plasmablastic lymphoma Orbital Burkitt lymphoma
12. Metastatic tumors		
13. Secondary tumors		

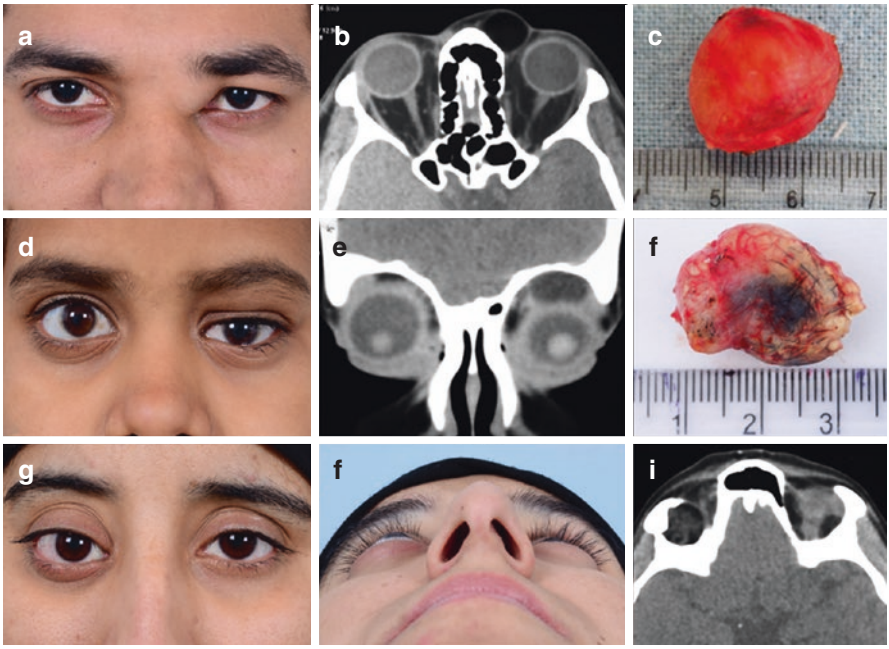

Fig. 12.1 Orbital dermoid cyst. (**a**) A 28-year-old male with an internal angular dermoid left orbit. (**b**) Axial CT orbit showing a cystic lesion in the left superomedial orbit. (**c**) Gross appearance of the intact dermoid of the same patient showing a well-circumscribed encapsulated lesion. (**d**) A 10-year-old female with a large dermoid in the superior left orbit. (**e**) Coronal CT orbit demonstrates downward displacement of the left globe by the cystic lesion (hypoglobus). (**f**) Gross appearance of the large dermoid with presence of hair on the tumor surface. (**g**) A 19-year-old female with right hypoglobus. (**h**) Worm's eye view shows right proptosis. (**i**) Axial CT orbit reveals the presence of a large deep orbital cystic lesion

tissues which causes proptosis (Fig. 12.1g–i). Sometimes, superficial dermoids rupture spontaneously or after trauma and produce an inflammatory reaction resembling cellulitis or dacryoadenitis. Rarely, squamous cell carcinoma may arise within these cysts.

The classic dermoid cyst can usually be diagnosed based on the clinical appearance of a subcutaneous firm mass located at the orbital rim. A computed tomography scan is preferred to assess any associated bony defects. It shows a cystic lesion with enhancement of the wall, but no significant enhancement of the lumen [2]. A bony defect is evident in dumbbell dermoid, and fluid levels and calcification are frequently seen. Histopathologically, an orbital dermoid cyst is lined by surface epithelium [2]. The cyst wall contains dermal appendages including sebaceous glands and sweat glands. The cyst lumen contains putty-like material composed of desquamated epithelial cells, sebaceous material, and hair.

The management of orbital dermoid cyst depends on the size, location, and symptoms. Asymptomatic small dermoids can be simply observed, while symptomatic large ones require complete surgical excision. Most anterior dermoid cysts can

be excised by anterior orbitotomy. Deeper and larger cysts require a lateral orbitotomy. Care should be taken to avoid surgical rupture of the cyst as its contents can incite an inflammatory reaction. If rupture occurs, copious irrigation and instillation of antibiotics or corticosteroids is advised.

12.2 Orbital Teratomatous Cyst

Teratoma is a congenital, multicystic mass arising from the primitive pluripotent germ cells that contains histologic structures representing all three embryonic germ layers: ectoderm, mesoderm, and endoderm [3]. Orbital teratoma is an uncommon condition that is almost always unilateral. Teratomas of the orbit are generally benign, and presents with severe unilateral proptosis at birth. The proptosis may increase over the first few days, and the resultant lid swelling and globe compression can lead to visual loss and corneal exposure. Larger lesions cause severe orbital disfigurement. The tumor can invade into the adjacent orbital tissue and extend posteriorly into the temporal fossa. Orbital teratoma should be ruled out in any neonate presenting with a large orbital mass.

On imaging of a teratoma, the scans demonstrate an enlarged orbit with a multiloculated mass. Histopathologically, a teratoma typically contains clear cysts lined by either epidermis or mucosal epithelium. A variety of tissues can be seen within the tumor including cerebral tissue, hyaline cartilage, choroid plexus, or rarely, well-differentiated tissues resembling a complete fetus or a portion of a fetus in the orbit [4].

Orbital exenteration is generally done in advanced cases with orbital disfigurement. Smaller orbital teratomas can be removed surgically, with preservation of the eye [5]. Aspiration of the fluid from a larger cyst to decrease the size of the mass allows complete surgical excision [6].

12.3 Orbital Mucocele

Orbital mucocele is an expansile lesion resulting from accumulation of mucoid secretion of a chronically inflamed paranasal sinus secondary to obstruction of the sinus ostium. It is often painless and demonstrates a fairly rapid growth. When a mucocele becomes secondarily infected, it is called a mucopyocele. It generally occurs in adults, but it is sometimes seen in children in association with cystic fibrosis. Most commonly, frontal sinus is involved (60–90%) which produces progressive proptosis that tends to displace the globe downward (Fig. 12.2a–d) [7]. Ethmoidal mucocele is less common, and maxillary and sphenoidal sinus involvement is very rare. The mass is generally visible and it is fluctuant to palpation beneath the orbital rim.

On imaging, a mucocele demonstrates opacification of the affected sinus and thickening of the mucosal lining, with erosion of the adjacent orbital bones [8]. Histopathologically, a mucocele is lined by the sinus mucosa, pseudostratified

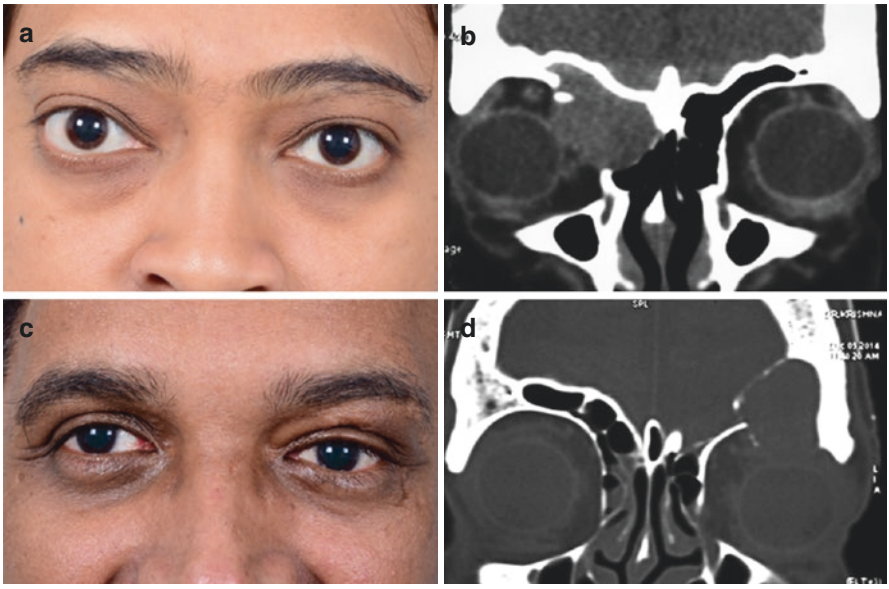

Fig. 12.2 Orbital mucocele. (**a**) A 32-year-old female with right proptosis. (**b**) Coronal CT orbit reveals an irregular homogenous lesion in the superomedial orbit with opacification of both ethmoid and frontal sinuses. (**c**) A 45-year-old man with left hypoglobus. (**d**) Coronal CT orbit shows left superior mass lesion with complete opacification of the left frontal sinus

columnar epithelium, with infiltration by the chronic inflammatory cells. The lumen contains mucous or pus.

The management of mucocele is complete surgical excision of the mucosal wall with marsupialization to avoid recurrence. Antibiotics to cover both aerobic and anaerobic bacteria should be administered before and after surgery.

12.4 Orbital Capillary Hemangioma

Periocular capillary hemangioma of infancy (strawberry hemangioma) can be superficial (located anterior to the orbital septum) or deep (located posterior to the septum). About 7% of periocular capillary hemangiomas arise posterior to the orbital septum [9]. Regarding its etiopathogenesis, due to the similar immunohistochemical characteristics with the placenta, it is believed that infantile hemangiomas could be of placental origin [10, 11]. Typically, capillary hemangiomas are not present at birth, but develop in the first few months of life and continue to enlarge over the first 6–12 months after the first year (proliferative phase), with 90% resolution occurring within 8 years of life (involutional phase). When located deeper within the orbit, it presents as progressive proptosis, which becomes more pronounced when the child strains or cries (Fig. 12.3a, b). In a child with proptosis, the diagnosis of orbital capillary hemangioma is more evident when associated with hemangioma

Fig. 12.3 Orbital capillary hemangioma. (**a**) A 19-month-old male with right upper lid fullness and mild right proptosis. (**b**) With crying, the fullness in the right upper lid increases with a prominent bulge in the right temporal fossa. (**c**) Coronal T2-weighted post-contrast MRI orbit reveals the presence of a diffuse mass in the deep right orbit which enhances well with contrast

of the eyelid. Lesions greater than 1 cm in diameter are more likely to cause complications, with an incidence of amblyopia upto 60% [9, 12]. Periocular capillary hemangioma of infancy may be seen in association with Kasabach–Merritt syndrome, which is characterized by large visceral hemangiomas, platelet entrapment, and thrombocytopenia.

On imaging, orbital capillary hemangiomas appear as a well-circumscribed homogenous soft tissue mass without adjacent bone destruction (Fig. 12.3c). With the use of contrast, the lesion shows enhancement. Histopathologically, an orbital capillary hemangioma is composed of lobules of proliferating small endothelially lined vascular spaces separated by thin fibrous septa.

Most tumors can be managed by observation, although those causing amblyopia should be treated with refraction and occlusive patching. Oral use or local injection of corticosteroids can hasten regression of the lesion. Oral prednisolone 2–4 mg/kg/day for 2–4 weeks is administered under the supervision of a pediatrician. The major risks include adrenal suppression and growth retardation. Intralesional corticosteroids are administered as a combination of triamcinolone 1 mL (40 mg/mL) and dexamethasone 1 mL (4 mg/mL). Interferon α-2a upto three million units/m^2 of body surface area can be given as daily subcutaneous injections for life-threatening or vision-threatening hemangiomas to cause complete regression of the lesions [13–15]. Propranolol is a nonselective beta blocker that can be used systemically for orbital capillary hemangiomas with high efficacy [16]. The recommended dosage of oral propranolol is 2–3 mg/kg/day until regression and additionally for a month to prevent recurrence. Surgical treatment is rarely necessary, but can be considered in those with visual symptoms not responding to pharmacologic modalities.

12.5 Orbital Schwannoma

Schwannoma (neurilemoma) is a benign, encapsulated tumor that arises from the cells forming the peripheral nerve sheath (Schwann cells). It develops as an eccentric growth from the nerves and causes proptosis (Fig. 12.4a–d). They are usually solitary lesions, and occur between the ages of 20 and 50 years [17]. Neurilemmomas

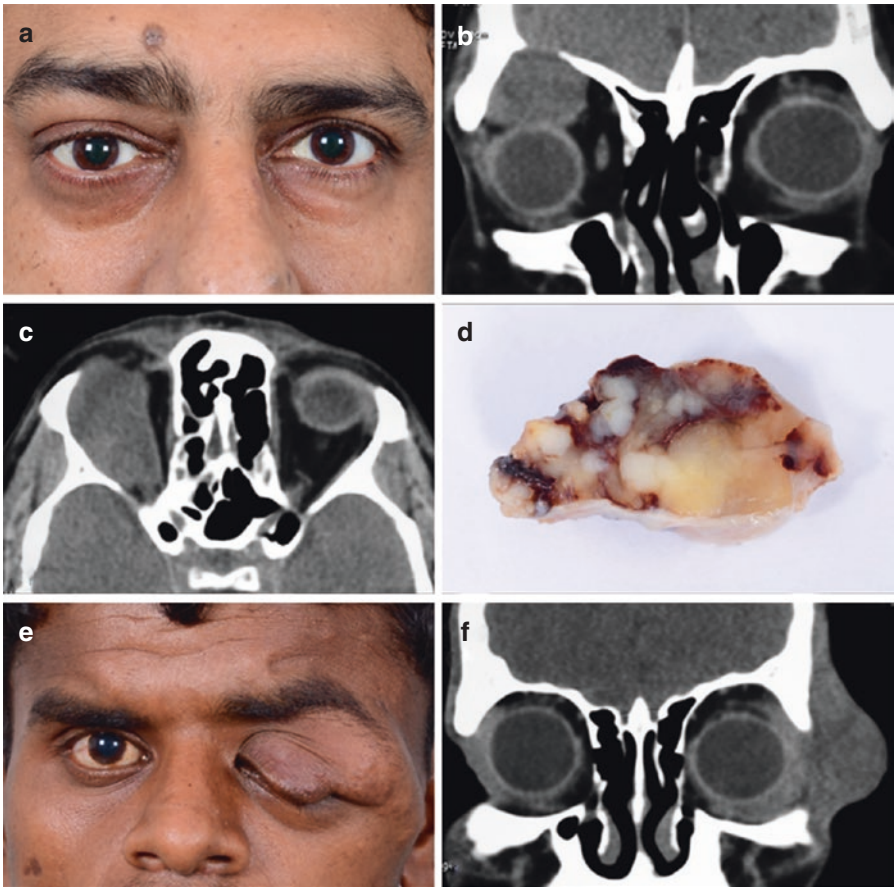

Fig. 12.4 Orbital peripheral nerve tumors. (**a**) A 48-year-old male with right proptosis. (**b**) Coronal CT orbit shows right superior orbital homogenous lesion. (**c**) Axial CT orbit shows an irregular homogenous mass extending upto the posterior orbit. (**d**) Gross appearance of an orbital schwannoma, multi-lobulated with a capsule. (**e**) A 20-year-old male with left orbital plexiform neurofibromatosis. (**f**) Coronal CT orbit illustrates left temporal fossa homogenous mass lesion with minimal orbital involvement

usually form along the course of the supraorbital or supratrochlear nerve, and less frequently along the infraorbital nerve.

On imaging, a neurilemmoma appears as an ovoid to elongated extraconal mass, although intraconal neurilemmomas also occur. Large cystoid spaces are sometimes present within the lesion. On histopathology, a schwannoma consists of benign proliferating Schwann cells, with Antoni A pattern (ribbons or fascicles of spindle cells) interspersed with Antoni B pattern (ovoid clear cells).

Surgical excision offers complete cure. Recurrences are common when the tumor is incompletely excised [21]. However, if the tumor has an extension upto the orbital

apex, the apical component is best left alone to avoid injury to the structures passing through the orbital apex and superior orbital fissure.

12.6 Orbital Neurofibroma

Neurofibromas in the orbit can occur in three different forms-as a solitary tumor, as a diffuse infiltration, and as a plexiform lesion. Isolated, solitary neurofibromas are generally not associated with neurofibromatosis. Diffuse neurofibromas occur as a part of the systemic syndrome in only 10% of patients [18]. On the other hand, plexiform lesions are typically suggestive of neurofibromatosis type 1. Patients with neurofibromatosis can have congenital absence of the sphenoid bone that can produce a pulsating proptosis.

Localized neurofibroma are solitary well-circumscribed tumors within the orbit that can produce proptosis and optic nerve compression. Diffuse and plexiform neurofibromas are seen in the first decade of life and cause the typical S-shaped curve to the upper eyelid due to the subcutaneous involvement, but the plexiform variant can cause severe disfigurement and morbidity secondary to involvement of the orbit, eyelids, intraocular structures, and maxillofacial region (Fig. 12.4e, f).

On imaging, a neurofibroma appears as a homogenous mass that can be either well-circumscribed or diffuse. Plexiform neurofibromas additionally show periorbital involvement. Histopathologically, it consists of Schwann cells and endoneural fibroblasts with distinct perineural sheath separating the axons within the involved nerve.

Symptomatic solitary tumors are managed by complete excision. Diffuse and plexiform lesions cannot be completely excised and hence, debulking is done to offer relief from compressive symptoms or for cosmesis.

12.7 Optic Nerve Glioma

Optic nerve gliomas are low-grade pilocytic (juvenile) astrocytomas that resemble those which occur elsewhere in the central nervous system. Although most of these are isolated lesions, an association with neurofibromatosis type1 (NF1) must be looked for, as the clinical behavior is different in this context. Approximately, 10% of patients with NF1 have optic pathway gliomas, and 30% of patients presenting with optic nerve gliomas have NF1 [19]. An optic nerve glioma in the background of NF1 offers a favorable prognosis [20]. Most lesions present in the first decade of life with a female preponderance. At the time of diagnosis, gliomas frequently involve the chiasma. Clinically, the usual presentations are proptosis, visual loss, motility restriction, optic atrophy, and unilateral disc edema. These tumors show an indolent growth or are non-progressive, with little or no change in the clinical status over long periods [21].

On imaging, optic nerve glioma has a characteristic ovoid appearance along the course of the optic nerve (Fig. 12.5a, b). A characteristic kink in the midportion of

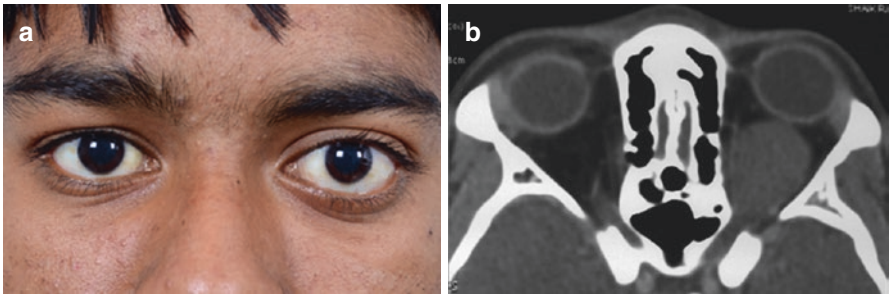

Fig. 12.5 Optic nerve glioma. (**a**) An 18-year-old male with left axial proptosis. (**b**) Axial CT orbit shows a homogenous ovoid mass along the course of the optic nerve extending upto the posterior orbit

the tumor is often present. Gadolinium-enhanced MRI is the best modality for diagnosis, monitoring disease progression, and response to treatment. Histopathologically, the tumor is composed of fibrillary astrocytes, which may develop many brightly eosinophilic nodes (called Rosenthal fibers) in their processes. Rarely, malignant degenerative features or mitoses are observed.

The general principle of management is essentially conservative. The patient is followed up periodically for vision, pupil, fundus, and visual field examination, while the tumor is monitored by imaging. Treatment is recommended in tumors which are either large or rapidly progressive. Patients in the younger age group are known to have a higher chance for progression [22]. In children less than 10 years of age, chemotherapy is the treatment of choice. In older children and adults, excision is performed when the tumor is still confined in the prechiasmatic optic nerve. With significant chiasmal or parachiasmal involvement and progressive growth, radiotherapy is treatment of choice [23].

12.8 Orbital Meningioma

Meningiomas affecting the ocular and orbital structures can arise from the optic nerve sheath or intracranially. Majority of the meningiomas involving the orbit are extensions from intracranial sites, most commonly the sphenoid wing. True primary optic nerve sheath meningiomas are rare. About 90% of the primary optic nerve sheath meningiomas originate within the intraorbital nerve sheath, while less than 10% are intracanalicular in origin [24].

Optic nerve sheath meningiomas typically affect middle-aged women (Fig. 12.6a, b). Bilateral and multifocal optic nerve sheath meningiomas are more likely to present in childhood in association with neurofibromatosis type 2 [25]. Visual loss is often seen, especially from tumors of the optic canal which can cause early visual disturbances. The classical triad of progressive visual loss, optic nerve atrophy, and presence of opticocilliary shunt vessels is pathognomonic of an optic nerve sheath meningiomas. Frequently, there is evidence of an underlying optic neuropathy, as

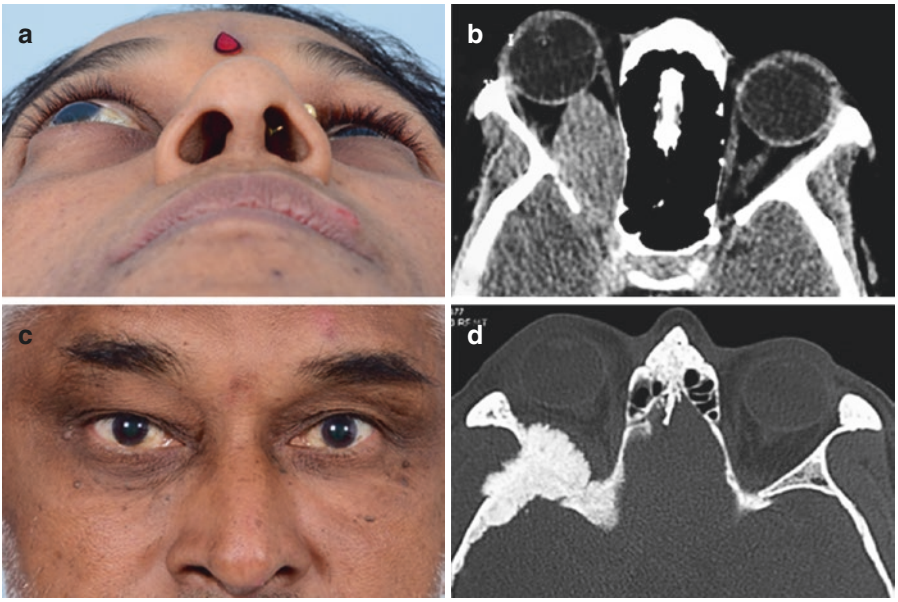

Fig. 12.6 Orbital meningioma. (**a**) A 46-year-old female with Worm's eye view demonstrates left proptosis. (**b**) Axial CT orbit shows a homogenous fusiform mass along the course of the optic nerve extending with optic foramen widening. (**c**) A 52-year-old male with right proptosis and bulging of right temporal fossa. (**d**) Axial CT orbit shows left sphenoidal wing hyperostosis

also peripapillary hemorrhages and disc swelling. Proptosis is present in most patients. Sphenoid wing meningioma arises from the arachnoid lining the sphenoid bones and secondarily invades the orbit. Like optic nerve sheath meningioma, the sphenoidal wing meningioma is also seen in middle-aged women. It presents as a slowly progressive abaxial proptosis, enlargement of the temporal fossa, and cranial nerve palsies (Fig. 12.6c, d). Visual disturbances occur late in the disease when the tumor compresses the optic nerve at the optic canal.

On imaging, optic nerve sheath meningiomas show fusiform enlargement in the arachnoid with a relatively normal optic nerve in its center. Areas of calcification are often seen in the tumors. On the other hand, a sphenoidal wing meningioma causes the characteristic bony hyperostosis, with a soft tissue tumor mass extending into the orbit, temporal fossa, and cranial cavity [25–27]. Histopathologically, meningiomas arise from meningothelial cap cells of the arachnoid with occasionally dispersed calcification (psammoma bodies).

For optic nerve sheath meningiomas, observation alone suffices where there is no significant visual deterioration, especially when the tumor is located at the orbital apex. Surgical resection is offered to patients with aggressive tumors with intracranial extension, in order to prevent spread to the contralateral optic nerve. The

surgical approach is either by a lateral orbitotomy, or via transcranial route by a neurosurgeon. Various new techniques of conformal radiotherapy are now used in the treatment of optic nerve sheath meningiomas including intensity-modulated radiotherapy (IMRT) and stereotactic fractionated radiotherapy (SFRT) [27]. Cyberknife surgery and proton beam therapy are now increasingly being used with good tumor control. Meningioma of the sphenoid wing is managed by surgical debulking in conjunction with a neurosurgical team, and subsequent postoperative radiation for the residual disease.

12.9 Orbital Rhabdomyosarcoma

Rhabdomyosarcoma is the most common primary orbital malignant tumor in the pediatric age group. Orbital rhabdomyosarcoma is primarily a disease of young children with a mean age at diagnosis of 10 years [28]. The presenting features include proptosis, globe displacement, ptosis, conjunctival and eyelid swelling, and a palpable orbital mass (Fig. 12.7a, b). Rhabdomyosarcoma is an aggressive neoplasm that can invade orbital bone and even extend into the cranial cavity. Metastasis most commonly occurs to lung and bone via hematogenous dissemination.

On imaging, rhabdomyosarcoma appears as a moderately well-circumscribed orbital mass that is limited to soft tissue without the involvement of extraocular muscles. Less frequently, it can erode into the adjacent orbital bones or sinuses. The tumor shows enhancement with contrast material. Histopathologically, the tumor is composed of cells that resemble histologically to striated muscle in various stages of embryogenesis. Four different histopathological types can be seen, and embryonal rhabdomyosarcoma is the most common variant in the orbit.

The management of orbital rhabdomyosarcoma has evolved over the last two decades. A multimodal management including a combination of surgery, irradiation, and chemotherapy is shown to give excellent results. Intergroup Rhabdomyosarcoma Study Group IV currently recommends a specific regimen

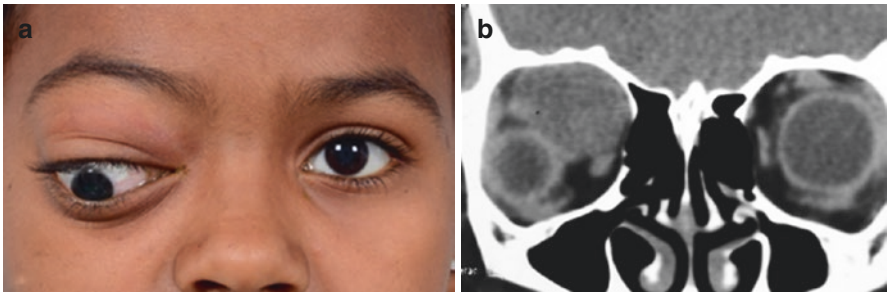

Fig. 12.7 Orbital rhabdomyosarcoma. (**a**) A 10-year-old female with right hypoglobus. (**b**) Coronal CT shows a large right superomedial orbital lesion displacing the globe downward and outward

including a combination of radiation and chemotherapy based on the tumor staging. An incisional biopsy is first performed to establish a histopathologic diagnosis, followed by chemotherapy consisting of vincristine, etoposide, cyclophosphamide/and ifosfamide [29–31]. Radiation is generally sandwiched between chemotherapy cycles, as deemed appropriate by the treating radiation oncologist.

12.10 Orbital Dermolipoma

Dermolipoma is a congenital lesion that is often detected in adulthood as the lesion tends to be very small in children. It is a choristoma and is seen as a pink-yellow mass in the superotemporal conjunctival fornix. It is a sessile, soft to firm mass, most commonly unilateral. It accounts for 3% of all orbital lesions [1]. Fine hair is sometimes found on the tumor surface (Fig. 12.8a, b). Dermolipoma is sometimes seen in association with Goldenhar syndrome.

On imaging, a dermolipoma appears as a well-circumscribed lesion, with its posterior border not very distinct from the superotemporal orbital fat and the lacrimal gland. Histopathologically, a dermolipoma is lined by stratified squamous epithelium, made up of mature fat, pilosebaceous units, and glandular acini.

