Intraocular Lymphoma

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Abstract

Intraocular lymphoma encompasses a heterogeneous spectrum of lymphoid neoplasms. These are extranodal, non-Hodgkin's lymphomas, and the majority are of B-cell origin. Historically, there have been several nomenclature and classification systems used to describe these intraocular neoplasms. At present, most experts classify these entities based upon site of involvement and whether the lymphoma is primary or secondary. Intraocular lymphoma can therefore be subdivided into: primary vitreoretinal lymphoma (PVRL), primary uveal lymphoma, and secondary intraocular manifestations of systemic lymphoma. PVRL is a high-grade, aggressive malignancy associated with central nervous system involvement and poor survival rates despite treatment. Primary uveal lymphoma is predominantly a low-grade, indolent lymphoma which may cause significant ocular morbidity, but carries an overall favorable prognosis for survival. As all forms of intraocular lymphoma can masquerade as infectious and inflammatory conditions, establishing the diagnosis can be challenging. Clinical features alone can be non-specific at times, therefore ancillary ophthalmic imaging and systemic imaging studies are invaluable in facilitating the diagnostic work-up for individuals with suspected intraocular lymphoma. Familiarity with the clinical features as well as a comprehensive understanding of the unique patterns of systemic involvement for each form of intraocular lymphoma is important in the management of these diseases.

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15.1 Introduction

Intraocular lymphoma can be broadly classified based upon site of involvement and whether the disease is primary or secondary. Intraocular lymphoma can be further subdivided into: primary vitreoretinal lymphoma, primary uveal lymphoma, and secondary intraocular manifestations of systemic lymphoma (Table 15.1). The vast majority are non-Hodgkin's B-cell lymphomas (rare T-cell variants exist). The distinction between forms of intraocular lymphoma is important, as the differential diagnosis, patterns of systemic involvement, and treatment strategies vary for each entity. Intraocular lymphoma frequently masquerades as inflammatory and infectious processes, resulting in delay in diagnosis and initiation of treatment. In the

Table 15.1 Clinical and imaging features of intraocular lymphoma

Lymphoma	Clinical features	Subtype	Imaging findings
Primary vitreoretinal lymphoma	Frequently bilateral vitreous cells retinal, sub-RPE infiltrates CNS involvement	High-grade DLBCL (majority)	FA: granular "leopard-spot" appearance
			ICG: hypofluorescent lesions in late phase
			OCT: sub-RPE infiltration, absence of macular edema
			FAF: autofluorescence in some cases
			MRI brain: potential CNS involvement
Primary uveal lymphoma	M>F usually unilateral clear vitreous diffuse choroidal thickening exudative retinal detachment	Low-grade EMZL (majority)	FA: foci of hyperfluorescence, staining in the late phase
			ICG: hypofluorescence corresponding to observed infiltrates
			OCT: choroidal thickening, "sea-sick" appearance
			USG: choroidal thickening, low internal reflectivity, extrascleral extension in some cases
			Systemic imaging: excludes potential systemic involvement
Secondary intraocular lymphoma	Variable: choroidal thickening iris infiltrates pseudohypopyon vitreous cells	Dependent upon systemic NHL	Majority demonstrate choroidal involvement with imaging findings similar to uveal lymphoma

RPE retinal pigment epithelium, *CNS* central nervous system, *DLBCL* diffuse large B-cell lymphoma, *FA* fluorescein angiography, *ICG* indocyanine green angiography, *OCT* optical coherence tomography, *FAF* fundus autofluorescence, *MRI* magnetic resonance imaging, *M* males, *F* females, *EMZL* extranodal marginal zone lymphoma, *USG* ultrasonography, *NHL* non-Hodgkin's lymphoma

following chapter, a discussion follows regarding each of the major forms of intraocular lymphoma, including a description of the typical clinical features, recommended examination and ancillary imaging investigations, patterns of systemic involvement, treatment strategies, and prognosis.

15.2 Primary Vitreoretinal Lymphoma

Primary vitreoretinal lymphoma (PVRL) is considered a variant of primary central nervous system lymphoma (PCNSL), with predominantly vitreoretinal involvement. PVRL has previously been termed primary intraocular lymphoma (PIOL or PCNSL-O), "reticulum cell sarcoma" and "microgliomatosis" [1, 2]. As the vitreous and retina are the major site of involvement, PVRL is the preferred name for this entity, particularly as earlier descriptors misleadingly suggest that the disease arises from reticulum or microglial cells.

