Chapter

Malignancies Masquerading as Uveitis

Teresa E. Fowler and Diego Espinosa-Heidmann

Abstract

Malignancy presenting as uveitis can be symptomatically mild and difficult to diagnose, often leading to delayed treatment and poor outcomes. In this chapter, we describe the range of malignancies reported to present with uveitis, both primary ocular malignancies and systemic malignancies which metastasize to the eye. We describe the range of clinical features and corresponding complaints that may be encountered with specific malignancies and provide a thorough review of diagnostic tools available to aid in diagnosis. The primary goal of this chapter is to aid in the diagnosis of intraocular malignancy to reduce treatment delays and improve patient outcomes.

Keywords: malignancy, uveitis, intraocular malignancy, metastatic ocular disease, lymphoma, leukemia, uveal melanoma

1. Introduction

The presence of intraocular cell does not always imply a primary inflammatory condition. It is reported that approximately 5% of patients initially diagnosed with uveitis have an underlying masquerade syndrome, about half of which are from a malignant process [1]. Intraocular cells in these cases may be inflammatory cells released in response to a separate primary condition or maybe entirely unrelated entities, such as heme, pigment, or malignant cells easily mistaken for inflammatory cells.

Although ocular immune privilege generally protects the eye from immune attack, malignant intraocular lesions may directly or indirectly incite an inflammatory response. Direct expression of antigenic proteins by a cancerous lesion can cause secondary uveitis [2, 3], with typical symptoms including redness, pain, photophobia, and blurred vision. Hematologic malignancies invading the eye may cause anterior chamber cell, vitritis, or retinochoroiditis clinically indistinguishable from an inflammatory uveitis flare. Malignancies manifesting as intraocular cells are important to keep on the differential but can present a diagnostic challenge, as their subjective and objective features can be nearly identical to the inflammatory uveitis triggered by infectious or noninfectious causes. Additionally, haze in the anterior or posterior chambers can impede the complete evaluation of the eye.

Malignancies are among the most feared uveitis masquerade syndromes, as delay in diagnosis and treatment can result in fatality. Clinical judgment and thorough evaluation are paramount in arriving at the correct diagnosis; intraocular

malignancies often come to light when an astute provider notes uveitis features with a negative workup and treatment failure with anti-inflammatory medications, pursuing further workup as detailed below.

1.1 Diagnostic tools

The provider caring for a patient with presumed uveitis who is not responding to anti-inflammatory treatments as expected has several diagnostic tools available for further investigation, some of which may be readily available in the office. A thorough ophthalmic exam is critical, with detailed documentation of the affected ocular segments. Since intraocular biopsy is invasive and poses a risk of vision-threatening complications, much of the diagnostic support for a diagnosis of intraocular malignancy relies on noninvasive testing.

1.1.1 Noninvasive or minimally invasive in-office testing

Fundus photography is helpful for monitoring the evolution of disease over time, as well as treatment response. These images can be used to document lesion dimensions, pigmentation, presence of drusen or lipofuscin, lacunae, vascular abnormalities, infarcts, and retinal atrophy. Fundus photography may also be helpful in patients with difficulty cooperating with the slit lamp and indirect examination. When a diagnosis of malignancy is uncertain, fundus photography provides a detailed snapshot that, in combination with a detailed clinical examination, can be monitored over time.

Optical coherence tomography (OCT) utilizes the reflection and scattering of light waves to create high-resolution cross-sectional imaging of the retinal layers [4]. OCT images have higher sensitivity for detecting retinal edema, thinning, atrophy, and subretinal fluid than clinical examination alone [5]. For some ocular malignancies, features such as subretinal fluid or nodularity have been shown to be associated with risk for metastasis, so OCT can be particularly helpful in understanding the full spectrum of disease in these patients [6]. OCT of the optic nerve can be helpful in monitoring nerve edema or atrophy. In cases with dense vitreous haze or a poor view of the posterior segment, OCT is of limited use and alternative testing methods must be employed. OCT is widely available, rapid, relatively inexpensive, and technically straightforward to perform, making it one of the best initial tests for understanding complex ophthalmic disease.