Dermolipoma is managed by observation when small and asymptomatic. Larger tumors are excised by a conjunctival approach by unroofing the lesion, with care taken to avoid injury to the lacrimal ducts and levator aponeurosis. After excision of the lesion, the conjunctiva overlying it can be easily reconstructed.

12.11 Lacrimal Gland Pleomorphic Adenoma

Pleomorphic adenoma (benign mixed tumor) accounts for accounts for 50% of all the epithelial tumors of the lacrimal gland. It is a disease of the young age, and it usually arises from the orbital lobe of the lacrimal gland. Pleomorphic adenoma

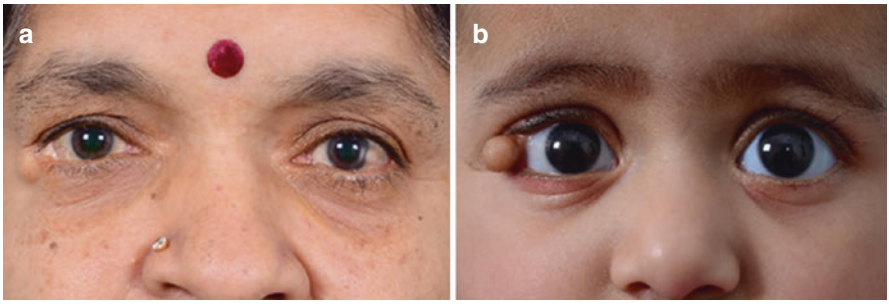

Fig. 12.8 Orbital dermolipoma. (**a**) A 63-year-old female with right dermolipoma, right lateral canthal cutaneous choristoma, left conjunctival dermoid (patient also had preauricular skin tags, all features suggestive of Goldenhar syndrome). (**b**) A 2-year-old female with a large right dermolipoma with fine hair on the tumor surface

presents as a unilateral progressive mass in the superotemporal orbit. It is generally painless and produces proptosis as it enlarges and grows into the orbit posteriorly. It causes downward displacement of eyeball and lid swelling (Fig. 12.9a, b). Rarely, the tumor demonstrates malignant transformation (pleomorphic adenocarcinoma).

On imaging, the tumor is seen as a well-circumscribed mass in the lacrimal gland fossa with an irregular surface. There is generally an associated pressure indentation of the lacrimal gland fossa, but without erosion of the orbital bones. The histopathology of pleomorphic adenoma reveals a combination of benign epithelial elements and mesenchymal elements, consisting of ducts, squamous cells, myxoid material, and cartilagenous tissue.

The diagnosis of pleomorphic adenoma of the lacrimal gland can be generally made based on the clinical and radiological findings. When the diagnosis is evident, an incisional biopsy is best avoided to avoid breaching the capsule. The tumor is excised with an intact capsule by a superolateral orbitotomy through an eyelid crease or a sub-brow incision with a trans-septal approach.

12.12 Adenoid Cystic Carcinoma of the Lacrimal Gland

Adenoid cystic carcinoma of the lacrimal gland is the most common malignant epithelial neoplasm of the lacrimal gland. The age at diagnosis has a bimodal pattern, with patients generally belonging to the first to second decade or the sixth to seventh decade. Periocular pain is frequently reported due to perineural invasion by the tumor. The tumor causes abaxial proptosis, with progressive downward and medial displacement of the globe (Fig. 12.9c, d).

Generally, CT demonstrates a round or elongated soft tissue mass with bone erosion, and moderate contrast enhancement. Histopathologically, the tumor is characterized by solid areas or cords of bland-appearing malignant epithelial cells arranged in various patterns. The typical pattern with cystic spaces lined by malignant cells is called the "Swiss cheese" pattern. Adenoid cystic carcinoma of the lacrimal gland has been subdivided into several histopathologic subtypes, namely cribriform, sclerosing, basaloid, comedocarcinoma, and tubular types [32].

Lacrimal gland adenocarcinoma is known to carry a dismal prognosis with fatality up to 60–80%. The tumor has a tendency for perineural infiltration and bone invasion, making it difficult to achieve surgically clear margins. Furthermore, distant metastasis occurs in about half of the patients. The rarity of this cancer makes it difficult to study the efficacy of various therapeutic modalities. Orbital exenteration is the widely accepted form of treatment. Neoadjuvant chemotherapy by the intra-arterial route or as systemic therapy has also been tried as a part of multimodal management [33]. Adjuvant radiotherapy for lacrimal gland carcinomas is indicated in all cases. Stereotactic radiotherapy, intensity-modulated radiation therapy (IMRT) technique, 3D conformal radiotherapy or proton radiotherapy deliver radiation more efficiently to the tumor site and reduce side effects to the normal orbital structures [34]. For those with a limited disease extent, tumor excision through lateral orbitotomy followed by adjuvant radiotherapy has achieved eye and vision salvage.

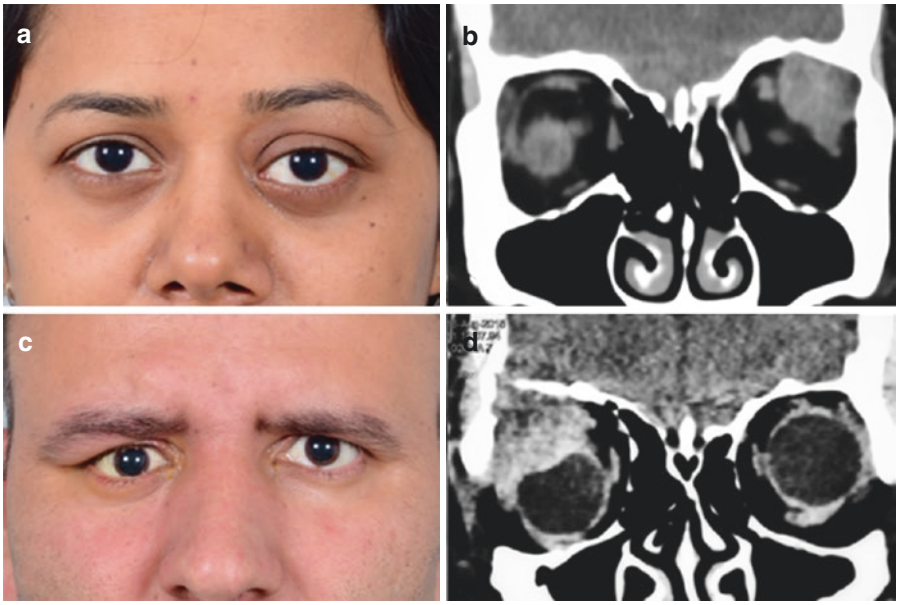

Fig. 12.9 Lacrimal gland tumors. (**a**) An 18-year-old female with left proptosis. (**b**) Coronal CT orbit reveals a left supertemporal homogenous orbital mass in the lacrimal fossa, with bony indentation and no bone destruction. (**c**) A 38-year-old male with right proptosis complaining of severe diplopia in right lateral gaze. (**d**) Coronal CT orbit shows a nonhomogenous ill-defined mass lesion in the right lacrimal fossa with evidence of bone destruction

12.13 Orbital Lymphoma

Lymphomas of the ocular adnexa constitute approximately 8–10% of all extranodal lymphomas. Orbital lymphoma is the most common orbital lymphoproliferative lesion, which form a spectrum ranging from reactive lymphoid hyperplasia to lymphomas. These lesions can involve the conjunctiva, eyelids, lacrimal glands, extraocular muscles, orbital soft tissue, or lacrimal sac, either individually or in combination.

Orbital lymphoma is a disease that occurs in the middle-age and the elderly. It is most commonly unilateral, although bilateral involvement is also known. Conjunctival lymphoma presents as a well-circumscribed "salmon-patch," while other orbital lymphomas most often cause proptosis or an eyelid swelling. Orbital involvement may present as an enlarged lacrimal gland, an enlarged extraocular muscle, or as a diffuse extraconal lesion (Fig. 12.10a–d). Most orbital lymphomas are primary tumors and are usually non-Hodgkin's lymphoma (NHL) of B-cell type. The most common primary lymphoma subtype is the low-grade malignant extranodal marginal zone B-cell lymphoma of MALT type (mucosa-associated lymphoid tissue). In those presenting with orbital lymphoma alone, systemic lymphoma eventually develops in one-thirds by 10 years, whereas only about 5% of patients with NHL develop ocular adnexal involvement during the course of their disease [35, 36].

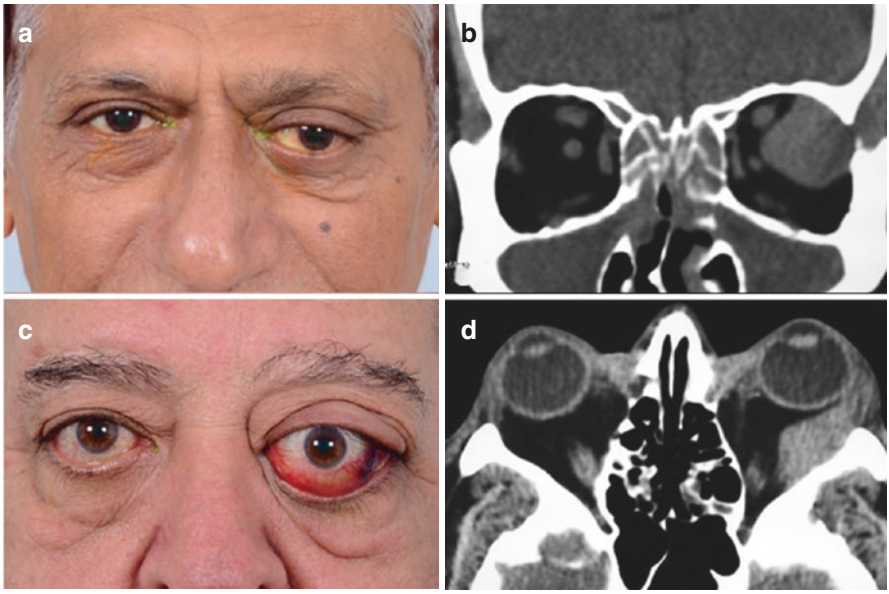

Fig. 12.10 Orbital lymphoma. (**a**) A 59-year-old male with left proptosis. (**b**) Coronal CT orbit reveals a left supertemporal orbital mass in the lacrimal fossa, with bony indentation and no bone destruction. (**c**) A 60-year-old male with left proptosis and conjunctival injection. (**d**) Axial CT orbit shows a mass lesion along the lateral rectus muscle extending upto the mid-orbit

A thorough systemic evaluation is warranted in all patients at the time of presentation. An incisional biopsy for a histopathological confirmation of the disease is mandatory. If the patient has associated systemic lymphoma, chemotherapy is recommended. Various regimens with or without immunotherapy are now available. In the absence of systemic lymphoma, small and well-circumscribed lesions are amenable to complete resection. Intralesional rituximab offers some benefit in the resolution of small orbital lesions. For larger lesions, a low dose radiotherapy offers an excellent local control with prolonged regression [37, 38]. Intravenous rituximab infusion followed by 90Y ibritumomab tiuxetan has also proven to be effective in early stage extranodal indolent B-cell lymphoma of the ocular adnexa [39].

12.14 Orbital Metastatic Tumors

Metastasis to the orbit occurs mainly by the hematogenous route. The primary tumor causing metastasis to the orbit is different in adults and children. In adults, the most common primary tumors metastasizing to the orbit are carcinomas of the breast, prostate gland, lung, and gastrointestinal tract [40]. Rarely, cutaneous and uveal melanoma can metastasize to the orbit. In children, orbital metastases occur from adrenal neuroblastoma, Wilms tumor, and Ewing tumor [40].

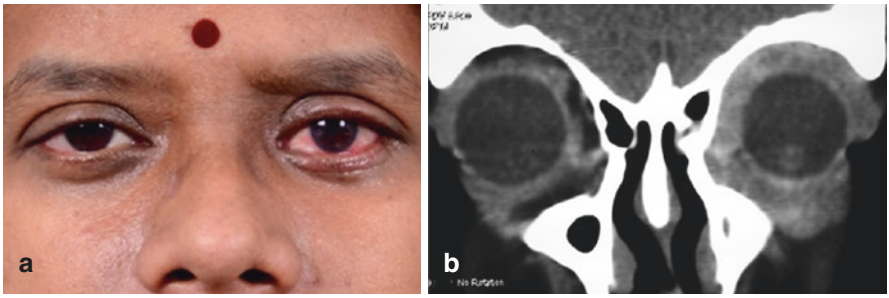

Fig. 12.11 Orbital metastatic tumors. (**a**) A 56-year-old female with a history of breast carcinoma post treatment presenting with left inferior orbital mass. (**b**) Coronal CT orbit shows a diffuse mass in the left orbit and the biopsy proved to be metastatic carcinoma from breast

The presenting features of orbital metastasis depend on the exact location of the tumor in the orbit and the type of primary neoplasm. Some of these lesions are confined to the extraocular muscles while others occur as solitary intraconal or extraconal mass producing rapidly progressive proptosis, pain, diplopia, ptosis, and eyelid swelling (Fig. 12.11a, b). Enophthalmos is seen in tumors which cause fibrosis of the orbital tissues, namely the scirrhous carcinoma of the breast and stomach [41, 42].

A thorough history, systemic examination and whole-body imaging is undertaken to diagnose the primary tumor. Imaging of the orbit for the size and location of the tumor is mandated. The diagnosis should be confirmed by an orbital incisional biopsy. The histopathology of orbital metastasis is same as that of the primary neoplasm. Once the orbital tumor is proven to be a metastasis, further management should involve a team of medical and surgical oncologists. The orbital tumor may subsequently require radiation therapy.

12.15 Orbital Secondary Tumors

An orbital secondary tumor is a malignant tumor that has extended into the orbit from the adjacent tissues around the orbit including eyelid, conjunctiva, intraocular structures, sinuses, nasopharynx, and brain. The main eyelid tumors that can involve the orbit secondarily include sebaceous gland carcinoma, squamous cell carcinoma, and basal cell carcinoma. Conjunctival tumors extending into the orbit include squamous cell carcinoma and melanoma (Fig. 12.12a, b). Intraocular tumors include uveal melanoma and retinoblastoma. Sinus tumors like carcinoma of the ethmoid or maxillary sinus and intracranial tumors like sphenoid wing meningioma also invade the orbit.

The clinical features of a secondary orbital tumor depend on the type and location of the primary neoplasm, with proptosis being the most common symptoms. Sometimes, the tumor is detected accidentally during follow-up for a previous eye and ocular adnexal tumor.

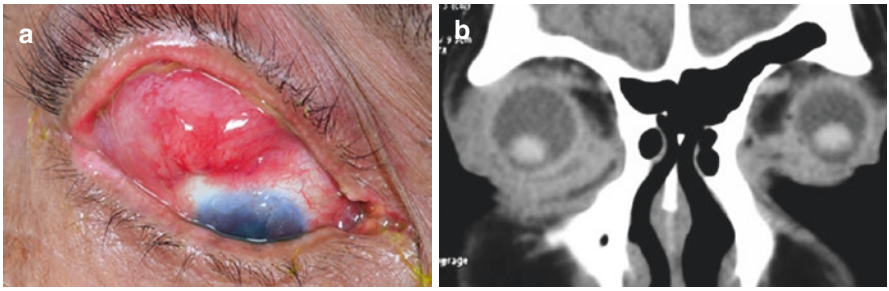

Fig. 12.12 Orbital secondary tumors. (**a**) A 59-year-old male with recurrent conjunctival squamous cell carcinoma right eye. (**b**) Coronal CT orbit shows diffuse right orbital involvement by extension of the conjunctival tumor

A detailed history, clinical exam, imaging, and an orbital biopsy are necessary to establish the diagnosis. Management depends on the extent of the lesion in the orbit. Smaller tumors may be managed by excision biopsy, while orbital exenteration is necessary for larger tumors. Subsequent chemotherapy and radiation therapy are essential in many cases.

In conclusion, orbit is an important site for a variety of primary and secondary tumors. Common tumors of the orbit maybe distinguished in most cases due to their characteristic clinical and radiological features. However, common tumors with atypical presentation or rare tumors of the orbit can cause a diagnostic dilemma. A well-planned biopsy of the tumor can yield correct diagnosis in such cases. Treatment of benign tumors is mainly observation or surgery, while malignant tumors are managed by using one or more of the various modalities of treatment available, as deemed appropriate by the treating ocular oncologist in conjunction with a medical oncologist.

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Tumors of the Conjunctiva and Ocular Surface

13

Fairooz P. Manjandavida and Shaifali Chahar

13.1 Introduction

The ocular surface is a functional unit that comprises eyelids, blink reflex, tear films, and tear glands, the conjunctival membrane covering the bulbar surface of eyeball and tarsal portion of the eyelids, the corneal epithelium, and the Bowman's zone [1]. Most important tumors that arise from the anatomical structures of the ocular surface include various forms of epithelial, stromal, caruncular, and secondary tumors. These tumors are seen in the clinical practice of a comprehensive ophthalmologist, cornea specialist, and an ocular oncologist. This chapter aims to discuss the spectrum of the lesions arising from the ocular surface varying along a continuum of benign to malignant.

13.2 Anatomical Consideration

Conjunctiva is a thin, translucent, vascularized mucous membrane covering the anterior part of the eyeball and lines the inside of the eyelids. It includes three portions namely: (a) bulbar conjunctiva that includes corneoconjunctival junction (limbus); (b) forniceal conjunctiva that includes superior, inferior and lateral conjunctival fornices; and (c) the palpebral conjunctiva that covers the back surface of the eyelids and includes mucocutaneous transitional zone in the lid margin.

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13.3 Histology

Conjunctiva is composed of epithelium and subepithelial stroma.

1. **Epithelium**
   Conjunctival epithelium is continuous with corneal epithelium near the limbus. At lid margin it forms the mucocutaneous epithelial zone continuing as the eyelid skin epidermis. Microscopically, the epithelium is stratified squamous non-keratinized. Bulbar and palpebral conjunctiva is made of cuboidal cells whereas cells in the fornices are stratified columnar. Melanocytes are scattered in basal layer. Goblet cells are most numerous in lower forniceal portions.
2. **Stroma** (Substantia propria)
   It is a fibro vascular connective tissue that contains collagen, elastin, blood vessels, lymphatics, nerves, and accessory lacrimal gland of Kraus. Similar to mucous membrane, conjunctiva also has its own associated lymphoid tissue. Stroma houses numerous lymphocytes, plasma cells, mast cells, and neutrophils.
   Caruncle is a fleshy prominence in the medial canthus that contains both conjunctival and cutaneous structures. Histologically, caruncle includes conjunctiva, hair follicles, sebaceous glands, sweat glands and accessory lacrimal tissue. Plica seminularis is a crescentic fold of conjunctiva lateral to the caruncle with thick epithelium and a highly vascular stroma.

13.4 Classification of Ocular Surface Tumors

The tumors of conjunctiva are grouped into two major categories: congenital and acquired. Classification of ocular surface tumors is summarized in Tables 13.1, 13.2, and 13.3.

Table 13.1 Classification of tumors of the ocular surface

S. no.	Type	Subtypes
1.	Congenital	• Choristomas. • Hamartomas.
2.	Acquired	• Epithelial. – Non-melanocytic – Melanocytic • Stromal. – Lymphoproliferative – Vascular – Fibrous – Neural – Histiocytic – Myogenic – Lipomatous • Caruncular. • Metastatic and secondary.

Table 13.2 Classification of epithelial tumors of conjunctiva

S. no.	Type	Benign	Malignant
1.	Non-melanocytic	• Squamous papilloma. • Reactive hyperplasia. • Hereditary intraepithelial dyskeratosis. • Keratoacanthoma. • Keratotic plaque. • Actinic keratosis. • Conjunctival intraepithelial neoplasia (CIN).	• Squamous cell carcinoma.
2.	Melanocytic	• Conjunctival melanocytic nevi. • Complexion-associated melanosis. • Primary acquired melanosis (PAM).	• Conjunctival melanoma.

Table 13.3 Classification of stromal tumors of conjunctiva

S. no.	Types	Benign	Malignant
1.	Lymphoproliferative	Benign reactive lymphoid hyperplasia	• Lymphoma.
2.	Vascular	• Capillary hemangioma. • Cavernous hemangioma. • Varix. • Racemose malformation. • Lymphangiectasia. • Lymphangioma (venolymphatic malformation). • Hemangiopericytoma. • Pyogenic granuloma.	• Kaposi's sarcoma. • Malignant hemangioendothelioma.
3.	Fibrous	• Fibroma. • Nodular fasciitis. • Benign fibrous histiocytoma.	• Fibrosarcoma. • Malignant fibrous histiocytoma.
4.	Neural	• Neurofibroma. • Schwannoma.	
5.	Histiocytic	• Xanthoma. • Xanthogranuloma.	
6.	Myxoid	• Myxoma.	
7.	Myogenic	• Leiomyoma.	• Leiomyosarcoma.
8.	Lipomatous	• Lipoma.	• Liposarcoma.
9.	Others		• Metastatic. • Secondary tumors. • Leukemic infiltrates.

13.5 Congenital Lesions of the Ocular Surface

13.5.1 Choristoma

Choristoma is a congenital lesion, which is defined as the presence of a normal tissue at an abnormal location. A simple choristoma has one type of tissue whereas, if a combination of displaced tissues is seen, it is termed as complex choristoma.

Epibulbar choristomas are the most common epibulbar tumors seen in children, dermoid and dermolipoma being the most common types. These can be associated with eyelid or uveal coloboma, Goldenhar syndrome, or organoid nevus syndrome [2].

13.5.1.1 Dermoid

Dermoid is a congenital lesion commonly seen involving the bulbar conjunctiva and often the corneoscleral limbus.

Clinical features: It presents as well-circumscribed, yellow-white firm, solitary mass most commonly occurring at inferotemporal limbus. Slit lamp biomicroscopy reveals fine hair arising from the lesion (Fig. 13.1). Size is variable from the more common small limbal dermoid to diffuse large dermoid covering the entire corneal surface and in few cases extensive dermoid lesions involving anterior chamber and the iris. Clinically, if encroachment of cornea is significant it can cause astigmatism and amblyopia.

Histology: It is a simple choristomatous malformation that consists of dense fibrous tissue lined by conjunctival epithelium with deeper dermal elements including hair follicles and sebaceous glands.

Treatment: If the lesion is small and vision is not affected, it can be observed. Indications for treatment include cosmetic reasons, chronic irritation, dellen formation, and amblyopia from astigmatism or involvement of visual axis. Larger dermoids can be excised by lamellar keratosclerectomy with amniotic membrane grafting if the defect is superficial or, closure using lamellar or full thickness corneal or sclerocorneal graft if the defect is deep or full thickness. While the cosmetic appearance does improve with surgery, the astigmatic error and visual acuity may not change significantly unless the child is treated early.

Systemic association: Goldenhar syndrome, less commonly Treacher Collins syndrome and nevus sebaceous of Jadassohn [2].

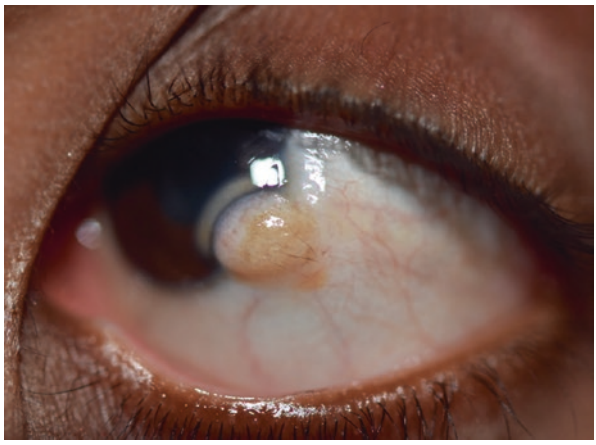

Fig. 13.1 Limbal dermoid: external image of left eye showing a yellowish white mass located at the limbus extending into the cornea with corneal opacity in a 19-year-old female. Multiple thin hair follicles are seen arising from the surface

13.5.1.2 Dermolipoma

Dermolipoma is a congenital lesion though it may remain asymptomatic and manifest only in adult life.

Clinical features: The lesion presents as a pale yellow, soft, fluctuant, mass protruding from the orbit through the conjunctival fornix superotemporally. The surface will often show fine hairs (Fig. 13.2). The lesion may extend posteriorly into the orbit and/or anteriorly toward the limbus. Main differential diagnosis is herniated orbital fat, which presents as subconjunctival yellowish mass with normal conjunctival surface, mobile and softer and does not show hair follicle on the surface like dermolipoma (Fig. 13.3).

Histology: It is lined by conjunctival epithelium on its surface, and subepithelial tissue has variable quantities of collagenous connective tissue and adipose elements. Pilosebaceous units and lacrimal gland tissue may occasionally be present.

Treatment: No treatment is required in majority of dermolipomas, unless for cosmetic considerations or in symptomatic patients with exuberant hair growth over the lesion. Visible portion of the dermolipoma may be debulked, and the ocular surface reconstructed with amniotic membrane graft.

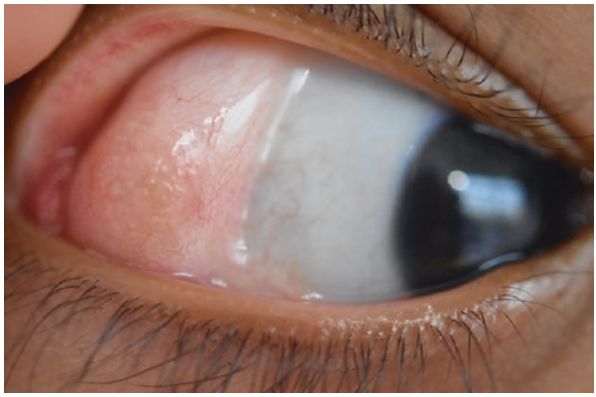

Fig. 13.2 Dermolipoma: a whitish-yellow subconjunctival lesion in the superotemporal bulbar conjunctiva of the left eye in a 5-year-old girl, with overlying conjunctival thickening and fine hair follicles

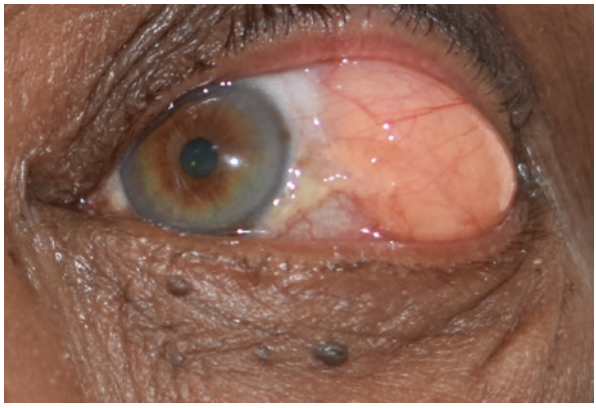

Fig. 13.3 Orbital fat prolapse: a 67-year-old gentleman who was referred for a mass with progressive growth in the left eye. Yellowish subconjunctival mass in the superotemporal bulbar conjunctiva with overlying normal conjunctiva noted. It is seen extending into the orbit

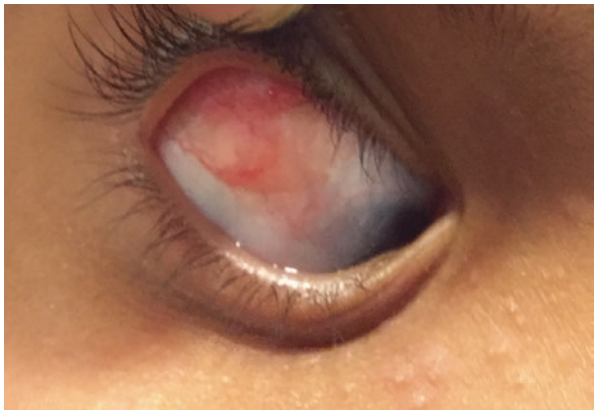

Fig. 13.4 Complex choristoma: a yellowish red ill-defined subconjunctival mass in a 2-year-old girl is seen in the superior bulbar conjunctiva. It was diagnosed to be lacrimal gland choristoma

13.5.1.3 Complex Choristoma

These are congenital, unilateral lesion containing tissues from two germ layers.

