Review Article

Adult onset retinoblastoma

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Retinoblastoma (RB) is the most common primary malignant intraocular tumor of childhood presenting usually before 5 years of age. RB in adults older than 20 years is extremely rare. A literature search using PubMed/PubMed Central, Scopus, Google Scholar, EMBASE, and Cochrane databases revealed only 45 cases till date. Over the past decade, there has been a significant increase in the number of such reports, indicating heightened level of suspicion among ophthalmologists. Compared to its pediatric counterpart, adult onset RB poses unique challenges in diagnosis and treatment. This article summarizes available literature on adult onset RB and its clinical and pathologic profile, genetics, association with retinocytoma, diagnostics, treatment, and outcomes.

Key words: Adult onset retinoblastoma, calcification, enucleation, globe salvage, immunohistochemistry, retinocytoma

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Retinoblastoma (RB), a tumor originating from the sensory retina, is the most common primary malignant intraocular tumor of childhood with a reported incidence ranging from 1 in 15,000 to 1 in 18,000 live births.[1] In 90% of cases, the diagnosis is made before 5 years of age.[2] RB is bilateral in 25–35% of cases with the average age of diagnosis of unilateral cases being 24 months and that of bilateral cases being 12 months.[3]

Its occurrence in adulthood is rare, and literature on this entity is scarce with majority being anecdotal case reports. There have been around 45 cases reported till date in adults 20 years or older. Ever since the oldest report was presented in 1919 from a 20-year-old white girl,[4] literature on this demographically rare variety of RB has been building progressively. There has been a flurry of reports in the previous decade with the largest series of eight cases published only recently.[5]

Adult onset RB can be quite different in presentation compared to its pediatric counterpart. Moreover, due to its rarity, it is usually not considered in the differential diagnosis of a retinal or intraocular mass in an adult[6] often leading to delayed diagnosis and dismal outcome. An increase in the number of case reports after the previous review article in 2000 and our own experience with such cases prompted us to review the literature again. In this paper, we present a comprehensive review of the historical aspects, clinical manifestations, pathology, pathogenesis, and potential association with retinocytoma, treatment, and outcomes of adult onset RB.

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Historical Background

The first case dates back to 1919 in a 20-year-old girl[4] followed by another report 10 years later in a 48-year-old gentleman.[7] Four more cases were reported between 1943 and 1948.[8-11] After another quiescence, in the decade between 1959 and 1968, seven cases were documented.[12-18] Literature reveals only four more cases in the 1970s and 1980s.[19-22] In 2000, Biswas *et al*. reported three cases and published the first comprehensive review on the subject[23] where they compiled data from 21 previous cases.[4,6-24] From 2005 onward, there has been a sudden proliferation of cases where 23 more cases have been published including 16 cases reported in the last 3 years.[5,25-39]

Pathogenesis

There are two explanations for the late presentation of RB:

i. *De novo* RB without antecedent lesion may be due to persistence of rare embryonal retinal cells which undergo malignant transformation in later life[22]
ii. The tumor may also arise from previously undiagnosed, spontaneously regressed/arrested RB often termed retinocytoma or retinoma which have been reactivated by additional oncogenic mutation.[19]

Reported Associations of Retinoblastoma with Retinocytoma

Retinocytoma is a rare clinically, well-characterized benign retinal tumor, carrying RB1 gene mutation. Retinocytomas were

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initially considered a type of spontaneously regressed tumor, but recent evidence suggests that it represents a premalignant lesion. It is frequently associated with cottage cheese calcification and retinal pigment epithelium hyperplasia.[40] Histopathology shows the presence of fleurettes with benign cytologic features. It is believed that RB arises if the second mutation occurs in immature retinoblasts, whereas retinocytoma is likely if the second event occurs in almost mature retinoblasts.[41,42] Another hypothesis states some mutations in RB1 do not inactivate the RB1 protein completely, leading to partial penetrance.[43]

