

REVIEW

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# Retinocytoma: understanding pathogenesis, diagnosis, and treatment approaches

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## Abstract

Retinocytoma, or retinoma, is a rare benign intraocular tumor primarily affecting the retina. It is often considered a precursor or a differentiated form of retinoblastoma, a malignant retinal tumor predominantly seen in children. Despite its non-aggressive nature and excellent prognosis, retinocytoma remains a significant area of interest due to its implications for genetic counseling, early detection, and management of ocular tumors. The pathogenesis of retinocytoma is closely linked to mutations in the *RB1* gene, which plays a vital role in regulating the cell cycle. The detection of *RB1* mutations in peripheral blood indicates germline disease, substantially elevating the risk of bilateral retinoblastoma development. Despite its benign nature, retinocytoma necessitates vigilant monitoring due to its potential to transform into retinoblastoma. Current treatment strategies primarily focus on observation and regular follow-up. However, more aggressive treatments are considered if malignant transformation is suspected. The prognosis is generally favorable, with most patients maintaining good visual acuity and a low risk of progression to retinoblastoma. We aim to present an up-to-date review on epidemiology, clinical features, pathogenesis, macroscopic and histopathological features, diagnostic criteria, prognosis, and management strategies.

**Keywords** Retinocytoma, Retinoma, Photoreceptor cells, *RB1* gene, Immunohistochemistry, Ocular tumors.

## Introduction

Retinocytoma, also known as retinoma, is a rare and benign intraocular tumor that primarily affects the retina [1]. It is often considered a precursor or a differentiated form of retinoblastoma, a malignant retinal tumor most commonly seen in children [2]. The term retinoma was first coined by Gallie et al. to replace the older term

“spontaneously regressing retinoblastoma.” [1]. The term retinocytoma was later proposed following the terminology for pineal gland tumors [3, 4]. The earliest description of “spontaneously regressing retinoblastoma” was published in 1956 [5]. At that time, compiled evidence of regression included four points: [1] a family history of the disease (which might not be present in all cases) [2], clinical diagnosis of bilateral retinoblastoma with removal of one eye (usually with histological proof) followed by arrest of growth in the other eye [3], a fundus image corresponding to that of verified cases, and [4] calcified tumor cells in phthisical eyes [5].

According to the International Classification of Diseases for Oncology (ICD-O), retinocytoma is coded as 9510/0 (Retinocytoma, C69.2), while retinoblastoma that has spontaneously regressed is coded as 9514/1 (Retinoblastoma, spontaneously regressed, C69.2) [6]. In the

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International Classification of Diseases, 11th Revision (ICD-11), retinocytoma is coded as XH5AV1 (Retinocytoma, neuroepitheliomatous neoplasm) and is also classified under 2F36 (Benign neoplasm of eye or ocular adnexa) [7].

## Methodology

This narrative review was conducted using the SANRA (Scale for Assessing Narrative Review Articles) criteria to ensure a structured approach in collecting, evaluating, and synthesizing the existing literature on retinocytoma [8].

A comprehensive search of electronic databases, including PubMed, MEDLINE, and Embase, was performed to identify relevant research published up to January 2023. The search strategy utilized a combination of keywords such as “retinocytoma,” “retinoma,” “RB1 gene mutation,” “ocular tumors,” and “retinal neoplasms.” To ensure comprehensiveness, reference lists of key articles were also reviewed to capture any additional relevant studies. The inclusion criteria were carefully defined to focus on studies providing substantial insights into retinocytoma. Articles included peer-reviewed publications and case studies detailing the clinical features, diagnostic methodologies, pathogenesis, prognosis, or management strategies of retinocytoma. In addition to research discussing imaging techniques, histopathological findings, or genetic analysis relevant to retinocytoma. Articles that exclusively focused on retinoblastoma without discussing retinocytoma, or published in languages other than English, were excluded.

The findings were synthesized using a thematic analysis framework. Publications were grouped into common themes, facilitating the development of a coherent narrative. This approach allowed the review to trace advancements in understanding retinocytoma, including its genetic basis, clinical presentation, and management. The narrative further highlighted the significance of innovations in imaging techniques and genetic testing in diagnosing and monitoring this rare condition.

A narrative review was chosen over a systematic review due to the sparse and heterogeneous nature of the available literature on retinocytoma. This approach enabled a broad exploration of current knowledge, identification of research gaps, and the presentation of a synthesized account that provides a foundation for future studies.

## Epidemiology

Retinocytoma is considerably less common than retinoblastoma. The exact prevalence is difficult to ascertain due to its rarity and often asymptomatic nature. Many cases are incidentally discovered during routine eye examinations or screenings in families with a history of retinoblastoma [9]. However, according to available

reports, retinocytoma accounts for 1.8–3.0% in USA [10, 11], 3.2% in Greece [12], and up to 11% in Switzerland of retinoblastoma patients and their families [13]. This wide variability in reported incidence between studies (1.8–11%) could be explained by geographic variation and diagnostic differences. A study by Singh et al. suggested that differences in access to healthcare and genetic predisposition among populations may explain the variation [10]. Variation in defining and diagnosing retinocytoma may also play a role [11]. Furthermore, advancements in imaging technologies, such as optical coherence tomography (OCT) and autofluorescence, have enhanced the identification of subtle lesions that might previously have gone unnoticed, thereby increasing the reported incidence. In histologically examined enucleated eyes, however, the reported incidence varies between 15.6 and 20.4% [14]. There is a slight predominance in males (53–58%), with a clear predilection for whites (82–85%) [10, 11]. Moreover, a family history of retinoblastoma is reported in approximately 13% of retinocytoma cases [15].

