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].

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 practices 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 amelanotic, 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 cir-

culation [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.

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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.*