Literature Review

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Uveitis Masquerade Syndrome

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The 'uveitis masquerade syndrome' is a large group of neoplastic and non-neoplastic conditions that mimic and are initially misdiagnosed as uveitis. These eye diseases account for approximately 5% of all presentations at tertiary referral uveitis clinics. Vitreoretinal lymphoma is one of the most common of the neoplastic conditions that present as uveitis. With a 5-year survival rate under 50%, it is vitally important to recognize this diagnosis promptly. Other malignancies that may masquerade as uveitis include systemic lymphomas, primary uveal lymphoma, leukemias, multiple myeloma, uveal melanoma, metastatic cancers, and in children, retinoblastoma, medulloepithelioma, and post-transplantation lymphoproliferative disorder. Paraneoplastic syndromes are also possible uveitis mimics. Non-neoplastic conditions that may present as uveitis include the ocular ischemic syndrome and other vascular eye diseases, central serous chorioretinopathy, inherited retinal diseases, rhegmatogenous retinal detachment, pigment dispersion syndrome, intraocular foreign bodies, and in children, juvenile xanthogranuloma and Coats disease. In this article, we review the uveitis masquerade syndrome. Our major focus is vitreoretinal lymphoma, but we also summarize the other neoplasms and non-neoplastic diseases that may masquerade as uveitis.

Key words:
Uveitis masquerade syndrome; Vitreoretinal lymphoma; Clinical registry.

Introduction

'Uveitis masquerade syndrome' refers to the constellation of unrelated eye diseases that present as intraocular inflammation, but are not uveitis. Large case series recently published by uveitis clinics in The Netherlands and Taiwan indicate that this syndrome accounts for approximately one in 20 tertiary referral uveitis consultations [1, 2]. A distinction is often made between neoplastic and non-neoplastic conditions that masquerade as uveitis, to highlight the key role the ophthalmologist plays in recognizing potentially life-threatening malignancies when a patient presents to them with 'uveitis'. In particular, vitreoretinal lymphoma (VRL) is the most common neoplastic uveitis mimic [3]. With a median survival of just over 2 years [4], prompt diagnosis of this serious malignancy is vital. In this narrative review of the uveitis masquerade syndrome, we focus on vitreoretinal lymphoma, providing a description of clinical features, investigations and treatments, plus a brief discussion of a recent international effort to improve outcomes. We complete the review with a summary of other neoplasms and non-neoplastic diseases that may masquerade as uveitis.

Vitreoretinal lymphoma

Vitreoretinal lymphoma is a highly aggressive intraocu-Vitreoretinal lymphoma is a highly aggressive intraocular malignancy and variant of primary central nervous system lymphoma (PCNSL) based in the vitreous, retina or subretina, and optic nerve [5]. While the tumor may be confined to the eye, termed primary VRL, involvement of extraocular central nervous system (CNS) compartments is found in approximately 40% of patients at the time of initial diagnosis, increasing to 70% over time [4]. Up to 20% of patients with PCNSL develop VRL over time [4]. The association between eye and brain disease is responsible for the high mortality rate of VRL [6].

Approximately 95% of VRLs are high-grade extranodal diffuse large B-cell lymphomas [6], but T-cell and natural killer cell VRLs are also reported [7-9]. 'Primary large B-cell lymphomas of immune-privileged sites' is a term added in the latest edition of the World Health Organization Classification of Hematolymphoid Tumors, aimed at recognizing shared biological characteristics among a set of aggressive B-cell lymphomas originating as primary tumors within the CNS, the vitreoretinal compartment, and the testes of immunocompetent individuals [10]. These lymphomas share immunophenotypic and molecular features [11], and have a propensity to migrate to other immune-privileged sites, with VRL showing a distinct tropism for the CNS [10].

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Epidemiology

Vitreoretinal lymphoma is a rare cancer [4, 12], although some studies indicate that the incidence is rising globally [13-18]. In British Colombia, the incidence of VRL doubled from 1990 to 2010 [13]. In the United States and Finland, the incidence of PCNSL has tripled over the past three decades [6, 17]. In Australia, increasing incidence of PCNSL has been linked to the overall increasing incidence of diffuse large B-cell lymphoma, including in younger adults [19]. The limited number of population-based studies complicates estimates of incidence, which is less than one per million persons per year [4].

A higher incidence of VRL is seen with increasing age [12, 20], in patients following solid-organ transplantation, and in those infected with human immunodeficiency virus (HIV) or living with acquired immunodeficiency syndrome (AIDS) [21, 22]. Approximately 3% of patients with AIDS developed PCNSL prior to the introduction of antiretroviral therapy, [23] which has reduced the prevalence of the malignancy [24, 25]. Most patients are over 60 years when they first present with VRL [26]. Some studies report a modest preponderance of women [13, 27]. Other articles describe VRL affecting men and women equally frequently [20]. There is no race predilection [20, 28].

Clinical features

Symptoms

Patients with VRL almost always complain of visual symptoms [26], although these symptoms are often non-specific [21]. Blurred vision, decreased vision, and floaters are common [26]. A recent report from Tokyo Medical and Dental University documented a median time from initial visual symptoms to diagnosis of 7 months [26]. Patients with associated CNS disease may have focal neurological deficits, generalized signs of increased intracranial pressure, or nonspecific cognitive and behavioral changes [21].

Signs

Vitreoretinal lymphoma is bilateral in 59-70% of patients [26, 29]. Typical ocular signs include vitreous cellular infiltration, and tumor deposits below the neural retina and retinal pigment epithelium [28]. Retinal vasculitis, retinal hemorrhage, cystoid macular edema [30], pseudonecrotic retinopathy [27], and optic nerve swelling [31] may occur. Anterior segment findings are uncommon, but include anterior chamber cells, iris infiltration, and pseudohypopyon [32]. The visual acuity may be unexpectedly good [33].

Diagnosis

Diagnosing VRL is often challenging due to the limited sensitivity of commonly used diagnostic tests to confirm ocular involvement [34]. The average time to diagnosis remains around 1 year [34, 35]. The preferred imaging modality for diagnosis of brain involvement is magnetic resonance imaging (MRI). Typical MRI features include T1-weighted gadolinium enhancement as a measure of blood-brain barrier disruption and tumor burden, and T2-weighted signal as a measure of vasogenic edema beyond MRI enhancement [36]. Diffusion restriction on diffusion-weighted imaging within the tumor lesion is also characteristic [21]. Whole-body fluorodeoxyglucose-positron emission tomography imaging is recommended by the International PCNSL Collaborative Group to exclude systemic involvement [36].

Ophthalmic imaging

Multimodal ophthalmic imaging – including spectral domain-optical coherence tomography (SD-OCT), fundus autofluorescence (FAF), fundus fluorescein angiography (FFA), indocyanine green angiography (ICGA) and B scan ultrasound – shows abnormalities that can increase the diagnostic suspicion of VRL. A 2021 consensus panel of ophthalmologist experts recommended all 5 imaging modalities to facilitate early diagnosis [37].

In one study of 55 eyes with VRL, vitreous opacities, retinal pigment epithelial abnormalities, and subretinal pigment epithelial (RPE) deposits were the most common presenting SD-OCT features, each present in just under two-thirds [38]. Pre-retinal deposits, intraretinal deposits, and subretinal deposits were also observed. The diagnostic value of SD-OCT has been assessed in another study comparing features in 45 eyes with VRL and 40 eyes with uveitis [39]. The highly sensitive features for VRL included vitreous cells, focal hyper-reflective sub-retinal infiltration, and diffuse RPE elevations, and the highly specific features included pre-retinal deposits, intra-retinal infiltration, banded hyper-reflective subretinal infiltration, and confluent RPE detachments. Combining two highly sensitive features with one specific feature, or one sensitive feature with two strongly specific features, yielded a sensitivity of 80% and a specificity of 95% for identifying VRL.

Vitreous cytology and flow cytometry

The gold standard for diagnosing VRL is cytological evaluation of the vitreous to identify lymphoma cells, often combined with immunophenotyping [20]. The lymphoma cells are large, with a high nuclear:cytoplasmic ratio, scant basophilic cytoplasm, and prominent nucleoli [40]. Cytomorphological assessment may be challenged by the paucicellular nature of vitrectomy specimens [34]. Poor cytological preservation of the fragile lymphoma cells that are also prone to apoptosis, and infiltration of the tumor with chronic inflammatory cells further complicate the evaluation [34, 41]. These factors lower the sensitivity of cytology, which ranges broadly from 37% to 73% [34]. Flow cytometry can assist in identifying a clonal B cell population with kappa and lambda light chain restriction, but this requires sufficient lymphoma cells [34].