PCNSL is an aggressive diffuse large B-cell lymphoma associated with poor survival (ranging from 1 to 8 years) depending upon factors such as Karnofsky performance status and age [3]. PCNSL originates in the brain parenchyma, leptomeninges, spinal cord, and the eyes [4]. In the United States, the age-adjusted incidence of PCNSL is 4.8 per million population [5]. As PVRL occurs as a subset of PCNSL, the exact incidence is unknown due to the small number of cases. In the United States, between 1999 and 2002, there were approximately 100 reported cases of PVRL which illustrates the rare nature of this disease [6]. Co-existence of PVRL with PCNSL is variable, with CNS disease manifesting prior to, at the same time of ocular presentation, or following ocular diagnosis. Of those with PCNSL, approximately 25% will have PVRL at the time of CNS diagnosis [7]. In contrast, 56–90% of individuals initially diagnosed PVRL will subsequently develop central nervous system within 8–29 months of follow-up [8–13]. The peak incidence of PVRL is in the fifth to seventh decades in immunocompetent individuals. In immunocompromised patients, such as those with autoimmune deficiency syndrome (AIDS), PVRL may occur at a younger age. The most common presenting symptoms are painless decrease in vision and floaters [10]. Those who are asymptomatic may be diagnosed during routine ophthalmic screening in the setting of known PCNSL. For PCNSL, common presenting symptoms may include personality changes or cognitive decline. Seizures are an unusual feature of this form of lymphoma.

15.2.1 Clinical Features

The hallmark clinical feature of PVRL is vitreous cells (Fig. 15.1a). Unlike more typical cases of posterior uveitis, lymphoma cells within the vitreous cavity may appear larger, and form sheets and/or clusters resulting in an "aurora borealis" appearance [12]. Vitreous haze may be present. Yellow-to white retinal, and particularly sub-retinal pigment epithelium (sub-RPE) infiltrates are characteristic. Bilateral disease is present in 80% of cases, and is typically asymmetric [8]. Anterior

