Diagnostic Challenges of Uveitis-Mimicking Adult-Onset Retinoblastoma: A Rare Case Report

Ahmet Özdemir[1], *Volkan Yeter*[1], *Yüksel Süllü*[1], *Bilge Can Meydan*[2]

ABSTRACT

Diffuse infiltrating retinoblastoma (DIRB) is a rare, aggressive retinoblastoma subtype that mimics uveitis and complicates diagnosis especially in adults often causing misdiagnosis, unnecessary therapy, and delay in definitive care.

We report a 19-year-old male presenting with decreased vision and photopsia in the right eye. He was initially diagnosed with pars planitis and received topical/subtenon steroids, followed by vitrectomy with cataract extraction; later, trabeculectomy was required for secondary glaucoma. Progressive visual decline and a suspicious anterior-segment lesion prompted enucleation. Histopathology confirmed DIRB with extensive anterior-segment infiltration and no extraocular extension.

This case underscores the need to consider retinoblastoma in refractory intraocular inflammation in young adults and to escalate evaluation with multimodal imaging and, when available, liquid biopsy (aqueous/vitreous). Multidisciplinary care is essential.

Keywords: Diffuse infiltrating retinoblastoma, pseudo-uveitis, secondary glaucoma, adult-onset retinoblastoma, vitreous sampling

INTRODUCTION

Retinoblastoma is the most common intraocular malignancy in childhood, with an estimated 5,000 new cases worldwide annually and an incidence of 1 in 15,000 live births. [1]Retinoblastoma typically presents with leukocoria and strabismus; however, it can mimic various ocular conditions, including uveitis, endophthalmitis, and orbital cellulitis-like presentations. [2] Among its subtypes, DIRB is particularly difficult to diagnose due to its unusual clinical presentation. This rare variant accounts for only 1–2% of all retinoblastoma cases and may present with ocular inflammation in 1–3% of patients. [3]

Unlike classic retinoblastoma, DIRB lacks a discrete mass lesion and is instead characterized by plaque-like retinal thickening. Anterior segment involvement often leads to pseudoinflammatory symptoms, which can result in misdiagnosis as uveitis or iritis. [4] Secondary glaucoma is reported in 17–22.8% of retinoblastoma cases, usually due to iris neovascularization. [5] However, in DIRB, secondary glaucoma may result from neoplastic seeding of the trabecular meshwork, further complicating both diagnosis and management.[6]

Adult-onset retinoblastoma is extremely rare, with only isolated case series reported in the literature. Kaliki et al.[3] described eight newly diagnosed adult patients, while Zhou et al.[5] reported six cases with variable genetic mutations, underscoring both the rarity and heterogeneity of this entity. In diffuse infiltrating variants, the absence of a discrete

1 Ondokuz Mayıs University, Ophthalmology, Samsun, Türkiye
2 Ondokuz Mayıs University, Pathology, Samsun, Türkiye

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Correspondence author:
Ahmet Özdemir
Email: dr_ahmet_ozdemir@hotmail.com

calcified mass, together with predominant anterior segment involvement such as keratic precipitates, iris neovascularization, and pseudoinflammatory deposits, frequently leads to misdiagnosis as uveitis or iridocyclitis. Such misinterpretations can result in prolonged corticosteroid use, multiple intraocular procedures, and delayed oncologic referral, thereby worsening visual and systemic prognosis. Recognizing these masquerade features is therefore critical in clinical practice, especially when inflammation persists despite appropriate therapy.[4]

Imaging plays a crucial role in evaluating retinoblastoma, not for definitive pathological diagnosis but to assess tumor extent and involvement. DIRBs exhibit extensive retinal, iris, and ciliary body infiltration, making radiological differentiation challenging. [7] Unlike other retinoblastoma subtypes, this variant rarely demonstrates calcification, reducing the reliability of ultrasonography and computed tomography but not rendering them entirely ineffective. [8] Magnetic resonance imaging (MRI) may reveal retinal detachment without a discrete mass, a distinguishing feature of this subtype.