Molecular studies

Molecular studies of aqueous or vitreous samples are useful supportive investigations when VRL is suspected. Genetic mutations that may be present in lymphoma cells include the single amplicon IGH gene arrangement and the L265P MYD88 gene mutation [42]. Small amounts of DNA can be extracted from ocular fluid samples for analysis by polymerase chain reaction (PCR) [43]. In studies with up to 200 patients, IGH gene rearrangement PCR was reported to have a sensitivity of 0.95-1.00 and a specificity

of 0.99-1.00 for VRL [44-46]. On the other hand, one study of 91 patients yielded a diagnostic accuracy ratio of 0.60 [47]. The use of MYD88 gene mutation analysis in VRL is a more recent development. Adding MYD88 gene mutation PCR to cytology plus IGH gene rearrangement PCR pushed testing sensitivity for VRL from 62% to 91%, with no change in 98% specificity, in one study of 69 patients [48]. Some clinical teams prefer the MYD88 gene mutation PCR as the sole tumor genetic test [49, 50].

Although considered an immunomodulatory cytokine, interleukin-10 (IL-10) acts as a growth factor for malignant B cells. Thus, IL-10 may be measured at increased levels in the ocular fluids of patients with VRL [42]. The concentration of IL-10 is typically compared with that of IL-6, an inflammatory cytokine produced by many cells including different types of leukocytes. A simple IL-10:IL-6 ratio can be calculated, with a value greater than one having 89% sensitivity for VRL in a systematic review [41]. However, more sophisticated mathematical approaches, the Interleukin Score for intraOcular Lymphoma Diagnosis (ISOLD) and the National Eye Institute Logistic Regression Model, have generated higher sensitivities and specificities of 0.93-0.94 and 0.95-1.00, respectively, in studies of 352 and 161 patients [51, 52].

Retinal or chorioretinal biopsy

A retinal or chorioretinal biopsy may be considered when there is ongoing suspicion of VRL in the face of negative vitreous biopsies [53]. In one study involving 29 patients suspected of having VRL, chorioretinal biopsies provided a specific histopathologic diagnosis in 17, and ruled out malignancy in 9 [54]. The risks of the procedure, including retinal detachment, hemorrhage, and post-surgical inflammation, need to be weighed [53].

Treatment

There is no established standard treatment protocol for patients with VRL, especially those with bilateral ocular lymphoma without brain involvement [6]. Thus, many local ocular and extraocular treatment approaches have been reported, including various combinations of chemotherapy, targeted therapy with monoclonal antibodies or small molecules, radiotherapy, and autologous stem cell transplantation. For example, the 17-center European Collaborative managed 78 patients with more than 25 different regimens [55]. of patients with VRL often requires an interdisciplinary medical team. The reported rates of cancer progression remain high, regardless of whether ocular, extraocular, or combined ocular and extraocular treatments are administered [56].

Ocular therapy

Local therapies for VRL include courses of intravitreally injected chemotherapeutic drugs and eye-targeted irradiation [57]. These measures effectively induce clinical remission of VRL and generally improve visual symptoms, but tumor recurrence and CNS progression continue to occur [58].

Nearly all patients receiving intravitreal methotrexate, an antimetabolite, achieve a complete intraocular response to treatment [59, 60]. Potential complications include corneal epitheliopathy, cataract, maculopathy, uveitis, and iris neovascularization [33]. Resistance to methotrexate is possible, but uncommon [61]. Intravitreal rituximab, a monoclonal antibody against the B-cell surface protein CD20, has been used as the sole treatment or in combination with methotrexate, demonstrating favorable rates of disease regression [62, 63]. Cataract, elevated intraocular pressure, uveitis, and occlusive retinal vasculopathy are reported side effects [33]. Intravitreal melphalan is a recently described alternative or second-line treatment [64, 65].

Ocular radiotherapy has a long history for the treatment of VRL, but it is now less commonly used in preference to intravitreal chemotherapy. Contemporary protocols involve 30–40 Gy delivered in fractions [66, 67]. Irradiation complications include cataract, retinopathy, cystoid macular edema, and optic atrophy.

Extraocular therapy

The treatment approach for PCNSL continues to evolve, with multiple targeted therapeutics currently under investigation [21]. CD19-directed chimeric antigen receptor (CAR) T-cell therapy is also being studied [68]. The United States National Cancer Institute maintains an electronic evidence-based resource that summarizes the current management of PCNSL [69]. As described in that resource, treatment usually involves an induction phase followed by a consolidation phase. Multi-drug induction therapy is based on high-dose methotrexate, usually delivered systemically. Whole-brain radiotherapy is avoided due to cognitive adverse events. Consolidation may include a variety of drugs, low-dose whole-brain radiotherapy, and autologous stem cell transplantation.

Prognosis

The prognosis of VRL is well known to be generally poor, reflecting the propensity for brain involvement [28]. However, there are few studies of population-based survival outcomes, and the figures are based on information sourced over 10 years ago. One study that used the Australian Cancer Database information from 2000 to 2014, showed the median survival time for patients with diffuse large B-cell VRL was 2.1 years, and the 5-year relative survival was 41% [12]. In a United States study that presented data from 1973 to 2014 from the National Cancer Institute's Surveillance, Epidemiology, and End Results database for the same VRL type, the 5-year overall survival rate was 41%, and the median overall survival time was 33 months [70].

The International Vitreoretinal B-cell Lymphoma Registry

Improving survival outcomes for VRL has been challenged by limited medical evidence to inform clinical practice [71], which is a common problem across rare diseases [72]. The potential value of a registry approach to address this issue has been voiced by several independent groups [62, 71, 73]. In response, the International Vitreoretinal B-Cell Lymphoma Registry was launched in 2021, to collect real-world contemporary diagnostic and treatment prac-

tices via a secure online platform [74]. Earlier this year, the International Vitreoretinal B-Cell Lymphoma Registry Group published its first report, describing presentation, diagnostic testing and initial treatments in a group of 80 patients who presented with new-onset or recurrent VRL over a recent 3-year period (January 1 2020 to December 31, 2022) [75].

Within this group of 80 patients with VRL, representation of women was slightly higher at 60%, and 70% were 60 years or older when the diagnosis was made. Active non-ocular CNS lymphoma was reported in 25% of patients, mostly in the brain, and 10% had non-ocular CNS lymphoma in remission. Relatively few patients (6%) had a non-CNS lymphoma, in remission for half at the time of diagnosis with VRL. In total, 132 eyes had VRL, meaning the tumor was bilateral in two-thirds. Ninety percent of the eyes presented with vitreous involvement, and there was retina co-involvement in 40%. Less than 10% of the eyes had retinal involvement alone. The majority of patients experienced some degree of visual burden from the cancer: one-third of the group had logMAR visual acuity of 1.00 or greater in their worse-seeing eye, and another one-quarter had a LogMAR visual acuity of 0.40-0.90 in that eye.

Ocular specimens were used to make the diagnosis of VRL across 80% of the patient group, with cytological assessment of the vitreous being much more common (73%) than histopathological assessment of retinochoroidal tissue (15%). The rates of diagnostic cytokine assays (IL-10 or IL-10:IL-6 ratio) and tumor gene analyses (MYD88 gene mutation or IGH gene re-arrangement PCR or next generation sequencing) were 20% and 30%, respectively. Approximately two-thirds of diagnoses made using an ocular specimen required at least two tests. In 20%, indirect evidence was used to make the diagnosis, including CNS specimen testing and imaging.

Within 6 months of being diagnosed with VRL, 95% of the patients had received treatment. Approximately one-half had ocular treatment alone, one-quarter had extraocular treatment alone, and another one-quarter had both ocular and extraocular treatment. Intravitreal chemotherapy was the standard initial local treatment approach, with 95% of the treated eyes given intravitreal methotrexate injections (400 μg). Systemic chemotherapy was the standard extraocular treatment, usually given alone, but sometimes combined with intrathecal chemotherapy and/or brain irradiation.

The first report from the International Vitreoretinal B-Cell Lymphoma Registry has demonstrated the feasibility of a worldwide collection of clinical data into a registry, as well as the capacity to publish real-world insights for a relatively large number of patients with VRL within a short timeframe [75]. The project continues to collect information with the aim of providing evidence-based information about the outcomes of standard diagnostic and therapeutic practices for VRL to the medical and general communities [76].

