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REVIEW ARTICLE

Retinoblastoma

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Abstract Retinoblastoma represents 3% of all childhood cancers, and is the most common intraocular malignancy of childhood. It is fatal, if untreated. White eye reflex, also known as leukocoria, is the commonest sign, followed by strabismus. The pediatricians have a very important role to play in the diagnosis of this relatively rare, but easily detectable tumor. Early diagnosis yields better results. 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 trans-pupillary thermotherapy, 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 modality of treatment. 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.

Keywords Eye · Retina · Malignant tumor · Retinoblastoma · Chemotherapy · Radiotherapy

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Introduction

Retinoblastoma was first described by Pawius in the sixteenth century [1]. But it was not until 1809 that retinoblastoma was discovered to originate from the retina, when Wardrop performed meticulous dissection on eyes with retinoblastoma, and called it fungus hematodes [1]. The incidence of retinoblastoma is 1 in every 15,000 to 18,000 live births [2]. There is no variation among different races and gender. There are an estimated 5000 new cases worldwide annually, with India alone contributing to 1500–2000 cases. A review of population-based cancer registries survey reported that the age-adjusted incidence of retinoblastoma in India is 1.3–12.3 per million children aged 0–14 y [3]. In countries of Asia and Africa, not only is the incidence higher, but the mortality rates for retinoblastoma is also higher, owing to the delay in diagnosis, advanced disease at presentation, lack of access to advanced medical facilities, and absence of standard management protocols.

Genetics of Retinoblastoma

Retinoblastoma is a malignancy associated with somatic mutation or germline mutation [2, 4]. 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 (Fig. 1). 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 to retinoblastoma, but also to other second cancers (most commonly pinealoblastoma, osteosarcoma and soft tissue sarcomas) [4]. 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

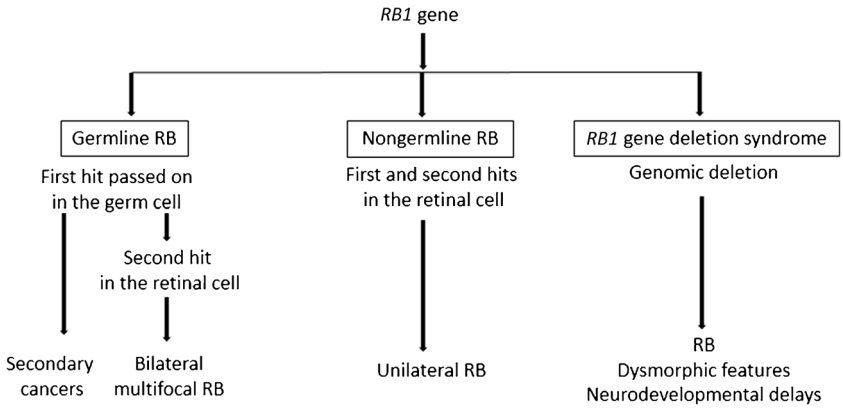

Fig. 1 Genetics of retinoblastoma

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 [4].

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].

Clinical Features

Retinoblastoma is usually diagnosed at an average age of 18 mo, with 95% of children diagnosed by 5 y of age. Germline retinoblastomas can present as early as first month and sporadic retinoblastomas are detected at an average age of 24 mo [2]. 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. The most common presenting symptom and sign is leukocoria. Strabismus is the second most common sign. The other common clinical features are as listed in Table 1.

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 towards it (endophytic) [2].

In the exophytic growth pattern, the tumor arises from the outer retinal layers and causes diffuse retinal detachment (Fig. 2a). It is most often associated with numerous small subretinal seeds. In contrast, an endophytic retinoblastoma arises from the inner retinal layers, progressively fills the vitreous cavity, and causes vitreous seeding (Fig. 2b). At times, the tumor may be 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 [5].