There is a possibility of malignant transformation of retinocytoma due to genomic instability and unknown stimulus.[41] Retinocytoma was observed in 1.8–15.6% of patients with childhood RB.[44,45] Singh *et al*. stated that the risk of malignant transformation of a retinocytoma into an RB is 4%.[40] Among all the cases of adult RB, histological features suggestive of accompanying retinocytoma at the base of malignant cells were reported in three cases.[18,24,25] As normal fundi were not previously documented in the majority of reported patients, most authors believe perhaps they did harbor a retinocytoma. In a recent retrospective series of eight cases, Kaliki *et al*. reported that they did not encounter benign retinocytoma/retinocytoma-like areas on histopathology in any of their cases. Yet, patients with retinocytoma must be kept under follow-up for several years due to the possibility of malignant transformation.

Genetic basis for progression of retinocytoma to retinoblastoma

Genetic studies on retinocytomas have been rarely performed. Sampieri *et al*. compared genetic mutations in retinocytomas and RBs and demonstrated that some copy number changes thought to belong to early (MDM4 gain) or late stage (MYCN and E2F3 gain) of RB are already present in retinocytoma at the same (for MDM4) or at lower (for MYCN and E2F3) copy number variations.[46] The authors suggest that MDM4 gain may be involved in the early transition from the normal retina to retinocytoma while MYCN and E2F3 progressive gain may represent driving factors of tumor progression. These results also confirm the premalignant nature of retinocytoma. Dimaras *et al*. demonstrated similar results and reported that although retinocytomas can remain unchanged throughout life, highly proliferative, clonal and aneuploid RBs commonly emerge, exhibiting altered gene copy number and expression of oncogenes (MYCN, E2F3, DEK, KIF14, and MDM4) and tumor suppressor genes (CDH11, p75NTR), and reduced expression of p16INK4a and p130.[44] The authors believe that RB1 inactivation in developing retina induces genomic instability, but senescence can block transformation at the stage of retinocytoma. However, stable retinocytoma is rarely clinically observed because progressive genomic instability commonly leads to highly proliferative RB.

There is a lack of genetic studies on adult onset RB specimens; thus, limiting current observations to childhood RB. It may be interesting to note genetic differences between childhood and adult onset RB, once such reports are available.

We suspect that most adult onset RBs harbor underlying retinocytomas and their reactivation much later in life, due to an unknown oncogenic stimulus, may lead to development of adult onset RB. Future publications on adult onset disease will do well to perform genetic analysis and comment on the presence of underlying retinocytoma from the enucleated specimens.

Histopathology and Immunohistochemistry

In childhood onset RB, it has been reported that well-differentiated tumors occur at an earlier age than poorly differentiated tumor.[47] This may represent de-differentiation seen in other carcinomas where less severe well-differentiated tumors progress to more severe poorly differentiated tumors.[48] However, combining all cases of adult onset RB, we did not see any difference in mean age between those with undifferentiated (mean age = 30 years) and poorly differentiated RB (mean age = 32.9 years), suggesting underlying pathogenic and potential genetic differences between childhood and adult onset RB.

Undifferentiated RB may need immunohistochemistry (IHC) for diagnosis.[36] IHC can help in confirmation of RB by identifying photoreceptors and glial cells. It can also indicate the level of differentiation of RB by identifying red and green cones found in rosettes and fleurettes and blue cones which do not form rosettes and fleurettes.[21]

There is no specific immunomarker for RB.[25] Literature shows that the most commonly employed IHC marker employed to confirm the presence of RB cells in adult onset disease was neuron-specific enolase (positive in nine out of ten cases). Other useful markers were synaptophysin (positive in five cases), CD56 (positive in three cases), and glial fibrillary acidic protein (positive in three cases). Other markers such as proliferating cell nuclear antigen, chromogranin A, S-antigen, S-100, vimentin, p53 protein were positive in individual cases only. Although a melanocytic marker, positive staining with S-100 is observed within the reactive stroma. In cases with dilemma, it is important to note that lack of staining with human melanoma black-45 and keratin almost rules out malignant melanoma and metastatic carcinoma.[31]