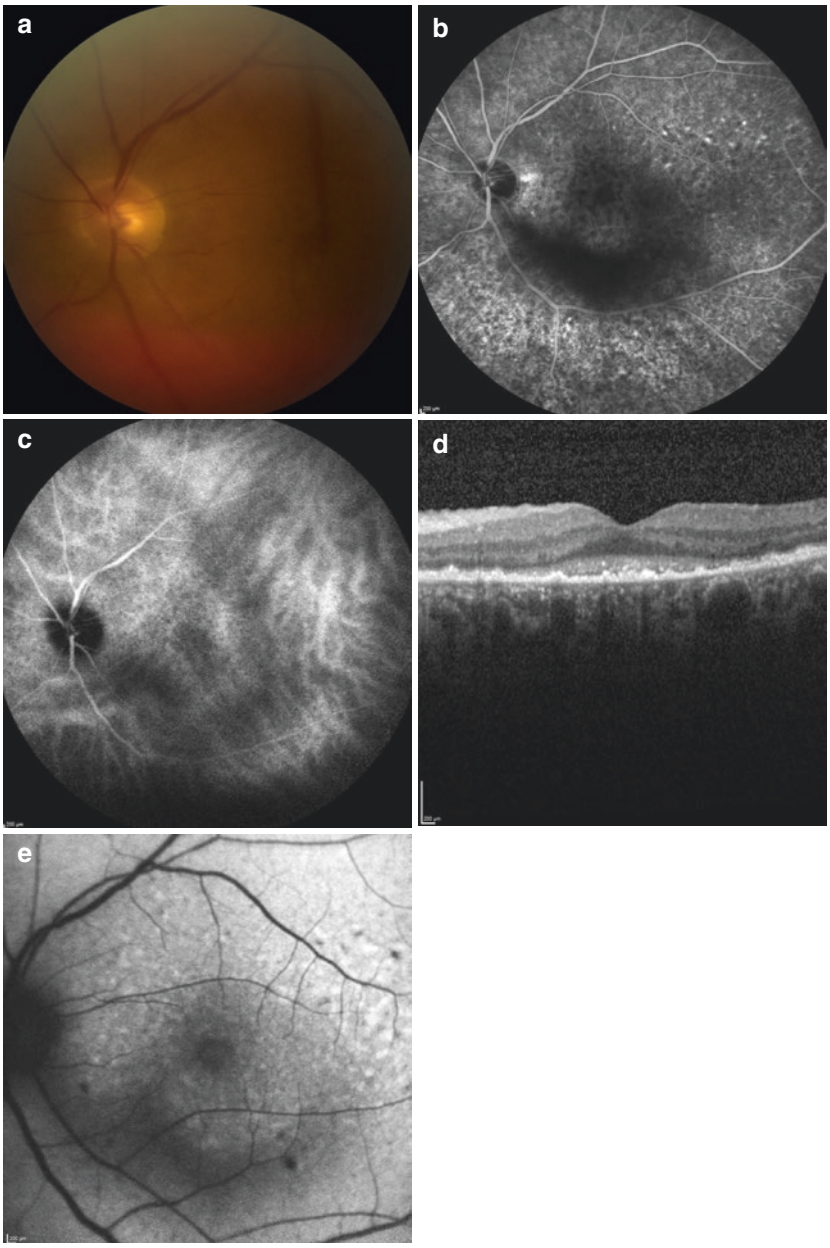

Fig. 15.1 A 64-year-old male presented with vitritis and decreased vision unresponsive to steroids. Soon after ocular presentation, he developed central nervous systemic lesions. Biopsy confirmed diffuse large B-cell lymphoma. Fundus photograph of the left eye demonstrates vitreous haze and mild vitreous cells (**a**). Fluorescein angiogram demonstrates a "leopard spot" appearance of the fundus (**b**). Indocyanine green angiography reveals hypofluorescent spots in the late phase of the angiogram (**c**). Optical coherent tomography (OCT) shows hyperreflective, nodular, infiltrate beneath the retinal pigment epithelium (**d**). Fundus autofluorescence demonstrates subtle autofluorescence corresponding to these infiltrates (**e**)

segment manifestations such as aqueous cells, keratic precipitates, and iris nodules have been reported, however these findings are non-specific [14]. Other less frequently reported features include perivasculitis [10], retinal artery occlusion [15], exudative retinal detachment [16], multifocal "punched-out" lesions of the retinal pigment epithelium (RPE) [17], disc edema, and optic atrophy [18]. Fundus photography is helpful to document the initial clinical findings and response to therapy.

15.2.2 Differential Diagnosis

Delayed diagnosis is common in PVRL due to the non-specific ophthalmic manifestations, many of which masquerade as inflammatory, infectious, and other neoplastic entities. In a series of 32 individuals with histologically confirmed PVRL, the average time between ocular symptoms and establishment of the diagnosis was 21 months [11]. The differential diagnosis includes such entities as sarcoidosis, syphilis, tuberculosis, birdshot retinochoroidopathy, multifocal chorioretinitis, acute posterior multifocal placoid pigmentary epitheliopathy (APMPPE), punctate inner choroidopathy, and serpiginous choroiditis [19]. When subretinal or choroidal involvement is present, other neoplastic entities such as metastases and potentially amelanotic melanoma should be considered. In immunocompromised patients, infections such as cytomegalovirus, toxoplasmosis, and pneumocystis choroiditis should be included in the differential diagnosis.

15.2.3 Fluorescein Angiography (FA)

The FA features of PVRL are typical and include: granularity giving rise to a "leopard spot" appearance to the fundus (Fig. 15.1b), blocked fluorescence, and late staining [20]. These features correlate histopathologically with clinically observed lymphoma cells located between the RPE and Bruch's membrane [20]. In contrast, fluorescein angiographic features which are common in posterior uveitis such as perivascular staining, vascular leakage, and petaloid leakage (cystoid macular edema) rarely occur in PVRL [20]. In a series of 53 patients with histopathologically confirmed PVRL, the fluorescein angiographic features were compared to 133 individuals with simulating conditions (infectious uveitis, autoimmune-mediated uveitis, and choroidal metastases) [21]. Small, round, hypofluorescent lesions (50–250 μm in diameter) were observed in the posterior pole in the early to late phase of the FA in 45% of PVRL patients, however these findings were observed in only 2% of non-lymphoma cases ($p < 0.001$) [21]. The FA features correlated with the clinically observed small, subtle, white punctuate lesions scattered throughout the fundus.

15.2.4 Indocyanine Green (ICG) Angiography

In PVRL, the lymphoma cells are typically confined to the vitreous cavity and sub-RPE space, rather than the choroid. ICG angiography is particularly useful in

characterizing the choroidal circulation, however this modality still demonstrates distinct features when compared to ICG angiograms obtained from individuals with simulating posterior uveitis. Small, round hypofluorescent lesions (Fig. 15.1c) that disappear in the later phase were observed in 26% of individuals with PVRL, but only 9% of non-lymphoma cases ($p = 0.014$) [21]. It has been suggested that this finding represents a reactive lymphocytic response within the choroid [22, 23].

15.2.5 Optical Coherence Tomography (OCT)

OCT findings are not diagnostic for PVRL, however they may be useful as an ancillary imaging technique in differentiating PVRL from other simulating forms of posterior uveitis. OCT has demonstrated that central foveal thickness is near normal in individuals with PVRL (mean: 231 μm, standard deviation: 45 μm), in contrast to the central foveal thickness in eyes with posterior uveitis in which foveal thickness is frequently increased due to the presence of macular edema (mean: 327 μm, standard deviation: 114 μm) ($p < 0.001$) [21]. In this same series, hyperreflective, nodular RPE lesions (Fig. 15.1d) were observed on the OCT in 42% of patients with PVRL compared to 15% of eyes with non-lymphoma diagnoses ($p = 0.076$) [21].