Patients with anterior extension of the tumor can present with white fluffy exudates in the anterior chamber resembling a hypopyon, called pseudohypopyon [2]. Neovascularization of iris and glaucoma are other clinical presentations seen in patients with advanced tumor (Fig. 2c). Orbital cellulitis-like picture occurs when a large tumor undergoes necrosis and induces inflammation in and around the eye (Fig. 2d). Retinoblastoma which has extended outside the confines of the eye is known as orbital retinoblastoma when the patient generally presents with proptosis.

Differential Diagnosis

The most important differential diagnosis is Coats' disease [6]. There are several other lesions that can simulate

Table 1 Clinical features of retinoblastoma

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

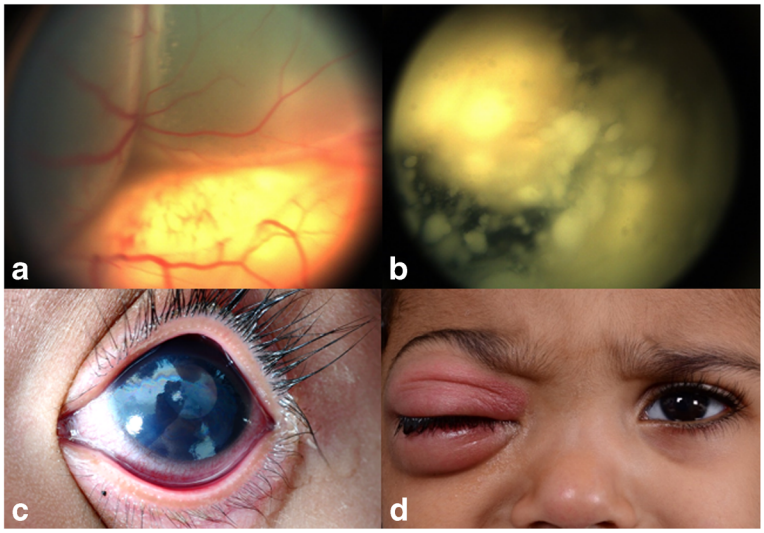

Fig. 2 Clinical presentation of retinoblastoma (**a**) Exophytic growth pattern with diffuse subretinal fluid (**b**) Endophytic growth pattern with diffuse vitreous seeds (**c**) Advanced retinoblastoma with neovascular glaucoma (**d**) Advanced retinoblastoma presenting as sterile orbital cellulitis

retinoblastoma and are known as pseudoretinoblastomas. The important differential diagnoses are listed in Table 2.

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 [7, 8]. CT scan also helps diagnose extraocular extension, while MRI is most appropriate to detect optic nerve invasion and to screen for pinealoblastoma in heritable retinoblastoma.

Table 2 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

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 [9]. The grouping is based on the tumor size, location, severity and presence of subretinal and vitreous seeds (Table 3).

Management

Management of a child with retinoblastoma is aimed at achieving the three sequential goals of life salvage, eye salvage and optimal vision. It involves identification of the tumor group and stage, decision-making regarding the appropriate therapeutic measure (Table 4), and meticulous follow-up for monitoring the treatment progress and detection of any recurrence.

Intravenous Chemotherapy

Currently, intravenous chemotherapy (IVC) is the most widely used treatment in India. Used as a combination triple drug therapy of vincristine, etoposide and carboplatin, and typically for 6 cycles, 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. 3a and b) [10–12]. 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 external beam radiation therapy (EBRT) or enucleation for tumor

Table 3 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 & 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 & 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

Rb Retinoblastoma

control [10]. A combination of chemotherapy and radiation in eyes with vitreous seeds has yielded globe salvage rates varying from 22 to 70% [13].

Periocular Chemotherapy

Periocular topotecan or carboplatin achieves rapid levels within the vitreous in 30 min which lasts for hours, and attains doses that are six to ten times higher than that achieved by IVC. Periocular chemotherapy (POC) is used for advanced groups D or E with diffuse vitreous seeds in which a higher local dose of chemotherapy is desired. It is administered by posterior sub-tenon injection in the quadrant closest to the location of the vitreous seeds. High-dose chemotherapy with concurrent periocular carboplatin has been tried as a primary management strategy, specifically in eyes with diffuse vitreous seeds [14]. 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. 3c and d) [14].