Other uveitis masquerades

Neoplastic conditions

Besides VRL, a variety of other malignancies may masquerade as uveitis, including systemic lymphomas, primary uveal lymphoma, leukemias, multiple myeloma, uveal melanoma, and metastatic cancers [3]. Certain neoplasia tend to occur in childhood, such as retinoblastoma, medulloepithelioma, and post-transplantation lymphoproliferative disorder. Paraneoplastic syndromes are also possible uveitis mimics. Finally, it is important to consider that some cancer therapeutics may cause uveitis or a uveitis masquerade. Checkpoint inhibitors, such as pembrolizumab, nivolumab, and ipilimumab, have been associated with anterior uveitis, and BRAF/MEK inhibitor treatment can be complicated by an accumulation of subretinal fluid, often bilaterally and multifocally, as well as macular edema, that may mimic uveitis [77].

Lymphomas

Systemic Hodgkin lymphomas and, more commonly, non-Hodgkin lymphomas may involve the eye. Systemic non-Hodgkin lymphoma may mimic Vogt-Koyanagi-Harada (VKH) syndrome and present with bilateral exudative retinal detachment and neurological symptoms, retinochoroidal lesions, retinal vasculitis, scleritis, endophthalmitis, and uveitis-glaucoma-hyphema (UGH) syndrome [78-84]. Primary uveal lymphomas, which are usually non-Hodgkin B-cell lymphomas, may show pseudohypopyon, retinal vasculitis, choroidal infiltrates, choroidal thickening and detachment, infiltration of the optic nerve, and episcleral extension [85-87]. Primary uveal lymphomas are more indolent than VRL and may have a prolonged course [87].

Other hematological malignancies

The eye may be indirectly or directly affected in leukemia, with involvement of the anterior segment, vitreous, retinal, choroid, and optic disc. Retinal hemorrhages are the most common manifestation and may be secondary to leukemic cell infiltration or blood dyscrasias such as thrombocytopenia and anemia [88]. Ocular manifestations are present in approximately one-half of adults with acute leukemia, particularly the myeloid forms, and in approximately one-quarter of adults with chronic leukemia [89-91]. Ocular involvement is less common in children with leukemia, estimated at 17% in one study [90]. Diagnosis may require anterior chamber and vitreous biopsies [88]. Patients with multiple myeloma may also present with non-granulomatous anterior uveitis, retinal vasculitis, panuveitis, optic nerve infiltration, and posterior scleritis, among other features [92-94].

Uveal melanoma

Unlike iris melanoma, which is easily visualized by slit-lamp examination, ciliary body and choroidal melanomas are often identified late due to their hidden location. Consequently, they have an ominous prognosis, with 50% of patients developing metastasis, generally involving the liver [95]. Five percent of patients present with ocular inflammation, such as anterior and posterior uveitis, scleritis, and panophthalmitis [96-98]. The tumor may be amelanot-

ic, mimicking sarcoid or tubercular choroidal granulomas [99, 100]. Ocular ultrasound shows internal hollowness; FAF aids in the visualization of orange lipofuscin pigmentation; and FFA and ICGA may demonstrate a double circulation [101]. Enhanced depth imaging (EDI)-OCT findings may also support the diagnosis [101].

Intraocular metastases

Intraocular metastases mostly involve the choroid (88%), much less frequently the iris (9%) and the ciliary body (2%), and they are rare in the retina [102-104]. The main primary cancer sites are the lung and breast, followed by the kidney, gastrointestinal tract, melanoma, and others [102, 105]. The characteristic choroidal lesion is yellowish, placoid, and associated with subretinal fluid. Solitary yellow or white nodules are typical of iris and ciliary body metastases [102]. Over a third of patients do not have a previous history of cancer, and the invading tumor may cause iridocyclitis, pseudohypopyon, vitritis, retinitis, and infiltration of the optic disc [102-104, 106-109]. Ocular ultrasound, OCT, FFA and ICGA, whole-body PET scan, and MRI can be helpful in making this diagnosis [103].

Pediatric malignancies

Diffuse infiltrating retinoblastoma accounts for approximately 2% of retinoblastomas and may present with pseudohypopyon, hyphema, tumor seeds on the corneal endothelium, iris nodules, vitreous hemorrhage and cells, retinal infiltrates, panuveitis, and endophthalmitis [110-115]. Ocular ultrasound and MRI may not corroborate the diagnosis in this type of retinoblastoma, and aqueous humor analysis may be required [115].

Intraocular medulloepithelioma is a rare congenital tumor, generally arising from the ciliary body, and rarely from the optic nerve, retinal stalk, or retina [116]. It is usually malignant, but can be benign [117]. Signs include granulomatous anterior uveitis, hyphema, cataract, neovascular glaucoma, vitreous hemorrhage, seeding of tumor cells in the vitreous and retina, and retinal detachment [116-120]. Treatment frequently requires enucleation, due to the high rate of recurrence after local resection [117].

Post-transplantation lymphoproliferative disorder is a rare disease associated with Epstein-Barr virus infection and immunosuppression after transplant surgery [121, 122]. The risk of eye involvement is 20% within 3 years, manifesting as bilateral granulomatous uveitis, iris nodules, secondary angle-closure glaucoma, and subretinal masses [121-125].

Paraneoplastic syndromes

Ocular paraneoplastic syndromes are indirect manifestations of distant malignancies, associated with development of an immune response against retinal components or induced by tumor-expressed growth factors [126, 127]. Specific conditions include cancer-associated retinopathy, cancer-associated cone dysfunction, melanoma-associated retinopathy, paraneoplastic optic neuropathy, paraneoplastic vitelliform maculopathy, and bilateral diffuse uveal melanocytic proliferation. They usually present acutely or subacutely with symptoms like photosensitivity, scotomas, glare, photopsia, altered color vision, and night blindness [126, 127]. Cancer-associated retinopathy is the most well characterized of these conditions, causing bilateral anterior chamber cellular reaction, mild vitritis, retinal vascular sheathing and narrowing, RPE mottling, and a flat electroretinogram (ERG) reflecting widespread rod and cone dysfunction [128].

Non-neoplastic conditions

A broad spectrum of non-neoplastic eye diseases may present as uveitis. These conditions include, but are not limited to, various vascular diseases, central serous chorioretinopathy (CSC), inherited retinal diseases, rhegmatogenous retinal detachment, pigment dispersion syndrome, and intraocular foreign bodies. Juvenile xanthogranuloma and Coats disease are pediatric conditions that may also be misdiagnosed as uveitis.

Vascular diseases

Ocular ischemic syndrome results from chronic hypoperfusion due to carotid artery stenosis, usually greater than 90%. In this condition, anterior chamber cells, keratic precipitates (KPs), and posterior synechiae may occur [129]. A poorly reactive pupil, dilated episcleral vessels, corneal edema, cataracts, retinal arteriolar narrowing and venular dilatation, mid-peripheral retinal hemorrhages, retinal microaneurysms, and retinal and optic disc neovascularization are other features. Iris neovascularization is present in two-thirds of patients, and neovascular glaucoma in one-half [129]. The FFA showed late and patchy choroidal filling, increased retinal arteriovenous circulation times, late retinal vascular leakage, retinal capillary non-perfusion, and macular edema [129]. Ocular ischemic syndrome can be a rare manifestation of giant cell arteritis, and the potential for this underlying pathology should always be considered [130, 131].

Vascular diseases, such as diabetic retinopathy, retinal vascular occlusions, and hypertensive retinochoroidopathy secondary to preeclampsia, can mimic posterior uveitis due to clinical manifestations that include retinal exudation and general vascular leakage, choroidal thickening and grayish spots, and serous retinal detachment [1, 2, 132].

In some reports, patients with sickle cell disease have been referred with hypertensive panuveitis due to the presence of fine KPs, anterior chamber cells, vitreous haze, and yellow subretinal lesions [133, 134]. In fact, the cells in the anterior chamber are erythrocytes that migrate from the vitreous cavity, and focal areas of presumed retinitis and retinochoroiditis with overlying vitreous haze are salmon-patch hemorrhages associated with vitreous hemorrhage. Uveitis-glaucoma-hyphema syndrome has been reported in a patient with sickle cell trait [135].

Coats disease is a unilateral idiopathic telangiectatic retinal disease that usually affects boys. Retinal exudation can simulate retinitis, while vitreous hemorrhage may be interpreted as vitritis [136]. Fluorescein angiography,

OCT and OCT-angiography can assist the precise diagnosis [137]. Interestingly, Coats-like conditions have been described in association with pars planitis [138, 139] and choroiditis [140].