Additional widely available noninvasive imaging includes fundus autofluorescence (FAF), a modality based on the differential absorption of specific wavelengths of light by ocular tissues. Lesions can be described as hyper- or hypo-autofluorescent based on their appearance. Hyperautofluorescence, seen as light coloration, indicates the presence of fluorophores excited by blue or green light and emitting light of longer wavelengths. Lipofuscin and related compounds are readily autofluorescent; thus, healthy RPE appears light on FA. Normal hypo-autofluorescent tissues include the vasculature since heme strongly absorbs blue and green wavelengths without excitation, and the optic nerve, which does not contain RPE or lipofuscin fluorophores. RPE and lipofuscin accumulation, as seen in choroidal melanomas and metastatic lesions, causes hyperautofluorescence, whereas nevi and congenital RPE hypertrophy appear hypo-autofluorescent. Areas of RPE atrophy appear dark and are referred to as "window defects."

Ultrasound biomicroscopy, a technique using high-frequency sound waves to look at the anterior segment, and B-scan ultrasound, using lower-frequency sound with a greater depth of focus, are noninvasive and can provide valuable clues to the underlying diagnosis. Biomicroscopy is particularly useful for lesions in the angle or far peripheral retina, where they may be difficult to view with a slit lamp or indirect exam. B-scan can be used to evaluate and measure posterior segment lesions, as well as for surgical planning, especially when the view is limited by vitreous haze or anterior segment pathology. The acoustic properties of the lesion are helpful in diagnosis; for example, choroidal melanoma likely has a dome or mushroom shape with moderate reflectivity, whereas retinoblastoma contains hyperreflective calcium deposits [7].

1.1.2 Evaluation for metastasis

In patients with suspected or confirmed malignancy, computed tomography (CT) and magnetic resonance imaging (MRI) imaging of sites suspected to be involved, including the CNS, are critical in evaluating for metastasis. Cerebrospinal fluid analysis via lumbar puncture with cytology and cytokine analysis can identify malignant cells unable to be seen on imaging. Suspicious brain lesions may require biopsy. The presence of intracranial or intrathecal lesions significantly changes both management and prognosis. Additional imaging may be indicated depending on the diagnosis.

1.1.3 Invasive testing and cytologic studies

For some intraocular malignancies, diagnostic vitrectomy or vitreous aspiration is the only means of a definitive diagnosis. Of course, either technique carries the risk of devastating complications leading to vision loss or loss of the eye and, in some cases, the risk of seeding the malignancy, so this decision should be carefully considered. Since the vitreous is relatively acellular, malignant cells can be scattered, and false negative results are possible. Malignant cells are especially sensitive to changing conditions, so samples must be delicately handled and rapidly processed. Careful fine-needle aspiration of retinal or choroidal tumors may be performed concurrently or at a later time for a more condensed sample of cells if vitrectomy is nondiagnostic [8].

Once the sample is obtained, it is processed through several testing techniques for diagnosis. Cytologic studies can differentiate inflammatory cells from malignant ones based on characteristic features. Malignant cells tend to be large with abnormally segmented nuclei, scant cytoplasm, and abundant nucleoli [9, 10]. Benign inflammatory cells, on the other hand, are smaller, with characteristic nuclear and cytoplasmic features based on cell type. The presence of necrotic cells is suggestive of malignancy, as these are not typically present in an uveitic reaction.

Immunophenotyping, a method for identifying cells based on expressed surface markers, can be used to differentiate cell populations. Malignancies arise from the uncontrolled proliferation of homogenous cell populations, which can be identified based on markers, such as CD19, CD20, and CD22 on the surface of B cells. Flow cytometry can sort cells based on the presence of several markers and may be diagnostic even when cytology is inconclusive [1]. The diagnosis can also be supported by polymerase chain reaction (PCR), a technique used to identify specific gene mutations or rearrangements present in sample tissue [11].

Cytokine analysis can be particularly helpful in differentiating inflammatory uveitis from malignancy. Interleukin (IL) cytokines are immune-modulating proteins secreted by inflammatory cells with a host of functions. For example, IL-6 is a pro-inflammatory signal secreted by B and T cells, whereas IL-10 is an inflammatory inhibitor produced by T helper cells. Specific cytokines may be released from malignant cells, so the cytokine profile of a sample identified by enzyme-linked immunosorbent assay (ELISA) can aid in diagnosis.