Although localized retinoblastomas have a favorable prognosis, with 90–95% five-year survival following enucleation or focal therapy [2], delayed diagnosis often leads to a more advanced disease stage. Extraocular extension significantly increases the risk of recurrence and metastasis, particularly if the tumor involves the conjunctiva, episclera, or orbital soft tissues. [9]

In this case report, we present a patient with DIRB initially misdiagnosed as intermediate uveitis. This case underscores the diagnostic challenges of this rare presentation and highlights the importance of recognizing atypical ocular inflammation as a potential manifestation of intraocular malignancy.

CASE REPORT

A 19-year-old male with no significant medical or family history presented to the ophthalmology department with complaints of decreased vision and photopsia in the right eye. Best-corrected visual acuity (BCVA) was 2/20 in the right eye and 20/20 in the left eye, with normal intraocular pressure (IOP) bilaterally. Slit-lamp examination revealed cataracts and minimal posterior synechiae. Dilated fundus examination showed clumps of vitreous seeds in the anterior vitreous, with the optic disc and macula not visible. B-scan ultrasonography was performed at presentation, which revealed diffuse vitreous seeds without any discrete intraocular mass or calcification. Based on these findings, a presumptive diagnosis of pars planitis sequelae was made, and treatment with subtenon triamcinolone acetonide and topical corticosteroids was initiated. Due to poor response to therapy, the patient underwent pars plana vitrectomy (PPV) with cataract extraction.

Postoperatively, BCVA improved to 6/20 in the right eye. However, at the three-month follow-up, IOP increased to 42 mmHg (compared to 12 mmHg in the left eye). Slit-lamp examination revealed fine keratic precipitates on the corneal endothelium, mild anterior chamber reaction (+/- cells), and numerous white deposits on the intraocular lens (IOL) surface. Fundus examination remained challenging due to anterior segment debris.

Given the elevated IOP, topical and systemic antiglaucoma therapy was initiated, including dorzolamide/timolol, brimonidine, and oral acetazolamide. However, IOP remained uncontrolled, necessitating trabeculectomy for secondary glaucoma secondary to uveitis. Following surgery, IOP normalized, but ultrasonographic evaluation remained inconclusive due to media opacities.

Over the next one and a half years, the patient reported progressive vision loss in the right eye. At the last visit, BCVA had declined to 3/20, with an IOP of 8 mmHg. Slit-lamp examination revealed non-granulomatous keratic precipitates, 1+ anterior chamber cells, and persistent white deposits on the IOL surface. Optical coherence tomography (OCT) imaging showed hyperreflective deposits along the retinal nerve fiber layer (RNFL) (Figure 1a-c).

The patient, who had not received systemic immunosuppressive therapy previously, was prescribed topical corticosteroids and subtenon triamcinolone. After one month of treatment with no significant improvement, fundus fluorescein angiography (FFA) was performed (Figure 2a-d). No optic disc leakage or staining was observed, and only mild vascular tortuosity was noted in the superior temporal arcade. The left eye remained unremarkable.

The patient missed follow-up appointments for nine months and returned with profound vision loss in the right eye, reduced to hand movement perception. IOP was measured as