Clinical features: They can have a varying size from small localized lesion to extensive lesion covering the entire bulbar surface and encroaching the cornea. Color varies according to the type of tissue involved. It can rarely present as osseous choristoma and lacrimal gland choristoma both of which are rare congenital lesions usually seen in the superotemporal quadrant [3, 4] (Fig. 13.4).

Histology: It has tissue from the ectoderm and mesoderm that may include adipose tissue, collagen, pilosebaceous structures, lacrimal gland, smooth muscle, cartilage, bone, nerves, and blood vessels.

Treatment: Asymptomatic small lesions can be observed; larger lesions can be dealt with excision and ocular surface reconstruction.

Systemic association: It may be associated with organoid nevus syndrome that has cutaneous feature of sebaceous nevus of Jadassohn [5].

13.6 Benign Tumors of the Epithelium: Non-melanocytic

13.6.1 Squamous Papilloma

Conjunctival squamous papilloma is a common, benign epithelial tumor. These can occur in any age group but are most commonly seen in young adults with a male predominance [6].

Etiology: Childhood papillomas are caused by infection with human papillomavirus (HPV type 6, 11, and 16) [7, 8]. These can be transmitted at birth via mother-to-infant, vertical transmission through an infected vagina. Papillomas in adults on the other hand, are mostly non-infectious but may have an association with HPV infection or immunocompromised status.

Clinical features: Childhood papilloma presents as sessile or pedunculated, pink or red fleshy finger-like or frond-like projection with irregular surface. Mostly the lesion is asymptomatic. Large lesion can cause a foreign body sensation, discharge, hemorrhagic tears, and a cosmetic blemish. It usually presents as a solitary lesion, but can be bilateral, multiple, and confluent. Childhood papillomas are commonly located in inferior fornix or bulbar conjunctiva but can appear in other parts of conjunctiva also.

Adult papilloma is unilateral and presents as a solitary lesion most commonly near limbus or bulbar conjunctiva. Usually it is broad-based sessile lesion, slightly pink in color than the childhood papilloma (Fig. 13.5). The pedunculated part can cover a part of the cornea when it grows interfering with the vision.

Histology: Childhood papillomas have a fibrovascular core with epithelial projections covered by non-keratinised acanthotic stratified squamous epithelium containing goblet cells, with intact basement membrane. Immunohistochemistry and molecular techniques have documented association with human papillomavirus in 92% cases [7, 8]. Adult papilloma reveals varying degree of pleomorphism and even dysplasia of epithelial cells. Histological variants include those with inverted growth pattern, which have a greater tendency for malignant transformation.

Treatment: Small childhood papillomas might resolve spontaneously. Larger papillomas require complete excision with a 'no-touch technique' to avoid spreading of the papillomavirus on ocular surface in conjunction with cryotherapy to the base and surrounding structures [9]. Cryotherapy can also be used for smaller lesions without excision, wherein the frozen lesion sloughs off the surface later [10].

Recurrence is common. Other modalities of treatment include topical medication with interferon alpha 2b (IFN α2b), or topical mitomycin C [11, 12], laser and

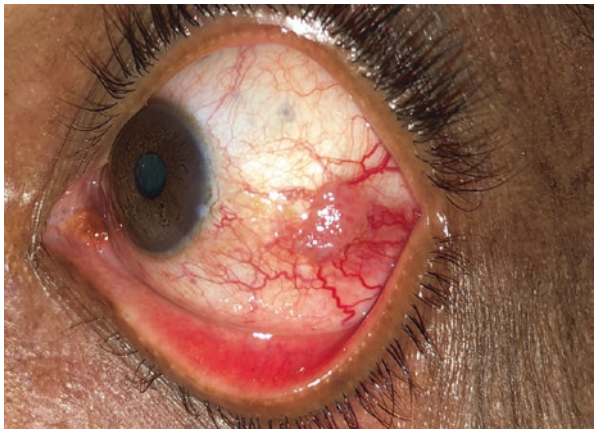

Fig. 13.5 Conjunctival papilloma: A pinkish, pedunculated conjunctival lesion in the bulbar conjunctiva away from the limbus in a 40-year-old immunocompromised male. Feeder vessels pointed out to suspicious malignancy, although histopathology confirmed conjunctival papilloma

dinitrochlorobenzene immunotherapy [13, 14]. Recent reports show significant role of oral cimetidine in treating recalcitrant and recurrent conjunctival papillomatosis. It is known to enhance the immune system by inhibiting certain T-cell functions [15].

13.6.2 Reactive Epithelial Hyperplasia (Pseudoepitheliomatous Hyperplasia, Pseudocarcinomatous Hyperplasia)

It is a benign reactive inflammatory proliferative lesion, occurring secondary to irritation by concurrent or preexisting stromal inflammation like pterygium, pinguecula, allergic conjunctivitis, or foreign body.

Clinical features: It appears as an elevated leukoplakic pink lesion in limbal area.

Histology: Inflammatory proliferation of the epithelial cells in the form of acanthosis, hyperkeratosis, or parakeratosis and subepithelial inflammation is seen. Mitotic figures can be observed but atypia is absent. Clinically and histologically this lesion can simulate conjunctival squamous cell carcinoma and, hence, be difficult to differentiate.

Treatment: Complete excision and additional cryotherapy.

13.6.3 Hereditary Benign Intraepithelial Dyskeratosis (HBID)

HBID is an autosomal dominant disorder of mucous membranes including conjunctiva. It is known to occur more commonly in descendants of inbred Caucasians, African-Americans and Native Americans (known as Haliwa Indians), though occurrence in other population is also seen [16, 17].

Clinical features: It presents in the first decade of life as a bilateral elevated fleshy v-shaped plaque on perilimbal, nasal or temporal bulbar conjunctiva with dilated blood vessels around it. Larger lesion can have associated corneal vascularization and opacification causing poor vision. This lesion does not have a malignant potential.

Histology: Lesion shows acanthosis, prominent dyskeratosis in epithelium, and severe chronic inflammation in stroma.

Treatment: Symptomatic treatment for smaller lesions with topical lubricants or topical steroids. Larger lesions require complete excision with ocular surface reconstruction.

13.6.4 Conjunctival Epithelial Cysts

These cysts may be congenital or acquired, the latter being more common in occurrence. The subtypes of cysts include (a) inclusion cysts that occur spontaneously or following surgery or trauma and (b) ductal cyst arising from accessory lacrimal glands.

Clinical features: These are smooth, translucent cystic lesion with clear fluid or occasionally turbid fluid with epithelial debris (Fig. 13.6).

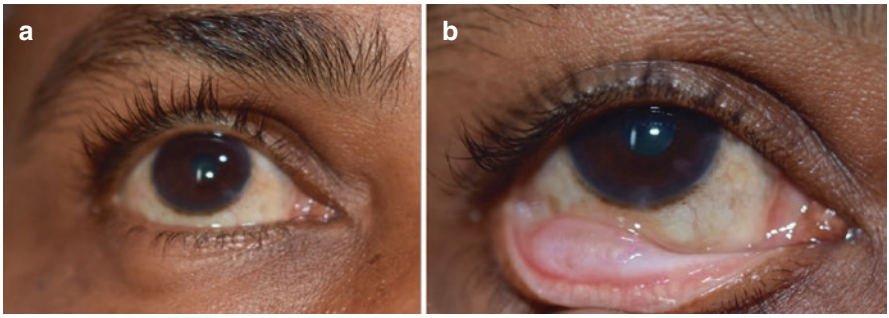

Fig. 13.6 Conjunctival inclusion cyst: (**a**) A 44-year-old female presented with fullness in the lower lid as seen here (**b**). On eversion of lower eyelid there is a well-defined subconjunctival transparent cystic lesion noted inferior to the lower edge of the tarsus

Histology: Inclusion cysts are lined by conjunctival epithelium. The lumen is filled with clear fluid or mucinous material, epithelial debris and/or keratin. Ductal cysts are lined by two layers of epithelium and contain PAS-positive material.

Treatment: The cysts may remain stable and asymptomatic, and rarely undergo spontaneous resolution. Excision is advised for a cyst that enlarges or becomes symptomatic.

13.6.4.1 Keratotic Plaque

This is a leukoplakic lesion developing commonly in limbal or bulbar conjunctiva usually in interpalpebral region.

Histology: There is thickening of epithelium with acanthosis, hyperkeratosis, or parakeratosis. Dyskeratosis is not present.

Treatment: It has little or no malignant potential and can be observed unless patient demands excision for cosmetic reasons.

13.6.4.2 Actinic Keratosis

Actinic keratosis is classified as a precancerous lesion of conjunctiva. Most commonly it is seen to develop after chronic sun exposure. It is a commonly seen focal leukoplakic lesion occurring in the interpalpebral area.

Clinical features: It presents as a flat, white plaque with frothy covering. It is usually located over chronically inflamed pinguecula or pterygium. Clinically, it may simulate conjunctival intraepithelial neoplasia (CIN). Rose Bengal staining can help in differentiating wherein positive staining is seen in cases of OSSN.

Histology: The epithelium exhibits acanthosis, hyperkeratosis, and parakeratosis with minimal dysplasia.

Treatment: Owing to suspicion of squamous cell carcinoma, lesion should be totally excised with additional cryotherapy. A close observation is maintained on other lesions until progression is documented.

13.6.5 Ocular Surface Squamous Neoplasia

Ocular surface squamous neoplasia (OSSN) is an umbrella term and, describes a spectrum of benign, premalignant, and malignant epithelial lesion of conjunctiva and cornea. It encompasses dysplasia, carcinoma in situ (CIN), and squamous cell carcinoma (SCC) [18]. Earlier terms used for this entity include 'intraepithelial epithelioma', 'Bowen's disease of the conjunctiva' or 'Bowenoid epithelioma' [19].

Epidemiology: The incidence of OSSN ranges from 0.02 to 3.5 per 1,00,000 population and varies geographically. It has greater frequency near the equator where sunlight exposure is more. CIN accounts for 39% of all premalignant and malignant lesions of the conjunctiva and 4% of all conjunctival lesions [20]. It predominantly occurs in men (75%) and frequently diagnosed in older individuals (75%).

Etiology: Lee et al. proposed the limbal transition zone/stem cell theory for OSSN development [18]. They postulated that alterations in limbus, where stem cells for corneal and conjunctival epithelium are located, along with other factors could cause abnormal maturation of the cells resulting in formation of OSSN. They based this theory on Tseng's concept of long-living cells and high proliferation rate of stem cells in limbal area [21].

Factors associated with the development of OSSN are

- Sunlight exposure: Ultraviolet B rays cause damage to DNA in human epithelium. This can lead to varying degree of somatic mutation causing OSSN. Lee et al. observed a relationship between lifetime exposure to solar ultraviolet light and risk of development of OSSN [18].
- Human papillomavirus: HPV type 16 has been associated with OSSN. There is a lack of evidence for a statistically significant association between anti-HPV antibody status and conjunctival neoplasia; hence it is assumed that HPV alone is incapable of causing OSSN [19].
- Acquired immunodeficiency syndrome: HIV infection has been reported to be an important risk factor for development of OSSN. Incidence of OSSN has increased since AIDS epidemic in sub-Saharan African countries [20].
- Systemic associations for development of OSSN include xeroderma pigmentosum and Papillon–Leferve syndrome.

Clinical Features: Clinically, it may be difficult to distinguish the spectrum of histological subtypes. Most lesions occur unilaterally in late adult life with ocular redness and irritation. Vision gets affected only if the lesion is big enough and encroaches the cornea. Bilateral presentation can sometimes be seen in immunocompromised individuals. The lesion appears commonly in the interpalpebral fissure, mostly at the limbus, although they can be found in any part of conjunctiva and cornea.

It appears as a fleshy or nodular, sessile minimally elevated lesion with surface keratin, feeder vessels, and secondary inflammation [9, 18] (Fig. 13.7a). Rose Bengal staining is helpful in the diagnosis and delineation of the tumor extent

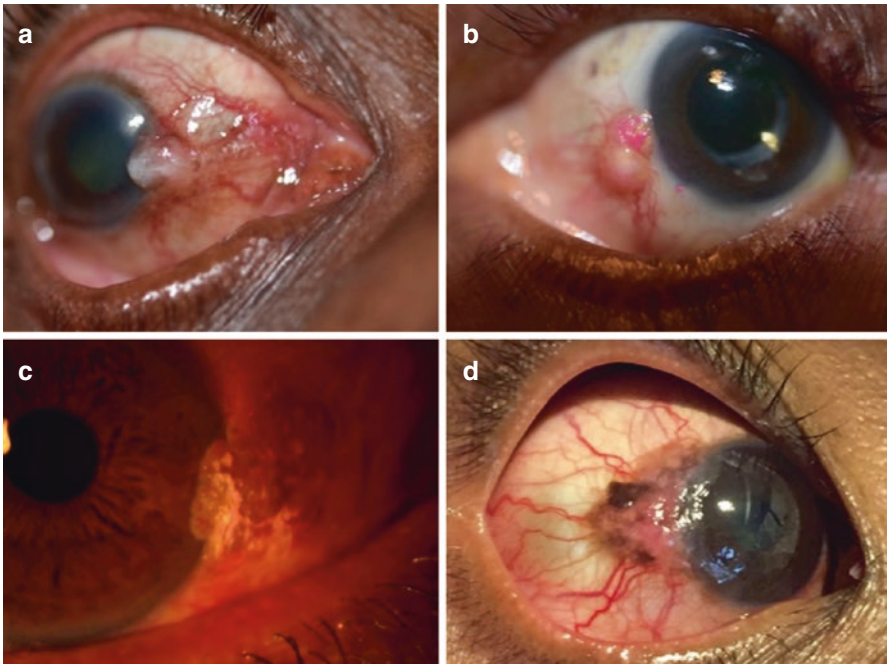

Fig. 13.7 Ocular surface squamous neoplasia: (**a**) A 68-year-old lady presented with rapidly growing mass in the right eye. It shows a nodular lesion located at the limbus with adjacent conjunctival thickening and keratin deposition extending into the peripheral cornea. Feeder vessels are prominent (**b**). A nodular lesion in the left eye of a 65-year-old gentleman with rose Bengal staining, keratin and feeder vessels is seen. The lesion was immobile with scleral fixity and possible invasion (**c**). The slit lamp photo shows conjunctival lesion with papillary fronds and surface keratin with advancing edge over the cornea with intrinsic vascularization (**d**). A reddish fleshy mass with scattered pigmentation and surface keratin as seen in pigmented OSSN. There is whitish gelatinous wavy contiguous lesion extending into the cornea

(Fig. 13.7b). Extension of tumor can be seen into the adjacent corneal epithelium from the limbus that clinically appears as a subtle wavy, advancing gray, superficial convex opacity that can be avascular or have very fine blood vessels (Fig. 13.7c, d). Mostly it is nonpigmented although pigmented conjunctival SCC is also reported (Fig. 13.7d).

Morphological subtypes of OSSN include:

- Placoid: variants include
  - Gelatinous
  - Leukoplakic plaque
  - Papilliform
  - Velvety
- Nodular
- Pigmented
- Diffuse

There are no consistent clinical criteria for distinguishing CIN from invasive SCC. Clinical features that favor suspicion of malignancy are extensive leukoplakia, presence of feeder vessels, and intrinsic vascularity. Nodular morphology and greater thickness must raise suspicion of invasive SCC. Scleral fixity in an OSSN indicates invasive SCC. Tarsal conjunctiva must be examined after everting the eyelid of patients with SCC to detect contiguous or multifocal involvement. Intraocular extension is seen in advanced cases where the tumor infiltrate the cornea and sclera. Orbital extension of conjunctival malignancy is not rare in advanced disease. Tumors extending to the caruncle and fornices should be radiologically evaluated for orbital extension. Metastasis to the regional lymph nodes may occur, but distant metastasis is rare. American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) classification takes into consideration the size, tumor location, and extent of involvement [22].

Histology: Histopathological evaluation helps differentiate between the lesions in the spectrum of OSSN.

- Dysplasia: The dysplastic lesions exhibit mild, moderate or severe cellular atypia that can have variable thickness in epithelium. There will be loss of cell polarity. These changes start from basal layer and move up and mostly superficial layers are normal.
- Carcinoma in situ: Histologically it may be difficult to distinguish between carcinoma in situ and SCC. Here the basement membrane is intact and it is confined within the epithelium. Mostly there is loss of cell maturation and full thickness is involved. Mitotic figures are seen and keratinization is common.
- Invasive squamous cell carcinoma: The basement membrane is breached and subepithelial tissue gets invaded in invasive SCC. Cellular pleomorphism with atypical mitotic figures is seen. Dyskeratosis is common and collection of keratinized cells (horn pearls) may be observed. Subepithelial tissue shows inflammation and islands of atypical epithelial cells.

Histopathological variants of invasive SCC with aggressive behavior include: [21]

- Spindle cell carcinoma.
- Mucoepidermoid carcinoma.
- Adenoid cell carcinoma.

Treatment

1. Surgery (no-touch technique)

   Surgical excision of OSSN involves excising the tumor using the 'no-touch' technique. Important steps during surgical excision include complete excision with 4 mm margin clearance. In the presence of corneal involvement, absolute alcohol assisted superficial epithelial keratectomy is performed with a 2 mm margin clearance. Entire tumor is excised along the limbus without touching the tumor. Double-freeze thaw cryotherapy is applied to the edge of the remaining bulbar conjunctiva. Lamellar sclerectomy is considered in indicated cases with scleral fixity suggesting invasion. Limbal cryotherapy should not exceed 6

o'clock hours. Ocular surface reconstruction may be needed after large excision with amniotic membrane transplantation [23–25]. In larger tumor excision, simple limbal epithelial transplant (SLET) can be combined to circumvent limbal stem cell deficiency.

2. Topical Medical Therapy (antineoplastic agents)

   The most commonly used topical agent is Interferon alpha 2b as immunotherapy. Other topical chemotherapeutic drugs include 5-fluorouracil (5-FU) and mitomycin C (MMC) [26].

   Interferon alpha 2b: Interferon (IFN) alpha 2b is currently the most accepted and favorable form of treatment for OSSN. Mechanism of action involved is the immunomodulatory effect of the drug. IFN alpha 2b is a cytokine that enhances the production of IL-2 and IFN-γ mRNA by the immune system and lowers the production of IL-10. This helps in recognition and targeting of neoplastic cells. In addition, it also has anti-proliferative and antiviral properties. Compared to other topical chemotherapeutic agents, IFN alpha 2b is well tolerated with negligible local side effects. It is used as primary therapy or as immune reduction to reduce the size of the tumor for further surgical excision. Topical dose recommended is one million IU administered 4 times daily for 6–12 months. It is reported to have a success rate of 85–100% [27–29]. It is also used as intralesional injection in the dose ranging from three million IU to ten million IU for larger lesions [28, 30]. IFN immunotherapy plays a major role in cases of high rate of recurrence like in immunosuppressed individuals with OSSN [31]. The long-term use of topical IFN helps to prevent recurrence by way of immunemodulation [30]. The most common complication is transient flu-like syndrome.

   5-Fluorouracil (5-FU): 5-FU is well tolerated and, effective in treatment of OSSN. It is a pyrimidine analog that blocks thymidine synthase, inhibiting DNA formation. This causes a reduction in RNA, which leads to poor cell growth and cell death [32]. 5-FU compounded as a 1% solution is used topically four times in a day for 2 weeks followed by 2 weeks treatment-free interval that comprises one cycle. Most common side effects include eyelid erythema, conjunctival hyperemia, and corneal punctate erosion.

   Mitomycin C (MMC): Mitomycin C is an alkylating agent with antineoplastic and antibiotic properties. Under aerobic condition, it generates free radicals causing cytotoxicity and lipid peroxidation. It binds to DNA, causes inhibition of DNA synthesis, and at higher concentration inhibits RNA transcription and protein synthesis [26, 33, 34]. There are several protocols used, but a dosage of 0.04%, four times a day, 4 days a week for 4 weeks (rule of 4) has been reported to give the best results [35]. Associated local complications include conjunctival hyperemia, punctate corneal erosions, and inadvertent prolonged use may lead to scleral melt.

3. Radiotherapy
   (a) Plaque brachytherapy: It is used to control gross or microscopic residual tumors. Commonly used materials are strontium-90 or ruthenium-106.
   (b) Stereotactic radiotherapy: In advanced ocular surface SCC with orbital extension, radiotherapy can be considered for eye salvage combined with chemotherapy.

4. Targeted therapies

   Epidermal growth factor receptor (EGFR) inhibitors: A potential option for treatment of OSSN is anti-EGFR monoclonal antibodies like cetuximab. EGFR-targeted therapies have been recommended for head and neck SCC. Intense expression of EGFR has been proven in conjunctival SCC and hence anti-EGFR is being explored as a therapy for conjunctival tumors also [40].

Prognosis: Ocular surface squamous neoplasia has a favorable prognosis in terms of metastasis and, mortality. Reported recurrence rate of OSSN is 15–52%. Lee and Hirst reported a 17% recurrence after excision of conjunctival dysplasia, 40% after excision of CIN and 30% for SCC of the conjunctiva [18]. With the modern techniques, the local recurrence rate is about 5% and regional metastasis of 2% [41]. Mucoepidermoid or spindle cell variants have the worst prognosis. Regional lymph node involvement precedes distant metastasis. Hence regular lymph node examination should be performed at every follow-up visit. Sites of metastasis include preauricular, submandibular and cervical lymph nodes, parotid gland, lungs, and bones.

13.7 Benign Tumors of the Epithelium: Melanocytic

13.7.1 Conjunctival Melanocytic Nevus

A conjunctival nevus is the most common melanocytic conjunctival tumor [20, 42].

Etiology: Nevi can occur in all races but is more common in Caucasians (89%) than Africans (6%) and Asians (5%). Nevi that appear at birth or within 6 months of life can be termed congenital nevi, and those appearing later as acquired nevi.

Clinical features: Typically, conjunctival nevi become apparent in the first to second decade of life. Clinically, it presents as a solitary, unilateral, discrete, slightly elevated, pigmented bulbar lesion of variable size most frequently in juxta-limbal area (Fig. 13.8a). Cystic spaces within the nevi are typical and can be frequently seen either by the naked eye or on slit lamp biomicroscopy (Fig. 13.8b). Clinically, feeder vessels may be observed in 64% of cases and intrinsic vascularity in 77% cases [43]. During adolescence the lesion might become inflamed. The extent of pigmentation is variable and some lesions may be virtually nonpigmented. But the lesion can vary in size, color, and location. Malignant transformation is reported to be less than 1% [42]. Clinical features that should raise a suspicion of malignancy include onset in adulthood, location other than bulbar conjunctiva, like fornices, palpebral conjunctiva, caruncle and plica seminularis, and recent growth of the nevus with a color change and increased thickness with prominent feeder vessels. Very rarely nevus can be amelanotic especially in Caucasian population.

Differential diagnosis includes primary acquired melanosis (PAM), melanoma, and pigmented OSSN.

Histology: Conjunctival nevi have a group of small nests of pigmented epithelial cells in the basal layer of the epithelium and ranges from junctional through

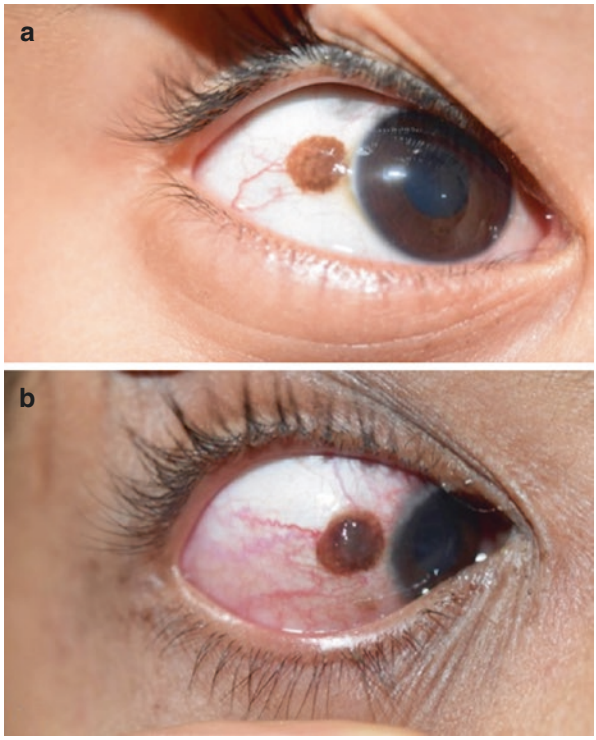

Fig. 13.8 Conjunctival nevus—(**a**) A 6-year-old boy presented with melanotic conjunctival lesion in the temporal bulbar conjunctiva of right eye slowly progressing since childhood. It shows varied pigmentation with microcysts and feeder vessels. (**b**) A 14-year-old female complains of redness in the existing melanotic mass. The central portion is more darkly pigmented than the peripheral rim. There are microcysts and macrocysts noted with surrounding congestion

compound to sub epithelial in type. These are the stages in the evolution of the nevus. Distinct cell types described in the nevi are balloon cells and spindle cells.

Positive immunostaining for HMB-45 and ki-67 are useful adjuncts in differentiating benign lesions from malignant entities [44]. Clinicopathological variants include spitz nevus, blue nevus, balloon cystic nevus, and inflamed juvenile conjunctival nevus (IJCN).

Treatment: Management of choice for most nevi is periodic (annual) observation with slit lamp measurements and serial imaging for comparison. In case of cosmetic concerns, documented growth or strong suspicion for malignancy, excision biopsy is performed.

13.7.1.1 Complexion-Associated Melanosis (CAM)

It is common in Asians and Africans, due to increased melanin production.

Clinical features: It occurs as bilateral, asymmetric, flat, patchy, brownish conjunctival pigmentation commonly scattered throughout the conjunctiva but more intense at the limbus, often for 360° and can involve the adjacent cornea and bulbar conjunctiva (Fig. 13.9). Uncommon areas of presentation are fornices or palpebral conjunctiva. Lesion can be more intense around the perforating branches of the anterior ciliary vessels or intrascleral nerve as it enters the sclera (Axenfeld loop).

Treatment: Observation.

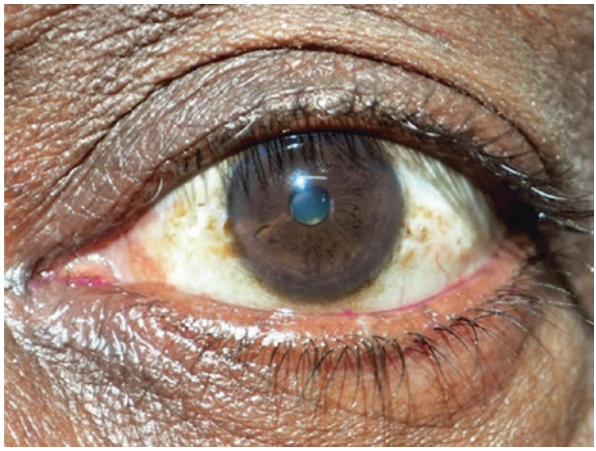

Fig. 13.9 Complexion-associated melanosis: Scattered flat pigmentation of the limbal and bulbar conjunctiva of a 65-year-old Asian male

13.7.1.2 Primary Acquired Melanosis (PAM)

Primary acquired melanosis is a benign conjunctival epithelial lesion. The clinical description dates back to 1892 by Hutchinson who called it 'senile freckle' [45]. Reese in 1966 termed it 'precancerous melanosis' and Zimmerman replaced it with 'benign acquired melanosis' [46, 47]. The term primary acquired melanosis was adopted by world health organization in 1980 [48].

'Primary' denotes that the lesion is not a result of systemic or local factor; 'acquired' distinguishes it from the congenital lesions; 'melanosis' indicates the proliferation of melanocytes rather than any other pigment accumulation or deposition.