2. Hematologic malignancies masquerading as uveitis

2.1 Leukemia

Leukemic cancers arise from bone marrow-derived blood cells. Acute leukemia and blast crises can rarely present with uveitis findings. Reported clinical findings range from low-grade anterior chamber cells to dense pseudohypopyon with intermixed heme [12]. Vitreous cell is less common in chronic leukemia but may be present in an acute blast crisis, and may be indicative of CNS involvement [13]. Anti-inflammatory agents are ineffective in treatment. Anterior chamber aspirate may reveal leukemic cells, with or without blast cells [13]. Patients with a known diagnosis of leukemia in remission should be evaluated for relapse when presenting with uveitic findings [13]. Intraocular findings more common in leukemia include retinal hemorrhages in all layers, often with white centers indicative of capillary rupture or leukemic cell aggregation.

2.2 Lymphoid malignancies

Lymphomas comprise a group of malignancies arising from B or T lymphocytes. Lymphoid malignancies occurring within the eye may be differentiated into vitreoretinal or uveal based on their origins. Systemic lymphoma spread hematogenously to the eye may present with visual decline, floaters, photophobia, or eye pain. The spectrum of clinical features similar to uveitis may include pseudohypopyon, anterior chamber cells, vitritis, white subretinal infiltrates, vascular inflammation, or choroiditis. Choroidal masses or whitening may be the primary feature. These malignant proliferations of B or T cells can easily be mistaken for inflammatory uveitis, and delays in an accurate diagnosis can lead to poor outcomes.

3. Central nervous system malignancies

3.1 Primary vitreoretinal lymphoma (PVRL)

The most common intraocular lymphoid malignancy, and one frequently misdiagnosed as uveitis, is PVRL. The vast majority of PVRL is non-Hodgkin B cell lymphomas [14], primarily involving the CNS, whereas rare cases arise from T cells [15]. The incidence of PVRL peaks in the 6th and 7th decades of life [16], with immunocompromised individuals being at higher risk than the general public. Human immunodeficiency virus (HIV) with a low CD-4 count is a known risk factor, so clinicians diagnosing uveitis in a known HIV-positive or otherwise immunocompromised patient should have PVRL on the differential [17]. PVRL is

often initially misdiagnosed, with patients being treated for alternative conditions for 10–21 months and undergoing four or more diagnostic procedures before the correct diagnosis is made [1, 10].

3.1.1 PVRL presentation and clinical features

Presenting complaints and clinical features vary. Two-thirds of patients have bilateral involvement [18], though findings can be highly asymmetric. Visual haze, blurriness, and floaters are common complaints [18]. Cells within the anterior segment may range from scarce to dense, sometimes evolving into a layered pseudohypopyon [19]. Patients generally do not develop posterior synechiae. In the posterior segment, vitritis with large, homogenous cells and lymphocyte clumping is often present. A heavy lymphocyte burden in the trabecular meshwork can lead to secondary glaucoma [16].

An important clinical finding suggestive of PRVL, though found in only one in five patients, is the presence of creamy yellow subretinal infiltrates composed of accumulated malignant lymphocytes beneath the RPE [20], which appear hyperreflective on OCT and hyperautofluorescent on FAF. These subretinal infiltrates can shift over time and may lead to areas of geographic atrophy. Subretinal fluid may be seen over infiltrates. Accumulation of atypical lymphocytes along vasculature can compromise perfusion and lead to ischemia, with downstream neovascular consequences. Involvement of the optic disc may be seen clinically as optic nerve head edema and elevation.

The symptoms of PVRL are often mild and insidious, leading to delayed presentation. It is estimated that symptoms are present for an average of 6 months before diagnosis, though patients treated for chronic smoldering uveitis for 2 years or more prior to PVRL diagnosis have been reported. Patients may temporarily improve with topical or systemic steroids, but later recur.

3.1.2 PVRL diagnosis and treatment

Workup often begins with negative blood work and chest x-ray to rule out causes of inflammatory uveitis. Office-based testing may include OCT, demonstrating subretinal infiltrates or subretinal fluid, FAF with hyperautofluorescent subretinal lesions, or fluorescein angiogram (FA) with hyperfluorescent lesions and window defects [21]. Hypocyanescence on indocyanine green angiography can be helpful in distinguishing PVRL from white dot syndromes [22].