Central serous chorioretinopathy

Central serous chorioretinopathy occurs secondary to choroidal vascular hyperpermeability [141], but is frequently mistaken for uveitis, particularly VKH syndrome and sympathetic ophthalmia [2, 142, 143]. An accurate diagnosis is essential, since CSC is a potential complication of corticosteroid therapy, and initially may improve paradoxically after corticosteroid treatment by decreasing vascular inflammation secondary to chronic subretinal fluid [2]. Similarly, in uveal effusion syndrome, anterior chamber cells, optic disc swelling, serous retinal detachment, and a thickened choroid, plus increased intraocular pressure secondary to angle closure, may mimic VKH syndrome [2, 144].

Inherited retinal diseases

In one case series of patients misreferred for treatment of posterior uveitis, almost 10% had retinitis pigmentosa [143]. Patients with this disease may have a cellular vitreous, macular edema, and retinal vascular leakage, but also degenerative changes including retinal 'bone spicules', paravenous chorioretinal atrophy, and retinal arteriolar narrowing [143, 145, 146]. The opposite has also been reported, with forms of intraocular inflammation such as syphilitic uveitis masquerading as retinitis pigmentosa [146]. Night blindness, an abnormal ERG, and results of genetic testing corroborate the diagnosis [143]. Other inherited retinal diseases may also masquerade as uveitis, such as X-linked retinoschisis, rod-cone dystrophy, and pigmented paravenous retinochoroidal atrophy [2, 147]. In addition, hereditary transthyretin amyloidosis, an autosomal dominant multisystem disease, can cause vitreous amyloidosis that simulates vitritis, along with retinal neovascularization and vitreous hemorrhage due to increased vitreous levels of vascular endothelial growth factor [148-150]. Analysis of vitreous aspirates display amyloid deposits with yellow-green birefringence when stained with Congo red [150].

Rhegmatogenous retinal detachment

In rare instances, acute and chronic rhegmatogenous retinal detachment may be associated with severe panuveitis, hypotony, or increased intraocular pressure [151-153]. Retinal breaks in the pars plicata have been reported to cause an anterior chamber reaction and increased intraocular pressure [154]. Of note, these presentations should be differentiated from Schwartz-Matsuo syndrome, a term used to describe the association of aqueous cells and elevated intraocular pressure with rhegmatogenous retinal detachment [152].

Pigment dispersion syndrome

In pigment dispersion syndrome, pigment released from the iris and/or ciliary body pigment epithelium deposits on anterior segment structures, sometimes simulating acute anterior uveitis [155]. Bilateral acute depigmentation of the iris is an unrelated condition, in which pigment may be released from the iris stroma [156]. This condition has been associated with the use of moxifloxacin [157, 158] and SARS-CoV-2 viral infection [159].

Intraocular foreign bodies

An intraocular foreign body may be immediately identifiable, but when lodged in sites that are difficult to visualize clinically – such as the angle, iris, and pars plicata – the patient may present with anterior, intermediate, posterior, or pan- uveitis [160-166]. Ultrasound biomicroscopy, anterior segment OCT, and computed tomography are important tools for identifying an occult foreign body [167, 168].

Juvenile xanthogranuloma

Juvenile xanthogranuloma is a non-Langerhans cell histiocytosis that mostly affects the skin, but involves the eye in up to 10% of cases [169]. The iris is the most common location, leading to iris nodules, iris heterochromia, anterior uveitis, hyphema, and secondary glaucoma; however, choroidal and retinal pathology are also reported [169-174]. Although the condition almost always manifests in childhood, it has been reported in adults [175, 176]. Fine-needle aspiration biopsy of the iris is sometimes required to make the diagnosis [177].

Conclusion

Uveitis masquerade syndrome poses a considerable diagnostic challenge. Recognizing VRL and other neoplastic and non-neoplastic conditions that may mimic uveitis is essential for timely and appropriate management. A thorough knowledge of the clinical presentations, coupled with multimodal ocular imaging, and supported by targeted pathological, radiological, and electrophysiological investigations, can empower the ophthalmologist to differentiate uveitis masquerades from true uveitis.

References

1. **Rothova A, Groen F, Ten Berge J, et al.** Causes and clinical manifestations of masquerade syndromes in intraocular inflammatory diseases. Retina. 2021;41(11):2318-24.
2. **Hsu YR, Wang LU, Chen FT, et al.** Clinical manifestations and implications of nonneoplastic uveitis masquerade syndrome. Am J Ophthalmol. 2022;238:75-85.
3. **Grange LK, Kouchouk A, Dalal MD, et al.** Neoplastic masquerade syndromes in patients with uveitis. Am J Ophthalmol. 2014;157(3):526-31.
4. **Farrall AL, Smith JR.** Eye involvement in primary central nervous system lymphoma. Surv Ophthalmol. 2020;65(5):548-61.
5. **Coupland SE, Heimann H, Bechrakis NE.** Primary intraocular lymphoma: a review of the clinical, histopathological and molecular biological features. Graefes Arch Clin Exp Ophthalmol. 2004;242(11):901-13.
6. **Sobolewska B, Chee SP, Zaguia F, et al**. Vitreoretinal lymphoma. Cancers (Basel). 2021;13(16):3921.
7. **Cimino L, Chan CC, Shen D, et al.** Ocular involvement in nasal natural killer T-cell lymphoma. Int Ophthalmol. 2009;29(4):275-9.
8. **Coupland SE, Anastassiou G, Bornfeld N, et al.** Primary intraocular lymphoma of T-cell type: report of a case and