Etiology: PAM is more prevalent in fair-skinned individuals and sunlight exposure might play a role in the development. It is reported to occur in patients with neurofibromatosis [49]. Also, cigarette smoking and hypertension have been observed to be independent factors in the development of PAM [50].

Clinical features: It usually presents in middle-aged or elderly individuals, may occur in young adults, and uncommon in children. Clinically, it appears as a unilateral, superficial, solitary, patchy, diffuse or multifocal, golden brown to dark chocolate pigmentation, which typically involves the interpalpebral area, but can occur in palpebral or forniceal conjunctiva (Fig. 13.10a). Rarely amelanotic PAM (sine pigmento) can be seen. PAM may show a waxing and waning phenomenon in which the lesion may lighten, darken, expand or shrink in size or remain stable for long time [51]. The overall risk of progression to melanoma is 9%. In cases of PAM with atypia the risk is 13% and almost no risk in PAM without atypia. The most significant factor to consider in risk of progression is the clock hours of involvement. Each additional clock hour involvement increases the risk by 1.7 times compared to 1 clock hour involvement of the conjunctiva [52] (Fig. 13.10b). Conjunctival malignant melanoma arising from PAM accounts to 75%.

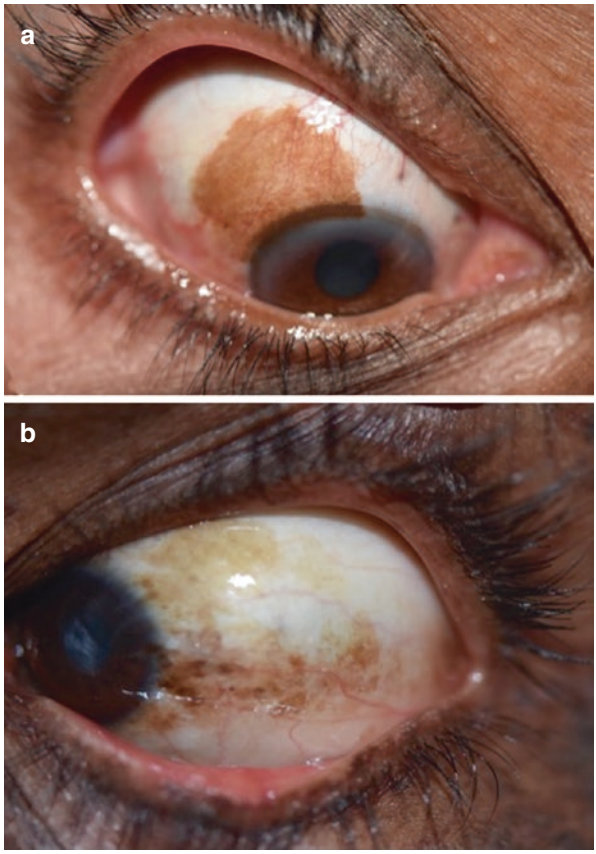

Fig. 13.10 Primary acquired melanosis: (**a**) Unilateral, patchy, flat, superficial brown conjunctival lesion in the right eye of a 55-year-old lady. (**b**) Diffuse, multifocal light to dark melanotic lesion in a 24-year-old male with xeroderma pigmentosum in the left eye. It carries high risk for malignant transformation

Histology: Histologically PAM is divided into two major groups-

- PAM without cellular atypia: It is a benign intraepithelial proliferation of epithelial melanocytes with no risk of malignant transformation.
- PAM with cellular atypia: It shows an increase in the number of intraepithelial melanocytes exhibiting pleomorphism. If severe, it can be regarded as 'melanoma in situ' and has a higher chance of evolving into conjunctival melanoma. The atypical melanocytes may be distributed along the epithelial basement membrane (basilar hyperplasia pattern), may be segregated into nests or may be dispersed upward into the epithelium (Pagetoid spread).

Treatment: Appropriate management approach remains controversial.

(a) Observation

PAM without atypia can be observed with periodic follow-up of each lesion with size, location, and appearance and serial pictures for documentation and

comparison [50]. Those that do not look like subtle common lesions must be biopsied.

(b) Surgery

Indication for biopsy of PAM include lesion equal to or greater than 5 mm, documented progression, change in color, thickening of the involved conjunctiva, distant nodule arising in the lesion, feeder vessels, involvement of cornea, involvement of palpebral conjunctiva or with a history of dysplastic nevus syndrome or close relative. Excision biopsy with cryotherapy to the excised margin (double-freeze thaw cycle) is recommended for suspicious looking lesions [53, 54]. PAM with atypia less than 3 o'clock hours can also be managed by cryotherapy alone.

(c) Topical mitomycin C

Diffuse PAM can be treated with 0.04% mitomycin C, although not as effective as in ocular surface squamous neoplasia [55].

Prognosis: Incidence of recurrence in PAM depends on presence or absence of atypia. In PAM with atypia recurrence rate can be as high as 60% if treated with excision alone, more in cases when incomplete excision is done or in cases of corneal involvement. The lesion might recur as malignant melanoma.

13.8 Conjunctival Malignant Melanoma

Conjunctival melanoma is a rare malignant tumor with a mortality rate of 23–30% [56, 57]. It accounts for 2–5% of ocular malignant melanomas. Cutaneous melanomas are 450–900 times more common than conjunctival melanoma but according to recent epidemiological analysis incidence of conjunctival melanoma is rising [58]. Overall incidence is between 0.24 and 0.8 cases per million. The reported incidence of CMM is on the rise. Over a period between 1973 and 1999, there was an increase in incidence from 0.27 to 0.54 million in United States, which was more pronounced in white men and in patients aged 60 years and older [58].

Etiology: Most commonly it affects middle-aged or elderly, fair-skinned individuals and recent studies suggest higher incidence in males [58]. Sunlight exposure is believed to be a causative factor though no clear evidence exists. Other risk factors are dysplastic nevus syndrome, neurofibromatosis, and xeroderma pigmentosum [59]. The main precursor lesions are PAM with atypia and conjunctival nevi. It arises from PAM in about 75% cases, preexisting nevus in 20% cases, and de novo in 5% cases [9].

Clinical Features: It may arise in any region of conjunctiva including bulbar, palpebral and forniceal conjunctiva, and in the caruncle and plica semilunaris. Most common site is the limbus. It is unilateral but can be multifocal. It appears as a pigmented fleshy mass with feeder vessels (Fig. 13.11). Amelanotic melanoma is a known variant reported among Caucasians. Three clinical and pathological forms exist: those arising from PAM with atypia, pre-existing nevus and those arising de novo [51]. Lesion is diffuse or multifocal with ill-defined margins particularly if arising from PAM. A subtle placoid thickening of the PAM on slit lamp examination can be noted.

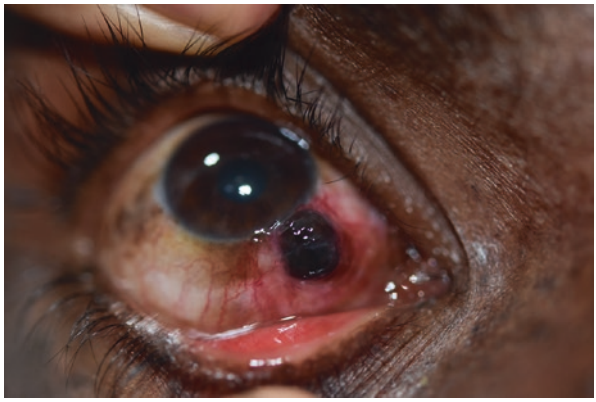

Fig. 13.11 A 24-year-old male with xeroderma pigmentosum presented with rapidly growing brownish lesion in the right eye. It shows nodular melanotic well-defined lesion with surface fixity in the inferonasal bulbar conjunctiva with surrounding PAM, large feeder vessels and conjunctival thickening

There may be a sudden appearance of one or more nodules in an otherwise flat lesion. When arising from a nevus or de novo, it appears as a dark pigmented, solitary, smooth, vascularized fleshy nodular lesion [51]. Other variants include primary corneal tumor, and implantation melanoma that develops secondary to contiguous touch from an eyelid margin melanoma [60]. Amelanotic melanoma can be confused with OSSN or lymphomas. Slit lamp biomicroscopy in such cases will reveal flecks of pigmentation somewhere in the lesion. Melanomas recurring after a prior excision tend to be amelanotic, fleshy and vascular [9].

Differential Diagnoses: Differential diagnoses include the precursor lesions—conjunctival nevus and PAM. Epithelial lesions such as squamous papilloma and OSSN may be confused with amelanotic melanoma. Staphylomas, subconjunctival hematoma, foreign bodies, and hematic cysts may also be confused clinically with melanoma. Although rare, metastatic cutaneous melanoma to the conjunctiva has been reported and also, epibulbar extension of uveal melanoma or melanocytoma should be considered in differential diagnosis [61, 62].

Histology: Histopathology shows sheets of melanoma cells within the sub epithelial stroma. Four types of atypical melanoma cells have been described: small polyhedral, spindle, balloon and round epithelioid cells with eosinophilic cytoplasm. These cells are positive for S-100 protein, tyrosinase, Melan-A, HMB-45, HMB-50, and microphthalmia conscription factor [51].

Prognosis: Histopathological features that predict an adverse prognosis for conjunctival melanoma include tumor thickness >2 mm, histological evidence of ulceration, mitotic figure count >1/mm^2, lymphovascular invasion, predominantly epithelioid histology, and microsatellitosis. The three features found to have significant correlation with regional lymph node metastasis are: tumor thickness >2 mm, histologic evidence of ulceration, and mitotic figure count >1/mm^2 [63].

Treatment: The primary treatment of conjunctival melanoma is complete excision with 4 mm wide surgical margins with a no-touch technique. Alcohol keratoepitheliectomy is done for the corneal epithelial component. In cases of suspected scleral involvement, partial lamellar sclerectomy can be done [23]. Double-freeze thaw cryotherapy to the surgical margins and bed is the standard of care [51]. In

case of extensive lesions; appropriate ocular surface reconstruction is done with amniotic membrane graft [25].

Postoperative adjuvant plaque brachytherapy is recommended if excision base is positive for tumor cells in histopathology. Areas of PAM with atypia, either around the excised melanoma or distant from it must be treated. This can be treated with surgical excision and cryotherapy or with topical chemotherapeutic agents like mitomycin C.

In cases of advanced tumor with deep corneal or scleral invasion or intraocular extension, extended enucleation with en-bloc excision of the tumor is the treatment of choice. Palliative treatment for advanced stages of conjunctival melanoma that has spread into orbit, in its aggressive phase includes exenteration. Targeted molecular therapies, which have revolutionized the treatment for cutaneous melanoma, have been described for the treatment of conjunctival melanoma in recent studies. A growing body of evidence demonstrates a common genetic kinship between conjunctival and cutaneous melanoma differentiating it from uveal melanoma. The drugs include ipilimumab (anti-CTLA4), vemurafinib and dabrafinib (BRAF-Kinase inhibitor), imatinib (kit/CD117), and nivolumab (anti-PD1) [64–69].

Regional lymph node metastasis is associated with poor prognosis. Feasibility of sentinel lymph node biopsy preoperatively in every case is debatable [70]. If present, regional metastases can be treated with neck dissection and adjuvant radiotherapy. Most patients with disseminated disease are treated with systemic chemotherapy.

Prognosis: Local recurrence after therapy is as high as 50–70% at 10 years. Overall mortality rate is 25% in 10 years and more than 30% in 15 years. Conjunctival melanoma American Joint Committee on Cancer (AJCC) Tumor/ Node/ Metastasis TNM. Staging predicts the prognosis and outcome [71].

13.9 Congenital Melanosis Oculi (Congenital Ocular Melanocytosis, Nevus of Ota)

This is a congenital pigmentary condition of the sclera and uvea involving the periocular skin, orbit, meninges and soft palate. Typically, there is no conjunctival pigmentation but this can be considered in clinical differential diagnosis of pigmented conjunctival lesion. Owing to diffuse pattern, it is confused with conjunctival PAM.

Clinical Features: Ocular surface appears gray or blue (not brown or black) because of Tyndall effect of pigmented melanin through episcleral and sclera. The overlying conjunctiva is freely mobile and pigmentation will not move as it is seen in the underlying layers (Fig. 13.12).

Risk of development of conjunctival melanoma is not described in literature. But risk of development of uveal melanoma is 1:400 and hence a thorough fundus examination is important at presentation and in follow-up visits to exclude uveal melanocytosis or melanoma [50]. Appropriate referral should be made if hairline pigmentation is observed as it can indicate meningeal melanoma and palate pigmentation that can indicate esophageal melanoma.

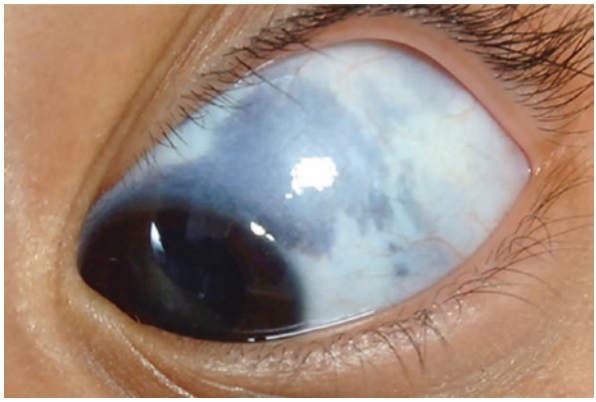

Fig. 13.12 Congenital melanosis oculi: Bluish episcleral discoloration of left eye is seen in a 10-year-old female with unilateral periocular pigmentation

13.10 Stromal Tumors of the Ocular Surface

13.10.1 Lymphoproliferative Tumors

Lymphoproliferative tumors of conjunctiva present as a spectrum, which may appear identical clinically, but vary from benign to malignant lesions. These includes

- Reactive lymphoid hyperplasia.
- Atypical lymphoid hyperplasia.
- Conjunctival lymphoma.

Conjunctival lymphoid tumors can appear as an isolated lesion but in one-third of patients it is a manifestation of coexisting systemic lymphoma either simultaneously or at follow-up [72, 73]. Lymphoid tumor of conjunctiva may involve additional ocular sites mainly orbit.

Clinical Features: Symptoms include an obvious conjunctival mass or occasionally non-specific symptoms like irritation, epiphora, ptosis, proptosis, blurred vision, or diplopia [73]. Clinically the lesion appears as diffuse, slightly elevated, subconjunctival orangish pink mass resembling smoked salmon (salmon patch) (Fig. 13.13a). Most common site is bulbar conjunctiva and fornices (Fig. 13.13b). It can be hidden under the eyelids if present in the superior and inferior quadrant. Caruncle or plica semilunaris can also get involved but it rarely occurs in palpebral conjunctiva [73]. In unilateral cases, chance of systemic lymphoma is 17%, and if bilateral the chance is 47%. Systemic lymphoma occurs in 15% of patients at 5 years and 28% in 10 years [74, 75].

Histology: Lesion shows solid sheets of lymphocytes, with overlap between benign reactive lymphoid hyperplasia, atypical lymphoid hyperplasia, and malignant lymphoma. Benign reactive lymphoid hyperplasia is generally polymorphic, with well-differentiated lymphocytes and plasma cells, while lymphoma tends to be more monomorphic and poorly differentiated. The vast majority of the lesions are non-Hodgkin's B-cell lymphoma, mostly low-grade; T-cell lymphoma being

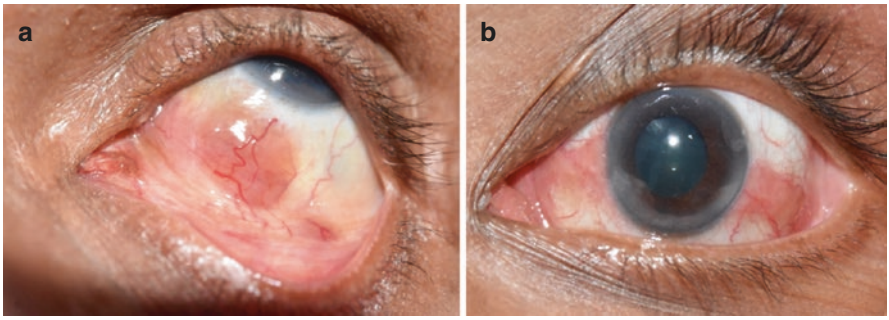

Fig. 13.13 Conjunctival Lymphoma: (**a**) A 57-year-old male showing orange red subconjunctival multifocal mass with feeder vessels in the inferobulbar and forniceal conjunctiva of left eye. (**b**) It shows orange colored lesion in the temporal and bulbar conjunctiva of the left eye of a 50-year-old lady with bilateral presentation. Histopathology revealed low-grade extranodal marginal zone non-Hodgkins B-cell lymphoma

extremely rare in conjunctiva. The main primary oculo-adnexal lymphoma subtypes include extra nodal marginal zone B-cell lymphoma (ENMZL), diffuse large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma [74].

Treatment: Modalities include excisional biopsy and low-dose external beam radiotherapy. Systemic involvement is managed with specific systemic chemotherapy protocols [73, 75]. A thorough systemic evaluation is also important to rule out systemic lymphoma. Main prognostic factors for developing systemic lymphoma include presence of lymphoma in the fornix or mid bulbar conjunctiva and presence of multifocal or bilateral tumors. Other factors include lymphoma subtype, and stage of the disease at presentation. Most cases of conjunctival lymphoma are low-grade B-cell non-Hodgkin's lymphomas where mortality is low.

13.11 Vascular Stromal Tumors

13.11.1 Capillary Hemangioma

Conjunctival capillary hemangioma is rare unlike its counterpart in the eyelids. According to the latest classification of vascular tumors by International Society for the Study of Vascular Anomalies (ISSVA), it is recognized as a benign vascular tumor [76].

Clinical Features: It presents at birth along with the eyelid lesion involving the conjunctiva, which may grow over several months and then regress spontaneously over several years. Spontaneous regression is often complete by 4–5 years of age.

Clinically it appears as focal or diffuse red elevated conjunctival lesion.

Histologically it shows lobules of proliferating endothelial cells separated by thin fibrous septa.

Treatment: Spontaneous regression is common and hence observation with follow-up in most cases suffices. Solitary conjunctival hemangioma can be excised [77].

13.11.2 Cavernous Hemangioma

Conjunctival cavernous hemangioma is rare, unlike the orbital counterpart. Cavernous hemangioma is not a vascular tumor, but rather a congenital vascular anomaly. It is classified as a venous malformation (VM) in the slow-flow lesion category by ISSVA [76]. Clinically, it presents as a red or blue lesion in deep conjunctival stroma.

Histologically, it presents dilated congested veins separated by connective tissue with smooth muscles in the walls of the blood vessels.

Treatment: Excision biopsy.

13.11.3 Varix

Varix is a rare vascular malformation of the conjunctiva. It is a mass of dilated venous channels ranging from a single channel to complex venous channels (Fig. 13.14). It is considered as a spectrum of lymphangioma. Often, conjunctival varix is an extension of an orbital varix. Management includes observation with symptomatic treatment. Surgical excision has the risk of prolonged bleeding.

13.11.4 Racemose Hemangioma

This lesion appears as loop of dilated vessels in conjunctival stroma without any direction and any inciting factor for vascularization. It is formed by dilated arteries and veins communicating directly without the capillary bed between them. Association with Wyburn-Mason syndrome is known. Similar malformation can occur in retina. Treatment includes observation.

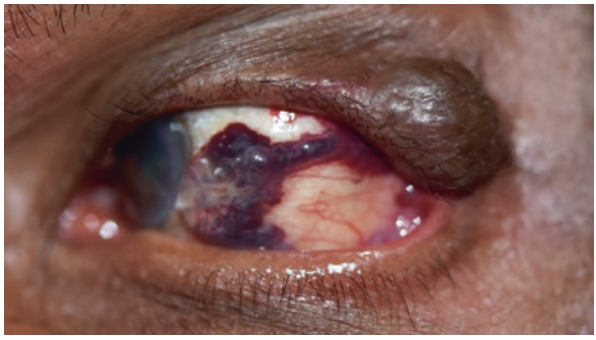

Fig. 13.14 Conjunctival varix: A 66-year-old gentleman showing dilated vascular channels in the bulbar conjunctiva extending from the eyelid and orbit of left eye

13.11.5 Lymphangiectasia

Lymphangiectasia is a condition of dilated, prominent lymphatic channels in conjunctiva.

There can be a communication with conjunctival veins and these dilated channels may be filled with blood (hemorrhagic lymphangiectasia). The surrounding conjunctiva may be edematous, and occasionally associated subconjunctival hemorrhage is present. It can have a spontaneous occurrence or following a trauma or inflammation. Usually no treatment is required unless it is a cosmetic blemish and patient is keen on excision.

13.11.6 Lymphangioma

Lymphangioma is a venolymphatic malformation appearing in the first decade of life. It can either occur as an isolated conjunctival lesion or may represent as the superficial component of the orbital lymphangioma.

Clinical Features: It appears as a multiloculated lesions made up of dilated cystic spaces containing clear fluids or blood (chocolate cysts).

Histology: Lesion shows a non-encapsulated, irregular mass composed of numerous cyst-like channels containing clear fluid and/or blood. The channels are lined by endothelial cells and separated by loose connective tissue [78].

Treatment: Surgical debulking is the treatment of choice, which alone might not eradicate the whole lesion. Other options include CO_2 laser-assisted debulking, β irradiation using strontium 90 applicator, and brachytherapy [79, 80]. Local injection with bleomycin, pingyamicin or picibanil is also considered as an option.

13.11.7 Hemangiopericytoma

Rarely seen in the conjunctiva, hemangiopericytoma appears as an elevated, pedunculated red mass [81].

Histology: It is a solid tumor composed of spindle-shaped pericytes and small blood vessels. According to recent literature it is considered as a vascular entity of solitary fibrous tumor.

Treatment: Wide surgical excision with tumor-free margins.

13.11.8 Pyogenic Granuloma

The term ‘pyogenic granuloma’ is a misnomer, as it is neither pyogenic nor granulomatous. It is a fibrovascular response to a tissue insult due to surgical or nonsurgical trauma or inflammation. Spontaneous lesions have also been reported. IVSSA classifies pyogenic granuloma as benign vascular tumor [76].

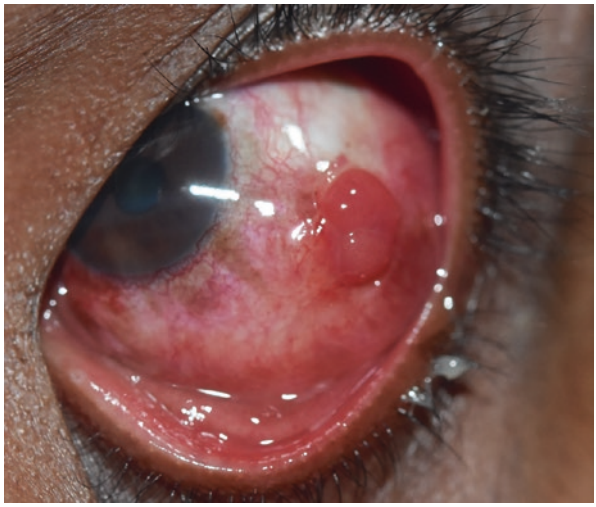

Fig. 13.15 Conjunctival pyogenic granuloma: A reddish, lobular, pedunculated, fleshy lesion with surrounding congestion in the left eye of a 30-year-old male who recently underwent conjunctival surgery

Clinical features: It can appear in any part of the conjunctiva and presents as a round or ovoid, typically pedunculated rarely broad-based, fleshy, red, richly vascularized mass (Fig. 13.15).

Histology: Granulation tissue with marked chronic inflammation and proliferation of numerous small caliber blood vessels is seen.

Treatment: Topical steroids work well if diagnosed early. In case of larger, unsightly, symptomatic, or bleeding lesions excision at the base followed by cauterization or cryotherapy to the excision base is the treatment of choice. Importance of detailed examination is important with slit lamp biomicroscopy, as the inciting factors like a suture knot or foreign body is commonly seen at the base in case of history of prior surgery or trauma. Inciting factor needs to be removed to prevent recurrence. Exuberant recurrence can be treated with low-dose plaque brachytherapy [82].

13.11.9 Kaposi's Sarcoma

It is a malignant tumor seen in immunocompromised individuals. The incidence has increased since the AIDS epidemic and it is diagnosed much more frequently now. Its importance lies in the fact that this lesion can be a first sign of an immunocompromised status [83].

Clinical features: It appears as a single or multiple, vascular red conjunctival mass associated with subconjunctival hemorrhage. They can become confluent and resemble hemorrhagic conjunctivitis [83].

Histology: Malignant spindle-shaped cells with elongated oval nuclei, well-formed capillary channels, and vascular slits containing blood but no endothelial lining is seen.

Treatment: It is treated by promptly instituting highly active antiretroviral therapy. It is known to involute with improvement of immune status.

13.12 Fibrous Tumors of Conjunctiva

13.12.1 Fibroma

It is a rare acquired, white stromal conjunctival tumor, which is slowly progressive in adults and clinically presents as a well-circumscribed lesion or a multi nodular lesion. Histology shows compact fibroblasts and collagen. Treatment is by complete surgical excision. Malignant fibrosarcoma has been reported [86, 87].

13.12.2 Nodular Fasciitis

Nodular fasciitis is a benign lesion that can occur at any age as a solitary white nodular tumor at the limbus or anterior to recti insertion. This nodule can grow quickly and show signs of inflammation. It is thought to originate from Tenon's capsule [88]. Treatment is with complete surgical excision. Recurrence can occur even after complete excision.

13.13 Neural Tumors of Ocular Surface

13.13.1 Neurofibroma

Neurofibroma is a peripheral nerve sheath tumor that appears as a solitary, circumscribed pink-yellow growing mass or diffuse plexiform mass. The latter is associated with neurofibromatosis type 1 (Von Recklinghausen's disease). Solitary tumor is usually treated by complete surgical excision [89].

13.13.2 Schwannoma (Neurilemmoma)

These are rare benign tumors that can occur in any part of conjunctiva.

Clinical features: It appears as a pink-yellow elevated mass, which grows slowly and can have dilated conjunctival or episcleral nutrient vessels.

Histology: It shows proliferation of Schwann cells of peripheral nerve sheath and is composed of spindle cells that may be arranged as Antoni A or Antoni B pattern.

Treatment: Complete excision along with tumor capsule [90].

13.13.3 Granular Cell Tumor

This is a rare benign tumor of disputed origin. This is also called as myoblastoma because originally it was thought to arise from striated muscles. Recently, it is suggested that it is a neural derivative probably from Schwann cells [91].

Clinical features: It appears as a pink, elevated, smooth mass of conjunctival stroma.

Histology: It shows groups and cords of cells with small round to oval nuclei and cytoplasm containing fine eosinophilic granules. Pseudoepitheliomatous hyperplasia of the overlying conjunctival epithelium is a recognized feature of the tumor.

Treatment: Excision biopsy.

13.14 Histiocytic Tumors of Ocular Surface

13.14.1 Xanthogranuloma

Juvenile xanthogranuloma, which is a benign dermatological condition of infants and young adults, can involve the conjunctiva.

Clinical features: It appears as solitary, orange-pink stromal mass, usually near the limbus. Occurrence has been reported in children and in adults [92, 93].

Histology: It shows typical findings of histiocytes and Touton giant cells along with lymphocytes, plasma cells, and eosinophils.

Treatment: It includes excision biopsy in most cases. When clinically suspected it may be observed for spontaneous resolution or treated with topical or systemic corticosteroids.

13.14.2 Xanthoma

Conjunctival xanthoma presents as a yellow sub epithelial mass on bulbar conjunctiva. Histology shows lipid-laden histiocytes, eosinophils and Touton giant cells. In xanthoma disseminatum multiple limbal lesions are seen in both eyes [94].