## Clinical features including examination

Retinocytoma is typically identified in patients with a known family history of retinoblastoma or through screening of individuals at risk for retinoblastoma [16]. Most patients (82%) are older than five years at the time of presentation [10], and the median age at diagnosis varies between 5 years to 15 years (range, 4–45 years) [10, 11]. The average age range is 23 [13] to 28.7 years [12]. The oldest patient described is an 88-year-old [11]. Many patients (41%) do not have symptoms, and visual acuity is normal in the majority [10]. Most cases are discovered incidentally in parents and relatives of children with retinoblastoma [17, 18]. Retinocytoma can occur in association with retinoblastoma in the same or the fellow eye [13]. It can also be discovered when an overlying retinoblastoma is treated or in association with phthisis bulbi, which can only be linked to retinoblastoma if other evidence, including genetic testing, is present [13, 19, 20]. When symptomatic, common symptoms include blurred vision (24%) and strabismus (18%) [10]. Cases presenting with exotropia, esotropia, and floaters secondary to vitreous seeding have been rarely reported [21–24]. A single case of swelling cataract and phacomorphic glaucoma in a patient with retinocytoma is described [25]. Leukocoria, a frequent presentation in retinoblastoma, is seen in younger patients [11]. Retinocytoma is unresponsive to chemotherapy, a feature that should raise suspicion of the diagnosis [26, 27]. It also does not show evidence of growth over time [26, 27].

Retinocytoma is most commonly unilateral, but 13% of cases can be bilateral [10, 13]. It is rare to have trilateral disease or a second malignancy [13, 28, 29]. The tumors

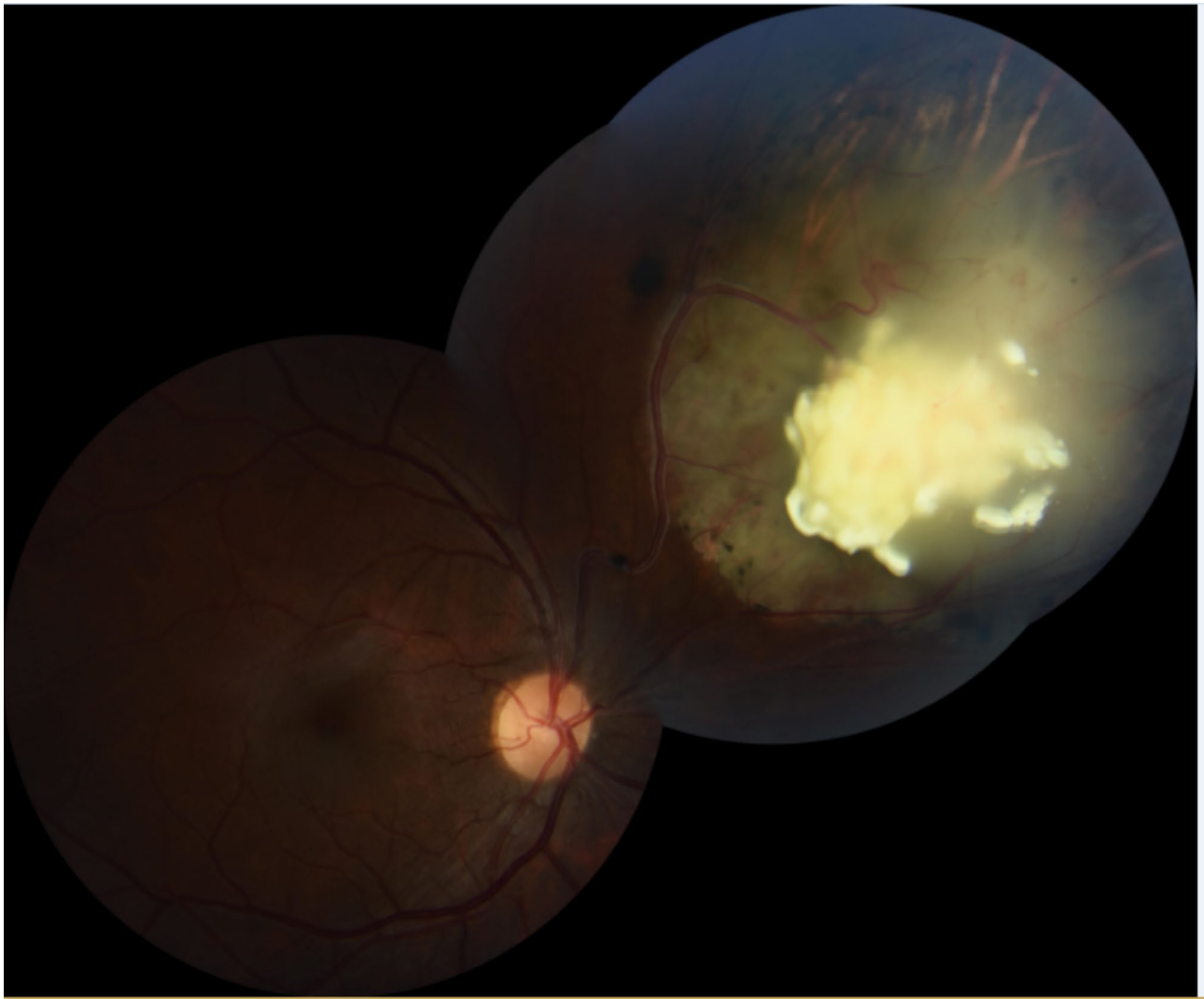
are usually small in size, with a median basal dimension of 6.0–6.25 mm (range, 0.3–15.0 mm) and a median thickness of 1.75–2.3 mm (range, 0.05–5.0 mm) [10, 11].