15.2.6 Fundus Autofluorescence (FAF)

While FAF is not routinely used in the work-up of PVRL, it may potentially highlight some unique features. In one series of five eyes, sub-RPE infiltrates exhibited weak autofluorescence (Fig. 15.1e) by FAF [24]. Brownish clumps on the surface of these lesions revealed bright autofluorescence. In contrast, diffuse retinal infiltrates or retinal whitening showed hypoautofluorescence. This method is useful in characterizing regions of RPE atrophy that appear hypoautofluorescent following therapy [24].

15.2.7 Additional Diagnostic Testing

As clinical findings are often non-specific, biopsy is the gold standard for definitive diagnosis of PVRL [25–29]. An exception is in setting of established PCNSL, with classic ocular findings. In these cases, the diagnosis of PVRL is straightforward, and most experts would concur that ocular biopsy is unnecessary for initiation of treatment. Collaboration with a cytopathologist with experience in diagnosing lymphoma is ideal. The majority of cases of PVRL are aggressive, diffuse large B-cell lymphoma (DLBCL). In a multi-center retrospective review of 221 patients with histologically confirmed PCNSL with ocular involvement, the subtype was determined to be DLBCL in 73%, T-cell in 2%, and type not specified in the remaining 25% [30]. Cytology demonstrates typical features. The cells in PVRL are 2–4 times larger than normal lymphocytes, demonstrate pleomorphism, and contain scant

cytoplasm [28]. The nuclei are large and may be round or oval-shaped, with conspicuous nuclear membranes, finger-like protrusions, and multiple, prominent, eccentrically located nucleoli. Mitotic figures are characteristic [28]. Electron microscopy demonstrates intranuclear inclusions, cytoplasmic crystalloids, pseudopodal cytoplasmic extensions, cytosomes, and autophagic vacuoles [31].

Several biopsy techniques can be employed to confirm diagnosis: vitreous biopsy, retinal biopsy, and sub-retinal biopsy. A common approach is to perform diagnostic 23-Gauge pars plana vitrectomy. Alternatively, 25-Gauge sutureless vitrectomy may be used for improved patient comfort and shorter operative times [27]. Proper surgical technique and handling of vitreous biopsy specimens are essential for optimizing diagnostic accuracy. Vitreous aspirates are typically have low cellularity and lymphoma cells are inherently fragile, making them prone to lysis at the time of sample collection. Biopsy techniques vary by treatment center. A frequently described approach is to procure an undiluted vitreous biopsy (approximately 1–2 mL) before the start of the saline infusion [25, 32]. Next, the saline infusion is initiated, and a second, dilute vitreous sample is procured in a separate syringe [33]. The vitreous cassette can also be submitted as an additional sample [27]. If fresh (unfixed) samples will be analyzed, the biopsy material should be sent to the laboratory within one hour of collection [25]. It is common for multiple vitreous biopsies to be performed to establish the correct diagnosis.

When sub-retinal infiltrates are the predominant clinical feature, a retinal or subretinal biopsy may be preferred. Subretinal biopsy techniques have been previously described in detail [34]. Briefly, a core vitrectomy is performed to allow entry into the subretinal space. Vitreous separation is induced and a thorough vitrectomy is then performed overlying the optimal biopsy site. The retina is incised to create an opening just large enough to allow entry of the vitreous cutter. Suction tubing is advanced through the retinectomy site and with a gentle cutting action, several samples are removed for analysis. Subretinal aspirates should be put into a cytofixative, such as herpes-glutamic acid buffer mediated organic solvent protection effect (H.O.P.E.) fixative or Cytolyt® (Cytyc Corporation) [25]. In a series of 84 patients who had undergone an initial pars plana vitrectomy without definite diagnosis, additional chorioretinal biopsy with analysis by immunohistochemistry and polymerase chain reaction (PCR) gene rearrangement studies was performed in three patients and confirmed the diagnosis of PVRL in all three [35].