review of the literature. Graefes Arch Clin Exp Ophthalmol. 2005;243(3):189-97.
9. **Low A, Chow RC, Ee Ling A, Khaliddin N.** Primary T-cell vitreoretinal non-hodgkin lymphoma: a case report and literature review. Cureus. 2023;15(7):e41341.
10. **Alaggio R, Amador C, Anagnostopoulos I, et al.** The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-48.
11. **Riemersma SA, Jordanova ES, Schop RF, et al.** Extensive genetic alterations of the HLA region, including homozygous deletions of HLA class II genes in B-cell lymphomas arising in immune-privileged sites. Blood. 2000;96(10):3569-77.
12. **Farrall AL, Smith JR.** Incidence and survival of ocular diffuse large B-cell lymphomas. Acta Ophthalmol. 2023;101(3):e353-4.
13. **Levasseur SD, Wittenberg LA, White VA.** Vitreoretinal lymphoma: a 20-year review of incidence, clinical and cytologic features, treatment, and outcomes. JAMA Ophthalmol. 2013;131(1):50-5.
14. **Hong JT, Chae JB, Lee JY, et al.** Ocular involvement in patients with primary CNS lymphoma. J Neurooncol. 2011;102(1):139-45.
15. **Sjö LD.** Ophthalmic lymphoma: epidemiology and pathogenesis. Acta Ophthalmol. 2009;87(thesis1):1-20.
16. **Haldorsen IS, Krossnes BK, Aarseth JH, et al.** Increasing incidence and continued dismal outcome of primary central nervous system lymphoma in Norway 1989-2003: time trends in a 15-year national survey. Cancer. 2007;110(8):1803-14.
17. **Corn BW, Marcus SM, Topham A, et al**. Will primary central nervous system lymphoma be the most frequent brain tumor diagnosed in the year 2000? Cancer. 1997;79(12):2409-13.
18. **Jones NP, Pockar S, Steeples LR.** Changing trends in uveitis in the United Kingdom: 5000 consecutive referrals to a tertiary referral centre. Ocul Immunol Inflamm. 2023;31(5):921-6.
19. **Farrall AL, Smith JR.** Changing incidence and survival of primary central nervous system lymphoma in Australia: a 33-year national population-based study. Cancers (Basel). 2021;13(3):403.
20. **Menean M, Giuffrè C, Cicinelli MV, et al**. A comprehensive overview of diagnosis, imaging and treatment of vitreoretinal lymphoma. Eur J Ophthalmol (in press).
21. **von Roemeling C, Ferreri AJM, Soussain C, et al.** Targets and treatments in primary CNS lymphoma. Leuk Lymphoma (in press).
22. **Steffen J, Coupland SE, Smith JR.** Primary vitreoretinal lymphoma in HIV infection. Ocul Immunol Inflamm. 2021;29(3):621-7.
23. **Hochberg FH, Miller DC**. Primary central nervous system lymphoma. J Neurosurg. 1988;68(6):835-53.
24. **Ferreira LB, Furtado JM, Charng J, et al.** Prevalence of toxoplasmic retinochoroiditis in an Australian adult population: a community-based study. Ophthalmol Retina. 2022;6(10):963-8.
25. **Shiels MS, Pfeiffer RM, Besson C, et al.** Trends in primary central nervous system lymphoma incidence and survival in the U.S. Br J Haematol. 2016;174(3):417-24.
26. **Motomura Y, Yoshifuji K, Tachibana T, et al.** Clinical factors for central nervous system progression and survival in primary vitreoretinal lymphoma. Br J Haematol. 2024;204(4):1279-87.
27. **Guan WX, Peng XY.** Vitreoretinal lymphoma with intraretinal infiltration, simulating retinal necrosis. Ophthalmol Retina. 2024;8(6):571-8.
28. **Chan CC, Rubenstein JL, Coupland SE, et al**. Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma Collaborative Group symposium. Oncologist. 2011;16(11):1589-99.
29. **Pichi F, Dolz-Marco R, Francis JH, et al.** Advanced OCT analysis of biopsy-proven vitreoretinal lymphoma. Am J Ophthalmol. 2022;238:16-26.
30. **Chiu S, Mudhar HS, Harrison B, et al.** Cystoid macular oedema as a presenting feature of vitreoretinal lymphoma. Ocul Oncol Pathol. 2020;6(5):318-22.
31. **Hernández RF, Rodriguez JEM, Trecu MS, Bhatti MT.** Not everything is ischemic optic neuropathy. Surv Ophthalmol (in press).
32. **Zamani G, Hajipour A, Ganjeifar B, et al.** Intraocular lymphoma masquerading as unilateral hypopyon anterior uveitis: a case report. J Ophthalmic Inflamm Infect. 2022;12(1):25.
33. **Kvopka M, Lake SR, Smith JR**. Intraocular chemotherapy for vitreoretinal lymphoma: a review. Clin Exp Ophthalmol. 2020;48(2):240-8.
34. **Sehgal A, Pulido JS, Mashayekhi A, et al**. Diagnosing vitreoretinal lymphomas - an analysis of the sensitivity of existing tools. Cancers (Basel). 2022;14(3):598.
35. **Pulido JS, Johnston PB, Nowakowski GS, et al.** The diagnosis and treatment of primary vitreoretinal lymphoma: a review. Int J Retina Vitreous. 2018;4:18.
36. **Barajas RF, Politi LS, Anzalone N, et al**. Consensus recommendations for MRI and PET imaging of primary central nervous system lymphoma: guideline statement from the International Primary CNS Lymphoma Collaborative Group (IPCG). Neuro Oncol. 2021;23(7):1056-71.
37. **Carbonell D, Mahajan S, Chee S-P, et al.** Consensus recommendations for the diagnosis of vitreoretinal lymphoma. Ocul Immunol Inflamm. 2021;29(3):507-20.
38. **Yang X, Dalvin LA, Mazloumi M, et al.** Spectral domain optical coherence tomography features of vitreoretinal lymphoma in 55 eyes. Retina. 2021;41(2):249-58.
39. **Guan W, Xiao Y, Zhao H, et al.** Spectral-domain optical coherence tomography biomarkers in vitreoretinal lymphoma. Clin Exp Ophthalmol. 2023;51(2):144-53.
40. **Sen HN, Bodaghi B, Hoang PL, Nussenblatt R.** Primary intraocular lymphoma: diagnosis and differential diagnosis. Ocul Immunol Inflamm. 2009;17(3):133-41.
41. **Huang RS, Mihalache A, Popovic MM, et al.** Diagnostic methods for primary vitreoretinal lymphoma: a systematic review. Surv Ophthalmol. 2024;69(3):456-64.
42. **Dawson AC, Williams KA, Appukuttan B, Smith JR.** Emerging diagnostic tests for vitreoretinal lymphoma: a review. Clin Exp Ophthalmol. 2018;46(8):945-54.
43. **Raja H, Salomão DR, Viswanatha DS, Pulido JS.** Prevalence of MYD88 L265P mutation in histologically proven, diffuse large B-cell vitreoretinal lymphoma. Retina. 2016;36(3):624-8.
44. **Lobo A, Okhravi N, Adamson P, et al. P**rotocol for the use of polymerase chain reaction in the detection of intraocular large B-cell lymphoma in ocular samples. J Mol Diagn. 2007;9(1):113-21.
45. **Sugita S, Takase H, Sugamoto Y, et al**. Diagnosis of intraocular lymphoma by polymerase chain reaction analysis

and cytokine profiling of the vitreous fluid. Jpn J Ophthalmol. 2009;53(3):209-14.
46. **Wang Y, Shen D, Wang VM, et al.** Molecular biomarkers for the diagnosis of primary vitreoretinal lymphoma. Int J Mol Sci. 2011;12(9):5684-97.
47. **Frenkel S, Pe'er J, Kaufman R, et al.** The importance of cytokines analysis in the diagnosis of vitreoretinal lymphoma. Acta Ophthalmol. 2020;98(6):e668-73.
48. **Bonzheim I, Giese S, Deuter C, et al.** High frequency of MYD88 mutations in vitreoretinal B-cell lymphoma: a valuable tool to improve diagnostic yield of vitreous aspirates. Blood. 2015;126(1):76-9.
49. **Giuffrè C, Cicinelli MV, Marchese A, et al.** Clinical experience in a large cohort of patients with vitreoretinal lymphoma in a single center. Ocul Immunol Inflamm. 2021;29(3):472-8.
50. **Demirci H, Rao RC, Elner VM, et al.** Aqueous humor-derived MYD88 L265P mutation analysis in vitreoretinal lymphoma: a potential less invasive method for diagnosis and treatment response assessment. Ophthalmol Retina. 2023;7(2):189-95.
51. **Costopoulos M, Touitou V, Golmard JL, et al.** ISOLD: a new highly sensitive interleukin score for intraocular lymphoma diagnosis. Ophthalmology. 2016;123(7):1626-8.
52. **Kuo DE, Wei MM, Knickelbein JE, et al.** Logistic regression classification of primary vitreoretinal lymphoma versus uveitis by interleukin 6 and interleukin 10 levels. Ophthalmology. 2020;127(7):956-62.
53. **Nguyen NV, Khan F, Cannon A, et al.** Diagnosis of primary vitreoretinal lymphoma masquerading infectious retinitis by retinal biopsy. J Ophthalmic Inflamm Infect. 2024;14(1):8.
54. **Mastropasqua R, Thaung C, Pavesio C, et al.** The role of chorioretinal biopsy in the diagnosis of intraocular lymphoma. Am J Ophthalmol. 2015;160(6):1127-32.e1.
55. **Riemens A, Bromberg J, Touitou V, et al.** Treatment strategies in primary vitreoretinal lymphoma: a 17-center European collaborative study. JAMA Ophthalmol. 2015;133(2):191-7.
56. **Castellino A, Pulido JS, Johnston PB, et al**. Role of systemic high-dose methotrexate and combined approaches in the management of vitreoretinal lymphoma: a single center experience 1990-2018. Am J Hematol. 2019;94(3):291-8.
57. **Gao J, Peng X, Wang L.** Efficacy and safety of first-line combination therapy versus monotherapy for vitreoretinal lymphoma: a systematic review and meta-analysis. BMC Ophthalmol. 2023;23(1):477.
58. **Soussain C, Malaise D, Cassoux N.** Primary vitreoretinal lymphoma: a diagnostic and management challenge. Blood. 2021;138(17):1519-34.
59. **Smith JR, Rosenbaum JT, Wilson DJ, et al.** Role of intravitreal methotrexate in the management of primary central nervous system lymphoma with ocular involvement. Ophthalmology. 2002;109(9):1709-16.
60. **Habot-Wilner Z, Frenkel S, Pe'er J.** Efficacy and safety of intravitreal methotrexate for vitreo-retinal lymphoma – 20 years of experience. Br J Haematol. 2021;194(1):92-100.
61. **Sen HN, Chan CC, Byrnes G, et al.** Intravitreal methotrexate resistance in a patient with primary intraocular lymphoma. Ocul Immunol Inflamm. 2008;16(1):29-33.
62. **Larkin KL, Saboo US, Comer GM, et al.** Use of intravitreal rituximab for treatment of vitreoretinal lymphoma. Br J Ophthalmol. 2014;98(1):99-103.
63. **Kakkassery V, Heindl LM, Rokohl AC, et al.** Primary vitreoretinal lymphoma therapy monitoring: significant vitreous haze reduction after intravitreal rituximab. Neurosignals. 2021;29(S1):1-7.
64. **Dalvin LA, Lim LS, Ancona-Lezama D, et al**. Tumor control and visual acuity outcomes in vitreoretinal lymphoma with and without sub-retinal pigment epithelium infiltration: analysis of 125 eyes of 70 patients at a single ocular oncology center. Ophthalmol Retina. 2019;3(11):998-1005. (doi:10.1016/j.oret.2019.05.021)
65. **Guneri Beser B, Demirci H.** Intravitreal melphalan injection as a second-line local therapy in vitreoretinal lymphoma: case series. Retina. 2024;44(2):353-9.
66. **Isobe K, Ejima Y, Tokumaru S, et al.** Treatment of primary intraocular lymphoma with radiation therapy: a multi-institutional survey in Japan. Leuk Lymphoma. 2006;47(9):1800-5.
67. **de la Fuente MI, Alderuccio JP, Reis IM, et al.** Bilateral radiation therapy followed by methotrexate-based chemotherapy for primary vitreoretinal lymphoma. Am J Hematol. 2019;94(4):455-60.
68. **Frigault MJ, Dietrich J, Gallagher K, et al.** Safety and efficacy of tisagenlecleucel in primary CNS lymphoma: a phase 1/2 clinical trial. Blood. 2022;139(15):2306-15.
69. PDQ® Adult Treatment Editorial Board. PDQ Primary CNS Lymphoma Treatment. Bethesda, MD: National Cancer Institute. Updated 02/12/2022. Available at: https://www.cancer.gov/types/lymphoma/hp/primary-cns-lymphoma-treatment-pdq. Accessed 19/07/2024.
70. **Ahmed AH, Foster CS, Shields CL.** Association of disease location and treatment with survival in diffuse large B-cell lymphoma of the eye and ocular adnexal region. JAMA Ophthalmol. 2017;135(10):1062-8.
71. **Raval V, Binkley E, Aronow ME, et al.** Primary central nervous system lymphoma - ocular variant: an interdisciplinary review on management. Surv Ophthalmol. 2021;66(6):1009-20.
72. **Rath A, Salamon V, Peixoto S, et al.** A systematic literature review of evidence-based clinical practice for rare diseases: what are the perceived and real barriers for improving the evidence and how can they be overcome? Trials. 2017;18(1):556.
73. **Fend F, Ferreri AJ, Coupland SE**. How we diagnose and treat vitreoretinal lymphoma. Br J Haematol. 2016;173(5):680-92.
74. **Smith JR, Farrall AL, Davis JL, et al**. The International Vitreoretinal B-Cell Lymphoma Registry: a protocol paper. BMJ Open. 2022;12(7):e060701.
75. The International Vitreoretinal B-Cell Lymphoma Registry Investigator Group. Presentation, diagnostic testing and initial treatment of vitreoretinal lymphoma. Ophthalmol Retina. 2024;8(1):72-80.
76. **Farrall AL, Radford MHB, Smith JR.** Comments on: Ophthalmic registries for rare eye diseases. Indian J Ophthalmol. 2023;71(3):1055-6.
77. **Touhami S, Audo I, Terrada C, et al.** Neoplasia and intraocular inflammation: from masquerade syndromes to immunotherapy-induced uveitis. Prog Retin Eye Res. 2019;72:100761.
78. **Gaucher D, Bodaghi B, Charlotte F, et al.** MALT-type B-cell lymphoma masquerading as scleritis or posterior uveitis. J Fr Ophtalmol. 2005;28(1):31-8.