Clinical Features

Presentation

Age

Age of presentation of adult RB cases ranged from 20 to 74 years. The majority (n = 39) were from 20 to 50 years with only five patients presenting above 50 years. Most common age of presentation was 20–30 years (n = 23) followed by 41–50 years (n = 9). Kaliki *et al*., in their recent series have reported a mean age at presentation of 30 years and range from 22 to 48 years, very similar to the previous reports.[5]

Sex

No predilection of adult onset RB for any sex was noted. Of the 45 cases, 24 were male, and 21 were female.

Laterality

All cases of adult RB have been unilateral till date. Among the 19 of 45 cases where data is available, RB affected the right eye in 13 cases and the left eye in 6 cases. The specifics of the eye involved are unavailable from other reports.

Presenting symptoms

Dimness of vision was the most common complaint followed by perception of floaters in the affected eye. Other symptoms

were pain and redness. One patient presented with leukocoria and three with proptosis and orbital mass. This is in sharp contrast to childhood RB where leukocoria and strabismus are the most common clinical presentation and vision loss reported in 5% of patients.[49] Duration of symptoms before diagnosis ranged from 3 days to 100 months with a mean duration of 15.1 months, and the median duration was 6 months in the first 36 cases and median of 12 months in the latest series of 8 cases.[5] This shows that symptoms of adult onset RB are insidious, and patients wait for a considerable period before seeking ophthalmic consultation.

Visual acuity

From available data of 18 cases, visual acuity at presentation ranged from 20/20 to no light perception. Half of the cases had 20/80 or better vision while the other half had 20/400 or worse.

Ocular findings

Findings are summarized in Tables 1 and 2. Solid intraocular mass is the universal presentation in all cases. However, in three cases, it was not identified initially on clinical examination but later confirmed on imaging.[5,26] The majority of the eyes (28 out of 45) had a single mass; one had two separate retinal lesions[23] whereas multiple lesions were noted in two eyes.[29,38] Data are not available on 13 cases. Intraocular mass was mostly whitish in color. Single cases of salmon colored[24] and partially pigmented masses[37] have been reported. Surprisingly, no cases of diffuse infiltrating variety, which is more common in older children, have been reported in adults. Among available data of 23 cases, anterior segment findings were noted in 11 cases showing keratic precipitates, anterior chamber seeds, iris neovascularization, and pseudohypopyon. Three cases had orbital disease.

Grouping

Grouping of RB in children is done according to the International Intraocular RB Classification (IIRC).[50] Using the IIRC for adult onset RB has its pitfalls but we, nevertheless, tried to classify eyes based on available data. Grouping of 17 adult RB cases up to 1986 was not possible due to lack of information in the reports. Among subsequent 27 cases, we found only two eyes that could be classified as Group B, 3 as Group C, 8 as Group D, and the majority (n = 12) as Group E. This shows most of the cases were fairly advanced before diagnosis.

Globe salvage

Unfortunately, only one of the adult onset RB eyes has been salvaged till date.[5] Globe was already destroyed in three cases of orbital RB[5,34] and others ended up in enucleation. Attempts to salvage the globe with chemo reduction and focal therapy in six cases were unsuccessful. This may be because of delayed presentation with advanced disease in most cases, or recurrences and more aggressive disease than childhood RB. However, with new targeted treatment modalities such as super selective intra-arterial chemotherapy and intravitreal chemotherapy, timely intervention at earliest may make globe salvage a reality in the near future even for adult onset RB.

Visual prognosis

There was a little hope of salvageable vision at the outset in most cases. The final outcome was dismal as, barring one, all eyes underwent enucleation either as primary management or subsequently due to the failure of conservative methods of treatment.