Supplemental techniques can be helpful for diagnostic confirmation of PVRL. Immunohistochemistry is useful for identifying markers for leukocytes (CD45), B-cells (CD20, CD79a, PAX-5), T-cells (CD45RO), and macrophages (CD68) [25]. Additionally, clonal cell populations can be established with antibodies directed against κ and λ light chains [28]. Flow cytometry provides a quantitative means by which to assess the proportion of cells that demonstrate these immunohistochemical markers. PCR gene rearrangement can detect monoclonality of the heavy chain variable (V), diversity (D), and joining (J) immunoglobulin gene segments. While supplementary studies may be helpful in establishing the diagnosis of PVRL, the small volume of vitreous aspirates is frequently inadequate for PCR analysis [36, 37]. PCR may be most successful in tissue specimens in which DNA

has been isolated by laser capture microdissection [36]. The measurement of IL-6 and IL-10 in aqueous or vitreous samples can also be helpful in establishing diagnosis, however an elevated IL-10/IL-6 ratio alone is not specific for PVRL [38, 39]. More recently, MYD88 mutations have been shown to be highly associated with PVRL. Identification of this mutation may in the future improve diagnostic accuracy [40].

15.2.8 Systemic Imaging and Evaluation

Due to the association between PVRL and PCNSL, individuals with ophthalmic disease should undergo systemic screening by an oncologist. In confirmed cases of PVRL, MRI of the brain with and without contrast should be performed to exclude central nervous systemic involvement. When CNS involvement is present, the lesions tend to be located in a periventricular distribution; this allows access to the cerebrospinal fluid (CSF) and leptomeninges. Leptomeningeal involvement occurs in 40% of cases [41]. Lumbar puncture may be obtained in selected cases depending upon local practice patterns. CSF samples that are positive typically demonstrate pleocytosis, elevated protein levels, and low or normal glucose. Cytologic identification of malignant lymphoma cells in the CSF is diagnostic. Flow cytometry is the most sensitive and specific marker of PCNSL [42]. Additional diagnostic imaging may include computed tomography scan of the chest, abdomen, and pelvis, testicular ultrasound (in elderly men), and HIV testing in the appropriate setting.

15.2.9 Treatment

PVRL is rare disease and therefore formal treatment consensus guidelines have not been established. Current therapeutic regimens vary depending upon patient factors and local expertise. When disease is limited to the eye and is unilateral, intravitreal therapy with either methotrexate or rituximab (or combination therapy) has been shown to be effective [43, 44]. Prior to the use of intravitreal chemotherapy, external beam radiotherapy (EBRT) was used as first line therapy. At present, the role of EBRT in patients with isolated ocular disease is controversial. EBRT remains a potentially important therapeutic option in patients with bilateral involvement, those who are unable to tolerate intravitreal chemotherapy, and in individuals who are unable return to clinic for multiple injections. In the present era, EBRT is reserved for patients under age 65 years, due to the concern for neurotoxicity in older individuals. In patients with both ocular and CNS disease, the majority are treated with high-dose intravenous chemotherapy. Methotrexate (8 g/m^2) is frequently used, either as monotherapy or as part of a combination regimen. There is consensus that regimens containing high-dose methotrexate, in combination with or without whole brain radiation therapy (WBRT) result in more successful control than regimens that do not contain high-dose methotrexate. Blood–brain barrier disruption (BBBD) has also been used successfully [45].

15.2.10 Prognosis

PVRL is a high-grade, aggressive lymphoma with poor prognosis. The majority of individuals (56–90%) ultimately develop CNS disease [11–13]. In a multicenter, retrospective study of 221 individuals with CNS lymphoma with vitreoretinal involvement, median progression-free survival and overall survival were 18 and 31 months, respectively [30]. Favorable prognostic factors include: age less than 60 years and high initial Karnofsky performance status. Poor prognostic indicators include: involvement of the brainstem and leptomeningeal disease. Vitreoretinal involvement concurrent with CNS disease does not seem to be a prognostic factor [46]. While current retrospective studies have shown that ocular treatment improves disease control and patient symptoms, no survival benefit from ocular therapy has yet been demonstrated [30].

15.3 Primary Uveal Lymphoma

Primary uveal lymphoma is classified based on the site of predominant uveal involvement as: choroidal, iridal, and ciliary body lymphoma. The majority of cases are primary choroidal lymphoma. This is generally a low-grade B-cell lymphoma with an indolent, benign course. Most uveal lymphoma are morphologically similar to extranodal marginal zone lymphoma (EMZL) that involves other systemic sites. Primary iridal lymphoma can be of either B-cell or T-cell origin. These are rare tumors, therefore the incidence of primarily iridal and ciliary body lymphoma is unknown. There are approximately 70–80 case published reports and small series of primary choroidal lymphoma [47].