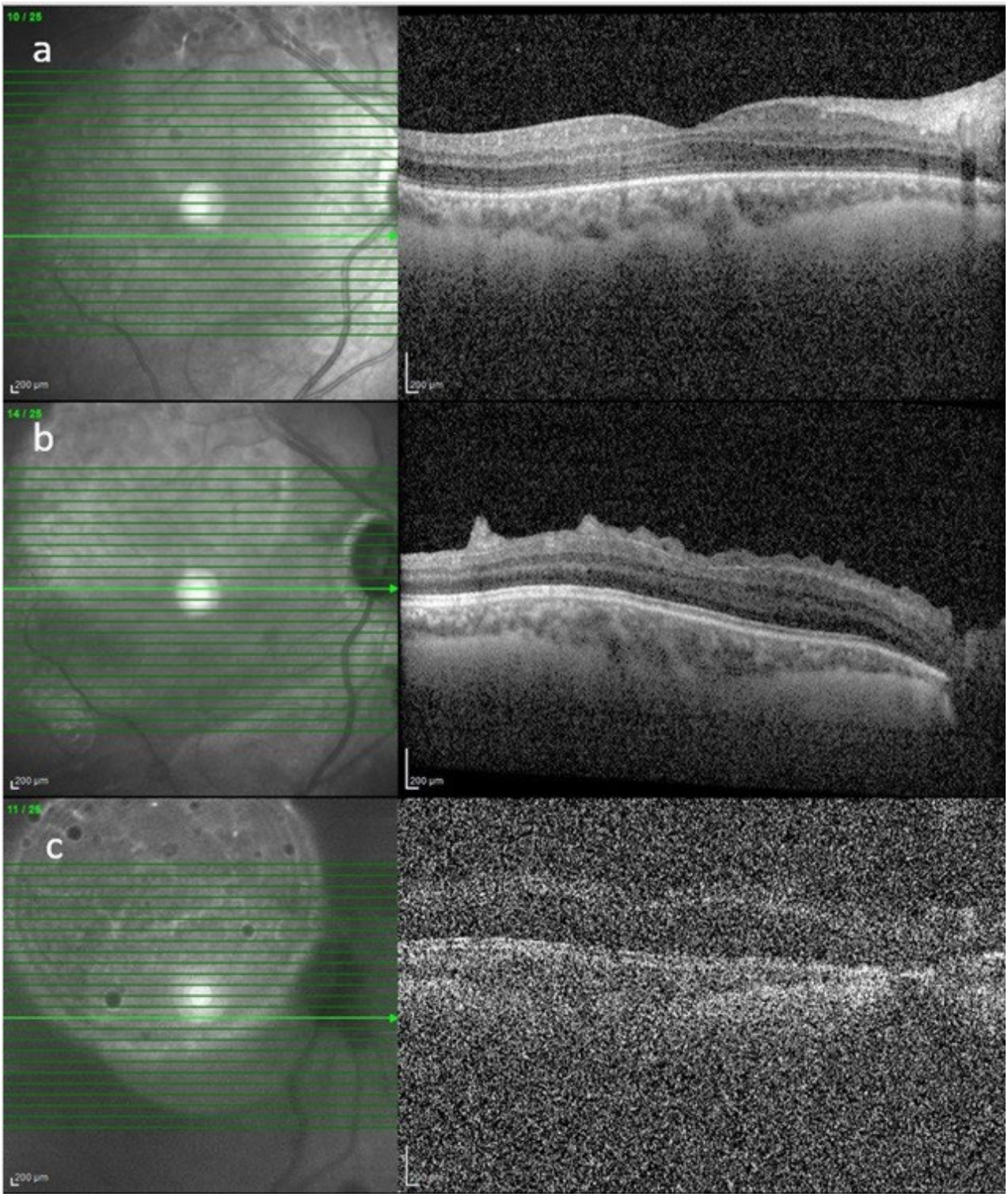

Figure 1. *Optical coherence tomography (OCT) findings of the right eye demonstrate progressive features of diffuse infiltrating retinoblastoma.*

(a) Initial OCT reveals diffuse retinal thickening with hyperreflective deposits localized to the inner retinal layers, indicative of early neoplastic infiltration.

(b) Follow-up OCT shows progressive irregularities in the retinal nerve fiber layer and increased hyperreflective deposits, consistent with advancing neoplastic involvement.

(c) Advanced-stage OCT highlights significant disruption of the retinal architecture, characterized by pronounced inner retinal hyperreflectivity and shadowing effects from dense vitreal deposits. Visualization is notably obscured by anterior segment deposits, resulting in reduced clarity of retinal details, suggestive of advanced disease progression.