Extraocular extension, metastasis, and death

Available records from published literature revealed extraocular extension in 5 of 27 cases. Of the 5 cases, 2 had orbital disease but no evidence of metastasis at presentation.[34] However, follow-up records are not available. Rest of the three cases had distant metastasis and unfortunately expired at 12, 16, and 60 months.[28,33]

Table 1: Cases of adult onset retinoblastoma reported till 1986

Author	Year	Age	Sex	Duration of SS (months)	Tumor characteristics		Treatment	Rosettes in histology
					Location	Size (mm)		
Maghy[4]	1919	20	Female	12	Whole eye	Whole	Enucleation	FW
Verhoeff[7]	1929	48	Male	6	Superonasal	10×15	Enucleation	FW
McCrea[8]	1943	20	Male	NS	NS	NS	Enucleation	NS
Rasmussen[9]	1944	48	Male	4	Anterior to equator	16×14	Enucleation	No
Rychener[10]	1948	33	Female	54	Posterior pole	6.5×7	Enucleation	FW
O'Day[11]	1948	29	Male	NS	Anterior to equator	NS	Enucleation	NS
Arseni and Opresco[12]	1959	53	Male	4	Posterior pole	NS	Enucleation	FW
Mehra and Hamid[13]	1961	45	Male	24	Anterior to equator	NS	Enucleation	FW
Finlay and Byron[14]	1962	74	Female	6	NS	NS	Enucleation	NS
Makley[15]	1963	52	Male	60	Whole eye	20×25	Enucleation	FW
Ohara *et al*.[16]	1963	43	Female	48	Optic nerve head	3.8×3.8	Enucleation	HW
Perz and Majewski[17]	1964	56	Male	5	NS	NS	Enucleation	NS
Lasch[18]	1968	40	Female	60	NS	NS	Enucleation	No
Kremlicka and Roubková[19]	1975	42	Male	4	Anterior to equator	8×18	Enucleation	FW
Berkeley and Kalita[20]	1977	60	Male	3	Whole eye	Whole	Enucleation	No
Takahashi *et al*.[21]	1983	26	Female	6	Superior	NS	Enucleation	HW
Neronova-Kotova[22]	1986	46	Female	24	NS	NS	Enucleation	NS

SS: Symptoms and signs, NS: Not specified, FW: Flexner–Wintersteiner rosettes, HW: Homer-Wright rosettes

Table 2: Recent reports of cases of adult onset retinoblastoma (1987-2015)