When PVRL is suspected, vitrectomy is performed to obtain vitreous samples and may be accompanied by a subretinal aspiration biopsy of selected lesions [23]. Cytology reveals a mix of typical inflammatory cells with malignant lymphocytes, distinguishable by their large size, atypical nuclei, scarce cytoplasm, and numerous nucleoli. Intermixed necrotic cells are not typical of inflammatory uveitis and, therefore, support the diagnosis of malignancy.

Immunohistochemical staining can be used to demonstrate B-cell-specific markers, such as CD19, CD20, CD22, and Pax-5 [24]. MYD88, a protein encoded on chromosome 3 with immune signaling functions, is found to be mutated in up to 70% of PVRL [25]. The ratio of interleukin 10 (IL-10), an anti-inflammatory cytokine, to IL-6, its pro-inflammatory counterpart, suggests malignancy when greater than 1 or benign inflammation when less than 1. Monoclonality on gene rearrangement studies is a feature of malignancy, as well as the predominance of a specific light chain

subtype. Even with all of these testing methods, false negatives are unfortunately common due to the paucicellular composition of vitreous, delicate tissue processing, and small sample sizes [10].

All patients undergoing workup for PVRL should undergo neuroimaging and cerebrospinal fluid analysis to evaluate for CNS involvement. CNS involvement is common, seen in up to 2/3 of PVRL patients [21], and confers a poor prognosis. Treatment involves intravitreal chemotherapy, generally with serial methotrexate [26, 27] and/or rituximab [28], and ocular radiation. Response to treatment may be monitored in the office using the imaging techniques described above [22]. Patients with CNS lesions require systemic or intrathecal chemotherapy, as well as extensive radiation. Despite aggressive treatment, the prognosis remains poor [21].

4. Non-hematologic malignancies masquerading as uveitis

4.1 Metastases from distant primary cancers

The vascularity of the choroid makes it a common area for metastatic invasion. Blurred vision in a patient with a recent or distant history of cancer, especially breast or lung cancer [29], should raise suspicion. Approximately 1/3 of patients diagnosed with a choroidal metastatic lesion do not have a known diagnosis of cancer prior to their presentation for eye complaints [29]. Clinical features include a unilateral dome-shaped choroidal elevation without significant pigmentation, with adjacent shifting subretinal fluid, which may require OCT for diagnosis. B-scan may demonstrate an echogenic lesion within the choroid, with or without overlying subretinal fluid or detachment (**Figures 1** and **2**).

4.2 Uveal melanoma

Melanoma of the uvea is the most frequently diagnosed primary ocular malignancy [30–33] and comprises approximately 5% of melanomas [34]. The prognosis is strongly correlated with the size of the primary tumor at diagnosis [35]; thus, prompt and accurate diagnosis is crucial as delay may be fatal. Uveal melanoma is most commonly observed in Caucasian [36] patients in their 6th to 7th decade of life [34, 37]. Symptomatic patients may complain of blurred vision, photopsias, or visual field defects, though a significant proportion is asymptomatic and identified on routine screening exams [31].

Small choroidal melanomas may be overlooked on early examinations or may be obscured from clinical views by the iris. Anterior or posterior chamber cells may be the first indication of a choroidal melanoma; in these cases, the intraocular cells are composed of inflammatory cells, pigment cells, and malignant cells [38]. In a pig model, inflammatory uveitis thought to be the result of an immunologic cross-reaction has been shown to develop in response to cutaneous melanoma [39], suggesting a potential mechanism for intraocular cells. Epithelioid cell-predominant melanomas have been shown to cause more inflammation than spindle or type A melanoma cells [40].

Clinical examination of uveal melanoma typically reveals a unilaterally elevated subretinal lesion with brown or gray coloration. If penetration through the Bruch membrane occurs, the tumor may extend into the vitreous via a stalk through the retina, taking on a “mushroom” shape. If the lesion is sharply defined or overlying drusen are present, a benign nevus or hypertrophy of the RPE should be considered.