13.14.3 Reticulohistiocytoma

This is a rare benign conjunctival lesion that usually occurs as a part of systemic disorder called 'multicentric reticulohistiocytosis.' Clinically reported cases are described as single, painless mass localized to cornea or limbus without systemic disease [95]. Histology shows large mononuclear cells and few multi-nucleated cells with finely granular ground-glass cytoplasm and large nuclei with prominent nucleoli. Treatment involves complete excision.

13.15 Myxoid Tumors

13.15.1 Myxoma

Conjunctival myxomas are rare benign stromal tumors occurring in adults.

Clinical features: It presents as a unilateral, well-circumscribed, solitary, freely movable pinkish fleshy lesion that can occur in any part of the conjunctiva but commonly seen in temporal, bulbar conjunctiva [96].

Histology: The lesion is hypocellular and composed of stellate and spindle-shaped cells with abundant mucoid material, sparse reticulin, and delicate collagen fibers in the stroma.

Treatment: Excision biopsy is curative. Eyelid and conjunctival myxomas may be associated with Carney's complex. Cardiac evaluation to rule out cardiac myxoma, which is a life-threatening condition, must be done in these cases.

13.16 Conjunctival Stromal Tumors (COST)

Based on a case series, Herwig et al. recently described a unique group of lesions termed as conjunctival stromal tumors (COST). Clinically, it resembles conjunctival myxoma, but carries different immunomarker profile with positive CD34 unlike in myxoma. The name COST was deduced from gastrointestinal stromal tumor (GIST) with a partially similar immunohistochemistry profile.

Clinical features: These are benign mesenchymal tumors most commonly occurring in bulbar conjunctiva in middle-aged patients. The clinical presentation is heterogeneous, occurring as translucent to reddish conjunctival lesions. Inflammatory stimulus from posterior blepharitis or a reactive process has been proposed for the pathogenesis of these lesions.

Histology: The lesion consists of spindle-shaped cells with pseudo nuclear inclusions and multinucleate cells in a collagenous-to-myxoid stroma. Positive markers for COST include CD34, vimentin, and partially for CD68; negative markers include S100 and smooth muscle actin. Most important differential diagnosis is myxoma which needs to be ruled out because of its association with Carney's complex as described previously.

Treatment: Excision biopsy. Local recurrence is common if incompletely excised [97].

13.17 Myogenic Tumors

13.17.1 Rhabdomyosarcoma

Rhabdomyosarcoma is the most common childhood primary orbital malignancy, but isolated conjunctival involvement is rare. Most commonly conjunctival component is seen in embryonal variety of rhabdomyosarcoma [98, 99].

Clinical features: It appears as a pink, rapidly growing, vascular conjunctival mass. Initially a non-inflamed pedicle of soft tissue can occur, but in most cases swelling and erythema precedes visible tumor formation.

Treatment: Complete surgical excision with protocol-based adjuvant chemotherapy and radiotherapy is the treatment of choice for rhabdomyosarcoma localized to the conjunctiva [98].

13.18 Lipomatous Tumor

13.18.1 Lipoma and Liposarcoma

Conjunctival lipoma occurs in adults. Clinically it appears as a yellow-pink stromal mass [9]. Histology shows variably sized adipocytes surrounded by stellate cells and loose myxoid stroma. Liposarcoma is the malignant counterpart, which appears similar to lipoma clinically. Histology shows numerous neoplastic cells containing stellate and hyperchromatic nuclei. Signet ring type cells can be seen with myxomatous stroma.

Treatment involves complete surgical excision [9].

13.19 Metastatic and Secondary Tumors

13.19.1 Metastatic Tumors

Metastatic tumors of conjunctiva are rare and occur in advanced stages of systemic malignancy when there is evidence of organ metastases most commonly from breast carcinoma or cutaneous melanoma. Clinically metastases will appear as a fleshy, yellow, or pink vascularized tumor. Metastases from cutaneous melanoma are pigmented lesions. These lesions can occur in any part of the conjunctiva. Treatment involves excision biopsy, radiotherapy, and/or chemotherapy [61].

13.19.2 Leukemic Infiltrates

Ocular involvement in leukemia is most commonly seen in choroid and retina, but conjunctival involvement is also well recognized. In fact, conjunctival involvement has been reported as the presenting manifestation of acute leukemia in some patients or a sign of relapse.

Clinical features: It can have variable presentation involving one or both eyes, have focal or diffuse infiltration of substantia propria, can occur on bulbar or palpebral conjunctiva or cause leukocytosis [100]. It has a spectrum of presentation, ranging from subconjunctival hemorrhage to direct infiltration of the tissue with leukemic cells but often manifests as a firm, non-tender, pink smooth mass associated with hemorrhage.

Histology: Conjunctival lesions are diffuse or patchy cellular invasions at level of substantia propria usually along blood vessels.

Treatment: It includes combination of chemotherapy and local radiotherapy. Local response is good in most cases although mortality is high due to systemic disease. Conjunctival leukemic involvement indicates a poor prognosis for the patient with a median survival of 3 months [100].

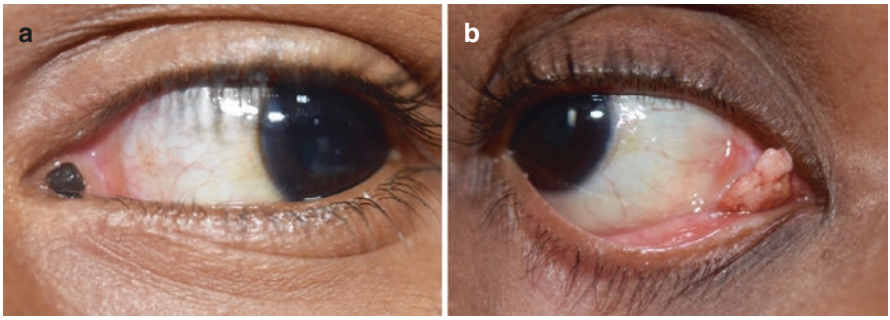

Fig. 13.16 Caruncular tumors (**a**) Melanotic lesion in the caruncle of the left eye of a 25-year-old female. (**b**) Sebaceous gland hypertrophy—Yellowish pedunculated mass is seen arising in the caruncle of the right eye of a 45-year-old female

13.19.3 Secondary Tumors

The conjunctiva can be secondarily involved by intraocular tumors, which can exhibit extra ocular extension, or tumors of adjacent structures, particularly by direct extension from the tumor of the eyelid. Most important is the sebaceous gland carcinoma of the eyelid which can exhibit pagetoid invasion and direct invasion into the conjunctival epithelium [9]. Extension of uveal melanoma through sclera into the conjunctiva can simulate conjunctival melanoma. Rhabdomyosarcoma of the orbit in children occasionally presents first with its conjunctival component.

13.20 Caruncular Tumors and Cysts

The caruncle is a unique anatomic structure containing elements of both conjunctiva and skin. The lesions occurring in the caruncle are similar to those that occur in mucous membranes and cutaneous structures [9, 101]. By histopathological analysis, 95% of the caruncular lesions are benign, and 5% are malignant [102]. The most common lesions in the caruncle include papilloma and nevus (Fig. 13.16a). Other lesions of caruncle include pyogenic granuloma, inclusion cysts, sebaceous hyperplasia, sebaceous adenoma, and oncocytoma (Fig. 13.16b).

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Eyelid Tumors: The Entire Spectrum

14

Fairooz P. Manjandavida and Shaifali Chahar

14.1 Anatomical Consideration

Eyelids form the covering over the eye, essential for normal functioning and integrity of the ocular surface and eyeball. It can be grossly divided into anterior lamella and posterior lamella. Anterior lamella consists of skin and orbicularis oculi muscle, while the posterior lamella is made up of tarsal conjunctiva and the tarsal plates, the main skeleton of the eyelids. The lid margin is a composite structure, containing hair follicles and glands associated with it, and opening of meibomian glands. It forms transition zone between the tarsal conjunctiva and the skin of the lid.

14.1.1 Gross Anatomy

1. Each eyelid consists of the following layers from anterior to posterior:
   (a) Skin—epidermis, dermis, and appendages
   (b) Subcutaneous areolar tissue
   (c) Layer of striated muscles—orbicularis oculi and levator palpebrae superioris in upper lid; and lower lid retractors in lower lid
   (d) Sub muscular areolar tissue—pre-tarsal space and pre-septal space
   (e) Fibrous layer—tarsal plate, septum orbitale, medial, and lateral palpebral ligaments
   (f) Layer of nonstriated muscle—Muller's muscle
   (g) Conjunctiva—tarsal conjunctiva

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Eyelid tumors, benign or malignant can take origin from any of these anatomical structures. These tumors are classified according to the cell of origin and their location.

To understand the cell of origin, microscopic anatomy of the eyelid is briefly described.

14.1.1.1 Epidermis

The epidermis is composed of six to seven layers of stratified squamous epithelium having:

(a) Keratin (stratum corneum)—thin layer of flat cells
(b) Granular cell layer (stratum granulosum)—one to two layers of cells containing keratohyaline granules
(c) Prickle cell layer (stratum spinosum)—polygonal, five cell thick layer with desmosomes, which are intercellular bridges
(d) Basal cell layer (stratum germinatum)—single row of columnar cells that gives rise to the superficial layers

Epidermis houses keratinocytes, melanocytes, Langerhans cells, and Merkel cells.

14.1.1.2 Dermis

Thicker than epidermis, dermis is composed of thin layer of connective tissue with rich network of elastic fibers, blood vessels, lymphatic, and nerves. Dermis lies over orbicularis oculi muscle. Skin appendages (adnexa) are present deep in the dermis or within the tarsus.

14.1.1.3 Glands of the Eyelids

(a) Sebaceous glands are seen in the caruncle, eyebrow hair and associated with thin hair covering the periocular skin.
(b) Meibomian glands are modified sebaceous glands located in tarsal plates.
(c) Gland of Zeiss are modified sebaceous glands associated with lash follicles.
(d) Gland of Moll are modified apocrine sweat glands, which open either in lash follicles or on anterior lid margin between lashes. They are also known as ciliary glands.
(e) Eccrine sweat glands are distributed throughout eyelid skin.

14.1.1.4 Vascular System

The venous and lymphatic system draining the eyelids forms the routes of metastases. The two main arterial sources are internal carotid artery and external carotid artery, anastomoses exists between the two systems. The venous drainage medially is into the angular vein, laterally into the superficial temporal vein and posteriorly into the orbital vein, anterior facial vein and pterygoid plexus. The medial one-third

of upper lid and medial two-third of lower lid portion of the eyelid drains into the submandibular lymph nodes and lateral two-third of upper lid and lateral one-third of lower lid drains to the preauricular lymph nodes that drain to deep cervical lymph nodes.

14.2 Terminologies

Terms used for clinical and histopathological description of eyelid tumors are described in Tables 14.1 and 14.2 respectively.

Table 14.1 Summary of terminologies used for clinical description of eyelid tumors

Clinical Terms	Description
Lesion	Any damage or abnormal change in the tissue
Macule	Flat area of skin discoloration without infiltration or elevation
Papule	Circumscribed, solid elevation of skin with no visible fluid, varying in area from a pinhead to 1 cm
Nodule	Solid area of raised skin resulting from growth of abnormal tissue
Cyst	Sac-like structures with cavity filled with fluid or semisolid materials
Crust	Dried skin exudate
Plaque	Broad, raised area on the skin
Scale	Thickening of horny layer keratin in form of readily detachable fragments
Vesicle	Circumscribed lesion containing fluid
Pustule	Circumscribed lesion containing pus
Ulcer	Circumscribed area of skin loss that extends through the epidermis into dermis

Table 14.2 Summary of terminologies used for histopathological description of eyelid tumors

Terms	Description
1. Hyperkeratosis	Increase in keratin layer
2. Dyskeratosis	Abnormal keratinization occurring prematurely within individual cells or groups of cells below the stratum granulosum; keratinization other than surface
3. Parakeratosis	Retention of nuclei into keratin layer
4. Acanthosis	Increase in squamous cell layer
5. Dysplasia	Presence of cells of an abnormal type within a tissue, which may signify a stage preceding the development of cancer
6. Carcinoma in situ	Dysplastic changes throughout the thickness of the epidermis and marked hyperkeratosis

14.3 Eyelid Tumors

As in other organs of the body, eyelid tumors are classified as benign or malignant and according to their cell of origin. A thorough clinical history and detailed ocular examination is most important for making an accurate clinical diagnosis of the lesion to clinically differentiate benign from malignant tumors. Histopathology gives a definitive diagnosis based on features seen in each type of lesions. Accordingly, appropriate management needs to be planned that differs according to the nature of the tumor. Differentiating features between benign and malignant tumors are summarized in Table 14.3.

Table 14.3 Differentiating features between benign and malignant eyelid tumors

S. no.	Features	Benign	Malignant
1.	History		
	(a) Presenting symptoms	– Painless or painful mass lesion, rarely ulceration or telangiectasia	– Painless mass lesion, ulceration and telangiectasia common
	(b) Rate of onset	– Weeks to months, insidious onset	– Sudden increase or growth
	(c) Past history and systemic association	– Family history is absent, systemic association can be seen	– Past history of lid tumor or family history of neoplasia can be present
2.	Clinical features		
	(a) Induration or ulceration	Absent mostly	Present
	(b) Color	Uniform color	Variable
	(c) Outline	Regular	Irregular
	(d) Growth	Limited growth	Invasion of neighboring structures
	(e) Lid architecture	Maintained	Loss of normal architecture
	(f) Lashes	Lashes intact	Lash loss seen
	(g) Vascularity	Absent	Intrinsic vessels and feeder vessels seen
3.	Microscopic features		
	(a) Cellular proliferation	None/mild (Low Ki-67, low mitotic index)	High (High mitotic index)
	(b) Cellular pleomorphism	None/mild dysplasia	Moderate–severe dysplasia
	(c) Cellular dedifferentiation	None/mild	Mild–severe
	(d) Necrosis	Absent	Occasionally
	(e) Basement membrane invasion	Absent	Frequent
	(f) Metastasis	Absent	Occasionally
4.	Treatment	Simple excision with or without lid reconstruction	Wide margin excision with lid reconstruction with or without chemotherapy or radiotherapy

Most eyelid tumors are cutaneous, epidermis being the most common layer of origin. Benign lesions are much more common and varied than malignant lesions. Malignant tumors comprise 20% of all tumors. A summary of classification of eyelid tumors is provided in Table 14.4. This is based primarily on World Health Organization (WHO) International Histological Classification of Tumor Series [1].

Table 14.4 Summary of benign and malignant eyelid tumors

S. no.	Tumor origin	Benign	Malignant
1.	Epidermis and Dermis	• Squamous papilloma • Basal cell papilloma • Actinic keratosis • Inverted follicular keratosis • Pseudoepitheliomatous hyperplasia • Epidermoid cyst • Dermoid cyst • Inclusion cyst • Sebaceous cyst	• Keratoacanthoma • Squamous cell carcinoma • Basal cell carcinoma
2.	Sebaceous gland	• Sebaceous adenoma • Sebaceous hyperplasia	• Sebaceous gland carcinoma
3.	Eccrine gland	• Syringoma • Eccrine hidrocystoma • Eccrine acrospiroma or hidradenoma • Pleomorphic adenoma	• Syringomatous carcinoma
4.	Apocrine gland	• Apocrine adenoma • Oncocytoma • Syringocystadenoma papilliferum	• Mucin producing sweat-gland adenocarcinoma
5.	Hair follicle	• Trichoepithelioma • Trichofolliculoma • Trichilemmoma • Pilomatrixoma	• Trichilemmal carcinoma
6.	Melanocytic	• Freckle/ephelis • Congenital melanocytic nevus • Acquired melanocytic nevus	• Malignant melanoma
7.	Vascular	• Capillary hemangioma • Port-wine stain/nevus flammeus • Cavernous hemangioma • Lymphangioma • Arterio-venous malformation • Pyogenic granuloma	• Kaposi's sarcoma • Angiosarcoma
8.	Fibrous tissue	• Fibroma • Nodular fasciitis	• Fibrosarcoma
9.	Fibrohistiocytic	• Xanthelasma • Xanthogranuloma • Fibrous histiocytoma • Angiofibroma	• Malignant fibrous histiocytic tumor

(continued)

Table 14.4 (continued)

S. no.	Tumor origin	Benign	Malignant
10.	Neurogenic	• Neurofibroma, plexiform neurofibroma • Schwannoma/neurilemmomas	• Merkel cell carcinoma
11.	Lipomatous	• Lipoma	• Liposarcoma
12.	Smooth muscles	• Leiomyoma	• Leiomyosarcoma
13.	Skeletal muscles	• Rhabdomyoma	• Rhabdomyosarcoma
14.	Miscellaneous	• Milia • Comedones • Chalazion • Molluscum contagiosum	• Eyelid lymphoma • Leukemic infiltration • Metastases

14.4 Benign Eyelid Tumors

14.4.1 Benign Epidermal Tumors and Cysts

14.4.1.1 Squamous Cell Papilloma

(Fibroepithelial polyp, skin tag, acrochordon)

A squamous cell papilloma is the most common benign epithelial eyelid tumor that can have variable clinical appearance. It is commonly seen in middle-aged or older adults.

Clinical features: It presents as a flesh-colored, pedunculated (narrow base) or sessile (broad based) lesion. Variable presentations include presence of a raspberry-like surface, skin tag, or a hyperkeratotic filiform lesion like cutaneous horn (Fig. 14.1).

Histology: Finger like projections of fibrovascular connective tissue covered with irregular acanthotic and hyperkeratotic squamous epithelium with or without chronic inflammation is seen.

Differential diagnoses include viral warts, seborrheic keratosis, and verruca vulgaris.

Treatment: Excision biopsy of the lesion.

14.4.1.2 Basal Cell Papilloma

(Seborrheic keratosis, seborrheic wart, senile verruca)

Basal cell papilloma or Seborrheic keratosis is a common, slow-growing condition found on the face, trunk and extremities of elderly individuals.

Clinical features: It presents as solitary or multiple, well-demarcated, greasy, warty plaques that vary in shape, size, surface, and pigmentation. The lesion is typically described to have a ‘stuck-on’ appearance (Fig. 14.2). Surface may appear papillary, cerebriform or have small keratin plugs. Sudden appearance of multiple

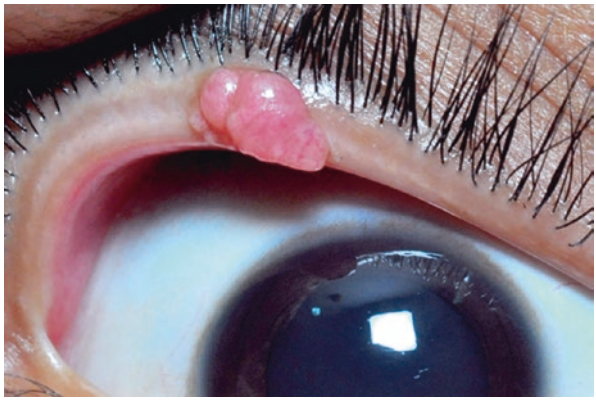

Fig. 14.1 Eyelid papilloma: upperlid of right eye showing fleshy pedunculated mass with papillary fronds

Fig. 14.2 Seborrheic keratosis: bilateral melanotic skin lesions are seen in upper lids. There is a well-demarcated, large greasy plaque like lesion with a 'stuck-on' appearance in the left upper lid

seborrheic keratosis (sign of Lesser–Trélat) or rapid growth of previous lesion must raise a suspicion of internal malignancy like intestinal adenocarcinomas [2].

Histology: The lesion is above the skin surface which shows expansion of squamous epithelium of the epidermis by proliferation of basal cells. There is acanthotic proliferation of basaloid cells with various degrees of hyperkeratosis and keratin filled cystic inclusions (horn-cysts or 'pseudo-horn' cysts). Pigmentation is due to transfer of melanin into keratinocytes.

Treatment: Excision biopsy.

14.4.1.3 Inverted Follicular Keratosis

Most frequently seen at the eyelid margin, this is a benign, solitary nodule or papillary keratotic mass with or without pigmentation. This can be mistaken for squamous cell carcinoma [3].

Histology: Proliferation of basaloid and squamous elements with variable pigmentation, acantholysis and chronic inflammation. Inverted follicular keratosis is a 'misnomer'. It should be considered as a form of irritated seborrheic keratosis [4].

Treatment: Excision biopsy.

14.4.1.4 Actinic Keratosis

(Solar keratosis, senile keratosis)

Actinic keratosis is the most common precancerous eyelid lesion. It has a low potential of transformation into low-grade squamous cell carcinoma (SCC). Currently, it is considered an incipient form of SCC [5].

Etiology: Common in elderly, fair skinned individuals with a history of excessive sunlight exposure.

Clinical features: It presents as single or multiple, small, erythematous, scaly, sessile lesions which are hyperkeratotic with fissured or nodular surface which may give rise to cutaneous horn.

Histology: Epithelium shows squamous dysplasia with loss of cell polarity and dysmaturation. It shows varying degree of hyperkeratosis, and parakeratosis with low mitotic activity. Histologically, four types of actinic keratosis are recognized: Hypertrophic, atrophic, acantholytic, and lichenoid. It can be seen at the margins of invasive SCC. Annual rate of malignant transformation shown by population-based studies is 0.01% [6].

Treatment: Excision biopsy, especially of suspicious lesions, with histopathological examination to rule out SCC. Topical chemotherapeutic agents or cryotherapy are other modalities of treatment of benign looking lesions.

14.4.1.5 Pseudoepitheliomatous (Pseudocarcinomatous) Hyperplasia

It can appear as an elevated lesion with irregular surface, sometimes with ulceration or crust anywhere on the eyelid. The lesion occurs as a result of trauma, surgical wound, burns, cryotherapy, insect bites, etc.

Histology: Lesion shows inflammatory cells with occasional multinucleate giant cells and eosinophils. Cytological atypia may occur. This lesion can be clinically and histopathologically confused with basal cell carcinoma (BCC) or SCC.

Treatment: Excision biopsy with additional cryotherapy is the most appropriate management.

14.4.1.6 Epidermoid Cyst

Epidermoid cyst is the most common type of benign periocular cutaneous lesion, resulting from proliferation of epidermal cells. Cyst formation may occur following trauma or surgery.

Clinically, it presents as solitary, elevated, round, firm, subcutaneous mass with smooth overlying skin, freely mobile or immobile if attached to underlying tarsus that progresses slowly (Fig. 14.3).

Histology shows cyst lined by squamous epithelium and cheesy material (keratin) produced by inner layer of squamous epithelium.

Treatment: Excision biopsy.

14.4.1.7 Dermoid Cyst

Dermoid cyst occurs at the site of the suture lines during the development of embryonic fissure. It is a form of congenital choristoma. Anterior lesions present as subcutaneous, smooth, well-circumscribed mobile nodule most commonly located at

Fig. 14.3 Epidermoid cyst: elevated non-tender subcutaneous nodule in the upper lid

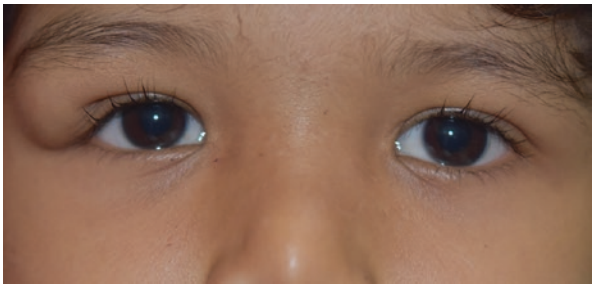

Fig. 14.4 Dermoid cyst: well-circumscribed soft mass in a child, gradually progressing in size. It is located at the lateral orbital rim overlying the frontozygomatic sutures

frontozygomatic suture causing a painless fullness of upper eyelid at lateral orbital rim (Fig. 14.4). Deeper cysts with orbital extension have limited mobility and larger cysts cause proptosis and diplopia. Computerized tomography imaging helps in detecting orbital extension.

Histology: Cyst walls are lined by keratinized epithelium containing adnexal structures as hair follicles, sebaceous glands and sweat glands. Cystic cavity is filled with sebaceous fluid, keratin, calcium, and cholesterol crystals.

Treatment: Excision biopsy is the treatment of choice. The cyst should be removed completely to avoid recurrence and ideally without rupture to avoid inflammation.

14.4.1.8 Epidermal Inclusion Cyst

These are subcutaneous lesions caused by implantation of epidermis into dermis following trauma or surgery. Clinically, the cyst presents as a slow-growing firm round lesion that contains keratin.

Treatment: Excision biopsy.

Milia are miniature variant of epidermal cysts. Comedones resemble epidermal cyst histologically. Clinically comedonal cyst can be a black head (opening on to the surface) or a white head (blocked opening).

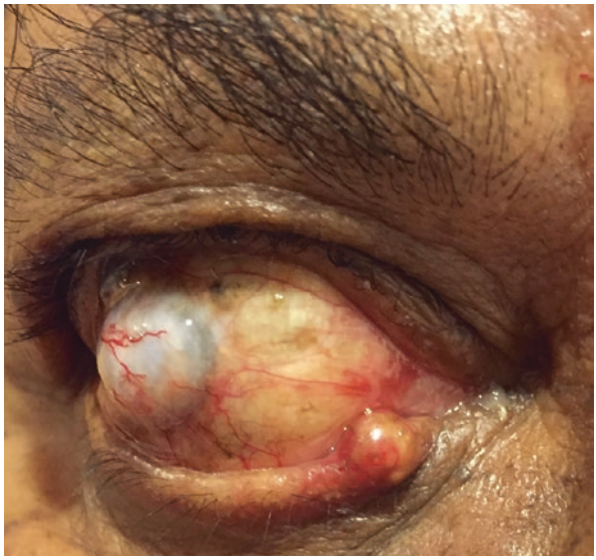

Fig. 14.5 Elevated nodular lesion in the lower lid margin. There is loss of lashed noted with sharp posterior lid margin. Sebaceous gland carcinoma is the differential diagnosis

14.4.1.9 Sebaceous Cyst

It is a sebum-containing cyst that forms as a result of blocked pilosebaceous follicle. It can appear clinically as an inclusion cyst, occasionally a punctum can be seen on the surface.

Treatment: Excision biopsy.

14.4.2 Benign Sebaceous Gland Tumors

14.4.2.1 Sebaceous Gland Adenoma

Most commonly seen on face and scalp of elderly individuals, sebaceous gland adenoma presents as yellow or reddish nodule, approximately 5 mm in size, and typically maintains lobular or organoid architecture (Fig. 14.5). Histopathologically, it has features of hyperplastic sebaceous gland surrounding centrally located dilated sebaceous duct. If seen in young individuals it should raise suspicion regarding Muir–Torre syndrome [7].

14.4.2.2 Sebaceous Gland Hyperplasia

Most commonly seen in elderly individuals, sebaceous gland hyperplasia shows similar histopathology to sebaceous gland adenoma. Clinically, it presents as a yellow, elevated soft umblicated nodule, 1–2 mm in size. Expansion and increased prominence of the peripherally located basaloid cells discriminates between sebaceous hyperplasia and sebaceous adenoma or sebaceoma. It can be mistaken for basal cell carcinoma.

Treatment: Excision biopsy. If subtotal excision is performed chances of regrowth are high. Sudden increase in size or number especially in younger individuals must be evaluated for internal malignancy (Muir–Torre syndrome) [7].

14.4.3 Benign Sweat Gland Tumors

Sweat glands in the eyelid are classified as being either apocrine or eccrine in origin. Histopathologically, the apocrine glands show decapitation secretion whereas eccrine glands are water-producing cysts. The former tends to be much more common in the eyelids than their eccrine counterparts.

The apocrine glands of Moll are exclusively localized at or near the eyelid margin and canthi whereas eccrine sweat glands are found several millimeters from the lid margin in pre-tarsal and pre-septal skin.

14.4.3.1 Benign Eccrine Gland Tumors

Syringoma

Syringoma is a benign proliferation of eccrine sweat gland, usually seen in young females.

It can bilaterally presents as multiple colored papules on face, eyelids, and cheeks (Fig. 14.6).