Author	Year	Age/sex	Tumor characteristics		Growth pattern	Extraocular spread	Treatment	Rosettes in histology
			Location	Size in mm				
Biswas *et al.*[23]	1996	32/male	Posterior pole + superotemporal	10×8	Mixed	No	Enucleation	HW + flurettes
Biswas *et al.*[23]	1996	21/male	Posterior pole	3×5	Endophytic	No	EBRT + chemo – enucleation	NS
Mietz *et al.*[6]	1996	26/female	Anterior to equator	12×2	Endophytic	No	EBRT + focal – enucleation	HW
Nork *et al.*[24]	1996	29/female	Nasal midperiphery	8×10	Exophytic	No	EBRT – enucleation	Bacillette
Biswas *et al.*[23]	2000	25/female	Superonasal	12.5×11	Mixed	No	Enucleation	No
Odashiro *et al.*[25]	2005	21/female	Inferotemporal	16×16	Mixed	No	Enucleation	FW + flurettes
Orellana *et al.*[26]	2009	23/male	Posterior pole	16×5	Mixed	No	Enucleation	No
Shrestha *et al.*[27]	2010	37/male	Nasal ciliary body	10×4	Exophytic	No	Enucleation	No
Nandedkar *et al.*[28]	2010	22/female	Whole eye	Whole eye	Mixed	Yes	Enucleation + chemo	No
Wells *et al.*[29]	2011	48/female	Superior	9×8.4	Mixed	No	EBRT + focal – enucleation	HW
Singh *et al.*[30]	2011	29/female	Posterior pole	11.5×4	Endophytic	No	Enucleation	HW
Zhang *et al.*[31]	2012	20/male	Nasal ciliary body	NS	Mixed	No	Enucleation with chemo	HW
Goel *et al.*[39]	2012	50/male	Posterior pole	Half of the globe	Endophytic	No	Enucleation	Rosettes with necrosis
Khetan *et al.*[32]	2013	33/female	Inferonasal	4×5	Endophytic	No	Focal – enucleation	No
Zafar *et al.*[33]	2013	25/male	NS	15×12	Mixed	Yes	Enucleation, chemo + EBRT	No
Chawla *et al.*[34]	2013	24/male	Whole eye + orbit	Whole eye	Mixed	Yes	EBRT + chemo	NS
Khetan *et al.*[35]	2014	30/female	Temporal	11×5.8	Exophytic	No	Focal + chemo – enucleation	NS
Yousef *et al.*[36]	2014	23/male	Inferotemporal	3.5×9.5	Endophytic	No	Focal + chemo – enucleation	FW + HW
Sharifzadeh *et al.*[37]	2014	29/female	Posterior pole	16×12.5	Mixed	No	Enucleation	FW
Zhang *et al.*[38]	2015	45/male	Posterior pole + inferonasal	NS	Endophytic	No	Enucleation	No
Kaliki *et al.*[5] (*n*=8)	2015	Mean age=30, 50% men	Individual cases NS	Mean=12×9	NS	Yes (*n*=3)	EBRT = 2 Enucleation = 5 Chemo = 3 Exentration + chemo + EBRT = 3	NS

EBRT: External beam radiotherapy, NS: Not specified, FW: Flexner–Wintersteiner rosettes, HW: Homer Wright rosettes

Differential Diagnosis

A diagnostic dilemma often exists as RB in adults is not expected due to its rarity. In the presence of inflammation, cataract or vitreous hemorrhage diagnosis becomes more challenging.[23] It can be misdiagnosed as:

i. Adult onset Coats disease[31]
ii. Retinal astrocytoma
iii. Metastatic carcinoma[5,29]
iv. Amelanotic melanoma[5,35,37]
v. Intraocular lymphoma
vi. Vasoproliferative tumor[5]
vii. Endophthalmitis or panophthalmitis
viii. Fungal granuloma[32]
ix. Ocular cystecercosis[23]
x. Retinal inflammatory diseases[26]
xi. Intraocular medulloepithelioma
xii. Retinocytoma
xiii. Neovascular glaucoma (in the presence of anterior segment signs with poor view of fundus).[38]

Ancillary Studies

The following ancillary tests can be considered to arrive at the correct diagnosis:

i. Ultrasound B-scan
ii. Computed tomography (CT)
iii. Magnetic resonance imaging (MRI)
iv. Fine needle aspiration biopsy (FNAB)
v. Metastatic workup.

Ultrasound B-scan

Ultrasound B-scan is the primary and most important study to confirm the presence of an intraocular mass arising from retina, to measure the dimensions of mass, to detect associated vitreous seeds or retinal detachment, and to exclude optic nerve invasion. It reveals dome-shaped solid mass with high surface reflectivity and variable internal reflectivity. However, an ultrasound scan may or may not reveal intralesional calcification, which is typical of RB in children.[51] Of 16 cases where ultrasound findings are available, only 5 had calcification confirming that this is not a consistent finding in adult onset RB. In addition, ultrasound B-scan remains invaluable to exclude other differentials.