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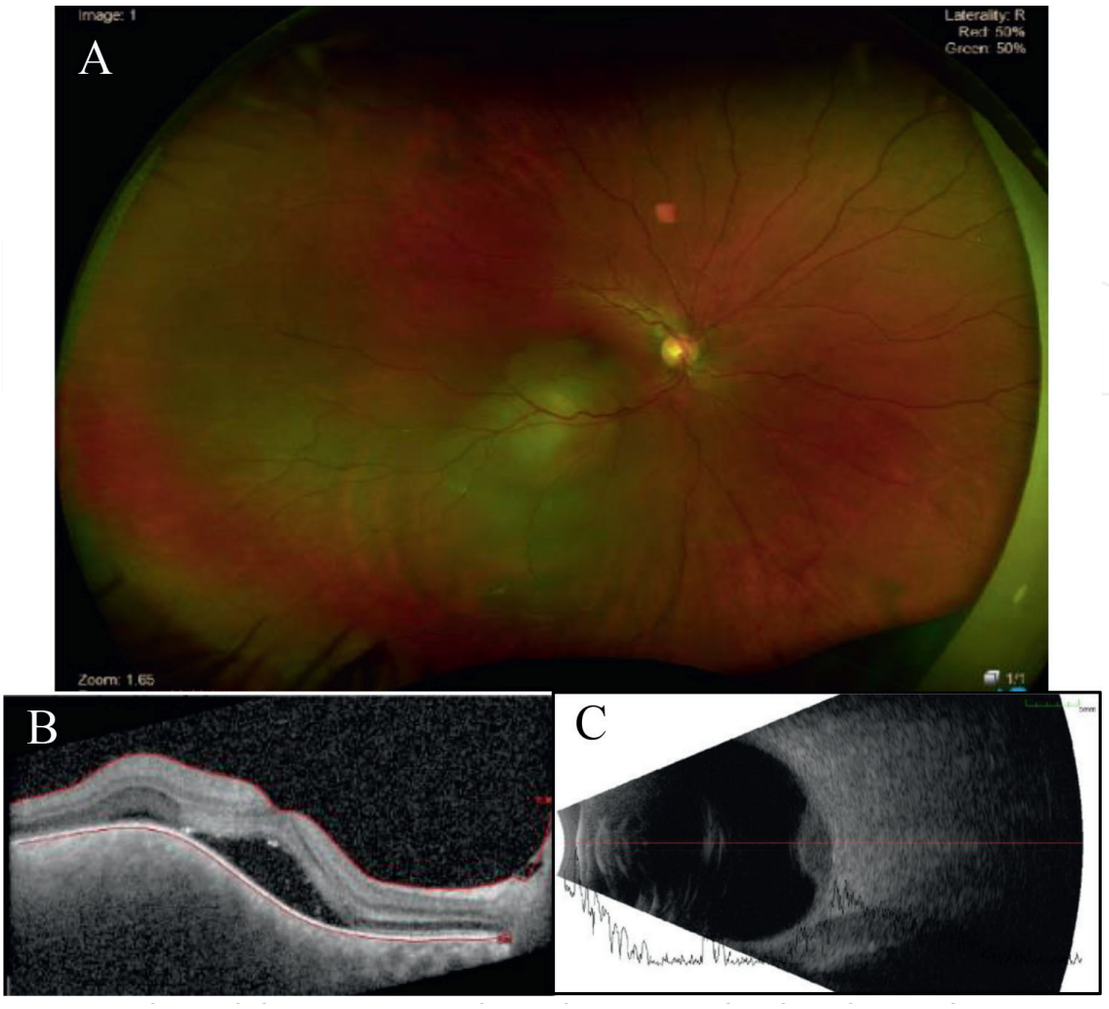

Figure 1.
Choroidal metastasis with exudative macular detachment from Ewing sarcoma. A patient with a known history of Ewing sarcoma undergoing systemic therapy presented with complaints of decreased visual acuity with constant distortion and intermittent flashes in the right eye (OD). (A) Fundus photograph of the right eye showing a choroidal mass within the inferior macula. (B) OCT of the right macula showing a fovea-involving exudative retinal detachment overlying the choroidal mass. (C) B-scan ultrasonography of the same patient demonstrating a choroidal mass lesion with medium reflectivity measuring 9.6 × 11 mm at its base and 3.5 mm in height. Images courtesy of Dr. Diego Espinosa-Heidmann.