Intra-Arterial Chemotherapy

Suzuki & Kaneko described the technique of 'selective ophthalmic artery infusion' in 2004 by the balloon technique, where a micro-balloon catheter positioned just distal to the orifice for the ophthalmic artery, by a transfemoral artery approach, is inflated and chemotherapy is injected with flow directed into the ophthalmic artery [15].

In 2006, Abramson and Gobin pioneered direct intra-arterial (ophthalmic artery) infusion or superselective intra-arterial chemotherapy (IAC) or "chemosurgery" [16]. The procedure is performed under general anesthesia using a sterile technique (Fig. 4a and b). Through a transfemoral approach, the ipsilateral internal carotid artery is catheterized, and the arterial anatomy visualized with serial angiography runs. The ostium of the ophthalmic artery is superselectively catheterized, and chemotherapeutic drugs injected [16].

IAC has emerged as an effective treatment for advanced retinoblastoma (Fig. 4c and d). It can be used as a primary therapy in advanced cases, or as a secondary therapy in recurrent cases. Shields et al. observed 94% globe salvage in group D eyes, and 91% vitreous seed regression, when IAC was used as a primary therapy [17–19].

Table 4 Decision-making in the management of retinoblastoma: treatment options

Primary tumor: Options for treatment	
Unilateral advanced (Groups D and E)	IAC, IVC, Enucleation
Unilateral less advanced (Groups A, B and C)	IAC, IVC, Focal therapy
Bilateral advanced (Groups D and E)	IVC + POC
Bilateral less advanced (Groups A, B and C)	IVC
Recurrent tumor: Options for treatment	
Solid tumor	IVC, IAC, Plaque radiation, Enucleation
Subretinal seeds	IVC, IAC
Vitreous seeds	IVitC

IAC Intra-arterial chemotherapy; *IVC* Intravenous chemotherapy; *POC* Periocular chemotherapy; *IVitC* Intravitreal chemotherapy

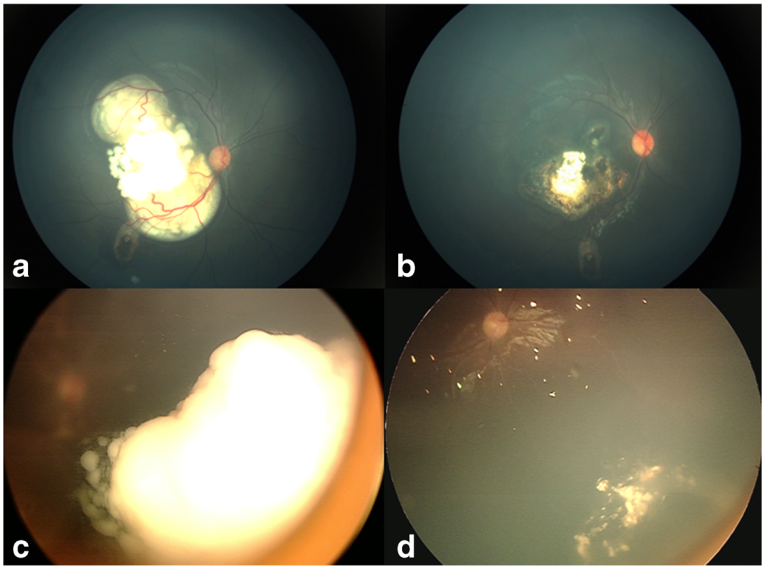

Fig. 3 Intravenous chemotherapy in retinoblastoma (**a**) A group C eye (**b**) After 6 cycles of standard-dose chemotherapy (**c**) A group D eye with fine diffuse vitreous seeds (**d**) Complete regression after 6 cycles of high-dose chemotherapy with 2 doses of concurrent periocular carboplatin

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. 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 [20]. Intravitreal chemotherapy (IVitC) achieves higher drug concentration within the vitreous and effectively causes regression of vitreous seeds, without associated systemic side effects.