Under indirect ophthalmoscopy, retinocytoma exhibits features resembling those of a partially treated retinoblastoma in an untreated eye. There are four clinical features of retinocytoma. These include the presence of a translucent retinal mass (88% of cases), intralesional calcification (63%), retinal pigment epithelial changes/disturbance/clumping (54%), and chorioretinal atrophy (54%) with or without staphyloma [10]. Any combination of two or three of the aforementioned is present in 83% and 46% of cases, respectively [10]. Occasional cases with calcified vitreous deposits/seeding are also reported [23, 30–32]. An intratumoral cystic pattern is rarely described (5.8%) [10]. Most cases are extra-macular [10]. Exophytic and endophytic pre-regression growth patterns have also

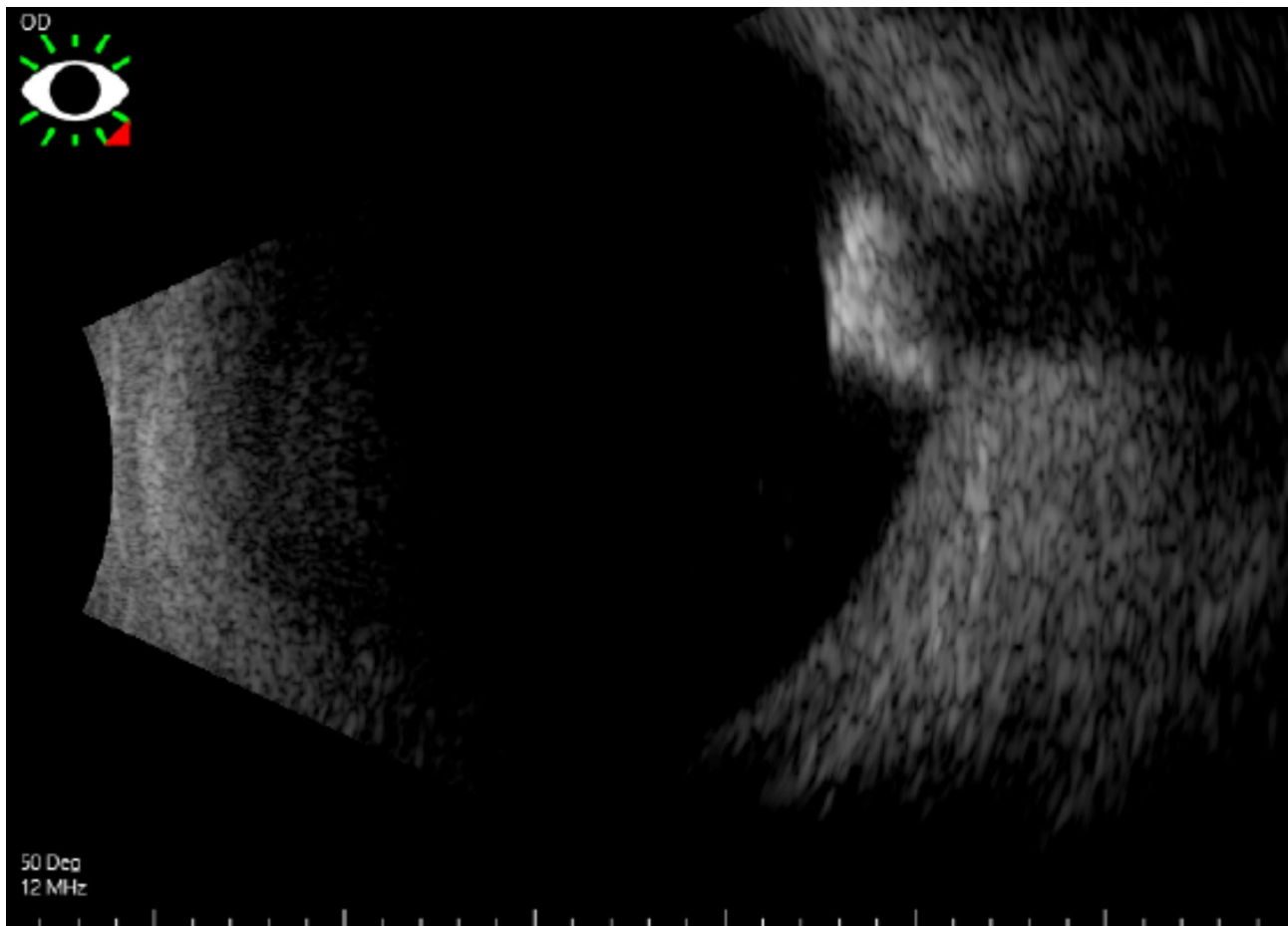
been described [12]. Figure 1 demonstrates an example of a color fundus photograph for an incidentally diagnosed retinocytoma.