Histology: A mixture of interconnected eccrine ducts is embedded in fibrous stroma. The walls of the ducts are usually lined by two rows of epithelial cells without myoepithelial cells.

Treatment: Cryotherapy, dermabrasion, or cauterization may be performed for aesthetic purpose.

Eccrine Hidrocystoma

Most common benign sweat-gland tumor of the eyelids, eccrine hidrocystoma, is seen in adults either as a solitary clear cystic lesion or with simultaneous bilateral involvement. It generally varies in size from 4 to 10 mm occurring near the eyelid margin (Fig. 14.7). Histopathologically, it shows markedly dilated sweat-gland duct.

Treatment: Excision, electrodessication, CO_2 laser vaporization, and laser treatment are some of the options**.**

Eccrine Acrospiroma

(Nodular hidradenoma, clear cell hidradenoma, solid cystic hidradenoma) [8, 9]

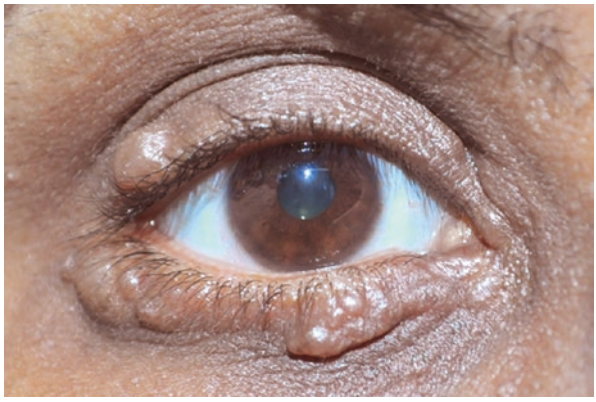

Fig. 14.6 Multiple skin-colored papules in the lower lid and upper lid is seen

Fig. 14.7 Solitary translucent cystic lesion seen arising from the eyelid skin medially

Eccrine acrospiroma ('acro': top most or end; 'spiroma': adenoma of sweat gland) is a benign lesion that resembles the cells and structures of ductal segment of eccrine sweat glands.

Clinically, it manifests as a single, slow-growing, well-circumscribed, mobile, cutaneous nodule ranging from 0.5 to 3 cm in diameter. Color changes on skin surface, skin thickening, serous discharge or tenderness can be seen sometimes.

Histology: Hidradenoma is composed of epithelial lobules within the dermis, showing tubular lumina lined by cuboidal or columnar cells with cystic spaces that contain faintly eosinophilic material. The solid component of the tumor is comprised of two types of cells, namely epidermoid cells and glycogen-rich clear cell. Malignant variant of these lesions is reported.

Primary skin tumors with follicular, sebaceous, or sweat gland should be differentiated. Hidradenomas can mimic cutaneous metastatic disease from clear cell tumors such as renal cell carcinoma [10]. In such cases, immunohistochemical analysis after an excision biopsy becomes essential to distinguish these entities.

Treatment: Excision biopsy with immunohistochemical analysis if required.

Pleomorphic Adenoma

(Benign mixed tumor, chondroid syringoma)

Pleomorphic adenoma is very rare in the eyelids. It arises from skin sweat glands and clinically appears as intradermal multilobulated firm or cystic subcutaneous nodule, which is slow growing. Histologically, it is identical to pleomorphic adenoma of the lacrimal glands. Like the counterpart it can also exhibit malignant transformation.

14.4.3.2 Benign Apocrine Gland Tumor

Even though multiple apocrine glands (Gland of moll) are distributed throughout the eyelid, benign tumors of apocrine origin are rare. These tumors are considered to be clinically and pathologically a diagnostic challenge.

Apocrine Adenoma

Apocrine adenoma is a rare benign tumor arising from the gland of Moll. According to the WHO classification of apocrine tumors, terms apocrine adenoma, tubular adenoma, tubulopapillary hidradenoma, and papillary tubular adenoma are synonyms [11]. Syringocystadenoma papilliferum, apocrine gland cyst (apocrine hidrocystoma or apocrine cystadenoma) and tubular papillary adenoma with apocrine differentiation (tubular apocrine adenoma) represent one spectrum with distinct architectural characteristics [12].

Clinical features: Apocrine adenoma presents a well-circumscribed, skin-colored, non-ulcerated nodule at the eyelid margin associated with telangiectasia. Tubular apocrine adenoma morphologically overlaps with papillary eccrine adenoma presenting as a spectrum.

Histology: Tubular papillary adenoma, as the name describes is composed of multiple tubules lined by dual layer of epithelium with an apocrine type or decapitation secretion within the luminal cell layer. Histopathological differentiation from other entities includes lack of papillary projections and cystic invaginations from the epidermis and absence of inflammatory plasma cells. Definitive diagnosis is made by histopathological analysis demonstrating characteristic features such as apical decapitation snouts, the limited presence of plasma cells.

Treatment: Excision biopsy.

Apocrine Hidrocystoma

(Cyst of Moll, cystadenoma, apocrine tubular adenoma)

Apocrine hidrocystoma presents a solitary nodule affecting middle-aged people. Clinically, it appears as a cystic lesion involving eyelid margin (Fig. 14.8). Multiple lesions are part of an autosomal recessive ectodermal dysplasia called Schopf–Schulz–Passarge syndrome [13].

Treatment: Excision, electrodessication, CO_2 laser vaporization, and laser treatment are some of the treatment options.

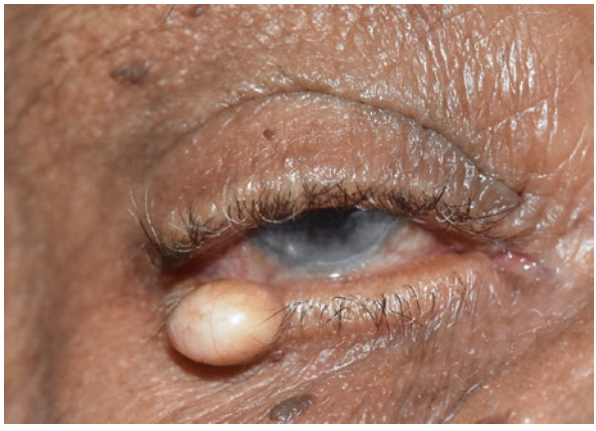

Fig. 14.8 Solitary whitish cyst involving the lower eyelid that is opaque with turbid secretion

Syringocystadenoma Papilleferum

It is a benign lesion that rarely affects the eyelids but is frequently misdiagnosed as basal cell or squamous cell carcinoma. It is believed to be derived from apocrine rather than eccrine sweat gland. It is seen in childhood, mostly at birth, and sometimes occurs around puberty.

Tumor is usually described as a skin-colored to pink, hairless, firm plaque of grouped nodules or as a solitary nodule. Cauliflower-like, verrucous, papillary, hyperkeratotic, or sometimes moist fleshy excrescences have also been described. Some tumors may show central umblication [14]. Most of the lesions enlarge slowly, although a few can increase significantly within a short period. Also, the lesion can develop ulceration and secondary infection. Malignant counterpart is described which is syringoadenocarcinoma papilliferum.

The diagnosis is clinically suspected and histologically confirmed. Ulceration or a rapid enlargement of an existing tumor is indicative of a malignant transformation.

Treatment: Excision biopsy

Oncocytoma

(Oxyphilic adenomas)

Oncocytomas are benign neoplasms of oncocytic cells, occurring at a variety of sites, commonly scalp. Ocular oncocytomas are most commonly seen in the caruncle, followed by lacrimal sac and very rarely on eyelids.

Clinically, this tumor presents as a slow-growing mass that is often tan red in color.

Histology: Oncocytoma probably represents an age-associated metaplastic and neoplastic transformation of the glandular epithelium.

Malignant oncocytomas occurring in the ocular adnexa have been reported. The differential diagnosis includes amelanocytic melanoma, amelanocytic nevus, benign epithelial tumors, pyogenic granulomas, and hemangiomas.

Treatment: Complete surgical excision with primary repair of the resulting defect. In case of incomplete excision, recurrence is common. The recurrence can be locally aggressive and occasionally turn malignant.

14.4.4 Benign Hair Follicle Tumors

14.4.4.1 Trichoepithelioma

Trichoepitheliomas are benign hamartomas arising from the walls of the hair follicle, most commonly seen in the fourth decade. Clinically, they present as a skin-colored, firm nodule without ulceration that increases in size over time. Large lesions can show surface telangiectasia. Multiple trichoepitheliomas are usually inherited and maybe associated with Spiegler–Brookler syndrome along with other adnexal tumors [15].

If ulceration is present, it can be misdiagnosed as basal cell carcinoma.

Histology: Numerous keratinous cysts, lacy pattern of tumor cells, dense stroma, minimal inflammation, and absence of abnormal hair follicles are seen.

Treatment: Excision biopsy with histopathological evaluation gives a definitive diagnosis.

14.4.4.2 Trichofolliculoma

Trichofolliculoma is an adnexal hamartoma of the skin with differentiation to a hair follicle tumor. Clinically, it presents as a solitary nodule of variable size with central depression. Typically, wool-like wisps of immature hair are seen emerging from the center.

Histology: Secondary hair follicle derived from a primary hair follicle lined by stratified squamous epithelium continuous with surface epithelium. Reactive granulomatous inflammation can be seen surrounding hair shaft fragment.

Treatment: Excision biopsy.

14.4.4.3 Trichilemmoma

Trichilemmoma is a benign tumor that arises from the outer layers of the hair follicle in adults. They appear as a small nodule with either smooth skin-colored papules or warty lesion with irregular rough surface with crusting or ulceration.

Histology: The lesion shows lobular acanthosis of glycogen-rich clear cells with palisading cells having distinct basal membrane in its periphery. Hair follicles may be seen in the lesion.

Multiple lesions should raise a suspicion of the autosomal dominant condition called Cowden's disease (multiple hamartoma syndrome) especially when associated with mucosal lesions like oral papillomas. Systemic evaluation for breast and thyroid carcinoma must be done in such cases [16].

Treatment: Excision biopsy

14.4.4.4 Pilomatrixoma

(Pilomatricoma, Calcifying epithelioma of Malherbe)

Pilomatricoma is the most common benign tumor derived from germinal matrix cells of the hair bulb. It presents as a slow-growing, deep, subcutaneous, pink or purple mobile mass that may be hard due to calcification, seen in upper eyelid or brow of a young patient. It can present as a part of autosomal dominant inherited disorder or systemic disease like Gardner's syndrome [17].

Histology: The tumor appears as a well-demarcated tumor that consists of two cell populations namely the basophilic basaloid cells at the periphery of the lesion, and pale ghost cells toward the center. Most of the tumors show varying degrees of calcifications that may elicit foreign body granulomatous inflammation.

Treatment: Excision biopsy.

14.5 Benign Melanocytic Tumors

14.5.1 Epithelial Pigmentation

14.5.1.1 Freckel/Ephelis

Freckles are flat, brown discoloration of sun-exposed areas, occurring as a result of increased melanin in epidermal basal layer. Histologically, there is hyperpigmentation of the basal cell layer but no elongation of the rete ridges. These can be clinically observed.

14.5.1.2 Lentigo Simplex

Lentigo simplex lesions are small, brown-black macules. Multiple lesions are seldom associated with gastrointestinal polyp and perioral lesion (Peutz–Jeghers syndrome) [18, 19].

14.5.1.3 Solar Lentigo

These lesions are brown macules seen in elderly due to sun exposure. Care should be taken to differentiate this lesion from lentigo maligna and if required biopsy can be done for histopathological confirmation. Clinically, these have uniform pigmentation and regular borders unlike the malignant counterpart.

14.5.1.4 Melanocytic Nevus

Melanocytic nevi are considered as hamartomas or benign tumor of neural crest-derived melanocytes. Histologically, the three main types described according to the location of the nevus cells, are:

1. Junctional nevus–located in the dermo-epidermal junction. It occurs in young individuals as uniform brown macule or plaque. It has a low potential for malignant transformation.
2. Compound nevus–which involves both dermo-epidermal junction and dermis. It occurs in middle-aged individuals as a raised papule, which is tan to dark brown in color. It has a low malignant potential (Fig. 14.9).
3. Intradermal nevus–located only in the dermis. It is the most common form, occurring in older age group as a papillomatous lesion that may show dilated vessels and protruding lashes. It has no malignant potential (Fig. 14.10).

Histopathologically nests of small to large nevus cell or occasionally balloon cells are seen with round to oval or elongated spindle-shaped nuclei with various amounts of melanin. Histopathological variants include balloon cell nevi, halo nevi, spitz nevi (juvenile melanoma), or dysplastic nevi (atypical moles). Spitz nevus and atypical/dysplastic nevus have a higher chance of malignant transformation. These can be congenital or acquired.

Fig. 14.9 Longstanding melanocytic nodular lesion in the lower lid. Lashes are intact and there is no vascularity

Fig. 14.10 Melanotic papillomatous lesion in the lower eyelid with varied pigmentation. There are hair follicles arising from the lesion

Congenital Melanocytic Nevus

Congenital melanocytic nevus is a benign tumor arising from the nevocytes that is seen in 1% of newborns. Clinical presentation includes either as a kissing or split nevus or a giant hairy nevus. Kissing or split nevus involves the upper and the lower eyelid because of nevocyte migration before embryonic separation of the lids (Fig. 14.11).

Arising commonly at the eyelid margin, lesions can be flat, elevated, dome-shaped, or pedunculated. Sized based classification of the congenital nevi depends on the largest diameter, and the lesion is classified as small (<1.5 cm), medium (1.5–19.9 cm), and large or giant nevi (>20 cm) [20]. The risk of malignant transformation is more common in large nevi (>4 cm) which is approximately 4.6% during a 30 years period [21]. The risk is particularly negligible in prepubertal years.

Treatment: The lesion can be cosmetically disfiguring, and sometimes affect visual development if mass on the upper lid causes mechanical ptosis covering the

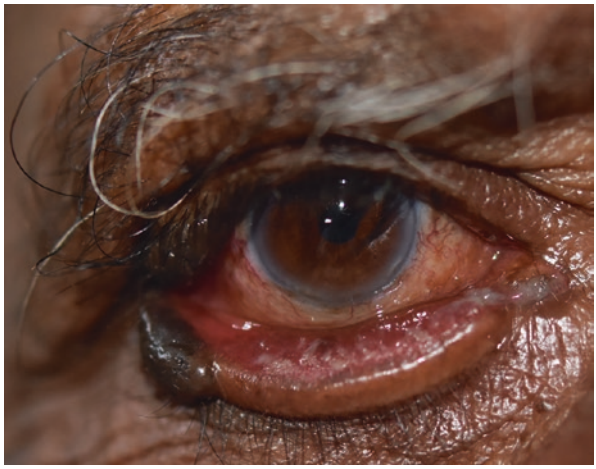

Fig. 14.11 Melanotic well-defined mass involving the lateral one-third of corresponding upper and lower lid. Senile ectropion with a mechanical component is also noted in the lowerlid.

visual axis. In such cases early management is required to prevent amblyopia. Superficial lesion can be treated with dermabrasion early in life. Lesions involving deep dermis require full thickness excision followed by lid reconstruction. Complete excision is important because residual tumor can grow, often with a more verrucous or thickened appearance making subsequent determination of malignant transformation and reconstruction difficult.

Acquired Melanocytic Nevus

Acquired nevi develop in childhood and may grow during adolescence.

Treatment is indicated for cosmetic concerns or if there is a concern about malignancy. Complete excision is warranted, as it may be clinically and histologically difficult to differentiate recurrence from melanoma.

14.5.1.5 Blue Nevus

Blue nevus is a variant of congenital nevus, which occurs as small nodule or flat, pigmented blue-gray lesion. This arises from dermal melanocytes and because of the deep location of the dendritic melanocytes the scattering of light by intervening dermal tissue (Tyndall phenomenon) it appears blue in color. Blue nevi are divided into two main histological groups: (1) common blue nevi which are loosely aggregated spindle shape or dendritiform cells with no mitotic activity; and the (2) cellular blue nevi with cells arranged in islands [22]. The blue nevus can rarely undergo malignant transformation. In the skin, multifocal blue nevi may be associated with lentigenes, atrial myxomas, mucocutaneous myxomas, and blue nevi (LAMB) syndrome found in association with the Carney Complex [23].

14.5.1.6 Nevus of Ota

(Oculodermal melanocytosis)

Oculodermal melanocytosis occurs as a unilateral bluish discoloration of the eyelid and periorbital skin, along with discoloration of bulbar surface. It can appear

at birth or develop in the first year of life or adolescence. It follows the distribution of the first and second divisions of the trigeminal nerve and arises from dermal melanocytes. Patients with nevus of Ota have a small risk of developing cutaneous or uveal melanoma [24]. The lifetime estimate for a white patient with oculodermal melanocytosis to develop uveal melanoma has been calculated in a study by Singh et al. to be 1 in 400 [24].

14.5.2 Benign Vascular Tumors and Malformations

14.5.2.1 Capillary Hemangioma

(Strawberry Nevus)

Capillary hemangioma is the most common vascular tumor of the eyelid. This is recognized as a benign vascular tumor according to the International Society for the Study of Vascular Anomalies (ISSVA) [25].

It presents at birth or within a week of birth. Superficial lesion presents as elevated, soft, bright reddish-purple lesions with surface invagination ('strawberry nevus'), which blanches on pressure and swell up on crying (Fig. 14.12). Subcutaneous or orbital lesion appears bluish in color. It grows rapidly during the first 6–12 months, and after a stable period, 30% regress by 3 years of age and 75–90% by 7 years of age [26]. A large lesion on upper eyelid can cause mechanical ptosis leading to amblyopia in infants. Skin of face and other parts of the body may be involved by the strawberry nevi.

Systemic associations: Extensive disease, which includes visceral capillary hemangioma, can cause sequestration of blood cells causing bleeding disorder (Kassabach–Merritt syndrome) [27].

Histology: Proliferation of varying sized vascular channels separated by fibrous septae. The capillaries may infiltrate the underlying subcutaneous lesion and muscle.

Treatment: Sight threatening, rapidly progressive or recurrent bleeding lesions warrant early intervention. Local treatment consists of intralesional steroid (triamcinolone + dexamethasone) injection. Intralesional triamcinolone is given in a dose of 6 mg/kg of body weight (maximum of 60 mg). Systemic steroids (1–2 mg/kg body weight tapered over 4–6 weeks) is used for extensive lesion. Most recent

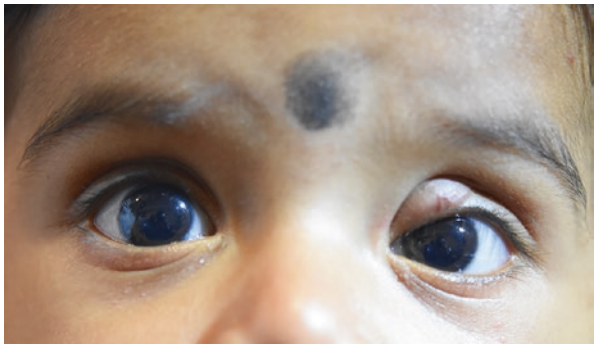

Fig. 14.12 Bluish soft lesion arising in the left upper lid since birth

studies have shown favorable result of systemic propranolol therapy (2 mg/kg body weight per day) for treatment of hemangiomas [28, 29].

14.5.2.2 Cavernous Hemangioma

Rarely seen in eyelids, cavernous hemangioma occurs in the second to fourth decade as a slowly progressive ill-defined lesion typically bluish in color if it is superficial, and if deeper overlying skin can appear normal (Fig. 14.12). Cavernous hemangioma is not a vascular tumor, but rather a congenital vascular anomaly. It is classified as a venous malformation (VM) in the slow-flow lesion category by ISSVA [25].

Histology: Large, dilated, blood-filled vascular spaces lined by a flat layer of endothelium. Lesion may show thrombosis, phlebitis, fibrosis of the septae, and calcification.

Treatment: Corticosteroids remain mainstay of therapy for massive eyelid hemangioma.

14.5.2.3 Port-Wine Stain

(Nevus flammeus)

Port-wine stain is a congenital, diffuse, flat mostly unilateral vascular formation of face involving the eyelid and periocular area (Fig. 14.13). It occurs in the distribution of trigeminal nerve. According to IVSSA classification, it falls under simple vascular malformations.

Clinically it is pink to purple and does not blanch on pressure. Overlying skin can become hypertrophied, friable and may bleed or become infected. Sturge–Weber syndrome (encephalotrigeminal angiomatosis) which can involve the face, leptomeninges, and eyes (as a trisystem disease involving all three or a bisystem disease involving face and leptomeninges or eyes) was reported in 10% of patients with eyelid port-wine stain [30]. Associated focal seizures, hemiparesis, hemianopia, ipsilateral glaucoma, episcleral hemangioma, iris heterochromia, and diffuse choroidal hemangioma can be seen [30].

Treatment: Laser can be used for treatment.

14.5.2.4 Lymphangiomas

Lymphangiomas are benign hamartomatous vascular lesions rarely seen on the eyelids. According to the IVSSA classification the lymphangiomas fall in simple vascular malformation IIa category that includes common venolymphatic malformations. Clinically presents as a soft bluish mass at birth or later. There can be a sudden increase in size due to hemorrhage in cystic spaces.

Treatment: Debulking can be done for extensive lesions. For smaller lesion either observation or excision is the treatment of choice.

14.5.2.5 Pyogenic Granuloma

Pyogenic granuloma is the most common acquired vascular lesion of eyelids that occurs following a trauma, surgery or chronic inflammatory lesions or rarely can be idiopathic. IVSSA classifies pyogenic granuloma as benign vascular tumor. The term ‘pyogenic granuloma’ is a misnomer as it is neither pyogenic nor a granuloma.

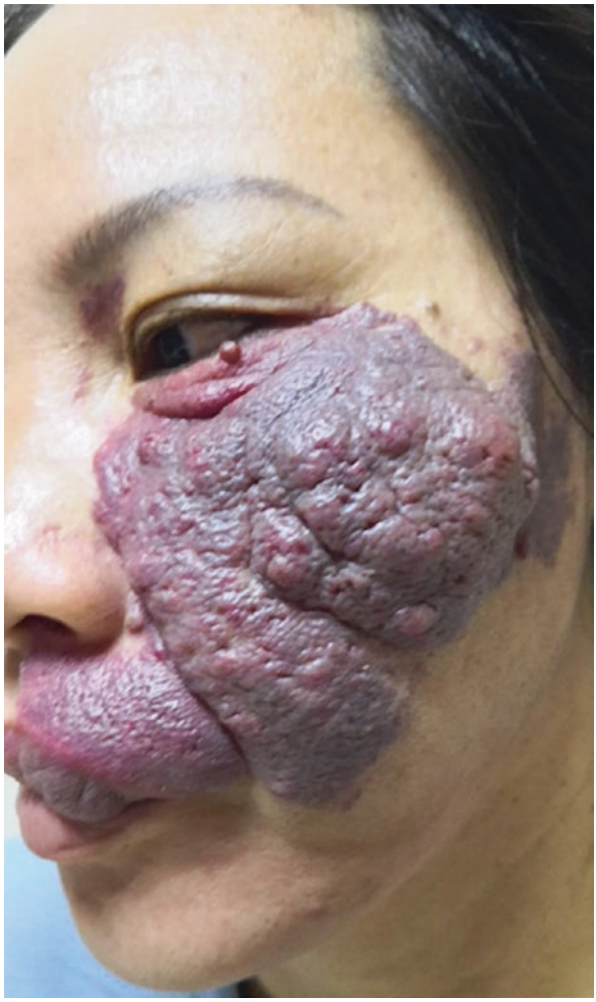

Fig. 14.13 Purple-colored diffuse lesion involving the lower eyelid and cheek. There is hypertrophy of skin with surface corrugation

Clinically it presents as a painful, friable, rapidly growing pedunculated lesion that can bleed on touch.

Histology: Excessive granulation tissue with inflammatory cells in a loose stroma with radiating capillaries extending from the pedunculated lesion.

Treatment: Excision biopsy.

14.5.3 Benign Histiocytic Tumors

14.5.3.1 Xanthelasma

Xanthelasma palpebrum is the most common form of cutaneous xanthoma.

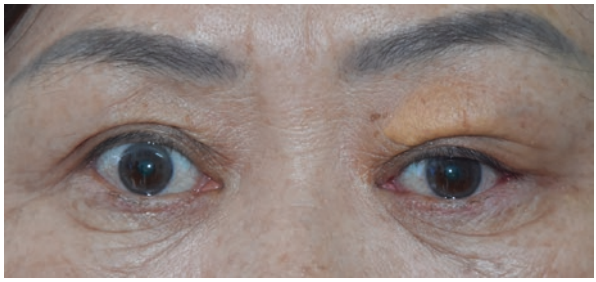

Fig. 14.14 Yellowish-orange discoloration of upper lid skin associated with mechanical blepharoptosis. There is upper lid fullness

It is mostly bilateral and appears as soft, yellow, well-defined plaques, most common on medial aspect of eyelid. If it occurs before the age of 40 years, it is most likely associated with familial hypercholesterolemia. Lipid abnormalities have been found in these patients, and hence a need to determine full lipid profile to screen for cardiovascular diseases is important [31–33].

Histology: Lipid laden foamy histiocytes clustered around blood vessels in the dermis.

Treatment: Excision biopsy and laser application. Recurrence is reported, higher in patients with persistently elevated cholesterol levels.

14.5.3.2 Xanthogranuloma

Xanthogranuloma is a chronic inflammatory lesion that is the most common non-Langerhans cell histiocytosis. Juvenile xanthogranuloma presents in children as yellowish-orange nodular subcutaneous lesion. Seventy one percent cases occur in children under 1 year of age. Systemic association with neurofibromatosis type 1 (NF 1) and juvenile chronic myelogenous leukemia is seen in these cases.

Adult-onset xanthogranuloma (AOX) is an isolated xanthogranuloma without systemic involvement presenting as yellowish-orange discoloration of eyelid skin with pre-septal and rarely orbital extension (Fig. 14.14) Other disorders affecting adults include necrobiotic xanthogranuloma (NXG), Erdheim–Chester disease and adult-onset asthma with periocular xanthogranuloma. NXG can rarely affect the eyelids and presents as subcutaneous skin lesion that ulcerates. Its importance lies in its association with paraproteinemia and multiple myeloma [34, 35]. Similarly, Erdheim–Chester disease is a devastating form of adult-onset xanthogranuloma which can lead to fibrosclerosis of orbit and internal organs [36].

Histology: Lesion contains non–Langerhans cell histiocytes, touton giant cells, lymphocytes and plasma cells.

Treatment: Intralesional corticosteroid injection has been successfully used in controlling symptoms and signs of AOX and occasionally NXG with eyelid and orbital involvement. The eyelid lesions in NXG can be successfully treated with radiotherapy or systemic steroids and chlorambucil.

14.5.4 Benign Neurogenic Tumors

14.5.4.1 Neurofibroma, Plexiform Neurofibroma

These are benign peripheral nerve sheath tumors arising from non-myelinated Schwann cells and/or perineural fibroblasts. Solitary neurofibroma is a rare entity. Multiple neurofibromas are part of type 1 neurofibromatosis syndrome. More commonly seen in eyelid and orbit are plexiform or diffuse type of neurofibromas.

Clinical features: Clinically solitary neurofibroma appears as a skin-colored nodule, generally occurring in adults. Plexiform neurofibroma is diffuse infiltrating tumor, generally presenting as s-shaped ptosis. The tumor has typical feel of 'bag of worms' on palpation. It is pathognomonic of NF1 occurring mostly in children and grows till puberty. Other ocular signs of neurofibromatosis include Lisch nodules on the iris, thickened corneal nerves and pulsatile proptosis (absence of greater wing of sphenoid). The hallmark of NF 1 is onset of dermal or plexiform neurofibromas. The diagnostic criteria include two or more of following features: (a) Six or more café-au-lait macule spots over 5-mm in greatest diameter in prepubertal individuals and over 15-mm in greatest diameter in post pubertal individuals, (b) Two or more neurofibromas of any type or one plexiform neurofibroma, (c) Freckling in the axillary or inguinal regions, (d) Optic nerve glioma, (e) Two or more Lisch nodules (iris hamartomas), (f) Distinctive osseous lesion such as sphenoid dysplasia, or tibial pseudarthrosis and/or (g) First-degree relative (parent, sibling, or offspring) with NF1 [37].