15.3.1 Clinical Features

Primary uveal lymphoma is most frequently a unilateral disease. When bilateral, the findings may be highly asymmetric. There is a male predominance, and most cases occur in the fifth to seventh decade. Symptoms can include painless, decreased vision, and metamorphopsia due to exudative retinal detachment. In advanced cases, pain and severely decreased vision may result from secondary angle-closure glaucoma. When extraocular extension is present, proptosis and diplopia can occur. A classic fundoscopic finding is the presence of either a placoid choroidal infiltrate, or multiple small, yellow, creamy choroidal infiltrates (Fig. 15.2a). In contrast to PVRL, the vitreous media remains clear. Diffuse thickening of the uveal tract may develop and can be associated with exudative retinal detachment. Occasionally, there may be episcleral extension appearing as a non-mobile “salmon” patch. There is frequent overlap between uveal and ocular adnexal lymphoma [48]. Ocular adnexal lymphoma and uveal lymphoma are similar morphologically and both follow an indolent course in most cases. For this reason, some experts consider uveal lymphoma to be a variant of ocular adnexal lymphoma [49].

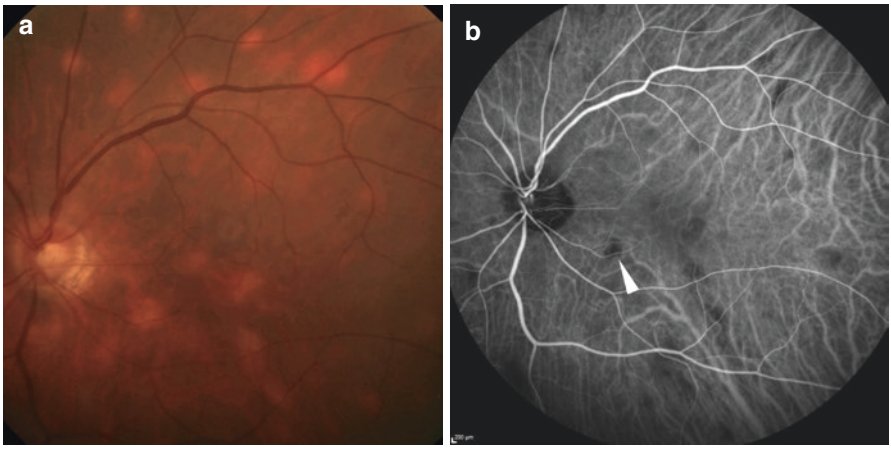

Fig. 15.2 A 72-year-old female was found to have multiple, bilateral, creamy choroidal infiltrates (**a**), which appeared as hypofluorescent foci on ICG (**b**)

15.3.2 Differential Diagnosis

The differential diagnosis of uveal lymphoma is broad and includes: the diffuse form of amelanotic uveal melanoma, uveal effusion syndrome, inflammation such as posterior scleritis, and choroidal metastases. Diffuse uveal melanoma can usually be distinguished based upon its pigmented appearance (although it may be amelanotic in some cases), presence of vascularity, and faster growth rate [50]. Uveal effusion syndrome is frequently bilateral, is associated with dilated episcleral vessels, and tends to occur in individuals with short axial lengths. Posterior scleritis is more common in women and is associated with autoimmune disease. Posterior scleritis also has characteristic ultrasonographic features such as high internal reflectivity and a classic "T-sign" on B-scan. In patients with choroidal metastases, there is frequently a prior history of malignancy. Additionally, B-scan ultrasonography typically confirms medium internal reflectivity.

15.3.3 Fluorescein Angiography (FA)

Fluorescein angiography may be non-specific as an ancillary imaging study for uveal lymphoma as it primarily defines features of the retinal circulation. In some cases, angiography may demonstrate early hypofluoresence with multiple foci of hyperfluorescence and staining in later phases of the angiogram. These angiographic features correlate with the clinically observed choroidal infiltrates.

15.3.4 Indocyanine Green (ICG) Angiography

ICG angiography provides a superior means for characterizing the choroid in comparison to FA, and is therefore the preferred imaging modality for uveal lymphoma. Multiple, round, hypofluorescent lesions (Fig. 15.2b) are typical and correspond to the areas of non-perfusion secondary to the clinically observed space-occupying choroidal infiltrates.

15.3.5 Optical Coherence Tomography (OCT)

OCT, particularly spectral-domain OCT may reveal choroidal thickening, choroidal folds, and an undulating "sea-sick" appearance (Fig. 15.3a, b) of the choroid [51]. Overlying exudative retinal detachment may be apparent on OCT. Enhanced depth imaging (EDI) OCT is particularly useful in characterizing choroidal features.

15.3.6 Ultrasonography

B-scan ultrasonography reveals variable uveal thickening. A-scan ultrasonography demonstrates low internal reflectivity. In addition to characterizing the size and extent of intraocular involvement, ultrasonography is useful in detecting occult extra-scleral extension (Fig. 15.3c). The extra-scleral component may appear as crescentic thickening outside the posterior scleral margin, or as a discrete mass (often near the optic nerve) [48]. Detection of extra-scleral disease is important as this provides a potential site for biopsy to confirm the diagnosis.