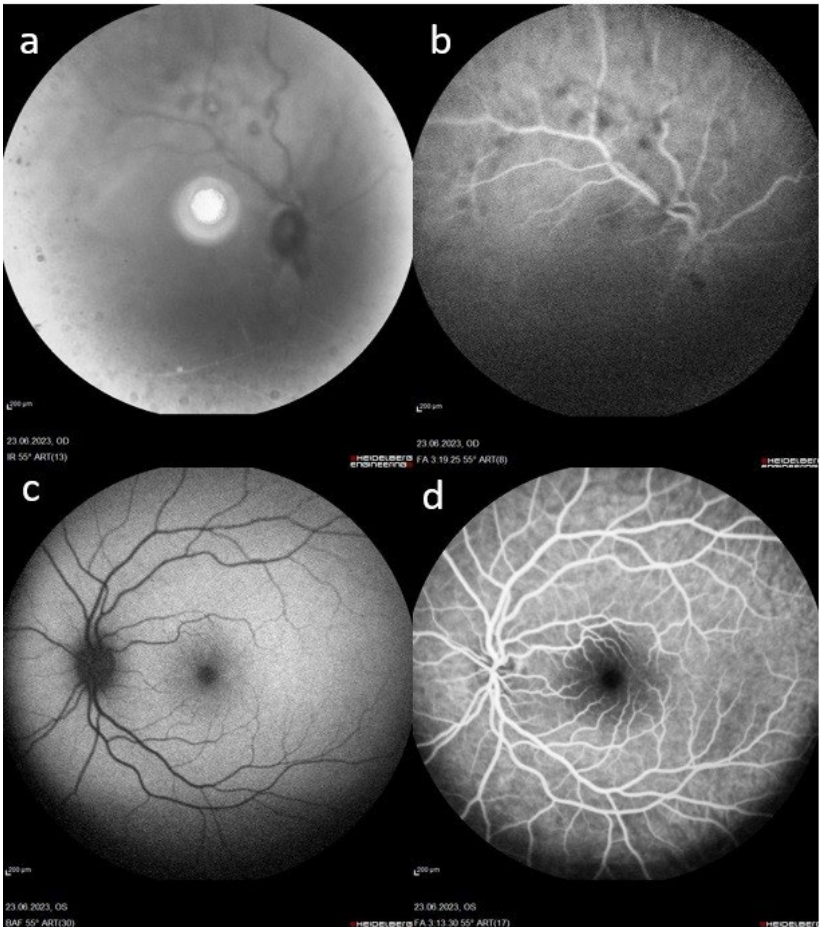

Figure 2. *Fundus imaging and fluorescein angiography (FFA) findings of the right and left eyes.*
(a) Fundus photograph of the right eye showing diffuse vitreous opacities without a discernible mass in the posterior pole. Visualization is partially obscured due to anterior segment deposits, limiting detailed assessment.
(b) FFA of the right eye in the mid-phase demonstrates mild vascular tortuosity without significant leakage or staining of the optic disc or retinal vessels, consistent with the subtle angiographic features of diffuse infiltrating retinoblastoma.
(c) Fundus photograph of the left (contralateral) eye, demonstrating a standard retinal structure for comparison.
(d) FFA of the left eye, captured in the mid-phase, reveals no vascular abnormalities or optic disc pathology, confirming the absence of neoplastic or inflammatory changes in the unaffected eye.

low, and both anterior chamber and fundus examinations were obscured by hyphema. An anterior chamber washout was planned. Intraoperatively, prominent iris neovascularization was observed, leading to an intravitreal bevacizumab injection. A vascularized loop-like structure was noted in the iridocorneal angle at the 5 o'clock position shown in Fig. 3a.

During surgery, a suspicious vascularized lesion adherent to the corneal endothelium was identified, raising concerns for ocular malignancy. Orbital MRI was performed, revealing a lesion adherent to the corneal endothelium without a distinct orbital mass. Despite initial intervention, recurrent hemorrhages complicated the clinical picture (Figure 3b). A second opinion from the ocular oncology team, combined with MRI findings, led to urgent enucleation due to progressive vision loss and strong suspicion of malignancy.

The enucleation specimen confirmed diffuse infiltrating retinoblastoma. Histological analysis revealed tumor cells forming rosettes with hyperchromatic nuclei and narrow cytoplasm (Grade 3) (Figure 3c-f).