79. **Sukon N, Tesavibul N, Choopong P, et al.** Extranodal natural killer/T-cell lymphoma presenting as hypopyon panuveitis: a case report. BMC Ophthalmol. 2022;22(1):46.
80. **Gauthier AC, Nguyen A, Munday WR, et al.** Anterior chamber non-hodgkin lymphoma of the iris masquerading as uveitis-glaucoma-hyphema syndrome. Ocul Oncol Pathol. 2016;2(4):230-3.
81. **Moussa K, Begaj T, Ma K, et al.** Systemic lymphoma masquerading as Vogt-Koyanagi-Harada syndrome: report of a case with multimodal imaging and histopathology. Am J Ophthalmol Case Rep. 2022;27:101643.
82. **Mathai A, Lall A, Jain R, Pathengay A.** Systemic non-Hodgkin's lymphoma masquerading as Vogt-Koyanagi-Harada disease in an HIV-positive patient. Clin Exp Ophthalmol. 2006;34(3):280-2.
83. **Panda P, Forooghian F, Goodglick T, et al.** Orbital lymphoma masquerading as panuveitis. Ocul Immunol Inflamm. 2010;18(3):181-3.
84. **Sonne SJ, Shieh WS, Srivastava SK, Smith BT**. Lymphoma masquerading as occlusive retinal vasculitis: a case study. Am J Ophthalmol Case Rep. 2020;19:100777.
85. **Rasić DM, Stanković Z, Terzić T, et al**. Primary extranodal marginal zone lymphoma of the uvea associated with massive diffuse epibulbar extension and focal infiltration of the optic nerve and meninges, clinically presented as uveitis masquerade syndrome: a case report. Med Oncol. 2010;27(3):1010-6.
86. **Wu RX, Yang T, Xu ZP.** Primary uveal lymphoma effectively treated with radiotherapy: a case report and literature review. J South Med Univ. 2018;38(4):371-4.
87. **Aronow ME, Portell CA, Sweetenham JW, Singh AD.** Uveal lymphoma: clinical features, diagnostic studies, treatment selection, and outcomes. Ophthalmology. 2014;121(1):334-41.
88. **Vishnevskia-Dai V, Sella King S, Lekach R, et al.** Ocular manifestations of leukemia and results of treatment with intravitreal methotrexate. Sci Rep. 2020;10(1):1994.
89. **Hafeez MU, Ali MH, Najib N, et al.** Ophthalmic manifestations of acute leukemia. Cureus. 2019;11(1):e3837.
90. **Reddy SC, Jackson N, Menon BS.** Ocular involvement in leukemia--a study of 288 cases. Ophthalmologica. 2003;217(6):441-5.
91. **Koshy J, John MJ, Thomas S, et al.** Ophthalmic manifestations of acute and chronic leukemias presenting to a tertiary care center in India. Indian J Ophthalmol. 2015;63(8):659-64.
92. **Guerriero S, Piscitelli D, Ciracì L, et al.** Hypertensive uveitis as a feature of multiple myeloma. Ocul Immunol Inflamm. 2010;18(2):104-6.
93. **Yew YC, Nurul-Fatin FS, Norazita AT.** Multiple myeloma masquerading as panuveitis in a middle-aged woman. Med J Malaysia. 2017;72(6):376-7.
94. **Singh RB, Singhal S, Sinha S, et al.** Ocular complications of plasma cell dyscrasias. Eur J Ophthalmol. 2023;33(5):1786-800.
95. **Buder K, Gesierich A, Gelbrich G, Goebeler M.** Systemic treatment of metastatic uveal melanoma: review of literature and future perspectives. Cancer Med. 2013;2(5):674-86.
96. **Kafkala C, Daoud YJ, Paredes I, Foster CS.** Masquerade scleritis. Ocul Immunol Inflamm. 2005;13(6):479-82.
97. **Fraser DJ Jr, Font RL.** Ocular inflammation and hemorrhage as initial manifestations of uveal malignant melanoma. Incidence and prognosis. Arch Ophthalmol. 1979;97(7):1311-4.
98. **Abdel-Aty A, Linderman WL, Kombo N, et al.** Necrotic uveal melanoma mimics orbital cellulitis: a review. Ocul Oncol Pathol. 2022;8(1):1-8.
99. **Berkowitz ST, Brock AL, Reichstein DA.** An amelanotic choroidal melanoma arising in a young man with tattoo-associated sarcoidosis. Am J Ophthalmol Case Rep. 2020;18:100655.
100. **Welch RJ, Newman JH, Honig SE, et al.** Choroidal amelanotic tumours: clinical differentiation of benign from malignant lesions in 5586 cases. Br J Ophthalmol. 2020;104(2):194-201.
101. **Kaliki S, Shields CL.** Uveal melanoma: relatively rare but deadly cancer. Eye. 2017;31(2):241-57.
102. **Shields CL, Shields JA, Gross NE, et al.** Survey of 520 eyes with uveal metastases. Ophthalmology. 1997;104(8):1265-76.
103. **Nguyen QL, Reynolds SB, Piri N, Rivas Perez HL.** Ophthalmic anterior segment metastasis masquerading as uveitis. BMJ Case Rep. 2021;14(3):e236405.
104. **Shields CL, McMahon JF, Atalay HT, et al.** Retinal metastasis from systemic cancer in 8 cases. JAMA Ophthalmol. 2014;132(11):1303-8.
105. **Shields CL, Welch RJ, Malik K, et al.** Uveal metastasis: clinical features and survival outcome of 2214 tumors in 1111 patients based on primary tumor origin. Middle East Afr J Ophthalmol. 2018;25(2):81-90.
106. **Liu W, Ma W, Guo R, Ji J.** Snowflakes in the eye - an uncommon presentation of iris metastasis of esophageal carcinoma and review of literature. Ocul Immunol Inflamm. 2022;30(7-8):1568-71.
107. **Soheilian M, Mirbabai F, Shahsavari M, et al.** Metastatic cutaneous melanoma to the vitreous cavity masquerading as intermediate uveitis. Eur J Ophthalmol. 2002;12(4):324-7.
108. **Ozawa H, Usui Y, Takano Y, et al.** Iris metastasis as the initial presentation of metastatic esophageal cancer diagnosed by fine needle aspiration biopsy: a case report. Medicine. 2021;100(22):e26232.
109. **Shields JA, Shields CL, Singh AD.** Metastatic neoplasms in the optic disc: the 1999 Bjerrum Lecture: part 2. Arch Ophthalmol. 2000;118(2):217-24.
110. **Bhatnagar R, Vine AK.** Diffuse infiltrating retinoblastoma. Ophthalmology. 1991;98(11):1657-61.
111. **Girard B, Le Hoang P, D'Hermies F, et al.** Diffuse infiltrating retinoblastoma. J Fr Ophtalmol. 1989;12(5):369-81.
112. **Shields CL, Ghassemi F, Tuncer S, et al.** Clinical spectrum of diffuse infiltrating retinoblastoma in 34 consecutive eyes. Ophthalmology. 2008;115(12):2253-8.
113. **Domínguez-Varela IA, Aguilera-Partida JA, Dalvin LA, et al.** Retinoblastoma in an older Hispanic child masquerading as pars planitis: a case report. Eur J Ophthalmol. 2022;32(3):NP71-4.
114. **Panigrahi A, Singh A, Gupta S, Gupta V.** Diffuse infiltrating retinoblastoma: a panuveitis masquerade. Can J Ophthalmol. 2023;58(6):e246-7.
115. **Traine PG, Schedler KJ, Rodrigues EB.** Clinical presentation and genetic paradigm of diffuse infiltrating retinoblastoma: a review. Ocul Oncol Pathol. 2016;2(3):128-32.
116. **Font RL, Rishi K.** Diffuse retinal involvement in malignant nonteratoid medulloepithelioma of ciliary body in an adult. Arch Ophthalmol. 2005;123(8):1136-8.
117. **Shields JA, Eagle RC Jr, Shields CL, Potter PD.** Congenital neoplasms of the nonpigmented ciliary epithelium (medulloepithelioma). Ophthalmology. 1996;103(12):1998-2006.