15.3.7 Additional Diagnostic Testing

As with other forms of intraocular lymphoma, biopsy remains the gold standard for establishing the diagnosis. Biopsy of the episcleral tumor nodule or choroidal aspirates may confirm diagnosis. Histopathologically, most cases of primary choroidal lymphoma are of the EMZL subtype. The lymphoma cells are usually centrocyte-like, monocytoid, and plasmacytoid type. Dutcher bodies, which are collections of intranuclear immunoglobulin, can be seen. Immunohistochemistry confirms expression of B-cell antigens (CD20 and CD-79a). Gene rearrangement studies or flow cytometry is supportive and can confirm the clonal nature of cell populations.

15.3.8 Systemic Imaging and Evaluation

Neuroimaging, including computed tomography and particularly magnetic resonance imaging of the orbits, may confirm uveal thickening. Neuroimaging is particularly useful for the detection of occult extra-scleral or orbital involvement, which as previously described, may also be observed on ultrasonography.

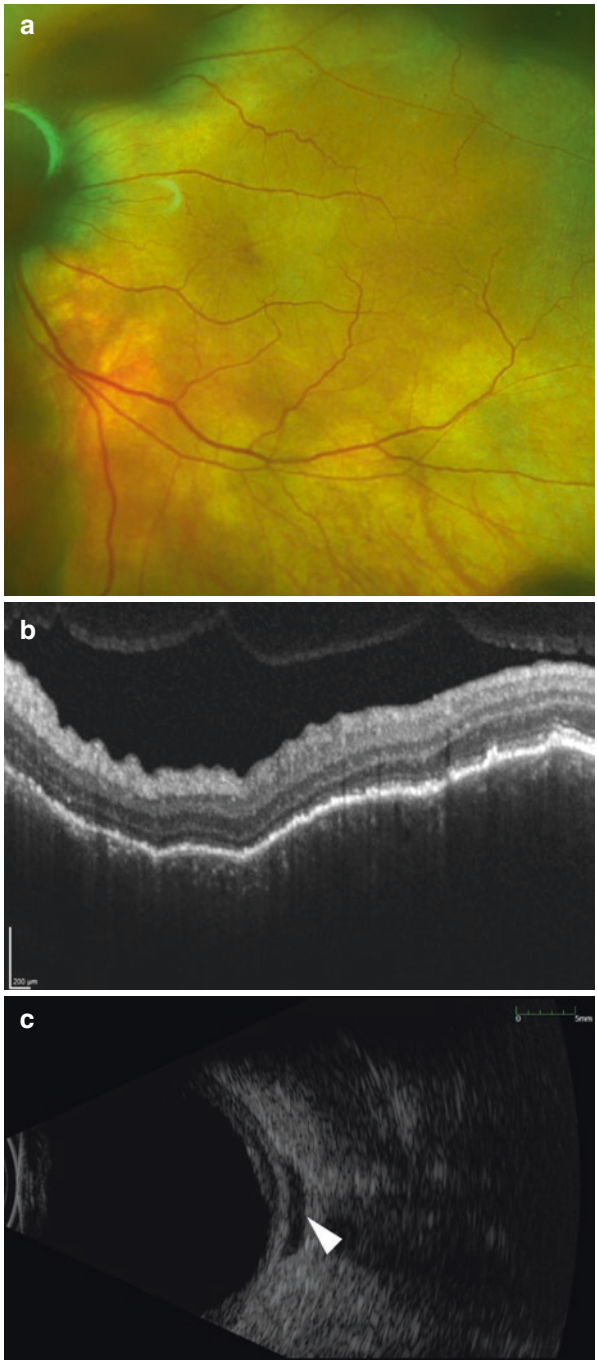

Fig. 15.3 A 67-year-old male with a known history of systemic lymphoplasmacytic lymphoma developed secondary intraocular manifestations. Fundus photograph of the left eye demonstrates a placoid area of amelanotic choroidal thickening (**a**). OCT reveals diffuse choroidal thickening and a "sea-sick" appearance of the choroid (**b**). B-scan ultrasonography detected occult extra-scleral extension (**c**)

Prior to initiation of localized treatment for uveal lymphoma, it is important to perform systemic imaging and laboratory studies to fully evaluate for the possibility of systemic involvement. Systemic evaluation varies by center and local expertise, but imaging studies may include: computed tomography or MRI of the neck, chest, abdomen, and pelvis. Laboratory evaluation may include: complete blood count, and serum protein electrophoresis, among others [52].