Ultrasonography facilitates tumor size assessment and delineates calcified lesions, characterized by acoustic solidity and shadowing resulting from intralesional calcification. A-scan ultrasonography shows a sharp anterior border, high internal reflectivity, and attenuation of orbital echoes posterior to the tumor [23, 33]. Figure 2 demonstrates an example of B-scan ultrasonography of the right eye with retinocytoma.

In optical coherence tomography (OCT), a hyper-reflective layer analogous to the preserved nerve fiber layer overlying the lesion, as well as symmetrical hyporeflective spaces in the underlying choroid with sudden disruption of the choroid in areas of choroidal atrophy, are described [34]. Vitreous seeding in retinocytoma can



**Fig. 1** Color fundus photograph of the right eye in a 30-year-old female, who was incidentally found to have a superonasal retinocytoma. The calcified tumor is endophytic, with surrounding patch of chorio-retinal atrophy



**Fig. 2** B-scan ultrasonography of the right eye showing a retinocytoma mass with calcifications, exhibiting high internal reflectivity and associated shadowing

also be detected using OCT [31]. However, OCT alone cannot differentiate between retinoblastoma and retinocytoma [35].

At early stages, retinoblastoma presents as small, intra retinal tumors with early calcifications and feeder vessels, while retinocytoma appears as a stable, translucent mass with limited vascularization [36]. At advanced stages, retinoblastoma demonstrates rapid growth, extensive calcifications, subretinal fluid, associated with sub-retinal and vitreous seeding, whereas retinocytoma remains non-progressive, with well-demarcated calcifications and no invasive features [37].

In recent years, swept-source OCT (SS-OCT) and OCT angiography (OCTA) have emerged as valuable tools in supporting the diagnosis of retinocytoma [22]. SS-OCT in retinocytoma often reveals significant thinning of the posterior ocular coat due to atrophic retinochoroidal layers, while OCTA, leveraging its three-dimensional imaging capabilities, typically demonstrates a well-defined superficial retinal plexus but may encounter limitations in assessing the deeper retinal and choroidal plexuses due to distortion and projection artifacts

caused by calcifications and scar tissue [22]. Fundus autofluorescence can show features similar to pre-treated RB [34, 38]. In retinocytoma, it shows a mixed pattern of hypoautofluorescence, isoautofluorescence, and hyperautofluorescence, with hypoautofluorescence in peripheral areas due to retinal pigment epithelium atrophy, isoautofluorescence and hyperautofluorescence in the central lesion, and hyperautofluorescence near areas of chorioretinal atrophy or exposed sclera from unmasking of scleral autofluorescence, resembling features seen in pre-treated retinoblastoma [34, 38]. It also shows features of tumor regression or arrest, including calcification, retinal pigment epithelium defects, lesion translucence, and chorioretinal atrophy [34, 38]. OCTA and multi-color imaging scans are also crucial in establishing the diagnosis and in identifying malignant transformation [39]. Multicolor imaging in retinocytoma shows central areas of hyperreflectivity caused by calcification, with bulging and calcification at different levels in the retina [39]. It also highlights chorioretinal atrophy and exposed sclera, especially on infrared reflectance channels. OCTA shows distorted retinal vessels over calcified areas but

has difficulty assessing deeper plexuses due to projection artifacts. It can also detect malignant changes by identifying new blood vessels and connections between retinal and tumor vessels. The choroidal vessels are visible in areas with retinal pigment epithelial atrophy [39]. Fluorescein angiography reveals tortuous, sclerosed feeder vessels and highlights specific features of retinocytoma, including limited intrinsic vascularity, a feeder artery of normal caliber, surrounding window defects, and minimal or absent dye leakage into the vitreous cavity [40]. In comparison, fluorescein angiography in retinoblastoma typically shows rapid filling of a feeder artery, a complex intratumoral vascular network, progressive hyperfluorescence due to intense tumor staining, and dye leakage into the vitreous cavity [41].

Magnetic resonance imaging (MRI) can also be helpful depending on T1 and T2 image characteristics, but generally, retinocytoma may be indistinguishable from retinoblastoma which appears as solid intraocular masses with intermediate to high signal intensity on T1-weighted images and low to intermediate signal intensity on T2-weighted images [42, 43].

The primary differential diagnosis for retinocytoma is retinoblastoma, mainly since both conditions can occur in the same patient or family [44]. Features that help distinguish retinocytoma from retinoblastoma include the minimal vascular proliferation, and the absence of symptoms [3]. Retinoblastoma generally does not show chorioretinal atrophy but does present with retinal pigment epithelium (RPE) alterations. Furthermore, prominent feeder vessels are commonly seen in retinoblastoma, although exudation is notably absent [45].

Other important considerations in the differential diagnosis include astrocytic hamartoma, which is commonly associated with tuberous sclerosis and typically presents as yellow, spherical lesions that may exhibit calcifications. Unlike retinocytoma, astrocytic hamartomas lack chorioretinal atrophy and retinal pigment epithelial (RPE) changes. However, not all astrocytic hamartomas are calcified, and while they can grow, their progression is typically slow and non-aggressive, distinguishing them from malignant retinal tumors such as retinoblastoma. Additionally, astrocytic hamartomas do not have prominent feeder vessels, though exudation may occasionally be present. Importantly, unlike astrocytic hamartomas, retinocytomas have no recognized associations with tuberous sclerosis or neurofibromatosis [46].