Immunohistochemistry revealed diffuse MAP-2 positivity and focal synaptophysin staining, consistent with retinoblastoma. Rare chromogranin positivity was also observed. In contrast, staining for pan-cytokeratin, Sox-10, GATA3, Melan-A, and HMB45 was negative, effectively excluding carcinoma, melanoma, and other small round blue cell tumors. The tumor demonstrated high proliferative activity, with approximately 10 mitoses and a mitotic karyorrhectic index (MKI) of 40.

The tumor occupied <5% of the vitreous cavity and exhibited focal choroidal invasion. Scleral involvement was confined to the inner one-third of the sclera, while the ciliary body, iris, and anterior chamber were extensively infiltrated. The optic nerve head was affected only at the prelaminar level, with no deeper optic nerve invasion. No extraocular extension was observed, and surgical margins were clean.

Following enucleation, systemic metastasis screening was conducted, including; complete blood count (CBC), lumbar puncture, bone marrow biopsy, positron emission tomography (PET) scan, brain MRI. No evidence of metastatic disease was detected. RB1 gene analysis was performed, and systemic chemotherapy was initiated due to the extensive anterior segment involvement (Table 1).

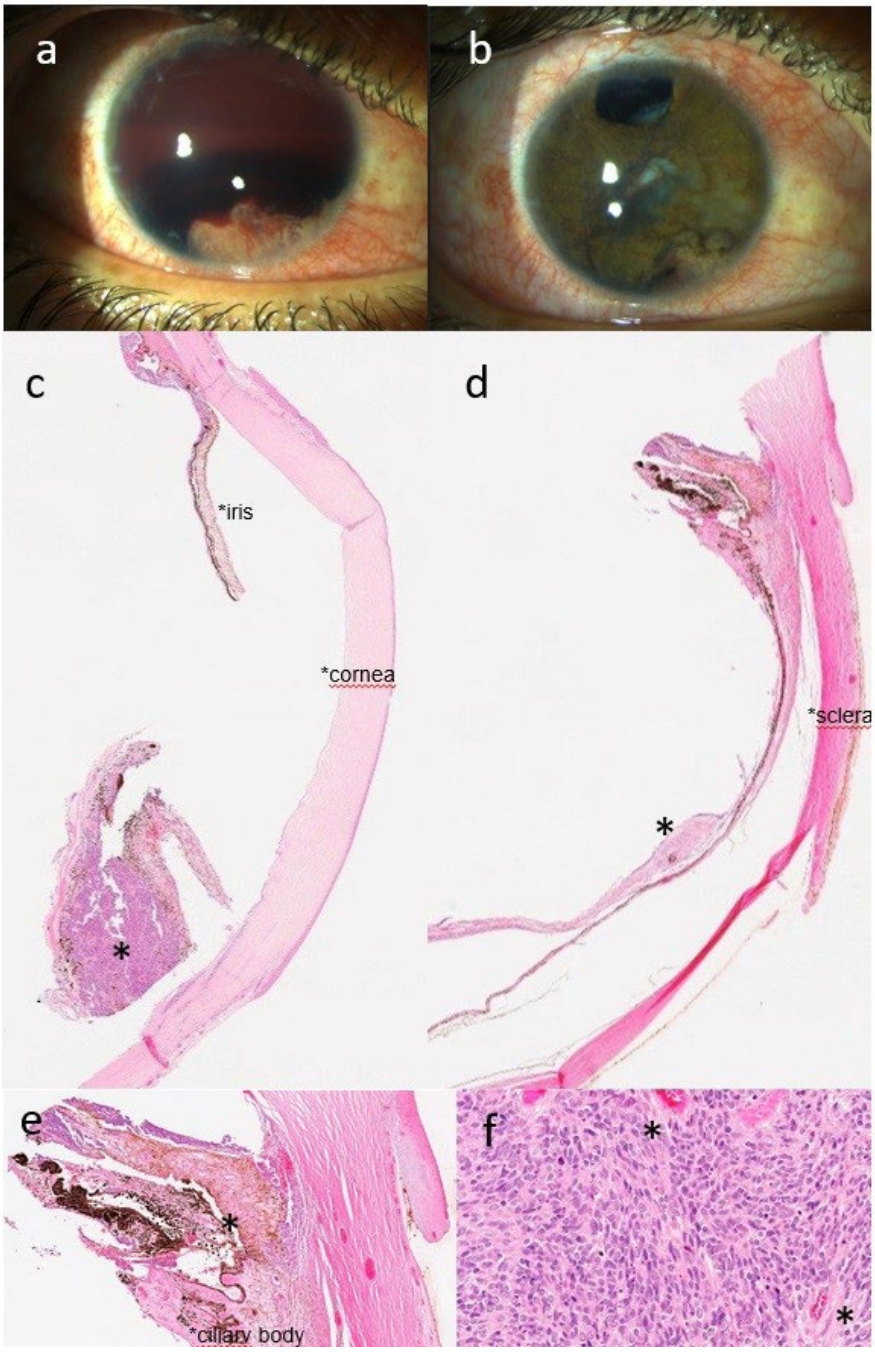

Figure 3. *Anterior segment and histopathological findings of the enucleated eye. (a) Slit-lamp photograph showing extensive tumor deposits on the corneal endothelium and iris vascularization, mimicking inflammatory nodules. (b) Clinical photograph at follow-up demonstrating recurrent anterior chamber hemorrhage and a vascular loop in the iridocorneal angle. (c) Low-power histology (H&E, ×5): Diffuse infiltrative tumor (*) involving the anterior chamber and attached to the corneal endothelium. (d) Intermediate-power histology (H&E, ×10): Prelaminar optic nerve involvement with tumor cells () but a tumor-free resection margin; sclera (*) also shown. (e) High-power histology (H&E, ×50): Tumoral infiltration (*) of the ciliary body and anterior uvea, extending into the corneal endothelium. (f) High-power histology (H&E, ×200): Homer Wright rosettes (*) characteristic of high-grade retinoblastoma.*