118. **Kanavi MR, Soheilian M, Kamrava K, Peyman GA.** Medulloepithelioma masquerading as chronic anterior granulomatous uveitis. Can J Ophthalmol. 2007;42(3):474-6.
119. **Chua J, Muen WJ, Reddy A, Brookes J.** The masquerades of a childhood ciliary body medulloepithelioma: a case of chronic uveitis, cataract, and secondary glaucoma. Case Rep Ophthalmol Med. 2012;2012:493493.
120. **Tadepalli SH, Shields CL, Shields JA, Honavar SG**. Intraocular medulloepithelioma - a review of clinical features, DICER 1 mutation, and management. Indian J Ophthalmol. 2019;67(6):755-62.
121. **Cook T, Grostern RJ, Barney NP, et al.** Posttransplantation lymphoproliferative disorder initially seen as iris mass and uveitis. Arch Ophthalmol. 2001;119(5):768-70.
122. **Rohrbach JM, Kröber SM, Teufel T, et al.** EBV-induced polymorphic lymphoproliferative disorder of the iris after heart transplantation. Graefes Arch Clin Exp Ophthalmol. 2004;242(1):44-50.
123. **Cho AS, Holland GN, Glasgow BJ, et al.** Ocular involvement in patients with posttransplant lymphoproliferative disorder. Arch Ophthalmol. 2001;119(2):183-9.
124. **O'Hara M, Lloyd WC 3rd, Scribbick FW, Gulley ML.** Latent intracellular Epstein-Barr Virus DNA demonstrated in ocular posttransplant lymphoproliferative disorder mimicking granulomatous uveitis with iris nodules in a child. J AAPOS. 2001;5(1):62-3.
125. **Iu LP, Yeung JC, Loong F, Chiang AK.** Successful treatment of intraocular post-transplant lymphoproliferative disorder with intravenous rituximab. Pediatr Blood Cancer. 2015;62(1):169-72.
126. **Przeździecka-Dołyk J, Brzecka A, Ejma M, et al.** Ocular paraneoplastic syndromes. Biomedicines. 2020;8(11):490.
127. **Sarkar P, Mehtani A, Gandhi HC, et al.** Paraneoplastic ocular syndrome: a pandora's box of underlying malignancies. Eye (Lond). 2022;36(7):1355-67.
128. **Shildkrot Y, Sobrin L, Gragoudas ES.** Cancer-associated retinopathy: update on pathogenesis and therapy. Semin Ophthalmol. 2011;26(4-5):321-8.
129. **Terelak-Borys B, Skonieczna K, Grabska-Liberek I.** Ocular ischemic syndrome - a systematic review. Med Sci Monit. 2012;18(8):RA138-44.
130. **Hamed LM, Guy JR, Moster ML, Bosley T.** Giant cell arteritis in the ocular ischemic syndrome. Am J Ophthalmol. 1992;113(6):702-5.
131. **Hayreh SS, Podhajsky PA, Zimmerman B.** Ocular manifestations of giant cell arteritis. Am J Ophthalmol. 1998;125(4):509-20.
132. **Fukui A, Tanaka H, Terao N, et al.** Changes in choroidal thickness and structure in preeclampsia with serous retinal detachment. J Clin Med. 2023;12(2):609.
133. **Makhoul D, Kolyvras N, Benchekroun S, et al.** Sickle cell crisis presenting as a masquerade syndrome complicated by macular ischemia. Ocul Immunol Inflamm. 2010;18(3):178-80.
134. **Campagnoli TR, Krawitz BD, Lin J, et al.** Salmon patch-associated vitreous hemorrhage in non-proliferative sickle cell retinopathy masquerading as infectious uveitis. Am J Ophthalmol Case Rep. 2022;25:101329.
135. **Sharma A, Ibarra MS, Piltz-Seymour JR, Syed NA.** An unusual case of uveitis-glaucoma-hyphema syndrome. Am J Ophthalmol. 2003;135(4):561-3.
136. **Lee DY, Chen SC, Sheu SJ.** Coats disease masquerading as acute posterior uveitis in a young adult. Kaohsiung J Med Sci. 2022;38(2):178-9.
137. **Brockmann C, Löwen J, Schönfeld S, et al.** Vascular findings in primarily affected and fellow eyes of middle-aged patients with Coats' disease using multimodal imaging. Br J Ophthalmol. 2021;105(10):1444.
138. **Chen PP, Chong LP.** Coats'-like response in a patient with pars planitis. Br J Ophthalmol. 1996;80(7):675-6.
139. **Suh DW, Pulido JS, Jampol LM, et al.** Coats'-like response in pars planitis. Retina. 1999;19(1):79-80.
140. **Verma S, Bhatia I, Banerjee M, Kumar V.** Coats like response in healed choroiditis. Ocul Immunol Inflamm. 2022;30(6):1527-9.
141. **Pauleikhoff LJB, Diederen RMH, Chang-Wolf JM, et al.** Choroidal hyperpermeability patterns correlate with disease severity in central serous chorioretinopathy: CERTAIN study report 2. Acta Ophthalmol (in press).
142. **Tandon R, Vanathi M, Verma L, Bharadwaj A.** Central serous retinopathy masquerading as sympathetic ophthalmia. Eye (Lond). 2003;17(5):666-7.
143. **Nagpal A, Biswas J.** Pseudouveitis--analysis of cases misdiagnosed as posterior uveitis. Ocul Immunol Inflamm. 2006;14(1):13-20.
144. **Liu Q, Hemarat K, Kayser DL, Stewart JM**. A case of posterior uveal effusion syndrome masquerading as uveitis. Retin Cases Brief Rep. 2017;11(Suppl 1):S124-7.
145. **Yoshida N, Ikeda Y, Notomi S, et al.** Clinical evidence of sustained chronic inflammatory reaction in retinitis pigmentosa. Ophthalmology. 2013;120(1):100-5.
146. **Thenappan A, Nanda A, Lee CS, Lee SY.** Retinitis pigmentosa masquerades: case series and review of the literature. J Clin Med. 2023;12(17):5620. (doi:10.3390/jcm12175620)
147. **Mautone L, Birtel J, Atiskova Y, et al.** X-linked retinoschisis masquerading uveitis. J Clin Med. 2023;12(11):3729.
148. **Terrier B, Colombat M, Beugnet C, et al.** Vitreous amyloidosis with autonomic neuropathy of the digestive tract associated with a novel transthyretin p.Gly87Arg variant in a Bangladeshi patient: a case report. J Med Case Rep. 2017;11(1):222.
149. **Treviño-Herrera AB, Bustamante-Vargas AP, Lisker-Cervantes A, et al.** Vitreous involvement as initial presentation of hereditary transthyretin amyloidosis related to the rare TTR Ile107Met (p.Ile127Met) pathogenic variant. Ophthalmic Genet. 2022;43(3):413-9.
150. **O'Hearn TM, Fawzi A, He S, et al.** Early onset vitreous amyloidosis in familial amyloidotic polyneuropathy with a transthyretin Glu54Gly mutation is associated with elevated vitreous VEGF. Br J Ophthalmol. 2007;91(12):1607-9.
151. **Lim WK, Chee SP.** Retinal detachment in atopic dermatitis can masquerade as acute panuveitis with rapidly progressive cataract. Retina. 2004;24(6):953-6.
152. **Joye AS, Bhisitkul RB, Pereira DDS, Gonzales JA**. Rhegmatogenous retinal detachment masquerading as exudative panuveitis with intense anterior chamber inflammatory reaction. American J Ophthalmol Case Rep. 2020;18:100618.
153. **Jarrett WH 2nd.** Rhematogenous retinal detachment complicated by severe intraocular inflammation, hypotony, and choroidal detachment. Trans Am Ophthalmol Soc. 1981;79:664-83.
154. **Uemura A.; Uto M.** Bilateral retinal detachment with large breaks of pars plicata associated with coloboma lentis and ocular hypertension. Jpn J Ophthalmol. 1992;36(1):97-102.
155. **Zeppieri M.** Pigment dispersion syndrome: a brief overview. J Clin Transl Res. 2022;8(5):344-50.