Other conditions that may mimic retinocytoma include congenital hypertrophy of the retinal pigment epithelium (CHRPE), and retinal hemangioblastoma [45, 47–49]. Both retinocytoma and CHRPE can present as well-defined, flat, pigmented lesions on fundus examination [50]. Retinocytoma may show areas of calcification and chorioretinal atrophy, which can sometimes mimic the

uniform pigmentation and surrounding halo effect seen in CHRPE [50]. However, CHRPE is typically non-calcified, stable over time, and lacks intrinsic vascularity or growth potential, helping to distinguish it from retinocytoma, which may display subtle vascular changes or calcifications on imaging [50].

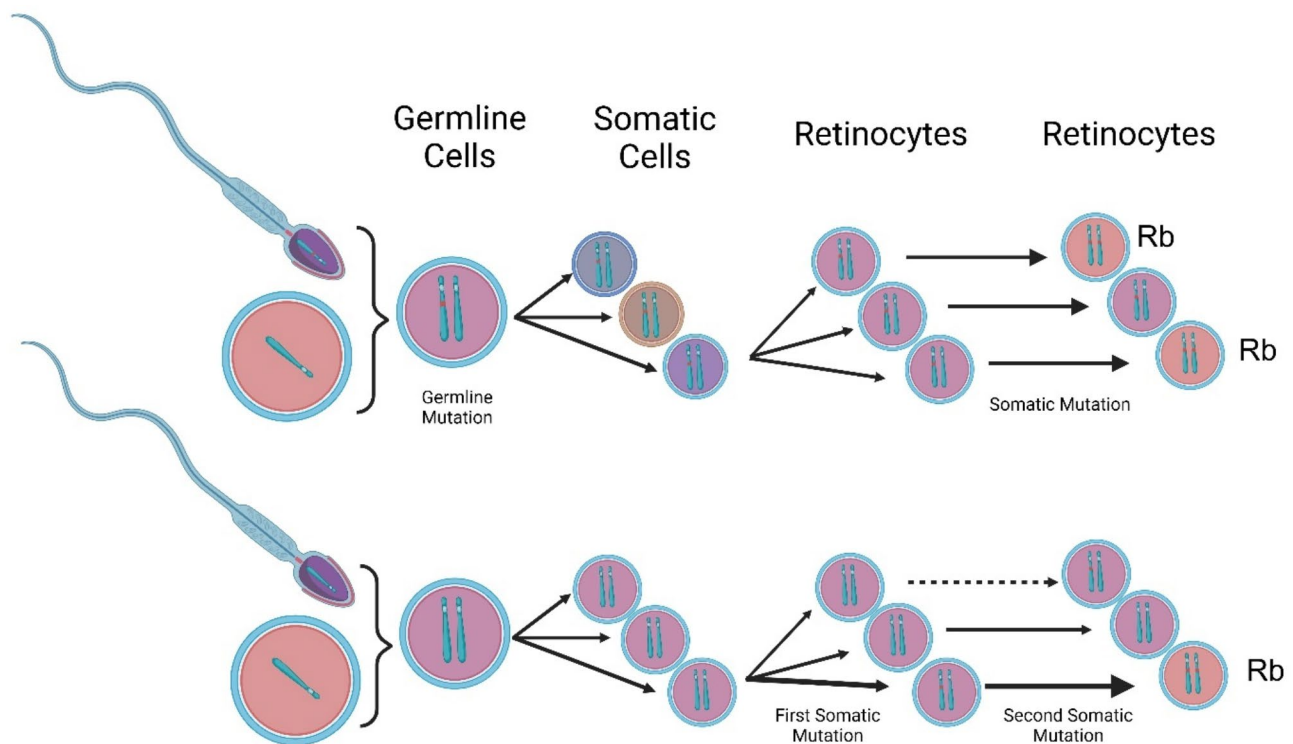
### Pathogenesis and etiology

The pathogenesis of retinocytoma is predominantly linked to mutations in the *RB1* gene, a tumor suppressor gene located on chromosome 13q14 [51]. The *RB1* gene plays a critical role in regulating the cell cycle by encoding the retinoblastoma protein (pRB), which controls the progression from the G1 to the S phase [52]. In its active form, pRB binds to and inhibits E2F transcription factors, thereby preventing uncontrolled cell proliferation [52].

Retinoblastoma and retinocytoma share the same genetic changes, although retinocytoma shows low penetrance to the *RB* gene [53]. Knudson's two-hit hypothesis states that both alleles of the *RB1* gene must be mutated to convert normal retinal cells into neoplastic retinoblastoma cells. Figure 3 illustrates the mechanism of *RB1* mutation based on Knudson's two-hit hypothesis. The presence of *RB1* mutations impairs the normal regulatory function of pRB, resulting in deregulated cell cycle progression and potential tumor formation [54]. However, unlike retinoblastoma, retinocytoma might stop at the M2 level and might not transform into retinoblastoma [55]. It could also arise if the second hit occurs at a later stage of cell maturation, when the precursor cell has limited mitotic capability and is unable to sequentially accumulate additional mutations [56, 57].