Table 1. *Clinical course and key interventions*

Time / Stage	Clinical findings	Intervention / Decision	Notes
Initial presentation	Decreased vision and photopsia (right eye); vitreous seeding; disc and macula not visible	Presumed pars planitis → topical + subtenon corticosteroids	No calcification; no discrete mass detected
Post-PPV + cataract	BCVA 6/20	Observation	Persistent anterior segment deposits
3 months	IOP 42 mmHg; fine keratic precipitates, mild AC reaction, white deposits on IOL	Multiple antiglaucoma medications → uncontrolled	Secondary glaucoma suspected
3–4 months		Trabeculectomy	IOP normalized
6–18 months	Progressive visual loss; OCT: hyperreflective foci along RNFL	Topical corticosteroids + subtenon triamcinolone	No systemic immunosuppression; insufficient response
~18 months	FFA: no disc leakage; mild vascular tortuosity	Observation	Findings inconsistent with inflammatory etiology
+9 months	Hand movements only; hyphema	Anterior chamber washout + intravitreal bevacizumab; vascular loop in angle	Suspicion of malignancy raised
Subsequent step	Orbital MRI: lesion adherent to corneal endothelium; no orbital mass	Enucleation	In consultation with ocular oncology
Pathology	Diffuse infiltrating RB; extensive iris/ciliary body/ anterior chamber involvement; prelaminar ONH; negative surgical margins	Systemic work-up negative; adjuvant chemotherapy started	No extraocular extension

DISCUSSION

DIRB is a rare and aggressive retinoblastoma variant that poses significant diagnostic challenges due to its atypical clinical presentation. Unlike classic retinoblastoma with a discrete calcified mass, DIRB shows diffuse retinal infiltration, often mimicking uveitis and delaying diagnosis with inappropriate treatments. [1, 2]

In the present case, the patient initially presented with decreased vision and photopsia, leading to a misdiagnosis of intermediate uveitis and subsequent anti-inflammatory treatment. Despite these interventions, disease progression continued, ultimately necessitating enucleation. This underscores the need for a heightened index of suspicion when evaluating ocular inflammation that does not respond to conventional therapy.