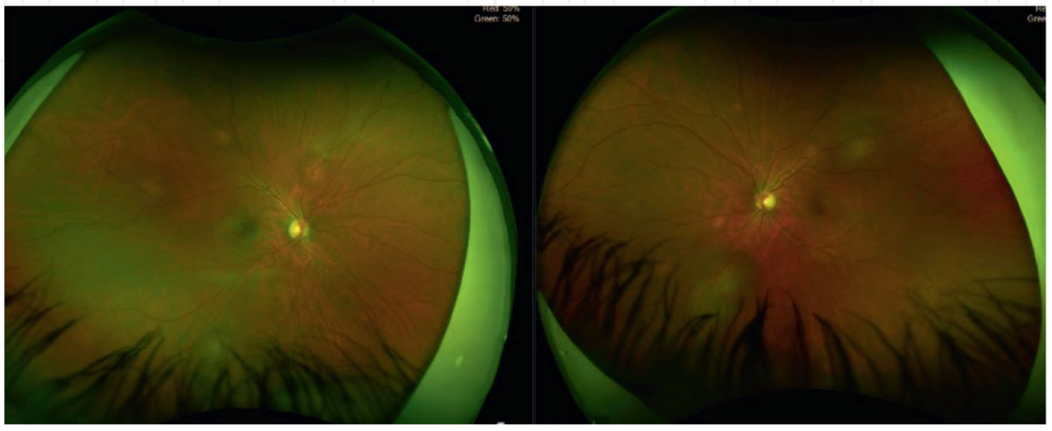

Figure 2.
Multifocal choroidal metastases from a primary neuroendocrine malignancy. Fundus photograph showing multiple orange-yellow choroidal lesions of varying sizes in the mid-periphery bilaterally. In this case, the primary malignancy was a high-grade neuroendocrine tumor identified in the lung. Image courtesy of Dr. Diego Espinosa-Heidmann.

Features suggestive of melanoma include thickness greater than 2 mm, subretinal fluid, orange lipofuscin, dilated or tortuous overlying vasculature, and close proximity to the optic nerve.

Ultrasound of a uveal melanoma demonstrates low to medium internal echogenicity with orbital shadowing beyond the lesion [41] and can be used to measure tumor dimensions and assess for orbital invasion. Ultrasound biomicroscopy may provide a better assessment of ciliary body tumors. Fluorescein angiography may show vessel irregularity or leakage around the tumor, as well as the classic "double circulation" sign with retinal and tumor vessels simultaneously visible [42]. A fine-needle aspiration biopsy provides a definitive histopathological diagnosis [43]. Melanoma has the propensity to spread hematogenously, with metastatic spread observed in up to 50% [44], and increasing tumor thickness has been shown to correlate with a higher risk of metastasis [6]. Once a primary tumor is identified, evaluation for the metastatic disease should proceed with imaging of the central nervous system, liver, and lungs. Prognosis strongly correlates with tumor size; survival is greater than 80% for tumors less than 10 mm but only approximately 40% for those with diameters greater than 16 mm [45].

Treatment of uveal melanoma historically included enucleation and localized radiotherapy until the mid-1970s, though there was concern that enucleation facilitated metastatic dissemination [46, 47]. The Collaborative Ocular Melanoma Study (COMS), a prospective multicenter randomized trial comparing treatment outcomes for uveal melanoma, began in 1985 and followed enrolled patients until 2003. The main conclusions from COMS include (1) equal 5-year survival for medium uveal melanoma patients treated with brachytherapy versus enucleation [48] and (2) no improvement in outcomes for large melanomas treated with radiation prior to enucleation compared to enucleation alone [49, 50]. Localized proton beam radiotherapy using externally applied protons, carbon, or helium particles has also shown promise in the treatment of large melanomas [51] (**Figure 3**).

4.3 Retinoblastoma

Retinoblastoma is a childhood cancer of neuroendocrine origin, the most recognized manifestation of which is leukocoria. An estimated 50% of patients referred to ocular oncologists with concern for retinoblastoma end up having alternate diagnoses [52]. In up to 3% of retinoblastoma patients, intraocular cell may be the presenting finding [53, 54], especially for the diffuse infiltrating subtype. Retinoblastoma should be on the differential for young patients presenting with signs and symptoms of uveitis without a clear underlying etiology (**Figure 4**).

4.3.1 Diffuse infiltrating retinoblastoma

Diffuse infiltrating retinoblastoma is a rare subtype of retinoblastoma known to mimic uveitis. Of the 7000–8000 retinoblastoma cases diagnosed annually [55], approximately 2% are diffuse infiltrating [54]. Rather than form a distinct mass, as in typical retinoblastoma, malignant cells in this subtype spread tangentially along and within the retina in an ill-defined and irregular pattern, with the tumor seeding throughout the eye. Suggested mechanisms behind this atypical growth pattern include immune dysregulation [56] or mutations of cell adhesion molecules [57], though strong evidence is lacking.