Computed tomography

CT detects extraocular extension and can detect RB associated intracranial tumor-pinealoblastoma, which is extremely rare in an adult.[51] CT has demonstrated intraocular calcification in only 25% cases (3 out of 12) till date. In two eyes of adult RB, ultrasound and CT gave contradictory results for calcification.[23]

Magnetic resonance imaging

MRI is specifically indicated if optic nerve invasion or intracranial extension is suspected.[51] MRI was done in six cases and successfully delineated the intraocular mass, excluded optic nerve, and extraocular spread in five cases and showed orbital apex involvement in one case of orbital RB.[34] However, MRI does not have specific features typical of RB in T1- or T2-weighted images or other sequences and hence, it is difficult to use MRI to conclusively diagnose the presence of RB. Once there is a good clinical or ultrasound/CT-guided evidence of RB, MRI helps to rule out optic nerve and extraocular/intracranial extension very well.

Diagnostic biopsy or cytology

In atypical cases of intraocular tumors defying accurate clinical diagnosis, sample obtained either by FNAB or from vitrectomy specimens has proved to be a useful adjunct diagnostic tool.[52] From available reports on adult onset RB, we found that aspiration cytology, biopsy, or vitrectomy samples were obtained in as many as 13 eyes due to diagnostic dilemma. The examination could provide limited information such as the presence of small round malignant cells in ten cases whereas in three cases smear was acellular. Cytology could differentiate nonmalignant masquerades such as Coats disease[31] or posterior uveitis[26] but was inconclusive in distinguishing primary and metastatic tumor and lead to delayed diagnosis in one case[28] and misdiagnosis in another.[5] In general, preoperative FNAB is not routinely performed in RB for risk of tumor seeding.[53] Despite the rare use of FNAB in the diagnosis of intraocular tumors, the risk of tumor recurrence in the socket was not increased after enucleation according to the literature.[53,54] Shields *et al*. stated some risks of RB dissemination after vitrectomy in eyes with unsuspected RB, in older pediatric patients.[55] Zafar *et al*. reported possible upstaging of tumor due to vitreous tap.[33] Vitrectomy or vitreous tap in unsuspected RB needs enucleation with chemotherapy or radiotherapy or both without delay to prevent systemic tumor dissemination.[55] Cases with diagnostic dilemma might benefit from FNAB followed by IHC staining of the specimens.

Metastatic workup

A patient of RB is always at risk of metastasis. Most metastases are detected within the first 2 years of diagnosis.[56] The standard metastatic workup for RB includes blood counts, bone marrow biopsy, cerebrospinal fluid cytology, liver function tests, abdominal ultrasound or CT, and chest X-ray or CT thorax. The previous reports also advise performing total body positron emission tomography and 99mTc-methylene diphosphonate whole body bone scan in suspected cases.

Treatment and Outcomes

Management of RB should be guided by the objectives to save life, retain anatomical integrity of the eye, preserve vision, and obtain good cosmetic results. The treatment option chosen for each individual case depends on the overall situation, including, size and location of the tumor, laterality, visual prognosis, threat of metastatic disease, and systemic status.[57]

Enucleation

Enucleation with orbital implant was the primary modality of treatment in the majority of reported cases of adult onset RB, due to the advanced stage of tumor and unilateral disease.[58] Although management of childhood RB has evolved over the past decade and newer modalities such as super selective intra-arterial chemotherapy and intravitreal chemotherapy for residual vitreous seeds favor eye salvage in most instances, there is little literature to support their use in adult onset RB thus far. Of the 17 cases reported up to 1986, no treatment records other than enucleation are available. Among the 27 subsequent cases reported, primary enucleation was done in 14 cases of which 1 case underwent preoperative radiation, 2 required additional postenucleation chemotherapy,[28,31] and 1 both chemo and radiotherapy.[33] Two cases underwent pars plana vitrectomy for retinal detachment with unsuspected RB ending up finally in enucleation.[26,29] Seven eyes had to be enucleated after the failure of other treatment modalities. No surgery was needed in one case of orbital RB but exenteration was done in other two.[5,34] As mentioned above, newer therapies may make globe salvage a reality in the near future even for adult onset RB.