DIRB often lacks the hallmark calcifications of classic retinoblastoma, making ultrasonography (USG) less reliable for diagnosis. In this case, USG revealed diffuse vitreous opacities without identifiable calcifications, which is consistent with previous reports describing heterogeneous echotexture and retinal thickening in DIRB. [3]

Only a few adult-onset retinoblastoma cases have been reported in the literature, and most presented with a classic nodular tumor containing. [3,5] In contrast, our case represents a diffuse infiltrating variant with predominant anterior-segment involvement and masquerade features of chronic uveitis, leading to a nearly two-year delay in diagnosis. To the best of our knowledge, such an anterior-predominant DIRB presentation in adulthood confirmed by histopathology and immunohistochemistry remains exceptionally rare, underscoring the novelty of this report.

MRI plays a crucial role in evaluating tumor extension and differentiating DIRB from other intraocular pathologies. In our patient, MRI findings demonstrated anterior segment involvement characterized by corneal endothelium-based irregularities, without optic nerve invasion. These findings align with previous studies, emphasizing the role of MRI in detecting anterior chamber seeding and subtle retinal detachment patterns in DIRB. [4]

Optical coherence tomography (OCT) provides valuable insights into structural retinal changes in DIRB. In this case, OCT revealed hyperreflective deposits on the retinal nerve fiber layer (RNFL), further supporting the diagnosis of a neoplastic process. While some reports describe exudative retinal detachment in DIRB cases, our patient exhibited minimal subretinal fluid, demonstrating the variability in its clinical presentation. [5]

Fundus fluorescein angiography (FFA) serves as a supplementary tool for evaluating vascular abnormalities in retinoblastoma. In our patient, FFA demonstrated mild vascular tortuosity without optic disc leakage or capillary dropout, which aligns with prior DIRB cases, where vascular abnormalities are often nonspecific. [6]

Histopathology remains the gold standard for confirming DIRB diagnosis. In this case, Homer Wright rosettes, anterior segment infiltration, and corneal endothelium-based tumor deposits mimicking inflammatory nodules were observed. The tumor extensively involved the iris, ciliary body, and corneal endothelium, while sparing the posterior segment, reinforcing the anterior-predominant nature of DIRB. Immunohistochemical analysis revealed diffuse MAP2 positivity and focal synaptophysin positivity, further supporting the neuronal origin of the tumor. [7]

Immunohistochemistry further supported the diagnosis in our case. Diffuse MAP-2 positivity and focal synaptophysin staining confirmed the neuroectodermal nature of the tumor, consistent with retinoblastoma. The absence of cytokeratin, Sox-10, and melanocytic markers (Melan-A, HMB45) excluded carcinoma and melanoma, while the lack of lymphoid markers and the morphological presence of Homer-Wright rosettes helped differentiate from intraocular lymphoma. Taken together, this immunoprofile is highly characteristic of retinoblastoma and essential for distinguishing it from other small round blue cell tumors encountered in the eye.

Vitreous sampling is an essential diagnostic tool in unexplained uveitis cases, particularly when inflammation persists despite appropriate treatment. In this case, the omission of cytological analysis during the initial vitrectomy represented a missed opportunity for early diagnosis. Given its utility in detecting malignant cells and confirming neoplastic etiology through molecular diagnostics, such as polymerase chain reaction (PCR) and next-generation sequencing, vitreous sampling should be strongly considered in refractory inflammatory presentations. [8-10] Recent studies have demonstrated that aqueous humor liquid biopsy combined with next-generation sequencing can reliably detect RB1 mutations and chromosomal alterations such as 6p gain, thereby facilitating earlier diagnosis and prognostication in retinoblastoma. [9] Although not performed in our case, such approaches represent a promising adjunct for future clinical practice.