The inactivation of the *RB1* gene leads to disruption of several vital cellular pathways; Firstly, the loss of functional pRB allows E2F transcription factors to remain active, promoting the expression of genes required for DNA synthesis and cell cycle progression. This uncontrolled cell division is a hallmark of tumorigenesis [58]. It is possible that proteins encoded by *RB1* gene variants retain part of the wild-type protein function. Therefore, in the presence of a partially functional RB1 protein, the precursor cells form a retinocytoma instead of a retinoblastoma. Also, the *RB1* gene plays a role in apoptosis, the programmed cell death mechanism eliminates damaged or abnormal cells [59]. In retinocytoma, impaired pRB function can disrupt apoptotic pathways, allowing the survival and accumulation of aberrant cells [60]. This is reflected in the tumor's histopathological appearance, where the retinal layers are relatively preserved, and the cells exhibit less aggressive behavior [61]. Recent evidence suggests that genetic instability and aneuploidy are key factors distinguishing retinoblastoma from retinocytoma suggesting that retinocytoma is genetically a precursor of retinoblastoma [62–64]. A study by Dimaras et





**Fig. 3** Knudson's two-hit hypothesis. If the first mutation is present in the germline, all somatic cells will carry one mutant allele. This increases the probability of a second mutation occurring during the somatic stage, which can affect multiple retinocytes in both eyes and other somatic precursor cells. If both mutations occur during the somatic stage, it leads to the development of unilateral unifocal retinoblastoma. Figure generated using BioRender

al. observed that retinomas, with their high expression of senescence-associated proteins like p16INK4a and p130, exhibit low-level genomic instability [62]. They observed that this instability, which is initially kept in check by cellular senescence, can escalate, leading to the malignant transformation to retinoblastoma. Moreover, based on molecular analysis, they suggested a clonal relationship between retinocytoma, and retinoblastoma based on the *RB1* gene mutation, underscoring the role of retinoma as a precursor lesion that, upon overcoming the senescence barrier, can evolve into highly proliferative and malignant retinoblastoma.

Also, epigenetic modification, through *RB1* promoter hypermethylation, might result in phenotypically variable tumor expression resulting in retinocytoma [65]. Despite the common genetic links between retinocytoma and retinoblastoma, the reasons why some individuals develop retinocytoma rather than retinoblastoma remain unclear [66]. Dryja et al. proposed another hypothesis suggesting that retinocytoma may result from low penetrance of retinoblastoma [67].

### Macroscopic and histopathological features

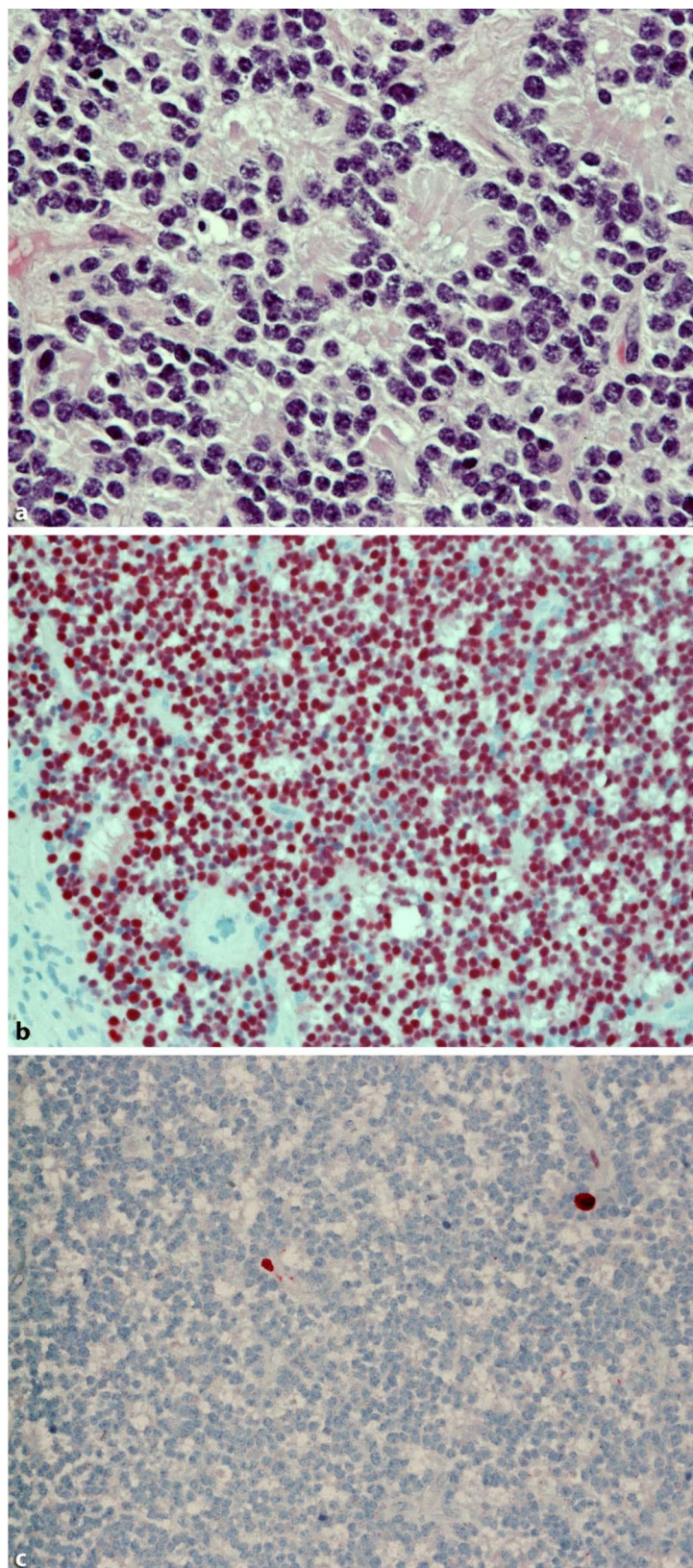
Macroscopically, retinocytoma appears as a translucent, slightly elevated retinal mass with well-defined borders [68]. The lesion often exhibits a lobulated or map-like

pattern, contributing to its similar appearance to retinoblastoma [69]. One of the hallmark macroscopic features is the presence of calcific foci, which appear as chalky-white patches within the tumor [37].