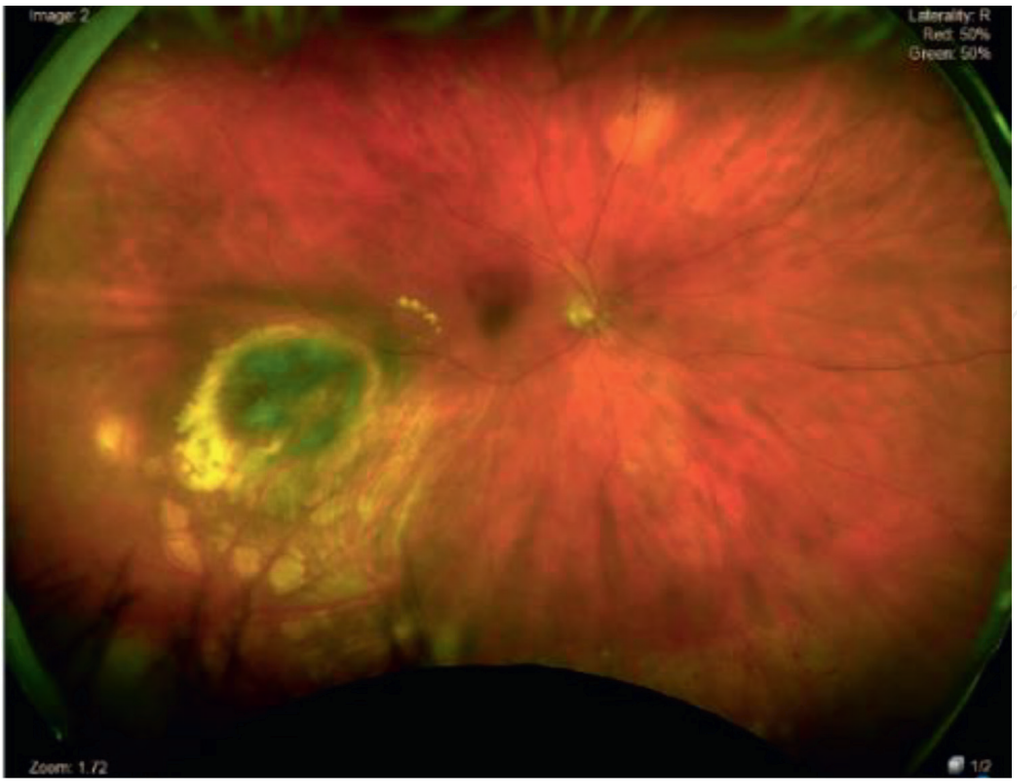

Figure 3.
Choroidal melanoma status post brachytherapy and thermotherapy. Fundus photograph of the right eye demonstrating an irregularly pigmented inferotemporal lesion with surrounding retinal atrophy consistent with a regressed choroidal melanoma. This lesion was closely monitored for recurrence. Image courtesy of Dr. Espinosa-Heidmann.