External beam radiotherapy

External beam radiotherapy (EBRT) was done in total of ten cases. Preoperative EBRT was given in one case before enucleation to prevent seeding.[24] Postenucleation EBRT even with chemotherapy was unable to control metastasis in one case.[33] Primary EBRT with subsequent chemotherapy (intra-arterial and intravitreal) and plaque radiotherapy was successful in the only reported case of globe salvage in IIRC Group D tumor (66 months follow-up).[5] However, EBRT with chemotherapy was only able to temporarily regress another Group D tumor for 18 months[23] and was unsuccessful in tumor regression in three cases.[5,6,29] It controlled local disease in one case of orbital RB[34] and played a crucial role along with chemotherapy and exenteration in treatment of two other cases.[5]

Systemic chemotherapy and chemoreduction

Six cycles (1 month apart) of carboplatin 500 mg/m^2 on day 1, vincristine 1.50 mg/m^2 on day 1, and etoposide 150 mg/m^2 on days 1 and 2 was the regime of chemotherapy used in adult RB cases.

Chemotherapy postenucleation was needed in four cases due to microscopic high-risk features.[28,29,31,33] It controlled orbital disease in three cases.[5,34] Chemotherapy with focal therapy (either transpupillary thermotherapy or cryotherapy) was able to induce initial regression in four cases but failed to prevent recurrence.[23,35,36]

Focal therapy (plaque brachytherapy, laser therapy, cryotherapy, transpupillary thermotherapy)

RB in adults may be more resistant to focal therapy than RB in children.[36] Five cases of IIRC Group C and D were treated with various combination of systemic chemotherapy, EBRT, and focal therapy.[6,29,32,35,36] One case was resistant[6] and others showed initial response but eventually had to be enucleated for recurrence. Khetan *et al*. reported a patient who underwent 11 cycles of chemotherapy in all combined with multiple treatments of transpupillary thermotherapy, laser using indirect ophthalmoscopy, and transconjunctival cryotherapy but tumor recurred after 2 years finally ending up in enucleation.[35]

It is important to recognize that out of 13 cases with primary enucleation, only 2 cases recurred with eventual

death probably representing aggressive disease.[28,33] However, all the five cases with focal therapy recurred (4 within 2 years and 1 at 42 months) indicating either improper case selection for therapy or poor response of adult RB to these modalities. Even after complete regression of a tumor, long follow-up at short intervals and a complete fundus evaluation at every visit is mandatory to detect early recurrences and deliver prompt management.[32]

Metastatic disease management

In spite of advanced local disease in most cases, metastatic disease has been reported in only three cases thus far. One patient, in spite of whole brain radiotherapy for metastatic suprasellar brain deposit, expired at 16 months.[33] The remaining two did not receive any treatment for metastasis and eventually died at 1 year and 5 years showing poor outcome.[5,28]

Conclusion

RB has evolved from a deadly childhood cancer to a largely curable cancer within the past 40 years.[31] RB should be considered as a possibility in adults with amelanotic whitish mass lesion in the fundus. Ultrasound and CT scan should be the first line of investigation. In case of dilemma, FNAB of the mass with IHC may yield useful results. As of today, globe salvage appears a far cry in eyes with adult onset RB. Early recognition of this entity and trials of appropriate focal therapy and new promising modalities like intraarterial, periocular, or intraocular chemotherapy is warranted for a better outcome. Many questions remain unanswered such as the genetic make-up of adult onset RB and its dependence on retinocytomas, best treatment patterns to allow globe salvage and long-term survival of adults with RB compared with childhood RB.[39] Long follow-up is required with proper attention to contra lateral eye of the patient and first-degree relatives.

Methods of literature search

PubMed and PubMed Central, Scopus, Google Scholar, EMBASE, Cochrane database for all reports in English using the keywords "Retinoblastoma in Adults," "Adult onset retinoblastoma," and filters such as date (from 1901 onward) and article type (case report, review). Reports in other native languages were translated in English using the "Google Translate" open access service to decipher useful information for this review.

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Conflicts of interest

There are no conflicts of interest.

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