Characteristically, retinocytoma displays benign histopathologic features. This includes bland round to oval nuclei with evenly dispersed chromatin, eosinophilic, occasionally clear cytoplasm with distinct cell borders, scattered fleurettes as evidence of prominent photoreceptor differentiation, a fibrillar eosinophilic stroma composed of elongated cytoplasmic processes, calcific foci within viable tumor, with no evidence of rosettes, mitoses, nuclear atypia, pleomorphism, or necrosis [62, 70, 71]. There is a well-vascularized ground substance with calcific foci, as well as RPE hyperplasia [71]. Multinucleate tumor giant cells have been occasionally described [72]. Figure 4 demonstrates the histopathological features of retinocytomas.

Usually, there is no evidence of retinal detachment [4]. The architecture of the normal retina is, however, obliterated. There is no evidence of invasion of the choroid, the optic nerve, or the vitreous [73].

Furthermore, evidence of retinocytoma can be seen in eyes enucleated for retinoblastoma [74]. Around 20% of retinoblastoma cases show evidence of photoreceptor differentiation, commonly localized to the base of the



**Fig. 4** Retinocytoma (Retinoma): Photoreceptor differentiation with numerous fleurettes (**a**, HE stain, original magnification 40x). Nuclear positivity for CRX (**b**, CRX, original magnification 20x). Negativity for Ki67 with a few reactive control cells (**c**, Ki67, original magnification 20x). Figure obtained with permission from Metz et al. (2017) [93]

tumor, supporting the notion that retinocytoma might be a precursor lesion to retinoblastoma [74].

Immunohistochemically, retinocytoma cells are positive for anti-RB antibodies, retinal S antigen, S-100 protein, and glial fibrillary acidic protein (GFAP) [70, 75, 76]. P16 (INK4a) immunostains are negative in areas of retinocytoma exhibiting fleurettes differentiation [77]. By electron microscopy, photoreceptor differentiation in the cytoplasm of tumor cells is depicted [4].

Retinoblastoma is the most important pathological differential diagnosis. In contrast to retinocytoma, it shows the proliferation of malignant cells with pleomorphism, mitosis, and necrosis [62, 70, 71]. Homer-Wright and Flexner-Wintersteiner rosettes are frequently seen [73]. P16 immunostain tends to be positive in retinoblastoma, especially in poorly differentiated tumors [77].

### Prognosis and prediction of retinocytoma

Retinocytoma can remain stable with no evidence of progression over an extended period [78]. However, risk of malignant transformation to retinoblastoma is reported, and ranges between 4% [10] to 12% [12], a tendency which appears to increase over time and reaches up to 15.3% by 10–20 years [11]. It appears that the only factor predictive of transformation is increasing thickness [36]. This tendency might be a plausible explanation for cases of retinoblastoma developing in adults [79].

In a comprehensive study spanning 20 years, Shields et al. explored the clinical features and long-term outcomes of retinocytoma in 62 patients [11]. The study included 78 tumors and reported that 3% of the 2,021 retinoblastoma patients had retinocytoma, with a median age of 5 years at presentation. Notably, malignant transformation of retinocytoma into retinoblastoma was documented in 2.7% of cases by two years, 9.2% by five years, and 15.3% by 10–20 years. Multivariate analysis identified increasing tumor thickness as the only predictor of transformation into retinoblastoma. Tumors that transformed had a mean thickness of 4.3 mm, compared to 2.4 mm in those that did not ( $p=0.003$ ). Each 1 mm increase in thickness corresponded to a hazard ratio of 2.83 for transformation. The average time to transformation was 9.8 years (117 months), with a range from 1.6 to 23.6 years.

Therefore, patients with the diagnosis of retinocytoma should be offered a lifelong close observation, and genetic counseling [80]. In addition, genetic counseling and frequent observation should be offered to their offspring. Genetic testing from blood [59] or saliva sample [33] can be used for the detection of germline *RB1* gene mutation to establish the diagnosis, which appears to be more common in young patients [11]. Two patterns of reactivation have been described in the literature: benign cystic growth or malignant transformation [12], which can be rapid with vitreous seeding [10, 70]. Furthermore,

ophthalmic examinations of parents and siblings of individuals with retinoblastoma should always be conducted to rule out the presence of retinoblastoma or asymptomatic retinocytoma [17, 81]. Occasional cases of retinocytoma might regress spontaneously [82]. However, aggressive endo- and exophytic growth prior to spontaneous regression have been reported [12].

### Management of retinocytoma

The management of retinocytoma focuses on regular monitoring, early detection of potential malignant transformation, and intervention when necessary to preserve vision and prevent complications [83]. Due to its benign nature, the primary approach involves vigilant observation and genetic counseling [11, 83].

Initial management begins with a comprehensive ophthalmic examination, including fundoscopy to identify the characteristic features of retinocytoma, such as a translucent retinal mass, calcific foci, and RPE changes [68, 84]. Detailed medical and family histories are also essential. Imaging studies, including OCT, B-scan ultrasonography, and brain and orbit MRI, help assess the tumor's size, location, and structural characteristics, documenting any signs of chorioretinal atrophy or calcification [23, 33, 42, 85, 86]. Genetic testing for *RB1* gene mutations using blood or saliva samples is conducted, employing methods such as Sanger sequencing to detect specific mutations [33, 59, 87].