156. **Tugal-Tutkun I, Urgancioglu M.** Bilateral acute depigmentation of the iris. Graefes Arch Clin Exp Ophthalmol. 2006;244(6):742-6.
157. **Wefers Bettink-Remeijer M, Brouwers K, van Langenhove L, et al.** Uveitis-like syndrome and iris transillumination after the use of oral moxifloxacin. Eye (Lond). 2009;23(12):2260-2.
158. **Gonul S, Bozkurt B.** Bilateral acute iris transillumination (BAIT) initially misdiagnosed as acute iridocyclitis. Arq Bras Oftalmol. 2015;78(2):115-7.
159. **Niedzwiecka E, Cantó San Miguel MP, Gonzalez Herrera M, Sánchez Rodriguez-Acosta I.** Bilateral acute depigmentation of the iris (BADI) following Covid-19 infection. Ocul Immunol Inflamm. 2023;31(6):1230-1.
160. **Saifaoui N, Mnasri H, Dubiez M, El-Belhadji M.** Case report: Intraocular foreign body masquerading as toxoplasma chorioretinitis. J Fr Ophtalmol. 2018;41(3):e113-5.
161. **Politis M, Rosin B, Amer R.** Ocular siderosis subsequent to a missed pars plana metallic foreign body that masqueraded as refractory intermediate uveitis. Ocul Immunol Inflamm. 2018;26(4):598-600.
162. **Yeh S, Ralle M, Phan IT, et al.** Occult intraocular foreign body masquerading as panuveitis: inductively coupled mass spectrometry and electrophysiologic analysis. J Ophthalmic Inflamm Infect. 2012;2(2):99-103.
163. **Mahmoud A, Messaoud R, Abid F, et al**. Anterior segment optical coherence tomography and retained vegetal intraocular foreign body masquerading as chronic anterior uveitis. J Ophthalmic Inflamm Infect. 2017;7(1):13.
164. **Alexandrakis G, Balachander R, Chaudhry NA, Filatov V.** An intraocular foreign body masquerading as idiopathic chronic iridocyclitis. Ophthalmic Surg Lasers. 1998;29(4):336-7.
165. **Kamath MG, Nayak IV, Satish KR.** Case report: intraocular foreign body in the angle masquerading as uveitis. Indian J Ophthalmol. 1991;39(3):138-9.
166. **Stangos AN, Pournaras CJ, Petropoulos IK.** Occult anterior-chamber metallic fragment post-phacoemulsification masquerading as chronic recalcitrant postoperative inflammation. Am J Ophthalmol. 2005;139(3):541-2.
167. **Wylegala E, Dobrowolski D, Nowińska A, Tarnawska D.** Anterior segment optical coherence tomography in eye injuries. Graefes Arch Clin Exp Ophthalmol. 2009;247(4):451-5.
168. **Cheng T, Zhao H, Chen Q, et al.** Efficiency of different imaging methods in detecting ocular foreign bodies. Med Phys. 2024;51(4):3124-9.
169. **Esen Baris M, Ciftci MD, Palamar M, Guven Yilmaz S**. Iris juvenile xanthogranuloma presenting with hypopyon. Ocul Immunol Inflamm. 2022;30(7-8):2014-6.
170. **DeBarge LR, Chan CC, Greenberg SC, et al.** Chorioretinal, iris, and ciliary body infiltration by juvenile xanthogranuloma masquerading as uveitis. Surv Ophthalmol. 1994;39(1):65-71.
171. **Zamir E, Wang RC, Krishnakumar S, et al.** Juvenile xanthogranuloma masquerading as pediatric chronic uveitis: a clinicopathologic study. Surv Ophthalmol. 2001;46(2):164-71.
172. **Lahri B, Hussain Z, Gupta N, et al**. Bilateral anterior uveitis as a presenting feature of juvenile xanthogranuloma in a neonate. Am J Ophthalmol Case Rep. 2023;31:101867.
173. **Longmuir S, Dumitrescu A, Kwon Y, et al.** Juvenile xanthogranulomatosis with bilateral and multifocal ocular lesions of the iris, cornealscleral limbus, and choroid. J AAPOS. 2011;15(6):598-600.
174. **Labalette P, Guilbert F, Jourdel D, et al.** Bilateral multifocal uveal juvenile xanthogranuloma in a young boy with systemic disease. Graefes Arch Clin Exp Ophthalmol. 2002;240(6):506-9.
175. **Parmley VC, George DP, Fannin LA.** Juvenile xanthogranuloma of the iris in an adult. Arch Ophthalmol. 1998;116(3):377-9.
176. **Sukavatcharin S, Cursino S, Li G, et al.** Xanthogranuloma of the iris simulating melanoma in an adult. Am J Ophthalmol. 2007;143(3):529-31.
177. **Karcioglu ZA, Mullaney PB.** Diagnosis and management of iris juvenile xanthogranuloma. J Pediatr Ophthalmol Strabismus. 1997;34(1):44-51.

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Abbreviation. *AIDS – acquired immunodeficiency syndrome, CAR – chimeric antigen receptor, CNS – central nervous system, CSC – central serous chorioretinopathy, EDI – enhanced depth imaging, ERG – electroretinogram, FAF – fundus autofluorescence, FFA – fundus fluorescein angiography, HIV – human immunodeficiency virus, ICGA – indocyanine green angiography, IL-10 – interleukin-10, ISOLD – Interleukin Score for intraOcular Lymphoma Diagnosis, KP – keratic precipitate, MRI – magnetic resonance imaging, PCNSL – primary central nervous system lymphoma, PCR – polymerase chain reaction, RPE – retinal pigment epithelial, SD-OCT – spectral domain-optical coherence tomography, UGH – uveitis-glaucoma-hyphema, VKH – Vogt-Koyanagi-Harada, VRL – vitreoretinal lymphoma.*