Histology: Proliferation of Schwann cells, fibroblasts, and nerve axons.

Treatment: Excision biopsy for solitary neurofibromas. Plexiform neurofibromas are difficult to excise completely hence debulking with ptosis repair is the treatment of choice.

14.5.4.2 Schwannoma/Neurilemmomas

Schwannomas (neurilemmomas) are benign neurogenic tumors of peripheral nerves. They originate from Schwann cells, which form the neural sheath. Eyelid schwannomas are presumed to originate from supraorbital, supratrochlear, and infraorbital nerves. Only a handful of cases of eyelid schwannomas are reported in literature. Malignant transformation has not been reported in eyelid.

Treatment: Excision biopsy.

14.5.5 Miscellaneous Benign Growths

14.5.5.1 Milia

These are pinhead sized lesions caused by occlusion of pilosebaceous units causing retention of keratin. Clinically appear in crops sometimes primarily or following trauma as white round superficial papules.

Treatment: Incision and expression of contents.

14.5.5.2 Chalazion

It is a chronic, sterile, lipogranulomatous inflammatory lesion which presents as a painless, slow-growing, firm nodule in the tarsal plate (Fig. 14.15) These are non-infectious, inflammatory lesions of meibomian gland in the eyelids. An infected lesion of meibomian glands is called internal hordeolum and that of glands of Zeiss is called external hordeolum. Marginal chalazion involves the gland of Zeiss, located on anterior lid margin.

Histology: Granuloma consists of giant cells, epithelioid cells and inflammatory cells around fat globules. Recurrent chalazion especially in elderly must raise the suspicion of eyelid sebaceous gland carcinoma.

Treatment: Incision and curettage. Intralesional steroid can be given. Sometimes it settles down with conservative treatment for posterior blepharitis.

14.5.5.3 Molluscum Contagiosum

It is an infectious lesion caused by DNA poxvirus. Clinically, it appears as small, pinkish or white papule or nodule with central umblication (Fig. 14.16). Associated follicular conjunctivitis is common.

Treatment: Excision, curettage, cryotherapy, or chemical cautery.

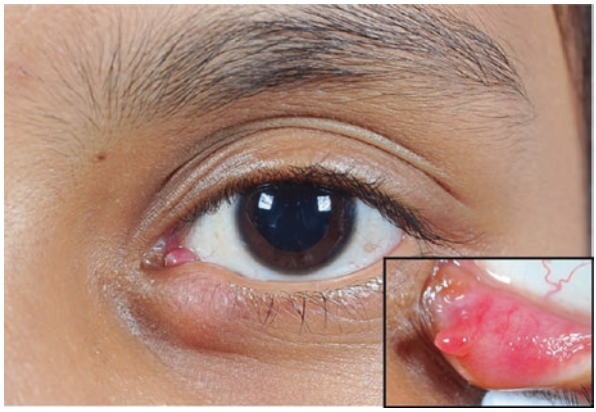

Fig. 14.15 Nodular firm mass in the lower eyelid involving the tarsus. On eyelid eversion there is a reddish protruding mass suggestive of a burst chalazion

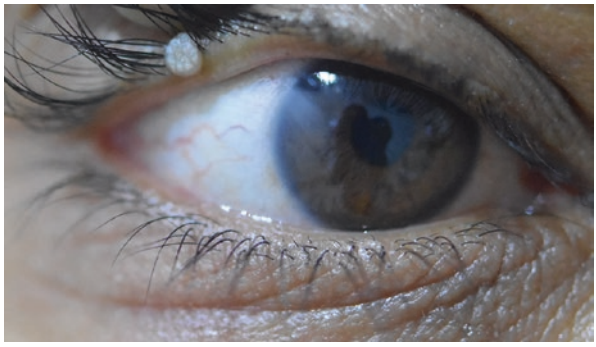

Fig. 14.16 Whitish elevated papule in the upper lid with waxy material and central umbilication

14.6 Malignant Eyelid Tumors

Eyelid malignancies are wide range of tumors with extremes from indolent types to very aggressive, life threatening ones. Similar to benign tumors, malignant eyelid tumors can take origin from any of the structures of the upper or lower eyelid and may involve medial or lateral canthi. As compared to their benign counterpart, malignant tumors are less common. Misdiagnosis is not rare, and it can mimic both inflammatory and benign lesions of eyelid. The most commonly identified malignant eyelid tumors are basal cell carcinoma (BCC), squamous cell carcinoma (SCC), sebaceous gland carcinoma (SGC), and malignant melanoma. The incidence of these malignant tumors varies in different regions. Basal cell carcinoma is considered the most common eyelid malignancy accounting for 90% of cases, followed by squamous cell carcinoma and sebaceous gland carcinoma. However, a study of Asian population reveals that sebaceous gland carcinoma has a higher incidence in India, China and other Asian countries [38–42].

Early diagnosis and treatment have proven to improve outcome. Optimal care to achieve full clearance with maximum preservation of function and cosmesis is a challenging task for treating ophthalmologist. Sometimes the treatment modalities require collaborated efforts with other specialists. Some of the aggressive types of lid tumors have a high metastatic potential that can be life threatening if not managed early and appropriately. The following segment describes few important malignant tumors commonly seen in practice.

14.6.1 Sebaceous Gland Carcinoma

Sebaceous gland carcinoma (SGC) arises de novo from cells of sebaceous glands (meibomian gland of eyelid and caruncle, rarely from gland of Zeiss) and occurs most often in periorbital area, especially eyelids. This is considered the most lethal of all ocular adnexal tumors [43].

14.6.1.1 Epidemiology

Incidence of SGC is variable in different regions. In the western countries, incidence of SGC is only 5% as compared to BCC (90%), while SGC is more common than BCC or SCC in Asian countries [40–42].

14.6.1.2 Etiology

Muir–Torre syndrome (MTS) has an important consideration when a patient is diagnosed with sebaceous carcinoma. Cohen et al. have reported sebaceous carcinoma in 24% of 124 MTS patients. MTS is an autosomal dominant condition of sebaceous tumors associated with gastrointestinal, endometrial, and urologic tumors [7]. Ocular or facial irradiation may be a risk factor. SGC occurring in young population may have a relation to immune dysfunction.

14.6.1.3 Clinical Features

Most frequently SGC affects the elderly with female predisposition. Majority of lesions arise from meibomian gland in tarsus, hence 65% occurrence in upper lid is noted as compared to 25% in lower eyelid, 5% in both eyelids, and 5% in the caruncle. Occasional cases have been reported from lacrimal gland and conjunctiva [41, 43]. The spreading variety of SGC occurs in pagetoid form which has diffuse intraepithelial infiltration resembling chronic blepharoconjunctivitis. This can involve eyelid or conjunctival epithelium.

SGC is notorious for highly variable clinical presentation and is a great masquerader. It manifests in three types:

1. Nodular type: It is most common presentation (Fig. 14.17a). The tumor appears as a firm, painless, sessile, round nodule fixed to tarsus (Fig. 14.17b), which might assume a yellow color due to lipid content. If it originates from gland of Zeiss, it appears at the lid margin. Malignant features of lash loss, distortion of meibomian gland architecture, rounding of posterior lid margin and feeder vessels must be noted. Any recurrent chalazia, especially in elderly, which is of unusual consistency and associated with loss of cilia, must raise a suspicion of nodular SGC.
2. Diffuse/Spreading SGC: Unilateral diffuse thickening is second common presentation. This can be very easily mistaken for chronic blepharitis.
3. Pagetoid spread: It refers to extension into the epithelium of palpebral, forniceal, or bulbar conjunctiva or even cornea. This can be misdiagnosed as an inflammatory condition.

14.6.1.4 Histopathology

Tumor consists of lobules of cells with pale, foamy, vacuolated lipid containing cytoplasm, pronounced nuclear pleomorphism and high mitotic activity. It can be well differentiated, moderately or poorly differentiated. The tumor may show lobular, comedocarcinoma, papillary, or mixed pattern.

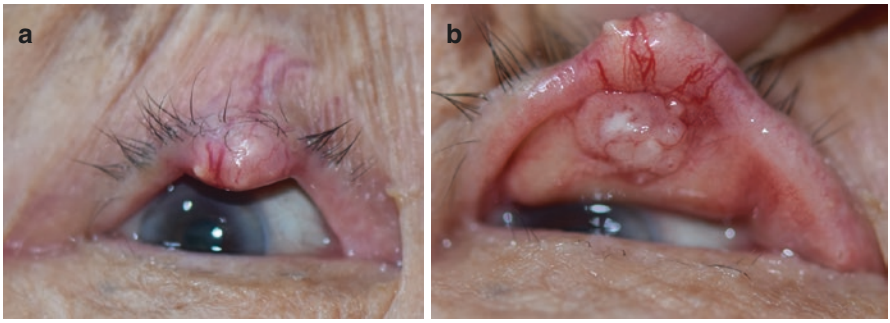

Fig. 14.17 (**a**) Upper lid yellowish nodule with dilated feeder vessels and lash loss. There is rounding of posterior lid margin and loss of meibomian gland architecture. (**b**) On eyelid eversion, there is nodular mass arising from the tarsus with intrinsic vascularity and ulceration

14.6.1.5 Differential Diagnosis

SGC is the most frequently misdiagnosed and mistreated condition leading to a mortality of 5–10%. Being the most lethal form of ocular tumor, it must be diagnosed early and accurately. It can mimic inflammatory conditions such as recurrent chalazion, blepharoconjunctivitis, and cicatricial pemphigoid. The squamous cell carcinoma may be misdiagnosed as SGC and vice versa.

14.6.1.6 Treatment

Full thickness wide margin (4 mm) excision biopsy of the eyelid is the preferred method of confirming the suspected clinical diagnosis. Frozen section or Mohs microsurgery is used at time of tumor excision, to evaluate the margins and histologically clear margins are a must before reconstruction is attempted. In case of diffuse spreading type multiple map biopsies of conjunctiva should be performed to confirm the extent of involvement. In advanced disease chemoreduction of the tumor is attained with systemic chemotherapy followed by excision biopsy. In the presence of orbital extension, exenteration may be considered.

14.6.1.7 Prognosis

Metastasis can occur in SGC, both local and regional. Thirty percent of cases show regional lymph node metastasis. Direct local growth beyond its original site is common in neglected or recurrent cases. Five-year tumor related death rate is approximately 10% [44].

14.6.2 Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common human malignancy and considered the most common malignant eyelid tumor accounting for 80–90% of all cases. It is a slow-growing, locally invasive but non-metastasizing tumor.

14.6.2.1 Etiology

Risk factor includes ultraviolet (UV) radiations exposure especially in fair skinned individuals, chronic sun exposure, inability to tan, immune dysfunction, previous radiation exposure, and infrequently prior trauma. Genetic diseases predisposing to BCC are Gorlin– Goltz syndrome, xeroderma pigmentosum, Basex syndrome, and Rombo syndrome (Table 14.5).

14.6.2.2 Clinical Features

BCC most frequently affects elderly patients with an average age of 60 years, with a male predisposition. Most commonly seen in the lower eyelids followed by medial canthus, upper eyelid, and lateral canthus.

Most common clinical types include

1. Nodular type: Presents as firm, shiny, pearly nodule, which can slowly enlarge. Surface telangiectasia is seen.

Table 14.5 Systemic associations of eyelid malignancies

S. no.	Entity	Eyelid tumors	Features	Genetics
1.	Xeroderma Pigmentosum	BCC SCC Melanoma	Lentigenous pigmentation in sun-exposed area	AR
2.	Gorlin–Goltz syndrome (nevoid basal cell carcinoma syndrome)	BCC	Odontogenic cysts Bifid ribs Palmar pits Ovarian tumors	AD
3.	Muir–Torre syndrome	SGC Keratoacanthoma Benign: sebaceous adenoma	Colorectal cancer Genitourinary cancer	AD
4.	Bazex syndrome	BCC	Eczematous, psoriasiform lesion Upper respiratory tract cancer Digestive tract cancer	XLD

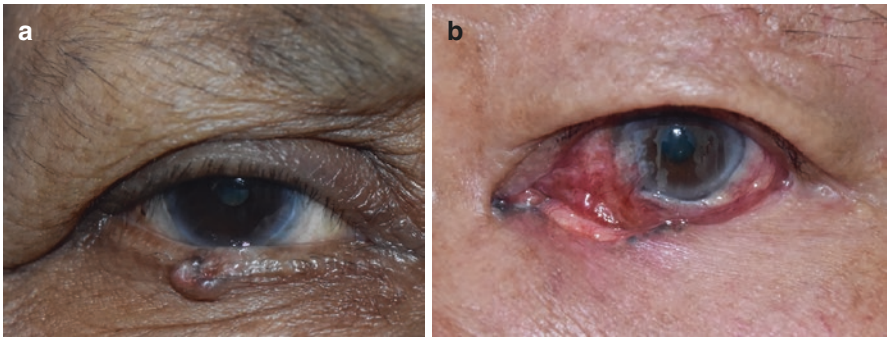

Fig. 14.18 (**a**) Nodular mass in the lower eyelid. (**b**) Flat diffuse lesion involving the entire lower eyelid and medial canthus with caruncular extension and ulceration. There is scattered pigmentation noted over the surface

2. Noduloulcerative type: Presents as nodular BCC with central ulceration (Fig. 14.18a) and telangiectasia with raised and rolled edges. It is known as 'rodent ulcer' (Fig. 14.18b) because it can slowly erode a large part of eyelid.
3. Sclerosing or morphoeic: It presents as flat, infiltrating lesion with induration and ill-defined margins. Lesion is much more extensive on palpation and histopathologic examination than inspection.
4. Cystic, pigmented, and adenoid types are also described.

14.6.2.3 Histology

Arises from the cells of basal layer of epidermis in the form of infiltrative nests, sheets, or strands with oval nuclei and scanty cytoplasm. These cells characteristically exhibit palisading pattern at the periphery. Typically, a gap is present between the nest of cells and the stroma. Necrosis is commonly observed. The cells can undergo squamous differentiation, or sebaceous and adenoid differentiation. Histologically important pattern of growth is circumscribed and infiltrative.

14.6.2.4 Differential Diagnosis

Any periocular nonhealing condition must warrant a high index of suspicion. Challenging cases included in differential diagnosis are trichoepithelioma, metastatic carcinoma, sebaceous gland carcinoma, squamous cell carcinoma, keratoacanthoma, and malignant melanoma.

14.6.2.5 Treatment

Treatment options for BCC consist of surgery, radiotherapy, and targeted immunotherapy as discussed in the following segments. Wide surgical excision with frozen section margin control or Mohs micrographic surgery is the first consideration for treatment of periocular BCC.

14.6.2.6 Prognosis

Depends on the size of BCC, location, and pattern of infiltrative growth and age of patient. Metastatic BCC is extremely rare (0.0028–0.01%). Mortality from eyelid and medial canthal BCC are rare.

14.6.3 Squamous Cell Carcinoma

Another most common malignant eyelid neoplasm, squamous cell carcinoma (SCC) arises from prickle-squamous cell layers of epidermis.

14.6.3.1 Etiology

Risk factors for development of SCC include UV light exposure, actinic damage, and exposure to arsenic, hydrocarbon, and radiation. Genetic disorders like xeroderma pigmentosum, albinism, or preexisting chronic skin lesions are also potential risk factors.

14.6.3.2 Clinical Features

Most commonly occurs in elderly individuals, with predominance among males, probably attributed to increased occupational sunlight exposure. It occurs in the lower eyelid, upper lid (Fig. 14.19), and medial canthus. It can present as:

1. Nodular SCC: Hyperkeratotic nodule with crusting and erosion
2. Ulcerating SCC: Erythematous, well-defined base with indurated, everted borders
3. Cutaneous horn with underlying invasive SCC

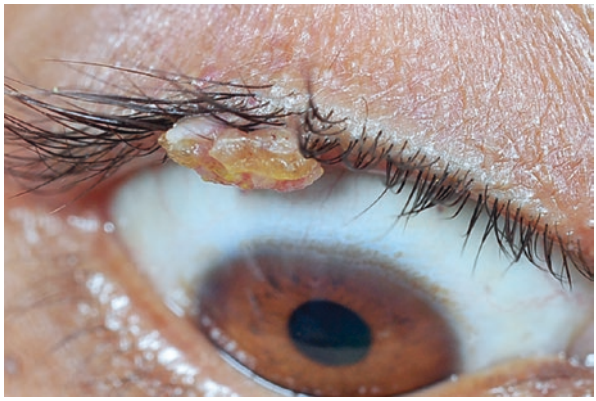

Fig. 14.19 Elevated and ulcerated lesion arising from the upper lid skin margin with crusting. Borders are everted with intrinsic vascularity

Well-differentiated tumors have gray white granular appearance because of the presence of keratin. Metastasis to regional lymph nodes is known in 20% of cases. Careful surveillance of regional lymph nodes is important part of initial management.

14.6.3.3 Histology

Tumor cells arise from squamous cell layer of the epidermis and can have variable degrees of differentiation. Well-differentiated tumors have polygonal cells with abundant acidophilic cytoplasm, prominent hyper chromatic nuclei. Characteristic keratin pearls are seen. Poorly differentiated tumors have irregularly shaped and sized cells, enlarged nuclei, abnormal mitoses, and little or no evidence of keratinization and loss of intercellular bridges.

14.6.3.4 Differential Diagnoses

SCC has no pathognomonic features that differentiate it from other lesions. It may mimic other types of skin lesion, benign and malignant. Histopathology can confirm the diagnosis.

14.6.3.5 Treatment

Treatment options for SCC consist of surgical excision, radiotherapy, orbital exenteration in case of advanced invasive tumor and targeted immunotherapy for locally advanced or metastatic SCC.

14.6.3.6 Prognosis

Eyelid SCC treated appropriately has excellent prognosis. Tendency to metastasize to regional lymph nodes is as high as 21% and, in advanced disease distant metastasis varies from 1 to 20%.

14.6.4 Keratoacanthoma

Keratoacanthoma is a dome-shaped nodule with central keratin filled crater and elevated rolled margins. It is debatable whether it is a benign lesion or variant of SCC [45].

Clinical features: Short history of few weeks with rapid growth and spontaneous gradual resolution over few months with some residual scarring can be seen. Multiple keratoacanthomas along with sebaceous adenomas are seen in Muir–Torre syndrome indicative of underlying malignancy usually colorectal adenocarcinoma [7, 46].

Histology: Cup-shaped nodular elevation with thickened epidermis containing well-differentiated squamous epithelium infiltrated by neutrophils surrounding central mass of keratin is seen.

Treatment: Spontaneous involution is reported in keratoacanthoma. However, complete surgical excision is preferred with margin clearance under the current belief of the lesion being low-grade SCC.

14.6.5 Melanoma of the Eyelid

Cutaneous melanoma represents less than 1% of all malignant neoplasms of the eyelid skin; it is potentially lethal. It could be primary or secondary metastatic eyelid melanoma.

14.6.5.1 Epidemiology

Most cases are reported from North America and Europe, and few from Asia. It commonly occurs in elderly individuals around sixth or seventh decade without any sex predilection.

14.6.5.2 Premalignant Precursor

1. Lentigo maligna (Melanoma in situ, intraepidermal melanoma, Hutchinson freckle)—It is the most common precursor lesion to melanoma. Histopathologically, it shows intraepidermal proliferation of atypical melanocytes that replaces basal layer of the epidermis. Clinically, it presents as expanding pigmented macule with irregular border in sun-exposed areas. The malignant transformation is signified by small nodular formations are typically seen along with areas of irregular pigmentation.
2. Dysplastic nevus

14.6.5.3 Clinical Features

Clinically, pigmentation though is a hallmark of cutaneous melanomas; half of the cases are non- pigmented. It can present as

1. Superficial spreading melanoma: It is a plaque like lesion with irregular borders and variable pigmentation.
2. Nodular melanoma: It presents as a blue-black nodule.

Clinical features highly suggestive of melanoma are recent onset of pigmented lesion, irregular margins, variegated shades of color, diameter more than 6 mm and most importantly thickness of the lesion. Important prognostic factor is the depth of

invasion that has been described by Clark and Breslow [47, 48]. Quantitative method by Breslow measures the depth of invasion in millimeters. Tumors of less than 0.75-mm thickness have an excellent prognosis, tumor thickness of 0.75–1.5 mm has fair prognosis and tumors more than 1.5-mm thickness have a poor prognosis [47].

14.6.5.4 Histology

Breach of epidermal basement membrane by atypical melanocytes is considered as malignant melanoma. Depth of invasion of melanocytes, ulceration and increased Ki67 index are important diagnostic and prognostic factors. There is marked cytological atypia. Specific features are consumption of epidermis, breach of epidermal basement membrane, pagetoid spread of melanocytes, nests of melanocytes with varying size and shape (lacking maturation), deep and atypical mitoses and increased apoptosis. Mitotic figures are common. Important histopathological prognostic factors include vertical growth pattern, increased Breslow thickness, ulceration, lymphovascular and perineural invasion and increased mitotic rates.

14.6.5.5 Treatment

Surgical excision with wide margins is the mainstay of early stage melanoma management. Wide local excision (5–7 mm) according to the thickness of the lesion has been proposed. Early stage melanoma requires 5–10 mm margin. Melanomas >2.0 mm thickness should have 20 mm margins. Lymph node dissection is indicated if sentinel lymph node biopsy is positive. Adjuvant therapy like radiotherapy can be considered in some patients. Targeted immunotherapy has been approved by FDA in 2014 for advanced melanoma.

14.6.5.6 Prognosis

Mortality from eyelid melanoma ranges from 6% to 58%. Local recurrence and lymph node spread even on complete excision is not rare. Hence long-term follow up is important for these patients.

14.6.6 Merkel Cell Tumor

It is an aggressive, primary cutaneous neuroendocrine malignant neoplasm arising from Merkel cells. Merkel cells are neuroendocrine receptors of touch in eyelid and conjunctiva.

Clinical features: Commonly seen in the elderly, it is a fast-growing tumor. It presents as well-demarcated violaceous nodule with intact overlying skin mostly in the upper eyelid.

Histology: It shows interconnecting sheets and cords (trabecular pattern) of tumor cells. Cells are uniform, round with scanty cytoplasm, large oval nuclei, prominent nucleoli, and abundant mitotic figures.

Treatment: Wide surgical excision with clear margins accompanied by adjuvant radiotherapy.

14.6.7 Kaposi's Sarcoma

It is a malignant vascular tumor that is seen in immunodeficiency syndrome (AIDS). It is the most common malignancy seen in AIDS patients and can be an initial presenting sign.

Clinical features: It presents as a pink, red-violet to brown, solitary or multifocal, circumscribed or diffuse subcutaneous lesion.

Histology: It has a network of proliferating endothelial cells forming slit like spaces surrounded by spindle-shaped mesenchymal cells and collagen.

Treatment: Improved viral loads and immunological status can cause spontaneous resolution of the tumor. Excision, cryotherapy and radiotherapy are other modalities of treatment.

14.6.8 Malignant Sweat Gland Tumors

Primary sweat-gland cancer can arise in the eyelid and orbit though extremely rare. Anatomically these can be eccrine carcinomas or apocrine adenocarcinomas.

14.6.8.1 Syringomatous Carcinoma

It is a malignant solid tumor originating in the eccrine glands and characterized by skin and skeletal muscle involvement, and perineural invasion. Most common feature is invasive plaques. Perineural and intraneural invasion is a particularly characteristic finding in syringomatous carcinoma. Other presentations can be solitary solid nodules or multiple nodules.

Most lesions are indolent and grow slowly. Tumor cells can grow from the dermis to subcutaneous tissue invasively and can infiltrate around vascular structures and endanger the nervous system, accounting for disease recurrence. Surgical excision is the treatment of choice but recurrence after excision is known.

14.6.8.2 Mucinous Adenocarcinoma

These are rare sweat-gland-derived tumors with predilection for eyelids. These are classified by WHO under the category of malignant tumors with apocrine and eccrine differentiation [1]. It can be primary or secondary as metastatic lesion. Therefore, warrants thorough systemic evaluation.

Clinical features: Clinically, the tumor presents as slow-growing, flesh colored, erythematous, or bluish nodule. It is locally aggressive but distant metastases are uncommon.

Histology: Tumor cells are embedded in abundant pool of mucin, separated by fibrous septae.

Treatment: Surgical excision either under frozen section control or by Mohs surgery is the treatment of choice and leads to lesser recurrence rate [49].

14.6.8.3 Endocrine Mucin Producing Sweat-Gland Carcinoma

It is a rare, low-grade cutaneous adnexal carcinoma with neuroendocrine differentiation.

Clinical Features: Clinical appearance of mucinous sweat-gland carcinomas of the eyelid is very variable. EMPSGC has largely been an under-reported entity until recently. It may represent the endocrine variant of mucinous carcinoma of the skin or precursor of invasive mucinous carcinoma. It is morphologically considered analogous to endocrine ductal carcinoma in situ or solid papillary carcinoma of breast [50–52].

It is slow-growing, flesh-colored, nonspecific papules, or nodules in the eyelids more common in the elderly age group (average age 60 years).

Histology: Lesion consists of gland formation or small clumps of well-differentiated epithelial cells present in large pools of basophilic mucin. Cancer cells are arranged in an adenoidal or cribriform fashion with mild atypia. Definitive diagnosis requires immunohistochemical staining wherein positivity to neuroendocrine markers is seen. The immunohistochemical profile of strong positivity for estrogen/progesterone receptors and cytokeratin 7 along with the histological resemblance to breast carcinoma makes it crucial to rule out the possibility of cutaneous metastases in all cases of EMPSGC [52].

Treatment: Excision biopsy with clear margins.

Prognosis: Although it can relapse locally, it is a low-grade carcinoma with fewer metastases and a good prognosis. The recurrence rate of tumors located on the eyelids had traditionally been estimated at 40%, based mainly on the study by Wright and Font in 1979.

14.6.9 Malignant Hair Follicle Tumors

14.6.9.1 Trichilemmal Carcinoma

Trichilemmal carcinoma is rare malignant adnexal tumor, which can involve the head and, rarely, the eyelid. It is derived from keratinocytes of the outer root sheath of hair follicles and can be locally invasive. It is seen on the sun-exposed areas of the elderly. Occurrence on eyelid is approximately 4% [53].

Clinical features: Clinically presents as an exophytic, nodular, or papular mass and can be associated with ulceration, telangiectasia, and conjunctival erosion. The differential diagnosis also includes basal cell carcinoma, squamous cell carcinoma, and keratoacanthoma.

Histology: Trichoepithelioma, basal cell carcinoma, and trichilemmal carcinoma may be difficult to distinguish from each other.

Treatment: Local excision with tumor-free margins is curative in most cases. Regular monitoring is important, as local recurrence in case of incomplete excision can be aggressive. Distant metastasis is rare.

14.6.10 Fibrosarcoma

Fibrosarcoma of the eyelid is a rare. It is highly malignant tumor and can be locally destructive and can metastasize. Clinically it presents as rapidly progressive, poorly circumscribed eyelid nodule. Juvenile fibrosarcoma can present as a second malignancy in retinoblastoma cases with or without prior radiotherapy [54].

Treatment: Wide surgical excision or orbital exenteration is recommended to minimize risk of local recurrence and metastasis.

14.6.11 Liposarcoma

Liposarcomas (LPS) account for 16–18% of the soft-tissue sarcomas, most common in adults and usually located in retroperitoneum or extremities. Despite the presence of large amount of adipose tissue in orbit, occurrence of primary liposarcoma in orbit, or as metastasis is very rare. Eyelid involvement is extremely rare and it can get involved as a local extension from orbit.

Excision biopsy is the treatment.