Nevertheless, several barriers limit its routine use in clinical practice. These include limited access to specialized ocular cytopathology, the small sample volume and low cellular yield, the requirement for advanced molecular platforms, and the risk of false-negative results. Moreover, vitreous manipulation carries theoretical risks of tumor seeding, making it essential to involve ocular oncologists in decision-making. In addition, recent advances suggest that aqueous humor liquid biopsy may provide a safer and more accessible alternative, enabling the detection of chromosomal alterations (e.g., 6p gain, RB1 mutations) through next-generation sequencing. Therefore, while vitreous or aqueous sampling could have enabled earlier diagnosis in our case, its application in daily practice must be balanced against resource availability, expertise, and patient safety.[9,10]

The lack of response to anti-inflammatory therapy and the progressive course in our patient can be explained by the unique biology of diffuse infiltrating retinoblastoma. Unlike typical uveitis, which often shows at least partial steroid responsiveness, DIRB demonstrates plaque-like infiltration without a discrete mass and may seed the trabecular meshwork, resulting in secondary glaucoma refractory to medical therapy. Although trabeculectomy temporarily normalized intraocular pressure, it could not address the

underlying neoplastic process. This highlights that the combination of steroid non-responsiveness, progressive white deposits on the intraocular lens, and atypical glaucoma mechanisms should raise suspicion for an underlying malignancy rather than chronic uveitis.[9]

Current diagnostic techniques each carry inherent limitations in the context of diffuse infiltrating retinoblastoma. Ultrasonography and computed tomography rely on calcification, which is typically absent in DIRB, while MRI is more useful for assessing anterior segment seeding and subtle retinal detachment patterns but cannot provide definitive diagnosis. Optical coherence tomography may reveal hyperreflective deposits or architectural disruption, yet these findings are nonspecific. Similarly, fundus fluorescein angiography often demonstrates only mild vascular tortuosity without classic neoplastic leakage. Histopathology therefore remains the gold standard, but it is generally available only after enucleation, underscoring the importance of earlier adjunctive tools such as aqueous or vitreous liquid biopsy. Molecular diagnostics, including RB1 mutation analysis and chromosomal copy number alterations (e.g., 6p gain), are increasingly recognized as promising but are not yet universally accessible. Prognostically, anterior segment involvement as in our case portends a higher risk of vision loss and potential extraocular spread, although clean surgical margins and absence of postlaminar optic nerve invasion are favorable features. Effective management of DIRB requires a multidisciplinary approach integrating ophthalmology, oncology, and pathology, with systemic chemotherapy considered in extensive anterior involvement, alongside genetic counseling and long-term surveillance.

DIRB carries a high risk of delayed diagnosis, leading to increased morbidity and potential metastasis. Given the high rate of anterior segment involvement in DIRB, early recognition is essential to prevent vision loss and extraocular spread.

Multidisciplinary management, including genetic counseling, advanced imaging, and histopathologic confirmation, is crucial for optimizing patient outcomes. Ancona-Lezama et al.[2] emphasized that individualized treatment strategies, such as enucleation and adjuvant chemotherapy, play a pivotal role in minimizing recurrence risk and improving survival in DIRB cases. [11]

This case highlights the importance of integrating vitreous sampling, OCT, and genomic analysis into standard diagnostic protocols for suspected retinoblastoma, particularly in atypical inflammatory presentations.

CONCLUSION

This case underscores the need to maintain a high index of suspicion for diffuse infiltrating retinoblastoma in young patients with treatment-resistant uveitis. Key clinical red flags include steroid non-responsiveness, atypical anterior segment deposits, and secondary glaucoma not explained by inflammatory mechanisms. In such scenarios, an escalated diagnostic pathway integrating multimodal imaging and, where available, aqueous or vitreous liquid biopsy should be strongly considered. Multidisciplinary collaboration between ophthalmologists, oncologists, and pathologists is essential for timely diagnosis and appropriate management. Future research should focus on validating liquid biopsy approaches and consolidating adult-onset case data to develop evidence-based diagnostic algorithms for this rare retinoblastoma variant.

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