Melphalan is now the most extensively used drug to control the vitreous disease in retinoblastoma. 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. 5a and b).

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. A combination of intravitreal melphalan and topotecan has also been used to achieve excellent regression in refractory vitreous seeds. The authors have used topotecan as monotherapy in achieving vitreous seed regression in 36 eyes (Fig. 5c and d). Topotecan is a very safe drug for intraocular use, is stable in solution and can be given as a 3-weekly injection.

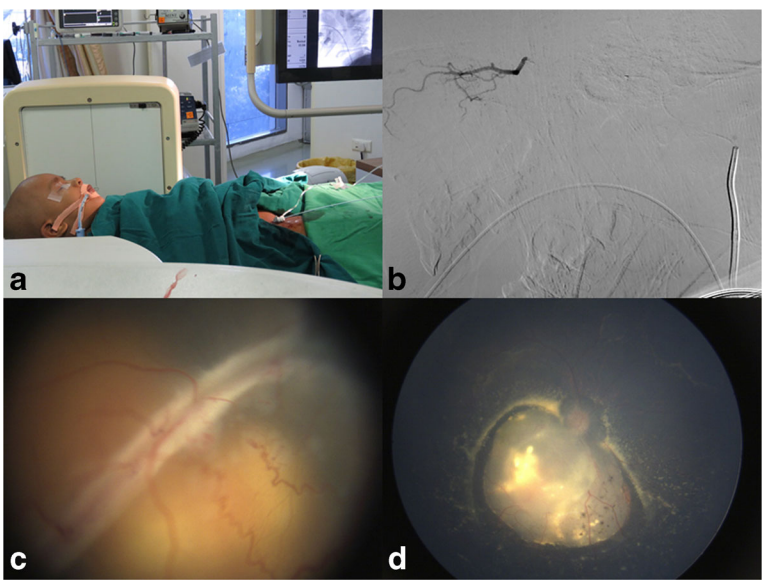

Fig. 4 Intra-arterial chemotherapy: Procedure in the cath lab (**a**) Patient under general anesthesia with a transfemoral cathether (**b**) An angiography performed with the microcatheter at the ostium of the ophthalmic artery, showing a patent ophthalmic artery (**c**) A group E eye with a very large tumor and diffuse subretinal fluid (**d**) After 3 cycles of intra-arterial chemotherapy

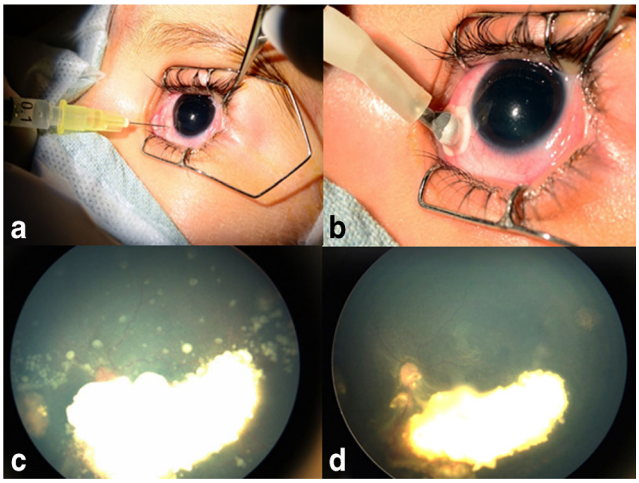

Fig. 5 Intravitreal chemotherapy (**a**) Pars plana intravitreal injection of topotecan at a dose of 30 μg in 0.15 ml with a 30-gauge needle (**b**) Triple freeze-thaw cryotherapy at the injection site (**c**) Before and (**d**) after 2 doses of intravitreal topotecan injections in an eye with recurrent diffuse vitreous seeds after 6 cycles of chemotherapy

Radiation Therapy

Retinoblastoma is a highly radiosensitive tumor, and radiation therapy can be curative. Radiation in the form of external beam radiation therapy 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 including recalcitrant cases, and as a part of multimodal treatment in orbital retinoblastoma. 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 [25]. It is now used as a secondary therapy for recurrent cases in tumors not amenable to focal therapy.