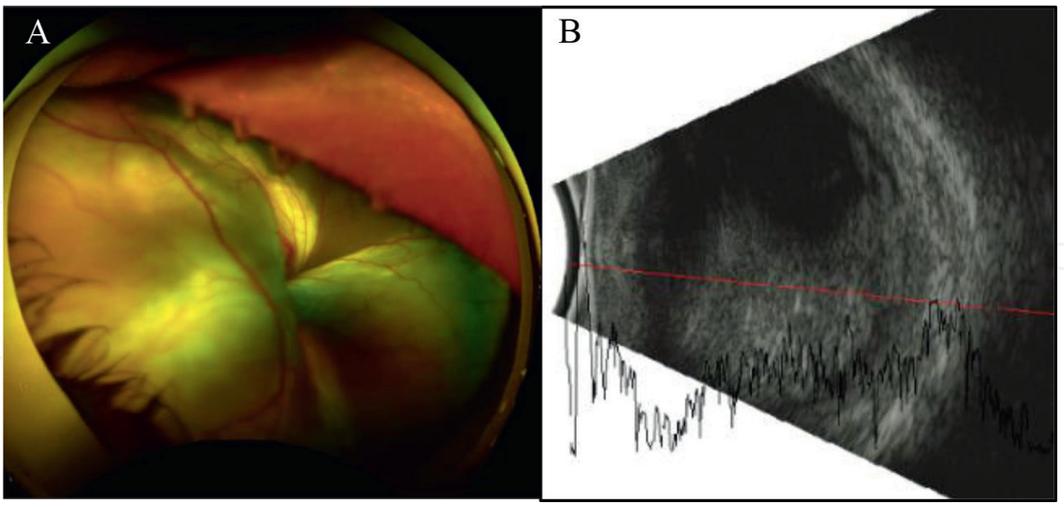

Figure 4.
Retinoblastoma in a 3-year-old child referred by a pediatrician due to leukocoria of the right eye. Family history included retinoblastoma requiring enucleation in an older sibling. (A) Fundus photograph showing a yellow-white mass in the posterior pole with associated exudative detachment, and (B) B-scan ultrasonography of the same eye demonstrating a large macula-involving elevated intraocular mass with high internal reflectivity. Images courtesy of Dr. Espinosa-Heidmann.

Much of our knowledge of this relatively rare disease comes from published case reports and series. The average age of presentation for this subtype is 4–5 years [54, 58], significantly later than typical retinoblastoma presenting between 1 and 2 years

of age [59], though there are published reports of cases diagnosed from 1 to 19 years [60]. An association has been shown with the *RB1* gene [57], though less than 5% have a known family history of retinoblastoma [58].

In children old enough to express symptoms, the most common presenting complaints include unilateral eye pain, floaters, and blurred vision [58]. The provider, patient, or family member may also notice injection or leukocoria [58]. Vitreous cell is the most common examination finding, reported in 79% of cases [58], followed by pseudohypopyon in 48% [58]. Intraocular pressure may be elevated in the affected eye [58]. Additional examination findings may include injections, cataracts, neovascularization of the iris, vitreous hemorrhages, or retinal detachments [54, 58].

Diffuse infiltrating retinoblastoma is often misdiagnosed as uveitis, especially when the presentation includes pain, conjunctival injection, and vitreous cells. Additional differential diagnoses include Coats disease, trauma, endophthalmitis, toxoplasmosis, or *Toxocara canis*, depending on presentation. The workup often begins with ultrasound, showing retinal thickening and calcification with hyperreflective vitreous cells [54]. On computed tomography, approximately 67% have a detectable mass and 89% exhibit patchy calcification [54]. As with typical retinoblastoma, diagnostic vitreous sampling is contraindicated due to the risk of metastasis. Therefore, diagnosis is largely based on clinical findings and confirmed with pathology after enucleation.

Treatment for diffuse infiltrating retinoblastoma often includes enucleation. When metastasis is present, intensive systemic chemotherapy [61] may be required with agents including vincristine, etoposide, methotrexate, or carboplatin, though drug resistance is a significant concern.

5. Conclusions

Intraocular cells in any segment of the eye are most commonly a sign of inflammation but may be a harbinger of an insidious underlying malignancy. Ophthalmologists should be suspicious of an alternative diagnosis in patients presenting with signs and symptoms of uveitis who do not improve, or initially improve and then recur, with anti-inflammatory treatments. There are a slew of diagnostic tools available, many of which are relatively easy to perform, widely available, and noninvasive. The malignancies described above are considered masquerade syndromes commonly mistaken for uveitis, and their prompt diagnosis can be lifesaving.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

OCT	optical coherence tomography
FAF	fundus autofluorescence
RPE	retinal pigment epithelium
PVRL	primary vitreoretinal lymphoma

DLBCL	diffuse large B-cell lymphoma
COMS	Collaborative Ocular Melanoma Study
HIV	Huma immunodeficiency virus
ELISA	enzyme-linked immunosorbent assay
PCR	polymerase chain reaction
FA	fundus autofluorescence
OD	oculus dexter
CT	computed tomography
MRI	magnetic resonance imaging
IL	interleukin

Author details

Teresa E. Fowler and Diego Espinosa-Heidmann*
Augusta University, Augusta, USA

*Address all correspondence to: deheidmann@augusta.edu

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