15.3.9 Treatment

When disease is limited to the choroid and/or uveal tract, management consists primarily of low-dose intensity-modulated radiotherapy (IMRT) alone (dose ranges from 23–36 Gy). When systemic disease is present, patients can be treated with chemotherapy or monoclonal antibody therapy (rituximab). In some cases, if systemic disease is minimal and asymptomatic, observation may be appropriate. In cases where systemic disease is more widespread, the lymphoma subtype is more aggressive, or the disease burden is causing symptoms, then various systemic therapies are available. Chemotherapy with combination rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP) is utilized for widespread systemic disease and more aggressive subtypes of lymphoma. Intravenous administration of rituximab may also be useful for cases of bilateral ocular involvement. Staging at the time of initial diagnosis and periodic systemic surveillance are important in monitoring response to therapy. Ideally, patients should be followed by a multidisciplinary team including an ocular oncologist, or ophthalmologist familiar with lymphoma, and a medical oncologist.

15.3.10 Prognosis

While there can be significant ocular morbidity associated with uveal lymphoma, overall mortality related to this condition is quite low and similar to age-matched controls without this disease [48]. Similar to ocular adnexal lymphoma, most uveal lymphoma are of the EMZL subtype. EMZL is typically a slowly progressive, indolent lymphoma which most often demonstrates an excellent response to treatment including radiation, chemotherapy, and monoclonal antibody therapy [48]. In one series of 13 eyes with biopsy proven primary choroidal lymphoma, systemic lymphoma eventually developed in two cases (3 and 7 years after the initial ocular diagnosis) [53].

15.4 Secondary Intraocular Manifestations of Systemic Lymphoma

Intraocular lymphoma secondary to systemic lymphoma most frequently involves the uveal tract. The clinical features are therefore similar to primary uveal lymphoma [54]. Retinal involvement without choroidal infiltration can rarely occur [54]. Other

unusual presentations of secondary intraocular lymphoma include: pseudohypopyon (layered lymphoma cells) and iris infiltration [55, 56]. While exceptionally rare, iridal lymphoma secondary to systemic non-lymphoma is probably more common than primary iridal lymphoma [47]. Diffuse large B-cell lymphoma is the most frequent subtype of systemic lymphoma associated with intraocular lymphoma. This is followed by multiple myeloma, extramedullary plasmacytoma, lymphoplasmocytic lymphoma/immunocytoma, and marginal zone B-cell lymphoma [54]. The morphologic and immunophenotypic features of secondary choroidal lymphoma are similar to its primary systemic counterpart. Initial staging evaluation and collaboration with an experienced oncology team are ideal in the management of individuals with systemic lymphoma with intraocular involvement.

15.5 Future Remarks

Intraocular lymphomas are a heterogeneous group of diseases. Each of the major forms: primary vitreoretinal lymphoma, primary uveal lymphoma, and secondary intraocular manifestations of systemic lymphoma are rare disease. Future efforts are needed to characterize these entities, in particular to further understand the relationship between ocular and systemic disease. It has been hypothesized that PVRL may originate from late-germinal center or post-germinal center lymphoid cells, however the neurotropic mechanisms that cause these cells to localize to the CNS is not well understood [57]. Human studies are not well suited for the investigation of intraocular lymphoma pathogenesis or treatment strategies because of the rare nature of the disease. Additionally, the variable presentation, limited volume of available ocular fluids, and fragility of lymphoma cells are challenges in studying these orphan diseases. Animal models have been helpful in the study of lymphoma pathogenesis and investigation of potential therapeutic strategies. The challenge in murine models for intraocular lymphoma is in replicating the clinical features, the behavior of the disease course, molecular profile, systemic immunity, and the microenvironment in humans.

In all fields of oncology, including ophthalmic tumors, there has been a recent trend towards applying standardized staging systems. Among these, a tumor-node-metastasis (TNM) staging system has been developed for ophthalmic neoplasms including ocular adnexal lymphoma and uveal melanoma under the guidance of the American Joint Committee on Cancer (AJCC) [58, 59]. TNM staging has not yet been developed for intraocular lymphoma. Ideally, a universal staging system of this form could be developed in order to facilitate characterization of the clinical and histomorphologic features of these lymphomas that are of prognostic significance, and to assess treatment outcomes.

Key Learning Points

- Intraocular lymphoma can be classified as primary vitreoretinal lymphoma, primary uveal lymphoma, and secondary intraocular manifestations of systemic lymphoma.

- Primary vitreoretinal lymphoma is an aggressive malignancy associated with primary central nervous system lymphoma and poor survival.
- Primary uveal lymphoma most frequently affects the choroid and is generally a low-grade, indolent lymphoma. While there can be significant ocular morbidity associated with this condition, overall survival is generally excellent.
- Secondary intraocular manifestations of systemic lymphoma bear clinical resemblance to uveal lymphoma. The choroid is most frequent affected site. Morphologically, the lymphoma mirrors its primary systemic counterpart.

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