Focal Therapy

Focal therapy in retinoblastoma includes cryotherapy, transpupillary thermotherapy, and laser therapy. These are used for consolidation once the tumor has attained a considerably lower volume with chemoreduction, usually after 2 or 3 cycles, or for the treatment of small recurrent tumors or subretinal seeds [26–28]. However, they can also be used as the sole therapy for small retinoblastomas (Group A or B). Transscleral cryotherapy involves freezing the tumor under visualization using indirect ophthalmoscopy. In thermotherapy, hyperthermia generated by infrared radiation at subphotocoagulation levels destroys the tumor. Photocoagulation using argon green laser (532 nm) is delivered with an indirect laser delivery system which causes tumor apoptosis.

Enucleation

Enucleation is the oldest form of treatment for retinoblastoma, and is still indicated in advanced cases [11]. 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 extra care needs to be taken when handling an eye with retinoblastoma to avoid accidental perforation that can potentially cause orbital seeding of the tumor. A primary orbital implant (silicone, polymethylmethacrylate, porous polyethylene, or hydroxyapatite) placed in the socket provides adequate static and dynamic cosmesis.

An enucleated eyeball is always submitted for pathology to assess for high risk factors (HRF). HRF include significant invasion of the uvea, anterior segment, or optic nerve. 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 [29]. 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. Adjuvant chemotherapy consists of a combination of vincristine, etoposide and carboplatin given 4-weekly for 6 cycles [29].

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% [30]. 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. 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 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% [30]. However, with an intensive multimodal management and careful monitoring, patients with orbital disease are known to do well (Fig. 6a–d).

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 [31]. 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 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 [31].

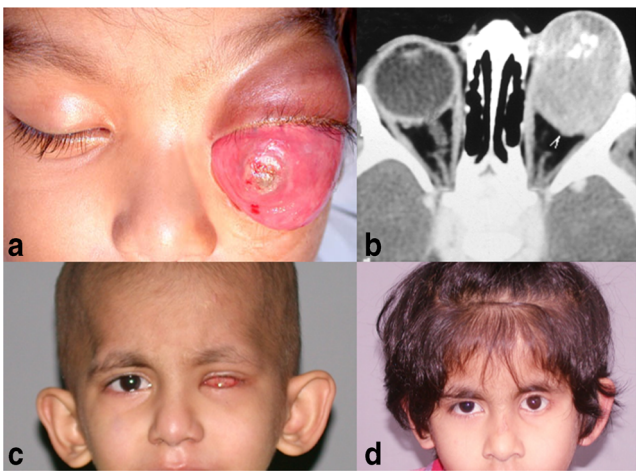

Fig. 6 Multimodal management in orbital retinoblastoma (**a**) External photograph of primary orbital retinoblastoma left eye taken during examination under anesthesia (**b**) Axial computed tomography image displaying extraocular extension of the intraocular tumor left eye (**c**) After 12 cycles of doses of high-dose chemotherapy, external beam radiotherapy and enucleation (**d**) Healthy child cured of orbital retinoblastoma, with a well-fitting prosthesis

Prenatal Genetics

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 [32].

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 [32].

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 the offspring can be tested for the same mutation. However, if no mutation is found in the blood, the tumor is nongermline (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 [3, 32].

Conclusions

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. A pediatrician plays a vital role in the diagnosis of the disease, and any case of leukocoria and strabismus must be referred urgently to an ophthalmologist for a thorough evaluation to rule out retinoblastoma. 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 the 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.

Contributions RR: Drafting of the manuscript and figure compilation; SGH: Concept, critical revision and will act as guarantor for the paper.

Compliance with Ethical Standards

Conflict of Interest None.

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