14.6.12 Rhabdomyosarcoma

It is one of the most common orbital malignancies in children that can involve eyelids in 3% of cases [55]. When anteriorly located, it can present as eyelid erythema, edema, and chemosis. This presentation can masquerade as infectious and inflammatory etiology.

Surgical biopsy and a combination of chemotherapy and radiotherapy offer the best chance of survival for the patients.

14.6.13 Lymphoid and Leukemic Tumors

These tumors occur in eyelid as primary tumor or manifestation of systemic disease.

Lymphomas present about 13% of primary malignant eyelid tumors, most common being B-cell lymphoma (marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue). Clinically lymphoma presents as a smooth subcutaneous mass without ulceration. It can be confined to the eyelid or have anterior orbital extension. T-cell lymphoma is rare in the eyelid, but when present can represent a part of mycosis fungoides (T-cell lymphoma of the skin). Skin ulceration is common in such cases that can simulate an infectious lesion.

Leukemic infiltration of the eyelid can occur in patients with systemic acute or chronic leukemia. Clinically, it presents as nodular or diffuse subcutaneous eyelid lesions. Primary leukemia affecting eyelid is called granulocytic sarcoma.

14.6.14 Metastatic

Eyelid metastases represent 1% of all malignant tumors. It presents as a rapidly progressive subcutaneous nodule, usually in patients with known cancer. The common primary sites in these cases are breast, lung, and cutaneous melanoma.

14.7 Basic Principles in Management of Eyelid Tumors

Goals in the management of eyelid tumors especially the malignant eyelid tumors are:

- To establish an early and accurate diagnosis
- Try for total eradication of the tumor with margin clearance
- Thorough examination and management of systemic symptoms if any in case of advanced cancer
- To preserve good eyelid function
- To achieve a good cosmetic result after reconstruction

The following segment deals with the basic principles of management modalities available in the armamentarium of the ocular oncologist dealing with these entities to achieve the best result for the patient. One single protocol cannot suit such a varied range of tumors, and treatment should be carefully tailored to suit the specific scenario. In case of advanced lesions or where risk of metastasis is suspected, full body metastatic workup is warranted with positron emission tomography (PET) CT scan.

14.7.1 Surgical Approach

14.7.1.1 Diagnostic Biopsy

(a) Incisional biopsy: A wedge-shaped part of the lesion including superficial and deepest part from the epicenter of the tumor is removed for histological examination.
(b) Punch biopsy: A 2 mm punch is used to take a piece of the lesion. This is a quick and simple diagnostic procedure that requires minimal equipments and can be performed as an outpatient procedure. The punch needs to be twisted in a 'drilling' motion targeted at the epicenter of the lesion so that adequate sample from deep and deepest layer of the lesion is obtained.
(c) Excisional biopsy: The entire lesion is removed and subjected to histopathological examination for definitive diagnosis. Excision can be a shave excision or a full thickness excision as per the nature of the lesion.

In case of a clinically benign looking lesion, simple excision without taking margins of healthy tissue will suffice while in a large lesion appropriate reconstruction should be planned to maintain function and cosmesis of the eyelid.

Principles of Surgical Excision

In case of suspected malignant lesion, smaller tumor can be removed with a 2–4 mm margin and defect closed directly, while awaiting histological confirmation of complete clearance. Aggressive tumors like BCC, SGC, SCC, and melanoma require wide margin excision with confirmation of tumor-free margins before reconstruction of the defect is attempted. Faster confirmation with reconstruction the same day can be achieved with standard frozen section or Mohs micrographic surgery.

Standard frozen section includes histological examination of the excised specimen at the same time of the surgery to confirm tumor-free margin. If positive, further excision is performed until margins are tumor free. Once it is confirmed that the margins are clear, appropriate reconstruction of the defect can be done the same day. The excised specimen can then be subjected to detailed histopathological examination for definitive diagnosis.

Mohs micrographic surgery with immediate reconstruction is a treatment of choice by few surgeons [56, 57]. Tumors that grow diffusely with indefinite margins and finger like extensions as seen in BCC, SCC, recurrent tumors, or canthal tumors, this technique maximizes total tumor clearance while minimizing sacrifice of normal tissue. The technique involves removal of gross mass with small peripheral margin of tumor that includes normal tissue with a 2 mm excision from base and edges of the wound. On achieving tumor-free margins reconstruction is done the same day.

Eyelid Reconstruction

Reconstruction technique depends on extent of tissue removed. A good reconstruction must ensure horizontal lid stabilization with minimum vertical tension, proper canthal fixation, and an epithelialized internal surface [58]. Anterior and posterior lamellae must be adequately reconstructed. In the laissez-faire approach wound edges are approximated as far as possible and defect is allowed to granulate and heal by secondary intention. Full thickness defects if small (less than one-third of eyelid) can be closed directly. Undermining should be sufficient for tension-free closure. Moderate sized defects (involving half of the eyelid) may require a flap. Larger defects require lid sharing procedures, free skin grafts, and/or rotation flaps.

14.7.2 Sentinel Lymph Node Biopsy (SLNB)

In a biopsy proven malignant eyelid tumor with high propensity for regional lymph node metastasis, careful watch on the lymph nodes is of utmost importance. The rate of metastasis is 0.0028–0.01% in BCC, 0–21% in SCC, 30% of in SGC, and 29% in melanoma.

SLNB in patients with conjunctiva and eyelid malignancies can be performed safely in clinically undetected regional lymph node metastasis [59]. SNLB for every case is debatable [60, 61]. Pfeiffer et al. reviewed the literature, and concluded that indications include: (a) SGC of >10 mm in size, (b) Eyelid melanoma ≥1 mm in thickness, >1 mitotic figure/hpf and/or ulceration, and (c) Merkel cell carcinoma of any size [62].

After injection of small volume of technetium Tc-99m sulfur colloid into the conjunctival cul-de-sac, lymphoscintigraphy is performed to detect dye uptake in the draining lymph nodes. If detected, small incisions are made to dissect the nodes for histopathological examination.

14.7.3 Radiation Therapy

Radiation therapy is indicated in selected cases of eyelid malignancy. Eyelid BCC is radiosensitive whereas SCC is radio resistant. Neck irradiation is advised in loco-regional lymph node metastasis. Treatment parameters include calculating a target tissue volume for the delivery of the radiation, total dose required which depends on tissue responsiveness, fractionation of the dose in sessions for better response and tissue tolerance as some of the critical structures like cornea, lens, optic nerve, and contralateral orbit are highly sensitive and at risk for exposure.

Techniques of delivery include

(a) ***External beam therapy:*** Initially, magnetic resonance imaging (MRI) or computerized tomography (CT) images of patient's anatomy in the treatment positions are taken. On simulation images, tumor area and normal anatomy is identified and contoured for dose delivery. Conformal radiation therapy helps to precisely identify the tumor as compared to conventional or standard EBRT.
(b) ***Intensity-modulated radiation therapy (IMRT):*** Where 'inverse planning' is used for deciding the dose before beam arrangement. A computer-generated plan is generated and a dynamically moving collimator is used to place the majority of hot spots within the tumor volume.
(c) ***Stereotactic radiotherapy:*** It uses highly focused precisely aimed radiation to treat tumors at very high dose per fraction.
(d) ***Gamma-knife radiosurgery:*** It uses gamma rays to focus on a single point.

Ocular side effects of radiations especially keratopathy and optic neuropathy should be carefully monitored.

14.7.4 Chemotherapy

Chemotherapeutic agents induce programmed cell death by DNA, RNA, and metabolic pathway alteration in both malignant and normal cells. Chemotherapy can have a curative effect or may be used as adjuvant therapy or for palliation.

Nonresectable BCC or metastatic BCC have shown to respond well to cisplatin with or without doxorubicin or paclitaxel. It can be used as an adjuvant to surgery and RT in aggressive infiltrating SCC and metastatic SGC.

14.7.5 Targeted Therapy for Advanced Malignant Tumors

1. Basal cell carcinoma (BCC)

   Targeted nonsurgical therapy has provided a new viable treatment alternative for locally advanced periocular BCC and metastatic BCC. The two targeted Sonic Hedgehog (SHH) pathway inhibitors approved by U.S food and Drug Administration for BCC are vismodegib and sonidegib [63–65]. Both drugs are formulated as capsules to be taken once daily (vismodegib 150 mg per oral P.O., and sonidegib 200 mg P.O). Outcome data on efficacy of these drugs are limited [66].
2. Squamous cell carcinoma

   Cemiplimab (LIBTAYO®) is a human programmed death receptor-1 (PD-1) monoclonal antibody that binds to PD-1 and blocks its interaction with programmed death ligands 1 (PD-L1) and 2 (PD-L2). This drug received approval in 2018 in the USA for the treatment of patients with metastatic cutaneous squamous cell carcinoma or locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation [67].

   The recent discovery of overexpression of the epidermal growth factor receptor (EGFR) in SCC has opened the door to consideration of targeted therapy in inoperable cases of advanced cutaneous SCC of the orbit and periocular region. EGFR inhibitors can be divided into small molecule tyrosine kinase inhibitors (e.g. gefitinib and erlotinib) and monoclonal antibodies to EGFR (e.g. cetuximab), which have greater specificity but require intravenous infusion [68–73].
3. Melanoma

   Programmed death-1 (PD-1) inhibitors are among the immunotherapies that have revolutionized the approach to treating advanced melanoma. Nivolumab and pembrolizumab, PD-1 monoclonal antibody inhibitors, became FDA-approved for treatment of advanced melanoma in 2014 [74, 75].

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Phakomatoses

15

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15.1 Introduction

Phakomatoses or neurocutaneous syndromes (NCS) are a group of disorders with manifestations involving the central and peripheral nervous system, the eye, the skin, and various viscera. The word Phakomatoses derived from the Greek word Phakos, was used by Van der Hoeve in 1932 to mean birth mark [1]. Most of these disorders have a well-defined pattern of inheritance. This disorder affects the tissues having neural crest origin embryologically [2]. Several of the NCS have mutations involving the RAS-miogen activated protein kinase (MAPK) pathway and have been called to be RASopathies [3].

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15.2 Neurofibromstosis Type 1

Neurofibromstosis type 1 (NF1) also known as von Recklinghausen disease is an autosomal dominant condition with incomplete penetrance. It is caused by mutation of the NF1 gene located on the long arm of chromosome 17 which encodes protein neurofibromin [4]. The diagnostic criteria for the diagnosis of NF1 is given in Table 15.1.

Neurofibromas are benign Schwann-cell tumors also composed of fibroblasts, mast cells, macrophages, endothelial cells, pericytes, and perineural cells [6]. These can be cutaneous, subcutaneous, plexiform and spinal. The pigmentary lesions of the skin include cafe-au-lait macules, axillary and inguinal freckling. Long-bone and sphenoid dysplasia resulting in short stature and facial hemiatrophy respectively and pseudoarthrosis are the skeletal abnormalities seen in these individuals. Cognitive and behavioral deficits including autism and attention deficit hyperactive disorder have been noted in this population [7, 8]. They are also prone to develop hypertension and several cardiovascular and cerebrovascular diseases. They have a higher risk of developing neurological and also nonnervous system malignancies [9].

The ophthalmic manifestation of NF 1 which are diagnostic, include Lisch nodules (Fig. 15.1), optic nerve gliomas and plexiform neurofibroma (Fig. 15.2) [5]. Lisch nodules are melanocytic hamartomas of the iris [10]. Optic nerve gliomas are low-grade pilocytic astrocytomas [11]. Other manifestations include enlarged corneal nerves, glaucoma, astrocytic hamartomas, capillary hemangioma of the retina, combined hypertrophy of the retina and retinal pigment epithelium, and choroidal nodules [12].

The recommended guidelines for screening include annual examination till the age of 8 years and biennially up to age 18 [13]. Treatment of optic nerve gliomas is considered in cases with documented clinical worsening or radiographic progression or both. Treatment options include chemotherapy, radiotherapy and rarely surgery. Plexiform neurofibromas when cosmetically disfiguring or causing amblyopia can be surgically resected but is associated with high risk of bleeding and recurrence.

Table 15.1 Diagnostic criteria for neurofibromatosis type I [5] at least 2 of the following signs must be present

Six or more cafe-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals
Two or more neurofibromas or one plexiform neurofibroma
Axillary or inguinal freckling
Optic pathway glioma
Two or more Lisch nodules (Fig. 15.1)
Characteristic skeletal dysplasia (sphenoid wing dysplasia, long-bone dysplasia)
An affected first-degree relative diagnosed by the above criteria

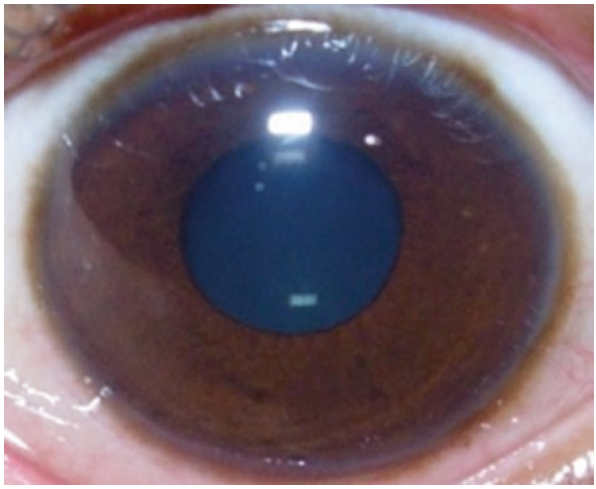

Fig. 15.1 Leish nodules

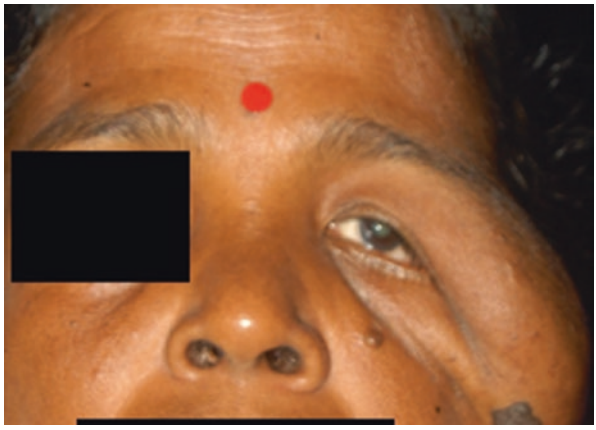

Fig. 15.2 External photo of a 48-year-old female showing plexiform neurofibroma of the left side

15.3 Neurofibromatosis Type 2

Neurofibromatosis 2 (NF2) is less common neurocutaneous syndrome affecting the NF2 gene on chromosome 22 which encodes the protein merlin or schwannomin [14, 15]. It has an autosomal dominant mode of inheritance in 50% of the cases and is sporadic in the other half. The characteristic clinical feature is bilateral vestibular schwannoma [16]. Other diagnostic criteria include family history of NF2 and other CNS tumor meningioma, schwannoma, glioma, neurofibroma, or cataract.

Individuals affected with vestibular schwannoma present with complaints of tinnitus, vertigo, or deafness [16]. Other neurological features include schwannomas of the other cranial, spinal and peripheral nerves, intracranial or intraspinal

meningiomas, and other central nervous system malignancies like ependymomas and gliomas. The dermatological features include cafe-au-lait macules, NF 2 plaques, subcutaneous and cutaneous schwannomas and neurofibromas.

The most common ophthalmologic feature is presenile posterior subcapsular cataract [17]. Cortical wedge-shaped opacities may also be present. The other ophthalmological features include epiretinal membrane (ERM), combined hamartoma of the retina and retinal pigment epithelium, optic pathway meningiomas, nystagmus, and strabismus. Annual evaluation by a neurologist, dermatologist, ophthalmologist, and audiologist is necessary from infancy in children of an affected parent [18].

15.4 Tuberous Sclerosis

Tuberous sclerosis or Bourneville disease is a multisystem disease with variable presentation that involves the brain, skin, kidneys, heart, eyes, and lungs. It is caused by mutation in gene TSC1 or TSC2 on chromosomes 9 and 16, respectively which codes for the proteins hamartin and tuberin, respectively [19].

The CNS lesions include cortical tubers, subendymal nodules, and subependymal astrocytoma [20]. The clinical manifestations include seizures, developmental delay and autism and behavioral disorders. The renal findings include renal cyst or angiomyolipoma which can progress to renal failure [21]. Cardiac rhabdomyoma, pulmonary lymphangioleiomyomatosis are other features. Dermatologic features include hypomelanotic macules (ash leaf spots), shagreen patches, facial angiofibromas or adenoma sebaceum, confetti skin lesions, and subungual fibromas [22]. Dental manifestations include enamel pits and intraoral fibromas [23].

Retinal astrocytic hamartoma is a classical ophthalmological feature (Fig. 15.3, b). It can be flat and translucent, nodular or transitional. The flat lesions are light

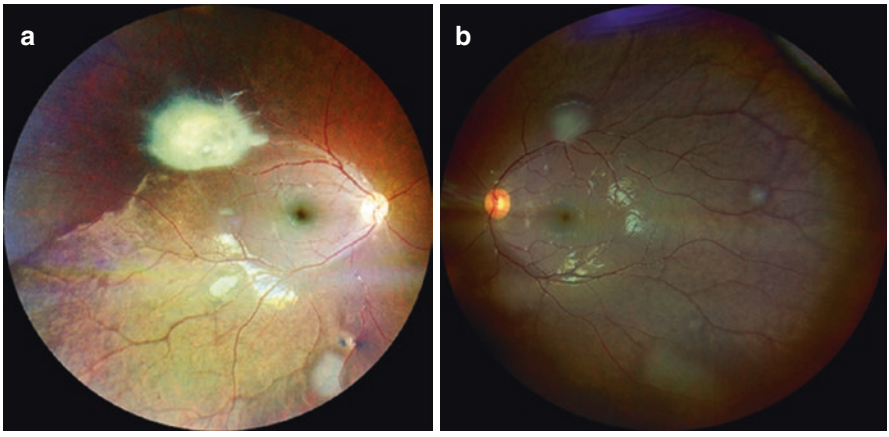

Fig. 15.3 (**a**, **b**) Fundus photos of the right and left eye respectively of a 12-year-old boy showing bilateral astrocytic hamartoma

gray or yellow in color with indistinct margins and are not calcified [24]. The nodular ones classically described as mulberry lesions are well demarcated, elevated and calcified. The transitional ones have features of both the flat and the nodular lesions [24]. The flat translucent lesions are superficial and located near the arcades whereas the nodular elevated lesions are located in the peripapillary area. These lesions are mostly nonprogressive in nature. These patients should be evaluated yearly as they can rarely develop subretinal fluid. Infrequently they can progress rapidly resulting in neovascular glaucoma [25].

Other ophthalmic manifestations include sectoral iris depigmentation, iris and ciliary hamartoma, retinal and choroidal colobomas, eyelid angiofibroma, and refractive error [26–28].

15.5 Wyburn-Mason Syndrome

Wyburn-Mason syndrome or racemose angioma is a rare, nonhereditary neurocutaneous syndrome characterized by arteriovenous malformation (AVM) of the brain, eye and the face. It is also referred to as Bonnet–Dechaume–Blanc syndrome. The manifestation of the disease varies among the individuals.

Patients with intracranial AVM can present with symptoms of seizures, vomiting, head ache, nerve palsy or raised intracranial pressure depending on the location of the AVM [29]. These occur as a result of compression on adjacent structures, ischemia, or bleeding [30]. The facial involvement can range from faint discoloration to large maxillofacial or mandibular AVM which can cause bleeding, facial disfigurement, and psychological stress [31]. There may not be apparent neurological features at initial presentation, but needs to be suspected in patients with retinal and facial vascular malformations [32].

The retina and orbit can be involved in the eye. The resulting symptoms include reduced visual acuity, field loss, proptosis, and congestion of the bulbar conjunctiva [29]. The retinal AVMs can also vary in size and location. The characteristic appearance of retinal AVMs is that of dilated and tortuous retinal vessels extending from the optic disc to the periphery. They have been classified into three distinct groups depending upon the severity of the vascular malformation. Group I AVMs possess an abnormal capillary plexus between the major vessels of the AVM. Group II AVMs lack an intervening capillary network between the artery and the vein. Group III are the most extensive AVMs, with dilated and tortuous vessels and inability to distinguish between arteries and veins [33]. These AVMs can result in macular ischemia, macular edema, vein occlusion, neovascular glaucoma, and serous retinal detachment [34]. These associated complications have to be treated accordingly, even though the AVMs cannot be treated.

15.6 Von Hippel–Lindau Disease

Von Hippel–Lindau disease (VHL) is an autosomal dominant condition caused by mutation of VHL gene located on Chromosome 3 [35]. It is a tumor suppressor gene, whose gene product is involved in the degradation of hypoxia-inducible factor (HIF) 1 and 2 [36]. HIF regulates the expression of several growth promoting genes including vascular endothelial growth factor which are responsible for angiogenesis, proliferation and metabolism. These individuals are predisposed to develop several benign and malignant CNS and visceral tumors.

Retinal capillary hemangioma is the most frequent manifestation of VHL. It can be unilateral/bilateral and solitary/multiple (Fig. 15.4). It is most commonly located in the retinal periphery but can be juxtapapillary as well [37]. It is a well-defined, globular and orange red lesion. The angiomas are supplied by a pair of dilated and tortuous retinal vessels, in which the artery and vein cannot be distinguished. Fluorescein angiography aids in visualization of these tumors. It can be associated with intraretinal/subretinal exudation and subretinal fluid and traction retinal detachment due to the fibrosis over the surface of the angioma and in the vitreous [38]. Long standing retinal detachment can lead to complications like retinal neovascularization, neovascular glaucoma, and cataract [39]. Other rare ocular manifestations of VHL include retinal twin vessels and retinal vascular hamartomas.

The treatment of angiomas involves ablation by laser photocoagulation, transpupillary thermotherapy, cryotherapy, photodynamic therapy or radiotherapy. Intravitreal anti-VEGF agents can be used in cases with associated macular edema.

In the CNS, hemangioblastomas occur and the most common location is cerebellar followed by spinal. Other systemic manifestations include pheochromocytoma,

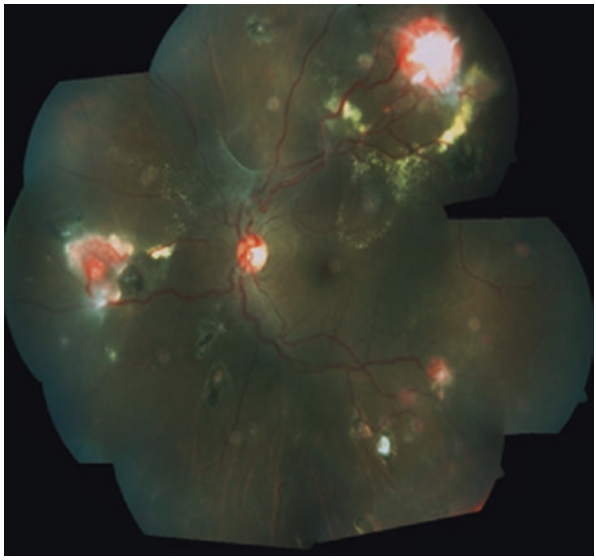

Fig. 15.4 Fundus photograph of the left eye of a 32-year-old man showing multiple retinal angiomas

renal cyst, renal carcinoma, pancreatic cyst, islet cell tumor, epididymal cystadenoma, and endolymphatic sac tumor. The National Institutes of Health recommends contrast-enhanced MR imaging of the brain and spine in VHL cases from age 11, every 2 years, along with annual physical and neurological examinations [40].

15.7 Sturge-Weber Syndrome

Sturge-Weber syndrome (SWS) or encephalotrigeminal angiomatosis is a sporadic neurocutaneous syndrome caused by mutation involving the GNAQ gene. It is characterized by facial Port-wine stain (PWS) involving the ophthalmic division of the trigeminal nerve, ipsilateral diffuse choroidal hemangioma, and ipsilateral leptomeningeal angioma.

PWS is a capillary malformation which is present since birth and increases in size with time (Fig. 15.5). PWS involving the entire division of ophthalmic division of trigeminal nerve have a higher risk of having associated ophthalmic and neurologic disease [41]. Following PWS, seizure is the next most common presentation in SWS. The onset is usually in the first 2 years of life and can be of different pattern. Other neurological manifestations of the disease include hemiparesis, head ache, stroke-like episodes, cognitive, and behavioral problems. Endocrinological abnormalities due to growth hormone deficiency and central hypothyroidism have been reported [42, 43].

The ophthalmic manifestation of SWS includes glaucoma and diffuse choroidal hemangioma. The pathogenesis leading to glaucoma in these cases are

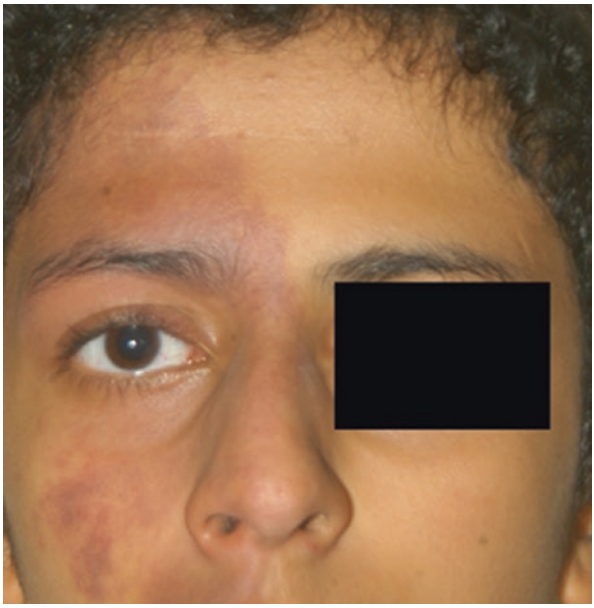

Fig. 15.5 External photograph of the face of a 14-year-old boy with SWS showing PWS

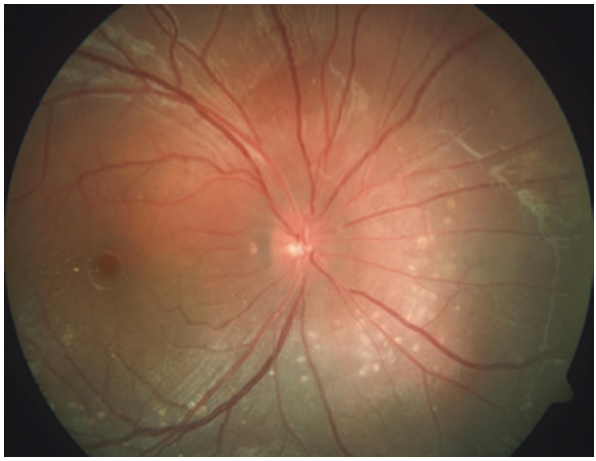

Fig. 15.6 Fundus image of the same patient in Fig. 15.4 showing ipsilateral diffuse choroidal hemangioma with a component of circumscribed choroidal hemangioma

developmental abnormality of anterior chamber angle and increased episcleral venous pressure leading to obstruction of aqueous outflow [44]. It is a unilateral glaucoma having bimodal peak of age of disease onset. Management of glaucoma includes both topical medication and surgical options. Involvement of the eyelids by PWS increases the risk of glaucoma.

Diffuse choroidal hemangioma gives a dark red hue to the fundus giving the 'tomato ketchup' appearance (Fig. 15.6). Though usually not resulting in visual complaints, rarely it can cause visual disturbance due to foveal distortion, refractive error, exudative retinal detachment, retinal pigment epithelial, and photoreceptor alteration. Treatment has to be individualized on a case-to-case basis depending on the extent of involvement and potential for visual recovery. The options include external beam radiotherapy, brachytherapy, and photodynamic therapy [45]. Oral propranolol also has been said to reduce the exudation in diffuse choroidal hemangioma [46]. Other ophthalmic manifestation in SWS includes conjunctival hemangioma, prominent episcleral vessels, and visual field defects due to leptomeningeal angioma.

In conclusion, neurocutaneous syndrome includes a group of diseases with wide variety of presentation which needs a multidisciplinary approach for management.

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