Genetic counseling for patients and their families is an integral part of management. It explains the nature of retinocytoma, the risk of malignant transformation, and the importance of regular monitoring [33, 59, 87]. Counseling also covers the hereditary aspects of *RB1* mutations and their implications for family members. Surveillance of family members, including ophthalmic examinations of parents and siblings, is necessary to detect any signs of retinocytoma or retinoblastoma. Genetic testing for family members can identify carriers of *RB1* mutations [33, 59, 87].

For stable retinocytomas with no signs of progression, continued observation with regular follow-up is the primary management strategy [10, 11]. One study suggests an observation protocol that involves close monitoring initially on a monthly basis, transitioning to every two months once stability is confirmed. Over time, the interval is gradually extended to every four months, and subsequently every six months. Long-term, continued observation every six months lifelong to ensure ongoing tumor stability is recommended [11]. Advanced imaging techniques, such as OCTA and SS-OCT, are invaluable in monitoring retinocytoma progression. These modalities provide detailed visualization of tumor vascularity, thickness, and adjacent retinal structures, which can aid



in identifying subtle changes suggestive of transformation [22].

Laser therapy or cryotherapy may be considered in specific cases, such as for tumors impacting vision, those demonstrating early signs of malignant transformation, or if complications such as vitreous hemorrhage occur, with the choice of therapy tailored to the individual clinical scenario and patient-specific factors [36, 88, 89]. In cases of confirmed malignant transformation to retinoblastoma, the treatment should be customized based on site of the tumor, extension, and thickness [36]. Treatment options include combination of systemic chemotherapy with focal consolidation therapy, intra-arterial chemotherapy, (which is an effective treatment option, delivering chemotherapy directly to the tumor and minimizing systemic side effects), Transpupillary thermotherapy laser, and radioactive plaque brachytherapy [90, 91].

A study by Kiratli et al. [92] reported two cases of retinocytoma, which were initially managed by observation to monitor tumor progression. In both cases, intra-arterial chemotherapy with 7.5 mg melphalan was administered, resulting in the rapid regression of the new developed growths while the original tumors remained unchanged. This approach successfully stabilized both patients' condition and visual acuity over the follow-up periods. Moreover, Yaman et al. reported a case involving a 12-year-old girl who underwent a single session of transpupillary thermotherapy laser to prevent malignant transformation [16]. During a 3.5-year follow-up period, the lesion's dimensions and the patient's visual acuity remained stable without additional treatment.

Occasional cases of retinocytoma may also result in vitreous hemorrhage necessitating vitrectomy [89], as long as there is no active intraocular retinoblastoma. In a case reported by Grassi et al. [89], a 35-year-old man with bilateral retinocytoma experienced persistent vitreous hemorrhage in his left eye for six months caused by an incomplete posterior vitreous detachment and was managed by a 23G pars plana vitrectomy, combined with endolaser and endodiathermy to treat the bleeding retinal vessel. This surgical procedure successfully cleared the hemorrhage and restored his visual acuity to 20/15 within six months.

## Conclusion

Retinocytoma, a benign retinal tumor, is typically associated with a favorable prognosis; however, its potential to transform into retinoblastoma underscores the need for lifelong surveillance. Early detection and routine follow-up are critical to preserving optimal visual outcomes and promptly identifying signs of malignant transformation, which, although uncommon, may become more likely over time.

Genetic counseling and testing play a role in managing retinocytoma, especially for individuals with a family history of retinoblastoma. Advances in diagnostic imaging and genetic testing have improved the ability to detect and monitor the tumor effectively.

Management primarily involves vigilant observation, with intervention strategies such as laser therapy, cryotherapy, systemic chemotherapy, and intra-ocular arterial chemotherapy reserved for cases showing signs of malignant transformation. This comprehensive approach ensures early intervention, maintaining vision, and mitigating the risks of progression to retinoblastoma.

## Abbreviations

RB1	Retinoblastoma 1 (gene)
pRB	Retinoblastoma protein
OCT	Optical Coherence Tomography
SS-OCT	Swept-Source Optical Coherence Tomography
OCTA	Optical Coherence Tomography Angiography
MRI	Magnetic Resonance Imaging
ICD-O	International Classification of Diseases for Oncology
ICD-11	International Classification of Diseases 11th Revision
CHRPE	Congenital Hypertrophy of the Retinal Pigment Epithelium
RPE	Retinal Pigment Epithelium
GFAP	Glial Fibrillary Acidic Protein
HE	Hematoxylin and Eosin (stain)
CRX	Cone-Rod Homeobox (gene)
Ki67	A cellular marker for proliferation

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## Author contributions

M.A.: Conceptualization, Supervision, Writing—original draft preparation, Review and editing. S.A.: Data curation, Methodology, Writing—review and editing. H.S.: Investigation, Writing—review and editing. M.M.: Validation, Writing—review and editing. Y.Y.: Resources, Supervision, Writing—review and editing. All authors have read and approved the final manuscript.

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## Declarations

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Not applicable. This review article did not involve human participants or animal subjects requiring ethical approval.

### Consent for publication

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### Competing interests

The authors declare no competing interests.

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